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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07D 403/04, 239/48, A61K 31/505
A1

(11) International Publication Number: **WO 99/41253**

(43) International Publication Date: 19 August 1999 (19.08.99)

(21) International Application Number: PCT/US99/03136

(22) International Filing Date: 12 February 1999 (12.02.99)

(30) Priority Data:
60/075,005 17 February 1998 (17.02.98) US

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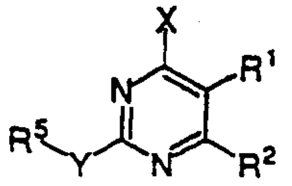
(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: ANTI-VIRAL PYRIMIDINE DERIVATIVES



(I)

(57) Abstract

Compounds and compositions which are useful for the treatment of viral infections, particularly human Cytomegalovirus infection. The compounds include novel pyrimidine-based derivatives having formula (I) wherein X is a member selected from the group consisting of $-NR^3R^4$, $-OR^3$, $-SR^3$, aryl, alkyl and arylalkyl; Y is a member selected from the group consisting of a covalent bond, $-N(R^6)-$, $-O-$, $-S-$, $-C(=O)-$ and alkylene; R^1 and R^2 are members independently selected from the group consisting of hydrogen, alkyl, -O-alkyl, -S-alkyl, aryl, arylalkyl, -O-aryl, -S-aryl, $-NO_2$, $-NR^7R^8$, $-C(O)R^9$, $-CO_2R^{10}$, $-C(O)NR^7R^8$, $-N(R^7)C(O)R^9$, $-N(R^7)CO_2R^{11}$, $-N(R^9)C(O)NR^7R^8$, $-S(O)_mNR^7R^8$, $-S(O)_nR^9$, -CN, halogen, and $-N(R^7)S(O)_mR^{11}$.

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1073 X 15 =16100

ANTI-VIRAL PYRIMIDINE DERIVATIVES

CROSS-REFERENCE TO RELATED APPLICATION

This application is a continuation in part of USSN 60/075,005, filed February 17, 1998, the disclosure of which is incorporated herein by reference in its entirety.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH

The invention described herein was not made with the aid of any federally sponsored grants.

FIELD OF THE INVENTION

The field of the invention is in novel substituted pyrimidine compounds and their use as pharmacologically active agents capable of suppressing and inhibiting viruses (*e.g.*, herpes viruses). The subject compounds and compositions are particularly useful in treating and suppressing human Cytomegalovirus.

BACKGROUND OF THE INVENTION

Cytomegalovirus (CMV) is a member of the herpes virus family. Other well-known members of the herpes virus family include, for example, herpes simplex virus, types I and II, Epstein-Barr virus and Varicella zoster virus. These viruses are related taxonomically, but each manifests in a clinically distinct manner. In the case of CMV, medical conditions arising from congenital infection include jaundice, respiratory distress and convulsive seizures which may result in mental retardation, neurologic disability or death. Infection in adults is frequently asymptomatic, but may manifest as mononucleosis, hepatitis, pneumonitis or retinitis, particularly in immunocompromised patients such as AIDS sufferers, chemotherapy patients, and organ transplant patients undergoing tissue rejection therapy.

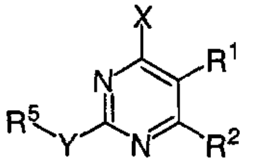
A variety of drugs have been developed to treat herpes virus infections, including naturally occurring proteins and synthetic nucleoside analogs. For example, the natural anti-viral protein interferon has been used in the treatment of herpes virus infections, as have the nucleoside analogs cytosine-arabinoside, adenine-arabinoside, iodoxyuridine and acyclovir, which is presently the treatment of choice for herpes simplex type II infection.

Unfortunately, drugs such as acyclovir that have proven sufficiently effective to treat infection by certain herpes viruses are not sufficiently effective to treat CMV.

Additionally, drugs currently used to treat CMV infection, such as 9-((1,3-dihydroxy-2-propoxy)methyl)guanidine (ganciclovir, DHPG) and phosphonoformic acid (foscarnet), lack the acceptable side effect and safety profiles of the drugs approved for treatment of other herpes viruses. Moreover, such drugs are ineffective to treat certain strains of CMV that have acquired drug resistance. Thus, despite advances in the development of anti-herpes virus drugs, there remains a need for therapeutic agents effective in treating CMV infection with an increased safety margin. The present invention provides such therapeutic agents in the form of surprisingly effective substituted pyrimidine compounds.

SUMMARY OF THE INVENTION

The present invention provides novel substituted pyrimidine compounds. The compounds have the general formula I:



(I)

in which X represents $-NR^3R^4$, $-OR^3$, $-SR^3$, aryl, alkyl or arylalkyl. The letter Y represents a covalent bond, $-N(R^6)-$, -O-, -S-, -C(=O)- or an alkylene group. R^1 and R^2 are independently selected from hydrogen, alkyl, -O-alkyl, -S-alkyl, aryl, arylalkyl, -O-aryl, -S-aryl, $-NO_2$, $-NR^7R^8$, $-C(O)R^9$, $-CO_2R^{10}$, $-C(O)NR^7R^8$ $-N(R^7)C(O)R^9$, $-N(R^7)CO_2R^{11}$, $-N(R^9)C(O)NR^7R^8$, $-S(O)_mNR^7R^8$, $-S(O)_nR^9$, -CN, halogen, and $-N(R^7)S(O)_mR^{11}$. The groups R^3 and R^4 are independently selected from hydrogen, alkyl, aryl or arylalkyl, or, when X is $-NR^3R^4$, R^3 and R^4 taken together with the nitrogen atom to which each is attached form a 5-, 6- or 7-membered aromatic or nonaromatic ring containing from one to three heteroatoms in the ring. R^5 and R^6 are independently hydrogen, alkyl, aryl or arylalkyl. R^7 and R^8 are each independently hydrogen, alkyl, aryl or arylalkyl, or, when attached to the same nitrogen atom can be combined with the nitrogen atom to form a 4-, 5-, 6- , 7- or 8-membered ring containing from one to three heteroatoms in the ring. R^9 and R^{10} are independently selected from hydrogen, alkyl, aryl and arylalkyl. R^{11} is selected from alkyl, aryl and arylalkyl. The subscript m is an integer of from 1 to 2 and the subscript n is an integer of from 1 to 3.

In addition to the above descriptions of R^1 to R^{11}, the formula above is meant to represent a number of compounds in which a second ring is fused to the pyrimidine ring. For example, R^1 can be joined to R^2, R^1 can be joined to R^3, R^3 can be joined to N^3(the nitrogen atom at the 3-position of the pyrimidine ring), R^5 can be joined to N^3, R^5 can be joined to N^1(the nitrogen atom at the 1-position of the pyrimidine ring) or R^2 can be joined to N^1 to form a fused 5-, 6-, or 7-membered ring.

Finally, the compounds of the present invention will typically have a molecular weight of from about 150 to about 750. The compounds provided in the above formula are meant to include all pharmaceutically acceptable salts thereof.

The compounds of the present invention are useful in therapeutic as well as prophylactic and diagnostic applications. Still further, the compounds are useful in the development of additional therapeutic agents as standards in a variety of assay formats. Accordingly, the present invention provides compositions containing the above compounds and pharmaceutically acceptable excipients or diagnostically acceptable excipients. The invention further provides methods of inhibiting or suppressing certain viruses, and methods of treating individuals infected with such viruses, particularly CMV. In addition to treatments for existing conditions, the present invention also provides methods for prophylactic treatments to prevent the onset of viral infection in patients undergoing, for example, organ transplants.

Other objects, features and advantages of the present invention will become apparent to those skilled in the art from the following description and claims.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 provides the structures of exemplary compounds of formula IIa.

Figure 2 provides the structures of exemplary compounds of formula IIb.

Figure 3 provides the structures of exemplary compounds of formula IIc.

Figure 4 provides the structures of exemplary compounds of formula IId.

Figure 5 provides the structures of exemplary compounds of formula IIe.

Figures 6-14 provide synthesis schemes for exemplary compounds of formulae IIa-IIe and also selected transformations for functional groups present on the compounds.

DETAILED DESCRIPTION OF THE INVENTION

Abbreviations and Definitions

The term "alkyl," by itself or as part of another substituent, means, unless otherwise stated, a straight or branched chain or cyclic hydrocarbon radical or combinations thereof, which may be fully saturated, mono- or polyunsaturated and can include di- and multi-radicals, having the number of carbon atoms designated (*i.e.* C1-C10 means one to ten carbons). Examples of saturated hydrocarbon radicals include straight or branched chain groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, homologs and isomers of, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. Other saturated hydrocarbon radicals include cyclopropylmethyl, cyclohexylmethyl and the like. An unsaturated alkyl group is one having one or more double bonds or triple bonds.

Examples of unsaturated alkyl groups include vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), ethynyl, 1- and 3-propynyl, 3-butynyl, and the higher homologs and isomers. The term "alkyl," unless otherwise noted, is also meant to include those derivatives of alkyl defined below as heteroalkyl, alkylene, heteroalkylene, cycloalkyl and heterocycloalkyl. Typically, an alkyl group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms being preferred in the present invention. The term "alkylene" by itself or as part of another substituent means a divalent radical derived from an alkane, as exemplified by $-CH_2CH_2CH_2CH_2-$. A "lower alkyl" or "lower alkylene" is a shorter chain alkyl or alkylene group, generally having eight or fewer carbon atoms. Unless otherwise indicated, the alkyl groups can be unsubstituted or substituted by the substituents indicated below.

The term "heteroalkyl," by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain radical consisting of the stated number of carbon atoms and from one to three heteroatoms selected from the group consisting of O, N, Si and S, and wherein the nitrogen and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) O, N and S may be placed at any interior position of the heteroalkyl group. The heteroatom Si may be placed at any position of the heteroalkyl group, including the position at which the alkyl group is attached to the remainder of the molecule. Examples include $-CH_2-CH_2-O-CH_3$, $-CH_2-CH_2-NH-CH_3$, $-CH_2-CH_2-N(CH_3)-CH_3$, $-CH_2-S-CH_2-CH_3$, $-CH_2-CH_2-S(O)-CH_3$, $-CH_2-CH_2-S(O)_2-CH_3$, $-CH=CH-O-CH_3$, $-Si(CH_3)_3$, $-CH_2-CH=N-OCH_3$, and $-CH=CH-N(CH_3)-CH_3$. Up to two heteroatoms may be consecutive, such as, for example, $-CH_2-NH-OCH_3$ and $-CH_2-O-Si(CH_3)_3$. The term "heteroalkylene" by itself or as part of another substituent means a divalent radical derived from heteroalkyl, as exemplified by $-CH_2-CH_2-S-CH_2CH_2-$ and $-CH_2-S-CH_2-CH_2-NH-CH_2-$.

The terms "cycloalkyl" and "heterocycloalkyl", by themselves or in combination with other terms, represent, unless otherwise stated, cyclic versions of "alkyl" and "heteroalkyl", respectively. Examples of cycloalkyl include cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, and the like. Examples of heterocycloalkyl include 1-(1,2,5,6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1-piperazinyl, 2-piperazinyl, and the like.

The terms "halo" or "halogen," by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Additionally, terms such as "fluoroalkyl," are meant to include monofluoroalkyl and polyfluoroalkyl. More particularly, the term "fluoroalkyl" also includes perfluoroalkyl, in which each hydrogen present in an alkyl group has been replaced by a fluorine.

The term "aryl," employed alone or in combination with other terms (*e.g.*, aryloxy, arylthioxy, arylalkyl) means, unless otherwise stated, an aromatic substituent which can be a single ring or multiple rings (up to three rings) which are fused together or linked covalently. The rings may each contain from zero to four heteroatoms selected from N, O, and S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. Non-limiting examples of aryl groups include phenyl, 1-naphthyl, 2-naphthyl, biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxalinyl, 5-quinoxalinyl, 3-quinolyl, and 6-quinolyl. Substituents for each of the above noted aryl ring systems are selected from the group of acceptable substituents described below.

As used herein, the term "bicyclic fused aryl-cycloalkyl" refers to those groups in which an aryl ring (or rings) is fused to a cycloalkyl group (including cycloheteroalkyl groups). The group can be attached to the remainder of the molecule through either an available valence on the aryl portion of the group, or an available valence on the cycloalkyl portion of the group. Examples of such bicyclic fused aryl-cycloalkyl groups are: indanyl, benzotetrahydrofuranyl, benzotetrahydropyranyl and 1,2,3,4-tetrahydronaphthyl.

Each of the above terms (*e.g.*, "alkyl" and "aryl" and "bicyclic fused aryl-cycloalkyl") will typically include both substituted and unsubstituted forms of the indicated radical. Preferred substituents for each type of radical are provided below. In the case of radicals containing both aryl (including heteroaryl) and alkyl (including, for example, heteroalkyl, cycloalkyl, and cycloheteroalkyl) portions, each of the portions can be substituted as indicated.

Substituents for the alkyl groups (including those groups often referred to as alkenyl, heteroalkyl, heteroalkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl) can be a variety of groups selected from: -OR', =O, =NR', =N-OR', -NR'R'', -SR', -halo, -SiR'R''R''', -OC(O)R', $-CO_2R'$, -CONR'R", -OC(O)NR'R", -NR"C(O)R', -NR"-C(O)-OR', $-NH-C(NH_2)=NH$, $-NR'C(NH_2)=NH$, $-NH-C(NH_2)=NR'$, -S(O)R', $-S(O)_2R'$, $-S(O)_2NR'R"$, -CN and $-NO_2$ in a number ranging from zero to (2N+1), where N is the total number of carbon atoms in such radical. R', R'' and R''' each independently refer to a hydrogen or C1-C10 alkyl group. Preferably, a substituted alkyl group will have from one to six independently selected substituents. More preferably, a substituted alkyl group will have from one to four independently selected substituents. Nevertheless, certain substituted alkyl groups (*e.g.*, perfluoroalkyl) will have a full 2N + 1 substituents (where N is the number of carbon atoms in a saturated alkyl group). Examples of substituted alkyl groups include: $-C(O)-CH_3$, $-C(O)CH_2OH$, $-CH_2-CH(CO_2H)-NH_2$ and $-Si(CH_3)_2-CH_2-C(O)-NH_2$.

Similarly, substituents for the aryl groups are varied and are selected from: -halo, -OR', -OC(O)R', -NR'R", -SR', -R', -CN, $-NO_2$, $-CO_2R'$, -CONR'R",

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-OC(O)NR'R", -NR"C(O)R', -NR"-C(O)-OR', -NH-C(NH_2)=NH, -NR'C(NH_2)=NH, -NH-C(NH_2)=NR', -S(O)R', -S(O)$_2$R', -S(O)$_2$NR'R", -N_3, -CH(Ph)$_2$, perfluoro(C1-C4)alkoxy, and perfluoro(C1-C4)alkyl, in a number ranging from zero to the total number of open valences on the aromatic ring system; and where R' and R" are independently selected from hydrogen, (C1-C8)alkyl, aryl, aryl-(C1-C4)alkyl, and aryloxy-(C1-C4)alkyl.

Two of the substituents on adjacent atoms of the aryl ring may optionally be replaced with a substituent of the formula -T-C(O)-(CH_2)$_s$-U-, wherein T and U are independently -NH-, -O-, -CH_2- or a single bond, and the subscript s is an integer of from 0 to 2. Alternatively, two of the substituents on adjacent atoms of the aryl ring may optionally be replaced with a substituent of the formula -A-(CH_2)$_p$-B-, wherein A and B are independently -CH_2-, -O-, -NH-, -S-, -S(O)-, -S(O)$_2$-, -S(O)$_2$NR'- or a single bond, and p is an integer of from 1 to 3. One or more of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, two of the substituents on adjacent atoms of the aryl ring may optionally be replaced with a substituent of the formula -(CH_2)$_q$-Z-(CH_2)$_r$-, where q and r are independently integers of from 1 to 3, and Z is -O-, -NR'-, -S-, -S(O)-, -S(O)$_2$-, or -S(O)$_2$NR'-. The substituent R' in -NR'- and -S(O)$_2$NR'- is selected from hydrogen or (C1-C6)alkyl.

As used herein, the term "heteroatom" is meant to include oxygen (O), nitrogen (N), sulfur (S) and silicon (Si).

The term "pharmaceutically acceptable salts" is meant to include salts of the active compounds which are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds of the present invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds of the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, oxalic, maleic, malonic, benzoic, succinic, suberic, fumaric, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (see, for example, Berge, S.M., et al, "Pharmaceutical Salts", *Journal of Pharmaceutical Science*, 1977, *66*, 1-19). Certain specific compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

The neutral forms of the compounds may be regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents, but otherwise the salts are equivalent to the parent form of the compound for the purposes of the present invention.

In addition to salt forms, the present invention provides compounds which are in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under physiological conditions to provide a compound of formula I.

Certain compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention.

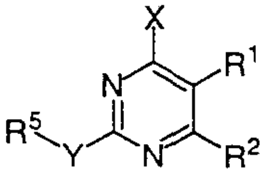
Certain compounds of the present invention possess asymmetric carbon atoms (optical centers) or double bonds; the racemates, diastereomers, geometric isomers and individual isomers are all intended to be encompassed within the scope of the present invention.

The compounds of the present invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (^3H), iodine-125 (^{125}I) or carbon-14 (^{14}C). All isotopic variations of the compounds of the present invention, whether radioactive or not, are intended to be encompassed within the scope of the present invention.

Embodiments of the Invention

Compounds

In one aspect, the present invention provides compounds of general formula I:



(I)

in which X represents $-NR^3R^4$, $-OR^3$, $-SR^3$, aryl, alkyl or arylalkyl. The letter Y represents a covalent bond, $-N(R^6)-$, -O-, -S-, -C(=O)- or an alkylene radical. Preferably, Y is $-N(R^6)-$ or -O-, in which R^6 is as defined below. More preferably, Y is $-N(R^6)-$. For those embodiments in which Y is an alkylene radical, the alkylene radical will typically have from 1 to 8 carbon atoms in the chain, with alkylene groups having from 1 to 3 carbon atoms being preferred.

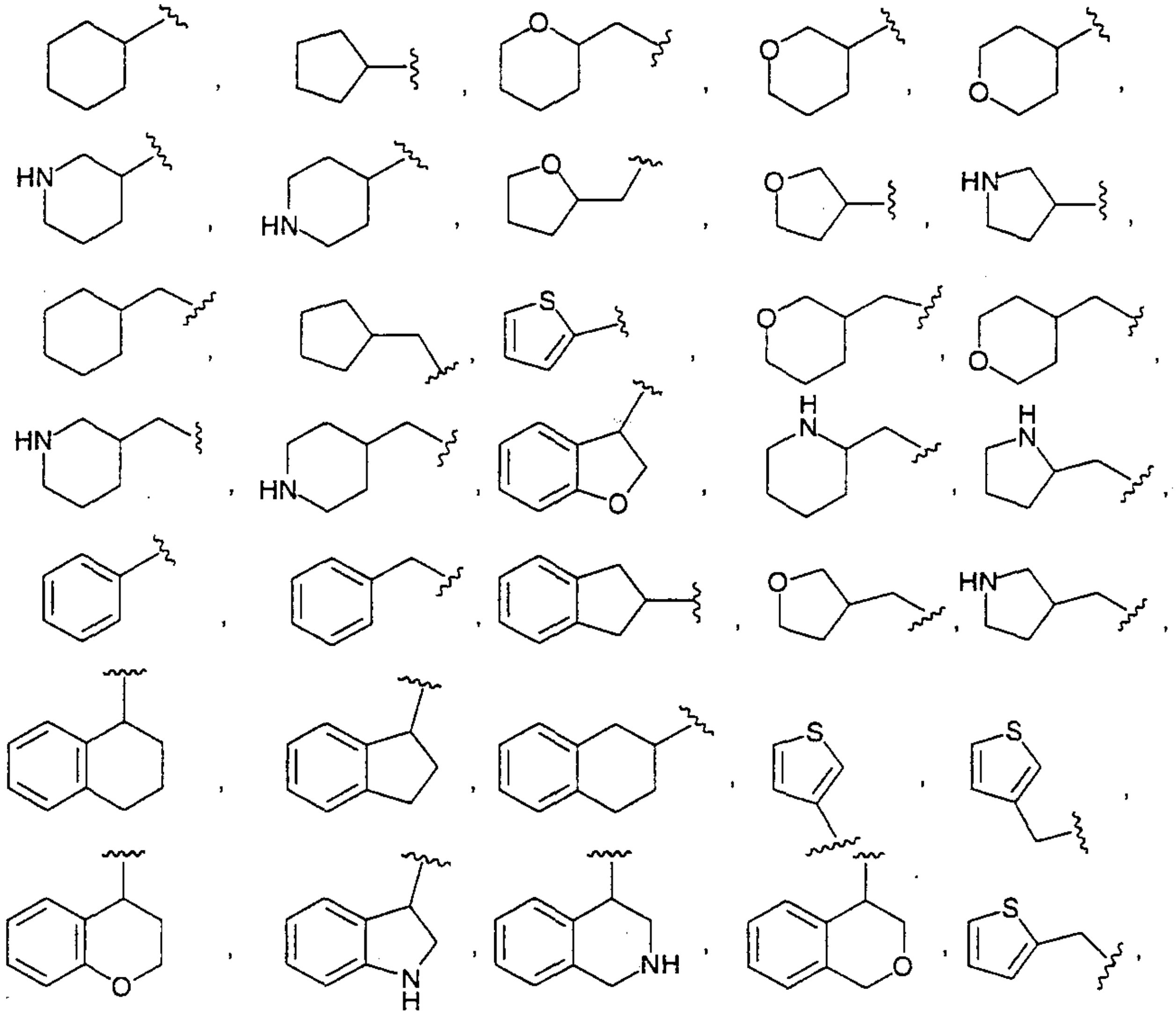
R^1 and R^2 are independently selected from hydrogen, alkyl, -O-alkyl, -S-alkyl, aryl, arylalkyl, -O-aryl, -S-aryl, -NO_2, -NR^7R^8, -C(O)R^9, -CO_2R^{10}, -C(O)NR^7R^8 -N(R^7)C(O)R^9, -N(R^7)CO_2R^{11}, -N(R^9)C(O)NR^7R^8, -S$(O)_m$$NR^7R^8$, -S$(O)_n$$R^9$, -CN, halogen, or -N($R^7$)S$(O)_m$$R^{11}$, in which R^7, R^8, R^9, R^{10} and R^{11} are as defined below.

In one group of preferred embodiments, R^1 is an electron-withdrawing group and R^2 is an electron-donating group. Within this group of embodiments, R^1 is preferably -NO_2, -S$(O)_m$$NR^7R^8$, -S$(O)_n$$R^9$, -CN, halogen, fluoroalkyl, -C(O)R^9, -CO_2R^{10} or -C(O)NR^7R^8. More preferably, R^1 is -CF_3, -NO_2, -CN, -S$(O)_m$$NR^7R^8$, or -$CO_2R^{10}$, with -$NO_2$ being the most preferred. The R^2 group is preferably hydrogen, lower alkyl, -O-alkyl, -S-alkyl, aryl, arylalkyl, -O-aryl or -S-aryl. More preferably, R^2 will be methyl, ethyl, n-propyl, isopropyl, methoxy, ethoxy, propoxy, methoxymethyl, methylthio, ethylthio or propylthio.

In another group of preferred embodiments, R^1 is an electron-donating group and R^2 is an electron-withdrawing group. Within this group of embodiments, R^1 is preferably hydrogen, lower alkyl, -O-alkyl, -S-alkyl, aryl, arylalkyl, -O-aryl or -S-aryl. More preferably, R^1 is methyl, ethyl, n-propyl, isopropyl, methoxy, ethoxy, propoxy, methylthio, ethylthio or propylthio. The R^2 group is preferably -NO_2, -S$(O)_m$$NR^7R^8$, -S$(O)_n$$R^9$, -CN, halogen, fluoroalkyl, -C(O)R^9, -CO_2R^{10} or -C(O)NR^7R^8. More preferably, R^2 is -CF_3, -NO_2, -CN, -S$(O)_m$$NR^7R^8$ or -CO_2R^{10}, with -NO_2 being the most preferred.

The groups R^3 and R^4 are independently hydrogen, alkyl, aryl or arylalkyl, or, taken together with the nitrogen atom to which each is attached form, a 5-, 6- or 7-membered ring containing from one to three heteroatoms in the ring. In one group of preferred embodiments, R^3 and R^4 are combined with the nitrogen atom to which each is attached, to form a 5- or 6-membered ring. The rings defined by R^3 and R^4 and the nitrogen atom can be saturated, unsaturated or aromatic, and can contain additional heteroatoms. Examples of suitable rings include: pyrrolidine, pyrrole, pyrazole, imidazole, imidazoline, thiazoline, piperidine, morpholine, and the like. In certain preferred embodiments, R^3 and R^4 are combined with the nitrogen atom to which each is attached to form a 5-membered ring containing two nitrogen atoms, preferably an imidazole ring, and most preferably a 2-alkylimidazole ring or a 5-alkylimidazole ring. Particularly preferred X groups are 2-methylimidazol-1yl, 2,4-dimethylimidazol-1yl, 2-ethylimidazol-1yl, 2-propylimidazol-1yl, 2-isopropylimidazol-1yl and 5-methylimidazol-1yl.

The R^5 group is an alkyl, aryl, arylalkyl or bicyclic fused aryl-cycloalkyl group. Preferred alkyl groups are those having from one to eight carbon atoms, either substituted or unsubstituted. Preferred aryl groups include substituted or unsubstituted phenyl, pyridyl, or naphthyl. Preferred arylalkyl groups include substituted and unsubstituted benzyl, phenethyl, pyridylmethyl and pyridylethyl. Particularly preferred R^5 groups are phenyl, 4-halophenyl, benzyl, n-butyl, propionyl, acetyl and methyl. Other preferred R^5 groups are those in which R^5 is combined with R^6 and the nitrogen atom to which each is attached to form a ring. Still other preferred R^5 groups (including some of the preferred fused bicyclic aryl-cycloalkyl groups) are selected from:



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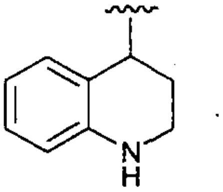

In the above radicals, and other groups described herein, the wavy line is used to indicate the point of attachment to the remainder of the molecule.

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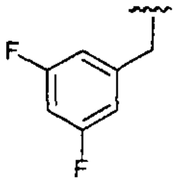
In one group of particularly preferred embodiments, R^5 is a radical selected from the group consisting of:



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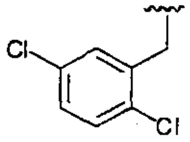

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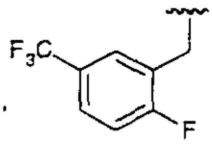

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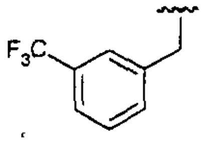

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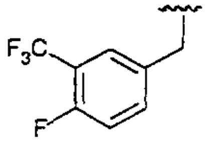

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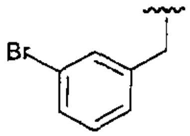

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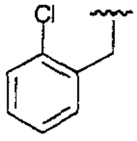

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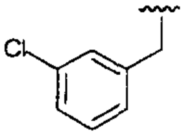

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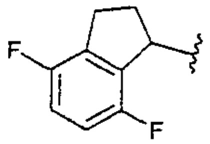

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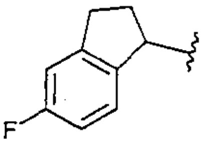

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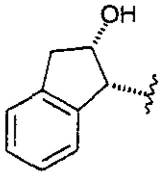

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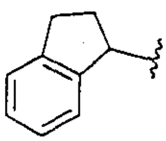
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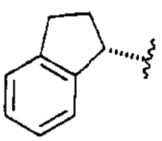
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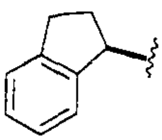
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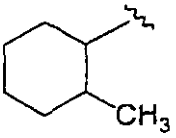
In another group of particularly preferred embodiments, R^5 is a radical selected from the group consisting of:



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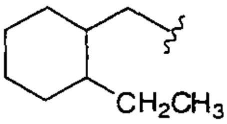

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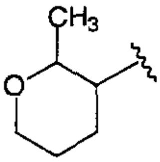

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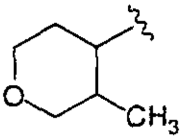

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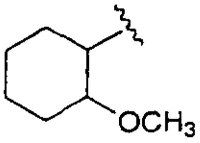

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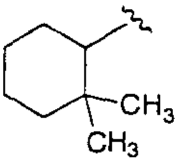

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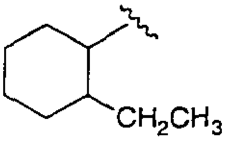

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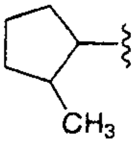

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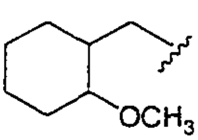

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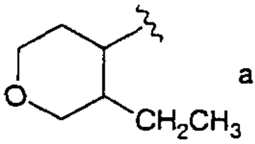

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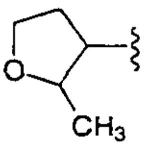

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The above group of radicals is meant to include those radicals having a mixture of stereochemistry as well as pure isomers and enantiomers (those having less than about 5% of another diastereomer or enantiomer, more preferably less than about 2% of another isomer, and most preferably less than about 1% of another isomer).

The R^6 group is typically hydrogen, alkyl, aryl or arylalkyl. Preferably, R^6 is hydrogen, a lower alkyl group having from one to three carbon atoms, a phenyl ring or a phenylalkyl group, such as, for example, a benzyl or a phenethyl group. R^7 and R^8 are each independently hydrogen, alkyl, aryl or arylalkyl, or, taken together with the nitrogen atom to which each is attached, form a 4-, 5-, 6-, 7- or 8-membered ring containing from one to three heteroatoms in the ring. Preferably, R^7 and R^8 are each independently a (C1-C8)alkyl group, or are combined to form a 5-, 6-, or 7-membered ring. R^9 and R^{10} are independently selected from hydrogen, alkyl, aryl and arylalkyl. In preferred embodiments, R^9 and R^{10} are independently selected from hydrogen, (C1-C8)alkyl, phenyl and phenyl(C1-C4)alkyl. R^{11} is alkyl, aryl or arylalkyl, preferably, (C1-C8)alkyl, phenyl and phenyl(C1-C4)alkyl.

In addition to the above descriptions of R^1 to R^{11}, the present formula above is meant to represent a number of compounds in which a second ring is fused to the pyrimidine ring, including structures in which one of the pyrimidine ring nitrogen atoms is at the ring junction. For the discussion below and the claims, the nitrogens are individually referred to as follows: N^1 is the nitrogen atom at the 1-position of the ring (which is between the carbon atom bearing $-R^2$ and the carbon atom bearing $-Y-R^5$). N^3 is the nitrogen atom at the 3-position of the pyrimidine ring (which is the nitrogen atom between the carbon bearing $-Y-R^5$ and the carbon atom bearing -X). Examples of fused rings are those in which R^1 is joined to R^2, R^1 is joined to R^3, R^3 is joined to N^3, R^5 is joined to N^3, R^5 is joined to N^1 or R^2 is joined to N^1 to form a fused 5-, 6-, or 7-membered ring. The ring formed by these combinations will contain 1-3 heteroatoms (*e.g.*, O, N or S) and can be either aromatic or nonaromatic. Preferably the additional ring formed is a 5- or 6-membered ring.

When R^1 and R^2 are combined to form a ring, the combination can be replaced with a substituent of the formula $-T-C(O)-(CH_2)_s-U-$, wherein T and U are independently selected from -NH-, -O-, $-CH_2-$ or a single bond, and the subscript s is an integer of from 0 to 2. Alternatively, the R^1 and R^2 radicals can be replaced with a substituent of the formula $-A-(CH_2)_p-B-$, wherein A and B are independently selected from $-CH_2-$, -O-, -NH-, -S-, -S(O)-, $-S(O)_2-$, $-S(O)_2NR'-$ or a single bond, and p is an integer of from 1 to 3. One or more of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, the R^1 and R^2 radicals can be replaced with a substituent of the formula $-(CH_2)_q-Z-(CH_2)_r-$, where q and r are independently integers of from 1 to 3, and Z is -O-, -NR'-, -S-, -S(O)-, $-S(O)_2-$, or $-S(O)_2NR'-$. The substituent R' in -NR'- and $-S(O)_2NR'-$ is selected from hydrogen or (C1-C6)alkyl.

The subscript m, in the groups above, is an integer of from 1 to 2, preferably 2. The subscript n, in the groups above, is an integer of from 1 to 3, preferably 2.

Finally, the compounds of the present invention typically have a molecular weight of from about 150 to about 750. The compounds provided in the above formula are meant to include all pharmaceutically acceptable salts thereof.

A number of substituent combinations on the pyrimidine ring are particularly preferred. For example, one group of preferred embodiments has the formula:

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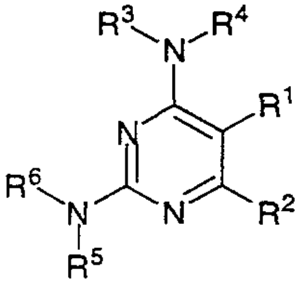
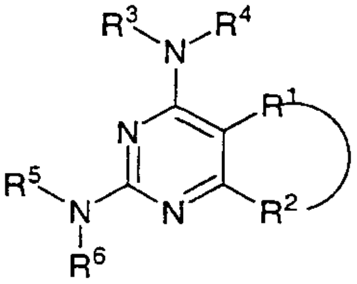


(IIa)

In compounds of general formula IIa, R^1 is preferably $-NO_2$, $-CF_3$, $-C(O)NR^7R^8$, $-CO_2R^{10}$, $-S(O)_2NR^7R^8$, $-S(O)_2R^9$, $-C(O)R^9$, $-SO_2NH_2$, or -CN and R^2 is preferably an alkyl group having from 1 to 8 carbon atoms. In the most preferred embodiments, the R^3 and R^4 groups are combined to form a 5-membered ring which is optionally fused to an aryl group. Examples of suitable 5-membered ring groups (and those which are optionally fused to an aryl group) include pyrrolidine, pyrrole, imidazole, pyrazole, benzimidazole, imidazoline, 1,2,4-triazole, 1,2,3-triazole, imidazolidin-2-one, and the like. More preferably, the R^3 and R^4 groups are combined to form an imidazole ring which is substituted or, optionally, is fused to an aryl group. Preferred substituted (and fused) imidazole rings include, for example, 2-methylimidazole, 2-ethylimidazole, 2-isopropylimidazole, 2-aminoimidazole, 5-methylimidazole, 5-ethylimidazole, 5-isopropylimidazole, 2,5-dimethylimidazole, benzimidazole, and 2-methylbenzimidazole. The R^5 and R^6 groups are independently selected from hydrogen, alkyl, aryl and arylalkyl, or can be combined with the nitrogen atom to which each is attached to form a ring which is optionally fused to an aryl group. Figure 1 provides exemplary structures of compounds within this preferred group of embodiments.

Another group of preferred embodiments are represented by the formula:

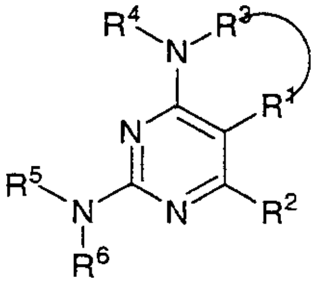


(IIb)

In this formula, the fused ring containing R^1 and R^2 is typically a heterocyclic ring in which the $-R^1-R^2-$ group is selected from, for example, -S(O)$_2$NR'C(O)-, -S(O)$_2$NR'C(O)NR"-, -NR'S(O)$_2$NR"C(O)-, -C(O)NR'C(O)-, -NR'C(O)NR"C(O)-, -NR'C(S)NR"C(O)-, -NR'C(S)NR"C(S)-, in which R' and R" are independently hydrogen or (C1-C8)alkyl. The R^3 and R^4 groups are preferably combined to form a 5-membered ring which is optionally fused to an aryl group. More preferably, the R^3 and R^4 groups are combined to form an imidazole ring which is optionally fused to an aryl group. The R^5 and R^6

groups are independently selected from hydrogen, alkyl, aryl and arylalkyl, or can be combined to form a ring which is optionally fused to an aryl group. Figure 2 provides exemplary structures of compounds within this preferred group of embodiments.

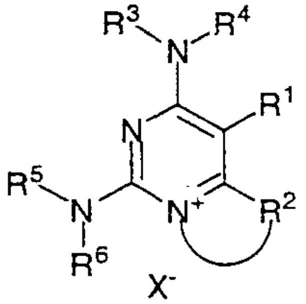
Yet another group of preferred embodiments is represented by the formula:



(IIc)

In this formula, the divalent radical -R^1—R^3- is typically an alkylene group, -C(O)NR'C(O)-, -C(O)NR'S$(O)_2$- or -S$(O)_2$NR'C(O)-, in which R' is a hydrogen or lower alkyl group. Preferably, R^2 and R^4 will each independently be an alkyl group, more preferably a lower alkyl group. The R^5 and R^6 groups are independently selected from hydrogen, alkyl, aryl and arylalkyl, or can be combined to form a ring which is optionally fused to an aryl group. Figure 3 provides exemplary structures of compounds within this preferred group of embodiments.

Still another group of preferred embodiments are represented by the formula:

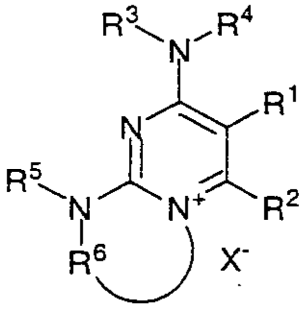


(IId)

In this formula, the fused ring portion defined by —R^2— is typically a (C3-C5)alkylene group, alkyleneamine group (*e.g.*, -$NHCH_2CH_2CH_2$-, -$NHCH_2CH_2$-), or a -NR'C(O)CH_2- group, in which R' is hydrogen or a lower alkyl group. R^1 is typically -NO_2, -S$(O)_2$NR^{7}R^8, -S$(O)_2$R^9, -CN, -CF_3, -C(O)R^9, -CO$_2$R^{10} or -C(O)NR^{7}R^8. More preferably, R^1 is -NO_2, -CN, -CF_3 or -CO$_2$R^{10}, with -NO_2 being the most preferred. The R^3 and R^4 groups are preferably combined to form a 5-membered ring which is optionally fused to an aryl group. More preferably, the R^3 and R^4 groups are combined to form an imidazole ring which is optionally fused to an aryl group. The R^5 and R^6 groups are independently selected from hydrogen, alkyl, aryl and arylalkyl, or can be combined to form a ring which is optionally fused to an aryl group. The symbol X^- represents a suitable counterion for the quaternary nitrogen. Preferred counterions are those which form pharmaceutically acceptable salts.

Figure 4 provides exemplary structures of compounds within this preferred group of embodiments.

Another group of preferred embodiments are represented by the formula:



(IIe)

In this formula, R^1 is preferably $-NO_2$, $-S(O)_2NR^7R^8$, $-S(O)_2R^9$, -CN, $-CF_3$, $-C(O)R^9$, $-CO_2R^{10}$ or $-C(O)NR^7R^8$. More preferably, R^1 is $-NO_2$, -CN, $-CF^3$ or $-CO_2R^{10}$, with $-NO_2$ being the most preferred. R^2 is preferably an alkyl group having from 1 to 8 carbon atoms. The R^3 and R^4 groups are preferably combined to form a 5-membered ring which is optionally fused to an aryl group. More preferably, the R^3 and R^4 groups are combined to form an imidazole ring which is optionally fused to an aryl group. R^5 is preferably hydrogen, (C1-C8)alkyl, phenyl, or phenylalkyl. The fused ring portion defined by $—R^6—$ is typically a (C3-C5)alkylene group or a substituted alkylene group (*e.g.*, $-C(O)CH_2CH_2CH_2-$, $-C(O)CH_2CH_2-$), or a $-NR'C(O)CH_2-$ group, in which R' is hydrogen or a lower alkyl group. The symbol X^- represents a suitable counterion for the quaternary nitrogen. Preferred counterions are those which form pharmaceutically acceptable salts. Figure 5 provides the structures of exemplary compounds of formula IIe.

Compositions

In another aspect, the invention provides compositions which are suitable for pharmaceutical or diagnostic use. The compositions comprise compounds of formula I provided above, in combination with a diagnostically or pharmaceutically acceptable carrier or excipient.

In one embodiment, the invention provides the subject compounds combined with a pharmaceutically acceptable excipient such as sterile saline or other medium, water, gelatin, an oil, etc. to form pharmaceutically acceptable compositions. The compositions and/or compounds may be administered alone or in combination with any convenient carrier, diluent, etc. and such administration may be provided in single or multiple dosages. Useful carriers include solid, semi-solid or liquid media including water and non-toxic organic solvents.

In another embodiment, the invention provides the subject compounds in the form of a pro-drug, which can be metabolically or chemically converted to the subject compound by the recipient host. A wide variety of pro-drug derivatives are known in the art such as those that rely on hydrolytic cleavage or oxidative activation of the prodrug.

The compositions may be provided in any convenient form, including tablets, capsules, lozenges, troches, hard candies, powders, sprays, creams, suppositories, etc. As such, the compositions, in pharmaceutically acceptable dosage units or in bulk, may be incorporated into a wide variety of containers. For example, dosage units may be included in a variety of containers including capsules, pills, etc.

The compositions may be advantageously combined and/or used in combination with other antiviral agents which are either therapeutic or prophylactic agents, and different from the subject compounds. The compositions may also be advantageously combined and/or used in combination with agents that treat or induce conditions often associated with the viral infections that are sensitive to the present compounds, such as anti-HIV agents or immunosuppressive agents. In many instances, administration in conjunction with the subject compositions enhances the efficacy of such agents. Exemplary antiviral agents include ganciclovir, foscarnet and cidofovir. Exemplary anti-HIV agents include indinavir, ritonavir, AZT, lamivudine and saquinavir. Exemplary immunosuppressive agents include cyclosporin and FK-506. The compositions may also be advantageously used as antiviral prophylactic treatment in combination with immunosuppressive protocols such as bone-marrow destruction (either by radiation or chemotherapy).

Methods of Use

In yet another aspect, the present invention provides novel methods for the use of the foregoing compounds and compositions. In particular, the invention provides novel methods for treating or preventing viruses from the herpes family, preferably, cytomegalovirus infections. The methods typically involve administering to a patient an effective formulation of one or more of the subject compositions.

The invention provides methods of using the subject compounds and compositions to treat disease or provide medicinal prophylaxis to individuals who possess a compromised immune system or are expected to suffer immunosuppressed conditions, such as patients prior to undergoing immunosuppressive therapy in connection with organ transplantation or anticancer chemotherapy. These methods generally involve administering to the host an effective amount of the subject compounds or pharmaceutically acceptable compositions.

The compositions and compounds of the invention and the pharmaceutically acceptable salts thereof can be administered in any effective way such as via oral, parenteral or topical routes. Generally, the compounds are administered in dosages ranging from about 2 mg up to about 2,000 mg per day, although variations will necessarily occur depending on the disease target, the patient, and the route of administration. Preferred dosages are administered orally in the range of about 0.05 mg/kg to about 20 mg/kg, more preferably in the range of about 0.05 mg/kg to about 2 mg/kg, most preferably in the range of about 0.05 mg/kg to about 0.2 mg per kg of body weight per day.

Preparation of the Compounds

The compounds of the present invention can be prepared using general synthesis schemes such as those outlined in Figures 6-14. One of skill in the art will understand that the syntheses provided below can be modified to use different starting materials and alternate reagents to accomplish the desired transformations. Accordingly, the description below, the Figures and the reagents are all expressed as non-limiting embodiments.

Briefly, the compounds of formula I, in which Y is -N(R^6)- can be prepared from a variety of known pyrimidinediones. As shown in Figure 6, the pyrimidine dione (**i**) can be converted to the corresponding dichloride (**ii**) by treatment with reagents such as, for example, $POCl_3$. Treatment of **ii** with the desired amines (including heterocyclic amines) provides the target compounds, typically as a mixture of isomers (**iii**). Separation of the isomers can be accomplished by traditional methods such as column chromatography or HPLC. Alternatively, **ii** can be hydrolyzed to a mono chloro compound (using, for example, sodium acetate, acetic acid, water and ethanol) to provide (**iv**) which upon treatment with a suitable amine, alkoxide or thiolate ion provides (**v**). Conversion of the 4-hydroxy group to a 4-chloro substituent and displacement with a suitably nucleophilic amine provides the targets (**vi**).

A number of pyrimidinediones are commercially available and can be used as starting materials for the above transformations, including, for example, 5-cyano-6-methyl-2,4-pyrimidinedione (**vii**), 6-methyl-2,4-pyrimidinedione-5-carboxamide (**x**), 6-methyl-2,4-pyrimidinedione-5-sulfonic acid (**xv**) and 6-methyl-5-nitro-2,4-pyrimidinedione. Each of these compounds can be converted to target compounds of formula (IIa) as illustrated in Figure 7. For example, 5-cyano-6-methyl-2,4-pyrimidinedione (**vii**) can be converted to a dichloride (**viii**) using reagents such as $POCl_3$, then further converted to target compounds (*e.g.*, **ix**) upon treatment with amines R^3-NH-R^4 (*e.g.*, 2-methylimidazole) and R^5-NH-R^6 (N-methylbenzylamine).

The carboxamide group of 6-methyl-2,4-pyrimidinedione-5-carboxamide (**x**) can be hydrolyzed to a carboxylic acid (**xi**) with aqueous base and then converted to an acid chloride (**xii**) with $POCl_3$ (forming a trichloride). Stepwise addition of amines or other suitable nucleophiles provides the target compounds (*e.g.*, **xiv**). Similarly, a trichloride (**xvi**) is formed by treating 6-methyl-2,4-pyrimidinedione-5-sulfonic acid (**xv**) with chlorinating agents such as $POCl_3$. Again, the stepwise addition of amines or other suitable nucleophiles produces the desired target species (**xviii**).

Yet another method for the preparation of compounds of formula IIa is shown in Figure 8. Treatment of either a β-ketoester (**xix**) or an α-methylene ester (**xxi**) with base (*e.g.*, sodium alkoxide) and an electrophile (*e.g.*, an alkylating agent, acylating agent, sulfonylating agent, and the like) provides a suitably derivatized β-ketoester (**xx**) which can be converted to a pyrimidinone (**xxiii**) upon treatment with a substituted guanidine (**xxii**), typically in acid (acetic acid) with heating. The substituents in the 5- and 6-positions (R^1 and R^2, respectively) are determined by the groups present on the derivatized β-ketoester. Chlorination of the pyrimidinone to produce (**xxiv**) and subsequent treatment with a nucleophilic nitrogen heterocycle (*e.g.*, imidazole, 2-alkylimidazole, pyrrolidine, piperidine and the like) as well as other amines provides the target compounds of formula IIa. Substituted guanidines used in this method of preparation can either be obtained from commercial sources or can be prepared by the treatment of a secondary amine with cyanamide. Additional literature methods for the preparation of substituted guanidines are known to those of skill in the art.

A number of transformations can be carried out to attach groups to an unsubstituted position on the pyrimidine ring, or to modify existing groups (see Figure 9). For example, a 4-chloro substituent (present, for example, in **xxv**) can be displaced with ammonia to produce a 4-aminopyrimidine (*e.g.*, **xxvi**). Treatment of the primary amine with succinic anhydride provides (**xxvii**) which upon treatment with acetic anhydride produces the succinimide compound **xxviii** (Figure 9A). Exocyclic amino groups can also be acylated using standard acylating agents as shown in Figure 9B. Metallation reactions can be carried out on pyrimidines which are unsubstituted in the 6-position (Figure 9C). For example, a 5-nitropyrimidine derivative (**xxxi**) can be catalytically (H_2) or chemically (*e.g.*, Fe/HCl) reduced to a 5-aminopyrimidine derivative (**xxxii**) which is then protected as a t-butyl carbamate (**xxxiii**). Treatment of the protected 5-aminopyrimidine derivative with a metallating agent such as sec-butyllithium provides a metallated intermediate (**xxxiv**) which can be acylated (**xxxv**), sulfonylated (**xxxvi**) or alkylated (**xxxvii**), as shown. Similarly (see Figure 9D), the pyrimidine derivative (**xxxviii**) can be metallated to produce intermediate (**xxxix**), then acylated (**xl**), sulfonylated (**xli**) or alkylated (**xlii**). Introduction of functional groups at the 5-position can be accomplished using similar metallation chemistry on, for example, the pyrimidine derivative (**xliii**), to produce intermediate (**xliv**) which can be acylated (**xlv**), sulfonylated (**xlvi**) and alkylated (**xlvii**).

Figure 10A-10D provides synthesis schemes for several compounds which follow the general methods shown in Figures 6-8. For example, Figure 10A illustrates the preparation of a substituted guanidine (**l**) from a secondary amine (**xlviii**) and a chloroimidate (**xlix**) and the conversion of ethyl cyanoacetate (**li**) to the ketoester (**lii**). Condensation of **l** and **lii** produces the pyrimidinone (**liii**) which can be chlorinated to provide **liv** and then treated with an amine nucleophile (*e.g.*, 2-methylimidazole) to provide the target **lv**. Figure 10B illustrates a similar route in which ethyl acetoactate (**lvi**) is acylated to provide the tricarbonyl compound (**lvii**). Condensation of **lvii** with the substituted guanidine (**lviii**) provides the pyrimidinone (**lix**) which is converted to the target (**lx**) using standard protocols. Figure 10C illustrates methodology in which a sulfonamide group is present in the starting material (**lxi**) and the substituted guanidine (**lxiii**) contains a nitrogen heterocycle. Accordingly, condensation of **lxii** and **lxiii** provides the pyrimidinone (**lxiv**) which is converted to the target (**lxv**) using $POCl_3$ (or other chlorinating agents) followed by reaction with an amine nucleophile (*e.g.*, 1,2,4-triazole). Additionally, the general methodology allows the preparation of compounds having -O-Ar, -S-Ar, -O-alkyl and -S-alkyl groups at the 2-position of the pyrimidine ring (Figure 10D). For example, treatment of the ketoester (**xx**) with the substituted guanidine (**lxvi**) provides the pyrimidinone (**lxvii**) which can be chlorinated and condensed with R^3-NH-R^4 to provide **lxix**. Removal of the protecting groups yields the 2-aminopyrimidine compound (**lxx**). Diazotization and subsequent chlorination can be carried out using standard procedures to provide **lxxi**. Diplacement of the chloride with either an oxygen-containing nucleophile or a sulfur-containing nucleophile provides the target compounds **lxxii** or **lxxiii**, respectively.

Figure 11 illustrates the preparation of several compounds of formula IIb. In one group of embodiments, substituted pyrimidines having a sulfonamide at the 5-position and an ester group at the 6-position (**lxxiv**) can be saponified to provide **lxxv**, which is then cyclized with dehydrating agents (*e.g.*, sulfuric acid or acetic anhydride) to the fused heterocycle shown as **lxxvi** (see Figure 11A). In other embodiments, diesters (**lxxvii**) are saponified to the diacid (**lxxviii**) and converted to a mixture of amides (**lxxix**, by sequential treatment with acetic anhydride and methylamine), which can then be cyclized by treatment with a dehydrating agent (*e.g.*, acetic anhydride) as indicated to provide a bicyclic system (**lxxx**, see Figure 11B). Yet another fused bicyclic system (**lxxxi**) can be prepared beginning with ethyl 2-oxocyclopentanecarboxylate, using methods outlined above for the conversion of a β-ketoester to a substituted pyrimidine (see Figure 11C). Still another group of embodiments can be prepared via manipulation of nitrile and ester substituents (see Figure 11D). Briefly, ethyl cyanoacetate is first condensed with ethyl oxalyl chloride and the resultant product is treated with a substituted guanidine (exemplified herein with N,N-diethylguanidine) to provide the substituted pyrimidinone (**lxxxii**). Treatment of **lxxxii** with $POCl_3$ (or other chlorinating agent) followed by an appropriate amine (*e.g.*, imidazole, 2-alkylimidazole, isopropylethylamine, pyrrolidine) provides the substituted pyrimidine (**lxxxiii**). Ester hydrolysis and Curtius rearrangement (using, for example, diphenylphosphoryl azide) provide the amino nitrile (**lxxxiv**). Conversion of the nitrile group to an amide by acid hydrolysis, and subsequent treatment with phosgene (or a phosgene equivalent such as diphosgene or dimethylcarbonate) provides the fused bicyclic system, **lxxxv** which can be further converted to **lxxxvi** on treatment with strong base (*e.g.*, NaH) and an alkylating agent (*e.g.*, MeI). Certain intermediates along these synthetic routes can be converted to other useful derivatives

(Figure 11E). For example, **lxxxvii** can be treated with Lawesson's reagent to provide the thioamide **lxxxviii**, which on treatment with phosgene (or a phosgene equivalent) provides the fused bicyclic system **lxxxix**. Alternatively, **lxxxvii** can be treated with sulfuryl chloride in the presence of a tertiary amine base to provide the fused bicyclic system **xc**. Figures 11F and 11G illustrate other methods of preparing compounds within the scope of formula IIb. In Figure 11F, a substituted pyrimidine (**xci**) having a sulfonamide at the 5-position and a carboxylic acid at the 6-position is prepared using methods analogous to those described above. Curtius rearrangement of the carboxylic acid group in **xci** to an amino group provides **xcii**, which is then cyclized to **xciii**, using phosgene or a phosgene equivalent. Figure 11G shows the preparation of a pyrimidine diester (**xciv**) and its conversion to the fused bicyclic system **xcvii**. Briefly, the silyl ester present in **xciv** is hydrolyzed to the acid which is subjected to a Curtius rearrangement to provide **xcv**. Conversion of the remaining ester group to an amide can be accomplished using standard procedures to provide **xcvi.** Cyclization of **xcvi** to **xcvii** can be carried out using phosgene or a phosgene equivalent.

Compounds of formula IIc can be prepared by methods outlined in Figure 12. In one group of embodiments (in Figure 12A), a 4-chloropyrimidine derivative (**xcviii**, prepared by methods described above), is treated with an amine (*e.g.*, allylamine) to provide **xcix**. The ester group is then converted to an N-methyl amide (**c**) upon treatment with methylamine in an alcohol solvent. Cyclization of **c** to **ci** occurs upon treatment with phosgene or an equivalent. Similarly, compounds having more electronegative groups in the ~~6~~-position can be prepared as shown in Figure 12B. For example, the chloropyrimidine **cii** can be produced using methods outlined above and then converted to the bicyclic compound **ciii**, using procedures described for **xcix**. Still other fused systems of formula IIc can be prepared as shown in Figure 12C. Here, a chloropyrimidine derivative (**civ**) is treated with a primary amine (*e.g.*, allylamine) to provide an amino moiety at the 4-position of the pyrimidine ring. Cyclization of the amino moiety onto a sulfonamide (present at the 5-position) can be accomplished with phosgene or an equivalent to provide the target (**cv**).

Preparation of compounds of formula IId can be accomplished, in one embodiment, as outlined in Figure 13. Briefly, ethyl nitroacetate can be condensed with a mixed anhydride (**cvi**) to provide a nitroketoester (**cvii**) which can then be converted to a pyrimidine (**cviii**) upon treatment with a suitably substituted guanidine. Removal of the protecting group, followed by treatment with $POCl_3$ effects chlorination of the pyrimidine ring and cyclization to form a pyrimidinium salt (**cix**). Treatment of **cix** with an amine nucleophile produces the target compound (**cx**). Other compounds in this group can be prepared by starting with ethyl 3,3,3-trifluoropropionate or ethyl cyanoacetate and varying both the substituted guanidine and the amino nucleophile which are used.

Preparation of certain compounds of formula IIe can be accomplished following procedures outlined in Figure 14. According to the scheme depicted in Figure 14, a suitably substituted guanidine (**cxi**, prepared from a protected hydroxypropylamine) is condensed with

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ethyl 2-nitroacetoacetate (or similarly ethyl 2-trifluoromethylacetoacetate) to provide the a pyrimidinone (**cxii**). Removal of the protecting group, chlorination and cyclization using procedures similar to those shown in Figure 13, produces the salt (**cxiii**). Subsequent treatment of **cxiii** with a nucleophilic amine produces the target (**cxiv**).

The compounds used as initial starting materials in this invention may be purchased from commercial sources or alternatively are readily synthesized by standard procedures which are well know to those of ordinary skill in the art.

Some of the compounds of the present invention will exist as stereoisomers, and the invention includes all active stereoisomeric forms of these compounds. In the case of optically active isomers, such compounds may be obtained from corresponding optically active precursors using the procedures described above or by resolving racemic mixtures. The resolution may be carried out using various techniques such as chromatography with a chiral solid support or a chiral solvent, repeated recrystallization of derived asymmetric salts, or derivatization, which techniques are well known to those of ordinary skill in the art.

The compounds of the invention may be labeled in a variety of ways. For example, the compounds may contain radioactive isotopes such as, for example, ^{3}H (tritium), ^{125}I (iodine-125) and ^{14}C (carbon-14). Similarly, the compounds may be advantageously joined, covalently or noncovalently, directly or through a linker molecule, to a wide variety of other compounds, which may provide pro-drugs or function as carriers, labels, adjuvents, coactivators, stabilizers, etc. Such labeled and joined compounds are contemplated within the present invention.

Analysis of Compounds

The subject compounds and compositions were demonstrated to have pharmacological activity in in vitro and in vivo assays, *e.g.*, they are capable of specifically modulating a cellular physiology to reduce an associated pathology or provide or enhance a prophylaxis.

Certain preferred compounds and compositions are capable of specifically inhibiting or suppressing cytomegalovirus infection. For the assessment of activity against human CMV, a method was used which is similar to that described in Kohler, *et al.*, *J. Virol.* **68:**6589-6597 (1994). Briefly, a recombinant human cytomegalovirus (HCMV) was made containing a marker gene (luciferase) under the control of the promoter for the late 28 kDa viral structural phosphoprotein pp28. Human foreskin fibroblast (HFF) cells were infected with the recombinant HCMV virus (MOI 5), placed into 96-well plates, and cultured under standard cell-culture conditions. Compounds that were evaluated for anti-HCMV activity were added to the infected cells 1 hour later. The level of luciferase expression was measured 24 hours after treatment with the test compounds. The biological activity of the test compounds is described by their IC$_{50}$ values, the concentration of test compound that reduces recombinant HCMV late gene expression (represented by luciferase expression in the HFF culture) by 50% relative to control (vehicle-treated) infected cells. As an additional control, the cytotoxicity of test compounds on untreated HFF cells was also evaluated in cultured cell growth experiments.

Table 1 provides biological data for selected compounds from the examples below.

TABLE 1

Compound	IC$_{50}$ (µM)
a	0.8
c	0.1
d	0.02
f	6.0
g	0.8
h	0.3
j	0.01
k	1.0
m	2.0
n	0.4
o	2.0
p	0.3
q	3.0
s	3.0
t	10.0
u	0.1

The following examples are offered by way of illustration and not by way of limitation.

EXAMPLES

^{1}H-NMR spectra were recorded on a Varian Gemini 400 MHz NMR spectrometer. Significant peaks are tabulated in the order: number of protons, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br s, broad singlet) and coupling constant(s) in Hertz. Electron Ionization (EI) mass spectra were recorded on a Hewlett Packard 5989A mass spectrometer. Mass spectrometry results are reported as the ratio of mass over charge, followed by the relative abundance of each ion (in parentheses). All reagents, starting materials and intermediates utilized in these examples are readily available from commercial sources or are readily prepared by methods known to those skilled in the art.

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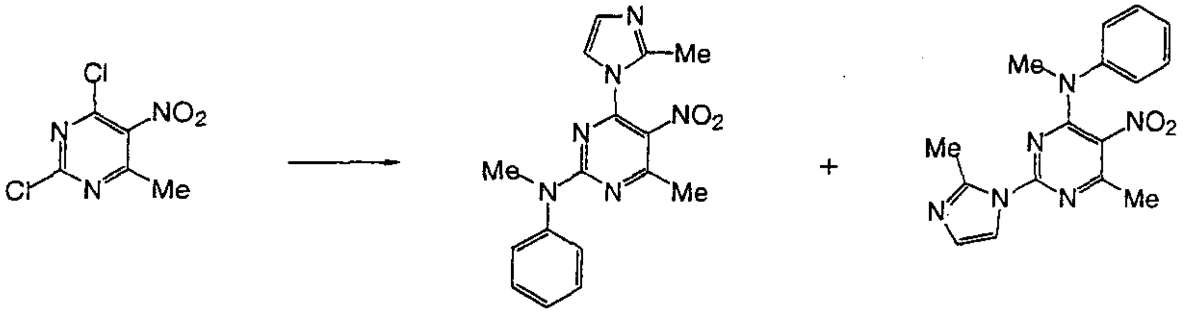
EXAMPLE 1

This example illustrates the synthesis of 2-(N-methylanilino)-4-(2-methylimidazol-1-yl)-6-methyl-5-nitropyrimidine (**a**) and an isomer 4-(N-methylanilino)-2-(2-methylimidazol-1-yl)-6-methyl-5-nitropyrimidine (**b**).



a **b**

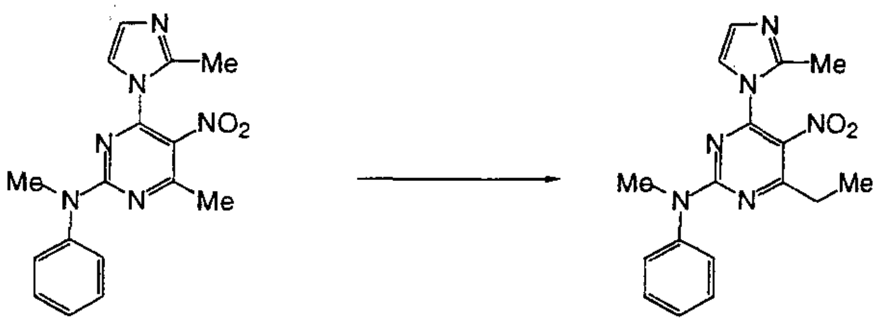
To a stirred cold (-78°C) solution of 2,4-dichloro-6-methyl-5-nitropyrimidine (2.25 g, 10.8 mmol, 1.0 eq) in THF (15 mL) was added 2-methylimidazole (977 mg, 11.9 mmol, 1.1 eq) in a solution of THF (15 mL) dropwise. After 1 hour, the dry ice bath was replaced with a water ice bath and stirring was continued for an additional 2 hours and 15 minutes. At this time N-methylaniline (4.6 mL, 43.2 mmol, 4.0 eq) was added. The reaction solution was stirred 1 hour and 15 minutes at -78°C and at room temperature overnight. At this time the solvent was removed and the residue was diluted with dichloromethane and washed three times with 0.1M HCl and three times with saturated aqueous NaCl solution. The organic phase was evaporated and the residue was purified by chromatography on silica gel (1:1 hexane/diethyl ether, 1% AcOH as eluant) to provide 209 mg of the target compound **a** (6%) along with an isomer (400 mg) and **b** (104.8 mg).

(**a**) ^{1}H NMR (400MHz) (CD_3OD): δ 2.26 (3H, br s); 2.58 (3H, br s); 3.61 (3H, s); 6.88 (1H, s); 7.02 (2H, d); 7.31-7.34 (3H, m); 7.43-7.48 (2H, m). Anal. calcd. for $C_{16}H_{16}N_6O_2$: C, 59.25; H, 4.97; N, 25.91. Found C, 59.16; H, 4.95; N, 25.86.

(**b**) ^{1}H NMR (400MHz) ($CDCl_3$): δ 2.40 (3H, s); 2.80 (3H, s); 3.55 (3H, s); 6.95 (1H, s); 7.13 (2H, m); 7.30-7.39 (3H, m); 7.86 (2H, s).

EXAMPLE 2

This example illustrates the synthesis of 2-(N-methylanilino)-4-(2-methylimidazol-1-yl)-6-ethyl-5-nitropyrimidine (**c**).



a **c**

To a stirred, cold (-78°C) solution of **a** (54.4 mg, 0.168 mmol, 1.0 eq) in THF (1.0 mL) was added $LiN(SiMe_3)_2$, (0.20 mmol, 0.20 mL, of a 1.0M/THF solution) dropwise. After stirring for 10 minutes, MeI (0.105 mL, 1.68 mmol, 10 eq) was added dropwise. The reaction was kept at -78°C for 40 minutes and stirred for an additional 4 hours at 0°C. A small portion of acetic acid (0.25 mL) was poured into the flask and the brown residue was evaporated to dryness. The residue was then dissolved in dichloromethane and washed three times with saturated aqueous NaCl solution and the organic phase was evaporated to dryness to provide a crude yellow oil.

Purification was carried out by column chromatography on silica gel with 1:1 hexane/diethyl ether, 1% AcOH, 3% MeOH as eluant, to provide 21.4 mg of the desired product (37%).

(**c**) ^1H NMR (400MHz) (CD_3OD): δ 1.29 (3H, br s); 2.28 (3H, br s); 2.86 (2H, br s); 3.63 (3H, s); 6.89 (1H, s); 7.02 (1H, s); 7.30-7.39 (3H, m); 7.42-7.49 (2H, m). MS ESI m/z (relative intensity): M+H, 339.2 (100); M+Na, 361.1 (15).

EXAMPLE 3

This example illustrates the synthesis of 2-(N-benzyl-N-methylamino)-4-(2-methylimidazol-1-yl)-6-methyl-5-nitropyrimidine (**d**), 2,4-bis-(N-benzyl-N-methylamino)-6-methyl-5-nitropyrimidine (**e**) and 4-(N-benzyl-N-methylamino)-2-(2-methylimidazol-1-yl)-6-methyl-5-nitropyrimidine (**f**).

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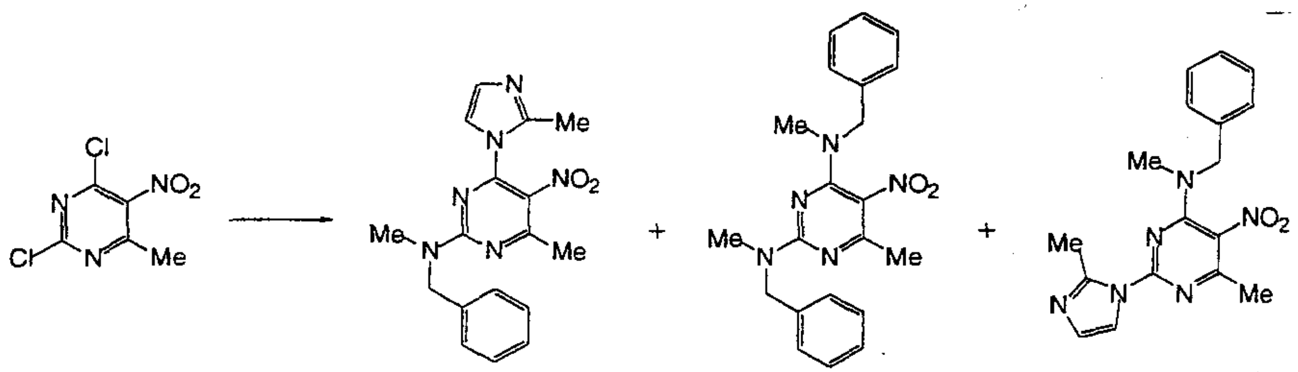


d e f

To a stirred, cold (-78°C) solution of 2,4-dichloro-6-methyl-5-nitropyrimidine (187.7 mg, 0.9 mmol, 1.0 eq) in THF (2.25 mL) and EtOH (2.25 mL) was added 2-methylimidazole (148 mg, 1.8 mmol, 2.0 eq) in a solution of EtOH (2.25 mL) dropwise. After 45 minutes, the dry ice bath was replaced with a water ice bath and the mixture was stirred for an additional 2.2 hours. At this time N-methylbenzylamine (0.465 mL, 3.6 mmol, 4.0 eq) was added. After stirring for 2.7 hours, the solvents were removed by evaporation. The residue was diluted with dichloromethane and washed three times with 0.1M HCl and three times with saturated aqueous NaCl solution. Solvent was removed from the organic phase and the residue was purified by chromatography on silica gel (1:1 hexane/diethyl ether, 1% AcOH, as eluant) to provide **d** (32 mg), **e** (116.3 mg) and **f** (104.8 mg).

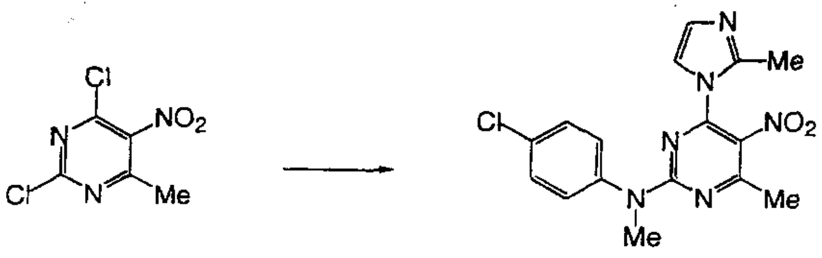
(**d**) ^{1}H NMR (400MHz) ($CDCl_3$): δ 2.30 (1.5H, s); 2.53 (1.5H, s); 2.57 (1.5H, s); 2.59 (1.5H, s); 3.15 (1.5H, s); 3.27 (1.5H, s); 4.88 (1H, s); 4.97 (1H, s); 6.87 (0.5H, s); 6.90 (0.5H, s); 6.96 (0.5H, s); 6.99 (0.5H, s); 7.16 (1H, d); 7.24-7.37 (4H, m). MS ESI m/z (relative intensity): M+H, 339.2 (100); M+Na, 361.1 (8)

(**e**) ^{1}H NMR (400MHz) ($CDCl_3$): δ 2.49 (3H, s); 2.79 (3H, s); 2.90-3.20 (3H, br m); 4.70-4.88 (4H, br m); 7.12-7.35 (10H, br m). MS ESI m/z (relative intensity): M+H, 378.2 (100); M+Na, 400.1 (15)

(**f**) ^{1}H NMR (400MHz) ($CDCl_3$): δ 2.52 (3H, s); 2.67 (3H, s); 2.90 (3H, s); 4.92 (2H, s); 6.89 (1H, s); 7.20 (2H, d); 7.28-7.35 (3H, m); 7.74 (1H, s). MS ESI m/z (relative intensity): M+H, 339.2 (100).

EXAMPLE 4

This example illustrates the synthesis of of 2-(N-methyl-4-chloroanilino)-4-(2-methylimidazol-1-yl)-6-methyl-5-nitropyrimidine (g).



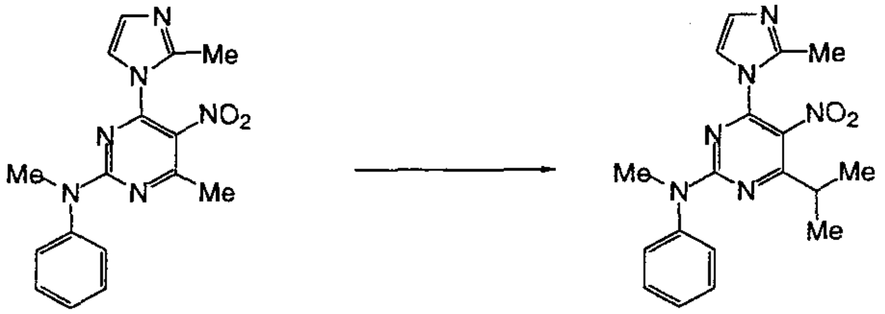
g

To a stirred, cold (-78°C) solution of 2,4-dichloro-6-methyl-5-nitropyrimidine (207.5 mg, 1.0 mmol, 1.0 eq) in THF (2.25 mL) and EtOH (2.25 mL) was added 2-methylimidazole (164 mg, 2.0 mmol, 2.0 eq) in a solution of EtOH (2.25 mL) dropwise. After 45 minutes, the dry ice bath was replaced with a water ice bath and stirring was continued for an additional 2.25 hours. 4-Chloro-N-methylaniline (0.485 mL, 4.0 mmol, 4.0 eq) was then added and the reaction solution was stirred for 2.7 hours. Solvent was removed by evaporation and the residue was diluted with dichloromethane, washed three times with 0.1M HCl, three times with saturated aqueous NaCl solution and dried over $MgSO_4$. Solvent was removed from the organic phase and the residue was purified by silica gel chromatography (1:1 hexane/diethyl ether, 1% AcOH as eluant) to provide g (55.9 mg, 15.6%).

(g) ^{1}H NMR (400MHz) (CD_3OD): δ 2.30 (3H, br s); 2.57 (3H, br s); 3.59 (3H, s); 6.91 (1H, s); 7.02 (1H, s); 7.36 (2H, d); 7.44 (2H,d). MS ESI m/z (relative intensity): M+H, 359.1 (100).

EXAMPLE 5

This example illustrates the synthesis of 2-(N-methylanilino)-4-(2-methylimidazol-1-yl)-6-isopropyl-5-nitropyrimidine (**h**).



a **h**

To a stirred, cold (-78°C) solution of **a** (38.6 mg, 0.12 mmol, 1.0 eq) in THF (0.5 mL) was added NaH (9.5 mg, 60% in oil 0.24 mmol, 2.0 eq). After stirring for 15 minutes, MeI (0.074 mL, 1.19 mmol, 10 eq) was added. The reaction was kept at -78°C for 2

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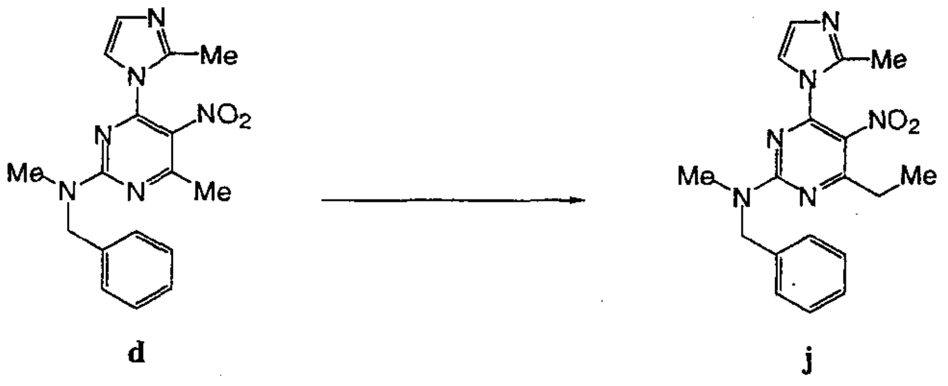
hours, then stirred an additional 2.5 hours at 0 °C. A small portion of acetic acid (0.25 mL) was poured into the flask and the brown mixture was evaporated to dryness. The residue was dissolved into dichloromethane, washed three times with water and three times with saturated aqueous NaCl solution. Solvent was removed from the organic phase and the product was purified by silica gel chromatography (1:1 hexane/diethyl ether, 1% AcOH as eluant) to provide the target compound (13.3 mg 33%).

(**h**) ^{1}H NMR (400MHz) ($CDCl_3$): δ 1.20-1.35 (6H, m); 2.29 (3H, br s); 3.24 (1H, m); 3.62 (3H, s); 4.92 (2H, s); 6.89 (1H, br s); 7.03 (1H, br s); 7.30-7.40 (3H, m); 7.71-7.48 (2H, m). MS ESI m/z (relative intensity): M+H, 353.1 (100).

EXAMPLE 6

This example illustrates the synthesis of 2-(N-benzyl-N-methylamino)-4-(2-methylimidazol-1-yl)-6-ethyl-5-nitropyrimidine (**j**).

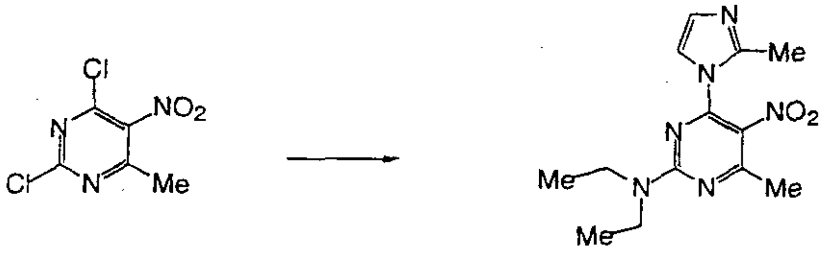


To a stirred, cold (-78°C) solution of **d** (57.7 mg, 0.170 mmol in THF (0.5 mL) was added $LiN(SiMe_3)_2$, (0.17 mL, 0.17 mmol, 1.0 eq, 1.0M/THF) dropwise. After stirring for 10 minutes, MeI (0.106 mL, 1.70 mmol, 10 eq) was added dropwise. The reaction was kept at -78°C for 2 hours and then stirred for an additional 3 hours at 0°C. A small portion of acetic acid (0.25 mL) was poured into the flask and the brown mixture was evaporated to dryness. The residue was dissolved into dichloromethane, washed three times with water, three times with saturated aqueous NaCl solution and the organic phase was evaporated to dryness. The target compound was obtained following silica gel chromatography (1:1 hexane/diethyl ether, 1% AcOH, 3% MeOH as eluant). Yield: 30.3 mg (50.4%).

(j) ^{1}H NMR (400MHz) (CD_3OD): δ 1.26-1.41 (3H,m); 2.21 (1.5H,s); 2.45 (1.5H, s); 2.86-2.94 (2H, m); 3.22 (1.5H, s); 3.35 (1.5H, s); 4.93 (1H, s); 5.05 (1H,s); 6.91 (0.5H, s); 6.94 (0.5H, s); 7.07 (0.5H, s); 7.12 (0.5H, s); 7.23-7.38 (5H, m). MS ESI m/z (relative intensity): M+H, 353.1 (100).

EXAMPLE 7

This example illustrates the synthesis of 2-(N,N-diethylamino)-4-(2-methylimidazol-1-yl)-6-methyl-5-nitropyrimidine (**k**).

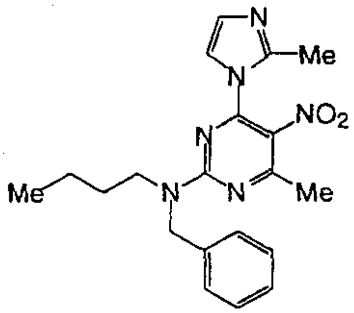


k

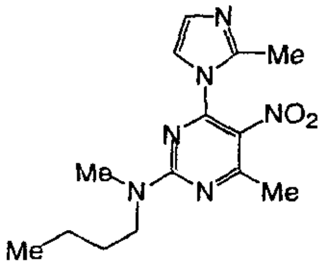
To a cooled (-78°C) solution of 2,4-dichloro-6-methyl-5-nitropyrimidine (208 mg, 1.0 mmol, 1.0 eq. in 2 mL each of EtOH and THF) was added 2-methylimidazole (164 mg, 2.0 mmol, 2.0eq.) in 2 mL of EtOH. The resulting mixture was stirred for 1 hour at -78°C, then for 2 hours at 0°C. Diethylamine (0.413 mL, 4.0 eq.) was added dropwise and the reaction was stirred overnight. The resulting mixture was diluted with dichloromethane, washed with 0.1N HCl, saturated NaCl, dried ($MgSO_4$), and filtered. Solvent was removed by evaporation and the residue was purified by silica gel chromatography to provide 35 mg of the target compound **k** as an oil.

(k) ^{1}H NMR (400MHz, $CDCl_3$): δ 1.15-1.23 (3H, m); 2.48 (3H, s); 2.53 (3H, s); 3.59-3.60 (2H, q); 3.68-3.70 (2H, q); 6.86 (1H, s); 6.95 (1H, s). MS ESI m/z (relative intensity): M+H, 291.2 (100).

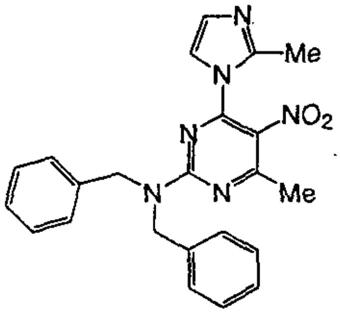
In a similar manner, the following compounds were prepared using the indicated amine in place of diethylamine. Each was obtained as a yellow oil.



m



n

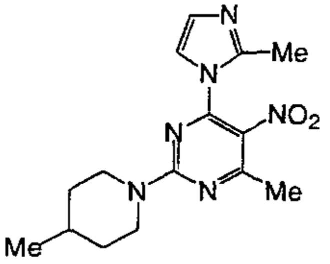


o

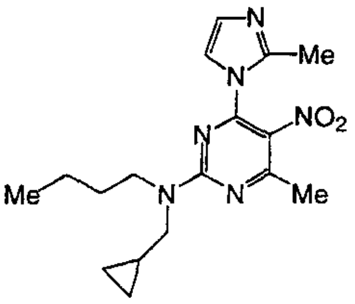
2-(N-benzylbutylamino)-4-(2-methylimidazol-1-yl)-6-methyl-5-nitropyrimidine – Compound **m** (N-butylbenzylamine) -- 40 mg. ^{1}H NMR (400MHz, $CDCl_3$): δ 0.86-0.95 (3H, m); 1.23-1.38 (2H, m); 1.51-1.68 (2H, m); 2.52 (3H, m); 3.52 (2H, t); 4.83 (1H, s); 6.80 (1H, s); 6.92 (1H, s); 7.13 (2H, d); 7.26-7.31 (3H, m). MS ESI m/z relative intensity: M+H, 381.2 (100).

2-(N-methylbutylamino)-4-(2-methylimidazol-1-yl)-6-methyl-5-nitropyrimidine Compound **n** (N-methylbutylamine) -- 68 mg. ^{1}H NMR (400MHz, $CDCl_3$): δ 0.95 (3H, t); 1.32 (2H, m); 2.51 (3H, br s); 2.55 (3H, s); 3.15-3.24 (3H, d); 3.58-3.72 (2H, t); 6.85 (1H, s); 6.95 (1H, s). MS ESI m/z (relative intensity) M+H, 305.4 (100).

2-(N,N-dibenzylamino)-4-(2-methylimidazol-1-yl)-6-methyl-5-nitropyrimidine Compound **o** (Dibenzylamine) -- 20 mg. ^{1}H NMR (400MHz, $CDCl_3$): δ 2.53 (3H, br s); 2.55 (3H, br s); 4.81 (2H, s); 4.96 (2H,s); 6.85 (1H, s); 6.95 (1H, s). MS ESI m/z (relative intensity) M+H, 415.6 (100).



p



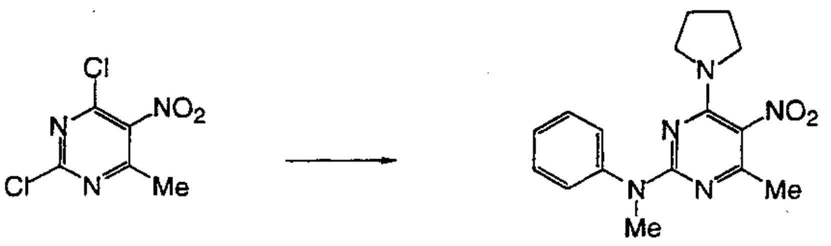
q

Compound **p** (4-methylpiperidine) -- 45 mg. ^{1}H NMR (400MHz, $CDCl_3$): δ 1.12-1.16 (3H, m); 2.46 (3H, s); 2.51 (3H, s); 3.40-3.47 (8H, m); 6.84 (1H, s); 6.99 (1H, s). MS ESI m/z (relative intensity): M+H, 317.1 (100).

Compound **q** (N-(cyclopropylmethyl)butylamine) -- 41 mg. ^{1}H NMR (400MHz, $CDCl_3$): δ 0.23-0.64 (4H, m); 0.89-0.93 (3H, m); 1.18 (1H, t); 1.59-1.73 (2H, m); 2.49-2.51 (3H, d); 2.54-2.55 (3H, d); 3.46-3.58 (2H, m). MS ESI m/z (relative intensity): M+H, 331.2 (100).

EXAMPLE 8

This example illustrates the synthesis of 2-(N-methylanilino)-4-pyrrolidino-6-methyl-5-nitropyrimidine (**r**).

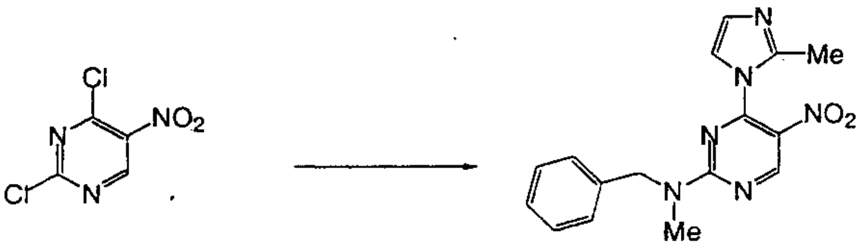


r

To a cooled (-78°C) solution of 2,4-dichloro-6-methyl-5-nitropyrimidine (208 mg, 1.0 mmol, 1.0 eq. in 2 mL each of EtOH and THF) is added of pyrrolidine (78mg, 1.1eq) in 1.0 mL of EtOH. The resulting solution is stirred for 1 hour at -78°C, then for 2 hours at 0°C. N-methylaniline (0.432 mL, 4.0 eq.) is added dropwise and the reaction is stirred overnight. The resulting mixture is diluted with dichloromethane, washed with 0.1N HCl, saturated NaCl, dried ($MgSO_4$), and filtered. Solvent is removed by evaporation and the residue is purified by chromatography to provide the target compound (**r**).

EXAMPLE 9

This example illustrates the synthesis of 2-(N-Methyl-N-benzylamino)-4-(2-methylimidazol-1-yl)-5-nitropyrimidine (s).



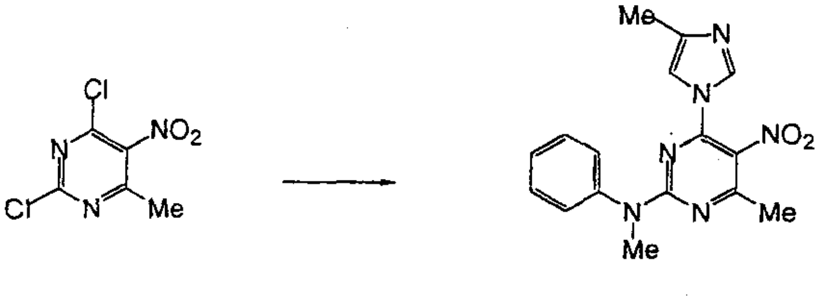
s

To a solution of 2,4-dichloro-5-nitropyrimidine (200 mg, 1.0 mmol) in dioxane (5 mL) at 80 °C was added 2-methylimidazole (85 mg, 1.0 mmol) and N-methyl-N-benzylamine (133 µL, 1 mmol). The solution was stirred overnight at 80 °C, cooled, and directly chromatographed (1/1 hexane diethyl ether) to yield the title compound (s).

(s) ^{1}H NMR (400MHz) (CD_3OD): δ 3.09 (s, 1.5H), 3.17 (s, 1.5H), 3.18 (s, 1.5H), 4.5-4.8 (m, 2H), 7.2-7.5 (m, 8H).

EXAMPLE 10

This example illustrates the synthesis of 2-(N-Methylanilino)-4-(4-methylimidazol-1-yl)-6-methyl-5-nitropyrimidine (**t**).



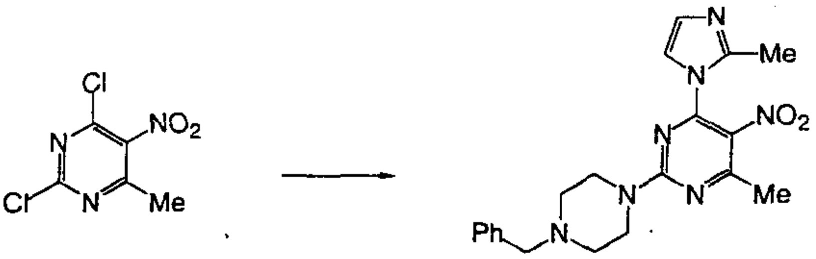
t

To a solution of 2,4-dichloro-6-methyl-5-nitropyrimidine (150 mg, 0.72 mmol) in dioxane (5 mL) at 80 °C was added 4-methylimidazole (60 mg, 0.72 mmol) and N-methylaniline (77 mg, 0.72 mmol). The solution was stirred overnight at 80 °C, cooled, and directly chromatographed (1/1 hexane diethyl ether) to yield the title compound (**t**).

(**t**) ^{1}H NMR (400MHz) (CD_3OD): δ 2.37 (s, 3H), 2.74 (s, 3H), 3.30 (s, 3H), 7.25-7.55 (m, 5H), 7.75 (s, 1H), 9.31 (s, 1H).

EXAMPLE 11

This example illustrates the synthesis of 2-(4-benzylpiperazin-1-yl)-4-(2-methylimidazol-1-yl)-6-methyl-5-nitropyrimidine (**u**).



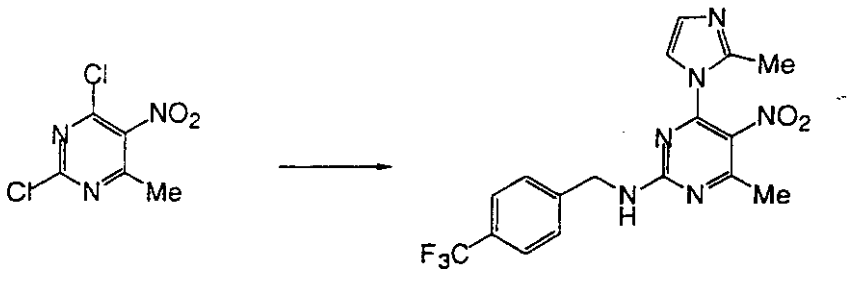
u

To a solution of 2,4-dichloro-6-methyl-5-nitropyrimidine (175 mg, 0.84 mmol) in dioxane (5 mL) at 80 °C was added 2-methylimidazole (85 mg, 0.84 mmol) and 1-benzylpiperazine (148 µL, 0.84 mmol). The solution was stirred overnight at 80 °C, cooled, and directly chromatographed (1/1 hexane diethyl ether) to yield the title compound (**u**).

(u) ^{1}H NMR (400MHz) (CD$_3$OD): δ 2.42 (s, 3H), 2.60 (s, 3H), 3.38 (br s, 4H), 3.80 (br s, 4H), 4.38 (s, 2H), 7.30-7.55 (m, 7H). MS ESI 347 m/e (relative intensity): M+H, 348.0 (100).

EXAMPLE 12

This example illustrates the synthesis of 2-(4-trifluoromethylbenzylamino)-4-(2-methylimidazol-1-yl)-6-methyl-5-nitropyrimidine (v).



v

To a stirred mixture of 2-chloro-4-hydroxy-6-methyl-5-nitropyrimidine (300 mg, 1.58 mmol, 1.0 eq) in absolute ethanol (20 mL) was added 4-(trifluoromethyl)-benzylamine (540 mg, 3.1 mmol, 2.0 eq), and sodium acetate (130 mg, 1.58 mmol, 1.0 eq). The mixture was slowly heated and the resulting solution refluxed for 22 hours. The mixture was then cooled and ethanol was removed *in vacuo*. The oily residue was dissolved in ethyl acetate and washed three times with 1M HCl, three times with saturated NaCl solution, then dried over $MgSO_4$. Removal of solvent provided a crude yellow solid intermediate which was dried under vacuum then dissolved in 4 mL of $POCl_3$ with heating (95-100°C) for 0.5 hours. The $POCl_3$ was removed by rotary evaporation and the crude brown product was purified using chromatography (1:1 hexane/dichloromethane) to provide a chloropyrimidine intermediate (313 mg), which was carried on directly without additional purification.

To a stirred solution of the above chloropyrimidine (150 mg, 0.4 mmol, 1.0 eq) in acetonitrile (2.5 mL) was added 2-methylimidazole (142 mg, 1.7 mmol, 4.0 eq). The resulting mixture was heated at reflux for 5 hours, cooled, and the solvent removed by rotary evaporation. The residue was dissolved in ethyl acetate, washed with 0.1M HCl, water, brine and dried over $MgSO_4$ to give a crude yellow solid following removal of solvent. The solid was purified using chromatography with 2.5% MeOH/dichloromethane to give a yellow oil. The title compound was obtained by precipitation from dichloromethane and hexane. Yield: 152.3 mg, 51% from the starting 2-chloro-4-hydroxy-6-methyl-5-nitropyrimidine.

(v) ^{1}H NMR (400MHz) CDCl$_3$ δ 2.28 (1.5H, s); 2.42 (1.5H, s); 2.55 (1.5H, s); 2.58 (1.5H, s); 4.71 (1H, d); 4.80 (1H, d); 6.67 (0.5H, br s); 6.80 (0.5H,br s); 6.88 (1H, d); 6.96 (1H, s); 7.41 (1H, d); 7.49 (1H, d); 7.62 (2H, d). MS ESI m/z (relative intensity): M+H 392.9 (100).

EXAMPLE 13

This example illustrates the preparation of 2-((1-phenyl-1-propyl)amino)-4-(imidazol-1-yl)-6-methyl-5-nitropyrimidine (**w**) using an alternate procedure for the addition of an imidazole group to the pyrimidine nucleus.

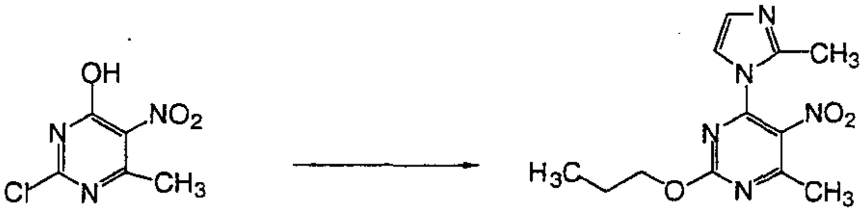
w

To a stirred solution of 2-((1-phenylpropyl)amino)-4-hydroxy-6-methyl-5-nitropyrimidine (78 mg, 0.27 mmol, 1.0 eq, prepared in a manner similar to that in Example 12 above) in pyridine (1 mL) was added trifluoroacetic anhydride (115 µL, 0.81 mmol, 3.0 eq). The mixture was stirred for 15 minutes, then imidazole (184 mg, 2.7 mmol, 10 eq) was added, and the mixture was stirred overnight. Pyridine was removed by rotary evaporation and the dark residue was dissolved in ethyl acetate and washed with 0.1M HCl, followed by brine. The crude solid obtained after removal of solvent was purified by chromatography on silica gel (2.5% MeOH/CH_2Cl_2) to give 36.1 mg (42%) of the title compound.

(**w**) ^1H NMR (400MHz) $CDCl_3$ δ 0.99 (3H, m); 1.73-2.02 (2H, m); 2.48 (3H, s); 4.81 (0.66H, dd); 5.07 (0.33H, dd); 6.16 (0.66H, d); 7.02 (0.33H, d); 7.08-7.12 (2H,m); 7.25-7.38 (5H, m); 7.89 (0.66H, s); 8.18 (0.33H, s). MS ESI m/z (relative intensity): M+H 339.2 (100).

EXAMPLE 14

This example illustrates the synthesis of pyrimidine derivatives having an alkoxy group in the 2-position, exemplified by 2-(1-propyloxy)-4-(2-methylimidazol-1yl)-6-methyl-5-nitropyrimidine (**x**).



x

To a flask charged with n-propanol (5 mL) was added NaH (128 mg, 60% in oil 3.19 mmol, 2.0 eq) and the mixture was stirred under nitrogen for 10 minutes. The resulting solution was transferred via canula into a flask containing a solution of 2-chloro-4-hydroxy-6-methyl-5-nitropyrimidine (302 mg, 1.6 mmol, 1.0 eq) in n-propanol (5 mL). The resulting mixture was heated in an oil bath at 100 °C for 1 hour, poured into a separatory funnel containing dilute HCl and extracted with dichloromethane. The organic phase was separated and washed with water, brine and dried over $MgSO_4$ to give a crude solid (yield 297 mg) after removal of solvent. The crude solid was heated in neat $POCl_3$ (3 mL) for 6 minutes at 85-90°C, cooled on ice, and the $POCl_3$ was removed *in vacuo*. The chloropyrimidine intermediate was purified via chromatography to provide 117 mg of the intermediate which was converted to the title compound using methods described in Example 12. The product was obtained as a yellow oil (191 mg, 43% from 2-chloro-4-hydroxy-6-methyl-5-nitropyrimidine).

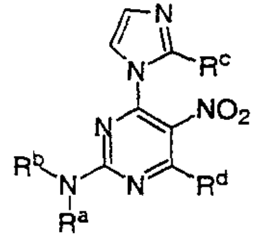
(x) ^1H NMR (400MHz) $CDCl_3$ δ 1.04 (3H, t); 1.86 (2H, dq); 2.52 (3H, s); 2.61 (3H, s); 4.38 (2H, t); 6.90 (1H, d); 6.98 (1H, d). MS ESI m/z (relative intensity): M+H 278.1 (100).

EXAMPLE 15

The compounds listed in Table 2 were prepared using the procedures outlined in Examples 12-13. Compounds were tested in the CMV assay described above and exhibited the following levels of activity: +, $IC_{50} > 500$ nM; ++, 100 nM < $IC_{50} \leq 500$ nM; +++, $IC_{50} \leq$ 100 nM.

17

TABLE 2



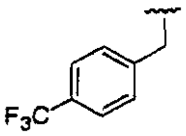
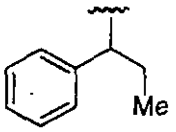
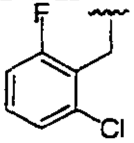
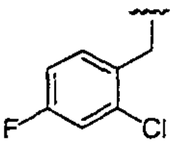
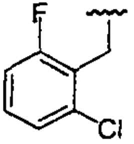
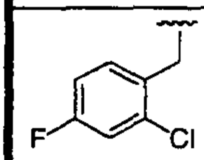
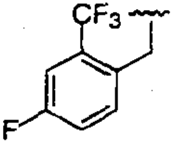
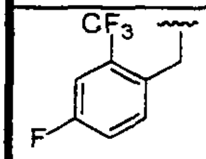
R^a	R^b	R^c	R^d	m/z (m+1)	Antiviral Activity
	H	Me	Me	392.9	++
	H	Me	Me	353.1	++
	H	Et	Me	391.1	++
	H	Et	Me	406.9	++
	H	Me	Me	377.1	++
	H	Et	Me	391.1	++
	H	Me	Me	411.1	++
	H	Et	Me	425.1	++

TABLE 2 (cont'd)

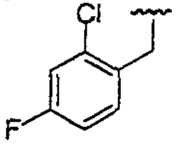
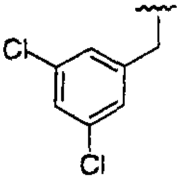
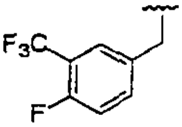
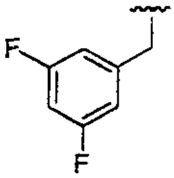
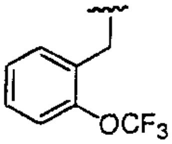
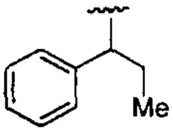
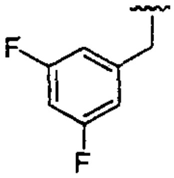
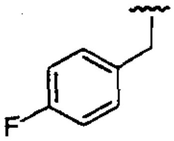
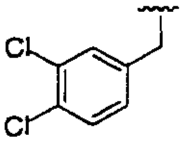
R^a	R^b	R^c	R^d	m/z (m+1)	Antiviral Activity
	H	Me	Me	377.1	++
	H	Me	Me	393.1	++
	H	Me	Me	411.1	+++
	H	Me	Me	361.1	+++
	H	Me	Me	409.1	++
	H	H	Me	339.2	+
	H	H	Me	347.1	+
	H	Me	Me	343.1	++
	H	Me	Me	393.1	++

TABLE 2 (cont'd)

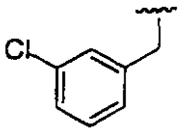
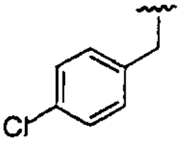
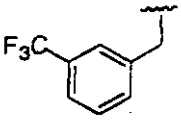
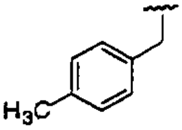
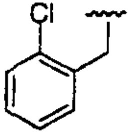
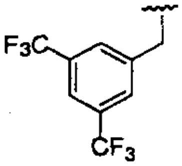
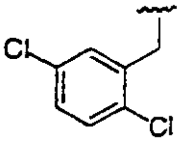
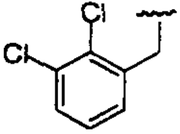
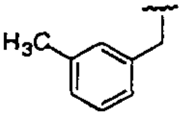
R^a	R^b	R^c	R^d	m/z (m+1)	Antiviral Activity
	H	Me	Me	359.1	+++
	H	Me	Me	359.1	++
	H	Me	Me	392.1	+++
	H	Me	Me	339.1	+
	H	Me	Me	359.1	+++
	H	Me	Me	461.1	+
	H	Me	Me	393.1	+++
	H	Me	Me	393.1	++
	H	Me	Me	339.1	++

TABLE 2 (cont'd)

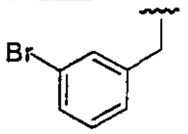
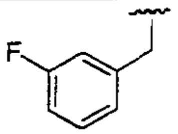
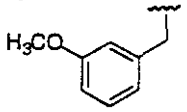
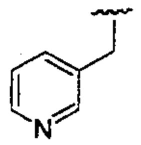
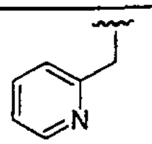
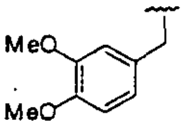
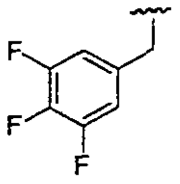
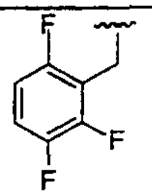
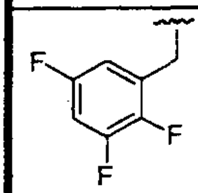
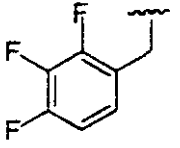
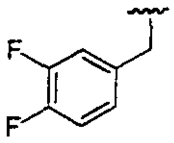
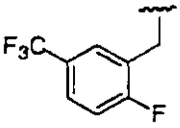
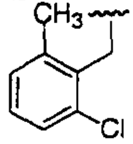
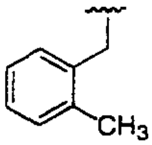
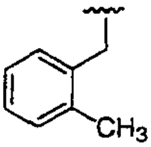
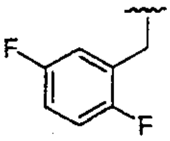
R^a	R^b	R^c	R^d	m/z (m+1)	Antiviral Activity
	H	Me	Me	403.0	+++
	H	Me	Me	343.1	++
	H	Me	Me	355.1	++
	H	Me	Me	326.1	+
	H	Me	Me	326.1	++
	H	Me	Me	385.1	++
	H	Me	Me	379.1	++
	H	Me	Me	379.1	++
	H	Me	Me	379.1	++
	H	Me	Me	379.1	++

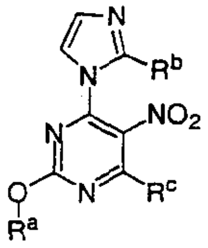
TABLE 2 (cont'd)

R^a	R^b	R^c	R^d	m/z (m+1)	Antiviral Activity
	H	Me	Me	361.1	++
	H	Me	Me	411.1	+++
	H	Me	Me	373.1	++
	H	H	Me	325.1	+
	H	Me	Me	339.1	++
	H	Me	Me	361.1	++

EXAMPLE 16

The compounds listed in Table 3 were prepared using procedures similar to those outlined in Examples 12-14. Compounds were tested in the CMV assay described above and exhibited the following levels of activity: +, $IC_{50} > 500$ nM.

TABLE 3

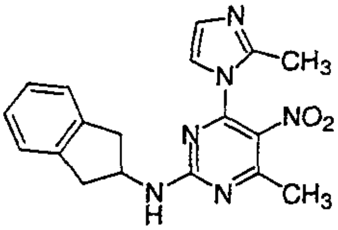


R^a	R^b	R^c	m/z (m+1)	Antiviral Activity
n-propyl	Me	Me	278.1	+
n-propyl	H	Me	264.1	+
n-butyl	Me	Me	292.2	+
n-butyl	H	Me	278.1	+
phenethyl	H	Me	326.1	+
methyl	Me	Me	250.1	+
ethyl	Me	Me	264.1	+
benzyl	H	Me	312.2	+
3-methoxy-1-butyl	H	Me	308.1	+
3-methoxy-1-butyl	Me	Me	322.3	+
3,3-dimethyl-1-butyl	H	Me	306.2	+
3,3-dimethyl-1-butyl	Me	Me	320.1	+

3

EXAMPLE 17

This example illustrates the synthesis of 2-(2-indanamino)-4-(2-methylimidazol-1-yl)-6-methyl-5-nitropyrimidine.

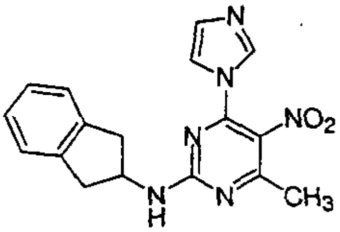


2-(2-Indanamino)-4-chloro-6-methyl-5-nitropyrimidine prepared according to the procedure of Example 12, but using 2-indanamine as the nucleophile, (56 mg, 0.18 mmol) was dissolved in 2.0 mL EtOH followed by the addition of 2-methylimidazole (38 mg, 0.46 mmol, 2.5 equiv). The resulting yellow solution was placed in an 80 °C bath and allowed to stir for 24 hours. The solution was then concentrated under reduced pressure. Purification by flash chromatography (SiO_2, 2% MeOH/CH_2Cl_2) gave 34 mg of the (52%) title compound as an amorphous yellow: mp 203–204 °C.

^{1}H NMR ($CDCl_3$, 400 MHz, mixture of rotamers) δ 7.28-7.13 (m, 5 H), 6.99 (s, 0.5 H), 6.96 (s, 0.5 H), 6.17 (d, J = 7.9 Hz, 0.5 H), 6.06 (d, J = 7.3 Hz, 0.5 H), 4.93 (m, 0.5 H), 4.73 (m, 0.5 H), 3.45-3.34 (m, 2 H), 2.94 (dd, J = 4.8, 16.2 Hz, 1 H), 2.89 (dd, J = 4.3, 16.0 Hz, 1 H), 2.71 (s, 1.5 H), 2.65 (s, 1.5 H), 2.63, s, 1.5 H), 2.53 (s, 1.5 H); MS ESI m/z (relative intensity): 351.2 (M + H, 100). Anal. calcd for $C_{18}H_{18}N_6O_2$: C, 61.70; H, 5.18; N, 23.99. Found: C, 61.08; H, 5.22; N, 23.57.

EXAMPLE 18

This example illustrates the synthesis of 2-(2-indanamino)-4-imidazol-1-yl-6-methyl-5-nitropyrimidine.



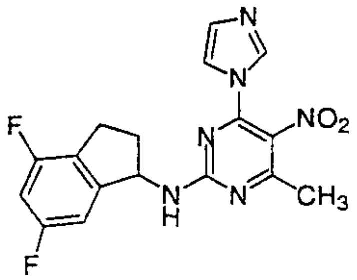
2-(2-Indanamino)-4-chloro-6-methyl-5-nitropyrimidine (66.8 mg, 0.22 mmol) was dissolved in 2.0 mL EtOH followed by the addition of imidazole (37 mg, 0.54 mmol, 2.5 equiv). The yellow solution was heated to 80 °C for 18 hours. The solution was then concentrated under reduced pressure and purified by flash chromatography (SiO_2, 2%

$MeOH/CH_2Cl_2$) to give 52.1 mg (71%) of the product as an amorphous yellow solid (0.155 mmol): mp 177-178 °C.

^1H NMR ($CDCl_3$, 400 MHz, mixture of rotamers) δ 8.23 (s, 0.5 H), 8.16 (s, 0.5 H), 7.28-7.11 (m, 6 H), 6.09 (broad s, 0.5 H), 5.91 (d, *J* = 7.2 Hz, 0.5 H), 4.93 (m, 0.5 H), 4.79 (m, 0.5 H), 3.40 (dd, *J* = 7.0, 15.9 Hz, 2 H), 2.91 (dd, *J* = 4.1, 15.8 Hz, 2 H), 2.56 (s, 1.5 H), 2.46 (s, 1.5 H);); MS ESI(relative abundance) 337.1 (M + H, 100). Anal. calcd for $C_{17}H_{16}N_6O_2$: C, 60.71; H, 4.79; N, 24.99. Found: C, 60.29; H, 4.89; N, 24.69.

EXAMPLE 19

This example illustrates the synthesis of 2-(4,6-difluoro-1-indanamino)-4-(imidazol-1-yl)-6-methyl-5-nitropyrimidine.

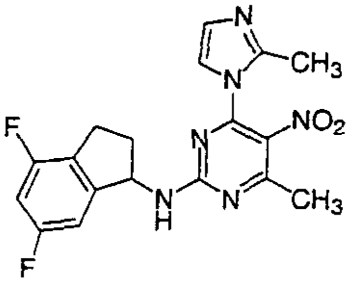


2-(4,6-Difluoro-1-indanamino)-4-chloro-6-methyl-5-nitropyrimidine prepared according to the procedure of Example 12, using 4,6-difluoro-1-indanamine as the nucleophile (56 mg, 0.16 mmol) was dissolved in 2.0 mL EtOH followed by the addition of imidazole (28 mg, 0.411 mmol, 2.5 equiv). The solution was heated to 80 °C for 23 hours. The solution was then concentrated under reduced pressure and purified by flash chromatography (SiO_2, 2% $MeOH/CH_2Cl_2$) to give 35.5 mg (58% yield) of the product as an amorphous yellow solid. mp 175-176 °C.

^1H NMR ($CDCl_3$, 400 MHz, mixture of rotamers) δ 8.09 (s, 0.5 H), 8.06 (s, 0.5 H), 7.26-7.10 (m, 2 H), 6.82 (dd, *J* = 7.6, 11.6 Hz, 1 H), 6.72 (dd, *J* = 8.8, 8.8 Hz, 1 H), 5.95 (broad s, 0.5 H), 5.82 (d, *J* = 8.4 Hz, 0.5 H), 5.72 (m, 0.5 H), 5.56 (m, 0.5 H), 3.05 (m, 1 H), 2.87 (m, 1 H), 2.73 (m, 1 H), 2.55 (s, 1.5 H), 2.49 (s, 1.5 H), 1.98 (m, 1 H);); MS ESI(relative abundance) 373.1 (M + H, 100). Anal. calcd for $C_{17}H_{14}F_2N_6O_2$: C, 54.84; H, 3.79; N, 22.57. Found: C, 54.95; H, 3.76; N, 22.32.

EXAMPLE 20

This example illustrates the synthesis of 2-(4,6-difluoro-1-indanamino)-4-(2-methylimidazol-1-yl)-6-methyl-5-nitropyrimidine.

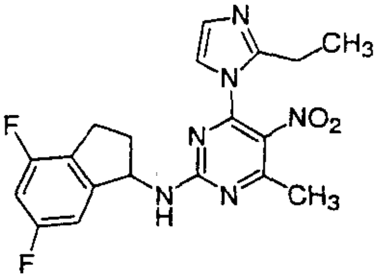


2-(4,6-Difluoro-1-indanamino)-4-chloro -6-methyl-5-nitropyrimidine (56 mg, 0.16 mmol) was dissolved in 2.0 mL EtOH followed by the addition of 2-methylimidazole (34 mg, 0.41 mmol, 2.5 equiv) and the solution was heated to 80 °C with stirring for 26 hours. The solution was then concentrated under reduced pressure and purified by flash chromatography (SiO_2, 2% MeOH/CH_2Cl_2) to give 42.6 mg (67% yield) of the as an amorphous yellow solid. mp 164-165 °C.

^{1}H NMR ($CDCl_3$, 400 MHz, mixture of rotamers) δ 6.98 (s, 1 H), 6.90 (s, 1 H), 6.81 (m, 1 H), 6.71 (m, 1 H), 5.87-5.81 (m, 1 H), 5.73 (m, 0.5 H), 5.54 (m, 0.5 H), 3.05 (m, 1 H), 2.82 (m, 1 H), 2.70 (m, 1 H), 2.60 (s, 1.5 H), 2.53 (s, 1.5 H), 2.51 (s, 1.5 H), 2.46 (s, 1.5 H), 1.98 (m, 1 H);); MS ESI(relative abundance) 387.1 (M + H, 100). Anal. calcd for $C_{18}H_{16}F_2N_6O_2$: C, 55.96; H, 4.17; N, 21.75. Found: C, 56.15; H, 4.59; N, 20.71.

EXAMPLE 21

This example illustrates the synthesis of 2-(4,6-difluoro-1-indanamino)-4-(2-ethylimidazol-1-yl)-6-methyl-5-nitropyrimidine.

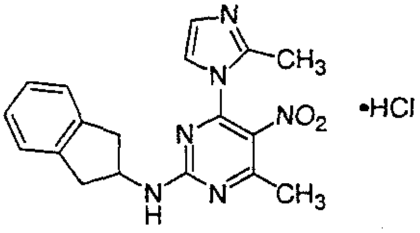


2-(4,6-Difluoro-1-indanamino)-4-chloro -6-methyl-5-nitropyrimidine (56 mg, 0.16 mmol) was dissolved in 2.0 mL EtOH followed by the addition of 2-ethylimidazole (39 mg, 0.41 mmol, 2.5 equiv) and the solution was heated to 80 °C for 23.5 hours. The solution was then concentrated under reduced pressure and purified by flash chromatography (SiO_2, 2% MeOH/CH_2Cl_2) to give 39.6 mg (60% yield) of the product as an amorphous yellow solid: mp 88-89 °C.

^{1}H NMR (CDCl$_3$, 400 MHz, mixture of rotamers) δ 7.02 (s, 1 H), 6.88 (s, 1 H), 6.81 (m, 1 H), 6.72 (m, 1 H), 5.85 (d, J = 9.0 Hz, 0.5 H), 5.81-5.70 (m, 1 H), 5.55 (m, 0.5 H), 3.04 (m, 1 H), 2.86-2.64 (m, 4 H), 2.60 (s, 1.5 H), 2.53 (s, 1.5 H), 1.98 (m, 1 H), 1.29 (t, J = 7.5 Hz, 3 H); MS ESI(relative abundance): 401.1 (M + H, 100). Anal. calcd for $C_{19}H_{18}F_2N_6O_2$: C, 57.00; H, 4.53; N, 20.99. Found: C, 56.93; H, 4.50; N, 20.71.

EXAMPLE 22

This example illustrates the synthesis of 2-(2-indanamino)-4-(2-methylimidazol-1-yl)-6-methyl-5-nitropyrimidine, monohydrochloride salt.

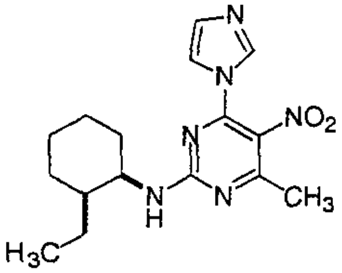


2-(2-Indanamino)-4-chloro-6-methyl-5-nitropyrimidine (310 mg, 1.02 mmol) prepared in Example 17was dissolved in 7 mL EtOH followed by the addition of 2-methylimidazole (600 mg, 7.3 mmol, 7.2 equiv). The resulting yellow solution was then heated at 80 °C with magnetic stirring. After 24 hours the solution was concentrated under reduced pressure and purified by flash chromatography (SiO$_2$, 2% MeOH/CH$_2$Cl$_2$) to give 303.6 mg of the free base as a yellow solid (0.867 mmol). The yellow solid was then dissolved in 3 mL anhydrous THF followed by the addition of 2 mL (8.0 mmol, 9.2 equiv) of a 4.0 M solution of HCl in 1,4-dioxane. A precipitate was immediatly formed, and the resulting slurry was allowed to stir for 10 min. The slurry was then concentrated under reduced pressure, taken up in 3 mL THF, and concentrated again. The resulting yellow solid was recrystallized from hot EtOAc to give 179 mg (45% yield) of the hydrochloride salt as light yellow needles: mp 184-185 °C.

^{1}H NMR (CD$_3$OD, 400 MHz, mixture of rotamers) δ 7.76 (d, J = 2.2 Hz, 0.5 H), 7.71 (d, J = 2.2 Hz, 0.5 H), 7.64 (d, J = 2.2 Hz, 0.5 H), 7.61 (d, J = 2.2 Hz, 0.5 H), 7.22 (m, 2 H), 7.15 (m, 2 H), 4.92 (m, 0.5 H), 4.72 (m, 0.5 H), 3.41-3.31 (m, 1 H), 2.97 (m, 1 H), 2.73 (s, 1.5 H), 2.72 (s, 1.5 H), 2.68 (s, 1.5 H), 2.65 (s, 1.5 H). Anal. calcd for $C_{18}H_{18}N_6O_2$•HCl: C, 55.89; H, 4.95; N, 21.73; Cl, 9.16. Found: C, 55.89; H, 5.00; N, 21.56; Cl, 9.14.

EXAMPLE 23

This example illustrates the synthesis of 2-(*cis*-2-ethylcyclohexylamino)-4-imidazol-1-yl-6-methyl-5-nitropyrimidine.



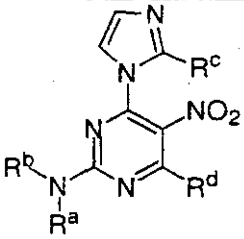
2-(*cis*-2-Ethylcyclohexylamino)-4-chloro-6-methyl-5-nitropyrimidine (58.6 mg, 0.196 mmol) was dissolved in 2.0 mL EtOH followed by the addition of imidazole (53mg, 0.78 mmol, 4.0 equiv). The resulting yellow solution was then heated to 80 °C with magnetic stirring. After 20 hours the solution was concentrated under reduced pressure and purified by flash chromatography (SiO_2, 2% $MeOH/CH_2Cl_2$) to give 39.5 mg (61% yield) of the title compound as an amorphous yellow solid: mp 123-124 °C.

^1H NMR ($CDCl_3$, 400 MHz, mixture of rotamers) δ 8.22 (s, 0.5 H), 8.17 (s, 0.5 H), 7.39-7.27 (m, 2 H), 5.92 (d, *J* = 7.8 Hz, 1 H), 4.57 (m, 0.5 H), 4.42 (m, 0.5 H), 2.65 (s, 1.5 H), 2.61 (m, 1.5 H), 2.02 (m, 1 H), 1.87-1.34 (m, 10 H), 1.02 (t, *J* = 7.0 Hz, 3 H); MS ESI(relative abundance): 331.2 (M + H, 100). Anal. calcd for $C_{16}H_{22}N_6O_2$: C, 58.17; H, 6.71; N, 25.44. Found: C, 58.01; H, 6.79; N, 25.30.

EXAMPLE 24

The compounds listed in Table 4 were prepared using the procedures outlined in Examples 17-23. Compounds were tested in the CMV assay described above and exhibited the following levels of activity: +, $IC_{50} > 500$ nM; ++, 100 nM $< IC_{50} \leq 500$ nM; +++, $IC_{50} \leq$ 100 nM.

TABLE 4



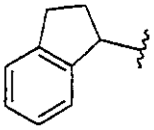
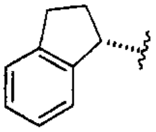
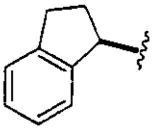
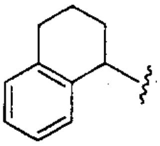
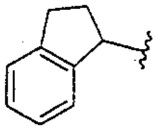
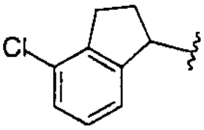
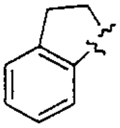
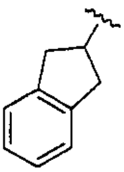
R^a	R^b	R^c	R^d	m/z (m+1) or mp (°C)	Antiviral Activity
	H	Me	Me	351.2	+++
	H	Me	Me	351.2	+++
	H	Me	Me	351.2	+++
	H	Me	Me	365.1	++
	Me	Me	Me	365.1	++
	H	Me	Me	385.1	+
		Me	Me	181-182 °C	++
	H	Me	Me	203-204 °C	+

TABLE 4 (cont'd)

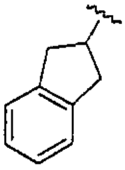
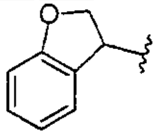
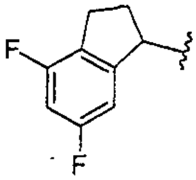
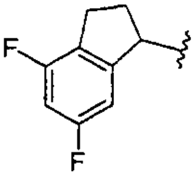
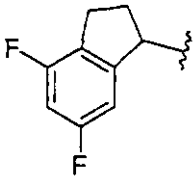
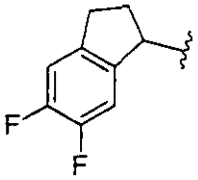
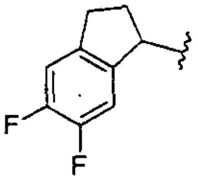
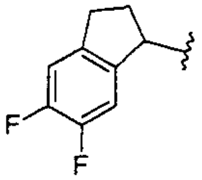
R^a	R^b	R^c	R^d	m/z (m+1) or mp (°C)	Antiviral Activity
	H	H	Me	177-178 °C	+
	H	Me	Me	353.1	++
	H	Et	Me	88-89 °C	++
	H	H	Me	175-176 °C	++
	H	Me	Me	164-165 °C	++
	H	H	Me	189-190 °C	++
	H	Et	Me	177-178 °C	++
	H	Me	Me	205-206 °C	++

TABLE 4 (cont'd)

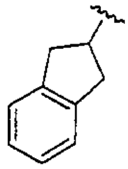
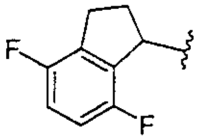
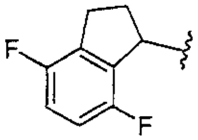
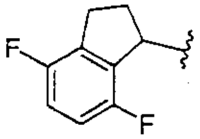
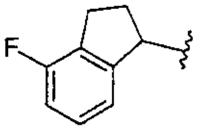
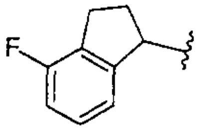
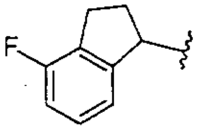
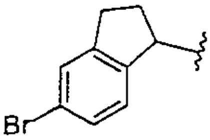
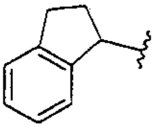
R^a	R^b	R^c	R^d	m/z (m+1) or mp (°C)	Antiviral Activity
	H	Et	Me	187-188 °C	+
	H	H	Me	153-154 °C	++
	H	Me	Me	140-141 °C	+++
	H	Et	Me	158-159 °C	+++
	H	H	Me	178-179 °C	++
	H	Me	Me	74-75 °C	++
	H	Et	Me	65-66 °C	++
	H	Me	Me	429.1	++
	H	H	Me	337.1	+++

TABLE 4 (cont'd)

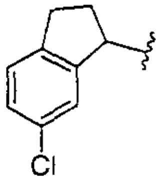
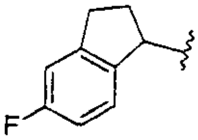
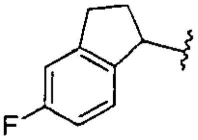
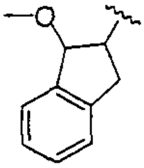
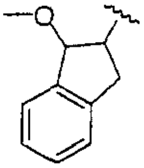
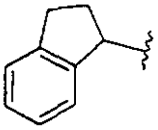
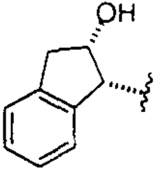
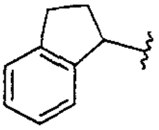
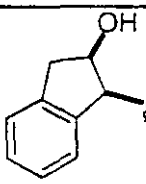
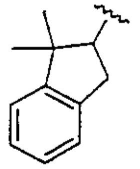
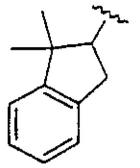
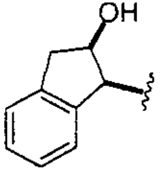
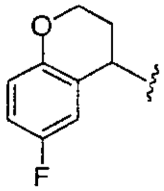
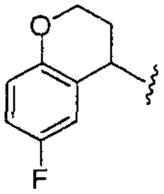
R^a	R^b	R^c	R^d	m/z (m+1) or mp (°C)	Antiviral Agents
	H	Me	Me	385.1	++
	H	H	Me	355.1	+++
	H	Me	Me	369.2	++
	H	H	Me	367.3	+
	H	Me	Me	381.2	+
	H	Et	Me	365.1	++
	H	Me	Me	367.3	+++
	H	Me	H	337.1	++
	H	H	Me	353.1	++

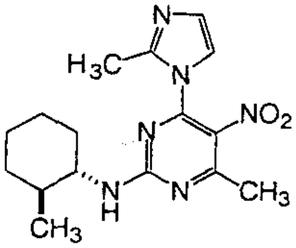
TABLE 4 (cont'd)

R^a	R^b	R^c	R^d	m/z (m+1) or mp (°C)	Antiviral Agents
	H	H	Me	365.1	+
	H	Me	Me	379.2	++
	H	Me	Me	367.2	
	H	H	Me	371.1	
	H	Me	Me	385.2	

EXAMPLE 24

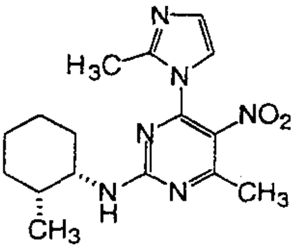
The compounds provided in this example were prepared using procedures outlined above. The starting materials are available as described above, or from commercial sources.

24.1 2-(N-(*trans*-2-methylcyclohexyl) amino)-4-(2-methylimidazol-1-yl)-6-methyl-5-nitropyrimidine



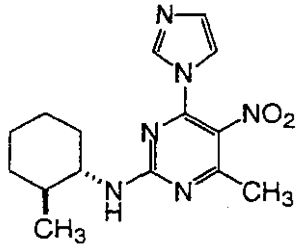
^{1}H NMR (400MHz, CDCl$_3$): δ 0.92(1.5H, d, J=7.2Hz); 0.94(1.5H, d, J=7.2Hz); 1.00-1.30(5H, m); 1.31-1.41(1H, m); 1.74-1.82(2H, m); 1.94-1.96(1H, m); 2.39(1.5H, s); 2.47(1.5H, s); 2.48(1.5H, s); 2.53(1.5H, s); 3.52(0.5H, dq, J=4.0, 9.8Hz); 3.69(0.5H, dq, J=4.0, 9.8Hz); 5.86(0.5H, d, J=9.2Hz), 5.98(0.5H, d, J=9.2Hz); 6.86(1H, s); 6.93(0.5H, s); 6.95(0.5H, s). MS ESI: m/z (relative intensity): M+H, 331.2 (100).

24.2 2-(N-(*cis*-2-methylcyclohexyl)amino)-4-(2-methylimidazol-1-yl)-6-methyl-5-nitropyrimidine



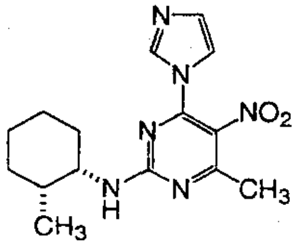
^{1}H NMR (400MHz, CDCl$_3$): δ 0.93(3H, d, J=7.2Hz); 1.22-1.41(3H, m); 1.48-1.68 (4H, m); 1.71-1.78(1H, m); 1.95(1H, m); 2.44(1.5H, s); 2.51(3H, s); 2.57(1.5H, s); 4.13(0.5H, m); 4.28(0.5H, m); 5.68(0.5H, d, J=9.0Hz), 5.59(0.5H, d, J=9.0Hz); 6.87(1H, s); 6.94(0.5H, s); 6.96(0.5H, s). MS ESI: m/z (relative intensity): M+H, 331.2 (100)

24.3 2-(N-(*trans*-2-methylcyclohexyl)amino)-4-(imidazol-1-yl)-6-methyl-5-nitropyrimidine



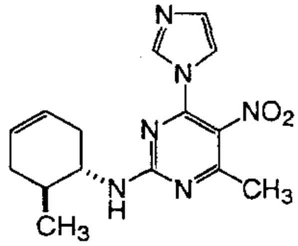
^{1}H NMR (400MHz, CDCl$_3$): δ 0.96(3H, d, J=6.5Hz); 1.11-1.29(3H, m); 1.33-1.39(2H, m); 1.70(1H, m); 1.75-1.83(2H, m) 2.05(1H, dd, J=2.8, 13.4Hz); 2.45(1.5H, s); 2.50(1.5H, s); 3.54(0.5H, dq, J=4.0, 9.8Hz); 3.70(0.5H, dq, J=4.0, 9.8Hz); 5.43(0.5H, s), 5.46(0.5H, s); 7.12(0.5H, s); 7.15(0.5H, s); 7.17(0.5H, s); 7.18(0.5H, s); 8.04 (0.5H, s); 8.08(0.5H, s). MS ESI: m/z (relative intensity): M+H, 317.2 (100).

24.4 2-(N-(*cis*-2-methylcyclohexyl)amino)-4-(imidazol-1-yl)-6-methyl-5-nitropyrimidine



^{1}H NMR (400MHz, CDCl$_3$): δ 0.93(3H, d, J=7.2Hz); 1.22-1.41(3H, m); 1.48-1.68 (4H, m); 1.76-1.82(1H, m); 1.94-1.99(1H, m); 2.48(1.5H, s); 2.52(1.5H, s); 4.15(0.5H, m); 4.29(0.5H, m); 5.65(0.5H, d, J=7.6Hz), 5.73(0.5H, d, J=7.6Hz); 7.16(1H, s); 7.21(1H, s); 8.04(0.5H, s); 8.10(0.5H, s). MS SEI m/z relative intensity:M+H, 317.2(100)

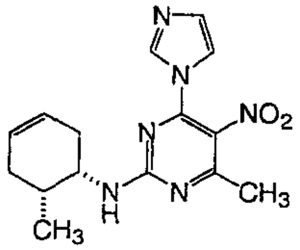
24.5 2-(N-(*trans*- 2-methyl-4-cyclohexenyl)amino)-4-(imidazol-1-yl)-6-methyl-5-nitropyrimidine



^{1}H NMR (400MHz, CDCl$_3$): δ 0.93(1.5H, d, J=6.8Hz); 1.00(1.5H, d, J=6.8Hz); 1.22(1H, m); 1.83-1.88(1H, m); 1.93-2.00(1H, m); 2.12(1H, m) 2.27(1H, m); 2.44(1.5H, s); 2.49(1.5H, s); 3.93(0.5H, dq, J=1.2, 7.2Hz); 4.08(0.5H, dq J=1.2, 7.2Hz);

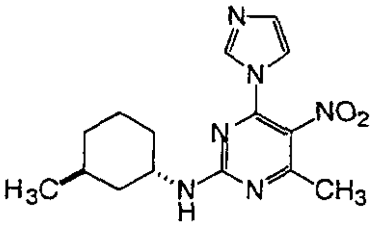
5.51(0.5H, d, J=7.0Hz), 5.60(1.5H, m); 5.68(0.5H, m); 7.13(1H, s); 7.16(1H, s); 8.00(0.5H, s); 8.07(0.5H, s). MS ESI: m/z (relative intensity): M+H, 315.2 (100).

24.6 2-(N-(*cis* - 2--methyl-4-cyclohexenyl)amino)-4-(imidazol-1-yl)-6-methyl-5-nitropyrimidine



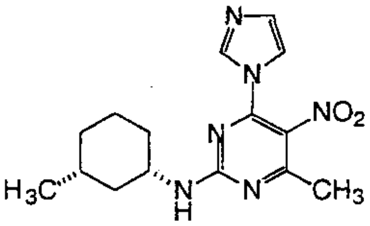
^{1}H NMR (400MHz, $CDCl_3$): δ 0.96(3H, d, J=6.8Hz); 1.26(1H, m); 1.84-1.92(1H, m); 2.10-2.18(1H, m); 2.27(1H, m) 2.42(1H, m); 2.47(1.5H, s); 2.51(1.5H, s); 4.32(0.5H, m); 4.47(0.5H, m); 5.63(1H, s), 5.72(1H, s); 5.79(0.5H, d, J=9.0Hz); 5.88(0.5H, d, J=9.0Hz); 7.13(0.5H, s); 7.15(0.5H, s); 7.17(0.5H,s); 7.21(0.5H, s); 8.03(0.5H, s); 8.08(0.5H, s). M ESI: m/z (relative intensity): M+H, 315.2 (100).

24.7 2-(N-(*trans*- 3-methylcyclohexyl)amino)-4-(imidazol-1-yl)-6-methyl-5-nitropyrimidine



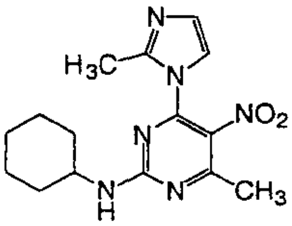
^{1}H NMR (400MHz, $CDCl_3$): δ 0.93(1.5H, d, J=6.5Hz); 0.96(0.5H, d, J=6.5Hz); 1.01-1.12(1H, m); 1.33-1.41(1H, m); 1.45-1.54(1H, m); 1.60-1.83(5H, m); 2.40(1.5H, s); 2.49(1.5H, s); 2.50(1.5H, s); 2.56(1.5H, s); 4.19(0.5H, m); 4.32(0.5H, m); 5.98(0.5H, d, J=6.0Hz), 6.03(0.5H, d, J=6.0Hz); 6.88(1H, s); 6.96(1H, s). MS ESI: m/z (relative intensity): M+H, 331.2 (100).

24.8 2-(N-*cis*-3-methylcyclohexyl)amino)-4-(imidazol-1-yl)-6-methyl-5-nitropyrimidine



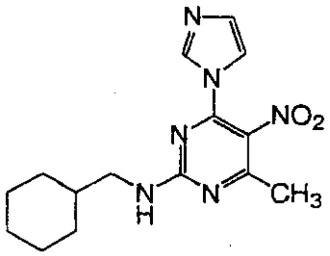
^{1}H NMR (400MHz, CDCl$_3$): δ 0.90(3H, d, J=6.5Hz); 1.08(1H, m); 1.29-1.38(1H, m); 1.42-1.52(1H, m); 1.60-1.70(1H, m); 1.76(1H, m); 1.92-2.03(4H, m); 2.36(1.5H, s); 2.46(1.5H, s); 2.49(1.5H, s); 2.54(1.5H, s); 3.73(0.5H, m); 3.91(0.5H, m); 6.06(0.5H, bs), 6.22(0.5H, bs); 6.85(1H, s); 6.93(1H, s). MS ESI: m/z (relative intensity): M+H, 331.2 (100).

24.9 2-Cyclohexylamino-4-(2-methylimidazol-1-yl)-6-methyl-5-nitropyrimidine



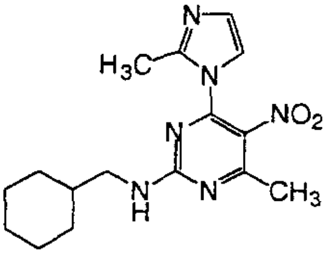
^{1}H NMR (400MHz, CDCl$_3$): δ 1.39(2H, m); 1.53(2H, m); 1.74(2H, m); 1.90(2H, m); 2.15(2H, m); 2.58(1.5H, s); 2.65(1.5H, s); 2.67(1.5H, s); 2.72(1.5H, s); 3.95(0.5H, m); 4.10(0.5H, m); 5.68(0.5H, d, J=4.0Hz), 5.79(0.5H, d, J=4.0Hz); 7.03(1H, s); 7.12(1H, s). MS ESI: m/z (relative intensity): M+H, 317.2 (100).

24.10 2-Cyclohexylmethylamino-4-(imidazol-1-yl)-6-methyl-5-nitropyrimidine



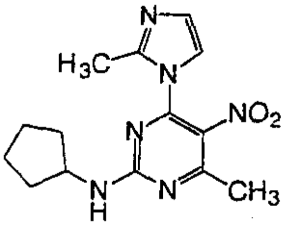
^{1}H NMR (400MHz, CDCl$_3$): δ 0.93-1.03(2H, m); 1.12-1.28(3H, m); 1.50-1.61(1H, m); 1.53-1.80(5H, m); 2.44(1.5H, s); 2.50(1.5H, s); 3.31(2H, dt, J=6.5, 24Hz); 5.88(0.5H, bs); 6.40(0.5H, bs); 7.10(0.5H, s); 7.13(1.5H, s), 7.19(0.5H, s); 8.07(1H, s). MS ESI m/z (relative intensity):M+H, 317.2(100)

24.11 2-Cyclohexylmethylamino-4-(2-methylimidazol-1-yl)-6-methyl-5-nitropyrimidine



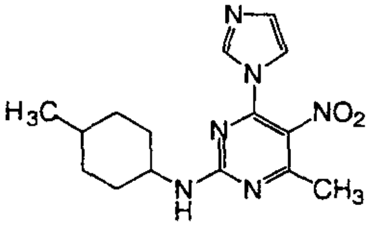
^{1}H NMR (400MHz, CDCl$_3$): δ 0.96(2H, m); 1.14-1.30(4H, m); 1.55(1H, m); 1.67(1H, m); 1.67-1.80(5H, m); 2.39(1.5H, s); 2.47(1.5H, s); 2.49(1.5H, s); 2.54(1.5H, s); 3.25(0.5H, t, J=6.3Hz); 3.35(0.5H, t, J=6.3Hz); 6.02(1H, bs), 6.86(1H, s); 6.95(1H, s). MS ESI m/z (relative intensity): M+H, 331.2 (100).

24.12 2-Cyclopentylamino-4-(2-methylimidazol-1-yl)-6-methyl-5-nitropyrimidine



^{1}H NMR (400MHz, CDCl$_3$): δ 1.21(1H, m); 1.49(1H, m); 1.60-1.78(4H, m); 2.38(1.5H, s); 2.47(1.5H, s); 2.55(1.5H, s); 4.21(0.5H, m); 4.37(0.5H, m); 5.86(0.5H, d, J=4.2Hz); 5.98(0.5H, d, J=4.2Hz); 6.86(1H, s); 6.95(1H, s). MS ESI: m/z (relative intensity): M+H, 303.2 (100).

24.13 2-(N-(4-Methylcyclohexyl)amino)-4-(imidazol-1-yl)-6-methyl-5-nitropyrimidine

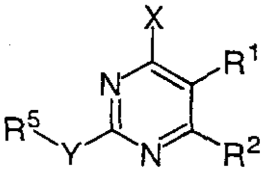


^{1}H NMR (400 MHz, CDCl$_3$): δ 1.03(1.5H, d, J=6.2Hz); 1.06(1.5H, d, J=6.2Hz); 1.08(1H, m); 1.15-1.28(1H, m); 1.30-1.42(2H, m); 1.43-1.55(1H, m); 1.70-1.84(4H, m); 1.85-1.96(2H, m); 2.18(1H, m); 2.54(1.5H, s); 2.64(3H, s); 2.69(1.5H, s); 3.84(0.5H, m); 4.02(0.5H, m); 5.97(0.5H, bs), 6.11(0.5H, bs); 7.01(1H, s); 7.10(1H, s). MS ESI: m/z (relative intensity): M+H, 331.1 (100).

All publications and patent applications cited in this specification are herein incorporated by reference as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference. Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.

WHAT IS CLAIMED IS:

1. A compound having the formula:



(I)

wherein

X is a member selected from the group consisting of $-NR^3R^4$, $-OR^3$, $-SR^3$, aryl, alkyl and arylalkyl;

Y is a member selected from the group consisting of a covalent bond, $-N(R^6)-$, -O-, -S-, -C(=O)- and alkylene;

R^1 and R^2 are members independently selected from the group consisting of hydrogen, alkyl, -O-alkyl, -S-alkyl, aryl, arylalkyl, -O-aryl, -S-aryl, $-NO_2$, $-NR^7R^8$, $-C(O)R^9$, $-CO_2R^{10}$, $-C(O)NR^7R^8$ $-N(R^7)C(O)R^9$, $-N(R^7)CO_2R^{11}$, $-N(R^9)C(O)NR^7R^8$, $-S(O)_mNR^7R^8$, $-S(O)_nR^9$, -CN, halogen, and $-N(R^7)S(O)_mR^{11}$;

R^3 and R^4 are members independently selected from the group consisting of hydrogen, alkyl, aryl and arylalkyl, or taken together with the nitrogen atom to which each is attached form a 5-, 6- or 7-membered ring containing from one to three heteroatoms in the ring;

R^5 is a member selected from the group consisting alkyl, aryl, arylalkyl and bicyclic fused aryl-cycloalkyl;

R^6 is a member selected from the group consisting of hydrogen, alkyl, aryl and arylalkyl; or is combined with R^5 and the nitrogen atom to which R^5 and R^6 are attached to form a 5-, 6-, 7- or 8-membered ring;

R^7 and R^8 are members independently selected from the group consisting of hydrogen, alkyl, aryl and arylalkyl, or, taken together with the nitrogen atom to which each is attached, form a 4-, 5-, 6-, 7- or 8-membered ring containing from one to three heteroatoms in the ring;

R^9 and R^{10} are members independently selected from the group consisting of hydrogen, alkyl, aryl and arylalkyl;

R^{11} is a member selected from the group consisting of alkyl, aryl and arylalkyl;

m is an integer of from 1 to 2;

n is an integer of from 1 to 3; and

optionally, a 5-, 6-, 7- or 8-member ring is formed by joining R^1 to R^2, R^1 to R^3, R^3 to N^3, R^5 to N^3, R^5 to N^1, or R^2 to N^1;

said compound having a molecular weight of from about 150 to about 750, with the proviso that when Y is a bond, then R^5 is other than an imidazole ring.

2. A compound in accordance with claim **1**, wherein R^1 is selected from the group consisting of $-NO_2$, $-S(O)_mNR^7R^8$, $-S(O)_nR^9$, -CN, fluoroalkyl, $-C(O)R^9$, $-CO_2R^{10}$ and $-C(O)NR^7R^8$ and R^2 is selected from the group consisting of hydrogen, alkyl, -O-alkyl, -S-alkyl, aryl, arylalkyl, -O-aryl and -S-aryl .

3. A compound in accordance with claim **2**, wherein X is $-NR^3R^4$, Y is selected from the group consisting of $-N(R^6)-$, -O- and -S; and R^2 is a member selected from the group consisting of hydrogen, alkyl, -S-alkyl, -O-alkyl and halogen.

4. A compound in accordance with claim **3**, wherein R^1 is selected from the group consisting of $-CF_3$, $-S(O)_mNR^7R^8$, $-CO_2R^{10}$, -CN and $-NO_2$, and R^2 is selected from the group consisting of hydrogen, (lower)alkyl, -O-(lower)alkyl and -S-(lower)alkyl.

5. A compound in accordance with claim **4**, wherein Y is $-N(R^6)-$ or -O-, R^1 is $-NO_2$, and R^2 is hydrogen or $(C_1\text{-}C_4)$alkyl.

6. A compound in accordance with claim **5**, wherein R^3 is joined to R^4 to form a 5-membered ring, together with the nitrogen to which both radicals are attached.

7. A compound in accordance with claim **6**, wherein said 5-membered ring contains two nitrogen atoms.

8. A compound in accordance with claim **7**, wherein said 5-membered ring is a substituted or unsubstituted imidazole ring.

9. A compound in accordance with claim **8**, wherein Y is $-N(R^6)-$, in which R^6 is hydrogen or lower alkyl, and R^5 is a member selected from the group consisting of alkyl, aryl, arylalkyl and bicyclic fused aryl-cycloalkyl.

10. A compound in accordance with claim **9**, wherein R^5 is selected from the group consisting of cycloalkyl, heterocycloalkyl, aryl, arylalkyl and bicyclic fused aryl-cycloalkyl, R^6 is selected from the group consisting of hydrogen, methyl, ethyl and propyl, and $-NR^3R^4$ is selected from the group consisting of imidazol-1-yl, 2-methylimidazol-1-yl, 2,4-dimethylimidazol-1-yl, 2-ethylimidazol-1-yl, 2-(1-propyl)imidazol-1-yl, 2-ethyl-4-methylimidazol-1-yl, and 2-(2-propyl)imidazol-1-yl.

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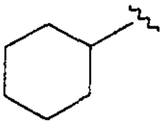
11. A compound in accordance with claim 10, wherein R^6 is selected from the group consisting of hydrogen, methyl and ethyl, $-NR^3R^4$ is selected from the group consisting of imidazol-1-yl, 2-methylimidazol-1yl, 2,4-dimethylimidazol-1-yl and 2-ethylimidazol-1-yl, and R^5 is an optionally substituted radical selected from the group consisting of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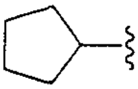
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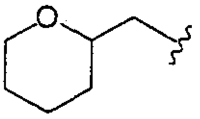
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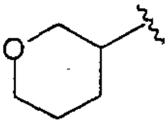
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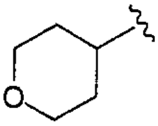
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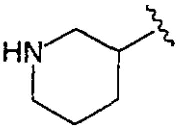

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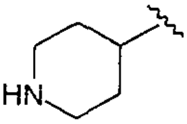

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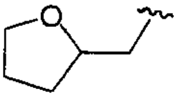
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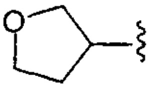
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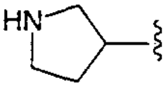

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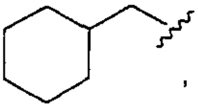
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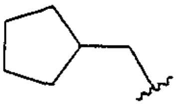
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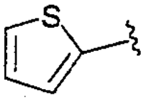
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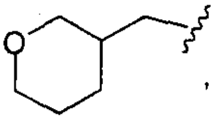
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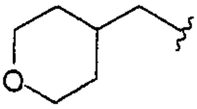
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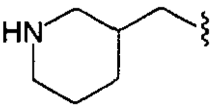

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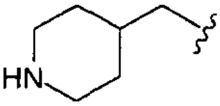

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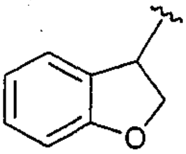
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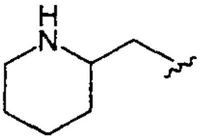

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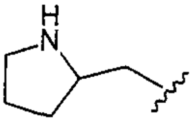

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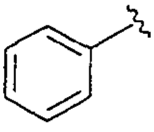
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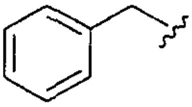
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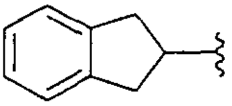
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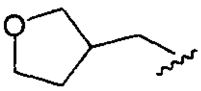
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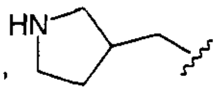

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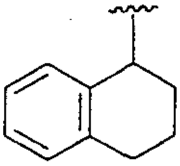
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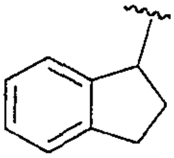
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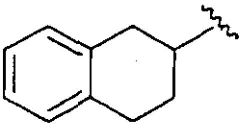
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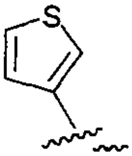
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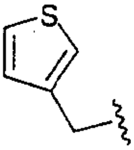
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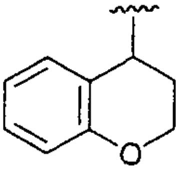
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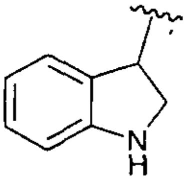
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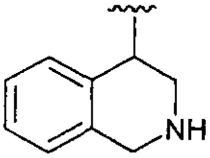

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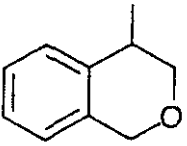
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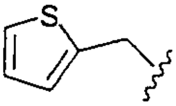
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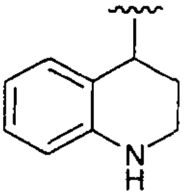
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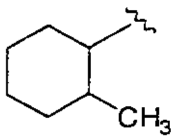
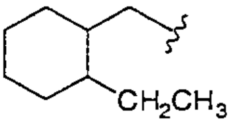
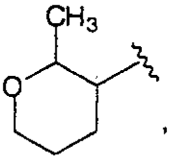
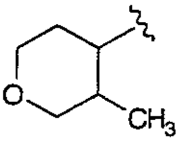
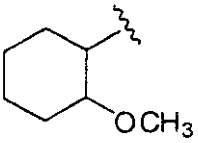
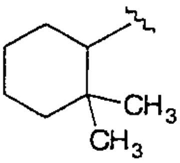
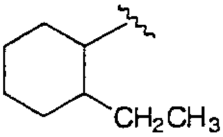
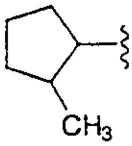
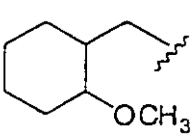
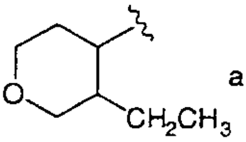
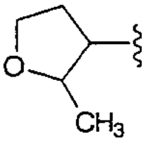
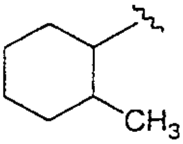
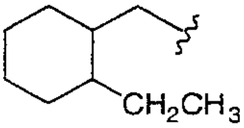
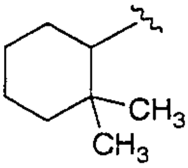
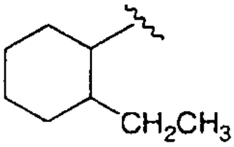
12. A compound in accordance with claim 11, wherein R^5 is a member selected from the group consisting of:

 ,
 ,
 ,
 ,

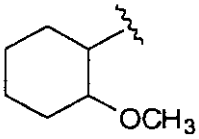
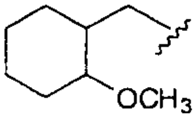
 ,
 ,
 ,
 ,

 ,
 and
 .

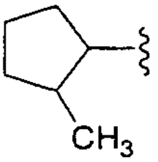
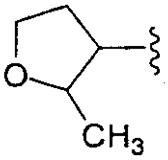
13. A compound in accordance with claim **12**, said compound being selected from the group consisting of

 ,
 ,
 and
 .

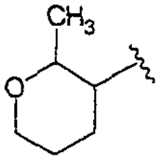
14. A compound in accordance with claim **12**, said compound being selected from the group consisting of

 and
 .

15. A compound in accordance with claim **12**, said compound being selected from the group consisting of

 and
 .

16. A compound in accordance with claim **12**, said compound being selected from the group consisting of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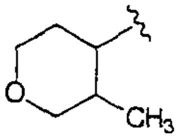
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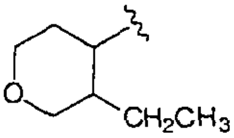
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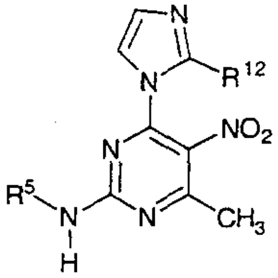
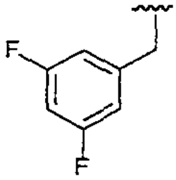
17. A compound in accordance with claim **1**, said compound having the formula:



wherein R^{12} is a member selected from the group consisting of hydrogen, methyl and ethyl; and R^5 is a member selected from the group consisting of: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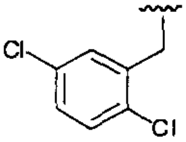
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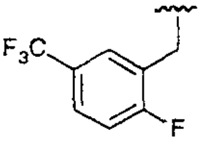
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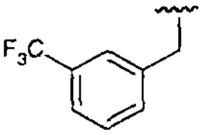
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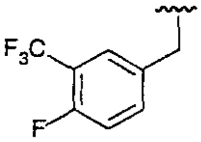
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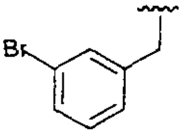
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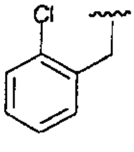
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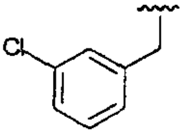
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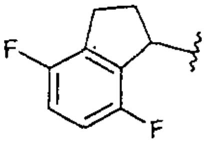
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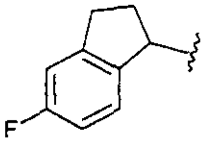
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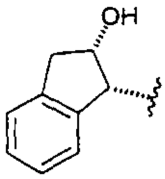
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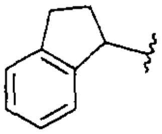
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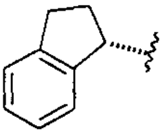
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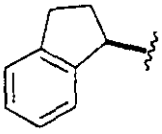
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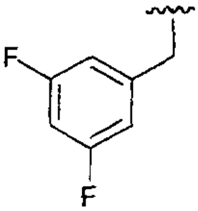
18. A compound in accordance with claim **17**, wherein R^{12} is methyl.

19. A compound in accordance with claim **18**, wherein R^5 is selected from the group consisting of: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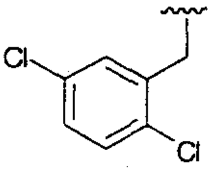
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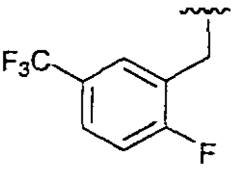
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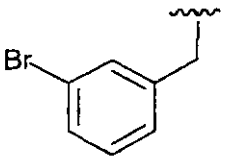
20. A compound in accordance with claim **18**, wherein R^5 is selected from the group consisting of:



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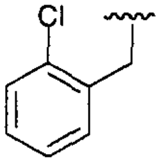

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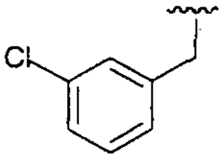

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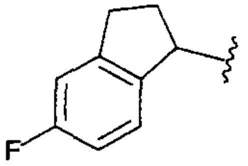
21. A compound in accordance with claim **18**, wherein R^5 is selected from the group consisting of:



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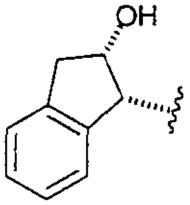

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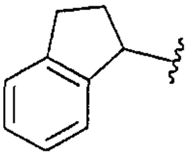
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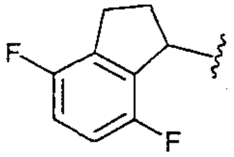
22. A compound in accordance with claim **18**, wherein R^5 is selected from the group consisting of:



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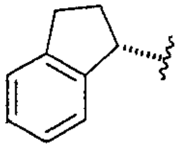
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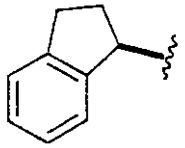
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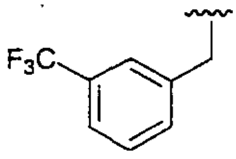
23. A compound in accordance with claim **18**, wherein R^5 is selected from the group consisting of:



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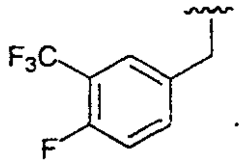

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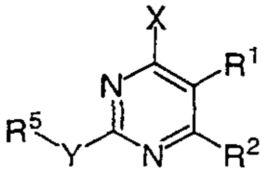
24. A pharmaceutical composition comprising a pharmaceutically or diagnostically acceptable excipient and a compound having the formula:



(I)

wherein

X is a member selected from the group consisting of $-NR^3R^4$, $-OR^3$, $-SR^3$, aryl, alkyl and arylalkyl;

Y is a member selected from the group consisting of a covalent bond, $-N(R^6)-$, -O-, -S-, -C(=O)- and alkylene;

R^1 and R^2 are members independently selected from the group consisting of hydrogen, alkyl, -O-alkyl, -S-alkyl, aryl, arylalkyl, -O-aryl, -S-aryl, $-NO_2$, $-NR^7R^8$, $-C(O)R^9$, $-CO_2R^{10}$, $-C(O)NR^7R^8$ $-N(R^7)C(O)R^9$, $-N(R^7)CO_2R^{11}$, $-N(R^9)C(O)NR^7R^8$, $-S(O)_mNR^7R^8$, $-S(O)_nR^9$, -CN, halogen, and $-N(R^7)S(O)_mR^{11}$;

R^3 and R^4 are members independently selected from the group consisting of hydrogen, alkyl, aryl and arylalkyl, or taken together with the nitrogen atom to which each is attached form a 5-, 6- or 7-membered ring containing from one to three heteroatoms in the ring;

R^5 is a member selected from the group consisting alkyl, aryl, arylalkyl and bicyclic fused aryl-cycloalkyl;

R^6 is a member selected from the group consisting of hydrogen, alkyl, aryl and arylalkyl; or is combined with R^5 and the nitrogen atom to which R^5 and R^6 are attached to form a 5-, 6-, 7- or 8-membered ring;

R^7 and R^8 are members independently selected from the group consisting of hydrogen, alkyl, aryl and arylalkyl, or, taken together with the nitrogen atom to which each is attached, form a 4-, 5-, 6-, 7- or 8-membered ring containing from one to three heteroatoms in the ring;

R^9 and R^{10} are members independently selected from the group consisting of hydrogen, alkyl, aryl and arylalkyl;

R^{11} is a member selected from the group consisting of alkyl, aryl and arylalkyl;

m is an integer of from 1 to 2;

n is an integer of from 1 to 3; and

optionally, a 5-, 6-, 7- or 8-member ring is formed by joining R^1 to R^2, R^1 to R^3, R^3 to N^3, R^5 to N^3, R^5 to N^1, or R^2 to N^1;

said compound having a molecular weight of from about 150 to about 750, with the proviso that when Y is a bond, then R^5 is other than an imidazole ring.

25. A composition in accordance with claim **24**, wherein R^1 is selected from the group consisting of -NO$_2$, -S(O)$_m$NR^{7}R^8, -S(O)$_n$R^9, -CN, fluoroalkyl, -C(O)R^9, -CO$_2$R^{10} and -C(O)NR^{7}R^8 and R^2 is selected from the group consisting of hydrogen, alkyl, -O-alkyl, -S-alkyl, aryl, arylalkyl, -O-aryl and -S-aryl .

26. A composition in accordance with claim **25**, wherein X is -NR^{3}R^4, Y is selected from the group consisting of -N(R^6)-, -O- and -S-; and -NO$_2$, and R^2 is a member selected from the group consisting of hydrogen, alkyl, -O-alkyl, -S-alkyl and halogen.

27. *A composition in accordance with claim* **26**, *wherein* R^1 *is selected* from the group consisting of -CF$_3$, -S(O)$_m$NR^{7}R^8, -CO$_2$R^{10}, -CN and -NO$_2$, and R^2 is selected from the group consisting of hydrogen, (lower)alkyl, -O-(lower)alkyl and -S-(lower)alkyl.

28. A composition in accordance with claim **27**, wherein Y is -N(R^6)- or -O-, R^1 is -NO$_2$, and R^2 is hydrogen or (C$_1$-C$_4$)alkyl.

29. A composition in accordance with claim **28**, wherein R^3 is joined to R^4 to form a 5-membered ring, together with the nitrogen to which both radicals are attached.

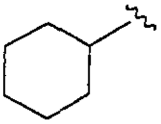
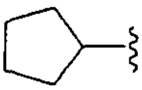
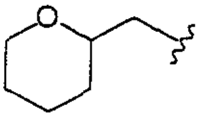
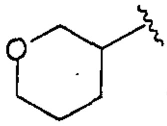
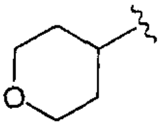
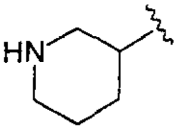
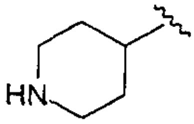
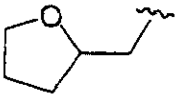
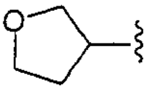
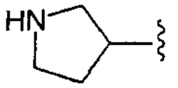
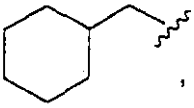
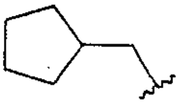
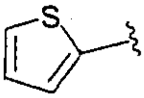
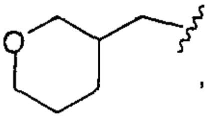
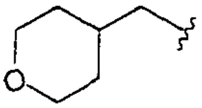
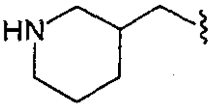
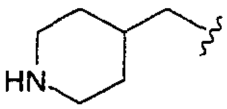
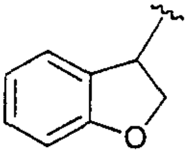
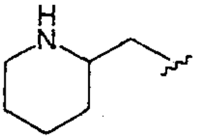
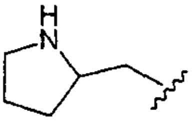
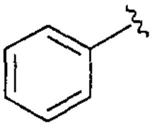
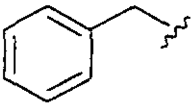
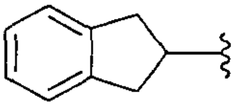
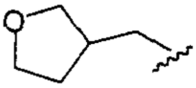
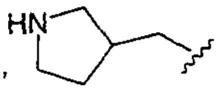
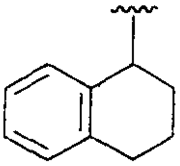
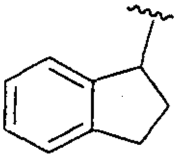
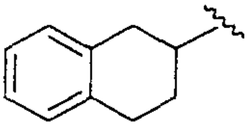
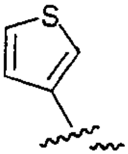
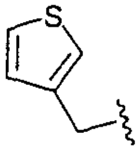
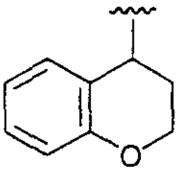
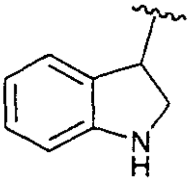
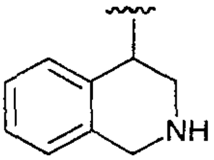
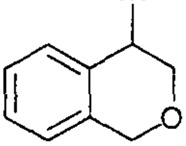
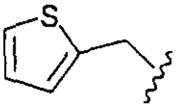
30. A composition in accordance with claim **29**, wherein said 5-membered ring contains two nitrogen atoms.

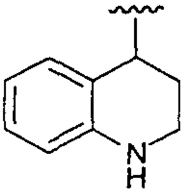
31. A composition in accordance with claim **30**, wherein said 5-membered ring is a substituted or unsubstituted imidazole ring.

32. A composition in accordance with claim **31**, wherein Y is -N(R^6)-, in which R^6 is hydrogen or lower alkyl, and R^5 is a member selected from the group consisting of alkyl, aryl, arylalkyl and bicyclic fused aryl-cycloalkyl.

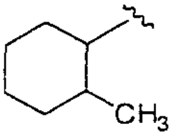
33. A composition in accordance with claim **32**, wherein R^5 is selected from the group consisting of cycloalkyl, heterocycloalkyl, aryl, arylalkyl and bicyclic fused aryl-cycloalkyl, R^6 is selected from the group consisting of hydrogen, methyl, ethyl and propyl, and -NR^{3}R^4 is selected from the group consisting of imidazol-1-yl, 2,4-dimethylimidazol-1-yl, 2-methylimidazol-1yl, 2-ethylimidazol-1-yl, 2-ethyl-4-methylimidazol-1-yl, 2-(1-propyl)imidazol-1-yl and 2-(2-propyl)imidazol-1-yl.

34. A composiuon in accordance with claim 33, wherein R^6 is selected from the group consisting of hydrogen, methyl and ethyl, $-NR^3R^4$ is selected from the group consisting of imidazol-1-yl, 2-methylimidazol-1yl, 2,4-dimethylimidazol-1-yl and 2-ethylimidazol-1-yl, and R^5 is an optionally substituted radical selected from the group consisting of

,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,

and .

35. A composition in accordance with claim **34**, wherein R^5 is a member selected from the group consisting of: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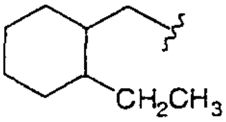
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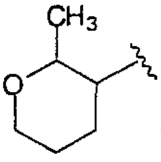
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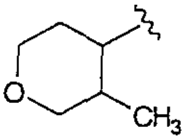
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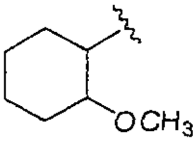
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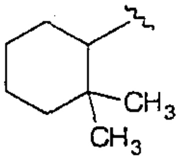
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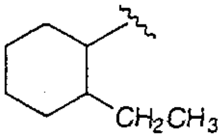
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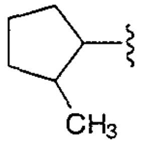
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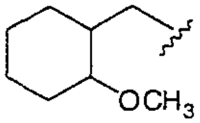
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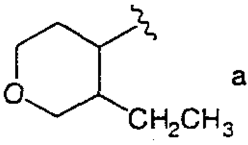
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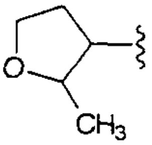
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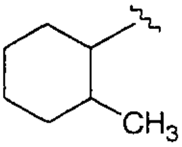
36. A composition in accordance with claim **35**, wherein R^5 is selected from the group consisting of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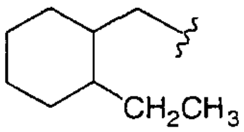
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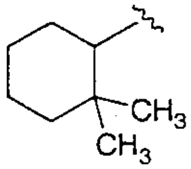
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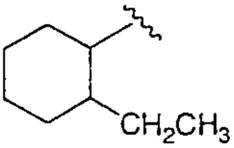
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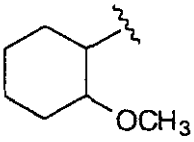
37. A composition in accordance with claim **35**, wherein R^5 is selected from the group consisting of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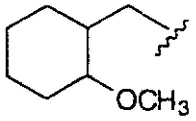
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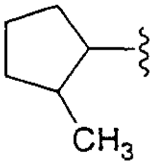
38. A composition in accordance with claim **35**, wherein R^5 is selected from the group consisting of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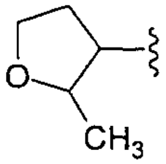
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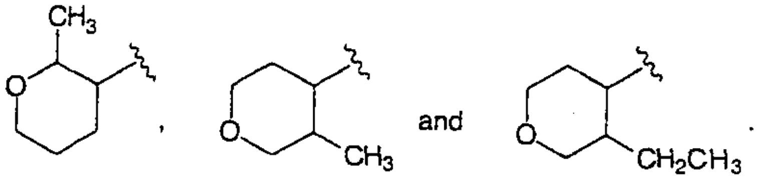
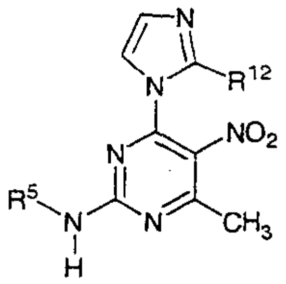
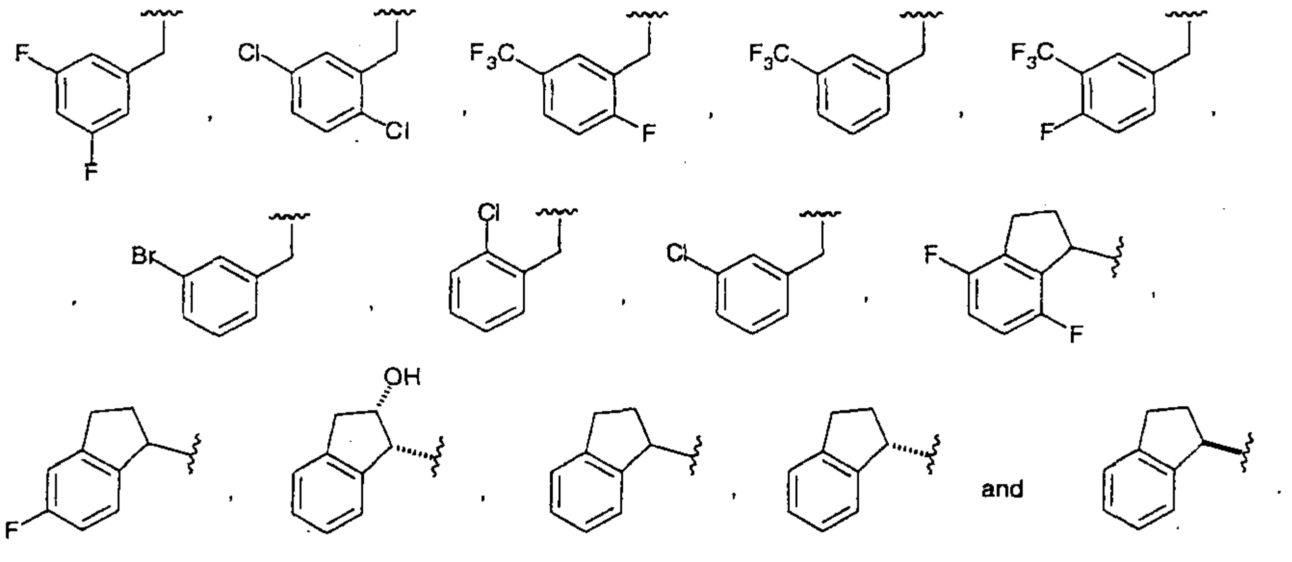
39. A composition in accordance with claim **35**, wherein R^5 is selected from the group consisting of



40. A composition in accordance with claim **1**, said compound having the formula:

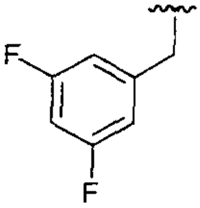


wherein R^{12} is a member selected from the group consisting of hydrogen, methyl and ethyl; and R^5 is a member selected from the group consisting of:



41. A composition in accordance with claim **40**, wherein R^{12} is methyl.

42. A composition in accordance with claim 41, wherein R^5 is selected from the group consisting of:



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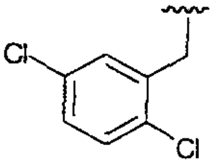

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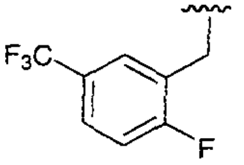

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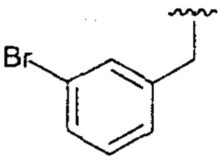
43. A composition in accordance with claim 41, wherein R^5 is selected from the group consisting of:



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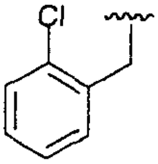

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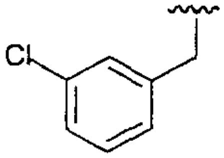

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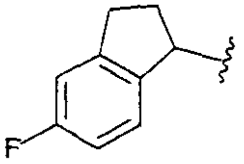
44. A composition in accordance with claim 41, wherein R^5 is selected from the group consisting of:



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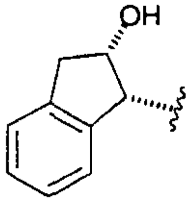

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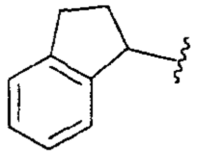

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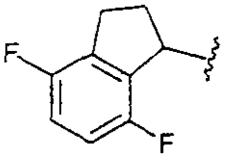
45. A composition in accordance with claim 41, wherein R^5 is selected from the group consisting of:



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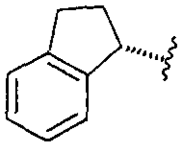

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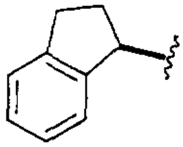

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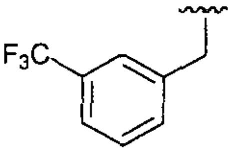
46. A composition in accordance with claim 41, wherein R^5 is selected from the group consisting of:



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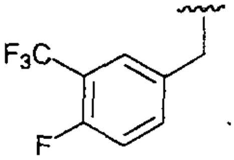

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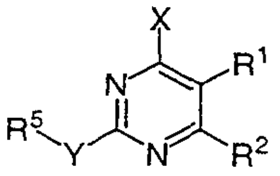
47. A method for preventing or suppressing a viral infection in a mammal, comprising administering to said mammal a viral infection suppressing amount of a compound having the formula:



(I)

wherein

X is a member selected from the group consisting of $-NR^3R^4$, $-OR^3$, $-SR^3$, aryl, alkyl and arylalkyl;

Y is a member selected from the group consisting of a covalent bond, $-N(R^6)-$, -O-, -S-, -C(=O)- and alkylene;

R^1 and R^2 are members independently selected from the group consisting of hydrogen, alkyl, -O-alkyl, -S-alkyl, aryl, arylalkyl, -O-aryl, -S-aryl, $-NO_2$, $-NR^7R^8$, $-C(O)R^9$, $-CO_2R^{10}$, $-C(O)NR^7R^8$ $-N(R^7)C(O)R^9$, $-N(R^7)CO_2R^{11}$, $-N(R^9)C(O)NR^7R^8$, $-S(O)_mNR^7R^8$, $-S(O)_nR^9$, -CN, halogen, and $-N(R^7)S(O)_mR^{11}$;

R^3 and R^4 are members independently selected from the group consisting of hydrogen, alkyl, aryl and arylalkyl, or taken together with the nitrogen atom to which each is attached form a 5-, 6- or 7-membered ring containing from one to three heteroatoms in the ring;

R^5 is a member selected from the group consisting alkyl, aryl, arylalkyl and bicyclic fused aryl-cycloalkyl;

R^6 is a member selected from the group consisting of hydrogen, alkyl, aryl and arylalkyl; or is combined with R^5 and the nitrogen atom to which R^5 and R^6 are attached to form a 5-, 6-, 7- or 8-membered ring;

R^7 and R^8 are members independently selected from the group consisting of hydrogen, alkyl, aryl and arylalkyl, or, taken together with the nitrogen atom to which each is attached, form a 4-, 5-, 6-, 7- or 8-membered ring containing from one to three heteroatoms in the ring;

R^9 and R^{10} are members independently selected from the group consisting of hydrogen, alkyl, aryl and arylalkyl;

R^{11} is a member selected from the group consisting of alkyl, aryl and arylalkyl;

m is an integer of from 1 to 2;

n is an integer of from 1 to 3; and

optionally, a 5-, 6-, 7- or 8-member ring is formed by joining R^1 to R^2, R^1 to R^3, R^3 to N^3, R^5 to N^3, R^5 to N^1, or R^2 to N^1;

said compound having a molecular weight of from about 150 to about 750.

48. A method in accordance with claim **47**, wherein said compound is administered in conjunction with an ancillary antiviral compound selected from the group consisting of ganciclovir, foscarnet, and cidofovir.

49. A method in accordance with claim **47**, wherein said compound is administered in conjunction with an anti-HIV compound.

50. A method in accordance with claim **47,** wherein said mammal is in an immunocompromised condition.

51. A method in accordance with claim **47,** wherein said administering is oral.

52. A method in accordance with claim **47,** wherein said administering is topical.

53. A method in accordance with claim **47**, wherein said administering is prophylactic to prevent the onset of viral infection in patients undergoing organ transplants.

54. A method in accordance with claim **47**, wherein said viral infection produces a disease selected from the group consisting of CMV-retinitis, CMV-mononucleosis, CMV-pneumonitis, and CMV-hepatitis.

55. A method in accordance with claim **47,** wherein said administering is parenteral.

56. A method in accordance with claim **1**, wherein R^1 is selected from the group consisting of $-NO_2$, $-S(O)_mNR^7R^8$, $-S(O)_nR^9$, -CN, fluoroalkyl, $-C(O)R^9$, $-CO_2R^{10}$ and $-C(O)NR^7R^8$ and R^2 is selected from the group consisting of hydrogen, alkyl, -O-alkyl, -S-alkyl, aryl, arylalkyl, -O-aryl and -S-aryl .

57. A method in accordance with claim **56**, wherein X is $-NR^3R^4$, Y is selected from the group consisting of $-N(R^6)-$, -O- and -S; and R^2 is a member selected from the group consisting of hydrogen, alkyl, -O-alkyl, -S-alkyl and halogen.

58. A method in accordance with claim **57**, wherein R^1 is selected from the group consisting of $-CF_3$, $-S(O)_mNR^7R^8$, $-CO_2R^{10}$, -CN and $-NO_2$, and R^2 is selected from the group consisting of hydrogen, (lower)alkyl, -O-(lower)alkyl and -S-(lower)alkyl.

59. A method in accordance with claim **58**, wherein Y is $-N(R^6)-$ or -O-, R^1 is $-NO_2$, and R^2 is hydrogen or $(C_1\text{-}C_4)$alkyl.

60. A method in accordance with claim **59**, wherein R^3 is joined to R^4 to form a 5-membered ring, together with the nitrogen to which both radicals are attached.

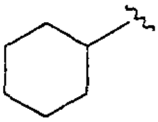
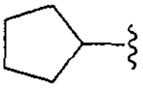
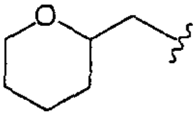
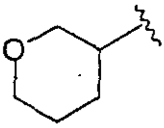
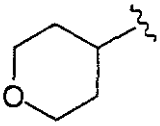
61. A method in accordance with claim **60**, wherein said 5-membered ring contains two nitrogen atoms.

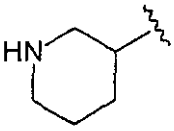
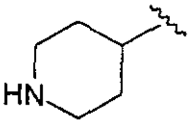
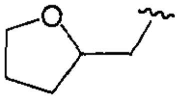
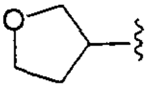
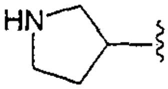
62. A method in accordance with claim **61**, wherein said 5-membered ring is a substituted or unsubstituted imidazole ring.

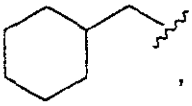
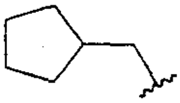
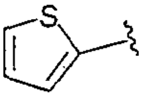
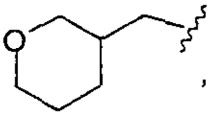
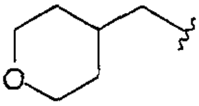
63. A method in accordance with claim **62**, wherein Y is $-N(R^6)-$, in which R^6 is hydrogen or lower alkyl, and R^5 is a member selected from the group consisting of alkyl, aryl, arylalkyl and bicyclic fused aryl-cycloalkyl.

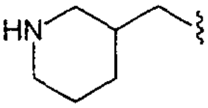
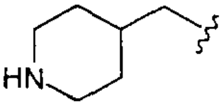
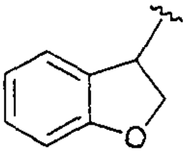
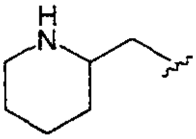
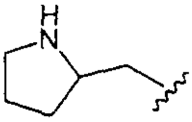
64. A method in accordance with claim **63**, wherein R^5 is selected from the group consisting of cycloalkyl, heterocycloalkyl, aryl, arylalkyl and bicyclic fused aryl-cycloalkyl, R^6 is selected from the group consisting of hydrogen, methyl, ethyl and propyl, and $-NR^3R^4$ is selected from the group consisting of imidazol-1-yl, 2-methylimidazol-1yl, 2,4-dimethylimidazol-1-yl, 2-ethylimidazol-1-yl, 2-ethyl-4-methylimidazol-1-yl, 2-(1-propyl)imidazol-1-yl and 2-(2-propyl)imidazol-1-yl.

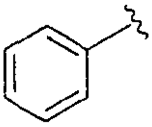
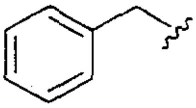
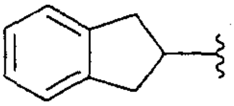
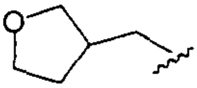
65. A method in accordance with claim **64**, wherein R is selected from the group consisting of hydrogen, methyl and ethyl, -NR^3R^4 is selected from the group consisting of imidazol-1-yl, 2-methylimidazol-1yl, 2,4-dimethylimidazol-1-yl and 2-ethylimidazol-1-yl, and R^5 is an optionally substituted radical selected from the group consisting of

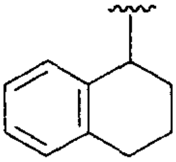
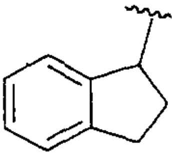
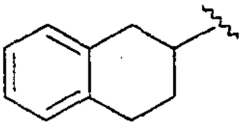
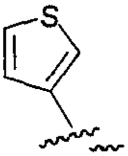
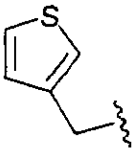
 ,  ,  ,  ,  ,

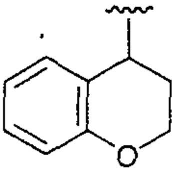
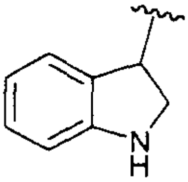
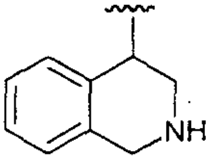
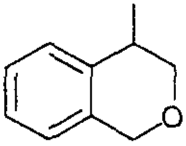
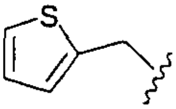
 ,  ,  ,  ,  ,

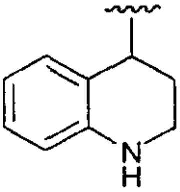
 ,  ,  ,  ,  ,

 ,  ,  ,  ,  ,

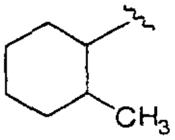
 ,  ,  ,  ,  ,

 ,  ,  ,  ,  ,

 ,  ,  ,  ,  ,

and  .

66. A method in accordance with claim **65**, wherein R^5 is a member selected from the group consisting of: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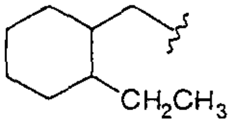
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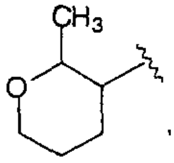
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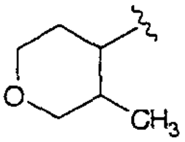
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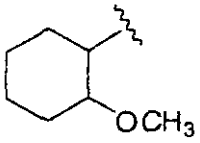
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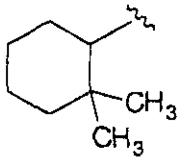
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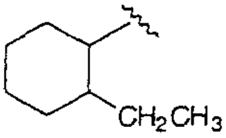
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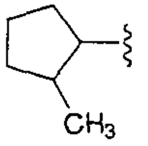
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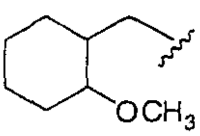
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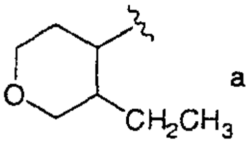
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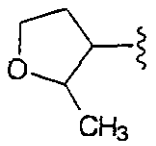
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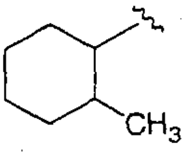
67. A method in accordance with claim **66**, wherein R^5 is selected from the group consisting of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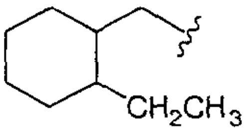
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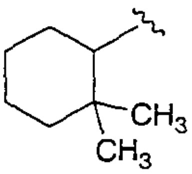
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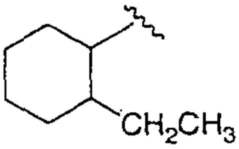
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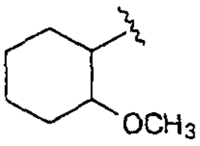
68. A method in accordance with claim **66**, wherein R^5 is selected from the group consisting of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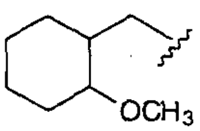
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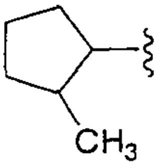
69. A method in accordance with claim **66**, wherein R^5 is selected from the group consisting of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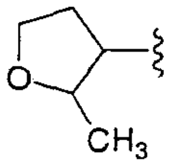
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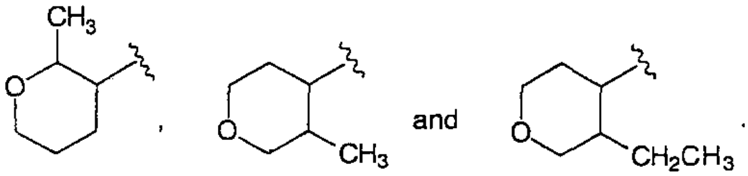
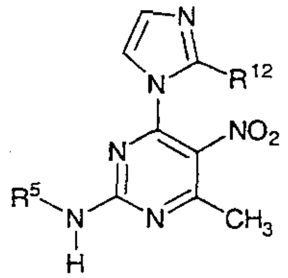
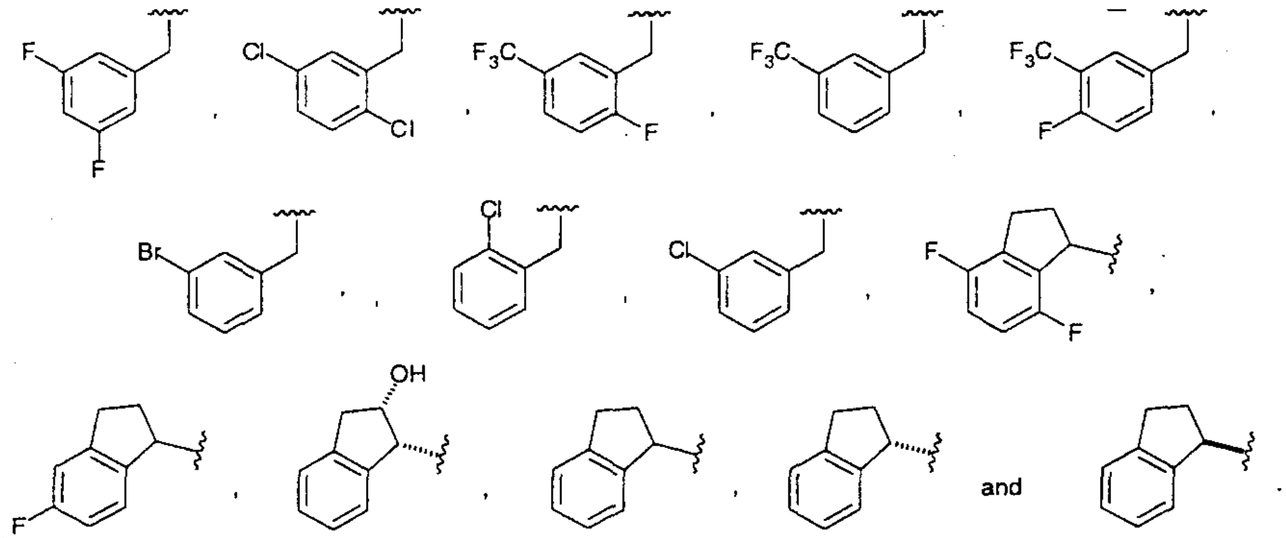
70. A method in accordance with claim **66**, wherein R^7 is selected from the group consisting of



71. A method in accordance with claim **1**, said compound having the formula:

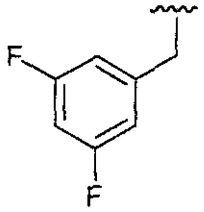


wherein R^{12} is a member selected from the group consisting of hydrogen, methyl and ethyl; and R^5 is a member selected from the group consisting of:



72. A method in accordance with claim **71**, wherein R^{12} is methyl.

73. A method in accordance with claim 72, wherein R^5 is selected from the group consisting of:



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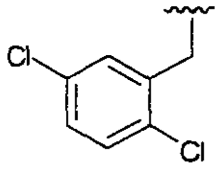

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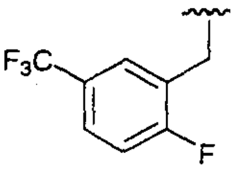

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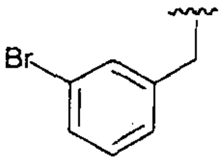
74. A method in accordance with claim 72, wherein R^5 is selected from the group consisting of:



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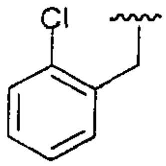

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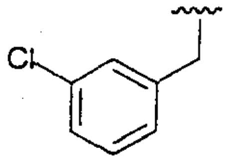

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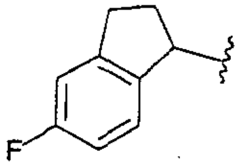
75. A method in accordance with claim 72, wherein R^5 is selected from the group consisting of:



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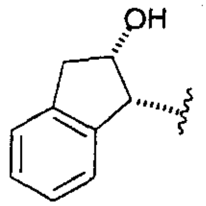

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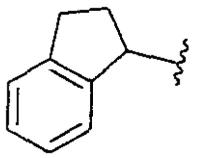

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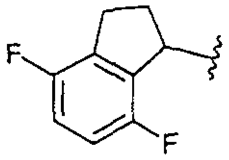
76. A method in accordance with claim 72, wherein R^5 is selected from the group consisting of:



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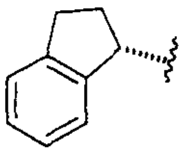

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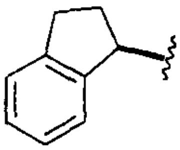

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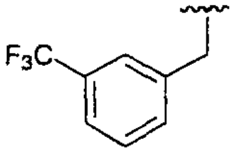
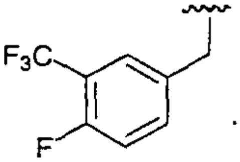
77. A method in accordance with claim 72, wherein R^5 is selected from the group consisting of:



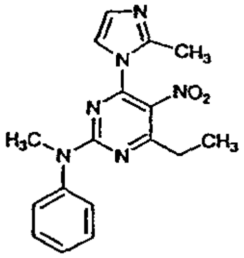
and

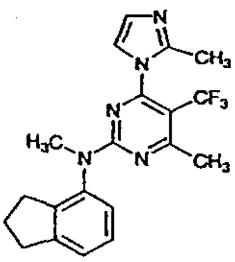


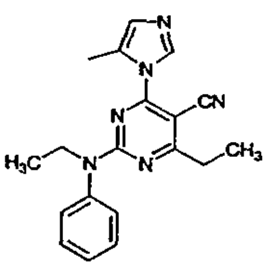
.

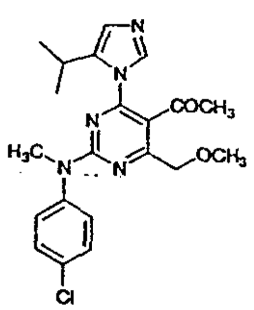
78. A method in accordance with claim **47**, said viral infection being a cytomegaloviral infection.

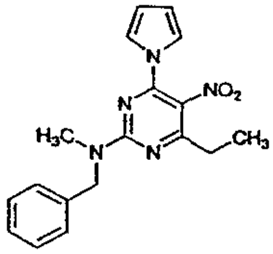
Figure 1

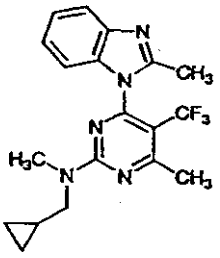

N
CH3
NO2
H3C
N
CH3

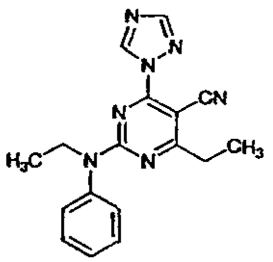

N
CH3
CF3
H3C
N
CH3

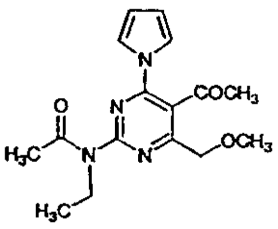

N
CN
H3C
N
CH3

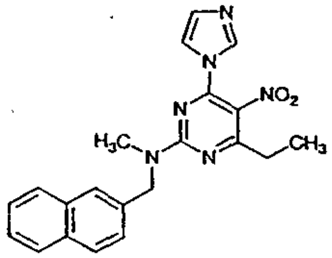

N
COCH3
H3C
N
OCH3
Cl

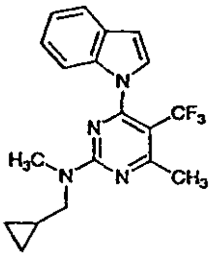

N
NO2
H3C
N
CH3

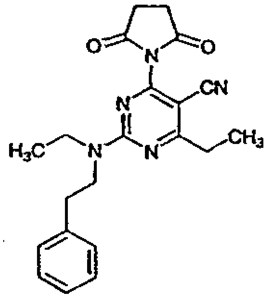

N
CH3
CF3
H3C
N
CH3

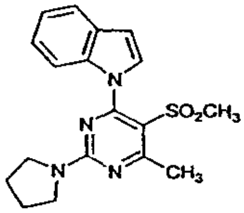

N
CN
H3C
N
CH3

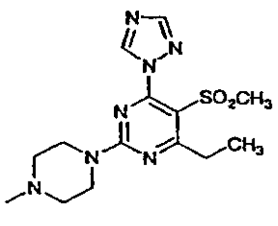

N
COCH3
O
H3C
N
OCH3
H3C


N
NO2
H3C
N
CH3


N
CF3
H3C
N
CH3


O
N
O
CN
H3C
N
CH3


N
SO2CH3
N
CH3


N
SO2CH3
N
CH3

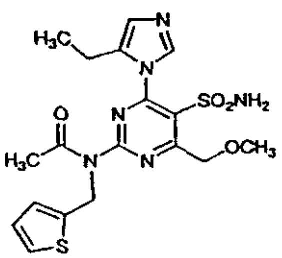
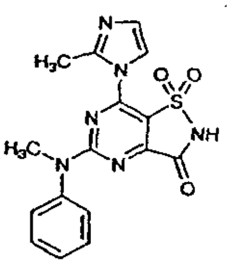
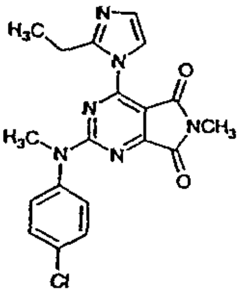
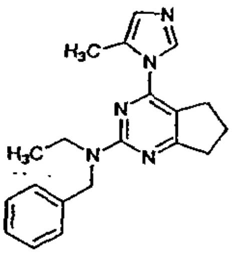
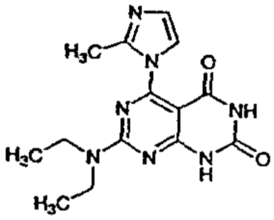

H3C
N
SO2NH2
O
H3C
N
OCH3
S

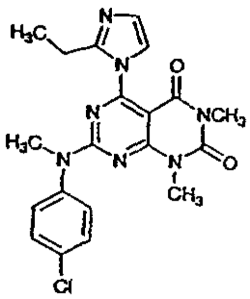
Figure 2

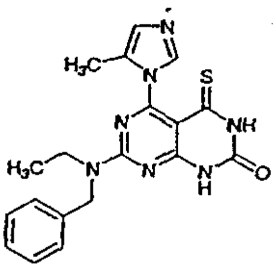

N
H3C
N
O
S
O
N
NH
H3C
N
N
O

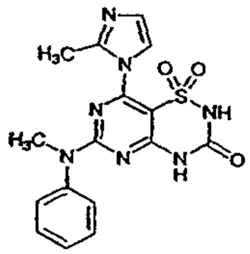

N
H3C
N
O
N
NCH3
H3C
N
N
O
Cl

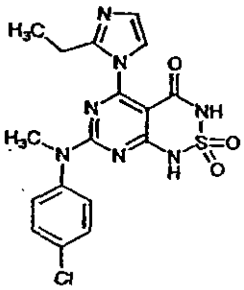

N
H3C
N
N
H3C
N
N


N
H3C
N
O
N
NH
H3C
N
N
N
H
O
H3C


H3C
N
N
O
N
NCH3
H3C
N
N
N
O
CH3
Cl


N
H3C
N
S
N
NH
H3C
N
N
N
H
O


N
H3C
N
O
S
O
N
NH
H3C
N
N
N
H
O


H3C
N
N
O
N
NH
H3C
N
N
N
H
S
O
O
Cl

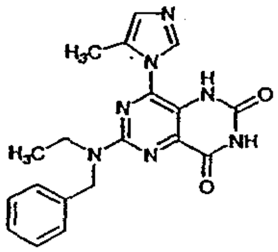

N
H3C
N
H
N
O
N
NH
H3C
N
N
O

Figure 3

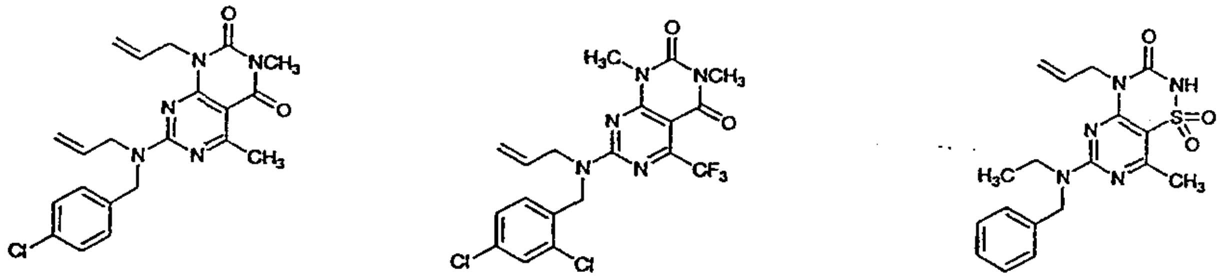


Figure 4

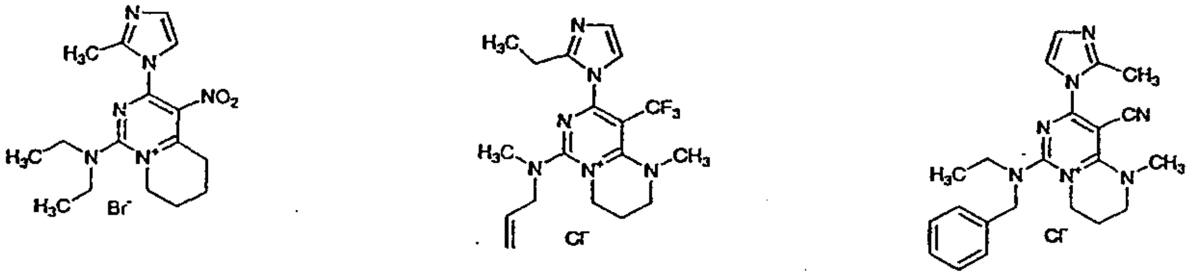


Figure 5

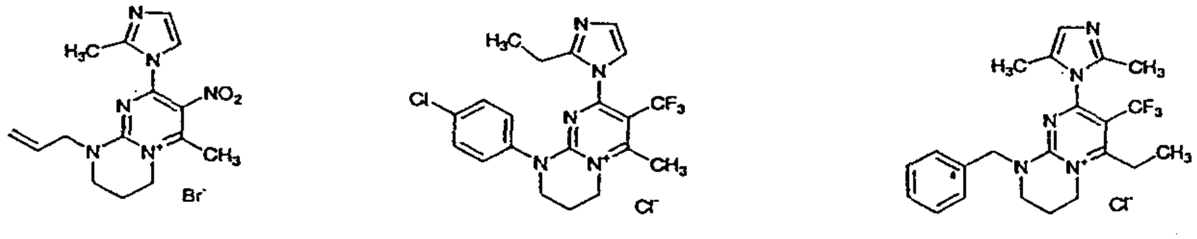


FIGURE 6

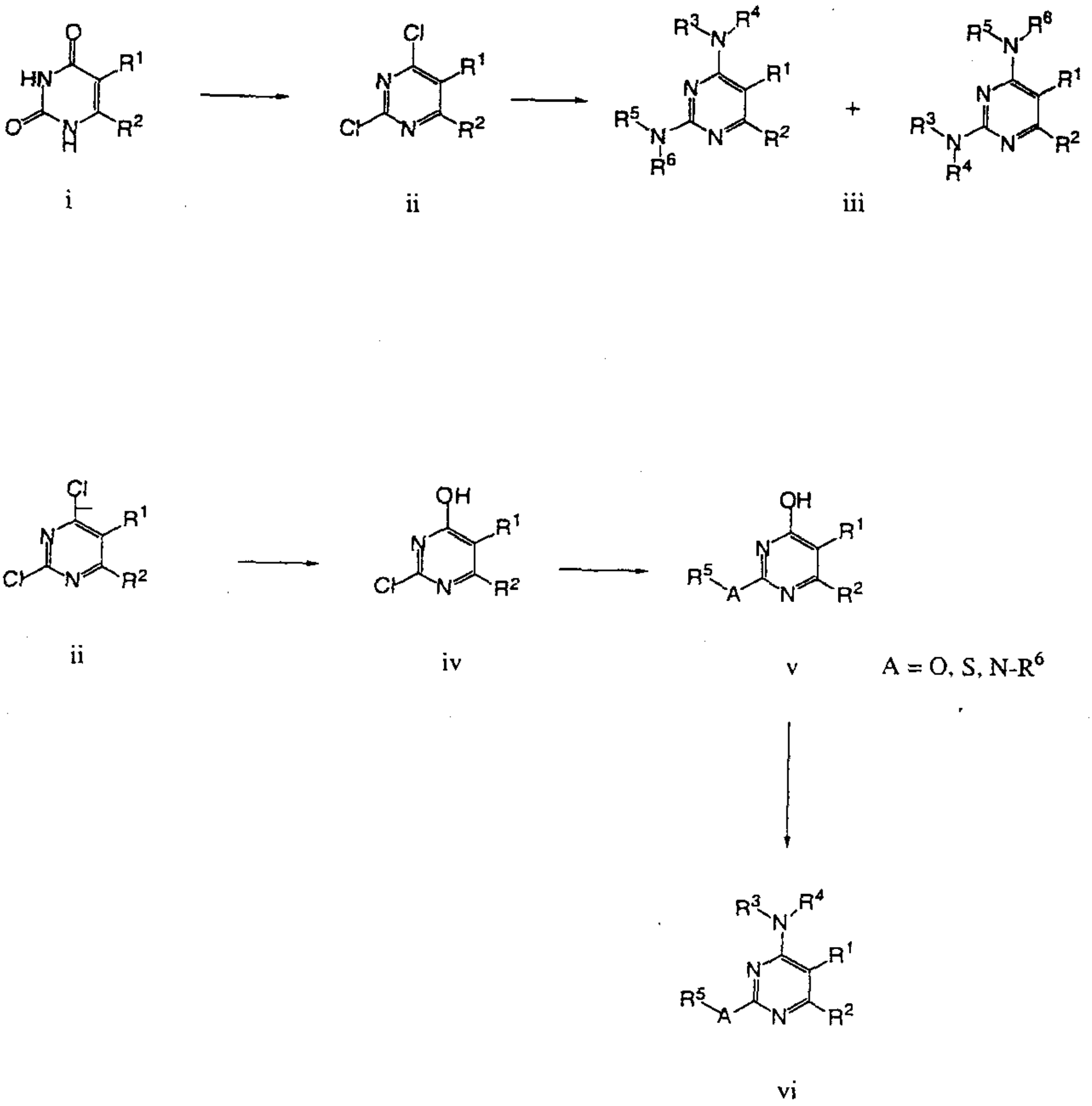


FIGURE 7

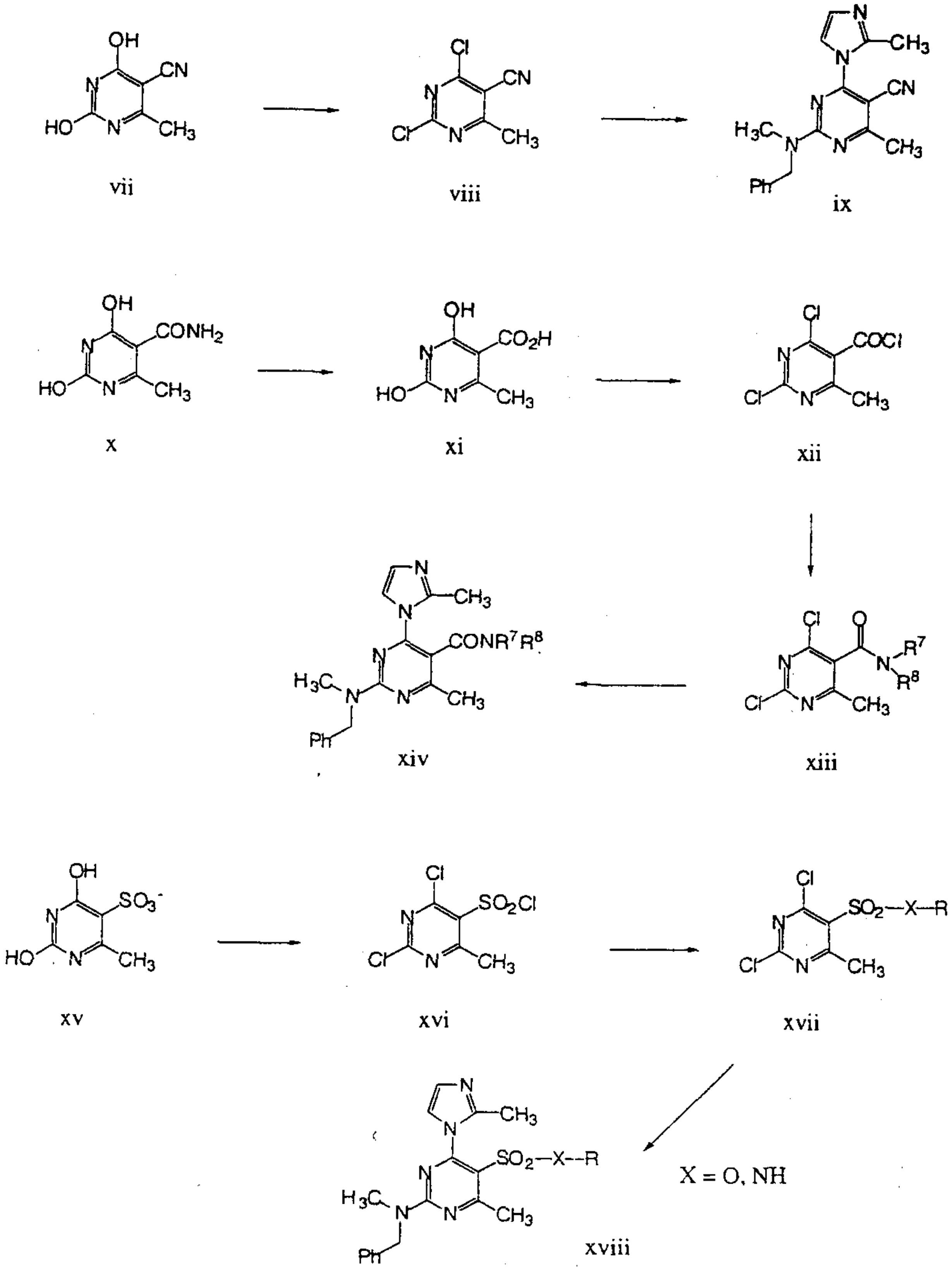

OH
CN
N
HO
N
CH3
vii
Cl
CN
N
Cl
N
CH3
viii
N
CH3
N
CN
N
H3C
N
N
CH3
Ph
ix
OH
CONH2
N
HO
N
CH3
x
OH
CO2H
N
HO
N
CH3
xi
Cl
COCl
N
Cl
N
CH3
xii
N
CH3
N
CONR7R8
N
H3C
N
N
CH3
Ph
xiv
Cl
O
N
R7
R8
N
Cl
N
CH3
xiii
OH
SO3-
N
HO
N
CH3
xv
Cl
SO2Cl
N
Cl
N
CH3
xvi
Cl
SO2—X—R
N
Cl
N
CH3
xvii
N
CH3
N
SO2—X—R
N
H3C
N
N
CH3
Ph
xviii
X = O, NH

FIGURE 8

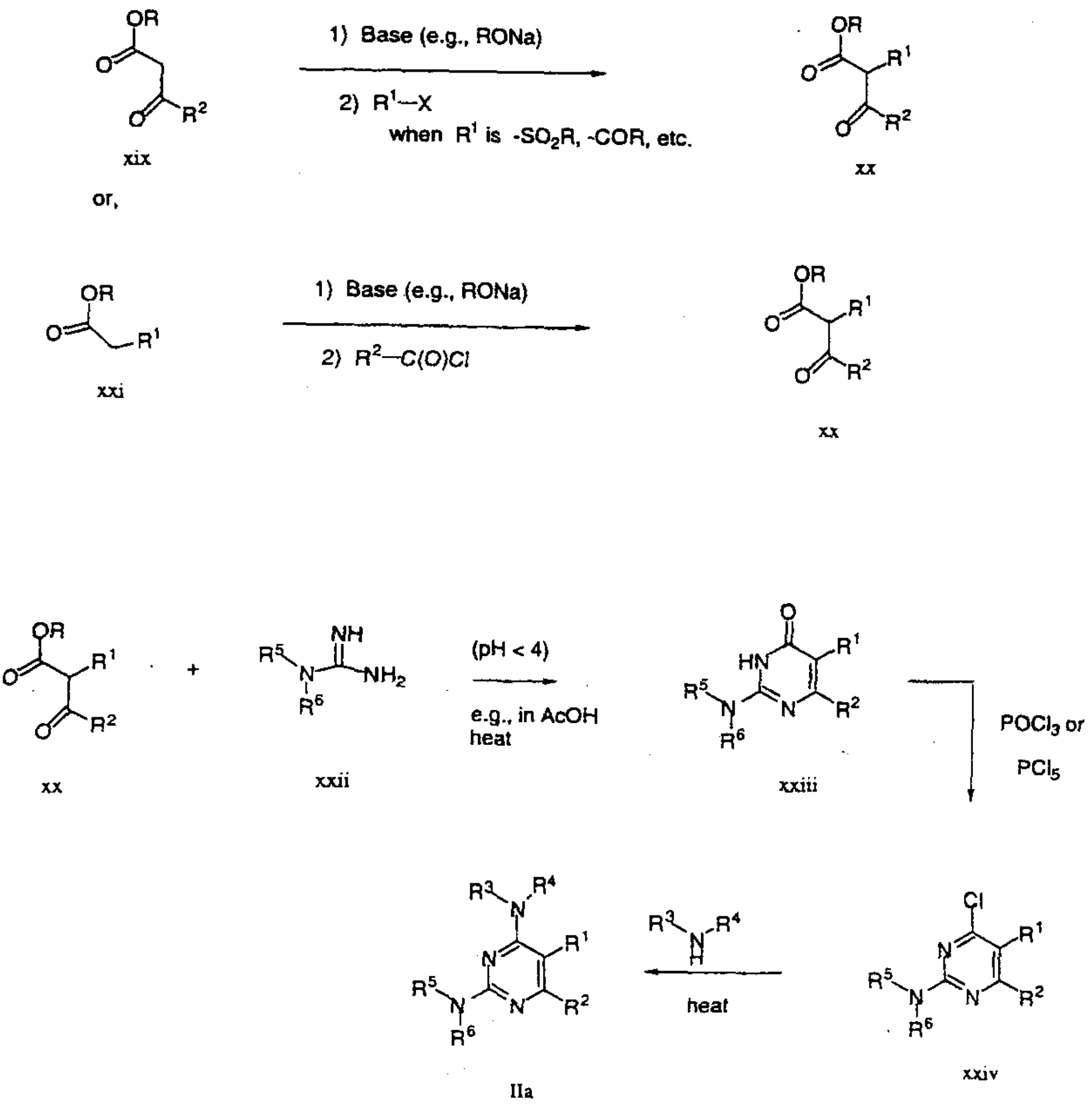

OR
R²
xix
1) Base (e.g., RONa)
2) R¹—X
when R¹ is -SO₂R, -COR, etc.
OR
R¹
R²
xx
or,
OR
R¹
xxi
1) Base (e.g., RONa)
2) R²—C(O)Cl
OR
R¹
R²
xx
OR
R¹
R²
xx
+
NH
R⁵
N
NH₂
R⁶
xxii
(pH < 4)
e.g., in AcOH
heat
O
HN
R¹
R⁵
N
N
R²
R⁶
xxiii
POCl₃ or
PCl₅
Cl
N
R¹
R⁵
N
N
R²
R⁶
xxiv
R³
N
R⁴
H
heat
R³
N
R⁴
N
R¹
R⁵
N
N
R²
R⁶
IIa

Figure 9A

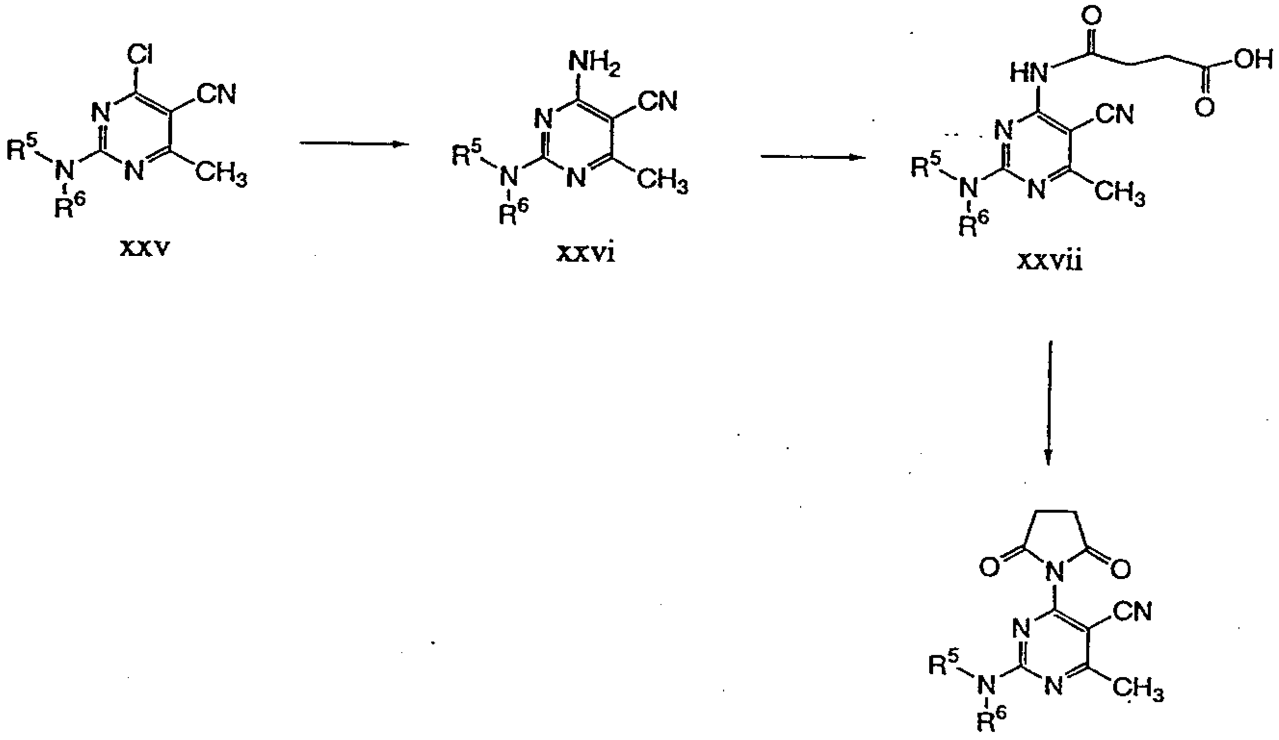


Figure 9B

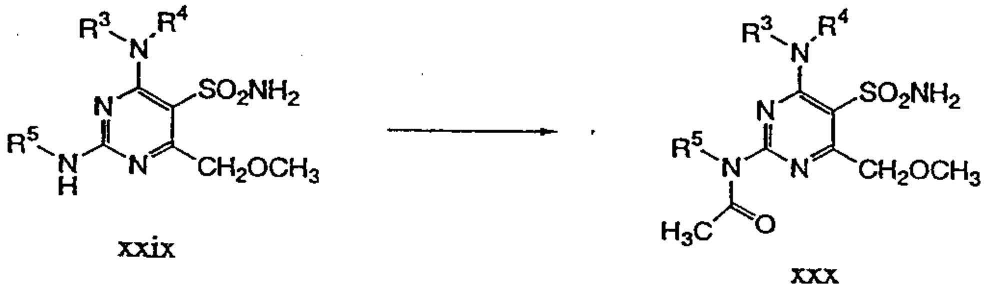


FIGURE 9C

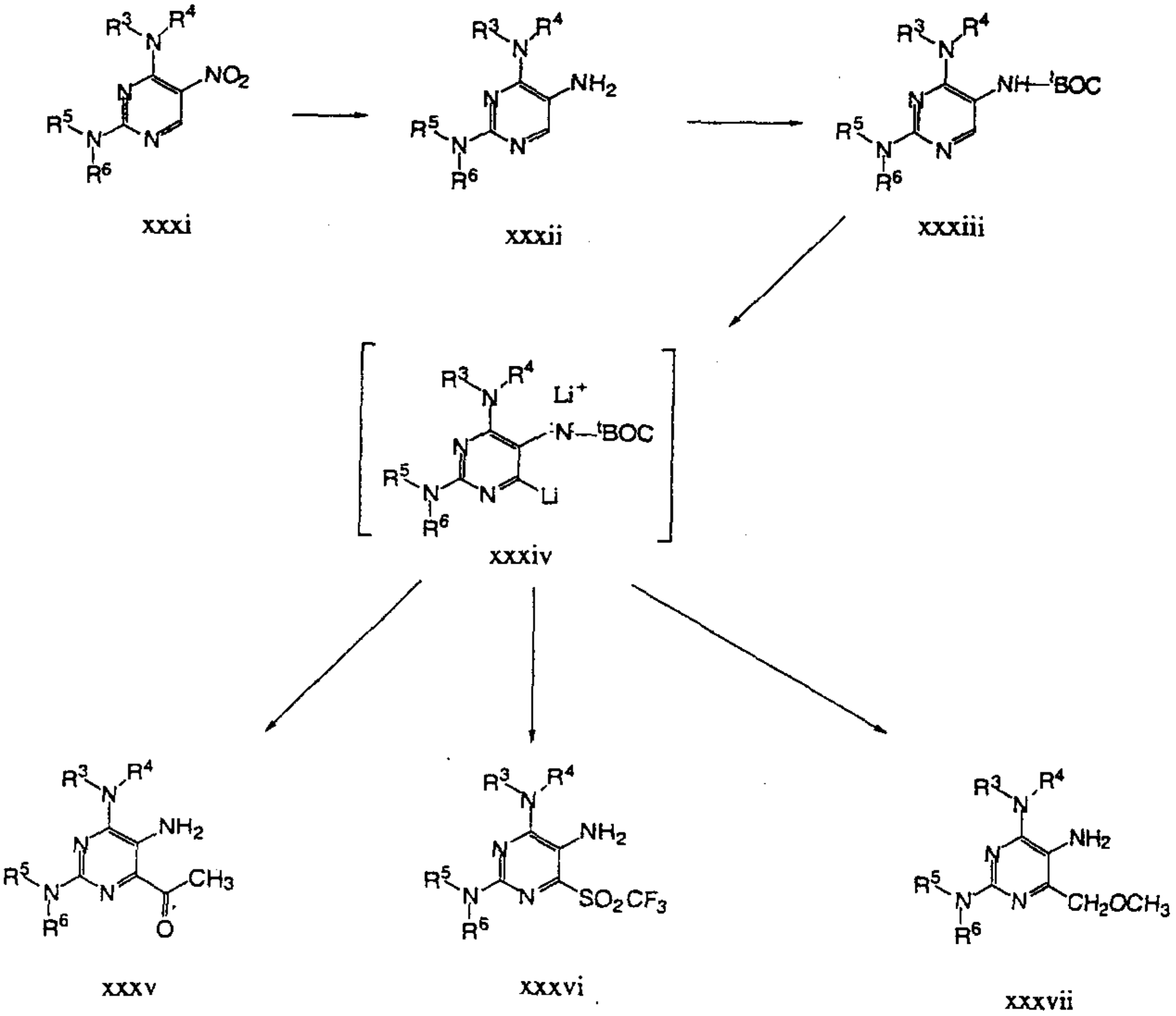
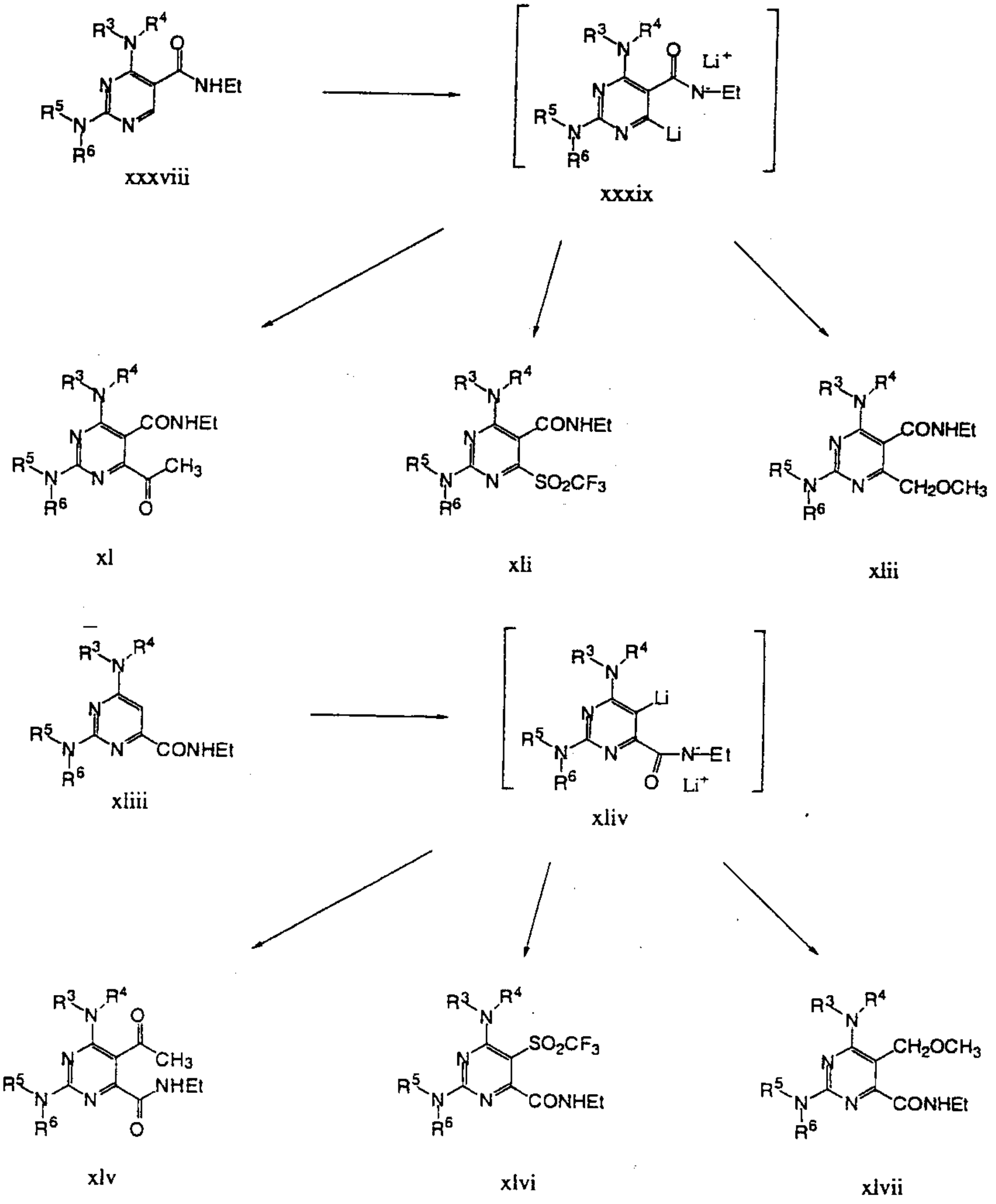

R3
R4
NO2
R5
R6
N
xxxi
NH2
xxxii
NH—tBOC
xxxiii
Li+
N—tBOC
Li
xxxiv
CH3
O
xxxv
SO2CF3
xxxvi
CH2OCH3
xxxvii

FIGURE 9D



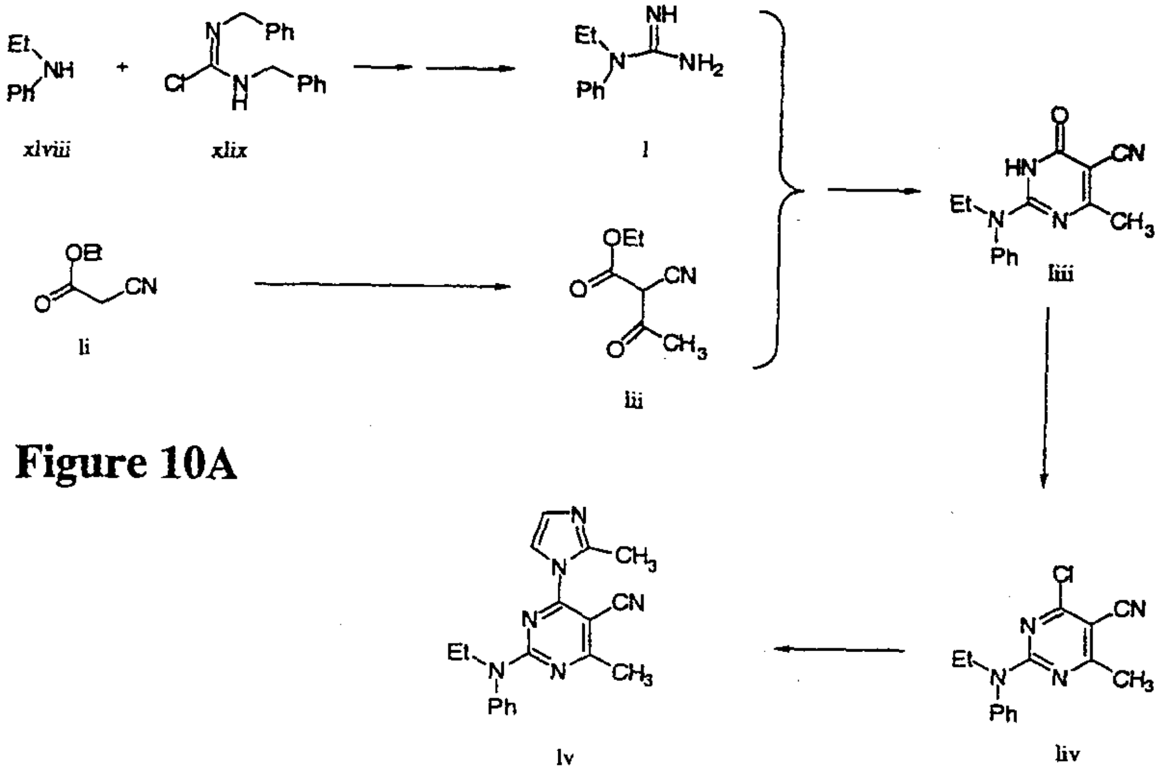


Figure 10A

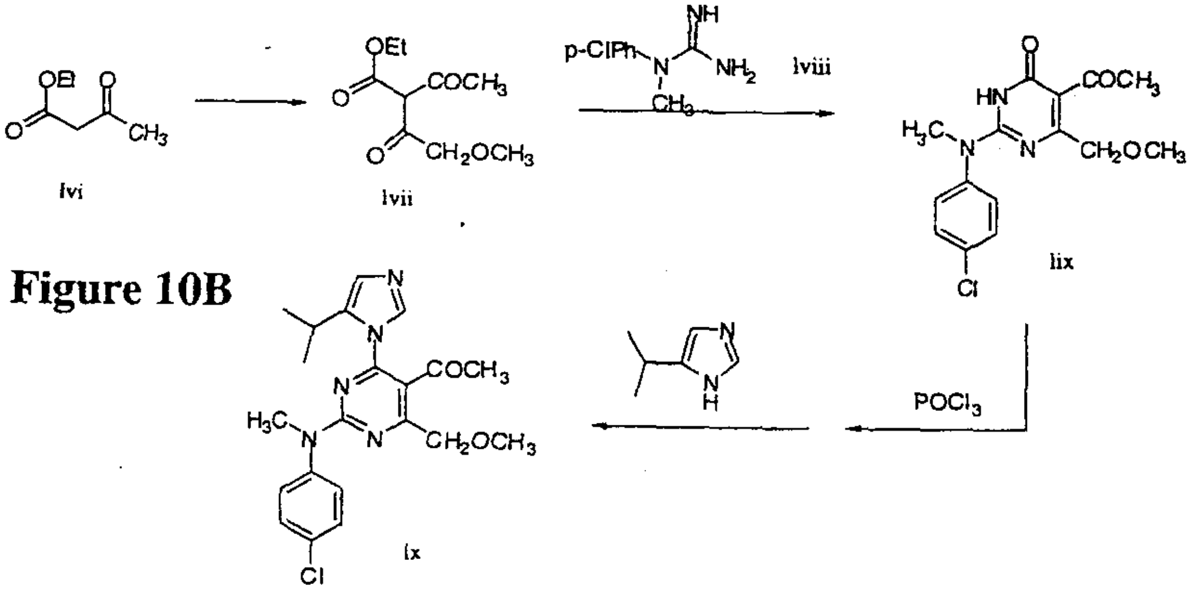


Figure 10B

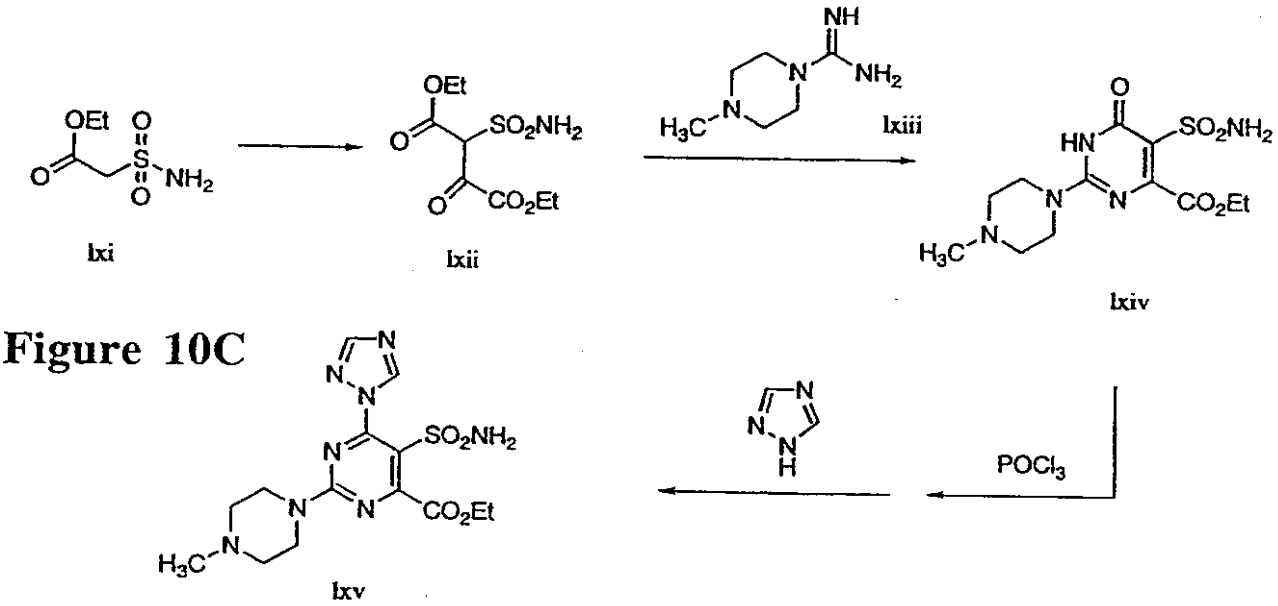


Figure 10C

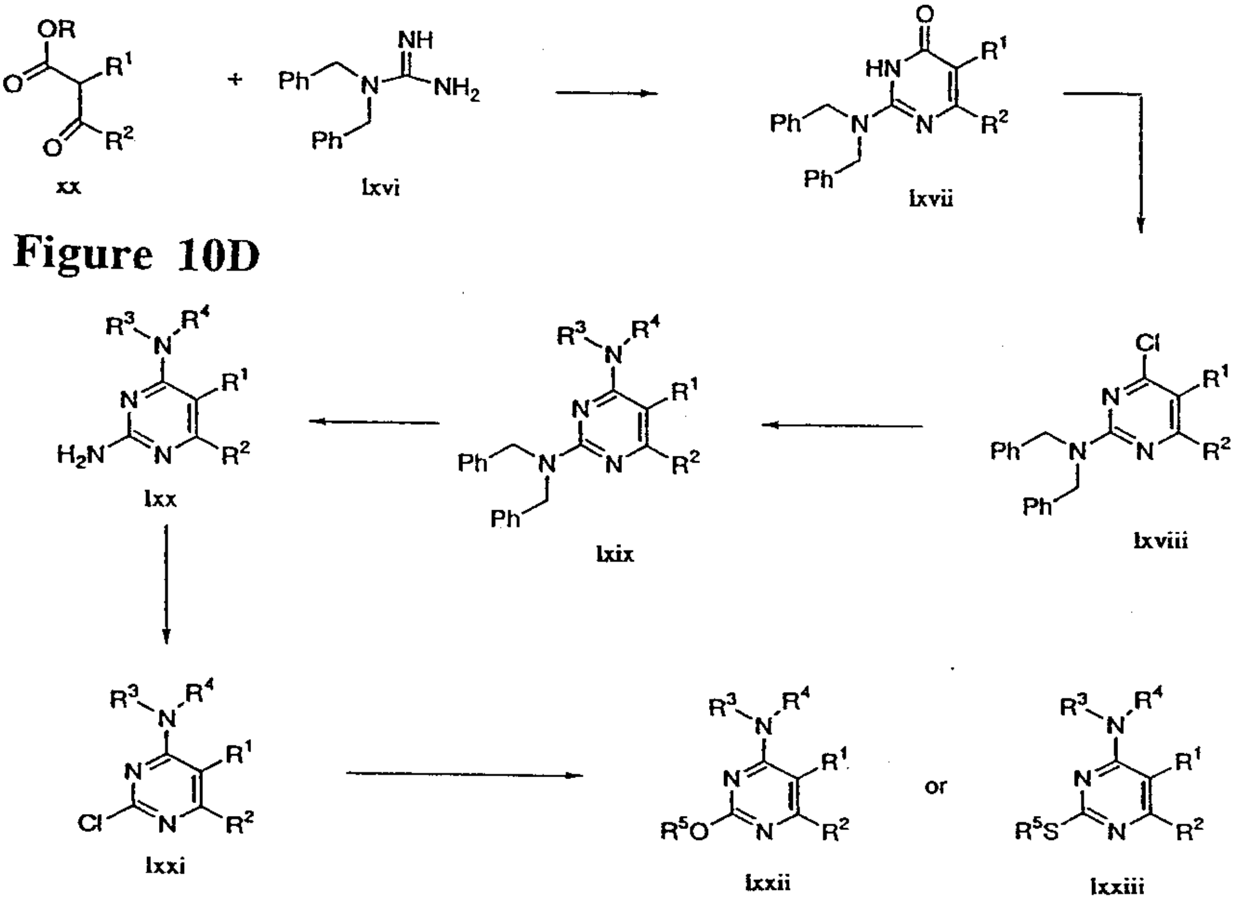


Figure 10D

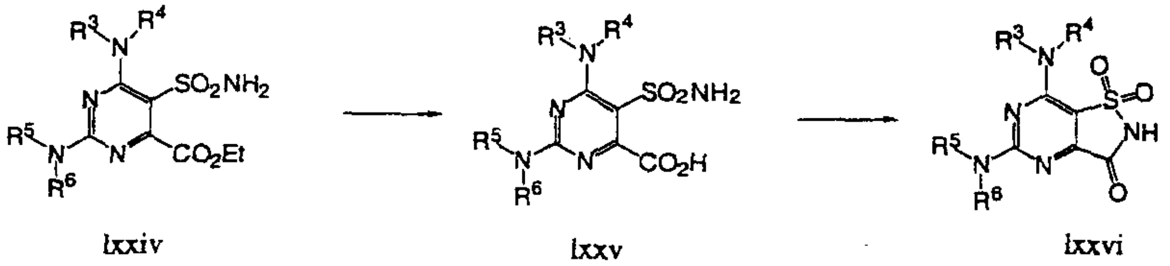


Figure 11A

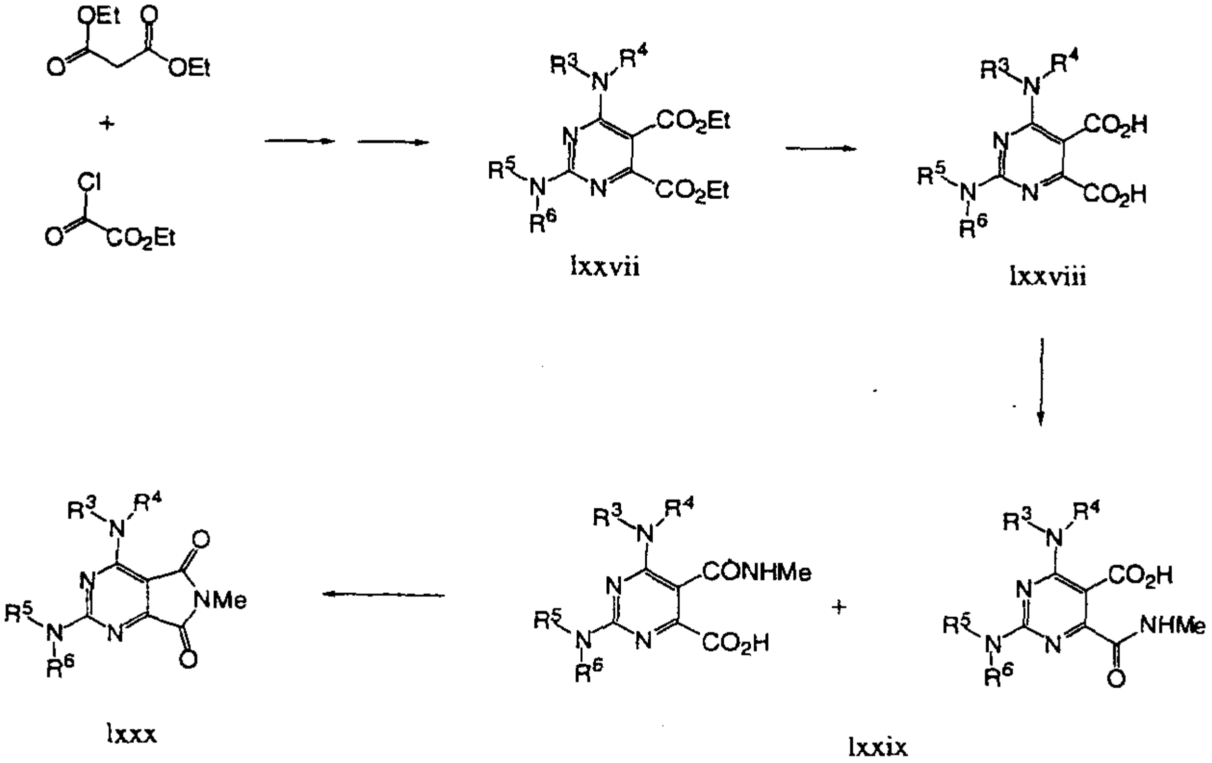


Figure 11B

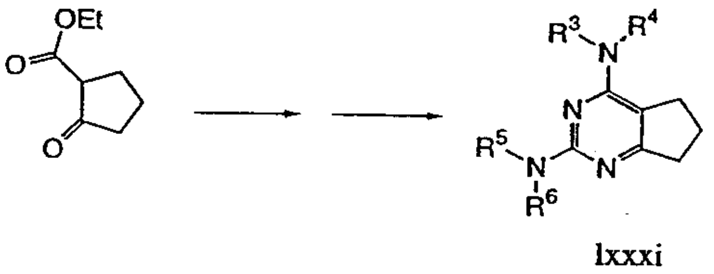


Figure 11C

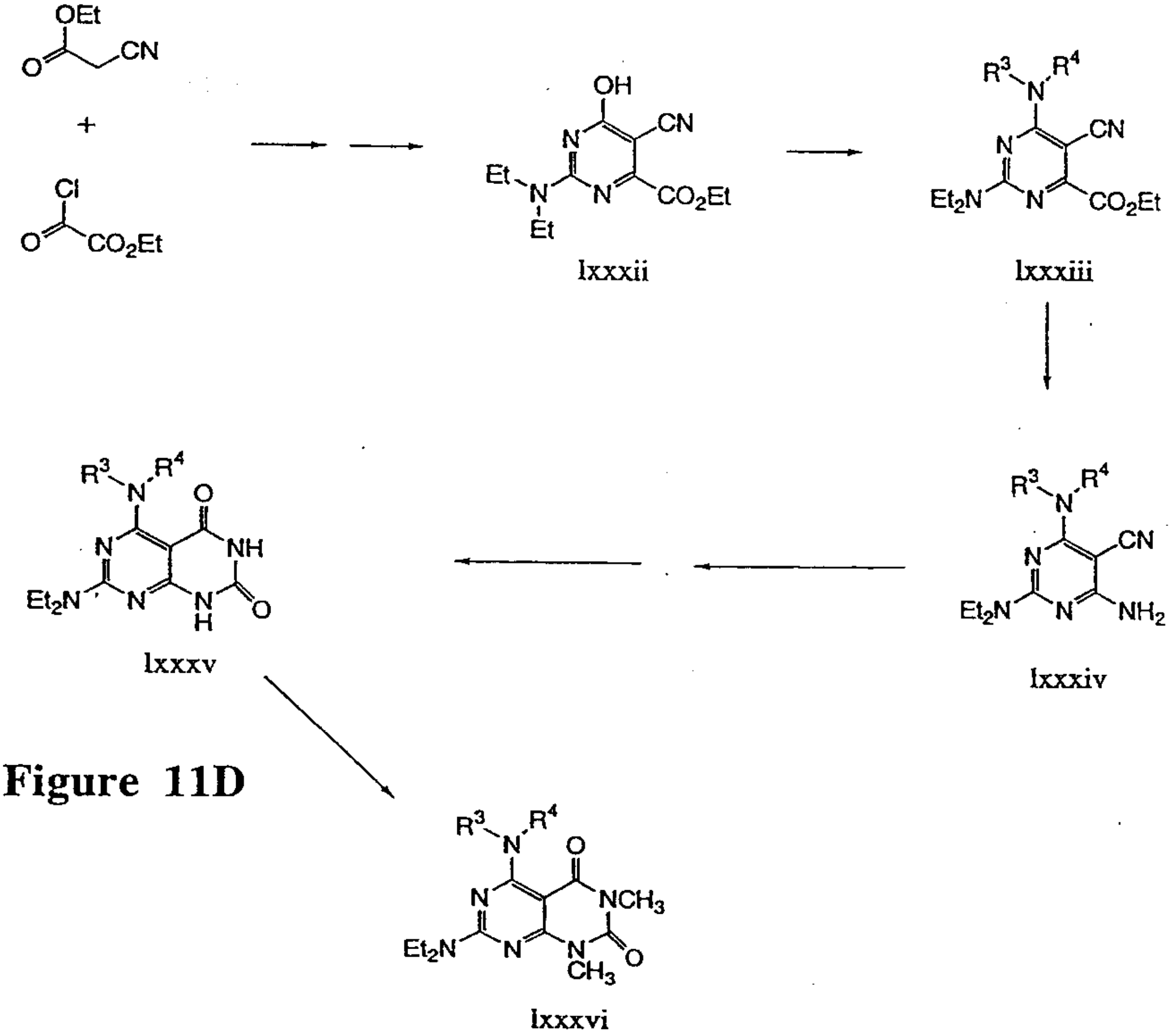


Figure 11D

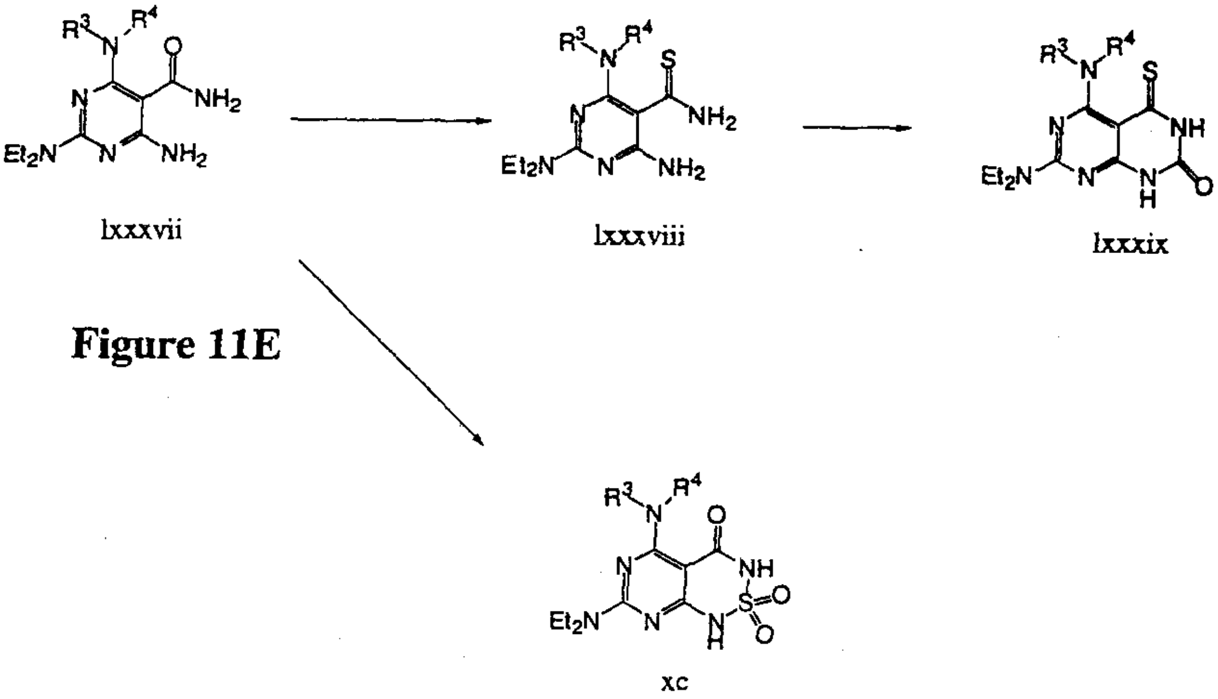


Figure 11E

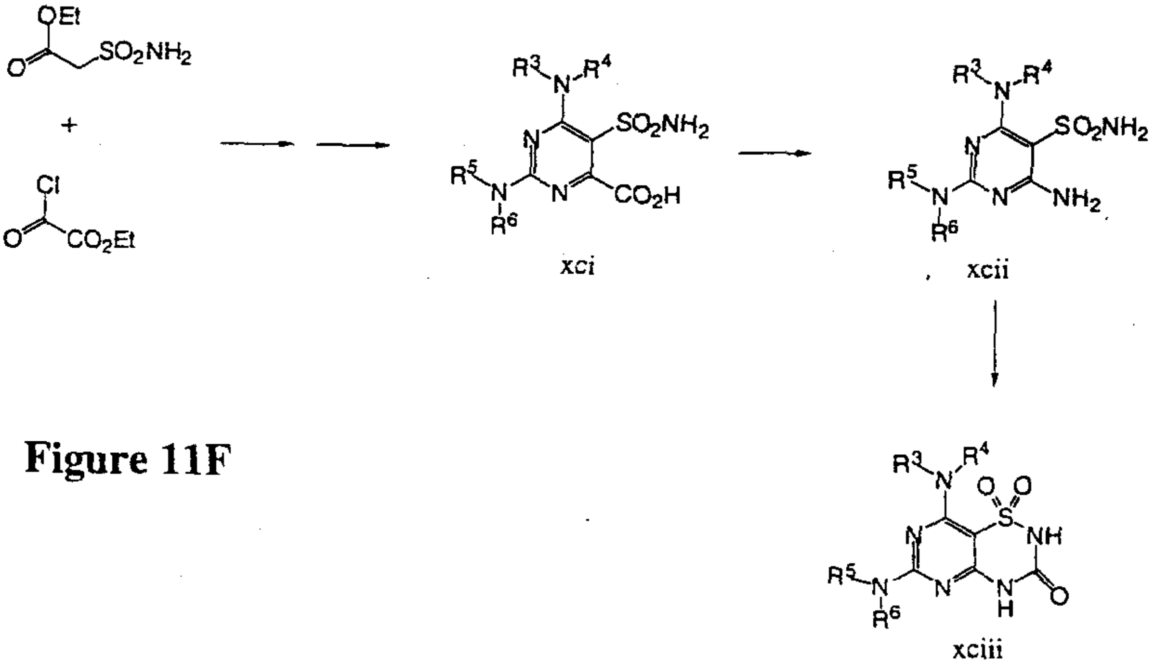
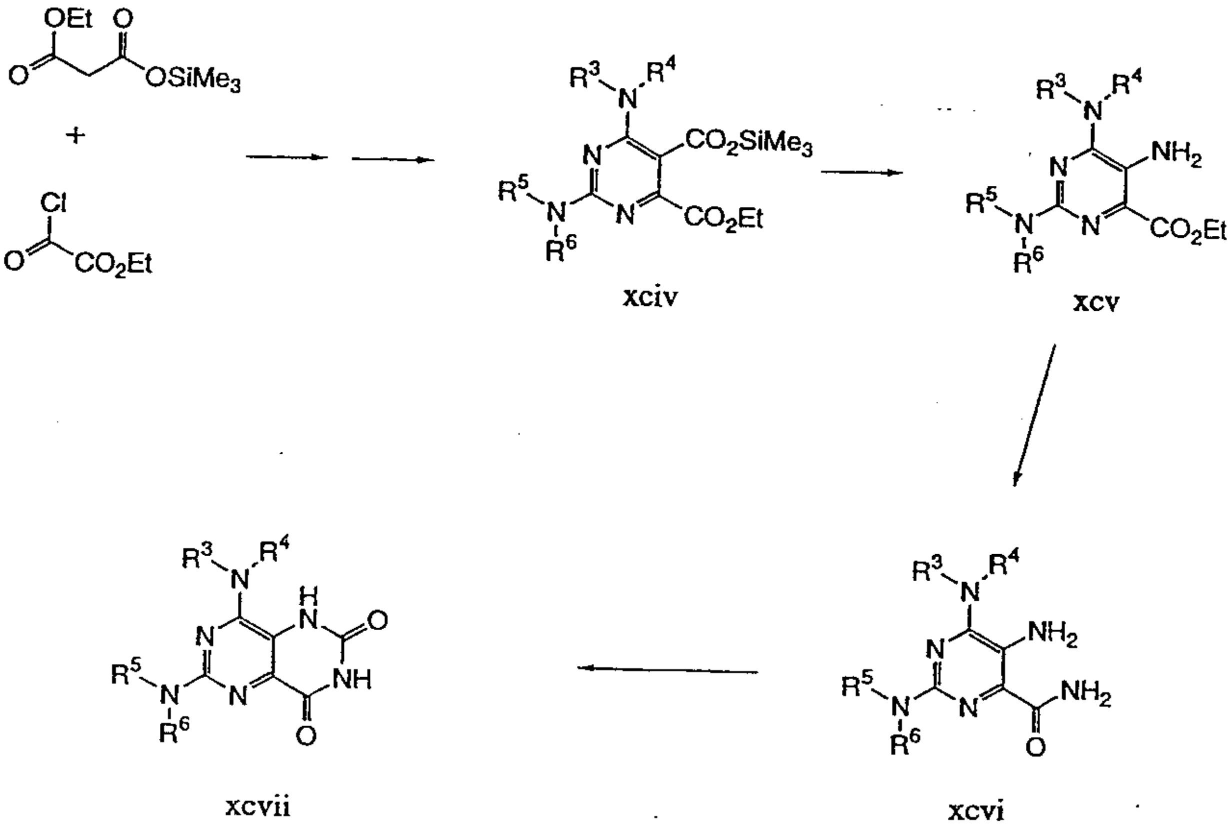


Figure 11F

Figure 11G


OEt
O
OSiMe3
+
Cl
O
CO2Et
R3
R4
N
CO2SiMe3
R5
R6
CO2Et
xciv
NH2
xcv
NH2
O
xcvi
H
NH
xcvii

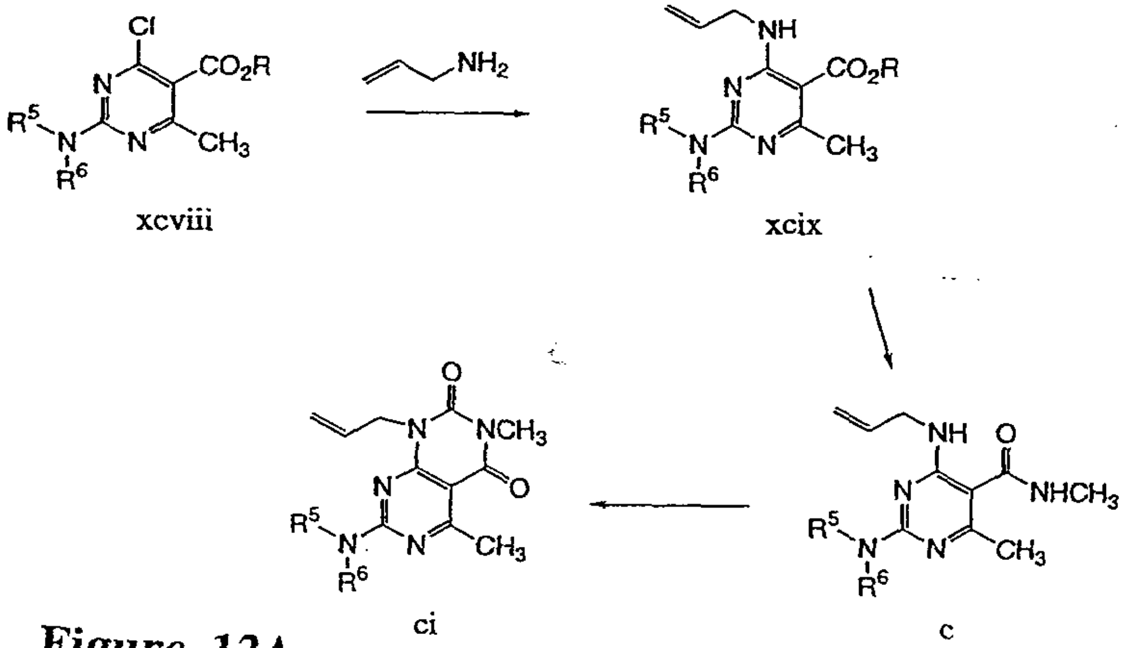


Figure 12A

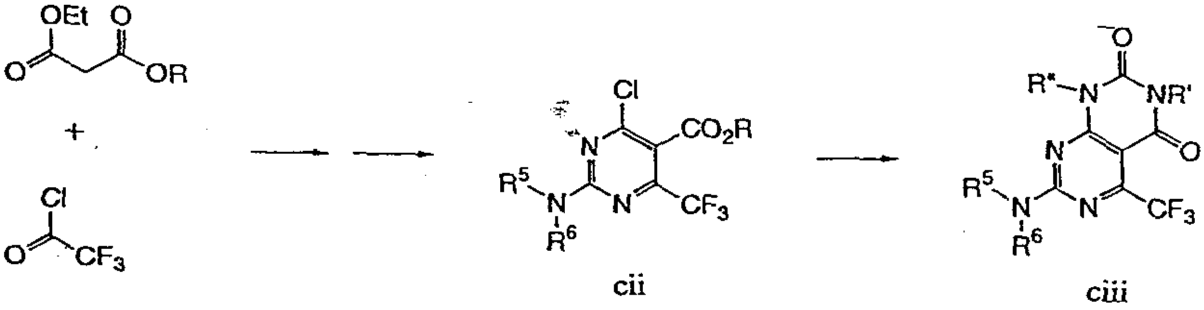


Figure 12B

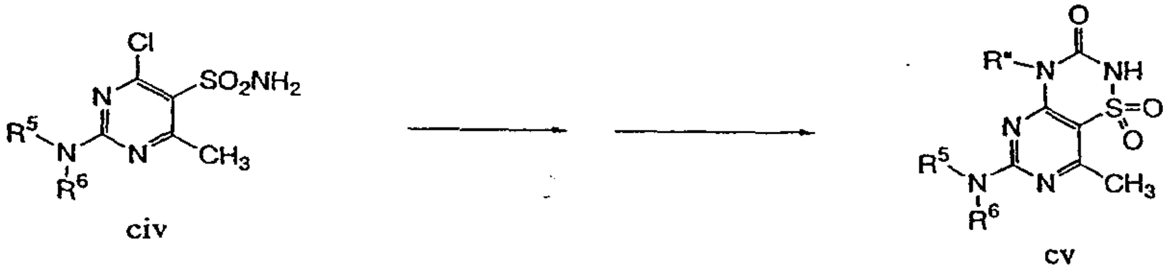


Figure 12C

FIGURE 13

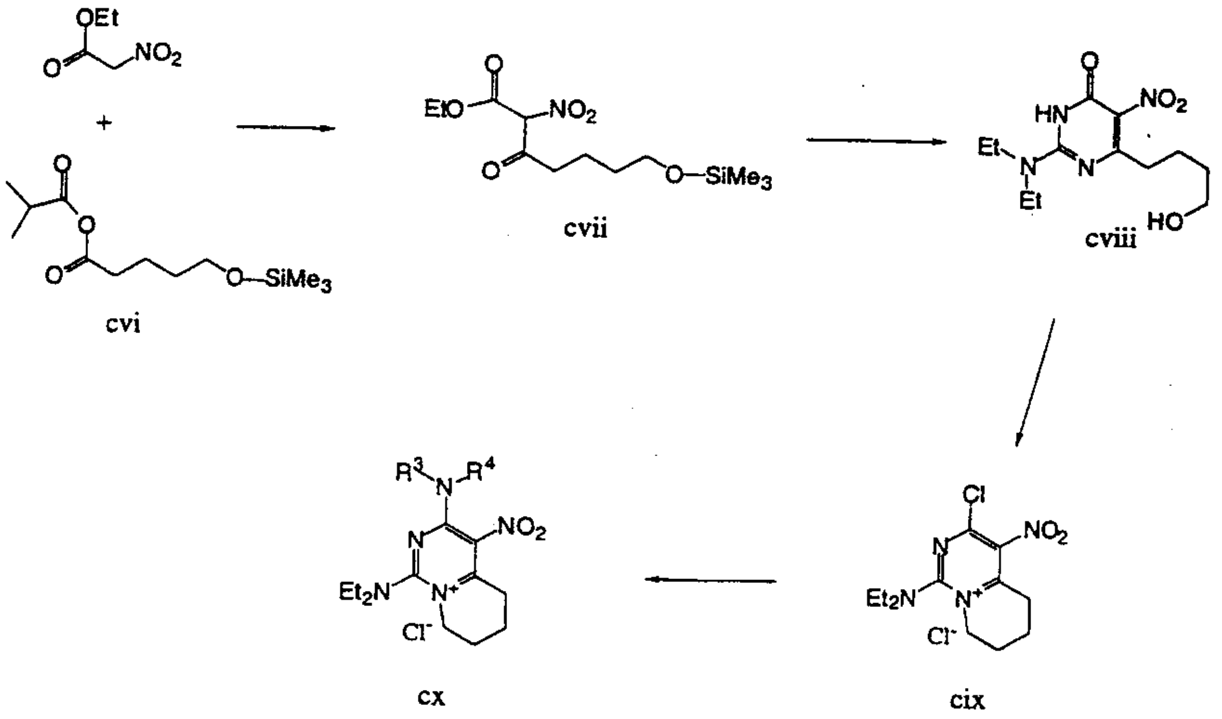
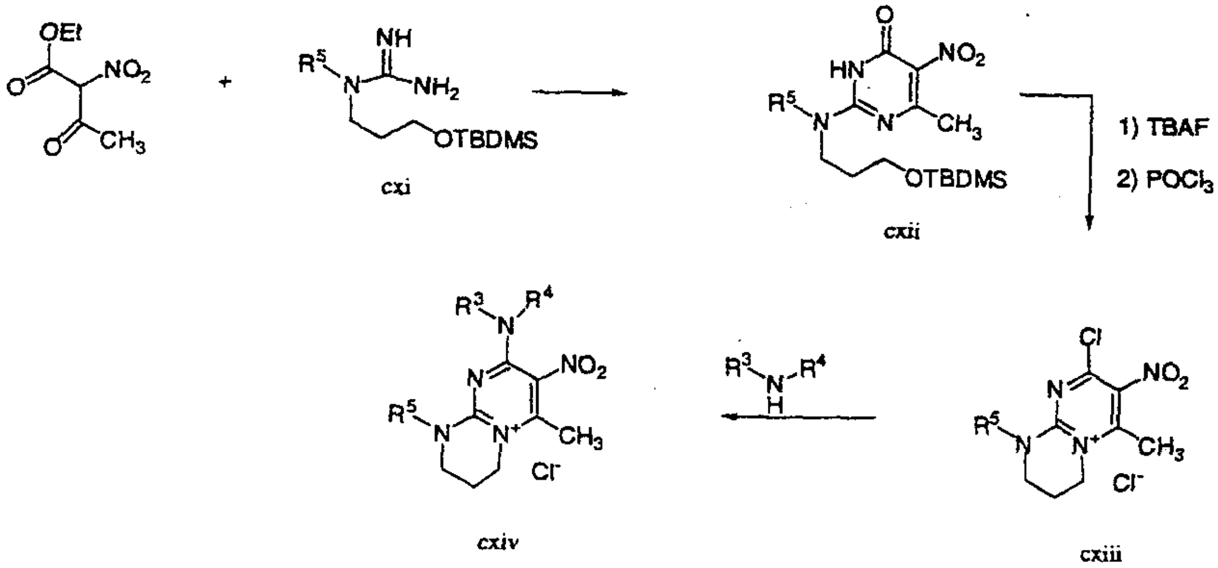

OEt
NO2
O
+
O
O
O
O–SiMe3
cvi
EtO
O
NO2
O
O–SiMe3
cvii
O
HN
NO2
Et
N
N
Et
HO
cviii
Cl
N
NO2
Et2N
N+
Cl-
cix
R3
N
R4
N
NO2
Et2N
N+
Cl-
cx

FIGURE 14


OEt
NO2
O
O
CH3
+
NH
R5
N
NH2
OTBDMS
cxi
O
HN
NO2
R5
N
N
CH3
OTBDMS
cxii
1) TBAF
2) POCl3
Cl
N
NO2
R5
N
N+
CH3
Cl-
cxiii
R3
N
R4
H
R3
N
R4
N
NO2
R5
N
N+
CH3
Cl-
cxiv

[19]中华人民共和国国家知识产权局

[51]Int. Cl⁷
C07D403/04
C07D239/48　A61K 31/505

[12]发明专利申请公开说明书

[21]申请号　99805084.9

[43]公开日　2001年5月30日

[11]公开号　CN 1297447A

[22]申请日　1999.2.12　[21]申请号　99805084.9
[30]优先权
[32]1998.2.17　[33]US [31]60/075,005
[86]国际申请　PCT/US99/03136　1999.2.12
[87]国际公布　WO99/41253　英　1999.8.19
[85]进入国家阶段日期　2000.10.16
[71]申请人　图拉列克股份有限公司
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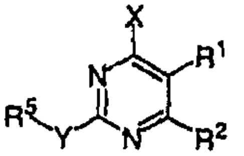
代理人　陈文青

权利要求书18页 说明书52页 附图页数18页

[54]发明名称　抗病毒嘧啶衍生物

[57]摘要

本发明揭示了用于治疗病毒感染,特别是巨细胞病毒感染的化合物和组 合物。化合物包括新颖的基于嘧啶的衍生物,它具有式(Ⅰ)结构,其中X选 自 $-NR^3R^4$、$-OR^3$、$-SR^3$、芳基、烷基和芳基烷基;Y选自共 价键、$-N(R^6)-$、$-O-$、$-S-$、$-C(=O)-$和亚烷基;R^1和R^2独立地选自氢、烷基、$-O-$烷基、$-S-$烷基、芳基、芳基烷基、$-O-$芳基、$-S-$芳基、$-NO_2$、$-NR^7R^8$、$-C(O)R^9$、$-C(O)_2R^{10}$、$-C(O)NR^7R^8$、$-N(R^7)C(O)R^9$、$-N(R^7)CO_2R^{11}$、$-N(R^9)C(O)NR^7R^8$、$-S(O)_mNR^7R^8$、$-S(O)_nR^9$、$-CN$、卤素和$-N(R^7)S(O)_mR^{11}$。



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ISSN 1008-4274

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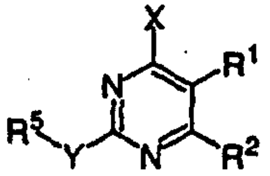
权 利 要 求 书

1. 一种化合物，它具有下式结构：



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其中

X 选自$-NR^3R^4$、$-OR^3$、$-SR^3$、芳基、烷基和芳烷基；

Y 选自共价键、$-N(R^6)-$、$-O-$、$-S-$、$-C(=O)-$和亚烷基；

R^1 和 R^2 独立地选自氢、烷基、-O-烷基、-S-烷基、芳基、芳基烷基、-O-芳基、-S-芳基、$-NO_2$、$-NR^7R^8$、$-C(O)R^9$、$-CO_2R^{10}$、$-C(O)NR^7R^8$-$N(R^7)C(O)R^9$、$-N(R^7)CO_2R^{11}$、$-N(R^9)C(O)NR^7R^8$、$-S(O)_mNR^7R^8$、$-S(O)_nR^9$、$-CN$、卤素和$-N(R^7)S(O)_mR^{11}$；

R^3 和 R^4 独立地选自氢、烷基、芳基或芳基烷基，或者，R^3 和 R^4 和与之连接的氮原子一起形成 5-、6-或 7-元环内含 1-3 个杂原子的芳环或非芳族环；

R^5 选自烷基、芳基、芳烷基和双环稠合的芳基-环烷基；

R^6 选自氢、烷基、芳基和芳基烷基；或与 R^5 并和与 R^5 和 R^6 连接的氮原子结合，形成 5-、6-、7-或 8-元环；

R^7 和 R^8 各自独立地选自氢、烷基、芳基或芳基烷基，或者 R^7 和 R^8 和与它们相连的氮原子连接在一起形成 4-、5-、6-、7-或 8-元环，环中含 1-3 个杂原子；

R^9 和 R^{10} 独立地选自氢、烷基、芳基和芳基烷基；

R^{11} 选自烷基、芳基和芳基烷基；

m 是 1-2 的整数；

n 是 1-3 的整数；

任选的是，R^1 与 R^2 连接、R^1 与 R^3 连接、R^3 与 N^3 连接、R^5 与 N^3 连接、R^5 与 N^1 连接或 R^2 与 N^1 连接形成了 5-、6-、7-或 8-元环，

所述的化合物的分子量为约 150~750，条件是当 Y 是键时，R^5 不是咪唑环。

2. 根据权利要求 1 所述的化合物，其中 R^1 选自$-NO_2$、$-S(O)_mNR^7R^8$、$-S(O)_nR^9$、

-CN、氟代烷基、$-C(O)R^9$、$-CO_2R^{10}$ 和 $-C(O)NR^7R^8$；R^2 选自氢、烷基、-O-烷基、-S-烷基、芳基、芳基烷基、-O-芳基和-S-芳基。

3. 根据权利要求 2 所述的化合物，其中 X 是 $-NR^3R^4$，Y 选自 $-N(R^6)-$、-O-和-S；R^2 选自氢、烷基、-S-烷基、-O-烷基和卤素。

4. 根据权利要求 3 所述的化合物，其中 R^1 选自 $-CF_3$、$-S(O)_mNR^7R^8$、$-CO_2R^{10}$、-CN 和 $-NO_2$，R^2 选自氢、(低级)烷基、-O-(低级)烷基和-S-(低级)烷基。

5. 根据权利要求 4 所述的化合物，其中 Y 是 $-N(R^6)-$ 或-O-，R^1 是 $-NO_2$，R^2 是氢或 (C_1-C_4) 烷基。

6. 根据权利要求 5 所述的化合物，其中 R^3 与 R^4 以及与之相连的氮原子连接在一起，形成 5-元环。

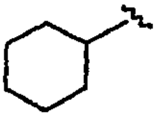
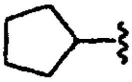
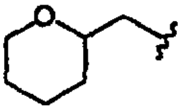
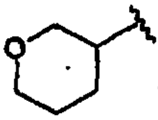
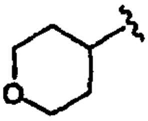
7. 根据权利要求 6 所述的化合物，其中所述的 5-元环含两个氮原子。

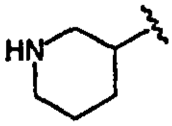
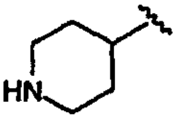
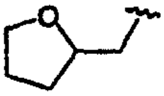
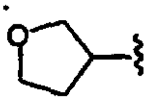
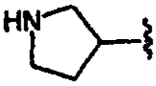
8. 根据权利要求 7 所述的化合物，其中所述的 5-元环是取代或未取代的咪唑环。

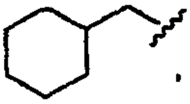
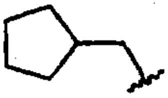
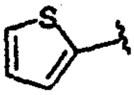
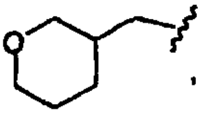
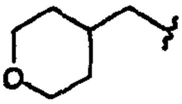
9. 根据权利要求 8 所述的化合物，其中 Y 是 $-N(R^6)-$，其中 R^6 是氢或低级烷基，R^5 选自烷基、芳基、芳基烷基和双环稠合的芳基-环烷基。

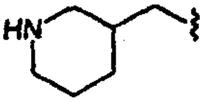
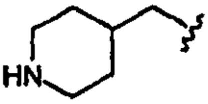
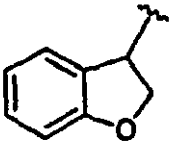
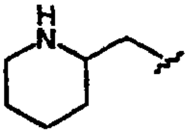
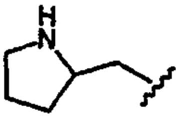
10. 根据权利要求 9 所述的化合物，其中 R^5 选自环烷基、杂环烷基、芳基、芳基烷基和双环稠合的芳基-环烷基，R^6 选自氢、甲基、乙基和丙基，$-NR^3R^4$ 选自咪唑-1-基、2-甲基咪唑-1-基、2,4-二甲基咪唑-1-基、2-乙基咪唑-1-基、2-(1-丙基)咪唑-1-基、2-乙基-4-甲基咪唑-1-基和 2-(2-丙基)咪唑-1-基。

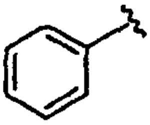
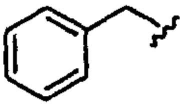
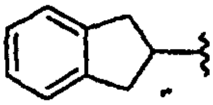
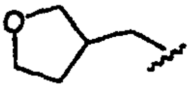
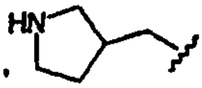
11. 根据权利要求 10 所述的化合物，其中 R^6 选自氢、甲基和乙基，$-NR^3R^4$ 选自咪唑-1-基、2-甲基咪唑-1-基、2,4-二甲基咪唑-1-基和 2-乙基咪唑-1-基，R^5 为选自下列的任选地取代的基团：

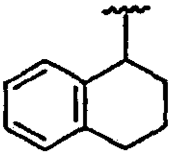
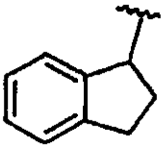
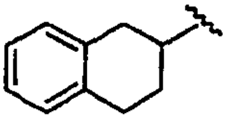
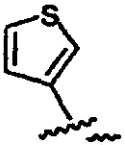
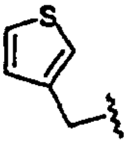
 ,  ,  ,  ,  ,

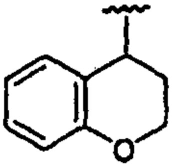
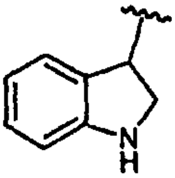
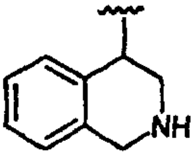
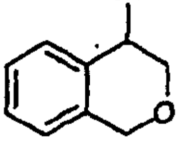
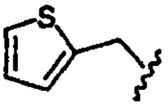
 ,  ,  ,  ,  ,

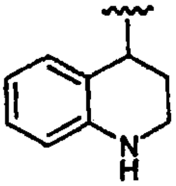
 ,  ,  ,  ,  ,

 ,  ,  ,  ,  ,

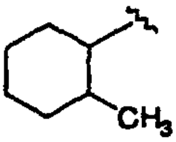
 ,  ,  ,  ,  ,

 ,  ,  ,  ,  ,

 ,  ,  ,  ,  ,

和  .

12. 根据权利要求 11 所述的化合物，其中 R^5 选自：



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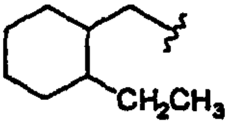

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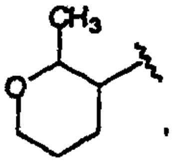

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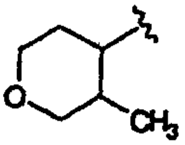

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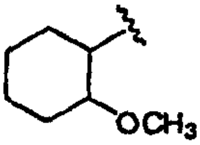

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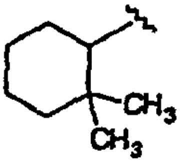

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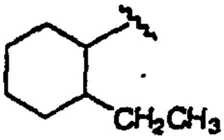

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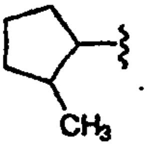

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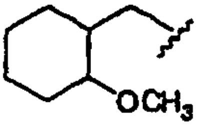

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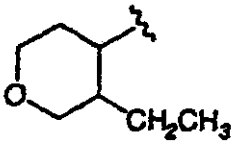

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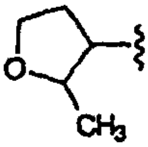

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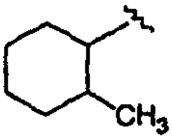
13. 根据权利要求 12 所述的化合物，其中所述的化合物选自：



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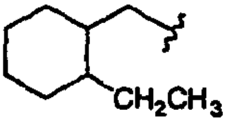

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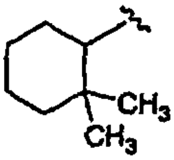

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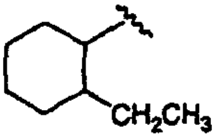

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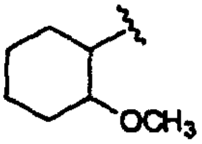
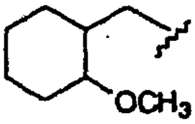
14. 根据权利要求 12 所述的化合物，其中所述的化合物选自：



和



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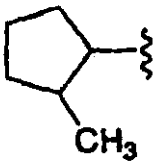
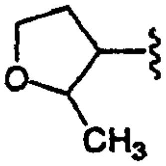
15. 根据权利要求 12 所述的化合物，其中所述的化合物选自：



和



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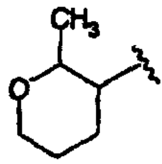
16. 根据权利要求 12 所述的化合物，所述的化合物选自：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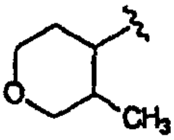
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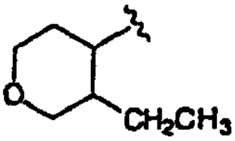
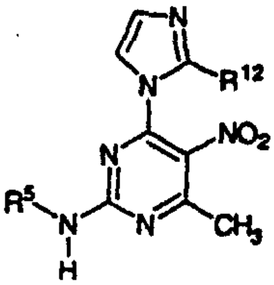
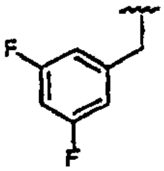
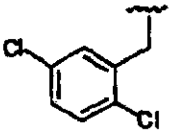

。

17．根据权利要求 1 所述的化合物，所述的化合物具有下式：



其中 R^{12} 选自氢、甲基和乙基；R^5 选自：


，

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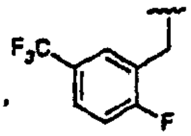
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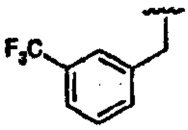
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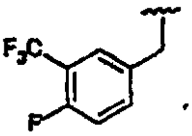
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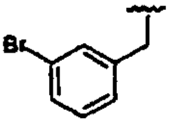
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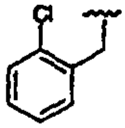
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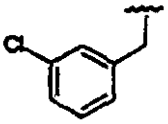
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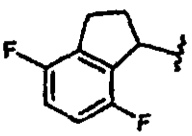
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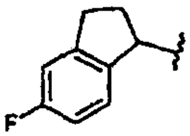
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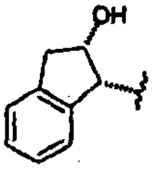
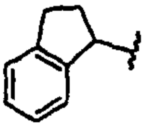
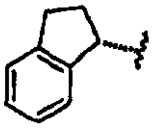
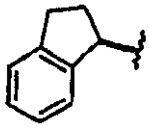
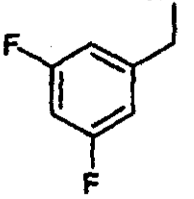
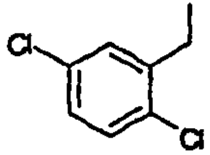

，

，

和

。

18．根据权利要求 17 所述的化合物，其中 R^{12} 是甲基。

19．根据权利要求 18 所述的化合物，其中 R^5 选自：


，

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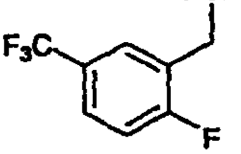
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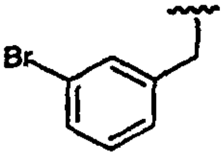
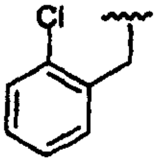
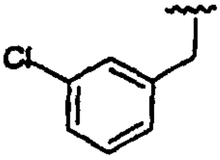
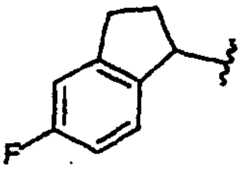
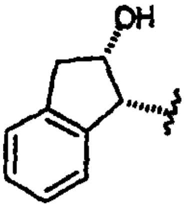
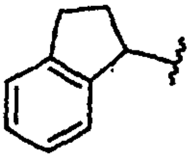
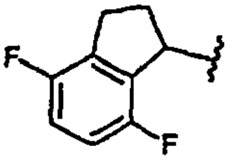
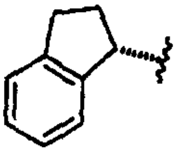
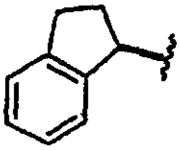
20．根据权利要求 18 所述的化合物，其中 R^5 选自：

，和。

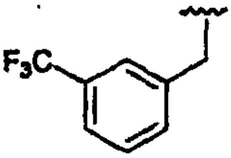
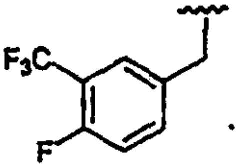
21．根据权利要求 18 所述的化合物，其中 R^5 选自：

，和。

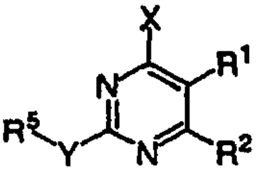
22．根据权利要求 18 所述的化合物，其中 R^5 选自：

，和。

23．根据权利要求 18 所述的化合物，其中 R^5 选自：

和。

24．一种药物组合物，包括药学上或诊断学上可接受的赋形剂和下式化合物：



(I)

其中

X 选自 $-NR^3R^4$、$-OR^3$、$-SR^3$、芳基、烷基和芳烷基；

Y 选自共价键、$-N(R^6)-$、$-O-$、$-S-$、$-C(=O)-$和亚烷基；

R^1 和 R^2 独立地选自氢、烷基、-O-烷基、-S-烷基、芳基、芳基烷基、-O-芳基、-S-芳基、$-NO_2$、$-NR^7R^8$、$-C(O)R^9$、$-CO_2R^{10}$、$-C(O)NR^7R^8$$-N(R^7)C(O)R^9$、$-N(R^7)CO_2R^{11}$、$-N(R^9)C(O)NR^7R^8$、$-S(O)_mNR^7R^8$、$-S(O)_nR^9$、-CN、卤素和$-N(R^7)S(O)_mR^{11}$；

R^3 和 R^4 独立地选自氢、烷基、芳基或芳基烷基，或者，R^3 和 R^4 和与之连接的氮原子一起形成 5-、6-或 7-元含 1-3 个环内杂原子的芳环或非芳族环；

R^5 选自烷基、芳基、芳烷基和双环稠合的芳基-环烷基；

R^6 选自氢、烷基、芳基和芳基烷基；或与 R^5 和与 R^5 并和 R^6 连接的氮原子结合，形成 5-、6-、7-或 8-元环；

R^7 和 R^8 各自独立地选自氢、烷基、芳基或芳基烷基，或者 R^7 和 R^8 和与它们相连的氮原子连接在一起形成 4-、5-、6-、7-或 8-元环，环中含 1-3 个杂原子；

R^9 和 R^{10} 独立地选自氢、烷基、芳基和芳基烷基；

R^{11} 选自烷基、芳基和芳基烷基；

m 是 1-2 的整数；

n 是 1-3 的整数；

任选的是，R^1 与 R^2 连接、R^1 与 R^3 连接、R^3 与 N^3 连接、R^5 与 N^3 连接、R^5 与 N^1 连接或 R^2 与 N^1 连接形成了 5-、6-、7-或 8-元环，

所述的化合物的分子量为约 150-750，条件是当 Y 是键时，R^5 不是咪唑环。

25. 根据权利要求 24 所述的组合物，其中 R^1 选自$-NO_2$、$-S(O)_mNR^7R^8$、$-S(O)_nR^9$、-CN、氟代烷基、$-C(O)R^9$、$-CO_2R^{10}$ 和$-C(O)NR^7R^8$；R^2 选自氢、烷基、-O-烷基、-S-烷基、芳基、芳基烷基、-O-芳基和-S-芳基。

26. 根据权利要求 25 所述的组合物，其中 X 是$-NR^3R^4$，Y 选自$-N(R^6)-$、-O-和-S-；和$-NO_2$，R^2 选自氢、烷基、-O-烷基-S-烷基、和卤素。

27. 根据权利要求 26 所述的化合物，其中 R^1 选自$-CF_3$、$-S(O)_mNR^7R^8$、$-CO_2R^{10}$、-CN 和$-NO_2$，R^2 选自氢、(低级)烷基、-O-(低级)烷基和-S-(低级)烷基。

28. 根据权利要求 27 所述的组合物，其中 Y 是$-N(R^6)-$或-O-，R^1 是$-NO_2$，R^2 是氢或(C_1-C_4)烷基。

29. 根据权利要求 28 所述的组合物，其中 R^3 与 R^4 以及与之相连的氮原子连接在一起，形成 5-元环。

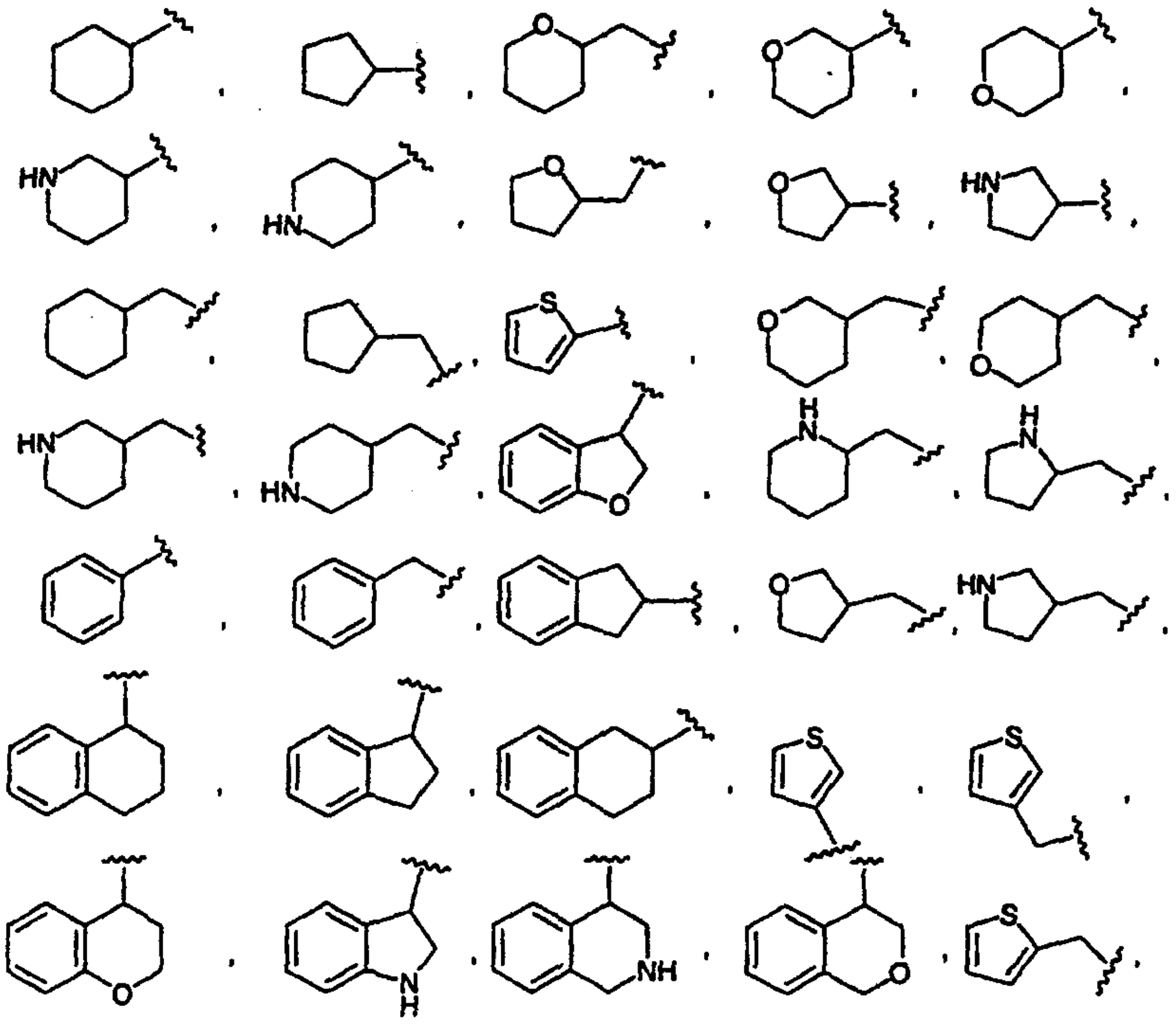
30. 根据权利要求 29 所述的组合物，其中所述的 5-元环含两个氮原子。

31. 根据权利要求 30 所述的组合物，其中所述的 5-元环是取代或未取代的咪唑环。

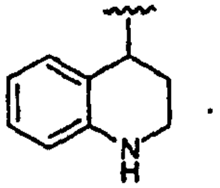
32. 根据权利要求 31 所述的组合物，其中 Y 是 $-N(R^6)-$，其中 R^6 是氢或低级烷基，R^5 选自烷基、芳基、芳基烷基和双环稠合的芳基-环烷基。

33. 根据权利要求 32 所述的组合物，其中 R^5 选自环烷基、杂环烷基、芳基、芳基烷基和双环稠合的芳基-环烷基，R^6 选自氢、甲基、乙基和丙基，$-NR^3R^4$ 选自咪唑-1-基、2,4-二甲基咪唑-1-基、2-甲基咪唑-1-基、2-乙基咪唑-1-基、2-(1-丙基)咪唑-1-基、2-乙基-4-甲基咪唑-1-基和 2-(2-丙基)咪唑-1-基。

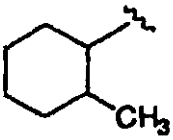
34. 根据权利要求 33 所述的组合物，其中 R^6 选自氢、甲基和乙基，$-NR^3R^4$ 选自咪唑-1-基、2-甲基咪唑-1-基、2,4-二甲基咪唑-1-基和 2-乙基咪唑-1-基，R^5 是选自下列的任选地取代的基团：



和



35．根据权利要求 34 所述的组合物，其中 R^5 选自：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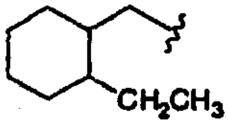
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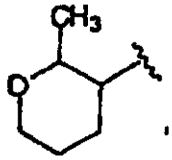
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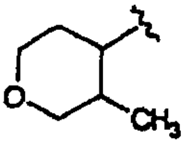
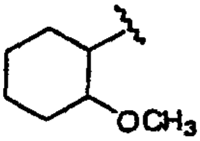
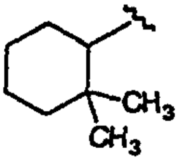

，

，

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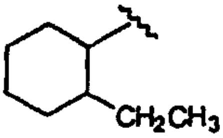
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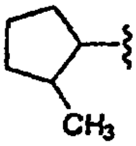
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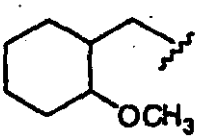
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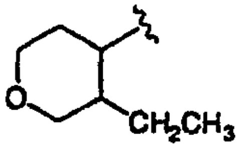
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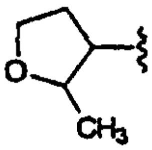
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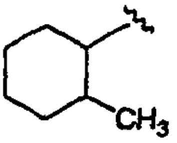
36．根据权利要求 35 所述的组合物，其中 R^5 选自：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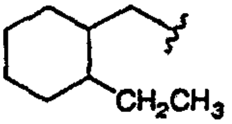
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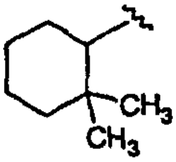
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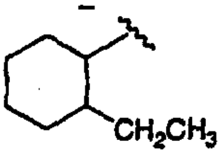
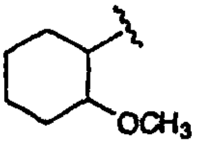

。

37．根据权利要求 35 所述的组合物，其中 R^5 选自：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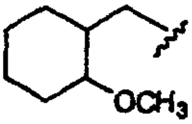
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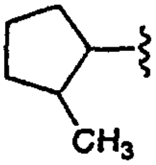
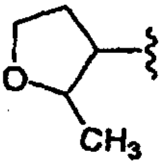
38．根据权利要求 35 所述的组合物，其中 R^5 选自：


和

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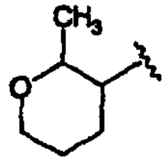
39．根据权利要求 35 所述的组合物，其中 R^5 选自：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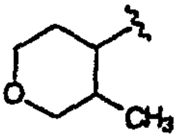
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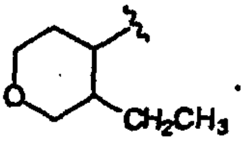
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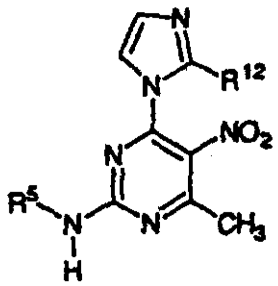
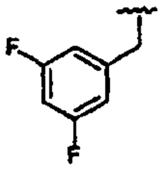
40．根据权利要求 1 所述的组合物合物，所述的化合物具有下式：



其中 R^{12} 选自氢、甲基和乙基；R^5 选自：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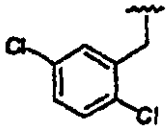
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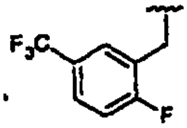
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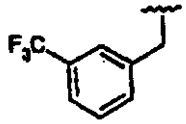
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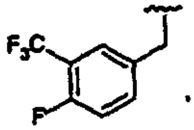
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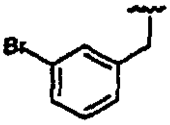
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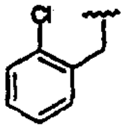
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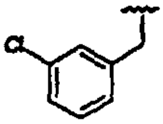
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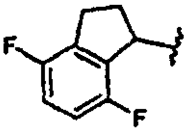
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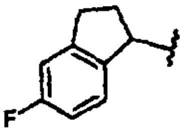
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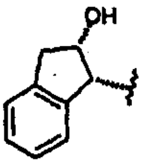
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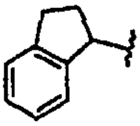
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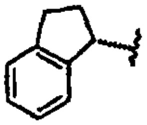
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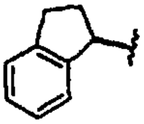
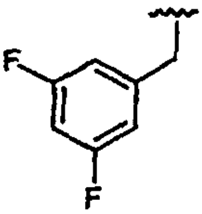

。

41．根据权利要求 40 所述的组合物，其中 R^{12} 是甲基。

42．根据权利要求 41 所述的组合物，其中 R^5 选自：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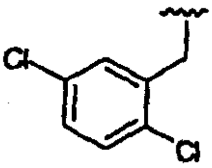
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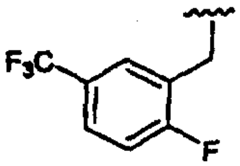
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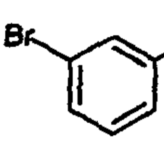
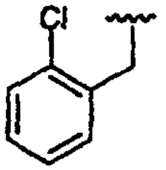
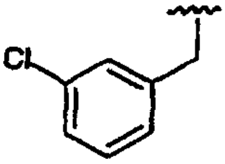
43．根据权利要求 41 所述的组合物，其中 R^5 选自：


，

和

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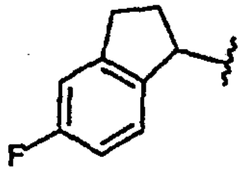
44．根据权利要求 41 所述的组合物，其中 R^5 选自：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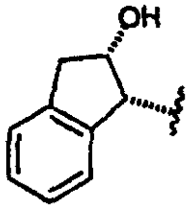
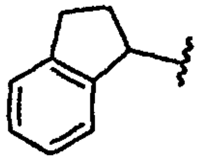
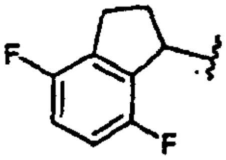
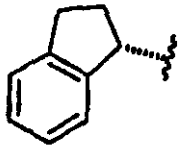
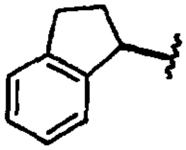

和

。

45．根据权利要求 41 所述的组合物，其中 R^5 选自：


，

和

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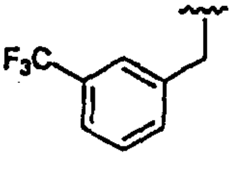
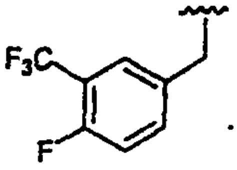
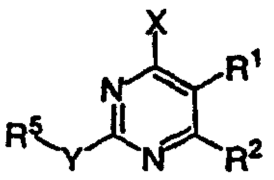
46．根据权利要求 41 所述的组合物，其中 R^5 选自：


和

。

47．一种预防或抑制哺乳动物病毒感染的方法，包括对所述的哺乳动物给予病毒感染抑制量的下式化合物：


(I)

其中

X 选自 $-NR^3R^4$、$-OR^3$、$-SR^3$、芳基、烷基和芳烷基；

Y 选自共价键、$-N(R^6)-$、-O-、-S-、-C(=O)-和亚烷基；

R^1 和 R^2 独立地选自氢、烷基、-O-烷基、-S-烷基、芳基、芳基烷基、-O-芳基、-S-芳基、$-NO_2$、$-NR^7R^8$、$-C(O)R^9$、$-CO_2R^{10}$、$-C(O)NR^7R^8$-$N(R^7)C(O)R^9$、$-N(R^7)CO_2R^{11}$、$-N(R^9)C(O)NR^7R^8$、$-S(O)_mNR^7R^8$、$-S(O)_nR^9$、-CN、卤素和 $-N(R^7)S(O)_mR^{11}$；

R^3 和 R^4 独立地选自氢、烷基、芳基或芳基烷基，或者，R^3 和 R^4 和与之连接的氮原子一起形成 5-、6-或 7-元含 1-3 个环内杂原子的芳环或非芳族环；

R^5 选自烷基、芳基、芳烷基和双环稠合的芳基-环烷基；

R^6 选自氢、烷基、芳基和芳基烷基；或与 R^5 并和与 R^5 和 R^6 连接的氮原子结合，形成 5-、6-、7-或 8-元环；

R^7 和 R^8 各自独立地选自氢、烷基、芳基或芳基烷基，或者 R^7 和 R^8 和与它们相连的氮原子连接在一起形成 4-、5-、6-、7-或 8-元环，环中含 1-3 个杂原子；

R^9 和 R^{10} 独立地选自氢、烷基、芳基和芳基烷基；

R^{11} 选自烷基、芳基和芳基烷基；

m 是 1-2 的整数；

n 是 1-3 的整数；

任选的是，R^1 与 R^2 连接、R^1 与 R^3 连接、R^3 与 N^3 连接、R^5 与 N^3 连接、R^5 与 N^1 连接或 R^2 与 N^1 连接形成了 5-、6-、7-或 8-元环，

所述的化合物的分子量为约 150-750。

48. 根据权利要求 47 所述的方法，其中所述的化合物与选自更昔洛韦、磷甲酸和 cidofovir 的辅助抗病毒化合物联合给药。

49. 根据权利要求 47 所述的方法，其中所述的化合物与抗-HIV 化合物联合给药。

50. 根据权利要求 47 所述的方法，其中所述的哺乳动物是处于受到免疫危险的状态。

51. 根据权利要求 47 所述的方法，其中所述的给药是口服给药。

52. 根据权利要求 47 所述的方法，其中所述的给药是局部外用给药。

53. 根据权利要求 47 所述的方法，其中所述的给药是预防性的，用来防止经器官移植的病人受到病毒感染。

54. 根据权利要求 47 所述的方法，其中所述的病毒感染产生了选自 CMV-视网膜炎、CMV-单核细胞增多症、CMV-肺炎和 CMV-肝炎的疾病。

55. 根据权利要求 47 所述的方法，其中所述的给药是非胃肠道给药。

56. 根据权利要求 1 所述的方法，其中 R^1 选自 $-NO_2$、$-S(O)_mNR^7R^8$、$-S(O)_nR^9$、

-CN、氟代烷基、-C(O)R^9、-CO_2R^{10}和-C(O)NR^7R^8；R^2选自氢、烷基、-O-烷基、-S-烷基、芳基、芳基烷基、-O-芳基和-S-芳基。

57．根据权利要求56所述的方法，其中X是-NR^3R^4，Y选自-N(R^6)-、-O-和-S；R^2选自氢、烷基、-O-烷基、-S-烷基和卤素。

58．根据权利要求57所述的方法，其中R^1选自-CF_3、-S(O)$_m$$NR^7R^8$、-$CO_2R^{10}$、-CN和-$NO_2$，$R^2$选自氢、(低级)烷基、-O-(低级)烷基和-S-(低级)烷基。

59．根据权利要求58所述的方法，其中Y是-N(R^6)-或-O-，R^1是-NO_2，R^2是氢或(C_1-C_4)烷基。

60．根据权利要求59所述的方法，其中R^3与R^4以及与之相连的氮原子连接在一起，形成5-元环。

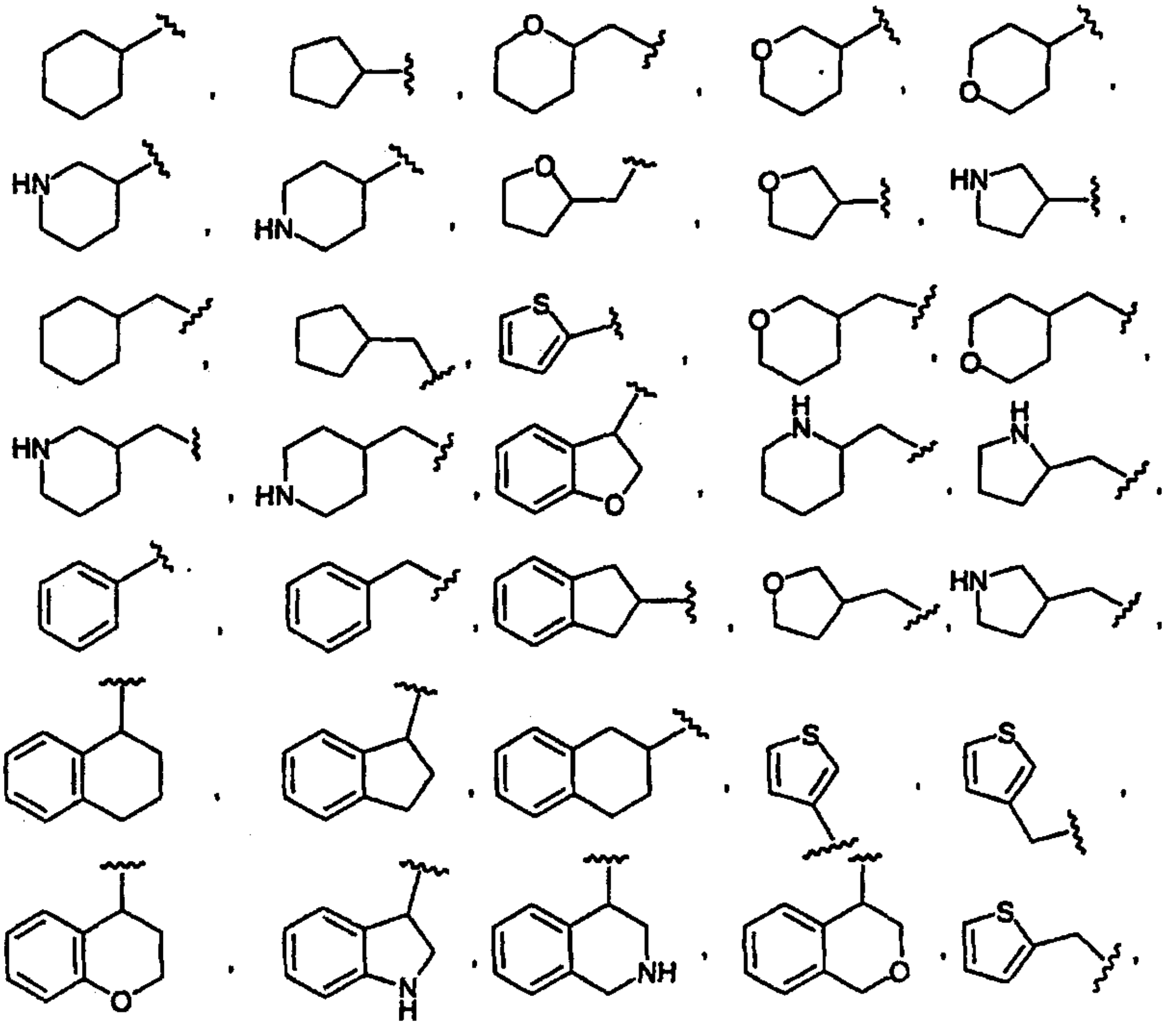
61．根据权利要求60所述的方法，其中所述的5-元环含两个氮原子。

62．根据权利要求61所述的方法，其中所述的5-元环是取代或未取代的咪唑环。

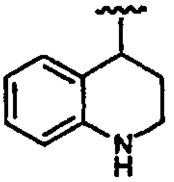
63．根据权利要求62所述的方法，其中Y是-N(R^6)-，其中R^6是氢或低级烷基，R^5选自烷基、芳基、芳基烷基和双环稠合的芳基-环烷基。

64．根据权利要求63所述的方法，其中R^5选自环烷基、杂环烷基、芳基、芳基烷基和双环稠合的芳基-环烷基，R^6选自氢、甲基、乙基和丙基，-NR^3R^4选自咪唑-1-基、2-甲基咪唑-1-基、2,4-二甲基咪唑-1-基、2-乙基咪唑-1-基、2-(1-丙基)咪唑-1-基、2-乙基-4-甲基咪唑-1-基和2-(2-丙基)咪唑-1-基。

65．根据权利要求64所述的方法，其中R^6选自氢、甲基和乙基，-NR^3R^4选自咪唑-1-基、2-甲基咪唑-1-基、2,4-二甲基咪唑-1-基和2-乙基咪唑-1-基，R^5是选自下列的任选地取代的基团：



和



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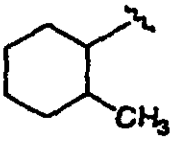
66. 根据权利要求 65 所述的方法，其中 R^5 选自：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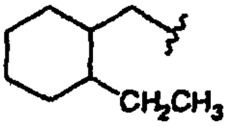
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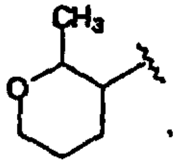
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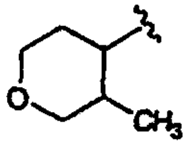
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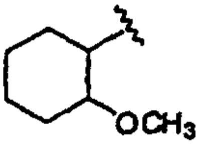
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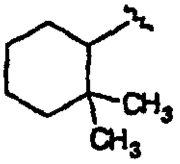
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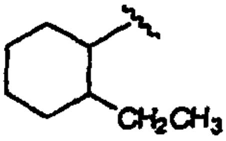
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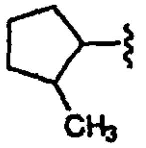
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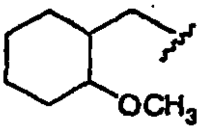
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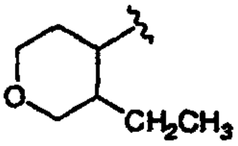
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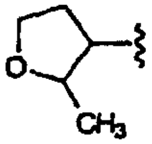
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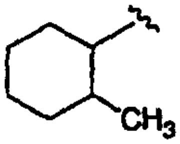
67. 根据权利要求 66 所述的方法，其中 R^5 选自：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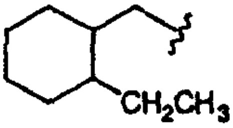
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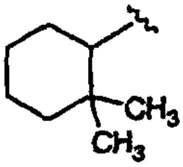
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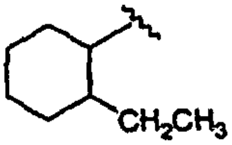
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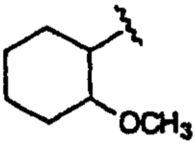
68. 根据权利要求 66 所述的方法，其中 R^5 选自：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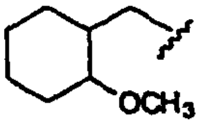
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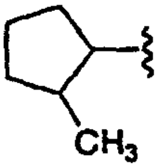
69. 根据权利要求 66 所述的方法，其中 R^5 选自：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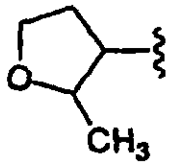
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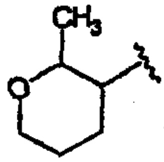
70. 根据权利要求 66 所述的方法，其中 R^5 选自：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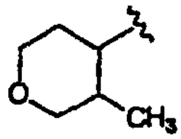
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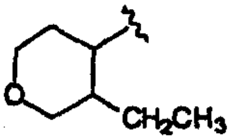
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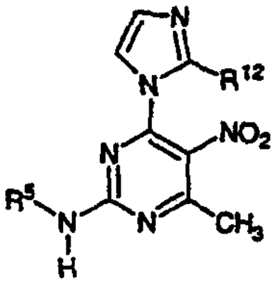
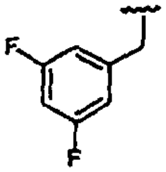
71．根据权利要求 1 所述的方法，其中所述的化合物具有下式：



其中 R^{12} 选自氢、甲基和乙基；R^5 选自：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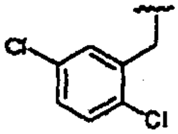
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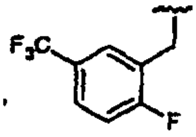
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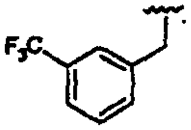
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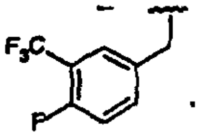
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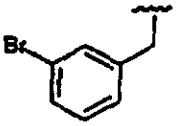
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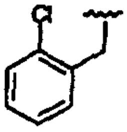
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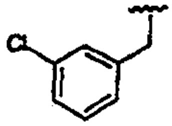
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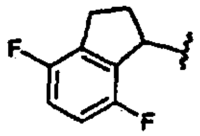
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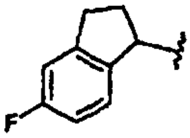
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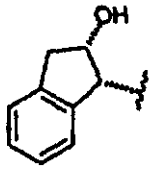
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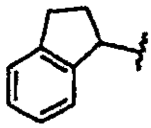
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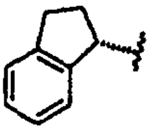
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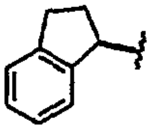
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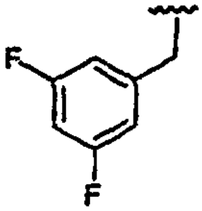
72．根据权利要求 71 所述的方法，其中 R^{12} 是甲基。

73．根据权利要求 72 所述的方法，其中 R^5 选自：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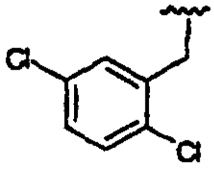
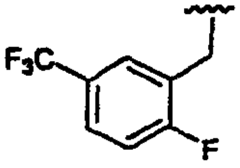

和

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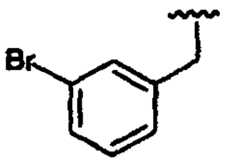
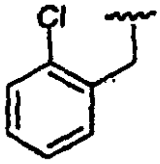
74．根据权利要求 72 所述的方法，其中 R^5 选自：


，

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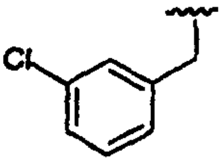
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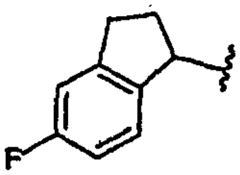
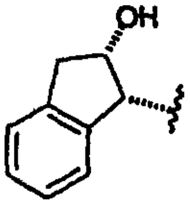
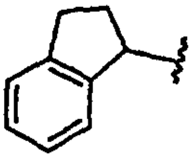
75．根据权利要求 72 所述的方法，其中 R^5 选自：


，

和

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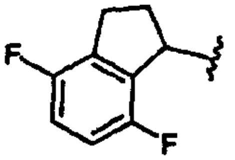
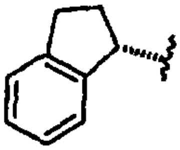
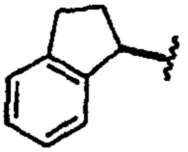
76．根据权利要求 72 所述的方法，其中 R^5 选自：


，

和

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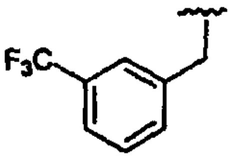
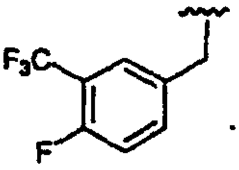
77．根据权利要求 72 所述的方法，其中 R^5 选自：


和

。

78．根据权利要求 47 所述的方法，所述的病毒感染是巨细胞病毒感染。

说　明　书

抗病毒嘧啶衍生物

相关的申请

本申请是 USSN 60/075,005(申请日 1998，2，17)的续展申请，在此全文并入供参考。

关于美国联邦政府资助的研究的声明

本文揭示的本发明不是由任何联邦政府基金资助进行的。

发明领域

本发明领域是新颖的取代嘧啶化合物，及它们作为能抑制病毒(如疱疹病毒)的药理活性药中的应用。主题化合物和组合物特别能用于治疗和抑制人体巨细胞病毒。

发明领域

巨细胞病毒(CMV)是疱疹病毒家族的一员。其它已知的疱疹病毒家族成员包括，例如，单纯疱疹病毒 I 型和 II 型，EB 病毒和水痘带状疱疹病毒。这些病毒在分类学上是相关的，但各自的临床表现截然不同。对于 CMV，起因于天生感染 CMV 的医学疾病包括黄疸、呼吸窘迫和痉挛性发作，它们会导致精神发育迟缓、神经病学上的伤残或死亡。成人感染通常是无症状的，但可表现为，特别是在免疫受危及的病人，如 AIDS 患者、化疗病人和经受组织排异治疗的器官移植病人中表现为，单核细胞增多症、肝炎、肺炎或视网膜炎。

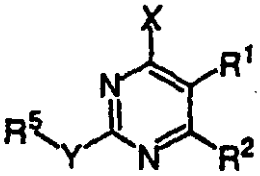
已开发出各种药物，包括天然形成的蛋白质和合成的核苷类似物，治疗疱疹病毒感染。例如，已用天然的抗病毒干扰素治疗疱疹病毒感染，如核苷类似物胞嘧啶-阿拉伯糖苷、腺嘌呤-阿拉伯糖苷、碘羟尿苷(iodoxyuridine)和阿昔洛韦是目前治疗单纯疱疹 II 型感染的选择药物。

不幸的是，已被证明能有效治疗某些疱疹病毒的药物，如阿昔洛韦不足以有效地治疗 CMV。另外，目前用于治疗 CMV 感染的药物，如 9-((1,3-二羟

基-2-丙氧基)甲基)胍(更昔洛韦，DHPG)和膦酰基甲酸(磷甲酸)缺少可接受的副作用和认可的治疗其它疱疹病毒的药物安全曲线。此外，这类药物对于已获得耐药性的某些 CMV 的治疗是无效的。因此，尽管已开发得到了抗疱疹病毒药，仍然需要安全极限增加的、能有效治疗 CMV 感染的治疗剂。本发明提供了令人惊奇地有效的这类治疗剂，取代的嘧啶化合物。

发明概述

本发明提供了新颖的取代嘧啶化合物。该类化合物具有通式 I：



(I)

其中 X 代表$-NR^3R^4$、$-OR^3$、$-SR^3$、芳基、烷基或芳烷基。字母 Y 代表共价键、$-N(R^6)-$、$-O-$、$-S-$、$-C(=O)-$或亚烷基。R^1 和 R^2 独立地选自氢、烷基、-O-烷基、-S-烷基、芳基、芳基烷基、-O-芳基、-S-芳基、$-NO_2$、$-NR^7R^8$、$-C(O)R^9$、$-CO_2R^{10}$、$-C(O)NR^7R^8-N(R^7)C(O)R^9$、$-N(R^7)CO_2R^{11}$、$-N(R^9)C(O)NR^7R^8$、$-S(O)_mNR^7R^8$、$-S(O)_nR^9$、-CN、卤素和$-N(R^7)S(O)_mR^{11}$。基团 R^3 和 R^4 独立地选自氢、烷基、芳基或芳基烷基，或者，当 X 是$-NR^3R^4$ 时，R^3 和 R^4 和与之连接的氮原子一起形成 5-、6-或 7-元芳环或非芳族环，环中含有 1-3 个杂原子。R^5 和 R^6 各自为氢、烷基、芳基或芳基烷基。R^7 和 R^8 各自独立地是氢、烷基、芳基或芳基烷基，或者当与相同的氮原子连接时可结合氮原子形成 4-、5-、6-、7-或 8-元环，环中含 1-3 个杂原子。R^9 和 R^{10} 独立地选自氢、烷基、芳基和芳基烷基。R^{11} 选自烷基、芳基和芳基烷基。下标 m 是 1-2 的整数，下标 n 是 1-3 的整数。

除了上述的 R^1 到 R^{11} 的定义外，上式还表示许多化合物，其中第二环与嘧啶环稠合。例如，R^1 可与 R^2 连接，R^1 可与 R^3 连接，R^3 可与 N^3(在嘧啶环的 3-位的氮原子)连接，R^5 可与 N^3 连接，R^5 可与 N^1(在嘧啶环 1-位上的氮原子)连接，或 R^2 可与 N^1(嘧啶环 1-位上的氮原子)连接，或 R^2 可与 N^1 连接形成稠合的 5-、6-或 7-元环。

最后，本发明化合物的分子量典型的是约 150-750。上式提供的化合物意味着也包括所有其药学上可接受的盐。

本发明化合物可用于治疗和预防以及诊断。进一步的是，本发明化合物可用于开发另外的治疗剂作为各种分析模式中的标准物。因此，本发明提供了含有上述化合物和药学上可接受的赋形剂或诊断学上可接受的赋形剂的组合物。本发明进一步提供了抑制某些病毒的方法，和治疗被这类病毒，特别是 CMV 感染的个体的方法。除了对现存疾病的治疗外，本发明也提供了预防性治疗以预防进行器官移植的病人被病毒侵染的方法。

本技术领域人员从下列阐述和权利要求书中可明显看出本发明的其它目的、特征和优点。

附图简述

图 1 提供了式 IIa 例举性化合物的结构。

图 2 提供了式 IIb 例举性化合物的结构。

图 3 提供了式 IIc 例举性化合物的结构。

图 4 提供了式 IId 例举性化合物的结构。

图 5 提供了式 IIe 例举性化合物的结构。

图 6-14 提供了式 IIa-e 例举性化合物的合成流程，也提供了化合物上官能团的选择性转化。

发明详述

缩写和定义

术语“烷基”本身或作为另一个取代基的部分，除非另作说明，表示直链或支链或环状的烃基团，或它们的组合，它们可为全饱和、单-不饱和或多-不饱和的，包括二元和多元基团，其碳原子数被指定(即 C1-C10 表示 1-10 个碳原子)。饱和烃基团的例子包括直链或支链基团，如甲基、乙基、正丙基、异丙基、正丁基、异丁基、叔丁基、仲丁基、如正戊基、正己基、正庚基、正辛基等的同类物或异构体等等。其它饱和的烃基包括环丙基甲基、环己基甲基等。不饱和烷基是有一个或多个双键或三键的基团。不饱和烷基的例子包括乙烯基、2-丙烯基、巴豆基、2-异戊烯基、2-(丁二烯基)、2,4-戊二烯基、3-(1,4-戊二烯基)、乙炔基、1-和 3-丙炔基、3-丁炔基和更高的同类物

和异构体。术语“烷基”，除非另作说明，也包括下面杂烷基、亚烷基、杂亚烷基、环烷基和杂环烷基的烷基的衍生物。典型的是，烷基有1-24个碳原子，优选的是这些基团有10个或更少的碳原子。术语“亚烷基”本身或作为另一个取代基的部分表示衍生自烷类的二价基团，如$-CH_2CH_2CH_2CH_2-$。“低级烷基”或“低级亚烷基”是较短链的烷基或亚烷基，通常有8个或更少的碳原子。除非另作说明，烷基可为未取代的，或被下列取代基取代。

术语“杂烷基”本身或与另一个术语的组合，除非另作说明，表示由所述碳原子数和1-3个选自O、N、Si和S的杂原子构成的稳定的直链或支链基团，其中氮原子和硫原子可任选地被氧化，氮杂原子可任选地被季铵化。杂原子O、N和S可在杂烷基的任何插入位置。杂原子Si可放在杂烷基的任何位置，包括在烷基与分子的剩余部分连接处的位置。例子包括$-CH_2-CH_2-O-CH_3$、$-CH_2-CH_2-NH-CH_3$、$-CH_2-CH_2-N(CH_3)-CH_3$、$-CH_2-S-CH_2-CH_3$、$-CH_2-CH_2-S(O)-CH_3$、$-CH_2-CH_2-S(O)_2-CH_3$、$-CH=CH-O-CH_3$、$-Si(CH_3)_3$、$-CH_2-CH=N=OCH_3$和$-CH=CH-N(CH_3)-CH_3$。最多可有两个连贯的杂原子，如$-CH_2-NH-OCH_3$和$-CH_2-O-Si(CH_3)_3$。术语“杂亚烷基”本身或作为另一个取代基的部分表示衍生自杂烷基的二价基团，如$-CH_2-CH_2-S-CH_2CH_2-$和$-CH_2-S-CH_2-CH_2-NH-CH_2-$。

术语“环烷基”和“杂环烷基”本身或与其它术语组合，除非另作说明，各自表示“烷基”和“杂烷基”的环状形式。环烷基的例子包括环戊基、环己基、1-环己烯基、3-环己烯基、环庚基等。杂环烷基的例子包括1-(1,2,5,6-四氢吡啶基)、1-哌啶基、2-哌啶基、3-哌啶基、4-吗啉基、3-吗啉基、四氢呋喃-2-基、四氢呋喃-3-基、四氢噻吩-2-基、四氢噻吩-3-基、1-哌嗪基、2-哌嗪基等。

术语“卤”或“卤素”本身或作为另一个取代基的部分，除非另作说明，表示氟、氯、溴或碘原子。另外，诸如“氟烷基”的术语包括单氟代烷基和多氟代烷基。更具体的是，术语“氟代烷基”也包括全氟代烷基，其中烷基中的每个氢都被氟取代。

术语“芳基”单独使用或与其它术语(如芳氧基、硫代芳基(arylthioxy)芳烷基)，除非另作说明，表示可为单环或共价稠合在一起或连接在一起的多环(最多为三环)的芳族取代基。该环可含有0-4个选自N、O和S的杂原子，

其中氮原子和硫原子可被任选地氧化，氮原子可被任选地季铵化。芳基的非限定性例子包括苯基、1-萘基、2-萘基、联苯基、1-吡咯基、2-吡咯基、3-吡咯基、3-吡唑基、2-咪唑基、4-咪唑基、吡嗪基、2-噁唑基、4-噁唑基、5-噁唑基、3-异噁唑基、4-异噁唑基、5-异噁唑基、2-噻唑基、4-噻唑基、5-噻唑基、2-呋喃基、3-呋喃基、2-噻吩基、3-噻吩基、2-吡啶基、3-吡啶基、4-吡啶基、2-嘧啶基、4-嘧啶基、5-苯并噻唑基、嘌呤基、2-苯并咪唑基、5-吲哚基、1-异喹啉基、5-异喹啉基、2-喹喔啉基、5-喹喔啉基、3-喹啉基和6-喹啉基。上述每个芳基环系统的取代基选自下述可接受的取代基。

本文使用的术语“双环稠合芳基-环烷基”指芳环与环烷基(包括环杂烷基)稠合的基团。该基团可通过在基团的芳基部分上可得的键，或通过在基团的环烷基部分上可得的键与分子的剩余部分连接。这类双环稠合的芳族-环烷基基团的例子是：2，3-二氢化茚基、苯并四氢呋喃基、苯并四氢吡喃基和 1，2，3，4-四氢萘基。

上述术语(如“烷基”和“芳基”和“双环稠合的芳基-环烷基”)每个都典型地包括该基团的取代和未取代形式。各类基团的优选的取代基如下。若基团含有芳基(包括杂芳基)和烷基(包括，如杂烷基、环烷基和环杂烷基)两部分，每个部分可被取代。

烷基(包括通常称为烯基、杂烷基、杂烯基、炔基、环烷基、杂环烷基、环烯基和杂环烯基)的取代基可为各种基团，选自：-OR'、=O、=NR'、=N-OR'、-NR'R''、-SR'、-卤素、-SiR'R''R'''、-OC(O)R'、$-CO_2R'$、-CONR'R''、-OC(O)NR'R''、-NR''C(O)R'、-NR''-C(O)-OR'、$-NH-C(NH_2)=NH$、$-NR'C(NH_2)=NH$、$-NR'-C(NH_2)=NR'$、-S(O)R'、$-S(O)_2R'$、$-S(O)_2NR'R''$、-CN 和$-NO_2$，取代基数范围为 0-(2N+1)，其中 N 是这类基团里的碳原子总数。R'、R''和 R'''各自独立地指氢或 C1-C10 烷基。优选的是，取代的烷基可有 1-6 个独立选定的基团。更优选的是，取代烷基有 1-4 个独立选定的基团。无论如何，特定的取代烷基(如全氟代烷基)有 2N+1 个全取代(其中 N 是饱和烷基里的碳原子数)。取代烷基的例子包括：$-C(O)-CH_3$、$-C(O)CH_2OH$、$-CH_2-CH(CO_2H)-NH_2$和 $Si(CH_3)_2-CH_2-C(O)-NH_2$。

相似的是，芳基的取代基是不同的，可选自：-卤素、-OR'、-OC(O)R'、

-NR'R''、-SR'、-R'、-CN、-NO$_2$、-CO$_2$R'、-CONR'R''、-OC(O)NR'R''、-NR''C(O)R'、-NR''-C(O)-OR'、-NH-C(NH$_2$)=NH、-NR'C(NH$_2$)=NH、-NH-C(NH$_2$)=NR'、-S(O)R'、-S(O)$_2$R'、-S(O)$_2$NR'R''、-N$_3$、-CH(Ph)$_2$、全氟代(C1-C4)烷氧基和全氟代(C1-C4)烷基，其取代基数范围从 0 到芳环系统上空价(打开价键)的总数；其中 R'和 R''独立地选自氢、(C1-C8)烷基、芳基、芳基-(C1-C4)烷基和芳氧基-(C1-C4)烷基。

芳环相邻原子上的两个取代基可任选地被式-TC(O)-(CH$_2$)$_s$-U-取代基所代替，其中 T 和 U 各自是-NH-、-O-、-CH$_2$-或单键，下标 s 是整数 0-2。或者，芳环相邻原子上的两个取代基可任选地被式-A-(CH$_2$)$_p$-B-的取代基所取代，其中 A 和 B 各自是-CH$_2$-、-O-、-NH-、-S-、S(O)-、-S(O)$_2$、-S(O)$_2$NR'-或单键，p 是整数 1-3。这样形成的新环上的一个或多个单键可任选地被双键替代。或者，芳环的相邻原子上的两个取代基可任选地被式-(CH$_2$)$_q$-Z-(CH$_2$)$_r$-所代替，其中 q 和 r 各自是整数 1-3，Z 是-O-、NR'-、-S-、-S(O)-、-S(O)$_2$-或-S(O)$_2$NR'-。NR'-和-S(O)$_2$NR'-里的取代基 R'选自氢或(C1-C6)烷基。

本文使用的术语“杂原子”包括氧(O)、氮(N)、硫(S)和硅(Si)。

术语“药学上可接受的盐”包括根据本文所定义的化合物上特定的取代基，通过与相应的无毒性酸或碱反应制备的活性化合物的盐。当本发明化合物含相对酸性的官能团时，在纯净态或在合适的惰性溶剂里，使这类化合物的中性形式与足量所需碱接触得到碱加成盐。药学上可接受的碱加成盐包括钠盐、钾盐、钙盐、铵盐、有机氨基或镁盐，或相似的盐。当本发明化合物含有相对碱性的官能团时，在纯净态或在合适的惰性溶剂里使这类化合物的中性形式与足量所需酸接触得到酸加成盐。药学上可接受的酸加成盐的例子包括衍生自如盐酸、氢溴酸、硝酸、碳酸、单氢碳酸、磷酸、单氢磷酸、二氢磷酸、硫酸、单氢硫酸、氢碘酸或膦酸等的无机酸的盐，以及衍生自相对无毒的有机酸，如乙酸、丙酸、异丁酸、草酸、马来酸、丙二酸、苯甲酸、琥珀酸、辛二酸、富马酸、扁桃酸、苯二甲酸、苯磺酸、对-甲苯磺酸、柠檬酸、酒石酸、甲磺酸等的盐。还包括的是氨基酸的盐，如精氨酸盐等，和像葡糖醛酸或半乳糖醛酸等的有机酸盐(例如，参见 Berge, S. M. 等，“药用盐”，药学科学杂志(Journal of Pharmaceutical Science), 1977, 66, 1-19)。本发

明特定的化合物含有碱性和酸性官能团，可将这些化合物转化为碱加成盐或酸加成盐。

通过使盐与碱或酸接触，并用常规的方法分离母体化合物，可再生出化合物的中性形式。母体形式的化合物的某些物理性质，如极性溶剂里的溶解度，会不同于各种盐形式，但其它方面盐与本发明化合物的母体形式在用于本发明目的时是等价的。

除了盐形式外，本发明提供了可为前体药物形式的化合物。本文揭示的化合物的前体药物是在生理条件下很容易地发生化学改变，得到式 I 化合物的那些化合物。

本发明某些化合物可以未溶剂化形式和溶剂化形式，包括水化形式存在。一般来说，溶剂化形式与未溶剂化形式是相当的，都包含于本发明的范围。

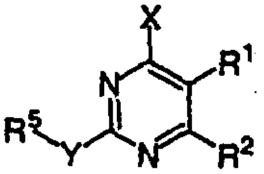
本发明的某些化合物具有手性碳原子(光学中心)或双键；外消旋物、非对映异构体、几何异构体和单个异构体(individual isomers)都在本发明的范围里。

本发明化合物在构成这类化合物的一个或多个原子上也可含有非天然比例的原子同位素。例如，化合物可用放射活性同位素，如氚(^3H)、碘-125(^{125}I)或碳-14(^{14}C)进行放射性标记。本发明化合物所有的同位素变体，不论是否有放射活性都包含在本发明的范围里。

发明的实施方案

化合物

本发明一个方面提供通式 I 化合物：



(I)

其中 X 代表—NR^3R^4、—OR^3、—SR^3、芳基、烷基或芳烷基。字母 Y 代表共价键、—N (R^6) —、—O—、—S—、—C (=O) —或亚烷基。y 优选的是 Y 是-N(R^6)-或-O-，其中 R^6 的定义同上。更优选的是，Y 是-N(R^6)-。对于 Y 是亚烷基的实施方案，亚烷基的链中典型地有 1—8 个碳原子，优选的是有 1—3 个碳原子

的亚烷基。

R^1 和 R^2 独立地选自氢、烷基、—O—烷基、—S—烷基、芳基、芳基烷基、—O—芳基、—S—芳基、$-NO_2$、$-NR^7R^8$、—C（O）R^9、$-CO_2R^{10}$、—C（O）NR^7R^8 —N（R^7）C（O）R^9、—N（R^7）CO_2R^{11}、—N（R^9）C（O）NR^7R^8、—S（O）$_mNR^7R^8$、—S（O）$_nR^9$、—CN、卤素或—N（R^7）S（O）$_mR^{11}$，其中 R^7、R^8、R^9、R^{10} 和 R^{11} 的定义如下。

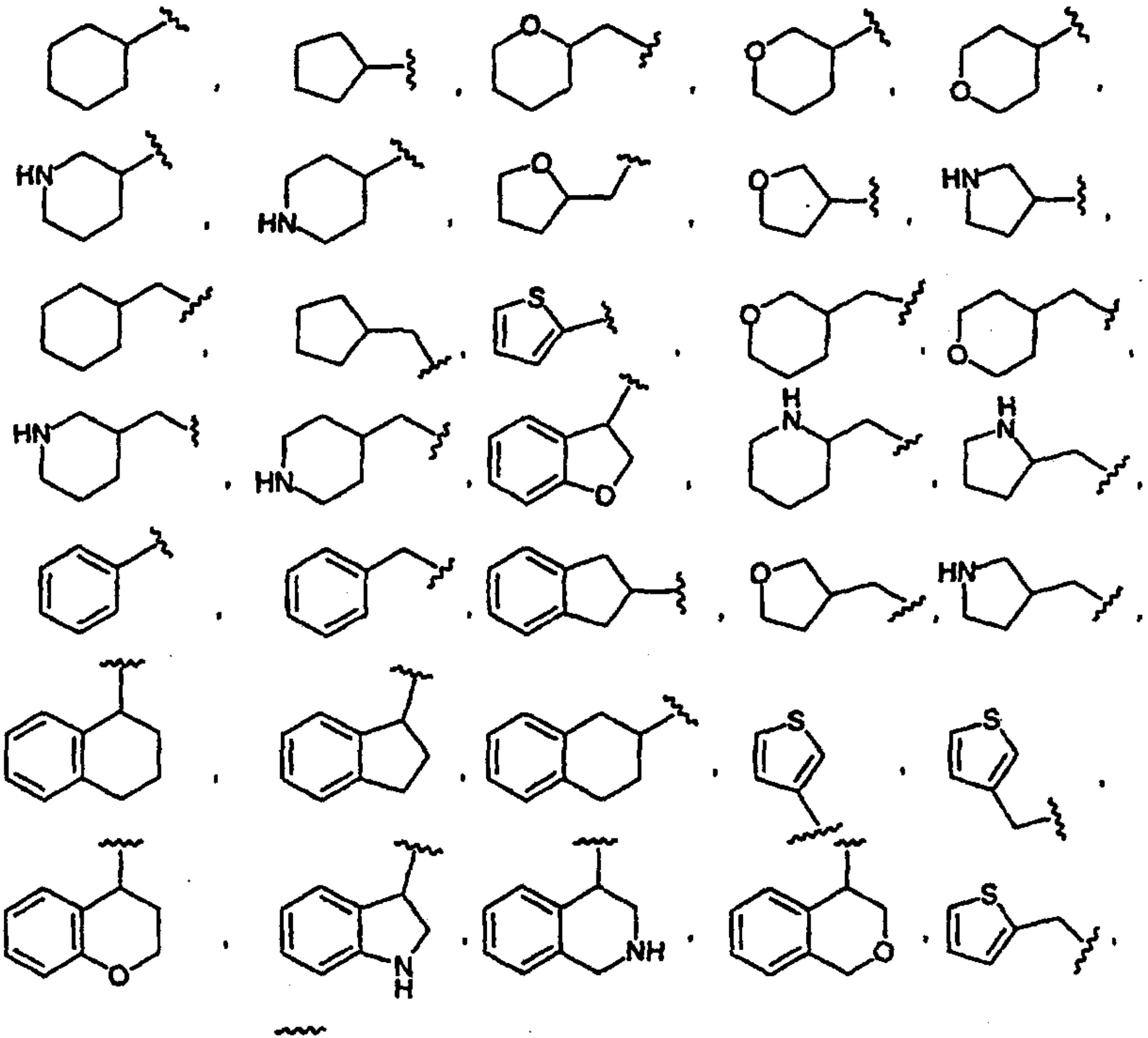
在一组优选的实施方案中，R^1 是吸电子基团，R^2 是供电子基团。在该组实施方案中，R^1 优选的是 $-NO_2$、—S（O）$_mNR^7R^8$、—S（O）$_nR^9$、—CN、卤素、氟代烷基、-C(O)R^9、$-CO_2R^{10}$ 或-C(O)NR^7R^8；更优选的是，R^1 是 $-CF_3$、$-NO_2$、—CN、—S（O）$_mNR^7R^8$ 或 $-CO_2R^{10}$，最好是 $-NO_2$。R^2 优选所是氢、低级烷基、—O—烷基、—S—烷基、芳基、芳基烷基、—O—芳基或—S—芳基。更好的是，R^2 是甲基、乙基、正丙基、异丙基、甲氧基、乙氧基、丙氧基、甲氧基甲基、甲硫基、乙硫基或丙硫基。

在另一组优选的实施方案中，R^1 是供电子基团，R^2 是吸电子基团。在该组实施方案中，R^1 优选的是氢、低级烷基、—O—烷基、—S—烷基、芳基、芳基烷基、—O—芳基或—S—芳基。更好的是，R^1 是甲基、乙基、正丙基、异丙基、甲氧基、乙氧基、丙氧基、甲硫基、乙硫基或丙硫基。R^2 优选的是 $-NO_2$、—S（O）$_mNR^7R^8$、—S（O）$_nR^9$、—CN、卤素、氟代烷基、-C(O)R^9、$-CO_2R^{10}$ 或-C(O)NR^7R^8；更优选的是，R^2 是 $-CF_3$、$-NO_2$、—CN、—S（O）$_mNR^7R^8$ 或 $-CO_2R^{10}$，最好是 $-NO_2$。

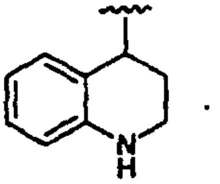
R^3 和 R^4 独立地是氢、烷基、芳基或芳基烷基，或者，R^3 和 R^4 和与之连接的氮原子一起形成 5—、6—或 7—元环中含 1—3 个杂原子的环。在一组优选的实施方案里，R^3 和 R^4 和与之连接的氮原子一起形成 5—或 6—元环。被 R^3、R^4 和氮原子围成的环可为饱和、不饱和或芳族的，可含有另外的杂原子。合适的环的例子包括吡咯烷、吡咯、吡唑、咪唑、咪唑啉、噻唑啉、哌啶、吗啉等。在特别优选的实施方案里，R^3 和 R^4 和与之连接的氮原子一起形成含两个氮原子的 5—元环，优选的是咪唑环，最好是 2—烷基咪唑环或 5—烷基咪唑环。特别优选的 X 基团是 2—甲基咪唑—1—基、2，4—二甲基咪唑—1—基、2—乙基咪唑—1—基、2—丙基咪唑—1—基、2—异丙基咪唑—1—基和 5—甲

基咪唑－1－基。

R^{5}基团是烷基、芳基、芳基烷基或双环稠合的芳基－环烷基。优选的烷基有1－8个碳原子，被取代或未取代的。优选的芳基包括取代或未取代的苯基、吡啶基或萘基。优选的芳基烷基包括取代和未取代的苄基、苯乙基、吡啶基甲基和吡啶基乙基。特别优选的R^{5}是苯基、4－卤代苯基、苄基、正丁基、丙酰基、乙酰基和甲基。其它优选的R^{5}基团是R^5、R^{6}和与之连接的氮原子一起形成环。其它优选的R^{5}基团（包括一些优选的稠合双环芳基－环烷基）选自：



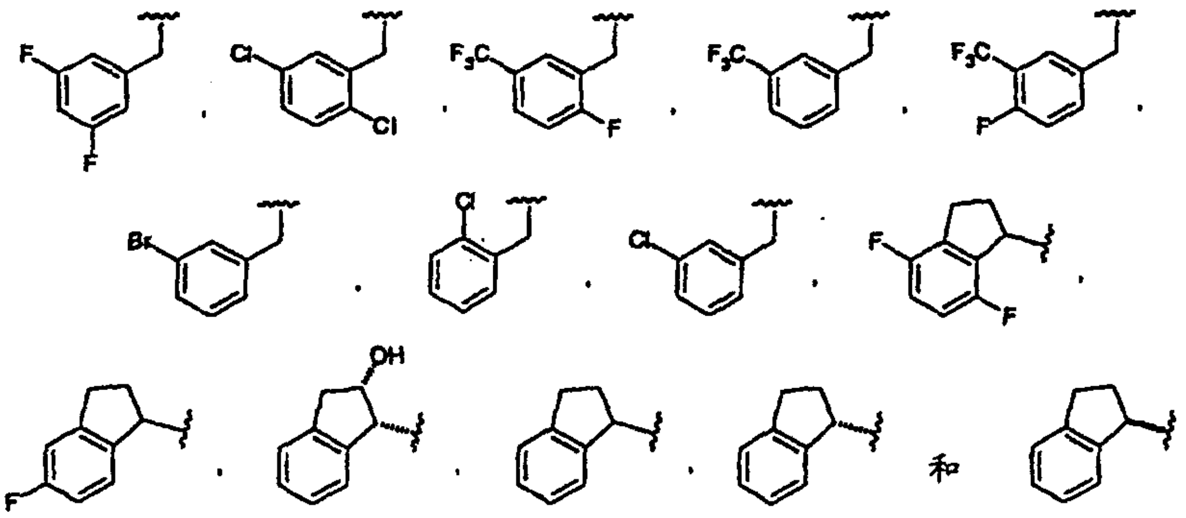
和



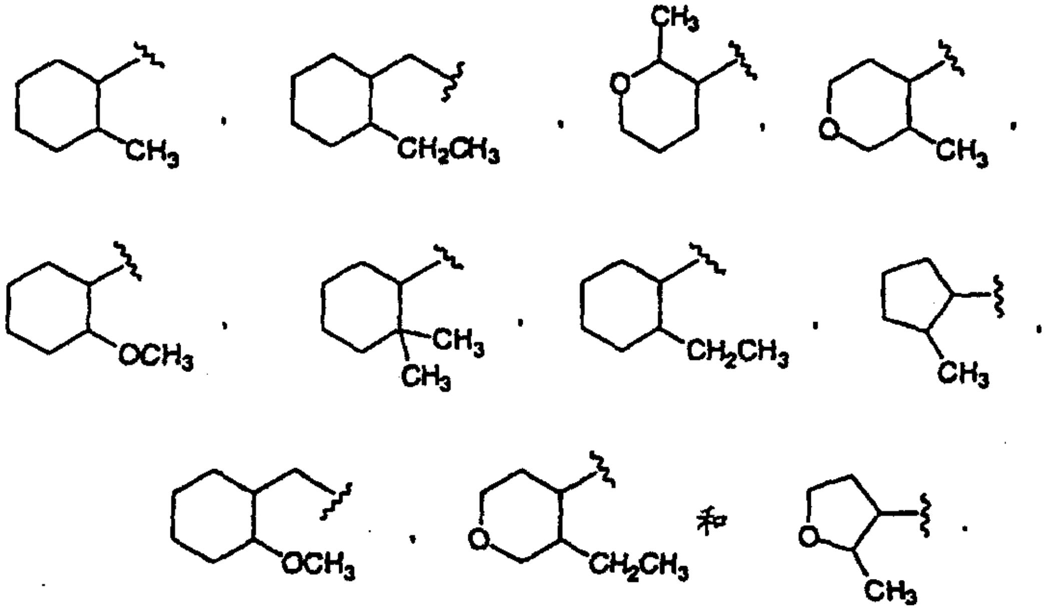
在上述基团和本文揭示的其它基团中，波纹线用来表示与分子剩余物的

连接点。

在特别优选的一组实施方案中，R^5 选自下列基团：



在特别优选的另一组实施方案中，R^5 选自下列基团：



上述基团表示包括有立体化学异构体的混合物以及纯异构体和对映异构体（那些有低于 5%的另一种非对映异构体或对映异构体，更优选的是低于约 2%的另一种异构体，最好是低于约 1%的另一种异构体）。

R^6 基团典型的是氢、烷基、芳基或芳基烷基。优选的是 R^6 是氢、有 1-3 个碳原子的低级烷基、苯环或苯基烷基，如苄基或苯乙基。R^7 和 R^8 各自独立地是氢、烷基、芳基或芳烷基，或与各自相连的氮原子结合在一起，形成 4-、5-、6-、7--或 8-元环，环中含 1-3 个杂原子。优选的是，R^7 和 R^8 各自独立地

是(C1-C8)烷基，或结合在一起，形成 5-、6-或 7-元环。R^9 和 R^{10} 独立地选自氢、烷基、芳基和芳烷基。在优选的实施方案中，R^9 和 R^{10} 独立地选自氢、(C1-C8)烷基、苯基和苯基(C1-C4)烷基。R^{11} 是烷基、芳基或芳烷基，优选的是(C1-C8)烷基、苯基和苯基(C1-C4)烷基。

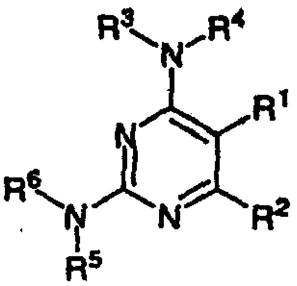
除了以上对 R^1 到 R^{11} 的叙述外，上式还代表了许多化合物，其中第二环稠合到嘧啶环上，包括其中嘧啶环氮原子之一是环连接点的结构。对于下面讨论的和权利要求书，氮各指：N^1 是在环 1-位的氮原子(它在带有-R^2 的碳原子和带有-Y-R^5 的碳原子之间)。N^3 是在嘧啶环 3-位处的氮原子(它在带有-Y-R^5 的碳原子和带有-X 的碳原子之间)。稠合环的例子是其中 R^1 与 R^2 连接，R^1 与 R^3 连接，R^3 与 N^3 连接，R^5 与 N^3 连接，R^5 与 N^1 连接，或 R^2 与 N^1 连接，形成稠合的 5-、6-或 7-元环。通过这些结合形成的环含有 1-3 个杂原子(如，O、N 或 S)，可为芳族或非芳族。优选的是所形成的另外的环是 5-或 6-元环。

当 R^1 和 R^2 结合在一起形成环时，该结合可被式$-T-C(O)-(CH_2)_s-U-$的取代基所代替，其中 T 和 U 独立地选自-NH-、-O-、$-CH_2-$或单键，下标 s 是 0-2 整数。或者，R^1 和 R^2 基团可被式$-A-(CH_2)_p-B-$的取代基所代替，其中 A 和 B 独立地选自$-CH_2-$、-O-、-NH-、-S-、-S(O)-、$-S(O)_2-$、$-S(O)_2NR'-$或单键，p 是整数 1-3。这样形成的新环的一个或多个单键可任选地被双键代替。或者，R^1 和 R^2 可被式$-(CH_2)_q-Z-(CH_2)_r-$的取代基所代替，其中 q 和 r 是独立的 1-3 的整数，Z 是-O-、-NR'-、-S-、-S(O)-、$-S(O)_2-$或$-S(O)_2NR'-$。-NR'-和$-S(O)_2NR'-$中的取代基 R' 选自氢或(C1-C6)烷基。

上述基团里的下标 m 是 1-2 整数，优选的是 2。下标 n 是整数 1-3，优选的是 2。

最后，本发明化合物典型的分子量为约 150-750。上式化合物也包括其所有的药学上可接受的盐。

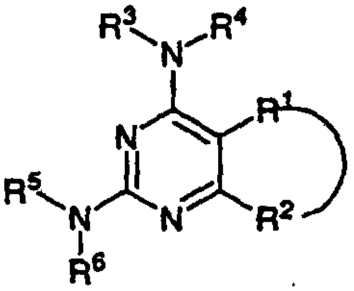
在嘧啶环上的许多取代基的组合尤为优选。例如，优选的实施方案中的一组具有下式：



(IIa)

在通式 IIa 化合物中，R^1 优选的是$-NO_2$、$-CF_3$、$-C(O)NR^7R^8$、$-CO_2R^{10}$、$-S(O)_2NR^7R^8$、$-S(O)_2R^9$、$-SO_2NH_2$ 或-CN，R^2 优选的是有 1-8 个碳原子的烷基。在最佳实施方案里，R^3 和 R^4 基团结合在一起，形成任选地与芳基稠合的 5-元环。合适的 5-元环基团(和任选地与芳基稠合的 5-元环基团)的例子包括吡咯烷、吡咯、咪唑、吡唑、苯并咪唑、咪唑啉、1,2,4-三唑、1,2,3-三唑、咪唑烷-2-酮等。更优选的是，R^3 和 R^4 结合在一起形成咪唑环，它被取代或任选地与芳基稠合。优选的取代(和稠合)的咪唑环包括，例如，2-甲基咪唑、2-乙基咪唑、2-异丙基咪唑、2-氨基咪唑、5-甲基咪唑、5-乙基咪唑、5-异丙基咪唑、2，5-二甲基咪唑、苯并咪唑和 2-甲基苯并咪唑。R^5 和 R^6 基团独立地选自氢、烷基、芳基和芳烷基，或可与之连接的氮原子结合，形成任选地与芳基稠合的环。图 1 提供了在该组优选的实施方案里化合物的例举性结构。

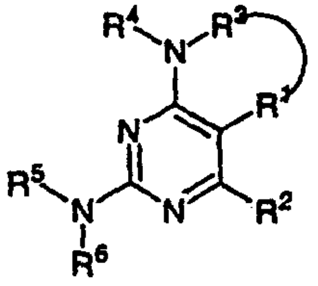
另一组优选的实施方案由下式代表：



(IIb)

在该式中，含 R^1 和 R^2 的稠合环典型的是杂环，其中$-R^1-R^2-$选自，如，$-S(O)_2NR'C(O)-$、$-S(O)_2NR'C(O)NR''-$、$-NR'S(O)_2NR''C(O)-$、$-C(O)NR'C(O)-$、$-NR'C(O)NR''C(O)-$、$-NR'C(S)NR''C(O)-$、$-NR'C(S)NR''C(S)-$，其中 R' 和 R'' 独立地是氢或(C1-C8)烷基。R^3 和 R^4 基团优选地结合，形成任选地与芳基稠合的 5-元环。更优选的是 R^3 和 R^4 结合，形成任选地与芳基稠合的咪唑环。R^5 和 R^6 独立地选自氢、烷基、芳基和芳烷基，或可结合形成任选地与芳基稠合的环。图 2 提供了该组优选实施方案中例举性化合物的结构。

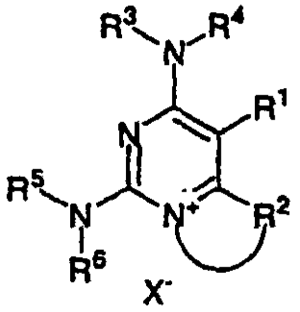
另一组优选的实施方案由下式代表：



(IIc)

在该式中，二价基团$-R^1-R^3-$典型的是亚烷基、$-C(O)NR'C(O)-$、$-C(O)NR'S(O)_2-$或$-S(O)_2NR'C(O)-$，其中 R'是氢或低级烷基。优选的是，R^2 和 R^4 各自独立地是烷基，更优选的是低级烷基。R^5 和 R^6 基团独立地选自氢、烷基、芳基和芳烷基，或可结合在一起形成任选地与芳基稠合的环。图 3 提供了该实施方案优选组中的例举性化合物结构。

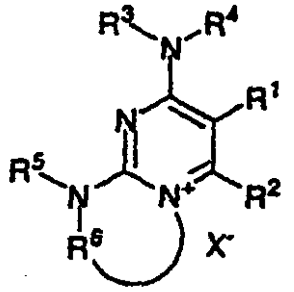
优选的实施方案的另一组由下式代表：



(IId)

在该式中，被$-R^2-$限定的稠合环部分典型的是(C3-C5)亚烷基、亚烷胺基团(如，$-NHCH_2CH_2CH_2-$、$-NHCH_2CH_2-$)或$-NR'C(O)CH_2-$基团，其中 R'是氢或低级烷基。R^1 典型的是$-NO_2$、$-S(O)_2NR^7N^8$、$-S(O)_2R^9$、$-CN$、$-CF_3$、$-C(O)R^9$、$-CO_2R^{10}$或$-C(O)NR^7R^8$。更优选的是，R^1 是$-NO_2$、$-CN$、$-CF_3$ 或$-CO_2R^{10}$，最好的是$-NO_2$。R^3 和 R^4 优选地结合形成任选地与芳基稠合的 5-元环。更优选的是，R^3 和 R^4 结合在一起形成任选地与芳基稠合的咪唑环。R^5 和 R^6 基团独立地选自氢、烷基、芳基和芳烷基，或可结合形成任选地与芳基稠合的环。符号 X^-代表季氮合适的相反离子。优选的相反离子是形成药学上可接受盐的相反离子。图 4 提供了该优选组中例举性化合物结构。

另一组优选实施方案由下式代表：



(IIe)

该式中，R^1 优选的是$-NO_2$、$-S(O)_2NR^7R^8$、$-S(O)_2R^9$、$-CN$、$-CF_3$、$-C(O)R^9$、$-CO_2R^{10}$或$-C(O)NR^7R^8$。更优选的是，R^1 是$-NO_2$、$-CN$、$-CF_3$或$-CO_2R^{10}$，最好的是$-NO_2$。R^2 优选的是有 1-8 个碳原子的烷基。R^3 和 R^4 基团优选地结合，形成任选地与芳基稠合的 5-元环。更优选的是，R^3 和 R^4 结合形成任选地与芳基稠合的咪唑环。R^5 优选的是氢、(C1-C8)烷基、苯基或苯基烷基。由$-R^6-$限定的稠合环部分典型的是(C3-C5)亚烷基或取代的亚烷基(如$-C(O)CH_2CH_2CH_2-$、$-C(O)CH_2CH_2-$)，或$-NR'C(O)CH_2-$基团，其中 R' 是氢或低级烷基。符号 X^-代表季氮合适的相反离子。优选的相反离子是形成药学上可接受盐的相反离子。图 5 提供了式 IIe 例举性化合物的结构。

组合物

本发明的另一方面提供了适合药用或诊断用的组合物。组合物包含上式 I 化合物与诊断学或药学上可接受的载体或赋形剂。

在一个实施方案中，本发明提供了与药学上可接受的赋形剂，如灭菌盐水或其它介质、水、明胶、油等，组合的主题化合物，形成药学上可接受的组合物。组合物和/或化合物可单独给予或与任何常规的载体、稀释剂等组合给予，这类给药可为单剂或多剂。有用的载体包括固体、半固体或液体介质，包括水和无毒的有机溶剂。

在另一个实施方案中，本发明提供了前体药物形式的主题化合物，它可通过接受者进行代谢或化学转化成为主题化合物。各种前体药物衍生物是本技术领域人员已知的，例如它们依赖于药物的水解裂解或氧化活化。

组合物可为任何常规形式，包括片剂、胶囊剂、糖锭、锭剂、硬糖、散剂、喷雾剂、霜剂、拴剂等。结果，以药学上可接受剂型单位的组合物或散装的组合物可放入各种容器。例如，单位剂量可放入各种容器，包括胶囊、

丸剂等。

组合物可有利地与其它不同于本发明主题化合物的治疗或预防用的抗病毒剂混合或结合使用。组合物也可有利地和治疗或减轻对本发明化合物敏感的病毒感染疾病的药物，如抗-HIV 药物或免疫抑制剂，组合和/或合用。在许多场合，结合本发明组合物给药能增强这类药物的效力。抗病毒药的例子包括更昔洛韦、磷甲酸和 cidofovir。抗-HIV 药物的例子包括 indinavir、ritonavir、AZT、lamivudine 和 saquinavir。免疫抑制剂的例子包括环孢素和 FK-506。组合物也可有利地与免疫抑制方案结合，如(通过辐射或化疗)破坏骨髓，用作抗病毒预防治疗。

使用方法

在另一方面，本发明提供了前述化合物和组合物的新颖的使用方法。特别是，本发明提供了用于治疗或预防疱疹家族病毒感染，特别是细胞巨化病毒感染。该方法典型地涉及对病人给予有效剂型的一种或多种主题组合物。

本发明对免疫系统受到损害或预期会患有免疫抑制疾病的个体，如经受与器官移植或抗癌化疗前有关的免疫抑制疗法的病人提供了将主题化合物和组合物用于治疗疾病或进行预防的使用方法。这些方法一般涉及对宿主给予有效量的主题化合物或药学上可接受的组合物。

本发明组合物和化合物及其药学上可接受的盐可以任何有效途径，如口服、非胃肠道给药或局部外用途径给药。一般来说，本化合物的给药剂量范围是约 2-2000 毫克/天，但根据被治疗的疾病、病人和给药途径，给药剂量会发生改变。优选的口服剂量范围是每天每千克体重约 0.05mg/kg 到约 20mg/kg，更好的是约 0.05mg/kg 到约 2mg/kg，最好是约 0.05 到约 0.2mg/kg。

化合物的制备

本发明化合物可用一般的合成流程，如图 6-14 列出的流程，进行制备。本技术领域人员可以明白，可用不同的起始物质和其它的试剂来改变下列合成以得到所需的转化。因此，如下所述，附图和试剂是非限定性的实施方案。

简单来说，Y 是$-N(R^6)-$的式 I 化合物可从各种已知的嘧啶二酮类中制得。

如图 6 所示，用诸如 $POCl_3$ 的试剂处理可将嘧啶二酮(i)转化为相应的二氯化物(ii)。用所需的胺(包括杂环胺)处理 ii 得到了目标化合物，典型的是异构体(iii)混合物。用传统的方法，如柱层析或 HPLC 可分离出异构体。或者，(例如，用乙酸钠、乙酸、水和乙醇) 水解 ii 为单氯代化合物，得到(iv)，用合适的胺、烷醇化物或硫醇盐离子对其进行处理，得到(v)。使 4-羟基转化为 4-氯取代基，并用合适的亲核胺取代得到目标物(vi)。

许多嘧啶二酮是市售的，可用作上述转化的起始物质，例如 5-氰基-6-甲基-2,4-嘧啶二酮(vii)、6-甲基-2,4-嘧啶二酮-5-甲酰胺(x)、6-甲基-2,4-嘧啶二酮-5-磺酸(xv)和 6-甲基-5-硝基-2,4-嘧啶二酮。这些化合物的每个可如图 7 所示转化为式(IIa)的目标化合物。例如，5-氰基-6-甲基-2,4-嘧啶二酮(vii)可用诸如 $POCl_3$ 的试剂转化为二氯化物(viii)，然后再用胺 R^3-NH-R^4(如 2-甲基咪唑)和 R^5-NH-R^6(N-甲基苄基胺)处理转化为目标化合物(如 ix)。

6-甲基-2,4-嘧啶二酮-5-甲酰胺(x)的甲酰胺基团可用含水碱水解成羧酸(xi)，然后用 $POCl_3$ 转化为酰氯(xii)(形成三氯化物)。逐步加入胺或其它合适的亲核试剂，得到目标化合物(如 xiv)。相似的是，通过用氯化试剂，如 $POCl_3$ 处理 6-甲基-2,4-嘧啶二酮-5-磺酸(xv)，形成三氯化物(xvi)。再者，逐步加入胺或其它合适的亲核试剂可产生所需的目标类(xviii)。

图 8 显示了制备式 IIa 化合物的另一个方法。用碱(如烷醇钠)和亲电试剂(如烷化剂、酰化剂、磺化剂等)处理β-酮酯(xix)或α-亚甲酯(xxi)，得到适当衍生的β-酮酯(xx)，它可用取代的胍(xxii)，典型的是在酸(乙酸)里，加热下处理，转化为嘧啶二酮(xxiii)。通过存在在衍生化的β-酮酯上的基团决定 5-位和 6-位(分别为 R^1 和 R^2)上的取代基。使嘧啶二酮氯化，得到(xxiv)，接着用亲核氮杂环(如咪唑、2-烷基咪唑、吡咯烷、哌啶等)以及其它胺处理，得到式 IIa 的目标化合物。用于该制备方法的取代胍可市售购得或用氨腈处理仲胺制得。用于制备取代的胍的另外的文献方法是本技术领域已知的。

对嘧啶环上的未取代位置处可作出许多转化以连接各种基团，或可对现存的基团进行改变(参见图 9)。例如，4-氯取代基(例如 xxv 中存在的)可用氨取代，得到 4-氨基嘧啶(如 xxvi)。用琥珀酸酐处理伯胺，得到(xxvii)，再用乙酸酐处理，产生琥珀酰亚胺化合物 xxviii(图 9A)。如图 9B 所示，用标

准的酰化剂也可酰化环外氨基。在嘧啶的未取代的 6-位上可进行金属化反应(图 9C)。例如，5-硝基嘧啶衍生物(xxxi)可被催化还原(H_2)或化学还原(如 Fe/HCl)为 5-氨基嘧啶衍生物(xxxii)，它然后被保护为氨基甲酸叔丁基酯(xxxiii)。用金属化试剂，如仲丁基锂，处理保护的 5-氨基嘧啶衍生物，可得到金属化中间体(xxxiv)，它可如图所示被酰化(xxxv)、磺化(xxxvi)或烷基化(xxxvii)。相似的是(参见图 9D)，嘧啶衍生物(xxxviii)可被金属化，产生中间体(xxxix)，然后酰化(xl)、磺化(xli)或烷基化(xlii)。在嘧啶衍生物(xliii)上用相似的金属化学，能在 5-位上引入官能团，产生中间体(xliv)，它可被酰化(xlv)、磺化(xlvi)和烷基化(xlvii)。

图 10A-10D 提供了一些化合物的合成流程，它遵从了图 6-8 显示的一般方法。例如，图 10A 显示了从仲胺(xlviii)和氯亚氨酸酯(chloroimidate)(xlix)可制备取代的胍(l)，氰基乙酸乙酯(li)转化为酮酯(lii)。l 和 lii 的缩合得到了嘧啶二酮(liii)，它可被氯化，产生 liv，然后用胺亲核试剂(如，2-甲基咪唑)处理，得到目标物 lv。图 10B 显示了相似的途径，其中乙酰乙酸乙酯(lvi)被酰化，得到三羰基化合物(lvii)。使 lvii 与取代的胍(lviii)缩合，得到嘧啶二酮(lix)，用标准方法将它转化为目标物(lx)。图 10C 显示了一般的方法，其中起始物质(lxi)中存在磺酰胺基团，取代的胍(lxiii)含有氮杂环。因此，使 lxii 和 lxiii 缩合得到了嘧啶二酮(lxiv)，用 $POCl_3$(或其它氯化剂)，然后与胺亲核剂(如 1，2,4-三唑)反应而转化为目标物(lxv)。另外，一般的方法可制得嘧啶环 2-位上具有-O-Ar、-S-Ar、-O-烷基和-S-烷基的化合物(图 10D)。例如，用取代胍(lxvi)处理酮酯(xx)，得到了嘧啶二酮(lxvii)，它可被氯化并与 R^3-NH-R^4 缩合，得到 lxix。除去保护基团，得到 2-氨基嘧啶化合物(lxx)。可用标准方法进行重氮化反应和接着的氯化反应，得到 lxxi。用含氧的亲核剂或含硫的亲核剂二取代氯化物，各自得到目标化合物 lxxii 或 lxxiii。

图 11 显示了式 IIb 化合物的制备。在一组实施方案中，皂化 5-位上有磺酰胺、6-位上有酯基团的取代嘧啶，得到 lxxv，然后用脱水剂(如硫酸或乙酸酐)环化成稠合杂环 lxxvi(参见图 11A)。在另一些实施方案中，二酯被皂化成二酸(lxxviii)，并转化为酰胺混合物(lxxix，通过用乙酸酐和甲胺连续处

理)，然后通过用脱水剂(如乙酸酐)处理环化，得到双环系统(lxxx,参见图 11B)。用将β-酮酯转化为取代嘧啶的上述方法，从 2-氧代环戊烷羧酸乙酯开始可制备另一个稠合双环系统(lxxxi)(参见图 11C)。通过操作腈和酯取代基可制备另一组实施方案(参见图 11D)。简单来说，氰基乙酸乙酯首先与乙基草酰氯缩合，所得的产物用取代胍(在此以 N，N-二乙基胍为例)处理，得到取代的嘧啶二酮(lxxxii)。用 $POCl_3$(或其它氯化剂)处理，然后用合适的胺(如，咪唑、2-烷基咪唑、异丙基乙胺、吡咯烷)处理，得到取代的嘧啶(lxxxiii)。酯水解并经 Curtius 重排(例如，用二苯基磷酰氮化物)，得到氨基腈(lxxxiv)。通过酸水解将腈基团转化为酰胺，接着用光气(或光气等价物，如双光气或碳酸二甲酯)处理，得到稠合双环系统，lxxxv,用强碱(如 NaH)和烷化剂(如 MeI)处理可进一步转化为 lxxxvi。这些合成途径中的某些中间体可被转化为其它有用的衍生物(图 11E)。例如 lxxxvii 可用 Lawesson 试剂处理，得到硫代酰胺 lxxxviii,用光气(或光气等价物)处理，得到稠合双环系统 lxxxix。或者，在叔胺碱的存在下用硫酰氯处理 lxxxvii，得到稠合双环系统 xc。图 11F 和 11G 显示了在式 IIb 范围里制备化合物的其它方法。在图 11F 中，用类似于上述的方法可制备 5-位有磺酰胺，6-位有羧酸的取代的嘧啶(xci)。xci 中的羧酸基经 Curtius 重排为氨基得到 xcii，然后用光气或光气等价物环化为 xciii。图 11G 显示嘧啶二酯(xciv)的制备及其转化为稠合双环系统 xcvii 的方法。简单来说，xciv 中存在的甲硅烷酯基被水解成酸，它进行 Curtius 重排，得到 xcv。用标准的方法可将剩余的酯基团转化为酰胺，得到 xcvi。用光气或光气等价物使 xcvi 环化为 xcvii。

通过图 12 的方法可制备式 IIc 化合物。在一组实施方案(图 12A)中，用胺(如烯丙基胺)处理 4-氯嘧啶衍生物(xcviii,用上述方法制备)，得到 xcix。用醇溶剂里的甲胺处理使酯基团然后转化为 N-甲基酰胺(c)。用光气或其等价物处理使 c 环化为 ci。相似的是，如图 12B 所示可制备 6-位有多个电负性基团的化合物。例如，用上述方法可制备氯代嘧啶 cii，然后用对于 xcix 的方法可转化为双环化合物 ciii。如图 12C 所示可制备另一个式 IIc 的稠合系统。在此，用伯胺(如烯丙基胺)处理氯代嘧啶衍生物(civ)，得到嘧啶环的 4-位上的氨基部分。用光气或其等价物可使氨基部分环化到磺酰胺(5-位上)上，得

到目标物(cv)。

在一个实施方案中，如图 13 所示，可制备式 IId 化合物。简单来说，硝基乙酸乙酯可用混合酸酐(cvi)缩合，得到硝基酮酯(cvii)，它用适当取代的脒处理，转化为嘧啶(cviii)。除去保护基团，然后用 $POCl_3$ 处理对嘧啶环进行氯代并环化，形成嘧啶鎓(pyrimidinium)盐(cix)。用胺亲核剂处理 cix 得到目标化合物(cx)。以 3，3，3-三氟丙酸乙酯或氰基乙酸乙酯为起始物，改变所用的取代的脒和氨基亲剂可制备该组中的其它化合物。

用图 14 列出的方法可制备式 IIe 的化合物。根据图 14 所示的流程，适当取代的脒(cxi，从被保护的羟丙基胺制备)与 2-硝基乙酰乙酸乙酯(或相似的 2-三氟甲基乙酰基乙酸乙酯)缩合，得到嘧啶二酮(cxii)。除去保护基团，用图 13 显示的相似方法进行氯代和环化，得到盐(cxiii)。接着用亲核的胺处理 cxiii，得到目标物(cxiv)。

用作本发明起始物的化合物可市售购得，或用本技术领域公知的标准方法容易地合成得到。

本发明的一些化合物存在着立体异构体，本发明包括这些化合物的所有的这些活性立体异构形式。对于光学活性异构体来说，这类化合物可用上述方法从相应的光学活性前体中得到，或通过拆分消旋混合物得到。可用本技术领域公知的各种技术，如带有手性固体载体或手性溶剂的色谱层析，衍生的不对称盐的重复重结晶，或衍生化，来进行拆分。

本发明化合物可以各种方式标记。例如，化合物可含放射性同位素，如 ^{3}H (氚)、^{125}I(碘-125)和 ^{14}C(碳-14)。相似的是，化合物可有利地与其它各种化合物共价或非共价、直接或通过连接基分子进行连接，所述的各种化合物能提供前体药物，或有作为载体、标记物、辅剂、助活化剂、稳定剂等的功能。这类标记的和连接的化合物也在本发明范围里。

化合物分析

主题化合物和组合物在体外和体内分析中显示出药理活性，如它们能特异性地调节细胞生理学，降低相关的致病性，或提供或增强了预防性。

某些优选的化合物和组合物能特异性地抑制巨细胞病毒感染。为了评价

对人 CMV 的活性，用与 Kohler 等在 J.Virol. 68:6589-6597(1994)揭示的相似方法进行评价。简单来说，在对后 28kDa 病毒结构的磷蛋白 pp28 促进子的控制下制备含标记基因(荧光素酶)的重组人巨细胞病毒(HCMV)。人体包皮成纤维(Human foreskin fibroblast,HFF)细胞用该重组 HCMV 病毒(MOI 5)感染，置于 96-孔板内，在标准细胞培养条件下培养。1 小时后，将待评估其抗 HCMV 活性的化合物加到感染的细胞中。用试验化合物处理后 24 小时测量荧光素酶的表达水平。试验化合物的生物活性由它们的 IC_{50} 值：相对于对照(赋形剂处理)的感染细胞，使重组 HCMV 后期基因表达(由 HFF 培养里的荧光素酶表达代表)减少 50%的试验化合物浓度，表示。作为另外的对照，在培养的细胞生长实验里也评估试验化合物对未处理 HFF 细胞的细胞毒性。

表 1 提供了从下列实施例选出的化合物的生物数据。

表 1

化合物	IC_{50}(μM)
a	0.8
c	0.1
d	0.02
f	6.0
g	0.8
h	0.3
j	0.01
k	1.0
m	2.0
n	0.4
o	2.0
p	0.3
q	3.0
s	3.0
t	10.0
u	0.1

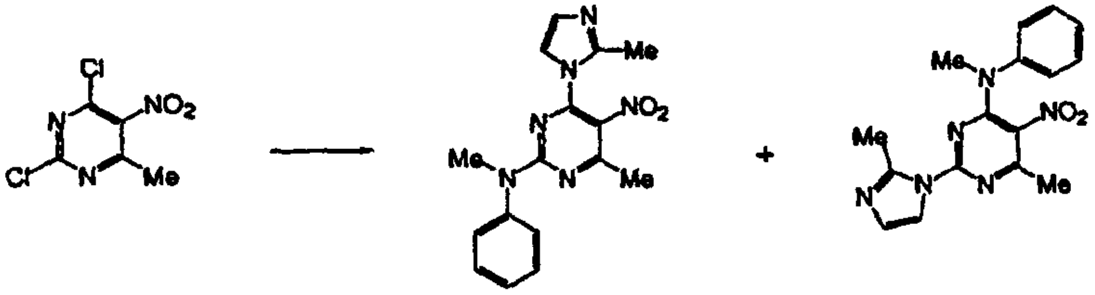
下列实施例仅供阐述，并非用于限定。

实施例

^{1}H-NMR 光谱在 Varian Gemini 400MHz NMR 光谱仪上记录。明显的峰被依次列表：质子数，峰数(s,单峰；d，双峰；t,三峰；q,四重峰；m,多重峰；br s,宽的单峰)，偶合常数(单位为 Hz)。电子离子化(EI)质谱在 Hewlett Packard 5989A 质谱仪上记录。质谱结果被记录为质量与电荷之比，然后是每个离子的相对丰度(在括号里)。用于实施例里的所有的试剂、起始物质和中间体都是市售可得，或可通过本技术领域公知的方法制得。

实施例 1

该实施例揭示了 2-(N-甲基苯胺基)-4-(2-甲基咪唑-1-基)-6-甲基-5-硝基嘧啶(a)和异构体 4-(N-甲基苯胺基)-2-(2-甲基咪唑-1-基)-6-甲基-5-硝基嘧啶(b)的合成。



a　　b

向搅拌着的 2,4-二氯-6-甲基-5-硝基嘧啶(2.25g, 10.8 毫摩尔，1.0 当量)在 THF(15 毫升)中的冷溶液(-78℃)中滴加入 2-甲基咪唑(977 毫克，11.9 毫摩尔，1.1 当量)在 THF(15 毫升)中的溶液。1 小时后，干冰浴用冰水浴代替，再搅拌 2 小时 15 分钟。此时加入 N-甲基苯胺(4.6ml, 43.2 毫摩尔，4.0 当量)。使反应溶液在-78℃下搅拌 1 小时 15 分钟，在室温下搅拌过夜。此时除去溶剂，残留物用二氯甲烷稀释，用 0.1MHCl 洗涤三次，用饱和 NaCl 水溶液洗涤三次。蒸发有机相，残留物经硅胶层析纯化(1：1 已烷/乙醚，1%AcOH 作为洗脱液)，得到 209 毫克目标化合物 a(6%)及其异构体(400 毫克)，和 b(104.8 毫克)。

(a) ^{1}H NMR (400MHz) (CD_3OD): δ 2.26 (3H, br s); 2.58 (3H, br s); 3.61 (3H, s); 6.88 (1H, s); 7.02 (2H, d); 7.31-7.34 (3H, m); 7.43-7.48 (2H, m). 计算值：$C_{16}H_{16}N_6O_2$: C, 59.25; H, 4.97; N, 25.91. 测定值：C, 59.16; H, 4.95; N, 25.86.

(b) ^{1}H NMR (400MHz) ($CDCl_3$): δ 2.40 (3H, s); 2.80 (3H, s); 3.55 (3H, s); 6.95 (1H, s); 7.13 (2H, m); 7.30-7.39 (3H, m); 7.86 (2H, s).

实施例 2

该实施例显示了 2-(N-甲基苯胺基)-4-(2-甲基咪唑-1-基)-6-乙基-5-硝基嘧啶(c)的合成。

a　　　　　　　　　　c

向搅拌着的 a(54.4 毫克，0.168 毫摩尔，1.0 当量)在 THF(1。0 毫升)中的冰冷溶液(-78℃)中滴加入 $LiN(SiMe_3)_2$,(0.20 毫摩尔，0.20 毫升，1.0M/THF 溶液)。搅拌 10 分钟后，滴加入 MeI(0.105ml, 1.68 毫摩尔，10 当量)。使反应在-78℃下保持 40 分钟，在 0℃下再搅拌 4 小时。将少量乙酸(0.25ml)倒入烧瓶，将褐色残留物蒸发至干。残留物然后溶于二氯甲烷，用饱和 NaCl 水溶液洗涤三次，蒸发有机相至干，得到粗制的黄色油。

通过硅胶柱层析纯化，用 1：1 已烷/乙醚、1%AcOH、3%MeOH 作为洗脱液，得到 21.4mg 所需的产物(37%)。

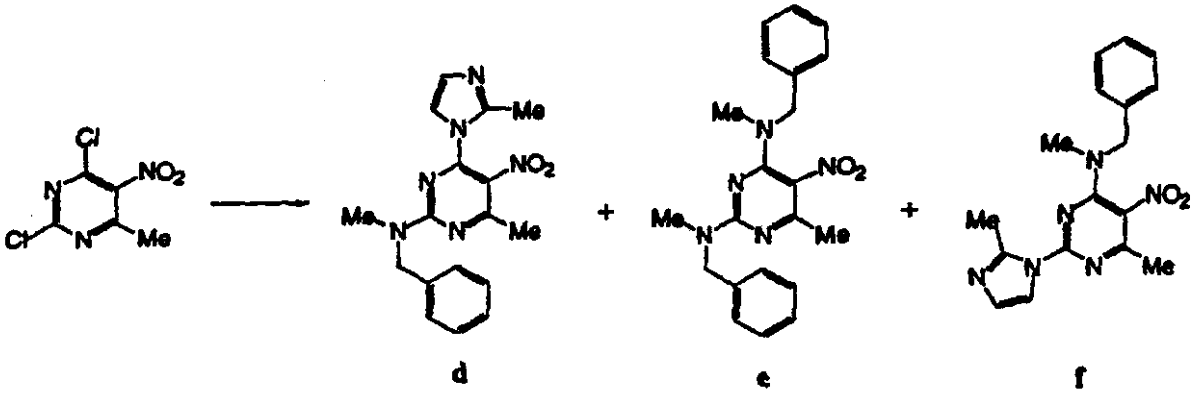
(c) ^{1}H NHR (400MHz) (CD_3OD)：δ 1.29(3H, br s)；2.28(3H, br s)；2.86(2H, br s)；3.63(3H, s)；6.89(1H, s)；7.02(1H, s)；7.30-7.39(3H, m)；7.42-7.49(2H, m)。

MS ESI m/z(相对强度)：M+H, 339.2(100)；M=Na, 361.1(15)。

实施例 3

该实施例显示了 2-(N-苄基-N-甲基氨基)-4-(2-甲基咪唑-1-基)-6-甲基-

5-硝基嘧啶(d)、2,4-双-(N-苄基-N-甲基氨基)-6-甲基-5-硝基嘧啶(e)和 4-(N-苄基-N-甲基氨基)-2-(2-甲基咪唑-1-基)-6-甲基-5-硝基嘧啶(f)的合成。



向搅拌着的 2,4-二氯-6-甲基-5-硝基嘧啶(187.7mg, 0.9 毫摩尔, 1.0 当量)在 THF(2.25 毫升)和 EtOH(2.25ml)中的冷溶液(-78℃)中滴加入 2-甲基咪唑(148 毫克, 1.8 毫摩尔, 2.0 当量)在 EtOH(2.25 毫升)中的溶液。45 分钟后，干冰浴用冰水浴代替，混合物再搅拌 2.2 小时。此时加入 N-甲基苄基胺(0.465ml, 3.6 毫摩尔, 4.0 当量)。搅拌 2.7 小时后，通过蒸发除去溶剂，残留物用二氯甲烷稀释，用 0.1MHCl 洗涤三次，用饱和 NaCl 水溶液洗涤三次。从有机相里除去溶剂，残留物经硅胶层析纯化(1：1 己烷/乙醚，1%AcOH 作为洗脱液)，得到 d(32mg),e(116.3mg)和 f(104.8mg)。

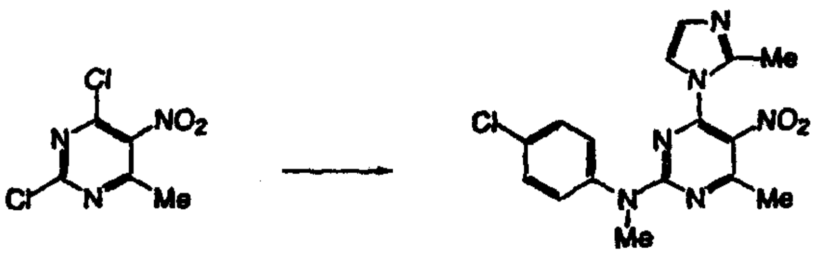
(d) ^{1}H NMR (400MHz) (CDCl$_3$): δ 2.30 (1.5H, s); 2.53 (1.5H, s); 2.57 (1.5H, s); 2.59 (1.5H, s); 3.15 (1.5H, s); 3.27 (1.5H, s); 4.88 (1H, s); 4.97 (1H, s); 6.87 (0.5H, s); 6.90 (0.5H, s); 6.96 (0.5H, s); 6.99 (0.5H, s); 7.16 (1H, d); 7.24-7.37 (4H, m). MS ESI m/z (相对强度): M+H, 339.2 (100); M+Na, 361.1 (8)

(e) ^{1}H NMR (400MHz) (CDCl$_3$): δ 2.49 (3H, s); 2.79 (3H, s); 2.90-3.20 (3H, br m); 4.70-4.88 (4H, br m); 7.12-7.35 (10H, br m). MS ESI m/z (相对强度):M+H, 378.2 (100); M+Na, 400.1 (15)

(f) ^{1}H NMR (400MHz) (CDCl$_3$): δ 2.52 (3H, s); 2.67 (3H, s); 2.90 (3H, s); 4.92 (2H, s); 6.89 (1H, s); 7.20 (2H, d); 7.28-7.35 (3H, m); 7.74 (1H, s). MS ESI m/z (相对强度): M+H, 339.2 (100).

实施例 4

该实施例显示了 2-(N-甲基-4-氯苯胺基)-4-(2-甲基咪唑-1-基)-6-甲基-5-硝基嘧啶(g)的合成。



g

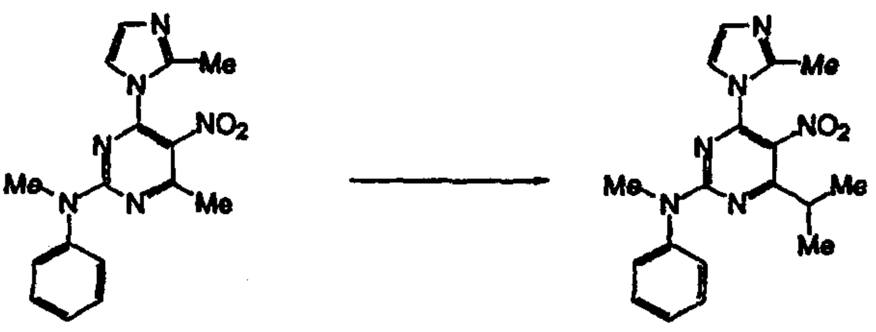
向搅拌着的 2,4-二氯-6-甲基-5-硝基嘧啶(207.5mg，1.0 毫摩尔，1.0 当量)在 THF(2.25 毫升)和 EtOH(2.25ml)中的冷溶液(-78℃)中滴加入 2-甲基咪唑(164 毫克，2.0 毫摩尔，2.0 当量)在 EtOH(2.25 毫升)中的溶液。45 分钟后，干冰浴用冰水浴代替，混合物再搅拌 2.25 小时。然后加入 4-氯-N-甲基苯胺(0.485ml，4.0 毫摩尔，4.0 当量)，使反应溶液搅拌 2.7 小时。通过蒸发除去溶剂，残留物用二氯甲烷稀释，用 0.1MHCl 洗涤三次，用饱和 NaCl 水溶液洗涤三次，用 $MgSO_4$ 干燥。从有机相里除去溶剂，残留物经硅胶层析纯化(1：1 己烷/乙醚，1%AcOH 作为洗脱液)，得到 g(55.9mg, 15.6%)。

(g) ^{1}H NMR (400MHz) (CD_3OD): δ 2.30 (3H, br s); 2.57 (3H, br s); 3.59 (3H, s); 6.91 (1H, s); 7.02 (1H, s); 7.36 (2H, d); 7.44 (2H,d).

MS ESI m/z(相对强度)：M+H，359.1(100)。

实施例 5

该实施例显示了 2-(N-甲基苯胺基)-4-(2-甲基咪唑-1-基)-6-异丙基-5-硝基嘧啶(h)的合成。



a　　h

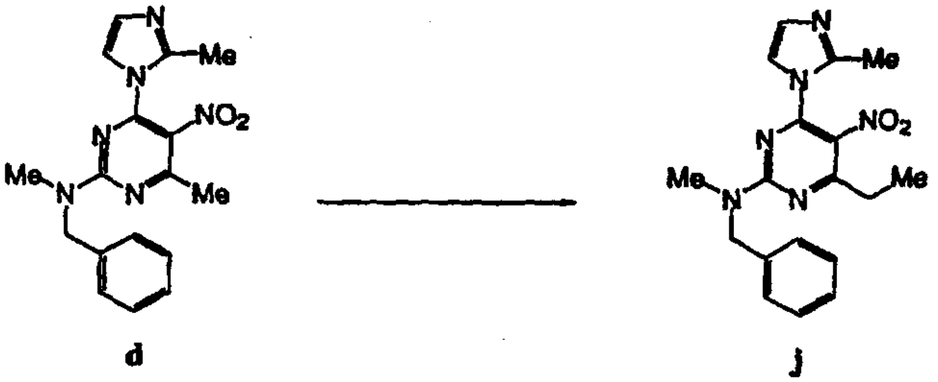
向 a(38.6mg，0.12 毫摩尔，1.0 当量)在 THF(0.5ml)中的搅拌的冰冷(-78℃)溶液里加入 NaH(9.5mg,60%在油中，0.24 毫摩尔，2.0 当量)。搅拌 15 分钟后，加入 MeI(0.074ml，1.19 毫摩尔，10 当量)。使反应在-78℃下保持 2

小时，然后在 0℃下再搅拌 2.5 小时。将少量乙酸(0.25 毫升)倒入烧瓶，将褐色残留物蒸发至干。残留物溶于二氯甲烷，用水洗涤三次，用饱和 NaCl 水溶液洗涤三次。从有机相除去溶剂，产物经硅胶层析(1：1 己烷/乙醚，1%AcOH 作为洗脱液)，得到目标化合物(13.3mg, 33%)。

(h) ^{1}H NMR (400MHz) ($CDCl_3$): δ 1.20-1.35 (6H, m); 2.29 (3H, br s); 3.24 (1H, m); 3.62 (3H, s); 4.92 (2H, s); 6.89 (1H, br s); 7.03 (1H, br s); 7.30-7.40 (3H, m); 7.71-7.48 (2H, m). MS ESI m/z (相对强度):M+H, 353.1 (100).

实施例 6

该实施例显示了 2-(N-苄基—N—甲基氨基)-4-(2-甲基咪唑-1-基)-6-乙基-5-硝基嘧啶(j)的合成。



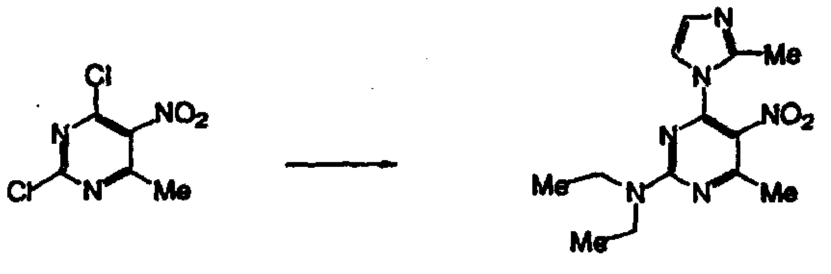
向搅拌着 d(57.7mg, 0.170 毫摩尔）在 THF（0.5 毫升）里的冰冷溶液（—78℃）里滴加入 $LiN(SiMe_3)_2$(0.17ml, 0.17 毫摩尔，1.0 当量，1.0M/THF)。搅拌 10 分钟后，滴加入 MeI(0.106ml, 1.70 毫摩尔，10 当量）。让反应在在-78℃下搅拌 2 小时，然后在 0℃下再搅拌 3 小时。将小部分乙酸（0.25ml)倒入烧瓶，褐色混合物蒸发至干。残留物溶于二氯甲烷，用水洗涤三次，用饱和 NaCl 水溶液洗涤三次，有机相蒸发至干。经硅胶层析纯化后（1：1 己烷/乙醚，1%AcOH, 3%MeOH 作为洗脱液），得到目标化合物。得率：30.3mg(50.4%)。

(j) ^{1}H NMR (400MHz) (CD_3OD): δ 1.26-1.41 (3H,m); 2.21 (1.5H,s); 2.45 (1.5H, s); 2.86-2.94 (2H, m); 3.22 (1.5H, s); 3.35 (1.5H, s); 4.93 (1H, s); 5.05 (1H,s); 6.91 (0.5H, s); 6.94 (0.5H, s); 7.07 (0.5H, s); 7.12 (0.5H, s); 7.23-7.38 (5H, m). MS ESI m/z (相对强度):M+H, 353.1 (100).

实施例 7

该实施例显示了 2-(N，N-二乙基氨基)-4-(2-甲基咪唑-1-基)-6-甲基-5-

硝基嘧啶(k)的合成。

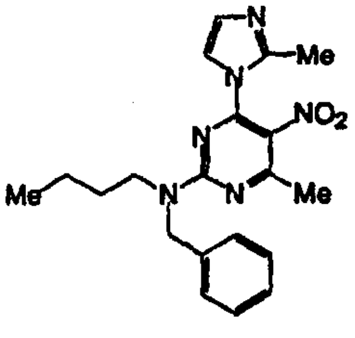


k

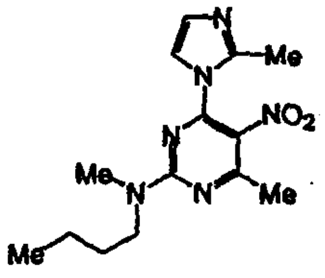
向搅拌着的2,4-二氯-6-甲基-5-硝基嘧啶(208mg, 1.0毫摩尔，1.0当量，在2毫升EtOH和2毫升THF中)的冷溶液(-78℃)中滴加入2-甲基咪唑(164毫克，2.0毫摩尔，2.0当量)在2毫升EtOH中的溶液。所得的溶液在-78℃下搅拌1小时，然后在0℃下搅拌2小时。滴加入二乙胺，使反应搅拌过夜。所得的混合物用二氯甲烷稀释，用0.1MHCl、饱和NaCl洗涤，干燥($MgSO_4$)，过滤。蒸发除去溶剂，残留物经硅胶层析纯化，得到35毫克目标化合物K的油状物。

(k) ^{1}H NMR (400MHz, $CDCl_3$): δ 1.15-1.23 (3H, m); 2.48 (3H, s); 2.53 (3H, s); 3.59-3.60 (2H, q); 3.68-3.70 (2H, q); 6.86 (1H, s); 6.95 (1H, s). *MS ESI* m/z (相对强度):M+H, 291.2 (100).

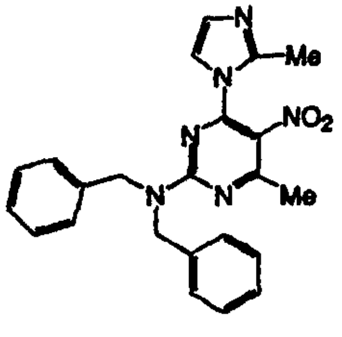
按照相似的方法，用指定的胺代替二乙胺，得到下列每个黄色油状物。



m



n

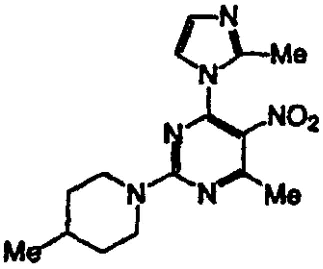


o

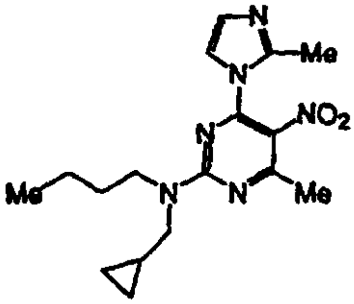
2-(N-苄基丁基氨基)-4-(2-甲基咪唑-1-基)-6-甲基-5-硝基嘧啶化合物m(N-丁基苄基胺)…40毫克。^{1}H NHR (400MHz)($CDCl_3$)：δ 0.86-0.95(3H,m);1.23-1.38(2H,m);1.51-1.68(2H,m);2.52(3H,m);3.52(2H,t);4.83(1H,s);6.80(1H,s);6.92(1H,s);7.13(2H,d);7.26-7.31(3H,m)。MS ESI m/z(相对强度)：M+H, 381.2(100)。

2-(N-甲基丁基氨基)-4-(2-甲基咪唑-1-基)-6-甲基-5-硝基嘧啶化合物 n(N-甲基丁基胺)…68 毫克。^{1}H NHR (400MHz)(CDCl$_3$)：δ 0.95(3H,t);1.32(2H,m); 2.51(3H,br s); 2.55(3H,s); 3.15-3.24(3H,d); 3.58-3.72(2H,t); 6.85(1H.s); 6.95(1H,s)。MS ESI m/z(相对强度)：M+H, 305.4(100)。

2-(N,N-二苄基氨基)-4-(2-甲基咪唑-1-基)-6-甲基-5-硝基嘧啶化合物 o(二苄基胺)…20 毫克。^{1}H NHR (400MHz)(CDCl$_3$)：δ 2.53(3H,br s); 2.55(3H,br s); 4.81(2H,s); 4.96(2H,s); 6.85(1H,s); 6.95(1H,s)。MS ESI m/z(相对强度)：M+H, 415.6(100)。



p



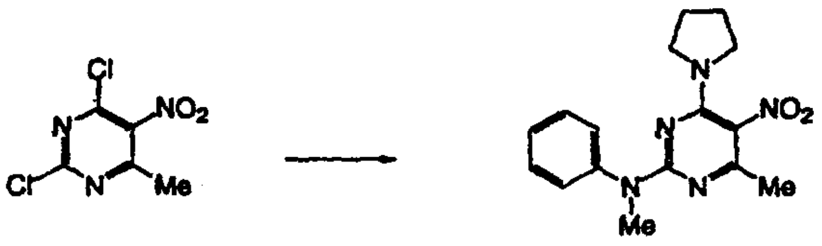
q

化合物 p(4-甲基哌啶)…45 毫克。^{1}H NHR (400MHz)(CDCl$_3$)：δ 1.12-1.16(3H,m); 2.46(3H,s);2.51(3H,s);3.40-3.47(8H,m); 6.84(1H,s); 6.99(1H,s)。MS ESI m/z(相对强度)：M+H, 317.1(100)。

化合物 q(N-(环丙基甲基)丁胺)…41 毫克。^{1}H NHR (400MHz)(CDCl$_3$)：δ 0.23-0.64(4H,m); 0.89-0.93(3H,m), 1.18(1H,t); 1.59-1.73(2H,m); 2.49-2.51(3H,d); 2.54-2.55(3H,d); 3.46-3.58(2H,m)。MS ESI m/z(相对强度)：M+H, 331.2(100)。

实施例 8

该实施例揭示了 2-(N-甲基苯胺基)-4-吡咯烷基-6-甲基-5-硝基嘧啶(r)的合成。

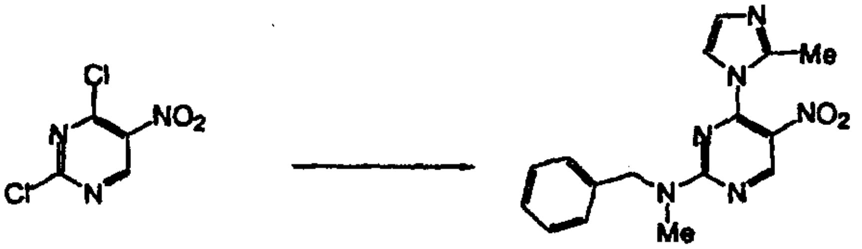


r

向搅拌着的 2,4-二氯-6-甲基-5-硝基嘧啶(208mg，1.0 毫摩尔，1.0 当量，在 2 毫升 EtOH 和 2 毫升 THF 中)的冷溶液(-78℃)中加入吡咯烷(78 毫克，1.1 当量)在 1.0 毫升 EtOH 中的溶液。所得的溶液在-78℃下搅拌 1 小时，然后在 0℃下搅拌 2 小时。滴加入 N-甲基苯胺(0.432 毫升，4.0 当量)，使反应搅拌过夜。所得的混合物用二氯甲烷稀释，用 0.1MHCl、饱和 NaCl 洗涤，干燥($MgSO_4$)，过滤。蒸发除去溶剂，残留物经硅胶层析纯化，得到目标化合物(r)。

实施例 9

该实施例显示了 2-(N-甲基-N-苄基氨基)-4-(2-甲基咪唑-1-基)-5-硝基嘧啶(s)的合成。



s

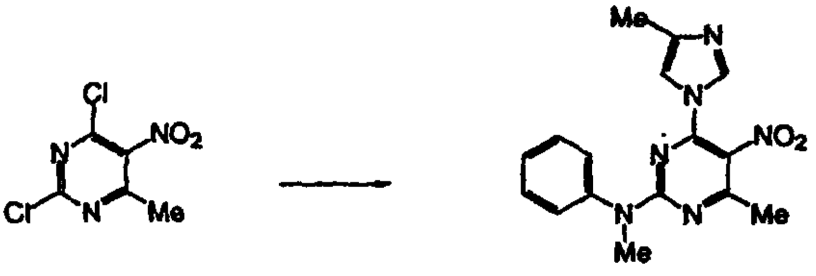
在 80℃下，向 2,4-二氯-5-硝基嘧啶(200 毫克，1.0 毫摩尔)在二噁烷(5 毫升)里的溶液中加入 2-甲基咪唑(85 毫克，1.0 毫摩尔)和 N-甲基-N-苄基胺(133 微升，1 毫摩尔)。使溶液在 80℃下搅拌过夜，冷却，直接进行层析(1/1 己烷/乙醚)，得到标题化合物(s)。

(s) ^{1}H NMR (400MHz) (CD_3OD): δ 3.09 (s, 1.5H), 3.17 (s, 1.5H), 3.18 (s, 1.5H), 4.5-4.8 (m, 2H), 7.2-7.5 (m, 8H).

实施例 10

该实施例显示了 2-(N-甲基苯胺基)-4-(4-甲基咪唑-1-基)-6-甲基-5-硝

基嘧啶(t)的合成。



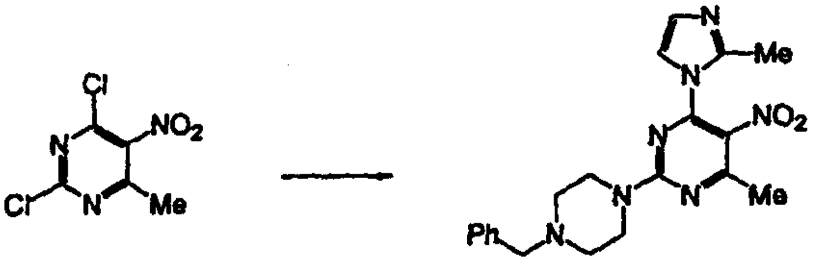
t

在 80℃下，向 2,4-二氯-6-甲基-5-硝基嘧啶(150 毫克，0.72 毫摩尔)在二噁烷(5 毫升)里的溶液中加入 4-甲基咪唑(60 毫克，0.72 毫摩尔)和 N-甲基-N-甲基苯胺(77 毫克，0.72 毫摩尔)。使溶液在 80℃下搅拌过夜，冷却，直接进行层析(1/1 己烷/乙醚)，得到标题化合物(t)。

(t) ^{1}H NMR (400MHz) (CD_3OD): δ 2.37 (s, 3H), 2.74 (s, 3H), 3.30 (s, 3H), 7.25-7.55 (m, 5H), 7.75 (s, 1H), 9.31 (s, 1H).

实施例 11

该实施例显示了 2-(4-苄基哌嗪-1-基)-4-(2-甲基咪唑-1-基)-6-甲基-5-硝基嘧啶(u)的合成。



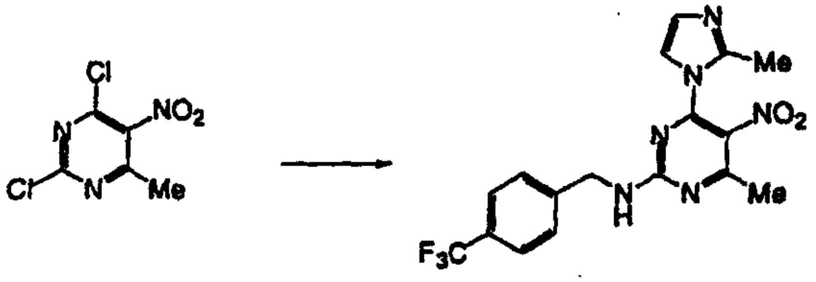
u

在 80℃下，向 2,4-二氯-6-甲基-5-硝基嘧啶(175 毫克，0.84 毫摩尔)在二噁烷(5 毫升)里的溶液中加入 4-甲基咪唑(60 毫克，0.72 毫摩尔)和 1-苄基哌嗪(148 微升，0.84 毫摩尔)。使溶液在 80℃下搅拌过夜，冷却，直接进行层析(1/1 己烷/乙醚)，得到标题化合物(u)。

(u) ^{1}H NMR (400MHz) (CD_3OD): δ 2.42 (s, 3H), 2.60 (s, 3H), 3.38 (br s, 4H), 3.80 (br s, 4H), 4.38 (s, 2H), 7.30-7.55 (m, 7H). MS ESI 347 m/e (相对强度): M+H, 348.0 (100).

实施例 12

该实施例显示了 2-(4-三氟甲基苄基氨基)-4-(2-甲基咪唑-1-基)-6-甲基-5-硝基嘧啶(v)的合成。



v

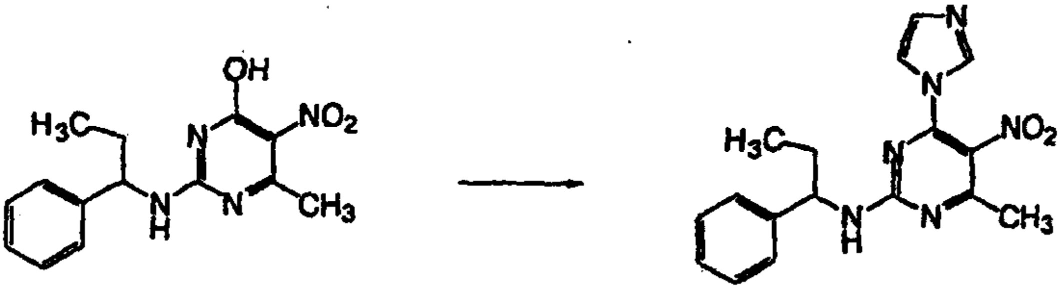
向 2-氯-4-羟基-6-甲基-5-硝基嘧啶(300 毫克，1.58 毫摩尔，1.0 当量)在无水乙醇(20 毫升)中的搅拌的混合物里加入 4-(三氟甲基)-苄基胺(540 毫克，3.1 毫摩尔，2.0 当量)和乙酸钠(130 毫克，1.58 毫摩尔，1.0 当量)。慢慢加热混合物，所得的溶液回流 22 小时。然后冷却混合物，真空除去乙醇。油状残留物溶于乙酸乙酯，用 1M HCl 洗涤三次，饱和 NaCl 溶液洗涤三次，然后用 $MgSO_4$ 干燥。除去溶剂得到粗制的黄色固体中间体，真空干燥，然后溶于 4 毫升 $POCl_3$。加热 (95~100℃)0.5 小时。通过旋转蒸发除去 $POCl_3$，粗制的褐色产物用层析纯化(1：1 己烷/二氯甲烷)，得到氯代嘧啶中间体(313 毫克)，它可用直接于下一步而无需另外的纯化。

向上述氯化嘧啶(150 毫克，0.4 毫摩尔，1.0 当量)在乙腈(2.5 毫升)中的搅拌溶液里加入 2-甲基咪唑(142 毫克，1.7 毫摩尔，4.0 当量)。所得的混合物回流加热 5 小时，冷却，通过旋转蒸发除去溶剂。残留物溶于乙酸乙酯，用 0.1MHCl、水、盐水洗涤，用 $MgSO_4$ 干燥，除去溶剂后得到粗制的黄色固体。固体经层析纯化，用 2.5%MeOH/二氯甲烷洗脱，得到黄色油。通过用二氯甲烷和己烷沉淀，得到标题化合物。得率：152.3mg，从起始的 2-氯-4-羟基-6-甲基-5-硝基嘧啶的得率为 51%。

(v) ^{1}H NMR (400MHz) $CDCl_3$ δ 2.28 (1.5H, s); 2.42 (1.5H, s); 2.55 (1.5H, s); 2.58 (1.5H, s); 4.71 (1H, d); 4.80 (1H, d); 6.67 (0.5H, br s); 6.80 (0.5H,br s); 6.88 (1H, d); 6.96 (1H, s); 7.41 (1H, d); 7.49 (1H, d); 7.62 (2H, d). MS ESI m/z (相对强度): M+H 392.9 (100).

实施例 13

该实施例揭示了用另外的方法将咪唑基团加到嘧啶核上，制备 2-((1-苯基-1-丙基)氨基)-4-(咪唑-1-基)-6-甲基-5-硝基嘧啶(w)。



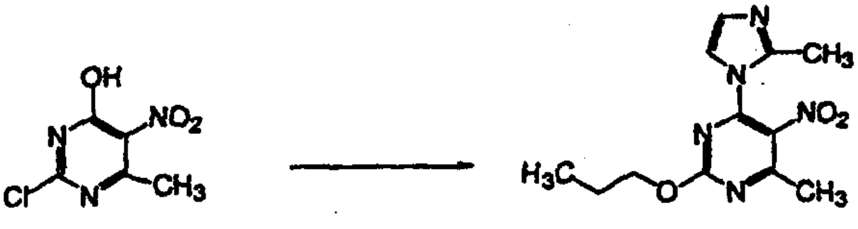
w

向 2-((1-苯基丙基)氨基)-4-羟基-6-甲基-5-硝基嘧啶(78 毫克，0.27 毫摩尔，1.0 当量，用与上述实施例 12 相似的方法制备)在吡啶(1 毫升)中的搅拌着的溶液里加入三氟乙酸酐(115 微升，0.81 毫摩尔，3.0 当量)。使混合物搅拌 15 分钟，然后加入咪唑(184 毫克，2.7 毫摩尔，10 当量)，让混合物搅拌过夜。通过旋转蒸发除去吡啶，将褐色残留物溶于乙酸乙酯，用 0.MHCl 洗涤，然后用盐水洗涤。除去溶剂后得到的粗制固体经硅胶层析纯化($2.5\%MeOH/CH_2Cl_2$)，得到 36.1 毫克(42%)标题化合物。

(w) ^1H NMR (400MHz) $CDCl_3$ δ 0.99 (3H, m); 1.73-2.02 (2H, m); 2.48 (3H, s); 4.81 (0.66H, dd); 5.07 (0.33H, dd); 6.16 (0.66H, d); 7.02 (0.33H, d); 7.08-7.12 (2H,m); 7.25-7.38 (5H, m); 7.89 (0.66H, s); 8.18 (0.33H, s). MS ESI m/z (相对强度): M+H 339.2 (100).

实施例 14

该实施例显示了在 2-位上有烷氧基的嘧啶衍生物，如 2-(1-丙氧基)-4-(2-甲基咪唑-1-基)-6-甲基-5-硝基嘧啶(x)，的合成。



x

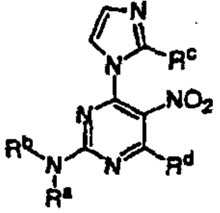
向加有正丙醇(5 毫升)的烧瓶中加入 NaH(128mg, 60%在油中，3.19 毫摩尔, 2.0 当量)，让混合物在氮气下搅拌 10 分钟。所得的溶液通过套管转移到含有 2-氯-4-羟基-6-甲基-5-硝基嘧啶(302 毫克，1.6 毫摩尔，1.0 当量)的正丙醇(5 毫升)溶液的烧瓶里。所得的混合物在 100℃油浴中加热 1 小时，倒入含有稀 HCl 的分液漏斗，用二氯甲烷萃取。分离有机相，用水、盐水洗涤，用 $MgSO_4$ 干燥，除去溶剂后得到粗制的固体(得率 297 毫克)。粗制的固体在纯净的 $POCl_3$(3ml)中在 85-90℃下加热 6 分钟，在冰上冷却，真空除去 $POCl_3$。氯嘧啶中间体经色谱层析纯化，得到 117 毫克中间体，用实施例 12 所述的方法将它转化为标题化合物。所得的产物是黄色油(191 毫克，从 2-氯-4-羟基-6-甲基-5-硝基嘧啶计算，得率为 43%)。

(x) ^{1}H NMR (400MHz) $CDCl_3$ δ 1.04 (3H, t); 1.86 (2H, dq); 2.52 (3H, s); 2.61 (3H, s); 4.38 (2H, t); 6.90 (1H, d); 6.98 (1H, d). MS ESI m/z (相对强度): M+H 278.1 (100).

实施例 15

用实施例 12-13 列出的方法制备表 2 列出的化合物。使化合物经上述的 CMV 分析法测试，并显示出下列水平的活性：＋IC_{50}>500nM；++，100nM<IC_{50}≤500nM；+++，IC_{50}≤100nM。

表　　2



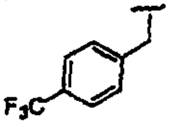
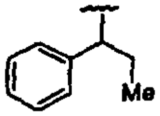
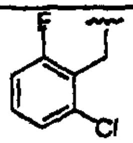
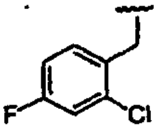
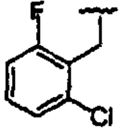
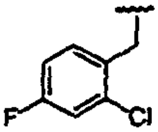
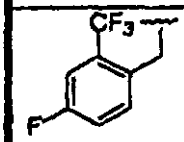
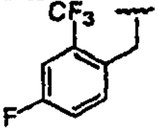
R^a	R^b	R^c	R^d	m/z (m+1)	抗病毒活性
	H	Me	Me	392.9	++
	H	Me	Me	353.1	++
	H	Et	Me	391.1	++
	H	Et	Me	406.9	++
	H	Me	Me	377.1	++
	H	Et	Me	391.1	++
	H	Me	Me	411.1	++
	H	Et	Me	425.1	++

表　　2（续）

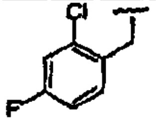
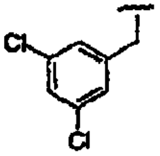
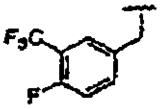
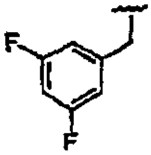
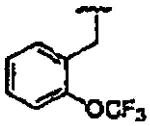
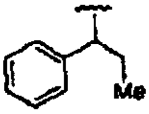
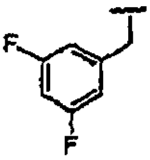
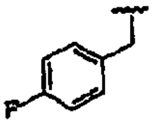
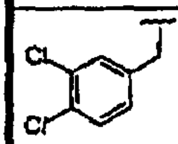
R^a	R^b	R^c	R^e	m/z（m+1）	抗病毒活性
	H	Me	Me	377.1	++
	H	Me	Me	393.1	++
	H	Me	Me	411.1	+++
	H	Me	Me	361.1	+++
	H	Me	Me	409.1	++
	H	H	Me	339.2	+
	H	H	Me	347.1	+
	H	Me	Me	343.1	++
	H	Me	Me	393.1	++

表　　2（续）

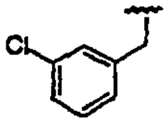
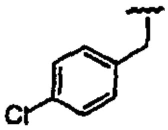
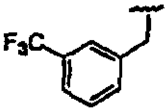
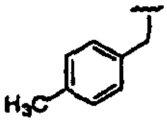
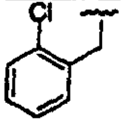
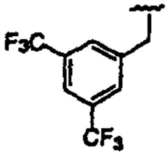
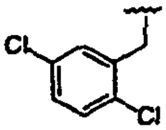
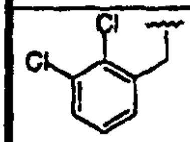
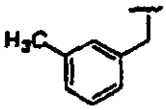
R^a	R^b	R^c	R^d	m/z (m+1)	抗病毒活性
	H	Me	Me	359.1	+++
	H	Me	Me	359.1	++
	H	Me	Me	392.1	+++
	H	Me	Me	339.1	+
	H	Me	Me	359.1	+++ –
	H	Me	Me	461.1	+
	H	Me	Me	393.1	+++
	H	Me	Me	393.1	++
	H	Me	Me	339.1	++

表　　2（续）

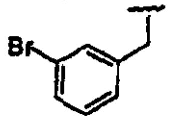
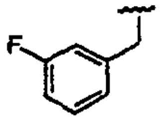
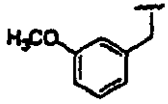
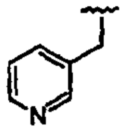
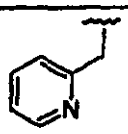
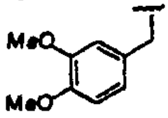
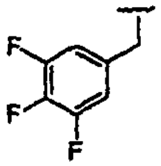
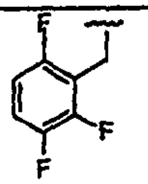
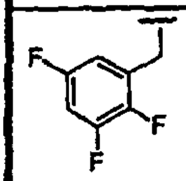
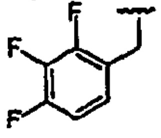
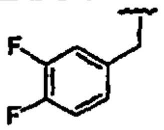
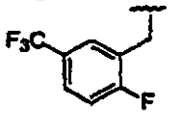
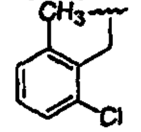
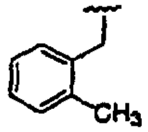
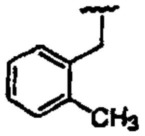
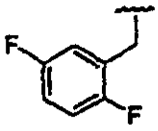
R^a	R^b	R^c	R^d	m/z (m+1)	抗病毒活性
	H	Me	Me	403.0	+++
	H	Me	Me	343.1	++
	H	Me	Me	355.1	++
	H	Me	Me	326.1	+
	H	Me	Me	326.1	++
	H	Me	Me	385.1	++
	H	Me	Me	379.1	++
	H	Me	Me	379.1	++
	H	Me	Me	379.1	++
	H	Me	Me	379.1	++

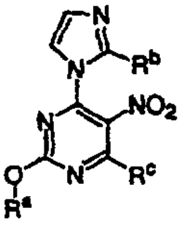
表　2（续）

R^a	R^b	R^c	R^d	m/z (m+1)	抗病毒活性
	H	Me	Me	361.1	++
	H	Me	Me	411.1	+++
	H	Me	Me	373.1	++
	H	H	Me	325.1	+
	H	Me	Me	339.1	++
	H	Me	Me	361.1	++

实施例16

用实施例12-14相似的方法制备列于表3的化合物。对化合物进行上述CMV试验，它们显示出＋,IC$_{50}$>500 nM的活性水平。

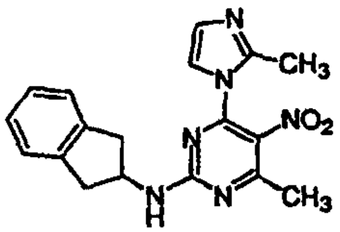
表 3



R^a	R^b	R^c	m/z (m+1)	抗病毒活性
正丙基	Me	Me	278.1	+
正丙基	H	Me	264.1	+
正丁基	Me	Me	292.2	+
正丁基	H	Me	278.1	+
苯乙基	H	Me	326.1	+
甲基	Me	Me	250.1	+
乙基	Me	Me	264.1	+
苄基	H	Me	312.2	+
3-甲氧基-1-丁基	H	Me	308.1	+
3-甲氧基-1-丁基	Me	Me	322.3	+
3,3-二甲基-1-丁基	H	Me	306.2	+
3,3-二甲基-1-丁基	Me	Me	320.1	+

实施例 17

该实施例显示了 2-(2-二氢化茚氨基)-4-(2-甲基咪唑-1-基)-6-甲基-5-硝基嘧啶的合成。

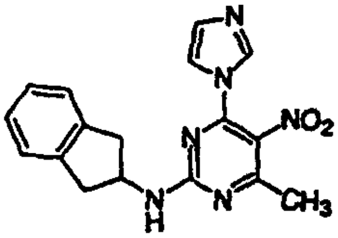


将根据实施例 12 的方法，但用 2-二氢化茚胺作为亲核剂，制备的 2-(2-二氢化茚氨基)-4-氯-6-甲基-5-硝基嘧啶(56 毫克，0.18 毫摩尔)，溶于 2.0 毫升 EtOH，然后加入 2-甲基咪唑(38 毫克，0.46 毫摩尔，2.5 当量)。所得的黄色溶液放在 80℃的水浴里，搅拌 24 小时。然后减压浓缩溶液。经快速层析纯化(SiO_2, 2%MeOH/CH_2Cl_2)，得到 34 毫克标题化合物(52%)的无定形黄色固体：熔点 203-204℃。

^{1}H NMR ($CDCl_3$, 400 MHz, 旋转异构体的混合物) δ 7.28-7.13 (m, 5 H), 6.99 (s, 0.5 H), 6.96 (s, 0.5 H), 6.17 (d, *J* = 7.9 Hz, 0.5 H), 6.06 (d, *J* = 7.3 Hz, 0.5 H), 4.93 (m, 0.5 H), 4.73 (m, 0.5 H), 3.45-3.34 (m, 2 H), 2.94 (dd, *J* = 4.8, 16.2 Hz, 1 H), 2.89 (dd, *J* = 4.3, 16.0 Hz, 1 H), 2.71 (s, 1.5 H), 2.65 (s, 1.5 H), 2.63, s, 1.5 H), 2.53 (s, 1.5 H); MS ESI m/z (相对强度): 351.2 (M + H, 100). 计算值: $C_{18}H_{18}N_6O_2$: C, 61.70; H, 5.18; N, 23.99. 测定值: C, 61.08; H, 5.22; N, 23.57.

实施例 18

该实施例显示了 2-(2-二氢化茚氨基)-4-咪唑-1-基-6-甲基-5-硝基嘧啶的合成。

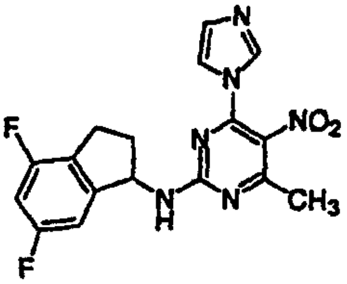


将 2-(2-二氢化茚氨基)-4-氯-6-甲基-5-硝基嘧啶(66.8mg, 0.22 毫摩尔)溶于 2.0mlEtOH，然后加入咪唑(37 毫克，0.54 毫摩尔，2.5 当量)。将黄色溶液加热到 80℃达 18 小时。然后真空减压浓缩溶液，经快速色谱层析纯化(SiO_2, 2%MeOH/CH_2Cl_2)，得到 52.1mg(71%)的无定形黄色固体产物(0.155 毫摩尔)：熔点 177-178℃。

^{1}H NMR ($CDCl_3$, 400MHz, 旋转异构体混合物) δ 8.23(s, 0.5H), 8.16(s, 0.5H), 7.28-7.11(m, 6H), 6.09(宽 s, 0.5H), 5.91(d, J=7.2Hz, 0.5H), 4.93(m, 0.5H), 4.79(m, 0.5H), 3.40(dd, J=7.0, 15.9Hz, 2H), 2.91(dd, J=4.1, 15.8Hz, 2H), 2.56(s, 1.5H), 2.46(s, 1.5H); MS ESI(相对丰度) 337.1(M+H, 100)。$C_{17}H_{16}N_6O_2$ 的计算值：C, 60.71; H, 4.79; N, 24.99。测定值：C, 60.29; H, 4.89; N, 24.69。

实施例 19

该实施例揭示了 2-(4,6-二氟-1-二氢化茚氨基)-4-(咪唑-1-基)-6 甲基-5-硝基嘧啶的合成。

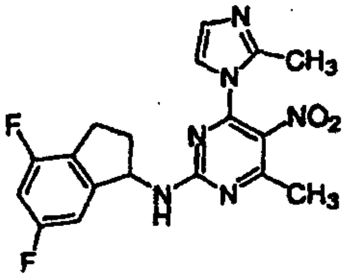


将根据实施例 12 的方法，用 4,6-二氟-1-二氢茚胺作为亲核剂制备的 2-(4,6-二氟-1-二氢化茚氨基)-4-氯-6-甲基-5-硝基嘧啶(56mg,0.16 毫摩尔)溶于 2.0mlEtOH，然后加入咪唑(28 毫克，0.411 毫摩尔，2.5 当量)。将溶液加热到 80℃达 23 小时。然后真空减压浓缩溶液，经快速层析纯化(SiO_2,2%MeOH/CH_2Cl_2)，得到 35.5mg(58%得率)的无定形黄色固体产物:熔点 175-176℃。

^{1}H NMR($CDCl_3$,400MHz,旋转异构体混合物)δ 8.09(s, 0.5H),8.06(s,0.5H0,7.26-7.10(m,2H),6.82(dd,J-7.6,11.6Hz,1H0,6.72(dd,J=8.8,8.8Hz,1H0,5.95(宽 s,0.5H), 5.82(d,J=8.4Hz,0.5H), 5.72(m,0.5H), 5.56(m,0.5H),3.05(m,1H),2.87(m,1H),2.73(m,1H),2.55(s,1.5H),2.49(s,1.5H),1.98(m,1H);MS ESI(相对丰度)373.1(M+H,100)。$C_{17}H_{14}F_2N_6O_2$ 的计算值：C,54.84;H,3.79;N,22.57。测定值：C,54.95;H,3.76;N,22.32。

实施例 20

该实施例显示了 2-(4,6-二氟-1-二氢化茚氨基)-4-(2-甲基咪唑-1-基)-6-甲基-5-硝基嘧啶的合成。

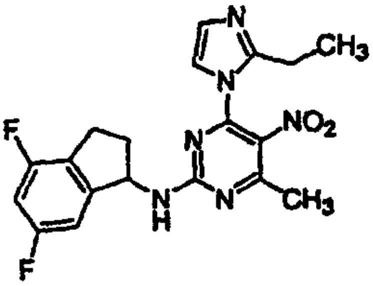


将 2-(4,6-二氟-1-二氢化茚氨基)-4-氯-6-甲基-5-硝基嘧啶(56mg,0.16 毫摩尔)溶于 2.0mlEtOH，然后加入 2-甲基咪唑(34 毫克，0.41 毫摩尔，2.5 当量)。将溶液加热到 80℃，搅拌下加热达 26 小时。然后真空减压浓缩溶液，经快速层析纯化(SiO_2,2%MeOH/CH_2Cl_2)，得到 42.6mg(67%得率)的无定形黄色固体产物:熔点 164-165℃。

^{1}H NMR($CDCl_3$,400MHz，旋转异构体混合物)δ 6.98(s,1H)，6.90(s,1H),6.81(m,1H),6.71(m,1H),5.87-5.81(m,1H)，5.73(m,0.5H)，5.54(m,0.5H)，3.05(m,1H)，2.82(m,1H)，2.70(m,1H)，2.60(s,1.5H)，2.53(s,1.5H),2.51(s,1.5H)，2.46(s,1.5H),1.98(m,1H);MS ESI(相对丰度)387.1(M+H,100)。$C_{18}H_{16}F_2N_6O_2$ 的计算值：C,55.96;H,4.17;N,21.75。测定值：C,56.15;H,4.59;N,20.71。

实施例 21

该实施例显示了 2-(4,6-二氟-1-二氢化茚氨基)-4-(2-乙基咪唑-1-基)-6-甲基-5-硝基嘧啶的合成。

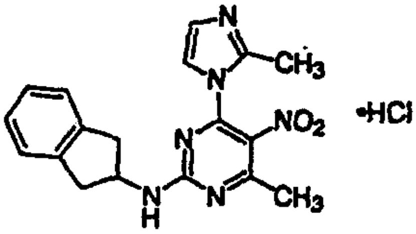


将 2-(4,6-二氟-1-二氢化茚氨基)-4-氯-6-甲基-5-硝基嘧啶(56mg,0.16 毫摩尔)溶于 2.0mlEtOH，然后加入 2-乙基咪唑(39 毫克，0.41 毫摩尔，2.5 当量)。将溶液加热到 80℃达 23.5 小时，然后真空减压浓缩溶液，经快速色谱层析纯化(SiO_2,2%MeOH/CH_2Cl_2)，得到 39.6mg(60%得率)的无定形黄色固体产物，熔点 88-89℃。

^{1}H NMR($CDCl_3$,400MHz,旋转异构体混合物)δ 7.02(s,1H0,6.88(s,1H)，6.81(m,1H),6.72(m,1H),5.85(d,J=9.0Hz,0.5H),5.81-5.70(m,1H)，1.29(t，J=7.5Hz,3H)；MS ESI(相对丰度):401.1(M+H,100)。$C_{19}H_{18}F_2N_6O_2$ 的计算值：C,57.00;H,4.53;N,20.99。测定值：C,56.93;H,4.50;N,20.71。

实施例 22

该实施例揭示了 2-(2-二氢化茚氨基)-4-(2-甲基咪唑-1-基)-6-甲基-5-硝基嘧啶，单盐酸盐的合成。

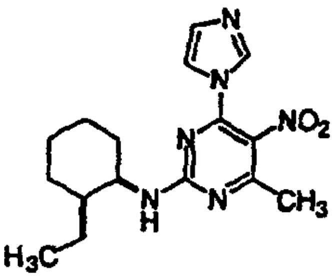


将根据实施例 17 的方法制备的 2-(2-二氢化茚氨基)-4-氯-6-甲基-5-硝基嘧啶(310 毫克，1.02 毫摩尔)溶于 7mlEtOH，然后加入 2-甲基咪唑(600 毫克，7.3 毫摩尔，7.2 当量)。将所得的黄色溶液然后加热到 80℃，同时进行磁搅拌。24 小时后，真空减压浓缩溶液，经快速层析纯化(SiO_2,2%MeOH/CH_2Cl_2)，得到 303.6mg 无定形黄色固体的游离碱(0.876 毫摩尔)。黄色固体然后溶于 3 毫升无水 THF 后，加入 2 毫升(8.0 毫摩尔，9.2 当量)4.0MHCl 在 1,4-二噁烷中的溶液。马上形成沉淀。让所得的浆状物搅拌 10 分钟。然后减压浓缩浆状物，溶于 3 毫升 THF，再浓缩。所得的黄色固体经热的 EtOAc 重结晶，得到 179 毫克(45%得率)淡黄色针晶的盐酸盐：熔点 184-185℃。

^{1}H NMR($CDCl_3$,400MHz,旋转异构体混合物)δ7.76(d,J=2.2Hz,0.5Hz)，7.71(d,J=2.2Hz,0.5H),7.64(d,J=2.2Hz,0.5H),7.61(d,J=2.2Hz,0.5H),7.22(m,2H),7.15(m,2H0,4.92(m,0.5H),4.72(m,0.5H),3.41-3.31(m,1H)，2.97(m,1H0,2.73(s,1.5H),2.72(s,1.5H),2.68(s,1.5H),2.65(s,1.5H)。$C_{18}H_{18}N_6O_2$·HCl 的计算值：C,55.89;H,4.95;N,21.73;Cl,9.16。测定值：C,55.89;H,5.00;N,21.56;Cl,9.14。

实施例 23

该实施例显示了 2-(顺-2-乙基环己基氨基)-4-咪唑-1-基-6-甲基-5-硝基嘧啶的合成。



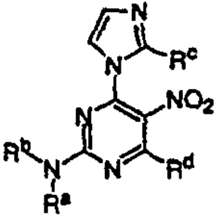
将 2-(顺-2-乙基环己基氨基)-4-氯-6-甲基-5-硝基嘧啶(58.6mg, 0.196 毫摩尔)溶于 2.0mlEtOH，然后加入咪唑(53 毫克，0.78 毫摩尔，4.0 当量)。将所得的黄色溶液加热到 80℃，进行磁搅拌。20 小时后真空减压浓缩溶液，经快速层析纯化(SiO_2, 2%MeOH/CH_2Cl_2)，得到 39.5mg(61%得率)的无定形黄色固体的标题化合物:熔点 123-124℃。

^{1}H NMR($CDCl_3$, 400MHz, 旋转异构体混合物)δ 8.22(s, 0.5H), 8.17(s, 0.5H), 7.39-7.27(m, 2H0, 5.92(d, J=7.8Hz, 1H), 4.57(m, 0.5H), 4.42(m, 0.5H), 2.65(s, 1.5H), 2.61(m, 1.5H), 2.02(m, 1H), 1.87-1.34(m, 10H), 1.02(t, J=7.0Hz, 3H); MS ESI(相对丰度)331.2(M+H, 100)。$C_{16}H_{22}N_6O_2$ 的计算值：C, 58.17; H, 6.71; N, 25.44。测定值：C, 58.01; H, 6.79; N, 25.30。

实施例 24

用实施例 17-23 列出的方法制备表 4 列出的化合物。化合物进行上述 CMV 试验，显示出下列活性水平：+，IC_{50}>500 nM; ++, 100nM<IC_{50}≤500nM; +++, IC_{50}≤100nM。

表 4



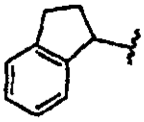
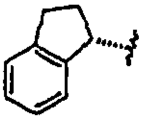
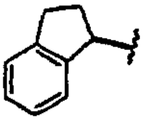
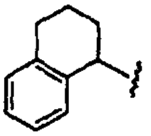
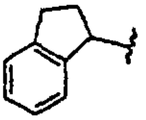
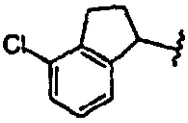
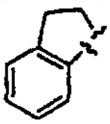
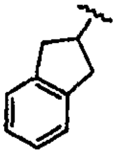
R^a	R^b	R^c	R^d	m/z (m+1) 或 mp (°C)	抗病毒活性
	H	Me	Me	351.2	+++
	H	Me	Me	351.2	+++
	H	Me	Me	351.2	+++
	H	Me	Me	365.1	++
	Me	Me	Me	365.1	++
	H	Me	Me	385.1	+
		Me	Me	181-182 °C	++
	H	Me	Me	203-204 °C	+

表　4(续)

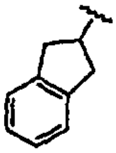
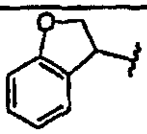
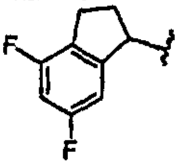
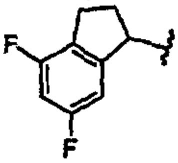
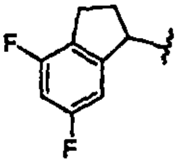
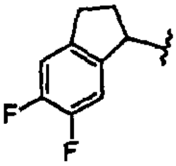
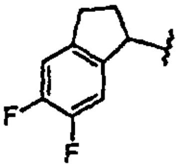
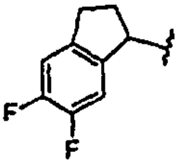
R^5	R^6	R^7	R^8	m/z (m+1) 或 mp (°C)	抗病毒活性
	H	H	Me	177-178 °C	+
	H	Me	Me	353.1	++
	H	Et	Me	88-89 °C	++
	H	H	Me	175-176 °C	++
	H	Me	Me	164-165 °C	++
	H	H	Me	189-190 °C	++
	H	Et	Me	177-178 °C	++
	H	Me	Me	205-206 °C	++

表 4(续)

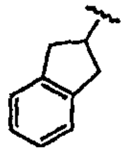
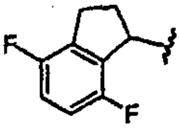
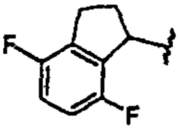
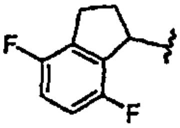
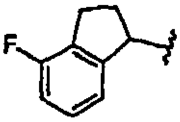
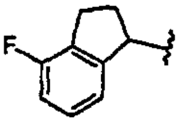
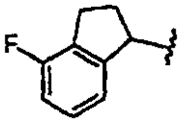
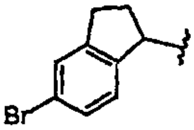
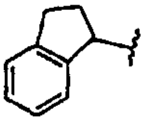
R^a	R^b	R^c	R^d	m/z (m+1) 或 mp (°C)	抗病毒活性
	H	Et	Me	187-188 °C	+
	H	H	Me	153-154 °C	++
	H	Me	Me	140-141 °C	+++
	H	Et	Me	158-159 °C	+++
	H	H	Me	178-179 °C	++
	H	Me	Me	74-75 °C	++
	H	Et	Me	65-66 °C	++
	H	Me	Me	429.1	++
	H	H	Me	337.1	+++

表 4(续)

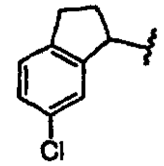
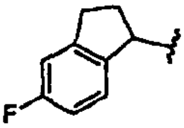
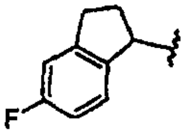
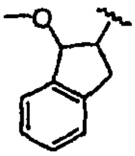
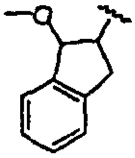
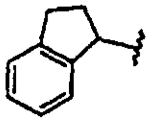
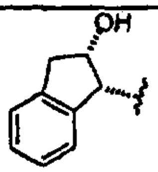
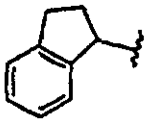
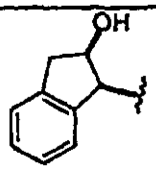
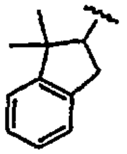
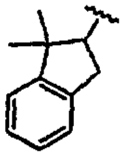
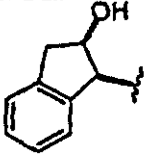
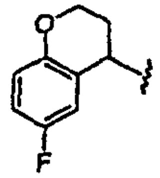
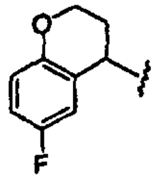
R^a	R^b	R^c	R^d	m/z (m+1) 或 mp (°C)	抗病毒活性
	H	Me	Me	385.1	++
	H	H	Me	355.1	+++
	H	Me	Me	369.2	++
	H	H	Me	367.3	+
	H	Me	Me	381.2	+
	H	Et	Me	365.1	++
	H	Me	Me	367.3	+++
	H	Me	H	337.1	++
	H	H	Me	353.1	++

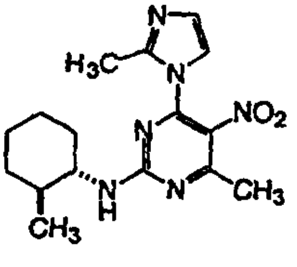
表 4(续)

R^a	R^b	R^c	R^d	m/z (m+1) 或 mp (°C)	抗病毒活性
	H	H	Me	365.1	+
	H	Me	Me	379.2	++
	H	Me	Me	367.2	
	H	H	Me	371.1	
	H	Me	Me	385.2	

实施例 24

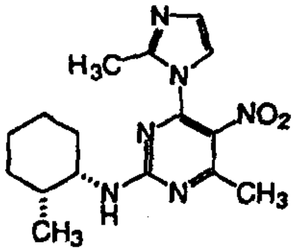
用上述方法制备此实施例中的化合物。起始物如上可得或由市售购得。

24.1 2-(N-(反-2-甲基环己基)氨基)-4-(2-甲基咪唑-1-基)-6-甲基-5-硝基嘧啶



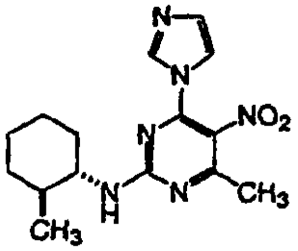
^{1}H NMR (400MHz, $CDCl_3$): δ 0.92(1.5H, d, J=7.2Hz); 0.94(1.5H, d, J=7.2Hz); 1.00-1.30(5H, m); 1.31-1.41(1H, m); 1.74-1.82(2H, m); 1.94-1.96(1H, m); 2.39(1.5H, s); 2.47(1.5H, s); 2.48(1.5H, s); 2.53(1.5H, s); 3.52(0.5H, dq, J=4.0, 9.8Hz); 3.69(0.5H, dq, J=4.0, 9.8Hz); 5.86(0.5H, d, J=9.2Hz), 5.98(0.5H, d, J=9.2Hz); 6.86(1H, s); 6.93(0.5H, s); 6.95(0.5H, s). MS ESI: m/z (相对强度): M+H, 331.2 (100).

24.2 2-(N-(顺-2-甲基环己基)氨基)-4-(2-甲基咪唑-1-基)-6-甲基-5-硝基嘧啶



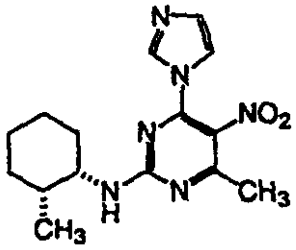
^{1}H NMR (400MHz, $CDCl_3$): δ 0.93(3H, d, J=7.2Hz); 1.22-1.41(3H, m); 1.48-1.68 (4H, m); 1.71-1.78(1H, m); 1.95(1H, m); 2.44(1.5H, s); 2.51(3H, s); 2.57(1.5H, s); 4.13(0.5H, m); 4.28(0.5H, m); 5.68(0.5H, d, J=9.0Hz), 5.59(0.5H, d, J=9.0Hz); 6.87(1H, s); 6.94(0.5H, s); 6.96(0.5H, s). MS ESI: m/z (相对强度): M+H, 331.2 (100)

24.3 2-(N-(反-2-甲基环己基)氨基)-4-(咪唑-1-基)-6-甲基-5-硝基嘧啶



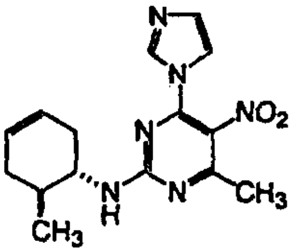
^{1}H NMR (400MHz, $CDCl_3$): δ 0.96(3H, d, J=6.5Hz); 1.11-1.29(3H, m); 1.33-1.39(2H, m); 1.70(1H, m); 1.75-1.83(2H, m) 2.05(1H, dd, J=2.8, 13.4Hz); 2.45(1.5H, s); 2.50(1.5H, s); 3.54(0.5H, dq, J=4.0, 9.8Hz); 3.70(0.5H, dq, J=4.0, 9.8Hz); 5.43(0.5H, s), 5.46(0.5H, s); 7.12(0.5H, s); 7.15(0.5H, s); 7.17(0.5H, s); 7.18(0.5H, s); 8.04 (0.5H, s); 8.08(0.5H, s). MS ESI: m/z (相对强度): M+H, 317.2 (100).

24.4 2-(N-(顺-2-甲基环己基)氨基)-4-(咪唑-1-基)-6-甲基-5-硝基嘧啶



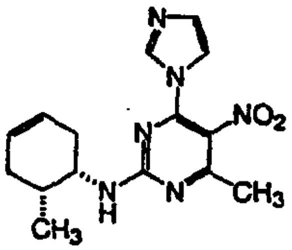
^{1}H NMR (400MHz, CDCl$_3$): δ 0.93(3H, d, J=7.2Hz); 1.22-1.41(3H, m); 1.48-1.68 (4H, m); 1.76-1.82(1H, m); 1.94-1.99(1H, m); 2.48(1.5H, s); 2.52(1.5H, s); 4.15(0.5H, m); 4.29(0.5H, m); 5.65(0.5H, d, J=7.6Hz), 5.73(0.5H, d, J=7.6Hz); 7.16(1H, s); 7.21(1H, s); 8.04(0.5H, s); 8.10(0.5H, s). MS SEI m/z (相对强度): M+H, 317.2(100)

24.5 2-(N-(反-2-甲基-4-环己烯基)氨基)-4-(咪唑-1-基)-6-甲基-5-硝基嘧啶



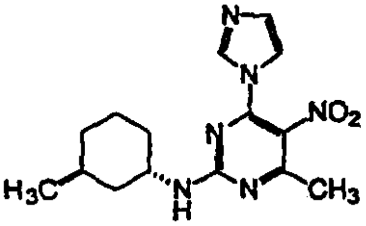
^{1}H NMR (400MHz, CDCl$_3$): δ 0.93(1.5H, d, J=6.8Hz); 1.00(1.5H, d, J=6.8Hz): 1.22(1H, m); 1.83-1.88(1H, m); 1.93-2.00(1H, m); 2.12(1H, m) 2.27(1H, m); 2.44(1.5H, s); 2.49(1.5H, s); 3.93(0.5H, dq, J=1.2, 7.2Hz); 4.08(0.5H, dq J=1.2, 7.2Hz); 5.51(0.5H, d, J=7.0Hz), 5.60(1.5H, m); 5.68(0.5H, m); 7.13(1H, s); 7.16(1H, s); 8.00(0.5H, s); 8.07(0.5H, s). MS ESI: m/z (相对强度):M+H, 315.2 (100).

24.6 2-(N-(顺-2-甲基-4-环己烯基)氨基)-4-(咪唑-1-基)-6-甲基-5-硝基嘧啶



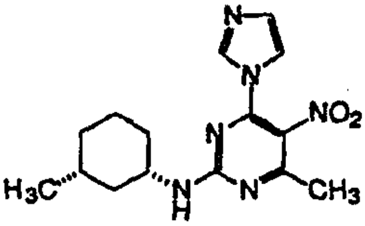
^{1}H NMR (400MHz, CDCl$_3$): δ 0.96(3H, d, J=6.8Hz); 1.26(1H, m); 1.84-1.92(1H, m); 2.10-2.18(1H, m); 2.27(1H, m) 2.42(1H, m); 2.47(1.5H, s); 2.51(1.5H, s); 4.32(0.5H, m); 4.47(0.5H, m); 5.63(1H, s), 5.72(1H, s); 5.79(0.5H, d, J=9.0Hz); 5.88(0.5H, d, J=9.0Hz); 7.13(0.5H, s); 7.15(0.5H, s); 7.17(0.5H,s); 7.21(0.5H, s); 8.03(0.5H, s); 8.08(0.5H, s). M ESI: m/z (相对强度): M+H, 315.2 (100).

24.7 2-(N-(反-3-甲基环己基)氨基)-4-(咪唑-1-基)-6-甲基-5-硝基嘧啶



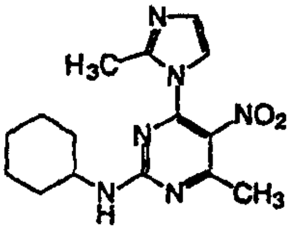
^{1}H NMR (400MHz, $CDCl_3$): δ 0.93(1.5H, d, J=6.5Hz); 0.96(0.5H, d, J=6.5Hz); 1.01-1.12(1H, m); 1.33-1.41(1H, m); 1.45-1.54(1H, m); 1.60-1.83(5H, m); 2.40(1.5H, s); 2.49(1.5H, s); 2.50(1.5H, s); 2.56(1.5H, s); 4.19(0.5H, m); 4.32(0.5H, m); 5.98(0.5H, d, J=6.0Hz), 6.03(0.5H, d, J=6.0Hz); 6.88(1H, s); 6.96(1H, s). MS ESI: m/z (相对强度): M+H, 331.2 (100).

24.8　2-(N-顺-3-甲基环己基)氨基)-4-(咪唑-1-基)-6-甲基-5-硝基嘧啶



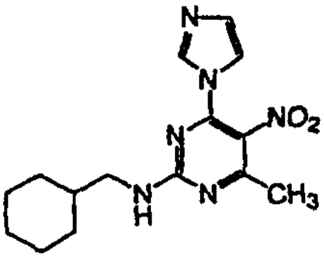
^{1}H NMR (400MHz, $CDCl_3$): δ 0.90(3H, d, J=6.5Hz); 1.08(1H, m); 1.29-1.38(1H, m); 1.42-1.52(1H, m); 1.60-1.70(1H, m); 1.76(1H, m); 1.92-2.03(4H, m); 2.36(1.5H, s); 2.46(1.5H, s); 2.49(1.5H, s); 2.54(1.5H, s); 3.73(0.5H, m); 3.91(0.5H, m); 6.06(0.5H, bs), 6.22(0.5H, bs); 6.85(1H, s); 6.93(1H, s). MS ESI: m/z (相对强度): M+H, 331.2 (100).

24.9　2-环己基氨基-4-(2-甲基咪唑-1-基)-6-甲基-5-硝基嘧啶



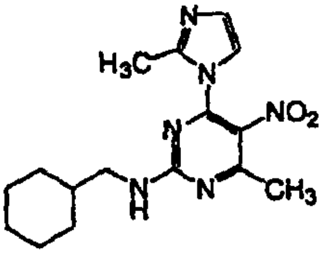
^{1}H NMR (400MHz, $CDCl_3$): δ 1.39(2H, m); 1.53(2H, m); 1.74(2H, m); 1.90(2H, m); 2.15(2H, m); 2.58(1.5H, s); 2.65(1.5H, s); 2.67(1.5H, s); 2.72(1.5H, s); 3.95(0.5H, m); 4.10(0.5H, m); 5.68(0.5H, d, J=4.0Hz), 5.79(0.5H, d, J=4.0Hz); 7.03(1H, s); 7.12(1H, s). MS ESI: m/z (相对强度): M+H, 317.2 (100).

24.10　2-环己基甲基氨基-4-(咪唑-1-基)-6-甲基-5-硝基嘧啶



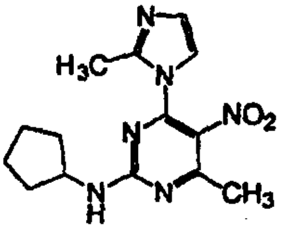
^{1}H NMR (400MHz, $CDCl_3$): δ 0.93-1.03(2H, m); 1.12-1.28(3H, m); 1.50-1.61(1H, m); 1.53-1.80(5H, m); 2.44(1.5H, s); 2.50(1.5H, s); 3.31(2H, dt, J=6.5, 24Hz); 5.88(0.5H, bs); 6.40(0.5H, bs); 7.10(0.5H, s); 7.13(1.5H, s), 7.19(0.5H, s); 8.07(1H, s). MS ESI m/z (相对强度): M+H, 317.2(100)

24.11 2-环己基甲基氨基-4-(2-甲基咪唑-1-基)-6-甲基-5-硝基嘧啶



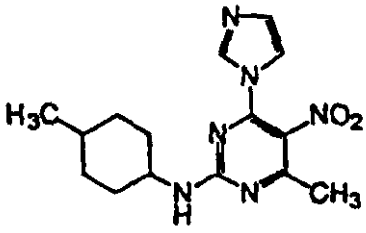
^{1}H NMR (400MHz, CDCl$_3$): δ 0.96(2H, m); 1.14-1.30(4H, m); 1.55(1H, m); 1.67(1H, m); 1.67-1.80(5H, m); 2.39(1.5H, s); 2.47(1.5H, s); 2.49(1.5H, s); 2.54(1.5H, s); 3.25(0.5H, t, J=6.3Hz); 3.35(0.5H, t, J=6.3Hz); 6.02(1H, bs), 6.86(1H, s); 6.95(1H, s). MS ESI m/z (相对强度): M+H, 331.2 (100).

24.12 2-环戊基氨基-4-(2-甲基咪唑-1-基)-6-甲基-5-硝基嘧啶



^{1}H NMR (400MHz, CDCl$_3$): δ 1.21(1H, m); 1.49(1H, m); 1.60-1.78(4H, m); 2.38(1.5H, s); 2.47(1.5H, s); 2.55(1.5H, s); 4.21(0.5H, m); 4.37(0.5H, m); 5.86(0.5H, d, J=4.2Hz); 5.98(0.5H, d, J=4.2Hz); 6.86(1H, s); 6.95(1H, s). MS ESI: m/z (相对强度): M+H, 303.2 (100).

24.13 2-(N-(4-甲基环己基)氨基)-4-(咪唑-1-基)-6-甲基-5-硝基嘧啶



^{1}H NMR (400 MHz, CDCl$_3$): δ 1.03(1.5H, d, J=6.2Hz); 1.06(1.5H, d, J=6.2Hz); 1.08(1H, m); 1.15-1.28(1H, m); 1.30-1.42(2H, m); 1.43-1.55(1H, m); 1.70-1.84(4H, m); 1.85-1.96(2H, m); 2.18(1H, m); 2.54(1.5H, s); 2.64(3H, s); 2.69(1.5H, s); 3.84(0.5H, m); 4.02(0.5H, m); 5.97(0.5H, bs), 6.11(0.5H, bs); 7.01(1H, s); 7.10(1H, s). MS ESI: m/z (相对强度): M+H, 331.1 (100).

在说明书中引用的所有公开物和专利申请在此并入本文供参考，恰如每个独立的公开物或专利申请特定地和单个地并入本文供参考。虽然本发明已以详细的方式进行了阐述，但它是为了便于理解而作出的阐述和例举，本技术领域人员应当明白可对其作出某些改变和修饰而不背离本发明的权利要求书的精神或范围。

说 明 书 附 图

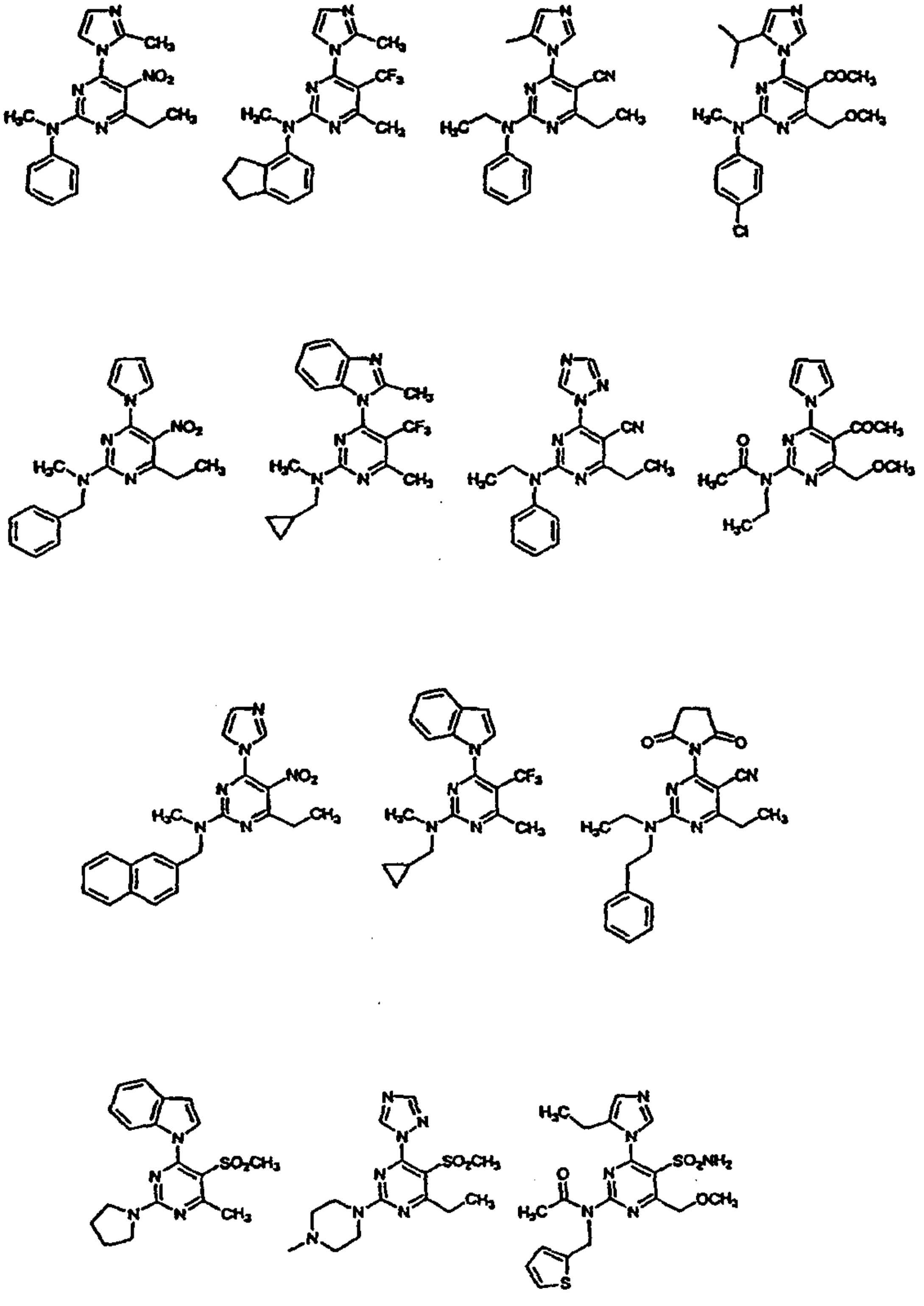
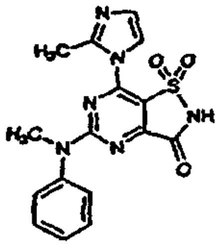


图 1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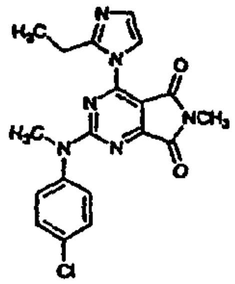
H3C
N
S
O
O
NH
N
H3C
N
N
O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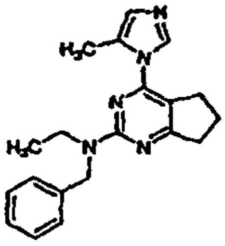
N
O
N
NCH3
H3C
N
N
O
Cl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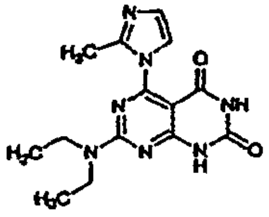
N
N
H3C
N
N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O
N
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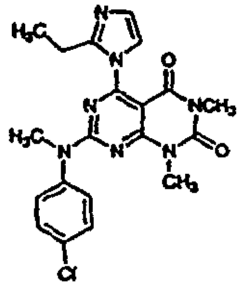
H3C
N
N
N
O
H
H3C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O
N
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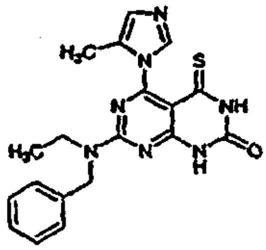
H3C
N
N
N
O
CH3
Cl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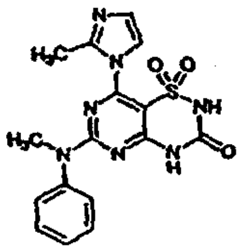
N
NH
H3C
N
N
N
O
H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NH
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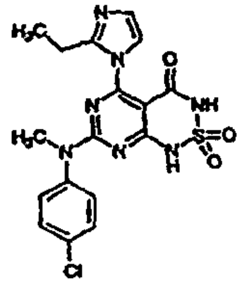
N
O
H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O
N
NH
H3C
N
N
N
S
O
O
H
Cl

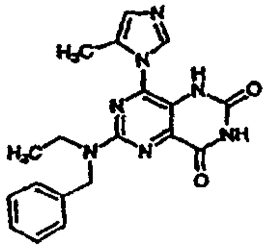
N
H3C
N
H
N
N
O
H3C
N
N
NH
O

图 2

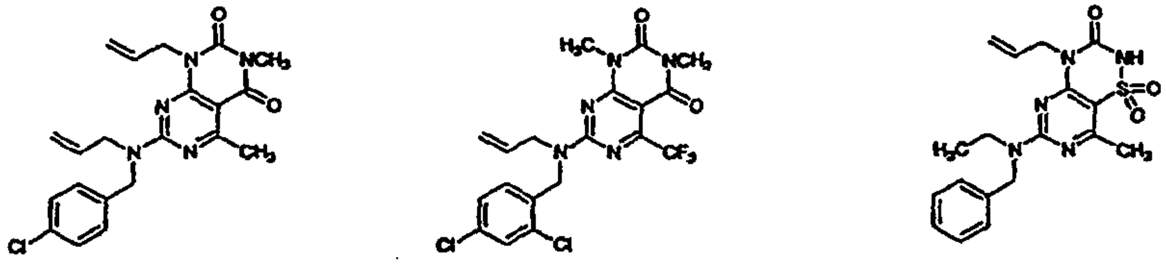

图 3

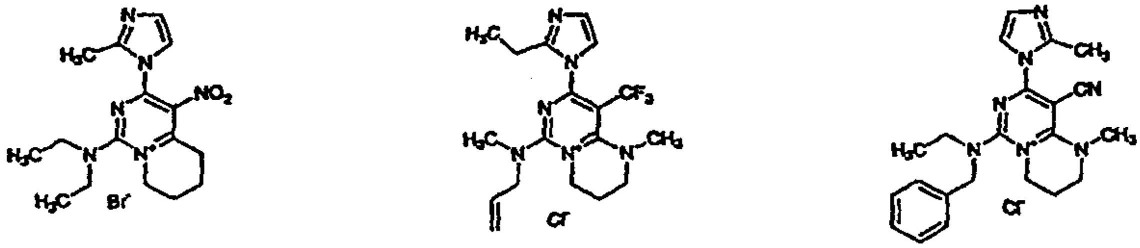

图 4

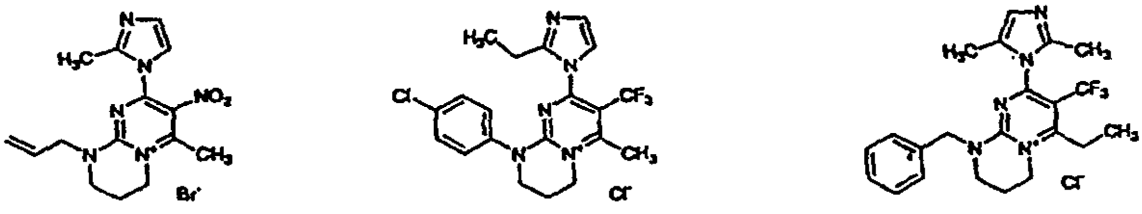

图 5

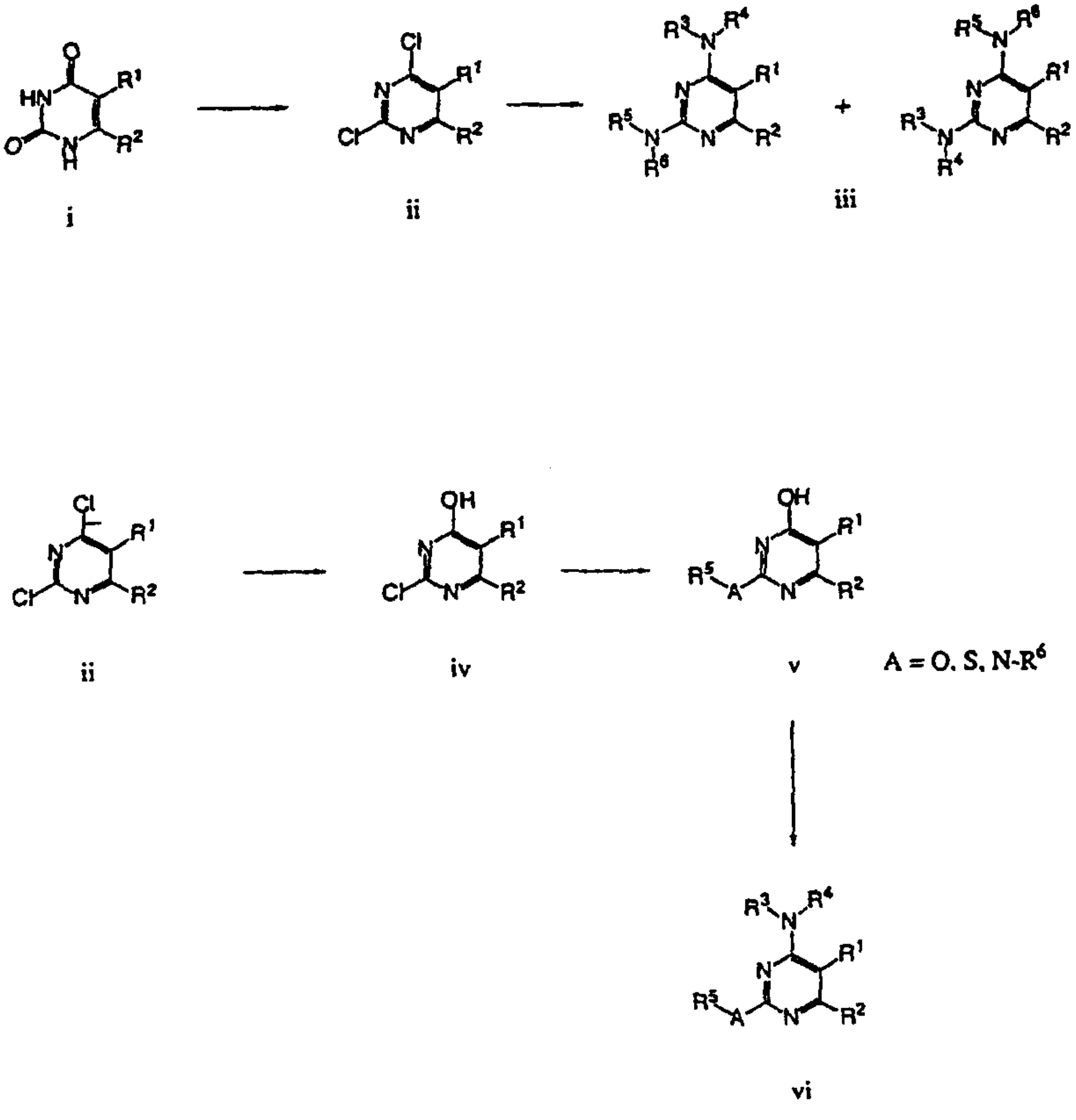

图 6

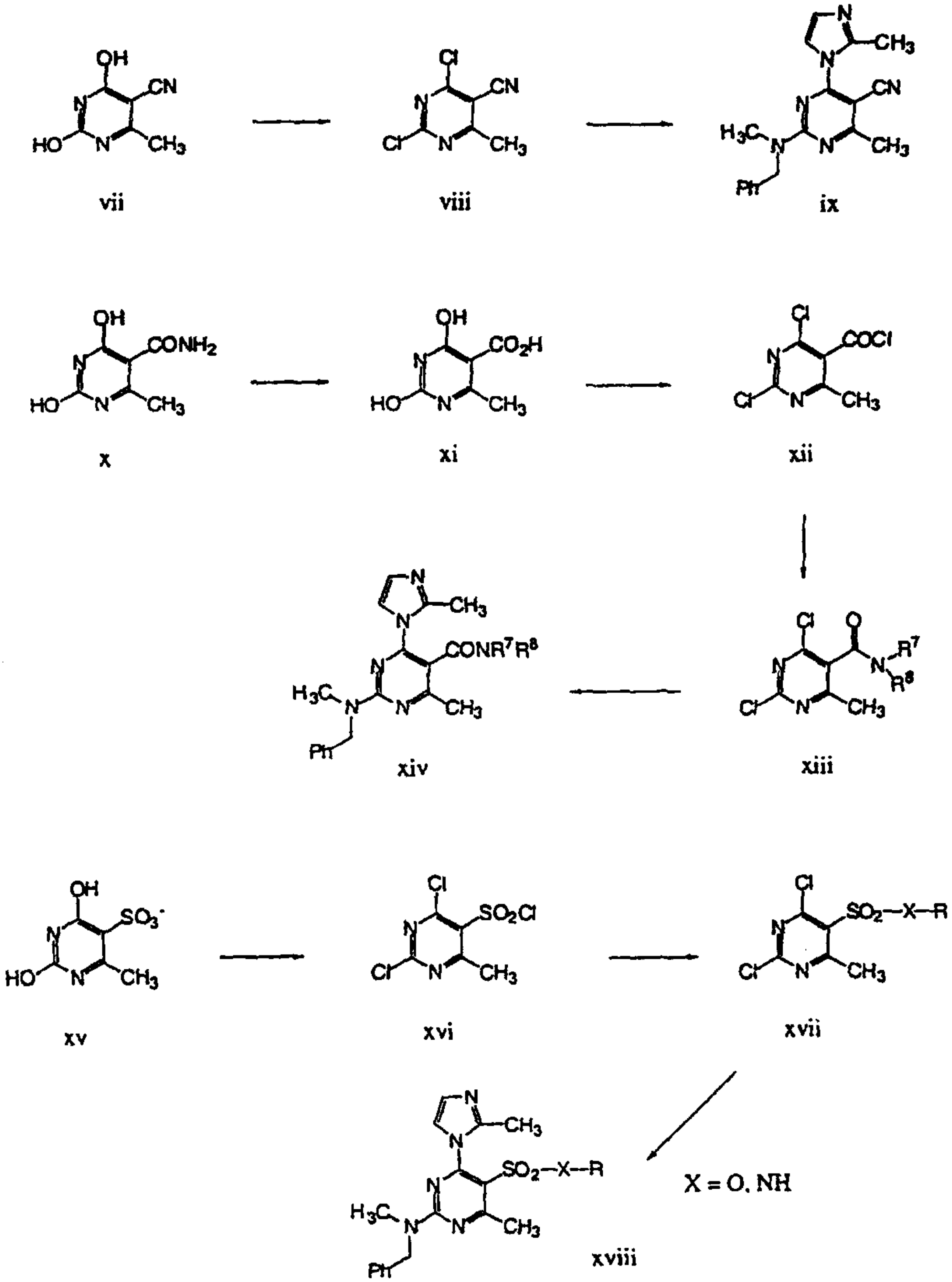

图 7

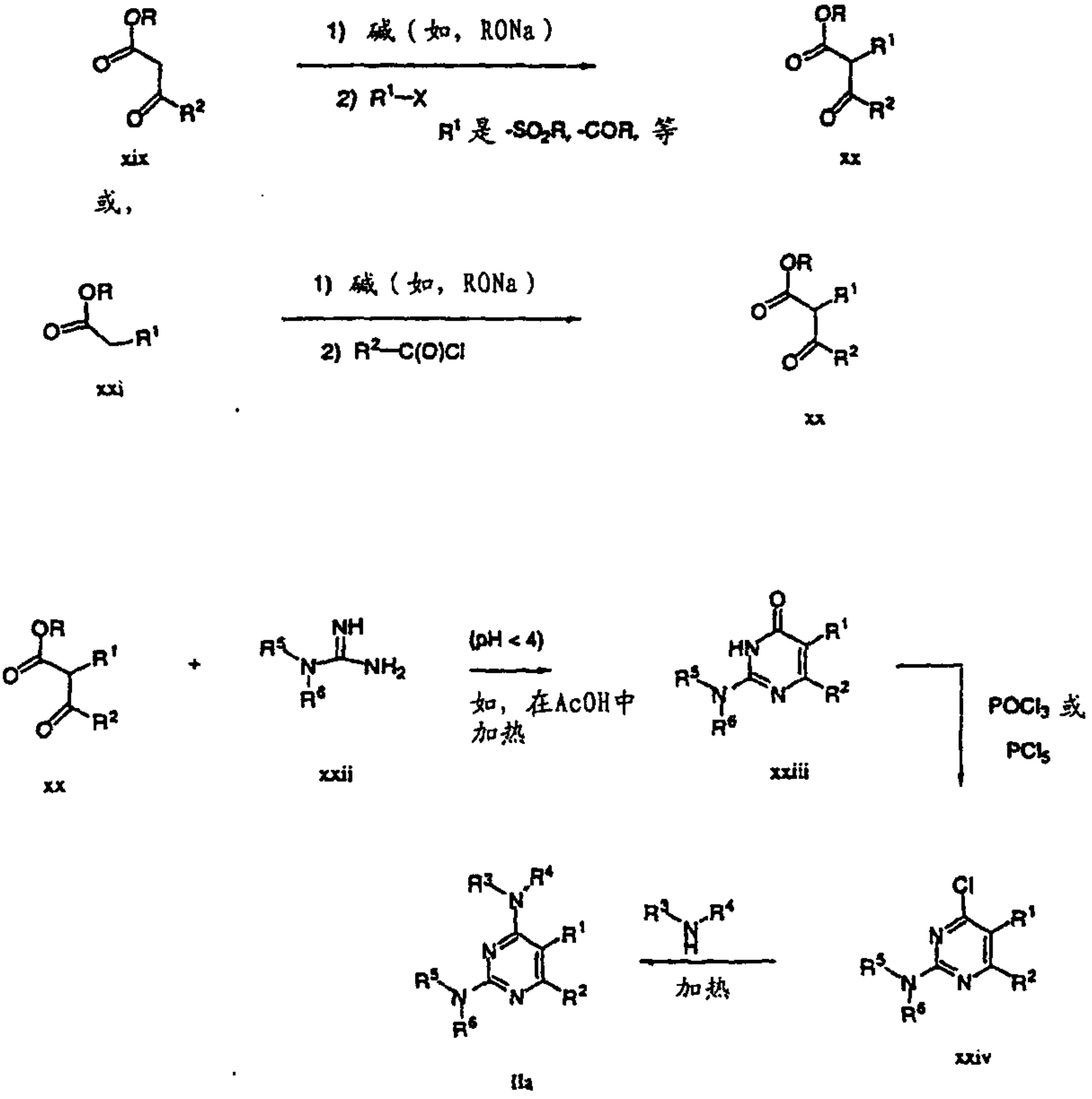
xix
1) 碱（如，RONa）
2) R^1—X
R^1 是 $-SO_2R$, -COR, 等
xx
或，
xxi
1) 碱（如，RONa）
2) R^2—C(O)Cl
xx
xx
xxii
(pH < 4)
如，在AcOH中加热
xxiii
$POCl_3$ 或 PCl_5
xxiv
加热
IIa

图 8

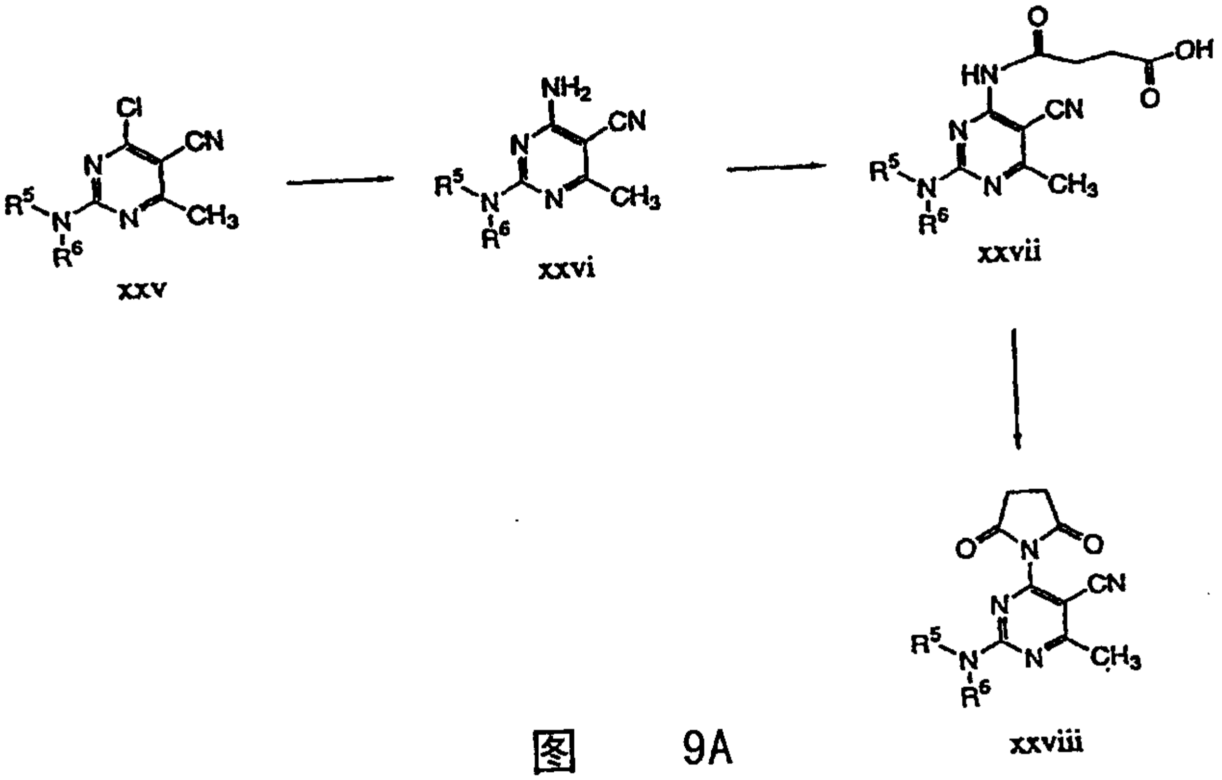
Cl
CN
N
R5
N
N
CH3
R6
xxv
NH2
CN
N
R5
N
N
CH3
R6
xxvi
O
HN
OH
O
CN
N
R5
N
N
CH3
R6
xxvii
O
N
O
CN
N
R5
N
N
CH3
R6
xxviii

图 9A


R3
R4
N
SO2NH2
N
R5
N
N
CH2OCH3
H
xxix
R3
R4
N
SO2NH2
N
R5
N
N
CH2OCH3
H3C
O
xxx

图 9B

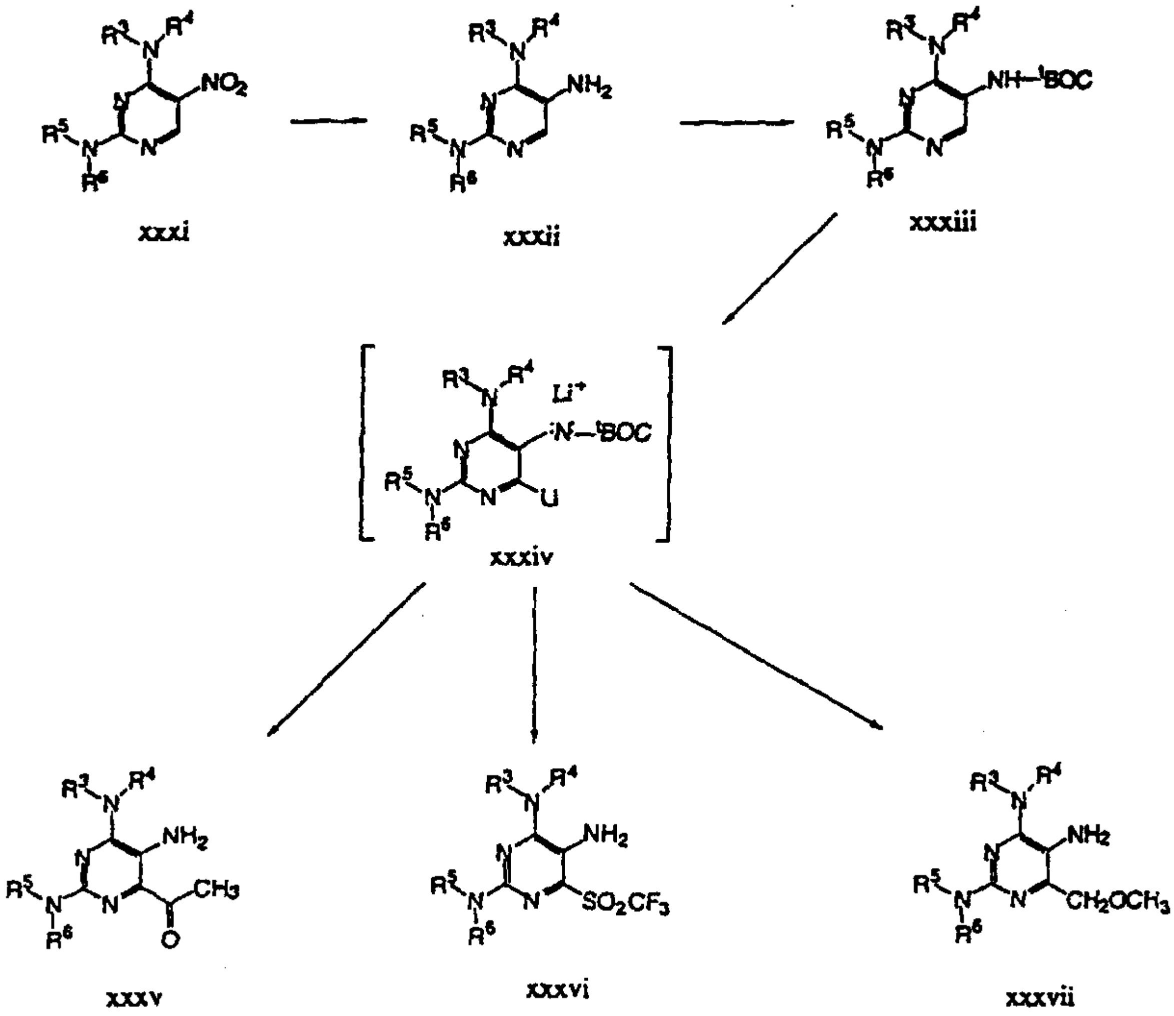
R3
R4
NO2
R5
R6
N
xxxi
NH2
xxxii
NH—tBOC
xxxiii
Li+
N—tBOC
Li
xxxiv
CH3
O
xxxv
SO2CF3
xxxvi
CH2OCH3
xxxvii

图　　9C

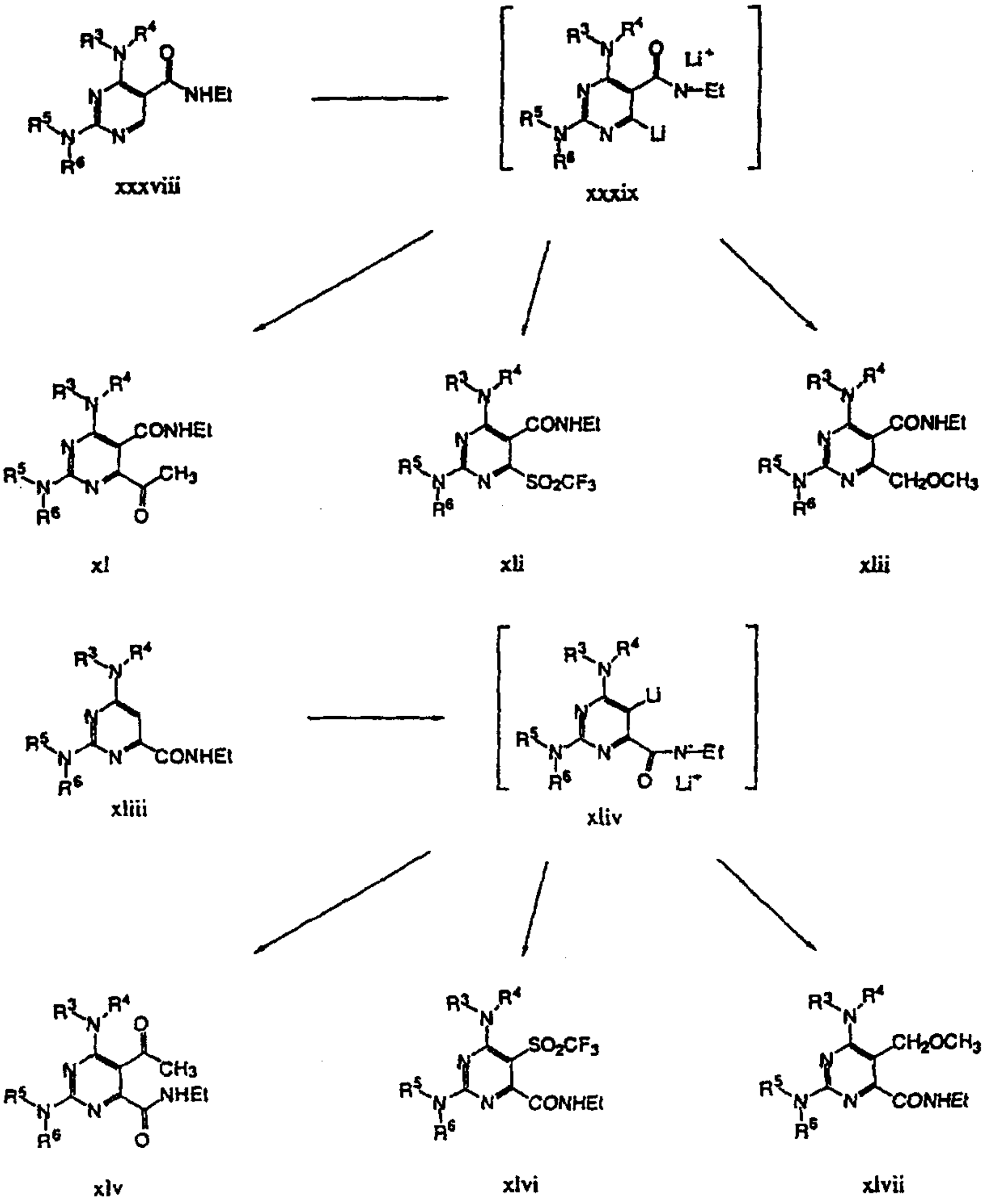
xxxviii
xxxix
xl
xli
xlii
xliii
xliv
xlv
xlvi
xlvii
NHEt
CONHEt
Li⁺
Li
SO₂CF₃
CH₂OCH₃
CH₃

图 9D

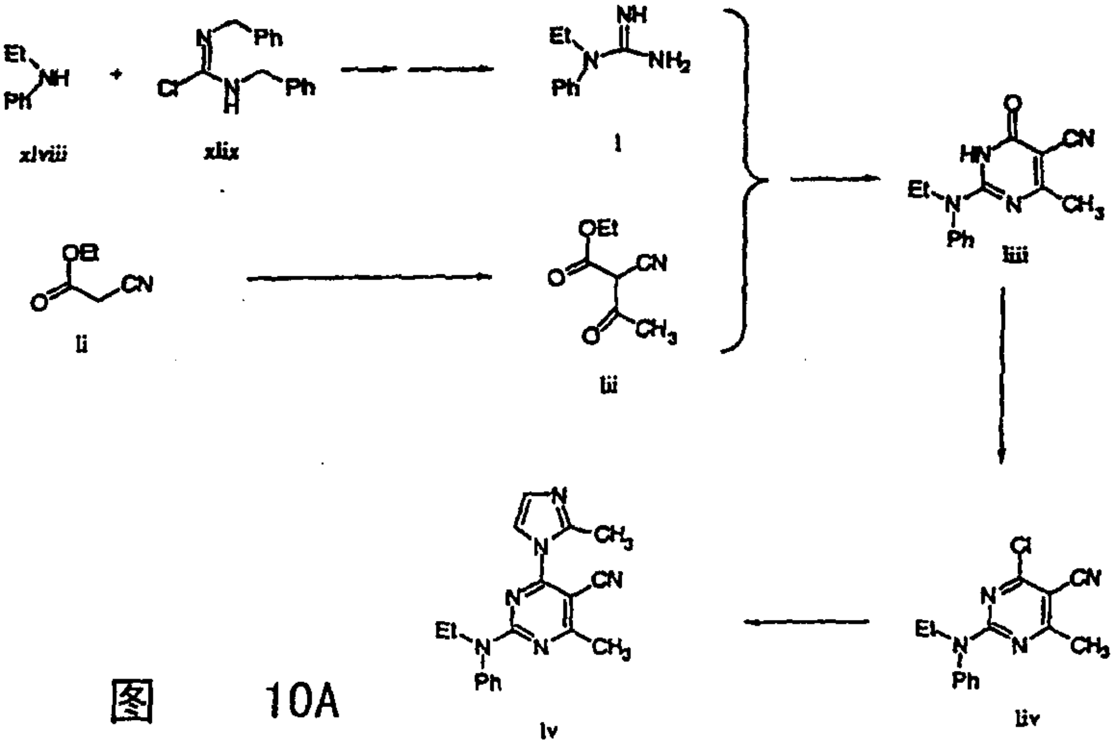
Et
NH
Ph
xlviii
+
N
Ph
Cl
N
H
Ph
xlix
NH
Et
N
NH2
Ph
l
OEt
O
CN
li
OEt
O
CN
O
CH3
lii
O
HN
CN
Et
N
N
CH3
Ph
liii
Cl
N
CN
Et
N
N
CH3
Ph
liv
N
N
CH3
N
CN
Et
N
N
CH3
Ph
lv

图 10A

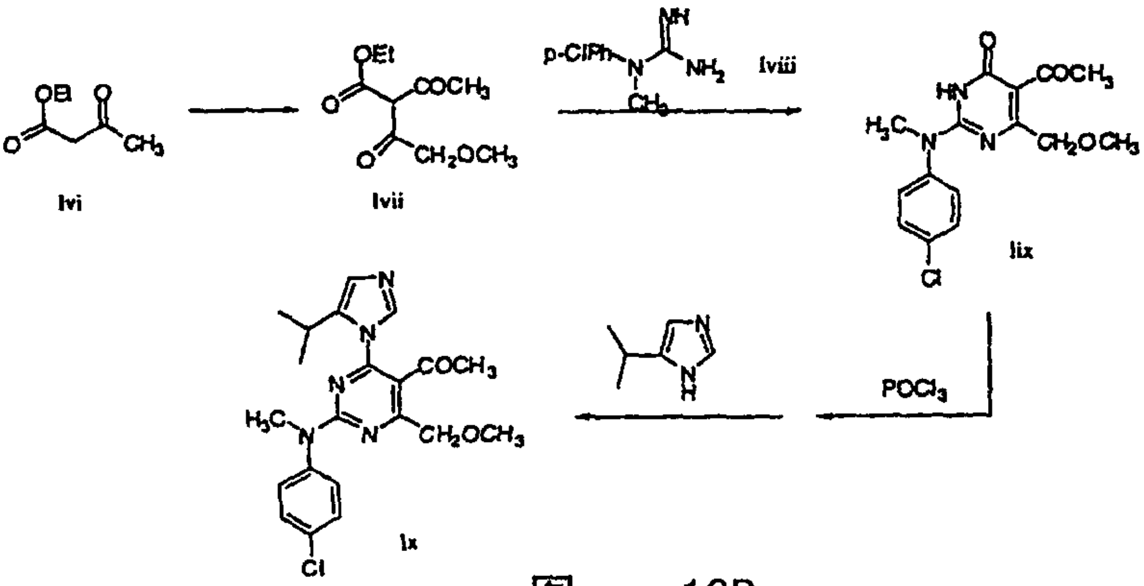
OEt
O
CH3
O
lvi
OEt
O
COCH3
O
CH2OCH3
lvii
NH
p-ClPh
N
NH2
CH3
lviii
O
HN
COCH3
H3C
N
N
CH2OCH3
Cl
lix
POCl3
N
N
H
N
N
N
COCH3
H3C
N
N
CH2OCH3
Cl
lx

图 10B

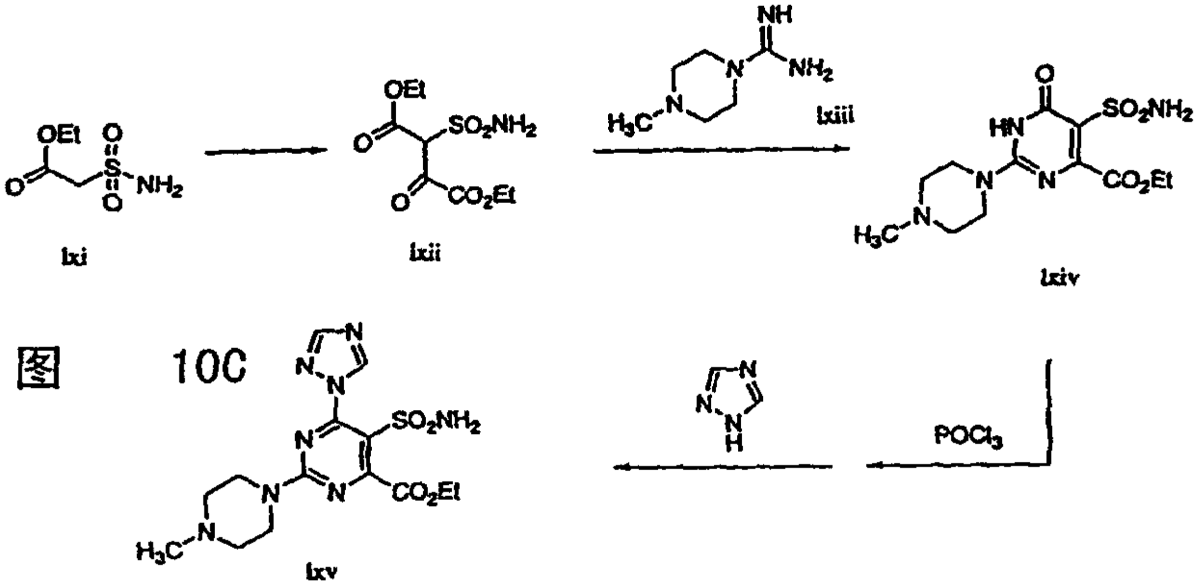
lxi
lxii
lxiii
lxiv
lxv
POCl3
OEt
SO2NH2
CO2Et
NH
NH2
H3C
HN
N
H

图 10C

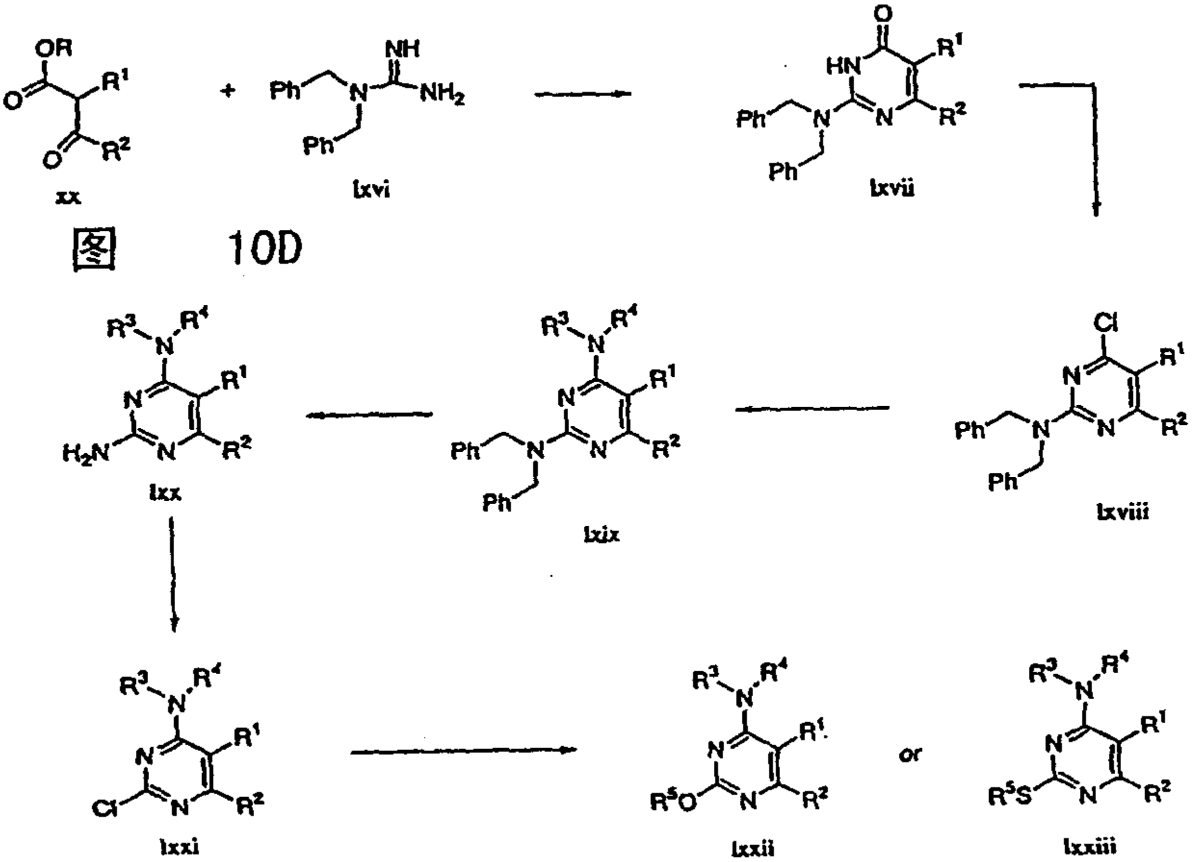
xx
lxvi
lxvii
lxviii
lxix
lxx
lxxi
lxxii
lxxiii
or
OR
R1
R2
R3
R4
R5O
R5S
Ph
NH
NH2
HN
H2N
Cl

图 10D

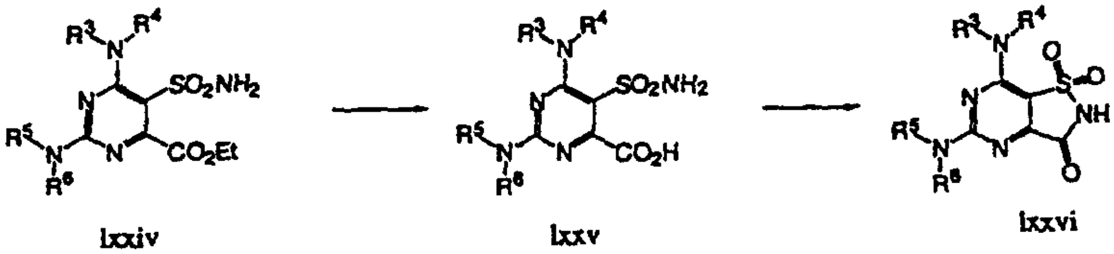
SO2NH2
CO2Et
CO2H
R3
R4
R5
R6
N
NH
O
lxxiv
lxxv
lxxvi

图 11A

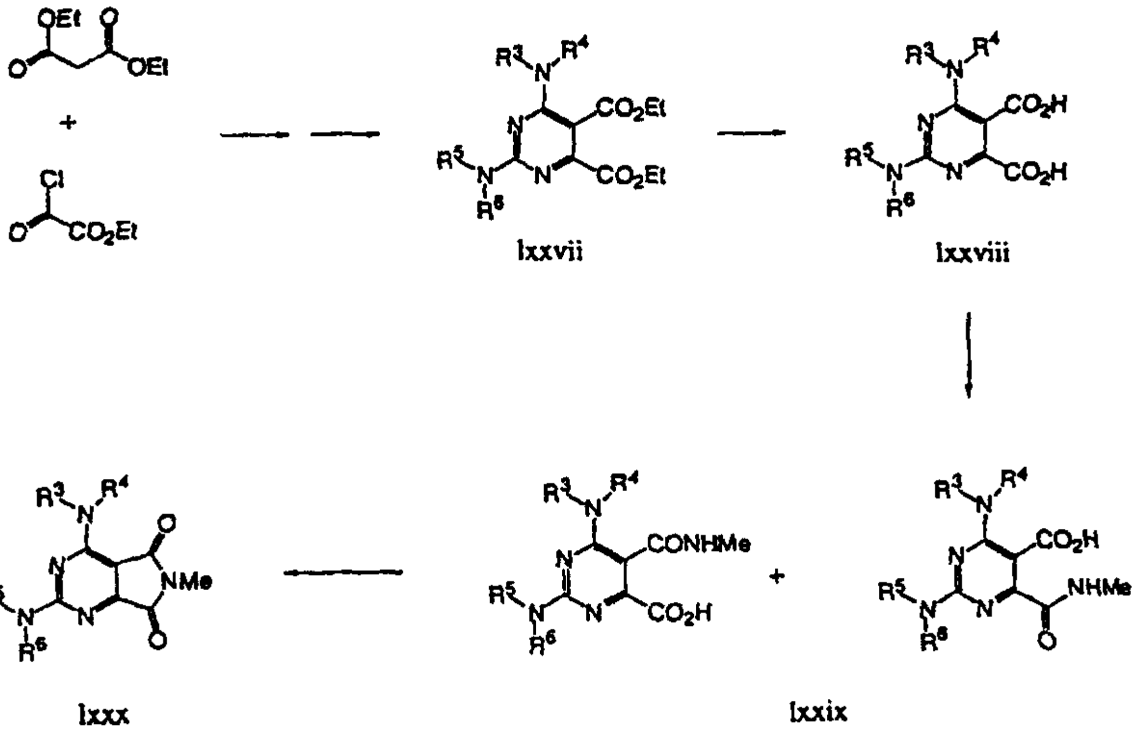
OEt
O
Cl
+
CO2Et
CO2H
CONHMe
NHMe
NMe
R3
R4
R5
R6
N
lxxvii
lxxviii
lxxix
lxxx

图 11B

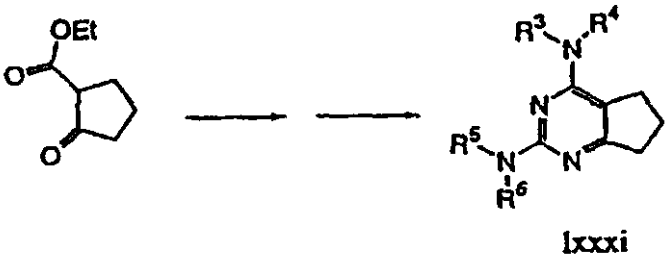
OEt
O
O
R3
R4
N
N
N
R5
N
R6
lxxxi

图 11C

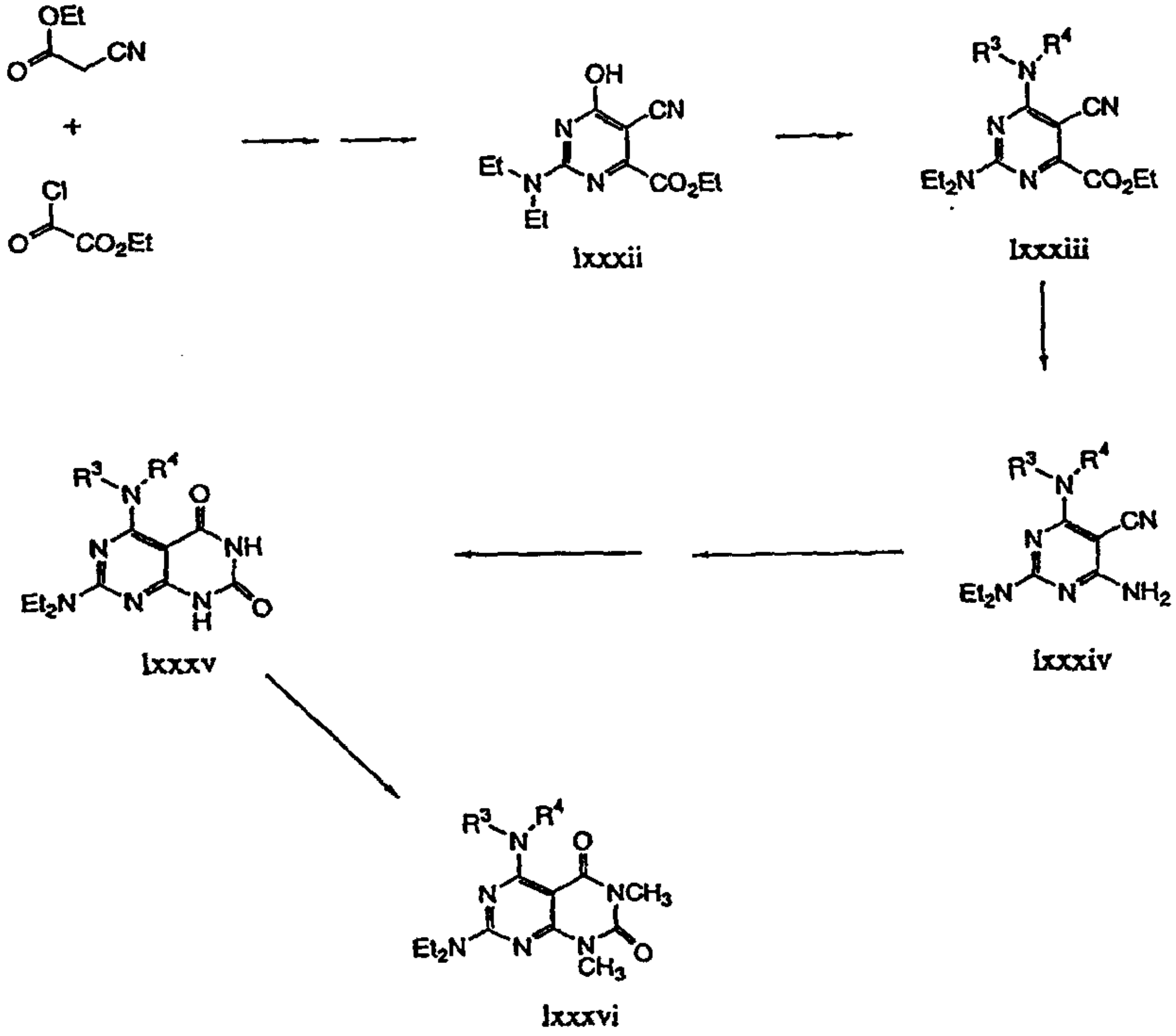
OEt
O
CN
+
Cl
O
CO2Et
OH
N
CN
Et
N
Et
N
CO2Et
lxxxii
R3
R4
N
N
CN
Et2N
N
CO2Et
lxxxiii
R3
R4
N
N
CN
Et2N
N
NH2
lxxxiv
R3
R4
N
O
N
NH
Et2N
N
N
H
O
lxxxv
R3
R4
N
O
N
NCH3
Et2N
N
N
CH3
O
lxxxvi

图 11D

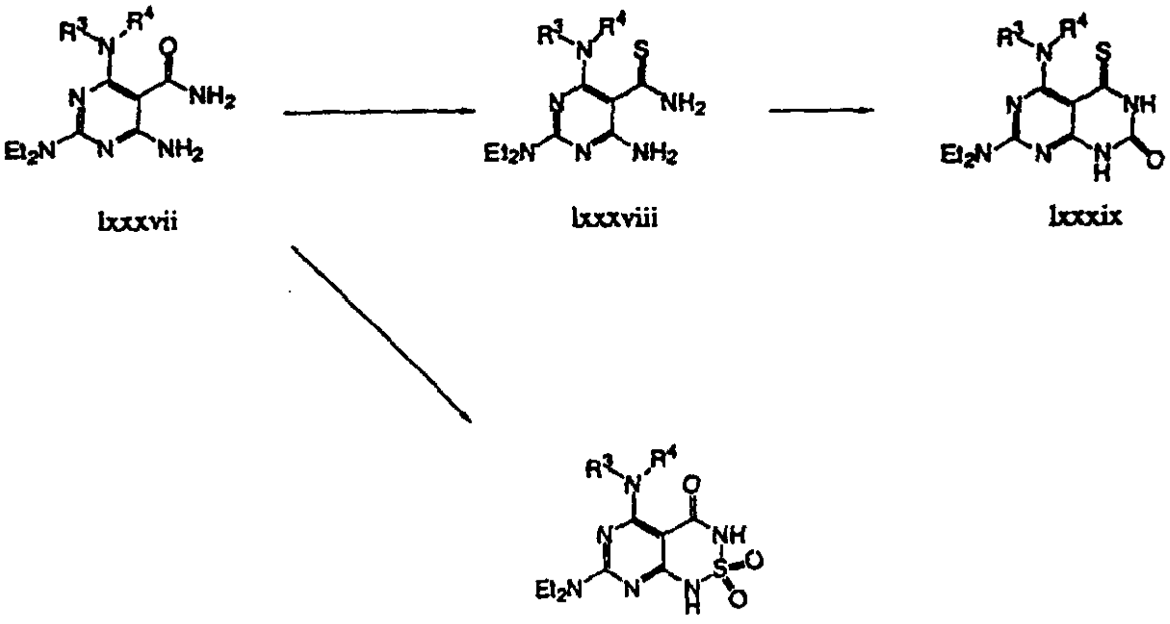

图 11E

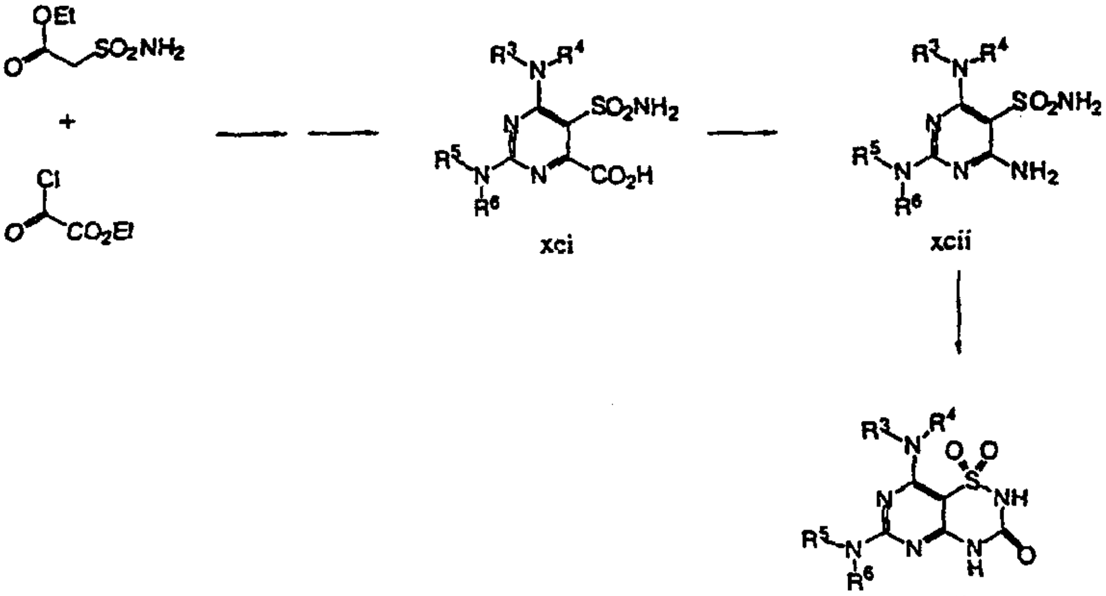

图 11F

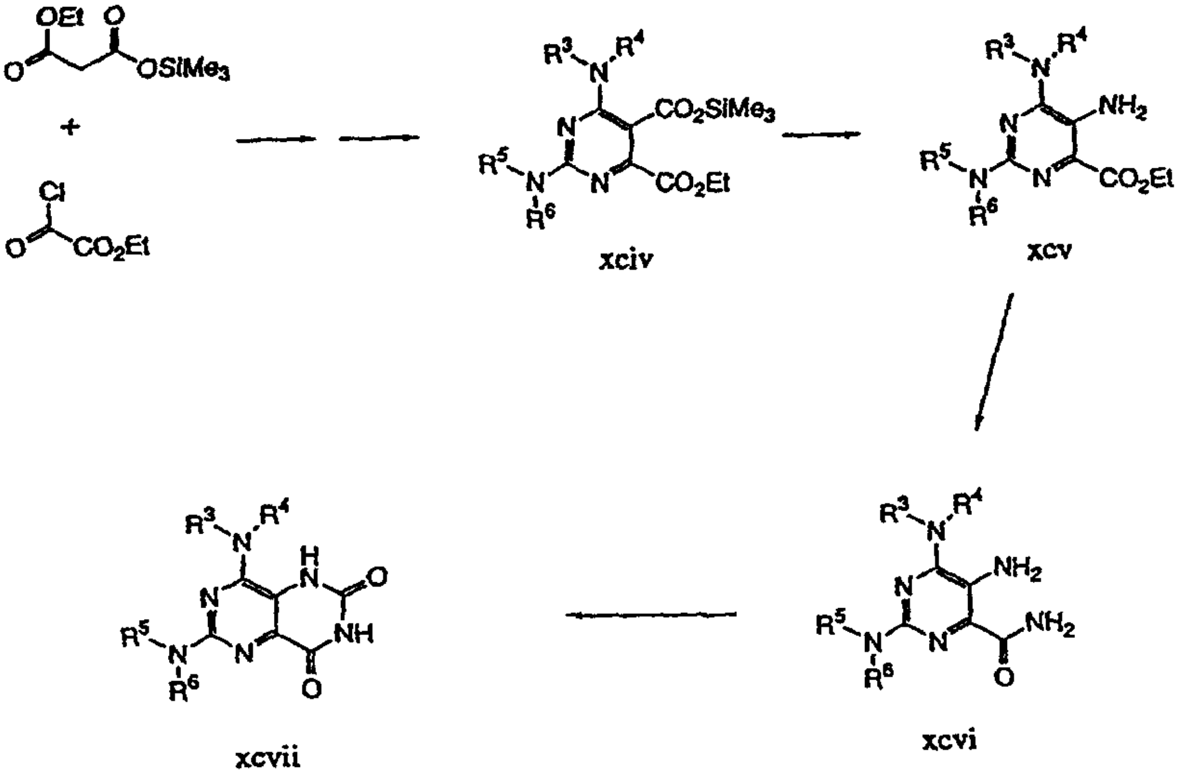
OEt
O
O
OSiMe3
+
Cl
O
CO2Et
R3
R4
N
N
CO2SiMe3
R5
N
N
CO2Et
R6
xciv
NH2
xcv
NH2
O
xcvi
H
N
O
NH
O
xcvii

图 11G

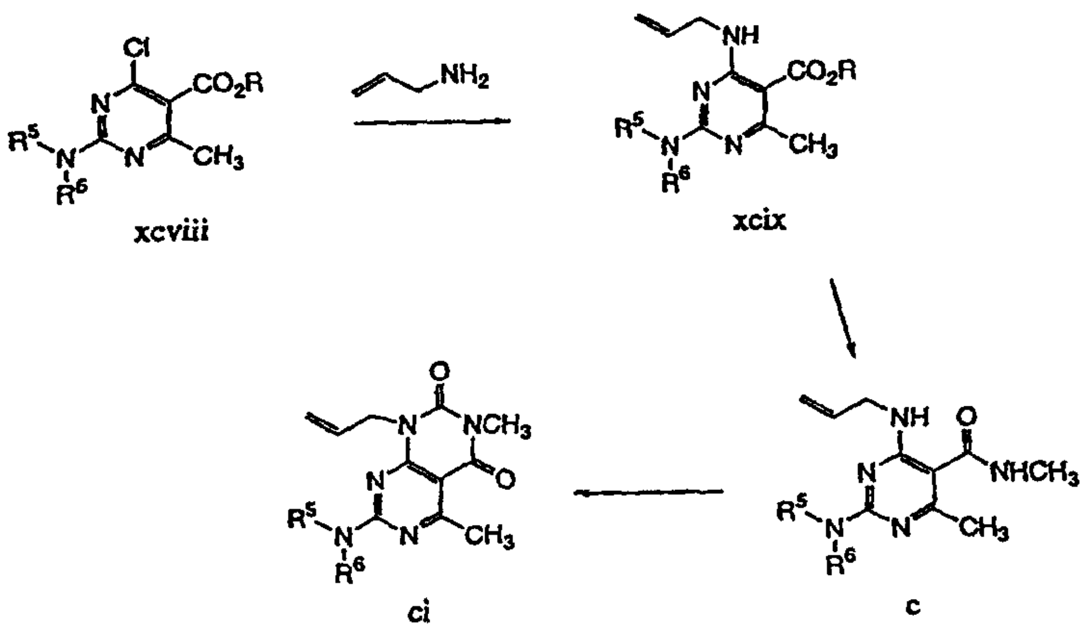

图 12A

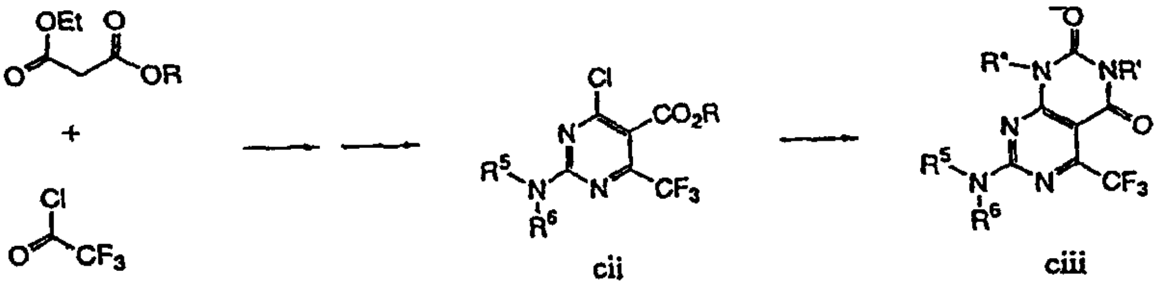

图 12B

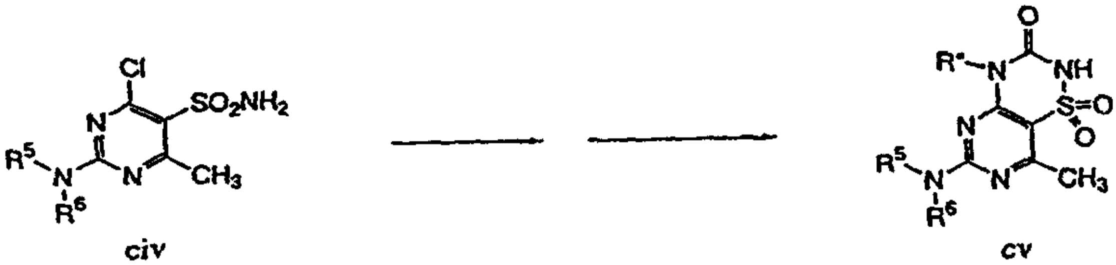

图 12C

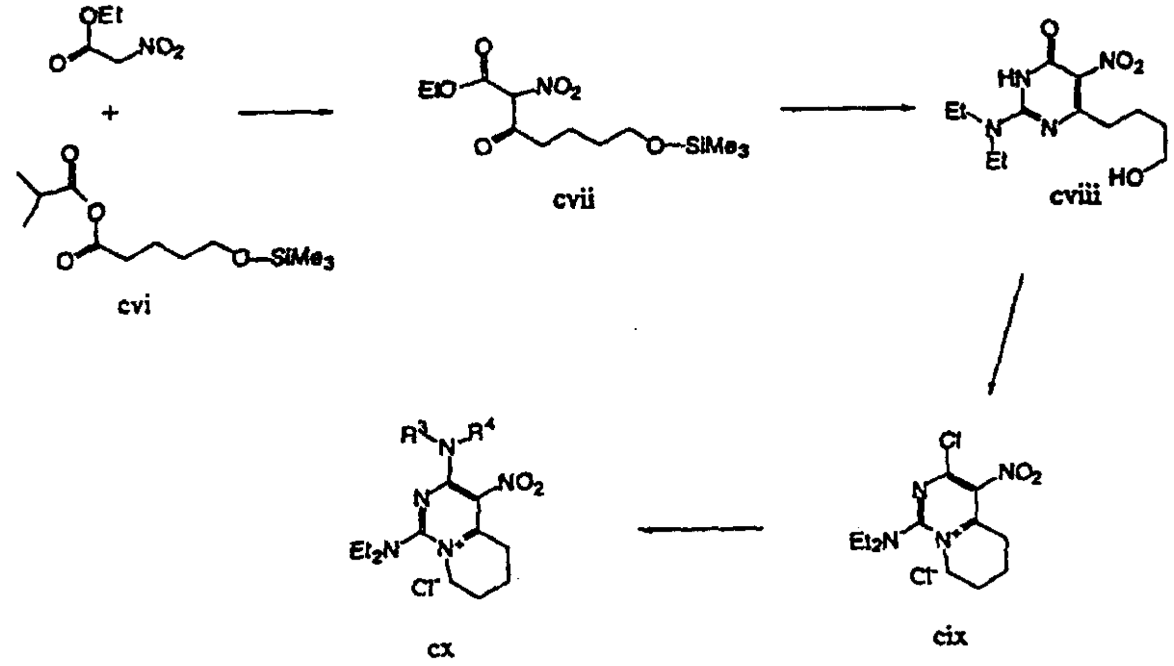
OEt
NO2
O
+
O
O
O
O—SiMe3
cvi
O
EtO
NO2
O
O—SiMe3
cvii
O
HN
NO2
Et
N
Et
N
HO
cviii
Cl
N
NO2
Et2N
N+
Cl-
cix
R3
N
R4
N
NO2
Et2N
N+
Cl-
cx

图 13

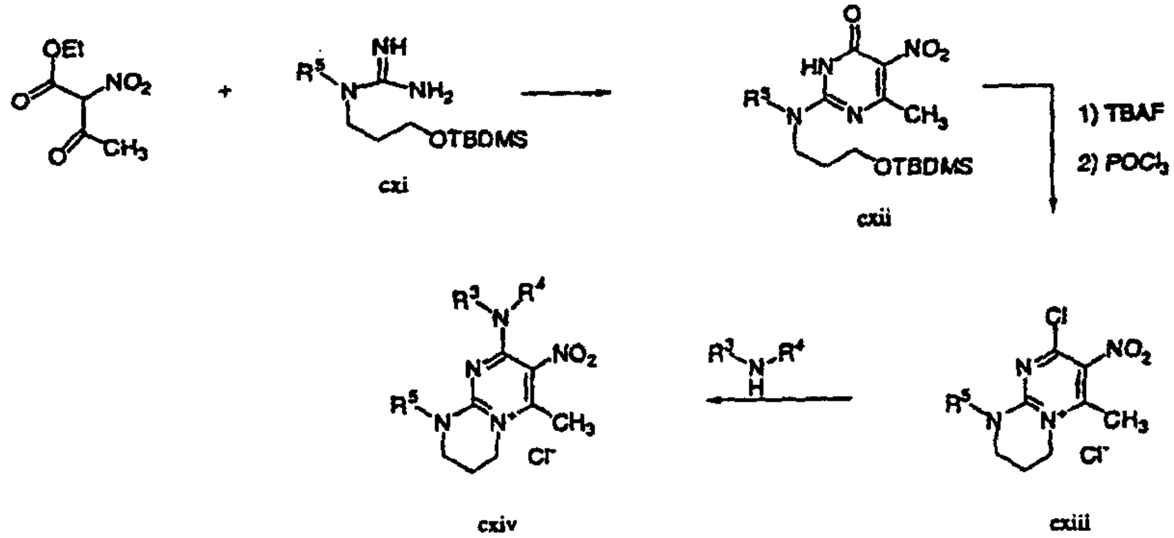
OEt
NO2
O
O
CH3
+
R5
NH
NH2
OTBDMS
cxi
O
HN
NO2
R5
N
N
CH3
OTBDMS
cxii
1) TBAF
2) POCl3
Cl
N
NO2
R5
N
N+
CH3
Cl-
cxiii
R3
N
R4
H
R3
N
R4
N
NO2
R5
N
N+
CH3
Cl-
cxiv

图 14