PROCESSES FOR PREPARING 4-(PHENOXY-5-METHYL-PYRIMIDIN-4-YLOXY) PIPERIDINE-1-CARBOXYLIC ACID DERIVATIVES AND RELATED COMPOUNDS

FIELD OF THE INVENTION

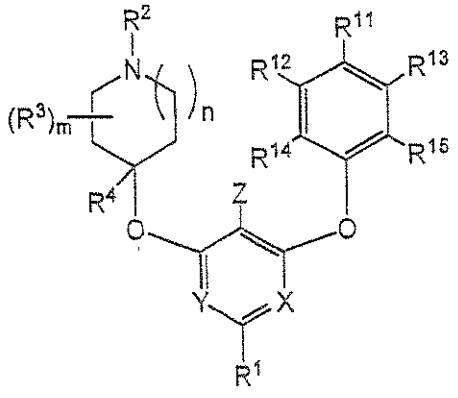
The present invention relates to processes for preparing aromatic ether compounds that are modulators of glucose metabolism and therefore useful in the treatment of metabolic disorders such as diabetes and obesity.

BACKGROUND OF THE INVENTION

Modulation of G-protein coupled receptors has been well-studied for controlling various metabolic disorders. Small molecule modulators of the receptor RUP3, a G-protein coupled-receptor described in, for example, GenBank (see, e.g., accession numbers XM_066873 and AY288416), have been shown to be useful for treating or preventing certain metabolic disorders. In particular, aromatic ethers and similar compounds, which are described in U.S. Ser. No. 10/888,747, are shown to be effective modulators of the RUP3 receptor and are useful in the treatment of various metabolic-related disorders such as type I diabetes, type II diabetes, inadequate glucose tolerance, insulin resistance, hyperglycemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, dyslipidemia or syndrome X. The aromatic ethers are also useful in controlling weight gain, controlling food intake, and inducing satiety in mammals. The promising nature of these RUP3 modulators in treating or preventing a number of common diseases evidences a need for more efficient processes of making these compounds. The processes described herein are directed toward this and other current needs.

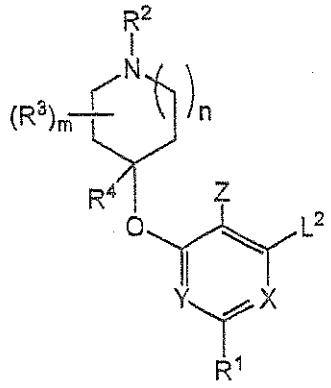
SUMMARY OF THE INVENTION

The present invention provides processes for preparing compounds of Formula I:



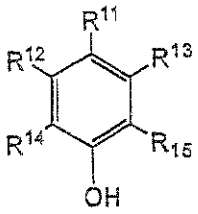
I

wherein constituent members are defined herein, comprising reacting a compound of Formula II:



II

with compound of Formula III:

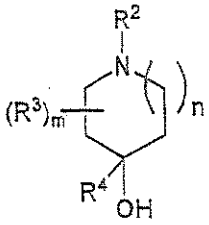


III

in the presence of a base, thereby forming the compound of Formula I.

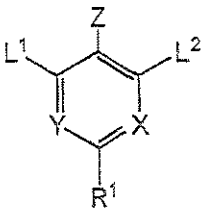
The present invention also provides processes for preparing compounds of Formula II by:

a) combining a compound of Formula IV:



IV

with a compound of Formula V:



V

to form a mixture; and

b) adding a base to the mixture, thereby forming the compound of Formula II.

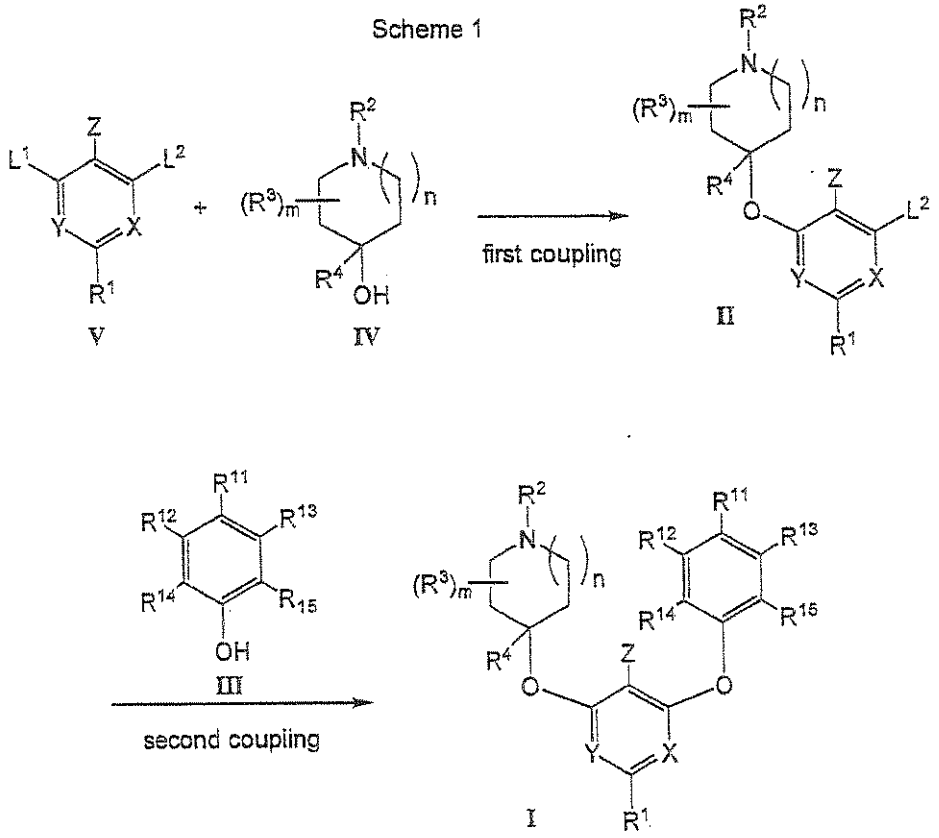
The present invention further provides bulk samples of the compound of Formula I or II prepared according to the processes herein.

DETAILED DESCRIPTION

The present invention is directed to processes and intermediates for the preparation of aromatic ethers that are useful as RUP3 modulators for the treatment of metabolic disorders such as diabetes and obesity.

Example processes and intermediates of the present invention are provided below in Scheme I, wherein constituent members of the formulae depicted therein are defined below.

Scheme 1



The present invention provides processes, such as exemplified in Scheme I, involving compounds of Formulas I, II, III, IV, and V, or salt forms thereof, wherein:

L^1 is a leaving group;

L^2 is a leaving group

X is N or CR^7;

Y is N or CR^8;

Z is C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylthioureyl, C_{1-4} alkylureyl, amino, C_{1-2} alkylamino, C_{2-4} dialkylamino, carbamimidoyl, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-7} cycloalkyl, C_{4-8} diacylamino, C_{2-6} dialkylcarboxamide, C_{2-6} dialkylthiocarboxamide, C_{2-6} dialkylsulfonamide, C_{2-6} dialkylsulfonylamino, formyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylcarboxamide, C_{1-4}

haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, halogen, aryl, heteroaryl, heterocycloalkyl, hydroxyl, hydroxycarbamimidoyl, hydroxylamino, nitro, or tetrazolyl; wherein said C_{1-8} alkyl, C_{3-7} cycloalkyl, and heterocycloalkyl are each optionally substituted with 1, 2, 3 or 4 groups selected from C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-7} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylureyl, amino, C_{1-2} alkylamino, C_{2-4} dialkylamino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, formyl, C_{1-4} haloalkoxy, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, halogen, hydroxyl, hydroxylamino, and nitro;

R^1 is H, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylureyl, amino, C_{1-4} alkylamino, C_{2-8} dialkylamino, carboxamide, cyano, C_{3-7} cycloalkyl, C_{2-6} dialkylcarboxamide, C_{2-6} dialkylsulfonamide, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, or hydroxyl;

R^2 is $-R^{22}$, $-CR^{23}R^{24}C(O)-R^{22}$, $-C(O)CR^{23}R^{24}-R^{22}$, $-C(O)-R^{22}$, $-CR^{23}R^{24}C(O)NR^{25}-R^{22}$, $-NR^{25}C(O)CR^{23}R^{24}-R^{22}$, $-C(O)NR^{23}-R^{22}$, $-NR^{23}C(O)-R^{22}$, $-C(O)O-R^{22}$, $-OC(O)-R^{22}$, $-C(S)-R^{22}$, $-C(S)NR^{23}-R^{22}$, $-NR^{23}C(S)-R^{22}$, $-C(S)O-R^{22}$, $-OC(S)-R^{22}$, $-CR^{23}R^{24}-R^{22}$, or $-S(O)_2-R^{22}$;

R^3 is C_{1-3} alkyl, C_{1-4} alkoxy, carboxy, cyano, C_{1-3} haloalkyl, or halogen;

R^4 is H, C_{1-8} alkyl or C_{3-7} cycloalkyl, wherein said C_{1-8} alkyl is optionally substituted with C_{1-4} alkoxy, C_{3-7} cycloalkyl, or heteroaryl;

R_7 and R_8 are each, independently, H, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylureyl, amino, C_{1-4} alkylamino, C_{2-8} dialkylamino, carboxamide, cyano, C_{3-7} cycloalkyl, C_{2-6} dialkylcarboxamide, C_{2-6} dialkylsulfonamide, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, or hydroxyl;

R^{11} is C_{1-5} acyl, C_{1-6} acylsulfonamide, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-6} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylthioureyl, C_{1-4} alkylureyl, amino, arylsulfonyl, carbamimidoyl, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-7} cycloalkyl, C_{3-7} cycloalkyloxy, C_{2-6} dialkylamino, C_{2-6} dialkylcarboxamide, C_{2-6} dialkylthiocarboxamide, guanidinyl, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, heterocycloalkyl, heterocycloalkyl-oxy, heterocycloalkylsulfonyl, heterocycloalkyl-carbonyl, heteroaryl, heteroarylcarbonyl, hydroxyl, nitro, C_{4-7} oxo-cycloalkyl, phenoxy, phenyl, sulfonamide, sulfonic acid, or thiol; and wherein said C_{1-5} acyl, C_{1-6} acylsulfonamide, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-6} alkylsulfonamide, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, arylsulfonyl, carbamimidoyl, C_{2-6} dialkylamino, heterocycloalkyl, heterocycloalkyl-carbonyl, heteroaryl, phenoxy and phenyl are each optionally substituted with 1 to 5 substituents selected independently from C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-7} alkyl, C_{1-4} alkylamino, C_{1-4} alkylcarboxamide, C_{2-6}

alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylureyl, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-7} cycloalkyl, C_{3-7} cycloalkyloxy, C_{2-6} dialkylamino, C_{2-6} dialkylcarboxamide, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, heteroaryl, heterocyclic, hydroxyl, nitro, phenyl, and phosphonooxy, wherein said C_{1-7} alkyl and C_{1-4} alkylcarboxamide are each optionally substituted with 1 to 5 substituents selected from C_{1-4} alkoxy and hydroxy;

R^{12}, R^{13}, R^{14}, and R^{15} are each, independently, H, C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylureyl, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-7} cycloalkyl, C_{2-6} dialkylcarboxamide, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, hydroxyl, or nitro;

R^{22} is H, C_{1-8} alkyl, C_{3-7} cycloalkyl, phenyl, heteroaryl, or heterocyclic each optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-7} alkyl, C_{1-4} alkylamino, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylthioureyl, C_{1-4} alkylureyl, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-7} cycloalkyl, C_{2-8} dialkylamino, C_{2-6} dialkylcarboxamide, C_{2-6} dialkylthiocarboxamide, C_{2-6} dialkylsulfonamide, C_{1-4} alkylthioureyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkyl, C_{1-4} haloalkylthio, halogen, heteroaryl, heterocyclic, hydroxyl, hydroxylamino, nitro, phenyl, phenoxy, and sulfonic acid, wherein said C_{1-7} alkyl, heteroaryl, phenyl and phenoxy are each optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylthioureyl, C_{1-4} alkylureyl, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-7} cycloalkyl, C_{2-8} dialkylamino, C_{2-6} dialkylcarboxamide, C_{2-6} dialkylthiocarboxamide, C_{2-6} dialkylsulfonamide, C_{1-4} alkylthioureyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkyl, C_{1-4} haloalkylthio, halogen, heterocyclic, hydroxyl, hydroxylamino, and nitro;

R^{23}, R^{24} and R^{25} are each, independently, H or C_{1-8} alkyl;

n is 0 or 1; and

m is 0, 1, 2, 3, or 4.

It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable subcombination. All combinations of the embodiments pertaining to the chemical groups represented by the variables (e.g., n, m, R_1, R_2, R_3, R_4, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, X, Y, Z, etc.) contained within the generic chemical formulae described herein [e.g. I, II, III, etc.] and process steps disclosed herein are specifically

embraced by the present invention just as if they were explicitly disclosed, to the extent that such combinations embrace compounds that result in stable compounds (ie., compounds that can be isolated, characterized and tested for biological activity). In addition, all subcombinations of the chemical groups listed in the embodiments describing such variables, as well as all subcombinations of process steps, are also specifically embraced by the present invention just as if each of such subcombination of chemical groups and process steps were explicitly disclosed herein.

In some embodiments, L^1 is halo.

In some embodiments, L^1 is Cl.

In some embodiments, L^2 is halo.

In some embodiments, L^2 is Cl.

In some embodiments, X is N.

In some embodiments, Y is N.

In some embodiments, both X and Y are N.

In some embodiments, Z is C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylthioureyl, C_{1-4} alkylureyl, amino, C_{1-2} alkylamino, C_{2-4} dialkylamino, carbamimidoyl, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-7} cycloalkyl, C_{4-8} diacylamino, C_{2-6} dialkylcarboxamide, C_{2-6} dialkylthiocarboxamide, C_{2-6} dialkylsulfonamide, C_{2-6} dialkylsulfonylamino, formyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylcarboxamide, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, halogen, aryl, heteroaryl, heterocycloalkyl, hydroxyl, hydroxycarbamimidoyl, hydroxylamino, nitro, or tetrazolyl.

In some embodiments, Z is C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{2-6} alkynyl, formyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, halogen, hydroxyl, or nitro.

In some embodiments, Z is C_{1-8} alkyl.

In some embodiments, Z is methyl, ethyl or propyl.

In some embodiments, Z is methyl.

In some embodiments, R^1 is H.

In some embodiments, R^2 is -C(O)O-R^{22}.

In some embodiments, R^2 is -C(O)O-R^{22} and R^{22} is C_{1-8} alkyl or C_{3-7} cycloalkyl.

In some embodiments, R^2 is -C(O)O-R^{22} and R^{22} is C_{1-4} alkyl.

In some embodiments, R^2 is -C(O)O-R^{22} and R^{22} is methyl, ethyl, or prop-1-yl, prop-2-yl.

In some embodiments, R^2 is -C(O)O-R^{22} and R^{22} is prop-2-yl.

In some embodiments, R^4 is H.

In some embodiments, n is 1.

In some embodiments, m is 0.

In some embodiments, R^{11} is C_{1-5} acyl, C_{1-6} acylsulfonamide, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-6} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylthioureyl, C_{1-4} alkylureyl, amino, arylsulfonyl, carbamimidoyl, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-7} cycloalkyl, C_{3-7} cycloalkyloxy, C_{2-6} dialkylamino, C_{2-6} dialkylcarboxamide, C_{2-6} dialkylthiocarboxamide, guanidinyl, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, heterocyclic, heterocycloalkyl-oxy, heterocycloalkylsulfonyl, heterocycloalkyl-carbonyl, heteroaryl, heteroarylcarbonyl, hydroxyl, nitro, C_{4-7} oxo-cycloalkyl, phenoxy, phenyl, sulfonamide, sulfonic acid, or thiol.

In some embodiments, R^{11} is C_{1-5} acyl, C_{1-6} acylsulfonamide, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-6} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, or C_{1-4} alkylsulfonyl.

In some embodiments, R^{11} is C_{1-4} alkylsulfinyl or C_{1-4} alkylsulfonyl.

In some embodiments, R^{11} is C_{1-4} alkylsulfonyl.

In some embodiments, R^{11} is methylsulfonyl or ethylsulfonyl.

In some embodiments, R^{11} is methylsulfonyl.

In some embodiments, R^{12}, R^{13}, R^{14}, and R^{15} are each, independently, H, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{2-6} alkynyl, cyano, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, hydroxyl, or nitro.

In some embodiments, R^{12}, R^{13}, R^{14}, and R^{15} are each, independently, H, C_{1-4} alkoxy, C_{1-8} alkyl, cyano, halogen, hydroxyl, or nitro.

In some embodiments, R^{12}, R^{13}, R^{14}, and R^{15} are each, independently, H or halogen.

In some embodiments, R^{15} is other than H.

In some embodiments, R^{15} is halogen.

In some embodiments, R^{15} is F.

In some embodiments, R^{12}, R^{13}, and R^{14} are each H and R^{15} is other than H.

In some embodiments, R^{11} is C_{1-4} alkylsulfonyl; R^{12}, R^{13}, and R^{14} are each H; and R^{15} is halogen.

In some embodiments:

X is N;

Y is N;

Z is C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{2-6} alkynyl, formyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, halogen, hydroxyl, or nitro;

R^1 is H;

R^2 is -C(O)O-R^{22};

R^4 is H;

R^{11} is C_{1-5} acyl, C_{1-6} acylsulfonamide, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-6} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, or C_{1-4} alkylsulfonyl;

R^{12}, R^{13}, R^{14}, and R^{15} are each, independently, H, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{2-6} alkynyl, cyano, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, hydroxyl, or nitro;

n is 1; and

m is 0 or 1.

In some embodiments:

X is N;

Y is N;

Z is C_{1-8} alkyl;

R^1 is H;

R^2 is -C(O)O-R^{22};

R^4 is H;

R^{11} is C_{1-5} acyl, C_{1-6} acylsulfonamide, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-6} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, or C_{1-4} alkylsulfonyl;

R^{12}, R^{13}, and R^{14} are each H;

R^{15} is C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{2-6} alkynyl, cyano, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, hydroxyl, or nitro;

n is 1; and

m is 0 or 1.

In some embodiments:

X is N;

Y is N;

Z is C_{1-8} alkyl;

R^1 is H;

R^2 is -C(O)O-R^{22};

R^4 is H;

R^{11} is C_{1-4} alkylsulfinyl or C_{1-4} alkylsulfonyl;

R^{12}, R^{13}, and R^{14} are each H;

R^{15} is C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{2-6} alkynyl, cyano, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, hydroxyl, or nitro;

R^{22} is C_{1-4} alkyl;

n is 1; and

m is 0.

In some embodiments:

X is N;

Y is N;

Z is methyl;

R^1 is H;

R^2 is -C(O)O-R^{22};

R^4 is H;

R^{11} is methylsulfonyl;

R^{12}, R^{13}, and R^{14} are each H;

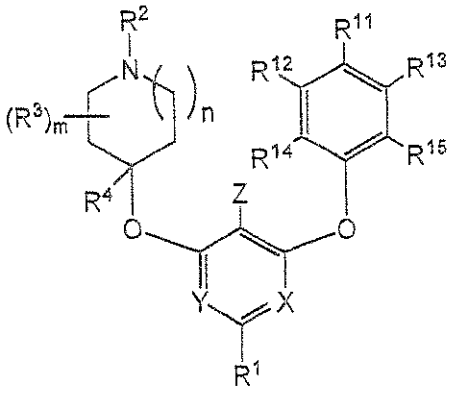
R^{15} is F;

R^{22} is prop-2-yl;

n is 1; and

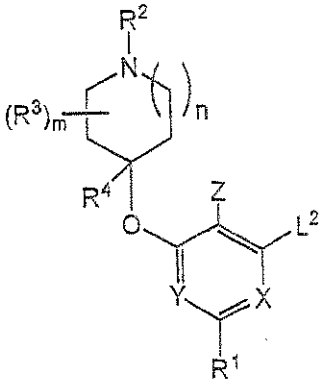
m is 0.

In some embodiments, the present invention provides a process for preparing a compound of Formula I:



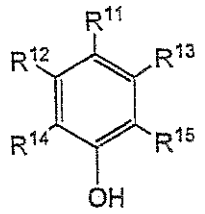
I

by reacting a compound of Formula II:



II

with compound of Formula III:



III

in the presence of a base, thereby forming the compound of Formula I.

The reacting of II with III can be further carried out in the presence of a salt, such as a tetrasubstituted ammonium salt or an iodide salt. A tetrasubstituted ammonium salt includes a salt of formula $[N(R)_4][X^1]$; where X^1 is any monoanion such as fluoride, chloride, bromide, iodide, and the like, and each R is, independently, C_{1-8} alkyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocyclic, or heterocyclic alkyl, each of which can be optionally substituted by halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, or C_{1-4} haloalkoxy. In some embodiments, the tetrasubstituted ammonium salt is a tetra(C_{1-8} alkyl)ammonium salt. In further embodiments, the tetrasubstituted ammonium salt is a tetrabutylammonium salt. In further embodiments, the tetrasubstituted ammonium salt is a halide salt. In further embodiments, the tetrasubstituted ammonium salt is an iodide salt. In further embodiments, the tetrasubstituted ammonium salt is tetrabutylammonium iodide. In further embodiments, the tetrasubstituted ammonium salt is a fluorine salt. In further embodiments, the tetrasubstituted ammonium salt is tetrabutylammonium fluoride $[(CH_3CH_2CH_2CH_2)_4NF]$.

The reacting of II with III can be further carried out in the presence of a salt, such as an alkali metal halide salt. Alkali metal halide salts are known in the art and include salts of formula M-Halide, wherein M is an alkali metal and halide is F, Cl, Br, and I. Examples of an alkali metal halide salt include, for example, NaF, NaCl, NaBr, NaI, KF, KCl, KBr, KI, CsF, CsCl, CsBr, CsI, and the like.

In the reacting of II with III, the base can be any that is routinely used in the art for similar coupling reactions. In some embodiments, the base is an alkali metal amide, alkali metal hydride, alkali metal carbonate, or an alkali metal hydrogencarbonate. In further embodiments, the base is an alkali metal carbonate. In yet a further embodiment, the base is K_2CO_3.

In some embodiments, the reacting of II with III can be carried out at elevated temperature. For example, the reaction mixture can be heated to a temperature of about 100 to about 150, about 120 to about 140, or about 130 to about 135 °C.

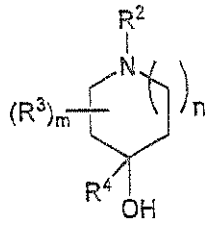
In some embodiments, the reacting of II with III is carried out in a solvent. Suitable solvents include, for example polar solvents or solvents having a boiling point above about 100 °C. Example polar solvents include dimethylsulfoxide (DMSO), dimethylformamide (DMF), dimethylacetate (DMA), N-methylpyrrolidine (NMP), acetonitrile, propionitrile, and the like. Example high boiling

solvents include DMSO, DMF, DMA, and the like. In some embodiments, the solvent includes DMSO.

In some embodiments, the reacting of II and III is carried out where the molar ratio of the compound of Formula II to Formula III is about 1:1. In some embodiments, the compound of Formula II is provided in slight molar excess relative to the amount of compound of Formula III. In further embodiments, the molar ratio of base to amount of compound of Formula III is about 2:1 to about 1:1, about 1.3:1 to about 1.1:1, or about 1.2:1. In yet further embodiments, the molar ratio of tetrasubstituted ammonium salt to amount of compound of Formula III is about 1:1 to about 0.1:1, about 0.8:1 to about 0.5:1, or about 0.7:1 to about 0.6:1.

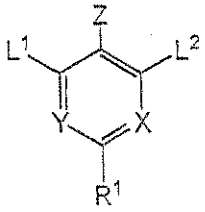
The compound Formula II can be prepared by:

a) combining a compound of Formula IV:



IV

with a compound of Formula V:



V

to form a mixture; and

b) adding a base to the mixture, thereby forming the compound of Formula II.

The base which is added to the mixture of IV and V can be any suitable base including, for example, C_{1-6} alkoxide salts, alkali metal amides, alkali metal hydrides, alkali metal carbonates, or alkali metal hydrogencarbonates. In some embodiments, the base is a C_{1-6} alkoxide salt such as an alkali salt of *t*-butoxide. In some embodiments, the base is potassium *t*-butoxide. Base can be optionally added in one or more portions such as, for example, two portions.

In some embodiments, the combining of IV and V as well as the adding step are carried out in a solvent. Example suitable solvents include ether solvents such as dimethoxymethane, tetrahydrofuran, 1,3-dioxane, 1,4-dioxane, furan, diethyl ether, ethylene glycol dimethyl ether, ethylene glycol diethyl ether, diethylene glycol dimethyl ether, diethylene glycol diethyl ether, triethylene glycol dimethyl ether, anisole, or t-butyl methyl ether. In some embodiments, the solvent

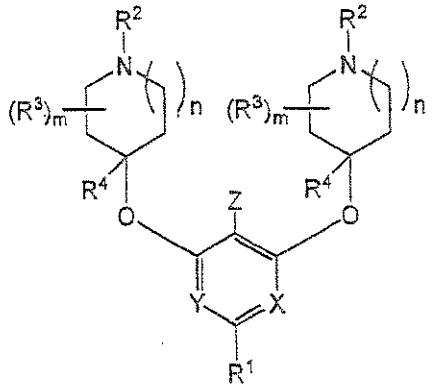
includes tetrahydrofuran. Other suitable solvents include DMF, DMA, NMP, DMSO, acetonitrile and propionitrile.

The adding of base can be optionally carried out at reduced temperature. For example, the addition can be carried out at a temperature below about 25, below about 15, below about 10, below about 5, or below about 0 °C.

In some embodiments, the molar ratio of compound IV to compound V is about 1:1. In further embodiments, the molar ratio of compound IV to compound V to base is about 1:1:1. In some embodiments, the molar ratio of base to compound V is about 1.02:1 to about 0.90:1 or about 1:1 to about 0.96:1.

The compounds of Formulas III, IV, and V can be prepared according to routine methods in the art. Example preparations of these compounds are provided such in U.S. App. Ser. No. 10/888,747, which is incorporated herein by reference in its entirety.

While routine isolation and purification procedures can yield substantially pure preparations (e.g., bulk samples) of the compound of Formula I, impurities which are characteristic of the procedures described herein can occasionally persist. For example, in the preparation of compounds of Formula II, compounds of Formula IIa can optionally be present as byproducts which optionally can be carried over to the preparation of Formula I if the byproduct is present in starting material II.

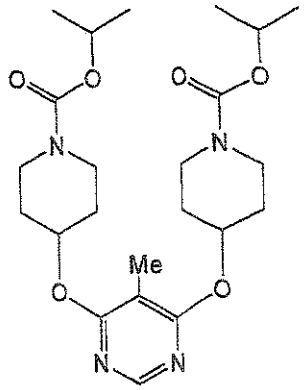


IIa

In some embodiments, bulk samples of Formula II made by the processes described herein can contain a detectable amount of compound of Formula IIa. The amount of compound of Formula IIa in preparations of Formula II can be, for example, less than about 5%, less than about 3%, less than about 2%, less than about 1%, less than about 0.5%, less than about 0.2%, less than about 0.1%, less than about 0.05%, less than about 0.02%, or less than about 0.01% by weight.

In some embodiments, bulk samples of Formula I made by the processes described herein can contain a detectable amount of compound of Formula IIa. The amount of compound of Formula IIa in preparations of Formula I can be, for example, less than about 5%, less than about 3%, less than about 2%, less than about 1%, less than about 0.5%, less than about 0.2%, less than about 0.1%, less than about 0.05%, less than about 0.02%, or less than about 0.01% by weight.

In some embodiments, the byproduct is compound of Formula IIb:



IIb.

The compound of Formula IIa and other byproducts can be detected and quantified by routine methods including, for example, proton nuclear magnetic resonance, high performance liquid chromatography, mass spectrometry, and the like. The amount of compound of Formula IIa and other byproducts in bulk samples prepared according to the processes herein can be reduced or substantially eliminated by routine methods such as recrystallization or chromatography techniques.

The term "bulk sample" is used herein consistently with its meaning in the art which, for example, refers to an amount of product prepared according to a given process or procedure. Bulk samples can be any size, but typically range from 1 mg on upward to several thousands of kilograms or more.

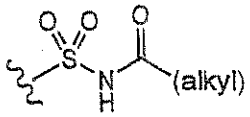
It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable subcombination.

The term "C_{i-j}" denotes the number of carbon atoms in the moiety to which the term refers. For example, C_{1-8} alkyl (where i is 1 and j is 8) refers to an alkyl group having 1 (C_1), 2 (C_2), 3 (C_3), 4 (C_4), 5 (C_5), 6 (C_6), 7 (C_7), or 8 (C_8) carbon atoms.

The term "acyl" denotes a carbonyl (C=O) substituted by an alkyl radical, wherein the definition of alkyl has the same definition as described herein. Some examples include, but are not limited to, acetyl, propionyl, n-butanoyl, *iso*-butanoyl, sec-butanoyl, t-butanoyl (i.e., pivaloyl), pentanoyl and the like.

The term "acyloxy" denotes –O- substituted by an acyl radical, wherein acyl has the same definition has described herein. Some examples include but are not limited to acetyloxy, propionyloxy, butanoyloxy, *iso*-butanoyloxy, sec-butanoyloxy, t-butanoyloxy and the like.

The term "acylsulfonamide" refers to a sulfonamide substituted by acyl on the sulfonamide N-atom, wherein the definitions for acyl and sulfonamide have the same meaning as described herein, and an acylsulfonamide can be represented by the following formula:



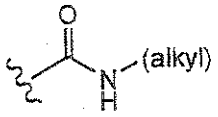
Some embodiments of the present invention include C_{1-5} acylsulfonamide, C_{1-4} acylsulfonamide, C_{1-3} acylsulfonamide, or C_{1-2} acylsulfonamide. Examples of acylsulfonamides include, but are not limited to, acetylsulfamoyl [$-S(=O)_2NHC(=O)Me$], propionylsulfamoyl [$-S(=O)_2NHC(=O)Et$], isobutyrylsulfamoyl, butyrylsulfamoyl, 2-methyl-butyrylsulfamoyl, 3-methyl-butyrylsulfamoyl, 2,2-dimethyl-propionylsulfamoyl, pentanoylsulfamoyl, 2-methyl-pentanoylsulfamoyl, 3-methyl-pentanoylsulfamoyl, 4-methyl-pentanoylsulfamoyl, and the like.

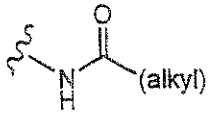
The term "alkenyl" denotes an alkyl radical containing having at least one carbon-carbon double bond. In some embodiments, the alkenyl group is C_{2-6} alkenyl, C_{2-5} alkenyl, C_{2-4} alkenyl, C_{2-3} alkenyl or C_2 alkenyl. Both *E* and *Z* isomers are embraced by the term "alkenyl." Furthermore, the term "alkenyl" includes groups with 1, 2, 3, 4 or more double bonds. Accordingly, if more than one double bond is present then the bonds may be all *E* or *Z* or a mixtures of *E* and *Z*. Examples of an alkenyl include vinyl, allyl, 2-butenyl, 3-butenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexanyl, 2,4-hexadienyl and the like.

The term "alkoxy" as used herein denotes a radical alkyl, as defined herein, attached directly to an oxygen atom. Examples include methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, t-butoxy, iso-butoxy, sec-butoxy and the like.

The term "alkyl" denotes a straight or branched hydrocarbon radical. In some embodiments, the alkyl group contains 1 to 8 carbons, 1 to 7 carbons, 1 to 6 carbons, 1 to 5 carbons, 1 to 4 carbons, 1 to 3 carbons, 1 or 2 carbons. Examples of alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, t-butyl, pentyl, iso-pentyl, t-pentyl, neo-pentyl, 1-methylbutyl [i.e., $-CH(CH_3)CH_2CH_2CH_3$], 2-methylbutyl [i.e., $-CH_2CH(CH_3)CH_2CH_3$], n-hexyl and the like.

The term "alkylcarboxamido" or "alkylcarboxamide" denotes a single alkyl group attached to the nitrogen or carbon of an amide group, wherein alkyl has the same definition as found herein. The alkylcarboxamide may be represented by the following:



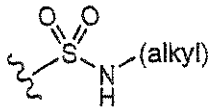


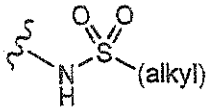
Examples include, but are not limited to, *N*-methylcarboxamide, *N*-ethylcarboxamide, *N*-n-propylcarboxamide, *N*-iso-propylcarboxamide, *N*-n-butylcarboxamide, *N*-sec-butylcarboxamide, *N*-iso-butylcarboxamide, *N*-t-butylcarboxamide and the like.

The term "alkylene" refers to a divalent alkyl group. In some embodiments, alkylene refers to, for example, $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, and the like. In some embodiments, alkylene refers to -CH-, $-CHCH_2-$, $-CHCH_2CH_2-$, and the like wherein these examples relate generally to "A".

The term "alkylsulfinyl" denotes -S(O)- substituted by alkyl, wherein the alkyl radical has the same definition as described herein. Examples include, but not limited to, methylsulfinyl, ethylsulfinyl, n-propylsulfinyl, iso-propylsulfinyl, n-butylsulfinyl, sec-butylsulfinyl, iso-butylsulfinyl, t-butyl, and the like.

The term "alkylsulfonamide" refers to the groups



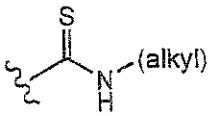


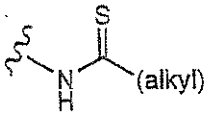
wherein alkyl has the same definition as described herein.

The term "alkylsulfonyl" denotes -$S(O)_2$- substituted by alkyl, wherein the alkyl radical has the same definition as described herein. Examples include, but are not limited to, methylsulfonyl, ethylsulfonyl, n-propylsulfonyl, iso-propylsulfonyl, n-butylsulfonyl, sec-butylsulfonyl, iso-butylsulfonyl, t-butyl, and the like.

The term "alkylthio" denotes -S- substituted by alkyl, wherein the alkyl radical has the same definition as described herein. Examples include, but not limited to, methylsulfanyl (i.e., CH_3S-), ethylsulfanyl, n-propylsulfanyl, iso-propylsulfanyl, n-butylsulfanyl, sec-butylsulfanyl, iso-butylsulfanyl, t-butyl, and the like.

The term "alkylthiocarboxamide" denotes a thioamide of the following formulae:





wherein alkyl has the same definition as described herein.

The term "alkylthioureyl" denotes the group of the formula: -NC(S)N- wherein one or both of the nitrogens are substituted with the same or different alkyl groups, and alkyl has the same definition as described herein. Examples of an alkylthioureyl include, but are not limited to, $CH_3NHC(S)NH$-, $NH_2C(S)NCH_3$-, $(CH_3)_2N(S)NH$-, $(CH_3)_2N(S)NH$-, $(CH_3)_2N(S)NCH_3$-, $CH_3CH_2NHC(S)NH$-, $CH_3CH_2NHC(S)NCH_3$-, and the like.

The term "alkylureyl" denotes the group of the formula: -NC(O)N- wherein one are both of the nitrogens are substituted with the same or different alkyl group, wherein alkyl has the same definition as described herein. Examples of an alkylureyl include, but not limited to, $CH_3NHC(O)NH$-, $NH_2C(O)NCH_3$-, $(CH_3)_2N(O)NH$-, $(CH_3)_2N(O)NH$-, $(CH_3)_2N(O)NCH_3$-, $CH_3CH_2NHC(O)NH$-, $CH_3CH_2NHC(O)NCH_3$-, and the like.

The term "alkynyl" denotes an alkyl group having at least one carbon-carbon triple bond. In some embodiments, the alkynyl group has 2 to 8 carbons, 2 to 7 carbons, 2 to 6 carbons, 2 to 5 carbons, 2 to 4 carbons, 2 to 3 carbons, or 2 carbons. Examples of alkynyl groups include, but are not limited to, ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl and the like.

Additionally, an alkynyl group can have 1, 2, 3, 4 or more triple bonds, forming for example, di- and tri-ynes.

The term "amino" denotes the group $-NH_2$.

The term "alkylamino" denotes amino substituted by alkyl, wherein the alkyl radical has the same meaning as described herein. Some examples include, but not limited to, methylamino, ethylamino, n-propylamino, iso-propylamino, n-butylamino, sec-butylamino, iso-butylamino, t-butylamino, and the like.

The term "aryl" denotes monocyclic or polycyclic aromatic hydrocarbons such as, for example, phenyl, naphthyl, anthracenyl, phenanthrenyl, indanyl, indenyl, and the like. In some embodiments, aryl groups have from 6 to about 20 carbon atoms.

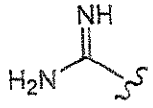
The term "arylalkyl" denotes alkyl substituted with an aryl group. Examples of an "arylalkyl" include benzyl, phenethylene and the like.

The term "arylcarboxamido" denotes an amide group substituted by an aryl group on the N-atom, wherein aryl has the same definition as found herein. An example is *N*-phenylcarboxamide.

The term "arylureyl" denotes the group -NC(O)N- where one of the nitrogens are substituted with an aryl.

The term "benzyl" denotes the group $-CH_2C_6H_5$.

The term "carbamimidoyl" refers to a group of the following chemical formula:



;

and in some embodiments, one or both hydrogens are replaced with another group. For example, one hydrogen can be replaced with a hydroxyl group to give a *N*-hydroxycarbamimidoyl group, or one hydrogen can be replaced with an alkyl group to give *N*-methylcarbamimidoyl, *N*-ethylcarbamimidoyl, *N*-propylcarbamimidoyl, *N*-butylcarbamimidoyl, and the like.

The term "carboalkoxy" refers to an alkyl ester of a carboxylic acid, wherein the alkyl group is as defined herein. Examples include, but not limited to, carbomethoxy, carboethoxy, carbopropoxy, carboisopropoxy, carbobutoxy, carbo-sec-butoxy, carbo-iso-butoxy, carbo-t-butoxy, carbo-n-pentoxy, carbo-iso-pentoxy, carbo-t-pentoxy, carbo-neo-pentoxy, carbo-n-hexyloxy, and the like.

The term "carboxamide" refers to the group $-CONH_2$.

The term "carboxy" or "carboxyl" denotes the group $-CO_2H$; also referred to as a carboxylic acid group.

The term "cyano" denotes the group –CN.

The term "cycloalkenyl" denotes a non-aromatic ring radical containing 3 to 6 ring carbons and at least one double bond; some embodiments contain 3 to 5 carbons; some embodiments contain 3 to 4 carbons. Examples include cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclopentenyl, cyclohexenyl, and the like.

The term "cycloalkyl" denotes a saturated, cyclic hydrocarbon containing, for example, 3 to 14, 1 to 10, 3 to 8, 3 to 7, 3 to 6, 3 to 5, or 3 to 4 carbons. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclopenyl, cyclohexyl, cycloheptyl and the like.

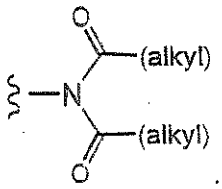
The term "cycloalkylalkyl" denotes an alkyl group substituted by a cycloalkyl group.

The term "cycloalkylene" refers to a divalent cycloalkyl radical. In some embodiments, the two bonding groups are on the same carbon, for example:



In some embodiments, the two bonding groups are on different carbons.

The term "diacylamino" denotes an amino group substituted with two acyl groups, wherein the acyl groups may be the same or different, such as:



Examples of diacylamino groups include, but limited to, diacetylamino, dipropionylamino, acetylpropionylamino and the like.

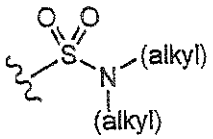
The term "dialkylamino" denotes an amino group substituted with two of the same or different alkyl radicals, wherein alkyl has the same definition as described herein. Some examples include, but not limited to, dimethylamino, methylethylamino, diethylamino, methylpropylamino, methylisopropylamino, ethylpropylamino, ethylisopropylamino, dipropylamino, propylisopropylamino and the like.

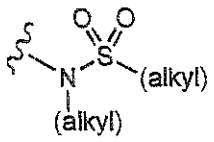
The term "dialkylcarboxamido" or "dialkylcarboxamide" denotes an amide substituted by two alkyl radicals, that are the same or different. Dialkylcarboxamidos can be represented by the following groups:



Examples of dialkylcarboxamides include, but are not limited to, *N*,*N*-dimethylcarboxamide, *N*-methyl-*N*-ethylcarboxamide, *N*,*N*-diethylcarboxamide, *N*-methyl-*N*-isopropylcarboxamide, and the like.

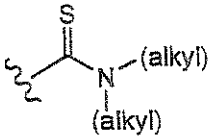
The term "dialkylsulfonamide" refers to one of the following groups shown below:

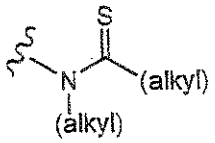




Examples include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, and the like.

The term "dialkylthiocarboxamido" or "dialkylthiocarboxamide" denotes a thioamide substituted by two alkyl radicals, that are the same or different, wherein alkyl has the same definition as described herein. Example dialkylthiocarboxamido groups can be represented by the following groups:





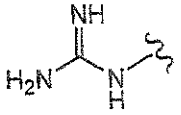
Examples of dialkylthiocarboxamides include, but are not limited to, *N*,*N*-dimethylthiocarboxamide, *N*-methyl-*N*-ethylthiocarboxamide and the like.

The term "dialkylsulfonylamino" refers to an amino group substituted with two alkylsulfonyl groups as defined herein.

The term "ethynylene" refers to –C≡C-.

The term "formyl" refers to the group –CHO.

The term "guanidine" refers to a group of the following chemical formula:



The term "haloalkoxy" denotes –O- substituted by haloalkyl. Examples include, but are not limited to, difluoromethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy, pentafluoroethoxy, and the like.

The term "haloalkyl" denotes an alkyl group, as defined herein, wherein the alkyl is substituted with one or more halogens. Examples of haloalkyl groups include, but are not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, chlorodifluoromethyl, 2,2,2-trifluoroethyl, pentafluoroethyl and the like.

The term "haloalkylcarboxamide" denotes an alkylcarboxamide group, defined herein, substituted with one or more halogens.

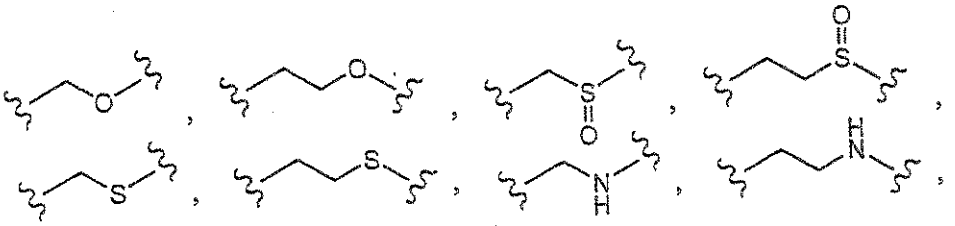
The term "haloalkylsulfinyl" denotes sulfoxide –S(O)- substituted by a haloalkyl radical, wherein the haloalkyl radical has the same definition as described herein. Examples include, but are not limited to, trifluoromethylsulfinyl, 2,2,2-trifluoroethylsulfinyl, 2,2-difluoroethylsulfinyl and the like.

The term "haloalkylsulfonyl" denotes -$S(O)_2$- substituted by a haloalkyl radical, wherein haloalkyl has the same definition as described herein. Examples include, but not limited to, trifluoromethylsulfonyl, 2,2,2-trifluoroethylsulfonyl, 2,2-difluoroethylsulfonyl and the like.

The term "haloalkylthio" denotes –S- substituted by a haloalkyl radical, wherein the haloalkyl has the same meaning as described herein. Examples include, but not limited to, trifluoromethylthio (i.e., CF_3S-), 1,1-difluoroethylthio, 2,2,2-trifluoroethylthio and the like.

The term "halogen" or "halo" denotes to a fluoro, chloro, bromo or iodo group.

The term "heteroalkylene" refers to alkylene interrupted or appended by a heteroatom-containing group selected from O, S, S(O), $S(O)_2$ and NH. Some examples include, but not limited to, the groups of the following formulae:



and the like.

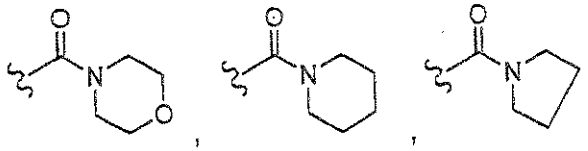
The term "heteroaryl" denotes an aromatic ring system that may be a single ring, two fused rings or three fused rings wherein at least one ring carbon is a heteroatom selected from, but not limited to, the group consisting of O, S and N, wherein the N can be optionally substituted with H, O, C_{1-4} acyl or C_{1-4} alkyl. Examples of heteroaryl groups include, but are not limited to, pyridyl, benzofuranyl, pyrazinyl, pyridazinyl, pyrimidinyl, triazinyl, quinoline, benzoxazole, benzothiazole, 1*H*-benzimidazole, isoquinoline, quinazoline, quinoxaline and the like. In some embodiments, the heteroatom is O, S, NH, examples include, but not limited to, pyrrole, indole, and the like.

The term "heteroarylalkyl" denotes an alkyl group substituted by a heteroaryl group.

The term "heterocyclic" denotes a non-aromatic, cyclic hydrocarbon (i.e., cycloalkyl or cycloalkenyl as defined herein) wherein one or more (e.g., one, two or three) ring carbons are replaced by a heteroatom selected from, but not limited to, the group consisting of O, S, N, wherein the N can be optionally substituted with H, O, C_{1-4} acyl or C_{1-4} alkyl, and ring carbon atoms are optionally substituted with oxo or a sulfido thus forming a carbonyl or thiocarbonyl group. The heterocyclic group can be a 3-, 4-, 5-, 6- or 7-membered ring. Examples of a heterocyclic group include but not limited to aziridin-1-yl, aziridin-2-yl, azetidin-1-yl, azetidin-2-yl, azetidin-3-yl, piperidin-1-yl, piperidin-4-yl, morpholin-4-yl, piperzin-1-yl, piperzin-4-yl, pyrrolidin-1-yl, pyrrolidin-3-yl, [1,3]-dioxolan-2-yl and the like.

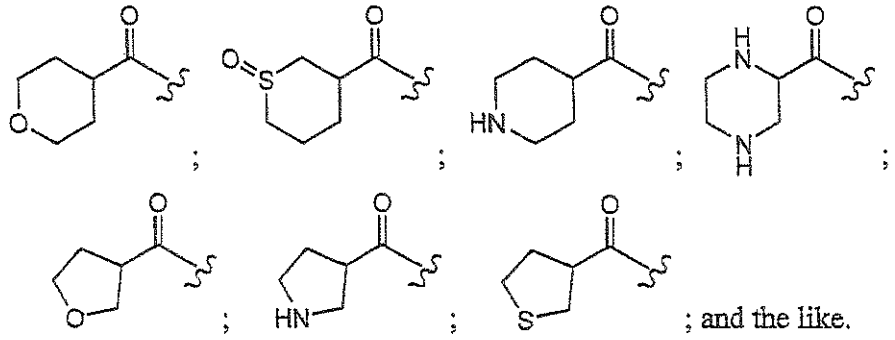
The term, "heterocyclicalkyl" denotes an alkyl group substituted by a heterocyclic group.

The term "heterocyclic-carbonyl" denotes a carbonyl group substituted by a heterocyclic group, as defined herein. In some embodiments, a ring nitrogen of the heterocyclic group is bonded to the carbonyl group forming an amide. Examples include, but are not limited to,

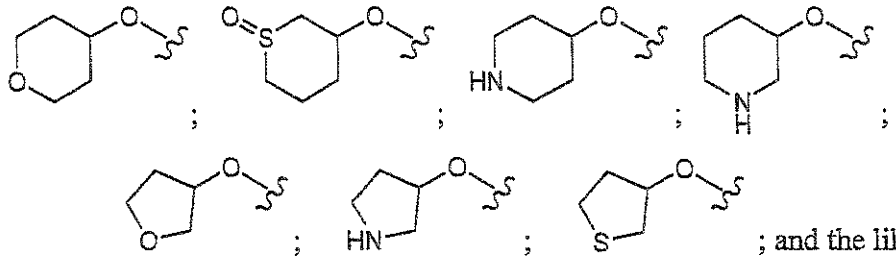


and the like.

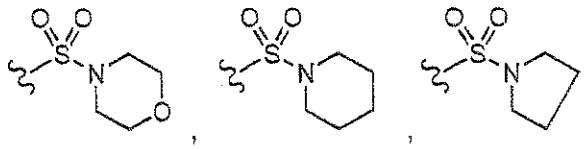
In some embodiments, a ring carbon is bonded to the carbonyl group forming a ketone group. Examples include, but are not limited to,



The term "heterocyclic-oxy" refers –O- substituted by a heterocyclic group, as defined herein. Examples include the following:



The term "heterocyclicsulfonyl" denotes SO_2 substituted with a heterocyclic group having a ring nitrogen, where the ring nitrogen is bonded directly to an SO_2 group forming an sulfonamide. Examples include, but not limited to,

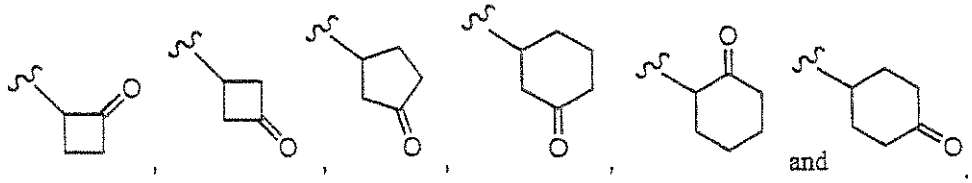


The term "hydroxyl" refers to the group -OH.

The term "hydroxylamino" refers to the group -NHOH.

The term "nitro" refers to the group $-NO_2$.

The term "oxo-cycloalkyl" refers to cycloalkyl, as defined herein, wherein one of the ring carbons is replaced with a carbonyl. Examples of oxo-cycloalkyl include, but are not limited to, 2-oxo-cyclobutyl, 3-oxo-cyclobutyl, 3-oxo-cyclopentyl, 4-oxo-cyclohexyl, and the like and represented by the following structures respectively:

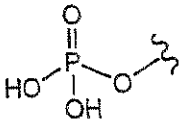


The term "perfluoroalkyl" denotes the group of the formula $-C_nF_{2n+1}$. Examples of perfluoroalkyls include CF_3, CF_2CF_3, $CF_2CF_2CF_3$, $CF(CF_3)_2$, $CF_2CF_2CF_2CF_3$, $CF_2CF(CF_3)_2$, $CF(CF_3)CF_2CF_3$ and the like.

The term "phenoxy" refers to the group C_6H_5O-.

The term "phenyl" refers to the group C_6H_5-.

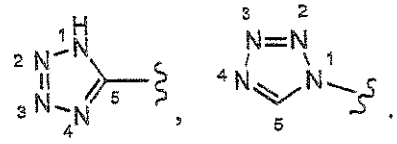
The term "phosphonooxy" refers to a group with the following chemical structure:



The term "sulfonamide" refers to the group $-SO_2NH_2$.

The term "sulfonic acid" refers to the group $-SO_3H$.

The term "tetrazolyl" refers to the five membered heteroaryl of the following formulae:



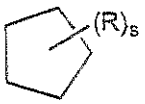
In some embodiments, the tetrazolyl group is further substituted at either the 1 or 5 position, resepectively, with a group selected from the group consisting of alkyl, haloalkyl and alkoxy.

The term "thiol" denotes the group –SH.

As used herein, the term "reacting" is used as known in the art and generally refers to the bringing together of chemical reagents in such a manner so as to allow their interaction at the molecular level to achieve a chemical or physical transformation of at least one chemical reagent.

As used herein, the term "substituted" refers to the replacement of a hydrogen moiety with a non-hydrogen moiety in a molecule or group.

For compounds in which a variable appears more than once, each variable can be a different moiety selected from the Markush group defining the variable. For example, where a structure is described having two R groups that are simultaneously present on the same compound; the two R groups can represent different moieties selected from the Markush group defined for R. In another example, when an optionally multiple substituent is designated in the form:



then it is understood that substituent R can occur *s* number of times on the ring, and R can be a different moiety at each occurrence.

As used herein, the term "leaving group" refers to a moiety that can be displaced by another moiety, such as by nucleophilic attack, during a chemical reaction. Leaving groups are well known in the art and include, for example, halogen including chloro, bromo, iodo, and the like.

The processes described herein can be monitored according to any suitable method known in the art. For example, product formation can be monitored by spectroscopic means, such as nuclear magnetic resonance spectroscopy (e.g., ^1H or ^{13}C) infrared spectroscopy, spectrophotometry (e.g.,

UV-visible), or mass spectrometry, or by chromatography such as high performance liquid chromatograpy (HPLC) or thin layer chromatography.

In some embodiments, preparation of compounds can involve the protection and deprotection of various chemical groups. The need for protection and deprotection, and the selection of appropriate protecting groups can be readily determined by one skilled in the art. The chemistry of protecting groups can be found, for example, in Greene and Wuts, et al., *Protective Groups in Organic Synthesis*, 3rd. Ed., Wiley & Sons, 1999, which is incorporated herein by reference in its entirety.

The reactions of the processes described herein can be carried out in suitable solvents which can be readily selected by one of skill in the art of organic synthesis. Suitable solvents can be substantially nonreactive with the starting materials (reactants), the intermediates, or products at the temperatures at which the reactions are carried out, e.g., temperatures which can range from the solvent's freezing temperature to the solvent's boiling temperature. A given reaction can be carried out in one solvent or a mixture of more than one solvent. Depending on the particular reaction step, suitable solvents for a particular reaction step can be selected. In some embodiments, reactions can be carried out in the absence of solvent, such as when at least one of the reagents is a liquid or gas.

Suitable solvents can include halogenated solvents such as carbon tetrachloride, bromodichloromethane, dibromochloromethane, bromoform, chloroform, bromochloromethane, dibromomethane, butyl chloride, dichloromethane, tetrachloroethylene, trichloroethylene, 1,1,1-trichloroethane, 1,1,2-trichloroethane, 1,1-dichloroethane, 2-chloropropane, hexafluorobenzene, 1,2,4-trichlorobenzene, o-dichlorobenzene, chlorobenzene, fluorobenzene, fluorotrichloromethane, chlorotrifluoromethane, bromotrifluoromethane, carbon tetrafluoride, dichlorofluoromethane, chlorodifluoromethane, trifluoromethane, 1,2-dichlorotetrafluorethane and hexafluoroethane.

Suitable ether solvents include: dimethoxymethane, tetrahydrofuran, 1,3-dioxane, 1,4-dioxane, furan, diethyl ether, ethylene glycol dimethyl ether, ethylene glycol diethyl ether, diethylene glycol dimethyl ether, diethylene glycol diethyl ether, triethylene glycol dimethyl ether, anisole, or t-butyl methyl ether.

Suitable protic solvents can include, by way of example and without limitation, water, methanol, ethanol, 2-nitroethanol, 2-fluoroethanol, 2,2,2-trifluoroethanol, ethylene glycol, 1-propanol, 2-propanol, 2-methoxyethanol, 1-butanol, 2-butanol, i-butyl alcohol, t-butyl alcohol, 2-ethoxyethanol, diethylene glycol, 1-, 2-, or 3- pentanol, neo-pentyl alcohol, t-pentyl alcohol, diethylene glycol monomethyl ether, diethylene glycol monoethyl ether, cyclohexanol, benzyl alcohol, phenol, or glycerol.

Suitable aprotic solvents can include, by way of example and without limitation, tetrahydrofuran (THF), dimethylformamide (DMF), dimethylacetamide (DMAC), 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU), 1,3-dimethyl-2-imidazolidinone (DMI), N-methylpyrrolidinone (NMP), formamide, N-methylacetamide, N-methylformamide, acetonitrile,

dimethyl sulfoxide, propionitrile, ethyl formate, methyl acetate, hexachloroacetone, acetone, ethyl methyl ketone, ethyl acetate, sulfolane, N,N-dimethylpropionamide, tetramethylurea, nitromethane, nitrobenzene, or hexamethylphosphoramide.

Suitable hydrocarbon solvents include benzene, cyclohexane, pentane, hexane, toluene, cycloheptane, methylcyclohexane, heptane, ethylbenzene, m-, o-, or p-xylene, octane, indane, nonane, or naphthalene.

Supercritical carbon dioxide can also be used as a solvent.

The reactions of the processes described herein can be carried out at appropriate temperatures which can be readily determined by the skilled artisan. Reaction temperatures will depend on, for example, the melting and boiling points of the reagents and solvent, if present; the thermodynamics of the reaction (e.g., vigorously exothermic reactions may need to be carried out at reduced temperatures); and the kinetics of the reaction (e.g., a high activation energy barrier may need elevated temperatures). "Elevated temperature" refers to temperatures above room temperature (about 25 °C) and "reduced temperature" refers to temperatures below room temperature.

The reactions of the processes described herein can be carried out in air or under an inert atomosphere. Typically, reactions containing reagents or products that are substantially reactive with air can be carried out using air-sensitive synthetic techniques that are well known to the skilled artisan.

In some embodiments, preparation of compounds can involve the addition of acids or bases to effect, for example, catalysis of a desired reaction or formation of salt forms such as acid addition salts.

Example acids can be inorganic or organic acids. Inorganic acids include hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, and nitric acid. Organic acids include formic acid, acetic acid, propionic acid, butanoic acid, methanesulfonic acid, p-toluene sulfonic acid, benzenesulfonic acid, trifluoroacetic acid, propiolic acid, butyric acid, 2-butynoic acid, vinyl acetic acid, pentanoic acid, hexanoic acid, heptanoic acid, octanoic acid, nonanoic acid and decanoic acid.

Example bases include lithium hydroxide, sodium hydroxide, potassium hydroxide, lithium carbonate, sodium carbonate, and potassium carbonate. Some example strong bases include, but are not limited to, hydroxide, alkoxides, metal amides, metal hydrides, metal dialkylamides and arylamines, wherein; alkoxides include lithium, sodium and potassium salts of methyl, ethyl and t-butyl oxides; metal amides include sodium amide, potassium amide and lithium amide; metal hydrides include sodium hydride, potassium hydride and lithium hydride; and metal dialkylamides include sodium and potassium salts of methyl, ethyl, n-propyl, i-propyl, n-butyl, t-butyl, trimethylsilyl and cyclohexyl substituted amides.

The compounds described herein can be asymmetric (e.g., having one or more stereocenters). All stereoisomers, such as enantiomers and diastereomers, are intended unless otherwise indicated. Compounds of the present invention that contain asymmetrically substituted carbon atoms can be

isolated in optically active or racemic forms. Methods on how to prepare optically active forms from optically active starting materials are known in the art, such as by resolution of racemic mixtures or by stereoselective synthesis.

The processes described herein can be stereoselective such that any given reaction starting with one or more chiral reagents enriched in one stereoisomer forms a product that is also enriched in one stereoisomer. The reaction can be conducted such that the product of the reaction substantially retains one or more chiral centers present in the starting materials. The reaction can also be conducted such that the product of the reaction contains a chiral center that is substantially inverted relative to a corresponding chiral center present in the starting materials.

Resolution of racemic mixtures of compounds can be carried out by any of numerous methods known in the art. An example method includes fractional recrystallizaion using a "chiral resolving acid" which is an optically active, salt-forming organic acid. Suitable resolving agents for fractional recrystallization methods are, for example, optically active acids, such as the D and L forms of tartaric acid, diacetyltartaric acid, dibenzoyltartaric acid, mandelic acid, malic acid, lactic acid or the various optically active camphorsulfonic acids such as α-camphorsulfonic acid. Other resolving agents suitable for fractional crystallization methods include stereoisomerically pure forms of α-methylbenzylamine (e.g., *S* and *R* forms, or diastereomerically pure forms), 2-phenylglycinol, norephedrine, ephedrine, N-methylephedrine, cyclohexylethylamine, 1,2-diaminocyclohexane, and the like.

Resolution of racemic mixtures can also be carried out by elution on a column packed with an optically active resolving agent (e.g., dinitrobenzoylphenylglycine). Suitable elution solvent composition can be determined by one skilled in the art.

Compounds of the invention can also include all isotopes of atoms occurring in the intermediates or final compounds. Isotopes include those atoms having the same atomic number but different mass numbers. For example, isotopes of hydrogen include tritium and deuterium.

Compounds of the invention can also include tautomeric forms, such as keto-enol tautomers. Tautomeric forms can be in equilibrium or sterically locked into one form by appropriate substitution.

The present invention also includes salt forms of the compounds described herein. Examples of salts (or salt forms) include, but are not limited to, mineral or organic acid salts of basic residues such as amines, alkali or organic salts of acidic residues such as carboxylic acids, and the like. Generally, the salt forms can be prepared by reacting the free base or acid with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid or base in a suitable solvent or various combinations of solvents. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, Pa., 1985, p. 1418, the disclosure of which is hereby incorporated by reference in its entirety.

Upon carrying out preparation of compounds according to the processes described herein, the usual isolation and purification operations such as concentration, filtration, extraction, solid-phase

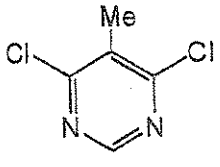
extraction, recrystallization, chromatography, and the like may be used, to isolate the desired products.

The invention will be described in greater detail by way of specific examples. The following examples are offered for illustrative purposes, and are not intended to limit the invention in any manner. Those of skill in the art will readily recognize a variety of noncritical parameters which can be changed or modified to yield essentially the same results.

EXAMPLES

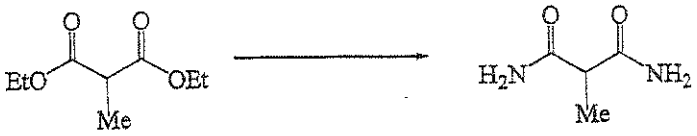
Example 1

Preparation of 4,6-Dichloro-5-Methylpyrimidine Intermediate (1).



1

Step 1.



A solution of diethyl-methylmalonate (0.11 mol) in methanol (100 mL) was added to a saturated solution of ammonia in methanol (7N, 200mL) containing sodium (0.2g, 0.08 eq) at 0°C. The mixture was allowed to stand in a stoppered flask at room temperature 2-3 days. The separated diamide was collected as a white solid by filtration, washed by methanol and dried.

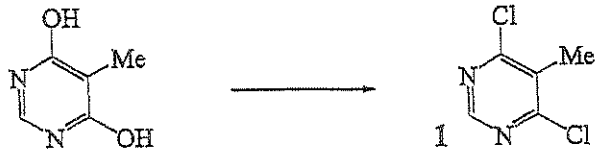
Step 2.



To a solution of Na (1.03 mol, 1.2 eq) in ethanol (2 L) was added diamide from Step 1 (0.86mol, 1 eq) as a solid. The mixture was heated to reflux and formamide (3.4 mol, 4 eq) was slowly added, the resulting mixture was refluxed for an additional 3h. The desired compound was filtered at room temperature as a white solid (as a sodium salt), washed by ethanol and dried.

The above solid was dissolved in water, which was acidified to pH=5 using concentrated solution of HCl (12 N). The mixture was stirred at 5 °C for 30 min. The white solid was filtered and dried under vacuum (60% yield).

Step 3.



1

To a mixture of pyrimidine derivative from Step 2 (0.38 mol, 1 eq) in $POCl_3$ (1.9 mol, 174 mL) was slowly added DMF (exothermic reaction, 0.152 mol, 11.7 mL). The resulting mixture was heated to reflux for 3 h, cooled to room temperature and poured into ice/water. The resulting white solid was filtered, washed with water and dried under vacuum (90% yield) to give 4,6-dichloro-5-methylpyrimidine (1).

Example 2

Preparation of 4-Hydroxy-Piperidine-1-Carboxylic Acid Isopropyl Ester Intermediate (2)

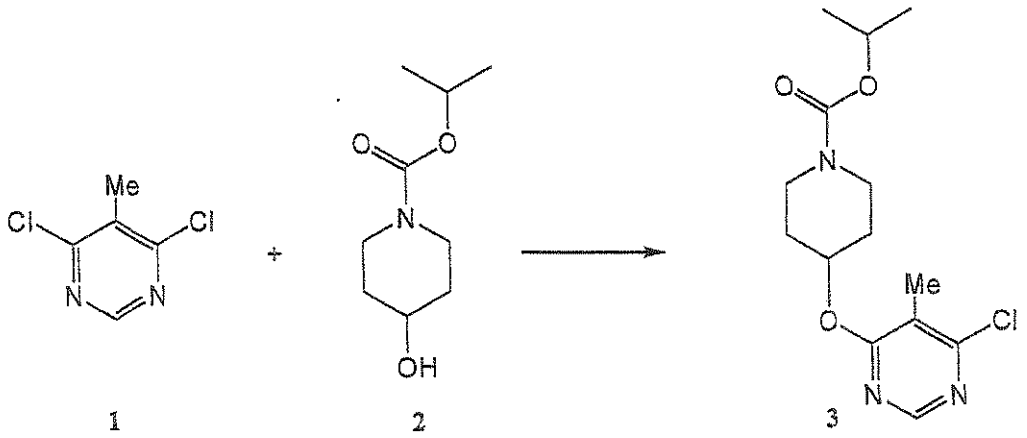


2

To a stirred mixture of 4-hydroxypiperidine (53.8 g, 1.000 eq), triethylamine (71.8 g, 1.334 equivalents), and ethyl acetate (498.8 g) was added neat isopropyl chloroformate (78.0 g, 1.1966 equivalents) at a rate sufficiently slow to maintain the reaction mixture temperature at 10° – 17 °C with reactor jacket cooling. After the addition had been completed, the reaction mixture was stirred at 20° C for 18 hours. Then water (100 g) was added, and the resulting mixture was stirred for 15 minutes before the phases were separated. The organic phase was washed with two 100-gram-portions of 20 wt% aqueous NaCl by stirring for 15 min at 150 rpm before separating the aqueous wash. After a final wash with water (100 g), the organic phase was concentrated by distillation on a rotary evaporator at reduced pressure to provide product (2) (91.1 g, 92.0 % yield) as light amber oil of 96.8 % purity by GC. Distillation of this crude product at 117-120° C, 0.3-1.0 torr gave a 95.7 % recovery of product (2) as a colorless oil collected at 112° -119° C.

Example 3

Preparation of 4-(6-chloro-5-methyl-pyrimidin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester intermediate (3)

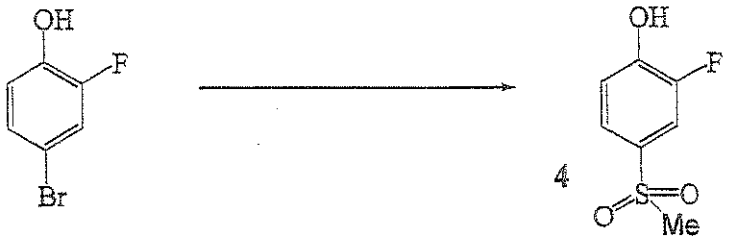


1 2 3

4,6-Dichloro-5-methylpyrimidine (1) (2.4235 Kg, 1.000 equivalents) and 4-hydroxypiperidine-1-carboxylic acid isopropyl ester (2) (2.8182 Kg, 1.012 equivalents) were dissolved in tetrahydrofuran (THF, 25.0028 Kg), and the resulting solution was cooled to -15 to -10° C. To the cold solution, potassium-tert-butoxide in tetrahydrofuran (1 M, 12.6051 Kg, 0.9399 equivalents) was added at a rate sufficiently slow to maintain the reaction mixture below 0° C with reactor jacket cooling. The reaction mixture was then stirred at about -5° C for about 2 hours before an additional portion of potassium-tert-butoxide in tetrahydrofuran (1 M, 0.5692 Kg, 0.0424 equivalents) was added to achieve > 97% conversion of the pyrimidine after an additional hour of stirring at about -5° C. Most of the solvent was then removed by distillation at 30-65° C, ≤80 torr. Addition of water (19.9681 Kg) to the evaporation residue precipitated the product. Distillative removal of THF was then completed at 30-65° C, ≤80 torr, and the resulting stirred slurry was cooled to 0° C for an hour. The solids were then collected by suction filtration, washed with water (8.011 Kg, 4° C), and vacuum dried to constant weight at 50° C, ≤40 torr to provide product (3) (4.491 Kg, 96.3% yield).

Example 4

Preparation of 2-fluoro-4-methanesulfonyl-phenol intermediate (4)



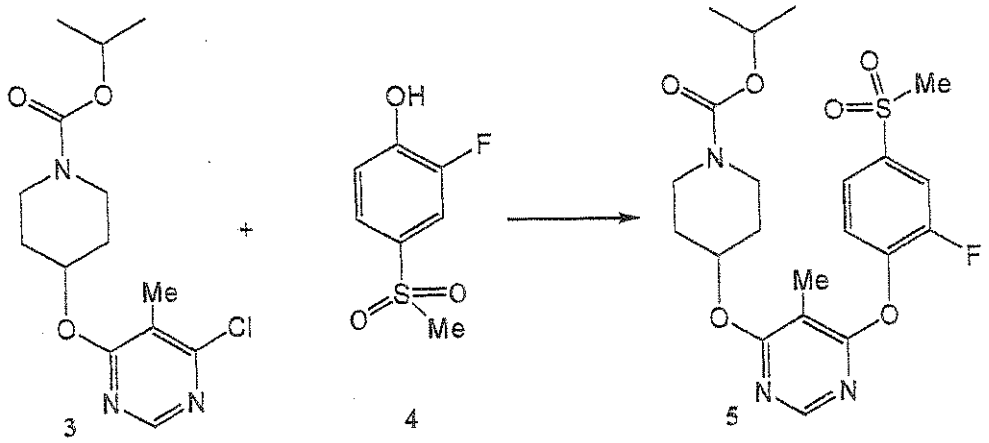
4

A stirred mixture of sodium methane sulfinic acid (51.0 g, 4.009 equivalents), 4-bromo-2-fluorophenol (23.8 g, 1.000 equivalent), copper(I) trifluoromethanesulfonate benzene complex (6.28 g, 0.1001 equivalents), N,N'-dimethylethylenediamine (DMEDA, 2.2 g, 0.2003 equivalents), and dimethylsulfoxide (DMSO, 104 g) was heated under nitrogen at 130° -135° C for 18 hours. Substantially all of the DMSO solvent was then removed from the reaction mixture by rotary

evaporation at 1 torr with a 120° C oil bath. To the brown oily distillation residue were added ethyl acetate (90 g) and water (100 g). After the resulting mixture had been heated and agitated to facilitate dissolution of the reaction mixture in the two liquid phases, it was filtered through a coarse sintered glass filter funnel containing a Whatman filter paper disc and 30 g of Celite. Addition of concentrated aqueous HCl (20 g) to the filtrate lowered the pH of the aqueous phase to less than 3. The phases were separated, and the aqueous phase was extracted two more times with ethyl acetate (90 g each). The combined organic phases were extracted with three 100-gram-portions of 1 M aqueous NaOH to extract the sodium salt of the phenoxide product into the aqueous phase. The aqueous phases were combined, acidified with cooling and concentrated aqueous HCl (40 g) to a pH less than 3, and then extracted with four 90-gram-portions of ethyl acetate to return the product as the free phenol to the organic phase. The organic phases were combined, dried over magnesium sulfate (15 grams), filtered, and concentrated by rotary evaporation at reduced pressure to provide product (4) (16.6 g, 70% yield) as a clear orange to brown oil, which solidified on standing.

Example 5

Preparation of 4-[6-(2-fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (5)

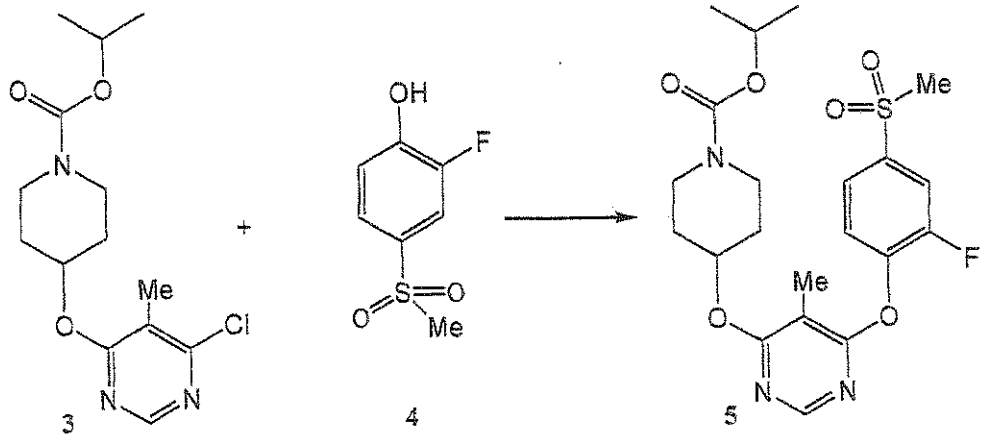


2-Fluoro-4-methanesulfonylphenol (4) (1.9863 Kg, 1.000 equivalent) and 4-(6'-chloro-5'-methylpyrimidin-4'-yloxypiperidine)-1-carboxylic acid isopropyl ester (3) (3.3656 Kg, 1.027 equivalents) were dissolved in dimethylsulfoxide (DMSO, 7.0160 Kg). To the resulting solution, tetrabutylammonium iodide promoter (2.5243 Kg, 0.6544 equivalents) and potassium carbonate (1.7422 Kg, 1.207 equivalents) were added. The reaction mixture was then stirred and heated at 130°-135° C internal temperature for about 24 hours, at which point conversion of phenol (4) to product (5) was >93%. The reaction mixture was then cooled to 50°-60° C and, with the assistance of additional DMSO (0.5050 Kg), added to water (36.1206 Kg) maintained at 25°-35° C throughout the addition. After the resulting slurry had been stirred at about 20° C for several hours, the precipitated solids were filtered, washed with water (8.1264 Kg, 20° C), and recrystallized from isopropyl alcohol (18.7195 Kg) by dissolution at 80° C and cooling to 2° C. The recrystallization mixture was stirred at 2° C for

two hours and then filtered. The filtered solid product was washed with a 2° C mixture of isopropanol (6.9792 Kg) and water (3.0329 Kg) and then recrystallized a second time from isopropanol (15.8899 Kg, 80° C). After having been cooled to and stirred at 2° C for two hours, the recrystallization mixture was filtered. The filtered solid product was washed with a 2° C mixture of isopropanol (5.8689 Kg) and water (2.590 Kg) and dried to constant weight at 50° C, ≤40 torr to provide product (5) (3.8937 Kg, 79.75% yield).

Example 6:

Preparation of 4-[6-(2-fluoro-4-methanesulfonyl-phenoxy)-5-methyl-pyrimidin-4-yloxy]-piperidine-1-carboxylic acid isopropyl ester (5)



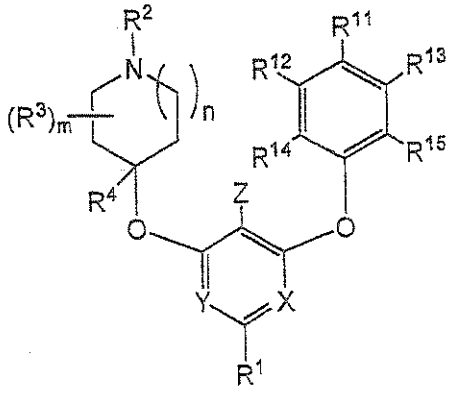
2-Fluoro-4-methanesulfonyl-phenol (4) (1.33g, 7.01mmol) and 4-(6-chloro-5-methyl-pyrimidin-4-yloxy)-piperidine-1-carboxylic acid isopropyl ester (3) (2.00g, 6.39mmol) were dissolved in DMSO (10mL). To the resulting solution, potassium iodide (0.21g, 1.27mmol) and potassium carbonate (0.97g, 7.01mmol) were added. The resulting mixture was heated to 130°C and stirred overnight. The crude was cooled to room temperature, poured into ice water (150 mL) and stirred for 2h. The precipitate was filtered, washed twice with water (2x10mL) and dried at 60°C in a vacuum oven (2.74g, 91%). The desired product was recrystallized from isopropanol (10mL) to afford 2.39g of the title compound (80%).

Various modifications of the invention, in addition to those described herein, will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims. Each reference cited in the present application is incorporated herein by reference in its entirety.

CLAIMS

What is claimed is:

1. A process for preparing a compound of Formula I:



I

wherein:

X is N or CR^7;

Y is N or CR^8;

Z is C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylthioureyl, C_{1-4} alkylureyl, amino, C_{1-2} alkylamino, C_{2-4} dialkylamino, carbamimidoyl, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-7} cycloalkyl, C_{4-8} diacylamino, C_{2-6} dialkylcarboxamide, C_{2-6} dialkylthiocarboxamide, C_{2-6} dialkylsulfonamide, C_{2-6} dialkylsulfonylamino, formyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylcarboxamide, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, halogen, aryl, heteroaryl, heterocycloalkyl, hydroxyl, hydroxycarbamimidoyl, hydroxylamino, nitro, or tetrazolyl; wherein said C_{1-8} alkyl, C_{3-7} cycloalkyl, and heterocycloalkyl are each optionally substituted with 1, 2, 3 or 4 groups selected from C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-7} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylureyl, amino, C_{1-2} alkylamino, C_{2-4} dialkylamino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, formyl, C_{1-4} haloalkoxy, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, halogen, hydroxyl, hydroxylamino, and nitro;

R^1 is H, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylureyl, amino, C_{1-4} alkylamino, C_{2-8} dialkylamino, carboxamide, cyano, C_{3-7} cycloalkyl, C_{2-6} dialkylcarboxamide, C_{2-6} dialkylsulfonamide, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, or hydroxyl;

R^2 is $-R^{22}$, $-CR^{23}R^{24}C(O)-R^{22}$, $-C(O)CR^{23}R^{24}-R^{22}$, $-C(O)-R^{22}$, $-CR^{23}R^{24}C(O)NR^{25}-R^{22}$, $-NR^{25}C(O)CR^{23}R^{24}-R^{22}$, $-C(O)NR^{23}-R^{22}$, $-NR^{23}C(O)-R^{22}$, $-C(O)O-R^{22}$, $-OC(O)-R^{22}$, $-C(S)-R^{22}$, $-C(S)NR^{23}-R^{22}$, $-NR^{23}C(S)-R^{22}$, $-C(S)O-R^{22}$, $-OC(S)-R^{22}$, $-CR^{23}R^{24}-R^{22}$, or $-S(O)_2-R^{22}$;

R^3 is C_{1-3} alkyl, C_{1-4} alkoxy, carboxy, cyano, C_{1-3} haloalkyl, or halogen;

R^4 is H, C_{1-8} alkyl or C_{3-7} cycloalkyl, wherein said C_{1-8} alkyl is optionally substituted with C_{1-4} alkoxy, C_{3-7} cycloalkyl, or heteroaryl;

R_7 and R_8 are each, independently, H, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylureyl, amino, C_{1-4} alkylamino, C_{2-8} dialkylamino, carboxamide, cyano, C_{3-7} cycloalkyl, C_{2-6} dialkylcarboxamide, C_{2-6} dialkylsulfonamide, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, or hydroxyl;

R^{11} is C_{1-5} acyl, C_{1-6} acylsulfonamide, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-6} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylthioureyl, C_{1-4} alkylureyl, amino, arylsulfonyl, carbamimidoyl, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-7} cycloalkyl, C_{3-7} cycloalkyloxy, C_{2-6} dialkylamino, C_{2-6} dialkylcarboxamide, C_{2-6} dialkylthiocarboxamide, guanidinyl, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, heterocycloalkyl, heterocycloalkyl-oxy, heterocycloalkylsulfonyl, heterocycloalkyl-carbonyl, heteroaryl, heteroarylcarbonyl, hydroxyl, nitro, C_{4-7} oxo-cycloalkyl, phenoxy, phenyl, sulfonamide, sulfonic acid, or thiol; and wherein said C_{1-5} acyl, C_{1-6} acylsulfonamide, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-6} alkylsulfonamide, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, arylsulfonyl, carbamimidoyl, C_{2-6} dialkylamino, heterocycloalkyl, heterocycloalkyl-carbonyl, heteroaryl, phenoxy and phenyl are each optionally substituted with 1 to 5 substituents selected independently from C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-7} alkyl, C_{1-4} alkylamino, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylureyl, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-7} cycloalkyl, C_{3-7} cycloalkyloxy, C_{2-6} dialkylamino, C_{2-6} dialkylcarboxamide, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, heteroaryl, heterocyclic, hydroxyl, nitro, phenyl, and phosphonooxy, wherein said C_{1-7} alkyl and C_{1-4} alkylcarboxamide are each optionally substituted with 1 to 5 substituents selected from C_{1-4} alkoxy and hydroxy;

R^{12}, R^{13}, R^{14}, and R^{15} are each, independently, H, C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylureyl, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-7} cycloalkyl, C_{2-6} dialkylcarboxamide, halogen, C_{1-4}

haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, hydroxyl, or nitro;

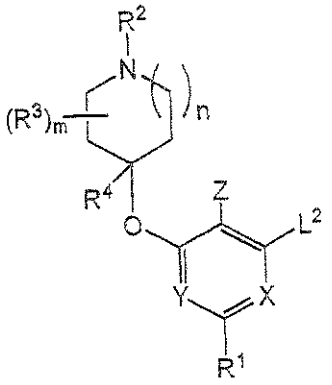
R^{22} is H, C_{1-8} alkyl, C_{3-7} cycloalkyl, phenyl, heteroaryl, or heterocyclic each optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-7} alkyl, C_{1-4} alkylamino, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylthioureyl, C_{1-4} alkylureyl, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-7} cycloalkyl, C_{2-8} dialkylamino, C_{2-6} dialkylcarboxamide, C_{2-6} dialkylthiocarboxamide, C_{2-6} dialkylsulfonamide, C_{1-4} alkylthioureyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkyl, C_{1-4} haloalkylthio, halogen, heteroaryl, heterocyclic, hydroxyl, hydroxylamino, nitro, phenyl, phenoxy, and sulfonic acid, wherein said C_{1-7} alkyl, heteroaryl, phenyl and phenoxy are each optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylthioureyl, C_{1-4} alkylureyl, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-7} cycloalkyl, C_{2-8} dialkylamino, C_{2-6} dialkylcarboxamide, C_{2-6} dialkylthiocarboxamide, C_{2-6} dialkylsulfonamide, C_{1-4} alkylthioureyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkyl, C_{1-4} haloalkylthio, halogen, heterocyclic, hydroxyl, hydroxylamino, and nitro;

R^{23}, R^{24} and R^{25} are each, independently, H or C_{1-8} alkyl;

n is 0 or 1; and

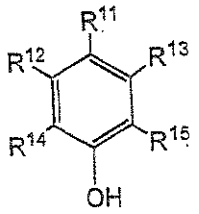
m is 0, 1, 2, 3, or 4;

wherein said process comprises reacting a compound of Formula II:



II

wherein L^2 is a leaving group, with compound of Formula III:



III

in the presence of a base and a salt, thereby forming the compound of Formula I.

2. The process of claim 1 wherein said salt is a tetra(C_{1-8} alkyl)ammonium salt is halide salt.

3. The process of claim 1 wherein said salt is a tetrasubstituted ammonium iodide salt.

4. The process of claim 1 wherein said salt is an alkali metal halide.

5. The process of claim 1 wherein said salt is KI.

6. The process of claim 1 wherein said base is an alkali metal amide, alkali metal hydride, alkali metal carbonate, or an alkali metal hydrogencarbonate.

7. The process of claim 1 wherein said base is K_2CO_3.

8. The process of claim 1 wherein said reacting is carried out at elevated temperature.

9. The process of claim 1 wherein said reacting is carried out at a temperature of about 120 to about 140 °C.

10. The process of claim 1 wherein said reacting is carried out in a solvent.

11. The process of claim 10 wherein said solvent comprises DMSO.

12. The process of claim 1 wherein L^2 is halo.

13. The process of claim 1 wherein L^2 is Cl.

14. The process of claim 1 wherein both X and Y are N.

15. The process of claim 1 wherein Z is C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{2-6} alkynyl, formyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, halogen, hydroxyl, or nitro.

16. The process of claim 1 wherein Z is methyl.

17. The process of claim 1 wherein R^1 is H.

18. The process of claim 1 wherein R^2 is -C(O)O-R^{22} and R^{22} is methyl, ethyl, or prop-1-yl, prop-2-yl.

19. The process of claim 1 wherein R^2 is -C(O)O-R^{22} and R^{22} is prop-2-yl.

20. The process of claim 1 wherein R^4 is H.

21. The process of claim 1 wherein n is 1.

22. The process of claim 1 wherein m is 0.

23. The process of claim 1 wherein R^{11} is C_{1-4} alkylsulfonyl.

24. The process of claim 1 wherein R^{11} is methylsulfonyl.

25. The process of claim 1 wherein R^{12}, R^{13}, R^{14}, and R^{15} are each, independently, H or halogen.

26. The process of claim 1 wherein R^{15} is F.

27. The process of claim 1 wherein R^{11} is C_{1-4} alkylsulfonyl; R^{12}, R^{13}, and R^{14} are each H; and R^{15} is halogen.

28. The process of claim 1 wherein:
X is N;
Y is N;
Z is methyl;
R^1 is H;
R^2 is -C(O)O-R^{22};
R^4 is H;
R^{11} is methylsulfonyl;

R^{12}, R^{13}, and R^{14} are each H;

R^{15} is F;

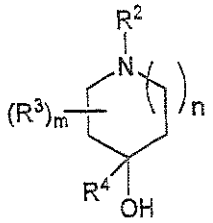
R^{22} is prop-2-yl;

n is 1; and

m is 0.

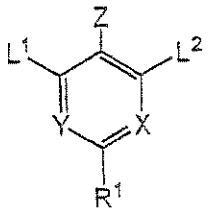
29. The process of claim 1 wherein said compound of Formula II is prepared by:

a) combining a compound of Formula IV:



IV

with a compound of Formula V:



V

wherein L^1 is a leaving group, to form a mixture; and

b) adding a base to said mixture, thereby forming the compound of Formula II.

30. The process of claim 29 wherein said base is C_{1-6} alkoxide salt, alkali metal amide, alkali metal hydride, alkali metal carbonate, or an alkali metal hydrogencarbonate.

31. The process of claim 29 wherein said base is potassium *t*-butoxide.

32. The process of claim 29 wherein said combining and adding are carried out in a solvent.

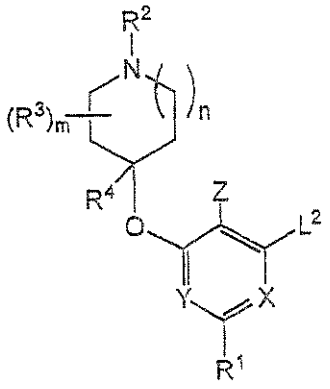
33. The process of claim 32 wherein said solvent comprises tetrahydrofuran.

34. The process of claim 29 wherein said adding is carried out at a temperature below about 10°C.

35. The process of claim 29 wherein L^1 is halo.

36. The process of claim 29 wherein L^1 is Cl.

37. A process for preparing a compound of Formula II:



II

wherein:

X is N or CR^7;

Y is N or CR^8;

Z is C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylthioureyl, C_{1-4} alkylureyl, amino, C_{1-2} alkylamino, C_{2-4} dialkylamino, carbamimidoyl, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-7} cycloalkyl, C_{4-8} diacylamino, C_{2-6} dialkylcarboxamide, C_{2-6} dialkylthiocarboxamide, C_{2-6} dialkylsulfonamide, C_{2-6} dialkylsulfonylamino, formyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylcarboxamide, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, halogen, aryl, heteroaryl, heterocycloalkyl, hydroxyl, hydroxycarbamimidoyl, hydroxylamino, nitro, or tetrazolyl; wherein said C_{1-8} alkyl, C_{3-7} cycloalkyl, and heterocycloalkyl are each optionally substituted with 1, 2, 3 or 4 groups selected from C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-7} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylureyl, amino, C_{1-2} alkylamino, C_{2-4} dialkylamino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, formyl, C_{1-4} haloalkoxy, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, halogen, hydroxyl, hydroxylamino, and nitro;

R^1 is H, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylureyl, amino, C_{1-4} alkylamino, C_{2-8} dialkylamino, carboxamide, cyano, C_{3-7} cycloalkyl, C_{2-6} dialkylcarboxamide, C_{2-6} dialkylsulfonamide, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, or hydroxyl;

R^2 is $-R^{22}$, $-CR^{23}R^{24}C(O)-R^{22}$, $-C(O)CR^{23}R^{24}-R^{22}$, $-C(O)-R^{22}$, $-CR^{23}R^{24}C(O)NR^{25}-R^{22}$, $-NR^{25}C(O)CR^{23}R^{24}-R^{22}$, $-C(O)NR^{23}-R^{22}$, $-NR^{23}C(O)-R^{22}$, $-C(O)O-R^{22}$, $-OC(O)-R^{22}$, $-C(S)-R^{22}$, $-C(S)NR^{23}-R^{22}$, $-NR^{23}C(S)-R^{22}$, $-C(S)O-R^{22}$, $-OC(S)-R^{22}$, $-CR^{23}R^{24}-R^{22}$, or $-S(O)_2-R^{22}$;

R^3 is C_{1-3} alkyl, C_{1-4} alkoxy, carboxy, cyano, C_{1-3} haloalkyl, or halogen;

R^4 is H, C_{1-8} alkyl or C_{3-7} cycloalkyl, wherein said C_{1-8} alkyl is optionally substituted with C_{1-4} alkoxy, C_{3-7} cycloalkyl, or heteroaryl;

R_7 and R_8 are each, independently, H, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylureyl, amino, C_{1-4} alkylamino, C_{2-8} dialkylamino, carboxamide, cyano, C_{3-7} cycloalkyl, C_{2-6} dialkylcarboxamide, C_{2-6} dialkylsulfonamide, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, or hydroxyl;

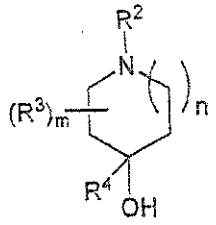
n is 0 or 1;

m is 0, 1, 2, 3, or 4; and

L^2 is a leaving group;

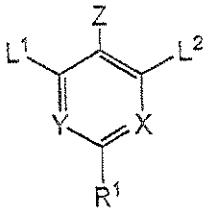
comprising:

a) combining a compound of Formula IV:



IV

with a compound of Formula V:



V

wherein L^1 is a leaving group, to form a mixture; and

b) adding a base to said mixture while maintaining the temperature of the mixture below about room temperature, thereby forming said compound of Formula II.

38. The process of claim 37 wherein said adding is carried out while maintaining the temperature of the mixture below about 0°C.

39. The process of claim 37 wherein said base is C_{1-6} alkoxide salt, alkali metal amide, alkali metal hydride, alkali metal carbonate, or an alkali metal hydrogencarbonate.

40. The process of claim 37 wherein said base is a potassium *t*-butoxide.

41. The process of claim 37 wherein said combining and adding are carried out in a solvent.

42. The process of claim 41 wherein said solvent comprises tetrahydrofuran.

43. The process of claim 37 wherein said mixture is cooled to a temperature of about -15 to about -10 °C prior to said adding.

44. The process of claim 37 wherein L^1 is halo.

45. The process of claim 37 wherein L^1 is Cl.