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(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.

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INHIBITION OF OLIG2 ACTIVITY

RELATED APPLICATIONS

[0001] The present application claims the benefit of priority from U.S. Provisional Application 62/126,382, filed February 27, 2015 which has been incorporated by reference in its entirety.

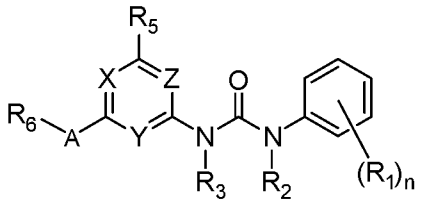
BACKGROUND OF THE INVENTION

[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), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI) (hereinafter "compounds of Formula (I), (II), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI)"), 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:

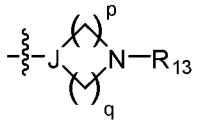
A is a bond, O, or $N(R_{10})$;

X, Y, and Z are each independently N, or $C(R_7)$ wherein at least one of X, Y, and Z are N;

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; 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_5 is 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 substituted or unsubstituted C_2-C_7heterocycloalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted C_2-C_7heteroaryl, $-(C(R_{14})(R_{15}))_mR_{21}$, $-(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$, or  ;

R_{11} and R_{12} are each independently H, or substituted or unsubstituted C_1-C_6alkyl; or R_{11} and R_{12} are taken together to form a 5-, 6-, 7-, or 8-membered heterocyclic ring;

J is C(H), or N;

R_{13} is H, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_2-C_7heterocycloalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted -C_1-C_4alkylC_6-C_{10}aryl, or substituted or unsubstituted -C_1-C_4alkylC_2-C_7heteroaryl;

each R_7 is 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_7heteroaryl;

each R_{14} and R_{15} are each independently H, or substituted or unsubstituted C_1-C_6alkyl; or R_{14} and R_{15} are taken together to form a 4-, 5-, 6-membered cycloalkyl ring;

R_{21} is halogen, -CN, $-NO_2$, -OH, $-OCF_3$, $-OCH_2F$, $-OCF_2H$, $-CF_3$, $-SR_{22}$, $-N(R_{22})S(=O)_2R_{23}$, $-S(=O)_2N(R_{22})_2$, $-S(=O)R_{23}$, $-S(=O)_2R_{23}$, $-C(=O)R_{23}$, $-CO_2R_{22}$, $-C(=O)N(R_{22})_2$, $-N(R_{22})C(=O)R_{23}$, 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;

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

R_{23} is substituted or unsubstituted C_1-C_6alkyl;

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

R_9 is substituted or unsubstituted C_1-C_6alkyl;

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

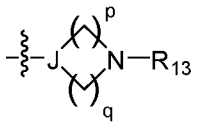
m is 2-6;

n is 0-5;

p is 1-3;

q is 1-3; or

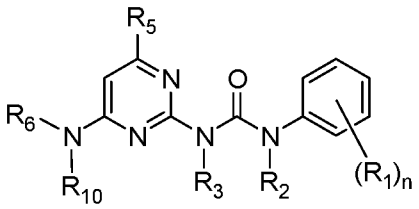
a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[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_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_6 is substituted or unsubstituted C_2-C_7heteroaryl. In a further embodiment is a compound of Formula (I) wherein R_6 is substituted or unsubstituted pyridyl. In another embodiment is a compound of Formula (I) wherein R_6 is  . In another embodiment is a compound of Formula (I) wherein R_{13} is H. In another embodiment is a compound of Formula (I) wherein R_{13} is substituted or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (I) wherein R_{13} is -CH_3. In another embodiment is a compound of Formula (I) wherein R_{13} is -CH_2CH_3. In another embodiment is a compound of Formula (I) wherein J is C(H). In another embodiment is a compound of Formula (I) wherein p is 2 and q is 1. In another embodiment is a compound of Formula (I) wherein p is 3 and q is 1. In another embodiment is a compound of Formula (I) wherein p is 2 and q is 2. In another embodiment of the aforementioned embodiments, is a compound of Formula (I) wherein J is N. In another embodiment is a compound of Formula (I) wherein p is 2 and q is 2. In another embodiment of the aforementioned embodiments, is a compound of Formula (I) wherein R_6 is substituted or unsubstituted C_2-C_7heterocycloalkyl. In another embodiment of the aforementioned embodiments, is a compound of Formula (I) wherein R_6 is substituted or unsubstituted morpholinyl. In another embodiment of the aforementioned embodiments, is a compound of Formula (I) wherein R_6 is substituted or unsubstituted piperidinyl. In another embodiment of the aforementioned embodiments, is a compound of Formula (I) wherein R_6 is -$(C(R_{14})(R_{15}))_mR_{21}$. In another embodiment of the aforementioned embodiments, is a compound of Formula (I) wherein R_{21} is -OH. In another embodiment of the aforementioned embodiments,

is a compound of Formula (I) wherein R_6 is $-(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$. In another embodiment of the aforementioned embodiments, is a compound of Formula (I) wherein R_{11} and R_{12} are each CH_3. In another embodiment of the aforementioned embodiments, is a compound of Formula (I) wherein R_{14} and R_{15} are each H. In another embodiment of the aforementioned embodiments, is a compound of Formula (I) wherein m is 2. In another embodiment of the aforementioned embodiments, is a compound of Formula (I) wherein m is 3. In another embodiment of the aforementioned embodiments, is a compound of Formula (I) wherein A is $N(R_{10})$. In another embodiment is a compound of Formula (I) wherein R_{10} is H or CH_3. In another embodiment of the aforementioned embodiments, is a compound of Formula (I) wherein A is O. In another embodiment of the aforementioned embodiments, is a compound of Formula (I) wherein A is a bond. In another embodiment of the aforementioned embodiments, 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 CH_3. In another embodiment is a compound of Formula (I) wherein R_5 is CH_2CH_3. In another embodiment of the aforementioned embodiments, is a compound of Formula (I) wherein n is 2. In another embodiment of the aforementioned embodiments, is a compound of Formula (I) wherein n is 1. In another embodiment of the aforementioned embodiments, is a compound of Formula (I) wherein n is 0. In another embodiment of the aforementioned embodiments, is a compound of Formula (I) wherein each R_1 is independently halogen, -CN, $-NO_2$, -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. In another embodiment is a compound of Formula (I) wherein each R_1 is independently halogen, -CN, -OH, $-CF_3$, substituted or unsubstituted C_1-C_6alkyl, or substituted or unsubstituted C_1-C_6alkoxy. In another embodiment of the aforementioned embodiments, is a compound of Formula (I) wherein two R_1 are taken together to form a substituted or unsubstituted heterocyclic ring or a substituted or unsubstituted carbocyclic ring. In another embodiment of the aforementioned embodiments, is a compound of Formula (I) wherein X is $C(R)_7$; Y is N; and Z is N. In another embodiment of the aforementioned embodiments, is a compound of Formula (I) wherein X is $C(R)_7$; Y is $C(R)_7$; and Z is N. In another embodiment of the aforementioned embodiments, is a compound of Formula (I) wherein X is $C(R)_7$; Y is N; and Z is $C(R)_7$. In another embodiment of the aforementioned embodiments, is a compound of Formula (I) wherein X is $C(R)_7$; Y is $C(R)_7$; and Z is $C(R)_7$. In another embodiment of the aforementioned embodiments, is a compound of Formula (I) wherein R_7 is H. In another

embodiment of the aforementioned embodiments, is a compound of Formula (I) wherein X is N; Y is N; and Z is N.

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



Formula (II);

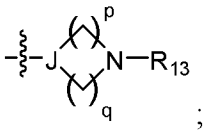
wherein:

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 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_5 is 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 substituted or unsubstituted C_2-C_7heterocycloalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted C_2-C_7heteroaryl, $-(C(R_{14})(R_{15}))_mR_{21}$, or



;

J is C(H);

R_{13} is H, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_2-C_7heterocycloalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted -C_1-C_4alkylC_6-C_{10}aryl, or substituted or unsubstituted -C_1-C_4alkylC_2-C_7heteroaryl;

each R_{14} and R_{15} are each independently H, or substituted or unsubstituted C_1-C_6alkyl; or R_{14} and R_{15} are taken together to form a 4-, 5-, 6-membered cycloalkyl ring;

R_{21} is halogen, -CN, -NO_2, -OH, -OCF_3, -OCH_2F, -OCF_2H, -CF_3, -SR_{22}, -$N(R_{22})S(=O)_2R_{23}$, -$S(=O)_2N(R_{22})_2$, -$S(=O)R_{23}$, -$S(=O)_2R_{23}$, -$C(=O)R_{23}$, -CO_2R_{22}, -$C(=O)N(R_{22})_2$, -$N(R_{22})C(=O)R_{23}$, 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 C_6-C_{10}aryl, or substituted or unsubstituted C_2-C_7heteroaryl;

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

R_{23} is substituted or unsubstituted C_1-C_6alkyl;

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

R_9 is substituted or unsubstituted C_1-C_6alkyl;

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

m is 2-6;

n is 0-5;

p is 1-3;

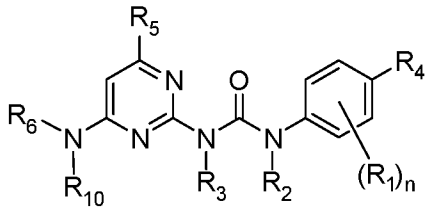
q is 1-3; or

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_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 of the aforementioned embodiments, is a compound of Formula (II) wherein R_6 is -$(C(R_{14})(R_{15}))_mR_{21}$. In another embodiment of the aforementioned embodiments, is a compound of Formula (II) wherein R_{21} is -OH, -$N(R_{22})S(=O)_2R_{23}$, -CO_2R_{22}, -$C(=O)N(R_{22})_2$, -$N(R_{22})C(=O)R_{23}$, substituted or unsubstituted C_1-C_6alkoxy, or substituted or unsubstituted C_2-C_7heteroaryl. In another embodiment of the aforementioned embodiments, is a compound of Formula (II) wherein R_{21} is -OH. In another embodiment of the aforementioned embodiments, is a compound of Formula (II) wherein R_{21} is -$N(R_{22})S(=O)_2R_{23}$. In another embodiment of the aforementioned embodiments, is a compound of Formula (II) wherein R_{21} is -$N(R_{22})C(=O)R_{23}$. In a further embodiment, is a compound of Formula (II) wherein R_{21} is –$N(R_{22})S(=O)_2R_{23}$. In another embodiment of the aforementioned embodiments, is a compound of Formula (II) wherein R_{21} is substituted or unsubstituted C_1-C_6alkoxy. In another embodiment of the

aforementioned embodiments, is a compound of Formula (II) wherein R_{21} is substituted or unsubstituted C_2-C_7heteroaryl. In another embodiment of the aforementioned embodiments, is a compound of Formula (II) wherein each R_{22} is independently H or unsubstituted C_1-C_6alkyl; and R_{23} is unsubstituted C_1-C_6alkyl. In another embodiment of the aforementioned embodiments, is a compound of Formula (II) wherein R_{14} and R_{15} are each independently H or substituted or unsubstituted C_1-C_6alkyl. In another embodiment of the aforementioned embodiments, is a compound of Formula (II) wherein R_{14} and R_{15} are each H. In another embodiment of the aforementioned embodiments, is a compound of Formula (II) wherein m is 2. In another embodiment of the aforementioned embodiments, is a compound of Formula (II) wherein m is 3. In another embodiment is a compound of Formula (II) wherein R_6 is substituted or unsubstituted C_2-C_7heteroaryl. In a further embodiment is a compound of Formula (II) wherein R_6 is substituted or unsubstituted pyridyl. In another embodiment of the aforementioned embodiments, is a compound of Formula (II) wherein R_6 is substituted or unsubstituted C_2-C_7heterocycloalkyl. In another embodiment of the aforementioned embodiments, is a compound of Formula (II) wherein R_6 is substituted or unsubstituted morpholinyl. In another embodiment of the aforementioned embodiments, is a compound of Formula (II) wherein R_6 is substituted or unsubstituted piperidinyl. In another embodiment is a compound of Formula (II) wherein R_{10} is H or CH_3.

[0008] In another aspect, described herein is a compound of Formula (IIA):



Formula (IIA);

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; 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, $-NO_2$, -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; or two R_1 are taken together to form a substituted or unsubstituted heterocyclic ring or a substituted or unsubstituted carbocyclic ring; wherein when n is 0, R_4 is not halogen;

R_5 is 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 $-(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$;

R_{11} and R_{12} are each independently H, or substituted or unsubstituted C_1-C_6alkyl; or R_{11} and R_{12} are taken together to form a 5-, 6-, 7-, or 8-membered heterocyclic ring;

R_{13} is H, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_2-C_7heterocycloalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted -C_1-C_4alkylC_6-C_{10}aryl, or substituted or unsubstituted -C_1-C_4alkylC_2-C_7heteroaryl;

each R_{14} and R_{15} are each independently H, or substituted or unsubstituted C_1-C_6alkyl; or R_{14} and R_{15} are taken together to form a 4-, 5-, 6-membered cycloalkyl ring;

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

R_9 is substituted or unsubstituted C_1-C_6alkyl;

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

m is 2-6;

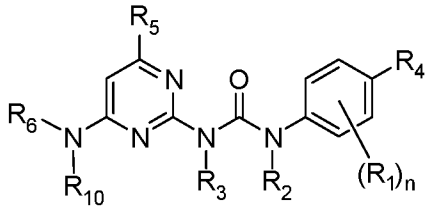
n is 0-4; or

a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[0009] In one embodiment is a compound of Formula (IIA) 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 (IIA) wherein R_2 and R_3 are each H. In another embodiment is a compound of Formula (IIA) 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 (IIA)

wherein R_2 and R_3 are taken together to form a 5-membered heterocyclic ring. In another embodiment of the aforementioned embodiments, is a compound of Formula (II) wherein R_6 is $-(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$ and R_{14} and R_{15} are each H. In another embodiment of the aforementioned embodiments, is a compound of Formula (II) wherein R_{11} and R_{12} are each independently H, or substituted or unsubstituted C_1-C_6alkyl. In another embodiment of the aforementioned embodiments, is a compound of Formula (II) wherein R_{11} and R_{12} are each independently unsubstituted C_1-C_6alkyl. In another embodiment of the aforementioned embodiments, is a compound of Formula (II) wherein R_{11} and R_{12} are each $-CH_3$. In another embodiment of the aforementioned embodiments, is a compound of Formula (II) wherein m is 2. In another embodiment of the aforementioned embodiments, is a compound of Formula (II) wherein m is 3. In another embodiment is a compound of Formula (II) wherein R_{10} is H or CH_3. In another embodiment of the aforementioned embodiments, is a compound of Formula (II) wherein n is 0. In another embodiment of the aforementioned embodiments, is a compound of Formula (II) wherein n is 1.

[0010] In another aspect, described herein is a compound of Formula (VI):



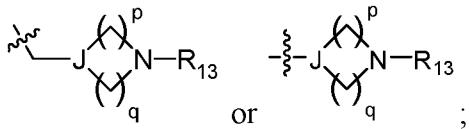
Formula (VI);

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; 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 or C_1-C_4alkyl; or R_2 and R_3 are taken together to form a 5- or 6-membered heterocyclic ring;

R_5 is substituted or unsubstituted C_1-C_6alkyl;

R_6 is unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_2-C_7heterocycloalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted C_2-C_7heteroaryl, $-(C(R_{14})(R_{15}))_mR_{21}$,  or ;

J is C(H);

R_{13} is H, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_2-C_7heterocycloalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted $-C_1$-C_4alkylC_6-C_{10}aryl, or substituted or unsubstituted $-C_1$-C_4alkylC_2-C_7heteroaryl;

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

R_{21} is halogen, $-CN$, $-NO_2$, $-OH$, $-OCF_3$, $-OCH_2F$, $-OCF_2H$, $-CF_3$, $-SR_{22}$, $-N(R_{22})S(=O)_2R_{23}$, $-S(=O)_2N(R_{22})_2$, $-S(=O)R_{23}$, $-S(=O)_2R_{23}$, $-C(=O)R_{23}$, $-CO_2R_{22}$, $-C(=O)N(R_{22})_2$, $-N(R_{22})C(=O)R_{23}$, substituted or unsubstituted C_1-C_6alkoxy, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_2-C_7heterocycloalkyl, or substituted or unsubstituted C_2-C_7heteroaryl;

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

R_{23} is substituted or unsubstituted C_1-C_6alkyl;

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

R_9 is substituted or unsubstituted C_1-C_6alkyl;

R_{10} is H;

m is 2-6;

n is 0-5;

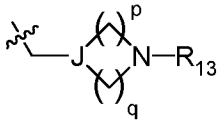
p is 1-3;

q is 1-3; or

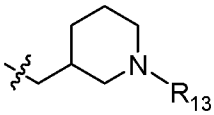
a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[0011] In some embodiments is a compound of Formula (VI) wherein R_2 and R_3 are each independently H or C_1-C_4alkyl. In another embodiment is a compound of Formula (VI) wherein R_2 and R_3 are each H. In another embodiment is a compound of Formula (VI) 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 (VI) wherein R_2 and R_3 are taken together to form a 5-membered heterocyclic ring. In another embodiment is a compound of Formula (VI) wherein R_6 is $-(C(R_{14})(R_{15}))_mR_{21}$. In another embodiment is a compound of Formula (VI) wherein R_{14} and R_{15} are each independently H, halogen, or unsubstituted C_1-C_6alkyl. In another embodiment is a

compound of Formula (VI) wherein R_{14} and R_{15} are each H. In another embodiment is a compound of Formula (VI) wherein R_{21} is -OH, $-N(R_{22})S(=O)_2R_{23}$, $-CO_2R_{22}$, $-C(=O)N(R_{22})_2$, $-N(R_{22})C(=O)R_{23}$, substituted or unsubstituted C_1-C_6alkoxy, or substituted or unsubstituted C_2-C_7heteroaryl. In another embodiment of the aforementioned embodiments, is a compound of Formula (VI) wherein R_{21} is -OH. In another embodiment of the aforementioned embodiments, is a compound of Formula (VI) wherein R_{21} is $-N(R_{22})S(=O)_2R_{23}$. In another embodiment of the aforementioned embodiments, is a compound of Formula (VI) wherein R_{21} is $-N(R_{22})C(=O)R_{23}$. In a further embodiment, R_{21} is $-N(R_{22})S(=O)_2R_{23}$. In another embodiment of the aforementioned embodiments, is a compound of Formula (VI) wherein R_{21} is substituted or unsubstituted C_1-C_6alkoxy. In another embodiment of the aforementioned embodiments, is a compound of Formula (VI) wherein R_{21} is substituted or unsubstituted C_2-C_7heteroaryl. In another embodiment is a compound of Formula (VI) wherein each R_{22} is independently H or unsubstituted C_1-C_6alkyl; and R_{23} is unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (VI) wherein m is 2. In another embodiment is a compound of Formula (VI) wherein m is 3. In another embodiment is a compound of Formula (VI) wherein R_6 is



. In another embodiment is a compound of Formula (VI) wherein R_6 is



. In another embodiment is a compound of Formula (VI) wherein R_{13} is H or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (VI) wherein each R_1 is independently halogen, $-OCF_3$, $-CF_3$, unsubstituted C_1-C_6alkyl, or unsubstituted C_1-C_6alkoxy. In another embodiment is a compound of Formula (VI) wherein each R_1 is independently halogen. In another embodiment is a compound of Formula (VI) wherein n is 1. In another embodiment is a compound of Formula (VI) wherein each R_1 is independently halogen. In another embodiment is a compound of Formula (VI) wherein n is 2. In another embodiment is a compound of Formula (VI) wherein each R_1 is independently halogen. In another embodiment is a compound of Formula (VI) wherein n is 0.

[0012] In another aspect is a pharmaceutical composition comprising a compound of Formula (I), (II), or (IIA) 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 (I), (II), (IIA), or (VI) or a pharmaceutically acceptable salt, solvate, or prodrug thereof, and at least one pharmaceutically acceptable excipient.

[0013] In another aspect is the use of a compound of Formula (I), (II), or (IIA) 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 is provided. The method includes contacting the cell with a compound of Formula (I), (II), or (IIA) including embodiments thereof.

[0014] In another aspect is the use of a compound of Formula (I), (II), (IIA), or (VI) 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 is provided. The method includes contacting the cell with a compound of Formula (I), (II), (IIA), or (VI) including embodiments thereof.

[0015] 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), or (IIA) 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), or (IIA) or a pharmaceutically acceptable salt, solvate, or prodrug thereof; wherein the disease is cancer or Down's Syndrome.

[0016] 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), (IIA), or (VI) 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), (IIA), or (VI) or a pharmaceutically acceptable salt, solvate, or prodrug thereof; wherein the disease is cancer or Down's Syndrome.

[0017] 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), or (IIA), 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), or (IIA) 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), or (IIA) or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[0018] 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), (IIA), or (VI) 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), or (IIA) 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), (IIA), or (VI) or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[0019] 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), or (IIA) 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 (I), (II), (IIA), or (VI) 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.

[0020] 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), or (IIA) 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 (I), (II), (IIA), or (VI) or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[0021] In another aspect is the use of a compound of Formula (I), (II), or (IIA) 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 (I), (II), (IIA), or (VI) in the manufacture of a medicament for the treatment of a disease, disorder, or condition that would benefit from inhibition of Olig2 activity.

[0022] 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

[0023] 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 bLHL 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.

[0024] 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.

[0025] 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.

[0026] 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.

[0027] 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.

[0028] 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.

[0029] 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).

[0030] The Olig2 targeted inhibitors described herein should prove unique in terms of efficacy and toxicity.

[0031] 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.

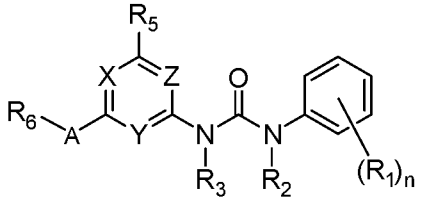
[0032] In another aspect, methods of inhibiting the activity of OLIG2 are provided. The methods include contacting an Olig2 protein with an effective amount of a compound provided herein (e.g., a compound of Formula (I), (II), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI). The compound may have 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.

[0033] 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), (IIA), (IIB), (IIC), (IID), (III), (IV), and (V)). 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

[0034] 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.

[0035] In one aspect, described herein is a compound of Formula (I):



Formula (I);

wherein:

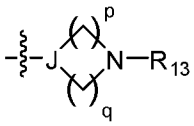
A is a bond, O, or $N(R_{10})$;

X, Y, and Z are each independently N, or $C(R_7)$ wherein at least one of X, Y, and Z are N;

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; 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_5 is 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 substituted or unsubstituted C_2-C_7heterocycloalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted C_2-C_7heteroaryl, $-(C(R_{14})(R_{15}))_mR_{21}$, $-(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$, or  ;

R_{11} and R_{12} are each independently H, or substituted or unsubstituted C_1-C_6alkyl; or R_{11} and R_{12} are taken together to form a 5-, 6-, 7-, or 8-membered heterocyclic ring;

J is C(H), or N;

R_{13} is H, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_2-C_7heterocycloalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted $-C_1$-C_4alkylC_6-C_{10}aryl, or substituted or unsubstituted $-C_1$-C_4alkylC_2-C_7heteroaryl;

each R_7 is 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_7heteroaryl;

each R_{14} and R_{15} are each independently H, or substituted or unsubstituted C_1-C_6alkyl; or R_{14} and R_{15} are taken together to form a 4-, 5-, 6-membered cycloalkyl ring;

R_{21} is halogen, -CN, -NO_2, -OH, -OCF_3, -OCH_2F, -OCF_2H, -CF_3, -SR_{22}, -$N(R_{22})S(=O)_2R_{23}$, -$S(=O)_2N(R_{22})_2$, -$S(=O)R_{23}$, -$S(=O)_2R_{23}$, -$C(=O)R_{23}$, -CO_2R_{22}, -$C(=O)N(R_{22})_2$, -$N(R_{22})C(=O)R_{23}$, 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;

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

R_{23} is substituted or unsubstituted C_1-C_6alkyl;

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

R_9 is substituted or unsubstituted C_1-C_6alkyl;

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

m is 2-6;

n is 0-5;

p is 1-3;

q is 1-3; or

a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[0036] In one embodiment is a compound of Formula (I) wherein A is O or N(R_{10}). In another embodiment is a compound of Formula (I) wherein A is O or N(H). In another embodiment is a compound of Formula (I) wherein A is O. In another embodiment is a compound of Formula (I) wherein A is N(R_{10}). In another embodiment is a compound of Formula (I) wherein A is N(H). In another embodiment is a compound of Formula (I) wherein A is N(CH_3). In another embodiment is a compound of Formula (I) wherein A is a bond.

[0037] In another embodiment is a compound of Formula (I) wherein R_6 is substituted or unsubstituted C_3-C_8cycloalkyl. In another embodiment is a compound of Formula (I) wherein R_6 is substituted or unsubstituted cyclopropyl. In another embodiment is a compound of Formula (I) wherein R_6 is substituted or unsubstituted cyclobutyl. In another embodiment is a compound of Formula (I) wherein R_6 is substituted or unsubstituted cyclopentyl. In another embodiment is a compound of Formula (I) wherein R_6 is substituted or unsubstituted cyclohexyl.

[0038] In another embodiment is a compound of Formula (I) wherein R_6 is substituted or unsubstituted C_2-C_7heteroaryl. In another embodiment is a compound of Formula (I) wherein R_6 is substituted or unsubstituted furanyl, thiophenyl, pyrrolyl, pyridyl, oxazolyl, thiazolyl, imidazolyl, isoxazolyl, isothiazolyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, oxadiazolyl,

thiadiazolyl, triazolyl, indolyl, benzothiophenyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, benzoxadiazolyl, benzothiadiazolyl, benzotriazolyl, pyrazolopyridinyl, imidazopyridinyl, pyrrolopyridinyl, pyrrolopyrimidinyl, indolizinyl, purinyl, furopyridinyl, thienopyridinyl, furopyrrolyl, furofuranyl, thienofuranyl, 1,4-dihydropyrrolopyrrolyl, thienopyrrolyl, thienothiophenyl, quinolinyl, isoquinolinyl, quinoxalinyl, furopyrazolyl, thienopyrazolyl, selenophenyl, selenazolyl, and benzoisoxazolyl. In another embodiment is a compound of Formula (I) wherein R_6 is substituted or unsubstituted pyridyl. In another embodiment is a compound of Formula (I) wherein R_6 is substituted pyridyl. In another embodiment is a compound of Formula (I) wherein R_6 is unsubstituted pyridyl.

[0039] In another embodiment is a compound of Formula (I) wherein R_6 is $-(C(R_{14})(R_{15}))_mR_{21}$. In another embodiment is a compound of Formula (I) wherein R_6 is $-(C(R_{14})(R_{15}))_mR_{21}$, and each R_{14} and R_{15} are H. In another embodiment is a compound of Formula (I) wherein R_6 is $-(C(R_{14})(R_{15}))_mR_{21}$, m is 2, and each R_{14} and R_{15} are H. In another embodiment is a compound of Formula (I) wherein R_6 is $-(CH_2)_mR_{21}$, m is 2, and R_{21} is substituted or unsubstituted C_2-C_7heterocycloalkyl. In another embodiment is a compound of Formula (I) wherein R_6 is $-(CH_2)_mR_{21}$, m is 2, and R_{21} is substituted or unsubstituted C_3-C_8cycloalkyl. In another embodiment is a compound of Formula (I) wherein R_6 is $-(CH_2)_mR_{21}$, m is 2, and R_{21} is substituted or unsubstituted C_6-C_{10}aryl. In another embodiment is a compound of Formula (I) wherein R_6 is $-(CH_2)_mR_{21}$, m is 2, and R_{21} is substituted or unsubstituted phenyl. In another embodiment is a compound of Formula (I) wherein R_6 is $-(CH_2)_mR_{21}$, m is 2, and R_{21} is substituted or unsubstituted C_2-C_7heteroaryl. In another embodiment is a compound of Formula (I) wherein R_6 is $-(CH_2)_mR_{21}$, m is 2, and R_{21} is -OH.

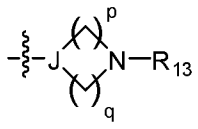
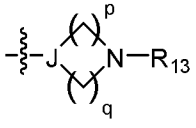
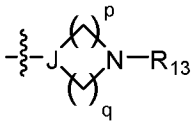
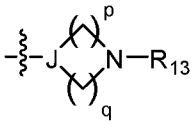
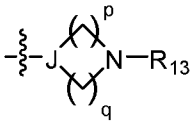
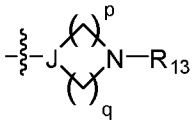
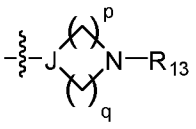
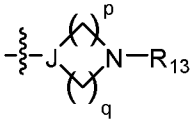
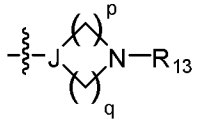
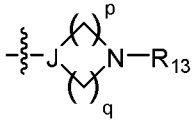
[0040] In another embodiment is a compound of Formula (I) wherein R_6 is $-(C(R_{14})(R_{15}))_mR_{21}$, m is 3, and each R_{14} and R_{15} are H. In another embodiment is a compound of Formula (I) wherein R_6 is $-(CH_2)_mR_{21}$, m is 3, and R_{21} is substituted or unsubstituted C_2-C_7heterocycloalkyl. In another embodiment is a compound of Formula (I) wherein R_6 is $-(CH_2)_mR_{21}$, m is 3, and R_{21} is substituted or unsubstituted C_3-C_8cycloalkyl. In another embodiment is a compound of Formula (I) wherein R_6 is $-(CH_2)_mR_{21}$, m is 3, and R_{21} is substituted or unsubstituted C_6-C_{10}aryl. In another embodiment is a compound of Formula (I) wherein R_6 is $-(CH_2)_mR_{21}$, m is 3, and R_{21} is substituted or unsubstituted phenyl. In another embodiment is a compound of Formula (I) wherein R_6 is $-(CH_2)_mR_{21}$, m is 3, and R_{21} is substituted or unsubstituted C_2-C_7heteroaryl. In another embodiment is a compound of Formula (I) wherein R_6 is $-(CH_2)_mR_{21}$, m is 3, and R_{21} is -OH.

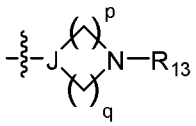
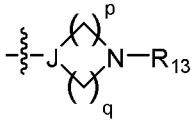
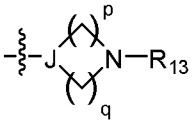
[0041] In another embodiment is a compound of Formula (I) wherein R_6 is $-(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$. In another embodiment is a compound of Formula (I) wherein R_6 is

$-(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$, m is 2, and each R_{14} and R_{15} are H. In another embodiment is a compound of Formula (I) wherein R_6 is $-(CH_2)_mN(R_{11})(R_{12})$, m is 2, and R_{11} and R_{12} are each H. In another embodiment is a compound of Formula (I) wherein R_6 is $-(CH_2)_mN(R_{11})(R_{12})$, m is 2, R_{11} is substituted or unsubstituted C_1-C_6alkyl, and R_{12} is H. In another embodiment is a compound of Formula (I) wherein R_6 is $-(CH_2)_mN(R_{11})(R_{12})$, m is 2, R_{11} is CH_3, and R_{12} is H. In another embodiment is a compound of Formula (I) wherein R_6 is $-(CH_2)_mN(R_{11})(R_{12})$, m is 2, R_{11} is substituted or unsubstituted C_1-C_6alkyl, and R_{12} is substituted or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (I) wherein R_6 is $-(CH_2)_mN(R_{11})(R_{12})$, m is 2, R_{11} is CH_3, and R_{12} is CH_3. In another embodiment is a compound of Formula (I) wherein R_6 is $-(CH_2)_mN(R_{11})(R_{12})$, m is 2, and R_{11} and R_{12} are taken together to form a 5-, 6-, 7-, or 8-membered heterocyclic ring. In another embodiment is a compound of Formula (I) wherein R_6 is $-(CH_2)_mN(R_{11})(R_{12})$, m is 2, and R_{11} and R_{12} are taken together to form a 5-membered heterocyclic ring. In another embodiment is a compound of Formula (I) wherein R_6 is $-(CH_2)_mN(R_{11})(R_{12})$, m is 2, and R_{11} and R_{12} are taken together to form a 6-membered heterocyclic ring.

[0042] 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 $-(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$, m is 3, and each R_{14} and R_{15} are H. In another embodiment is a compound of Formula (I) wherein R_6 is $-(CH_2)_mN(R_{11})(R_{12})$, m is 3, and R_{11} and R_{12} are each H. In another embodiment is a compound of Formula (I) wherein R_6 is $-(CH_2)_mN(R_{11})(R_{12})$, m is 3, R_{11} is substituted or unsubstituted C_1-C_6alkyl, and R_{12} is H. In another embodiment is a compound of Formula (I) wherein R_6 is $-(CH_2)_mN(R_{11})(R_{12})$, m is 3, R_{11} is CH_3, and R_{12} is H. In another embodiment is a compound of Formula (I) wherein R_6 is $-(CH_2)_mN(R_{11})(R_{12})$, m is 3, R_{11} is substituted or unsubstituted C_1-C_6alkyl, and R_{12} is substituted or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (I) wherein R_6 is $-(CH_2)_mN(R_{11})(R_{12})$, m is 3, R_{11} is CH_3, and R_{12} is CH_3. In another embodiment is a compound of Formula (I) wherein R_6 is $-(CH_2)_mN(R_{11})(R_{12})$, m is 3, and R_{11} and R_{12} are taken together to form a 5-, 6-, 7-, or 8-membered heterocyclic ring. In another embodiment is a compound of Formula (I) wherein R_6 is $-(CH_2)_mN(R_{11})(R_{12})$, m is 3, and R_{11} and R_{12} are taken together to form a 5-membered heterocyclic ring. In another embodiment is a compound of Formula (I) wherein R_6 is $-(CH_2)_mN(R_{11})(R_{12})$, m is 3, and R_{11} and R_{12} are taken together to form a 6-membered heterocyclic ring.

[0043] In another embodiment is a compound of Formula (I) wherein R_6 is substituted or unsubstituted C_2-C_7heterocycloalkyl. In another embodiment is a compound of Formula (I)

wherein R_6 is  . In another embodiment is a compound of Formula (I) wherein R_6 is  and J is C(H). In another embodiment is a compound of Formula (I) wherein R_6 is  , J is C(H), p is 1, and q is 1. In another embodiment is a compound of Formula (I) wherein R_6 is  , J is C(H), p is 2, and q is 1. In another embodiment is a compound of Formula (I) wherein R_6 is  , J is C(H), p is 3, and q is 1. In another embodiment is a compound of Formula (I) wherein R_6 is  , J is C(H), p is 2, and q is 2. In another embodiment is a compound of Formula (I) wherein R_6 is  , J is C(H), p is 1, q is 1, and R_{13} is substituted or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (I) wherein R_6 is  , J is C(H), p is 2, q is 1, and R_{13} is substituted or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (I) wherein R_6 is  , J is C(H), p is 3, q is 1, and R_{13} is substituted or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (I) wherein R_6 is  , J is C(H), p is 2, q is 2, and R_{13} is substituted or unsubstituted C_1-C_6alkyl.

[0044] In another embodiment is a compound of Formula (I) wherein R_6 is  and J is N. In another embodiment is a compound of Formula (I) wherein R_6 is  , J is N, p is 2, and q is 2. In another embodiment is a compound of Formula (I) wherein R_6 is  , J is N, p is 2, q is 2, and R_{13} is substituted or unsubstituted C_1-C_6alkyl.

[0045] 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 $-CF_3$. 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 $-CH_3$. 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 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 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.

[0046] 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. In another embodiment is a compound of Formula (I) wherein R_2 and R_3 are each H.

[0047] 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.

[0048] 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.

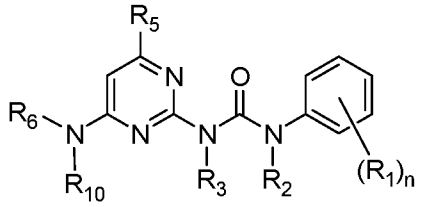
[0049] In another embodiment is a compound of Formula (I) wherein n is 0.

[0050] In another embodiment is a compound of Formula (I) 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. In another embodiment is a compound of Formula (I) wherein each R_1 is independently halogen, -CN, -OH, $-CF_3$, substituted or unsubstituted C_1-C_6alkyl, or substituted or unsubstituted C_1-C_6alkoxy. In another embodiment is a compound of Formula (I) wherein each R_1 is independently halogen, -CN, $-OCF_3$, $-OCH_2F$, $-OCF_2H$, $-CF_3$, 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. In another embodiment is a compound of Formula (I) wherein each R_1 is independently halogen, -CN, $-OCF_3$, $-OCH_2F$, $-OCF_2H$, $-CF_3$, substituted or unsubstituted C_1-C_6alkyl, or substituted or unsubstituted C_1-C_6alkoxy. In another embodiment is a compound of Formula (I) wherein each R_1 is independently halogen, -CN, $-OCF_3$, $-OCH_2F$, $-OCF_2H$, $-CF_3$, 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 (I) wherein each R_1 is independently halogen, -CN, $-OCF_3$, $-OCH_2F$, $-OCF_2H$, $-CF_3$, 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 (I) wherein n is 3, and each R_1 is independently halogen. In another embodiment is a compound of Formula (I) wherein n is 2, and each R_1 is independently halogen. In another embodiment is a compound of Formula (I) wherein n is 2, and each R_1 is independently F or Cl. In another embodiment is a compound of Formula (I) wherein n is 2, and each R_1 is F. In another embodiment is a compound of Formula (I) wherein n is 2, and each R_1 is independently Cl. In another

embodiment is a compound of Formula (I) wherein n is 2, and each R_1 is independently halogen or $-CF_3$. In another embodiment is a compound of Formula (I) wherein n is 2, and each R_1 is independently F or $-CF_3$. In another embodiment is a compound of Formula (I) wherein n is 2, and each R_1 is independently Cl or $-CF_3$. In another embodiment is a compound of Formula (I) wherein n is 1, and R_1 is halogen. In another embodiment is a compound of Formula (I) wherein n is 1, and R_1 is F. In another embodiment is a compound of Formula (I) wherein n is 1, and R_1 is Cl. In another embodiment is a compound of Formula (I) wherein n is 1, and R_1 is $-CF_3$. In another embodiment is a compound of Formula (I) wherein n is 1, and R_1 is substituted or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (I) wherein n is 1, and R_1 is CH_3. In another embodiment is a compound of Formula (I) wherein n is 1, and R_1 is substituted or unsubstituted C_1-C_6alkoxy. In another embodiment is a compound of Formula (I) wherein n is 1, and R_1 is $-OCH_3$. In another embodiment is a compound of Formula (I) wherein n is 1, and R_1 is $-OCF_3$. In another embodiment is a compound of Formula (I) wherein n is 1, and R_1 is $-OCF_2H$.

[0051] In a further embodiment of the aforementioned embodiments of Formula (I), X is $C(R_7)$; Y is N; and Z is N. In a further embodiment of the aforementioned embodiments of Formula (I), X is C(H); Y is N; and Z is N. In a further embodiment of the aforementioned embodiments of Formula (I), X is $C(R_7)$; Y is $C(R_7)$; and Z is N. In a further embodiment of the aforementioned embodiments of Formula (I), X is C(H); Y is C(H); and Z is N. In a further embodiment of the aforementioned embodiments of Formula (I), X is $C(R_7)$; Y is N; and Z is $C(R_7)$. In a further embodiment of the aforementioned embodiments of Formula (I), X is C(H); Y is N; and Z is C(H). In a further embodiment of the aforementioned embodiments of Formula (I), X is $C(R_7)$; Y is $C(R_7)$; and Z is $C(R_7)$. In a further embodiment of the aforementioned embodiments of Formula (I), X is C(H); Y is C(H); and Z is C(H).

[0052] In another aspect, described herein is a compound of Formula (II):



Formula (II);

wherein:

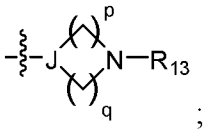
each R_1 is independently halogen, -CN, $-NO_2$, -OH, $-OCF_3$, $-OCH_2F$, $-OCF_2H$, $-CF_3$, $-SR_8$, $-N(R_8)S(=O)_2R_9$, $-S(=O)_2N(R_8)_2$, $-S(=O)R_9$, $-S(=O)_2R_9$, $-C(=O)R_9$, $-CO_2R_8$, $-N(R_8)_2$, $-C(=O)N(R_8)_2$, $-N(R_8)C(=O)R_9$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6alkoxy, substituted or unsubstituted 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_5 is 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 substituted or unsubstituted C_2-C_7heterocycloalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted C_2-C_7heteroaryl, $-(C(R_{14})(R_{15}))_mR_{21}$, or



;

J is C(H);

R_{13} is H, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_2-C_7heterocycloalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted -C_1-C_4alkylC_6-C_{10}aryl, or substituted or unsubstituted -C_1-C_4alkylC_2-C_7heteroaryl;

each R_{14} and R_{15} are each independently H, or substituted or unsubstituted C_1-C_6alkyl; or R_{14} and R_{15} are taken together to form a 4-, 5-, 6-membered cycloalkyl ring;

R_{21} is halogen, -CN, $-NO_2$, -OH, $-OCF_3$, $-OCH_2F$, $-OCF_2H$, $-CF_3$, $-SR_{22}$, $-N(R_{22})S(=O)_2R_{23}$, $-S(=O)_2N(R_{22})_2$, $-S(=O)R_{23}$, $-S(=O)_2R_{23}$, $-C(=O)R_{23}$, $-CO_2R_{22}$, $-C(=O)N(R_{22})_2$, $-N(R_{22})C(=O)R_{23}$, 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 C_6-C_{10}aryl, or substituted or unsubstituted C_2-C_7heteroaryl;

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

R_{23} is substituted or unsubstituted C_1-C_6alkyl;

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

R_9 is substituted or unsubstituted C_1-C_6alkyl;

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

m is 2-6;

n is 0-5;

p is 1-3;

q is 1-3; or

a pharmaceutically acceptable salt, solvate, or prodrug thereof.

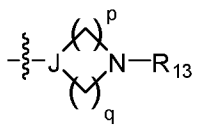
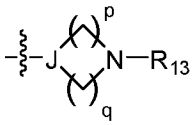
[0053] In another embodiment is a compound of Formula (II) wherein R_6 is substituted or unsubstituted C_3-C_8cycloalkyl. In another embodiment is a compound of Formula (II) wherein R_6 is substituted or unsubstituted cyclopropyl. In another embodiment is a compound of Formula (II) wherein R_6 is substituted or unsubstituted cyclobutyl. In another embodiment is a compound of Formula (II) wherein R_6 is substituted or unsubstituted cyclopentyl. In another embodiment is a compound of Formula (II) wherein R_6 is substituted or unsubstituted cyclohexyl.

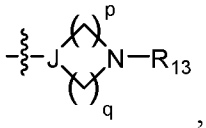
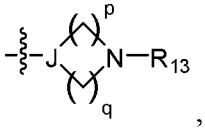
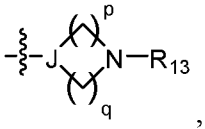
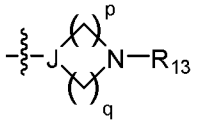
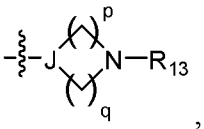
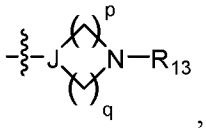
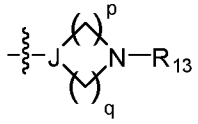
[0054] In another embodiment is a compound of Formula (II) wherein R_6 is substituted or unsubstituted C_2-C_7heteroaryl. In another embodiment is a compound of Formula (II) wherein R_6 is substituted or unsubstituted furanyl, thiophenyl, pyrrolyl, pyridyl, oxazolyl, thiazolyl, imidazolyl, isoxazolyl, isothiazolyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, oxadiazolyl, thiadiazolyl, triazolyl, indolyl, benzothiophenyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, benzoxadiazolyl, benzothiadiazolyl, benzotriazolyl, pyrazolopyridinyl, imidazopyridinyl, pyrrolopyridinyl, pyrrolopyrimidinyl, indolizinyl, purinyl, furopyridinyl, thienopyridinyl, furopyrrolyl, furofuranyl, thienofuranyl, 1,4-dihydropyrrolopyrrolyl, thienopyrrolyl, thienothiophenyl, quinolinyl, isoquinolinyl, quinoxalinyl, furopyrazolyl, thienopyrazolyl, selenophenyl, selenazolyl, and benzoisoxazolyl. In another embodiment is a compound of Formula (II) wherein R_6 is substituted or unsubstituted pyridyl. In another embodiment is a compound of Formula (II) wherein R_6 is substituted pyridyl. In another embodiment is a compound of Formula (II) wherein R_6 is unsubstituted pyridyl.

[0055] In another embodiment is a compound of Formula (II) wherein R_6 is -$(C(R_{14})(R_{15}))_mR_{21}$. In another embodiment is a compound of Formula (II) wherein R_6 is -$(C(R_{14})(R_{15}))_mR_{21}$, and each R_{14} and R_{15} are H. In another embodiment is a compound of Formula (II) wherein R_6 is -$(C(R_{14})(R_{15}))_mR_{21}$, m is 2, and each R_{14} and R_{15} are H. In another embodiment is a compound of Formula (II) wherein R_6 is -$(CH_2)_mR_{21}$, m is 2, and R_{21} is substituted or unsubstituted C_2-C_7heterocycloalkyl. In another embodiment is a compound of Formula (II) wherein R_6 is -$(CH_2)_mR_{21}$, m is 2, and R_{21} is substituted or unsubstituted C_3-C_8cycloalkyl. In another embodiment is a compound of Formula (II) wherein R_6 is -$(CH_2)_mR_{21}$, m is 2, and R_{21} is substituted C_6-C_{10}aryl. In another embodiment is a compound of Formula (II) wherein R_6 is -$(CH_2)_mR_{21}$, m is 2, and R_{21} is substituted phenyl. In another embodiment is a compound of Formula (II) wherein R_6 is -$(CH_2)_mR_{21}$, m is 2, and R_{21} is substituted or

unsubstituted C_2-C_7heteroaryl. In another embodiment is a compound of Formula (II) wherein R_6 is -$(CH_2)_mR_{21}$, m is 2, and R_{21} is -OH. In another embodiment is a compound of Formula (II) wherein R_6 is -$(CH_2)_mR_{21}$, m is 2, and R_{21} is -$N(R_{22})S(=O)_2R_{23}$. In another embodiment is a compound of Formula (II) wherein R_6 is -$(CH_2)_mR_{21}$, m is 2, and R_{21} is -$N(R_{22})C(=O)R_{23}$. In another embodiment is a compound of Formula (II) wherein R_6 is -$(CH_2)_mR_{21}$, m is 2, and R_{21} is substituted or unsubstituted C_1-C_6alkoxy. In another embodiment of the aforementioned embodiments, is a compound of Formula (II) wherein each R_{22} is independently H or unsubstituted C_1-C_6alkyl; and R_{23} is unsubstituted C_1-C_6alkyl.

[0056] In another embodiment is a compound of Formula (II) wherein R_6 is -$(C(R_{14})(R_{15}))_mR_{21}$, m is 3, and each R_{14} and R_{15} are H. In another embodiment is a compound of Formula (II) wherein R_6 is -$(CH_2)_mR_{21}$, m is 3, and R_{21} is substituted or unsubstituted C_2-C_7heterocycloalkyl. In another embodiment is a compound of Formula (II) wherein R_6 is -$(CH_2)_mR_{21}$, m is 3, and R_{21} is substituted or unsubstituted C_3-C_8cycloalkyl. In another embodiment is a compound of Formula (II) wherein R_6 is -$(CH_2)_mR_{21}$, m is 3, and R_{21} is substituted C_6-C_{10}aryl. In another embodiment is a compound of Formula (II) wherein R_6 is -$(CH_2)_mR_{21}$, m is 3, and R_{21} is substituted phenyl. In another embodiment is a compound of Formula (II) wherein R_6 is -$(CH_2)_mR_{21}$, m is 3, and R_{21} is substituted or unsubstituted C_2-C_7heteroaryl. In another embodiment is a compound of Formula (II) wherein R_6 is -$(CH_2)_mR_{21}$, m is 3, and R_{21} is -OH. In another embodiment is a compound of Formula (II) wherein R_6 is -$(CH_2)_mR_{21}$, m is 3, and R_{21} is -$N(R_{22})S(=O)_2R_{23}$. In another embodiment is a compound of Formula (II) wherein R_6 is -$(CH_2)_mR_{21}$, m is 3, and R_{21} is -$N(R_{22})C(=O)R_{23}$. In another embodiment is a compound of Formula (II) wherein R_6 is -$(CH_2)_mR_{21}$, m is 3, and R_{21} is substituted or unsubstituted C_1-C_6alkoxy. In another embodiment of the aforementioned embodiments, is a compound of Formula (II) wherein each R_{22} is independently H or unsubstituted C_1-C_6alkyl; and R_{23} is unsubstituted C_1-C_6alkyl.

[0057] In another embodiment is a compound of Formula (II) wherein R_6 is substituted or unsubstituted C_2-C_7heterocycloalkyl. In another embodiment is a compound of Formula (II) wherein R_6 is  and J is C(H). In another embodiment is a compound of Formula (II) wherein R_6 is  , J is C(H), p is 1, and q is 1. In another embodiment is a

compound of Formula (II) wherein R_6 is  , J is C(H), p is 2, and q is 1. In another embodiment is a compound of Formula (II) wherein R_6 is  , J is C(H), p is 3, and q is 1. In another embodiment is a compound of Formula (II) wherein R_6 is  , J is C(H), p is 2, and q is 2. In another embodiment is a compound of Formula (II) wherein R_6 is  , J is C(H), p is 1, q is 1, and R_{13} is substituted or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (II) wherein R_6 is  , J is C(H), p is 2, q is 1, and R_{13} is substituted or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (II) wherein R_6 is  , J is C(H), p is 3, q is 1, and R_{13} is substituted or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (II) wherein R_6 is  , J is C(H), p is 2, q is 2, and R_{13} is substituted or unsubstituted C_1-C_6alkyl.

[0058] In another embodiment is a compound of Formula (II) wherein R_5 is halogen. In another embodiment is a compound of Formula (II) wherein R_5 is $-CF_3$. In another embodiment is a compound of Formula (II) wherein R_5 is substituted or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (II) wherein R_5 is $-CH_3$. In another embodiment is a compound of Formula (II) wherein R_5 is $-CH_2CH_3$. In another embodiment is a compound of Formula (II) wherein R_5 is substituted or unsubstituted C_1-C_6heteroalkyl. In another embodiment is a compound of Formula (II) wherein R_5 is substituted or unsubstituted C_2-C_7heterocycloalkyl. In another embodiment is a compound of Formula (II) wherein R_5 is substituted or unsubstituted C_3-C_8cycloalkyl. In another embodiment is a compound of Formula

(II) wherein R_5 is substituted or unsubstituted C_6-C_{10}aryl. In another embodiment is a compound of Formula (II) wherein R_5 is substituted or unsubstituted C_2-C_7heteroaryl.

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

[0060] 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.

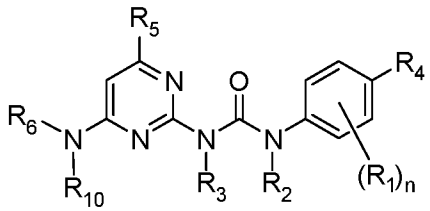
[0061] In another embodiment is a compound of Formula (II) wherein R_2 and R_3 are taken together to form a 5- or 6-membered heterocyclic ring. In another embodiment is a compound of Formula (II) wherein R_2 and R_3 are taken together to form a 5-membered heterocyclic ring. In another embodiment is a compound of Formula (II) wherein R_2 and R_3 are taken together to form 6-membered heterocyclic ring.

[0062] In another embodiment is a compound of Formula (II) wherein n is 0.

[0063] 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 $-OCF_2H$.

[0064] In another embodiment, described herein is a compound of Formula (IIA):



Formula (IIA);

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; 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, $-NO_2$, -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; or two R_1 are taken together to form a substituted or unsubstituted heterocyclic ring or a substituted or unsubstituted carbocyclic ring; wherein when n is 0, R_4 is not halogen;

R_5 is 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 $-(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$;

R_{11} and R_{12} are each independently H, or substituted or unsubstituted C_1-C_6alkyl; or R_{11} and R_{12} are taken together to form a 5-, 6-, 7-, or 8-membered heterocyclic ring;

R_{13} is H, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_2-C_7heterocycloalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted -C_1-C_4alkylC_6-C_{10}aryl, or substituted or unsubstituted -C_1-C_4alkylC_2-C_7heteroaryl;

each R_{14} and R_{15} are each independently H, or substituted or unsubstituted C_1-C_6alkyl; or R_{14} and R_{15} are taken together to form a 4-, 5-, 6-membered cycloalkyl ring;

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

R_9 is substituted or unsubstituted C_1-C_6alkyl;

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

m is 2-6;

n is 0-4; or

a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[0065] In one embodiment is a compound of Formula (IIA) wherein R_6 is -$(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$, and each R_{14} and R_{15} are H. In another embodiment is a compound of Formula (IIA) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, and R_{11} and R_{12} are each H. In another embodiment is a compound of Formula (IIA) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, R_{11} is substituted or unsubstituted C_1-C_6alkyl, and R_{12} is H. In another embodiment is a compound of Formula (IIA) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, R_{11} is CH_3, and R_{12} is H. In another embodiment is a compound of Formula (IIA) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, R_{11} is substituted or unsubstituted C_1-C_6alkyl, and R_{12} is substituted or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIA) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, R_{11} is CH_3, and R_{12} is CH_3. In another embodiment is a compound of Formula (IIA) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, and R_{11} and R_{12} are taken together to form a 5-, 6-, 7-, or 8-membered heterocyclic ring. In another embodiment is a compound of Formula (IIA) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, and R_{11} and R_{12} are taken together to form a 5-membered heterocyclic ring. In another embodiment is a compound of Formula (IIA) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, and R_{11} and R_{12} are taken together to form a 6-membered heterocyclic ring.

[0066] In another embodiment is a compound of Formula (IIA) wherein R_6 is -$(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$, m is 2, and each R_{14} and R_{15} are H. In another embodiment is a compound of Formula (IIA) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, m is 2, and R_{11} and R_{12} are each H. In another embodiment is a compound of Formula (IIA) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, m is 2, R_{11} is substituted or unsubstituted C_1-C_6alkyl, and R_{12} is H. In another embodiment is a compound of Formula (IIA) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, m is 2, R_{11} is CH_3, and R_{12} is H. In another embodiment is a compound of Formula (IIA) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, m is 2, R_{11} is substituted or unsubstituted C_1-C_6alkyl, and R_{12} is substituted or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIA) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, m is 2, R_{11} is CH_3, and R_{12} is CH_3. In another embodiment is a compound of Formula (IIA) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, m is 2, and R_{11} and R_{12} are taken together to form a 5-, 6-, 7-, or 8-membered heterocyclic ring. In another embodiment is a compound of Formula (IIA) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, m is 2, and R_{11} and R_{12} are taken together to form a 5-membered heterocyclic ring. In another embodiment is a compound of Formula (IIA) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, m is 2, and R_{11} and R_{12} are taken together to form a 6-membered heterocyclic ring.

[0067] In another embodiment is a compound of Formula (IIA) wherein R_6 is -$(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$. In another embodiment is a compound of Formula (IIA) wherein R_6 is -$(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$, m is 3, and each R_{14} and R_{15} are H. In another embodiment is a

compound of Formula (IIA) wherein R_6 is $-(CH_2)_mN(R_{11})(R_{12})$, m is 3, and R_{11} and R_{12} are each H. In another embodiment is a compound of Formula (IIA) wherein R_6 is $-(CH_2)_mN(R_{11})(R_{12})$, m is 3, R_{11} is substituted or unsubstituted C_1-C_6alkyl, and R_{12} is H. In another embodiment is a compound of Formula (IIA) wherein R_6 is $-(CH_2)_mN(R_{11})(R_{12})$, m is 3, R_{11} is CH_3, and R_{12} is H. In another embodiment is a compound of Formula (IIA) wherein R_6 is $-(CH_2)_mN(R_{11})(R_{12})$, m is 3, R_{11} is substituted or unsubstituted C_1-C_6alkyl, and R_{12} is substituted or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIA) wherein R_6 is $-(CH_2)_mN(R_{11})(R_{12})$, m is 3, R_{11} is CH_3, and R_{12} is CH_3. In another embodiment is a compound of Formula (IIA) wherein R_6 is $-(CH_2)_mN(R_{11})(R_{12})$, m is 3, and R_{11} and R_{12} are taken together to form a 5-, 6-, 7-, or 8-membered heterocyclic ring. In another embodiment is a compound of Formula (IIA) wherein R_6 is $-(CH_2)_mN(R_{11})(R_{12})$, m is 3, and R_{11} and R_{12} are taken together to form a 5-membered heterocyclic ring. In another embodiment is a compound of Formula (IIA) wherein R_6 is $-(CH_2)_mN(R_{11})(R_{12})$, m is 3, and R_{11} and R_{12} are taken together to form a 6-membered heterocyclic ring.

[0068] In another embodiment is a compound of Formula (IIA) wherein R_5 is halogen. In another embodiment is a compound of Formula (IIA) wherein R_5 is $-CF_3$. In another embodiment is a compound of Formula (IIA) wherein R_5 is substituted or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIA) wherein R_5 is $-CH_3$. In another embodiment is a compound of Formula (IIA) wherein R_5 is $-CH_2CH_3$. In another embodiment is a compound of Formula (IIA) wherein R_5 is substituted or unsubstituted C_1-C_6heteroalkyl. In another embodiment is a compound of Formula (IIA) wherein R_5 is substituted or unsubstituted C_2-C_7heterocycloalkyl. In another embodiment is a compound of Formula (IIA) wherein R_5 is substituted or unsubstituted C_3-C_8cycloalkyl. In another embodiment is a compound of Formula (IIA) wherein R_5 is substituted or unsubstituted C_6-C_{10}aryl. In another embodiment is a compound of Formula (IIA) wherein R_5 is substituted or unsubstituted C_2-C_7heteroaryl.

[0069] In another embodiment is a compound of Formula (IIA) 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 (IIA) wherein R_2 and R_3 are each H.

[0070] In another embodiment is a compound of Formula (IIA) 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 (IIA) wherein R_2 is H, and R_3 is C_1-C_4alkyl. In another embodiment is a compound of Formula (IIA) wherein R_2 is H, and R_3 is CH_3. In another embodiment is a compound of Formula (IIA) wherein R_2 is H, and R_3 is C_3-C_6cycloalkyl. In another embodiment is a compound of Formula (IIA) wherein R_2 is H,

and R_3 is cyclopropyl. In another embodiment is a compound of Formula (IIA) wherein R_2 is H, and R_3 is cyclopentyl. In another embodiment is a compound of Formula (IIA) wherein R_2 is CH_3, and R_3 is CH_3. In another embodiment is a compound of Formula (IIA) wherein R_2 is C_1-C_4alkyl, and R_3 is H. In another embodiment is a compound of Formula (IIA) wherein R_2 is CH_3, and R_3 is H. In another embodiment is a compound of Formula (IIA) wherein R_2 is C_3-C_6cycloalkyl, and R_3 is H. In another embodiment is a compound of Formula (IIA) wherein R_2 is cyclopropyl, and R_3 is H. In another embodiment is a compound of Formula (IIA) wherein R_2 is cyclopentyl, and R_3 is H.

[0071] In another embodiment is a compound of Formula (IIA) 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 (IIA) wherein R_2 and R_3 are taken together to form a 5-membered heterocyclic ring. In another embodiment is a compound of Formula (IIA) wherein R_2 and R_3 are taken together to form 6-membered heterocyclic ring.

[0072] In another embodiment is a compound of Formula (IIA) wherein n is 0.

[0073] In another embodiment is a compound of Formula (IIA) 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 (IIA) 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 (IIA) 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 (IIA) 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 (IIA) 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 (IIA) 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 (IIA) wherein n is 3, and each R_1 is independently halogen. In another embodiment is a compound of Formula (IIA) wherein n is 2, and each R_1 is independently halogen. In another embodiment is a compound of Formula (IIA) wherein n is 2, and each R_1 is independently F or Cl. In another embodiment is a compound of Formula (IIA) wherein n is 2, and each R_1 is F. In another embodiment is a compound of Formula (IIA) wherein n is 2, and each R_1 is independently Cl. In another embodiment is a compound of Formula (IIA) wherein n is 1, and R_1 is halogen. In another embodiment is a compound of Formula (IIA) wherein n is 1, and R_1 is F. In another embodiment is a compound of Formula (IIA) wherein n is 1, and R_1 is Cl. In another embodiment is a compound of Formula (IIA) wherein n is 1, and R_1 is substituted or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIA) wherein n is 1, and R_1 is CH_3. In another embodiment is a compound of Formula (IIA) wherein n is 1, and R_1 is substituted or unsubstituted C_1-C_6alkoxy. In another embodiment is a compound of Formula (IIA) wherein n is 1, and R_1 is -OCH_3. In another embodiment is a compound of Formula (IIA) wherein n is 1, and R_1 is -OCF_3. In another embodiment is a compound of Formula (IIA) wherein n is 1, and R_1 is -OCF_2H.

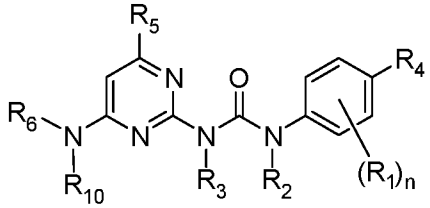
[0074] In another embodiment is a compound of Formula (IIA) wherein R_4 is H, halogen, -CN, -NO_2, -OH, -OCF_3, -OCH_2F, -OCF_2H, -SR_8, -$N(R_8)S(=O)_2R_9$, -$S(=O)_2N(R_8)_2$, -$S(=O)R_9$, -$S(=O)_2R_9$, -$C(=O)R_9$, -CO_2R_8, -$N(R_8)_2$, -$C(=O)N(R_8)_2$, -$N(R_8)C(=O)R_9$, substituted or unsubstituted C_1-C_6alkyl, or substituted or unsubstituted C_1-C_6alkoxy. In another embodiment is a compound of Formula (IIA) wherein R_4 is H, halogen, -CN, -OH, -OCF_3, substituted or unsubstituted C_1-C_6alkyl, or substituted or unsubstituted C_1-C_6alkoxy. In another embodiment is a compound of Formula (IIA) wherein R_4 is H. In another embodiment is a compound of Formula (IIA) wherein R_4 is halogen. In another embodiment is a compound of Formula (IIA) wherein R_4 is F. In another embodiment is a compound of Formula (IIA) wherein R_4 is Cl. In another embodiment is a compound of Formula (IIA) wherein R_4 is Br. In another embodiment is a compound of Formula (IIA) wherein R_4 is -CF_3. In another embodiment is a compound of Formula (IIA) wherein R_4 is -OCF_3. In another embodiment is a compound of Formula (IIA) R_4 is -CH_3. In another embodiment is a compound of Formula (IIA) wherein R_4 is -OCH_3.

[0075] In another embodiment is a compound of Formula (IIA) wherein n is 0 and R_4 is H. In another embodiment is a compound of Formula (IIA) wherein n is 0 and R_4 is halogen. In another embodiment is a compound of Formula (IIA) wherein n is 0 and R_4 is F. In another embodiment is a compound of Formula (IIA) wherein n is 0 and R_4 is Cl. In another embodiment is a compound of Formula (IIA) wherein n is 0 and R_4 is Br. In another embodiment is a compound of Formula (IIA) wherein n is 0 and R_4 is -CF_3. In another embodiment is a compound of Formula (IIA) wherein n is 0 and R_4 is -OCF_3. In another

embodiment is a compound of Formula (IIA) wherein n is 0 and R_4 is -CH_3. In another embodiment is a compound of Formula (IIA) wherein n is 0 and R_4 is -OCH_3.

[0076] In another embodiment is a compound of Formula (IIA) wherein n is 1, R_1 is Cl, and R_4 is Cl. In another embodiment is a compound of Formula (IIA) wherein n is 1, R_1 is -CH_3, and R_4 is Cl. In another embodiment is a compound of Formula (IIA) wherein n is 1, R_1 is -OCH_3, and R_4 is Cl. In another embodiment is a compound of Formula (IIA) wherein n is 1, R_1 is -CF_3, and R_4 is Cl. In another embodiment is a compound of Formula (IIA) wherein n is 1, R_1 is -OCF_3, and R_4 is Cl. In another embodiment is a compound of Formula (IIA) wherein n is 1, R_1 is Cl, and R_4 is F. In another embodiment is a compound of Formula (IIA) wherein n is 1, R_1 is -CH_3, and R_4 is F. In another embodiment is a compound of Formula (IIA) wherein n is 1, R_1 is -OCH_3, and R_4 is F. In another embodiment is a compound of Formula (IIA) wherein n is 1, R_1 is -CF_3, and R_4 is F. In another embodiment is a compound of Formula (IIA) wherein n is 1, R_1 is -OCF_3, and R_4 is F. In another embodiment is a compound of Formula (IIA) wherein n is 1, R_1 is Cl, and R_4 is H. In another embodiment is a compound of Formula (IIA) wherein n is 1, R_1 is -CH_3, and R_4 is H. In another embodiment is a compound of Formula (IIA) wherein n is 1, R_1 is -OCH_3, and R_4 is H. In another embodiment is a compound of Formula (IIA) wherein n is 1, R_1 is -CF_3, and R_4 is H. In another embodiment is a compound of Formula (IIA) wherein n is 1, R_1 is -OCF_3, and R_4 is H. In another embodiment is a compound of Formula (IIA) wherein n is 1, R_1 is Cl, and R_4 is -OCH_3. In another embodiment is a compound of Formula (IIA) wherein n is 1, R_1 is -CH_3, and R_4 is -OCH_3. In another embodiment is a compound of Formula (IIA) wherein n is 1, R_1 is -OCH_3, and R_4 is -OCH_3. In another embodiment is a compound of Formula (IIA) wherein n is 1, R_1 is -CF_3, and R_4 is -OCH_3. In another embodiment is a compound of Formula (IIA) wherein n is 1, R_1 is -OCF_3, and R_4 is -OCH_3. In another embodiment is a compound of Formula (IIA) wherein n is 1, R_1 is Cl, and R_4 is -OCF_3. In another embodiment is a compound of Formula (IIA) wherein n is 1, R_1 is -CH_3, and R_4 is -OCF_3. In another embodiment is a compound of Formula (IIA) wherein n is 1, R_1 is -OCH_3, and R_4 is -OCF_3. In another embodiment is a compound of Formula (IIA) wherein n is 1, R_1 is -CF_3, and R_4 is -OCF_3. In another embodiment is a compound of Formula (IIA) wherein n is 1, R_1 is -OCF_3, and R_4 is -OCF_3.

[0077] In another embodiment, described herein is a compound of Formula (IIA'):



Formula (IIA');

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; 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, F, Cl, Br, I, -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; or two R_1 are taken together to form a substituted or unsubstituted heterocyclic ring or a substituted or unsubstituted carbocyclic ring; wherein when n is 0, R_4 is not Cl;

R_5 is 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 -$(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$;

R_{11} and R_{12} are each independently H, or substituted or unsubstituted C_1-C_6alkyl; or R_{11} and R_{12} are taken together to form a 5-, 6-, 7-, or 8-membered heterocyclic ring;

R_{13} is H, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_2-C_7heterocycloalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted -C_1-C_4alkylC_6-C_{10}aryl, or substituted or unsubstituted -C_1-C_4alkylC_2-C_7heteroaryl;

each R_{14} and R_{15} are each independently H, or substituted or unsubstituted C_1-C_6alkyl; or R_{14} and R_{15} are taken together to form a 4-, 5-, 6-membered cycloalkyl ring;

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

R_9 is substituted or unsubstituted C_1-C_6alkyl;

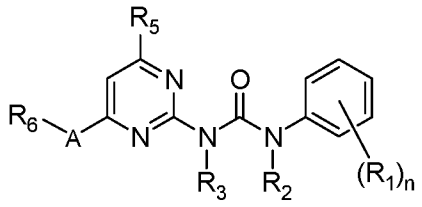
R_{10} is H, or C_1-C_4alkyl;

m is 2-6;

n is 0-4; or

a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[0078] In another embodiment, described herein is a compound of Formula (IIB):



Formula (IIB);

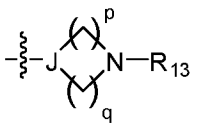
wherein:

A is O;

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; 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_5 is 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 substituted or unsubstituted C_2-C_7heterocycloalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted C_2-C_7heteroaryl, -$(C(R_{14})(R_{15}))_mR_{21}$, -$(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$, or  ;

R_{11} and R_{12} are each independently H, or substituted or unsubstituted C_1-C_6alkyl; or R_{11} and R_{12} are taken together to form a 5-, 6-, 7-, or 8-membered heterocyclic ring;

J is C(H);

R_{13} is H, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_2-C_7heterocycloalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted -C_1-C_4alkylC_6-C_{10}aryl, or substituted or unsubstituted -C_1-C_4alkylC_2-C_7heteroaryl;

each R_{14} and R_{15} are each independently H, or substituted or unsubstituted C_1-C_6alkyl; or R_{14} and R_{15} are taken together to form a 4-, 5-, 6-membered cycloalkyl ring;

R_{21} is halogen, -CN, -NO_2, -OH, -OCF_3, -OCH_2F, -OCF_2H, -CF_3, -SR_{22}, -$N(R_{22})S(=O)_2R_{23}$, -$S(=O)_2N(R_{22})_2$, -$S(=O)R_{23}$, -$S(=O)_2R_{23}$, -$C(=O)R_{23}$, -CO_2R_{22}, -$C(=O)N(R_{22})_2$, -$N(R_{22})C(=O)R_{23}$, 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;

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

R_{23} is substituted or unsubstituted C_1-C_6alkyl;

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

R_9 is substituted or unsubstituted C_1-C_6alkyl;

m is 2-6;

n is 0-5;

p is 1-3;

q is 1-3; or

a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[0079] In another embodiment is a compound of Formula (IIB) wherein R_6 is substituted or unsubstituted C_3-C_8cycloalkyl. In another embodiment is a compound of Formula (IIB) wherein R_6 is substituted or unsubstituted cyclopropyl. In another embodiment is a compound of Formula (IIB) wherein R_6 is substituted or unsubstituted cyclobutyl. In another embodiment is a compound of Formula (IIB) wherein R_6 is substituted or unsubstituted cyclopentyl. In another embodiment is a compound of Formula (IIB) wherein R_6 is substituted or unsubstituted cyclohexyl.

[0080] In another embodiment is a compound of Formula (IIB) wherein R_6 is substituted or unsubstituted C_2-C_7heteroaryl. In another embodiment is a compound of Formula (IIB) wherein R_6 is substituted or unsubstituted furanyl, thiophenyl, pyrrolyl, pyridyl, oxazolyl, thiazolyl, imidazolyl, isoxazolyl, isothiazolyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, oxadiazolyl, thiadiazolyl, triazolyl, indolyl, benzothiophenyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, benzoxadiazolyl, benzothiadiazolyl, benzotriazolyl, pyrazolopyridinyl, imidazopyridinyl, pyrrolopyridinyl, pyrrolopyrimidinyl, indolizinyl, purinyl, furopyridinyl, thienopyridinyl,

furopyrrolyl, furofuranyl, thienofuranyl, 1,4-dihydropyrrolopyrrolyl, thienopyrrolyl, thienothiophenyl, quinolinyl, isoquinolinyl, quinoxalinyl, furopyrazolyl, thienopyrazolyl, selenophenyl, selenazolyl, and benzoisoxazolyl. In another embodiment is a compound of Formula (IIB) wherein R_6 is substituted or unsubstituted pyridyl. In another embodiment is a compound of Formula (IIB) wherein R_6 is substituted pyridyl. In another embodiment is a compound of Formula (IIB) wherein R_6 is unsubstituted pyridyl.

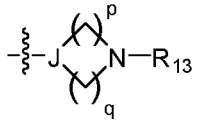
[0081] In another embodiment is a compound of Formula (IIB) wherein R_6 is -$(C(R_{14})(R_{15}))_mR_{21}$. In another embodiment is a compound of Formula (IIB) wherein R_6 is -$(C(R_{14})(R_{15}))_mR_{21}$, and each R_{14} and R_{15} are H. In another embodiment is a compound of Formula (IIB) wherein R_6 is -$(C(R_{14})(R_{15}))_mR_{21}$, m is 2, and each R_{14} and R_{15} are H. In another embodiment is a compound of Formula (I) wherein R_6 is -$(CH_2)_mR_{21}$, m is 2, and R_{21} is substituted or unsubstituted C_2-C_7heterocycloalkyl. In another embodiment is a compound of Formula (IIB) wherein R_6 is -$(CH_2)_mR_{21}$, m is 2, and R_{21} is substituted or unsubstituted C_3-C_8cycloalkyl. In another embodiment is a compound of Formula (IIB) wherein R_6 is -$(CH_2)_mR_{21}$, m is 2, and R_{21} is substituted or unsubstituted C_6-C_{10}aryl. In another embodiment is a compound of Formula (IIB) wherein R_6 is -$(CH_2)_mR_{21}$, m is 2, and R_{21} is substituted or unsubstituted phenyl. In another embodiment is a compound of Formula (IIB) wherein R_6 is -$(CH_2)_mR_{21}$, m is 2, and R_{21} is substituted or unsubstituted C_2-C_7heteroaryl. In another embodiment is a compound of Formula (IIB) wherein R_6 is -$(CH_2)_mR_{21}$, m is 2, and R_{21} is -OH.

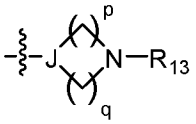
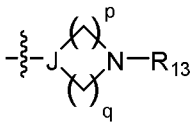
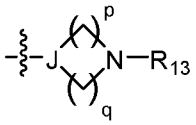
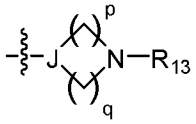
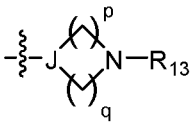
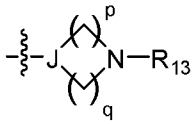
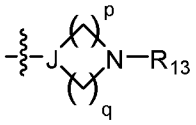
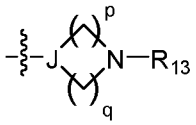
[0082] In another embodiment is a compound of Formula (IIB) wherein R_6 is -$(C(R_{14})(R_{15}))_mR_{21}$, m is 3, and each R_{14} and R_{15} are H. In another embodiment is a compound of Formula (IIB) wherein R_6 is -$(CH_2)_mR_{21}$, m is 3, and R_{21} is substituted or unsubstituted C_2-C_7heterocycloalkyl. In another embodiment is a compound of Formula (IIB) wherein R_6 is -$(CH_2)_mR_{21}$, m is 3, and R_{21} is substituted or unsubstituted C_3-C_8cycloalkyl. In another embodiment is a compound of Formula (IIB) wherein R_6 is -$(CH_2)_mR_{21}$, m is 3, and R_{21} is substituted or unsubstituted C_6-C_{10}aryl. In another embodiment is a compound of Formula (IIB) wherein R_6 is -$(CH_2)_mR_{21}$, m is 3, and R_{21} is substituted or unsubstituted phenyl. In another embodiment is a compound of Formula (IIB) wherein R_6 is -$(CH_2)_mR_{21}$, m is 3, and R_{21} is substituted or unsubstituted C_2-C_7heteroaryl. In another embodiment is a compound of Formula (IIB) wherein R_6 is -$(CH_2)_mR_{21}$, m is 3, and R_{21} is -OH.

[0083] In another embodiment is a compound of Formula (IIB) wherein R_6 is -$(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$. In another embodiment is a compound of Formula (IIB) wherein R_6 is -$(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$, m is 2, and each R_{14} and R_{15} are H. In another embodiment is a compound of Formula (IIB) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, m is 2, and R_{11} and R_{12} are each H. In another embodiment is a compound of Formula (IIB) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$,

m is 2, R_{11} is substituted or unsubstituted C_1-C_6alkyl, and R_{12} is H. In another embodiment is a compound of Formula (IIB) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, m is 2, R_{11} is CH_3, and R_{12} is H. In another embodiment is a compound of Formula (IIB) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, m is 2, R_{11} is substituted or unsubstituted C_1-C_6alkyl, and R_{12} is substituted or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIB) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, m is 2, R_{11} is CH_3, and R_{12} is CH_3. In another embodiment is a compound of Formula (IIB) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, m is 2, and R_{11} and R_{12} are taken together to form a 5-, 6-, 7-, or 8-membered heterocyclic ring. In another embodiment is a compound of Formula (IIB) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, m is 2, and R_{11} and R_{12} are taken together to form a 5-membered heterocyclic ring. In another embodiment is a compound of Formula (IIB) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, m is 2, and R_{11} and R_{12} are taken together to form a 6-membered heterocyclic ring.

[0084] In another embodiment is a compound of Formula (IIB) wherein R_6 is -$(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$. In another embodiment is a compound of Formula (IIB) wherein R_6 is -$(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$, m is 3, and each R_{14} and R_{15} are H. In another embodiment is a compound of Formula (IIB) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, m is 3, and R_{11} and R_{12} are each H. In another embodiment is a compound of Formula (IIB) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, m is 23, R_{11} is substituted or unsubstituted C_1-C_6alkyl, and R_{12} is H. In another embodiment is a compound of Formula (IIB) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, m is 3, R_{11} is CH_3, and R_{12} is H. In another embodiment is a compound of Formula (IIB) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, m is 3, R_{11} is substituted or unsubstituted C_1-C_6alkyl, and R_{12} is substituted or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIB) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, m is 3, R_{11} is CH_3, and R_{12} is CH_3. In another embodiment is a compound of Formula (IIB) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, m is 3, and R_{11} and R_{12} are taken together to form a 5-, 6-, 7-, or 8-membered heterocyclic ring. In another embodiment is a compound of Formula (IIB) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, m is 3, and R_{11} and R_{12} are taken together to form a 5-membered heterocyclic ring. In another embodiment is a compound of Formula (IIB) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, m is 3, and R_{11} and R_{12} are taken together to form a 6-membered heterocyclic ring.

[0085] In another embodiment is a compound of Formula (IIB) wherein R_6 is substituted or unsubstituted C_2-C_7heterocycloalkyl. In another embodiment is a compound of Formula (IIB) wherein R_6 is  and J is C(H). In another embodiment is a compound of Formula

(IIB) wherein R_6 is  , J is C(H), p is 1, and q is 1. In another embodiment is a compound of Formula (IIB) wherein R_6 is  , J is C(H), p is 2, and q is 1. In another embodiment is a compound of Formula (IIB) wherein R_6 is  , J is C(H), p is 3, and q is 1. In another embodiment is a compound of Formula (IIB) wherein R_6 is  , J is C(H), p is 2, and q is 2. In another embodiment is a compound of Formula (IIB) wherein R_6 is  , J is C(H), p is 1, q is 1, and R_{13} is substituted or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIB) wherein R_6 is  , J is C(H), p is 2, q is 1, and R_{13} is substituted or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIB) wherein R_6 is  , J is C(H), p is 3, q is 1, and R_{13} is substituted or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIB) wherein R_6 is  , J is C(H), p is 2, q is 2, and R_{13} is substituted or unsubstituted C_1-C_6alkyl.

[0086] In another embodiment is a compound of Formula (IIB) wherein R_5 is halogen. In another embodiment is a compound of Formula (IIB) wherein R_5 is $-CF_3$. In another embodiment is a compound of Formula (IIB) wherein R_5 is substituted or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIB) wherein R_5 is $-CH_3$. In another embodiment is a compound of Formula (IIB) wherein R_5 is $-CH_2CH_3$. In another embodiment is a compound of Formula (IIB) wherein R_5 is substituted or unsubstituted C_1-C_6heteroalkyl. In another embodiment is a compound of Formula (IIB) wherein R_5 is

substituted or unsubstituted C_2-C_7heterocycloalkyl. In another embodiment is a compound of Formula (IIB) wherein R_5 is substituted or unsubstituted C_3-C_8cycloalkyl. In another embodiment is a compound of Formula (IIB) wherein R_5 is substituted or unsubstituted C_6-C_{10}aryl. In another embodiment is a compound of Formula (IIB) wherein R_5 is substituted or unsubstituted C_2-C_7heteroaryl.

[0087] In another embodiment is a compound of Formula (IIB) 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 (IIB) wherein R_2 and R_3 are each H.

[0088] In another embodiment is a compound of Formula (IIB) 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 (IIB) wherein R_2 is H, and R_3 is C_1-C_4alkyl. In another embodiment is a compound of Formula (IIB) wherein R_2 is H, and R_3 is CH_3. In another embodiment is a compound of Formula (IIB) wherein R_2 is H, and R_3 is C_3-C_6cycloalkyl. In another embodiment is a compound of Formula (IIB) wherein R_2 is H, and R_3 is cyclopropyl. In another embodiment is a compound of Formula (IIB) wherein R_2 is H, and R_3 is cyclopentyl. In another embodiment is a compound of Formula (IIB) wherein R_2 is CH_3, and R_3 is CH_3. In another embodiment is a compound of Formula (IIB) wherein R_2 is C_1-C_4alkyl, and R_3 is H. In another embodiment is a compound of Formula (IIB) wherein R_2 is CH_3, and R_3 is H. In another embodiment is a compound of Formula (IIB) wherein R_2 is C_3-C_6cycloalkyl, and R_3 is H. In another embodiment is a compound of Formula (IIB) wherein R_2 is cyclopropyl, and R_3 is H. In another embodiment is a compound of Formula (IIB) wherein R_2 is cyclopentyl, and R_3 is H.

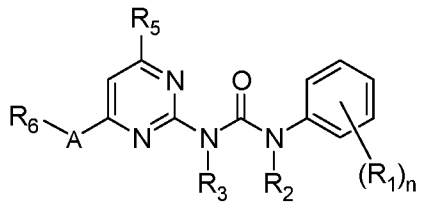
[0089] In another embodiment is a compound of Formula (IIB) wherein R_2 and R_3 are taken together to form a 5- or 6-membered heterocyclic ring. In another embodiment is a compound of Formula (IIB) wherein R_2 and R_3 are taken together to form a 5-membered heterocyclic ring. In another embodiment is a compound of Formula (IIB) wherein R_2 and R_3 are taken together to form 6-membered heterocyclic ring.

[0090] In another embodiment is a compound of Formula (IIB) wherein n is 0.

[0091] In another embodiment is a compound of Formula (IIB) 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. In another

embodiment is a compound of Formula (IIB) wherein each R_1 is independently halogen, -CN, -OH, $-CF_3$, substituted or unsubstituted C_1-C_6alkyl, or substituted or unsubstituted C_1-C_6alkoxy. In another embodiment is a compound of Formula (IIB) wherein each R_1 is independently halogen, -CN, $-OCF_3$, $-OCH_2F$, $-OCF_2H$, $-CF_3$, 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. In another embodiment is a compound of Formula (IIB) wherein each R_1 is independently halogen, -CN, $-OCF_3$, $-OCH_2F$, $-OCF_2H$, $-CF_3$, substituted or unsubstituted C_1-C_6alkyl, or substituted or unsubstituted C_1-C_6alkoxy. In another embodiment is a compound of Formula (IIB) wherein each R_1 is independently halogen, -CN, $-OCF_3$, $-OCH_2F$, $-OCF_2H$, $-CF_3$, 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 (IIB) wherein each R_1 is independently halogen, -CN, $-OCF_3$, $-OCH_2F$, $-OCF_2H$, $-CF_3$, 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 (IIB) wherein n is 3, and each R_1 is independently halogen. In another embodiment is a compound of Formula (IIB) wherein n is 2, and each R_1 is independently halogen. In another embodiment is a compound of Formula (IIB) wherein n is 2, and each R_1 is independently F or Cl. In another embodiment is a compound of Formula (IIB) wherein n is 2, and each R_1 is F. In another embodiment is a compound of Formula (IIB) wherein n is 2, and each R_1 is independently Cl. In another embodiment is a compound of Formula (IIB) wherein n is 2, and each R_1 is independently halogen or $-CF_3$. In another embodiment is a compound of Formula (IIB) wherein n is 2, and each R_1 is independently F or $-CF_3$. In another embodiment is a compound of Formula (IIB) wherein n is 2, and each R_1 is independently Cl or $-CF_3$. In another embodiment is a compound of Formula (IIB) wherein n is 1, and R_1 is halogen. In another embodiment is a compound of Formula (IIB) wherein n is 1, and R_1 is F. In another embodiment is a compound of Formula (IIB) wherein n is 1, and R_1 is Cl. In another embodiment is a compound of Formula (IIB) wherein n is 1, and R_1 is $-CF_3$. In another embodiment is a compound of Formula (IIB) wherein n is 1, and R_1 is substituted or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIB) wherein n is 1, and R_1 is CH_3. In another embodiment is a compound of Formula (IIB) wherein n is 1, and R_1 is substituted or unsubstituted C_1-C_6alkoxy. In another embodiment is a compound of Formula (IIB) wherein n is 1, and R_1 is $-OCH_3$. In another embodiment is a compound of Formula (IIB) wherein n is 1, and R_1 is $-OCF_3$. In another embodiment is a compound of Formula (IIB) wherein n is 1, and R_1 is $-OCF_2H$.

[0092] In another embodiment, described herein is a compound of Formula (IIC):



Formula (IIC);

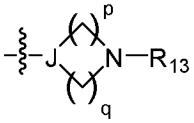
wherein:

A is a bond;

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; 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_5 is 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 substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted C_2-C_7heteroaryl, -$(C(R_{14})(R_{15}))_mR_{21}$, -$(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$, or  ;

R_{11} and R_{12} are each independently H, or substituted or unsubstituted C_1-C_6alkyl; or R_{11} and R_{12} are taken together to form a 5-, 6-, 7-, or 8-membered heterocyclic ring;

J is C(H);

R_{13} is H, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_2-C_7heterocycloalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted -C_1-C_4alkylC_6-C_{10}aryl, or substituted or unsubstituted -C_1-C_4alkylC_2-C_7heteroaryl;

each R_{14} and R_{15} are each independently H, or substituted or unsubstituted C_1-C_6alkyl; or R_{14} and R_{15} are taken together to form a 4-, 5-, 6-membered cycloalkyl ring;

R_{21} is halogen, -CN, -NO_2, -OH, -OCF_3, -OCH_2F, -OCF_2H, -CF_3, -SR_{22}, -$N(R_{22})S(=O)_2R_{23}$, -$S(=O)_2N(R_{22})_2$, -$S(=O)R_{23}$, -$S(=O)_2R_{23}$, -$C(=O)R_{23}$, -CO_2R_{22}, -$C(=O)N(R_{22})_2$, -$N(R_{22})C(=O)R_{23}$, 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;

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

R_{23} is substituted or unsubstituted C_1-C_6alkyl;

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

R_9 is substituted or unsubstituted C_1-C_6alkyl;

m is 2-6;

n is 0-5;

p is 1-3;

q is 1-3; or

a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[0093] In another embodiment is a compound of Formula (IIC) wherein R_6 is substituted or unsubstituted C_3-C_8cycloalkyl. In another embodiment is a compound of Formula (IIC) wherein R_6 is substituted or unsubstituted cyclopropyl. In another embodiment is a compound of Formula (IIC) wherein R_6 is substituted or unsubstituted cyclobutyl. In another embodiment is a compound of Formula (IIC) wherein R_6 is substituted or unsubstituted cyclopentyl. In another embodiment is a compound of Formula (IIC) wherein R_6 is substituted or unsubstituted cyclohexyl.

[0094] In another embodiment is a compound of Formula (IIC) wherein R_6 is substituted or unsubstituted C_2-C_7heteroaryl. In another embodiment is a compound of Formula (IIC) wherein R_6 is substituted or unsubstituted furanyl, thiophenyl, pyrrolyl, pyridyl, oxazolyl, thiazolyl, imidazolyl, isoxazolyl, isothiazolyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, oxadiazolyl, thiadiazolyl, triazolyl, indolyl, benzothiophenyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, benzoxadiazolyl, benzothiadiazolyl, benzotriazolyl, pyrazolopyridinyl, imidazopyridinyl, pyrrolopyridinyl, pyrrolopyrimidinyl, indolizinyl, purinyl, furopyridinyl, thienopyridinyl, furopyrrolyl, furofuranyl, thienofuranyl, 1,4-dihydropyrrolopyrrolyl, thienopyrrolyl, thienothiophenyl, quinolinyl, isoquinolinyl, quinoxalinyl, furopyrazolyl, thienopyrazolyl, selenophenyl, selenazolyl, and benzoisoxazolyl. In another embodiment is a compound of Formula (IIC) wherein R_6 is substituted or unsubstituted pyridyl. In another embodiment is a

compound of Formula (IIC) wherein R_6 is substituted pyridyl. In another embodiment is a compound of Formula (IIC) wherein R_6 is unsubstituted pyridyl.

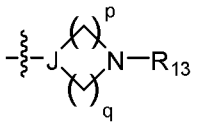
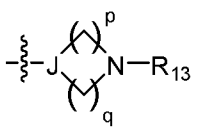
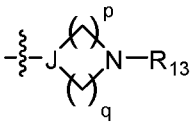
[0095] In another embodiment is a compound of Formula (IIC) wherein R_6 is -$(C(R_{14})(R_{15}))_mR_{21}$. In another embodiment is a compound of Formula (IIC) wherein R_6 is -$(C(R_{14})(R_{15}))_mR_{21}$, and each R_{14} and R_{15} are H. In another embodiment is a compound of Formula (IIC) wherein R_6 is -$(C(R_{14})(R_{15}))_mR_{21}$, m is 2, and each R_{14} and R_{15} are H. In another embodiment is a compound of Formula (I) wherein R_6 is -$(CH_2)_mR_{21}$, m is 2, and R_{21} is substituted or unsubstituted C_2-C_7heterocycloalkyl. In another embodiment is a compound of Formula (IIC) wherein R_6 is -$(CH_2)_mR_{21}$, m is 2, and R_{21} is substituted or unsubstituted C_3-C_8cycloalkyl. In another embodiment is a compound of Formula (IIC) wherein R_6 is -$(CH_2)_mR_{21}$, m is 2, and R_{21} is substituted or unsubstituted C_6-C_{10}aryl. In another embodiment is a compound of Formula (IIC) wherein R_6 is -$(CH_2)_mR_{21}$, m is 2, and R_{21} is substituted or unsubstituted phenyl. In another embodiment is a compound of Formula (IIC) wherein R_6 is -$(CH_2)_mR_{21}$, m is 2, and R_{21} is substituted or unsubstituted C_2-C_7heteroaryl. In another embodiment is a compound of Formula (IIC) wherein R_6 is -$(CH_2)_mR_{21}$, m is 2, and R_{21} is -OH.

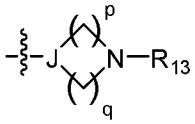
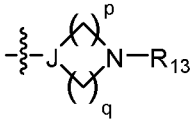
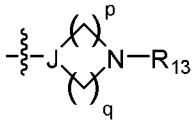
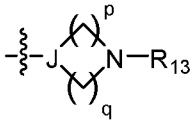
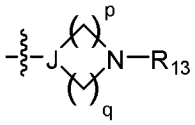
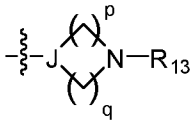
[0096] In another embodiment is a compound of Formula (IIC) wherein R_6 is -$(C(R_{14})(R_{15}))_mR_{21}$, m is 3, and each R_{14} and R_{15} are H. In another embodiment is a compound of Formula (IIC) wherein R_6 is -$(CH_2)_mR_{21}$, m is 3, and R_{21} is substituted or unsubstituted C_2-C_7heterocycloalkyl. In another embodiment is a compound of Formula (IIC) wherein R_6 is -$(CH_2)_mR_{21}$, m is 3, and R_{21} is substituted or unsubstituted C_3-C_8cycloalkyl. In another embodiment is a compound of Formula (IIC) wherein R_6 is -$(CH_2)_mR_{21}$, m is 3, and R_{21} is substituted or unsubstituted C_6-C_{10}aryl. In another embodiment is a compound of Formula (IIC) wherein R_6 is -$(CH_2)_mR_{21}$, m is 3, and R_{21} is substituted or unsubstituted phenyl. In another embodiment is a compound of Formula (IIC) wherein R_6 is -$(CH_2)_mR_{21}$, m is 3, and R_{21} is substituted or unsubstituted C_2-C_7heteroaryl. In another embodiment is a compound of Formula (IIC) wherein R_6 is -$(CH_2)_mR_{21}$, m is 3, and R_{21} is -OH.

[0097] In another embodiment is a compound of Formula (IIC) wherein R_6 is -$(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$. In another embodiment is a compound of Formula (IIC) wherein R_6 is -$(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$, m is 2, and each R_{14} and R_{15} are H. In another embodiment is a compound of Formula (IIC) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, m is 2, and R_{11} and R_{12} are each H. In another embodiment is a compound of Formula (IIC) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, m is 2, R_{11} is substituted or unsubstituted C_1-C_6alkyl, and R_{12} is H. In another embodiment is a compound of Formula (IIC) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, m is 2, R_{11} is CH_3, and R_{12} is H. In another embodiment is a compound of Formula (IIC) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, m is 2, R_{11} is substituted or unsubstituted C_1-C_6alkyl, and R_{12} is substituted or unsubstituted C_1-

C_6alkyl. In another embodiment is a compound of Formula (IIC) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, m is 2, R_{11} is CH_3, and R_{12} is CH_3. In another embodiment is a compound of Formula (IIC) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, m is 2, and R_{11} and R_{12} are taken together to form a 5-, 6-, 7-, or 8-membered heterocyclic ring. In another embodiment is a compound of Formula (IIC) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, m is 2, and R_{11} and R_{12} are taken together to form a 5-membered heterocyclic ring. In another embodiment is a compound of Formula (IIC) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, m is 2, and R_{11} and R_{12} are taken together to form a 6-membered heterocyclic ring.

[0098] In another embodiment is a compound of Formula (IIC) wherein R_6 is -$(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$. In another embodiment is a compound of Formula (IIC) wherein R_6 is -$(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$, m is 3, and each R_{14} and R_{15} are H. In another embodiment is a compound of Formula (IIC) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, m is 3, and R_{11} and R_{12} are each H. In another embodiment is a compound of Formula (IIC) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, m is 23, R_{11} is substituted or unsubstituted C_1-C_6alkyl, and R_{12} is H. In another embodiment is a compound of Formula (IIC) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, m is 3, R_{11} is CH_3, and R_{12} is H. In another embodiment is a compound of Formula (IIC) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, m is 3, R_{11} is substituted or unsubstituted C_1-C_6alkyl, and R_{12} is substituted or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIC) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, m is 3, R_{11} is CH_3, and R_{12} is CH_3. In another embodiment is a compound of Formula (IIC) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, m is 3, and R_{11} and R_{12} are taken together to form a 5-, 6-, 7-, or 8-membered heterocyclic ring. In another embodiment is a compound of Formula (IIC) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, m is 3, and R_{11} and R_{12} are taken together to form a 5-membered heterocyclic ring. In another embodiment is a compound of Formula (IIC) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, m is 3, and R_{11} and R_{12} are taken together to form a 6-membered heterocyclic ring.

[0099] In another embodiment is a compound of Formula (IIC) wherein R_6 is  and J is C(H). In another embodiment is a compound of Formula (IIC) wherein R_6 is  , J is C(H), p is 1, and q is 1. In another embodiment is a compound of Formula (IIC) wherein R_6 is  , J is C(H), p is 2, and q is 1. In another embodiment is a

compound of Formula (IIC) wherein R_6 is  , J is C(H), p is 3, and q is 1. In another embodiment is a compound of Formula (IIC) wherein R_6 is  , J is C(H), p is 2, and q is 2. In another embodiment is a compound of Formula (IIC) wherein R_6 is  , J is C(H), p is 1, q is 1, and R_{13} is substituted or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIC) wherein R_6 is  , J is C(H), p is 2, q is 1, and R_{13} is substituted or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIC) wherein R_6 is  , J is C(H), p is 3, q is 1, and R_{13} is substituted or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIC) wherein R_6 is  , J is C(H), p is 2, q is 2, and R_{13} is substituted or unsubstituted C_1-C_6alkyl.

[00100] In another embodiment is a compound of Formula (IIC) wherein R_5 is halogen. In another embodiment is a compound of Formula (IIC) wherein R_5 is $-CF_3$. In another embodiment is a compound of Formula (IIC) wherein R_5 is substituted or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIC) wherein R_5 is $-CH_3$. In another embodiment is a compound of Formula (IIC) wherein R_5 is $-CH_2CH_3$. In another embodiment is a compound of Formula (IIC) wherein R_5 is substituted or unsubstituted C_1-C_6heteroalkyl. In another embodiment is a compound of Formula (IIC) wherein R_5 is substituted or unsubstituted C_2-C_7heterocycloalkyl. In another embodiment is a compound of Formula (IIC) wherein R_5 is substituted or unsubstituted C_3-C_8cycloalkyl. In another embodiment is a compound of Formula (IIC) wherein R_5 is substituted or unsubstituted C_6-C_{10}aryl. In another embodiment is a compound of Formula (IIC) wherein R_5 is substituted or unsubstituted C_2-C_7heteroaryl.

[00101] In another embodiment is a compound of Formula (IIC) 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 (IIC) wherein R_2 and R_3 are each H.

[00102] In another embodiment is a compound of Formula (IIC) 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 (IIC) wherein R_2 is H, and R_3 is C_1-C_4alkyl. In another embodiment is a compound of Formula (IIC) wherein R_2 is H, and R_3 is CH_3. In another embodiment is a compound of Formula (IIC) wherein R_2 is H, and R_3 is C_3-C_6cycloalkyl. In another embodiment is a compound of Formula (IIC) wherein R_2 is H, and R_3 is cyclopropyl. In another embodiment is a compound of Formula (IIC) wherein R_2 is H, and R_3 is cyclopentyl. In another embodiment is a compound of Formula (IIC) wherein R_2 is CH_3, and R_3 is CH_3. In another embodiment is a compound of Formula (IIC) wherein R_2 is C_1-C_4alkyl, and R_3 is H. In another embodiment is a compound of Formula (IIC) wherein R_2 is CH_3, and R_3 is H. In another embodiment is a compound of Formula (IIC) wherein R_2 is C_3-C_6cycloalkyl, and R_3 is H. In another embodiment is a compound of Formula (IIC) wherein R_2 is cyclopropyl, and R_3 is H. In another embodiment is a compound of Formula (IIC) wherein R_2 is cyclopentyl, and R_3 is H.

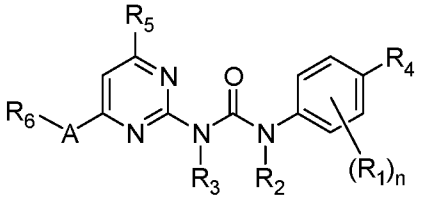
[00103] In another embodiment is a compound of Formula (IIC) wherein R_2 and R_3 are taken together to form a 5- or 6-membered heterocyclic ring. In another embodiment is a compound of Formula (IIC) wherein R_2 and R_3 are taken together to form a 5-membered heterocyclic ring. In another embodiment is a compound of Formula (IIC) wherein R_2 and R_3 are taken together to form 6-membered heterocyclic ring.

[00104] In another embodiment is a compound of Formula (IIC) wherein n is 0.

[00105] In another embodiment is a compound of Formula (IIC) 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. In another embodiment is a compound of Formula (IIC) wherein each R_1 is independently halogen, -CN, -OH, $-CF_3$, substituted or unsubstituted C_1-C_6alkyl, or substituted or unsubstituted C_1-C_6alkoxy. In another embodiment is a compound of Formula (IIC) wherein each R_1 is independently halogen, -CN, $-OCF_3$, $-OCH_2F$, $-OCF_2H$, $-CF_3$, 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. In another embodiment is a compound of Formula (IIC) wherein each R_1 is independently halogen, -CN, $-OCF_3$, $-OCH_2F$, $-OCF_2H$, $-CF_3$, substituted or unsubstituted C_1-C_6alkyl, or substituted or unsubstituted C_1-C_6alkoxy. In another embodiment is a compound of Formula (IIC) wherein each R_1 is independently halogen, -CN, $-OCF_3$, $-OCH_2F$, $-OCF_2H$, $-CF_3$, 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 (IIC) wherein each R_1 is independently halogen, -CN, $-OCF_3$, $-OCH_2F$, $-OCF_2H$, $-CF_3$, 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 (IIC) wherein n is 3, and each R_1 is independently halogen. In another embodiment is a compound of Formula (IIC) wherein n is 2, and each R_1 is independently halogen. In another embodiment is a compound of Formula (IIC) wherein n is 2, and each R_1 is independently F or Cl. In another embodiment is a compound of Formula (IIC) wherein n is 2, and each R_1 is F. In another embodiment is a compound of Formula (IIC) wherein n is 2, and each R_1 is independently Cl. In another embodiment is a compound of Formula (IIC) wherein n is 2, and each R_1 is independently halogen or $-CF_3$. In another embodiment is a compound of Formula (IIC) wherein n is 2, and each R_1 is independently F or $-CF_3$. In another embodiment is a compound of Formula (IIC) wherein n is 2, and each R_1 is independently Cl or $-CF_3$. In another embodiment is a compound of Formula (IIC) wherein n is 1, and R_1 is halogen. In another embodiment is a compound of Formula (IIC) wherein n is 1, and R_1 is F. In another embodiment is a compound of Formula (IIC) wherein n is 1, and R_1 is Cl. In another embodiment is a compound of Formula (IIC) wherein n is 1, and R_1 is $-CF_3$. In another embodiment is a compound of Formula (IIC) wherein n is 1, and R_1 is substituted or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIC) wherein n is 1, and R_1 is CH_3. In another embodiment is a compound of Formula (IIC) wherein n is 1, and R_1 is substituted or unsubstituted C_1-C_6alkoxy. In another embodiment is a compound of Formula (IIC) wherein n is 1, and R_1 is $-OCH_3$. In another embodiment is a compound of Formula (IIC) wherein n is 1, and R_1 is $-OCF_3$. In another embodiment is a compound of Formula (IIC) wherein n is 1, and R_1 is $-OCF_2H$.

[00106] In another embodiment, described herein is a compound of Formula (IID):



Formula (IID);

wherein:

A is a bond;

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; 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, $-NO_2$, -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; or two R_1 are taken together to form a substituted or unsubstituted heterocyclic ring or a substituted or unsubstituted carbocyclic ring; wherein when n is 0, R_4 is not halogen;

R_5 is 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 substituted or unsubstituted C_2-C_7heterocycloalkyl;

R_{11} and R_{12} are each independently H, or substituted or unsubstituted C_1-C_6alkyl; or R_{11} and R_{12} are taken together to form a 5-, 6-, 7-, or 8-membered heterocyclic ring;

J is C(H);

R_{13} is H, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_2-C_7heterocycloalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted -C_1-C_4alkylC_6-C_{10}aryl, or substituted or unsubstituted -C_1-C_4alkylC_2-C_7heteroaryl;

each R_{14} and R_{15} are each independently H, or substituted or unsubstituted C_1-C_6alkyl; or R_{14} and R_{15} are taken together to form a 4-, 5-, 6-membered cycloalkyl ring;

R_{21} is halogen, -CN, -NO_2, -OH, -OCF_3, -OCH_2F, -OCF_2H, -CF_3, -SR_{22}, -$N(R_{22})S(=O)_2R_{23}$, -$S(=O)_2N(R_{22})_2$, -$S(=O)R_{23}$, -$S(=O)_2R_{23}$, -$C(=O)R_{23}$, -CO_2R_{22}, -$C(=O)N(R_{22})_2$, -$N(R_{22})C(=O)R_{23}$, 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;

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

R_{23} is substituted or unsubstituted C_1-C_6alkyl;

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

R_9 is substituted or unsubstituted C_1-C_6alkyl;

m is 2-6;

n is 0-4;

p is 1-3;

q is 1-3; or

a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[00107] In one embodiment is a compound of Formula (IID) wherein R_6 is unsubstituted C_2-C_7heterocycloalkyl. In another embodiment is a compound of Formula (IID) wherein R_6 is substituted C_2-C_7heterocycloalkyl. In another embodiment is a compound of Formula (IID) wherein R_6 is substituted or unsubstituted morpholinyl. In another embodiment is a compound of Formula (IID) wherein R_6 is substituted or unsubstituted piperazinyl. In another embodiment is a compound of Formula (IID) wherein R_6 is substituted or unsubstituted piperidinyl.

[00108] In another embodiment is a compound of Formula (IID) wherein R_5 is halogen. In another embodiment is a compound of Formula (IID) wherein R_5 is -CF_3. In another embodiment is a compound of Formula (IID) wherein R_5 is substituted or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IID) wherein R_5 is -CH_3. In another embodiment is a compound of Formula (IID) wherein R_5 is -CH_2CH_3. In another embodiment is a compound of Formula (IID) wherein R_5 is substituted or unsubstituted C_1-C_6heteroalkyl. In another embodiment is a compound of Formula (IID) wherein R_5 is substituted or unsubstituted C_2-C_7heterocycloalkyl. In another embodiment is a compound of

Formula (IID) wherein R_5 is substituted or unsubstituted C_3-C_8cycloalkyl. In another embodiment is a compound of Formula (IID) wherein R_5 is substituted or unsubstituted C_6-C_{10}aryl. In another embodiment is a compound of Formula (IID) wherein R_5 is substituted or unsubstituted C_2-C_7heteroaryl.

[00109] In another embodiment is a compound of Formula (IID) 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 (IID) wherein R_2 and R_3 are each H.

[00110] In another embodiment is a compound of Formula (IID) 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 (IID) wherein R_2 is H, and R_3 is C_1-C_4alkyl. In another embodiment is a compound of Formula (IID) wherein R_2 is H, and R_3 is CH_3. In another embodiment is a compound of Formula (IID) wherein R_2 is H, and R_3 is C_3-C_6cycloalkyl. In another embodiment is a compound of Formula (IID) wherein R_2 is H, and R_3 is cyclopropyl. In another embodiment is a compound of Formula (IID) wherein R_2 is H, and R_3 is cyclopentyl. In another embodiment is a compound of Formula (IID) wherein R_2 is CH_3, and R_3 is CH_3. In another embodiment is a compound of Formula (IID) wherein R_2 is C_1-C_4alkyl, and R_3 is H. In another embodiment is a compound of Formula (IID) wherein R_2 is CH_3, and R_3 is H. In another embodiment is a compound of Formula (IID) wherein R_2 is C_3-C_6cycloalkyl, and R_3 is H. In another embodiment is a compound of Formula (IID) wherein R_2 is cyclopropyl, and R_3 is H. In another embodiment is a compound of Formula (IID) wherein R_2 is cyclopentyl, and R_3 is H.

[00111] In another embodiment is a compound of Formula (IID) 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 (IID) wherein R_2 and R_3 are taken together to form a 5-membered heterocyclic ring. In another embodiment is a compound of Formula (IID) wherein R_2 and R_3 are taken together to form 6-membered heterocyclic ring.

[00112] In another embodiment is a compound of Formula (IID) wherein n is 0.

[00113] In another embodiment is a compound of Formula (IID) 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. In another embodiment is a compound of Formula (IID) wherein each R_1 is independently halogen, -CN, -

OH, $-CF_3$, substituted or unsubstituted C_1-C_6alkyl, or substituted or unsubstituted C_1-C_6alkoxy. In another embodiment is a compound of Formula (IID) wherein each R_1 is independently halogen, -CN, $-OCF_3$, $-OCH_2F$, $-OCF_2H$, $-CF_3$, 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. In another embodiment is a compound of Formula (IID) wherein each R_1 is independently halogen, -CN, $-OCF_3$, $-OCH_2F$, $-OCF_2H$, $-CF_3$, substituted or unsubstituted C_1-C_6alkyl, or substituted or unsubstituted C_1-C_6alkoxy. In another embodiment is a compound of Formula (IID) wherein each R_1 is independently halogen, -CN, $-OCF_3$, $-OCH_2F$, $-OCF_2H$, $-CF_3$, 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 (IID) wherein each R_1 is independently halogen, -CN, $-OCF_3$, $-OCH_2F$, $-OCF_2H$, $-CF_3$, 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 (IID) wherein n is 3, and each R_1 is independently halogen. In another embodiment is a compound of Formula (IID) wherein n is 2, and each R_1 is independently halogen. In another embodiment is a compound of Formula (IID) wherein n is 2, and each R_1 is independently F or Cl. In another embodiment is a compound of Formula (IID) wherein n is 2, and each R_1 is F. In another embodiment is a compound of Formula (IID) wherein n is 2, and each R_1 is independently Cl. In another embodiment is a compound of Formula (IID) wherein n is 2, and each R_1 is independently halogen or $-CF_3$. In another embodiment is a compound of Formula (IID) wherein n is 2, and each R_1 is independently F or $-CF_3$. In another embodiment is a compound of Formula (IID) wherein n is 2, and each R_1 is independently Cl or $-CF_3$. In another embodiment is a compound of Formula (IID) wherein n is 1, and R_1 is halogen. In another embodiment is a compound of Formula (IID) wherein n is 1, and R_1 is F. In another embodiment is a compound of Formula (IID) wherein n is 1, and R_1 is Cl. In another embodiment is a compound of Formula (IID) wherein n is 1, and R_1 is $-CF_3$. In another embodiment is a compound of Formula (IID) wherein n is 1, and R_1 is substituted or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IID) wherein n is 1, and R_1 is CH_3. In another embodiment is a compound of Formula (IID) wherein n is 1, and R_1 is substituted or unsubstituted C_1-C_6alkoxy. In another embodiment is a compound of Formula (IID) wherein n is 1, and R_1 is $-OCH_3$. In another embodiment is a compound of Formula (IID) wherein n is 1, and R_1 is $-OCF_3$. In another embodiment is a compound of Formula (IID) wherein n is 1, and R_1 is $-OCF_2H$.

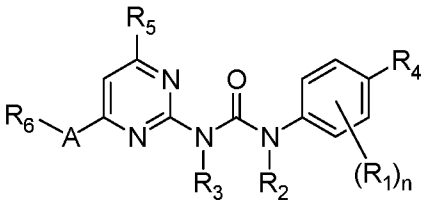
[00114] In another embodiment is a compound of Formula (IID) wherein R_4 is H, halogen, -CN, -NO_2, -OH, -OCF_3, -OCH_2F, -OCF_2H, -SR_8, -$N(R_8)S(=O)_2R_9$, -$S(=O)_2N(R_8)_2$, -$S(=O)R_9$, -$S(=O)_2R_9$, -$C(=O)R_9$, -CO_2R_8, -$N(R_8)_2$, -$C(=O)N(R_8)_2$, -$N(R_8)C(=O)R_9$, substituted or unsubstituted C_1-C_6alkyl, or substituted or unsubstituted C_1-C_6alkoxy. In another embodiment is a compound of Formula (IID) wherein R_4 is H, halogen, -CN, -OH, -OCF_3, substituted or unsubstituted C_1-C_6alkyl, or substituted or unsubstituted C_1-C_6alkoxy. In another embodiment is a compound of Formula (IID) wherein R_4 is H. In another embodiment is a compound of Formula (IID) wherein R_4 is halogen. In another embodiment is a compound of Formula (IID) wherein R_4 is F. In another embodiment is a compound of Formula (IID) wherein R_4 is Cl. In another embodiment is a compound of Formula (IID) wherein R_4 is Br. In another embodiment is a compound of Formula (IID) wherein R_4 is -CF_3. In another embodiment is a compound of Formula (IID) wherein R_4 is -OCF_3. In another embodiment is a compound of Formula (IID) R_4 is -CH_3. In another embodiment is a compound of Formula (IID) wherein R_4 is -OCH_3.

[00115] In another embodiment is a compound of Formula (IID) wherein n is 0 and R_4 is H. In another embodiment is a compound of Formula (IID) wherein n is 0 and R_4 is halogen. In another embodiment is a compound of Formula (IID) wherein n is 0 and R_4 is F. In another embodiment is a compound of Formula (IID) wherein n is 0 and R_4 is Cl. In another embodiment is a compound of Formula (IID) wherein n is 0 and R_4 is Br. In another embodiment is a compound of Formula (IID) wherein n is 0 and R_4 is -CF_3. In another embodiment is a compound of Formula (IID) wherein n is 0 and R_4 is -OCF_3. In another embodiment is a compound of Formula (IID) wherein n is 0 and R_4 is -CH_3. In another embodiment is a compound of Formula (IID) wherein n is 0 and R_4 is -OCH_3.

[00116] In another embodiment is a compound of Formula (IID) wherein n is 1, R_1 is Cl, and R_4 is Cl. In another embodiment is a compound of Formula (IID) wherein n is 1, R_1 is -CH_3, and R_4 is Cl. In another embodiment is a compound of Formula (IID) wherein n is 1, R_1 is -OCH_3, and R_4 is Cl. In another embodiment is a compound of Formula (IID) wherein n is 1, R_1 is -CF_3, and R_4 is Cl. In another embodiment is a compound of Formula (IID) wherein n is 1, R_1 is -OCF_3, and R_4 is Cl. In another embodiment is a compound of Formula (IID) wherein n is 1, R_1 is Cl, and R_4 is F. In another embodiment is a compound of Formula (IID) wherein n is 1, R_1 is -CH_3, and R_4 is F. In another embodiment is a compound of Formula (IID) wherein n is 1, R_1 is -OCH_3, and R_4 is F. In another embodiment is a compound of Formula (IID) wherein n is 1, R_1 is -CF_3, and R_4 is F. In another embodiment is a compound of Formula (IID) wherein n is 1, R_1 is -OCF_3, and R_4 is F. In another embodiment is a compound of Formula (IID) wherein n is 1, R_1 is Cl, and R_4 is H. In another embodiment is a compound of Formula (IID) wherein n is 1, R_1 is -CH_3, and R_4 is H. In another embodiment is a compound of Formula (IID) wherein n is 1, R_1

is -OCH_3, and R_4 is H. In another embodiment is a compound of Formula (IID) wherein n is 1, R_1 is -CF_3, and R_4 is H. In another embodiment is a compound of Formula (IID) wherein n is 1, R_1 is -OCF_3, and R_4 is H. In another embodiment is a compound of Formula (IID) wherein n is 1, R_1 is Cl, and R_4 is -OCH_3. In another embodiment is a compound of Formula (IID) wherein n is 1, R_1 is -CH_3, and R_4 is -OCH_3. In another embodiment is a compound of Formula (IID) wherein n is 1, R_1 is -OCH_3, and R_4 is -OCH_3. In another embodiment is a compound of Formula (IID) wherein n is 1, R_1 is -CF_3, and R_4 is -OCH_3. In another embodiment is a compound of Formula (IID) wherein n is 1, R_1 is -OCF_3, and R_4 is -OCH_3. In another embodiment is a compound of Formula (IID) wherein n is 1, R_1 is Cl, and R_4 is -OCF_3. In another embodiment is a compound of Formula (IID) wherein n is 1, R_1 is -CH_3, and R_4 is -OCF_3. In another embodiment is a compound of Formula (IID) wherein n is 1, R_1 is -OCH_3, and R_4 is -OCF_3. In another embodiment is a compound of Formula (IID) wherein n is 1, R_1 is -CF_3, and R_4 is -OCF_3. In another embodiment is a compound of Formula (IID) wherein n is 1, R_1 is -OCF_3, and R_4 is -OCF_3.

[00117] In another embodiment, described herein is a compound of Formula (IID'):



Formula (IID');

wherein:

A is a bond;

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; 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, F, Cl, Br, I, -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; or two R_1 are taken together to form a substituted or unsubstituted heterocyclic ring or a substituted or unsubstituted carbocyclic ring; wherein when n is 0, R_4 is not Cl;

R_5 is 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 substituted or unsubstituted C_2-C_7heterocycloalkyl;

R_{11} and R_{12} are each independently H, or substituted or unsubstituted C_1-C_6alkyl; or R_{11} and R_{12} are taken together to form a 5-, 6-, 7-, or 8-membered heterocyclic ring;

J is C(H);

R_{13} is H, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_2-C_7heterocycloalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted -C_1-C_4alkylC_6-C_{10}aryl, or substituted or unsubstituted -C_1-C_4alkylC_2-C_7heteroaryl;

each R_{14} and R_{15} are each independently H, or substituted or unsubstituted C_1-C_6alkyl; or R_{14} and R_{15} are taken together to form a 4-, 5-, 6-membered cycloalkyl ring;

R_{21} is halogen, -CN, $-NO_2$, -OH, $-OCF_3$, $-OCH_2F$, $-OCF_2H$, $-CF_3$, $-SR_{22}$, $-N(R_{22})S(=O)_2R_{23}$, $-S(=O)_2N(R_{22})_2$, $-S(=O)R_{23}$, $-S(=O)_2R_{23}$, $-C(=O)R_{23}$, $-CO_2R_{22}$, $-C(=O)N(R_{22})_2$, $-N(R_{22})C(=O)R_{23}$, 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;

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

R_{23} is substituted or unsubstituted C_1-C_6alkyl;

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

R_9 is substituted or unsubstituted C_1-C_6alkyl;

m is 2-6;

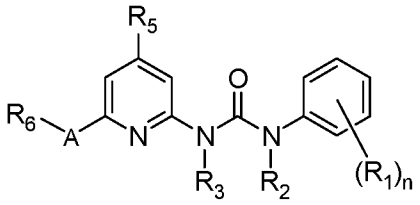
n is 0-4;

p is 1-3;

q is 1-3; or

a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[00118] In another aspect, described herein is a compound of Formula (III):



Formula (III);

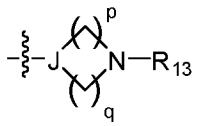
wherein:

A is a bond, O, or $N(R_{10})$;

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; 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_5 is 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_3-C_8cycloalkyl, substituted or unsubstituted C_6-C_{10}aryl, or substituted or unsubstituted C_2-C_7heteroaryl;

R_6 is substituted or unsubstituted C_2-C_7heterocycloalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted C_2-C_7heteroaryl, $-(C(R_{14})(R_{15}))_mR_{21}$, $-(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$, or  ;

R_{11} and R_{12} are each independently H, or substituted or unsubstituted C_1-C_6alkyl; or R_{11} and R_{12} are taken together to form a 5-, 6-, 7-, or 8-membered heterocyclic ring;

J is C(H), or N;

R_{13} is H, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_2-C_7heterocycloalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted -C_1-C_4alkylC_6-C_{10}aryl, or substituted or unsubstituted -C_1-C_4alkylC_2-C_7heteroaryl;

each R_{14} and R_{15} are each independently H, or substituted or unsubstituted C_1-C_6alkyl; or R_{14} and R_{15} are taken together to form a 4-, 5-, 6-membered cycloalkyl ring;

R_{21} is halogen, -CN, -NO_2, -OH, -OCF_3, -OCH_2F, -OCF_2H, -CF_3, -SR_{22}, -$N(R_{22})S(=O)_2R_{23}$, -$S(=O)_2N(R_{22})_2$, -$S(=O)R_{23}$, -$S(=O)_2R_{23}$, -$C(=O)R_{23}$, -CO_2R_{22}, -$C(=O)N(R_{22})_2$, -$N(R_{22})C(=O)R_{23}$, 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;

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

R_{23} is substituted or unsubstituted C_1-C_6alkyl;

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

R_9 is substituted or unsubstituted C_1-C_6alkyl;

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

m is 2-6;

n is 0-5;

p is 1-3;

q is 1-3; or

a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[00119] In another embodiment is a compound of Formula (III) wherein A is O, or N(R_{10}). In another embodiment is a compound of Formula (III) wherein A is O, CH_2, or N(H). In another embodiment is a compound of Formula (III) wherein A is O. In another embodiment is a compound of Formula (III) wherein A is N(R_{10}). In another embodiment is a compound of Formula (III) wherein A is N(H). In another embodiment is a compound of Formula (III) wherein A is N(CH_3). In another embodiment is a compound of Formula (III) wherein A is a bond.

[00120] In another embodiment is a compound of Formula (III) wherein R_6 is substituted or unsubstituted C_3-C_8cycloalkyl. In another embodiment is a compound of Formula (III) wherein R_6 is substituted or unsubstituted cyclopropyl. In another embodiment is a compound of Formula (III) wherein R_6 is substituted or unsubstituted cyclobutyl. In another embodiment is a compound of Formula (III) wherein R_6 is substituted or unsubstituted cyclopentyl. In another embodiment is a compound of Formula (III) wherein R_6 is substituted or unsubstituted cyclohexyl.

[00121] In another embodiment is a compound of Formula (III) wherein R_6 is substituted or unsubstituted C_2-C_7heteroaryl. In another embodiment is a compound of Formula (III) wherein R_6 is substituted or unsubstituted furanyl, thiophenyl, pyrrolyl, pyridyl, oxazolyl, thiazolyl,

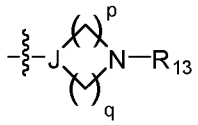
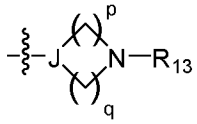
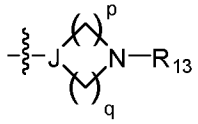
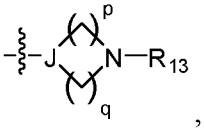
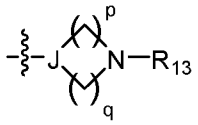
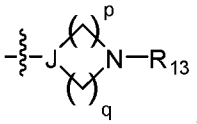
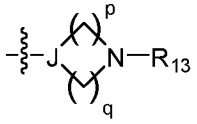
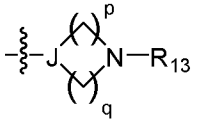
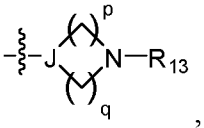
imidazolyl, isoxazolyl, isothiazolyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, oxadiazolyl, thiadiazolyl, triazolyl, indolyl, benzothiophenyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, benzoxadiazolyl, benzothiadiazolyl, benzotriazolyl, pyrazolopyridinyl, imidazopyridinyl, pyrrolopyridinyl, pyrrolopyrimidinyl, indolizinyl, purinyl, furopyridinyl, thienopyridinyl, furopyrrolyl, furofuranyl, thienofuranyl, 1,4-dihydropyrrolopyrrolyl, thienopyrrolyl, thienothiophenyl, quinolinyl, isoquinolinyl, quinoxalinyl, furopyrazolyl, thienopyrazolyl, selenophenyl, selenazolyl, and benzoisoxazolyl. In another embodiment is a compound of Formula (III) wherein R_6 is substituted or unsubstituted pyridyl. In another embodiment is a compound of Formula (III) wherein R_6 is substituted pyridyl. In another embodiment is a compound of Formula (III) wherein R_6 is unsubstituted pyridyl.

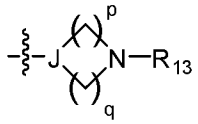
[00122] In another embodiment is a compound of Formula (III) wherein R_6 is -$(C(R_{14})(R_{15}))_mR_{21}$. In another embodiment is a compound of Formula (III) wherein R_6 is -$(C(R_{14})(R_{15}))_mR_{21}$, and each R_{14} and R_{15} are H. In another embodiment is a compound of Formula (III) wherein R_6 is -$(C(R_{14})(R_{15}))_mR_{21}$, m is 2, and each R_{14} and R_{15} are H. In another embodiment is a compound of Formula (III) wherein R_6 is -$(CH_2)_mR_{21}$, m is 2, and R_{21} is substituted or unsubstituted C_2-C_7heterocycloalkyl. In another embodiment is a compound of Formula (III) wherein R_6 is -$(CH_2)_mR_{21}$, m is 2, and R_{21} is substituted or unsubstituted C_3-C_8cycloalkyl. In another embodiment is a compound of Formula (III) wherein R_6 is -$(CH_2)_mR_{21}$, m is 2, and R_{21} is substituted or unsubstituted C_6-C_{10}aryl. In another embodiment is a compound of Formula (III) wherein R_6 is -$(CH_2)_mR_{21}$, m is 2, and R_{21} is substituted or unsubstituted phenyl. In another embodiment is a compound of Formula (III) wherein R_6 is -$(CH_2)_mR_{21}$, m is 2, and R_{21} is substituted or unsubstituted C_2-C_7heteroaryl. In another embodiment is a compound of Formula (III) wherein R_6 is -$(CH_2)_mR_{21}$, m is 2, and R_{21} is -OH.

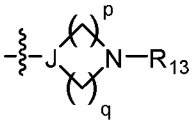
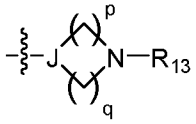
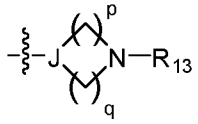
[00123] In another embodiment is a compound of Formula (III) wherein R_6 is -$(C(R_{14})(R_{15}))_mR_{21}$, m is 3, and each R_{14} and R_{15} are H. In another embodiment is a compound of Formula (III) wherein R_6 is -$(CH_2)_mR_{21}$, m is 3, and R_{21} is substituted or unsubstituted C_2-C_7heterocycloalkyl. In another embodiment is a compound of Formula (III) wherein R_6 is -$(CH_2)_mR_{21}$, m is 3, and R_{21} is substituted or unsubstituted C_3-C_8cycloalkyl. In another embodiment is a compound of Formula (III) wherein R_6 is -$(CH_2)_mR_{21}$, m is 3, and R_{21} is substituted or unsubstituted C_6-C_{10}aryl. In another embodiment is a compound of Formula (III) wherein R_6 is -$(CH_2)_mR_{21}$, m is 3, and R_{21} is substituted or unsubstituted phenyl. In another embodiment is a compound of Formula (III) wherein R_6 is -$(CH_2)_mR_{21}$, m is 3, and R_{21} is substituted or unsubstituted C_2-C_7heteroaryl. In another embodiment is a compound of Formula (III) wherein R_6 is -$(CH_2)_mR_{21}$, m is 3, and R_{21} is -OH.

[00124] 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 -$(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$, m is 2, and each R_{14} and R_{15} are H. In another embodiment is a compound of Formula (III) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, m is 2, and R_{11} and R_{12} are each H. In another embodiment is a compound of Formula (III) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, m is 2, R_{11} is substituted or unsubstituted C_1-C_6alkyl, and R_{12} is H. In another embodiment is a compound of Formula (III) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, m is 2, R_{11} is CH_3, and R_{12} is H. In another embodiment is a compound of Formula (III) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, m is 2, R_{11} is substituted or unsubstituted C_1-C_6alkyl, and R_{12} is substituted or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (III) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, m is 2, R_{11} is CH_3, and R_{12} is CH_3. In another embodiment is a compound of Formula (III) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, m is 2, and R_{11} and R_{12} are taken together to form a 5-, 6-, 7-, or 8-membered heterocyclic ring. In another embodiment is a compound of Formula (III) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, m is 2, and R_{11} and R_{12} are taken together to form a 5-membered heterocyclic ring. In another embodiment is a compound of Formula (III) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, m is 2, and R_{11} and R_{12} are taken together to form a 6-membered heterocyclic ring.

[00125] 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 -$(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$, m is 3, and each R_{14} and R_{15} are H. In another embodiment is a compound of Formula (III) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, m is 3, and R_{11} and R_{12} are each H. In another embodiment is a compound of Formula (III) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, m is 3, R_{11} is substituted or unsubstituted C_1-C_6alkyl, and R_{12} is H. In another embodiment is a compound of Formula (III) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, m is 3, R_{11} is CH_3, and R_{12} is H. In another embodiment is a compound of Formula (III) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, m is 3, R_{11} is substituted or unsubstituted C_1-C_6alkyl, and R_{12} is substituted or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (III) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, m is 3, R_{11} is CH_3, and R_{12} is CH_3. In another embodiment is a compound of Formula (III) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, m is 3, and R_{11} and R_{12} are taken together to form a 5-, 6-, 7-, or 8-membered heterocyclic ring. In another embodiment is a compound of Formula (III) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, m is 3, and R_{11} and R_{12} are taken together to form a 5-membered heterocyclic ring. In another embodiment is a compound of Formula (III) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, m is 3, and R_{11} and R_{12} are taken together to form a 6-membered heterocyclic ring.

[00126] In another embodiment is a compound of Formula (III) wherein R_6 is substituted or unsubstituted C_2-C_7heterocycloalkyl. In another embodiment is a compound of Formula (III) wherein R_6 is  . In another embodiment is a compound of Formula (III) wherein R_6 is  and J is C(H). In another embodiment is a compound of Formula (III) wherein R_6 is  , J is C(H), p is 1, and q is 1. In another embodiment is a compound of Formula (III) wherein R_6 is  , J is C(H), p is 2, and q is 1. In another embodiment is a compound of Formula (III) wherein R_6 is  , J is C(H), p is 3, and q is 1. In another embodiment is a compound of Formula (III) wherein R_6 is  , J is C(H), p is 2, and q is 2. In another embodiment is a compound of Formula (III) wherein R_6 is  , J is C(H), p is 1, q is 1, and R_{13} is substituted or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (III) wherein R_6 is  , J is C(H), p is 2, q is 1, and R_{13} is substituted or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (III) wherein R_6 is  , J is C(H), p is 3, q is 1, and R_{13} is substituted or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (III)

wherein R_6 is  , J is C(H), p is 2, q is 2, and R_{13} is substituted or unsubstituted C_1-C_6alkyl.

[00127] In another embodiment is a compound of Formula (III) wherein R_6 is  and J is N. In another embodiment is a compound of Formula (III) wherein R_6 is  , J is N, p is 2, and q is 2. In another embodiment is a compound of Formula (III) wherein R_6 is  , J is N, p is 2, q is 2, and R_{13} is substituted or unsubstituted C_1-C_6alkyl.

[00128] 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 $-CF_3$. 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 $-CH_3$. 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 substituted or unsubstituted C_1-C_6heteroalkyl. 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 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.

[00129] 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. In another embodiment is a compound of Formula (III) wherein R_2 and R_3 are each H.

[00130] 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.

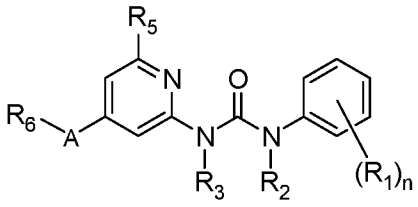
[00131] In another embodiment is a compound of Formula (III) wherein R_2 and R_3 are taken together to form a 5- or 6-membered heterocyclic ring. In another embodiment is a compound of Formula (III) wherein R_2 and R_3 are taken together to form a 5-membered heterocyclic ring. In another embodiment is a compound of Formula (III) wherein R_2 and R_3 are taken together to form 6-membered heterocyclic ring.

[00132] In another embodiment is a compound of Formula (III) wherein n is 0.

[00133] In another embodiment is a compound of 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. In another embodiment is a compound of Formula (III) wherein each R_1 is independently halogen, -CN, -OH, -CF_3, substituted or unsubstituted C_1-C_6alkyl, or substituted or unsubstituted C_1-C_6alkoxy. In another embodiment is a compound of Formula (III) wherein each R_1 is independently halogen, -CN, -OCF_3, -OCH_2F, -OCF_2H, -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. In another embodiment is a compound of Formula (III) wherein each R_1 is independently halogen, -CN, -OCF_3, -OCH_2F, -OCF_2H, -CF_3, substituted or unsubstituted C_1-C_6alkyl, or substituted or unsubstituted C_1-C_6alkoxy. In another embodiment is a compound of Formula (III) wherein each R_1 is independently halogen, -CN, -OCF_3, -OCH_2F, -OCF_2H, -CF_3, 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 (III) wherein each R_1 is independently halogen, -CN, -OCF_3, -OCH_2F, -OCF_2H, -CF_3, 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 (III)

wherein n is 3, and each R_1 is independently halogen. In another embodiment is a compound of Formula (III) wherein n is 2, and each R_1 is independently halogen. In another embodiment is a compound of Formula (III) wherein n is 2, and each R_1 is independently F or Cl. In another embodiment is a compound of Formula (III) wherein n is 2, and each R_1 is F. In another embodiment is a compound of Formula (III) wherein n is 2, and each R_1 is independently Cl. In another embodiment is a compound of Formula (III) wherein n is 2, and each R_1 is independently halogen or $-CF_3$. In another embodiment is a compound of Formula (III) wherein n is 2, and each R_1 is independently F or $-CF_3$. In another embodiment is a compound of Formula (III) wherein n is 2, and each R_1 is independently Cl or $-CF_3$. In another embodiment is a compound of Formula (III) wherein n is 1, and R_1 is halogen. In another embodiment is a compound of Formula (III) wherein n is 1, and R_1 is F. In another embodiment is a compound of Formula (III) wherein n is 1, and R_1 is Cl. In another embodiment is a compound of Formula (III) wherein n is 1, and R_1 is $-CF_3$. In another embodiment is a compound of Formula (III) wherein n is 1, and R_1 is substituted or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (III) wherein n is 1, and R_1 is CH_3. In another embodiment is a compound of Formula (III) wherein n is 1, and R_1 is substituted or unsubstituted C_1-C_6alkoxy. In another embodiment is a compound of Formula (III) wherein n is 1, and R_1 is $-OCH_3$. In another embodiment is a compound of Formula (III) wherein n is 1, and R_1 is $-OCF_3$. In another embodiment is a compound of Formula (III) wherein n is 1, and R_1 is $-OCF_2H$.

[00134] In another aspect, described herein is a compound of Formula (IV):



Formula (IV);

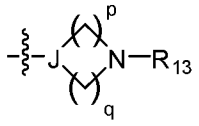
wherein:

A is a bond, O, or $N(R_{10})$;

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; 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_5 is 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 substituted or unsubstituted C_2-C_7heterocycloalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted C_2-C_7heteroaryl, $-(C(R_{14})(R_{15}))_mR_{21}$, $-(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$, or  ;

R_{11} and R_{12} are each independently H, or substituted or unsubstituted C_1-C_6alkyl; or R_{11} and R_{12} are taken together to form a 5-, 6-, 7-, or 8-membered heterocyclic ring;

J is C(H), or N;

R_{13} is H, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_2-C_7heterocycloalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted -C_1-C_4alkylC_6-C_{10}aryl, or substituted or unsubstituted -C_1-C_4alkylC_2-C_7heteroaryl;

each R_{14} and R_{15} are each independently H, or substituted or unsubstituted C_1-C_6alkyl; or R_{14} and R_{15} are taken together to form a 4-, 5-, 6-membered cycloalkyl ring;

R_{21} is halogen, -CN, $-NO_2$, -OH, $-OCF_3$, $-OCH_2F$, $-OCF_2H$, $-CF_3$, $-SR_{22}$, $-N(R_{22})S(=O)_2R_{23}$, $-S(=O)_2N(R_{22})_2$, $-S(=O)R_{23}$, $-S(=O)_2R_{23}$, $-C(=O)R_{23}$, $-CO_2R_{22}$, $-C(=O)N(R_{22})_2$, $-N(R_{22})C(=O)R_{23}$, 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;

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

R_{23} is substituted or unsubstituted C_1-C_6alkyl;

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

R_9 is substituted or unsubstituted C_1-C_6alkyl;

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

m is 2-6;

n is 0-5;

p is 1-3;

q is 1-3; or

a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[00135] In another embodiment is a compound of Formula (IV) wherein A is O, or $N(R_{10})$. In another embodiment is a compound of Formula (IV) wherein A is O, or N(H). In another embodiment is a compound of Formula (IV) wherein A is O. In another embodiment is a compound of Formula (IV) wherein A is $N(R_{10})$. In another embodiment is a compound of Formula (IV) wherein A is N(H). In another embodiment is a compound of Formula (IV) wherein A is $N(CH_3)$. In another embodiment is a compound of Formula (IV) wherein A is a bond.

[00136] In another embodiment is a compound of Formula (IV) wherein R_6 is substituted or unsubstituted C_3-C_8cycloalkyl. In another embodiment is a compound of Formula (IV) wherein R_6 is substituted or unsubstituted cyclopropyl. In another embodiment is a compound of Formula (IV) wherein R_6 is substituted or unsubstituted cyclobutyl. In another embodiment is a compound of Formula (IV) wherein R_6 is substituted or unsubstituted cyclopentyl. In another embodiment is a compound of Formula (IV) wherein R_6 is substituted or unsubstituted cyclohexyl.

[00137] In another embodiment is a compound of Formula (IV) wherein R_6 is substituted or unsubstituted C_2-C_7heteroaryl. In another embodiment is a compound of Formula (IV) wherein R_6 is substituted or unsubstituted furanyl, thiophenyl, pyrrolyl, pyridyl, oxazolyl, thiazolyl, imidazolyl, isoxazolyl, isothiazolyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, oxadiazolyl, thiadiazolyl, triazolyl, indolyl, benzothiophenyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, benzoxadiazolyl, benzothiadiazolyl, benzotriazolyl, pyrazolopyridinyl, imidazopyridinyl, pyrrolopyridinyl, pyrrolopyrimidinyl, indolizinyl, purinyl, furopyridinyl, thienopyridinyl, furopyrrolyl, furofuranyl, thienofuranyl, 1,4-dihydropyrrolopyrrolyl, thienopyrrolyl, thienothiophenyl, quinolinyl, isoquinolinyl, quinoxalinyl, furopyrazolyl, thienopyrazolyl, selenophenyl, selenazolyl, and benzoisoxazolyl. In another embodiment is a compound of Formula (IV) wherein R_6 is substituted or unsubstituted pyridyl. In another embodiment is a compound of Formula (IV) wherein R_6 is substituted pyridyl. In another embodiment is a compound of Formula (IV) wherein R_6 is unsubstituted pyridyl.

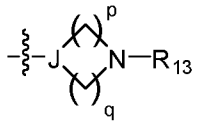
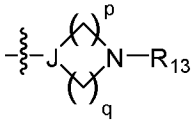
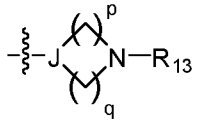
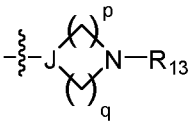
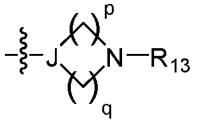
[00138] In another embodiment is a compound of Formula (IV) wherein R_6 is -$(C(R_{14})(R_{15}))_mR_{21}$. In another embodiment is a compound of Formula (IV) wherein R_6 is -$(C(R_{14})(R_{15}))_mR_{21}$, and each R_{14} and R_{15} are H. In another embodiment is a compound of Formula (IV) wherein R_6 is -$(C(R_{14})(R_{15}))_mR_{21}$, m is 2, and each R_{14} and R_{15} are H. In another embodiment is a compound of Formula (IV) wherein R_6 is -$(CH_2)_mR_{21}$, m is 2, and R_{21} is substituted or unsubstituted C_2-C_7heterocycloalkyl. In another embodiment is a compound of

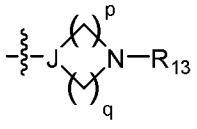
Formula (IV) wherein R_6 is $-(CH_2)_mR_{21}$, m is 2, and R_{21} is substituted or unsubstituted C_3-C_8cycloalkyl. In another embodiment is a compound of Formula (IV) wherein R_6 is $-(CH_2)_mR_{21}$, m is 2, and R_{21} is substituted or unsubstituted C_6-C_{10}aryl. In another embodiment is a compound of Formula (IV) wherein R_6 is $-(CH_2)_mR_{21}$, m is 2, and R_{21} is substituted or unsubstituted phenyl. In another embodiment is a compound of Formula (IV) wherein R_6 is $-(CH_2)_mR_{21}$, m is 2, and R_{21} is substituted or unsubstituted C_2-C_7heteroaryl. In another embodiment is a compound of Formula (IV) wherein R_6 is $-(CH_2)_mR_{21}$, m is 2, and R_{21} is -OH.

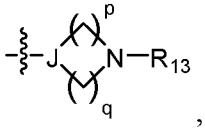
[00139] In another embodiment is a compound of Formula (IV) wherein R_6 is $-(C(R_{14})(R_{15}))_mR_{21}$, m is 3, and each R_{14} and R_{15} are H. In another embodiment is a compound of Formula (IV) wherein R_6 is $-(CH_2)_mR_{21}$, m is 3, and R_{21} is substituted or unsubstituted C_2-C_7heterocycloalkyl. In another embodiment is a compound of Formula (IV) wherein R_6 is $-(CH_2)_mR_{21}$, m is 3, and R_{21} is substituted or unsubstituted C_3-C_8cycloalkyl. In another embodiment is a compound of Formula (IV) wherein R_6 is $-(CH_2)_mR_{21}$, m is 3, and R_{21} is substituted or unsubstituted C_6-C_{10}aryl. In another embodiment is a compound of Formula (IV) wherein R_6 is $-(CH_2)_mR_{21}$, m is 3, and R_{21} is substituted or unsubstituted phenyl. In another embodiment is a compound of Formula (IV) wherein R_6 is $-(CH_2)_mR_{21}$, m is 3, and R_{21} is substituted or unsubstituted C_2-C_7heteroaryl. In another embodiment is a compound of Formula (IV) wherein R_6 is $-(CH_2)_mR_{21}$, m is 3, and R_{21} is -OH.

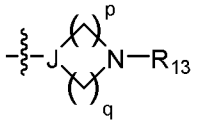
[00140] In another embodiment is a compound of Formula (IV) wherein R_6 is $-(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$. In another embodiment is a compound of Formula (IV) wherein R_6 is $-(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$, m is 2, and each R_{14} and R_{15} are H. In another embodiment is a compound of Formula (IV) wherein R_6 is $-(CH_2)_mN(R_{11})(R_{12})$, m is 2, and R_{11} and R_{12} are each H. In another embodiment is a compound of Formula (IV) wherein R_6 is $-(CH_2)_mN(R_{11})(R_{12})$, m is 2, R_{11} is substituted or unsubstituted C_1-C_6alkyl, and R_{12} is H. In another embodiment is a compound of Formula (IV) wherein R_6 is $-(CH_2)_mN(R_{11})(R_{12})$, m is 2, R_{11} is CH_3, and R_{12} is H. In another embodiment is a compound of Formula (IV) wherein R_6 is $-(CH_2)_mN(R_{11})(R_{12})$, m is 2, R_{11} is substituted or unsubstituted C_1-C_6alkyl, and R_{12} is substituted or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IV) wherein R_6 is $-(CH_2)_mN(R_{11})(R_{12})$, m is 2, R_{11} is CH_3, and R_{12} is CH_3. In another embodiment is a compound of Formula (IV) wherein R_6 is $-(CH_2)_mN(R_{11})(R_{12})$, m is 2, and R_{11} and R_{12} are taken together to form a 5-, 6-, 7-, or 8-membered heterocyclic ring. In another embodiment is a compound of Formula (IV) wherein R_6 is $-(CH_2)_mN(R_{11})(R_{12})$, m is 2, and R_{11} and R_{12} are taken together to form a 5-membered heterocyclic ring. In another embodiment is a compound of Formula (IV) wherein R_6 is $-(CH_2)_mN(R_{11})(R_{12})$, m is 2, and R_{11} and R_{12} are taken together to form a 6-membered heterocyclic ring.

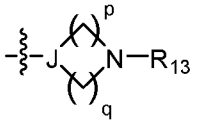
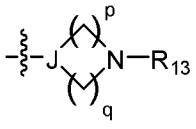
[00141] In another embodiment is a compound of Formula (IV) wherein R_6 is -$(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$. In another embodiment is a compound of Formula (IV) wherein R_6 is -$(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$, m is 3, and each R_{14} and R_{15} are H. In another embodiment is a compound of Formula (IV) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, m is 3, and R_{11} and R_{12} are each H. In another embodiment is a compound of Formula (IV) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, m is 3, R_{11} is substituted or unsubstituted C_1-C_6alkyl, and R_{12} is H. In another embodiment is a compound of Formula (IV) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, m is 3, R_{11} is CH_3, and R_{12} is H. In another embodiment is a compound of Formula (IV) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, m is 3, R_{11} is substituted or unsubstituted C_1-C_6alkyl, and R_{12} is substituted or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IV) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, m is 3, R_{11} is CH_3, and R_{12} is CH_3. In another embodiment is a compound of Formula (IV) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, m is 3, and R_{11} and R_{12} are taken together to form a 5-, 6-, 7-, or 8-membered heterocyclic ring. In another embodiment is a compound of Formula (IV) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, m is 3, and R_{11} and R_{12} are taken together to form a 5-membered heterocyclic ring. In another embodiment is a compound of Formula (IV) wherein R_6 is -$(CH_2)_mN(R_{11})(R_{12})$, m is 3, and R_{11} and R_{12} are taken together to form a 6-membered heterocyclic ring.

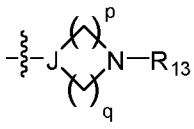
[00142] In another embodiment is a compound of Formula (IV) wherein R_6 is substituted or unsubstituted C_2-C_7heterocycloalkyl. In another embodiment is a compound of Formula (IV) wherein R_6 is  . In another embodiment is a compound of Formula (IV) wherein R_6 is  and J is C(H). In another embodiment is a compound of Formula (IV) wherein R_6 is  , J is C(H), p is 1, and q is 1. In another embodiment is a compound of Formula (IV) wherein R_6 is  , J is C(H), p is 2, and q is 1. In another embodiment is a compound of Formula (IV) wherein R_6 is  , J is C(H), p is 3, and q is 1. In another embodiment is a compound of Formula (IV) wherein R_6 is

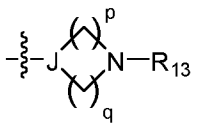


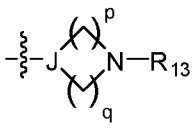
, J is C(H), p is 2, and q is 2. In another embodiment is a compound of Formula (IV) wherein R_6 is  , J is C(H), p is 1, q is 1, and R_{13} is substituted or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IV) wherein R_6 is



, J is C(H), p is 2, q is 1, and R_{13} is substituted or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IV) wherein R_6 is  , J is C(H), p is 3, q is 1, and R_{13} is substituted or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IV) wherein R_6 is  , J is C(H), p is 2, q is 2, and R_{13} is substituted or unsubstituted C_1-C_6alkyl.

[00143] In another embodiment is a compound of Formula (IV) wherein R_6 is  and J is N. In another embodiment is a compound of Formula (IV) wherein R_6 is



, J is N, p is 2, and q is 2. In another embodiment is a compound of Formula (IV) wherein R_6 is  , J is N, p is 2, q is 2, and R_{13} is substituted or unsubstituted C_1-C_6alkyl.

[00144] In another embodiment is a compound of Formula (IV) wherein R_5 is halogen. In another embodiment is a compound of Formula (IV) wherein R_5 is $-CF_3$. In another embodiment is a compound of Formula (IV) wherein R_5 is substituted or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IV) wherein R_5 is $-CH_3$. In another embodiment is a compound of Formula (IV) wherein R_5 is $-CH_2CH_3$. In another embodiment is a compound of Formula (IV) wherein R_5 is substituted or unsubstituted C_1-C_6heteroalkyl. In

another embodiment is a compound of Formula (IV) wherein R_5 is substituted or unsubstituted C_2-C_7heterocycloalkyl. In another embodiment is a compound of Formula (IV) wherein R_5 is substituted or unsubstituted C_3-C_8cycloalkyl. In another embodiment is a compound of Formula (IV) wherein R_5 is substituted or unsubstituted C_6-C_{10}aryl. In another embodiment is a compound of Formula (IV) wherein R_5 is substituted or unsubstituted C_2-C_7heteroaryl.

[00145] In another embodiment is a compound of Formula (IV) 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 (IV) wherein R_2 and R_3 are each H.

[00146] In another embodiment is a compound of Formula (IV) 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 (IV) wherein R_2 is H, and R_3 is C_1-C_4alkyl. In another embodiment is a compound of Formula (IV) wherein R_2 is H, and R_3 is CH_3. In another embodiment is a compound of Formula (IV) wherein R_2 is H, and R_3 is C_3-C_6cycloalkyl. In another embodiment is a compound of Formula (IV) wherein R_2 is H, and R_3 is cyclopropyl. In another embodiment is a compound of Formula (IV) wherein R_2 is H, and R_3 is cyclopentyl. In another embodiment is a compound of Formula (IV) wherein R_2 is CH_3, and R_3 is CH_3. In another embodiment is a compound of Formula (IV) wherein R_2 is C_1-C_4alkyl, and R_3 is H. In another embodiment is a compound of Formula (IV) wherein R_2 is CH_3, and R_3 is H. In another embodiment is a compound of Formula (IV) wherein R_2 is C_3-C_6cycloalkyl, and R_3 is H. In another embodiment is a compound of Formula (IV) wherein R_2 is cyclopropyl, and R_3 is H. In another embodiment is a compound of Formula (IV) wherein R_2 is cyclopentyl, and R_3 is H.

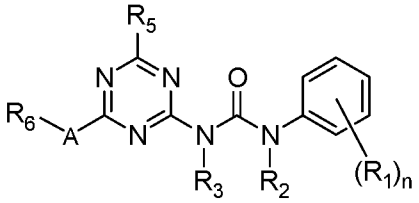
[00147] In another embodiment is a compound of Formula (IV) wherein R_2 and R_3 are taken together to form a 5- or 6-membered heterocyclic ring. In another embodiment is a compound of Formula (IV) wherein R_2 and R_3 are taken together to form a 5-membered heterocyclic ring. In another embodiment is a compound of Formula (IV) wherein R_2 and R_3 are taken together to form 6-membered heterocyclic ring.

[00148] In another embodiment is a compound of Formula (IV) wherein n is 0.

[00149] In another embodiment is a compound of Formula (IV) 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. In another

embodiment is a compound of Formula (IV) wherein each R_1 is independently halogen, -CN, -OH, $-CF_3$, substituted or unsubstituted C_1-C_6alkyl, or substituted or unsubstituted C_1-C_6alkoxy. In another embodiment is a compound of Formula (IV) wherein each R_1 is independently halogen, -CN, $-OCF_3$, $-OCH_2F$, $-OCF_2H$, $-CF_3$, 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. In another embodiment is a compound of Formula (IV) wherein each R_1 is independently halogen, -CN, $-OCF_3$, $-OCH_2F$, $-OCF_2H$, $-CF_3$, substituted or unsubstituted C_1-C_6alkyl, or substituted or unsubstituted C_1-C_6alkoxy. In another embodiment is a compound of Formula (IV) wherein each R_1 is independently halogen, -CN, $-OCF_3$, $-OCH_2F$, $-OCF_2H$, $-CF_3$, 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 (IV) wherein each R_1 is independently halogen, -CN, $-OCF_3$, $-OCH_2F$, $-OCF_2H$, $-CF_3$, 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 (IV) wherein n is 3, and each R_1 is independently halogen. In another embodiment is a compound of Formula (IV) wherein n is 2, and each R_1 is independently halogen. In another embodiment is a compound of Formula (IV) wherein n is 2, and each R_1 is independently F or Cl. In another embodiment is a compound of Formula (IV) wherein n is 2, and each R_1 is F. In another embodiment is a compound of Formula (IV) wherein n is 2, and each R_1 is independently Cl. In another embodiment is a compound of Formula (IV) wherein n is 2, and each R_1 is independently halogen or $-CF_3$. In another embodiment is a compound of Formula (IV) wherein n is 2, and each R_1 is independently F or $-CF_3$. In another embodiment is a compound of Formula (IV) wherein n is 2, and each R_1 is independently Cl or $-CF_3$. In another embodiment is a compound of Formula (IV) wherein n is 1, and R_1 is halogen. In another embodiment is a compound of Formula (IV) wherein n is 1, and R_1 is F. In another embodiment is a compound of Formula (IV) wherein n is 1, and R_1 is Cl. In another embodiment is a compound of Formula (IV) wherein n is 1, and R_1 is $-CF_3$. In another embodiment is a compound of Formula (IV) wherein n is 1, and R_1 is substituted or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IV) wherein n is 1, and R_1 is CH_3. In another embodiment is a compound of Formula (IV) wherein n is 1, and R_1 is substituted or unsubstituted C_1-C_6alkoxy. In another embodiment is a compound of Formula (IV) wherein n is 1, and R_1 is $-OCH_3$. In another embodiment is a compound of Formula (IV) wherein n is 1, and R_1 is $-OCF_3$. In another embodiment is a compound of Formula (IV) wherein n is 1, and R_1 is $-OCF_2H$.

[00150] In another aspect, described herein is a compound of Formula (V):



Formula (V);

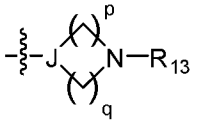
wherein:

A is a bond, O, or $N(R_{10})$;

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; 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_5 is halogen, -CN, -OH, $-CF_3$, 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 substituted or unsubstituted C_2-C_7heterocycloalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted C_2-C_7heteroaryl, $-(C(R_{14})(R_{15}))_mR_{21}$, $-(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$, or  ;

R_{11} and R_{12} are each independently H, or substituted or unsubstituted C_1-C_6alkyl; or R_{11} and R_{12} are taken together to form a 5-, 6-, 7-, or 8-membered heterocyclic ring;

J is C(H), or N;

R_{13} is H, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_2-C_7heterocycloalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted -C_1-C_4alkylC_6-C_{10}aryl, or substituted or unsubstituted -C_1-C_4alkylC_2-C_7heteroaryl;

each R_{14} and R_{15} are each independently H, or substituted or unsubstituted C_1-C_6alkyl; or R_{14} and R_{15} are taken together to form a 4-, 5-, 6-membered cycloalkyl ring;

R_{21} is halogen, -CN, -NO_2, -OH, -OCF_3, -OCH_2F, -OCF_2H, -CF_3, -SR_{22}, -$N(R_{22})S(=O)_2R_{23}$, -$S(=O)_2N(R_{22})_2$, -$S(=O)R_{23}$, -$S(=O)_2R_{23}$, -$C(=O)R_{23}$, -CO_2R_{22}, -$C(=O)N(R_{22})_2$, -$N(R_{22})C(=O)R_{23}$, 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;

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

R_{23} is substituted or unsubstituted C_1-C_6alkyl;

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

R_9 is substituted or unsubstituted C_1-C_6alkyl;

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

m is 2-6;

n is 0-5;

p is 1-3;

q is 1-3; or

a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[00151] In another embodiment is a compound of Formula (V) wherein A is O, or N(R_{10}). In another embodiment is a compound of Formula (V) wherein A is O, or N(H). In another embodiment is a compound of Formula (V) wherein A is O. In another embodiment is a compound of Formula (V) wherein A is N(R_{10}). In another embodiment is a compound of Formula (V) wherein A is N(H). In another embodiment is a compound of Formula (V) wherein A is N(CH_3). In another embodiment is a compound of Formula (V) wherein A is a bond.

[00152] In another embodiment is a compound of Formula (V) wherein R_6 is substituted or unsubstituted C_3-C_8cycloalkyl. In another embodiment is a compound of Formula (V) wherein R_6 is substituted or unsubstituted cyclopropyl. In another embodiment is a compound of Formula (V) wherein R_6 is substituted or unsubstituted cyclobutyl. In another embodiment is a compound of Formula (V) wherein R_6 is substituted or unsubstituted cyclopentyl. In another embodiment is a compound of Formula (V) wherein R_6 is substituted or unsubstituted cyclohexyl.

[00153] In another embodiment is a compound of Formula (V) wherein R_6 is substituted or unsubstituted C_2-C_7heteroaryl. In another embodiment is a compound of Formula (V) wherein R_6 is substituted or unsubstituted furanyl, thiophenyl, pyrrolyl, pyridyl, oxazolyl, thiazolyl, imidazolyl, isoxazolyl, isothiazolyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, oxadiazolyl,

thiadiazolyl, triazolyl, indolyl, benzothiophenyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, benzoxadiazolyl, benzothiadiazolyl, benzotriazolyl, pyrazolopyridinyl, imidazopyridinyl, pyrrolopyridinyl, pyrrolopyrimidinyl, indolizinyl, purinyl, furopyridinyl, thienopyridinyl, furopyrrolyl, furofuranyl, thienofuranyl, 1,4-dihydropyrrolopyrrolyl, thienopyrrolyl, thienothiophenyl, quinolinyl, isoquinolinyl, quinoxalinyl, furopyrazolyl, thienopyrazolyl, selenophenyl, selenazolyl, and benzoisoxazolyl. In another embodiment is a compound of Formula (V) wherein R_6 is substituted or unsubstituted pyridyl. In another embodiment is a compound of Formula (V) wherein R_6 is substituted pyridyl. In another embodiment is a compound of Formula (V) wherein R_6 is unsubstituted pyridyl.

[00154] In another embodiment is a compound of Formula (V) wherein R_6 is -$(C(R_{14})(R_{15}))_mR_{21}$. In another embodiment is a compound of Formula (V) wherein R_6 is -$(C(R_{14})(R_{15}))_mR_{21}$, and each R_{14} and R_{15} are H. In another embodiment is a compound of Formula (V) wherein R_6 is -$(C(R_{14})(R_{15}))_mR_{21}$, m is 2, and each R_{14} and R_{15} are H. In another embodiment is a compound of Formula (V) wherein R_6 is -$(CH_2)_mR_{21}$, m is 2, and R_{21} is substituted or unsubstituted C_2-C_7heterocycloalkyl. In another embodiment is a compound of Formula (V) wherein R_6 is -$(CH_2)_mR_{21}$, m is 2, and R_{21} is substituted or unsubstituted C_3-C_8cycloalkyl. In another embodiment is a compound of Formula (V) wherein R_6 is -$(CH_2)_mR_{21}$, m is 2, and R_{21} is substituted or unsubstituted C_6-C_{10}aryl. In another embodiment is a compound of Formula (V) wherein R_6 is -$(CH_2)_mR_{21}$, m is 2, and R_{21} is substituted or unsubstituted phenyl. In another embodiment is a compound of Formula (V) wherein R_6 is -$(CH_2)_mR_{21}$, m is 2, and R_{21} is substituted or unsubstituted C_2-C_7heteroaryl. In another embodiment is a compound of Formula (V) wherein R_6 is -$(CH_2)_mR_{21}$, m is 2, and R_{21} is -OH.

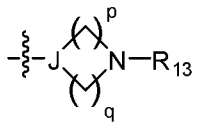
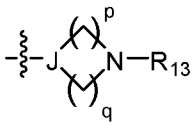
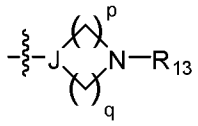
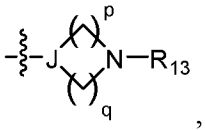
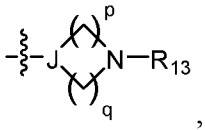
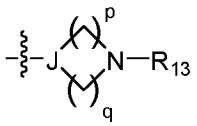
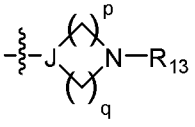
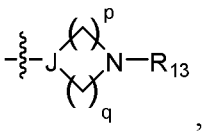
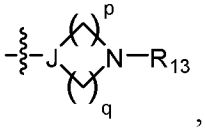
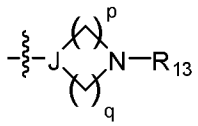
[00155] In another embodiment is a compound of Formula (V) wherein R_6 is -$(C(R_{14})(R_{15}))_mR_{21}$, m is 3, and each R_{14} and R_{15} are H. In another embodiment is a compound of Formula (V) wherein R_6 is -$(CH_2)_mR_{21}$, m is 3, and R_{21} is substituted or unsubstituted C_2-C_7heterocycloalkyl. In another embodiment is a compound of Formula (V) wherein R_6 is -$(CH_2)_mR_{21}$, m is 3, and R_{21} is substituted or unsubstituted C_3-C_8cycloalkyl. In another embodiment is a compound of Formula (V) wherein R_6 is -$(CH_2)_mR_{21}$, m is 3, and R_{21} is substituted or unsubstituted C_6-C_{10}aryl. In another embodiment is a compound of Formula (V) wherein R_6 is -$(CH_2)_mR_{21}$, m is 3, and R_{21} is substituted or unsubstituted phenyl. In another embodiment is a compound of Formula (V) wherein R_6 is -$(CH_2)_mR_{21}$, m is 3, and R_{21} is substituted or unsubstituted C_2-C_7heteroaryl. In another embodiment is a compound of Formula (V) wherein R_6 is -$(CH_2)_mR_{21}$, m is 3, and R_{21} is -OH.

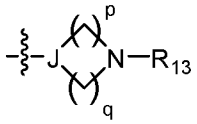
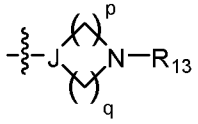
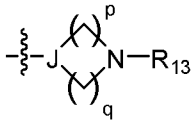
[00156] In another embodiment is a compound of Formula (V) wherein R_6 is -$(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$. In another embodiment is a compound of Formula (V) wherein R_6 is

$-(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$, m is 2, and each R_{14} and R_{15} are H. In another embodiment is a compound of Formula (V) wherein R_6 is $-(CH_2)_mN(R_{11})(R_{12})$, m is 2, and R_{11} and R_{12} are each H. In another embodiment is a compound of Formula (V) wherein R_6 is $-(CH_2)_mN(R_{11})(R_{12})$, m is 2, R_{11} is substituted or unsubstituted C_1-C_6alkyl, and R_{12} is H. In another embodiment is a compound of Formula (V) wherein R_6 is $-(CH_2)_mN(R_{11})(R_{12})$, m is 2, R_{11} is CH_3, and R_{12} is H. In another embodiment is a compound of Formula (V) wherein R_6 is $-(CH_2)_mN(R_{11})(R_{12})$, m is 2, R_{11} is substituted or unsubstituted C_1-C_6alkyl, and R_{12} is substituted or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (V) wherein R_6 is $-(CH_2)_mN(R_{11})(R_{12})$, m is 2, R_{11} is CH_3, and R_{12} is CH_3. In another embodiment is a compound of Formula (V) wherein R_6 is $-(CH_2)_mN(R_{11})(R_{12})$, m is 2, and R_{11} and R_{12} are taken together to form a 5-, 6-, 7-, or 8-membered heterocyclic ring. In another embodiment is a compound of Formula (V) wherein R_6 is $-(CH_2)_mN(R_{11})(R_{12})$, m is 2, and R_{11} and R_{12} are taken together to form a 5-membered heterocyclic ring. In another embodiment is a compound of Formula (V) wherein R_6 is $-(CH_2)_mN(R_{11})(R_{12})$, m is 2, and R_{11} and R_{12} are taken together to form a 6-membered heterocyclic ring.

[00157] In another embodiment is a compound of Formula (V) wherein R_6 is $-(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$. In another embodiment is a compound of Formula (V) wherein R_6 is $-(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$, m is 3, and each R_{14} and R_{15} are H. In another embodiment is a compound of Formula (V) wherein R_6 is $-(CH_2)_mN(R_{11})(R_{12})$, m is 3, and R_{11} and R_{12} are each H. In another embodiment is a compound of Formula (V) wherein R_6 is $-(CH_2)_mN(R_{11})(R_{12})$, m is 3, R_{11} is substituted or unsubstituted C_1-C_6alkyl, and R_{12} is H. In another embodiment is a compound of Formula (V) wherein R_6 is $-(CH_2)_mN(R_{11})(R_{12})$, m is 3, R_{11} is CH_3, and R_{12} is H. In another embodiment is a compound of Formula (V) wherein R_6 is $-(CH_2)_mN(R_{11})(R_{12})$, m is 3, R_{11} is substituted or unsubstituted C_1-C_6alkyl, and R_{12} is substituted or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (V) wherein R_6 is $-(CH_2)_mN(R_{11})(R_{12})$, m is 3, R_{11} is CH_3, and R_{12} is CH_3. In another embodiment is a compound of Formula (V) wherein R_6 is $-(CH_2)_mN(R_{11})(R_{12})$, m is 3, and R_{11} and R_{12} are taken together to form a 5-, 6-, 7-, or 8-membered heterocyclic ring. In another embodiment is a compound of Formula (V) wherein R_6 is $-(CH_2)_mN(R_{11})(R_{12})$, m is 3, and R_{11} and R_{12} are taken together to form a 5-membered heterocyclic ring. In another embodiment is a compound of Formula (V) wherein R_6 is $-(CH_2)_mN(R_{11})(R_{12})$, m is 3, and R_{11} and R_{12} are taken together to form a 6-membered heterocyclic ring.

[00158] In another embodiment is a compound of Formula (V) wherein R_6 is substituted or unsubstituted C_2-C_7heterocycloalkyl. In another embodiment is a compound of Formula (V)

wherein R_6 is  . In another embodiment is a compound of Formula (V) wherein R_6 is  and J is C(H). In another embodiment is a compound of Formula (V) wherein R_6 is  , J is C(H), p is 1, and q is 1. In another embodiment is a compound of Formula (V) wherein R_6 is  , J is C(H), p is 2, and q is 1. In another embodiment is a compound of Formula (V) wherein R_6 is  , J is C(H), p is 3, and q is 1. In another embodiment is a compound of Formula (V) wherein R_6 is  , J is C(H), p is 2, and q is 2. In another embodiment is a compound of Formula (V) wherein R_6 is  , J is C(H), p is 1, q is 1, and R_{13} is substituted or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (V) wherein R_6 is  , J is C(H), p is 2, q is 1, and R_{13} is substituted or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (V) wherein R_6 is  , J is C(H), p is 3, q is 1, and R_{13} is substituted or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (V) wherein R_6 is  , J is C(H), p is 2, q is 2, and R_{13} is substituted or unsubstituted C_1-C_6alkyl.

[00159] In another embodiment is a compound of Formula (V) wherein R_6 is  and J is N. In another embodiment is a compound of Formula (V) wherein R_6 is  , J is N, p is 2, and q is 2. In another embodiment is a compound of Formula (V) wherein R_6 is  , J is N, p is 2, q is 2, and R_{13} is substituted or unsubstituted C_1-C_6alkyl.

[00160] In another embodiment is a compound of Formula (V) wherein R_5 is halogen. In another embodiment is a compound of Formula (V) wherein R_5 is $-CF_3$. In another embodiment is a compound of Formula (V) wherein R_5 is unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (V) wherein R_5 is $-CH_3$. In another embodiment is a compound of Formula (V) wherein R_5 is $-CH_2CH_3$. In another embodiment is a compound of Formula (V) wherein R_5 is substituted or unsubstituted C_1-C_6heteroalkyl. In another embodiment is a compound of Formula (V) wherein R_5 is substituted or unsubstituted C_2-C_7heterocycloalkyl. In another embodiment is a compound of Formula (V) wherein R_5 is substituted or unsubstituted C_3-C_8cycloalkyl. In another embodiment is a compound of Formula (V) wherein R_5 is substituted or unsubstituted C_6-C_{10}aryl. In another embodiment is a compound of Formula (V) wherein R_5 is substituted or unsubstituted C_2-C_7heteroaryl.

[00161] In another embodiment is a compound of Formula (V) 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 (V) wherein R_2 and R_3 are each H.

[00162] In another embodiment is a compound of Formula (V) 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 (V) wherein R_2 is H, and R_3 is C_1-C_4alkyl. In another embodiment is a compound of Formula (V) wherein R_2 is H, and R_3 is CH_3. In another embodiment is a compound of Formula (V) wherein R_2 is H, and R_3 is C_3-C_6cycloalkyl. In another embodiment is a compound of Formula (V) wherein R_2 is H, and R_3 is cyclopropyl. In another embodiment is a compound of Formula (V) wherein R_2 is H, and R_3 is cyclopentyl. In another embodiment is a compound of Formula (V) wherein R_2 is CH_3, and R_3 is CH_3. In another embodiment is a compound of Formula (V) wherein R_2 is C_1-C_4alkyl, and R_3 is H. In another embodiment is a compound of Formula (V) wherein R_2 is CH_3, and R_3 is H. In another embodiment is a compound of Formula (V) wherein R_2 is C_3-C_6cycloalkyl, and

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

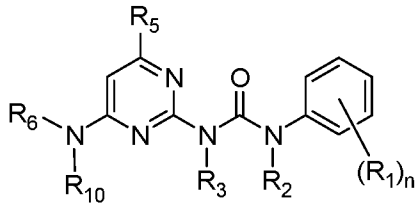
[00163] In another embodiment is a compound of Formula (V) wherein R_2 and R_3 are taken together to form a 5- or 6-membered heterocyclic ring. In another embodiment is a compound of Formula (V) wherein R_2 and R_3 are taken together to form a 5-membered heterocyclic ring. In another embodiment is a compound of Formula (V) wherein R_2 and R_3 are taken together to form 6-membered heterocyclic ring.

[00164] In another embodiment is a compound of Formula (V) wherein n is 0.

[00165] In another embodiment is a compound of Formula (V) 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. In another embodiment is a compound of Formula (V) wherein each R_1 is independently halogen, -CN, -OH, $-CF_3$, substituted or unsubstituted C_1-C_6alkyl, or substituted or unsubstituted C_1-C_6alkoxy. In another embodiment is a compound of Formula (V) wherein each R_1 is independently halogen, -CN, $-OCF_3$, $-OCH_2F$, $-OCF_2H$, $-CF_3$, 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. In another embodiment is a compound of Formula (V) wherein each R_1 is independently halogen, -CN, $-OCF_3$, $-OCH_2F$, $-OCF_2H$, $-CF_3$, substituted or unsubstituted C_1-C_6alkyl, or substituted or unsubstituted C_1-C_6alkoxy. In another embodiment is a compound of Formula (V) wherein each R_1 is independently halogen, -CN, $-OCF_3$, $-OCH_2F$, $-OCF_2H$, $-CF_3$, 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 (V) wherein each R_1 is independently halogen, -CN, $-OCF_3$, $-OCH_2F$, $-OCF_2H$, $-CF_3$, 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 (V) wherein n is 3, and each R_1 is independently halogen. In another embodiment is a compound of Formula (V) wherein n is 2, and each R_1 is independently halogen. In another embodiment is a compound of Formula (V) wherein n is 2, and each R_1 is independently F or Cl. In another embodiment is a compound of Formula (V) wherein n is 2, and each R_1 is F. In another embodiment is a

compound of Formula (V) wherein n is 2, and each R_1 is independently Cl. In another embodiment is a compound of Formula (V) wherein n is 2, and each R_1 is independently halogen or $-CF_3$. In another embodiment is a compound of Formula (V) wherein n is 2, and each R_1 is independently F or $-CF_3$. In another embodiment is a compound of Formula (V) wherein n is 2, and each R_1 is independently Cl or $-CF_3$. In another embodiment is a compound of Formula (V) wherein n is 1, and R_1 is halogen. In another embodiment is a compound of Formula (V) wherein n is 1, and R_1 is F. In another embodiment is a compound of Formula (V) wherein n is 1, and R_1 is Cl. In another embodiment is a compound of Formula (V) wherein n is 1, and R_1 is $-CF_3$. In another embodiment is a compound of Formula (V) wherein n is 1, and R_1 is substituted or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (V) wherein n is 1, and R_1 is CH_3. In another embodiment is a compound of Formula (V) wherein n is 1, and R_1 is substituted or unsubstituted C_1-C_6alkoxy. In another embodiment is a compound of Formula (V) wherein n is 1, and R_1 is $-OCH_3$. In another embodiment is a compound of Formula (V) wherein n is 1, and R_1 is $-OCF_3$. In another embodiment is a compound of Formula (V) wherein n is 1, and R_1 is $-OCF_2H$.

[00166] In another aspect, described herein is a compound of Formula (VI):



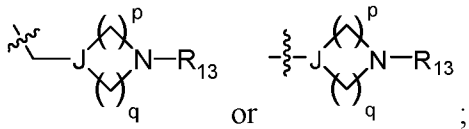
Formula (VI);

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; 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 or C_1-C_4alkyl; or R_2 and R_3 are taken together to form a 5- or 6-membered heterocyclic ring;

R_5 is substituted or unsubstituted C_1-C_6alkyl;

R_6 is unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_2-C_7heterocycloalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted C_2-C_7heteroaryl, $-(C(R_{14})(R_{15}))_mR_{21}$,  or ;

J is C(H);

R_{13} is H, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_2-C_7heterocycloalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted $-C_1$-C_4alkylC_6-C_{10}aryl, or substituted or unsubstituted $-C_1$-C_4alkylC_2-C_7heteroaryl;

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

R_{21} is halogen, $-CN$, $-NO_2$, $-OH$, $-OCF_3$, $-OCH_2F$, $-OCF_2H$, $-CF_3$, $-SR_{22}$, $-N(R_{22})S(=O)_2R_{23}$, $-S(=O)_2N(R_{22})_2$, $-S(=O)R_{23}$, $-S(=O)_2R_{23}$, $-C(=O)R_{23}$, $-CO_2R_{22}$, $-C(=O)N(R_{22})_2$, $-N(R_{22})C(=O)R_{23}$, substituted or unsubstituted C_1-C_6alkoxy, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_2-C_7heterocycloalkyl, or substituted or unsubstituted C_2-C_7heteroaryl;

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

R_{23} is substituted or unsubstituted C_1-C_6alkyl;

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

R_9 is substituted or unsubstituted C_1-C_6alkyl;

R_{10} is H;

m is 2-6;

n is 0-5;

p is 1-3;

q is 1-3; or

a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[00167] In another embodiment is a compound of Formula (VI) wherein R_6 is substituted or unsubstituted C_3-C_8cycloalkyl. In another embodiment is a compound of Formula (VI) wherein R_6 is substituted or unsubstituted cyclopropyl. In another embodiment is a compound of Formula (VI) wherein R_6 is substituted or unsubstituted cyclobutyl. In another embodiment is a compound of Formula (VI) wherein R_6 is substituted or unsubstituted cyclopentyl. In another embodiment is a compound of Formula (VI) wherein R_6 is substituted or unsubstituted cyclohexyl.

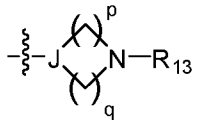
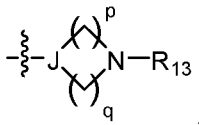
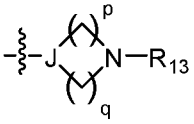
[00168] In another embodiment is a compound of Formula (VI) wherein R_6 is substituted or unsubstituted C_2-C_7heteroaryl. In another embodiment is a compound of Formula (VI) wherein R_6 is substituted or unsubstituted furanyl, thiophenyl, pyrrolyl, pyridyl, oxazolyl, thiazolyl, imidazolyl, isoxazolyl, isothiazolyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, oxadiazolyl, thiadiazolyl, triazolyl, indolyl, benzothiophenyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, benzoxadiazolyl, benzothiadiazolyl, benzotriazolyl, pyrazolopyridinyl, imidazopyridinyl, pyrrolopyridinyl, pyrrolopyrimidinyl, indolizinyl, purinyl, furopyridinyl, thienopyridinyl, furopyrrolyl, furofuranyl, thienofuranyl, 1,4-dihydropyrrolopyrrolyl, thienopyrrolyl, thienothiophenyl, quinolinyl, isoquinolinyl, quinoxalinyl, furopyrazolyl, thienopyrazolyl, selenophenyl, selenazolyl, and benzoisoxazolyl. In another embodiment is a compound of Formula (VI) wherein R_6 is substituted or unsubstituted pyridyl. In another embodiment is a compound of Formula (VI) wherein R_6 is substituted pyridyl. In another embodiment is a compound of Formula (VI) wherein R_6 is unsubstituted pyridyl.

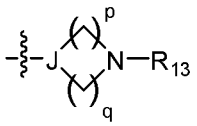
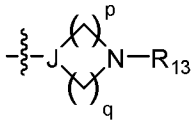
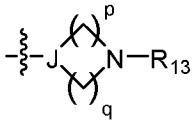
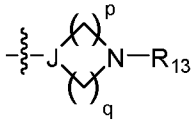
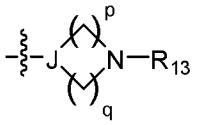
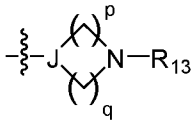
[00169] In another embodiment is a compound of Formula (VI) wherein R_6 is unsubstituted C_1-C_4alkyl. In another embodiment is a compound of Formula (VI) wherein R_6 is $-CH_3$. In another embodiment is a compound of Formula (VI) wherein R_6 is $-CH_2CH_3$. In another embodiment is a compound of Formula (VI) wherein R_6 is $-CH_2CH_2CH_3$.

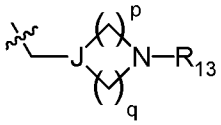
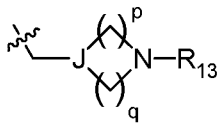
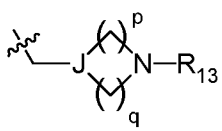
[00170] In another embodiment is a compound of Formula (VI) wherein R_6 is $-(C(R_{14})(R_{15}))_mR_{21}$. In another embodiment is a compound of Formula (VI) wherein R_6 is $-(C(R_{14})(R_{15}))_mR_{21}$, and each R_{14} and R_{15} are H or halogen. In another embodiment is a compound of Formula (VI) wherein R_6 is $-(C(R_{14})(R_{15}))_mR_{21}$, and each R_{14} and R_{15} are H or halogen. In another embodiment is a compound of Formula (VI) wherein R_6 is $-(C(R_{14})(R_{15}))_mR_{21}$, m is 2, and each R_{14} and R_{15} are H. In another embodiment is a compound of Formula (VI) wherein R_6 is $-(CH_2)_mR_{21}$, m is 2, and R_{21} is substituted or unsubstituted C_2-C_7heterocycloalkyl. In another embodiment is a compound of Formula (VI) wherein R_6 is $-(CH_2)_mR_{21}$, m is 2, and R_{21} is substituted or unsubstituted C_2-C_7heteroaryl. In another embodiment is a compound of Formula (VI) wherein R_6 is $-(CH_2)_mR_{21}$, m is 2, and R_{21} is -OH. In another embodiment is a compound of Formula (VI) wherein R_6 is $-(CH_2)_mR_{21}$, m is 2, and R_{21} is $-N(R_{22})S(=O)_2R_{23}$. In another embodiment is a compound of Formula (VI) wherein R_6 is $-(CH_2)_mR_{21}$, m is 2, and R_{21} is $-N(H)S(=O)_2CH_3$. In another embodiment is a compound of Formula (VI) wherein R_6 is $-(CH_2)_mR_{21}$, m is 2, and R_{21} is $-N(R_{22})C(=O)R_{23}$. In another embodiment is a compound of Formula (VI) wherein R_6 is $-(CH_2)_mR_{21}$, m is 2, and R_{21} is $-N(H)C(=O)CH_3$. In another embodiment is a compound of Formula (VI) wherein R_6 is $-(CH_2)_mR_{21}$, m is 2, and R_{21} is $-C(=O)N(R_{22})_2$. In another embodiment is a compound of Formula (VI) wherein R_6 is $-(CH_2)_mR_{21}$, m is 2, and R_{21} is $-C(=O)NH_2$. In another embodiment is a

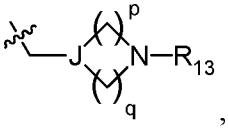
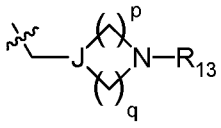
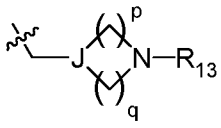
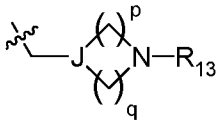
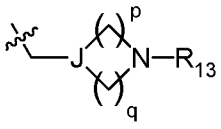
compound of Formula (VI) wherein R_6 is $-(CH_2)_mR_{21}$, m is 2, and R_{21} is $-CO_2R_{22}$. In another embodiment is a compound of Formula (VI) wherein R_6 is $-(CH_2)_mR_{21}$, m is 2, and R_{21} is $-CO_2Et$.

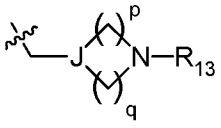
[00171] In another embodiment is a compound of Formula (VI) wherein R_6 is $-(C(R_{14})(R_{15}))_mR_{21}$, m is 3, and each R_{14} and R_{15} are H. In another embodiment is a compound of Formula (VI) wherein R_6 is $-(CH_2)_mR_{21}$, m is 3, and R_{21} is substituted or unsubstituted C_2-C_7heterocycloalkyl. In another embodiment is a compound of Formula (VI) wherein R_6 is $-(CH_2)_mR_{21}$, m is 3, and R_{21} is substituted or unsubstituted C_3-C_8cycloalkyl. In another embodiment is a compound of Formula (VI) wherein R_6 is $-(CH_2)_mR_{21}$, m is 3, and R_{21} is substituted C_6-C_{10}aryl. In another embodiment is a compound of Formula (VI) wherein R_6 is $-(CH_2)_mR_{21}$, m is 3, and R_{21} is substituted phenyl. In another embodiment is a compound of Formula (VI) wherein R_6 is $-(CH_2)_mR_{21}$, m is 3, and R_{21} is substituted or unsubstituted C_2-C_7heteroaryl. In another embodiment is a compound of Formula (VI) wherein R_6 is $-(CH_2)_mR_{21}$, m is 3, and R_{21} is -OH. In another embodiment is a compound of Formula (VI) wherein R_6 is $-(CH_2)_mR_{21}$, m is 3, and R_{21} is $-N(R_{22})S(=O)_2R_{23}$. In another embodiment is a compound of Formula (VI) wherein R_6 is $-(CH_2)_mR_{21}$, m is 3, and R_{21} is $-N(H)S(=O)_2CH_3$. In another embodiment is a compound of Formula (VI) wherein R_6 is $-(CH_2)_mR_{21}$, m is 3, and R_{21} is $-N(R_{22})C(=O)R_{23}$. In another embodiment is a compound of Formula (VI) wherein R_6 is $-(CH_2)_mR_{21}$, m is 3, and R_{21} is $-N(H)C(=O)CH_3$. In another embodiment is a compound of Formula (VI) wherein R_6 is $-(CH_2)_mR_{21}$, m is 3, and R_{21} is $-C(=O)N(R_{22})_2$. In another embodiment is a compound of Formula (VI) wherein R_6 is $-(CH_2)_mR_{21}$, m is 3, and R_{21} is $-C(=O)NH_2$. In another embodiment is a compound of Formula (VI) wherein R_6 is $-(CH_2)_mR_{21}$, m is 3, and R_{21} is $-CO_2R_{22}$. In another embodiment is a compound of Formula (VI) wherein R_6 is $-(CH_2)_mR_{21}$, m is 3, and R_{21} is $-CO_2Et$.

[00172] In another embodiment is a compound of Formula (VI) wherein R_6 is substituted or unsubstituted C_2-C_7heterocycloalkyl. In another embodiment is a compound of Formula (VI) wherein R_6 is  and J is C(H). In another embodiment is a compound of Formula (VI) wherein R_6 is  , J is C(H), p is 1, and q is 1. In another embodiment is a compound of Formula (VI) wherein R_6 is  , J is C(H), p is 2, and q is 1. In

another embodiment is a compound of Formula (VI) wherein R_6 is  , J is C(H), p is 3, and q is 1. In another embodiment is a compound of Formula (VI) wherein R_6 is  , J is C(H), p is 2, and q is 2. In another embodiment is a compound of Formula (VI) wherein R_6 is  , J is C(H), p is 1, q is 1, and R_{13} is substituted or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (VI) wherein R_6 is  , J is C(H), p is 2, q is 1, and R_{13} is substituted or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (VI) wherein R_6 is  , J is C(H), p is 3, q is 1, and R_{13} is substituted or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (VI) wherein R_6 is  , J is C(H), p is 2, q is 2, and R_{13} is substituted or unsubstituted C_1-C_6alkyl.

[00173] In another embodiment is a compound of Formula (VI) wherein R_6 is substituted or unsubstituted C_2-C_7heterocycloalkyl. In another embodiment is a compound of Formula (VI) wherein R_6 is  and J is C(H). In another embodiment is a compound of Formula (VI) wherein R_6 is  , J is C(H), p is 1, and q is 1. In another embodiment is a compound of Formula (VI) wherein R_6 is  , J is C(H), p is 2, and q is 1. In another embodiment is a compound of Formula (VI) wherein R_6 is


, J is C(H), p is 3, and q is 1. In another embodiment is a compound of Formula (VI) wherein R_6 is 
, J is C(H), p is 2, and q is 2. In another embodiment is a compound of Formula (VI) wherein R_6 is 
, J is C(H), p is 1, q is 1, and R_{13} is substituted or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (VI) wherein R_6 is 
, J is C(H), p is 2, q is 1, and R_{13} is substituted or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (VI) wherein R_6 is 
, J is C(H), p is 3, q is 1, and R_{13} is substituted or unsubstituted C_1-C_6alkyl.

In another embodiment is a compound of Formula (VI) wherein R_6 is 
, J is C(H), p is 2, q is 2, and R_{13} is substituted or unsubstituted C_1-C_6alkyl.

[00174] In another embodiment is a compound of Formula (VI) wherein R_5 is substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (VI) wherein R_5 is unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (VI) wherein R_5 is unsubstituted -CH_3. In another embodiment is a compound of Formula (VI) wherein R_5 is unsubstituted -CH_2CH_3.

[00175] In another embodiment is a compound of Formula (VI) wherein R_2 and R_3 are each H. In another embodiment is a compound of Formula (VI) wherein R_2 and R_3 are each independently H or C_1-C_4alkyl; and at least one of R_2 and R_3 is not H. In another embodiment is a compound of Formula (VI) wherein R_2 is H, and R_3 is C_1-C_4alkyl. In another embodiment is a compound of Formula (VI) wherein R_2 is H, and R_3 is CH_3. In another embodiment is a compound of Formula (VI) wherein R_2 is CH_3, and R_3 is CH_3. In another embodiment is a compound of Formula (VI) wherein R_2 is C_1-C_4alkyl, and R_3 is H. In another embodiment is a compound of Formula (VI) wherein R_2 is CH_3, and R_3 is H.

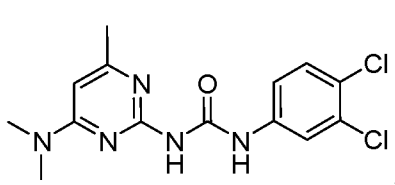
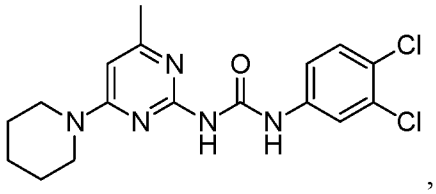
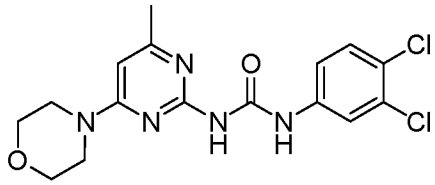
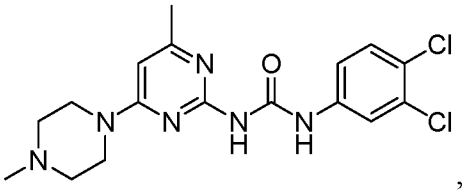
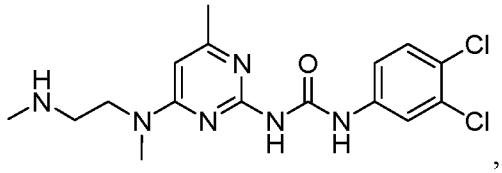
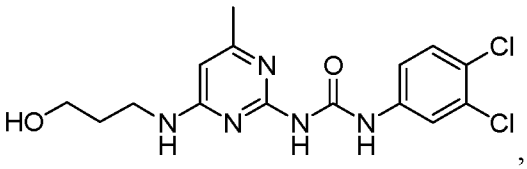
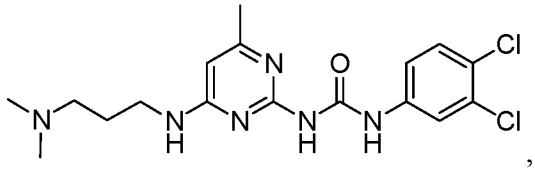
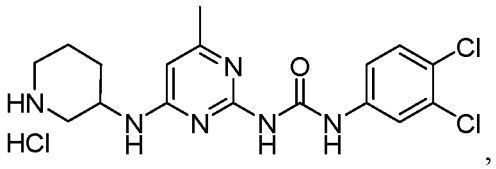
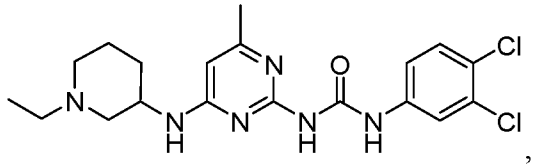
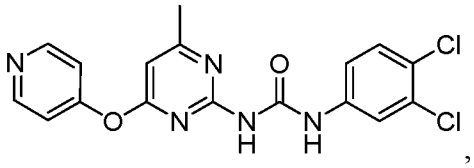
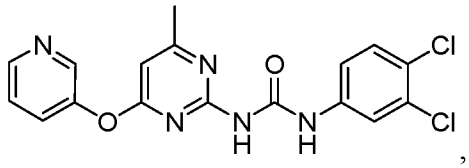
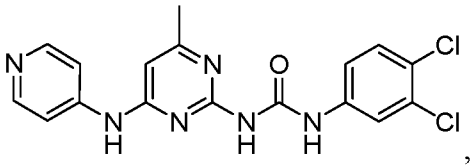
[00176] In another embodiment is a compound of Formula (VI) wherein R_2 and R_3 are taken together to form a 5- or 6-membered heterocyclic ring. In another embodiment is a compound of Formula (VI) wherein R_2 and R_3 are taken together to form a 5-membered heterocyclic ring. In another embodiment is a compound of Formula (VI) wherein R_2 and R_3 are taken together to form 6-membered heterocyclic ring.

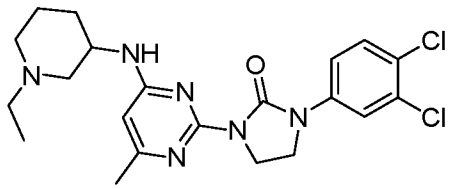
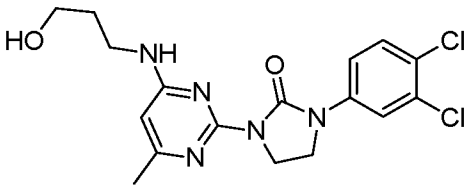
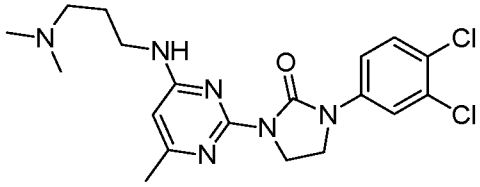
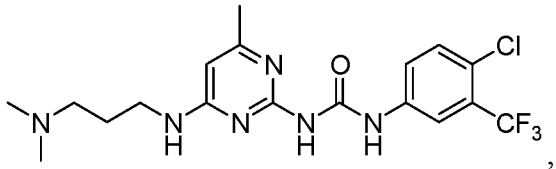
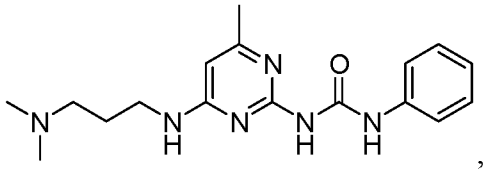
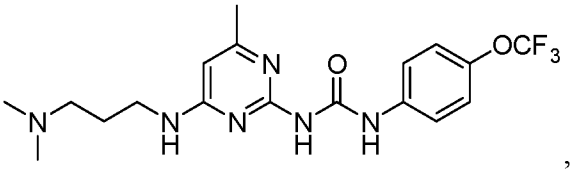
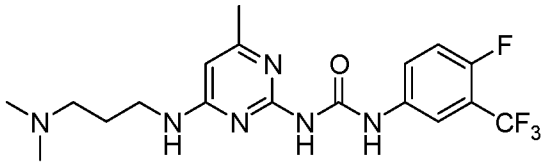
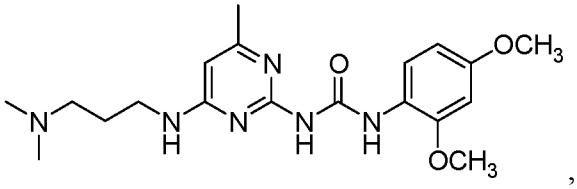
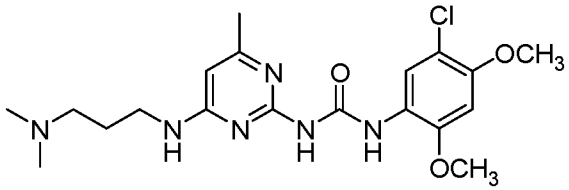
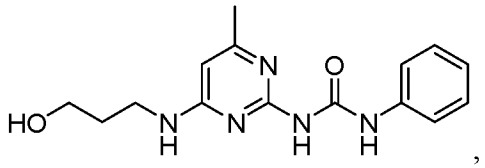
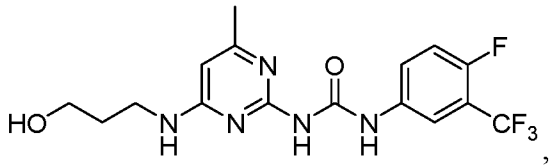
[00177] In another embodiment is a compound of Formula (VI) wherein n is 0.

[00178] In another embodiment is a compound of Formula (VI) 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 (VI) 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 (VI) 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 (VI) 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 (VI) 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 (VI) 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 (VI) wherein n is 3, and each R_1 is independently halogen. In another embodiment is a compound of Formula (VI) wherein n is 2, and each R_1 is independently halogen. In another embodiment is a compound of Formula (VI) wherein n is 2, and each R_1 is independently F or Cl. In another embodiment is a compound of Formula (VI) wherein n is 2, and one R_1 is F and one R_1 is -CF_3. In another embodiment is a compound of Formula (VI) wherein n is 2, and each R_1 is F. In another embodiment is a compound of Formula (VI) wherein n is 2, and each R_1 is Cl. In another embodiment is a compound of Formula (VI) wherein n is 2, and one R_1 is F and one R_1 is Cl. In another embodiment is a

compound of Formula (VI) wherein n is 1, and R_1 is halogen. In another embodiment is a compound of Formula (VI) wherein n is 1, and R_1 is F. In another embodiment is a compound of Formula (VI) wherein n is 1, and R_1 is Cl. In another embodiment is a compound of Formula (VI) wherein n is 1, and R_1 is substituted or unsubstituted C_1-C_6alkyl. In another embodiment is a compound of Formula (VI) wherein n is 1, and R_1 is CH_3. In another embodiment is a compound of Formula (VI) wherein n is 1, and R_1 is -CF_3. In another embodiment is a compound of Formula (VI) wherein n is 1, and R_1 is substituted or unsubstituted C_1-C_6alkoxy. In another embodiment is a compound of Formula (VI) wherein n is 1, and R_1 is -OCH_3. In another embodiment is a compound of Formula (VI) wherein n is 1, and R_1 is -OCF_3. In another embodiment is a compound of Formula (VI) wherein n is 1, and R_1 is -OCF_2H.

[00179] In another embodiment is a compound selected from:


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

[00180] 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.

[00181] Any combination of the groups described above for the various variables is contemplated herein.

[00182] Throughout the specification, groups and substituents thereof can be chosen to provide stable moieties and compounds.

Further Forms of Compounds

[00183] 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.

[00184] In some situations, compounds may exist as tautomers. All tautomers are included within the formulas described herein.

[00185] 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.

[00186] 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.

[00187] 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).

[00188] Prodrug forms of the herein described compounds, wherein the prodrug is metabolized *in vivo* to produce a compound of Formula (I), (II), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI) 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.

[00189] 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).

[00190] 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.

[00191] 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.

[00192] 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.

[00193] 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.

[00194] 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.

[00195] 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.

[00196] In some embodiments, compounds described herein, such as compounds of Formula (I), (II), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI), 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.

[00197] 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.

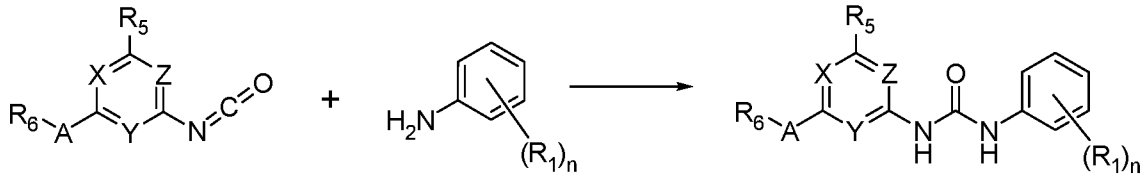
[00198] Throughout the specification, groups and substituents thereof can be chosen to provide stable moieties and compounds.

Synthesis of Compounds

[00199] 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.

[00200] In some embodiments, compounds of Formula (I), (II), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI) are prepared according to the synthetic route shown in Scheme 1.

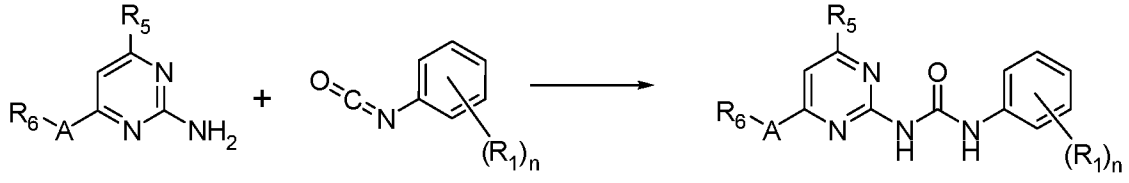
Scheme 1



[00201] As depicted in Scheme 1, addition of the amine to the isocyanate gives the urea.

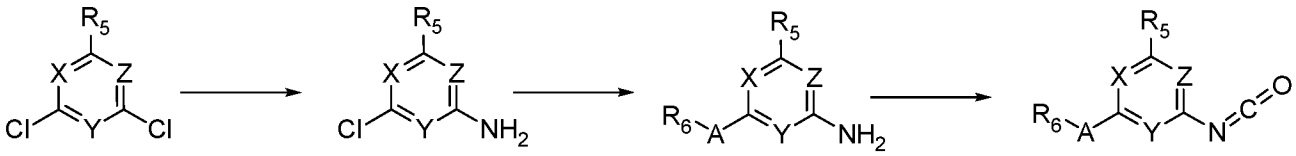
[00202] Through a similar protocol, additional compounds of Formula (I), (II), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI) are prepared as shown in Scheme 2.

Scheme 2

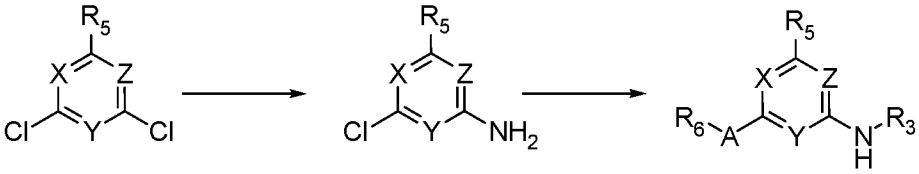


[00203] In some embodiments, the isocyanate and amine synthetic intermediates are prepared according to Schemes 3-4.

Scheme 3: Synthesis of pyridine/pyrimidine isocyanate (A=O, NR_{10})



Scheme 4: Synthesis of pyridine/pyrimidine amine (A=O, NR_{10})



[00204] In other embodiments, the starting materials and reagents used for the synthesis of the compounds described herein are synthesized or are obtained from commercial sources, such as, but not limited to, Sigma-Aldrich, FischerScientific (Fischer Chemicals), and AcrosOrganics.

[00205] 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

[00206] 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.

[00207] 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.

[00208] The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

[00209] 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.

[00210] 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.

[00211] 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.

[00212] 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).

[00213] 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.

[00214] 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).

[00215] An "alkoxy" refers to a "-O-alkyl" group, where alkyl is as defined herein.

[00216] 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).

[00217] 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).

[00218] "Amino" refers to a -NH_2 group.

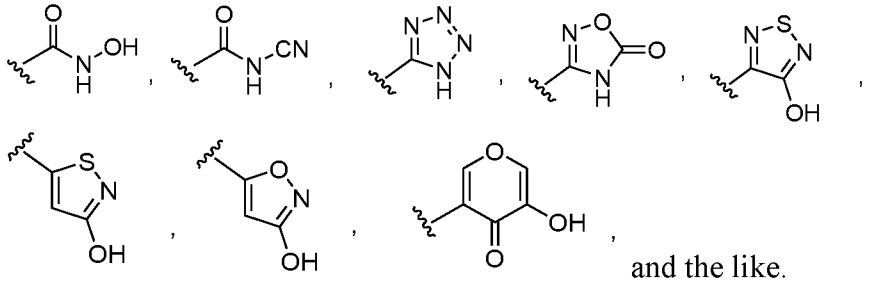
[00219] The term "alkylamine" or "alkylamino" refers to the -N(alkyl)$_x$H$_y$ group, where alkyl is as defined herein and x and y are selected from the group x=1, y=1 and x=2, y=0. When x=2, the alkyl groups, taken together with the nitrogen to which they are attached, can optionally form a cyclic ring system. "Dialkylamino" refers to a -N(alkyl)$_2$ group, where alkyl is as defined herein.

[00220] 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).

[00221] 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).

[00222] 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.

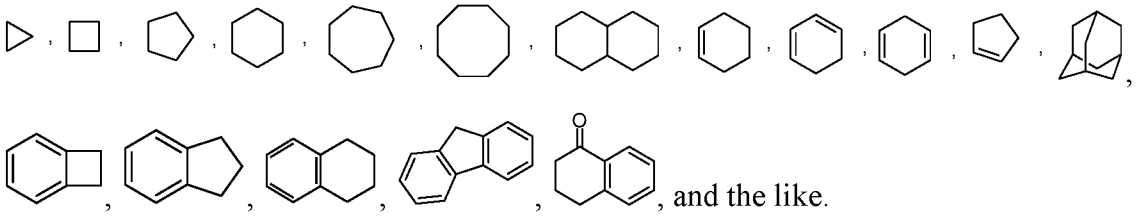
[00223] "Carboxy" refers to -CO_2H. In some embodiments, carboxy moieties may be replaced with a "carboxylic acid bioisostere", which refers to a functional group or moiety that exhibits similar physical and/or chemical properties as a carboxylic acid moiety. A carboxylic acid bioisostere has similar 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.

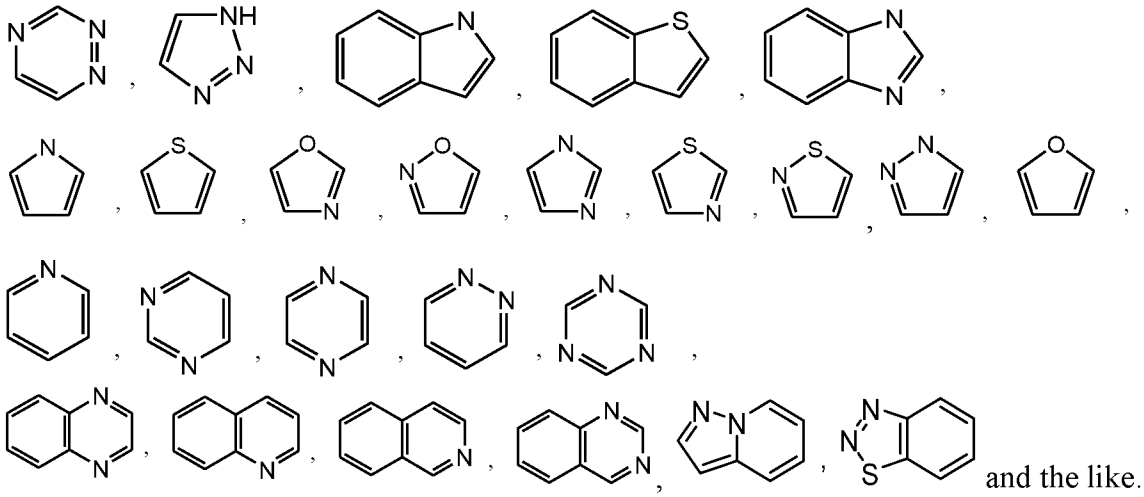
[00224] The term "cycloalkyl" refers to a monocyclic or polycyclic non-aromatic radical, wherein each of the atoms forming the ring (i.e. skeletal atoms) is a carbon atom. Cycloalkyls may be saturated, or partially unsaturated. Cycloalkyls may be fused with an aromatic ring (in which case the cycloalkyl 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:



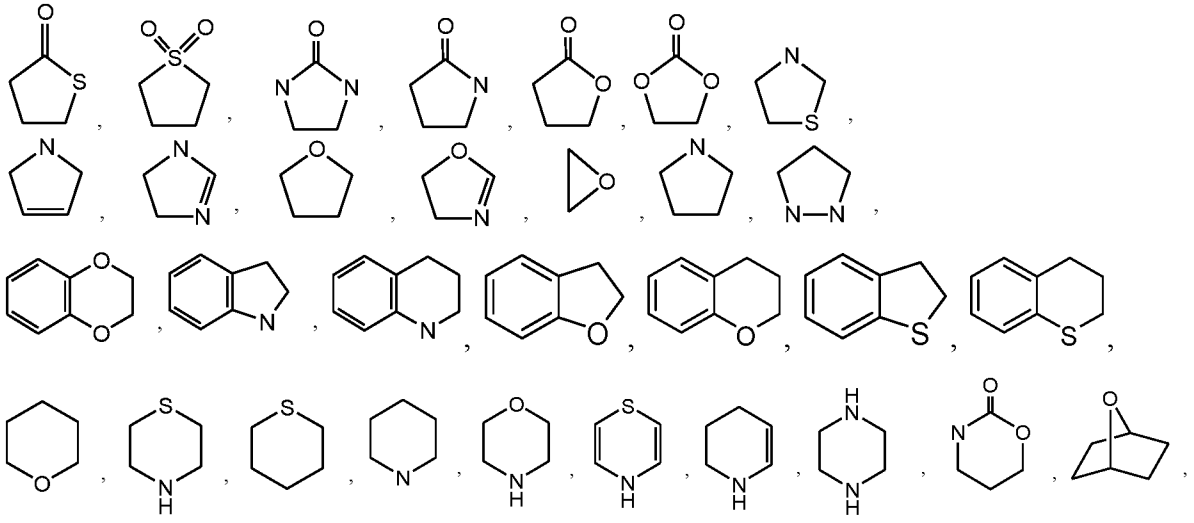
and the like.

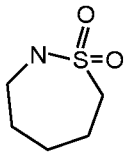
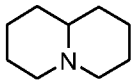
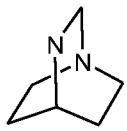
[00225] The terms "heteroaryl" or, alternatively, "heteroaromatic" refers to an aryl group that includes one or more ring heteroatoms selected from nitrogen, oxygen and sulfur. An *N*-containing "heteroaromatic" or "heteroaryl" moiety refers to an aromatic group in which at least one of the skeletal 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.

[00226] 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).

[00227] 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.

[00228] The term "halo" or, alternatively, "halogen" means fluoro, chloro, bromo and iodo.

[00229] 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.

[00230] 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.

[00231] 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.

[00232] 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.

[00233] 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.

[00234] 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.

[00235] 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.

[00236] 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), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI), 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.

[00237] The terms "kit" and "article of manufacture" are used as synonyms.

[00238] 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.

[00239] 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.

[00240] 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.

[00241] 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.

[00242] 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.

[00243] 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.

[00244] 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.

[00245] 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.

[00246] 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.

[00247] 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.

[00248] 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.

[00249] 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).

[00250] 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.

[00251] 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.

[00252] 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.

[00253] 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.

[00254] 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), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI), 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), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI), 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.

[00255] The term "pharmaceutical composition" refers to a mixture of a compound of Formula (I), (II), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI) 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.

[00256] 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), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI) 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.

[00257] 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.

[00258] "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.

[00259] 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.

[00260] 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.

[00261] 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.

[00262] 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.

[00263] "Bioavailability" refers to the percentage of the weight of the compound disclosed herein (e.g. compound of Formula (I), (II), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI)), 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.

[00264] "Blood plasma concentration" refers to the concentration of a compound of Formula (I), (II), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI) 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.

[00265] 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.

[00266] 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

[00267] In another aspect is a pharmaceutical composition comprising a compound of Formula (I), (II), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, and at least one pharmaceutically acceptable excipient.

[00268] In another aspect is the use of a compound of Formula (I), (II), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI), 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), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI), including embodiments thereof.

[00269] 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), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI), 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), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI), or a pharmaceutically acceptable salt, solvate, or prodrug thereof; wherein the disease is cancer or Down's Syndrome.

[00270] 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), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI), 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), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI), 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), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI), or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[00271] 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), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI), 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.

[00272] 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), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI), or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[00273] In another aspect is the use of a compound of Formula (I), (II), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI) 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.

[00274] 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.

[00275] 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.

[00276] 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), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI) is administered once; (ii) the compound of Formula (I), (II), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI) is administered to the mammal multiple times over the span of one day; (iii) continually; or (iv) continuously.

[00277] In any of the aforementioned aspects are further embodiments that include multiple administrations of the effective amount of the compound of Formula (I), (II), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI), including further embodiments in which (i) the compound of Formula (I), (II), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI) is administered in a single dose; (ii) the time between multiple administrations is every 6 hours; (iii) the compound of Formula (I), (II), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI) 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), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI) is temporarily suspended or the dose of the compound of Formula (I), (II), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI) being administered is temporarily reduced; at the end of the drug holiday, dosing of the compound of Formula (I), (II), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI) is resumed. The length of the drug holiday can vary from 2 days to 1 year.

[00278] 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

[00279] 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.

[00280] A pharmaceutical composition, as used herein, refers to a mixture of a compound of Formula (I), (II), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI) 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), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI) can be used singly or in combination with one or more therapeutic agents as components of mixtures (as in combination therapy).

[00281] 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), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI) 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.

[00282] 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.

[00283] 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.

[00284] The pharmaceutical compositions will include at least one compound of Formula (I), (II), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI) 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.

[00285] 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.

[00286] 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), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI)), 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.

[00287] 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.

[00288] 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.

[00289] 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.

[00290] 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), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI) 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), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI) 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.

[00291] The pharmaceutical solid dosage forms described herein can include a compound of Formula (I), (II), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI) 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.

[00292] 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.

[00293] 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.

[00294] In order to release the compound of Formula (I), (II), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI) 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.

[00295] 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.

[00296] 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.

[00297] 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.

[00298] 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.

[00299] 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.

[00300] 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.

[00301] 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.

[00302] Suitable antioxidants for use in the solid dosage forms described herein include, for example, e.g., butylated hydroxytoluene (BHT), sodium ascorbate, and tocopherol.

[00303] 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.

[00304] 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.

[00305] 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), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI) 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.

[00306] 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.

[00307] In various embodiments, the particles of the compound of Formula (I), (II), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI) 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.

[00308] 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.

[00309] 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), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI) *in vivo*.

[00310] 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.

[00311] 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.

[00312] 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.

[00313] 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.

[00314] 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.

[00315] 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), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI). 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.

[00316] 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.

[00317] 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:

[00318] 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;

[00319] 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;

[00320] Poly Vinyl Acetate Phthalate (PVAP). PVAP dissolves in pH >5, and it is much less permeable to water vapor and gastric fluids.

[00321] 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.

[00322] 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.

[00323] In other embodiments, the formulations described herein, which include a compound of Formula (I), (II), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI) 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.

[00324] 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.

[00325] In some embodiments, pharmaceutical formulations are provided that include particles of the compounds described herein, e.g. compounds of Formula (I), (II), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI), 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.

[00326] 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).

[00327] 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.

[00328] 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.

[00329] 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.

[00330] 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.

[00331] 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.

[00332] 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.

[00333] 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.

[00334] 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.

[00335] 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.

[00336] 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.

[00337] 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.

[00338] 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.

[00339] 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.

[00340] 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.

[00341] 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.

[00342] 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.

[00343] Generally, an agent, such as a compound of Formula (I), (II), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI), 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.

[00344] 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.

[00345] 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

[00346] 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.

[00347] 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.

[00348] 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.

[00349] 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.

[00350] 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%.

[00351] 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.

[00352] 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.

[00353] 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.

[00354] 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.

[00355] 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

[00356] The compounds of Formula (I), (II), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI), 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.

[00357] 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), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI), 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.

[00358] 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.

[00359] As a non-limiting example, the compounds of Formula (I), (II), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI) described herein can be co-administered with conventional chemotherapeutic agents including alkylating agents (*e.g.,* cyclophosphamide, ifosfamide, chlorambucil, busulfan, melphalan, mechlorethamine, uramustine, thiotepa, nitrosoureas, *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.

[00360] The compounds of Formula (I), (II), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI) 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.

[00361] Additionally, the compounds of Formula (I), (II), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI) 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.*).

[00362] In further embodiments, the compounds of Formula (I), (II), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI) described herein can also be co-administered with STAT 3 inhibitors or Janus Kinase inhibitors.

[00363] 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.

[00364] 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.

[00365] 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).

[00366] In any case, the multiple therapeutic agents (one of which is a compound of Formula (I), (II), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI) 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.

[00367] 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.

[00368] 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.

[00369] 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.

[00370] 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

[00371] 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.

[00372] 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.

[00373] 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.

[00374] 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.

[00375] 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.

[00376] 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

[00377] 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.

[00378] HPLC methods: Platform (Methods 1-3): Agilent 1100 series HPLC, comprised of pumps, degasser and UV detector, equipped with an auto-sampler. MS detector (APCI) PE Sciex API 150 EX. Platform (Method 4): Agilent 1290 series HPLC, comprised of binary pumps, degasser and UV detector, equipped with an auto-sampler. MS detector AJS-ES.

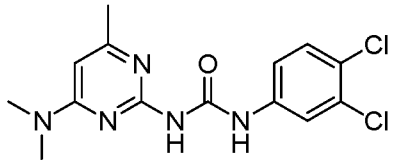
[00379] Method 1: Column - Zorbax C18, size 4.6 mm X 7.5 cm; Solvent A: 0.05 % TFA in water, Solvent B: 0.05 % TFA in acetonitrile; Flow rate – 0.7 mL/min; Gradient: 5 % B to 100 % B in 9 min, hold at 100 % B for 4 min and 100 % B to 5 % B in 0.5 min; UV detector – channel 1 = 220 nm, channel 2 = 254 nm.

[00380] Method 2: Column - Zorbax C18, size 4.6 mm X 7.5 cm; Solvent A: 0.05 % TFA in water, Solvent B: 0.05 % TFA in acetonitrile; Flow rate – 0.7 mL/min; Gradient: 5 % B to 100 % B in 5 min, hold at 100 % B for 2 min and 100 % B to 5 % B in 0.5 min; UV detector – channel 1 = 220 nm, channel 2 = 254 nm.

[00381] Method 3: Column - SunFireTM (Waters) C18, size 2.1 mm X 50 mm; Solvent A: 0.05 % TFA in water, Solvent B: 0.05 % TFA in acetonitrile; Flow rate – 0.8 mL/min; Gradient: 10 % B to 90 % B in 2.4 min, hold at 90 % B for 1.25 min and 90 % B to 10 % B in 0.25 min, hold at 10 % B for 1.5 min.; UV detector – channel 1 = 220 nm, channel 2 = 254 nm.

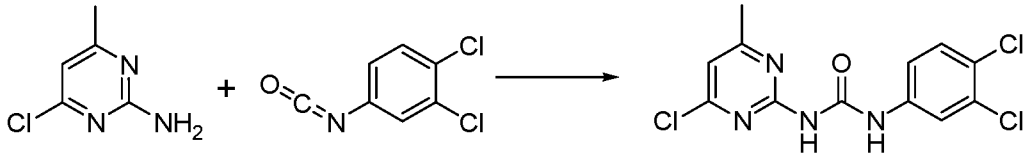
[00382] Method 4: Column - Zorbax Eclipse Plus C18, size 2.1 X 50 mm; Solvent A: 0.10 % formic acid in water, Solvent B: 0.00 % formic acid in acetonitrile; Flow rate – 0.7 mL/min; Gradient: 5 % B to 95 % B in 5 min and hold at 95 % B for 2 min; UV detector – channel 1 = 254 nm, channel 2 = 254 nm.

Example 1: **Synthesis of (N-methyl{2-[3-(3,4-dichlorophenyl)ureido]-6-methyl-4-pyrimidinyl}amino)methane (2)**



2

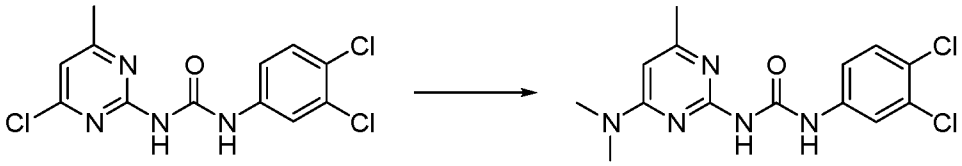
[00383] Step 1: 1-(4-Chloro-6-methyl-2-pyrimidinyl)-3-(3,4-dichlorophenyl)urea (**1**)



1

[00384] A mixture of 3,4-dichloro phenyl isocyanate (5 g, 26.6 mmol) and 2-amino-4-chloro-6-methylpyrimidine (3.82 g, 26.6 mmol) and 1,4-dioxane (130.0 mL) was heated at reflux for 15 hours. The mixture was cooled and MeOH (50 mL) was added. A white precipitate was collected by filtration and dried to give compound (**1**) (6 g, 69%). LC/MS: Rt = 3.4 min, *m/z* = 333.3-335.3 [MH^+].

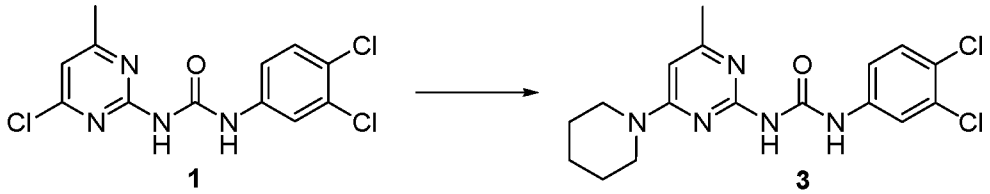
[00385] Step 2: 1-(N-Methyl{2-[3-(3,4-dichlorophenyl)ureido]-6-methyl-2-pyrimidinyl}amino)methane (**2**)



1 **2**

[00386] A mixture of 1-(4-chloro-6-methyl-2-pyrimidinyl)-3-(3,4-dichlorophenyl)urea (**1**) (83 mg, 0.25 mmol), dimethylamine (0.125 mL, 0.25 mmol, 2M solution in THF), diisopropylethylamine (50 µL) and dimethylacetamide (3.0 mL) was heated to 90-95 °C overnight. The mixture was cooled and MeOH (3.0 mL) was added. White precipitates formed which were filtered to afford the title compound (**2**) (45.0 mg, 52%). %). LC/MS: Rt = 2.85 min, *m/z* = 340.3-344.2 [MH^+].

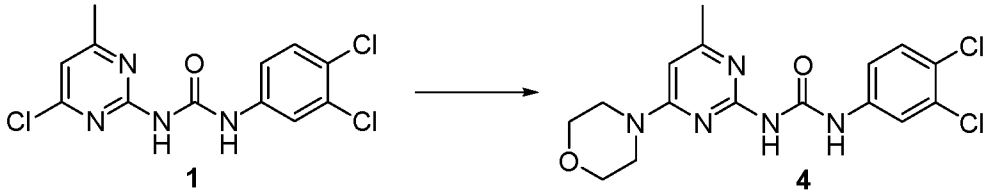
Example 2: Synthesis of 1-(3,4-dichlorophenyl)-3-(6-methyl-4-piperidino-2-pyrimidinyl)urea (3)



1 **3**

[00387] A mixture of 1-(4-chloro-6-methyl-2-pyrimidinyl)-3-(3,4-dichlorophenyl)urea (**1**) (83 mg, 0.25 mmol), piperidine (106 mg, 1.25 mmol) and dimethylacetamide (3.0 mL) was heated to 90-95°C overnight. The mixture was cooled and MeOH (3.0 mL) was added. White precipitates formed which were filtered to afford the title compound (**3**) (63.0 mg, 66%). LC/MS: Rt = 2.95 min, *m/z* = 381.9-384.3 [MH^+].

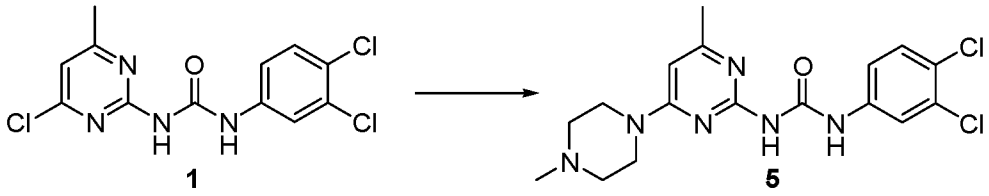
Example 3: Synthesis of 1-(3,4-dichlorophenyl)-3-(6-methyl-4-morpholino-2-pyrimidinyl) urea (4)



1 **4**

[00388] A mixture of 1-(4-chloro-6-methyl-2-pyrimidinyl)-3-(3,4-dichlorophenyl)urea (**1**) (83 mg, 0.25 mmol), morpholine (105 mg, 1.25 mmol) and dimethylacetamide (3.0 mL) was heated to 90-95°C overnight. The mixture was cooled and MeOH (3.0 mL) was added. A white solid precipitate was collected by filtration and dried to give the title compound (**4**) (61 mg, 64%). LC/MS: Rt = 3.12 min, *m/z* = 382.3-384.6 [MH^+].

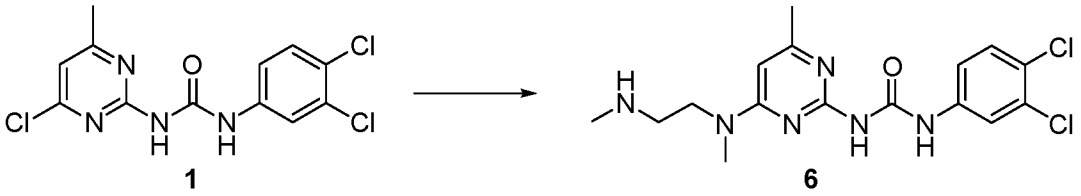
Example 4: Synthesis of 1-(3,4-dichlorophenyl)-3-{6-methyl-4-(4-methyl-piperazin-1-yl-)pyrimidin-2-yl}-urea (5)



1 **5**

[00389] A mixture of 1-(2-chloro-6-methyl-2-pyrimidinyl)-3-(3,4-dichlorophenyl)urea (**1**) (83 mg, 0.25 mmol), 1-methylpiperazine (27.0 mg, 0.27 mmol), diisopropylethylamine (52 µL) and dimethylacetamide (3.0 mL) was heated to 90-95 °C overnight. The mixture was cooled and MeOH (3.0 mL) was added. White precipitates formed which were filtered to give the title compound (**5**) (55 mg, 56%). LC/MS: Rt = 2.82 min, *m/z* = 397.4-399.4 [MH^+].

Example 5: Synthesis of 1-(N-methyl{2-[3-(3,4-dichlorophenyl)ureido]-6-methyl-4-pyrimidinyl}amino)-2-(methylamino)ethane (6)

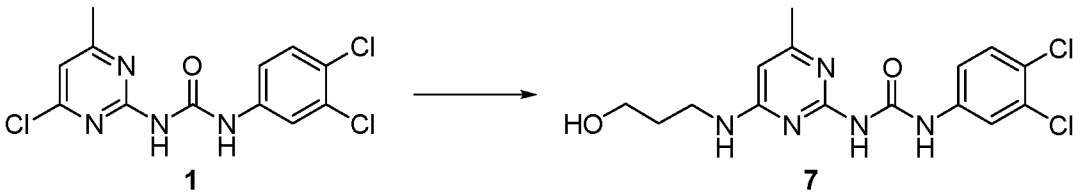


1 **6**

[00390] A mixture of 1-(4-chloro-6-methyl-2-pyrimidinyl)-3-(3,4-dichlorophenyl)urea (**1**) (166 mg, 0.5 mmol), N,N'-dimethylethane-1,2-diamine (450 mg, 5 mmol), and 1,4-dioxane (4.0 mL)

was heated to 90-95°C overnight. The mixture was cooled and MeOH (5.0 mL) was added. White precipitates formed which were filtered to give the title compound (**6**) (140 mg, 73%). LC/MS: Rt = 2.92 min, *m/z* = 384.3-386.4 [MH^+].

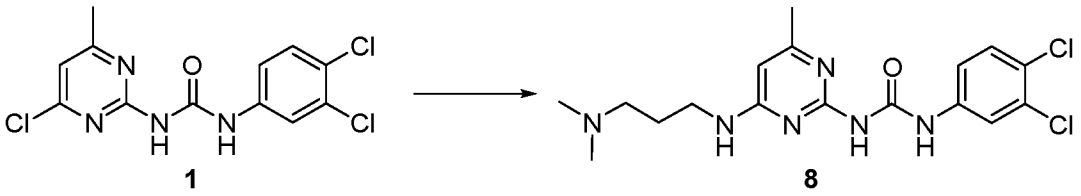
Example 6: Synthesis of 3-{2-[3-(3,4-dichlorophenyl)ureido]-6-methyl-pyrimidin-4-yl}-aminopropanol (7)



1 **7**

[00391] A mixture of 1-(4-chloro-6-methyl-2-pyrimidinyl)-3-(3,4-dichlorophenyl)urea (**1**) (166 mg, 0.5 mmol), 3-aminopropanol (73.0 mg, 0.5 mmol), and 1,4-dioxane (4.0 mL) was heated to 90-95°C overnight. The mixture was cooled and MeOH (3.0 mL) was added. White precipitates formed which were filtered to give the title compound (**7**) (90 mg, 56%). LC/MS: Rt = 3.06 min, *m/z* = 372.2-374.5 [MH^+].

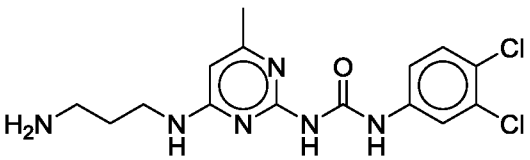
Example 7: Synthesis of 1-{2-[3-(3,4-Dichlorophenyl)ureido]-6-methyl-pyrimidin-4-yl}-amino-3-(dimethylamino)propane (8)



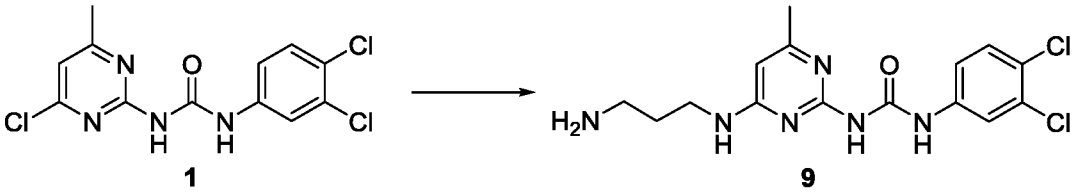
1 **8**

[00392] A mixture of 1-(4-chloro-6-methyl-2-pyrimidinyl)-3-(3,4-dichlorophenyl)urea (**1**) (166 mg, 0.5 mmol), N,N'-dimethyl-1,3-propanediamine (510mg, 5.0 mmol), and 1,4-dioxane (4.0 mL) was heated to 90-95°C overnight. The mixture was cooled and MeOH (3.0 mL) was added. White precipitates formed which were filtered to give the title compound (**8**) (64 mg, 33%). LC/MS: Rt = 2.96 min, *m/z* = 397.2-399.4 [MH^+].

Example 8: Synthesis of 1-(4-((2-aminopropyl)amino)-6-methylpyrimidin-2-yl)-3-(3,4-dichlorophenyl)urea (9)



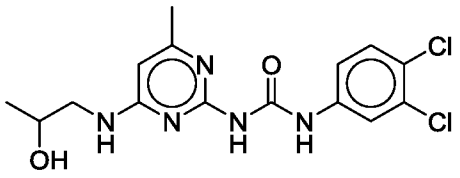
9



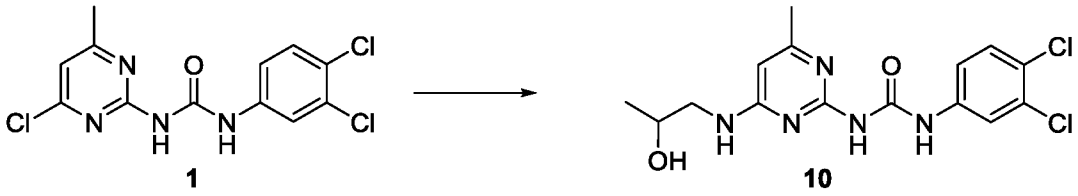
1 **9**

[00393] A mixture of 1-(4-chloro-6-methyl-2-pyrimidinyl)-3-(3,4-dichlorophenyl)urea (1) (1.05g, 3.2mmol) and toluene (4.7 mL) was heated to reflux with stirring. To this was added 1,3-propanediamine (0.32 mL, 3.8 mmol), and triethylamine (0.66 mL, 4.7 mmol) and reflux continued. Upon cooling a precipitate formed which was filtered and washed with methanol and diethyl ether to give the title compound (**9**) (1.01g, 83%). LC/MS: Method 4: Rt = 1.44 min, m/z = 368.1-370.1 [MH+].

Example 9: Synthesis of 1-{2-[3-(3,4-Dichlorophenyl)ureido]-6-methyl-4-pyrimidinylamino}-2-propanol (10)



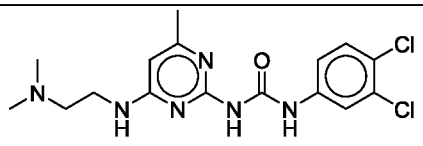
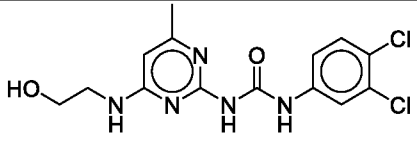
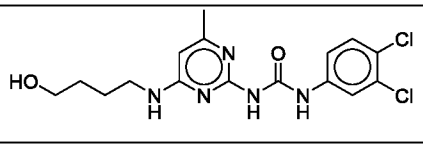
10

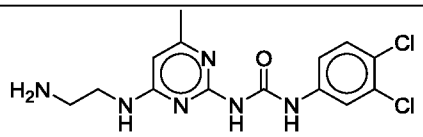
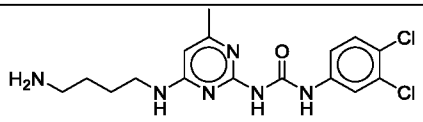
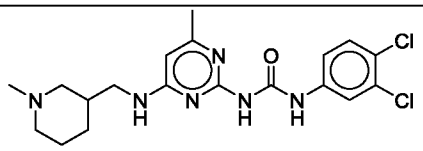
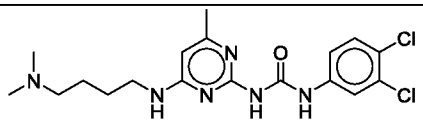
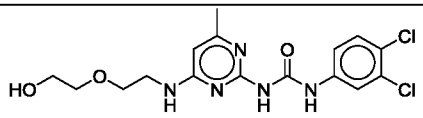
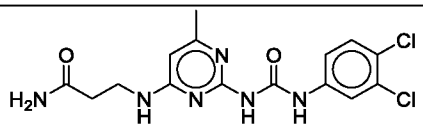
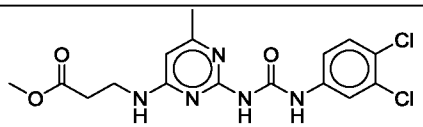
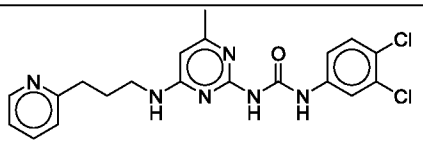
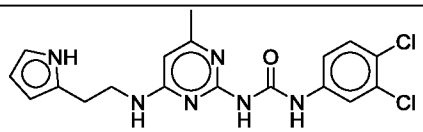


1 **10**

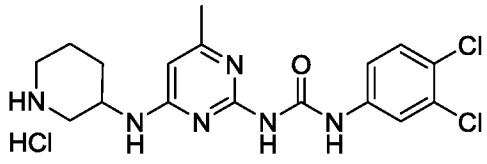
[00394] 1-(4-Chloro-6-methyl-2-pyrimidinyl)-3-(3,4-dichlorophenyl)urea (1) (0.2g, 0.56mmol) was suspended in 2-propanol (1.1mL). To this was added triethylamine (0.12 mL, 0.89mmol) and then 1-aminopropan-2-ol (0.06mL, 0.70mmol), and the mixture was heated to reflux with stirring overnight. Upon cooling a precipitate formed which was filtered and washed with absolute ethanol to give the title compound (**10**) (6.4mg, 3%). LC/MS: Method 4: Rt = 2.22 min, m/z = 370.1-372.1 [MH+]).

[00395] The following examples were prepared according to similar procedures described for Examples 1-9:

Cpd ID	Example ID	Structure	HPLC Method	Yield (mass/%)	RT (min)	MH^+
11	**10**		**4**	**0.24 g, 21**	**2.48**	**383.2-385.1**
12	**11**		**4**	**27 mg, 18**	**1.70**	**356.1-358.1**
13	**12**		**4**	**14 mg, 11**	**2.18**	**384.1-386.1**

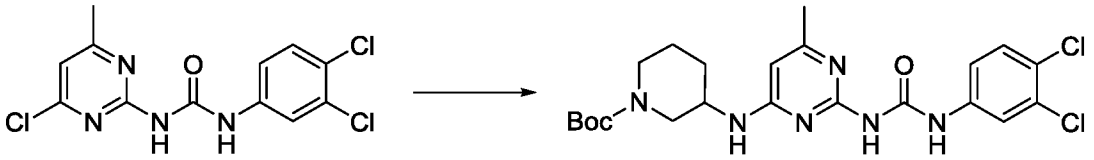
14	**13**		**4**	**16 mg, 71**	**1.80**	**355.1-357.1**
15	**14**		**4**	**0.14 g, 60**	**1.89**	**383.1-385.1**
16	**15**			**15 mg, 8**	**1.74**	**423.2-425.2**
17	**16**		**4**	**0.23 g, 87**	**2.30**	**411.2-413.2**
18	**17**		**4**	**0.19 g, 82**	**2.01**	**400.1-402.1**
19	**18**		**4**	**17 mg, 9**	**2.11**	**383.1-385.1**
20	**19**		**4**	**11 mg, 41**	**2.62**	**398.1-400.1**
21	**20**		**4**	**0.20 g, 73**	**1.96**	**431.2-433.2**
22	**21**		**4**	**0.20 g, 78**	**2.85**	**405.1-407.1**

Example 22: Synthesis of (±)-2-[3-(3,4-dichlorophenyl)ureido]-6-methyl-4-(3-piperidylamino)pyrimidine hydrochloride (24)



24

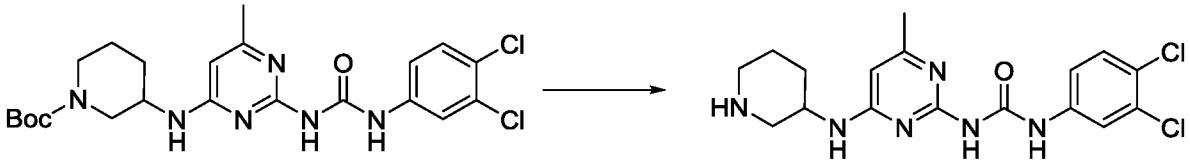
[00396] Step 1: tert-butyl 2-(2-(3-(3,4-dichlorophenyl)ureido)-6-methylpyrimidin-4-ylamino)piperidine-1-carboxylate (**23**)



1 23

[00397] A mixture of 1-(4-chloro-6-methyl-2-pyrimidinyl)-3-(3,4-dichlorophenyl)urea (**1**) (905 mg, 2.75 mmol), 1-boc-3-amino-piperidine (901 mg, 4.5 mmol), and dimethylacetamide (9.0 mL) was heated at 85°C for 5 hours. The mixture was cooled and added to water. White solids formed that were filtered and washed with 1M HCl and EA and dried (1.03 g, 76%).

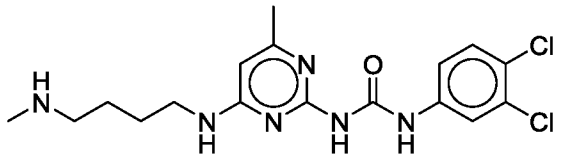
[00398] Step 2: (±)-2-[3-(3,4-dichlorophenyl)ureido]-6-methyl-4-(3-piperidylamino)pyrimidine hydrochloride (**24**)



23 24

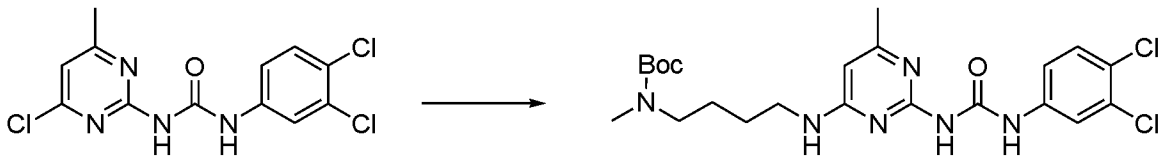
[00399] The BOC derivative (**9**) (741 mg, 1.5 mmol) was suspended into a 9:1 mixture of DCM: MeOH (7.5 mL) and HCl (4M in dioxane, 7.5 mL) was added. The reaction mixture was stirred overnight at room temperature. Volatiles were removed in vacuo to yield the title compound (**10**) as a hydrochloride salt (500 mg). LC/MS: Rt = 3.18 min, *m/z* = 395.1 [MH^+].

Example 23: Synthesis of 1-(3,4-dichlorophenyl)-3-(4-methyl-6-((4-(methylamino)butyl)amino)pyrimidin-2-yl)urea (26)



26

[00400] Step 1: (4-{2-[3-(3,4-Dichloro-phenyl)-ureido]-6-methyl-pyrimidin-4-ylamino}-butyl)-methyl-carbamic acid tert-butyl ester (**25**)

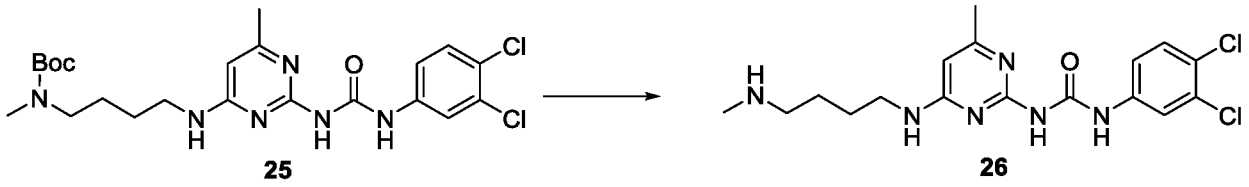


1 25

[00401] A mixture of 1-(4-chloro-6-methyl-2-pyrimidinyl)-3-(3,4-dichlorophenyl)urea (**1**) (1.4g, 4.3mmol) and toluene (6.5 mL) was heated to reflux with stirring. To this was added N-(4-Aminobutyl)-N-methyl carbamic acid tert-butyl ester (1.0 g, 5.2 mmol), and triethylamine (0.91 mL, 6.4 mmol) and reflux continued for 30 minutes. Upon cooling methanol was added

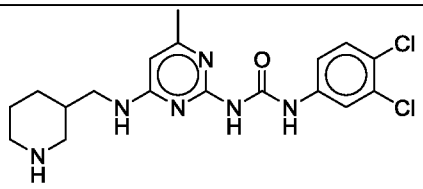
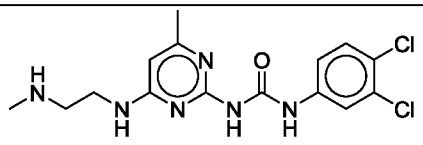
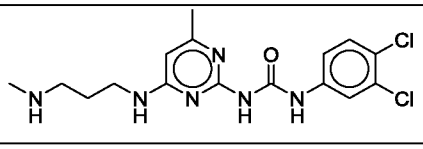
and the precipitate formed was filtered and washed with diethyl ether to give the title compound (**25**) (2.0 g, 90%). LC/MS: Rt = 3.97 min, m/z = 497.2-499.2 [MH+].

[00402] Step 2: 1-(3,4-dichlorophenyl)-3-(4-methyl-6-((4-(methylamino)butyl)amino)pyrimidin-2-yl)urea

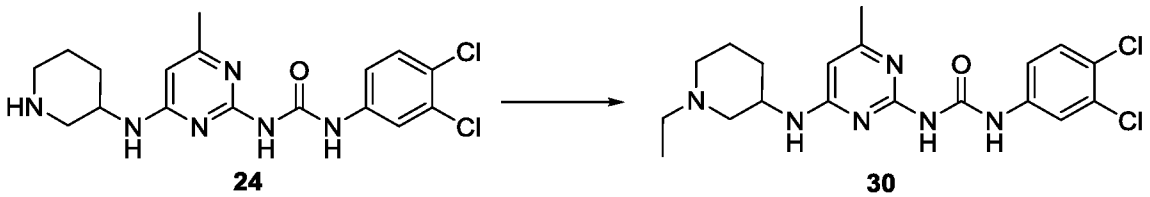


[00403] The BOC derivative (**25**) (2.5g, 4.7 mmol) was suspended in DCM (15 mL) to which trifluoroacetic acid (9 mL, 118 mmol) was added. The reaction mixture was stirred for 30 minutes at room temperature. This mixture was treated with 1N NaOH solution (4.7 mL, 4.7 mmol) and the mixture stirred for 30 minutes. The layers were separated and the organics washed with water and brine before drying and being concentrated to yield the title product (**26**) LC/MS: Method 4: Rt = 2.31 min, *m/z* = 397.2-399.2 [MH^+].

[00404] The following examples were prepared according to similar procedures described for Examples 22-23:

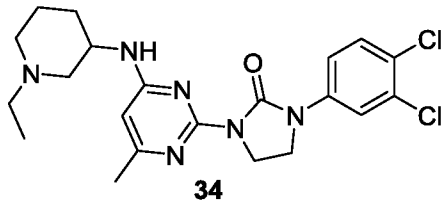
Cpd ID	Example ID	Structure	HPLC Method	Yield (mass/%)	RT (min)	MH^+
27	**24**		**4**	**1.7 g, 91**	**2.24**	**409.2-411.2**
28	**25**		**4**	**69 mg, 97**	**1.77**	**370.1-372.1**
29	**26**		**4**	**0.37 g, 92**	**0.35**	**383.2-385.1**

Example 27: Synthesis of (±)-2-[3-(3,4-dichlorophenyl)ureido]-4-(1-ethyl-piperidin-3-yl-amino)-6-methylpyrimidine (30)



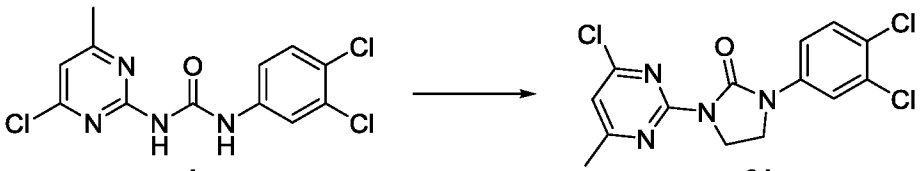
[00405] To a solution of 2-[3-(3,4-dichlorophenyl)ureido]-6-methyl-4-(3-piperidylamino)pyrimidine (**24**) (215 mg, 0.5 mmol) in DCM (2.5 mL) was added acetaldehyde (141 µL, 2.5 mmol) and then sodium cyanoborohydride (63 mg, 1.00 mmol). The reaction mixture was stirred for 3 hours and then diluted with DCM (10 mL) and washed with water, $NaHCO_3$ solution, and water. The organic layer was dried (Na_2SO_4), filtered and concentrated. The residue was purified on silica plate (eluent: DCM:MeOH:NH_4OH: 400:50:2 v/v) to give the title compound (**30**) (50 mg, 24%). LC/MS: Rt = 3.05 min, *m/z* = 423.4 [MH^+].

Example 28: Synthesis of (±)-1-(3,4-dichlorophenyl)-3-[4-(1-ethyl-3-piperidylamino)-6-methyl-2-pyrimidinyl]-2-imidazolidinone (34)



34

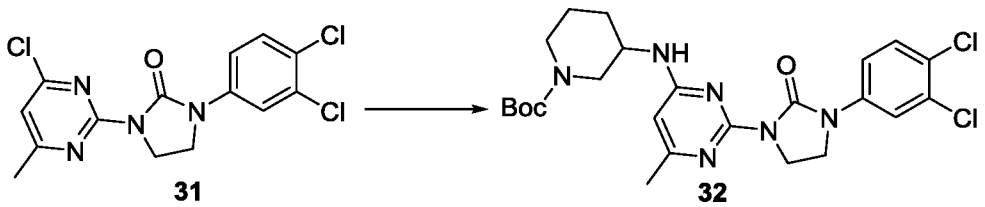
[00406] Step 1: 3-(4-Chloro-6-methyl-2-pyrimidinyl)-1-(3,4-dichlorophenyl)-2-imidazolidinone (**31**)



1 **31**

[00407] A mixture of 1-(4-chloro-6-methyl-2-pyrimidinyl)-3-(3,4-dichlorophenyl)urea (**1**) (150 mg, 0.45 mmol), 1,2-dibromoethane (847 mg, 4.53 mmol), K_2CO_3 (607 mg, 4.53 mmol) in acetone (4.5 mL) was heated to reflux for 3 hours. The reaction mixture was cooled, poured into water (25.0 mL) and extracted with EA (2x25 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to dryness. The residue was purified by chromatography (silica column, eluent 0-40% EA in Hexane, gradient) to yield compound (**31**) (100 mg, 61.2%). LC/MS: Rt = 4.15 min, *m/z* = 357.2 [MH^+].

[00408] Step 2: (±)-tert-butyl 3-(2-(3-(3,4-dichlorophenyl)-2-oxoimidazolidin-1-yl)-6-methylpyrimidin-4-ylamino)piperidine-1-carboxylate (**32**)



31 **32**

[00409] A mixture of 3-(4-chloro-6-methyl-2-pyrimidinyl)-1-(3,4-dichlorophenyl)-2-imidazolidinone (**31**) (100 mg, 0.28 mmol), 1-Boc-3-aminopiperidine (901 mg, 4.5 mmol),

DIPEA (73 mg, 0.56 mmol) and DMA (3.0 mL) was heated at 85°C for 5 hrs. The reaction was cooled and added to water. White solids formed that were filtered and washed with 0.1M HCl and EA and dried (100 mg) to yield compound (**32**).

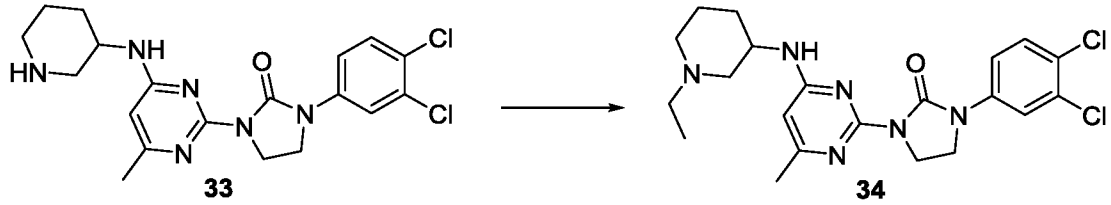
[00410] Step 3: (±)-1-(3,4-Dichlorophenyl)-3-[6-methyl-4-(3-piperidylamino)-2-pyrimidinyl]-2-imidazolidinone (**33**)



32 **33**

[00411] Compound (**32**) (100 mg, 0.192 mmol) was suspended in DCM (10.0 mL) and TFA (10.0 mL) was added. The mixture was stirred overnight at room temperature. Volatiles were removed in vacuo to yield 1-(4-chloro-6-methyl-2-pyrimidinyl)-3-(3,4-dichlorophenyl)-2-imidazolidinone (**33**) (100 mg) as a TFA salt.

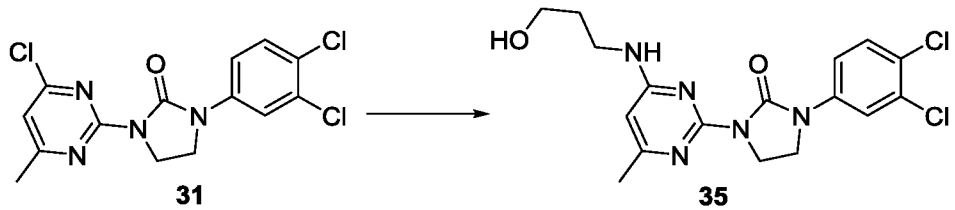
[00412] Step 4: (±)-1-(3,4-Dichlorophenyl)-3-[4-(1-ethyl-3-piperidylamino)-6-methyl-2-pyrimidinyl]-2-imidazolidinone (**34**)



33 **34**

[00413] To a solution of (±)-1-(3,4-dichlorophenyl)-3-[6-methyl-4-(3-piperidylamino)-2-pyrimidinyl]-2-imidazolidinone (**33**) (100 mg, 0.237 mmol) in DCM (2.5 mL) was added acetaldehyde (52 mg, 1.187 mmol) and then sodium cyanoborohydride (29 mg, 0.475 mmol). The reaction mixture was stirred for 3 hours and then diluted with DCM (10 mL). The reaction mixture was washed with water, $NaHCO_3$ solution and water. The organic layer was dried (Na_2SO_4), filtered and concentrated to yield crude product which was purified on silica plate (eluent, DCM: MeOH: NH_4OH: 400: 50: 2) to yield the title compound (**34**) (15 mg, 14%). LC/MS: Rt = 0.05 min, *m/z* = 450.6 [MH^+].

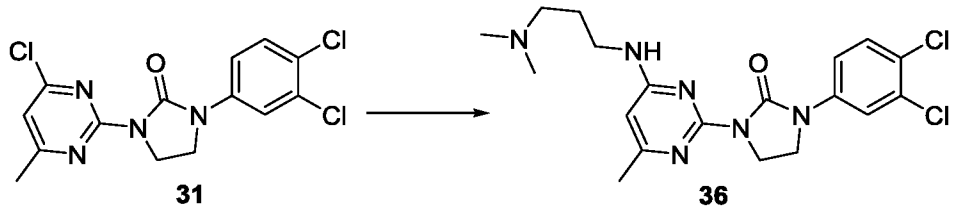
Example 29: Synthesis of 3-(3,4-dichlorophenyl)-1-[4-(3-hydroxypropylamino)-6-methyl-2-pyrimidinyl]-2-imidazolidinone (35)



31 **35**

[00414] 3-(4-Chloro-6-methyl-2-pyrimidinyl)-1-(3,4-dichlorophenyl)-2-imidazolidinone (**31**) (50 mg, 0.14 mmol), 3-aminopropanol (16 mg, 0.21 mmol), DIPEA (271 mg, 2.1 mmol) were taken into DMA (3.0 mL) and heated at 80 ºC for 12 hours. Then the reaction mixture was cooled and water was added. The desired compound precipitated which was crystallized using MeOH and DCM mixture. The resulting crystals were filtered and dried to give the title compound (**35**) (25 mg, 45%). LC/MS: Rt = 4.24 min, *m/z* = 397.3 [MH^+].

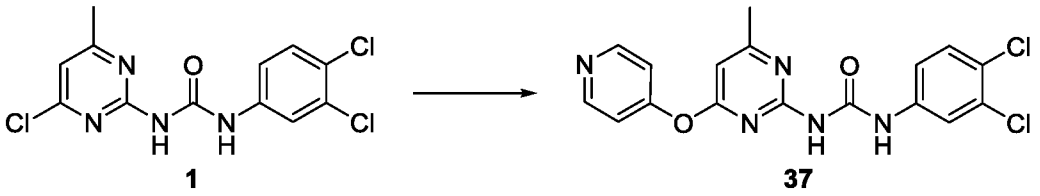
Example 30: Synthesis of 3-(3,4-dichlorophenyl)-1-{4-[3-(dimethylamino)propylamino]-6-methyl-2-pyrimidinyl}-2-imidazolidinone (36)



31 **36**

[00415] 3-(4-Chloro-6-methyl-2-pyrimidinyl)-1-(3,4-dichlorophenyl)-2-imidazolidinone (**31**) (50 mg, 0.14 mmol), 3-(dimethylamino)propylamine (21 mg, 0.21 mmol), DIPEA (271 mg, 2.1 mmol) were taken into DMA (3.0 mL) and heated at 80ºC for 12 hours. The reaction mixture was cooled and water added. The desired compound precipitated which was crystallized using MeOH and DCM mixture. The resulting crystals were filtered and dried to give the title compound (**36**) (25 mg, 45%). LC/MS: Rt = 4.16 min, *m/z* = 424.3 [MH^+].

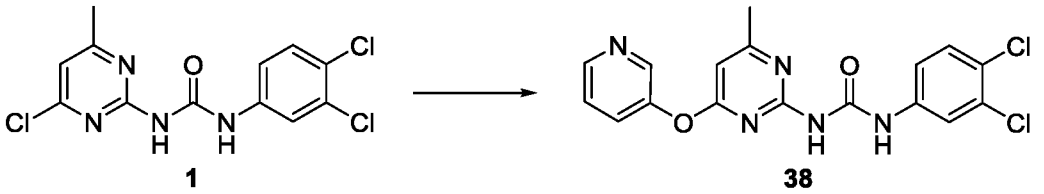
Example 31: Synthesis of 1-(3,4-dichlorophenyl)-3-[6-methyl-4-(4-pyridyloxy)-2-pyrimidinyl]-urea (37)



1 **37**

[00416] A mixture of 1-(4-chloro-6-methyl-2-pyrimidinyl)-3-(3,4-dichlorophenyl)urea (**1**) (50 mg, 0.15 mmol), K_2CO_3 (42.0 mg, 0.30 mmol) and 4-hydroxypyridine (21.0 mg, 0.225 mmol) in 1,4-dioxane was stirred at 100ºC for 4 hours. The reaction mixture was cooled, diluted with water and extracted with EA (2x10 mL). The organic layers were dried (Na_2SO_4), filtered and concentrated to yield title compound (**37**) (28.0 mg, 48%) as a solid. LC/MS: Rt = 3.09 min, *m/z* = 390.4 [MH^+].

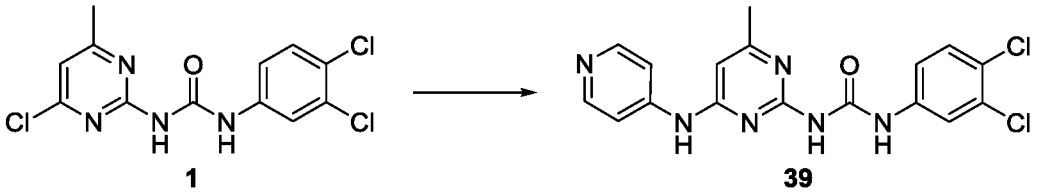
Example 32: Synthesis of 1-(3,4-dichlorophenyl)-3-[6-methyl-4-(3-pyridyloxy)-2-pyrimidinyl]-urea (38)



1 38

[00417] A mixture of 1-(4-chloro-6-methyl-2-pyrimidinyl)-3-(3,4-dichlorophenyl)urea (**1**) (50 mg, 0.15 mmol), K_2CO_3 (42 mg, 0.30 mmol) and 3-hydroxypyridine (21mg, 0.225 mmol) in 1,4-dioxane was stirred at 100°C for 4 hours. This reaction mixture was cooled, diluted with water and extracted with EA (2x10 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated to yield title compound (**38**) (29 mg, 50%) as a solid. LC/MS: Rt = 3.26 min, *m/z* = 390.4 [MH^+].

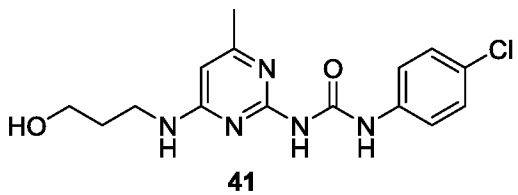
Example 33: Synthesis of 2-[3-(3,4-dichlorophenyl)ureido]-6-methyl-4-(4-pyridylamino)-pyrimidine (39)



1 39

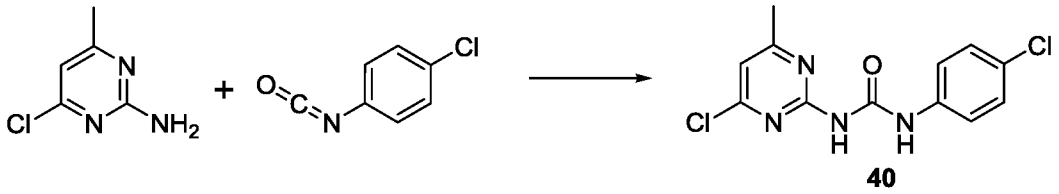
[00418] A mixture of 1-(4-chloro-6-methyl-2-pyrimidinyl)-3-(3,4-dichlorophenyl)urea (**1**) (50 mg, 0.15 mmol), 4-aminopyridine (21.0 mg, 0.225 mmol), diisopropylethylamine (52 µL, 0.30 mmol) was heated in DMA (1.5 mL) for 4 hours. The reaction mixture was cooled, diluted with water and extracted with EA (2x10 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated to yield the title compound (**39**) (30 mg, 52%) as a solid. LC/MS: Rt = 0.04 min, *m/z* = 389.3 [MH^+].

Example 34: Synthesis of 3-{2-[3-(p-Chlorophenyl)ureido]-6-methyl-4-pyrimidinylamino}-propanol (41)



41

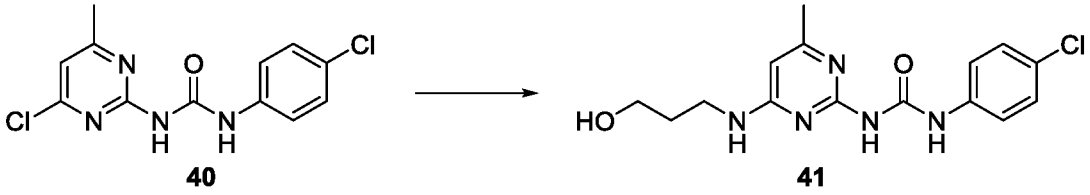
[00419] Step 1: 1-(4-Chloro-6-methyl-2-pyrimidinyl)-3-(p-chlorophenyl)urea (**40**)



40

[00420] A mixture of 2-amino-4-chloro-6-methylpyrimidine (72 mg, 0.5 mmol) and 4-chlorophenyl isocyanate (115 mg, 0.75 mmol) in 1,4-dioxane (1 mL) was heated for 3 hours at 100°C. The mixture was concentrated in vacuo and the residue was triturated with MeOH, filtered and dried to yield compound (**40**) (72 mg, 49%) as a white solid.

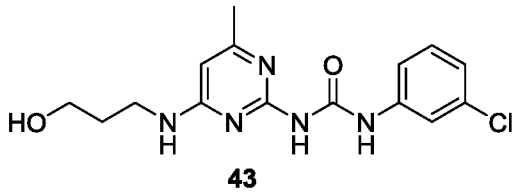
[00421] Step 2: 3-{2-[3-(p-Chlorophenyl)ureido]-6-methyl-4-pyrimidinylamino}-propanol (**41**)



40 41

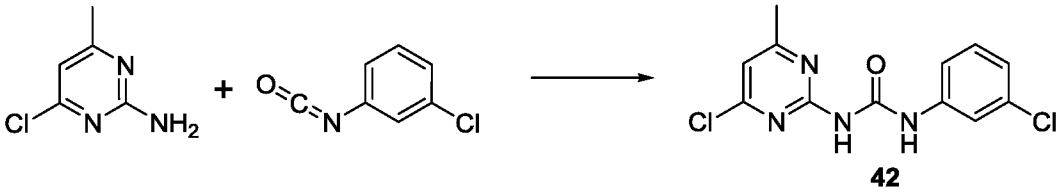
[00422] A mixture of 1-(4-chloro-6-methyl-2-pyrimidinyl)-3-(p-chlorophenyl)urea (**40**) (36 mg, 0.12 mmol) and 3-amino-1-propanol (46 mg, 0.61 mmol) in DMA (1 mL) was heated for 3 hours at 100 °C. The mixture was cooled. A white precipitate was filtered and air-dried to yield the title compound (**41**) (20 mg, 49%). LC/MS: Rt = 0.30 min, *m/z* = 336.6 [MH^+].

Example 35: Synthesis of 3-{2-[3-(m-chlorophenyl)ureido]-6-methyl-4-pyrimidinylamino}-propanol (43)



43

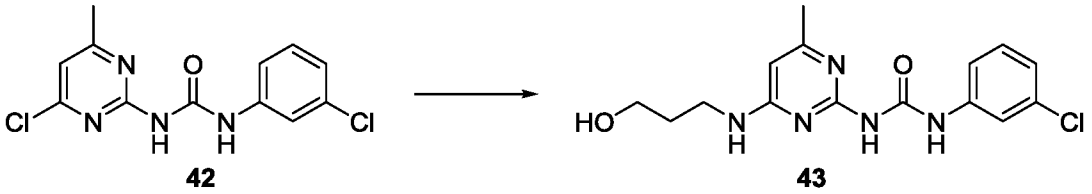
[00423] Step 1: 1-(4-Chloro-6-methyl-2-pyrimidinyl)-3-(m-chlorophenyl)urea (**42**)



42

[00424] A mixture of 2-amino-4-chloro-6-methylpyrimidine (72 mg, 0.5 mmol) and 3-chlorophenyl isocyanate (115 mg, 0.75 mmol) in 1,4-dioxane (1 mL) was heated for 3 hours at 100 °C. The mixture was concentrated in vacuo and the residue was triturated with MeOH, filtered and dried to yield compound (**42**) (115 mg, 88%) as a white solid.

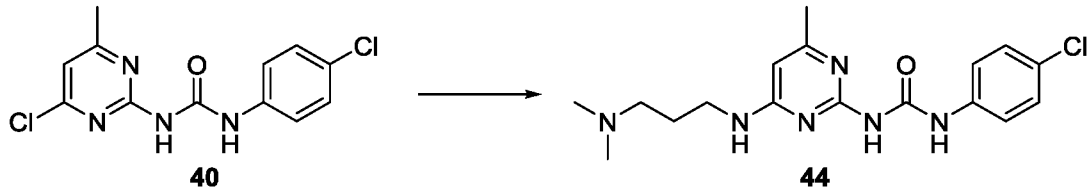
[00425] Step 2: 3-{2-[3-(m-Chlorophenyl)ureido]-6-methyl-4-pyrimidinylamino}-propanol (**43**)



42 43

[00426] A mixture of 1-(4-chloro-6-methyl-2-pyrimidinyl)-3-(m-chlorophenyl)urea (**38**) (58 mg, 0.22 mmol) and 3-amino-1-propanol (50 mg, 0.66 mmol) in DMA (1 mL) was heated for 3 hours at 100 °C. The mixture was cooled. A white precipitate was filtered and air-dried to yield the title compound (**43**) (54 mg, 82%). LC/MS: Rt = 0.11 min, *m/z* = 336.6 [MH^+].

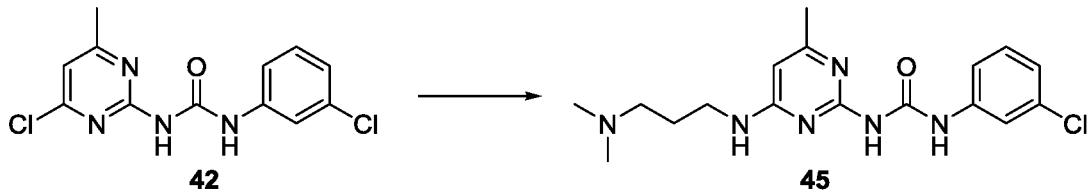
Example 36: Synthesis of 1-{2-[3-(4-chloro-phenyl)ureido]-6-methyl-4-pyrimidin-ylamino}-3-(dimethylamino)propane (44)



40 44

[00427] A mixture of 3-(4-chlorophenyl)-1-(4-chloro-6-methyl-2-pyrimidinyl)urea (**40**) (36.0 mg, 0.121 mmol) and 3-(dimethylamino)-1-propylamine (37.1 mg, 0.364 mmol) in DMA (1.0 mL) was heated for 3 hours at 100 °C. The mixture was cooled. A white precipitate was filtered and air-dried to yield the title compound (**44**) (26 mg, 59%). LC/MS: Rt = 0.53 min, *m/z* = 363.4 [MH^+].

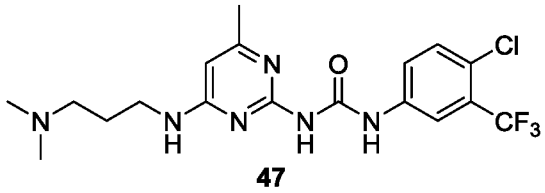
Example 37: Synthesis of 1-{2-[3-(3-Chloro-phenyl)ureido]-6-methyl-4-pyrimidin-ylamino}-3-(dimethyl-amino)propane (45)



42 45

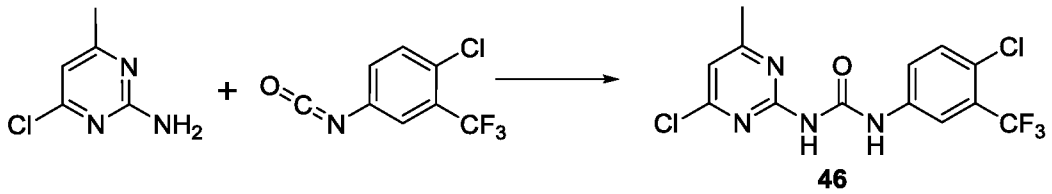
[00428] A mixture of 3-(3-chloro-phenyl)-1-(4-chloro-6-methyl-2-pyrimidinyl)urea (**42**) (58 mg, 0.22 mmol) and 3-(dimethylamino)-1-propylamine (135 mg, 0.66 mmol) in DMA (1.0 mL) was heated for 3 hours at 100 °C. The mixture was cooled. A white precipitate was filtered and air-dried to yield the title compound (**45**) (22 mg, 31%). LC/MS: Rt = 3.84 min, *m/z* = 363.6 [MH^+].

Example 38: Synthesis of 1-(2-{3-[4-chloro-3-(trifluoromethyl)phenyl]ureido}-6-methyl-4-pyrimidinylamino)-3-(dimethylamino)propane (47)



47

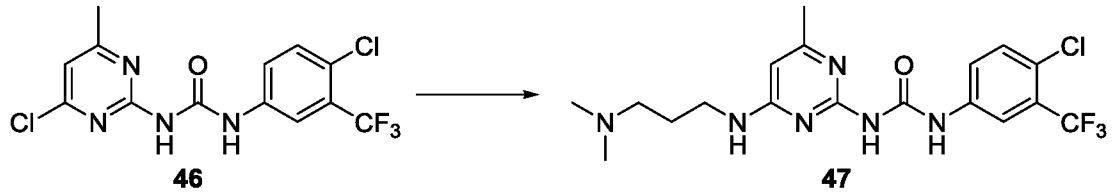
[00429] Step 1: 3-(4-Chloro-6-methyl-2-pyrimidinyl)-1-[4-chloro-3-(trifluoromethyl) phenyl]urea (**46**)



46

[00430] A mixture of 2-amino-4-chloro-6-methylpyrimidine (72.0 mg, 0.5 mmol) and 4-chloro-(3-trifluoromethyl)phenyl isocyanate (166.2 mg, 0.75 mmol) in 1,4-dioxane (1.0 mL) was heated for 3 hours at 100 ºC. The reaction mixture was cooled and precipitate product was filtered, washed with 1,4-dioxane and dried to yield compound (**46**) (129 mg, 70%) as a white solid.

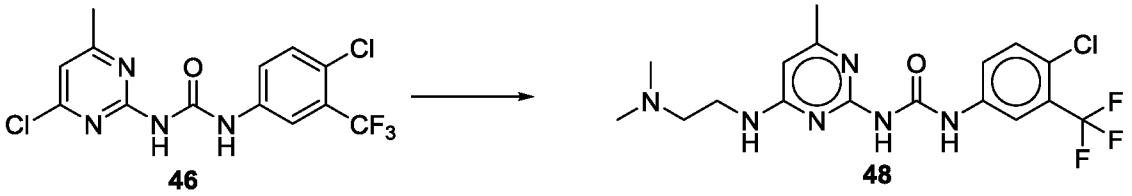
[00431] Step 2: 1-(2-{3-[4-Chloro-3-(trifluoromethyl)phenyl]ureido}-6-methyl-4-pyrimidinylamino)-3-(dimethylamino)propane (**47**)



46 **47**

[00432] A mixture of 3-(4-chloro-6-methyl-2-pyrimidinyl)-1-[4-chloro-3-(trifluoromethyl) phenyl]urea (**46**) (129 mg, 0.35 mmol) and 3-(dimethylamino)-1-propylamine (107 mg, 1.05 mmol) in DMA (1.0 mL) was heated for 3 hrs at 100 ºC. The mixture was cooled and a white precipitate was filtered, washed with water and air dried to yield the title compound (**47**) (128 mg, 85%). LC/MS: Rt = 0.17 min, *m/z* = 431.3 [MH^+].

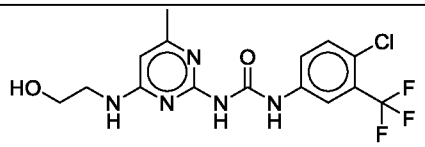
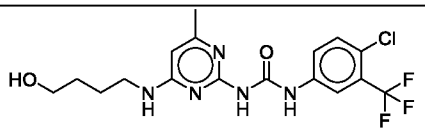
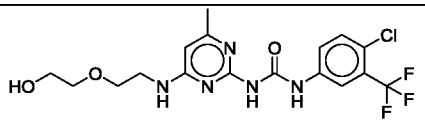
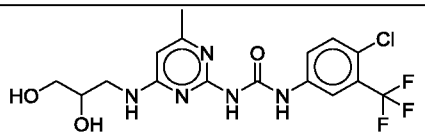
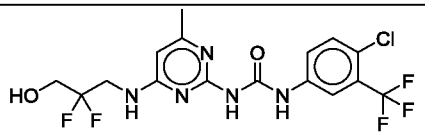
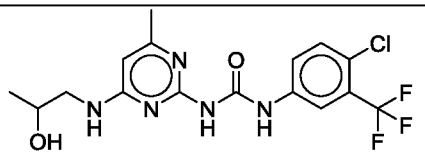
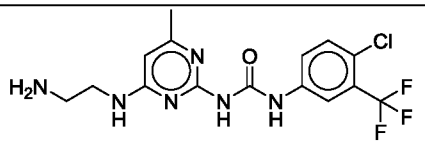
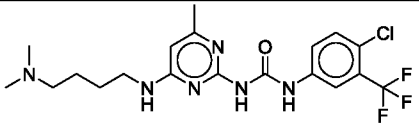
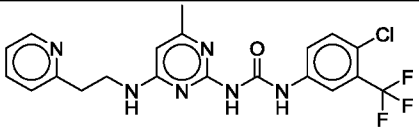
Example 39: Synthesis of 1-(4-chloro-3-(trifluoromethyl)phenyl)-3-(4-((2-(dimethylamino)ethyl)amino)-6-methylpyrimidin-2-yl)urea (48)

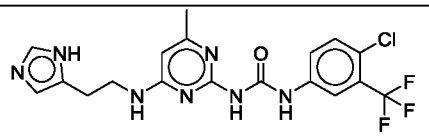
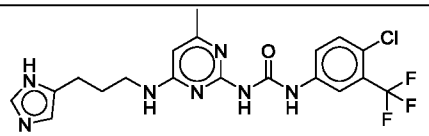
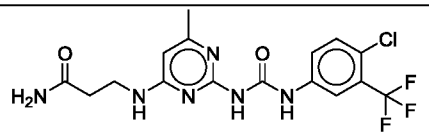
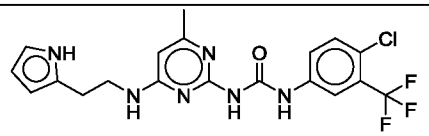


46 **48**

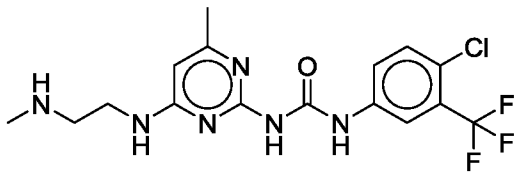
[00433] A suspension of 3-(4-chloro-6-methyl-2-pyrimidinyl)-1-[4-chloro-3-(trifluoromethyl) phenyl]urea (**46**) (100 mg, 0.26 mmol), N,N-dimethylethylene-diamine (28 mg, 0.31 mmol) and trimethylamine (39 mg, 0.39 mmol) in 2-propanol (1 mL) was heated to reflux at 90ºC. After 30 minutes the mixture was cooled to ambient temperature and diluted with MeOH. The title compound (**48**) was filtered as a white solid (85mg, 78%). LC/MS: Method 4: Rt = 1.96 min, m/z = 418.2-420.2 [MH+].

[00434] The following examples were prepared according to similar procedures described for Examples 38-39:

Cpd ID	Example ID	Structure	HPLC Method	Yield (mass/%)	RT (min)	MH^+
49	**40**		**4**	**88mg, 82**	**2.23**	**390.1-392.1**
50	**41**		**4**	**82mg, 72**	**2.25**	**419.2-421.2**
51	**42**		**4**	**99mg, 83**	**2.23**	**435.2-437.2**
52	**43**		**4**	**92mg, 80**	**2.12**	**421.2-423.2**
53	**44**		**4**	**23mg, 19**	**2.66**	**441.1-443.1**
54	**45**		**4**	**83mg, 75**	**2.16**	**405.2-407.2**
55	**46**		**4**	**96mg, 90**	**1.79**	**389.2-391.2**
56	**47**		**4**	**82mg, 67**	**1.80**	**445.2-447.2**
57	**48**		**4**	**108mg, 87**	**2.02**	**451.2-453.2**

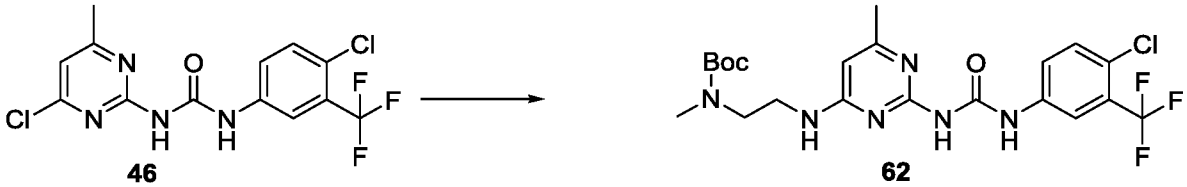
58	**49**		**4**	**91mg, 76**	**1.78**	**441.2-443.2**
59	**50**		**4**	**43mg, 35**	**1.71**	**454.2-456.2**
60	**51**		**4**	**52mg, 46**	**2.01**	**418.2-420.1**
61	**52**		**4**	**10mg, 17**	**2.82**	**439.2-441.2**

Example 53: 1-(4-chloro-3-(trifluoromethyl)phenyl)-3-(4-methyl-6-((2-(methylamino)ethyl)amino)pyrimidin-2-yl)urea (63)



63

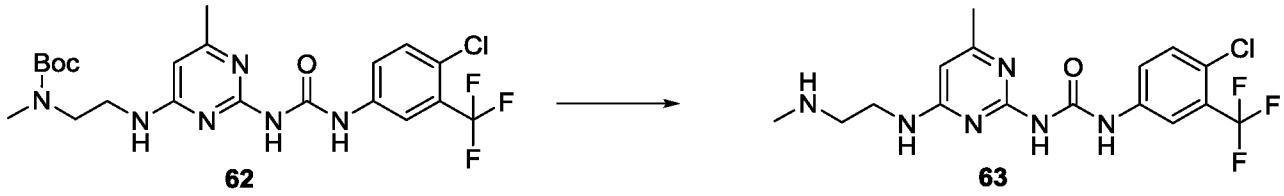
[00435] Step 1: tert-butyl (2-((2-(3-(4-chloro-3-(trifluoromethyl)phenyl)ureido)-6-methylpyrimidin-4-yl)amino)ethyl)(methyl)carbamate (**62**)



46 **62**

[00436] A mixture of 3-(4-chloro-6-methyl-2-pyrimidinyl)-1-[4-chloro-3-(trifluoromethyl) phenyl]urea (**46**) (100 mg, 0.26 mmol), N-(2-Aminoethyl)-N-methyl carbamic acid tert-butyl ester (56mg, 0.31mmol), and triethylamine (40 mg, 0.39 mmol) was heated to reflux with stirring in 2-propanol (1 mL) for 30 minutes. Upon cooling methanol was added and the precipitate formed was filtered to give the title compound (**62**) (97mg, 70%). LC/MS: Rt = 3.11 min, m/z = 504.2-506.2 [MH+].

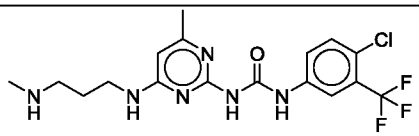
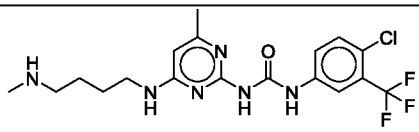
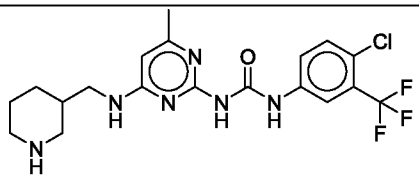
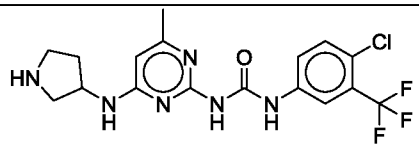
[00437] Step 2: 1-(4-chloro-3-(trifluoromethyl)phenyl)-3-(4-methyl-6-((2-(methylamino)ethyl)amino)pyrimidin-2-yl)urea (**63**)



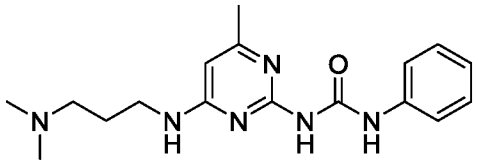
62 63

[00438] The BOC derivative (**62**) (97 mg, 0.18 mmol) was suspended in DCM (1.8 mL) to which trifluoroacetic acid (0.15mL, 1.8mmol) was added. The reaction mixture was stirred for 3 hours before addition of more trifluoroacetic acid (0.15 mL). This mixture was warmed to 45°C and stirred overnight. The solvent was removed under reduced pressure to obtain a yellow gel ehich was mixed with saturated $NaHCO_3$ solution. No precipitation was observed, thus the solvent was removed under reduced pressure and the resulting residue was purified by flash chromatography (gradient elution, 0-20% 3M NH_3 in MeOH over CH_2Cl_2) to obtain the desired compound as a white solid (**63**) (51 mg, 66%). LC/MS: Method 4: Rt = 1.80 min, *m/z* = 404.2-406.2 [MH^+].

[00439] The following examples were prepared according to similar procedures described for Example 53:

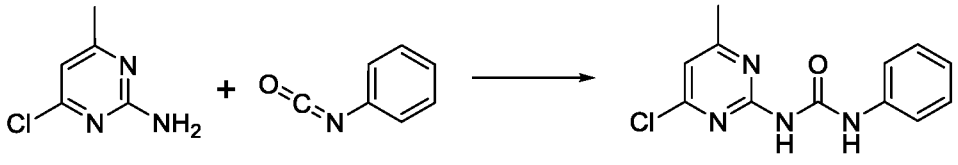
Cpd ID	Example ID	Structure	HPLC Method	Yield (mass/%)	RT (min)	MH^+
64	**54**		**4**	**66mg, 86**	**1.72**	**417.2-419.2**
65	**55**		**4**	**37mg, 48**	**1.73**	**431.2-433.2**
66	**56**		**4**	**100mg, 88**	**1.78**	**443.2-445.1**
67	**57**		**4**	**62mg, 85**	**1.78**	**415.1-417.1**

Example 58: Synthesis of 1-(4-((3-(dimethylamino)propyl)amino)-6-methylpyrimidin-2-yl)-3-phenylurea (69)



69

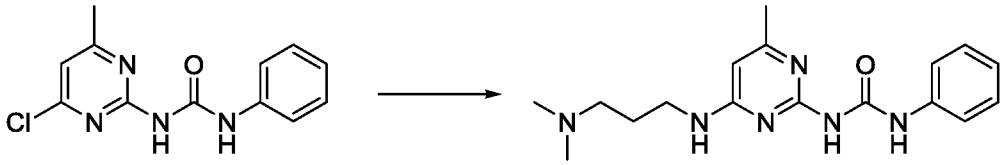
[00440] Step 1: 1-(4-Chloro-6-methyl-2-pyrimidinyl)-3-phenylurea (**68**)



68

[00441] A mixture of 2-amino-4-chloro-6-methylpyrimidine (72.0 mg, 0.5 mmol) and phenyl isocyanate (90.0 mg, 0.75 mmol) in 1,4-dioxane (1.00 mL) was heated for 3 hours at 100 °C. Volatiles were removed under vacuum and the residue was triturated with MeOH, filtered and dried to yield compound (**68**) (78.0 mg, 58%) as a white solid.

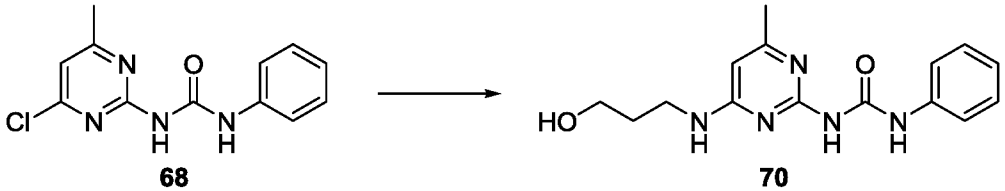
[00442] Step 2: 1-(4-((3-(dimethylamino)propyl)amino)-6-methylpyrimidin-2-yl)-3-phenylurea (**69**)



68 **69**

[00443] A mixture of 1-(4-chloro-6-methyl-2-pyrimidinyl)-3-phenylurea (**68**) (37.0 mg, 0.143 mmol), and 3-(dimethylamino)-1-propylamine (107 mg, 1.05 mmol) in DMA (1.0 mL) was heated for 3 hours at 100 °C. The reaction mixture was cooled and treated with water. A white precipitate was filtered and air dried to yield the title compound (**69**) (41 mg, 87%). LC/MS: Rt = 4.41 min, *m/z* = 329.4 [MH^+].

Example 59: Synthesis of 1-(4-((3-hydroxypropyl)amino)-6-methylpyrimidin-2-yl)-3-phenylurea (70)

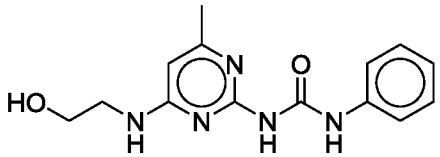


68 **70**

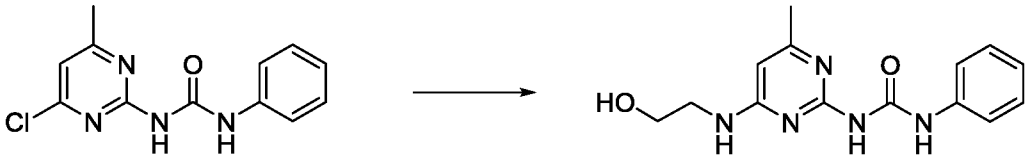
[00444] A mixture of 1-(4-chloro-6-methyl-2-pyrimidinyl)-3-phenylurea (**68**) (37 mg, 0.143 mmol) and 3-amino-1-propanol (54 mg, 0.715 mmol) in DMA (1.0 mL) was heated for 3 hours at 100 °C. The mixture was cooled and treated with water. A white precipitate was filtered and

air-dried to yield the title compound (**70**) (23 mg, 53%). LC/MS: Rt = 0.05 min, *m/z* = 423.1 [MH^+].

Example 60: Synthesis of 1-(4-((2-aminopropyl)amino)-6-methylpyrimidin-2-yl)-3-(3,4-dichlorophenyl)urea (71)



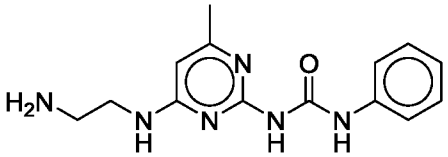
71



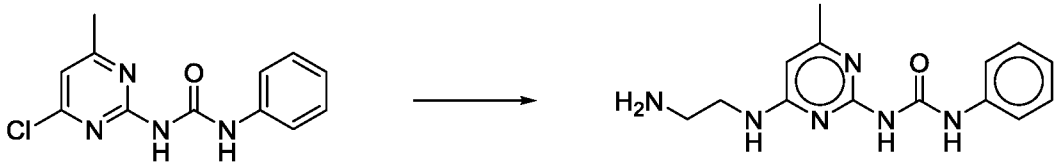
68 **71**

[00445] A mixture of 1-(4-chloro-6-methyl-2-pyrimidinyl)-3-phenylurea (**68**) (0.3g, 1.1 mmol) and toluene (1.5 mL) was treated with triethylamine (0.21mL, 1.5mmol) and 2-aminoethanol (0.08 mL, 1.2 mmol), and then heated to reflux with stirring.. Upon cooling a precipitate formed which was filtered and washed with methanol and diethyl ether to give the title compound (**71**) (0.26 g, 85%). LC/MS: Method 4: Rt = 1.75 min, m/z = 288.1 [MH+].

Example 61: Synthesis of 1-(4-((2-aminoethyl)amino)-6-methylpyrimidin-2-yl)-3-phenylurea (72)



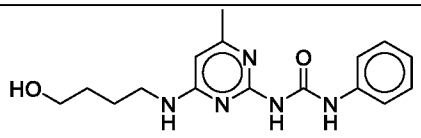
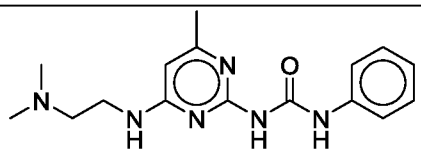
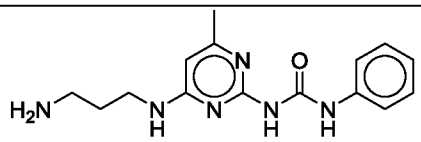
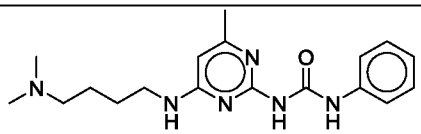
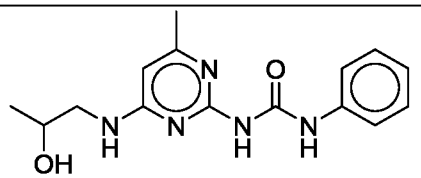
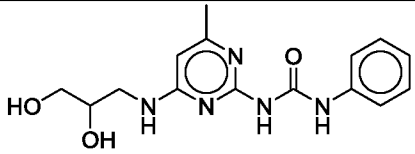
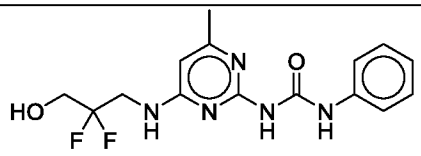
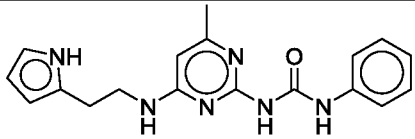
72



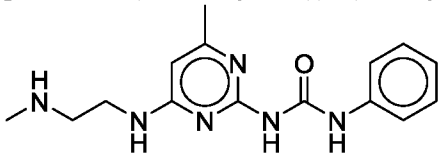
68 **72**

[00446] 1-(4-chloro-6-methyl-2-pyrimidinyl)-3-phenylurea (**68**) (0.2 g, 0.76 mmol) was suspended in 2-propanol (1.5mL). To this was added triethylamine (0.15 mL, 1.1 mmol) and then ethane-1,2-diamine (0.06 mL, 0.91 mmol), and the mixture was heated to reflux with stirring overnight. Upon cooling a precipitate formed which was filtered to give the title compound (**72**) (0.21 g, 91%). LC/MS: Method 4: Rt = 0.86 min, m/z = 287.2 [MH+] .

[00447] The following examples were prepared according to similar procedures described for Examples 58-61:

Cpd ID	Example ID	Structure	HPLC Method	Yield (mass/%)	RT (min)	MH^+
73	62		4	110mg, 32	1.96	316.2
74	63		4	61mg, 44	0.36	315.2
75	64		4	61mg, 22	0.41	301.2
76	65		4	80mg, 32	0.36	343.3
77	66		4	23mg, 15	0.34	302.2
78	67		4	72mg, 60	1.29	318.2
79	68		4	22mg, 17	1.64	338.2
80	69		4	28mg, 20	1.97	337.2

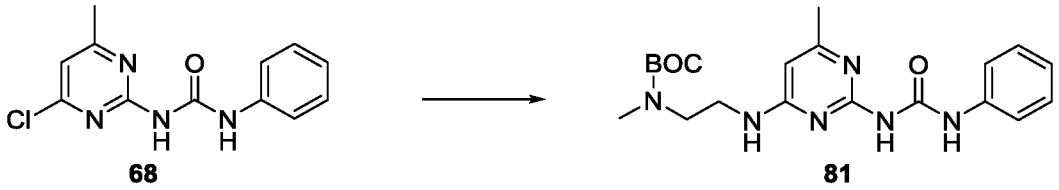
Example 70: 1-(4-methyl-6-((2-(methylamino)ethyl)amino)pyrimidin-2-yl)-3-phenylurea



82

(82)

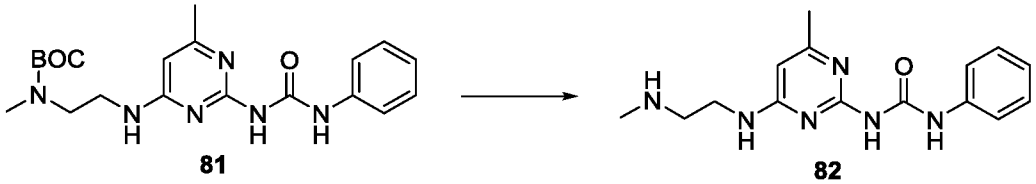
[00448] Step 1: *tert*-butyl methyl(2-((6-methyl-2-(3-phenylureido)pyrimidin-4-yl)amino)ethyl)carbamate (**81**)



68 81

[00449] A mixture of 1-(4-chloro-6-methyl-2-pyrimidinyl)-3-phenylurea (**68**) (200 mg, 0.78 mmol) and toluene (1.2 mL) was treated with N-(2-aminoethyl)-N-methyl carbamic acid tert-butyl ester (0.17 mL, 0.94 mmol), and triethylamine (0.16 mL, 1.2 mmol) and this was heated to reflux with stirring. Upon cooling methanol was added and the precipitate formed was filtered and washed with diethyl ether to give the title compound (**81**) (212 mg, 64%). LC/MS: Method 4: Rt = 0.36 min, m/z = 401.3 [MH+].

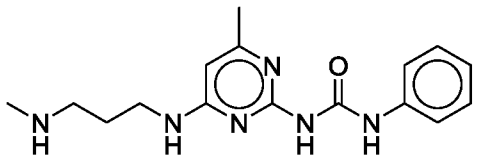
[00450] Step 2: 1-(4-methyl-6-((2-(methylamino)ethyl)amino)pyrimidin-2-yl)-3-phenylurea



81 82

[00451] The BOC derivative (**81**) (0.2 g, 0.5 mmol) was suspended in DCM (5 mL) to which trifluoroacetic acid (0.98 mL, 12 mmol) was added. The reaction mixture was stirred for 15 minutes at room temperature before evaporation of the solvent. This mixture was treated with DCM and 1N NaOH solution (0.5mL, 0.5 mmol) and the mixture stirred for 10-30 minutes. The suspension was filtered to yield the title product (**82**) as a white solid (145 mg, 86%) LC/MS: Method 4: Rt = 0.36 min, *m/z* = 301.2 [MH^+].

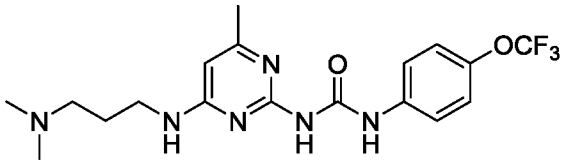
Example 71: 1-(4-methyl-6-((3-(methylamino)propyl)amino)pyrimidin-2-yl)-3-phenylurea (83)



83

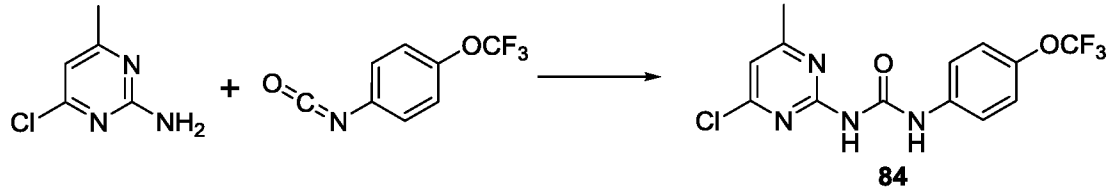
[00452] Example **71** was prepared by a procedure similar to example **70** from 1-(4-chloro-6-methyl-2-pyrimidinyl)-3-phenylurea (**68**) and N-(3-aminopropyl)-N-methyl carbamic acid tert-butyl ester. (28 mg, 11%) LC/MS: Method 4: Rt = 0.38 min, *m/z* = 315.2 [MH^+].

Example 72: Synthesis of 1-(4-((3-(dimethylamino)propyl)amino)-6-methylpyrimidin-2-yl)-3-(4-(trifluoromethoxy)phenyl)urea (85)



85

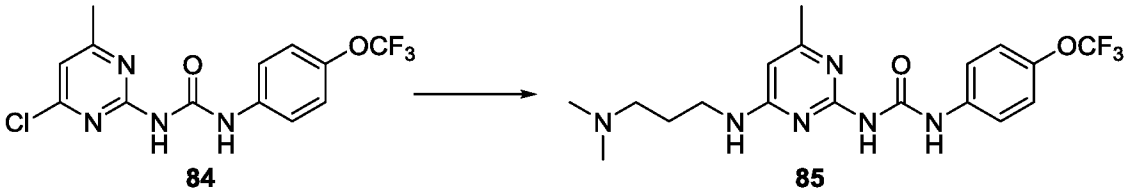
[00453] Step 1: 1-(4-Chloro-6-methyl-2-pyrimidinyl)-3-(p-trifluoromethoxyphenyl)urea (**84**)



84

[00454] A mixture of 2-amino-4-chloro-6-methylpyrimidine (72.0 mg, 0.5 mmol) and 4-(trifluoromethoxy)phenyl isocyanate (152.0 mg, 0.75 mmol) in dioxane (1.00 mL) was heated for 3 hours at 100 °C. Volatiles were removed under vacuum and the residue was triturated with MeOH, filtered and dried to yield compound (**84**) (120.0 mg, 69%) as a white solid.

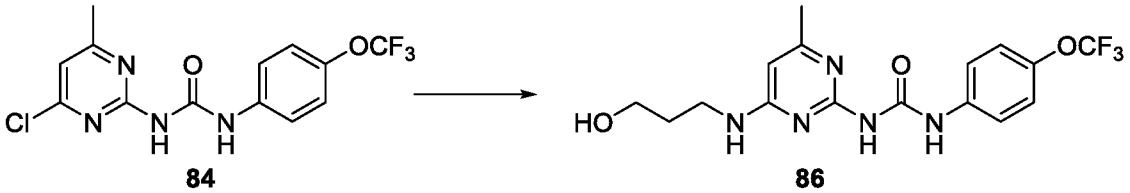
[00455] Step 2: 1-(4-((3-(dimethylamino)propyl)amino)-6-methylpyrimidin-2-yl)-3-(4-(trifluoromethoxy)phenyl)urea (**85**)



84 **85**

[00456] A mixture of 1-(4-chloro-6-methyl-2-pyrimidinyl)-3-(p-trifluoromethoxyphenyl)urea (**25**) (60 mg, 0.173 mmol), and 3-(dimethylamino)-1-propylamine (54 mg, 1.05 mmol) in DMA (1.0 mL) was heated for 3 hrs at 100 °C. The reaction mixture was cooled and treated with water. A white precipitate was filtered and air dried to yield the title compound (**26**) (41 mg, 57%). LC/MS: Rt = 0.33 min, *m/z* = 413.3 [MH^+].

Example 73: Synthesis of 1-(4-((3-hydroxypropyl)amino)-6-methylpyrimidin-2-yl)-3-(4-(trifluoromethoxy)phenyl)urea (86)

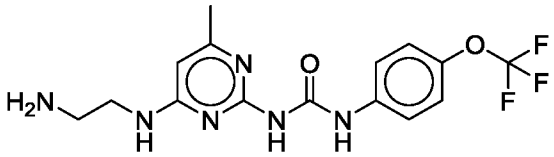


84 **86**

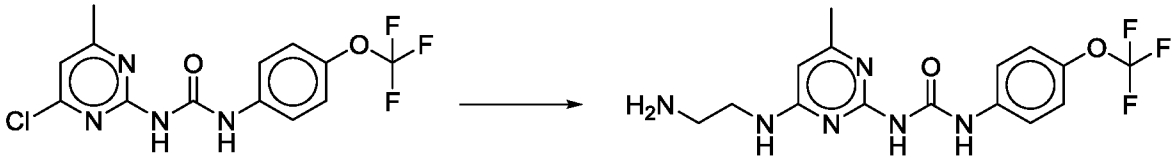
[00457] A mixture of 1-(4-chloro-6-methyl-2-pyrimidinyl)-3-(p-trifluoromethoxyphenyl)urea (**84**) (60 mg, 0.17 mmol) and 3-amino-1-propanol (65 mg, 0.86 mmol) in DMA (1.0 mL) was

heated for 3 hours at 100 °C. The mixture was cooled. A white precipitate was filtered and air-dried to yield the title compound (**86**) (35 mg, 52%). LC/MS: Rt = 0.13 min, *m/z* = 386.4 [MH^+].

Example 74: Synthesis of 1-(4-((2-aminoethyl)amino)-6-methylpyrimidin-2-yl)-3-(4-(trifluoromethoxy)phenyl)urea (87)



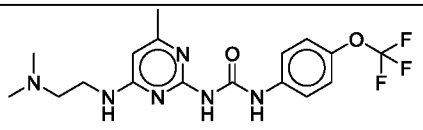
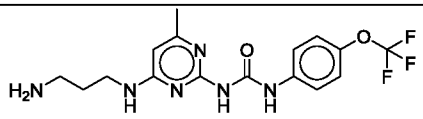
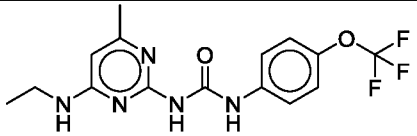
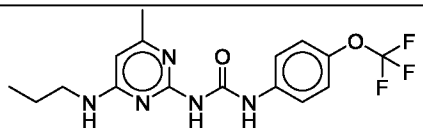
87

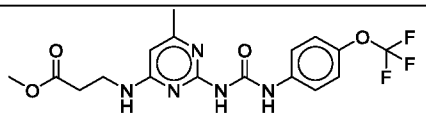
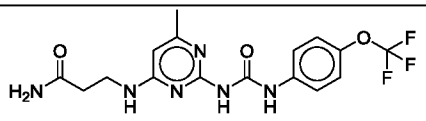
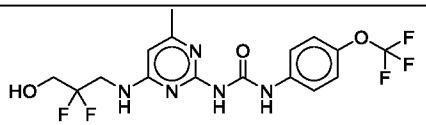
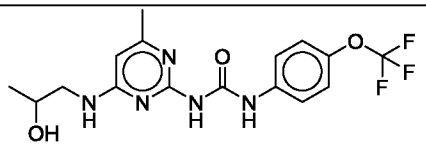
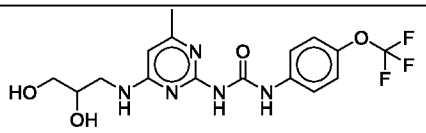


84 **87**

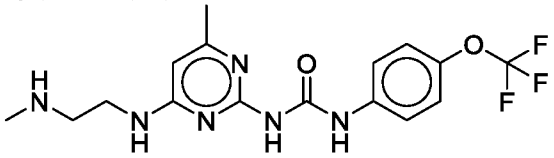
[00458] A mixture of 1-(4-chloro-6-methyl-2-pyrimidinyl)-3-(p-trifluoromethoxyphenyl)urea (**84**) (75 mg, 0.21 mmol) was suspended in 2-propanol (0.4 mL). To this mixture was added triethylamine (0.04 mL, 0.32mmol) and then ethane-1,2-diamine (0.02 mL, 0.25 mmol), and the mixture was heated to reflux with stirring for several hours. Upon cooling and dilution with methanol (3mL), a precipitate formed which was filtered to give the title compound (**87**) (54 mg, 68%). LC/MS: Method 4: Rt = 1.50 min, m/z = 386.4 [MH^+].

[00459] The following examples were prepared according to similar procedures described for Examples 72-74:

Cpd ID	Example ID	Structure	HPLC Method	Yield (mass/%)	RT (min)	MH^+
88	**75**		**4**	**33 mg, 39**	**1.45**	**400.2**
89	**76**		**4**	**45 mg, 54**	**1.59**	**386.2**
90	**77**		**4**	**54 mg, 71**	**2.27**	**357.2**
91	**78**		**4**	**64 mg, 80**	**2.45**	**371.2**

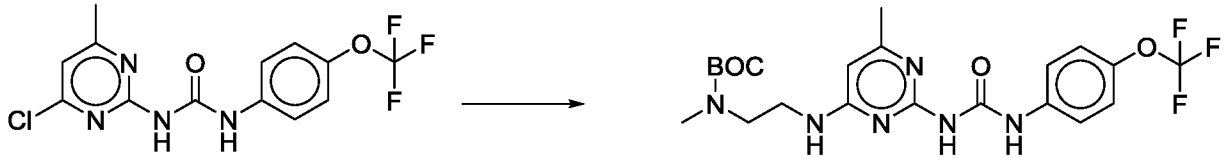
92	**79**		**4**	**66 mg, 74**	**2.34**	**415.2**
93	**80**		**4**	**55 mg, 64**	**1.94**	**399.2**
94	**81**		**4**	**18 mg, 20**	**2.32**	**422.2**
95	**82**		**4**	**52 mg, 62**	**2.01**	**386.2**
96	**83**		**4**	**38 mg, 44**	**1.90**	**403.2**

Example 84: Synthesis of 1-(4-methyl-6-((2-(methylamino)ethyl)amino)pyrimidin-2-yl)-3-(4-(trifluoromethoxy)phenyl)urea (98)



98

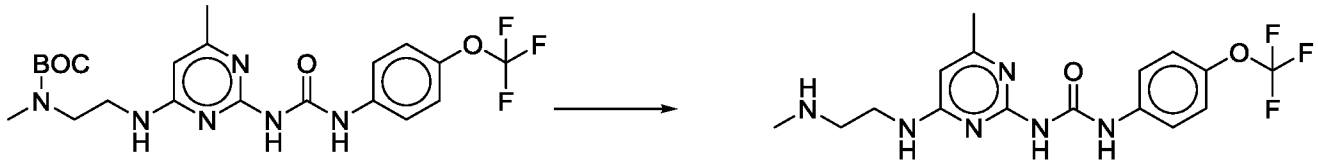
[00460] Step 1: *tert*-Butyl methyl(2-((6-methyl-2-(3-(4-(trifluoromethoxy)phenyl)ureido)pyrimidin-4-yl)amino)ethyl)carbamate (**97**)



84 **97**

[00461] A mixture of 1-(4-chloro-6-methyl-2-pyrimidinyl)-3-(p-trifluoromethoxyphenyl)urea (**84**) (75 mg, 0.22 mmol) and 2-propanol (0.43 mL) was treated with N-(2-aminoethyl)-N-methyl carbamic acid tert-butyl ester (0.05 mL, 0.25 mmol), and triethylamine (0.05 mL, 0.32 mmol) and this was heated to reflux with stirring for 5 hours. Upon cooling methanol (3 mL) was added and the precipitate formed was filtered to give the title compound (**97**) (68 mg, 65%). LC/MS: Method 4: Rt = 2.74 min, m/z = 485.3 [MH+].

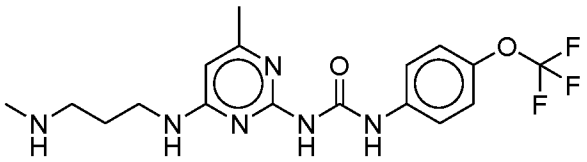
[00462] Step 2: 1-(4-methyl-6-((2-(methylamino)ethyl)amino)pyrimidin-2-yl)-3-(4-(trifluoromethoxy)phenyl)urea



97 98

[00463] The BOC derivative (**97**) (75 mg, 0.16 mmol) was suspended in DCM (0.12 mL) to which trifluoroacetic acid (0.12 mL, 1.6 mmol) was added. After 5 hours at room temperature the mixture was treated with saturated sodium bicarbonate solution until a pH of 8 was reached. The suspension so formed was filtered to yield the title product (**98**) as a white solid (59 mg, 97%) LC/MS: Method 4: Rt = 1.50 min, *m/z* = 385.2 [MH^+].

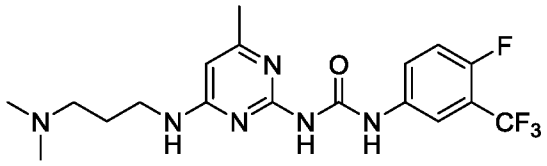
Example 85: 1-[4-Methyl-6-(3-methylamino-propylamino)-pyrimidin-2-yl]-3-(4-trifluoromethoxy-phenyl)-urea (99)



99

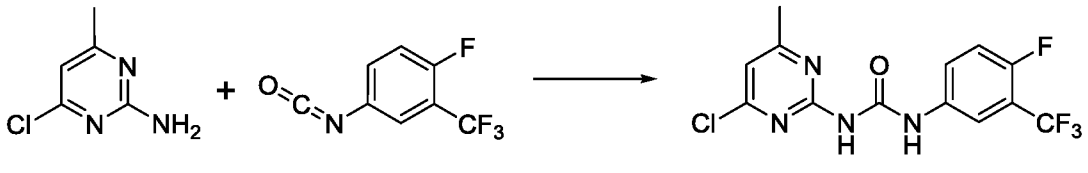
[00464] Example **85** was prepared by a procedure similar to example **84** from 1-(4-chloro-6-methyl-2-pyrimidinyl)-3-(p-trifluoromethoxyphenyl)urea (**84**) and N-(3-aminopropyl)-N-methyl carbamic acid tert-butyl ester except the intermediate carbamate was first purified by preparative TLC eluting with 10% 1M NH_4OH in MeOH/90% DCM (36 mg, 41%) LC/MS: Method 4: Rt = 1.57 min, *m/z* = 400.2 [MH^+].

Example 86: Synthesis of 3-(dimethylamino)-1-(2-{3-[4-fluoro-3-(trifluoromethyl)phenyl]ureido}-6-methyl-4-pyrimidinylamino)propane (101)



101

[00465] Step 1: 1-(4-Chloro-6-methyl-2-pyrimidinyl)-3-[4-fluoro-3-(trifluoromethyl)-phenyl]urea (**100**)

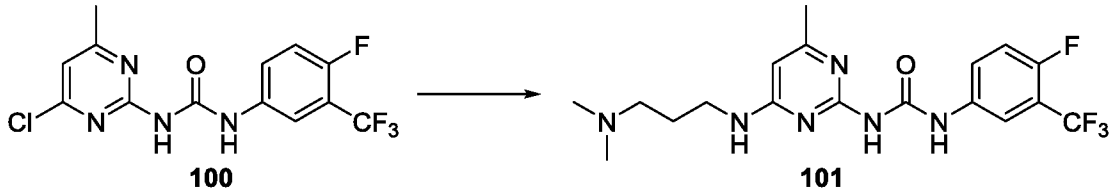


100

[00466] A mixture of 2-amino-4-chloro-6-methylpyrimidine (72 mg, 0.5 mmol) and 4-fluoro-3-(trifluoromethyl)phenyl isocyanate (154 mg, 0.75 mmol) in 1,4-dioxane (1 mL) was heated for 3

hours at 100 °C. The reaction mixture was cooled and precipitated product was filtered, washed with 1,4-dioxane and dried to yield compound (**100**) (144 mg, 83%) as a white solid.

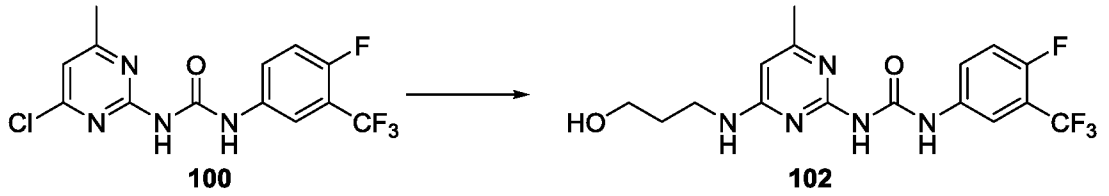
[00467] Step 2: 3-(Dimethylamino)-1-(2-{3-[4-fluoro-3-(trifluoromethyl)phenyl]ureido}-6-methyl-4-pyrimidinylamino)propane (**101**)



100 **101**

[00468] A mixture of 1-(4-chloro-6-methyl-2-pyrimidinyl)-3-[4-fluoro-3-(trifluoromethyl)-phenyl]urea (**100**) (60 mg, 0.172 mmol) and 3-(dimethylamino)-1-propylamine (53 mg, 0.516 mmol) in DMA (1 mL) was heated for 3 hours at 100 °C. The mixture was cooled and treated with water. A white precipitate was filtered and air-dried to yield the title compound (**101**) (50 mg, 70%). LC/MS: Rt = 0.32 min, *m/z* = 415.5 [MH^+].

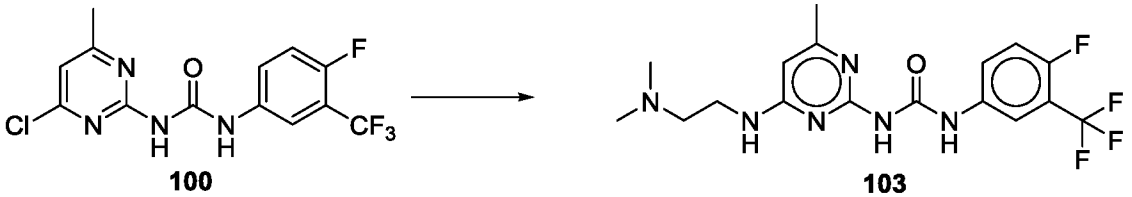
Example 87: Synthesis of 1-(4-fluoro-3-(trifluoromethyl)phenyl)-3-(4-((3-hydroxypropyl)amino)-6-methylpyrimidin-2-yl)urea (102)



100 **102**

[00469] A mixture of 1-(4-chloro-6-methyl-2-pyrimidinyl)-3-[4-fluoro-3-(trifluoromethyl)-phenyl]urea (**100**) (84 mg, 0.24 mmol) and 3-amino-1-propanol (91 mg, 1.2 mmol) in DMA (1.0 mL) was heated for 3 hours at 100 °C. The mixture was cooled and treated with water. A white precipitate was filtered and air-dried to yield the title compound (**102**) (66 mg, 71%). LC/MS: Rt = 0.21 min, *m/z* = 388.5 [MH^+].

Example 88: Synthesis of 1-(4-fluoro-3-(trifluoromethyl)phenyl)-3-(4-((2-(dimethylamino)ethyl)amino)-6-methylpyrimidin-2-yl)urea (103)

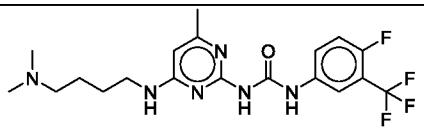
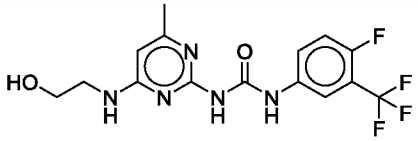
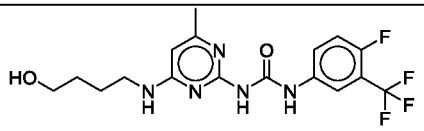
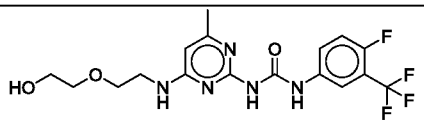
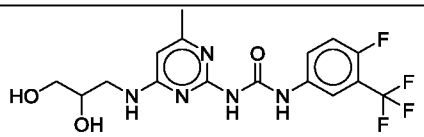
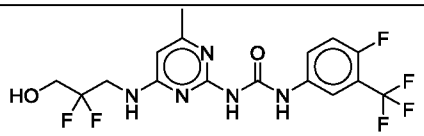
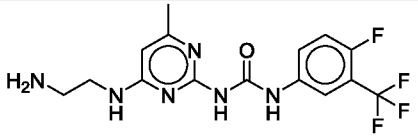
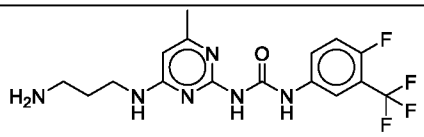
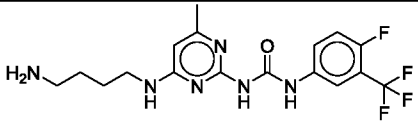
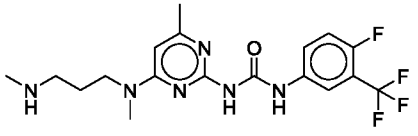


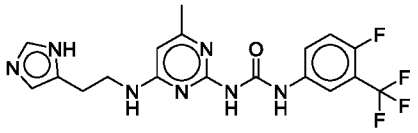
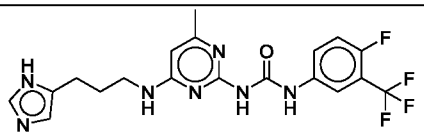
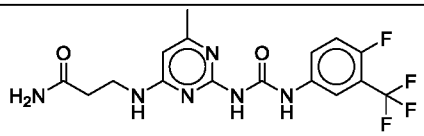
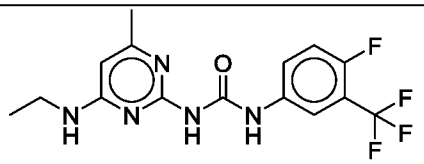
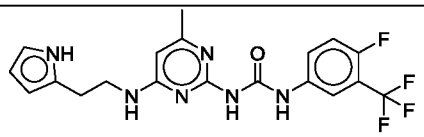
100 **103**

[00470] A suspension of 3-(4-fluoro-6-methyl-2-pyrimidinyl)-1-[4-chloro-3-(trifluoromethyl) phenyl]urea (**100**) (100 mg, 0.26 mmol), N,N-dimethylethylene-diamine (0.04 mL, 0.33 mmol) and trimethylamine (0.06 mL, 0.41 mmol) in 2-propanol (1mL) was heated to reflux at 90°C. After 30 minutes the mixture was cooled to ambient temperature and diluted with MeOH. The

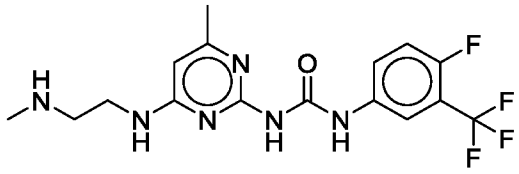
title compound (**103**) was filtered as a white solid. (65 mg, 57%). LC/MS: Method 4: Rt = 1.57 min, m/z = 401.2 [MH+].

[00471] The following examples were prepared according to similar procedures described for Examples 86-88:

Cpd ID	Example ID	Structure	HPLC Method	Yield (mass/%)	RT (min)	MH^+
104	**89**		**4**	**37 mg, 30**	**1.68**	**429.3**
105	**90**		**4**	**56 mg, 52**	**1.86**	**374.2**
106	**91**		**4**	**80 mg, 70**	**2.07**	**403.2**
107	**92**		**4**	**72 mg, 60**	**1.93**	**418.2**
108	**93**		**4**	**35 mg, 61**	**1.90**	**404.2**
109	**94**		**4**	**24 mg, 39**	**2.40**	**426.2**
110	**95**		**4**	**17 mg, 32**	**1.57**	**373.2**
111	**96**		**4**	**30 mg, 54**	**1.57**	**387.2**
112	**97**		**4**	**41 mg, 71**	**1.61**	**401.2**
113	**98**		**4**	**51 mg, 86**	**1.73**	**415.2**

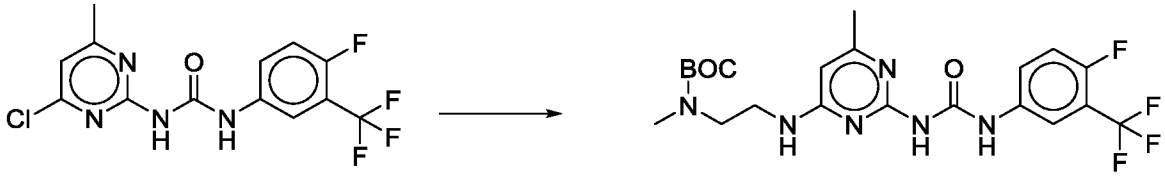
114	**99**		**4**	**27 mg, 44**	**1.52**	**424.2**
115	**100**		**4**	**41 mg, 65**	**1.61**	**438.2**
116	**101**		**4**	**40 mg, 70**	**1.90**	**402.2**
117	**102**		**4**	**40 mg, 78**	**2.29**	**359.2**
118	**103**		**4**	**23 mg, 38**	**2.54**	**423.2**

Example 104: Synthesis of 1-(4-fluoro-3-(trifluoromethyl)phenyl)-3-(4-methyl-6-((2-(methylamino)ethyl)amino)pyrimidin-2-yl)urea (120)



120

[00472] Step 1: *tert*-Butyl (2-((2-(3-(4-fluoro-3-(trifluoromethyl)phenyl)ureido)-6-methylpyrimidin-4-yl)amino)ethyl)(methyl)carbamate (**119**)

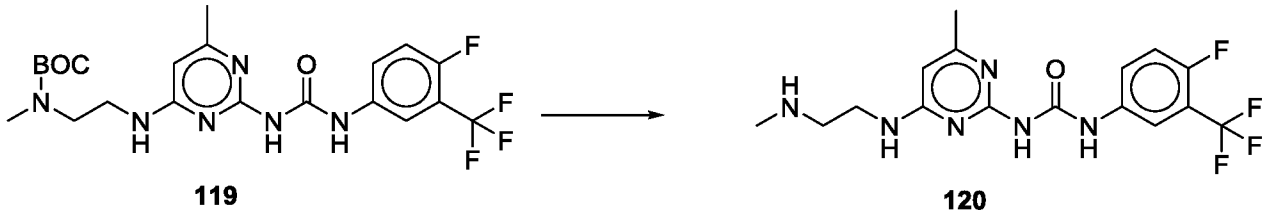


100 **119**

[00473] A mixture of 1-(4-chloro-6-methyl-2-pyrimidinyl)-3-[4-fluoro-3-(trifluoromethyl)-phenyl]urea (**100**) (100 mg, 0.27 mmol) and 2-propanol (1 mL) was treated with N-(2-aminoethyl)-N-methyl carbamic acid tert-butyl ester (0.06 mL, 0.32 mmol), and triethylamine (0.06 mL, 0.41 mmol) and this was heated to reflux with stirring for 30 minutes. Upon cooling

ethanol was added and the precipitate formed was filtered to give the title compound (**119**) (116 mg, 83%). LC/MS: Method 4: Rt = 2.77 min, m/z = 487.3 [MH+].

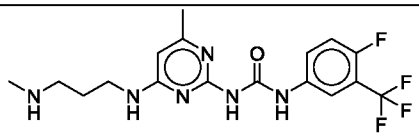
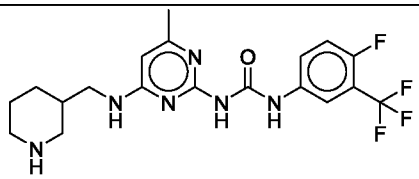
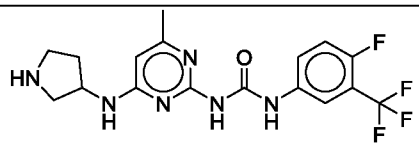
[00474] Step 2: 1-(4-fluoro-3-(trifluoromethyl)phenyl)-3-(4-methyl-6-((2-(methylamino)ethyl)amino)pyrimidin-2-yl)urea



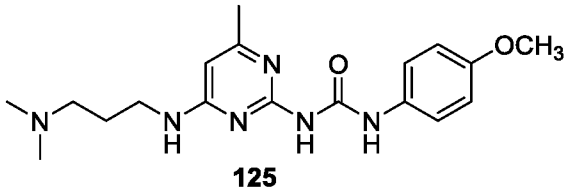
119 **120**

[00475] The BOC derivative (**119**) (116 mg, 0.12 mmol) was suspended in DCM (1.2 mL) to which trifluoroacetic acid (0.18 mL, 2.26 mmol) was added. After 3 hours at room temperature, the mixture was warmed to 45°C and stirred overnight. After cooling the solvent was evaporated and the residue treated with saturated sodium bicarbonate solution. The solvent was evaporated and the resulting residue was purified by flash chromatography (gradient elution, 0-25% 3M NH_3 in MeOH over CH_2Cl_2) to obtain the desired compound as a white solid (**120**) (77 mg, 84%). LC/MS: Method 4: Rt = 1.38 min, *m/z* = 387.2 [MH^+].

[00476] The following examples were prepared according to similar procedures described for Example 104:

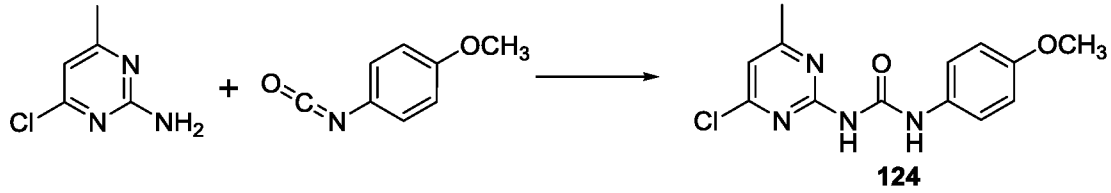
Cpd ID	Example ID	Structure	HPLC Method	Yield (mass/%)	RT (min)	MH^+
121	**105**		**4**	**69 mg, 60**	**1.57**	**401.2**
122	**106**		**4**	**89 mg, 73**	**1.51**	**428.2**
123	**107**		**4**	**75 mg, 66**	**1.49**	**400.2**

Example 108: Synthesis of 1-(4-((3-(dimethylamino)propyl)amino)-6-methylpyrimidin-2-yl)-3-(4-methoxy)phenyl)urea (125)



125

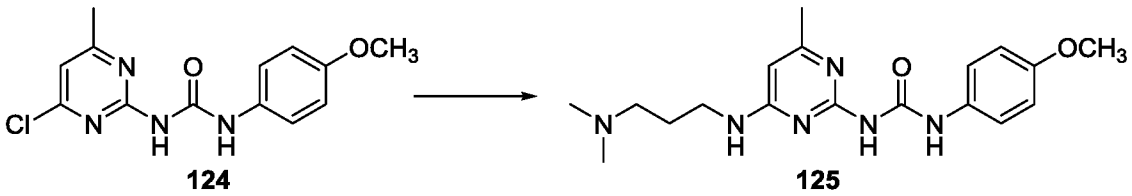
[00477] Step 1: 1-(4-Chloro-6-methyl-2-pyrimidinyl)-3-(4-methoxyphenyl)urea (**124**)



124

[00478] A mixture of 2-amino-4-chloro-6-methylpyrimidine (2.6 g, 17.6 mmol) and 4-methoxyphenyl isocyanate (2.7 g, 17.6 mmol) in toluene (31 mL) was refluxed under a stream of N_2 overnight. On cooling the suspension was filtered, washed with EtOH and Et_2O and dried to yield compound (**124**) (5.1 g, 65%) as a white solid. LC/MS: Method 4: Rt = 2.95 min, *m/z* = 293.1 [MH^+].

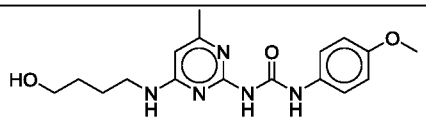
[00479] Step 2: 1-(4-((3-(Dimethylamino)propyl)amino)-6-methylpyrimidin-2-yl)-3-(4-(methoxy)phenyl)urea (**125**)

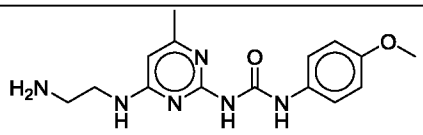
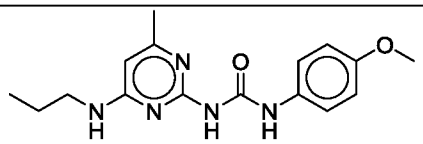
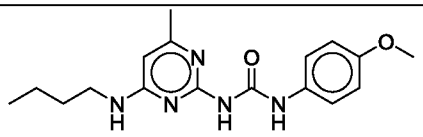
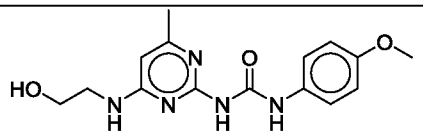
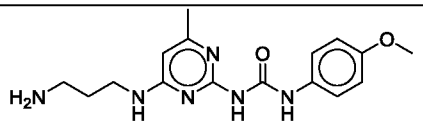
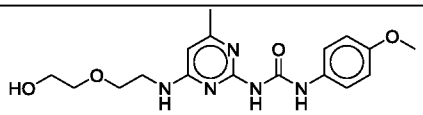
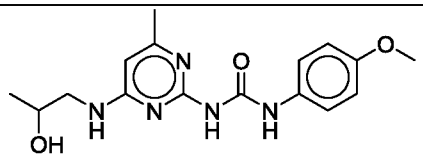
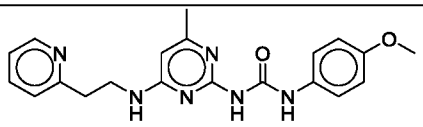
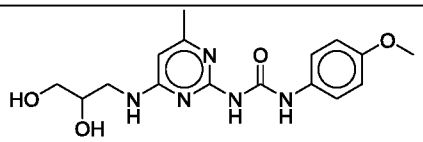
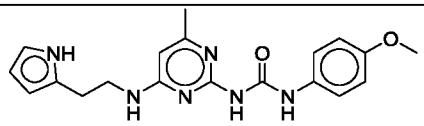
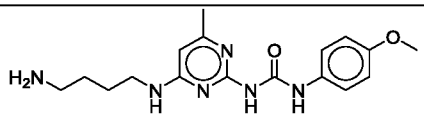
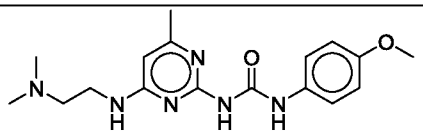


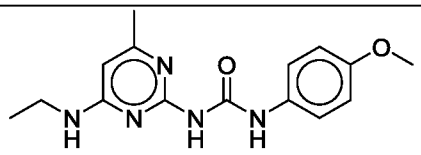
124 **125**

[00480] A mixture of 1-(4-chloro-6-methyl-2-pyrimidinyl)-3-(p-methoxyphenyl)urea (**124**) (100 mg, 0.32 mmol), and 3-(dimethylamino)-1-propylamine (0.05 mL, 0.39 mmol) and triethylamine (0.07 mL, 0.49 mmol) in 2-propanol (0.5 mL) was heated for 2 hrs at 80 °C. The reaction mixture was cooled and the white precipitate was filtered to yield the title compound (**125**) (53 mg, 43%). LC/MS: Method 4: Rt = 1.02 min, *m/z* = 359.3 [MH^+].

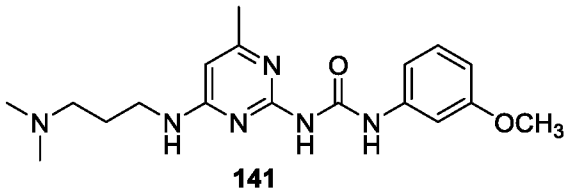
[00481] The following examples were prepared according to similar procedures described for Example 108:

Cpd ID	Example ID	Structure	HPLC Method	Yield (mass/%)	RT (min)	MH^+
126	**109**		**4**	**206 mg, 77**	**1.61**	**346.2**

127	110		4	83 mg, 31	1.1	317.2
128	111		4	100 mg, 40	1.97	316.2
129	112		4	222 mg, 85	2.22	330.2
130	113		4	189 mg, 78	1.48	318.2
131	114		4	229 mg, 75	1.05	331.2
132	115		4	120 mg, 42	1.52	362.2
133	116		4	86 mg, 69	1.51	333.2
134	117		4	100 mg, 70	1.28	379.2
135	118		4	80 mg, 61	1.36	348.2
136	119		4	5 mg, 4	1.94	367.2
137	120		4	82 mg, 66	1.07	345.3
138	121		4	28 mg, 21	1.12	345.2

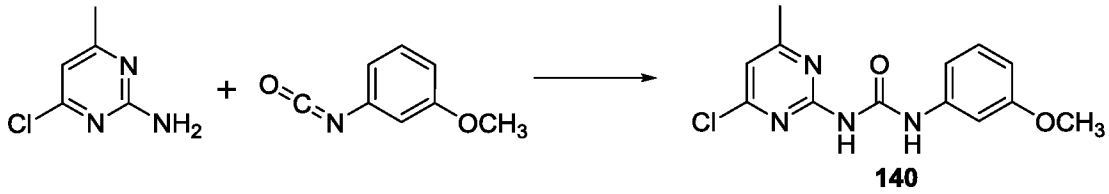
139	122		4	9mg, 8	1.76	302.2

Example 123: Synthesis of 1-(4-((3-(dimethylamino)propyl)amino)-6-methylpyrimidin-2-yl)-3-(3-methoxy)phenyl)urea (141)



141

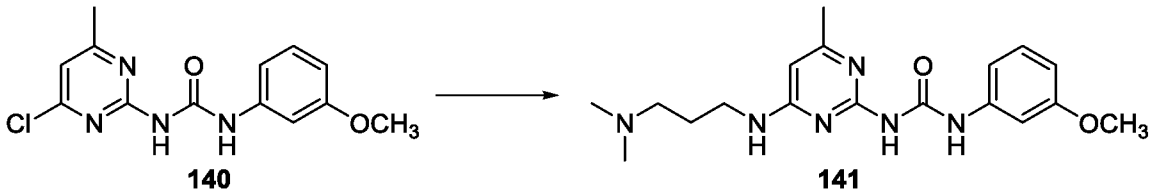
[00482] Step 1: 1-(4-Chloro-6-methyl-2-pyrimidinyl)-3-(3-methoxyphenyl)urea (**140**)



140

[00483] A mixture of 2-amino-4-chloro-6-methylpyrimidine (3 g, 20.9 mmol) and 3-methoxyphenyl isocyanate (3.4 g, 23.0 mmol) in N, N-dimethylacetamide (28 mL) was heated for 80 minutes at 100 °C. Upon cooling the mixture was diluted with MeOH (75mL), filtered and dried to yield compound (**140**) (3.1 g, 51%) as a white solid.

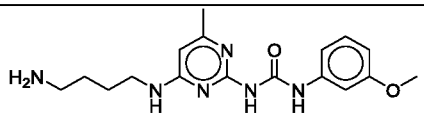
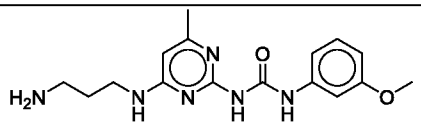
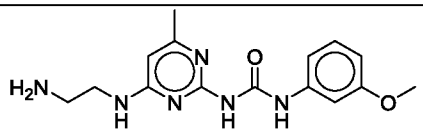
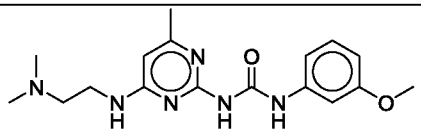
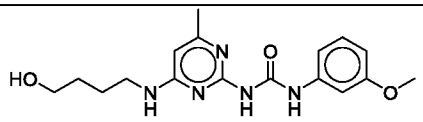
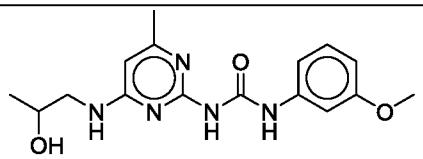
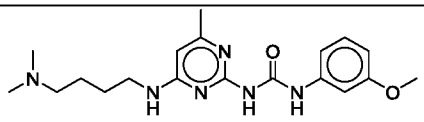
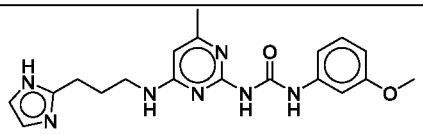
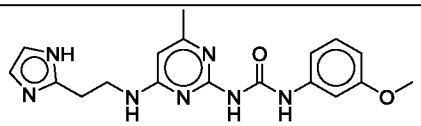
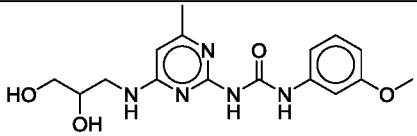
[00484] Step 2: 1-(4-((3-(dimethylamino)propyl)amino)-6-methylpyrimidin-2-yl)-3-(3-(methoxy)phenyl)urea (**141**)



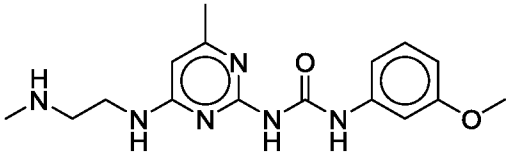
140 **141**

[00485] 1-(4-Chloro-6-methyl-2-pyrimidinyl)-3-(3-methoxyphenyl)urea (**140**) (75 mg, 0.26 mmol), and 3-(dimethylamino)-1-propylamine (0.04 mL, 0.31 mmol) and triethylamine (0.05 mL, 0.38mmol) in 2-propanol (0.5 mL) was heated for 23 hrs at 80 °C. The reaction mixture was cooled and diluted with 2-propanol (3 mL). A white precipitate was filtered and washed with ethanol to yield the title compound (**141**) (18 mg, 19%). LC/MS: Method 4: Rt = 0.32 min, *m/z* = 359.3 [MH^+].

[00486] The following examples were prepared according to similar procedures described for Example 123:

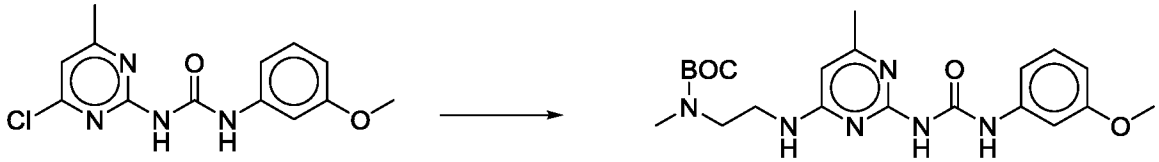
Cpd ID	Example ID	Structure	HPLC Method	Yield (mass/%)	RT (min)	MH^+
142	124		4	10 mg, 11	0.34	345.3
143	125		4	9 mg, 10	1.08	331.2
144	126		4	16 mg, 19	0.34	317.2
145	127		4	22 mg, 25	0.34	345.3
146	128		4	21 mg, 29	0.33	346.2
147	129		4	5 mg, 6	1.60	332.2
148	130		4	15 mg, 15	1.21	373.3
149	131		4	29 mg, 29	1.23	382.2
150	132		4	24 mg, 26	1.24	368.2
151	133		4	17 mg, 19	1.45	348.2

Example 134: Synthesis of 1-(3-methoxyphenyl)-3-(4-methyl-6-((2-(methylamino)ethyl)amino)pyrimidin-2-yl)urea (153)



153

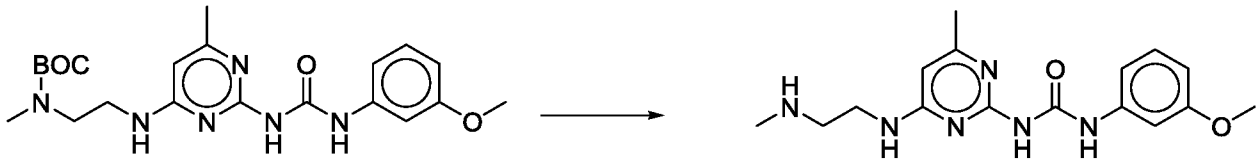
[00487] Step 1: *tert*-butyl (2-((2-(3-(3-methoxyphenyl)ureido)-6-methylpyrimidin-4-yl)amino)ethyl)(methyl)carbamate (**152**)



140 **152**

[00488] A mixture of 1-(4-chloro-6-methylpyrimidin-2-yl)-3-(3-methoxyphenyl)urea (**140**) (75 mg, 0.26 mmol) and 2-propanol (1 mL) was treated with N-(2-aminoethyl)-N-methyl carbamic acid tert-butyl ester (0.06 mL, 0.31 mmol), and triethylamine (0.05 mL, 0.38 mmol) and this was heated to reflux with stirring for 30 minutes. Upon cooling methanol (5 mL) was added and the precipitate formed was filtered to give the title compound (**152**) (69 mg, 62%).

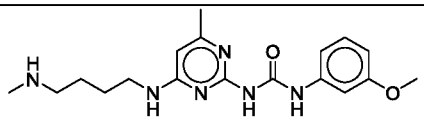
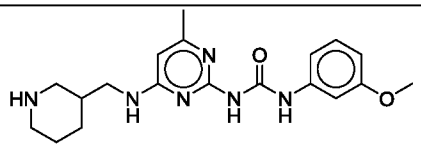
[00489] Step 2: 1-(3-methoxyphenyl)-3-(4-methyl-6-((2-(methylamino)ethyl)amino)pyrimidin-2-yl)urea



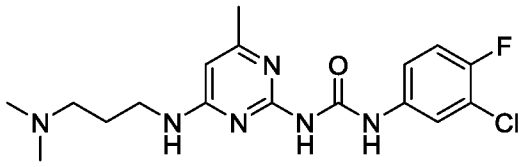
152 **153**

[00490] The BOC derivative (**152**) (69 mg, 0.16 mmol) was suspended in DCM (0.11 mL) to which trifluoroacetic acid (0.12 mL, 1.5 mmol) was added. After 2 hours at room temperature the mixture was treated with saturated sodium bicarbonate solution. The title product was filtered as a white solid (**153**) (19 mg, 37%). LC/MS: Method 4: Rt = 0.95 min, *m/z* = 331.2 [MH^+].

[00491] The following examples were prepared according to similar procedures described for Example 134:

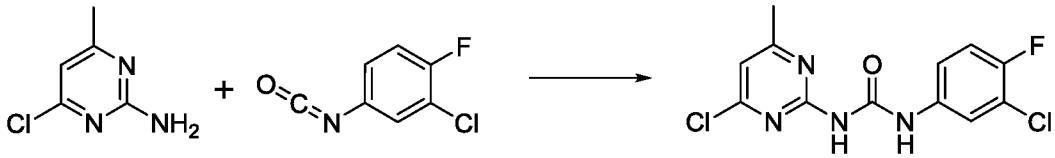
Cpd ID	Example ID	Structure	HPLC Method	Yield (mass/%)	RT (min)	MH^+
154	135		4	23 mg, 25	1.23	359.3
155	136		4	19 mg, 20	1.33	371.3

Example 137: Synthesis of 1-(3-chloro-4-fluorophenyl)-3-(4-((3-(dimethylamino)propyl)amino)-6-methylpyrimidin-2-yl)urea (157)



157

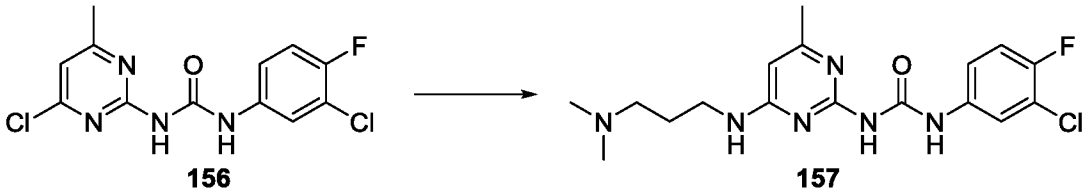
[00492] Step 1: 1-(3-chloro-4-fluorophenyl)-3-(4-chloro-6-methylpyrimidin-2-yl)urea (**156**)



156

[00493] A mixture of 2-amino-4-chloro-6-methylpyrimidine (5 g, 34 mmol) and 4-methoxyphenyl isocyanate (5.9 g, 34 mmol) in toluene (60 mL) was refluxed under a stream of N_2 overnight. On cooling, the suspension was filtered, washed with MeOH and Et_2O and dried to yield compound (**156**) (5.1 g, 48%) as a white solid. LC/MS: Method 4: Rt = 0.23 min, *m/z* = 315.0-317.1 [MH^+].

[00494] Step 2: 1-(4-((3-(dimethylamino)propyl)amino)-6-methylpyrimidin-2-yl)-3-(4-(methoxy)phenyl)urea (**157**)

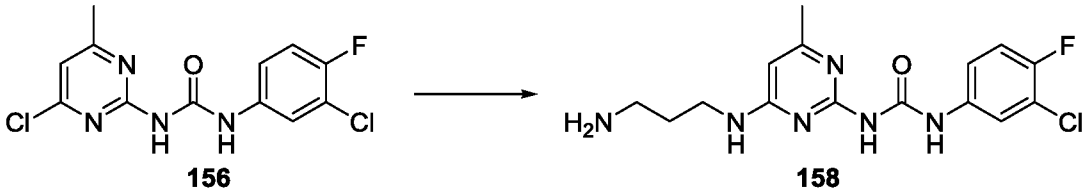


156 **157**

[00495] A mixture of 1-(3-chloro-4-fluorophenyl)-3-(4-chloro-6-methylpyrimidin-2-yl)urea (**156**) (100 mg, 0.30 mmol), and 3-(dimethylamino)-1-propylamine (0.04 mL, 0.36 mmol) and triethylamine (0.06 mL, 0.45 mmol) in 2-propanol (0.5 mL) was heated for 2 hrs at 80 ºC. The

reaction mixture was cooled and the white precipitate was filtered to yield the title compound (**157**) (83 mg, 69%). LC/MS: Method 4: Rt = 1.38 min, *m/z* = 382.2-384.2 [MH^+].

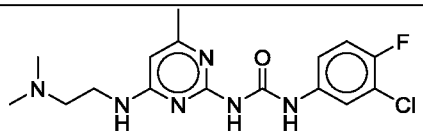
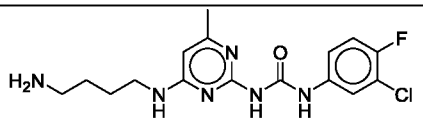
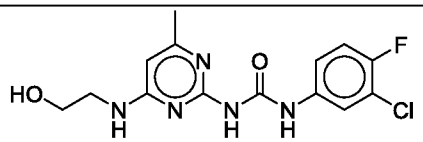
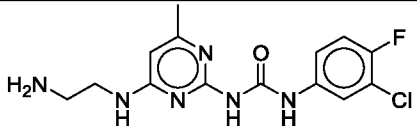
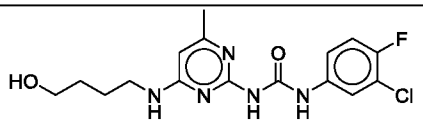
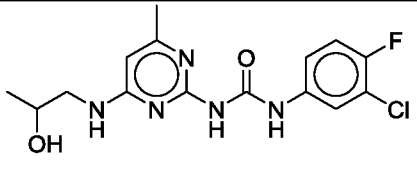
Example 138: Synthesis of 1-(4-((3-aminopropyl)amino)-6-methylpyrimidin-2-yl)-3-(3-chloro-4-fluorophenyl)urea (158)

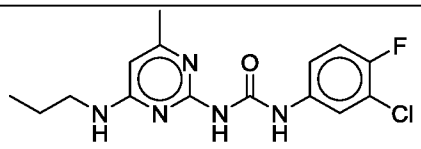
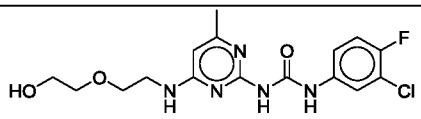
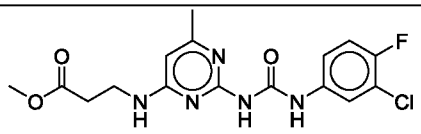


156 **158**

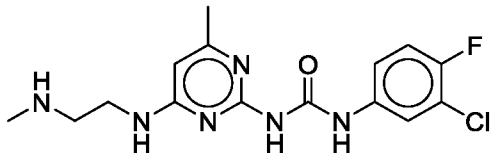
[00496] A mixture of 1-(3-chloro-4-fluorophenyl)-3-(4-chloro-6-methylpyrimidin-2-yl)urea (**156**) (148 mg, 0.45 mmol), and 1,3-diaminopropane (0.05 mL, 0.54 mmol) and triethylamine (0.06 mL, 0.45 mmol) in toluene (0.7 mL) was heated at reflux for 1.5 hrs. The reaction mixture was cooled and the white precipitate was filtered, then washed with MeOH and Et_2O to yield the title compound (**158**) (83 mg, 69%). LC/MS: Method 4: Rt = 0.39 min, *m/z* = 353.1-356.2 [MH^+].

[00497] The following examples were prepared according to similar procedures described for Example 137-138:

Cpd ID	Example ID	Structure	HPLC Method	Yield (mass/%)	RT (min)	MH^+
159	**139**		**4**	**150 mg, 76**	**0.38**	**367.2-370.2**
160	**140**		**4**	**140 mg, 76**	**0.36**	**367.2-369.2**
161	**141**		**4**	**80 mg, 59**	**0.34**	**340.1-342.1**
162	**142**		**4**	**102 mg, 67**	**1.52**	**339.1-341.1**
163	**143**		**4**	**109 mg, 71**	**2.02**	**368.2-370.2**
164	**144**		**4**	**155 mg, 67**	**1.99**	**354.2-356.1**

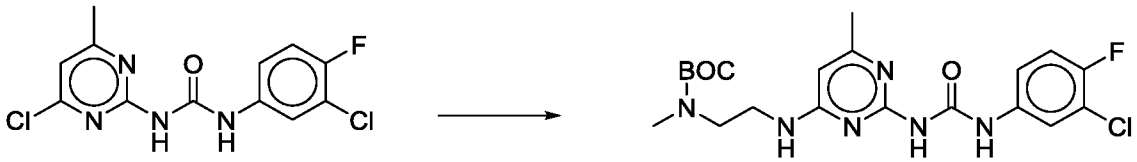
165	**145**		**4**	**201 mg, 86**	**0.32**	**338.2-340.2**
166	**146**		**4**	**37 mg, 15**	**0.35**	**384.2-386.2**
167	**147**		**4**	**56 mg, 22**	**2.33**	**382.2-384.2**

Example 148: Synthesis of 1-(3-chloro-4-fluorophenyl)-3-(4-methyl-6-((2-(methylamino)ethyl)amino)pyrimidin-2-yl)urea (169)



169

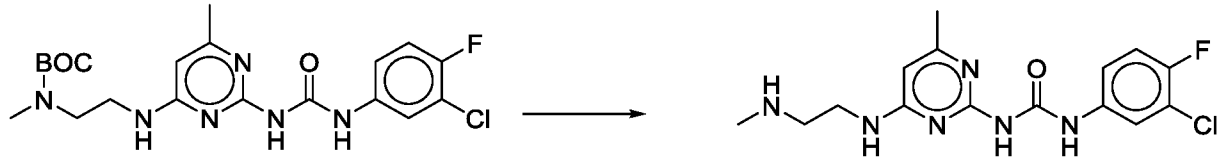
[00498] Step 1: *tert*-Butyl (2-((2-(3-(3-chloro-4-fluorophenyl)ureido)-6-methylpyrimidin-4-yl)amino)ethyl)(methyl)carbamate (**168**)



156 **168**

[00499] A mixture of 1-(3-chloro-4-fluorophenyl)-3-(4-chloro-6-methylpyrimidin-2-yl)urea (**156**) (206 mg, 0.62 mmol) and toluene (2.3 mL) was treated with N-(2-aminoethyl)-N-methyl carbamic acid tert-butyl ester (0.14 mL, 0.74 mmol), and triethylamine (0.13 mL, 0.93 mmol) and this was heated to reflux with stirring for 1 hour. Upon cooling the precipitate formed was filtered and washed with MeOH and Et_2O to give the title compound (**168**) (189 mg, 64%). LC/MS: Method 4: Rt = 0.33 min, *m/z* = 453.2-455.2 [MH^+].

[00500] Step 2: 1-(3-Chloro-4-fluorophenyl)-3-(4-methyl-6-((2-(methylamino)ethyl)amino)pyrimidin-2-yl)urea (**169**)

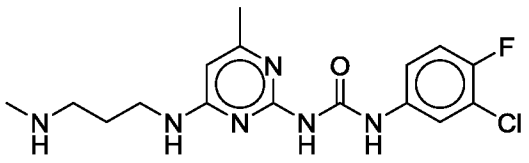


168 **169**

[00501] The BOC derivative (**168**) (189 mg, 0.40 mmol) was suspended in DCM (5 mL) to which trifluoroacetic acid (0.77 mL, 9.9 mmol) was added. After 15 minutes at room

temperature the solvent was evaporated and the residue treated with DCM and 1N sodium hydroxide solution. The title product was filtered and washed with water to yield a white solid (**169**) after drying. (117 mg, 79%) LC/MS: Method 4: Rt = 0.36 min, *m/z* = 353.2-355.2 [MH^+].

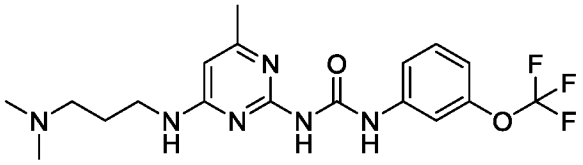
Example 149: Synthesis of 1-(3-chloro-4-fluorophenyl)-3-(4-methyl-6-((3-(methylamino)propyl)amino)pyrimidin-2-yl)urea (170)



170

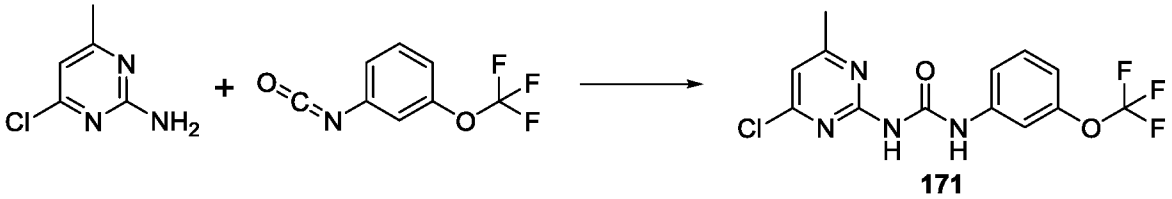
[00502] Example 149 was prepared in a similar manner to example 148 from 1-(3-chloro-4-fluorophenyl)-3-(4-chloro-6-methylpyrimidin-2-yl)urea (156) and N-(3-aminopropyl)-N-methyl carbamic acid tert-butyl ester (165 mg, 93%). LC/MS: Method 4: Rt = 0.38 min, m/z = 367.2-369.2 [MH+].

Example 150: Synthesis of 1-(4-((3-(dimethylamino)propyl)amino)-6-methylpyrimidin-2-yl)-3-(3-(trifluoromethoxy)phenyl)urea (172)



172

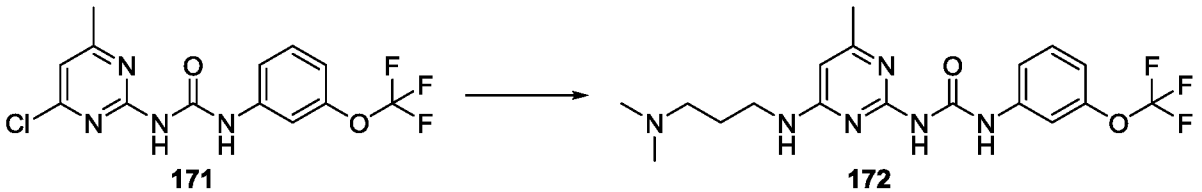
[00503] Step 1: 1-(4-Chloro-6-methylpyrimidin-2-yl)-3-(3-(trifluoromethoxy)phenyl)urea (**171**)



171

[00504] A mixture of 2-amino-4-chloro-6-methylpyrimidine (179 mg, 1.2 mmol) and 3-trifluoromethoxyphenyl isocyanate (278 mg, 1.4 mmol) in toluene (1.7 mL) was refluxed for 7 hours. On cooling, MeOH (5mL) was added and the suspension was filtered, washed with Et_2O and dried to yield compound (**171**) (66 mg, 15%) as a white solid.

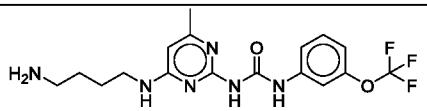
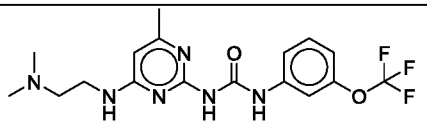
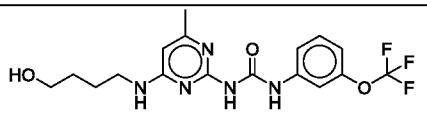
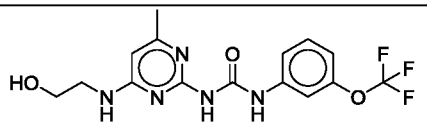
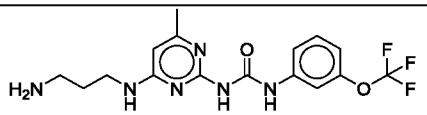
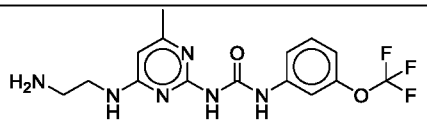
[00505] Step 2: 1-(4-((3-(Dimethylamino)propyl)amino)-6-methylpyrimidin-2-yl)-3-(3-(trifluoromethoxy)phenyl)urea (**172**)



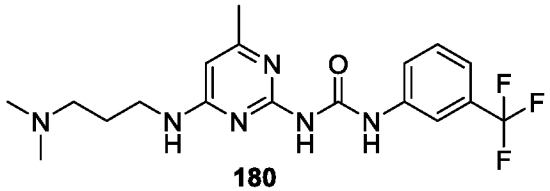
171 **172**

[00506] A mixture of 1-(4-chloro-6-methylpyrimidin-2-yl)-3-(3-(trifluoromethoxy)phenyl)urea (**171**) (66 mg, 0.19 mmol), and 3-(dimethylamino)-1-propylamine (0.03 mL, 0.22 mmol) and triethylamine (0.04 mL, 0.28 mmol) in 2-propanol (0.5 mL) was heated overnight at 80 ºC. The reaction mixture was cooled, diluted with MeOH (5mL), and the white precipitate was filtered to yield the title compound (**172**) (14 mg, 17%). LC/MS: Method 4: Rt = 1.65 min, *m/z* = 413.2 [MH^+].

[00507] The following examples were prepared according to similar procedures described for Example 150:

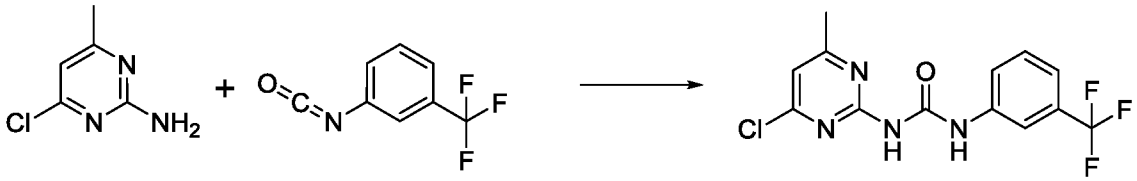
Cpd ID	Example ID	Structure	HPLC Method	Yield (mass/%)	RT (min)	MH^+
173	**151**		**4**	**50 mg, 58**	**1.65**	**399.2**
174	**152**		**4**	**46 mg, 53**	**1.68**	**399.2**
175	**153**		**4**	**47 mg, 66**	**2.10**	**400.2**
176	**154**		**4**	**48 mg, 60**	**2.02**	**373.2**
177	**155**		**4**	**18 mg, 21**	**1.51**	**386.2**
178	**156**		**4**	**22 mg, 28**	**1.52**	**371.2**

Example 157: Synthesis of 1-(4-((3-(dimethylamino)propyl)amino)-6-methylpyrimidin-2-yl)-3-(3-(trifluoromethyl)phenyl)urea (180)



180

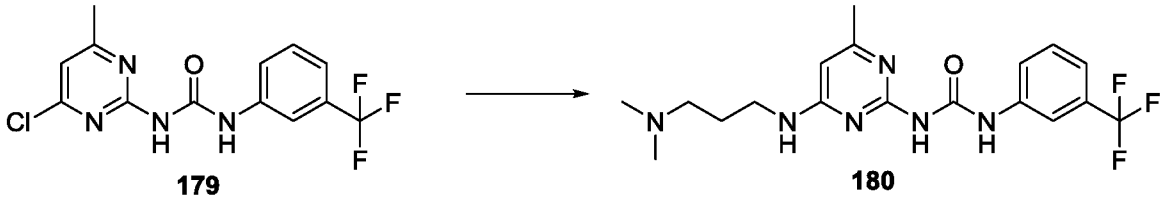
[00508] Step 1: 1-(4-chloro-6-methylpyrimidin-2-yl)-3-(3-(trifluoromethyl)phenyl)urea (**179**)



179

[00509] A mixture of 2-amino-4-chloro-6-methylpyrimidine (2.6 g, 17.6 mmol) and 3-trifluoromethylphenyl isocyanate (3.9 g, 17.6 mmol) in toluene (31 mL) was refluxed overnight. On cooling the suspension was filtered, washed with MeOH and Et_2O and dried to yield compound (**179**) (4.4 g, 72%) as a white solid. LC/MS: Method 4: Rt = 3.65 min, *m/z* = 331.1 [MH^+].

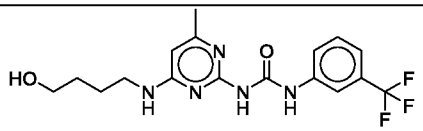
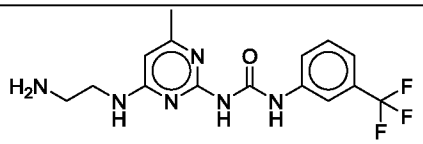
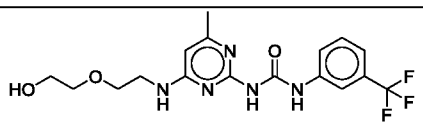
[00510] Step 2: 1-(4-((3-(dimethylamino)propyl)amino)-6-methylpyrimidin-2-yl)-3-(3-(trifluoromethyl)phenyl)urea (**180**)

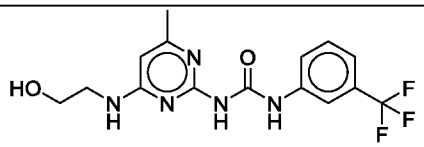
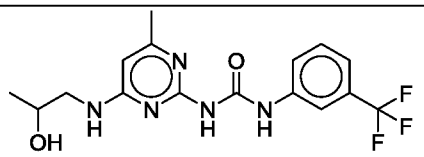
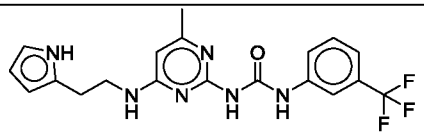
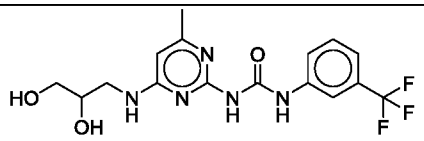
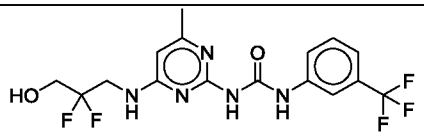
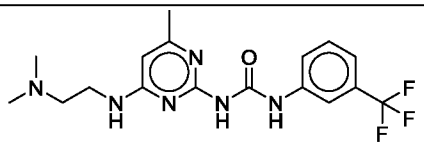
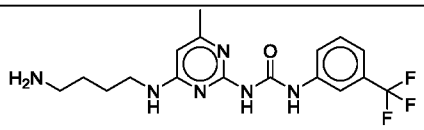
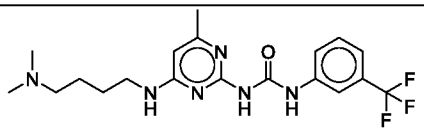
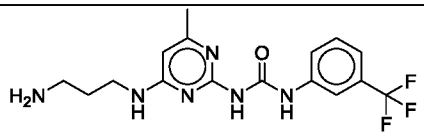


179 180

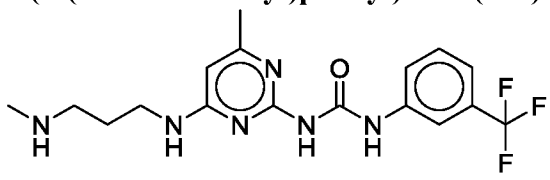
[00511] A mixture of 1-(4-chloro-6-methylpyrimidin-2-yl)-3-(3-(trifluoromethyl)phenyl)urea (**179**) (100 mg, 0.29 mmol), and 3-(dimethylamino)-1-propylamine (0.04 mL, 0.34 mmol) and triethylamine (0.06 mL, 0.43 mmol) in 2-propanol (0.5 mL) was heated for 2 hours at 80 °C. The reaction mixture was cooled and the white precipitate was filtered to yield the title compound (**180**) (61 mg, 54%). LC/MS: Method 4: Rt = 1.46 min, *m/z* = 397.2 [MH^+].

[00512] The following examples were prepared according to similar procedures described for Example 157:

Cpd ID	Example ID	Structure	HPLC Method	Yield (mass/%)	RT (min)	MH^+
181	**158**		**4**	**200 mg, 76**	**2.10**	**384.2**
182	**159**		**4**	**105 mg, 40**	**1.64**	**355.2**
183	**160**		**4**	**148 mg, 53**	**2.04**	**400.2**

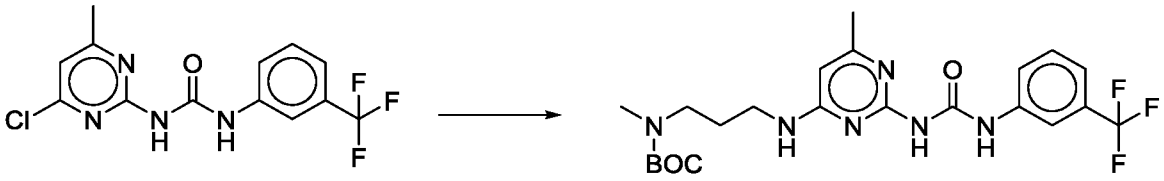
184	**161**		**4**	**145 mg, 59**	**1.96**	**356.2**
185	**162**		**4**	**208 mg, 81**	**2.05**	**370.2**
186	**163**		**4**	**135 mg, 46**	**2.51**	**405.2**
187	**164**		**4**	**192 mg, 69**	**1.87**	**386.2**
188	**165**		**4**	**54 mg, 18**	**2.21**	**406.2**
189	**166**		**4**	**54 mg, 47**	**1.67**	**383.2**
190	**167**		**4**	**56 mg, 46**	**1.62**	**383.2**
191	**168**		**4**	**16 mg, 9**	**1.56**	**411.2**
192	**169**		**4**	**20 mg, 9**	**1.59**	**369.2**

Example 170: Synthesis of 1-(4-methyl-6-((3-(methylamino)propyl)amino)pyrimidin-2-yl)-3-(3-(trifluoromethyl)phenyl)urea (194)



194

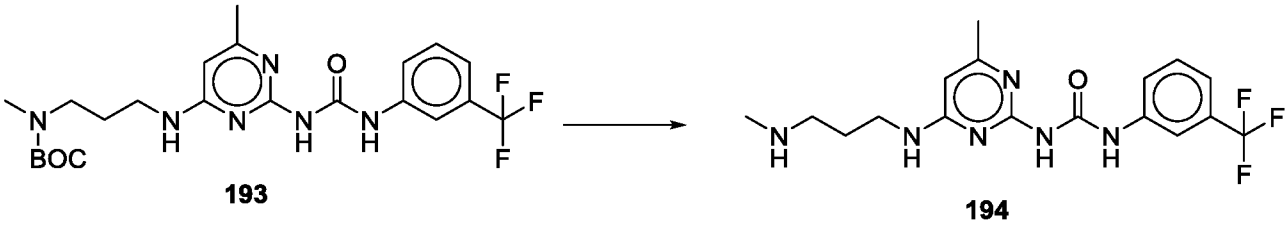
[00513] Step 1: *tert*-butyl methyl(3-((6-methyl-2-(3-(3-(trifluoromethyl)phenyl)ureido)pyrimidin-4-yl)amino)propyl)carbamate (**193**)



179 193

[00514] A mixture of 1-(4-chloro-6-methylpyrimidin-2-yl)-3-(3-(trifluoromethyl)phenyl)urea (**179**) (189mg, 0.54mmol) and 2-propanol (5 mL) was treated with N-(3-aminopropyl)-N-methyl carbamic acid tert-butyl ester (0.13g, 0.65mmol), and triethylamine (0.11mL, 0.81mmol) and this was heated to reflux with stirring for 30 minutes. Upon cooling the precipitate formed was filtered and washed with MeOH and Et_2O to give the title compound (**193**) (122mg, 44%). LC/MS: Method 4: Rt 2.90 min, *m/z* = 483.3 [MH^+].

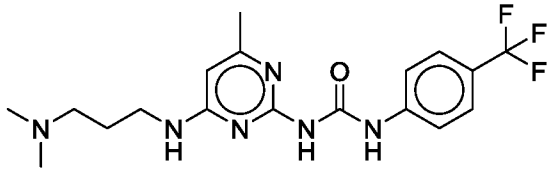
[00515] Step 2: 1-(4-methyl-6-((3-(methylamino)propyl)amino)pyrimidin-2-yl)-3-(3-(trifluoromethyl)phenyl)urea



193 194

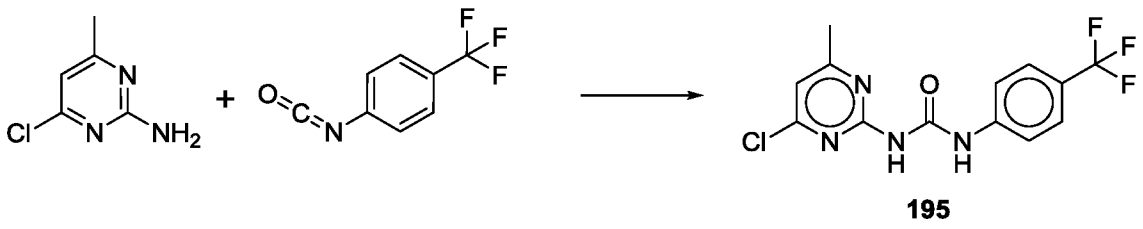
[00516] The BOC derivative (**193**) (122 mg, 0.24 mmol) was suspended in DCM (5 mL) to which trifluoroacetic acid (0.46 mL, 6.0 mmol) was added. After 15 minutes at room temperature the solvent was evaporated and the residue treated with DCM and 1N sodium hydroxide solution (0.24 mL). The title product was filtered as a white solid (**194**), washed with water and dried (60 mg, 62%) LC/MS: Method 4: Rt 1.55 min, *m/z* = 383.2 [MH^+].

Example 171: Synthesis of 1-(4-((3-(dimethylamino)propyl)amino)-6-methylpyrimidin-2-yl)-3-(4-(trifluoromethyl)phenyl)urea (196)



196

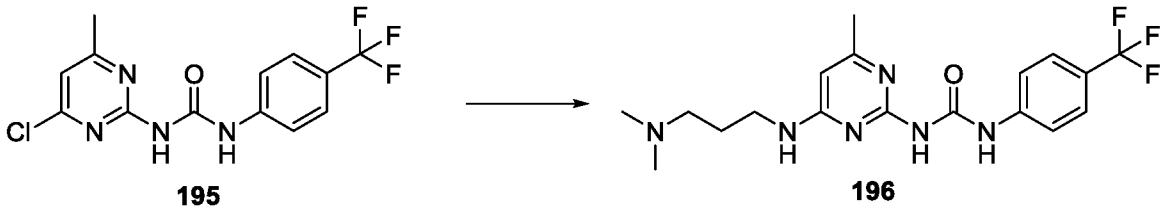
[00517] Step 1: 1-(4-Chloro-6-methylpyrimidin-2-yl)-3-(4-(trifluoromethyl)phenyl)urea (**195**)



195

[00518] A mixture of 2-amino-4-chloro-6-methylpyrimidine (0.82 g, 5.7 mmol) and 4-trifluoromethylphenyl isocyanate (0.91 mL, 6.3 mmol) in N,N-dimethylacetamide (7.6 mL) was heated at 100 °C for 20 minutes. On cooling the mixture was diluted with MeOH (20 mL). The slurry was filtered and washed with MeOH and dried to yield compound (**195**) (0.98 g, 52%) as a white solid.

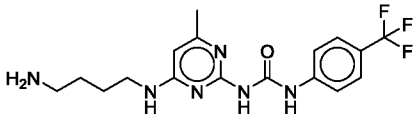
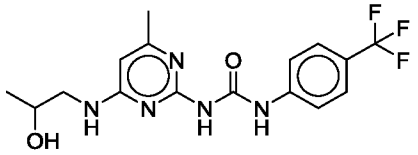
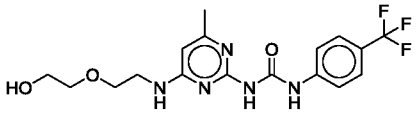
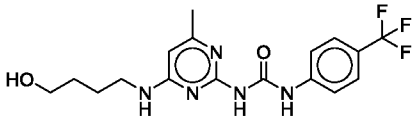
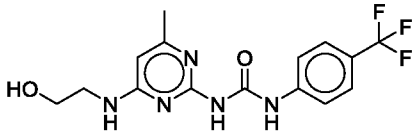
[00519] Step 2: 1-(4-((3-(Dimethylamino)propyl)amino)-6-methylpyrimidin-2-yl)-3-(4-(trifluoromethyl)phenyl)urea (**196**)

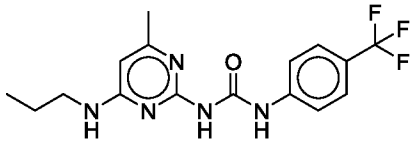
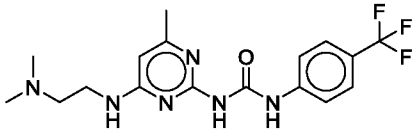
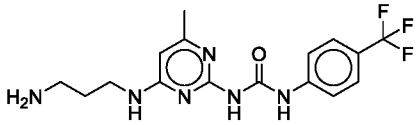
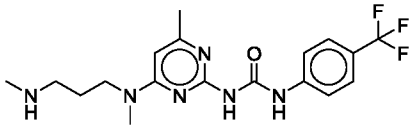
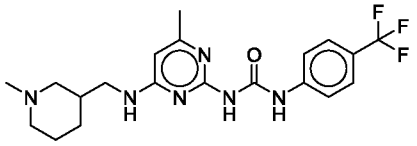
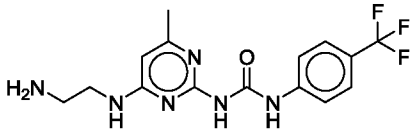


195 **196**

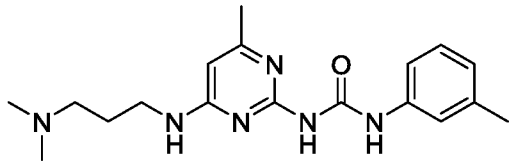
[00520] A mixture of 1-(4-chloro-6-methylpyrimidin-2-yl)-3-(4-(trifluoromethyl)phenyl)urea (**195**) (75 mg, 0.23 mmol), and 3-(dimethylamino)-1-propylamine (0.03 mL, 0.27 mmol) and triethylamine (0.05 mL, 0.34 mmol) in 2-propanol (0.5 mL) was heated overnight at 80 °C. The reaction mixture was cooled and the white precipitate was filtered to yield the title compound (**196**) (8 mg, 8%). LC/MS: Method 4: Rt = 1.70 min, *m/z* = 397.2 [MH^+].

[00521] The following examples were prepared according to similar procedures described for Example 171:

Cpd ID	Example ID	Structure	HPLC Method	Yield (mass/%)	RT (min)	MH^+
197	**172**		**4**	**16 mg, 19**	**2.02**	**383.2**
198	**173**		**4**	**26 mg, 31**	**2.01**	**371.2**
199	**174**		**4**	**26 mg, 29**	**1.98**	**401.2**
200	**175**		**4**	**60 mg, 83**	**2.07**	**384.2**
201	**176**		**4**	**53 mg, 65**	**1.93**	**356.2**

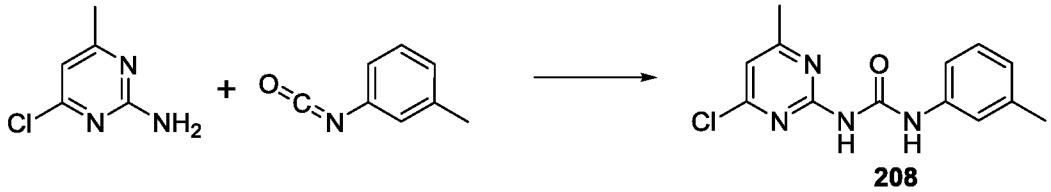
202	**177**		**4**	**55 mg, 66**	**2.46**	**354.2**
203	**178**		**4**	**26 mg, 30**	**1.67**	**384.2**
204	**179**		**4**	**12 mg, 14**	**2.07**	**369.2**
205	**180**		**4**	**6 mg, 6**	**1.81**	**398.2**
206	**181**		**4**	**28 mg, 38**	**1.68**	**423.3**
207	**182**		**4**	**16 mg, 9**	**1.69**	**355.2**

Example 183: Synthesis of 1-(4-((3-(dimethylamino)propyl)amino)-6-methylpyrimidin-2-yl)-3-(m-tolyl)urea (209)



209

[00522] Step 1: 1-(4-Chloro-6-methyl-2-pyrimidinyl)-3-(3-methylphenyl)urea (**208**)

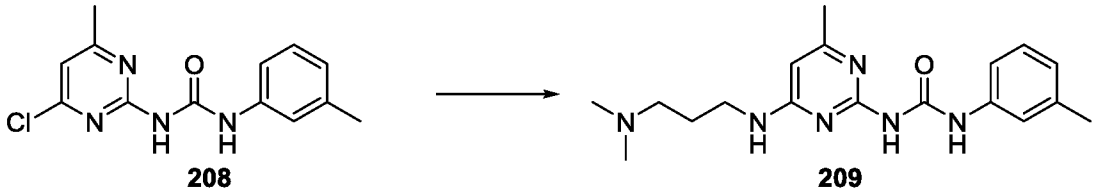


208

[00523] A mixture of 2-amino-4-chloro-6-methylpyrimidine (10 g, 68 mmol) and 3-methylphenyl isocyanate (11.1 g, 83 mmol) in N, N-dimethylacetamide (50 mL) was stirred at room temperature for 1 hour then heated for 2 hours at 70 ºC. Upon cooling the mixture was stirred overnight. The slurry which formed was filtered, washed with ethanol and dried to yield

compound (**208**) (8.0 g, 43%) as a white solid. LC/MS: Method 4: Rt = 0.25 min, *m/z* = 277.1 [MH^+].

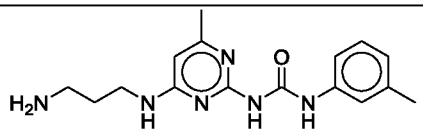
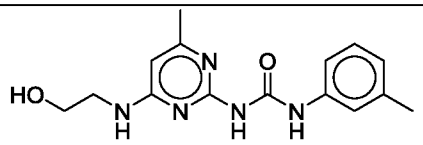
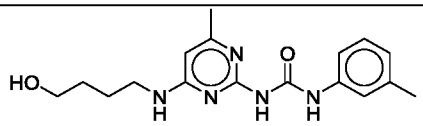
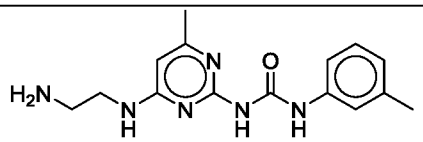
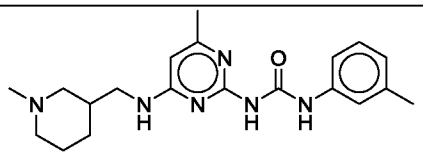
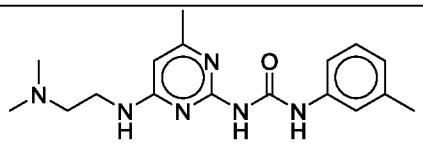
[00524] Step 2: 1-(4-((3-(Dimethylamino)propyl)amino)-6-methylpyrimidin-2-yl)-3-(m-tolyl)urea (**209**)

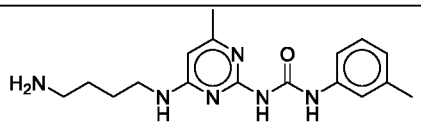
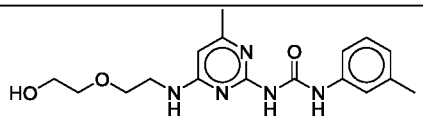
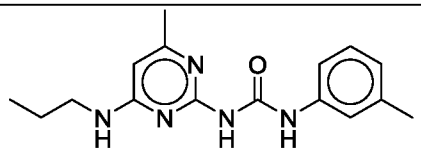
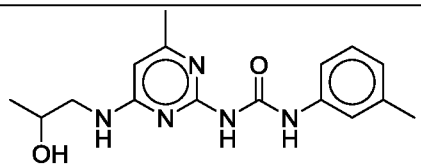
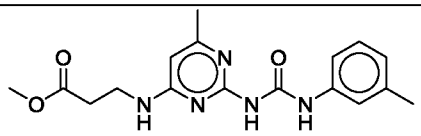
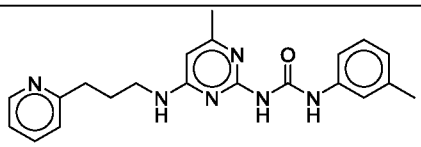
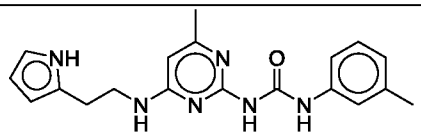
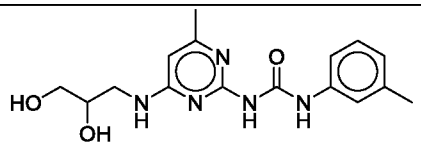
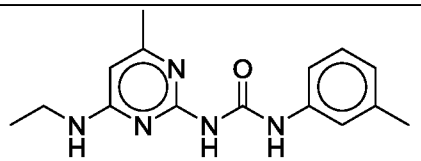
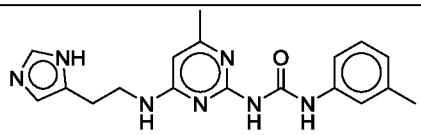
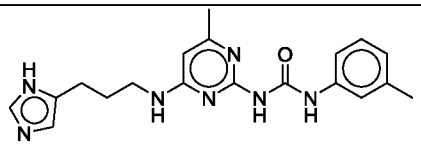
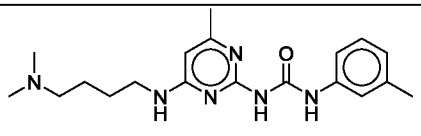


208 **209**

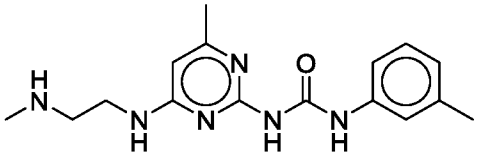
[00525] 1-(4-Chloro-6-methyl-2-pyrimidinyl)-3-(3-methoxyphenyl)urea (**208**) (0.2 g, 0.70 mmol), and 3-(dimethylamino)-1-propylamine (0.11 mL, 0.81 mmol) and triethylamine (0.15 mL, 1.1 mmol) in 2-propanol (1.2 mL) was heated overnight at 70 °C. The reaction mixture was cooled and filtered. The solids were washed with ethanol to yield the title compound (**209**) (0.19 g, 77%). LC/MS: Method 4: Rt = 0.35 min, *m/z* = 343.3 [MH^+].

[00526] The following examples were prepared according to similar procedures described for Example 183:

Cpd ID	Example ID	Structure	HPLC Method	Yield (mass/%)	RT (min)	MH^+
210	**184**		**4**	**159 mg, 72**	**1.29**	**315.2**
211	**185**		**4**	**185 mg, 88**	**1.56**	**302.2**
212	**186**		**4**	**170 mg, 74**	**1.20**	**330.2**
213	**187**		**4**	**65 mg, 31**	**0.36**	**301.2**
214	**188**		**4**	**115 mg, 59**	**0.34**	**369.3**
215	**189**		**4**	**50 mg, 22**	**0.35**	**329.3**

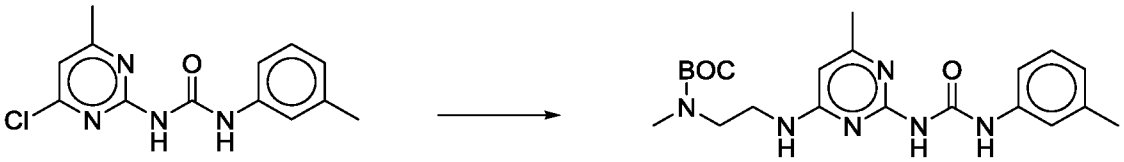
216	190		4	225 mg, 98	0.34	329.2
217	191		4	108 mg, 45	1.64	346.2
218	192		4	156 mg, 74	2.07	300.2
219	193		4	190 mg, 86	1.69	316.2
220	194		4	100 mg, 39	2.00	344.2
221	195		4	195 mg, 70	1.41	377.3
222	196		4	195 mg, 75	2.26	351.2
223	197		4	195 mg, 80	1.57	332.2
224	198		4	110 mg, 52	1.90	286.2
225	199		4	14 mg, 7	1.37	352.2
226	200		4	120 mg, 59	1.32	366.2
227	201		4	130 mg, 52	1.29	357.3

Example 202: Synthesis of 1-(4-methyl-6-((2-(methylamino)ethyl)amino)pyrimidin-2-yl)-3-(m-tolyl)urea (229)



229

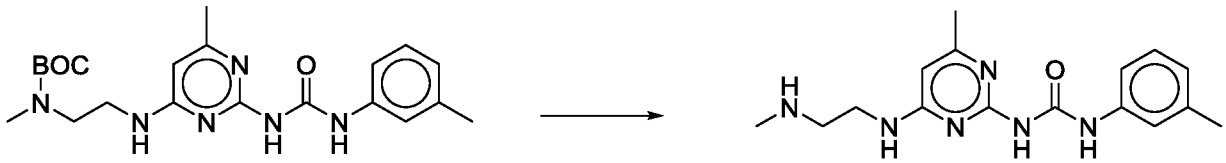
[00527] Step 1: *tert*-Butyl methyl(2-((6-methyl-2-(3-(m-tolyl)ureido)pyrimidin-4-yl)amino)ethyl)carbamate (**228**)



208 **228**

[00528] A mixture of 1-(4-chloro-6-methylpyrimidin-2-yl)-3-(m-tolyl)urea (**208**) (200 mg, 0.70 mmol) and 2-propanol (1.2 mL) was treated with N-(2-aminoethyl)-N-methyl carbamic acid tert-butyl ester (1.2 mL, 16.7 mmol), and triethylamine (0.15 mL, 1.1 mmol) and this was heated to reflux with stirring overnight. Upon cooling, the mixture was filtered and the solids washed with ethanol to give the title compound (**228**) (240 mg, 83%). LC/MS: Method 4: Rt = 0.33 min, *m/z* = 415.3 [MH^+].

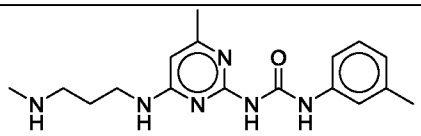
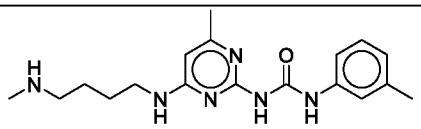
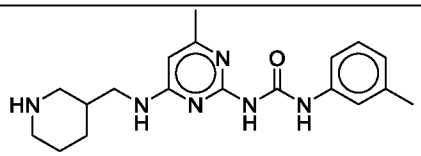
[00529] Step 2: 1-(4-Methyl-6-((2-(methylamino)ethyl)amino)pyrimidin-2-yl)-3-(m-tolyl)urea (**229**)



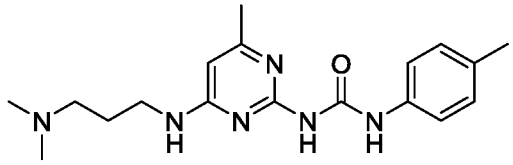
228 **229**

[00530] The BOC derivative (**228**) (226 mg, 0.53 mmol) was suspended in DCM (0.7 mL) to which trifluoroacetic acid (0.7 mL, 9 mmol) was added. After 2 hours at room temperature the mixture was treated with saturated sodium bicarbonate solution to achieve a pH of 8. The title product was filtered as a white solid (**229**) (165 mg, 100%). LC/MS: Method 4: Rt = 0.35 min, *m/z* = 315.2 [MH^+].

[00531] The following examples were prepared according to similar procedures described for Example 202:

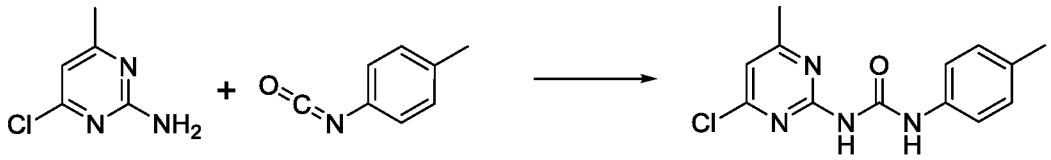
Cpd ID	Example ID	Structure	HPLC Method	Yield (mass/%)	RT (min)	MH^+
230	203		4	180 mg, 81	0.35	329.3
231	204		4	120 mg, 46	1.29	343.3
232	205		4	200 mg, 78	1.25	355.3

Example 206: Synthesis of 1-(4-((3-(dimethylamino)propyl)amino)-6-methylpyrimidin-2-yl)-3-(p-tolyl)urea (234)



234

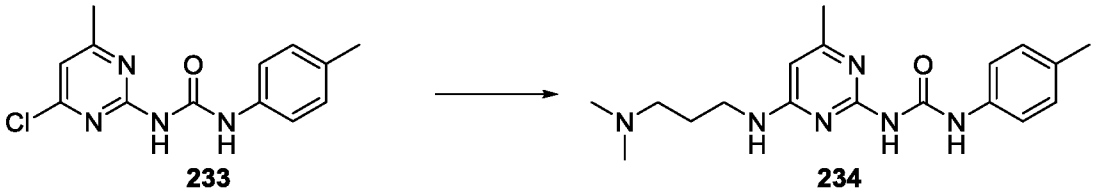
[00532] Step 1: 1-(4-Chloro-6-methylpyrimidin-2-yl)-3-(p-tolyl)urea (**233**)



233

[00533] A mixture of 2-amino-4-chloro-6-methylpyrimidine (3 g, 20 mmol) and 4-methylphenyl isocyanate (3.3 g, 25 mmol) in N, N-dimethylacetamide (15 mL) was stirred at room temperature for 1 hour, heated for 2 hours at 70 °C, then maintained at 50°C overnight. Upon cooling the mixture was stirred overnight. The slurry which formed was filtered, washed with ethanol and dried to yield compound (**233**) (3.3 g, 59%) as a white solid. LC/MS: Method 4: Rt = 3.28 min, *m/z* = 277.1 [MH^+].

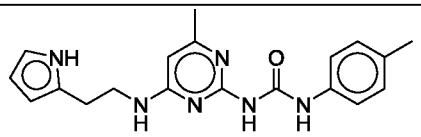
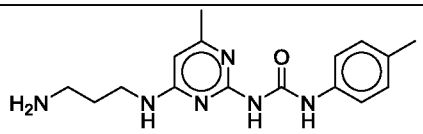
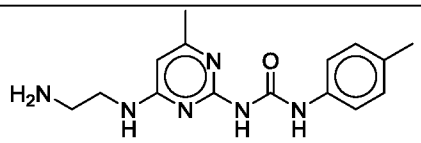
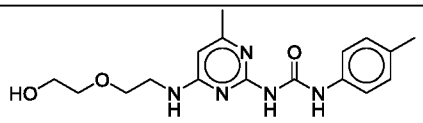
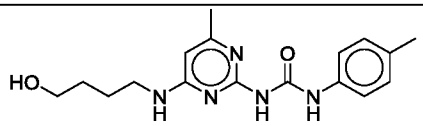
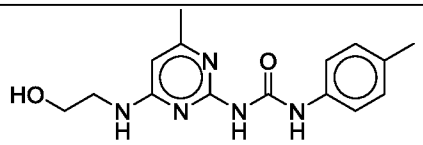
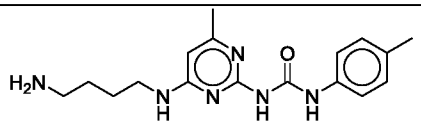
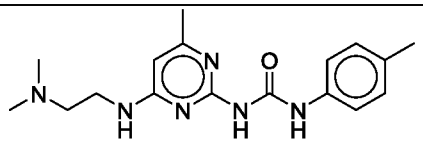
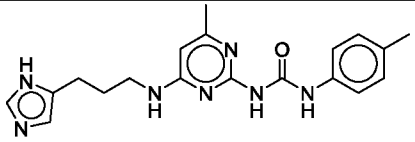
[00534] Step 2: 1-(4-((3-(Dimethylamino)propyl)amino)-6-methylpyrimidin-2-yl)-3-(p-tolyl)urea (**234**)

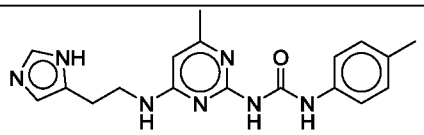
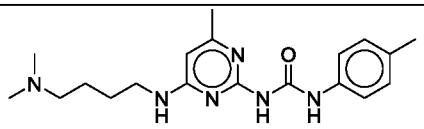
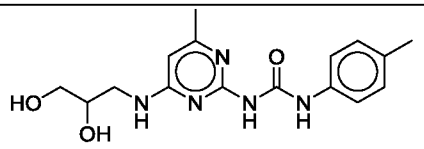


233 **234**

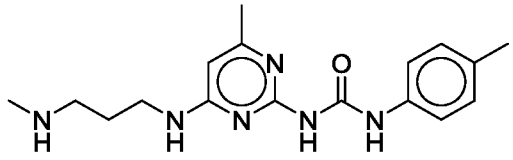
[00535] 1-(4-Chloro-6-methylpyrimidin-2-yl)-3-(p-tolyl)urea (**233**) (0.2 g, 0.70 mmol), and 3-(dimethylamino)-1-propylamine (0.11 mL, 0.81 mmol) and triethylamine (0.15 mL, 1.1 mmol) in 2-propanol (1.2 mL) was heated overnight at 70 ºC. The reaction mixture was cooled and filtered. The solids were washed with ethanol to yield the title compound (**234**) (0.19 g, 77%). LC/MS: Method 4: Rt = 1.32 min, *m/z* = 343.3 [MH^+].

[00536] The following examples were prepared according to similar procedures described for Example 206:

Cpd ID	Example ID	Structure	HPLC Method	Yield (mass/%)	RT (min)	MH^+
235	**207**		**4**	**195 mg, 75**	**2.21**	**351.2**
236	**208**		**4**	**155 mg, 70**	**1.12**	**315.2**
237	**209**		**4**	**150 mg, 68**	**1.12**	**301.2**
238	**210**		**4**	**193 mg, 80**	**1.66**	**346.2**
239	**211**		**4**	**185 mg, 76**	**1.70**	**330.2**
240	**212**		**4**	**144 mg, 68**	**1.61**	**302.2**
241	**213**		**4**	**150 mg, 65**	**1.30**	**329.2**
242	**214**		**4**	**108 mg, 45**	**1.69**	**330.2**
243	**215**		**4**	**25 mg, 12**	**1.31**	**366.2**

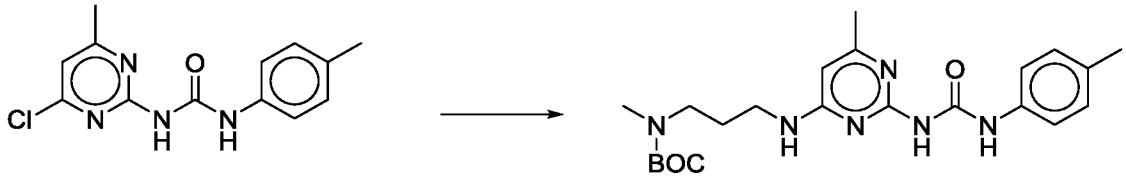
244	**216**		**4**	**40 mg, 21**	**1.27**	**352.2**
245	**217**		**4**	**80 mg, 32**	**1.38**	**357.3**
246	**218**		**4**	**140 mg, 57**	**1.57**	**332.2**

Example 219: Synthesis of 1-(4-methyl-6-((3-(methylamino)propyl)amino)pyrimidin-2-yl)-3-(p-tolyl)urea (248)



248

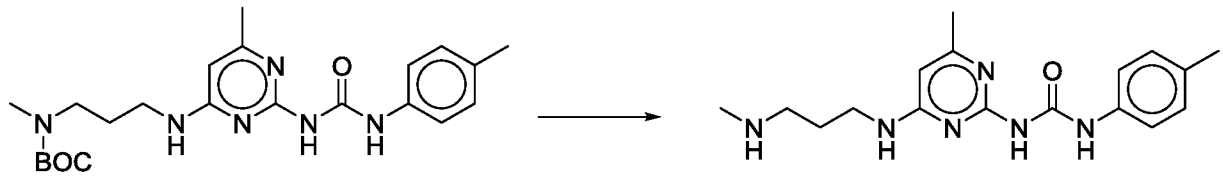
[00537] Step 1: *tert*-Butyl methyl(3-((6-methyl-2-(3-(p-tolyl)ureido)pyrimidin-4-yl)amino)propyl)carbamate (**247**)



233 **247**

[00538] A mixture of 1-(4-chloro-6-methylpyrimidin-2-yl)-3-(p-tolyl)urea (**233**) (200 mg, 0.70 mmol) and 2-propanol (0.96 mL) was treated with N-(3-aminopropyl)-N-methyl carbamic acid tert-butyl ester (0.1 mL, 0.84 mmol), and triethylamine (0.15 mL, 1.1 mmol) and this was heated to 70 °C with stirring overnight. Upon cooling, the precipitate formed was dried to give the title compound (**247**) (164 mg, 53%).

[00539] Step 2: 1-(4-Methyl-6-((3-(methylamino)propyl)amino)pyrimidin-2-yl)-3-(p-tolyl)urea (**248**)

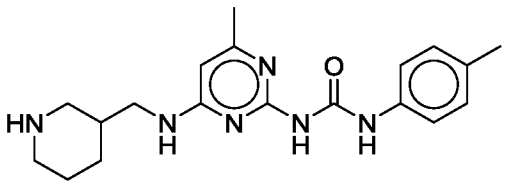


247 **248**

[00540] The BOC derivative (**247**) (251 mg, 0.56 mmol) was suspended in DCM (0.75 mL) to which trifluoroacetic acid (0.71 mL, 9.7 mmol) was added. After 2 hours at room temperature

the solvent was evaporated and the residue treated with saturated sodium bicarbonate solution sufficient to achieve a pH of 8. The title product was filtered as a white solid (**248**), washed with water and dried (160 mg, 82%). LC/MS: Method 4: Rt 1.22 min, *m/z* = 329.2 [MH^+].

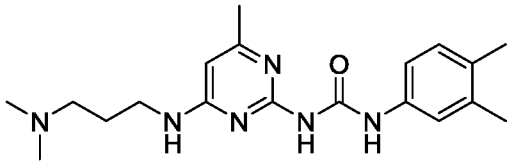
Example 220: Synthesis of 1-(4-methyl-6-((piperidin-3-ylmethyl)amino)pyrimidin-2-yl)-3-(p-tolyl)urea (249)



249

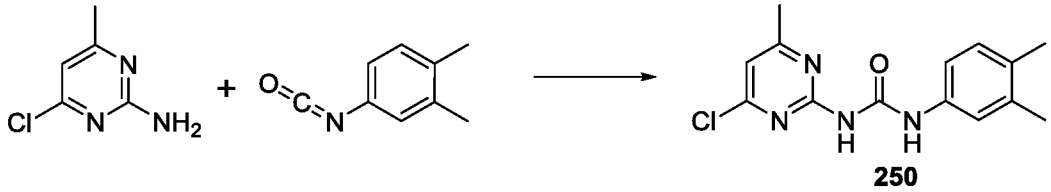
[00541] Example 220 was prepared in a similar manner to example 219 from 1-(4-chloro-6-methylpyrimidin-2-yl)-3-(p-tolyl)urea (**233**) and *tert*-butyl 3-(aminomethyl)piperidine-1-carboxylate. (180 mg, 71%) LC/MS: Method 4: Rt = 1.31 min, m/z = 355.3 [MH+].

Example 221: Synthesis of 1-(4-((3-(dimethylamino)propyl)amino)-6-methylpyrimidin-2-yl)-3-(3,4-dimethylphenyl)urea (251)



251

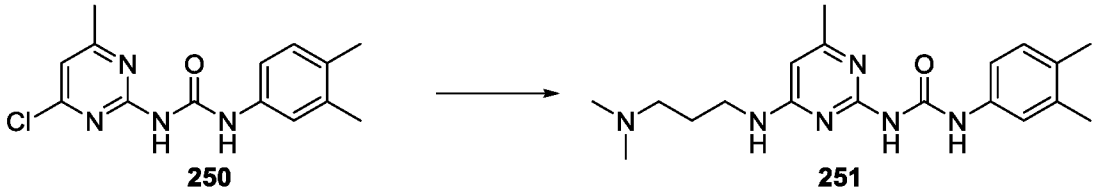
[00542] Step 1: 1-(4-Chloro-6-methylpyrimidin-2-yl)-3-(3,4-dimethylphenyl)urea (**250**)



250

[00543] A mixture of 2-amino-4-chloro-6-methylpyrimidine (10 g, 68 mmol) and 3, 4-dimethylphenyl isocyanate (12.3 g, 83 mmol) in N, N-dimethylacetamide (60 mL) was stirred at room temperature for 1 hour then heated overnight at 50 ºC. Upon cooling the mixture was stirred overnight. The slurry which formed was filtered, washed with ether and dried to yield compound (**250**) (4.8 g, 24%) as a white solid. LC/MS: Method 4: Rt = 0.25 min, *m/z* = 277.1 [MH^+]. This material was used directly in the next step.

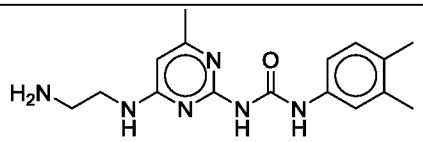
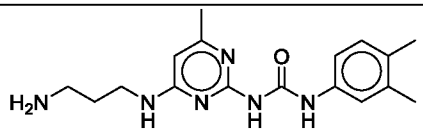
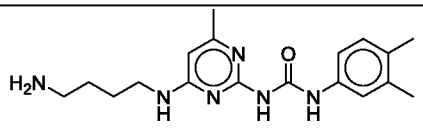
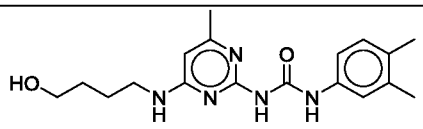
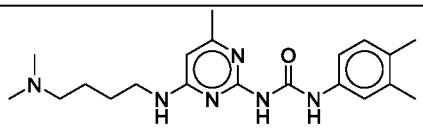
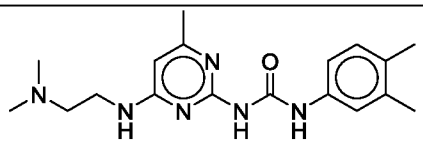
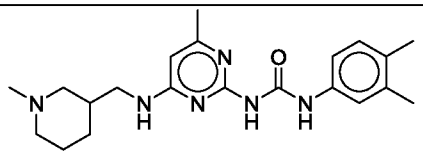
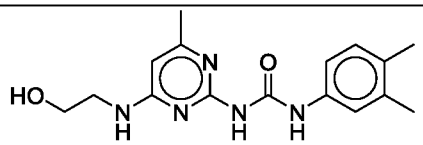
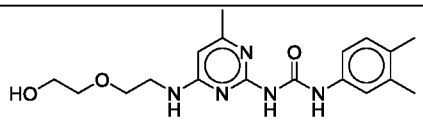
[00544] Step 2: 1-(4-((3-(Dimethylamino)propyl)amino)-6-methylpyrimidin-2-yl)-3-(3,4-dimethylphenyl)urea (**251**)

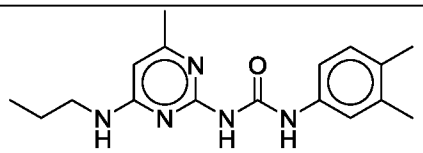
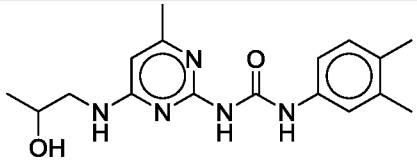
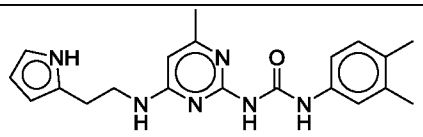
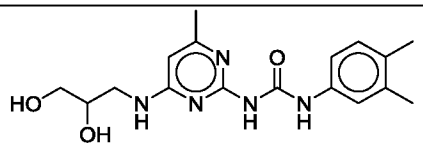
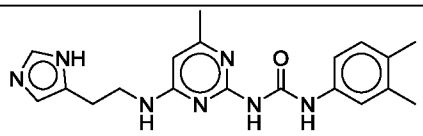
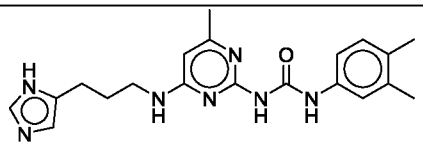


250 **251**

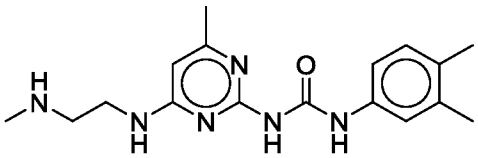
[00545] 1-(4-Chloro-6-methylpyrimidin-2-yl)-3-(3,4-dimethylphenyl)urea (**250**) (0.2 g, 0.67 mmol), and 3-(dimethylamino)-1-propylamine (0.11 mL, 0.81 mmol) and triethylamine (0.14 mL, 1.0 mmol) in 2-propanol (1.1 mL) was heated overnight at 70 ºC. The reaction mixture was cooled and filtered. The solids were washed with ethanol to yield the title compound (**251**) (198 mg, 83%). LC/MS: Method 4: Rt = 0.35 min, *m/z* = 357.3 [MH^+].

[00546] The following examples were prepared according to similar procedures described for Example 221:

Cpd ID	Example ID	Structure	HPLC Method	Yield (mass/%)	RT (min)	MH^+
252	**222**		**4**	**85 mg, 31**	**0.36**	**301.2**
253	**223**		**4**	**50 mg, 23**	**2.07**	**329.2**
254	**224**		**4**	**39 mg, 17**	**2.10**	**343.3**
255	**225**		**4**	**42 mg, 18**	**2.66**	**344.2**
256	**226**		**4**	**75 mg, 30**	**0.38**	**371.3**
257	**227**		**4**	**50 mg, 22**	**0.35**	**329.3**
258	**228**		**4**	**20 mg, 10**	**0.40**	**383.3**
259	**229**		**4**	**38 mg, 24**	**2.34**	**316.2**
260	**230**		**4**	**91 mg, 38**	**1.82**	**360.2**

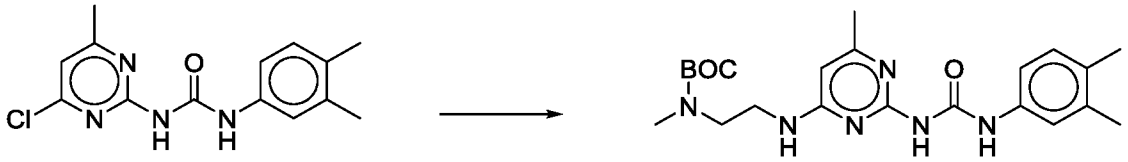
261	**231**		**4**	**127 mg, 61**	**0.33**	**314.2**
262	**232**		**4**	**130 mg, 56**	**1.29**	**330.2**
263	**233**		**4**	**195 mg, 76**	**2.44**	**365.3**
264	**234**		**4**	**195 mg, 81**	**1.75**	**346.2**
265	**235**		**4**	**25 mg, 13**	**1.62**	**366.2**
266	**236**		**4**	**20 mg, 10**	**1.50**	**380.2**

Example 237: Synthesis of 1-(3,4-dimethylphenyl)-3-(4-methyl-6-((2-(methylamino)ethyl)amino)pyrimidin-2-yl)urea (268)



268

[00547] Step 1: *tert*-Butyl (2-((2-(3-(3,4-dimethylphenyl)ureido)-6-methylpyrimidin-4-yl)amino)ethyl)(methyl)carbamate (**267**)

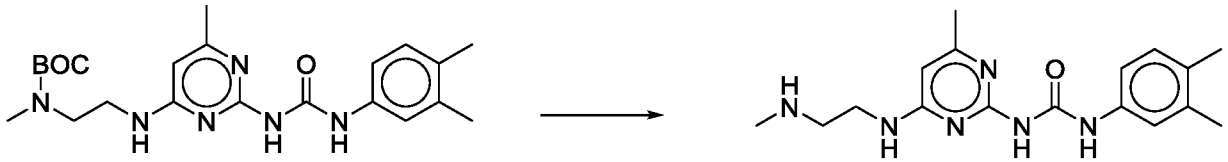


250 **267**

[00548] A mixture of 1-(4-chloro-6-methylpyrimidin-2-yl)-3-(3,4-dimethylphenyl)urea (**250**) (200 mg, 0.70 mmol) and 2-propanol (1.2 mL) was treated with N-(2-aminoethyl)-N-methyl carbamic acid tert-butyl ester (1.2 mL, 16.7 mmol), and triethylamine (0.15 mL, 1.1 mmol) and

this was heated to reflux with stirring overnight. Upon cooling, the mixture was filtered and the solids washed with ethanol to give the title compound (**267**) (168 mg, 59%).

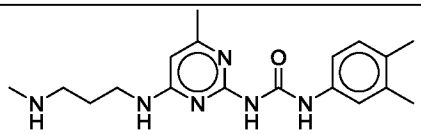
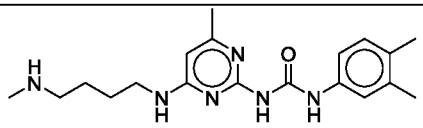
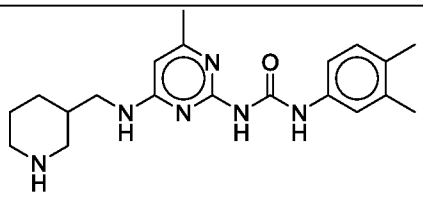
[00549] Step 2: 1-(3,4-Dimethylphenyl)-3-(4-methyl-6-((2-(methylamino)ethyl)amino)pyrimidin-2-yl)urea (**268**)



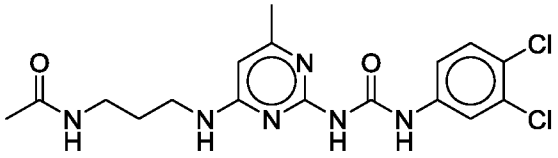
267 **268**

[00550] The BOC derivative (**267**) (167 mg, 0.38 mmol) was suspended in DCM (0.5 mL) to which trifluoroacetic acid (0.48 mL, 6 mmol) was added. After 2 hours at room temperature the mixture was treated with saturated sodium bicarbonate solution to achieve a pH of 8. The title product was filtered as a white solid (**268**) (115 mg, 93%). LC/MS: Method 4: Rt = 0.37 min, *m/z* = 329.2 [MH^+].

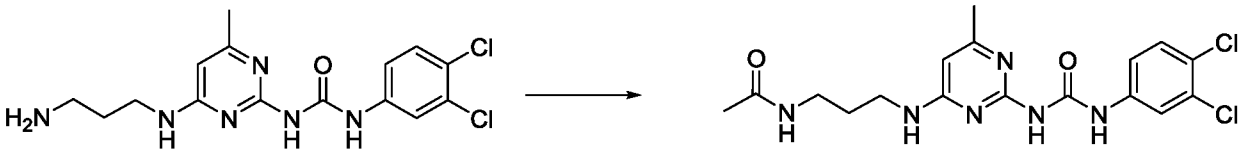
[00551] The following examples were prepared according to similar procedures described for Example 237:

Cpd ID	Example ID	Structure	HPLC Method	Yield (mass/%)	RT (min)	MH^+
269	**238**		**4**	**100 mg, 50**	**0.37**	**343.2**
270	**239**		**4**	**84 mg, 37**	**0.36**	**357.3**
271	**240**		**4**	**109 mg, 45**	**0.35**	**369.3**

Example 241: Synthesis of N-(3-((2-(3-(3,4-dichlorophenyl)ureido)-6-methylpyrimidin-4-yl)amino)propyl)acetamide (272)



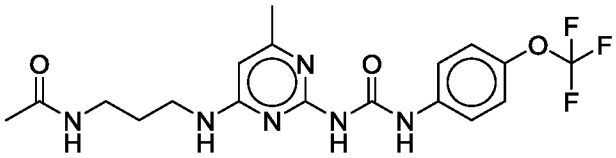
272



9 272

[00552] A mixture of 1-(4-((3-aminopropyl)amino)-6-methylpyrimidin-2-yl)-3-(3,4-dichlorophenyl)urea (**9**) (100 mg, 0.27 mmol), acetic anhydride (0.03 mL, 0.29 mmol), pyridine (0.14 mL, 1.7 mmol) and a catalytic amount of N,N-dimethylaminopyridine in DCM (0.54 mL) was stirred at room temperature for 2.5 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 (**272**) (75 mg, 64%). LC/MS: Method 4: Rt = 2.07 min, *m/z* = 411.2-413.2 [MH^+].

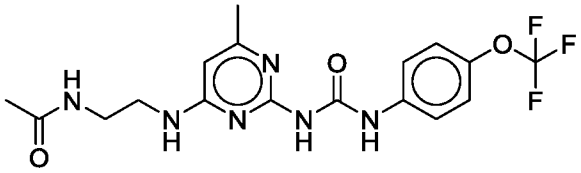
Example 242: Synthesis of N-(3-((6-methyl-2-(3-(4-(trifluoromethoxy)phenyl)ureido)pyrimidin-4-yl)amino)propyl)acetamide (273)



273

[00553] Example 242 was prepared by a similar procedure to that described for example 241 from 1-(4-((3-aminopropyl)amino)-6-methylpyrimidin-2-yl)-3-(3-(trifluoromethoxy)phenyl)urea (**89**) (11 mg, 20%). LC/MS: Method 4: Rt = 2.02 min, *m/z* = 427.2 [MH^+].

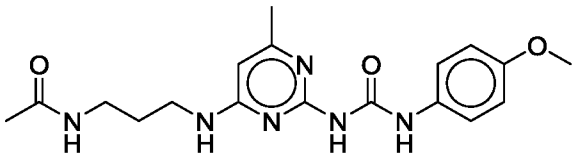
Example 243: Synthesis of N-(3-((6-methyl-2-(3-(4-(trifluoromethoxy)phenyl)ureido)pyrimidin-4-yl)amino)ethyl)acetamide (274)



274

[00554] Example 243 was prepared by a similar procedure to that described for example 241 from 1-(4-((3-aminoethyl)amino)-6-methylpyrimidin-2-yl)-3-(4-(trifluoromethoxy)phenyl)urea (**87**) (11 mg, 20%). LC/MS: Method 4: Rt = 2.02 min, *m/z* = 427.2 [MH^+].

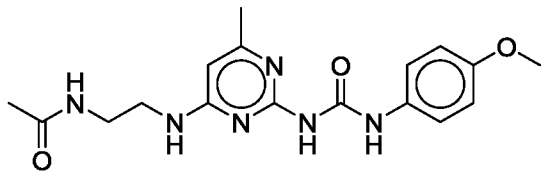
Example 244: Synthesis of N-(3-((2-(3-(4-methoxyphenyl)ureido)-6-methylpyrimidin-4-yl)amino)propyl)acetamide (275)



275

[00555] Example 244 was prepared by a similar procedure to that described for example 241 from 1-(4-((3-aminopropyl)amino)-6-methylpyrimidin-2-yl)-3-(4-methoxyphenyl)urea (**131**) (47 mg, 56%). LC/MS: Method 4: Rt = 1.44 min, *m/z* = 373.2 [MH^+].

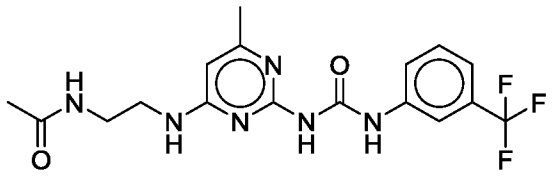
Example 245: Synthesis of N-(2-((2-(3-(4-methoxyphenyl)ureido)-6-methylpyrimidin-4-yl)amino)ethyl)acetamide (276)



276

[00556] Example 245 was prepared by a similar procedure to that described for example 241 from 1-(4-((2-aminoethyl)amino)-6-methylpyrimidin-2-yl)-3-(4-methoxyphenyl)urea (**127**) (19 mg, 49%). LC/MS: Method 4: Rt = 1.37 min, *m/z* = 359.2 [MH^+].

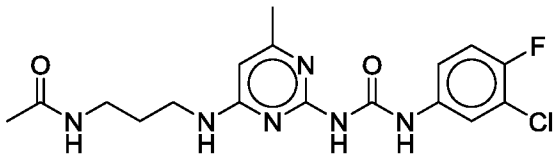
Example 246: Synthesis of N-(2-((2-(3-(4-methoxyphenyl)ureido)-6-methylpyrimidin-4-yl)amino)ethyl)acetamide (277)



277

[00557] Example 246 was prepared by a similar procedure to that described for example 241 from 1-(4-((2-aminoethyl)amino)-6-methylpyrimidin-2-yl)-3-(3-(trifluoromethyl)phenyl)urea (**182**) (12 mg, 33%). LC/MS: Method 4: Rt = 1.87 min, *m/z* = 397.2 [MH^+].

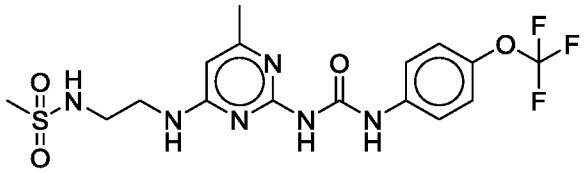
Example 247: Synthesis of N-(3-((2-(3-(3-chloro-4-fluorophenyl)ureido)-6-methylpyrimidin-4-yl)amino)propyl)acetamide (278)



278

[00558] Example 247 was prepared by a similar procedure to that described for example 241 from 1-(4-((3-aminopropyl)amino)-6-methylpyrimidin-2-yl)-3-(3-chloro-4-fluorophenyl)urea (**158**) (24 mg, 43%). LC/MS: Method 4: Rt = 1.83 min, *m/z* = 395.2 [MH^+].

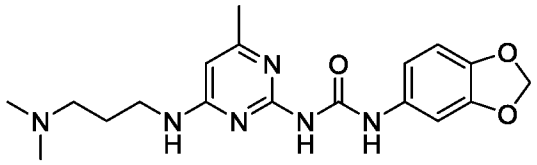
Example 248: Synthesis of N-(2-((6-methyl-2-(3-(4-(trifluoromethoxy)phenyl)-ureido)-pyrimidin-4-yl)-ethyl)methanesulfonamide (279)



279

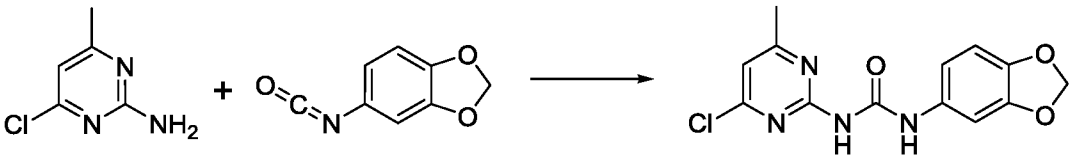
[00559] To a mixture of 1-(4-((3-aminoethyl)amino)-6-methylpyrimidin-2-yl)-3-(4-(trifluoromethoxy)phenyl)urea (**87**), (53 mg, 0.14 mmol) and triethylamine (0.04 mL, 0.28 mmol) in DCM (0.48 mL) that was cooled to 0°C was added, methanesulfonyl chloride (0.01 mL, 0.16 mmol), and this was stirred at room temperature for 5 hours. At this time the mixture was diluted with MeOH (5 mL) and the resulting solids filtered. This material was purified by silica gel chromatography using a gradient of 0-10% MeOH in DCM. Evaporation of the appropriate fractions afforded the title product (**279**) (5 mg, 7%). LC/MS: Method 4: Rt = 2.14 min, m/z = 449.1 [MH+].

Example 249: Synthesis of 1-(benzo[d][1,3]dioxol-5-yl)-3-(4-((3-(dimethylamino)propyl)amino)-6-methylpyrimidin-2-yl)urea (281)



281

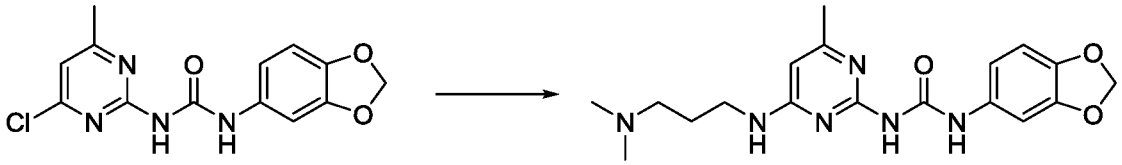
[00560] Step 1: 1-(Benzo[d][1,3]dioxol-5-yl)-3-(4-chloro-6-methylpyrimidin-2-yl)urea (**280**)



280

[00561] A mixture of 2-amino-4-chloro-6-methylpyrimidine (0.51 g, 3.5 mmol) and 2H-benzo[d]1,3-dioxolan-5-isocyanate (0.64 g, 3.9 mmol) in toluene (4.7 mL) was heated with stirring for 2 hours at 100 °C, then at 50 °C overnight. Upon cooling, the mixture was diluted with methanol (10 mL) and the slurry which formed was filtered, triturated with methanol and dried to yield compound (**280**) (0.48 g, 44%). This material was used directly in the next step.

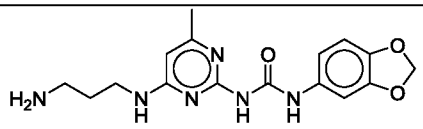
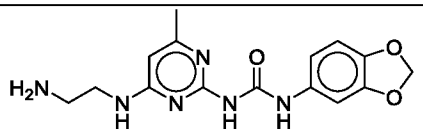
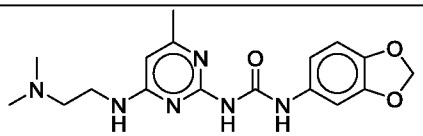
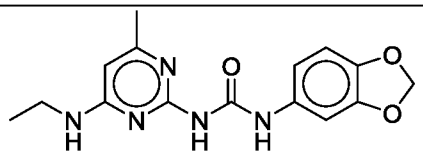
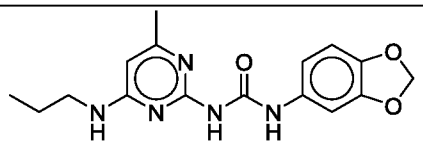
[00562] Step 2: 1-(Benzo[d][1,3]dioxol-5-yl)-3-(4-((3-(dimethylamino)propyl)amino)-6-methylpyrimidin-2-yl)urea (**281**)



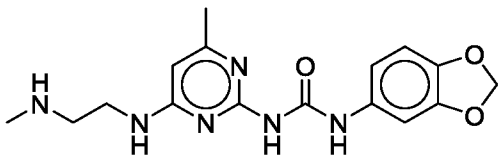
280 281

[00563] A mixture of 1-(benzo[d][1,3]dioxol-5-yl)-3-(4-chloro-6-methylpyrimidin-2-yl)urea (**280**) (0.1 g, 0.33 mmol), and 3-(dimethylamino)-1-propylamine (0.05 mL, 0.40 mmol) and triethylamine (0.07 mL, 0.5 mmol) in 2-propanol (0.66 mL) was heated overnight at 80 °C. The reaction mixture was cooled and filtered and this solid was purified by preparative TLC eluting with 30% 1M NH_4OH in MeOH/70% DCM to yield the title compound (**281**) (27 mg, 31%). LC/MS: Method 4: Rt = 0.98 min, *m/z* = 373.2 [MH^+].

[00564] The following examples were prepared according to similar procedures described for Example 249:

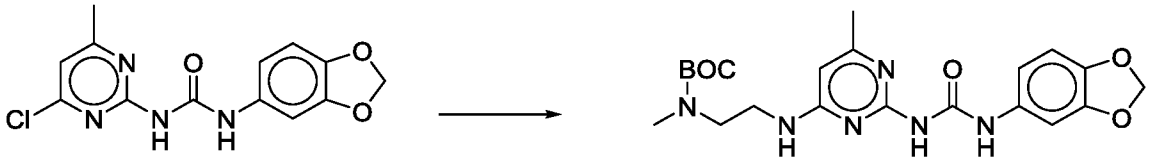
Cpd ID	Example ID	Structure	HPLC Method	Yield (mass/%)	RT (min)	MH^+
282	**250**		**4**	**12 mg, 18**	**0.99**	**345.2**
283	**251**		**4**	**23 mg, 31**	**0.93**	**331.2**
284	**252**		**4**	**33 mg, 40**	**1.10**	**359.2**
285	**253**		**4**	**59 mg, 76**	**1.68**	**316.2**
286	**254**		**4**	**65 mg, 81**	**1.85**	**330.2**

Example 255: Synthesis of 1-(benzo[d][1,3]dioxol-5-yl)-3-(4-methyl-6-((2-(methylamino)ethyl)amino)pyrimidin-2-yl)urea (288)



288

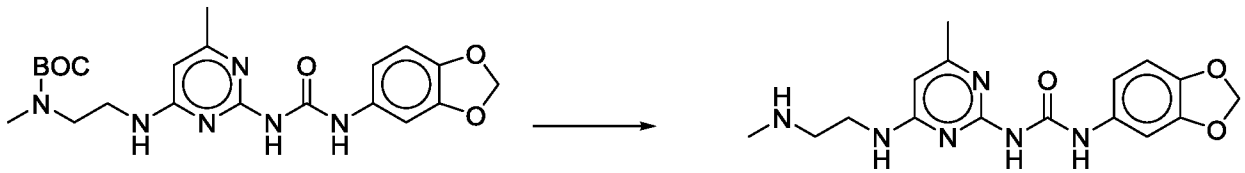
[00565] Step 1: *tert*-Butyl (2-((2-(3-(benzo[d][1,3]dioxol-5-yl)ureido)-6-methylpyrimidin-4-yl)amino)ethyl)(methyl)carbamate (**287**)



280 **287**

[00566] A mixture of 1-(benzo[d][1,3]dioxol-5-yl)-3-(4-chloro-6-methylpyrimidin-2-yl)urea (**280**) (82 mg, 0.27 mmol) and 2-propanol (0.5 mL) was treated with N-(2-aminoethyl)-N-methyl carbamic acid tert-butyl ester (0.06 mL, 0.32 mmol), and triethylamine (0.06 mL, 0.40 mmol) and this was heated to 80 °C with stirring overnight. Upon cooling the reaction was diluted with MeOH (3mL) and the precipitate formed was filtered to give the title compound (**287**) (85 mg, 72%). LC/MS: Method 4: Rt = 2.14 min, *m/z* = 445.3 [MH^+].

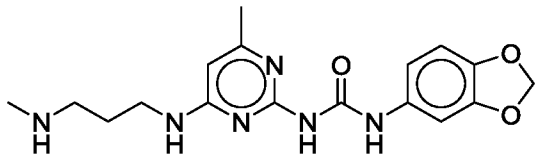
[00567] Step 2: 1-(Benzo[d][1,3]dioxol-5-yl)-3-(4-methyl-6-((2-(methylamino)ethyl)amino)pyrimidin-2-yl)urea



287 **288**

[00568] The BOC derivative (**287**) (85 mg, 0.19 mmol) was suspended in DCM (0.15 mL) to which trifluoroacetic acid (0.14 mL, 1.9 mmol) was added. After 40 minutes at room temperature the solvent was evaporated and the residue treated with saturated sodium bicarbonate solution to achieve a pH of 8. The title product was filtered and washed with water to yield a white solid (**288**) after drying (30 mg, 46%). LC/MS: Method 4: Rt = 0.94 min, *m/z* = 345.2 [MH^+].

Example 256: Synthesis of 1-(benzo[d][1,3]dioxol-5-yl)-3-(4-methyl-6-((3-(methylamino)propyl)amino)pyrimidin-2-yl)urea (289)

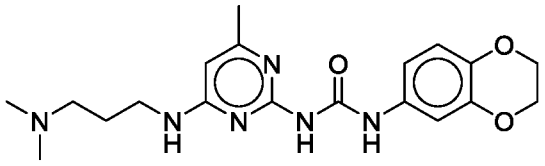


289

[00569] Example 262 was prepared in a similar manner to example 261 from 1-(benzo[d][1,3]dioxol-5-yl)-3-(4-chloro-6-methylpyrimidin-2-yl)urea (**287**) and N-(3-

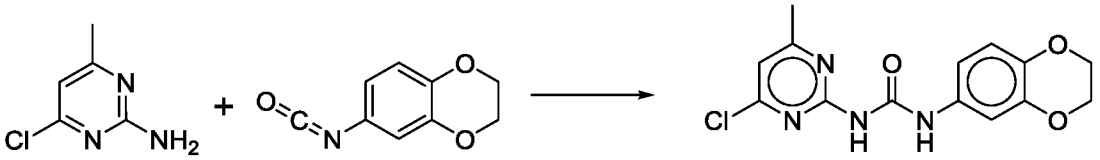
aminopropyl)-N-methyl carbamic acid tert-butyl ester. (17 mg, 19%) LC/MS: Method 4: Rt = 1.01 min, m/z = 359.2 [MH+].

Example 257: Synthesis of 1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-3-(4-((3-(dimethylamino)propyl)amino)-6-methylpyrimidin-2-yl)urea (291)



291

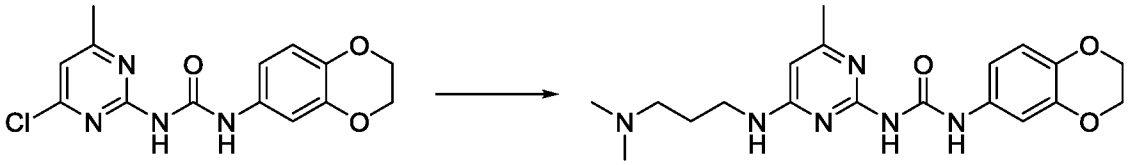
[00570] Step 1: 1-(4-Chloro-6-methylpyrimidin-2-yl)-3-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)urea (**290**)



290

[00571] A mixture of 2-amino-4-chloro-6-methylpyrimidine (2.1 g, 15 mmol) and 2H, 3H-benzo[e]1,4-dioxan-6-isocyanate (3 g, 16 mmol) in toluene (19.9 mL) was heated with stirring for 1 hour at 100 °C, then at 50 °C overnight. Upon cooling the mixture was diluted with methanol (20mL) and the slurry which formed was filtered, triturated with methanol and dried to yield compound (**290**) (2.8 g, 59%). This material was used directly in the next step.

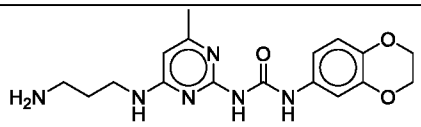
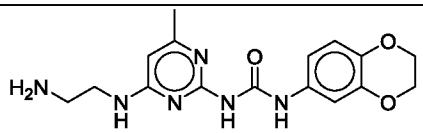
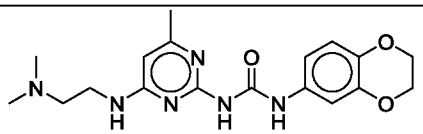
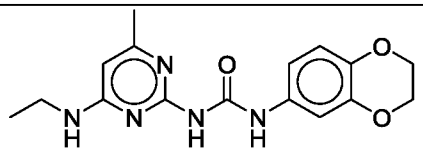
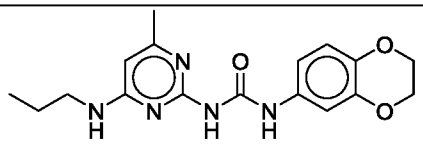
[00572] Step 2: 1-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)-3-(4-((3-(dimethylamino)propyl)amino)-6-methylpyrimidin-2-yl)urea (**291**)



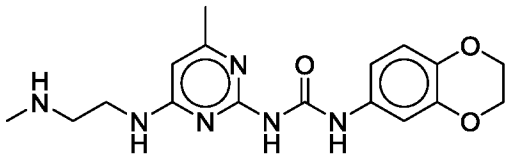
290 **291**

[00573] A mixture of 1-(4-chloro-6-methylpyrimidin-2-yl)-3-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)urea (**290**) (75 mg, 0.23 mmol), and 3-(dimethylamino)-1-propylamine (0.04 mL, 0.28 mmol) and triethylamine (0.05 mL, 0.35 mmol) in 2-propanol (0.47 mL) was heated for 5 hours at 80 °C. The reaction mixture was cooled and filtered and this solid was purified by preparative TLC eluting with 30% 1M NH4OH in MeOH/70% DCM to yield the title compound (**291**) (17 mg, 19%). LC/MS: Method 4: Rt = 1.04 min, *m/z* = 387.3 [MH^+].

[00574] The following examples were prepared according to similar procedures described for Example 257:

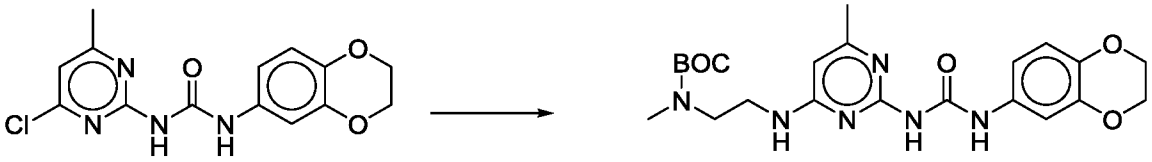
Cpd ID	Example ID	Structure	HPLC Method	Yield (mass/%)	RT (min)	MH^+
292	258		4	185 mg, 83	0.91	359.2
293	259		4	188 mg, 87	1.02	345.2
294	260		4	47 mg, 54	1.14	373.2
295	261		4	58 mg, 75	1.60	330.2
296	262		4	68 mg, 85	1.78	344.2

Example 263: Synthesis of 1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-3-(4-methyl-6-((2-(methylamino)ethyl)amino)pyrimidin-2-yl)urea (298)



298

[00575] Step 1: *tert*-Butyl (2-((2-(3-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)ureido)-6-methylpyrimidin-4-yl)amino)ethyl)(methyl)carbamate (**297**)

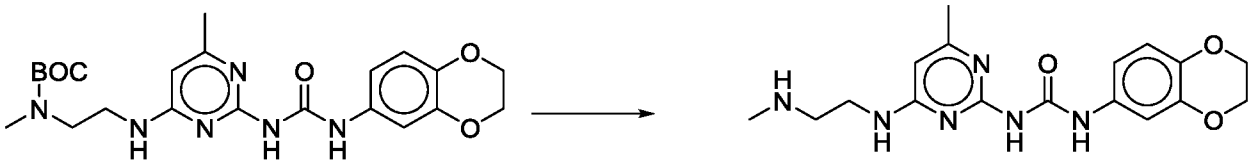


290 **297**

[00576] A mixture of 1-(4-chloro-6-methylpyrimidin-2-yl)-3-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)urea (**290**) (75 mg, 0.23 mmol) and 2-propanol (0.48 mL) was treated with N-(2-aminoethyl)-N-methyl carbamic acid tert-butyl ester (0.05 mL, 0.28 mmol), and triethylamine (0.05 mL, 0.35 mmol) and this was heated to 80 °C with stirring overnight. Upon cooling, the reaction was diluted with MeOH (3 mL) and the precipitate formed was filtered and further

washed with MeOH to give the title compound (**297**) (76 mg, 70%). LC/MS: Method 4: Rt = 2.10 min, *m/z* = 459.3 [MH^+].

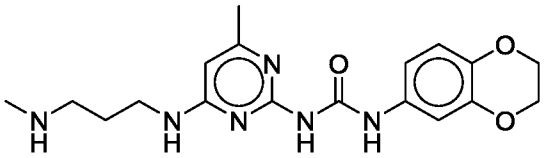
[00577] Step 2: 1-(benzo[d][1,3]dioxol-5-yl)-3-(4-methyl-6-((2-(methylamino)ethyl)amino)pyrimidin-2-yl)urea



297 **298**

[00578] The BOC derivative (**297**) (76 mg, 0.16 mmol) was suspended in DCM (0.1 mL) to which trifluoroacetic acid (0.12 mL, 1.6 mmol) was added. After 3.5 hours at room temperature the solvent was evaporated and the residue treated with saturated sodium bicarbonate solution to achieve a pH of 8. The title product was filtered and washed with water to yield a white solid (**298**) after drying. (42 mg, 71%) LC/MS: Method 4: Rt = 1.03 min, *m/z* = 359.2 [MH^+].

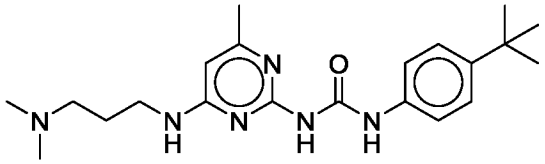
Example 264: Synthesis of 1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-3-(4-methyl-6-((3-(methylamino)propyl)amino)pyrimidin-2-yl)urea (299)



299

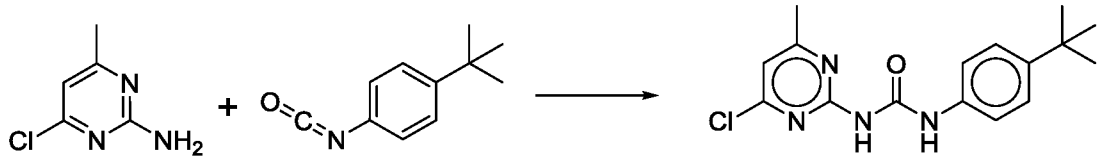
[00579] Example 262 was prepared in a similar manner to example 261 from 1-(4-chloro-6-methylpyrimidin-2-yl)-3-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)urea (**290**) and N-(3-aminopropyl)-N-methyl carbamic acid tert-butyl ester. (57 mg, 64%) LC/MS: Method 4: Rt = 1.03 min, m/z = 373.2 [MH+].

Example 265: Synthesis of 1-(4-(tert-butyl)phenyl)-3-(4-((3-(dimethylamino)propyl)amino)-6-methylpyrimidin-2-yl)urea (301)



301

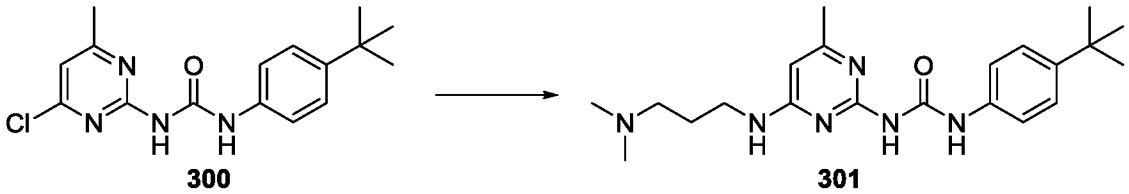
[00580] Step 1: 1-(4-(tert-Butyl)phenyl)-3-(4-chloro-6-methylpyrimidin-2-yl)urea (**300**)



300

[00581] A mixture of 2-amino-4-chloro-6-methylpyrimidine (2.0 g, 14 mmol) and 4-tert-butylphenyl isocyanate (2.9 g, 16 mmol) in toluene (12.7 mL) was stirred for 1 hour at room temperature, then heated at 110 °C overnight. Upon cooling the slurry which formed was filtered, washed with ether and dried to yield compound (**300**) (2.3 g, 53%). This material was used directly in the next step.

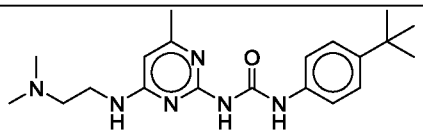
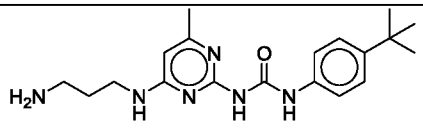
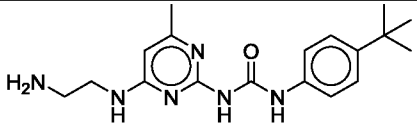
[00582] Step 2: 1-(4-(tert-Butyl)phenyl)-3-(4-((3-(dimethylamino)propyl)amino)-6-methylpyrimidin-2-yl)urea (**301**)



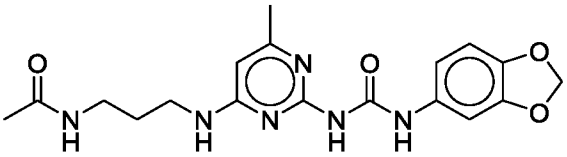
300 301

[00583] A mixture of 1-(4-(tert-butyl)phenyl)-3-(4-chloro-6-methylpyrimidin-2-yl)urea (**300**) (100 mg, 0.30 mmol), and 3-(dimethylamino)-1-propylamine (0.05 mL, 0.36 mmol) and triethylamine (0.06 mL, 0.45 mmol) in 2-propanol (0.5 mL) was heated for 2 hours at 80 °C. The reaction mixture was cooled and filtered to yield the title compound (**301**) (80 mg, 66%).
LC/MS: Method 4: Rt = 1.72 min, *m/z* = 385.3 [MH^+].

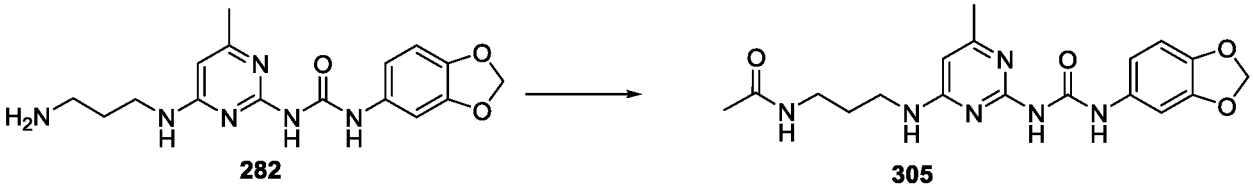
[00584] The following examples were prepared according to similar procedures described for Example 265:

Cpd ID	Example ID	Structure	Method	Yield (mass/%)	RT (min)	MH^+
302	**266**		**4**	**95 mg, 78**	**1.65**	**371.3**
303	**267**		**4**	**80 mg, 34**	**1.64**	**357.3**
304	**268**		**4**	**183 mg, 85**	**1.67**	**343.2**

Example 269: Synthesis of N-(3-((2-(3-(benzo[d][1,3]dioxol-5-yl)ureido)-6-methylpyrimidin-4-yl)amino)propyl)acetamide (305)



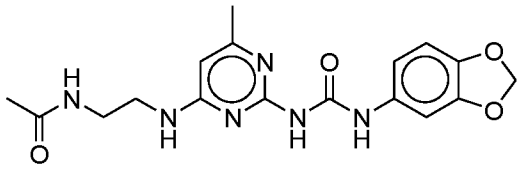
305



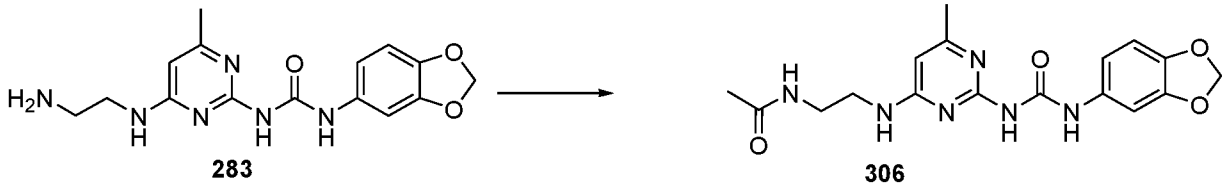
282 **305**

[00585] A mixture of 1-(4-((3-aminopropyl)amino)-6-methylpyrimidin-2-yl)-3-(benzo[d][1,3]dioxol-5-yl)urea (**282**) (75 mg, 0.22 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 (0.44 mL) was stirred at room temperature for 2 hours. At this time another aliquot of acetic anhydride (0.01 mL) was added and stirring continued overnight. The mixture was diluted with DCM (3 mL) and the resulting solids were filtered and dried to yield the title product (**305**) (39 mg, 47%). LC/MS: Method 4: Rt = 1.45 min, *m/z* = 387.2 [MH^+].

Example 270: Synthesis of N-{2-[2-(3-benzo[1,3]dioxol-5-yl-ureido)-6-methyl-pyrimidin-4-ylamino]-ethyl}-acetamide (306)



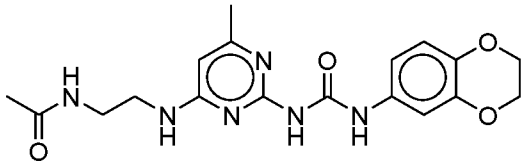
306



283 **306**

[00586] A mixture of 1-[4-(2-amino-ethylamino)-6-methyl-pyrimidin-2-yl]-3-benzo[1,3]dioxol-5-yl-urea (**283**) (75 mg, 0.23 mmol), acetic anhydride (0.02 mL, 0.25 mmol), pyridine (0.11 mL, 1.4 mmol) and a catalytic amount of N,N-dimethylaminopyridine in DCM (0.44 mL) was stirred at room temperature for 1 hour. The mixture was diluted with DCM (3mL) and the resulting solids were filtered and dried to yield the title product (**306**) (63 mg, 74%). LC/MS: Method 4: Rt = 1.34 min, *m/z* = 373.2 [MH^+].

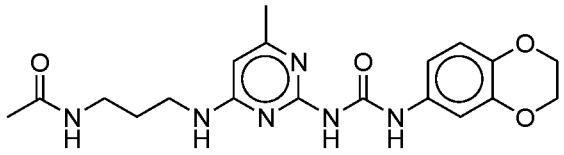
Example 271: Synthesis of N-(2-{2-[3-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-ureido]-6-methyl-pyrimidin-4-ylamino}-ethyl)-acetamide (307)



307

[00587] Example 271 was prepared by a similar procedure to that described for example 270 from 1-[4-(2-Amino-ethylamino)-6-methyl-pyrimidin-2-yl]-3-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-urea (**293**) (36 mg, 43%). LC/MS: Method 4: Rt = 1.43 min, *m/z* = 387.2 [MH^+].

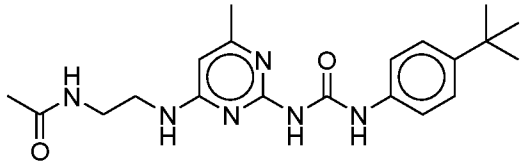
Example 272: Synthesis of N-(3-{2-[3-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-ureido]-6-methyl-pyrimidin-4-ylamino}-propyl)-acetamide (308)



308

[00588] Example 272 was prepared by a similar procedure to that described for example 270 from 1-[4-(3-amino-propylamino)-6-methyl-pyrimidin-2-yl]-3-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-urea (**292**) (58 mg, 69%). LC/MS: Method 4: Rt = 1.49 min, *m/z* = 401.2 [MH^+].

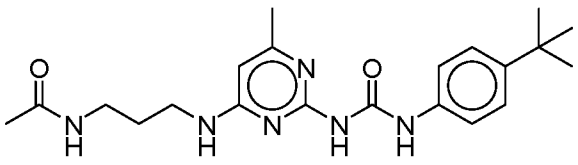
Example 273: Synthesis of N-(2-{2-[3-(4-tert-butyl-phenyl)-ureido]-6-methyl-pyrimidin-4-ylamino}-ethyl)-acetamide (309)



309

[00589] Example 273 was prepared by a similar procedure to that described for example 270 from 1-[4-(2-amino-ethylamino)-6-methyl-pyrimidin-2-yl]-3-(4-tert-butyl-phenyl)-urea (**293**) except the mixture was diluted with Et_2O (5 mL) prior to filtration of the solid product (40 mg, 21%). LC/MS: Method 4: Rt = 2.15 min, *m/z* = 385.3 [MH^+].

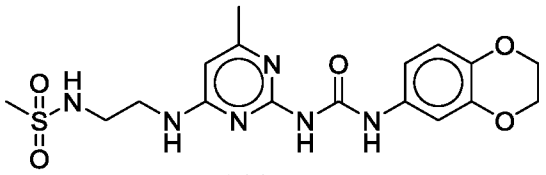
Example 274: Synthesis of N-(3-{2-[3-(4-tert-butyl-phenyl)-ureido]-6-methyl-pyrimidin-4-ylamino}-propyl)-acetamide (310)



310

[00590] Example 274 was prepared by a similar procedure to that described for example 270 from 1-[4-(3-amino-propylamino)-6-methyl-pyrimidin-2-yl]-3-(4-tert-butyl-phenyl)-urea (**303**) except the mixture was diluted with Et_2O (5 mL) prior to filtration of the solid product (40 mg, 21%). LC/MS: Method 4: Rt = 2.22 min, *m/z* = 399.3 [MH^+].

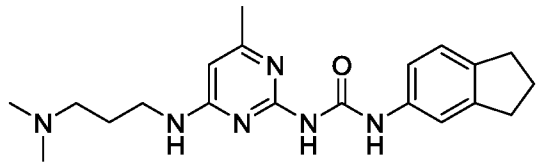
Example 275: Synthesis of N-2-(3-(2,3-dihydro-benzo[1, 4]dioxin-6-yl)-ureido)-6-methyl-pyrimidin-4-yl)-ethyl)methanesulfonamide (311)



311

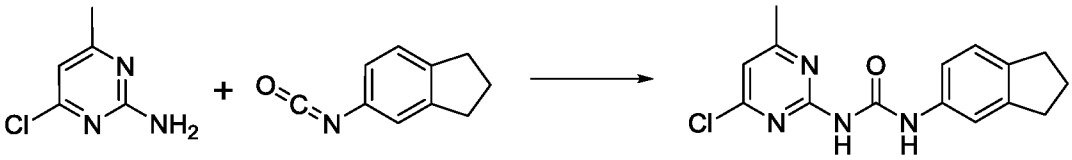
[00591] To a mixture of 1-(4-((3-aminoethyl)amino)-6-methylpyrimidin-2-yl)-3-(3-(trifluoromethoxy)phenyl)urea (**87**), (53 mg, 0.14 mmol) and triethylamine (0.04 mL , 0.28mmol) in DCM (0.48 mL) that was cooled to 0°C was added, methanesulfonyl chloride (0.01mL, 0.16 mmol), and this was stirred at room temperature for 5 hours. At this time the mixture was diluted with MeOH (5 mL) and the resulting solids filtered. This material was purified by silica gel chromatography using a gradient of 0-10% MeOH in DCM. Evaporation of the appropriate fractions afforded the title product (**311**) (5 mg, 7%). LC/MS: Method 4: Rt = 2.14 min, m/z = 449.1 [MH+].

Example 276: Synthesis of 1-(2,3-dihydro-1H-inden-5-yl)-3-(4-((3-(dimethylamino)propyl)amino)-6-methylpyrimidin-2-yl)urea (313)



313

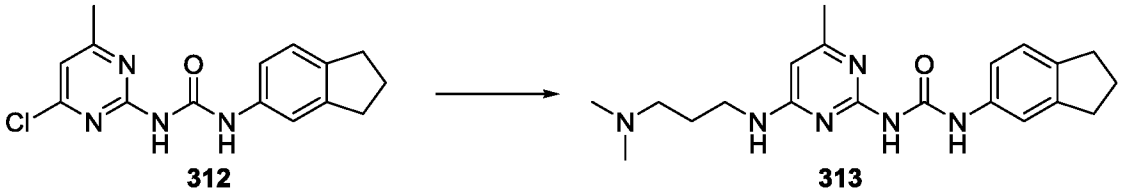
[00592] Step 1: 1-(4-Chloro-6-methylpyrimidin-2-yl)-3-(2,3-dihydro-1H-inden-5-yl)urea (**312**)



312

[00593] A mixture of 2-amino-4-chloro-6-methylpyrimidine (1.5 g, 10 mmol) and 5-indanyl isocyanate (2.0 g, 12 mmol) in toluene (9.5 mL) was stirred at room temperature for 1 hour then heated overnight at 110 ºC. Upon cooling the mixture was stirred overnight. The slurry which formed was filtered, washed with ether and dried to yield compound (**312**) (2.5g, 82%). LC/MS: Method 4: Rt = 3.79 min, *m/z* = 303.1 [MH^+]. This material was used directly in the next step.

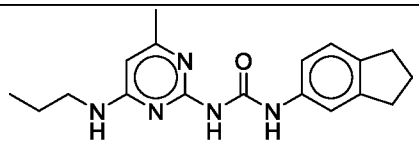
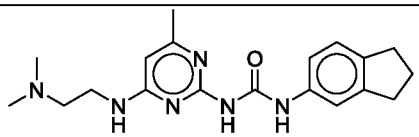
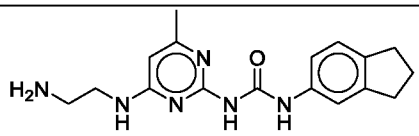
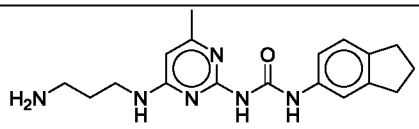
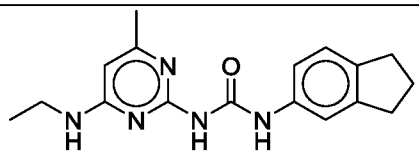
[00594] Step 2: 1-(2,3-Dihydro-1H-inden-5-yl)-3-(4-((3-(dimethylamino)propyl)amino)-6-methylpyrimidin-2-yl)urea (**313**)



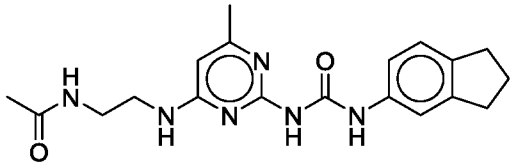
312 **313**

[00595] A mixture of 1-(4-chloro-6-methylpyrimidin-2-yl)-3-(2,3-dihydro-1H-inden-5-yl)urea (**312**) (0.1 g, 0.33 mmol), and 3-(dimethylamino)-1-propylamine (0.05 mL, 0.40 mmol) and triethylamine (0.07 mL, 0.5 mmol) in 2-propanol (0.66 mL) was heated for 2 hours at 80 °C. The reaction mixture was cooled and filtered to yield the title compound (**313**) (90 mg, 70%).
LC/MS: Method 4: Rt = 1.41 min, *m/z* = 369.3 [MH^+].

[00596] The following examples were prepared according to similar procedures described for Example 276:

Cpd ID	Example ID	Structure	HPLC Method	Yield (mass/%)	RT (min)	MH^+
314	**277**		**4**	**80 mg, 74**	**2.31**	**326.2**
315	**278**		**4**	**95 mg, 77**	**1.44**	**355.3**
316	**279**		**4**	**75 mg, 70**	**1.37**	**327.2**
317	**280**		**4**	**80 mg, 68**	**1.42**	**341.2**
318	**281**		**4**	**8 mg, 8**	**2.21**	**312.2**

Example 282: Synthesis of N-(2-{2-[3-(2,3-dihydro-1H-inden-5-yl)-ureido]-6-methyl-pyrimidin-4-ylamino}-ethyl)-acetamide (319)



319

[00597] A mixture of 1-[4-(2-amino-ethylamino)-6-methyl-pyrimidin-2-yl]-3--(2,3-dihydro-1H-inden-5-yl)-urea (**316**) (62 mg, 0.19 mmol), acetic anhydride (0.02 mL, 0.21 mmol), pyridine (0.10 mL, 1.2 mmol) and a catalytic amount of N,N-dimethylaminopyridine in DCM (0.38 mL) was stirred at room temperature for 3 hours. The mixture was cooled in a freezer then diluted with diethyl ether (5 mL). The resulting solids were filtered and dried to yield the title product (**319**) (40 mg, 57%). LC/MS: Method 4: Rt = 1.87 min, m/z = 369.2 [MH+].

Example 283: GBM4 and GBM8 Viability Assay

[00598] 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.

[00599] 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. Table 1 below shows 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)
2	NT	NT	173	NT	A
3	NT	NT	174	NT	B
4	C	B	175	NT	A
5	C	NT	176	NT	A
6	B	B	177	NT	A
7	A	A	178	NT	A
8	A	A	180	NT	A
9	NT	A	181	NT	A
10	NT	A	182	NT	A
11	NT	A	183	NT	B
12	NT	A	184	NT	A
13	NT	A	185	NT	A
14	NT	A	186	NT	A
15	NT	A	187	NT	A
16	NT	A	188	NT	A
17	NT	A	189	NT	B
18	NT	A	190	NT	A
19	NT	B	191	NT	A
20	NT	A	192	NT	A
21	NT	B	194	NT	A
22	NT	A	196	NT	A
24	A	A	197	NT	A

Cpd #	GBM4 IC50 (uM)	GBM8 IC50 (uM)	Cpd #	GBM4 IC50 (uM)	GBM8 IC50 (uM)
26	NT	A	198	NT	A
27	NT	A	199	NT	A
28	NT	A	200	NT	A
29	NT	A	201	NT	A
30	C	C	202	NT	A
34	C	B	203	NT	A
35	NT	A	204	NT	B
36	NT	A	205	NT	B
37	B	NT	206	NT	B
38	C	B	207	NT	A
39	B	B	209	NT	A
41	NT	A	210	NT	A
43	NT	A	211	NT	A
44	NT	A	212	NT	A
45	NT	A	213	NT	A
47	NT	A	214	NT	B
48	NT	B	215	NT	A
49	NT	A	216	NT	A
50	NT	A	217	NT	A
51	NT	A	218	NT	A
52	NT	A	219	NT	A
53	NT	A	220	NT	B
54	NT	A	221	NT	B

Cpd #	GBM4 IC50 (uM)	GBM8 IC50 (uM)	Cpd #	GBM4 IC50 (uM)	GBM8 IC50 (uM)
55	NT	A	222	NT	A
56	NT	B	223	NT	A
57	NT	B	224	NT	A
58	NT	B	225	NT	A
59	NT	A	226	NT	A
60	NT	A	227	NT	A
61	NT	A	229	NT	B
63	NT	B	230	NT	A
64	NT	A	231	NT	B
65	NT	A	232	NT	A
66	NT	A	234	NT	A
67	NT	A	235	NT	A
69	NT	B	236	NT	A
70	NT	B	237	NT	A
71	NT	B	238	NT	B
72	NT	B	239	NT	A
73	NT	B	240	NT	A
74	NT	B	241	NT	A
75	NT	B	242	NT	B
76	NT	B	243	NT	A
77	NT	B	244	NT	B
78	NT	A	245	NT	B
79	NT	B	246	NT	A

Cpd #	GBM4 IC50 (uM)	GBM8 IC50 (uM)	Cpd #	GBM4 IC50 (uM)	GBM8 IC50 (uM)
80	NT	B	248	NT	B
82	NT	B	249	NT	B
83	NT	B	251	NT	A
85	NT	A	252	NT	A
86	NT	A	253	NT	A
87	NT	A	254	NT	A
88	NT	A	255	NT	A
89	NT	A	256	NT	A
90	NT	A	257	NT	A
91	NT	A	258	NT	B
92	NT	A	259	NT	A
93	NT	A	260	NT	B
94	NT	A	261	NT	A
95	NT	A	262	NT	A
96	NT	A	263	NT	A
98	NT	A	264	NT	A
99	NT	A	265	NT	A
101	NT	A	266	NT	A
102	NT	A	268	NT	B
103	NT	A	269	NT	A
104	NT	A	270	NT	A
105	NT	A	271	NT	A
106	NT	A	272	NT	B

Cpd #	GBM4 IC50 (uM)	GBM8 IC50 (uM)	Cpd #	GBM4 IC50 (uM)	GBM8 IC50 (uM)
107	NT	A	273	NT	A
108	NT	A	274	NT	A
109	NT	A	275	NT	A
110	NT	A	276	NT	A
111	NT	A	277	NT	B
112	NT	A	278	NT	A
113	NT	B	279	NT	A
114	NT	A	281	NT	B
115	NT	A	282	NT	A
116	NT	A	283	NT	A
117	NT	A	284	NT	B
118	NT	A	285	NT	A
120	NT	A	286	NT	A
121	NT	A	288	NT	A
122	NT	A	289	NT	B
123	NT	A	291	NT	A
125	NT	A	292	NT	A
126	NT	A	293	NT	B
127	NT	A	294	NT	A
128	NT	A	295	NT	A
129	NT	A	296	NT	A
130	NT	A	298	NT	A
131	NT	A	299	NT	B

Cpd #	GBM4 IC50 (uM)	GBM8 IC50 (uM)	Cpd #	GBM4 IC50 (uM)	GBM8 IC50 (uM)
132	NT	A	301	NT	A
133	NT	A	302	NT	B
134	NT	B	303	NT	A
135	NT	A	304	NT	A
136	NT	A	305	NT	A
137	NT	A	306	NT	B
138	NT	A	307	NT	A
139	NT	A	308	NT	A
141	NT	B	309	NT	A
142	NT	B	310	NT	A
143	NT	B	311	NT	A
144	NT	B			
145	NT	B			
146	NT	B			
147	NT	B			
148	NT	B			
149	NT	B			
150	NT	B			
151	NT	B			
153	NT	B			
154	NT	B			
155	NT	B			
157	NT	A			

Cpd #	GBM4 IC50 (uM)	GBM8 IC50 (uM)	Cpd #	GBM4 IC50 (uM)	GBM8 IC50 (uM)
158	NT	A			
159	NT	B			
160	NT	A			
161	NT	A			
162	NT	A			
163	NT	A			
164	NT	A			
165	NT	A			
166	NT	A			
167	NT	B			
169	NT	A			
170	NT	A			
172	NT	A			
173	NT	A			

IC50: A <1 μM; 1 μM ≤ B ≤10 μM; 10 μM < C ≤30 μM; NT = not tested

Example 284: Phase II Clinical Trial of Compounds of Formula (I), (II), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI) in Patients with Recurrent Rb Positive Glioblastoma

[00600] The purpose of this phase II trial is to determine the efficacy of a compound of Formula (I), (II), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI) (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.

[00601] Patients: Eligible subjects will be men and women 18 years and older

[00602] 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.

[00603] Study Design: A total of 30 patients with recurrent Glioblastoma or Gliosarcoma will be treated with a compound of Formula (I), (II), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI) 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.

[00604] 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.

[00605] 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).

[00606] 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), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI) 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

[00607] 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 285: Phase II Clinical Trial of the Safety and Efficacy of Compounds of Formula (I), (II), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI) in Adults With Recurrent or Refractory Medulloblastoma.

[00608] The purpose of this phase II trial is to how well a compound of Formula (I), (II), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI) works in treating adult patients with recurrent or refractory medulloblastoma.

[00609] Patients: Eligible subjects will be men and women 22 years and older.

[00610] 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

[00611] Study Design: Patients receive a compound of Formula (I), (II), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI) 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.

[00612] 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.

[00613] 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), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI) 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 286: Phase I/II Clinical Trial of the Safety, Tolerability, and Anti-tumor Efficacy of Compounds of Formula (I), (II), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI) in the Treatment of Recurrent Malignant Astrocytomas

[00614] 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), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI) 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.

[00615] Patients: Eligible subjects will be men and women ages 18 and older

[00616] Criteria**:**

[00617] 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), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI)
- 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 ≥ 100 g/L (transfusions are allowed) Plasma total bilirubin level ≤ 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

[00618] Study Design:

[00619] 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), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI) 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), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI) in patients with recurrent or progressive glioblastoma and to assess the safety and toxicity of the compound of Formula (I), (II), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI) 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), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI) 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), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI), 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).

[00620] In the second phase, 12 patients will be enrolled and treated with the identified RP2D of the compound of Formula (I), (II), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI) 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), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI).

[00621] 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)

[00622] 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), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI).
- 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), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI) 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), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI)

- 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), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI)

- 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 287: Pharmaceutical Compositions

Example 287A: Parenteral Composition

[00623] To prepare a parenteral pharmaceutical composition suitable for administration by injection, 100 mg of a compound of Formula (I), (II), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI) 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.

[00624] In another embodiment, the following ingredients are mixed to form an injectable formulation:

Ingredient	Amount
Compound of Formula (I), (II), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI)	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

[00625] 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 287B: Oral Composition

[00626] To prepare a pharmaceutical composition for oral delivery, 100 mg of a compound of Formula (I), (II), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI) 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.

[00627] 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), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI)	200
Cornstarch	50
croscarmellose sodium	25
Lactose	120
magnesium stearate	5

[00628] 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), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI)	200
lactose, spray-dried	148
magnesium stearate	2

[00629] In yet another embodiment, the following ingredients are mixed to form a solution/suspension for oral administration:

Ingredient	**Amount**
Compound of Formula (I), (II), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI)	1 g
Anhydrous Sodium Carbonate	0.1 g
Ethanol (200 proof), USP	10 mL
Purified Water, USP	90 mL
Aspartame	0.003g

Example 287C: Sublingual (Hard Lozenge) Composition

[00630] To prepare a pharmaceutical composition for buccal delivery, such as a hard lozenge, mix 100 mg of a compound of Formula (I), (II), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI) 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 287D: Inhalation Composition

[00631] To prepare a pharmaceutical composition for inhalation delivery, 20 mg of a compound of Formula (I), (II), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI) 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 287E: Rectal Gel Composition

[00632] To prepare a pharmaceutical composition for rectal delivery, 100 mg of a compound of Formula (I), (II), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI) 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 287F: Suppository Formulation

[00633] A suppository of total weight 2.5 g is prepared by mixing a compound of Formula (I), (II), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI) with Witepsol™ 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), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI)	500
Witepsol® H-15	balance

Example 287G: Topical Gel Composition

[00634] To prepare a pharmaceutical topical gel composition, 100 mg of a compound of Formula (I), (II), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI) 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.

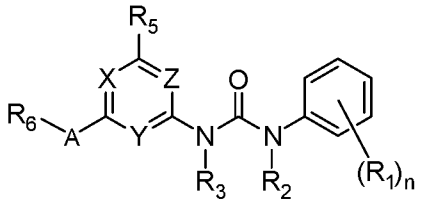
Example 287H: Ophthalmic Solution Composition

[00635] To prepare a pharmaceutical opthalmic solution composition, 100 mg of a compound of Formula (I), (II), (IIA), (IIB), (IIC), (IID), (III), (IV), (V) or (VI) 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.

[00636] 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:

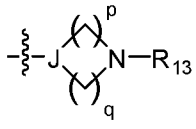
A is a bond, O, or $N(R_{10})$;

X, Y, and Z are each independently N, or $C(R_7)$ wherein at least one of X, Y, and Z are N;

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; 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_5 is 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 substituted or unsubstituted C_2-C_7heterocycloalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted C_2-C_7heteroaryl, $-(C(R_{14})(R_{15}))_mR_{21}$, $-(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$, or  ;

R_{11} and R_{12} are each independently H, or substituted or unsubstituted C_1-C_6alkyl; or R_{11} and R_{12} are taken together to form a 5-, 6-, 7-, or 8-membered heterocyclic ring;

J is C(H), or N;

R_{13} is H, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_2-C_7heterocycloalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted -C_1-C_4alkylC_6-C_{10}aryl, or substituted or unsubstituted -C_1-C_4alkylC_2-C_7heteroaryl;

each R_7 is 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_7heteroaryl;

each R_{14} and R_{15} are each independently H, or substituted or unsubstituted C_1-C_6alkyl; or R_{14} and R_{15} are taken together to form a 4-, 5-, 6-membered cycloalkyl ring;

R_{21} is halogen, -CN, $-NO_2$, -OH, $-OCF_3$, $-OCH_2F$, $-OCF_2H$, $-CF_3$, $-SR_{22}$, $-N(R_{22})S(=O)_2R_{23}$, $-S(=O)_2N(R_{22})_2$, $-S(=O)R_{23}$, $-S(=O)_2R_{23}$, $-C(=O)R_{23}$, $-CO_2R_{22}$, $-C(=O)N(R_{22})_2$, $-N(R_{22})C(=O)R_{23}$, 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;

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

R_{23} is substituted or unsubstituted C_1-C_6alkyl;

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

R_9 is substituted or unsubstituted C_1-C_6alkyl;

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

m is 2-6;

n is 0-5;

p is 1-3;

q is 1-3; 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.

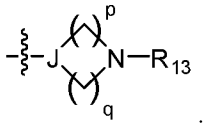
4. The compound of claim 1, wherein R_2 and R_3 are taken together to form a 5- or 6-membered heterocyclic ring.

5. The compound of claim 4, wherein R_2 and R_3 are taken together to form a 5-membered heterocyclic ring.

6. The compound of any one of claims 1-5, wherein R_6 is substituted or unsubstituted C_2-C_7heteroaryl.

7. The compound of claim 6, wherein R_6 is substituted or unsubstituted pyridyl.

8. The compound of claim 7, wherein R_6 is unsubstituted pyridyl.

9. The compound of any one of claims 1-5, wherein R_6 is  .

10. The compound of claim 9, wherein R_{13} is H.

11. The compound of claim 9, wherein R_{13} is substituted or unsubstituted C_1-C_6alkyl.

12. The compound of claim 11, wherein R_{13} is $-CH_3$.

13. The compound of claim 11, wherein R_{13} is $-CH_2CH_3$.

14. The compound of any one of claims 9-13, wherein J is C(H).

15. The compound of claim 14, wherein p is 2 and q is 1.

16. The compound of claim 14, wherein p is 3 and q is 1.

17. The compound of claim 14, wherein p is 2 and q is 2.

18. The compound of any one of claims 9-13, wherein J is N.

19. The compound of claim 18, wherein p is 2 and q is 2.

20. The compound of any one of claims 1-5, wherein R_6 is substituted or unsubstituted C_2-C_7heterocycloalkyl.

21. The compound of claim 20, wherein R_6 is substituted or unsubstituted morpholinyl.

22. The compound of claim 20, wherein R_6 is substituted or unsubstituted piperidinyl.

23. The compound of any one of claims 1-5, wherein R_6 is $-(C(R_{14})(R_{15}))_mR_{21}$.

24. The compound of claim 23, wherein R_{21} is -OH.

25. The compound of any one of claims 1-5, wherein R_6 is $-(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$.

26. The compound of claim 25, wherein R_{11} and R_{12} are each CH_3.

27. The compound of any one of claims 23-26, wherein R_{14} and R_{15} are each H.

28. The compound of any one of claims 23-27, wherein m is 2.

29. The compound of any one of claims 23-27, wherein m is 3.

30. The compound of any one of claims 1-29, wherein A is $N(R_{10})$.

31. The compound of claim 30, wherein R_{10} is H or CH_3.

32. The compound of any one of claims 1-29, wherein A is O.

33. The compound of any one of claims 1-29, wherein A is a bond.

34. The compound of any one of claims 1-33, wherein R_5 is substituted or unsubstituted C_1-C_6alkyl.

35. The compound of claim 34, wherein R_5 is CH_3.

36. The compound of claim 34, wherein R_5 is CH_2CH_3.

37. The compound of any one of claims 1-36, wherein n is 2.

38. The compound of any one of claims 1-36, wherein n is 1.

39. The compound of any one of claims 1-36, wherein n is 0.

40. The compound of any one of claims 1-38, wherein each R_1 is independently halogen, -CN, $-NO_2$, -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.

41. The compound of claim 40, wherein each R_1 is independently halogen, -CN, -OH, $-CF_3$, substituted or unsubstituted C_1-C_6alkyl, or substituted or unsubstituted C_1-C_6alkoxy.

42. The compound of any one of claims 1-37, wherein two R_1 are taken together to form a substituted or unsubstituted heterocyclic ring or a substituted or unsubstituted carbocyclic ring.

43. The compound of any one of claims 1-42, wherein X is $C(R_7)$; Y is N; and Z is N.

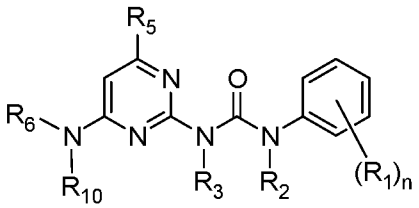
44. The compound of any one of claims 1-42, wherein X is $C(R_7)$; Y is $C(R_7)$; and Z is N.

45. The compound of any one of claims 1-42, wherein X is $C(R_7)$; Y is N; and Z is $C(R_7)$.

46. The compound of any one of claims 1-42, wherein X is $C(R_7)$; Y is $C(R_7)$; and Z is $C(R_7)$.

47. The compound of any one of claims 1-46, wherein R_7 is H.

48. A compound having the structure of Formula (II):



Formula (II);

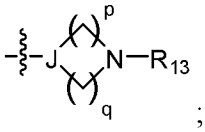
wherein:

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 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_5 is 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 substituted or unsubstituted C_2-C_7heterocycloalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted C_2-C_7heteroaryl, $-(C(R_{14})(R_{15}))_mR_{21}$, or



;

J is C(H);

R_{13} is H, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_2-C_7heterocycloalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted -C_1-C_4alkylC_6-C_{10}aryl, or substituted or unsubstituted -C_1-C_4alkylC_2-C_7heteroaryl;

each R_{14} and R_{15} are each independently H, or substituted or unsubstituted C_1-C_6alkyl; or R_{14} and R_{15} are taken together to form a 4-, 5-, 6-membered cycloalkyl ring;

R_{21} is halogen, $-CN$, $-NO_2$, -OH, $-OCF_3$, $-OCH_2F$, $-OCF_2H$, $-CF_3$, $-SR_{22}$, $-N(R_{22})S(=O)_2R_{23}$, $-S(=O)_2N(R_{22})_2$, $-S(=O)R_{23}$, $-S(=O)_2R_{23}$, $-C(=O)R_{23}$, $-CO_2R_{22}$, $-C(=O)N(R_{22})_2$, $-N(R_{22})C(=O)R_{23}$, 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 C_6-C_{10}aryl, or substituted or unsubstituted C_2-C_7heteroaryl;

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

R_{23} is substituted or unsubstituted C_1-C_6alkyl;

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

R_9 is substituted or unsubstituted C_1-C_6alkyl;

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

m is 2-6;

n is 0-5;

p is 1-3;

q is 1-3; or

a pharmaceutically acceptable salt, solvate, or prodrug thereof.

49. The compound of claim 48, wherein R_2 and R_3 are each independently H, -CN, C_1-C_4alkyl, C_3-C_6cycloalkyl, or C_2-C_7heterocycloalkyl.

50. The compound of claim 49, wherein R_2 and R_3 are each H.

51. The compound of claim 48, wherein R_2 and R_3 are taken together to form a 5- or 6-membered heterocyclic ring.

52. The compound of claim 51, wherein R_2 and R_3 are taken together to form a 5-membered heterocyclic ring.

53. The compound of any one of claims 48-52, wherein R_6 is $-(C(R_{14})(R_{15}))_mR_{21}$.

54. The compound of any one of claims 48-53, wherein R_{21} is -OH, $-N(R_{22})S(=O)_2R_{23}$, $-CO_2R_{22}$, $-C(=O)N(R_{22})_2$, $-N(R_{22})C(=O)R_{23}$, substituted or unsubstituted C_1-C_6alkoxy, or substituted or unsubstituted C_2-C_7heteroaryl.

55. The compound of claim 54, wherein R_{21} is -OH.

56. The compound of claim 54, wherein R_{21} is $-N(R_{22})S(=O)_2R_{23}$.

57. The compound of claim 54, wherein R_{21} is $-N(R_{22})C(=O)R_{23}$.

58. The compound of claim 54, wherein R_{21} is substituted or unsubstituted C_1-C_6alkoxy.

59. The compound of claim 54, wherein R_{21} is substituted or unsubstituted C_2-C_7heteroaryl.

60. The compound of any one of claims 48-59, wherein each R_{22} is independently H or unsubstituted C_1-C_6alkyl; and R_{23} is unsubstituted C_1-C_6alkyl.

61. The compound of any one of claims 48-60, wherein R_{14} and R_{15} are each independently H, or substituted or unsubstituted C_1-C_6alkyl.

62. The compound of any one of claims 48-60, wherein R_{14} and R_{15} are each H.

63. The compound of any one of claims 48-62, wherein m is 2.

64. The compound of any one of claims 48-62, wherein m is 3.

65. The compound of any one of claims 48-52, wherein R_6 is substituted or unsubstituted C_2-C_7heteroaryl.

66. The compound of claim 65, wherein R_6 is substituted or unsubstituted pyridyl.

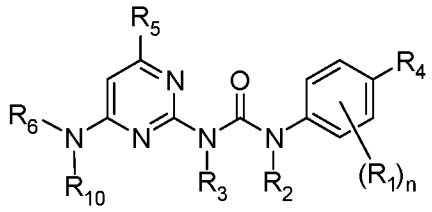
67. The compound of any one of claims 48-52, wherein R_6 is substituted or unsubstituted C_2-C_7heterocycloalkyl.

68. The compound of claim 67, wherein R_6 is substituted or unsubstituted morpholinyl.

69. The compound of claim 67, wherein R_6 is substituted or unsubstituted piperidinyl.

70. The compound of any one of claims 48-69, wherein R_{10} is H or CH_3.

71. A compound having the structure of Formula (IIA):



Formula (IIA);

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; 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, -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; or two R_1 are taken together to form a substituted or unsubstituted heterocyclic ring or a substituted or unsubstituted carbocyclic ring; wherein when n is 0, R_4 is not halogen;

R_5 is 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 -$(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$;

R_{11} and R_{12} are each independently H, or substituted or unsubstituted C_1-C_6alkyl; or R_{11} and R_{12} are taken together to form a 5-, 6-, 7-, or 8-membered heterocyclic ring;

R_{13} is H, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_2-C_7heterocycloalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or

unsubstituted -C_1-C_4alkylC_6-C_{10}aryl, or substituted or unsubstituted -C_1-C_4alkylC_2-C_7heteroaryl;

each R_{14} and R_{15} are each independently H, or substituted or unsubstituted C_1-C_6alkyl; or R_{14} and R_{15} are taken together to form a 4-, 5-, 6-membered cycloalkyl ring;

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

R_9 is substituted or unsubstituted C_1-C_6alkyl;

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

m is 2-6;

n is 0-4; or

a pharmaceutically acceptable salt, solvate, or prodrug thereof.

72. The compound of claim 71, wherein R_2 and R_3 are each independently H, -CN, C_1-C_4alkyl, C_3-C_6cycloalkyl, or C_2-C_7heterocycloalkyl.

73. The compound of claim 72, wherein R_2 and R_3 are each H.

74. The compound of claim 71, wherein R_2 and R_3 are taken together to form a 5- or 6-membered heterocyclic ring.

75. The compound of claim 74, wherein R_2 and R_3 are taken together to form a 5-membered heterocyclic ring.

76. The compound of any one of claims 71-75, wherein R_6 is -$(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$ and R_{14} and R_{15} are each H.

77. The compound of claim 76, wherein R_{11} and R_{12} are each independently H, or substituted or unsubstituted C_1-C_6alkyl.

78. The compound of claim 77, wherein R_{11} and R_{12} are each independently unsubstituted C_1-C_6alkyl.

79. The compound of claim 78, wherein R_{11} and R_{12} are each -CH_3.

80. The compound of any one of claims 71-79, wherein m is 2.

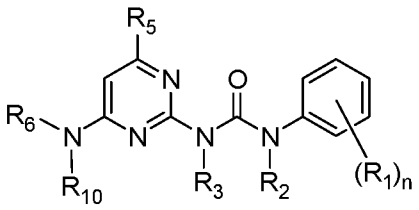
81. The compound of any one of claims 71-79, wherein m is 3.

82. The compound of any one of claims 71-81, wherein R_{10} is H or CH_3.

83. The compound of any one of claims 71-82, wherein n is 0.

84. The compound of any one of claims 71-82, wherein n is 1.

85. A compound having the structure of Formula (VI):



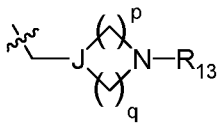
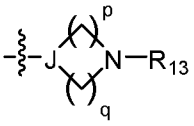
Formula (VI);

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; 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 or C_1-C_4alkyl; or R_2 and R_3 are taken together to form a 5- or 6-membered heterocyclic ring;

R_5 is substituted or unsubstituted C_1-C_6alkyl;

R_6 is unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_2-C_7heterocycloalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted C_2-C_7heteroaryl, -$(C(R_{14})(R_{15}))_mR_{21}$,  or  ;

J is C(H);

R_{13} is H, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_2-C_7heterocycloalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted -C_1-C_4alkylC_6-C_{10}aryl, or substituted or unsubstituted -C_1-C_4alkylC_2-C_7heteroaryl;

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

R_{21} is halogen, -CN, -NO_2, -OH, -OCF_3, -OCH_2F, -OCF_2H, -CF_3, -SR_{22}, -$N(R_{22})S(=O)_2R_{23}$, -$S(=O)_2N(R_{22})_2$, -$S(=O)R_{23}$, -$S(=O)_2R_{23}$, -$C(=O)R_{23}$, -CO_2R_{22}, -$C(=O)N(R_{22})_2$, -$N(R_{22})C(=O)R_{23}$, substituted or unsubstituted C_1-C_6alkoxy, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_2-C_7heterocycloalkyl, or substituted or unsubstituted C_2-C_7heteroaryl;

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

R_{23} is substituted or unsubstituted C_1-C_6alkyl;

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

R_9 is substituted or unsubstituted C_1-C_6alkyl;

R_{10} is H;

m is 2-6;

n is 0-5;

p is 1-3;

q is 1-3; or

a pharmaceutically acceptable salt, solvate, or prodrug thereof.

86. The compound of claim 85, wherein R_2 and R_3 are each independently H or C_1-C_4alkyl.

87. The compound of claim 86, wherein R_2 and R_3 are each H.

88. The compound of claim 85, wherein R_2 and R_3 are taken together to form a 5- or 6-membered heterocyclic ring.

89. The compound of claim 88, wherein R_2 and R_3 are taken together to form a 5-membered heterocyclic ring.

90. The compound of any one of claims 85-89, wherein R_6 is $-(C(R_{14})(R_{15}))_mR_{21}$.

91. The compound of any one of claims 85-90, wherein each R_{14} and R_{15} are each independently H, halogen, or unsubstituted C_1-C_6alkyl.

92. The compound of any one of claims 85-90, wherein R_{14} and R_{15} are each H.

93. The compound of any one of claims 85-92, wherein R_{21} is -OH, $-N(R_{22})S(=O)_2R_{23}$, $-CO_2R_{22}$, $-C(=O)N(R_{22})_2$, $-N(R_{22})C(=O)R_{23}$, substituted or unsubstituted C_1-C_6alkoxy, or substituted or unsubstituted C_2-C_7heteroaryl.

94. The compound of claim 93, wherein R_{21} is -OH.

95. The compound of claim 93, wherein R_{21} is $-N(R_{22})S(=O)_2R_{23}$.

96. The compound of claim 93, wherein R_{21} is $-N(R_{22})C(=O)R_{23}$.

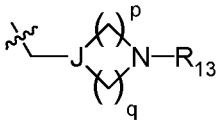
97. The compound of claim 93, wherein R_{21} is substituted or unsubstituted C_1-C_6alkoxy.

98. The compound of claim 93, wherein R_{21} is substituted or unsubstituted C_2-C_7heteroaryl.

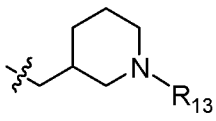
99. The compound of any one of claims 85-98, wherein each R_{22} is independently H or unsubstituted C_1-C_6alkyl; and R_{23} is unsubstituted C_1-C_6alkyl.

100. The compound of any one of claims 85-99, wherein m is 2.

101. The compound of any one of claims 85-99, wherein m is 3.

102. The compound of any one of claims 85-89, wherein R_6 is 

.

103. The compound of any one of claims 85-89, wherein R_6 is 

.

104. The compound of claim 102 or 103, wherein R_{13} is H or unsubstituted C_1-C_6alkyl,

105. The compound of any one of claims 85-104, wherein each R_1 is independently halogen, $-OCF_3$, $-CF_3$, unsubstituted C_1-C_6alkyl, or unsubstituted C_1-C_6alkoxy.

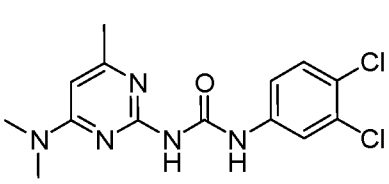
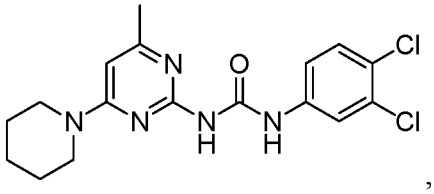
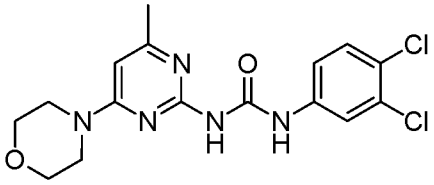
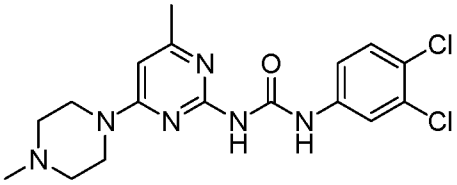
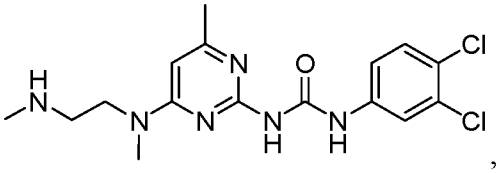
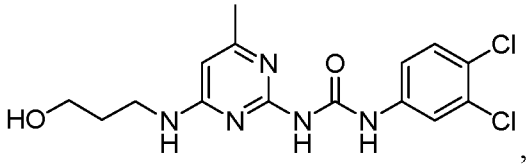
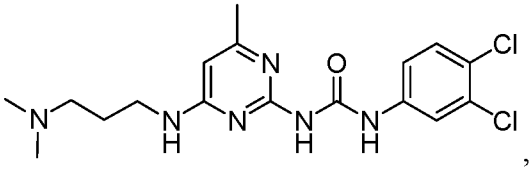
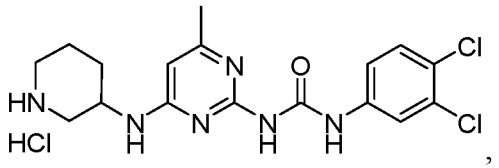
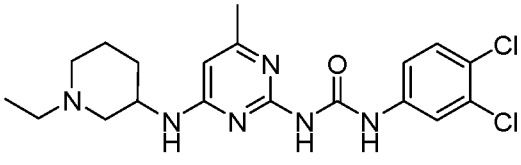
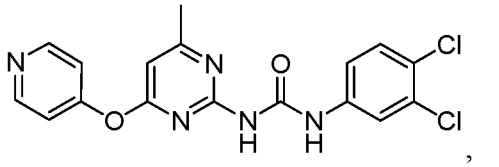
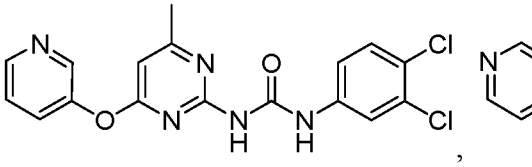
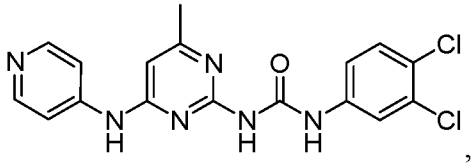
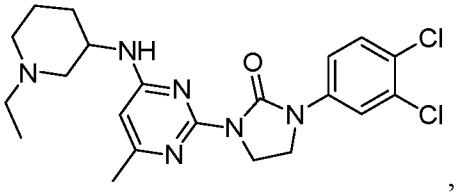
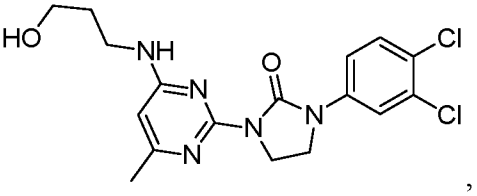
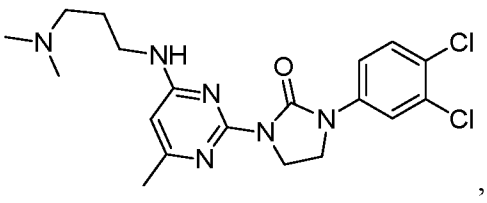
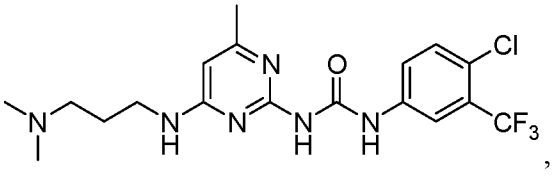
106. The compound of any one of claims 85-104, wherein each R_1 is independently halogen.

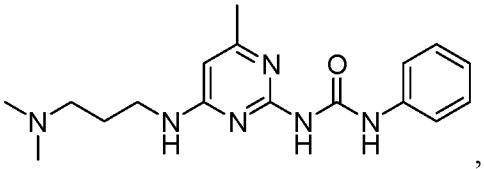
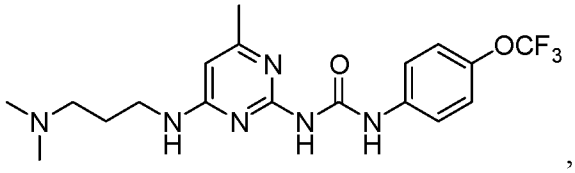
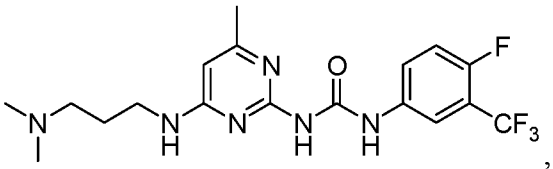
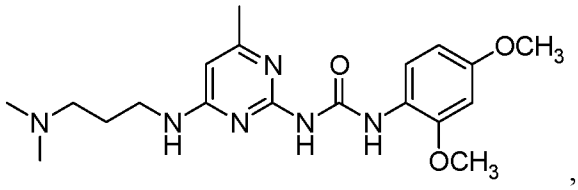
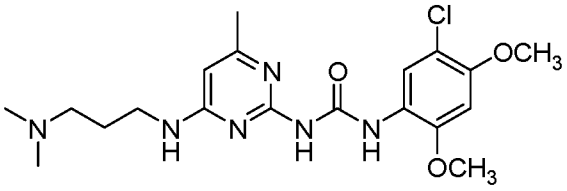
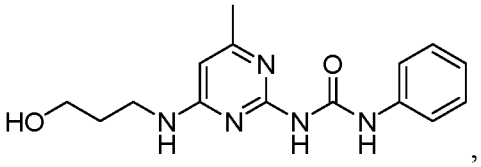
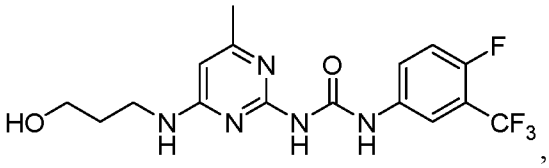
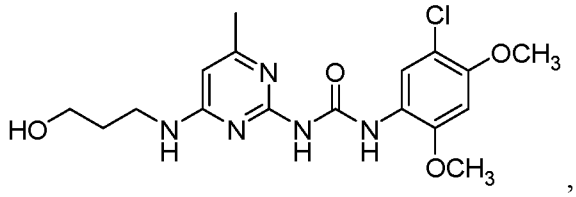
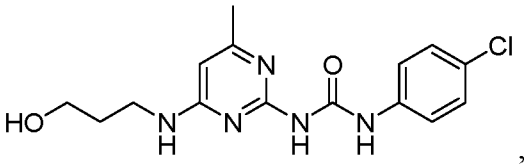
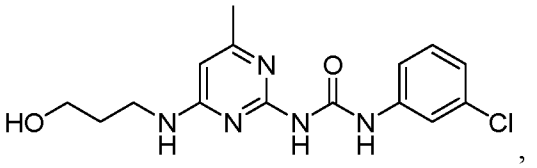
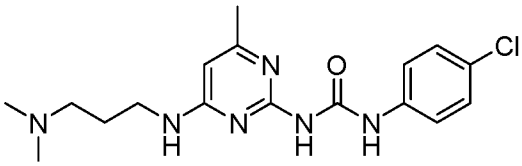
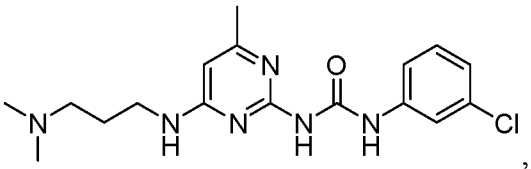
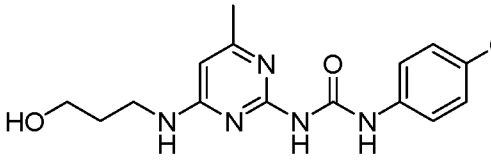
107. The compound of any one of claims 85-106, wherein n is 1.

108. The compound of any one of claims 85-106, wherein n is 2.

109. The compound of any one of claims 85-104, wherein n is 0.

110. A compound having a structure selected from:


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

111. A pharmaceutical composition comprising a compound of any one of claims 1-110, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, and at least one pharmaceutically acceptable excipient.

112. 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 1-110, or a pharmaceutically acceptable salt, solvate, or prodrug thereof; wherein the disease is cancer or Down's Syndrome.

113. The method of claim 112, wherein the disease is cancer.

114. The method of claim 113, wherein the cancer is brain cancer, glioblastoma multiforme, medulloblastoma, astrocytomas, brain stem gliomas, meningiomas, oligodendrogliomas, melanoma, lung cancer, breast cancer, or leukemia.

115. The method of claim 112, wherein the disease is Down's Syndrome.

116. A method for inhibiting the activity of Olig2 in a cell comprising contacting the cell with a compound of any one of claims 1-110, or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2016/019932

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/17; A61K 31/33; A61K 31/395 (2016.01)
CPC - C07D 251/18; A61K 31/395; A61K 31/33; A61K 31/53; C07D 251/00; C07D 251/14 (2016.05)
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - A61K 31/17; A61K 31/33; A61K 31/395 (2016.01)
CPC - C07D 251/18; A61K 31/395; A61K 31/33; A61K 31/53; C07D 251/00; C07D 251/14 (2016.05)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 514/183; 514/241; 514/245; IPC(8) - A61K 31/17; A61K 31/33; A61K 31/395 (2016.01); CPC - C07D 251/18; A61K 31/395; A61K 31/33; A61K 31/53; C07D 251/00; C07D 251/14 (2016.05) (keyword delimited)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase, STN, PubChem, Google Patents, Google Scholar
Search terms used: 1,3,5-triazole urea phenyl halo heterocycloalkyl

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PUBCHEM, Substance Record for SID 104352562, Create Date: 2011-02-18. [retrieved on 06 June 2016]. Retrieved from the Internet. < https://pubchem.ncbi.nlm.nih.gov/substance/104352562/version/1#section=Top >. entire document	1-3, 20
A	PUBCHEM, Substance Record for SID 125468769, Create Date: 2011-11-30. [retrieved on 26 March 2016]. Retrieved from the Internet. < https://pubchem.ncbi.nlm.nih.gov/substance/125468769/version/1#section=Top >. entire document	1-3, 20
A	US 2006/0004005 A1 (SATTIGERI et al) 05 January 2006 (05.01.2006) entire document	1-3, 20

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
06 June 2016	08 JUL 2016
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300	Authorized officer Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2016/019932

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

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

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 14-19, 27-47, 54-64, 70, 80-84, 91-101, 104-109, 111-116
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

See Extra Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-3, 20

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

Continued from Box No. III Observations where unity of invention is lacking

Claims 1-3 and 20 have been analyzed subject to the restriction that the claims read on the compound having the structure of Formula (I) as described in the Lack of Unity of Invention (See Box IV). The claims are restricted to a compound having the structure of Formula (I): wherein: A is a bond; X, Y, and Z are each independently N; each R1 is halogen; R2 and R3 are each independently H; R5 is halogen; R6 substituted C2 heterocycloalkyl; and n is 0; or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I+: claims 1-13, 20-26, 48-53, 65-69, 71-79, 85-90, 102, 103, and 110 are drawn to compounds having the structure of Formula (I), Formula (II), Formula (IIA), and Formula (VI), or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

The first invention of Group I+ is restricted based on the proviso that at least one of X, Y, and Z are N and is restricted to a compound having the structure of Formula (I): wherein: A is a bond; X, Y, and Z are each independently N; each R1 is halogen; R2 and R3 are each independently H; R5 is halogen; R6 substituted C2 heterocycloalkyl; and n is 0; or a pharmaceutically acceptable salt, solvate, or prodrug thereof. It is believed that claims 1-3 and 20 read on this first named invention and thus these claims will be searched without fee to the extent that they read on the above embodiment.

Applicant is invited to elect additional formula(e) for each additional compound to be searched in a specific combination by paying an additional fee for each set of election. Each additional elected formula(e) requires the selection of a single definition for each compound variable. An exemplary election would a compound having the structure of Formula (I): wherein: A is a bond; X is C(R7), Y and Z are each independently N; each R1 is -CN; R2 and R3 are each independently -CN; R5 is -CN; R6 unsubstituted C4 cycloalkyl; R7 is –CN; and n is 5; or a pharmaceutically acceptable salt, solvate, or prodrug thereof. Additional formula(e) will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined.

The inventions listed in Groups I+ do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The Groups I+ formulae do not share a significant structural element requiring the selection of alternatives for the compound variables X, Y, Z, A, R1, R2, R3, R5, R6, and n.

The Groups I+ share the technical features of a compound having the core structure of Formula (I) and species thereof; a compound having the core structure of Formula (II); a compound having the core structure of Formula (IIA); a compound having the core structure of Formula (VI); or a pharmaceutically acceptable salt, solvate, or prodrug thereof. However, these shared technical features do not represent a contribution over the prior art.

Specifically, Substance Record for SID 125468769 to PubChem a compound having the core structure of Formula (I): wherein A is a bond; X, Y, and Z are each independently N; R1 is absent; R2 and R3 are each independently H; R5 is halogen; and n is 0 (PubChem, Pg. 3;...see shown structure...); a compound having the core structure of Formula (II): wherein R1 is absent; R2 and R3 are each independently H; R5 is halogen; and n is 0 (PubChem, Pg. 3;...see shown structure...); a compound having the core structure of Formula (IIA): wherein R1 is absent; R2 and R3 are each independently H; R4 is H; R5 is halogen; and n is 0 (PubChem, Pg. 3;...see shown structure...); a compound having the core structure of Formula (VI) wherein R1 is absent; R2 and R3 are each independently H; R5 is halogen; and n is 0 (PubChem, Pg. 3;...see shown structure...).

The inventions listed in Groups I+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.

(19)中华人民共和国国家知识产权局

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A61K 31/17(2006.01)
A61K 31/33(2006.01)
A61K 31/395(2006.01)

权利要求书10页 说明书174页

(54)发明名称

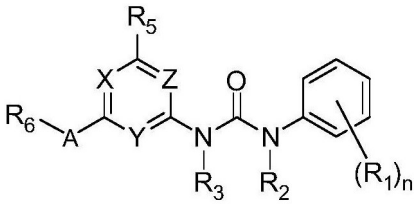
OLIG2活性的抑制

(57)摘要

本文描述了抑制Olig2活性的化合物和含有此类化合物的药物组合物。本文还描述了单独地以及与其他化合物联合地使用此类Olig2抑制剂治疗癌症和其他疾病的方法。特别是,该Olig2抑制剂可用来治疗胶质母细胞瘤。

CN 107530304 A

1.具有式(I)结构的化合物,或其药学上可接受的盐、溶剂化物或前药:



式(I);

其中:

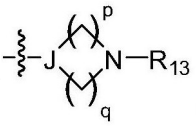
A为键、O或N(R_{10});

X、Y和Z各自独立地为N或C(R_7),其中X、Y和Z中的至少一个为N;

每个R_1独立地为卤素、-CN、-NO_2、-OH、-OCF_3、-OCH_2F、-OCF_2H、-CF_3、-SR_8、-N(R_8)S(=O)$_2R_9$、-S(=O)$_2$N(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、取代或未取代的C_1-C_6烷基、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基;或者两个R_1合起来形成取代或未取代的杂环或者取代或未取代的碳环;

R_2和R_3各自独立地为H、-CN、C_1-C_4烷基、C_3-C_6环烷基或C_2-C_7杂环烷基;或者R_2和R_3合起来形成5元或6元杂环;

R_5为卤素、-CN、-OH、-CF_3、取代或未取代的C_1-C_6烷基、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基;

R_6为取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_2-C_7杂芳基、-(C(R_{14})(R_{15}))$_m$$R_{21}$、-(C($R_{14}$)($R_{15}$))$_m$N($R_{11}$)($R_{12}$)或  ;

R_{11}和R_{12}各自独立地为H、或取代或未取代的C_1-C_6烷基;或者R_{11}和R_{12}合起来形成5、6、7或8元杂环;

J为C(H)或N;

R_{13}为H、取代或未取代的C_1-C_6烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的-C_1-C_4烷基C_6-C_{10}芳基、或取代或未取代的-C_1-C_4烷基C_2-C_7杂芳基;

每个R_7独立地为H、卤素、-CN、-OH、-CF_3、取代或未取代的C_1-C_6烷基、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基;

每个R_{14}和R_{15}各自独立地为H、或取代或未取代的C_1-C_6烷基;或者R_{14}和R_{15}合起来形成4、5、6元环烷基环;

R_{21}为卤素、-CN、-NO_2、-OH、-OCF_3、-OCH_2F、-OCF_2H、-CF_3、-SR_{22}、-N(R_{22})S(=O)$_2R_{23}$、-S(=O)$_2$N(R_{22})$_2$、-S(=O)R_{23}、-S(=O)$_2R_{23}$、-C(=O)R_{23}、-CO_2R_{22}、-C(=O)N(R_{22})$_2$、-N(R_{22})C(=O)R_{23}、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环

烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基；

每个R_{22}独立地为H、或取代或未取代的C_1-C_6烷基；

R_{23}为取代或未取代的C_1-C_6烷基；

每个R_8独立地为H、或取代或未取代的C_1-C_6烷基；

R_9为取代或未取代的C_1-C_6烷基；

R_{10}为H或未取代的C_1-C_4烷基；

m为2-6；

n为0-5；

p为1-3；

q为1-3。

2.如权利要求1所述的化合物，其中R_2和R_3各自独立地为H、-CN、C_1-C_4烷基、C_3-C_6环烷基或C_2-C_7杂环烷基。

3.如权利要求2所述的化合物，其中R_2和R_3各自为H。

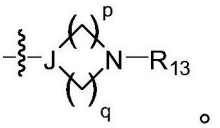
4.如权利要求1所述的化合物，其中R_2和R_3合起来形成5元或6元杂环。

5.如权利要求4所述的化合物，其中R_2和R_3合起来形成5元杂环。

6.如权利要求1-5中任一项所述的化合物，其中R_6为取代或未取代的C_2-C_7杂芳基。

7.如权利要求6所述的化合物，其中R_6为取代或未取代的吡啶基。

8.如权利要求7所述的化合物，其中R_6为未取代的吡啶基。

9.如权利要求1-5中任一项所述的化合物，其中R_6为  。

10.如权利要求9所述的化合物，其中R_{13}为H。

11.如权利要求9所述的化合物，其中R_{13}为取代或未取代的C_1-C_6烷基。

12.如权利要求11所述的化合物，其中R_{13}为$-CH_3$。

13.如权利要求11所述的化合物，其中R_{13}为$-CH_2CH_3$。

14.如权利要求9-13中任一项所述的化合物，其中J为C(H)。

15.如权利要求14所述的化合物，其中p为2且q为1。

16.如权利要求14所述的化合物，其中p为3且q为1。

17.如权利要求14所述的化合物，其中p为2且q为2。

18.如权利要求9-13中任一项所述的化合物，其中J为N。

19.如权利要求18所述的化合物，其中p为2且q为2。

20.如权利要求1-5中任一项所述的化合物，其中R_6为取代或未取代的C_2-C_7杂环烷基。

21.如权利要求20所述的化合物，其中R_6为取代或未取代的吗啉基。

22.如权利要求20所述的化合物，其中R_6为取代或未取代的哌啶基。

23.如权利要求1-5中任一项所述的化合物，其中R_6为$-(C(R_{14})(R_{15}))_mR_{21}$。

24.如权利要求23所述的化合物，其中R_{21}为-OH。

25.如权利要求1-5中任一项所述的化合物，其中R_6为$-(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$。

26.如权利要求25所述的化合物，其中R_{11}和R_{12}各自为CH_3。

27.如权利要求23-26中任一项所述的化合物，其中R_{14}和R_{15}各自为H。

28.如权利要求23-27中任一项所述的化合物，其中m为2。

29.如权利要求23-27中任一项所述的化合物，其中m为3。

30.如权利要求1-29中任一项所述的化合物，其中A为$N(R_{10})$。

31.如权利要求30所述的化合物，其中R_{10}为H或CH_3。

32.如权利要求1-29中任一项所述的化合物，其中A为O。

33.如权利要求1-29中任一项所述的化合物，其中A为键。

34.如权利要求1-33中任一项所述的化合物，其中R_5为取代或未取代的C_1-C_6烷基。

35.如权利要求34所述的化合物，其中R_5为CH_3。

36.如权利要求34所述的化合物，其中R_5为CH_2CH_3。

37.如权利要求1-36中任一项所述的化合物，其中n为2。

38.如权利要求1-36中任一项所述的化合物，其中n为1。

39.如权利要求1-36中任一项所述的化合物，其中n为0。

40.如权利要求1-38中任一项所述的化合物，其中每个R_1独立地为卤素、-CN、$-NO_2$、-OH、$-CF_3$、取代或未取代的C_1-C_6烷基、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基。

41.如权利要求40所述的化合物，其中每个R_1独立地为卤素、-CN、-OH、$-CF_3$、取代或未取代的C_1-C_6烷基、或取代或未取代的C_1-C_6烷氧基。

42.如权利要求1-37中任一项所述的化合物，其中两个R_1合起来形成取代或未取代的杂环或者取代或未取代的碳环。

43.如权利要求1-42中任一项所述的化合物，其中X为$C(R_7)$；Y为N；且Z为N。

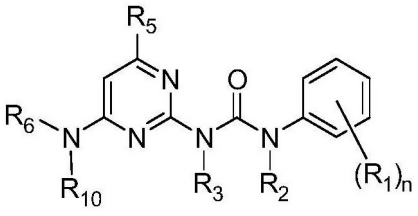
44.如权利要求1-42中任一项所述的化合物，其中X为$C(R_7)$；Y为$C(R_7)$；且Z为N。

45.如权利要求1-42中任一项所述的化合物，其中X为$C(R_7)$；Y为N；且Z为$C(R_7)$。

46.如权利要求1-42中任一项所述的化合物，其中X为$C(R_7)$；Y为$C(R_7)$；且Z为$C(R_7)$。

47.如权利要求1-46中任一项所述的化合物，其中R_7为H。

48.具有式(II)结构的化合物，或其药学上可接受的盐、溶剂化物或前药：



式(II)；

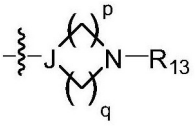
其中：

每个R_1独立地为卤素、-CN、$-NO_2$、-OH、$-OCF_3$、$-OCH_2F$、$-OCF_2H$、$-CF_3$、$-SR_8$、$-N(R_8)S(=O)_2R_9$、$-S(=O)_2N(R_8)_2$、$-S(=O)R_9$、$-S(=O)_2R_9$、$-C(=O)R_9$、$-CO_2R_8$、$-N(R_8)_2$、$-C(=O)N(R_8)_2$、$-N(R_8)C(=O)R_9$、取代或未取代的C_1-C_6烷基、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基；或者两个R_1合起来形成取代或未取代的杂环

或者取代或未取代的碳环；

R_2和R_3各自独立地为H、-CN、C_1-C_4烷基、C_3-C_6环烷基或C_2-C_7杂环烷基；或者R_2和R_3合起来形成5元或6元杂环；

R_5为卤素、-CN、-OH、$-CF_3$、取代或未取代的C_1-C_6烷基、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基；

R_6为取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_2-C_7杂芳基、$-(C(R_{14})(R_{15}))_mR_{21}$或  ；

J为C(H)；

R_{13}为H、取代或未取代的C_1-C_6烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的-C_1-C_4烷基C_6-C_{10}芳基、或取代或未取代的-C_1-C_4烷基C_2-C_7杂芳基；

每个R_{14}和R_{15}各自独立地为H、或取代或未取代的C_1-C_6烷基；或者R_{14}和R_{15}合起来形成4、5、6元环烷基环；

R_{21}为卤素、-CN、$-NO_2$、-OH、$-OCF_3$、$-OCH_2F$、$-OCF_2H$、$-CF_3$、$-SR_{22}$、$-N(R_{22})S(=O)_2R_{23}$、$-S(=O)_2N(R_{22})_2$、$-S(=O)R_{23}$、$-S(=O)_2R_{23}$、$-C(=O)R_{23}$、$-CO_2R_{22}$、$-C(=O)N(R_{22})_2$、$-N(R_{22})C(=O)R_{23}$、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基；

每个R_{22}独立地为H、或取代或未取代的C_1-C_6烷基；

R_{23}为取代或未取代的C_1-C_6烷基；

每个R_8独立地为H、或取代或未取代的C_1-C_6烷基；

R_9为取代或未取代的C_1-C_6烷基；

R_{10}为H或未取代的C_1-C_4烷基；

m为2-6；

n为0-5；

p为1-3；

q为1-3。

49.如权利要求48所述的化合物，其中R_2和R_3各自独立地为H、-CN、C_1-C_4烷基、C_3-C_6环烷基或C_2-C_7杂环烷基。

50.如权利要求49所述的化合物，其中R_2和R_3各自为H。

51.如权利要求48所述的化合物，其中R_2和R_3合起来形成5元或6元杂环。

52.如权利要求51所述的化合物，其中R_2和R_3合起来形成5元杂环。

53.如权利要求48-52中任一项所述的化合物，其中R_6为$-(C(R_{14})(R_{15}))_mR_{21}$。

54.如权利要求48-53中任一项所述的化合物，其中R_{21}为-OH、$-N(R_{22})S(=O)_2R_{23}$、$-CO_2R_{22}$、$-C(=O)N(R_{22})_2$、$-N(R_{22})C(=O)R_{23}$、取代或未取代的C_1-C_6烷氧基、或取代或未取代的C_2-C_7杂芳基。

55.如权利要求54所述的化合物，其中R_{21}为-OH。

56.如权利要求54所述的化合物，其中R_{21}为-N(R_{22})S(=O)$_2R_{23}$。

57.如权利要求54所述的化合物，其中R_{21}为-N(R_{22})C(=O)R_{23}。

58.如权利要求54所述的化合物，其中R_{21}为取代或未取代的C_1-C_6烷氧基。

59.如权利要求54所述的化合物，其中R_{21}为取代或未取代的C_2-C_7杂芳基。

60.如权利要求48-59中任一项所述的化合物，其中每个R_{22}独立地为H或未取代的C_1-C_6烷基；且R_{23}为未取代的C_1-C_6烷基。

61.如权利要求48-60中任一项所述的化合物，其中R_{14}和R_{15}各自独立地为H、或取代或未取代的C_1-C_6烷基。

62.如权利要求48-60中任一项所述的化合物，其中R_{14}和R_{15}各自为H。

63.如权利要求48-62中任一项所述的化合物，其中m为2。

64.如权利要求48-62中任一项所述的化合物，其中m为3。

65.如权利要求48-52中任一项所述的化合物，其中R_6为取代或未取代的C_2-C_7杂芳基。

66.如权利要求65所述的化合物，其中R_6为取代或未取代的吡啶基。

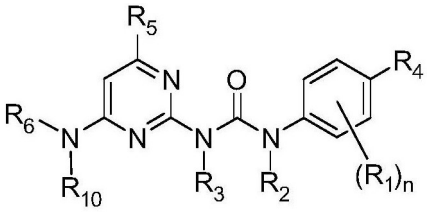
67.如权利要求48-52中任一项所述的化合物，其中R_6为取代或未取代的C_2-C_7杂环烷基。

68.如权利要求67所述的化合物，其中R_6为取代或未取代的吗啉基。

69.如权利要求67所述的化合物，其中R_6为取代或未取代的哌啶基。

70.如权利要求48-69中任一项所述的化合物，其中R_{10}为H或CH_3。

71.具有式(IIA)结构的化合物，或其药学上可接受的盐、溶剂化物或前药：



式(IIA)；

其中：

每个R_1独立地为卤素、-CN、-NO_2、-OH、-OCF_3、-OCH_2F、-OCF_2H、-SR_8、-N(R_8)S(=O)$_2R_9$、-S(=O)$_2$N(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、取代或未取代的C_1-C_6烷基、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基；或者两个R_1合起来形成取代或未取代的杂环或者取代或未取代的碳环；

R_2和R_3各自独立地为H、-CN、C_1-C_4烷基、C_3-C_6环烷基或C_2-C_7杂环烷基；或者R_2和R_3合起来形成5元或6元杂环；

R_4为H、卤素、-CN、-NO_2、-OH、-OCF_3、-OCH_2F、-OCF_2H、-SR_8、-N(R_8)S(=O)$_2R_9$、-S(=O)$_2$N(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、取代或未取代的C_1-C_6烷基、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基；或者两个R_1合起来形成取代或未取代的杂环或者取代或未取

代的碳环;其中当n为0时,

R_4不是卤素;

R_5为卤素、-CN、-OH、$-CF_3$、取代或未取代的C_1-C_6烷基、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基;

R_6为$-(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$;

R_{11}和R_{12}各自独立地为H、或取代或未取代的C_1-C_6烷基;或者R_{11}和R_{12}合起来形成5、6、7或8元杂环;

R_{13}为H、取代或未取代的C_1-C_6烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的-C_1-C_4烷基C_6-C_{10}芳基、或取代或未取代的-C_1-C_4烷基C_2-C_7杂芳基;

每个R_{14}和R_{15}各自独立地为H、或取代或未取代的C_1-C_6烷基;或者R_{14}和R_{15}合起来形成4、5、6元环烷基环;

每个R_8独立地为H、或取代或未取代的C_1-C_6烷基;

R_9为取代或未取代的C_1-C_6烷基;

R_{10}为H或C_1-C_4烷基;

m为2-6;

n为0-4。

72.如权利要求71所述的化合物,其中R_2和R_3各自独立地为H、-CN、C_1-C_4烷基、C_3-C_6环烷基或C_2-C_7杂环烷基。

73.如权利要求72所述的化合物,其中R_2和R_3各自为H。

74.如权利要求71所述的化合物,其中R_2和R_3合起来形成5元或6元杂环。

75.如权利要求74所述的化合物,其中R_2和R_3合起来形成5元杂环。

76.如权利要求71-75中任一项所述的化合物,其中R_6为$-(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$且$R_{14}$和$R_{15}$各自为H。

77.如权利要求76所述的化合物,其中R_{11}和R_{12}各自独立地为H、或取代或未取代的C_1-C_6烷基。

78.如权利要求77所述的化合物,其中R_{11}和R_{12}各自独立地为未取代的C_1-C_6烷基。

79.如权利要求78所述的化合物,其中R_{11}和R_{12}各自为$-CH_3$。

80.如权利要求71-79中任一项所述的化合物,其中m为2。

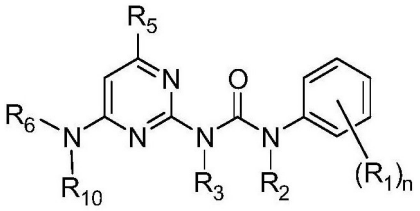
81.如权利要求71-79中任一项所述的化合物,其中m为3。

82.如权利要求71-81中任一项所述的化合物,其中R_{10}为H或CH_3。

83.如权利要求71-82中任一项所述的化合物,其中n为0。

84.如权利要求71-82中任一项所述的化合物,其中n为1。

85.具有式(VI)结构的化合物,或其药学上可接受的盐、溶剂化物或前药:



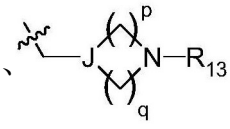
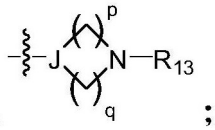
式(VI)；

其中：

每个R_1独立地为卤素、-CN、$-NO_2$、-OH、$-OCF_3$、$-OCH_2F$、$-OCF_2H$、$-CF_3$、$-SR_8$、$-N(R_8)S(=O)_2R_9$、$-S(=O)_2N(R_8)_2$、$-S(=O)R_9$、$-S(=O)_2R_9$、$-C(=O)R_9$、$-CO_2R_8$、$-N(R_8)_2$、$-C(=O)N(R_8)_2$、$-N(R_8)C(=O)R_9$、取代或未取代的C_1-C_6烷基、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基；或者两个R_1合起来形成取代或未取代的杂环或者取代或未取代的碳环；

R_2和R_3各自独立地为H或C_1-C_4烷基；或者R_2和R_3合起来形成5元或6元杂环；

R_5为取代或未取代的C_1-C_6烷基；

R_6为未取代的C_1-C_4烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_2-C_7杂芳基、$-(C(R_{14})(R_{15}))_mR_{21}$、  或  ；

J为C(H)；

R_{13}为H、取代或未取代的C_1-C_6烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的-C_1-C_4烷基C_6-C_{10}芳基、或取代或未取代的-C_1-C_4烷基C_2-C_7杂芳基；

每个R_{14}和R_{15}各自独立地为H、卤素、或取代或未取代的C_1-C_6烷基；

R_{21}为卤素、-CN、$-NO_2$、-OH、$-OCF_3$、$-OCH_2F$、$-OCF_2H$、$-CF_3$、$-SR_{22}$、$-N(R_{22})S(=O)_2R_{23}$、$-S(=O)_2N(R_{22})_2$、$-S(=O)R_{23}$、$-S(=O)_2R_{23}$、$-C(=O)R_{23}$、$-CO_2R_{22}$、$-C(=O)N(R_{22})_2$、$-N(R_{22})C(=O)R_{23}$、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、或取代或未取代的C_2-C_7杂芳基；

每个R_{22}独立地为H、或取代或未取代的C_1-C_6烷基；

R_{23}为取代或未取代的C_1-C_6烷基；

每个R_8独立地为H、或取代或未取代的C_1-C_6烷基；

R_9为取代或未取代的C_1-C_6烷基；

R_{10}为H；

m为2-6；

n为0-5；

p为1-3；

q为1-3。

86.如权利要求85所述的化合物，其中R_2和R_3各自独立地为H或C_1-C_4烷基。

87.如权利要求86所述的化合物，其中R_2和R_3各自为H。

88.如权利要求85所述的化合物，其中R_2和R_3合起来形成5元或6元杂环。

89.如权利要求88所述的化合物，其中R_2和R_3合起来形成5元杂环。

90.如权利要求85-89中任一项所述的化合物，其中R_6为$-(C(R_{14})(R_{15}))_mR_{21}$。

91.如权利要求85-90中任一项所述的化合物，其中每个R_{14}和R_{15}各自独立地为H、卤素或未取代的C_1-C_6烷基。

92.如权利要求85-90中任一项所述的化合物，其中R_{14}和R_{15}各自为H。

93.如权利要求85-92中任一项所述的化合物，其中R_{21}为-OH、$-N(R_{22})S(=O)_2R_{23}$、$-CO_2R_{22}$、$-C(=O)N(R_{22})_2$、$-N(R_{22})C(=O)R_{23}$、取代或未取代的C_1-C_6烷氧基、或取代或未取代的C_2-C_7杂芳基。

94.如权利要求93所述的化合物，其中R_{21}为-OH。

95.如权利要求93所述的化合物，其中R_{21}为$-N(R_{22})S(=O)_2R_{23}$。

96.如权利要求93所述的化合物，其中R_{21}为$-N(R_{22})C(=O)R_{23}$。

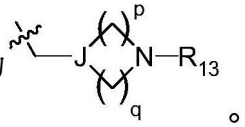
97.如权利要求93所述的化合物，其中R_{21}为取代或未取代的C_1-C_6烷氧基。

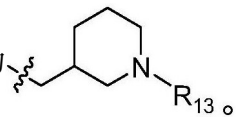
98.如权利要求93所述的化合物，其中R_{21}为取代或未取代的C_2-C_7杂芳基。

99.如权利要求85-98中任一项所述的化合物，其中每个R_{22}独立地为H或未取代的C_1-C_6烷基；且R_{23}为未取代的C_1-C_6烷基。

100.如权利要求85-99中任一项所述的化合物，其中m为2。

101.如权利要求85-99中任一项所述的化合物，其中m为3。

102.如权利要求85-89中任一项所述的化合物，其中R_6为  。

103.如权利要求85-89中任一项所述的化合物，其中R_6为  。

104.如权利要求102或103所述的化合物，其中R_{13}为H或未取代的C_1-C_6烷基。

105.如权利要求85-104中任一项所述的化合物，其中每个R_1独立地为卤素、$-OCF_3$、$-CF_3$、未取代的C_1-C_6烷基或未取代的C_1-C_6烷氧基。

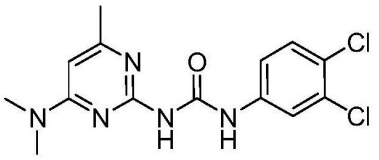
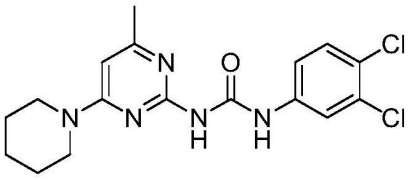
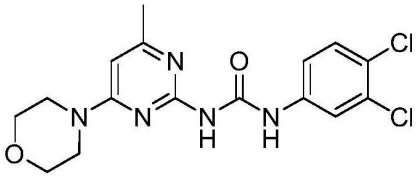
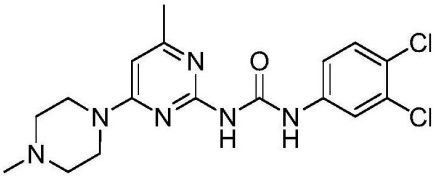
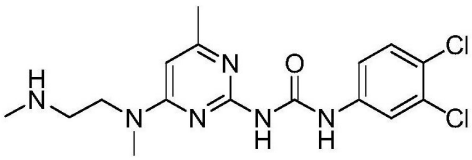
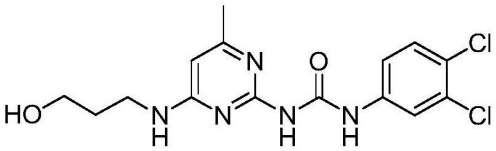
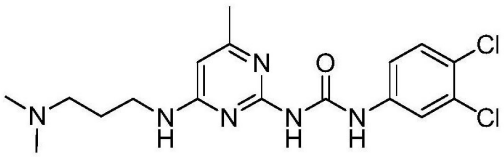
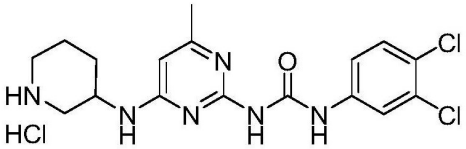
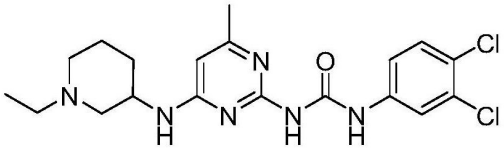
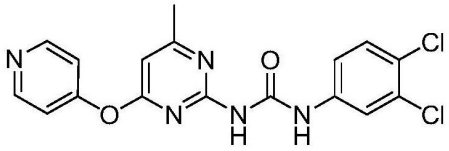
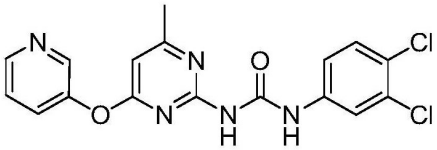
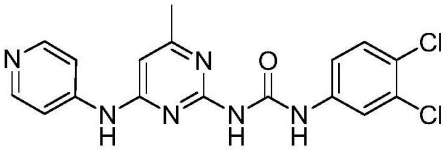
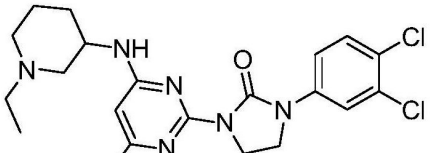
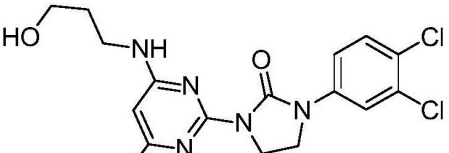
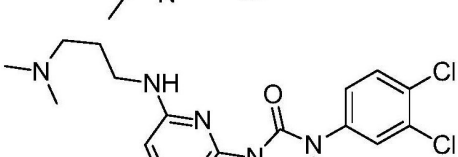
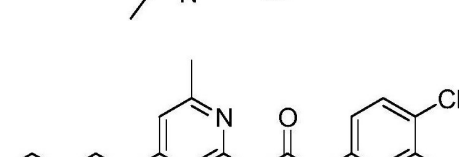
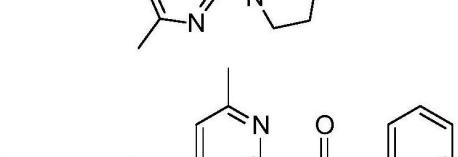
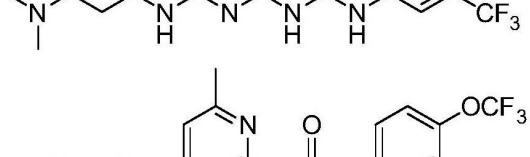
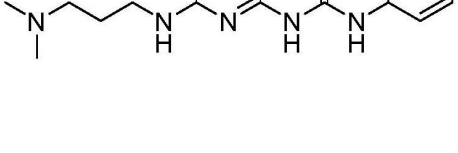
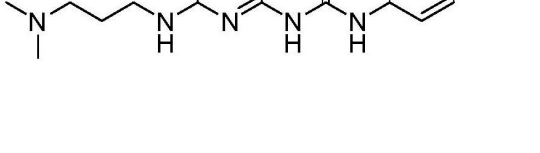
106.如权利要求85-104中任一项所述的化合物，其中每个R_1独立地为卤素。

107.如权利要求85-106中任一项所述的化合物，其中n为1。

108.如权利要求85-106中任一项所述的化合物，其中n为2。

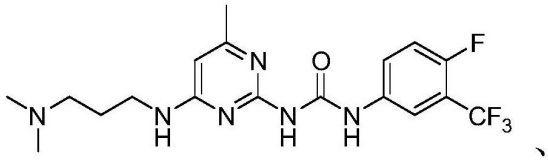
109.如权利要求85-104中任一项所述的化合物，其中n为0。

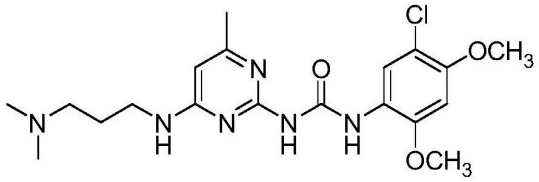
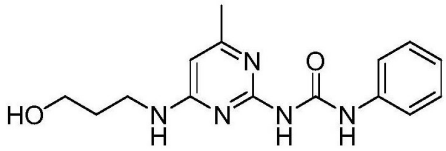
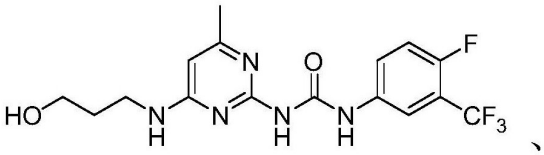
110.一种化合物，其具有选自以下的结构：

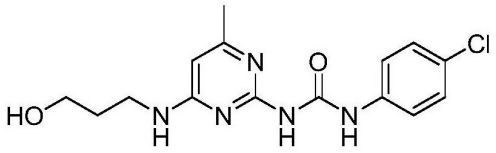
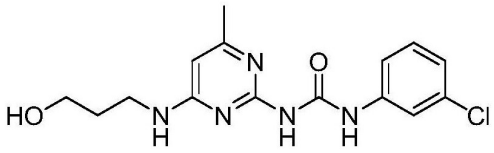
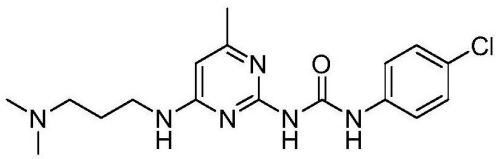
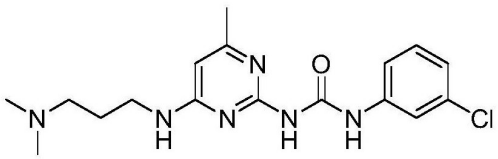
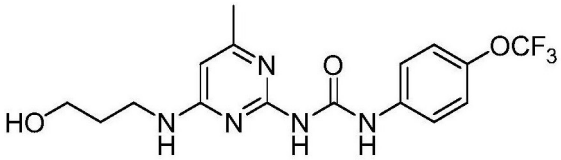

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和

或其药学上可接受的盐、溶剂化物或前药。

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111.一种药物组合物，其包含如权利要求1-110中任一项所述的化合物，或其药学上可接受的盐、溶剂化物或前药，以及至少一种药学上可接受的赋形剂。

112.一种治疗受试者的疾病的方法，其包括向有需要的受试者施用包含如权利要求1-110中任一项所述的化合物或其药学上可接受的盐、溶剂化物或前药的组合物；其中所述疾病为癌症或唐氏综合征。

113.如权利要求112所述的方法，其中所述疾病为癌症。

114.如权利要求113所述的方法，其中所述癌症为脑癌、多形性胶质母细胞瘤、髓母细胞瘤、星形细胞瘤、脑干胶质瘤、脑膜瘤、少突神经胶质瘤、黑素瘤、肺癌、乳腺癌或白血病。

115.如权利要求112所述的方法，其中所述疾病为唐氏综合征。

116.一种抑制细胞中Olig2的活性的方法，其包括使该细胞接触如权利要求1-110中任一项所述的化合物或其药学上可接受的盐、溶剂化物或前药。

OLIG2活性的抑制

相关申请

[0001] 本申请要求2015年2月27日提交的美国临时申请62/126,382的优先权,该临时申请通过引用以其全文而并入。

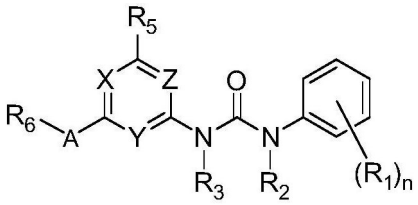
发明背景

[0002] 现有的脑瘤治疗剂引起明显的全身毒性,却仅能使患者的生存期中值延长6个月。这种毒性导致存活的少数患者在认知、内分泌紊乱和运动效应方面长期为严重的病患困扰。目前,脑瘤基本上无法治愈,生存期中值为15个月。

发明内容

[0003] 本文描述了式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物(下文称为"式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物")、包含此类化合物的组合物及其使用方法,其用于抑制Olig2活性。

[0004] 在一方面,本文描述了式(I)化合物,或其药学上可接受的盐、溶剂化物或前药:



式(I);

其中:

A为键、O或N(R_{10});

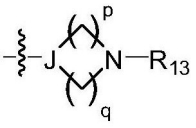
X、Y和Z各自独立地为N或C(R_7),其中X、Y和Z中的至少一个为N;

每个R_1独立地为卤素、-CN、-NO_2、-OH、-OCF_3、-OCH_2F、-OCF_2H、-CF_3、-SR_8、-N(R_8)S(=O)$_2R_9$、-S(=O)$_2$N(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、取代或未取代的C_1-C_6烷基、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基;或者两个R_1合起来形成取代或未取代的杂环或者取代或未取代的碳环;

R_2和R_3各自独立地为H、-CN、C_1-C_4烷基、C_3-C_6环烷基或C_2-C_7杂环烷基;或者R_2和R_3合起来形成5元或6元杂环;

R_5为卤素、-CN、-OH、-CF_3、取代或未取代的C_1-C_6烷基、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基;

R_6为取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_2-

C_7杂芳基、-(C(R_{14})(R_{15}))$_m$$R_{21}$、-(C($R_{14}$)($R_{15}$))$_m$N($R_{11}$)($R_{12}$)或  ；

R_{11}和R_{12}各自独立地为H、或取代或未取代的C_1-C_6烷基；或者R_{11}和R_{12}合起来形成5、6、7或8元杂环；

J为C(H)或N；

R_{13}为H、取代或未取代的C_1-C_6烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的-C_1-C_4烷基C_6-C_{10}芳基、或取代或未取代的-C_1-C_4烷基C_2-C_7杂芳基；

每个R_7独立地为H、卤素、-CN、-OH、-CF_3、取代或未取代的C_1-C_6烷基、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基；

每个R_{14}和R_{15}各自独立地为H、或取代或未取代的C_1-C_6烷基；或者R_{14}和R_{15}合起来形成4、5、6元环烷基环；

R_{21}为卤素、-CN、-NO_2、-OH、-OCF_3、-OCH_2F、-OCF_2H、-CF_3、-SR_{22}、-N(R_{22})S(=O)$_2$$R_{23}$、-S(=O)$_2$N($R_{22}$)$_2$、-S(=O)$R_{23}$、-S(=O)$_2$$R_{23}$、-C(=O)$R_{23}$、-$CO_2R_{22}$、-C(=O)N($R_{22}$)$_2$、-N($R_{22}$)C(=O)$R_{23}$、取代或未取代的$C_1$-$C_6$烷基、取代或未取代的$C_1$-$C_6$烷氧基、取代或未取代的$C_1$-$C_6$杂烷基、取代或未取代的$C_2$-$C_7$杂环烷基、取代或未取代的$C_3$-$C_8$环烷基、取代或未取代的$C_6$-$C_{10}$芳基、或取代或未取代的$C_2$-$C_7$杂芳基；

每个R_{22}独立地为H、或取代或未取代的C_1-C_6烷基；

R_{23}为取代或未取代的C_1-C_6烷基；

每个R_8独立地为H、或取代或未取代的C_1-C_6烷基；

R_9为取代或未取代的C_1-C_6烷基；

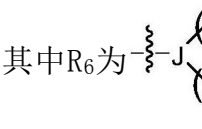
R_{10}为H或未取代的C_1-C_4烷基；

m为2-6；

n为0-5；

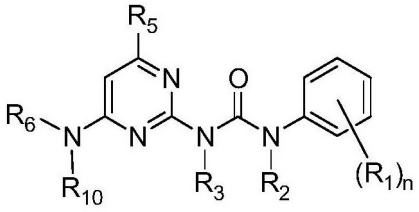
p为1-3；

q为1-3。

[0005] 在一个实施方案中为式(I)化合物，其中R_2和R_3各自独立地为H、-CN、C_1-C_4烷基、C_3-C_6环烷基或C_2-C_7杂环烷基。在另一个实施方案中为式(I)化合物，其中R_2和R_3各自为H。在另一个实施方案中为式(I)化合物，其中R_2和R_3合起来形成5元或6元杂环。在另一个实施方案中为式(I)化合物，其中R_2和R_3合起来形成5元杂环。在另一个实施方案中为式(I)化合物，其中R_6为取代或未取代的C_2-C_7杂芳基。在进一步的实施方案中为式(I)化合物，其中R_6为取代或未取代的吡啶基。在另一个实施方案中为式(I)化合物，其中R_6为  。在另一个实施方案中为式(I)化合物，其中R_{13}为H。在另一个实施方案中为式(I)化合物，其中R_{13}为取代或未取代的C_1-C_6烷基。在另一个实施方案中为式(I)化合物，其中R_{13}为-CH_3。在另一个实施方案中为式(I)化合物，其中R_{13}为-CH_2CH_3。在另一个实施方案中为式(I)化合物，其中J

为C(H)。在另一个实施方案中为式(I)化合物,其中p为2且q为1。在另一个实施方案中为式(I)化合物,其中p为3且q为1。在另一个实施方案中为式(I)化合物,其中p为2且q为2。在上述实施方案的另一个实施方案中为式(I)化合物,其中J为N。在另一个实施方案中为式(I)化合物,其中p为2且q为2。在上述实施方案的另一个实施方案中为式(I)化合物,其中R_6为取代或未取代的C_2-C_7杂环烷基。在上述实施方案的另一个实施方案中为式(I)化合物,其中R_6为取代或未取代的吗啉基。在上述实施方案的另一个实施方案中为式(I)化合物,其中R_6为取代或未取代的哌啶基。在上述实施方案的另一个实施方案中为式(I)化合物,其中R_6为-(C(R_{14})(R_{15}))$_m$$R_{21}$。在上述实施方案的另一个实施方案中为式(I)化合物,其中R_{21}为-OH。在上述实施方案的另一个实施方案中为式(I)化合物,其中R_6为-(C(R_{14})(R_{15}))$_m$N(R_{11})(R_{12})。在上述实施方案的另一个实施方案中为式(I)化合物,其中R_{11}和R_{12}各自为CH_3。在上述实施方案的另一个实施方案中为式(I)化合物,其中R_{14}和R_{15}各自为H。在上述实施方案的另一个实施方案中为式(I)化合物,其中m为2。在上述实施方案的另一个实施方案中为式(I)化合物,其中m为3。在上述实施方案的另一个实施方案中为式(I)化合物,其中A为N(R_{10})。在另一个实施方案中为式(I)化合物,其中R_{10}为H或CH_3。在上述实施方案的另一个实施方案中为式(I)化合物,其中A为O。在上述实施方案的另一个实施方案中为式(I)化合物,其中A为键。在上述实施方案的另一个实施方案中为式(I)化合物,其中R_5为取代或未取代的C_1-C_6烷基。在另一个实施方案中为式(I)化合物,其中R_5为CH_3。在另一个实施方案中为式(I)化合物,其中R_5为CH_2CH_3。在上述实施方案的另一个实施方案中为式(I)化合物,其中n为2。在上述实施方案的另一个实施方案中为式(I)化合物,其中n为1。在上述实施方案的另一个实施方案中为式(I)化合物,其中n为0。在上述实施方案的另一个实施方案中为式(I)化合物,其中每个R_1独立地为卤素、-CN、-NO_2、-OH、-CF_3、取代或未取代的C_1-C_6烷基、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基。在另一个实施方案中为式(I)化合物,其中每个R_1独立地为卤素、-CN、-OH、-CF_3、取代或未取代的C_1-C_6烷基、或取代或未取代的C_1-C_6烷氧基。在上述实施方案的另一个实施方案中为式(I)化合物,其中两个R_1合起来形成取代或未取代的杂环或者取代或未取代的碳环。在上述实施方案的另一个实施方案中为式(I)化合物,其中X为C(R)$_7$;Y为N;且Z为N。在上述实施方案的另一个实施方案中为式(I)化合物,其中X为C(R)$_7$;Y为C(R)$_7$;且Z为N。在上述实施方案的另一个实施方案中为式(I)化合物,其中X为C(R)$_7$;Y为N;且Z为C(R)$_7$。在上述实施方案的另一个实施方案中为式(I)化合物,其中X为C(R)$_7$;Y为C(R)$_7$;且Z为C(R)$_7$。在上述实施方案的另一个实施方案中为式(I)化合物,其中R_7为H。在上述实施方案的另一个实施方案中为式(I)化合物,其中X为N;Y为N;且Z为N。

[0006] 在另一方面,本文描述了式(II)化合物,或其药学上可接受的盐、溶剂化物或前药:



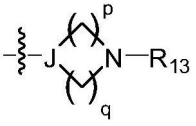
式(II)；

其中：

每个R_1独立地为卤素、-CN、$-NO_2$、-OH、$-OCF_3$、$-OCH_2F$、$-OCF_2H$、$-CF_3$、$-SR_8$、$-N(R_8)S(=O)_2R_9$、$-S(=O)_2N(R_8)_2$、$-S(=O)R_9$、$-S(=O)_2R_9$、$-C(=O)R_9$、$-CO_2R_8$、$-N(R_8)_2$、$-C(=O)N(R_8)_2$、$-N(R_8)C(=O)R_9$、取代或未取代的C_1-C_6烷基、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基；或者两个R_1合起来形成取代或未取代的杂环或者取代或未取代的碳环；

R_2和R_3各自独立地为H、-CN、C_1-C_4烷基、C_3-C_6环烷基或C_2-C_7杂环烷基；或者R_2和R_3合起来形成5元或6元杂环；

R_5为卤素、-CN、-OH、$-CF_3$、取代或未取代的C_1-C_6烷基、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基；

R_6为取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_2-C_7杂芳基、$-(C(R_{14})(R_{15}))_mR_{21}$或  ；

J为C(H)；

R_{13}为H、取代或未取代的C_1-C_6烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的-C_1-C_4烷基C_6-C_{10}芳基、或取代或未取代的-C_1-C_4烷基C_2-C_7杂芳基；

每个R_{14}和R_{15}各自独立地为H、或取代或未取代的C_1-C_6烷基；或者R_{14}和R_{15}合起来形成4、5、6元环烷基环；

R_{21}为卤素、-CN、$-NO_2$、-OH、$-OCF_3$、$-OCH_2F$、$-OCF_2H$、$-CF_3$、$-SR_{22}$、$-N(R_{22})S(=O)_2R_{23}$、$-S(=O)_2N(R_{22})_2$、$-S(=O)R_{23}$、$-S(=O)_2R_{23}$、$-C(=O)R_{23}$、$-CO_2R_{22}$、$-C(=O)N(R_{22})_2$、$-N(R_{22})C(=O)R_{23}$、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基；

每个R_{22}独立地为H、或取代或未取代的C_1-C_6烷基；

R_{23}为取代或未取代的C_1-C_6烷基；

每个R_8独立地为H、或取代或未取代的C_1-C_6烷基；

R_9为取代或未取代的C_1-C_6烷基；

R_{10}为H或未取代的C_1-C_4烷基；

m为2-6；

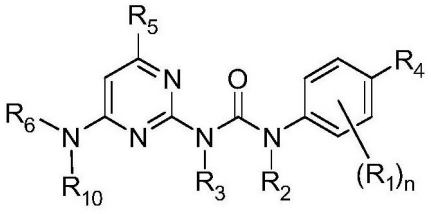
n为0-5；

p为1-3；

q为1-3。

[0007] 在一个实施方案中为式(II)化合物，其中R_2和R_3各自独立地为H、-CN、C_1-C_4烷基、C_3-C_6环烷基或C_2-C_7杂环烷基。在另一个实施方案中为式(II)化合物，其中R_2和R_3各自为H。在另一个实施方案中为式(II)化合物，其中R_2和R_3合起来形成5元或6元杂环。在另一个实施方案中为式(II)化合物，其中R_2和R_3合起来形成5元杂环。在上述实施方案的另一个实施方案中为式(II)化合物，其中R_6为-(C(R_{14})(R_{15}))$_m$$R_{21}$。在上述实施方案的另一个实施方案中为式(II)化合物，其中R_{21}为-OH、-N(R_{22})S(=O)$_2$$R_{23}$、-$CO_2R_{22}$、-C(=O)N($R_{22}$)$_2$、-N($R_{22}$)C(=O)$R_{23}$、取代或未取代的$C_1$-$C_6$烷氧基、或取代或未取代的$C_2$-$C_7$杂芳基。在上述实施方案的另一个实施方案中为式(II)化合物，其中R_{21}为-OH。在上述实施方案的另一个实施方案中为式(II)化合物，其中R_{21}为-N(R_{22})S(=O)$_2$$R_{23}$。在上述实施方案的另一个实施方案中为式(II)化合物，其中R_{21}为-N(R_{22})C(=O)R_{23}。在进一步的实施方案中为式(II)化合物，其中R_{21}为-N(R_{22})S(=O)$_2$$R_{23}$。在上述实施方案的另一个实施方案中为式(II)化合物，其中R_{21}为取代或未取代的C_1-C_6烷氧基。在上述实施方案的另一个实施方案中为式(II)化合物，其中R_{21}为取代或未取代的C_2-C_7杂芳基。在上述实施方案的另一个实施方案中为式(II)化合物，其中每个R_{22}独立地为H或未取代的C_1-C_6烷基；且R_{23}为未取代的C_1-C_6烷基。在上述实施方案的另一个实施方案中为式(II)化合物，其中R_{14}和R_{15}各自独立地为H或取代或未取代的C_1-C_6烷基。在上述实施方案的另一个实施方案中为式(II)化合物，其中R_{14}和R_{15}各自为H。在上述实施方案的另一个实施方案中为式(II)化合物，其中m为2。在上述实施方案的另一个实施方案中为式(II)化合物，其中m为3。在另一个实施方案中为式(II)化合物，其中R_6为取代或未取代的C_2-C_7杂芳基。在进一步的实施方案中为式(II)化合物，其中R_6为取代或未取代的吡啶基。在上述实施方案的另一个实施方案中为式(II)化合物，其中R_6为取代或未取代的C_2-C_7杂环烷基。在上述实施方案的另一个实施方案中为式(II)化合物，其中R_6为取代或未取代的吗啉基。在上述实施方案的另一个实施方案中为式(II)化合物，其中R_6为取代或未取代的哌啶基。在另一个实施方案中为式(II)化合物，其中R_{10}为H或CH_3。

[0008] 在另一方面，本文描述了式(IIA)化合物，或其药学上可接受的盐、溶剂化物或前药：



式(IIA)；

其中：

每个R_1独立地为卤素、-CN、-NO_2、-OH、-OCF_3、-OCH_2F、-OCF_2H、-SR_8、-N(R_8)S(=O)$_2$$R_9$、-S(=O)$_2$N($R_8$)$_2$、-S(=O)$R_9$、-S(=O)$_2$$R_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$、取代或未取代的$C_1$-$C_6$烷基、取代或未取代的$C_1$-$C_6$烷氧基、取代或未取代的$C_1$-$C_6$杂烷基、取代或未取代的$C_2$-$C_7$杂环烷基、取代或未取代的$C_3$-$C_8$环烷基、取代或未取代的$C_6$-$C_{10}$芳基、或取代或未取代的$C_2$-$C_7$杂芳基；或者两个$R_1$合起来形成取代或未取代的杂环或者取

代或未取代的碳环；

R_2和R_3各自独立地为H、-CN、C_1-C_4烷基、C_3-C_6环烷基或C_2-C_7杂环烷基；或R_2和R_3合起来形成5元或6元杂环；

R_4为H、卤素、-CN、-NO_2、-OH、-OCF_3、-OCH_2F、-OCF_2H、-SR_8、-N(R_8)S(=O)$_2R_9$、-S(=O)$_2$N(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、取代或未取代的C_1-C_6烷基、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基；或者两个R_1合起来形成取代或未取代的杂环或者取代或未取代的碳环；其中当n为0时，R_4不是卤素；

R_5为卤素、-CN、-OH、-CF_3、取代或未取代的C_1-C_6烷基、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基；

R_6为-(C(R_{14})(R_{15}))$_m$N(R_{11})(R_{12})；

R_{11}和R_{12}各自独立地为H、或取代或未取代的C_1-C_6烷基；或R_{11}和R_{12}合起来形成5、6、7或8元杂环；

R_{13}为H、取代或未取代的C_1-C_6烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的-C_1-C_4烷基C_6-C_{10}芳基、或取代或未取代的-C_1-C_4烷基C_2-C_7杂芳基；

每个R_{14}和R_{15}各自独立地为H、或取代或未取代的C_1-C_6烷基；或R_{14}和R_{15}合起来形成4、5、6元环烷基环；

每个R_8独立地为H、或取代或未取代的C_1-C_6烷基；

R_9为取代或未取代的C_1-C_6烷基；

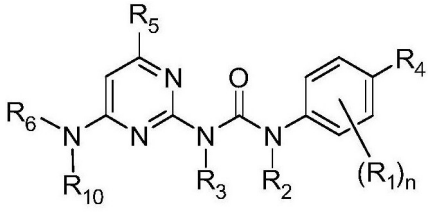
R_{10}为H或C_1-C_4烷基；

m为2-6；

n为0-4。

[0009] 在一个实施方案中为式(IIA)化合物，其中R_2和R_3各自独立地为H、-CN、C_1-C_4烷基、C_3-C_6环烷基或C_2-C_7杂环烷基。在另一个实施方案中为式(IIA)化合物，其中R_2和R_3各自为H。在另一个实施方案中为式(IIA)化合物，其中R_2和R_3合起来形成5元或6元杂环。在另一个实施方案中为式(IIA)化合物，其中R_2和R_3合起来形成5元杂环。在上述实施方案的另一个实施方案中为式(II)化合物，其中R_6为-(C(R_{14})(R_{15}))$_m$N(R_{11})(R_{12})且R_{14}和R_{15}各自为H。在上述实施方案的另一个实施方案中为式(II)化合物，其中R_{11}和R_{12}各自独立地为H、或取代或未取代的C_1-C_6烷基。在上述实施方案的另一个实施方案中为式(II)化合物，其中R_{11}和R_{12}各自独立地为未取代的C_1-C_6烷基。在上述实施方案的另一个实施方案中为式(II)化合物，其中R_{11}和R_{12}各自为-CH_3。在上述实施方案的另一个实施方案中为式(II)化合物，其中m为2。在上述实施方案的另一个实施方案中为式(II)化合物，其中m为3。在另一个实施方案中为式(II)化合物，其中R_{10}为H或CH_3。在上述实施方案的另一个实施方案中为式(II)化合物，其中n为0。在上述实施方案的另一个实施方案中为式(II)化合物，其中n为1。

[0010] 在另一方面，本文描述了式(VI)化合物，或其药学上可接受的盐、溶剂化物或前药：



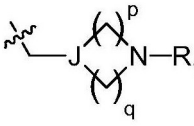
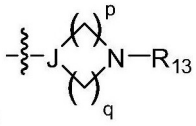
式(VI)；

其中：

每个R_1独立地为卤素、-CN、$-NO_2$、-OH、$-OCF_3$、$-OCH_2F$、$-OCF_2H$、$-CF_3$、$-SR_8$、$-N(R_8)S(=O)_2R_9$、$-S(=O)_2N(R_8)_2$、$-S(=O)R_9$、$-S(=O)_2R_9$、$-C(=O)R_9$、$-CO_2R_8$、$-N(R_8)_2$、$-C(=O)N(R_8)_2$、$-N(R_8)C(=O)R_9$、取代或未取代的C_1-C_6烷基、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基；或者两个R_1合起来形成取代或未取代的杂环或者取代或未取代的碳环；

R_2和R_3各自独立地为H或C_1-C_4烷基；或R_2和R_3合起来形成5元或6元杂环；

R_5为取代或未取代的C_1-C_6烷基；

R_6为未取代的C_1-C_4烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_2-C_7杂芳基、$-(C(R_{14})(R_{15}))_mR_{21}$、  或  ；

J为C(H)；

R_{13}为H、取代或未取代的C_1-C_6烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的$-C_1-C_4$烷基C_6-C_{10}芳基、或取代或未取代的$-C_1-C_4$烷基C_2-C_7杂芳基；

每个R_{14}和R_{15}各自独立地为H、卤素、或取代或未取代的C_1-C_6烷基；

R_{21}为卤素、-CN、$-NO_2$、-OH、$-OCF_3$、$-OCH_2F$、$-OCF_2H$、$-CF_3$、$-SR_{22}$、$-N(R_{22})S(=O)_2R_{23}$、$-S(=O)_2N(R_{22})_2$、$-S(=O)R_{23}$、$-S(=O)_2R_{23}$、$-C(=O)R_{23}$、$-CO_2R_{22}$、$-C(=O)N(R_{22})_2$、$-N(R_{22})C(=O)R_{23}$、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、或取代或未取代的C_2-C_7杂芳基；

每个R_{22}独立地为H、或取代或未取代的C_1-C_6烷基；

R_{23}为取代或未取代的C_1-C_6烷基；

每个R_8独立地为H、或取代或未取代的C_1-C_6烷基；

R_9为取代或未取代的C_1-C_6烷基；

R_{10}为H；

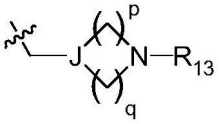
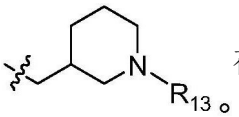
m为2-6；

n为0-5；

p为1-3；

q为1-3。

[0011] 在一些实施方案中为式(VI)化合物，其中R_2和R_3各自独立地为H或C_1-C_4烷基。在另一个实施方案中为式(VI)化合物，其中R_2和R_3各自为H。在另一个实施方案中为式(VI)化合

物，其中R_2和R_3合起来形成5元或6元杂环。在另一个实施方案中为式(VI)化合物，其中R_2和R_3合起来形成5元杂环。在另一个实施方案中为式(VI)化合物，其中R_6为$-(C(R_{14})(R_{15}))_mR_{21}$。在另一个实施方案中为式(VI)化合物，其中$R_{14}$和$R_{15}$各自独立地为H、卤素或未取代的$C_1$-$C_6$烷基。在另一个实施方案中为式(VI)化合物，其中$R_{14}$和$R_{15}$各自为H。在另一个实施方案中为式(VI)化合物，其中R_{21}为$-OH$、$-N(R_{22})S(=O)_2R_{23}$、$-CO_2R_{22}$、$-C(=O)N(R_{22})_2$、$-N(R_{22})C(=O)R_{23}$、取代或未取代的C_1-C_6烷氧基、或取代或未取代的C_2-C_7杂芳基。在上述实施方案的另一个实施方案中为式(VI)化合物，其中R_{21}为$-OH$。在上述实施方案的另一个实施方案中为式(VI)化合物，其中R_{21}为$-N(R_{22})S(=O)_2R_{23}$。在上述实施方案的另一个实施方案中为式(VI)化合物，其中R_{21}为$-N(R_{22})C(=O)R_{23}$。在进一步的实施方案中，R_{21}为$-N(R_{22})S(=O)_2R_{23}$。在上述实施方案的另一个实施方案中为式(VI)化合物，其中R_{21}为取代或未取代的C_1-C_6烷氧基。在上述实施方案的另一个实施方案中为式(VI)化合物，其中R_{21}为取代或未取代的C_2-C_7杂芳基。在另一个实施方案中为式(VI)化合物，其中每个R_{22}独立地为H或未取代的C_1-C_6烷基；且R_{23}为未取代的C_1-C_6烷基。在另一个实施方案中为式(VI)化合物，其中m为2。在另一个实施方案中为式(VI)化合物，其中m为3。在另一个实施方案中为式(VI)化合物，其中R_6为  。在另一个实施方案中为式(VI)化合物，其中R_6为  。在另一个实施方案中为式(VI)化合物，其中R_{13}为H或未取代的C_1-C_6烷基。在另一个实施方案中为式(VI)化合物，其中每个R_1独立地为卤素、$-OCF_3$、$-CF_3$、未取代的C_1-C_6烷基或未取代的C_1-C_6烷氧基。在另一个实施方案中为式(VI)化合物，其中每个R_1独立地为卤素。在另一个实施方案中为式(VI)化合物，其中n为1。在另一个实施方案中为式(VI)化合物，其中每个R_1独立地为卤素。在另一个实施方案中为式(VI)化合物，其中n为2。在另一个实施方案中为式(VI)化合物，其中每个R_1独立地为卤素。在另一个实施方案中为式(VI)化合物，其中n为0。

[0012] 在另一方面为一种药物组合物，其包含式(I)、(II)或(IIA)化合物或其药学上可接受的盐、溶剂化物或前药，以及至少一种药学上可接受的赋形剂。在另一方面为一种药物组合物，其包含式(I)、(II)、(IIA)或(VI)化合物或其药学上可接受的盐、溶剂化物或前药，以及至少一种药学上可接受的赋形剂。

[0013] 在另一方面，提供了式(I)、(II)或(IIA)化合物或其药学上可接受的盐、药学上可接受的溶剂化物或药学上可接受的前药在配制用于抑制细胞中Olig2活性的药物中的用途。该方法包括使该细胞接触式(I)、(II)或(IIA)化合物，包括其实施方案。

[0014] 在另一方面，提供了式(I)、(II)、(IIA)或(VI)化合物或其药学上可接受的盐、药学上可接受的溶剂化物或药学上可接受的前药在配制用于抑制细胞中Olig2活性的药物中的用途。该方法包括使该细胞接触式(I)、(II)、(IIA)或(VI)化合物，包括其实施方案。

[0015] 在另一方面是一种治疗受试者中将会受益于Olig2活性抑制的疾病、病症或状况的方法，其包括向有需要的受试者施用包含式(I)、(II)或(IIA)化合物或其药学上可接受的盐、溶剂化物或前药的组合物。在一些实施方案中是一种治疗受试者中将会受益于Olig2活性抑制的疾病、病症或状况的方法，其包括向有需要的受试者施用包含式(I)、(II)或(IIA)化合物或其药学上可接受的盐、溶剂化物或前药的组合物；其中该疾病为癌症或唐氏综合征。

[0016] 在另一方面是一种治疗受试者中将会受益于Olig2活性抑制的疾病、病症或状况的方法，其包括向有需要的受试者施用包含式(I)、(II)、(IIA)或(VI)化合物或其药学上可接受的盐、溶剂化物或前药的组合物。在一些实施方案中是一种治疗受试者中将会受益于Olig2活性抑制的疾病、病症或状况的方法，其包括向有需要的受试者施用包含式(I)、(II)、(IIA)或(VI)化合物或其药学上可接受的盐、溶剂化物或前药的组合物；其中该疾病为癌症或唐氏综合征。

[0017] 在另一方面是一种治疗受试者的疾病的方法，其包括向有需要的受试者施用包含式(I)、(II)或(IIA)化合物或其药学上可接受的盐、溶剂化物或前药的组合物；其中该疾病为癌症或唐氏综合征。在一些实施方案中是一种治疗受试者的癌症的方法，其包括向有需要的受试者施用包含式(I)、(II)或(IIA)化合物或其药学上可接受的盐、溶剂化物或前药的组合物。在一些实施方案中是一种治疗受试者的唐氏综合征的方法，其包括向有需要的受试者施用包含式(I)、(II)或(IIA)化合物或其药学上可接受的盐、溶剂化物或前药的组合物。

[0018] 在另一方面是一种治疗受试者的疾病的方法，其包括向有需要的受试者施用包含式(I)、(II)、(IIA)或(VI)化合物或其药学上可接受的盐、溶剂化物或前药的组合物；其中该疾病为癌症或唐氏综合征。在一些实施方案中是一种治疗受试者的癌症的方法，其包括向有需要的受试者施用包含式(I)、(II)或(IIA)化合物或其药学上可接受的盐、溶剂化物或前药的组合物。在一些实施方案中是一种治疗受试者的唐氏综合征的方法，其包括向有需要的受试者施用包含式(I)、(II)、(IIA)或(VI)化合物或其药学上可接受的盐、溶剂化物或前药的组合物。

[0019] 在另一个实施方案中是一种治疗受试者的癌症的方法，其包括向有需要的受试者施用包含式(I)、(II)或(IIA)化合物或其药学上可接受的盐、溶剂化物或前药的组合物，其中该癌症为脑癌、多形性胶质母细胞瘤、髓母细胞瘤、星形细胞瘤、脑干胶质瘤、脑膜瘤、少突神经胶质瘤、黑素瘤、肺癌、乳腺癌或白血病。在另一个实施方案中是一种治疗受试者的癌症的方法，其包括向有需要的受试者施用包含式(I)、(II)、(IIA)或(VI)化合物或其药学上可接受的盐、溶剂化物或前药的组合物，其中该癌症为脑癌、多形性胶质母细胞瘤、髓母细胞瘤、星形细胞瘤、脑干胶质瘤、脑膜瘤、少突神经胶质瘤、黑素瘤、肺癌、乳腺癌或白血病。

[0020] 在另一方面是一种抑制细胞中Olig2的活性的方法，其包括使该细胞接触式(I)、(II)或(IIA)化合物或其药学上可接受的盐、溶剂化物或前药。在另一方面是一种抑制细胞中Olig2的活性的方法，其包括使该细胞接触式(I)、(II)、(IIA)或(VI)化合物或其药学上可接受的盐、溶剂化物或前药。

[0021] 在另一方面是式(I)、(II)或(IIA)化合物在制备用于治疗将会受益于Olig2活性抑制的疾病、病症或状况的药物中的用途。在另一方面是式(I)、(II)、(IIA)或(VI)化合物在制备用于治疗将会受益于Olig2活性抑制的疾病、病症或状况的药物中的用途。

[0022] 通过以下详细描述，本文所述的化合物、组合物、方法和用途的其他目标、特征和优点将会变得显而易见。然而，应当理解，尽管该详细描述和具体实例表示了具体的实施方案，但其仅以说明的方式给出，因为根据该详细描述，本公开内容的精神和范围内的各种变化和修改将会变得显而易见。

具体实施方式

[0023] 本文所述的化合物是神经和GBM(多形性胶质母细胞瘤)干细胞转录抑制物OLIG2(例如,对于人类为NM_005806、NP_005797)的调节剂或抑制剂。OLIG2(本文也称为Olig2)是少突胶质细胞转录因子2。该蛋白质是bHLH(碱性螺旋-环-螺旋)家族的成员。该bHLH家族是转录因子家族,这些转录因子含有以由环连接的两个α螺旋为特征的结构基序。含有bLHL结构域的转录因子通常是二聚化的。通常,螺旋之一含有碱性氨基酸残基,其促进与DNA结合。OLIG2通常局限于非疾病状态的中枢神经系统(CNS),在其中它是祖细胞命运的必需调节剂。OLIG2同型二聚化并且与E12或E47蛋白质异型二聚化,然后结合并抑制p21基因启动子以及其他效应。P21是干细胞和肿瘤抑制物,并被OLIG2直接抑制。P21被肿瘤抑制物p53激活。p53以完整的野生型形式存在于近70％的原发性GBM患者样品中。OLIG2在所有弥漫性神经胶质瘤中高度表达,并且发现于几乎100％的CD133干细胞标志物阳性GBM细胞中。重要的是,OLIG2通常不会在正常脑中以及CNS以外的组织中发现,除非它们是恶性的,如T-细胞白血病、黑素瘤、肺癌和乳腺癌。没有其他神经或神经胶质标志物基因并且没有其他转录抑制物表现出与脑癌的一致关联。相比之下,膜受体(EGFR、PDGFR等)在患者中不均匀地表达,并且针对它们的各种方法已经在GBM治疗中取得了有限的成功。

[0024] 弥漫性神经胶质瘤中Olig2的表达可能是由于这些肿瘤的转化的干细胞来源引起的。已经发现,存在于患者GBM中的一小群细胞表达神经干细胞标志物,包括CD133和巢蛋白,等等。从现有GBM中分离的CD133(+)细胞在原位植入小鼠中时是高度致瘤性的。在一项研究中,从患者GBM中提取的少至100个CD133(+)细胞在植入到受体小鼠的脑中时产生侵袭性肿瘤,而100,000个CD133(-)GBM细胞不能产生肿瘤。与这些发现一致,显著高百分比的GBM紧密靠近脑中的神经干细胞生发区而发生,即神经干细胞经历恶性转化并从生发区迁移一些距离并建立GBM。

[0025] 关于GBM癌症干细胞(CSC)的另一个重要的发现是CD133(+)细胞比由CD133(-)组成的大多数肿瘤块对用于治疗GBM的辐射和细胞毒性剂的耐受性明显更强。这提示常规的放射/化学疗法放过GBM内的CSC,并且除非这些细胞被靶向,否则肿瘤总是复发,具有致死作用。此外,GBM存活的极少数患者在认知、内分泌平衡和其他功能方面由于化学和放射毒性而终身致病。

[0026] Olig2在GBM CSC中高度表达,但仅被正常脑低水平表达,并且在神经系统外的组织中检测不到。Olig2抑制剂将提供优于常规化疗的治疗优点。与采用目前使用的治疗方法的情况相比,低全身毒性将与GBM的长期临床管理更兼容。

[0027] 脑癌患者的高死亡率使得这种疾病成为男性、女性和儿童中癌症相关死亡的主要原因。原发性脑瘤实际上是最常见的儿童实体瘤,也是仅次于白血病的第二大癌症死亡原因。现有治疗的毒性在存活的少数患者中引起严重的终身发病。开发对脑癌有效的低毒性小分子口服药物将代表显著的进步。而且,这些化合物在干细胞驱动且高表达Olig2的其他癌症中也可能是有效的。这些癌症包括T细胞白血病、皮肤癌、小细胞肺癌和乳腺癌。而且,这些癌症经常转移到脑。这将关系到全球数百万的患者。

[0028] 在本文描述的一些实施方案中是抑制Olig2的小分子,Olig2是对胶质母细胞瘤和其他脑癌,即髓母细胞瘤、星形细胞瘤、脑干胶质瘤、脑膜瘤和少突神经胶质瘤的存活和增

殖至关重要的转录因子。特别是，Olig2主要在脑中检测到，在神经系统外通常检测不到，并且在胶质母细胞瘤中高度表达。这意味着Olig2抑制应该对患者具有相对较低的毒性。Olig2也在黑素瘤、肺癌、乳腺癌和T细胞白血病中过表达，因此Olig2抑制剂也可应用于这些癌症的治疗。

[0029] 没有其他转录因子或标志物像Olig2一样表现出与脑癌的一致关联，所以对于胶质母细胞瘤，Olig2抑制应该有利地与其他信号传导途径抑制剂相当。Olig2是一个稳定的靶标，因为其二聚化环的铰链区与其所在类别的其他蛋白质(碱性螺旋-环-螺旋蛋白质)相比是独特的。

[0030] 本文描述的Olig2靶向抑制剂在功效和毒性方面应证明是独特的。

[0031] 用于治疗脑癌的现有药剂、治疗剂和方法包括替莫唑胺(TMZ-Temodar)、辐射、环磷酰胺、卡莫司汀、卡铂以及偶尔补充阿瓦斯丁(Avastin)。所有这些仅仅是略微有效的标准脑癌治疗剂，并且它们的毒性非常高。目前没有用于脑瘤的脑癌干细胞抑制剂。

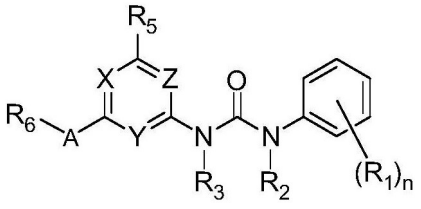
[0032] 在另一方面，提供了抑制OLIG2活性的方法。该方法包括使Olig2蛋白质接触有效量的本文提供的化合物(例如式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物)。该化合物可以具有本文提供的通式的结构(或其上述任何实施方案)。在一些实施方案中，抑制Olig2蛋白的方法在细胞内进行。因此，在某些实施方案中，提供了抑制细胞内Olig2的活性的方法。该方法包括使细胞与有效量的本文提供的化合物接触。该化合物可以具有本文提供的通式的结构(或其上述任何实施方案)。在一些实施方案中，该细胞是原核生物或真核生物细胞。该细胞可以是真核生物细胞(例如原生动物细胞、真菌细胞、植物细胞或动物细胞)。在一些实施方案中，该细胞是哺乳动物细胞，例如人细胞、牛细胞、猪细胞、马细胞、犬细胞和猫细胞、小鼠细胞或大鼠细胞。在一些实施方案中，该细胞是人细胞。该细胞可以形成器官或生物体的一部分。在某些实施方案中，该细胞不形成器官或生物体的一部分。

[0033] 在另一方面，提供了一种抑制细胞内Olig2的活性的方法。该方法包括使细胞接触本文提供的化合物(例如式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)和(V))。在一些实施方案中，该化合物结合Olig2的二聚化环的铰链区。在一些实施方案中，该化合物抑制Olig2的二聚化。

化合物

[0034] 本文所述的化合物抑制细胞内Olig2的活性，并且可用于治疗对Olig2活性的抑制具有有益效果的疾病或状况。

[0035] 在一方面，本文描述了式(I)化合物，或其药学上可接受的盐、溶剂化物或前药：



式(I)；

其中：

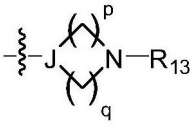
A为键、O或N(R10)；

X、Y和Z各自独立地为N或C(R7)，其中X、Y和Z中的至少一个为N；

每个R1独立地为卤素、-CN、-NO2、-OH、-OCF3、-OCH2F、-OCF2H、-CF3、-SR8、-N(R8)S(=O)2R9、-S(=O)2N(R8)2、-S(=O)R9、-S(=O)2R9、-C(=O)R9、-CO2R8、-N(R8)2、-C(=O)N(R8)2、-N(R8)C(=O)R9、取代或未取代的C1-C6烷基、取代或未取代的C1-C6烷氧基、取代或未取代的C1-C6杂烷基、取代或未取代的C2-C7杂环烷基、取代或未取代的C3-C8环烷基、取代或未取代的C6-C10芳基、或取代或未取代的C2-C7杂芳基；或者两个R1合起来形成取代或未取代的杂环或者取代或未取代的碳环；

R2和R3各自独立地为H、-CN、C1-C4烷基、C3-C6环烷基或C2-C7杂环烷基；或者R2和R3合起来形成5元或6元杂环；

R5为卤素、-CN、-OH、-CF3、取代或未取代的C1-C6烷基、取代或未取代的C1-C6烷氧基、取代或未取代的C1-C6杂烷基、取代或未取代的C2-C7杂环烷基、取代或未取代的C3-C8环烷基、取代或未取代的C6-C10芳基、或取代或未取代的C2-C7杂芳基；

R6为取代或未取代的C2-C7杂环烷基、取代或未取代的C3-C8环烷基、取代或未取代的C2-C7杂芳基、-(C(R14)(R15))mR21、-(C(R14)(R15))mN(R11)(R12)或  ；

R11和R12各自独立地为H、或取代或未取代的C1-C6烷基；或者R11和R12合起来形成5、6、7或8元杂环；

J为C(H)或N；

R13为H、取代或未取代的C1-C6烷基、取代或未取代的C2-C7杂环烷基、取代或未取代的C3-C8环烷基、取代或未取代的-C1-C4烷基C6-C10芳基、或取代或未取代的-C1-C4烷基C2-C7杂芳基；

每个R7独立地为H、卤素、-CN、-OH、-CF3、取代或未取代的C1-C6烷基、取代或未取代的C1-C6烷氧基、取代或未取代的C1-C6杂烷基、取代或未取代的C2-C7杂环烷基、取代或未取代的C3-C8环烷基、取代或未取代的C6-C10芳基、或取代或未取代的C2-C7杂芳基；

每个R14和R15各自独立地为H、或取代或未取代的C1-C6烷基；或者R14和R15合起来形成4、5、6元环烷基环；

R21为卤素、-CN、-NO2、-OH、-OCF3、-OCH2F、-OCF2H、-CF3、-SR22、-N(R22)S(=O)2R23、-S(=O)2N(R22)2、-S(=O)R23、-S(=O)2R23、-C(=O)R23、-CO2R22、-C(=O)N(R22)2、-N(R22)C(=O)R23、取代或未取代的C1-C6烷氧基、取代或未取代的C1-C6杂烷基、取代或未取代的C2-C7杂环烷基、取代或未取代的C3-C8环烷基、取代或未取代的C6-C10芳基、或取代或未取代的C2-C7杂芳基；

每个R22独立地为H、或取代或未取代的C1-C6烷基；

R23为取代或未取代的C1-C6烷基；

每个R8独立地为H、或取代或未取代的C1-C6烷基；

R9为取代或未取代的C1-C6烷基；

R10为H或未取代的C1-C4烷基；

m为2-6；

n为0-5；

p为1-3；

q为1-3。

[0036] 在一个实施方案中为式(I)化合物，其中A为O或N(R_{10})。在另一个实施方案中为式(I)化合物，其中A为O或N(H)。在另一个实施方案中为式(I)化合物，其中A为O。在另一个实施方案中为式(I)化合物，其中A为N(R_{10})。在另一个实施方案中为式(I)化合物，其中A为N(H)。在另一个实施方案中为式(I)化合物，其中A为N(CH_3)。在另一个实施方案中为式(I)化合物，其中A为键。

[0037] 在另一个实施方案中为式(I)化合物，其中R_6为取代或未取代的C_3-C_8环烷基。在另一个实施方案中为式(I)化合物，其中R_6为取代或未取代的环丙基。在另一个实施方案中为式(I)化合物，其中R_6为取代或未取代的环丁基。在另一个实施方案中为式(I)化合物，其中R_6为取代或未取代的环戊基。在另一个实施方案中为式(I)化合物，其中R_6为取代或未取代的环己基。

[0038] 在另一个实施方案中为式(I)化合物，其中R_6为取代或未取代的C_2-C_7杂芳基。在另一个实施方案中为式(I)化合物，其中R_6为取代或未取代的呋喃基、噻吩基、吡咯基、吡啶基、噁唑基、噻唑基、咪唑基、异噁唑基、异噻唑基、吡唑基、哒嗪基、嘧啶基、吡嗪基、噁二唑基、噻二唑基、三唑基、吲哚基、苯并噻吩基、苯并噁唑基、苯并噻唑基、苯并咪唑基、苯并噁二唑基、苯并噻二唑基、苯并三唑基、吡唑并吡啶基、咪唑并吡啶基、吡咯并吡啶基、吡咯并嘧啶基、吲嗪基、嘌呤基、呋喃并吡啶基、噻吩并吡啶基、呋喃并吡咯基、呋喃并呋喃基、噻吩并呋喃基、1,4-二氢吡咯并吡咯基、噻吩并吡咯基、噻吩并噻吩基、喹啉基、异喹啉基、喹喔啉基、呋喃并吡唑基、噻吩并吡唑基、硒吩基、硒唑基和苯并异噁唑基。在另一个实施方案中为式(I)化合物，其中R_6为取代或未取代的吡啶基。在另一个实施方案中为式(I)化合物，其中R_6为取代的吡啶基。在另一个实施方案中为式(I)化合物，其中R_6为未取代的吡啶基。

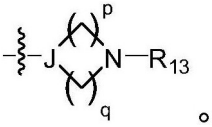
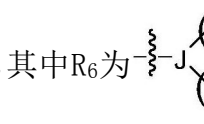
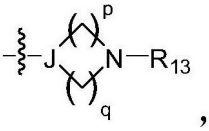
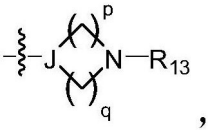
[0039] 在另一个实施方案中为式(I)化合物，其中R_6为-(C(R_{14})(R_{15}))$_m$$R_{21}$。在另一个实施方案中为式(I)化合物，其中$R_6$为-(C($R_{14}$)($R_{15}$))$_m$$R_{21}$，且每个$R_{14}$和$R_{15}$为H。在另一个实施方案中为式(I)化合物，其中$R_6$为-(C($R_{14}$)($R_{15}$))$_m$$R_{21}$，m为2，且每个$R_{14}$和$R_{15}$为H。在另一个实施方案中为式(I)化合物，其中$R_6$为-($CH_2$)$_m$$R_{21}$，m为2，且$R_{21}$为取代或未取代的$C_2$-$C_7$杂环烷基。在另一个实施方案中为式(I)化合物，其中R_6为-(CH_2)$_m$$R_{21}$，m为2，且$R_{21}$为取代或未取代的$C_3$-$C_8$环烷基。在另一个实施方案中为式(I)化合物，其中$R_6$为-($CH_2$)$_m$$R_{21}$，m为2，且$R_{21}$为取代或未取代的$C_6$-$C_{10}$芳基。在另一个实施方案中为式(I)化合物，其中$R_6$为-($CH_2$)$_m$$R_{21}$，m为2，且$R_{21}$为取代或未取代的苯基。在另一个实施方案中为式(I)化合物，其中R_6为-(CH_2)$_m$$R_{21}$，m为2，且$R_{21}$为取代或未取代的$C_2$-$C_7$杂芳基。在另一个实施方案中为式(I)化合物，其中$R_6$为-($CH_2$)$_m$$R_{21}$，m为2，且$R_{21}$为-OH。

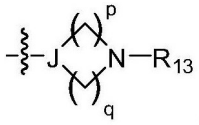
[0040] 在另一个实施方案中为式(I)化合物，其中R_6为-(C(R_{14})(R_{15}))$_m$$R_{21}$，m为3，且每个$R_{14}$和$R_{15}$为H。在另一个实施方案中为式(I)化合物，其中$R_6$为-($CH_2$)$_m$$R_{21}$，m为3，且$R_{21}$为取代或未取代的$C_2$-$C_7$杂环烷基。在另一个实施方案中为式(I)化合物，其中R_6为-(CH_2)$_m$$R_{21}$，m为3，且$R_{21}$为取代或未取代的$C_3$-$C_8$环烷基。在另一个实施方案中为式(I)化合物，其中$R_6$为-($CH_2$)$_m$$R_{21}$，m为3，且$R_{21}$为取代或未取代的$C_6$-$C_{10}$芳基。在另一个实施方案中为式(I)化合物，其中$R_6$为-($CH_2$)$_m$$R_{21}$，m为3，且$R_{21}$为取代或未取代的苯基。在另一个实施方案中为式(I)化合物，其中R_6为-(CH_2)$_m$$R_{21}$，m为3，且$R_{21}$为取代或未取代的$C_2$-$C_7$杂芳基。在另一个实施方案中为

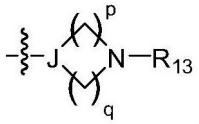
式(I)化合物,其中R_6为-$(CH_2)_mR_{21}$,m为3,且R_{21}为-OH。

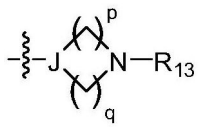
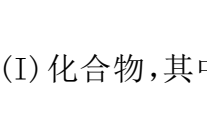
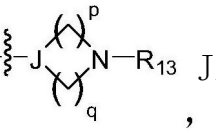
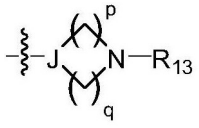
[0041] 在另一个实施方案中为式(I)化合物,其中R_6为-$(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$。在另一个实施方案中为式(I)化合物,其中$R_6$为-$(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$,m为2,且每个$R_{14}$和$R_{15}$为H。在另一个实施方案中为式(I)化合物,其中$R_6$为-$(CH_2)_mN(R_{11})(R_{12})$,m为2,且$R_{11}$和$R_{12}$各自为H。在另一个实施方案中为式(I)化合物,其中R_6为-$(CH_2)_mN(R_{11})(R_{12})$,m为2,$R_{11}$为取代或未取代的$C_1$-$C_6$烷基,且$R_{12}$为H。在另一个实施方案中为式(I)化合物,其中$R_6$为-$(CH_2)_mN(R_{11})(R_{12})$,m为2,$R_{11}$为$CH_3$,且$R_{12}$为H。在另一个实施方案中为式(I)化合物,其中$R_6$为-$(CH_2)_mN(R_{11})(R_{12})$,m为2,$R_{11}$为取代或未取代的$C_1$-$C_6$烷基,且$R_{12}$为取代或未取代的$C_1$-$C_6$烷基。在另一个实施方案中为式(I)化合物,其中$R_6$为-$(CH_2)_mN(R_{11})(R_{12})$,m为2,$R_{11}$为$CH_3$,且$R_{12}$为$CH_3$。在另一个实施方案中为式(I)化合物,其中$R_6$为-$(CH_2)_mN(R_{11})(R_{12})$,m为2,且$R_{11}$和$R_{12}$合起来形成5、6、7或8元杂环。在另一个实施方案中为式(I)化合物,其中R_6为-$(CH_2)_mN(R_{11})(R_{12})$,m为2,且$R_{11}$和$R_{12}$合起来形成5元杂环。在另一个实施方案中为式(I)化合物,其中R_6为-$(CH_2)_mN(R_{11})(R_{12})$,m为2,且$R_{11}$和$R_{12}$合起来形成6元杂环。

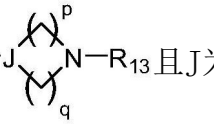
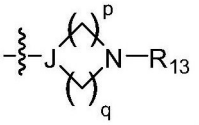
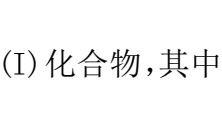
[0042] 在另一个实施方案中为式(I)化合物,其中R_6为-$(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$。在另一个实施方案中为式(I)化合物,其中$R_6$为-$(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$,m为3,且每个$R_{14}$和$R_{15}$为H。在另一个实施方案中为式(I)化合物,其中$R_6$为-$(CH_2)_mN(R_{11})(R_{12})$,m为3,且$R_{11}$和$R_{12}$各自为H。在另一个实施方案中为式(I)化合物,其中R_6为-$(CH_2)_mN(R_{11})(R_{12})$,m为3,$R_{11}$为取代或未取代的$C_1$-$C_6$烷基,且$R_{12}$为H。在另一个实施方案中为式(I)化合物,其中$R_6$为-$(CH_2)_mN(R_{11})(R_{12})$,m为3,$R_{11}$为$CH_3$,且$R_{12}$为H。在另一个实施方案中为式(I)化合物,其中$R_6$为-$(CH_2)_mN(R_{11})(R_{12})$,m为3,$R_{11}$为取代或未取代的$C_1$-$C_6$烷基,且$R_{12}$为取代或未取代的$C_1$-$C_6$烷基。在另一个实施方案中为式(I)化合物,其中$R_6$为-$(CH_2)_mN(R_{11})(R_{12})$,m为3,$R_{11}$为$CH_3$,且$R_{12}$为$CH_3$。在另一个实施方案中为式(I)化合物,其中$R_6$为-$(CH_2)_mN(R_{11})(R_{12})$,m为3,且$R_{11}$和$R_{12}$合起来形成5、6、7或8元杂环。在另一个实施方案中为式(I)化合物,其中R_6为-$(CH_2)_mN(R_{11})(R_{12})$,m为3,且$R_{11}$和$R_{12}$合起来形成5元杂环。在另一个实施方案中为式(I)化合物,其中R_6为-$(CH_2)_mN(R_{11})(R_{12})$,m为3,且$R_{11}$和$R_{12}$合起来形成6元杂环。

[0043] 在另一个实施方案中为式(I)化合物,其中R_6为取代或未取代的C_2-C_7杂环烷基。在另一个实施方案中为式(I)化合物,其中R_6为  在另一个实施方案中为式(I)化合物,其中R_6为  且J为C(H)。在另一个实施方案中为式(I)化合物,其中R_6为  ,J为C(H),p为1,且q为1。在另一个实施方案中为式(I)化合物,其中R_6为  ,J为C(H),p为2,且q为1。在另一个实施方案中为式(I)化合物,其中R_6为


J为C(H)，p为3，且q为1。在另一个实施方案中为式(I)化合物，其中R_6为


J为C(H)，p为2，且q为2。在另一个实施方案中为式(I)化合物，其中R_6为


J为C(H)，p为1，q为1，且R_{13}为取代或未取代的C_1-C_6烷基。在另一个实施方案中为式(I)化合物，其中R_6为 
J为C(H)，p为2，q为1，且R_{13}为取代或未取代的C_1-C_6烷基。在另一个实施方案中为式(I)化合物，其中R_6为 
J为C(H)，p为3，q为1，且R_{13}为取代或未取代的C_1-C_6烷基。在另一个实施方案中为式(I)化合物，其中R_6为 
J为C(H)，p为2，q为2，且R_{13}为取代或未取代的C_1-C_6烷基。

[0044] 在另一个实施方案中为式(I)化合物，其中R_6为  且J为N。在另一个实施方案中为式(I)化合物，其中R_6为 
J为N，p为2，且q为2。在另一个实施方案中为式(I)化合物，其中R_6为 
J为N，p为2，q为2，且R_{13}为取代或未取代的C_1-C_6烷基。

[0045] 在另一个实施方案中为式(I)化合物，其中R_5为卤素。在另一个实施方案中为式(I)化合物，其中R_5为-CF_3。在另一个实施方案中为式(I)化合物，其中R_5为取代或未取代的C_1-C_6烷基。在另一个实施方案中为式(I)化合物，其中R_5为-CH_3。在另一个实施方案中为式(I)化合物，其中R_5为-CH_2CH_3。在另一个实施方案中为式(I)化合物，其中R_5为取代或未取代的C_1-C_6杂烷基。在另一个实施方案中为式(I)化合物，其中R_5为取代或未取代的C_2-C_7杂环烷基。在另一个实施方案中为式(I)化合物，其中R_5为取代或未取代的C_3-C_8环烷基。在另一个实施方案中为式(I)化合物，其中R_5为取代或未取代的C_6-C_{10}芳基。在另一个实施方案中为式(I)化合物，其中R_5为取代或未取代的C_2-C_7杂芳基。

[0046] 在另一个实施方案中为式(I)化合物，其中R_2和R_3各自独立地为H、-CN、C_1-C_4烷基、C_3-C_6环烷基或C_2-C_7杂环烷基。在另一个实施方案中为式(I)化合物，其中R_2和R_3各自为H。

[0047] 在另一个实施方案中为式(I)化合物，其中R_2和R_3各自独立地为H、-CN、C_1-C_4烷基、C_3-C_6环烷基或C_2-C_7杂环烷基；且R_2和R_3中的至少一个不是H。在另一个实施方案中为式(I)化合物，其中R_2为H，且R_3为C_1-C_4烷基。在另一个实施方案中为式(I)化合物，其中R_2为H，且R_3为CH_3。在另一个实施方案中为式(I)化合物，其中R_2为H，且R_3为C_3-C_6环烷基。在另一个实施方案中为式(I)化合物，其中R_2为H，且R_3为环丙基。在另一个实施方案中为式(I)化合物，其中R_2为H，且R_3为环戊基。在另一个实施方案中为式(I)化合物，其中R_2为CH_3，且R_3为CH_3。在另一个实施方案中为式(I)化合物，其中R_2为C_1-C_4烷基，且R_3为H。在另一个实施方案中为式(I)化合物，其中R_2为CH_3，且R_3为H。在另一个实施方案中为式(I)化合物，其中R_2为C_3-C_6环烷基，且R_3为H。在另一个实施方案中为式(I)化合物，其中R_2为环丙基，且R_3为H。在另一个实施方案中为式(I)化合物，其中R_2为环戊基，且R_3为H。

[0048] 在另一个实施方案中为式(I)化合物，其中R_2和R_3合起来形成5元或6元杂环。在另一个实施方案中为式(I)化合物，其中R_2和R_3合起来形成5元杂环。在另一个实施方案中为式(I)化合物，其中R_2和R_3合起来形成6元杂环。

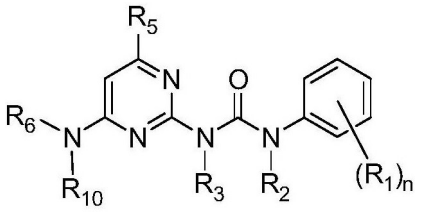
[0049] 在另一个实施方案中为式(I)化合物，其中n为0。

[0050] 在另一个实施方案中为式(I)化合物，其中每个R_1独立地为卤素、-CN、$-NO_2$、-OH、$-OCF_3$、$-OCH_2F$、$-OCF_2H$、$-CF_3$、$-SR_8$、$-N(R_8)S(=O)_2R_9$、$-S(=O)_2N(R_8)_2$、$-S(=O)R_9$、$-S(=O)_2R_9$、$-C(=O)R_9$、$-CO_2R_8$、$-N(R_8)_2$、$-C(=O)N(R_8)_2$、$-N(R_8)C(=O)R_9$、取代或未取代的C_1-C_6烷基、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基。在另一个实施方案中为式(I)化合物，其中每个R_1独立地为卤素、-CN、-OH、$-CF_3$、取代或未取代的C_1-C_6烷基、或取代或未取代的C_1-C_6烷氧基。在另一个实施方案中为式(I)化合物，其中每个R_1独立地为卤素、-CN、$-OCF_3$、$-OCH_2F$、$-OCF_2H$、$-CF_3$、取代或未取代的C_1-C_6烷基、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基。在另一个实施方案中为式(I)化合物，其中每个R_1独立地为卤素、-CN、$-OCF_3$、$-OCH_2F$、$-OCF_2H$、$-CF_3$、取代或未取代的C_1-C_6烷基、或取代或未取代的C_1-C_6烷氧基。在另一个实施方案中为式(I)化合物，其中每个R_1独立地为卤素、-CN、$-OCF_3$、$-OCH_2F$、$-OCF_2H$、$-CF_3$、取代或未取代的C_1-C_6烷基、或取代或未取代的C_1-C_6烷氧基，且n为3。在另一个实施方案中为式(I)化合物，其中每个R_1独立地为卤素、-CN、$-OCF_3$、$-OCH_2F$、$-OCF_2H$、$-CF_3$、取代或未取代的C_1-C_6烷基、或取代或未取代的C_1-C_6烷氧基，且n为2。在另一个实施方案中为式(I)化合物，其中n为3，且每个R_1独立地为卤素。在另一个实施方案中为式(I)化合物，其中n为2，且每个R_1独立地为卤素。在另一个实施方案中为式(I)化合物，其中n为2，且每个R_1独立地为F或Cl。在另一个实施方案中为式(I)化合物，其中n为2，且每个R_1为F。在另一个实施方案中为式(I)化合物，其中n为2，且每个R_1独立地为Cl。在另一个实施方案中为式(I)化合物，其中n为2，且每个R_1独立地为卤素或$-CF_3$。在另一个实施方案中为式(I)化合物，其中n为2，且每个R_1独立地为F或$-CF_3$。在另一个实施方案中为式(I)化合物，其中n为2，且每个R_1独立地为Cl或$-CF_3$。在另一个实施方案中为式(I)化合物，其中n为1，且R_1为卤素。在另一个实施方案中为式(I)化合物，其中n为1，且R_1为F。在另一个实施方案中为式(I)化合物，其中n为1，且R_1为Cl。在另一个实施方案中为式(I)化合物，其中n为1，且R_1为$-CF_3$。在另一个实施方案中为式(I)化合物，其中n为1，且R_1

为取代或未取代的C_1-C_6烷基。在另一个实施方案中为式(I)化合物，其中n为1，且R_1为CH_3。在另一个实施方案中为式(I)化合物，其中n为1，且R_1为取代或未取代的C_1-C_6烷氧基。在另一个实施方案中为式(I)化合物，其中n为1，且R_1为$-OCH_3$。在另一个实施方案中为式(I)化合物，其中n为1，且R_1为$-OCF_3$。在另一个实施方案中为式(I)化合物，其中n为1，且R_1为$-OCF_2H$。

[0051] 在式(I)的上述实施方案的进一步实施方案中，X为C(R_7)；Y为N；且Z为N。在式(I)的上述实施方案的进一步实施方案中，X为C(H)；Y为N；且Z为N。在式(I)的上述实施方案的进一步实施方案中，X为C(R_7)；Y为C(R_7)；且Z为N。在式(I)的上述实施方案的进一步实施方案中，X为C(H)；Y为C(H)；且Z为N。在式(I)的上述实施方案的进一步实施方案中，X为C(R_7)；Y为N；且Z为C(R_7)。在式(I)的上述实施方案的进一步实施方案中，X为C(H)；Y为N；且Z为C(H)。在式(I)的上述实施方案的进一步实施方案中，X为C(R_7)；Y为C(R_7)；且Z为C(R_7)。在式(I)的上述实施方案的进一步实施方案中，X为C(H)；Y为C(H)；且Z为C(H)。

[0052] 在另一方面，本文描述了式(II)化合物，或其药学上可接受的盐、溶剂化物或前药：



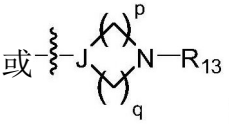
式(II)；

其中：

每个R_1独立地为卤素、-CN、$-NO_2$、-OH、$-OCF_3$、$-OCH_2F$、$-OCF_2H$、$-CF_3$、$-SR_8$、$-N(R_8)S(=O)_2R_9$、$-S(=O)_2N(R_8)_2$、$-S(=O)R_9$、$-S(=O)_2R_9$、$-C(=O)R_9$、$-CO_2R_8$、$-N(R_8)_2$、$-C(=O)N(R_8)_2$、$-N(R_8)C(=O)R_9$、取代或未取代的C_1-C_6烷基、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基；或者两个R_1合起来形成取代或未取代的杂环或者取代或未取代的碳环；

R_2和R_3各自独立地为H、-CN、C_1-C_4烷基、C_3-C_6环烷基或C_2-C_7杂环烷基；或者R_2和R_3合起来形成5元或6元杂环；

R_5为卤素、-CN、-OH、$-CF_3$、取代或未取代的C_1-C_6烷基、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基；

R_6为取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_2-C_7杂芳基、$-(C(R_{14})(R_{15}))_mR_{21}$或  ；

J为C(H)；

R_{13}为H、取代或未取代的C_1-C_6烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的$-C_1$-C_4烷基C_6-C_{10}芳基、或取代或未取代的$-C_1$-C_4烷基C_2-C_7杂芳基；

每个R_{14}和R_{15}各自独立地为H、或取代或未取代的C_1-C_6烷基;或者R_{14}和R_{15}合起来形成4、5、6元环烷基环;

R_{21}为卤素、-CN、$-NO_2$、-OH、$-OCF_3$、$-OCH_2F$、$-OCF_2H$、$-CF_3$、$-SR_{22}$、$-N(R_{22})S(=O)_2R_{23}$、$-S(=O)_2N(R_{22})_2$、$-S(=O)R_{23}$、$-S(=O)_2R_{23}$、$-C(=O)R_{23}$、$-CO_2R_{22}$、$-C(=O)N(R_{22})_2$、$-N(R_{22})C(=O)R_{23}$、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基;

每个R_{22}独立地为H、或取代或未取代的C_1-C_6烷基;

R_{23}为取代或未取代的C_1-C_6烷基;

每个R_8独立地为H、或取代或未取代的C_1-C_6烷基;

R_9为取代或未取代的C_1-C_6烷基;

R_{10}为H或未取代的C_1-C_4烷基;

m为2-6;

n为0-5;

p为1-3;

q为1-3。

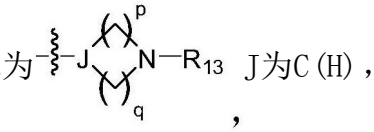
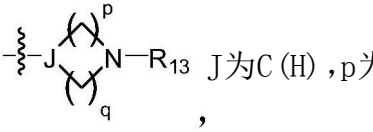
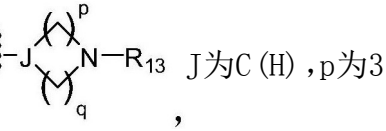
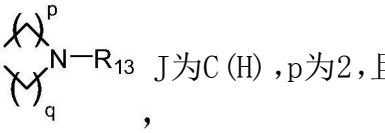
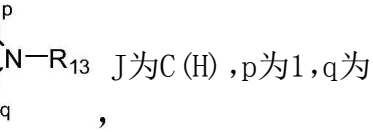
[0053] 在另一个实施方案中为式(II)化合物,其中R_6为取代或未取代的C_3-C_8环烷基。在另一个实施方案中为式(II)化合物,其中R_6为取代或未取代的环丙基。在另一个实施方案中为式(II)化合物,其中R_6为取代或未取代的环丁基。在另一个实施方案中为式(II)化合物,其中R_6为取代或未取代的环戊基。在另一个实施方案中为式(II)化合物,其中R_6为取代或未取代的环己基。

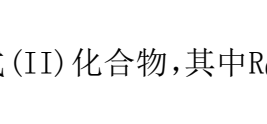
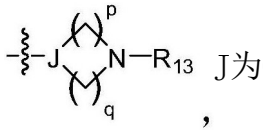
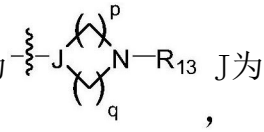
[0054] 在另一个实施方案中为式(II)化合物,其中R_6为取代或未取代的C_2-C_7杂芳基。在另一个实施方案中为式(II)化合物,其中R_6为取代或未取代的呋喃基、噻吩基、吡咯基、吡啶基、噁唑基、噻唑基、咪唑基、异噁唑基、异噻唑基、吡唑基、哒嗪基、嘧啶基、吡嗪基、噁二唑基、噻二唑基、三唑基、吲哚基、苯并噻吩基、苯并噁唑基、苯并噻唑基、苯并咪唑基、苯并噁二唑基、苯并噻二唑基、苯并三唑基、吡唑并吡啶基、咪唑并吡啶基、吡咯并吡啶基、吡咯并嘧啶基、吲嗪基、嘌呤基、呋喃并吡啶基、噻吩并吡啶基、呋喃并吡咯基、呋喃并呋喃基、噻吩并呋喃基、1,4-二氢吡咯并吡咯基、噻吩并吡咯基、噻吩并噻吩基、喹啉基、异喹啉基、喹喔啉基、呋喃并吡唑基、噻吩并吡唑基、硒吩基、硒唑基和苯并异噁唑基。在另一个实施方案中为式(II)化合物,其中R_6为取代或未取代的吡啶基。在另一个实施方案中为式(II)化合物,其中R_6为取代的吡啶基。在另一个实施方案中为式(II)化合物,其中R_6为未取代的吡啶基。

[0055] 在另一个实施方案中为式(II)化合物,其中R_6为$-(C(R_{14})(R_{15}))_mR_{21}$。在另一个实施方案中为式(II)化合物,其中$R_6$为$-(C(R_{14})(R_{15}))_mR_{21}$,且每个$R_{14}$和$R_{15}$为H。在另一个实施方案中为式(II)化合物,其中$R_6$为$-(C(R_{14})(R_{15}))_mR_{21}$,m为2,且每个$R_{14}$和$R_{15}$为H。在另一个实施方案中为式(II)化合物,其中$R_6$为$-(CH_2)_mR_{21}$,m为2,且$R_{21}$为取代或未取代的$C_2$-$C_7$杂环烷基。在另一个实施方案中为式(II)化合物,其中R_6为$-(CH_2)_mR_{21}$,m为2,且R_{21}为取代或未取代的C_3-C_8环烷基。在另一个实施方案中为式(II)化合物,其中R_6为$-(CH_2)_mR_{21}$,m为2,且R_{21}为取代的C_6-C_{10}芳基。在另一个实施方案中为式(II)化合物,其中R_6为$-(CH_2)_mR_{21}$,m为2,且R_{21}为取代的苯基。在另一个实施方案中为式(II)化合物,其中R_6为$-(CH_2)_mR_{21}$,m为2,且R_{21}为取代或

未取代的C_2-C_7杂芳基。在另一个实施方案中为式(II)化合物，其中R_6为-$(CH_2)_mR_{21}$，m为2，且R_{21}为-OH。在另一个实施方案中为式(II)化合物，其中R_6为-$(CH_2)_mR_{21}$，m为2，且R_{21}为-N(R_{22})S(=O)$_2R_{23}$。在另一个实施方案中为式(II)化合物，其中R_6为-$(CH_2)_mR_{21}$，m为2，且R_{21}为-N(R_{22})C(=O)R_{23}。在另一个实施方案中为式(II)化合物，其中R_6为-$(CH_2)_mR_{21}$，m为2，且R_{21}为取代或未取代的C_1-C_6烷氧基。在上述实施方案的另一个实施方案中为式(II)化合物，其中每个R_{22}独立地为H或未取代的C_1-C_6烷基；且R_{23}为未取代的C_1-C_6烷基。

[0056] 在另一个实施方案中为式(II)化合物，其中R_6为-$(C(R_{14})(R_{15}))_mR_{21}$，m为3，且每个$R_{14}$和$R_{15}$为H。在另一个实施方案中为式(II)化合物，其中$R_6$为-$(CH_2)_mR_{21}$，m为3，且$R_{21}$为取代或未取代的$C_2$-$C_7$杂环烷基。在另一个实施方案中为式(II)化合物，其中R_6为-$(CH_2)_mR_{21}$，m为3，且R_{21}为取代或未取代的C_3-C_8环烷基。在另一个实施方案中为式(II)化合物，其中R_6为-$(CH_2)_mR_{21}$，m为3，且R_{21}为取代的C_6-C_{10}芳基。在另一个实施方案中为式(II)化合物，其中R_6为-$(CH_2)_mR_{21}$，m为3，且R_{21}为取代的苯基。在另一个实施方案中为式(II)化合物，其中R_6为-$(CH_2)_mR_{21}$，m为3，且R_{21}为取代或未取代的C_2-C_7杂芳基。在另一个实施方案中为式(II)化合物，其中R_6为-$(CH_2)_mR_{21}$，m为3，且R_{21}为-OH。在另一个实施方案中为式(II)化合物，其中R_6为-$(CH_2)_mR_{21}$，m为3，且R_{21}为-N(R_{22})S(=O)$_2R_{23}$。在另一个实施方案中为式(II)化合物，其中R_6为-$(CH_2)_mR_{21}$，m为3，且R_{21}为-N(R_{22})C(=O)R_{23}。在另一个实施方案中为式(II)化合物，其中R_6为-$(CH_2)_mR_{21}$，m为3，且R_{21}为取代或未取代的C_1-C_6烷氧基。在上述实施方案的另一个实施方案中为式(II)化合物，其中每个R_{22}独立地为H或未取代的C_1-C_6烷基；且R_{23}为未取代的C_1-C_6烷基。

[0057] 在另一个实施方案中为式(II)化合物，其中R_6为取代或未取代的C_2-C_7杂环烷基。在另一个实施方案中为式(II)化合物，其中R_6为  且J为C(H)。在另一个实施方案中为式(II)化合物，其中R_6为  J为C(H)，p为1，且q为1。在另一个实施方案中为式(II)化合物，其中R_6为  J为C(H)，p为2，且q为1。在另一个实施方案中为式(II)化合物，其中R_6为  J为C(H)，p为3，且q为1。在另一个实施方案中为式(II)化合物，其中R_6为  J为C(H)，p为2，且q为2。在另一个实施方案中为式(II)化合物，其中R_6为  J为C(H)，p为1，q为1，且R_{13}为取代或未取代的C_1-C_6烷

基。在另一个实施方案中为式(II)化合物,其中R_6为  ,J为C(H),p为2,q为1,且R_{13}为取代或未取代的C_1-C_6烷基。在另一个实施方案中为式(II)化合物,其中R_6为  ,J为C(H),p为3,q为1,且R_{13}为取代或未取代的C_1-C_6烷基。在另一个实施方案中为式(II)化合物,其中R_6为  ,J为C(H),p为2,q为2,且R_{13}为取代或未取代的C_1-C_6烷基。

[0058] 在另一个实施方案中为式(II)化合物,其中R_5为卤素。在另一个实施方案中为式(II)化合物,其中R_5为-CF_3。在另一个实施方案中为式(II)化合物,其中R_5为取代或未取代的C_1-C_6烷基。在另一个实施方案中为式(II)化合物,其中R_5为-CH_3。在另一个实施方案中为式(II)化合物,其中R_5为-CH_2CH_3。在另一个实施方案中为式(II)化合物,其中R_5为取代或未取代的C_1-C_6杂烷基。在另一个实施方案中为式(II)化合物,其中R_5为取代或未取代的C_2-C_7杂环烷基。在另一个实施方案中为式(II)化合物,其中R_5为取代或未取代的C_3-C_8环烷基。在另一个实施方案中为式(II)化合物,其中R_5为取代或未取代的C_6-C_{10}芳基。在另一个实施方案中为式(II)化合物,其中R_5为取代或未取代的C_2-C_7杂芳基。

[0059] 在另一个实施方案中为式(II)化合物,其中R_2和R_3各自独立地为H、-CN、C_1-C_4烷基、C_3-C_6环烷基或C_2-C_7杂环烷基。在另一个实施方案中为式(II)化合物,其中R_2和R_3各自为H。

[0060] 在另一个实施方案中为式(II)化合物,其中R_2和R_3各自独立地为H、-CN、C_1-C_4烷基、C_3-C_6环烷基或C_2-C_7杂环烷基;且R_2和R_3中的至少一个不是H。在另一个实施方案中为式(II)化合物,其中R_2为H,且R_3为C_1-C_4烷基。在另一个实施方案中为式(II)化合物,其中R_2为H,且R_3为CH_3。在另一个实施方案中为式(II)化合物,其中R_2为H,且R_3为C_3-C_6环烷基。在另一个实施方案中为式(II)化合物,其中R_2为H,且R_3为环丙基。在另一个实施方案中为式(II)化合物,其中R_2为H,且R_3为环戊基。在另一个实施方案中为式(II)化合物,其中R_2为CH_3,且R_3为CH_3。在另一个实施方案中为式(II)化合物,其中R_2为C_1-C_4烷基,且R_3为H。在另一个实施方案中为式(II)化合物,其中R_2为CH_3,且R_3为H。在另一个实施方案中为式(II)化合物,其中R_2为C_3-C_6环烷基,且R_3为H。在另一个实施方案中为式(II)化合物,其中R_2为环丙基,且R_3为H。在另一个实施方案中为式(II)化合物,其中R_2为环戊基,且R_3为H。

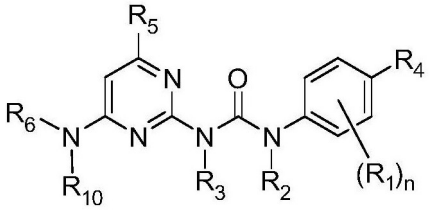
[0061] 在另一个实施方案中为式(II)化合物,其中R_2和R_3合起来形成5元或6元杂环。在另一个实施方案中为式(II)化合物,其中R_2和R_3合起来形成5元杂环。在另一个实施方案中为式(II)化合物,其中R_2和R_3合起来形成6元杂环。

[0062] 在另一个实施方案中为式(II)化合物,其中n为0。

[0063] 在另一个实施方案中为式(II)化合物,其中每个R_1独立地为卤素、-CN、-NO_2、-OH、-OCF_3、-OCH_2F、-OCF_2H、-SR_8、-N(R_8)S(=O)$_2R_9$、-S(=O)$_2$N(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、取代或未取代的C_1-C_6烷基、取代或未

取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基。在另一个实施方案中为式(II)化合物，其中每个R_1独立地为卤素、-CN、-OH、取代或未取代的C_1-C_6烷基、或取代或未取代的C_1-C_6烷氧基。在另一个实施方案中为式(II)化合物，其中每个R_1独立地为卤素、-CN、$-OCF_3$、$-OCH_2F$、$-OCF_2H$、取代或未取代的C_1-C_6烷基、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基。在另一个实施方案中为式(II)化合物，其中每个R_1独立地为卤素、-CN、$-OCF_3$、$-OCH_2F$、$-OCF_2H$、取代或未取代的C_1-C_6烷基、或取代或未取代的C_1-C_6烷氧基。在另一个实施方案中为式(II)化合物，其中每个R_1独立地为卤素、-CN、$-OCF_3$、$-OCH_2F$、$-OCF_2H$、取代或未取代的C_1-C_6烷基、或取代或未取代的C_1-C_6烷氧基，且n为3。在另一个实施方案中为式(II)化合物，其中每个R_1独立地为卤素、-CN、$-OCF_3$、$-OCH_2F$、$-OCF_2H$、取代或未取代的C_1-C_6烷基、或取代或未取代的C_1-C_6烷氧基，且n为2。在另一个实施方案中为式(II)化合物，其中n为3，且每个R_1独立地为卤素。在另一个实施方案中为式(II)化合物，其中n为2，且每个R_1独立地为卤素。在另一个实施方案中为式(II)化合物，其中n为2，且每个R_1独立地为F或Cl。在另一个实施方案中为式(II)化合物，其中n为2，且每个R_1为F。在另一个实施方案中为式(II)化合物，其中n为2，且每个R_1独立地为Cl。在另一个实施方案中为式(II)化合物，其中n为1，且R_1为卤素。在另一个实施方案中为式(II)化合物，其中n为1，且R_1为F。在另一个实施方案中为式(II)化合物，其中n为1，且R_1为Cl。在另一个实施方案中为式(II)化合物，其中n为1，且R_1为取代或未取代的C_1-C_6烷基。在另一个实施方案中为式(II)化合物，其中n为1，且R_1为CH_3。在另一个实施方案中为式(II)化合物，其中n为1，且R_1为取代或未取代的C_1-C_6烷氧基。在另一个实施方案中为式(II)化合物，其中n为1，且R_1为$-OCH_3$。在另一个实施方案中为式(II)化合物，其中n为1，且R_1为$-OCF_3$。在另一个实施方案中为式(II)化合物，其中n为1，且R_1为$-OCF_2H$。

[0064] 在另一个实施方案中，本文描述了式(IIA)化合物，或其药学上可接受的盐、溶剂化物或前药：



式(IIA)；

其中：

每个R_1独立地为卤素、-CN、$-NO_2$、-OH、$-OCF_3$、$-OCH_2F$、$-OCF_2H$、$-SR_8$、$-N(R_8)S(=O)_2R_9$、$-S(=O)_2N(R_8)_2$、$-S(=O)R_9$、$-S(=O)_2R_9$、$-C(=O)R_9$、$-CO_2R_8$、$-N(R_8)_2$、$-C(=O)N(R_8)_2$、$-N(R_8)C(=O)R_9$、取代或未取代的C_1-C_6烷基、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基；或者两个R_1合起来形成取代或未取代的杂环或者取代或未取代的碳环；

R_2和R_3各自独立地为H、-CN、C_1-C_4烷基、C_3-C_6环烷基或C_2-C_7杂环烷基；或者R_2和R_3合起

来形成5元或6元杂环；

R_4为H、卤素、-CN、$-NO_2$、-OH、$-OCF_3$、$-OCH_2F$、$-OCF_2H$、$-SR_8$、$-N(R_8)S(=O)_2R_9$、$-S(=O)_2N(R_8)_2$、$-S(=O)R_9$、$-S(=O)_2R_9$、$-C(=O)R_9$、$-CO_2R_8$、$-N(R_8)_2$、$-C(=O)N(R_8)_2$、$-N(R_8)C(=O)R_9$、取代或未取代的C_1-C_6烷基、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基；或者两个R_1合起来形成取代或未取代的杂环或者取代或未取代的碳环；其中当n为0时，R_4不是卤素；

R_5为卤素、-CN、-OH、$-CF_3$、取代或未取代的C_1-C_6烷基、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基；

R_6为$-(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$；

R_{11}和R_{12}各自独立地为H、或取代或未取代的C_1-C_6烷基；或者R_{11}和R_{12}合起来形成5、6、7或8元杂环；

R_{13}为H、取代或未取代的C_1-C_6烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的-C_1-C_4烷基C_6-C_{10}芳基、或取代或未取代的-C_1-C_4烷基C_2-C_7杂芳基；

每个R_{14}和R_{15}各自独立地为H、或取代或未取代的C_1-C_6烷基；或者R_{14}和R_{15}合起来形成4、5、6元环烷基环；

每个R_8独立地为H、或取代或未取代的C_1-C_6烷基；

R_9为取代或未取代的C_1-C_6烷基；

R_{10}为H或C_1-C_4烷基；

m为2-6；

n为0-4。

[0065] 在一个实施方案中为式(IIA)化合物，其中R_6为$-(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$，且每个$R_{14}$和$R_{15}$为H。在另一个实施方案中为式(IIA)化合物，其中R_6为$-(CH_2)_mN(R_{11})(R_{12})$，且$R_{11}$和$R_{12}$各自为H。在另一个实施方案中为式(IIA)化合物，其中R_6为$-(CH_2)_mN(R_{11})(R_{12})$，$R_{11}$为取代或未取代的$C_1$-$C_6$烷基，且$R_{12}$为H。在另一个实施方案中为式(IIA)化合物，其中R_6为$-(CH_2)_mN(R_{11})(R_{12})$，$R_{11}$为$CH_3$，且$R_{12}$为H。在另一个实施方案中为式(IIA)化合物，其中R_6为$-(CH_2)_mN(R_{11})(R_{12})$，$R_{11}$为取代或未取代的$C_1$-$C_6$烷基，且$R_{12}$为取代或未取代的$C_1$-$C_6$烷基。在另一个实施方案中为式(IIA)化合物，其中R_6为$-(CH_2)_mN(R_{11})(R_{12})$，$R_{11}$为$CH_3$，且$R_{12}$为$CH_3$。在另一个实施方案中为式(IIA)化合物，其中$R_6$为$-(CH_2)_mN(R_{11})(R_{12})$，且$R_{11}$和$R_{12}$合起来形成5、6、7或8元杂环。在另一个实施方案中为式(IIA)化合物，其中R_6为$-(CH_2)_mN(R_{11})(R_{12})$，且$R_{11}$和$R_{12}$合起来形成5元杂环。在另一个实施方案中为式(IIA)化合物，其中R_6为$-(CH_2)_mN(R_{11})(R_{12})$，且$R_{11}$和$R_{12}$合起来形成6元杂环。

[0066] 在另一个实施方案中为式(IIA)化合物，其中R_6为$-(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$，m为2，且每个$R_{14}$和$R_{15}$为H。在另一个实施方案中为式(IIA)化合物，其中R_6为$-(CH_2)_mN(R_{11})(R_{12})$，m为2，且$R_{11}$和$R_{12}$各自为H。在另一个实施方案中为式(IIA)化合物，其中R_6为$-(CH_2)_mN(R_{11})(R_{12})$，m为2，$R_{11}$为取代或未取代的$C_1$-$C_6$烷基，且$R_{12}$为H。在另一个实施方案中为式(IIA)化合物，其中R_6为$-(CH_2)_mN(R_{11})(R_{12})$，m为2，$R_{11}$为$CH_3$，且$R_{12}$为H。在另一个实施方案中为式(IIA)

化合物，其中R_6为-$(CH_2)_mN(R_{11})(R_{12})$，m为2，$R_{11}$为取代或未取代的$C_1$-$C_6$烷基，且$R_{12}$为取代或未取代的$C_1$-$C_6$烷基。在另一个实施方案中为式(IIA)化合物，其中R_6为-$(CH_2)_mN(R_{11})(R_{12})$，m为2，$R_{11}$为$CH_3$，且$R_{12}$为$CH_3$。在另一个实施方案中为式(IIA)化合物，其中$R_6$为-$(CH_2)_mN(R_{11})(R_{12})$，m为2，且$R_{11}$和$R_{12}$合起来形成5、6、7或8元杂环。在另一个实施方案中为式(IIA)化合物，其中R_6为-$(CH_2)_mN(R_{11})(R_{12})$，m为2，且$R_{11}$和$R_{12}$合起来形成5元杂环。在另一个实施方案中为式(IIA)化合物，其中R_6为-$(CH_2)_mN(R_{11})(R_{12})$，m为2，且$R_{11}$和$R_{12}$合起来形成6元杂环。

[0067] 在另一个实施方案中为式(IIA)化合物，其中R_6为-$(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$。在另一个实施方案中为式(IIA)化合物，其中$R_6$为-$(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$，m为3，且每个$R_{14}$和$R_{15}$为H。在另一个实施方案中为式(IIA)化合物，其中R_6为-$(CH_2)_mN(R_{11})(R_{12})$，m为3，且$R_{11}$和$R_{12}$各自为H。在另一个实施方案中为式(IIA)化合物，其中R_6为-$(CH_2)_mN(R_{11})(R_{12})$，m为3，$R_{11}$为取代或未取代的$C_1$-$C_6$烷基，且$R_{12}$为H。在另一个实施方案中为式(IIA)化合物，其中R_6为-$(CH_2)_mN(R_{11})(R_{12})$，m为3，$R_{11}$为$CH_3$，且$R_{12}$为H。在另一个实施方案中为式(IIA)化合物，其中R_6为-$(CH_2)_mN(R_{11})(R_{12})$，m为3，$R_{11}$为取代或未取代的$C_1$-$C_6$烷基，且$R_{12}$为取代或未取代的$C_1$-$C_6$烷基。在另一个实施方案中为式(IIA)化合物，其中R_6为-$(CH_2)_mN(R_{11})(R_{12})$，m为3，$R_{11}$为$CH_3$，且$R_{12}$为$CH_3$。在另一个实施方案中为式(IIA)化合物，其中$R_6$为-$(CH_2)_mN(R_{11})(R_{12})$，m为3，且$R_{11}$和$R_{12}$合起来形成5、6、7或8元杂环。在另一个实施方案中为式(IIA)化合物，其中R_6为-$(CH_2)_mN(R_{11})(R_{12})$，m为3，且$R_{11}$和$R_{12}$合起来形成5元杂环。在另一个实施方案中为式(IIA)化合物，其中R_6为-$(CH_2)_mN(R_{11})(R_{12})$，m为3，且$R_{11}$和$R_{12}$合起来形成6元杂环。

[0068] 在另一个实施方案中为式(IIA)化合物，其中R_5为卤素。在另一个实施方案中为式(IIA)化合物，其中R_5为-CF_3。在另一个实施方案中为式(IIA)化合物，其中R_5为取代或未取代的C_1-C_6烷基。在另一个实施方案中为式(IIA)化合物，其中R_5为-CH_3。在另一个实施方案中为式(IIA)化合物，其中R_5为-CH_2CH_3。在另一个实施方案中为式(IIA)化合物，其中R_5为取代或未取代的C_1-C_6杂烷基。在另一个实施方案中为式(IIA)化合物，其中R_5为取代或未取代的C_2-C_7杂环烷基。在另一个实施方案中为式(IIA)化合物，其中R_5为取代或未取代的C_3-C_8环烷基。在另一个实施方案中为式(IIA)化合物，其中R_5为取代或未取代的C_6-C_{10}芳基。在另一个实施方案中为式(IIA)化合物，其中R_5为取代或未取代的C_2-C_7杂芳基。

[0069] 在另一个实施方案中为式(IIA)化合物，其中R_2和R_3各自独立地为H、-CN、C_1-C_4烷基、C_3-C_6环烷基或C_2-C_7杂环烷基。在另一个实施方案中为式(IIA)化合物，其中R_2和R_3各自为H。

[0070] 在另一个实施方案中为式(IIA)化合物，其中R_2和R_3各自独立地为H、-CN、C_1-C_4烷基、C_3-C_6环烷基或C_2-C_7杂环烷基；且R_2和R_3中的至少一个不是H。在另一个实施方案中为式(IIA)化合物，其中R_2为H，且R_3为C_1-C_4烷基。在另一个实施方案中为式(IIA)化合物，其中R_2为H，且R_3为CH_3。在另一个实施方案中为式(IIA)化合物，其中R_2为H，且R_3为C_3-C_6环烷基。在另一个实施方案中为式(IIA)化合物，其中R_2为H，且R_3为环丙基。在另一个实施方案中为式(IIA)化合物，其中R_2为H，且R_3为环戊基。在另一个实施方案中为式(IIA)化合物，其中R_2为CH_3，且R_3为CH_3。在另一个实施方案中为式(IIA)化合物，其中R_2为C_1-C_4烷基，且R_3为H。在另一个实施方案中为式(IIA)化合物，其中R_2为CH_3，且R_3为H。在另一个实施方案中为式(IIA)化合物，其中R_2为C_3-C_6环烷基，且R_3为H。在另一个实施方案中为式(IIA)化合物，其中R_2为环丙基，且R_3为H。在另一个实施方案中为式(IIA)化合物，其中R_2为环戊基，且R_3为H。

[0071] 在另一个实施方案中为式(IIA)化合物，其中R_2和R_3合起来形成5元或6元杂环。在另一个实施方案中为式(IIA)化合物，其中R_2和R_3合起来形成5元杂环。在另一个实施方案中为式(IIA)化合物，其中R_2和R_3合起来形成6元杂环。

[0072] 在另一个实施方案中为式(IIA)化合物，其中n为0。

[0073] 在另一个实施方案中为式(IIA)化合物，其中每个R_1独立地为卤素、-CN、$-NO_2$、-OH、$-OCF_3$、$-OCH_2F$、$-OCF_2H$、$-SR_8$、$-N(R_8)S(=O)_2R_9$、$-S(=O)_2N(R_8)_2$、$-S(=O)R_9$、$-S(=O)_2R_9$、$-C(=O)R_9$、$-CO_2R_8$、$-N(R_8)_2$、$-C(=O)N(R_8)_2$、$-N(R_8)C(=O)R_9$、取代或未取代的C_1-C_6烷基、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基。在另一个实施方案中为式(IIA)化合物，其中每个R_1独立地为卤素、-CN、-OH、取代或未取代的C_1-C_6烷基、或取代或未取代的C_1-C_6烷氧基。在另一个实施方案中为式(IIA)化合物，其中每个R_1独立地为卤素、-CN、$-OCF_3$、$-OCH_2F$、$-OCF_2H$、取代或未取代的C_1-C_6烷基、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基。在另一个实施方案中为式(IIA)化合物，其中每个R_1独立地为卤素、-CN、$-OCF_3$、$-OCH_2F$、$-OCF_2H$、取代或未取代的C_1-C_6烷基、或取代或未取代的C_1-C_6烷氧基。在另一个实施方案中为式(IIA)化合物，其中每个R_1独立地为卤素、-CN、$-OCF_3$、$-OCH_2F$、$-OCF_2H$、取代或未取代的C_1-C_6烷基、或取代或未取代的C_1-C_6烷氧基，且n为3。在另一个实施方案中为式(IIA)化合物，其中每个R_1独立地为卤素、-CN、$-OCF_3$、$-OCH_2F$、$-OCF_2H$、取代或未取代的C_1-C_6烷基、或取代或未取代的C_1-C_6烷氧基，且n为2。在另一个实施方案中为式(IIA)化合物，其中n为3，且每个R_1独立地为卤素。在另一个实施方案中为式(IIA)化合物，其中n为2，且每个R_1独立地为卤素。在另一个实施方案中为式(IIA)化合物，其中n为2，且每个R_1独立地为F或Cl。在另一个实施方案中为式(IIA)化合物，其中n为2，且每个R_1为F。在另一个实施方案中为式(IIA)化合物，其中n为2，且每个R_1独立地为Cl。在另一个实施方案中为式(IIA)化合物，其中n为1，且R_1为卤素。在另一个实施方案中为式(IIA)化合物，其中n为1，且R_1为F。在另一个实施方案中为式(IIA)化合物，其中n为1，且R_1为Cl。在另一个实施方案中为式(IIA)化合物，其中n为1，且R_1为取代或未取代的C_1-C_6烷基。在另一个实施方案中为式(IIA)化合物，其中n为1，且R_1为CH_3。在另一个实施方案中为式(IIA)化合物，其中n为1，且R_1为取代或未取代的C_1-C_6烷氧基。在另一个实施方案中为式(IIA)化合物，其中n为1，且R_1为$-OCH_3$。在另一个实施方案中为式(IIA)化合物，其中n为1，且R_1为$-OCF_3$。在另一个实施方案中为式(IIA)化合物，其中n为1，且R_1为$-OCF_2H$。

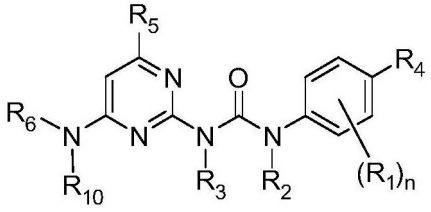
[0074] 在另一个实施方案中为式(IIA)化合物，其中R_4为H、卤素、-CN、$-NO_2$、-OH、$-OCF_3$、$-OCH_2F$、$-OCF_2H$、$-SR_8$、$-N(R_8)S(=O)_2R_9$、$-S(=O)_2N(R_8)_2$、$-S(=O)R_9$、$-S(=O)_2R_9$、$-C(=O)R_9$、$-CO_2R_8$、$-N(R_8)_2$、$-C(=O)N(R_8)_2$、$-N(R_8)C(=O)R_9$、取代或未取代的C_1-C_6烷基、或取代或未取代的C_1-C_6烷氧基。在另一个实施方案中为式(IIA)化合物，其中R_4为H、卤素、-CN、-OH、$-OCF_3$、取代或未取代的C_1-C_6烷基、或取代或未取代的C_1-C_6烷氧基。在另一个实施方案中为式(IIA)化合物，其中R_4为H。在另一个实施方案中为式(IIA)化合物，其中R_4为卤素。在另一个实施方案中为式(IIA)化合物，其中R_4为F。在另一个实施方案中为式(IIA)化合物，其中R_4为Cl。在另一个实施方案中为式(IIA)化合物，其中R_4为Br。在另一个实施方案中为式(IIA)化

合物，其中R_4为$-CF_3$。在另一个实施方案中为式(IIA)化合物，其中R_4为$-OCF_3$。在另一个实施方案中为式(IIA)化合物，R_4为$-CH_3$。在另一个实施方案中为式(IIA)化合物，其中R_4为$-OCH_3$。

[0075] 在另一个实施方案中为式(IIA)化合物，其中n为0且R_4为H。在另一个实施方案中为式(IIA)化合物，其中n为0且R_4为卤素。在另一个实施方案中为式(IIA)化合物，其中n为0且R_4为F。在另一个实施方案中为式(IIA)化合物，其中n为0且R_4为Cl。在另一个实施方案中为式(IIA)化合物，其中n为0且R_4为Br。在另一个实施方案中为式(IIA)化合物，其中n为0且R_4为$-CF_3$。在另一个实施方案中为式(IIA)化合物，其中n为0且R_4为$-OCF_3$。在另一个实施方案中为式(IIA)化合物，其中n为0且R_4为$-CH_3$。在另一个实施方案中为式(IIA)化合物，其中n为0且R_4为$-OCH_3$。

[0076] 在另一个实施方案中为式(IIA)化合物，其中n为1，R_1为Cl，且R_4为Cl。在另一个实施方案中为式(IIA)化合物，其中n为1，R_1为$-CH_3$，且R_4为Cl。在另一个实施方案中为式(IIA)化合物，其中n为1，R_1为$-OCH_3$，且R_4为Cl。在另一个实施方案中为式(IIA)化合物，其中n为1，R_1为$-CF_3$，且R_4为Cl。在另一个实施方案中为式(IIA)化合物，其中n为1，R_1为$-OCF_3$，且R_4为Cl。在另一个实施方案中为式(IIA)化合物，其中n为1，R_1为Cl，且R_4为F。在另一个实施方案中为式(IIA)化合物，其中n为1，R_1为$-CH_3$，且R_4为F。在另一个实施方案中为式(IIA)化合物，其中n为1，R_1为$-OCH_3$，且R_4为F。在另一个实施方案中为式(IIA)化合物，其中n为1，R_1为$-CF_3$，且R_4为F。在另一个实施方案中为式(IIA)化合物，其中n为1，R_1为$-OCF_3$，且R_4为F。在另一个实施方案中为式(IIA)化合物，其中n为1，R_1为Cl，且R_4为H。在另一个实施方案中为式(IIA)化合物，其中n为1，R_1为$-CH_3$，且R_4为H。在另一个实施方案中为式(IIA)化合物，其中n为1，R_1为$-OCH_3$，且R_4为H。在另一个实施方案中为式(IIA)化合物，其中n为1，R_1为$-CF_3$，且R_4为H。在另一个实施方案中为式(IIA)化合物，其中n为1，R_1为$-OCF_3$，且R_4为H。在另一个实施方案中为式(IIA)化合物，其中n为1，R_1为Cl，且R_4为$-OCH_3$。在另一个实施方案中为式(IIA)化合物，其中n为1，R_1为$-CH_3$，且R_4为$-OCH_3$。在另一个实施方案中为式(IIA)化合物，其中n为1，R_1为$-OCH_3$，且R_4为$-OCH_3$。在另一个实施方案中为式(IIA)化合物，其中n为1，R_1为$-CF_3$，且R_4为$-OCH_3$。在另一个实施方案中为式(IIA)化合物，其中n为1，R_1为$-OCF_3$，且R_4为$-OCH_3$。在另一个实施方案中为式(IIA)化合物，其中n为1，R_1为Cl，且R_4为$-OCF_3$。在另一个实施方案中为式(IIA)化合物，其中n为1，R_1为$-CH_3$，且R_4为$-OCF_3$。在另一个实施方案中为式(IIA)化合物，其中n为1，R_1为$-OCH_3$，且R_4为$-OCF_3$。在另一个实施方案中为式(IIA)化合物，其中n为1，R_1为$-CF_3$，且R_4为$-OCF_3$。在另一个实施方案中为式(IIA)化合物，其中n为1，R_1为$-OCF_3$，且R_4为$-OCF_3$。

[0077] 在另一个实施方案中，本文描述了了式(IIA')化合物，或其药学上可接受的盐、溶剂化物或前药：



式(IIA')；

其中：

每个R_1独立地为卤素、-CN、$-NO_2$、-OH、$-OCF_3$、$-OCH_2F$、$-OCF_2H$、$-SR_8$、$-N(R_8)S(=O)_2R_9$、$-S(=O)_2N(R_8)_2$、$-S(=O)R_9$、$-S(=O)_2R_9$、$-C(=O)R_9$、$-CO_2R_8$、$-N(R_8)_2$、$-C(=O)N(R_8)_2$、$-N(R_8)C(=O)R_9$、取代或未取代的C_1-C_6烷基、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基；或者两个R_1合起来形成取代或未取代的杂环或者取代或未取代的碳环；

R_2和R_3各自独立地为H、-CN、C_1-C_4烷基、C_3-C_6环烷基或C_2-C_7杂环烷基；或者R_2和R_3合起来形成5元或6元杂环；

R_4为H、F、Cl、Br、I、-CN、$-NO_2$、-OH、$-OCF_3$、$-OCH_2F$、$-OCF_2H$、$-SR_8$、$-N(R_8)S(=O)_2R_9$、$-S(=O)_2N(R_8)_2$、$-S(=O)R_9$、$-S(=O)_2R_9$、$-C(=O)R_9$、$-CO_2R_8$、$-N(R_8)_2$、$-C(=O)N(R_8)_2$、$-N(R_8)C(=O)R_9$、取代或未取代的C_1-C_6烷基、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基；或者两个R_1合起来形成取代或未取代的杂环或者取代或未取代的碳环；其中当n为0时，R_4不是Cl；

R_5为卤素、-CN、-OH、$-CF_3$、取代或未取代的C_1-C_6烷基、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基；

R_6为$-(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$；

R_{11}和R_{12}各自独立地为H、或取代或未取代的C_1-C_6烷基；或者R_{11}和R_{12}合起来形成5、6、7或8元杂环；

R_{13}为H、取代或未取代的C_1-C_6烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的-C_1-C_4烷基C_6-C_{10}芳基、或取代或未取代的-C_1-C_4烷基C_2-C_7杂芳基；

每个R_{14}和R_{15}各自独立地为H、或取代或未取代的C_1-C_6烷基；或者R_{14}和R_{15}合起来形成4、5、6元环烷基环；

每个R_8独立地为H、或取代或未取代的C_1-C_6烷基；

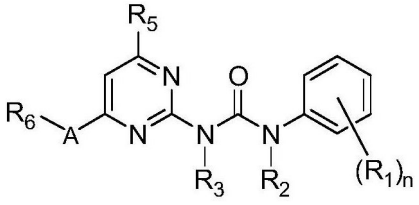
R_9为取代或未取代的C_1-C_6烷基；

R_{10}为H或C_1-C_4烷基；

m为2-6；

n为0-4。

[0078] 在另一个实施方案中，本文描述了式(IIB)化合物，或其药学上可接受的盐、溶剂化物或前药：



式(IIB)；

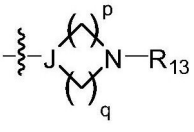
其中：

A为O；

每个R_1独立地为卤素、-CN、$-NO_2$、-OH、$-OCF_3$、$-OCH_2F$、$-OCF_2H$、$-CF_3$、$-SR_8$、$-N(R_8)S(=O)_2R_9$、$-S(=O)_2N(R_8)_2$、$-S(=O)R_9$、$-S(=O)_2R_9$、$-C(=O)R_9$、$-CO_2R_8$、$-N(R_8)_2$、$-C(=O)N(R_8)_2$、$-N(R_8)C(=O)R_9$、取代或未取代的C_1-C_6烷基、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基；或者两个R_1合起来形成取代或未取代的杂环或者取代或未取代的碳环；

R_2和R_3各自独立地为H、-CN、C_1-C_4烷基、C_3-C_6环烷基或C_2-C_7杂环烷基；或者R_2和R_3合起来形成5元或6元杂环；

R_5为卤素、-CN、-OH、$-CF_3$、取代或未取代的C_1-C_6烷基、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基；

R_6为取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_2-C_7杂芳基、$-(C(R_{14})(R_{15}))_mR_{21}$、$-(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$或  ；

R_{11}和R_{12}各自独立地为H、或取代或未取代的C_1-C_6烷基；或者R_{11}和R_{12}合起来形成5、6、7或8元杂环；

J为C(H)；

R_{13}为H、取代或未取代的C_1-C_6烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的-C_1-C_4烷基C_6-C_{10}芳基、或取代或未取代的-C_1-C_4烷基C_2-C_7杂芳基；

每个R_{14}和R_{15}各自独立地为H、或取代或未取代的C_1-C_6烷基；或者R_{14}和R_{15}合起来形成4、5、6元环烷基环；

R_{21}为卤素、-CN、$-NO_2$、-OH、$-OCF_3$、$-OCH_2F$、$-OCF_2H$、$-CF_3$、$-SR_{22}$、$-N(R_{22})S(=O)_2R_{23}$、$-S(=O)_2N(R_{22})_2$、$-S(=O)R_{23}$、$-S(=O)_2R_{23}$、$-C(=O)R_{23}$、$-CO_2R_{22}$、$-C(=O)N(R_{22})_2$、$-N(R_{22})C(=O)R_{23}$、取代或未取代的C_1-C_6烷基、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基；

每个R_{22}独立地为H、或取代或未取代的C_1-C_6烷基；

R_{23}为取代或未取代的C_1-C_6烷基；

每个R_8独立地为H、或取代或未取代的C_1-C_6烷基；

R_9为取代或未取代的C_1-C_6烷基；

m为2-6；

n为0-5；

p为1-3；

q为1-3。

[0079] 在另一个实施方案中为式(IIB)化合物，其中R_6为取代或未取代的C_3-C_8环烷基。在

另一个实施方案中为式(IIB)化合物，其中R_6为取代或未取代的环丙基。在另一个实施方案中为式(IIB)化合物，其中R_6为取代或未取代的环丁基。在另一个实施方案中为式(IIB)化合物，其中R_6为取代或未取代的环戊基。在另一个实施方案中为式(IIB)化合物，其中R_6为取代或未取代的环己基。

[0080] 在另一个实施方案中为式(IIB)化合物，其中R_6为取代或未取代的C_2-C_7杂芳基。在另一个实施方案中为式(IIB)化合物，其中R_6为取代或未取代的呋喃基、噻吩基、吡咯基、吡啶基、噁唑基、噻唑基、咪唑基、异噁唑基、异噻唑基、吡唑基、哒嗪基、嘧啶基、吡嗪基、噁二唑基、噻二唑基、三唑基、吲哚基、苯并噻吩基、苯并噁唑基、苯并噻唑基、苯并咪唑基、苯并噁二唑基、苯并噻二唑基、苯并三唑基、吡唑并吡啶基、咪唑并吡啶基、吡咯并吡啶基、吡咯并嘧啶基、吲嗪基、嘌呤基、呋喃并吡啶基、噻吩并吡啶基、呋喃并吡咯基、呋喃并呋喃基、噻吩并呋喃基、1,4-二氢吡咯并吡咯基、噻吩并吡咯基、噻吩并噻吩基、喹啉基、异喹啉基、喹喔啉基、呋喃并吡唑基、噻吩并吡唑基、硒吩基、硒唑基和苯并异噁唑基。在另一个实施方案中为式(IIB)化合物，其中R_6为取代或未取代的吡啶基。在另一个实施方案中为式(IIB)化合物，其中R_6为取代的吡啶基。在另一个实施方案中为式(IIB)化合物，其中R_6为未取代的吡啶基。

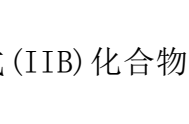
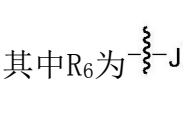
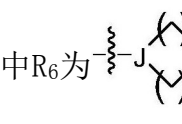
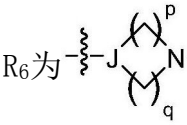
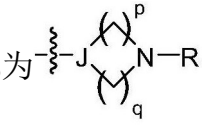
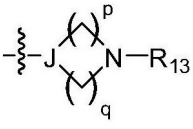
[0081] 在另一个实施方案中为式(IIB)化合物，其中R_6为-(C(R_{14})(R_{15}))$_m$$R_{21}$。在另一个实施方案中为式(IIB)化合物，其中$R_6$为-(C($R_{14}$)($R_{15}$))$_m$$R_{21}$，且每个$R_{14}$和$R_{15}$为H。在另一个实施方案中为式(IIB)化合物，其中R_6为-(C(R_{14})(R_{15}))$_m$$R_{21}$，m为2，且每个$R_{14}$和$R_{15}$为H。在另一个实施方案中为式(I)化合物，其中$R_6$为-$(CH_2)_m$$R_{21}$，m为2，且$R_{21}$为取代或未取代的$C_2$-$C_7$杂环烷基。在另一个实施方案中为式(IIB)化合物，其中R_6为-$(CH_2)_m$$R_{21}$，m为2，且$R_{21}$为取代或未取代的$C_3$-$C_8$环烷基。在另一个实施方案中为式(IIB)化合物，其中R_6为-$(CH_2)_m$$R_{21}$，m为2，且$R_{21}$为取代或未取代的$C_6$-$C_{10}$芳基。在另一个实施方案中为式(IIB)化合物，其中R_6为-$(CH_2)_m$$R_{21}$，m为2，且$R_{21}$为取代或未取代的苯基。在另一个实施方案中为式(IIB)化合物，其中R_6为-$(CH_2)_m$$R_{21}$，m为2，且$R_{21}$为取代或未取代的$C_2$-$C_7$杂芳基。在另一个实施方案中为式(IIB)化合物，其中R_6为-$(CH_2)_m$$R_{21}$，m为2，且$R_{21}$为-OH。

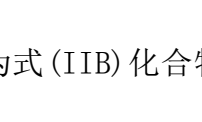
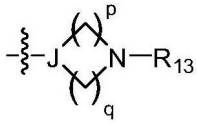
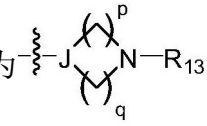
[0082] 在另一个实施方案中为式(IIB)化合物，其中R_6为-(C(R_{14})(R_{15}))$_m$$R_{21}$，m为3，且每个$R_{14}$和$R_{15}$为H。在另一个实施方案中为式(IIB)化合物，其中R_6为-$(CH_2)_m$$R_{21}$，m为3，且$R_{21}$为取代或未取代的$C_2$-$C_7$杂环烷基。在另一个实施方案中为式(IIB)化合物，其中R_6为-$(CH_2)_m$$R_{21}$，m为3，且$R_{21}$为取代或未取代的$C_3$-$C_8$环烷基。在另一个实施方案中为式(IIB)化合物，其中R_6为-$(CH_2)_m$$R_{21}$，m为3，且$R_{21}$为取代或未取代的$C_6$-$C_{10}$芳基。在另一个实施方案中为式(IIB)化合物，其中R_6为-$(CH_2)_m$$R_{21}$，m为3，且$R_{21}$为取代或未取代的苯基。在另一个实施方案中为式(IIB)化合物，其中R_6为-$(CH_2)_m$$R_{21}$，m为3，且$R_{21}$为取代或未取代的$C_2$-$C_7$杂芳基。在另一个实施方案中为式(IIB)化合物，其中R_6为-$(CH_2)_m$$R_{21}$，m为3，且$R_{21}$为-OH。

[0083] 在另一个实施方案中为式(IIB)化合物，其中R_6为-(C(R_{14})(R_{15}))$_m$N(R_{11})(R_{12})。在另一个实施方案中为式(IIB)化合物，其中R_6为-(C(R_{14})(R_{15}))$_m$N(R_{11})(R_{12})，m为2，且每个R_{14}和R_{15}为H。在另一个实施方案中为式(IIB)化合物，其中R_6为-$(CH_2)_m$N(R_{11})(R_{12})，m为2，且R_{11}和R_{12}各自为H。在另一个实施方案中为式(IIB)化合物，其中R_6为-$(CH_2)_m$N(R_{11})(R_{12})，m为2，R_{11}为取代或未取代的C_1-C_6烷基，且R_{12}为H。在另一个实施方案中为式(IIB)化合物，其中R_6为-$(CH_2)_m$N(R_{11})(R_{12})，m为2，R_{11}为CH_3，且R_{12}为H。在另一个实施方案中为式(IIB)化合物，其

中R_6为-$(CH_2)_mN(R_{11})(R_{12})$，m为2，$R_{11}$为取代或未取代的$C_1$-$C_6$烷基，且$R_{12}$为取代或未取代的$C_1$-$C_6$烷基。在另一个实施方案中为式(IIB)化合物，其中R_6为-$(CH_2)_mN(R_{11})(R_{12})$，m为2，$R_{11}$为$CH_3$，且$R_{12}$为$CH_3$。在另一个实施方案中为式(IIB)化合物，其中$R_6$为-$(CH_2)_mN(R_{11})(R_{12})$，m为2，且$R_{11}$和$R_{12}$合起来形成5、6、7或8元杂环。在另一个实施方案中为式(IIB)化合物，其中R_6为-$(CH_2)_mN(R_{11})(R_{12})$，m为2，且$R_{11}$和$R_{12}$合起来形成5元杂环。在另一个实施方案中为式(IIB)化合物，其中R_6为-$(CH_2)_mN(R_{11})(R_{12})$，m为2，且$R_{11}$和$R_{12}$合起来形成6元杂环。

[0084] 在另一个实施方案中为式(IIB)化合物，其中R_6为-$(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$。在另一个实施方案中为式(IIB)化合物，其中$R_6$为-$(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$，m为3，且每个$R_{14}$和$R_{15}$为H。在另一个实施方案中为式(IIB)化合物，其中R_6为-$(CH_2)_mN(R_{11})(R_{12})$，m为3，且$R_{11}$和$R_{12}$各自为H。在另一个实施方案中为式(IIB)化合物，其中R_6为-$(CH_2)_mN(R_{11})(R_{12})$，m为23，$R_{11}$为取代或未取代的$C_1$-$C_6$烷基，且$R_{12}$为H。在另一个实施方案中为式(IIB)化合物，其中R_6为-$(CH_2)_mN(R_{11})(R_{12})$，m为3，$R_{11}$为$CH_3$，且$R_{12}$为H。在另一个实施方案中为式(IIB)化合物，其中R_6为-$(CH_2)_mN(R_{11})(R_{12})$，m为3，$R_{11}$为取代或未取代的$C_1$-$C_6$烷基，且$R_{12}$为取代或未取代的$C_1$-$C_6$烷基。在另一个实施方案中为式(IIB)化合物，其中R_6为-$(CH_2)_mN(R_{11})(R_{12})$，m为3，$R_{11}$为$CH_3$，且$R_{12}$为$CH_3$。在另一个实施方案中为式(IIB)化合物，其中$R_6$为-$(CH_2)_mN(R_{11})(R_{12})$，m为3，且$R_{11}$和$R_{12}$合起来形成5、6、7或8元杂环。在另一个实施方案中为式(IIB)化合物，其中R_6为-$(CH_2)_mN(R_{11})(R_{12})$，m为3，且$R_{11}$和$R_{12}$合起来形成5元杂环。在另一个实施方案中为式(IIB)化合物，其中R_6为-$(CH_2)_mN(R_{11})(R_{12})$，m为3，且$R_{11}$和$R_{12}$合起来形成6元杂环。

[0085] 在另一个实施方案中为式(IIB)化合物，其中R_6为取代或未取代的C_2-C_7杂环烷基。在另一个实施方案中为式(IIB)化合物，其中R_6为  且J为C(H)。在另一个实施方案中为式(IIB)化合物，其中R_6为  ，J为C(H)，p为1，且q为1。在另一个实施方案中为式(IIB)化合物，其中R_6为  ，J为C(H)，p为2，且q为1。在另一个实施方案中为式(IIB)化合物，其中R_6为  ，J为C(H)，p为3，且q为1。在另一个实施方案中为式(IIB)化合物，其中R_6为  ，J为C(H)，p为2，且q为2。在另一个实施方案中为式(IIB)化合物，其中R_6为  ，J为C(H)，p为1，q为1，且R_{13}为取代或未取代的C_1-C_6

烷基。在另一个实施方案中为式(IIB)化合物，其中R_6为  ，J为C(H)，p为2，q为1，且R_{13}为取代或未取代的C_1-C_6烷基。在另一个实施方案中为式(IIB)化合物，其中R_6为  ，J为C(H)，p为3，q为1，且R_{13}为取代或未取代的C_1-C_6烷基。在另一个实施方案中为式(IIB)化合物，其中R_6为  ，J为C(H)，p为2，q为2，且R_{13}为取代或未取代的C_1-C_6烷基。

[0086] 在另一个实施方案中为式(IIB)化合物，其中R_5为卤素。在另一个实施方案中为式(IIB)化合物，其中R_5为-CF_3。在另一个实施方案中为式(IIB)化合物，其中R_5为取代或未取代的C_1-C_6烷基。在另一个实施方案中为式(IIB)化合物，其中R_5为-CH_3。在另一个实施方案中为式(IIB)化合物，其中R_5为-CH_2CH_3。在另一个实施方案中为式(IIB)化合物，其中R_5为取代或未取代的C_1-C_6杂烷基。在另一个实施方案中为式(IIB)化合物，其中R_5为取代或未取代的C_2-C_7杂环烷基。在另一个实施方案中为式(IIB)化合物，其中R_5为取代或未取代的C_3-C_8环烷基。在另一个实施方案中为式(IIB)化合物，其中R_5为取代或未取代的C_6-C_{10}芳基。在另一个实施方案中为式(IIB)化合物，其中R_5为取代或未取代的C_2-C_7杂芳基。

[0087] 在另一个实施方案中为式(IIB)化合物，其中R_2和R_3各自独立地为H、-CN、C_1-C_4烷基、C_3-C_6环烷基或C_2-C_7杂环烷基。在另一个实施方案中为式(IIB)化合物，其中R_2和R_3各自为H。

[0088] 在另一个实施方案中为式(IIB)化合物，其中R_2和R_3各自独立地为H、-CN、C_1-C_4烷基、C_3-C_6环烷基或C_2-C_7杂环烷基；且R_2和R_3中的至少一个不是H。在另一个实施方案中为式(IIB)化合物，其中R_2为H，且R_3为C_1-C_4烷基。在另一个实施方案中为式(IIB)化合物，其中R_2为H，且R_3为CH_3。在另一个实施方案中为式(IIB)化合物，其中R_2为H，且R_3为C_3-C_6环烷基。在另一个实施方案中为式(IIB)化合物，其中R_2为H，且R_3为环丙基。在另一个实施方案中为式(IIB)化合物，其中R_2为H，且R_3为环戊基。在另一个实施方案中为式(IIB)化合物，其中R_2为CH_3，且R_3为CH_3。在另一个实施方案中为式(IIB)化合物，其中R_2为C_1-C_4烷基，且R_3为H。在另一个实施方案中为式(IIB)化合物，其中R_2为CH_3，且R_3为H。在另一个实施方案中为式(IIB)化合物，其中R_2为C_3-C_6环烷基，且R_3为H。在另一个实施方案中为式(IIB)化合物，其中R_2为环丙基，且R_3为H。在另一个实施方案中为式(IIB)化合物，其中R_2为环戊基，且R_3为H。

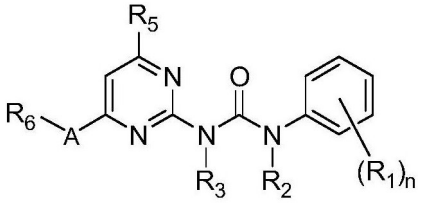
[0089] 在另一个实施方案中为式(IIB)化合物，其中R_2和R_3合起来形成5元或6元杂环。在另一个实施方案中为式(IIB)化合物，其中R_2和R_3合起来形成5元杂环。在另一个实施方案中为式(IIB)化合物，其中R_2和R_3合起来形成6元杂环。

[0090] 在另一个实施方案中为式(IIB)化合物，其中n为0。

[0091] 在另一个实施方案中为式(IIB)化合物，其中每个R_1独立地为卤素、-CN、-NO_2、-OH、-OCF_3、-OCH_2F、-OCF_2H、-CF_3、-SR_8、-N(R_8)S(=O)$_2R_9$、-S(=O)$_2$N(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、取代或未取代的C_1-C_6烷

基、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基。在另一个实施方案中为式(IIB)化合物，其中每个R_1独立地为卤素、-CN、-OH、$-CF_3$、取代或未取代的C_1-C_6烷基、或取代或未取代的C_1-C_6烷氧基。在另一个实施方案中为式(IIB)化合物，其中每个R_1独立地为卤素、-CN、$-OCF_3$、$-OCH_2F$、$-OCF_2H$、$-CF_3$、取代或未取代的C_1-C_6烷基、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基。在另一个实施方案中为式(IIB)化合物，其中每个R_1独立地为卤素、-CN、$-OCF_3$、$-OCH_2F$、$-OCF_2H$、$-CF_3$、取代或未取代的C_1-C_6烷基、或取代或未取代的C_1-C_6烷氧基。在另一个实施方案中为式(IIB)化合物，其中每个R_1独立地为卤素、-CN、$-OCF_3$、$-OCH_2F$、$-OCF_2H$、$-CF_3$、取代或未取代的C_1-C_6烷基、或取代或未取代的C_1-C_6烷氧基，且n为3。在另一个实施方案中为式(IIB)化合物，其中每个R_1独立地为卤素、-CN、$-OCF_3$、$-OCH_2F$、$-OCF_2H$、$-CF_3$、取代或未取代的C_1-C_6烷基、或取代或未取代的C_1-C_6烷氧基，且n为2。在另一个实施方案中为式(IIB)化合物，其中n为3，且每个R_1独立地为卤素。在另一个实施方案中为式(IIB)化合物，其中n为2，且每个R_1独立地为卤素。在另一个实施方案中为式(IIB)化合物，其中n为2，且每个R_1独立地为F或Cl。在另一个实施方案中为式(IIB)化合物，其中n为2，且每个R_1为F。在另一个实施方案中为式(IIB)化合物，其中n为2，且每个R_1独立地为Cl。在另一个实施方案中为式(IIB)化合物，其中n为2，且每个R_1独立地为卤素或$-CF_3$。在另一个实施方案中为式(IIB)化合物，其中n为2，且每个R_1独立地为F或$-CF_3$。在另一个实施方案中为式(IIB)化合物，其中n为2，且每个R_1独立地为Cl或$-CF_3$。在另一个实施方案中为式(IIB)化合物，其中n为1，且R_1为卤素。在另一个实施方案中为式(IIB)化合物，其中n为1，且R_1为F。在另一个实施方案中为式(IIB)化合物，其中n为1，且R_1为Cl。在另一个实施方案中为式(IIB)化合物，其中n为1，且R_1为$-CF_3$。在另一个实施方案中为式(IIB)化合物，其中n为1，且R_1为取代或未取代的C_1-C_6烷基。在另一个实施方案中为式(IIB)化合物，其中n为1，且R_1为CH_3。在另一个实施方案中为式(IIB)化合物，其中n为1，且R_1为取代或未取代的C_1-C_6烷氧基。在另一个实施方案中为式(IIB)化合物，其中n为1，且R_1为$-OCH_3$。在另一个实施方案中为式(IIB)化合物，其中n为1，且R_1为$-OCF_3$。在另一个实施方案中为式(IIB)化合物，其中n为1，且R_1为$-OCF_2H$。

[0092] 在另一个实施方案中，本文描述了式(IIC)化合物，或其药学上可接受的盐、溶剂化物或前药：



式(IIC)；

其中：

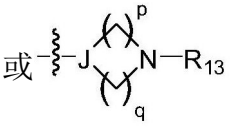
A为键；

每个R_1独立地为卤素、-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

$(R_8)C(=O)R_9$、取代或未取代的C_1-C_6烷基、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基;或者两个R_1合起来形成取代或未取代的杂环或者取代或未取代的碳环;

R_2和R_3各自独立地为H、-CN、C_1-C_4烷基、C_3-C_6环烷基或C_2-C_7杂环烷基;或者R_2和R_3合起来形成5元或6元杂环;

R_5为卤素、-CN、-OH、$-CF_3$、取代或未取代的C_1-C_6烷基、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基;

R_6为取代或未取代的C_3-C_8环烷基、取代或未取代的C_2-C_7杂芳基、$-(C(R_{14})(R_{15}))_mR_{21}$、$-(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$或  ;

R_{11}和R_{12}各自独立地为H、或取代或未取代的C_1-C_6烷基;或者R_{11}和R_{12}合起来形成5、6、7或8元杂环;

J为C(H);

R_{13}为H、取代或未取代的C_1-C_6烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的-C_1-C_4烷基C_6-C_{10}芳基、或取代或未取代的-C_1-C_4烷基C_2-C_7杂芳基;

每个R_{14}和R_{15}各自独立地为H、或取代或未取代的C_1-C_6烷基;或者R_{14}和R_{15}合起来形成4、5、6元环烷基环;

R_{21}为卤素、-CN、$-NO_2$、-OH、$-OCF_3$、$-OCH_2F$、$-OCF_2H$、$-CF_3$、$-SR_{22}$、$-N(R_{22})S(=O)_2R_{23}$、$-S(=O)_2N(R_{22})_2$、$-S(=O)R_{23}$、$-S(=O)_2R_{23}$、$-C(=O)R_{23}$、$-CO_2R_{22}$、$-C(=O)N(R_{22})_2$、$-N(R_{22})C(=O)R_{23}$、取代或未取代的C_1-C_6烷基、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基;

每个R_{22}独立地为H、或取代或未取代的C_1-C_6烷基;

R_{23}为取代或未取代的C_1-C_6烷基;

每个R_8独立地为H、或取代或未取代的C_1-C_6烷基;

R_9为取代或未取代的C_1-C_6烷基;

m为2-6;

n为0-5;

p为1-3;

q为1-3。

[0093] 在另一个实施方案中为式(IIC)化合物,其中R_6为取代或未取代的C_3-C_8环烷基。在另一个实施方案中为式(IIC)化合物,其中R_6为取代或未取代的环丙基。在另一个实施方案中为式(IIC)化合物,其中R_6为取代或未取代的环丁基。在另一个实施方案中为式(IIC)化合物,其中R_6为取代或未取代的环戊基。在另一个实施方案中为式(IIC)化合物,其中R_6为取代或未取代的环己基。

[0094] 在另一个实施方案中为式(IIC)化合物，其中R_6为取代或未取代的C_2-C_7杂芳基。在另一个实施方案中为式(IIC)化合物，其中R_6为取代或未取代的呋喃基、噻吩基、吡咯基、吡啶基、噁唑基、噻唑基、咪唑基、异噁唑基、异噻唑基、吡唑基、哒嗪基、嘧啶基、吡嗪基、噁二唑基、噻二唑基、三唑基、吲哚基、苯并噻吩基、苯并噁唑基、苯并噻唑基、苯并咪唑基、苯并噁二唑基、苯并噻二唑基、苯并三唑基、吡唑并吡啶基、咪唑并吡啶基、吡咯并吡啶基、吡咯并嘧啶基、吲嗪基、嘌呤基、呋喃并吡啶基、噻吩并吡啶基、呋喃并吡咯基、呋喃并呋喃基、噻吩并呋喃基、1,4-二氢吡咯并吡咯基、噻吩并吡咯基、噻吩并噻吩基、喹啉基、异喹啉基、喹喔啉基、呋喃并吡唑基、噻吩并吡唑基、硒吩基、硒唑基和苯并异噁唑基。在另一个实施方案中为式(IIC)化合物，其中R_6为取代或未取代的吡啶基。在另一个实施方案中为式(IIC)化合物，其中R_6为取代的吡啶基。在另一个实施方案中为式(IIC)化合物，其中R_6为未取代的吡啶基。

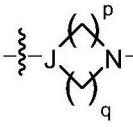
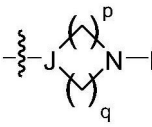
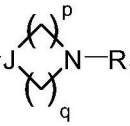
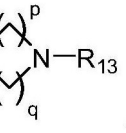
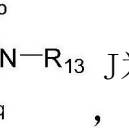
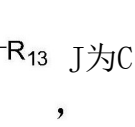
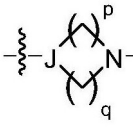
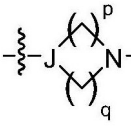
[0095] 在另一个实施方案中为式(IIC)化合物，其中R_6为-(C(R_{14})(R_{15}))$_m$$R_{21}$。在另一个实施方案中为式(IIC)化合物，其中$R_6$为-(C($R_{14}$)($R_{15}$))$_m$$R_{21}$，且每个$R_{14}$和$R_{15}$为H。在另一个实施方案中为式(IIC)化合物，其中R_6为-(C(R_{14})(R_{15}))$_m$$R_{21}$，m为2，且每个$R_{14}$和$R_{15}$为H。在另一个实施方案中为式(I)化合物，其中$R_6$为-$(CH_2)_m$$R_{21}$，m为2，且$R_{21}$为取代或未取代的$C_2$-$C_7$杂环烷基。在另一个实施方案中为式(IIC)化合物，其中R_6为-$(CH_2)_m$$R_{21}$，m为2，且$R_{21}$为取代或未取代的$C_3$-$C_8$环烷基。在另一个实施方案中为式(IIC)化合物，其中R_6为-$(CH_2)_m$$R_{21}$，m为2，且$R_{21}$为取代或未取代的$C_6$-$C_{10}$芳基。在另一个实施方案中为式(IIC)化合物，其中R_6为-$(CH_2)_m$$R_{21}$，m为2，且$R_{21}$为取代或未取代的苯基。在另一个实施方案中为式(IIC)化合物，其中R_6为-$(CH_2)_m$$R_{21}$，m为2，且$R_{21}$为取代或未取代的$C_2$-$C_7$杂芳基。在另一个实施方案中为式(IIC)化合物，其中R_6为-$(CH_2)_m$$R_{21}$，m为2，且$R_{21}$为-OH。

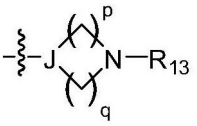
[0096] 在另一个实施方案中为式(IIC)化合物，其中R_6为-(C(R_{14})(R_{15}))$_m$$R_{21}$，m为3，且每个$R_{14}$和$R_{15}$为H。在另一个实施方案中为式(IIC)化合物，其中R_6为-$(CH_2)_m$$R_{21}$，m为3，且$R_{21}$为取代或未取代的$C_2$-$C_7$杂环烷基。在另一个实施方案中为式(IIC)化合物，其中R_6为-$(CH_2)_m$$R_{21}$，m为3，且$R_{21}$为取代或未取代的$C_3$-$C_8$环烷基。在另一个实施方案中为式(IIC)化合物，其中R_6为-$(CH_2)_m$$R_{21}$，m为3，且$R_{21}$为取代或未取代的$C_6$-$C_{10}$芳基。在另一个实施方案中为式(IIC)化合物，其中R_6为-$(CH_2)_m$$R_{21}$，m为3，且$R_{21}$为取代或未取代的苯基。在另一个实施方案中为式(IIC)化合物，其中R_6为-$(CH_2)_m$$R_{21}$，m为3，且$R_{21}$为取代或未取代的$C_2$-$C_7$杂芳基。在另一个实施方案中为式(IIC)化合物，其中R_6为-$(CH_2)_m$$R_{21}$，m为3，且$R_{21}$为-OH。

[0097] 在另一个实施方案中为式(IIC)化合物，其中R_6为-(C(R_{14})(R_{15}))$_m$N(R_{11})(R_{12})。在另一个实施方案中为式(IIC)化合物，其中R_6为-(C(R_{14})(R_{15}))$_m$N(R_{11})(R_{12})，m为2，且每个R_{14}和R_{15}为H。在另一个实施方案中为式(IIC)化合物，其中R_6为-$(CH_2)_m$N(R_{11})(R_{12})，m为2，且R_{11}和R_{12}各自为H。在另一个实施方案中为式(IIC)化合物，其中R_6为-$(CH_2)_m$N(R_{11})(R_{12})，m为2，R_{11}为取代或未取代的C_1-C_6烷基，且R_{12}为H。在另一个实施方案中为式(IIC)化合物，其中R_6为-$(CH_2)_m$N(R_{11})(R_{12})，m为2，R_{11}为CH_3，且R_{12}为H。在另一个实施方案中为式(IIC)化合物，其中R_6为-$(CH_2)_m$N(R_{11})(R_{12})，m为2，R_{11}为取代或未取代的C_1-C_6烷基，且R_{12}为取代或未取代的C_1-C_6烷基。在另一个实施方案中为式(IIC)化合物，其中R_6为-$(CH_2)_m$N(R_{11})(R_{12})，m为2，R_{11}为CH_3，且R_{12}为CH_3。在另一个实施方案中为式(IIC)化合物，其中R_6为-$(CH_2)_m$N(R_{11})(R_{12})，m为2，且R_{11}和R_{12}合起来形成5、6、7或8元杂环。在另一个实施方案中为式(IIC)化合物，其中R_6为-

$(CH_2)_mN(R_{11})(R_{12})$，m为2，且$R_{11}$和$R_{12}$合起来形成5元杂环。在另一个实施方案中为式(IIC)化合物，其中R_6为$-(CH_2)_mN(R_{11})(R_{12})$，m为2，且$R_{11}$和$R_{12}$合起来形成6元杂环。

[0098] 在另一个实施方案中为式(IIC)化合物，其中R_6为$-(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$。在另一个实施方案中为式(IIC)化合物，其中$R_6$为$-(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$，m为3，且每个$R_{14}$和$R_{15}$为H。在另一个实施方案中为式(IIC)化合物，其中R_6为$-(CH_2)_mN(R_{11})(R_{12})$，m为3，且$R_{11}$和$R_{12}$各自为H。在另一个实施方案中为式(IIC)化合物，其中R_6为$-(CH_2)_mN(R_{11})(R_{12})$，m为23，$R_{11}$为取代或未取代的$C_1$-$C_6$烷基，且$R_{12}$为H。在另一个实施方案中为式(IIC)化合物，其中R_6为$-(CH_2)_mN(R_{11})(R_{12})$，m为3，$R_{11}$为$CH_3$，且$R_{12}$为H。在另一个实施方案中为式(IIC)化合物，其中R_6为$-(CH_2)_mN(R_{11})(R_{12})$，m为3，$R_{11}$为取代或未取代的$C_1$-$C_6$烷基，且$R_{12}$为取代或未取代的$C_1$-$C_6$烷基。在另一个实施方案中为式(IIC)化合物，其中R_6为$-(CH_2)_mN(R_{11})(R_{12})$，m为3，$R_{11}$为$CH_3$，且$R_{12}$为$CH_3$。在另一个实施方案中为式(IIC)化合物，其中$R_6$为$-(CH_2)_mN(R_{11})(R_{12})$，m为3，且$R_{11}$和$R_{12}$合起来形成5、6、7或8元杂环。在另一个实施方案中为式(IIC)化合物，其中R_6为$-(CH_2)_mN(R_{11})(R_{12})$，m为3，且$R_{11}$和$R_{12}$合起来形成5元杂环。在另一个实施方案中为式(IIC)化合物，其中R_6为$-(CH_2)_mN(R_{11})(R_{12})$，m为3，且$R_{11}$和$R_{12}$合起来形成6元杂环。

[0099] 在另一个实施方案中为式(IIC)化合物，其中R_6为  且J为C(H)。在另一个实施方案中为式(IIC)化合物，其中R_6为  J为C(H)，p为1，且q为1。在另一个实施方案中为式(IIC)化合物，其中R_6为  J为C(H)，p为2，且q为1。在另一个实施方案中为式(IIC)化合物，其中R_6为  J为C(H)，p为3，且q为1。在另一个实施方案中为式(IIC)化合物，其中R_6为  J为C(H)，p为2，且q为2。在另一个实施方案中为式(IIC)化合物，其中R_6为  J为C(H)，p为1，q为1，且R_{13}为取代或未取代的C_1-C_6烷基。在另一个实施方案中为式(IIC)化合物，其中R_6为  J为C(H)，p为2，q为1，且R_{13}为取代或未取代的C_1-C_6烷基。在另一个实施方案中为式(IIC)化合物，其中R_6为  J为C(H)，p为3，q为1，且R_{13}为取代或未取代的C_1-C_6烷基。在另一个实施

方案中为式(IIC)化合物，其中R_6为  ，J为C(H)，p为2，q为2，且R_{13}为取代或未取代的C_1-C_6烷基。

[0100] 在另一个实施方案中为式(IIC)化合物，其中R_5为卤素。在另一个实施方案中为式(IIC)化合物，其中R_5为-CF_3。在另一个实施方案中为式(IIC)化合物，其中R_5为取代或未取代的C_1-C_6烷基。在另一个实施方案中为式(IIC)化合物，其中R_5为-CH_3。在另一个实施方案中为式(IIC)化合物，其中R_5为-CH_2CH_3。在另一个实施方案中为式(IIC)化合物，其中R_5为取代或未取代的C_1-C_6杂烷基。在另一个实施方案中为式(IIC)化合物，其中R_5为取代或未取代的C_2-C_7杂环烷基。在另一个实施方案中为式(IIC)化合物，其中R_5为取代或未取代的C_3-C_8环烷基。在另一个实施方案中为式(IIC)化合物，其中R_5为取代或未取代的C_6-C_{10}芳基。在另一个实施方案中为式(IIC)化合物，其中R_5为取代或未取代的C_2-C_7杂芳基。

[0101] 在另一个实施方案中为式(IIC)化合物，其中R_2和R_3各自独立地为H、-CN、C_1-C_4烷基、C_3-C_6环烷基或C_2-C_7杂环烷基。在另一个实施方案中为式(IIC)化合物，其中R_2和R_3各自为H。

[0102] 在另一个实施方案中为式(IIC)化合物，其中R_2和R_3各自独立地为H、-CN、C_1-C_4烷基、C_3-C_6环烷基或C_2-C_7杂环烷基；且R_2和R_3中的至少一个不是H。在另一个实施方案中为式(IIC)化合物，其中R_2为H，且R_3为C_1-C_4烷基。在另一个实施方案中为式(IIC)化合物，其中R_2为H，且R_3为CH_3。在另一个实施方案中为式(IIC)化合物，其中R_2为H，且R_3为C_3-C_6环烷基。在另一个实施方案中为式(IIC)化合物，其中R_2为H，且R_3为环丙基。在另一个实施方案中为式(IIC)化合物，其中R_2为H，且R_3为环戊基。在另一个实施方案中为式(IIC)化合物，其中R_2为CH_3，且R_3为CH_3。在另一个实施方案中为式(IIC)化合物，其中R_2为C_1-C_4烷基，且R_3为H。在另一个实施方案中为式(IIC)化合物，其中R_2为CH_3，且R_3为H。在另一个实施方案中为式(IIC)化合物，其中R_2为C_3-C_6环烷基，且R_3为H。在另一个实施方案中为式(IIC)化合物，其中R_2为环丙基，且R_3为H。在另一个实施方案中为式(IIC)化合物，其中R_2为环戊基，且R_3为H。

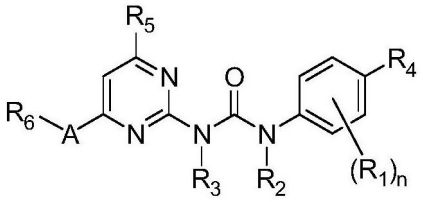
[0103] 在另一个实施方案中为式(IIC)化合物，其中R_2和R_3合起来形成5元或6元杂环。在另一个实施方案中为式(IIC)化合物，其中R_2和R_3合起来形成5元杂环。在另一个实施方案中为式(IIC)化合物，其中R_2和R_3合起来形成6元杂环。

[0104] 在另一个实施方案中为式(IIC)化合物，其中n为0。

[0105] 在另一个实施方案中为式(IIC)化合物，其中每个R_1独立地为卤素、-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、-$N(R_8)_2$、-$C(=O)N(R_8)_2$、-$N(R_8)C(=O)R_9$、取代或未取代的C_1-C_6烷基、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基。在另一个实施方案中为式(IIC)化合物，其中每个R_1独立地为卤素、-CN、-OH、-CF_3、取代或未取代的C_1-C_6烷基、或取代或未取代的C_1-C_6烷氧基。在另一个实施方案中为式(IIC)化合物，其中每个R_1独立地为卤素、-CN、-OCF_3、-OCH_2F、-OCF_2H、-CF_3、取代或未取代的C_1-C_6烷基、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7

杂芳基。在另一个实施方案中为式(IIC)化合物，其中每个R_1独立地为卤素、-CN、-OCF_3、-OCH_2F、-OCF_2H、-CF_3、取代或未取代的C_1-C_6烷基、或取代或未取代的C_1-C_6烷氧基。在另一个实施方案中为式(IIC)化合物，其中每个R_1独立地为卤素、-CN、-OCF_3、-OCH_2F、-OCF_2H、-CF_3、取代或未取代的C_1-C_6烷基、或取代或未取代的C_1-C_6烷氧基，且n为3。在另一个实施方案中为式(IIC)化合物，其中每个R_1独立地为卤素、-CN、-OCF_3、-OCH_2F、-OCF_2H、-CF_3、取代或未取代的C_1-C_6烷基、或取代或未取代的C_1-C_6烷氧基，且n为2。在另一个实施方案中为式(IIC)化合物，其中n为3，且每个R_1独立地为卤素。在另一个实施方案中为式(IIC)化合物，其中n为2，且每个R_1独立地为卤素。在另一个实施方案中为式(IIC)化合物，其中n为2，且每个R_1独立地为F或Cl。在另一个实施方案中为式(IIC)化合物，其中n为2，且每个R_1为F。在另一个实施方案中为式(IIC)化合物，其中n为2，且每个R_1独立地为Cl。在另一个实施方案中为式(IIC)化合物，其中n为2，且每个R_1独立地为卤素或-CF_3。在另一个实施方案中为式(IIC)化合物，其中n为2，且每个R_1独立地为F或-CF_3。在另一个实施方案中为式(IIC)化合物，其中n为2，且每个R_1独立地为Cl或-CF_3。在另一个实施方案中为式(IIC)化合物，其中n为1，且R_1为卤素。在另一个实施方案中为式(IIC)化合物，其中n为1，且R_1为F。在另一个实施方案中为式(IIC)化合物，其中n为1，且R_1为Cl。在另一个实施方案中为式(IIC)化合物，其中n为1，且R_1为-CF_3。在另一个实施方案中为式(IIC)化合物，其中n为1，且R_1为取代或未取代的C_1-C_6烷基。在另一个实施方案中为式(IIC)化合物，其中n为1，且R_1为CH_3。在另一个实施方案中为式(IIC)化合物，其中n为1，且R_1为取代或未取代的C_1-C_6烷氧基。在另一个实施方案中为式(IIC)化合物，其中n为1，且R_1为-OCH_3。在另一个实施方案中为式(IIC)化合物，其中n为1，且R_1为-OCF_3。在另一个实施方案中为式(IIC)化合物，其中n为1，且R_1为-OCF_2H。

[0106] 在另一个实施方案中，本文描述了式(IID)化合物，或其药学上可接受的盐、溶剂化物或前药：



式(IID)；

其中：

A为键；

每个R_1独立地为卤素、-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、-$N(R_8)_2$、-$C(=O)N(R_8)_2$、-$N(R_8)C(=O)R_9$、取代或未取代的C_1-C_6烷基、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基；或者两个R_1合起来形成取代或未取代的杂环或者取代或未取代的碳环；

R_2和R_3各自独立地为H、-CN、C_1-C_4烷基、C_3-C_6环烷基或C_2-C_7杂环烷基；或者R_2和R_3合起来形成5元或6元杂环；

R_4为H、卤素、-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、取代或未取代的C_1-C_6烷基、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基；或者两个R_1合起来形成取代或未取代的杂环或者取代或未取代的碳环；其中当n为0时，R_4不是卤素；

R_5为卤素、-CN、-OH、-CF_3、取代或未取代的C_1-C_6烷基、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基；

R_6为取代或未取代的C_2-C_7杂环烷基；

R_{11}和R_{12}各自独立地为H、或取代或未取代的C_1-C_6烷基；或者R_{11}和R_{12}合起来形成5、6、7或8元杂环；

J为C(H)；

R_{13}为H、取代或未取代的C_1-C_6烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的-C_1-C_4烷基C_6-C_{10}芳基、或取代或未取代的-C_1-C_4烷基C_2-C_7杂芳基；

每个R_{14}和R_{15}各自独立地为H、或取代或未取代的C_1-C_6烷基；或者R_{14}和R_{15}合起来形成4、5、6元环烷基环；

R_{21}为卤素、-CN、-NO_2、-OH、-OCF_3、-OCH_2F、-OCF_2H、-CF_3、-SR_{22}、-N(R_{22})S(=O)$_2R_{23}$、-S(=O)$_2$N$(R_{22})_2$、-S(=O)R_{23}、-S(=O)$_2R_{23}$、-C(=O)R_{23}、-CO_2R_{22}、-C(=O)N$(R_{22})_2$、-N(R_{22})C(=O)R_{23}、取代或未取代的C_1-C_6烷基、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基；

每个R_{22}独立地为H、或取代或未取代的C_1-C_6烷基；

R_{23}为取代或未取代的C_1-C_6烷基；

每个R_8独立地为H、或取代或未取代的C_1-C_6烷基；

R_9为取代或未取代的C_1-C_6烷基；

m为2-6；

n为0-4；

p为1-3；

q为1-3。

[0107] 在一个实施方案中为式(IID)化合物，其中R_6为未取代的C_2-C_7杂环烷基。在另一个实施方案中为式(IID)化合物，其中R_6为取代的C_2-C_7杂环烷基。在另一个实施方案中为式(IID)化合物，其中R_6为取代或未取代的吗啉基。在另一个实施方案中为式(IID)化合物，其中R_6为取代或未取代的哌嗪基。在另一个实施方案中为式(IID)化合物，其中R_6为取代或未取代的哌啶基。

[0108] 在另一个实施方案中为式(IID)化合物，其中R_5为卤素。在另一个实施方案中为式(IID)化合物，其中R_5为-CF_3。在另一个实施方案中为式(IID)化合物，其中R_5为取代或未取代的C_1-C_6烷基。在另一个实施方案中为式(IID)化合物，其中R_5为-CH_3。在另一个实施方案中为式(IID)化合物，其中R_5为-CH_2CH_3。在另一个实施方案中为式(IID)化合物，其中R_5为取

代或未取代的C_1-C_6杂烷基。在另一个实施方案中为式(IID)化合物，其中R_5为取代或未取代的C_2-C_7杂环烷基。在另一个实施方案中为式(IID)化合物，其中R_5为取代或未取代的C_3-C_8环烷基。在另一个实施方案中为式(IID)化合物，其中R_5为取代或未取代的C_6-C_{10}芳基。在另一个实施方案中为式(IID)化合物，其中R_5为取代或未取代的C_2-C_7杂芳基。

[0109] 在另一个实施方案中为式(IID)化合物，其中R_2和R_3各自独立地为H、-CN、C_1-C_4烷基、C_3-C_6环烷基或C_2-C_7杂环烷基。在另一个实施方案中为式(IID)化合物，其中R_2和R_3各自为H。

[0110] 在另一个实施方案中为式(IID)化合物，其中R_2和R_3各自独立地为H、-CN、C_1-C_4烷基、C_3-C_6环烷基或C_2-C_7杂环烷基；且R_2和R_3中的至少一个不是H。在另一个实施方案中为式(IID)化合物，其中R_2为H，且R_3为C_1-C_4烷基。在另一个实施方案中为式(IID)化合物，其中R_2为H，且R_3为CH_3。在另一个实施方案中为式(IID)化合物，其中R_2为H，且R_3为C_3-C_6环烷基。在另一个实施方案中为式(IID)化合物，其中R_2为H，且R_3为环丙基。在另一个实施方案中为式(IID)化合物，其中R_2为H，且R_3为环戊基。在另一个实施方案中为式(IID)化合物，其中R_2为CH_3，且R_3为CH_3。在另一个实施方案中为式(IID)化合物，其中R_2为C_1-C_4烷基，且R_3为H。在另一个实施方案中为式(IID)化合物，其中R_2为CH_3，且R_3为H。在另一个实施方案中为式(IID)化合物，其中R_2为C_3-C_6环烷基，且R_3为H。在另一个实施方案中为式(IID)化合物，其中R_2为环丙基，且R_3为H。在另一个实施方案中为式(IID)化合物，其中R_2为环戊基，且R_3为H。

[0111] 在另一个实施方案中为式(IID)化合物，其中R_2和R_3合起来形成5元或6元杂环。在另一个实施方案中为式(IID)化合物，其中R_2和R_3合起来形成5元杂环。在另一个实施方案中为式(IID)化合物，其中R_2和R_3合起来形成6元杂环。

[0112] 在另一个实施方案中为式(IID)化合物，其中n为0。

[0113] 在另一个实施方案中为式(IID)化合物，其中每个R_1独立地为卤素、-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、-$N(R_8)_2$、-$C(=O)N(R_8)_2$、-$N(R_8)C(=O)R_9$、取代或未取代的C_1-C_6烷基、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基。在另一个实施方案中为式(IID)化合物，其中每个R_1独立地为卤素、-CN、-OH、-CF_3、取代或未取代的C_1-C_6烷基、或取代或未取代的C_1-C_6烷氧基。在另一个实施方案中为式(IID)化合物，其中每个R_1独立地为卤素、-CN、-OCF_3、-OCH_2F、-OCF_2H、-CF_3、取代或未取代的C_1-C_6烷基、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基。在另一个实施方案中为式(IID)化合物，其中每个R_1独立地为卤素、-CN、-OCF_3、-OCH_2F、-OCF_2H、-CF_3、取代或未取代的C_1-C_6烷基、或取代或未取代的C_1-C_6烷氧基。在另一个实施方案中为式(IID)化合物，其中每个R_1独立地为卤素、-CN、-OCF_3、-OCH_2F、-OCF_2H、-CF_3、取代或未取代的C_1-C_6烷基、或取代或未取代的C_1-C_6烷氧基，且n为3。在另一个实施方案中为式(IID)化合物，其中每个R_1独立地为卤素、-CN、-OCF_3、-OCH_2F、-OCF_2H、-CF_3、取代或未取代的C_1-C_6烷基、或取代或未取代的C_1-C_6烷氧基，且n为2。在另一个实施方案中为式(IID)化合物，其中n为3，且每个R_1独立地为卤素。在另一个实施方案中为式(IID)化合物，其中n为2，且每个R_1独立地为卤素。在另一个实施方案中为式(IID)化合物，其中n为2，且每个R_1独立

地为F或Cl。在另一个实施方案中为式(IID)化合物，其中n为2，且每个R_1为F。在另一个实施方案中为式(IID)化合物，其中n为2，且每个R_1独立地为Cl。在另一个实施方案中为式(IID)化合物，其中n为2，且每个R_1独立地为卤素或$-CF_3$。在另一个实施方案中为式(IID)化合物，其中n为2，且每个R_1独立地为F或$-CF_3$。在另一个实施方案中为式(IID)化合物，其中n为2，且每个R_1独立地为Cl或$-CF_3$。在另一个实施方案中为式(IID)化合物，其中n为1，且R_1为卤素。在另一个实施方案中为式(IID)化合物，其中n为1，且R_1为F。在另一个实施方案中为式(IID)化合物，其中n为1，且R_1为Cl。在另一个实施方案中为式(IID)化合物，其中n为1，且R_1为$-CF_3$。在另一个实施方案中为式(IID)化合物，其中n为1，且R_1为取代或未取代的C_1-C_6烷基。在另一个实施方案中为式(IID)化合物，其中n为1，且R_1为CH_3。在另一个实施方案中为式(IID)化合物，其中n为1，且R_1为取代或未取代的C_1-C_6烷氧基。在另一个实施方案中为式(IID)化合物，其中n为1，且R_1为$-OCH_3$。在另一个实施方案中为式(IID)化合物，其中n为1，且R_1为$-OCF_3$。在另一个实施方案中为式(IID)化合物，其中n为1，且R_1为$-OCF_2H$。

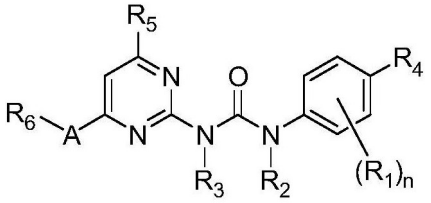
[0114] 在另一个实施方案中为式(IID)化合物，其中R_4为H、卤素、-CN、$-NO_2$、-OH、$-OCF_3$、$-OCH_2F$、$-OCF_2H$、$-SR_8$、$-N(R_8)S(=O)_2R_9$、$-S(=O)_2N(R_8)_2$、$-S(=O)R_9$、$-S(=O)_2R_9$、$-C(=O)R_9$、$-CO_2R_8$、$-N(R_8)_2$、$-C(=O)N(R_8)_2$、$-N(R_8)C(=O)R_9$、取代或未取代的C_1-C_6烷基、或取代或未取代的C_1-C_6烷氧基。在另一个实施方案中为式(IID)化合物，其中R_4为H、卤素、-CN、-OH、$-OCF_3$、取代或未取代的C_1-C_6烷基、或取代或未取代的C_1-C_6烷氧基。在另一个实施方案中为式(IID)化合物，其中R_4为H。在另一个实施方案中为式(IID)化合物，其中R_4为卤素。在另一个实施方案中为式(IID)化合物，其中R_4为F。在另一个实施方案中为式(IID)化合物，其中R_4为Cl。在另一个实施方案中为式(IID)化合物，其中R_4为Br。在另一个实施方案中为式(IID)化合物，其中R_4为$-CF_3$。在另一个实施方案中为式(IID)化合物，其中R_4为$-OCF_3$。在另一个实施方案中为式(IID)化合物，R_4为$-CH_3$。在另一个实施方案中为式(IID)化合物，其中R_4为$-OCH_3$。

[0115] 在另一个实施方案中为式(IID)化合物，其中n为0且R_4为H。在另一个实施方案中为式(IID)化合物，其中n为0且R_4为卤素。在另一个实施方案中为式(IID)化合物，其中n为0且R_4为F。在另一个实施方案中为式(IID)化合物，其中n为0且R_4为Cl。在另一个实施方案中为式(IID)化合物，其中n为0且R_4为Br。在另一个实施方案中为式(IID)化合物，其中n为0且R_4为$-CF_3$。在另一个实施方案中为式(IID)化合物，其中n为0且R_4为$-OCF_3$。在另一个实施方案中为式(IID)化合物，其中n为0且R_4为$-CH_3$。在另一个实施方案中为式(IID)化合物，其中n为0且R_4为$-OCH_3$。

[0116] 在另一个实施方案中为式(IID)化合物，其中n为1，R_1为Cl，且R_4为Cl。在另一个实施方案中为式(IID)化合物，其中n为1，R_1为$-CH_3$，且R_4为Cl。在另一个实施方案中为式(IID)化合物，其中n为1，R_1为$-OCH_3$，且R_4为Cl。在另一个实施方案中为式(IID)化合物，其中n为1，R_1为$-CF_3$，且R_4为Cl。在另一个实施方案中为式(IID)化合物，其中n为1，R_1为$-OCF_3$，且R_4为Cl。在另一个实施方案中为式(IID)化合物，其中n为1，R_1为Cl，且R_4为F。在另一个实施方案中为式(IID)化合物，其中n为1，R_1为$-CH_3$，且R_4为F。在另一个实施方案中为式(IID)化合物，其中n为1，R_1为$-OCH_3$，且R_4为F。在另一个实施方案中为式(IID)化合物，其中n为1，R_1为$-CF_3$，且R_4为F。在另一个实施方案中为式(IID)化合物，其中n为1，R_1为$-OCF_3$，且R_4为F。在另一个实施方案中为式(IID)化合物，其中n为1，R_1为Cl，且R_4为H。在另一个实施方案中为式(IID)

化合物，其中n为1，R_1为-CH_3，且R_4为H。在另一个实施方案中为式(IID)化合物，其中n为1，R_1为-OCH_3，且R_4为H。在另一个实施方案中为式(IID)化合物，其中n为1，R_1为-CF_3，且R_4为H。在另一个实施方案中为式(IID)化合物，其中n为1，R_1为-OCF_3，且R_4为H。在另一个实施方案中为式(IID)化合物，其中n为1，R_1为Cl，且R_4为-OCH_3。在另一个实施方案中为式(IID)化合物，其中n为1，R_1为-CH_3，且R_4为-OCH_3。在另一个实施方案中为式(IID)化合物，其中n为1，R_1为-OCH_3，且R_4为-OCH_3。在另一个实施方案中为式(IID)化合物，其中n为1，R_1为-CF_3，且R_4为-OCH_3。在另一个实施方案中为式(IID)化合物，其中n为1，R_1为-OCF_3，且R_4为-OCH_3。在另一个实施方案中为式(IID)化合物，其中n为1，R_1为Cl，且R_4为-OCF_3。在另一个实施方案中为式(IID)化合物，其中n为1，R_1为-CH_3，且R_4为-OCF_3。在另一个实施方案中为式(IID)化合物，其中n为1，R_1为-OCH_3，且R_4为-OCF_3。在另一个实施方案中为式(IID)化合物，其中n为1，R_1为-CF_3，且R_4为-OCF_3。在另一个实施方案中为式(IID)化合物，其中n为1，R_1为-OCF_3，且R_4为-OCF_3。

[0117] 在另一个实施方案中，本文描述了式(IID')化合物，或其药学上可接受的盐、溶剂化物或前药：



式(IID')；

其中：

A为键；

每个R_1独立地为卤素、-CN、-NO_2、-OH、-OCF_3、-OCH_2F、-OCF_2H、-CF_3、-SR_8、-N(R_8)S(=O)$_2R_9$、-S(=O)$_2$N(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、取代或未取代的C_1-C_6烷基、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基；或者两个R_1合起来形成取代或未取代的杂环或者取代或未取代的碳环；

R_2和R_3各自独立地为H、-CN、C_1-C_4烷基、C_3-C_6环烷基或C_2-C_7杂环烷基；或者R_2和R_3合起来形成5元或6元杂环；

R_4为H、F、Cl、Br、I、-CN、-NO_2、-OH、-OCF_3、-OCH_2F、-OCF_2H、-SR_8、-N(R_8)S(=O)$_2R_9$、-S(=O)$_2$N(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、取代或未取代的C_1-C_6烷基、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基；或者两个R_1合起来形成取代或未取代的杂环或者取代或未取代的碳环；其中当n为0时，R_4不是Cl；

R_5为卤素、-CN、-OH、-CF_3、取代或未取代的C_1-C_6烷基、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基；

R_6为取代或未取代的C_2-C_7杂环烷基；

R_{11}和R_{12}各自独立地为H、或取代或未取代的C_1-C_6烷基；或者R_{11}和R_{12}合起来形成5、6、7或8元杂环；

J为C(H)；

R_{13}为H、取代或未取代的C_1-C_6烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的-C_1-C_4烷基C_6-C_{10}芳基、或取代或未取代的-C_1-C_4烷基C_2-C_7杂芳基；

每个R_{14}和R_{15}各自独立地为H、或取代或未取代的C_1-C_6烷基；或者R_{14}和R_{15}合起来形成4、5、6元环烷基环；

R_{21}为卤素、-CN、-NO_2、-OH、-OCF_3、-OCH_2F、-OCF_2H、-CF_3、-SR_{22}、-N(R_{22})S(=O)$_2R_{23}$、-S(=O)$_2$N(R_{22})$_2$、-S(=O)R_{23}、-S(=O)$_2R_{23}$、-C(=O)R_{23}、-CO_2R_{22}、-C(=O)N(R_{22})$_2$、-N(R_{22})C(=O)R_{23}、取代或未取代的C_1-C_6烷基、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基；

每个R_{22}独立地为H、或取代或未取代的C_1-C_6烷基；

R_{23}为取代或未取代的C_1-C_6烷基；

每个R_8独立地为H、或取代或未取代的C_1-C_6烷基；

R_9为取代或未取代的C_1-C_6烷基；

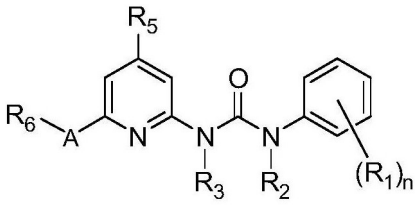
m为2-6；

n为0-4；

p为1-3；

q为1-3。

[0118] 在另一方面，本文描述了式(III)化合物，或其药学上可接受的盐、溶剂化物或前药：



式(III)；

其中：

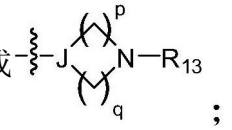
A为键、O或N(R_{10})；

每个R_1独立地为卤素、-CN、-NO_2、-OH、-OCF_3、-OCH_2F、-OCF_2H、-CF_3、-SR_8、-N(R_8)S(=O)$_2R_9$、-S(=O)$_2$N(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、取代或未取代的C_1-C_6烷基、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基；或者两个R_1合起来形成取代或未取代的杂环或者取代或未取代的碳环；

R_2和R_3各自独立地为H、-CN、C_1-C_4烷基、C_3-C_6环烷基或C_2-C_7杂环烷基；或者R_2和R_3合起

来形成5元或6元杂环；

R_5为卤素、-CN、-OH、$-CF_3$、取代或未取代的C_1-C_6烷基、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基；

R_6为取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_2-C_7杂芳基、$-(C(R_{14})(R_{15}))_mR_{21}$、$-(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$或  ；

R_{11}和R_{12}各自独立地为H、或取代或未取代的C_1-C_6烷基；或者R_{11}和R_{12}合起来形成5、6、7或8元杂环；

J为C(H)或N；

R_{13}为H、取代或未取代的C_1-C_6烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的-C_1-C_4烷基C_6-C_{10}芳基、或取代或未取代的-C_1-C_4烷基C_2-C_7杂芳基；

每个R_{14}和R_{15}各自独立地为H、或取代或未取代的C_1-C_6烷基；或者R_{14}和R_{15}合起来形成4、5、6元环烷基环；

R_{21}为卤素、-CN、$-NO_2$、-OH、$-OCF_3$、$-OCH_2F$、$-OCF_2H$、$-CF_3$、$-SR_{22}$、$-N(R_{22})S(=O)_2R_{23}$、$-S(=O)_2N(R_{22})_2$、$-S(=O)R_{23}$、$-S(=O)_2R_{23}$、$-C(=O)R_{23}$、$-CO_2R_{22}$、$-C(=O)N(R_{22})_2$、$-N(R_{22})C(=O)R_{23}$、取代或未取代的C_1-C_6烷基、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基；

每个R_{22}独立地为H、或取代或未取代的C_1-C_6烷基；

R_{23}为取代或未取代的C_1-C_6烷基；

每个R_8独立地为H、或取代或未取代的C_1-C_6烷基；

R_9为取代或未取代的C_1-C_6烷基；

R_{10}为H或C_1-C_4烷基；

m为2-6；

n为0-5；

p为1-3；

q为1-3。

[0119] 在另一个实施方案中为式(III)化合物，其中A为O或N(R_{10})。在另一个实施方案中为式(III)化合物，其中A为O、CH_2或N(H)。在另一个实施方案中为式(III)化合物，其中A为O。在另一个实施方案中为式(III)化合物，其中A为N(R_{10})。在另一个实施方案中为式(III)化合物，其中A为N(H)。在另一个实施方案中为式(III)化合物，其中A为N(CH_3)。在另一个实施方案中为式(III)化合物，其中A为键。

[0120] 在另一个实施方案中为式(III)化合物，其中R_6为取代或未取代的C_3-C_8环烷基。在另一个实施方案中为式(III)化合物，其中R_6为取代或未取代的环丙基。在另一个实施方案中为式(III)化合物，其中R_6为取代或未取代的环丁基。在另一个实施方案中为式(III)化合物，其中R_6为取代或未取代的环戊基。在另一个实施方案中为式(III)化合物，其中R_6为取

代或未取代的环己基。

[0121] 在另一个实施方案中为式(III)化合物，其中R_6为取代或未取代的C_2-C_7杂芳基。在另一个实施方案中为式(III)化合物，其中R_6为取代或未取代的呋喃基、噻吩基、吡咯基、吡啶基、噁唑基、噻唑基、咪唑基、异噁唑基、异噻唑基、吡唑基、哒嗪基、嘧啶基、吡嗪基、噁二唑基、噻二唑基、三唑基、吲哚基、苯并噻吩基、苯并噁唑基、苯并噻唑基、苯并咪唑基、苯并噁二唑基、苯并噻二唑基、苯并三唑基、吡唑并吡啶基、咪唑并吡啶基、吡咯并吡啶基、吡咯并嘧啶基、吲嗪基、嘌呤基、呋喃并吡啶基、噻吩并吡啶基、呋喃并吡咯基、呋喃并呋喃基、噻吩并呋喃基、1,4-二氢吡咯并吡咯基、噻吩并吡咯基、噻吩并噻吩基、喹啉基、异喹啉基、喹喔啉基、呋喃并吡唑基、噻吩并吡唑基、硒吩基、硒唑基和苯并异噁唑基。在另一个实施方案中为式(III)化合物，其中R_6为取代或未取代的吡啶基。在另一个实施方案中为式(III)化合物，其中R_6为取代的吡啶基。在另一个实施方案中为式(III)化合物，其中R_6为未取代的吡啶基。

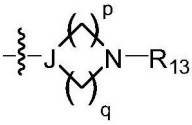
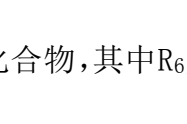
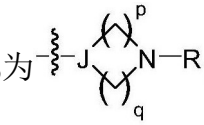
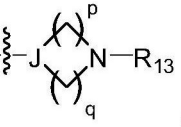
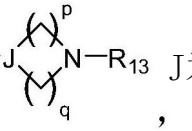
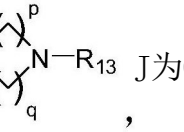
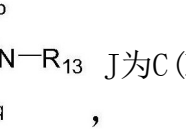
[0122] 在另一个实施方案中为式(III)化合物，其中R_6为-(C(R_{14})(R_{15}))$_m$$R_{21}$。在另一个实施方案中为式(III)化合物，其中$R_6$为-(C($R_{14}$)($R_{15}$))$_m$$R_{21}$，且每个$R_{14}$和$R_{15}$为H。在另一个实施方案中为式(III)化合物，其中R_6为-(C(R_{14})(R_{15}))$_m$$R_{21}$，m为2，且每个$R_{14}$和$R_{15}$为H。在另一个实施方案中为式(III)化合物，其中R_6为-(CH_2)$_m$$R_{21}$，m为2，且$R_{21}$为取代或未取代的$C_2$-$C_7$杂环烷基。在另一个实施方案中为式(III)化合物，其中R_6为-(CH_2)$_m$$R_{21}$，m为2，且$R_{21}$为取代或未取代的$C_3$-$C_8$环烷基。在另一个实施方案中为式(III)化合物，其中R_6为-(CH_2)$_m$$R_{21}$，m为2，且$R_{21}$为取代或未取代的$C_6$-$C_{10}$芳基。在另一个实施方案中为式(III)化合物，其中R_6为-(CH_2)$_m$$R_{21}$，m为2，且$R_{21}$为取代或未取代的苯基。在另一个实施方案中为式(III)化合物，其中R_6为-(CH_2)$_m$$R_{21}$，m为2，且$R_{21}$为取代或未取代的$C_2$-$C_7$杂芳基。在另一个实施方案中为式(III)化合物，其中R_6为-(CH_2)$_m$$R_{21}$，m为2，且$R_{21}$为-OH。

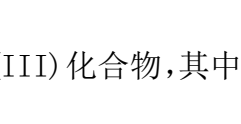
[0123] 在另一个实施方案中为式(III)化合物，其中R_6为-(C(R_{14})(R_{15}))$_m$$R_{21}$，m为3，且每个$R_{14}$和$R_{15}$为H。在另一个实施方案中为式(III)化合物，其中R_6为-(CH_2)$_m$$R_{21}$，m为3，且$R_{21}$为取代或未取代的$C_2$-$C_7$杂环烷基。在另一个实施方案中为式(III)化合物，其中R_6为-(CH_2)$_m$$R_{21}$，m为3，且$R_{21}$为取代或未取代的$C_3$-$C_8$环烷基。在另一个实施方案中为式(III)化合物，其中R_6为-(CH_2)$_m$$R_{21}$，m为3，且$R_{21}$为取代或未取代的$C_6$-$C_{10}$芳基。在另一个实施方案中为式(III)化合物，其中R_6为-(CH_2)$_m$$R_{21}$，m为3，且$R_{21}$为取代或未取代的苯基。在另一个实施方案中为式(III)化合物，其中R_6为-(CH_2)$_m$$R_{21}$，m为3，且$R_{21}$为取代或未取代的$C_2$-$C_7$杂芳基。在另一个实施方案中为式(III)化合物，其中R_6为-(CH_2)$_m$$R_{21}$，m为3，且$R_{21}$为-OH。

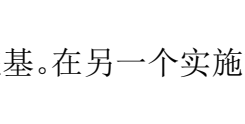
[0124] 在另一个实施方案中为式(III)化合物，其中R_6为-(C(R_{14})(R_{15}))$_m$N(R_{11})(R_{12})。在另一个实施方案中为式(III)化合物，其中R_6为-(C(R_{14})(R_{15}))$_m$N(R_{11})(R_{12})，m为2，且每个R_{14}和R_{15}为H。在另一个实施方案中为式(III)化合物，其中R_6为-(CH_2)$_m$N(R_{11})(R_{12})，m为2，且R_{11}和R_{12}各自为H。在另一个实施方案中为式(III)化合物，其中R_6为-(CH_2)$_m$N(R_{11})(R_{12})，m为2，R_{11}为取代或未取代的C_1-C_6烷基，且R_{12}为H。在另一个实施方案中为式(III)化合物，其中R_6为-(CH_2)$_m$N(R_{11})(R_{12})，m为2，R_{11}为CH_3，且R_{12}为H。在另一个实施方案中为式(III)化合物，其中R_6为-(CH_2)$_m$N(R_{11})(R_{12})，m为2，R_{11}为取代或未取代的C_1-C_6烷基，且R_{12}为取代或未取代的C_1-C_6烷基。在另一个实施方案中为式(III)化合物，其中R_6为-(CH_2)$_m$N(R_{11})(R_{12})，m为2，R_{11}为CH_3，且R_{12}为CH_3。在另一个实施方案中为式(III)化合物，其中R_6为-(CH_2)$_m$N(R_{11})(R_{12})，m为2，

且R_{11}和R_{12}合起来形成5、6、7或8元杂环。在另一个实施方案中为式(III)化合物，其中R_6为-$(CH_2)_mN(R_{11})(R_{12})$，m为2，且$R_{11}$和$R_{12}$合起来形成5元杂环。在另一个实施方案中为式(III)化合物，其中R_6为-$(CH_2)_mN(R_{11})(R_{12})$，m为2，且$R_{11}$和$R_{12}$合起来形成6元杂环。

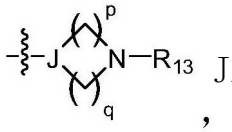
[0125] 在另一个实施方案中为式(III)化合物，其中R_6为-$(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$。在另一个实施方案中为式(III)化合物，其中$R_6$为-$(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$，m为3，且每个$R_{14}$和$R_{15}$为H。在另一个实施方案中为式(III)化合物，其中R_6为-$(CH_2)_mN(R_{11})(R_{12})$，m为3，且$R_{11}$和$R_{12}$各自为H。在另一个实施方案中为式(III)化合物，其中R_6为-$(CH_2)_mN(R_{11})(R_{12})$，m为3，$R_{11}$为取代或未取代的$C_1$-$C_6$烷基，且$R_{12}$为H。在另一个实施方案中为式(III)化合物，其中R_6为-$(CH_2)_mN(R_{11})(R_{12})$，m为3，$R_{11}$为$CH_3$，且$R_{12}$为H。在另一个实施方案中为式(III)化合物，其中R_6为-$(CH_2)_mN(R_{11})(R_{12})$，m为3，$R_{11}$为取代或未取代的$C_1$-$C_6$烷基，且$R_{12}$为取代或未取代的$C_1$-$C_6$烷基。在另一个实施方案中为式(III)化合物，其中R_6为-$(CH_2)_mN(R_{11})(R_{12})$，m为3，$R_{11}$为$CH_3$，且$R_{12}$为$CH_3$。在另一个实施方案中为式(III)化合物，其中$R_6$为-$(CH_2)_mN(R_{11})(R_{12})$，m为3，且$R_{11}$和$R_{12}$合起来形成5、6、7或8元杂环。在另一个实施方案中为式(III)化合物，其中R_6为-$(CH_2)_mN(R_{11})(R_{12})$，m为3，且$R_{11}$和$R_{12}$合起来形成5元杂环。在另一个实施方案中为式(III)化合物，其中R_6为-$(CH_2)_mN(R_{11})(R_{12})$，m为3，且$R_{11}$和$R_{12}$合起来形成6元杂环。

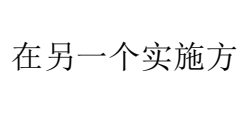
[0126] 在另一个实施方案中为式(III)化合物，其中R_6为取代或未取代的C_2-C_7杂环烷基。在另一个实施方案中为式(III)化合物，其中R_6为  。在另一个实施方案中为式(III)化合物，其中R_6为  且J为C(H)。在另一个实施方案中为式(III)化合物，其中R_6为  ，J为C(H)，p为1，且q为1。在另一个实施方案中为式(III)化合物，其中R_6为  ，J为C(H)，p为2，且q为1。在另一个实施方案中为式(III)化合物，其中R_6为  ，J为C(H)，p为3，且q为1。在另一个实施方案中为式(III)化合物，其中R_6为  ，J为C(H)，p为2，且q为2。在另一个实施方案中为式(III)化合物，其中R_6为  ，J为C(H)，p为1，q为1，且R_{13}为取代或未取代的C_1-C_6烷基。在另一个实施方案

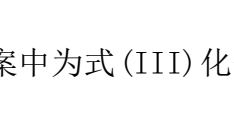
中为式(III)化合物，其中R_6为  J为C(H)，p为2，q为1，且R_{13}为取代或未取代的

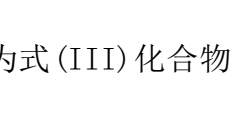
C_1-C_6烷基。在另一个实施方案中为式(III)化合物，其中R_6为  J为C(H)，p为3，

q为1，且R_{13}为取代或未取代的C_1-C_6烷基。在另一个实施方案中为式(III)化合物，其中R_6为

 J为C(H)，p为2，q为2，且R_{13}为取代或未取代的C_1-C_6烷基。

[0127] 在另一个实施方案中为式(III)化合物，其中R_6为  且J为N。在另一个

实施方案中为式(III)化合物，其中R_6为  J为N，p为2，且q为2。在另一个实施

方案中为式(III)化合物，其中R_6为  J为N，p为2，q为2，且R_{13}为取代或未取代

的C_1-C_6烷基。

[0128] 在另一个实施方案中为式(III)化合物，其中R_5为卤素。在另一个实施方案中为式(III)化合物，其中R_5为-CF_3。在另一个实施方案中为式(III)化合物，其中R_5为取代或未取代的C_1-C_6烷基。在另一个实施方案中为式(III)化合物，其中R_5为-CH_3。在另一个实施方案中为式(III)化合物，其中R_5为-CH_2CH_3。在另一个实施方案中为式(III)化合物，其中R_5为取代或未取代的C_1-C_6杂烷基。在另一个实施方案中为式(III)化合物，其中R_5为取代或未取代的C_3-C_8环烷基。在另一个实施方案中为式(III)化合物，其中R_5为取代或未取代的C_6-C_{10}芳基。在另一个实施方案中为式(III)化合物，其中R_5为取代或未取代的C_2-C_7杂芳基。

[0129] 在另一个实施方案中为式(III)化合物，其中R_2和R_3各自独立地为H、-CN、C_1-C_4烷基、C_3-C_6环烷基或C_2-C_7杂环烷基。在另一个实施方案中为式(III)化合物，其中R_2和R_3各自为H。

[0130] 在另一个实施方案中为式(III)化合物，其中R_2和R_3各自独立地为H、-CN、C_1-C_4烷基、C_3-C_6环烷基或C_2-C_7杂环烷基；且R_2和R_3中的至少一个不是H。在另一个实施方案中为式(III)化合物，其中R_2为H，且R_3为C_1-C_4烷基。在另一个实施方案中为式(III)化合物，其中R_2为H，且R_3为CH_3。在另一个实施方案中为式(III)化合物，其中R_2为H，且R_3为C_3-C_6环烷基。在另一个实施方案中为式(III)化合物，其中R_2为H，且R_3为环丙基。在另一个实施方案中为式(III)化合物，其中R_2为H，且R_3为环戊基。在另一个实施方案中为式(III)化合物，其中R_2为CH_3，且R_3为CH_3。在另一个实施方案中为式(III)化合物，其中R_2为C_1-C_4烷基，且R_3为H。在另一个实施方案中为式(III)化合物，其中R_2为CH_3，且R_3为H。在另一个实施方案中为式(III)化合物，其中R_2为C_3-C_6环烷基，且R_3为H。在另一个实施方案中为式(III)化合物，其中R_2为环

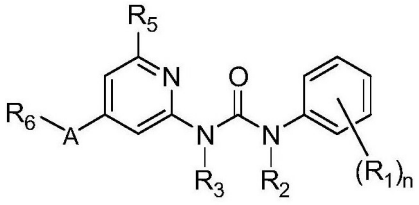
丙基，且R_3为H。在另一个实施方案中为式(III)化合物，其中R_2为环戊基，且R_3为H。

[0131] 在另一个实施方案中为式(III)化合物，其中R_2和R_3合起来形成5元或6元杂环。在另一个实施方案中为式(III)化合物，其中R_2和R_3合起来形成5元杂环。在另一个实施方案中为式(III)化合物，其中R_2和R_3合起来形成6元杂环。

[0132] 在另一个实施方案中为式(III)化合物，其中n为0。

[0133] 在另一个实施方案中为式(III)化合物，其中每个R_1独立地为卤素、-CN、$-NO_2$、-OH、$-OCF_3$、$-OCH_2F$、$-OCF_2H$、$-CF_3$、$-SR_8$、$-N(R_8)S(=O)_2R_9$、$-S(=O)_2N(R_8)_2$、$-S(=O)R_9$、$-S(=O)_2R_9$、$-C(=O)R_9$、$-CO_2R_8$、$-N(R_8)_2$、$-C(=O)N(R_8)_2$、$-N(R_8)C(=O)R_9$、取代或未取代的C_1-C_6烷基、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基。在另一个实施方案中为式(III)化合物，其中每个R_1独立地为卤素、-CN、-OH、$-CF_3$、取代或未取代的C_1-C_6烷基、或取代或未取代的C_1-C_6烷氧基。在另一个实施方案中为式(III)化合物，其中每个R_1独立地为卤素、-CN、$-OCF_3$、$-OCH_2F$、$-OCF_2H$、$-CF_3$、取代或未取代的C_1-C_6烷基、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基。在另一个实施方案中为式(III)化合物，其中每个R_1独立地为卤素、-CN、$-OCF_3$、$-OCH_2F$、$-OCF_2H$、$-CF_3$、取代或未取代的C_1-C_6烷基、或取代或未取代的C_1-C_6烷氧基。在另一个实施方案中为式(III)化合物，其中每个R_1独立地为卤素、-CN、$-OCF_3$、$-OCH_2F$、$-OCF_2H$、$-CF_3$、取代或未取代的C_1-C_6烷基、或取代或未取代的C_1-C_6烷氧基，且n为3。在另一个实施方案中为式(III)化合物，其中每个R_1独立地为卤素、-CN、$-OCF_3$、$-OCH_2F$、$-OCF_2H$、$-CF_3$、取代或未取代的C_1-C_6烷基、或取代或未取代的C_1-C_6烷氧基，且n为2。在另一个实施方案中为式(III)化合物，其中n为3，且每个R_1独立地为卤素。在另一个实施方案中为式(III)化合物，其中n为2，且每个R_1独立地为卤素。在另一个实施方案中为式(III)化合物，其中n为2，且每个R_1独立地为F或Cl。在另一个实施方案中为式(III)化合物，其中n为2，且每个R_1为F。在另一个实施方案中为式(III)化合物，其中n为2，且每个R_1独立地为Cl。在另一个实施方案中为式(III)化合物，其中n为2，且每个R_1独立地为卤素或$-CF_3$。在另一个实施方案中为式(III)化合物，其中n为2，且每个R_1独立地为F或$-CF_3$。在另一个实施方案中为式(III)化合物，其中n为2，且每个R_1独立地为Cl或$-CF_3$。在另一个实施方案中为式(III)化合物，其中n为1，且R_1为卤素。在另一个实施方案中为式(III)化合物，其中n为1，且R_1为F。在另一个实施方案中为式(III)化合物，其中n为1，且R_1为Cl。在另一个实施方案中为式(III)化合物，其中n为1，且R_1为$-CF_3$。在另一个实施方案中为式(III)化合物，其中n为1，且R_1为取代或未取代的C_1-C_6烷基。在另一个实施方案中为式(III)化合物，其中n为1，且R_1为CH_3。在另一个实施方案中为式(III)化合物，其中n为1，且R_1为取代或未取代的C_1-C_6烷氧基。在另一个实施方案中为式(III)化合物，其中n为1，且R_1为$-OCH_3$。在另一个实施方案中为式(III)化合物，其中n为1，且R_1为$-OCF_3$。在另一个实施方案中为式(III)化合物，其中n为1，且R_1为$-OCF_2H$。

[0134] 在另一方面，本文描述了式(IV)化合物，或其药学上可接受的盐、溶剂化物或前药：



式(IV)；

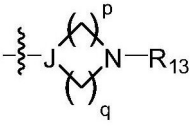
其中：

A为键、O或N(R10)；

每个R1独立地为卤素、-CN、-NO2、-OH、-OCF3、-OCH2F、-OCF2H、-CF3、-SR8、-N(R8)S(=O)2R9、-S(=O)2N(R8)2、-S(=O)R9、-S(=O)2R9、-C(=O)R9、-CO2R8、-N(R8)2、-C(=O)N(R8)2、-N(R8)C(=O)R9、取代或未取代的C1-C6烷基、取代或未取代的C1-C6烷氧基、取代或未取代的C1-C6杂烷基、取代或未取代的C2-C7杂环烷基、取代或未取代的C3-C8环烷基、取代或未取代的C6-C10芳基、或取代或未取代的C2-C7杂芳基；或者两个R1合起来形成取代或未取代的杂环或者取代或未取代的碳环；

R2和R3各自独立地为H、-CN、C1-C4烷基、C3-C6环烷基或C2-C7杂环烷基；或者R2和R3合起来形成5元或6元杂环；

R5为卤素、-CN、-OH、-CF3、取代或未取代的C1-C6烷基、取代或未取代的C1-C6烷氧基、取代或未取代的C1-C6杂烷基、取代或未取代的C2-C7杂环烷基、取代或未取代的C3-C8环烷基、取代或未取代的C6-C10芳基、或取代或未取代的C2-C7杂芳基；

R6为取代或未取代的C2-C7杂环烷基、取代或未取代的C3-C8环烷基、取代或未取代的C2-C7杂芳基、-(C(R14)(R15))mR21、-(C(R14)(R15))mN(R11)(R12)或  ；

R11和R12各自独立地为H、或取代或未取代的C1-C6烷基；或者R11和R12合起来形成5、6、7或8元杂环；

J为C(H)或N；

R13为H、取代或未取代的C1-C6烷基、取代或未取代的C2-C7杂环烷基、取代或未取代的C3-C8环烷基、取代或未取代的-C1-C4烷基C6-C10芳基、或取代或未取代的-C1-C4烷基C2-C7杂芳基；

每个R14和R15各自独立地为H、或取代或未取代的C1-C6烷基；或者R14和R15合起来形成4、5、6元环烷基环；

R21为卤素、-CN、-NO2、-OH、-OCF3、-OCH2F、-OCF2H、-CF3、-SR22、-N(R22)S(=O)2R23、-S(=O)2N(R22)2、-S(=O)R23、-S(=O)2R23、-C(=O)R23、-CO2R22、-C(=O)N(R22)2、-N(R22)C(=O)R23、取代或未取代的C1-C6烷基、取代或未取代的C1-C6烷氧基、取代或未取代的C1-C6杂烷基、取代或未取代的C2-C7杂环烷基、取代或未取代的C3-C8环烷基、取代或未取代的C6-C10芳基、或取代或未取代的C2-C7杂芳基；

每个R22独立地为H、或取代或未取代的C1-C6烷基；

R23为取代或未取代的C1-C6烷基；

每个R8独立地为H、或取代或未取代的C1-C6烷基；

R_9为取代或未取代的C_1-C_6烷基；

R_{10}为H或C_1-C_4烷基；

m为2-6；

n为0-5；

p为1-3；

q为1-3。

[0135] 在另一个实施方案中为式(IV)化合物，其中A为O或N(R_{10})。在另一个实施方案中为式(IV)化合物，其中A为O或N(H)。在另一个实施方案中为式(IV)化合物，其中A为O。在另一个实施方案中为式(IV)化合物，其中A为N(R_{10})。在另一个实施方案中为式(IV)化合物，其中A为N(H)。在另一个实施方案中为式(IV)化合物，其中A为N(CH_3)。在另一个实施方案中为式(IV)化合物，其中A为键。

[0136] 在另一个实施方案中为式(IV)化合物，其中R_6为取代或未取代的C_3-C_8环烷基。在另一个实施方案中为式(IV)化合物，其中R_6为取代或未取代的环丙基。在另一个实施方案中为式(IV)化合物，其中R_6为取代或未取代的环丁基。在另一个实施方案中为式(IV)化合物，其中R_6为取代或未取代的环戊基。在另一个实施方案中为式(IV)化合物，其中R_6为取代或未取代的环己基。

[0137] 在另一个实施方案中为式(IV)化合物，其中R_6为取代或未取代的C_2-C_7杂芳基。在另一个实施方案中为式(IV)化合物，其中R_6为取代或未取代的呋喃基、噻吩基、吡咯基、吡啶基、噁唑基、噻唑基、咪唑基、异噁唑基、异噻唑基、吡唑基、哒嗪基、嘧啶基、吡嗪基、噁二唑基、噻二唑基、三唑基、吲哚基、苯并噻吩基、苯并噁唑基、苯并噻唑基、苯并咪唑基、苯并噁二唑基、苯并噻二唑基、苯并三唑基、吡唑并吡啶基、咪唑并吡啶基、吡咯并吡啶基、吡咯并嘧啶基、吲嗪基、嘌呤基、呋喃并吡啶基、噻吩并吡啶基、呋喃并吡咯基、呋喃并呋喃基、噻吩并呋喃基、1,4-二氢吡咯并吡咯基、噻吩并吡咯基、噻吩并噻吩基、喹啉基、异喹啉基、喹喔啉基、呋喃并吡唑基、噻吩并吡唑基、硒吩基、硒唑基和苯并异噁唑基。在另一个实施方案中为式(IV)化合物，其中R_6为取代或未取代的吡啶基。在另一个实施方案中为式(IV)化合物，其中R_6为取代的吡啶基。在另一个实施方案中为式(IV)化合物，其中R_6为未取代的吡啶基。

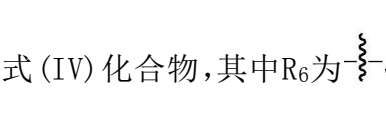
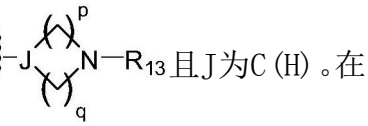
[0138] 在另一个实施方案中为式(IV)化合物，其中R_6为-(C(R_{14})(R_{15}))$_m$$R_{21}$。在另一个实施方案中为式(IV)化合物，其中$R_6$为-(C($R_{14}$)($R_{15}$))$_m$$R_{21}$，且每个$R_{14}$和$R_{15}$为H。在另一个实施方案中为式(IV)化合物，其中$R_6$为-(C($R_{14}$)($R_{15}$))$_m$$R_{21}$，m为2，且每个$R_{14}$和$R_{15}$为H。在另一个实施方案中为式(IV)化合物，其中$R_6$为-$(CH_2)_m$$R_{21}$，m为2，且$R_{21}$为取代或未取代的$C_2$-$C_7$杂环烷基。在另一个实施方案中为式(IV)化合物，其中R_6为-$(CH_2)_m$$R_{21}$，m为2，且$R_{21}$为取代或未取代的$C_3$-$C_8$环烷基。在另一个实施方案中为式(IV)化合物，其中R_6为-$(CH_2)_m$$R_{21}$，m为2，且$R_{21}$为取代或未取代的$C_6$-$C_{10}$芳基。在另一个实施方案中为式(IV)化合物，其中$R_6$为-$(CH_2)_m$$R_{21}$，m为2，且$R_{21}$为取代或未取代的苯基。在另一个实施方案中为式(IV)化合物，其中R_6为-$(CH_2)_m$$R_{21}$，m为2，且$R_{21}$为取代或未取代的$C_2$-$C_7$杂芳基。在另一个实施方案中为式(IV)化合物，其中R_6为-$(CH_2)_m$$R_{21}$，m为2，且$R_{21}$为-OH。

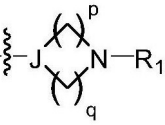
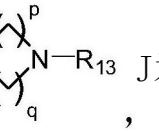
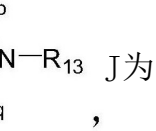
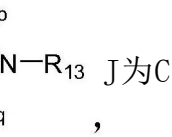
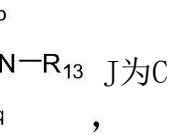
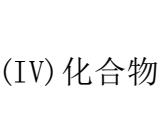
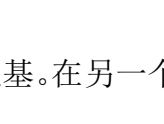
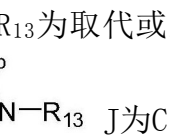
[0139] 在另一个实施方案中为式(IV)化合物，其中R_6为-(C(R_{14})(R_{15}))$_m$$R_{21}$，m为3，且每个$R_{14}$和$R_{15}$为H。在另一个实施方案中为式(IV)化合物，其中$R_6$为-$(CH_2)_m$$R_{21}$，m为3，且$R_{21}$为取代

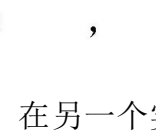
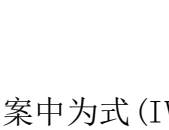
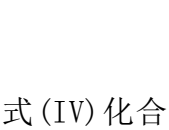
或未取代的C_2-C_7杂环烷基。在另一个实施方案中为式(IV)化合物，其中R_6为-$(CH_2)_mR_{21}$，m为3，且R_{21}为取代或未取代的C_3-C_8环烷基。在另一个实施方案中为式(IV)化合物，其中R_6为-$(CH_2)_mR_{21}$，m为3，且R_{21}为取代或未取代的C_6-C_{10}芳基。在另一个实施方案中为式(IV)化合物，其中R_6为-$(CH_2)_mR_{21}$，m为3，且R_{21}为取代或未取代的苯基。在另一个实施方案中为式(IV)化合物，其中R_6为-$(CH_2)_mR_{21}$，m为3，且R_{21}为取代或未取代的C_2-C_7杂芳基。在另一个实施方案中为式(IV)化合物，其中R_6为-$(CH_2)_mR_{21}$，m为3，且R_{21}为-OH。

[0140] 在另一个实施方案中为式(IV)化合物，其中R_6为-$(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$。在另一个实施方案中为式(IV)化合物，其中$R_6$为-$(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$，m为2，且每个$R_{14}$和$R_{15}$为H。在另一个实施方案中为式(IV)化合物，其中$R_6$为-$(CH_2)_mN(R_{11})(R_{12})$，m为2，且$R_{11}$和$R_{12}$各自为H。在另一个实施方案中为式(IV)化合物，其中R_6为-$(CH_2)_mN(R_{11})(R_{12})$，m为2，$R_{11}$为取代或未取代的$C_1$-$C_6$烷基，且$R_{12}$为H。在另一个实施方案中为式(IV)化合物，其中$R_6$为-$(CH_2)_mN(R_{11})(R_{12})$，m为2，$R_{11}$为$CH_3$，且$R_{12}$为H。在另一个实施方案中为式(IV)化合物，其中$R_6$为-$(CH_2)_mN(R_{11})(R_{12})$，m为2，$R_{11}$为取代或未取代的$C_1$-$C_6$烷基，且$R_{12}$为取代或未取代的$C_1$-$C_6$烷基。在另一个实施方案中为式(IV)化合物，其中$R_6$为-$(CH_2)_mN(R_{11})(R_{12})$，m为2，$R_{11}$为$CH_3$，且$R_{12}$为$CH_3$。在另一个实施方案中为式(IV)化合物，其中$R_6$为-$(CH_2)_mN(R_{11})(R_{12})$，m为2，且$R_{11}$和$R_{12}$合起来形成5、6、7或8元杂环。在另一个实施方案中为式(IV)化合物，其中R_6为-$(CH_2)_mN(R_{11})(R_{12})$，m为2，且$R_{11}$和$R_{12}$合起来形成5元杂环。在另一个实施方案中为式(IV)化合物，其中R_6为-$(CH_2)_mN(R_{11})(R_{12})$，m为2，且$R_{11}$和$R_{12}$合起来形成6元杂环。

[0141] 在另一个实施方案中为式(IV)化合物，其中R_6为-$(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$。在另一个实施方案中为式(IV)化合物，其中$R_6$为-$(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$，m为3，且每个$R_{14}$和$R_{15}$为H。在另一个实施方案中为式(IV)化合物，其中$R_6$为-$(CH_2)_mN(R_{11})(R_{12})$，m为3，且$R_{11}$和$R_{12}$各自为H。在另一个实施方案中为式(IV)化合物，其中R_6为-$(CH_2)_mN(R_{11})(R_{12})$，m为3，$R_{11}$为取代或未取代的$C_1$-$C_6$烷基，且$R_{12}$为H。在另一个实施方案中为式(IV)化合物，其中$R_6$为-$(CH_2)_mN(R_{11})(R_{12})$，m为3，$R_{11}$为$CH_3$，且$R_{12}$为H。在另一个实施方案中为式(IV)化合物，其中$R_6$为-$(CH_2)_mN(R_{11})(R_{12})$，m为3，$R_{11}$为取代或未取代的$C_1$-$C_6$烷基，且$R_{12}$为取代或未取代的$C_1$-$C_6$烷基。在另一个实施方案中为式(IV)化合物，其中$R_6$为-$(CH_2)_mN(R_{11})(R_{12})$，m为3，$R_{11}$为$CH_3$，且$R_{12}$为$CH_3$。在另一个实施方案中为式(IV)化合物，其中$R_6$为-$(CH_2)_mN(R_{11})(R_{12})$，m为3，且$R_{11}$和$R_{12}$合起来形成5、6、7或8元杂环。在另一个实施方案中为式(IV)化合物，其中R_6为-$(CH_2)_mN(R_{11})(R_{12})$，m为3，且$R_{11}$和$R_{12}$合起来形成5元杂环。在另一个实施方案中为式(IV)化合物，其中R_6为-$(CH_2)_mN(R_{11})(R_{12})$，m为3，且$R_{11}$和$R_{12}$合起来形成6元杂环。

[0142] 在另一个实施方案中为式(IV)化合物，其中R_6为取代或未取代的C_2-C_7杂环烷基。在另一个实施方案中为式(IV)化合物，其中R_6为  。在另一个实施方案中为式(IV)化合物，其中R_6为  且J为C(H)。在另一个实施方案中为式(IV)化合物，其

中R_6为  J为C(H)，p为1，且q为1。在另一个实施方案中为式(IV)化合物，其中R_6为  J为C(H)，p为2，且q为1。在另一个实施方案中为式(IV)化合物，其中R_6为  J为C(H)，p为3，且q为1。在另一个实施方案中为式(IV)化合物，其中R_6为  J为C(H)，p为2，且q为2。在另一个实施方案中为式(IV)化合物，其中R_6为  J为C(H)，p为1，q为1，且R_{13}为取代或未取代的C_1-C_6烷基。在另一个实施方案中为式(IV)化合物，其中R_6为  J为C(H)，p为2，q为1，且R_{13}为取代或未取代的C_1-C_6烷基。在另一个实施方案中为式(IV)化合物，其中R_6为  J为C(H)，p为3，q为1，且R_{13}为取代或未取代的C_1-C_6烷基。在另一个实施方案中为式(IV)化合物，其中R_6为  J为C(H)，p为2，q为2，且R_{13}为取代或未取代的C_1-C_6烷基。

[0143] 在另一个实施方案中为式(IV)化合物，其中R_6为  且J为N。在另一个实施方案中为式(IV)化合物，其中R_6为  J为N，p为2，且q为2。在另一个实施方案中为式(IV)化合物，其中R_6为  J为N，p为2，q为2，且R_{13}为取代或未取代的C_1-C_6烷基。

[0144] 在另一个实施方案中为式(IV)化合物，其中R_5为卤素。在另一个实施方案中为式(IV)化合物，其中R_5为$-CF_3$。在另一个实施方案中为式(IV)化合物，其中R_5为取代或未取代的C_1-C_6烷基。在另一个实施方案中为式(IV)化合物，其中R_5为$-CH_3$。在另一个实施方案中为式(IV)化合物，其中R_5为$-CH_2CH_3$。在另一个实施方案中为式(IV)化合物，其中R_5为取代或未

取代的C_1-C_6杂烷基。在另一个实施方案中为式(IV)化合物，其中R_5为取代或未取代的C_2-C_7杂环烷基。在另一个实施方案中为式(IV)化合物，其中R_5为取代或未取代的C_3-C_8环烷基。在另一个实施方案中为式(IV)化合物，其中R_5为取代或未取代的C_6-C_{10}芳基。在另一个实施方案中为式(IV)化合物，其中R_5为取代或未取代的C_2-C_7杂芳基。

[0145] 在另一个实施方案中为式(IV)化合物，其中R_2和R_3各自独立地为H、-CN、C_1-C_4烷基、C_3-C_6环烷基或C_2-C_7杂环烷基。在另一个实施方案中为式(IV)化合物，其中R_2和R_3各自为H。

[0146] 在另一个实施方案中为式(IV)化合物，其中R_2和R_3各自独立地为H、-CN、C_1-C_4烷基、C_3-C_6环烷基或C_2-C_7杂环烷基；且R_2和R_3中的至少一个不是H。在另一个实施方案中为式(IV)化合物，其中R_2为H，且R_3为C_1-C_4烷基。在另一个实施方案中为式(IV)化合物，其中R_2为H，且R_3为CH_3。在另一个实施方案中为式(IV)化合物，其中R_2为H，且R_3为C_3-C_6环烷基。在另一个实施方案中为式(IV)化合物，其中R_2为H，且R_3为环丙基。在另一个实施方案中为式(IV)化合物，其中R_2为H，且R_3为环戊基。在另一个实施方案中为式(IV)化合物，其中R_2为CH_3，且R_3为CH_3。在另一个实施方案中为式(IV)化合物，其中R_2为C_1-C_4烷基，且R_3为H。在另一个实施方案中为式(IV)化合物，其中R_2为CH_3，且R_3为H。在另一个实施方案中为式(IV)化合物，其中R_2为C_3-C_6环烷基，且R_3为H。在另一个实施方案中为式(IV)化合物，其中R_2为环丙基，且R_3为H。在另一个实施方案中为式(IV)化合物，其中R_2为环戊基，且R_3为H。

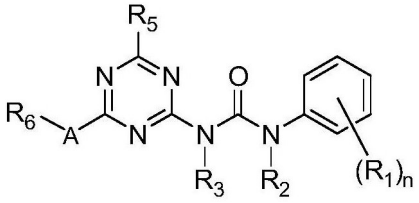
[0147] 在另一个实施方案中为式(IV)化合物，其中R_2和R_3合起来形成5元或6元杂环。在另一个实施方案中为式(IV)化合物，其中R_2和R_3合起来形成5元杂环。在另一个实施方案中为式(IV)化合物，其中R_2和R_3合起来形成6元杂环。

[0148] 在另一个实施方案中为式(IV)化合物，其中n为0。

[0149] 在另一个实施方案中为式(IV)化合物，其中每个R_1独立地为卤素、-CN、$-NO_2$、-OH、$-OCF_3$、$-OCH_2F$、$-OCF_2H$、$-CF_3$、$-SR_8$、$-N(R_8)S(=O)_2R_9$、$-S(=O)_2N(R_8)_2$、$-S(=O)R_9$、$-S(=O)_2R_9$、$-C(=O)R_9$、$-CO_2R_8$、$-N(R_8)_2$、$-C(=O)N(R_8)_2$、$-N(R_8)C(=O)R_9$、取代或未取代的C_1-C_6烷基、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基。在另一个实施方案中为式(IV)化合物，其中每个R_1独立地为卤素、-CN、-OH、$-CF_3$、取代或未取代的C_1-C_6烷基、或取代或未取代的C_1-C_6烷氧基。在另一个实施方案中为式(IV)化合物，其中每个R_1独立地为卤素、-CN、$-OCF_3$、$-OCH_2F$、$-OCF_2H$、$-CF_3$、取代或未取代的C_1-C_6烷基、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基。在另一个实施方案中为式(IV)化合物，其中每个R_1独立地为卤素、-CN、$-OCF_3$、$-OCH_2F$、$-OCF_2H$、$-CF_3$、取代或未取代的C_1-C_6烷基、或取代或未取代的C_1-C_6烷氧基。在另一个实施方案中为式(IV)化合物，其中每个R_1独立地为卤素、-CN、$-OCF_3$、$-OCH_2F$、$-OCF_2H$、$-CF_3$、取代或未取代的C_1-C_6烷基、或取代或未取代的C_1-C_6烷氧基，且n为3。在另一个实施方案中为式(IV)化合物，其中每个R_1独立地为卤素、-CN、$-OCF_3$、$-OCH_2F$、$-OCF_2H$、$-CF_3$、取代或未取代的C_1-C_6烷基、或取代或未取代的C_1-C_6烷氧基，且n为2。在另一个实施方案中为式(IV)化合物，其中n为3，且每个R_1独立地为卤素。在另一个实施方案中为式(IV)化合物，其中n为2，且每个R_1独立地为卤素。在另一个实施方案中为式(IV)化合物，其中n为2，且每个R_1独立地为F或Cl。在另

一个实施方案中为式(IV)化合物，其中n为2，且每个R_1为F。在另一个实施方案中为式(IV)化合物，其中n为2，且每个R_1独立地为Cl。在另一个实施方案中为式(IV)化合物，其中n为2，且每个R_1独立地为卤素或$-CF_3$。在另一个实施方案中为式(IV)化合物，其中n为2，且每个R_1独立地为F或$-CF_3$。在另一个实施方案中为式(IV)化合物，其中n为2，且每个R_1独立地为Cl或$-CF_3$。在另一个实施方案中为式(IV)化合物，其中n为1，且R_1为卤素。在另一个实施方案中为式(IV)化合物，其中n为1，且R_1为F。在另一个实施方案中为式(IV)化合物，其中n为1，且R_1为Cl。在另一个实施方案中为式(IV)化合物，其中n为1，且R_1为$-CF_3$。在另一个实施方案中为式(IV)化合物，其中n为1，且R_1为取代或未取代的C_1-C_6烷基。在另一个实施方案中为式(IV)化合物，其中n为1，且R_1为CH_3。在另一个实施方案中为式(IV)化合物，其中n为1，且R_1为取代或未取代的C_1-C_6烷氧基。在另一个实施方案中为式(IV)化合物，其中n为1，且R_1为$-OCH_3$。在另一个实施方案中为式(IV)化合物，其中n为1，且R_1为$-OCF_3$。在另一个实施方案中为式(IV)化合物，其中n为1，且R_1为$-OCF_2H$。

[0150] 在另一方面，本文描述了式(V)化合物，或其药学上可接受的盐、溶剂化物或前药：



式(V)；

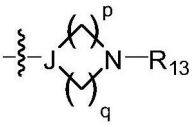
其中：

A为键、O或$N(R_{10})$；

每个R_1独立地为卤素、-CN、$-NO_2$、-OH、$-OCF_3$、$-OCH_2F$、$-OCF_2H$、$-CF_3$、$-SR_8$、$-N(R_8)S(=O)_2R_9$、$-S(=O)_2N(R_8)_2$、$-S(=O)R_9$、$-S(=O)_2R_9$、$-C(=O)R_9$、$-CO_2R_8$、$-N(R_8)_2$、$-C(=O)N(R_8)_2$、$-N(R_8)C(=O)R_9$、取代或未取代的C_1-C_6烷基、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基；或者两个R_1合起来形成取代或未取代的杂环或者取代或未取代的碳环；

R_2和R_3各自独立地为H、-CN、C_1-C_4烷基、C_3-C_6环烷基或C_2-C_7杂环烷基；或者R_2和R_3合起来形成5元或6元杂环；

R_5为卤素、-CN、-OH、$-CF_3$、未取代的C_1-C_6烷基、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基；

R_6为取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_2-C_7杂芳基、$-(C(R_{14})(R_{15}))_mR_{21}$、$-(C(R_{14})(R_{15}))_mN(R_{11})(R_{12})$或  ；

R_{11}和R_{12}各自独立地为H、或取代或未取代的C_1-C_6烷基；或者R_{11}和R_{12}合起来形成5、6、7或8元杂环；

J为C(H)或N；

R_{13}为H、取代或未取代的C_1-C_6烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的-C_1-C_4烷基C_6-C_{10}芳基、或取代或未取代的-C_1-C_4烷基C_2-C_7杂芳基；

每个R_{14}和R_{15}各自独立地为H、或取代或未取代的C_1-C_6烷基；或者R_{14}和R_{15}合起来形成4、5、6元环烷基环；

R_{21}为卤素、-CN、-NO_2、-OH、-OCF_3、-OCH_2F、-OCF_2H、-CF_3、-SR_{22}、-$N(R_{22})S(=O)_2R_{23}$、-$S(=O)_2N(R_{22})_2$、-$S(=O)R_{23}$、-$S(=O)_2R_{23}$、-$C(=O)R_{23}$、-CO_2R_{22}、-$C(=O)N(R_{22})_2$、-$N(R_{22})C(=O)R_{23}$、取代或未取代的C_1-C_6烷基、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基；

每个R_{22}独立地为H、或取代或未取代的C_1-C_6烷基；

R_{23}为取代或未取代的C_1-C_6烷基；

每个R_8独立地为H、或取代或未取代的C_1-C_6烷基；

R_9为取代或未取代的C_1-C_6烷基；

R_{10}为H或C_1-C_4烷基；

m为2-6；

n为0-5；

p为1-3；

q为1-3。

[0151] 在另一个实施方案中为式(V)化合物，其中A为O或$N(R_{10})$。在另一个实施方案中为式(V)化合物，其中A为O或N(H)。在另一个实施方案中为式(V)化合物，其中A为O。在另一个实施方案中为式(V)化合物，其中A为$N(R_{10})$。在另一个实施方案中为式(V)化合物，其中A为N(H)。在另一个实施方案中为式(V)化合物，其中A为$N(CH_3)$。在另一个实施方案中为式(V)化合物，其中A为键。

[0152] 在另一个实施方案中为式(V)化合物，其中R_6为取代或未取代的C_3-C_8环烷基。在另一个实施方案中为式(V)化合物，其中R_6为取代或未取代的环丙基。在另一个实施方案中为式(V)化合物，其中R_6为取代或未取代的环丁基。在另一个实施方案中为式(V)化合物，其中R_6为取代或未取代的环戊基。在另一个实施方案中为式(V)化合物，其中R_6为取代或未取代的环己基。

[0153] 在另一个实施方案中为式(V)化合物，其中R_6为取代或未取代的C_2-C_7杂芳基。在另一个实施方案中为式(V)化合物，其中R_6为取代或未取代的呋喃基、噻吩基、吡咯基、吡啶基、噁唑基、噻唑基、咪唑基、异噁唑基、异噻唑基、吡唑基、哒嗪基、嘧啶基、吡嗪基、噁二唑基、噻二唑基、三唑基、吲哚基、苯并噻吩基、苯并噁唑基、苯并噻唑基、苯并咪唑基、苯并噁二唑基、苯并噻二唑基、苯并三唑基、吡唑并吡啶基、咪唑并吡啶基、吡咯并吡啶基、吡咯并嘧啶基、吲嗪基、嘌呤基、呋喃并吡啶基、噻吩并吡啶基、呋喃并吡咯基、呋喃并呋喃基、噻吩并呋喃基、1,4-二氢吡咯并吡咯基、噻吩并吡咯基、噻吩并噻吩基、喹啉基、异喹啉基、喹喔啉基、呋喃并吡唑基、噻吩并吡唑基、硒吩基、硒唑基和苯并异噁唑基。在另一个实施方案中为式(V)化合物，其中R_6为取代或未取代的吡啶基。在另一个实施方案中为式(V)化合物，其中R_6为取代的吡啶基。在另一个实施方案中为式(V)化合物，其中R_6为未取代的吡啶基。

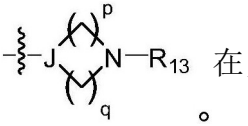
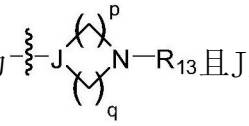
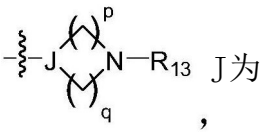
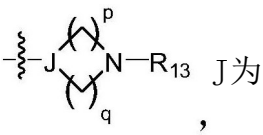
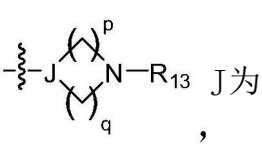
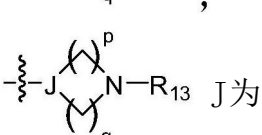
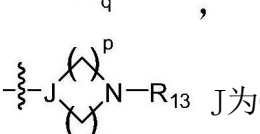
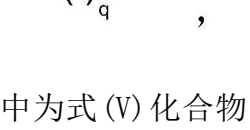
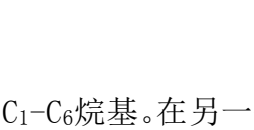
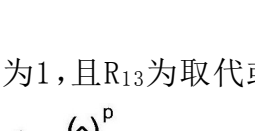
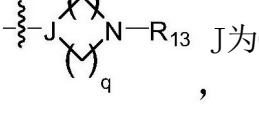
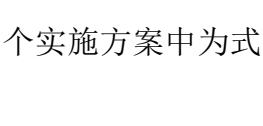
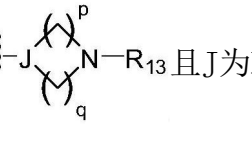
[0154] 在另一个实施方案中为式(V)化合物，其中R_6为-(C(R_{14})(R_{15}))$_m$$R_{21}$。在另一个实施方案中为式(V)化合物，其中$R_6$为-(C($R_{14}$)($R_{15}$))$_m$$R_{21}$，且每个$R_{14}$和$R_{15}$为H。在另一个实施方案中为式(V)化合物，其中$R_6$为-(C($R_{14}$)($R_{15}$))$_m$$R_{21}$，m为2，且每个$R_{14}$和$R_{15}$为H。在另一个实施方案中为式(V)化合物，其中$R_6$为-($CH_2$)$_m$$R_{21}$，m为2，且$R_{21}$为取代或未取代的$C_2$-$C_7$杂环烷基。在另一个实施方案中为式(V)化合物，其中R_6为-(CH_2)$_m$$R_{21}$，m为2，且$R_{21}$为取代或未取代的$C_3$-$C_8$环烷基。在另一个实施方案中为式(V)化合物，其中$R_6$为-($CH_2$)$_m$$R_{21}$，m为2，且$R_{21}$为取代或未取代的$C_6$-$C_{10}$芳基。在另一个实施方案中为式(V)化合物，其中$R_6$为-($CH_2$)$_m$$R_{21}$，m为2，且$R_{21}$为取代或未取代的苯基。在另一个实施方案中为式(V)化合物，其中R_6为-(CH_2)$_m$$R_{21}$，m为2，且$R_{21}$为取代或未取代的$C_2$-$C_7$杂芳基。在另一个实施方案中为式(V)化合物，其中$R_6$为-($CH_2$)$_m$$R_{21}$，m为2，且$R_{21}$为-OH。

[0155] 在另一个实施方案中为式(V)化合物，其中R_6为-(C(R_{14})(R_{15}))$_m$$R_{21}$，m为3，且每个$R_{14}$和$R_{15}$为H。在另一个实施方案中为式(V)化合物，其中$R_6$为-($CH_2$)$_m$$R_{21}$，m为3，且$R_{21}$为取代或未取代的$C_2$-$C_7$杂环烷基。在另一个实施方案中为式(V)化合物，其中R_6为-(CH_2)$_m$$R_{21}$，m为3，且$R_{21}$为取代或未取代的$C_3$-$C_8$环烷基。在另一个实施方案中为式(V)化合物，其中$R_6$为-($CH_2$)$_m$$R_{21}$，m为3，且$R_{21}$为取代或未取代的$C_6$-$C_{10}$芳基。在另一个实施方案中为式(V)化合物，其中$R_6$为-($CH_2$)$_m$$R_{21}$，m为3，且$R_{21}$为取代或未取代的苯基。在另一个实施方案中为式(V)化合物，其中R_6为-(CH_2)$_m$$R_{21}$，m为3，且$R_{21}$为取代或未取代的$C_2$-$C_7$杂芳基。在另一个实施方案中为式(V)化合物，其中$R_6$为-($CH_2$)$_m$$R_{21}$，m为3，且$R_{21}$为-OH。

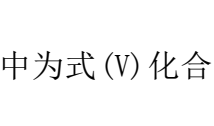
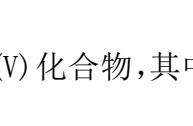
[0156] 在另一个实施方案中为式(V)化合物，其中R_6为-(C(R_{14})(R_{15}))$_m$N(R_{11})(R_{12})。在另一个实施方案中为式(V)化合物，其中R_6为-(C(R_{14})(R_{15}))$_m$N(R_{11})(R_{12})，m为2，且每个R_{14}和R_{15}为H。在另一个实施方案中为式(V)化合物，其中R_6为-(CH_2)$_m$N(R_{11})(R_{12})，m为2，且R_{11}和R_{12}各自为H。在另一个实施方案中为式(V)化合物，其中R_6为-(CH_2)$_m$N(R_{11})(R_{12})，m为2，R_{11}为取代或未取代的C_1-C_6烷基，且R_{12}为H。在另一个实施方案中为式(V)化合物，其中R_6为-(CH_2)$_m$N(R_{11})(R_{12})，m为2，R_{11}为CH_3，且R_{12}为H。在另一个实施方案中为式(V)化合物，其中R_6为-(CH_2)$_m$N(R_{11})(R_{12})，m为2，R_{11}为取代或未取代的C_1-C_6烷基，且R_{12}为取代或未取代的C_1-C_6烷基。在另一个实施方案中为式(V)化合物，其中R_6为-(CH_2)$_m$N(R_{11})(R_{12})，m为2，R_{11}为CH_3，且R_{12}为CH_3。在另一个实施方案中为式(V)化合物，其中R_6为-(CH_2)$_m$N(R_{11})(R_{12})，m为2，且R_{11}和R_{12}合起来形成5、6、7或8元杂环。在另一个实施方案中为式(V)化合物，其中R_6为-(CH_2)$_m$N(R_{11})(R_{12})，m为2，且R_{11}和R_{12}合起来形成5元杂环。在另一个实施方案中为式(V)化合物，其中R_6为-(CH_2)$_m$N(R_{11})(R_{12})，m为2，且R_{11}和R_{12}合起来形成6元杂环。

[0157] 在另一个实施方案中为式(V)化合物，其中R_6为-(C(R_{14})(R_{15}))$_m$N(R_{11})(R_{12})。在另一个实施方案中为式(V)化合物，其中R_6为-(C(R_{14})(R_{15}))$_m$N(R_{11})(R_{12})，m为3，且每个R_{14}和R_{15}为H。在另一个实施方案中为式(V)化合物，其中R_6为-(CH_2)$_m$N(R_{11})(R_{12})，m为3，且R_{11}和R_{12}各自为H。在另一个实施方案中为式(V)化合物，其中R_6为-(CH_2)$_m$N(R_{11})(R_{12})，m为3，R_{11}为取代或未取代的C_1-C_6烷基，且R_{12}为H。在另一个实施方案中为式(V)化合物，其中R_6为-(CH_2)$_m$N(R_{11})(R_{12})，m为3，R_{11}为CH_3，且R_{12}为H。在另一个实施方案中为式(V)化合物，其中R_6为-(CH_2)$_m$N(R_{11})(R_{12})，m为3，R_{11}为取代或未取代的C_1-C_6烷基，且R_{12}为取代或未取代的C_1-C_6烷基。在另一个实施方案中为式(V)化合物，其中R_6为-(CH_2)$_m$N(R_{11})(R_{12})，m为3，R_{11}为CH_3，且R_{12}为CH_3。在另一个实施方案中为式(V)化合物，其中R_6为-(CH_2)$_m$N(R_{11})(R_{12})，m为3，且R_{11}和R_{12}合

起来形成5、6、7或8元杂环。在另一个实施方案中为式(V)化合物，其中R_6为$-(CH_2)_mN(R_{11})(R_{12})$，m为3，且$R_{11}$和$R_{12}$合起来形成5元杂环。在另一个实施方案中为式(V)化合物，其中R_6为$-(CH_2)_mN(R_{11})(R_{12})$，m为3，且$R_{11}$和$R_{12}$合起来形成6元杂环。

[0158] 在另一个实施方案中为式(V)化合物，其中R_6为取代或未取代的C_2-C_7杂环烷基。在另一个实施方案中为式(V)化合物，其中R_6为  。在另一个实施方案中为式(V)化合物，其中R_6为  且J为C(H)。在另一个实施方案中为式(V)化合物，其中R_6为  J为C(H)，p为1，且q为1。在另一个实施方案中为式(V)化合物，其中R_6为  ，  J为C(H)，p为2，且q为1。在另一个实施方案中为式(V)化合物，其中R_6为  ，  J为C(H)，p为3，且q为1。在另一个实施方案中为式(V)化合物，其中R_6为  ，  J为C(H)，p为2，且q为2。在另一个实施方案中为式(V)化合物，其中R_6为  ，  J为C(H)，p为1，q为1，且R_{13}为取代或未取代的C_1-C_6烷基。在另一个实施方案中为式(V)化合物，其中R_6为  ，J为C(H)，p为2，q为1，且R_{13}为取代或未取代的C_1-C_6烷基。在另一个实施方案中为式(V)化合物，其中R_6为  ，J为C(H)，p为3，q为1，且R_{13}为取代或未取代的C_1-C_6烷基。在另一个实施方案中为式(V)化合物，其中R_6为，J为C(H)，p为2，q为2，且R_{13}为取代或未取代的C_1-C_6烷基。

[0159] 在另一个实施方案中为式(V)化合物，其中R_6为且J为N。在另一个实

施方案中为式(V)化合物，其中R_6为  ，J为N，p为2，且q为2。在另一个实施方案中为式(V)化合物，其中R_6为  ，J为N，p为2，q为2，且R_{13}为取代或未取代的C_1-C_6烷基。

[0160] 在另一个实施方案中为式(V)化合物，其中R_5为卤素。在另一个实施方案中为式(V)化合物，其中R_5为-CF_3。在另一个实施方案中为式(V)化合物，其中R_5为未取代的C_1-C_6烷基。在另一个实施方案中为式(V)化合物，其中R_5为-CH_3。在另一个实施方案中为式(V)化合物，其中R_5为-CH_2CH_3。在另一个实施方案中为式(V)化合物，其中R_5为取代或未取代的C_1-C_6杂烷基。在另一个实施方案中为式(V)化合物，其中R_5为取代或未取代的C_2-C_7杂环烷基。在另一个实施方案中为式(V)化合物，其中R_5为取代或未取代的C_3-C_8环烷基。在另一个实施方案中为式(V)化合物，其中R_5为取代或未取代的C_6-C_{10}芳基。在另一个实施方案中为式(V)化合物，其中R_5为取代或未取代的C_2-C_7杂芳基。

[0161] 在另一个实施方案中为式(V)化合物，其中R_2和R_3各自独立地为H、-CN、C_1-C_4烷基、C_3-C_6环烷基或C_2-C_7杂环烷基。在另一个实施方案中为式(V)化合物，其中R_2和R_3各自为H。

[0162] 在另一个实施方案中为式(V)化合物，其中R_2和R_3各自独立地为H、-CN、C_1-C_4烷基、C_3-C_6环烷基或C_2-C_7杂环烷基；且R_2和R_3中的至少一个不是H。在另一个实施方案中为式(V)化合物，其中R_2为H，且R_3为C_1-C_4烷基。在另一个实施方案中为式(V)化合物，其中R_2为H，且R_3为CH_3。在另一个实施方案中为式(V)化合物，其中R_2为H，且R_3为C_3-C_6环烷基。在另一个实施方案中为式(V)化合物，其中R_2为H，且R_3为环丙基。在另一个实施方案中为式(V)化合物，其中R_2为H，且R_3为环戊基。在另一个实施方案中为式(V)化合物，其中R_2为CH_3，且R_3为CH_3。在另一个实施方案中为式(V)化合物，其中R_2为C_1-C_4烷基，且R_3为H。在另一个实施方案中为式(V)化合物，其中R_2为CH_3，且R_3为H。在另一个实施方案中为式(V)化合物，其中R_2为C_3-C_6环烷基，且R_3为H。在另一个实施方案中为式(V)化合物，其中R_2为环丙基，且R_3为H。在另一个实施方案中为式(V)化合物，其中R_2为环戊基，且R_3为H。

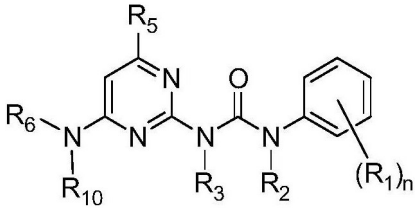
[0163] 在另一个实施方案中为式(V)化合物，其中R_2和R_3合起来形成5元或6元杂环。在另一个实施方案中为式(V)化合物，其中R_2和R_3合起来形成5元杂环。在另一个实施方案中为式(V)化合物，其中R_2和R_3合起来形成6元杂环。

[0164] 在另一个实施方案中为式(V)化合物，其中n为0。

[0165] 在另一个实施方案中为式(V)化合物，其中每个R_1独立地为卤素、-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、-$N(R_8)_2$、-$C(=O)N(R_8)_2$、-$N(R_8)C(=O)R_9$、取代或未取代的C_1-C_6烷基、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基。在另一个实施方案中为式(V)化合物，其中每个R_1独立地为卤素、-CN、-OH、-CF_3、取代或未取代的C_1-C_6烷基、或取代或未取代的C_1-C_6烷氧基。在另一个实施方案中为式(V)化合物，其中每个R_1独立地为卤素、-CN、-OCF_3、-OCH_2F、-OCF_2H、-CF_3、取代或未取代的C_1-C_6烷基、取代或未

取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基。在另一个实施方案中为式(V)化合物，其中每个R_1独立地为卤素、-CN、$-OCF_3$、$-OCH_2F$、$-OCF_2H$、$-CF_3$、取代或未取代的C_1-C_6烷基、或取代或未取代的C_1-C_6烷氧基。在另一个实施方案中为式(V)化合物，其中每个R_1独立地为卤素、-CN、$-OCF_3$、$-OCH_2F$、$-OCF_2H$、$-CF_3$、取代或未取代的C_1-C_6烷基、或取代或未取代的C_1-C_6烷氧基，且n为3。在另一个实施方案中为式(V)化合物，其中每个R_1独立地为卤素、-CN、$-OCF_3$、$-OCH_2F$、$-OCF_2H$、$-CF_3$、取代或未取代的C_1-C_6烷基、或取代或未取代的C_1-C_6烷氧基，且n为2。在另一个实施方案中为式(V)化合物，其中n为3，且每个R_1独立地为卤素。在另一个实施方案中为式(V)化合物，其中n为2，且每个R_1独立地为卤素。在另一个实施方案中为式(V)化合物，其中n为2，且每个R_1独立地为F或Cl。在另一个实施方案中为式(V)化合物，其中n为2，且每个R_1为F。在另一个实施方案中为式(V)化合物，其中n为2，且每个R_1独立地为Cl。在另一个实施方案中为式(V)化合物，其中n为2，且每个R_1独立地为卤素或$-CF_3$。在另一个实施方案中为式(V)化合物，其中n为2，且每个R_1独立地为F或$-CF_3$。在另一个实施方案中为式(V)化合物，其中n为2，且每个R_1独立地为Cl或$-CF_3$。在另一个实施方案中为式(V)化合物，其中n为1，且R_1为卤素。在另一个实施方案中为式(V)化合物，其中n为1，且R_1为F。在另一个实施方案中为式(V)化合物，其中n为1，且R_1为Cl。在另一个实施方案中为式(V)化合物，其中n为1，且R_1为$-CF_3$。在另一个实施方案中为式(V)化合物，其中n为1，且R_1为取代或未取代的C_1-C_6烷基。在另一个实施方案中为式(V)化合物，其中n为1，且R_1为CH_3。在另一个实施方案中为式(V)化合物，其中n为1，且R_1为取代或未取代的C_1-C_6烷氧基。在另一个实施方案中为式(V)化合物，其中n为1，且R_1为$-OCH_3$。在另一个实施方案中为式(V)化合物，其中n为1，且R_1为$-OCF_3$。在另一个实施方案中为式(V)化合物，其中n为1，且R_1为$-OCF_2H$。

[0166] 在另一方面，本文描述了式(VI)化合物，或其药学上可接受的盐、溶剂化物或前药：



式(VI)；

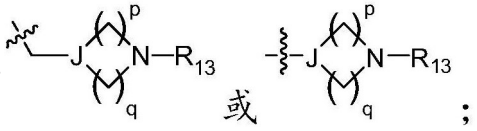
其中：

每个R_1独立地为卤素、-CN、$-NO_2$、-OH、$-OCF_3$、$-OCH_2F$、$-OCF_2H$、$-CF_3$、$-SR_8$、$-N(R_8)S(=O)_2R_9$、$-S(=O)_2N(R_8)_2$、$-S(=O)R_9$、$-S(=O)_2R_9$、$-C(=O)R_9$、$-CO_2R_8$、$-N(R_8)_2$、$-C(=O)N(R_8)_2$、$-N(R_8)C(=O)R_9$、取代或未取代的C_1-C_6烷基、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基；或者两个R_1合起来形成取代或未取代的杂环或者取代或未取代的碳环；

R_2和R_3各自独立地为H或C_1-C_4烷基；或者R_2和R_3合起来形成5元或6元杂环；

R_5为取代或未取代的C_1-C_6烷基；

R_6为未取代的C_1-C_4烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷

基、取代或未取代的C_2-C_7杂芳基、-(C(R_{14})(R_{15}))$_m$$R_{21}$、  ;

J为C(H);

R_{13}为H、取代或未取代的C_1-C_6烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的-C_1-C_4烷基C_6-C_{10}芳基、或取代或未取代的-C_1-C_4烷基C_2-C_7杂芳基;

每个R_{14}和R_{15}各自独立地为H、卤素、或取代或未取代的C_1-C_6烷基;

R_{21}为卤素、-CN、-NO_2、-OH、-OCF_3、-OCH_2F、-OCF_2H、-CF_3、-SR_{22}、-N(R_{22})S(=O)$_2$$R_{23}$、-S(=O)$_2$N($R_{22}$)$_2$、-S(=O)$R_{23}$、-S(=O)$_2$$R_{23}$、-C(=O)$R_{23}$、-$CO_2R_{22}$、-C(=O)N($R_{22}$)$_2$、-N($R_{22}$)C(=O)$R_{23}$、取代或未取代的$C_1$-$C_6$烷氧基、取代或未取代的$C_1$-$C_6$杂烷基、取代或未取代的$C_2$-$C_7$杂环烷基、或取代或未取代的$C_2$-$C_7$杂芳基;

每个R_{22}独立地为H、或取代或未取代的C_1-C_6烷基;

R_{23}为取代或未取代的C_1-C_6烷基;

每个R_8独立地为H、或取代或未取代的C_1-C_6烷基;

R_9为取代或未取代的C_1-C_6烷基;

R_{10}为H;

m为2-6;

n为0-5;

p为1-3;

q为1-3。

[0167] 在另一个实施方案中为式(VI)化合物,其中R_6为取代或未取代的C_3-C_8环烷基。在另一个实施方案中为式(VI)化合物,其中R_6为取代或未取代的环丙基。在另一个实施方案中为式(VI)化合物,其中R_6为取代或未取代的环丁基。在另一个实施方案中为式(VI)化合物,其中R_6为取代或未取代的环戊基。在另一个实施方案中为式(VI)化合物,其中R_6为取代或未取代的环己基。

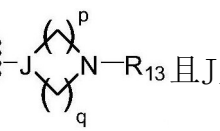
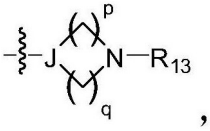
[0168] 在另一个实施方案中为式(VI)化合物,其中R_6为取代或未取代的C_2-C_7杂芳基。在另一个实施方案中为式(VI)化合物,其中R_6为取代或未取代的呋喃基、噻吩基、吡咯基、吡啶基、噁唑基、噻唑基、咪唑基、异噁唑基、异噻唑基、吡唑基、哒嗪基、嘧啶基、吡嗪基、噁二唑基、噻二唑基、三唑基、吲哚基、苯并噻吩基、苯并噁唑基、苯并噻唑基、苯并咪唑基、苯并噁二唑基、苯并噻二唑基、苯并三唑基、吡唑并吡啶基、咪唑并吡啶基、吡咯并吡啶基、吡咯并嘧啶基、吲嗪基、嘌呤基、呋喃并吡啶基、噻吩并吡啶基、呋喃并吡咯基、呋喃并呋喃基、噻吩并呋喃基、1,4-二氢吡咯并吡咯基、噻吩并吡咯基、噻吩并噻吩基、喹啉基、异喹啉基、喹喔啉基、呋喃并吡唑基、噻吩并吡唑基、硒吩基、硒唑基和苯并异噁唑基。在另一个实施方案中为式(VI)化合物,其中R_6为取代或未取代的吡啶基。在另一个实施方案中为式(VI)化合物,其中R_6为取代的吡啶基。在另一个实施方案中为式(VI)化合物,其中R_6为未取代的吡啶基。

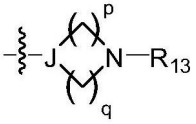
[0169] 在另一个实施方案中为式(VI)化合物,其中R_6为未取代的C_1-C_4烷基。在另一个实施方案中为式(VI)化合物,其中R_6为-CH_3。在另一个实施方案中为式(VI)化合物,其中R_6为-

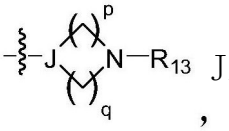
CH_2CH_3。在另一个实施方案中为式(VI)化合物，其中R_6为$-CH_2CH_2CH_3$。

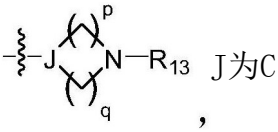
[0170] 在另一个实施方案中为式(VI)化合物，其中R_6为$-(C(R_{14})(R_{15}))_mR_{21}$。在另一个实施方案中为式(VI)化合物，其中$R_6$为$-(C(R_{14})(R_{15}))_mR_{21}$，且每个$R_{14}$和$R_{15}$为H或卤素。在另一个实施方案中为式(VI)化合物，其中R_6为$-(C(R_{14})(R_{15}))_mR_{21}$，且每个$R_{14}$和$R_{15}$为H或卤素。在另一个实施方案中为式(VI)化合物，其中R_6为$-(C(R_{14})(R_{15}))_mR_{21}$，m为2，且每个$R_{14}$和$R_{15}$为H。在另一个实施方案中为式(VI)化合物，其中$R_6$为$-(CH_2)_mR_{21}$，m为2，且$R_{21}$为取代或未取代的$C_2$-$C_7$杂环烷基。在另一个实施方案中为式(VI)化合物，其中R_6为$-(CH_2)_mR_{21}$，m为2，且R_{21}为取代或未取代的C_2-C_7杂芳基。在另一个实施方案中为式(VI)化合物，其中R_6为$-(CH_2)_mR_{21}$，m为2，且R_{21}为-OH。在另一个实施方案中为式(VI)化合物，其中R_6为$-(CH_2)_mR_{21}$，m为2，且R_{21}为$-N(R_{22})S(=O)_2R_{23}$。在另一个实施方案中为式(VI)化合物，其中R_6为$-(CH_2)_mR_{21}$，m为2，且R_{21}为$-N(H)S(=O)_2CH_3$。在另一个实施方案中为式(VI)化合物，其中R_6为$-(CH_2)_mR_{21}$，m为2，且R_{21}为$-N(R_{22})C(=O)R_{23}$。在另一个实施方案中为式(VI)化合物，其中R_6为$-(CH_2)_mR_{21}$，m为2，且R_{21}为$-N(H)C(=O)CH_3$。在另一个实施方案中为式(VI)化合物，其中R_6为$-(CH_2)_mR_{21}$，m为2，且R_{21}为$-C(=O)N(R_{22})_2$。在另一个实施方案中为式(VI)化合物，其中R_6为$-(CH_2)_mR_{21}$，m为2，且R_{21}为$-C(=O)NH_2$。在另一个实施方案中为式(VI)化合物，其中R_6为$-(CH_2)_mR_{21}$，m为2，且R_{21}为$-CO_2R_{22}$。在另一个实施方案中为式(VI)化合物，其中R_6为$-(CH_2)_mR_{21}$，m为2，且R_{21}为$-CO_2Et$。

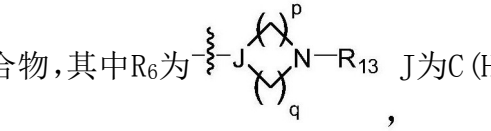
[0171] 在另一个实施方案中为式(VI)化合物，其中R_6为$-(C(R_{14})(R_{15}))_mR_{21}$，m为3，且每个$R_{14}$和$R_{15}$为H。在另一个实施方案中为式(VI)化合物，其中$R_6$为$-(CH_2)_mR_{21}$，m为3，且$R_{21}$为取代或未取代的$C_2$-$C_7$杂环烷基。在另一个实施方案中为式(VI)化合物，其中R_6为$-(CH_2)_mR_{21}$，m为3，且R_{21}为取代或未取代的C_3-C_8环烷基。在另一个实施方案中为式(VI)化合物，其中R_6为$-(CH_2)_mR_{21}$，m为3，且R_{21}为取代的C_6-C_{10}芳基。在另一个实施方案中为式(VI)化合物，其中R_6为$-(CH_2)_mR_{21}$，m为3，且R_{21}为取代的苯基。在另一个实施方案中为式(VI)化合物，其中R_6为$-(CH_2)_mR_{21}$，m为3，且R_{21}为取代或未取代的C_2-C_7杂芳基。在另一个实施方案中为式(VI)化合物，其中R_6为$-(CH_2)_mR_{21}$，m为3，且R_{21}为-OH。在另一个实施方案中为式(VI)化合物，其中R_6为$-(CH_2)_mR_{21}$，m为3，且R_{21}为$-N(R_{22})S(=O)_2R_{23}$。在另一个实施方案中为式(VI)化合物，其中R_6为$-(CH_2)_mR_{21}$，m为3，且R_{21}为$-N(H)S(=O)_2CH_3$。在另一个实施方案中为式(VI)化合物，其中R_6为$-(CH_2)_mR_{21}$，m为3，且R_{21}为$-N(R_{22})C(=O)R_{23}$。在另一个实施方案中为式(VI)化合物，其中R_6为$-(CH_2)_mR_{21}$，m为3，且R_{21}为$-N(H)C(=O)CH_3$。在另一个实施方案中为式(VI)化合物，其中R_6为$-(CH_2)_mR_{21}$，m为3，且R_{21}为$-C(=O)N(R_{22})_2$。在另一个实施方案中为式(VI)化合物，其中R_6为$-(CH_2)_mR_{21}$，m为3，且R_{21}为$-C(=O)NH_2$。在另一个实施方案中为式(VI)化合物，其中R_6为$-(CH_2)_mR_{21}$，m为3，且R_{21}为$-CO_2R_{22}$。在另一个实施方案中为式(VI)化合物，其中R_6为$-(CH_2)_mR_{21}$，m为3，且R_{21}为$-CO_2Et$。

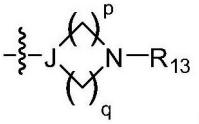
[0172] 在另一个实施方案中为式(VI)化合物，其中R_6为取代或未取代的C_2-C_7杂环烷基。在另一个实施方案中为式(VI)化合物，其中R_6为  且J为C(H)。在另一个实施方案中为式(VI)化合物，其中R_6为  ，J为C(H)，p为1，且q为1。在另一个实施方案，

中为式(VI)化合物，其中R_6为  J为C(H)，p为2，且q为1。在另一个实施方案中，

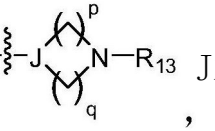
为式(VI)化合物，其中R_6为  J为C(H)，p为3，且q为1。在另一个实施方案中为，

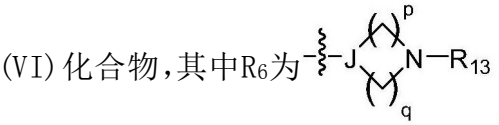
式(VI)化合物，其中R_6为  J为C(H)，p为2，且q为2。在另一个实施方案中为式，

(VI)化合物，其中R_6为  J为C(H)，p为1，q为1，且R_{13}为取代或未取代的C_1-C_6烷，

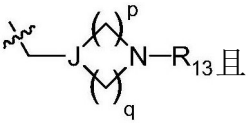
基。在另一个实施方案中为式(VI)化合物，其中R_6为  J为C(H)，p为2，q为1，且，

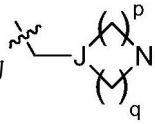
R_{13}为取代或未取代的C_1-C_6烷基。在另一个实施方案中为式(VI)化合物，其中R_6为

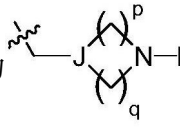
 J为C(H)，p为3，q为1，且R_{13}为取代或未取代的C_1-C_6烷基。在另一个实施方案，

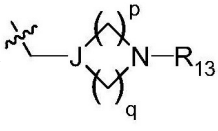
中为式(VI)化合物，其中R_6为  J为C(H)，p为2，q为2，且R_{13}为取代或未取代的，

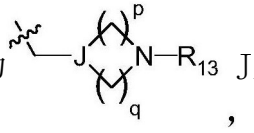
C_1-C_6烷基。

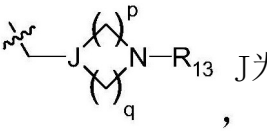
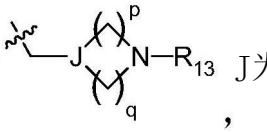
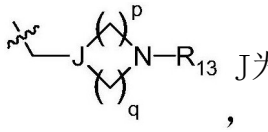
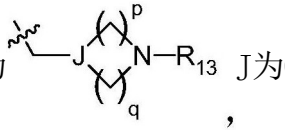
[0173] 在另一个实施方案中为式(VI)化合物，其中R_6为取代或未取代的C_2-C_7杂环烷基。在另一个实施方案中为式(VI)化合物，其中R_6为  且J为C(H)。在另一个实施

方案中为式(VI)化合物，其中R_6为  J为C(H)，p为1，且q为1。在另一个实施方，

案中为式(VI)化合物，其中R_6为  J为C(H)，p为2，且q为1。在另一个实施方案，

中为式(VI)化合物，其中R_6为  J为C(H)，p为3，且q为1。在另一个实施方案中，

为式(VI)化合物，其中R_6为  J为C(H)，p为2，且q为2。在另一个实施方案中为，

式(VI)化合物，其中R_6为  ，J为C(H)，p为1，q为1，且R_{13}为取代或未取代的C_1-C_6烷基。在另一个实施方案中为式(VI)化合物，其中R_6为  ，J为C(H)，p为2，q为1，且R_{13}为取代或未取代的C_1-C_6烷基。在另一个实施方案中为式(VI)化合物，其中R_6为  ，J为C(H)，p为3，q为1，且R_{13}为取代或未取代的C_1-C_6烷基。在另一个实施方案中为式(VI)化合物，其中R_6为  ，J为C(H)，p为2，q为2，且R_{13}为取代或未取代的C_1-C_6烷基。

[0174] 在另一个实施方案中为式(VI)化合物，其中R_5为取代的C_1-C_6烷基。在另一个实施方案中为式(VI)化合物，其中R_5为未取代的C_1-C_6烷基。在另一个实施方案中为式(VI)化合物，其中R_5为未取代的-CH_3。在另一个实施方案中为式(VI)化合物，其中R_5为未取代的-CH_2CH_3。

[0175] 在另一个实施方案中为式(VI)化合物，其中R_2和R_3各自为H。在另一个实施方案中为式(VI)化合物，其中R_2和R_3各自独立地为H或C_1-C_4烷基；且R_2和R_3中的至少一个不是H。在另一个实施方案中为式(VI)化合物，其中R_2为H，且R_3为C_1-C_4烷基。在另一个实施方案中为式(VI)化合物，其中R_2为H，且R_3为CH_3。在另一个实施方案中为式(VI)化合物，其中R_2为CH_3，且R_3为CH_3。在另一个实施方案中为式(VI)化合物，其中R_2为C_1-C_4烷基，且R_3为H。在另一个实施方案中为式(VI)化合物，其中R_2为CH_3，且R_3为H。

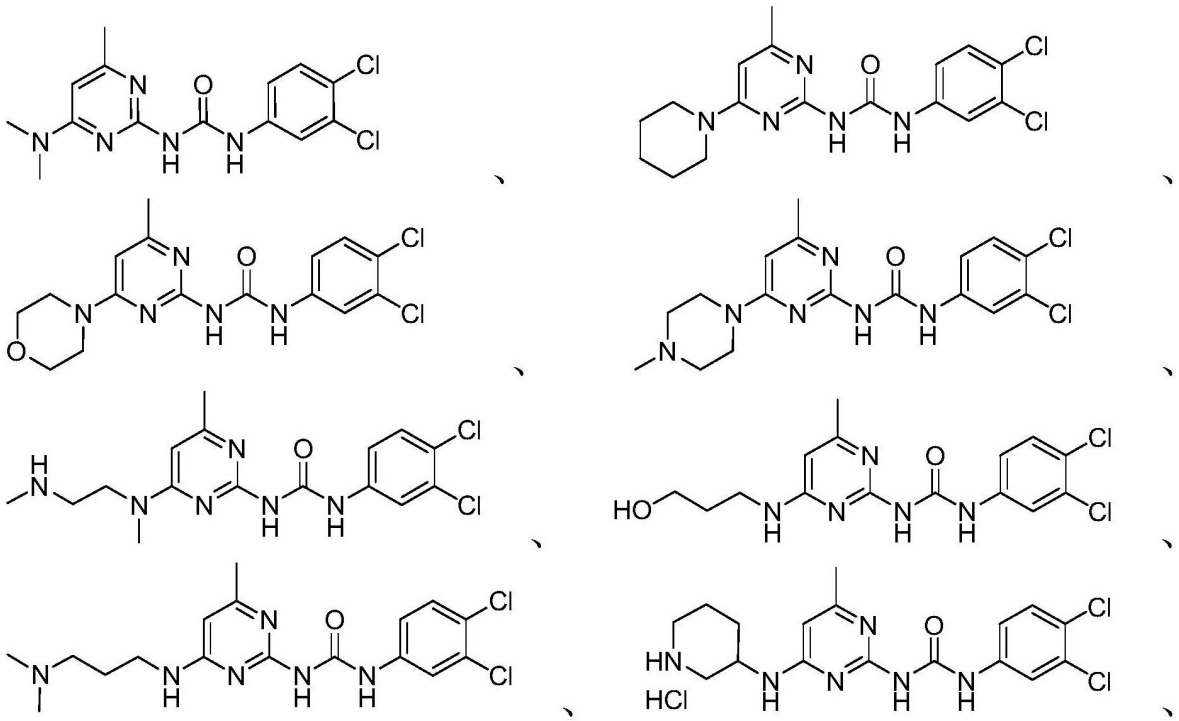
[0176] 在另一个实施方案中为式(VI)化合物，其中R_2和R_3合起来形成5元或6元杂环。在另一个实施方案中为式(VI)化合物，其中R_2和R_3合起来形成5元杂环。在另一个实施方案中为式(VI)化合物，其中R_2和R_3合起来形成6元杂环。

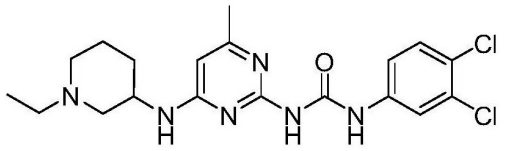
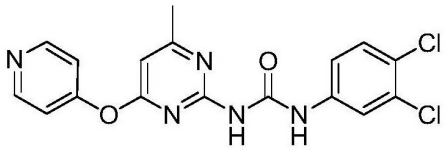
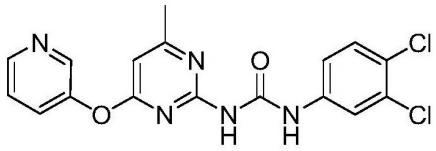
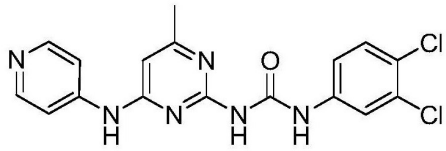
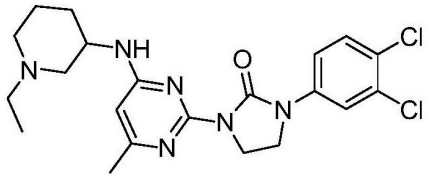
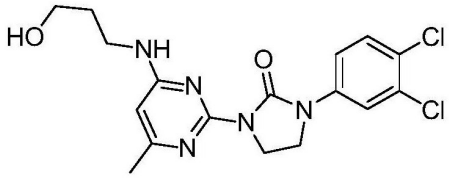
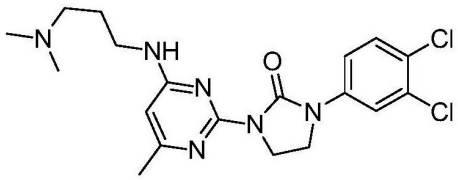
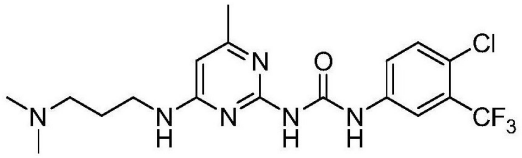
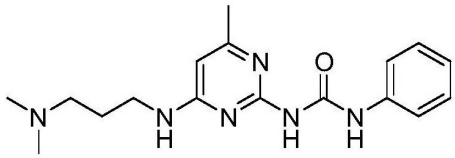
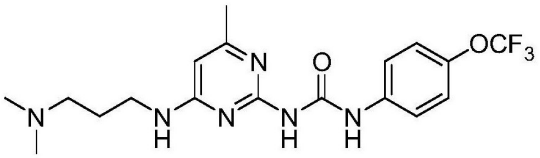
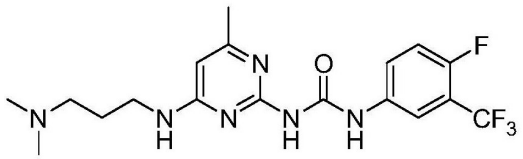
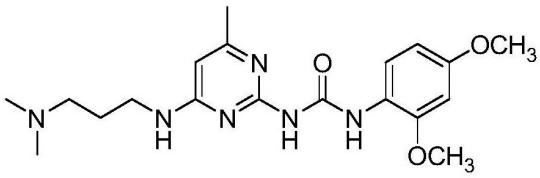
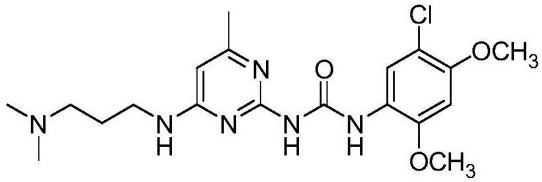
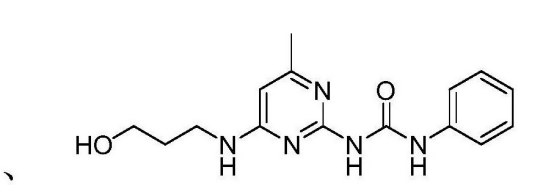
[0177] 在另一个实施方案中为式(VI)化合物，其中n为0。

[0178] 在另一个实施方案中为式(VI)化合物，其中每个R_1独立地为卤素、-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、-$N(R_8)_2$、-$C(=O)N(R_8)_2$、-$N(R_8)C(=O)R_9$、取代或未取代的C_1-C_6烷基、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基。在另一个实施方案中为式(VI)化合物，其中每个R_1独立地为卤素、-CN、-OH、取代或未取代的C_1-C_6烷基、或取代或未取代的C_1-C_6烷氧基。在另一个实施方案中为式(VI)化合物，其中每个R_1独立地为卤素、-CN、-OCF_3、-OCH_2F、-OCF_2H、取代或未取代的C_1-C_6烷基、取代或未取代的C_1-C_6烷氧基、取代或未取代的C_1-C_6杂烷基、取代或未取代的C_2-C_7杂环烷基、取代或未取代的C_3-C_8环烷基、取代或未取代的C_6-C_{10}芳基、或取代或未取代的C_2-C_7杂芳基。在另一个实施方案中为式(VI)化合物，其中每个R_1独立地为卤素、-CN、-OCF_3、-OCH_2F、-OCF_2H、取代或未取代的

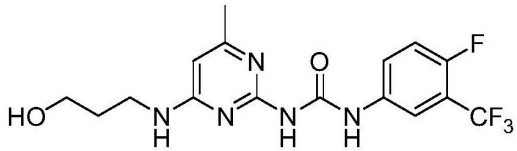
C_1-C_6烷基、或取代或未取代的C_1-C_6烷氧基。在另一个实施方案中为式(VI)化合物，其中每个R_1独立地为卤素、-CN、-OCF_3、-OCH_2F、-OCF_2H、取代或未取代的C_1-C_6烷基、或取代或未取代的C_1-C_6烷氧基，且n为3。在另一个实施方案中为式(VI)化合物，其中每个R_1独立地为卤素、-CN、-OCF_3、-OCH_2F、-OCF_2H、取代或未取代的C_1-C_6烷基、或取代或未取代的C_1-C_6烷氧基，且n为2。在另一个实施方案中为式(VI)化合物，其中n为3，且每个R_1独立地为卤素。在另一个实施方案中为式(VI)化合物，其中n为2，且每个R_1独立地为卤素。在另一个实施方案中为式(VI)化合物，其中n为2，且每个R_1独立地为F或Cl。在另一个实施方案中为式(VI)化合物，其中n为2，且一个R_1为F且一个R_1为-CF_3。在另一个实施方案中为式(VI)化合物，其中n为2，且每个R_1为F。在另一个实施方案中为式(VI)化合物，其中n为2，且每个R_1为Cl。在另一个实施方案中为式(VI)化合物，其中n为2，且一个R_1为F且一个R_1为Cl。在另一个实施方案中为式(VI)化合物，其中n为1，且R_1为卤素。在另一个实施方案中为式(VI)化合物，其中n为1，且R_1为F。在另一个实施方案中为式(VI)化合物，其中n为1，且R_1为Cl。在另一个实施方案中为式(VI)化合物，其中n为1，且R_1为取代或未取代的C_1-C_6烷基。在另一个实施方案中为式(VI)化合物，其中n为1，且R_1为CH_3。在另一个实施方案中为式(VI)化合物，其中n为1，且R_1为-CF_3。在另一个实施方案中为式(VI)化合物，其中n为1，且R_1为取代或未取代的C_1-C_6烷氧基。在另一个实施方案中为式(VI)化合物，其中n为1，且R_1为-OCH_3。在另一个实施方案中为式(VI)化合物，其中n为1，且R_1为-OCF_3。在另一个实施方案中为式(VI)化合物，其中n为1，且R_1为-OCF_2H。

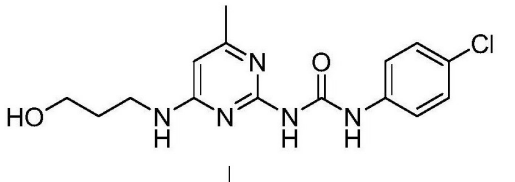
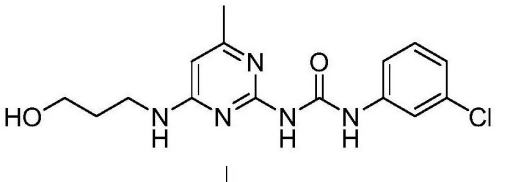
[0179] 在另一个实施方案中为选自以下的化合物：



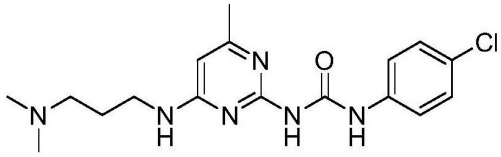
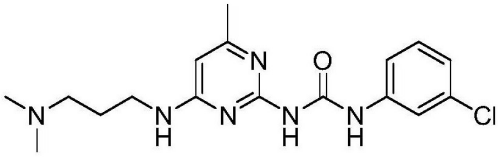

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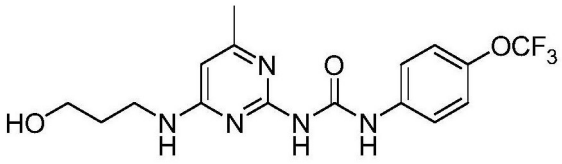
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或其药学上可接受的盐、溶剂化物或前药。

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[0180] 氘(D或^{2}H)是氢的稳定的、非放射性同位素，并且原子量为2.0144。氢作为同位素^{1}H(氢或氕)、D(^{2}H或氘)和T(^{3}H或氚)的混合物天然存在。氘的天然丰度为0.015％。通常，在含有H原子的化学化合物中，H原子实际上代表H和D的混合物，其中约0.015％为D。在一些实施方案中，本文所述的富含氘的化合物通过用氘交换质子或通过富含氘的起始材料和/或中间体来得到。

[0181] 本文考虑了上文针对各种变量描述的基团的任何组合。

[0182] 在整篇说明书中，可以选择基团及其取代基以提供稳定的部分和化合物。

化合物的其他形式

[0183] 在一些情况下，本文所述的化合物可以以非对映异构体、对映异构体或其他立体异构体形式存在。本文提供的化合物包括所有非对映异构、对映异构和差向异构的形式以及其适当的混合物。可以通过色谱法或通过形成非对映异构体并经由重结晶或色谱法或其任意组合分离来进行立体异构体的分离。(Jean Jacques,Andre Collet,Samuel H.Wilen,“Enantiomers,Racemates and Resolutions”,John Wiley And Sons,Inc.,1981，因该公开内容而通过引用并入本文)。还可通过立体选择性合成获得立体异构体。

[0184] 在某些情况下，化合物可以以互变异构体存在。所有互变异构体都被包括在本文所述的通式中。

[0185] 本文所述的方法和组合物包括无定形形式以及结晶形式(也称为多晶型物)的使用。本文所述的化合物可为药学上可接受的盐的形式。同样，具有相同类型活性的这些化合物的活性代谢物也被包括在本公开内容的范围内。此外，本文所述的化合物可以以非溶剂化形式存在以及以用药学上可接受的溶剂如水、乙醇等溶剂化的形式存在。本文示出的化合物的溶剂化形式也被认为在本文中公开。

[0186] 在一些实施方案中，本文描述的化合物可制备成前药。“前药”是指在体内转变成母体药物的药剂。前药通常是有用的，因为在一些情况下，前药可能比母体药物更容易施用。例如，它们可以通过口服给药而成为生物可用的，而母体药物则不能。前药在药物组合物中也可具有比母体药物改善的溶解度。前药的一个非限制性实例是本文所述的化合物，其作为酯(“前药”)施用以促进跨细胞膜的输送——在细胞膜中水溶性不利于移动性，但随后其一旦处于水溶性有益的细胞内，即被代谢水解成羧酸，即活性实体。前药的另一实例可为与酸基团键合的短肽(聚氨基酸)，其中该肽被代谢，从而显露出活性部分。在某些实施方案中，当在体内给药时，前药被化学转化成该化合物的生物学、药学或治疗活性形式。在某些实施方案中，前药通过一个或多个步骤或过程而被酶促代谢成该化合物的生物学、药学或治疗活性形式。

[0187] 为了产生前药，修饰药学活性的化合物，使得该活性化合物在体内施用时再生。前药可设计成改变药物的代谢稳定性或输送特性、掩饰副作用或毒性、改善药物味道或改变药物的其他特性或性质。在一些实施方案中，凭借对体内药效过程和药物代谢的了解，一旦确定了药学活性化合物，就可以设计出该化合物的前药。(参见，例如Nograd y(1985)

Medicinal Chemistry A Biochemical Approach,Oxford University Press,New York,第388-392页;Silverman(1992),The Organic Chemistry of Drug Design and Drug Action,Academic Press,Inc.,SanDiego,第352-401页,Saulnier等人(1994),Bioorganic and Medicinal Chemistry Letters,Vol.4,p.1985;Rooseboom等人,Pharmacological Reviews,56:53-102,2004;Miller等人,J.Med.Chem.Vol.46,no.24,第5097-5116页,2003;Aesop Cho,"Recent Advances in Oral Prodrug Discovery",Annual Reports in Medicinal Chemistry,Vol.41,395-407,2006)。

[0188] 本文所述的化合物的前药形式(其中该前药在体内代谢产生如本文所述的式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物)包括在权利要求书的范围内。在一些情况下,一些本文描述的化合物可为另一种衍生物或活性化合物的前药。

[0189] 前药通常是有用的,因为在一些情况下,它们可比母体药物更易于施用。例如,它们可通过口服施用而可生物利用,而母体药物则不能。前药在药物组合物中也可具有比母体药物改善的溶解度。前药可设计成可逆的药物衍生物,以用作提高药物向位点特异性组织输送的调节剂。在一些实施方案中,前药的设计增加有效水溶性。参见,例如Fedorak等人,Am.J.Physiol.,269:G210-218(1995);McLoed等人,Gastroenterol,106:405-413(1994);Hochhaus等人,Biomed.Chrom.,6:283-286(1992);J.Larsen和H.Bundgaard,Int.J.Pharmaceutics,37,87(1987);J.Larsen等人,Int.J.Pharmaceutics,47,103(1988);Sinkula等人,J.Pharm.Sci.,64:181-210(1975);T.Higuchi和V.Stella,Pro-drugs as Novel Delivery Systems,A.C.S.学术讨论会丛刊第14卷;和Edward B.Roche,Bioreversible Carriers in Drug Design,American Pharmaceutical Association and Pergamon Press,1987,全部这些公开内容均并入本文。

[0190] 本文所述化合物的芳族环部分上的位点可能易受各种代谢反应的影响,因此在芳族环结构上并入适当的取代基,仅举例来说,如卤素,可以减少、最小化或排除这个代谢途径。

[0191] 可对本文所述的化合物进行同位素(例如,用放射性同位素)标记或通过其他手段标记,包括但不限于,使用生色团或荧光部分、生物发光标签、可光活化标签或化学发光标签。

[0192] 本文所述的化合物包括同位素标记的化合物,该同位素标记的化合物与记载在本文示出的多个通式和结构中的那些相同,但事实上一个或多个原子被具有与自然界中通常发现的原子质量或质量数不同的原子质量或质量数的原子所替换。可并入所示化合物中的同位素的实例包括氢、碳、氮、氧、硫、氟和氯的同位素,例如,分别为^{2}H、^{3}H、^{13}C、^{14}C、^{15}N、^{18}O、^{17}O、^{35}S、^{18}F、^{36}Cl。某些本文所述的同位素标记的化合物,例如,其中并入了放射性同位素如^{3}H和^{14}C的那些,在药物和/或底物组织分布测定中是有用的。另外,用同位素如氘(即^{2}H)的取代可提供由更高的代谢稳定性导致的某些治疗优势,例如,延长的体内半衰期或减低的剂量要求。

[0193] 在另外的或进一步的实施方案中,本文所述的化合物当施用到有需要的生物体时被代谢,以生成代谢物,该代谢物随后用来产生所需的效果,包括所需的治疗效果。

[0194] 本文所述的化合物可形成为和/或用作药学上可接受的盐。药学上可接受的盐的类型包括但不限于:(1)通过化合物的游离碱形式与如下药学上可接受的无机酸或有机酸

反应而形成的酸加成盐，所述无机酸例如是盐酸、氢溴酸、硫酸、磷酸、偏磷酸等；所述有机酸例如是乙酸、丙酸、己酸、环戊烷丙酸、乙醇酸、丙酮酸、乳酸、丙二酸、琥珀酸、苹果酸、马来酸、富马酸、三氟乙酸、酒石酸、柠檬酸、苯甲酸、3-(4-羟基苯甲酰基)苯甲酸、肉桂酸、扁桃酸、甲磺酸、乙磺酸、1,2-乙二磺酸、2-羟基乙磺酸、苯磺酸、甲苯磺酸、2-萘磺酸、4-甲基双环-[2.2.2]辛-2-烯-1-羧酸、葡庚糖酸、4,4'-亚甲基双-(3-羟基-2-烯-1-羧酸)、3-苯基丙酸、三甲基乙酸、叔丁基乙酸、月桂基硫酸、葡糖酸、谷氨酸、羟基萘甲酸、水杨酸、硬脂酸、黏康酸、丁酸、苯乙酸、苯丁酸、丙戊酸等；(2)母体化合物中存在的酸性质子被金属离子例如碱金属离子(例如，锂、钠、钾)、碱土金属离子(例如，镁或钙)或铝离子替换时形成的盐。在一些情况下，本文所述的化合物可与诸如但不限于乙醇胺、二乙醇胺、三乙醇胺、氨丁三醇、N-甲基葡糖胺、二环己胺、三(羟甲基)甲胺的有机碱配位。在其他情况下，本文所述的化合物可与诸如但不限于精氨酸、赖氨酸等氨基酸形成盐。用于与包含酸性质子的化合物形成盐的可接受的无机碱包括但不限于氢氧化铝、氢氧化钙、氢氧化钾、碳酸钠、氢氧化钠等。

[0195] 应理解，对药学上可接受的盐的提及包括其溶剂加成形式或结晶形式，特别是溶剂化物或多晶型物。溶剂化物含有化学计量或非化学计量的量的溶剂，并且可在与药学上可接受的溶剂如水、乙醇等结晶的过程中形成。当溶剂为水时形成水合物，或当溶剂为醇时形成醇合物。可在本文所述的过程期间方便地制备或形成本文所述化合物的溶剂化物。另外，本文提供的化合物可以以非溶剂化形式以及溶剂化形式存在。通常，对于本文提供的化合物和方法而言，溶剂化形式与非溶剂化形式被视为是等同的。

[0196] 在一些实施方案中，本文所述的化合物，如式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物呈多种形式，包括但不限于，无定形形式、研磨形式和纳米颗粒形式。另外，本文所述的化合物包括结晶形式，也称为多晶型物。多晶型物包括化合物的相同元素组成的不同晶体堆积排列。多晶型物通常具有不同的X射线衍射图、熔点、密度、硬度、晶体形状、光学性质、稳定性和溶解度。诸如重结晶溶剂、结晶速率和储存温度等多种因素可导致单晶体形式占主导。

[0197] 药学上可接受的盐、多晶型物和/或溶剂化物的筛选和表征可采用包括但不限于热分析、X射线衍射、光谱法、气相吸附和显微术等多种技术来实现。热分析方法针对热化学降解或热物理过程，包括但不限于多晶型转变，并且这类方法被用于分析多晶型形式之间的关系、确定重量损失、发现玻璃化转变温度，或用于赋形剂相容性研究。这类方法包括但不限于差示扫描量热法(DSC)、调制差示扫描量热法(MDCS)、热重分析(TGA)以及热重和红外分析(TG/IR)。X射线衍射方法包括但不限于单晶和粉末衍射仪和同步加速器源。所用的多种光谱学技术包括但不限于拉曼、FTIR、UV-VIS和NMR(液态和固态)。多种显微镜技术包括但不限于偏振光显微术、具有能量色散X射线分析(EDX)的扫描电子显微术(SEM)、具有EDX的环境扫描电子显微术(在气体气氛或水蒸汽气氛中)、IR显微术和拉曼显微术。

[0198] 在整篇说明书中，可选择基团及其取代基以提供稳定的部分和化合物。

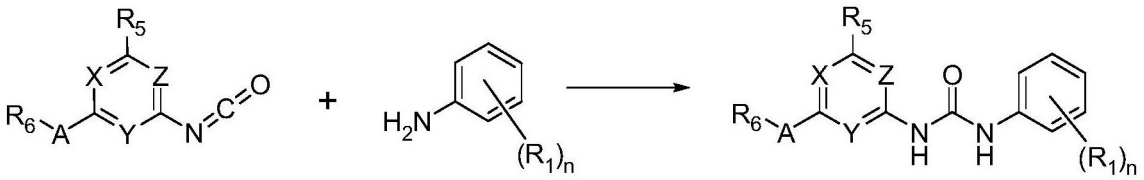
化合物的合成

[0199] 在一些实施方案中，采用化学文献中描述的手段、采用本文所述的方法或通过其组合来实现本文所述化合物的合成。另外，本文示出的溶剂、温度及其他反应条件可以变化。

[0200] 在一些实施方案中，式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或

(VI)化合物根据方案1中所示的合成路线来制备。

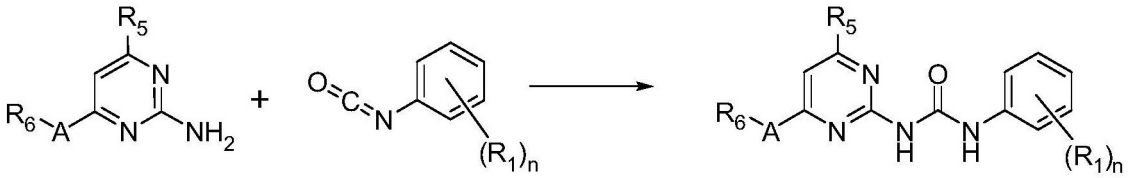
方案1



[0201] 如方案1所示,将胺加入到异氰酸酯中得到脲。

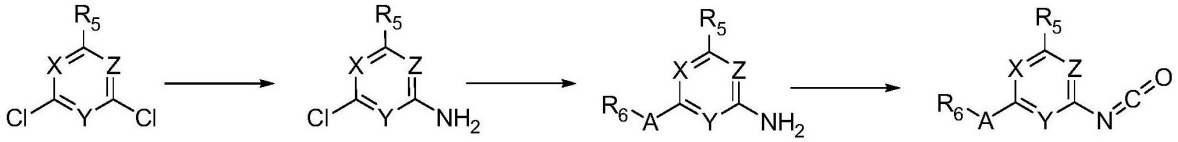
[0202] 通过类似的方案,另外的式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物如方案2所示制备。

方案2

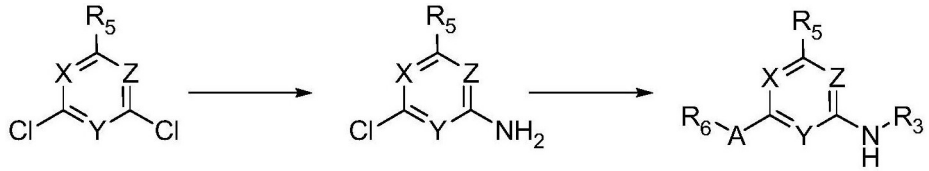


[0203] 在一些实施方案中,根据方案3-4制备异氰酸酯和胺合成中间体。

方案3:吡啶/嘧啶异氰酸酯(A=O、NR_{10})的合成



方案4:吡啶/嘧啶胺(A=O、NR_{10})的合成



[0204] 在其他实施方案中,合成或从诸如但不限于Sigma-Aldrich、FischerScientific(Fischer Chemicals)和AcrosOrganics等商业来源获得用于合成本文所述化合物的起始材料和试剂。

[0205] 在进一步的实施方案中,本文所述的化合物和具有不同取代基的其他相关化合物采用本文所述的技术和材料以及本领域中公认的技术和材料来合成,诸如例如以下文献中所述:Fieser和Fieser的Reagents for Organic Synthesis,1-17卷(John Wiley and Sons,1991);Rodd的Chemistry of Carbon Compounds,1-5卷和增刊(Elsevier Science Publishers,1989);Organic Reactions,1-40卷(John Wiley and Sons,1991),Larock的Comprehensive Organic Transformations(VCH Publishers Inc.,1989),March,Advanced Organic Chemistry第四版,(Wiley 1992);Carey和Sundberg,Advanced Organic Chemistry第四版,A和B卷(Plenum 2000,2001),以及Greene和Wuts,Protective Groups in Organic Synthesis第三版(Wiley 1999)(所有这些的公开内容都通过引用并入本文)。

某些术语

[0206] 除非另有定义,否则本文中使用的所有技术和科学术语都具有与所请求保护的主题所属的通常理解的相同含义。在本文术语有多个定义的情况下,以本节中的定义为准。本

文引用的所有专利、专利申请、出版物和公开的核苷酸和氨基酸序列(例如,可从GenBank或其他数据库中获得的序列)通过引用而并入。当引用URL或其他这样的标识符或地址时,应理解,这样的标识符可能改变,并且因特网上的具体信息可能瞬息即逝,但通过搜索因特网可以找到同等的信息。对其的引用证明了这类信息的可用性和公开传播。

[0207] 应当理解,前面的一般描述和以下的详细描述仅是示例性和解释性的,并非限制所请求保护的任何主题。在本申请中,除非另有说明,否则单数的使用包括复数。必须指出,除非上下文另有明确规定,否则如在说明书和所附权利要求中所用的,单数形式“一个”、“一种”和“该”包括复数个指示物。在本申请中,除非另有说明,否则“或”的使用表示“和/或”。此外,术语“包括”以及其他形式如“包含”和“含有”的使用并不是限制性的。

[0208] 本文使用的章节标题仅用于组织目的,不应被解释为限制所描述的主题。

[0209] 标准化学术语的定义可在参考文献中找到,包括但不限于,Carey和Sundberg“Advanced Organic Chemistry第4版”A卷(2000)和B卷(2001),Plenum Press,New York。除非另有说明,常规方法包括质谱法、NMR、HPLC、蛋白质化学、生物化学、重组DNA技术和药理学。

[0210] 除非提供了具体定义,否则结合本文所述的分析化学、合成有机化学、医药和药物化学所使用的命名法及其实验室程序和技术都是本领域公认的。标准技术可用于化学合成、化学分析、药物制备、配制和递送以及治疗患者。标准技术可用于重组DNA、寡核苷酸合成和组织培养和转化(例如,电穿孔,脂转染)。例如,反应和纯化技术可使用制造商规格的试剂盒来进行,或以如本领域通常实现的方式进行,或如本文所述进行。前述技术和程序通常可用常规方法并且如在本说明书中引用和讨论的各种一般和更具体的参考文献中所描述地进行。

[0211] 应当理解,本文所述的方法和组合物不限于本文所述的特定方法、方案、细胞系、构建体和试剂,因此这些可以变化。还应理解,本文使用的术语仅用于描述特定实施方案的目的,并非意在限制本文所述的方法、化合物、组合物的范围。

[0212] 如本文所用的,C_1-C_x包括C_1-C_2、C_1-C_3...C_1-C_x。C_1-C_x是指构成其所指部分的碳原子的数目(不包括可选的取代基)。

[0213] “烷基”基团是指脂肪烃基团。烷基基团可包括或不包括不饱和单元。烷基部分可为“饱和烷基”基团,这意味着其不含任何不饱和单元(即,碳-碳双键或碳-碳三键)。烷基基团还可为“不饱和烷基”部分,这意味着其含有至少一个不饱和单元。烷基部分,无论是饱和的还是不饱和的,均可以是支链、直链或环状的。

[0214] “烷基”基团可具有1至12个碳原子(每当其出现在本文中时,数值范围如“1至6”指代给定范围内的每个整数;例如,“1至6个碳原子”表示烷基基团可由1个碳原子、2个碳原子、3个碳原子等直到6个碳原子组成并包括6个碳原子,尽管本定义也涵盖了没有指定数值范围的术语“烷基”的存在)。本文所述化合物的烷基基团均可被指定为“C_1-C_6烷基”或类似的名称。仅举例而言,“C_1-C_6烷基”表示烷基链中有一至六个碳原子,即,该烷基链选自甲基、乙基、正丙基、异丙基、正丁基、异丁基、仲丁基、叔丁基、正戊基、异戊基、新戊基、己基、丙烯-3-基(烯丙基)、环丙基甲基、环丁基甲基、环戊基甲基、环己基甲基。烷基基团可以是取代或未取代的。根据结构,烷基基团可以是单价或二价基团(即,亚烷基基团)。

[0215] “烷氧基”是指“-O-烷基”基团,其中烷基如本文所定义。

[0216] 术语“烯基”是指这样的烷基基团类型，其中该烷基基团的前两个原子形成不是芳族基团一部分的双键。即，烯基基团从原子-C(R)＝CR_2开始，其中R指代该烯基基团的剩余部分，其可以是相同或不同的。烯基基团的非限制性实例包括-CH＝CH_2、-C(CH_3)＝CH_2、-CH＝$CHCH_3$、-CH＝C(CH_3)$_2$和-C(CH_3)＝$CHCH_3$。烯基部分可以是支链、直链或环状的(在这种情况下，其也被称为“环烯基”基团)。烯基基团可具有2至6个碳。烯基基团可以是取代或未取代的。根据结构，烯基基团可以是单价或二价基团(即，亚烯基基团)。

[0217] 术语“炔基”是指这样的烷基基团类型，其中该烷基基团的前两个原子形成三键。即，炔基基团从原子-C≡C-R开始，其中R指代该炔基基团的剩余部分。炔基基团的非限制性实例包括-C≡CH、-C≡CCH_3、-C≡CCH_2CH_3和-C≡$CCH_2CH_2CH_3$。炔基部分的“R”部分可以是支链、直链或环状的。炔基基团可具有2至6个碳。炔基基团可以是取代或未取代的。根据结构，炔基基团可以是单价或二价基团(即，亚炔基基团)。

[0218] “氨基”是指-NH_2基团。

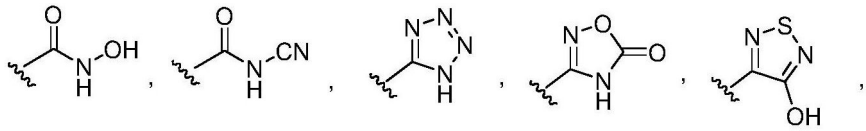
[0219] 术语“烷基胺”或“烷基氨基”是指-N(烷基)$_x$$H_y$基团，其中烷基如本文所定义，并且x和y选自x＝1，y＝1和x＝2，y＝0。当x＝2时，烷基基团连同它们附接的氮一起可任选地形成环状环系。“二烷基氨基”是指-N(烷基)$_2$基团，其中烷基如本文所定义。

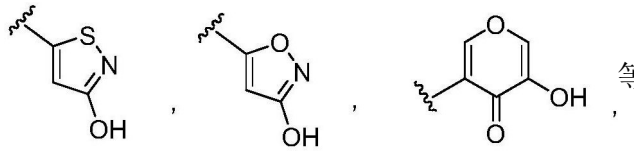
[0220] 术语“芳族”是指具有包含4n+2个π电子的离域π电子体系的平面环，其中n为整数。芳族环可由五、六、七、八、九个或多于九个原子形成。芳族化合物可任选地被取代。术语“芳族”即包括芳基基团(例如，苯基，萘基)又包括杂芳基基团(例如，吡啶基，喹啉基)。

[0221] 如本文所用的，术语“芳基”是指其中构成环的每个原子均为碳原子的芳族环。芳环可以由五、六、七、八、九个或多于九个碳原子形成。芳基基团可任选地被取代。芳基基团的实例包括但不限于苯基和萘基。根据结构，芳基基团可以是单价或二价基团(即，亚芳基基团)。

[0222] 术语“碳环”是指其中构成该环的每个原子均为碳原子的环。碳环可以是芳基或环烷基。

[0223] “羧基”是指-CO_2H。在一些实施方案中，羧基部分可被“羧酸生物电子等排体”替代，“羧酸生物电子等排体”是指表现出与羧酸部分类似的物理和/或化学性质的官能团或部分。羧酸生物电子等排体具有与羧酸基团类似的生物学性质。具有羧酸部分的化合物可具有与羧酸生物电子等排体交换的羧酸部分，并且具有与含羧酸的化合物相比类似的物理和/或生物学性质。例如，在一个实施方案中，羧酸生物电子等排体将在生理学pH下电离至与羧酸基团大致相同的程度。羧酸的生物电子等排体的实例包括但不限于

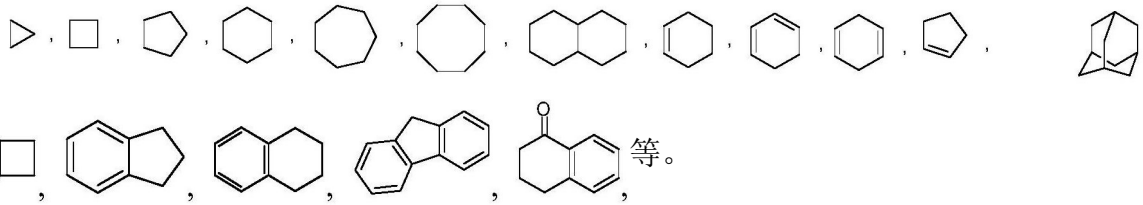




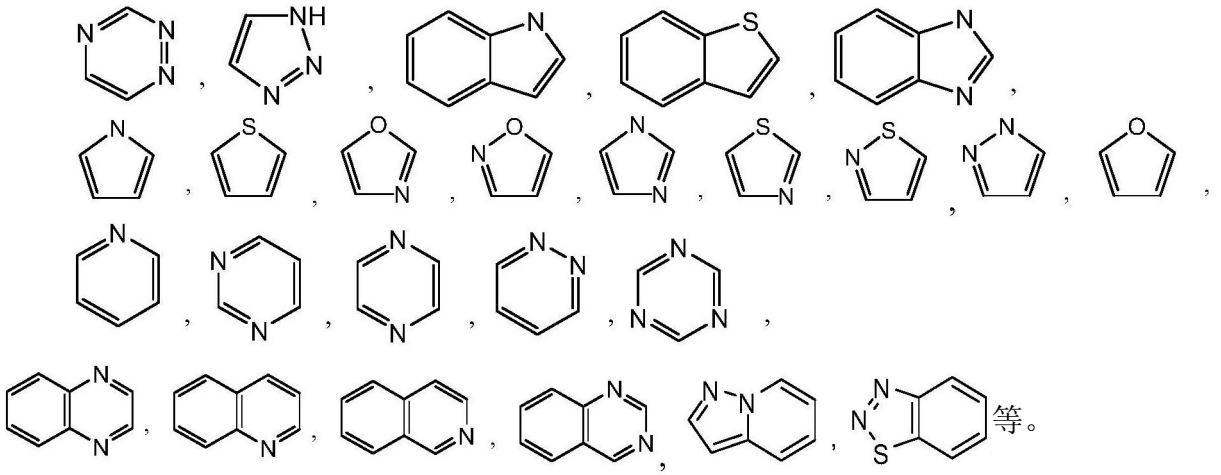
等。

[0224] 术语“环烷基”是指单环或多环非芳族基团，其中构成环的每个原子(即，骨架原子)均为碳原子。环烷基可以是饱和或部分不饱和的。环烷基可与芳族环稠合(在这种情况下，环烷基通过非芳族环碳原子键合)。环烷基基团包括具有3至10个环原子的基团。环烷基

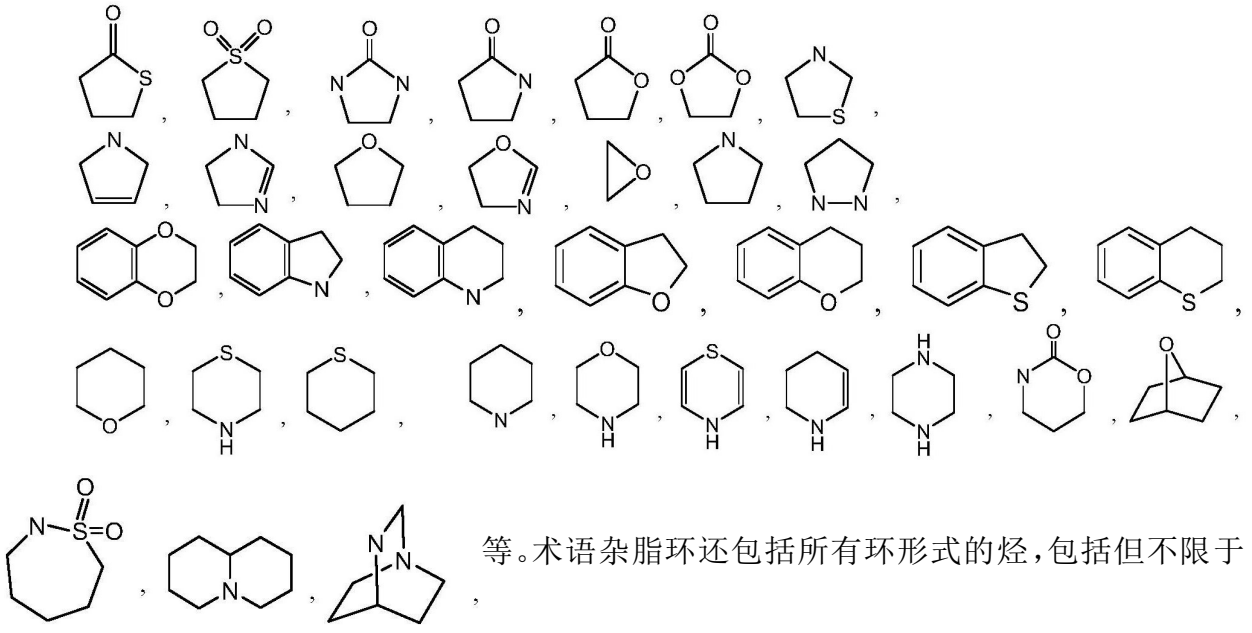
基团的说明性实例包括但不限于以下部分：



[0225] 术语“杂芳基”或“杂芳族”是指包含一个或多个选自氮、氧和硫的环杂原子的芳基。含N的“杂芳族”或“杂芳基”部分是指其中该环的至少一个骨架原子为氮原子的芳族基团。多环杂芳基基团可以是稠合或非稠合的。杂芳基基团的说明性实例包括以下部分：



[0226] “杂环烷基”基团或“杂脂环”基团是指其中至少一个骨架环原子为选自氮、氧和硫的杂原子的环烷基基团。该基团可与芳基或杂芳基稠合。也被称为非芳族杂环的杂环烷基基团的说明性实例包括：



单糖、二糖和寡糖。除非另有说明，杂环烷基在环中具有2至10个碳。应当理解，当提及杂环烷基中的碳原子数时，该杂环烷基中的碳原子数不同于构成该杂环烷基(即，该杂环烷基环的骨架原子)的总原子数(包括杂原子)。

[0227] 术语“杂环”是指其中至少一个骨架环原子为选自氮、氧和硫的杂原子的环。杂环

可以是杂芳基或杂环烷基。

[0228] 术语“卤代”或“卤素”表示氟、氯、溴和碘。

[0229] 术语“卤代烷基”是指被一个或多个卤素取代的烷基基团。卤素可能相同或可能不同。卤代烷基的非限制性实例包括-CH_2Cl、-CF_3、-CHF_2、-CH_2CF_3、-CF_2CF_3、-$CF(CH_3)_2$等。

[0230] 术语“氟烷基”和“氟烷氧基”分别包括被一个或多个氟原子取代的烷基和烷氧基基团。氟烷基的非限制性实例包括-CF_3、-CHF_2、-CH_2F、-CH_2CF_3、-CF_2CF_3、-$CF_2CF_2CF_3$、-$CF(CH_3)_3$等。氟烷氧基基团的非限制性实例包括-OCF_3、-$OCHF_2$、-OCH_2F、-OCH_2CF_3、-OCF_2CF_3、-$OCF_2CF_2CF_3$、-$OCF(CH_3)_2$等。

[0231] 术语“杂烷基”是指这样的烷基基团，其中一个或多个骨架链原子选自除了碳以外的原子，例如，氧、氮、硫、磷、硅或它们的组合。杂原子可位于杂烷基基团的任何内部位置。实例包括但不限于-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和-CH＝CH-N(CH_3)-CH_3。另外，最多两个杂原子可以是连续的，如举例而言，-CH_2-NH-OCH_3和-CH_2-O-Si(CH_3)$_3$。除了杂原子数目之外，“杂烷基”可具有1至6个碳原子。

[0232] 术语“键”或“单键”是指两个原子或(当通过键连接的原子被认为是较大子结构的一部分时)两个部分之间的化学键。

[0233] 术语“部分”是指分子的特定区段或官能团。化学部分通常是嵌入分子中或附加于分子上的识别到的化学实体。

[0234] 如本文所用的，自己出现并且没有数字表示的取代基“R”是指选自烷基、卤代烷基、杂烷基、烯基、环烷基、芳基、杂芳基(通过环碳键合的)和杂环烷基的取代基。

[0235] 术语“任选取代的”或“取代的”是指所提到的基团可被一个或多个另外的基团取代，该一个或多个另外的基团单独且独立地选自烷基、环烷基、芳基、杂芳基、杂环烷基、-OH、烷氧基、芳氧基、烷基硫基、芳基硫基、烷基亚砜、芳基亚砜、烷基砜、芳基砜、-CN、炔、C_1-C_6烷基炔、卤代、酰基、酰氧基、-CO_2H、-CO_2-烷基、硝基、卤代烷基、氟烷基以及氨基，包括单取代和二取代的氨基基团(例如-NH_2、-NHR、-N(R)$_2$)及其被保护的衍生物。举例而言，可选的取代基可以是L^sR^s，其中每个L^s独立地选自键、-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_6烷基)-或-(C_2-C_6烯基)-；并且每个R^s独立地选自H、(C_1-C_6烷基)、(C_3-C_8环烷基)、芳基、杂芳基、杂环烷基和C_1-C_6杂烷基。可以形成上述取代基的保护性衍生物的保护基团可以在例如上述Greene和Wuts等资源中找到。

[0236] 本文所述的方法和制剂包括使用具有式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)结构的化合物的结晶形式(也称为多晶型物)或药学上可接受的盐，以及具有相同类型活性的这些化合物的活性代谢物。在某些情况下，化合物可以以互变异构体存在。所有互变异构体都被包括在本文所示化合物的范围内。此外，本文所述的化合物可以以非溶剂化形式存在，以及以用药学上可接受的溶剂如水、乙醇等溶剂化的形式存在。本文示出的化合物的溶剂化形式也被认为在本文中公开。

[0237] 术语“药剂盒”和“制品”作为同义词使用。

[0238] 术语“受试者”或“患者”包括哺乳动物和非哺乳动物。哺乳动物的实例包括但不限

于哺乳动物纲的任何成员:人、非人灵长类动物如黑猩猩及其他猿类和猴物种;农场动物如牛、马、绵羊、山羊、猪;家养动物如兔、狗和猫;实验动物,包括啮齿动物如大鼠、小鼠和豚鼠,等等。非哺乳动物的实例包括但不限于鸟类、鱼类等。在本文提供的方法和组合物的一个实施方案中,哺乳动物为人。

[0239] 术语"疾病"或"状况"是指能够用本文提供的化合物或方法治疗的患者或受试者的身体状况或健康状态。在实施方案中,该疾病是与Olig2或异常Olig2活性相关的(例如,引起的)疾病(例如脑癌、多形性胶质母细胞瘤、髓母细胞瘤、星形细胞瘤、脑干胶质瘤、脑膜瘤、少突神经胶质瘤、黑素瘤、肺癌、乳腺癌、白血病或唐氏综合征)。疾病、病症或状况的实例包括但不限于脑癌、多形性胶质母细胞瘤、髓母细胞瘤、星形细胞瘤、脑干胶质瘤、脑膜瘤、少突神经胶质瘤、黑素瘤、肺癌、乳腺癌、白血病、唐氏综合征、结直肠癌、乳头状甲状腺癌、肝细胞癌、阿尔茨海默病、帕金森病、亨廷顿病、额颞叶痴呆、克罗伊茨费尔特-雅各布病(Creutzfeldt-Jakob disease)、Gerstmann-Sträussler-Scheinker综合征、朊病毒病、神经变性疾病、癌症、心血管疾病、高血压、X综合征、抑郁症、焦虑症、青光眼、人免疫缺陷病毒(HIV)或获得性免疫缺陷综合征(AIDS)、神经变性、阿尔茨海默病、帕金森病、认知增强、库欣综合征、阿狄森病、骨质疏松症、虚弱、肌肉脆弱、炎症性疾病、骨关节炎、类风湿性关节炎、哮喘和鼻炎、肾上腺功能相关疾病、病毒感染、免疫缺陷、免疫调节、自身免疫性疾病、变态反应、伤口愈合、强迫行为、多药耐药性、成瘾、精神病、厌食症、恶病质、创伤后应激综合征、术后骨折、医学分解代谢、主要精神病性抑郁症、轻度认知障碍、精神病、痴呆、高血糖症、应激障碍、抗精神病药诱发的体重增加、精神错乱、抑郁症患者的认知损害、唐氏综合征患者的认知恶化、与干扰素-α治疗相关的精神病、慢性疼痛、与胃食管返流疾病有关的疼痛、产后精神病、产后抑郁症、早产儿神经性障碍、偏头痛、中风、动脉瘤、大脑动脉瘤、脑动脉瘤、脑发作(brain attack)、脑血管意外、局部缺血、血栓形成、动脉栓塞、出血、短暂性脑缺血发作、贫血、栓塞、全身性灌注不足、静脉血栓形成、关节炎、再灌注损伤、皮肤疾病或状况、痤疮、寻常痤疮、急性毛发角化病、前髓细胞性白血病、秃发、红斑痤疮、丑角样鱼鳞病、着色性干皮病、角化病、神经母细胞瘤、渐进性骨化性纤维发育不良、湿疹、酒渣鼻、光损伤、皱纹或美容性状况。在一些情况下,"疾病"或"状况"是指癌症。在另外一些情况下,"癌症"是指人类癌症和癌、肉瘤、腺癌、淋巴瘤、白血病等,包括实体瘤和淋巴癌、肾癌、乳腺癌、肺癌、膀胱癌、结肠癌、卵巢癌、前列腺癌、胰腺癌、胃癌、脑癌、头颈癌、皮肤癌、子宫癌、睾丸癌、神经胶质瘤、食道癌和肝癌,包括肝癌、淋巴瘤、包括B型急性淋巴母细胞性淋巴瘤、非霍奇金淋巴瘤(例如,伯基特、小细胞和大细胞淋巴瘤)、霍奇金淋巴瘤、白血病(包括AML、ALL和CML)或多发性骨髓瘤。

[0240] 如本文所用的,术语"癌症"是指在哺乳动物中发现的所有类型的癌症、赘生物或恶性肿瘤,包括白血病、癌和肉瘤。可以用本文提供的化合物或方法治疗的示例性癌症包括甲状腺癌、内分泌系统癌、脑癌、乳腺癌、子宫颈癌、结肠癌、头颈癌、肝癌、肾癌、肺癌、非小细胞肺癌、黑素瘤、间皮瘤、卵巢癌、肉瘤、胃癌、子宫癌或髓母细胞瘤。其他实例包括霍奇金病、非霍奇金淋巴瘤、多发性骨髓瘤、神经母细胞瘤、神经胶质瘤、多形性胶质母细胞瘤、卵巢癌、横纹肌肉瘤、原发性血小板增多症、原发性巨球蛋白血症、原发性脑瘤、癌症、恶性胰腺胰岛素瘤、恶性类癌、膀胱癌、恶变前皮肤病损、睾丸癌、淋巴瘤、甲状腺癌、神经母细胞瘤、食道癌、泌尿生殖道癌、恶性高钙血症、子宫内膜癌、肾上腺皮质癌、内分泌或外分泌性

胰腺肿瘤、甲状腺髓样癌、髓样甲状腺癌、黑素瘤、结直肠癌、乳头状甲状腺癌、肝细胞癌或前列腺癌。

[0241] 术语“白血病”泛指造血器官的进行性、恶性疾病，并且通常其特征在于血液和骨髓中白细胞及其前体的变形增殖和发育。通常基于以下标准对白血病进行临床分类：(1)急性或慢性疾病的持续时间和性质；(2)涉及的细胞类型；髓样(骨髓原性)、淋巴样(淋巴原性)或单核细胞性；以及(3)白血病或白细胞缺乏(亚白血病)血液中异常细胞数的增加或不增加。可以用本文提供的化合物或方法治疗的示例性白血病包括，例如急性非淋巴细胞白血病、慢性淋巴细胞白血病、急性粒细胞性白血病、慢性粒细胞性白血病、急性早幼粒细胞白血病、成人T细胞白血病、白细胞不增多性白血病、白血性白血病(leukocythemic leukemia)、嗜碱细胞性白血病、母细胞性白血病、牛白血病、慢性髓细胞性白血病、皮肤白血病、干细胞性白血病、嗜酸性白血病、格罗斯白血病、毛细胞白血病、成血细胞白血病、成血细胞性白血病、组织细胞性白血病、干细胞白血病、急性单核细胞白血病、白细胞减少性白血病、淋巴性白血病、淋巴母细胞性白血病、淋巴细胞白血病、淋巴原性白血病、淋巴样白血病、淋巴肉瘤细胞性白血病、肥大细胞白血病、巨核细胞白血病、小原粒型白血病、单核细胞性白血病、成髓细胞白血病、髓细胞性白血病、骨髓性粒细胞性白血病、粒单核细胞白血病、内格利白血病、血浆细胞白血病、多发性骨髓瘤、浆细胞白血病、前髓细胞性白血病、Rieder细胞性白血病、希林白血病、干细胞白血病、亚白血病性白血病或未分化细胞性白血病。

[0242] 术语“肉瘤”通常是指由诸如胚性结缔组织的物质组成的肿瘤，并且通常由嵌入纤丝状或均质物质中的紧密堆积的细胞组成。可以用本文提供的化合物或方法治疗的肉瘤包括软骨肉瘤、纤维肉瘤、淋巴肉瘤、黑素肉瘤、黏液肉瘤、骨肉瘤、Abemethy肉瘤、脂肪肉瘤、脂肉瘤、软组织腺泡状肉瘤、成釉细胞肉瘤、葡萄状肉瘤、绿色瘤、绒毛膜癌、胚胎性癌肉瘤、维尔姆斯瘤肉瘤、子宫内膜肉瘤、间质肉瘤、尤因肉瘤、筋膜肉瘤、成纤维细胞肉瘤、巨细胞肉瘤、粒细胞肉瘤、霍奇金肉瘤、皮肤特发性多发性色素沉着出血性肉瘤、B细胞免疫母细胞肉瘤、淋巴瘤、T细胞免疫母细胞肉瘤、晏森肉瘤、卡波西肉瘤、枯否细胞肉瘤、血管肉瘤、白血病性肉瘤、恶性间叶瘤肉瘤、骨周肉瘤、网状细胞肉瘤、劳斯肉瘤、浆液囊性肉瘤、滑膜肉瘤或毛细血管肉瘤(telangiectaltic sarcoma)。

[0243] 术语“黑素瘤”是指由皮肤和其他器官的黑素细胞系统引起的肿瘤。可以用本文提供的化合物或方法治疗的黑素瘤包括，例如肢端雀斑样痣黑素瘤、无黑素性黑素瘤、良性幼年型黑素瘤、Cloudman黑素瘤、S91黑素瘤、Harding-Passey黑素瘤、幼年型黑素瘤、恶性雀斑样痣黑素瘤、恶性黑色素瘤、结节性黑素瘤、甲下黑素瘤(subungal melanoma)或浅表扩散性黑素瘤。

[0244] 术语“癌”是指由上皮细胞组成的恶性新生长，其倾向于浸润周围组织并引起转移。可以用本文提供的化合物或方法来治疗的示例性癌包括，例如，甲状腺髓样癌、家族性甲状腺髓样癌、腺泡癌(acinar carcinoma)、腺泡癌(acinous carcinoma)、囊性腺样癌、腺样囊性癌、腺癌、肾上腺皮质癌、肺泡癌、肺泡细胞癌、基底细胞癌(basal cell carcinoma)、基底细胞癌(carcinoma basocellulare)、基底细胞样癌、基底鳞状细胞癌、细支气管肺泡癌、细支气管癌、支气管原癌、脑样癌、胆管细胞癌、绒毛膜癌、胶样癌、粉刺状癌、子宫体癌、筛状癌、胸廓癌、皮肤癌、柱状癌、柱状细胞癌、导管癌、硬癌、胚胎性癌、髓样

癌、表皮样癌(epiermoid carcinoma)、腺样上皮细胞癌、外植癌、溃疡性癌、纤维癌、胶样癌(gelatiniforni carcinoma)、胶状癌、巨细胞癌(giant cell carcinoma)、巨细胞癌(carcinoma gigantocellulare)、腺癌、粒层细胞癌、发母质癌、多血癌、肝细胞癌、许特尔(Hurthle)细胞癌、胶样癌、肾上腺样癌、幼稚型胚胎性癌、原位癌、表皮内癌、上皮内癌、克罗姆佩柯赫尔癌(Krompecher's carcinoma)、库尔契茨基细胞癌(Kulchitzky-cell carcinoma)、大细胞癌、豆状癌(lenticular carcinoma)、豆状癌(carcinoma lenticulare)、脂瘤癌、淋巴上皮癌、髓样癌(carcinoma medullare)、髓样癌(medullary carcinoma)、黑色素癌、软癌、粘液癌(mucinous carcinoma)、粘液癌(carcinoma muciparum)、粘液细胞癌、粘液表皮样癌、粘液癌(carcinoma mucosum)、粘液癌(mucous carcinoma)、粘液瘤样癌、鼻咽癌、燕麦细胞癌、骨化性癌、骨样癌、乳头状癌、门静脉周癌、浸润前癌、棘细胞癌、粉刺癌、肾细胞癌、贮备细胞癌、肉瘤样癌、施奈德(schneiderian)癌、硬癌、阴囊癌、印戒细胞癌、单纯癌、小细胞癌、马铃薯状癌、球状细胞癌、梭细胞癌、海绵样癌(carcinoma spongiosum)、鳞状癌、鳞状细胞癌、绳捆癌、血管扩张性癌(carcinoma telangiectaticum)、血管扩张性癌(carcinoma telangiectodes)、移形细胞癌、结节性皮癌(carcinoma tuberosum)、结节性皮癌(tuberous carcinoma)、疣状癌或绒毛状癌。

[0245] "与异常Olig2活性相关的癌症"(本文中也被称为"Olig2相关癌症")是由异常Olig2活性(例如突变的Olig2基因)引起的癌症。Olig2相关癌症可包括脑癌、多形性胶质母细胞瘤、髓母细胞瘤、星形细胞瘤、脑干胶质瘤、脑膜瘤、少突神经胶质瘤、黑素瘤、肺癌、乳腺癌、白血病、T细胞白血病。

[0246] 如本文所用的,术语"治疗"或"处理"包括缓解、缓和或改善疾病或状况症状、预防其他症状、改善或预防症状的潜在原因、抑制疾病或状况,例如,阻止疾病或状况的发展、减轻疾病或状况、致使疾病或状况消退、减轻由疾病或状况引起的病状,或预防性和/或治疗性地停止疾病或状况的症状。例如,在本文提出的某些方法中,通过减少癌症发生率和/或导致癌症缓解来成功地治疗癌症。在一些实施方案中,本文提出的某些方法通过减少唐氏综合征的发生率或减轻唐氏综合征的一种或多种症状或降低唐氏综合征的一种或多种症状的严重程度来成功地治疗唐氏综合征。

[0247] 如本文所用的,通过施用特定化合物或药物组合物来改善特定疾病、病症或状况的症状是指可归因于该化合物或组合物的施用或与之相关的严重程度的任何减轻、发作的延迟、进展的减缓或持续时间的缩短,无论是永久的还是暂时的,持续的还是短暂的。

[0248] 如本文所用的,术语"调节"指直接或间接地与靶蛋白相互作用以便改变靶蛋白的活性,仅举例而言,包括抑制靶标的活性或限制或降低靶标的活性。

[0249] 如本文所用的,术语"调节剂"是指改变靶标活性的化合物。例如,与不存在调节剂的情况下活性的量值相比,调节剂可导致靶标的某种活性的量值增大或减小。在某些实施方案中,调节剂是减小靶标的一种或多种活性的量值的抑制剂。在某些实施方案中,抑制剂完全阻止靶标的一种或多种活性。在一些实施方案中,Olig2调节剂是降低细胞内Olig2的活性的化合物。在一些实施方案中,Olig2疾病调节剂是降低与Olig2相关的疾病(例如癌症或唐氏综合征)的一种或几种症状的严重程度的化合物。

[0250] 如本文所用的,术语"靶活性"是指能够被调节剂调节的生物活性。某些示例性的靶活性包括但不限于结合亲和力、信号转导、酶活性、肿瘤生长、炎症或与炎症相关的过程,

以及与疾病或状况相关的一种或多种症状的改善。

[0251] 如本文所用的，术语Olig2活性的“抑制”或“抑制剂”是指对少突胶质细胞转录因子2活性的抑制。对于蛋白质-抑制剂相互作用，这些术语的意思是，相对于不存在抑制剂(例如Olig2抑制剂或Olig2抑制剂化合物)时蛋白质(例如Olig2，转录因子)的活性或功能，负面影响(例如降低)蛋白质的活性或功能(例如降低由Olig2调节的基因转录)。在一些实施方案中，抑制是指疾病或疾病症状的减轻。在一些实施方案中，抑制是指信号转导途径或信号传导途径活性的降低(例如，涉及Olig2的转录调节或由Olig2调节的转录的途径的减少)。因此，抑制至少部分地包括部分地或完全地阻断刺激，减少、防止或延迟激活，或灭活、脱敏或下调信号转导或酶活性或蛋白质(例如Olig2)的量。在一些实施方案中，抑制是指Olig2的抑制。

[0252] 如本文所用的，针对制剂、组合物或成分而言的术语“可接受的”是指对所治疗的受试者的总体健康没有持续的不利影响。

[0253] 如本文所用的，“药学上可接受的”是指不消除化合物的生物学活性或性质并且相对无毒的物质，如载体或稀释剂，即，该物质可施用至个体而不导致不期望的生物学效果或不以有害的方式与包含该化合物的组合物的任何组分相互作用。

[0254] 如本文所用的，术语“药物组合”是指由超过一种活性成分的混合或组合产生的产物，并且其包括活性成分的固定组合和非固定组合。术语“固定组合”指一种活性成分例如式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物和辅剂二者以单个实体或剂量的形式同时施用至患者。术语“非固定组合”指一种活性成分例如式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物和辅剂作为单独的实体同时、并行或无特定间隔时间限制地顺序施用至患者，其中这样的施用在该患者体内提供这两种化合物的有效水平。后者还适用于鸡尾酒疗法，例如，三种或更多种活性成分的施用。

[0255] 术语“药物组合物”指本文所述的式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物与其他化学组分如载体、稳定剂、稀释剂、分散剂、悬浮剂、增稠剂和/或赋形剂的混合物。药物组合物有助于化合物向生物体的施用。本领域中有多种施用化合物的技术，包括但不限于：静脉内施用、口服施用、气雾剂施用、肠胃外施用、眼科施用、肺部施用和局部施用。

[0256] 如本文所用的，术语“有效量”或“治疗有效量”是指所施用的足量的药剂或化合物，其将在一定程度上减轻所治疗疾病或状况的一种或多种症状。结果可以是疾病体征、症状或病因的减少和/或缓解，或生物系统的任何其他期望的改变。例如，用于治疗用途的“有效量”是包含本文所述式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物的组合物提供疾病症状的临床显著减轻所需的量。在任何个别情况下，合适的“有效”量均可采用诸如剂量递增研究等技术来确定。

[0257] 如本文所用的，术语“增强”是指所需效果的效力或持续时间的增加或延长。因此，关于增强治疗剂的效果，术语“增强”是指在效力或持续时间方面增加或延长其他治疗剂对系统的效果的能力。如本文所用的，“增强有效量”是指足以增强另一治疗剂在所需系统中的效果的量。

[0258] “接触”按照其一般的普通含义而使用，并且是指使至少两种不同的物质(例如化学化合物，包括生物分子，或细胞)充分接近以便发生反应、相互作用或物理接触的过程。然

而，应当理解，所得的反应产物可以直接从添加的试剂之间的反应产生，或从可在反应混合物中产生的、来自一种或多种添加试剂的中间体产生。术语“接触”可以包括使两种物质反应、相互作用或物理接触，其中这两种物质可以是本文所述的化合物和蛋白质或酶(例如Olig2)。在一些实施方案中，该蛋白质可以是Olig2。在一些实施方案中，接触包括使本文所述的化合物与参与转录的蛋白质或酶相互作用。

[0259] 如本文使用的，术语“共同施用”等意在包括选定治疗剂向单个患者的施用，并且旨在包括这样的治疗方案：其中药剂通过相同或不同的施用途径施用或在相同或不同的时间施用。

[0260] 如本文所用的，术语“赋形剂”或“载体”是指有助于将化合物并入细胞或组织中的相对无毒的化合物或药剂。

[0261] 术语“稀释剂”是指用于在递送前稀释目的化合物的化学化合物。因为稀释剂可以提供更稳定的环境，所以它们还可发用来稳定化合物。溶解在缓冲溶液中的盐(其也可提供pH控制或维持)在本领域中用作稀释剂，包括但不限于磷酸盐缓冲盐水溶液。

[0262] 本文公开的化合物的“代谢物”是化合物被代谢时所形成的该化合物的衍生物。术语“活性代谢物”是指化合物被代谢时所形成的该化合物的生物活性衍生物。如本文所用的，术语“代谢”是指特定物质被生物体改变的过程(包括但不限于水解反应和由酶催化的反应)的总和。因此，酶可使化合物产生特异性的结构改变。例如，细胞色素P450催化多种氧化和还原反应，而尿苷二磷酸葡糖醛酸转移酶催化已激活的葡糖醛酸分子转移至芳族醇、脂族醇、羧酸、胺和游离巯基基团。其他关于代谢的信息可从The Pharmacological Basis of Therapeutics，第九版，McGraw-Hill(1996)获得。本文公开的化合物的代谢物可通过向宿主施用化合物并分析来自该宿主的组织样品而鉴别，或通过将化合物与肝细胞一起体外温育并分析所得化合物而鉴别。

[0263] “生物利用度”是指本文公开的化合物(例如，式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物)被递送至所研究的动物或人的全身循环中的重量百分比。通常将静脉内施用时药物的总暴露(AUC(0-∞))定义为100％生物利用度(F％)。“口服生物利用度”是指与静脉内注射相比，当药物组合物口服时本文公开的化合物被吸收至全身循环中的程度。

[0264] “血浆浓度”是指受试者血液的血浆组分中本文公开的式(I)、式(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物的浓度。应理解，由于代谢的可变性和/或与其他治疗剂的可能的相互作用，本文所述化合物的血浆浓度可在受试者之间显著变化。根据本文公开的一个实施方案，本文公开的化合物的血浆浓度可随受试者而变化。类似地，诸如最大血浆浓度(Cmax)或达到最大血浆浓度的时间(Tmax)或血浆浓度时间曲线下总面积(AUC(0-∞))等值可随受试者而变化。由于这种可变性，构成化合物的“治疗有效量”所需的量可随受试者而变化。

[0265] 如本文所用的，“改善”是指疾病或状况的改善或与疾病或状况相关的症状的至少部分缓解。

[0266] 如本文所用的，“免疫细胞”包括免疫系统的细胞和在免疫应答中行使功能或活性的细胞，例如，但不限于T-细胞、B细胞、淋巴细胞、巨噬细胞、树突细胞、嗜中性粒细胞、嗜酸性粒细胞、嗜碱性粒细胞、肥大细胞、浆细胞、白细胞、抗原呈递细胞和自然杀伤细胞。

治疗方法

[0267] 在另一方面是一种药物组合物，其包含式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物，或其药学上可接受的盐、溶剂化物或前药，以及至少一种药学上可接受的赋形剂。

[0268] 在另一方面提供了式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物或其药学上可接受的盐、药学上可接受的溶剂化物或药学上可接受的前药的用途，其用于配制用于抑制细胞内Olig2的活性的药物。所述方法包括使该细胞接触式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物，包括其实施方案。

[0269] 在又一方面是治疗受试者中将受会益于Olig2活性抑制的疾病、病症或状况的方法，该方法包括向有需要的受试者施用包含式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物或其药学上可接受的盐、溶剂化物或前药的组合物。在一些实施方案中是治疗受试者中将会受益于Olig2活性抑制的疾病、病症或状况的方法，该方法包括向有需要的受试者施用包含式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物或其药学上可接受的盐、溶剂化物或前药的组合物；其中该疾病是癌症或唐氏综合征。

[0270] 在另一方面是治疗受试者的疾病的方法，该方法包括向有需要的受试者施用包含式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物或其药学上可接受的盐、溶剂化物或前药的组合物；其中该疾病是癌症或唐氏综合征。在一些实施方案中是治疗受试者的癌症的方法，该方法包括向有需要的受试者施用包含式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物或其药学上可接受的盐、溶剂化物或前药的组合物。在一些实施方案中是治疗受试者的唐氏综合征的方法，该方法包括向有需要的受试者施用包含式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物或其药学上可接受的盐、溶剂化物或前药的组合物。

[0271] 在另一实施方案中是治疗受试者的癌症的方法，该方法包括向有需要的受试者施用包含式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物或其药学上可接受的盐、溶剂化物或前药的组合物，其中该癌症是脑癌、多形性胶质母细胞瘤、髓母细胞瘤、星形细胞瘤、脑干胶质瘤、脑膜瘤、少突神经胶质瘤、黑素瘤、肺癌、乳腺癌或白血病。

[0272] 在另一方面是抑制细胞中Olig2的活性的方法，该方法包括使该细胞接触式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物，或其药学上可接受的盐、溶剂化物或前药。

[0273] 在另一方面是式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物或其药学上可接受的盐、溶剂化物或前药在制备用于治疗将受会益于Olig2活性抑制的疾病、病毒或状况的药物中的用途。

[0274] 在一个方面，本文提供了一种药物组合物，其包含有效量的本文提供的化合物和药学上可接受的赋形剂。在又一方面，提供了进一步包含第二药物活性成分的组合物。

[0275] 在某些实施方案中，本文提供了一种药物组合物，其含有：i)生理上可接受的载体、稀释剂和/或赋形剂；和ii)一种或多种本文所述的化合物。

[0276] 在任何前述方面是进一步的实施方案，其包括单次施用有效量的本文公开的化合物，包括以下进一步的实施方案，其中：(i)施用式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、

(III)、(IV)、(V)或(VI)化合物一次;(ii)在一天的跨度内向哺乳动物多次施用式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物;(iii)频繁地施用;或(iv)连续地施用。

[0277] 在任何前述方面是进一步的实施方案,其包括多次施用有效量的式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物,包括以下进一步的实施方案,其中:(i)以单剂量施用式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物;(ii)多次施用之间的时间是每6小时一次;(iii)每8小时向哺乳动物施用式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物。在进一步或替代的实施方案中,所述方法包括休药期,其中暂停式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物的施用或暂时减少所施用的式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物的剂量;在休药期结束时,恢复式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物的剂量。休药期的时间长度可以从2天至1年不等。

[0278] 在一个方面,向人施用本文所述的化合物。在一些实施方案中,口服施用本文所述的化合物。

药物组合物和施用方法的实例

[0279] 可采用有助于将活性化合物加工成药学上可使用的制剂的一种或多种生理上可接受的载体(包括赋形剂和助剂),以常规方式配制药物组合物。适当的制剂取决于所选择的施用途径。关于用于本文所述药物组合物的合适赋形剂的其他细节可见,例如,Remington:The Science and Practice of Pharmacy,第19版(Easton,Pa.:Mack Publishing Company,1995);Hoover,John E.,Remington's Pharmaceutical Sciences,Mack Publishing Co.,Easton,Pennsylvania 1975;Liberman,H.A.和Lachman,L.编,Pharmaceutical Dosage Forms,Marcel Decker,New York,N.Y.,1980;以及Pharmaceutical Dosage Forms and Drug Delivery Systems,第7版(Lippincott Williams&Wilkins,1999),其公开内容通过引用并入本文。

[0280] 如本文所用的,药物组合物指本文所述的式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物与其他化学组分如载体、稳定剂、稀释剂、分散剂、悬浮剂、增稠剂和/或赋形剂的混合物。药物组合物有助于化合物向生物体的施用。在实施本文提供的治疗或使用方法时,治疗有效量的本文所述化合物以药物组合物形式施用于患有待治疗的疾病、病症或状况的哺乳动物。在一些实施方案中,该哺乳动物为人。治疗有效量可根据疾病的严重程度、受试者的年龄和相对健康、所用化合物的效力及其他因素而广泛变化。式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或VI)化合物可单独使用,或与作为混合物成分的一种或多种治疗剂联合使用(如在联合疗法中)。

[0281] 本文所述的药物制剂可通过多种施用途径施用至受试者,包括但不限于口服、肠胃外(例如,静脉内、皮下、肌肉内)、鼻内、含服、局部、直肠或经皮施用途径。此外,包含式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物的本文所述药物组合物可被配制成任何合适的剂型,包括但不限于水性口服分散体、液体、凝胶、糖浆、酏剂、浆液、悬浮液、气雾剂、控制释放制剂、快速熔化制剂、泡腾制剂、冻干制剂、片剂、粉剂、丸剂、糖衣丸、胶囊、延缓释放制剂、延长释放制剂、脉冲释放制剂、多颗粒制剂,以及混合的立即

释放制剂和控制释放制剂。

[0282] 可以以局部而非全身的方式施用所述化合物和/或组合物，例如，经由将化合物直接注射至器官或组织中，通常在贮库型制品或持续释放制剂中。这类长效制剂可通过植入(例如，皮下或肌肉内植入)或通过肌肉内注射来施用。此外，可以在靶向药物递送系统中，例如在用器官特异性抗体包被的脂质体中施用药物。所述脂质体将被靶向该器官且被该器官选择性地吸收。此外，药物可以以快速释放制剂的形式、以延长释放制剂的形式或以立即释放制剂的形式来提供。

[0283] 包含本文所述化合物的药物组合物可以以常规方式制备，仅举例而言，例如通过常规混合、溶解、制粒、糖衣丸制作、水飞、乳化、封装、包埋或压缩过程制备。

[0284] 药物组合物将包含至少一种本文所述的式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物，作为呈游离酸或游离碱形式或药学上可接受的盐形式的活性成分。此外，本文所述的方法和药物组合物包括使用结晶形式(也称为多晶型物)以及具有相同类型活性的这些化合物的活性代谢物。在某些情况下，化合物可以以互变异构体存在。所有互变异构体都被包括在本文所示化合物的范围内。另外，本文所述的化合物可以以非溶剂化形式存在，以及以用药学上可接受的溶剂如水、乙醇等溶剂化的形式存在。本文示出的化合物的溶剂化形式也被认为在本文中公开。

[0285] 在某些实施方案中，本文提供的组合物还可包含一种或多种防腐剂以抑制微生物活性。合适的防腐剂包括季铵化合物，如苯扎氯铵、溴化十六烷基三甲铵和氯化十六烷基吡啶鎓。

[0286] 可通过将一种或多种固体赋形剂与一种或多种本文所述化合物(例如，式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物)混合，任选地研磨所得的混合物，并且如果期望，则在添加合适的助剂后加工颗粒剂混合物以获得片剂、丸剂或胶囊，从而获得用于口服使用的药物制剂。合适的赋形剂包括，例如，填料如糖，包括乳糖、蔗糖、甘露糖醇或山梨糖醇；纤维素制剂，例如玉米淀粉、小麦淀粉、米淀粉、马铃薯淀粉、明胶、黄蓍胶、甲基纤维素、微晶纤维素、羟丙基甲基纤维素、羧甲基纤维素钠；或其他填料，如：聚乙烯吡咯烷酮(PVP或聚维酮)或磷酸钙。如果期望，可添加崩解剂，如交联的交联羧甲基纤维素钠、聚乙烯吡咯烷酮、琼脂，或海藻酸或其盐，如海藻酸钠。

[0287] 为糖衣丸芯提供合适的包衣。为此，可使用浓缩的糖溶液，该浓缩糖溶液可任选地含有阿拉伯胶、滑石、聚乙烯吡咯烷酮、卡波姆凝胶、聚乙二醇和/或二氧化钛、漆溶液以及合适的有机溶剂或溶剂混合物。可将染料或颜料添加至片剂或糖衣丸包衣中以用于标识或用于表征活性化合物剂量的不同组合。

[0288] 可口服使用的药物制剂包括由明胶制成的推入配合胶囊，以及由明胶和增塑剂如甘油或山梨糖醇制成的密封软胶囊。推入配合胶囊可含有与填料如乳糖、粘合剂如淀粉和/或润滑剂如滑石或硬脂酸镁以及可选的稳定剂混合的活性成分。在软胶囊中，活性化合物可溶解或悬浮在合适的液体如脂肪油、液体石蜡或液体聚乙二醇中。此外，可添加稳定剂。

[0289] 在一些实施方案中，本文公开的固体剂型可为片剂的形式(包括悬浮片剂、快速熔化片剂、咬合崩解片剂、快速崩解片剂、泡腾片剂或囊片剂)、丸剂、粉剂(包括无菌包装的粉剂、可分配的粉剂或泡腾粉剂)、胶囊(包括软胶囊或硬胶囊，例如，由动物来源的明胶或植物来源的HPMC制成的胶囊，或“撒布胶囊”)、固体分散体、固溶体、生物溶蚀性剂型、控制释

放制剂、脉冲释放剂型、多颗粒剂型、微丸、颗粒剂或气雾剂。在其他实施方案中，该药物制剂为粉剂形式。在另外其他的实施方案中，该药物制剂为片剂形式，包括但不限于快速熔化片剂。此外，本文所述化合物的药物制剂可以以单一胶囊或多个胶囊剂型的形式施用。在一些实施方案中，该药物制剂以两个或三个或四个胶囊或片剂的形式施用。

[0290] 在一些实施方案中，通过将本文所述的式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物的颗粒与一种或多种药用赋形剂混合以形成大块共混组合物来制备固体剂型，例如，片剂、泡腾片剂和胶囊。当提及这些大块共混混合物是均一的时，意味着本文所述的式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物的颗粒均匀地分散在整个组合物中，使得该组合物可被细分成等效的单位剂型，如片剂、丸剂和胶囊。单个单位剂量还可包含薄膜包衣，该薄膜包衣在经口摄取或与稀释剂接触时崩解。这些制剂可通过常规药理学技术来制备。

[0291] 本文所述的药物固体剂型可包含本文所述的式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物，以及一种或多种药学上可接受的添加剂，诸如相容性载体、粘合剂、填充剂、悬浮剂、调味剂、甜味剂、崩解剂、分散剂、表面活性剂、润滑剂、着色剂、稀释剂、增溶剂、润湿剂、增塑剂、稳定剂、渗透促进剂、湿润剂、消泡剂、抗氧化剂、防腐剂，或它们的一种或多种组合。在另外其他方面，采用标准包衣程序，如Remington's Pharmaceutical Sciences，第20版(2000)中所述的那些程序，围绕本文所述化合物的制剂提供薄膜包衣。在一个实施方案中，包覆本文所述化合物的一些或全部颗粒。在另一实施方案中，对本文所述化合物的一些或全部颗粒进行微胶囊化。在又一实施方案中，本文所述化合物的颗粒不是微胶囊化的并且是未包衣的。

[0292] 用于本文所述固体剂型的合适载体包括但不限于阿拉伯胶、明胶、胶体二氧化硅、甘油磷酸钙、乳酸钙、麦芽糖糊精、甘油、硅酸镁、酪蛋白酸钠、大豆卵磷脂、氯化钠、磷酸三钙、磷酸氢二钾、硬脂酰乳酸钠、角叉菜胶、甘油单酯、甘油二酯、预胶化淀粉、羟丙基甲基纤维素、羟丙基甲基纤维素乙酸酯硬脂酸酯、蔗糖、微晶纤维素、乳糖、甘露糖醇等。

[0293] 用于本文所述固体剂型的合适填充剂包括但不限于乳糖、碳酸钙、磷酸钙、磷酸氢钙、硫酸钙、微晶纤维素、纤维素粉末、右旋糖、葡萄糖结合剂、葡聚糖、淀粉、预胶化淀粉、羟丙基甲基纤维素(HPMC)、羟丙基甲基纤维素邻苯二甲酸酯、羟丙基甲基纤维素乙酸酯硬脂酸酯(HPMCAS)、蔗糖、木糖醇、乳糖醇、甘露糖醇、山梨糖醇、氯化钠、聚乙二醇等。

[0294] 为了尽可能有效地从固体剂型基体释放式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物，常常在制剂中使用崩解剂，特别当剂型用粘合剂压缩时。当水分被吸收到该剂型中时，崩解剂有助于通过溶胀或毛细管作用破坏剂型基体。用于本文所述固体剂型的合适的崩解剂包括但不限于天然淀粉如玉米淀粉或马铃薯淀粉、预胶化淀粉如National 1551或Amijel®，或羟基乙酸淀粉钠如Promogel®或Explotab®、纤维素如木制品、甲基结晶纤维素，例如，Avicel®、Avicel®PH101、Avicel®PH102、Avicel®PH105、Elcema®P100、Emcocel®、Vivacel®、Ming Tia®和Solka-Floc®、甲基纤维素、交联羧甲基纤维素或交联的纤维素，如交联的羧甲基纤维素钠(Ac-Di-Sol®)、交联的羧甲基纤维素，或交联的交联羧甲基纤维素、交联的淀粉如淀粉羟乙酸钠、交联的聚合物如交聚维酮，交联的聚乙烯吡咯烷酮、海藻酸盐如海藻酸或海藻酸的盐如海藻酸钠、粘土如

Veegum®HV(硅酸镁铝)、胶如琼脂、瓜尔豆胶、槐豆胶、刺梧桐胶、果胶或黄蓍胶、羟基乙酸淀粉钠、膨润土、天然海绵、表面活性剂、树脂如阳离子交换树脂、柑橘渣、十二烷基硫酸钠、十二烷基硫酸钠与淀粉的组合,等等。

[0295] 粘合剂为固体口服剂型制剂赋予粘结性:对于粉末填充胶囊制剂,它们帮助形成可填充至软壳胶囊或硬壳胶囊中的栓塞,对于片剂制剂,它们确保该片剂在压缩后保持完整并帮助保证压缩或填充步骤之前的共混均一性。适合用作本文所述固体剂型中的粘合剂的材料包括但不限于羧甲基纤维素、甲基纤维素(例如,Methocel®)、羟丙基甲基纤维素(例如,羟丙甲纤维素USP Pharmacoat-603、羟丙基甲基纤维素乙酸酯硬脂酸酯(Aqoate HS-LF和HS)、羟乙基纤维素、羟丙基纤维素(例如,Klucel®)、乙基纤维素(例如,Ethocel®)和微晶纤维素(例如,Avicel®)、微晶右旋糖、直链淀粉、硅酸镁铝、多糖酸、膨润土、明胶、聚乙烯吡咯烷酮/醋酸乙烯酯共聚物、交聚维酮、聚维酮、淀粉、预胶化淀粉、黄蓍胶、糊精、糖如蔗糖(例如,Dipac®)、葡萄糖、右旋糖、糖蜜、甘露糖醇、山梨糖醇、木糖醇(例如,Xylitab®)、乳糖、天然或合成胶如阿拉伯胶、黄蓍胶、茄替胶、isapol husks的粘液、淀粉、聚乙烯吡咯烷酮(例如,Povidone® CL、Kollidon® CL、Polyplasdone® XL-10和Povidone®K-12)、落叶松阿拉伯半乳聚糖、Veegum®、聚乙二醇、蜡、海藻酸钠等。

[0296] 通常,将20-70%的粘合剂水平用于粉末填充的明胶胶囊制剂。片剂制剂中的粘合剂使用水平随直接压缩、湿法制粒、辊压或其他赋形剂如本身可作为中等粘合剂的填料的使用而变化。在一些实施方案中,配制者决定制剂的粘合剂水平,但片剂制剂中最高达70%的粘合剂使用水平是常见的。

[0297] 用于本文所述固体剂型的合适的润滑剂或助流剂包括但不限于硬脂酸、氢氧化钙、滑石、玉米淀粉、硬脂酰富马酸钠、碱金属和碱土金属盐(如铝盐、钙盐、镁盐、锌盐)、硬脂酸、硬脂酸钠、硬脂酸镁、硬脂酸锌、蜡、Stearowet®、硼酸、苯甲酸钠、乙酸钠、氯化钠、亮氨酸、聚乙二醇或甲氧基聚乙二醇如Carbowax™、PEG 4000、PEG 5000、PEG 6000、丙二醇、油酸钠、甘油二十二烷酸酯、棕榈酸硬脂酸甘油酯、苯甲酸甘油酯、月桂基硫酸镁或月桂基硫酸钠等。

[0298] 用于本文所述固体剂型的合适的稀释剂包括但不限于糖(包括乳糖、蔗糖和葡萄糖)、多糖(包括葡萄糖结合剂和麦芽糖糊精)、多元醇(包括甘露糖醇、木糖醇和山梨糖醇)、环糊精等。

[0299] 用于本文所述固体剂型的合适的湿润剂包括,例如,油酸、单硬脂酸甘油酯、失水山梨糖醇单油酸酯、失水山梨糖醇单月桂酸酯、三乙醇胺油酸酯、聚氧乙烯失水山梨糖醇单油酸酯、聚氧乙烯失水山梨糖醇单月桂酸酯、季铵化合物(例如,Polyquat10®)、油酸钠、月桂基硫酸钠、硬脂酸镁、多库酯钠、三醋精、维生素E TPGS等。

[0300] 用于本文所述固体剂型的合适的表面活性剂包括,例如,月桂基硫酸钠、失水山梨糖醇单油酸酯、聚氧乙烯失水山梨糖醇单油酸酯、聚山梨醇酯、泊洛沙姆、胆汁盐、单硬脂酸甘油酯、环氧乙烷与环氧丙烷的共聚物例如Pluronic®(BASF)等。

[0301] 用于本文所述固体剂型的合适的悬浮剂包括但不限于聚乙烯吡咯烷酮，例如聚乙烯吡咯烷酮K12、聚乙烯吡咯烷酮K17、聚乙烯吡咯烷酮K25或聚乙烯吡咯烷酮K30、聚乙二醇(例如聚乙二醇可具有约300至约6000，或约3350至约4000，或约5400至约7000的分子量)、乙烯基吡咯烷酮/乙酸乙烯酯共聚物(S630)、羧甲基纤维素钠、甲基纤维素、羟丙基甲基纤维素、聚山梨醇酯-80、羟乙基纤维素、海藻酸钠、树胶，诸如例如黄蓍胶和阿拉伯胶、瓜尔豆胶、三仙胶(包括黄原胶)、糖、纤维素材料，例如羧甲基纤维素钠、甲基纤维素、羧甲基纤维素钠、羟丙基甲基纤维素、羟乙基纤维素、聚山梨醇酯-80、海藻酸钠、聚乙氧基化失水山梨糖醇单月桂酸酯、聚乙氧基化失水山梨糖醇单月桂酸酯、聚维酮等。

[0302] 用于本文所述固体剂型的合适的表面抗氧化剂包括，例如，丁基化羟基甲苯(BHT)、抗坏血酸钠和生育酚。

[0303] 在本文所述的固体剂型中使用的添加剂之间存在相当大的重叠。因此，上文列出的添加剂应被认为仅仅是示例性的而非限制可包含在本文所述药物组合物的固体剂型中的添加剂的类型。

[0304] 在其他实施方案中，药物制剂的一层或多层被塑化。说明性地，增塑剂通常是高沸点的固体或液体。可按重量(w/w)计以包衣组合物的约0.01％至约50％添加合适的增塑剂。增塑剂包括但不限于邻苯二甲酸二乙酯、柠檬酸酯、聚乙二醇、甘油、乙酰化甘油酯、三醋精、聚丙二醇、聚乙二醇、柠檬酸三乙酯、癸二酸二丁酯、硬脂酸、硬脂醇、硬脂酸酯和蓖麻油。

[0305] 压缩片剂是通过压缩上述制剂的大块共混物而制备的固体剂型。在多个实施方案中，设计成在口中溶解的压缩片剂将包含一种或多种调味剂。在其他实施方案中，压缩片剂将包含围绕最终的压缩片剂的薄膜。在一些实施方案中，薄膜包衣可提供本文所述的式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物从制剂中的延迟释放。在其他实施方案中，薄膜包衣有助于患者顺应性(例如，Opadry®包衣或糖包衣)。包括Opadry®在内的薄膜包衣通常为片剂重量的约1％至约3％。在其他实施方案中，压缩片剂包含一种或多种赋形剂。

[0306] 例如，可通过将上述化合物的制剂的大块共混物放置在胶囊内而制备胶囊。在一些实施方案中，将制剂(非水性悬浮液和溶液)放置在软明胶胶囊中。在其他实施方案中，将制剂放置在标准明胶胶囊或非明胶胶囊如包含HPMC的胶囊中。在其他实施方案中，将制剂放置在撒布胶囊中，其中该胶囊可整体吞咽，或可在用餐前将该胶囊打开并将内容物洒在食物上。在一些实施方案中，将治疗剂量分成多个(例如，两个、三个或四个)胶囊。在一些实施方案中，制剂的全部剂量都以胶囊的形式递送。

[0307] 在多个实施方案中，将本文所述的式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物的颗粒与一种或多种赋形剂干燥共混并压缩成块，如片剂，该块的硬度足以提供在口服施用后少于约30分钟、少于约35分钟、少于约40分钟、少于约45分钟、少于约50分钟、少于约55分钟或少于约60分钟之内基本上崩解的药物组合物，从而将该制剂释放至胃肠液中。

[0308] 在另一方面，剂型可包括微胶囊化的制剂。在一些实施方案中，微胶囊化材料中存在一种或多种其他的相容性物质。示例性的物质包括但不限于pH调节剂、侵蚀促进剂、消泡

剂、抗氧化剂、调味剂和载体物质如粘合剂、悬浮剂、崩解剂、填充剂、表面活性剂、增溶剂、稳定剂、润滑剂、湿润剂和稀释剂。

[0309] 用于本文所述的微胶囊化的物质包括与本文所述化合物相容的物质，其充分地将该化合物与其他不相容赋形剂隔离。与本文所述化合物相容的物质是延缓式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物的体内释放的那些物质。

[0310] 可用于延缓包含本文所述化合物的制剂的释放的示例性微胶囊化物质包括但不限于羟丙基纤维素醚(HPC)如Klucel®或Nisso HPC、低取代羟丙基纤维素醚(L-HPC)、羟丙基甲基纤维素醚(HPMC)(如Seppifilm-LC、Pharmacoat®、Metolose SR、Methocel®-E、Opadry YS、PrimaFlo、Benecel MP824和Benecel MP843)、甲基纤维素聚合物如Methocel®-A、羟丙基甲基纤维素乙酸酯硬脂酸酯Aqoat(HF-LS、HF-LG、HF-MS)和Metolose®、乙基纤维素(EC)及其混合物(如E461、Ethocel®、Aqualon®-EC、Surelease®)、聚乙烯醇(PVA)如Opadry AMB、羟乙基纤维素如Natrosol®、羧甲基纤维素和羧甲基纤维素的盐(CMC)如Aqualon®-CMC、聚乙烯醇和聚乙二醇共聚物如Kollicoat IR®、单甘油酯(Myverol)、三酸甘油酯(KLX)、聚乙二醇、改性食品淀粉、丙烯酸聚合物和丙烯酸聚合物与纤维素醚的混合物(如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和Eudragit®NE 40D)、邻苯二甲酸乙酸纤维素、sepifilms如HPMC与硬脂酸的混合物、环糊精以及这些物质的混合物。

[0311] 在另外其他的实施方案中，向微胶囊化物质中掺入增塑剂如聚乙二醇，例如，PEG 300、PEG 400、PEG 600、PEG 1450、PEG 3350和PEG 800、硬脂酸、丙二醇、油酸和三醋精。在其他实施方案中，可用于延缓药物组合物的释放的微胶囊化物质来自USP或国家处方集(NF)。在另外其他的实施方案中，微胶囊化物质为Klucel。在另外其他的实施方案中，微胶囊化物质为甲基纤维素(methocel)。

[0312] 本文所述的微胶囊化化合物可通过包括例如喷雾干燥法、转盘-溶剂法、热熔法、喷雾冷却法、流化床、静电沉积、离心挤出、旋转悬浮分离、在液-气法或固-气界面处聚合、压力挤出或喷雾溶剂萃取浴在内的方法来配制。除这些之外，还可使用几种化学技术，例如，复凝聚、溶剂蒸发、聚合物-聚合物不相容性、在液体介质中的界面聚合、原位聚合、液体内干燥和在液体介质中的去溶剂化。此外，也可使用其他方法，诸如辊压、挤出/滚圆、凝聚或纳米颗粒包覆。

[0313] 在另外其他的实施方案中，还可根据本公开内容制备泡腾粉末。泡腾盐已被用于将药物分散在水中以供口服施用。泡腾盐是含有在干燥混合物中的药剂的颗粒或粗粉，该混合物通常由碳酸氢钠、柠檬酸和/或酒石酸组成。当将这样的盐加入水中时，酸和碱反应释放出二氧化碳气体，从而引起“泡腾”。泡腾盐的实例包括例如以下成分：碳酸氢钠或碳酸氢钠与碳酸钠、柠檬酸和/或酒石酸的混合物。任何导致二氧化碳释放的酸碱组合均可用于代替碳酸氢钠与柠檬酸和酒石酸的组合，只要这些成分适合于制药用途并产生约6.0或更

高的pH。

[0314] 在其他实施方案中，本文描述的包含本文所述化合物的制剂为固体分散体。制备这类固体分散体的方法包括但不限于例如第4,343,789号、第5,340,591号、第5,456,923号、第5,700,485号、第5,723,269号美国专利和第2004/0013734号美国专利公开。在另外其他的实施方案中，本文所述的制剂为固溶体。固溶体将物质与活性剂及其他赋形剂合并在一起，使得对混合物加热导致药物溶解，然后将所得组合物冷却以产生固体共混物，该固体共混物可进一步配制或直接添加至胶囊中或压缩成片剂。生产这类固溶体的方法包括但不限于例如第4,151,273号、第5,281,420号和第6,083,518号美国专利。

[0315] 包含含有本文所述化合物的本文所述制剂的药物口服固体剂型可被进一步配制，以提供式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物的控制释放。控制释放是指本文所述化合物在延长的时间段内根据所需释放曲线从其所掺入的剂型中的释放。例如，控制释放曲线包括持续释放、延长释放、脉冲释放和延迟释放曲线。与立即释放组合物相比，控制释放组合物允许根据预定曲线在延长的时间段内将药剂递送至受试者。这样的释放速率可在延长的时间段内提供治疗有效水平的药剂，从而与常规的快速释放剂型相比提供更长的药理学响应时间，同时使副作用最小化。这种更长的响应时间提供了无法用相应的短效立即释放制剂实现的许多固有益处。

[0316] 在一些实施方案中，本文所述的固体剂型可被配制成肠溶包衣延迟释放口服剂型，即，配制为利用肠溶包衣来实现在胃肠道的小肠中的释放的本文所述药物组合物的口服剂型。肠溶包衣剂型可为含有活性成分和/或其他组合物组分(其本身是包覆或未涂包覆的)的颗粒剂、粉末、微丸、珠粒或颗粒的压缩或模制或挤出的片剂/模塑片(包覆或未包覆的)。肠溶包衣口服剂型还可为含有本身包覆或未包覆的固体载体或组合物的微丸、珠粒或颗粒剂的胶囊(包覆或未包覆的)。

[0317] 如本文所用的术语“延迟释放”是指这样的递送，其使得释放可以在肠道中的一些通常可预测的位置完成，该位置比如果没有延迟释放改变时释放会完成的位置更居于远端。在一些实施方案中，延迟释放的方法是包衣。任何包衣均应施加至足够的厚度，以使得整个包衣在pH低于约5的胃肠液中不溶解，但在pH约5及以上时能溶解。包衣可以由以下物质制成：

[0318] 丙烯酸聚合物。丙烯酸聚合物的性能(主要是它们在生物流体中的溶解度)可以基于取代的程度和类型而变化。合适的丙烯酸聚合物的实例包括甲基丙烯酸共聚物和甲基丙烯酸铵共聚物。Eudragit系列E、L、S、RL、RS和NE(Rohm Pharma)在溶解于有机溶剂时、作为水性分散体或干粉可用。Eudragit系列RL、NE和RS在胃肠道中不可溶，但可渗透且主要用于结肠靶向。Eudragit系列E在胃中溶解。Eudragit系列L、L-30D和S在胃中不可溶，但在肠中溶解；

[0319] 纤维素衍生物。合适的纤维素衍生物的实例是：乙基纤维素；纤维素的偏醋酸酯与邻苯二甲酸酐的反应混合物。基于取代的程度和类型，性能可以变化。纤维素醋酸酯邻苯二甲酸酯(CAP)在pH>6时溶解。Aquateric(FMC)是基于水性的体系，而且是颗粒<1μm的喷雾干燥的CAP假胶乳。Aquateric中的其他组分可以包括Pluronics、吐温和乙酰化甘油单酯。其他合适的纤维素衍生物包括：纤维素醋酸酯偏苯三酸酯(Eastman)；甲基纤维素(Pharmacoat,Methocel)；羟丙基甲基纤维素邻苯二甲酸酯(HPMCP)；羟丙基甲基纤维素琥

珀酸酯(HPMCS);和羟丙基甲基纤维素醋酸酯琥珀酸酯(例如AQOAT(Shin Etsu))。基于取代的程度和类型,性能可以变化。举例来说,HPMCP例如HP-50、HP-55、HP-55S、HP-55F级是合适的。基于取代的程度和类型,性能可以变化。例如,合适级别的羟丙基甲基纤维素醋酸酯琥珀酸酯包括但不限于AS-LG(LF),其在pH 5时溶解;AS-MG(MF),其在pH 5.5时溶解;和AS-HG(HF),其在更高的pH时溶解。这些聚合物作为颗粒或细粉提供,以用于水性分散体;

[0320] 聚乙烯基醋酸酯邻苯二甲酸酯(PVAP)。PVAP在pH>5时溶解,而且它对水汽和胃液具有相当低的渗透性。

[0321] 在一些实施方案中,包衣可以含有而且通常确实含有增塑剂和其他可能的包衣赋形剂,例如着色剂、滑石和/或硬脂酸镁。合适的增塑剂包括柠檬酸三乙酯(Citroflex 2)、三醋精(三醋酸甘油酯)、乙酰基柠檬酸三乙酯(Citroflec A2)、Carbowax 400(聚乙二醇400)、邻苯二甲酸二乙酯、柠檬酸三丁酯、乙酰化甘油单酯、甘油、脂肪酸酯、丙二醇和邻苯二甲酸二丁酯。特别地,阴离子羧酸丙烯酸聚合物通常将含有10-25重量%的增塑剂,特别是邻苯二甲酸二丁酯、聚乙二醇、柠檬酸三乙酯和三醋精。使用常规的包衣技术例如喷雾或锅包衣来施加包衣。包衣厚度必须足以确保口服剂型在到达肠道中的所需局部递送部位前保持完整。

[0322] 除了增塑剂之外,还可将着色剂、防粘剂、表面活性剂、消泡剂、润滑剂(例如,巴西棕榈蜡或PEG)添加至包衣中以将包衣材料溶解或分散并改善包衣性能和所包覆的产品。

[0323] 在其他实施方案中,采用脉冲剂型递送包含本文所述的式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物的本文所述制剂。脉冲剂型能够在控制的滞后时间之后的预定时间点或在特定部位处提供一个或多个立即释放脉冲。脉冲剂型可采用多种脉冲制剂来施用,包括但不限于第5,011,692号、第5,017,381号、第5,229,135号、第5,840,329号、第4,871,549号、第5,260,068号、第5,260,069号、第5,508,040号、第5,567,441号和第5,837,284号美国专利中描述的那些。

[0324] 许多其他类型的控制释放体系适合与本文所述的制剂一起使用。这类递送系统的实例包括,例如,基于聚合物的体系,诸如聚乳酸和聚乙醇酸、聚酸酐和聚己内酯;为脂质的基于非聚合物多孔基体的体系,包括甾醇如胆固醇、胆固醇酯和脂肪酸,或中性脂肪如甘油单酯、甘油二酯和甘油三酯;水凝胶释放体系;硅橡胶体系;基于肽的体系;蜡包衣、生物溶蚀性剂型、采用常规粘合剂的压缩片剂,等等。参见,例如,Liberman等人,Pharmaceutical Dosage Forms,第2版,Vol.1,pp.209-214(1990);Singh等人,Encyclopedia of Pharmaceutical Technology,第2版,pp.751-753(2002);第4,327,725号、第4,624,848号、第4,968,509号、第5,461,140号、第5,456,923号、第5,516,527号、第5,622,721号、第5,686,105号、第5,700,410号、第5,977,175号、第6,465,014号和第6,932,983号美国专利。

[0325] 在一些实施方案中,提供了药物制剂,其包含本文所述化合物例如式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物的颗粒,和至少一种分散剂或悬浮剂,以供口服施用至受试者。该制剂可以是用于悬浮的粉末和/或颗粒,并且在与水混合时获得基本均匀的悬浮液。

[0326] 用于口服施用的液体制剂剂型可为水性悬浮液,其选自包括但不限于药学上可接受的水性口服分散体、乳液、溶液、酏剂、凝胶和糖浆。参见,例如,Singh等人,Encyclopedia of Pharmaceutical Technology,第2版,pp.754-757(2002)。

[0327] 本文所述的水性悬浮液和分散体可保持在如The USP Pharmacists' Pharmacopeia(2005版,第905章)中定义的均匀状态持续至少4小时。通过符合测定整个组合物的均匀性的取样方法来测定均匀性。在一个实施方案中,可通过持续少于1分钟的物理搅拌将水性悬浮液再悬浮成均匀悬浮液。在另一实施方案中,可通过持续少于45秒的物理搅拌将水性悬浮液再悬浮成均匀悬浮液。在又一实施方案中,可通过持续少于30秒的物理搅拌将水性悬浮液再悬浮成均匀悬浮液。在又一实施方案中,不需要搅拌来维持均匀的水性分散体。

[0328] 本文所述的药物组合物可包含甜味剂,诸如但不限于,阿拉伯胶糖浆、乙酰舒泛K、阿力甜、茴芹、苹果、阿斯巴甜、香蕉、巴伐利亚奶油、浆果、黑醋栗、奶油硬糖、柠檬酸钙、樟脑、焦糖、樱桃、樱桃奶油、巧克力、肉桂、泡泡糖、柑橘、柑橘宾治(citrus punch)、柑橘奶油、棉花糖、可可、可乐、冷樱桃、冷柑橘、甜蜜素、cylamate、右旋糖、桉树、丁香酚、果糖、水果宾治、姜、甘草次酸酯、甘草(甘草)糖浆、葡萄、葡萄柚、蜂蜜、异麦芽糖、柠檬、酸橙、柠檬奶油、甘草酸单铵(MagnaSweet®)、麦芽糖醇、甘露糖醇、枫树、棉花糖、薄荷醇、薄荷奶油、混合浆果、新橙皮苷DC、纽甜、橙、梨、桃、胡椒薄荷、胡椒薄荷奶油、Prosweet®粉、覆盆子、根汁饮料、朗姆酒、糖精、黄樟素、山梨糖醇、留兰香、留兰香奶油、草莓、草莓奶油、甜叶菊、三氯蔗糖、蔗糖、糖精钠、糖精、阿斯巴甜、乙酰磺胺酸钾、甘露糖醇、塔林糖、三氯蔗糖、山梨糖醇、瑞士奶油、塔格糖、橘子、索默坦蛋白质、图提芙蒂、香草、胡桃、西瓜、野樱桃、冬青、木糖醇或这些调味成分的任何组合,例如茴香-薄荷醇、樱桃-茴香、肉桂-橙、樱桃-肉桂、巧克力-薄荷、蜂蜜-柠檬、柠檬-酸橙、柠檬-薄荷、薄荷醇-桉树、橙-奶油、香草-薄荷以及它们的混合物。

[0329] 在一些实施方案中,本文所述的药物制剂可为自乳化药物递送体系(SEDDS)。乳液是一种不混溶相通常以小液滴的形式在另一相中的分散体。通常,通过剧烈的机械分散产生乳液。SEDDS与乳液或微乳液相反,其在添加至过量的水中时自发形成乳液而无需任何外部的机械分散或搅拌。SEDDS的优点是只需要轻柔的混合即可将小液滴分布在整个溶液中。此外,水或水相可在施用之前添加,这确保了不稳定或疏水性活性成分的稳定性。因此,SEDDS提供了用于口服和肠胃外递送疏水性活性成分的有效递送体系。SEDDS可提供疏水性活性成分的生物利用度的改善。生产自乳化剂型的方法包括但不限于例如第5,858,401号、第6,667,048号和第6,960,563号美国专利。

[0330] 在本文所述的水性分散体或悬浮液中使用的上文列出的添加剂之间存在重叠,因为给定的添加剂通常由本领域的不同从业者进行不同分类,或者通常因几种不同功能中的任一种而使用。因此,上文列出的添加剂应被认为仅仅是示例性的,而非限制可包含在本文所述制剂中的添加剂的类型。

[0331] 用于鼻内制剂的潜在赋形剂包括例如第4,476,116号、第5,116,817号和第6,391,452号美国专利。盐水中的制剂溶液采用苄醇或其他合适的防腐剂、碳氟化合物和/或其他增溶剂或分散剂。参见,例如,Ansel,H.C.等人,Pharmaceutical Dosage Forms and Drug Delivery Systems,第六版(1995)。优选地,这些组合物和制剂用合适的非毒性的药学上可接受的成分制备。适当载体的选择高度取决于所需的鼻剂型例如溶液、悬浮液、乳膏或凝胶的确切性质。除活性成分外,鼻剂型通常含有大量水。还可存在微量的其他成分如pH调节

剂、乳化剂或分散剂、防腐剂、表面活性剂、胶凝剂或缓冲剂以及其他稳定剂和增溶剂。优选地，鼻剂型应与鼻分泌物是等渗的。

[0332] 对于通过吸入施用，本文所述的化合物可以是作为气雾剂、薄雾剂或粉剂的形式。通过使用合适的推进剂例如二氯二氟甲烷、三氯氟甲烷，二氯四氟乙烷、二氧化碳或其他合适的气体，以来自加压包装或喷雾器的气雾剂喷雾形式方便地递送本文所述的药物组合物。在加压气雾剂的情况下，可通过提供用于递送计量量的阀门来确定剂量单位。例如仅举例而言，用于吸入器或吹入器的明胶的胶囊和筒匣可被配制成含有本文所述化合物与合适粉末基底如乳糖或淀粉的粉末混合物。

[0333] 包含本文所述化合物的含服制剂可采用多种制剂来施用，该制剂包括但不限于第4,229,447号、第4,596,795号、第4,755,386号和第5,739,136号美国专利。此外，本文所述的含服剂型可进一步包含生物溶蚀性(可水解的)聚合物载体，该载体还用于将该剂型粘附至口腔粘膜。制备了含服剂型以便在预定时间段内逐渐溶蚀，其中基本上一直提供化合物的递送。含服药物递送避免了口服药物施用所遇到的缺点，例如，缓慢吸收、活性剂被存在于胃肠道中的流体降解和/或肝脏中的首过失活。对于生物溶蚀性(可水解的)聚合物载体，实际上可使用任何这样的载体，只要期望的药物释放特性不受损害，并且该载体与本文所述的化合物以及含服剂量单位中可能存在的任何其他组分相容。通常，聚合物载体包括粘附至含服粘膜的湿表面的亲水性(水溶性和水溶胀性)聚合物。本文中有用的聚合物载体的实例包括丙烯酸聚合物和共聚物，例如被称为“卡波姆”(Carbopol®，其可从B.F.Goodrich获得，是一种这样的聚合物)的那些。还可以将其他组分掺入本文所述的含服剂型中，包括但不限于崩解剂、稀释剂、粘合剂、润滑剂、调味剂、着色剂、防腐剂等。对于含服或舌下施用，组合物可采取以常规方式配制的片剂、锭剂或凝胶的形式。

[0334] 本文所述的经皮制剂可采用多种装置施用，包括但不限于第3,598,122号、第3,598,123号、第3,710,795号、第3,731,683号、第3,742,951号、第3,814,097号、第3,921,636号、第3,972,995号、第3,993,072号、第3,993,073号、第3,996,934号、第4,031,894号、第4,060,084号、第4,069,307号、第4,077,407号、第4,201,211号、第4,230,105号、第4,292,299号、第4,292,303号、第5,336,168号、第5,665,378号、第5,837,280号、第5,869,090号、第6,923,983号、第6,929,801号和第6,946,144号美国专利。

[0335] 本文所述的经皮剂型可掺有本领域中常规的某些药学上可接受的赋形剂。在一个实施方案中，本文所述的经皮制剂包含至少三种组分：(1)化合物的制剂；(2)渗透促进剂；和(3)水性佐剂。此外，经皮制剂可包含其他组分，诸如但不限于，胶凝剂、乳膏和软膏基底，等等。在一些实施方案中，经皮制剂可进一步包括织造或非织造衬底材料，以增强吸收并防止经皮制剂从皮肤上去除。在其他实施方案中，本文所述的经皮制剂可维持饱和或超饱和状态，以促进向皮肤内的分散。

[0336] 适用于经皮施用本文所述化合物的制剂可采用经皮递送装置和经皮递送贴片，并可以是溶解和/或分散在聚合物或胶粘剂中的亲脂性乳液或缓冲的水性溶液。这样的贴片可被构造用于药物剂的连续递送、脉冲递送或按需递送。更进一步地，本文所述化合物的经皮递送可通过离子电渗贴片等手段来实现。另外，经皮贴片可提供本文所述化合物的控制递送。可通过使用速率控制膜或通过将化合物捕陷在聚合物基体或凝胶内来减缓吸收的速率。相反，可使用吸收增强剂增加吸收。吸收增强剂或载体可包含可吸收的药学上可接受的

溶剂以帮助穿过皮肤。例如，经皮装置为绷带的形式，其包含衬底膜、含有化合物和可选的载体的储层、可选的速率控制障碍层，用于在延长的时间段内在控制和预定的速率下向宿主的皮肤递送该化合物，以及用于将该装置固定于皮肤的手段。

[0337] 适用于肌肉内、皮下或静脉内注射的制剂可包含生理学上可接受的无菌水性溶液或非水性溶液、分散体、悬浮液或乳液，以及用于重构成无菌可注射溶液或分散体的无菌粉末。合适的水性和非水性载体、稀释剂、溶剂或媒介物的实例包括水、乙醇、多元醇(丙二醇、聚乙二醇、甘油、氢化蓖麻油等)、它们的合适混合物、植物油(如橄榄油)以及可注射的有机酯如油酸乙酯。例如，可通过使用包衣如卵磷脂、在分散体的情况下通过维持所需的颗粒大小，以及通过使用表面活性剂来维持适当的流动性。适用于皮下注射的制剂也可含有添加剂如防腐剂、湿润剂、乳化剂和分散剂。可通过诸如对羟基苯甲酸酯、氯丁醇、苯酚、山梨酸等多种抗菌剂和抗真菌剂来确保防止微生物生长。还可期望包含等渗剂，如糖、氯化钠等。可通过使用延缓吸收的药剂如单硬脂酸铝和明胶来实现可注射药物形式的延长吸收。

[0338] 对于静脉内注射，本文所述化合物可配制在水性溶液中，优选配制在生理学相容的缓冲液如Hank溶液、Ringer溶液或生理盐水缓冲液中。对于经粘膜施用，在制剂中使用适合于待渗透的屏障的渗透剂。这类渗透剂一般是本领域所公认的。对于其他肠胃外注射，合适的制剂可包含水性或非水性溶液，优选具有生理学相容的缓冲液或赋形剂。这类赋形剂一般是本领域所公认的。

[0339] 肠胃外注射可涉及推注或连续输注。用于注射的制剂可以以单位剂型呈现，例如，在添加有防腐剂的安瓿或多剂量容器中。本文所述的药物组合物可为适用于作为无菌悬浮液、溶液或在油性或水性媒介物中的乳液进行肠胃外注射的形式，并且可含有调配剂，如悬浮剂、稳定剂和/或分散剂。用于肠胃外施用的药物制剂包含为水溶性形式的活性化合物的水性溶液。另外，活性化合物的悬浮液可制备成合适的油性注射悬浮液。合适的亲脂性溶剂或媒介物包括脂肪油，诸如芝麻油或合成脂肪酸酯，如油酸乙酯或甘油三酯，或脂质体。水性注射悬浮液可含有增加悬浮液粘度的物质，如羧甲基纤维素钠、山梨糖醇或葡聚糖。任选地，该悬浮液还可含有合适的稳定剂或增加该化合物溶解度的药剂，以允许制备高度浓缩的溶液。或者，活性成分可为粉末形式，以供在使用前用合适的媒介物例如无菌无热原水重建。

[0340] 在某些实施方案中，可采用药物化合物的递送体系，例如，脂质体和乳液。在某些实施方案中，本文提供的组合物还包含粘膜粘着聚合物，其选自例如羧甲基纤维素、卡波姆(丙烯酸聚合物)、聚(甲基丙烯酸甲酯)、聚丙烯酰胺、聚卡波非、丙烯酸/丙烯酸丁酯共聚物、海藻酸钠和葡聚糖。

[0341] 在一些实施方案中，本文所述的化合物可局部施用并被配制成多种可局部施用的组合物，诸如溶液、悬浮液、洗剂、凝胶、糊剂、药棒、香膏、乳膏或软膏。这类药物化合物可含有增溶剂、稳定剂、张力增强剂、缓冲剂和防腐剂。

[0342] 本文所述化合物还可配制为直肠组合物，如灌肠剂、直肠凝胶、直肠泡沫、直肠气雾剂、栓剂、胶冻栓剂或保留灌肠剂，该组合物含有常规栓剂基底，如可可脂或其他甘油酯，以及合成聚合物，如聚乙烯吡咯烷酮、PEG等。在组合物的栓剂形式中，首先熔化低熔点蜡，诸如但不限于任选地与可可脂组合的脂肪酸甘油酯混合物。

[0343] 通常，诸如式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合

物的药剂以有效改善或预防疾病或病症症状的发展的量(即,治疗有效量)施用。因此,治疗有效量可以是能够至少部分预防或逆转疾病或病症的量。获得有效量所需的剂量可根据药剂、制剂、疾病或病症以及药剂所施用至的个体而变化。

[0344] 有效量的确定还可涉及这样的体外测定,其中将不同剂量的药剂施用至培养中的细胞,并且确定有效改善一些或全部症状的药剂浓度,以便计算体内所需的浓度。有效量还可基于动物体内研究。

[0345] 药剂可在疾病或病症的症状出现之前、同时和之后施用。在一些实施方案中,将药剂施用至具有疾病或病症的家族史的受试者,或具有可指示疾病或病症倾向性的表型的受试者,或具有使受试者倾向于患上疾病或病症的表型的受试者。

给药方法和治疗方案的实例

[0346] 本文所述的化合物可在制备用于治疗癌症或治疗将会至少部分地受益于Olig2抑制的疾病或状况的药物中使用。另外,用于在有需要的受试者中治疗本文所述的任何疾病和状况的方法包括以治疗有效量向所述受试者施用含有至少一种本文所述化合物或其药学上可接受的盐、药学上可接受的前药或药学上可接受的溶剂化物的药物组合物。

[0347] 可施用含有本文所述化合物的组合物以用于预防性和/或治疗性处理。在治疗性应用中,以足以治愈或至少部分阻止疾病或状况的症状的量将该组合物施用至已经罹患该疾病或状况的患者。对于该用途而言有效的量将取决于该疾病或状况的严重程度和进程、既往疗法、患者的健康状态、体重和对药物的响应,以及治疗医师的判断。

[0348] 在预防性应用中,将含有本文所述化合物的组合物施用至易患特定疾病、病症或状况或存在其风险的患者。这样的量被定义为“预防有效量或剂量”。在该用途中,准确的量也取决于患者的健康状态、体重等。当用于患者时,对于该用途的有效量将取决于该疾病、病症或状况的严重程度和进程、既往疗法、患者的健康状态和对药物的响应,以及治疗医师的判断。

[0349] 在患者的状况没有改善的情况下,根据医生的判断,化合物的施用可长期进行,即持续延长的一段时间,包括患者生命的整个持续时间,以便改善或以其他方式控制或限制患者疾病或状况的症状。

[0350] 在患者的状况确实改善的情况下,根据医生的判断,化合物的施用可连续给予;或者,所施用药物的剂量可暂时减少或暂时停止一段时间(即,“休药期”)。休药期的长度可在2天至1年之间不等,仅举例而言,包括2天、3天、4天、5天、6天、7天、10天、12天、15天、20天、28天、35天、50天、70天、100天、120天、150天、180天、200天、250天、280天、300天、320天、350天或365天。休药期期间的剂量减少可为约10%至约100%,仅举例而言,包括约10%、约15%、约20%、约25%、约30%、约35%、约40%、约45%、约50%、约55%、约60%、约65%、约70%、约75%、约80%、约85%、约90%、约95%或约100%。

[0351] 一旦患者的状况发生改善,即在必要时施用维持剂量。随后,可根据症状将施用剂量或频率或二者降低至保持疾病、症状或状况改善的水平。然而,在症状有任何复发时,患者可能需要长期的间歇性治疗。

[0352] 与这样的量相对应的所给予药剂的量将会根据诸如具体化合物、疾病或状况及其严重程度、需要治疗的受试者或宿主的特性(例如,重量)等因素而变化,但也可根据个例的具体情况以本领域公认的方式确定,包括,例如,所施用的具体化合物、施用途径、所治疗的

状况和所治疗的受试者或宿主。然而，通常，对于成年人治疗所采用的剂量一般在每日约0.02mg至每日约5000mg的范围内，在一些实施方案中，在每日约1mg至每日约1500mg的范围内。期望的剂量可方便地以单一剂量呈现，或作为同时(或在较短的一段时间内)施用或以适当间隔施用(例如，每日两次、三次、四次或更多次子剂量)的分剂量。

[0353] 本文所述的药物组合物可以为适用于单次施用准确剂量的单位剂型。在单位剂型中，制剂被分成含有适量的一种或多种化合物的单位剂量。单位剂量可为含有离散量制剂的包装的形式。非限制性实例为包装的片剂或胶囊，和在小瓶或安瓿中的粉剂。可将水性悬浮液组合物包装在不可重新盖紧的单剂量容器中。或者，可使用可重新盖紧的多剂量容器，在这种情况下组合物中一般包含防腐剂。仅举例而言，用于肠胃外注射的制剂可以以包括但不限于安瓿的单位剂型呈现，或呈现于添加有防腐剂的多剂量容器中。

[0354] 适合于本文所述化合物的每日剂量为约0.01mg/kg至约20mg/kg。在一个实施方案中，每日剂量为约0.1mg/kg至约10mg/kg。在包括但不限于人的较大哺乳动物中的指定每日剂量在约0.5mg至约1000mg的范围内，其方便地以单剂量或分剂量(包括但不限于每日至多四次)或以延长释放的形式施用。适用于口服施用的单位剂型包含约1至约500mg的活性成分。在一个实施方案中，单位剂量为约1mg、约5mg、约10mg、约20mg、约50mg、约100mg、约200mg、约250mg、约400mg或约500mg。前述范围仅仅是建议性的，因为关于个体治疗方案的变量数目很大，并且与这些推荐值相当大的偏差并不罕见。这些剂量可根据多种变量而变化，不限于所用化合物的活性、待治疗的疾病或状况、施用方式、个体受试者的要求、所治疗的疾病或状况的严重程度，以及从业者的判断。

[0355] 这类治疗方案的毒性和疗效可通过细胞培养物或实验动物中的标准药学程序来确定，包括但不限于对LD_{50}(对50％群体致死的剂量)和ED_{50}(在50％群体中治疗有效的剂量)的确定。毒性与治疗效果之间的剂量比为治疗指数，且可表示为LD_{50}与ED_{50}之比。表现出高治疗指数的化合物是优选的。从细胞培养测定和动物研究中获得的数据可用于制定用于人的剂量范围。这类化合物的剂量优选落入包括具有最小毒性的ED_{50}的循环浓度的范围内。该剂量可根据所采用的剂型和所使用的施用途径而在该范围内变化。

联合治疗

[0356] 式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物及其组合物还可与针对其对于待治疗状况的治疗价值而选择的其他治疗剂联合使用。通常，本文所述的组合物以及(在采用联合疗法的实施方案中)其他药剂不必在同一药物组合物中施用，并且可能由于不同的物理和化学特征而必须通过不同途径予以施用。在可能的情况下，在同一药物组合物中的施用方式和施用适当性的确定完全在临床医生的知识之内。初始施用可根据本领域公认的既定方案进行，然后根据观察到的效果，可由临床医生修改施用方式和施用时间。

[0357] 在某些情况下，将至少一种本文所述化合物与另一种治疗剂联合施用可能是合适的。仅举例而言，如果患者在接受一种本文化合物如式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物时经历的一种副作用为恶心，则将抗恶心剂与初始治疗剂联合施用可能是合适的。或者，仅举例而言，可通过施用佐剂来增强一种本文所述化合物的治疗有效性(即，该佐剂自身可能具有微小的治疗益处，但与另一治疗剂组合时，对患者的总体治疗益处得到增强)。或者，仅举例而言，可通过将一种本文所述的化合物与同样

具有治疗益处的另一治疗剂(其也包括治疗方案)一起施用来增加患者所经历的益处。在任何情况下,无论所治疗的疾病、症状或状况如何,患者所经历的总体益处可简单地为两种治疗剂的累加,或者患者可经历协同益处。

[0358] 对于治疗应用,本发明的化合物或药物可以单独施用或者与常规化学疗法、放射疗法、激素疗法和/或免疫疗法联合地共同施用。

[0359] 作为非限制性实例,本文所述的式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物可以与常规化疗剂共同施用,所述化疗剂包括烷化剂(例如,环磷酰胺、异环磷酰胺、苯丁酸氮芥、白消安、美法仑、氮芥、乌拉莫司汀、噻替派、亚硝基脲等)、抗代谢物(例如,5-氟尿嘧啶、硫唑嘌呤、甲氨蝶呤、甲酰四氢叶酸、卡培他滨、阿糖胞苷、氟尿苷、氟达拉滨、吉西他滨、培美曲塞、雷替曲塞等)、植物生物碱(例如,长春新碱、长春碱、长春瑞滨、长春地辛、鬼臼毒素、紫杉醇、多西他赛等)、拓扑异构酶抑制剂(例如,伊立替康、拓扑替康、安吖啶、依托泊苷(VP16)、依托泊苷磷酸盐、替尼泊苷等)、抗肿瘤抗生素(例如,多柔比星、阿霉素、柔红霉素、表柔比星、放线菌素、博来霉素、丝裂霉素、米托蒽醌、普卡霉素等)、铂基化合物(例如顺铂、奥沙利铂(oxaloplatin)、卡铂等),等等。

[0360] 本文所述的式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物也可以与常规激素治疗剂共同施用,所述常规激素治疗剂包括但不限于类固醇(例如,地塞米松)、非那雄胺、芳香酶抑制剂、它莫西芬和促性腺激素释放激素激动剂(GnRH),如戈舍瑞林。

[0361] 另外,本文所述的式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物可以与常规免疫治疗剂共同施用,所述常规免疫治疗剂包括但不限于免疫刺激剂(例如,卡介苗(BCG)、左旋咪唑、白细胞介素-2、α-干扰素等)、单克隆抗体(例如,抗-CD20、抗-HER2、抗-CD52、抗-HLA-DR和抗-VEGF单克隆抗体)、免疫毒素(例如,抗-CD33单克隆抗体-加利车霉素缀合物、抗-CD22单克隆抗体-假单胞菌外毒素缀合物等)和放射免疫治疗剂(例如,与^{111}In、^{90}Y或^{131}I缀合的抗-CD20单克隆抗体等)。

[0362] 在进一步的实施方案中,本文所述的式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物也可以与STAT 3抑制剂或Janus激酶抑制剂共同施用。

[0363] 所用化合物的具体选择将取决于主治医师的诊断及其对患者状况的判断以及适当的治疗方案。所述化合物可并行施用(例如,同时施用、基本上同时施用或在同一治疗方案内施用)或顺序施用,这取决于疾病、病症或状况的性质,患者的状况,和所用化合物的实际选择。在评价所治疗的疾病和患者的状况后,施用顺序的确定和治疗方案期间每种治疗剂的重复施用次数完全在医生的知识范围之内。

[0364] 当药物以治疗组合使用时,治疗有效剂量可能改变。文献中描述了用于实验性地确定供联合治疗方案使用的药物及其他试剂的治疗有效剂量的方法。例如,文献中广泛描述了使用节律性给药,即提供更频繁、更低的剂量,以使毒副作用减至最小。联合治疗进一步包括在不同时间开始和停止的周期性治疗,以辅助患者的临床管理。

[0365] 对于本文所述的联合疗法,共同施用的化合物的剂量当然将取决于所采用的共同药物的类型、所采用的具体药物、所治疗的疾病或状况,等等。此外,当与一种或多种生物活性剂共同施用时,本文提供的化合物可与该生物活性剂同时或顺序施用。如果顺序施用,则主治医师将决定将蛋白质与该生物活性剂联合施用的适当顺序。

[0366] 在任何情况下，多种治疗剂(其中一种为本文所述的式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物)可以以任意顺序施用或甚至同时施用。如果同时施用，则所述多种治疗剂可以以统一的单一形式或多种形式提供(仅举例而言，作为单一丸剂或两种单独的丸剂)。治疗剂的一种可以以多个剂量给予，或者两者都可以以多个剂量给予。如果不是同时施用，则多个剂量之间的时间选择可在大于零周到少于四周之间不等。此外，组合方法、组合物和制剂并不限于仅使用两种药剂；也想到多种治疗组合的使用。

[0367] 应当理解，可根据多种因素来修改用于治疗、预防或改善寻求缓解的状况的剂量方案。这些因素包括受试者所罹患的病症或状况，以及受试者的年龄、体重、性别、饮食和医疗状况。因此，实际采用的剂量方案可广泛变化，因此可偏离本文所述的剂量方案。

[0368] 构成本文公开的联合疗法的药剂可为组合剂型或用于基本同时施用的单独剂型。构成联合疗法的药剂也可顺序施用，其中治疗化合物通过需要两步施用的方案施用。该两步施用方案可需要活性剂的顺序施用或单独活性剂的间隔施用。多个施用步骤之间的时间段可为几分钟至数小时，这取决于每种药剂的性质，如药剂的效力、溶解度、生物利用度、血浆半衰期和动力学谱。靶分子浓度的昼夜变化还可确定最佳给药间隔。

[0369] 此外，本文所述化合物还可与可为患者提供额外或协同益处的程序联合使用。仅举例而言，预期患者将通过本文所述的方法得到治疗性和/或预防性益处，其中将本文公开化合物的药物组合物和/或与其他治疗剂的组合与遗传测试相组合，以确定该个体是否为已知与某些疾病或状况相关的突变基因的携带者。

[0370] 本文所述的化合物和联合疗法可在疾病或状况发生之前、期间或之后施用，并且施用含有化合物的组合物的时机可以变化。因此，例如，所述化合物可用作预防剂，并可连续施用至倾向于发生状况或疾病的受试者，以便防止疾病或状况的发生。该化合物和组合物可在症状发作期间施用于受试者，或在发作之后尽可能快地施用于受试者。化合物的施用可在症状发作的最初48小时内进行，优选在症状发作的最初48小时内，更优选在症状发作的最初6小时内，最优选地在症状发作的3小时内。初始施用可经由任何可行的途径，例如静脉内注射、推注、经约5分钟至约5小时的输注、丸剂、胶囊、经皮贴片、含服递送等，或它们的组合。优选地，在检测到或怀疑疾病或状况发作之后在可行时尽快施用化合物，并且施用持续治疗该疾病所需的时间长度，例如，1天至约3个月。针对每名受试者的治疗时间长度可以不同，并且可采用已知的标准来确定。例如，化合物或含有该化合物的制剂可施用至少2周，优选约1个月至约5年。

药剂盒/制品

[0371] 为了用于本文所述的治疗应用，本文还描述了药剂盒和制品。这类药剂盒可包含被区室化以接纳一个或多个容器(如小瓶、管等)的载具、包装或容器，每个容器均包含将在本文所述方法中使用的一个单独的元件。合适的容器包括例如瓶子、小瓶、注射器和试管。该容器可由多种材料如玻璃或塑料形成。

[0372] 本文提供的制品含有包装材料。用于包装药物产品的包装材料包括但不限于例如第5,323,907、5,052,558和5,033,252号美国专利中描述的那些。药物包装材料的实例包括但不限于泡罩包装、瓶子、管、吸入器、泵、袋、小瓶、容器、注射器、瓶子以及适合于所选制剂和预期施用方式和治疗的任何包装材料。本文提供的化合物和组合物的众多制剂被设想为针对将会受益于Olig2活性抑制的任何疾病、病症或状况的多种治疗。

[0373] 例如,所述容器可包含一种或多种本文所述的化合物,任选地在组合物中或与如本文公开的另一种药剂组合。任选地,该容器具有无菌入口(例如,该容器可以是静脉内溶液袋或具有可被皮下注射针刺穿的塞子的小瓶)。任选地,这类药剂盒包含化合物以及识别描述或标签,或与其在本文所述方法中的应用相关的说明书。

[0374] 药剂盒一般可包含一个或多个额外的容器,每个容器均具有从使用本文所述化合物的商业和用户观点出发所期望的多种材料(如任选地呈浓缩形式的试剂,和/或装置)中的一种或多种。这类材料的非限制性实例包括但不限于缓冲液、稀释剂、过滤器、针头、注射器;载具、包装、容器、小瓶和/或列出内容物的管标签以及/或者使用说明书,以及具有使用说明的包装插页。通常还将包括一套说明书。

[0375] 标签可处于容器上或与容器相关联。当构成标签的字母、数字或其他字符附接、模制或蚀刻到容器本身中时,该标签可处于该容器上;当标签存在于还容纳容器的器皿或载具内时,该标签可与该容器相关联,例如作为包装插页。标签可用于指示内容物将用于特定的治疗应用。标签还可指示内容物的使用指南,如在本文所述方法中的使用指南。

[0376] 在某些实施方案中,所述药物组合物可以呈现在包装或分配器装置中,该包装或装置可以含有一种或多种含有本文提供的化合物的单位剂型。例如,该包装可以包含金属或塑料箔,如泡罩包装。该包装或分配器装置可以附有施用说明书。该包装或分配器还可以附有监管药物生产、使用或销售的政府机构所规定形式的、与容器相关联的通知,该通知反映出该机构对用于人类或兽医给药的药物形式的批准。例如,这样的通知可以是由美国食品药品管理局对处方药批准的标签或批准的产品插页。也可以制备在相容的药物载体中配制的、含有本文提供的化合物的组合物,将其置于适当的容器中,并且标示出用于治疗所示状况。

实施例

[0377] 这些实施例仅出于说明目的而提供,并非限制本文提供的权利要求的范围。用于合成本文所述化合物的起始材料和试剂可以是合成的或可从诸如但不限于Sigma-Aldrich Corp.、Acros Organics、Fluka和Fisher Scientific的商业来源获得。

[0378] HPLC方法:平台(方法1-3):Agilent 1100系列HPLC,包含泵、脱气器和UV检测器,配备有自动进样器。MS检测器(APCI)PE Sciex API 150 EX。平台(方法4):Agilent 1290系列HPLC,包含二元泵、脱气器和UV检测器,配备有自动进样器。MS检测器AJS-ES。

[0379] 方法1:柱——Zorbax C18,尺寸4.6mm×7.5cm;溶剂A:0.05%TFA水溶液,溶剂B:0.05%TFA的乙腈溶液;流速——0.7mL/min;梯度:在9min内从5%B到100%B,在100%B下保持4min,并且在0.5min内从100%B到5%B;UV检测器-通道1=220nm,通道2=254nm。

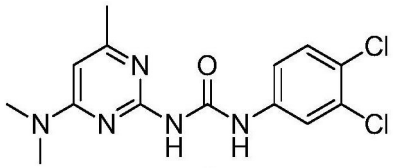
[0380] 方法2:柱——Zorbax C18,尺寸4.6mm×7.5cm;溶剂A:0.05%TFA水溶液,溶剂B:0.05%TFA的乙腈溶液;流速——0.7mL/min;梯度:在5min内从5%B到100%B,在100%B下保持2min,并且在0.5min内从100%B到5%B;UV检测器-通道1=220nm,通道2=254nm。

[0381] 方法3:柱——SunFireTM(Waters)C18,尺寸2.1mm×50mm;溶剂A:0.05%TFA水溶液,溶剂B:0.05%TFA的乙腈溶液;流速——0.8mL/min;梯度:在2.4min内从10%B到90%B,在90%B下保持1.25min,并且在0.25min内从90%B到10%B,在10%B下保持1.5min;UV检测器-通道1=220nm,通道2=254nm。

[0382] 方法4:柱——Zorbax Eclipse Plus C18,尺寸2.1×50mm;溶剂A:0.10%甲酸水

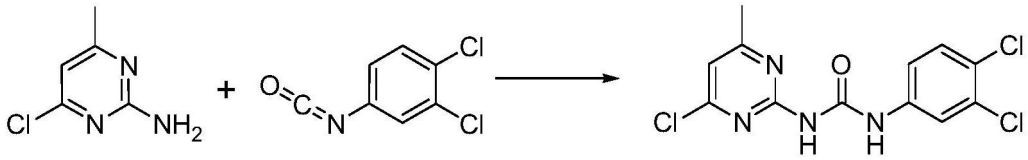
溶液，溶剂B：0.00％甲酸的乙腈溶液；流速——0.7mL/min；梯度：在5min内从5％B到95％B，并且在95％B下保持2min；UV检测器-通道1＝254nm，通道2＝254nm。

实施例1：(N-甲基{2-[3-(3,4-二氯苯基)脲基]-6-甲基-4-嘧啶基}氨基)甲烷(2)的合成



2

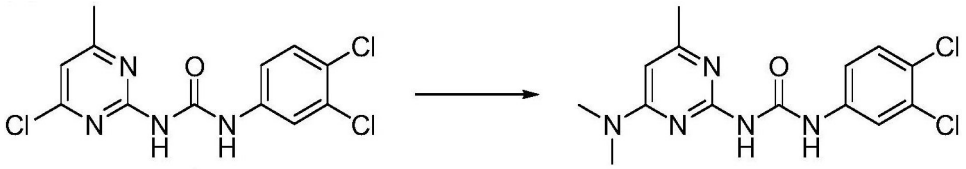
[0383] 步骤1：1-(4-氯-6-甲基-2-嘧啶基)-3-(3,4-二氯苯基)脲(1)



1

[0384] 将3,4-二氯苯基异氰酸酯(5g，26.6mmol)和2-氨基-4-氯-6-甲基嘧啶(3.82g，26.6mmol)以及1,4-二氧杂环己烷(130.0mL)的混合物在回流下加热15小时。冷却该混合物，并添加MeOH(50mL)。通过过滤收集白色沉淀物并干燥，得到化合物(1)(6g，69％)。LC/MS：Rt＝3.4min，m/z＝333.3-335.3[MH^+]。

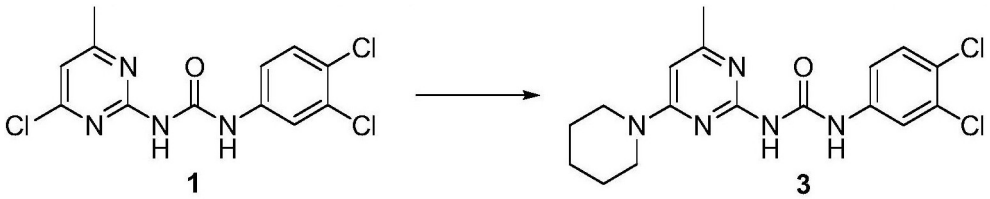
[0385] 步骤2：1-(N-甲基{2-[3-(3,4-二氯苯基)脲基]-6-甲基-2-嘧啶基}氨基)甲烷(2)



1 2

[0386] 将1-(4-氯-6-甲基-2-嘧啶基)-3-(3,4-二氯苯基)脲(1)(83mg，0.25mmol)、二甲胺(0.125mL，0.25mmol，在THF中的2M溶液)、二异丙基乙胺(50μL)和二甲基乙酰胺(3.0mL)的混合物加热到90-95℃过夜。冷却该混合物，并添加MeOH(3.0mL)。过滤所形成的白色沉淀物以提供标题化合物(2)(45.0mg，52％)。LC/MS：Rt＝2.85min，m/z＝340.3-344.2[MH^+]。

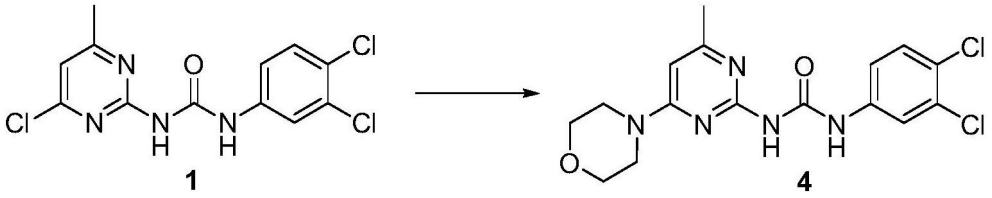
实施例2：1-(3,4-二氯苯基)-3-(6-甲基-4-哌啶子基-2-嘧啶基)脲(3)的合成



1 3

[0387] 将1-(4-氯-6-甲基-2-嘧啶基)-3-(3,4-二氯苯基)脲(1)(83mg，0.25mmol)、哌啶(106mg，1.25mmol)和二甲基乙酰胺(3.0mL)的混合物加热到90-95℃过夜。冷却该混合物，并添加MeOH(3.0mL)。过滤所形成的白色沉淀物以提供标题化合物(3)(63.0mg，66％)。LC/MS：Rt＝2.95min，m/z＝381.9-384.3[MH^+]。

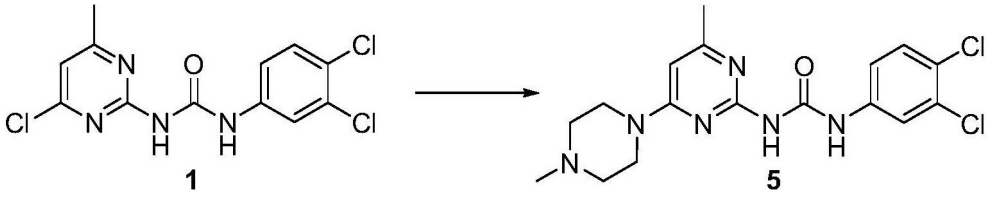
实施例3：1-(3,4-二氯苯基)-3-(6-甲基-4-吗啉代-2-嘧啶基)脲(4)的合成



1 4

[0388] 将1-(4-氯-6-甲基-2-嘧啶基)-3-(3,4-二氯苯基)脲(1)(83mg,0.25mmol)、吗啉(105mg,1.25mmol)和二甲基乙酰胺(3.0mL)的混合物加热到90-95℃过夜。冷却该混合物,并添加MeOH(3.0mL)。通过过滤收集白色固体沉淀物并干燥,得到标题化合物(4)(61mg,64%)。LC/MS:Rt=3.12min,m/z=382.3-384.6[MH^+]。

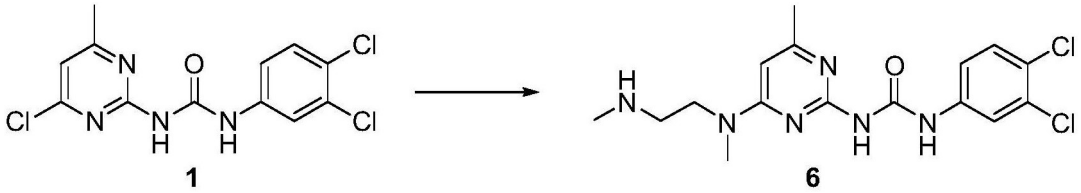
实施例4:1-(3,4-二氯苯基)-3-{6-甲基-4-(4-甲基-哌嗪-1-基-)嘧啶-2-基}-脲(5)的合成



1 5

[0389] 将1-(2-氯-6-甲基-2-嘧啶基)-3-(3,4-二氯苯基)脲(1)(83mg,0.25mmol)、1-甲基哌嗪(27.0mg,0.27mmol)、二异丙基乙胺(52μL)和二甲基乙酰胺(3.0mL)的混合物加热到90-95℃过夜。冷却该混合物,并添加MeOH(3.0mL)。过滤所形成的白色沉淀物以得到标题化合物(5)(55mg,56%)。LC/MS:Rt=2.82min,m/z=397.4-399.4[MH^+]。

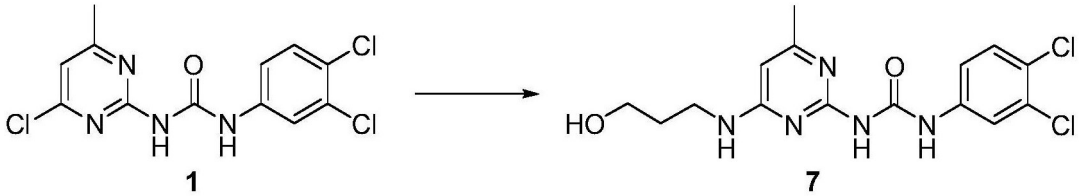
实施例5:1-(N-甲基{2-[3-(3,4-二氯苯基)脲基]-6-甲基-4-嘧啶基}氨基)-2-(甲氨基)乙烷(6)的合成



1 6

[0390] 将1-(4-氯-6-甲基-2-嘧啶基)-3-(3,4-二氯苯基)脲(1)(166mg,0.5mmol)、N,N'-二甲基乙烷-1,2-二胺(450mg,5mmol)和1,4-二氧杂环己烷(4.0mL)的混合物加热到90-95℃过夜。冷却该混合物,并添加MeOH(5.0mL)。过滤所形成的白色沉淀物以得到标题化合物(6)(140mg,73%)。LC/MS:Rt=2.92min,m/z=384.3-386.4[MH^+]。

实施例6:3-{2-[3-(3,4-二氯苯基)脲基]-6-甲基-嘧啶-4-基}-氨基丙醇(7)的合成

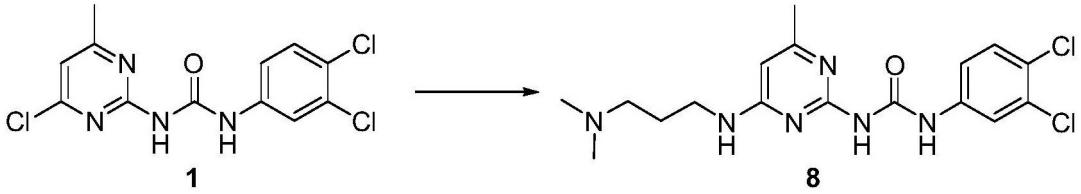


1 7

[0391] 将1-(4-氯-6-甲基-2-嘧啶基)-3-(3,4-二氯苯基)脲(1)(166mg,0.5mmol)、3-氨基丙醇(73.0mg,0.5mmol)和1,4-二氧杂环己烷(4.0mL)的混合物加热到90-95℃过夜。冷却该混合物,并添加MeOH(3.0mL)。过滤所形成的白色沉淀物以得到标题化合物(7)(90mg,56%)。LC/MS:Rt=3.06min,m/z=372.2-374.5[MH^+]。

实施例7:1-{2-[3-(3,4-二氯苯基)脲基]-6-甲基-嘧啶-4-基}-氨基-3-(二甲氨基)丙

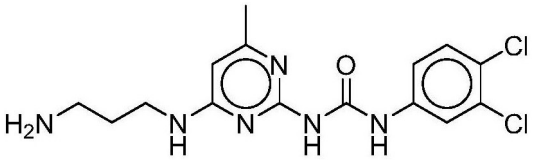
烷(8)的合成



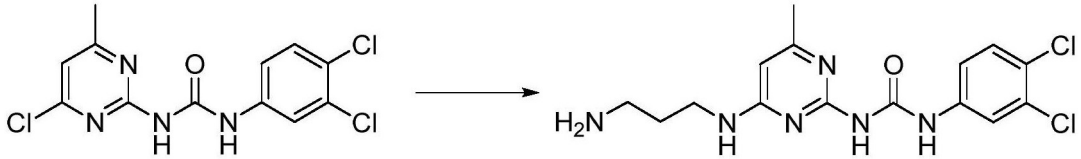
1 8

[0392] 将1-(4-氯-6-甲基-2-嘧啶基)-3-(3,4-二氯苯基)脲(1)(166mg,0.5mmol)、N,N'-二甲基-1,3-丙二胺(510mg,5.0mmol)和1,4-二氧杂环己烷(4.0mL)的混合物加热到90-95℃过夜。冷却该混合物,并添加MeOH(3.0mL)。过滤所形成的白色沉淀物以得到标题化合物(8)(64mg,33%)。LC/MS:Rt=2.96min,m/z=397.2-399.4[MH^+]。

实施例8:1-(4-((2-氨丙基)氨基)-6-甲基嘧啶-2-基)-3-(3,4-二氯苯基)脲(9)的合成



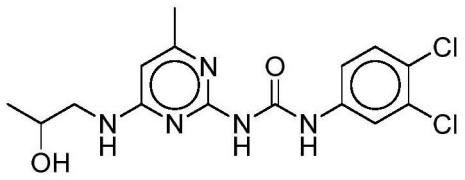
9



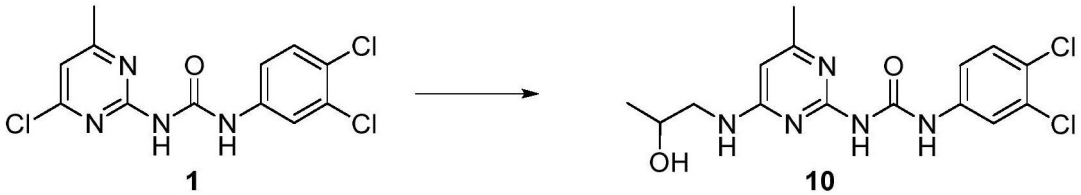
1 9

[0393] 将1-(4-氯-6-甲基-2-嘧啶基)-3-(3,4-二氯苯基)脲(1)(1.05g,3.2mmol)和甲苯(4.7mL)的混合物在搅拌下加热至回流。向其中添加1,3-丙二胺(0.32mL,3.8mmol)和三乙胺(0.66mL,4.7mmol),并继续回流。在冷却后形成沉淀物,将其过滤并用甲醇和二乙醚洗涤,得到标题化合物(9)(1.01g,83%)。LC/MS:方法4:Rt=1.44min,m/z=368.1-370.1[MH+]。

实施例9:1-{2-[3-(3,4-二氯苯基)脲基]-6-甲基-4-嘧啶基氨基}-2-丙醇(10)的合成



10



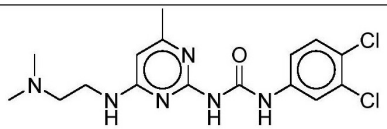
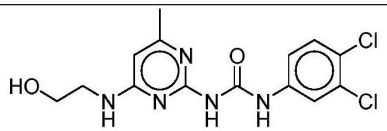
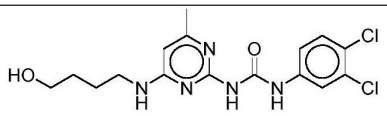
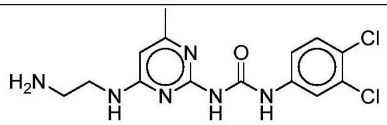
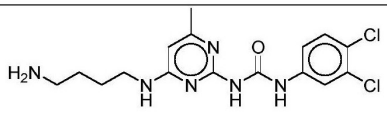
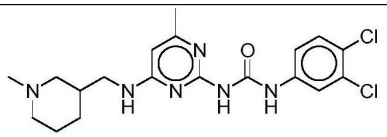
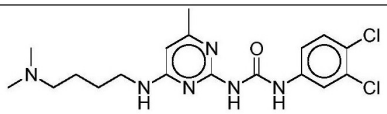
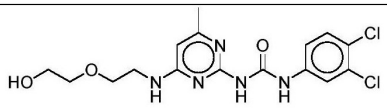
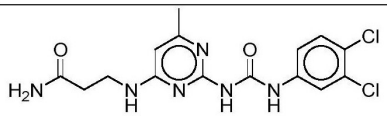
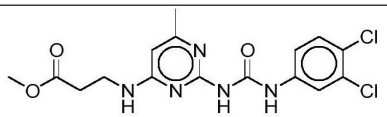
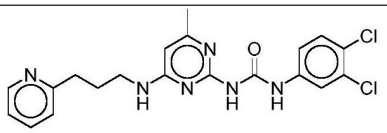
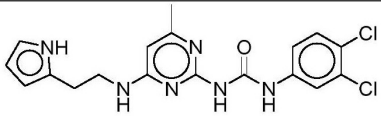
1 10

[0394] 将1-(4-氯-6-甲基-2-嘧啶基)-3-(3,4-二氯苯基)脲(1)(0.2g,0.56mmol)悬浮在2-丙醇(1.1mL)中。向其中添加三乙胺(0.12mL,0.89mmol),然后添加1-氨基丙-2-醇(0.06mL,0.70mmol),并将混合物在搅拌下加热至回流过夜。在冷却后形成沉淀物,将其过

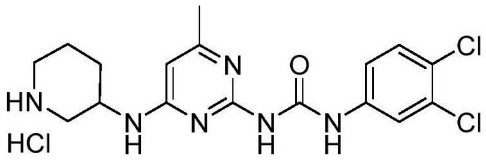
滤并用无水乙醇洗涤，得到标题化合物(10)(6.4mg，3％)。LC/MS：方法4：Rt＝2.22min，m/z＝370.1-372.1[MH+]。

[0395] 根据针对实施例1-9描述的类似过程制备下列实施例：

化合物ID	实施例ID	结构	HPLC方法	产率(质量/%)	RT(min)	MH^+

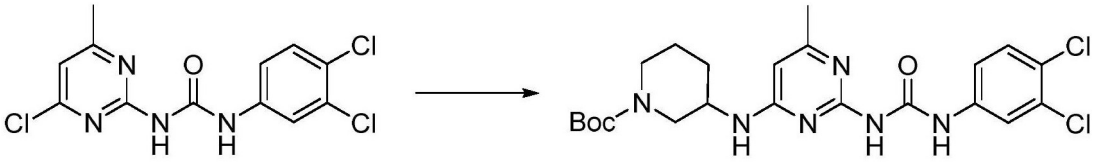
11	**10**		**4**	**0.24 g, 21**	**2.48**	**383.2-385.1**
12	**11**		**4**	**27 mg, 18**	**1.70**	**356.1-358.1**
13	**12**		**4**	**14 mg, 11**	**2.18**	**384.1-386.1**
14	**13**		**4**	**16 mg, 71**	**1.80**	**355.1-357.1**
15	**14**		**4**	**0.14 g, 60**	**1.89**	**383.1-385.1**
16	**15**			**15 mg, 8**	**1.74**	**423.2-425.2**
17	**16**		**4**	**0.23 g, 87**	**2.30**	**411.2-413.2**
18	**17**		**4**	**0.19 g, 82**	**2.01**	**400.1-402.1**
19	**18**		**4**	**17 mg, 9**	**2.11**	**383.1-385.1**
20	**19**		**4**	**11 mg, 41**	**2.62**	**398.1-400.1**
21	**20**		**4**	**0.20 g, 73**	**1.96**	**431.2-433.2**
22	**21**		**4**	**0.20 g, 78**	**2.85**	**405.1-407.1**

实施例22：(±)-2-[3-(3,4-二氯苯基)脲基]-6-甲基-4-(3-哌啶基氨基)嘧啶盐酸盐(24)的合成



24

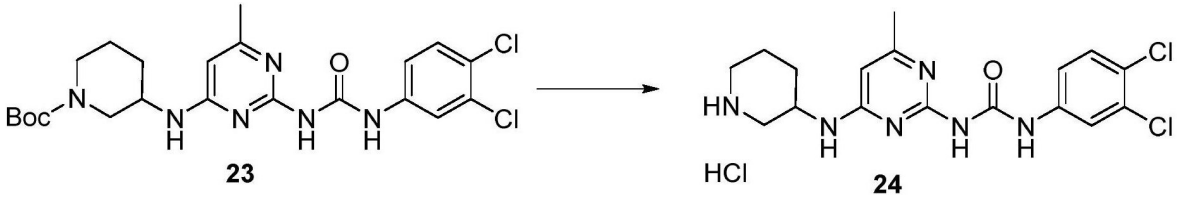
[0396] 步骤1:2-(2-(3-(3,4-二氯苯基)脲基)-6-甲基嘧啶-4-基氨基)哌啶-1-甲酸叔丁酯(23)



1 23

[0397] 将1-(4-氯-6-甲基-2-嘧啶基)-3-(3,4-二氯苯基)脲(1)(905mg,2.75mmol)、1-boc-氨基-哌啶(901mg,4.5mmol)和二甲基乙酰胺(9.0mL)的混合物在85℃下加热5小时。将该混合物冷却并加至水中。形成白色固体,将其过滤并用1M HCl和EA洗涤并干燥(1.03g,76%)。

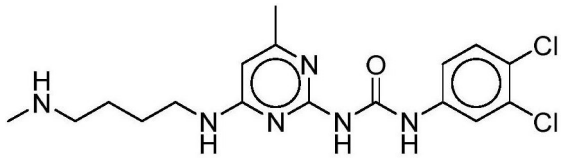
[0398] 步骤2:(±)-2-[3-(3,4-二氯苯基)脲基]-6-甲基-4-(3-哌啶基氨基)嘧啶盐酸盐(24)



23 24

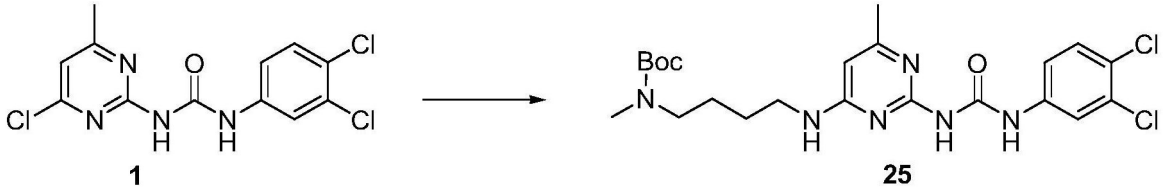
[0399] 将BOC衍生物(9)(741mg,1.5mmol)悬浮于DCM:MeOH的9:1混合物(7.5mL)中,并且添加HCl(在二氧杂环己烷中4M,7.5mL)。将反应混合物在室温下搅拌过夜。在真空中除去挥发物,产生作为盐酸盐的标题化合物(10)(500mg)。LC/MS:Rt=3.18min,m/z=395.1[MH^+]。

实施例23:1-(3,4-二氯苯基)-3-(4-甲基-6-((4-(甲氨基)丁基)氨基)嘧啶-2-基)脲(26)的合成



26

[0400] 步骤1:(4-{2-[3-(3,4-二氯-苯基)-脲基]-6-甲基-嘧啶-4-基氨基}-丁基)-甲基-氨基甲酸叔丁酯(25)

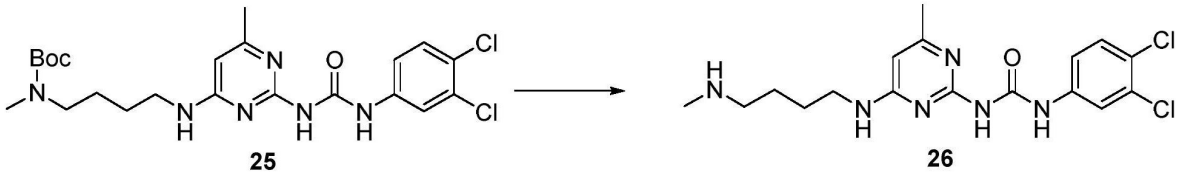


1 25

[0401] 将1-(4-氯-6-甲基-2-嘧啶基)-3-(3,4-二氯苯基)脲(1)(1.4g,4.3mmol)和甲苯(6.5mL)的混合物在搅拌下加热至回流。向其中添加N-(4-氨基丁基)-N-甲基氨基甲酸叔丁

酯(1.0g,5.2mmol)和三乙胺(0.91mL,6.4mmol),并继续回流30分钟。在冷却后添加甲醇,将所形成的沉淀物过滤并用二乙醚洗涤,得到标题化合物(25)(2.0g,90%)。LC/MS:Rt=3.97min,m/z=497.2-499.2[MH+]。

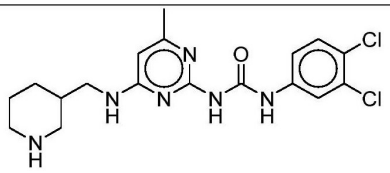
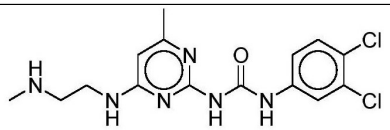
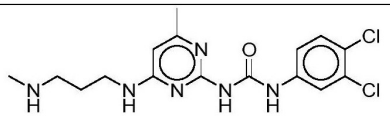
[0402] 步骤2:1-(3,4-二氯苯基)-3-(4-甲基-6-((4-(甲氨基)丁基)氨基)嘧啶-2-基)脲



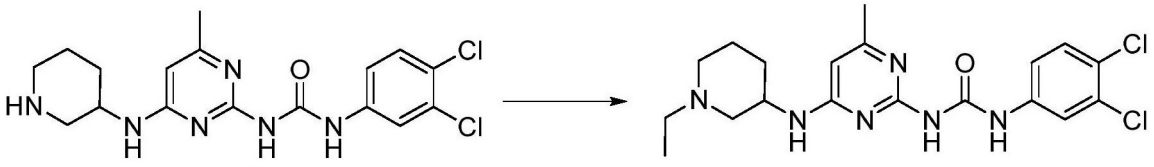
25 26

[0403] 将BOC衍生物(25)(2.5g,4.7mmol)悬浮在DCM(15mL)中,向其中添加三氟乙酸(9mL,118mmol)。将反应混合物在室温下搅拌30分钟。用1N NaOH溶液(4.7mL,4.7mmol)处理该混合物,并将混合物搅拌30分钟。分离各层,用水和盐水洗涤有机物,然后干燥并浓缩,产生标题产物(26)。LC/MS:方法4:Rt=2.31min,m/z=397.2-399.2[MH^+]。

[0404] 根据针对实施例22-23描述的类似过程制备下列实施例:

化合物ID	实施例ID	结构	HPLC方法	产率(质量/%)	RT (min)	MH^+
27	24		4	1.7 g, 91	2.24	409.2-411.2
28	25		4	69 mg, 97	1.77	370.1-372.1
29	26		4	0.37 g, 92	0.35	383.2-385.1

实施例27:(±)-2-[3-(3,4-二氯苯基)脲基]-4-(1-乙基-哌啶-3-基-氨基)-6-甲基嘧啶(30)的合成

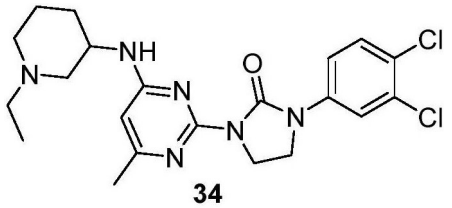


24 30

[0405] 向2-[3-(3,4-二氯苯基)脲基]-6-甲基-4-(3-哌啶基氨基)嘧啶(24)(215mg,0.5mmol)的DCM(2.5mL)溶液中添加乙醛(141μL,2.5mmol),然后添加氰基硼氢化钠(63mg,1.00mmol)。将反应混合物搅拌3小时,然后用DCM(10mL)稀释,并用水、$NaHCO_3$溶液和水洗涤。将有机层干燥(Na_2SO_4)、过滤并浓缩。将残余物在硅胶板上纯化(洗脱液:DCM:MeOH:NH_4OH:400:50:2v/v),得到标题化合物(30)(50mg,24%)。LC/MS:Rt=3.05min,m/z=423.4[MH^+]。

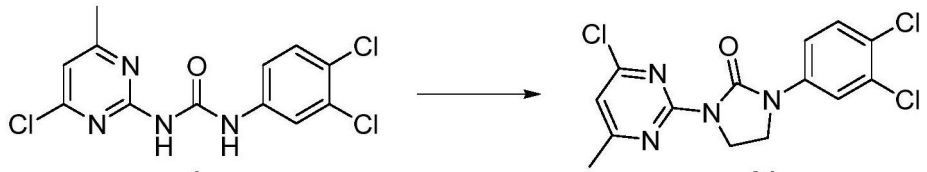
实施例28:(±)-1-(3,4-二氯苯基)-3-[4-(1-乙基-3-哌啶基氨基)-6-甲基-2-嘧啶

基]-2-咪唑烷酮(34)的合成



34

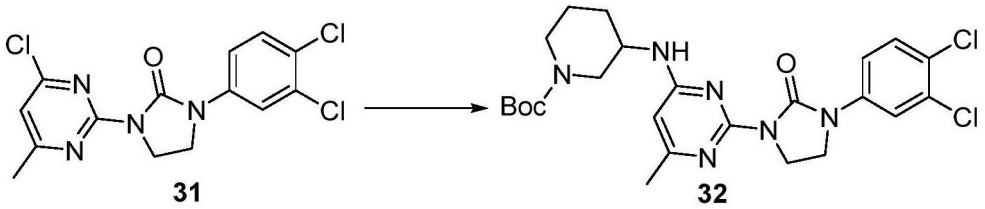
[0406] 步骤1:3-(4-氯-6-甲基-2-嘧啶基)-1-(3,4-二氯苯基)-2-咪唑烷酮(31)



1 31

[0407] 将1-(4-氯-6-甲基-2-嘧啶基)-3-(3,4-二氯苯基)脲(1)(150mg,0.45mmol)、1,2-二溴乙烷(847mg,4.53mmol)、K_2CO_3(607mg,4.53mmol)在丙酮(4.5mL)中的混合物加热至回流3小时。将反应混合物冷却,倒入水(25.0mL)中,并用EA(2×25mL)萃取。将有机层干燥(Na_2SO_4)、过滤并蒸发至干。残余物通过色谱法(硅胶柱,洗脱液0-40%EA的己烷溶液,梯度)纯化,产生化合物(31)(100mg,61.2%)。LC/MS:Rt=4.15min,m/z=357.2[MH^+]。

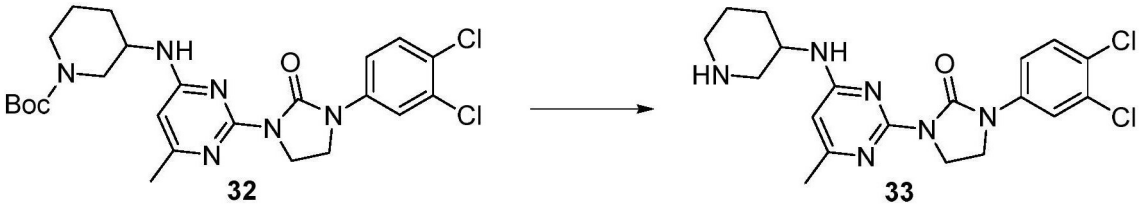
[0408] 步骤2:(±)-3-(2-(3-(3,4-二氯苯基)-2-氧代咪唑烷-1-基)-6-甲基嘧啶-4-基氨基)哌啶-1-甲酸叔丁酯(32)



31 32

[0409] 将3-(4-氯-6-甲基-2-嘧啶基)-1-(3,4-二氯苯基)-2-咪唑烷酮(31)(100mg,0.28mmol)、1-Boc-3-氨基哌啶(901mg,4.5mmol)、DIPEA(73mg,0.56mmol)和DMA(3.0mL)的混合物在85℃下加热5小时。将反应冷却并加至水中。将所形成的白色固体过滤并用0.1M HCl和EA洗涤并干燥(100mg),产生化合物(32)。

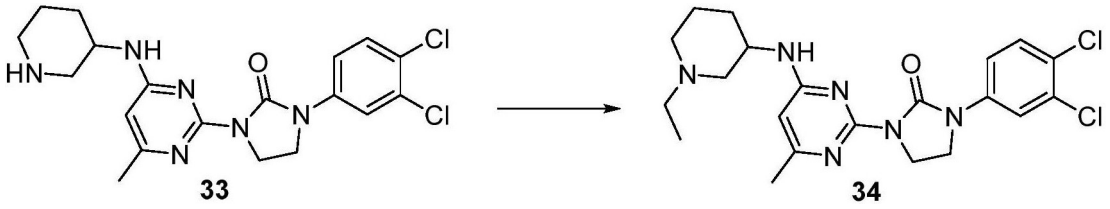
[0410] 步骤3:(±)-1-(3,4-二氯苯基)-3-[6-甲基-4-(3-哌啶基氨基)-2-嘧啶基]-2-咪唑烷酮(33)



32 33

[0411] 将化合物(32)(100mg,0.192mmol)悬浮在DCM(10.0mL)中,并添加TFA(10.0mL)。将混合物在室温下搅拌过夜。在真空中除去挥发物,产生作为TFA盐的1-(4-氯-6-甲基-2-嘧啶基)-3-(3,4-二氯苯基)-2-咪唑烷酮(33)(100mg)。

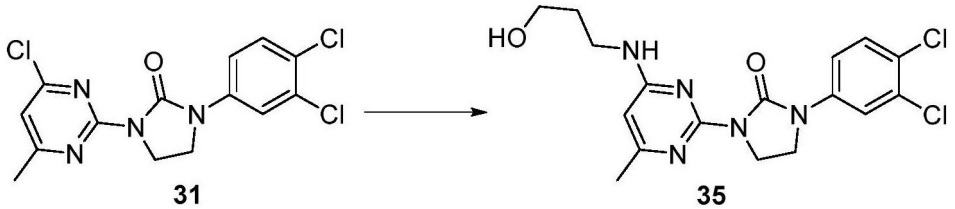
[0412] 步骤4:(±)-1-(3,4-二氯苯基)-3-[4-(1-乙基-3-哌啶基氨基)-6-甲基-2-嘧啶基]-2-咪唑烷酮(34)



33 34

[0413] 向(±)-1-(3,4-二氯苯基)-3-[6-甲基-4-(3-哌啶基氨基)-2-嘧啶基]-2-咪唑烷酮(33)(100mg,0.237mmol)的DCM(2.5mL)溶液中添加乙醛(52mg,1.187mmol),然后添加氰基硼氢化钠(29mg,0.475mmol)。将反应混合物搅拌3小时,然后用DCM(10mL)稀释。用水、$NaHCO_3$溶液和水洗涤反应混合物。将有机层干燥(Na_2SO_4)、过滤并浓缩,产生粗产物,将该粗产物在硅胶板上纯化(洗脱液,DCM:MeOH:NH_4OH:400:50:2),产生标题化合物(34)(15mg,14%)。LC/MS:Rt=0.05min,m/z=450.6[MH^+]。

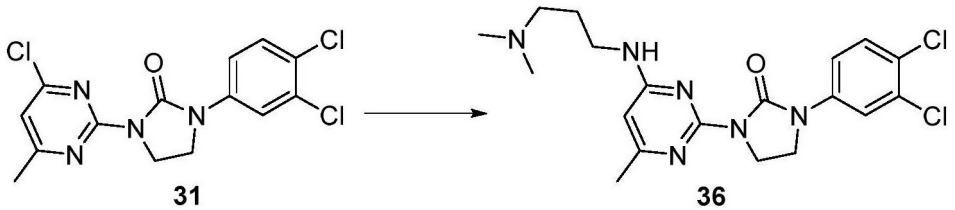
实施例29:3-(3,4-二氯苯基)-1-[4-(3-羟丙基氨基)-6-甲基-2-嘧啶基]-2-咪唑烷酮(35)的合成



31 35

[0414] 将3-(4-氯-6-甲基-2-嘧啶基)-1-(3,4-二氯苯基)-2-咪唑烷酮(31)(50mg,0.14mmol)、3-氨基丙醇(16mg,0.21mmol)、DIPEA(271mg,2.1mmol)投入DMA(3.0mL)中,并在80℃下加热12小时。然后冷却反应混合物并添加水。沉淀的所需化合物利用MeOH和DCM混合物来结晶。过滤并干燥所得晶体,得到标题化合物(35)(25mg,45%)。LC/MS:Rt=4.24min,m/z=397.3[MH^+]。

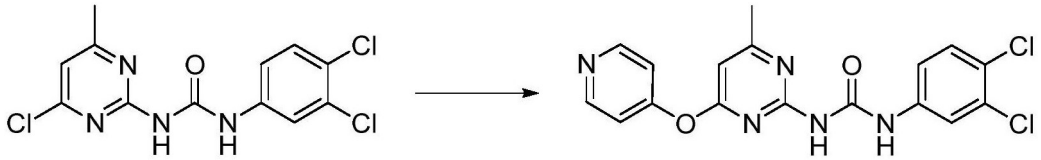
实施例30:3-(3,4-二氯苯基)-1-{4-[3-(二甲氨基)丙氨基]-6-甲基-2-嘧啶基}-2-咪唑烷酮(36)的合成



31 36

[0415] 将3-(4-氯-6-甲基-2-嘧啶基)-1-(3,4-二氯苯基)-2-咪唑烷酮(31)(50mg,0.14mmol)、3-(二甲氨基)丙胺(21mg,0.21mmol)、DIPEA(271mg,2.1mmol)投入DMA(3.0mL)中,并在80℃下加热12小时。冷却反应混合物并添加水。沉淀的所需化合物利用MeOH和DCM混合物来结晶。过滤并干燥所得晶体,得到标题化合物(36)(25mg,45%)。LC/MS:Rt=4.16min,m/z=424.3[MH^+]。

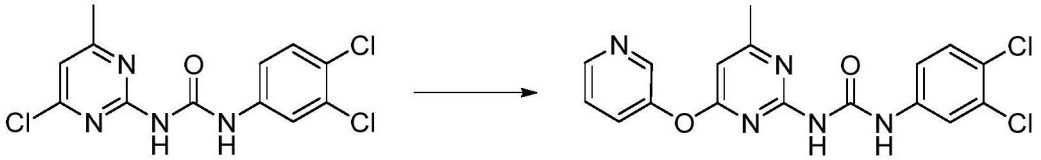
实施例31:1-(3,4-二氯苯基)-3-[6-甲基-4-(4-吡啶基氧基)-2-嘧啶基]-脲(37)的合成



1 37

[0416] 将1-(4-氯-6-甲基-2-嘧啶基)-3-(3,4-二氯苯基)脲(1)(50mg,0.15mmol)、K_2CO_3(42.0mg,0.30mmol)和4-羟基吡啶(21.0mg,0.225mmol)在1,4-二氧杂环己烷中的混合物在100℃下搅拌4小时。将反应混合物冷却,用水稀释,并用EA(2×10mL)萃取。将有机层干燥(Na_2SO_4)、过滤并浓缩,产生呈固体的标题化合物(37)(28.0mg,48%)。LC/MS:Rt=3.09min,m/z=390.4[MH^+]。

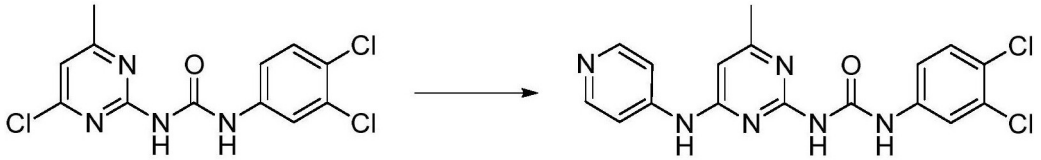
实施例32:1-(3,4-二氯苯基)-3-[6-甲基-4-(3-吡啶基氧基)-2-嘧啶基]-脲(38)的合成



1 38

[0417] 将1-(4-氯-6-甲基-2-嘧啶基)-3-(3,4-二氯苯基)脲(1)(50mg,0.15mmol)、K_2CO_3(42mg,0.30mmol)和3-羟基吡啶(21mg,0.225mmol)在1,4-二氧杂环己烷中的混合物在100℃下搅拌4小时。将该反应混合物冷却,用水稀释,并用EA(2×10mL)萃取。将有机层干燥(Na_2SO_4)、过滤并浓缩,产生呈固体的标题化合物(38)(29mg,50%)。LC/MS:Rt=3.26min,m/z=390.4[MH^+]。

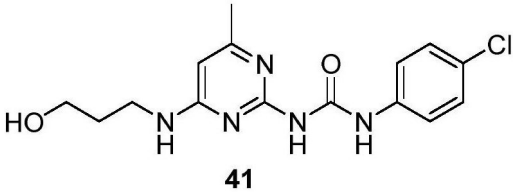
实施例33:2-[3-(3,4-二氯苯基)脲基]-6-甲基-4-(4-吡啶基氨基)嘧啶(39)的合成



1 39

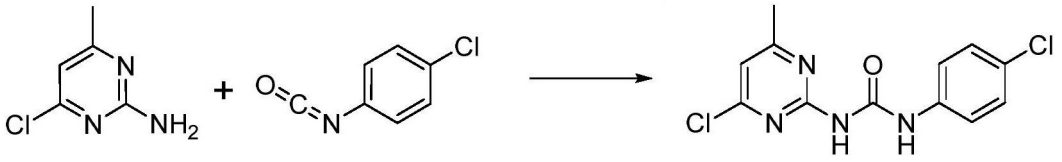
[0418] 将1-(4-氯-6-甲基-2-嘧啶基)-3-(3,4-二氯苯基)脲(1)(50mg,0.15mmol)、4-氨基吡啶(21.0mg,0.225mmol)、二异丙基乙胺(52μL,0.30mmol)的混合物在DMA(1.5mL)中加热4小时。将反应混合物冷却,用水稀释,并用EA(2×10mL)萃取。将有机层干燥(Na_2SO_4)、过滤并浓缩,产生呈固体的标题化合物(39)(30mg,52%)。LC/MS:Rt=0.04min,m/z=389.3[MH^+]。

实施例34:3-{2-[3-(对氯苯基)脲基]-6-甲基-4-嘧啶基氨基}-丙醇(41)的合成



41

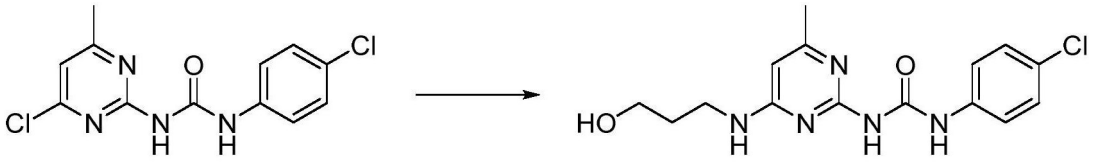
[0419] 步骤1:1-(4-氯-6-甲基-2-嘧啶基)-3-(对氯苯基)脲(40)



40

[0420] 将2-氨基-4-氯-6-甲基嘧啶(72mg,0.5mmol)和4-氯-苯基异氰酸酯(115mg,0.75mmol)在1,4-二氧杂环己烷(1mL)中的混合物在100℃下加热3小时。在真空中浓缩该混合物,将残余物与MeOH一起研磨、过滤并干燥,产生呈白色固体的化合物(40)(72mg,49%)。

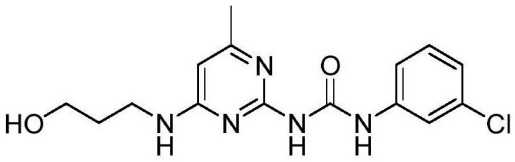
[0421] 步骤2:3-{2-[3-(对氯苯基)脲基]-6-甲基-4-嘧啶基氨基}-丙醇(41)



40 41

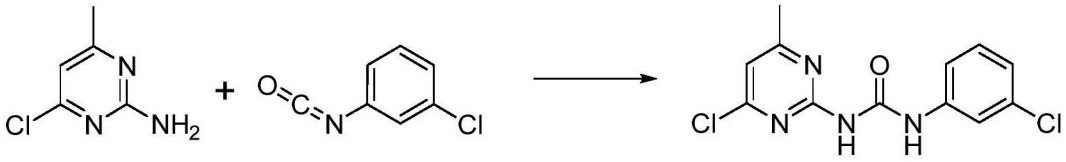
[0422] 将1-(4-氯-6-甲基-2-嘧啶基)-3-(对氯苯基)脲(40)(36mg,0.12mmol)和3-氨基-1-丙醇(46mg,0.61mmol)在DMA(1mL)中的混合物在100℃下加热3小时。冷却该混合物。过滤白色沉淀物并风干,产生标题化合物(41)(20mg,49%)。LC/MS:Rt=0.30min,m/z=336.6[MH^+]。

实施例35:3-{2-[3-(间氯苯基)脲基]-6-甲基-4-嘧啶基氨基}-丙醇(43)的合成



43

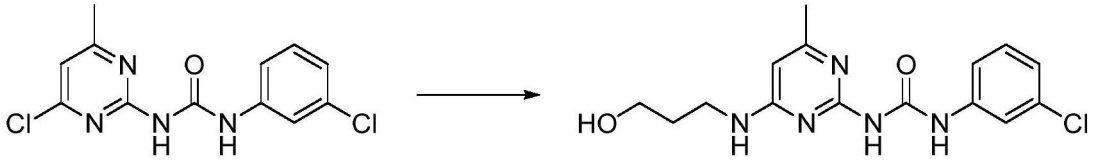
[0423] 步骤1:1-(4-氯-6-甲基-2-嘧啶基)-3-(间氯苯基)脲(42)



42

[0424] 将2-氨基-4-氯-6-甲基嘧啶(72mg,0.5mmol)和3-氯-苯基异氰酸酯(115mg,0.75mmol)在1,4-二氧杂环己烷(1mL)中的混合物在100℃下加热3小时。在真空中浓缩该混合物,将残余物与MeOH一起研磨、过滤并干燥,产生呈白色固体的化合物(42)(115mg,88%)。

[0425] 步骤2:3-{2-[3-(间氯苯基)脲基]-6-甲基-4-嘧啶基氨基}-丙醇(43)

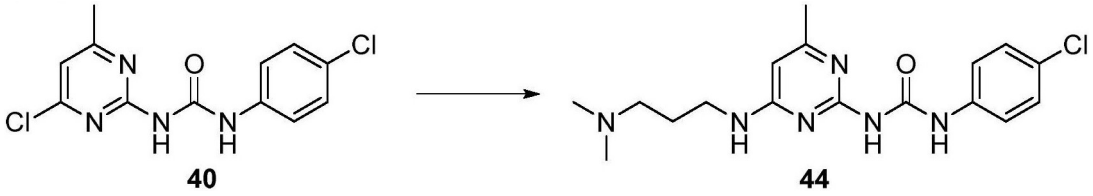


42 43

[0426] 将1-(4-氯-6-甲基-2-嘧啶基)-3-(间氯苯基)脲(38)(58mg,0.22mmol)和3-氨基-1-丙醇(50mg,0.66mmol)在DMA(1mL)中的混合物在100℃下加热3小时。冷却该混合物。过滤

白色沉淀物并风干,产生标题化合物(43)(54mg,82%)。LC/MS:Rt=0.11min,m/z=336.6[MH+]。

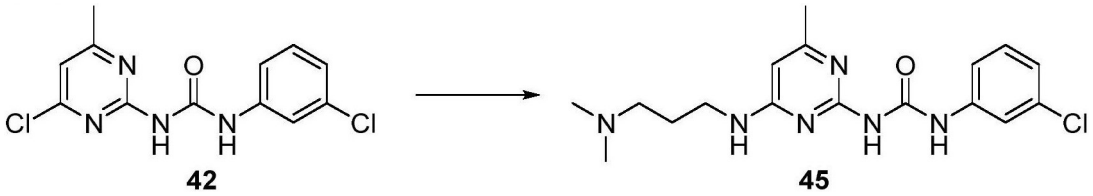
实施例36:1-{2-[3-(4-氯-苯基)脲基]-6-甲基-4-嘧啶-基氨基}-3-(二甲氨基)丙烷(44)的合成



40 44

[0427] 将3-(4-氯苯基)-1-(4-氯-6-甲基-2-嘧啶基)脲(40)(36.0mg,0.121mmol)和3-(二甲氨基)-1-丙胺(37.1mg,0.364mmol)在DMA(1.0mL)中的混合物在100℃下加热3小时。冷却该混合物。过滤白色沉淀物并风干,产生标题化合物(44)(26mg,59%)。LC/MS:Rt=0.53min,m/z=363.4[MH+]。

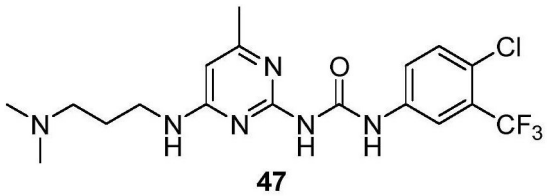
实施例37:1-{2-[3-(3-氯-苯基)脲基]-6-甲基-4-嘧啶-基氨基}-3-(二甲氨基)丙烷(45)的合成



42 45

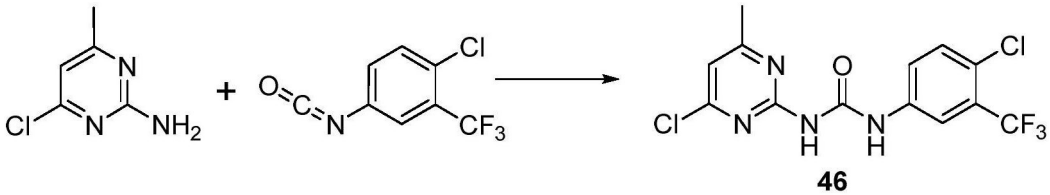
[0428] 将3-(3-氯-苯基)-1-(4-氯-6-甲基-2-嘧啶基)脲(42)(58mg,0.22mmol)和3-(二甲氨基)-1-丙胺(135mg,0.66mmol)在DMA(1.0mL)中的混合物在100℃下加热3小时。冷却该混合物。过滤白色沉淀物并风干,产生标题化合物(45)(22mg,31%)。LC/MS:Rt=3.84min,m/z=363.6[MH+]。

实施例38:1-(2-{3-[4-氯-3-(三氟甲基)苯基]脲基}-6-甲基-4-嘧啶基氨基)-3-(二甲氨基)丙烷(47)的合成



47

[0429] 步骤1:3-(4-氯-6-甲基-2-嘧啶基)-1-[4-氯-3-(三氟甲基)苯基]脲(46)

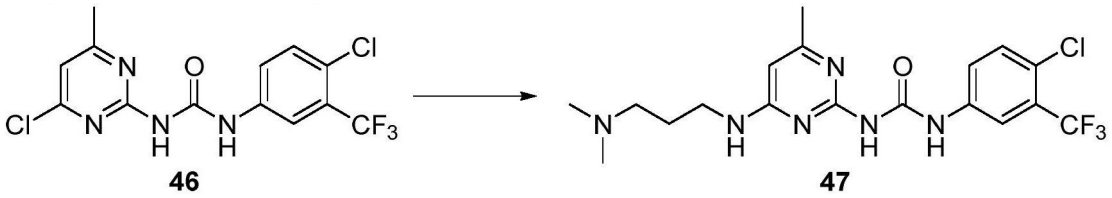


46

[0430] 将2-氨基-4-氯-6-甲基嘧啶(72.0mg,0.5mmol)和4-氯-(3-三氟甲基)苯基异氰酸酯(166.2mg,0.75mmol)在1,4-二氧杂环己烷(1.0mL)中的混合物在100℃下加热3小时。冷却反应混合物,将沉淀产物过滤、用1,4-二氧杂环己烷洗涤并干燥,产生呈白色固体的化合物(46)(129mg,70%)。

[0431] 步骤2:1-(2-{3-[4-氯-3-(三氟甲基)苯基]脲基}-6-甲基-4-嘧啶基氨基)-3-(二

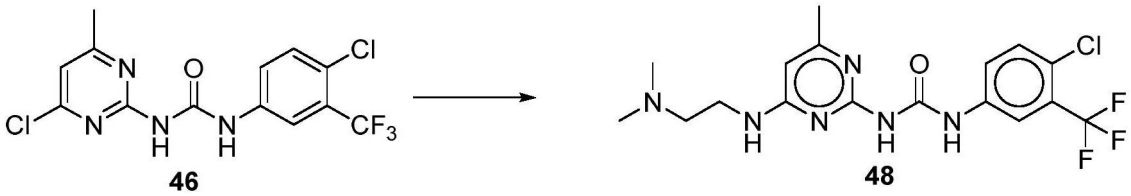
甲氨基)丙烷(47)



46 47

[0432] 将3-(4-氯-6-甲基-2-嘧啶基)-1-[4-氯-3-(三氟甲基)苯基]脲(46)(129mg,0.35mmol)和3-(二甲氨基)-1-丙胺(107mg,1.05mmol)在DMA(1.0mL)中的混合物在100℃下加热3小时。冷却该混合物,并将白色沉淀物过滤、用水洗涤并风干,产生标题化合物(47)(128mg,85%)。LC/MS:Rt=0.17min,m/z=431.3[MH^+]。

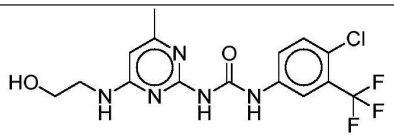
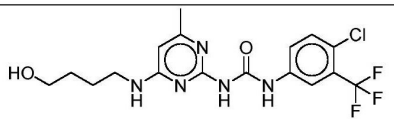
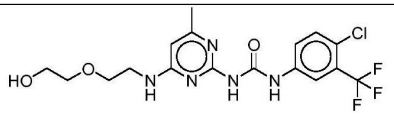
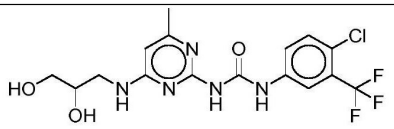
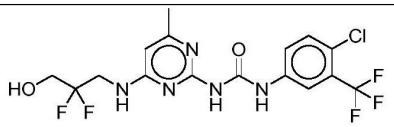
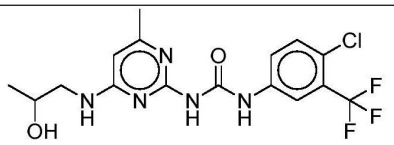
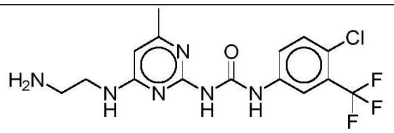
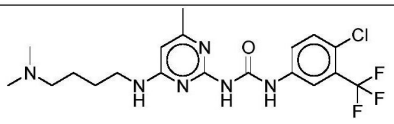
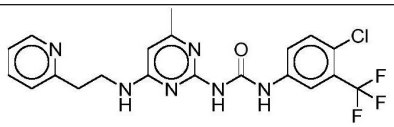
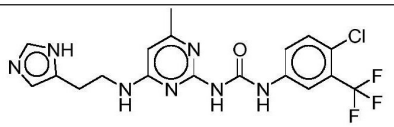
实施例39:1-(4-氯-3-(三氟甲基)苯基)-3-(4-((2-(二甲氨基)乙基)氨基)-6-甲基嘧啶-2-基)脲(48)的合成

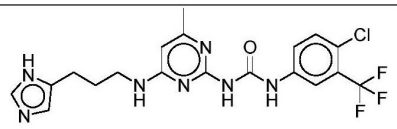
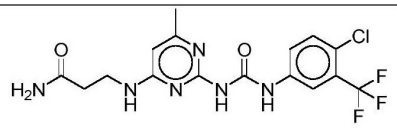
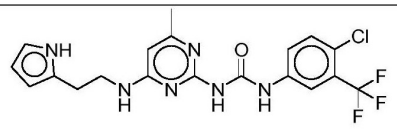


46 48

[0433] 将3-(4-氯-6-甲基-2-嘧啶基)-1-[4-氯-3-(三氟甲基)苯基]脲(46)(100mg,0.26mmol)、N,N-二甲基乙烯-二胺(28mg,0.31mmol)和三甲胺(39mg,0.39mmol)在2-丙醇(1mL)中的悬浮液在90℃下加热至回流。30分钟后,将混合物冷却至环境温度,并用MeOH稀释。过滤出呈白色固体的标题化合物(48)(85mg,78%)。LC/MS:方法4:Rt=1.96min,m/z=418.2-420.2[MH+]。

[0434] 根据针对实施例38-39描述的类似过程制备下列实施例:

化合物 ID	实施例 ID	结构	HPLC 方法	产率 (质量/%)	RT (min)	MH^+
49	40		4	88mg, 82	2.23	390.1-392.1
50	41		4	82mg, 72	2.25	419.2-421.2
51	42		4	99mg, 83	2.23	435.2-437.2
52	43		4	92mg, 80	2.12	421.2-423.2
53	44		4	23mg, 19	2.66	441.1-443.1
54	45		4	83mg, 75	2.16	405.2-407.2
55	46		4	96mg, 90	1.79	389.2-391.2
56	47		4	82mg, 67	1.80	445.2-447.2
57	48		4	108mg, 87	2.02	451.2-453.2
58	49		4	91mg, 76	1.78	441.2-443.2

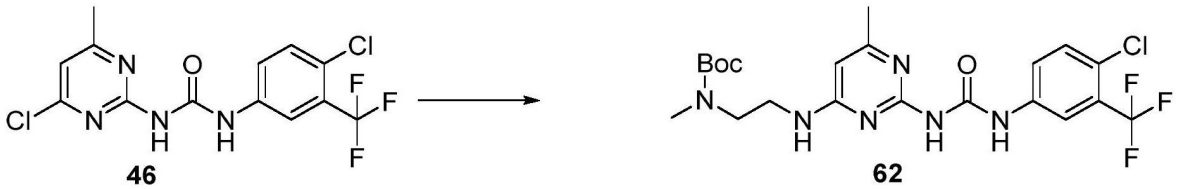
59	**50**		**4**	**43mg, 35**	**1.71**	**454.2-456.2**
60	**51**		**4**	**52mg, 46**	**2.01**	**418.2-420.1**
61	**52**		**4**	**10mg, 17**	**2.82**	**439.2-441.2**

实施例53:1-(4-氯-3-(三氟甲基)苯基)-3-(4-甲基-6-((2-(甲氨基)乙基)氨基)-嘧啶-2-基)脲(63)



63

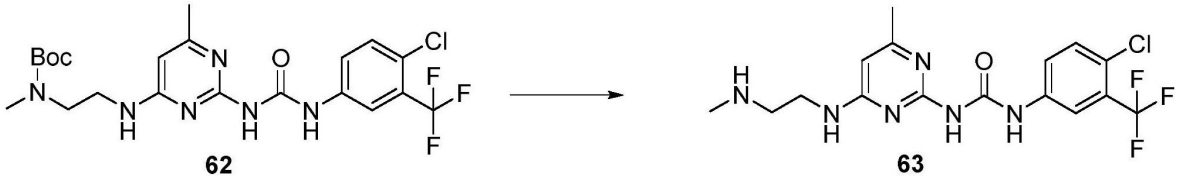
[0435] 步骤1:(2-((2-(3-(4-氯-3-(三氟甲基)苯基)脲基)-6-甲基嘧啶-4-基)氨基)乙基)(甲基)氨基甲酸叔丁酯(62)



46 **62**

[0436] 将3-(4-氯-6-甲基-2-嘧啶基)-1-[4-氯-3-(三氟甲基)苯基]脲(46)(100mg,0.26mmol)、N-(2-氨乙基)-N-甲基氨基甲酸叔丁酯(56mg,0.31mmol)和三乙胺(40mg,0.39mmol)的混合物在2-丙醇(1mL)中在搅拌下加热至回流30分钟。在冷却后添加甲醇,将所形成的沉淀物过滤,得到标题化合物(62)(97mg,70%)。LC/MS:Rt=3.11min,m/z=504.2-506.2[MH+]。

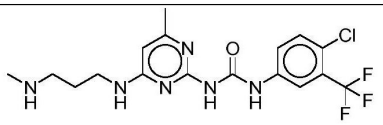
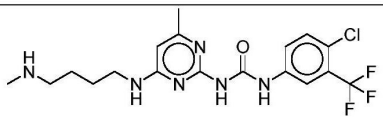
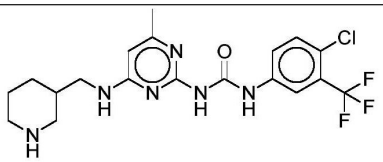
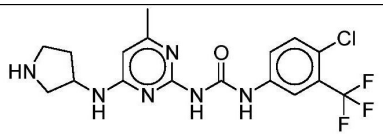
[0437] 步骤2:1-(4-氯-3-(三氟甲基)苯基)-3-(4-甲基-6-((2-(甲氨基)乙基)氨基)-嘧啶-2-基)脲(63)



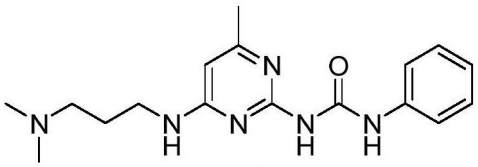
62 **63**

[0438] 将BOC衍生物(62)(97mg,0.18mmol)悬浮在DCM(1.8mL)中,向其中添加三氟乙酸(0.15mL,1.8mmol)。将反应混合物搅拌3小时,然后添加更多三氟乙酸(0.15mL)。将该混合物升温至45℃并搅拌过夜。在减压下除去溶剂,获得黄色凝胶物,其与饱和$NaHCO_3$溶液混合。未观察到沉淀,因此在减压下除去溶剂,所得残余物通过急骤色谱法纯化(梯度洗脱,相对于CH_2Cl_2,0-20%的3M NH_3在MeOH中的溶液),获得呈白色固体的所需化合物(63)(51mg,66%)。LC/MS:方法4:Rt=1.80min,m/z=404.2-406.2[MH^+]。

[0439] 根据针对实施例53描述的类似过程制备下列实施例：

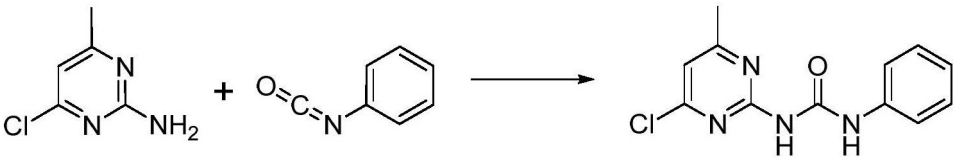
化合物ID	实施例ID	结构	HPLC方法	产率(质量/%)	RT(min)	MH^+
64	54		4	66mg, 86	1.72	417.2-419.2
65	55		4	37mg, 48	1.73	431.2-433.2
66	56		4	100mg, 88	1.78	443.2-445.1
67	57		4	62mg, 85	1.78	415.1-417.1

实施例58:1-(4-((3-(二甲氨基)丙基)氨基)-6-甲基嘧啶-2-基)-3-苯基脲(69)的合成



69

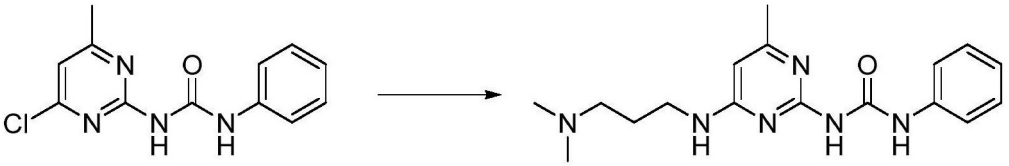
[0440] 步骤1:1-(4-氯-6-甲基-2-嘧啶基)-3-苯基脲(68)



68

[0441] 将2-氨基-4-氯-6-甲基嘧啶(72.0mg,0.5mmol)和异氰酸苯酯(90.0mg,0.75mmol)在1,4-二氧杂环己烷(1.00mL)中的混合物在100℃下加热3小时。在真空下除去挥发物,并将残余物与MeOH一起研磨、过滤并干燥,产生呈白色固体的化合物(68)(78.0mg,58%)。

[0442] 步骤2:1-(4-((3-(二甲氨基)丙基)氨基)-6-甲基嘧啶-2-基)-3-苯基脲(69)

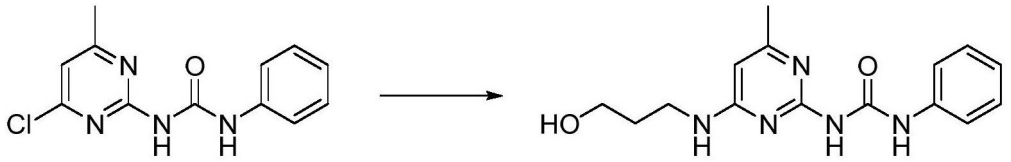


68 69

[0443] 将1-(4-氯-6-甲基-2-嘧啶基)-3-苯基脲(68)(37.0mg,0.143mmol)和3-(二甲氨基)-1-丙胺(107mg,1.05mmol)在DMA(1.0mL)中的混合物在100℃下加热3小时。冷却反应混合物并用水处理。过滤白色沉淀物并风干,产生标题化合物(69)(41mg,87%)。LC/MS:Rt=

4.41min,m/z＝329.4[MH+]。

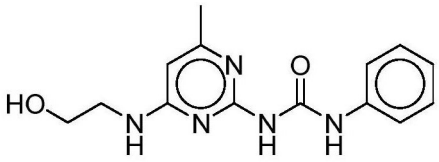
实施例59:1-(4-((3-羟丙基)氨基)-6-甲基嘧啶-2-基)-3-苯基脲(70)的合成



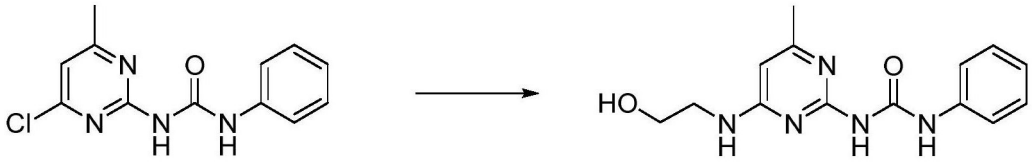
68 70

[0444] 将1-(4-氯-6-甲基-2-嘧啶基)-3-苯基脲(68)(37mg,0.143mmol)和3-氨基-1-丙醇(54mg,0.715mmol)在DMA(1.0mL)中的混合物在100℃下加热3小时。冷却该混合物并用水处理。过滤白色沉淀物并风干,产生标题化合物(70)(23mg,53%)。LC/MS:Rt＝0.05min,m/z＝423.1[MH+]。

实施例60:1-(4-((2-氨丙基)氨基)-6-甲基嘧啶-2-基)-3-(3,4-二氯苯基)脲(71)的合成



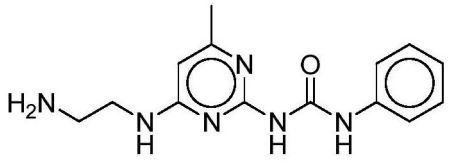
71



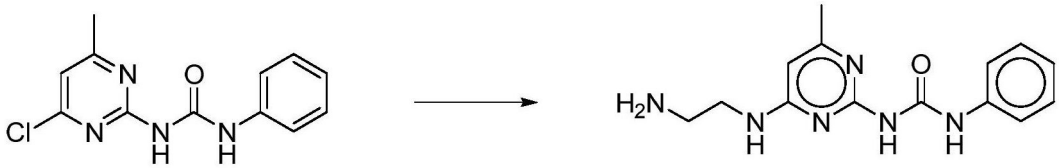
68 71

[0445] 用三乙胺(0.21mL,1.5mmol)和2-氨基乙醇(0.08mL,1.2mmol)处理1-(4-氯-6-甲基-2-嘧啶基)-3-苯基脲(68)(0.3g,1.1mmol)和甲苯(1.5mL)的混合物,并随后在搅拌下加热至回流。在冷却后形成沉淀物,将其过滤并用甲醇和二乙醚洗涤,得到标题化合物(71)(0.26g,85%)。LC/MS:方法4:Rt＝1.75min,m/z＝288.1[MH+]。

实施例61:1-(4-((2-氨乙基)氨基)-6-甲基嘧啶-2-基)-3-苯基脲(72)的合成



72

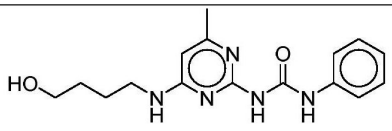
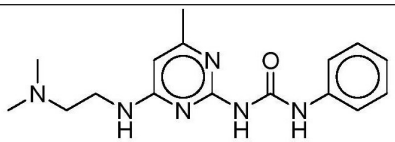
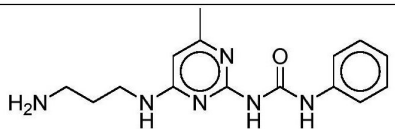
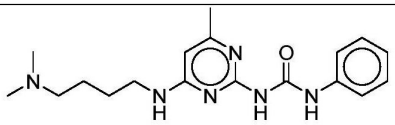
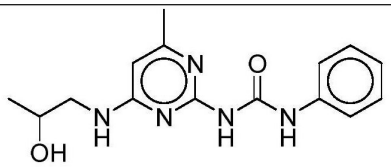
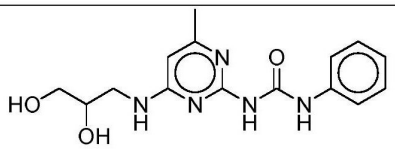
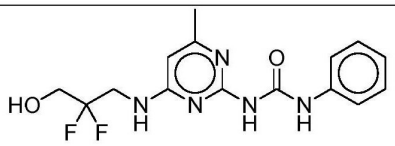
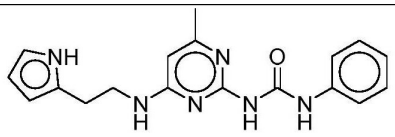


68 72

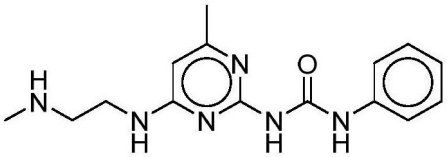
[0446] 将1-(4-氯-6-甲基-2-嘧啶基)-3-苯基脲(68)(0.2g,0.76mmol)悬浮在2-丙醇(1.5mL)中。向其中添加三乙胺(0.15mL,1.1mmol),然后添加乙烷-1,2-二胺(0.06mL,0.91mmol),并将混合物在搅拌下加热至回流过夜。在冷却后形成沉淀物,过滤得到标题化

合物(72)(0.21g,91%)。LC/MS:方法4:Rt＝0.86min,m/z＝287.2[MH+]。

[0447] 根据针对实施例58-61所述的类似过程制备下列实施例:

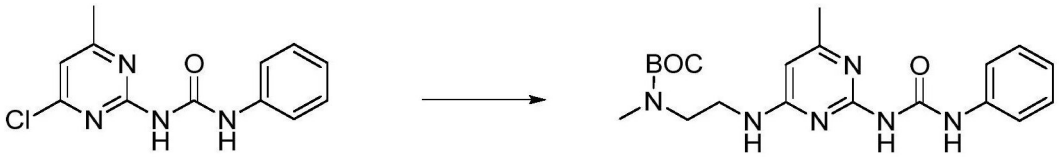
化合物ID	实施例ID	结构	HPLC方法	产率(质量/%)	RT(min)	MH^+
73	62		4	110mg, 32	1.96	316.2
74	63		4	61mg, 44	0.36	315.2
75	64		4	61mg, 22	0.41	301.2
76	65		4	80mg, 32	0.36	343.3
77	66		4	23mg, 15	0.34	302.2
78	67		4	72mg, 60	1.29	318.2
79	68		4	22mg, 17	1.64	338.2
80	69		4	28mg, 20	1.97	337.2

实施例70:1-(4-甲基-6-((2-(甲氨基)乙基)氨基)嘧啶-2-基)-3-苯基脲(82)



82

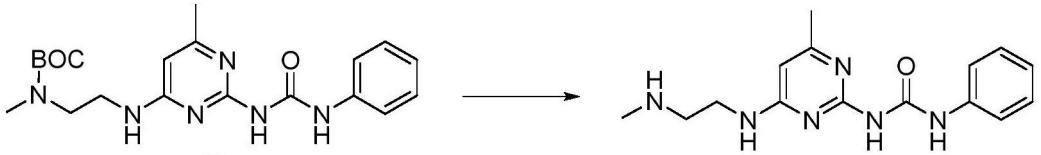
[0448] 步骤1:甲基(2-((6-甲基-2-(3-苯基脲基)嘧啶-4-基)氨基)乙基)氨基甲酸叔丁酯(81)



68 81

[0449] 用N-(2-氨乙基)-N-甲基氨基甲酸叔丁酯(0.17mL,0.94mmol)和三乙胺(0.16mL,1.2mmol)处理1-(4-氯-6-甲基-2-嘧啶基)-3-苯基脲(68)(200mg,0.78mmol)和甲苯(1.2mL)的混合物,并将其在搅拌下加热至回流。在冷却后添加甲醇,将所形成的沉淀物过滤并用二乙醚洗涤,得到标题化合物(81)(212mg,64%)。LC/MS:方法4:Rt=0.36min,m/z=401.3[MH+]。

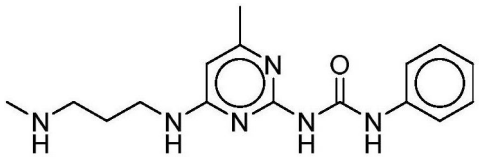
[0450] 步骤2:1-(4-甲基-6-((2-(甲氨基)乙基)氨基)嘧啶-2-基)-3-苯基脲



81 82

[0451] 将BOC衍生物(81)(0.2g,0.5mmol)悬浮在DCM(5mL)中,向其中添加三氟乙酸(0.98mL,12mmol)。将反应混合物在室温下搅拌15分钟,然后蒸发溶剂。用DCM和1N NaOH溶液(0.5mL,0.5mmol)处理该混合物,并将混合物搅拌10-30分钟。过滤悬浮液,产生呈白色固体的标题产物(82)(145mg,86%)。LC/MS:方法4:Rt=0.36min,m/z=301.2[MH^+]。

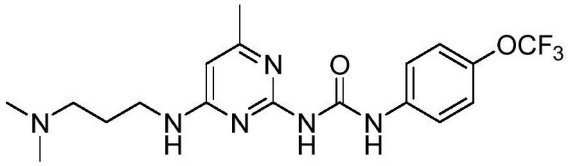
实施例71:1-(4-甲基-6-((3-(甲氨基)丙基)氨基)嘧啶-2-基)-3-苯基脲(83)



83

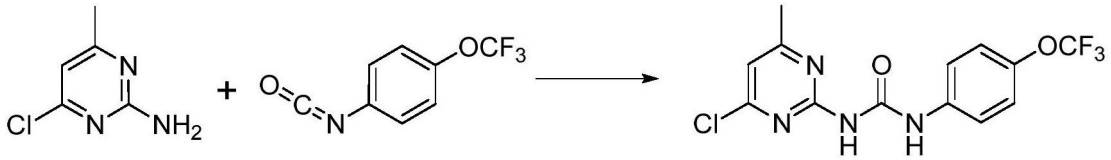
[0452] 通过与实施例70类似的过程,由1-(4-氯-6-甲基-2-嘧啶基)-3-苯基脲(68)和N-(3-氨丙基)-N-甲基氨基甲酸叔丁酯制备实施例71(28mg,11%)。LC/MS:方法4:Rt=0.38min,m/z=315.2[MH^+]。

实施例72:1-(4-((3-(二甲氨基)丙基)氨基)-6-甲基嘧啶-2-基)-3-(4-(三氟甲氧基)苯基)脲(85)的合成



85

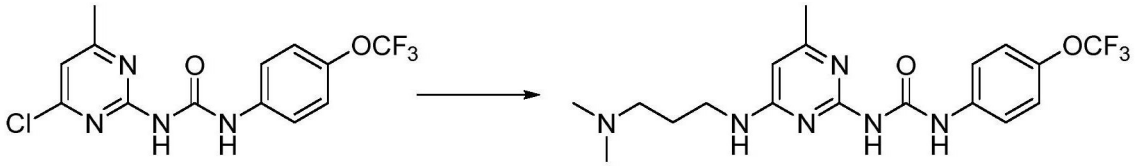
[0453] 步骤1:1-(4-氯-6-甲基-2-嘧啶基)-3-(对三氟甲氧基苯基)脲(84)



84

[0454] 将2-氨基-4-氯-6-甲基嘧啶(72.0mg,0.5mmol)和4-(三氟甲氧基)苯基异氰酸酯(152.0mg,0.75mmol)在二氧杂环己烷(1.00mL)中的混合物在100℃下加热3小时。在真空下除去挥发物,并将残余物与MeOH一起研磨、过滤并干燥,产生呈白色固体的化合物(84)(120.0mg,69%)。

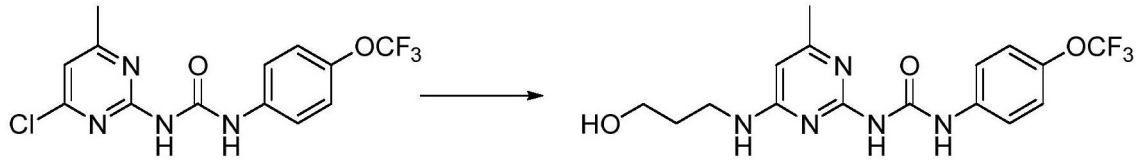
[0455] 步骤2:1-(4-((3-(二甲氨基)丙基)氨基)-6-甲基嘧啶-2-基)-3-(4-(三氟甲氧基)苯基)脲(85)



84 85

[0456] 将1-(4-氯-6-甲基-2-嘧啶基)-3-(对三氟甲氧基苯基)脲(25)(60mg,0.173mmol)和3-(二甲氨基)-1-丙胺(54mg,1.05mmol)在DMA(1.0mL)中的混合物在100℃下加热3小时。冷却反应混合物并用水处理。过滤白色沉淀物并风干,产生标题化合物(26)(41mg,57%)。LC/MS:Rt=0.33min,m/z=413.3[MH^+]。

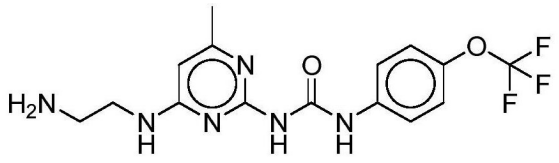
实施例73:1-(4-((3-羟丙基)氨基)-6-甲基嘧啶-2-基)-3-(4-(三氟甲氧基)苯基)脲(86)的合成



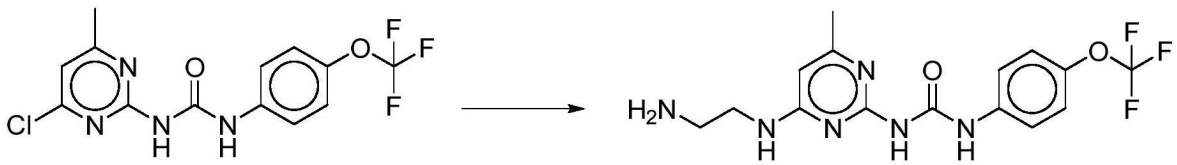
84 86

[0457] 将1-(4-氯-6-甲基-2-嘧啶基)-3-(对三氟甲氧基苯基)脲(84)(60mg,0.17mmol)和3-氨基-1-丙醇(65mg,0.86mmol)在DMA(1.0mL)中的混合物在100℃下加热3小时。冷却该混合物。过滤白色沉淀物并风干,产生标题化合物(86)(35mg,52%)。LC/MS:Rt=0.13min,m/z=386.4[MH^+]。

实施例74:1-(4-((2-氨乙基)氨基)-6-甲基嘧啶-2-基)-3-(4-(三氟甲氧基)苯基)脲(87)的合成



87

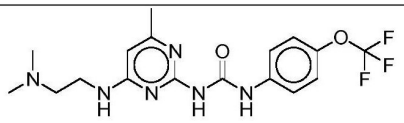
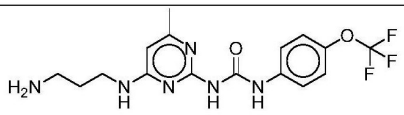
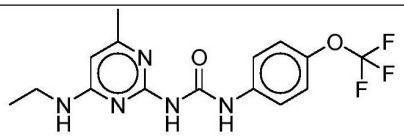
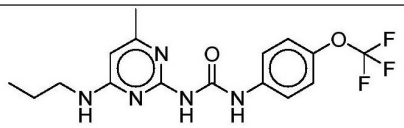
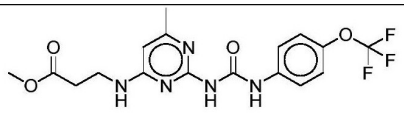
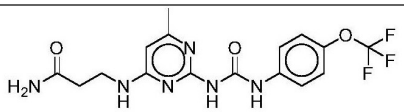
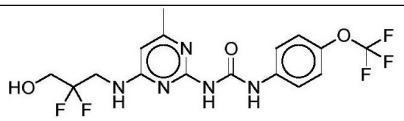
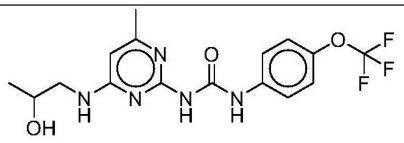
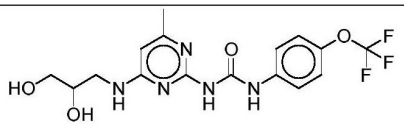


84 87

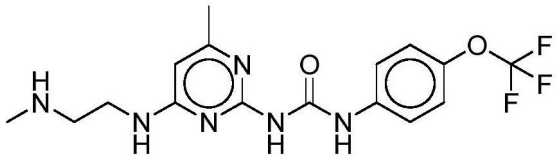
[0458] 将1-(4-氯-6-甲基-2-嘧啶基)-3-(对三氟甲氧基苯基)脲(84)(75mg,0.21mmol)的混合物悬浮在2-丙醇(0.4mL)中。向该混合物中添加三乙胺(0.04mL,0.32mmol),然后添加乙烷-1,2-二胺(0.02mL,0.25mmol),并将该混合物在搅拌下加热至回流数小时。在冷却

并用甲醇(3mL)稀释时形成沉淀物,过滤该沉淀物得到标题化合物(87)(54mg,68%)。LC/MS:方法4:Rt=1.50min,m/z=386.4[MH^+]。

[0459] 根据针对实施例72-74所述的类似过程制备下列实施例:

化合物ID	实施例ID	结构	HPLC方法	产率(质量/%)	RT(min)	MH^+
88	75		4	33 mg, 39	1.45	400.2
89	76		4	45 mg, 54	1.59	386.2
90	77		4	54 mg, 71	2.27	357.2
91	78		4	64 mg, 80	2.45	371.2
92	79		4	66 mg, 74	2.34	415.2
93	80		4	55 mg, 64	1.94	399.2
94	81		4	18 mg, 20	2.32	422.2
95	82		4	52 mg, 62	2.01	386.2
96	83		4	38 mg, 44	1.90	403.2

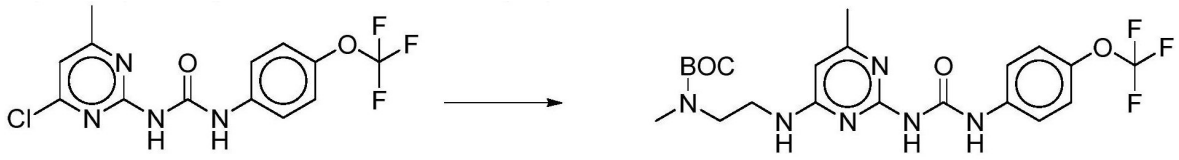
实施例84:1-(4-甲基-6-((2-(甲氨基)乙基)氨基)嘧啶-2-基)-3-(4-(三氟甲氧基)苯基)脲(98)的合成



98

[0460] 步骤1:甲基(2-((6-甲基-2-(3-(4-(三氟甲氧基)苯基)脲基)嘧啶-4-基)氨基)乙

基)氨基甲酸叔丁酯(97)



84 97

[0461] 用N-(2-氨乙基)-N-甲基氨基甲酸叔丁酯(0.05mL,0.25mmol)和三乙胺(0.05mL,0.32mmol)处理1-(4-氯-6-甲基-2-嘧啶基)-3-(对三氟甲氧基苯基)脲(84)(75mg,0.22mmol)和2-丙醇(0.43mL)的混合物,并将其在搅拌下加热至回流5小时。在冷却后添加甲醇(3mL),将所形成的沉淀物过滤得到标题化合物(97)(68mg,65%)。LC/MS:方法4:Rt=2.74min,m/z=485.3[MH+]。

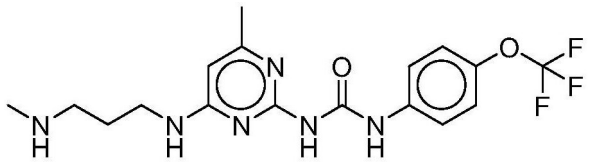
[0462] 步骤2:1-(4-甲基-6-((2-(甲氨基)乙基)氨基)嘧啶-2-基)-3-(4-(三氟甲氧基)苯基)脲



97 98

[0463] 将BOC衍生物(97)(75mg,0.16mmol)悬浮在DCM(0.12mL)中,向其中添加三氟乙酸(0.12mL,1.6mmol)。在室温下5小时后,用饱和碳酸氢钠溶液处理该混合物直到达到pH 8。过滤所形成的悬浮液,产生呈白色固体的标题产物(98)(59mg,97%)。LC/MS:方法4:Rt=1.50min,m/z=385.2[MH^+]。

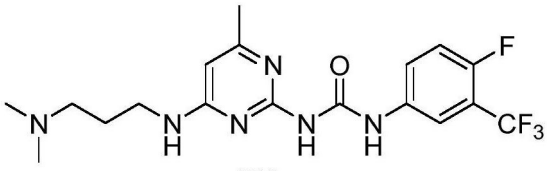
实施例85:1-[4-甲基-6-(3-甲氨基-丙氨基)-嘧啶-2-基]-3-(4-三氟甲氧基-苯基)-脲(99)



99

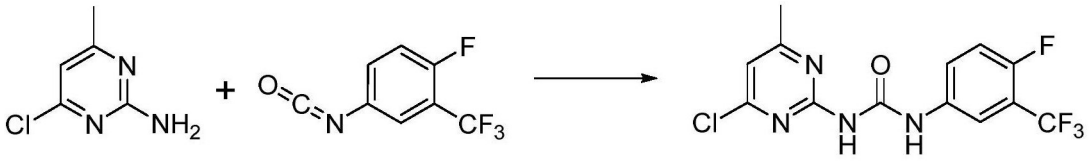
[0464] 通过与实施例84类似的过程,由1-(4-氯-6-甲基-2-嘧啶基)-3-(对三氟甲氧基苯基)脲(84)和N-(3-氨丙基)-N-甲基氨基甲酸叔丁酯制备实施例85,不同之处在于中间体氨基甲酸酯先通过制备型TLC纯化(用含10%1M NH_4OH的MeOH/90%DCM(36mg,41%)洗脱)。LC/MS:方法4:Rt=1.57min,m/z=400.2[MH^+]。

实施例86:3-(二甲氨基)-1-(2-{3-[4-氟-3-(三氟甲基)苯基]脲基}-6-甲基-4-嘧啶基氨基)-丙烷(101)的合成



101

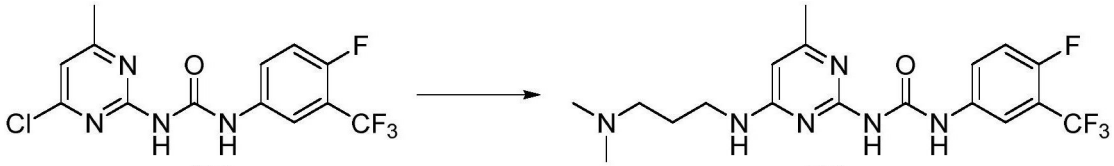
[0465] 步骤1:1-(4-氯-6-甲基-2-嘧啶基)-3-[4-氟-3-(三氟甲基)-苯基]脲(100)



100

[0466] 将2-氨基-4-氯-6-甲基嘧啶(72mg,0.5mmol)和4-氟-3-(三氟甲基)苯基异氰酸酯(154mg,0.75mmol)在1,4-二氧杂环己烷(1mL)中的混合物在100℃下加热3小时。冷却该反应混合物,将沉淀产物过滤、用1,4-二氧杂环己烷洗涤并干燥,产生呈白色固体的化合物(100)(144mg,83%)。

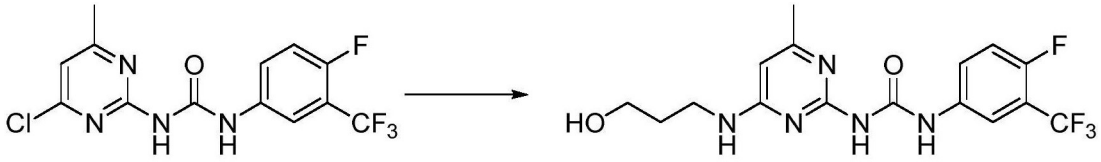
[0467] 步骤2:3-(二甲氨基)-1-(2-{3-[4-氟-3-(三氟甲基)苯基]脲基}-6-甲基-4-嘧啶基氨基)-丙烷(101)



100 101

[0468] 将1-(4-氯-6-甲基-2-嘧啶基)-3-[4-氟-3-(三氟甲基)-苯基]脲(100)(60mg,0.172mmol)和3-(二甲氨基)-1-丙胺(53mg,0.516mmol)在DMA(1mL)中的混合物在100℃下加热3小时。冷却该混合物并用水处理。过滤白色沉淀物并风干,产生标题化合物(101)(50mg,70%)。LC/MS:Rt=0.32min,m/z=415.5[MH^+]。

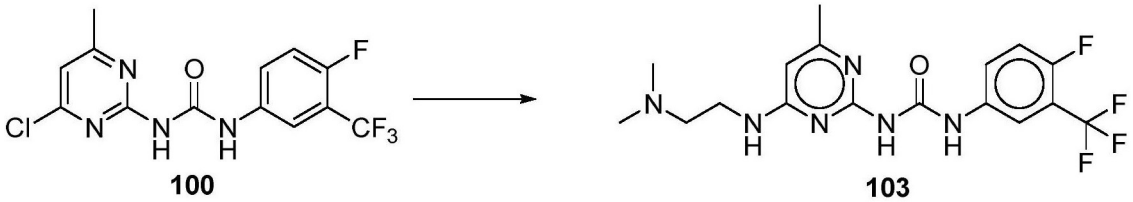
实施例87:1-(4-氟-3-(三氟甲基)苯基)-3-(4-((3-羟丙基)氨基)-6-甲基嘧啶-2-基)脲(102)的合成



100 102

[0469] 将1-(4-氯-6-甲基-2-嘧啶基)-3-[4-氟-3-(三氟甲基)-苯基]脲(100)(84mg,0.24mmol)和3-氨基-1-丙醇(91mg,1.2mmol)在DMA(1.0mL)中的混合物在100℃下加热3小时。冷却该混合物并用水处理。过滤白色沉淀物并风干,产生标题化合物(102)(66mg,71%)。LC/MS:Rt=0.21min,m/z=388.5[MH^+]。

实施例88:1-(4-氟-3-(三氟甲基)苯基)-3-(4-((2-(二甲氨基)乙基)氨基)-6-甲基嘧啶-2-基)脲(103)的合成

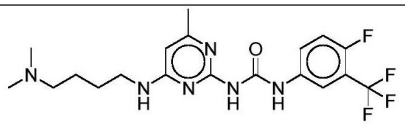
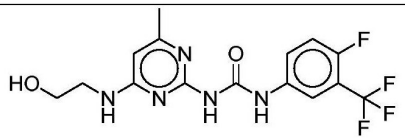
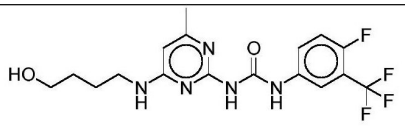
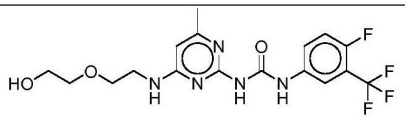
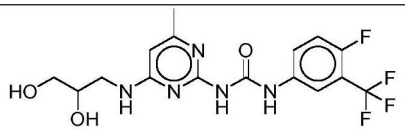
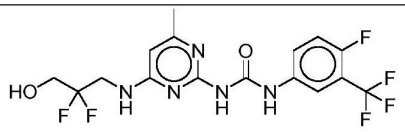


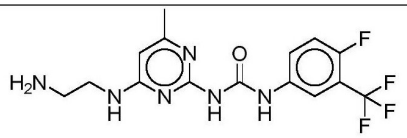
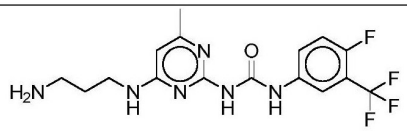
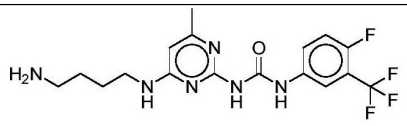
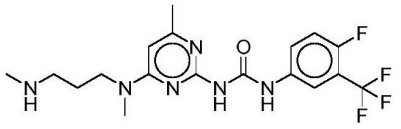
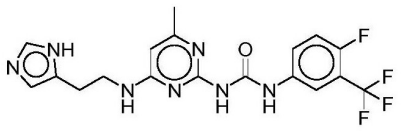
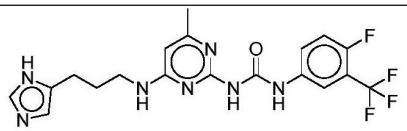
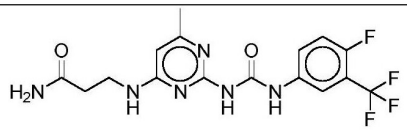
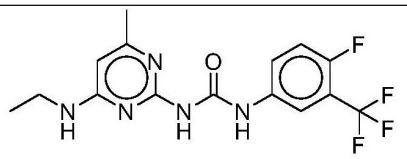
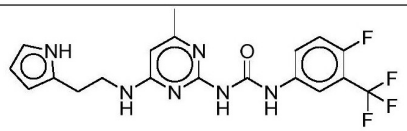
100 103

[0470] 将3-(4-氟-6-甲基-2-嘧啶基)-1-[4-氯-3-(三氟甲基)苯基]脲(100)(100mg,0.26mmol)、N,N-二甲基乙烯-二胺(0.04mL,0.33mmol)和三甲胺(0.06mL,0.41mmol)在2-丙醇(1mL)中的悬浮液在90℃下加热至回流。30分钟后,将该混合物冷却至环境温度,并用

MeOH稀释。过滤得到呈白色固体的标题化合物(103)(65mg,57％)。LC/MS:方法4:Rt＝1.57min,m/z＝401.2[MH+]。

[0471] 根据针对实施例86-88所述的类似过程制备下列实施例:

化合物ID	实施例ID	结构	HPLC方法	产率 (质量/%)	RT (min)	MH^+
104	89		4	37 mg, 30	1.68	429.3
105	90		4	56 mg, 52	1.86	374.2
106	91		4	80 mg, 70	2.07	403.2
107	92		4	72 mg, 60	1.93	418.2
108	93		4	35 mg, 61	1.90	404.2
109	94		4	24 mg, 39	2.40	426.2

110	**95**		**4**	**17 mg, 32**	**1.57**	**373.2**
111	**96**		**4**	**30 mg, 54**	**1.57**	**387.2**
112	**97**		**4**	**41 mg, 71**	**1.61**	**401.2**
113	**98**		**4**	**51 mg, 86**	**1.73**	**415.2**
114	**99**		**4**	**27 mg, 44**	**1.52**	**424.2**
115	**100**		**4**	**41 mg, 65**	**1.61**	**438.2**
116	**101**		**4**	**40 mg, 70**	**1.90**	**402.2**
117	**102**		**4**	**40 mg, 78**	**2.29**	**359.2**
118	**103**		**4**	**23 mg, 38**	**2.54**	**423.2**

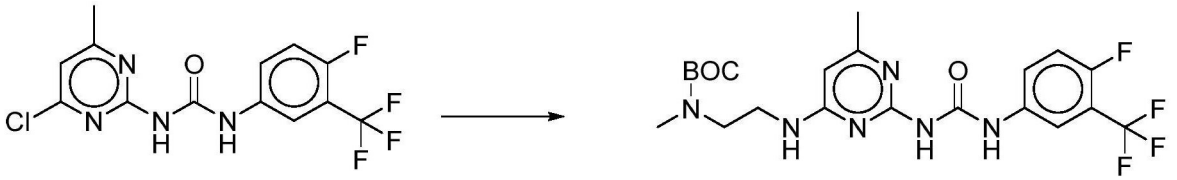
实施例104:1-(4-氟-3-(三氟甲基)苯基)-3-(4-甲基-6-((2-(甲氨基)乙基)氨基)-嘧啶-2-基)脲(120)的合成



120

[0472] 步骤1:(2-((2-(3-(4-氟-3-(三氟甲基)苯基)脲基)-6-甲基嘧啶-4-基)氨基)乙

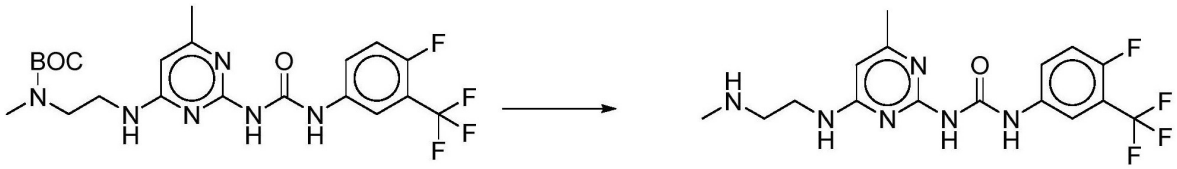
基)(甲基)氨基甲酸叔丁酯(119)



100 119

[0473] 用N-(2-氨乙基)-N-甲基氨基甲酸叔丁酯(0.06mL,0.32mmol)和三乙胺(0.06mL,0.41mmol)处理1-(4-氯-6-甲基-2-嘧啶基)-3-[4-氟-3-(三氟甲基)-苯基]脲(100)(100mg,0.27mmol)和2-丙醇(1mL)的混合物,并将其在搅拌下加热至回流30分钟。在冷却后添加乙醇,将所形成的沉淀物过滤,得到标题化合物(119)(116mg,83%)。LC/MS:方法4:Rt=2.77min,m/z=487.3[MH+]。

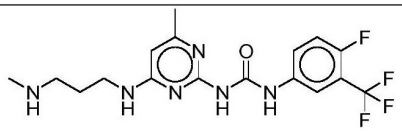
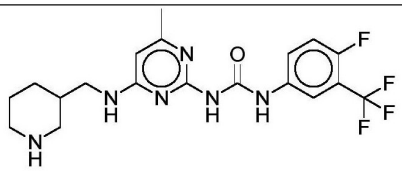
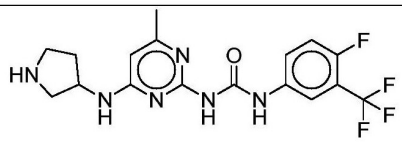
[0474] 步骤2:1-(4-氟-3-(三氟甲基)苯基)-3-(4-甲基-6-((2-(甲氨基)乙基)氨基)-嘧啶-2-基)脲



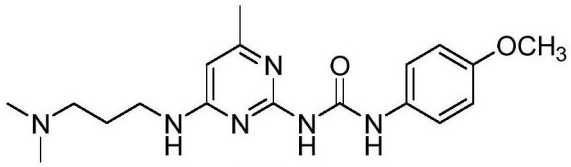
119 120

[0475] 将BOC衍生物(119)(116mg,0.12mmol)悬浮在DCM(1.2mL)中,向其中添加三氟乙酸(0.18mL,2.26mmol)。在室温下3小时后,将混合物升温至45℃并搅拌过夜。冷却后,蒸发溶剂,并用饱和碳酸氢钠溶液处理残余物。蒸发溶剂,所得残余物通过急骤色谱法纯化(梯度洗脱,相对于CH_2Cl_2,0-25%的3M NH_3在MeOH中的溶液),获得呈白色固体的所需化合物(120)(77mg,84%)。LC/MS:方法4:Rt=1.38min,m/z=387.2[MH^+]。

[0476] 根据针对实施例104所述的类似过程制备下列实施例:

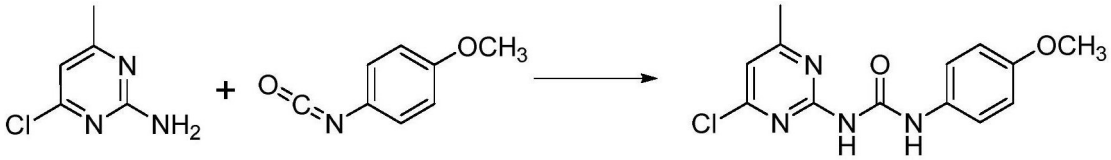
化合物ID	实施例ID	结构	HPLC方法	产率(质量/%)	RT(min)	MH^+
121	105		4	69 mg, 60	1.57	401.2
122	106		4	89 mg, 73	1.51	428.2
123	107		4	75 mg, 66	1.49	400.2

实施例108:1-(4-((3-(二甲氨基)丙基)氨基)-6-甲基嘧啶-2-基)-3-(4-甲氧基)苯基)脲(125)的合成



125

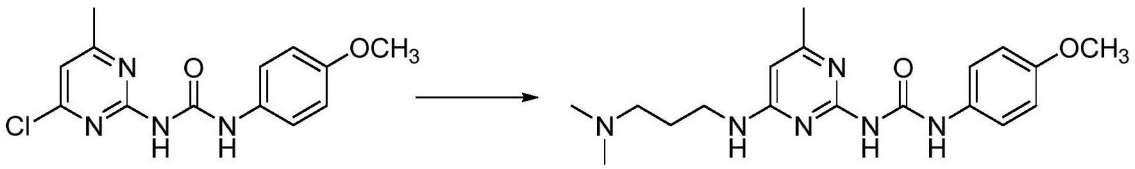
[0477] 步骤1:1-(4-氯-6-甲基-2-嘧啶基)-3-(4-甲氧基苯基)脲(124)



124

[0478] 将2-氨基-4-氯-6-甲基嘧啶(2.6g,17.6mmol)和4-甲氧基苯基异氰酸酯(2.7g,17.6mmol)在甲苯(31mL)中的混合物在N_2气流下回流过夜。冷却后过滤悬浮液,用EtOH和Et_2O洗涤并干燥,产生呈白色固体的化合物(124)(5.1g,65%)。LC/MS:方法4:Rt=2.95min,m/z=293.1[MH^+]。

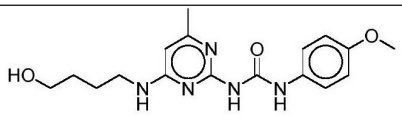
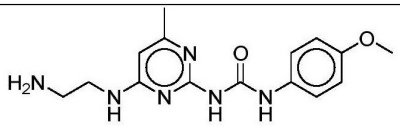
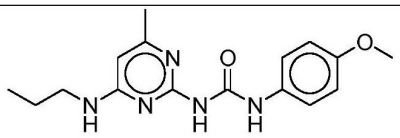
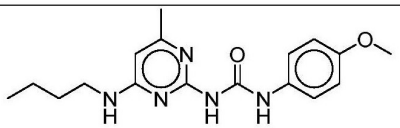
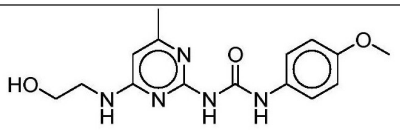
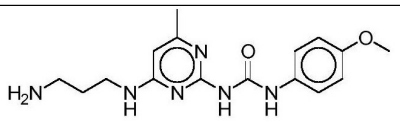
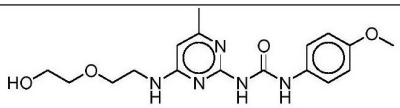
[0479] 步骤2:1-(4-((3-(二甲氨基)丙基)氨基)-6-甲基嘧啶-2-基)-3-(4-(甲氧基)苯基)脲(125)

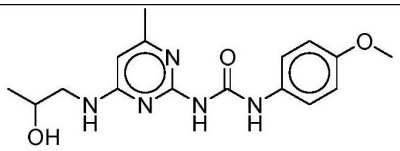
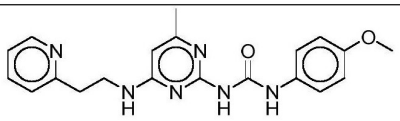
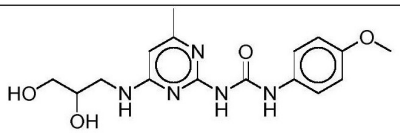
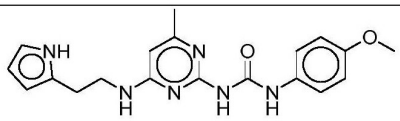
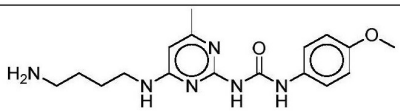
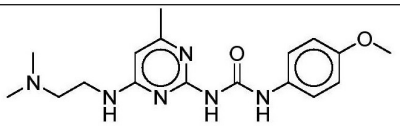
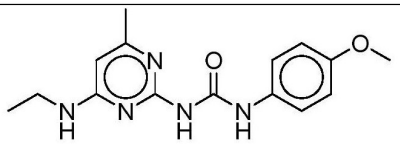


124 125

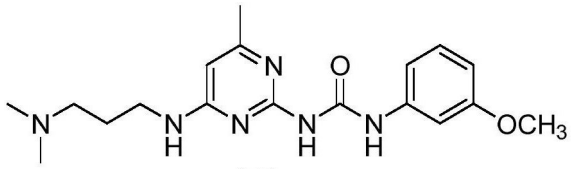
[0480] 将1-(4-氯-6-甲基-2-嘧啶基)-3-(对甲氧基苯基)脲(124)(100mg,0.32mmol)和3-(二甲氨基)-1-丙胺(0.05mL,0.39mmol)以及三乙胺(0.07mL,0.49mmol)在2-丙醇(0.5mL)中的混合物在80℃下加热2小时。冷却该反应混合物,并过滤白色沉淀物,产生标题化合物(125)(53mg,43%)。LC/MS:方法4:Rt=1.02min,m/z=359.3[MH^+]。

[0481] 根据针对实施例108所述的类似过程制备下列实施例:

化合物 ID	实施例 ID	结构	HPLC 方法	产率 (质量/%)	RT (min)	MH^+
126	109		4	206 mg, 77	1.61	346.2
127	110		4	83 mg, 31	1.1	317.2
128	111		4	100 mg, 40	1.97	316.2
129	112		4	222 mg, 85	2.22	330.2
130	113		4	189 mg, 78	1.48	318.2
131	114		4	229 mg, 75	1.05	331.2
132	115		4	120 mg, 42	1.52	362.2

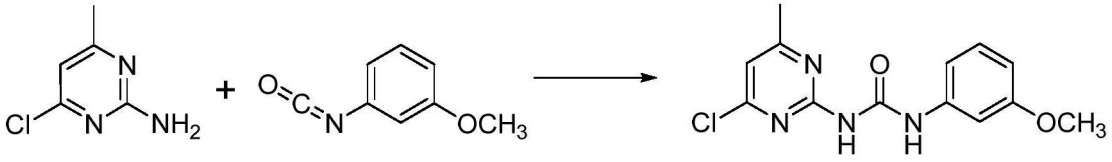
133	**116**		**4**	**86 mg, 69**	**1.51**	**333.2**
134	**117**		**4**	**100 mg, 70**	**1.28**	**379.2**
135	**118**		**4**	**80 mg, 61**	**1.36**	**348.2**
136	**119**		**4**	**5 mg, 4**	**1.94**	**367.2**
137	**120**		**4**	**82 mg, 66**	**1.07**	**345.3**
138	**121**		**4**	**28 mg, 21**	**1.12**	**345.2**
139	**122**		**4**	**9 mg,8**	**1.76**	**302.2**

实施例123:1-(4-((3-(二甲氨基)丙基)氨基)-6-甲基嘧啶-2-基)-3-(3-甲氧基)苯基)脲(141)的合成



141

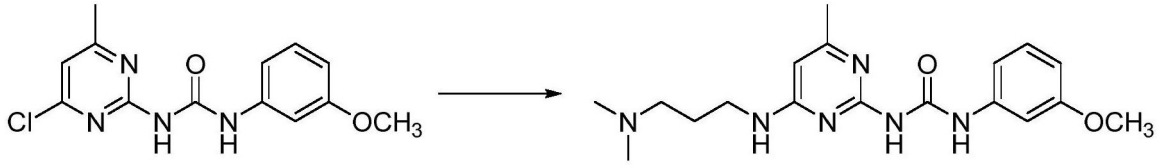
[0482] 步骤1:1-(4-氯-6-甲基-2-嘧啶基)-3-(3-甲氧基苯基)脲(140)



140

[0483] 将2-氨基-4-氯-6-甲基嘧啶(3g,20.9mmol)和3-甲氧基苯基异氰酸酯(3.4g,23.0mmol)在N,N-二甲基乙酰胺(28mL)中的混合物在100℃下加热80分钟。冷却后用MeOH(75mL)稀释混合物,过滤并干燥,产生呈白色固体的化合物(140)(3.1g,51%)。

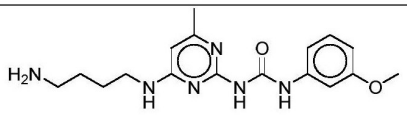
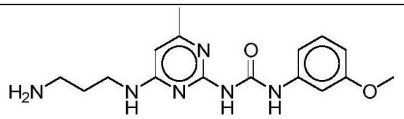
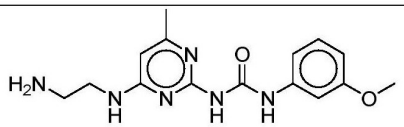
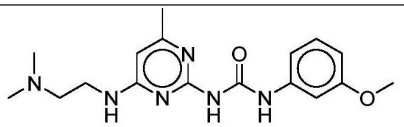
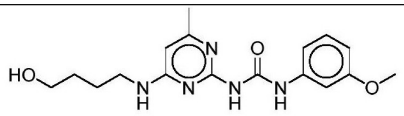
[0484] 步骤2:1-(4-((3-(二甲氨基)丙基)氨基)-6-甲基嘧啶-2-基)-3-(3-(甲氧基)苯基)脲(141)

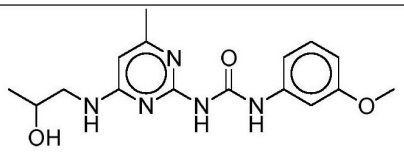
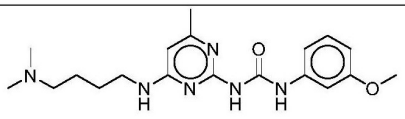
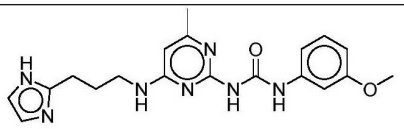
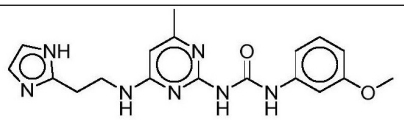
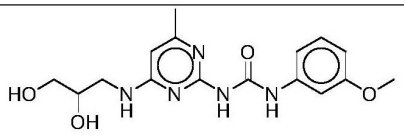


140 141

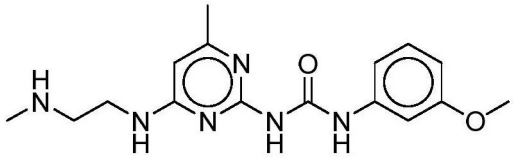
[0485] 将在2-丙醇(0.5mL)中的1-(4-氯-6-甲基-2-嘧啶基)-3-(3-甲氧基苯基)脲(140)(75mg,0.26mmol)和3-(二甲氨基)-1-丙胺(0.04mL,0.31mmol)以及三乙胺(0.05mL,0.38mmol)在80℃下加热23小时。冷却反应混合物并用2-丙醇(3mL)稀释。过滤白色沉淀物并用乙醇洗涤,产生标题化合物(141)(18mg,19%)。LC/MS:方法4:Rt=0.32min,m/z=359.3[MH^+]。

[0486] 根据针对实施例123所述的类似过程制备下列实施例:

化合物ID	实施例ID	结构	HPLC方法	产率(质量/%)	RT(min)	MH^+
142	124		4	10 mg, 11	0.34	345.3
143	125		4	9 mg, 10	1.08	331.2
144	126		4	16 mg, 19	0.34	317.2
145	127		4	22 mg, 25	0.34	345.3
146	128		4	21 mg, 29	0.33	346.2

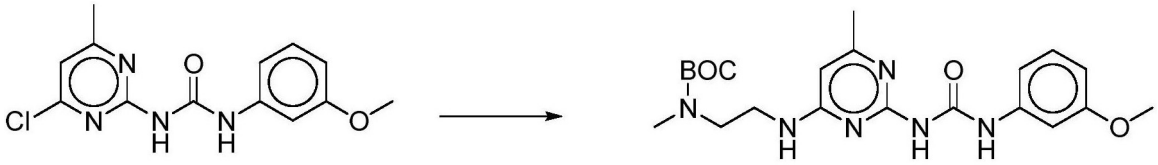
147	**129**		**4**	**5 mg, 6**	**1.60**	**332.2**
148	**130**		**4**	**15 mg, 15**	**1.21**	**373.3**
149	**131**		**4**	**29 mg, 29**	**1.23**	**382.2**
150	**132**		**4**	**24 mg, 26**	**1.24**	**368.2**
151	**133**		**4**	**17 mg, 19**	**1.45**	**348.2**

实施例134:1-(3-甲氧基苯基)-3-(4-甲基-6-((2-(甲氨基)乙基)氨基)嘧啶-2-基)脲(153)的合成



153

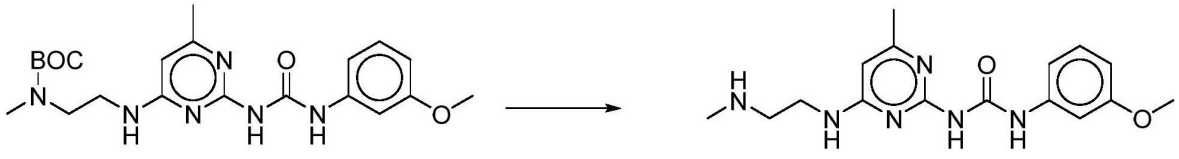
[0487] 步骤1:(2-((2-(3-(3-甲氧基苯基)脲基)-6-甲基嘧啶-4-基)氨基)乙基)(甲基)氨基甲酸叔丁酯(152)



140 **152**

[0488] 用N-(2-氨乙基)-N-甲基氨基甲酸叔丁酯(0.06mL,0.31mmol)和三乙胺(0.05mL,0.38mmol)处理1-(4-氯-6-甲基嘧啶-2-基)-3-(3-甲氧基苯基)脲(140)(75mg,0.26mmol)和2-丙醇(1mL)的混合物,并将其在搅拌下加热至回流30分钟。在冷却后添加甲醇(5mL),将所形成的沉淀物过滤,得到标题化合物(152)(69mg,62%)。

[0489] 步骤2:1-(3-甲氧基苯基)-3-(4-甲基-6-((2-(甲氨基)乙基)氨基)嘧啶-2-基)脲

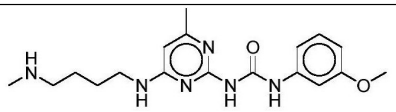
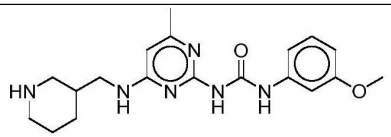


152 **153**

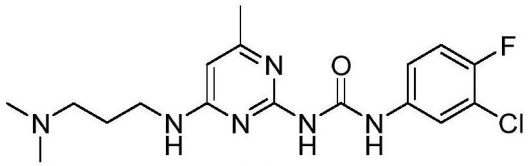
[0490] 将BOC衍生物(152)(69mg,0.16mmol)悬浮在DCM(0.11mL)中,向其中添加三氟乙酸

(0.12mL,1.5mmol)。在室温下2小时后,用饱和碳酸氢钠溶液处理该混合物。过滤得到呈白色固体的标题产物(153)(19mg,37%)。LC/MS:方法4:Rt=0.95min,m/z=331.2[MH^+]。

[0491] 根据针对实施例134所述的类似过程制备下列实施例:

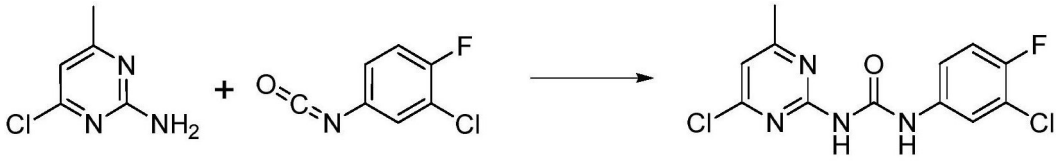
化合物ID	实施例ID	结构	HPLC方法	产率(质量/%)	RT(min)	MH^+
154	135		4	23 mg, 25	1.23	359.3
155	136		4	19 mg, 20	1.33	371.3

实施例137:1-(3-氯-4-氟苯基)-3-(4-((3-(二甲氨基)丙基)氨基)-6-甲基嘧啶-2-基)脲(157)的合成



157

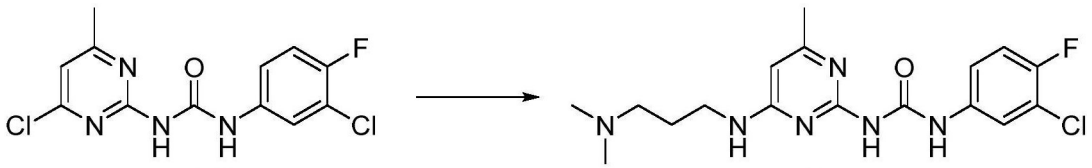
[0492] 步骤1:1-(3-氯-4-氟苯基)-3-(4-氯-6-甲基嘧啶-2-基)脲(156)



156

[0493] 将2-氨基-4-氯-6-甲基嘧啶(5g,34mmol)和4-甲氧基苯基异氰酸酯(5.9g,34mmol)在甲苯(60mL)中的混合物在N_2气流下回流过夜。冷却后过滤该悬浮液,用MeOH和Et_2O洗涤并干燥,产生呈白色固体的化合物(156)(5.1g,48%)。LC/MS:方法4:Rt=0.23min,m/z=315.0-317.1[MH^+]。

[0494] 步骤2:1-(4-((3-(二甲氨基)丙基)氨基)-6-甲基嘧啶-2-基)-3-(4-(甲氧基)苯基)脲(157)

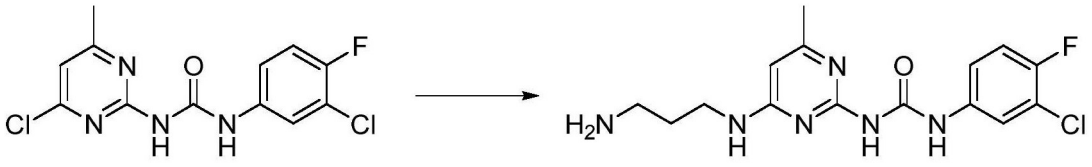


156 157

[0495] 将1-(3-氯-4-氟苯基)-3-(4-氯-6-甲基嘧啶-2-基)脲(156)(100mg,0.30mmol)和3-(二甲氨基)-1-丙胺(0.04mL,0.36mmol)以及三乙胺(0.06mL,0.45mmol)在2-丙醇(0.5mL)中的混合物在80℃下加热2小时。冷却该反应混合物,并过滤白色沉淀物,得到标题化合物(157)(83mg,69%)。LC/MS:方法4:Rt=1.38min,m/z=382.2-384.2[MH^+]。

实施例138:1-(4-((3-氨丙基)氨基)-6-甲基嘧啶-2-基)-3-(3-氯-4-氟苯基)脲(158)

的合成

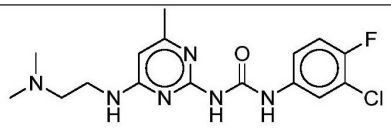
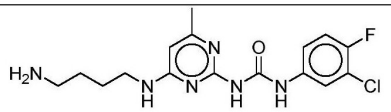
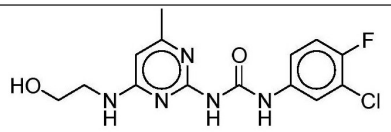
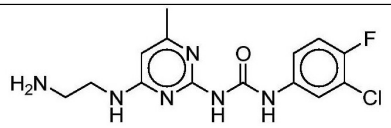
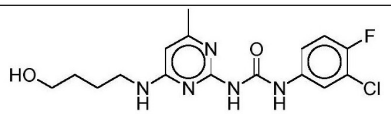
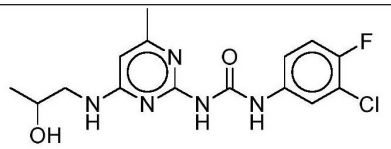
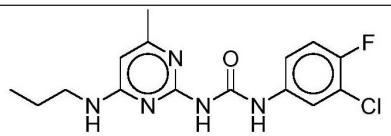
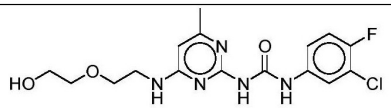
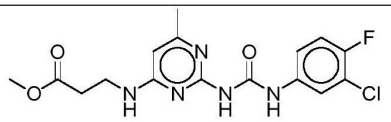


156 158

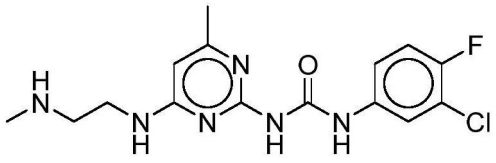
[0496] 将1-(3-氯-4-氟苯基)-3-(4-氯-6-甲基嘧啶-2-基)脲(156)(148mg,0.45mmol)和1,3-丙二胺(0.05mL,0.54mmol)以及三乙胺(0.06mL,0.45mmol)在甲苯(0.7mL)中的混合物加热回流1.5小时。冷却该反应混合物,并过滤白色沉淀物,然后用MeOH和Et_2O洗涤,产生标题化合物(158)(83mg,69%)。LC/MS:方法4:Rt=0.39min,m/z=353.1-356.2[MH^+]。

[0497] 根据针对实施例137-138所述的类似过程制备下列实施例:

化合物ID	实施例ID	结构	HPLC方法	产率(质量/%)	RT(min)	MH^+

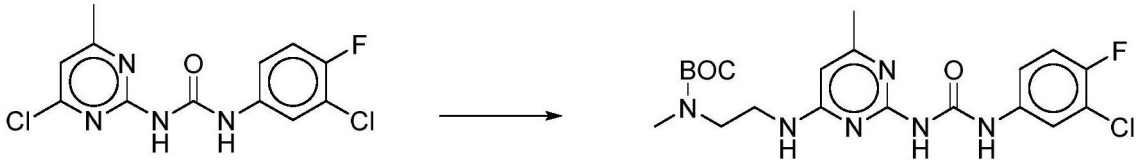
159	**139**		**4**	**150 mg, 76**	**0.38**	**367.2-370.2**
160	**140**		**4**	**140 mg, 76**	**0.36**	**367.2-369.2**
161	**141**		**4**	**80 mg, 59**	**0.34**	**340.1-342.1**
162	**142**		**4**	**102 mg, 67**	**1.52**	**339.1-341.1**
163	**143**		**4**	**109 mg, 71**	**2.02**	**368.2-370.2**
164	**144**		**4**	**155 mg, 67**	**1.99**	**354.2-356.1**
165	**145**		**4**	**201 mg, 86**	**0.32**	**338.2-340.2**
166	**146**		**4**	**37 mg, 15**	**0.35**	**384.2-386.2**
167	**147**		**4**	**56 mg, 22**	**2.33**	**382.2-384.2**

实施例148:1-(3-氯-4-氟苯基)-3-(4-甲基-6-((2-(甲氨基)乙基)氨基)嘧啶-2-基)脲(169)的合成



169

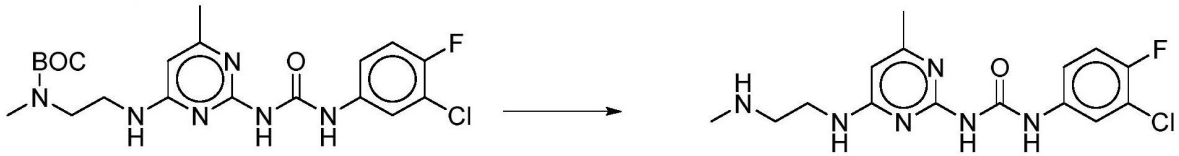
[0498] 步骤1:(2-((2-(3-(3-氯-4-氟苯基)脲基)-6-甲基嘧啶-4-基)氨基)乙基)(甲基)氨基甲酸叔丁酯(168)



156 168

[0499] 用N-(2-氨乙基)-N-甲基氨基甲酸叔丁酯(0.14mL,0.74mmol)和三乙胺(0.13mL,0.93mmol)处理1-(3-氯-4-氟苯基)-3-(4-氯-6-甲基嘧啶-2-基)脲(156)(206mg,0.62mmol)和甲苯(2.3mL)的混合物,并将其在搅拌下加热至回流1小时。在冷却后将所形成的沉淀物过滤并用MeOH和Et_2O洗涤,得到标题化合物(168)(189mg,64%)。LC/MS:方法4:Rt=0.33min,m/z=453.2-455.2[MH^+]。

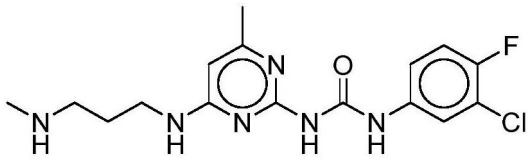
[0500] 步骤2:1-(3-氯-4-氟苯基)-3-(4-甲基-6-((2-(甲氨基)乙基)氨基)嘧啶-2-基)脲(169)



168 169

[0501] 将BOC衍生物(168)(189mg,0.40mmol)悬浮在DCM(5mL)中,向其中添加三氟乙酸(0.77mL,9.9mmol)。在室温下15分钟后,蒸发溶剂并用DCM和1N氢氧化钠溶液处理残余物。过滤标题产物,并用水洗涤,干燥后产生白色固体(169)(117mg,79%)。LC/MS:方法4:Rt=0.36min,m/z=353.2-355.2[MH^+]。

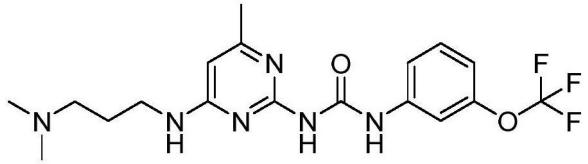
实施例149:1-(3-氯-4-氟苯基)-3-(4-甲基-6-((3-(甲氨基)丙基)氨基)嘧啶-2-基)脲(170)的合成



170

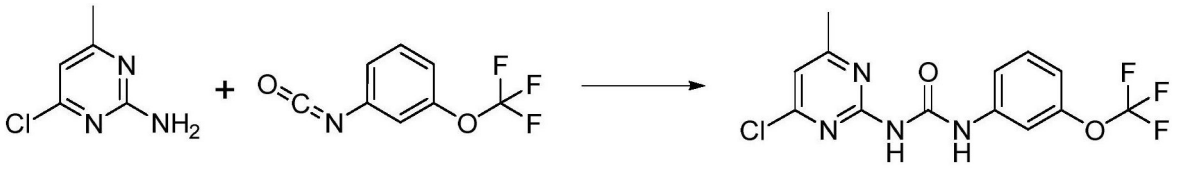
[0502] 以与实施例148类似的方式,由1-(3-氯-4-氟苯基)-3-(4-氯-6-甲基嘧啶-2-基)脲(156)和N-(3-氨丙基)-N-甲基氨基甲酸叔丁酯(165mg,93%)制备实施例149。LC/MS:方法4:Rt=0.38min,m/z=367.2-369.2[MH+]。

实施例150:1-(4-((3-(二甲氨基)丙基)氨基)-6-甲基嘧啶-2-基)-3-(3-(三氟甲氧基)苯基)脲(172)的合成



172

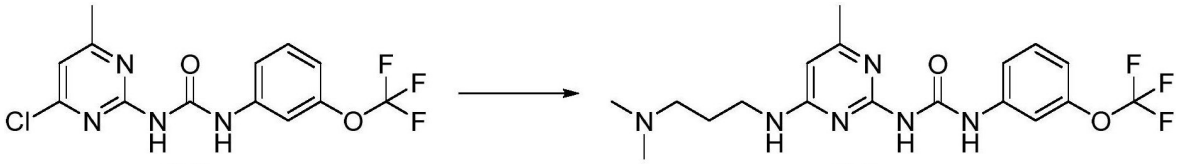
[0503] 步骤1:1-(4-氯-6-甲基嘧啶-2-基)-3-(3-(三氟甲氧基)-苯基)脲(171)



171

[0504] 将2-氨基-4-氯-6-甲基嘧啶(179mg,1.2mmol)和3-三氟甲氧基苯基异氰酸酯(278mg,1.4mmol)在甲苯(1.7mL)中的混合物回流7小时。冷却后添加MeOH(5mL)并过滤悬浮液,用Et_2O洗涤并干燥,产生呈白色固体的化合物(171)(66mg,15%)。

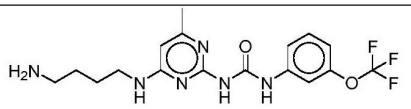
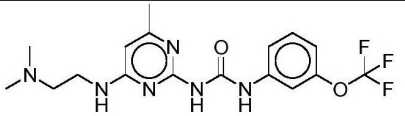
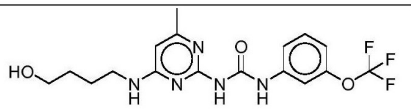
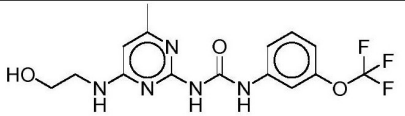
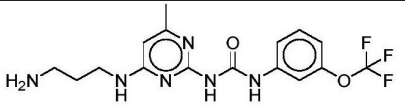
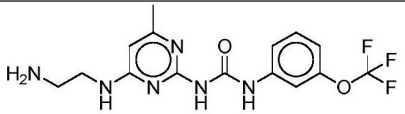
[0505] 步骤2:1-(4-((3-(二甲氨基)丙基)氨基)-6-甲基嘧啶-2-基)-3-(3-(三氟甲氧基)苯基)脲(172)



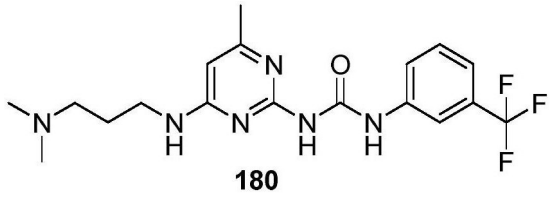
171 172

[0506] 将1-(4-氯-6-甲基嘧啶-2-基)-3-(3-(三氟甲氧基)苯基)脲(171)(66mg,0.19mmol)和3-(二甲氨基)-1-丙胺(0.03mL,0.22mmol)以及三乙胺(0.04mL,0.28mmol)在2-丙醇(0.5mL)中的混合物在80℃下加热过夜。冷却该反应混合物,用MeOH(5mL)稀释,并过滤白色沉淀物,产生标题化合物(172)(14mg,17%)。LC/MS:方法4:Rt=1.65min,m/z=413.2[MH^+]。

[0507] 根据针对实施例150所述的类似过程制备下列实施例:

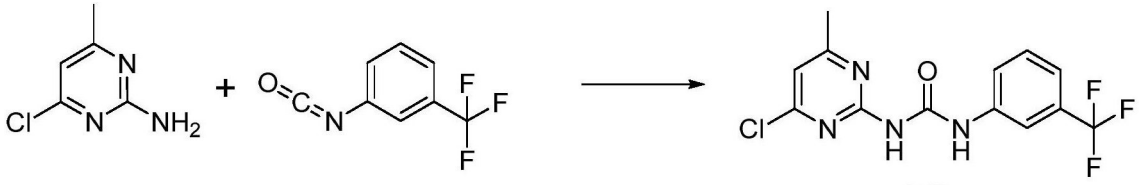
化合物 ID	实施例 ID	结构	HPLC 方法	产率 (质量/%)	RT (min)	MH^+
173	151		4	50 mg, 58	1.65	399.2
174	152		4	46 mg, 53	1.68	399.2
175	153		4	47 mg, 66	2.10	400.2
176	154		4	48 mg, 60	2.02	373.2
177	155		4	18 mg, 21	1.51	386.2
178	156		4	22 mg, 28	1.52	371.2

实施例157:1-(4-((3-(二甲氨基)丙基)氨基)-6-甲基嘧啶-2-基)-3-(3-(三氟甲基)苯基)脲(180)的合成



180

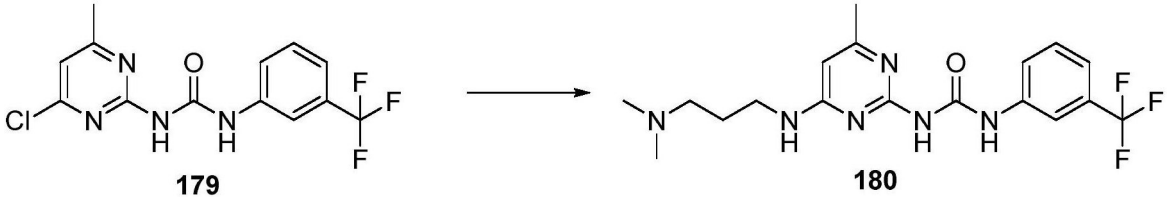
[0508] 步骤1:1-(4-氯-6-甲基嘧啶-2-基)-3-(3-(三氟甲基)-苯基)脲(179)



179

[0509] 将2-氨基-4-氯-6-甲基嘧啶(2.6g,17.6mmol)和3-三氟甲基苯基异氰酸酯(3.9g,17.6mmol)在甲苯(31mL)中的混合物回流过夜。冷却后过滤悬浮液,用MeOH和Et_2O洗涤并干燥,产生呈白色固体的化合物(179)(4.4g,72%)。LC/MS:方法4:Rt=3.65min,m/z=331.1[MH^+]。

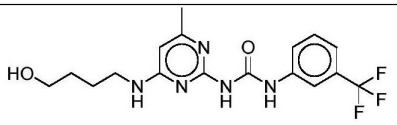
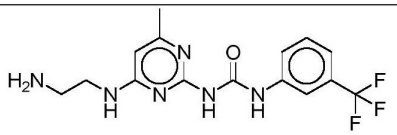
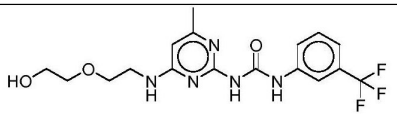
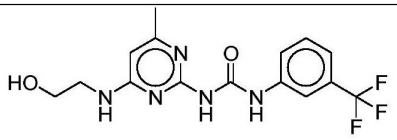
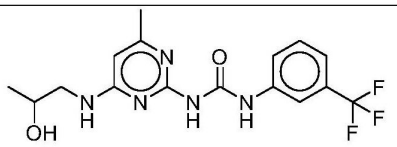
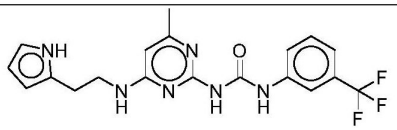
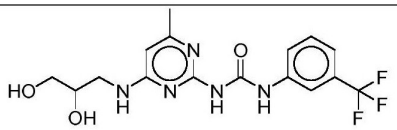
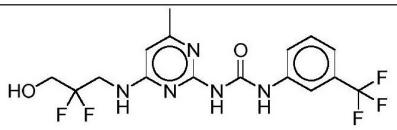
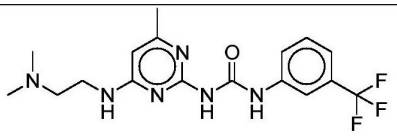
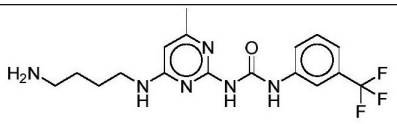
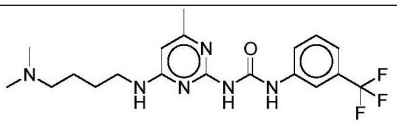
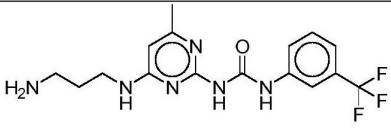
[0510] 步骤2:1-(4-((3-(二甲氨基)丙基)氨基)-6-甲基嘧啶-2-基)-3-(3-(三氟甲基)苯基)脲(180)



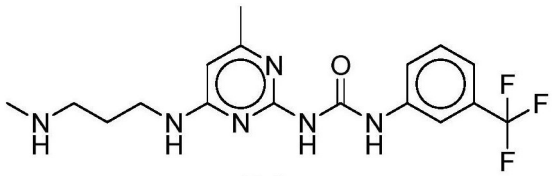
179 180

[0511] 将1-(4-氯-6-甲基嘧啶-2-基)-3-(3-(三氟甲基)苯基)脲(179)(100mg,0.29mmol)和3-(二甲氨基)-1-丙胺(0.04mL,0.34mmol)以及三乙胺(0.06mL,0.43mmol)在2-丙醇(0.5mL)中的混合物在80℃下加热2小时。冷却该反应混合物,并过滤白色沉淀物,产生标题化合物(180)(61mg,54%)。LC/MS:方法4:Rt=1.46min,m/z=397.2[MH^+]。

[0512] 根据针对实施例157所述的类似过程制备下列实施例:

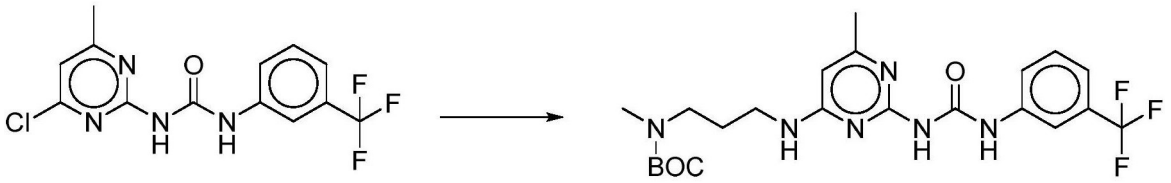
化合物 ID	实施例 ID	结构	HPLC 方法	产率 (质量/%)	RT (min)	MH^+
181	158		4	200 mg,76	2.10	384.2
182	159		4	105 mg, 40	1.64	355.2
183	160		4	148 mg, 53	2.04	400.2
184	161		4	145 mg, 59	1.96	356.2
185	162		4	208 mg, 81	2.05	370.2
186	163		4	135 mg, 46	2.51	405.2
187	164		4	192 mg, 69	1.87	386.2
188	165		4	54 mg, 18	2.21	406.2
189	166		4	54 mg, 47	1.67	383.2
190	167		4	56 mg, 46	1.62	383.2
191	168		4	16 mg, 9	1.56	411.2
192	169		4	20 mg, 9	1.59	369.2

实施例170:1-(4-甲基-6-((3-(甲氨基)丙基)氨基)嘧啶-2-基)-3-(3-(三氟甲基)苯基)脲(194)的合成



194

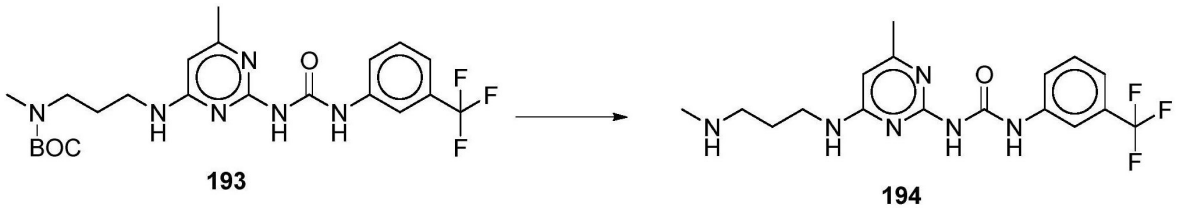
[0513] 步骤1:甲基(3-((6-甲基-2-(3-(3-(三氟甲基)苯基)脲基)嘧啶-4-基)氨基)丙基)氨基甲酸叔丁酯(193)



179 193

[0514] 用N-(3-氨丙基)-N-甲基氨基甲酸叔丁酯(0.13g,0.65mmol)和三乙胺(0.11mL,0.81mmol)处理1-(4-氯-6-甲基嘧啶-2-基)-3-(3-(三氟甲基)苯基)脲(179)(189mg,0.54mmol)和2-丙醇(5mL)的混合物,并将其在搅拌下加热至回流30分钟。在冷却后将所形成的沉淀物过滤并用MeOH和Et_2O洗涤,得到标题化合物(193)(122mg,44%)。LC/MS:方法4:Rt 2.90min,m/z=483.3[MH^+]。

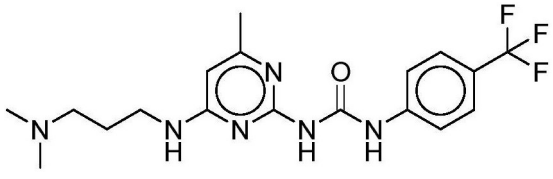
[0515] 步骤2:1-(4-甲基-6-((3-(甲氨基)丙基)氨基)嘧啶-2-基)-3-(3-(三氟甲基)苯基)脲



193 194

[0516] 将BOC衍生物(193)(122mg,0.24mmol)悬浮在DCM(5mL)中,向其中添加三氟乙酸(0.46mL,6.0mmol)。在室温下15分钟后,蒸发溶剂,用DCM和1N氢氧化钠溶液(0.24mL)处理残余物。过滤得到呈白色固体的标题产物(194),用水洗涤并干燥(60mg,62%)。LC/MS:方法4:Rt 1.55min,m/z=383.2[MH^+]。

实施例171:1-(4-((3-(二甲氨基)丙基)氨基)-6-甲基嘧啶-2-基)-3-(4-(三氟甲基)苯基)脲(196)的合成



196

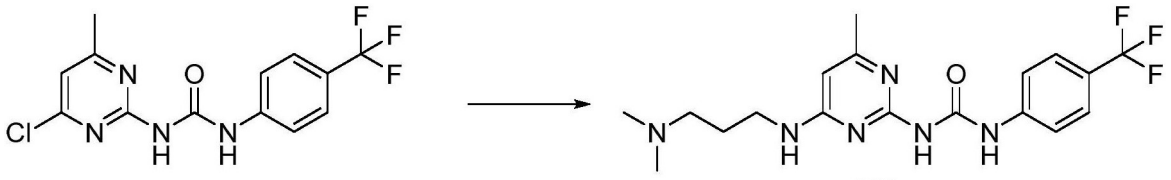
[0517] 步骤1:1-(4-氯-6-甲基嘧啶-2-基)-3-(4-(三氟甲基)-苯基)脲(195)



195

[0518] 将2-氨基-4-氯-6-甲基嘧啶(0.82g,5.7mmol)和4-三氟甲基苯基异氰酸酯(0.91mL,6.3mmol)在N,N-二甲基乙酰胺(7.6mL)中的混合物在100℃下加热20分钟。在冷却后用MeOH(20mL)稀释该混合物。过滤浆液,用MeOH洗涤并干燥,产生呈白色固体的化合物(195)(0.98g,52%)。

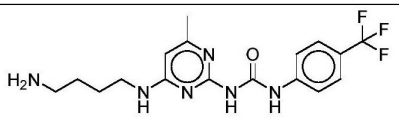
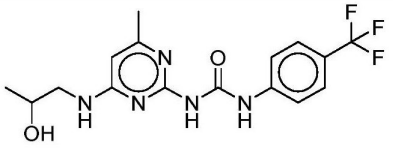
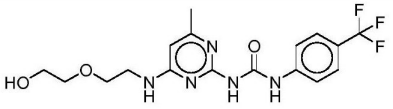
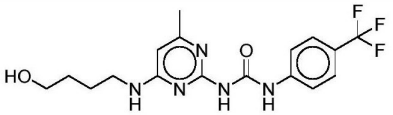
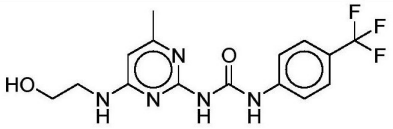
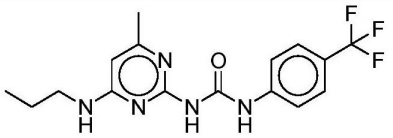
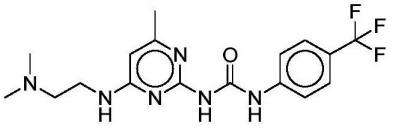
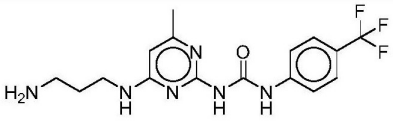
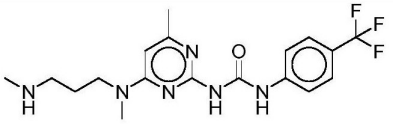
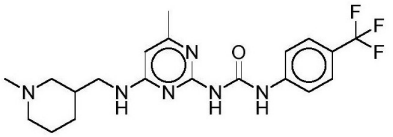
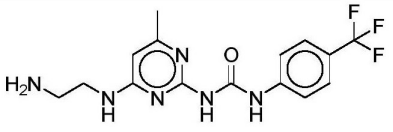
[0519] 步骤2:1-(4-((3-(二甲氨基)丙基)氨基)-6-甲基嘧啶-2-基)-3-(4-(三氟甲基)苯基)脲(196)



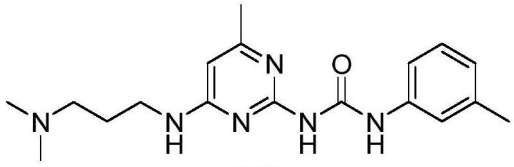
195 196

[0520] 将1-(4-氯-6-甲基嘧啶-2-基)-3-(4-(三氟甲基)苯基)脲(195)(75mg,0.23mmol)和3-(二甲氨基)-1-丙胺(0.03mL,0.27mmol)以及三乙胺(0.05mL,0.34mmol)在2-丙醇(0.5mL)中的混合物在80℃下加热过夜。冷却该反应混合物,并过滤白色沉淀物,产生标题化合物(196)(8mg,8%)。LC/MS:方法4:Rt=1.70min,m/z=397.2[MH^+]。

[0521] 根据针对实施例171所述的类似过程制备下列实施例:

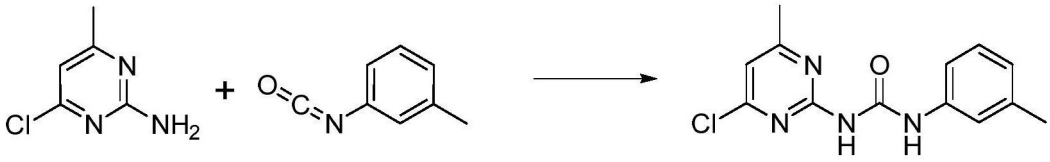
化合物 ID	实施例 ID	结构	HPLC 方法	产率 (质量/%)	RT (min)	MH^+
197	172		4	16 mg, 19	2.02	383.2
198	173		4	26 mg, 31	2.01	371.2
199	174		4	26 mg, 29	1.98	401.2
200	175		4	60 mg, 83	2.07	384.2
201	176		4	53 mg, 65	1.93	356.2
202	177		4	55 mg, 66	2.46	354.2
203	178		4	26 mg, 30	1.67	384.2
204	179		4	12 mg, 14	2.07	369.2
205	180		4	6 mg, 6	1.81	398.2
206	181		4	28 mg, 38	1.68	423.3
207	182		4	16 mg, 9	1.69	355.2

实施例183:1-(4-((3-(二甲氨基)丙基)氨基)-6-甲基嘧啶-2-基)-3-(间甲苯基)脲(209)的合成



209

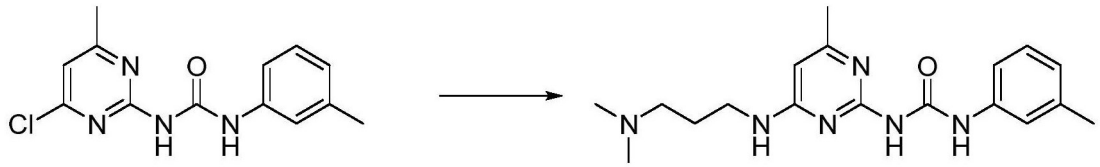
[0522] 步骤1:1-(4-氯-6-甲基-2-嘧啶基)-3-(3-甲基苯基)脲(208)



208

[0523] 将2-氨基-4-氯-6-甲基嘧啶(10g,68mmol)和3-甲基苯基异氰酸酯(11.1g,83mmol)的N,N-二甲基乙酰胺(50mL)中的混合物在室温下搅拌1小时,然后在70℃下加热2小时。在冷却后将该混合物搅拌过夜。过滤所形成的浆液,用乙醇洗涤并干燥,产生呈白色固体的化合物(208)(8.0g,43%)。LC/MS:方法4:Rt=0.25min,m/z=277.1[MH^+]。

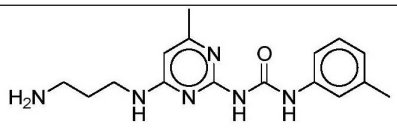
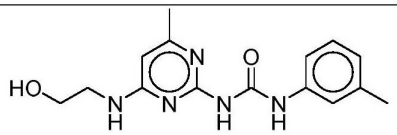
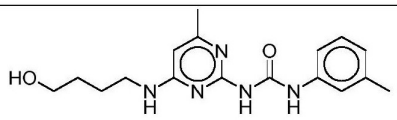
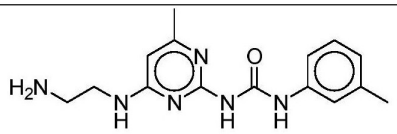
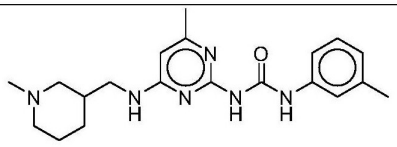
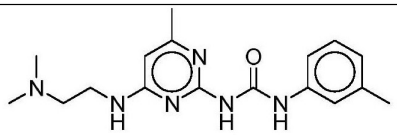
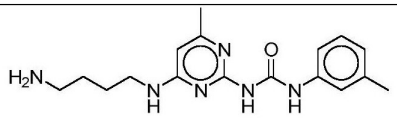
[0524] 步骤2:1-(4-((3-(二甲氨基)丙基)氨基)-6-甲基嘧啶-2-基)-3-(间甲苯基)脲(209)

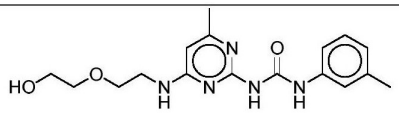
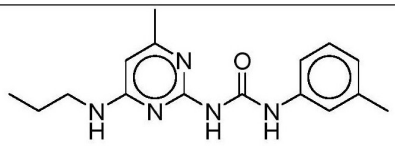
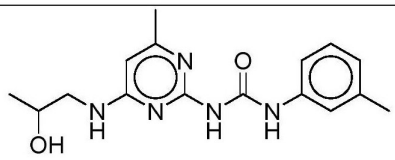
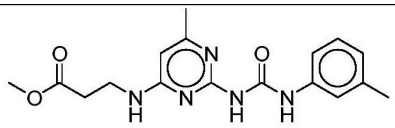
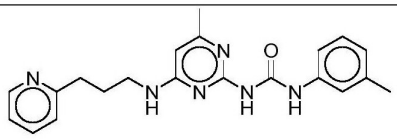
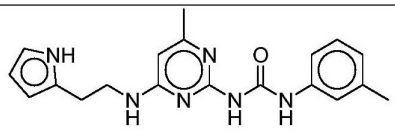
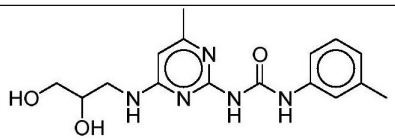
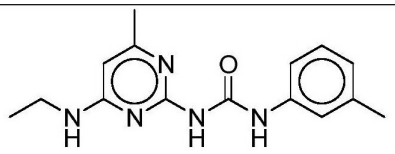
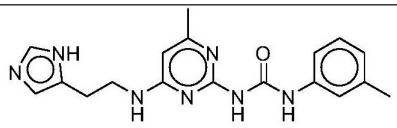
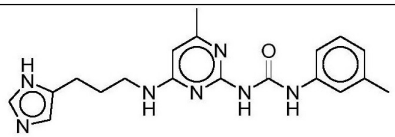
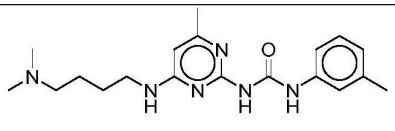


208 209

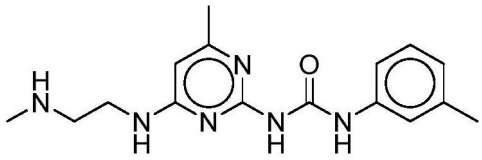
[0525] 将在2-丙醇(1.2mL)中的1-(4-氯-6-甲基-2-嘧啶基)-3-(3-甲氧基苯基)脲(208)(0.2g,0.70mmol)和3-(二甲氨基)-1-丙胺(0.11mL,0.81mmol)以及三乙胺(0.15mL,1.1mmol)在70℃下加热过夜。冷却并过滤该反应混合物。用乙醇洗涤固体,产生标题化合物(209)(0.19g,77%)。LC/MS:方法4:Rt=0.35min,m/z=343.3[MH^+]。

[0526] 根据针对实施例183所述的类似过程制备下列实施例:

化合物 ID	实施例 ID	结构	HPLC 方法	产率 (质量/%)	RT (min)	MH^+
210	184		4	159 mg, 72	1.29	315.2
211	185		4	185 mg, 88	1.56	302.2
212	186		4	170 mg, 74	1.20	330.2
213	187		4	65 mg, 31	0.36	301.2
214	188		4	115 mg, 59	0.34	369.3
215	189		4	50 mg, 22	0.35	329.3
216	190		4	225 mg, 98	0.34	329.2

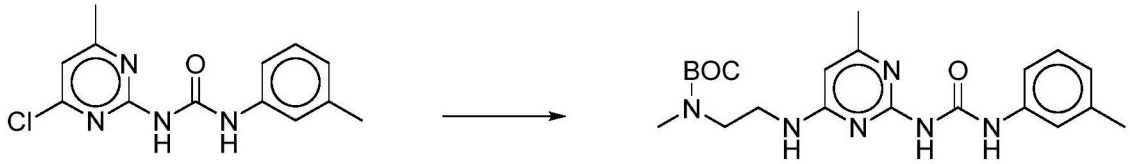
217	**191**		**4**	**108 mg, 45**	**1.64**	**346.2**
218	**192**		**4**	**156 mg, 74**	**2.07**	**300.2**
219	**193**		**4**	**190 mg, 86**	**1.69**	**316.2**
220	**194**		**4**	**100 mg, 39**	**2.00**	**344.2**
221	**195**		**4**	**195 mg, 70**	**1.41**	**377.3**
222	**196**		**4**	**195 mg, 75**	**2.26**	**351.2**
223	**197**		**4**	**195 mg, 80**	**1.57**	**332.2**
224	**198**		**4**	**110 mg, 52**	**1.90**	**286.2**
225	**199**		**4**	**14 mg, 7**	**1.37**	**352.2**
226	**200**		**4**	**120 mg, 59**	**1.32**	**366.2**
227	**201**		**4**	**130 mg, 52**	**1.29**	**357.3**

实施例202:1-(4-甲基-6-((2-(甲氨基)乙基)氨基)嘧啶-2-基)-3-(间甲苯基)脲(229)的合成



229

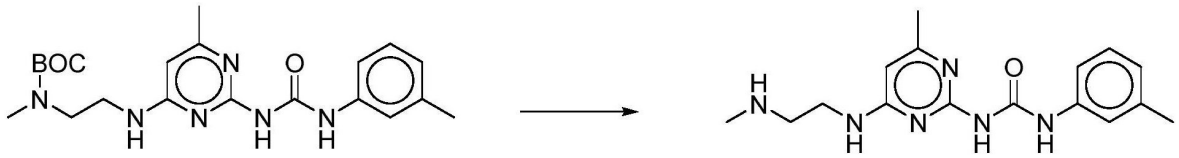
[0527] 步骤1:甲基(2-((6-甲基-2-(3-(间甲苯基)脲基)嘧啶-4-基)氨基)乙基)氨基甲酸叔丁酯(228)



208 228

[0528] 用N-(2-氨乙基)-N-甲基氨基甲酸叔丁酯(1.2mL,16.7mmol)和三乙胺(0.15mL,1.1mmol)处理1-(4-氯-6-甲基嘧啶-2-基)-3-(间甲苯基)脲(208)(200mg,0.70mmol)和2-丙醇(1.2mL)的混合物,并将其在搅拌下加热至回流过夜。在冷却后过滤该混合物,并用乙醇洗涤固体,得到标题化合物(228)(240mg,83%)。LC/MS:方法4:Rt=0.33min,m/z=415.3[MH^+]。

[0529] 步骤2:1-(4-甲基-6-((2-(甲氨基)乙基)氨基)嘧啶-2-基)-3-(间甲苯基)脲(229)

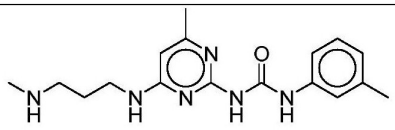
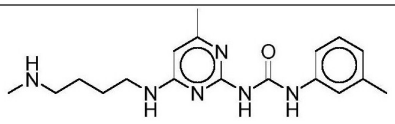
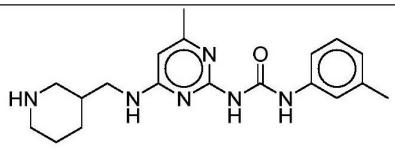


228 229

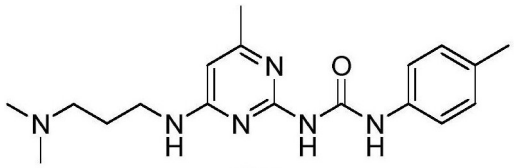
[0530] 将BOC衍生物(228)(226mg,0.53mmol)悬浮在DCM(0.7mL)中,向其中添加三氟乙酸(0.7mL,9mmol)。在室温下2小时后,用饱和碳酸氢钠溶液处理混合物达到pH 8。过滤得到呈白色固体的标题产物(229)(165mg,100%)。LC/MS:方法4:Rt=0.35min,m/z=315.2[MH^+]。

[0531] 根据针对实施例202所述的类似过程制备下列实施例:

化合	实施	结构	HPLC	产率 (质	RT	MH^+

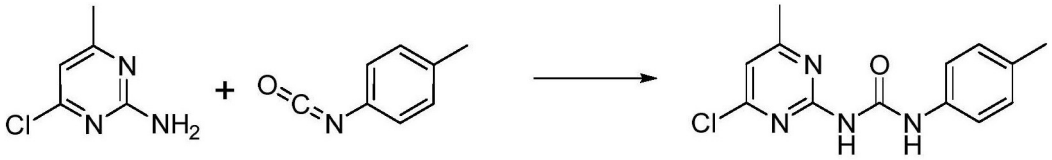
物 ID	例 ID		方法	量/%)	(min)	
230	203		4	180 mg, 81	0.35	329.3
231	204		4	120 mg, 46	1.29	343.3
232	205		4	200 mg, 78	1.25	355.3

实施例206:1-(4-((3-(二甲氨基)丙基)氨基)-6-甲基嘧啶-2-基)-3-(对甲苯基)脲(234)的合成



234

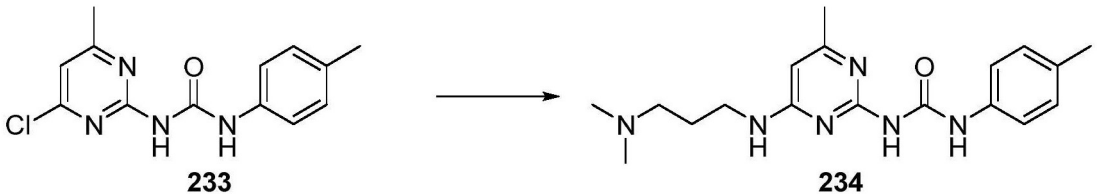
[0532] 步骤1:1-(4-氯-6-甲基嘧啶-2-基)-3-(对甲苯基)脲(233)



233

[0533] 将2-氨基-4-氯-6-甲基嘧啶(3g,20mmol)和4-甲基苯基异氰酸酯(3.3g,25mmol)在N,N-二甲基乙酰胺(15mL)中的混合物在室温下搅拌1小时,在70℃下加热2小时,然后维持在50℃下过夜。在冷却后将该混合物搅拌过夜。过滤所形成的浆液,用乙醇洗涤并干燥,产生呈白色固体的化合物(233)(3.3g,59%)。LC/MS:方法4:Rt=3.28min,m/z=277.1[MH^+]。

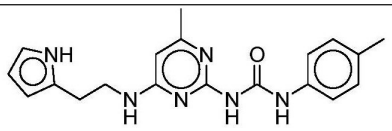
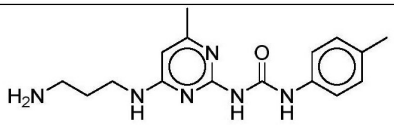
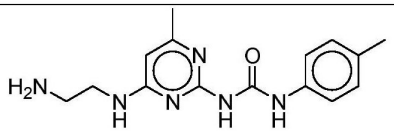
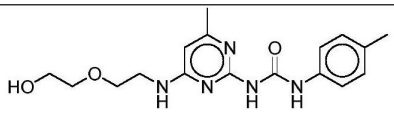
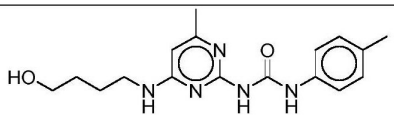
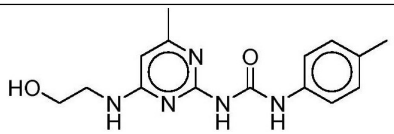
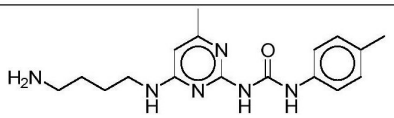
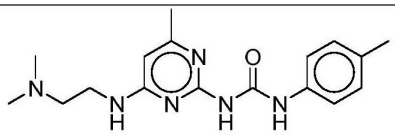
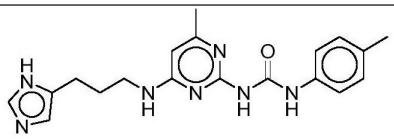
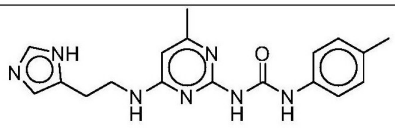
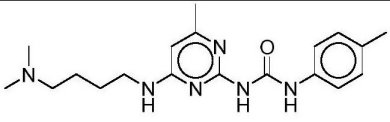
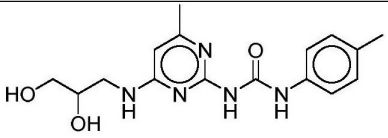
[0534] 步骤2:1-(4-((3-(二甲氨基)丙基)氨基)-6-甲基嘧啶-2-基)-3-(对甲苯基)脲(234)



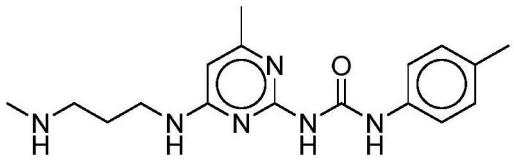
233 234

[0535] 将在2-丙醇(1.2mL)中的1-(4-氯-6-甲基嘧啶-2-基)-3-(对甲苯基)脲(233)(0.2g,0.70mmol)和3-(二甲氨基)-1-丙胺(0.11mL,0.81mmol)以及三乙胺(0.15mL,1.1mmol)在70℃下加热过夜。冷却并过滤该反应混合物。用乙醇洗涤固体,产生标题化合物(234)(0.19g,77%)。LC/MS:方法4:Rt=1.32min,m/z=343.3[MH^+]。

[0536] 根据针对实施例206所述的类似过程制备下列实施例:

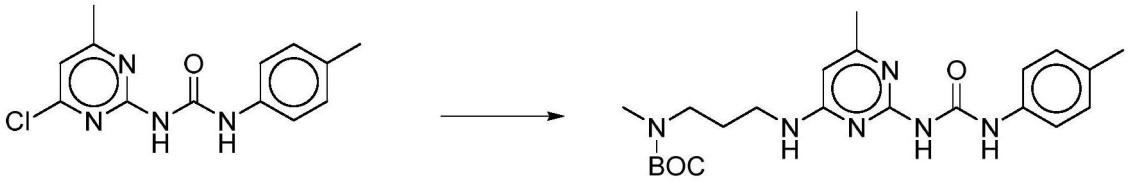
化合物 ID	实施例 ID	结构	HPLC 方法	产率 (质量/%)	RT (min)	MH^+
235	207		4	195 mg, 75	2.21	351.2
236	208		4	155 mg, 70	1.12	315.2
237	209		4	150 mg, 68	1.12	301.2
238	210		4	193 mg, 80	1.66	346.2
239	211		4	185 mg, 76	1.70	330.2
240	212		4	144 mg, 68	1.61	302.2
241	213		4	150 mg, 65	1.30	329.2
242	214		4	108 mg, 45	1.69	330.2
243	215		4	25 mg, 12	1.31	366.2
244	216		4	40 mg, 21	1.27	352.2
245	217		4	80 mg, 32	1.38	357.3
246	218		4	140 mg, 57	1.57	332.2

实施例219:1-(4-甲基-6-((3-(甲氨基)丙基)氨基)嘧啶-2-基)-3-(对甲苯基)脲(248)的合成



248

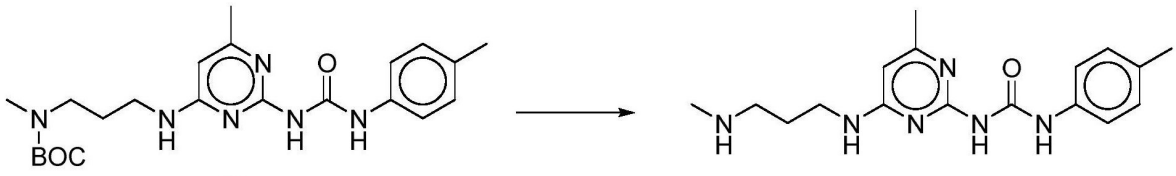
[0537] 步骤1:甲基(3-((6-甲基-2-(3-(对甲苯基)脲基)嘧啶-4-基)氨基)丙基)氨基甲酸叔丁酯(247)



233 247

[0538] 用N-(3-氨丙基)-N-甲基氨基甲酸叔丁酯(0.1mL,0.84mmol)和三乙胺(0.15mL,1.1mmol)处理1-(4-氯-6-甲基嘧啶-2-基)-3-(对甲苯基)脲(233)(200mg,0.70mmol)和2-丙醇(0.96mL)的混合物,并将其在搅拌下加热到70℃过夜。在冷却后干燥所形成的沉淀物,得到标题化合物(247)(164mg,53%)。

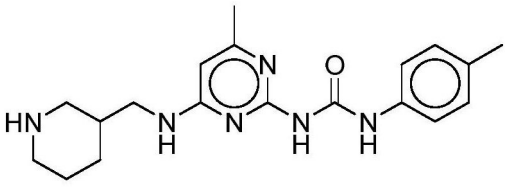
[0539] 步骤2:1-(4-甲基-6-((3-(甲氨基)丙基)氨基)嘧啶-2-基)-3-(对甲苯基)脲(248)



247 248

[0540] 将BOC衍生物(247)(251mg,0.56mmol)悬浮在DCM(0.75mL)中,向其中添加三氟乙酸(0.71mL,9.7mmol)。在室温下2小时后,蒸发溶剂,并用足以达到pH 8的饱和碳酸氢钠溶液处理残余物。过滤得到呈白色固体的标题产物(248),用水洗涤并干燥(160mg,82%)。LC/MS:方法4:Rt 1.22min,m/z=329.2[MH^+]。

实施例220:1-(4-甲基-6-((哌啶-3-基甲基)氨基)嘧啶-2-基)-3-(对甲苯基)脲(249)的合成

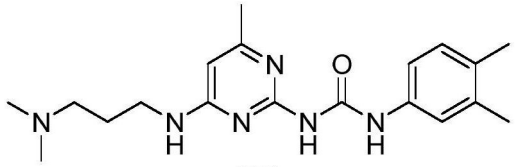


249

[0541] 以与实施例219类似的方式,由1-(4-氯-6-甲基嘧啶-2-基)-3-(对甲苯基)脲(233)和3-(氨甲基)哌啶-1-甲酸叔丁酯制备实施例220(180mg,71%)。LC/MS:方法4:Rt=1.31min,m/z=355.3[MH+]。

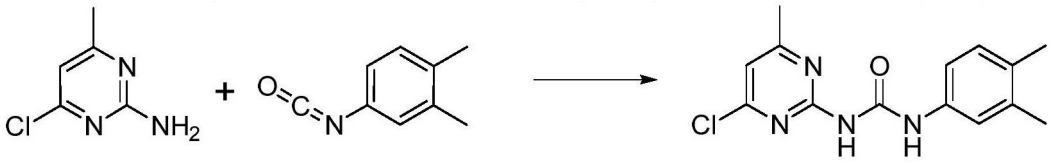
实施例221:1-(4-((3-(二甲氨基)丙基)氨基)-6-甲基嘧啶-2-基)-3-(3,4-二甲基苯

基)脲(251)的合成



251

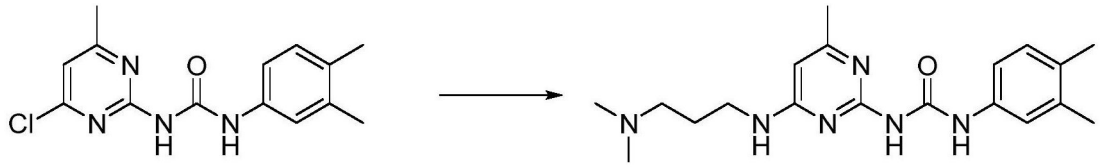
[0542] 步骤1:1-(4-氯-6-甲基嘧啶-2-基)-3-(3,4-二甲基苯基)脲(250)



250

[0543] 将2-氨基-4-氯-6-甲基嘧啶(10g,68mmol)和3,4-二甲基苯基异氰酸酯(12.3g,83mmol)在N,N-二甲基乙酰胺(60mL)中的混合物在室温下搅拌1小时,然后在50℃下加热过夜。在冷却后将混合物搅拌过夜。过滤所形成的浆液,用醚洗涤并干燥,产生呈白色固体的化合物(250)(4.8g,24%)。LC/MS:方法4:Rt=0.25min,m/z=277.1[MH^+]。该物质直接用于下一步。

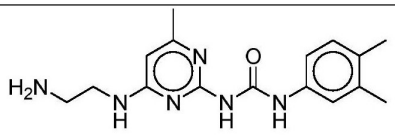
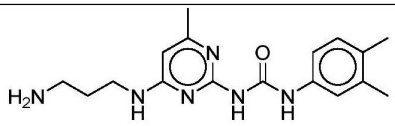
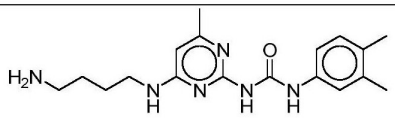
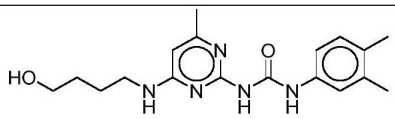
[0544] 步骤2:1-(4-((3-(二甲氨基)丙基)氨基)-6-甲基嘧啶-2-基)-3-(3,4-二甲基苯基)脲(251)

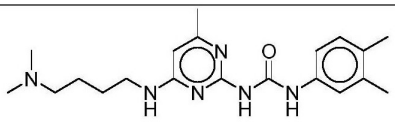
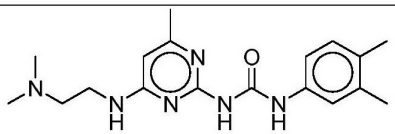
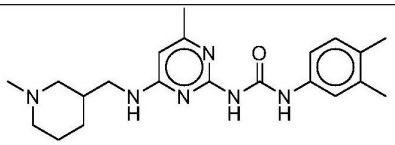
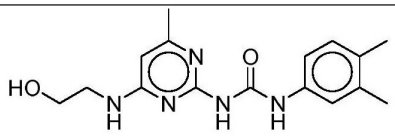
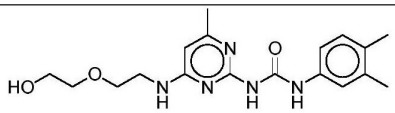
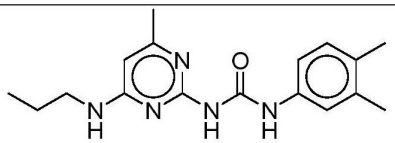
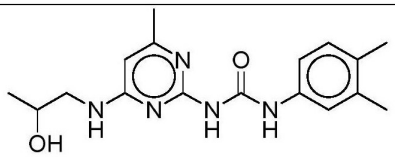
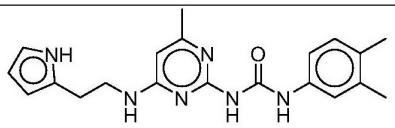
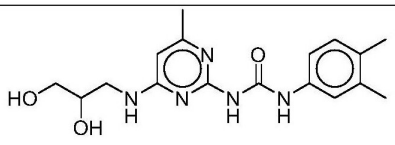
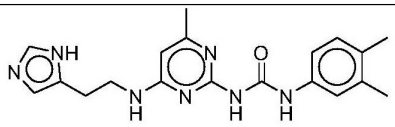
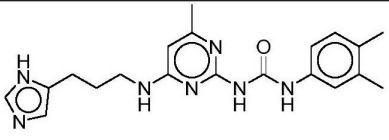


250 251

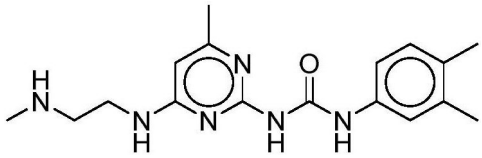
[0545] 将在2-丙醇(1.1mL)中的1-(4-氯-6-甲基嘧啶-2-基)-3-(3,4-二甲基苯基)脲(250)(0.2g,0.67mmol)和3-(二甲氨基)-1-丙胺(0.11mL,0.81mmol)以及三乙胺(0.14mL,1.0mmol)在70℃下加热过夜。冷却并过滤该反应混合物。用乙醇洗涤固体,产生标题化合物(251)(198mg,83%)。LC/MS:方法4:Rt=0.35min,m/z=357.3[MH^+]。

[0546] 根据针对实施例221所述的类似过程制备下列实施例:

化合物 ID	实施例 ID	结构	HPLC 方法	产率 (质量 /%)	RT (min)	MH^+
252	222		4	85 mg, 31	0.36	301.2
253	223		4	50 mg, 23	2.07	329.2
254	224		4	39 mg, 17	2.10	343.3
255	225		4	42 mg, 18	2.66	344.2

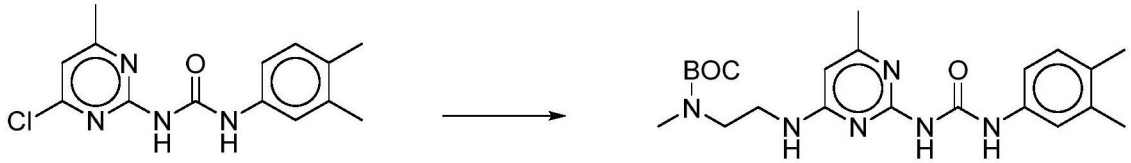
256	**226**		**4**	**75 mg, 30**	**0.38**	**371.3**
257	**227**		**4**	**50 mg, 22**	**0.35**	**329.3**
258	**228**		**4**	**20 mg, 10**	**0.40**	**383.3**
259	**229**		**4**	**38 mg, 24**	**2.34**	**316.2**
260	**230**		**4**	**91 mg, 38**	**1.82**	**360.2**
261	**231**		**4**	**127 mg, 61**	**0.33**	**314.2**
262	**232**		**4**	**130 mg, 56**	**1.29**	**330.2**
263	**233**		**4**	**195 mg, 76**	**2.44**	**365.3**
264	**234**		**4**	**195 mg, 81**	**1.75**	**346.2**
265	**235**		**4**	**25 mg, 13**	**1.62**	**366.2**
266	**236**		**4**	**20 mg, 10**	**1.50**	**380.2**

实施例237:1-(3,4-二甲基苯基)-3-(4-甲基-6-((2-(甲氨基)乙基)氨基)嘧啶-2-基)脲(268)的合成



268

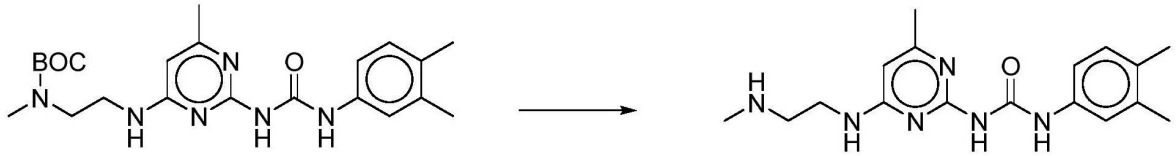
[0547] 步骤1：(2-((2-(3-(3,4-二甲基苯基)脲基)-6-甲基嘧啶-4-基)氨基)乙基)(甲基)氨基甲酸叔丁酯(267)



250 267

[0548] 用N-(2-氨乙基)-N-甲基氨基甲酸叔丁酯(1.2mL,16.7mmol)和三乙胺(0.15mL,1.1mmol)处理1-(4-氯-6-甲基嘧啶-2-基)-3-(3,4-二甲基苯基)脲(250)(200mg,0.70mmol)和2-丙醇(1.2mL)的混合物,并将其在搅拌下加热至回流过夜。在冷却后过滤该混合物,并用乙醇洗涤固体,得到标题化合物(267)(168mg,59%)。

[0549] 步骤2:1-(3,4-二甲基苯基)-3-(4-甲基-6-((2-(甲氨基)乙基)氨基)嘧啶-2-基)脲(268)

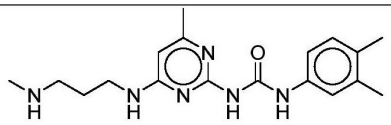
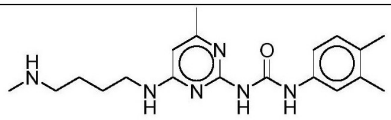
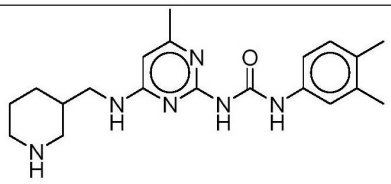


267 268

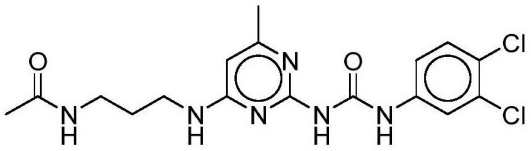
[0550] 将BOC衍生物(267)(167mg,0.38mmol)悬浮在DCM(0.5mL)中,向其中添加三氟乙酸(0.48mL,6mmol)。在室温下2小时后,用饱和碳酸氢钠溶液处理混合物达到pH 8。过滤得到呈白色固体的标题产物(268)(115mg,93%)。LC/MS:方法4:Rt＝0.37min,m/z＝329.2[MH^+]。

[0551] 根据针对实施例237所述的类似过程制备下列实施例:

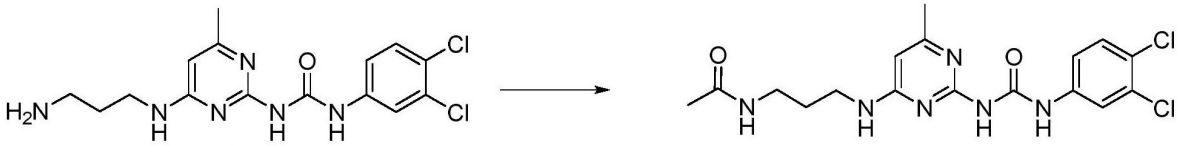
化合物ID	实施例ID	结构	HPLC方法	产率(质量/%)	RT(min)	MH^+

269	**238**		**4**	**100 mg, 50**	**0.37**	**343.2**
270	**239**		**4**	**84 mg, 37**	**0.36**	**357.3**
271	**240**		**4**	**109 mg, 45**	**0.35**	**369.3**

实施例241:N-(3-((2-(3-(3,4-二氯苯基)脲基)-6-甲基嘧啶-4-基)氨基)丙基)乙酰胺(272)的合成



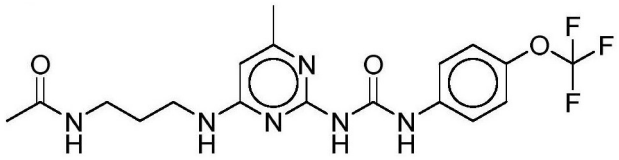
272



9 **272**

[0552] 将1-(4-((3-氨丙基)氨基)-6-甲基嘧啶-2-基)-3-(3,4-二氯苯基)脲(9)(100mg,0.27mmol)、乙酸酐(0.03mL,0.29mmol)、吡啶(0.14mL,1.7mmol)和催化量的N,N-二甲基氨基吡啶在DCM(0.54mL)中的混合物在室温下搅拌2.5小时。此时将该混合物冷却至-20℃,然后用MeOH(5mL)稀释。过滤并干燥产生的固体,得到标题产物(272)(75mg,64%)。LC/MS:方法4:Rt=2.07min,m/z=411.2-413.2[MH^+]。

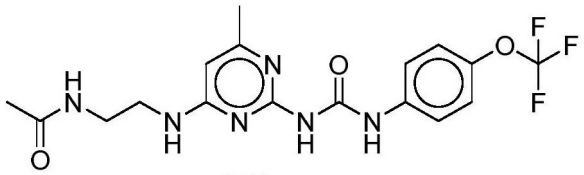
实施例242:N-(3-((6-甲基-2-(3-(4-(三氟甲氧基)苯基)脲基)嘧啶-4-基)氨基)丙基)乙酰胺(273)的合成



273

[0553] 通过与针对实施例241所述类似的过程,由1-(4-((3-氨丙基)氨基)-6-甲基嘧啶-2-基)-3-(3-(三氟甲氧基)苯基)脲(89)制备实施例242(11mg,20%)。LC/MS:方法4:Rt=2.02min,m/z=427.2[MH^+]。

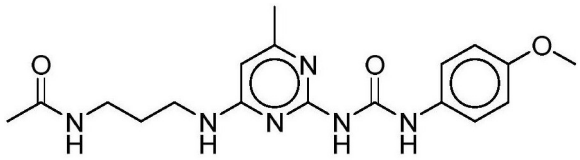
实施例243:N-(3-((6-甲基-2-(3-(4-(三氟甲氧基)苯基)脲基)嘧啶-4-基)氨基)乙基)乙酰胺(274)的合成



274

[0554] 通过与针对实施例241所述类似的过程,由1-(4-((3-氨乙基)氨基)-6-甲基嘧啶-2-基)-3-(4-(三氟甲氧基)苯基)脲(87)制备实施例243(11mg,20%)。LC/MS:方法4:Rt=2.02min,m/z=427.2[MH^+]。

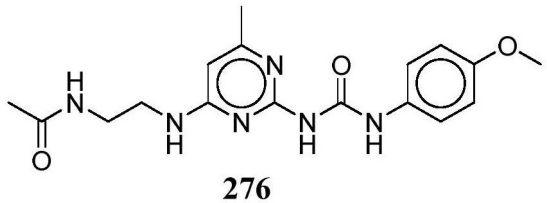
实施例244:N-(3-((2-(3-(4-甲氧基苯基)脲基)-6-甲基嘧啶-4-基)氨基)丙基)乙酰胺(275)的合成



275

[0555] 通过与针对实施例241所述类似的过程,由1-(4-((3-氨丙基)氨基)-6-甲基嘧啶-2-基)-3-(4-甲氧基苯基)脲(131)制备实施例244(47mg,56%)。LC/MS:方法4:Rt=1.44min,m/z=373.2[MH^+]。

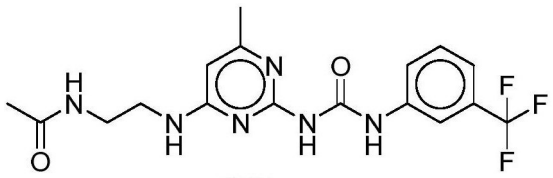
实施例245:N-(2-((2-(3-(4-甲氧基苯基)脲基)-6-甲基嘧啶-4-基)氨基)乙基)乙酰胺(276)的合成



276

[0556] 通过与针对实施例241所述类似的过程,由1-(4-((2-氨乙基)氨基)-6-甲基嘧啶-2-基)-3-(4-甲氧基苯基)脲(127)制备实施例245(19mg,49%)。LC/MS:方法4:Rt=1.37min,m/z=359.2[MH^+]。

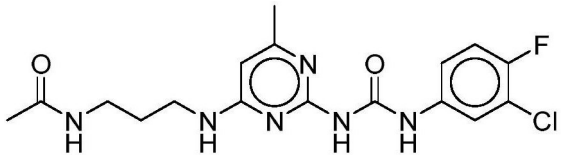
实施例246:N-(2-((2-(3-(4-甲氧基苯基)脲基)-6-甲基嘧啶-4-基)氨基)乙基)乙酰胺(277)的合成



277

[0557] 通过与针对实施例241所述类似的过程,由1-(4-((2-氨乙基)氨基)-6-甲基嘧啶-2-基)-3-(3-(三氟甲基)苯基)脲(182)制备实施例246(12mg,33%)。LC/MS:方法4:Rt=1.87min,m/z=397.2[MH^+]。

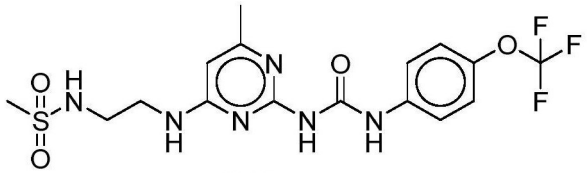
实施例247:N-(3-((2-(3-(3-氯-4-氟苯基)脲基)-6-甲基嘧啶-4-基)氨基)丙基)乙酰胺(278)的合成



278

[0558] 通过与针对实施例241所述类似的过程，由1-(4-((3-氨丙基)氨基)-6-甲基嘧啶-2-基)-3-(3-氯-4-氟苯基)脲(158)制备实施例247(24mg，43％)。LC/MS：方法4：Rt＝1.83min，m/z＝395.2[MH+]。

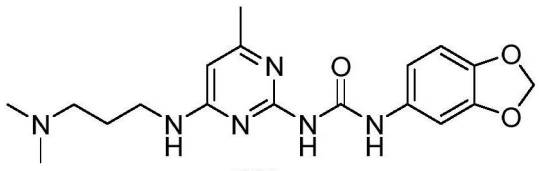
实施例248：N-(2-((6-甲基-2-(3-(4-(三氟甲氧基)苯基)脲基)嘧啶-4-基)-乙基)甲基磺酰胺(279)的合成



279

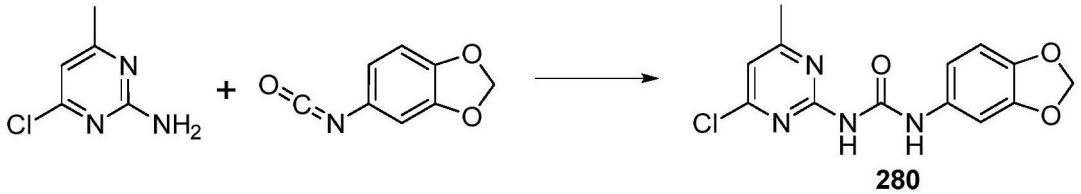
[0559] 向冷却至0℃的、1-(4-((3-氨乙基)氨基)-6-甲基嘧啶-2-基)-3-(4-(三氟甲氧基)苯基)脲(87)(53mg，0.14mmol)和三乙胺(0.04mL，0.28mmol)在DCM(0.48mL)中的混合物添加甲基磺酰氯(0.01mL，0.16mmol)，并将其在室温下搅拌5小时。此时用MeOH(5mL)稀释混合物，并过滤所得固体。通过利用在DCM中的0-10％MeOH梯度的硅胶色谱法纯化该物质。蒸发适当的级分，提供标题产物(279)(5mg，7％)。LC/MS：方法4：Rt＝2.14min，m/z＝449.1[MH+]。

实施例249：1-(苯并[d][1,3]二氧戊环-5-基)-3-(4-((3-(二甲氨基)丙基)氨基)-6-甲基嘧啶-2-基)脲(281)的合成



281

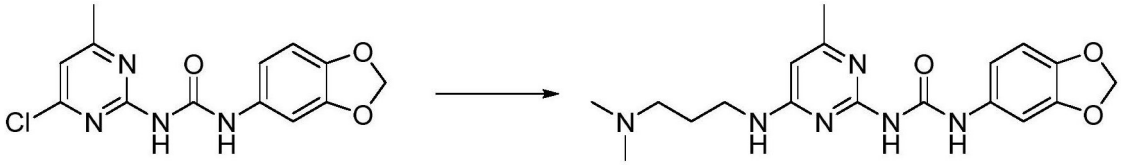
[0560] 步骤1：1-(苯并[d][1,3]二氧戊环-5-基)-3-(4-氯-6-甲基嘧啶-2-基)脲(280)



280

[0561] 将2-氨基-4-氯-6-甲基嘧啶(0.51g，3.5mmol)和2H-苯并[d]1,3-二氧戊环-5-异氰酸酯(0.64g，3.9mmol)在甲苯(4.7mL)中的混合物在100℃下搅拌加热2小时，然后在50℃下过夜。冷却后，用甲醇(10mL)稀释混合物，过滤所形成的浆液，与甲醇一起研磨并干燥，产生化合物(280)(0.48g，44％)。该物质直接用于下一步。

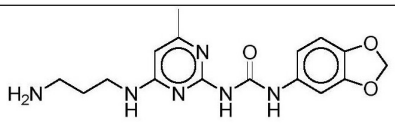
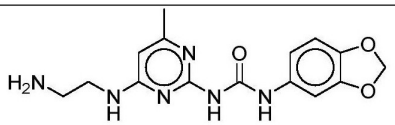
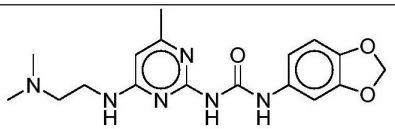
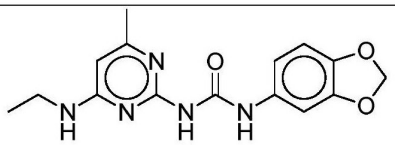
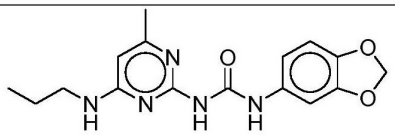
[0562] 步骤2：1-(苯并[d][1,3]二氧戊环-5-基)-3-(4-((3-(二甲氨基)丙基)氨基)-6-甲基嘧啶-2-基)脲(281)



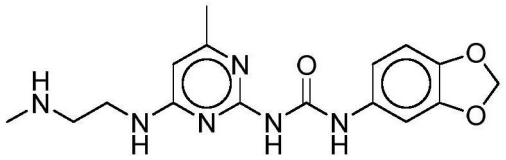
280 281

[0563] 将1-(苯并[d][1,3]二氧戊环-5-基)-3-(4-氯-6-甲基嘧啶-2-基)脲(280)(0.1g,0.33mmol)和3-(二甲氨基)-1-丙胺(0.05mL,0.40mmol)以及三乙胺(0.07mL,0.5mmol)在2-丙醇(0.66mL)中的混合物在80℃下加热过夜。将反应混合物冷却并过滤,通过制备型TLC(用MeOH中的30％1M NH_4OH/70％DCM洗脱)纯化该固体,产生标题化合物(281)(27mg,31％)。LC/MS:方法4:Rt＝0.98min,m/z＝373.2[MH^+]。

[0564] 根据针对实施例249所述的类似过程制备下列实施例:

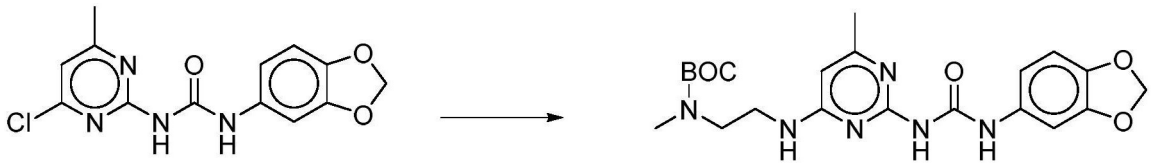
化合物ID	实施例ID	结构	HPLC方法	产率(质量/%)	RT(min)	MH^+
282	250		4	12 mg, 18	0.99	345.2
283	251		4	23 mg, 31	0.93	331.2
284	252		4	33 mg, 40	1.10	359.2
285	253		4	59 mg, 76	1.68	316.2
286	254		4	65 mg, 81	1.85	330.2

实施例255:1-(苯并[d][1,3]二氧戊环-5-基)-3-(4-甲基-6-((2-(甲氨基)乙基)氨基)嘧啶-2-基)脲(288)的合成



288

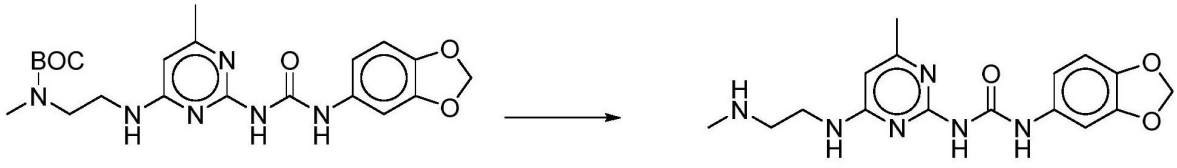
[0565] 步骤1:(2-((2-(3-(苯并[d][1,3]二氧戊环-5-基)脲基)-6-甲基嘧啶-4-基)氨基)乙基)(甲基)氨基甲酸叔丁酯(287)



280 287

[0566] 用N-(2-氨乙基)-N-甲基氨基甲酸叔丁酯(0.06mL,0.32mmol)和三乙胺(0.06mL,0.40mmol)处理1-(苯并[d][1,3]二氧戊环-5-基)-3-(4-氯-6-甲基嘧啶-2-基)脲(280)(82mg,0.27mmol)和2-丙醇(0.5mL)的混合物,并将其在搅拌下加热至80℃过夜。在冷却后用MeOH(3mL)稀释该反应,将所形成的沉淀物过滤,得到标题化合物(287)(85mg,72%)。LC/MS:方法4:Rt=2.14min,m/z=445.3[MH^+]。

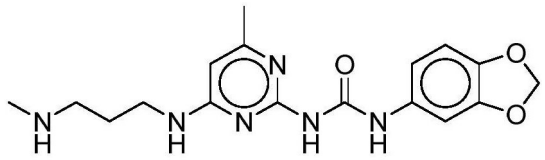
[0567] 步骤2:1-(苯并[d][1,3]二氧戊环-5-基)-3-(4-甲基-6-((2-(甲氨基)乙基)氨基)嘧啶-2-基)脲



287 288

[0568] 将BOC衍生物(287)(85mg,0.19mmol)悬浮在DCM(0.15mL)中,向其中添加三氟乙酸(0.14mL,1.9mmol)。在室温下40分钟后,蒸发溶剂,并用饱和碳酸氢钠溶液处理残余物以达到pH 8。过滤标题产物,并用水洗涤,干燥后产生白色固体(288)(30mg,46%)。LC/MS:方法4:Rt=0.94min,m/z=345.2[MH^+]。

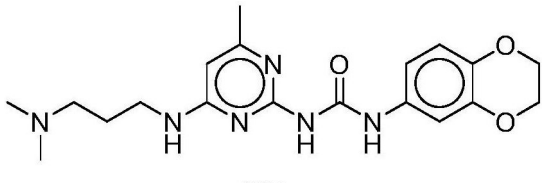
实施例256:1-(苯并[d][1,3]二氧戊环-5-基)-3-(4-甲基-6-((3-(甲氨基)丙基)氨基)嘧啶-2-基)脲(289)的合成



289

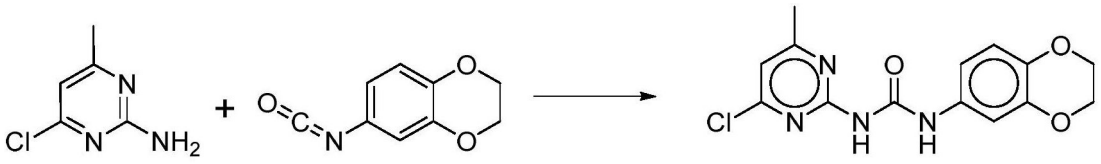
[0569] 以与实施例261类似的方式,由1-(苯并[d][1,3]二氧戊环-5-基)-3-(4-氯-6-甲基嘧啶-2-基)脲(287)和N-(3-氨丙基)-N-甲基氨基甲酸叔丁酯制备实施例262(17mg,19%)。LC/MS:方法4:Rt=1.01min,m/z=359.2[MH+]。

实施例257:1-(2,3-二氢苯并[b][1,4]二噁英-6-基)-3-(4-((3-(二甲氨基)丙基)氨基)-6-甲基嘧啶-2-基)脲(291)的合成



291

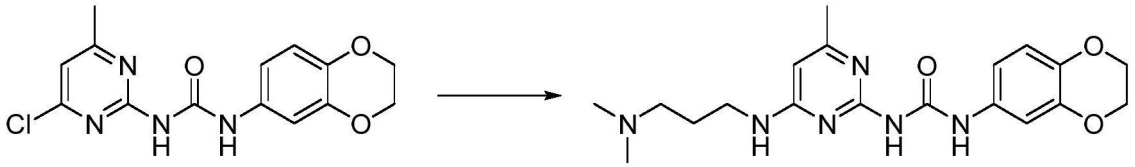
[0570] 步骤1:1-(4-氯-6-甲基嘧啶-2-基)-3-(2,3-二氢苯并[b][1,4]二噁英-6-基)脲(290)



290

[0571] 将2-氨基-4-氯-6-甲基嘧啶(2.1g,15mmol)和2H,3H-苯并[e]1,4-二噁烷-6-异氰酸酯(3g,16mmol)在甲苯(19.9mL)中的混合物在100℃下搅拌加热1小时,然后在50℃下过夜。冷却后,用甲醇(20mL)稀释该混合物,过滤所形成的浆液,与甲醇一起研磨并干燥,产生化合物(290)(2.8g,59%)。该物质直接用于下一步。

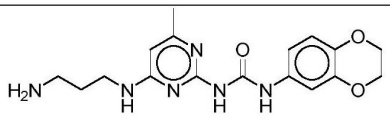
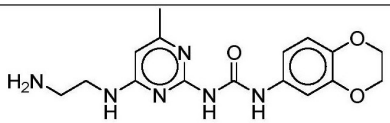
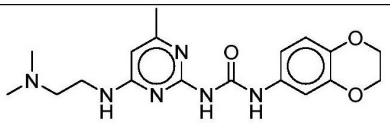
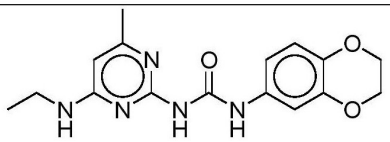
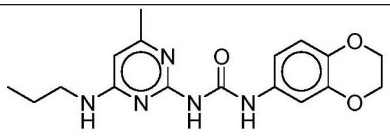
[0572] 步骤2:1-(2,3-二氢苯并[b][1,4]二噁英-6-基)-3-(4-((3-(二甲氨基)丙基)氨基)-6-甲基嘧啶-2-基)脲(291)



290 291

[0573] 将1-(4-氯-6-甲基嘧啶-2-基)-3-(2,3-二氢苯并[b][1,4]二噁英-6-基)脲(290)(75mg,0.23mmol)和3-(二甲氨基)-1-丙胺(0.04mL,0.28mmol)以及三乙胺(0.05mL,0.35mmol)在2-丙醇(0.47mL)中的混合物在80℃下加热5小时。将反应混合物冷却并过滤,通过制备型TLC(用MeOH中的30%1M NH_4OH/70%DCM洗脱)纯化该固体,产生标题化合物(291)(17mg,19%)。LC/MS:方法4:Rt=1.04min,m/z=387.3[MH^+]。

[0574] 根据针对实施例257所述的类似过程制备下列实施例:

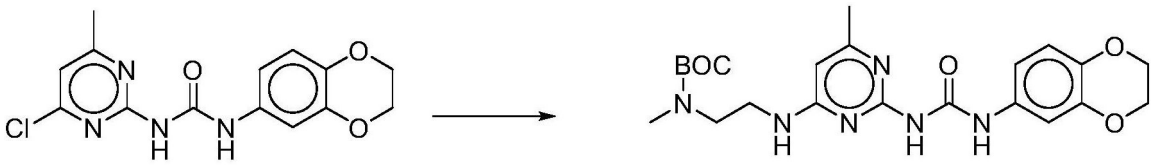
化合物ID	实施例ID	结构	HPLC方法	产率(质量/%)	RT(min)	MH^+
292	258		4	185 mg, 83	0.91	359.2
293	259		4	188 mg, 87	1.02	345.2
294	260		4	47 mg, 54	1.14	373.2
295	261		4	58 mg, 75	1.60	330.2
296	262		4	68 mg, 85	1.78	344.2

实施例263:1-(2,3-二氢苯并[b][1,4]二噁英-6-基)-3-(4-甲基-6-((2-(甲氨基)乙基)氨基)嘧啶-2-基)脲(298)的合成



298

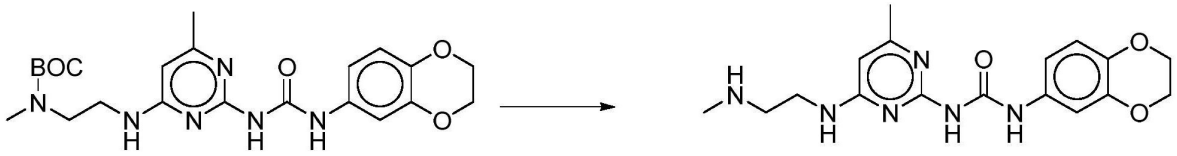
[0575] 步骤1:(2-((2-(3-(2,3-二氢苯并[b][1,4]二噁英-6-基)脲基)-6-甲基嘧啶-4-基)氨基)乙基)(甲基)氨基甲酸叔丁酯(297)



290 297

[0576] 用N-(2-氨乙基)-N-甲基氨基甲酸叔丁酯(0.05mL,0.28mmol)和三乙胺(0.05mL,0.35mmol)处理1-(4-氯-6-甲基嘧啶-2-基)-3-(2,3-二氢苯并[b][1,4]二噁英-6-基)脲(290)(75mg,0.23mmol)和2-丙醇(0.48mL)的混合物,并将其在搅拌下加热至80℃过夜。在冷却后用MeOH(3mL)稀释该反应,将所形成的沉淀物过滤并进一步用MeOH洗涤,得到标题化合物(297)(76mg,70%)。LC/MS:方法4:Rt=2.10min,m/z=459.3[MH^+]。

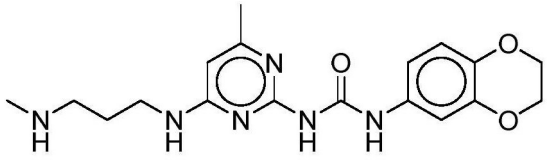
[0577] 步骤2:1-(苯并[d][1,3]二氧戊环-5-基)-3-(4-甲基-6-((2-(甲氨基)乙基)氨基)嘧啶-2-基)脲



297 298

[0578] 将BOC衍生物(297)(76mg,0.16mmol)悬浮在DCM(0.1mL)中,向其中添加三氟乙酸(0.12mL,1.6mmol)。在室温下3.5小时后,蒸发溶剂,并用饱和碳酸氢钠溶液处理残余物以达到pH 8。过滤标题产物,并用水洗涤,干燥后产生白色固体(298)(42mg,71%)。LC/MS:方法4:Rt=1.03min,m/z=359.2[MH^+]。

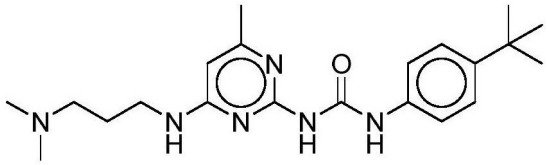
实施例264:1-(2,3-二氢苯并[b][1,4]二噁英-6-基)-3-(4-甲基-6-((3-(甲氨基)丙基)氨基)嘧啶-2-基)脲(299)的合成



299

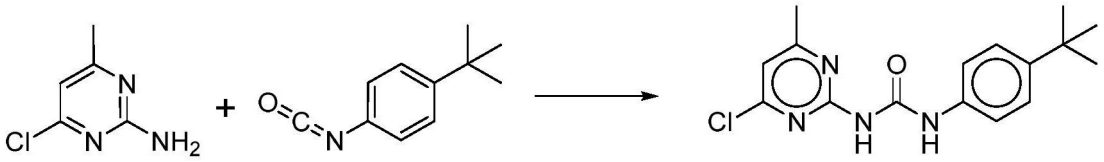
[0579] 以与实施例261类似的方式,由1-(4-氯-6-甲基嘧啶-2-基)-3-(2,3-二氢苯并[b][1,4]二噁英-6-基)脲(290)和N-(3-氨丙基)-N-甲基氨基甲酸叔丁酯制备实施例262(57mg,64%)。LC/MS:方法4:Rt=1.03min,m/z=373.2[MH+]。

实施例265:1-(4-(叔丁基)苯基)-3-(4-((3-(二甲氨基)丙基)氨基)-6-甲基嘧啶-2-基)脲(301)的合成



301

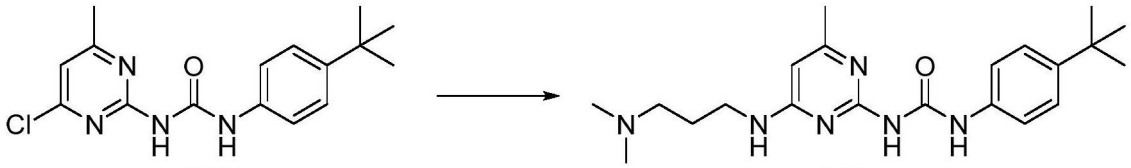
[0580] 步骤1:1-(4-(叔丁基)苯基)-3-(4-氯-6-甲基嘧啶-2-基)脲(300)



300

[0581] 将2-氨基-4-氯-6-甲基嘧啶(2.0g,14mmol)和4-叔丁基苯基异氰酸酯(2.9g,16mmol)在甲苯(12.7mL)中的混合物在室温下搅拌1小时,然后在110℃下加热过夜。冷却后,过滤所形成的浆液,用醚洗涤并干燥,产生化合物(300)(2.3g,53%)。该物质直接用于下一步。

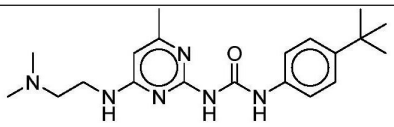
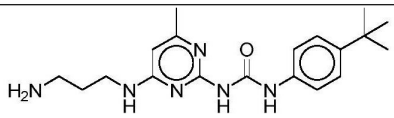
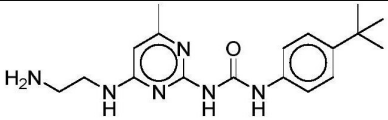
[0582] 步骤2:1-(4-(叔丁基)苯基)-3-(4-((3-(二甲氨基)丙基)氨基)-6-甲基嘧啶-2-基)脲(301)



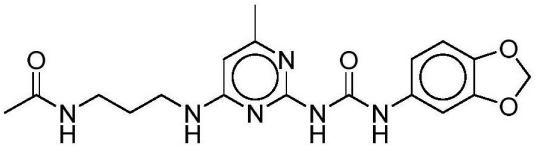
300 301

[0583] 将1-(4-(叔丁基)苯基)-3-(4-氯-6-甲基嘧啶-2-基)脲(300)(100mg,0.30mmol)和3-(二甲氨基)-1-丙胺(0.05mL,0.36mmol)以及三乙胺(0.06mL,0.45mmol)在2-丙醇(0.5mL)中的混合物在80℃下加热2小时。冷却该反应混合物并过滤,产生标题化合物(301)(80mg,66%)。LC/MS:方法4:Rt=1.72min,m/z=385.3[MH^+]。

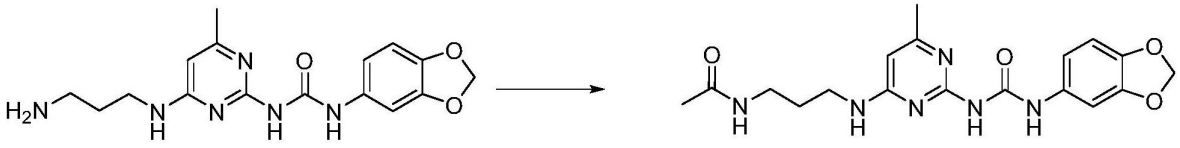
[0584] 根据针对实施例265所述的类似过程制备下列实施例:

化合物ID	实施例ID	结构	方法	产率(质量/%)	RT(min)	MH^+
302	266		4	95 mg, 78	1.65	371.3
303	267		4	80 mg, 34	1.64	357.3
304	268		4	183 mg, 85	1.67	343.2

实施例269:N-(3-((2-(3-(苯并[d][1,3]二氧戊环-5-基)脲基)-6-甲基嘧啶-4-基)氨基)丙基)乙酰胺(305)的合成



305



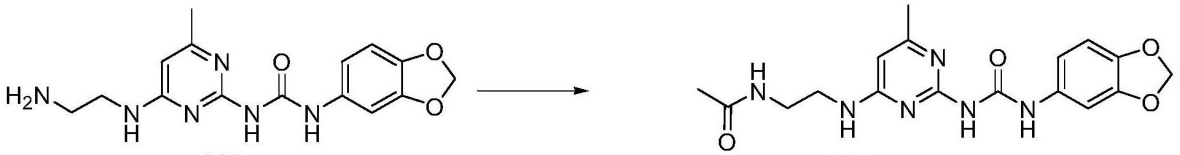
282 305

[0585] 将1-(4-((3-氨丙基)氨基)-6-甲基嘧啶-2-基)-3-(苯并[d][1,3]二氧戊环-5-基)脲(282)(75mg,0.22mmol)、乙酸酐(0.02mL,0.24mmol)、吡啶(0.11mL,1.3mmol)和催化量的N,N-二甲基氨基吡啶在DCM(0.44mL)中的混合物在室温下搅拌2小时。此时,添加另一份乙酸酐(0.01mL),并继续搅拌过夜。用DCM(3mL)稀释该混合物,过滤并干燥所产生的固体,得到标题产物(305)(39mg,47%)。LC/MS:方法4:Rt=1.45min,m/z=387.2[MH^+]。

实施例270:N-{2-[2-(3-苯并[1,3]二氧戊环-5-基-脲基)-6-甲基-嘧啶-4-基氨基]-乙基}-乙酰胺(306)的合成



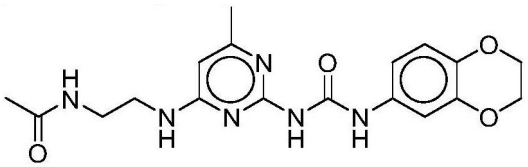
306



283 306

[0586] 将1-[4-(2-氨基-乙氨基)-6-甲基-嘧啶-2-基]-3-苯并[1,3]二氧戊环-5-基-脲(283)(75mg,0.23mmol)、乙酸酐(0.02mL,0.25mmol)、吡啶(0.11mL,1.4mmol)和催化量的N,N-二甲基氨基吡啶在DCM(0.44mL)中的混合物在室温下搅拌1小时。用DCM(3mL)稀释该混合物,过滤并干燥所产生的固体,得到标题产物(306)(63mg,74%)。LC/MS:方法4:Rt=1.34min,m/z=373.2[MH^+]。

实施例271:N-(2-{2-[3-(2,3-二氢-苯并[1,4]二噁英-6-基)-脲基]-6-甲基-嘧啶-4-基氨基}-乙基)-乙酰胺(307)的合成

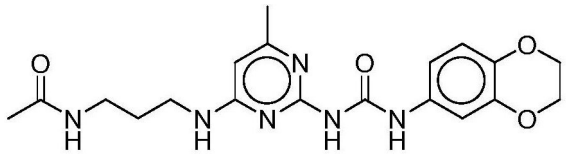


307

[0587] 通过与针对实施例270所述类似的过程,由1-[4-(2-氨基-乙氨基)-6-甲基-嘧啶-

2-基]-3-(2,3-二氢-苯并[1,4]二噁英-6-基)-脲(293)制备实施例271(36mg,43%)。LC/MS:方法4:Rt=1.43min,m/z=387.2[MH+]。

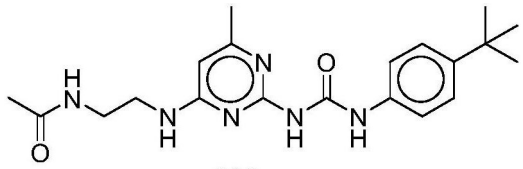
实施例272:N-(3-{2-[3-(2,3-二氢-苯并[1,4]二噁英-6-基)-脲基]-6-甲基-嘧啶-4-基氨基}-丙基)-乙酰胺(308)的合成



308

[0588] 通过与针对实施例270所述类似的过程,由1-[4-(3-氨基-丙氨基)-6-甲基-嘧啶-2-基]-3-(2,3-二氢-苯并[1,4]二噁英-6-基)-脲(292)制备实施例272(58mg,69%)。LC/MS:方法4:Rt=1.49min,m/z=401.2[MH+]。

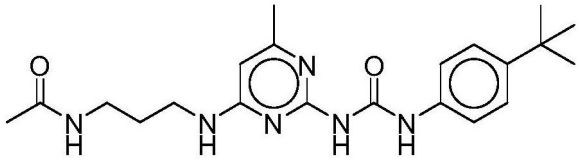
实施例273:N-(2-{2-[3-(4-叔丁基-苯基)-脲基]-6-甲基-嘧啶-4-基氨基}-乙基)-乙酰胺(309)的合成



309

[0589] 通过与针对实施例270所述类似的过程,除了用Et_2O(5mL)稀释混合物然后过滤固体产物之外,由1-[4-(2-氨基-乙氨基)-6-甲基-嘧啶-2-基]-3-(4-叔丁基-苯基)-脲(293)制备实施例273(40mg,21%)。LC/MS:方法4:Rt=2.15min,m/z=385.3[MH+]。

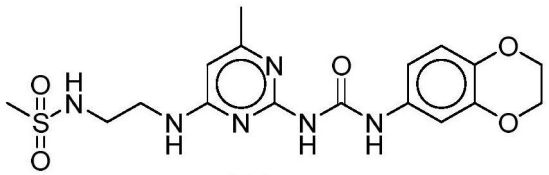
实施例274:N-(3-{2-[3-(4-叔丁基-苯基)-脲基]-6-甲基-嘧啶-4-基氨基}-丙基)-乙酰胺(310)的合成



310

[0590] 通过与针对实施例270所述类似的过程,除了用Et_2O(5mL)稀释混合物然后过滤固体产物之外,由1-[4-(3-氨基-丙氨基)-6-甲基-嘧啶-2-基]-3-(4-叔丁基-苯基)-脲(303)制备实施例274(40mg,21%)。LC/MS:方法4:Rt=2.22min,m/z=399.3[MH+]。

实施例275:N-2-(3-(2,3-二氢-苯并[1,4]二噁英-6-基)-脲基)-6-甲基-嘧啶-4-基)-乙基)甲基磺酰胺(311)的合成



311

[0591] 向冷却至0℃的、1-(4-((3-氨乙基)氨基)-6-甲基嘧啶-2-基)-3-(3-(三氟甲氧基)苯基)脲(87)(53mg,0.14mmol)和三乙胺(0.04mL,0.28mmol)在DCM(0.48mL)中的混合物

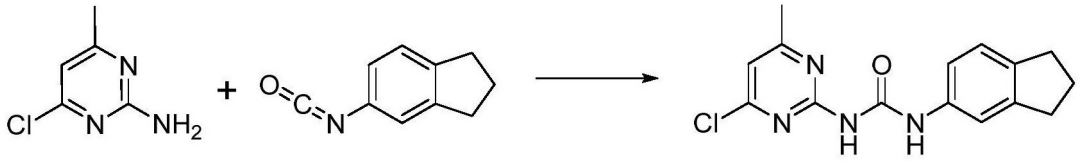
中添加甲基磺酰氯(0.01mL,0.16mmol),并将其在室温下搅拌5小时。此时用MeOH(5mL)稀释该混合物,并过滤所得固体。通过利用在DCM中的0-10％MeOH梯度的硅胶色谱法纯化该物质。蒸发适当的级分,提供标题产物(311)(5mg,7％)。LC/MS:方法4:Rt＝2.14min,m/z＝449.1[MH+]。

实施例276:1-(2,3-二氢-1H-茚-5-基)-3-(4-((3-(二甲氨基)丙基)氨基)-6-甲基嘧啶-2-基)脲(313)的合成



313

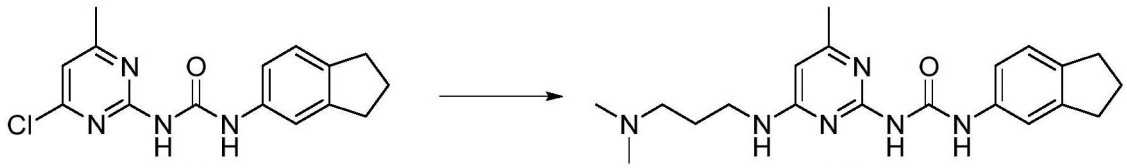
[0592] 步骤1:1-(4-氯-6-甲基嘧啶-2-基)-3-(2,3-二氢-1H-茚-5-基)脲(312)



312

[0593] 将2-氨基-4-氯-6-甲基嘧啶(1.5g,10mmol)和5-茚满基异氰酸酯(2.0g,12mmol)在甲苯(9.5mL)中的混合物在室温下搅拌1小时,然后在110℃下加热过夜。在冷却后将混合物搅拌过夜。过滤所形成的浆液,用醚洗涤并干燥,产生化合物(312)(2.5g,82％)。LC/MS:方法4:Rt＝3.79min,m/z＝303.1[MH^+]。该物质直接用于下一步。

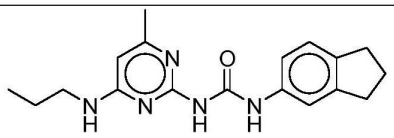
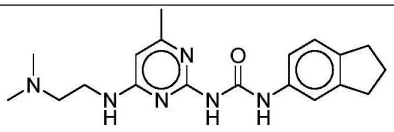
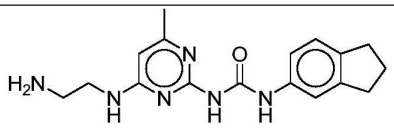
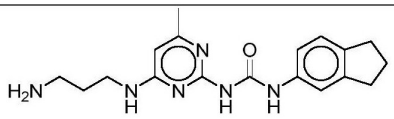
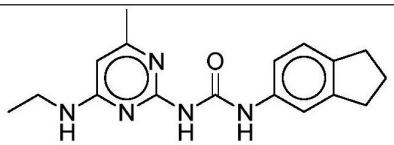
[0594] 步骤2:1-(2,3-二氢-1H-茚-5-基)-3-(4-((3-(二甲氨基)丙基)氨基)-6-甲基嘧啶-2-基)脲(313)



312 313

[0595] 将1-(4-氯-6-甲基嘧啶-2-基)-3-(2,3-二氢-1H-茚-5-基)脲(312)(0.1g,0.33mmol)和3-(二甲氨基)-1-丙胺(0.05mL,0.40mmol)以及三乙胺(0.07mL,0.5mmol)在2-丙醇(0.66mL)中的混合物在80℃下加热2小时。冷却该反应混合物并过滤,产生标题化合物(313)(90mg,70％)。LC/MS:方法4:Rt＝1.41min,m/z＝369.3[MH^+]。

[0596] 根据针对实施例276所述的类似过程制备下列实施例:

化合物 ID	实施例 ID	结构	HPLC 方法	产率 (质量/%)	RT (min)	MH^+
314	277		4	80 mg, 74	2.31	326.2
315	278		4	95 mg, 77	1.44	355.3
316	279		4	75 mg, 70	1.37	327.2
317	280		4	80 mg, 68	1.42	341.2
318	281		4	8 mg, 8	2.21	312.2

实施例282:N-(2-{2-[3-(2,3-二氢-1H-茚-5-基)-脲基]-6-甲基-嘧啶-4-基氨基}-乙基)-乙酰胺(319)的合成



319

[0597] 将1-[4-(2-氨基-乙氨基)-6-甲基-嘧啶-2-基]-3-(2,3-二氢-1H-茚-5-基)-脲(316)(62mg,0.19mmol)、乙酸酐(0.02mL,0.21mmol)、吡啶(0.10mL,1.2mmol)和催化量的N,N-二甲基氨基吡啶在DCM(0.38mL)中的混合物在室温下搅拌3小时。在冰箱中冷却该混合物,然后用二乙醚(5mL)稀释。过滤并干燥所得固体,得到标题产物(319)(40mg,57%)。LC/MS:方法4:Rt=1.87min,m/z=369.2[MH+]。

实施例283:GBM4和GBM8活力试验

[0598] 从NSA增殖试剂盒(Neurocult)和NeuroCult补充剂(Stemcell Tech目录号05751)制备细胞培养基,并用20μL的10μg/mL rh EGF、10μL的10μg/mL rh bFGF和10μL的0.2%肝素处理。在该培养基中,在超低附着组织培养瓶中培养人胶质母细胞瘤,直到达到1x10^6个细胞/ml(GBM4和GBM8是来源于这些人类患者组织的不同神经球细胞培养物)。分离GBM4和GBM8细胞,并将含有4000个人胶质母细胞瘤细胞/90uL的10mL培养基转移到超低结合96孔板,并在37℃下温育过夜。第二天,将10μL在试验介质中测试化合物的1%DMSO溶液添加到含有细胞悬浮液的孔中,并将混合物在37℃下温育3天。此时,从培养箱中取出板并使其达到室温。约30分钟后,向每个孔添加50μL的Cell Titer Glo溶液,并将板以低速振动1分钟。

10分钟后,使用Tecan Safire2读板记录发光。

[0599] 使用与仅含DMSO的对照孔相比的发光减少来确定细胞生长抑制百分比。使用Prism(San Diego)曲线拟合程序内的4参数拟合来拟合化合物的连续稀释液,使用发光的%抑制来计算IC_{50}。以下表1显示了本文所述化合物的GBM4IC50和GBM8IC50。

表1

化合物编号	GBM4 IC50 (uM)	GBM8 IC50 (uM)	化合物编号	GBM4 IC50 (uM)	GBM8 IC50 (uM)
2	NT	NT	173	NT	A
3	NT	NT	174	NT	B
4	C	B	175	NT	A
5	C	NT	176	NT	A
6	B	B	177	NT	A
7	A	A	178	NT	A
8	A	A	180	NT	A
9	NT	A	181	NT	A
10	NT	A	182	NT	A
11	NT	A	183	NT	B
12	NT	A	184	NT	A
13	NT	A	185	NT	A
14	NT	A	186	NT	A
15	NT	A	187	NT	A
16	NT	A	188	NT	A
17	NT	A	189	NT	B
18	NT	A	190	NT	A

化合物编号	GBM4 IC50 (uM)	GBM8 IC50 (uM)	化合物编号	GBM4 IC50 (uM)	GBM8 IC50 (uM)
19	NT	B	191	NT	A
20	NT	A	192	NT	A
21	NT	B	194	NT	A
22	NT	A	196	NT	A
24	A	A	197	NT	A
26	NT	A	198	NT	A
27	NT	A	199	NT	A
28	NT	A	200	NT	A
29	NT	A	201	NT	A
30	C	C	202	NT	A
34	C	B	203	NT	A
35	NT	A	204	NT	B
36	NT	A	205	NT	B
37	B	NT	206	NT	B
38	C	B	207	NT	A
39	B	B	209	NT	A
41	NT	A	210	NT	A
43	NT	A	211	NT	A
44	NT	A	212	NT	A
45	NT	A	213	NT	A
47	NT	A	214	NT	B
48	NT	B	215	NT	A

化合物编号	GBM4 IC50 (uM)	GBM8 IC50 (uM)	化合物编号	GBM4 IC50 (uM)	GBM8 IC50 (uM)
49	NT	A	216	NT	A
50	NT	A	217	NT	A
51	NT	A	218	NT	A
52	NT	A	219	NT	A
53	NT	A	220	NT	B
54	NT	A	221	NT	B
55	NT	A	222	NT	A
56	NT	B	223	NT	A
57	NT	B	224	NT	A
58	NT	B	225	NT	A
59	NT	A	226	NT	A
60	NT	A	227	NT	A
61	NT	A	229	NT	B
63	NT	B	230	NT	A
64	NT	A	231	NT	B
65	NT	A	232	NT	A
66	NT	A	234	NT	A
67	NT	A	235	NT	A
69	NT	B	236	NT	A
70	NT	B	237	NT	A
71	NT	B	238	NT	B
72	NT	B	239	NT	A

化合物编号	GBM4 IC50 (uM)	GBM8 IC50 (uM)	化合物编号	GBM4 IC50 (uM)	GBM8 IC50 (uM)
73	NT	B	240	NT	A
74	NT	B	241	NT	A
75	NT	B	242	NT	B
76	NT	B	243	NT	A
77	NT	B	244	NT	B
78	NT	A	245	NT	B
79	NT	B	246	NT	A
80	NT	B	248	NT	B
82	NT	B	249	NT	B
83	NT	B	251	NT	A
85	NT	A	252	NT	A
86	NT	A	253	NT	A
87	NT	A	254	NT	A
88	NT	A	255	NT	A
89	NT	A	256	NT	A
90	NT	A	257	NT	A
91	NT	A	258	NT	B
92	NT	A	259	NT	A
93	NT	A	260	NT	B
94	NT	A	261	NT	A
95	NT	A	262	NT	A
96	NT	A	263	NT	A

化合物编号	GBM4 IC50 (uM)	GBM8 IC50 (uM)	化合物编号	GBM4 IC50 (uM)	GBM8 IC50 (uM)
98	NT	A	264	NT	A
99	NT	A	265	NT	A
101	NT	A	266	NT	A
102	NT	A	268	NT	B
103	NT	A	269	NT	A
104	NT	A	270	NT	A
105	NT	A	271	NT	A
106	NT	A	272	NT	B
107	NT	A	273	NT	A
108	NT	A	274	NT	A
109	NT	A	275	NT	A
110	NT	A	276	NT	A
111	NT	A	277	NT	B
112	NT	A	278	NT	A
113	NT	B	279	NT	A
114	NT	A	281	NT	B
115	NT	A	282	NT	A
116	NT	A	283	NT	A
117	NT	A	284	NT	B
118	NT	A	285	NT	A
120	NT	A	286	NT	A
121	NT	A	288	NT	A

化合物编号	GBM4 IC50 (uM)	GBM8 IC50 (uM)	化合物编号	GBM4 IC50 (uM)	GBM8 IC50 (uM)
122	NT	A	289	NT	B
123	NT	A	291	NT	A
125	NT	A	292	NT	A
126	NT	A	293	NT	B
127	NT	A	294	NT	A
128	NT	A	295	NT	A
129	NT	A	296	NT	A
130	NT	A	298	NT	A
131	NT	A	299	NT	B
132	NT	A	301	NT	A
133	NT	A	302	NT	B
134	NT	B	303	NT	A
135	NT	A	304	NT	A
136	NT	A	305	NT	A
137	NT	A	306	NT	B
138	NT	A	307	NT	A
139	NT	A	308	NT	A
141	NT	B	309	NT	A
142	NT	B	310	NT	A
143	NT	B	311	NT	A
144	NT	B			
145	NT	B			

化合物编号	GBM4 IC50 (uM)	GBM8 IC50 (uM)	化合物编号	GBM4 IC50 (uM)	GBM8 IC50 (uM)
146	NT	B			
147	NT	B			
148	NT	B			
149	NT	B			
150	NT	B			
151	NT	B			
153	NT	B			
154	NT	B			
155	NT	B			
157	NT	A			
158	NT	A			
159	NT	B			
160	NT	A			
161	NT	A			
162	NT	A			
163	NT	A			
164	NT	A			
165	NT	A			
166	NT	A			
167	NT	B			
169	NT	A			
170	NT	A			

化合物编号	GBM4 IC50 (uM)	GBM8 IC50 (uM)	化合物编号	GBM4 IC50 (uM)	GBM8 IC50 (uM)
172	NT	A			
173	NT	A			

IC50:A<1M;1M≤B≤10M;10M<C≤30M;NT=未测试

实施例284:式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物在复发性Rb阳性胶质母细胞瘤患者中的II期临床试验

[0600] 该II期试验的目的是确定式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物在Rb阳性的复发性多形性胶质母细胞瘤或神经胶质肉瘤患者中的功效(以6个月时的无进展生存率测量)。总共治疗30名患者;15名接受计划中的手术切除并在术前接受7天的药物,随后在从手术中恢复后接受药物,而其余15名接受药物,不进行计划中的手术过程。

[0601] 患者:具有资格的受试者是18岁及以上的男性和女性。

[0602] 标准:

入选标准:

●具有经放射照相证实的复发性颅内多形性胶质母细胞瘤或神经胶质肉瘤的患者符合本方案的资格。患者必须有Rb阳性疾病的证明材料。

●所有患者必须签署知情同意书,表明他们了解本研究的研究性质。患者必须对发布他们受保护的健康信息签字授权。患者必须在用研究药物治疗前进行登记。治疗必须在登记后7天内进行;如果治疗延迟超过7天,则必须重复针对资格、病史和体检的实验室检查。

●患者必须先前进行过外线束放射治疗和替莫唑胺化疗;对使用的既往化疗的次数没有限制;患者可在其第一次、第二次或第三次复发时接受治疗

●患者必须>18岁,且预期寿命>8周。

●患者必须具有>60的Karnofsky体能状态。

●登记时:患者必须已经从先前治疗的毒性作用中恢复:距离任何研究药物>28天[注意:FDA批准的药剂的标签外使用不认为对本方案而言是研究性的],距离先前的细胞毒性疗法>28天,距离亚硝基脲>42天,距离贝伐珠单抗>28天,并且距离非细胞毒性剂例如干扰素、他莫昔芬、沙利度胺、顺式视黄酸和厄洛替尼>7天。与非细胞毒性剂的定义有关的任何问题都应发送给研究组。

●患者在开始治疗前必须具有足够的骨髓功能(WBC>3,000/μl,ANC>1,500/mm^3,血小板计数>100,000/mm^3,并且血红蛋白>10gm/dl)、足够的肝功能(SGOT和胆红素<2倍ULN)以及足够的肾功能(肌酸酐<1.5mg/dL)。所有患者在研究前均需进行EKG,且患者必须具有正常的QT间期。这些检查必须在登记前14天内进行。可通过输血达到血红蛋白的合格水平。

●患者必须通过MRI扫描显示肿瘤进展的明确放射照相证据。扫描应在登记前14天内进行,并且类固醇剂量应该已经稳定至少7天。如果类固醇剂量在成像和登记的日期之间增加,则需要新的基线MRI。在整个肿瘤测量的方案治疗期间必须使用相同类型的扫描,即

MRI。无法进行MR成像的患者将不具备资格。

●只有下列所有条件都满足，最近接受了复发性或进行性肿瘤切除的患者才具备资格：

○他们已经从手术的影响中恢复。

○复发性颅内多形性胶质母细胞瘤或神经胶质肉瘤切除后的残留疾病对于本研究的资格来说不做强制要求。为了最佳评估术后残留疾病的程度，MRI应在登记前14天内，在即刻术后期不晚于96小时或术后至少4周内进行。如果96小时的扫描超过登记前14天，则需重新扫描。如果类固醇剂量在成像和登记日期之间增加，则需要在类固醇剂量稳定至少7天的情况下进行新基线MRI。

●患者必须具有失败的既往放疗和替莫唑胺，并且从完成放疗到进入本研究必须具有大于或等于42天的间隔。

●采用包括间质近距离放疗、立体定向放射外科术或Gliadel晶片等既往治疗的患者必须确认有真正的进行性疾病，而不是基于PET扫描、MR光谱分析或疾病手术记录的放射性坏死。

●在计划的指定手术切除前，将会招募15名患者的子集。只有患者是手术候选者、不具有急性颅内出血的证据并且能够在术前7天的窗口内开始方案治疗时，才能在术前入选。

●在研究治疗期间和停止后3个月内，具有生殖能力的男性和女性患者必须在适当情况下使用已批准的避孕方法(例如宫内节育器[IUD]、避孕药或阻隔装置)。具有生育能力的女性在登记前14天内必须记录为β-HCG妊娠试验阴性。

●来自先前手术的肿瘤组织块或切片必须可供进行IHC Rb染色。肿瘤阴性(Rb阴性)的患者将从该研究中排除。

排除标准：

●患者不得患有研究人员认为不能通过适当的治疗而充分控制或将会损害患者耐受该治疗的能力的任何重大医学疾病。

●(除了非黑素瘤皮肤癌或子宫颈原位癌之外)具有任何其他癌症病史的患者均不合格，除非完全缓解并且停止该疾病的所有治疗至少3年。

●患者不得有活动性感染或严重的间发医学疾病。具有急性颅内出血史的患者也将被排除。

●患者不得处于妊娠/哺乳期，且必须同意进行适当的避孕。

●患者不得具有会掩盖毒性或危险地改变药物代谢的任何疾病。

●由于药物相互作用的可能性，正在使用诱导酶的抗癫痫药物或引起CYP3A酶诱导或抑制的其他药物的患者将不合格，除非停止治疗至少14天。

●EKG上的QT间隔延长的先天性或其他原因的患者将被排除。

[0603] 研究设计：用式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物以每天125mg的剂量治疗总共30名复发性胶质母细胞瘤或神经胶质肉瘤患者，连续21天，然后中断治疗7天(周期长度为28天)。在这30名患者中，15名在针对进展的指定预期手术切除前接受7天的药物，然后在从手术中恢复后以相同的剂量继续使用药物。治疗每28天重复一次，如无疾病进展，则患者可接受12个周期的治疗。此时，患者可选择在12个周期后继续进行研究，最多可达24个周期。

[0604] 登记后，必须提交可从先前手术获得的块或切片以供诊断检查(确定多形性胶质母细胞瘤或神经胶质肉瘤)和Rb状态确定。只有Rb阳性肿瘤患者才可进行治疗，并且在任何治疗前必须已知Rb肿瘤状态。还获得来自先前手术的附加组织以评估肿瘤中的分子异常。这些研究回顾性地进行，并且无需在登记之前执行。

[0605] 监测包括在每个周期(每4周)开始之前进行临床和神经学检查。在每个周期的第1天和第15天检查分类全血细胞计数。每4周进行肝和肾功能检查。毒性和剂量修改基于NCI CTCAE版本4。疾病状态在每个周期(每4周)进行临床评估，并在每个第二周期(每8周)后进行放射照相评估。

[0606] 主要结果测量指标：

●由无进展生存率确定的功效[时间范围:1-2年][指定为安全性问题:否]

●确定式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物在Rb阳性的复发性多形性胶质母细胞瘤或神经胶质肉瘤患者中的功效，通过6个月时的无进展生存率来衡量。总共治疗30名患者;15名进行计划的预期手术切除并在术前接受7天的药物治疗，随后在从手术中恢复后接受药物，而15名接受药物治疗，不进行计划的手术过程。

[0607] 次要结果测量指标：

●有不良事件的参与者数目，作为安全性和耐受性的量度[时间范围:1-2年][指定为安全性问题:是]

实施例285:式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物在患有复发性或难治性成髓母细胞瘤的成人中的安全性和功效的II期临床试验。

[0608] 该II期试验的目的在于确定式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物在治疗复发性或难治性髓母细胞瘤成人患者中的效果如何。

[0609] 患者:具有资格的受试者为22岁及以上的男性和女性。

[0610] 标准：

入选标准：

●经组织学确诊为对标准疗法而言为复发性、进行性或难治性并且没有已知治愈性疗法的髓母细胞瘤(包括后窝PNET)的患者符合资格;在研究前MRI中必须有残留的可测量疾病或病变的证据，如章节中所述;具有可测量的脊柱疾病的患者符合资格

●应在治疗机构确诊，且组织(无论来自诊断还是复发，还是优选来自两个时间点)必须可用于生物学研究

●患有神经功能缺陷的患者应具有在登记前稳定至少1周的缺陷;这将会记录在数据库中

●东部肿瘤协作组(ECOG)体能状态为0-2

●在进入研究前4周内无其他骨髓抑制性化疗或免疫治疗(如果先前使用亚硝基脲，则为6周)

●在开始治疗前，地塞米松剂量也应稳定或降低至少1周(7天)

●放疗(XRT)对于颅脊椎照射(>＝23Gy)而言在进入研究前>＝3个月;对于原发性肿瘤的局部照射而言>＝8周;对于症状性转移部位的焦点照射而言在进入研究前>＝2周

●进入研究前停用所有集落刺激因子>＝1周(GCSF、GM CSF、红细胞生成素)

●嗜中性粒细胞绝对计数(ANC)>＝1000/μL

●血小板计数>＝50,000/uL(独立于输血)

●血红蛋白>＝8.0gm/dL(可接受RBC输注)

●肌酸酐清除率或放射性同位素GFR>＝70ml/min/1.73m2或

●血清肌酸酐＝<2.0mg/dL

●总胆红素＝<1.5倍年龄的正常值上限(ULN)

●血清谷丙转氨酶(SGPT)(丙氨酸氨基转移酶[ALT])＝<2.5倍机构ULN

●血清谷草转氨酶(SGOT)(天冬氨酸氨基转移酶[AST])＝<2.5倍机构ULN

●血清白蛋白>＝2.5g/dL

●在进入本研究之前,患者必须已经从所有先前治疗的重要急性毒性中恢复,并符合所有其他合格性标准

●对于具有生育能力的女性,在最后一次给药后12个月内应避免妊娠;具有生育能力的女性不得处于妊娠或哺乳期;具有生育能力的女性患者在开始治疗前24小时内必须为血清或尿妊娠试验阴性

●具有生育能力的女性需要采用2种形式的可接受的避孕措施,包括在参与研究期间和最后一次剂量后的12个月内采用一种阻隔法;出于医学或个人原因,100%承诺禁欲被认为是可接受的避孕形式。所有患者均应接受研究人员或OB/妇科医生或具有本专业领域资格的其他医师的避孕咨询

●必须签署根据机构准则的知情同意书

排除标准:

●患有将会损害患者耐受方案治疗的能力或可能干扰研究过程或结果的任何临床上重大的无关全身性疾病(严重感染或重大的心脏、肺、肝或其他器官功能障碍)的患者

●接受任何其他抗癌或试验药物治疗的患者

●无法进行随访或获得评估治疗毒性所需的随访研究的患者

●由治疗医生确定的预期寿命<12周

●无法吞咽胶囊

●吸收不良综合征或会干扰肠内吸收的其他病症

●充血性心力衰竭史

●需要药物治疗的室性心律失常史

●未受控制的低钙血症、低镁血症、低钠血症或低钾血症,定义为尽管电解质补充充足,但是低于机构的正常值下限

●先天性长QT综合征

[0611] 研究设计:患者在第1-28天每天一次PO接受式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物。在不存在疾病进展或不可接受的毒性的情况下,每28天重复治疗,最多26个疗程。

[0612] 主要结果:

●使用RECIST标准进行评分的客观反应率(PR和CR)[时间范围:至多12个月][指定为安全性问题:否]

●对三个层级中的每一个建立真实、未知的客观反应率的百分之九十五置信区间估计值。对三个层级中的每一个均说明性地报告具有确定的完全反应、部分反应和疾病稳定的

患者的比例。还提供时间与客观反应的累积发生率函数。

[0613] 次要结果：

●持续的客观反应的持续时间[时间范围：从随后确认的证明完全或部分反应的初始扫描直到研究中记录的进展或死亡中的较早者，评估至多12个月][指定为安全性问题：否]

●无进展生存率[时间范围：从式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物初始治疗的日期直到研究中进展或死亡中的最早者，评估至多12个月][指定为安全性问题：否]

●移植后前6个月期间的医疗费用

●患者和移植物存活

实施例286：式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物在复发性恶性星形细胞瘤治疗中的安全性、耐受性和抗肿瘤功效的I/II期临床试验

[0614] 这是单中心、标签开放、非随机化的I/IIa期研究，用以研究式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物在复发性恶性星形细胞瘤(胶质母细胞瘤、神经胶质肉瘤、间变性星形细胞瘤、间变性少突神经胶质瘤、间变性寡星形细胞瘤和间变性室管膜瘤)患者中的安全性、耐受性和抗肿瘤功效。患者接受治疗最多5个周期。治疗周期被定义为28天+7天休息(周期1-4期间为28+7天，第5周期为28天)。随后的周期在满足治疗延续标准后才开始。伴随的支持治疗是允许的。

[0615] 患者：具有资格的受试者为18岁及以上的男性和女性。

[0616] 标准：

[0617] 入选标准：

●已被告知本研究的性质，并已提供书面知情同意书

●至少18岁

●ECOG体能为0、1或2，或KPS(Karnofsky体能状态)≥60。

●病理证实为WHO 4级星形细胞瘤(胶质母细胞瘤或神经胶质肉瘤)或WHO 3级间变性星形细胞瘤、间变性少突神经胶质瘤、间变性寡星形细胞瘤或间变性室管膜瘤。

●至少一次失败的化疗和放疗治疗后，记录为复发性胶质母细胞瘤、神经胶质肉瘤、间变性星形细胞瘤、间变性少突神经胶质瘤、间变性寡星形细胞瘤或间变性室管膜瘤

●至少3个月的预期生存期

●距离细胞减灭术(如果进行的话)至少2周，距离贝伐珠单抗或其他化疗4周(如果先前化疗是亚硝基脲则为6周)，并且距离放疗结束12周。

●能够如方案中所规定的那样定期进行无成像染料和有成像染料的MRI扫描

●在施用式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物的第一剂量之前，停用诱导CYP2C9和CYP3A4的药物至少七(7)天

●保留主要器官功能，即：血液白细胞计数≥3.0x10^9/L，血液嗜中性粒细胞绝对计数≥1.5x10^9/L，血液血小板计数≥100x10^9/L，血液血红蛋白≥100g/L(允许输血)，血浆总胆红素水平≤1.5倍“正常”(即参考)范围的机构上限(ULN)，血浆AST(天冬氨酸氨基转移酶)或ALT≤2.5倍“正常”范围的机构上限(ULN)，血浆肌酸酐≤1.5倍“正常”范围的机构上限(ULN)，12导联ECG具有正常描迹；或变化是临床上不显著的，且无需医疗干预，并且QTc<500ms，在研究治疗第一天之前停用抑制或诱导CYP2C9或CYP3A4的药物至少七(7)天。

排除标准：

●正处于感染或其他重要的最近或正在发生的疾病，其根据研究人员的观点对患者造成不可接受的风险

●在随机分组前，过去28天内有3级或以上的便秘，或在过去14天内有2级便秘。(如果在便秘的最佳控制下便秘降至≤1级，则过去14天内具有2级便秘的患者可被重新筛选。)

●共存的未受控制的医疗状况，包括但不限于活动性心脏病和明显的痴呆症

●乙型肝炎或丙型肝炎，或需要抗逆转录病毒治疗的HIV感染

●除基底细胞皮肤癌之外的活动性恶性肿瘤

●前3年期间有其他活动性恶性肿瘤

●4周内有大手术

●先前的立体定向或伽玛刀放射外科手术或质子辐射，除非根据功能性神经成像(PET、动态MRI、MRS、SPECT)或通过重新手术确认有明确进展，记录有复发的组织学确认。

●先前的抗肿瘤治疗，如下：距离放疗至少12周；距离替莫唑胺或贝伐珠单抗的先前治疗至少4周，距离BCNU或CCNU 6周。

●不同意使用可接受的避孕方法(口服避孕药、IUD)的具有生育能力的女性(WOCBP)。对于本研究的目的，WOCBP包括已经经历月经初潮、尚未经历输卵管结扎并且不处于绝经后的任何女性。绝经后定义为：在不存在其他原因的情况下闭经≥连续12个月。

●医学上未受控制的1型或2型糖尿病

●妊娠或哺乳期

●在4周内正在参与任何其他研究性临床试验。

●在药物优化后，东部肿瘤协作组(ECOG)体能状态>2(参见附录4)，或KPS<60

●预期寿命少于3个月

●对研究产品具有禁忌症或已知或疑似超敏反应

●必须服用具有窄治疗范围的诱导或有效抑制CYP2C9或为CYP3A4敏感底物的伴随药物的患者不得参与

●由研究人员判断，由于任何原因不适合参与该试验

[0618] 研究设计：

[0619] 该试验分为两期。在I期招募10-20名患者，并用300-520mg式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物BID治疗28天。I期的主要终点是确定式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物在复发性或进行性胶质母细胞瘤患者中的推荐2期剂量(RP2D)，并评估式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物在该患者群体中的安全性和毒性。该研究具有3+3设计，第一队列用400mg式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物BID治疗28天，重复最多5个周期。如果发生剂量限制性毒性(DLT)如嗜中性白细胞减少，则中断给药，个体患者将会在正常化后根据标准化程序以相同或较低的剂量水平重新开始。如果处于特定剂量水平的前三名患者有两名或三名在用式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物治疗的前28天期间经历DLT，则后续患者将会以较低剂量水平治疗。如果在前三名患者的前28天给药期间发生一例DLT，则另外3名患者将会以相同的剂量水平治疗。如果6名患者中有2名显示DLT，则接下来的患者将会以较低剂量水平治疗。6

名患者中无DLT或最多具有一例DLT的最高剂量水平将为RPTD。关于后续队列的剂量调整的所有评估在治疗的前28天期间完成。非进行性患者可治疗总共五个为期28天的周期(24周)。

[0620] 在II期中,招募12名患者并用式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物所鉴别的RP2D治疗28天,重复五个周期。II期的主要终点是评估在24周时无进展的患者的比例,并评估式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物的安全性、耐受性和不良事件概况。

[0621] 主要结果:

●I期-确定推荐的II期剂量。[时间范围:8个月][指定为安全性问题:是]

●II期-确定抗肿瘤作用[时间范围:4个月][指定为安全性问题:是]

●I期-有不良事件的参与者数目,作为安全性和耐受性的量度[时间范围:6个月][指定为安全性问题:是]

●身体/神经学检查(病理学发现及其质量和数量)

●不良事件(每剂量水平的质量和数量)

●生命体征、ECG、实验室参数(病理学发现的质量和数量、实验室参数、描述性统计数据)

[0622] 次要结果:

●肾I期-最大耐受剂量(MTD)[时间范围:8个月][指定为安全性问题:是]

以鉴别式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物的MTD。

●I期-最佳反应的分子标志物[时间范围:8个月][指定为安全性问题:是]

以评估可预测最佳反应亚群组的潜在分子标志物

●I期-IGF(胰岛素样生长因子)-1R途径的分子标志物[时间范围:8个月][指定为安全性问题:是]

以评价用式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物治疗后在恶性星形细胞瘤患者中的IGF-1R途径活化/抑制的替代分子标志物

●II期-进展时间(TTP)和总生存率(OS)[时间范围:4个月][指定为安全性问题:是]

以确定用式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物治疗的患者的进展时间(TTP)和总生存率(OS)

●II期-总反应率[时间范围:4个月][指定为安全性问题:是]

以评估使用式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物治疗后在复发性恶性星形细胞瘤中的总反应率(ORR)

●II期-反应的成像证据[时间范围:4个月][指定为安全性问题:是]

通过RANO标准来鉴别MRI(磁共振成像)序列上的反应的替代成像证据(另外特别注意T2-FLAIR、DWI(弥散加权成像)、灌注MRI和多像素MRS(磁共振波谱法)序列)。

实施例287:药物组合物

实施例287A:肠胃外组合物

[0623] 为制备适合通过注射施用的肠胃外药物组合物,将100mg式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物溶于DMSO中并随后与10mL的0.9%无菌盐水混合。将混合物并入适合通过注射给药的单位剂型中。

[0624] 在另一个实施方案中，将下列成分混合以形成可注射制剂。

成分	量
式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物	1.2 g
乙酸钠缓冲溶液(0.4M)	2.0mL
HCl (1N)或 NaOH (1M)	适量至合适的 pH
水(经蒸馏，无菌)	适量至 20mL

[0625] 合并除水外的所有上述成分，并且如果必要的话进行搅拌，如果必要的话，稍微加热。然后加入足量的水。

实施例287B：口服组合物

[0626] 为制备用于口服递送的药物组合物，将100mg式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物与750mg淀粉混合。将混合物并入适合口服给药的口服剂量单位如硬明胶胶囊中。

[0627] 在另一个实施方案中，将下列成分紧密地混合并压成单一刻痕片剂。

成分	每片中的量，mg
式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物	200
玉米淀粉	50
交联羧甲基纤维素钠	25
乳糖	120
硬脂酸镁	5

[0628] 在又一实施方案中，将下列成分紧密地混合并装入硬壳明胶胶囊中。

成分	每片中的量，mg
式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物	200
喷雾干燥的乳糖	148
硬脂酸镁	2

[0629] 在又一实施方案中，将下列成分混合以形成用于口服给药的溶液/悬浮液。

成分	量
式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物	1 g
无水碳酸钠	0.1 g
乙醇(200 标准(proof)), USP	10 mL
纯净水, USP	90 mL
阿斯巴甜	0.003g

实施例287C:舌下(硬锭剂)组合物

[0630] 为制备用于含服递送的药物组合物,如硬锭剂,将100mg式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物与420mg糖粉混合,该糖粉已与1.6mL低度玉米糖浆、2.4mL蒸馏水和0.42mL薄荷提取物混合。将混合物轻轻地混合并倒入模具中以形成适于含服给药的锭剂。

实施例287D:吸入组合物

[0631] 为制备用于吸入递送的药物组合物,将20mg式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物与50mg无水柠檬酸以及100mL的0.9%氯化钠溶液混合。将混合物并入适合吸入给药的吸入递送单元如喷雾器中。

实施例287E:直肠凝胶组合物

[0632] 为制备用于直肠递送的药物组合物,将100mg式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物与2.5g甲基纤维素(1500mPa)、100mg对羟基苯甲酸甲酯、5g甘油和100mL纯净水混合。然后将所得凝胶混合物并入适合直肠给药的直肠递送单元如注射器中。

实施例287F:栓剂制剂

[0633] 通过将式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物与Witepsol™ H-15(饱和植物脂肪酸的甘油三酯;Riches-Nelson,Inc.,New York)混合来制备总重量为2.5g的栓剂,且其具有下列组成:

成分	每个栓剂中的量, mg
式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物	500
Witepsol® H-15	余量

实施例287G:局部凝胶组合物

[0634] 为制备局部凝胶药物组合物,将100mg式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物与1.75g羟丙基纤维素、10mL丙二醇、10mL肉豆蔻酸异丙酯和100mL纯化的乙醇USP混合。然后将所得凝胶混合物并入适合局部给药的容器如管中。

实施例287H:眼用溶液组合物

[0635] 为制备眼用溶液药物组合物，将100mg式(I)、(II)、(IIA)、(IIB)、(IIC)、(IID)、(III)、(IV)、(V)或(VI)化合物与在100mL纯净水中的0.9g的NaCl混合，并用0.2微米过滤器过滤。然后将所得等渗溶液并入适合于眼部给药的眼用递送单元如滴眼剂容器中。

[0636] 本文描述的实例和实施方案仅用于说明目的，并且在一些实施方案中，各种修改或改变将包括在本发明的精神以及所附权利要求的范围内。