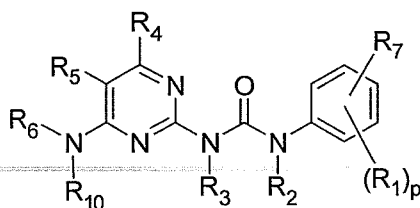


subject in need thereof a composition comprising a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein the cancer is brain cancer, glioblastoma multiforme, medulloblastoma, astrocytomas, brain stem gliomas, meningiomas, oligodendrogliomas, melanoma, lung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

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

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

[0017a] In another aspect is a compound of Formula (III):



Formula (III);

wherein:

each R_1 is independently halogen, -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, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆alkoxy, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₂-C₇heterocycloalkyl, substituted or unsubstituted C₃-C₈cycloalkyl, substituted or unsubstituted C₆-C₁₀aryl, or substituted or unsubstituted C₂-C₇heteroaryl;

R_2 and R_3 are each independently H, -CN, C₁-C₄alkyl, C₃-C₆cycloalkyl, or C₂-C₇heterocycloalkyl; or R_2 and R_3 are taken together to form a 5- or 6-membered heterocyclic ring;

R_4 and R_5 are independently H, halogen, -CN, -OH, -CF₃, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆alkoxy, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₂-C₇heterocycloalkyl, substituted or unsubstituted C₃-C₈cycloalkyl, substituted or unsubstituted C₆-C₁₀aryl, or substituted or unsubstituted C₂-C₉heteroaryl;

R₆ is H, unsubstituted C₁-C₆alkyl, -(C(R₁₄)(R₁₅))_mR₁₇, -(C(R₁₄)(R₁₅))_mN(R₁₁)(R₁₂), -(C(R₁₄)(R₁₅))_mOR₁₃, -(C(R₁₄)(R₁₅))_nR₁₆, or -OR₂₂;

R₇ is substituted or unsubstituted phenoxy or -C(=O)R₂₃;

each R₈ is independently H or substituted or unsubstituted C₁-C₆alkyl;

each R₉ is independently substituted or unsubstituted C₁-C₆alkyl;

R₁₀ is H or unsubstituted C₁-C₄alkyl;

R₁₁ is H, substituted or unsubstituted C₁-C₆alkyl, -C(=O)R₁₉, or -S(=O)₂R₁₉;

R₁₂ is H or substituted or unsubstituted C₁-C₆alkyl;

R₁₃ is H or substituted or unsubstituted C₁-C₆alkyl;

each R₁₄ and R₁₅ is each independently H, halogen, or substituted or unsubstituted C₁-C₆alkyl;

R₁₆ is substituted or unsubstituted C₂-C₇heterocycloalkyl or -C(=O)N(R₁₈)₂;

R₁₇ is -C(=O)R₂₀, -CO₂R₂₁, -C(=O)N(R₂₁)₂, or substituted or unsubstituted C₂-C₉heteroaryl;

each R₁₈ is independently H, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₂-C₇heterocycloalkyl, or substituted or unsubstituted C₃-C₈cycloalkyl; or two R₁₈ are taken together to form a heterocycloalkyl ring;

R₁₉ is substituted or unsubstituted C₁-C₆alkyl;

R₂₀ is substituted or unsubstituted C₁-C₆alkyl;

each R₂₁ is independently H, or substituted or unsubstituted C₁-C₆alkyl; or two R₂₁ are taken together to form a heterocycloalkyl ring;

R₂₂ is H, or substituted or unsubstituted C₁-C₆alkyl;

R₂₃ is substituted or unsubstituted C₆-C₁₀aryl;

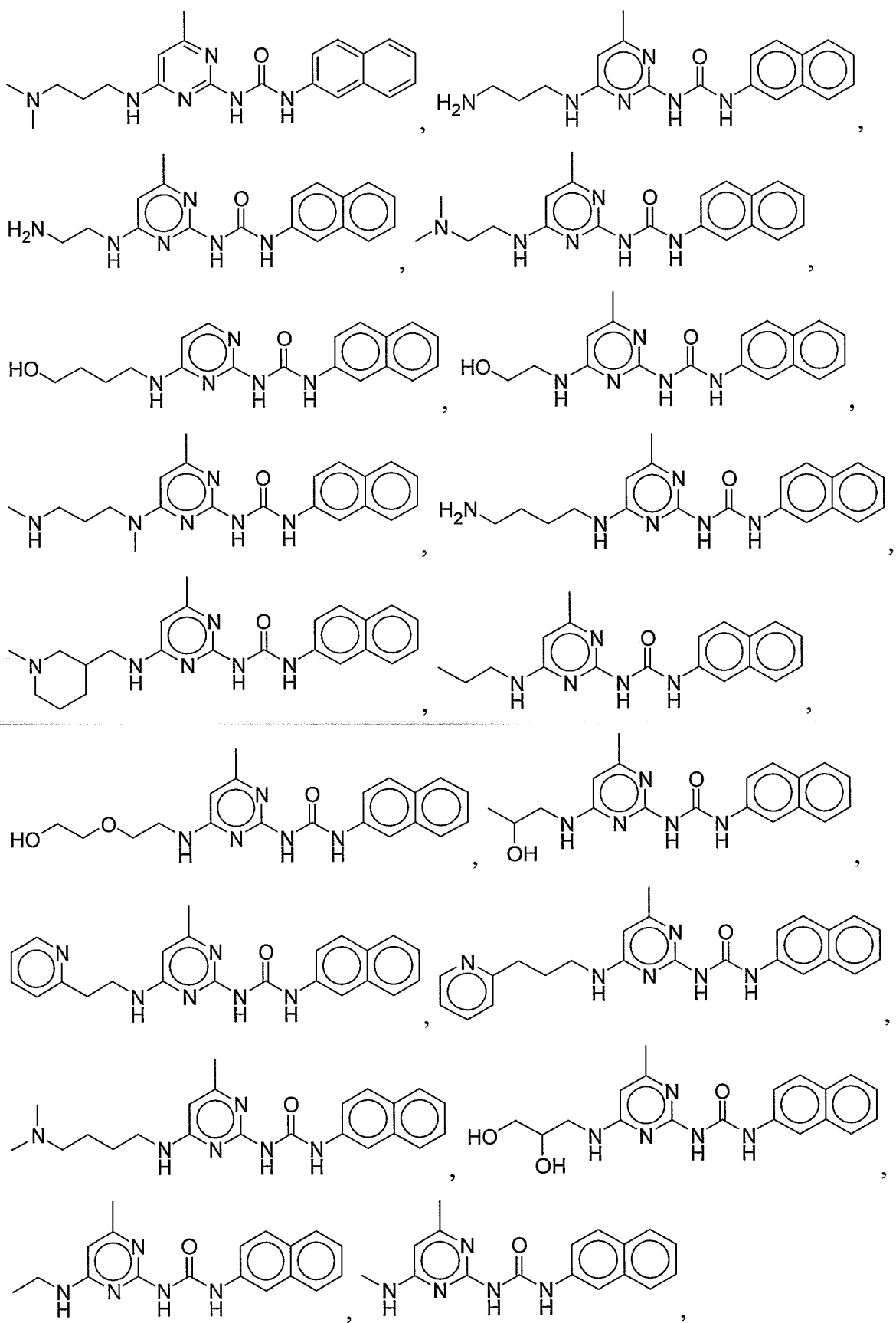
m is 2-6;

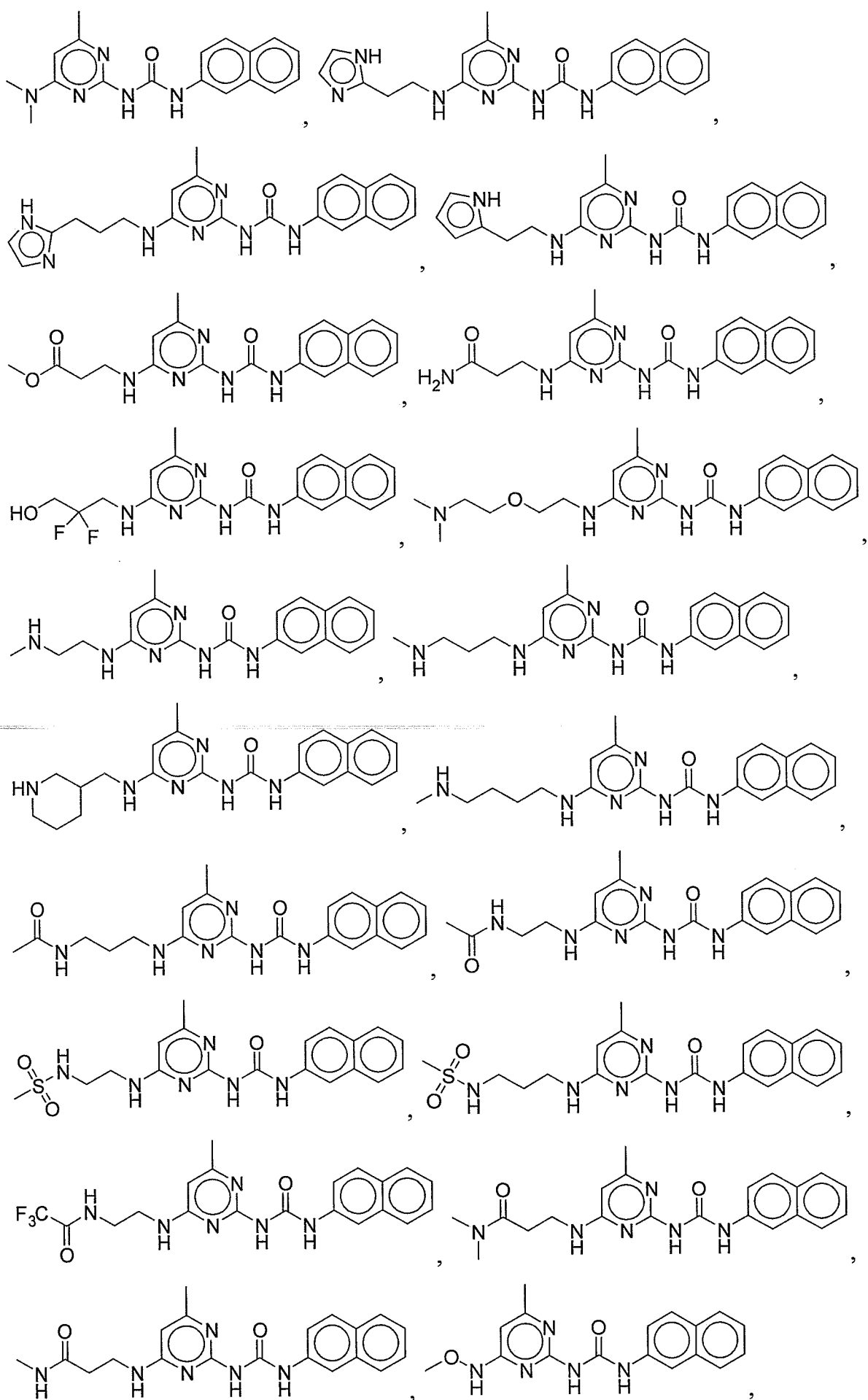
n is 1-5; and

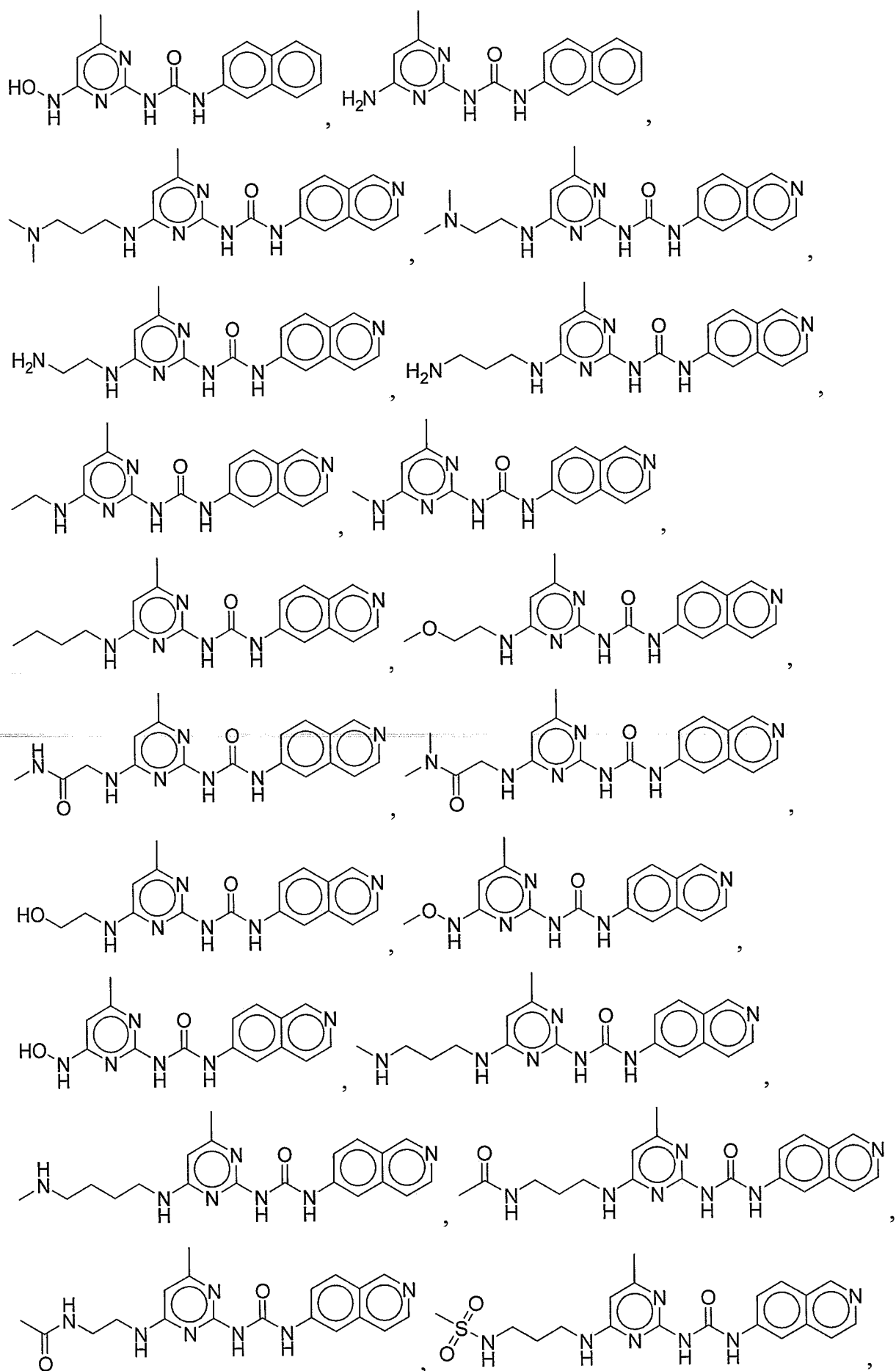
p is 0-4; or

a pharmaceutically acceptable salt, solvate, or prodrug thereof.

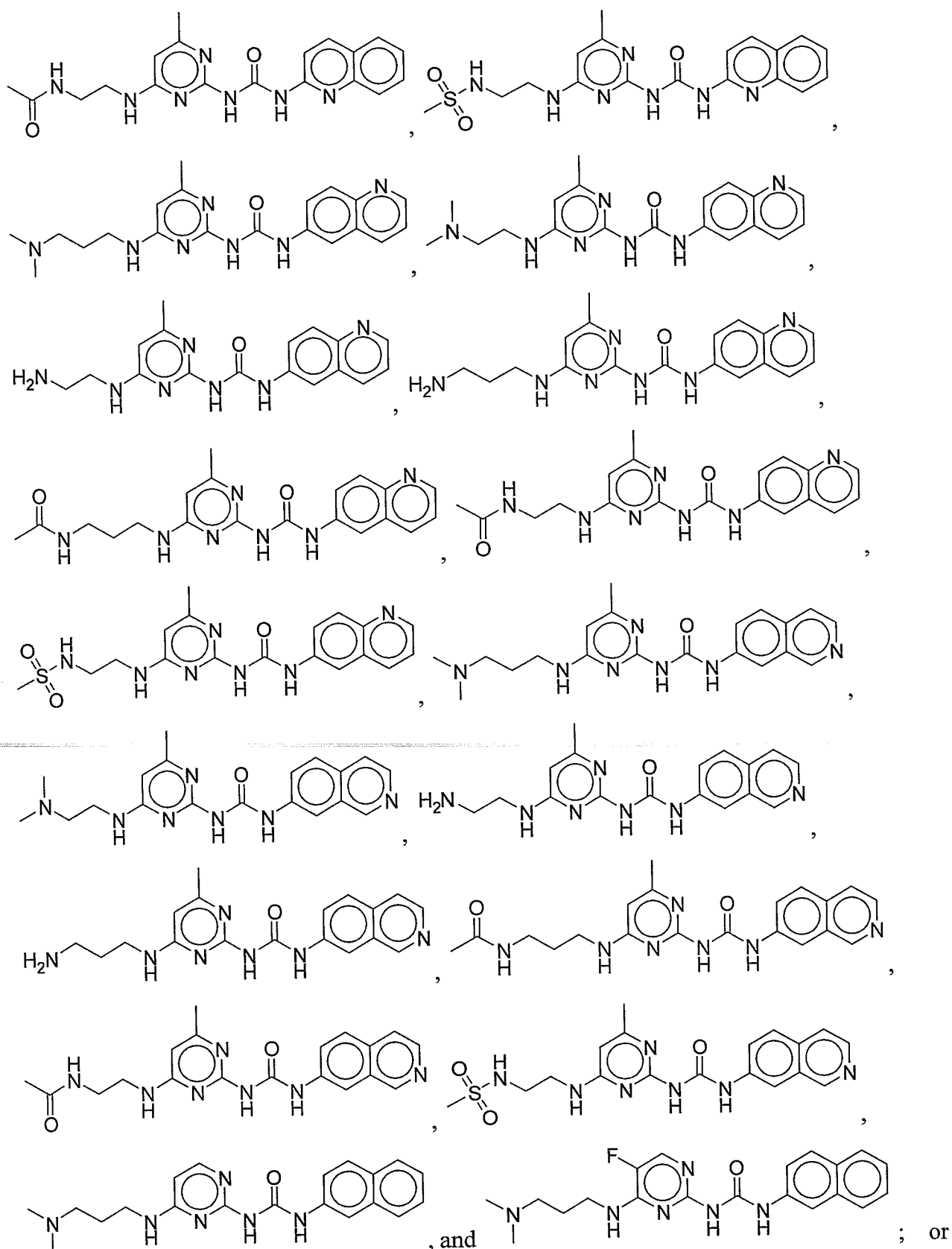
[0017b] In another aspect is a compound selected from:





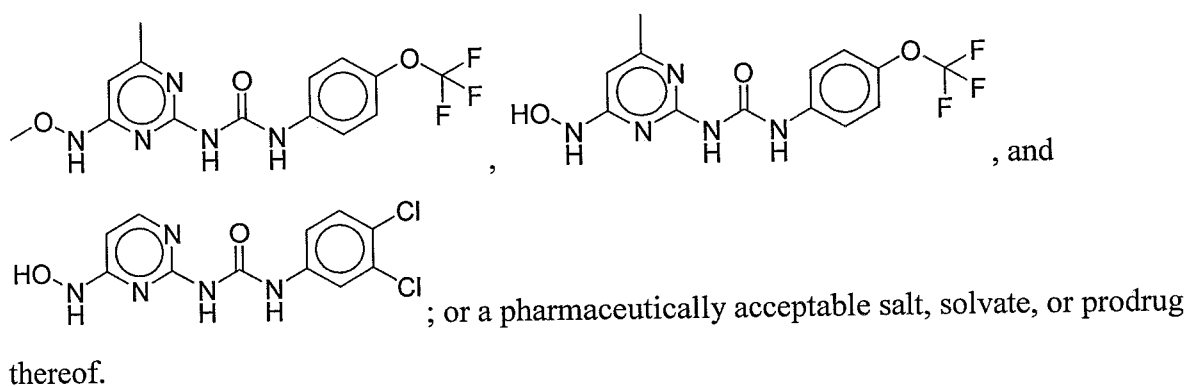




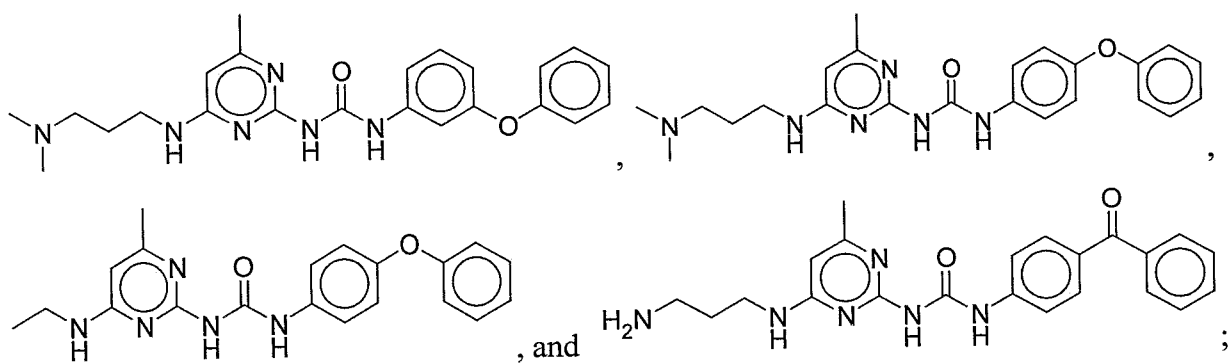


a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[0017c] In another aspect is a compound selected from:

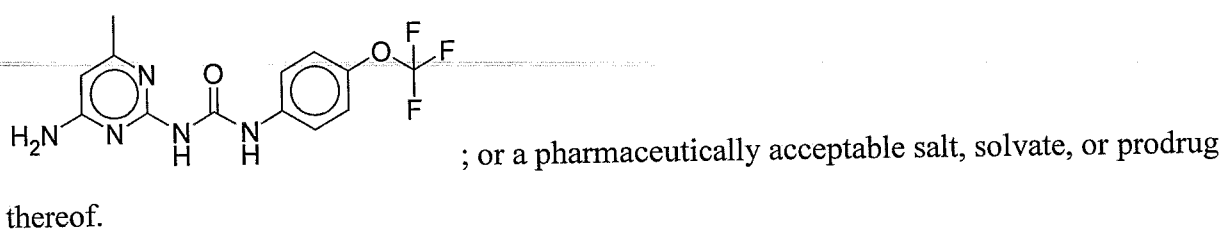


[0017d] In another aspect is a compound selected from:

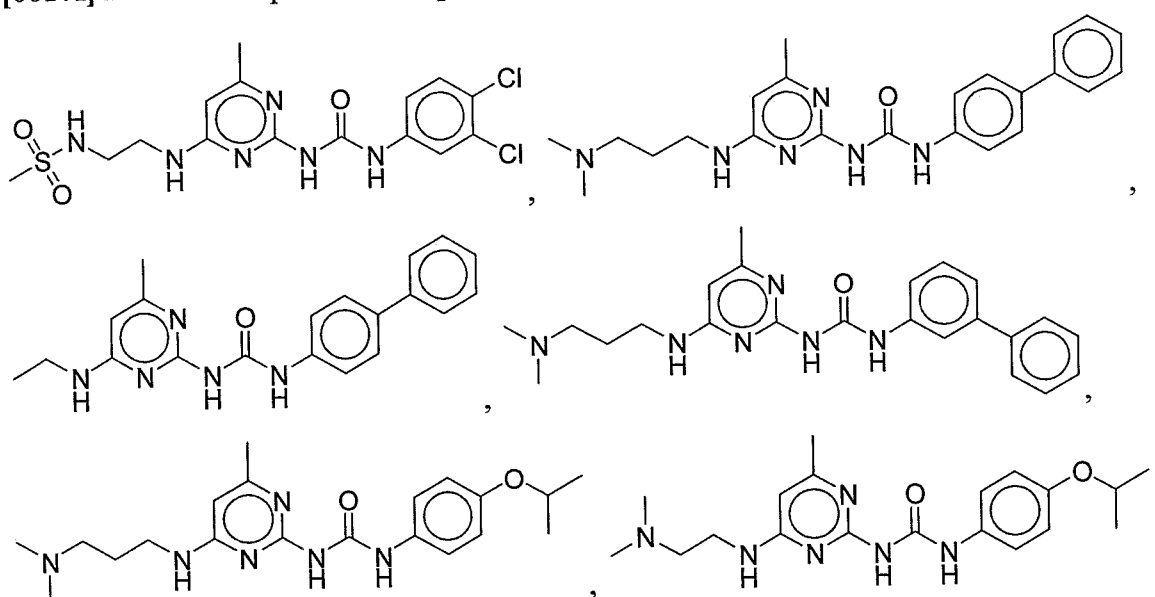


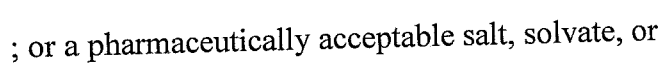
or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[0017e] In another aspect is a compound having the structure:



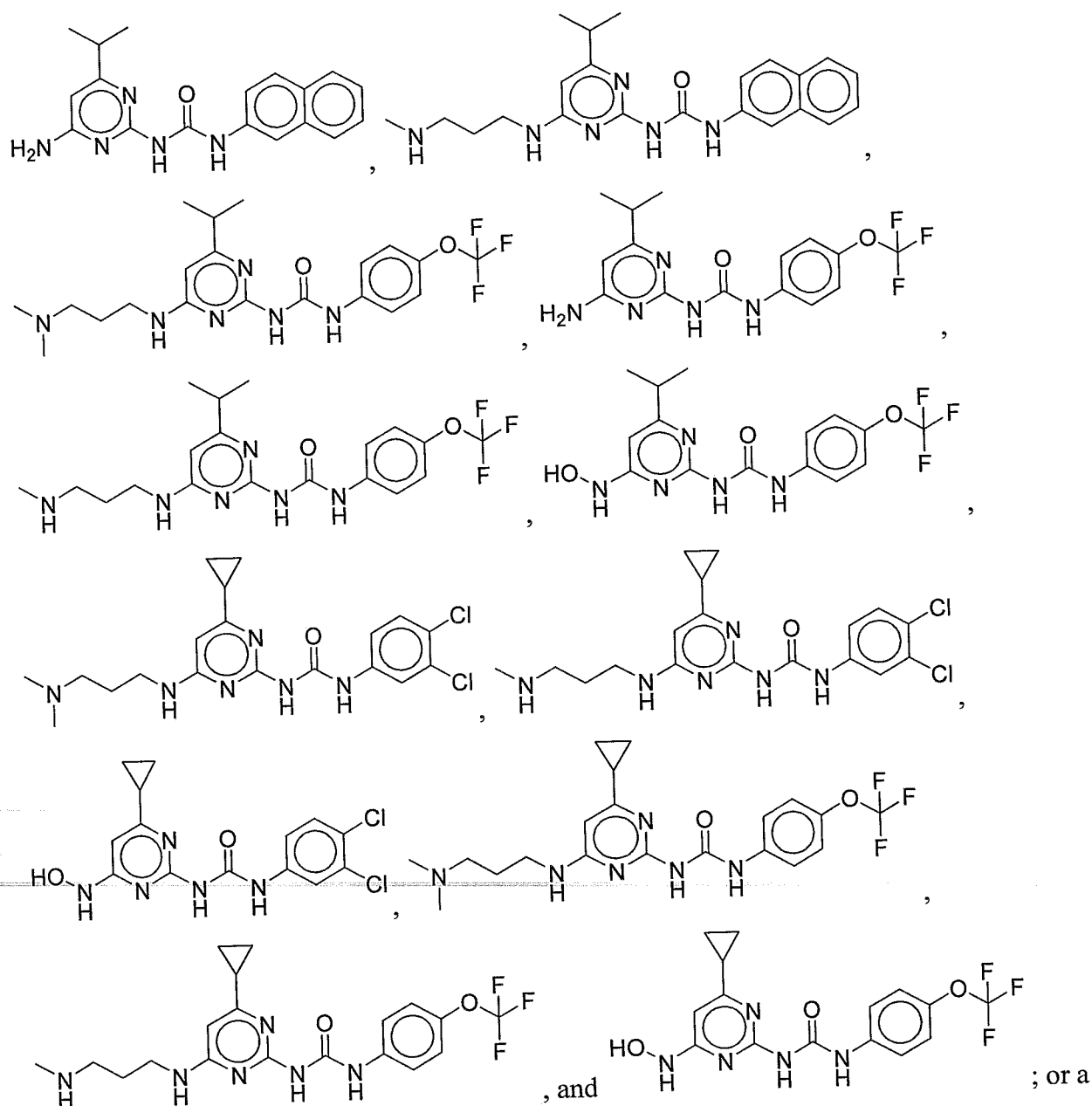
[0017f] In another aspect is a compound selected from:



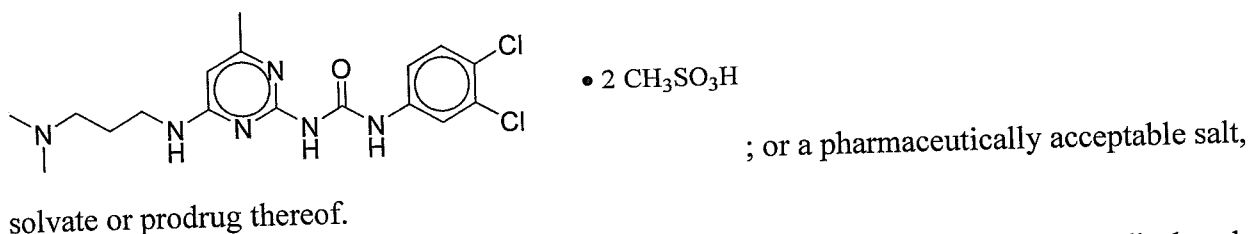


[0017g] In another aspect is a compound selected from:





[0017h] In another aspect is a compound having the structure of:



solvate or prodrug thereof.

[0017i] In another aspect is a pharmaceutical composition comprising a compound as disclosed herein, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, and at least one pharmaceutically acceptable excipient.

[0017j] In another aspect is a use of a compound as disclosed herein, or a pharmaceutically acceptable salt, solvate, or prodrug thereof in the manufacture of a medicament for the treatment of a disease in a subject; wherein the disease is cancer or Down's Syndrome.

[0017k] In another aspect is a use of a compound as disclosed herein, or a pharmaceutically acceptable salt, solvate, or prodrug thereof in the manufacture of a medicament for the inhibition of the activity of Olig2 in a cell.

[0017l] In another aspect is a compound as disclosed herein for use in therapy.

[0017m] In another aspect is a compound as disclosed herein for use as a medicament.

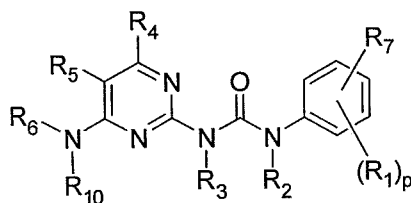
[0018] Other objects, features and advantages of the compounds, compositions, methods, and uses described herein will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific embodiments,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

DETAILED DESCRIPTION

[0019] The compounds described herein are modulators or inhibitors of the neural and GBM (glioblastoma multiforme) stem cell transcriptional repressor OLIG2 (e.g. NM_005806, NP_005797 for human). OLIG2 (also written herein as Olig2) is the oligodendrocyte transcription factor 2. This protein is a member of the bHLH (basic helix-loop-helix) family. The bHLH family is a family of transcription factors that contain the structure motif characterized by two alpha helices connected by a loop. The transcription factors containing bHLH domains are generally dimeric. Generally one of the helices contains basic amino acid residues that facilitate binding to DNA. OLIG2 is normally restricted to the central nervous system (CNS) in non-disease states, where it is an essential regulator of progenitor cell fate. OLIG2 homodimerizes and heterodimerizes 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

WHAT IS CLAIMED IS:

1. A compound of Formula (III):



Formula (III);

wherein:

each R_1 is independently halogen, -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, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆alkoxy, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₂-C₇heterocycloalkyl, substituted or unsubstituted C₃-C₈cycloalkyl, substituted or unsubstituted C₆-C₁₀aryl, or substituted or unsubstituted C₂-C₇heteroaryl;

R_2 and R_3 are each independently H, -CN, C₁-C₄alkyl, C₃-C₆cycloalkyl, or C₂-C₇heterocycloalkyl; or R_2 and R_3 are taken together to form a 5- or 6-membered heterocyclic ring;

R_4 and R_5 are independently H, halogen, -CN, -OH, -CF₃, substituted or unsubstituted C₁-C₆alkyl, substituted or unsubstituted C₁-C₆alkoxy, substituted or unsubstituted C₁-C₆heteroalkyl, substituted or unsubstituted C₂-C₇heterocycloalkyl, substituted or unsubstituted C₃-C₈cycloalkyl, substituted or unsubstituted C₆-C₁₀aryl, or substituted or unsubstituted C₂-C₉heteroaryl;

R_6 is H, unsubstituted C₁-C₆alkyl, -(C(R₁₄)(R₁₅))_mR₁₇, -(C(R₁₄)(R₁₅))_mN(R₁₁)(R₁₂), -(C(R₁₄)(R₁₅))_mOR₁₃, -(C(R₁₄)(R₁₅))_nR₁₆, or -OR₂₂;

R_7 is substituted or unsubstituted phenoxy or -C(=O)R₂₃;

each R_8 is independently H or substituted or unsubstituted C₁-C₆alkyl;

each R_9 is independently substituted or unsubstituted C₁-C₆alkyl;

R_{10} is H or unsubstituted C₁-C₄alkyl;

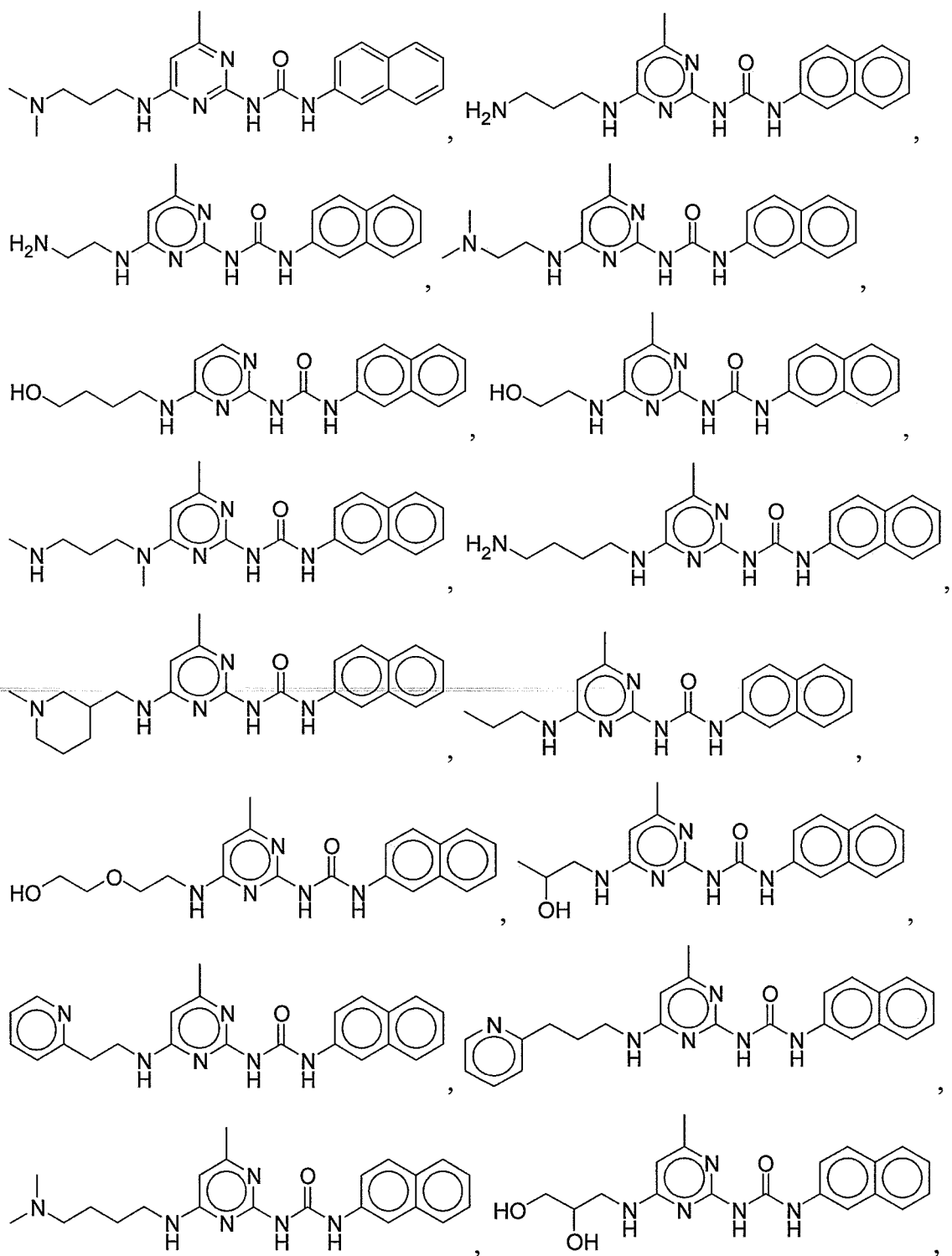
R_{11} is H, substituted or unsubstituted C₁-C₆alkyl, -C(=O)R₁₉, or -S(=O)₂R₁₉;

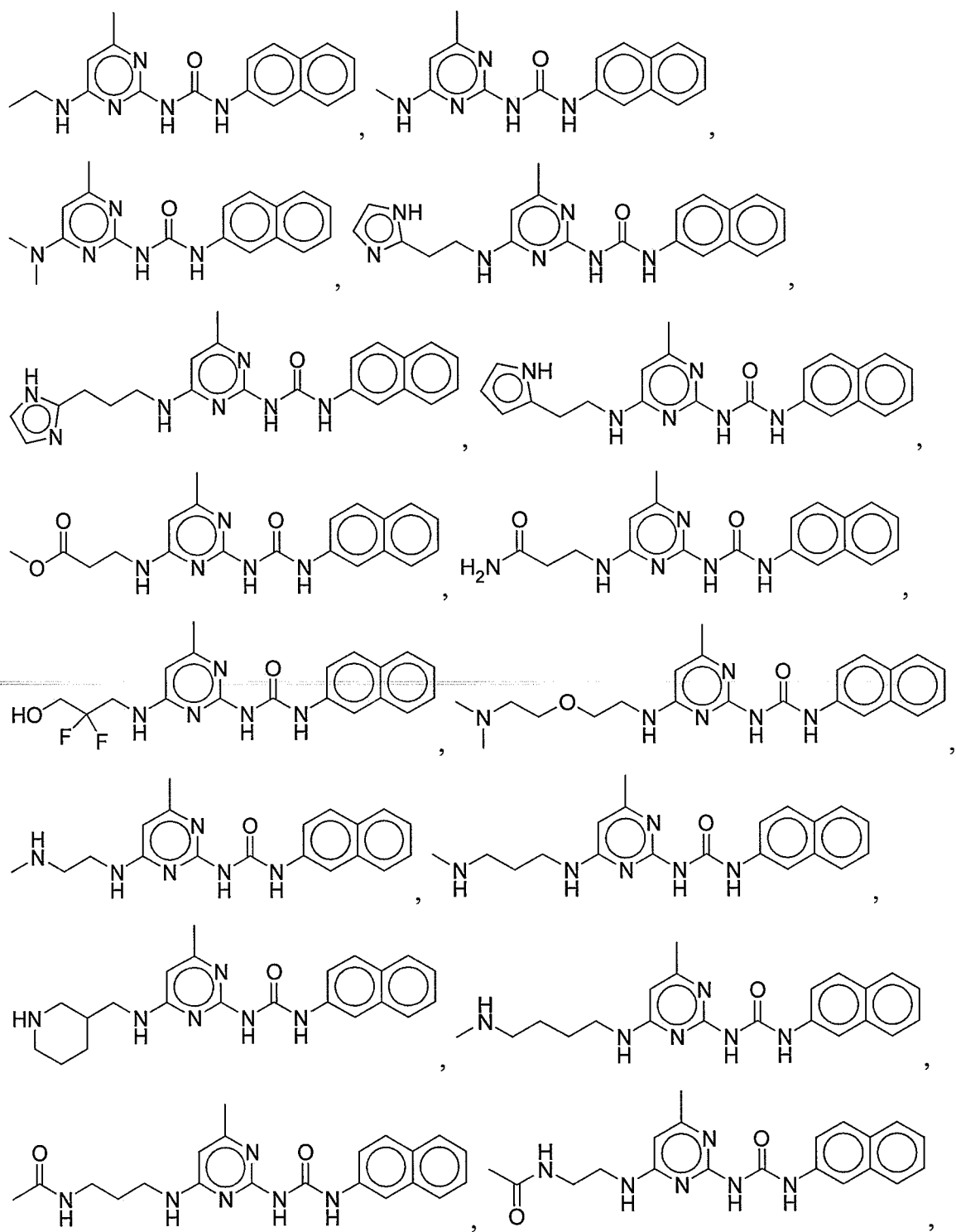
R_{12} is H or substituted or unsubstituted C₁-C₆alkyl;

R_{13} is H or substituted or unsubstituted C_1 - C_6 alkyl;
 each R_{14} and R_{15} is each independently H, halogen, or substituted or unsubstituted C_1 - C_6 alkyl;
 R_{16} is substituted or unsubstituted C_2 - C_7 heterocycloalkyl or $-C(=O)N(R_{18})_2$;
 R_{17} is $-C(=O)R_{20}$, $-CO_2R_{21}$, $-C(=O)N(R_{21})_2$, or substituted or unsubstituted C_2 - C_9 heteroaryl;
 each R_{18} is independently H, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_2 - C_7 heterocycloalkyl, or substituted or unsubstituted C_3 - C_8 cycloalkyl; or two R_{18} are taken together to form a heterocycloalkyl ring;
 R_{19} is substituted or unsubstituted C_1 - C_6 alkyl;
 R_{20} is substituted or unsubstituted C_1 - C_6 alkyl;
 each R_{21} is independently H, or substituted or unsubstituted C_1 - C_6 alkyl; or two R_{21} are taken together to form a heterocycloalkyl ring;
 R_{22} is H, or substituted or unsubstituted C_1 - C_6 alkyl;
 R_{23} is substituted or unsubstituted C_6 - C_{10} aryl;
 m is 2-6;
 n is 1-5; and
 p is 0-4; or

a pharmaceutically acceptable salt, solvate, or prodrug thereof.

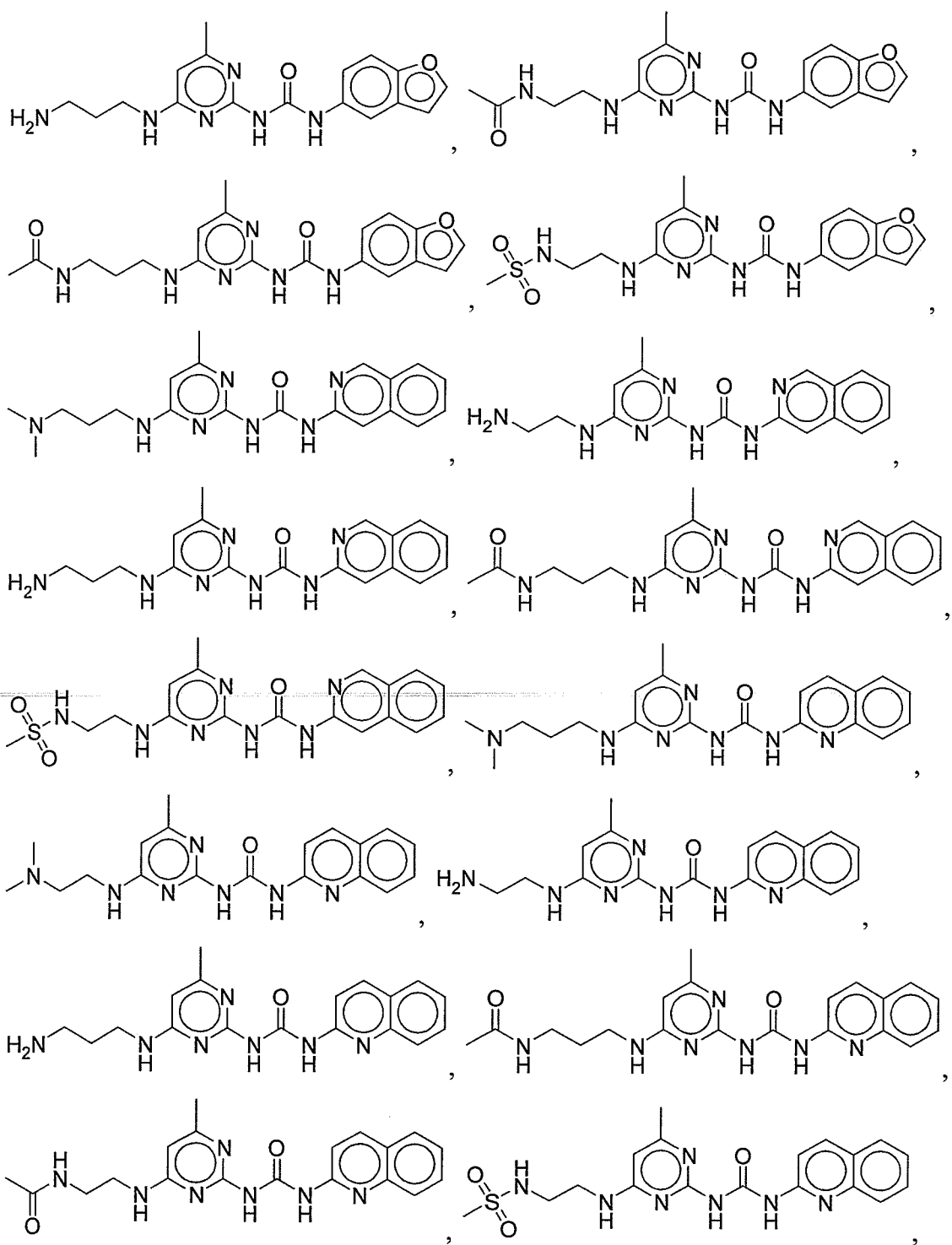
2. The compound of claim 1, wherein R_2 and R_3 are each independently H, $-CN$, C_1 - C_4 alkyl, C_3 - C_6 cycloalkyl, or C_2 - C_7 heterocycloalkyl.
3. The compound of claims 1 or 2, R_5 is H.
4. The compound of any one of claims 1-3, wherein R_4 is halogen, $-CN$, $-OH$, $-CF_3$, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_1 - C_6 alkoxy, substituted or unsubstituted C_1 - C_6 heteroalkyl.
5. The compound of any one of claims 1-4, wherein R_{10} is H.
6. The compound of any one of claims 1-5, wherein R_7 is substituted or unsubstituted phenoxy.
7. The compound of any one of claims 1-5, wherein R_7 is $-C(=O)R_{23}$.
8. A compound selected from:

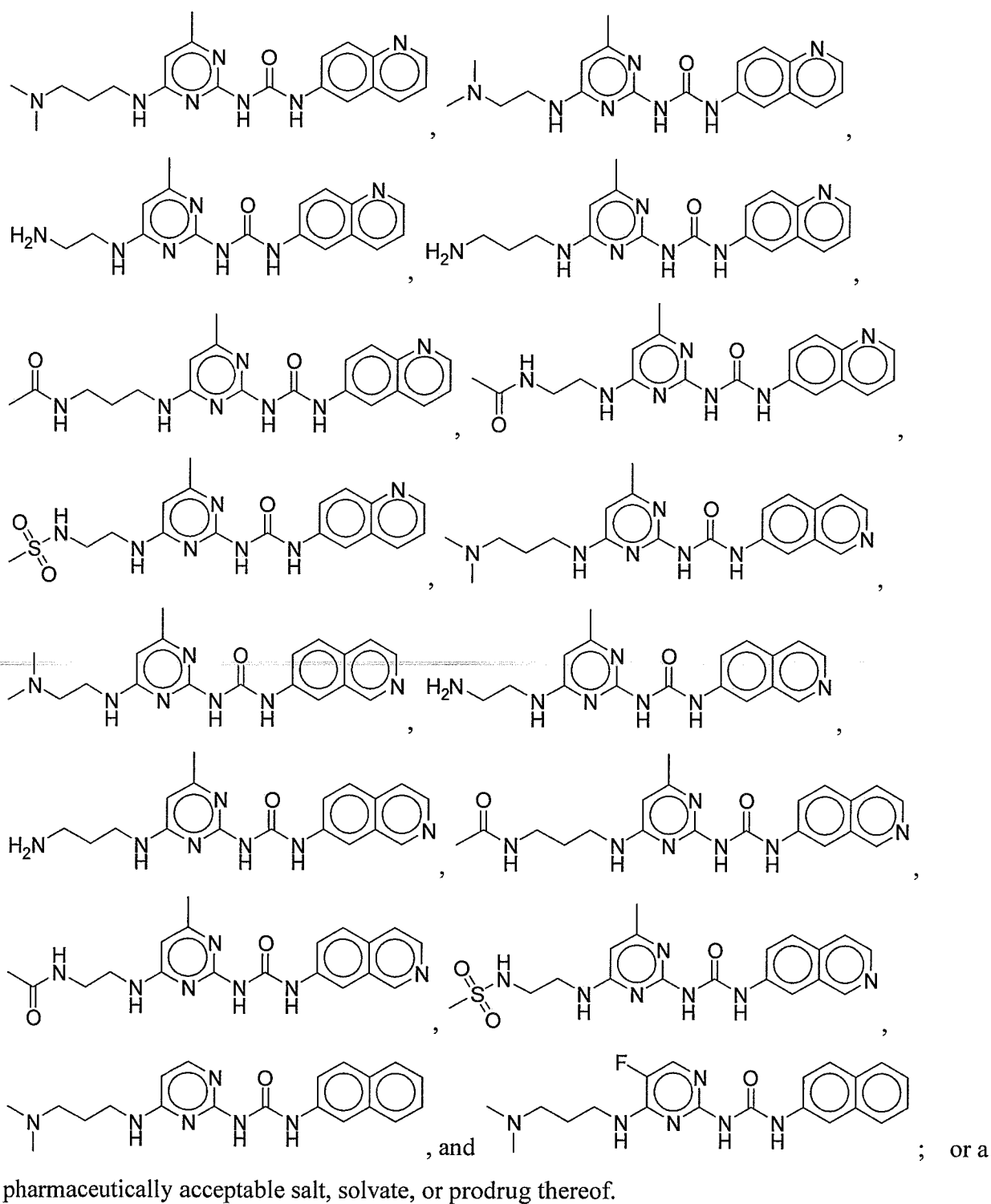




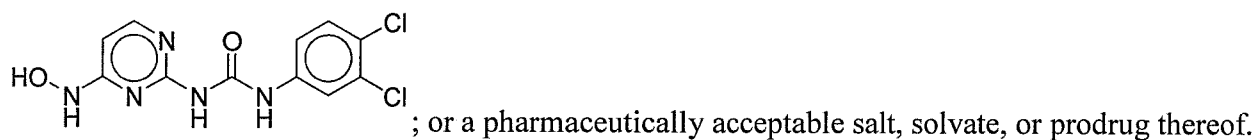
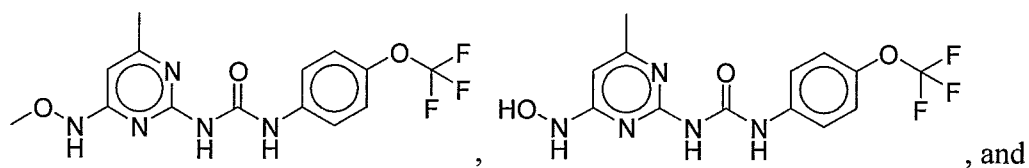




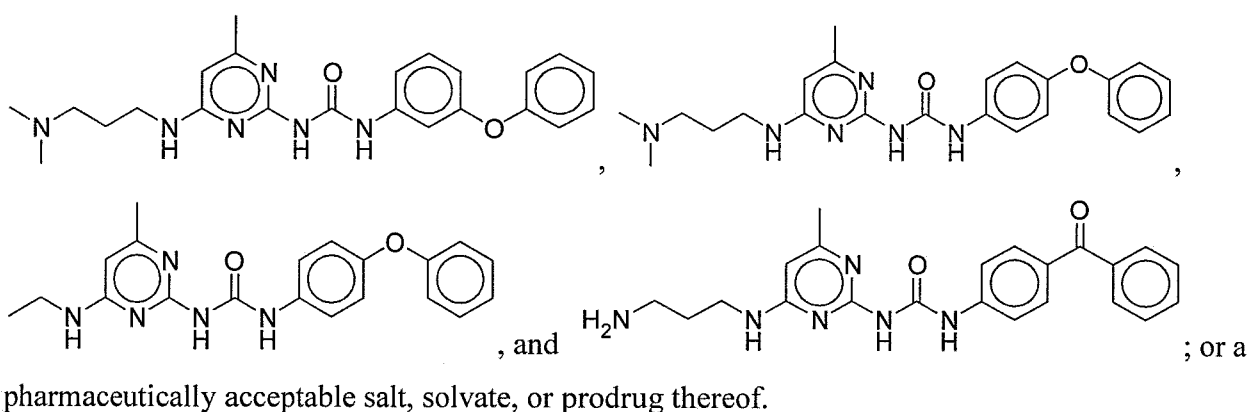




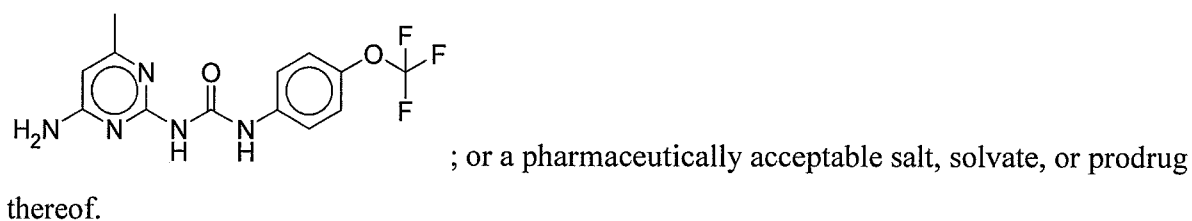
9. A compound selected from:



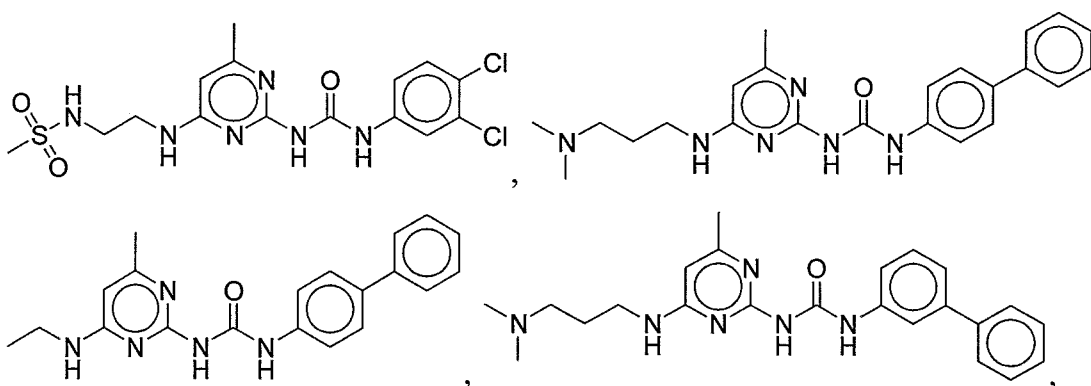
10. A compound selected from:

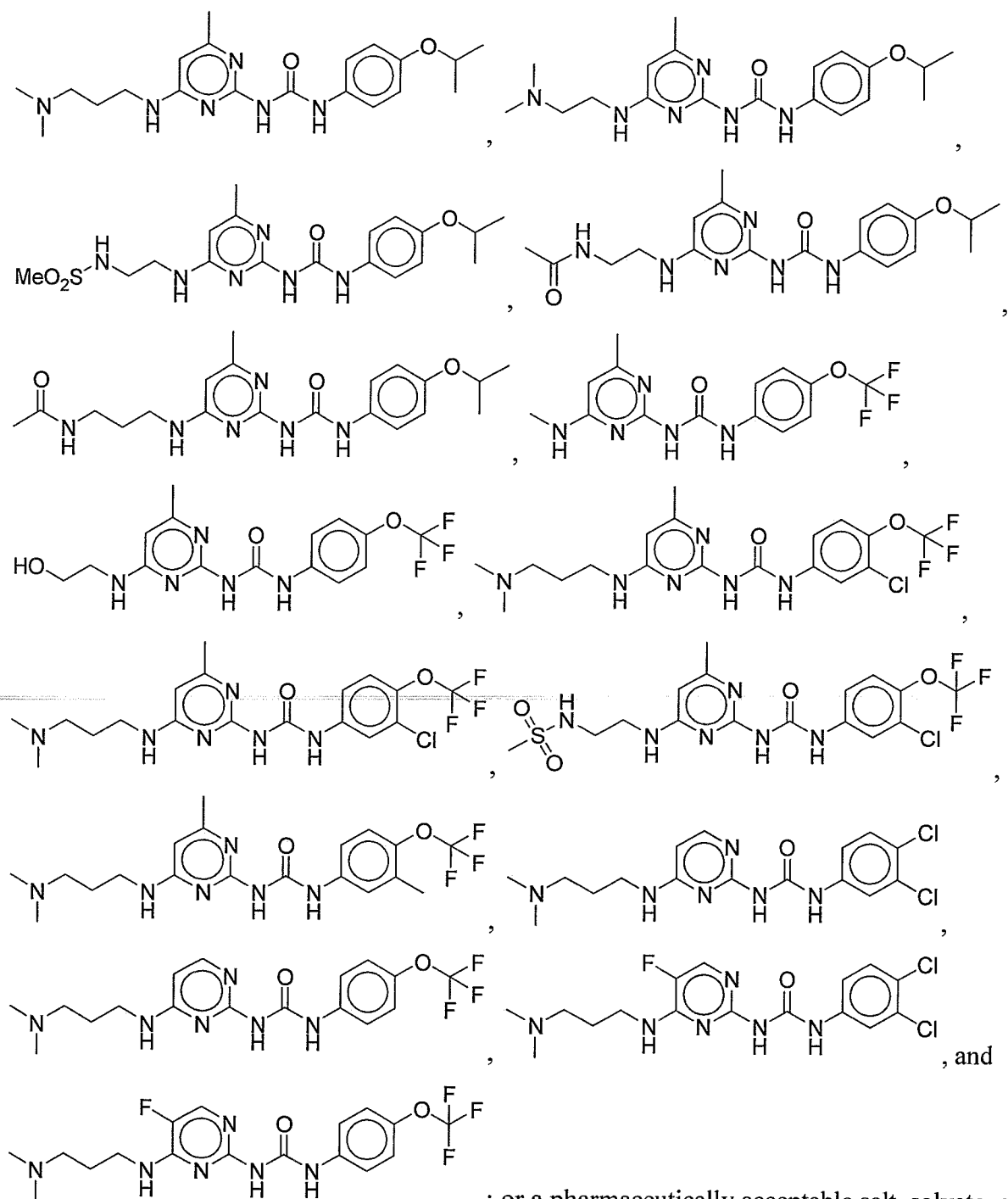


11. A compound having the structure:



12. A compound selected from:

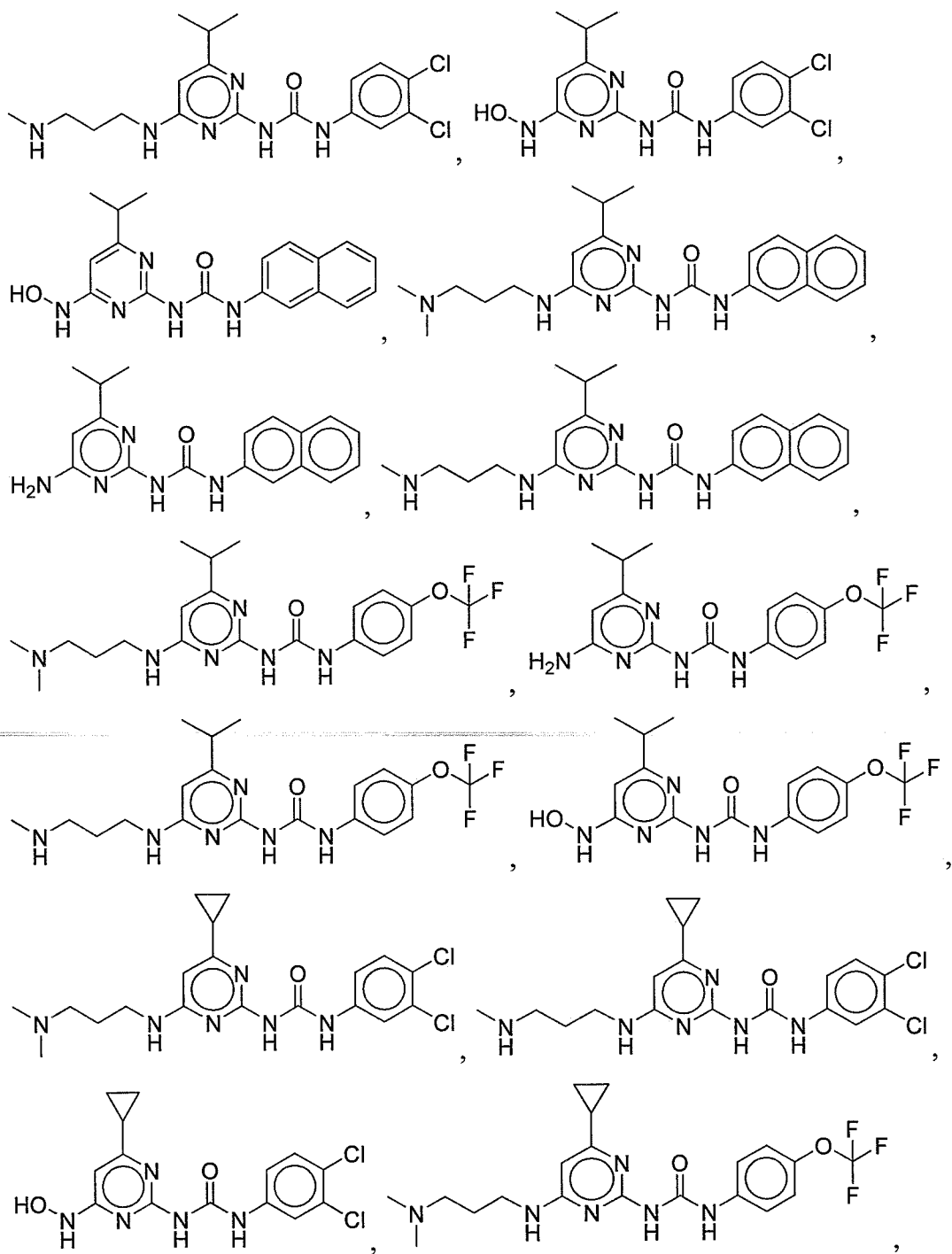


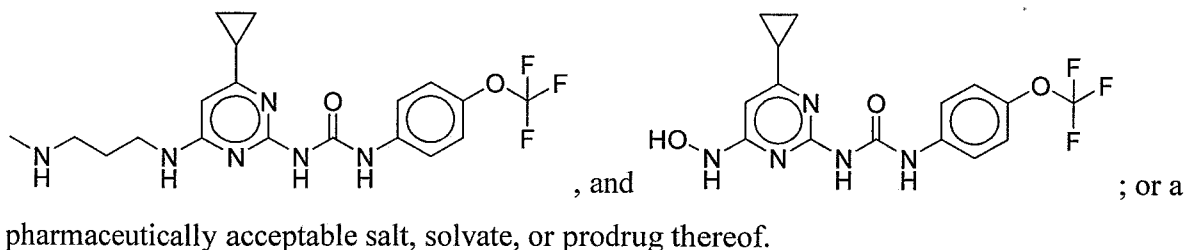


; or a pharmaceutically acceptable salt, solvate, or

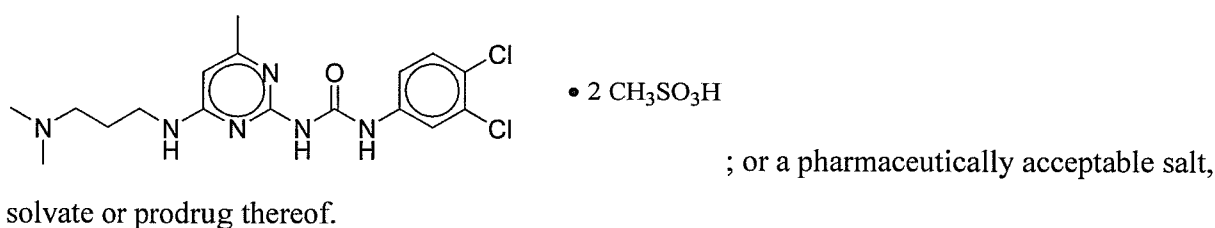
prodrug thereof.

13. A compound selected from:





14. A compound having the structure of:



15. A pharmaceutical composition comprising a compound of any one of claims 1-14, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, and at least one pharmaceutically acceptable excipient.

16. Use of a compound of any one of claims 1-14, or a pharmaceutically acceptable salt, solvate, or prodrug thereof in the manufacture of a medicament for the treatment of a disease in a subject; wherein the disease is cancer or Down's Syndrome.

17. Use of a compound of any one of claims 1-14, or a pharmaceutically acceptable salt, solvate, or prodrug thereof in the manufacture of a medicament for the inhibition of the activity of Olig2 in a cell.

18. A compound of any one of claims 1-14 for use in therapy.

19. A compound of any one of claims 1-14 for use as a medicament.