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(71) Applicant (for all designated States except US): **GLAXO GROUP LIMITED** [GB/GB]; Glaxo Wellcome House, Berkeley, Middlesex UB6 0NN (GB).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **CALLAHAN, James, Francis** [US/US]; 709 Swedeland Road, King Of Prussia, Pennsylvania 19406 (US). **BOEHM, Jeffrey** [US/US]; 709 Swedeland Road, King Of Prussia, Pennsylvania 19406 (US). **WAN, Zehong** [CN/US]; 709 Swedeland Road, King Of Prussia, Pennsylvania 19406 (US). **YAN, Hongxing** [CN/US]; 709 Swedeland Road, King Of Prussia, Pennsylvania 19406 (US).

(74) Agents: **DINNER, Dara, L.** et al.; GLAXOSMITHKLINE, CORPORATE INTELLECTUAL PROPERTY, UW2220, 709 Swedeland Road, P.o. Box 1539, King Of Prussia, Pennsylvania 19406-0939 (US).

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(54) Title: PROCESS FOR PREPARING PYRIDO[2,3-D]PYRIMIDIN-7-ONE AND 3,4-DIHYDROPYRIMIDO[4,5-D]PYRIMIDIN-2(1H)-ONE DERIVATIVES

(57) Abstract: The present invention is directed to a novel method of preparing of 2,4,8- trisubstituted pyrido[2,3-d]pyrimidin-7-one pharmacophores of Formula (II) or (Ha) wherein GHs CH₂ Or NH; G2 is CH or nitrogen; Rx is chloro, bromo, iodo, or O-S(O)₂CF₃; Rg is a C₁₋₁₀ alkyl; m is 0, or an integer having a value of 1, or 2; R₃ is a C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl C₁₋₁₀ alkyl, aryl, arylC₁₋₁₀ alkyl, heteroaryl, heteroarylC₁₋₁₀ alkyl, heterocyclic or a heterocyclylC₁₋₁₀ alkyl moiety, and wherein each of these moieties may be optionally substituted. which comprises reacting a compound of the formula: wherein Ry is chloro, bromo, iodo, O-S(O)₂CF₃; and Rg is a C₁₋₁₀ alkyl; with a olefin forming reagent in a suitable base to yield a compound of Formula (II), or (Ha) wherein m=0 and oxidizing the sulphur as necessary or desired.

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Process for Preparing Pyrido[2,3-*d*]pyrimidin-7-one and 3,4-Dihydropyrimido[4,5-*d*]pyrimidin-2(1*H*)-one Derivatives

Field of the Invention

This invention relates to a novel process to produce pyrido[2,3-*d*]pyrimidin-7-one containing compounds or 3,4-dihydropyrimido[4,5-*d*]pyrimidin-2(1*H*)-one containing compounds.

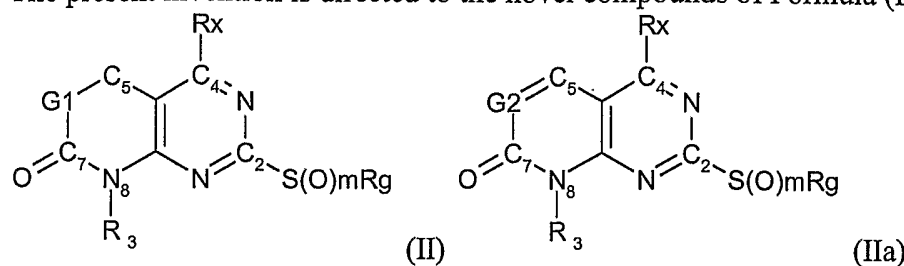
Background of the Invention

Preparation of 2,4,8-trisubstituted pyrido[2,3-*d*]pyrimidin-7-one has been demonstrated by a small, but limited, number of methods. In general, these methods either include lengthy synthetic sequence (e.g., more than 5 steps in the longest linear sequence from commercially available starting materials) or are not conducive for use in structure-activity relationship studies [e.g., not amenable to multi-dimensional (> or = 2-D) array syntheses]. Doherty, J. B. *et al.*, (Merck, US 6,809,199) discloses an eight-step method to prepare intermediates with structures similar to (II) wherein C4 and N8 have already been substituted with phenyl groups. Mauro, A. *et al.* (Pharmacia, US 2004/0009993) reported a nine-step method to prepare intermediates with structures similar to (II) wherein C4 is substituted with C₁-C₆ alkyl or C₁-C₆ arylalkyl and N8 has been connected with a phenyl group. Adams, J.L. *et al.* (SmithKline Beecham: WO 02/059083; WO 03/088972; Tetrahedron Letters, 2003, Vol. 44, pages 4567-4570) discloses a four-step method to prepare intermediates with structures similar to (II) wherein the C4 position has already been substituted via a Suzuki cross coupling reaction and N8 is substituted with alkyl or aryl.

However, despite all of these methods there still remains a need for an efficient method to prepare 2,4,8-trisubstituted pyrido[2,3-*d*]pyridine-7-one that can independently optimize the substituents at C2 and C4.

Summary of the Invention

The present invention is directed to the novel compounds of Formula (II):



5 wherein

G1 is CH₂ or NH;

G2 is CH or nitrogen;

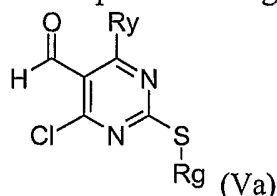
Rx is chloro, bromo, iodo, or O-S(O)₂CF₃;

R_g is a C₁₋₁₀ alkyl;

10 m is 0, or an integer having a value of 1, or 2;

R₃ is a C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl C₁₋₁₀ alkyl, aryl, arylC₁₋₁₀ alkyl, heteroaryl, heteroarylC₁₋₁₀ alkyl, heterocyclic or a heterocyclylC₁₋₁₀ alkyl moiety, and wherein each of these moieties may be optionally substituted.

15 The present invention is also directed to a novel process to make compounds of Formula (II) wherein m = 0, which comprises reacting a compound of the formula:



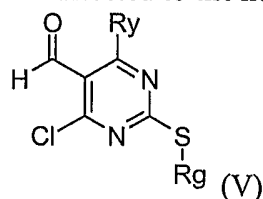
wherein

Ry is chloro, bromo, iodo, O-S(O)₂CF₃; and

20 R_g is a C₁₋₁₀ alkyl;

with a olefin forming reagent in a suitable base to yield a compound of Formula (II), wherein G2 is CH, which may optionally be reduced to a compound of Formula (IIa) under standard reducing conditions if desired.

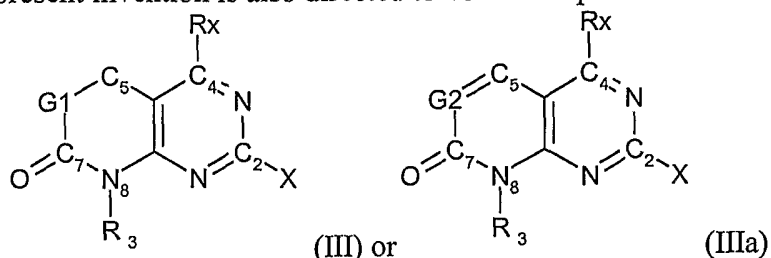
25 The present invention is also directed to the novel compounds of Formula (V)



wherein

Ry is bromo, iodo, O-S(O)₂CF₃; and
Rg is a C₁₋₁₀ alkyl.

The present invention is also directed to novel compounds of Formula (III):



wherein

G1 is CH₂ or NH;

G2 is CH or nitrogen;

10 Rx is chloro, bromo, iodo, or O-S(O)₂CF₃;

X is R₂, OR₂', S(O)_mR₂', (CH₂)_nN(R₁₁)S(O)_mR₂', (CH₂)_nN(R₁₁)C(O)R₂',
(CH₂)_nNR₄R₁₄, or (CH₂)_nN(R₂') (R₂''), or N(R₁₀')-R_h-NH-C(=N-CN)NR_qR_q';

X₁ is N(R₁₁), O, S(O)_m, or CR₁₀R₂₀;

R_h is selected from an optionally substituted C₁₋₁₀ alkyl, -CH₂-C(O)-CH₂-,

15 -CH₂CH₂-O-CH₂-CH₂-, -CH₂-C(O)N(R₁₀')CH₂-CH₂-, -CH₂-
N(R₁₀')C(O)CH₂-, -CH₂-CH(OR₁₀')-CH₂-, -CH₂-C(O)O-CH₂-CH₂-, or -CH₂-
CH₂-O-C(O)CH₂-;

R_q and R_q' are independently selected at each occurrence from hydrogen, C₁₋₁₀

20 alkyl, C₃₋₇cycloalkyl, C₃₋₇cycloalkylC₁₋₁₀alkyl, C₅₋₇ cycloalkenyl, C₅₋₇
cycloalkenyl-C₁₋₁₀alkyl, aryl, arylC₁₋₁₀alkyl, heteroaryl, heteroarylC₁₋₁₀alkyl,
heterocyclic, or a heterocyclylC₁₋₁₀alkyl moiety, wherein all of the moieties,
excluding hydrogen, are optionally substituted, or R_q and R_q' together with the
nitrogen to which they are attached form a 5 to 7 membered optionally substituted
ring, which ring may contain an additional heteroatom selected from oxygen,
25 nitrogen or sulfur;

R₂ is hydrogen, C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkylalkyl, aryl, arylC₁₋₁₀
alkyl, heteroaryl, heteroarylC₁₋₁₀alkyl, heterocyclic, or a heterocyclylC₁₋₁₀alkyl
moiety, and wherein each of these moieties, excluding hydrogen, may be
optionally substituted; or R₂ is the moiety

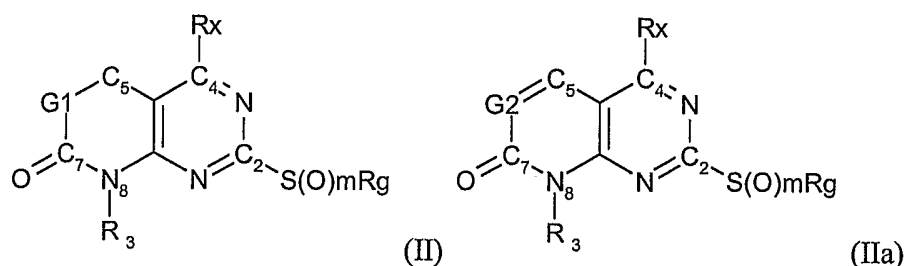
30 (CR₁₀R₂₀)_qX₁(CR₁₀R₂₀)_qC(A₁)(A₂)(A₃), or C(A₁)(A₂)(A₃);

R₂' is hydrogen, C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkylalkyl, aryl, arylC₁₋₁₀
alkyl, heteroaryl, heteroarylC₁₋₁₀alkyl, heterocyclic, or a heterocyclylC₁₋₁₀alkyl

- moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;
- R₂'' is hydrogen, C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkylalkyl, aryl, arylC₁₋₁₀ alkyl, heteroaryl, heteroarylC₁₋₁₀ alkyl, heterocyclic, or a heterocyclylC₁₋₁₀ alkyl
- 5 moiety, and wherein these moieties, excluding hydrogen, may be optionally substituted; or
- wherein R₂'' is the moiety (CR₁₀R₂₀)_tX₁(CR₁₀R₂₀)_qC(A₁)(A₂)(A₃);
- A₁ is an optionally substituted C₁₋₁₀ alkyl, heterocyclic, heterocyclic C₁₋₁₀ alkyl, heteroaryl, heteroaryl C₁₋₁₀ alkyl, aryl, or aryl C₁₋₁₀ alkyl;
- 10 A₂ is an optionally substituted C₁₋₁₀ alkyl, heterocyclic, heterocyclic C₁₋₁₀ alkyl, heteroaryl, heteroaryl C₁₋₁₀ alkyl, aryl, or aryl C₁₋₁₀ alkyl;
- A₃ is hydrogen or is an optionally substituted C₁₋₁₀ alkyl;
- R₃ is a C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl C₁₋₁₀ alkyl, aryl, arylC₁₋₁₀ alkyl, heteroaryl, heteroarylC₁₋₁₀ alkyl, heterocyclic or a heterocyclylC₁₋₁₀ alkyl
- 15 moiety, and wherein each of these moieties may be optionally substituted;
- R₄ and R₁₄ are each independently selected from hydrogen, C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkylC₁₋₄alkyl, aryl, aryl-C₁₋₄ alkyl, heterocyclic, heterocyclic C₁₋₄ alkyl, heteroaryl or a heteroaryl C₁₋₄ alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or the
- 20 R₄ and R₁₄ together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 4 to 7 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or nitrogen;
- R₁₀ and R₂₀ are independently selected from hydrogen or C₁₋₄alkyl;
- R₁₀' is independently selected at each occurrence from hydrogen or C₁₋₄alkyl;
- 25 R₁₁ is independently selected from hydrogen or C₁₋₄alkyl;
- n' is independently selected at each occurrence from 0 or an integer having a value of 1 to 10;
- m is independently selected at each occurrence from 0 or an integer having a value of 1 or 2;
- 30 q is 0 or an integer having a value of 1 to 10;
- q' is 0, or an integer having a value of 1 to 6; or
- t is an integer having a value of 2 to 6.

The present invention is also directed to a process for making a compound

35 Formula (III) or (IIIa), which comprises reacting a compound of formula (II) or (IIa)



wherein

G1 is CH₂ or NH;

5 G2 is CH or nitrogen;

Rx is chloro, bromo, iodo, or O-S(O)₂CF₃;

R_g is a C₁₋₁₀ alkyl;

m is an integer having a value of 1, or 2;

10 R₃ is a C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl C₁₋₁₀ alkyl, aryl, arylC₁₋₁₀ alkyl, heteroaryl, heteroarylC₁₋₁₀ alkyl, heterocyclic or a heterocyclylC₁₋₁₀ alkyl moiety, and wherein each of these moieties may be optionally substituted.

with the compound X-Y,

wherein X is R₂, OR₂', S(O)_mR₂', (CH₂)_n'N(R₁₁)S(O)_mR₂',

15 (CH₂)_n'N(R₁₁)C(O)R₂', (CH₂)_n'NR₄R₁₄, or (CH₂)_n'N(R₂') (R₂''), or N(R₁₀')-R_h-NH-C(=N-CN)NR_qR_q'; and R₂, R₂', m, n', R₁₁, R₁₀', R_h and R_qR_q' are as defined according to Formula (III) herein; and

Y is hydrogen, a metal, a boronic acid derivative, or a trialkyl tin derivative, in an anhydrous organic solvent which does not contain a nucleophile to yield a compound

20 of Formula (III); provided that

when Y is hydrogen then

a) X= OR₂', or X is S(O)_mR₂' (and m=0); or

b) X is (CH₂)_n'N(R₁₀')S(O)_mR₂', (CH₂)_n'N(R₁₀')C(O)R₂', (CH₂)_n'NR₄R₁₄, or (CH₂)_n'N(R₂') (R₂'') and n'=0; or

25 c) X=R₂ and R₂ = (CR₁₀R₂₀)_q'X₁(CR₁₀R₂₀)_qC(A₁)(A₂)(A₃), q'=0, and X₁ is N(R₁₀'), O, S(O)_m and m=0.

d) when X is N(R₁₀')-R_h-NH-C(=N-CN)NR_qR_q'; and

when Y is a metal, such as Li, Mg, or any other appropriate metal or metal complexes; then

30 a) X is R₂, and R₂ is C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkylC₁₋₁₀ alkyl, aryl, arylC₁₋₁₀ alkyl, heteroaryl, heteroaryl C₁₋₁₀ alkyl, heterocyclic, or a heterocyclylC₁₋₁₀ alkyl moiety; and

when Y is a boronic acid, (B(OH)₂) or boronic ester derivatives

a) $X = R_2$, and $R_2 = \text{aryl}$, or heteroaryl; and

when Y is a trialkyl tin derivative, such as $(C_{1-4} \text{ alkyl})_3\text{Sn}$, then

a) $X = R_2$, and $R_2 = \text{aryl}$, or heteroaryl.

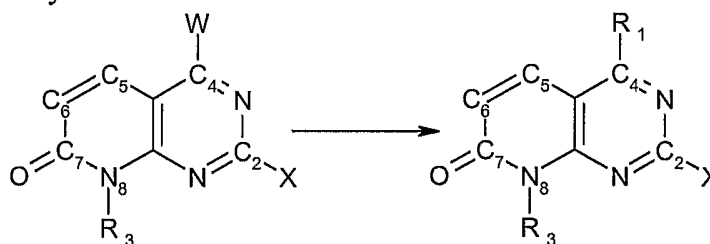
5 Detailed Description of the Invention

The present invention is an alternative process for preparation of compounds having a pyrido[2,3-*d*]pyrimidin-7-one template or a 3,4-dihydropyrimido[4,5-*d*]pyrimidin-2(1*H*)-one derivatives.

This novel process provides for facile variation of the C4 position in the both
10 of these templates, and therefore ease of use in the making of a combinatorial array.

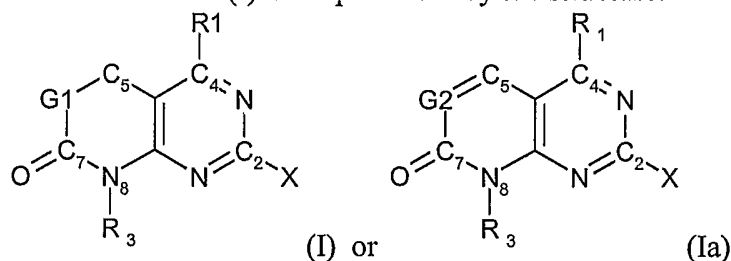
The process as will be described herein provides for different (R_1) substituents to be introduced at the C4 position of the compounds with the general structure of **Formula I**, late in a synthetic sequence after the pyrido[2,3-*d*]pyrimidin-7-one or the 3,4-dihydropyrimido[4,5-*d*]pyrimidin-2(1*H*)-one template has already been substituted
15 with a substituent ("X" in Formula I) at the C2 position and with another substituent (" R_3 " in Formula I) at the N8 position.

Generically the reaction is:



wherein W is a leaving group such as chlorine, bromine, iodine, $\text{OS}(\text{O})\text{CF}_3$; and R_1 ,
20 R_3 and X are as defined in Formula (I).

Compounds of Formula (I) are represented by the structure:



wherein

25 G1 is CH_2 , or NH;

G2 is CH or nitrogen;

R_1 is an aryl, aryl C_{2-10} alkyl, heteroaryl, heteroaryl C_{2-10} alkyl; aryl C_{2-10} alkenyl, aryl C_{2-10} alkynyl, heteroaryl C_{2-10} alkenyl, heteroaryl C_{2-10} alkynyl,

- C₂₋₁₀alkenyl, or C₂₋₁₀ alkynyl moiety, which moieties may be optionally substituted;
- X is R₂, OR₂', S(O)_mR₂', (CH₂)_n'N(R₁₀')S(O)_mR₂', (CH₂)_n'N(R₁₀')C(O)R₂', (CH₂)_n'NR₄R₁₄, (CH₂)_n'N(R₂') (R₂''), or N(R₁₀')-R_h-NH-C(=N-CN)NR_qR_q';
- 5 X₁ is N(R₁₁), O, S(O)_m, or CR₁₀R₂₀;
- R_h is selected from an optionally substituted C₁₋₁₀ alkyl, -CH₂-C(O)-CH₂-, -CH₂CH₂-O- CH₂-CH₂-, -CH₂-C(O)N(R₁₀')CH₂-CH₂-, -CH₂-N(R₁₀')C(O)CH₂-, -CH₂-CH(OR₁₀')-CH₂-, -CH₂-C(O)O-CH₂-CH₂-, or -CH₂-CH₂-O-C(O) CH₂-;
- 10 R_q and R_q' are independently selected at each occurrence from hydrogen, C₁₋₁₀ alkyl, C₃₋₇cycloalkyl, C₃₋₇cycloalkylC₁₋₁₀alkyl, C₅₋₇ cycloalkenyl, C₅₋₇ cycloalkenyl-C₁₋₁₀alkyl, aryl, arylC₁₋₁₀ alkyl, heteroaryl, heteroarylC₁₋₁₀ alkyl, heterocyclic, or a heterocyclylC₁₋₁₀ alkyl moiety, wherein all of the moieties, excluding hydrogen, are optionally substituted, or R_q and R_q' together with the
- 15 nitrogen to which they are attached form a 5 to 7 membered optionally substituted ring, which ring may contain an additional heteroatom selected from oxygen, nitrogen or sulfur;
- R₂ is hydrogen, C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkylalkyl, aryl, arylC₁₋₁₀ alkyl, heteroaryl, heteroarylC₁₋₁₀ alkyl, heterocyclic, or a heterocyclylC₁₋₁₀ alkyl moiety,
- 20 and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or
- R₂ is the moiety (CR₁₀R₂₀)_q'X₁(CR₁₀R₂₀)_qC(A₁)(A₂)(A₃), or (CR₁₀R₂₀)_q'C(A₁)(A₂)(A₃);
- R₂' is hydrogen, C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkylalkyl, aryl, arylC₁₋₁₀ alkyl, heteroaryl, heteroarylC₁₋₁₀ alkyl, heterocyclic, or a heterocyclylC₁₋₁₀ alkyl
- 25 moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;
- R₂'' is hydrogen, C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkylalkyl, aryl, arylC₁₋₁₀ alkyl, heteroaryl, heteroarylC₁₋₁₀ alkyl, heterocyclic, or a heterocyclylC₁₋₁₀ alkyl
- 30 moiety, and wherein these moieties, excluding hydrogen, may be optionally substituted; or
- wherein R₂''' is the moiety (CR₁₀R₂₀)_tX₁(CR₁₀R₂₀)_qC(A₁)(A₂)(A₃);
- A₁ is an optionally substituted C₁₋₁₀ alkyl, heterocyclic, heterocyclic C₁₋₁₀ alkyl, heteroaryl, heteroaryl C₁₋₁₀ alkyl, aryl, or aryl C₁₋₁₀ alkyl;
- 35 A₂ is an optionally substituted C₁₋₁₀ alkyl, heterocyclic, heterocyclic C₁₋₁₀ alkyl, heteroaryl, heteroaryl C₁₋₁₀ alkyl, aryl, or aryl C₁₋₁₀ alkyl;
- A₃ is hydrogen or is an optionally substituted C₁₋₁₀ alkyl;

- R₃ is C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl C₁₋₁₀ alkyl, aryl, arylC₁₋₁₀ alkyl, heteroarylC₁₋₁₀ alkyl, or a heterocyclylC₁₋₁₀ alkyl moiety, and wherein each of these moieties may be optionally substituted;
- 5 R₄ and R₁₄ are each independently selected at each occurrence from hydrogen, C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkylC₁₋₄alkyl, aryl, aryl-C₁₋₄ alkyl, heterocyclic, heterocyclic C₁₋₄ alkyl, heteroaryl or a heteroaryl C₁₋₄ alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or the R₄ and R₁₄ together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 4 to 7 members, which ring
- 10 optionally contains an additional heteroatom selected from oxygen, sulfur or nitrogen;
- R₁₀ and R₂₀ are independently selected at each occurrence from hydrogen or C₁₋₄alkyl;
- R₁₀' is independently selected at each occurrence from hydrogen or C₁₋₄alkyl;
- 15 R₁₁ is independently selected at each occurrence from hydrogen or C₁₋₄alkyl;
- n' is independently selected at each occurrence from 0 or an integer having a value of 1 to 10;
- m is independently selected at each occurrence from 0 or an integer having a value of 1 or 2;
- 20 q is 0 or an integer having a value of 1 to 10;
- q' is 0, or an integer having a value of 1 to 6;
- t is an integer having a value of 2 to 6; or
- a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof.
- 25 Compounds of Formula (I) having a similar template are described in WO 01/64679, WO 02/059083, and WO 03/088972 whose disclosures are incorporated by reference in their entirety herein.
- It should be noted that the difference between compounds of Formula (I) and (Ia), as well as (II) and (IIa), (III) and (IIIa) lie in the unsaturation of the ring at the C5
- 30 position and the 6-position of the ring which may be a carbon or a nitrogen. The remaining variables on the ring are the same otherwise, e.g. R_x, R₁, R₃, etc. for each formula. Unless otherwise specified, the substitution applicable to Formula (I) is also applicable to Formula (Ia), etc.
- For all of the formulas herein having an R₁ substituent, R₁ is suitably an aryl,
- 35 aryl C₂₋₁₀ alkyl, heteroaryl, heteroaryl C₂₋₁₀ alkyl; aryl C₂₋₁₀ alkenyl, arylC₂₋₁₀ alkynyl, heteroaryl C₂₋₁₀ alkenyl, heteroaryl C₂₋₁₀ alkynyl, C₂₋₁₀ alkenyl, or C₂₋₁₀ alkynyl moiety, which moieties may be optionally substituted.

In one embodiment R_1 is an optionally substituted aryl, or an optionally substituted heteroaryl ring. Preferably, R_1 is an optionally substituted aryl, more preferably an optionally substituted phenyl.

R_1 may be substituted one or more times, suitably 1 to 4 times, independently at each occurrence by halogen, C_{1-4} alkyl, halo-substituted- C_{1-4} alkyl, cyano, nitro, aryl, aryl- C_{1-4} alkyl, $(CR_{10}R_{20})_vNR_dR_d'$, $(CR_{10}R_{20})_vC(O)R_{12}$, SR_5 , $S(O)R_5$, $S(O)_2R_5$, $(CR_{10}R_{20})_vOR_{13}$, $(CR_{10}R_{20})_vC(Z)NR_4R_{14}$, $(CR_{10}R_{20})_vC(Z)OR_8$, $(CR_{10}R_{20})_vCOR_a$, $(CR_{10}R_{20})_vC(O)H$, $ZC(Z)R_{11}$, $N(R_{10}')C(Z)R_{11}$, $N(R_{10}')S(O)_2R_7$, $C(Z)N(R_{10}')(CR_{10}R_{20})_vR_b$, $C(Z)O(CR_{10}R_{20})_vR_b$, $N(R_{10}')C(Z)(CR_{10}R_{20})_vR_b$; $N(R_{10}')C(Z)N(R_{10}')(CR_{10}R_{20})_vR_b$; or $N(R_{10}')OC(Z)(CR_{10}R_{20})_vR_b$.

Suitably, R_b is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl- C_{1-10} alkyl, aryl, aryl- C_{1-10} alkyl, heteroaryl, heteroaryl- C_{1-10} alkyl, heterocyclic, or a heterocyclyl- C_{1-10} alkyl moiety, which moieties excluding hydrogen, may all be optionally substituted.

In one embodiment of the invention when the R_1 moiety is phenyl, and the phenyl ring is substituted by the moiety (R_1'') wherein R_1'' is selected from $C(Z)N(R_{10}')(CR_{10}R_{20})_vR_b$, $C(Z)O(CR_{10}R_{20})_vR_b$, $N(R_{10}')C(Z)(CR_{10}R_{20})_vR_b$, $N(R_{10}')C(Z)N(R_{10}')(CR_{10}R_{20})_vR_b$, or $N(R_{10}')OC(Z)(CR_{10}R_{20})_vR_b$. The phenyl ring may also be additionally substituted by the substituent $(R_1')_g$, wherein g is 0 or an integer having a value of 1, 2, 3, or 4. In one embodiment of the invention, g is 0, 1 or 2. When the R_1 moiety is substituted by R_1'' then these substituents are preferably in the 3- or 4-position of the phenyl ring.

Suitably, the R_1' moiety is independently selected at each occurrence from halogen, C_{1-4} alkyl, halo-substituted- C_{1-4} alkyl, cyano, nitro, $(CR_{10}R_{20})_vNR_dR_d'$, $(CR_{10}R_{20})_vC(O)R_{12}$, SR_5 , $S(O)R_5$, $S(O)_2R_5$, or $(CR_{10}R_{20})_vOR_{13}$.

In one embodiment of the invention, R_1 is substituted by $C(Z)N(R_{10}')(CR_{10}R_{20})_vR_b$, or $N(R_{10}')C(Z)(CR_{10}R_{20})_vR_b$, and R_1' is independently selected at each occurrence from C_{1-4} alkyl, such as methyl, or halogen, such as fluorine or chlorine or bromine, or halo-substituted- C_{1-4} alkyl, such as CF_3 . In a further embodiment R_1 is an aryl moiety, preferably a phenyl ring.

In another embodiment of the invention R_1 is substituted by $C(Z)N(R_{10}')(CR_{10}R_{20})_vR_b$, and R_1' is independently selected at each occurrence from C_{1-4} alkyl, such as methyl, or halogen, such as fluorine, chlorine or bromine.

In one embodiment, R_1' is independently selected at each occurrence from halogen, C_{1-4} alkyl, or halo-substituted- C_{1-4} alkyl. In another embodiment, R_1' is

independently selected at each occurrence from fluorine, chlorine, methyl, or CF₃. In a further embodiment R₁ is an aryl moiety, preferably a phenyl ring.

In one embodiment, R₁ is an aryl moiety, preferably a phenyl ring, optionally substituted one or more times by halogen, C₁₋₄ alkyl, or halo-substituted-C₁₋₄ alkyl.

- 5 More preferably, the phenyl ring is substituted in the 2, 4, or 6-position, or di-substituted in the 2,4- position, such as 2-fluoro, 3-fluoro, 4-fluoro, 2,4-difluoro, or 2-methyl-4-fluoro; or tri-substituted in the 2,4,6-position such as 2,4,6-trifluoro.

- In another embodiment R₁ is an aryl moiety, preferably a phenyl ring, optionally substituted one or more times by halogen, C₁₋₄ alkyl, halo-substituted-
 10 C₁₋₄ alkyl, SR₅, S(O)R₅, S(O)₂R₅, (CR₁₀R₂₀)_vOR₁₃, (CR₁₀R₂₀)_vC(Z)NR₄R₁₄, C(Z)N(R₁₀') (CR₁₀R₂₀)_vR_b, and (CR₁₀R₂₀)_vC(Z)OR₈. In one embodiment, R₈ is hydrogen, or C₁₋₄ alkyl, R₁₃ is hydrogen, or C₁₋₄ alkyl, such as methyl; R_b is suitably hydrogen, C₁₋₄ alkyl, aryl, or heteroaryl. Preferably, R₁ is a phenyl substituted by 2-methoxy, 3-methoxy, 4-methoxy, 2-chloro, 3-chloro, 4-chloro, 2-
 15 fluoro, 3- fluoro, 4-fluoro, ,4-difluoro, 2,4,6-trifluoro, 3,4-difluoro, 3,5-difluoro, 2-methyl-4-fluoro, 2-methyl-4-chloro, 2-methylsulfanyl, 3-methylsulfanyl, 4-methylsulfanyl, 2-phenyl, 3-phenyl, 4-phenyl, 2-methyl, 3-methyl, 4-methyl, 3-fluoro-4-phenyl, 2-hydroxy, 3-hydroxy, 4-hydroxy, 2-methylsulfonyl, 3-methylsulfonyl, 4-methylsulfonyl, 3-N-cyclopropylamide, 2-methyl-3-fluoro-5-N-cyclopropylamide, 2-
 20 C(O)OH, 3-C(O)OH, 4-C(O)OH, 2-methyl-5-C(O)OH, 2-methyl-3-C(O)OH, 2-methyl-4-C(O)OH, 2-methyl-3-F-5-C(O)OH, 4-F-phenyl-1-amide, 2-ethyl-5-C(O)OH, 2-ethyl-3-C(O)OH, 2-ethyl-4-C(O)OH, 2-methyl-5-dimethylamide, 2-methyl-4-dimethylamide, 5-dimethylamide, and 4-dimethylamide.

- 25 A preferred R₁ moiety is 4-methyl-*N*-1,3-thiazol-2-ylbenzamide, *N*-(4-fluorophenyl)-4-methylbenzamide, 4-methyl-*N*-propylbenzamide, 4-methyl-*N*-isopropylbenzamide, 2-methyl-4-fluorophenyl, or 2-methyl-3-fluorophenyl, and 2-methyl-4-chlorophenyl.

- Suitably, when R₁ is a heteroaryl moiety, the ring is not attached to the
 30 pharmacophore via one of the heteroatoms, such as nitrogen to form a charged ring. For instance, a pyridinyl ring would be attached through a carbon atom to yield a 2-, 3- or 4-pyridyl moiety, which is optionally substituted.

- If R₁ is substituted by C(Z)N(R₁₀') (CR₁₀R₂₀)_vR_b, C(Z)O(CR₁₀R₂₀)_vR_b, or N(R₁₀')C(Z)(CR₁₀R₂₀)_vR_b; N(R₁₀')C(Z)N(R₁₀') (CR₁₀R₂₀)_vR_b;
 35 N(R₁₀')OC(Z)(CR₁₀R₂₀)_vR_b; it is preferably in the 4 or 5 position of the ring. If the ring is additionally substituted by R₁', and R₁ is a phenyl ring, then the additional substituents are present in the ortho position, if a second R₁' moiety is also

substituted on the ring, then preferably, this second R₁' substitution is not in the other ortho position.

Suitably, R_a' is C₁₋₄ alkyl, halo-substituted C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₇ cycloalkyl, C₅₋₇ cycloalkenyl, aryl, arylC₁₋₄ alkyl, heteroaryl, heteroarylC₁₋₄ alkyl, heterocyclyl, heterocyclylC₁₋₄ alkyl, (CR₁₀R₂₀)_vOR₇, (CR₁₀R₂₀)_vS(O)_mR₇, (CR₁₀R₂₀)_vN(R₁₀')S(O)₂R₇, or (CR₁₀R₂₀)_vNR₄R₁₄; and wherein the aryl, arylalkyl, heteroaryl, heteroaryl alkyl may be optionally substituted.

Suitably, R_d and R_d' are each independently selected from hydrogen, C₁₋₄ alkyl, C₃₋₅ cycloalkyl, C₃₋₅ cycloalkylC₁₋₄alkyl, or the R_d and R_d' together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 5 to 6 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR₉', and wherein the R_d and R_d' moieties which are C₁₋₄ alkyl, C₃₋₆cycloalkyl, C₃₋₆cycloalkylC₁₋₄ alkyl, and the R₄ and R₁₄ cyclized ring are optionally substituted, 1 to 4 times, independently by halogen; halosubstituted C₁₋₄ alkyl; hydroxy; hydroxy substituted C₁₋₄alkyl; C₁₋₄ alkoxy; halosubstituted C₁₋₄ alkoxy; S(O)_mR_f; C(O)R_j; C(O)OR_j; C(O)NR₄'R₁₄', NR₄'C(O)C₁₋₄alkyl; S(O)₂NR₄'R₁₄'C₁₋₄ alkyl; NR₄'R₁₄'S(O)₂C₁₋₄ alkyl; or NR₄'R₁₄'.

Suitably R₉' is independently selected at each occurrence from hydrogen, or C₁₋₄ alkyl.

Suitably, Z is independently at each occurrence selected from oxygen or sulfur.

Suitably, m is independently selected at each occurrence from 0 or an integer having a value of 1 or 2.

Suitably, v is 0 or an integer having a value of 1 to 2.

Suitably, v' is 0 or an integer having a value of 1 or 2.

Suitably, R₁₀ and R₂₀ are independently selected at each occurrence from hydrogen or C₁₋₄ alkyl.

Suitably, R₁₀' is independently selected at each occurrence from hydrogen or C₁₋₄ alkyl.

Suitably, R₁₁ is independently selected at each occurrence from hydrogen, or C₁₋₄ alkyl.

Suitably, R₁₂ is independently selected at each occurrence from hydrogen, C₁₋₄ alkyl, halo-substituted C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl C₁₋₄ alkyl, C₅₋₇ cycloalkenyl, C₅₋₇cycloalkenyl C₁₋₄ alkyl, aryl, arylC₁₋₄ alkyl, heteroaryl, heteroarylC₁₋₄ alkyl, heterocyclyl, or heterocyclylC₁₋₄ alkyl, and wherein these moieties, excluding hydrogen, may be optionally substituted.

- Suitably, R₁₃ is independently selected at each occurrence from hydrogen, C₁₋₄ alkyl, halo-substituted C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₇ cycloalkyl, C₃₋₇cycloalkylC₁₋₄ alkyl, C₅₋₇ cycloalkenyl, C₅₋₇cycloalkenyl C₁₋₄ alkyl, aryl, arylC₁₋₄ alkyl, heteroaryl, heteroarylC₁₋₄ alkyl, heterocyclyl, or a heterocyclylC₁₋₄ alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted and wherein these moieties, excluding hydrogen, may be optionally substituted 1 to 4 times by halogen; halosubstituted C₁₋₄ alkyl; C₁₋₄ alkyl; hydroxy; hydroxy substituted C₁₋₄alkyl; C₁₋₄alkoxy; halosubstituted C₁₋₄ alkoxy; S(O)_mC₁₋₄ alkyl; -C(O), C(O)C₁₋₄ alkyl; or NR_{21'}R_{31'}.
- Suitably, R_{21'} and R_{31'} are each independently selected from hydrogen or C₁₋₄ alkyl, or R_{21'} and R_{31'} together with the nitrogen to which they are attached cyclize to form a 5 to 7 membered ring which optionally contains an additional heteroatom selected from oxygen, nitrogen or sulfur.
- The R_b moieties, excluding hydrogen, may be optionally substituted, one or more times, preferably 1 to 4 times independently at each occurrence by halogen, such as fluorine, chlorine, bromine or iodine; hydroxy; hydroxy substituted C₁₋₁₀alkyl; C₁₋₁₀ alkoxy, such as methoxy or ethoxy; halosubstituted C₁₋₁₀ alkoxy; OR₈, such as methoxy, ethoxy or phenoxy; SR₅, S(O)R₅, S(O)₂R₅, such as methyl thio, methylsulfinyl or methyl sulfonyl; C(O)R_j; C(O)OR_j; C(O)NR_{4''}R_{14''}; cyano; nitro; NR₁₅R₂₅; -Z'-(CR₁₀R₂₀)_s-Z'; C₁₋₁₀alkyl; such as methyl, ethyl, propyl, isopropyl, t-butyl, n-butyl, etc.; C₃₋₇cycloalkyl or a C₃₋₇cycloalkyl C₁₋₁₀ alkyl group, such as cyclopropyl, or cyclopropyl methyl, or cyclopropyl ethyl, etc.; halosubstituted C₁₋₁₀ alkyl, such CF₂CF₂H, CH₂CF₃, or CF₃; an optionally substituted aryl, such as phenyl, or an optionally substituted aryl C₁₋₁₀alkyl, such as benzyl or phenethyl; an optionally substituted heterocyclic or heterocyclic C₁₋₁₀alkyl, or an optionally substituted heteroaryl or heteroaryl C₁₋₁₀alkyl, and wherein these aryl, heteroaryl, and heterocyclic containing moieties may also be substituted one to two times by halogen, hydroxy, hydroxy substituted alkyl, C₁₋₁₀ alkoxy, S(O)_malkyl, amino, mono & di-substituted C₁₋₄ alkyl amino, C₁₋₄ alkyl, or CF₃.
- Suitably, when R_b is an optionally substituted C₁₋₁₀alkyl, the moiety includes but is not limited to a methyl, ethyl, n-propyl, isopropyl, t-butyl, n-butyl, isobutyl, 1,2-dimethylpropyl, 2,2-dimethylpropyl, heptyl, 2-methylpropyl; a halosubstituted alkyl, such as 2,2,2-trifluoroethyl, trifluoromethyl, 2-fluoroethyl; a cyano substituted alkyl, such as cyanomethyl, cyanoethyl; an alkoxy, thio or hydroxy substituted alkyl, such as 2-methoxy-ethyl, 2-hydroxy propyl or serinol, or an ethylthioethyl.

In an alternative embodiment, when R_b is an optionally substituted C_{1-10} alkyl the moiety is a methyl, ethyl, n-propyl, isopropyl, t-butyl, n-butyl, or 2,2-dimethylpropyl or 2-hydroxy propyl group.

Suitably, when R_b is an optionally substituted heteroaryl, heteroaryl alkyl
 5 they are as defined in the definition section, and include but are not limited, to furyl, pyranyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, imidazolyl, pyrazolyl, oxadiazolyl, oxathiadiazolyl, triazolyl, tetrazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, and uracil, indolyl, isoindolyl, indazolyl, indoliziny, azaindolyl, benzoxazolyl, benzimidazolyl, benzothiazolyl,
 10 benzofuranyl, benzothiophenyl, quinolyl, isoquinolyl, quinazolinyl, quinoxaliny, naphthyridinyl, cinnoliny, purinyl, and phthalazinyl.

Suitably, when R_b is an optionally substituted heterocyclic, heterocyclic alkyl, they are as defined in the definition section,

In one embodiment of the invention, when R_b is an optionally substituted
 15 heteroaryl, heteroaryl alkyl, heterocyclic or heterocyclic alkyl, the moiety is a 1,3-thiazol-2-yl, 5-methyl-1,3-thiazol-2-yl, isoquinoline, 3-thiophene, indol-5yl, pyridin-3-yl, pyridine-4-yl, indazolyl, benzothiazolyl, 2-methyl-1,3-benzothiazol-5-yl, pyrazol-3-yl, 4-morpholino, 2-furanyl, 2-furanylmethyl, 2-thienyl, 2-thienylmethyl, tetrahydro-2H-pyran-4yl, tetrahydro-2H-pyran-4yl methyl, tetrahydro-2-furanyl, or
 20 tetrahydro-2-furanylmethyl, 1*H*-imidazol-4-yl or 1*H*-imidazol-4-ylethyl.

In an alternative embodiment, when R_b is an optionally substituted heteroaryl the moiety is a 1,3-thiazol-2-yl or 5-methyl-1,3-thiazol-2-yl, isoquinolinyl, thiophene, pyridinyl, indazolyl, benzothiazolyl, e.g. 2-methyl-1,3-benzothiazol-5-yl.

25 In another embodiment, the heteroaryl ring is an optionally substituted thiazolyl, pyridyl, or thiophene ring.

Suitably, when R_b is an optionally substituted aryl or arylalkyl moiety, the aryl containing is unsubstituted or substituted independently at each occurrence one or more times by halogen, alkyl, cyano, OR_8 , SR_5 , $S(O)_2R_5$, $C(O)R_j$, $C(O)OR_j$,
 30 $-Z'-(CR_{10}R_{20})_s-Z'$, halosubstituted C_{1-10} alkyl, or an optionally substituted aryl.

In one embodiment, R_b is a phenyl, or naphthylene, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,3-difluorophenyl, 2,4-difluorophenyl, 3,4-difluorophenyl, 3,5-difluorophenyl, 3-chlorophenyl, 4-chlorophenyl, 3-chloro-4-fluorophenyl, 2-methyl phenyl, 3-methylphenyl, 4-methylphenyl, 6-methyl phenyl,
 35 2-methyl phenyl, 3-amino phenyl, 3,4-dimethyl phenyl, 4-methyl-3-fluorophenyl, 4-trifluorophenyl, 4-ethoxyphenyl, 4-methoxyphenyl, 3-cyanophenyl, 4-cyanophenyl, 4-thiomethylphenyl, 4-acetylphenyl, 4-dimethylaminophenyl, benzyl, phenethyl,

phenylpropyl, 2,3-difluoro-benzyl, 3,5-difluoro-benzyl, biphenyl, 4'-fluorobiphenyl, 4-sulfonamido-2-methylphenyl, or 3-phenyloxyphenyl, 4-phenyloxyphenyl, 4-(1-piperidinylsulfonyl)-phenyl, or 3-(aminocarbonyl)phenyl.

In another embodiment, R_b is a phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,4-difluorophenyl, 3,4-difluorophenyl, 3,5-difluorophenyl, 3-chlorophenyl, 4-chlorophenyl, 3-chloro-4-fluorophenyl, 4-methyl-3-fluorophenyl, 4-trifluorophenyl, 2-methylphenyl, 3-methylphenyl, 4-ethoxyphenyl, 4-methoxyphenyl, 3-cyanophenyl, 4-cyanophenyl, 4-thiomethylphenyl, 4-acetylphenyl, 4-dimethylaminophenyl, biphenyl, 4'-fluorobiphenyl, 4-sulfonamido-2-methylphenyl, 3-phenyloxyphenyl, benzyl, or phenethyl.

Suitably, when R_b is an optionally substituted cycloalkyl or cycloalkyl alkyl moiety, the moiety is a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, or a cyclopentylmethyl. In another embodiment, R_b is a cyclopropyl or cyclopropylmethyl group.

In another embodiment, R_b is hydrogen, or an optionally substituted alkyl.

In another embodiment, R_b is C_{1-10} alkyl, heteroaryl, or aryl, all optionally substituted.

The moiety $-Z'-(CR_{10}R_{20})_s-Z'$ forms a cyclic ring, such as a dioxalane ring.

Suitably Z' is independently selected at each occurrence from oxygen, or sulfur.

Suitably, s is independently selected at each occurrence from 0 or an integer having a value of 1, 2, or 3.

For each of the integer variables where appropriate, e.g. n , n' , m , q' , s , t , or v' , etc. they are independently chosen at each occurrence.

Suitably, R_5 is independently selected at each occurrence from hydrogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl or $NR_{4'}R_{14'}$, excluding the moieties SR_5 being $SNR_{4'}R_{14'}$, $S(O)_2R_5$ being SO_2H and $S(O)R_5$ being SOH .

Suitably, R_f is hydrogen, C_{1-10} alkyl, aryl, aryl C_{1-10} alkyl, heteroaryl, heteroaryl C_{1-10} alkyl, heterocyclic, or a heterocyclic C_{1-10} alkyl moiety, and wherein these moieties, excluding hydrogen, may be optionally substituted.

Suitably, R_j is C_{1-10} alkyl, aryl, aryl C_{1-10} alkyl, heteroaryl, heteroaryl C_{1-10} alkyl, heterocyclic, or a heterocyclic C_{1-10} alkyl moiety.

Suitably, R_8 is independently selected at each occurrence from hydrogen, C_{1-4} alkyl, halo-substituted C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl C_{1-4} alkyl, C_{5-7} cycloalkenyl, C_{5-7} cycloalkenyl C_{1-4} alkyl, aryl, aryl C_{1-4} alkyl, heteroaryl, heteroaryl C_{1-4} alkyl, heterocyclyl, or a heterocyclyl C_{1-4} alkyl moiety, and wherein these moieties, excluding hydrogen, may be optionally

substituted independently at each occurrence, 1 to 4 times, by halogen;
 halosubstituted C₁₋₄ alkyl; C₁₋₄ alkyl; C₃₋₅cycloalkyl; C₃₋₅cycloalkyl C₁₋₄alkyl;
 halosubstituted C₁₋₄ alkyl; hydroxy; hydroxy substituted C₁₋₄alkyl; C₁₋₄alkoxy;
 halosubstituted C₁₋₄ alkoxy; S(O)_mC₁₋₄ alkyl; -C(O), C(O)C₁₋₄ alkyl; NR₂₁'R₃₁';
 5 or an aryl or aryl C₁₋₄ alkyl, and wherein these aryl containing moieties may also be
 substituted one to two times independently at each occurrence, by halogen, hydroxy,
 hydroxy substituted alkyl, C₁₋₄ alkoxy, S(O)_mC₁₋₄alkyl, amino, mono & di-
 substituted C₁₋₄ alkylamino, C₁₋₄ alkyl, or CF₃.

Suitably, R₁₅ and R₂₅ are each independently selected at each occurrence from
 10 hydrogen, C₁₋₄ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkylC₁₋₄alkyl, aryl, or aryl-C₁₋₄
 alkyl, heteroaryl or heteroaryl C₁₋₄ alkyl moiety, and wherein these moieties, excluding
 hydrogen may be optionally substituted; or R₁₅ and R₂₅ together with the nitrogen
 which they are attached form an optionally substituted heterocyclic ring of 4 to 7
 members, which ring optionally contains an additional heteroatom selected from oxygen,
 15 sulfur or NR₉; and wherein these moieties are optionally substituted 1 to 4 times,
 independently at each occurrence by halogen; hydroxy; hydroxy substituted C₁₋₁₀alkyl;
 C₁₋₁₀ alkoxy; halosubstituted C₁₋₁₀ alkoxy; SR₅, S(O)R₅, S(O)₂R₅; C(O)R_j;
 C(O)OR_j; C(O)NR₄'R₁₄'; NR₄'C(O)C₁₋₁₀alkyl; NR₄'C(O)aryl; NR₄'R₁₄'; cyano; nitro;
 C₁₋₁₀ alkyl; C₃₋₇cycloalkyl; C₃₋₇cycloalkyl C₁₋₁₀ alkyl; halosubstituted C₁₋₁₀ alkyl;
 20 aryl, arylC₁₋₄ alkyl, heteroaryl, or heteroC₁₋₄ alkyl, heterocyclic and heterocyclicC₁₋₄
 alkyl and wherein these aryl, heterocyclic and heteroaryl containing moieties may also be
 substituted one to two times independently at each occurrence by halogen, C₁₋₄ alkyl,
 hydroxy, hydroxy substituted C₁₋₄ alkyl, C₁₋₁₀ alkoxy, S(O)_malkyl, amino, mono & di-
 substituted C₁₋₄ alkyl amino, C₁₋₄ alkyl, or CF₃.

Suitably, R₄ and R₁₄ are each independently selected at each occurrence from
 25 hydrogen, C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkylC₁₋₄alkyl, aryl, aryl-C₁₋₄
 alkyl, heterocyclic, heterocyclic.C₁₋₄ alkyl, heteroaryl or heteroaryl C₁₋₄ alkyl; or the
 R₄ and R₁₄ together with the nitrogen which they are attached form an unsubstituted
 or substituted heterocyclic ring of 4 to 7 members, which ring optionally contains an
 30 additional heteroatom selected from oxygen, sulfur or nitrogen; and wherein the
 C₁₋₁₀ alkyl, C₃₋₇cycloalkyl, C₃₋₇cycloalkylC₁₋₄ alkyl, aryl, aryl-C₁₋₄ alkyl,
 heteroaryl and heteroaryl C₁₋₄ alkyl moieties, and the R₄ and R₁₄ cyclized ring are
 optionally substituted, 1 to 4 times, independently at each occurrence, by halogen;
 hydroxy; hydroxy substituted C₁₋₁₀alkyl; C₁₋₁₀ alkoxy; halosubstituted C₁₋₁₀
 35 alkoxy; C₁₋₁₀ alkyl; halosubstituted C₁₋₁₀ alkyl; SR₅; S(O)R₅; S(O)₂R₅; C(O)R_j;
 C(O)OR_j; C(O)NR₄'R₁₄'; (CR₁₀R₂₀)_nN(R₁₀')C(Z)OR₇;
 (CR₁₀R₂₀)_nN(R₁₀')C(Z)NR_dR_d'; NR₄'C(O)C₁₋₁₀alkyl; NR₄'C(O)aryl; NR₄'R₁₄';

cyano; nitro; C₃₋₇cycloalkyl; C₃₋₇cycloalkyl C₁₋₁₀ alkyl; C₁₋₁₀ alkyl substituted one or more times by an optionally substituted aryl; an unsubstituted or substituted aryl, or arylC₁₋₄ alkyl; an unsubstituted or substituted heteroaryl, or heteroaryl C₁₋₄ alkyl; an unsubstituted or substituted heterocyclic, or heterocyclic C₁₋₄ alkyl, and

- 5 wherein these aryl, heterocyclic and heteroaryl containing moieties are substituted one to two times independently at each occurrence by halogen; C₁₋₄ alkyl, hydroxy; hydroxy substituted C₁₋₄ alkyl; C₁₋₄ alkoxy; S(O)_malkyl; amino, mono & di-substituted C₁₋₄ alkyl amino, or CF₃.

- Suitably, when R₄ and R₁₄ together with the nitrogen cyclize to form an
10 optionally substituted ring, such as described above, such rings include, but are not limited to pyrrolidine, piperidine, piperazine, diazepine, azepine, morpholine, and thiomorpholine (including oxidizing the sulfur).

- Suitably, R_{4'} and R_{14'} are each independently selected at each occurrence from hydrogen or C₁₋₄ alkyl, or R_{4'} and R_{14'} can cyclize together with the nitrogen to
15 which they are attached to form an optionally substituted 5 to 7 membered ring which optionally contains an additional heteroatom from oxygen, sulfur or NR_{9'}. Suitably, when R_{4'} and R_{14'} cyclize to form an optionally substituted ring, such rings include, but are not limited to pyrrolidine, piperidine, piperazine, morpholine, and thiomorpholine (including oxidizing the sulfur).

- 20 Suitably, R_{4''} and R_{14''} are each independently selected from hydrogen or C₁₋₁₀ alkyl, or R_{4''} and R_{14''} can cyclize together with the nitrogen to which they are attached to form an optionally substituted 5 to 7 membered ring which optionally contains an additional heteroatom selected from oxygen, sulfur or NR_{9'}. Suitably, when R_{4''} and R_{14''} cyclize to form an optionally substituted ring, such rings include,
25 but are not limited to pyrrolidine, piperidine, piperazine, diazepine, azepine, morpholine, and thiomorpholine (including oxidizing the sulfur).

- Suitably, R₆ is independently selected from hydrogen, C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, heterocyclyl, heterocyclyl C₁₋₁₀alkyl, aryl, arylC₁₋₁₀ alkyl, heteroaryl or a heteroarylC₁₋₁₀ alkyl moiety, and wherein these moieties, excluding hydrogen may
30 be optionally substituted independently, one or more times, suitably 1 to 2 times, by halogen; hydroxy; hydroxy substituted C₁₋₁₀alkyl; C₁₋₁₀ alkoxy; halosubstituted C₁₋₁₀ alkoxy; S(O)_m alkyl; C(O); NR_{4'}R_{14'}; C₁₋₁₀ alkyl; C₃₋₇cycloalkyl; C₃₋₇cycloalkyl C₁₋₁₀ alkyl; halosubstituted C₁₋₁₀ alkyl; an unsubstituted aryl or arylalkyl, or an aryl or arylalkyl substituted one or two times by halogen, hydroxy,
35 hydroxy substituted alkyl, C₁₋₁₀ alkoxy, S(O)_malkyl, amino, mono & di-substituted C₁₋₄ alkyl amino, C₁₋₄ alkyl, or CF₃.

Suitably, R₉ is hydrogen, C(Z)R₆, optionally substituted C₁₋₁₀ alkyl, optionally substituted aryl or optionally substituted aryl-C₁₋₄ alkyl. The alkyl, aryl and arylalkyl moieties may be optionally substituted 1 or 2 times, independently by halogen; hydroxy; hydroxy substituted C₁₋₁₀alkyl; C₁₋₁₀ alkoxy; halosubstituted C₁₋₁₀ alkoxy; S(O)_m alkyl; -C(O); NR₄R₁₄; C₁₋₁₀ alkyl, C₃₋₇cycloalkyl; C₃₋₇cycloalkyl C₁₋₁₀ alkyl; halosubstituted C₁₋₁₀ alkyl; an aryl or aryl C₁₋₄ alkyl, and wherein these aryl containing moieties may also be substituted one or two times independently by halogen, hydroxy, hydroxy substituted alkyl, C₁₋₁₀ alkoxy, S(O)_mC₁₋₄ alkyl, amino, mono & di-substituted C₁₋₄ alkyl amino, C₁₋₄ alkyl, or CF₃.

Suitably, R₃ is a C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl C₁₋₁₀ alkyl, aryl, arylC₁₋₁₀ alkyl, heteroaryl, heteroarylC₁₋₁₀ alkyl, heterocyclic, or heterocyclylC₁₋₁₀ alkyl moiety, which moieties may be optionally substituted 1 to 4 times, independently at each occurrence by hydrogen, halogen, nitro, C₁₋₁₀ alkyl, halo-substituted C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀alkynyl, C₃₋₇cycloalkyl, C₃₋₇cycloalkylC₁₋₁₀ alkyl, C₅₋₇cycloalkenyl, C₅₋₇cycloalkenylC₁₋₁₀ alkyl, (CR₁₀R₂₀)_nOR₆, (CR₁₀R₂₀)_nSH, (CR₁₀R₂₀)_nS(O)_mR₇, (CR₁₀R₂₀)_nN(R₁₀')S(O)₂R₇, (CR₁₀R₂₀)_nNR₁₆R₂₆, (CR₁₀R₂₀)_nCN, (CR₁₀R₂₀)_nS(O)₂NR₁₆R₂₆, (CR₁₀R₂₀)_nC(Z)R₆, (CR₁₀R₂₀)_nOC(Z)R₆, (CR₁₀R₂₀)_nC(Z)OR₆, (CR₁₀R₂₀)_nC(Z)NR₁₆R₂₆, (CR₁₀R₂₀)_nN(R₁₀')C(Z)R₆, (CR₁₀R₂₀)_nN(R₁₀')C(=N(R₁₀'))NR₁₆R₂₆, (CR₁₀R₂₀)_nOC(Z)NR₁₆R₂₆, (CR₁₀R₂₀)_nN(R₁₀')C(Z)NR₁₆R₂₆, or (CR₁₀R₂₀)_nN(R₁₀')C(Z)OR₇.

In one embodiment, the R₃ moieties are optionally substituted 1 to 4 times, independently at each occurrence by halogen, nitro, C₁₋₄ alkyl, halo-substituted C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄alkynyl, C₃₋₆cycloalkyl, C₃₋₆cycloalkylC₁₋₄ alkyl, C₅₋₆cycloalkenyl, C₅₋₆cycloalkenylC₁₋₄ alkyl, (CR₁₀R₂₀)_nOR₆, (CR₁₀R₂₀)_nSH, (CR₁₀R₂₀)_nS(O)_mR₇, (CR₁₀R₂₀)_nNHS(O)₂R₇, (CR₁₀R₂₀)_nS(O)₂NR₁₆R₂₆, (CR₁₀R₂₀)_nNR₁₆R₂₆, (CR₁₀R₂₀)_nCN, (CR₁₀R₂₀)_nC(Z)R₆, (CR₁₀R₂₀)_nOC(Z)R₆, (CR₁₀R₂₀)_nC(Z)OR₆, (CR₁₀R₂₀)_nN(R₁₀')C(Z)R₆, or (CR₁₀R₂₀)_nC(Z)NR₁₆R₂₆.

In one embodiment the R₃ moieties are optionally substituted independently, one or more times, suitably 1 to 4 times, independently at each occurrence by halogen, C₁₋₁₀alkyl, (CR₁₀R₂₀)_nOR₆, cyano, nitro, (CR₁₀R₂₀)_nNR₁₆R₂₆, or halosubstituted C₁₋₁₀alkyl. Further to this embodiment, R₃ is a phenyl ring, optionally substituted independently, one or more times, suitably 1 to 4 times, independently at each occurrence by halogen, C₁₋₁₀ alkyl, hydroxy, C₁₋₁₀ alkoxy, cyano, nitro, amino, or halosubstituted C₁₋₁₀ alkyl. In another embodiment, the R₃

substituents are selected independently from halogen, such as fluorine, chlorine, bromine or iodine, or C₁₋₁₀ alkyl, such as methyl.

In one embodiment the R₃ moieties are an optionally substituted C₁₋₁₀ alkyl, optionally substituted C₃₋₇cycloalkyl, optionally substituted C₃₋₇cycloalkylalkyl, or optionally substituted aryl. In another embodiment, the R₃ moiety is an optionally substituted C₁₋₁₀ alkyl, or an optionally substituted aryl. In another embodiment, R₃ is an optionally substituted phenyl.

Suitably, in one embodiment when R₃ is an aryl moiety, it is an optionally substituted phenyl ring. The phenyl is optionally substituted one or more times, independently at each occurrence, suitably 1 to 4 times by halogen, C₁₋₄ alkyl, or halo-substituted-C₁₋₄ alkyl. The phenyl ring may be substituted in the 2, 4, or 6-position, or di-substituted in the 2,4- position or 2,6-position, such as 2-fluoro, 4-fluoro, 2,4-difluoro, 2,6-difluoro, or 2-methyl-4-fluoro; or tri-substituted in the 2,4,6-position, such as 2,4,6-trifluoro.

In one embodiment of the invention, the R₃ optional substituents are independently selected from halogen, alkyl, hydroxy, alkoxy, cyano, nitro, amino, or halosubstituted alkyl. In another embodiment, the optional substituents are independently selected from halogen, or alkyl.

Suitably, R₇ is C₁₋₆alkyl, aryl, arylC₁₋₆alkyl, heterocyclic, heterocyclylC₁₋₆alkyl, heteroaryl, or heteroarylC₁₋₆alkyl; and wherein each of these moieties may be optionally substituted one or two times independently, by halogen; hydroxy; hydroxy substituted C₁₋₁₀alkyl; C₁₋₁₀ alkoxy; halosubstituted C₁₋₁₀ alkoxy; S(O)_m alkyl; C(O); NR₄R₁₄; C₁₋₁₀ alkyl; C₃₋₇cycloalkyl; C₃₋₇cycloalkylC₁₋₁₀ alkyl; halosubstituted C₁₋₁₀ alkyl; an aryl or arylalkyl moiety, and wherein these aryl containing moieties may also be substituted one to two times by halogen, hydroxy, hydroxy substituted alkyl, C₁₋₁₀ alkoxy, S(O)_malkyl, amino, mono & di-substituted C₁₋₄ alkyl amino, C₁₋₄ alkyl, or CF₃.

Suitably, R₁₆ and R₂₆ are each independently selected from hydrogen, or C₁₋₄ alkyl; or the R₁₆ and R₂₆ together with the nitrogen which they are attached form an unsubstituted or substituted heterocyclic ring of 4 to 7 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR₉.

Suitably, n is 0 or an integer having a value of 1 to 10, and is independently selected at each occurrence.

Suitably, X is R₂, OR₂', S(O)_mR₂', (CH₂)_n'N(R₁₁)S(O)_mR₂', (CH₂)_n'N(R₁₁)C(O)R₂', (CH₂)_n'NR₄R₁₄, (CH₂)_n'N(R₂')R₂'', or N(R₁₀')R_hNH-C(=N-CN)NR_qR_q'.

Suitably, n' is independently selected at each occurrence from 0 or an integer having a value of 1 to 10;

Suitably, R_h is selected from an optionally substituted C_{1-10} alkyl, $-CH_2CH_2-O-$, $-CH_2-CH_2-$, $-CH_2-O-CH_2-$, $-CH_2-C(O)N(R_{10'})CH_2-CH_2-$,
 5 $-CH_2-N(R_{10'})C(O)CH_2-$, $-CH_2-CH(OR_{10'})-CH_2-$, $-CH_2-C(O)O-CH_2-CH_2-$, or $-CH_2-CH_2-O-C(O)CH_2-$.

Suitably, R_q and $R_{q'}$ are independently selected from hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl C_{1-10} alkyl, C_{5-7} cycloalkenyl, C_{5-7} cycloalkenyl- C_{1-10} alkyl, aryl, aryl C_{1-10} alkyl, heteroaryl, heteroaryl C_{1-10} alkyl, heterocyclic, or a
 10 heterocyclyl C_{1-10} alkyl moiety, wherein all of the moieties are optionally substituted, or R_q and $R_{q'}$ together with the nitrogen to which they are attached form a 5 to 7 membered optionally substituted ring, which ring may contain an additional heteroatom selected from oxygen, nitrogen or sulphur.

Suitably, X_1 is $N(R_{10'})$, O, $S(O)_m$, or $CR_{10}R_{20}$. In one embodiment of the
 15 invention, X_1 is $N(R_{10'})$, or O.

Suitably, R_2 is independently selected from hydrogen, optionally substituted C_{1-10} alkyl, optionally substituted C_{3-7} cycloalkyl, optionally substituted C_{3-7} cycloalkylalkyl, optionally substituted aryl, optionally substituted aryl C_{1-10} alkyl, optionally substituted heteroaryl, optionally substituted
 20 heteroaryl C_{1-10} alkyl, optionally substituted heterocyclic, optionally substituted heterocyclyl C_{1-10} alkyl moiety; or R_2 is the moiety $(CR_{10}R_{20})_qX_1(CR_{10}R_{20})_qC(A_1)(A_2)(A_3)$, or $(CR_{10}R_{20})_qC(A_1)(A_2)(A_3)$.

Suitably q' is 0, or an integer having a value of 1 to 6.

Suitably q is 0, or an integer having a value of 1 to 10.

25

The R_2 moieties, excluding hydrogen, may be optionally substituted one or more times, preferably 1 to 4 times, independently at each occurrence by C_{1-10} alkyl, halo-substituted C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl C_{1-10} alkyl, C_{5-7} cycloalkenyl, C_{5-7} cycloalkenyl C_{1-10} alkyl,
 30 halogen, $-C(O)$, cyano, nitro, aryl, aryl C_{1-10} alkyl, heterocyclic, heterocyclic C_{1-10} alkyl, heteroaryl, heteroaryl C_{1-10} alkyl, $(CR_{10}R_{20})_nOR_6$, $(CR_{10}R_{20})_nSH$, $(CR_{10}R_{20})_nS(O)_mR_7$, $(CR_{10}R_{20})_nN(R_{10'})S(O)_2R_7$, $(CR_{10}R_{20})_nNR_eR_e'$, $(CR_{10}R_{20})_nNR_eR_e'C_{1-4}alkyl$ NR_eR_e' , $(CR_{10}R_{20})_nCN$, $(CR_{10}R_{20})_nS(O)_2NR_eR_e'$, $(CR_{10}R_{20})_nC(Z)R_6$, $(CR_{10}R_{20})_nOC(Z)R_6$,
 35 $(CR_{10}R_{20})_nC(Z)OR_6$, $(CR_{10}R_{20})_nC(Z)NR_eR_e'$, $(CR_{10}R_{20})_nN(R_{10'})C(Z)R_6$, $(CR_{10}R_{20})_nN(R_{10'})C(=N(R_{10'}))NR_eR_e'$, $(CR_{10}R_{20})_nC(=NOR_6)NR_eR_e'$,

$(\text{CR}_{10}\text{R}_{20})_n\text{OC}(\text{Z})\text{NR}_e\text{R}_{e'}$, $(\text{CR}_{10}\text{R}_{20})_n\text{N}(\text{R}_{10}')\text{C}(\text{Z})\text{NR}_e\text{R}_{e'}$, or $(\text{CR}_{10}\text{R}_{20})_n\text{N}(\text{R}_{10}')\text{C}(\text{Z})\text{OR}_7$.

Suitably, R_e and $\text{R}_{e'}$ are each independently selected at each occurrence from hydrogen, C_{1-4} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl C_{1-4} alkyl, aryl, aryl- C_{1-4} alkyl, heterocyclic, heterocyclic C_{1-4} alkyl, heteroaryl or a heteroaryl C_{1-4} alkyl moiety, which moieties may be optionally substituted; or R_e and $\text{R}_{e'}$ together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 4 to 7 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or nitrogen; and wherein each of these moieties, including the cyclized ring and excluding hydrogen, may be substituted 1 to 4 times, independently at each occurrence by halogen; hydroxy; hydroxy substituted C_{1-10} alkyl; C_{1-10} alkoxy; halosubstituted C_{1-10} alkoxy; C_{1-10} alkyl; halosubstituted C_{1-4} alkyl; $\text{S}(\text{O})\text{mR}_f$; $\text{C}(\text{O})\text{R}_j$; $\text{C}(\text{O})\text{OR}_j$; $(\text{CR}_{10}\text{R}_{20})_n\text{N}(\text{R}_{10}')\text{C}(\text{Z})\text{OR}_7$; $(\text{CR}_{10}\text{R}_{20})_n\text{N}(\text{R}_{10}')\text{C}(\text{Z})\text{NR}_d\text{R}_{d'}$; $\text{C}(\text{O})\text{NR}_4'\text{R}_{14}'$; $\text{NR}_4'\text{C}(\text{O})\text{C}_{1-10}$ alkyl; $\text{NR}_4'\text{C}(\text{O})$ aryl; cyano; nitro; C_{1-10} alkyl; C_{3-7} cycloalkyl; C_{3-7} cycloalkyl C_{1-10} alkyl; halosubstituted C_{1-10} alkyl; aryl, aryl C_{1-4} alkyl, heterocyclic, heterocyclic C_{1-4} alkyl, heteroaryl, or hetero C_{1-4} alkyl, and wherein these aryl, heterocyclic or heteroaryl containing moieties may be optionally substituted one to two times independently at each occurrence by halogen, C_{1-4} alkyl, hydroxy, hydroxy substituted C_{1-4} alkyl, C_{1-10} alkoxy, $\text{S}(\text{O})\text{malkyl}$, amino, mono & di-substituted C_{1-4} alkyl amino, C_{1-4} alkyl, or CF_3 .

Suitably, R_f is independently selected at each occurrence from hydrogen, C_{1-10} alkyl, aryl, aryl C_{1-10} alkyl, heteroaryl, heteroaryl C_{1-10} alkyl, heterocyclic, heterocyclic C_{1-10} alkyl or $\text{NR}_4'\text{R}_{14}'$, and wherein these moieties, excluding hydrogen, and $\text{NR}_4'\text{R}_{14}'$, may be optionally substituted.

In one embodiment of the present invention X is R_2 , OR_2 , $(\text{CH}_2)_n\text{NR}_4\text{R}_{14}$, or $(\text{CH}_2)_n\text{N}(\text{R}_2')(\text{R}_2'')$. In another embodiment of the present invention, X is R_2 , and R_2 is $(\text{CR}_{10}\text{R}_{20})_q\text{X}_1(\text{CR}_{10}\text{R}_{20})_q\text{C}(\text{A}_1)(\text{A}_2)(\text{A}_3)$, or $(\text{CR}_{10}\text{R}_{20})_q\text{C}(\text{A}_1)(\text{A}_2)(\text{A}_3)$.

When X is R_2 and R_2 is an optionally substituted heterocyclic or heterocyclic alkyl, the heterocyclic containing moiety is suitably selected from tetrahydropyrrole, tetrahydropyran, tetrahydrofuran, tetrahydrothiophene (including oxidized versions of the sulfur moiety), aziridinyl, pyrrolinyl, pyrrolidinyl, 2-oxo-1-pyrrolidinyl, 3-oxo-1-pyrrolidinyl, 1,3-benzodioxol-5-yl, imidazolynyl, imidazolidinyl, indolynyl, pyrazolynyl, pyrazolidinyl, piperidinyl, piperazinyl, morpholino and thiomorpholino (including oxidized versions of the sulfur moiety).

In one embodiment, R_2 is an optionally substituted piperidinyl or piperazinyl ring.

In another embodiment, when R₂ is an optionally substituted heterocyclic or heterocyclic alkyl ring the ring is substituted one or more times independently by an optionally substituted heterocyclic, heterocyclic alkyl, aryl, arylalkyl, alkyl, (CR₁₀R₂₀)_nNR_eR_e', or (CR₁₀R₂₀)_nN(R₁₀')C(Z)OR₇. The second heterocyclic ring is suitably selected from an optionally substituted tetrahydropyrrole, tetrahydropyran, tetrahydrofuran, tetrahydrothiophene (including oxidized versions of the sulfur moiety), aziridinyl, pyrrolinyl, pyrrolidinyl, 2-oxo-1-pyrrolidinyl, 3-oxo-1-pyrrolidinyl, 1,3-benzodioxol-5-yl, imidazolyl, imidazolidinyl, indolyl, pyrazolyl, pyrazolidinyl, piperidinyl, piperazinyl, diazepine, morpholino or thiomorpholino (including oxidized versions of the sulfur moiety). Suitably, the second heterocyclic ring is selected from morpholino, piperidine, or pyrrolidinyl.

In one embodiment, R₂ is a 4-amino-1-piperidinyl, 1,1-dimethylethyl[oxy]carbonyl}amino)-1-piperidinyl, 4-methyl-1-piperazinyl, 4-ethyl-1-piperazinyl, 4-propyl-1-piperazinyl, 4-butyl-1-piperazinyl, 4-(methylamino)-1-piperidinyl, 1,1-dimethylethyl-4-piperidinyl}methylcarbamate, 4-phenyl-1-piperazinyl, 1,4'-bipiperidin-1'-yl, 4-(1-pyrrolidinyl)-1-piperidinyl, 4-methyl-1,4'-bipiperidin-1'-yl, 4-(4-morpholinyl)-1-piperidinyl, 4-(diphenylmethyl)-1-piperazinyl, or 4-methylhexahydro-1H-1,4-diazepin-1-yl.

Suitably, R₂' is independently selected at each occurrence from hydrogen, C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkylalkyl, aryl, arylC₁₋₁₀ alkyl, heteroaryl, heteroarylC₁₋₁₀ alkyl, heterocyclic, or a heterocyclC₁₋₁₀ alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted 1 to 4 times, independently, at each occurrence, by C₁₋₁₀ alkyl, halo-substituted C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₇ cycloalkyl, C₃₋₇cycloalkylC₁₋₁₀alkyl, C₅₋₇cycloalkenyl, C₅₋₇ cycloalkenylC₁₋₁₀ alkyl, halogen, -C(O), cyano, nitro, aryl, aryl C₁₋₁₀ alkyl, heteroaryl, heteroarylC₁₋₁₀ alkyl, heterocyclic, heterocyclC₁₋₁₀ alkyl, (CR₁₀R₂₀)_nOR₆, (CR₁₀R₂₀)_nSH, (CR₁₀R₂₀)_nS(O)_mR₇, (CR₁₀R₂₀)_nN(R₁₀')S(O)₂R₇, (CR₁₀R₂₀)_nNR_eR_e', (CR₁₀R₂₀)_nNR_eR_e'C₁₋₄alkylNR_eR_e', (CR₁₀R₂₀)_nCN, (CR₁₀R₂₀)_nS(O)₂NR_eR_e', (CR₁₀R₂₀)_nC(Z)R₆, (CR₁₀R₂₀)_nOC(Z)R₆, (CR₁₀R₂₀)_nC(Z)OR₆, (CR₁₀R₂₀)_nC(Z)NR_eR_e', (CR₁₀R₂₀)_nN(R₁₀')C(Z)R₆, (CR₁₀R₂₀)_nN(R₁₀')C(=N(R₁₀'))NR_eR_e', (CR₁₀R₂₀)_nC(=NOR₆) NR_eR_e', (CR₁₀R₂₀)_nOC(Z) NR_eR_e', (CR₁₀R₂₀)_nN(R₁₀')C(Z)NR_eR_e', or (CR₁₀R₂₀)_nN(R₁₀')C(Z)OR₇.

In one embodiment, when X is (CH₂)_nN(R₂')R₂'', one of R₂', or R₂'', is hydrogen, or methyl.

In one embodiment, when R_2' is an optionally substituted heterocyclic or heterocyclyl C_{1-10} alkyl the heterocyclic containing moiety is substituted one or more times independently by C_{1-10} alkyl, aryl, heterocyclic, $(CR_{10}R_{20})_nNR_eR_e'$, $(CR_{10}R_{20})_nN(R_{10}')C(Z)OR_7$, or $(CR_{10}R_{20})_nC(Z)OR_6$. More specifically, methyl, ethyl, $NHC(O)O-CCH_3$, $N(CH_3)C(O)O-CCH_3$, amino, methylamino, dimethylamino, phenyl, piperidine, pyrrolidine, 1-ethylpropyl, 4-methyl-1,4'-bipiperidin-1'-yl, 1,4'-bipiperidin-1'-yl, morpholino,

In one embodiment, when X is $(CH_2)_nN(R_2')(R_2'')$, R_2' is an optionally substituted C_{1-10} alkyl, cycloalkyl, heterocyclic, heterocyclyl C_{1-10} alkyl, heteroarylalkyl. Suitably, when R_2' is an optionally substituted cycloalkyl it is an a cyclohexyl ring. In one embodiment the cyclohexyl ring is optionally substituted one or more times by $(CR_{10}R_{20})_nNR_eR_e'$.

Suitably, when R_2' is an optionally substituted heterocyclic, or a heterocyclyl C_{1-10} alkyl, the ring is selected from tetrahydropyrrole, tetrahydropyran, tetrahydrofuran, tetrahydrothiophene (including oxidized versions of the sulfur moiety), aziridinyl, pyrrolinyl, pyrrolidinyl, 2-oxo-1-pyrrolidinyl, 3-oxo-1-pyrrolidinyl, 1,3-benzdioxol-5-yl, imidazolynyl, imidazolidinyl, indolynyl, pyrazolynyl, pyrazolidinyl, piperidinyl, piperazinyl, diazepine, hexahydro-1-H-azepine, morpholino or thiomorpholino (including oxidized versions of the sulfur moiety). Preferably, the ring is a piperidine, piperazine, pyrrolidinyl, 2-oxo-1-pyrrolidinyl, morpholino, hexahydro-1-H-azepine ring. In one embodiment, the rings are substituted one or more times, suitably 1 to 4 times, independently by C_{1-10} alkyl, aryl, arylalkyl, $(CR_{10}R_{20})_nNR_eR_e'$, or $(CR_{10}R_{20})_nN(R_{10}')C(Z)OR_7$.

In one embodiment, $(CH_2)_nN(R_2')(R_2'')$ is 1-(phenylmethyl)-4-piperidinamine, 2-[4-(phenylmethyl)-1-piperazinyl]ethylamine, 2-(1-piperidinyl)ethylamine, 2-(1-methyl-2-pyrrolidinyl)ethylamine, 1-[(phenylmethyl)-3-pyrrolidinyl]amine, 3-[(1-pyrrolidinyl)propyl]amine, 3-[(hexahydro-1-H-azepin-1-yl)propyl]amine, (1-methyl-4-piperidinyl)amine, 3-[(4-morpholinyl)propyl]amine, 3-[(2-oxo-1-pyrrolidinyl)propyl]amine, 2-[(4-morpholinyl)ethyl]amine, 2-[(1-pyrrolidinyl)ethyl]-amine, or [(1-ethyl-2-pyrrolidinyl)methyl]amino.

In one embodiment when X is $(CH_2)_nN(R_2')(R_2'')$, and R_2' is an optionally substituted C_{1-10} alkyl, the alkyl is substituted one or more times independently by $(CR_{10}R_{20})_nNR_eR_e'$ or $(CR_{10}R_{20})_nNR_eR_e'C_{1-4}alkylNR_eR_e'$. In one embodiment R_e and R_e' are independently an optionally substituted C_{1-4} alkyl, such as methyl, ethyl, isopropyl, n-butyl, or t-butyl. Preferably, $(CH_2)_nN(R_2')(R_2'')$ is 3-(dimethylamino)propyl(methyl)amine, 3-(diethylamino)propylamine, propylamine, (2,2-dimethylpropyl)amine, (2-hydroxypropyl)amino, 2-(dimethylamino)ethylamine,

- 2-(dimethylamino)ethyl(methyl)amine, 3-(dimethylamino)propylamine,
 2-(dimethylamino)ethyl(methyl)amine, 3-(diethylamino)propylamine,
 2-(methylamino)ethylamine, [(1-methylethyl)amino]ethylamine,
 3-(diethylamino)propylamine, 3-(dibutylamino)propylamine,
 5 3-[(1-methylethyl)amino]propylamine, 3-(1,1-dimethylethyl)aminopropylamine,
 3-(dimethylamino)-2,2-dimethylpropylamine, 4-(diethylamino)-1-methylbutylamine,
 or 3-[[3-(dimethylamino)propyl]-(methyl)amino]propyl(methyl)amine.

- Suitably R_2'' is selected from hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7}
 10 cycloalkylalkyl, aryl, aryl C_{1-10} alkyl, heteroaryl, heteroaryl C_{1-10} alkyl, heterocyclic,
 or a heterocyclyl C_{1-10} alkyl moiety, and wherein these moieties, excluding hydrogen,
 may be optionally substituted 1 to 4 times, independently at each occurrence, by C_{1-10}
 alkyl, halo-substituted C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7}
 cycloalkyl, C_{3-7} cycloalkyl C_{1-10} alkyl, C_{5-7} cycloalkenyl, C_{5-7} cycloalkenyl C_{1-10}
 15 alkyl, halogen, -C(O), cyano, nitro, aryl, aryl C_{1-10} alkyl, heteroaryl, heteroaryl C_{1-10}
 alkyl, heterocyclic, heterocyclyl C_{1-10} alkyl, $(CR_{10}R_{20})_nOR_6$, $(CR_{10}R_{20})_nSH$,
 $(CR_{10}R_{20})_nS(O)_mR_7$, $(CR_{10}R_{20})_nN(R_{10}')S(O)_2R_7$, $(CR_{10}R_{20})_nNR_eR_e'$,
 $(CR_{10}R_{20})_nNR_eR_e'C_{1-4}alkyl$ NR_eR_e' , $(CR_{10}R_{20})_nCN$, $(CR_{10}R_{20})_nS(O)_2$
 NR_eR_e' , $(CR_{10}R_{20})_nC(Z)R_6$, $(CR_{10}R_{20})_nOC(Z)R_6$, $(CR_{10}R_{20})_nC(Z)OR_6$,
 20 $(CR_{10}R_{20})_nC(Z)NR_eR_e'$, $(CR_{10}R_{20})_nN(R_{10}')C(Z)R_6$,
 $(CR_{10}R_{20})_nN(R_{10}')C(=N(R_{10}'))NR_eR_e'$, $(CR_{10}R_{20})_nC(=NOR_6)NR_eR_e'$,
 $(CR_{10}R_{20})_nOC(Z)NR_eR_e'$, $(CR_{10}R_{20})_nN(R_{10}')C(Z)NR_eR_e'$, or
 $(CR_{10}R_{20})_nN(R_{10}')C(Z)OR_7$; or wherein R_2'' is the moiety
 $(CR_{10}R_{20})_tX_1(CR_{10}R_{20})_qC(A_1)(A_2)(A_3)$;

- 25 Suitably, t is an integer having a value of 2 to 6.

Suitably, q is 0 or an integer having a value of 1 to 10.

Suitably, A_1 is an optionally substituted C_{1-10} alkyl, heterocyclic,
 heterocyclic C_{1-10} alkyl, heteroaryl, heteroaryl C_{1-10} alkyl, aryl, or aryl C_{1-10} alkyl.

- Suitably, A_2 is an optionally substituted C_{1-10} alkyl, heterocyclic,
 30 heterocyclic C_{1-10} alkyl, heteroaryl, heteroaryl C_{1-10} alkyl, aryl, or aryl C_{1-10} alkyl.

Suitably, A_3 is hydrogen or is an optionally substituted C_{1-10} alkyl.

- The A_1 , A_2 , and A_3 C_{1-10} alkyl moieties may optionally substituted one or
 more times independently at each occurrence, preferably from 1 to 4 times, with
 halogen, such as chlorine, fluorine, bromine, or iodine; halo-substituted C_{1-10} alkyl,
 35 such as CF_3 , or CHF_2CF_3 ; C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl,
 C_{3-7} cycloalkyl C_{1-10} alkyl, C_{5-7} cycloalkenyl, C_{5-7} cycloalkenyl C_{1-10} alkyl,
 $(CR_{10}R_{20})_nOR_6$, $(CR_{10}R_{20})_nSH$, $(CR_{10}R_{20})_nS(O)_mR_7$,

- (CR₁₀R₂₀)_nN(R₁₀')S(O)₂R₇, (CR₁₀R₂₀)_nNR₄R₁₄, (CR₁₀R₂₀)_nCN,
 (CR₁₀R₂₀)_nS(O)₂NR₄R₁₄, (CR₁₀R₂₀)_nC(Z)R₆, (CR₁₀R₂₀)_nOC(Z)R₆,
 (CR₁₀R₂₀)_nC(Z)OR₆, (CR₁₀R₂₀)_nC(Z)NR₄R₁₄, (CR₁₀R₂₀)_nN(R₁₀')C(Z)R₆,
 (CR₁₀R₂₀)_nN(R₁₀')C(=N(R₁₀'))NR₄R₁₄, (CR₁₀R₂₀)_nOC(Z)NR₄R₁₄,
 5 (CR₁₀R₂₀)_nN(R₁₀')C(Z)NR₄R₁₄, or (CR₁₀R₂₀)_nN(R₁₀')C(Z)OR₇.

In another embodiment of the present invention, X is R₂, and R₂ is (CR₁₀R₂₀)_q'X₁(CR₁₀R₂₀)_qC(A₁)(A₂)(A₃), or (CR₁₀R₂₀)_q'C(A₁)(A₂)(A₃). In a further embodiment, q' is 0.

- In another embodiment when R₂ is the moiety
 10 (CR₁₀R₂₀)_q'X₁(CR₁₀R₂₀)_qC(A₁)(A₂)(A₃), q' is 0, X₁ is nitrogen, q is 0 or 1, A₁ is an optionally substituted heterocyclic or heterocyclic alkyl, and A₂ is an optionally substituted aryl. More specifically, R₂ is 2-phenyl-2-(1-pyrrolidinyl)ethyl]amino, or 1-phenyl-2-(1-pyrrolidinyl)ethyl]amino. In another embodiment, A₁ is an optionally substituted aryl or arylalkyl, and A₂ is an optionally substituted aryl or arylalkyl.

- 15 In one embodiment of the invention, one or more of the A₁, A₂ and A₃ moieties are substituted with (CR₁₀R₂₀)_nOR₆. In another embodiment of the invention, the R₆ substituent in (CR₁₀R₂₀)_nOR₆ is hydrogen.

- In yet another embodiment of the present invention, X is R₂ and R₂ is C(A₁)(A₂)(A₃), such as CH(CH₂OH)₂, or C(CH₃)(CH₂OH)₂; or
 20 X₁(CR₁₀R₂₀)_qCH(CH₂OH)₂, or X₁(CR₁₀R₂₀)_qC(CH₃)(CH₂OH)₂; and further wherein X₁ is oxygen or nitrogen.

- In another embodiment X is S(O)_mR₂', (CH₂)_nNR₄R₁₄, or (CH₂)_nN(R₂)(R₂'). In yet another embodiment, X is (CH₂)_nNR₄R₁₄, or (CH₂)_nN(R₂)(R₂').
 25 Suitably, when X is (CH₂)_nNR₄R₁₄, and R₄ and R₁₄ are C₁₋₁₀ alkyl, aryl, aryl-C₁₋₄ alkyl, heterocyclic, heterocyclic C₁₋₄ alkyl, heteroaryl or heteroaryl C₁₋₄ alkyl, the C₁₋₄ alkyl may be substituted one or more times, independently at each occurrence with NR₄'R₁₄'; halogen, hydroxy, alkoxy, C(O)NR₄'R₁₄'; or NR₄'C(O)C₁₋₁₀alkyl. Preferably, the C₁₋₄ alkyl is substituted with NR₄'R₁₄'.

- 30 In one embodiment at least one of R₄ and R₁₄ may be hydrogen when R₄ and R₁₄ are not cyclized. In another embodiment neither R₄ nor R₁₄ is hydrogen.

- In one embodiment when X is (CH₂)_nNR₄R₁₄, one of R₄ and R₁₄ are hydrogen, and the other is an optionally substituted heteroaryl C₁₋₄ alkyl. Suitably, the optionally substituted heteroaryl alkyl is an imidazolyl alkyl, such as a 1*H*-
 35 imidazol-2-yl-methyl group.

In one embodiment when X is (CH₂)_nNR₄R₁₄ and one of R₄ and R₁₄ is a heteroaryl C₁₋₄ alkyl moiety, then the heteroaryl ring is selected from thienyl,

pyrrolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, imidazolyl, pyrazolyl, triazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, benzoxazolyl, benzimidazolyl, and benzothiazolyl. Suitably, the heteroaryl C₁₋₄ alkyl is selected from pyrrolyl, oxazolyl, thiazolyl, isoxazolyl, imidazolyl, benzoxazolyl, benzimidazolyl, and benzothiazolyl.

In another embodiment when X is (CH₂)_nNR₄R₁₄ and one of R₄ and R₁₄ is a heterocyclic C₁₋₄ alkyl moiety, then the heterocyclic ring is selected from tetrahydropyrrole, tetrahydropyran, tetrahydrofuran, pyrrolinyl, pyrrolidinyl, imidazolyl, imidazolidinyl, indolyl, pyrazolyl, pyrazolidinyl, piperidinyl, piperazinyl, and morpholino. Suitably, the heterocyclic C₁₋₄ alkyl moiety is selected from pyrrolinyl, pyrrolidinyl, piperidinyl, piperazinyl, and morpholino.

In another embodiment when X is (CH₂)_nNR₄R₁₄ and R₄ and R₁₄ together with the nitrogen cyclize to form an optionally substituted ring, such as described above, such rings include, but are not limited to pyrrolidine, piperidine, piperazine, diazepine, and morpholine. In one embodiment when X is (CH₂)_nNR₄R₁₄, the R₄ and R₁₄ substituents cyclize to form a heterocyclic 5 or 6 membered ring, which ring is optionally substituted as defined herein. When the R₄ and R₁₄ substituents cyclize to form a 4 to 7 membered ring, the optional substituents are suitably selected from an optionally substituted alkyl, an optionally substituted aryl, an optionally substituted heteroaryl, optionally substituted heterocyclic, (CR₁₀R₂₀)_nN(R_{10'})C(Z)OR₇, NR₄R₁₄, or a C₁₋₁₀ alkyl substituted one or more times by an optionally substituted aryl. Such substituents more specifically include phenyl, pyrrolidinyl, morpholino, piperazinyl, 4-methyl-1-piperazinyl, piperidinyl, 2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl, 5-chloro-2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl, diphenylmethyl, methyl, ethyl, propyl, butyl, amino, methylamino, and dimethylamino.

In one embodiment the X substituent is a 1,4'-bipiperin-1-yl ring which may be optionally substituted such as in 4-methyl-1,4'-bipiperin-1-yl; 4-piperidinylamino, 4-amino-1-piperidinyl, 2,2,6,6-tetramethyl-4-piperidinylamino, 4-methyl-1-piperazinyl, (4-morpholinyl)-1-piperidinyl, (4-methyl-1-piperazinyl)-1-piperidinyl, 4-ethyl-1-piperazinyl, (2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)-1-piperidinyl, 5-chloro-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)-1-piperidinyl, 4-(1-pyrrolidinyl)-1-piperidinyl, 4-(diphenylmethyl)-1-piperazinyl, 4-methylhexahydro-1*H*-1,4-diazepin-1-yl, 4-propyl-1-piperazinyl, or 4-butyl-1-piperazinyl.

In another embodiment, when X is (CH₂)_nN(R_{2'})(R_{2''}), and R_{2'} is an optionally substituted C₁₋₁₀ alkyl moiety, and the alkyl is substituted by (CR₁₀R₂₀)_nNR_eR_{e'}, and R_e and R_{e'} are hydrogen, or an optionally substituted C₁₋₁₀ alkyl. Suitably, the X moiety is 3-(diethylamino)propylamino, 3-

(dimethylamino)propyl(methyl)amino, 3-(dimethylamino)propyl(methyl)amino, 2-(dimethylamino)ethylamino, 1-methylethylamino-propylamino, (1,1-dimethylethyl)aminopropylamino, (1-methylethyl)aminoethylamino, 2-(methylamino)ethylamino, 2-aminoethyl(methyl)amino, or a 2-(dimethylamino)ethyl(methyl)amino.

In another embodiment when X is $(CH_2)_nN(R_{2'}) (R_{2''})$, and $R_{2'}$ moiety is an optionally substituted heteroaryl C_{1-10} alkyl, the heteroaryl moiety is suitably an optionally substituted imidazole.

In one embodiment at least one of R_4 and R_{14} may be hydrogen when R_4 and R_{14} are not cyclized. In another embodiment neither R_4 and R_{14} is hydrogen.

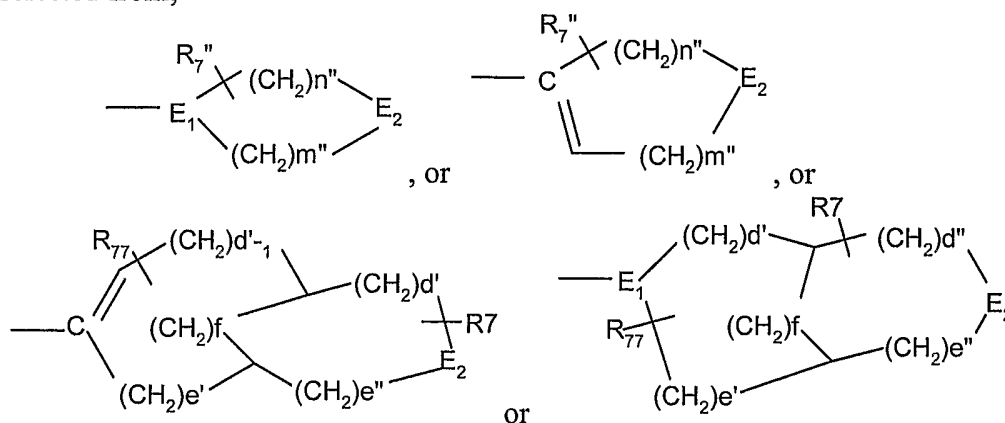
In one embodiment R_3 is a 2,6-difluoro phenyl, R_1 is a phenyl ring substituted by and R_1 is selected from $C(Z)N(R_{10'})(CR_{10}R_{20})_vR_b$, or $C(Z)O(CR_{10}R_{20})_vR_b$, or $N(R_{10'})C(Z)(CR_{10}R_{20})_vR_b$ and also substituted by R_1' independently selected at each occurrence from hydrogen, fluorine, or methyl; g is 1 or 2. Preferably, R_1 is substituted by $C(Z)N(R_{10'})(CR_{10}R_{20})_vR_b$ and R_1' independently selected at each occurrence from hydrogen, fluorine, or methyl. In another embodiment, the R_b moiety is selected from thiazolyl, C_{1-10} alkyl or an optionally substituted aryl. In another embodiment the R_b moiety is propyl or 4-fluorophenyl.

In another embodiment, X is suitably selected from (1*H*-imidazol-2-ylmethyl)amino or 4-methyl-1,4'-bipiperidin-1'-yl, 2,2,6,6-tetramethyl-4-piperidiny)amino, 4-amino-1-piperidiny, 3-(diethylamino)propylamino, 3-(dimethylamino)propyl(methyl)amino, 3-(dimethylamino)propyl(methyl)amino, 2-(dimethylamino)ethylamino, 1-methylethylamino-propylamino, (1,1-dimethylethyl)aminopropylamino, (1-methylethyl)aminoethylamino, 2-(methylamino)ethylamino, 2-aminoethyl(methyl)amino, or 2-(dimethylamino)ethyl(methyl)amino.

In one embodiment, R_3 is a 2,6-difluoro phenyl, R_1 is phenyl, R_1' is independently selected at each occurrence from hydrogen, fluorine, or methyl; g is 1 or 2; and the phenyl ring is also substituted in the 3- or 4-position by $C(Z)N(R_{10'})(CR_{10}R_{20})_vR_b$, R_b moiety is C_{1-10} alkyl or an optionally substituted aryl, preferably propyl or 4-fluorophenyl, X is $(CH_2)_nN(R_{2'}) (R_{2''})$, and n is 0. In another embodiment, X is $(CH_2)_nN(R_{2'}) (R_{2''})$, $R_{2''}$ is hydrogen, n is 0, and $R_{2'}$ is an alkyl substituted by $(CR_{10}R_{20})_nNR_eR_e'$. In a further embodiment, R_e and R_e' are independently selected from an optionally substituted C_{1-4} alkyl, such as methyl, ethyl, isopropyl, n-butyl, or t-butyl, preferably ethyl.

In another embodiment of the present invention, for compounds of Formula (I) the X term may also be the B-Non-Ar-cyc moiety as disclosed in US 6,809,199 whose disclosure is incorporated by reference herein.

As represented by the disclosure in US 6,809,199, Non-Ar-Cyc is suitably
5 selected from;



wherein

- d is an integer having a value of 1, 2, 3, or 4;
10 d' is 0, or an integer having a value of 1, 2, or 3;
d'' is 0, or an integer having a value of 1, 2, or 3;
e is 0, or is an integer having a value of 1, 2, 3, or 4;
e' is 0, or an integer having a value of 1, 2, or 3;
e'' is 0, or an integer having a value of 1, 2, or 3;
15 f is 0, or is an integer having a value of 1, 2, or 3;
d + e is 2, 3, 4, 5, or 6;
d' + e'' = d
e' + e'' = m

- Suitably, R₇, R₇₇ and R_{77''} are each independently selected from hydrogen,
20 C₁₋₆ alkyl-group, C₂₋₆ alkenyl-group, C₄₋₆ cycloalkyl-C₀₋₆ alkyl-group, N(C₀₋₄ alkyl)(C₀₋₄ alkyl)-C₁₋₄ alkyl-N(C₀₋₄ alkyl)-group, -N(C₀₋₄ alkyl)(C₀₋₄ alkyl) group, C₁₋₃ alkyl-CO-C₀₋₄ alkyl-group, C₀₋₆ alkyl-O-C(O)-C₀₋₄ alkyl-group, C₀₋₆alkyl-C(O)-O-C₀₋₄alkyl-group, N(C₀₋₄ alkyl)(C₀₋₄ alkyl)-(C₀₋₄ alkyl)C(O)(C₀₋₄ alkyl)-group, phenyl-C₀₋₄ alkyl-group, pyridyl-C₀₋₄ alkyl-group, pyrimidinyl-C₀₋₄ alkyl-group, pyrazinyl-C₀₋₄ alkyl-group, thiophenyl-C₀₋₄ alkyl-group, pyrazolyl-C₀₋₄ alkyl-group, imidazolyl-C₀₋₄ alkyl-group, triazolyl-C₀₋₄ alkyl-group, azetidyl-C₀₋₄ alkyl-group, pyrrolidinyl-C₀₋₄ alkyl-group, isoquinolinyl-C₀₋₄alkyl-group, indanyl-C₀₋₄ alkyl-group, benzothiazolyl-C₀₋₄ alkyl-group, any of the groups optionally substituted with 1-6 substituents, each substituent independently being -OH, -N(C₀₋₄ alkyl)(C₀₋

alkyl), C₁₋₄alkyl, C₁₋₆alkoxyl, C₁₋₆alkyl-CO—C₀₋₄alkyl-, pyrrolidinyl-C₀₋₄alkyl-, or halogen; or R₇ together with a bond from an absent ring hydrogen is =O.

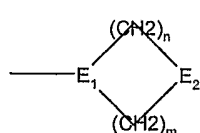
- Suitably, B is -C₁₋₆alkyl-, -C₀₋₃alkyl-O-C₀₋₃alkyl-, -C₀₋₃alkyl-NH-C₀₋₃alkyl-, -C₀₋₃alkyl-NH-C₃₋₇cycloalkyl-, -C₀₋₃alkyl-N(C₀₋₃alkyl)-C(O)-C₀₋₃alkyl-, -C₀₋₃alkyl-NH--SO₂-C₀₋₃alkyl-, -C₀₋₃alkyl-, -C₀₋₃alkyl-S-C₀₋₃alkyl-, -C₀₋₃alkyl-SO₂-C₀₋₃alkyl-, -C₀₋₃alkyl-PH-C₀₋₃alkyl-, C₀₋₃alkyl-C(O)-C₀₋₃alkyl, or a direct bond.

Suitably, E₁ is CH, N, or CR₆₆; or B and E₁ together form a double bond, i.e., -CH=C.

Suitably, E₂ is CH₂, CHR₇₇, C(OH)R₇₇ NH, NR₇₇, O, S, -S(O)-, or -S(O)₂-.

- 10 Suitably, R₆₆ is independently selected from at each occurrence from halogen, C₀₋₄alkyl, -C(O)-O (C₀₋₄alkyl), or -C(O)-N(C₀₋₄alkyl)-(C₀₋₄alkyl).

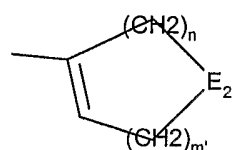
In an alternative embodiment of this invention, Non-Ary Cyc is:



n = 1 to 4
m = 0 to 4
n+m = 2 to 6

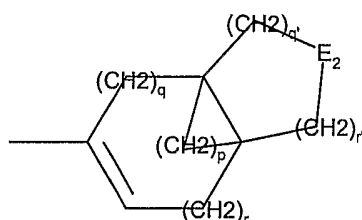
E₁ = CH, CR₆₆, N or B-E₁ can equal double bond (C=C); or

15



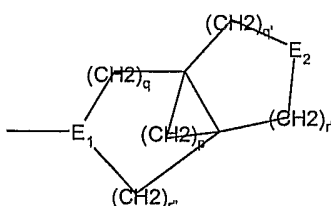
n = 1 to 4
m' = 0 to 3
n+m' = 1 to 5

; or



p = 0 to 3
q = 0 to 4
q' = 0 to 4
r = 0 to 4
r' = 0 to 4
q+q'+r+r' = 2 to 6

; or



p = 0 to 3
q = 0 to 4
q' = 0 to 4
r' = 0 to 4
r'' = 0 to 4
q+q'+r'+r'' = 2 to 7

- 20 In another embodiment of the present invention, for compound of Formula (I) herein, the X term may also be the X moiety as disclosed in WO 2004/073628, published September 2004, Boehm et al., whose disclosure is incorporated by reference herein.

The term "halo" or "halogens" is used herein to mean the halogens, chloro, fluoro, bromo and iodo.

As used herein, the term "alkyl" refers to straight or branched hydrocarbon chains containing the specified number of carbon atoms. For example, C₁₋₆alkyl means a straight or branched alkyl containing at least 1, and at most 6, carbon atoms.

5 Examples of "alkyl" as used herein include, but are not limited to, methyl, ethyl, n-propyl, n-butyl, n-pentyl, isobutyl, isopropyl, sec-butyl, *tert*-butyl or t-butyl and hexyl and the like.

As used herein, the term "alkenyl" refers to straight or branched hydrocarbon chains containing the specified number of carbon atoms and containing at least one double bond. For example, C₂₋₆alkenyl means a straight or branched alkenyl
10 containing at least 2, and at most 6, carbon atoms and containing at least one double bond. Examples of "alkenyl" as used herein include, but are not limited to ethenyl, 2-propenyl, 3-butenyl, 2-butenyl, 2-pentenyl, 3-pentenyl, 3-methyl-2-butenyl, 3-methylbut-2-enyl, 3-hexenyl, 1,1-dimethylbut-2-enyl and the like.

As used herein, the term "alkoxy" refers to straight or branched chain alkoxy groups containing the specified number of carbon atoms. For example, C₁₋₆alkoxy
15 means a straight or branched alkoxy containing at least 1, and at most 6, carbon atoms. Examples of "alkoxy" as used herein include, but are not limited to, methoxy, ethoxy, propoxy, prop-2-oxy, butoxy, but-2-oxy, 2-methylprop-1-oxy, 2-methylprop-2-oxy, pentoxy and hexyloxy.

As used herein, the term "cycloalkyl" refers to cyclic radicals, such as a non-aromatic hydrocarbon ring containing a specified number of carbon atoms. For
20 example, C₃₋₇cycloalkyl means a non-aromatic ring containing at least three, and at most seven, ring carbon atoms. Representative examples of "cycloalkyl" as used herein include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and
25 cycloheptyl and the like.

The term "cycloalkenyl" is used herein to mean cyclic radicals, such as a non-aromatic hydrocarbon ring containing a specified number of carbon atoms preferably of 5 to 7 carbons, which have at least one bond including but not limited to cyclopentenyl, cyclohexenyl, and the like.

30 The term "alkenyl" is used herein at all occurrences to mean straight or branched chain radical of 2-10 carbon atoms, unless the chain length is limited thereto, including, but not limited to ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl and the like.

The term "aryl" is used herein to mean phenyl, naphthyl, and indene.

35 The terms "heteroaryl ring", "heteroaryl moiety", and "heteroaryl" are used herein to mean a monocyclic five- to seven- membered unsaturated hydrocarbon ring containing at least one heteroatom selected from oxygen, nitrogen and sulfur. Examples

of heteroaryl rings include, but are not limited to, furyl, pyranyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, imidazolyl, pyrazolyl, oxadiazolyl, oxathiadiazolyl, triazolyl, tetrazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, and uracil. The terms "heteroaryl ring", "heteroaryl moiety", and "heteroaryl" shall also used herein to refer to fused aromatic rings comprising at least one heteroatom selected from oxygen, nitrogen and sulfur. Each of the fused rings may contain five or six ring atoms. Examples of fused aromatic rings include, but are not limited to, indolyl, isoindolyl, indazolyl, indoliziny, azaindolyl, benzoxazolyl, benzimidazolyl, benzothiazolyl, benzofuranyl, benzothiophenyl, quinolyl, isoquinolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, cinnolinyl, purinyl, and phthalazinyl.

The terms "heterocyclic rings", "heterocyclic moieties", and "heterocyclyl" is used herein to mean a monocyclic three- to seven-membered saturated or non-aromatic, unsaturated hydrocarbon ring containing at least one heteroatom selected from nitrogen, oxygen, sulphur or oxidized sulphur moieties, such as S(O)_m, and m is 0 or an integer having a value of 1 or 2. The terms "heterocyclic rings", "heterocyclic moieties", and "heterocyclyl" shall also refer to fused rings, saturated or partially unsaturated, and wherein one of the rings may be aromatic, or heteroaromatic. Each of the fused rings may have from four to seven ring atoms. Examples of heterocyclyl groups include, but are not limited to, the saturated or partially saturated versions of the heteroaryl moieties as defined above, such as tetrahydropyrrole, tetrahydropyran, tetrahydrofuran, tetrahydrothiophene (including oxidized versions of the sulfur moiety), azepine, diazepine, aziridinyl, pyrrolinyl, pyrrolidinyl, 2-oxo-1-pyrrolidinyl, 3-oxo-1-pyrrolidinyl, 1,3-benzdioxol-5-yl, imidazolyl, imidazolidinyl, indolyl, pyrazolyl, pyrazolidinyl, piperidinyl, piperazinyl, morpholino and thiomorpholino (including oxidized versions of the sulfur moiety).

The term "arylalkyl" or "heteroarylalkyl" or "heterocyclicalkyl" is used herein to mean a C₁₋₄ alkyl (as defined above) attached to an aryl, heteroaryl or heterocyclic moiety (as also defined above) unless otherwise indicated.

The term "sulfinyl" is used herein to mean the oxide S(O) of the corresponding sulfide, the term "thio" refers to the sulfide, and the term "sulfonyl" refers to the fully oxidized S (O)₂ moiety.

The term "aroyl" is used herein to mean C(O)Ar, wherein Ar is as phenyl, naphthyl, or aryl alkyl derivative such as defined above, such group include but are not limited to benzyl and phenethyl.

The term "alkanoyl" is used herein to mean C(O)C₁₋₁₀ alkyl wherein the alkyl is as defined above.

As used herein, the term "optionally" means that the subsequently described event(s) may or may not occur, and includes both event(s) which occur and events that do not occur.

As used herein, the term "substituted" refers to substitution with the named
5 substituent or substituents, multiple degrees of substitution being allowed unless otherwise stated.

As used herein, "optionally substituted" unless specifically defined shall mean such groups as halogen, such as fluorine, chlorine, bromine or iodine; hydroxy; hydroxy substituted C₁₋₁₀alkyl; C₁₋₁₀ alkoxy, such as methoxy or ethoxy;
10 halosubstituted C₁₋₁₀ alkoxy; S(O)_m alkyl, such as methyl thio, methylsulfinyl or methyl sulfonyl; a ketone (-C(O)), or an aldehyde (-C(O)R_{6'}), such as C(O)C₁₋₁₀ alkyl or C(O)aryl, wherein R_{6'} is hydrogen, C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, heterocyclyl, heterocyclyl C₁₋₁₀alkyl, aryl, arylC₁₋₁₀ alkyl, heteroaryl or heteroarylC₁₋₁₀ alkyl (and wherein the R_{6'} moieties, excluding hydrogen, may
15 themselves be optionally substituted 1 or 2 times, independently by halogen; hydroxy; hydroxy substituted alkyl; C₁₋₄ alkoxy; S(O)_mC₁₋₄ alkyl; amino, mono & di-substituted C₁₋₄ alkyl amino; C₁₋₄ alkyl, or CF₃); C(O)OR_{6'}; NR_{4'}R_{14'}, wherein R_{4'} and R_{14'} are each independently hydrogen or C₁₋₄ alkyl, such as amino or mono or -disubstituted C₁₋₄ alkyl or wherein the R_{4'}R_{14'} can cyclize together with the nitrogen
20 to which they are attached to form a 5 to 7 membered ring which optionally contains an additional heteroatom selected from O/N/S; C₁₋₁₀ alkyl, C₃₋₇cycloalkyl, or C₃₋₇cycloalkyl C₁₋₁₀ alkyl group, such as methyl, ethyl, propyl, isopropyl, t-butyl, etc. or cyclopropyl methyl; halosubstituted C₁₋₁₀ alkyl, such CF₂CF₂H, or CF₃; an optionally substituted aryl, such as phenyl, or an optionally substituted arylalkyl, such
25 as benzyl or phenethyl, wherein these aryl containing moieties may also be substituted one to two times by halogen; hydroxy; hydroxy substituted alkyl; C₁₋₄ alkoxy; S(O)_m C₁₋₄ alkyl; amino, mono & di-substituted C₁₋₄ alkyl amino; C₁₋₄ alkyl, or CF₃.

As used herein, the term "pharmaceutically acceptable" means a compound which is suitable for pharmaceutical use. Salts and solvates of compounds of the
30 invention which are suitable for use in medicine are those wherein the counterion or associated solvent is pharmaceutically acceptable. However, salts and solvates having non-pharmaceutically acceptable counterions or associated solvents are within the scope of the present invention, for example, for use as intermediates in the preparation of other compounds of the invention and their pharmaceutically acceptable salts and solvates.

As used herein, the term "pharmaceutically acceptable derivative", means any
35 pharmaceutically acceptable salt, solvate or prodrug e.g. ester, of a compound of the invention, which upon administration to the recipient is capable of providing (directly or

indirectly) a compound of the invention, or an active metabolite or residue thereof. Such derivatives are recognizable to those skilled in the art, without undue experimentation. Nevertheless, reference is made to the teaching of Burger's Medicinal Chemistry and Drug Discovery, 5th Edition, Vol 1: Principles and Practice, which is incorporated
5 herein by reference to the extent of teaching such derivatives. In one embodiment of the present invention the pharmaceutically acceptable derivatives are salts, solvates, esters, carbamates and phosphate esters. In another embodiment pharmaceutically acceptable derivatives are salts, solvates and esters. In yet another embodiment, pharmaceutically acceptable derivatives are salts and esters, in particular salts.

10 Suitable pharmaceutically acceptable salts are well known to those skilled in the art and include basic salts of inorganic and organic acids, such as hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methane sulphonic acid, ethane sulphonic acid, acetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid,
15 phenylacetic acid and mandelic acid.

The compounds of the present invention may be in the form of and/or may be administered as a pharmaceutically acceptable salt. For a review on suitable salts see Berge *et al.*, J. Pharm. Sci., 1977, 66, 1-19.

Typically, a pharmaceutical acceptable salt may be readily prepared by using a
20 desired acid or base as appropriate. The salt may precipitate from solution and be collected by filtration or may be recovered by evaporation of the solvent.

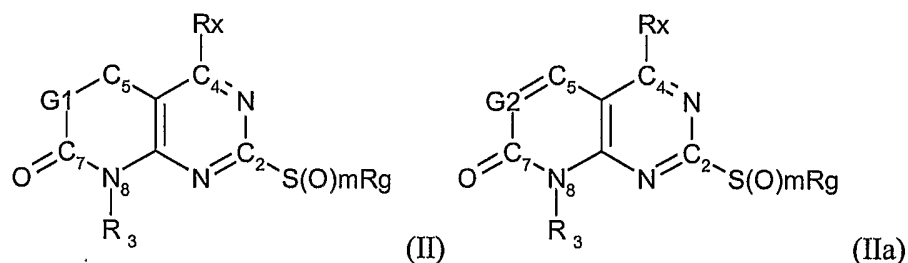
Pharmaceutically acceptable salts of compounds of Formula (I) may suitably be formed with a pharmaceutically acceptable cation, for instance, if a substituent group comprises a carboxy moiety. Suitable pharmaceutically acceptable cations are
25 well known to those skilled in the art and include alkaline, alkaline earth, ammonium and quaternary ammonium cations.

Those skilled in the art of organic chemistry will appreciate that many organic compounds can form complexes with solvents in which they are reacted or from which they are precipitated or crystallized. These complexes are known as
30 "solvates". As used herein, the term "solvate" refers to a complex of variable stoichiometry formed by a solute (in this invention, a compound of formula (I) or a salt thereof) and a solvent. Such solvents for the purpose of the invention may not interfere with the biological activity of the solute. Examples of suitable solvents include water, methanol, ethanol and acetic acid. Preferably the solvent used is a
35 pharmaceutically acceptable solvent. Examples of suitable pharmaceutically acceptable solvents include water, ethanol and acetic acid. Most preferably the

solvent used is water. A complex with water is known as a "hydrate". Solvates of the compound of the invention are within the scope of the invention.

Compounds of Formula (II) are represented by the structure:

5



wherein

G1 is CH₂ or NH;

G2 is CH or nitrogen;

10 Rx is chloro, bromo, iodo, or O-S(O)₂CF₃;

R_g is a C₁₋₁₀ alkyl;

m is 0, or an integer having a value of 1, or 2;

R₃ is a C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl C₁₋₁₀ alkyl, aryl, arylC₁₋₁₀ alkyl, heteroaryl, heteroarylC₁₋₁₀ alkyl, heterocyclic or a heterocyclylC₁₋₁₀ alkyl

15 moiety, and wherein each of these moieties may be optionally substituted.

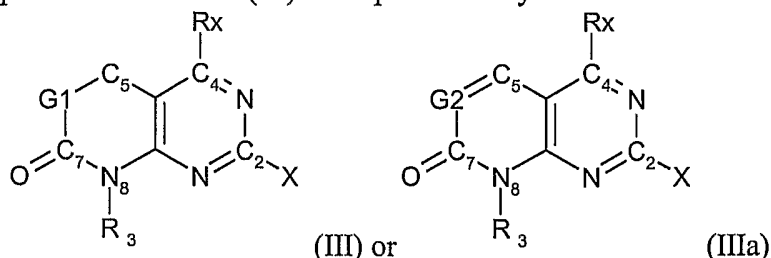
The optional substituents for the R₃ moiety are as defined herein for compounds of Formula (I).

In one embodiment of the invention, Rx is chloro. In another embodiment, R_g is methyl. In a further embodiment, m is 0. In another embodiment m is 1, and R₃ is an optionally substituted phenyl (as defined in Formula (I)).

In another embodiment, m is 0, R_g is methyl, Rx is chloro and R₃ is an optionally substituted phenyl (as defined in Formula (I)).

25

Compounds of Formula (III) are represented by the structure:



wherein

G1 is CH₂ or NH:

G2 is CH or nitrogen;

R_x is chloro, bromo, iodo, or O-S(O)₂CF₃;

X is R₂, OR₂', S(O)_mR₂', (CH₂)_n'N(R₁₁)S(O)_mR₂', (CH₂)_n'N(R₁₁)C(O)R₂',
(CH₂)_n'NR₄R₁₄, or (CH₂)_n'N(R₂') (R₂''), or N(R₁₀')-R_h-NH-C(=N-CN)NR_qR_q';

5 X₁ is N(R₁₁), O, S(O)_m, or CR₁₀R₂₀;

R_h is selected from an optionally substituted C₁₋₁₀ alkyl, -CH₂-C(O)-CH₂-,
-CH₂-O-CH₂-, -CH₂-C(O)N(R₁₀')CH₂-CH₂-, -CH₂-N(R₁₀')C(O)CH₂-,
-CH₂-CH(OR₁₀')-CH₂-, -CH₂-C(O)O-CH₂-CH₂-, or -CH₂-CH₂-O-C(O)CH₂-;

10 R_q and R_q' are independently selected at each occurrence from hydrogen, C₁₋₁₀
alkyl, C₃₋₇cycloalkyl, C₃₋₇cycloalkylC₁₋₁₀alkyl, C₅₋₇ cycloalkenyl, C₅₋₇
cycloalkenyl-C₁₋₁₀alkyl, aryl, arylC₁₋₁₀ alkyl, heteroaryl, heteroarylC₁₋₁₀ alkyl,
heterocyclic, or a heterocyclylC₁₋₁₀ alkyl moiety, wherein all of the moieties,
excluding hydrogen, are optionally substituted, or R_q and R_q' together with the
15 nitrogen to which they are attached form a 5 to 7 membered optionally substituted
ring, which ring may contain an additional heteroatom selected from oxygen,
nitrogen or sulfur;

R₂ is hydrogen, C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkylalkyl, aryl, arylC₁₋₁₀
alkyl, heteroaryl, heteroarylC₁₋₁₀ alkyl, heterocyclic, or a heterocyclylC₁₋₁₀ alkyl
moiety, and wherein each of these moieties, excluding hydrogen, may be
20 optionally substituted; or R₂ is the moiety

(CR₁₀R₂₀)_qX₁(CR₁₀R₂₀)_qC(A₁)(A₂)(A₃), or C(A₁)(A₂)(A₃);

R₂' is hydrogen, C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkylalkyl, aryl, arylC₁₋₁₀
alkyl, heteroaryl, heteroarylC₁₋₁₀ alkyl, heterocyclic, or a heterocyclylC₁₋₁₀ alkyl
moiety, and wherein each of these moieties, excluding hydrogen, may be
25 optionally substituted;

R₂'' is hydrogen, C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkylalkyl, aryl, arylC₁₋₁₀
alkyl, heteroaryl, heteroarylC₁₋₁₀ alkyl, heterocyclic, or a heterocyclylC₁₋₁₀ alkyl
moiety, and wherein these moieties, excluding hydrogen, may be optionally
substituted; or

30 wherein R₂'' is the moiety (CR₁₀R₂₀)_tX₁(CR₁₀R₂₀)_qC(A₁)(A₂)(A₃);

A₁ is an optionally substituted C₁₋₁₀ alkyl, heterocyclic, heterocyclic C₁₋₁₀ alkyl,
heteroaryl, heteroaryl C₁₋₁₀ alkyl, aryl, or aryl C₁₋₁₀ alkyl;

A₂ is an optionally substituted C₁₋₁₀ alkyl, heterocyclic, heterocyclic C₁₋₁₀ alkyl,
heteroaryl, heteroaryl C₁₋₁₀ alkyl, aryl, or aryl C₁₋₁₀ alkyl;

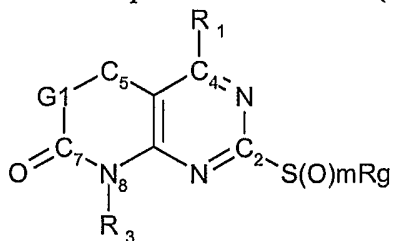
35 A₃ is hydrogen or is an optionally substituted C₁₋₁₀ alkyl;

- R₃ is a C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl C₁₋₁₀ alkyl, aryl, arylC₁₋₁₀ alkyl, heteroaryl, heteroarylC₁₋₁₀ alkyl, heterocyclic or a heterocyclylC₁₋₁₀ alkyl moiety, and wherein each of these moieties may be optionally substituted;
- R₄ and R₁₄ are each independently selected from hydrogen, C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkylC₁₋₄alkyl, aryl, aryl-C₁₋₄ alkyl, heterocyclic, heterocyclic C₁₋₄ alkyl, heteroaryl or a heteroaryl C₁₋₄ alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or the R₄ and R₁₄ together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 4 to 7 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or nitrogen;
- R₉' is independently selected at each occurrence from hydrogen, or C₁₋₄ alkyl;
- R₁₀ and R₂₀ are independently selected from hydrogen or C₁₋₄alkyl;
- R₁₀' is independently selected at each occurrence from hydrogen or C₁₋₄alkyl;
- R₁₁ is independently selected from hydrogen or C₁₋₄alkyl;
- n' is independently selected at each occurrence from 0 or an integer having a value of 1 to 10;
- m is independently selected at each occurrence from 0 or an integer having a value of 1 or 2;
- q is 0 or an integer having a value of 1 to 10;
- q' is 0, or an integer having a value of 1 to 6; or
- t is an integer having a value of 2 to 6.

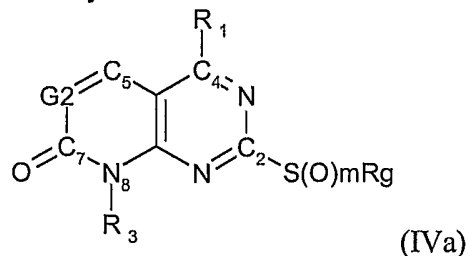
Suitably, R_x is chloro, bromo, iodo, or O-S(O)₂CF₃. In an embodiment of the invention, R_x is chloro.

- The X term moieties and their substituent groups, etc. are as defined herein for compounds of Formula (I).

Compounds of Formula (IV) are represented by the structure:



(IV) or



- wherein
- G₁ is CH₂ or NH;
- G₂ is CH or nitrogen;

R₁ is an aryl, aryl C₂₋₁₀ alkyl, heteroaryl, heteroaryl C₂₋₁₀ alkyl; aryl C₂₋₁₀ alkenyl, aryl C₂₋₁₀ alkynyl, heteroaryl C₂₋₁₀ alkenyl, heteroaryl C₂₋₁₀ alkynyl, C₂₋₁₀ alkenyl, or C₂₋₁₀ alkynyl moiety, which moieties may be optionally substituted;

5 R_g is an optionally substituted C₁₋₁₀ alkyl;

m is 0 or an integer having the value of 1 or 2;

R₃ is a C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl C₁₋₁₀ alkyl, aryl, aryl C₁₋₁₀ alkyl, heteroaryl, heteroaryl C₁₋₁₀ alkyl, heterocyclic or a heterocyclic C₁₋₁₀ alkyl moiety, and wherein each of these moieties may be optionally substituted.

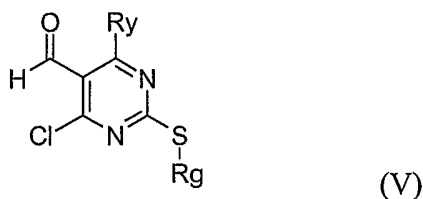
10

Suitably R₁ and R₃ are substituted as defined herein for compounds of Formula (I). In one embodiment, R₁ is an optionally substituted aryl or heteroaryl ring, preferably and optionally substituted aryl.

In another embodiment R_g is methyl. In a further embodiment, m is 0 or 2.

15

Compounds of Formula (V) are represented by the formula:



wherein

20 Ry is chloro, bromo, iodo, O-S(O)₂CF₃; and

Rg is a C₁₋₁₀ alkyl.

In one embodiment of the invention, Ry is bromo, iodo, or O-S(O)₂CF₃.

In another embodiment of the invention, Rg is methyl.

25

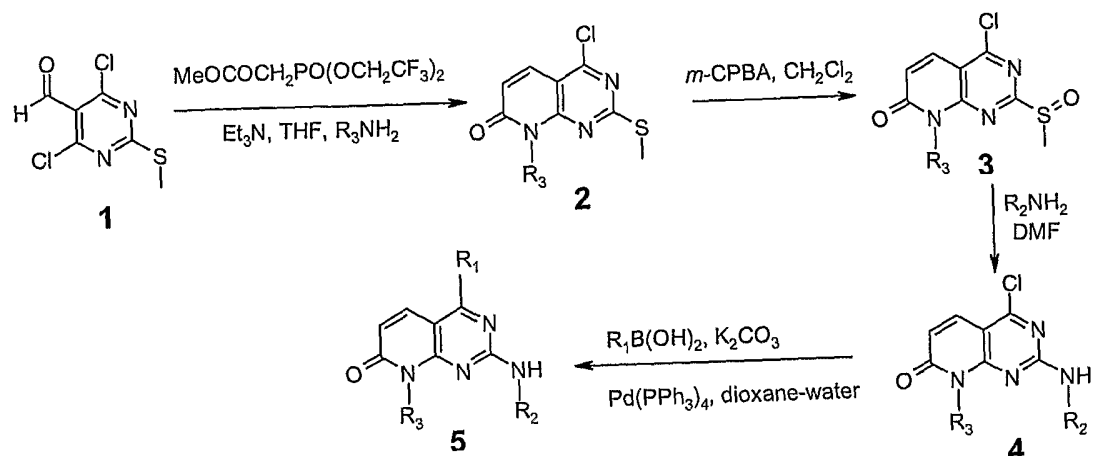
The general preparation of analogs around the pyrido[2,3-*d*]pyrimidin-7-one template is shown in the Schemes, **Schemes 1 to 4** below. While a particular formula with particular substituent groups is shown herein, e.g. Rg as methyl, or Rx or LG2 as chloro, the synthesis is applicable to all formulas and all substituent groups as described herein.

30

The synthesis described herein, Schemes 1 to 4, start with a 4,6-Ry substituted-2-methylsulfanyl-pyrimidine-5-carboxaldehyde (**1**), such as described in Formula (V). Treatment of **1**, **Scheme 1**, with an optionally substituted aniline in the presence of an olefin forming agent, such as bis(2,2,2-trifluoroethyl)-

(methoxycarbonylmethyl)-phosphonate or an acylating agent, such as acetic acid anhydride affords the pyrido[2,3-*d*]pyrimidin-7-one, **2**. Oxidation of **2** with a peracid, such as 3-chloroperoxybenzoic acid (*m*-CPBA) yields compound **3**. This is followed by substitution of **3** in C2 position with a suitable X moiety as described in Formula (I) herein. In this scheme, substitution of the C2 position is demonstrated with serinol to furnish compound **4**. Palladium (0) mediated Suzuki cross-coupling affords compound **5**. Other cross coupling reactions known in the art may also be suitable for use herein.

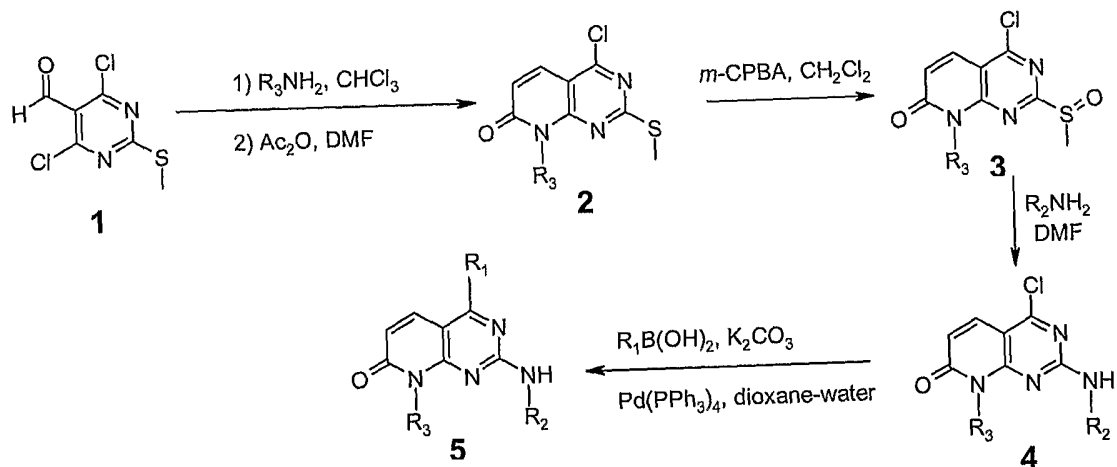
Scheme 1: Route 1

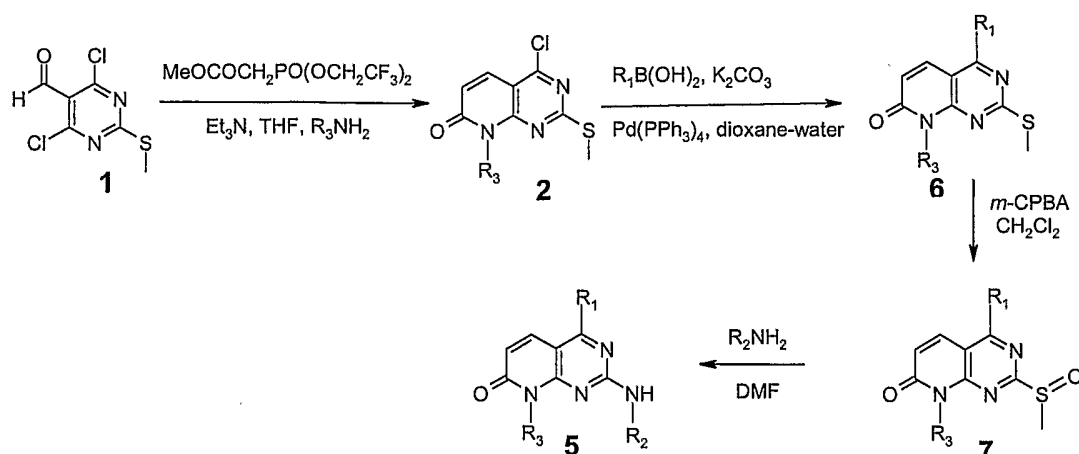
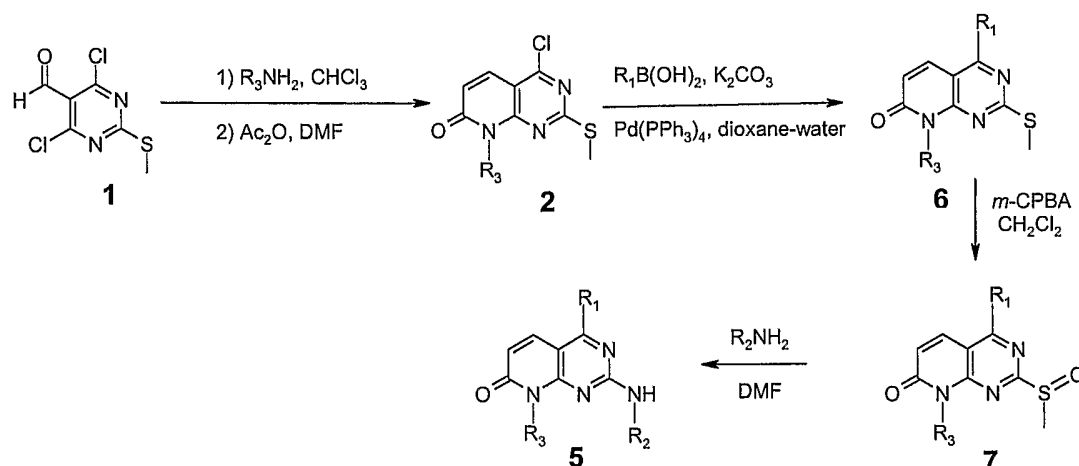


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Scheme 2: Route 2

10



Scheme 3: Route 3**5 Scheme 4: Route 4**

In **Routes 1 & 3; Schemes 1 & 3**, Compound **1** to Compound **2**, while the olefin forming reagent Bis(2,2,2-trifluoroethyl)(methoxycarbonylmethyl)phosphonate is used, alternative cyclization reagents, include, but are not limited to Bis(2,2,2-trifluoroethyl)-(ethoxycarbonylmethyl)phosphonate, Bis(2,2,2-trifluoroethyl)-(isopropoxycarbonylmethyl)phosphonate, (Diethoxy-phosphoryl)-acetic acid methyl ester, (Diisopropoxy-phosphoryl)-acetic acid methyl ester, (Diphenyloxy-phosphoryl)-acetic acid methyl ester, (Diethoxy-phosphoryl)-acetic acid ethyl ester, (Diisopropoxy-phosphoryl)-acetic acid ethyl ester, or (Diphenyloxy-phosphoryl)-acetic acid ethyl ester.

While this reaction as shown in **Scheme 1** and **Scheme 3** uses triethylamine as a base, suitable alternative bases can include, but are not limited to pyridine, diisopropyl ethyl amine, or pyrrolidone, or combinations thereof.

Further, while the reaction scheme as shown in **Scheme 1** and **Scheme 3** utilizes tetrahydrofuran as a solvent, it is recognized that suitable alternative organic solvents can be used. Such solvents include, but are not limited to chloroform, methylene chloride, acetonitrile, toluene, DMF, or n-methylpyrrolidine, or combinations thereof.

The reaction temperature of this particular step in the reaction scheme can be varied from room temperature to > 100 °C, i.e. reflux temperature of the solvent. Alternatively, this reaction process step may be performed under suitable microwave conditions.

In **Routes 2 & 4, Schemes 2 & 4**, Compound **1** to Compound **2**, while the reagent acetic anhydride is shown, this reagent can be replaced with acetyl chloride, or any other suitably acylating reagent.

Further, while the reaction scheme as shown in **Scheme 2** and **Scheme 4** utilizes chloroform as a solvent, it is recognized that suitable alternative organic solvents can be used. Such solvents include, but are not limited to tetrahydrofuran, methylene chloride, acetonitrile, toluene, DMF, n-methylpyrrolidine, or dioxane, or combinations thereof.

The reaction temperature of this particular step in the reaction scheme can be varied from room temperature to > 100 °C, i.e. reflux temperature of the solvent. Alternatively, this reaction process step may be performed under suitable microwave conditions.

In **Routes 1 & 2; Schemes 1 & 2**, Compound **2** to Compound **3**, or for **Routes 3 & 4, Schemes 3 & 4**, Compound **6** to Compound **7**, while the oxidizing reagent 3-chloroperoxybenzoic acid (*m*-CPBA) is used, alternative reagents, include but are not limited to hydrogen peroxide, sodium periodate, potassium periodate, Oxone, OsO₄, catalytic tertiary amine *N*-oxide, peracids, such as aryl peracids, i.e. perbenzoic and the aforementioned *m*-CPBA, or alkylperacids, as such peracetic acid and pertrifluoroacetic acid, oxygen, ozone, organic peroxides, peroxide (H₂O₂), and inorganic peroxides, potassium and zinc permanganate, potassium persulfate. It is recognized that the peroxide agents can be used in combination with sodium tungstate, acetic acid or sodium hyperchlorite.

It is recognized that the oxidation process may in fact yield Compound **3**, or Compound **7**, but may also result in the corresponding sulfone, as well as the sulfoxide, or mixtures thereof.

This reaction step, while demonstrated in the schematics with methylene chloride as the solvent, may use alternative organic solvents other than primary amines or alcohols which include, but are not limited to chloroform, acetone, DMF,

THF, acetonitrile, dioxane, or DMSO, or combinations thereof. This reaction step may be conducted at about 0 °C to room temperature.

In **Routes 1 & 2; Schemes 1 & 2**, Compound **3** to Compound **4**, or for **Route 3 & 4, Schemes 3 & 4**, Compound **7** to Compound **5**, the reaction solvent of DMF may alternatively be replaced with other suitable anhydrous organic solvents, which does not contain a nucleophile, which include but are not limited to THF, methylene chloride, acetone, acetonitrile, toluene, chloroform, n-methyl-pyrrolidine, or dioxane, or combinations thereof.

This temperature step may be conducted at room temperature to > 100 °C, i.e. reflux temperature of the solvent. Alternatively, this reaction process step may be performed under suitable microwave conditions.

In **Routes 1 & 2, Schemes 1 & 2**, Compound **4** to Compound **5**, or for **Routes 3-4, Schemes 3-4**, Compound **2** to Compound **6** wherein Compound **2** or **4** are coupled to arylboronic acids, heteroarylboronic acids or the corresponding boronic acid esters under standard Suzuki coupling conditions. These reaction conditions utilize a palladium catalyst, such as tetrakis(triphenylphosphine)palladium (0), which has been shown to provide good yields of either compound **5** or **6**. The reaction conditions may be from room temperature to about 250°C, by heating in an oil bath, or with microwave irradiation. If desired, these Suzuki coupling reactions may be run under microwave conditions.

The aryl or heteroaryl boronic acid or ester intermediates can be synthesized either by the palladium catalyzed coupling of an aryl halide and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane or the transmetalation of an aryl halide with a Grignard reagent, e.g., isopropylmagnesium bromide followed by a trialkylborate (e.g., triethylborate) in a suitable solvent like THF.

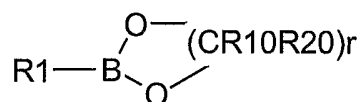
Alternatively, the coupling reaction of **2** or **4** may be performed utilizing aryl or heteroaryl organozinc, organocopper, organotin, or other organometallic reagents known to afford cross-coupling products such as **5** or **6** [See for example: Solberg, J.; Undheim, K. *Acta Chemica Scandinavia* **1989**, 62-68, whose disclosure is incorporated by reference herein]. Using the reaction procedures described in the aforementioned WO 02/059083, it has been found that compounds of Formula (III) as described herein, were unable to be synthesized following those procedures. The present invention provides for an alternative method to synthesize compounds of Formula (I) having differing R₁ substituents on the C4 position of the pyrido[2,3-*d*]pyrimidin-7-one pharmacophore. These substituents may be introduced to this

position after the pyrido[2,3-*d*]pyrimidine-7-one pharmacophore is substituted with functional groups at the C₂ and N₈ position. This particular substitution has not previously been available using the reaction conditions as set forth in WO 02/059083.

While it is possible to produce individual compounds using the process illustrated herein, a benefit for these reaction pathways lies in its ability to optimize leads and to make arrays for combinatorial chemistry, with various R₁, R₂, and R₃ substituents.

Another aspect of the invention is a process to make compounds of Formula (I) as defined herein, which comprises reacting a compound of Formula (III), as defined herein with a coupling agent selected from an arylboronic acid, or a heteroarylboronic acid or their corresponding boronic acid esters, with a suitable palladium catalyst to yield a compound of Formula (I). This coupling process takes place under standard Suzuki conditions.

Suitably the arylboronic acids, heteroarylboronic acids, or their corresponding boronic acid esters are R₁-boronic acid or an R₁-boronic acid ester; e.g. R₁B(OH)₂, R₁B(O-C₁₋₄ alkyl)₂, or



wherein R₁, R₁₀, and R₂₀ is as defined for compounds of Formula (I) herein; and r is an integer having a value of 2 to 6.

The coupling conditions include the use of appropriate solvents. These solvents include, but are not limited to dioxane, THF, DMF, DMSO, NMP, acetone, water, or a combination or a mixture thereof. Preferably, the solvent is THF/H₂O, or dioxane/H₂O.

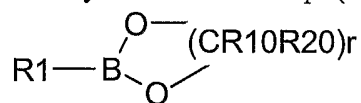
The coupling conditions also include the presence of catalytic amount of catalysts and these catalysts include, but not limited to tetrakis(triphenylphosphine)-palladium (0), PdCl₂, Pd(OAc)₂, (CH₃CN)₂PdCl₂, Pd(dppf)₂, or [1,1'-bis(diphenylphosphino)-ferrocene]-dichloropalladium(II).

The coupling reaction may or may not require the presence of a base. Suitable bases include, but are not limited to NaHCO₃, KHCO₃, Na₂CO₃, K₂CO₃, KOAc or combination or mixture thereof. Preferably, the base is K₂CO₃ and KOAc.

The coupling reaction may or may not require heating. The heating can be carried out with a regular oil bath or microwave irradiations and the temperature can be varied from room temperature to >100 °C, i.e. reflux temperature of the solvent. The coupling reaction may or may not require a sealed reaction vessel and the internal pressure can be varied from one atmosphere to 100 atmospheres.

The aryl or heteroaryl boronic acid or ester intermediates containing the R₁ moiety, used in the Suzuki coupling reactions may or may not be commercially available and they can be prepared by utilizing proper methods in the literature known to those with appropriate training. Examples of these methods include, but not limited to palladium catalyzed coupling of an aryl halide and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane or the transmetalation of an aryl halide with a Grignard reagent, e.g., isopropylmagnesium bromide followed by a trialkylborate (e.g., triethylborate) in a suitable solvent. These solvents include, but not limited to CH₂Cl₂, chloroform, CH₃CN, benzene, THF, hexane, ethyl ether, *tert*-butyl methyl ether, DMSO, DMF, toluene, *n*-methyl-pyrrolidine, dioxane. The reaction temperature can be varied from -78 °C to >100 °C, i.e. reflux temperature of the solvent. Alternatively, this reaction process step may or may not be performed under suitable microwave irradiation conditions. This reaction may or may not require a sealed reaction vessel and the internal pressure can be varied from one atmosphere to 100 atmospheres.

One embodiment of the invention are the arylboronic acids and esters which are generically referred to as R₁B(OH)₂, R₁B(O-C₁₋₄ alkyl)₂, or



wherein

R₁₀ and R₂₀ are independently selected from hydrogen or C₁₋₄ alkyl;

r is an integer having a value of 2 to 6;

R₁ is an optionally substituted phenyl, as defined according to Formula (I).

Suitably, the phenyl ring is substituted by one or more times independently at each occurrence by halogen, C₁₋₄ alkyl, halo-substituted-C₁₋₄ alkyl, cyano, nitro, (CR₁₀R₂₀)_v, NR_dR_d', (CR₁₀R₂₀)_vC(O)R₁₂, SR₅, S(O)R₅, S(O)₂R₅, or (CR₁₀R₂₀)_vOR₁₃, (CR₁₀R₂₀)_vC(Z)NR₄R₁₄, (CR₁₀R₂₀)_vC(Z)OR₈, (CR₁₀R₂₀)_vCOR_a', (CR₁₀R₂₀)_vC(O)H, SR₅, S(O)R₅, S(O)₂R₅, (CR₁₀R₂₀)_vOR₈, ZC(Z)R₁₁, N(R₁₀')C(Z)R₁₁, N(R₁₀')S(O)₂R₇, C(Z)N(R₁₀') (CR₁₀R₂₀)_vR_b, C(Z)O(CR₁₀R₂₀)_vR_b, N(R₁₀')C(Z)(CR₁₀R₂₀)_vR_b; N(R₁₀')C(Z)N(R₁₀') (CR₁₀R₂₀)_vR_b; or N(R₁₀')OC(Z)(CR₁₀R₂₀)_vR_b; and wherein R_a' is C₁₋₄ alkyl, halo-substituted C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₇ cycloalkyl, C₅₋₇ cycloalkenyl, aryl, arylC₁₋₄ alkyl, heteroaryl, heteroarylC₁₋₄ alkyl, heterocyclyl, heterocyclylC₁₋₄ alkyl, (CR₁₀R₂₀)_vOR₇, (CR₁₀R₂₀)_vS(O)_mR₇, (CR₁₀R₂₀)_v N(R₁₀')S(O)₂R₇, or (CR₁₀R₂₀)_vNR₄R₁₄;

and wherein the aryl, arylalkyl, heteroaryl, heteroaryl alkyl may be optionally substituted;

R_b is hydrogen, C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkylC₁₋₁₀ alkyl, aryl, arylC₁₋₁₀alkyl, heteroaryl, heteroarylC₁₋₁₀ alkyl, heterocyclic, or a heterocyclylC₁₋₁₀ alkyl moiety, which moieties excluding hydrogen, may all be optionally substituted;

R_d and R_{d'} are each independently selected from hydrogen, C₁₋₄ alkyl, C₃₋₅ cycloalkyl, C₃₋₅ cycloalkylC₁₋₄alkyl, or the R_d and R_{d'} together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 5 to 6 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR_{9'}, and wherein the R_d and R_{d'} moieties which are C₁₋₄ alkyl, C₃₋₆cycloalkyl, C₃₋₆cycloalkylC₁₋₄ alkyl, and the R₄ and R₁₄ cyclized ring are optionally substituted;

R₇ is C₁₋₆alkyl, aryl, arylC₁₋₆alkyl, heterocyclic, heterocyclylC₁₋₆ alkyl, heteroaryl, or heteroarylC₁₋₆alkyl; and wherein each of these moieties may be optionally substituted;

R₈ is independently selected at each occurrence from hydrogen, C₁₋₄ alkyl, halo-substituted C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl C₁₋₄ alkyl, C₅₋₇ cycloalkenyl, C₅₋₇cycloalkenyl C₁₋₄ alkyl, aryl, arylC₁₋₄ alkyl, heteroaryl, heteroarylC₁₋₄ alkyl, heterocyclyl, or a heterocyclylC₁₋₄ alkyl moiety, and wherein these moieties, excluding hydrogen, may be optionally substituted independently at each occurrence;

R_{9'} is independently selected at each occurrence from hydrogen, or C₁₋₄ alkyl;

m is independently selected at each occurrence from 0 or an integer having a value of 1 or 2;

v is independently selected at each occurrence from 0, or an integer having a value of 1 to 2.

v' is independently selected at each occurrence from 0 or an integer having a value of 1 or 2;

R₄ and R₁₄ are each independently selected at each occurrence from hydrogen, C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkylC₁₋₄alkyl, aryl, aryl-C₁₋₄ alkyl, heterocyclic, heterocyclic C₁₋₄ alkyl, heteroaryl or heteroaryl C₁₋₄ alkyl; or the R₄ and R₁₄ together with the nitrogen which they are attached form an unsubstituted or substituted heterocyclic ring of 4 to 7 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or nitrogen; and wherein all of these moieties, excluding hydrogen, are optionally substituted;

- R_{4'} and R_{14'} are each independently selected at each occurrence from hydrogen or C₁₋₄ alkyl, or R_{4'} and R_{14'} can cyclize together with the nitrogen to which they are attached to form an optionally substituted 5 to 7 membered ring which optionally contains an additional heteroatom selected from oxygen, sulfur or NR_{9'};
- R₅ is independently selected at each occurrence from hydrogen, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl or NR_{4'}R_{14'}, excluding the moieties SR₅ being SNR_{4'}R_{14'}, S(O)₂R₅ being SO₂H and S(O)R₅ being SOH;
- R₁₀ and R₂₀ are independently selected at each occurrence from hydrogen or C₁₋₄ alkyl;
- R_{10'} is independently selected at each occurrence from hydrogen or C₁₋₄ alkyl;
- R₁₁ is independently selected at each occurrence from hydrogen, or C₁₋₄ alkyl;
- R₁₂ is independently selected at each occurrence from hydrogen, C₁₋₄ alkyl, halo-substituted C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl C₁₋₄ alkyl, C₅₋₇ cycloalkenyl, C₅₋₇cycloalkenyl C₁₋₄ alkyl, aryl, arylC₁₋₄ alkyl, heteroaryl, heteroarylC₁₋₄ alkyl, heterocyclyl, or heterocyclylC₁₋₄ alkyl, and wherein these moieties, excluding hydrogen, may be optionally substituted; and
- R₁₃ is independently selected at each occurrence from hydrogen, C₁₋₄ alkyl, halo-substituted C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₇ cycloalkyl, C₃₋₇cycloalkylC₁₋₄ alkyl, C₅₋₇ cycloalkenyl, C₅₋₇cycloalkenyl C₁₋₄ alkyl, aryl, arylC₁₋₄ alkyl, heteroaryl, heteroarylC₁₋₄ alkyl, heterocyclyl, or a heterocyclylC₁₋₄ alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted.

25

- In one embodiment, the phenyl ring is substituted by C(Z)N(R_{10'})(CR₁₀R₂₀)_v R_b, or N(R_{10'})C(Z)(CR₁₀R₂₀)_vR_b, and optionally another substituent (R_{1'})_g, and g is 1 or 2. R_b is suitably as defined in Formula (I) herein. Suitably, R_{1'} is independently selected at each occurrence from halogen, C₁₋₄ alkyl, halo-substituted-C₁₋₄ alkyl, cyano, nitro, (CR₁₀R₂₀)_vNR_dR_{d'}, (CR₁₀R₂₀)_vC(O)R₁₂, SR₅, S(O)R₅, S(O)₂R₅, or (CR₁₀R₂₀)_vOR₁₃. Preferably R_{1'} is independently selected at each occurrence from C₁₋₄ alkyl, such as methyl, or halogen, such as fluorine or chlorine or bromine, or halo-substituted-C₁₋₄ alkyl, such as CF₃.

35

In one embodiment, the C(Z)N(R_{10'})(CR₁₀R₂₀)_v R_b, is substituted on the phenyl ring in the 4-position or the 5-position, preferably the 5-position. If an R_{1'} moiety is present, it is preferably in the 2-position, and R_{1'} is independently selected

at each occurrence from C₁₋₄ alkyl, such as methyl, or halogen, such as fluorine or chlorine or bromine. Preferably the aryl is 4-methyl-*N*-1,3-thiazol-2-ylbenzamide, *N*-(4-fluorophenyl)-4-methylbenzamide, or 4-methyl-*N*-propylbenzamide.

In another embodiment the phenyl ring is substituted one or more times, preferably 1
5 to 4 times by R_{1'} and R_{1'} is independently selected at each occurrence from halogen, C₁₋₄ alkyl, halo-substituted-C₁₋₄ alkyl, cyano, nitro, (CR₁₀R₂₀)_vNR_dR_d', (CR₁₀R₂₀)_vC(O)R₁₂, SR₅, S(O)R₅, S(O)₂R₅, or (CR₁₀R₂₀)_vOR₁₃. Preferably, the phenyl ring is di-substituted in the 2,4-position. In another embodiment R_{1'} is
10 independently selected at each occurrence from C₁₋₄ alkyl, such as methyl, or halogen, such as fluorine or chlorine or bromine, or halo-substituted-C₁₋₄ alkyl, such as CF₃. Preferably, the aryl is phenyl, 2-methyl-4-fluorophenyl, 2-methylphenyl, 2-chlorophenyl, 2-fluorophenyl, or 2-methyl-3-fluorophenyl.

Another aspect of the invention is another process to make compounds of
15 Formula (I) as defined herein, which comprises reacting a compound of Formula (III), as defined herein utilizing aryl or heteroaryl organozinc, organocopper, organotin, or other organometallic reagents known in the art to afford a cross-coupling product of the desired R₁ moiety in the C₄ position of the template yielding a compound of Formula (I).

20 This coupling reaction may be performed utilizing aryl or heteroaryl organozinc (e.g., R₁-ZnBr, R₁-ZnCl, R₁-Zn-R₁), organocopper [e.g., (R₁)₂-CuLi], organotin (e.g., R₁-Sn(CH₃)₃, R₁-Sn(CH₂CH₂CH₂CH₃)₃), or other organometallic reagents to afford the cross-coupling product. The R₁ aryl and heteroaryl moiety is as defined for Formula (I) herein. If the desired aryl or hetero aryl organozinc (e.g.,
25 R₁-ZnBr, R₁-ZnCl, R₁-Zn-R₁), organocopper [e.g., (R₁)₂-CuLi], organotin (e.g., R₁-Sn(CH₃)₃, R₁-Sn(CH₂CH₂CH₂CH₃)₃), or other organometallic reagent is not commercially available, they can readily be prepared by utilizing proper methods, known in the literature.

These types of coupling reactions require the use of appropriate solvents.
30 Such solvents include, but are not limited to dioxane, THF, methylene chloride, chloroform, benzene, hexane, ethyl ether, *tert*-butyl methyl ether or a combination or a mixture thereof.

The coupling reaction may, or may not, require the presence of catalytic amount of a catalyst. Such catalysts include, but are not limited to
35 tetrakis(triphenylphosphine)palladium (0), PdCl₂, Pd(OAc)₂, (CH₃CN)₂PdCl₂, Pd(dppf)₂.

The reaction temperature can be varied from -78 °C to >100 °C, i.e. reflux temperature of the solvent. Alternatively, this reaction process step may be performed under suitable microwave irradiation conditions, if needed. This reaction may, or may not, require a sealed reaction vessel and the internal pressure can be varied from one atmosphere to 100 atmospheres.

Suitably, the R₁ moiety is as defined for compounds of Formula (I) herein.

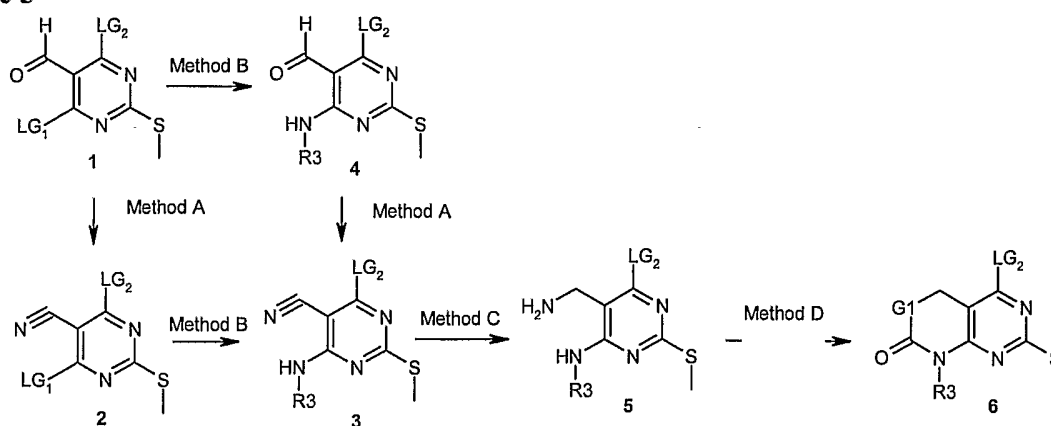
In one embodiment, the R₁ moiety is an optionally substituted aryl ring, preferably a phenyl ring. In another embodiment, the phenyl ring is substituted by C(Z)N(R_{10'})(CR₁₀R₂₀)_v R_b, or N(R_{10'})C(Z)(CR₁₀R₂₀)_v R_b, and optionally another substituent (R_{1'})_g, and g is 1 or 2. R_b is suitably as defined in Formula (I) herein. Suitably, R_{1'} is independently selected at each occurrence from halogen, C₁₋₄ alkyl, halo-substituted-C₁₋₄ alkyl, cyano, nitro, (CR₁₀R₂₀)_v NR_dR_{d'}, (CR₁₀R₂₀)_v C(O)R₁₂, SR₅, S(O)R₅, S(O)₂R₅, or (CR₁₀R₂₀)_v OR₁₃. Preferably R_{1'} is independently selected at each occurrence from C₁₋₄ alkyl, such as methyl, or halogen, such as fluorine or chlorine or bromine, or halo-substituted-C₁₋₄ alkyl, such as CF₃.

In one embodiment, the C(Z)N(R_{10'})(CR₁₀R₂₀)_v R_b, is substituted on the phenyl ring in the 4-position or the 5-position, preferably the 5-position. If an R_{1'} moiety is present, it is preferably in the 2-position, and R_{1'} is independently selected at each occurrence from C₁₋₄ alkyl, such as methyl, or halogen, such as fluorine or chlorine or bromine. Preferably the aryl is 4-methyl-N-1,3-thiazol-2-ylbenzamide, N-(4-fluorophenyl)-4-methylbenzamide, or 4-methyl-N-propylbenzamide.

In another embodiment the phenyl ring is substituted one or more times, preferably 1 to 4 times by R_{1'} and R_{1'} is independently selected at each occurrence from halogen, C₁₋₄ alkyl, halo-substituted-C₁₋₄ alkyl, cyano, nitro, (CR₁₀R₂₀)_v NR_dR_{d'}, (CR₁₀R₂₀)_v C(O)R₁₂, SR₅, S(O)R₅, S(O)₂R₅, or (CR₁₀R₂₀)_v OR₁₃. Preferably, the phenyl ring is di-substituted in the 2,4-position.

In another embodiment R_{1'} is independently selected at each occurrence from C₁₋₄ alkyl, such as methyl, or halogen, such as fluorine or chlorine or bromine, or halo-substituted-C₁₋₄ alkyl, such as CF₃. Preferably, the aryl moiety is a 2-methyl-4-fluorophenyl.

Additional methods to produce compounds of Formula (II), wherein G₁ is NH, are shown in Scheme 5 below.

Scheme 5

Method A is for conversion of **1** to **2**. Examples of the methods include, but are not limited to condensation with NH_2OH followed by treatment with thionyl chloride (SOCl_2) [e.g., Santilli et al., *J. Heterocycl. Chem.* (1971), 445-53] or oxidation of $-\text{CHO}$ group to $-\text{COOH}$ followed by formation of a primary amide ($-\text{CONH}_2$) and treatment with POCl_3 . Suitable Method A can also be utilized to furnish the conversion of **4** to **3** – **Scheme 5**.

Leaving groups (LG, described as Leaving group 1 (LG1) & LG2) in **1** (or **2**), or elsewhere, can be independently selected from $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, or $-\text{OTf}$ and these groups can be installed through the transformation of another functional group (e.g. $-\text{OH}$) by following the methods well known in the art (e.g., treatment of the $-\text{OH}$ compound with POCl_3).

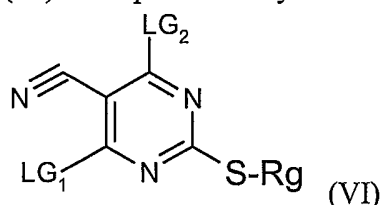
Method B is for selective displacement of suitable aldehyde **1** or nitrile **2** with an amine ($\text{R}_3\text{-NH}_2$). This type of displacement may be achieved using triethylamine and the desired amine R_3NH_2 in chloroform at room temperature for 10 minutes. The reaction was very effective for a range of alkyl amines (78-95 % yield). For aryl or heteroaryl amines, elevated temperatures (reflux), longer reaction time (24 hours) and presence of NaH (or Na) may be necessary for reaction completion. Use of the base could be omitted when 3 or more equivalent of the desired amine were used. Other suitable bases include but are not limited to pyridine, diisopropyl ethylamine or pyrrolidine, which may also be used in an appropriate organic solvent, including but not limited to THF, diethyl ether, DCM, DMF, DMSO, toluene or dioxane.

Method C is for the reduction of nitrile **3** to amine **5**. **5** may be considered a primary amine (NH_2), a secondary amine (because of $-\text{NH}(\text{R}_3)$) or an amine (as it contains basic nitrogen). This method includes, but is not limited to BH_3 in

appropriate organic solvent, such as THF, DCM, toluene, DMSO, diethyl ether or dioxane. Other suitable reduction reagents, include but are not limited to NaBH₄, LAH or DIBAL. Method C may require elevated temperatures (e.g., heating, refluxing or irradiating with microwave). Another example of the method is
 5 hydrogenation (H₂) in the presence of transition metals (e.g., Pd/C, Raney-Ni, PdCl₂).

Method D is for the cyclization of **5** to **6**. This method requires the presence of a cyclization reagent (e.g., CDI, COCl₂, tri-phosgene, or phenyl chloroformate methyl chloroformate). Presence of a suitable base may help the reaction to go to
 10 completion and examples of the base include, but not limited to triethyl amine, diisopropylethylamine or pyrrolidine. Reaction solvent can be DCM, THF, toluene, DMSO, or DMF.

Compounds of Formula (VI) are represented by the formula:



15 wherein

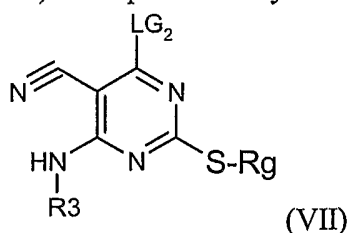
LG2 is chloro, bromo, iodo, or O-S(O)₂CF₃;

LG1 is chloro, bromo, iodo, or O-S(O)₂CF₃; and

Rg is an optionally substituted C₁₋₁₀ alkyl.

20 In one embodiment, LG2 is chloro. IN a further embodiment, LG1 is chloro. In another embodiment, Rg is methyl.

Compounds of Formula (VII) are represented by the formula:



25 wherein

LG2 is chloro, bromo, iodo, O-S(O)₂CF₃;

Rg is an optionally substituted C₁₋₁₀ alkyl;

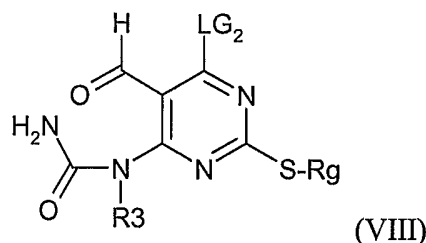
R3 is a C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl C₁₋₁₀ alkyl, aryl, arylC₁₋₁₀ alkyl, heteroaryl, heteroarylC₁₋₁₀ alkyl, heterocyclic or a heterocyclC₁₋₁₀ alkyl

30 moiety, and wherein each of these moieties may be optionally substituted.

Suitably R₃ is substituted as defined herein for compounds of Formula (I).

In one embodiment, R_g is methyl. In another embodiment, LG₂ is chloro.

- 5 Another aspect of the invention are compounds of Formula (VIII) represented by the formula:



wherein

LG₂ is chloro, bromo, iodo, O-S(O)₂CF₃;

- 10 R_g is an optionally substituted C₁₋₁₀ alkyl;

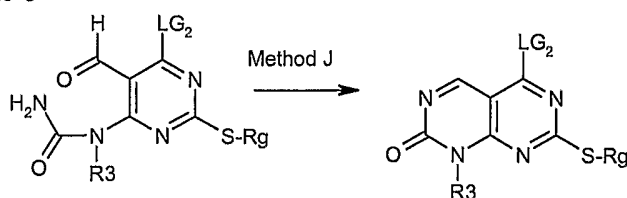
R₃ is a C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl C₁₋₁₀ alkyl, aryl, arylC₁₋₁₀ alkyl, heteroaryl, heteroarylC₁₋₁₀ alkyl, heterocyclic or a heterocyclylC₁₋₁₀ alkyl moiety, and wherein each of these moieties may be optionally substituted.

- 15 Suitably R₃ is substituted as defined herein for compounds of Formula (I).

In an embodiment of the invention LG₂ is chloro. In another embodiment, R_g is methyl. In another embodiment, LG₂ is chloro, R_g is methyl, and R₃ is an optionally substituted phenyl.

- 20 Another aspect of the present invention is the novel process, shown in **Scheme- 6** below, to make the transformation of a compound of Formula (VIII) to a compound of Formula (II) wherein Rx is now defined as LG₂, and m=0.

Scheme 6



25

13

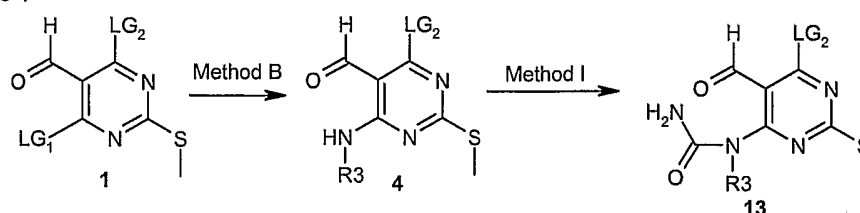
14

Method J is for imine formation to convert compound **13** to a compound of Formula (II) wherein m is 0, compound **14**. This can be achieved by following various strategies known in the art. Strategies include, but are not limited to treatment with an acid including TFA, HOAc, HCl, H₂SO₄ or a Lewis acid (e.g., AlCl₃). This

conversion may require elevated temperatures (e.g., heat, solvent reflux, microwave irradiation) in appropriate organic solvents (e.g., THF, CH₂Cl₂, toluene, DMSO, CH₃CN or dioxane).

- 5 Compounds of Formula (VIII) (compound **13**- **Scheme 7**) may be made by reacting the compound **4** using **Method I** as described below. Compound **4** may be obtained from compound **1** using Method B as described above.

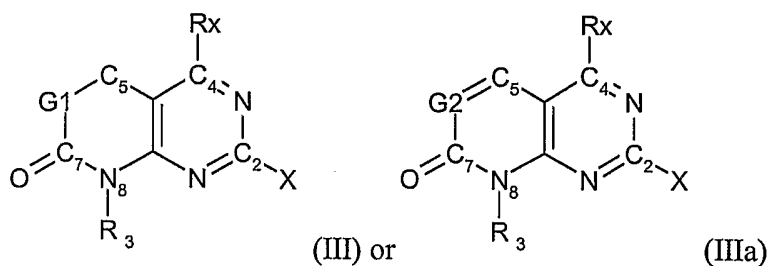
Scheme 7



10

- Method I** is for urea formation to convert **4** to **13**. This can be achieved by following strategies well-established in the art. Strategies include, but are not limited to reaction with suitably substituted isocyanate, such as ClSO₂NCO (or Me₃SiNCO) in a aprotic organic solvent, such as toluene, methylene chloride, chloroform, benzene, THF, hexane, optionally with a non-nucleophilic base, such as triethylamine, diisopropyl ethylamine, pyridine, followed by reaction with ammonia or H₂O; or by reaction with COCl₂ (CDI, or triphosgene) or methylchloroformate or other chloroformates in an aprotic organic solvent, such as toluene, methylene chloride, chloroform, benzene, THF, hexane, optionally with a non-nucleophilic base, such as triethylamine, diisopropyl ethylamine, pyridine, followed by treatment with NH₃ (or NH₄OH); or by reaction with ClCO₂Me (or ClCO₂Et) in a aprotic organic solvent, such as toluene, methylene chloride, chloroform, benzene, THF, hexane, optionally with a non-nucleophilic base, such as triethylamine, diisopropyl ethylamine, pyridine followed by treatment with NH₃ (or NH₄OH) or reaction with NH₂CO₂(*t*-Bu), followed by reaction with ammonia. This reaction may, or may not, require heating (e.g, temperature between r.t. and 250 °C). The heating can be carried out in any manner and may include the use of an oil bath or microwave irradiation.

- 30 Another aspect of the invention is a process for making a compound of Formula (III):



wherein

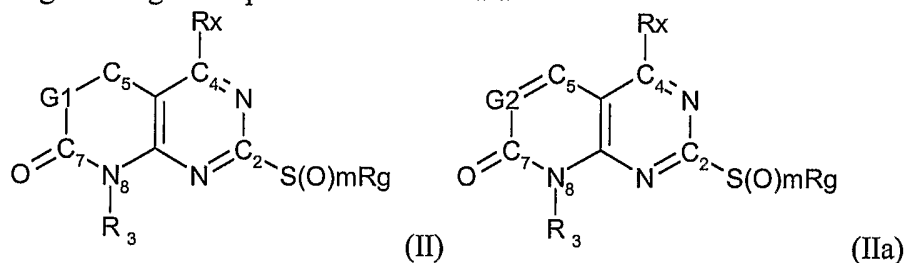
G1 is CH₂ or NH;

5 G2 is CH or nitrogen;

Rx is chloro, bromo, iodo, or O-S(O)₂CF₃;

and wherein X and R₃ are as defined above for compounds of Formula (I);

comprising reacting a compound of the formula



10

wherein

G1 is CH₂ or NH;

G2 is carbon or nitrogen;

Rx is chloro, bromo, iodo, or O-S(O)₂CF₃;

15 R_g is a C₁₋₁₀ alkyl;

m is an integer having a value of 1, or 2;

R₃ is a C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl C₁₋₁₀ alkyl, aryl, arylC₁₋₁₀ alkyl, heteroaryl, heteroarylC₁₋₁₀ alkyl, heterocyclic or a heterocyclylC₁₋₁₀ alkyl

moiety, and wherein each of these moieties may be optionally substituted;

20 with X-Y wherein X is R₂, OR₂', S(O)_mR₂', (CH₂)_nN(R₁₁)S(O)_mR₂', (CH₂)_nN(R₁₁)C(O)R₂', (CH₂)_nNR₄R₁₄, or (CH₂)_nN(R₂') (R₂''), or N(R₁₀')-R_h-NH-C(=N-CN)NR_qR_q'; and R₂, R₂', m, n', R₁₁, R₁₀', R_h and R_qR_q' are as defined according to Formula (I or III) herein; and

25 Y is hydrogen, a metal, a boronic acid derivative, or a trialkyl tin derivative, in an anhydrous organic solvent which does not contain a nucleophile to yield a compound of Formula (III).

In the transformation of (II) to (III), when Y is hydrogen then X is the following:

a) X= OR₂', or X is S(O)_mR₂' (and m=0); or

- b) X is $(\text{CH}_2)_n\text{N}(\text{R}_{10'})\text{S}(\text{O})_m\text{R}_2'$, $(\text{CH}_2)_n\text{N}(\text{R}_{10'})\text{C}(\text{O})\text{R}_2'$, $(\text{CH}_2)_n\text{NR}_4\text{R}_{14}$, or $(\text{CH}_2)_n\text{N}(\text{R}_2')(\text{R}_2'')$ and $n'=0$; or
 c) $\text{X}=\text{R}_2$ and $\text{R}_2 = (\text{CR}_{10}\text{R}_{20})_q\text{X}_1(\text{CR}_{10}\text{R}_{20})_q\text{C}(\text{A}_1)(\text{A}_2)(\text{A}_3)$, $q'=0$, and X_1 is $\text{N}(\text{R}_{10'})$, O, $\text{S}(\text{O})_m$ and $m=0$.
 5 d) when X is $\text{N}(\text{R}_{10'})\text{-R}_h\text{-NH-C(=N-CN)NR}_q\text{R}_{q'}$.

In the transformation of (II) to (III), when Y is a metal, such as Li, Mg, or any other appropriate metal or metal complex; then X is the following:

- a) X is R_2 , and R_2 is C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl C_{1-10} alkyl, aryl, aryl C_{1-10} alkyl, heteroaryl, heteroaryl C_{1-10} alkyl, heterocyclic, or a
 10 heterocyclyl C_{1-10} alkyl moiety.

In the transformation of (II) to (III), when Y is a boronic acid, $(\text{B}(\text{OH})_2)$ or boronic ester derivatives; then X is the following

- a) $\text{X}=\text{R}_2$, and $\text{R}_2=\text{aryl}$, or heteroaryl.

When Y is a trialkyl tin derivative, such as $(\text{C}_{1-4}\text{ alkyl})_3\text{Sn}$, then

- 15 a) $\text{X}=\text{R}_2$, and $\text{R}_2=\text{aryl}$, or heteroaryl.

It is recognized that for compounds of Formula (II) or (III) when G1 is NH, the nitrogen may need to be protected under standard conditions, and then deprotected after the transformation, as desired.

- 20 The anhydrous organic solvents include, but are not limited to CH_2Cl_2 , chloroform, CH_3CN , benzene, THF, hexane, ethyl ether, *tert*-butyl methyl ether, DMSO, DMF and toluene.

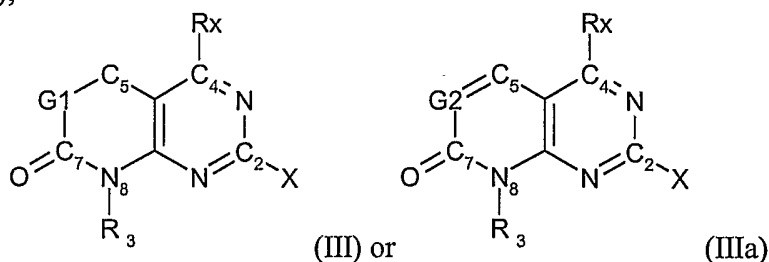
- This reaction may or may not require heating (e.g., temperature between r.t. and 300°C) and the heating can be carried out with, but not limited to a regular oil
 25 bath or microwave irradiations;

This reaction may or may not require the presence of bases, and the bases include, but are not limited to triethyl amine, diisopropyl ethyl amine, NaH, *n*-Buli, *tert*-BuLi, *tert*-BuOK, Li_2CO_3 , Cs_2CO_3 and pyridine. It is recognized that some of these bases will be incompatible with the organic solvents specified above.

- 30 This reaction may or may not be carried out in a sealed reaction vessel and the internal pressure may be higher than one atmosphere (e.g., between 1 and 100 atmospheres).

- This reaction may or may not require the presence of catalytic amount of catalysts containing transition metals (e.g., Pd, Cu, Ni or W). These catalysts include
 35 but are not limited to Pd/C, $\text{Pd}(\text{PPh}_3)_4$ and PdCl_2 .

Another aspect of the invention is a process for making a compound of Formula (III),



5 wherein

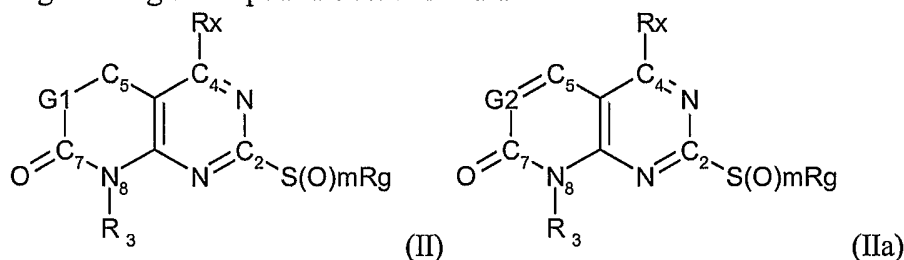
G1 is CH₂ or NH;

G2 is CH or nitrogen;

Rx is chloro, bromo, iodo, or O-S(O)₂CF₃;

and wherein X and R₃ are as defined above for compounds of Formula (III);

10 comprising reacting a compound of the formula



wherein

G1 is CH₂ or NH;

15 G2 is CH or nitrogen;

Rx is chloro, bromo, iodo, or O-S(O)₂CF₃;

R_g is a C₁₋₁₀ alkyl;

m is an integer having a value of 1, or 2;

R₃ is a C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl C₁₋₁₀ alkyl, aryl, arylC₁₋₁₀

20 alkyl, heteroaryl, heteroarylC₁₋₁₀ alkyl, heterocyclic or a heterocyclylC₁₋₁₀ alkyl

moiety, and wherein each of these moieties may be optionally substituted;

with X-Y wherein X is R₂, OR₂', S(O)_mR₂', (CH₂)_n'N(R₁₁)S(O)_mR₂',

(CH₂)_n'N(R₁₁)C(O)R₂', (CH₂)_n'NR₄R₁₄, or (CH₂)_n'N(R₂') (R₂''), or

N(R₁₀')-R_h-NH-C(=N-CN)NR_qR_q'; and R₂, R₂', m, n', R₁₁, R₁₀', R_h and R_qR_q'

25 are as defined according to Formula (I or III) herein; and

and Y is NH₂, NH(R₁₀), OH, or SH, in an anhydrous organic solvent to yield a compound of Formula (III), provided that

- a) X is R₂ and R₂ is hydrogen, C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkylalkyl, aryl, arylC₁₋₁₀ alkyl, heteroaryl, heteroarylC₁₋₁₀ alkyl, heterocyclic, or a heterocyclylC₁₋₁₀ alkyl; or
- b) X is (CH₂)_nN(R₁₀')S(O)_mR₂', (CH₂)_nN(R₁₀')C(O)R₂', (CH₂)_nNR₄R₁₄,
 5 (CH₂)_nN(R₂') (R₂''), and n' is greater than 2.

The anhydrous organic solvents include, but are not limited to CH₂Cl₂, chloroform, CH₃CN, benzene, THF, hexane, ethyl ether, *tert*-butyl methyl ether, DMSO, DMF and toluene, DMF, acetone, toluene, n-methyl-pyrrolidine, or dioxane,
 10 or a combination or mixture thereof.

This reaction may or may not require heating (e.g., temperature between room temperature and 300 °C) and the heating can be carried out with, but not limited to a regular oil bath or microwave irradiations;

This reaction may or may not require the presence of bases, and the bases
 15 include, but are not limited to triethyl amine, diisopropyl ethyl amine, NaH, n-Buli, *tert*-BuLi, *tert*-BuOK, Li₂CO₃, Cs₂CO₃ and pyridine. It is recognized that some of these bases will be incompatible with the organic solvents specified above.

This reaction may or may not be carried out in a sealed reaction vessel and the internal pressure may be higher than one atmosphere (e.g., between 1 and 100
 20 atmospheres).

This reaction may or may not require the presence of catalytic amount of catalysts containing transition metals (e.g., Pd, Cu, Ni or W). These catalysts include but are not limited to Pd/C, Pd(PPh₃)₄ and PdCl₂. It is recognized that use of these
 25 metals is generally not needed for simple transformations.

Exemplified compounds of Formulas (II):

- 4-Chloro-8-(4-trifluoromethyl-phenyl)-2-methylsulfanyl-8H-pyrido[2,3-d]pyrimidin-
 7-one; 4-Chloro-8-(4-trifluoromethyl -phenyl)-2-methylsulfinyl-8H-
 pyrido[2,3-d]pyrimidin-
 30 7-one;
 4-Chloro-8-(2,4-difluoro-phenyl)-2-methylsulfanyl-8H-pyrido[2,3-d]pyrimidin-7-one;
 4-Chloro-8-(2,4-difluoro-phenyl)-2-methylsulfinyl-8H-pyrido[2,3-d]pyrimidin-7-one;
 4-Chloro-8-(2,6-difluoro-phenyl)-2-methylsulfanyl-8H-pyrido[2,3-d]pyrimidin-7-one;
 2-(Hydroxy-hydroxymethyl-ethylamino)-4-Chloro-8-(2,6-difluoro-phenyl)-8H-
 35 pyrido[2,3-d]pyrimidin-7-one; and
 4-Chloro-8-(2,6-difluoro-phenyl)-2-methylsulfinyl-8H-pyrido[2,3-d]pyrimidin-7-one.

Exemplified compounds of Formula (III):

- 2-(Hydroxy-hydroxymethyl-ethylamino)-4-Chloro-8-(4-trifluoromethyl-phenyl)-8H-pyrido[2,3-d]pyrimidin-7-one; 2-(Hydroxy-hydroxymethyl-ethylamino)-4-Chloro-8-(2,4-difluoro-phenyl)-8H-pyrido[2,3-d]pyrimidin-7-one;

Exemplified compounds of Formula (I) which may be produced using the processes described herein include:

- 2-(Hydroxy-hydroxymethyl-ethylamino)-4-(2-methylsulfonyl-phenyl)-8-(4-trifluoromethyl-phenyl)-8H-pyrido[2,3-d]pyrimidin-7-one
- 2-(Hydroxy-hydroxymethyl-ethylamino)-4-(3-methylsulfonyl-phenyl)-8-(4-trifluoromethyl-phenyl)-8H-pyrido[2,3-d]pyrimidin-7-one
- 2-(Hydroxy-hydroxymethyl-ethylamino)-4-phenyl-8-(4-trifluoromethyl-phenyl)-8H-pyrido[2,3-d]pyrimidin-7-one
- 2-(Hydroxy-hydroxymethyl-ethylamino)-4-(3-chlorophenyl)-8-(4-trifluoromethyl-phenyl)-8H-pyrido[2,3-d]pyrimidin-7-one
- 2-(Hydroxy-hydroxymethyl-ethylamino)-4-(4-chlorophenyl)-8-(4-trifluoromethyl-phenyl)-8H-pyrido[2,3-d]pyrimidin-7-one
- 2-(Hydroxy-hydroxymethyl-ethylamino)-4-(3,4-difluorophenyl)-8-(4-trifluoromethyl-phenyl)-8H-pyrido[2,3-d]pyrimidin-7-one
- 2-(Hydroxy-hydroxymethyl-ethylamino)-4-(2-chlorophenyl)-8-(4-trifluoromethyl-phenyl)-8H-pyrido[2,3-d]pyrimidin-7-one
- 2-(Hydroxy-hydroxymethyl-ethylamino)-4-(4-methoxyphenyl)-8-(4-trifluoromethyl-phenyl)-8H-pyrido[2,3-d]pyrimidin-7-one
- 2-(Hydroxy-hydroxymethyl-ethylamino)-4-(3-methoxyphenyl)-8-(4-trifluoromethyl-phenyl)-8H-pyrido[2,3-d]pyrimidin-7-one
- 2-(Hydroxy-hydroxymethyl-ethylamino)-4-(2-methoxyphenyl)-8-(4-trifluoromethyl-phenyl)-8H-pyrido[2,3-d]pyrimidin-7-one
- 8-(2,4-Difluoro-phenyl)-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-4-(3-methylsulfonyl-phenyl)-8H-pyrido[2,3-d]pyrimidin-7-one
- 8-(2,4-Difluoro-phenyl)-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-4-(4-methylsulfonyl-phenyl)-8H-pyrido[2,3-d]pyrimidin-7-one
- 8-(2,4-Difluoro-phenyl)-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-4-(2-methylsulfonyl-phenyl)-8H-pyrido[2,3-d]pyrimidin-7-one
- 8-(2,4-Difluoro-phenyl)-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-4-(3,4-difluorophenyl)-8H-pyrido[2,3-d]pyrimidin-7-one
- 8-(2,4-Difluoro-phenyl)-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-4-(2-

- methoxyphenyl)-8H-pyrido[2,3-d]pyrimidin-7-one
- 8-(2,4-Difluoro-phenyl)-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-4-(4-methoxyphenyl)-8H-pyrido[2,3-d]pyrimidin-7-one
- 8-(2,4-Difluoro-phenyl)-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-4-(2-biphenyl)-8H-pyrido[2,3-d]pyrimidin-7-one
- 5 8-(2,4-Difluoro-phenyl)-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-4-(3-biphenyl)-8H-pyrido[2,3-d]pyrimidin-7-one
- 8-(2,4-Difluoro-phenyl)-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-4-(2-tolyl)-8H-pyrido[2,3-d]pyrimidin-7-one
- 10 8-(2,4-Difluoro-phenyl)-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-4-(3-fluoro-4-biphenyl)-8H-pyrido[2,3-d]pyrimidin-7-one
- 8-(2,4-Difluoro-phenyl)-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-4-(4-chlorophenyl)-8H-pyrido[2,3-d]pyrimidin-7-one
- 8-(2,4-Difluoro-phenyl)-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-4-(3-chlorophenyl)-8H-pyrido[2,3-d]pyrimidin-7-one
- 15 8-(2,4-Difluoro-phenyl)-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-4-(3-fluorophenyl)-8H-pyrido[2,3-d]pyrimidin-7-one
- 8-(2,4-Difluoro-phenyl)-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-4-(3-methoxyphenyl)-8H-pyrido[2,3-d]pyrimidin-7-one
- 20 8-(2,4-Difluoro-phenyl)-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-4-(3,5-difluorophenyl)-8H-pyrido[2,3-d]pyrimidin-7-one
- 8-(2,6-Difluoro-phenyl)-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-4-(2-methylthiophenyl)-8H-pyrido[2,3-d]pyrimidin-7-one
- 8-(2,6-Difluoro-phenyl)-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-4-(3-methylthiophenyl)-8H-pyrido[2,3-d]pyrimidin-7-one
- 25 8-(2,6-Difluoro-phenyl)-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-4-(4-methoxyphenyl)-8H-pyrido[2,3-d]pyrimidin-7-one
- 8-(2,6-Difluoro-phenyl)-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-4-(3-methoxyphenyl)-8H-pyrido[2,3-d]pyrimidin-7-one
- 30 8-(2,6-Difluoro-phenyl)-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-4-phenyl-8H-pyrido[2,3-d]pyrimidin-7-one
- 8-(2,6-Difluoro-phenyl)-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-4-(4-methylthiophenyl)-8H-pyrido[2,3-d]pyrimidin-7-one
- 8-(2,6-Difluoro-phenyl)-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-4-(2-methoxyphenyl)-8H-pyrido[2,3-d]pyrimidin-7-one
- 35 8-(2,6-Difluoro-phenyl)-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-4-(2-hydroxylphenyl)-8H-pyrido[2,3-d]pyrimidin-7-one

- 8-(2,6-Difluoro-phenyl)-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-4-(3-hydroxyphenyl)-8H-pyrido[2,3-d]pyrimidin-7-one
- 8-(2,6-Difluoro-phenyl)-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-4-(4-hydroxyphenyl)-8H-pyrido[2,3-d]pyrimidin-7-one
- 5 8-(2,6-Difluoro-phenyl)-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-4-(4-methylsulfonylphenyl)-8H-pyrido[2,3-d]-pyrimidin-7-one
- 8-(2,6-Difluoro-phenyl)-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-4-(3-methylsulfonylphenyl)-8H-pyrido[2,3-d]-pyrimidin-7-one
- 8-(2,6-Difluoro-phenyl)-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-4-(2-methylsulfonylphenyl)-8H-pyrido[2,3-d] pyrimidin-7-one
- 10 8-(2,6-Difluoro-phenyl)-4-(4-fluoro-2-methyl-phenyl)-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-8H-pyrido[2,3-d]pyrimidin-7-one
- 3-{8-(2,6-difluorophenyl)-2-[(1*H*-imidazol-2-ylmethyl)amino]-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl}-4-methyl-*N*-1,3-thiazol-2-ylbenzamide
- 15 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-propylbenzamide; ; or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof.

20 Synthetic Examples

- The invention will now be described by reference to the following examples which are merely illustrative and are not to be construed as a limitation of the scope of the present invention. All temperatures are given in degrees centigrade, all solvents are highest available purity and all reactions run under anhydrous conditions
- 25 in an Ar atmosphere where necessary.

List of Abbreviations

EDC: 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride	dppf: 1,1'-Bis(diphenylphosphino)-ferrocene
DMAP: 4-(Dimethylamino)pyridine	DMSO: Dimethylsulfoxide
m-CPBA: 3-Chlorobenzenecarboperoxoic acid	EtOAc: Ethyl acetate
THF: Tetrahydrofuran	DIPEA or DIEA: <i>N,N</i> -Diisopropylethylamine
DCM: Dichloromethane	SPE: Solid phase extraction
TFA: Trifluoroacetic anhydride	MDAP: Mass directed auto preparation
HATU: <i>O</i> -(7-Azabenzotriazol-1-yl)-	HBTU: <i>O</i> -Benzotriazol-1-yl- <i>N,N,N',N'</i> -

<i>N,N,N',N'</i> -tetramethyluronium hexafluorophosphate	tetramethyluronium hexafluorophosphate
NIS: <i>N</i> -Iodosuccinimide	HOBT: 1-Hydroxybenzotriazole hydrate
DMF: <i>N,N</i> -Dimethylformamide	HPLC: High Pressure Liquid Chromatography
IPA: isopropyl alcohol	M: molar
DSC: differential scanning calorimetry	mmol: millimoles
L: liters	mol: moles
mL: milliliters	aq: aqueous
mg: milligrams	eq: equivalents
g: grams	h: hours
rt: room temperature	mp: melting point
eq: equivalents	min: minutes
dppf=1,1'-bis(diphenylphosphino)ferrocene	satd: saturated
NMP = 1-methyl-2-pyrrolidinone	

LC-MS Experimental Conditions:

Liquid Chromatograph

System: Shimadzu LC system with SCL-10A Controller and dual UV detector

5 Autosampler: Leap CTC with a Valco six port injector

Column: Aquasil/Aquasil (C18 40x1 mm)

Inj. Vol.(μ L): 2.0Solvent A: H₂O, 0.02% TFA

Solvent B: MeCN, 0.018% TFA

10 Gradient: linear

Channel A: UV 214 nm

Channel B: ELS

Step	Time (min)	Dura.(min)	Flow (μ L/min)	Sol.A	Sol.B
0	0.00	0.00	300.00	95.00	5.00
15 1	0.00	0.01	300.00	95.00	5.00
2	0.01	3.20	300.00	10.00	90.00
3	3.21	1.00	300.00	10.00	90.00
4	4.21	0.10	300.00	95.00	5.00
5	4.31	0.40	300.00	95.00	5.00

20

Mass Spectrometer: PE Sciex Single Quadrupole LC/MS API-150

Polarity: Positive
Acquisition mode: Profile

General Procedures

5 Nuclear magnetic resonance spectra were recorded at 400 MHz using on a Bruker AC 400 spectrometer. CDCl_3 is deuteriochloroform, DMSO-d_6 is hexadeuteriodimethylsulfoxide, and CD_3OD (or MeOD) is tetradeuteriomethanol. Chemical shifts are reported in parts per million (δ) downfield from the internal standard tetramethylsilane (TMS) or the NMR solvent. Abbreviations for NMR data
10 are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, app = apparent, br = broad. J indicates the NMR coupling constant measured in Hertz. Mass spectra were taken on a instruments, using electrospray (ES) ionization techniques. All temperatures are reported in degrees Celsius. Other abbreviations are as described in the ACS Style
15 Guide (American Chemical Society, Washington, DC, 1986).

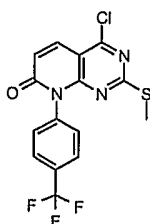
Analtech Silica Gel GF and E. Merck Silica Gel 60 F-254 thin layer plates were used for thin layer chromatography. Both flash and gravity chromatography were carried out on E. Merck Kieselgel 60 (230-400 mesh) silica gel. Preparative
20 hplc were performed using a Gilson Preparative System using a Luna 5u C18(2) 100A reverse phase column eluting with a 10-80 gradient (0.1%TFA in acetonitrile/0.1% aqueous TFA) or a 10-80 gradient (acetonitrile/water). The CombiFlash system used for purification in this application was purchased from Isco, Inc. CombiFlash purification was carried out using a prepacked SiO_2 column, a detector with UV wavelength at 254nm and mixed solvents.

25 Heating of reaction mixtures with microwave irradiations was carried out on either a Smith Creator (purchased from Personal Chemistry, Forboro/MA, now owned by Biotage), a Emrys Optimizer (purchased from Personal Chemistry) or an Explorer (provided by CEM Discover, Matthews/NC) microwave.

30

Example 1

4-Chloro-2-methylsulfanyl-8-(4-trifluoromethyl-phenyl)-8H-pyrido[2,3-d] pyrimidin-7-one

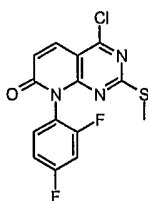


A solution of 4,6-dichloro-2-methylsulfanyl-pyrimidine-5-carbaldehyde (1.0g, 4.5mmol) and Et_3N (1.26mL, 9.0mmol) in THF (25mL) was mixed with 4-trifluoromethylaniline (0.62mL, 4.9mmol). The resultant mixture was stirred at room temperature for 2 hours before bis(2,2,2-trifluoroethyl)(methoxycarbonylmethyl)-

- phosphonate (0.95mL, 4.5mmol) was added. After stirring at room temperature for additional 12 hours, the mixture was diluted with dichloromethane (50mL) and washed with H₂O (2 x 25mL). The organic layer was dried over Na₂SO₄, filtered and concentrated. This crude product was further purified by washing with a mixture of
- 5 THF / Hexane (1 : 3, 2 x 10mL) to provide the title compound (1.17g, 70%): MS (ES) *m/z* 372 (M+H)⁺; ¹H-NMR(CDCl₃) δ 2.18 (s, 3H), 6.79 (d, *J* = 9.8 Hz, 1H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.83 (d, *J* = 8.4 Hz, 2H), 8.03 (d, *J* = 9.8 Hz, 1H).

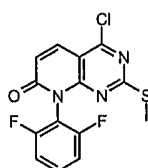
Example 2

10 4-Chloro-2-methylsulfanyl-8-(2,4-difluoro-phenyl)-8H-pyrido[2,3-*d*]pyrimidin-7-one



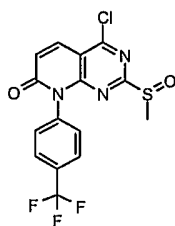
- A solution of 4,6-dichloro-2-methylsulfanyl-pyrimidine-5-carbaldehyde (1.0g, 4.5mmol) and Et₃N (1.26mL, 9.0mmol) in THF (25mL) was mixed with 2,4-difluoroaniline (0.50mL, 4.9mmol).
- The resultant mixture was stirred at room temperature for 2 hours before bis(2,2,2-trifluoroethyl) (methoxycarbonyl-methyl)phosphonate (0.95mL, 4.5mmol) was added. After stirring at room temperature for additional 48 hours, the mixture was diluted with dichloromethane (50mL) and then washed with H₂O (2 x 25mL). The organic layer was dried over Na₂SO₄, filtered and concentrated. This
- 20 crude product was applied to flash chromatography (EtOAc / Hexane, 1 : 5) to provide the title compound (0.79g, 52%): MS (ES) *m/z* 340 (M+H)⁺; ¹H-NMR(CDCl₃) δ 2.24 (s, 3H), 6.79 (d, *J* = 9.8 Hz, 1H), 7.06 (m, 2H), 7.29 (m, 1H), 8.03 (d, *J* = 9.8 Hz, 1H).

Example 3



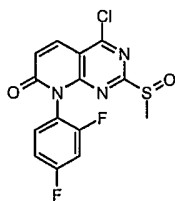
4-Chloro-2-methylsulfanyl-8-(2,6-difluoro-phenyl)-8H-pyrido[2,3-*d*]pyrimidin-7-one

- A solution of 4-Chloro-6-(2,6-difluoro-phenylamino)-2-methylsulfanyl-pyrimidine-5-carbaldehyde (200mg, 0.63mmol) in DMF (4.0mL) and Ac₂O (2.0mL) was heated with "Smith Creator" (microwave, 160°C) for 30minutes. The mixture was
- 30 concentrate under vacuum. Flash chromatography (EtOAc / Hexane, 1 : 5) then provided the title compound (50%): MS (ES) *m/z* 340 (M+H)⁺; ¹H-NMR(CDCl₃) δ 2.24 (s, 3H), 6.80 (d, *J* = 9.8 Hz, 1H), 7.12 (m, 2H), 7.49 (m, 1H), 8.04 (d, *J* = 9.8 Hz, 1H).

Example 4

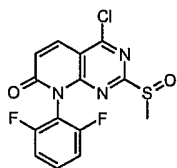
4-Chloro-2-methylsulfinyl-8-(4-trifluoromethyl-phenyl)-8H-pyrido[2,3-d] pyrimidin-7-one

A solution of 4-Chloro-2-methylsulfonyl-8-(4-trifluoromethyl-phenyl)-8H-pyrido[2,3-d] pyrimidin-7-one (1.0g, 2.7mmol) in dichloromethane (50mL) was mixed with *m*-CPBA (0.63g, 4.0mmol). The resultant mixture was stirred at room temperature for 10 minutes and concentrated under vacuum. Flash chromatography (EtOAc / Hexane, 3 : 1) then provided the title compound (0.86g, 82%): MS (ES) m/z 388 (M+H)⁺; ¹H-NMR(CDCl₃) δ 2.80 (s, 3H), 7.03 (d, *J* = 9.9 Hz, 1H), 7.39 (d, *J* = 8.0 Hz, 2H), 7.86 (d, *J* = 8.0 Hz, 2H), 8.19 (d, *J* = 9.9 Hz, 1H).

Example 5

4-Chloro-2-methylsulfinyl-8-(2,4-difluoro-phenyl)-8H-pyrido[2,3-d] pyrimidin-7-one

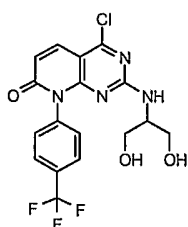
A solution of 4-Chloro-2-methylsulfonyl-8-(2,4-difluoro-phenyl)-8H-pyrido[2,3-d] pyrimidin-7-one (1.0g, 2.9mmol) in dichloromethane (50mL) was mixed with *m*-CPBA (0.69g, 4.4mmol). The resultant mixture was stirred at room temperature for 10 minutes and concentrated under *vacou*. Flash chromatography (EtOAc / Hexane, 3 : 1) then provided the title compound (1.02g, 97%): MS (ES) m/z 356 (M+H)⁺; ¹H-NMR(CDCl₃) δ 2.84 (m, 3H), 7.01 (d, *J* = 9.9 Hz, 1H), 7.09 (m, 2H), 7.29 (m, 1H), 8.16 (d, *J* = 9.9 Hz, 1H).

Example 6

4-Chloro-2-methylsulfinyl-8-(2,6-difluoro-phenyl)-8H-pyrido[2,3-d] pyrimidin-7-one A solution of 4-Chloro-2-methylsulfinyl-8-(2,6-difluoro-phenyl)-8H-pyrido[2,3-d] pyrimidin-7-one (1.0g, 2.9mmol) in dichloromethane (50mL) was mixed with *m*-CPBA (0.69g, 4.4mmol). The resultant mixture was stirred at room

temperature for 10 minutes and concentrated under *vacou*. Flash chromatography (EtOAc / Hexane, 3 : 1) then provided the title compound (0.91g, 87%): MS (ES) m/z 356 (M+H)⁺; ¹H-NMR(CDCl₃) δ 2.85 (s, 3H), 7.03 (d, J = 9.6 Hz, 1H), 7.15 (m, 2H),

10 7.53 (m, 1H), 8.18 (d, J = 9.6 Hz, 1H).

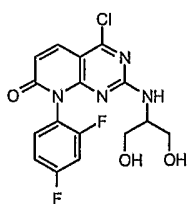
Example 7

4-Chloro-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-8-(4-trifluoromethyl-phenyl)-8H-pyrido[2,3-d]pyrimidin-7-one

A solution of 4-Chloro-2-methylsulfinyl-8-(4-trifluoromethyl-phenyl)-8H-pyrido[2,3-d] pyrimidin-7-one (0.29g, 0.75mmol) in dichloromethane (30mL) was mixed with a solution of serinol (0.075g, 0.82mmol) in DMF (0.75mL). The resultant mixture

was stirred at room temperature for 1 hour before concentrated under vacuum. Flash chromatography (EtOAc : Hexane, 3 : 1) then provided the title compound (0.14g, 45%): MS (ES) m/z 415 (M+H)⁺; ¹H-NMR(CDCl₃) δ 2.25 (s, br, 2H), 3.66 (m, br, 5H), 6.15 (m, br, 1H), 6.55 (d, J = 9.2 Hz, 1H), 7.36 (m, 2H), 7.81 (d, J = 8.1 Hz, 2H), 7.92 (d, J = 9.2 Hz, 1H).

25

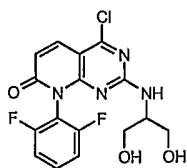
Example 8

4-Chloro-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-8-(2,4-difluoro-phenyl)-8H-pyrido[2,3-d]pyrimidin-7-one

A solution of 4-Chloro-2-methylsulfinyl-8-(2,4-difluoro-phenyl)-8H-pyrido[2,3-d] pyrimidin-7-one (0.24g, 0.67mmol) in dichloromethane (24mL) was mixed with a solution of serinol

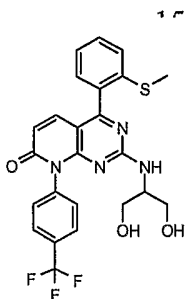
(0.065g, 0.71mmol) in DMF (0.65mL). The resultant mixture was stirred at room temperature for 1 hour before concentrated under vacuum. Flash chromatography (EtOAc / Hexane, 3 : 1) then provided the title compound (0.12g, 46%): MS (ES) m/z 383 (M+H)⁺; ¹H-NMR(CDCl₃) δ 2.15 (s, br, 2H), 3.75 (m, br, 5H), 6.10 (m, br, 1H), 6.55 (m, 1H), 7.04 (m, 2H), 7.28 (m, 1H), 7.90 (m, 1H).

35

Example 9

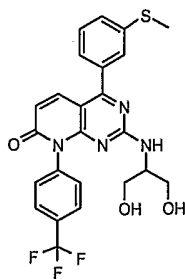
4-Chloro-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-8-(2,6-difluoro-phenyl)-8H-pyrido[2,3-d]pyrimidin-7-one

A solution of 4-Chloro-2-methylsulfinyl-8-(2,6-difluoro-phenyl)-8H-pyrido[2,3-d]pyrimidin-7-one (0.90g, 2.53mmol) in dichloromethane (90mL) was mixed with a solution of serinol (0.24g, 2.66mmol) in DMF (2.0mL). The resultant mixture was stirred at room temperature for 1 hour before concentrated under vacuum. Flash chromatography (EtOAc / Hexane, 3 : 1) then provided the title compound (0.40g, 42%): MS (ES) m/z 383 (M+H)⁺; ¹H-NMR(CDCl₃) δ 1.95 (s, br, 2H), 3.90 (m, br, 5H), 6.05 (m, br, 1H), 6.56 (d, J = 9.6 Hz, 1H), 7.10 (m, 2H), 7.48 (d, J = 8.1 Hz, 2H), 7.94 (d, J = 9.6 Hz, 1H).

Example 10

4-(2-Methylsulfonyl-phenyl)-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-8-(4-trifluoromethyl-phenyl)-8H-pyrido[2,3-d]pyrimidin-7-one

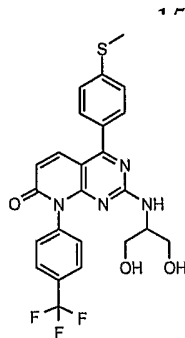
A solution of 4-Chloro-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-8-(4-trifluoromethyl-phenyl)-8H-pyrido[2,3-d]pyrimidin-7-one (50mg, 0.12mmol) in dioxane / H₂O (3 : 1, 4.8mL) was mixed with 2-methylthiophenyl boronic acid (30.4mg, 0.18mmol) and K₂CO₃ (50.1mg, 0.36mmol). The resultant mixture was bubbled with argon for 5 minutes, and added by Pd(PPh₃)₄ (2.8mg, 0.0024mmol). The reaction tube was sealed and heated with "Smith Creator" (microwave, 150°C) for 15minutes. The mixture was concentrated under vacuo. Flash chromatography (EtOAc / Hexane, 3 : 1) then provided the title compound (88%): MS (ES) m/z 503 (M+H)⁺; ¹H-NMR(CDCl₃) δ 2.48 (s, 3H), 2.65 (s, br, 2H), 3.70 (m, br, 5H), 6.20 (m, br, 1H), 6.45 (m, 1H), 7.43 (m, 6H), 7.68 (m, 1H), 7.83 (m, 2H).

Example 11

4-(3-Methylsulfanyl-phenyl)-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-8-(4-trifluoromethyl-phenyl)-8H-pyrido[2,3-d]pyrimidin-7-one

The title compound was prepared by following the procedure in Example 10 except 3-methylthiophenyl boronic acid was used in the coupling step (76%): MS (ES) m/z 503 ($M+H$)⁺; ¹H-NMR(CDCl₃) δ 2.49 (s, br, 2H), 2.54 (s, 3H), 3.68 (m, br, 5H),

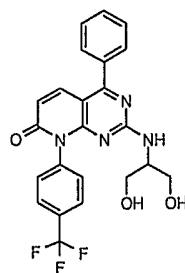
5.90 (s, br, 1H), 6.47 (s, b, 1H), 7.45 (m, 6H), 7.65 (m, 1H), 7.82 (m, 2H).

Example 12

4-(4-Methylsulfanyl-phenyl)-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-8-(4-trifluoromethyl-phenyl)-8H-pyrido[2,3-d]pyrimidin-7-one

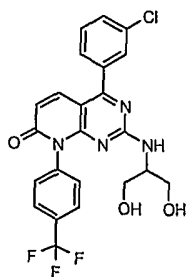
The title compound was prepared by following the procedure in Example 10 except 4-methylthiophenyl boronic acid was used in the coupling step (56%): MS (ES) m/z 503 ($M+H$)⁺; ¹H-NMR(CDCl₃) δ 2.40 (s, br, 2H), 2.58 (s, 3H), 3.69 (m, br, 5H), 5.85 (s, br, 1H), 6.48 (m, 1H), 7.40 (m, 2H), 7.48 (m, 2H), 7.56 (m, 2H), 7.67 (m,

1H), 7.83 (m, 2H).

Example 13

4-phenyl-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-8-(4-trifluoromethyl-phenyl)-8H-pyrido[2,3-d]pyrimidin-7-one

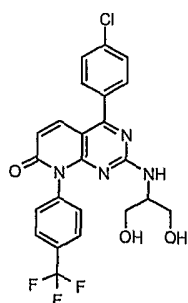
The title compound was prepared by following the procedure in Example 10 except phenyl boronic acid was used in the coupling step (82%): MS (ES) m/z 457 ($M+H$)⁺; ¹H-NMR(CDCl₃) δ 1.81 (s, br, 2H), 3.68 (m, br, 5H), 6.10 (m, br, 1H), 6.47 (m, 1H), 7.40 (m, 2H), 7.59 (m, 5H), 7.82 (m, 3H).



10

Example 144-(3-chlorophenyl)-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-8-(4-trifluoromethyl-phenyl)-8H-pyrido[2,3-d]pyrimidin-7-one

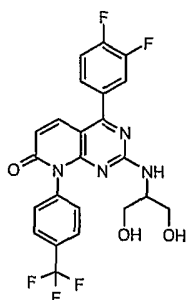
The title compound was prepared by following the procedure in Example 10 except 3-chlorophenyl boronic acid was used in the coupling step (76%): MS (ES) m/z 491 ($M+H$)⁺; ¹H-NMR(CDCl₃) δ 1.66 (s, br, 2H), 3.73 (m, br, 5H), 6.15 (m, br, 1H), 6.50 (m, 1H), 7.52 (m, 6H), 7.75 (m, 1H), 7.84 (m, 2H).



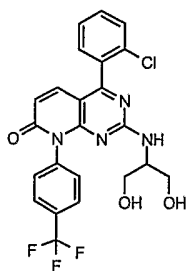
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Example 154-(4-chlorophenyl)-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-8-(4-trifluoromethyl-phenyl)-8H-pyrido[2,3-d]pyrimidin-7-one

The title compound was prepared by following the procedure in Example 10 except 4-chlorophenyl boronic acid was used in the coupling step (72%): MS (ES) m/z 491 ($M+H$)⁺; ¹H-NMR(CDCl₃) δ 1.61 (s, br, 2H), 3.73 (m, br, 5H), 6.05 (m, br, 1H), 6.50 (m, 1H), 7.41 (m, 2H), 7.58 (m, 4H), 7.76 (m, 1H), 7.84 (m, 2H).

**Example 16**4-(3,4-difluorophenyl)-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-8-(4-trifluoromethyl-phenyl)-8H-pyrido[2,3-d]pyrimidin-7-one

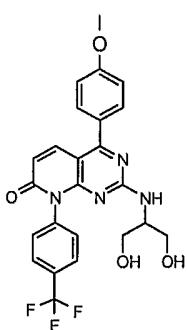
The title compound was prepared by following the procedure in Example 10 except 3,4-difluorophenyl boronic acid was used in the coupling step (65%): MS (ES) m/z 493 ($M+H$)⁺; ¹H-NMR(CDCl₃) δ 2.06 (s, br, 2H), 3.72 (m, br, 5H), 6.05 (m, br, 1H), 6.50 (m, 1H), 7.42 (m, 5H), 7.76 (m, 1H), 7.83 (m, 2H).

Example 17

4-(2-Chlorophenyl)-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-8-(4-trifluoromethyl-phenyl)-8H-pyrido[2,3-d]pyrimidin-7-one

The title compound was prepared by following the procedure in Example 10 except 2-chlorophenyl boronic acid was used in the coupling step (72%). MS (ES) m/z 491 (M+H)⁺; ¹H-NMR(CDCl₃) δ 3.60 (m, br, 5H), 6.10 (m, br, 1H), 6.45 (m, 1H), 7.32 (m, 2H), 7.50 (m, 5H), 7.80 (m, 2H).

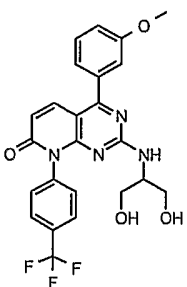
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Example 18

4-(4-Methoxyphenyl)-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-8-(4-trifluoromethyl-phenyl)-8H-pyrido[2,3-d]pyrimidin-7-one

The title compound was prepared by following the procedure in Example 10 except [4-(methoxy)phenyl]boronic acid was used in the coupling step (66%). MS (ES) m/z 487 (M+H)⁺; ¹H-NMR(CDCl₃) δ 1.85 (s, br, 2H), 3.69 (m, br, 5H), 3.92 (s, 3H), 6.10 (m, br, 1H), 6.47 (m, 1H), 7.07 (m, 2H), 7.40 (m, 2H), 7.60

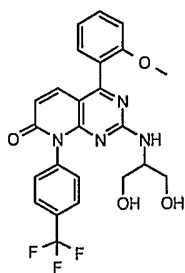
20 (m, 2H), 7.84 (m, 3H).

Example 19

4-(3-Methoxyphenyl)-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-8-(4-trifluoromethyl-phenyl)-8H-pyrido[2,3-d]pyrimidin-7-one

The title compound was prepared by following the procedure in Example 10 except [3-(methoxy)phenyl]boronic acid was used in the coupling step (65%): MS (ES) m/z 487 (M+H)⁺; ¹H-NMR(CDCl₃) δ 2.90 (s, br, 2H), 3.61 (m, br, 5H), 3.88 (s, 3H),

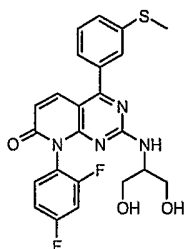
30 6.05 (m, br, 1H), 6.45 (m, 1H), 7.09 (m, 2H), 7.45 (m, 4H), 7.80 (m, 3H).

Example 20

4-(2-Methoxyphenyl)-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-8-(4-trifluoromethyl-phenyl)-8H-pyrido[2,3-d]pyrimidin-7-one

The title compound was prepared by following the procedure in Example 10 except [2-(methoxy)phenyl]boronic acid was used in the coupling step (75%): MS (ES) m/z 487 (M+H)⁺; ¹H-NMR(CDCl₃) δ 2.20 (s, br, 2H), 3.69 (m, br, 5H), 3.84 (s, 3H), 6.05 (m, br, 1H), 6.41 (m, 1H), 7.12 (m, 2H), 7.47 (m, 5H), 7.83 (m, 2H).

10 6.05 (m, br, 1H), 6.41 (m, 1H), 7.12 (m, 2H), 7.47 (m, 5H), 7.83 (m, 2H).

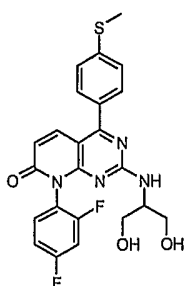
Example 21

4-(3-Methylsulfanyl-phenyl)-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-8-(2,4-difluorophenyl)-8H-pyrido[2,3-d]pyrimidin-7-one

A solution of 4-Chloro-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-8-(2,4-difluoro-phenyl)-8H-pyrido[2,3-d]pyrimidin-7-one (50mg, 0.13mmol) in dioxane / H₂O (3 : 1, 4.8mL) was

20 mixed with 3-methylthiophenyl boronic acid (33.8mg, 0.20mmol) and K₂CO₃ (54.3mg, 0.39mmol). The resultant mixture was bubbled with argon for 5 minutes followed by the addition of Pd(PPh₃)₄ (3.0mg, 0.0026mmol). The reaction tube was sealed and heated with "Smith Creator" (microwave, 150°C) for 15minutes. The mixture was concentrated under vacuo. Flash chromatography (EtOAc / Hexane, 3 : 1) 25 then provided the title compound (90%): MS (ES) m/z 471 (M+H)⁺; ¹H-NMR(CDCl₃) δ 2.40 (s, br, 2H), 2.40 (s, 3H), 3.90 (m, br, 5H), 6.00 (m, br, 1H), 6.45 (m, 1H), 7.15 (m, 2H), 7.40 (m, 5H), 7.85 (m, 1H).

30

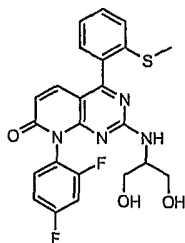
Example 22

4-(4-Methylsulfanyl-phenyl)-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-8-(2,4-difluorophenyl)-8H-pyrido[2,3-d]pyrimidin-7-one

The title compound was prepared by following the procedure in Example 21 except 4-methylthiophenyl boronic acid was used in the coupling step (95%): MS (ES) m/z 471 (M+H)⁺; ¹H-NMR(CDCl₃) δ 2.35 (s, br, 2H), 2.57 (s, 3H), 3.76 (m, br, 5H),

6.05 (m, br, 1H), 6.46 (m, 1H), 7.05 (m, 2H), 7.27 (m, 1H), 7.39 (m, 2H), 7.55 (m, 2H), 7.81 (m, 1H).

Example 23



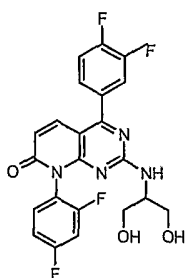
4-(2-Methylsulfanyl-phenyl)-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-8-(2,4-difluorophenyl)-8H-pyrido[2,3-d]pyrimidin-7-one

The title compound was prepared by following the procedure in Example 21 except 2-methylthiophenyl boronic acid was used in the coupling step (72%): MS (ES) m/z 471 (M+H)⁺; ¹H-

NMR(CDCl₃) δ 2.45 (s, 3H), 2.55 (s, br, 2H), 3.72 (m, br, 5H), 6.05 (m, br, 1H), 6.40 (m, 1H), 7.05 (m, 2H), 7.40 (m, 6H).

15

Example 24



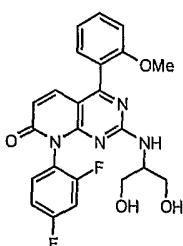
4-(3,4-difluorophenyl)-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-8-(2,4-difluorophenyl)-8H-pyrido[2,3-d]pyrimidin-7-one

The title compound was prepared by following the procedure in Example 21 except 3,4-difluorophenyl boronic acid was used in the coupling step (56%): MS (ES) m/z 461 (M+H)⁺; ¹H-

NMR(CDCl₃) δ 2.25 (s, br, 2H), 3.77 (m, br, 5H), 6.15 (m, br, 1H), 6.48 (m, 1H), 7.06 (m, 2H), 7.49 (m, 4H), 7.74 (m, 1H).

25

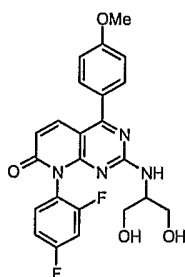
Example 25



4-(2-Methoxyphenyl)-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-8-(2,4-difluorophenyl)-8H-pyrido[2,3-d]pyrimidin-7-one

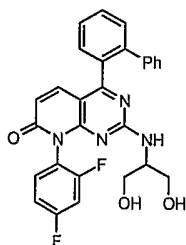
The title compound was prepared by following the procedure in Example 21 except 2-methoxyphenyl boronic acid was used in the coupling step (89%): MS (ES) m/z 455 (M+H)⁺; ¹H-

NMR(CDCl₃) δ 2.85 (s, br, 2H), 3.67 (m, br, 5H), 3.81 (s, 3H), 6.10 (m, br, 1H), 6.38 (m, 1H), 7.07 (m, 5H), 7.30 (s, 1H), 7.38 (m, 1H), 7.50 (m, 1H).

Example 26

10 7.58 (m, 2H), 7.83 (m, 1H).

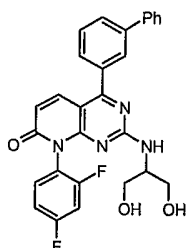
4-(4-Methoxyphenyl)-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-8-(2,4-difluorophenyl)-8H-pyrido[2,3-d]pyrimidin-7-one The title compound was prepared by following the procedure in Example 21 except 4-methoxyphenyl boronic acid was used in the coupling step (70%): MS (ES) m/z 455 (M+H)⁺; ¹H-NMR(CDCl₃) δ 2.60 (s, br, 2H), 3.73 (m, br, 5H), 3.91 (s, 3H), 6.15 (m, br, 1H), 6.45 (m, 1H), 7.05 (m, 4H), 7.38 (s, 1H),

Example 27

20

4-(2-Biphenyl)-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-8-(2,4-difluorophenyl)-8H-pyrido[2,3-d]pyrimidin-7-one

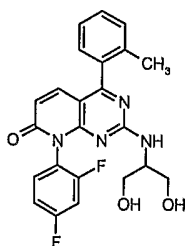
The title compound was prepared by following the procedure in Example 21 except 2-biphenyl boronic acid was used in the coupling step (89%): MS (ES) m/z 501 (M+H)⁺; ¹H-NMR(CDCl₃) δ 2.06 (s, br, 2H), 3.73 (m, br, 5H), 6.15 (m, br, 1H), 6.18 (s, br, 1H), 7.00 (m, 2H), 7.25 (m, 7H), 7.58 (m, 4H).

Example 28

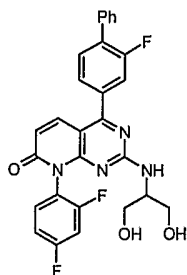
30

4-(3-Biphenyl)-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-8-(2,4-difluorophenyl)-8H-pyrido[2,3-d]pyrimidin-7-one

The title compound was prepared by following the procedure in Example 21 except 3-biphenyl boronic acid was used in the coupling step (92%): MS (ES) m/z 501 (M+H)⁺; ¹H-NMR(CDCl₃) δ 2.10 (s, br, 2H), 3.72 (m, br, 5H), 6.10 (m, br, 1H), 6.47 (m, 1H), 7.06 (m, 2H), 7.60 (m, 8H), 7.82 (m, 3H).

Example 29

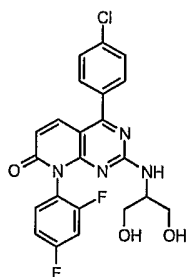
4-(2-Tolyl)-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-8-(2,4-difluorophenyl)-8H-pyrido[2,3-d]pyrimidin-7-one The title compound was prepared by following the procedure in Example 21 except 2-tolyl boronic acid was used in the coupling step (66%): MS (ES) m/z 439 (M+H)⁺; ¹H-NMR(CDCl₃) δ 2.24 (s, 3H), 2.96 (s, br, 2H), 3.68 (m, br, 5H), 6.10 (m, br, 1H), 6.39 (m, 1H), 7.04 (m, 2H), 7.40 (m, 6H).

Example 30

4-(3-Fluoro-4-biphenyl)-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-8-(2,4-difluorophenyl)-8H-pyrido[2,3-d]pyrimidin-7-one

The title compound was prepared by following the procedure in Example 21 except 3-fluoro-4-biphenyl boronic acid was used in the coupling step (48%): MS (ES) m/z 519 ($M+H$)⁺; ¹H-

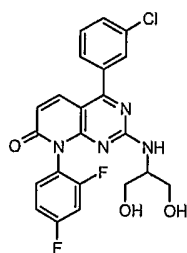
NMR(CDCl₃) δ 2.15 (s, br, 2H), 3.78 (m, br, 5H), 6.05 (m, br, 1H), 6.50 (m, 1H), 7.06 (m, 2H), 7.28 (m, 1H), 7.52 (m, 8H), 7.86 (m, 1H).

Example 31

4-(4-Chlorophenyl)-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-8-(2,4-difluorophenyl)-8H-pyrido[2,3-d]pyrimidin-7-one

The title compound was prepared by following the procedure in Example 21 except 4-chlorophenyl boronic acid was used in the coupling step (70%): MS (ES) m/z 459 ($M+H$)⁺; ¹H-

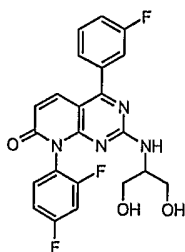
NMR(CDCl₃) δ 2.83 (s, br, 2H), 3.72 (m, br, 5H), 6.15 (m, br, 1H), 6.46 (m, 1H), 7.04 (m, 2H), 7.28 (m, 1H), 7.53 (m, 4H), 7.72 (m, 1H).

Example 32

4-(3-Chlorophenyl)-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-8-(2,4-difluorophenyl)-8H-pyrido[2,3-d]pyrimidin-7-one

The title compound was prepared by following the procedure in Example 21 except 3-chlorophenyl boronic acid was used in the coupling step (49%). MS (ES) m/z 459 ($M+H$)⁺; ¹H-

NMR(CDCl₃) δ 2.55 (s, br, 2H), 3.74 (m, br, 5H), 6.10 (m, br, 1H), 6.47 (m, 1H), 7.05 (m, 2H), 7.28 (m, 1H), 7.53 (m, 4H), 7.73 (m, 1H).

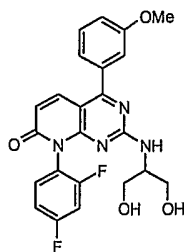
Example 33

4-(3-Fluorophenyl)-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-8-(2,4-difluorophenyl)-8H-pyrido[2,3-d]pyrimidin-7-one

The title compound was prepared by following the procedure in Example 21 except 3-fluorophenyl boronic acid was used in the coupling step (64%): MS (ES) m/z 443 ($M+H$)⁺; ¹H-

NMR(CDCl₃) δ 2.05 (s, br, 2H), 3.79 (m, br, 5H), 6.10 (m, br, 1H), 6.49 (m, 1H), 7.07 (m, 2H), 7.42 (m, 5H), 7.77 (m, 1H).

Example 34

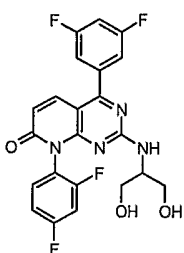


4-(3-Methoxyphenyl)-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-8-(2,4-difluorophenyl)-8H-pyrido[2,3-d]pyrimidin-7-one

The title compound was prepared by following the procedure in Example 21 except 3-methoxyphenyl boronic acid was used in the coupling step (89%): MS (ES) m/z 455 (M+H)⁺; ¹H-NMR(CDCl₃) δ 2.07 (s, br, 2H), 3.83 (m, br, 5H), 3.91 (s, 3H), 6.15 (m, br, 1H), 6.47 (m, 1H), 7.10 (m, 5H), 7.28 (m, 1H), 7.47 (m, 1H), 7.82 (m, 1H).

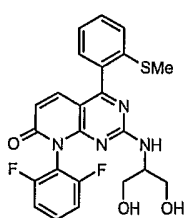
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Example 35



4-(3,5-Difluorophenyl)-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-8-(2,4-difluorophenyl)-8H-pyrido[2,3-d]pyrimidin-7-one The title compound was prepared by following the procedure in Example 21 except 3,5-difluorophenyl boronic acid was used in the coupling step (89%): MS (ES) m/z 461 (M+H)⁺; ¹H-NMR(CDCl₃) δ 2.05 (s, br, 2H), 3.89 (m, br, 5H), 6.10 (m, br, 1H), 6.51 (m, 1H), 7.08 (m, 5H), 7.28 (m, 1H), 7.75 (m, 1H).

Example 36



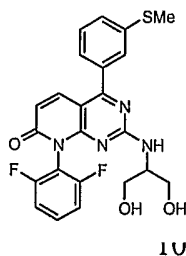
4-(2-Methylsulfanyl-phenyl)-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-8-(2,6-difluorophenyl)-8H-pyrido[2,3-d]pyrimidin-7-one

A solution of 4-Chloro-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-8-(2,6-difluoro-phenyl)-8H-pyrido[2,3-d]pyrimidin-7-one (50mg, 0.13mmol) in dioxane / H₂O (3 : 1, 4.8mL) was mixed with 2-methylthiophenyl boronic acid (33.8mg, 0.20mmol) and K₂CO₃ (54.3mg, 0.39mmol). The resultant mixture was bubbled with argon for 5 minutes, and added by Pd(PPh₃)₄ (3.0mg, 0.0026mmol). The reaction tube was sealed and heated with "Smith Creator" (microwave, 150°C) for 15minutes. The mixture was concentrated under vacuo. Flash chromatography (EtOAc / Hexane, 3 : 1) then provided the title compound (89%): MS (ES) m/z 471 (M+H)⁺; ¹H-NMR(CDCl₃) δ

35

2.45 (s, 3H), 2.55 (s, br, 2H), 3.72 (m, br, 5H), 6.25 (m, br, 1H), 6.41 (m, 1H), 7.11 (m, 2H), 7.30 (m, 2H), 7.45 (m, 2H), 7.51 (m, 2H).

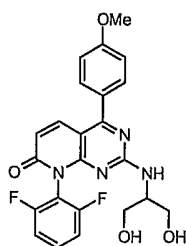
Example 37



4-(3-Methylsulfonyl-phenyl)-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-8-(2,6-difluorophenyl)-8H-pyrido[2,3-d]pyrimidin-7-one

The title compound was prepared by following the procedure in Example 36 except 3-methylthiophenyl boronic acid was used in the coupling step (71%): MS (ES) m/z 471 (M+H)⁺; ¹H-NMR(CDCl₃) δ 2.50 (s, br, 2H), 2.55 (s, 3H), 3.72 (m, br, 5H), 6.25 (m, br, 1H), 6.47 (m, 1H), 7.11 (m, 2H), 7.35 (m, 1H), 7.46 (m, 4H), 7.77 (m, 1H).

Example 38

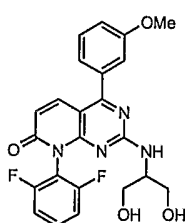


4-(4-Methoxyphenyl)-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-8-(2,6-difluorophenyl)-8H-pyrido[2,3-d]pyrimidin-7-one

The title compound was prepared by following the procedure in Example 36 except 4-methoxyphenyl boronic acid was used in the coupling step (70%): MS (ES) m/z 455 (M+H)⁺; ¹H-NMR(CDCl₃) δ 1.80 (s, br, 2H), 3.77 (m, br, 5H), 3.92 (s, 3H), 6.10 (m, br, 1H), 6.47 (m, 1H), 7.12 (m, 4H), 7.50 (m, 1H), 7.62 (m, 2H), 7.86 (m, 1H).

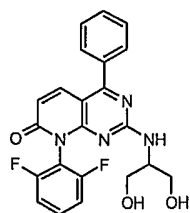
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Example 39



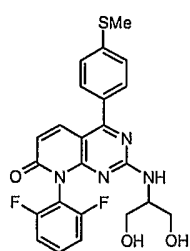
4-(3-Methoxyphenyl)-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-8-(2,6-difluorophenyl)-8H-pyrido[2,3-d]pyrimidin-7-one

The title compound was prepared by following the procedure in Example 36 except 3-methoxyphenyl boronic acid was used in the coupling step (79%): MS (ES) m/z 455 (M+H)⁺; ¹H-NMR(CDCl₃) δ 2.25 (s, br, 2H), 3.75 (m, br, 5H), 3.90 (s, 3H), 6.15 (m, br, 1H), 6.46 (m, 1H), 7.15 (m, 5H), 7.47 (m, 2H), 7.82 (m, 1H).

Example 40

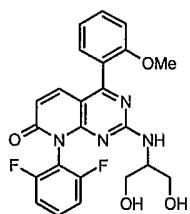
4-phenyl-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-8-(2,6-difluorophenyl)-8H-pyrido[2,3-d]pyrimidin-7-one The title compound was prepared by following the procedure in Example 36 except phenyl boronic acid was used in the coupling step (89%): MS (ES) m/z 425 (M+H)⁺; ¹H-NMR(CDCl₃) δ 2.16 (s, br, 2H), 3.83 (m, br, 5H), 6.15 (m, br, 1H), 6.47 (m, 1H), 7.13 (m, 2H), 7.55 (m, 6H), 7.80 (m, 1H).

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Example 41

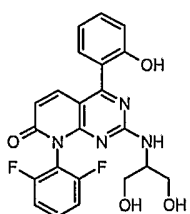
4-(4-Methylsulfanylphenyl)-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-8-(2,6-difluorophenyl)-8H-pyrido[2,3-d]pyrimidin-7-one The title compound was prepared by following the procedure in Example 36 except 4-methylthiophenyl boronic acid was used in the coupling step (67%): MS (ES) m/z 471 (M+H)⁺; ¹H-NMR(CDCl₃) δ 2.50 (s, 3H), 2.57 (s, br, 2H), 3.72 (m, br, 5H), 6.20 (m, br, 1H), 6.46 (m, 1H), 7.11 (m, 2H), 7.39 (m, 2H), 7.45 (m, 1H), 7.56 (m, 2H), 7.81 (m, 1H).

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Example 42

4-(2-Methoxyphenyl)-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-8-(2,6-difluorophenyl)-8H-pyrido[2,3-d]pyrimidin-7-one The title compound was prepared by following the procedure in Example 36 except 2-methoxyphenyl boronic acid was used in the coupling step (91%): MS (ES) m/z 455 (M+H)⁺; ¹H-NMR(CDCl₃) δ 2.70 (s, br, 2H), 3.68 (m, br, 5H), 3.82 (s, 3H), 6.20 (m, br, 1H), 6.40 (m, 1H), 7.08 (m, 4H), 7.48 (m, 4H).

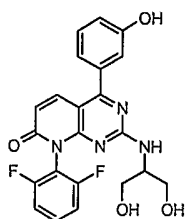
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Example 43

4-(2-Hydroxyphenyl)-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-8-(2,6-difluorophenyl)-8H-pyrido[2,3-d]pyrimidin-7-one A solution of 4-Chloro-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-8-(2,6-difluorophenyl)-8H-pyrido[2,3-d]pyrimidin-7-one (50mg, 0.13mmol) in dioxane / H₂O (3 : 1, 4.8mL) was mixed with 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (44.0mg, 0.20mmol) and K₂CO₃ (71.9mg, 0.52mmol). The resultant

- mixture was bubbled with argon for 5 minutes, and added by Pd(PPh₃)₄ (3.0mg, 0.0026mmol). The reaction tube was sealed and heated with "Smith Creator" (microwave, 150°C) for 15minutes. The mixture was concentrated under vaco. Flash chromatography (EtOAc / Hexane, 3 : 1) then afforded the title compound (82%): MS (ES) *m/z* 441 (M+H)⁺; ¹H-NMR(CDCl₃) δ 1.65 (s, br, 2H), 3.80 (m, br, 5H), 6.05 (m, br, 1H), 6.54 (m, 1H), 7.15 (m, 4H), 7.48 (m, 3H), 7.98 (m, 1H).

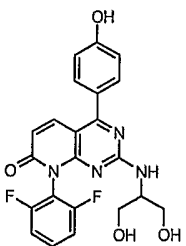
Example 44



4-(3-Hydroxyphenyl)-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-8-(2,6-difluorophenyl)-8H-pyrido[2,3-d]pyrimidin-7-one

- The title compound was prepared by following the procedure in Example 43 except 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol was used in the coupling step (13%): MS (ES) *m/z* 441 (M+H)⁺; ¹H-NMR-(CD₃OD) δ 2.18 (m, br, 5H), 4.92 (m, 1H), 5.50 (m, 1H), 5.65 (m, 4H), 5.86 (m, 1H), 6.08 (m, 1H), 6.44 (m, 1H).

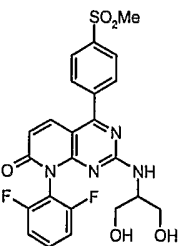
Example 45



4-(4-Hydroxyphenyl)-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-8-(2,6-difluorophenyl)-8H-pyrido[2,3-d]pyrimidin-7-one

- The title compound was prepared by following the procedure in Example 43 except 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol was used in the coupling step (56%): MS (ES) *m/z* 441 (M+H)⁺; ¹H-NMR(CD₃OD) δ 2.18 (m, br, 5H), 4.91 (m, 1H), 5.48 (m, 2H), 5.71 (m, 2H), 6.07 (m, 3H), 6.51 (m, 1H).

Example 46



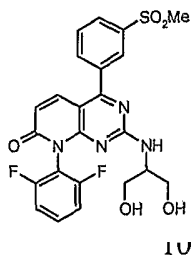
4-(4-Methylsulfonyl-phenyl)-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-8-(2,6-difluorophenyl)-8H-pyrido[2,3-d]pyrimidin-7-one

A solution of 4-(4-Methylsulfonyl-phenyl)-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-8-(2,6-difluorophenyl)-8H-pyrido[2,3-d]pyrimidin-7-one (50mg, 0.11mmol) in methylene chloride (3mL) was mixed with *m*CPBA (80.0mg, 0.33mmol).

- After stirring at room temperature for 30 minutes, the mixture was concentrated under vaco. Flash chromatography (EtOAc / Hexane, 10 : 1) then provided the title compound (61%): MS (ES) *m/z* 502 (M+H)⁺; ¹H-NMR(CDCl₃) δ

2.06 (s, br, 2H), 3.16 (s, 3H), 3.77 (m, br, 5H), 6.20 (m, br, 1H), 6.51 (m, 1H), 7.13 (m, 2H), 7.51 (m, 1H), 7.68 (m, 1H), 7.85 (m, 2H), 8.15 (m, 2H).

Example 47

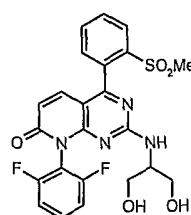


4-(3-Methylsulfonyl-phenyl)-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-8-(2,6-difluorophenyl)-8H-pyrido[2,3-d]pyrimidin-7-one

The title compound was prepared from 4-(3-methylsulfonyl-phenyl)-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-8-(2,6-difluorophenyl)-8H-pyrido[2,3-d]pyrimidin-7-one by following the procedure in Example 46 (64%): MS (ES) m/z 503 ($M+H$)⁺; ¹H-NMR(CDCl₃) δ 2.09 (s, br, 2H), 3.16 (s, 3H), 3.78 (m, br, 5H), 6.35 (m, br, 1H), 6.55 (m, 1H), 7.14 (m, 2H), 7.50 (m, 1H), 7.70 (m, 1H), 7.81 (m, 1H), 7.95 (m, 1H), 8.17 (m, 1H), 8.30 (s, br, 1H).

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Example 48



4-(2-Methylsulfonyl-phenyl)-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-8-(2,6-difluorophenyl)-8H-pyrido[2,3-d]pyrimidin-7-one

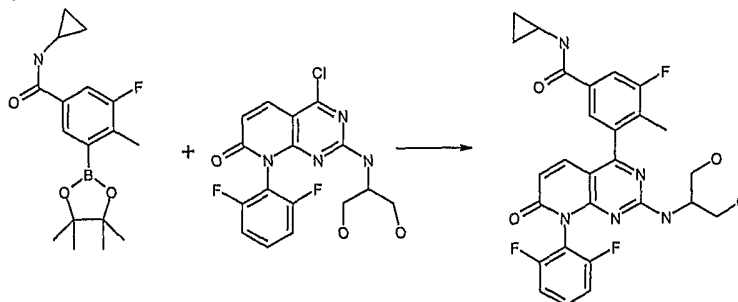
The title compound was prepared from 4-(2-methylsulfonyl-phenyl)-2-(2-hydroxy-1-hydroxymethyl-ethylamino)-8-(2,6-difluorophenyl)-8H-pyrido[2,3-d]pyrimidin-7-one by following the procedure in Example 46 (62%): MS (ES) m/z 503 ($M+H$)⁺; ¹H-NMR(CDCl₃) δ 2.27 (s, br, 2H), 3.28 (s, 3H), 3.77 (m, br, 5H), 6.20 (s, br, 1H), 6.41 (m, 1H), 7.13 (m, 2H), 7.25 (m, 1H), 7.48 (m, 2H), 7.81 (m, 2H), 8.26 (m, 1H).

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Example 49

N-cyclopropyl-3-(8-(2,6-difluorophenyl)-2-([2-hydroxy-1-(hydroxymethyl)ethyl]amino)-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-4-yl)-5-fluoro-4-methylbenzamide

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3-Fluoro-4-methylbenzoic acid (1.54 g, 0.01 mol) is dissolved in trifluoromethanesulfonic acid (10 mL) and cooled to about 0 °C. NIS (2.25 g, 0.01 mol) is added in several portions over a 6 h period while maintaining the reaction temperature at about 0 °C. The mixture is allowed to warm to rt. overnight. The reaction mixture is then poured over ice and extracted with ethyl acetate (3x). The organic layers are washed (Na₂S₂O₅) and concentrated. The material is carried on crude.

The crude acid from above (~1.5 g) is dissolved in thionyl chloride (75 mL) and heated to 80 °C for about 2 h. The mixture is then cooled to room temperature and stirred under N₂ overnight. The mixture is concentrated in vacuo and dissolved in 15 mL DCM. Na₂CO₃ (3g) is added along with the cyclopropyl amine (0.69 mL, 0.01 moles (hereinafter "mol")). The mixture is allowed to stir overnight and purified via flash chromatography (5% MeOH / CH₂Cl₂) to afford 0.904g of *N*-cyclopropyl-3-fluoro-5-iodo-4-methylbenzamide

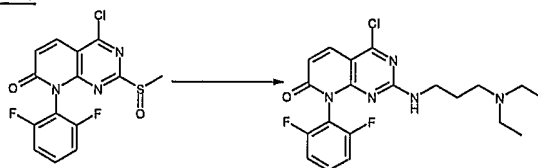
N-cyclopropyl-3-fluoro-5-iodo-4-methylbenzamide (0.904 g, 2.83 mmol) is dissolved in DMF (30 mL). Bis-pinicalato-diborane (1.44 g, 2.83 mmol) is added followed by PdCl₂.dppf (55 mg) and potassium acetate (1.38 g, 14.15 mmol). The mixture are stirred for about 18 h, concentrated *in vacuo* and purified via flash chromatography to afford *N*-cyclopropyl-3-fluoro-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (60 mg).

4-Chloro-8-(2,6-difluorophenyl)-2-{[2-hydroxy-1-(hydroxymethyl)ethyl]-amino}pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (0.056 g, 0.17 mmol), *N*-cyclopropyl-3-fluoro-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (0.065 g, 0.17 mmol), K₂CO₃ (0.07 g, 0.51 mmol) and tetrakis triphenyl phosphine palladium (10 mg, 0.05eq) are dissolved in dioxane / water (3:1, 10 mL) and heated to about 100 °C for about 3 h. The mixture is concentrated and purified via reverse phase HPLC to afford the title compound (9 mg, yellow powder, mp 214.2-217.5): LC-MS *m/z* 540 (M+H)⁺, 1.69 min (ret time). HPLC indicates 96% pure.

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Example 50

4-chloro-2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one



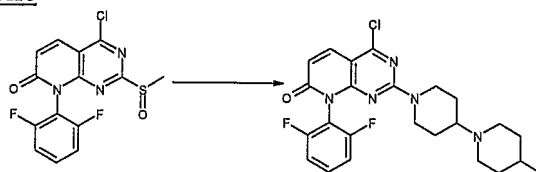
To the compound 4-chloro-8-(2,6-difluorophenyl)-2-(methylsulfinyl)-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (1.59 g, 4.47 mmol) in dichloromethane (89.4

mL) were added *N,N*-diethyl-1,3-propanediamine (0.845 mL, 5.36 mol) and triethylamine (1.26 uL, 8.94 mmol). The mixture was stirred at rt overnight. Some white precipitate was formed during the reaction. Filtration followed by wash with ethyl acetate/dichloromethane/methanol afforded the title compound (1.028 g, 60%).

5 LC-MS m/z 383 ($M+H$)⁺.

Example 51

4-chloro-8-(2,6-difluorophenyl)-2-(4-methyl-1,4'-bipiperidin-1'-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one



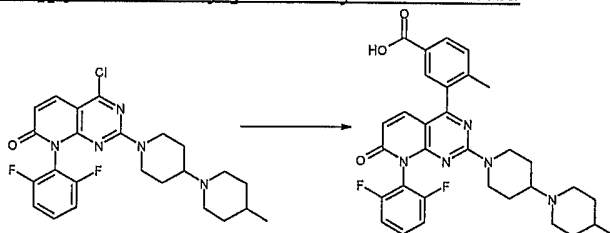
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To the compound 4-chloro-8-(2,6-difluorophenyl)-2-(methylsulfinyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (1.39 g, 3.9 mmol) in dichloromethane (80 mL) were added 4-methyl-1,4'-bipiperidine (0.75 g, 5.85 mol) and triethylamine (1.03 mL, 11.7 mmol). The mixture was stirred at about -20°C overnight. Filtration followed by concentration, the crude was purified with flash chromatography to afford the title compound (0.904 g, 51%). LC-MS m/z 474 ($M+H$)⁺.

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Example 52

3-[8-(2,6-difluorophenyl)-2-(4-methyl-1,4'-bipiperidin-1'-yl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid



To a stirring solution of 3-iodo-4-methylbenzoic acid (60 g, 0.22 mol, 1 eq) in degassed DMF (1400 mL, 23.3 vol.) was charged 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane (81.4 g, 0.32 mol, 1.4 eq) followed by potassium acetate (112 g, 1.14 mole, 5eq) and [1,1'-bis(diphenylphosphino)ferrocene]-dichloropalladium(II) (18.7 g, 0.02 mole, 0.1eq). The resulting mixture was placed under a nitrogen atmosphere and was heated to 80 °C with the exclusion of light overnight. The mixture was then concentrated under high vacuum and the residue partitioned between EtOAc and 2M HCl. The mixture was then filtered and the layers separated. The aqueous phase was re-extracted with EtOAc. The combined

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organics were then washed with brine, dried and evaporated to yield a brown solid that was applied to a silica plug then eluted with 2:1 cyclohexane : ethyl acetate.

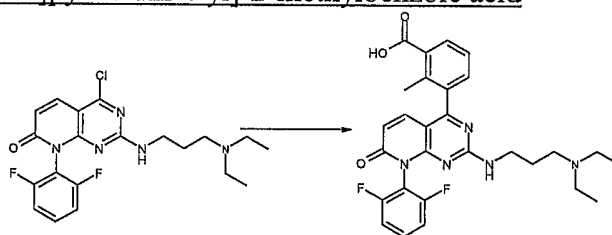
Fractions were then combined and evaporated to yield a brown foam that was triturated with cyclohexane, collected by filtration then dried in *vacuo* to yield 4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid. δ (CDCl₃) 8.50-8.49 (1H, d), 8.04-8.02 (1H, dd), 7.27-7.25 (1H, d), 2.61 (3H, s), 1.36 (12H, s).

To the compound 4-chloro-8-(2,6-difluorophenyl)-2-(4-methyl-1,4'-bipiperidin-1'-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (47.5 mg, 0.1 mmol) in dioxane (3 mL) and water (1 mL) were added 4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid (38.4 mg, 0.15 mol), potassium carbonate (83 mg, 0.6 mmol) and tetrakis(triphenylphosphine)palladium(0) (4.6 mL, 0.005 mmol). The mixture was heated with microwave at about 150°C for about 15 min. The mixture was concentrated & then mixed with DMSO (0.75 mL) and water (0.25 mL).

Separation by HPLC afforded the title compound (39 mg, 68%). LC-MS *m/z* 574 (M+H)⁺.

Example 53

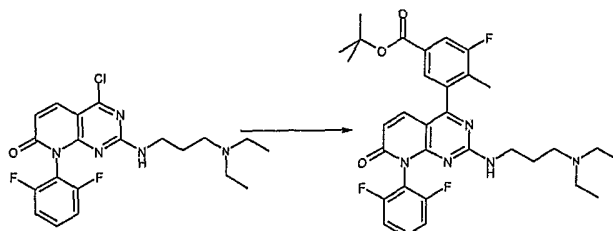
3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-2-methylbenzoic acid



To the compound 4-chloro-2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (176 mg, 0.418 mmol) in dioxane (4.5 mL) and water (1.5 mL) was added 2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid (173 mg, 0.626 mol), potassium carbonate (289 mg, 2.09 mmol) and tetrakis(triphenylphosphine)palladium(0) (24.2 mg, 0.0259 mmol). The mixture was heated with microwave at about 150 °C for about 15 min. The mixture was filtered. Separation by HPLC with TFA afforded the title compound (238 mg, 99%). LC-MS *m/z* 522 (M+H)⁺.

Example 54

1,1-dimethylethyl 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-5-fluoro-4-methylbenzoate trifluoroacetate



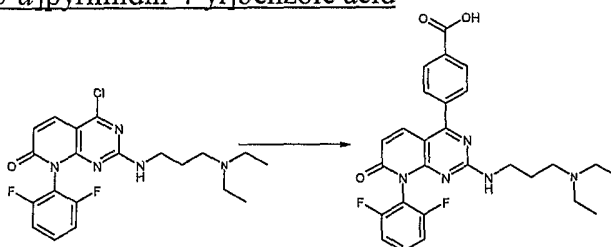
5

To the compound 4-chloro-2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (600 mg, 1.422 mmol) in dioxane (15 mL) and water (5 mL) were added 1,1-dimethylethyl 3-fluoro-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (542 mg, 2.132 mol),
 10 potassium carbonate (590 mg, 4.26 mmol) and tetrakis(triphenylphosphine)-palladium(0) (82 mg, 0.071 mmol). The mixture was heated with microwave at 150°C for 15 minutes. The mixture was filtered. Separation by HPLC with TFA afforded the crude title compound.

15

Example 55

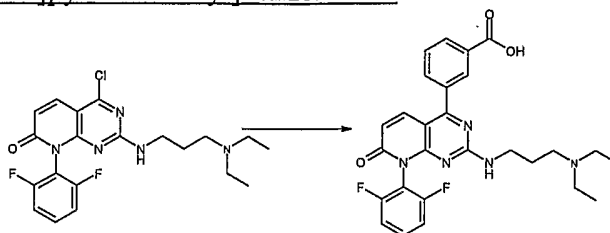
4-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]benzoic acid



To the compound 4-chloro-2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (168.75 mg, 0.40 mmol) in
 20 dioxane (12 mL) and water (4 mL) were added 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid (148.85 mg, 0.60 mol), potassium carbonate (208 mg, 1.20 mmol) and tetrakis(triphenylphosphine)palladium(0) (23 mg, 0.02 mmol). The mixture was heated with microwave at 150°C for 15 min. The mixture was
 25 concentrated. It was mixed with DMSO (0.75 mL) and water (0.25 mL). Separation by HPLC afforded the title compound (147 mg, 72%). LC-MS *m/z* 508 (*M*+*H*)⁺.

Example 56

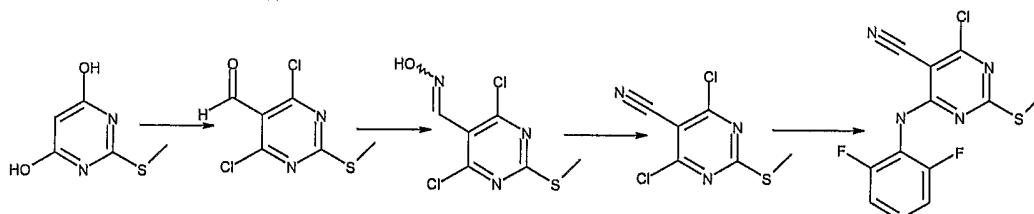
3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]benzoic acid



- 5 To the compound 4-chloro-2-[[3-(diethylamino)propyl]amino]-8-(2,6-difluorophenyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (210.5 mg, 0.50 mmol) in dioxane (15 mL) and water (5 mL) were added 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid (125 mg, 0.75 mol), potassium carbonate (210 mg, 1.20 mmol) and tetrakis(triphenylphosphine)palladium(0) (29 mg, 0.025 mmol). The mixture was
- 10 heated with microwave at about 150^oC for about 15 min. The mixture was concentrated, then mixed with DMSO (0.75 mL) and water (0.25 mL). Separation by HPLC afforded the title compound (467 mg, 32%). LC-MS *m/z* 508 (M+H)⁺.

Example 57

- 15 5-Chloro-1-(2,6-difluorophenyl)-7-(methylthio)-3,4-dihydropyrimido[4,5-*d*]pyrimidin-2(1*H*)-one
57a) 4-chloro-6-[(2,6-difluorophenyl)amino]-2-(methylthio)-5-pyrimidinecarbonitrile



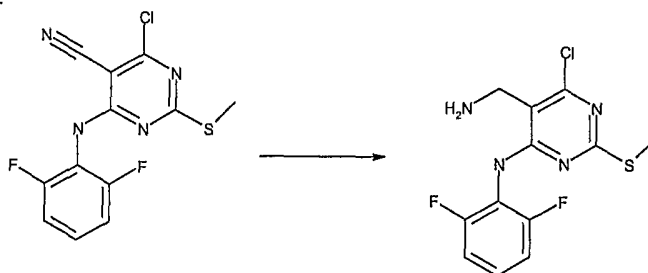
- 20 To the solution of phosphorus oxychloride (65 mL, 0.70 mol) in trichloroethylene (46.5 mL) was added DMF (25 mL, 0.32 mol) slowly to keep the temperature between 5 °C to 10 °C. The solution was then warmed up to room temperature before 6-hydroxy-2-(methylthio)-4(1*H*)-pyrimidinone (25 g, 0.16 mol) was added in portions. The resultant reaction mixture was heated at 80 °C overnight
- 25 followed by concentration under vacuum. The resulting slurry like residue was poured into ice, stirred for about 2 hours then filtered to afford the crude product. The crude product was further purified by recrystallization with hexane to afford 4,6-dichloro-2-(methylthio)-5-pyrimidinecarbaldehyde (21.3 g, 61%). ¹H-NMR (CDCl₃) δ 2.66 (s, 3 H), 10.4 (s, 1 H).

To the mixture of hydroxylamine hydrochloride (139 mg, 2.0 mmol), HOAc (0.113 mL, 2.0 mmol) and EtOH (5 mL) was added 4,6-dichloro-2-(methylthio)-5-pyrimidinecarbaldehyde (223 mg, 1.0 mmol) to room temperature. The solution was then heated at 50 °C for about 1 hour, 60 °C for about 30 minutes and 70 °C for about 30 minutes before it was concentrated under vacuum and washed with H₂O (10-20 mL) to afford 4,6-dichloro-2-(methylthio)-5-pyrimidinecarbaldehyde oxime (190 mg, 80%). LC-MS *m/z* 238 (M + H)⁺ 1.57 minute, 1.65 minute; ¹H-NMR (CDCl₃) δ 2.62, 2.65 (3 H), 7.53, 8.30 (1 H).

To 4,6-dichloro-2-(methylthio)-5-pyrimidinecarbaldehyde oxime (2.38 g, 10 mmol) was added SOCl₂ (21.8 mL, 0.30 mol) slowly at room temperature. The solution was then heated at 75 °C for about 3 hours before it was concentrated under vacuum. The residue SOCl₂ was removed by evaporation with toluene (5 mL) under vacuum. The resulting solid was washed with EtOH/H₂O (10 mL, 1 : 1) to afford 4,6-dichloro-2-(methylthio)-5-pyrimidinecarbonitrile (2.04 g, 93%). LC-MS *m/z* 220 (M + H)⁺ 1.99 minute; ¹H-NMR (CDCl₃) δ 2.64 (3 H).

To the solution of 4,6-dichloro-2-(methylthio)-5-pyrimidinecarbonitrile (2.20 g, 10.0 mmol) in DMF (10 mL) was added 2,6-difluoroaniline (2.17 mL, 20.0 mmol). The solution was stirred at 50 °C for about 60 minutes. The mixture was slowly added into a solution of MeOH (20 mL) and water (30 mL). The resultant solid was filtered and washed with MeOH / H₂O (20 mL, 1:1) to give 4-chloro-6-[(2,6-difluorophenyl)amino]-2-(methylthio)-5-pyrimidinecarbonitrile as a white solid (2.82 g, 90 %). LC-MS *m/z* 313 (M + H)⁺; ¹H-NMR (CDCl₃) δ 2.33 (s, 3 H), 6.94 (s, 1 H), 7.04 (m, 2 H), 7.35 (m, 1 H).

25 57b) 5-(Aminomethyl)-6-chloro-N-(2,6-difluorophenyl)-2-(methylthio)-4-pyrimidinamine

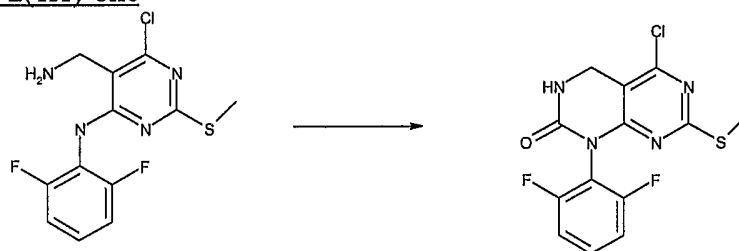


To the solution of 4-chloro-6-[(2,6-difluorophenyl)amino]-2-(methylthio)-5-pyrimidinecarbonitrile (0.938 g) was added borane•THF complex (1.0 M, 15 mL). The reaction mixture was then heated at reflux for about 4 h until all the starting material disappeared. The solution was cooled to r.t., mixed with HCl solution (6 M, 5 mL), and stirred at room temperature for about 30 minutes. The solution was then mixed with NaOH solution (3 M) to pH 9.0-10.0. The organic phase was

separated and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (50 mL), collected, dried over Na₂SO₄ and concentrated to afford the title compound 0.97 g (quantative). LC-MS *m/z* 317 (M+H)⁺, 1.5 min (ret. time).

5

57c) 5-Chloro-1-(2,6-difluorophenyl)-7-(methylthio)-3,4-dihydropyrimido[4,5-d]pyrimidin-2(1H)-one

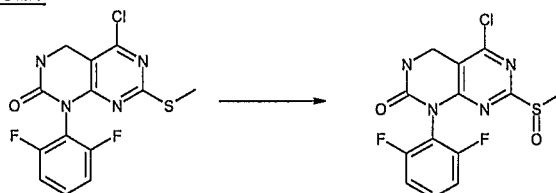


To the solution of 5-(aminomethyl)-6-chloro-*N*-(2,6-difluorophenyl)-2-(methylthio)-4-pyrimidinamine (0.317 g) in CH₂Cl₂ (5 mL) was added the mixture of carbonyl diimidazole (0.178 g) in CH₂Cl₂ (5 mL). The resultant mixture was stirred for about 3 hours at r.t., mixed with CH₂Cl₂ (10 mL) and washed with HCl (1 N, 2 x 10 mL) and H₂O (20 mL). The organic layers were collected, dried over Na₂SO₄, filtered and concentrated to provide the title compound (0.279 g, 81%). LC-MS *m/z* 343 (M+H)⁺, 1.75 min (ret. time); ¹H-NMR (400 MHz, CDCl₃) δ 7.44-7.40 (m, 1H), 7.07-7.03 (m, 2H), 5.84 (br, 1H), 4.62 (s, 2H), 2.19 (s, 3H).

20

Example 58

5-chloro-1-(2,6-difluorophenyl)-7-(methylsulfinyl)-3,4-dihydropyrimido[4,5-d]pyrimidin-2(1H)-one

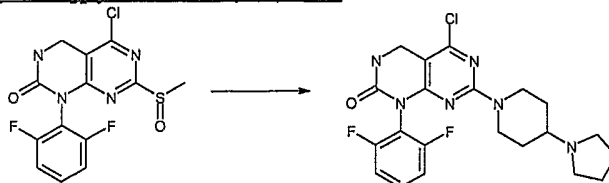


To a solution of 3-[8-(2,6-difluorophenyl)-2-(methylthio)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-d]pyrimidin-4-yl]-4-methylbenzoic acid (1.71 g, 5 mmol) in CH₂Cl₂ (60 mL) was added *m*-CPBA (1.17 g, 5.2 mmol). The mixture was stirred at room temperature for 10 minutes, then directly loaded onto a column. Flash chromatography (mobile phase EtOAc/Hexane) afforded the title compound as a white solid 1.58 g (88 %). LC-MS *m/z* 358 (M + H)⁺.

25

Example 59

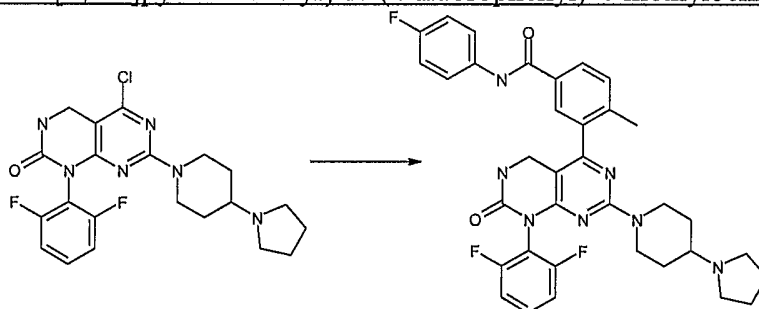
5-chloro-1-(2,6-difluorophenyl)-7-[4-(1-pyrrolidinyl)-1-piperidinyl]-3,4-dihydropyrimido[4,5-*d*]pyrimidin-2(1*H*)-one



- 5 To a solution of 5-chloro-1-(2,6-difluorophenyl)-7-(methylsulfinyl)-3,4-dihydropyrimido[4,5-*d*]pyrimidin-2(1*H*)-one (250 mg, 0.70 mmol) in DCM (10 mL) were added 4-(1-pyrrolidinyl)piperidine (323 mg, 2.1 mmol) and *N,N*-diisopropylethylamine (0.3 mL, 1.7 mmol). The resultant solution was stirred at room temperature over night. The result mixture was concentrated. CombiFlash
10 chromatography (mobile phase DCM/DCM[90]+MeOH[7]+NH₄OH[3]) provided the title compound as a white solid (253 mg, 81 %). LC-MS *m/z* 449 (*M* + *H*)⁺

Example 60

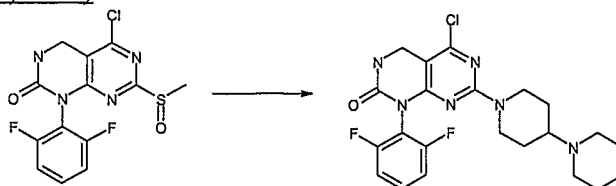
- 15 3-{8-(2,6-difluorophenyl)-7-oxo-2-[4-(1-pyrrolidinyl)-1-piperidinyl]-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl}-*N*-(4-fluorophenyl)-4-methylbenzamide



- To a solution of 5-chloro-1-(2,6-difluorophenyl)-7-[4-(1-pyrrolidinyl)-1-piperidinyl]-3,4-dihydropyrimido[4,5-*d*]pyrimidin-2(1*H*)-one (18 mg, 0.04 mmol) in dioxane (1.5 mL)/water (0.5 mL) were added potassium carbonate (34 mg, 0.25
20 mmol), tetrakis(triphenylphosphine)palladium(0) (2.3 mg, 0.002 mmol) and *N*-(4-fluorophenyl)-4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (22 mg, 0.062 mmol). The reaction mixture was bubbled with N₂ for 5 mins, then microwaved at about 150⁰C for about 30 mins. The reaction mixture was concentrated. CombiFlash chromatography (mobile phase DCM/DCM[90]+
25 MeOH[7]+ NH₄OH[3]) provided the title compound as a white solid (14 mg, 54%). LC-MS *m/z* 642 (*M* + *H*)⁺; ¹H-NMR (CD₃OD) δ 1.32 (m, 2 H), 1.80 (m, 4 H), 1.88 (m, 2 H), 2.24 (m, 1 H), 2.33 (s, 3 H), 2.62 (m, 4 H), 2.74 (t, 2 H), 4.17 (m, 2 H), 4.40 (m, 2 H), 7.12 (m, 4 H), 7.52 (m, 2 H), 7.72 (m, 2 H), 7.82 (s, 1 H), 7.98 (d, 1 H).

Example 61

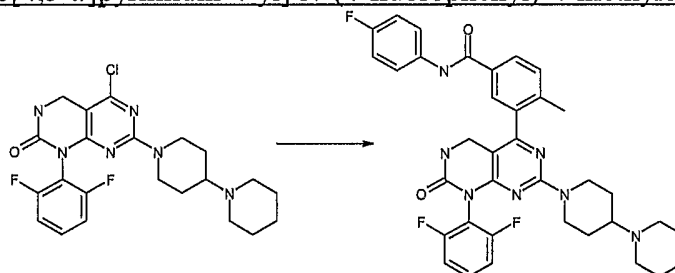
7-(1,4'-bipiperidin-1'-yl)-5-chloro-1-(2,6-difluorophenyl)-3,4-dihydropyrimido[4,5-*d*]pyrimidin-2(1*H*)-one



- 5 To a solution of 5-chloro-1-(2,6-difluorophenyl)-7-(methylsulfinyl)-3,4-dihydropyrimido[4,5-*d*]pyrimidin-2(1*H*)-one (200 mg, 0.56 mmol) in DCM (10 mL) were added 1,4'-bipiperidine (270 mg, 1.61 mmol) and *N,N*-diisopropylethylamine (0.3 mL, 1.7 mmol). The resultant solution was stirred at room temperature over night. The result mixture was concentrated. CombiFlash chromatography (mobile
10 phase DCM/DCM[90]+MeOH[7]+NH₄OH[3]) provided the title compound as a white solid (298 mg, 83 %). LC-MS *m/z* 463 (*M* + *H*)⁺.

Example 62

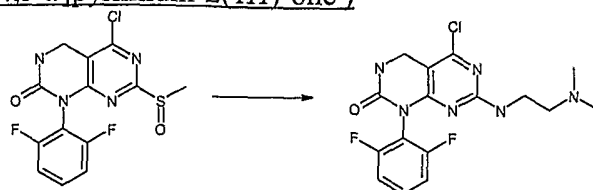
- 3-[2-(1,4'-bipiperidin-1'-yl)-8-(2,6-difluorophenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-*N*-(4-fluorophenyl)-4-methylbenzamide



- To a solution of compound 7-(1,4'-bipiperidin-1'-yl)-5-chloro-1-(2,6-difluorophenyl)-3,4-dihydropyrimido[4,5-*d*]pyrimidin-2(1*H*)-one (18 mg, 0.04 mmol) in dioxane (1.5 mL)/water (0.5 mL) were added potassium carbonate (34 mg, 0.25 mmol), tetrakis(triphenylphosphine)palladium(0) (2.3 mg, 0.002 mmol) and *N*-(4-fluorophenyl)-4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (22 mg, 0.062 mmol). The reaction mixture was bubbled with N₂ for 5 mins, then microwaved at about 150°C for about 30 mins. The reaction mixture was concentrated. CombiFlash chromatography (mobile phase DCM/DCM[90]+MeOH
20 [7]+NH₄OH[3]) provided the title compound as a white solid (13 mg, 51%). LC-MS *m/z* 656 (*M* + *H*)⁺; ¹H-NMR (CD₃OD) δ 1.37 (m, 2 H), 1.48 (m, 2 H), 1.60 (m, 4 H), 1.80 (m, 2 H), 2.33 (s, 3 H), 2.56 (m, 5 H), 2.72 (t, 2 H), 4.17 (m, 2 H), 4.46 (m, 2 H), 7.12 (m, 4 H), 7.52 (m, 2 H), 7.72 (m, 2 H), 7.82 (s, 1 H), 7.98 (d, 1 H).

Example 63

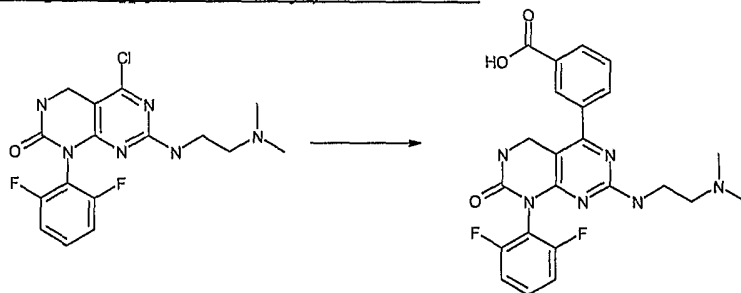
5-chloro-1-(2,6-difluorophenyl)-7-{[2-(dimethylamino)ethyl]amino}-3,4-dihydropyrimido[4,5-*d*]pyrimidin-2(1*H*)-one



- 5 To a solution of 5-chloro-1-(2,6-difluorophenyl)-7-(methylsulfinyl)-3,4-dihydropyrimido[4,5-*d*]pyrimidin-2(1*H*)-one (800 mg, 2.23 mmol) in DCM (45 mL) were added *N,N*-dimethylethylenediamine (0.36 mL, 3.23 mmol) and triethylamine (0.63 mL, 4.5 mmol). The resultant solution was stirred at room temperature over night. The result mixture was concentrated. CombiFlash chromatography (mobile
10 phase DCM/DCM[90]+MeOH[7]+NH₄OH[3]) provided the title compound as a white solid (730 mg, 85 %). LC-MS *m/z* 383 (*M* + *H*)⁺.

Example 64

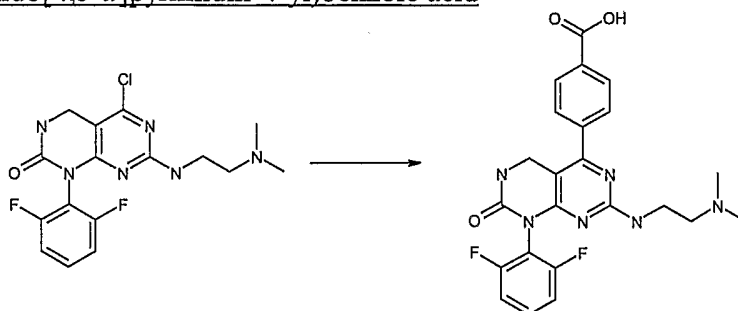
- 15 3-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)benzoic acid



- To a solution of 5-chloro-1-(2,6-difluorophenyl)-7-{[2-(dimethylamino)-ethyl]amino}-3,4-dihydropyrimido[4,5-*d*]pyrimidin-2(1*H*)-one (100 mg, 0.26 mmol) in dioxane (9 mL)/water (3 mL) were added potassium carbonate (217 mg, 1.57 mmol), tetrakis(triphenylphosphine)palladium(0) (15 mg, 0.013 mmol) and 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid (65 mg, 0.39 mmol). The reaction mixture was bubbled with N₂ for 5 mins, then microwaved at about 150°C for about 30 mins. The reaction mixture was concentrated. To the concentrated mixture were added DMSO (2 mL), H₂O (0.5 mL) and AcOH (0.05 mL). Separation
25 via a HPLC then provided the title compound as a white solid (120 mg, 98%). LC-MS *m/z* 469 (*M* + *H*)⁺.

Example 65

4-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)benzoic acid

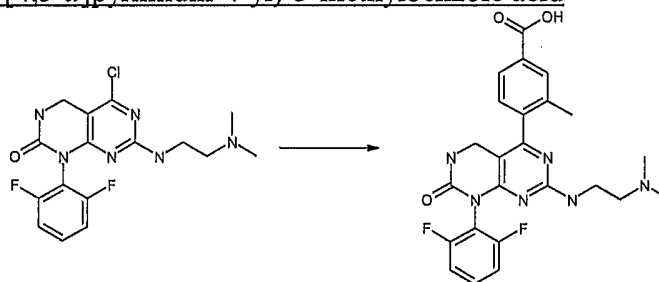


- 5 To a solution of 5-chloro-1-(2,6-difluorophenyl)-7-{[2-(dimethylamino)-ethyl]-amino}-3,4-dihydropyrimido[4,5-*d*]pyrimidin-2(1*H*)-one (150 mg, 0.39 mmol) in dioxane (12 mL)/water (4 mL) were added potassium carbonate (325 mg, 2.36 mmol), tetrakis(triphenylphosphine)palladium(0) (23 mg, 0.019 mmol) and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid (146 mg, 0.59 mmol).
- 10 The reaction mixture was bubbled with N₂ for about 5 mins, then microwaved at about 150°C for about 30 mins. The reaction mixture was concentrated. To the concentrated mixture were added DMSO (2 mL), H₂O (0.5 mL) and AcOH (0.05 mL). Separation via a HPLC then provided the title compound as a white solid (142 mg, 77%). LC-MS *m/z* 469 (M + H)⁺.

15

Example 66

4-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-3-methylbenzoic acid

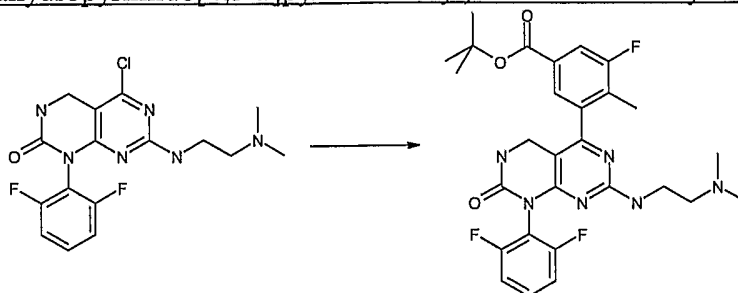


- 20 To a solution of 5-chloro-1-(2,6-difluorophenyl)-7-{[2-(dimethylamino)ethyl]-amino}-3,4-dihydropyrimido[4,5-*d*]pyrimidin-2(1*H*)-one (200 mg, 0.52 mmol) in dioxane (15 mL)/water (5 mL) were added potassium carbonate (433 mg, 3.14 mmol), tetrakis(triphenylphosphine)palladium(0) (31 mg, 0.027 mmol) and 3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid (205 mg, 0.78 mmol). The reaction mixture was bubbled with N₂ for about 10
- 25 mins, then microwaved at 150°C for about 30 mins. The reaction mixture was concentrated. To the concentrated mixture were added DMSO (2 mL), H₂O (0.5

mL) and AcOH (0.05 mL). Gilson with TFA provided the title compound as a white solid (310 mg, 99%). LC-MS m/z 483 ($M + H$)⁺.

Example 67

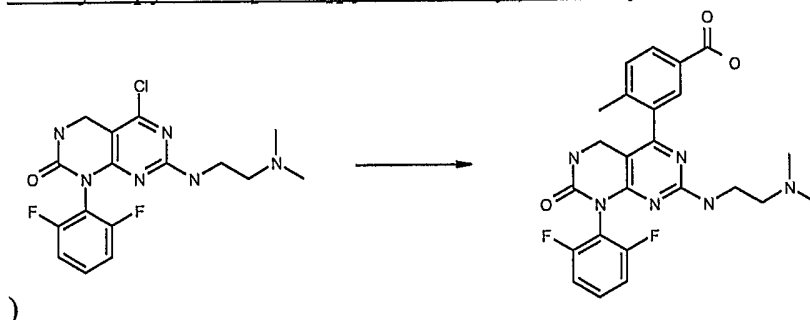
- 5 1,1-dimethylethyl 3-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-5-fluoro-4-methylbenzoate



- To a solution of 5-chloro-1-(2,6-difluorophenyl)-7-{[2-(dimethylamino)ethyl]amino}-3,4-dihydropyrimido[4,5-*d*]pyrimidin-2(1*H*)-one (200 mg, 0.52 mmol) in dioxane (15 mL)/water (5 mL) were added potassium carbonate (433 mg, 3.14 mmol), tetrakis(triphenylphosphine)palladium(0) (31 mg, 0.027 mmol) and (5-{[(1,1-dimethylethyl)oxy]carbonyl}-3-fluoro-2-methylphenyl)boronic acid (159 mg, 0.63 mmol). The reaction mixture was bubbled with N₂ for 10 mins, then microwaved at 150°C for 30 mins. The reaction mixture was concentrated. To the concentrated mixture were added DMSO (2 mL), H₂O (0.5 mL) and AcOH (0.05 mL). Separation via a HPLC then provided the title compound as a white solid (270 mg, 88%). LC-MS m/z 587 ($M + H$)⁺.

Example 68

- 20 3-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-4-methylbenzoic acid



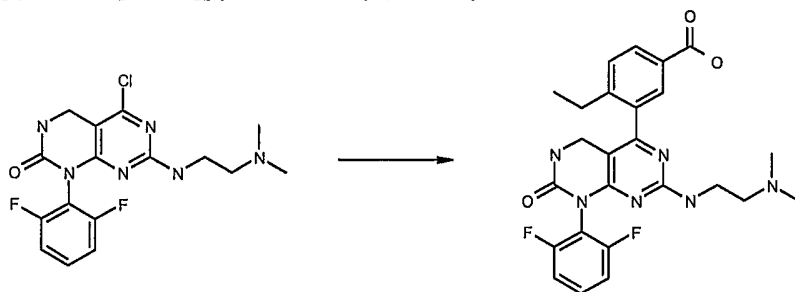
- To the solution of 5-chloro-1-(2,6-difluorophenyl)-7-{[2-(dimethylamino)ethyl]amino}-3,4-dihydropyrimido[4,5-*d*]pyrimidin-2(1*H*)-one (191 mg, 0.50 mmol) in dioxane (15 mL) and water (5 mL) were added 4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid (197 mg, 0.75 mmol),

K₂CO₃ (415 mg, 3.0 mmol) and tetrakis(triphenyl-phosphine)palladium(0) (23 mg, 0.025 mmol). The reaction mixture was heated to 150 °C for about 15 minutes with microwave. The reaction mixture was concentrated to dry then was added DMSO (2 mL), water (0.5 mL) and HOAc (1 drop). The solution was filtered and applied to the reverse phase HPLC to afford the titled compound 0.24 g (quantitative). LC-MS *m/z* 483 (M + H)⁺; ¹H-NMR (CD₃OD) 2.36 (s, 3 H), 2.76 (s, 6H), 3.16 (s, 2 H), 3.56 (s, 2 H), 4.13 (s, 2 H), 7.21 (m, 1 H), 7.53 (m, 2 H), 7.95 (s, 1 H), 8.09 (d, *J* = 7.6 Hz, 1 H).

10

Example 69

3-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-4-ethylbenzoic acid

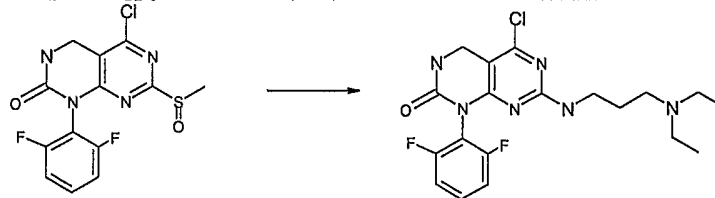


The title compound was prepared by following the procedure in Example 68 except 3-(dihydroxyboranyl)-4-ethylbenzoic acid was used in the coupling reaction (yield: 38%). LC-MS *m/z* 497 (M + H)⁺; ¹H-NMR (CD₃OD) 1.22 (t, *J* = 7.6 Hz, 3 H), 2.68 (s, 2 H), 2.77 (s, 6 H), 3.16 (m, 2 H), 3.53 (m, 2 H), 4.13 (m, 2 H), 7.18 (m, 2 H), 7.55 (m, 2 H), 7.86 (s, 1 H), 8.10 (m 1 H).

20

Example 70

5-chloro-7-{[3-(diethylamino)propyl]amino}-1-(2,6-difluorophenyl)-3,4-dihydropyrimido[4,5-*d*]pyrimidin-2(1H)-one trifluoroacetate

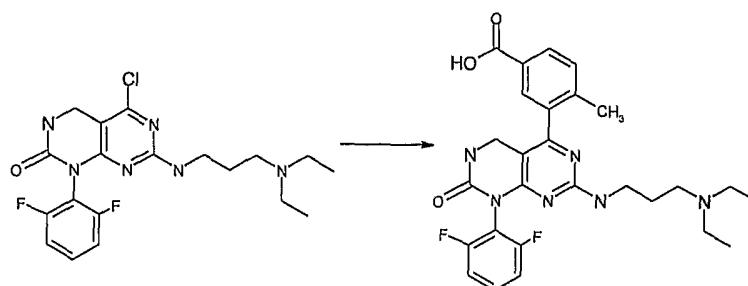


To 5-chloro-1-(2,6-difluorophenyl)-7-(methylsulfinyl)-3,4-dihydropyrimido[4,5-*d*]pyrimidin-2(1H)-one (275 mg, 0.767 mmol) in dichloromethane (15 mL) was added *N,N*-diethyl-1,3-propyldiamine (0.181 mL, 1.15 mmol) and triethylamine (0.215 mL, 1.53 mmol). The mixture was stirred over

night. The mixture was concentrated and separated by Gilson HPLC (with 0.1% TFA) to afford the title compound (207 mg, 64%).

Example 71

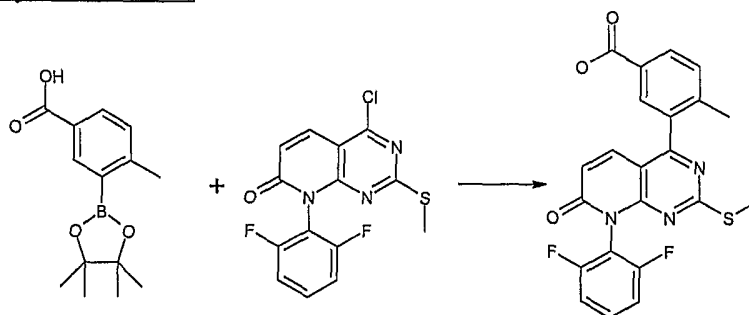
5 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methylbenzoic acid



To 5-chloro-7-{[3-(diethylamino)propyl]amino}-1-(2,6-difluorophenyl)-3,4-dihydropyrimido[4,5-*d*]pyrimidin-2(1*H*)-one (207 mg, 0.488 mmol) in 1,4-dioxane (7.5 mL) and water (2.5 mL) was added 4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid (0.192 g, 0.733 mmol), tetrakis(triphenylphosphine)-palladium(0) (28.3 mg, 0.024 mmol), and potassium carbonate (270 mg, 1.95 mmol). The mixture was heated with microwave for about 15 min at 150°C, and then allowed to cool to room temperature. The mixture was concentrated and separated by HPLC to afford the title compound (66 mg, 26%). LC-MS *m/z* 525 (M+H)⁺.

Example 72

20 3-[8-(2,6-difluorophenyl)-2-(methylthio)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-4-yl]-4-methylbenzoic acid

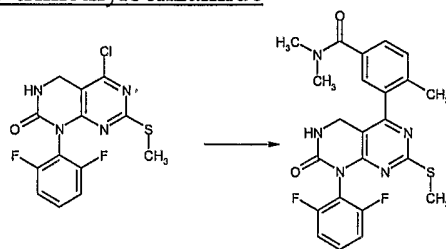


The solution of 4-chloro-8-(2,6-difluorophenyl)-2-(methylthio)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (1.70 g, 5.00 mmol) in DME (150 mL) and H₂O (50 mL), in a pressure flask (500 mL, Chemglass), was added 4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) benzoic acid (1.97 g, 7.50 mmol) and K₂CO₃ (4.15

g, 30.0 mmol). The resulting mixture was degassed with Argon for 5 minutes, mixed with $\text{Pd}(\text{PPh}_3)_4$ (0.232 g, 0.20 mmol) and heated with a preheated oil bath (160°C) under vigorous stirring for 30 minutes. The reaction mixture was filtered through celite, concentrated under vacuum to remove DME. It was then mixed with EtOAc (200 mL) and AcOH (2.5 mL), and shaken. The layers were separated. The organic layer was collected, further washed with brine (70 mL), dried over Na_2SO_4 , filtered, concentrated and purified via a flash chromatography (load column with DCM, mobile phase EtOAc/Hexane) to afford the title compound as a white solid 2.15g (98 %). LC-MS (ES) m/z 440 ($\text{M} + \text{H}^+$); ^1H -NMR (CD_3OD) δ 2.27 (s, 3 H), 2.31 (s, 3 H), 6.71 (d, $J = 9.6 \text{ Hz}$, 1 H), 7.28 (t, $J = 8.2 \text{ Hz}$, 2 H), 7.57 (d, $J = 8.4 \text{ Hz}$, 1 H), 7.64 (m, 2 H), 8.00 (d, $J = 1.6 \text{ Hz}$, 1 H), 8.14 (dd, $J_1 = 7.6 \text{ Hz}$, $J_2 = 1.6 \text{ Hz}$, 1 H).

Example 73

3-[8-(2,6-difluorophenyl)-2-(methylthio)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-d]pyrimidin-4-yl]-N,N,4-trimethylbenzamide



4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid (1 g, 3.8 mmol) was taken up in CH_2Cl_2 (200 mL) and was treated with oxalyl chloride (0.44 mL, 5 mmol) and DMF (1 drop). One hour after gas evolution had ceased, the solvents were pumped off *in vacuo*, and the residue stripped from toluene. This was again taken up in CH_2Cl_2 (200 mL), and excess dimethyl amine was bubbled into the mixture, which was then sealed off and stirred overnight at room temperature. The solvents were pumped off to give the crude *N,N*,4-trimethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide, which was used without further purification in the next step.

5-chloro-1-(2,6-difluorophenyl)-7-(methylthio)-3,4-dihydropyrimido[4,5-d]pyrimidin-2(1H)-one (0.102 g, 0.298 mmol), *N,N*,4-trimethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide from above, (0.129 g, 0.447 mmol), and K_2CO_3 (0.123 g, 0.894 mmol), were taken up in dioxane (6 mL) and water (1.2 mL). The mixture was degassed with argon for 30 min and tetrakis(triphenylphosphine)palladium(0) (0.026 g, 0.022 mmol) was added. The mixture was then heated under argon at 95°C for 18 h. The solvents were pumped off, and after aqueous workup, the crude material was flashed on silica gel (15 g), eluted with a

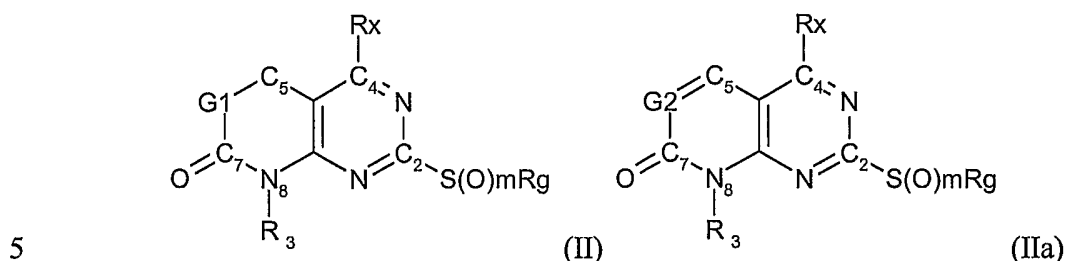
EtOAc / CH₂Cl₂ gradient to give the title compound as a white amorphous solid. mp 144-147°C. LC-MS m/z 470 (M+H)⁺, 2.02 min (ret time).

5 All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

10 The above description fully discloses the invention including preferred embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are within the scope of the following Claims. Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. Therefore, the Examples herein are to be construed as merely illustrative and not a limitation of the
15 scope of the present invention in any way. The embodiments of the invention in which an exclusive property or privilege is Claimed are defined as follows.

What is Claimed Is:

1. A compound of the formula:



wherein

G1 is CH₂ or NH;

G2 is CH or nitrogen;

- 10 Rx is chloro, bromo, iodo, or O-S(O)₂CF₃;

R_g is a C₁₋₁₀ alkyl;

m is 0, or an integer having a value of 1, or 2;

R₃ is a C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl C₁₋₁₀ alkyl, aryl, arylC₁₋₁₀ alkyl, heteroaryl, heteroarylC₁₋₁₀ alkyl, heterocyclic or a heterocyclylC₁₋₁₀ alkyl

- 15 moiety, and wherein each of these moieties may be optionally substituted.

2. The compound according to Claim 1 which is Formula (II).

3. The compound according to Claim 1 which is Formula (IIa).

20

4. The compound according to Claims 1 wherein R_g is methyl.

5. The compound according to Claim 4 wherein m is 0.

- 25 6. The compound according to Claim 4 wherein m is 1.

7. The compound according to Claim 1 wherein Rx is chloro.

8. The compound according to Claim 1 wherein R₃ is an optionally substituted aryl.

30

9. The compound according to Claim 8 wherein R₃ is optionally substituted independently, one or more times, independently at each occurrence by halogen,

C₁₋₁₀ alkyl, hydroxy, C₁₋₁₀ alkoxy, cyano, nitro, amino, or halosubstituted C₁₋₁₀ alkyl.

10. The compound according to Claim 9 wherein R₃ is a phenyl substituted one or more times independently by fluorine, chlorine, or methyl.

11. The compound according to Claim 8 wherein R₃ is phenyl, 4-trifluoromethyl-phenyl, 2-fluorophenyl, 2,6-difluoro-phenyl, 2,4-difluoro-phenyl, 2-chlorophenyl, 2-methylphenyl, or 2, 6-dimethylphenyl.

10

12. The compound according to Claim 1 which is:

4-Chloro-8-(4-trifluoromethyl-phenyl)-2-methylsulfanyl-8H-pyrido[2,3-d]pyrimidin-7-one;

15 4-Chloro-8-(4-trifluoromethyl -phenyl)-2-methylsulfinyl-8H-pyrido[2,3-d]pyrimidin-7-one;

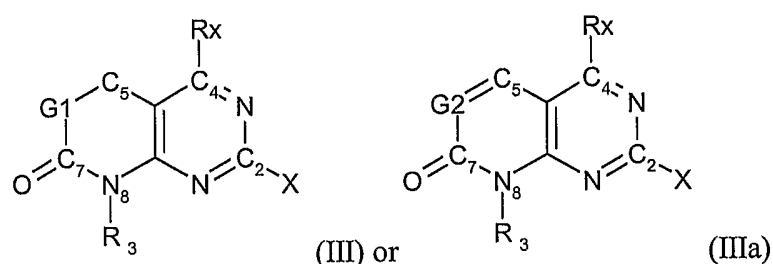
4-Chloro-8-(2,4-difluoro-phenyl)-2-methylsulfanyl-8H-pyrido[2,3-d]pyrimidin-7-one;

4-Chloro-8-(2,4-difluoro-phenyl)-2-methylsulfinyl-8H-pyrido[2,3-d]pyrimidin-7-one;

4-Chloro-8-(2,6-difluoro-phenyl)-2-methylsulfanyl-8H-pyrido[2,3-d]pyrimidin-7-one; and

20 4-Chloro-8-(2,6-difluoro-phenyl)-2-methylsulfinyl-8H-pyrido[2,3-d]pyrimidin-7-one.

13. A compound of the formula:



25

wherein

G1 is CH₂ or NH;

G2 is CH or nitrogen;

Rx is chloro, bromo, iodo, or O-S(O)₂CF₃;

30 X is R₂, OR₂', S(O)_mR₂', (CH₂)_nN(R₁₁)S(O)_mR₂', (CH₂)_nN(R₁₁)C(O)R₂', (CH₂)_nNR₄R₁₄, or (CH₂)_nN(R₂') (R₂''), or N(R₁₀')-R_h-NH-C(=N-CN)NR_qR_q';
X₁ is N(R₁₁), O, S(O)_m, or CR₁₀R₂₀;

- R_h is selected from an optionally substituted C_{1-10} alkyl, $-CH_2-C(O)-CH_2-$, $-CH_2CH_2-O-CH_2-CH_2-$, $-CH_2-C(O)N(R_{10'})CH_2-CH_2-$, $-CH_2-N(R_{10'})C(O)CH_2-$, $-CH_2-CH(OR_{10'})-CH_2-$, $-CH_2-C(O)O-CH_2-CH_2-$, or $-CH_2-CH_2-O-C(O)CH_2-$;
- 5 R_q and $R_{q'}$ are independently selected at each occurrence from hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl C_{1-10} alkyl, C_{5-7} cycloalkenyl, C_{5-7} cycloalkenyl- C_{1-10} alkyl, aryl, aryl C_{1-10} alkyl, heteroaryl, heteroaryl C_{1-10} alkyl, heterocyclic, or a heterocyclyl C_{1-10} alkyl moiety, wherein all of the moieties, excluding hydrogen, are optionally substituted, or R_q and $R_{q'}$ together with the
- 10 nitrogen to which they are attached form a 5 to 7 membered optionally substituted ring, which ring may contain an additional heteroatom selected from oxygen, nitrogen or sulfur;
- R_2 is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylalkyl, aryl, aryl C_{1-10} alkyl, heteroaryl, heteroaryl C_{1-10} alkyl, heterocyclic, or a heterocyclyl C_{1-10} alkyl
- 15 moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or R_2 is the moiety $(CR_{10}R_{20})_qX_1(CR_{10}R_{20})_qC(A_1)(A_2)(A_3)$, or $C(A_1)(A_2)(A_3)$;
- R_2' is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylalkyl, aryl, aryl C_{1-10} alkyl, heteroaryl, heteroaryl C_{1-10} alkyl, heterocyclic, or a heterocyclyl C_{1-10} alkyl
- 20 moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;
- R_2'' is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylalkyl, aryl, aryl C_{1-10} alkyl, heteroaryl, heteroaryl C_{1-10} alkyl, heterocyclic, or a heterocyclyl C_{1-10} alkyl
- 25 moiety, and wherein these moieties, excluding hydrogen, may be optionally substituted; or wherein R_2'' is the moiety $(CR_{10}R_{20})_tX_1(CR_{10}R_{20})_qC(A_1)(A_2)(A_3)$;
- A_1 is an optionally substituted C_{1-10} alkyl, heterocyclic, heterocyclic C_{1-10} alkyl, heteroaryl, heteroaryl C_{1-10} alkyl, aryl, or aryl C_{1-10} alkyl;
- A_2 is an optionally substituted C_{1-10} alkyl, heterocyclic, heterocyclic C_{1-10} alkyl,
- 30 heteroaryl, heteroaryl C_{1-10} alkyl, aryl, or aryl C_{1-10} alkyl;
- A_3 is hydrogen or is an optionally substituted C_{1-10} alkyl;
- R_3 is a C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl C_{1-10} alkyl, aryl, aryl C_{1-10} alkyl, heteroaryl, heteroaryl C_{1-10} alkyl, heterocyclic or a heterocyclyl C_{1-10} alkyl
- moiety, and wherein each of these moieties may be optionally substituted;
- 35 R_4 and R_{14} are each independently selected from hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl C_{1-4} alkyl, aryl, aryl- C_{1-4} alkyl, heterocyclic, heterocyclic C_{1-4} alkyl, heteroaryl or a heteroaryl C_{1-4} alkyl moiety, and wherein

- each of these moieties, excluding hydrogen, may be optionally substituted; or the R₄ and R₁₄ together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 4 to 7 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or nitrogen;
- 5 R₁₀ and R₂₀ are independently selected from hydrogen or C₁₋₄alkyl;
R₁₀' is independently selected at each occurrence from hydrogen or C₁₋₄alkyl;
R₁₁ is independently selected from hydrogen or C₁₋₄alkyl;
n' is independently selected at each occurrence from 0 or an integer having a value of 1 to 10;
- 10 m is independently selected at each occurrence from 0 or an integer having a value of 1 or 2;
q is 0 or an integer having a value of 1 to 10;
q' is 0, or an integer having a value of 1 to 6; or
t is an integer having a value of 2 to 6.
- 15
14. The compound according to Claim 13 which is Formula (III).
15. The compound according to Claim 13 which is Formula (IIIa).
- 20 16. The compound according to Claim 13 wherein R_x is chloro.
17. The compound according to Claim 13 wherein R₃ is an optionally substituted aryl.
- 25 18. The compound according to Claim 17 wherein R₃ is optionally substituted independently, one or more times, independently at each occurrence by halogen, C₁₋₁₀ alkyl, hydroxy, C₁₋₁₀ alkoxy, cyano, nitro, amino, or halosubstituted C₁₋₁₀ alkyl.
- 30 19. The compound according to Claim 18 wherein R₃ is phenyl substituted one or more times independently by fluorine, chlorine or methyl.
20. The compound according to Claim 18 wherein R₃ is phenyl, 4-trifluoromethyl-phenyl, 2-fluorophenyl, 2,6-difluoro-phenyl, 2,4-difluoro-phenyl, 2-chlorophenyl, 2-methylphenyl, or 2, 6-dimethylphenyl.
- 35

21. The compound according to Claim 13 wherein X is R₂, and R₂ is (CR₁₀R₂₀)_qX₁(CR₁₀R₂₀)_qC(A₁)(A₂)(A₃), or C(A₁)(A₂)(A₃).
22. The compound according to Claim 21 wherein at least one of A₁, A₂ or A₃ is a C₁₋₁₀ alkyl substituted by (CR₁₀R₂₀)_nOR₆; and wherein
 5 n is 0, or an integer having a value of 1 to 10;
 m is 0 or an integer having a value of 1 or 2;
 R₆ is independently selected from hydrogen, C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, heterocyclyl, heterocyclyl C₁₋₁₀alkyl, aryl, arylC₁₋₁₀ alkyl, heteroaryl or a
 10 heteroarylC₁₋₁₀ alkyl moiety, and wherein these moieties, excluding hydrogen may be optionally substituted independently at each occurrence, one or more times, by halogen; hydroxy; hydroxy substituted C₁₋₁₀alkyl; C₁₋₁₀ alkoxy; halosubstituted C₁₋₁₀ alkoxy; S(O)_m alkyl; C(O); NR₄R₁₄'; C₁₋₁₀ alkyl; C₃₋₇cycloalkyl; C₃₋₇cycloalkyl C₁₋₁₀ alkyl; halosubstituted C₁₋₁₀ alkyl; an
 15 unsubstituted aryl or arylalkyl, or an aryl or arylalkyl substituted one or two times by halogen, hydroxy, hydroxy substituted alkyl, C₁₋₁₀ alkoxy, S(O)_malkyl, amino, mono & di-substituted C₁₋₄ alkyl amino, C₁₋₄ alkyl, or CF₃;
 R₄' and R₁₄' are each independently selected at each occurrence from hydrogen or C₁₋₄ alkyl, or R₄' and R₁₄' can cyclize together with the nitrogen to which they
 20 are attached to form an optionally substituted 5 to 7 membered ring which optionally contains an additional heteroatom selected from oxygen, sulfur or NR₉'; and
 R₉' is independently selected at each occurrence from hydrogen, or C₁₋₄ alkyl.
23. The compound according to Claim 21 wherein X₁ N(R₁₀'), q is 1 or 2, q' is 0, and R₆ is hydrogen.
24. The compound according to Claim 13 wherein X is (CH₂)_nNR₄R₁₄, or (CH₂)_nN(R₂') (R₂'').
25. The compound according to Claim 24 wherein X is (CH₂)_nNR₄R₁₄, and R₄ and R₁₄ are independently selected from hydrogen, optionally substituted C₁₋₁₀ alkyl, optionally substituted aryl, optionally substituted aryl-C₁₋₄ alkyl, optionally substituted heterocyclic, optionally substituted heterocyclic C₁₋₄ alkyl, optionally substituted heteroaryl or optionally substituted heteroaryl C₁₋₄ alkyl.

26. The compound according to Claim 25 wherein the C₁₋₁₀ alkyl may be substituted one or more times, independently at each occurrence with NR_{4'}R_{14'}; halogen, hydroxy, alkoxy, C(O)NR_{4'}R_{14'}; or NR_{4'}C(O)C₁₋₁₀alkyl; and wherein R_{4'} and R_{14'} are independently selected at each occurrence from hydrogen or C₁₋₄ alkyl, or R_{4'} and R_{14'} together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members, which ring optionally contains an additional heteroatom selected from NR_{9'}; and R_{9'} is independently selected at each occurrence from hydrogen, or C₁₋₄ alkyl.
27. The compound according to Claim 24 wherein X is (CH₂)_nN(R_{2'})(R_{2''}), and R_{2'} is an optionally substituted C₁₋₁₀ alkyl, cycloalkyl, heterocyclic, heterocyclyl C₁₋₁₀ alkyl, heteroarylalkyl.
28. The compound according to Claim 27 wherein the R_{2'} moieties, excluding hydrogen, are optionally substituted 1 to 4 times, independently, at each occurrence, by C₁₋₁₀ alkyl, halo-substituted C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₇ cycloalkyl, C₃₋₇cycloalkylC₁₋₁₀alkyl, C₅₋₇cycloalkenyl, C₅₋₇ cycloalkenylC₁₋₁₀ alkyl, halogen, -C(O), cyano, nitro, aryl, aryl C₁₋₁₀ alkyl, aryl, aryl C₁₋₁₀ alkyl, heterocyclic, heterocyclic C₁₋₁₀ alkyl, heteroaryl, heteroaryl C₁₋₁₀ alkyl, (CR₁₀R₂₀)_nOR₆, (CR₁₀R₂₀)_nSH, (CR₁₀R₂₀)_nS(O)_mR₇, (CR₁₀R₂₀)_nN(R_{10'})S(O)₂R₇, (CR₁₀R₂₀)_nNR_eR_{e'}, (CR₁₀R₂₀)_nNR_eR_{e'}C₁₋₄alkylNR_eR_{e'}, (CR₁₀R₂₀)_nCN, (CR₁₀R₂₀)_nS(O)₂NR_eR_{e'}, (CR₁₀R₂₀)_nC(Z)R₆, (CR₁₀R₂₀)_nOC(Z)R₆, (CR₁₀R₂₀)_nC(Z)OR₆, (CR₁₀R₂₀)_nC(Z)NR_eR_{e'}, (CR₁₀R₂₀)_nN(R_{10'})C(Z)R₆, (CR₁₀R₂₀)_nN(R_{10'})C(=N(R_{10'}))NR_eR_{e'}, (CR₁₀R₂₀)_nC(=NOR₆) NR_eR_{e'}, (CR₁₀R₂₀)_nOC(Z) NR_eR_{e'}, (CR₁₀R₂₀)_nN(R_{10'})C(Z) NR_eR_{e'}, or (CR₁₀R₂₀)_nN(R_{10'})C(Z)OR₇; and wherein R₆ is independently selected at each occurrence from hydrogen, C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, heterocyclyl, heterocyclyl C₁₋₁₀alkyl, aryl, arylC₁₋₁₀ alkyl, heteroaryl or heteroarylC₁₋₁₀ alkyl, wherein each of these moieties, excluding hydrogen are optionally substituted; R₇ is independently selected at each occurrence from C₁₋₆alkyl, aryl, arylC₁₋₆alkyl, heterocyclic, heterocyclylC₁₋₆ alkyl, heteroaryl, or heteroarylC₁₋₆alkyl moiety, and wherein each of these moieties may be optionally substituted; R_e and R_{e'} are each independently selected at each occurrence from hydrogen, C₁₋₄ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkylC₁₋₄alkyl, aryl, aryl-C₁₋₄ alkyl, heterocyclic, heterocyclic C₁₋₄ alkyl, heteroaryl or a heteroaryl C₁₋₄ alkyl moiety; or R_e and R_{e'}

together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 4 to 7 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or nitrogen; and

wherein each of these moieties, excluding hydrogen, may be substituted 1 to 4 times, independently at each occurrence by halogen; hydroxy; hydroxy substituted C₁₋₁₀alkyl; C₁₋₁₀ alkoxy; halosubstituted C₁₋₁₀ alkoxy; amino, mono & di-substituted C₁₋₄ alkyl amino, S(O)_mR_f; C(O)R_j; C(O)OR_j; (CR₁₀R₂₀)_nN(R_{10'})C(Z)OR₇; (CR₁₀R₂₀)_nN(R_{10'})C(Z)NR_dR_{d'}; C(O)NR_{4'}R_{14'}; NR_{4'}C(O)C₁₋₁₀alkyl; NR_{4'}C(O)aryl; cyano; nitro; C₁₋₁₀ alkyl; C₃₋₇cycloalkyl; C₃₋₇cycloalkyl C₁₋₁₀ alkyl; halosubstituted C₁₋₁₀ alkyl; aryl, aryl C₁₋₄ alkyl, heterocyclic, heterocyclicC₁₋₄ alkyl, heteroaryl, or heteroC₁₋₄alkyl, and wherein these aryl, heterocyclic, and heteroaryl containing moieties may be optionally substituted one to two times independently at each occurrence by halogen, C₁₋₄ alkyl, hydroxy, hydroxy substituted C₁₋₄ alkyl, C₁₋₁₀ alkoxy, S(O)_malkyl, amino, mono & di-substituted C₁₋₄ alkyl amino, C₁₋₄ alkyl, or CF₃;

R_f is independently selected at each occurrence from C₁₋₁₀alkyl, aryl, aryl C₁₋₁₀alkyl, heteroaryl, heteroaryl C₁₋₁₀alkyl, heterocyclic, or a heterocyclic C₁₋₁₀alkyl moiety, and wherein these moieties may all be optionally substituted;

R_{4'} and R_{14'} are each independently selected at each occurrence from hydrogen or C₁₋₄ alkyl, or R_{4'} and R_{14'} can cyclize together with the nitrogen to which they are attached to form a 5 to 7 membered ring which optionally contains an additional heteroatom selected from oxygen, sulfur or NR_{9'};

R_j is independently selected at each occurrence from hydrogen, C₁₋₄alkyl, aryl, aryl C₁₋₄alkyl, heteroaryl, heteroaryl C₁₋₄alkyl, heterocyclic, or a heterocyclic C₁₋₄alkyl moiety, and wherein these moieties, excluding hydrogen, may be optionally substituted; and

n is independently selected at each occurrence from 0 or an integer having a value of 1 to 10.

30

29. The compound according to Claim 27 wherein R_{2'} is a heterocyclic or a heterocyclic alkyl substituted one or more times, independently by C₁₋₁₀ alkyl, aryl, arylalkyl, (CR₁₀R₂₀)_nNR_eR_{e'}, or (CR₁₀R₂₀)_nN(R_{10'})C(Z)OR₇.

35

30. The compound according to Claim 13 wherein the (CH₂)_nN(R_{2'})(R_{2''}) moiety is 1-(phenylmethyl)-4-piperidinamine, 2-[4-(phenylmethyl)-1-piperazinyl]ethylamine, 2-(1-piperidinyl)ethylamine, 2-(1-methyl-2-pyrrolidinyl)ethylamine, 1-[(phenylmethyl)-3-

pyrrolidinyl]amine, 3-[(1-pyrrolidinyl)propyl]amine, 3-[(hexahydro-1H-azepin-1-yl)propyl]amine, (1-methyl-4-piperidinyl)amine, 3-[(4-morpholinyl)propyl]amine, 3-[(2-oxo-1-pyrrolidinyl)propyl]amine, 2-[(4-morpholinyl)ethyl]amine, 2-[(1-pyrrolidinyl)ethyl]amine, or [(1-ethyl-2-pyrrolidinyl)methyl]amine.

5

31. The compound according to Claim 13 wherein R_2' is a C_{1-10} alkyl substituted by $(CR_{10}R_{20})_nNR_eR_{e'}$ or $(CR_{10}R_{20})_nNR_eR_{e'}C_{1-4}alkylNR_eR_{e'}$.

32. The compound according to Claim 31 wherein R_e and $R_{e'}$ are independently
10 selected from methyl, ethyl, isopropyl, n-butyl, or t-butyl.

33. The compound according to Claim 13 wherein $(CH_2)_nN(R_2')(R_2'')$ is
3-(dimethylamino)propyl(methyl)amine, 3-(diethylamino)propylamine, propylamine,
(2,2-dimethylpropyl)amine, (2-hydroxypropyl)amino, 2-(dimethylamino)ethylamine,
15 2-(dimethylamino)ethyl(methyl)amine, 3-(dimethylamino)propylamine,
2-(dimethylamino)ethyl(methyl)amine, 3-(diethylamino)propylamine,
2-(methylamino)ethylamine, [(1-methylethyl)amino]ethylamine,
3-(diethylamino)propylamine, 3-(dibutylamino)propylamine,
3-[(1-methylethyl)amino]propylamine, 3-(1,1-dimethylethyl)aminopropylamine,
20 3-(dimethylamino)-2,2-dimethylpropylamine, 4-(diethylamino)-1-methylbutylamine,
or 3-[[3-(dimethylamino)propyl]-(methyl)amino]propyl(methyl)amine.

34. The compound according to Claim 13 wherein R_3 is an aryl optionally
substituted one or more times independently at each occurrence with halogen, nitro,
25 C_{1-10} alkyl, halo-substituted C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl,
 C_{3-7} cycloalkyl, C_{3-7} cycloalkyl C_{1-10} alkyl, C_{5-7} cycloalkenyl,
 C_{5-7} cycloalkenyl C_{1-10} alkyl, $(CR_{10}R_{20})_nOR_6$, $(CR_{10}R_{20})_nSH$,
 $(CR_{10}R_{20})_nS(O)_mR_7$, $(CR_{10}R_{20})_nN(R_{10'})S(O)_2R_7$, $(CR_{10}R_{20})_nNR_{16}R_{26}$,
 $(CR_{10}R_{20})_nCN$, $(CR_{10}R_{20})_nS(O)_2NR_{16}R_{26}$, $(CR_{10}R_{20})_nC(Z)R_6$,
30 $(CR_{10}R_{20})_nOC(Z)R_6$, $(CR_{10}R_{20})_nC(Z)OR_6$, $(CR_{10}R_{20})_nC(Z)NR_{16}R_{26}$,
 $(CR_{10}R_{20})_nN(R_{10'})C(Z)R_6$, $(CR_{10}R_{20})_nN(R_{10'})C(=N(R_{10'}))NR_{16}R_{26}$,
 $(CR_{10}R_{20})_nOC(Z)NR_{16}R_{26}$, $(CR_{10}R_{20})_nN(R_{10'})C(Z)NR_{16}R_{26}$, or
 $(CR_{10}R_{20})_nN(R_{10'})C(Z)OR_7$; and wherein
 R_6 is independently selected from hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl,
35 heterocyclyl, heterocyclyl C_{1-10} alkyl, aryl, aryl C_{1-10} alkyl, heteroaryl or a
heteroaryl C_{1-10} alkyl moiety, and wherein these moieties, excluding hydrogen
may be optionally substituted;

- R₇ is C₁₋₆alkyl, aryl, arylC₁₋₆alkyl, heterocyclic, heterocyclylC₁₋₆ alkyl, heteroaryl, or heteroarylC₁₋₆alkyl; and wherein each of these moieties may be optionally substituted;
- R_{10'} is independently selected at each occurrence from hydrogen or C₁₋₄ alkyl;
- 5 R₁₀ and R₂₀ are independently selected at each occurrence from hydrogen or C₁₋₄ alkyl;
- R₁₆ and R₂₆ are each independently selected from hydrogen, or C₁₋₄ alkyl; or the R₁₆ and R₂₆ together with the nitrogen which they are attached form an unsubstituted or substituted heterocyclic ring of 4 to 7 members, which ring
- 10 optionally contains an additional heteroatom selected from oxygen, sulfur or NR_{9'};
- R_{9'} is independently selected at each occurrence from hydrogen, or C₁₋₄ alkyl;
- n is independently selected at each occurrence from 0 or an integer having a value of 1 to 10;
- 15 m is independently selected from 0 or an integer having a value of 1 or 2;
- Z is independently at each occurrence selected from oxygen or sulfur.

35. The compound according to Claim 33 wherein R₃ is an optionally substituted phenyl.

20

36. The compound according to Claim 35 wherein the optional substituents on the phenyl ring are independently selected at each occurrence from halogen, C₁₋₁₀alkyl, (CR₁₀R₂₀)_nOR₆, cyano, nitro, (CR₁₀R₂₀)_nNR₁₆R₂₆, or halosubstituted C₁₋₁₀alkyl.

25

37. The compound according Claim 24 wherein the phenyl is substituted one or more times by halogen, hydroxy, alkoxy, amino or CF₃.

38. The compound according to Claim 36 wherein R₃ is phenyl, 4-trifluoromethyl-phenyl, 2-fluorophenyl, 2,6-difluoro-phenyl, 2,4-difluoro-phenyl, 2-chlorophenyl, 2-methylphenyl, or 2, 6-dimethylphenyl.

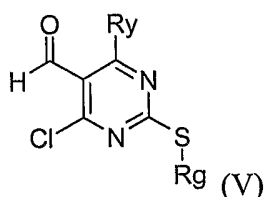
39. The compound according to Claim 13 which is:
2-(Hydroxy-hydroxymethyl-ethylamino)-4-Chloro-8-(4-trifluoromethyl -phenyl)-
35 8H-pyrido[2,3-d]pyrimidin-7-one;
2-(Hydroxy-hydroxymethyl-ethylamino)-4-Chloro-8-(2,4-difluoro-phenyl)-8H-pyrido[2,3-d]pyrimidin-7-one; and

2-(Hydroxy-hydroxymethyl-ethylamino)-4-Chloro-8-(2,6-difluoro-phenyl)-8H-pyrido[2,3-*d*]pyrimidin-7-one.

40. The compound according to Claim 13 which is:

- 5 4-Chloro-8-(2,6-difluorophenyl)-2-[[2-hydroxy-1-(hydroxymethyl)ethyl]-amino]pyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
 4-chloro-2-[[3-(diethylamino)propyl]amino]-8-(2,6-difluorophenyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
 4-chloro-8-(2,6-difluorophenyl)-2-(4-methyl-1,4'-bipiperidin-1'-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
 10 5-chloro-7-[[3-(diethylamino)propyl]amino]-1-(2,6-difluorophenyl)-3,4-dihydropyrimido[4,5-*d*]pyrimidin-2(1*H*)-one trifluoroacetate;
 5-chloro-1-(2,6-difluorophenyl)-7-[4-(1-pyrrolidinyl)-1-piperidinyl]-3,4-dihydropyrimido[4,5-*d*]pyrimidin-2(1*H*)-one; or
 15 5-chloro-1-(2,6-difluorophenyl)-7-[[2-(dimethylamino)ethyl]amino]-3,4-dihydropyrimido[4,5-*d*]pyrimidin-2(1*H*)-one.

41. A compound of the formula:



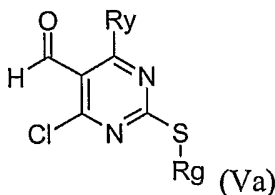
wherein

Ry is bromo, iodo, O-S(O)₂CF₃; and

Rg is a C₁₋₁₀ alkyl.

- 25 42. The compound according to Claim 41 wherein Rg is methyl.

43. A process for making a compound of Formula (II) and (IIa) according to Claim 1 wherein m = 0, and G1 or G2 are CH, which comprises reacting a compound of the formula:



wherein

Ry is chloro, bromo, iodo, O-S(O)₂CF₃; and

Rg is a C₁₋₁₀ alkyl;

with an olefin forming reagent in a suitable base to yield a compound of Formula (IIa), and optionally reducing to yield a compound of Formula (II).

5

44. The process according to Claim 43 wherein the olefin forming reagent is selected from Bis(2,2,2-trifluoroethyl)(methoxycarbonylmethyl)phosphonate, Bis(2,2,2-trifluoroethyl)-(ethoxycarbonylmethyl)phosphonate, Bis(2,2,2-trifluoroethyl)-(isopropoxycarbonylmethyl)phosphonate, (Diethoxy-phosphoryl)-
10 acetic acid methyl ester, (Diisopropoxy-phosphoryl)-acetic acid methyl ester, (Diphenyloxy-phosphoryl)-acetic acid methyl ester, (Diethoxy-phosphoryl)-acetic acid ethyl ester, (Diisopropoxy-phosphoryl)-acetic acid ethyl ester, or (Diphenyloxy-phosphoryl)-acetic acid ethyl ester.

15 45. The process according to Claim 44 wherein the base is selected from triethylamine, pyridine, diisopropyl ethyl amine, or pyrrolidone, or combinations thereof.

46. The process according to Claims 43 wherein the process further comprises an
20 organic solvent.

47. The process according to Claim 46 wherein the solvent is chloroform, methylene chloride, acetonitrile, toluene, DMF, or n-methylpyrrolidine, or combinations thereof.

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48. The process according to Claim 43 wherein the olefin forming reagent is Bis(2,2,2-trifluoroethyl)(methoxycarbonylmethyl)phosphonate, and the base is triethylamine.

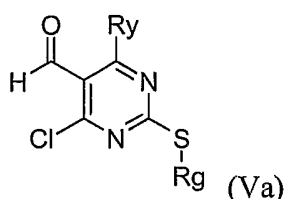
30 49. The process according to Claim 43 wherein Rx is chloro.

50. The process according to Claim 43 wherein Rg is methyl.

51. The process according to Claim 43 which further comprises reacting the
35 compound of formula (II) or (IIa) with an oxidizing agent to yield the corresponding sulfone or sulfoxide of formula (II), or (IIa) or a mixture thereof.

52. The process according to Claim 51 wherein the oxidizing reagent is 3-chloroperoxybenzoic acid, hydrogen peroxide, sodium periodate, potassium periodate, Oxone, OsO₄, catalytic tertiary amine *N*-oxide, a peracid, oxygen, ozone, an organic peroxide, an inorganic peroxide, potassium permanganate, zinc permanganate, potassium persulfate, or sodium hyperchlorite, or a combination of hydrogen peroxide and sodium tungstate, acetic acid or sodium hyperchlorite.

53. A process for making a compound of Formula (II), or (IIa) according to Claim 1 wherein *m* = 0, and G1 or G2 are CH, which comprises reacting a compound of the formula:



wherein

Ry is chloro, bromo, iodo, O-S(O)₂CF₃; and

Rg is a C₁₋₁₀ alkyl;

with an acylating agent in an organic solvent to yield a compound of Formula (IIa), and optionally reducing to yield a compound of Formula (II).

54. The process according to Claim 53 wherein the acylating agent is acetic anhydride or acetyl chloride.

55. The process according to Claim 53 wherein the solvent is chloroform, tetrahydrofuran, methylene chloride, acetonitrile, toluene, DMF, *n*-methylpyrrolidine, or dioxane, or a combination or mixture thereof.

56. The process according to Claim 53 wherein Rx is chloro.

57. The process according to Claim 53 which further comprises reacting the compound of Formula (II) with an oxidizing agent to yield the corresponding sulfone or sulfoxide of Formula (II), or a mixture thereof.

58. The process according to Claim 57 wherein the oxidizing reagent is 3-chloroperoxybenzoic acid, hydrogen peroxide, sodium periodate, potassium periodate, Oxone, OsO₄, catalytic tertiary amine *N*-oxide, a peracid, oxygen, ozone,

peroxide, an organic peroxide, potassium permanganate, zinc permanganate, potassium persulfate, or sodium hyperchlorite.

59. A process for making a compound Formula (III), or (IIIa) according to Claim 7, which process comprises reacting a compound of Formula (II) or (IIa) according to Claim 1 with the compound X-Y, wherein X is as defined for compounds of Formula (III), and Y is NH₂, NH(R₁₀), OH, or SH in an anhydrous organic solvent to yield a compound of Formula (III), provided that

- 10 a) X is R₂ and R₂ is hydrogen, C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkylalkyl, aryl, arylC₁₋₁₀ alkyl, heteroaryl, heteroarylC₁₋₁₀ alkyl, heterocyclic, or a heterocyclylC₁₋₁₀ alkyl; or
- b) X is (CH₂)_n'N(R₁₀')S(O)_mR₂', (CH₂)_n'N(R₁₀')C(O)R₂', (CH₂)_n'NR₄R₁₄, (CH₂)_n'N(R₂') (R₂''), and n' is greater than 2.

15 60. The process according to Claim 59 wherein the solvent methylene chloride, chloroform, acetonitrile, benzene, THF, hexane, ethyl ether, *tert*-butyl methyl ether, DMSO, DMF, toluene, DMF, acetone, n-methyl-pyrrolidine, or dioxane, or a combination or mixture thereof.

20 61. The process according to Claim 59 which further comprises a base.

62. The process according to Claim 61 wherein the base is triethyl amine, diisopropyl ethyl amine, NaH, n-BuLi, *tert*-BuLi, *tert*-BuOK, Li₂CO₃, Cs₂CO₃ or pyridine.

25

63. A process for making a compound Formula (III), or (IIIa) according to Claim 7, which comprises reacting a compound of Formula (II) or (IIa) according to Claim 1 with the compound X-Y, wherein X is as defined for compounds of Formula (III), and

30 Y is hydrogen, a metal, a boronic acid derivative, or a trialkyl tin derivative, in an anhydrous organic solvent which does not contain a nucleophile to yield a compound of Formula (III) or (IIIa); provided that

when Y is hydrogen then

- a) X= OR₂', or X is S(O)_mR₂' (and m=0); or
- 35 b) X is (CH₂)_n'N(R₁₀')S(O)_mR₂', (CH₂)_n'N(R₁₀')C(O)R₂', (CH₂)_n'NR₄R₁₄, or (CH₂)_n'N(R₂') (R₂'') and n'=0; or
- c) X=R₂ and R₂ = (CR₁₀R₂₀)_qX₁(CR₁₀R₂₀)_qC(A₁)(A₂)(A₃), q'=0, and X₁ is N(R₁₀'), O, S(O)_m and m=0.

d) when X is $N(R_{10'})-R_h-NH-C(=N-CN)NR_qR_q'$; and

when Y is a metal, such as Li, Mg, or any other appropriate metal or metal complexes; then

5 a) X is R_2 , and R_2 is C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl C_{1-10} alkyl, aryl, aryl C_{1-10} alkyl, heteroaryl, heteroaryl C_{1-10} alkyl, heterocyclic, or a heterocyclyl C_{1-10} alkyl moiety; and

when Y is a boronic acid, $(B(OH)_2)$ or boronic ester derivatives

a) $X=R_2$, and R_2 = aryl, or heteroaryl; and

when Y is a trialkyl tin derivative, such as $(C_{1-4} \text{ alkyl})_3Sn$, then

10 a) $X=R_2$, and R_2 = aryl, or heteroaryl.

64. The process according to Claim 63 wherein the anhydrous organic solvent is selected from CH_2Cl_2 , chloroform, CH_3CN , benzene, THF, hexane, ethyl ether, *tert*-butyl methyl ether, DMSO, DMF and toluene.

15

65. The process according to Claim 63 which further comprises a base.

66. The process according to Claim 65 wherein the base is triethyl amine, diisopropyl ethyl amine, NaH, *n*-Buli, *tert*-BuLi, *tert*-BuOK, Li_2CO_3 , Cs_2CO_3 or
20 pyridine.

67. A process to make a compound of Formula (I) and (Ia) as defined herein which comprises reacting a compound of Formula (III), or (IIIa) according to Claim 7 with a coupling agent selected from an arylboronic acid, a heteroarylboronic acid or their
25 corresponding boronic acid esters, with a palladium catalyst, in a solvent, to yield a compound of Formula (I) or (Ia).

68. The process according to Claim 67 wherein the palladium catalyst is tetrakis(triphenylphosphine)palladium (0), $PdCl_2$, $Pd(OAc)_2$, $(CH_3CN)_2PdCl_2$,
30 $Pd(dppf)_2$, or [1,1'-bis(diphenylphosphino)-ferrocene]-dichloropalladium(II).

69. The process according to Claim 68 wherein the palladium catalyst is tetrakis(triphenylphosphine)palladium (0).

35 70. The process according to Claim 67 wherein the solvent is dioxane, THF, DMF, DMSO, NMP, acetone, water, or a combination or a mixture thereof.

71. The process according to Claim 70 wherein the solvent is THF and H₂O, or dioxane and H₂O.

72. The process according to Claim 67 which further comprises a base.

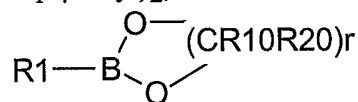
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73. The process according to Claim 72 wherein the base is NaHCO₃, KHCO₃, Na₂CO₃, K₂CO₃, KOAc or a combination or mixture thereof.

74. The process according to Claim 72 wherein the base is K₂CO₃ or KOAc or a combination or mixture thereof.

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75. The process according to Claim 67 wherein the arylboronic acid is R₁B(OH)₂, R₁B(O-C₁₋₄ alkyl)₂, or



wherein

15 R₁₀ and R₂₀ are independently selected from hydrogen or C₁₋₄ alkyl;

r is an integer having a value of 2 to 6; and

R₁ is an optionally substituted phenyl.

76. The process according to Claim 75 wherein the phenyl ring is substituted by one or more times independently at each occurrence by halogen, C₁₋₄ alkyl, halo-substituted-C₁₋₄ alkyl, cyano, nitro, (CR₁₀R₂₀)_vNR_dR_d', (CR₁₀R₂₀)_vC(O)R₁₂, SR₅, S(O)R₅, S(O)₂R₅, or (CR₁₀R₂₀)_vOR₁₃, (CR₁₀R₂₀)_vC(Z)NR₄R₁₄, (CR₁₀R₂₀)_vC(Z)OR₈, (CR₁₀R₂₀)_vCOR_a', (CR₁₀R₂₀)_vC(O)H, ZC(Z)R₁₁, N(R₁₀')C(Z)R₁₁, N(R₁₀')S(O)₂R₇, C(Z)N(R₁₀') (CR₁₀R₂₀)_vR_b, C(Z)O(CR₁₀R₂₀)_vR_b, N(R₁₀')C(Z)(CR₁₀R₂₀)_vR_b; N(R₁₀')C(Z)N(R₁₀') (CR₁₀R₂₀)_vR_b; or N(R₁₀')OC(Z)(CR₁₀R₂₀)_vR_b; and wherein R_a' is C₁₋₄ alkyl, halo-substituted C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₇ cycloalkyl, C₅₋₇ cycloalkenyl, aryl, arylC₁₋₄ alkyl, heteroaryl, heteroarylC₁₋₄ alkyl, heterocyclyl, heterocyclylC₁₋₄ alkyl, (CR₁₀R₂₀)_vOR₇, (CR₁₀R₂₀)_vS(O)_mR₇, (CR₁₀R₂₀)_v N(R₁₀')S(O)₂R₇, or (CR₁₀R₂₀)_vNR₄R₁₄; and wherein the aryl, arylalkyl, heteroaryl, heteroaryl alkyl may be optionally substituted; R_b is hydrogen, C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkylC₁₋₁₀ alkyl, aryl, arylC₁₋₁₀alkyl, heteroaryl, heteroarylC₁₋₁₀ alkyl, heterocyclic, or a

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- heterocyclylC₁₋₁₀ alkyl moiety, which moieties excluding hydrogen, may all be optionally substituted;
- R_d and R_{d'} are each independently selected from hydrogen, C₁₋₄ alkyl, C₃₋₅ cycloalkyl, C₃₋₅ cycloalkylC₁₋₄alkyl, or the R_d and R_{d'} together with the
- 5 nitrogen which they are attached form an optionally substituted heterocyclic ring of 5 to 6 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR_{9'}, and wherein the R_d and R_{d'} moieties which are C₁₋₄ alkyl, C₃₋₆cycloalkyl, C₃₋₆cycloalkylC₁₋₄ alkyl, and the R₄ and R₁₄ cyclized ring are optionally substituted;
- 10 R₇ is C₁₋₆alkyl, aryl, arylC₁₋₆alkyl, heterocyclic, heterocyclylC₁₋₆ alkyl, heteroaryl, or heteroarylC₁₋₆alkyl; and wherein each of these moieties may be optionally substituted;
- R₈ is independently selected at each occurrence from hydrogen, C₁₋₄ alkyl, halo-substituted C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₇ cycloalkyl, C₃₋₇
- 15 cycloalkyl C₁₋₄ alkyl, C₅₋₇ cycloalkenyl, C₅₋₇cycloalkenyl C₁₋₄ alkyl, aryl, arylC₁₋₄ alkyl, heteroaryl, heteroarylC₁₋₄ alkyl, heterocyclyl, or a heterocyclylC₁₋₄ alkyl moiety, and wherein these moieties, excluding hydrogen, may be optionally substituted independently at each occurrence;
- R_{9'} is independently selected at each occurrence from hydrogen, or C₁₋₄ alkyl;
- 20 m is independently selected at each occurrence from 0 or an integer having a value of 1 or 2;
- v is independently selected at each occurrence from 0, or an integer having a value of 1 to 2.
- v' is independently selected at each occurrence from 0 or an integer having a value of
- 25 1 or 2;
- R₄ and R₁₄ are each independently selected at each occurrence from hydrogen, C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkylC₁₋₄alkyl, aryl, aryl-C₁₋₄ alkyl, heterocyclic, heterocyclic C₁₋₄ alkyl, heteroaryl or heteroaryl C₁₋₄ alkyl; or the R₄ and R₁₄ together with the nitrogen which they are attached form an
- 30 unsubstituted or substituted heterocyclic ring of 4 to 7 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or nitrogen; and wherein all of these moieties, excluding hydrogen, are optionally substituted;
- R_{4'} and R_{14'} are each independently selected at each occurrence from hydrogen or
- 35 C₁₋₄ alkyl, or R_{4'} and R_{14'} can cyclize together with the nitrogen to which they are attached to form an optionally substituted 5 to 7 membered ring which

- optionally contains an additional heteroatom selected from oxygen, sulfur or NR₉';
- R₅ is independently selected at each occurrence from hydrogen, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl or NR₄'R₁₄', excluding the moieties SR₅ being
- 5 SNR₄'R₁₄', S(O)₂R₅ being SO₂H and S(O)R₅ being SOH;
- R₁₀ and R₂₀ are independently selected at each occurrence from hydrogen or C₁₋₄ alkyl;
- R₁₀' is independently selected at each occurrence from hydrogen or C₁₋₄ alkyl;
- R₁₁ is independently selected at each occurrence from hydrogen, or C₁₋₄ alkyl;
- 10 R₁₂ is independently selected at each occurrence from hydrogen, C₁₋₄ alkyl, halo-substituted C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl C₁₋₄ alkyl, C₅₋₇ cycloalkenyl, C₅₋₇cycloalkenyl C₁₋₄ alkyl, aryl, arylC₁₋₄ alkyl, heteroaryl, heteroarylC₁₋₄ alkyl, heterocyclyl, or heterocyclylC₁₋₄ alkyl, and wherein these moieties, excluding hydrogen, may be optionally
- 15 substituted; and
- R₁₃ is independently selected at each occurrence from hydrogen, C₁₋₄ alkyl, halo-substituted C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₇ cycloalkyl, C₃₋₇cycloalkylC₁₋₄ alkyl, C₅₋₇ cycloalkenyl, C₅₋₇cycloalkenyl C₁₋₄ alkyl, aryl, arylC₁₋₄ alkyl, heteroaryl, heteroarylC₁₋₄ alkyl, heterocyclyl, or a
- 20 heterocyclylC₁₋₄ alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted.

77. The process according to Claim 76 wherein the phenyl ring is substituted one or more times independently at each occurrence by halogen, C₁₋₄ alkyl, halo-

25 substituted-C₁₋₄ alkyl, SR₅, S(O)R₅, S(O)₂R₅, (CR₁₀R₂₀)_v'OR₁₃, (CR₁₀R₂₀)_vC(Z)NR₄R₁₄, C(Z)N(R₁₀') (CR₁₀R₂₀)_vR_b, and (CR₁₀R₂₀)_vC(Z)OR₈.

78. The process according to Claim 77 wherein R₈ is hydrogen, or C₁₋₄ alkyl, R₁₃ is hydrogen, or C₁₋₄ alkyl, such as methyl; R_b is suitably hydrogen, C₁₋₄ alkyl, aryl,

30 or heteroaryl.

79. The proves according to Claim 78 wherein the phenyl ring is substituted by 2-methoxy, 3-methoxy, 4-methoxy, 2-chloro, 3-chloro, 4-chloro, 2-fluoro, 3- fluoro, 4-fluoro, ,4-difluoro, 2,4,6-trifluoro, 3,4-difluoro, 3,5-difluoro, 2-methyl-4-fluoro, 2-

35 methyl-4-chloro, 2-methylsulfanyl, 3-methylsulfanyl, 4-methylsulfanyl, 2-phenyl, 3-phenyl, 4-phenyl, 2-methyl, 3-methyl, 4-methyl, 3-fluoro-4-phenyl, 2-hydroxy, 3-hydroxy, 4-hydroxy, 2-methylsulfonyl, 3-methylsulfonyl, 4-methylsulfonyl, 3-N-

- cyclopropylamide, 2-methyl-3-fluoro-5-N-cyclopropylamide, 2-C(O)OH, 3-C(O)OH, 4-C(O)OH, 2-methyl-5-C(O)OH, 2-methyl-3-C(O)OH, 2-methyl-4-C(O)OH, 2-methyl-3-F-5-C(O)OH, 4-F-phenyl-1-amide, 2-ethyl-5-C(O)OH, 2-ethyl-3-C(O)OH, 2-ethyl-4-C(O)OH, 2-methyl-5-dimethylamide, 2-methyl-4-dimethylamide, 5-dimethylamide, and 4-dimethylamide.

80. The process according to Claim 77 wherein the phenyl is di-substituted independently at each occurrence by halogen, C₁₋₄ alkyl, or halo-substituted-C₁₋₄ alkyl.

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81. The process according to Claim 75 wherein the aryl is phenyl, 2-methyl-4-fluorophenyl, 2-methylphenyl, 2-chlorophenyl, 2-fluorophenyl, or 2-methyl-3-fluorophenyl, 2-methyl-4-fluorophenyl, and 2-methyl-4-chlorophenyl.

82. The process according to Claim 75 wherein the phenyl is substituted in the 4- or 5-position by C(Z)N(R_{10'})(CR₁₀R₂₀)_v R_b, Z is oxygen, and R_b is an optionally substituted C₁₋₁₀alkyl, or an optionally substituted heteroaryl.

83. The process according to Claim 82 wherein the phenyl ring is also substituted one or more times independently at each occurrence by halogen, C₁₋₄ alkyl, or halo-substituted-C₁₋₄ alkyl.

84. The process according to Claim 81 wherein the aryl is 4-methyl-N-1,3-thiazol-2-ylbenzamide, N-(4-fluorophenyl)-4-methylbenzamide, 4-methyl-N-isopropylbenzamide or 4-methyl-N-propylbenzamide.

85. A process for making compounds of Formula (I) and (Ia) as defined herein, which comprises reacting a compound of Formula (III) or (IIIa), according to Claim 7 with an R₁-ZnBr, R₁-ZnCl, R₁-Zn-R₁, (R₁)₂-CuLi, R₁-Sn(CH₃)₃, R₁-Sn(CH₂CH₂CH₂CH₃)₃, or other R₁-organometallic reagents with an organic solvent, to yield a compound of Formula (I) or (Ia).

86. The process according to Claim 85 wherein the solvent is dioxane, THF, methylene chloride, chloroform, benzene, hexane, ethyl ether, *tert*-butyl methyl ether or a combination or a mixture thereof.

87. The process according to Claim 85 which further comprises a catalyst.

88. The process according to Claim 87 wherein the catalyst is tetrakis(triphenylphosphine)palladium (0), PdCl₂, Pd(OAc)₂, (CH₃CN)₂PdCl₂, or Pd(dppf)₂.

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89. The process according to Claim 85 wherein the R₁-moiety in the organometallic reagent is a phenyl ring substituted by one or more times independently at each occurrence by halogen, C₁₋₄ alkyl, halo-substituted-C₁₋₄ alkyl, cyano, nitro, (CR₁₀R₂₀)_v'NR_dR_d', (CR₁₀R₂₀)_v'C(O)R₁₂, SR₅, S(O)R₅, S(O)₂R₅,
 10 or (CR₁₀R₂₀)_v'OR₁₃, (CR₁₀R₂₀)_vC(Z)NR₄R₁₄, (CR₁₀R₂₀)_vC(Z)OR₈, (CR₁₀R₂₀)_vCOR_a', (CR₁₀R₂₀)_vC(O)H, SR₅, S(O)R₅, S(O)₂R₅, (CR₁₀R₂₀)_vOR₈, ZC(Z)R₁₁, N(R₁₀')C(Z)R₁₁, N(R₁₀')S(O)₂R₇, C(Z)N(R₁₀') (CR₁₀R₂₀)_vR_b, C(Z)O(CR₁₀R₂₀)_vR_b, N(R₁₀')C(Z)(CR₁₀R₂₀)_vR_b; N(R₁₀')C(Z)N(R₁₀') (CR₁₀R₂₀)_vR_b; or N(R₁₀')OC(Z)(CR₁₀R₂₀)_vR_b; and wherein
 15 R_a' is C₁₋₄ alkyl, halo-substituted C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₇ cycloalkyl, C₅₋₇ cycloalkenyl, aryl, arylC₁₋₄ alkyl, heteroaryl, heteroarylC₁₋₄ alkyl, heterocyclyl, heterocyclylC₁₋₄ alkyl, (CR₁₀R₂₀)_vOR₇, (CR₁₀R₂₀)_vS(O)_mR₇, (CR₁₀R₂₀)_v N(R₁₀')S(O)₂R₇, or (CR₁₀R₂₀)_vNR₄R₁₄; and wherein the aryl, arylalkyl, heteroaryl, heteroaryl alkyl may be optionally substituted;
 20 R_b is hydrogen, C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkylC₁₋₁₀ alkyl, aryl, arylC₁₋₁₀alkyl, heteroaryl, heteroarylC₁₋₁₀ alkyl, heterocyclic, or a heterocyclylC₁₋₁₀ alkyl moiety, which moieties excluding hydrogen, may all be optionally substituted;
 25 R_d and R_d' are each independently selected from hydrogen, C₁₋₄ alkyl, C₃₋₅ cycloalkyl, C₃₋₅ cycloalkylC₁₋₄alkyl, or the R_d and R_d' together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 5 to 6 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR₉', and wherein the R_d and R_d' moieties which
 30 are C₁₋₄ alkyl, C₃₋₆cycloalkyl, C₃₋₆cycloalkylC₁₋₄ alkyl, and the R₄ and R₁₄ cyclized ring are optionally substituted;
 R₇ is C₁₋₆alkyl, aryl, arylC₁₋₆alkyl, heterocyclic, heterocyclylC₁₋₆ alkyl, heteroaryl, or heteroarylC₁₋₆alkyl; and wherein each of these moieties may be optionally substituted;
 35 R₈ is independently selected at each occurrence from hydrogen, C₁₋₄ alkyl, halo-substituted C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl C₁₋₄ alkyl, C₅₋₇ cycloalkenyl, C₅₋₇cycloalkenyl C₁₋₄ alkyl, aryl,

- arylC₁₋₄ alkyl, heteroaryl, heteroarylC₁₋₄ alkyl, heterocyclyl, or a heterocyclylC₁₋₄ alkyl moiety, and wherein these moieties, excluding hydrogen, may be optionally substituted independently at each occurrence;
- R₉' is independently selected at each occurrence from hydrogen, or C₁₋₄ alkyl;
- 5 m is independently selected at each occurrence from 0 or an integer having a value of 1 or 2;
- v is independently selected at each occurrence from 0, or an integer having a value of 1 to 2.
- v' is independently selected at each occurrence from 0 or an integer having a value of 10 1 or 2;
- R₄ and R₁₄ are each independently selected at each occurrence from hydrogen, C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkylC₁₋₄alkyl, aryl, aryl-C₁₋₄ alkyl, heterocyclic, heterocyclic C₁₋₄ alkyl, heteroaryl or heteroaryl C₁₋₄ alkyl; or the R₄ and R₁₄ together with the nitrogen which they are attached form an 15 unsubstituted or substituted heterocyclic ring of 4 to 7 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or nitrogen; and wherein all of these moieties, excluding hydrogen, are optionally substituted;
- R₄' and R₁₄' are each independently selected at each occurrence from hydrogen or 20 C₁₋₄ alkyl, or R₄' and R₁₄' can cyclize together with the nitrogen to which they are attached to form an optionally substituted 5 to 7 membered ring which optionally contains an additional heteroatom selected from oxygen, sulfur or NR₉';
- R₅ is independently selected at each occurrence from hydrogen, C₁₋₄ alkyl, C₂₋₄ 25 alkenyl, C₂₋₄ alkynyl or NR₄'R₁₄', excluding the moieties SR₅ being SNR₄'R₁₄', S(O)₂R₅ being SO₂H and S(O)R₅ being SOH;
- R₁₀ and R₂₀ are independently selected at each occurrence from hydrogen or C₁₋₄ alkyl;
- R₁₀' is independently selected at each occurrence from hydrogen or C₁₋₄ alkyl;
- 30 R₁₁ is independently selected at each occurrence from hydrogen, or C₁₋₄ alkyl;
- R₁₂ is independently selected at each occurrence from hydrogen, C₁₋₄ alkyl, halo-substituted C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl C₁₋₄ alkyl, C₅₋₇ cycloalkenyl, C₅₋₇cycloalkenyl C₁₋₄ alkyl, aryl, arylC₁₋₄ alkyl, heteroaryl, heteroarylC₁₋₄ alkyl, heterocyclyl, or heterocyclylC₁₋₄ 35 alkyl, and wherein these moieties, excluding hydrogen, may be optionally substituted; and

R₁₃ is independently selected at each occurrence from hydrogen, C₁₋₄ alkyl, halo-substituted C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₇ cycloalkyl, C₃₋₇cycloalkylC₁₋₄ alkyl, C₅₋₇ cycloalkenyl, C₅₋₇cycloalkenyl C₁₋₄ alkyl, aryl, arylC₁₋₄ alkyl, heteroaryl, heteroarylC₁₋₄ alkyl, heterocyclyl, or a
5 heterocyclylC₁₋₄ alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted.

90. The process according to Claim 89 wherein the phenyl ring is substituted one or more times independently at each occurrence by halogen, C₁₋₄ alkyl, halo-substituted-C₁₋₄ alkyl, SR₅, S(O)R₅, S(O)₂R₅, (CR₁₀R₂₀)_vOR₁₃,
10 (CR₁₀R₂₀)_vC(Z)NR₄R₁₄, C(Z)N(R₁₀') (CR₁₀R₂₀)_vR_b, and (CR₁₀R₂₀)_vC(Z)OR₈.

91. The process according to Claim 90 wherein R₈ is hydrogen, or C₁₋₄ alkyl, R₁₃ is hydrogen, or C₁₋₄ alkyl, such as methyl; R_b is suitably hydrogen, C₁₋₄ alkyl, aryl,
15 or heteroaryl.

92. The proves according to Claim 78 wherein the phenyl ring is substituted by 2-methoxy, 3-methoxy, 4-methoxy, 2-chloro, 3-chloro, 4-chloro, 2-fluoro, 3- fluoro, 4-fluoro, ,4-difluoro, 2,4,6-trifluoro, 3,4-difluoro, 3,5-difluoro, 2-methyl-4-fluoro, 2-
20 methyl-4-chloro, 2-methylsulfanyl, 3-methylsulfanyl, 4-methylsulfanyl, 2-phenyl, 3-phenyl, 4-phenyl, 2-methyl, 3-methyl, 4-methyl, 3-fluoro-4-phenyl, 2-hydroxy, 3-hydroxy, 4-hydroxy, 2-methylsulfonyl, 3-methylsulfonyl, 4-methylsulfonyl, 3-N-cyclopropylamide, 2-methyl-3-fluoro-5-N-cyclopropylamide, 2-C(O)OH, 3-C(O)OH, 4-C(O)OH, 2-methyl-5-C(O)OH, 2-methyl-3-C(O)OH, 2-methyl-4-C(O)OH, 2-
25 methyl-3-F-5-C(O)OH, 4-F-phenyl1-amide, 2-ethyl-5-C(O)OH, 2-ethyl-3-C(O)OH, 2-ethyl-4-C(O)OH, 2-methyl-5-dimethylamide, 2-methyl-4-dimethylamide, 5-dimethylamide, and 4-dimethylamide.

93. The process according to Claim 89 wherein the phenyl ring is substituted one or more times independently at each occurrence by halogen, C₁₋₄ alkyl, or halo-substituted-C₁₋₄ alkyl.
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94. The process according to Claim 93 wherein the phenyl is di-substituted independently at each occurrence by fluorine or methyl.
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95. The process according to Claim 87 wherein the aryl is phenyl, 2-methyl-4-fluorophenyl, 2-methylphenyl, 2-chlorophenyl, 2-fluorophenyl, 2-methyl-4-chlorophenyl, or 2-methyl-3-fluorophenyl.
- 5 96. The process according to Claim 87 wherein the phenyl is substituted in the 4- or 5-position by $C(Z)N(R_{10})(CR_{10}R_{20})_vR_b$, Z is oxygen, and R_b is an optionally substituted C_{1-10} alkyl, or an optionally substituted heteroaryl.
- 10 97. The process according to Claim 96 wherein the phenyl ring is also substituted one or more times independently at each occurrence by halogen, C_{1-4} alkyl, or halo-substituted- C_{1-4} alkyl.
- 15 98. The process according to Claim 83 wherein the aryl is 4-methyl-*N*-1,3-thiazol-2-ylbenzamide, *N*-(4-fluorophenyl)-4-methylbenzamide, 4-methyl-*N*-isopropylbenzamide or 4-methyl-*N*-propylbenzamide.