5-ALKYLPYRIDO[2,3-d]PYRIMIDINES TYROSINE KINASE INHIBITORS

FIELD OF THE INVENTION

This invention relates to 5-alkylpyridopyrimidines as inhibitors of cyclin-dependent kinases, particularly cyclin-dependent kinase 4. The compounds of the invention are useful for the treatment of inflammation, cell proliferative diseases such as cancer and restenosis, and neurodegenerative diseases such as Alzheimer's disease.

SUMMARY OF THE RELATED ART

Cyclin-dependent kinases and related serine/threonine protein kinases are cellular enzymes that perform essential functions in regulating cell division and proliferation. The cyclin-dependent kinase catalytic units, of which nine have been identified, are activated by regulatory units known as cyclines. The cyclin-dependent kinases include (Cdk) Cdk1, Cdk2, Cdk4, Cdk5, Cdk6, and Wee-1 kinase. Increased activity or temporally abnormal activation of these kinases results in development of human tumors and other proliferative disorders such as restenosis. Compounds that inhibit Cdks, either by blocking the interaction between a cyclin and its kinase partner, or by binding to and inactivating the kinase, cause inhibition of cell proliferation and thus are useful for treating tumors and other abnormally proliferating cells.

Several compounds that inhibit Cdks have demonstrated both preclinical and clinical anti-tumor activity. For example, flavopiridol is a flavonoid that is a potent inhibitor of Cdk2 and Cdk4, and has been shown to inhibit several types of breast and lung cancer cells (Kaur et al., *J. Natl. Cancer Inst.*, 1992;84:1736-1740; Kaur et al., *Int. J. Oncol.*, 1996;9:1143-1168). In addition, Olomoucine [2-(hydroxyethylamine)-6-benzylamine-9-methylpurine] is a potent inhibitor of Cdk2 and Cdk5 (Vesely et al., *Eur. J. Biochem.*, 1994;224:771-786), and has been shown to inhibit proliferation of approximately 60 different human tumor cell

lines used by the National Cancer Institute (NCI) to screen for new cancer therapies (Abraham et al., *Biol. Cell*, 1995;83:105-120).

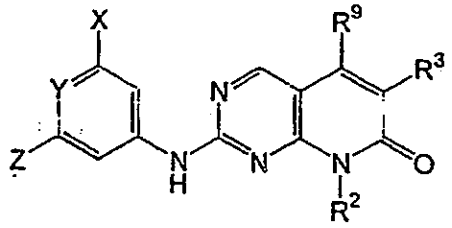
In addition to treating cancer, Cdk inhibitors have been shown to treat cardiovascular disorders such as restenosis and atherosclerosis. Other diseases in which Cdk inhibitors are useful include those caused by a variety of infectious agents, including DNA and RNA viruses, and inflammatory disorders such as rheumatoid arthritis.

An object of this invention is to provide a group of small molecular weight organic compounds that are potent Cdk inhibitors, and as such are useful for preventing and treating diseases caused by abnormally proliferating cells.

SUMMARY OF THE INVENTION

This invention provides 5-alkyl pyridopyrimidines that are useful for treating inflammation, cell proliferative diseases such as cancer and restenosis, and neurodegenerative diseases such as Alzheimer's disease. The compounds of the invention display unexpected improvements in pharmacokinetic properties over prior art compounds, including unanticipated metabolic stability and low clearance rates. In addition, the compounds of the invention are unexpectedly selective inhibitors of Cdk4. The compounds of the invention are readily synthesized, and can be administered to patients by a variety of methods.

A first aspect of the present invention provides a compound of Formula I:



I

and pharmaceutically acceptable salts, esters, amides, and prodrugs thereof, wherein:

R^2 is (a) hydrogen;

(b) lower alkyl optionally substituted with one, two, or three groups independently selected from halogen, hydroxy, lower alkoxy, amino, mono- or dialkylamino, carboxy, alkoxycarbonyl, thio alkyl, nitrile, aryl, heteroaryl, or a carbocyclic group containing from 3 to 7 members, up to two of which members are optionally heteroatoms independently selected from oxygen, sulfur, and nitrogen; or

(c) a carbocyclic group containing from 3 to 7 members, up to two of which members are optionally heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the carbocyclic group is unsubstituted or substituted with one, two, or three groups independently selected from halogen, hydroxy, lower alkyl, lower alkoxy, amino, mono- or dialkylamino, aryl, and heteroaryl;

R^3 is hydrogen, lower alkyl, lower alkoxy, halogen, trifluoromethyl, lower alkynyl, lower alkenyl, nitrile, nitro, $-COR^4$, $-CO_2R^4$, $-CONR^4R^5$, $CONOR^5$, $-SO_2NR^4R^5$, $-SO_2R^4$, $-SO_3R^4$, $P(O)(OR^4)(OR^5)$, or

$$\begin{array}{l} | \\ R^4 \end{array}$$

$-NR^4R^5$;

Y is N or CR^7;

R^9 is lower alkyl, haloalkyl, or aryl;

X and Z are independently hydrogen, halogen, lower alkyl, lower alkoxy, trifluoromethyl, hydroxy, nitrile, nitro, $-NR^4R^5$, $-N(O)R^4R^5$, $-NR^4R^5R^6W$, $-SR^4$, $-C(O)R^4$, $-CO_2R^4$, $-CONR^4R^5$, $-SO_2NR^4R^5$, $-SO_2R^4$, $-SO_3R^4$, $P(O)(OR^4)(OR^5)$, $-T(CH_2)_mQR^4$, $-C(O)T(CH_2)_mQR^4$, or $-NR^4C(O)T(CH_2)_mQR^5$;

m is 1-6;

T is O, S, NR^4, $N(O)R^4$, NR^4R^5W, or CR^4R^5;

Q is O, S, NR^4, $N(O)R^4$, NR^4R^5W, CO_2, or a carbocyclic group containing from 3 to 7 members, up to four of which members are optionally heteroatoms

independently selected from oxygen, sulfur, and nitrogen, wherein the carbocyclic group is unsubstituted or substituted with one, two, or three groups independently selected from halogen, hydroxy, hydroxyalkyl, lower alkyl, lower alkoxy, alkoxycarbonyl, alkylcarbonyl, alkylcarbonylamino, aminoalkyl, trifluoromethyl, N-hydroxyacetamide, trifluoromethylalkyl, amino, or mono or dialkylamino;

R^6 is lower alkyl, haloalkyl, or aryl;

R^7 is NR^4R^5, $N(O)R^4R^5$, $NR^4R^5R^9W$, OH, OR^4, SR^4, halo, COR^4, $(CH_2)_nR^4$, CO_2R^4, $CONR^4R^5$, $C(O)NR^4SO_2R^5$, $S(O)R^4$, SO_2R^4, $SO_2NR^4R^5$, SO_3R^4, $(CH_2)_nP(O)(OR^4)_2$, $NR^4SO_2R^5$, aldehyde, nitrile, nitro, alkyl, alkoxyalkyl, $T(CH_2)_mQR^4$, $C(O)T(CH_2)_mQR^4$, $NR^4C(O)T(CH_2)_mQR^5$, or $T(CH_2)_mCO_2R^4$;

n is 0 to 6;

W is an anion;

R^4 and R^5 are independently hydrogen, lower alkyl, lower alkenyl, lower alkynyl, $(CH_2)_nAr$, arylalkyl, aryl, heteroaryl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, or heteroaryl, or R^4 and R^5 together with the nitrogen to which they are attached form a carbocyclic ring containing 3 to 8 members, up to four of which members are optionally carbonyl groups or heteroatoms independently selected from oxygen, sulfur, S(O), $S(O)_2$, and nitrogen, wherein the carbocyclic group is unsubstituted or substituted with one, two, three, or four groups independently selected from halogen, hydroxy, hydroxyalkyl, lower alkyl, lower alkoxy, alkoxycarbonyl, alkylcarbonyl, alkylcarbonylamino, aminoalkyl, aminoalkylcarbonyl, trifluoromethyl, trifluoromethylalkyl, trifluoromethylalkylaminoalkyl, amino, mono- or dialkylamino, N-hydroxyacetamido, aryl, heteroaryl, carboxyalkyl, $NR^{10}SO_2R^{11}$, $C(O)NR^{10}R^{11}$, $NR^{10}C(O)R^{11}$, $C(O)OR^{10}$, $C(O)NR^{10}SO_2R^{11}$, $(CH_2)_nS(O)_nR^{10}$, $(CH_2)_n$-heteroaryl, $O(CH_2)_n$-heteroaryl, $(CH_2)_nC(O)NR^{10}R^{11}$, $O(CH_2)_nC(O)OR^{10}$;

and R^4 additionally can be lower alkyl unsubstituted or substituted with one, two, or three groups independently selected from halogen, 5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl-sulfanyl, 5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl-sulfinyl, 5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl-sulfonyl, or a carbocyclic group containing from 3 to 7 members, up to four of which members are optionally heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the carbocyclic group is unsubstituted or substituted with one, two, or three groups independently selected from halogen, hydroxy, hydroxyalkyl, lower alkyl, lower alkoxy, alkoxycarbonyl, alkylcarbonyl, alkylcarbonylamino, aminoalkyl, trifluoromethyl, N-hydroxyacetamide, trifluoromethylalkyl, amino, or mono- or dialkylamino; and

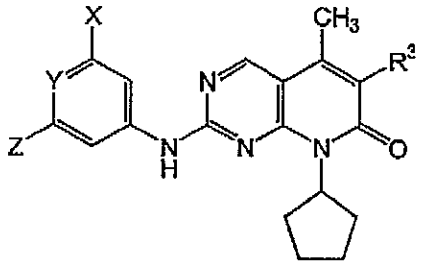
R^{10} and R^{11} are independently hydrogen, halogen, lower alkyl, lower alkoxy, or alkylcarbonyl ;

with the proviso that when, R^3 is hydrogen, lower alkyl, lower alkoxy, halogen, nitrile, nitro, $-CO_2R^4$, $CONR^4OR^5$, or $-NR^4R^5$, then R^9 is not C_1-C_3 alkyl.

Embodiments may provide preferred compounds of Formula I wherein Y is CR^7. Of this group, preferred compounds may be those wherein R^7 is NR^4R^5, and R^4 and R^5 can be taken

together with the N to which they are attached to form a ring such as piperazine, piperidine, pyrrolidine, morpholine, each of which can be optionally substituted.

A second aspect of the present invention provides a compound of the Formula II



II

and pharmaceutically acceptable salts, esters, amides, and prodrugs thereof, wherein:

R^3 is trifluoromethyl, lower alkynyl, lower alkenyl, $-COR^4$, $CONR^4OR^5$, $-SO_2NR^4R^5$, $-SO_2R^4$, $-SO_3R^4$, or $-P(O)(OR^4)(OR^5)$;
|
R^4

Y is N or CR^7;

X and Z are independently hydrogen, halogen, lower alkyl, lower alkoxy, trifluoromethyl, hydroxy, nitrile, nitro, $-NR^4R^5$, $-N(O)R^4R^5$, $-NR^4R^5R^6W$, $-SR^4$, $-C(O)R^4$, $-CO_2R^4$, $-CONR^4R^5$, $-SO_2NR^4R^5$, $-SO_2R^4$, $-SO_3R^4$, $P(O)(OR^4)(OR^5)$, $-T(CH_2)_mQR^4$, $-C(O)T(CH_2)_mQR^4$, or $-NR^4C(O)T(CH_2)_mQR^5$;

m is 1 to 6;

T is O, S, NR^4, $N(O)R^4$, NR^4R^5W, or CR^4R^5;

Q is O, S, NR^4, $N(O)R^4$, NR^4R^5W, CO_2, or a carbocyclic group containing from 3 to 7 members, up to four of which members are optionally heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the carbocyclic group is unsubstituted or substituted with one, two, or three groups independently selected from halogen, hydroxy, hydroxyalkyl, lower alkyl, lower alkoxy, alkoxycarbonyl, alkylcarbonyl, alkylcarbonylamino, aminoalkyl, trifluoromethyl, N-hydroxyacetamide, trifluoromethylalkyl, amino, or mono or dialkylamino;

R^6 is lower alkyl, haloalkyl, or aryl;

R^7 is NR^4R^5, $N(O)R^4R^5$, $NR^4R^5R^9X$, OH, OR^4, SR^4, halo, COR^4, $(CH_2)_nR^4$, CO_2R^4, $CONR^4R^5$, $C(O)NR^4SO_2R^5$, $S(O)R^4$, SO_2R^4, $SO_2NR^4R^5$, SO_3R^4, $(CH_2)_nP(O)(OR^4)_2$, $NR^4SO_2R^5$, aldehyde, nitrile, nitro, alkyl, alkoxyalkyl, $T(CH_2)_mQR^9$, $C(O)T(CH_2)_mQR^9$, $NR^9C(O)T(CH_2)_mQR^{10}$, or $T(CH_2)_mCO_2R^4$;

n is 0 to 6;

W is an anion;

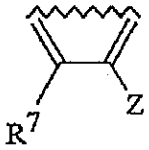
R^4 and R^5 are independently hydrogen, lower alkyl, lower alkenyl, lower alkynyl, $(CH_2)_nAr$, arylalkyl, aryl, heteroaryl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, or heteroaryl, or R^4 and R^5 together with the nitrogen to which they are attached form a carbocyclic ring containing 3 to 8 members, up to four of which members are optionally carbonyl groups or heteroatoms independently selected from oxygen, sulfur, S(O), $S(O)_2$, and nitrogen, wherein the carbocyclic group is unsubstituted or substituted with one, two, three, or four groups independently selected from halogen, hydroxy, hydroxyalkyl, lower alkyl, lower alkoxy, alkoxycarbonyl, alkylcarbonyl, alkylcarbonylamino, aminoalkyl, aminoalkylcarbonyl, trifluoromethyl, trifluoromethylalkyl, trifluoromethylalkylaminoalkyl, amino, mono- or dialkylamino, N-hydroxyacetamido, aryl, heteroaryl, carboxyalkyl, $NR^{10}SO_2R^{11}$, $C(O)NR^{10}R^{11}$, $NR^{10}C(O)R^{11}$, $C(O)OR^{10}$, $C(O)NR^{10}SO_2R^{11}$, $(CH_2)_nS(O)_nR^{10}$, $(CH_2)_n$-heteroaryl, $O(CH_2)_n$-heteroaryl, $(CH_2)_nC(O)NR^{10}R^{11}$, $O(CH_2)_nC(O)OR^{10}$;

R^9 is lower alkyl, haloalkyl, or aryl;

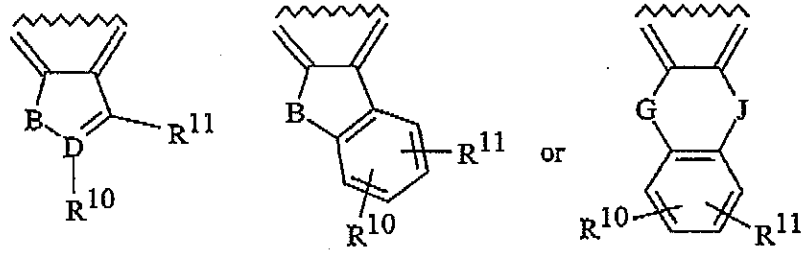
and R^4 additionally can be lower alkyl unsubstituted or substituted with one, two, or three groups independently selected from halogen, 5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl-sulfanyl, 5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl-sulfinyl, 5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl-sulfonyl, or a carbocyclic group containing from 3 to 7 members, up to four of which members are optionally heteroatoms independently selected from oxygen, sulfur and nitrogen, wherein the carbocyclic group is unsubstituted or

substituted with one, two, or three groups independently selected from halogen, hydroxy, hydroxyalkyl, lower alkyl, lower alkoxy, alkoxycarbonyl, alkylcarbonyl, alkylcarbonylamino, aminoalkyl, trifluoromethyl, N-hydroxyacetamide, trifluoromethylalkyl, amino, or mono- or dialkylamino;

and when Y is CR^7, it is part of the part structure



wherein R^7 and Z are as defined above, or can be taken together with the carbons to which they are attached to form



wherein:

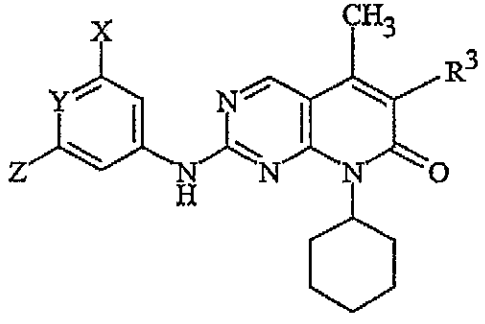
G and J are independently CH_2, NH, or O;

B is NH, S, CH_2, or O;

D is C or N, provided that R^{10} is nothing when D is N; and

R^{10} and R^{11} are independently hydrogen, halogen, lower alkyl, lower alkoxy, or alkylcarbonyl.

A third aspect of the present invention provides a compound of the Formula III



III

and pharmaceutically acceptable salts, esters, amides, and prodrugs thereof, wherein:

R^3 is trifluoromethyl, lower alkynyl, lower alkenyl, $-COR^4$, $CONR^4OR^5$, $-SO_2NR^4R^5$, $-SO_2R^4$, $-SO_3R^4$, or $-P(O)(OR^4)(OR^5)$; with R^4 below the carbonyl;

Y is N or CR^7;

X and Z are independently hydrogen, halogen, lower alkyl, lower alkoxy, trifluoromethyl, hydroxy, nitrile, nitro, $-NR^4R^5$, $-N(O)R^4R^5$, $-NR^4R^5R^6W$, $-SR^4$, $-C(O)R^4$, $-CO_2R^4$, $-CONR^4R^5$, $-SO_2NR^4R^5$, $-SO_2R^4$, $-SO_3R^4$, $P(O)(OR^4)(OR^5)$, $-T(CH_2)_mQR^4$, $-C(O)T(CH_2)_mQR^4$, or $-NR^4C(O)T(CH_2)_mQR^5$;

m is 1 to 6;

T is O, S, NR^4, $N(O)R^4$, NR^4R^5W, or CR^4R^5;

Q is O, S, NR^4, $N(O)R^4$, NR^4R^5W, CO_2, or a carbocyclic group containing from 3 to 7 members, up to four of which members are optionally heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the carbocyclic group is unsubstituted or substituted with one, two, or three groups independently selected from halogen, hydroxy, hydroxyalkyl, lower alkyl, lower alkoxy, alkoxycarbonyl, alkylcarbonyl, alkylcarbonylamino, aminoalkyl, trifluoromethyl, N-hydroxyacetamide, trifluoromethylalkyl, amino, or mono or dialkylamino;

R^6 is lower alkyl, haloalkyl, or aryl;

R^7 is NR^4R^5, $N(O)R^4R^5$, $NR^4R^5R^9X$, OH, OR^4, SR^4, halo, COR^4, $(CH_2)_nR^4$, CO_2R^4, $CONR^4R^5$, $C(O)NR^4SO_2R^5$, $S(O)R^4$, SO_2R^4, $SO_2NR^4R^5$, SO_3R^4, $(CH_2)_nP(O)(OR^4)_2$, $NR^4SO_2R^5$, aldehyde, nitrile, nitro, alkyl, alkoxyalkyl, $T(CH_2)_mQR^9$, $C(O)T(CH_2)_mQR^9$, $NR^9C(O)T(CH_2)_mQR^{10}$, or $T(CH_2)_mCO_2R^4$;

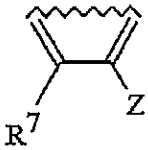
n is 0 to 6;

W is an anion;

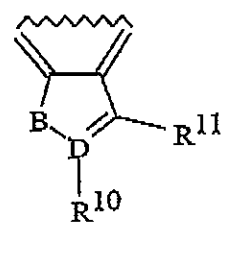
R^4 and R^5 are independently hydrogen, lower alkyl, lower alkenyl, lower alkynyl, $(CH_2)_nAr$, arylalkyl, aryl, heteroaryl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, or heteroaryl, or R^4 and R^5 together with the nitrogen to which they are attached form a carbocyclic ring containing 3 to 8 members, up to four of which members are optionally carbonyl groups or heteroatoms independently selected from oxygen, sulfur, S(O), $S(O)_2$, and nitrogen, wherein the carbocyclic group is unsubstituted or substituted with one, two, three, or four groups independently selected from halogen, hydroxy, hydroxyalkyl, lower alkyl, lower alkoxy, alkoxycarbonyl, alkylcarbonyl, alkylcarbonylamino, aminoalkyl, trifluoromethyl, trifluoromethylalkyl, trifluoromethylalkylaminoalkyl, amino, mono- or dialkylamino, N-hydroxyacetamido, aryl, heteroaryl, carboxyalkyl, $NR^{10}SO_2R^{11}$, $C(O)NR^{10}R^{11}$, $NR^{10}C(O)R^{11}$, $C(O)OR^{10}$, $C(O)NR^{10}SO_2R^{11}$, $(CH_2)_nS(O)_nR^{10}$, $(CH_2)_n$-heteroaryl, $O(CH_2)_n$-heteroaryl, $(CH_2)_nC(O)NR^{10}R^{11}$, $O(CH_2)_nC(O)OR^{10}$;

and R^4 additionally can be lower alkyl unsubstituted or substituted with one, two, or three groups independently selected from halogen, 5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl-sulfanyl, 5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl-sulfinyl, 5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl-sulfonyl, or a carbocyclic group containing from 3 to 7 members, up to four of which members are optionally heteroatoms independently selected from oxygen, sulfur and nitrogen, wherein the carbocyclic group is unsubstituted or substituted with one, two, or three groups independently selected from halogen, hydroxy, hydroxyalkyl, lower alkyl, lower alkoxy, alkoxycarbonyl, alkylcarbonyl, alkylcarbonylamino, aminoalkyl, trifluoromethyl, N-hydroxyacetamide, trifluorometbylalkyl, amino, or mono- or dialkylamino;

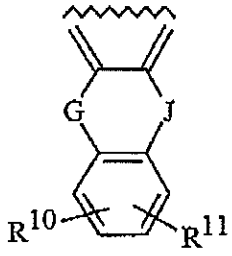
and when Y is CR^7, it is part of the part structure



wherein R^7 and Z are as defined above, or can be taken together with the carbons to which they are attached to form



or



wherein:

G and J are independently CH_2, NH, or O;

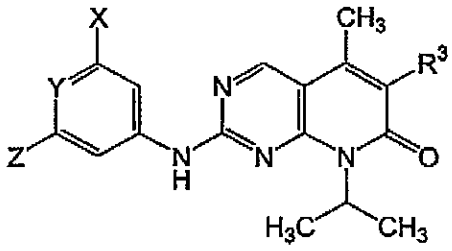
B is NH, S, CH_2, or O;

D is C or N, provided that R^{10} is nothing when D is N; and

R^9 is lower alkyl, haloalkyl, or aryl;

R^{10} and R^{11} are independently hydrogen, halogen, lower alkyl, lower alkoxy, or alkylcarbonyl.

A fourth aspect of the present invention provides a compound of the Formula IV



IV

and pharmaceutically acceptable salts, esters, amides, and prodrugs thereof,

wherein:

R^3 is trifluoromethyl, lower alkynyl, lower alkenyl, $-COR^4$, $CONR^4OR^5$, $-SO_2NR^4R^5$, $-SO_2R^4$, $-SO_3R^4$, or $-P(O)(OR^4)(OR^5)$;

R^4

Y is N or CR^7;

X and Z are independently hydrogen, halogen, lower alkyl, lower alkoxy, trifluoromethyl, hydroxy, nitrile, nitro, $-NR^4R^5$, $-N(O)R^4R^5$, $-NR^4R^5R^6W$, $-SR^4$, $-C(O)R^4$, $-CO_2R^4$, $-CONR^4R^5$, $-SO_2NR^4R^5$, $-SO_2R^4$, $-SO_3R^4$, $P(O)(OR^4)(OR^5)$, $-T(CH_2)_mQR^4$, $-C(O)T(CH_2)_mQR^4$, or $-NR^4C(O)T(CH_2)_mQR^5$;

m is 1 to 6;

T is O, S, NR^4, $N(O)R^4$, NR^4R^5W, or CR^4R^5;

Q is O, S, NR^4, $N(O)R^4$, NR^4R^5W, CO_2, or a carbocyclic group containing from 3 to 7 members, up to four of which members are optionally heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the carbocyclic group is unsubstituted or substituted with one, two, or three groups independently selected from halogen, hydroxy, hydroxyalkyl, lower alkyl, lower alkoxy, alkoxycarbonyl, alkylcarbonyl, alkylcarbonylamino, aminoalkyl, trifluoromethyl, N-hydroxyacetamide, trifluoromethylalkyl, amino, or mono or dialkylamino;

R^6 is lower alkyl, haloalkyl, or aryl;

R^7 is NR^4R^5, $N(O)R^4R^5$, $NR^4R^5R^9X$, OH, OR^4, SR^4, halo, COR^4, $(CH_2)_nR^4$, CO_2R^4, $CONR^4R^5$, $C(O)NR^4SO_2R^5$, $S(O)R^4$, SO_2R^4, $SO_2NR^4R^5$, SO_3R^4, $(CH_2)_nP(O)(OR^4)_2$, $NR^4SO_2R^5$, aldehyde, nitrile, nitro, alkyl, alkoxyalkyl, $T(CH_2)_mQR^9$, $C(O)T(CH_2)_mQR^9$, $NR^9C(O)T(CH_2)_mQR^{10}$, or $T(CH_2)_mCO_2R^4$;

n is 0 to 6;

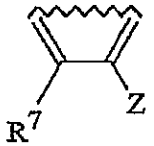
W is an anion;

R^4 and R^5 are independently hydrogen, lower alkyl, lower alkenyl, lower alkynyl, $(CH_2)_nAr$, arylalkyl, aryl, heteroaryl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, or heteroaryl, or R^4 and R^5 together with the nitrogen to which they are attached form a carbocyclic ring containing 3 to 8 members, up to four of which members are optionally carbonyl groups

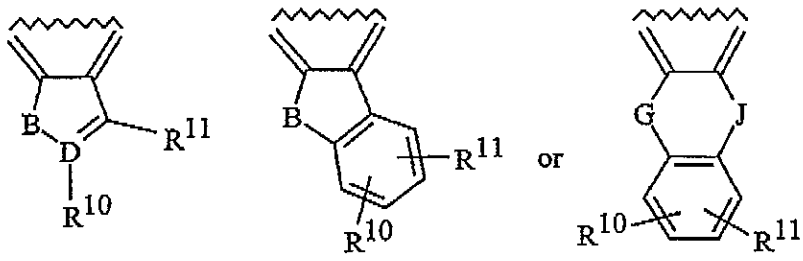
or heteroatoms independently selected from oxygen, sulfur, S(O), $S(O)_2$, and nitrogen, wherein the carbocyclic group is unsubstituted or substituted with one, two, three, or four groups independently selected from halogen, hydroxy, hydroxyalkyl, lower alkyl, lower alkoxy, alkoxycarbonyl, alkylcarbonyl, alkylcarbonylamino, aminoalkyl, aminoalkylcarbonyl, trifluoromethyl, trifluoromethylalkyl, trifluoromethylalkylaminoalkyl, amino, mono- or dialkylamino, N-hydroxyacetamido, aryl, heteroaryl, carboxyalkyl, $NR^{10}SO_2R^{11}$, $C(O)NR^{10}R^{11}$, $NR^{10}C(O)R^{11}$, $C(O)NR^{10}SO_2R^{11}$, $(CH_2)_nS(O)_nR^{10}$, $(CH_2)_n$-heteroaryl, $O(CH_2)_n$-heteroaryl, $(CH_2)_nC(O)NR^{10}R^{11}$, $O(CH_2)_nC(O)OR^{10}$;

and R^4 additionally can be lower alkyl unsubstituted or substituted with one, two, or three groups independently selected from halogen, 5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl-sulfanyl, 5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl-sulfinyl, 5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl-sulfonyl, or a carbocyclic group containing from 3 to 7 members, up to four of which members are optionally heteroatoms independently selected from oxygen, sulfur and nitrogen, wherein the carbocyclic group is unsubstituted or substituted with one, two, or three groups independently selected from halogen, hydroxy, hydroxyalkyl, lower alkyl, lower alkoxy, alkoxycarbonyl, alkylcarbonyl, alkylcarbonylamino, aminoalkyl, trifluoromethyl, N-hydroxyacetamide, trifluoromethylalkyl, amino, or mono- or dialkylamino;

and when Y is CR^7, it is part of the part structure



wherein R^7 and Z are as defined above, or can be taken together with the carbons to which they are attached to form



wherein:

G and J are independently CH_2, NH, or O;

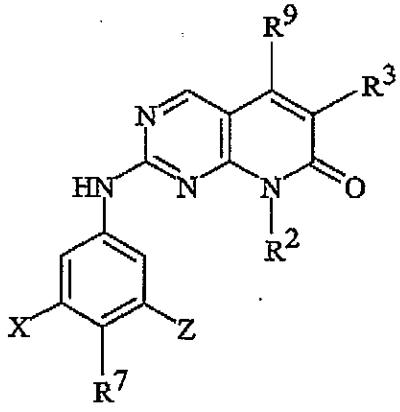
B is NH, S, CH_2, or O;

D is C or N, provided that R^{10} is nothing when D is N;

R^9 is lower alkyl, haloalkyl, or aryl; and

R^{10} and R^{11} are independently hydrogen, halogen, lower alkyl, lower alkoxy, or alkylcarbonyl.

A fifth aspect of the present invention provides a compound of the Formula V



V

and pharmaceutically acceptable salts, esters, amides, and prodrugs thereof, wherein:

R^2 is (a) hydrogen;

(b) lower alkyl optionally substituted with one, two, or three groups independently selected from halogen, hydroxy, lower alkoxy, amino, mono- or dialkylamino, carboxy, alkoxycarbonyl, thioalkyl,

nitrile, aryl, heteroaryl, or a carbocyclic group containing from 3 to 7 members, up to two of which members are optionally heteroatoms independently selected from oxygen, sulfur, and nitrogen; or

(c) a carbocyclic group containing from 3 to 7 members, up to two of which members are optionally heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the carbocyclic group is unsubstituted or substituted with one, two, or three groups independently selected from consisting of halogen, hydroxy, lower alkyl, lower alkoxy, amino, mono- or dialkylamino, aryl, and heteroaryl;

R^3 is hydrogen, lower alkyl, lower alkoxy, halogen, trifluoromethyl, lower alkynyl, lower alkenyl, nitrile, nitro, $-COR^4$, $-CO_2R^4$, $-CONR^4R^5$, $CONR^4OR^5$, $-SO_2NR^4R^5$, $-SO_2R^4$, $-SO_3R^4$,

$$\begin{array}{l} | \\ R^4 \end{array}$$

$P(O)(OR^4)(OR^5)$, or $-NR^4R^5$;

R^9 is lower alkyl, haloalkyl, or aryl;

X and Z are independently hydrogen, halogen, lower alkyl, lower alkoxy, trifluoromethyl, hydroxy, nitrile, nitro, $-NR^4R^5$, $-N(O)R^4R^5$, $-NR^4R^5R^6W$, $-SR^4$, $-C(O)R^4$, $-CO_2R^4$, $-CONR^4R^5$, $-SO_2NR^4R^5$, $-SO_2R^4$, $-SO_3R^4$, $P(O)(OR^4)(OR^5)$, $-T(CH_2)_mQR^4$, $-C(O)T(CH_2)_mQR^4$, or $-NR^4C(O)T(CH_2)_mQR^5$;

m is 1 to 6;

T is O, S, NR^4, $N(O)R^4$, NR^4R^5W, or CR^4R^5;

Q is O, S, NR^4, $N(O)R^4$, NR^4R^5W, CO_2, or a carbocyclic group containing from 3 to 7 members, up to four of which members are optionally heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the carbocyclic group is unsubstituted or substituted with one, two, or three groups independently selected from halogen, hydroxy, hydroxyalkyl,

lower alkyl, lower alkoxy, alkoxycarbonyl, alkylcarbonyl, alkylcarbonylamino, aminoalkyl, trifluoromethyl, N-hydroxyacetamide, trifluoromethylalkyl, amino, or mono or dialkylamino;

R^6 is lower alkyl, haloalkyl, or aryl;

R^7 is NR^4R^5, $N(O)R^4R^5$, $NR^4R^5R^9W$, OH, OR^4, SR^4, halo, COR^4, $(CH_2)_nR^4$, $(CH_2)_nR^4$, CO_2R^4, $CONR^4R^5$, $C(O)NR^4SO_2R^5$, $S(O)R^4$, SO_2R^4, $SO_2NR^4R^5$, SO_3R^4, $(CH_2)_nP(O)(OR^4)_2$, $NR^4SO_2R^5$, aldehyde, nitrile, nitro, alkyl, alkoxyalkyl, $T(CH_2)_mQR^4$, $C(O)T(CH_2)_mQR^4$, $NR^4C(O)T(CH_2)_mQR^5$, or $T(CH_2)_mCO_2R^4$;

n is 0 to 6;

W is an anion;

R^4 and R^5 are independently hydrogen, lower alkyl, lower alkenyl, lower alkynyl, $(CH_2)_nAr$, arylalkyl, aryl, heteroaryl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, or heteroaryl, or R^4 and R^5 together with the nitrogen to which they are attached form a carbocyclic ring containing 3 to 8 members, up to four of which members are optionally carbonyl groups or heteroatoms independently selected from oxygen, sulfur, S(O), $S(O)_2$, and nitrogen, wherein the carbocyclic group is unsubstituted or substituted with one, two, three, or four groups independently selected from halogen, hydroxy, hydroxyalkyl, lower alkyl, lower alkoxy, alkoxycarbonyl, alkylcarbonyl, alkylcarbonylamino, aminoalkyl, aminoalkylcarbonyl, trifluoromethyl, trifluoromethylalkyl, trifluoromethylalkylaminoalkyl, mono- or dialkylamino, N-hydroxyacetamido, aryl, heteroaryl, carboxyalkyl, $NR^{10}SO_2R^{11}$, $C(O)NR^{10}R^{11}$, $NR^{10}C(O)R^{11}$, $C(O)OR^{10}$, $C(O)NR^{10}SO_2R^{11}$, $(CH_2)_nS(O)_nR^{10}$, $(CH_2)_n$-heteroaryl, $O(CH_2)_n$-heteroaryl, $(CH_2)_nC(O)NR^{10}R^{11}$, $O(CH_2)_nC(O)OR^{10}$;

and R^4 additionally can be lower alkyl unsubstituted or substituted with one, two, or three groups independently selected from halogen, 5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl-sulfanyl, 5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl-sulfinyl, 5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl-sulfonyl, or a

carbocyclic group containing from 3 to 7 members, up to four of which members are optionally heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the carbocyclic group is unsubstituted or substituted with one, two, or three groups independently selected from halogen, hydroxy, hydroxyalkyl, lower alkyl, lower alkoxy, alkoxycarbonyl, alkylcarbonyl, alkylcarbonylamino, aminoalkyl, trifluoromethyl, N-hydroxyacetamide, trifluoromethylalkyl, amino, or mono- or dialkylamino; and

R^{10} and R^{11} are independently hydrogen, halogen, lower alkyl, lower alkoxy, or alkylcarbonyl;

with the proviso that when, R^3 is hydrogen, lower alkyl, lower alkoxy, halogen, nitrile, nitro, $-CO_2R^4$, $CONR^4OR^5$, or $-NR^4R^5$, then R^9 is not C_1-C_3 alkyl.

The present invention also provides pharmaceutical compositions that comprise a compound of Formula I together with a pharmaceutically acceptable diluent, carrier, or excipient.

An embodiment may provide methods for inhibiting cyclin-dependent kinase and growth factor-mediated kinase enzymes.

Another embodiment may provide a method of treating subjects suffering from diseases caused by cellular proliferation. The method may entail inhibiting proliferation of tumorigenic cells of epithelial origin and vascular smooth muscle proliferation, and/or cellular migration by administering a therapeutically effective amount of a compound of Formula I to a subject in need of treatment.

The invention also provides compounds useful in the diagnosis and treatment of cancer, psoriasis, vascular smooth muscle cell proliferation associated with atherosclerosis and postsurgical vascular stenosis and restenosis in mammals.

Yet another embodiment may provide a method for treating subjects suffering from diseases caused by DNA tumor viruses such as herpes viruses.

A sixth aspect of the present invention provides a pharmaceutical composition comprising a compound as defined in the first aspect, in combination with a pharmaceutically acceptable carrier, diluent, or excipient.

A seventh aspect of the present invention provides a use of a therapeutically effective amount of a compound as defined in the first aspect, in the manufacture of a medicament for the treatment of proliferative disorders selected from the group consisting of cancer, psoriasis, vascular smooth muscle proliferation associated with a disorder selected from the group consisting of atherosclerosis, postsurgical vascular stenosis, and restenosis in mammals.

An eighth aspect of the present invention provides a use of a compound as defined in the first aspect, in the manufacture of a medicament for inhibiting a cyclin-dependent kinase.

A ninth aspect of the present invention provides a use of a compound as defined in the first aspect, in the manufacture of a medicament for inhibiting a growth factor-mediated tyrosine kinase.

A tenth aspect of the present invention provides a use of a therapeutically effective amount of a compound as defined in the first aspect, in the manufacture of a medicament for the treatment of a subject suffering from diseases caused by vascular smooth muscle cell proliferation.

An eleventh aspect of the present invention provides a use of a therapeutically effective amount of a compound as defined in the first aspect, in the manufacture of a medicament for the treatment of a subject suffering from cancer.

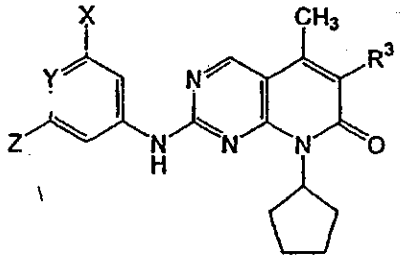
A twelfth aspect of the present invention provides a use of an effective amount of a compound as defined in the first aspect, in the manufacture of a medicament for the diagnosis and/or treatment of cancer, psoriasis, vascular smooth muscle cell proliferation associated with atherosclerosis and postsurgical vascular stenosis and restenosis in a mammal.

A thirteenth aspect of the present invention provides a use of an effective amount of a compound as defined in the first aspect, in the manufacture of a medicament for treating a mammal suffering from a disease caused by a DNA tumor virus.

DETAILED DESCRIPTION OF THE INVENTION

The novel compounds encompassed by the instant invention are those described by the general Formula I set forth above, and the pharmaceutically acceptable salts, esters, amides, and prodrugs thereof.

In addition to the compounds of Formula I, the invention encompasses, in a preferred embodiment, compounds of Formula II:

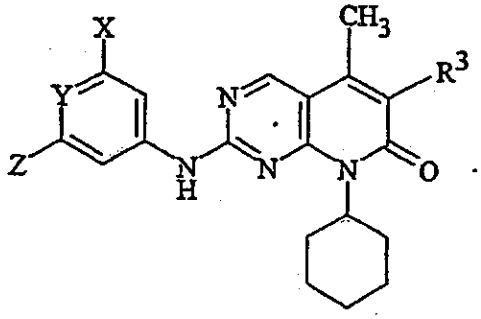


II

wherein X, Y, Z, and R^3 are as defined above for Formula I.

Preferred compounds of Formula II are those in which X and Z are independently hydrogen, Cl, or F; Y is CR^7; and R^3 is hydrogen, Cl, F, Br, or CN.

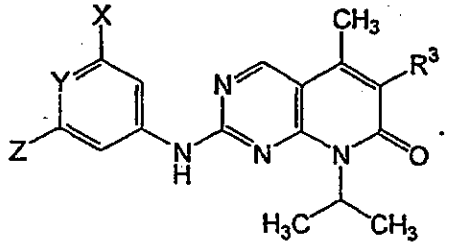
In addition, the present invention also encompasses preferred compounds of the Formula III:



III

Especially preferred compounds of Formula III are those in which X and Z are independently hydrogen, Cl, or F; Y is CR^7; and R^3 is hydrogen, Cl, F, Br, or CN.

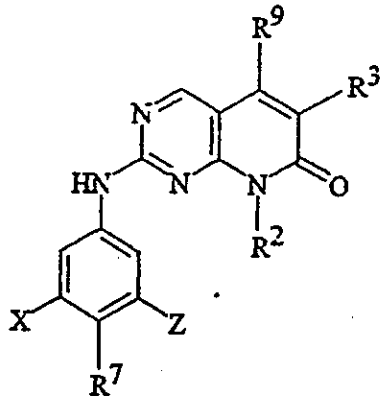
In addition, the present invention also encompasses, as a further preferred embodiment, compounds of the Formula IV:



IV

Preferred compounds of Formula IV are those in which X and Z are independently hydrogen, Cl, or F; Y is CR^7; and R^3 is hydrogen, Cl, F, Br, or CN.

The most preferred invention compounds have the Formula V



V

wherein:

R^2 is alkyl or cycloalkyl;

R^3 is hydrogen or halo;

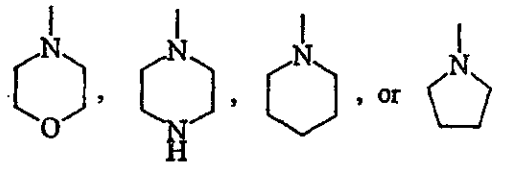
R^9 is alkyl;

X and Z independently are hydrogen or halo;

R^7 is NR^4R^5; and

R^4 and R^5 are taken together with the nitrogen to which they are attached to form a 5- or 6-membered carbocyclic ring, optionally containing an oxygen, nitrogen, or sulfur heteroatom, and optionally substituted with alkyl or substituted alkyl groups.

Especially preferred compounds of Formula V are those wherein R^7 is



, and such groups are optionally substituted by alkyl, acyl, amide, or the like.

Unless otherwise expressly stated, the following definitions are adhered to throughout this disclosure.

By "alkyl," "lower alkyl," and "C_1-C_{10} alkyl" in the present invention is meant a straight or branched hydrocarbon radical having from 1 to 10 carbon atoms and includes, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, iso-pentyl, n-hexyl, and the like.

By the term "halogen" in the present invention is meant fluorine, bromine, chlorine, and iodine.

"Alkenyl" means straight and branched hydrocarbon radicals having from 2 to 6 carbon atoms and one double bond and includes ethenyl, 3-buten-1-yl, 2-ethenylbutyl, 3-hexen-1-yl, and the like.

"Alkynyl" means straight and branched hydrocarbon radicals having from 2 to 6 carbon atoms and one triple bond and includes ethynyl, 3-butyn-1-yl, propynyl, 2-butyn-1-yl, 3-pentyn-1-yl, and the like.

"Cycloalkyl" means a monocyclic or polycyclic hydrocarbyl group such as cyclopropyl, cycloheptyl, cyclooctyl, cyclodecyl, cyclobutyl, adamantyl, norpinanyl, decalinyl, norbornyl, cyclohexyl, and cyclopentyl. Such groups can be substituted with groups such as hydroxy, keto, amino, alkyl, and dialkylamino, and the like. Also included are rings in which 1 to 3 heteroatoms replace carbons. Such groups are termed "heterocyclyl," which means a cycloalkyl group also bearing at least one heteroatom selected from O, S, or N, examples being oxiranyl, pyrrolidinyl, piperidyl, tetrahydropyran, and morpholine.

By "alkoxy," "lower alkoxy," and "C_1-C_{10} alkoxy" is meant straight or branched chain alkoxy groups having 1-10 carbon atoms, such as, for example, methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, sec-butoxy, tert-butoxy, pentoxy, 2-pentyloxy, isopentoxy, neopentoxy, hexoxy, 2-hexoxy, 3-hexoxy, and 3-methylpentoxy. In addition, alkoxy refers to polyethers such as -O-$(CH_2)_2$-O-CH_3, and the like.

"Alkanoyl" groups are alkyl groups linked through a carbonyl, i.e., C_1-C_5-C(O)-. Such groups include formyl, acetyl, propionyl, butyryl, and isobutyryl.

"Acyl" means an alkyl or aryl (Ar) group bonded through a carbonyl group, i.e., R-C(O)-. For example, acyl includes a C_1-C_6 alkanoyl, including substituted alkanoyl, wherein the alkyl portion can be substituted by NR^4R^5 or a carboxylic or heterocyclic group. Typical acyl groups include acetyl, benzoyl, and the like.

"Amide" is an amino carbonyl group such as -$CONR^4R^5$.

The alkyl, alkenyl, alkoxy, and alkynyl groups described above are optionally substituted, preferably by 1 to 3 groups selected from NR^4R^5, phenyl, substituted phenyl, thio C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxy, carboxy, C_1-C_6 alkoxycarbonyl, halo, nitrile, cycloalkyl, and a 5- or 6-membered carbocyclic ring or heterocyclic ring having 1 or 2 heteroatoms selected from nitrogen, substituted nitrogen, oxygen, and sulfur. "Substituted nitrogen" means nitrogen bearing C_1-C_6 alkyl or $(CH_2)_nPh$ where n is 1, 2, or 3. Perhalo and polyhalo substitution is also included.

Examples of substituted alkyl groups include 2-aminoethyl, 2-hydroxyethyl, pentachloroethyl, trifluoromethyl, 2-diethylaminoethyl, 2-dimethylaminopropyl, ethoxycarbonylmethyl, 3-phenylbutyl, methanylsulfanylmethyl, methoxymethyl, 3-hydroxypentyl, 2-carboxybutyl, 4-chlorobutyl, 3-cyclopropylpropyl, pentafluoroethyl, 3-morpholinopropyl, piperazinylmethyl, and 2-(4-methylpiperazinyl)ethyl.

Examples of substituted alkynyl groups include 2-methoxyethynyl, 2-ethylsulfanylethynyl, 4-(1-piperazinyl)-3-(butynyl), 3-phenyl-5-hexynyl, 3-diethylamino-3-butynyl, 4-chloro-3-butynyl, 4-cyclobutyl-4-hexenyl, and the like.

Typical substituted alkoxy groups include aminomethoxy, trifluoromethoxy, 2-diethylaminoethoxy, 2-ethoxycarbonylethoxy, 3-hydroxypropoxy, 6-carboxhexyloxy, and the like.

Further, examples of substituted alkyl, alkenyl, and alkynyl groups include dimethylaminomethyl, carboxymethyl, 4-dimethylamino-3-buten-1-yl, 5-ethylmethylamino-3-pentyn-1-yl, 4-morpholinobutyl, 4-tetrahydropyrinidylbutyl, 3-imidazolidin-1-ylpropyl, 4-tetrahydrothiazol-3-yl-butyl, phenylmethyl, 3-chlorophenylmethyl, and the like.

The term "anion" means a negatively charged counterion such as chloride, bromide, trifluoroacetate, and triethylammonium.

By "heteroaryl" is meant one or more aromatic ring systems of 5-, 6-, or 7-membered rings containing at least one and up to four heteroatoms selected from nitrogen, oxygen, or sulfur. Such heteroaryl groups include, for example, thienyl, furanyl, thiazolyl, triazolyl, imidazolyl, (is)oxazolyl, oxadiazolyl,

tetrazolyl, pyridyl, thiadiazolyl, oxadiazolyl, oxathiadiazolyl, thiatriazolyl, pyrimidinyl, (iso)quinolinyl, napthyridinyl, phthalimidyl, benzimidazolyl, and benzoxazolyl. A preferred heteroaryl is pyridine.

By "aryl" is meant an aromatic carbocyclic group having a single ring (e.g., phenyl), multiple rings (e.g., biphenyl), or multiple condensed rings in which at least one is aromatic, (e.g., 1,2,3,4-tetrahydronaphthyl, naphthyl, anthryl, or phenanthryl), which can be mono-, di-, or trisubstituted with, e.g., halogen, lower alkyl, lower alkoxy, lower alkylthio, trifluoromethyl, lower acyloxy, aryl, heteroaryl, and hydroxy. A preferred aryl is phenyl.

The term "cancer" includes, but is not limited to, the following cancers: breast, ovary, cervix, prostate, testis, esophagus, glioblastoma, neuroblastoma, stomach, skin, keratoacanthoma, lung, epidermoid carcinoma, large cell carcinoma, adenocarcinoma, bone, colon, adenocarcinoma, adenoma, pancreas, adenocarcinoma, thyroid, follicular carcinoma, undifferentiated carcinoma, papillary carcinoma, seminoma, melanoma, sarcoma, bladder carcinoma, liver carcinoma and biliary passages, kidney carcinoma, myeloid disorders, lymphoid disorders, Hodgkin's, hairy cells, buccal cavity and pharynx (oral), lip, tongue, mouth, pharynx, small intestine, colon-rectum, large intestine, rectum, brain and central nervous system, and leukemia.

The term "pharmaceutically acceptable salts, esters, amides, and prodrugs" as used herein refers to those carboxylate salts, amino acid addition salts, esters, amides, and prodrugs of the compounds of the present invention which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of patients without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the invention. The term "salts" refers to the relatively nontoxic, inorganic and organic acid addition salts of compounds of the present invention. These salts can be prepared in situ during the final isolation and purification of the compounds or by separately reacting the purified compound in its free base form with a suitable organic or inorganic acid and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, nitrate, acetate, oxalate, valerate, oleate, palmitate, stearate, laurate, borate, benzoate, lactate,

phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate mesylate, glucoheptonate, lactobionate and laurylsulphonate salts, and the like. These may include cations based on the alkali and alkaline earth metals, such as sodium, lithium, potassium, calcium, magnesium and the like, as well as non-toxic ammonium, quaternary ammonium, and amine cations including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like. (See, for example, Berge S.M. et al., "Pharmaceutical Salts," *J. Pharm. Sci.*, 1977;66:1-19 which is incorporated herein by reference.)

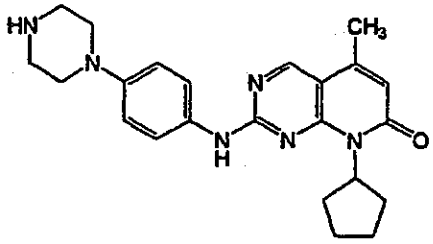
Examples of pharmaceutically acceptable, non-toxic esters of the compounds of this invention include C_1-C_6 alkyl esters wherein the alkyl group is a straight or branched chain. Acceptable esters also include C_5-C_7 cycloalkyl esters as well as arylalkyl esters such as, but not limited to benzyl. C_1-C_4 alkyl esters are preferred. Esters of the compounds of the present invention may be prepared according to conventional methods.

Examples of pharmaceutically acceptable, non-toxic amides of the compounds of this invention include amides derived from ammonia, primary C_1-C_6 alkyl amines and secondary C_1-C_6 dialkyl amines wherein the alkyl groups are straight or branched chain. In the case of secondary amines the amine may also be in the form of a 5- or 6-membered heterocycle containing one nitrogen atom. Amides derived from ammonia, C_1-C_3 alkyl primary amines and C_1-C_2 dialkyl secondary amines are preferred. Amides of the compounds of the invention may be prepared according to conventional methods.

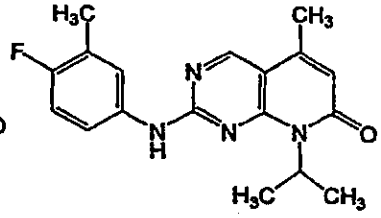
The term "prodrug" refers to compounds that are rapidly transformed in vivo to yield the parent compound of the above formulae, for example, by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are hereby incorporated by reference.

Representative compounds of the invention are shown below in Table 1.

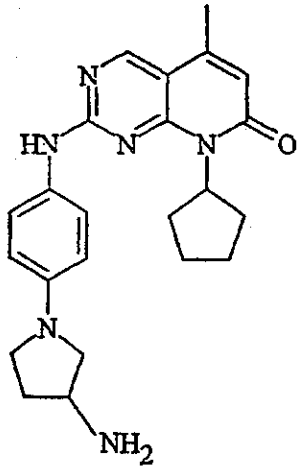
TABLE 1



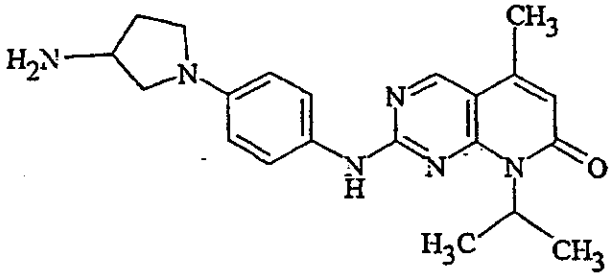
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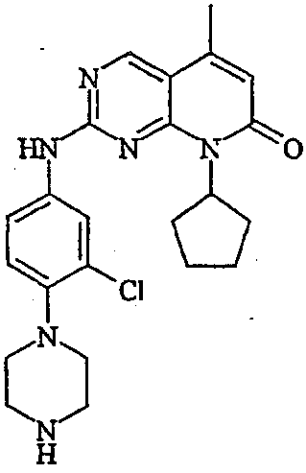
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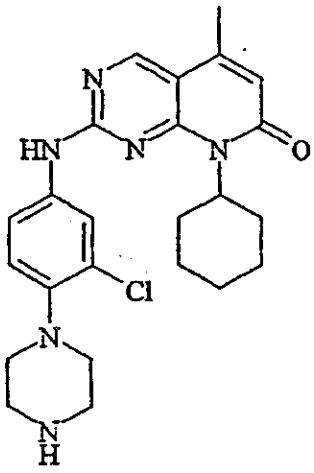
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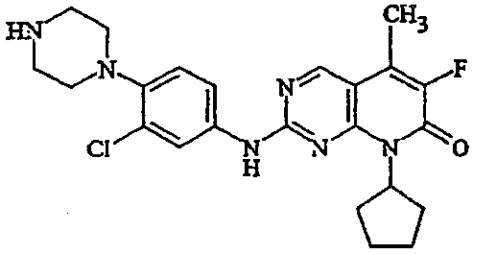


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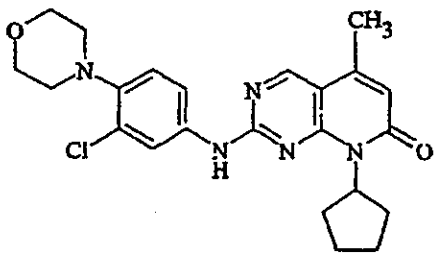


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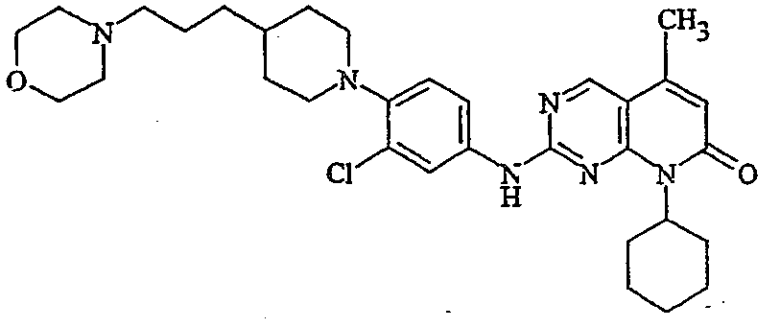
TABLE 1 (cont)



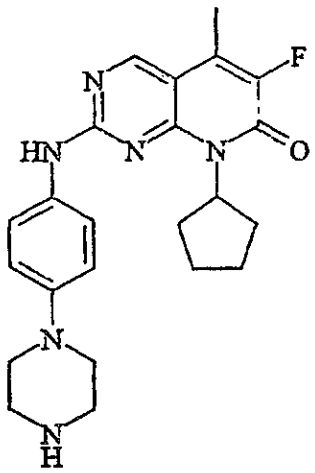
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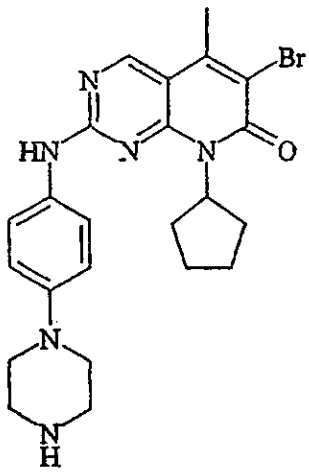
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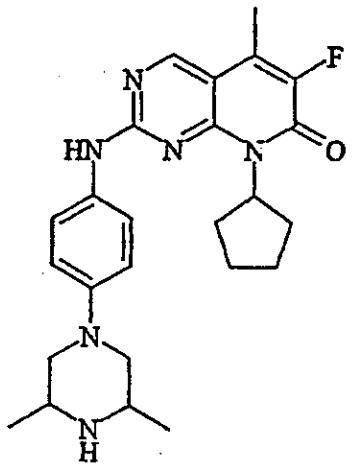


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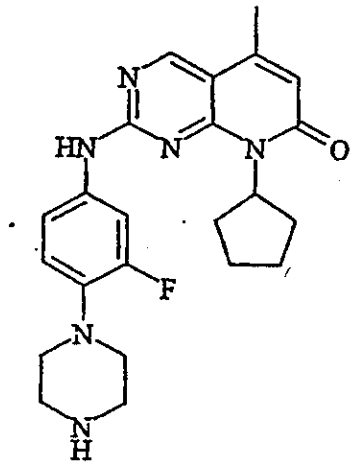


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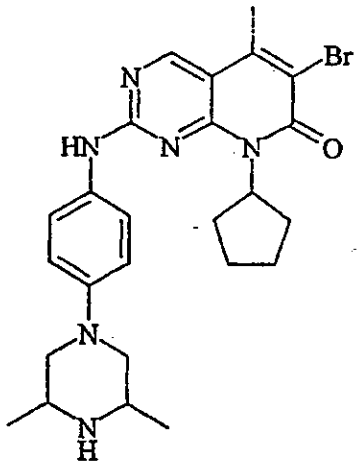
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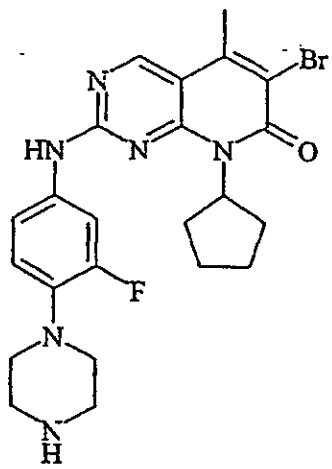
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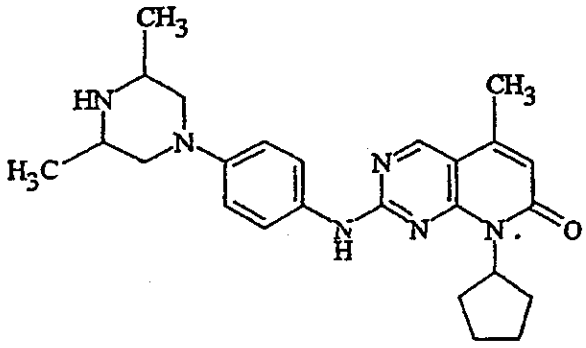


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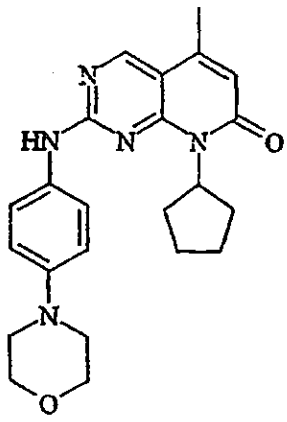


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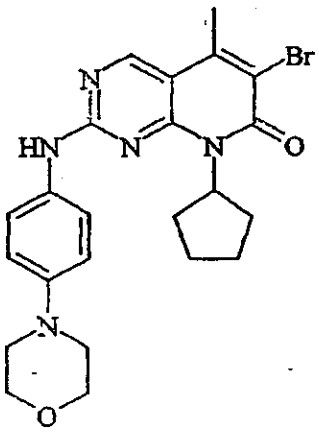
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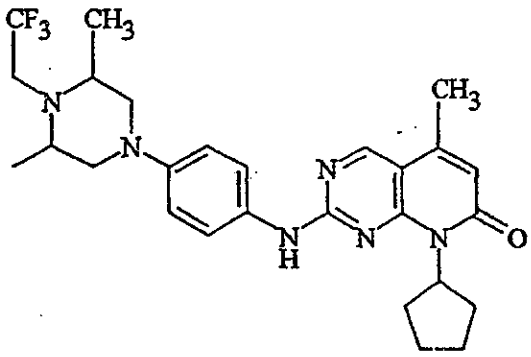
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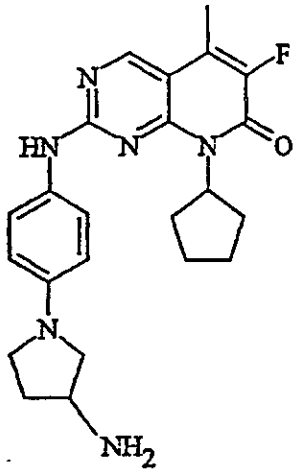


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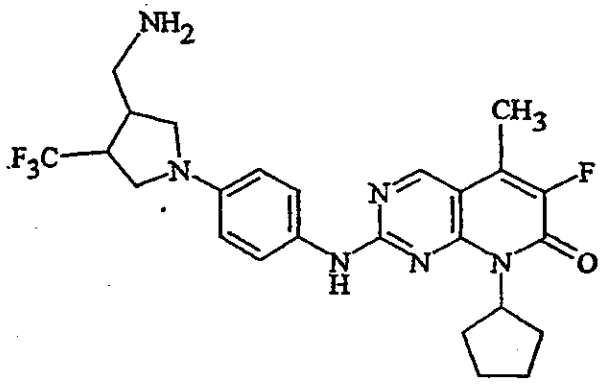


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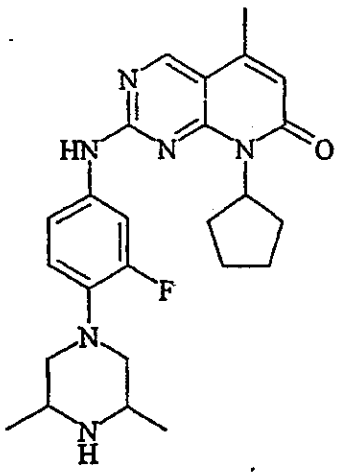
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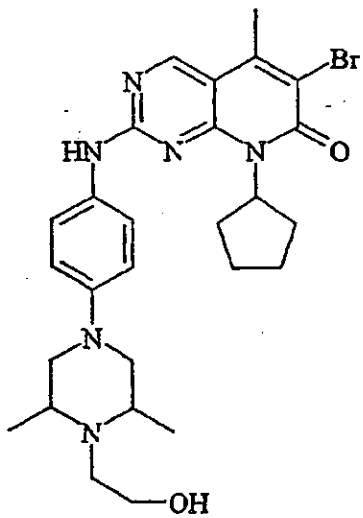
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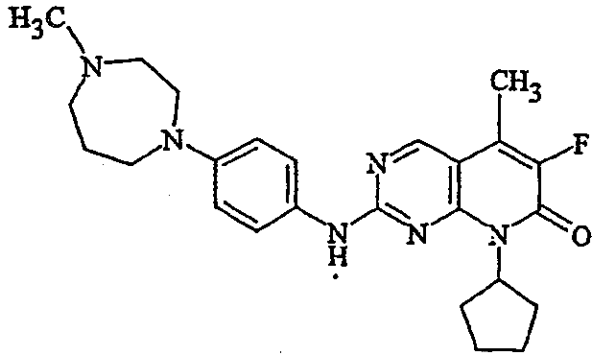


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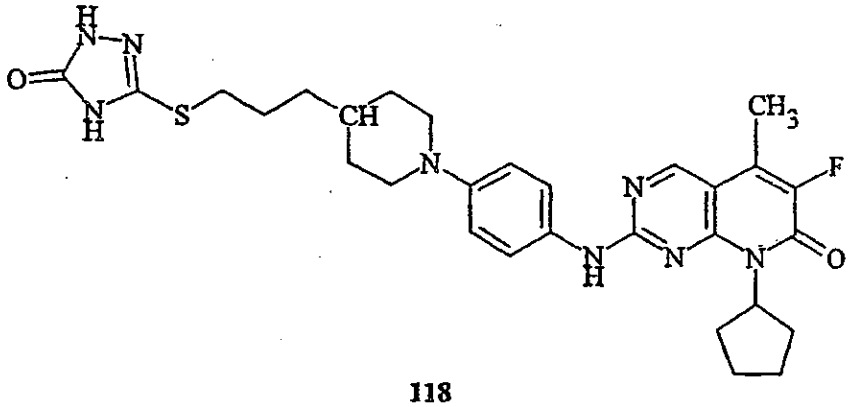


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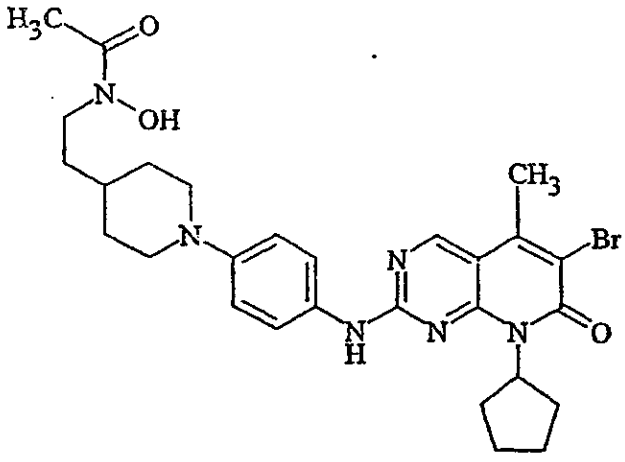
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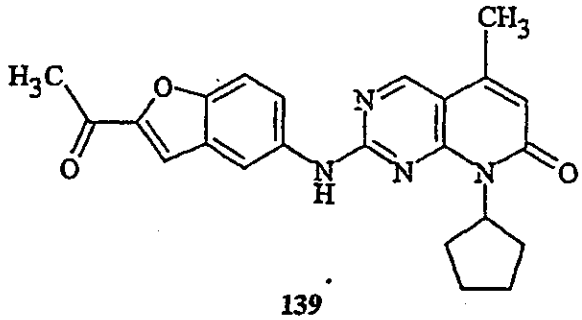


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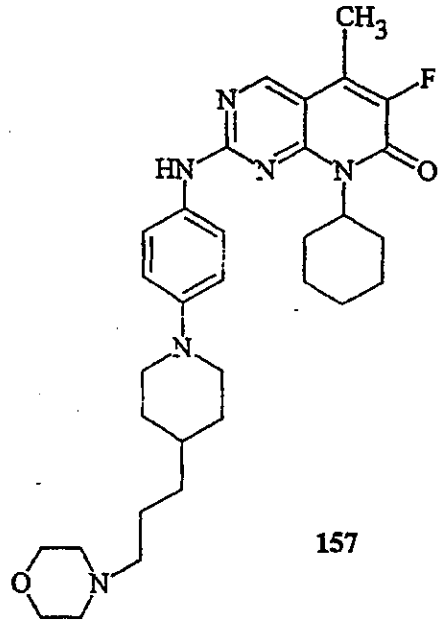


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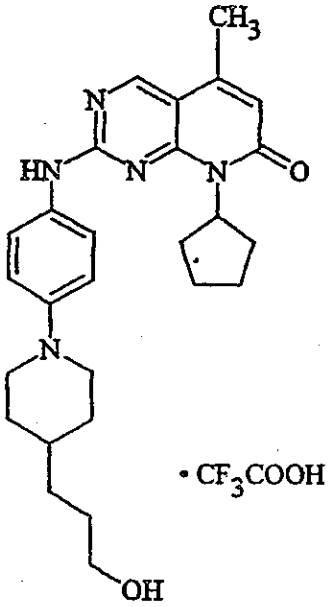


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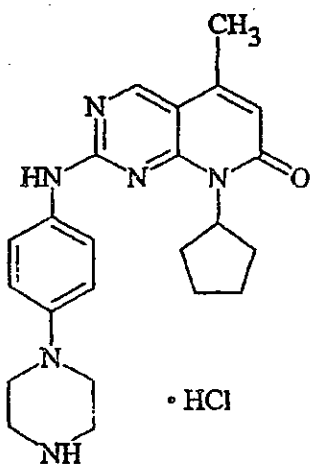


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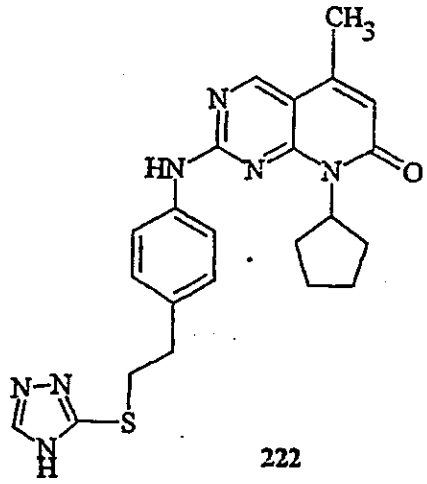


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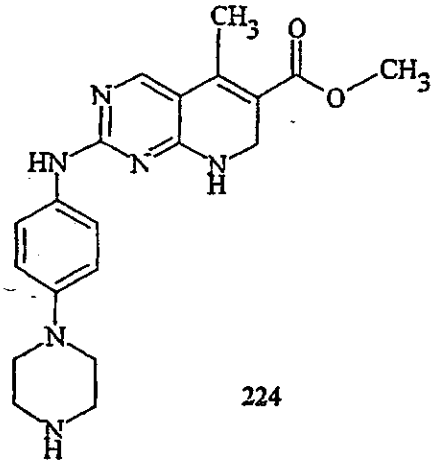


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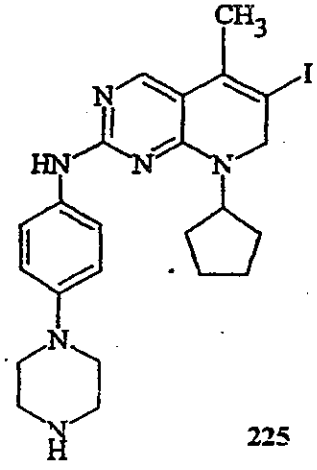


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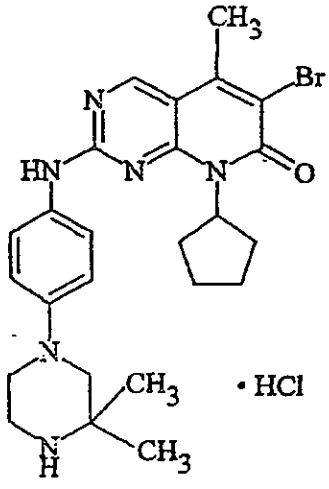


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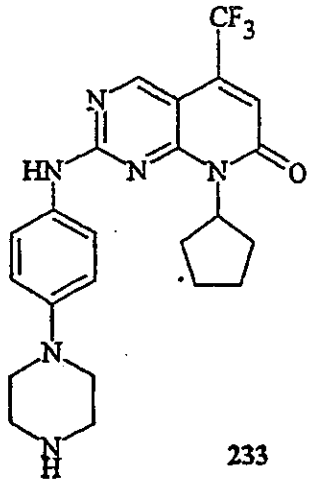


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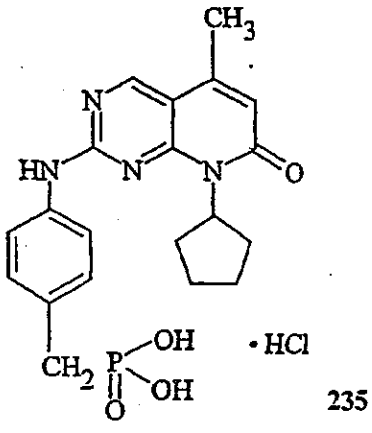


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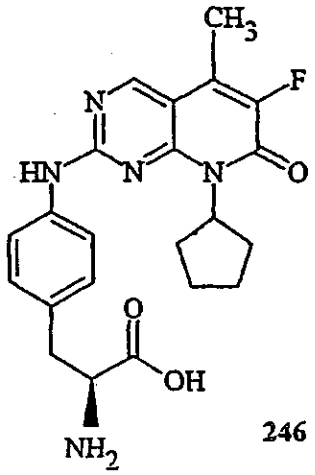


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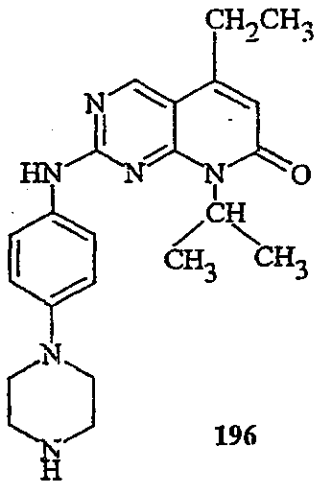


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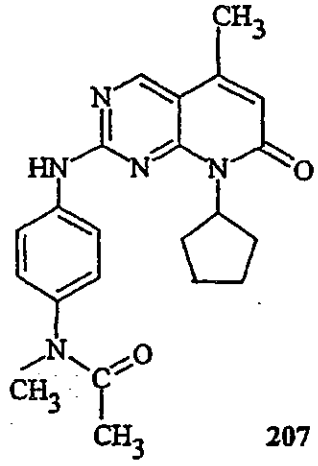


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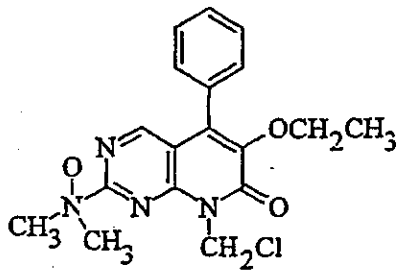


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TABLE 1 (cont)



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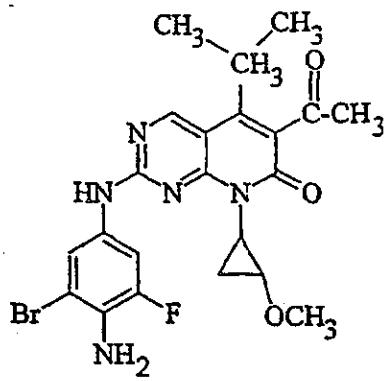
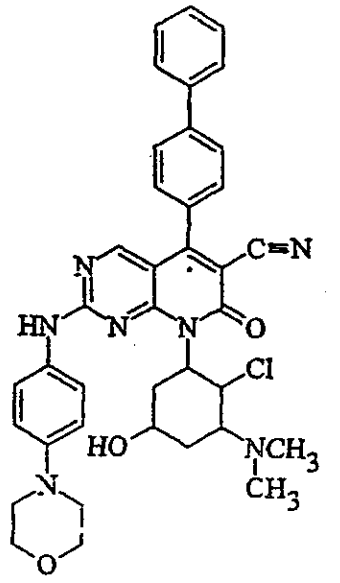
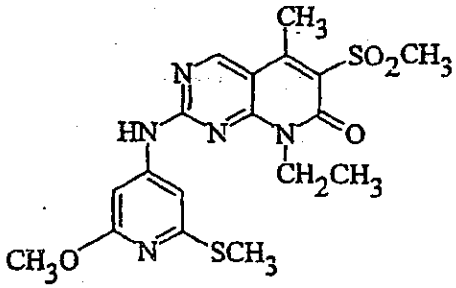


TABLE 1 (cont)





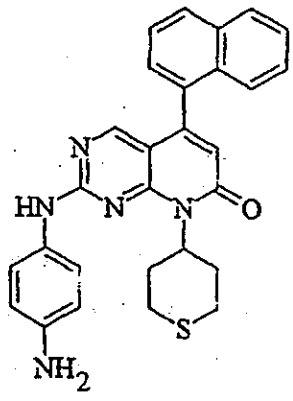
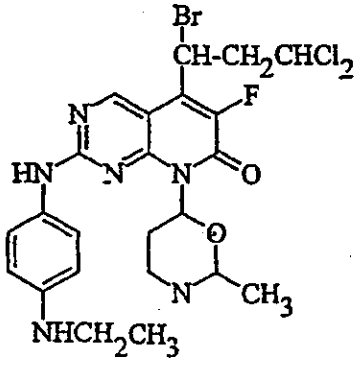


TABLE 1 (cont)



The compounds of the present invention are useful for treating cancer (for example, leukemia and cancer of the lung, breast, prostate, and skin such as melanoma) and other proliferative diseases including but not limited to psoriasis, HSV, HIV, restenosis, and atherosclerosis. To utilize a compound of the present invention to treat cancer, a patient having cancer is administered a therapeutically effective amount of a pharmaceutically acceptable composition comprising an invention compound.

A further embodiment of this invention is a method of treating subjects suffering from diseases caused by vascular smooth muscle cell proliferation. Compounds within the scope of the present invention effectively inhibit vascular smooth muscle cell proliferation and migration. The method entails inhibiting vascular smooth muscle proliferation, and/or migration by administering an effective amount of a compound of Formula I to a subject in need of treatment.

The compounds of the present invention can be formulated and administered in a wide variety of oral and parenteral dosage forms, including transdermal and rectal administration. It will be recognized to those skilled in the art that the following dosage forms may comprise as the active component, either a compound of Formula I or a corresponding pharmaceutically acceptable salt, ester, amide, prodrug, or solvate of a compound of Formula I.

A further embodiment of this invention is a pharmaceutical composition comprising a compound of Formula I together with a pharmaceutically acceptable carrier, diluent, or excipient therefor. For preparing pharmaceutical compositions with the compounds of the present invention, pharmaceutically acceptable carriers

can be either a solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispensable granules. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid such as talc or starch which is in a mixture with the finely divided active component. In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

The compositions of this invention preferably contain from about 5% to about 70% or more of the active compound. Suitable carriers include magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. A preferred form for oral use are capsules, which include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogenous mixture is then poured into convenient size molds, allowed to cool, and thereby to solidify.

Liquid form preparations include solutions, suspensions, and emulsions such as water or water/propylene glycol solutions. For parenteral injection, liquid preparations can be formulated in solution in aqueous polyethylene glycol solution, isotonic saline, 5% aqueous glucose, and the like. Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizing and thickening agents as desired. Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water and mixing with a viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, or other well-known suspending agents.

Also included are solid form preparations that are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like. Waxes, polymers, microparticles, and the like can be utilized to prepare sustained-release dosage forms. Also, osmotic pumps can be employed to deliver the active compound uniformly over a prolonged period.

The pharmaceutical preparations of the invention are preferably in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

The therapeutically effective dose of a compound of Formula I will generally be from about 1 mg/kg to about 100 mg/kg of body weight per day. Typical adult doses will be about 50 mg to about 800 mg per day. The quantity of active component in a unit dose preparation may be varied or adjusted from about 0.1 mg to about 500 mg, preferably about 0.5 mg to 100 mg according to the particular application and the potency of the active component. The composition can, if desired, also contain other compatible therapeutic agents. A subject in need of treatment with a compound of Formula I is administered a dosage of about 1 mg to about 500 mg per day, either singly or in multiple doses over a 24-hour period.

The compounds of the present invention are capable of binding to and inhibiting the activity of proteins having the ability to phosphorylate other proteins, such as cdks, PDGFr, FGFr, c-Src, and EGFr-FL. Cdks form complexes with cyclins, and these complexes phosphorylate key proteins allowing cells to proceed through the cell cycle (Meijer L., *Progress in Cell Cycle Research*, 1995;1:351-363). The compounds of this invention inhibit this phosphorylation

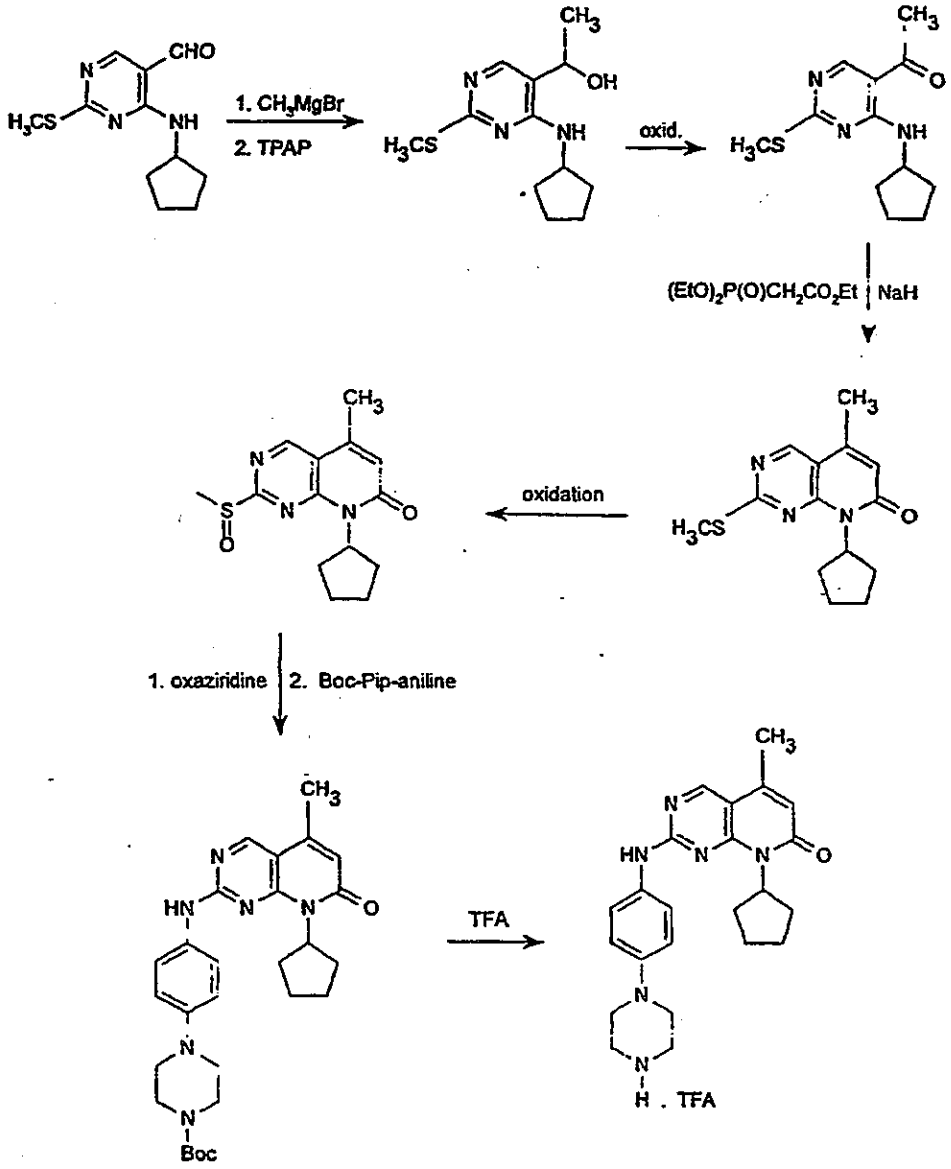
and therefore can be used as anti-proliferative agents for the treatment of cancer and/or restenosis and other proliferative diseases.

Because of their inhibitory activity against cdks and other kinases, the compounds of the present invention are also useful research tools for studying the mechanism of action of those kinases, both in vitro and in vivo.

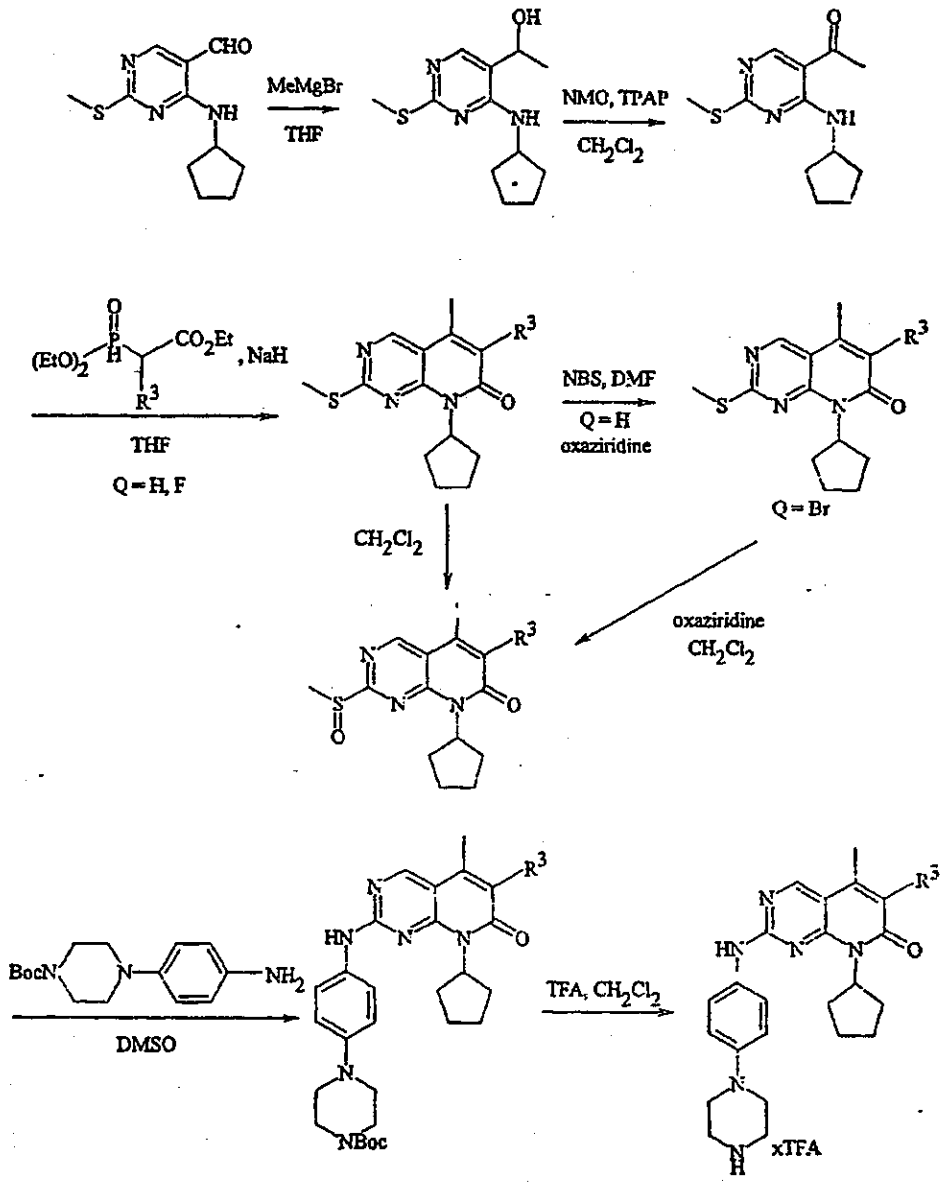
The examples presented below are intended to illustrate particular embodiments of the invention, and are not intended to limit the scope of the specification or the claims in any way.

An illustration of the preparation of compounds of the present invention is shown in Schemes 1 and 2.

Scheme 1


CHO
H_3CS
N
NH
1. CH_3MgBr
2. TPAP
CH_3
OH
oxid.
O
$(EtO)_2P(O)CH_2CO_2Et$
NaH
oxidation
S
1. oxaziridine
2. Boc-Pip-aniline
HN
TFA
Boc
H . TFA

Scheme 2


CHO
MeMgBr
THF
OH
NMO, TPAP
CH_2Cl_2
O
$(EtO)_2$
CO_2Et
, NaH
R^3
THF
Q = H, F
NBS, DMF
Q = H
oxaziridine
Q = Br
CH_2Cl_2
oxaziridine
CH_2Cl_2
BocN
NH_2
DMSO
HN
NBoc
TFA, CH_2Cl_2
xTFA

Those having skill in the art will recognize that the starting materials may be varied and additional steps employed to produce compounds encompassed by the present invention, as demonstrated by the following examples.

As shown in Schemes 1 and 2, a 4-substituted amino-2-methansulfanyl-pyrimidine-5-carboxaldehyde is reacted with an organometallic compound, such as, for example, a Grignard reagent, to afford the corresponding secondary alcohol. The alcohol is subsequently oxidized to the ketone. The ketone is then reacted with a trialkyl phosphonoacetate in the presence of base to produce the corresponding 8-substituted-5-alkyl-2-methylsulfanyl-8H-pyrido[2,3-d]pyrimidin-7-one. The pyrido-pyrimidine then can be halogenated at the 6-position with a common halogenating agent, such as, for example, N-bromosuccinimide (NBS). The 2-methylsulfanyl derivative is oxidized to the corresponding methylsulfoxide, which is subsequently treated with a desired aniline to afford the 2-phenylamino invention compound.

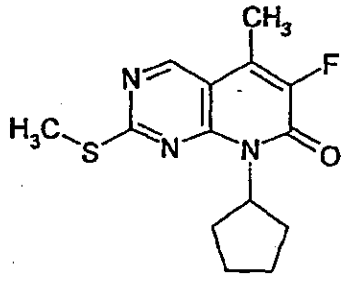
When carrying out various reactions to prepare invention compounds, it may be desirable to derivatize reactive groups such as amines, alcohols, and acids, with protecting groups that are readily removed when desired. Such protecting groups simply avoid unwanted side reactions. Use of protecting groups is common in the art of organic chemistry, as described by Greeve and Wuts in *Protective Groups in Organic Synthesis,* John Wiley and Sons, New York (2nd ed, 1991). Typical hydroxy protecting groups include either forming groups such as benzyl, and acyl groups such as tert-butoxycarbonyl(Boc), formyl, and acetyl. Amino protecting groups include benzyl, acyl such as acetyl, and trialkylsilyl groups. Carboxylic acid groups typically are protected by conversion to an ester that can be easily hydrolyzed, for example, trichloroethyl, tert-butyl, benzyl, and the like.

Some of the invention compounds have one or more chiral centers, and thus can exist as individual optical isomers and mixtures thereof. Compound 246 (Table 1), for example, can exist as an RS racemate, or as the individual R or S isomer. All individual isomers and mixtures thereof are included in this invention. Individual isomers are readily prepared by a chiral synthesis, or by conventional resolution techniques well-known to those skilled in the art.

The invention is illustrated further by the following detailed examples which are not to be construed as limiting the invention in scope or spirit to the specific procedures described in them. The starting materials and various intermediates utilized in the synthesis of invention compounds may be obtained from commercial sources, prepared from commercially available organic compounds, or prepared using well-known synthetic methods. The disclosures in this application of all articles and references, including patents, are incorporated herein by reference.

EXAMPLE 1

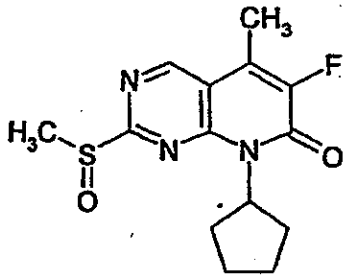
8-Cyclopentyl-6-fluoro-5-methyl-2-methylsulfanyl-8H-pyrido[2,3-d]pyrimidin-7-one



NaH (771 mg, 19.3 mmol) is suspended in dry THF (20 mL), and the mixture is cooled to 0°C in an ice bath. Triethyl 2-fluoro-2-phosphonoacetate (3.9 mL, 19.3 mmol) is added dropwise with stirring, and the solution is stirred at room temperature for 30 minutes. A solution of 1-(4-cyclopentylamino-2-methylsulfanyl-pyrimidin-5-yl)-ethanone in dry THF (40 mL) is added via a cannula, and the reaction mixture is stirred at 24°C for 12 hours. The reaction is quenched by the addition of H_2O (0.5 mL), and the THF is evaporated in vacuo. The residue is partitioned between ethyl acetate and saturated aqueous sodium chloride. The aqueous layer is extracted twice with fresh ethyl acetate, and the combined organic layers are dried over $MgSO_4$. After removal of the drying agent and evaporation of the solvent, the crude product is purified by chromatography on silica gel (eluting with 20%-30% ethyl acetate in hexanes) to give the titled compound as a colorless solid (0.61 g, 23%).

EXAMPLE 2

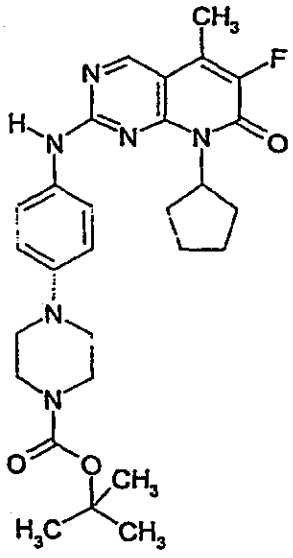
8-Cyclopentyl-6-fluoro-2-methanesulfinyl-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one



8-Cyclopentyl-6-fluoro-5-methyl-2-methylsulfanyl-8H-pyrido[2,3-d]pyrimidin-7-one (0.61 g, 2.08 mmol) from Example 1 and 3-phenyl-1-*p*-nitrophenylsulfonyloxaziridine (0.65 g, 2.5 mmol) are dissolved in CH_2Cl_2 (20 mL) and stirred for 12 hours at 24°C. Following evaporation of the solvent, the crude product is purified by silica gel chromatography (eluting with 80%-100% ethyl acetate in hexanes) to provide the sulfoxide product as a white solid (0.55 g, 86%).

EXAMPLE 3

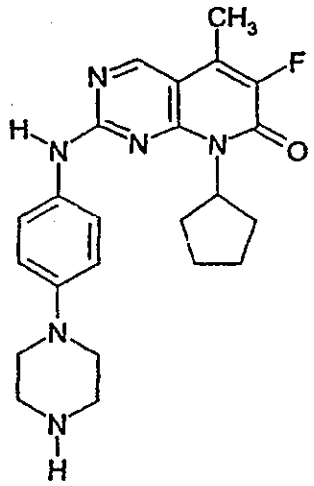
4-[4-(8-Cyclopentyl-6-fluoro-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino)-phenyl]-piperazine-1-carboxylic acid tert-butyl ester



8-Cyclopentyl-6-fluoro-2-methanesulfinyl-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (0.3 g, 0.97 mmol) from Example 2 and 4-(*N*-Boc-piperazin-1-yl)aniline (0.548 g, 1.94 mmol) are suspended in 1,4-dioxane (5 mL) and heated to 80°C for 12 hours. Anhydrous DMSO (2.5 mL) is added, and the temperature is raised to 100°C. Heating is continued for 24 hours, after which the reaction mixture is cooled to 24°C and partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The organic layer is separated and washed with H_2O, and then with saturated aqueous sodium chloride. After drying over anhydrous $MgSO_4$, the solvent is evaporated, and the residue is purified by silica gel chromatography to provide the titled compound as a yellow solid (0.23 g, 45%).

EXAMPLE 4

8-Cyclopentyl-6-fluoro-5-methyl-2-(4-piperazin-1-yl-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one

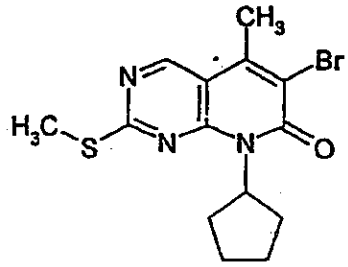


4-[4-(8-Cyclopentyl-6-fluoro-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino)-phenyl]-piperazine-1-carboxylic acid tert-butyl ester (0.23 g, 0.44 mmol) from Example 3 is dissolved in a 1:1 mixture of trifluoroacetic acid (TFA)/CH_2Cl_2 (20 mL) and stirred at room temperature for 1 hour. Evaporation of the solvents, followed by the addition of anhydrous diethyl ether, gave an orange solid (**compound 34**) that is collected by filtration (0.21 g, 74%). Mp 254-255°C.

$C_{23}H_{27}N_6OF \cdot 1.93$ TFA: Calcd C, 50.21; H, 4.54; N, 13.08. Found: C, 49.83; H, 4.45; N, 12.99.

EXAMPLE 5

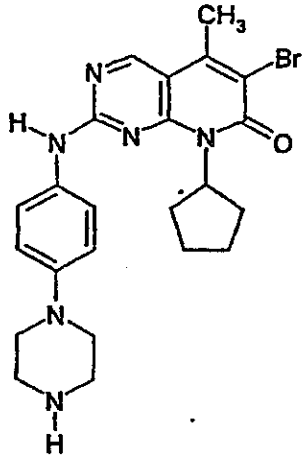
6-Bromo-8-cyclopentyl-5-methyl-2-methylsulfanyl-8H-pyrido[2,3-d]pyrimidin-7-one



8-Cyclopentyl-5-methyl-2-methylsulfanyl-8H-pyrido[2,3-d]pyrimidin-7-one (1 g, 3.64 mmol) is dissolved in dry DMF (15 mL) and *N*-bromosuccinimide (0.97 g, 5.45 mmol) is added followed by benzoylperoxide (0.13 g, 0.5 mmol). The resulting solution is stirred for 12 hours at 24°C. The mixture is then partitioned between ethyl acetate and H_2O. The organic layer is washed with H_2O, and then with saturated aqueous sodium chloride solution and dried over $MgSO_4$. Removal of the drying agent and evaporation of the solvent gave the desired title product (0.86 g, 66%) which is used without further purification.

EXAMPLE 6

6-Bromo-8-cyclopentyl-5-methyl-2-(4-piperazin-1-yl-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one

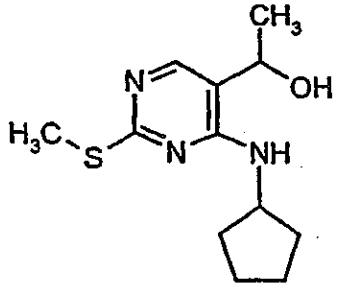


6-Bromo-8-cyclopentyl-5-methyl-2-methylsulfanyl-8H-pyrido[2,3-d]pyrimidin-7-one is oxidized as described in Example 2. The sulfoxide is reacted with 4-(N-Boc-piperazin-1-yl)aniline as described in Example 3. The N-Boc protecting group is removed by hydrolysis as described above for 8-cyclopentyl-6-fluoro-5-methyl-2-methylsulfanyl-8H-pyrido[2,3-d]pyrimidin-7-one to provide 6-Bromo-8-cyclopentyl-5-methyl-2-(4-piperazin-1-yl-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**compound 35**). Mp >200°C (dec).

$C_{23}H_{27}N_6OBr$ 1.9 TFA: Calcd C, 45.90; H, 4.15; N, 11.97. Found: C, 45.53; H, 4.09; N, 11.76.

EXAMPLE 7

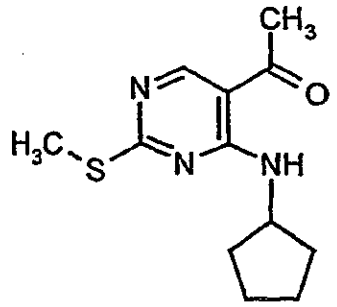
1-(4-Cyclopentylamino-2-methylsulfanyl-pyrimidin-5-yl)-ethan-1-ol



4-Cyclopentylamino-2-methanesulfanyl-pyrimidine-5-carboxaldehyde (1.1 g, 4.64 mmol) is dissolved in tetrahydrofuran (30 mL) under nitrogen and then cooled with an ice bath. To this clear solution is slowly added methyl magnesium bromide (4.4 mL, 13.2 mmol, 3 M in ether). The reaction is stirred for 1 hour with the ice bath still in place. The reaction is quenched with a small amount of saturated aqueous ammonium chloride and then partitioned between water and ethyl acetate. The layers are separated, and the aqueous layer is extracted with ethyl acetate. The combined organic layers are washed with brine and then dried over magnesium sulfate. After filtration, the solvent is removed in vacuo to yield the titled compound as an oil (1.09 g, 90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.42-1.59 (m, 5H), 1.60-1.76 (m, 4H), 2.04-2.06 (m, 2H), 2.49 (s, 3H), 4.38-4.43 (m, 1H), 4.69-4.74 (m, 1H), 6.28-6.30 (d, 1H), 7.57 (s, 1H).

EXAMPLE 8

1-(4-Cyclopentylamino-2-methylsulfanyl-pyrimidin-5-yl)-ethanone

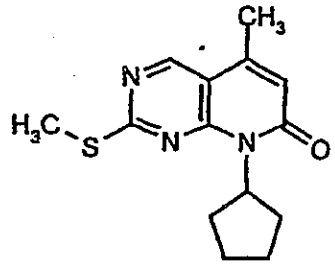


1-(4-Cyclopentylamino-2-methylsulfanyl-pyrimidin-5-yl)-ethan-1-ol (1.09 g, 4.3 mmol) from Example 7 is dissolved in 100 mL of dichloromethane. The solution is purged by bubbling nitrogen gas through it for 2 minutes. To the reaction solution are added, in order: powdered molecular sieves (4 angstrom), *N*-methyl morpholine oxide (1.07 g, 8.6 g), and tetrapropylammonium perruthenate (0.227 g, 0.645 mmol). The reaction mixture is stirred at 24°C for 2 hours, and small amounts of additional catalyst are periodically added. The reaction mixture is then run through a silica column (1:1, ethyl acetate:hexanes) to yield the titled compound as a light yellow solid (0.74 g, 70%). ^{1}H NMR

(400 MHz, $CDCl_3$): δ 1.51-1.78 (m, 6H), 2.02-2.08 (m, 2H), 2.49 (s, 3H), 2.53 (s, 3H), 4.47-4.53 (m, 1H), 8.53 (s, 1H), 9.21 (s, 1H); MS (M+1) 252.2.

EXAMPLE 9

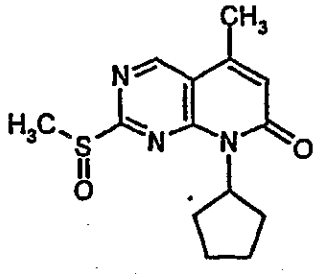
8-Cyclopentyl-5-methyl-2-methylsulfanyl-8H-pyrido[2,3-d]pyrimidin-7-one



A cooled (5°C) flask containing tetrahydrofuran (50 mL) is charged with sodium hydride (1.05 g, 26.3 mmol, 60% dispersion in mineral oil) under nitrogen, and 1.0 g of triethyl phosphonoacetate is added. The cooling bath is removed, and the mixture is stirred at 24°C until it becomes a homogeneous solution. The solution is diluted by the dropwise addition of a solution of 1-(4-cyclopentylamino-2-methylsulfanyl-pyrimidin-5-yl)-ethanone (3.0 g, 11.9 mmol) in tetrahydrofuran (25 mL). The reaction mixture is heated to reflux for 2 hours. The reaction mixture is cooled to 24°C, and diluted 50 mL of water and 50 mL of ethyl acetate. Following separation of the layers, the organic layer is dried over magnesium sulfate and concentrated in vacuo to near dryness. Hexane is added, and the solid is stirred vigorously for 5 minutes before being filtered to yield the titled compound as a light pale orange solid (3.01 g, 92%). ^1H NMR (400 MHz, $CDCl_3$): δ 1.63-2.36 (m, 8H), 2.38 (s, 3H), 2.59 (s, 3H), 5.84-5.93 (m, 1H), 6.39 (s, 1H), 8.66 (s, 1H).

EXAMPLE 10

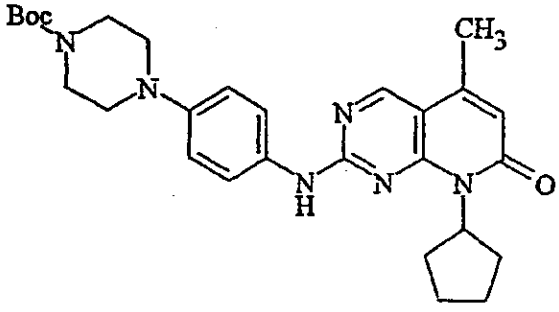
8-Cyclopentyl-2-methanesulfinyl-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one



8-Cyclopentyl-5-methyl-2-methylsulfanyl-8H-pyrido[2,3-d]pyrimidin-7-one (1.0 g, 3.63 mmol) from Example 9 is dissolved in dichloromethane (15 mL), and (±)-*trans*-2-(phenylsulfonyl)-3-phenyloxaziridine is added. The reaction mixture is stirred at 24°C for 12 hours, and then the solution is passed through a silica column (2% MeOH in CH_2Cl_2) to yield the titled sulfoxide as a white solid (0.67 g, 64%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.53-2.19 (m, 8H), 2.45 (s, 3H), 2.87 (s, 3H), 5.75-5.84 (m, 1H), 6.64 (s, 1H), 9.19 (s, 1H).

EXAMPLE 11

4-[4-(8-Cyclopentyl-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino)-phenyl]-piperazine-1-carboxylic acid tert-butyl ester

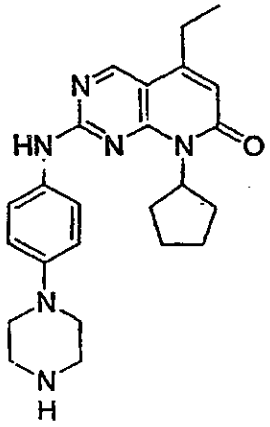


8-Cyclopentyl-2-methanesulfinyl-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (0.7 g, 2.4 mmol) from Example 10 and 4-(4′-*N*-Boc-piperazinyl)-aniline are dissolved in dimethylsulfoxide (8 mL) and heated to 90°C overnight. The reaction mixture is cooled to room temperature and partitioned between water and ethyl acetate. The organic layer is washed with sodium hydrogen carbonate, brine, and then dried over magnesium sulfate. Removal of the drying agent and

concentration in vacuo gives the titled product as a yellow solid that is recrystallized from water and acetonitrile (0.55 g, 45%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.45 (s, 9H), 1.56-1.87 (m, 6H), 2.23-2.28 (m, 2H), 2.31 (s, 3H), 3.07 (m, 4H), 3.55 (m, 4H), 5.77-5.81 (m, 1H), 6.19 (s, 1H), 6.90 (d, 2H), 7.42-7.44 (d, 2H), 7.47 (s, 1H), 8.55 (s, 1H); MS (M+1) 505.1. The Boc protecting group is removed by stirring in a 1:1 mixture of trifluoroacetic acid/dichloromethane to give (Compound 1). Mp >215°C (dec).

EXAMPLE 12

8-Cyclopentyl-5-ethyl-2-(4-piperazin-1-yl-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one **(Compound 193)**



1-(4-Cyclopentylamino-2-methylsulfanyl-pyrimidin-5-yl)-propan-1-ol. 4-Cyclopentylamino-2-methylsulfanyl-pyrimidine-5-carbaldehyde (4.07 g, 17.1 mmol) was dissolved in THF (60 mL) under nitrogen then cooled with an ice bath. To this clear solution EtMgBr (13.4 mL, 40.3 mmol, Aldrich 3M in ether) was slowly added. The reaction was stirred for 15 minutes with the ice bath still in place. The reaction was quenched with a small amount of sat. aq. NH_4Cl then partitioned between water and EtOAc. The layers were separated, the organic layer dried over $MgSO_4$, and after filtration, the solvent was removed in vacuo to yield 1-(4-cyclopentylamino-2-methylsulfanyl-pyrimidin-5-yl)-propan-1-ol as an oil (4.55 g, 99%) which was used without further purification.

1-(4-Cyclopentylamino-2-methylsulfanyl-pyrimidin-5-yl)-propan-1-one. 1-(4-Cyclopentylamino-2-methylsulfanyl-pyrimidin-5-yl)-propan-1-ol (4.55 g, 17.1 mmol) was dissolved in toluene (80 mL) to which manganese (IV) oxide (3.72 g, 42.8 mmol, Aldrich <5 micron, activated, ~85%) was subsequently added. The reaction was brought to reflux for 16 hours. The reaction was cooled to room temperature and filtered though a celite pad. The filtrate then was concentrated in vacuo to yield the product as a light yellow oil (3.79 g, 84%).

8-Cyclopentyl-5-ethyl-2-methylsulfanyl-8H-pyrido[2,3-d]pyrimidin-7-one. Under nitrogen, a cooled flask with THF (50 mL) was charged with NaH (1.23 g, 30.7 mmol, 60% dispersion in mineral oil) to which was added triethyl phosphonoacetate (6.09 mL, 30.7 mmol). The cooling bath was removed, and the reaction mixture was stirred at ambient temperature until everything dissolved. A solution of the 1-(4-cyclopentylamino-2-methylsulfanyl-pyrimidin-5-yl)-propan-1-one (3.0 g, 11.9 mmol) in THF (70 mL) was slowly added to the preformed anion. Then the reaction mixture was brought to reflux for 60 hours. The reaction was cooled to room temperature and diluted with water and EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give a waxy solid. The solid residue was triturated with hexanes to give a white solid after filtration (2.67 g, 66%).

8-Cyclopentyl-5-ethyl-2-methanesulfinyl-8H-pyrido[2,3-d]pyrimidin-7-one. 8-Cyclopentyl-5-ethyl-2-methylsulfanyl-8H-pyrido[2,3-*d*]pyrimidin-7-one (2.57 g, 8.88 mmol) was dissolved in CH_2Cl_2 (50 mL), and 2-benzene-sulfonyl-3-phenyl-oxaziridine was added. The reaction mixture was stirred for 16 hours at room temperature. Then the solution was evaporated in vacuo to give an orange oil. EtOAc was added and a white precipitate formed. This precipitate was filtered and washed with hexanes to yield a white solid (2.12 g, 78%).

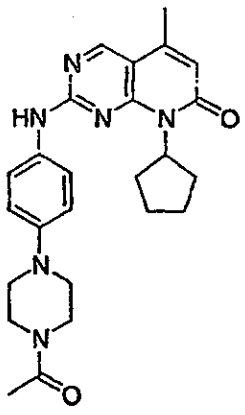
4-[4-(8-Cyclopentyl-5-ethyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino)-phenyl]-piperazine-1-carboxylic acid tert-butyl ester. The sulfoxide, 8-cyclopentyl-5-ethyl-2-methanesulfinyl-8H-pyrido[2,3-*d*]pyrimidin-7-one (0.2 g,

0.654 mmol) and 4-(4'-*N*-Boc-piperazinyl)-aniline were dissolved in DMSO (5 mL) and heated to 70°C for 16 hours. The reaction mixture was cooled to room temperature and partitioned between water and EtOAc. The organic layer was washed with brine then dried over $MgSO_4$. After filtration and concentrate in vacuo, orange solid was obtained which was purified by column chromatography to yield the product as a yellow solid (0.160 g, 47%).

8-Cyclopentyl-5-ethyl-2-(4-piperazin-1-yl-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (235)·4-[4-(8-Cyclopentyl-5-ethyl-7-oxo-7,8-dihydro-pyrido[2,3-*d*]pyrimidin-2-ylamino)-phenyl]-piperazine-1-carboxylic acid tert-butyl ester was dissolved in dichloromethane (2 mL), and trifluoroacetic acid (0.5 mL) was added. This mixture was stirred at room temperature for 15 hours. The solvent was evaporated, then the solid was suspended in diethyl ether and filtered to give a fluffy gray solid (128 mg, 75%). ^1H NMR (400 MHz, DMSO-d_6): δ 1.17 (m, 3H), 1.52-1.83 (m, 6H), 2.20 (m, 2H), 2.75 (m, 2H), 3.22 (m, 4H), 5.78 (m, 1H), 6.10 (s, 1H), 6.95 (d, 2H), 7.53 (d, 2H), 8.73 (s, 2H), 8.79 (s, 1H), 9.76 (s, 1H); CHN for $C_{23}H_{30}N_6O$ + 1.21 TFA.

EXAMPLE 13

2-[4-(4-Acetyl-piperazin-1-yl)-phenylamino]-8-cyclopentyl-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one **(Compound 198)**

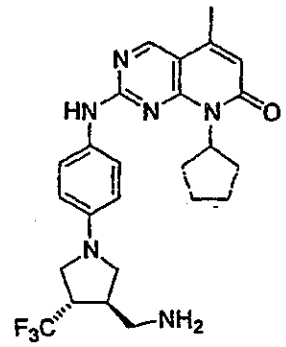


1-[4-(4-Amino-phenyl)-piperazin-1-yl]-ethane (0.075 g, 0.343 mmol) and 8-cyclopentyl-5-methyl-2-methanesulfinyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one

(0.100 g, 0.343 mmol) were dissolved in DMSO (5 mL) and heated to 70°C for 16 hours. At this point, 20 mg more of the aniline was added, and heating was continued for an additional 4 hours. The reaction was cooled to room temperature and partitioned between water and EtOAc. The organic layer was washed with brine then dried over $MgSO_4$. Filtration and concentration in vacuo gave an orange solid which was purified by column chromatography to yield a yellow solid (0.049 g, 32%). Mp 261-263°C.

EXAMPLE 14

2-[4-((3R,4S)-Aminomethyl-trifluoromethyl-pyrrolidin-1-yl)-phenylamino]-8-cyclopentyl-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one **(Compound 216)**



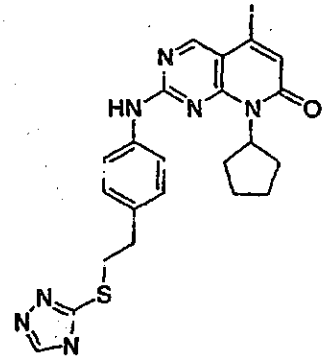
[(3R,4S)-1-(4-Amino-phenyl)-trifluoromethyl-pyrrolidin-3-ylmethyl]-carbamic acid tert-butyl ester. ((3*S*,4*S*)-4-Trifluoromethyl-pyrrolidin-3-ylmethyl)-carbamic acid *tert*-butyl ester (1.0 g, 3.72 mmol), *p*-fluoro-nitrobenzene (0.36 mL, 3.38 mmol) and diisopropyl ethyl amine (0.65 mL, 3.72 mmol) were dissolved in acetonitrile (10 mL) and refluxed for 24 hours. The solvent was removed, and the mixture was triturated with hexanes and filtered to yield a crude yellow solid (1.4 g). This product was dissolved in THF and treated with Raney Nickel under a hydrogen atmosphere until no further change in pressure was observable. Following removal of the catalyst by filtration, the product aniline was obtained by evaporation of the solvent and used without further purification.

{(3R,4S)-[4-(8-Cyclopentyl-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-α]pyrimidin-2-ylamino)-phenyl]-trifluoromethyl-pyrrolidin-3-ylmethyl}-carbamic acid tert-butyl ester (222). [(3*R*,4*S*)-1-(4-Amino-phenyl)-

trifluoromethyl-pyrrolidin-3-ylmethyl]-carbamic acid tert-butyl ester and 8-cyclopentyl-5-methyl-2-methanesulfinyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one were coupled and deprotected as previously described for Example 11.
CHN for $C_{25}H_{29}N_6O_1F_3$ + 1.6 TFA, mp >130°C (dec).

EXAMPLE 15

8-Cyclopentyl-5-methyl-2-{4-[2-(4H-[1,2,4]triazol-3-ylsulfanyl)-ethyl]-phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one **(Compound 222)**



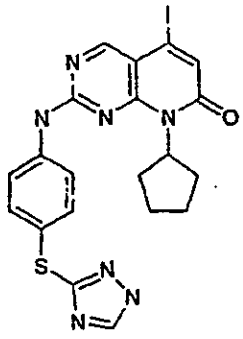
4-[2(4H-[1,2,4]triazol-3-ylsulfanyl)-ethyl]-phenylamine. To a suspension of hexane rinsed 60% sodium hydride (0.83 g), in dimethylformamide (5 mL) at 0°C, was added a solution of 3-mercapto-1,2,4-triazole (2.0 g) in dimethylformamide (10 mL) in portions. After 45 minutes 4-nitrophenethyl bromide (4.1 g) was added, and the reaction mixture was stirred at room temperature for 18 hours. 1 M Hydrochloric acid (70 mL) was added and the aqueous phase was extracted with diethyl ether (3 × 100 mL), and the combined organic extracts were concentrated to dryness. The resulting solid was collected, washed with diethyl ether (2 × 10 mL) and dried to yield the nitrobenzene intermediate (3.17 g). *MS*: MH+, 251; MH- 248.9. A solution of this intermediate (1.0 g) was reduced using Raney Nickel (0.5 g) and hydrogen in THF (100 mL). The sample was concentrated to dryness to yield the title compound (0.88 g), *MS*: MH+, 221; MH-, 219.

8-Cyclopentyl-5-methyl-2-{4-[2-(4H-[1,2,4]triazol-3-ylsulfanyl)-ethyl]-phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one. A solution of 8-cyclopentyl-5-methyl-2-methanesulfinyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (0.02 g), 4-[2(4*H*-

[1,2,4]triazol-3-ylsulfanyl)-ethyl]-phenylamine (0.0166 g) and trifluoroacetic acid (0.06 mL) in acetonitrile (2 mL) was heated at 80°C for 18 hours. The reaction mixture was cooled and the solvent removed in vacuo. 1 M Sodium hydroxide (4 mL) was added and the aqueous phase was extracted with diethyl ether (3 × 4 mL); sodium chloride (20 mg) was added after the first extraction. The aqueous layer was acidified to pH = 1 and extracted with a mixture of ethyl acetate/dichloromethane (9:1) (3 × 4 mL). The combined ethyl acetate/dichloromethane extracts were concentrated to dryness and purified by column chromatography using a gradient of ethyl acetate 60% to 100% in hexanes. Concentration of the appropriate fractions yielded Compound 222 (0.014 g). ^{1}H NMR (d_6-DMSO): δ 1.58 (2H, m), 1.7 (2H, m), 1.88 (2H, m), 2.2 (2H, m), 2.38 (3H, s), 2.9 (2H, m), 3.4 (2H, m), 5.7 (1H, s), 5.8 (1H, m), 7.18 (2H, d, J = 9), 7.6 (2H, d, J = 9), 8.78 (1H, s).

EXAMPLE 16

8-Cyclopentyl-5-methyl-2-[4-(1H-[1,2,4]triazol-3-ylsulfanyl)-phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one **(Compound 223)**



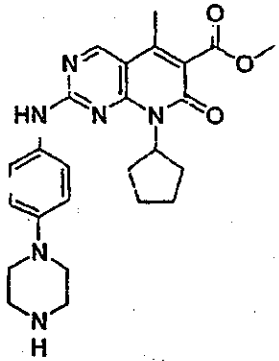
4-(1H-[1,2,4]triazol-3-ylsulfanyl)-phenylamine. To a suspension of hexanes rinsed 60% sodium hydride (1.16 g) in dimethylformamide (10 mL) at 0°C was added a solution of 3-mercapto-1,2,4-triazole (4.0 g) in dimethylformamide (20 mL) dropwise. After 20 minutes, 1-fluoro-4-nitrobenzene (5 g) in dimethylformamide (20 mL) was added, and the reaction mixture was stirred at room temperature for 2 hours, then at 60°C for 18 hours. 1 M Hydrochloric acid (100 mL) was added, and the solid was collected and dried. A second crop of solid (2.1 g) was recovered by crystallization from the mother

liquors. To the combined solids was added dichloromethane (300 mL) and 1 M sodium hydroxide (200 mL). The dichloromethane was further extracted with 1 M sodium hydroxide (100 mL). The combined aqueous phases were extracted with dichloromethane (2 x 300 mL) then acidified to pH = 1. The solid formed was collected and dried to yield the nitrobenzene derivative (1.96 g). This product was reduced using Raney Nickel and hydrogen in tetrahydrofuran (100 mL). Following removal of the catalyst, the sample was concentrated to dryness to yield the desired product (1.7 g), *MS*: MH+, 192.9; MH-, 190.0.

8-Cyclopentyl-5-methyl-2-[4-(1H-[1,2,4]triazol-3-ylsulfanyl)-phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one. This compound was prepared from 4-(1H-[1,2,4]triazol-3-ylsulfanyl)-phenylamine and 8-cyclopentyl-5-methyl-2-methanesulfinyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one by the procedure of Example 15 to give Compound 223. ^{1}H NMR (D_6-DMSO): δ 1.58 (2H, m), 1.75 (2H, m), 1.90 (2H, m), 2.2 (2H, m), 2.38 (3H, s), 5.82 (1H, m), 6.20 (1H, s), 7.4 (2H, d, J = 9), 7.73 (2H, d, J = 9), 8.85 (1H, bs), 8.82 (1H, s).

EXAMPLE 17

8-Cyclopentyl-5-methyl-7-oxo-2-(4-piperazin-1-yl-phenylamino)-7,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid methyl ester **(Compound 224)**



4-[4-(6-Bromo-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-*d*]pyrimidin-2-ylamino)-phenyl]-piperazine-1-carboxylic acid *tert*-butyl ester (300 mg, 0.515 mmol), $Pd(OAc)_2$ (23 mg, 0.05 mmol), 1,2-bis(diphenylphosphino)-propane 64 mg, 0.155 mmol), and triethylamine (0.18 mL, 1.29 mmol) were combined in methanol and pressurized to 500 PSI in

CO gas. The reaction mixture was heated to 100°C and stirred for 14 hours, then allowed to cool to 24°C. Evaporation of the solvent, followed by chromatography on SiO_2 (45%-50% EtOAc in Hexanes) gave a yellow oil. This oil was dissolved in CH_2Cl_2 (10 mL) and treated with 2 M HCl in diethyl ether (10 mL) at room temperature. A white precipitate formed. After stirring for 3 hours at room temperature, the solvent was evaporated. The residue was re-suspended in anhydrous diethyl ether and filtered to give the titled compound as a yellow solid (34 mg), mp 195-205°C. ^1H NMR (d_6-DMSO): δ 1.52 (br s, 2H), 1.71 (br s, 2H), 1.82 (br s, 2H), 2.14 (br s, 2H), 2.30 (s, 3H), 3.18 (s, 4H), 3.27 (s, 4H), 3.76 (s, 3H), 5.8 (s, 1H), 6.96 (d, J = 8 Hz, 2H), 7.53 (d, J = 8 Hz, 2H), 8.85 (s, 1H), 9.04 (s, 1H), 9.97 (s, 1H).

EXAMPLE 18

The following compounds are prepared essentially according to the procedures described in Examples 1 to 17 and as illustrated in Schemes 1 and 2:

(a) 8-Cyclopentyl-5-methyl-2-(4-piperazin-1-yl-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one trifluoroacetic acid salt (**Compound 1**), mp >215°C (dec);

(b) 8-(1-Methylethyl)-5-methyl-2-(4-piperazin-1-yl-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 2**), mp >235°C (dec);

(c) 8-Cyclopentyl-5-methyl-2-(4-fluoro-3-methylphenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 3**);

(d) 8-(1-Methylethyl)-5-methyl-2-(4-fluoro-3-methylphenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 4**);

(e) 8-Cyclohexyl-5-methyl-2-(4-fluoro-3-methylphenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 5**);

(f) 8-Cyclohexyl-5-methyl-2-[4-(4-propanoylpiperazin-1-yl)phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 6**);

(g) 8-Cyclopentyl-5-methyl-2-[4-(4-propanoylpiperazin-1-yl)phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one trifluoroacetic acid salt (**Compound 7**), mp 235-237°C;

(h) 8-(1-Methylethyl)-5-methyl-2-[4-(4-propanoylpiperazin-1-yl)phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 8**);

(i) 8-Cyclohexyl-5-methyl-2-(4-piperazin-1-yl-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 9**);

(j) 8-Cyclopentyl-5-methyl-2-(4-pyridylphenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 10**);

(k) 8-(1-Methylethyl)-5-methyl-2-(4-pyridylphenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 11**);

(l) 8-Cyclopentyl-5-methyl-2-[4-(3-aminopyrrolidinyl)phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one trifluoroacetic acid salt (**Compound 12**), mp >195°C (dec);

(m) 8-(1-Methylethyl)-5-methyl-2-[4-(3-aminopyrrolidinyl)phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 13**), mp >227-229°C;

(n) N-(1-{4-[(8-cyclopentyl-5-methyl-7-oxo(8-hydropyridino[2,3-d]-pyrimidin-2-yl))amino]phenyl}pyrrolidin-3-yl)-3,3-dimethylbutanamide (**Compound 14**);

(o) N-(1-{4-[(5-methyl-8-(1-methylethyl)-7-oxo(8-hydropyridino[2,3-d]-pyrimidin-2-yl))amino]phenyl}pyrrolidin-3-yl)-3,3-dimethylbutanamide (**Compound 15**);

(p) 8-Cyclopentyl-5-methyl-2-(3-chloro-4-piperazin-1-yl-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 16**), mp 234-237°C;

(q) 8-Cyclohexyl-5-methyl-2-(3-chloro-4-piperazin-1-yl-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 17**);

(r) 8-(1-Methylethyl)-5-methyl-2-(3-chloro-4-piperazin-1-yl-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 18**);

(s) 8-Cyclopentyl-6-fluoro-5-methyl-2-(3-chloro-4-piperazin-1-yl-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 19**);

(t) 8-Cyclohexyl-6-fluoro-5-methyl-2-(3-chloro-4-piperazin-1-yl-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 21**);

(u) 8-(1-Methylethyl)-6-fluoro-5-methyl-2-(3-chloro-4-piperazin-1-yl-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 20**);

(v) 8-Cyclopentyl-5-methyl-2-(3-chloro-4-morpholin-4-yl-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 22**);

(w) 8-(1-Methylethyl)-5-methyl-2-(3-chloro-4-morpholin-4-yl-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 23**);

(x) 8-Cyclohexyl-5-methyl-2-(3-chloro-4-morpholin-4-yl-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 24**);

(y) 2-({3-chloro-4-[4-(3-morpholin-4-ylpropyl)piperidyl]phenyl}amino)-8-cyclopentyl-5-methyl-8-hydropyridino[2,3-d]pyrimidin-7-one (**Compound 25**);

(z) 2-({3-chloro-4-[4-(3-morpholin-4-ylpropyl)piperidyl]phenyl}amino)-8-(1-methylethyl)-5-methyl-8-hydropyridino[2,3-d]pyrimidin-7-one (**Compound 26**);

(aa) 2-({3-chloro-4-[4-(3-morpholin-4-ylpropyl)piperidyl]phenyl}amino)-8-cyclohexyl-5-methyl-8-hydropyridino[2,3-d]pyrimidin-7-one (**Compound 27**);

(bb) 2-({3-chloro-4-[4-(3-piperazinylpropyl)piperidyl]phenyl}amino)-8-cyclopentyl-6-fluoro-5-methyl-8-hydropyridino[2,3-d]pyrimidin-7-one (**Compound 28**);

(cc) 2-({3-chloro-4-[4-(3-piperazinylpropyl)piperidyl]phenyl}amino)-8-(1-methylethyl)-6-fluoro-5-methyl-8-hydropyridino[2,3-d]pyrimidin-7-one (**Compound 29**);

(dd) 2-({3-chloro-4-[4-(3-piperazinylpropyl)piperidyl]phenyl}amino)-8-cyclohexyl-6-fluoro-5-methyl-8-hydropyridino[2,3-d]pyrimidin-7-one (**Compound 30**), mp >80°C (dec);

(ee) 2-({3-chloro-4-[4-(3-piperazinylpropyl)piperidyl]phenyl}amino)-8-cyclopentyl-5-methyl-8-hydropyridino[2,3-d]pyrimidin-7-one (**Compound 31**);

(ff) 2-({3-chloro-4-[4-(3-piperazinylpropyl)piperidyl]phenyl}amino)-8-(1-methylethyl)-5-methyl-8-hydropyridino[2,3-d]pyrimidin-7-one (**Compound 32**);

(gg) 2-({3-chloro-4-[4-(3-piperazinylpropyl)piperidyl]phenyl}amino)-8-cyclohexyl-5-methyl-8-hydropyridino[2,3-d]pyrimidin-7-one (**Compound 33**);

(gg2) 8-Cyclopentyl-2-[4-(piperazin-1-yl)-phenylamino]-6-fluoro-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one trifluoroacetate (**Compound 34**), mp 254-255°C;

(gg3) 8-Cyclopentyl-2-[4-(piperazin-1-yl)-phenylamino]-6-bromo-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one trifluoroacetate (**Compound 35**), mp >200°C;

(hh) 8-Cyclopentyl-2-[4-(3,5-dimethyl-piperazin-1-yl)-phenylamino]-6-fluoro-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one hydrochloride (**Compound 36**), mp >220°C;

(ii) 8-Cyclopentyl-2-(3-fluoro-4-piperazin-1-yl-phenylamino)-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 37**);

(jj) 6-Bromo-8-cyclopentyl-2-[4-(3,5-dimethyl-piperazin-1-yl)-phenylamino]-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one hydrochloride (**Compound 38**), mp >230°C;

(kk) 8-Cyclopentyl-6-fluoro-2-(3-fluoro-4-piperazin-1-yl-phenylamino)-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 39**);

(ll) 6-Bromo-8-cyclopentyl-2-(3-fluoro-4-piperazin-1-yl-phenylamino)-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 40**);

(mm) 8-Cyclopentyl-2-[4-(3,5-dimethyl-piperazin-1-yl)-phenylamino]-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one hydrochloride (**Compound 41**);

(nn) 2-(3-Chloro-4-piperazin-1-yl-phenylamino)-8-cyclopentyl-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 42**);

(oo) 2-(3-Chloro-4-piperazin-1-yl-phenylamino)-8-cyclopentyl-6-fluoro-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 43**);

(pp) 6-Bromo-2-(3-chloro-4-piperazin-1-yl-phenylamino)-8-cyclopentyl-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 44**);

(qq) 8-Cyclopentyl-5-methyl-2-(4-morpholin-4-yl-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one trifluoroacetate (**Compound 45**), mp 227-229°C;

(rr) 8-Cyclopentyl-6-fluoro-5-methyl-2-(4-morpholin-4-yl-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 46**);

(ss) 6-Bromo-8-cyclopentyl-5-methyl-2-(4-morpholin-4-yl-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 47**);

(tt) 8-Cyclopentyl-2-(3-fluoro-4-morpholin-4-yl-phenylamino)-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 48**);

(uu) 8-Cyclopentyl-6-fluoro-2-(3-fluoro-4-morpholin-4-yl-phenylamino)-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 49**);

(vv) 6-Bromo-8-cyclopentyl-2-(3-fluoro-4-morpholin-4-yl-phenylamino)-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 50**);

(ww) 2-(3-Chloro-4-morpholin-4-yl-phenylamino)-8-cyclopentyl-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 51**);

(xx) 2-(3-Chloro-4-morpholin-4-yl-phenylamino)-8-cyclopentyl-6-fluoro-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 52**);

(yy) 6-Bromo-2-(3-chloro-4-morpholin-4-yl-phenylamino)-8-cyclopentyl-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 53**);

(zz) 8-Cyclopentyl-5-methyl-2-{4-[4-(2,2,2-trifluoro-ethyl)-piperazin-1-yl]-phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 54**), mp 198-199°C;

(aaa) 8-Cyclopentyl-6-fluoro-5-methyl-2-{4-[4-(2,2,2-trifluoro-ethyl)-piperazin-1-yl]-phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 55**);

(bbb) 6-Bromo-8-cyclopentyl-5-methyl-2-{4-[4-(2,2,2-trifluoro-ethyl)-piperazin-1-yl]-phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 56**);

(ccc) 8-Cyclopentyl-5-methyl-2-{4-[4-(3-piperazin-1-yl-propyl)-piperidin-1-yl]-phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one trifluoroacetate (**Compound 57**), mp >80°C (dec);

(ddd) 8-Cyclopentyl-6-fluoro-5-methyl-2-{4-[4-(3-piperazin-1-yl-propyl)-piperidin-1-yl]-phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 58**), mp >230°C;

(eee) 6-Bromo-8-cyclopentyl-5-methyl-2-{4-[4-(3-piperazin-1-yl-propyl)-piperidin-1-yl]-phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 59**);

(fff) 8-Cyclopentyl-5-methyl-2-{4-[4-(3-morpholin-4-yl-propyl)-piperidin-1-yl]-phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 60**);

(ggg) 8-Cyclopentyl-6-fluoro-5-methyl-2-{4-[4-(3-morpholin-4-yl-propyl)-piperidin-1-yl]-phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 61**);

(hhh) 6-Bromo-8-cyclopentyl-5-methyl-2-{4-[4-(3-morpholin-4-yl-propyl)-piperidin-1-yl]-phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 62**);

(iii) 6-Bromo-8-cyclopentyl-5-methyl-2-{4-[4-(3-morpholin-4-yl-propyl)-piperidin-1-yl]-phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 63**);

(jjj) 2-(4-{4-[3-(3-Amino-pyrrolidin-1-yl)-propyl]-piperidin-1-yl}-phenylamino)-8-cyclopentyl-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 64**);

(kkk) 2-(4-{4-[3-(3-Amino-pyrrolidin-1-yl)-propyl]-piperidin-1-yl}-phenylamino)-8-cyclopentyl-6-fluoro-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 65**);

(lll) 2-(4-{4-[3-(3-Amino-pyrrolidin-1-yl)-propyl]-piperidin-1-yl}-phenylamino)-6-bromo-8-cyclopentyl-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 66**);

(mmm) 8-Cyclopentyl-2-{3-fluoro-4-[4-(3-piperazin-1-yl-propyl)-piperidin-1-yl]-phenylamino}-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 67**);

(nnn) 8-Cyclopentyl-6-fluoro-2-{3-fluoro-4-[4-(3-piperazin-1-yl-propyl)-piperidin-1-yl]-phenylamino}-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 68**);

(ooo) 6-Bromo-8-cyclopentyl-2-{3-fluoro-4-[4-(3-piperazin-1-yl-propyl)-piperidin-1-yl]-phenylamino}-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 69**);

(ppp) 8-Cyclopentyl-2-{3-fluoro-4-[4-(3-morpholin-4-yl-propyl)-piperidin-1-yl]-phenylamino}-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 70**);

(qqq) 8-Cyclopentyl-6-fluoro-2-{3-fluoro-4-[4-(3-morpholin-4-yl-propyl)-piperidin-1-yl]-phenylamino}-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 71**);

(rrr) 6-Bromo-8-cyclopentyl-2-{3-fluoro-4-[4-(3-morpholin-4-yl-propyl)-piperidin-1-yl]-phenylamino}-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 72**);

(sss) 2-[4-(3-Amino-pyrrolidin-1-yl)-phenylamino]-8-cyclopentyl-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 73**), mp >215°C (dec);

(ttt) 2-[4-(3-Amino-pyrrolidin-1-yl)-phenylamino]-8-cyclopentyl-6-fluoro-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 74**);

(uuu) 2-[4-(3-Amino-pyrrolidin-1-yl)-phenylamino]-6-bromo-8-cyclopentyl-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 75**);

(vvv) 2-[4-(3-Amino-pyrrolidin-1-yl)-3-fluoro-phenylamino]-8-cyclopentyl-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 76**);

(www) 2-[4-(3-Amino-pyrrolidin-1-yl)-3-fluoro-phenylamino]-8-cyclopentyl-6-fluoro-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 77**);

(xxx) 2-[4-(3-Amino-pyrrolidin-1-yl)-3-fluoro-phenylamino]-6-bromo-8-cyclopentyl-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 78**);

(yyy) 8-Cyclopentyl-5-methyl-2-{4-[3-(2,2,2-trifluoro-ethylamino)-pyrrolidin-1-yl]-phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one trifluoroacetate (**Compound 79**), mp >160°C (dec);

(zzz) 8-Cyclopentyl-6-fluoro-5-methyl-2-{4-[3-(2,2,2-trifluoro-ethylamino)-pyrrolidin-1-yl]-phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 80**);

(aaaa) 6-Bromo-8-cyclopentyl-5-methyl-2-{4-[3-(2,2,2-trifluoro-ethylamino)-pyrrolidin-1-yl]-phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 81**);

(bbbb) 2-[4-(3-Amino-pyrrolidin-1-yl)-3-chloro-phenylamino]-8-cyclopentyl-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one trifluoroacetate (**Compound 82**), mp >215°C (dec);

(cccc) 2-[4-(3-Amino-pyrrolidin-1-yl)-3-chloro-phenylamino]-8-cyclopentyl-6-fluoro-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 83**), mp 221°C;

(dddd) 2-[4-(3-Amino-pyrrolidin-1-yl)-3-chloro-phenylamino]-6-bromo-8-cyclopentyl-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 84**);

(eeee) 2-[4-(3-Aminomethyl-4-trifluoromethyl-pyrrolidin-1-yl)-phenylamino]-8-cyclopentyl-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one **(Compound 85)**;

(ffff) 2-[4-(3-Aminomethyl-4-trifluoromethyl-pyrrolidin-1-yl)-phenylamino]-8-cyclopentyl-6-fluoro-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one **(Compound 86)**;

(gggg) 2-[4-(3-Aminomethyl-4-trifluoromethyl-pyrrolidin-1-yl)-phenylamino]-6-bromo-8-cyclopentyl-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one **(Compound 87)**;

(hhhh) 2-[4-(3-Trifloroethylaminomethyl-pyrrolidin-1-yl)-phenylamino]-8-cyclopentyl-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one **(Compound 88)**;

(iiii) 2-[4-(3-Trifloroethylaminomethyl-pyrrolidin-1-yl)-phenylamino]-8-cyclopentyl-6-fluoro-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one **(Compound 89)**;

(jjjj) 2-[4-(3-Trifloroethylaminomethyl-pyrrolidin-1-yl)-phenylamino]-6-bromo-8-cyclopentyl-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one **(Compound 90)**;

(kkkk) 8-Cyclopentyl-2-[4-(3,3-dimethyl-piperazin-1-yl)-phenylamino]-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one hydrochloride **(Compound 91)**, mp >150°C (dec);

(llll) 8-Cyclopentyl-2-[4-(3,3-dimethyl-piperazin-1-yl)-phenylamino]-6-fluoro-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one **(Compound 92)**;

(mmmm) 6-Bromo-8-cyclopentyl-2-[4-(3,3-dimethyl-piperazin-1-yl)-phenylamino]-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one hydrochloride **(Compound 93)**, mp >200°C (dec);

(nnnn) 8-Cyclopentyl-5-methyl-2-[4-(3,3,4-trimethyl-piperazin-1-yl)-phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one **(Compound 94)**;

(oooo) 8-Cyclopentyl-6-fluoro-5-methyl-2-[4-(3,3,4-trimethyl-piperazin-1-yl)-phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one **(Compound 95)**;

(pppp) 6-Bromo-8-cyclopentyl-5-methyl-2-[4-(3,3,4-trimethyl-piperazin-1-yl)-phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one **(Compound 96)**;

(qqqq) 2-[4-(4-Acetyl-piperazin-1-yl)-phenylamino]-8-cyclopentyl-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 97**);

(rrrr) 2-[4-(4-Acetyl-piperazin-1-yl)-phenylamino]-8-cyclopentyl-6-fluoro-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 98**), mp 267-269°C;

(ssss) 2-[4-(4-Acetyl-piperazin-1-yl)-phenylamino]-6-bromo-8-cyclopentyl-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 99**);

(tttt) 8-Cyclopentyl-2-{4-[4-(2-hydroxy-ethyl)-3,5-dimethyl-piperazin-1-yl]-phenylamino}-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 100**), mp 156-159°C;

(uuuu) 8-Cyclopentyl-6-fluoro-2-{4-[4-(2-hydroxy-ethyl)-3,5-dimethyl-piperazin-1-yl]-phenylamino}-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 101**);

(vvvv) 6-Bromo-8-cyclopentyl-2-{4-[4-(2-hydroxy-ethyl)-3,5-dimethyl-piperazin-1-yl]-phenylamino}-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 102**);

(wwww) 8-Cyclopentyl-5-methyl-2-(4-perhydro-1,4-diazepin-1-yl-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one hydrochloride (**Compound 103**), mp 172°C (dec);

(xxxx) 8-Cyclopentyl-6-fluoro-5-methyl-2-(4-perhydro-1,4-diazepin-1-yl-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one hydrochloride (**Compound 104**), mp 192°C (dec);

(yyyy) 6-Bromo-8-cyclopentyl-5-methyl-2-(4-perhydro-1,4-diazepin-1-yl-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 105**);

(zzzz) 8-Cyclopentyl-5-methyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 106**), mp 211-213°C;

(aaaaa) 8-Cyclopentyl-6-fluoro-5-methyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 107**);

(bbbbb) 6-Bromo-8-cyclopentyl-5-methyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 108**);

(ccccc) 8-Cyclopentyl-5-methyl-2-[4-(4-methyl-perhydro-1,4-diazepin-1-yl)-phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 109**), mp >185°C (dec);

(ddddd) 8-Cyclopentyl-6-fluoro-5-methyl-2-[4-(4-methyl-perhydro-1,4-diazepin-1-yl)-phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 110**);

(eeeee) 6-Bromo-8-cyclopentyl-5-methyl-2-[4-(4-methyl-perhydro-1,4-diazepin-1-yl)-phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 111**);

(fffff) {4-[4-(8-Cyclopentyl-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino)-phenyl]-piperazin-1-yl}-acetic acid (**Compound 112**);

(ggggg) {4-[4-(8-Cyclopentyl-6-fluoro-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino)-phenyl]-piperazin-1-yl}-acetic acid (**Compound 113**);

(hhhhh) {4-[4-(6-Bromo-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino)-phenyl]-piperazin-1-yl}-acetic acid (**Compound 114**);

(iiiii) 8-Cyclopentyl-5-methyl-2-(4-{4-[3-(1H-tetrazol-5-yl)-propyl]-piperidin-1-yl}-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 115**);

(jjjjj) 8-Cyclopentyl-6-fluoro-5-methyl-2-(4-{4-[3-(1H-tetrazol-5-yl)-propyl]-piperidin-1-yl}-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 116**);

(kkkkk) 6-Bromo-8-cyclopentyl-5-methyl-2-(4-{4-[3-(1H-tetrazol-5-yl)-propyl]-piperidin-1-yl}-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 117**);

(lllll) 8-Cyclopentyl-5-methyl-2-(4-{4-[3-(5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-ylsulfanyl)-propyl]-piperidin-1-yl}-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 118**);

(mmmmm) 8-Cyclopentyl-6-fluoro-5-methyl-2-(4-{4-[3-(5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-ylsulfanyl)-propyl]-piperidin-1-yl}-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 119**);

(nnnnn) 6-Bromo-8-cyclopentyl-5-methyl-2-(4-{4-[3-(5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-ylsulfanyl)-propyl]-piperidin-1-yl}-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 120**);

(ooooo) 8-Cyclopentyl-5-methyl-2-(4-{4-[3-(5-oxo-4,5-dihydro-1H-1,2,4-triazole-3-sulfinyl)-propyl]-piperidin-1-yl}-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 121**);

(ppppp) 8-Cyclopentyl-6-fluoro-5-methyl-2-(4-{4-[3-(5-oxo-4,5-dihydro-1H-1,2,4-triazole-3-sulfinyl)-propyl]-piperidin-1-yl}-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 122**);

(qqqqq) 6-Bromo-8-cyclopentyl-5-methyl-2-(4-{4-[3-(5-oxo-4,5-dihydro-1H-1,2,4-triazole-3-sulfinyl)-propyl]-piperidin-1-yl}-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 123**);

(rrrrr) 8-Cyclopentyl-5-methyl-2-(4-{4-[3-(5-oxo-4,5-dihydro-1H-1,2,4-triazole-3-sulfonyl)-propyl]-piperidin-1-yl}-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 124**);

(sssss) 8-Cyclopentyl-6-fluoro-5-methyl-2-(4-{4-[3-(5-oxo-4,5-dihydro-1H-1,2,4-triazole-3-sulfonyl)-propyl]-piperidin-1-yl}-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 125**);

(ttttt) 6-Bromo-8-cyclopentyl-5-methyl-2-(4-{4-[3-(5-oxo-4,5-dihydro-1H-1,2,4-triazole-3-sulfonyl)-propyl]-piperidin-1-yl}-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 126**);

(uuuuu) N-(2-{1-[4-(8-Cyclopentyl-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino)-phenyl]-piperidin-4-yl}-ethyl)-N-hydroxy-acetamide (**Compound 127**);

(vvvvv) N-(2-{1-[4-(8-Cyclopentyl-6-fluoro-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino)-phenyl]-piperidin-4-yl}-ethyl)-N-hydroxy-acetamide (**Compound 128**);

(wwwww) N-(2-{1-[4-(6-Bromo-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino)-phenyl]-piperidin-4-yl}-ethyl)-N-hydroxy-acetamide (**Compound 129**);

(xxxxx) N-(3-{1-[4-(8-Cyclopentyl-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino)-phenyl]-piperidin-4-yl}-propyl)-N-hydroxy-acetamide (**Compound 130**);

(yyyyy) N-(3-{1-[4-(8-Cyclopentyl-6-fluoro-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino)-phenyl]-piperidin-4-yl}-propyl)-N-hydroxy-acetamide (**Compound 131**);

(zzzzz) N-(3-{1-[4-(6-Bromo-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino)-phenyl]-piperidin-4-yl}-propyl)-N-hydroxy-acetamide (**Compound 132**);

(aaaaaa) 2-(Benzofuran-5-ylamino)-8-cyclopentyl-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 133**);

(bbbbbb) 8-Cyclopentyl-2-(1H-indol-5-ylamino)-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 134**);

(cccccc) 2-(Benzo[b]thiophen-5-ylamino)-8-cyclopentyl-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 135**);

(dddddd) 8-Cyclopentyl-2-(2,3-dimethyl-1H-indol-5-ylamino)-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 136**);

(eeeeee) 2-(9H-Carbazol-3-ylamino)-8-cyclopentyl-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 137**);

(ffffff) 8-Cyclopentyl-2-(1H-indazol-5-ylamino)-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 138**);

(gggggg) 2-(2-Acetyl-benzofuran-5-ylamino)-8-cyclopentyl-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 139**);

(hhhhhh) 8-Cyclopentyl-5-methyl-2-(4-morpholin-4-yl-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 140**), mp 227-229°C;

(iiiiii) 8-Cyclopentyl-2-[4-(3,5-dimethyl-piperazin-1-yl)-phenylamino]-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 141**);

(jjjjjj) 2-(3-Chloro-4-piperazin-1-yl-phenylamino)-8-cyclopentyl-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one trifluoroacetate (**Compound 142**), mp 234-237°C;

(kkkkkk) 8-Cyclopentyl-5-methyl-2-(4-piperidin-1-yl-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 143**);

(llllll) 8-Cyclopentyl-5-methyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 144**);

(mmmmmm) N-{1-[4-(8-Cyclopentyl-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino)-phenyl]-piperidin-4-yl}-acetamide (**Compound 145**);

(nnnnnn) 8-Cyclopentyl-5-methyl-2-(4-piperazin-1-yl-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one trifluoroacetate (**Compound 146**), mp 237-240°C;

(oooooo) 8-Cyclopentyl-6-fluoro-5-methyl-2-(4-piperazin-1-yl-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 147**), mp 254-255°C;

(pppppp) 6-Iodo-8-cyclopentyl-5-methyl-2-(4-piperazin-1-yl-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 148**);

(qqqqqq) 2-[3-Chloro-4-(3-amino-pyrrolidin-1-yl)-phenylamino]-8-cyclopentyl-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one trifluoroacetate (**Compound 149**), mp >215°C (dec);

(rrrrrr) 8-Cyclopentyl-5-methyl-2-[4-(4-(2,2,2-trifluoroethyl)-piperazin-1-yl)-phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 150**), mp 198-199°C;

(ssssss) 8-Cyclopentyl-2-(4-fluoro-phenylamino)-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 151**), mp 217-220°C;

(tttttt) 8-Cyclopentyl-5-methyl-2-phenylamino-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 152**), mp 180-183°C;

(uuuuuu) 8-Cyclopentyl-2-(3,4-dichlorophenylamino)-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 153**), mp 225-230°C;

(vvvvvv) 8-Isopropyl-5-methyl-2-(4-piperazin-1-yl-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one trifluoroacetate (**Compound 154**), mp >235°C (dec);

(wwwwww) 8-Isopropyl-5-methyl-2-[4-(4-propionyl-piperazin-1-yl)-phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 155**);

(xxxxxx) 8-Cyclohexyl-5-methyl-2-(4-piperazin-1-yl-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 156**);

(yyyyyy) 2-{4-[4-(3-Morpholin-4-yl-propyl)-piperidin-1-yl]-phenylamino}-8-cyclohexyl-6-fluoro-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 157**), mp 206-209°C;

(zzzzzz) 8-Cyclopentyl-5-methyl-2-[4-(2H-1,2,4-triazol-3-ylsulfanylmethyl)-phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 158**);

(aaaaaaa) 8-Cyclopentyl-5-methyl-2-[4-(2H-1,2,4-triazole-3-sulfinylmethyl)-phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 159**);

(bbbbbbb) 8-Cyclopentyl-5-methyl-2-[4-(2H-1,2,4-triazole-3-sulfonylmethyl)-phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 160**);

(ccccccc) 8-Cyclopentyl-5-methyl-2-[4-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-ylmethyl)-phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 161**);

(ddddddd) 8-Cyclopentyl-5-methyl-2-{4-[2-(2H-1,2,4-triazol-3-ylsulfanyl)-ethyl]-phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 162**);

(eeeeeee) 8-Cyclopentyl-5-methyl-2-{4-[2-(2H-1,2,4-triazole-3-sulfinyl)-ethyl]-phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 163**);

(fffffff) 8-Cyclopentyl-5-methyl-2-{4-[2-(2H-1,2,4-triazole-3-sulfonyl)-ethyl]-phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 164**);

(ggggggg) 8-Cyclopentyl-5-methyl-2-{4-[2-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-ethyl]-phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 165**);

(hhhhhhh) 8-Cyclopentyl-5-methyl-2-[4-(3H-1,2,3-triazol-4-ylsulfanylmethyl)-phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 166**);

(iiiiiii) 8-Cyclopentyl-5-methyl-2-{4-[2-(3H-1,2,3-triazol-4-ylsulfanyl)-ethyl]-phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 167**);

(jjjjjjj) 8-Cyclopentyl-5-methyl-2-{4-[4-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-piperidin-1-yl]-phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one **(Compound 168)**;

(kkkkkkk) 8-Cyclopentyl-5-methyl-2-{4-[4-(2H-1,2,4-triazol-3-ylsulfanyl)-piperidin-1-yl]-phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one **(Compound 169)**;

(lllllll) 8-Cyclopentyl-5-methyl-2-{4-[4-(2H-1,2,4-triazole-3-sulfinyl)-piperidin-1-yl]-phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one **(Compound 170)**;

(mmmmmmm) 8-Cyclopentyl-5-methyl-2-{4-[4-(2H-1,2,4-triazole-3-sulfonyl)-piperidin-1-yl]-phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one **(Compound 171)**, mp 235-237°C;

(nnnnnnn) 8-Cyclopentyl-5-methyl-2-{4-[4-(2H-tetrazol-5-yl)-piperidin-1-yl]-phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one **(Compound 172)**;

(ooooooo) 1-[4-(8-Cyclopentyl-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino)-phenyl]-piperidine-4-carboxylic acid (1H-tetrazol-5-yl)-amide **(Compound 173)**;

(ppppppp) 8-Cyclopentyl-5-methyl-2-{4-[4-(3H-1,2,3-triazol-4-ylsulfanyl)-piperidin-1-yl]-phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one **(Compound 173)**;

(qqqqqqq) 3-[4-(8-Cyclopentyl-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino)-phenyl]-N-(1H-tetrazol-5-yl)-propionamide **(Compound 174)**;

(rrrrrrr) 2-[4-(8-Cyclopentyl-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino)-phenoxy]-N-(1H-tetrazol-5-yl)-acetamide **(Compound 175)**;

(sssssss) 8-Cyclopentyl-5-methyl-2-[4-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-ylmethoxy)-phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one **(Compound 176)**, mp >195°C (dec);

(ttttttt) 8-Cyclopentyl-5-methyl-2-(4-{4-[2-(2H-1,2,4-triazole-3-sulfinyl)-ethyl]-piperidin-1-yl}-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one **(Compound 177)**;

(uuuuuuu) 8-Cyclopentyl-5-methyl-2-(4-{4-[2-(2H-1,2,4-triazole-3-sulfonyl)-ethyl]-piperidin-1-yl}-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 178**);

(vvvvvvv) 8-Cyclopentyl-5-methyl-2-(4-{4-[2-(3H-1,2,3-triazol-4-ylsulfanyl)-ethyl]-piperidin-1-yl}-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 179**);

(wwwwwww) 8-Cyclopentyl-5-methyl-2-(4-{4-[2-(2H-1,2,4-triazol-3-ylsulfanyl)-ethyl]-piperidin-1-yl}-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 180**), mp 234-237°C;

(xxxxxxx) 8-Cyclopentyl-5-methyl-2-(4-{4-[2-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-ethyl]-piperidin-1-yl}-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 181**);

(yyyyyyy) 8-Cyclopentyl-5-methyl-2-{4-[4-(2-oxo-2,3-dihydro-1,2,3,5-oxathiadiazol-4-yl)-piperidin-1-yl]-phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 182**);

(zzzzzzz) 8-Cyclopentyl-2-{4-[4-(2,2-dioxo-2,3-dihydro-1,2,3,5-oxathiadiazol-4-yl)-piperidin-1-yl]-phenylamino}-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 183**);

(aaaaaaaa) 8-Cyclopentyl-5-methyl-2-{4-[4-(1-oxo-2,5-dihydro-1H-1,2.3,5-thiatriazol-4-yl)-piperidin-1-yl]-phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 184**);

(bbbbbbbb) 8-Cyclopentyl-2-{4-[4-(1,1-dioxo-2,5-dihydro-1H-1,2,3,5-thiatriazol-4-yl)-piperidin-1-yl]-phenylamino}-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 185**);

(cccccccc) N-{1-[4-(8-Cyclopentyl-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino)-phenyl]-piperidine-4-carbonyl}-methanesulfonamide (**Compound 186**);

(ddddddd) 8-Cyclopentyl-5-methyl-2-{4-[3-(2H-1,2,4-triazol-3-ylsulfanyl)-pyrrolidin-1-yl]-phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 187**);

(eeeeeeee) 8-Cyclopentyl-5-methyl-2-{4-[3-(2H-1,2,4-triazole-3-sulfinyl)-pyrrolidin-1-yl]-phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 188**);

(ffffffff) 8-Cyclopentyl-5-methyl-2-{4-[3-(2H-1,2,4-triazole-3-sulfonyl)-pyrrolidin-1-yl]-phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 189**);

(gggggggg) 8-Cyclopentyl-5-methyl-2-{4-[3-(3H-1,2,3-triazol-4-ylsulfanyl)-pyrrolidin-1-yl]-phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 190**);

(hhhhhhhh) 8-Cyclopentyl-5-methyl-2-{4-[3-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-pyrrolidin-1-yl]-phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 191**);

(iiiiiiii) 8-Cyclopentyl-5-methyl-2-{4-[4-(3-hydroxypropyl)piperidin-1-yl]-phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one trifluoroacetate (**Compound 192**), mp 180-184°C;

(jjjjjjjj) 8-Cyclopentyl-5-propyl-2-(4-piperazin-1-yl-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one trifluoroacetate (**Compound 193**);

(kkkkkkkk) 8-Cyclopentyl-5-ethyl-2-(4-piperazin-1-yl-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 194**);

(llllllll) 8-(1-Methylethyl)-5-ethyl-2-(4-piperazin-1-yl-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 195**), mp >235°C (dec);

(mmmmmmmm) 8-(1-Methylethyl)-5-ethyl-2-(4-piperazin-1-yl-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one trifluoroacetate (**Compound 196**), mp >235°C (dec);

(nnnnnnnn) 8-Cyclopentyl-5-methyl-2-[4-(3-hydroxypyrrolidin-1-yl)phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 197**), mp 225-226°C;

(oooooooo) 8-Cyclopentyl-5-ethyl-2-[4-(4-acetylpiperazin-1-yl)phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 198**);

(pppppppp) 8-Cyclopentyl-5-methyl-6-fluoro-2-[4-(4-acetylpiperidin-1-yl)phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 199**), mp 267-269°C;

(qqqqqqqq) 8-Cyclopropyl-5-methyl-2-[4-(4-acetamidopiperidin-1-yl)phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 200**), mp 221°C (dec);

(qqqqqqqr) 8-Cyclopropyl-5-methyl-6-fluoro-2-[4-(4-acetamidopiperidin-1-yl) phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 201**), mp >250°C;

(rrrrrrr) 8-Cyclopentyl-5-methyl-2-[4-(homopiperazin-1-yl)phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one hydrochloride (**Compound 202**), mp 172°C (dec);

(sssssssss) 8-Cyclopentyl-5-methyl-6-fluoro-2-[4-(homopiperazin-1-yl)phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one hydrochloride (**Compound 203**), mp 192°C (foam);

(ttttttt) 8-Cyclopentyl-5-methyl-6-fluoro-2-[4-(3,3-dimethyl-4-acetylpiperazin-1-yl)phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 204**), mp 200-204°C;

(uuuuuuuu) 8-Cyclopentyl-5-methyl-2-[4-(3,3-dimethyl-4-acetylpiperazin-1-yl)phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 205**), mp 192-196°C;

(vvvvvvvv) 8-Cyclopentyl-5-methyl-6-fluoro-2-[4-(4-methylpiperazin-1-yl)phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one trifluoroacetate (**Compound 206**);

(wwwwwwww) 8-Cyclopentyl-5-methyl-2-[4-(N-methylacetamido)phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 207**), mp 185-187°C;

(xxxxxxxx) 8-Cyclopentyl-5-methyl-2-{4-[2-(2-hydroxyethoxy)ethylamino]phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 208**), mp 122-126°C;

(yyyyyyyy) 8-Cyclopentyl-5-methyl-2-[4-(3-oxopiperazin-1-yl)phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 209**), mp >235°C (dec);

(*zzzzzzzz*) 8-Cyclopentyl-5-methyl-2-[4-(2-methoxyethoxy)phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 210**), mp 156-157°C;

(aaaaaaaaa) 8-Cyclopentyl-5-methyl-2-(9H carbazol-3-yl amino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 211**);

(bbbbbbbbb) 8-Cyclopentyl-5-methyl-2-(1H-indazol-5-yl)amino-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 212**);

(ccccccccc) 8-Cyclopentyl-5-methyl-2-(2-acetylbenzofuran-5-yl)amino-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 213**);

(ddddddddd) 8-Cyclopentyl-5-methyl-2-[(4-piperidin-1-yl)phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 214**);

(eeeeeeeee) 8-Cyclopentyl-5-methyl-2-(2,3-dimethylindol-5-yl)amino-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 215**);

(fffffffff) 8-Cyclopentyl-5-isopropyl-2-[4-(3,5-methyl-4R-aminomethylpyrrolidin-1-yl)phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 216**);

(ggggggggg) 8-Cyclopentyl-5-methyl-2-{4-[4-(2-hydroxyethyl)piperazin-1-yl)]phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 217**), mp 171-173°C;

(hhhhhhhhh) 8-Cyclopentyl-5-methyl-2-{4-[4-(3-morpholinopropyl)piperidin-1-yl]phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one trifuoroacetic acid salt (**Compound 218**), mp 178-181°C;

(iiiiiiiii) 8-Cyclopentyl-5-methyl-2-(benzofuran-5-yl)amino-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 219**);

(jjjjjjjjj) 8-Cyclopentyl-5-methyl-2-(indol-5-yl)amino-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 220**); and

(kkkkkkkkk) 8-Cyclopentyl-5-methyl-2-(thionaphthen-5-yl)amino-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 221**);.

8-Cyclopentyl-6-iodo-5-methyl-2-(4-piperazin-1-yl-phenylamino)-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (**Compound 225**), mp 185-198°C (dec);

8-Cyclopentyl-2-{4-[1-(3,5-dimethyl-piperazin-1-yl)-methanoyl]-phenylamino}-5-methyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (**Compound 226**), mp 181 (foam);

8-Cyclopentyl-2-[4-(3,5-dimethyl-piperazin-1-yl)-phenylamino]-5-trifluoromethyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (**Compound 227**), mp 200(foam);

6-Bromo-8-cyclopentyl-2-[4-(3,3-dimethyl-piperazin-1-yl)-phenylamino]-5-methyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (**Compound 228**), mp >200 (dec);

8-Cyclopentyl-2-[4-(3,5-dimethyl-piperazin-1-yl)-phenylamino]-6-iodo-5-methyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (**Compound 229**), mp 225-226°C (dec);

6-Chloro-8-cyclopentyl-2-[4-(3,5-dimethyl-piperazin-1-yl)-phenylamino]-5-methyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (**Compound 230**), mp >250°C;

8-Cyclopentyl-5-methyl-2-[4-(1H-[1,2,4]triazol-3-ylsulfanyl)-phenylamino]-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (**Compound 231**);

4-[4-(8-Cyclopentyl-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-*d*]pyrimidin-2-ylamino)-phenyl]-piperazine-1-carbaldehyde (**Compound 232**), mp 244-247°C;

8-Cyclopentyl-2-(4-piperazin-1-yl-phenylamino)-5-trifluoromethyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (**Compound 233**), mp >275°C (dec);

8-(1-Ethyl-propyl)-5-methyl-2-(4-piperazin-1-yl-phenylamino)-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (**Compound 234**), mp >180°C (dec);

[4-(8-Cyclopentyl-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-*d*]pyrimidin-2-ylamino)-benzyl]-phosphonic acid (**Compound 235**), mp >250°C;

6-Chloro-8-cyclopentyl-5-methyl-2-(4-piperazin-1-yl-phenylamino)-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (**Compound 236**), mp 188°C (dec);

2-[4-(3,5-Dimethyl-piperazin-1-yl)-phenylamino]-8-(1-ethyl-propyl)-5-methyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (**Compound 237**), mp >185°C (dec);

8-Cyclopentyl-2-[4-(2-hydroxy-ethylamino)-phenylamino]-5-methyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (**Compound 238**), mp 197-200°C;

3-[4-(8-Cyclopentyl-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-*d*]pyrimidin-2-ylamino)-phenyl]-*N*,*N*-diethyl-propionamide (**Compound 239**), mp 138-140°C;

8-Cyclopentyl-6-fluoro-2-[4-(2-hydroxy-ethyl)-phenylamino]-5-methyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (**Compound 240**), mp 241-244°C;

8-Cyclopentyl-2-[4-(2-hydroxy-ethyl)-phenylamino]-5-methyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (**Compound 241**), mp 191-194°C;

4-(8-Cyclopentyl-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-*d*]pyrimidin-2-ylamino)-benzoic acid (**Compound 242**);

8-Cyclopentyl-2-[4-(3,3-dimethyl-piperazin-1-yl)-phenylamino]-5-methyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (**Compound 243**), mp >150°C (dec);

[4-(8-Cyclopentyl-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-*d*]pyrimidin-2-ylamino)-benzyl]-phosphonic acid diethyl ester (**Compound 244**), mp >250°C (foam);

8-Cyclopentyl-6-fluoro-2-[4-(2-methoxy-ethylamino)-phenylamino]-5-methyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (**Compound 245**), mp 147-149°C;

(S)-2-Amino-3-[4-(8-cyclopentyl-6-fluoro-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-*d*]pyrimidin-2-ylamino)-phenyl]-propionic acid (**Compound 246**), mp 238°C (dec);

8-Cyclopentyl-2-[4-(2-methoxy-ethoxy)-phenylamino]-5-methyl-8*H*-pyrido[2,3-d]pyrimidin-7-one (**Compound 247**), mp 156-157°C;

8-Cyclopentyl-2-(4-isopropylamino-phenylamino)-5-methyl-8*H*-pyrido[2,3-d]pyrimidin-7-one (**Compound 248**), mp 216-220°C;

8-Cyclopentyl-2-(4-hydroxy-3,5-dimethyl-phenylamino)-5-methyl-8*H*-pyrido[2,3-d]pyrimidin-7-one (**Compound 249**), mp 252-254°C;

8-Cyclopentyl-6-fluoro-2-(4-hydroxy-3,5-dimethyl-phenylamino)-5-methyl-8*H*-pyrido[2,3-d]pyrimidin-7-one (**Compound 250**), mp 241-248°C;

8-Cyclopentyl-6-fluoro-2-(4-hydroxy-3,5-dimethyl-phenylamino)-5-methyl-8*H*-pyrido[2,3-d]pyrimidin-7-one (**Compound 251**), mp 240°C (dec).

EXAMPLE 19

Biological Assays

Several of the invention compounds have been evaluated in standard assays routinely used to measure inhibition of cyclin-dependent kinase enzymes and other serine/threonine protein kinases. The assays were carried out as follows:

Cdk1 and Cdk2 enzyme assays for IC_{50} determinations and kinetic evaluation are performed as follows. 96-well filter plates (Millipore

MADVN6550) are used. The total volume is 0.1 mL 20 mM TRIS (pH 7.4), 50 mM NaCl, 1 mM dithiothreitol, 10 mM $MgCl_2$, 12 mM ATP containing 0.25 μCi [^{32}P]ATP, 20 ng enzyme (Cdk2/cyclin E, Cdk2/cyclin A, or Cdk1/cyclin B), 1 μg retinoblastoma protein, and appropriate dilutions of the particular invention compound. All components except the ATP are added to the wells, and the plate is placed on a plate mixer for 2 minutes. The reaction is initiated by addition of [^{32}P]ATP, and the plate is incubated at 25°C for 15 minutes. The reaction is terminated by addition of 0.1 mL 20% TCA. The plate is kept at 4°C for at least 1 hour to allow the substrate to precipitate. The wells are then washed five times with 0.2 mL 10% TCA, and ^{32}P incorporation is determined with a beta plate counter (Wallac Inc., Gaithersburg, MD).

The Cdk4 enzyme assay for IC_{50} determination and kinetic evaluation is performed as follows. 96-well filter plates (Millipore MADVN6550) are used. The total volume is 0.1 mL containing a final concentration of 20 mM TRIS (tris[hydroxymethyl]aminomethane) (pH 7.4), 50 mM NaCl, 1 mM dithiothreitol, 10 mM $MgCl_2$, 25 μM ATP containing 0.25 μCi [^{32}P]ATP, 20 ng Cdk4, 1 μg retinoblastoma protein, and appropriate dilutions of a compound of the present invention. All components except the ATP are added to the wells, and the plate is placed on a plate mixer for 2 minutes. The reaction is started by adding [^{32}P]ATP, and the plate is incubated at 25°C for 15 minutes. The reaction is terminated by addition of 0.1 mL 20% trichloroacetic acid (TCA). The plate is kept at 4°C for at least 1 hour to allow the substrate to precipitate. The wells are then washed five times with 0.2 mL 10% TCA, and ^{32}P incorporation is determined with a beta plate counter (Wallac Inc., Gaithersburg, MD).

For PDGF receptor (PDGFr) and FGF receptor (FGFr) tyrosine kinase assays, full-length cDNAs for the mouse PDGF-β and human FGF1(flg) receptor tyrosine kinases are obtained from J. Escobedo and prepared as described previously (Escobedo et al., *J. Biol. Chem.*, 1988;262:1482-1487). PCR primers are designed to amplify a fragment of DNA that codes for the intracellular tyrosine kinase domain. The fragment is inserted into a baculovirus vector, cotransfected with AcMNPV DNA, and the recombinant virus is isolated. SF9

insect cells are infected with the virus to overexpress the protein, and the cell lysate is used for the assay.

PDGFr and FGFr enzyme assays are performed in 96-well plates (100 µL/incubation/well), and conditions are optimized to measure the incorporation of ^{32}P from [$\gamma^{32}P$]ATP into a glutamate-tyrosine co-polymer substrate. Briefly, to each well is added 82.5 µL incubation buffer containing 25 mM Hepes (pH 7.0), 150 mM NaCl, 0.1% Triton X-100, 0.2 mM PMSF, 0.2 mM Na_3VO_4, 10 mM $MnCl_2$, and 750 µg/mL Poly (4:1) glutamate-tyrosine followed by 2.5 µL inhibitor and 5 µL enzyme lysate (7.5 µg/µL FGFr or 6.0 µg/µL PDGFr) to initiate the reaction. Following a 10-minute incubation at 25°C, 10 mL [$\gamma^{32}P$]ATP (0.4 µCi plus 50 µM ATP) is added to each well, and samples are incubated for an additional 10 minutes at 25°C. The reaction is terminated by the addition of 100 µL 30% trichloroacetic acid (TCA) containing 20 mM sodium pyrophosphate and precipitation of material onto glass fiber mats (Wallac). Filters are washed three times with 15% TCA containing 100 mM sodium pyrophosphate, and the radioactivity retained on the filters is counted in a Wallac 1250 Betaplate reader. Nonspecific activity is defined as radioactivity retained on the filters following incubation of samples with buffer alone (no enzyme). Specific enzymatic activity (enzyme plus buffer) is defined as total activity minus nonspecific activity. The concentration of a compound that inhibited specific activity by 50% (IC_{50}) is determined based on the inhibition curve.

The c-Src protein kinase assay is carried out as follows. c-Src kinase is purified from baculovirus infected insect cell lysates using an antipeptide monoclonal antibody directed against the N-terminal amino acids (amino acids 2-17) of c-Src. The antibody, covalently linked to 0.65 µm latex beads, is added to a suspension of insect cell lysis buffer comprised of 150 mM NaCl, 50 mM Tris (pH 7.5), 1 mM DTT, 1% NP-40, 2 mM EGTA, 1 mM sodium vanadate, 1 mM PMSF, 1 µg/mL each of leupeptin, pepstatin, and aprotinin. Insect cell lysate containing c-Src protein is incubated with these beads for 3 to 4 hours at 4°C with rotation. At the end of the lysate incubation, the beads are rinsed three times in

lysis buffer, resuspended in lysis buffer containing 10% glycerol, and frozen. These latex beads are thawed, rinsed three times in assay buffer (40 mM Tris (pH 7.5), 5 mM μg Cl_2) and suspended in the same buffer. In a Millipore 96-well plate with a 0.65 μm polyvinylidine membrane bottom are added the reaction components: 10 μL c-Src beads, 10 μL 2.5 mg/mL poly GluTyr substrate, 5 μM ATP containing 0.2 μCi [^{32}P]ATP, 5 μL DMSO containing inhibitors or as a solvent control, and buffer to make the final volume 125 μL. The reaction is started at room temperature by addition of ATP and quenched 10 minutes later by the addition of 125 μL 30% TCA, 0.1 M sodium pyrophosphate for 5 minutes on ice. The plate is then filtered and the wells washed with two 250-mL aliquots of 15% TCA, 0.1 M pyrophosphate. The filters are then punched, counted in a liquid scintillation counter, and the data examined for inhibitory activity in comparison to a known inhibitor such as erbstatin. The method has been described by Thompson et al., *J. Med. Chem.*, 1994;37:598-609.

The results of the foregoing assays for several representative invention compounds are presented in Table 1. The metabolic stability of representative Compounds was evaluated in human liver microsomes (HLM) and is given in Table 1 as the time in minutes (T Half) required for one-half of the parent compound to disappear after being added to a HLM homogluate.

Table 1
(Page 1 of 3)

Compound No.	MP degrees C	CYCK1B IC_{50}	CYCK2A IC_{50}	CYCK2E IC_{50}	CYCK4 IC_{50}	FGF IC_{50}	CSRC IC_{50}	T HALF HLM
		µM	µM	µM	µM	µM	µM	min
1	>215 (dec)	>5	>5	>5	0.007	1.077	NA	83
2	>235 (dec)	>5	>5	>5	0.265	NA	NA	NA
7	235-237	>1.5	>1.7	>5	NA	NA	NA	6
12	>195 (dec)	>5	>1.7	>5	0.064	NA	NA	43
16	234-237	>5	>5	>5	0.028	NA	NA	67
45	227-229	1.12	5.38	>5	NA	36.7	NA	NA
57	>80 (dec)	>5	>5	>5	0.151	NA	6.08	NA
58	>230	>5	>5	>5	0.154	35.7		
73	>215 (dec)	>1.7	>1.7	>5	0.061	>5	NA	80
79	>160 (dec)	>5	>5	>5	0.975	NA	34	8
82	>215 (dec)	>1.7	>1.7	>5	0.061	>5	NA	
100	156-159					5.44	1.2468	
106	211-213	>5	>5	>5	0.018	1.96		
109	>185 (dec)	>5	13	>5	0.040	1.15	NA	NA
147	254-255	>5	>5	>5	0.03	NA	NA	61
148	>200	2.615	0.439	0.95	0.005	NA	NA	73
150	198-199	>5	>5	>5	0.295	NA	NA	NA
151	217-220	>1.7	6.98	39	2.45	NA	>50	11
152	180-183	>1.7	4.91	>5	2.15	NA	>50	4
153	225-230	>1.7	>5	>5	>5	NA	>50	24
157	206-209	>40	>40	NA	21.5	>50	>50	11
192	180-184	>5	>5	>5	0.114	NA	NA	NA

NA = Data not available.

Table 1
(Page 2 of 3)

Compound No.	MP degrees C	CYCK1B IC_{50}	CYCK2A IC_{50}	CYCK2E IC_{50}	CYCK4 IC_{50}	FGF IC_{50}	CSRC IC_{50}	T HALF HLM
		µM	µM	µM	µM	µM	µM	min
193		>5	>5	>5	0.655			
196	>235 (dec)	1.64	>5	>5	2.8			
197	225-226	>5	>5	>5	0.26			
198	261-263	>5	13.5	>5	0.103	43.6		
199	267-269	>5	44.8	>5	0.141	16.5		
200	221 (dec)	>5	>5	>5	0.285	19.3		
201	>250	>5	6.94	>5	0.175			
202	172 (dec)	>5	9.305	>5	0.052			
203	192	24.5	17.565	>5	0.085			
204	200-204	>5	>5	>5	0.31			
205	192-196	>5	>5	>5	0.37			
206		>5	>5	>5	0.042			
207	185-187	>5	>5	>5	0.480			
208	122-126	>5	>5	>5	0.450			
216	>130 (dec)					>5	10.2	
217	171-173	>5	>5	>5	0.035			
218	178-181	8.12	>5	>5	0.46	18.75	15.2	
222		>5	2.9	>5	1.35			
225	185-198 (dec)	1.865	0.4425	0.365	0.005			
226	181	>5	2.85	3.65	0.17			
227	200	>5	>5	>5	>5			
228	>200 (dec)	>5	1.33	2.05	0.02			

NA = Data not available.

Table 1
(Page 3 of 3)

Compound No.	MP degrees C	CYCK1B IC_{50}	CYCK2A IC_{50}	CYCK2E IC_{50}	CYCK4 IC_{50}	FGF IC_{50}	CSRC IC_{50}	T HALF HLM
		μM	μM	μM	μM	μM	μM	min
229	225-226 (dec)	1.74	0.5465	0.725	0.015			
232	244-247	>5	6.31	>5	0.1605			
236	188 (dec)	5.39	1.625	1.5	0.0155			
238	197-200	>5	>5	>5	0.225			
241	191-194	>5	>5	3.4	0.423			
245	147-149	>5	>5	>5	0.375			
246	238 (dec)	>5	19.4	>5	1.05			
250	246-248	>5	>5	>5	>5			
251	>240 (dec)	>5	6.52	4.7	0.27			

NA = Data not available.

Various properties of preferred 5-methylpyridopyrimidin-7-ones such as 8-cyclopentyl-5-methyl-2-[(4-piperazinylphenyl)-amino]-8-hydropyridino[2,3-d]pyrimidin-7-one (**Compound 1**), including IC_{50}, stability, and clearance rate, are displayed in Table 2.

Table 2

Compound	5-Me	IC_{50} (μM)							T½ in HLM (min)	Clearance (mL/min/kg)
		Cdk1/ cyclin B	Cdk2/ cyclin A	Cdk2/ cyclin E	Cdk4	FGFr	c-Src	PDGFr		
1	Yes	>5	>5	>5	0.007	1.077			83	25.5 (n = 2)
57	Yes	>5	>5	>5	0.151		6.08			
73	Yes	>1.7	>1.7	>5	0.061	>5			80	
79	Yes	>5	>5	>5	0.975	NA	34		8	
152	Yes	>1.7	4.91	>5	2.15	NA	>50		4	

From the results displayed in Table 2, it is clear that Compound 1 and other invention compounds specifically inhibit Cdk4, and has relatively little effect on Cdk1 and Cdk2. Furthermore, Compound 1 is relatively more stable, and cleared at a slower rate, compared to prior art compounds. These results indicate that the methyl group in the 5-position confers unique properties onto the pyridopyrimidine and is a preferred embodiment.

Formulation Examples

As noted above, the invention compounds will typically be formulated with common excipients, diluents, and carriers to provide compositions that are well-suited for convenient administration to mammals. The following examples illustrate typical compositions that are provided in a further embodiment of this invention.

EXAMPLE 20

Tablet Formulation

Ingredient	Amount
Compound 12	50 mg
Lactose	80 mg
Cornstarch (for mix)	10 mg
Cornstarch (for paste)	8 mg
Magnesium Stearate (1%)	2 mg
	150 mg

Compound 12 is mixed with the lactose and cornstarch (for mix) and blended to uniformity to a powder. The cornstarch (for paste) is suspended in 6 mL of water and heated with stirring to form a paste. The paste is added to the mixed powder, and the mixture is granulated. The wet granules are passed through a No. 8 hard screen and dried at 50°C. The mixture is lubricated with 1% magnesium stearate and compressed into a tablet. The tablets are administered to a patient at the rate of 1 to 4 each day for prevention and treatment of atherosclerosis.

EXAMPLE 21

Parenteral Solution

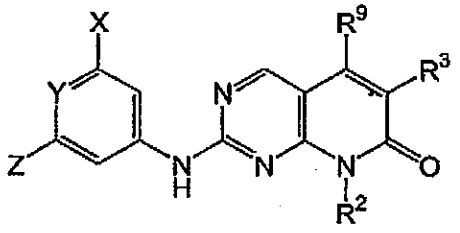
In a solution of 700 mL of propylene glycol and 200 mL of water for injection is added 20.0 g of Compound 38. The mixture is stirred and the pH is adjusted to 5.5 with hydrochloric acid. The volume is adjusted to 1000 mL with water for injection. The solution is sterilized, filled into 5.0 mL ampoules, each containing 2.0 mL (40 mg of Compound 38), and sealed under nitrogen. The solution is administered by injection to a patient suffering from cancer and in need of treatment.

The invention and the manner and process of making and using it, are now described in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, to make and use the same. It is to be understood that the foregoing describes preferred embodiments of the present

invention and that modifications may be made therein without departing from the spirit or scope of the present invention as set forth in the claims. To particularly point out and distinctly claim the subject matter regarded as invention, the following claims conclude this specification.

What is claimed is:

1. A compound of the formula



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and pharmaceutically acceptable salts, esters, amides, and prodrugs thereof, wherein:

R^2 is (a) hydrogen;

(b) lower alkyl optionally substituted with one, two, or three groups independently selected from halogen, hydroxy, lower alkoxy, amino, mono- or dialkylamino, carboxy, alkoxycarbonyl, thioalkyl, nitrile, aryl, heteroaryl, or a carbocyclic group containing from 3 to 7 members, up to two of which members are optionally heteroatoms independently selected from oxygen, sulfur, and nitrogen; or

(c) a carbocyclic group containing from 3 to 7 members, up to two of which members are optionally heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the carbocyclic group is unsubstituted or substituted with one, two, or three groups independently selected from consisting of halogen, hydroxy, lower alkyl, lower alkoxy, amino, mono- or dialkylamino, aryl, and heteroaryl;

R^3 is hydrogen, lower alkyl, lower alkoxy, halogen, trifluoromethyl, lower alkynyl, lower alkenyl, nitrile, nitro, $-COR^4$, $-CO_2R^4$, $-CONR^4R^5$, $CONR^4OR^5$, $-SO_2NR^4R^5$, $-SO_2R^4$, $-SO_3R^4$,

R^4

$P(O)(OR^4)(OR^5)$, or $-NR^4R^5$;

Y is N or CR^7;

R^9 is lower alkyl, haloalkyl, or aryl;

X and Z are independently hydrogen, halogen, lower alkyl, lower alkoxy, trifluoromethyl, hydroxy, nitrile, nitro, $-NR^4R^5$, $-N(O)R^4R^5$, $-NR^4R^5R^6W$, $-SR^4$, $-C(O)R^4$, $-CO_2R^4$, $-CONR^4R^5$, $-SO_2NR^4R^5$, $-SO_2R^4$, $-SO_3R^4$, $P(O)(OR^4)(OR^5)$, $-T(CH_2)_mQR^4$, $-C(O)T(CH_2)_mQR^4$, or $-NR^4C(O)T(CH_2)_mQR^5$;

m is 1 to 6;

T is O, S, NR^4, $N(O)R^4$, NR^4R^5W, or CR^4R^5;

Q is O, S, NR^4, $N(O)R^4$, NR^4R^5W, CO_2, or a carbocyclic group containing from 3 to 7 members, up to four of which members are optionally heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the carbocyclic group is unsubstituted or substituted with one, two, or three groups independently selected from halogen, hydroxy, hydroxyalkyl, lower alkyl, lower alkoxy, alkoxycarbonyl, alkylcarbonyl, alkylcarbonylamino, aminoalkyl, trifluoromethyl, N-hydroxyacetamide, trifluoromethylalkyl, amino, or mono or dialkylamino;

R^6 is lower alkyl, haloalkyl, or aryl;

R^7 is NR^4R^5, $N(O)R^4R^5$, $NR^4R^5R^9W$, OH, OR^4, SR^4, halo, COR^4, $(CH_2)_nR^4$, CO_2R^4, $CONR^4R^5$, $C(O)NR^4SO_2R^5$, $S(O)R^4$, SO_2R^4, $SO_2NR^4R^5$, SO_3R^4, $(CH_2)_nP(O)(OR^4)_2$, $NR^4SO_2R^5$, aldehyde, nitrile, nitro, alkyl, alkoxyalkyl, $T(CH_2)_mQR^4$, $C(O)T(CH_2)_mQR^4$, $NR^4C(O)T(CH_2)_mQR^5$, or $T(CH_2)_mCO_2R^4$;

n is 0 to 6;

W is an anion;

R^4 and R^5 are independently hydrogen, lower alkyl, lower alkenyl, lower alkynyl, $(CH_2)_nAr$, arylalkyl, aryl, heteroaryl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, or heteroaryl, or R^4 and R^5 together with the nitrogen to which they are attached form a carbocyclic ring containing 3 to

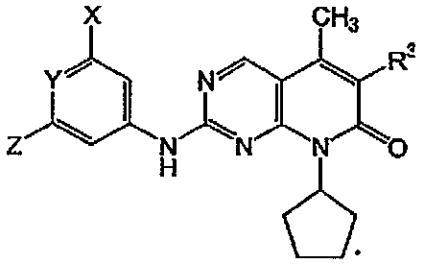
8 members, up to four of which members are optionally carbonyl groups or heteroatoms independently selected from oxygen, sulfur, S(O), $S(O)_2$, and nitrogen, wherein the carbocyclic group is unsubstituted or substituted with one, two, three, or four groups independently selected from halogen, hydroxy, hydroxyalkyl, lower alkyl, lower alkoxy, alkoxycarbonyl, alkylcarbonyl, alkylcarbonylamino, aminoalkyl, aminoalkylcarbonyl, trifluoromethyl, trifluoromethylalkyl, trifluoromethylalkylaminoalkyl, mono- or dialkylamino, N-hydroxyacetamido, aryl, heteroaryl, carboxyalkyl, $NR^{10}SO_2R^{11}$, $C(O)NR^{10}R^{11}$, $NR^{10}C(O)R^{11}$, $C(O)OR^{10}$, $C(O)NR^{10}SO_2R^{11}$, $(CH_2)_nS(O)_nR^{10}$, $(CH_2)_n$-heteroaryl, $O(CH_2)_n$-heteroaryl, $(CH_2)_nC(O)NR^{10}R^{11}$, $O(CH_2)_nC(O)OR^{10}$;

and R^4 additionally can be lower alkyl unsubstituted or substituted with one, two, or three groups independently selected from halogen, 5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl-sulfanyl, 5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl-sulfinyl, 5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl-sulfonyl, or a carbocyclic group containing from 3 to 7 members, up to four of which members are optionally heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the carbocyclic group is unsubstituted or substituted with one, two, or three groups independently selected from halogen, hydroxy, hydroxyalkyl, lower alkyl, lower alkoxy, alkoxycarbonyl, alkylcarbonyl, alkylcarbonylamino, aminoalkyl, trifluoromethyl, N-hydroxyacetamide, trifluoromethylalkyl, amino, or mono- or dialkylamino; and

R^{10} and R^{11} are independently hydrogen, halogen, lower alkyl, lower alkoxy, or alkylcarbonyl;

with the proviso that when, R^3 is hydrogen, lower alkyl, lower alkoxy, halogen, nitrile, nitro, $-CO_2R^4$, $CONR^4OR^5$, or $-NR^4R^5$, then R^9 is not C_1-C_3 alkyl.

2. A compound of the Formula II



II

and pharmaceutically acceptable salts, esters, amides, and prodrugs thereof, wherein:

R^3 is trifluoromethyl, lower alkynyl, lower alkenyl, $-COR^4$, $CONR^4OR^5$, $-SO_2NR^4R^5$, $-SO_2R^4$, $-SO_3R^4$, or $-P(O)(OR^4)(OR^5)$;

Y is N or CR^7;

X and Z are independently hydrogen, halogen, lower alkyl, lower alkoxy, trifluoromethyl, hydroxy, nitrile, nitro, $-NR^4R^5$, $-N(O)R^4R^5$, $-NR^4R^5R^6W$, $-SR^4$, $-C(O)R^4$, $-CO_2R^4$, $-CONR^4R^5$, $-SO_2NR^4R^5$, $-SO_2R^4$, $-SO_3R^4$, $P(O)(OR^4)(OR^5)$, $-T(CH_2)_mQR^4$, $-C(O)T(CH_2)_mQR^4$, or $-NR^4C(O)T(CH_2)_mQR^5$;

m is 1 to 6;

T is O, S, NR^4, $N(O)R^4$, NR^4R^5W, or CR^4R^5;

Q is O, S, NR^4, $N(O)R^4$, NR^4R^5W, CO_2, or a carbocyclic group containing from 3 to 7 members, up to four of which members are optionally heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the carbocyclic group is unsubstituted or substituted with one, two, or three groups independently selected from halogen, hydroxy, hydroxyalkyl, lower alkyl, lower alkoxy, alkoxycarbonyl, alkylcarbonyl, alkylcarbonylamino, aminoalkyl, trifluoromethyl, N-hydroxyacetamide, trifluoromethylalkyl, amino, or mono or dialkylamino;

R^6 is lower alkyl, haloalkyl, or aryl;

R^7 is NR^4R^5, $N(O)R^4R^5$, $NR^4R^5R^9X$, OH, OR^4, SR^4, halo, COR^4, $(CH_2)_nR^4$, CO_2R^4, $CONR^4R^5$, $C(O)NR^4SO_2R^5$, $S(O)R^4$, SO_2R^4, $SO_2NR^4R^5$, SO_3R^4, $(CH_2)_nP(O)(OR^4)_2$, $NR^4SO_2R^5$, aldehyde, nitrile, nitro, alkyl, alkoxyalkyl, $T(CH_2)_mQR^9$, $C(O)T(CH_2)_mQR^9$, $NR^9C(O)T(CH_2)_mQR^{10}$, or $T(CH_2)_mCO_2R^4$;

n is 0 to 6;

W is an anion;

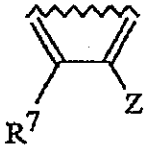
R^4 and R^5 are independently hydrogen, lower alkyl, lower alkenyl, lower alkynyl, $(CH_2)_nAr$, arylalkyl, aryl, heteroaryl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, or heteroaryl, or R^4 and R^5 together with the nitrogen to which they are attached form a carbocyclic ring containing 3 to 8 members, up to four of which members are optionally carbonyl groups or heteroatoms independently selected from oxygen, sulfur, S(O), $S(O)_2$, and nitrogen, wherein the carbocyclic group is unsubstituted or substituted with one, two, three, or four groups independently selected from halogen, hydroxy, hydroxyalkyl, lower alkyl, lower alkoxy, alkoxycarbonyl, alkylcarbonyl, alkylcarbonylamino, aminoalkyl, aminoalkylcarbonyl, trifluoromethyl, trifluoromethylalkyl, trifluoromethylalkylaminoalkyl, amino, mono- or dialkylamino, N-hydroxyacetamido, aryl, heteroaryl, carboxyalkyl, $NR^{10}SO_2R^{11}$, $C(O)NR^{10}R^{11}$, $NR^{10}C(O)R^{11}$, $C(O)OR^{10}$, $C(O)NR^{10}SO_2R^{11}$, $(CH_2)_nS(O)_nR^{10}$, $(CH_2)_n$-heteroaryl, $O(CH_2)_n$-heteroaryl, $(CH_2)_nC(O)NR^{10}R^{11}$, $O(CH_2)_nC(O)OR^{10}$;

R^9 is lower alkyl, haloalkyl, or aryl;

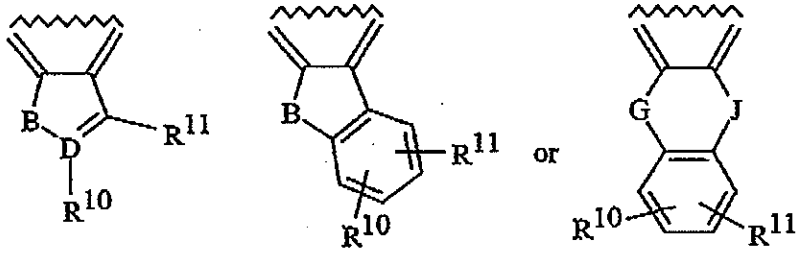
and R^4 additionally can be lower alkyl unsubstituted or substituted with one, two, or three groups independently selected from halogen, 5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl-sulfanyl, 5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl-sulfinyl, 5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl-sulfonyl, or a carbocyclic group containing from 3 to 7 members, up to four of which members are optionally heteroatoms independently selected from oxygen, sulfur and nitrogen, wherein the carbocyclic group is unsubstituted or

substituted with one, two, or three groups independently selected from halogen, hydroxy, hydroxyalkyl, lower alkyl, lower alkoxy, alkoxycarbonyl, alkylcarbonyl, alkylcarbonylamino, aminoalkyl, trifluoromethyl, N-hydroxyacetamide, trifluoromethylalkyl, amino, or mono- or dialkylamino;

and when Y is CR^7, it is part of the part structure



wherein R^7 and Z are as defined above, or can be taken together with the carbons to which they are attached to form



wherein:

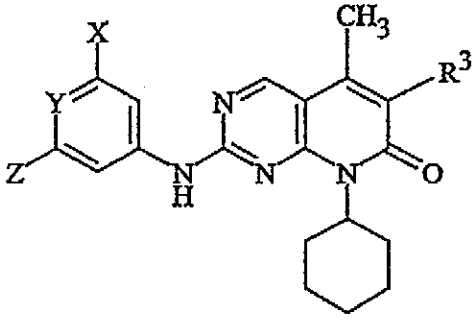
G and J are independently CH_2, NH, or O;

B is NH, S, CH_2, or O;

D is C or N, provided that R^{10} is nothing when D is N; and

R^{10} and R^{11} are independently hydrogen, halogen, lower alkyl, lower alkoxy, or alkylcarbonyl.

3. A compound of the Formula III



III

and pharmaceutically acceptable salts, esters, amides, and prodrugs thereof, wherein:

R^3 is trifluoromethyl, lower alkynyl, lower alkenyl, $-COR^4$, $CONR^4OR^5$, $-SO_2NR^4R^5$, $-SO_2R^4$, $-SO_3R^4$, or $-P(O)(OR^4)(OR^5)$; with R^4 as a substituent;

Y is N or CR^7;

X and Z are independently hydrogen, halogen, lower alkyl, lower alkoxy, trifluoromethyl, hydroxy, nitrile, nitro, $-NR^4R^5$, $-N(O)R^4R^5$, $-NR^4R^5R^6W$, $-SR^4$, $-C(O)R^4$, $-CO_2R^4$, $-CONR^4R^5$, $-SO_2NR^4R^5$, $-SO_2R^4$, $-SO_3R^4$, $P(O)(OR^4)(OR^5)$, $-T(CH_2)_mQR^4$, $-C(O)T(CH_2)_mQR^4$, or $-NR^4C(O)T(CH_2)_mQR^5$;

m is 1 to 6;

T is O, S, NR^4, $N(O)R^4$, NR^4R^5W, or CR^4R^5;

Q is O, S, NR^4, $N(O)R^4$, NR^4R^5W, CO_2, or a carbocyclic group containing from 3 to 7 members, up to four of which members are optionally heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the carbocyclic group is unsubstituted or substituted with one, two, or three groups independently selected from halogen, hydroxy, hydroxyalkyl, lower alkyl, lower alkoxy, alkoxycarbonyl, alkylcarbonyl, alkylcarbonylamino, aminoalkyl, trifluoromethyl, N-hydroxyacetamide, trifluoromethylalkyl, amino, or mono or dialkylamino;

R^6 is lower alkyl, haloalkyl, or aryl;

R^7 is NR^4R^5, $N(O)R^4R^5$, $NR^4R^5R^9X$, OH, OR^4, SR^4, halo, COR^4, $(CH_2)_nR^4$, CO_2R^4, $CONR^4R^5$, $C(O)NR^4SO_2R^5$, $S(O)R^4$, SO_2R^4, $SO_2NR^4R^5$, SO_3R^4, $(CH_2)_nP(O)(OR^4)_2$, $NR^4SO_2R^5$, aldehyde, nitrile, nitro, alkyl, alkoxyalkyl, $T(CH_2)_mQR^9$, $C(O)T(CH_2)_mQR^9$, $NR^9C(O)T(CH_2)_mQR^{10}$, or $T(CH_2)_mCO_2R^4$;

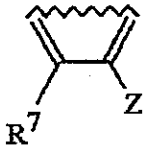
n is 0 to 6;

W is an anion;

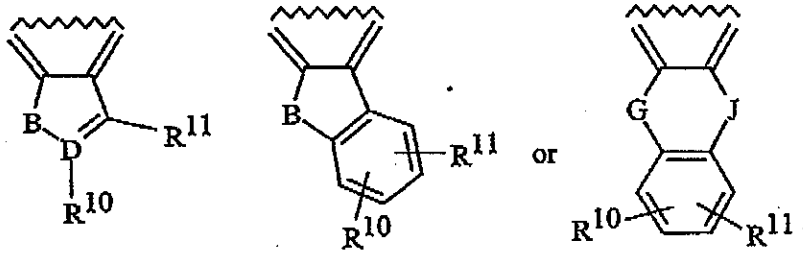
R^4 and R^5 are independently hydrogen, lower alkyl, lower alkenyl, lower alkynyl, $(CH_2)_nAr$, arylalkyl, aryl, heteroaryl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, or heteroaryl, or R^4 and R^5 together with the nitrogen to which they are attached form a carbocyclic ring containing 3 to 8 members, up to four of which members are optionally carbonyl groups or heteroatoms independently selected from oxygen, sulfur, S(O), $S(O)_2$, and nitrogen, wherein the carbocyclic group is unsubstituted or substituted with one, two, three, or four groups independently selected from halogen, hydroxy, hydroxyalkyl, lower alkyl, lower alkoxy, alkoxycarbonyl, alkylcarbonyl, alkylcarbonylamino, aminoalkyl, trifluoromethyl, trifluoromethylalkyl, trifluoromethylalkylaminoalkyl, amino, mono- or dialkylamino, N-hydroxyacetamido, aryl, heteroaryl, carboxyalkyl, $NR^{10}SO_2R^{11}$, $C(O)NR^{10}R^{11}$, $NR^{10}C(O)R^{11}$, $C(O)OR^{10}$, $C(O)NR^{10}SO_2R^{11}$, $(CH_2)_nS(O)_nR^{10}$, $(CH_2)_n$-heteroaryl, $O(CH_2)_n$-heteroaryl, $(CH_2)_nC(O)NR^{10}R^{11}$, $O(CH_2)_nC(O)OR^{10}$;

and R^4 additionally can be lower alkyl unsubstituted or substituted with one, two, or three groups independently selected from halogen, 5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl-sulfanyl, 5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl-sulfinyl, 5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl-sulfonyl, or a carbocyclic group containing from 3 to 7 members, up to four of which members are optionally heteroatoms independently selected from oxygen, sulfur and nitrogen, wherein the carbocyclic group is unsubstituted or substituted with one, two, or three groups independently selected from halogen, hydroxy, hydroxyalkyl, lower alkyl, lower alkoxy, alkoxycarbonyl, alkylcarbonyl, alkylcarbonylamino, aminoalkyl, trifluoromethyl, N-hydroxyacetamide, trifluoromethylalkyl, amino, or mono- or dialkylamino;

and when Y is CR^7, it is part of the part structure



wherein R^7 and Z are as defined above, or can be taken together with the carbons to which they are attached to form



wherein:

G and J are independently CH_2, NH, or O;

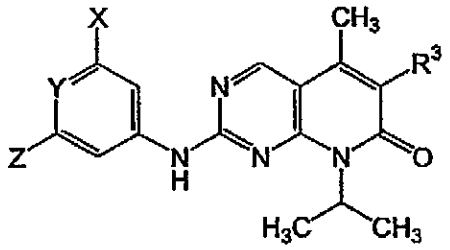
B is NH, S, CH_2, or O;

D is C or N, provided that R^{10} is nothing when D is N; and

R^9 is lower alkyl, haloalkyl, or aryl;

R^{10} and R^{11} are independently hydrogen, halogen, lower alkyl, lower alkoxy, or alkylcarbonyl.

4. A compound of the Formula IV



IV

and pharmaceutically acceptable salts, esters, amides, and prodrugs thereof,

wherein:

R^3 is trifluoromethyl, lower alkynyl, lower alkenyl, $-COR^4$, $CONR^4OR^5$, $-SO_2NR^4R^5$, $-SO_2R^4$, $-SO_3R^4$, or $-P(O)(OR^4)(OR^5)$;

R^4

Y is N or CR^7;

X and Z are independently hydrogen, halogen, lower alkyl, lower alkoxy, trifluoromethyl, hydroxy, nitrile, nitro, $-NR^4R^5$, $-N(O)R^4R^5$, $-NR^4R^5R^6W$, $-SR^4$, $-C(O)R^4$, $-CO_2R^4$, $-CONR^4R^5$, $-SO_2NR^4R^5$, $-SO_2R^4$, $-SO_3R^4$, $P(O)(OR^4)(OR^5)$, $-T(CH_2)_mQR^4$, $-C(O)T(CH_2)_mQR^4$, or $-NR^4C(O)T(CH_2)_mQR^5$;

m is 1 to 6;

T is O, S, NR^4, $N(O)R^4$, NR^4R^5W, or CR^4R^5;

Q is O, S, NR^4, $N(O)R^4$, NR^4R^5W, CO_2, or a carbocyclic group containing from 3 to 7 members, up to four of which members are optionally heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the carbocyclic group is unsubstituted or substituted with one, two, or three groups independently selected from halogen, hydroxy, hydroxyalkyl, lower alkyl, lower alkoxy, alkoxycarbonyl, alkylcarbonyl, alkylcarbonylamino, aminoalkyl, trifluoromethyl, N-hydroxyacetamide, trifluoromethylalkyl, amino, or mono or dialkylamino;

R^6 is lower alkyl, haloalkyl, or aryl;

R^7 is NR^4R^5, $N(O)R^4R^5$, $NR^4R^5R^9X$, OH, OR^4, SR^4, halo, COR^4, $(CH_2)_nR^4$, CO_2R^4, $CONR^4R^5$, $C(O)NR^4SO_2R^5$, $S(O)R^4$, SO_2R^4, $SO_2NR^4R^5$, SO_3R^4, $(CH_2)_nP(O)(OR^4)_2$, $NR^4SO_2R^5$, aldehyde, nitrile, nitro, alkyl, alkoxyalkyl, $T(CH_2)_mQR^9$, $C(O)T(CH_2)_mQR^9$, $NR^9C(O)T(CH_2)_mQR^{10}$, or $T(CH_2)_mCO_2R^4$;

n is 0 to 6;

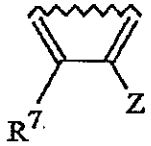
W is an anion;

R^4 and R^5 are independently hydrogen, lower alkyl, lower alkenyl, lower alkynyl, $(CH_2)_nAr$, arylalkyl, aryl, heteroaryl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, or heteroaryl, or R^4 and R^5 together with the nitrogen to which they are attached form a carbocyclic ring containing 3 to 8 members, up to four of which members are optionally carbonyl groups

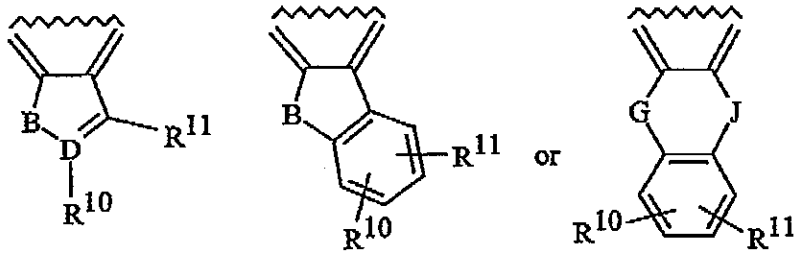
or heteroatoms independently selected from oxygen, sulfur, S(O), $S(O)_2$, and nitrogen, wherein the carbocyclic group is unsubstituted or substituted with one, two, three, or four groups independently selected from halogen, hydroxy, hydroxyalkyl, lower alkyl, lower alkoxy, alkoxycarbonyl, alkylcarbonyl, alkylcarbonylamino, aminoalkyl, aminoalkylcarbonyl, trifluoromethyl, trifluoromethylalkyl, trifluoromethylalkylaminoalkyl, amino, mono- or dialkylamino, N-hydroxyacetamido, aryl, heteroaryl, carboxyalkyl, $NR^{10}SO_2R^{11}$, $C(O)NR^{10}R^{11}$, $NR^{10}C(O)R^{11}$, $C(O)NR^{10}SO_2R^{11}$, $(CH_2)_nS(O)_nR^{10}$, $(CH_2)_n$-heteroaryl, $O(CH_2)_n$-heteroaryl, $(CH_2)_nC(O)NR^{10}R^{11}$, $O(CH_2)_nC(O)OR^{10}$;

and R^4 additionally can be lower alkyl unsubstituted or substituted with one, two, or three groups independently selected from halogen, 5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl-sulfanyl, 5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl-sulfinyl, 5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl-sulfonyl, or a carbocyclic group containing from 3 to 7 members, up to four of which members are optionally heteroatoms independently selected from oxygen, sulfur and nitrogen, wherein the carbocyclic group is unsubstituted or substituted with one, two, or three groups independently selected from halogen, hydroxy, hydroxyalkyl, lower alkyl, lower alkoxy, alkoxycarbonyl, alkylcarbonyl, alkylcarbonylamino, aminoalkyl, trifluoromethyl, N-hydroxyacetamide, trifluoromethylalkyl, amino, or mono- or dialkylamino;

and when Y is CR^7, it is part of the part structure



wherein R^7 and Z are as defined above, or can be taken together with the carbons to which they are attached to form



wherein:

G and J are independently CH_2, NH, or O;

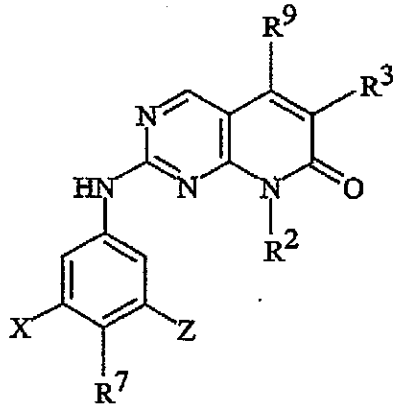
B is NH, S, CH_2, or O;

D is C or N, provided that R^{10} is nothing when D is N;

R^9 is lower alkyl, haloalkyl, or aryl; and

R^{10} and R^{11} are independently hydrogen, halogen, lower alkyl, lower alkoxy, or alkylcarbonyl.

5. A compound of Formula V



V

and pharmaceutically acceptable salts, esters, amides, and prodrugs thereof, wherein:

R^2 is (a) hydrogen;

(b) lower alkyl optionally substituted with one, two, or three groups independently selected from halogen, hydroxy, lower alkoxy, amino, mono- or dialkylamino, carboxy, alkoxycarbonyl, thioalkyl,

nitrile, aryl, heteroaryl, or a carbocyclic group containing from 3 to 7 members, up to two of which members are optionally heteroatoms independently selected from oxygen, sulfur, and nitrogen; or

(c) a carbocyclic group containing from 3 to 7 members, up to two of which members are optionally heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the carbocyclic group is unsubstituted or substituted with one, two, or three groups independently selected from consisting of halogen, hydroxy, lower alkyl, lower alkoxy, amino, mono- or dialkylamino, aryl, and heteroaryl;

R^3 is hydrogen, lower alkyl, lower alkoxy, halogen, trifluoromethyl, lower alkynyl, lower alkenyl, nitrile, nitro, $-COR^4$, $-CO_2R^4$, $-CONR^4R^5$, $CONR^4OR^5$, $-SO_2NR^4R^5$, $-SO_2R^4$, $-SO_3R^4$,

$$\begin{array}{l} | \\ R^4 \end{array}$$

$P(O)(OR^4)(OR^5)$, or $-NR^4R^5$;

R^9 is lower alkyl, haloalkyl, or aryl;

X and Z are independently hydrogen, halogen, lower alkyl, lower alkoxy, trifluoromethyl, hydroxy, nitrile, nitro, $-NR^4R^5$, $-N(O)R^4R^5$, $-NR^4R^5R^6W$, $-SR^4$, $-C(O)R^4$, $-CO_2R^4$, $-CONR^4R^5$, $-SO_2NR^4R^5$, $-SO_2R^4$, $-SO_3R^4$, $P(O)(OR^4)(OR^5)$, $-T(CH_2)_mQR^4$, $-C(O)T(CH_2)_mQR^4$, or $-NR^4C(O)T(CH_2)_mQR^5$;

m is 1 to 6;

T is O, S, NR^4, $N(O)R^4$, NR^4R^5W, or CR^4R^5;

Q is O, S, NR^4, $N(O)R^4$, NR^4R^5W, CO_2, or a carbocyclic group containing from 3 to 7 members, up to four of which members are optionally heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the carbocyclic group is unsubstituted or substituted with one, two, or three groups independently selected from halogen, hydroxy, hydroxyalkyl,

lower alkyl, lower alkoxy, alkoxycarbonyl, alkylcarbonyl, alkylcarbonylamino, aminoalkyl, trifluoromethyl, N-hydroxyacetamide, trifluoromethylalkyl, amino, or mono or dialkylamino;

R^6 is lower alkyl, haloalkyl, or aryl;

R^7 is NR^4R^5, $N(O)R^4R^5$, $NR^4R^5R^9W$, OH, OR^4, SR^4, halo, COR^4, $(CH_2)_nR^4$, $(CH_2)_nR^4$, CO_2R^4, $CONR^4R^5$, $C(O)NR^4SO_2R^5$, $S(O)R^4$, SO_2R^4, $SO_2NR^4R^5$, SO_3R^4, $(CH_2)_nP(O)(OR^4)_2$, $NR^4SO_2R^5$, aldehyde, nitrile, nitro, alkyl, alkoxyalkyl, $T(CH_2)_mQR^4$, $C(O)T(CH_2)_mQR^4$, $NR^4C(O)T(CH_2)_mQR^5$, or $T(CH_2)_mCO_2R^4$;

n is 0 to 6;

W is an anion;

R^4 and R^5 are independently hydrogen, lower alkyl, lower alkenyl, lower alkynyl, $(CH_2)_nAr$, arylalkyl, aryl, heteroaryl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, or heteroaryl, or R^4 and R^5 together with the nitrogen to which they are attached form a carbocyclic ring containing 3 to 8 members, up to four of which members are optionally carbonyl groups or heteroatoms independently selected from oxygen, sulfur, S(O), $S(O)_2$, and nitrogen, wherein the carbocyclic group is unsubstituted or substituted with one, two, three, or four groups independently selected from halogen, hydroxy, hydroxyalkyl, lower alkyl, lower alkoxy, alkoxycarbonyl, alkylcarbonyl, alkylcarbonylamino, aminoalkyl, aminoalkylcarbonyl, trifluoromethyl, trifluoromethylalkyl, trifluoromethylalkylaminoalkyl, mono- or dialkylamino, N-hydroxyacetamido, aryl, heteroaryl, carboxyalkyl, $NR^{10}SO_2R^{11}$, $C(O)NR^{10}R^{11}$, $NR^{10}C(O)R^{11}$, $C(O)OR^{10}$, $C(O)NR^{10}SO_2R^{11}$, $(CH_2)_nS(O)_nR^{10}$, $(CH_2)_n$-heteroaryl, $O(CH_2)_n$-heteroaryl, $(CH_2)_nC(O)NR^{10}R^{11}$, $O(CH_2)_nC(O)OR^{10}$;

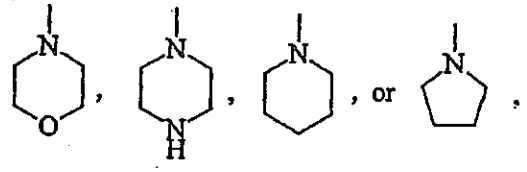
and R^4 additionally can be lower alkyl unsubstituted or substituted with one, two, or three groups independently selected from halogen, 5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl-sulfanyl, 5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl-sulfinyl, 5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl-sulfonyl, or a

carbocyclic group containing from 3 to 7 members, up to four of which members are optionally heteroatoms independently selected from oxygen, sulfur, and nitrogen, wherein the carbocyclic group is unsubstituted or substituted with one, two, or three groups independently selected from halogen, hydroxy, hydroxyalkyl, lower alkyl, lower alkoxy, alkoxycarbonyl, alkylcarbonyl, alkylcarbonylamino, aminoalkyl, trifluoromethyl, N-hydroxyacetamide, trifluoromethylalkyl, amino, or mono- or dialkylamino; and

R^{10} and R^{11} are independently hydrogen, halogen, lower alkyl, lower alkoxy, or alkylcarbonyl;

with the proviso that when, R^3 is hydrogen, lower alkyl, lower alkoxy, halogen, nitrile, nitro, $-CO_2R^4$, $CONR^4OR^5$, or $-NR^4R^5$, then R^9 is not C_1-C_3 alkyl.

6. A compound according to Claim 5 wherein R^7 is selected from



and wherein such groups are optionally substituted by alkyl, aryl, or amide.

7. A compound selected from the group consisting of:

(a) 8-Cyclopentyl-5-methyl-2-(4-piperazin-1-yl-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 1**);

(b) 8-(1-Methylethyl)-5-methyl-2-(4-piperazin-1-yl-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 2**);

(c) 8-Cyclopentyl-5-methyl-2-(4-fluoro-3-methylphenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 3**);

(d) 8-(1-Methylethyl)-5-methyl-2-(4-fluoro-3-methylphenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 4**);

(e) 8-Cyclohexyl-5-methyl-2-(4-fluoro-3-methylphenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 5**);

(f) 8-Cyclohexyl-5-methyl-2-[4-(4-propanoylpiperazin-1-yl)phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 6**);

(g) 8-Cyclopentyl-5-methyl-2-[4-(4-propanoylpiperazin-1-yl)phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 7**);

(h) 8-(1-Methylethyl)-5-methyl-2-[4-(4-propanoylpiperazin-1-yl)phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 8**);

(i) 8-Cyclohexyl-5-methyl-2-(4-piperazin-1-yl-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 9**);

(j) 8-Cyclopentyl-5-methyl-2-(4-pyridylphenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 10**);

(k) 8-(1-Methylethyl)-5-methyl-2-(4-pyridylphenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 11**);

(l) 8-Cyclopentyl-5-methyl-2-[4-(3-aminopyrrolidinyl)-phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 12**);

(m) 8-(1-Methylethyl)-5-methyl-2-[4-(3-aminopyrrolidinyl)-phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 13**);

(n) N-(1-{4-[(8-cyclopentyl-5-methyl-7-oxo(8-hydropyridino-[2,3-d]pyrimidin-2-yl))amino]phenyl}pyrrolidin-3-yl)-3,3-dimethylbutanamide (**Compound 14**);

(o) N-(1-{4-[(5-methyl-8-(1-methylethyl)-7-oxo(8-hydropyridino[2,3-d]pyrimidin-2-yl))amino]phenyl}pyrrolidin-3-yl)-3,3-dimethylbutanamide (**Compound 15**);

(p) 8-Cyclopentyl-5-methyl-2-(3-chloro-4-piperazin-1-yl-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 16**);

(q) 8-Cyclohexyl-5-methyl-2-(3-chloro-4-piperazin-1-yl-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 17**);

(r) 8-(1-Methylethyl)-5-methyl-2-(3-chloro-4-piperazin-1-yl-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 18**);

(s) 8-Cyclopentyl-6-fluoro-5-methyl-2-(3-chloro-4-piperazin-1-yl-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 19**);

(t) 8-Cyclohexyl-6-fluoro-5-methyl-2-(3-chloro-4-piperazin-1-yl-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 21**);

(u) 8-(1-Methylethyl)-6-fluoro-5-methyl-2-(3-chloro-4-piperazin-1-yl-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 20**);

(v) 8-Cyclopentyl-5-methyl-2-(3-chloro-4-morpholin-4-yl-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 22**);

(w) 8-(1-Methylethyl)-5-methyl-2-(3-chloro-4-morpholin-4-yl-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 23**);

(x) 8-Cyclohexyl-5-methyl-2-(3-chloro-4-morpholin-4-yl-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 24**);

(y) 2-({3-chloro-4-[4-(3-morpholin-4-ylpropyl)piperidyl]-phenyl}amino)-8-cyclopentyl-5-methyl-8-hydropyridino[2,3-d]pyrimidin-7-one (**Compound 25**);

(z) 2-({3-chloro-4-[4-(3-morpholin-4-ylpropyl)piperidyl]-phenyl}amino)-8-(1-methylethyl)-5-methyl-8-hydropyridino[2,3-d]-pyrimidin-7-one (**Compound 26**);

(aa) 2-({3-chloro-4-[4-(3-morpholin-4-ylpropyl)piperidyl]-phenyl}amino)-8-cyclohexyl-5-methyl-8-hydropyridino[2,3-d]pyrimidin-7-one (**Compound 27**);

(bb) 2-({3-chloro-4-[4-(3-piperazinylpropyl)piperidyl]phenyl}-amino)-8-cyclopentyl-6-fluoro-5-methyl-8-hydropyridino[2,3-d]pyrimidin-7-one (**Compound 28**);

(cc) 2-({3-chloro-4-[4-(3-piperazinylpropyl)piperidyl]-phenyl}amino)-8-(1-methylethyl)-6-fluoro-5-methyl-8-hydropyridino-[2,3-d]pyrimidin-7-one (**Compound 29**);

(dd) 2-({3-chloro-4-[4-(3-piperazinylpropyl)piperidyl]-phenyl}amino)-8-cyclohexyl-6-fluoro-5-methyl-8-hydropyridino-[2,3-d]pyrimidin-7-one (**Compound 30**);

(ee) 2-({3-chloro-4-[4-(3-piperazinylpropyl)piperidyl]-phenyl}amino)-8-cyclopentyl-5-methyl-8-hydropyridino[2,3-d]pyrimidin-7-one (**Compound 31**);

(ff) 2-({3-chloro-4-[4-(3-piperazinylpropyl)piperidyl]-phenyl}amino)-8-(1-methylethyl)-5-methyl-8-hydropyridino-[2,3-d]pyrimidin-7-one (**Compound 32**);

(gg) 2-({3-chloro-4-[4-(3-piperazinylpropyl)piperidyl]-phenyl}amino)-8-cyclohexyl-5-methyl-8-hydropyridino[2,3-d]pyrimidin-7-one (**Compound 33**);

(gg2) 8-Cyclopentyl-2-[4-(piperazin-1-yl)-phenylamino]-6-fluoro-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one trifluoroacetate (**Compound 34**);

(gg3) 8-Cyclopentyl-2-[4-(piperazin-1-yl)-phenylamino]-6-bromo-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one trifluoroacetate (**Compound 35**);

(hh) 8-Cyclopentyl-2-[4-(3,5-dimethyl-piperazin-1-yl)-phenylamino]-6-fluoro-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one hydrochloride (**Compound 36**);

(ii) 8-Cyclopentyl-2-(3-fluoro-4-piperazin-1-yl-phenylamino)-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 37**);

(jj) 6-Bromo-8-cyclopentyl-2-[4-(3,5-dimethyl-piperazin-1-yl)-phenylamino]-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one hydrochloride (**Compound 38**);

(kk) 8-Cyclopentyl-6-fluoro-2-(3-fluoro-4-piperazin-1-yl-phenylamino)-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 39**);

(ll) 6-Bromo-8-cyclopentyl-2-(3-fluoro-4-piperazin-1-yl-phenylamino)-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 40**);

(mm) 8-Cyclopentyl-2-[4-(3,5-dimethyl-piperazin-1-yl)-phenylamino]-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 41**);

(nn) 2-(3-Chloro-4-piperazin-1-yl-phenylamino)-8-cyclopentyl-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 42**);

(oo) 2-(3-Chloro-4-piperazin-1-yl-phenylamino)-8-cyclopentyl-6-fluoro-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 43**);

(pp) 6-Bromo-2-(3-chloro-4-piperazin-1-yl-phenylamino)-8-cyclopentyl-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 44**);

(qq) 8-Cyclopentyl-5-methyl-2-(4-morpholin-4-yl-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one trifluoroacetate (**Compound 45**);

(rr) 8-Cyclopentyl-6-fluoro-5-methyl-2-(4-morpholin-4-yl-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 46**);

(ss) 6-Bromo-8-cyclopentyl-5-methyl-2-(4-morpholin-4-yl-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 47**);

(tt) 8-Cyclopentyl-2-(3-fluoro-4-morpholin-4-yl-phenylamino)-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 48**);

(uu) 8-Cyclopentyl-6-fluoro-2-(3-fluoro-4-morpholin-4-yl-phenylamino)-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 49**);

(vv) 6-Bromo-8-cyclopentyl-2-(3-fluoro-4-morpholin-4-yl-phenylamino)-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 50**);

(ww) 2-(3-Chloro-4-morpholin-4-yl-phenylamino)-8-cyclopentyl-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 51**);

(xx) 2-(3-Chloro-4-morpholin-4-yl-phenylamino)-8-cyclopentyl-6-fluoro-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 52**);

(yy) 6-Bromo-2-(3-chloro-4-morpholin-4-yl-phenylamino)-8-cyclopentyl-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 53**);

(zz) 8-Cyclopentyl-5-methyl-2-{4-[4-(2,2,2-trifluoro-ethyl)-piperazin-1-yl]-phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 54**);

(aaa) 8-Cyclopentyl-6-fluoro-5-methyl-2-{4-[4-(2,2,2-trifluoro-ethyl)-piperazin-1-yl]-phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 55**);

(bbb) 6-Bromo-8-cyclopentyl-5-methyl-2-{4-[4-(2,2,2-trifluoro-ethyl)-piperazin-1-yl]-phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 56**);

(ccc) 8-Cyclopentyl-5-methyl-2-{4-[4-(3-piperazin-1-yl-propyl)-piperidin-1-yl]-phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one trifluoroacetate (**Compound 57**);

(ddd) 8-Cyclopentyl-6-fluoro-5-methyl-2-{4-[4-(3-piperazin-1-yl-propyl)-piperidin-1-yl]-phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 58**);

(eee) 6-Bromo-8-cyclopentyl-5-methyl-2-{4-[4-(3-piperazin-1-yl-propyl)-piperidin-1-yl]-phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 59**);

(fff) 8-Cyclopentyl-5-methyl-2-{4-[4-(3-morpholin-4-yl-propyl)-piperidin-1-yl]-phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 60**);

(ggg) 8-Cyclopentyl-6-fluoro-5-methyl-2-{4-[4-(3-morpholin-4-yl-propyl)-piperidin-1-yl]-phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 61**);

(hhh) 6-Bromo-8-cyclopentyl-5-methyl-2-{4-[4-(3-morpholin-4-yl-propyl)-piperidin-1-yl]-phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 62**);

(iii) 6-Bromo-8-cyclopentyl-5-methyl-2-{4-[4-(3-morpholin-4-yl-propyl)-piperidin-1-yl]-phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 63**);

(jjj) 2-(4-{4-[3-(3-Amino-pyrrolidin-1-yl)-propyl]-piperidin-1-yl}-phenylamino)-8-cyclopentyl-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 64**);

(kkk) 2-(4-{4-[3-(3-Amino-pyrrolidin-1-yl)-propyl]-piperidin-1-yl}-phenylamino)-8-cyclopentyl-6-fluoro-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 65**);

(lll) 2-(4-{4-[3-(3-Amino-pyrrolidin-1-yl)-propyl]-piperidin-1-yl}-phenylamino)-6-bromo-8-cyclopentyl-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 66**);

(mmm) 8-Cyclopentyl-2-{3-fluoro-4-[4-(3-piperazin-1-yl-propyl)-piperidin-1-yl]-phenylamino}-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 67**);

(nnn) 8-Cyclopentyl-6-fluoro-2-{3-fluoro-4-[4-(3-piperazin-1-yl-propyl)-piperidin-1-yl]-phenylamino}-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 68**);

(ooo) 6-Bromo-8-cyclopentyl-2-{3-fluoro-4-[4-(3-piperazin-1-yl-propyl)-piperidin-1-yl]-phenylamino}-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 69**);

(ppp) 8-Cyclopentyl-2-{3-fluoro-4-[4-(3-morpholin-4-yl-propyl)-piperidin-1-yl]-phenylamino}-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 70**);

(qqq) 8-Cyclopentyl-6-fluoro-2-{3-fluoro-4-[4-(3-morpholin-4-yl-propyl)-piperidin-1-yl]-phenylamino}-5-methyl-8H-pyrido[2,3-d]-pyrimidin-7-one (**Compound 71**);

(rrr) 6-Bromo-8-cyclopentyl-2-{3-fluoro-4-[4-(3-morpholin-4-yl-propyl)-piperidin-1-yl]-phenylamino}-5-methyl-8H-pyrido[2,3-d]-pyrimidin-7-one (**Compound 72**);

(sss) 2-[4-(3-Amino-pyrrolidin-1-yl)-phenylamino]-8-cyclopentyl-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 73**);

(ttt) 2-[4-(3-Amino-pyrrolidin-1-yl)-phenylamino]-8-cyclopentyl-6-fluoro-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 74**);

(uuu) 2-[4-(3-Amino-pyrrolidin-1-yl)-phenylamino]-6-bromo-8-cyclopentyl-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 75**);

(vvv) 2-[4-(3-Amino-pyrrolidin-1-yl)-3-fluoro-phenylamino]-8-cyclopentyl-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 76**);

(www) 2-[4-(3-Amino-pyrrolidin-1-yl)-3-fluoro-phenylamino]-8-cyclopentyl-6-fluoro-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 77**);

(xxx) 2-[4-(3-Amino-pyrrolidin-1-yl)-3-fluoro-phenylamino]-6-bromo-8-cyclopentyl-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 78**);

(yyy) 8-Cyclopentyl-5-methyl-2-{4-[3-(2,2,2-trifluoro-ethylamino)-pyrrolidin-1-yl]-phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one trifluoroacetate (**Compound 79**);

(zzz) 8-Cyclopentyl-6-fluoro-5-methyl-2-{4-[3-(2,2,2-trifluoro-ethylamino)-pyrrolidin-1-yl]-phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 80**);

(aaaa) 6-Bromo-8-cyclopentyl-5-methyl-2-{4-[3-(2,2,2-trifluoro-ethylamino)-pyrrolidin-1-yl]-phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 81**);

(bbbb) 2-[4-(3-Amino-pyrrolidin-1-yl)-3-chloro-phenylamino]-8-cyclopentyl-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one trifluoroacetate (**Compound 82**);

(cccc) 2-[4-(3-Amino-pyrrolidin-1-yl)-3-chloro-phenylamino]-8-cyclopentyl-6-fluoro-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 83**);

(dddd) 2-[4-(3-Amino-pyrrolidin-1-yl)-3-chloro-phenylamino]-6-bromo-8-cyclopentyl-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 84**);

(eeee) 2-[4-(3-Aminomethyl-4-trifluoromethyl-pyrrolidin-1-yl)-phenylamino]-8-cyclopentyl-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 85**);

(ffff) 2-[4-(3-Aminomethyl-4-trifluoromethyl-pyrrolidin-1-yl)-phenylamino]-8-cyclopentyl-6-fluoro-5-methyl-8H-pyrido[2,3-d]-pyrimidin-7-one (**Compound 86**);

(gggg) 2-[4-(3-Aminomethyl-4-trifluoromethyl-pyrrolidin-1-yl)-phenylamino]-6-bromo-8-cyclopentyl-5-methyl-8H-pyrido[2,3-d]-pyrimidin-7-one (**Compound 87**);

(hhhh) 2-[4-(3-Trifloroethylaminomethyl-pyrrolidin-1-yl)-phenylamino]-8-cyclopentyl-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 88**);

(iiii) 2-[4-(3-Trifloroethylaminomethyl-pyrrolidin-1-yl)-phenylamino]-8-cyclopentyl-6-fluoro-5-methyl-8H-pyrido[2,3-d]-pyrimidin-7-one (**Compound 89**);

(jjjj) 2-[4-(3-Trifloroethylaminomethyl-pyrrolidin-1-yl)-phenylamino]-6-bromo-8-cyclopentyl-5-methyl-8H-pyrido[2,3-d]-pyrimidin-7-one (**Compound 90**);

(kkkk) 8-Cyclopentyl-2-[4-(3,3-dimethyl-piperazin-1-yl)-phenylamino]-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one hydrochloride (**Compound 91**);

(llll) 8-Cyclopentyl-2-[4-(3,3-dimethyl-piperazin-1-yl)-phenylamino]-6-fluoro-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 92**);

(mmmm) 6-Bromo-8-cyclopentyl-2-[4-(3,3-dimethyl-piperazin-1-yl)-phenylamino]-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one hydrochloric (**Compound 93**);

(nnnn) 8-Cyclopentyl-5-methyl-2-[4-(3,3,4-trimethyl-piperazin-1-yl)-phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 94**);

(oooo) 8-Cyclopentyl-6-fluoro-5-methyl-2-[4-(3,3,4-trimethyl-piperazin-1-yl)-phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 95**);

(pppp) 6-Bromo-8-cyclopentyl-5-methyl-2-[4-(3,3,4-trimethyl-piperazin-1-yl)-phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 96**);

(qqqq) 2-[4-(4-Acetyl-piperazin-1-yl)-phenylamino]-8-cyclopentyl-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 97**);

(rrrr) 2-[4-(4-Acetyl-piperazin-1-yl)-phenylamino]-8-cyclopentyl-6-fluoro-5-methyl-8H-pyrido[2,3-*d*]pyrimidin-7-one (**Compound 98**);

(ssss) 2-[4-(4-Acetyl-piperazin-1-yl)-phenylamino]-6-bromo-8-cyclopentyl-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 99**);

(tttt) 8-Cyclopentyl-2-{4-[4-(2-hydroxy-ethyl)-3,5-dimethyl-piperazin-1-yl]-phenylamino}-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 100**);

(uuuu) 8-Cyclopentyl-6-fluoro-2-{4-[4-(2-hydroxy-ethyl)-3,5-dimethyl-piperazin-1-yl]-phenylamino}-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 101**);

(vvvv) 6-Bromo-8-cyclopentyl-2-{4-[4-(2-hydroxy-ethyl)-3,5-dimethyl-piperazin-1-yl]-phenylamino}-5-methyl-8H-pyrido[2,3-d]-pyrimidin-7-one (**Compound 102**);

(wwww) 8-Cyclopentyl-5-methyl-2-(4-perhydro-1,4-diazepin-1-yl-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one hydrochloride (**Compound 103**);

(xxxx) 8-Cyclopentyl-6-fluoro-5-methyl-2-(4-perhydro-1,4-diazepin-1-yl-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one hydrochloride (**Compound 104**);

(yyyy) 6-Bromo-8-cyclopentyl-5-methyl-2-(4-perhydro-1,4-diazepin-1-yl-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 105**);

(zzzz) 8-Cyclopentyl-5-methyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 106**);

(aaaaa) 8-Cyclopentyl-6-fluoro-5-methyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 107**);

(bbbbb) 6-Bromo-8-cyclopentyl-5-methyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 108**);

(ccccc) 8-Cyclopentyl-5-methyl-2-[4-(4-methyl-perhydro-1,4-diazepin-1-yl)-phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 109**);

(ddddd) 8-Cyclopentyl-6-fluoro-5-methyl-2-[4-(4-methyl-perhydro-1,4-diazepin-1-yl)-phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 110**);

(eeeee) 6-Bromo-8-cyclopentyl-5-methyl-2-[4-(4-methyl-perhydro-1,4-diazepin-1-yl)-phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 111**);

(fffff) {4-[4-(8-Cyclopentyl-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino)-phenyl]-piperazin-1-yl}-acetic acid (**Compound 112**);

(ggggg) {4-[4-(8-Cyclopentyl-6-fluoro-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino)-phenyl]-piperazin-1-yl}-acetic acid (**Compound 113**);

(hhhhh) {4-[4-(6-Bromo-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino)-phenyl]-piperazin-1-yl}-acetic acid (**Compound 114**);

(iiiii) 8-Cyclopentyl-5-methyl-2-(4-{4-[3-(1H-tetrazol-5-yl)-propyl]-piperidin-1-yl}-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 115**);

(jjjjj) 8-Cyclopentyl-6-fluoro-5-methyl-2-(4-{4-[3-(1H-tetrazol-5-yl)-propyl]-piperidin-1-yl}-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 116**);

(kkkkk) 6-Bromo-8-cyclopentyl-5-methyl-2-(4-{4-[3-(1H-tetrazol-5-yl)-propyl]-piperidin-1-yl}-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 117**);

(lllll) 8-Cyclopentyl-5-methyl-2-(4-{4-[3-(5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-ylsulfanyl)-propyl]-piperidin-1-yl}-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 118**);

(mmmmm) 8-Cyclopentyl-6-fluoro-5-methyl-2-(4-{4-[3-(5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-ylsulfanyl)-propyl]-piperidin-1-yl}-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 119**);

(nnnnn) 6-Bromo-8-cyclopentyl-5-methyl-2-(4-{4-[3-(5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-ylsulfanyl)-propyl]-piperidin-1-yl}-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 120**);

(ooooo) 8-Cyclopentyl-5-methyl-2-(4-{4-[3-(5-oxo-4,5-dihydro-1H-1,2,4-triazole-3-sulfinyl)-propyl]-piperidin-1-yl}-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 121**);

(ppppp) 8-Cyclopentyl-6-fluoro-5-methyl-2-(4-{4-[3-(5-oxo-4,5-dihydro-1H-1,2,4-triazole-3-sulfinyl)-propyl]-piperidin-1-yl}-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 122**);

(qqqqq) 6-Bromo-8-cyclopentyl-5-methyl-2-(4-{4-[3-(5-oxo-4,5-dihydro-1H-1,2,4-triazole-3-sulfinyl)-propyl]-piperidin-1-yl}-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 123**);

(rrrrr) 8-Cyclopentyl-5-methyl-2-(4-{4-[3-(5-oxo-4,5-dihydro-1H-1,2,4-triazole-3-sulfonyl)-propyl]-piperidin-1-yl}-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 124**);

(sssss) 8-Cyclopentyl-6-fluoro-5-methyl-2-(4-{4-[3-(5-oxo-4,5-dihydro-1H-1,2,4-triazole-3-sulfonyl)-propyl]-piperidin-1-yl}-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 125**);

(ttttt) 6-Bromo-8-cyclopentyl-5-methyl-2-(4-{4-[3-(5-oxo-4,5-dihydro-1H-1,2,4-triazole-3-sulfonyl)-propyl]-piperidin-1-yl}-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 126**);

(uuuuu) N-(2-{1-[4-(8-Cyclopentyl-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino)-phenyl]-piperidin-4-yl}-ethyl)-N-hydroxy-acetamide (**Compound 127**);

(vvvvv) N-(2-{1-[4-(8-Cyclopentyl-6-fluoro-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino)-phenyl]-piperidin-4-yl}-ethyl)-N-hydroxy-acetamide (**Compound 128**);

(wwwww) N-(2-{1-[4-(6-Bromo-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino)-phenyl]-piperidin-4-yl}-ethyl)-N-hydroxy-acetamide (**Compound 129**);

(xxxxx) N-(3-{1-[4-(8-Cyclopentyl-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino)-phenyl]-piperidin-4-yl}-propyl)-N-hydroxy-acetamide (**Compound 130**);

(yyyyy) N-(3-{1-[4-(8-Cyclopentyl-6-fluoro-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino)-phenyl]-piperidin-4-yl}-propyl)-N-hydroxy-acetamide (**Compound 131**);

(zzzzz) N-(3-{1-[4-(6-Bromo-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino)-phenyl]-piperidin-4-yl}-propyl)-N-hydroxy-acetamide (**Compound 132**);

(aaaaaa) 2-(Benzofuran-5-ylamino)-8-cyclopentyl-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 133**);

(bbbbbb) 8-Cyclopentyl-2-(1H-indol-5-ylamino)-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 134**);

(cccccc) 2-(Benzo[b]thiophen-5-ylamino)-8-cyclopentyl-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 135**);

(dddddd) 8-Cyclopentyl-2-(2,3-dimethyl-1H-indol-5-ylamino)-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 136**);

(eeeeee) 2-(9H-Carbazol-3-ylamino)-8-cyclopentyl-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 137**);

(ffffff) 8-Cyclopentyl-2-(1H-indazol-5-ylamino)-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 138**);

(gggggg) 2-(2-Acetyl-benzofuran-5-ylamino)-8-cyclopentyl-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 139**);

(hhhhhh) 8-Cyclopentyl-5-methyl-2-(4-morpholin-4-yl-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 140**);

(iiiiii) 8-Cyclopentyl-2-[4-(3,5-dimethyl-piperazin-1-yl)-phenylamino]-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 141**);

(jjjjjj) 2-(3-Chloro-4-piperazin-1-yl-phenylamino)-8-cyclopentyl-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one trifluoroacetate (**Compound 142**);

(kkkkkk) 8-Cyclopentyl-5-methyl-2-(4-piperidin-1-yl-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 143**);

(llllll) 8-Cyclopentyl-5-methyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 144**);

(mmmmmm) N-{1-[4-(8-Cyclopentyl-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino)-phenyl]-piperidin-4-yl}-acetamide (**Compound 145**);

(nnnnnn) 8-Cyclopentyl-5-methyl-2-(4-piperazin-1-yl-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one trifluoroacetate (**Compound 146**);

(oooooo) 8-Cyclopentyl-6-fluoro-5-methyl-2-(4-piperazin-1-yl-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 147**);

(pppppp) 6-Bromo-8-cyclopentyl-5-methyl-2-(4-piperazin-1-yl-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 148**);

(qqqqqq) 2-[3-Chloro-4-(3-amino-pyrrolidin-1-yl)-phenylamino]-8-cyclopentyl-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one trifluoroacetate (**Compound 149**);

(rrrrrr) 8-Cyclopentyl-5-methyl-2-[4-(4-(2,2,2-trifluoroethyl)-piperazin-1-yl)-phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 150**);

(ssssss) 8-Cyclopentyl-2-(4-fluoro-phenylamino)-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 151**);

(ttttt) 8-Cyclopentyl-5-methyl-2-phenylamino-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 152**);

(uuuuuu) 8-Cyclopentyl-2-(3,4-dichlorophenylamino)-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 153**);

(vvvvvv) 8-Isopropyl-5-methyl-2-(4-piperazin-1-yl-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one trifluoroacetate (**Compound 154**);

(wwwwww) 8-Isopropyl-5-methyl-2-[4-(4-propionyl-piperazin-1-yl)-phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 155**);

(xxxxxx) 8-Cyclohexyl-5-methyl-2-(4-piperazin-1-yl-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 156**);

(yyyyyy) 2-{4-[4-(3-Morpholin-4-yl-propyl)-piperidin-1-yl]-phenylamino}-8-cyclohexyl-6-fluoro-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 157**);

(zzzzzz) 8-Cyclopentyl-5-methyl-2-[4-(2H-1,2,4-triazol-3-ylsulfanylmethyl)-phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 158**);

(aaaaaaa) 8-Cyclopentyl-5-methyl-2-[4-(2H-1,2,4-triazole-3-sulfinylmethyl)-phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 159**);

(bbbbbbb) 8-Cyclopentyl-5-methyl-2-[4-(2H-1,2,4-triazole-3-sulfonylmethyl)-phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 160**);

(ccccccc) 8-Cyclopentyl-5-methyl-2-[4-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-ylmethyl)-phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 161**);

(ddddddd) 8-Cyclopentyl-5-methyl-2-{4-[2-(2H-1,2,4-triazol-3-ylsulfanyl)-ethyl]-phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 162**);

(eeeeeee) 8-Cyclopentyl-5-methyl-2-{4-[2-(2H-1,2,4-triazole-3-sulfinyl)-ethyl]-phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 163**);

(fffffff) 8-Cyclopentyl-5-methyl-2-{4-[2-(2H-1,2,4-triazole-3-sulfonyl)-ethyl]-phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 164**);

(gggggggg) 8-Cyclopentyl-5-methyl-2-{4-[2-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-ethyl]-phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 165**);

(hhhhhhh) 8-Cyclopentyl-5-methyl-2-[4-(3H-1,2,3-triazol-4-ylsulfanylmethyl)-phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 166**);

(iiiiiii) 8-Cyclopentyl-5-methyl-2-{4-[2-(3H-1,2,3-triazol-4-ylsulfanyl)-ethyl]-phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 167**);

(jjjjjjj) 8-Cyclopentyl-5-methyl-2-{4-[4-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-piperidin-1-yl]-phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 168**);

(kkkkkkk) 8-Cyclopentyl-5-methyl-2-{4-[4-(2H-1,2,4-triazol-3-ylsulfanyl)-piperidin-1-yl]-phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 169**);

(lllllll) 8-Cyclopentyl-5-methyl-2-{4-[4-(2H-1,2,4-triazole-3-sulfinyl)-piperidin-1-yl]-phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 170**);

(mmmmmmm) 8-Cyclopentyl-5-methyl-2-{4-[4-(2H-1,2,4-triazole-3-sulfonyl)-piperidin-1-yl]-phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 171**), mp 235-237°C;

(nnnnnnn) 8-Cyclopentyl-5-methyl-2-{4-[4-(2H-tetrazol-5-yl)-piperidin-1-yl]-phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 172**);

(ooooooo) 1-[4-(8-Cyclopentyl-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino)-phenyl]-piperidine-4-carboxylic acid (1H-tetrazol-5-yl)-amide (**Compound 173**);

(ppppppp) 8-Cyclopentyl-5-methyl-2-{4-[4-(3H-1,2,3-triazol-4-ylsulfanyl)-piperidin-1-yl]-phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 173**);

(qqqqqqq) 3-[4-(8-Cyclopentyl-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino)-phenyl]-N-(1H-tetrazol-5-yl)-propionamide (**Compound 174**);

(rrrrrr) 2-[4-(8-Cyclopentyl-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino)-phenoxy]-N-(1H-tetrazol-5-yl)-acetamide (**Compound 175**);

(sssssss) 8-Cyclopentyl-5-methyl-2-[4-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-ylmethoxy)-phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 176**);

(tttttt) 8-Cyclopentyl-5-methyl-2-(4-{4-[2-(2H-1,2,4-triazole-3-sulfinyl)-ethyl]-piperidin-1-yl}-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 177**);

(uuuuuuu) 8-Cyclopentyl-5-methyl-2-(4-{4-[2-(2H-1,2,4-triazole-3-sulfonyl)-ethyl]-piperidin-1-yl}-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 178**);

(vvvvvvv) 8-Cyclopentyl-5-methyl-2-(4-{4-[2-(3H-1,2,3-triazol-4-ylsulfanyl)-ethyl]-piperidin-1-yl}-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 179**);

(wwwwwww) 8-Cyclopentyl-5-methyl-2-(4-{4-[2-(2H-1,2,4-triazol-3-ylsulfanyl)-ethyl]-piperidin-1-yl}-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 180**);

(xxxxxxx) 8-Cyclopentyl-5-methyl-2-(4-{4-[2-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-ethyl]-piperidin-1-yl}-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 181**);

(yyyyyyy) 8-Cyclopentyl-5-methyl-2-{4-[4-(2-oxo-2,3-dihydro-1,2,3,5-oxathiadiazol-4-yl)-piperidin-1-yl]-phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 182**);

(zzzzzzz) 8-Cyclopentyl-2-{4-[4-(2,2-dioxo-2,3-dihydro-1,2,3,5-oxathiadiazol-4-yl)-piperidin-1-yl]-phenylamino}-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 183**);

(aaaaaaaa) 8-Cyclopentyl-5-methyl-2-{4-[4-(1-oxo-2,5-dihydro-1H-1,2,3,5-thiatriazol-4-yl)-piperidin-1-yl]-phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 184**);

(bbbbbbbb) 8-Cyclopentyl-2-{4-[4-(1,1-dioxo-2,5-dihydro-1H-1,2,3,5-thiatriazol-4-yl)-piperidin-1-yl]-phenylamino}-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 185**);

(cccccccc) N-{1-[4-(8-Cyclopentyl-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino)-phenyl]-piperidine-4-carbonyl}-methanesulfonamide (**Compound 186**);

(dddddddd) 8-Cyclopentyl-5-methyl-2-{4-[3-(2H-1,2,4-triazol-3-ylsulfanyl)-pyrrolidin-1-yl]-phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 187**);

(eeeeeeee) 8-Cyclopentyl-5-methyl-2-{4-[3-(2H-1,2,4-triazole-3-sulfinyl)-pyrrolidin-1-yl]-phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 188**);

(ffffffff) 8-Cyclopentyl-5-methyl-2-{4-[3-(2H-1,2,4-triazole-3-sulfonyl)-pyrrolidin-1-yl]-phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 189**);

(gggggggg) 8-Cyclopentyl-5-methyl-2-{4-[3-(3H-1,2,3-triazol-4-ylsulfanyl)-pyrrolidin-1-yl]-phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 190**);

(hhhhhhhh) 8-Cyclopentyl-5-methyl-2-{4-[3-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-pyrrolidin-1-yl]-phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 191**);

(iiiiiiii) 8-Cyclopentyl-5-methyl-2-{4-[4-(3-hydroxypropyl)piperidin-1-yl]-phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one trifluoroacetate (**Compound 192**);

(jjjjjjjj) 8-Cyclopentyl-5-methyl-2-(4-piperazin-1-yl-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one trifluoroacetate (**Compound 193**);

(kkkkkkkk) 8-Cyclopentyl-5-ethyl-2-(4-piperazin-1-yl-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 194**);

(lllllll) 8-(1-Methylethyl)-5-ethyl-2-(4-piperazin-1-yl-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 195**);

(mmmmmmmm) 8-(Methylethyl)-5-ethyl-2-(4-piperazin-1-yl-phenylamino)-8H-pyrido[2,3-d]pyrimidin-7-one trifluoroacetate (**Compound 196**);

(nnnnnnnn) 8-Cyclopentyl-5-methyl-2-[4-(3-hydroxypyrrolidin-1-yl)phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 197**);

(ooooooo) 8-Cyclopentyl-5-methyl-2-[4-(4-acetylpiperazin-1-yl)phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 198**);

(ppppppp) 8-Cyclopentyl-5-methyl-6-fluoro-2-[4-(4-acetylpiperidin-1-yl)phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 199**);

(qqqqqqqq) 8-Cyclopropyl-5-methyl-2-[4-(4-acetamidopiperidin-1-yl)phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 200**);

(rrrrrrr) 8-Cyclopentyl-5-methyl-2-[4-(homopiperazin-1-yl)phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one hydrochloride (**Compound 202**);

(sssssssss) 8-Cyclopentyl-5-methyl-6-fluoro-2-[4-(homopiperazin-1-yl)phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one hydrochloride (**Compound 203**);

(ttttttt) 8-Cyclopentyl-5-methyl-6-fluoro-2-[4-(3,3-dimethyl-4-acetylpiperazin-1-yl)phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 204**);

(uuuuuuuu) 8-Cyclopentyl-5-methyl-2-[4-(3,3-dimethyl-4-acetylpiperazin-1-yl)phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 205**);

(vvvvvvvv) 8-Cyclopentyl-5-methyl-6-fluoro-2-[4-(4-methylpiperazin-1-yl)phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 206**);

(wwwwwwww) 8-Cyclopentyl-5-methyl-2-[4-(N-methylacetamido)phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 207**);

(xxxxxxxx) 8-Cyclopentyl-5-methyl-2-{4-[2-(2-hydroxyethoxy)ethylamino]phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 208**);

(yyyyyyyy) 8-Cyclopentyl-5-methyl-2-[4-(3-oxopiperazin-1-yl)phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 209**);

(zzzzzzzz) 8-Cyclopentyl-5-methyl-2-[4-(2-methoxyethoxy)phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 210**);

(aaaaaaaaa) 8-Cyclopentyl-5-methyl-2-(carbozol-3-yl)amino-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 211**);

(bbbbbbbbb) 8-Cyclopentyl-5-methyl-2-(isoindazol-5-yl)amino-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 212**);

(ccccccccc) 8-Cyclopentyl-5-methyl-2-(2-acetylbenzofuran-5-yl)amino-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 213**);

(ddddddddd) 8-Cyclopentyl-5-methyl-2-[(4-piperidin-1-yl)phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 214**);

(eeeeeeeee) 8-Cyclopentyl-5-methyl-2-(2,3-dimethylindol-5-yl)amino-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 215**);

(fffffffff) 8-Cyclopentyl-5-methyl-2-[4-(3,5-methyl-4R-aminomethylpyrrolidin-1-yl)phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 216**);

(ggggggggg) 8-Cyclopentyl-5-methyl-2-{4-[4-(2-hydroxyethyl)piperazin-1-yl)]phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 217**);

(hhhhhhhhh) 8-Cyclopentyl-5-methyl-2-{4-[4-(3-morpholinopropyl)piperidin-1-yl]phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 218**);

(iiiiiiiii) 8-Cyclopentyl-5-methyl-2-(benzofuran-5-yl)amino-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 219**);

(jjjjjjjjj) 8-Cyclopentyl-5-methyl-2-(indol-5-yl)amino-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 220**); and

(kkkkkkkkk) 8-Cyclopentyl-5-methyl-2-(thionaphthen-5-yl)amino-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 221**).

8. A compound selected from the group consisting of:

8-Cyclopentyl-6-iodo-5-methyl-2-(4-piperazin-1-yl-phenylamino)-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (**Compound 225**);

8-Cyclopentyl-2-{4-[1-(3,5-dimethyl-piperazin-1-yl)-methanoyl]-phenylamino}-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (Compound 226);

8-Cyclopentyl-2-[4-(3,5-dimethyl-piperazin-1-yl)-phenylamino]-5-trifluoromethyl-8H-pyrido[2,3-d]pyrimidin-7-one (Compound 227);

6-Bromo-8-cyclopentyl-2-[4-(3,3-dimethyl-piperazin-1-yl)-phenylamino]-5-methyl-8H-pyrido[2,3-*d*]pyrimidin-7-one (**Compound 228**);

8-Cyclopentyl-2-[4-(3,5-dimethyl-piperazin-1-yl)-phenylamino]-6-iodo-5-methyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (**Compound 229**);

6-Chloro-8-cyclopentyl-2-[4-(3,5-dimethyl-piperazin-1-yl)-phenylamino]-5-methyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (**Compound 230**);

8-Cyclopentyl-5-methyl-2-[4-(1H-[1,2,4]triazol-3-ylsulfanyl)-phenylamino]-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (**Compound 231**);

4-[4-(8-Cyclopentyl-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-*d*]pyrimidin-2-ylamino)-phenyl]-piperazine-1-carbaldehyde (**Compound 232**);

8-Cyclopentyl-2-(4-piperazin-1-yl-phenylamino)-5-trifluoromethyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (**Compound 233**);

8-(1-Ethyl-propyl)-5-methyl-2-(4-piperazin-1-yl-phenylamino)-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (**Compound 234**);

[4-(8-Cyclopentyl-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-*d*]pyrimidin-2-ylamino)-benzyl]-phosphonic acid (**Compound 235**);

6-Chloro-8-cyclopentyl-5-methyl-2-(4-piperazin-1-yl-phenylamino)-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (**Compound 236**);

2-[4-(3,5-Dimethyl-piperazin-1-yl)-phenylamino]-8-(1-ethyl-propyl)-5-methyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (**Compound 237**);

8-Cyclopentyl-2-[4-(2-hydroxy-ethylamino)-phenylamino]-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 238**);

3-[4-(8-Cyclopentyl-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino)-phenyl]-N,N-diethyl-propionamide (**Compound 239**);

8-Cyclopentyl-6-fluoro-2-[4-(2-hydroxy-ethyl)-phenylamino]-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 240**);

8-Cyclopentyl-2-[4-(2-hydroxy-ethyl)-phenylamino]-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 241**);

4-(8-Cyclopentyl-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino)-benzoic acid (**Compound 242**);

8-Cyclopentyl-2-[4-(3,3-dimethyl-piperazin-1-yl)-phenylamino]-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 243**);

[4-(8-Cyclopentyl-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino)-benzyl]-phosphonic acid diethyl ester (**Compound 244**);

8-Cyclopentyl-6-fluoro-2-[4-(2-methoxy-ethylamino)-phenylamino]-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 245**);

(S)-2-Amino-3-[4-(8-cyclopentyl-6-fluoro-5-methyl-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino)-phenyl]-propionic acid (**Compound 246**);

8-Cyclopentyl-2-[4-(2-methoxy-ethoxy)-phenylamino]-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 247**);

8-Cyclopentyl-2-(4-isopropylamino-phenylamino)-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 248**);

8-Cyclopentyl-2-(4-hydroxy-3,5-dimethyl-phenylamino)-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 249**);

8-Cyclopentyl-6-fluoro-2-(4-hydroxy-3,5-dimethyl-phenylamino)-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 250**);

8-Cyclopentyl-6-fluoro-2-(4-hydroxy-3,5-dimethyl-phenylamino)-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 251**).

9. A pharmaceutical composition comprising a compound selected from Claim 1 in combination with a pharmaceutically acceptable carrier, diluent, or excipient.

10. Use of a therapeutically effective amount of a compound according to Claim 1, in the manufacture of a medicament for the treatment of proliferative disorders selected from the group consisting of cancer, psoriasis, vascular smooth muscle proliferation associated with a disorder selected from the group consisting of atherosclerosis, postsurgical vascular stenosis, and restenosis in mammals.

11. Use of a compound selected from Claim 1, in the manufacture of a medicament for inhibiting a cyclin-dependent kinase.

12. Use of a compound of Claim 11 wherein said cyclin-dependent kinase is cdk4.

13. Use of a compound selected from Claim 1, in the manufacture of a medicament for inhibiting a growth factor-mediated tyrosine kinase.

14. Use of a compound of Claim 13 wherein said growth factor-mediated tyrosine kinase is platelet derived growth factor (PDGF).

15. Use of a compound of Claim 13 wherein said growth factor-mediated tyrosine kinase according to Claim 13 is fibroblast growth factor (FGF).

16. Use of a therapeutically effective amount of a compound selected from Claim 1, in the manufacture of a medicament for the treatment of a subject suffering from diseases caused by vascular smooth muscle cell proliferation.

17. Use of a therapeutically effective amount of a compound selected from Claim 1 in the manufacture of a medicament for the treatment of a subject suffering from cancer.

18. 6-Bromo-8-cyclopentyl-2-[4-(3,5-dimethylpipeerazin-1-yl)-phenylamino]-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one.

19. 8-Cyclopentyl-6-fluoro-5-methyl-2-[4-(piperazin-1-yl)phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one.

20. 8-Cyclopentyl-5-methyl-2-(carbazol-3-yl)-8H-pyrido[2,3-d]pyrimidin-7-one.

21. A compound selected from

8-Cyclopentyl-5-methyl-2-(carbozol-3-yl)amino-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 211**);

8-Cyclopentyl-5-methyl-2-(isoindazol-5-yl)amino-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 212**);

8-Cyclopentyl-5-methyl-2-(2-acetylbenzofuran-5-yl)amino-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 213**);

8-Cyclopentyl-5-methyl-2-[(4-piperidin-1-yl)phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 214**);

8-Cyclopentyl-5-methyl-2-(2,3-dimethylindol-5-yl)amino-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 215**);

8-Cyclopentyl-5-methyl-2-[4-(3,5-methyl-4R-aminomethylpyrrolidin-1-yl)phenylamino]-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 216**);

8-Cyclopentyl-5-methyl-2-{4-[4-(2-hydroxyethyl)piperazin-1-yl)]phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 217**);

8-Cyclopentyl-5-methyl-2-{4-[4-(3-morpholinopropyl)piperidin-1-yl]phenylamino}-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 217**);

8-Cyclopentyl-5-methyl-2-(benzofuran-5-yl)amino-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 219**);

8-Cyclopentyl-5-methyl-2-(indol-5-yl)amino-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 220**); and

8-Cyclopentyl-5-methyl-2-(thionaphthen-5-yl)amino-8H-pyrido[2,3-d]pyrimidin-7-one (**Compound 221**).

22. Use of an effective amount of a compound in Claim 1 in the manufacture of a medicament for the diagnosis and/or treatment of cancer, psoriasis, vascular smooth muscle cell proliferation associated with atherosclerosis and postsurgical vascular stenosis and restenosis in a mammal.

23. Use of an effective amount of a compound of Claim 1 in the manufacture of a medicament for treating a mammal suffering from a disease caused by a DNA tumor virus.