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(54) Title: BARBITURIC ACID ANALOGS AS THERAPEUTIC AGENTS

(57) Abstract: This invention pertains to active barbituric acid analogs which inhibit HIF-1 activity (e.g., the interaction between HIF-1α and p300) and thereby inhibit angiogenesis, tumorigenesis, and proliferative conditions, such as cancer. The present invention also pertains to pharmaceutical compositions comprising such compounds, and the use of such compounds and compositions, both in vitro and in vivo, to inhibit HIF-1 activity, and to inhibit angiogenesis, tumorigenesis, and proliferative conditions, such as cancer.

BARBITURIC ACID ANALOGS AS THERAPEUTIC AGENTS

RELATED APPLICATION

This application claims priority to United Kingdom patent application GB 0013655.6 filed 05 June 2000, the contents of which are incorporated herein by reference in their entirety.

TECHNICAL FIELD

This invention pertains generally to the field of antiproliferative compounds, and more specifically to certain active compounds which inhibit HIF-1 activity (e.g., the interaction between HIF-1α and p300), and thereby inhibit angiogenesis, tumorigenesis, and proliferative conditions, such as cancer. The present invention also pertains to pharmaceutical compositions comprising such compounds, and the use of such compounds and compositions, both in vitro and in vivo, to inhibit the interaction between HIF-1α and p300, and to inhibit angiogenesis, tumorigenesis, and proliferative conditions, such as cancer.

BACKGROUND

Solid tumour growth is dependent upon the supply of nutrients and oxygen from the blood. Typically a tumour mass will not grow beyond 2-3 mm^3 unless new blood vessels are formed within the tumour. Such "pre-vascular" tumours and dormant micrometastases maintain their small volume due to a balance of cell proliferation and cell death; they are generally asymptomatic and hence clinically undetected. The formation of new blood vessels (vasculature) within a tumour, by a process known as angiogenesis or neovascularisation, permits further growth, and it is

typically vascularised solid tumours which are detected and which require treatment. Thus, angiogenesis is an essential component of tumorigenesis and the pathogenesis of cancer, and is a recognized target for cancer therapy.

The phenomenon of angiogenesis has many features, for instance intra- and intercellular signalling, tissue remodelling and endothelial cell proliferation. In addition, it has the significant feature that angiogenic endothelial cells have not suffered the unpredictable and undefined mutational changes which characterise tumour cells.

The fundamental stimulus for angiogenesis is believed to be localized tissue "hypoxia," in which tumour cells become starved of oxygen. This condition is typically observed within solid tumours, and the hypoxic environment is believed to arise largely as a result of the rapid aberrant proliferation of the cancer cell, and thus inability of the tumor to maintain an adequate and organised vasculature to supply oxygen to cells within the tumor. When the tumour cells become starved of oxygen, they respond by the expression and secretion of proteins important for stimulating angiogenesis. This response, known as hypoxia adaptation, leads to vascularisation, and facilitates further tumour growth. The most powerful and predominant angiogenic factors appear to be VEGF (Vascular Endothelial Growth Factor) and bFGF (basic Fibroblast Growth Factor).

Recent studies on the inhibition of angiogenesis, taking several approaches, have clearly demonstrated that efficient inhibition of this process can block tumour growth in animal models. Probably the most dramatic examples of induced tumour regression under experimental conditions using an anti-angiogenic strategy have recently been provided by the

studies using the naturally occurring polypeptides angiostatin and endostatin. These studies, in addition to the apparent efficacy, have shown no toxicity and no acquired drug resistance. In addition, promising anti-angiogenic strategies are in clinical development using small molecules targeting several aspects of blood vessel growth, e.g., VEGF/VEGF receptor, integrin ($\alpha v\beta 3$) : vitronectin interaction, or the inhibition of matrix metalloproteinases. The only clear undesirable side effects to an anti-angiogenic strategy that has been determined so far is a reversible loss of female fertility.

Therefore, inhibition of angiogenesis is an attractive aim in pharmaceutical discovery because it should be clinically efficacious and because the genetic homogeneity of the target tissue renders it unlikely to acquire drug resistance. Disruption of signal transduction pathways that mediate adaptation to hypoxia and angiogenesis may represent potentially effective anti-cancer strategies. It is important to realize that the target of an anti-angiogenesis therapy would primarily be the endothelial cell rather than the cancer cell. One advantage that the endothelial cell would offer as a cellular target is that it is not an immortalised cell line, and multi-drug resistance mechanisms operating in cancer cells would presumably be absent.

There are several control points influencing angiogenesis which may be considered as targets for intervention, and one of particular interest is the transcription factor Hypoxia-Inducible Factor 1 (HIF-1). HIF-1 has been shown to play an essential role in cellular responses to hypoxia. Upon hypoxic stimulation, HIF-1 is known to activate genes that contain Hypoxic Response Elements (HREs) in their promoters, and thus up-regulate a series of gene products that promote cell survival under conditions of low oxygen availability.

The list of HIF-responsive genes is constantly expanding, but known gene products include glycolytic enzymes such as lactate dehydrogenase, (LDH-A), enolase-1 (ENO-1), and aldolase A; glucose transporters GLUT 1 & 3; vascular endothelial growth factor (VEGF); inducible nitric oxide synthase (NOS-2); and erythropoietin (EPO). The switch of the cell to anaerobic glycolysis, and the up-regulation of angiogenesis by VEGF is geared at maximizing cell survival under conditions of low oxygen tension by reducing the requirement for oxygen, and increasing vasculature to maximise oxygen delivery to tissues. Induction of NOS-2, and the subsequent increase in NO would effectively promote a state of vasodilation in the hypoxic microenvironment thereby maximizing blood flow and oxygen delivery to cells. Increased EPO production by the tubular interstitial cells of the kidney is geared at promoting erythropoiesis, and increasing red blood cell number to further facilitate oxygen delivery to hypoxic tissues.

The HIF-1 transcription complex has recently been shown to comprise a heterodimer of two basic helix-loop-helix proteins, HIF-1α and HIF-1β (also known as ARNT, Aryl Hydrocarbon Receptor Nuclear Translocator). See, for example, Wood et al., 1996. Oxygen tension regulates the expression levels of both factors.

HIF-1α is a member of the basic-helix-loop-helix PAS domain protein family and is an approximately 120 kDa protein containing 2x transactivation domains (TAD) in its carboxy-terminal half and DNA binding activity located in the N-terminal half of the molecule. HIF-1α is constitutively degraded by the ubiquitin-proteosome pathway under conditions of normoxia, a process that is facilitated by binding of the von Hippel-Lindau (VHL) tumor suppressor

protein to HIF-1α. Under conditions of hypoxia, degradation of HIF-1α is blocked and active HIF-1α accumulates. The subsequent dimerization of HIF-1α with ARNT leads to the formation of active HIF transcription complexes in the nucleus, which can bind to and activate HREs on HIF-responsive genes.

Recent evidence suggests that nuclear translocation is a function intrinsic to HIF-1α and does not require ARNT. Indeed, ARNT has recently been postulated to function to lock HIF-1α in the nucleus and protect it from proteolytic degradation, enabling the active complex to bind DNA and activate transcription. Studies in a mouse hepatoma cell line found to be deficient in ARNT showed that HIF-1 activity was not induced by hypoxia. Furthermore, in animal tumour model studies using this cell line, reduced VEGF expression was observed associated with decreased tumour vascularity and growth rate. In a separate approach, a targeted gene disruption of ARNT in the mouse was found to cause embryonic lethality (day 10.5) with angiogenic abnormalities similar to those observed for VEGF deficiency. Associated studies confirmed that these $ARNT^{-/-}$ embryonic stem cells were unable to induce genes such as VEGF in response to hypoxia.

It is known that HIF-1 activity is sustained by the p300/CBP co-activator family of proteins and that recruitment of the transcriptional adapter protein p300 to the HIF-1 complex is an essential step to activate HIF-responsive genes. The protein p300 physically interacts with the activation domain of HIF-1α to facilitate the transcription of target genes, and this interaction has been shown to be mediated by the N-terminal CH1 domain of p300. It is believed that histone acetyl transferase (HAT) activity of p300 is required to allow the HIF-1 complex to access chromatin and bind to

sites on DNA. Since there are known to be multiple HIF-1 binding sites on a single promoter, p300 has also been postulated to physically link several HIF-1 complexes to maximally activate transcription. A recent study demonstrating that binding of adenoviral protein E1A to p300 completely abolished HIF-dependent transcriptional activation demonstrates an essential role for p300 in HIF activation. Indeed, a mutant E1A molecule selectively deficient for p300 binding failed to block HIF-dependent transcriptional activation, providing convincing evidence that pharmaceutical intervention at the level of HIF-1α/p300 would completely inactivate the complex.

Several lines of evidence support the importance of HIF-1 as a viable therapeutic target in angiogenesis. HIF-1$\alpha^{-/-}$ mice show an embryonic lethal phenotype, which is characterised by a lack of cephalic vascularisation. Teratocarcinomas generated from HIF-1$\alpha^{-/-}$ mice were 75% smaller than wildtype tumours, the reduced size resulting from increased levels of apoptosis. Furthermore, inactivation of ARNT in a mouse hepatoma cell line resulted in retarded angiogenesis and tumour growth. Other studies have documented the levels of HIF-1α with a highly metastatic and aggressive tumour phenotype, for example in the human prostrate cell line PC3 which has high levels of HIF-1α and is very metastatic. More recently, a transgenic mouse approach has been taken to demonstrate the importance of the HIF-1α/p300 interaction for tumourigenesis.

Additional discussion of hypoxia, HIF-1, and related topics is provided in following recent review articles: Brown et al., 2000; Semenza et al., 1999a; Semenza et al., 1999b; Richard et al., 1999; Taylor et al., 1999; and Wenger et al., 1999.

Several components of the HIF-1 complex offer potential sites where a small molecule drug could cause disruption and inactivate the transcription of HIF-responsive genes. Essential interactions required to activate transcription include the HIF-1α/ARNT interaction, the HIF-1α/p300 interaction, and the HIF-1/DNA interaction. One target of particular interest is the HIF-1α/p300 interaction. This interaction offers a more attractive target than HIF-1α/ARNT since disruption of dimerization would presumably liberate ARNT, which has other functions within the cell.

Methods of identifying compounds which modulate a transcriptional response to hypoxia in a cell are described in Livingston et al., 2000. Similar methods are also described in Arany et al., 1996.

One aim of the present invention is the provision of small drug-like molecules which interfere with the pro-angiogenic response of tumour cells to hypoxic conditions. There is a pressing need for such anticancer compounds, since present drugs are of low efficacy, have many deleterious side-effects, and often give rise to drug-resistance in the tumour.

Such molecules desirably have one or more of the following properties and/or effects:

(a) easily gain access to and act upon endothelial cells of the tumor vasculature;

(b) down-regulate HIF-1 activity;

(c) inhibit the formation of the HIF-1 complex;

(d) inhibit the interactions of the HIF-1 complex;

(e) inhibit the HIF-1α/p300 interaction;

(f) inhibit the transcription of HIF-responsive genes, for example, the VEGF gene;

(g) inhibit the hypoxic response of tumours;

(h) inhibit angiogenesis;

(i) promote tumour cell apoptosis;

(j) inhibit tumour growth; and,

(k) complement the activity of traditional chemotherapeutic agents.

A number of barbituric acid derivatives are known, and, as discussed below, some have been reported to have biological activity.

Pan et al., 1997, describe certain 5-(phenylmethylene) barbituric acid analogs which apparently inhibit tyrosine protein kinase (TPK) of HL-60 leukemia cells and normal rat spleen cells.

Fellahi et al., 1995, describe certain 2-substituted-5-(1,2-diarylethyl)-4,6-dichloropyrimidine derivatives which apparently are active against a wide range of bacterial flora of the axilla and foot, and in particular, against Corynebacterium xerosis and Arcanobacterium haemolyticum of the human axilla.

Naguib et al., 1993, describe certain 5-benzylbarbituric acid derivatives which apparently are potent and specific inhibitors of uridine phosphorylase.

Miyazaki et al., 1987, describe certain barbituric acid derivatives which apparently showed excellent maintenance effect on the survival and function of adult rat hepatocytes in primary culture.

Rehse et al., 1982, describe certain barbituric acid derivatives which were synthesized and tested for anticoagulant activity, but found to be inactive.

Vida et al., 1974, describe certain 5-substituted-5-proprionoxybarbituric acid derivatives which apparently had analgesic activity in mice.

Weinryb et al., 1971, describe certain barbiturates, including 5,5-dibromobarbiturate and 5-bromo-5-phenylbarbiturate, which apparently were potent inhibitors of basal adenylate cylcase activity in particulate fractions from guinea pig heart and lung.

SUMMARY OF THE INVENTION

One aspect of the invention pertains to active compounds, as described herein, which inhibit HIF-1 activity, e.g., in a cell.

Another aspect of the invention pertains to active compounds, as described herein, which inhibit the interaction between HIF-1α and p300, e.g., in a cell.

Another aspect of the invention pertains to active compounds, as described herein, which inhibit angiogenesis.

Another aspect of the invention pertains to active compounds, as described herein, which treat a proliferative condition, such as cancer.

Another aspect of the present invention pertains to a composition comprising a compound as described herein and a pharmaceutically acceptable carrier.

Another aspect of the present invention pertains to methods of inhibiting HIF-1α activity in a cell, comprising contacting said cell with an effective amount of an active compound, as described herein.

Another aspect of the present invention pertains to methods of inhibiting the interaction between HIF-1α and p300 in a cell, comprising contacting said cell with an effective amount of an active compound, as described herein.

Another aspect of the present invention pertains to methods of inhibiting angiogenesis, comprising contacting a cell with an effective amount of an active compound, as described herein, whether *in vitro* or *in vivo*.

Another aspect of the present invention pertains to methods of treating a proliferative condition in a patient comprising administering to said patient a therapeutically-effective amount of an active compound, as described herein. In one preferred embodiment, the proliferative condition is cancer.

Another aspect of the present invention pertains to an active compound, as described herein, for use in a method of treatment of the human or animal body.

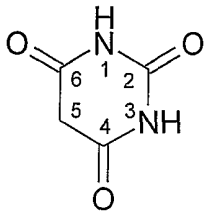
Another aspect of the present invention pertains to use of an active compound, as described herein, for the manufacture of a medicament for use in the treatment of a proliferative condition. In one preferred embodiment, the proliferative condition is cancer.

As will be appreciated by one of skill in the art, features and preferred embodiments of one aspect of the invention will also pertain to other aspects of the invention.

DETAILED DESCRIPTION OF THE INVENTION

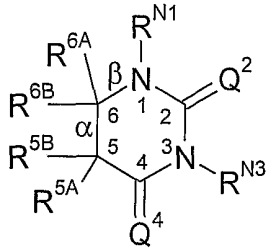
Compounds

The well known compound, barbituric acid, has the following formula:



(1)

The present invention pertains to certain barbituric acid analogs, specifically, compounds of the formula:



(2)

wherein:

Q^2 is =O, =S, or $=NR^{N2}$;

Q^4 is =O, =S, or $=NR^{N4}$;

α is a single bond or a double bond;

β is a single bond or a double bond;

with the proviso that α and β are not both double bonds, and that if β is a double bond, R^{N1} is absent;

and wherein:

(i) R^{5B} is -H and R^{5A} is R^{C5}; or,

(ii) R^{5A} and R^{5B} together are =O, α is a single bond, and β is a single bond; or,

(iii) R^{5A} and R^{5B} together are $=CHR^{C5}$, wherein R^{C5} may be cis- or trans-, α is a single bond, and β is a single bond;

and wherein:

(iv) R^{6B} is -H and R^{6A} is R^{C6}; or,

(v) R^{6A} and R^{6B} together are =O, α is a single bond, and β is a single bond; or,

(vi) R^{6A} and R^{6B} together are =CHR^{C6}, wherein R^{C6} may be cis- or trans-, α is a single bond, and β is a single bond;

or wherein:

R^{5A} and R^{6A}, together form a bidentate structure, R^{56}, which, together with the two carbon atoms to which it is attached, forms a cyclic structure with five or six ring atoms, wherein 1 or 2 of said ring atoms are nitrogen, and the remainder are carbon, and wherein the bonds between said ring atoms of the cyclic structure are single or double bonds, as permitted by the valencies of the ring atoms; and,

R^{5B} and R^{6B}, if present, are both -H;

and wherein:

each one of R^{N1}, R^{N2}, R^{N3}, and R^{N4} is a nitrogen substituent, and is independently hydrogen, optionally substituted C_{1-7}alkyl (including, e.g., C_{1-7}haloalkyl, C_{1-7}hydroxyalkyl, C_{1-7}aminoalkyl, C_{1-7}carboxyalkyl, C_{5-20}aryl-C_{1-7}alkyl), optionally substituted C_{3-20}heterocyclyl, or optionally substituted C_{5-20}aryl (including, e.g., C_{5-20}haloaryl, C_{1-7}alkyl-C_{5-20}aryl);

and wherein:

each one of R^{C5} and R^{C6} is a carbon substituent, and is independently optionally substituted C_{1-7}alkyl (including, e.g., C_{1-7}haloalkyl, C_{1-7}hydroxyalkyl, C_{1-7}aminoalkyl, C_{1-7}carboxyalkyl, C_{5-20}aryl-C_{1-7}alkyl), optionally substituted C_{3-20}heterocyclyl, or optionally substituted C_{5-20}aryl (including, e.g., C_{5-20}haloaryl, C_{1-7}alkyl-C_{5-20}aryl);

or a pharmaceutically acceptable salt, solvate, amide, ester, N-oxide, chemically protected form, and prodrug thereof.

Q^2 and Q^4

In one embodiment, Q^2 is =O or =S; and Q^4 is =O or =S.

In one embodiment, Q^2 is =O and Q^4 is =O; or Q^2 is =S and Q^4 is =O.

In one embodiment, Q^2 is =O and Q^4 is =O.

In one embodiment, Q^2 is =S and Q^4 is =O.

Nitrogen Subsituents, R^N

Each one of R^{N1}, R^{N2}, R^{N3}, and R^{N4} is a nitrogen substituent, and is independently hydrogen, optionally substituted C_{1-7}alkyl (including, e.g., C_{1-7}haloalkyl, C_{1-7}hydroxyalkyl, C_{1-7}aminoalkyl, C_{1-7}carboxyalkyl, C_{5-20}aryl-C_{1-7}alkyl), optionally substituted C_{3-20}heterocyclyl, or optionally substituted C_{5-20}aryl (including, e.g., C_{5-20}haloaryl, C_{1-7}alkyl-C_{5-20}aryl).

In one embodiment, each one of R^{N1}, R^{N2}, R^{N3}, and R^{N4} is independently hydrogen, optionally substituted C_{1-7}alkyl (including, e.g., C_{1-7}hydroxyalkyl, C_{1-7}haloalkyl, C_{1-7}aminoalkyl), or optionally substituted C_{5-20}aryl (including, e.g., C_{5-20}haloaryl, C_{1-7}alkyl-C_{5-20}aryl).

In one embodiment, each one of R^{N1}, R^{N2}, R^{N3}, and R^{N4} is independently hydrogen, saturated aliphatic C_{1-7}alkyl, saturated aliphatic C_{1-7}haloalkyl, saturated aliphatic C_{1-7}hydroxyalkyl, saturated aliphatic C_{1-7}aminoalkyl,

saturated aliphatic C_{1-7}carboxyalkyl, C_{5-20}aryl-C_{1-7}alkyl, C_{5-20}carboaryl, or C_{5-20}haloaryl.

In one embodiment, each one of R^{N1}, R^{N2}, R^{N3}, and R^{N4} is independently -H, -Me, -Et, $-CH_2COOH$, -Ph, $-C_6H_4F$, $-C_6H_4Cl$, $-C_6H_4Br$, $-C_6H_4-OCH_3$, or $-C_6H_4-CH_3$.

In one embodiment, each one of R^{N1}, R^{N2}, R^{N3}, and R^{N4} is independently -H, -Me, -Et, $-CH_2COOH$, -Ph, or $-C_6H_4Cl$.

In one embodiment, R^{N1} is -H or other than -H; and each one of R^{N2}, R^{N3}, and R^{N4} is -H.

In one embodiment, R^{N3} is -H or other than -H; and each one of R^{N1}, R^{N2}, and R^{N4} is -H.

In one embodiment, each one of R^{N1}, R^{N2}, R^{N3}, and R^{N4} is -H.

5-(Substituted Methylene) Compounds

In one embodiment:

Q^2 is =O, =S, or $=NR^{N2}$;

Q^4 is =O, =S, or $=NR^{N4}$;

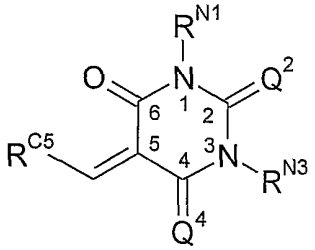
R^{5A} and R^{5B} together are $=CHR^{C5}$, wherein R^{C5} may be cis- or trans-;

R^{6A} and R^{6B} together are =O;

α is a single bond; and,

β is a single bond;

and the compounds have the following formula:



(3)

In one embodiment:

Q^2 is =O;

Q^4 is =O;

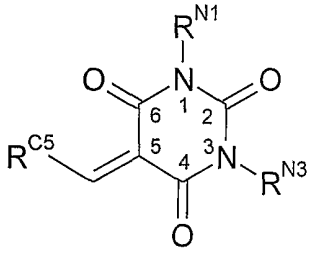
R^{5A} and R^{5B} together are $=CHR^{C5}$, wherein R^{C5} may be cis- or trans-;

R^{6A} and R^{6B} together are =O;

α is a single bond; and,

β is a single bond;

and the compounds have the following formula:



(4)

In one embodiment:

Q^2 is =S;

Q^4 is =O;

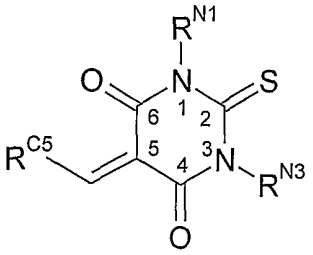
R^{5A} and R^{5B} together are $=CHR^{C5}$, wherein R^{C5} may be cis- or trans-;

R^{6A} and R^{6B} together are =O;

α is a single bond; and,

β is a single bond;

and the compounds have the following formula:



(5)

In the above formulae, R^{C5} is, as mentioned above, optionally substituted C_{1-7}alkyl (including, e.g.,

C_{1-7}haloalkyl, C_{1-7}hydroxyalkyl, C_{1-7}aminoalkyl, C_{1-7}carboxyalkyl, C_{5-20}aryl-C_{1-7}alkyl), optionally substituted C_{3-20}heterocyclyl, or optionally substituted C_{5-20}aryl (including, e.g., C_{5-20}haloaryl, C_{1-7}alkyl-C_{5-20}aryl).

In one embodiment, R^{C5} is C_{1-7}alkyl, and is optionally substituted. In one embodiment, R^{C5} is C_{3-6}cycloalkyl, and is optionally substituted. In one embodiment, R^{C5} is partially unsaturated C_{3-6}cycloalkyl, for example, cyclohexenyl.

In one embodiment, R^{C5} is C_{5-20}aryl-C_{1-7}alkyl, and is optionally substituted, for example, phenyl-ethenyl (styryl), furanyl-ethenyl, and thiophenyl-ethenyl.

In one embodiment, R^{C5} is C_{3-20}heterocyclyl, and is optionally substituted. In one embodiment, R^{C5} is C_{5-7}heterocyclyl, and is optionally substituted.

In one embodiment, R^{C5} is C_{5-20}aryl, and is optionally substituted.

In one embodiment, R^{C5} is C_{5-20}carboaryl, and is optionally substituted. In one embodiment, R^{C5} is phenyl, naphthyl, anthracenyl, or phenanthryl, and is optionally substituted. In one embodiment, R^{C5} is phenyl, and is optionally substituted.

In one embodiment, R^{C5} is C_{5-20}heteroaryl, and is optionally substituted. In one embodiment, R^{C5} is furanyl, thiophenyl, pyrrolyl, indolyl, or benzopyronyl (e.g., chromonyl), and is optionally substituted. In one embodiment, R^{C5} is furanyl, thiophenyl, or pyrrolyl, and is optionally substituted, for example, nitrothiophenyl.

In one embodiment, R^{C5} is cyclohexenyl, phenyl, furanyl, thiophenyl, pyrrolyl, indolyl, or benzopyronyl (e.g., chromonyl), and is optionally substituted.

In one embodiment, R^{C5} is phenyl, and is optionally substituted.

Examples of substituents include, but are not limited to, hydrogen, halo, hydroxy, ether (including, e.g., C_{1-7}alkoxy, C_{5-20}aryloxy), oxo, formyl, acyl, carboxy, carboxylate, acyloxy, amido, acylamido, amino, cyano, nitro, sulfhydryl, thioether, sulfonamino, sulfinamino, sulfamyl, sulfonamido, C_{1-7}alkyl (including, e.g., C_{1-7}haloalkyl, C_{1-7}hydroxyalkyl, C_{1-7}carboxyalkyl, C_{1-7}aminoalkyl, C_{5-20}aryl-C_{1-7}alkyl), optionally substiuted C_{3-20}heterocyclyl, optionally substituted C_{5-20}aryl (including, e.g., C_{5-20}heteroaryl, C_{1-7}alkyl-C_{5-20}aryl and C_{5-20}haloaryl).

5-(Phenylmethylene) Compounds

In one embodiment:

Q^2 is =O, =S, or $=NR^{N2}$;

Q^4 is =O, =S, or $=NR^{N4}$;

R^{5A} and R^{5B} together are $=CHR^{C5}$, wherein R^{C5} may be cis- or trans-;

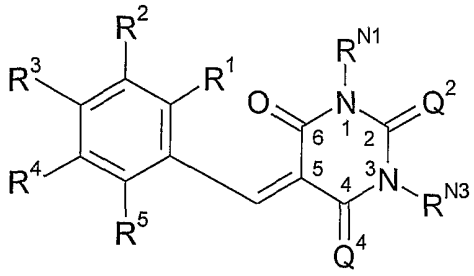
R^{C5} is an optionally substituted phenyl group;

R^{6A} and R^{6B} together are =O;

α is a single bond; and,

β is a single bond;

and the compounds have the following formula:



(6)

In one embodiment:

Q^2 is =O;

Q^4 is =O;

R^{5A} and R^{5B} together are $=CHR^{C5}$, wherein R^{C5} may be cis- or trans-;

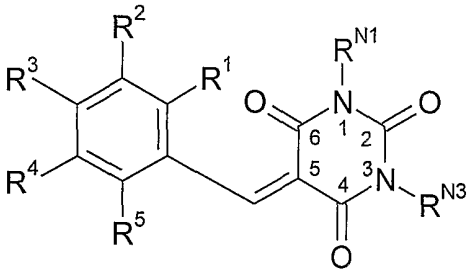
R^{C5} is an optionally substituted phenyl group;

R^{6A} and R^{6B} together are =O;

α is a single bond; and,

β is a single bond;

and the compounds have the following formula:



(7)

In one embodiment:

Q^2 is =S;

Q^4 is =O;

R^{5A} and R^{5B} together are $=CHR^{C5}$, wherein R^{C5} may be cis- or trans-;

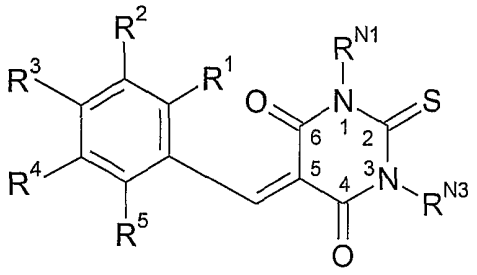
R^{C5} is an optionally substituted phenyl group;

R^{6A} and R^{6B} together are =O;

α is a single bond; and,

β is a single bond;

and the compounds have the following formula:



(8)

In the above formulae, each one of R^1 through R^5 is a phenyl substituent, and is independently hydrogen, halo, hydroxy, ether (e.g., C_{1-7}alkoxy, C_{5-20}aryloxy), formyl, acyl, carboxy, carboxylate, amido, acylamido, amino, nitro, optionally substituted C_{1-7}alkyl (including, e.g., C_{1-7}haloalkyl), optionally substituted C_{3-20}heterocyclyl, or optionally substituted C_{5-20}aryl.

Also, two of R^1 through R^5, preferably adjacent groups, may together form a bidentate structure which, together with the two carbon atoms to which it is attached, forms a cyclic structure with five or six ring atoms, which ring atoms are carbon, nitrogen, or oxygen, and wherein the bonds between said ring atoms of the cyclic structure are single or double bonds, as permitted by the valencies of the ring atoms. Examples of such bidentate structures include, but are not limited to, $-(CH_2)_3-$, $-(CH_2)_4-$, $-O-CH_2-O-$, and $-O-CH_2CH_2-O-$, and substituted and/or unsaturated forms thereof.

In one embodiment, each one of R^1 through R^5 is hydrogen, halo, hydroxy, C_{1-7}alkoxy, optionally substituted C_{5-20}aryloxy, optionally substituted C_{5-20}aryl-C_{1-7}alkoxy, acyl, amino (e.g., with from 0 to 2 optionally substituted C_{1-7}alkyl substituents), or optionally substituted C_{1-7}alkyl (including, e.g., C_{1-7}haloalkyl).

In one embodiment, each one of R^1 through R^5 is independently selected from:

-H;

-F, -Cl, -Br, and -I;

-OH;

$-OCH_3$, $-OCH_2CH_3$, $-OC(CH_3)_3$, and $-OCH_2Ph$;

$-C(=O)H$;

$-C(=O)CH_3$, $-C(=O)CH_2CH_3$, $-C(=O)C(CH_3)_3$, and $-C(=O)Ph$;

-COOH;

$-COOCH_3$, $-COOCH_2CH_3$, and $-COOC(CH_3)_3$;

$-C(=O)NH_2$, $-C(=O)NHCH_3$, $-C(=O)N(CH_3)_2$, and $-C(=O)NHCH_2CH_3$;

$-NHC(=O)CH_3$, $-NHC(=O)CH_2CH_3$, $-NHC(=O)Ph$, succinimidyl, and maleimidyl;

$-NH_2$, $-NHCH_3$, $-NHCH(CH_3)_2$, $-N(CH_3)_2$, and $-N(CH_2CH_3)_2$;

$-NO_2$;

$-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, and $-CH(CH_3)_2$;

$-CF_3$, $-CHF_2$, $-CH_2F$, $-CCl_3$, $-CBr_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, and $-CH_2CF_3$;

$-OCF_3$, $-OCHF_2$, $-OCH_2F$, $-OCCl_3$, $-OCBr_3$, $-OCH_2CH_2F$, $-OCH_2CHF_2$, and $-OCH_2CF_3$;

$-CH_2OH$, $-CH_2CH_2OH$, and $-CH(OH)CH_2OH$;

$-CH_2NH_2$, $-CH_2CH_2NH_2$, and $-CH_2CH_2N(CH_3)_2$; and,

optionally substituted phenyl.

In one embodiment, each one of R^1 through R^5 is independently selected from: -H, -F, -Cl, -Br, -I, $-NMe_2$, $-NEt_2$, -OH, $-OCH_3$, $-OCH_2CH_3$, -OPh, $-OCH_2Ph$, $-C(=O)CH_3$, $-CONH_2$, $-CONHCH_3$, $-NO_2$, $-CH_3$, $-CH_2CH_3$, $-CF_3$, $-OCF_3$, $-CH_2OH$, -Ph, and $-CH_2Ph$.

In one embodiment, each one of R^1 through R^5 is independently selected from: -H, -F, -Cl, -Br, -I, $-NMe_2$, $-NEt_2$, -OH, -OMe, -OEt, -CONHMe, $-NO_2$, and $-CF_3$.

In one embodiment, each one of R^1 through R^5 is independently selected from: -H, $-NMe_2$, -OH, -OMe, -OEt, and $-NO_2$.

In one embodiment, each one of R^1 through R^5 is independently selected from: -H, -F, -Cl, -Br, and -I.

Fused 5 & 6 Membered Ring Compounds

In one embodiment, R^{5A} and R^{6A}, together form a bidentate structure, R^{56}, which, together with the two carbon atoms to which it is attached, forms a cyclic structure with five ring atoms, wherein 1 or 2 of said ring atoms are nitrogen, and the remainder are carbon, and wherein the bonds between said ring atoms of the cyclic structure are single or double bonds, as permitted by the valencies of the ring atoms; and, R^{5B} and R^{6B}, if present, are both -H.

In one embodiment:

Q^2 is =O, =S, or $=NR^{N2}$;

Q^4 is =O, =S, or $=NR^{N4}$;

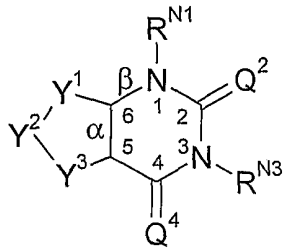
α is a single or a double bond;

β is a single bond;

R^{5A} and R^{6A}, together form a bidentate structure, R^{56}, which, together with the two carbon atoms to which it is attached, forms a cyclic structure with five ring atoms, wherein 1 or 2 of said ring atoms are nitrogen, and the remainder are carbon; and,

R^{5B} and R^{6B} are both absent;

and the compounds have the following formula:



(9)

wherein 1 or 2 of Y^1, Y^2, and Y^3 are (optionally substituted) nitrogen atoms, and the remainder are (optionally substituted) carbon atoms, and the bonds between C-5 and Y^3, Y^3 and Y^2, Y^2 and Y^1, and Y^1 and C-6 are single or double bonds, as permitted by the valencies of the respective atoms.

In one embodiment:

Q^2 is =O, =S, or $=NR^{N2}$;

Q^4 is =O, =S, or $=NR^{N4}$;

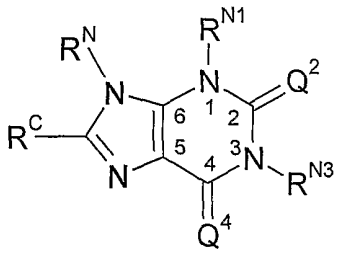
α is a single or double bond;

β is a single or double bond;

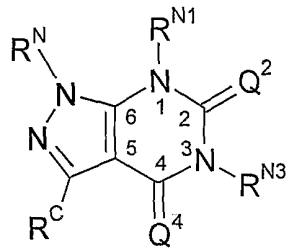
R^{5A} and R^{6A}, together form a bidentate structure, R^{56}; and,

R^{5B} and R^{6B} are both absent;

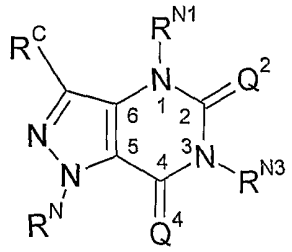
and the compounds have one of the following formulae:



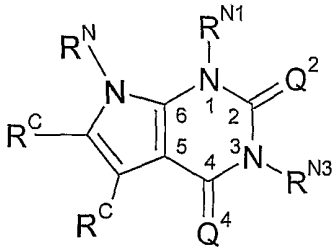
(10)



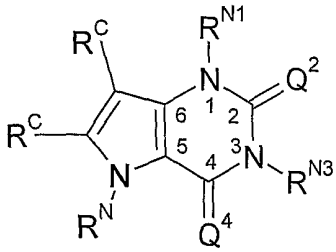
(11)



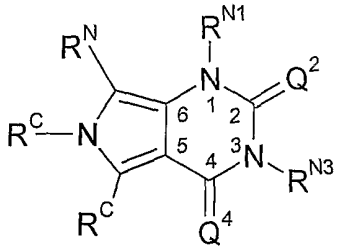
(12)



(13)



(14)



(15)

In one embodiment:

Q^2 is =O, =S, or $=NR^{N2}$;

Q^4 is =O, =S, or $=NR^{N4}$;

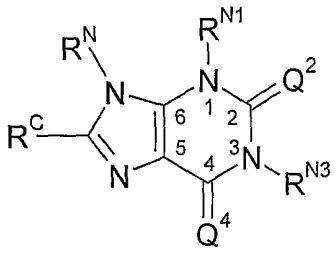
α is a double bond;

β is a single bond;

R^{5A} and R^{6A}, together form a bidentate structure, R^{56}; and,

R^{5B} and R^{6B} are both absent;

and the compounds have the following formula:



(10)

In one embodiment:

Q^2 is =O;

Q^4 is =O;

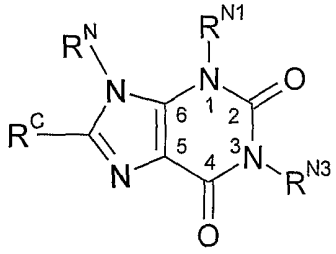
α is a double bond;

β is a single bond;

R^{5A} and R^{6A}, together form a bidentate structure, R^{56}; and,

R^{5B} and R^{6B} are both absent;

and the compounds have the following formula:



(16)

In one embodiment of the preceding formula, R^N is C_{1-7}hydroxyalkyl, and is optionally substituted with a substituent, R^{CH}.

In one embodiment:

Q^2 is =O;

Q^4 is =O;

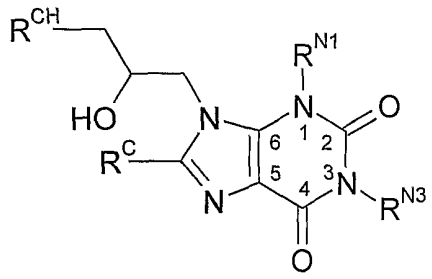
α is a double bond;

β is a single bond;

R^{5A} and R^{6A}, together form a bidentate structure, R^{56}; and,

R^{5B} and R^{6B} are both absent;

and the compounds have the following formula:



(17)

In the above formulae, each R^C is a carbon substituent, and is independently hydrogen, halo, hydroxy, ether (including, e.g., C_{1-7}alkoxy), formyl, acyl, carboxy, carboxylate, acyloxy, amido, acylamido, amino, cyano, nitro, sulfhydryl, thioether, sulfonamino, sulfinamino, sulfamyl, sulfonamido, optionally substituted C_{1-7}alkyl (including, e.g., C_{1-7}haloalkoxy, C_{1-7}hydroxyalkyl, C_{1-7}carboxyalkyl, C_{1-7}aminoalkyl, C_{5-20}aryl-C_{1-7}alkyl), optionally substituted C_{3-20}heterocyclyl, or optionally substituted C_{5-20}aryl (including, e.g., C_{5-20}heteroaryl, C_{1-7}alkyl-C_{5-20}aryl and C_{5-20}haloaryl).

In one embodiment, R^C is hydrogen, C_{1-7}alkyl, hydroxy, C_{1-7}alkoxy, amino, or C_{5-20}aryl.

In one embodiment, R^C is -H, -Me, -Et, -OH, -OMe, -OEt, $-NH_2$, $-NMe_2$, $-NEt_2$, -Ph, $-C_6H_5Cl$, $-C_6H_5OCH_3$.

In the above formulae, each R^N is a nitrogen substituent, and is as defined above for R^{N1}, R^{N2}, R^{N3}, and R^{N4}.

In the above formulae, R^{CH} is a C_{1-7}hydroxyalkyl substituent, and is hydrogen, halo, hydroxy, ether (including, e.g., C_{1-7}alkoxy), oxo, formyl, acyl, carboxy, carboxylate, acyloxy, amido, acylamido, amino, cyano, nitro, sulfhydryl, thioether, sulfonamino, sulfinamino, sulfamyl, sulfonamido, C_{1-7}alkyl (including, e.g., C_{1-7}haloalkoxy, C_{1-7}hydroxyalkyl,

C_{1-7}carboxyalkyl, C_{1-7}aminoalkyl, C_{5-20}aryl-C_{1-7}alkyl), C_{3-20}heterocyclyl, C_{5-20}aryl (including, e.g., C_{5-20}heteroaryl, C_{1-7}alkyl-C_{5-20}aryl and C_{5-20}haloaryl).

In one embodiment, R^{CH} is hydrogen, C_{1-7}alkyl, C_{1-7}alkoxy, C_{3-20}heterocyclyl, C_{3-20}heterocyclyloxy, C_{5-20}aryl, C_{5-20}aryloxy, and substituted forms thereof, for example, para-chlorophenoxy and (N-meta-chlorophenyl)piperazinyl.

Fused 6 & 6 Membered Ring Compounds

In one embodiment, R^{5A} and R^{6A}, together form a bidentate structure, R^{56}, which, together with the two carbon atoms to which it is attached, forms a cyclic structure with six ring atoms, wherein 1 or 2 of said ring atoms are nitrogen, and the remainder are carbon, and wherein the bonds between said ring atoms of the cyclic structure are single or double bonds, as permitted by the valencies of the ring atoms; and, R^{5B} and R^{6B}, if present, are both -H.

In one embodiment:

Q^2 is =O, =S, or $=NR^{N2}$;

Q^4 is =O, =S, or $=NR^{N4}$;

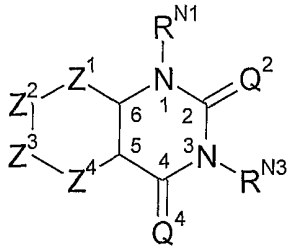
α is a single or double bond;

β is a single or double bond;

R^{5A} and R^{6A}, together form a bidentate structure, R^{56}, which, together with the two carbon atoms to which it is attached, forms a cyclic structure with six ring atoms, wherein 1 or 2 of said ring atoms are nitrogen, and the remainder are carbon; and,

R^{5B} and R^{6B} are both -H, if present;

and the compounds have the following formula:



(18)

wherein 1 or 2 of Z^1, Z^2, Z^3, and Z^4 are (optionally substituted) nitrogen atoms, and the remainder are (optionally substituted) carbon atoms, and the bonds between C-5 and Z^4, Z^4 and Z^3, Z^3 and Z^2, Z^2 and Z^1, and Z^1 and C-6 may be single or double bonds, as permitted by the valencies of the respective atoms.

In one embodiment:

Q^2 is =O, =S, or $=NR^{N2}$;

Q^4 is =O, =S, or $=NR^{N4}$;

α is a single or double bond;

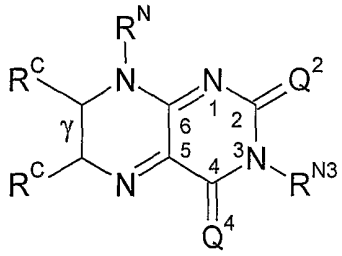
β is a single or double bond;

γ is a single or double bond;

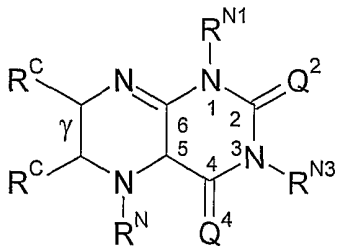
R^{5A} and R^{6A}, together form a bidentate structure, R^{56}; and,

R^{5B} and R^{6B} are both absent;

and the compounds have one of the following formulae:



(19)



(20)

In one embodiment:

Q^2 is =O, =S, or $=NR^{N2}$;

Q^4 is =O, =S, or $=NR^{N4}$;

α is a single bond;

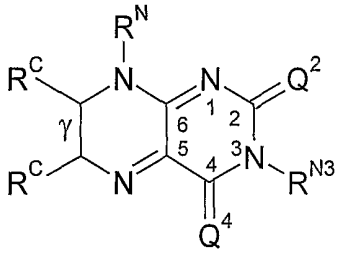
β is a double bond;

γ is a single or double bond;

R^{5A} and R^{6A}, together form a bidentate structure, R^{56}; and,

R^{5B} and R^{6B} are both absent;

and the compounds have the following formula:



(19)

In one embodiment:

Q^2 is =O, =S, or $=NR^{N2}$;

Q^4 is =O, =S, or $=NR^{N4}$;

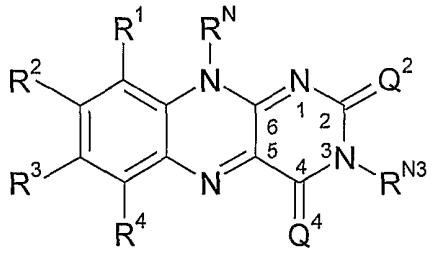
α is a single bond;

β is a double bond;

R^{5A} and R^{6A}, together form a bidentate structure, R^{56}; and,

R^{5B} and R^{6B} are both absent;

and the compounds have the following formula:



(21)

In one embodiment:

Q^2 is =O, =S, or $=NR^{N2}$;

Q^4 is =O, =S, or $=NR^{N4}$;

α is a double bond;

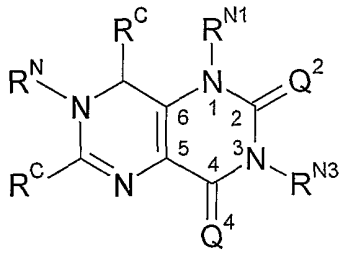
β is a single bond;

R^{5A} and R^{6A}, together form a bidentate structure, R^{56};

and,

R^{5B} and R^{6B} are both absent;

and the compounds have the following formula:



(22)

In one embodiment:

Q^2 is =O, =S, or $=NR^{N2}$;

Q^4 is =O, =S, or $=NR^{N4}$;

α is a double bond;

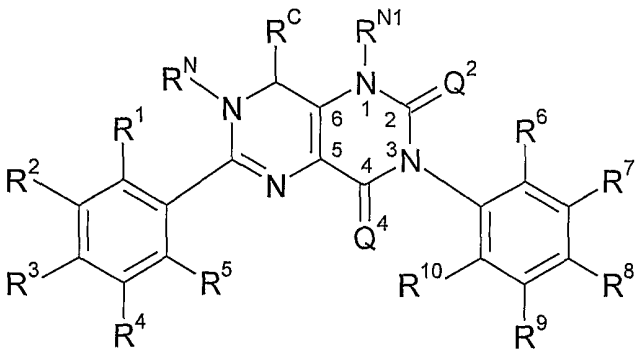
β is a single bond;

R^{5A} and R^{6A}, together form a bidentate structure, R^{56};

and,

R^{5B} and R^{6B} are both absent;

and the compounds have the following formula:



(23)

In one embodiment:

Q^2 is =O;

Q^4 is =O;

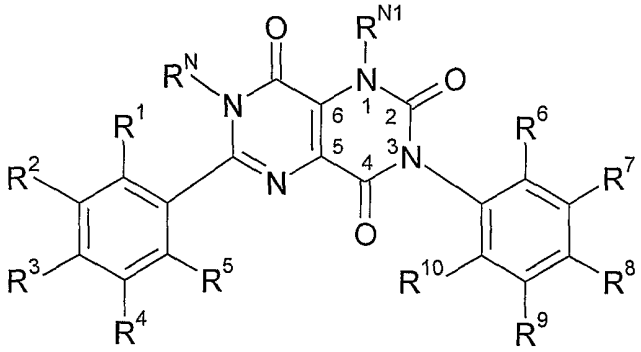
α is a double bond;

β is a single bond;

R^{5A} and R^{6A}, together form a bidentate structure, R^{56}; and,

R^{5B} and R^{6B} are both absent;

and the compounds the following formula:



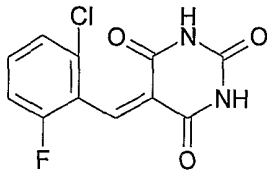
(24)

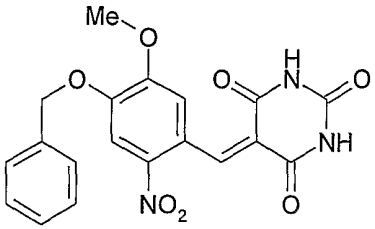
In the above formulae, R^{N1}, R^{N2}, R^{N3}, R^{N4}, R^N and R^C are independently nitrogen and carbon substituents, respectively, and are as defined above.

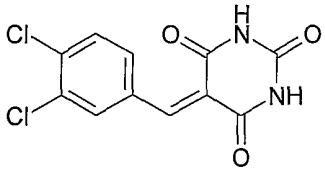
In the above formulae, R^1 through R^5 and R^6 through R^{10} are independently phenyl substituents, as defined above for R^1 through R^5.

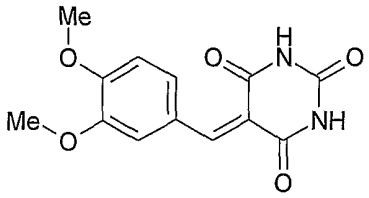
Examples of Specific Embodiments

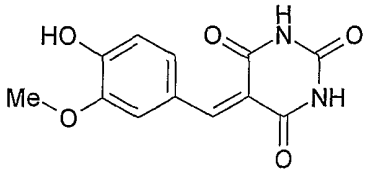
Some individual embodiments of the present invention include the following compounds:

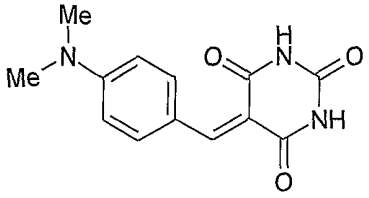
(1)  PX069119

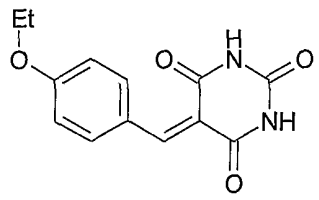
(2)  PX069153

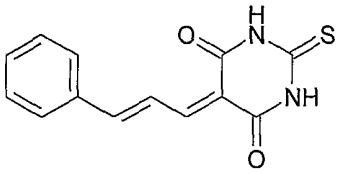
(3)  PX072002

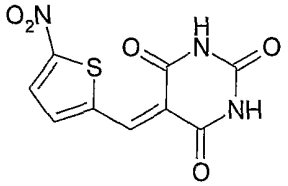
(4)  PX072004

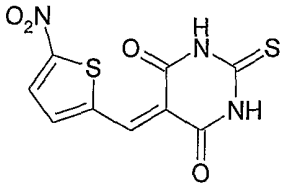
(5)  PX072008

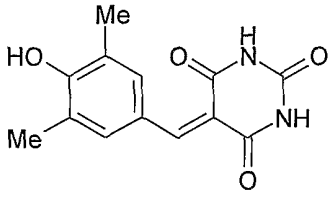
(6)  PX072009

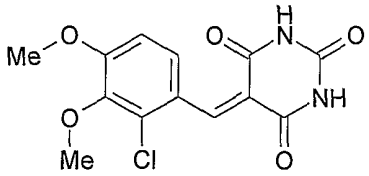
(7)  PX072012

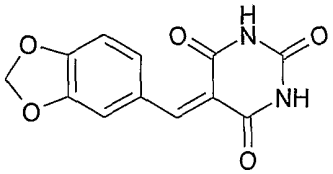
(8)  PX072015

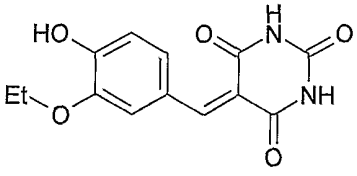
(9)  PX074037

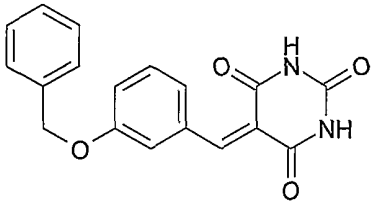
(10)  PX074038

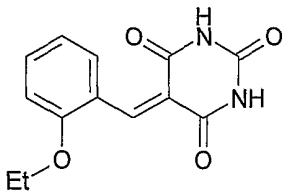
(11)  PX074100

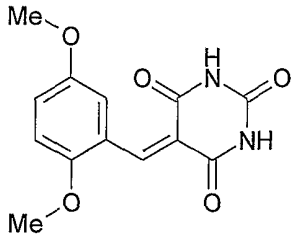
(12)  PX074728

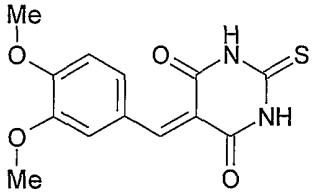
(13)  PX075240

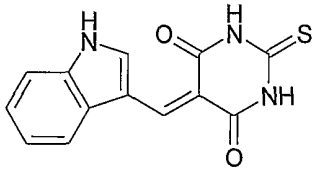
(14)  PX075244

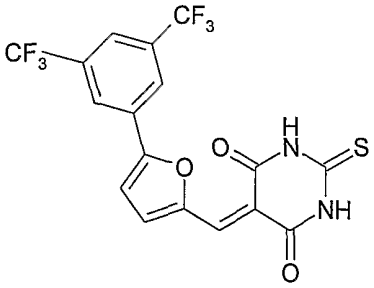
(15)  PX075245

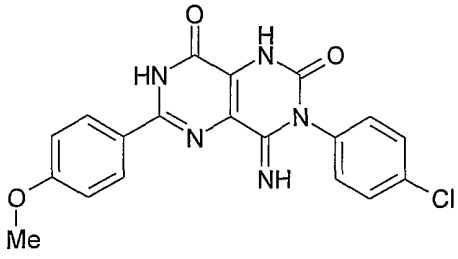
(16)  PX075248

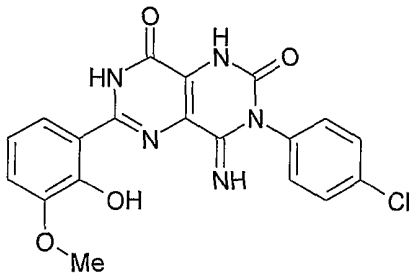
(17)  PX075257

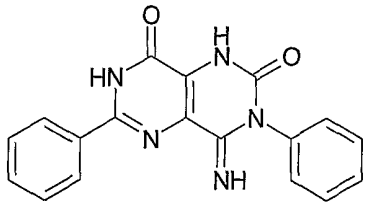
(18)  PX075262

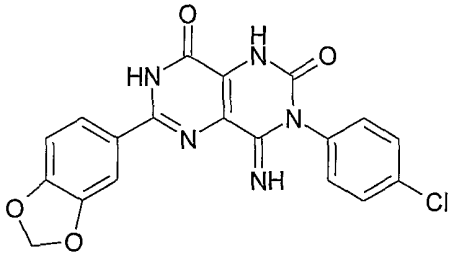
(19)  PX075276

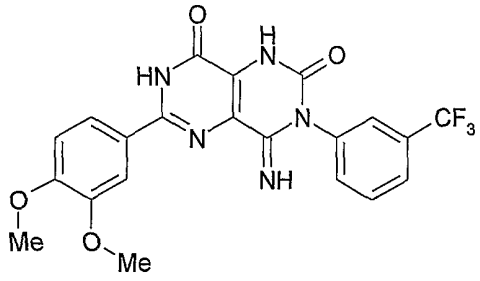
(20)  PX075367

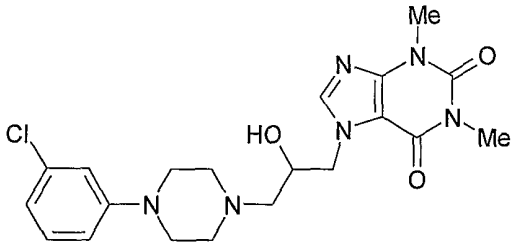
(21)  PX081770

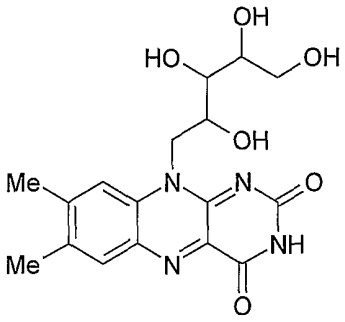
(22)  PX081958

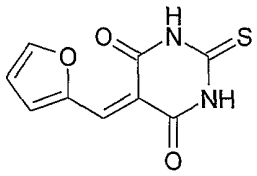
(23)  PX082132

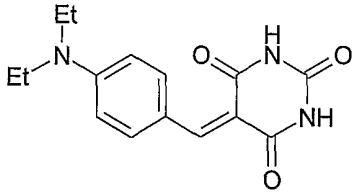
(24)  PX082202

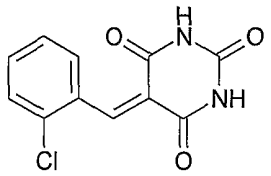
(25)  PX082229

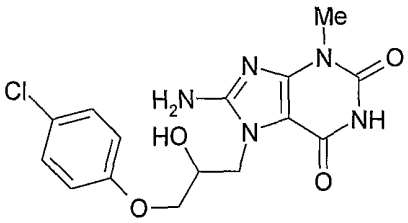
(26)  PX082796

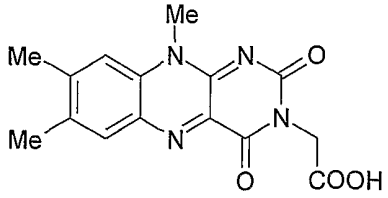
(27)  PX083033

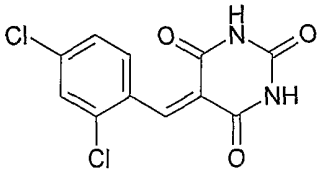
(28)  PX083634

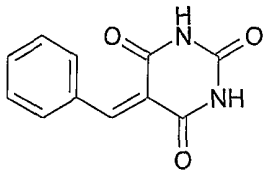
(29)  PX083675

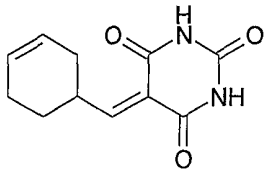
(30)  PX083677

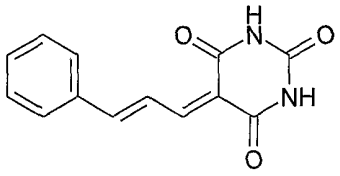
(31)  PX084819

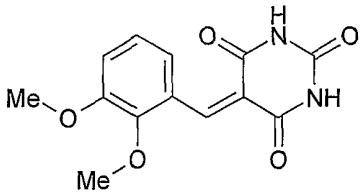
(32)  PX088992

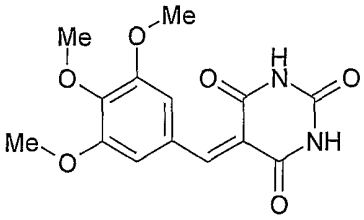
(33)  PX089367

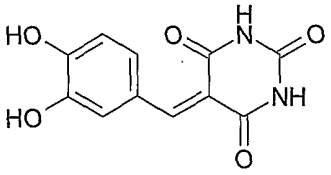
(34)  PX089368

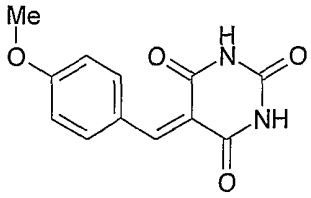
(35)  PX089369

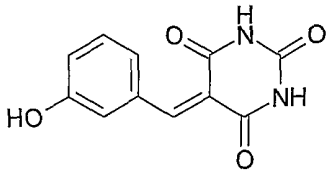
(36)  PX089370

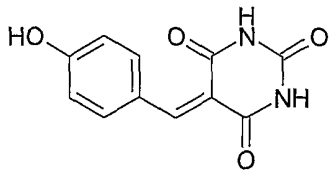
(37)  PX089371

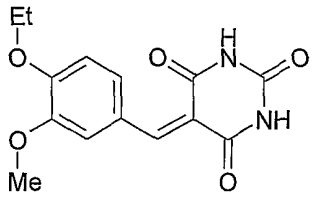
(38)  PX089372

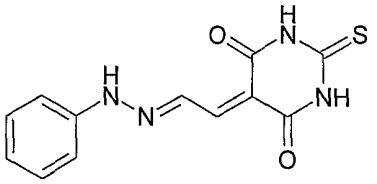
(39)  PX089374

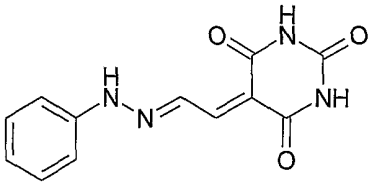
(40)  PX089375

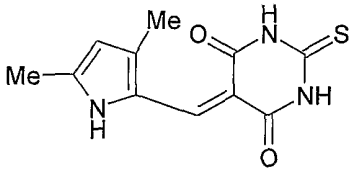
(41)  PX089376

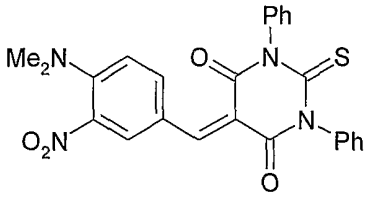
(42)  PX089377

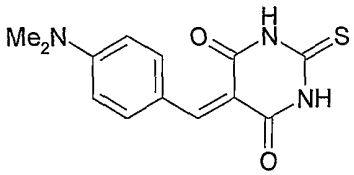
(43)  PX089378

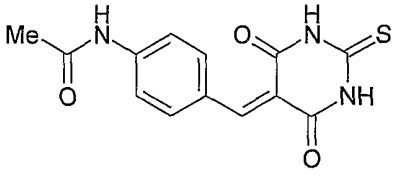
(44)  PX089619

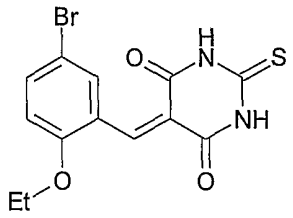
(45)  PX089620

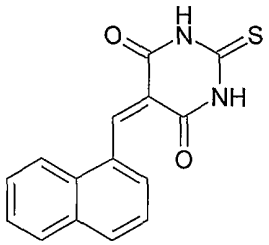
(46)  PX089624

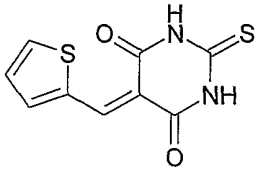
(47)  PX089626

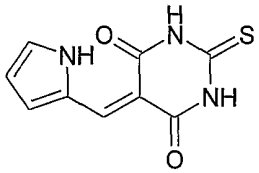
(48)  PX089631

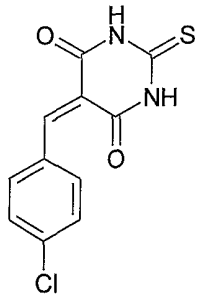
(49)  PX089632

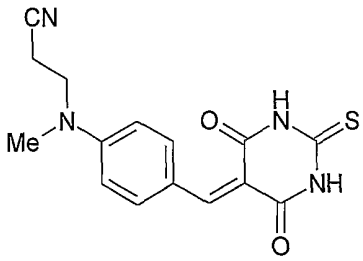
(50)  PX089633

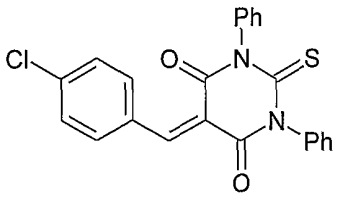
(51)  PX089635

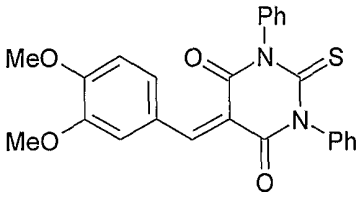
(52)  PX089638

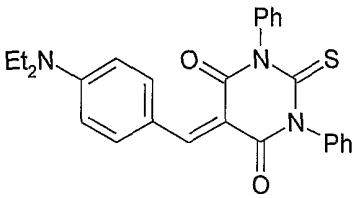
(53)  PX089639

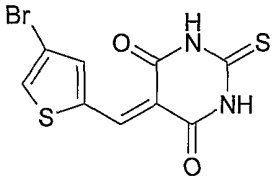
(54)  PX089640

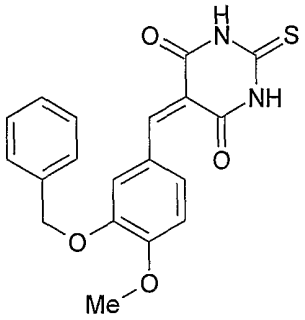
(55)  PX089643

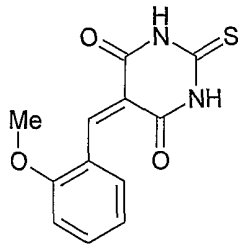
(56)  PX089645

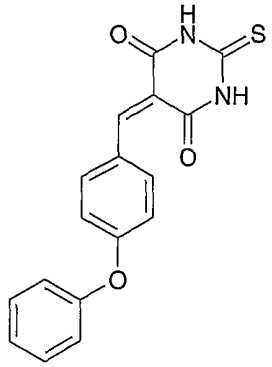
(57)  PX089646

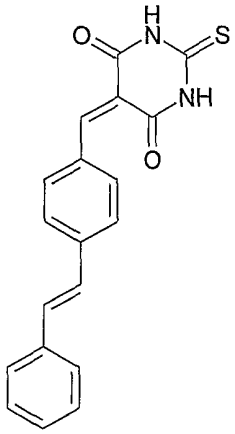
(58)  PX089647

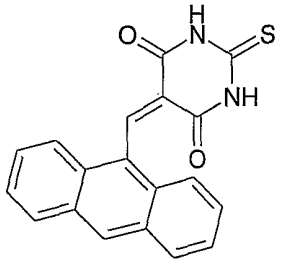
(59)  PX089648

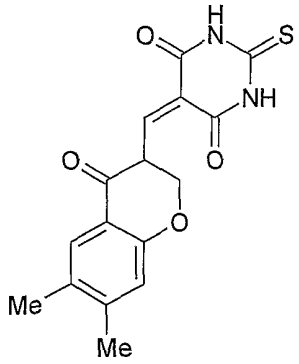
(60)  PX105990

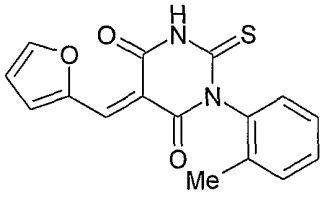
(61)  PX105993

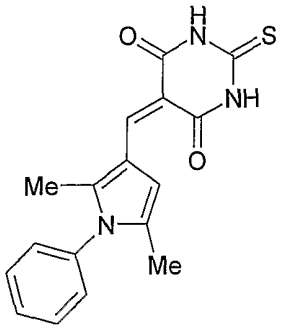
(62)  PX106021

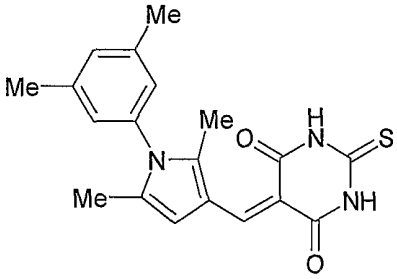
(63)  PX106027

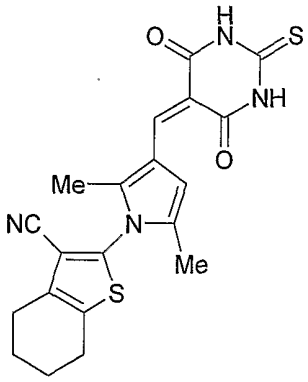
(64)  PX106031

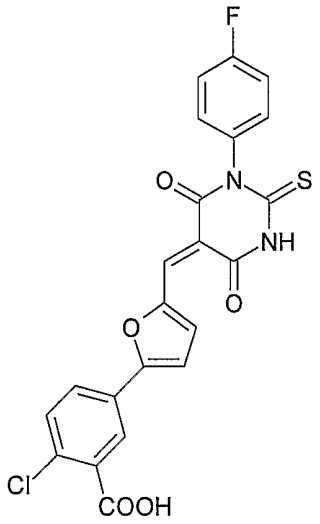
(65)  PX106036

(66)  PX106130

(67)  PX106151

(68)  PX106155

(69)  PX106174

(70) 

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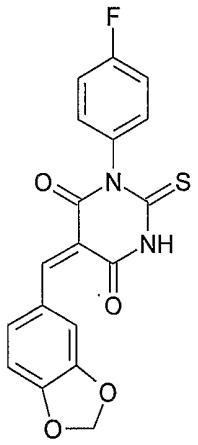
(71) 

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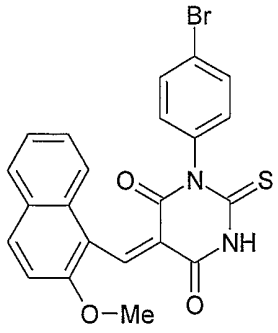
(72) 

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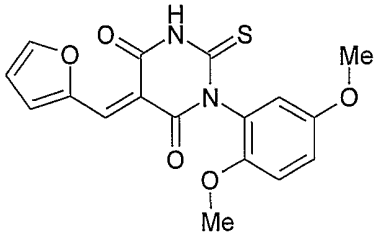
(73) 

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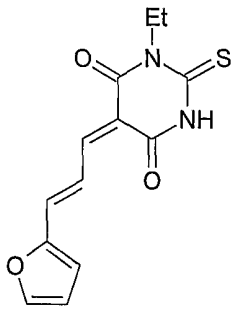
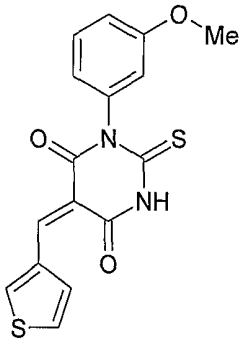
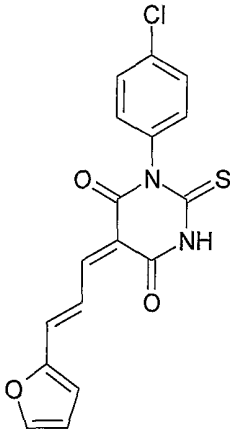
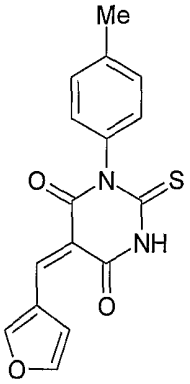
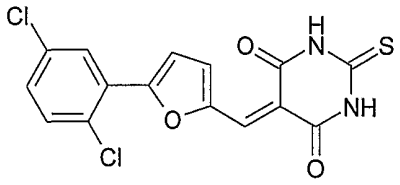
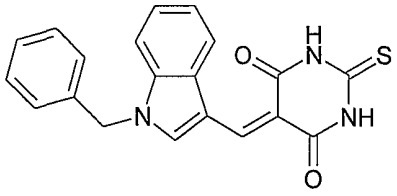
(74)  PX106281

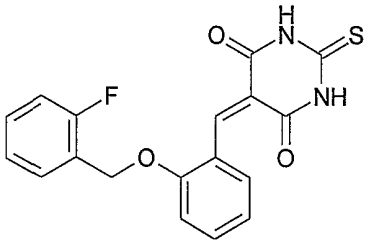
(75)  PX106287

(76)  PX106291

(77)  PX106297

(78)  PX106326

(79)  PX106341

(80)  PX106343

Substituents

The term "substituent" is used herein in the conventional sense and refers to a chemical moiety which is covalently attached to, appended to, or if appropriate, fused to, a parent group. A wide variety of substituents are well known, and methods for their formation and introduction into a variety of parent groups are also well known. Examples of substituents include, but are not limited to, the following:

Hydrogen: -H. Note that if the substituent at a particular position is hydrogen, it may be convenient to refer to the compound as being "unsubstituted" at this position.

Halo: -F, -Cl, -Br, and -I.

Hydroxy: -OH.

Ether: -OR, wherein R is an ether substituent, for example, a C_{1-7}alkyl group (resulting in a C_{1-7}alkoxy group, discussed below), a C_{3-20}heterocyclyl group (resulting in a C_{3-20}hetercyclyloxy group), or a C_{5-20}aryl group (resulting in a C_{5-20}aryloxy group), preferably a C_{1-7}alkyl group.

C_{1-7}alkoxy: -OR, wherein R is a C_{1-7}alkyl group. Examples of C_{1-7}alkoxy groups include, but are not limited to, $-OCH_3$ (methoxy), $-OCH_2CH_3$ (ethoxy) and $-OC(CH_3)_3$ (tert-butoxy).

Oxo (keto): =O.

Imino: =NR, wherein R is an imino substituent, for example, for example, hydrogen, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably H or a C_{1-7}alkyl group.

Formyl (carbaldehyde): $-C(=O)H$.

Acyl (keto): $-C(=O)R$, wherein R is an acyl substituent, for example, a C_{1-7}alkyl group (also referred to as C_{1-7}alkylacyl), a C_{3-20}heterocyclyl group (also referred to as C_{3-20}heterocyclylacyl), or a C_{5-20}aryl group (also referred to as C_{5-20}arylacyl), preferably a C_{1-7}alkyl group. Examples of acyl groups include, but are not limited to, $-C(=O)CH_3$ (acetyl), $-C(=O)CH_2CH_3$ (propionyl), $-C(=O)C(CH_3)_3$ (butyryl), and $-C(=O)Ph$ (benzoyl).

Carboxy (carboxylic acid): $-C(=O)OH$.

Carboxylate (carboxylic acid ester): $-C(=O)OR$, wherein R is an ester substituent, for example, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7}alkyl group. Examples of carboxylate groups include, but are not limited to, $-COOCH_3$, $-COOCH_2CH_3$, and $-COOC(CH_3)_3$.

Acyloxy (reverse ester): -OC(=O)R, wherein R is an acyloxy substituent, for example, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7}alkyl group. Examples of acyloxy groups include, but are not limited to, $-OC(=O)CH_3$ (acetoxy), $-OC(=O)CH_2CH_3$, and $-OC(=O)C(CH_3)_3$.

Amido (carbamoyl, carbamyl, aminocarbonyl): $-C(=O)NR^1R^2$, wherein R^1 and R^2 are independently amino substituents, as defined for amino groups. Examples of amido groups include, but are not limited to, $-C(=O)NH_2$, $-C(=O)NHCH_3$, $-C(=O)NH(CH_3)_2$, and $-C(=O)NHCH_2CH_3$.

Acylamido (acylamino): $-NR^1C(=O)R^2$, wherein R^1 is an amide substituent, for example, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7}alkyl group, and R^2 is an acyl substituent, for example, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7}alkyl group. Examples of acylamide groups include, but are not limited to, $-NHC(=O)CH_3$, $-NHC(=O)CH_2CH_3$, and -NHC(=O)Ph. R^1 and R^2 may together form a cyclic structure, as in, for example, succinimidyl and maleimidyl:

succinimidyl maleimidyl

Amino: $-NR^1R^2$, wherein R^1 and R^2 are independently amino substituents, for example, hydrogen, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably H or a C_{1-7}alkyl group. R^1 and R^2, taken together with the nitrogen atom may form a heterocyclic ring having from 4 to

8 ring atoms (for example, aziridinyl, azetidinyl, pyridyl). Examples of amino groups include, but are not limited to, $-NH_2$, $-NHCH_3$, $-NHCH(CH_3)_2$, $-N(CH_3)_2$, and $-N(CH_2CH_3)_2$.

Cyano (nitrile, carbonitrile): $-CN$.

Nitro: $-NO_2$.

Sulfhydryl (thiol, mercapto): $-SH$.

Thioether: $-SR$, wherein R is a thioether substituent, for example, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7}alkyl group (also referred to herein as thioC_{1-7}alkyl). Examples of thioC_{1-7}alkyl groups include, but are not limited to, $-SCH_3$ and $-SCH_2CH_3$.

Sulfonamino: $-NR^1S(=O)_2R$, wherein R^1 is an amino substituent, as defined for amino groups, and R is a sulfonamino substituent, for example, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7}alkyl group. Examples of sulfonamino groups include, but are not limited to, $-NHS(=O)_2CH_3$ and $-N(CH_3)S(=O)_2C_6H_5$.

Sulfinamino: $-NR^1S(=O)R$, wherein R^1 is an amino substituent, as defined for amino groups, and R is a sulfinamino substituent, for example, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7}alkyl group. Examples of sulfinamino groups include, but are not limited to, $-NHS(=O)CH_3$ and $-N(CH_3)S(=O)C_6H_5$.

Sulfamyl: $-S(=O)NR^1R^2$, wherein R^1 and R^2 are independently amino substituents, as defined for amino groups. Examples of sulfamyl groups include, but are not limited to, $-S(=O)NH_2$ and $-S(=O)N(CH_3)_2$.

Sulfonamido: $-S(=O)_2NR^1R^2$, wherein R^1 and R^2 are independently amino substituents, as defined for amino groups. Examples of sulfonamido groups include, but are not limited to, $-S(=O)_2NH_2$ and $-S(=O)_2N(CH_3)_2$.

C_{1-7}alkyl: The term "C_{1-7}alkyl," as used herein, pertains to monovalent alkyl groups having from 1 to 7 carbon atoms, which may be aliphatic or alicyclic, or a combination thereof, and which may be saturated, partially unsaturated, or fully unsaturated.

The term "aliphatic," as used herein, pertains to groups which are linear or branched, but not cyclic. The term "alicyclic," as used herein, pertains to groups which have one ring, or two or more rings (e.g., spiro, fused, bridged), but which are not aromatic. The term "saturated," as used herein, pertains to groups which do not have any carbon-carbon double bonds or carbon-carbon triple bonds. The term "unsaturated," as used herein, pertains to groups which have at least one carbon-carbon double bond or carbon-carbon triple bond.

Examples of saturated linear C_{1-7}alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, n-butyl, and n-pentyl (amyl).

Examples of saturated branched C_{1-7}alkyl groups include, but are not limited to, iso-propyl, iso-butyl, sec-butyl, tert-butyl, and neo-pentyl.

Examples of saturated alicylic (carbocyclic) C_{1-7}alkyl groups (also referred to as "C_{3-7}cycloalkyl" groups) include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl, as well as groups which comprise such

groups, including, but not limited to, cyclopropylmethyl and cyclohexylmethyl.

Examples of unsaturated C_{1-7}alkyl groups which have one or more carbon-carbon double bonds (also referred to as "C_{2-7}alkenyl" groups) include, but are not limited to, ethenyl (vinyl) and 2-propenyl (allyl).

Examples of unsaturated C_{1-7}alkyl groups which have one or more carbon-carbon triple bonds (also referred to as "C_{2-7}alkynyl" groups) include, but are not limited to, ethynyl (ethinyl) and 2-propynyl (propargyl).

Examples of unsaturated alicylic (carbocyclic) C_{1-7}alkyl groups which have one or more carbon-carbon double bonds (also referred to as "C_{3-7}cycloalkenyl" groups) include, but are not limited to, cyclopropenyl and cyclohexenyl, as well as groups which comprise such groups, including but not limited to cyclopropenylmethyl and cyclohexenylmethyl.

C_{3-20}heterocyclyl: The term "C_{3-20}heterocyclyl," as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from a ring atom of an alicyclic (i.e., non-aromatic cyclic) compound, said compound having one ring, or two or more rings (e.g., spiro, fused, bridged), having from 3 to 20 ring atoms, of which from 1 to 10 are ring heteroatoms, including, but not limited to, nitrogen, oxygen, and sulfur. Preferably, each ring has from 3 to 7 ring atoms, of which from 1 to 4 are ring heteroatoms. "C_{3-20}" denotes ring atoms, whether carbon atoms or heteroatoms.

Examples of monocyclic C_{3-20}heterocyclyl groups include, but are not limited to, those derived from:

N_1: aziridine (C_3), azetidine (C_4), pyrrolidine (tetrahydropyrrole) (C_5), pyrroline (e.g., 3-pyrroline, 2,5-dihydropyrrole) (C_5), 2H-pyrrole or 3H-pyrrole (isopyrrole, isoazole) (C_5), piperidine (C_6), dihydropyridine (C_6), tetrahydropyridine (C_6), azepine (C_7);

O_1: oxirane (C_3), oxetane (C_4), oxolane (tetrahydrofuran) (C_5), oxole (dihydrofuran) (C_5), oxane (tetrahydropyran) (C_6), dihydropyran (C_6), pyran (C_6), oxepin (C_7);

S_1: thiirane (C_3), thietane (C_4), thiolane (tetrahydrothiophene) (C_5), thiane (tetrahydrothiopyran) (C_6), thiepane (C_7);

O_2: dioxolane (C_5), dioxane (C_6), and dioxepane (C_7);

O_3: trioxane (C_6);

N_2: imidazolidine (C_5), pyrazolidine (diazolidine) (C_5), imidazoline (C_5), pyrazoline (dihydropyrazole) (C_5), piperazine (C_6);

N_1O_1: tetrahydrooxazole (C_5), dihydrooxazole (C_5), tetrahydroisoxazole (C_5), dihydroisoxazole (C_5), morpholine (C_6), tetrahydrooxazine (C_6), dihydrooxazine (C_6), oxazine (C_6);

N_1S_1: thiazoline (C_5), thiazolidine (C_5), thiomorpholine (C_6);

N_2O_1: oxadiazine (C_6);

O_1S_1: oxathiole (C_5) and oxathiane (thioxane) (C_6); and,

$N_1O_1S_1$: oxathiazine (C_6).

C_{5-20}aryl: The term "C_{5-20}aryl," as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from a ring atom of an aromatic compound, said compound having one ring, or two or more fused rings, and having from 5 to 20 ring atoms. The ring atoms may be all carbon atoms, as in "carboaryl groups," or may include one or more heteroatoms (including but not limited to oxygen, nitrogen, and sulfur), as in "heteroaryl groups." In the latter case, the group may conveniently be referred to as a "C_{5-20}heteroaryl" group, wherein "C_{5-20}" denotes ring atoms, whether carbon atoms or heteroatoms. Preferably, each ring has from 3 to 7 ring atoms, of which from 0 to 4 are ring heteroatoms.

Examples of carboaryl groups include, but are not limited to, those derived from benzene (i.e., phenyl) (C_6), naphthalene (C_{10}), azulene (C_{10}), anthracene (C_{14}), phenanthrene (C_{14}), naphthacene (C_{18}), and pyrene (C_{16}).

Examples of aryl groups which comprise fused rings, at least one of which is an aromatic ring, include, but are not limited to, groups derived from indene (C_9), isoindene (C_9), and fluorene (C_{13}).

Examples of monocyclic heteroaryl groups include, but are not limited to, those derived from:

N_1: pyrrole (azole) (C_5), pyridine (azine) (C_6);

O_1: furan (oxole) (C_5);

S_1: thiophene (thiole) (C_5);

N_1O_1: oxazole (C_5), isoxazole (C_5), isoxazine (C_6);

N_2O_1: oxadiazole (furazan) (C_5);

N_3O_1: oxatriazole (C_5);

N_1S_1: thiazole (C_5), isothiazole (C_5);

N_2: imidazole (1,3-diazole) (C_5), pyrazole (1,2-diazole) (C_5), pyridazine (1,2-diazine) (C_6), pyrimidine (1,3-diazine) (C_6) (e.g., cytosine, thymine, uracil), pyrazine (1,4-diazine) (C_6);

N_3: triazole (C_5), triazine (C_6); and,

N_4: tetrazole (C_5).

Examples of heterocyclic groups (some of which are also heteroaryl groups) which comprise fused rings, include, but are not limited to:

C_9heterocyclic groups (with 2 fused rings) derived from benzofuran (O_1), isobenzofuran (O_1), indole (N_1), isoindole (N_1), purine (N_4) (e.g., adenine, guanine), benzimidazole (N_2), benzoxazole (N_1O_1), benzisoxazole (N_1O_1), benzodioxole (O_2), benzofurazan (N_2O_1), benzotriazole (N_3), benzothiofuran (S_1), benzothiazole (N_1S_1), benzothiadiazole (N_2S);

C_{10}heterocyclic groups (with 2 fused rings) derived from benzodioxan (O_2), quinoline (N_1), isoquinoline (N_1), benzoxazine (N_1O_1), benzodiazine (N_2), pyridopyridine (N_2), quinoxaline (N_2), quinazoline (N_2);

C_{13}heterocyclic groups (with 3 fused rings) derived from carbazole (N_1), dibenzofuran (O_1), dibenzothiophene (S_1); and,

C_{14}heterocyclic groups (with 3 fused rings) derived from acridine (N_1), xanthene (O_1), phenoxathiin (O_1S_1), phenazine (N_2), phenoxazine (N_1O_1), phenothiazine (N_1S_1), thianthrene (S_2), phenanthridine (N_1), phenanthroline (N_2), phenazine (N_2).

Heterocyclic groups (including heteroaryl groups) which have a nitrogen ring atom in the form of an -NH- group may be N-substituted, that is, as -NR-. For example, pyrrole may be N-methyl substituted, to give N-methypyrrole. Examples

of N-substitutents include, but are not limited to C_{1-7}alkyl, C_{3-20}heterocyclyl, C_{5-20}aryl, and acyl groups.

Heterocyclic groups (including heteroaryl groups) which have a nitrogen ring atom in the form of an -N= group may be substituted in the form of an N-oxide, that is, as $-N(\rightarrow O)=$ (also denoted $-N^{+}(\rightarrow O^{-})=$). For example, quinoline may be substituted to give quinoline N-oxide; pyridine to give pyridine N-oxide; benzofurazan to give benzofurazan N-oxide (also known as benzofuroxan).

Cyclic groups may additionally bear one or more oxo (=O) groups on ring carbon atoms. Monocyclic examples of such groups include, but are not limited to, those derived from:

C_5: cyclopentanone, cyclopentenone, cyclopentadienone;
C_6: cyclohexanone, cyclohexenone, cyclohexadienone;
O_1: furanone (C_5), pyrone (C_6);
N_1: pyrrolidone (pyrrolidinone) (C_5), piperidinone (piperidone) (C_6), piperidinedione (C_6);
N_2: imidazolidone (imidazolidinone) (C_5), pyrazolone (pyrazolinone) (C_5), piperazinone (C_6), piperazinedione (C_6), pyridazinone (C_6), pyrimidinone (C_6) (e.g., cytosine), pyrimidinedione (C_6) (e.g., thymine, uracil), barbituric acid (C_6);
N_1S_1: thiazolone (C_5), isothiazolone (C_5);
N_1O_1: oxazolinone (C_5).

Polycyclic examples of such groups include, but are not limited to, those derived from:

C_9: indenedione;
N_1: oxindole (C_9);
O_1: benzopyrone (e.g., coumarin, isocoumarin, chromone) (C_{10});
N_1O_1: benzoxazolinone (C_9), benzoxazolinone (C_{10});

N_2: quinazolinedione (C_{10});

N_4: purinone (C_9) (e.g., guanine).

Still more examples of cyclic groups which bear one or more oxo (=O) groups on ring carbon atoms include, but are not limited to, those derived from:

cyclic anhydrides (-C(=O)-O-C(=O)- in a ring), including but not limited to maleic anhydride (C_5), succinic anhydride (C_5), and glutaric anhydride (C_6);

cyclic carbonates (-O-C(=O)-O- in a ring), such as ethylene carbonate (C_5) and 1,2-propylene carbonate (C_5);

imides (-C(=O)-NR-C(=O)- in a ring), including but not limited to, succinimide (C_5), maleimide (C_5), phthalimide, and glutarimide (C_6);

lactones (cyclic esters, -O-C(=O)- in a ring), including, but not limited to, β-propiolactone, γ-butyrolactone, δ-valerolactone (2-piperidone), and ε-caprolactone;

lactams (cyclic amides, -NR-C(=O)- in a ring), including, but not limited to, β-propiolactam (C_4), γ-butyrolactam (2-pyrrolidone) (C_5), δ-valerolactam (C_6), and ε-caprolactam (C_7);

cyclic carbamates (-O-C(=O)-NR- in a ring), such as 2-oxazolidone (C_5);

cyclic ureas (-NR-C(=O)-NR- in a ring), such as 2-imidazolidone (C_5) and pyrimidine-2,4-dione (e.g., thymine, uracil) (C_6).

The above C_{1-7}alkyl, C_{3-20}heterocyclyl, and C_{5-20}aryl groups, whether alone or part of another substituent, may themselves optionally be substituted with one or more groups selected from themselves and the preceding substituents (e.g., halo, hydroxy, carboxylic acid) to give substituted C_{1-7}alkyl groups, substituted C_{3-20}heterocyclyl groups, and substituted C_{5-20}aryl groups, respectively. Unless otherwise specified,

a reference to a such a group is also a reference to the corresponding substituted group. Specific examples of such substituted groups are discussed below.

C_{1-7}haloalkyl group: The term "C_{1-7}haloalkyl group," as used herein, pertains to a C_{1-7}alkyl group in which at least one hydrogen atom has been replaced with a halogen atom (e.g., F, Cl, Br, I). If more than one hydrogen atom has been replaced with a halogen atom, the halogen atoms may independently be the same or different. Every hydrogen atom may be replaced with a halogen atom, in which case the group may conveniently be referred to as a C_{1-7}perhaloalkyl group." Examples of C_{1-7}haloalkyl groups include, but are not limited to, $-CF_3$, $-CHF_2$, $-CH_2F$, $-CCl_3$, $-CBr_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, and $-CH_2CF_3$.

C_{1-7}haloalkoxy: -OR, wherein R is a C_{1-7}haloalkyl group. Examples of C_{1-7}haloalkoxy groups include, but are not limited to, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, $-OCCl_3$, $-OCBr_3$, $-OCH_2CH_2F$, $-OCH_2CHF_2$, and $-OCH_2CF_3$.

C_{1-7}hydroxyalkyl: The term "C_{1-7}hydroxyalkyl group," as used herein, pertains to a C_{1-7}alkyl group in which at least one hydrogen atom has been replaced with a hydroxy group. Examples of C_{1-7}hydroxyalkyl groups include, but are not limited to, $-CH_2OH$, $-CH_2CH_2OH$, and $-CH(OH)CH_2OH$.

C_{1-7}carboxyalkyl: The term "C_{1-7}carboxyalkyl group," as used herein, pertains to a C_{1-7}alkyl group in which at least one hydrogen atom has been replaced with a carboxy group. Examples of C_{1-7}carboxyalkyl groups include, but are not limited to, $-CH_2COOH$ and $-CH_2CH_2COOH$.

C_{1-7}aminoalkyl: The term "C_{1-7}aminoalkyl group," as used herein, pertains to a C_{1-7}alkyl group in which at least one

hydrogen atom has been replaced with an amino group. Examples of C_{1-7}aminoalkyl groups include, but are not limited to, $-CH_2NH_2$, $-CH_2CH_2NH_2$, and $-CH_2CH_2N(CH_3)_2$.

C_{1-7}alkyl-C_{5-20}aryl: The term "C_{1-7}alkyl-C_{5-20}aryl," as used herein, describes certain C_{5-20}aryl groups which have been substituted with a C_{1-7}alkyl group. Examples of such groups include, but are not limited to, tolyl, xylyl, mesityl, and cumenyl.

C_{1-7}alkyl-C_{5-20}aryloxy: The term "C_{1-7}alkyl-C_{5-20}aryloxy," as used herein, describes certain C_{5-20}aryloxy groups which have been substituted with a C_{1-7}alkyl group. Examples of such groups include, but are not limited to, tolyloxy, xylyloxy, mesityloxy, and cumenyloxy.

C_{5-20}aryl-C_{1-7}alkyl: The term "C_{5-20}aryl-C_{1-7}alkyl," as used herein, describers certain C_{1-7}alkyl groups which have been substituted with a C_{5-20}aryl group. Examples of such groups include, but are not limited to, benzyl, tolylmethyl, phenylethyl, and triphenylmethyl (trityl).

C_{5-20}aryl-C_{1-7}alkoxy: The term "C_{5-20}aryl-C_{1-7}alkoxy," as used herein, describes certain C_{1-7}alkoxy groups which have been substituted with a C_{5-20}aryl group. Examples of such groups include, but are not limited to, benzyloxy, tolylmethoxy, and phenylethoxy.

C_{5-20}haloaryl: The term "C_{5-20}haloaryl," as used herein, describes certain C_{5-20}aryl groups which have been substituted with one or more halo groups. Examples of such groups include, but are not limited to, halophenyl (e.g., fluorophenyl, chlorophenyl, bromophenyl, or iodophenyl, whether ortho-, meta-, or para-substituted), dihalophenyl, trihalophenyl, tetrahalophenyl, and pentahalophenyl.

Included in the above are the well known ionic, salt, solvate, and protected forms of these substituents. For example, a reference to carboxylic acid (-COOH) also includes the anionic (carboxylate) form ($-COO^-$), a salt or solvate thereof, as well as conventional protected forms. Similarly, a reference to an amino group includes the protonated form ($-N^+HR^1R^2$), a salt or solvate of the amino group, for example, a hydrochloride salt, as well as conventional protected forms of an amino group. Similarly, a reference to a hydroxyl group also includes the anionic form ($-O^-$), a salt or solvate thereof, as well as conventional protected forms of a hydroxyl group.

Acronyms

For convenience, many chemical moieties are represented herein using well known abbreviations, including but not limited to, methyl (Me), ethyl (Et), n-propyl (nPr), iso-propyl (iPr), n-butyl (nBu), tert-butyl (tBu), n-hexyl (nHex), cyclohexyl (cHex), phenyl (Ph), biphenyl (biPh), benzyl (Bn), naphthyl (naph), methoxy (MeO), ethoxy (EtO), benzoyl (Bz), and acetyl (Ac).

For convenience, many chemical compounds are represented herein using well known abbreviations, including but not limited to, methanol (MeOH), ethanol (EtOH), iso-propanol (i-PrOH), methyl ethyl ketone (MEK), acetic acid (AcOH), dichloromethane (methylene chloride, DCM), trifluoroacetic acid (TFA), dimethylformamide (DMF), and tetrahydrofuran (THF).

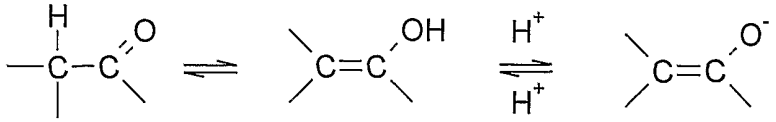
Isomers, Salts, Solvates, Protected Forms, and Prodrugs

A certain compound may exist in one or more particular geometric, optical, enantiomeric, diasteriomeric, epimeric, stereoisomeric, tautomeric, conformational, or anomeric forms, including but not limited to, cis- and trans-forms; E- and Z-forms; c-, t-, and r- forms; endo- and exo-forms; R-, S-, and meso-forms; D- and L-forms; (+) and (-) forms; keto-, enol-, and enolate-forms; syn- and anti-forms; synclinal- and anticlinal-forms; α- and β-forms; axial and equatorial forms; boat-, chair-, twist-, envelope-, and halfchair-forms; and combinations thereof, hereinafter collectively referred to as "isomers" (or "isomeric forms").

Note that, except as discussed below for tautomeric forms, specifically excluded from the term "isomers," as used herein, are structural (or constitutional) isomers (i.e., isomers which differ in the connections between atoms rather than merely by the position of atoms in space). For example, a reference to a methoxy group, $-OCH_3$, is not to be construed as a reference to its structural isomer, a hydroxymethyl group, $-CH_2OH$. Similarly, a reference to ortho-chlorophenyl is not to be construed as a reference to its structural isomer, meta-chlorophenyl. However, a reference to a class of structures may well include structurally isomeric forms falling within that class (e.g., C_{1-7}alkyl includes n-propyl and iso-propyl; butyl includes n-, iso-, sec-, and tert-butyl; methoxyphenyl includes ortho-, meta-, and para-methoxyphenyl).

The above exclusion does not pertain to tautomeric forms, for example, keto-, enol-, and enolate-forms, as in, for example, the following tautomeric pairs: keto/enol (illustrated below), imine/enamine, amide/imino alcohol,

amidine/amidine, nitroso/oxime, thioketone/enethiol, N-nitroso/hyroxyazo, and nitro/aci-nitro.



Note that specifically included in the term "isomer" are compounds with one or more isotopic substitutions. For example, H may be in any isotopic form, including ^{1}H, ^{2}H (D), and ^{3}H (T); C may be in any isotopic form, including ^{12}C, ^{13}C, and ^{14}C; O may be in any isotopic form, including ^{16}O and ^{18}O; and the like.

Unless otherwise specified, a reference to a particular compound includes all such isomeric forms, including racemic and other mixtures thereof. Methods for the preparation (e.g., asymmetric synthesis) and separation (e.g., fractional crystallisation and chromatographic means) of such isomeric forms are either known in the art or are readily obtained by adapting the methods taught herein in a known manner.

Unless otherwise specified, a reference to a particular compound also includes ionic, salt, hydrate, and protected forms of thereof, for example, as discussed below.

It may be convenient or desirable to prepare, purify, and/or handle a corresponding salt of the active compound, for example, a pharmaceutically-acceptable salt. Examples of pharmaceutically acceptable salts are discussed in Berge et al., 1977, "Pharmaceutically Acceptable Salts," J. Pharm. Sci., Vol. 66, pp. 1-19.

For example, if the compound is anionic, or has a functional group which may be anionic (e.g., -COOH may be $-COO^{-}$), then

a salt may be formed with a suitable cation. Examples of suitable inorganic cations include, but are not limited to, alkali metal ions such as Na+ and K+, alkaline earth cations such as Ca^{2+} and Mg^{2+}, and other cations such as Al^{+3}. Examples of suitable organic cations include, but are not limited to, ammonium ion (i.e., NH_4^+) and substituted ammonium ions (e.g., NH_3R^+, $NH_2R_2^+$, NHR_3^+, NR_4^+). Examples of some suitable substituted ammonium ions are those derived from: ethylamine, diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine. An example of a common quaternary ammonium ion is $N(CH_3)_4^+$.

If the compound is cationic, or has a functional group which may be cationic (e.g., $-NH_2$ may be $-NH_3^+$), then a salt may be formed with a suitable anion. Examples of suitable inorganic anions include, but are not limited to, those derived from the following inorganic acids: hydrochloric, hydrobromic, hydroiodic, sulfuric, sulfurous, nitric, nitrous, phosphoric, and phosphorous. Examples of suitable organic anions include, but are not limited to, anions from the following organic acids: acetic, propionic, succinic, gycolic, stearic, lactic, malic, tartaric, citric, ascorbic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetyoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and valeric.

It may be convenient or desirable to prepare, purify, and/or handle a corresponding solvate of the active compound. The term "solvate" is used herein in the conventional sense to refer to a complex of solute (e.g., active compound, salt of active compound) and solvent. If the solvent is water, the solvate may be conveniently referred to as a hydrate, for example, a mono-hydrate, a di-hydrate, a tri-hydrate, etc.

It may be convenient or desirable to prepare, purify, and/or handle the active compound in a chemically protected form. The term "chemically protected form," as used herein, pertains to a compound in which one or more reactive functional groups are protected from undesirable chemical reactions, that is, are in the form of a protected or protecting group (also known as a masked or masking group). By protecting a reactive functional group, reactions involving other unprotected reactive functional groups can be performed, without affecting the protected group; the protecting group may be removed, usually in a subsequent step, without substantially affecting the remainder of the molecule. See, for example, Protective Groups in Organic Synthesis (T. Green and P. Wuts, Wiley, 1991).

For example, a hydroxy group may be protected as an ether (-OR) or an ester (-OC(=O)R), for example, as: a t-butyl ether; a benzyl, benzhydryl (diphenylmethyl), or trityl (triphenylmethyl) ether; a trimethylsilyl or t-butyldimethylsilyl ether; or an acetyl ester (-OC(=O)CH_3, -OAc).

For example, an aldehyde or ketone group may be protected as an acetal or ketal, respectively, in which the carbonyl group (>C=O) is converted to a diether (>C$(OR)_2$), by reaction with, for example, a primary alcohol. The aldehyde or ketone group is readily regenerated by hydrolysis using a large excess of water in the presence of acid.

For example, an amine group may be protected, for example, as an amide or a urethane, for example, as: a methyl amide (-NHCO-CH_3); a benzyloxy amide (-NHCO-$OCH_2C_6H_5$, -NH-Cbz); as a t-butoxy amide (-NHCO-$OC(CH_3)_3$, -NH-Boc); a 2-biphenyl-2-propoxy amide (-NHCO-$OC(CH_3)_2C_6H_4C_6H_5$, -NH-Bpoc), as a 9-fluorenylmethoxy amide (-NH-Fmoc), as a 6-nitroveratryloxy

amide (-NH-Nvoc), as a 2-trimethylsilylethyloxy amide (-NH-Teoc), as a 2,2,2-trichloroethyloxy amide (-NH-Troc), as an allyloxy amide (-NH-Alloc), as a 2(-phenylsulphonyl)ethyloxy amide (-NH-Psec); or, in suitable cases, as an N-oxide (>NO•).

For example, a carboxylic acid group may be protected as an ester or an amide, for example, as: a benzyl ester; a t-butyl ester; a methyl ester; or a methyl amide.

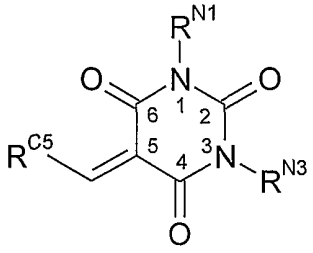
For example, a thiol group may be protected as a thioether (-SR), for example, as: a benzyl thioether; an acetamidomethyl ether ($-S-CH_2NHC(=O)CH_3$).

It may be convenient or desirable to prepare, purify, and/or handle the active compound in the form of a prodrug. The term "prodrug," as used herein, pertains to a compound which, when metabolised, yields the desired active compound. Typically, the prodrug is inactive, or less active than the active compound, but may provide advantageous handling, administration, or metabolic properties. For example, some prodrugs are esters of the active compound; during metabolysis, the ester group is cleaved to yield the active drug. Also, some prodrugs are activated enzymatically to yield the active compound, or a compound which, upon further chemical reaction, yields the active compound. For example, the prodrug may be a sugar derivative or other glycoside conjugate, or may be an amino acid ester derivative.

Synthesis

The compounds of the present invention may be prepared using well known methods, or by adapting well known methods in well known ways.

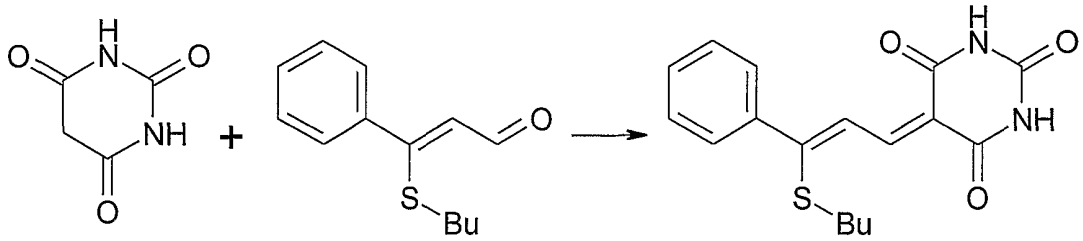
For example, compounds of the type:



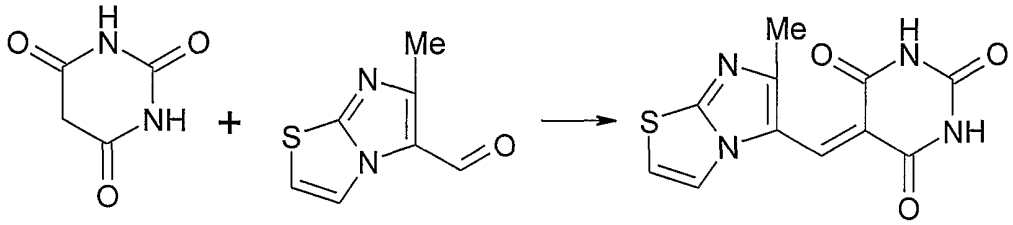
may be readily prepared by the acylation reaction of a parent ring system (e.g., barbituric acid) with an aldehyde, ketone, dinitrile, or other reactive species.

Many examples of such reactions have been reported in the chemical literature, including, but not limited to, the following:

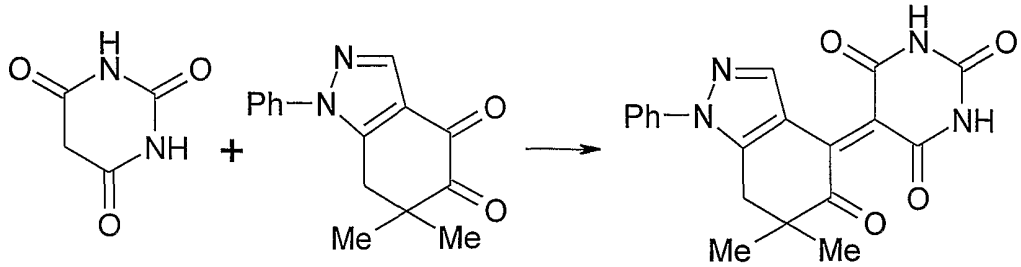
Scheme 1 - Das et al., 1996



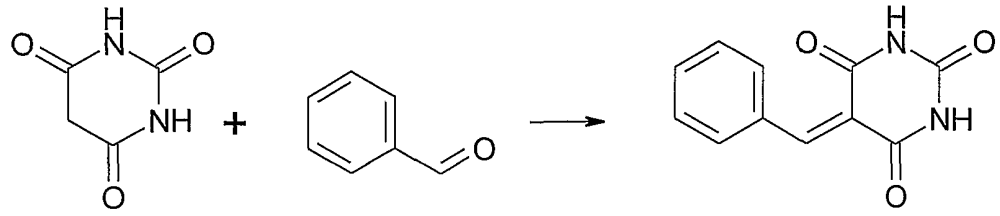
Scheme 2 - Andreani et al., 1996



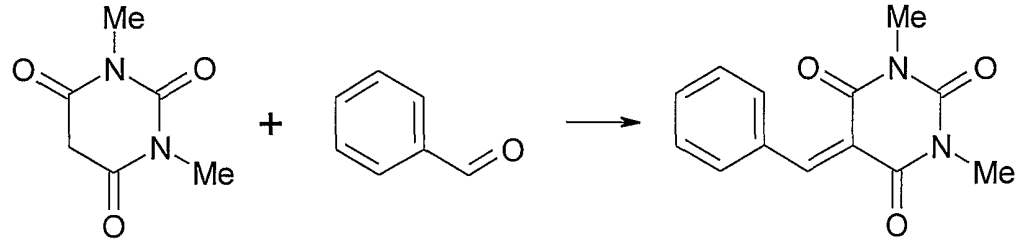
Scheme 3 - Strakov et al., 1996



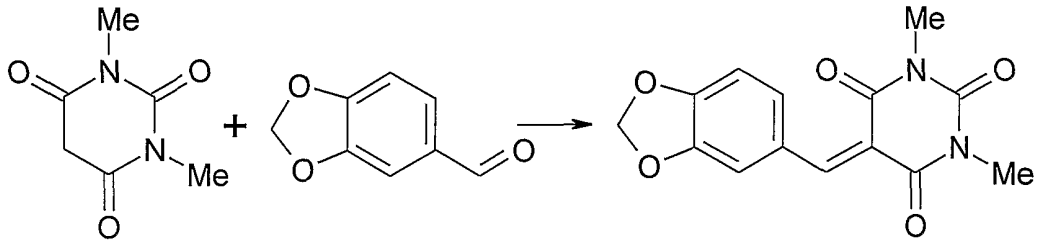
Scheme 4 - Cremlyn et al., 1992



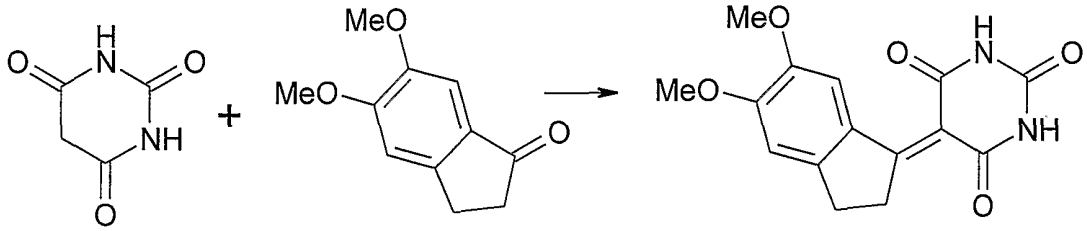
Scheme 5 - Rao et al., 1993



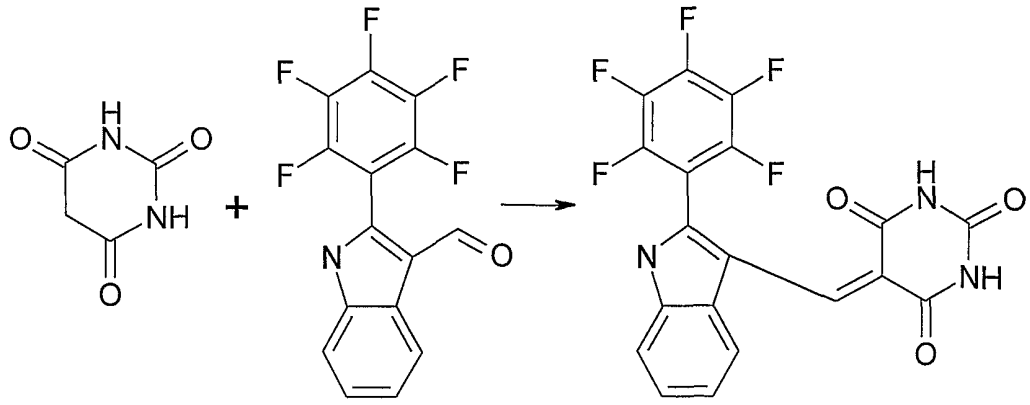
Scheme 6 - Figueroa-Villar et al., 1992



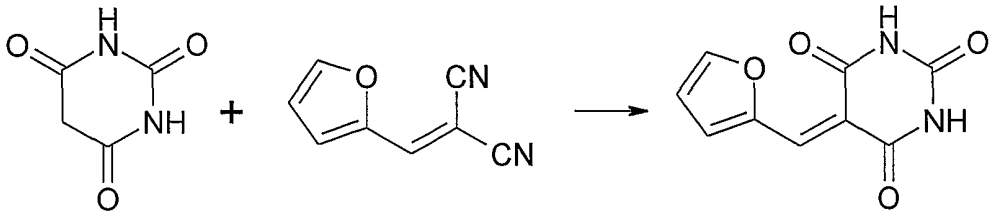
Scheme 7 - Chan et al., 1991



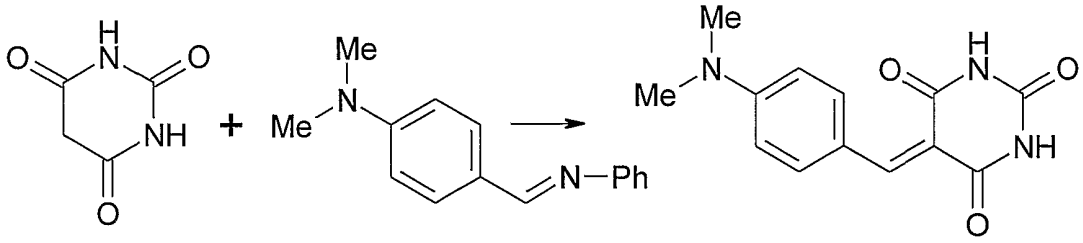
Scheme 8 - Joshi et al., 1990



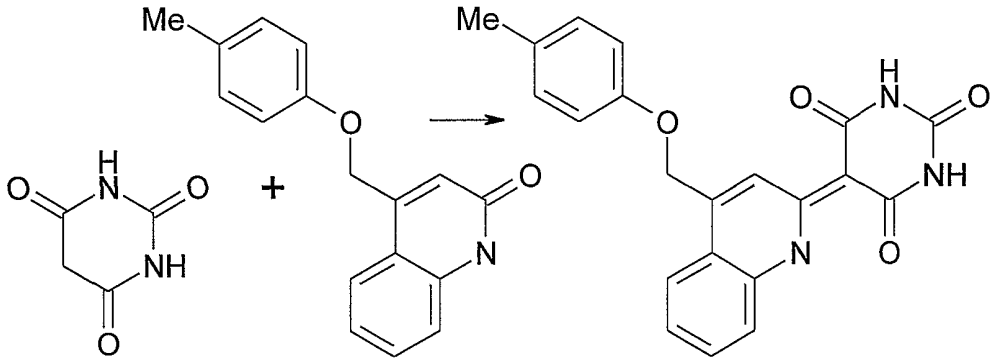
Scheme 9 - Abdel-Latif, 1991



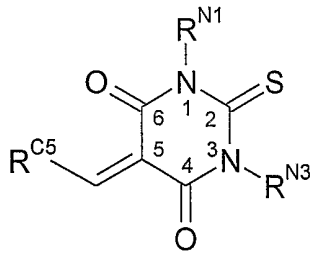
Scheme 10 - Hennig et al., 1992



Scheme 11 - Kulkarni et al., 1996



Compounds of the type:

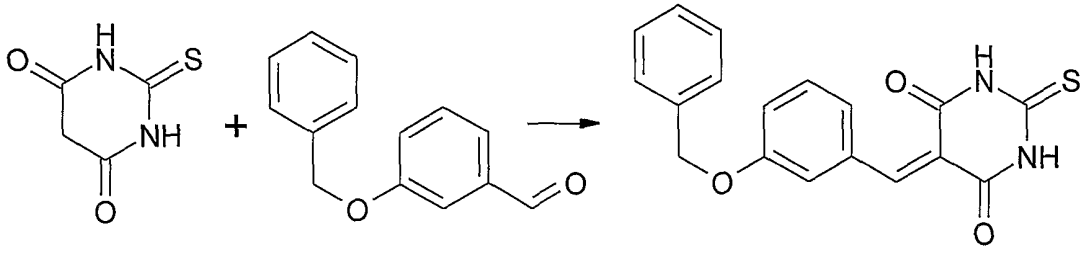


may be readily prepared using methods similar to those described above.

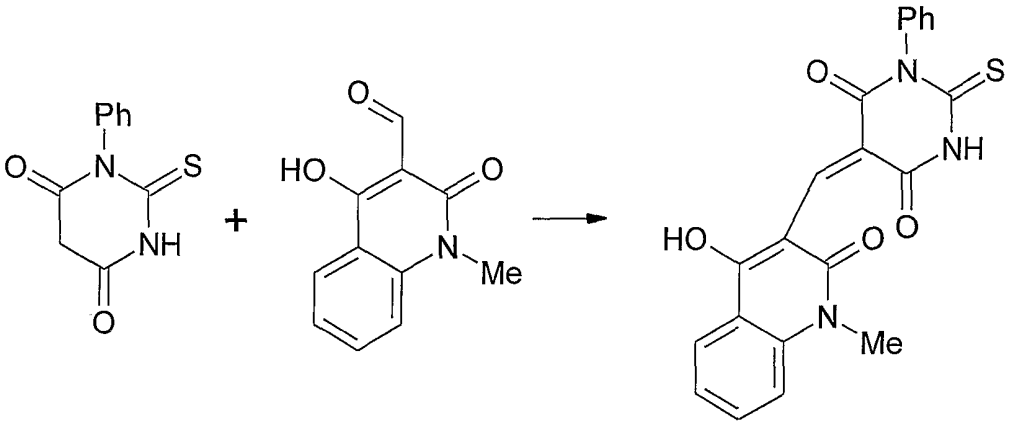
For example, such compounds may be prepared by reaction of a suitable aldehyde or dinitrile with a suitable thio-barbituric acid derivative. Examples of such reactions have

been reported in the chemical literature, including, but not limited to, the following:

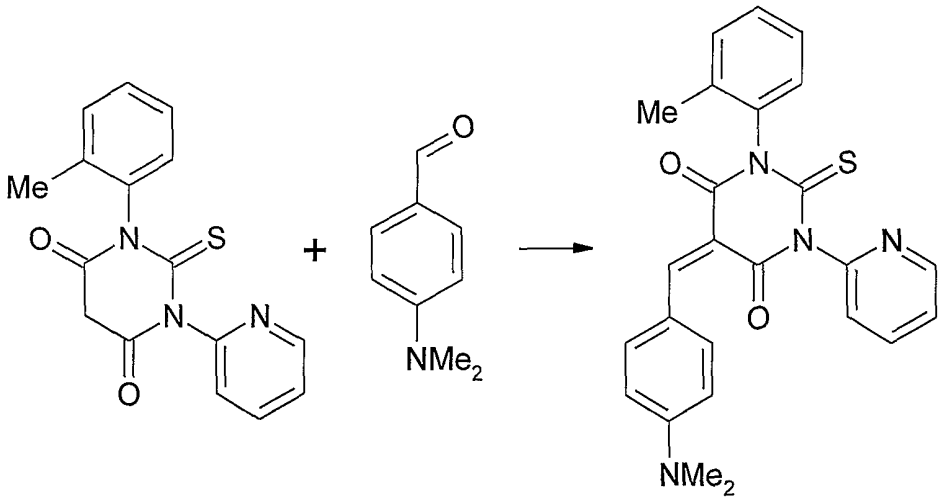
Scheme 12 - Guerein et al., 1999



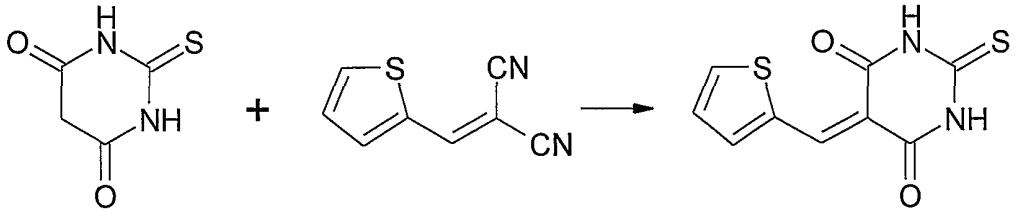
Scheme 13 - Ismail et al., 1997



Scheme 14 - Shalmashi et al., 1994

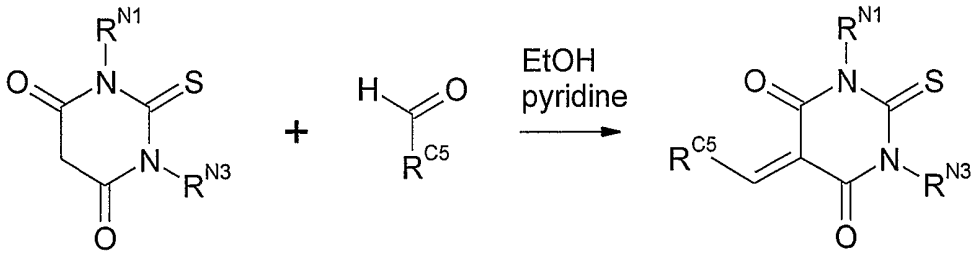


Scheme 15 - Abdel-Latif, 1991



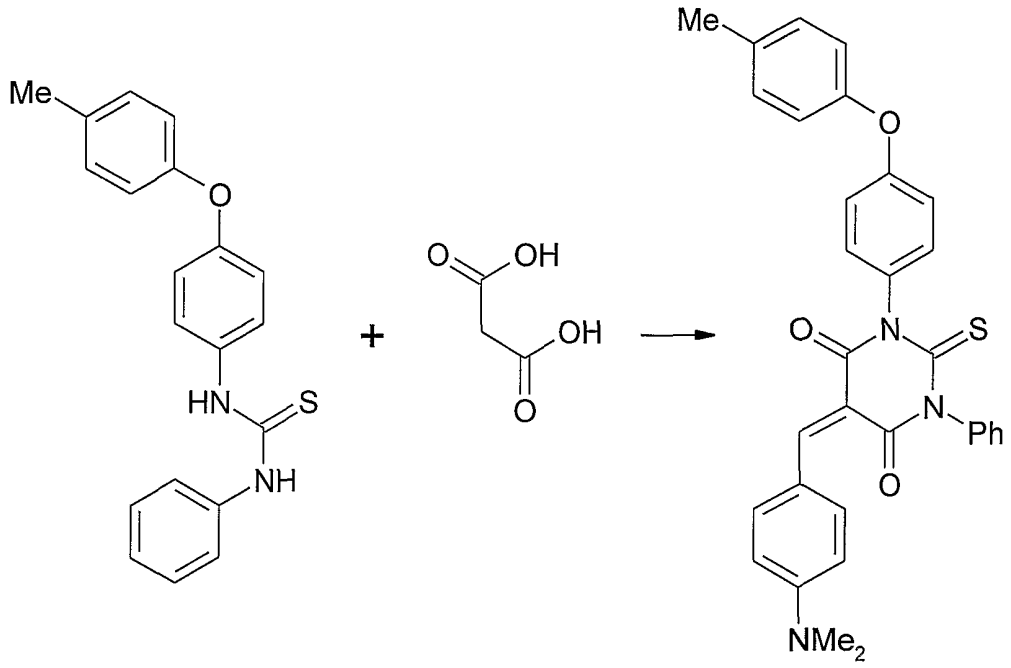
In one method (see also the Examples below), thiobarbituric acid and aldehyde are dissolved in ethanol. A catalytic amount of pyridine is added, and the reaction mixture is heated, e.g., to 60°C for 5 hours or, where R^{N1} and/or R^{N3} is phenyl, for 24 hours. In some cases, a precipitate is formed while in other cases, a coloured solution results. Ethanol is evaporated off and the residue washed, e.g., with petroleum ether (bp 40-60°C).

Scheme 16



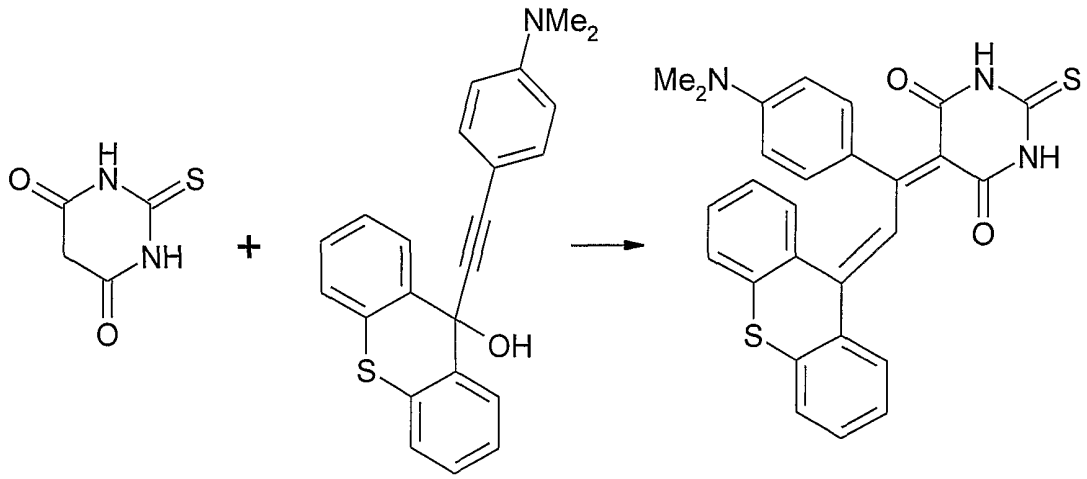
Also, such compounds may be prepared by reaction of a suitable thiourea with a suitable malonic acid. Examples of such reactions have been reported in the chemical literature, including, but not limited to, the following:

Scheme 17 - Swarup et al., 1991



Also, such compounds may be prepared by addition of a suitable thio-barbituric acid to a suitable acetylenic compound. Examples of such reactions have been reported in the chemical literature, including, but not limited to, the following:

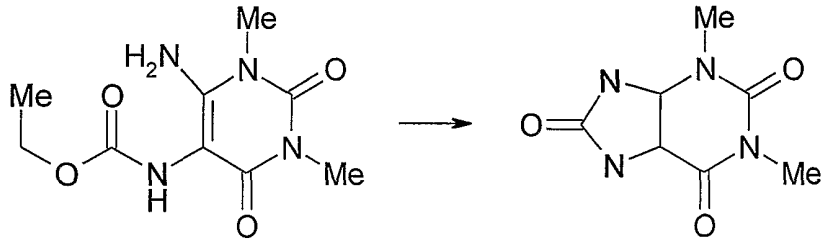
Scheme 18 - Nakatsuji, 1988



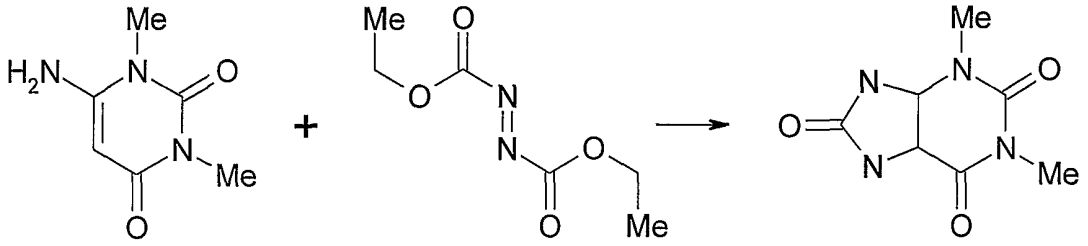
Compounds in which a five or six membered heterocyclic ring is fused to the barbituric acid ring may be prepared using

known methods, or by adapting known methods in known ways. Examples of such reactions have been reported in the chemical literature, including, but not limited to, the following:

Scheme 19 - Taylor et al., 1974



Scheme 20 - Taylor et al., 1974



Uses

The present invention provides active compounds which are capable of inhibiting HIF-1 activity (for example, capable of inhibiting the interaction between HIF-1α and p300), as well as methods of inhibiting HIF-1 activity, comprising contacting a cell with an effective amount of an active compound, whether *in vitro* or *in vivo*.

The term "active," as used herein, pertains to compounds which are capable of inhibiting HIF-1 activity, and specifically includes both compounds with intrinsic activity (drugs) as well as prodrugs of such compounds, which prodrugs may themselves exhibit little or no intrinsic activity.

One of ordinary skill in the art is readily able to determine whether or not a candidate compound is active, that is, capable of inhibiting HIF-1 activity, for example, capable of inhibiting the interaction between HIF-1α and p300. For example, assays which may conveniently be used to assess the inhibition offered by a particular compound are described in the examples below.

For example, a sample of cells (e.g., from a tumour) may be grown in vitro and a candidate compound brought into contact with the cells, and the effect of the compound on those cells observed. As examples of "effect," the morphological status of the cells may be determined (e.g., alive or dead), or the expression levels of genes regulated by the HIF-1 transcription factor. Where the candidate compound is found to exert an influence on the cells, this may be used as a prognostic or diagnostic marker of the efficacy of the compound in methods of treating a patient carrying the tumour or a tumour of the same cellular type.

Thus, in one aspect, the present invention provides angiogenesis inhibitors, as well as methods of inhibiting angiogenesis, comprising contacting a cell (e.g., a tumour cell, an endothelial cell, etc.) with an effective amount of an active compound, whether *in vitro* or *in vivo*. The term "angiogenesis inhibitor" as used herein, pertains to an active compound which inhibits angiogenesis, that is, which inhibits the progress of angiogenesis, and includes both a reduction in the rate of progress and a halt in the rate of progress.

Thus, in one aspect, the present invention provides antiproliferative agents. The term "antiproliferative agent" as used herein, pertain to a compound which treats a

proliferative condition (i.e., a compound which is useful in the treatment of a proliferative condition).

The terms "cell proliferation," "proliferative condition," "proliferative disorder," and "proliferative disease," are used interchangeably herein and pertain to an unwanted or uncontrolled cellular proliferation of excessive or abnormal cells which is undesired, such as, neoplastic or hyperplastic growth, whether in vitro or in vivo. Examples of proliferative conditions include, but are not limited to, pre-malignant and malignant cellular proliferation, including but not limited to, malignant neoplasms and tumours, cancers, leukemias, psoriasis, bone diseases, fibroproliferative disorders (e.g., of connective tissues), and atherosclerosis. Any type of cell may be treated, including but not limited to, lung, colon, breast, ovarian, prostate, liver, pancreas, brain, and skin.

Antiproliferative compounds of the present invention have application in the treatment of cancer, and so the present invention further provides anticancer agents. The term "anticancer agent" as used herein, pertains to a compound which treats a cancer (i.e., a compound which is useful in the treatment of a cancer). The anti-cancer effect may arise through one or more mechanisms, including but not limited to, the regulation of cell proliferation, the inhibition of angiogenesis (the formation of new blood vessels), the inhibition of metastasis (the spread of a tumour from its origin), the inhibition of invasion (the spread of tumour cells into neighbouring normal structures), or the promotion of apoptosis (programmed cell death).

The active compounds of the present invention are particularly applicable to proliferative conditions (e.g., cancers) which are characterized by so-called "solid"

tumours, and which rely on angiogenesis, and the vasculature arising therefrom.

The invention further provides active compounds for use in a method of treatment of the human or animal body. Such a method may comprise administering to such a subject a therapeutically-effective amount of an active compound, preferably in the form of a pharmaceutical composition.

The term "treatment," as used herein in the context of treating a condition, pertains generally to treatment and therapy, whether of a human or an animal (e.g., in veterinary applications), in which some desired therapeutic effect is achieved, for example, the inhibition of the progress of the condition, and includes a reduction in the rate of progress, a halt in the rate of progress, amelioration of the condition, and cure of the condition. Treatment as a prophylactic measure is also included.

The term "therapeutically-effective amount," as used herein, pertains to that amount of an active compound, or a material, composition or dosage from comprising an active compound, which is effective for producing some desired therapeutic effect, commensurate with a reasonable benefit/risk ratio.

The invention further provides the use of an active compound for the manufacture of a medicament, for example, for the treatment of a proliferative condition, as discussed above.

The invention further provides a method of treatment of the human or animal body, the method comprising administering to a subject in need of treatment a therapeutically-effective amount of an active compound, preferably in the form of a pharmaceutical composition.

Active compounds may also be used, as described above, in combination therapies, that is, in conjunction with other agents, for example, cytotoxic agents.

Active compounds may also be used as part of an in vitro assay, for example, in order to determine whether a candidate host is likely to benefit from treatment with the compound in question.

Active compounds may also be used as a standard, for example, in an assay, in order to identify other active compounds, other antiproliferative agents, etc.

Administration

The active compound or pharmaceutical composition comprising the active compound may be administered to a subject by any convenient route of administration, whether systemically/peripherally or at the site of desired action, including but not limited to, oral (e.g, by ingestion); topical (including transdermal, intranasal, ocular, buccal, and sublingual); pulmonary (e.g., by inhalation therapy using, for example, an aerosol); rectal; vaginal; parenteral, for example, by injection, including subcutaneous, intradermal, intramuscular, intravenous, intraarterial, intracardiac, intrathecal, intraspinal, intracapsular, subcapsular, intraorbital, intraperitoneal, intratracheal, subcuticular, intraarticular, subarachnoid, and intrasternal.

The subject may be a eukaryote, an animal, a vertebrate animal, a mammal, a rodent (e.g., a guinea pig, a hamster, a rat, a mouse), murine (e.g., a mouse), a simian (e.g., a chimpanzee), or a human.

Formulations

While it is possible for the active ingredient to be administered alone, it is preferable to present it as a pharmaceutical composition (e.g., formulation) comprising at least one active ingredient, as defined above, together with one or more pharmaceutically acceptable carriers, excipients, buffers, adjuvants, stabilisers, or other materials well known to those skilled in the art and optionally other therapeutic agents.

Thus, the present invention further provides pharmaceutical compositions, as defined above, and methods of making a pharmaceutical composition comprising admixing at least one active ingredient, as defined above, together with one or more pharmaceutically acceptable carriers, excipients, buffers, adjuvants, stabilisers, or other materials, as described herein.

The term "pharmaceutically acceptable" as used herein pertains to compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of a subject (e.g., human) without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio. Each carrier, excipient, etc. must also be "acceptable" in the sense of being compatible with the other ingredients of the formulation.

The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients.

In general, the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then if necessary shaping the product.

Formulations may be in the form of liquids, solutions, suspensions, emulsions, tablets, losenges, granules, powders, capsules, cachets, pills, ampoules, suppositories, pessaries, ointments, gels, pastes, creams, sprays, foams, lotions, oils, boluses, electuaries, or aerosols.

Formulations suitable for oral administration (e.g., by ingestion) may be presented as discrete units such as capsules, cachets or tablets, each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion; as a bolus; as an electuary; or as a paste.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder (*e.g.*, povidone, gelatin, hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (*e.g.*, sodium starch glycolate, cross-linked povidone, cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying

proportions to provide the desired release profile. Tablets may optionally be provided with an enteric coating, to provide release in parts of the gut other than the stomach.

Formulations suitable for topical administration (e.g., transdermal, intranasal, ocular, buccal, and sublingual) may be formulated as an ointment, cream, suspension, lotion, powder, solution, past, gel, spray, aerosol, or oil. Alternatively, a formulation may comprise a patch or a dressing such as a bandage or adhesive plaster impregnated with active ingredients and optionally one or more excipients or diluents.

Formulations suitable for topical administration in the mouth include losenges comprising the active ingredient in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the active ingredient.

Formulations suitable for nasal administration, wherein the carrier is a solid, include a coarse powder having a particle size, for example, in the range of about 20 to about 500 microns which is administered in the manner in which snuff is taken, i.e., by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable formulations wherein the carrier is a liquid for administration as, for example, nasal spray,

nasal drops, or by aerosol administration by nebuliser, include aqueous or oily solutions of the active ingredient.

Formulations suitable for topical administration via the skin include ointments, creams, and emulsions. When formulated in an ointment, the active ingredient may optionally be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base. If desired, the aqueous phase of the cream base may include, for example, at least about 30% w/w of a polyhydric alcohol, i.e., an alcohol having two or more hydroxyl groups such as propylene glycol, butane-1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol and mixtures thereof. The topical formulations may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethylsulfoxide and related analogues.

When formulated as a topical emulsion, the oily phase may optionally comprise merely an emulsifier (otherwise known as an emulgent), or it may comprises a mixture of at lease one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabiliser. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabiliser(s) make up the so-called emulsifying wax, and the wax together with the oil and/or fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations.

Suitable emulgents and emulsion stabilisers include Tween 60, Span 80, cetostearyl alcohol, myristyl alcohol, glyceryl

monostearate and sodium lauryl sulphate. The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties, since the solubility of the active compound in most oils likely to be used in pharmaceutical emulsion formulations may be very low. Thus the cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters known as Crodamol CAP may be used, the last three being preferred esters. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

Formulations suitable for rectal administration may be presented as a suppository with a suitable base comprising, for example, cocoa butter or a salicylate.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient, such carriers as are known in the art to be appropriate.

Formulations suitable for parenteral administration (e.g., by injection, including cutaneous, subcutaneous, intramuscular, intravenous and intradermal), include aqueous and non-aqueous isotonic, pyrogen-free, sterile injection solutions which may contain anti-oxidants, buffers, preservatives, stabilisers, bacteriostats and solutes which

render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents, and liposomes or other microparticulate systems which are designed to target the compound to blood components or one or more organs. Examples of suitable isotonic vehicles for use in such formulations include Sodium Chloride Injection, Ringer's Solution, or Lactated Ringer's Injection. Typically, the concentration of the active ingredient in the solution is from about 1 ng/ml to about 10 µg/ml, for example from about 10 ng/ml to about 1 µg/ml. The formulations may be presented in unit-dose or multi-dose sealed containers, for example, ampoules and vials, and may be stored in a freese-dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules, and tablets. Formulations may be in the form of liposomes or other microparticulate systems which are designed to target the active compound to blood components or one or more organs.

Dosage

It will be appreciated that appropriate dosages of the active compounds, and compositions comprising the active compounds, can vary from patient to patient. Determining the optimal dosage will generally involve the balancing of the level of therapeutic benefit against any risk or deleterious side effects of the treatments of the present invention. The selected dosage level will depend on a variety of factors including, but not limited to, the activity of the particular compound, the route of administration, the time of administration, the rate of excretion of the compound, the duration of the treatment,

other drugs, compounds, and/or materials used in combination, and the age, sex, weight, condition, general health, and prior medical history of the patient. The amount of compound and route of administration will ultimately be at the discretion of the physician, although generally the dosage will be to achieve local concentrations at the site of action which achieve the desired effect.

Administration *in vivo* can be effected in one dose, continuously or intermittently throughout the course of treatment. Methods of determining the most effective means and dosage of administration are well known to those of skill in the art and will vary with the formulation used for therapy, the purpose of the therapy, the target cell being treated, and the subject being treated. Single or multiple administrations can be carried out with the dose level and pattern being selected by the treating physician.

In general, a suitable dose of the active compound is in the range of about 0.1 to about 250 mg per kilogram body weight of the subject per day. Where the active ingredient is a salt, an ester, prodrug, or the like, the amount administered is calculated on the basis the parent compound and so the actual weight to be used is increased proportionately.

EXAMPLES

The following are examples are provided solely to illustrate the present invention and are not intended to limit the scope of the invention, as described herein.

Chemical Synthesis

Several compounds of the present invention were synthesized according to the general method illustrated in Scheme 16 above.

Thiobarbituric acid (250 mmol/dm^3, 1.25 eq.) and aldehyde (200 mmol/dm^3, 1 eq.) were dissolved in ethanol. A catalytic amount of pyridine (0.2 mmol/dm^3, 0.001 eq.) was added, and the reaction mixture was heated, e.g., to 60°C for 5 hours or, where R^{N1} and/or R^{N3} is phenyl, for 24 hours. In some cases, a precipitate was formed while in other cases, a coloured solution resulted. Ethanol was evaporated off and the residue washed with petroleum ether (bp 40-60°C). Structures were confirmed using APCI mass spectrometry (Hewlett Packard MS 59893B) and ^1H NMR (Bruker 250 MHz).

Example 1

5-(3-Phenyl-allylidene)-2-thioxo-dihydro-pyrimidine-4,6-dione (PX072015) (8)

Using the general method and 3-Phenyl-propenal gave a 63% yield of the desired product, 5-(3-Phenyl-allylidene)-2-thioxo-dihydro-pyrimidine-4,6-dione, MS: 258 (M^-).

Example 2

5-(5-Nitro-thiophen-2-ylmethylene)-2-thioxo-dihydro-pyrimidine-4,6-dione (PX074038) (10)

Using the general method and 5-Nitro-thiophene-2-carbaldehyde gave a 97% yield of the desired product, 5-(5-Nitro-thiophen-2-ylmethylene)-2-thioxo-dihydro-pyrimidine-4,6-dione, MS: 283 (M^-), Mp = 285°C (decomposes).

Example 3

5-(3,4-Dimethoxy-benzylidene)-2-thioxo-dihydro-pyrimidine-4,6-dione (PX075262) (18)

Using the general method and 3,4-Dimethoxy-benzaldehyde gave a 86% yield of the desired product, 5-(3,4-Dimethoxy-benzylidene)-2-thioxo-dihydro-pyrimidine-4,6-dione, MS: 277, 291 (M^-).

Example 4

5-(1H-Indol-3-ylmethylene)-2-thioxo-dihydro-pyrimidine-4,6-dione (PX075276) (19)

Using the general method and 1H-Indole-3-carbaldehyde gave a 96% yield of the desired product, 5-(1H-Indol-3-ylmethylene)-2-thioxo-dihydro-pyrimidine-4,6-dione, MS: 270 (M^-), ^1H NMR δ: 12.2(2H,bs,NH), 9.5(1H,s,CH), 8.7(1H,s,CH), 7.9(1H,m,CH), 7.6(1H,m,CH), 7.3(2H,m,CH), Mp = 320°C (decomposes).

Example 5

5-(Furan-2-ylmethylene)-2-thioxo-dihydro-pyrimidine-4,6-dione (PX083634) (28)

Using the general method and Furan-2-carbaldehyde gave a 77% yield of the desired product, 5-Furan-2-ylmethylene-2-thioxo-dihydro-pyrimidine-4,6-dione, MS: 194, 222 (M^-).

Example 6

5-(4-dimethylamino-benzylidene)-2-thioxo-dihydro-pyrimidine-4,6-dione (PX089631) (48)

Using the general method and 4-dimethylamino benzaldehyde gave a 98% yield of the desired product, 5-(4-dimethylamino-

benzylidene)-2-thioxo-dihydro-pyrimidine-4,6-dione, MS: 275 (M^-), ^1H NMR δ: 12.1(2H,bs,NH), 8.5(2H,d,CH), 8.1(1H,s,CH), 6.9 (2H,d,CH), 3.2(6H,s,CH_3), Mp = 272°C (decomposes).

Example 7

N-[4-(4,6-Dioxo-2-thioxo-tetrahydro-pyrimidin-5-ylidenemethyl)-phenyl]-acetamide (PX089632) (49)

Using the general method and N-(4-Formyl-phenyl)-acetamide gave a 82% yield of the desired product, N-[4-(4,6-Dioxo-2-thioxo-tetrahydro-pyrimidin-5-ylidenemethyl)-phenyl]-acetamide, MS: 289 (M^-).

Example 8

5-(Naphthalen-1-ylmethylene)-2-thioxo-dihydro-pyrimidine-4,6-dione (PX089635) (51)

Using the general method and Naphthalene-1-carbaldehyde gave a 96% yield of the desired product, 5-Naphthalen-1-ylmethylene-2-thioxo-dihydro-pyrimidine-4,6-dione, MS: 281 (M^-), Mp = 280°C (decomposes).

Example 9

5-(1H-pyrrol-2-ylmethylene)-2-thioxo-dihydro-pyrimidine-4,6-dione (PX089639) (53)

Using the general method and 1H-pyrrole-2-carbaldehyde gave a 90% yield of the desired product, 5-(1H-pyrrol-2-ylmethylene)-2-thioxo-dihydro-pyrimidine-4,6-dione, MS: 221 (M^-), ^1H NMR δ: 13.0(1H,s,NH), 12.3(1H,s,NH), 8.1(1H,s,CH), 7.7(1H,s,CH), 7.4(1H,s,NH), 6.5(1H,s,CH), Mp = 280°C (decomposes).

Example 10

5-(4-Chloro-benzylidene)-2-thioxo-dihydro-pyrimidine-4,6-dione (PX089640) (54)

Using the general method and 4-Chloro-benzaldehyde gave a 18% yield of the desired product, 5-(4-Chloro-benzylidene)-2-thioxo-dihydro-pyrimidine-4,6-dione, MS: 266, 268 (M^-).

Example 11

5-(4-Chloro-benzylidene)-1,3-diphenyl-2-thioxo-dihydro-pyrimidine-4,6-dione (PX089645) (56)

Using 1,3-Diphenyl-2-thioxo-dihydro-pyrimidine-4,6-dione and 4-Chloro-benzaldehyde gave a 95% yield of the desired product, 5-(4-Chloro-benzylidene)-1,3-diphenyl-2-thioxo-dihydro-pyrimidine-4,6-dione, MS: 418 (M^-).

Example 12

5-(4-Bromo-thiophen-2-ylmethylene)-2-thioxo-dihydro-pyrimidine-4,6-dione (PX089648) (59)

Using the general method and 4-Bromo-thiophene-2-carbaldehyde gave a 92% yield of the desired product, 5-(4-Bromo-thiophen-2-ylmethylene)-2-thioxo-dihydro-pyrimidine-4,6-dione, MS: 316, 318 (M^-), ^1H NMR δ: 12.4(2H,s,NH), 8.5(1H,S,CH), 8.4(1H,S,CH), 8.3(1H,S,CH), Mp = 230°C (decomposes).

Example 13

5-(3-Benzyloxy-4-methoxy-benzylidene)-2-thioxo-dihydro-pyrimidine-4,6-dione (PX105990) (60)

Using the general method and 3-Benzyloxy-4-methoxy-benzaldehyde gave a 11% yield of the desired product, 5-(3-Benzyloxy-4-methoxy-benzylidene)-2-thioxo-dihydro-

pyrimidine-4,6-dione, MS: 253, 367 (M^-).

Example 14

5-(2-Methoxy-benzylidene)-2-thioxo-dihydro-pyrimidine-4,6-dione (PX105993) (61)

Using the general method and 2-Methoxy-benzaldehyde gave a 91% yield of the desired product, 5-(2-Methoxy-benzylidene)-2-thioxo-dihydro-pyrimidine-4,6-dione, MS: 247, 261 (M^-).

Example 15

5-(4-Phenoxy-benzylidene)-2-thioxo-dihydro-pyrimidine-4,6-dione (PX106021) (62)

Using the general method and 4-Phenoxy-benzaldehyde gave a 78% yield of the desired product, 5-(4-Phenoxy-benzylidene)-2-thioxo-dihydro-pyrimidine-4,6-dione, MS: 247, 324 (M^-).

Example 16

5-(4-Styryl-benzylidene)-2-thioxo-dihydro-pyrimidine-4,6-dione (PX106027) (63)

Using the general method and 4-Styryl-benzaldehyde gave a 78% yield of the desired product, 5-(4-Styryl-benzylidene)-2-thioxo-dihydro-pyrimidine-4,6-dione, MS: 334 (M^-).

Example 17

5-(Anthracen-9-ylmethylene)-2-thioxo-dihydro-pyrimidine-4,6-dione (PX106031) (64)

Using the general method and Anthracene-9-carbaldehyde gave a 86% yield of the desired product, 5-Anthracen-9-ylmethylene-2-thioxo-dihydro-pyrimidine-4,6-dione, MS: 332 (M^-).

Example 18

5-(6,7-Dimethyl-4-oxo-4H-chromen-3-ylmethylene)-2-thioxo-dihydro-pyrimidine-4,6-dione (PX106036) (65)

Using the general method and 6,7-Dimethyl-4-oxo-4H-chromene-3-carbaldehyde gave a 29% yield of the desired product, 5-(6,7-Dimethyl-4-oxo-4H-chromen-3-ylmethylene)-2-thioxo-dihydro-pyrimidine-4,6-dione, MS: 418 (M^-).

Primary Assay

Candidate compounds were assessed for their ability to inhibit the interaction between HIF-1α and p300 using a high throughput fluorescence-based screening assay (DELFIA) as follows.

Some of the compounds were obtained from commercial sources (e.g., Sigma Aldrich, Fancy Road, Poole, Dorset, BH12 4QH, United Kingdom; Maybridge Chemical Company Ltd., Trevillet, Tintagel, Cornwall, PL34 0HW, United Kingdom; Menai Organics Ltd., Unit 5, Menai Technology Centre, Deiniol Road, Bangor, Gwynedd, North Wales, LL57 2UP, United Kingdom; Contact Services, P.O. Box 32, Strakhovoi Uchastock, Dolgoprudny, Moscow Region, 131700, Russia) and were used without further purification.

Some of the compounds were synthesized, as described herein.

A plasmid expressing His-HIF-1α fusion protein was constructed by PCR, by amplifying and subcloning a fragment of the human HIF-1α cDNA (NCBI GenBank, accession number AH006957) corresponding to the C-terminal 390 amino acids into vector pET28a (Novagen®, Madison, WI, USA). A plasmid containing the N-terminal 595 amino acids of human p300 (NCBI GenBank, accession number U01877) inserted into vector

pGEX2T (Pharmacia®, Little Chalfont, Bucks, UK) was used for the production of GST-p300 fusion protein. The recombinant proteins were produced in E. coli. His-HIF-1α was purified using Ni-NTA agarose beads, according to manufacture's method (Qiagen®, Crawley, West Sussex, UK). GST-p300 was purified using Glutathione-sepharose beads (Amersham Pharmacia®, Little Chalfont, Bucks, UK) according to manufacturer's instructions. A titration of every batch of p300 was carried out in order to determine the optimum dilution of the protein to obtain at least a 10:1 ratio signal to noise in the binding assay.

The assay was performed in 96-well Polysorb plates (Nalge Nunc International®, Rochester, NY, USA) as follows. Plates were coated with His-HIF-1α at 50 ng/well in 100 mL PBS and incubated overnight at 4°C. The plates were then washed 3 times with deionized water and blocked with 100 µL/well 3% BSA in PBS for 3 hours at 4°C. After washing 3 times as before, GST-p300 was added at the appropriate dilution (1:800 in this screening) in binding buffer (50 mM HEPES pH 7.5, 50 mM NaCl, 0.1% BSA, 0.5 mM DTT). The reaction was incubated at room temperature for 1 hour. Plates were washed 3 times and anti-GST Europium-conjugated antibody (from Wallac®, Turku, Finland) was added at 50 ng/well in 100 mL of binding buffer. After 45 minutes incubation, plates were washed 3 times as before. Then, 100 µL/well enhancement solution (from Wallac®, Catalog No. 1244-105) was added and allowed to react for 15 minutes at room temperature. Plates were read on a Victor 2 plate reader (from Wallac®).

IC50 data (concentration of compound required to cause a 50% inhibition of the signal; or a different % inhibition, as

indicated) for several compounds of the present invention, as determined using this assay, are shown in Table 1.

Secondary cell-based assays

Compounds with inhibition activity, as determined using the primary assay, were subsequently evaluated using one or more secondary assays.

VEGF-Luciferase

This cell-based reporter assay involves the use of a luciferase reporter gene under the direct control of the VEGF promoter. Induction of HIF using desferoxamine leads to the transcription of luciferase through activation of the VEGF (Vascular Endothelial Growth Factor) promoter, which in turn leads to an increase in luciferase activity, which can be measured using most commercially available luciferase assay kits. Molecules that disrupt the HIF complex cause inhibition of HIF-dependent luciferase activation and lead to a reduction in luciferase activity. This assay allows the activity of the compounds to be assessed against the VEGF promoter, which is essential for VEGF production and subsequent angiogenesis.

Hepatoma 3B (hep3B) cells (ATCC Ref. No. HB-8064) were plated in 24-well plates at 2 x 10^4/well in 500 µL DMEM/10% FCS, and were transfected the following day using Fugene 6 (Roche Biochemicals®, Lewes, E. Sussex, UK). Transfection mixtures per well contained 6 µL 10% Fugene, 200 ng VEGF-luciferase reporter (rat VEGF promoter, NCBI GenBank, accession number U22373, Levy et al., 1995) and 2 ng TK-renilla (Promega®, Madison, WI, USA) (for transfection efficiency control). Transfection was performed as recommended by manufacturer. Compounds were added the

following day. After 1 hour incubation at 37°C, desferoxamine (Sigma®, Dorset, UK) was added at 100 µM to induce HIF activity. Duplicate wells without desferoxamine were run in parallel. Cells were harvested 15 hours later, and luciferase activity was measured using Dual Luciferase Assay System (Promega®, see also Technical Manual, Part #TM040, Instructions for Use of Products E1910 and E1960, revised 5/99).

IC50 data (concentration of compound required to cause a 50% inhibition of the luciferase signal; or a different % inhibition, if indicated), for several compounds of the present invention, as determined using this assay, are shown in Table 1.

VEGF-ELISA

This assay employs the quantitative sandwich enzyme immunoassay technique. A monoclonal antibody (R&D Systems®, Abingdon, Oxon, UK) specific for VEGF was pre-coated onto a microplate. To this was added a sample containing VEGF. After washing, a second anti-VEGF antibody coupled to horseradish peroxidase was added. After incubation and washing, the amount of bound antibody, and hence VEGF, was measured using a colorigenic substrate for horseradish peroxidase. Typically, cells were plated at a concentration of 2.5×10^4 cells/well, and incubated with either 100 µM desferroxamine or at 0.1% O_2 for 17 hours at 37°C. 200 µL of supernatant were removed and the VEGF quantitated using the Quantikine® ELISA kit from R&D Systems® (catalog # DVE00) exactly according to the manufacturer's instructions. The assay is calibrated each time using recombinant human VEGF.

IC50 data (concentration of compound required to cause a 50% inhibition of the absorbance signal; or a different % inhibition, if indicated), for several compounds of the present invention, as determined using this assay, are shown in Table 1.

Table 1

No.	Ref. No.	Primary Assay	Secondary Assay	
		Inhibition IC50 (μM)	VEGF-luciferase IC50 (μM)	VEGF-ELISA IC50 (μM)
1	PX069119	250	-	-
2	PX069153	200	-	-
3	PX072002	225	-	-
4	PX072004	250	-	-
5	PX072008	300	-	-
6	PX072009	500	-	-
7	PX072012	175	-	-
8	PX072015	20(a)	18	-
9	PX074037	100	35	30
10	PX074038	20	50	-
11	PX074100	500	-	-
12	PX074728	125	-	-
13	PX075240	100	-	-
14	PX075244	500	-	-
15	PX075245	125	-	-
16	PX075248	450	-	-
17	PX075257	350	-	-
18	PX075262	65	-	-
19	PX075276	30	10.8	18.8
20	PX075367	45	50	75
21	PX081770	125	-	-
22	PX081958	125	-	-
23	PX082132	125	-	-
24	PX082202	250	-	-
25	PX082229	125	-	-
26	PX082796	150	-	-
27	PX083033	4	20	-
28	PX083634	65	50	-
29	PX083675	35	50	75

Table 1

No.	Ref. No.	Primary Assay	Secondary Assay	
		Inhibition IC50 (μM)	VEGF-luciferase IC50 (μM)	VEGF-ELISA IC50 (μM)
30	PX083677	400	-	-
31	PX084819	10	50	-
32	PX088992	10	20	-
33	PX089367	200	-	-
34	PX089368	350	-	-
35	PX089369	225	-	-
36	PX089370	225	-	-
37	PX089371	400	-	-
38	PX089372	500	-	-
39	PX089374	230	-	-
40	PX089375	200	-	-
41	PX089376	200	-	-
42	PX089377	400	-	-
43	PX089378	500	-	-
44	PX089619	180	-	-
45	PX089620	80	-	-
46	PX089624	45	12.5	6.2
47	PX089626	40	75	-
48	PX089631	25	16.3	27.5
49	PX089632	15	-	-
50	PX089633	70	50	-
51	PX089635	80	-	-
52	PX089638	130	-	-
53	PX089639	20	25	50
54	PX089640	100	-	-
55	PX089643	55	87.5	100
56	PX089645	80	-	200
57	PX089646	100	-	-
58	PX089647	100	-	-
59	PX089648	45	30	32.5
60	PX105990	20	100(f)	-
61	PX105993	80	-	-
62	PX106021	40(b)	100	80
63	px106027	20(c)	75	-
64	PX106031	80(d)	50	-
65	PX106036	20	50	-

Table 1

No.	Ref. No.	Primary Assay	Secondary Assay	
		Inhibition IC50 (μM)	VEGF-luciferase IC50 (μM)	VEGF-ELISA IC50 (μM)
66	PX106130	29	-	-
67	PX106151	160	40	75
68	PX106155	10	27.5	45
69	PX106174	43	-	-
70	PX106244	40	-	-
71	PX106255	3	-	-
72	PX106265	50	32	-
73	PX106274	29	-	-
74	PX106281	35	28	30
75	PX106287	80(e)	100	-
76	PX106291	80	-	-
77	PX106297	32	100	-
78	PX106326	40	50	-
79	PX106341	49	57.5	20
80	PX106343	49	100	-

(a) 58%; (b) 53%; (c) 55%; (d) 78%; (e) 35%; (f) 30%.

REFERENCES

A number of patents and publications are cited above in order to more fully describe and disclose the invention and the state of the art to which the invention pertains. Full citations for these references are provided below. Each of these references is incorporated herein by reference in its entirety into the present disclosure.

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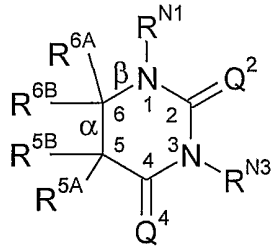
CLAIMS

1. A method of inhibiting HIF-1 activity in a cell, comprising contacting said cell with an effective amount of a compound having the following formula:



(2)

wherein:

Q^2 is =O, =S, or $=NR^{N2}$;

Q^4 is =O, =S, or $=NR^{N4}$;

α is a single bond or a double bond;

β is a single bond or a double bond;

with the proviso that α and β are not both double bonds, and that if β is a double bond, R^{N1} is absent;

and wherein:

(i) R^{5B} is -H and R^{5A} is R^{C5}; or,

(ii) R^{5A} and R^{5B} together are =O, α is a single bond, and β is a single bond; or,

(iii) R^{5A} and R^{5B} together are $=CHR^{C5}$, wherein R^{C5} may be cis- or trans-, α is a single bond, and β is a single bond;

and wherein:

(iv) R^{6B} is -H and R^{6A} is R^{C6}; or,

(v) R^{6A} and R^{6B} together are =O, α is a single bond, and β is a single bond; or,

(vi) R^{6A} and R^{6B} together are $=CHR^{C6}$, wherein R^{C6} may be cis- or trans-, α is a single bond, and β is a single bond;

or wherein:

R^{5A} and R^{6A}, together form a bidentate structure, R^{56}, which, together with the two carbon atoms to which it is attached, forms a cyclic structure with five or six ring atoms, wherein 1 or 2 of said ring atoms are nitrogen, and the remainder are carbon, and wherein the bonds between said ring atoms of the cyclic structure are single or double bonds, as permitted by the valencies of the ring atoms; and,

R^{5B} and R^{6B}, if present, are both -H;

and wherein:

each one of R^{N1}, R^{N2}, R^{N3}, and R^{N4} is a nitrogen substituent, and is independently hydrogen, optionally substituted C_{1-7}alkyl, optionally substituted C_{3-20}heterocyclyl, or optionally substituted C_{5-20}aryl;

and wherein:

each one of R^{C5} and R^{C6} is a carbon substituent, and is independently optionally substituted C_{1-7}alkyl, optionally substituted C_{3-20}heterocyclyl, or optionally substituted C_{5-20}aryl;

or a pharmaceutically acceptable salt, solvate, amide, ester, N-oxide, chemically protected form, or prodrug thereof.

2. A method according to claim 1, wherein Q^2 is =O or =S; and Q^4 is =O or =S.

3. A method according to claim 1, wherein Q^2 is =O and Q^4 is =O; or Q^2 is =S and Q^4 is =O.

4. A method according to claim 1, wherein Q^2 is =O and Q^4 is =O.

5. A method according to claim 1, wherein Q^2 is =S and Q^4 is =O.

6. A method according to any one of claims 1-5, wherein each one of R^{N1}, R^{N2}, R^{N3}, and R^{N4} is independently hydrogen, saturated aliphatic C_{1-7}alkyl, saturated aliphatic C_{1-7}haloalkyl, saturated aliphatic C_{1-7}hydroxyalkyl, saturated aliphatic C_{1-7}aminoalkyl, saturated aliphatic C_{1-7}carboxyalkyl, C_{5-20}aryl-C_{1-7}alkyl, C_{5-20}carboaryl, or C_{5-20}haloaryl.

7. A method according to any one of claims 1-5, wherein each one of R^{N1}, R^{N2}, R^{N3}, and R^{N4} is independently -H, -Me, -Et, $-CH_2COOH$, -Ph, $-C_6H_4F$, $-C_6H_4Cl$, $-C_6H_4Br$, $-C_6H_4-OCH_3$, or $-C_6H_4-CH_3$.

8. A method according to any one of claims 1-7, wherein R^{N1} is -H or other than -H; and, each one of R^{N2}, R^{N3}, and R^{N4} is -H.

9. A method according to any one of claims 1-7, wherein R^{N3} is -H or other than -H; and each one of R^{N1}, R^{N2}, and R^{N4} is -H.

10. A method according to any one of claims 1-7, wherein each one of R^{N1}, R^{N2}, R^{N3}, and R^{N4} is -H.

11. A method according to any one of claims 1-10, wherein:

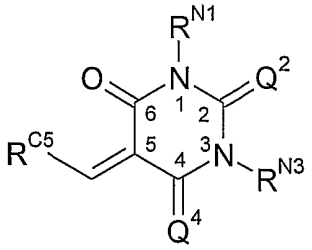
R^{5A} and R^{5B} together are $=CHR^{C5}$, wherein R^{C5} may be cis- or trans-;

R^{6A} and R^{6B} together are =O;

α is a single bond; and,

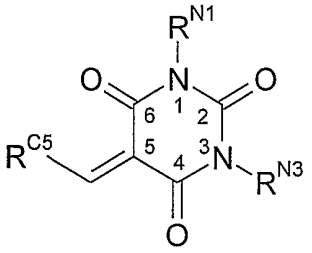
β is a single bond;

and the compound has the following formula:



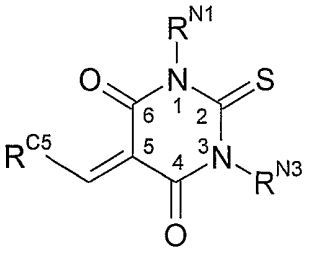
(3)

12. A method according to claim 11, wherein Q^2 is =O and Q^4 is =O and the compound has the following formula:



(4)

13. A method according to claim 11, wherein Q^2 is =S and Q^4 is =O and the compound has the following formula:



(5)

14. A method according to any one of claims 11-13, wherein R^{C5} is optionally substituted C_{1-7}alkyl.

15. A method according to any one of claims 11-13, wherein R^{C5} is optionally substituted C_{3-6}cycloalkyl.

16. A method according to any one of claims 11-13, wherein R^{C5} is optionally substituted partially unsaturated C_{3-6}cycloalkyl.

17. A method according to any one of claims 11-13, wherein R^{C5} is optionally substituted cyclohexenyl.

18. A method according to any one of claims 11-13, wherein R^{C5} is optionally substituted C_{5-20}aryl-C_{1-7}alkyl.

19. A method according to any one of claims 11-13, wherein R^{C5} is optionally substituted phenyl-ethenyl, furanyl-ethenyl, or thiophenyl-ethenyl.

20. A method according to any one of claims 11-13, wherein R^{C5} is optionally substituted C_{3-20}heterocyclyl.

21. A method according to any one of claims 11-13, wherein R^{C5} is optionally substituted C_{5-20}aryl.

22. A method according to any one of claims 11-13, wherein R^{C5} is optionally substituted C_{5-20}carboaryl.

23. A method according to any one of claims 11-13, wherein and R^{C5} is optionally substituted phenyl, naphthyl, anthracenyl, or phenanthryl.

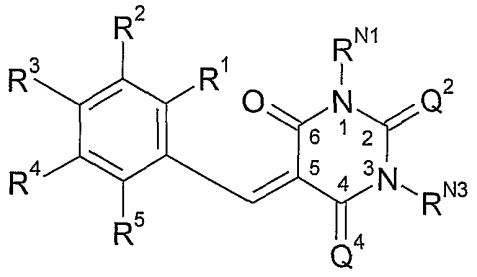
24. A method according to any one of claims 11-13, wherein R^{C5} is optionally substituted C_{5-20}heteroaryl.

25. A method according to any one of claims 11-13, wherein R^{C5} is optionally substituted furanyl, thiophenyl, pyrrolyl, indolyl, or benzopyronyl.

26. A method according to any one of claims 11-13, wherein R^{C5} is optionally substituted cyclohexenyl, phenyl, furanyl, thiophenyl, pyrrolyl, indolyl, or benzopyronyl.

27. A method according to any one of claims 11-13, wherein R^{C5} is an optionally substituted phenyl group.

28. A method according to any one of claims 11-13, wherein the compound has the following formula:



(6)

wherein:

each one of R^1 through R^5 is a phenyl substituent, and is independently hydrogen, halo, hydroxy, ether, formyl, acyl, carboxy, carboxylate, amido, acylamido, amino, nitro, optionally substituted C_{1-7}alkyl, optionally substituted C_{3-20}heterocyclyl, or optionally substituted C_{5-20}aryl; and,

two of R^1 through R^5 may together form a bidentate structure which, together with the two carbon atoms to which it is attached, forms a cyclic structure with five or six ring atoms.

29. A method according to claim 28, wherein:

each one of R^1 through R^5 is independently hydrogen, halo, hydroxy, C_{1-7}alkoxy, optionally substituted C_{5-20}aryloxy, optionally substituted C_{5-20}aryl-C_{1-7}alkoxy, acyl, amino, or optionally substituted C_{1-7}alkyl; and,

two of R^1 through R^5 may form a bidentate structure selected from $-(CH_2)_3-$, $-(CH_2)_4-$, $-O-CH_2-O-$, and $-O-CH_2CH_2-O-$;

30. A method according to claim 28, wherein each one of R^1 through R^5 is independently selected from: -H, -F, -Cl, -Br, -I, $-NMe_2$, $-NEt_2$, -OH, $-OCH_3$, $-OCH_2CH_3$, -OPh, $-OCH_2Ph$, $-C(=O)CH_3$, $-CONH_2$, $-CONHCH_3$, $-NO_2$, $-CH_3$, $-CH_2CH_3$, $-CF_3$, $-OCF_3$, $-CH_2OH$, -Ph, and $-CH_2Ph$.

31. A method according to any one of claims 1-10, wherein:

R^{5A} and R^{6A}, together form a bidentate structure, R^{56}, which, together with the two carbon atoms to which it is attached, forms a cyclic structure with five or six ring atoms, wherein 1 or 2 of said ring atoms are nitrogen, and the remainder are carbon, and wherein the bonds between said ring atoms of the cyclic structure are single or double bonds, as permitted by the valencies of the ring atoms; and,

R^{5B} and R^{6B}, if present, are both -H.

32. A method according to claim 31, wherein said cyclic structure has five ring atoms.

33. A method according to claim 31, wherein:

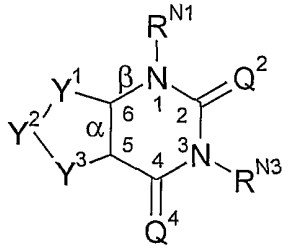
α is a single or double bond;

β is a single bond;

R^{5A} and R^{6A}, together form a bidentate structure, R^{56}, which, together with the two carbon atoms to which it is attached, forms a cyclic structure with <u>five</u> ring atoms, wherein 1 or 2 of said ring atoms are nitrogen, and the remainder are carbon; and,

R^{5B} and R^{6B} are both absent;

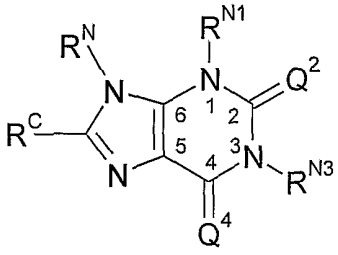
and the compound has the following formula:



(9)

wherein 1 or 2 of Y^1, Y^2, and Y^3 are optionally substituted nitrogen atoms, and the remainder are optionally substituted carbon atoms, and the bonds between C-5 and Y^3, Y^3 and Y^2, Y^2 and Y^1, and Y^1 and C-6 are single or double bonds, as permitted by the valencies of the respective atoms.

34. A method according to claim 32 or 33, wherein the compound has the following formula:



(10)

wherein:

R^C is a carbon substituent, and is independently hydrogen, halo, hydroxy, ether, formyl, acyl, carboxy, carboxylate, acyloxy, amido, acylamido, amino, cyano, nitro, sulfhydryl, thioether, sulfonamino, sulfinamino, sulfamyl, sulfonamido, optionally substituted C_{1-7}alkyl, optionally substituted C_{3-20}heterocyclyl, or optionally subsituted C_{5-20}aryl; and,

R^N is as defined for R^{N1}, R^{N2}, R^{N3}, and R^{N4}.

35. A method according to claim 34, wherein R^C is hydrogen, C_{1-7}alkyl, hydroxy, C_{1-7}alkoxy, amino, or C_{5-20}aryl.

36. A method according to claim 34, wherien R^C is -H, -Me, -Et, -OH, -OMe, -OEt, $-NH_2$, $-NMe_2$,$-NEt_2$, -Ph, $-C_6H_5Cl$, $-C_6H_5OCH_3$.

37. A method according to claim 31, wherein said cyclic structure has six ring atoms.

38. A method according to claim 31, wherein:

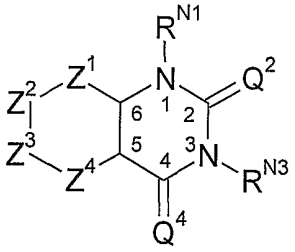
α is a single or double bond;

β is a single or double bond;

R^{5A} and R^{6A}, together form a bidentate structure, R^{56}, which, together with the two carbon atoms to which it is attached, forms a cyclic structure with six ring atoms, wherein 1 or 2 of said ring atoms are nitrogen, and the remainder are carbon; and,

R^{5B} and R^{6B} are both -H, if present;

and the compound has the following formula:



(18)

wherein 1 or 2 of Z^1, Z^2, Z^3, and Z^4 are optionally substituted nitrogen atoms, and the remainder are optionally substituted carbon atoms, and the bonds between C-5 and Z^4, Z^4 and Z^3, Z^3 and Z^2, Z^2 and Z^1, and Z^1 and C-6 may be single or double bonds, as permitted by the valencies of the respective atoms.

39. A method according to claim 38, wherein

α is a single or double bond;

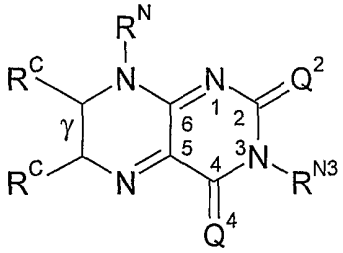
β is a single or double bond;

γ is a single or double bond;

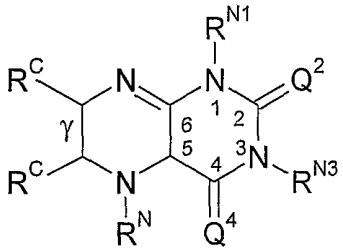
R^{5A} and R^{6A}, together form a bidentate structure, R^{56}; and,

R^{5B} and R^{6B} are both absent;

and the compound has one of the following formulae:



(19)



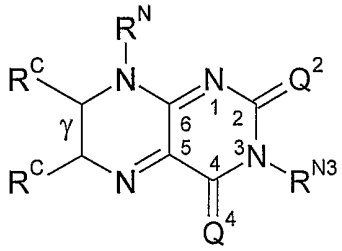
(20)

wherein:

each R^C is a carbon substituent, and is independently hydrogen, halo, hydroxy, ether, formyl, acyl, carboxy, carboxylate, acyloxy, amido, acylamido, amino, cyano, nitro, sulfhydryl, thioether, sulfonamino, sulfinamino, sulfamyl, sulfonamido, optionally substituted C_{1-7}alkyl, optionally substituted C_{3-20}heterocyclyl, or optionally subsituted C_{5-20}aryl; and,

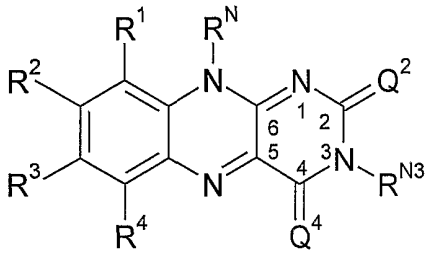
R^N is as defined for R^{N1}, R^{N2}, R^{N3}, and R^{N4}.

40. A method according to claim 39, wherein the compound has the following formula:



(19)

41. A method according to claim 38, wherein the compound has the following formula:



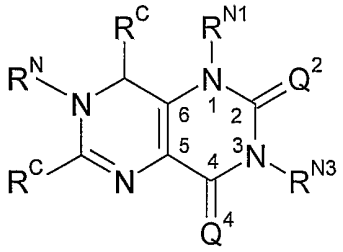
(21)

wherein:

each one of R^1 through R^4 is a phenyl substituent, and is independently hydrogen, halo, hydroxy, ether, formyl, acyl, carboxy, carboxylate, amido, acylamido, amino, nitro, optionally substituted C_{1-7}alkyl, optionally substituted C_{3-20}heterocyclyl, or optionally substituted C_{5-20}aryl; and,

two of R^1 through R^4 may together form a bidentate structure which, together with the two carbon atoms to which it is attached, forms a cyclic structure with five or six ring atoms.

42. A method according to claim 38, wherein the compound has the following formula:



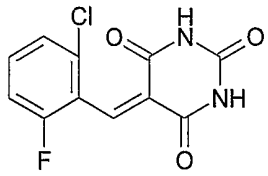
(22)

wherein:

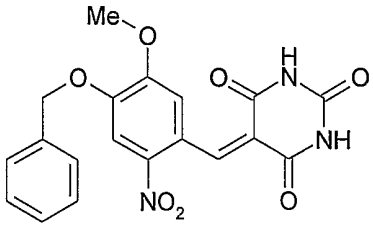
each R^C is a carbon substituent, and is independently hydrogen, halo, hydroxy, ether, formyl, acyl, carboxy, carboxylate, acyloxy, amido, acylamido, amino, cyano, nitro, sulfhydryl, thioether, sulfonamino, sulfinamino, sulfamyl, sulfonamido, optionally substituted C_{1-7}alkyl, optionally substituted C_{3-20}heterocyclyl, or optionally subsituted C_{5-20}aryl; and,

R^N is as defined for R^{N1}, R^{N2}, R^{N3}, and R^{N4}.

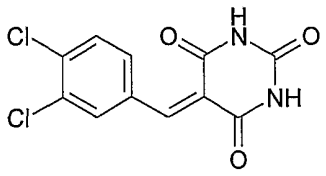
43. A method according to claim 1, wherein the compound is:

(1)  PX069119

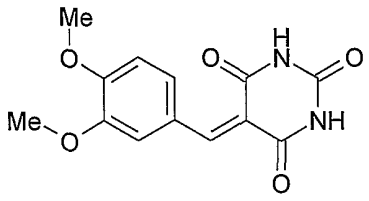
44. A method according to claim 1, wherein the compound is:

(2)  PX069153

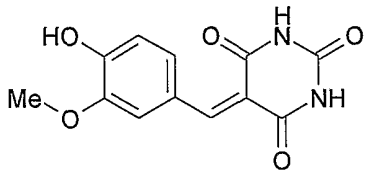
45. A method according to claim 1, wherein the compound is:

(3)  PX072002

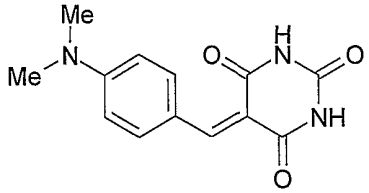
46. A method according to claim 1, wherein the compound is:

(4)  PX072004

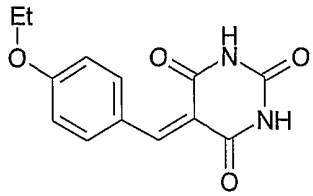
47. A method according to claim 1, wherein the compound is:

(5)  PX072008

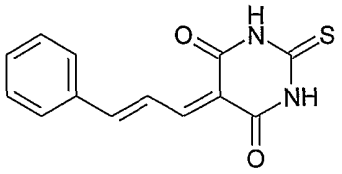
48. A method according to claim 1, wherein the compound is:

(6)  PX072009

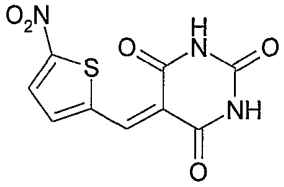
49. A method according to claim 1, wherein the compound is:

(7)  PX072012

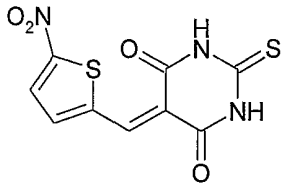
50. A method according to claim 1, wherein the compound is:

(8)  PX072015

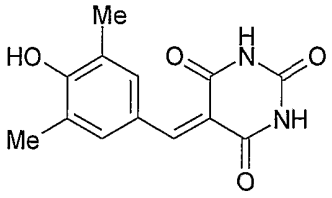
51. A method according to claim 1, wherein the compound is:

(9)  PX074037

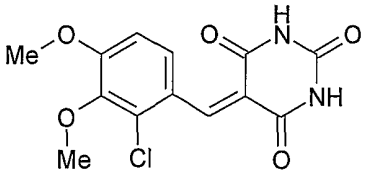
52. A method according to claim 1, wherein the compound is:

(10)  PX074038

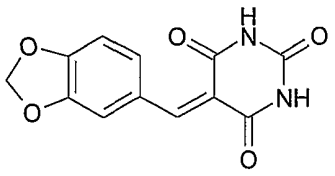
53. A method according to claim 1, wherein the compound is:

(11)  PX074100

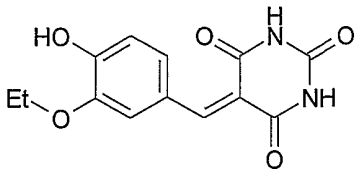
54. A method according to claim 1, wherein the compound is:

(12)  PX074728

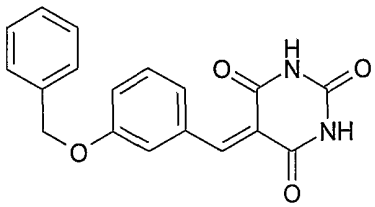
55. A method according to claim 1, wherein the compound is:

(13)  PX075240

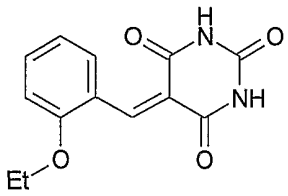
56. A method according to claim 1, wherein the compound is:

(14)  PX075244

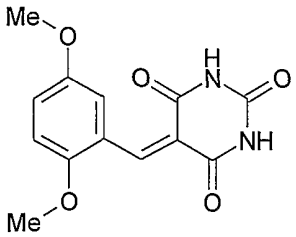
57. A method according to claim 1, wherein the compound is:

(15)  PX075245

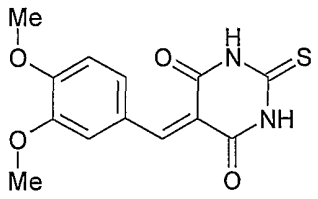
58. A method according to claim 1, wherein the compound is:

(16)  PX075248

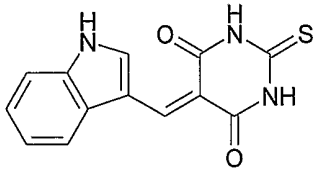
59. A method according to claim 1, wherein the compound is:

(17)  PX075257

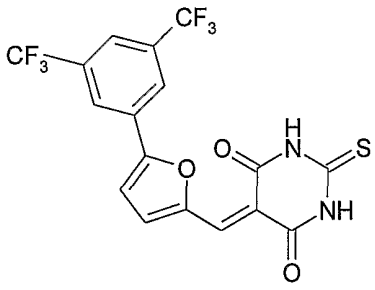
60. A method according to claim 1, wherein the compound is:

(18)  PX075262

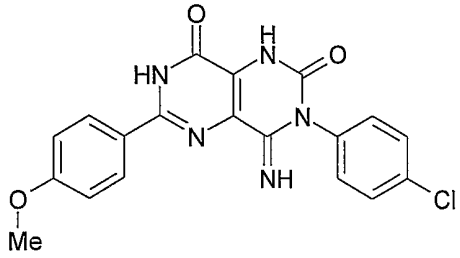
61. A method according to claim 1, wherein the compound is:

(19)  PX075276

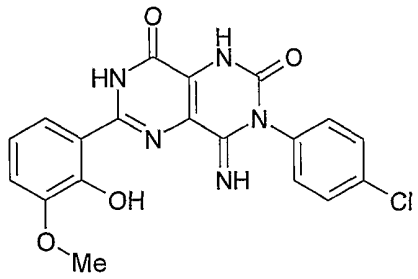
62. A method according to claim 1, wherein the compound is:

(20)  PX075367

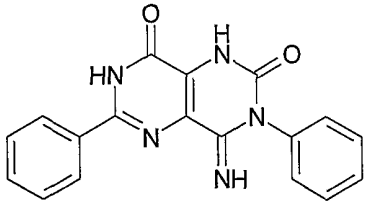
63. A method according to claim 1, wherein the compound is:

(21)  PX081770

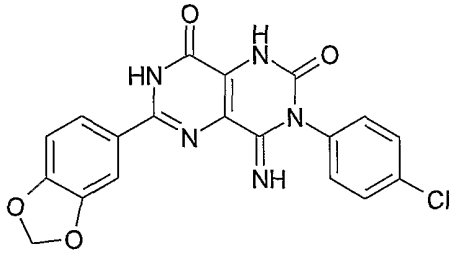
64. A method according to claim 1, wherein the compound is:

(22)  PX081958

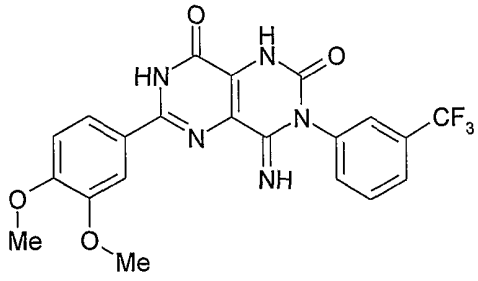
65. A method according to claim 1, wherein the compound is:

(23)  PX082132

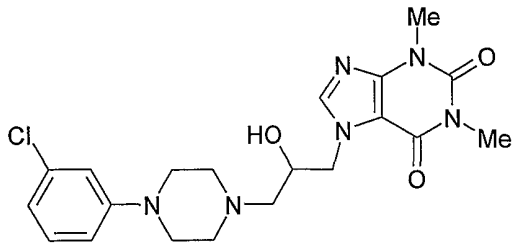
66. A method according to claim 1, wherein the compound is:

(24)  PX082202

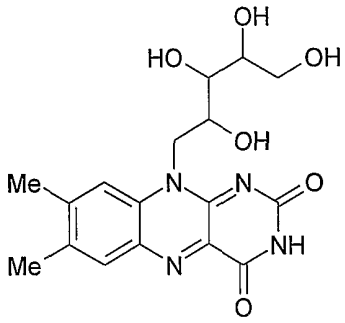
67. A method according to claim 1, wherein the compound is:

(25)  PX082229

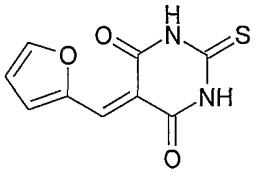
68. A method according to claim 1, wherein the compound is:

(26)  PX082796

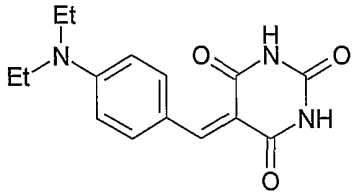
69. A method according to claim 1, wherein the compound is:

(27)  PX083033

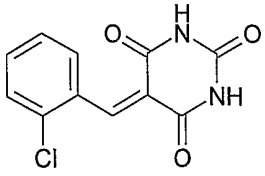
70. A method according to claim 1, wherein the compound is:

(28)  PX083634

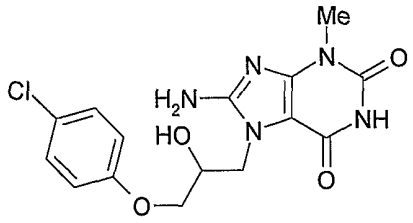
71. A method according to claim 1, wherein the compound is:

(29)  PX083675

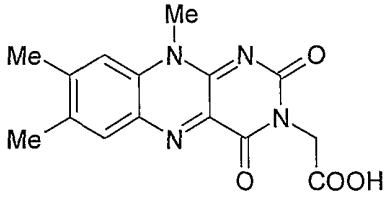
72. A method according to claim 1, wherein the compound is:

(30)  PX083677

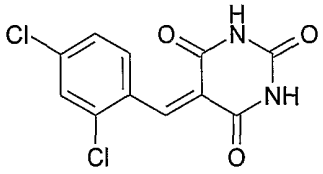
73. A method according to claim 1, wherein the compound is:

(31)  PX084819

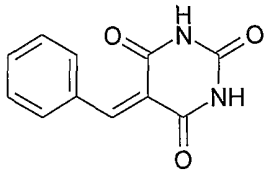
74. A method according to claim 1, wherein the compound is:

(32)  PX088992

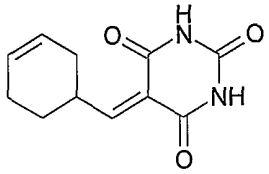
75. A method according to claim 1, wherein the compound is:

(33)  PX089367

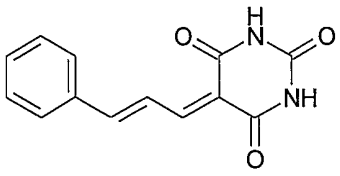
76. A method according to claim 1, wherein the compound is:

(34)  PX089368

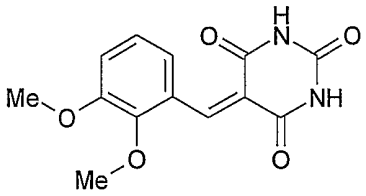
77. A method according to claim 1, wherein the compound is:

(35)  PX089369

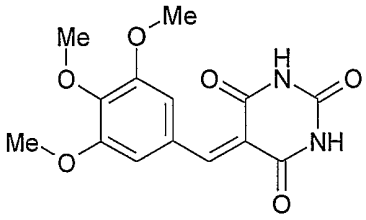
78. A method according to claim 1, wherein the compound is:

(36)  PX089370

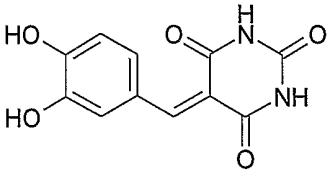
79. A method according to claim 1, wherein the compound is:

(37)  PX089371

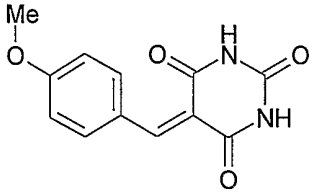
80. A method according to claim 1, wherein the compound is:

(38)  PX089372

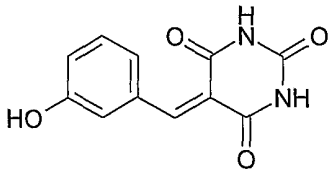
81. A method according to claim 1, wherein the compound is:

(39)  PX089374

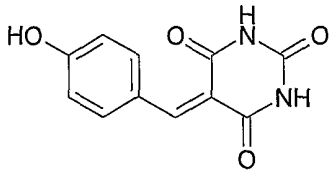
82. A method according to claim 1, wherein the compound is:

(40)  PX089375

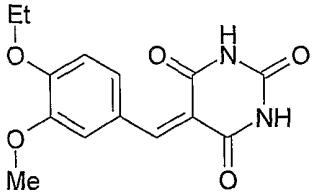
83. A method according to claim 1, wherein the compound is:

(41)  PX089376

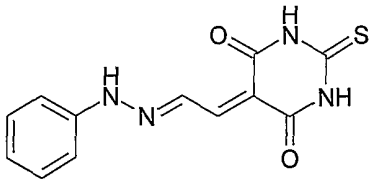
84. A method according to claim 1, wherein the compound is:

(42)  PX089377

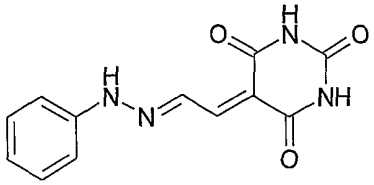
85. A method according to claim 1, wherein the compound is:

(43)  PX089378

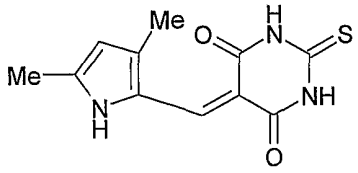
86. A method according to claim 1, wherein the compound is:

(44)  PX089619

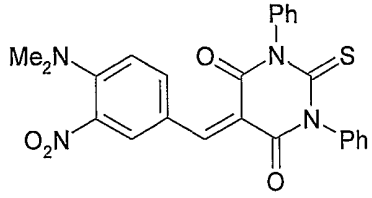
87. A method according to claim 1, wherein the compound is:

(45)  PX089620

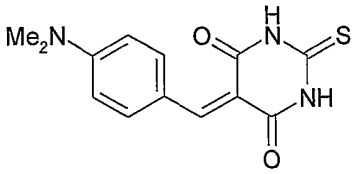
88. A method according to claim 1, wherein the compound is:

(46)  PX089624

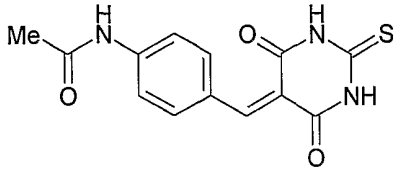
89. A method according to claim 1, wherein the compound is:

(47)  PX089626

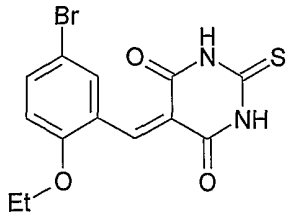
90. A method according to claim 1, wherein the compound is:

(48)  PX089631

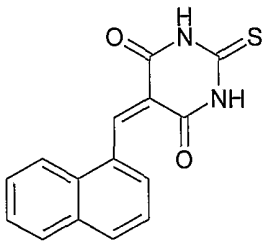
91. A method according to claim 1, wherein the compound is:

(49)  PX089632

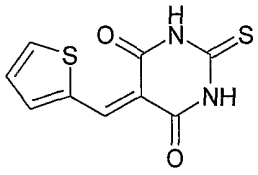
92. A method according to claim 1, wherein the compound is:

(50)  PX089633

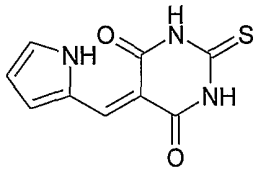
93. A method according to claim 1, wherein the compound is:

(51)  PX089635

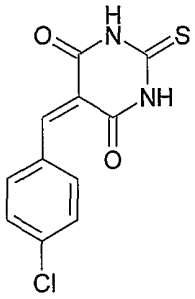
94. A method according to claim 1, wherein the compound is:

(52)  PX089638

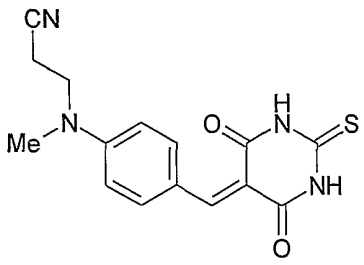
95. A method according to claim 1, wherein the compound is:

(53)  PX089639

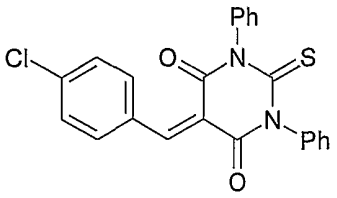
96. A method according to claim 1, wherein the compound is:

(54)  PX089640

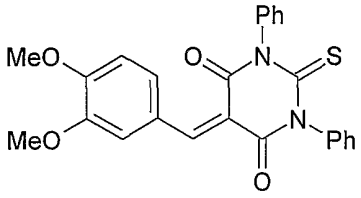
97. A method according to claim 1, wherein the compound is:

(55)  PX089643

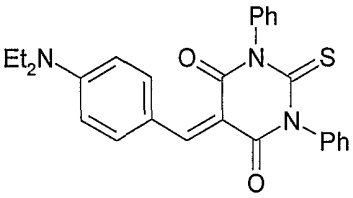
98. A method according to claim 1, wherein the compound is:

(56)  PX089645

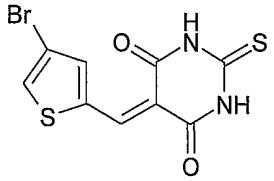
99. A method according to claim 1, wherein the compound is:

(57)  PX089646

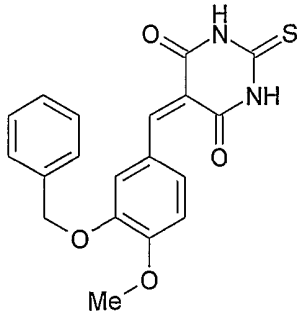
100. A method according to claim 1, wherein the compound is:

(58)  PX089647

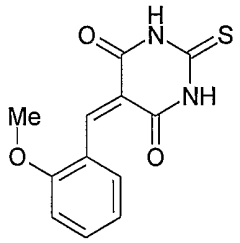
101. A method according to claim 1, wherein the compound is:

(59)  PX089648

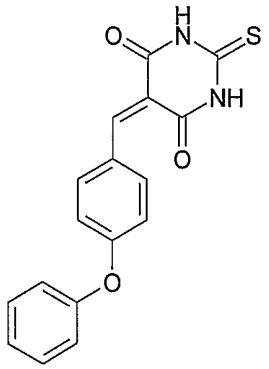
102. A method according to claim 1, wherein the compound is:

(60)  PX105990

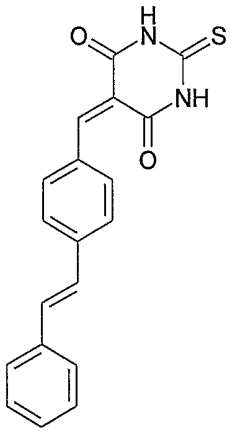
103. A method according to claim 1, wherein the compound is:

(61)  PX105993

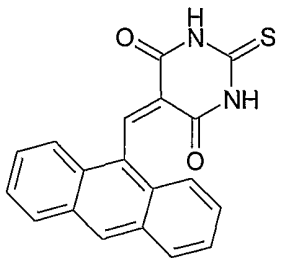
104. A method according to claim 1, wherein the compound is:

(62)  PX106021

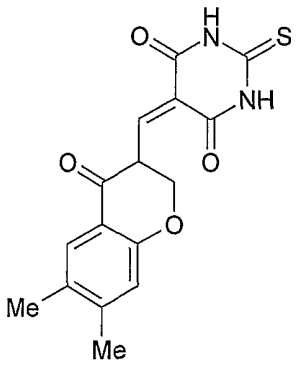
105. A method according to claim 1, wherein the compound is:

(63)  PX106027

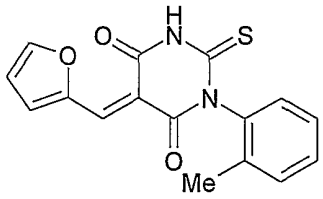
106. A method according to claim 1, wherein the compound is:

(64)  PX106031

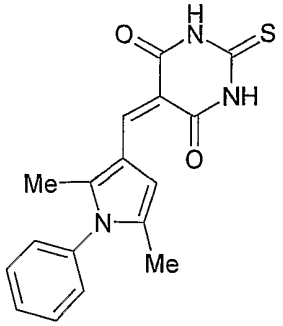
107. A method according to claim 1, wherein the compound is:

(65)  PX106036

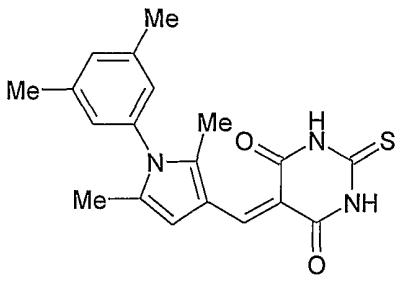
108. A method according to claim 1, wherein the compound is:

(66)  PX106130

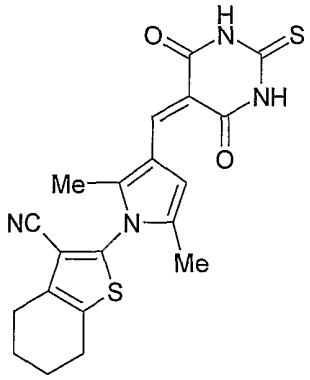
109. A method according to claim 1, wherein the compound is:

(67)  PX106151

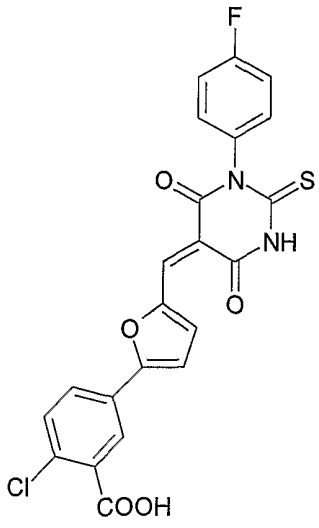
110. A method according to claim 1, wherein the compound is:

(68)  PX106155

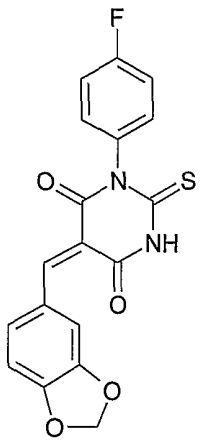
111. A method according to claim 1, wherein the compound is:

(69)  PX106174

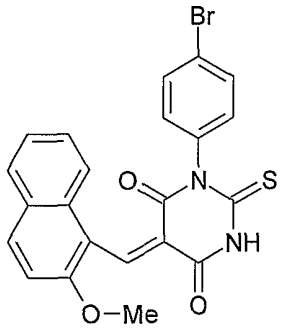
112. A method according to claim 1, wherein the compound is:

(70)  PX106244

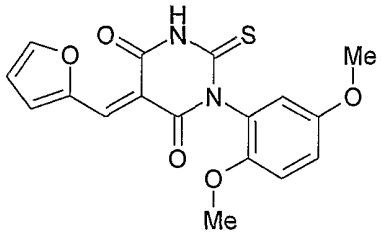
113. A method according to claim 1, wherein the compound is:

(71)  PX106255

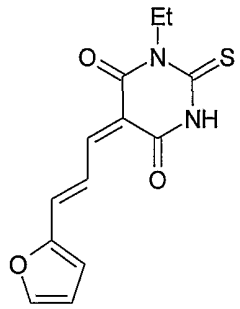
114. A method according to claim 1, wherein the compound is:

(72)  PX106265

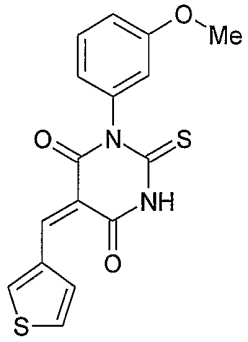
115. A method according to claim 1, wherein the compound is:

(73)  PX106274

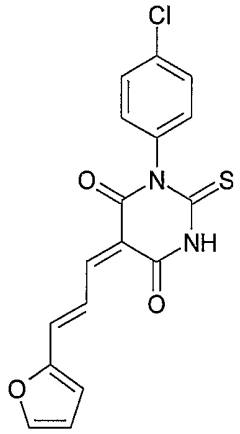
116. A method according to claim 1, wherein the compound is:

(74)  PX106281

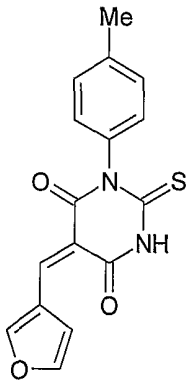
117. A method according to claim 1, wherein the compound is:

(75)  PX106287

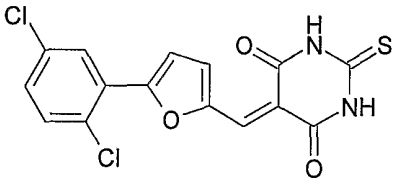
118. A method according to claim 1, wherein the compound is:

(76)  PX106291

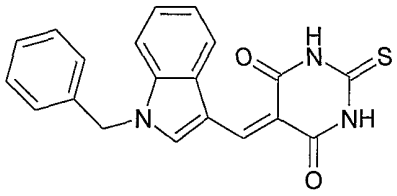
119. A method according to claim 1, wherein the compound is:

(77)  PX106297

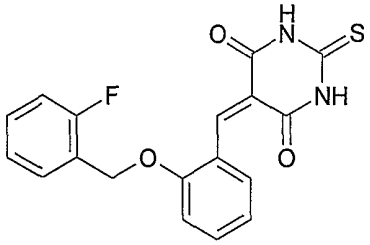
120. A method according to claim 1, wherein the compound is:

(78)  PX106326

121. A method according to claim 1, wherein the compound is:

(79)  PX106341

122. A method according to claim 1, wherein the compound is:

(80)  PX106343

123. A method of inhibiting the interaction between HIF-1α and p300 in a cell, comprising contacting said cell with an effective amount of a compound as defined in any one of claims 1-122.

124. A method of inhibiting angiogenesis, comprising contacting a cell with an effective amount of a compound as defined in any one of claims 1-122.

125. A method of treating a proliferative condition in a patient comprising administering to said patient a therapeutically-effective amount of a compound as defined in any one of claims 1-122.

126. A method according to claim 125, wherein the proliferative condition is cancer.

127. A compound as defined in any one of claims 1-122 for use in a method of treatment of the human or animal body.

128. Use of a compound as defined in any one of claims 1-122 for the manufacture of a medicament for use in the treatment of a proliferative condition.

129. Use according to claim 128, wherein the proliferative condition is cancer.

130. A compound as defined in any one of claims 1-122, or a pharmaceutically acceptable salt, solvate, amide, ester, N-oxide, chemically protected form, or prodrug thereof.

131. A compound as defined in claim 50 (PX072015), or a pharmaceutically acceptable salt, solvate, amide, ester, N-oxide, chemically protected form, or prodrug thereof.

132. A compound as defined in claim 52 (PX074038), or a pharmaceutically acceptable salt, solvate, amide, ester, N-oxide, chemically protected form, or prodrug thereof.

133. A compound as defined in claim 60 (PX075262), or a pharmaceutically acceptable salt, solvate, amide, ester, N-oxide, chemically protected form, or prodrug thereof.

134. A compound as defined in claim 61 (PX075276), or a pharmaceutically acceptable salt, solvate, amide, ester, N-oxide, chemically protected form, or prodrug thereof.

135. A compound as defined in claim 70 (PX083634), or a pharmaceutically acceptable salt, solvate, amide, ester, N-oxide, chemically protected form, or prodrug thereof.

136. A compound as defined in claim 90 (PX089631), or a pharmaceutically acceptable salt, solvate, amide, ester, N-oxide, chemically protected form, or prodrug thereof.

137. A compound as defined in claim 91 (PX089632), or a pharmaceutically acceptable salt, solvate, amide, ester, N-oxide, chemically protected form, or prodrug thereof.

138. A compound as defined in claim 93 (PX089635), or a pharmaceutically acceptable salt, solvate, amide, ester, N-oxide, chemically protected form, or prodrug thereof.

139. A compound as defined in claim 95 (PX089639), or a pharmaceutically acceptable salt, solvate, amide, ester, N-oxide, chemically protected form, or prodrug thereof.

140. A compound as defined in claim 96 (PX089640), or a pharmaceutically acceptable salt, solvate, amide, ester, N-oxide, chemically protected form, or prodrug thereof.

141. A compound as defined in claim 98 (PX089645), or a pharmaceutically acceptable salt, solvate, amide, ester, N-oxide, chemically protected form, or prodrug thereof.

142. A compound as defined in claim 101 (PX089648), or a pharmaceutically acceptable salt, solvate, amide, ester, N-oxide, chemically protected form, or prodrug thereof.

143. A compound as defined in claim 102 (PX105990), or a pharmaceutically acceptable salt, solvate, amide, ester, N-oxide, chemically protected form, or prodrug thereof.

144. A compound as defined in claim 103 (PX105993), or a pharmaceutically acceptable salt, solvate, amide, ester, N-oxide, chemically protected form, or prodrug thereof.

145. A compound as defined in claim 104 (PX106021), or a pharmaceutically acceptable salt, solvate, amide, ester, N-oxide, chemically protected form, or prodrug thereof.

146. A compound as defined in claim 105 (PX106027), or a pharmaceutically acceptable salt, solvate, amide, ester, N-oxide, chemically protected form, or prodrug thereof.

147. A compound as defined in claim 106 (PX106031), or a pharmaceutically acceptable salt, solvate, amide, ester, N-oxide, chemically protected form, or prodrug thereof.

148. A compound as defined in claim 107 (PX106036), or a pharmaceutically acceptable salt, solvate, amide, ester, N-oxide, chemically protected form, or prodrug thereof.

149. A composition comprising a compound as defined in any one of claims 130-150 and a pharmaceutically acceptable carrier.