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Pyridino `2, 3-D! pyrimidine derivatives as selective KDR and FGFR inhibitors

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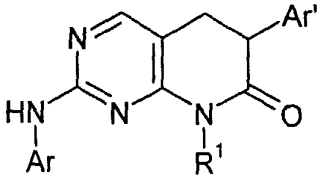
(54) Title: PYRIDINO '2, 3-D! PYRIMIDINE DERIVATIVES AS SELECTIVE KDR AND FGFR INHIBITORS



(I)

(57) Abstract: Disclosed are novel dihydropridinone compounds of the formula (I) wherein Ar, Ar' and R^1 are as defined in the description, that are selective inhibitors of both KDR and FGFR kinases. These compounds and their pharmaceutically acceptable salts are anti-proliferative agents useful in the treatment or control of solid tumors, in particular breast, colon lung and prostate tumors. Also, disclosed are pharmaceutical compositions containing these compounds and their preparation.

5,8-Dihydro-6H-pyrido[2,3-d]pyrimidin-7-ones

PRIORITY TO PROVISIONAL APPLICATION(S) UNDER 35 U.S.C. §119(e)

This application claims priority under 35 U.S.C. §119(e) of provisional applications(s) Ser. No. 60/434,969, filed on Dec. 20, 2002 and Ser. No. 60/513,615, filed on Oct. 23, 2003.

FIELD OF THE INVENTION

The present invention is directed to novel dihydropyridinone compounds that inhibit KDR (kinase insert domain-containing receptor) and FGFR (fibroblast growth factor receptor) kinases. These compounds and their pharmaceutically acceptable salts have antiproliferative activity and are useful in the treatment or control of cancer, in particular solid tumors. In addition these compounds have advantageous bioavailability profiles. This invention is also directed to pharmaceutical compositions containing such compounds and to methods of treating or controlling cancer, most particularly the treatment or control of breast, lung, colon and prostate tumors.

BACKGROUND OF THE INVENTION

Protein kinases are a class of proteins (enzymes) that regulate a variety of cellular functions. This is accomplished by the phosphorylation of specific amino acids on protein substrates resulting in conformational alteration of the substrate protein. The conformational change modulates the activity of the substrate or its ability to interact with other binding partners. The enzyme activity of the protein kinase refers to the rate at which the kinase adds phosphate groups to a substrate. It can be measured, for example, by determining the amount of a substrate that is converted to a product as a function of time.

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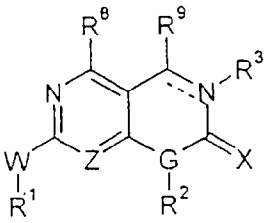
Phosphorylation of a substrate occurs at the active-site of a protein kinase.

Tyrosine kinases are a subset of protein kinases that catalyze the transfer of the terminal phosphate of adenosine triphosphate (ATP) to tyrosine residues on protein substrates. These kinases play an important part in the propagation of growth factor signal transduction that leads to cellular proliferation, differentiation and migration.

For example, fibroblast growth factor (FGF) and vascular endothelial growth factor (VEGF) have been recognized as important mediators of tumor promoted angiogenesis. VEGF activates endothelial cells by signaling through two high affinity receptors, one of which is the kinase insert domain-containing receptor (KDR). See, Hennequin L. F. et. al., J. Med. Chem. 2002, 45(6), pp 1300. FGF activates endothelial cells by signaling through the FGF receptor (FGFR). Solid tumors depend upon the formation of new blood vessels (angiogenesis) to grow. Accordingly, inhibitors of the receptors FGFR and KDR that interfere with the growth signal transduction, and thus slow down or prevent

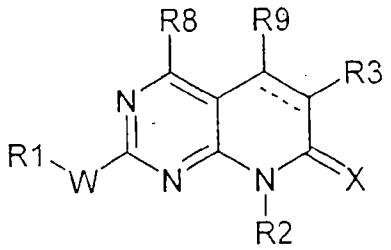
angiogenesis, are useful agents in the prevention and treatment of solid tumors. See, Klohs W.E. et. al., Current Opinion in Biotechnology 1999, 10, p.544.

There are several examples of small molecule inhibitors of protein kinase catalytic activity. In particular, small molecule inhibitors typically block the phosphorylation of substrates by tightly interacting with the protein kinase ATP binding site (or "active site"). See, WO 98/24432 and Hennequin L. F. et. al., J. Med. Chem. 2002, 45(6), pp1300. Several of these compounds inhibit multiple targets. For example, WO 99/61444 (Warner-Lambert) discloses bicyclic pyrimidines and bicyclic 3,4-dihydropyrimidines of formula

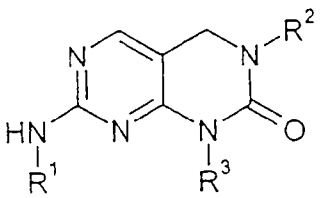


that are asserted to inhibit cyclin dependent kinases Cdk1, Cdk2 and Cdk4 as well as the growth factor receptor tyrosine kinase enzymes PDGFR and FGFR. Some compounds are also asserted to inhibit Cdk6.

WO 01/55148A1 discloses a method for treating neurodegenerative diseases in mammals comprising administering an effective amount of a cyclin-dependent kinase inhibitors, preferably using Cdk inhibitors of formula

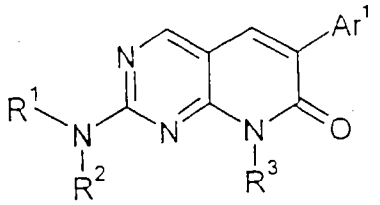


U.S. Patent No. 6,150,373 discloses bicyclic nitrogen heterocycles of formula



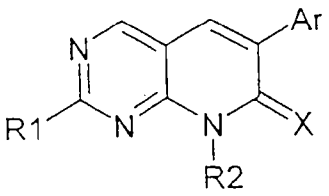
that are stated to inhibit the T-cell tyrosine kinase $p56^{lck}$.

WO 02/18380 A1 discloses 7-oxo pyridopyrimidines of formula



that are stated to inhibit p38 mediated cellular functions and are thus inhibitors of cellular proliferation.

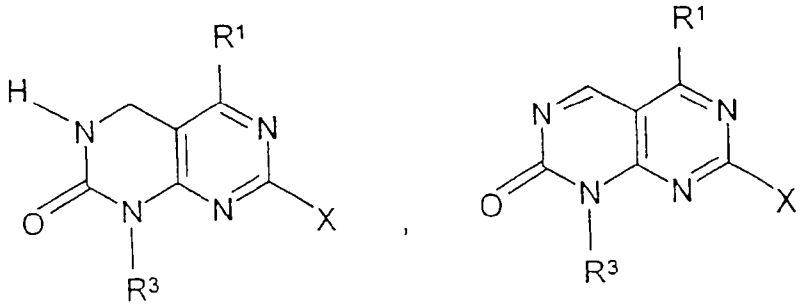
WO 96/34867 discloses 6-aryl pyrido [2,3-d] pyrimidine 7-imines, 7-ones, and 7-thiones of formula



are inhibitors of protein kinases, and useful in treating cellular proliferation mediated diseases.

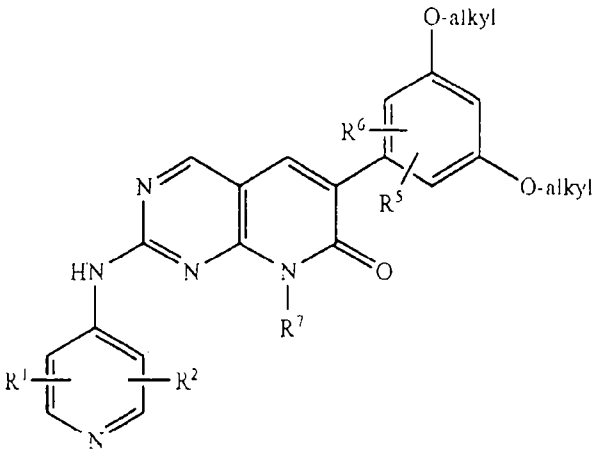
WO 98/33798 discloses pyrido [2,3-d] pyrimidines and 4-aminopyrimidines as inhibitors of cellular proliferation. Specifically, this publication discloses a group of 7,8-dihydro-2-(amino and thio)pyrido[2,3-d]pyrimidines and 2,4-diaminopyrimidines that are potent inhibitors of cyclin-dependent kinases (Cdks) and growth mediated kinases.

WO 01/64679 A1 discloses 1,5-disubstituted-3,4-dihydro-1H-pyrimido[4,5-D]pyrimidin-2-one compounds of formula



that are stated to be useful in treating CSBP/P38 kinase mediated diseases.

WO 02/12237 A2 discloses a process for preparing 2-(4-pyridyl)amino-6-dialkoxyphenyl-pyrido[2,3-d]pyrimidin-7-ones, and WO 02/12238 A2 discloses 2-(4-pyridyl)amino-6-dialkoxyphenyl-pyrido[2,3-d]pyrimidin-7-ones of formula (I).



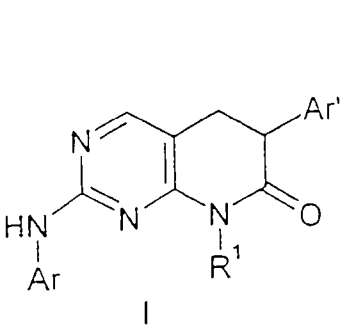
(I)

These compounds are asserted to be useful in treating diseases resulting from uncontrolled cell growth.

There continues to be a need for easily synthesized, small-molecule compounds effective in inhibiting the catalytic activity of protein kinases, in particular FGFR and KDR kinases for treating one or more types of solid tumors. It is particularly desirable to provide small molecule inhibitors that are selective for FGFR and KDR. This is desirable because the potential concomitant inhibition of targets involved in angiogenesis could provide better efficacy. On the other hand, toxicity and other undesirable complications may follow from inhibiting multiple targets. It is preferable that such small molecule inhibitors also possess advantageous bioavailability profiles. It is therefore desirable to provide such compounds and pharmaceutical compositions containing these compounds.

SUMMARY OF THE INVENTION

The present invention relates to novel dihydropyridinone compounds capable of selectively inhibiting the activity of KDR and FGFR. These compounds are useful for the treatment or control of cancer, in particular the treatment or control of solid tumors. In particular this invention relates to compounds of formulas I and II:



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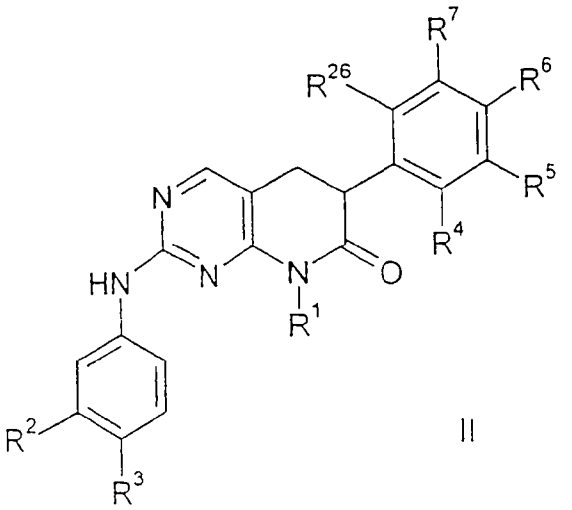


II

with the proviso that Ar is not 2-pyridyl or substituted 2-pyridyl.

The present invention also relates to pharmaceutical compositions comprising a therapeutically effective amount of one or more compounds of formulas I and II, and a pharmaceutically acceptable carrier or excipient.

The present invention further relates to a method for treating solid tumors, in particular breast, lung, prostate or colon tumors, by administering to a human patient in need of such therapy an effective amount of a compound of formulas I or II, and/or a pharmaceutically acceptable salt thereof.

The present invention is further directed to novel intermediate compounds useful in the preparation of compounds of formulas I and II.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

As used herein, the following terms shall have the following definitions.

"Alkenyl" denotes a straight-chain or branched aliphatic hydrocarbon having at least one set of carbon-carbon double bond, for example vinyl, 2-butenyl, and 3-methyl-2-butenyl.

"Alkynyl" denotes a straight-chain or branched aliphatic hydrocarbon having at least one set of carbon-carbon triple bond, for example ethynyl, and 2-butynyl.

"Alkyl" denotes a straight-chain or branched saturated aliphatic hydrocarbon having 1 to 10, preferably 1 to 6, and more preferably 1 to 4 carbon atoms. Alkyl groups having 1 to 6 carbon atoms are also referred to herein as "lower alkyl." Typical lower alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, t-butyl, 2-butyl, pentyl and hexyl. As used herein the sample designation C_{1-4} alkyl means alkyl having from 1 to 4 carbon atoms.

"Alkoxy" means an alkyl radical that is attached to the remainder of the molecule by oxygen (RO-), e.g. methoxy, ethoxy.

"Aryl" means an aromatic carbocyclic radical, for example a 6-10 membered aromatic or partially aromatic ring system. A partially aromatic ring system is one with two fused rings with one of the two rings being aromatic, for example tetrahydro-naphthyl. Preferred aryl groups include, but are not limited to, phenyl, naphthyl, tolyl and xylyl.

"Cycloalkyl" means a non-aromatic, partially or completely saturated cyclic aliphatic hydrocarbon group containing 3 to 8 atoms. Examples of cycloalkyl groups include cyclopropyl, cyclopentyl and cyclohexyl.

"Effective amount" or "therapeutically effective amount" means an amount of at least one compound for formulas I and II, or a pharmaceutically acceptable salt or ester thereof, that significantly inhibits proliferation of tumor cells, including human tumor cell lines.

"Halogen" means fluorine, chlorine, bromine or iodine, preferably chlorine or fluorine.

"Hetero atom" means an atom selected from N, O and S, preferably N. If the hetero atom is N, it can be present as -NH- or -N-lower alkyl-. If the hetero atom is S, it can be present as S, SO or SO_2.

"Heteroaryl" means an aromatic heterocyclic ring system containing up to two rings. Preferred heteroaryl groups include, but are not limited to, thienyl, furyl, indolyl, pyrrolyl, pyridinyl, pyrazinyl, oxazolyl, thiaxolyl, quinolinyl, pyrimidinyl, imidazole and tetrazolyl.

"Heterocycle" or "heterocyclyl" means a 3- to 10-membered saturated or partially unsaturated non-aromatic monovalent cyclic radical having from one to 3 hetero atoms selected from nitrogen, oxygen or sulfur or a combination thereof. Examples of preferred heterocycles are piperidine, piperazine, pyrrolidine, and morpholine.

"Hydroxy" is a prefix indicating the presence of a monovalent OH group.

"IC_{50}" refers to the concentration of a particular compound according to the invention required to inhibit 50% of a specific measured activity. IC_{50} can be measured, inter alia, as is described in Example 15, infra.

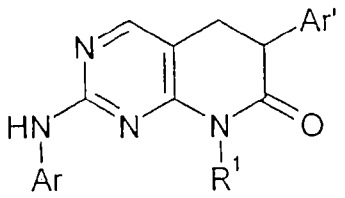
"Pharmaceutically acceptable salt" refers to conventional acid-addition salts or base-addition salts that retain the biological effectiveness and properties of the compounds of formula I and are formed from suitable non-toxic organic or inorganic acids or organic or inorganic bases. Sample acid-addition salts include those derived from inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, sulfamic acid, phosphoric acid and nitric acid, and those derived from organic acids such as p-toluenesulfonic acid, salicylic acid, methanesulfonic acid, oxalic acid, succinic acid, citric acid, malic acid, lactic acid, fumaric acid, and the like. Sample base-addition salts include those derived from ammonium, potassium, sodium and,

quaternary ammonium hydroxides, such as for example, tetramethylammonium hydroxide. The chemical modification of a pharmaceutical compound (i.e. drug) into a salt is a technique well known to pharmaceutical chemists to obtain improved physical and chemical stability, hygroscopicity, flowability and solubility of compounds. See, e.g., H. Ansel et. al., Pharmaceutical Dosage Forms and Drug Delivery Systems (6th Ed. 1995) at pp. 196 and 1456-1457.

"Pharmaceutically acceptable," such as pharmaceutically acceptable carrier, excipient, etc., means pharmacologically acceptable and substantially non-toxic to the subject to which the particular compound is administered.

"Substituted," as in, for example, substituted alkyl, lower alkyl, aryl, cycloalkyl, cycloaryl and heteroaryl, means that the substitution can occur at one or more positions and, unless otherwise indicated, that the substituents at each substitution site are independently selected from the specified options.

In one embodiment, this invention relates to compounds of formula



I

or a pharmaceutical acceptable salt thereof, wherein

Ar and Ar' are independently selected from the group consisting of aryl, substituted aryl, heteroaryl and substituted heteroaryl, with the proviso that for Ar, the heteroaryl is not 2-pyridyl and substituted heteoraryl is not substituted 2-pyridyl;

R^1 is selected from the group consisting of

H;

C_{1-10} alkyl;

C_{1-10} alkyl independently substituted by up to three groups selected from aryl, heteroaryl, heterocycle, cycloalkyl, NR^8R^9, OR^{10}, SR^{10}, halogen, COR^{11}, CO_2R^{11}, $CONR^{11}R^{12}$, $SO_2NR^{11}R^{12}$, SOR^{11}, SO_2R^{11}, CN and NO_2, wherein the aryl, heteroaryl, heterocycle and cycloalkyl groups may each independently be substituted by up to three groups selected from NR^8R^9, OR^{10}, SR^{10}, halogen, COR^{11}, CO_2R^{11}, $CONR^{11}R^{12}$, $SO_2NR^{11}R^{12}$, SOR^{11}, SO_2R^{11}, CN and NO_2;

aryl;

aryl independently substituted by up to three groups selected from lower alkyl, NR^8R^9, OR^{10}, SR^{10}, halogen, COR^{11}, CO_2R^{11}, $CONR^{11}R^{12}$, $SO_2NR^{11}R^{12}$, SOR^{11}, SO_2R^{11}, CN and NO_2;

heteroaryl;

heteroaryl independently substituted by up to three groups selected from lower alkyl, NR^8R^9, OR^{10}, SR^{10}, halogen, COR^{11}, CO_2R^{11}, $CONR^{11}R^{12}$, $SO_2NR^{11}R^{12}$, SOR^{11}, SO_2R^{11}, CN and NO_2;

heterocycle;

heterocycle independently substituted by up to three groups selected from lower alkyl, NR^8R^9, OR^{10}, SR^{10}, halogen, COR^{11}, CO_2R^{11}, $CONR^{11}R^{12}$, $SO_2NR^{11}R^{12}$, SOR^{11}, SO_2R^{11}, CN and NO_2;

C_{3-10} cycloalkyl;

C_{3-10} cycloalkyl independently substituted by up to three groups selected from lower alkyl, substituted lower alkyl, NR^8R^9, OR^{10}, SR^{10}, halogen, COR^{11}, CO_2R^{11}, $CONR^{11}R^{12}$, $SO_2NR^{11}R^{12}$, SOR^{11}, SO_2R^{11}, CN and NO_2;

C_{2-10} alkenyl;

C_{2-10} alkenyl independently substituted by up to three groups selected from cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocycloalkyl, NR^8R^9, OR^{10}, SR^{10}, halogen, COR^{11}, CO_2R^{11}, $CONR^{11}R^{12}$, $SO_2NR^{11}R^{12}$, SOR^{11}, SO_2R^{11}, CN and NO_2;

C_{2-10} alkynyl; and

C_{2-10} alkynyl independently substituted by up to three groups selected from NR^8R^9, OR^{10}, SR^{10}, halogen, COR^{11}, CO_2R^{11}, $CONR^{11}R^{12}$, $SO_2NR^{11}R^{12}$, SOR^{11}, SO_2R^{11}, CN and NO_2; and wherein

R^8, R^9 and R^{10} are independently H or lower alkyl;

R^{11} and R^{12} are independently selected from the group consisting of

H;

unsubstituted lower alkyl; lower alkyl substituted by hydroxy, alkoxy or $NR^{21}R^{22}$;

unsubstituted cycloalkyl; cycloalkyl substituted by hydroxy, alkoxy, lower alkyl or $NR^{21}R^{22}$;

unsubstituted heterocycle; heterocycle substituted by hydroxy, alkoxy, lower alkyl or $NR^{21}R^{22}$;

or alternatively $NR^{11}R^{12}$ forms a ring having 3 to 7 atoms, the ring having no or at least one additional heteroatoms, with the proviso that if the heteroatom is N, the heteroatom may be substituted by one or more substituents selected from the group consisting of lower alkyl, OR^{13}, COR^{14}, CO_2R^{14}, $CONR^{14}R^{15}$, SO_2R^{14}, and $SO_2NR^{14}R^{15}$;

R^{13} is selected from the group consisting of

H;

COR^{14};

$CONR^{14}R^{15}$;

unsubstituted lower alkyl; lower alkyl substituted by hydroxy, alkoxy or $NR^{21}R^{22}$;

unsubstituted cycloalkyl; cycloalkyl substituted by hydroxy, alkoxy, lower alkyl or $NR^{21}R^{22}$;

unsubstituted heterocycle; and heterocycle substituted by hydroxy, alkoxy, lower alkyl or $NR^{21}R^{22}$;

R^{14} and R^{15} are independently selected from the group consisting of

H;

unsubstituted lower alkyl; lower alkyl substituted by hydroxy, alkoxy or $NR^{21}R^{22}$;

unsubstituted cycloalkyl; cycloalkyl substituted by hydroxy, alkoxy, lower alkyl or $NR^{21}R^{22}$;

unsubstituted heterocycle; heterocycle substituted by hydroxy, alkoxy, lower alkyl or $NR^{21}R^{22}$;

or alternatively $NR^{14}R^{15}$ forms a ring having 3 to 7 atoms, the ring having no or at least one hetero atoms, with the proviso that if the heteroatom is N, the heteroatom may be substituted by one or more substituents selected from the group consisting of lower alkyl, OR^{23}, COR^{23}, CO_2R^{23}, $CONR^{23}R^{24}$, SO_2R^{23}, $SO_2NR^{23}R^{24}$;

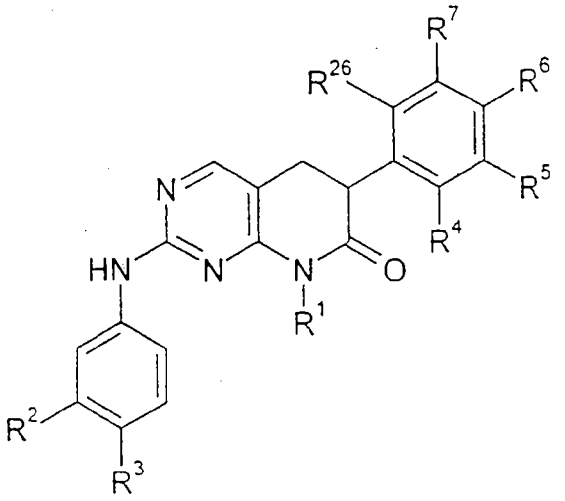
R^{21} is selected from the group consisting of H, lower alkyl, COR^{23} or CO_2R^{23};

R^{22}, R^{23} and R^{24} are independently selected from the group consisting of H or lower alkyl;

or alternatively $NR^{21}R^{22}$ or $NR^{23}R^{24}$ independently forms a ring having 3 to 7 atoms, the ring having no or at least one additional heteroatoms selected from the group consisting of N, O, or S, with the proviso that if the heteroatom is N, the heteroatom may be in the form of -NH or NR^{25}, and if the hetero atom is S, it may be in the form of $S(O)_m$ where m = 0, 1 or 2; and

R^{25} is lower alkyl.

In another embodiment, this invention relates to compounds of formula



II

or a pharmaceutically acceptable salt thereof, where

R^1 is selected from the group consisting of

H;

C_{1-10} alkyl;

C_{1-10} alkyl independently substituted by up to three groups selected from aryl, heteroaryl, heterocycle, cycloalkyl, NR^8R^9, OR^{10}, SR^{10}, halogen, COR^{11}, CO_2R^{11}, $CONR^{11}R^{12}$, $SO_2NR^{11}R^{12}$, SOR^{11}, SO_2R^{11}, CN and NO_2, wherein the aryl, heteroaryl, heterocycle and cycloalkyl groups may each independently be substituted by up to three groups selected from NR^8R^9, OR^{10}, SR^{10}, halogen, COR^{11}, CO_2R^{11}, $CONR^{11}R^{12}$, $SO_2NR^{11}R^{12}$, SOR^{11}, SO_2R^{11}, CN and NO_2;

aryl;

aryl independently substituted by up to three groups selected from lower alkyl, NR^8R^9, OR^{10}, SR^{10}, halogen, COR^{11}, CO_2R^{11}, $CONR^{11}R^{12}$, $SO_2NR^{11}R^{12}$, SOR^{11}, SO_2R^{11}, CN and NO_2;

heteroaryl;

heteroaryl independently substituted by up to three groups selected from lower alkyl, NR^8R^9, OR^{10}, SR^{10}, halogen, COR^{11}, CO_2R^{11}, $CONR^{11}R^{12}$, $SO_2NR^{11}R^{12}$, SOR^{11}, SO_2R^{11}, CN and NO_2;

heterocycle;

heterocycle independently substituted by up to three groups selected from lower alkyl, NR^8R^9, OR^{10}, SR^{10}, halogen, COR^{11}, CO_2R^{11}, $CONR^{11}R^{12}$, $SO_2NR^{11}R^{12}$, SOR^{11}, SO_2R^{11}, CN and NO_2;

C_{3-10} cycloalkyl;

C_{3-10} cycloalkyl independently substituted by up to three groups selected from lower alkyl, substituted lower alkyl, NR^8R^9, OR^{10}, SR^{10}, halogen, COR^{11}, CO_2R^{11}, $CONR^{11}R^{12}$, $SO_2NR^{11}R^{12}$, SOR^{11}, SO_2R^{11}, CN and NO_2;

C_{2-10} alkenyl;

C_{2-10} alkenyl independently substituted by up to three groups selected from cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocycloalkyl, NR^8R^9, OR^{10}, SR^{10}, halogen, COR^{11}, CO_2R^{11}, $CONR^{11}R^{12}$, $SO_2NR^{11}R^{12}$, SOR^{11}, SO_2R^{11}, CN and NO_2;

C_{2-10} alkynyl; and

C_{2-10} alkynyl independently substituted by up to three groups selected from NR^8R^9, OR^{10}, SR^{10}, halogen, COR^{11}, CO_2R^{11}, $CONR^{11}R^{12}$, $SO_2NR^{11}R^{12}$, SOR^{11}, SO_2R^{11}, CN and NO_2; and wherein R^8, R^9 and R^{10} are independently H or lower alkyl;

R^2 and R^3 are independently selected from the group consisting of

$NR^{11}R^{12}$;

OR^{13};

SR^{16};

halogen;

COR^{14};

CO_2R^{14};

$CONR^{14}R^{15}$;

$SO_2NR^{14}R^{15}$;

SO_2R^{14};

CN;

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NO_2;

$(CH_2)_n$heteroaryl;

$(CH_2)_n$heterocycle;

C_1-C_{10} alkyl;

C_3-C_{10} cycloalkyl;

C_2-C_{10} alkenyl;

C_2-C_{10} alkynyl;

where n is 0, 1, 2, or 3 and the aryl, heteroaryl, heterocycle, alkyl, cycloalkyl, alkenyl, and alkynyl groups are unsubstituted or substituted by up to three groups selected from $NR^{11}R^{12}$; OR^{13}; SR^{16}; halogen; COR^{14}; CO_2R^{14}; $CONR^{14}R^{15}$; $SO_2NR^{14}R^{15}$; SO_2R^{14}; CN; and NO_2;

or alternatively, R^2 and R^3 together form a ring having 3 to 7 atoms fused to the phenyl ring that they are attached to, the ring having no or at least one additional heteroatoms, with the proviso that if the heteroatom is N, the heteroatom may be substituted by at least one substituent selected from the group consisting of lower alkyl; lower alkyl substituted by hydroxy, alkoxy or $NR^{11}R^{12}$; $NR^{11}R^{12}$; OR^{13}; SR^{16}; COR^{14}; CO_2R^{14}; $CONR^{14}R^{15}$; $SO_2NR^{14}R^{15}$; SO_2R^{14}; and CN;

R^4, R^5, R^6, R^7 and R^{26} are independently selected from the group, with at least one being H, consisting of

H;

unsubstituted lower alkyl; lower alkyl substituted by hydroxy, alkoxy or halogen;

$NR^{21}R^{22}$;

OR^{23};

SR^{23};

halogen;

NO_2;

COR^{23};

CO_2R^{23};

$CONR^{23}R^{24}$;

$SO_2NR^{23}R^{24}$;

SO_2R^{23}; and

CN;

R^{11} and R^{12} are independently selected from the group consisting of

H;

unsubstituted lower alkyl; lower alkyl substituted by hydroxy, alkoxy or $NR^{21}R^{22}$;

unsubstituted cycloalkyl; cycloalkyl substituted by hydroxy, alkoxy, lower alkyl or $NR^{21}R^{22}$;

unsubstituted heterocycle; and heterocycle substituted by hydroxy, alkoxy, lower alkyl or $NR^{21}R^{22}$;

or alternatively $NR^{11}R^{12}$ forms a ring having 3 to 7 atoms, the ring having no or at least one additional heteroatoms, with the proviso that if the hetero atom is N, the heteroatom may be substituted by one or more substituents selected from the group consisting of lower alkyl, COR^{14}, CO_2R^{14}, $CONR^{14}R^{15}$, SO_2R^{14}, and $SO_2NR^{14}R^{15}$;

R^{13} is selected from the group consisting of

H;

COR^{14};

$CONR^{14}R^{15}$;

unsubstituted lower alkyl; lower alkyl substituted by hydroxy, alkoxy or $NR^{21}R^{22}$;

unsubstituted cycloalkyl; cycloalkyl substituted by hydroxy, alkoxy, lower alkyl or $NR^{21}R^{22}$;

unsubstituted heterocycle; and heterocycle substituted by hydroxy, alkoxy, lower alkyl or $NR^{21}R^{22}$;

R^{14} and R^{15} are independently selected from the group consisting of

H;

unsubstituted lower alkyl; lower alkyl substituted by hydroxy, alkoxy or $NR^{21}R^{22}$;

unsubstituted cycloalkyl; cycloalkyl substituted by hydroxy, alkoxy, lower alkyl or $NR^{21}R^{22}$;

unsubstituted heterocycle; and heterocycle substituted by hydroxy, alkoxy, lower alkyl or $NR^{21}R^{22}$;

or alternatively $NR^{14}R^{15}$ forms a ring having 3 to 7 atoms, the ring having no or at least one additional heteroatoms, with the proviso that if the heteroatom is N, the heteroatom may be substituted by one or more substituents selected from the group consisting of one or more lower alkyl, COR^{23}, CO_2R^{23}, $CONR^{23}R^{24}$, SO_2R^{23}, and $SO_2NR^{23}R^{24}$;

R^{16} is selected from the group consisting of

unsubstituted lower alkyl; lower alkyl substituted by hydroxy, alkoxy or $NR^{21}R^{22}$;

unsubstituted cycloalkyl; cycloalkyl substituted by hydroxy, alkoxy, lower alkyl or $NR^{21}R^{22}$,

unsubstituted heterocycle; and heterocycle substituted by hydroxy, alkoxy, lower alkyl or $NR^{21}R^{22}$;

R^{21} is selected from the group consisting of H, lower alkyl, COR^{23} or CO_2R^{23};

R^{22}, R^{23} and R^{24} are independently selected from the group consisting of H or lower alkyl, or alternatively $NR^{21}R^{22}$ or $NR^{23}R^{24}$ independently forms a ring having 3 to 7 atoms, the ring having no or at least one additional heteroatom selected from the group consisting of N, O, and S, with the proviso that if the heteroatom is N, the heteroatom may be in the form of -NH or NR^{25}, and if the hetero atom is S, it may be in the form of $S(O)_m$ where m = 0, 1 or 2; and

R^{25} is lower alkyl.

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In one embodiment, this invention is directed to a pharmaceutical composition comprising a therapeutically effective amount of the compounds above and a pharmaceutically acceptable carrier or excipient.

In another embodiment, this invention is directed to a method for treating cancer comprising administering to a patient in need of such treatment a therapeutically effective amount of the compounds above. The cancer is breast, lung, colon or prostate.

In yet another embodiment, this invention is directed to a method of controlling cancer comprising administering to a patient in need of such treatment a therapeutically effective amount of the compounds above. The cancer is breast, lung, colon or prostate.

The following compounds are preferred embodiments according to the present invention:

6-(4-Methoxy-phenyl)-8-phenyl-2-phenylamino-5,8-dihydro-6H-pyrido[2,3-d]pyrimidin-7-one (Example 1f);

6-(2,6-Dichloro-phenyl)-8-phenyl-2-phenylamino-5,8-dihydro-6H-pyrido[2,3--d]pyrimidin-7-one (Example 2c);

6-(3,5-Dimethoxy-phenyl)-8-phenyl-2-phenylamino-5,8-dihydro-6H-pyrido[2,3- -d]pyrimidin-7-one (Example 3d);

8-Phenyl-2-phenylamino-6-O-tolyl-5,8-dihydro-6H-pyrido[2,3-d]pyrimidin-7-- one (Example 4c);

6,8-Diphenyl-2-phenylamino-5,8-dihydro-6H-pyrido[2,3-d]pyrimidin-7-one (Example 5c);

6-(2,5-Dimethoxy-phenyl)-8-phenyl-2-phenylamino-5,8-dihydro-6H-pyrido[2,3- -d]pyrimidin-7-one (Example 6c);

6-(2-Methoxy-phenyl)-8-phenyl-2-phenylamino-5,8-dihydro-6H-pyrido[2,3-d]pyrimidin-7-one (Example 7c);

6-(3,5-Bis-trifluromethyl-phenyl)-8-phenyl-2-phenylamino-5,8-dihydro-6H-pyrido[2,3-d]pyrimidin-7-one (example 8d);

8-Phenyl-2-phenylamino-6-pyridin-4-yl-5,8-dihydro-6H-pyrido[2,3-d]pyrimid- in-

7-one (Example 9c);

8-Phenyl-2-phenylamino-6-pyridin-3-yl-5,8-dihydro-6H-pyrido[2,3-d]pyrimid- in-7-one (Example 10c);

6-(3,4-Dimethoxy-phenyl)-8-phenyl-2-phenylamino-5,8-dihydro-6H-pyrido[2,3- - d]pyrimidin-7-one (Example 11c);

6-(4-Methoxy-phenyl)-2-(6-methoxy-pyridin-3-ylamino)-8-phenyl-5,8-dihydro- - 6H-pyrido[2,3-d]pyrimidine-7-one (Example 12d);

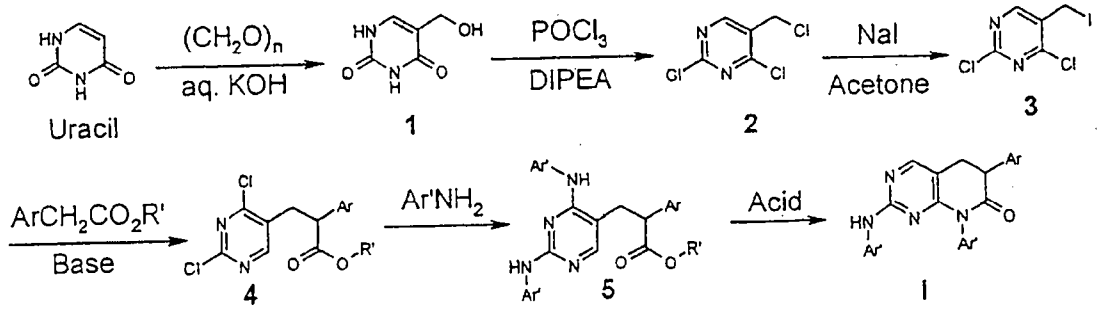
8-Isobutyl-6-(4-methoxy-phenyl)-2-phenylamino-5,8-dihydro-6H-pyrido[2,3-d-]pyrimidine-7-one (Example 13b); and

8 Cyclopropylmethyl-6-(4-methoxy-phenyl)-2-phenylamino-5,8-dihydro-6H-pyrid- o[2,3-d]pyrimidine-7-one (Example 14b).

General Synthesis of Compounds According to the Invention

The compounds of the present invention can be prepared by any conventional means. Suitable processes for synthesizing these compounds are provided in the examples. Generally, compounds of Formula I can be prepared according to the below-described synthetic route.

Scheme 1



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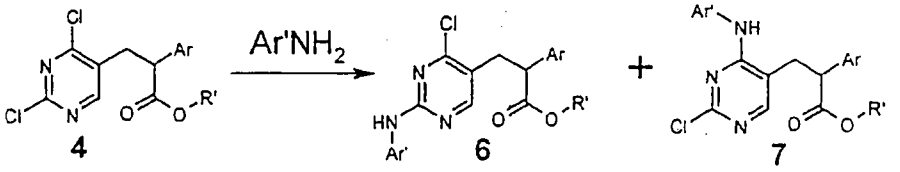
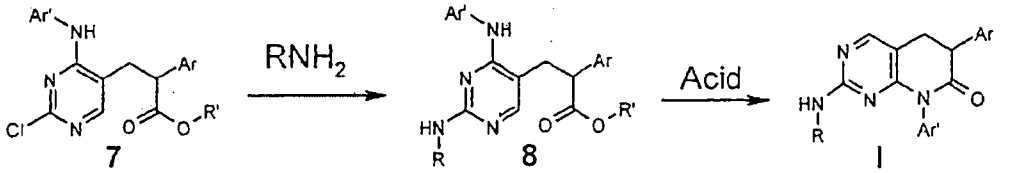
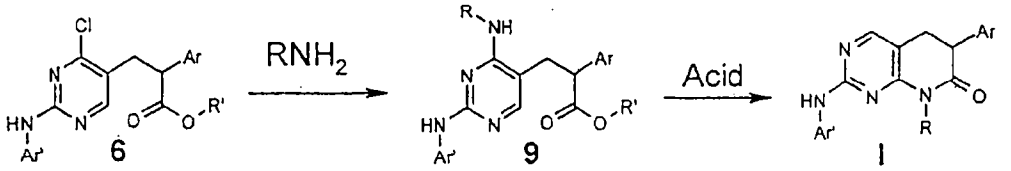
Scheme 2



Scheme 3



Scheme 4



Compositions/Formulations

In an alternative embodiment, the present invention relates to pharmaceutical compositions comprising at least one compound of formula I, or a pharmaceutically acceptable salt or ester thereof.

These pharmaceutical compositions can be administered orally, for example in the form of tablets, coated tablets, dragees, hard or soft gelatin capsules, solutions, emulsions or suspensions. They can also be administered rectally, for example, in the form of suppositories, or parenterally, for example, in the form of injection solutions.

The pharmaceutical compositions of the present invention comprising compounds of formulas I and II, and/or the salts thereof, may be manufactured in a manner that is known

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in the art, e.g., by means of conventional mixing, encapsulating, dissolving, granulating, emulsifying, entrapping, dragee-making, or lyophilizing processes. These pharmaceutical preparations can be formulated with therapeutically inert, inorganic or organic carriers. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts can be used as such carriers for tablets, coated tablets, dragees and hard gelatin capsules. Suitable carriers for soft gelatin capsules include vegetable oils, waxes and fats. Depending on the nature of the active substance, no carriers are generally required in the case of soft gelatin capsules. Suitable carriers for the manufacture of solutions and syrups are water, polyols, saccharose, invert sugar and glucose. Suitable carriers for injection are water, alcohols, polyols, glycerine, vegetable oils, phospholipids and surfactants. Suitable carriers for suppositories are natural or hardened oils, waxes, fats and semi-liquid polyols.

The pharmaceutical preparations can also contain preserving agents, solubilizing agents, stabilizing agents, wetting agents, emulsifying agents, sweetening agents, coloring agents, flavoring agents, salts for varying the osmotic pressure, buffers, coating agents or antioxidants. They can also contain other therapeutically valuable substances, including additional active ingredients other than those of formulas I and II.

Dosages

As mentioned above, the compounds of the present invention, including the compounds of formula I, are useful in the treatment or control of cell proliferative disorders, in particular oncological disorders. These compounds and formulations containing said compounds are particularly useful in the treatment or control of solid tumors, such as, for example, breast, colon, lung and prostate tumors. Thus, the present invention is further directed to a method for treating such solid tumors by administering to a patient in need of such therapy an effective amount of a compound of formulas I and II, and/or their salt.

A therapeutically effective amount of a compound in accordance with this invention means an amount of compound that is effective to prevent, alleviate or ameliorate symptoms of disease or prolong the survival of the subject being treated. Determination of a

therapeutically effective amount is within the skill in the art.

The therapeutically effective amount or dosage of a compound according to this invention can vary within wide limits and may be determined in a manner known in the art. Such dosage will be adjusted to the individual requirements in each particular case including the specific compound(s) being administered, the route of administration, the condition being treated, as well as the patient being treated. In general, in the case of oral or parenteral administration to adult humans weighing approximately 70 Kg, a daily dosage of about 10 mg to about 10,000 mg, preferably from about 200 mg to about 1,000 mg, should be appropriate, although the upper limit may be exceeded when indicated. The daily dosage can be administered as a single dose or in divided doses, or for parenteral administration, it may be given as continuous infusion.

The present invention is also directed to the following novel intermediates useful in the synthesis of compounds of formulas I and II:

3-(2,4-Dichloro-pyrimidin-5-yl)-2-(4-methoxy-phenyl)-propionic acid methyl ester (Example 1d);

3-(2,4-Diphenylamino-pyrimidin-5-yl)-2-(4-methoxy-phenyl)-propionic acid methyl ester (Example 1e);

2-(2,6-Dichloro-phenyl)-3-(2,4-dichloro-pyrimidin-5-yl)-propionic acid methyl ester (Example 2a);

3-(2,4-Diphenylamino-pyrimidin-5-yl)-2-(2,6-Dichloro-phenyl)-propionic acid methyl ester (Example 2b);

3-(2,4-Dichloro-pyrimidin-5-yl)-2-(3,5-dimethoxy-phenyl)-propionic acid methyl ester (Example 3b);

3-(2,4-Diphenylamino-pyrimidin-5-yl)-2-(3,5-dimethoxy-phenyl)-propionic acid methyl ester (Example 3c);

3-(2,4-Dichloro-pyrimidin-5-yl)-2-O-tolyl-propionic acid methyl ester (Example 4a);

3-(2,4-Diphenylamino-pyrimidin-5-yl)-2-O-tolyl-propionic acid methyl ester (Example 4b)

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3-(2,4-Dichloro-pyrimidin-5-yl)-2-phenyl-propionic acid methyl ester (Example 5a);

3-(2,4-Diphenylamino-pyrimidin-5-yl)-2-phenyl-propionic acid methyl ester (Example 5b);

3-(2,4-Dichloro-pyrimidin-5-yl)-2-(2,5-dimethoxy-phenyl)-propionic acid ethyl ester (Example 6a);

3-(2,4-Diphenylamino-pyrimidin-5-yl)-2-(2,5-dimethoxy-phenyl propionic acid ethyl ester (Example 6b);

3-(2,4-Dichloro-pyrimidin-5-yl)-2-(2-methoxy-phenyl)-propionic acid methyl ester (Example 7a);

3-(2,4-Diphenylamino-pyrimidin-5-yl)-2-(2-methoxy-phenyl) propionic acid ethyl ester (Example 7b);

2-(3,5-Bis-trifluoromethyl-phenyl)-3-(2,4-dichloro-pyrimidin-5-yl)-propio- nic acid methyl ester (Example 8b);

3-(2,4-Diphenylamino-pyrimidin-5-yl)-2-(3,5-bis-trifluoromethyl-phenyl)-p- ropionic acid methyl ester (Example 8c);

3-(2,4-Dichloro-pyrimidin-5-yl)-2-pyridin-4-yl-propionic acid ethyl ester (Example 9a);

3-(2,4-Diphenylamino-pyrimidin-5-yl)-2-pyridin-4-yl-propionic acid ethyl ester (Example 9b);

3-(2,4-Dichloro-pyrimidin-5-yl)-2-pyridin-3-yl-propionic acid ethyl ester (Example 10a);

3-(2,4-Diphenylamino-pyrimidin-5-yl)-2-pyridin-3-yl-propionic acid ethyl ester (Example 10b);

3-(2,4-Dichloro-pyrimidin-5-yl)-2-(3,4-dimethoxy-phenyl)-propionic acid ethyl ester (Example 11a);

3-(2,4-Diphenylamino-pyrimidin-5-yl)-2-(3,4-dimethoxy-phenyl)-propionic acid ethyl ester (Example 11b);

3-(4 Chloro-2-phenylamino-pyrimidin-5-yl)-2-(4-methoxy-phenyl)-propionic acid methyl ester (Example 12a);

3-(2 Chloro-4-phenylamino-pyrimidin-5-yl)-2-(4-methoxy-phenyl)-propionic acid

methyl ester;

(Example 12b); 3-[2-(6-Methoxy-pyridin-3-ylamino)-4-phenylamino-pyrimidin-5-yl]-2-(4-met- hoxy-phenyl)-propionic acid methyl ester (Example 12c);

3-(2-Phenylamino-4-isobutylamino-pyrimidin-5-yl)-2-(4-methoxy-phenyl)-propionic acid methyl ester (Example 13a); and

3-(2-Phenylamino-4-cyclopropylmethylamino-pyrimidin-5-yl)-2-(4-methoxy-phenyl)-propionic acid methyl ester (Example 14a).

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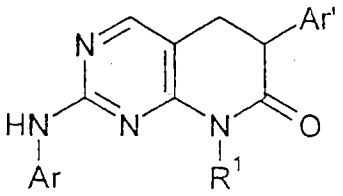
THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A compound of formula



I

or a pharmaceutical acceptable salt thereof, wherein

Ar and Ar' are independently selected from the group consisting of aryl, substituted aryl, heteroaryl and substituted heteroaryl, with the proviso that for Ar, the heteroaryl is not 2-pyridyl and substituted heteoraryl is not substituted 2-pyridyl;

R^1 is selected from the group consisting of

H;

C_{1-10} alkyl;

C_{1-10} alkyl independently substituted by up to three groups selected from aryl, heteroaryl, heterocycle, cycloalkyl, NR^8R^9, OR^{10}, SR^{10}, halogen, COR^{11}, CO_2R^{11}, $CONR^{11}R^{12}$, $SO_2NR^{11}R^{12}$, SOR^{11}, SO_2R^{11}, CN and NO_2, wherein the aryl, heteroaryl, heterocycle and cycloalkyl groups may each independently be substituted by up to three groups selected from NR^8R^9, OR^{10}, SR^{10}, halogen, COR^{11}, CO_2R^{11}, $CONR^{11}R^{12}$, $SO_2NR^{11}R^{12}$, SOR^{11}, SO_2R^{11}, CN and NO_2;

aryl;

aryl independently substituted by up to three groups selected from lower alkyl, NR^8R^9, OR^{10}, SR^{10}, halogen, COR^{11}, CO_2R^{11}, $CONR^{11}R^{12}$, $SO_2NR^{11}R^{12}$, SOR^{11}, SO_2R^{11}, CN and NO_2;

heteroaryl;

heteroaryl independently substituted by up to three groups selected from lower alkyl, NR^8R^9, OR^{10}, SR^{10}, halogen, COR^{11}, CO_2R^{11}, $CONR^{11}R^{12}$, $SO_2NR^{11}R^{12}$, SOR^{11}, SO_2R^{11}, CN and NO_2;

heterocycle;

heterocycle independently substituted by up to three groups selected from lower alkyl, NR^8R^9, OR^{10}, SR^{10}, halogen, COR^{11}, CO_2R^{11}, $CONR^{11}R^{12}$, $SO_2NR^{11}R^{12}$, SOR^{11}, SO_2R^{11}, CN and NO_2;

C_{3-10} cycloalkyl;

C_{3-10} cycloalkyl independently substituted by up to three groups selected from lower alkyl, substituted lower alkyl, NR^8R^9, OR^{10}, SR^{10}, halogen, COR^{11}, CO_2R^{11}, $CONR^{11}R^{12}$, $SO_2NR^{11}R^{12}$, SOR^{11}, SO_2R^{11}, CN and NO_2;

C_{2-10} alkenyl;

C_{2-10} alkenyl independently substituted by up to three groups selected from cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocycloalkyl, NR^8R^9, OR^{10}, SR^{10}, halogen, COR^{11}, CO_2R^{11}, $CONR^{11}R^{12}$, $SO_2NR^{11}R^{12}$, SOR^{11}, SO_2R^{11}, CN and NO_2;

C_{2-10} alkynyl; and

C_{2-10} alkynyl independently substituted by up to three groups selected from NR^8R^9, OR^{10}, SR^{10}, halogen, COR^{11}, CO_2R^{11}, $CONR^{11}R^{12}$, $SO_2NR^{11}R^{12}$, SOR^{11}, SO_2R^{11}, CN and NO_2; and wherein

R^8, R^9 and R^{10} are independently H or lower alkyl;

R^{11} and R^{12} are independently selected from the group consisting of

H;

unsubstituted lower alkyl; lower alkyl substituted by hydroxy, alkoxy or $NR^{21}R^{22}$;

unsubstituted cycloalkyl; cycloalkyl substituted by hydroxy, alkoxy, lower alkyl or $NR^{21}R^{22}$;

unsubstituted heterocycle; heterocycle substituted by hydroxy, alkoxy, lower alkyl or $NR^{21}R^{22}$;

or alternatively $NR^{11}R^{12}$ forms a ring having 3 to 7 atoms, the ring having no or at least one additional heteroatoms, with the proviso that if the heteroatom is N, the heteroatom may be substituted by one or more substituents selected from the group consisting of lower alkyl, OR^{13}, COR^{14}, CO_2R^{14}, $CONR^{14}R^{15}$, SO_2R^{14}, and $SO_2NR^{14}R^{15}$;

R^{13} is selected from the group consisting of

H;

COR^{14};

$CONR^{14}R^{15}$;

unsubstituted lower alkyl; lower alkyl substituted by hydroxy, alkoxy or $NR^{21}R^{22}$;

unsubstituted cycloalkyl; cycloalkyl substituted by hydroxy, alkoxy, lower alkyl or $NR^{21}R^{22}$;

unsubstituted heterocycle; and heterocycle substituted by hydroxy, alkoxy, lower alkyl or $NR^{21}R^{22}$;

R^{14} and R^{15} are independently selected from the group consisting of

H;

unsubstituted lower alkyl; lower alkyl substituted by hydroxy, alkoxy or $NR^{21}R^{22}$;

unsubstituted cycloalkyl; cycloalkyl substituted by hydroxy, alkoxy, lower alkyl or $NR^{21}R^{22}$;

unsubstituted heterocycle; heterocycle substituted by hydroxy, alkoxy, lower alkyl or $NR^{21}R^{22}$;

or alternatively $NR^{14}R^{15}$ forms a ring having 3 to 7 atoms, the ring having no or at least one hetero atoms, with the proviso that if the heteroatom is N, the heteroatom may be substituted by one or more substituents selected from the group consisting of lower alkyl, OR^{23}, COR^{23}, CO_2R^{23}, $CONR^{23}R^{24}$, SO_2R^{23}, $SO_2NR^{23}R^{24}$;

R^{21} is selected from the group consisting of H, lower alkyl, COR^{23} or CO_2R^{23};

R^{22}, R^{23} and R^{24} are independently selected from the group consisting of H or lower alkyl;

or alternatively $NR^{21}R^{22}$ or $NR^{23}R^{24}$ independently forms a ring having 3 to 7 atoms, the ring having no or at least one additional heteroatoms selected from the group consisting of N, O, or S, with the proviso that if the heteroatom is N, the heteroatom may be in the form of -NH or NR^{25}, and if the hetero atom is S, it may be in the form of $S(O)_m$ where m = 0, 1 or 2; and

R^{25} is lower alkyl.

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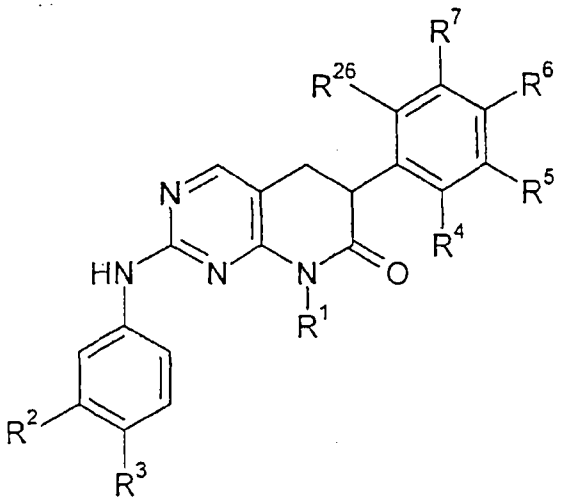
2. The compound of claim 1 wherein Ar is a substituted heteroaryl, with the proviso that the substituted heteroaryl is not 2-pyridyl.

3. The compound of claim 1 wherein Ar' is aryl, substituted aryl or heteroaryl.

4. The compound of claim 1 wherein R^1 is aryl, substituted aryl or heteroaryl.

5. A compound of formula



II

or a pharmaceutically acceptable salt thereof, where

R^1 is selected from the group consisting of

H;

C_{1-10} alkyl;

C_{1-10} alkyl independently substituted by up to three groups selected from aryl, heteroaryl, heterocycle, cycloalkyl, NR^8R^9, OR^{10}, SR^{10}, halogen, COR^{11}, CO_2R^{11}, $CONR^{11}R^{12}$, $SO_2NR^{11}R^{12}$, SOR^{11}, SO_2R^{11}, CN and NO_2, wherein the aryl, heteroaryl, heterocycle and cycloalkyl groups may each independently be substituted by up to three groups selected from NR^8R^9, OR^{10}, SR^{10}, halogen, COR^{11}, CO_2R^{11}, $CONR^{11}R^{12}$, $SO_2NR^{11}R^{12}$, SOR^{11}, SO_2R^{11}, CN and NO_2;

aryl;

aryl independently substituted by up to three groups selected from lower alkyl, NR^8R^9, OR^{10}, SR^{10}, halogen, COR^{11}, CO_2R^{11}, $CONR^{11}R^{12}$, $SO_2NR^{11}R^{12}$, SOR^{11}, SO_2R^{11}, CN and NO_2;

heteroaryl;

heteroaryl independently substituted by up to three groups selected from lower alkyl, NR^8R^9, OR^{10}, SR^{10}, halogen, COR^{11}, CO_2R^{11}, $CONR^{11}R^{12}$, $SO_2NR^{11}R^{12}$, SOR^{11}, SO_2R^{11}, CN and NO_2;

heterocycle;

heterocycle independently substituted by up to three groups selected from lower alkyl, NR^8R^9, OR^{10}, SR^{10}, halogen, COR^{11}, CO_2R^{11}, $CONR^{11}R^{12}$, $SO_2NR^{11}R^{12}$, SOR^{11}, SO_2R^{11}, CN and NO_2;

C_{3-10} cycloalkyl;

C_{3-10} cycloalkyl independently substituted by up to three groups selected from lower alkyl, substituted lower alkyl, NR^8R^9, OR^{10}, SR^{10}, halogen, COR^{11}, CO_2R^{11}, $CONR^{11}R^{12}$, $SO_2NR^{11}R^{12}$, SOR^{11}, SO_2R^{11}, CN and NO_2;

C_{2-10} alkenyl;

C_{2-10} alkenyl independently substituted by up to three groups selected from cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocycloalkyl, NR^8R^9, OR^{10}, SR^{10}, halogen, COR^{11}, CO_2R^{11}, $CONR^{11}R^{12}$, $SO_2NR^{11}R^{12}$, SOR^{11}, SO_2R^{11}, CN and NO_2;

C_{2-10} alkynyl; and

C_{2-10} alkynyl independently substituted by up to three groups selected from NR^8R^9, OR^{10}, SR^{10}, halogen, COR^{11}, CO_2R^{11}, $CONR^{11}R^{12}$, $SO_2NR^{11}R^{12}$, SOR^{11}, SO_2R^{11}, CN and NO_2; and wherein R^8, R^9 and R^{10} are independently H or lower alkyl;

R^2 and R^3 are independently selected from the group consisting of

$NR^{11}R^{12}$;

OR^{13};

SR^{16};

halogen;

COR^{14};

CO_2R^{14};

$CONR^{14}R^{15}$;

$SO_2NR^{14}R^{15}$;

SO_2R^{14};

CN;

NO_2;

$(CH_2)_n$heteroaryl;

$(CH_2)_n$heterocycle;

C_1-C_{10} alkyl;

C_3-C_{10} cycloalkyl;

C_2-C_{10} alkenyl;

C_2-C_{10} alkynyl;

where n is 0, 1, 2, or 3 and the aryl, heteroaryl, heterocycle, alkyl, cycloalkyl, alkenyl, and alkynyl groups are unsubstituted or substituted by up to three groups selected from $NR^{11}R^{12}$; OR^{13}; SR^{16}; halogen; COR^{14}; CO_2R^{14}; $CONR^{14}R^{15}$; $SO_2NR^{14}R^{15}$; SO_2R^{14}; CN; and NO_2;

or alternatively, R^2 and R^3 together form a ring having 3 to 7 atoms fused to the phenyl ring that they are attached to, the ring having no or at least one additional heteroatoms, with the proviso that if the heteroatom is N, the heteroatom may be substituted by at least one substituent selected from the group consisting of lower alkyl; lower alkyl substituted by hydroxy, alkoxy or $NR^{11}R^{12}$; $NR^{11}R^{12}$; OR^{13}; SR^{16}; COR^{14}; CO_2R^{14}; $CONR^{14}R^{15}$; $SO_2NR^{14}R^{15}$; SO_2R^{14}; and CN;

R^4, R^5, R^6, R^7 and R^{26} are independently selected from the group, with at least one being H, consisting of

H;

unsubstituted lower alkyl; lower alkyl substituted by hydroxy, alkoxy or halogen;

$NR^{21}R^{22}$;

OR^{23};

SR^{23};

halogen;

NO_2;

COR^{23};

CO_2R^{23};

$CONR^{23}R^{24}$;

$SO_2NR^{23}R^{24}$;

SO_2R^{23}; and

CN;

R^{11} and R^{12} are independently selected from the group consisting of

H;

unsubstituted lower alkyl; lower alkyl substituted by hydroxy, alkoxy or $NR^{21}R^{22}$;

unsubstituted cycloalkyl; cycloalkyl substituted by hydroxy, alkoxy, lower alkyl or $NR^{21}R^{22}$;

unsubstituted heterocycle; and heterocycle substituted by hydroxy, alkoxy, lower alkyl or $NR^{21}R^{22}$;

or alternatively $NR^{11}R^{12}$ forms a ring having 3 to 7 atoms, the ring having no or at least one additional heteroatoms, with the proviso that if the hetero atom is N, the heteroatom may be substituted by one or more substituents selected from the group consisting of lower alkyl, COR^{14}, CO_2R^{14}, $CONR^{14}R^{15}$, SO_2R^{14}, and $SO_2NR^{14}R^{15}$;

R^{13} is selected from the group consisting of

H;

COR^{14};

$CONR^{14}R^{15}$;

unsubstituted lower alkyl; lower alkyl substituted by hydroxy, alkoxy or $NR^{21}R^{22}$;

unsubstituted cycloalkyl; cycloalkyl substituted by hydroxy, alkoxy, lower alkyl or $NR^{21}R^{22}$;

unsubstituted heterocycle; and heterocycle substituted by hydroxy, alkoxy, lower alkyl or $NR^{21}R^{22}$;

R^{14} and R^{15} are independently selected from the group consisting of

H;

unsubstituted lower alkyl; lower alkyl substituted by hydroxy, alkoxy or $NR^{21}R^{22}$;

unsubstituted cycloalkyl; cycloalkyl substituted by hydroxy, alkoxy, lower alkyl or $NR^{21}R^{22}$;

unsubstituted heterocycle; and heterocycle substituted by hydroxy, alkoxy, lower alkyl or $NR^{21}R^{22}$;

or alternatively $NR^{14}R^{15}$ forms a ring having 3 to 7 atoms, the ring having no or at least one additional heteroatoms, with the proviso that if the heteroatom is N, the heteroatom may be substituted by one or more substituents selected from the

group consisting of one or more lower alkyl, COR^{23}, CO_2R^{23}, $CONR^{23}R^{24}$, SO_2R^{23}, and $SO_2NR^{23}R^{24}$;

R^{16} is selected from the group consisting of

unsubstituted lower alkyl; lower alkyl substituted by hydroxy, alkoxy or $NR^{21}R^{22}$;

unsubstituted cycloalkyl; cycloalkyl substituted by hydroxy, alkoxy, lower alkyl or $NR^{21}R^{22}$,

unsubstituted heterocycle; and heterocycle substituted by hydroxy, alkoxy, lower alkyl or $NR^{21}R^{22}$;

R^{21} is selected from the group consisting of H, lower alkyl, COR^{23} or CO_2R^{23};

R^{22}, R^{23} and R^{24} are independently selected from the group consisting of H or lower alkyl, or alternatively $NR^{21}R^{22}$ or $NR^{23}R^{24}$ independently forms a ring having 3 to 7 atoms, the ring having no or at least one additional heteroatom selected from the group consisting of N, O, and S, with the proviso that if the heteroatom is N, the heteroatom may be in the form of -NH or NR^{25}, and if the hetero atom is S, it may be in the form of $S(O)_m$ where m = 0, 1 or 2; and

R^{25} is lower alkyl.

6. The compound of claim 5 wherein R^6 is OR^{23}.

7. The compound of claim 5 wherein R^4 and R^{26} are halogen.

8. The compound of claim 5 wherein R^5 and R^7 are OR^{23}.

9. The compound of claim 5 wherein R^{26} is an unsubstituted lower alkyl.

10. The compound of claim 5 wherein R^4, R^5, R^6 and R^{26} are H.

11. The compound of claim 5 wherein R^5 and R^{26} are OR^{22}.

12. The compound of claim 5 wherein R^{26} is OR^{23}.

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13. The compound of claim 5 wherein R^6 and R^7 are OR^{23}.

14. The compound of claim 5 wherein R^6 is OR^{23}.

15. A compound selected from the group:

6-(4-Methoxy-phenyl)-8-phenyl-2-phenylamino-5,8-dihydro-6H-pyrido[2,3-d]pyrimidin-7-one (Example 1f);

6-(2,6-Dichloro-phenyl)-8-phenyl-2-phenylamino-5,8-dihydro-6H-pyrido[2,3--d]pyrimidin-7-one (Example 2c);

6-(3,5-Dimethoxy-phenyl)-8-phenyl-2-phenylamino-5,8-dihydro-6H-pyrido[2,3- -d]pyrimidin-7-one (Example 3d);

8-Phenyl-2-phenylamino-6-O-tolyl-5,8-dihydro-6H-pyrido[2,3-d]pyrimidin-7-- one (Example 4c);

6,8-Diphenyl-2-phenylamino-5,8-dihydro-6H-pyrido[2,3-d]pyrimidin-7-one (Example 5c);

6-(2,5-Dimethoxy-phenyl)-8-phenyl-2-phenylamino-5,8-dihydro-6H-pyrido[2,3- -d]pyrimidin-7-one (Example 6c); and

6-(2-Methoxy-phenyl)-8-phenyl-2-phenylamino-5,8-dihydro-6H-pyrido[2,3-d]pyrimidin-7-one (Example 7c).

16. A compound selected from the group:

6-(3,5-Bis-trifluromethyl-phenyl)-8-phenyl-2-phenylamino-5,8-dihydro-6H-pyrido[2,3-d]pyrimidin-7-one (example 8d);

8-Phenyl-2-phenylamino-6-pyridin-4-yl-5,8-dihydro-6H-pyrido[2,3-d]pyrimid- in-7-one (Example 9c);

8-Phenyl-2-phenylamino-6-pyridin-3-yl-5,8-dihydro-6H-pyrido[2,3-d]pyrimid- in-7-one (Example 10c);

6-(3,4-Dimethoxy-phenyl)-8-phenyl-2-phenylamino-5,8-dihydro-6H-pyrido[2,3- -d]pyrimidin-7-one (Example 11c);

6-(4-Methoxy-phenyl)-2-(6-methoxy-pyridin-3-ylamino)-8-phenyl-5,8-dihydro- -

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6H-pyrido[2,3-d]pyrimidine-7-one (Example 12d);

8-Isobutyl-6-(4-methoxy-phenyl)-2-phenylamino-5,8-dihydro-6H-pyrido[2,3-d-]pyrimidine-7-one (Example 13b); and

8 Cyclopropylmethyl-6-(4-methoxy-phenyl)-2-phenylamino-5,8-dihydro-6H-pyrid-o[2,3-d]pyrimidine-7-one (Example 14b).

17. A compound selected from the group:

3-(2,4-Dichloro-pyrimidin-5-yl)-2-(4-methoxy-phenyl)-propionic acid methyl ester (Example 1d);

3-(2,4-Diphenylamino-pyrimidin-5-yl)-2-(4-methoxy-phenyl)-propionic acid methyl ester (Example 1e);

2-(2,6-Dichloro-phenyl)-3-(2,4-dichloro-pyrimidin-5-yl)-propionic acid methyl ester (Example 2a);

3-(2,4-Diphenylamino-pyrimidin-5-yl)-2-(2,6-Dichloro-phenyl)-propionic acid methyl ester (Example 2b);

3-(2,4-Dichloro-pyrimidin-5-yl)-2-(3,5-dimethoxy-phenyl)-propionic acid methyl ester (Example 3b);

3-(2,4-Diphenylamino-pyrimidin-5-yl)-2-(3,5-dimethoxy-phenyl)-propionic acid methyl ester (Example 3c);

3-(2,4-Dichloro-pyrimidin-5-yl)-2-O-tolyl-propionic acid methyl ester (Example 4a);

3-(2,4-Diphenylamino-pyrimidin-5-yl)-2-O-tolyl-propionic acid methyl ester (Example 4b)

3-(2,4-Dichloro-pyrimidin-5-yl)-2-phenyl-propionic acid methyl ester (Example 5a); and

3-(2,4-Diphenylamino-pyrimidin-5-yl)-2-phenyl-propionic acid methyl ester (Example 5b).

18. A compound selected from the group:

3-(2,4-Dichloro-pyrimidin-5-yl)-2-(2,5-dimethoxy-phenyl)-propionic acid ethyl ester (Example 6a);

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3-(2,4-Diphenylamino-pyrimidin-5-yl)-2-(2,5-dimethoxy-phenyl propionic acid ethyl ester (Example 6b);

3-(2,4-Dichloro-pyrimidin-5-yl)-2-(2-methoxy-phenyl)-propionic acid methyl ester (Example 7a);

3-(2,4-Diphenylamino-pyrimidin-5-yl)-2-(2-methoxy-phenyl) propionic acid ethyl ester (Example 7b);

2-(3,5-Bis-trifluoromethyl-phenyl)-3-(2,4-dichloro-pyrimidin-5-yl)-propio- nic acid methyl ester (Example 8b);

3-(2,4-Diphenylamino-pyrimidin-5-yl)-2-(3,5-bis-trifluoromethyl-phenyl)-p- ropionic acid methyl ester (Example 8c);

3-(2,4-Dichloro-pyrimidin-5-yl)-2-pyridin-4-yl-propionic acid ethyl ester (Example 9a);

3-(2,4-Diphenylamino-pyrimidin-5-yl)-2-pyridin-4-yl-propionic acid ethyl ester (Example 9b);

3-(2,4-Dichloro-pyrimidin-5-yl)-2-pyridin-3-yl-propionic acid ethyl ester (Example 10a); and

3-(2,4-Diphenylamino-pyrimidin-5-yl)-2-pyridin-3-yl-propionic acid ethyl ester (Example 10b).

19. A compound selected from the group:

3-(2,4-Dichloro-pyrimidin-5-yl)-2-(3,4-dimethoxy-phenyl)-propionic acid ethyl ester (Example 11a);

3-(2,4-Diphenylamino-pyrimidin-5-yl)-2-(3,4-dimethoxy-phenyl)-propionic acid ethyl ester (Example 11b);

3-(4 Chloro-2-phenylamino-pyrimidin-5-yl)-2-(4-methoxy-phenyl)-propionic acid methyl ester (Example 12a);

3-(2 Chloro-4-phenylamino-pyrimidin-5-yl)-2-(4-methoxy-phenyl)-propionic acid methyl ester (Example 12b);

3-[2-(6-Methoxy-pyridin-3-ylamino)-4-phenylamino-pyrimidin-5-yl]-2-(4-met- hoxy-phenyl)-propionic acid methyl ester (Example 12c);

3-(2-Phenylamino-4-isobutylamino-pyrimidin-5-yl)-2-(4-methoxy-phenyl)-pro-

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pionic acid methyl ester (Example 13a); and

3-(2-Phenylamino-4-cyclopropylmethylamino-pyrimidin-5-yl)-2-(4-methoxy-phenyl)-propionic acid methyl ester (Example 14a).

20. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 1 and a pharmaceutically acceptable carrier or excipient.

21. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 9 and a pharmaceutically acceptable carrier or excipient.

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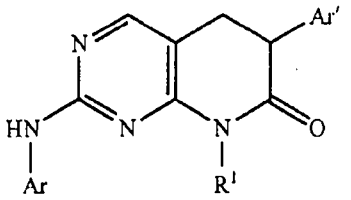
ABSTRACT

The invention provides 5,8-dihydro-6H-pyrido[2,3-d]pyrimidin-7-one compounds that are selective inhibitors of KDR and FGFR kinases, and are useful in the treatment of cancers. The compounds have the generic structure I

I



where Ar, Ar', and R^1 are as set forth in the present specification. The invention also provides pharmaceutical compositions containing these compounds and methods for their use.