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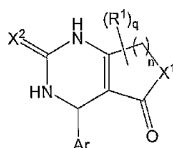
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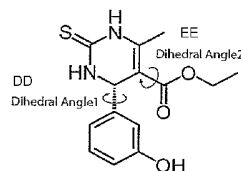
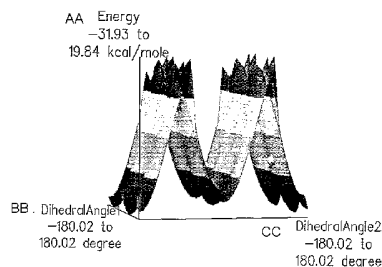
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(54) Title: BICYCLIC DIHYDROPYRIMIDINES AND USES THEREOF



(I)



(57) Abstract: The present invention provides compounds having formula (I): (I) and pharmaceutically acceptable derivatives thereof; as described generally and in subclasses herein, which compounds are useful as kinesin inhibitors (e.g., Eg5 inhibitors), and thus are useful, for example, for the treatment of proliferative disorders e.g., cancer. The invention additionally provides methods for preparing compounds of the invention, compositions comprising them, and methods for the use thereof in the treatment of various disorders where Eg5 is involved. In certain embodiments, the present invention provides for compounds, compositions, methods and systems for inhibiting cell growth. More specifically, the present invention provides for methods, compounds and compositions which are capable of inhibiting mitosis in metabolically active cells. Compounds, compositions and methods of the present invention inhibit the activity of a protein involved in the assembly and maintenance of the mitotic spindle. One class of proteins which acts on the mitotic spindle is the family of mitotic kinesins, a subset of the kinesin superfamily.

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BICYCLIC DIHYDROPYRIMIDINES AND USES THEREOF**PRIORITY**

[0001] The present application claims priority to U.S. Provisional Patent Application No.: 60/642,360 filed January 7, 2005; The entire contents of which are incorporated herein by reference.

GOVERNMENT SUPPORT

[0002] The work described in the present application was supported, in part, by grant number CA78048 from the National Cancer Institute, and grant number GM62566 from the National Institute of General Medical Sciences. The U.S. government may have certain rights in this invention.

BACKGROUND OF THE INVENTION

[0003] Cell-permeable small molecules can rapidly perturb the function of their targets and are therefore powerful tools to dissect dynamic cellular processes. However, such modulators are not available for most of the proteins involved in essential processes, and many of the ones that are available are nonspecific. The only known small molecules that specifically affect the mitotic machinery target tubulin (E. Hamel, *Med. Res. Rev.* **16**, 207 (1996)), a subunit of the microtubules in the mitotic spindle.

[0004] In all eukaryotic cells, the formation of a microtubule based dynamic structure, commonly known as the spindle, is essential for the accurate segregation of chromosomes during cell division (T. Wittmann, A. Hyman, A. Desai, *Nat Cell Biol* **2001**, 3, E28-34). Many approved anti-cancer drugs such as taxanes (Taxol) or vinca alkaloids (Vinblastine) directly target the dynamic process of microtubule polymerization and depolymerization. However, microtubule based structures are also important for other cellular processes, including the organization of intracellular structures as well as intracellular transport, and perturbing these processes results in undesired side effects. Because the above-mentioned drugs do not selectively target the spindle-associated microtubules, the application of those compounds is severely limited (E. K. Rowinsky, *Clin Cancer Res* **1999**, 5, 481-486).

[0005] One class of proteins involved in the assembly and maintenance of the mitotic spindle is the family of mitotic kinesins, a subset of the kinesin superfamily. This superfamily contains over 100 proteins, whose other functions include organelle

transport and membrane organization (R.D. Vale and R.J. Fletterick, *Annu. Rev. Cell Dev. Biol.* **13**, 745 (1997)). Interestingly, motor proteins involved in the formation of the spindle are generally not associated with other microtubule-based structures (1. T. Wittmann, A. Hyman, A. Desai, *Nat Cell Biol* **2001**, 3, E28-34; 2. E. K. Rowinsky, *Clin Cancer Res* **1999**, 5, 481-486; and 3. M. Schliwa, G. Woehlke, *Nature* **2003**, 422, 759-765). The first evidence that mitotic kinesins are important in establishing spindle bipolarity came from genetic studies: temperature-sensitive mutants in the BimC family of kinesins do not form bipolar spindles at the restrictive temperature (A.P. Enos and N.R. Morris, *Cell* **60**, 1019 (1990); I. Hagan and M. Yanagida, *Nature* **356**, 74 (1992); M.A. Hoyt *et al.*, *J. Cell Biol.* **118**, 109 (1992)). Inhibition of the BimC kinesin Eg5 with Eg5-specific antibodies also induced monoasters similar to those observed after treatment with monastrol (A. Blangy *et al.*, *Cell* **83**, 1159 (1995); K.E. Sawin *et al.*, *Nature* **359**, 540 (1992)). Like other kinesins, Eg5 can drive the movement of microtubules *in vitro* (T.M. Kapoor and T.J. Mitchison, *Proc. Natl. Acad. Sci. U.S.A.* **96**, 9106 (1999)).

[0006] Enzymes in the kinesin superfamily use the free energy of ATP hydrolysis to drive intracellular movement and influence cytoskeleton organization (R.D. Vale and R.J. Fletterick, *Annu. Rev. Cell. Dev. Biol.* **13**, 745-777 (1997)). More than 90 members of this family are known. Historically, kinesins have been proposed to move cellular cargo along polar microtubule tracks. More recently it has been shown that these ATPases can modulate dynamics of the underlying microtubule network (A. Desai *et al.*, *Cell* **96**, 69-78 (1999)), couple movement of cargo to the microtubule polymerization or depolymerization (K.W. Wood *et al.*, *Cell* **91**, 357-366 (1997)), and crosslink microtubules in dynamic structures (D.J. Sharp *et al.*, *J. Cell Biol.* **144**, 125-138 (1999)). Kinesins thus play central roles in mitotic and meiotic spindle formation, chromosome alignment and separation, axonal transport, endocytosis, secretion, and membrane trafficking. The cargo associated with these motor proteins includes intracellular vesicles, organelles, chromosomes, kinetochores, intermediate filaments, microtubules, and even other motors (reviewed in C. E. Walczak and T.J. Mitchison, *Cell* **85**, 943-946 (1996); and N. Hirokawa, *Science* **279**, 519-526 (1998)).

[0007] For many of these processes, more than one kinesin is implicated, and the specific cargo associated with a given motor protein has been difficult to establish. For example, conventional kinesin (R.D. Vale *et al.*, *Cell* **42**, 39-50 (1985)) (the

founding member of the family) is one of a subset of kinesins involved in organelle transport in mammalian cells. This group includes KIF1, KIF2, KIFC2/C3, and KIF4; and more recently, 18 new murine KIFs have been reported, many of which may functionally overlap with the transport kinesins (reviewed in N. Hirokawa, *Science* **279**, 519-526 (1998)). It thus has been difficult to tie down the *in vivo* function(s) of conventional kinesin. Experiments using antisense techniques and microinjection of inhibitory antibodies have been further complicated by recent observations of efficient endoplasmic reticulum to Golgi transport in the absence of microtubules, albeit under restricted conditions (reviewed in G.S. Bloom and L.S. Goldstein, *J. Cell Biol.* **140**, 1277-1280 (1998)). Similar problems have been encountered in dissecting the function of kinesins in mitosis. Extensive genetic analysis of motors in *Saccharomyces cerevisiae* has linked all but one of the six kinesins to spindle function. None of these five motors are individually required for the viability of yeast, implying that more than one motor is associated with essential aspects of spindle movement (W.S. Saunders and M.A. Hoyt, *Cell* **70**, 451-458 (1992); M.A. Hoyt *et al.*, *Proc. Natl. Acad. Sci USA* **94**, 12747-12748 (1997)). Immunodepletion and add-back approaches in *Xenopus* extract spindle assembly assays have provided similarly ambiguous data (C.E. Walczak *et al.*, *Curr. Biol.* **8**, 903-913 (1998)).

[0008] Small molecules that conditionally activate or inactivate a protein are valuable tools for analyzing cellular functions of proteins (D.T. Hung *et al.*, *Chem. Biol.* **3**, 623-639 (1996)). Their use provides an alternative to conventional biochemical and genetic approaches. However, to date there have been few reports of small molecules that can reversibly alter the function of motor proteins. Butanedione monoxime has been used to probe the role of myosin in cell movement (L.P. Cramer and T.J. Mitchison, *J. Cell Biol.* **131**, 179-189 (1995)), but its specificity has been questioned (G. Steinberg and J.R. McIntosh, *Eur. J. Cell Biol.* **77**, 284-293 (1998)). A natural product inhibitor of kinesin has been reported (R. Sakowicz *et al.*, *Science* **280**, 292-295 (1998)), but is thought not to be selective for different kinesins and thus is not useful for probing the role of one specific kinesin in a complex process. Hyman *et al.* (A.A. Hyman *et al.*, *Nature (London)* **359**, 533-536 (1992)) have used ATP analogs to distinguish between microtubule motility at kinetochores driven by a kinesin and a dynein, but again, this approach is unlikely to distinguish between different kinesins.

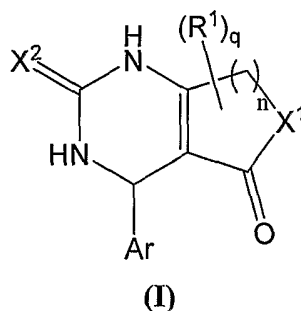
Thus currently there is a lack of small molecule activators or inhibitors that are specific for one member of the kinesin family.

[0009] Therefore, there remains a need for inhibitory molecules with specificity for a particular member of a kinesin class. Such compounds would be useful as an anti-mitotic and also as an anti-cancer, anti-tumor compound. For example, as discussed above, one important member of the Kinesin Family is Eg5, a plus-end-directed motor, which is thought to generate force to push the two poles of the mitotic soindle apart. Blocking of Eg5 protein function by means of small molecules or antibodies results in the collapse of the spindle, ultimatly preventing cell division. Accordingly, inhibition of mitotic kinesines, such as Eg5, is an attractive target for the development of novel anti-mitotic drugs.

SUMMARY OF THE INVENTION

[0010] The present invention provides compounds, compositions, methods and systems for inhibiting cell growth. More specifically, the present invention provides methods, compounds and compositions that are capable of inhibiting mitosis in metabolically active cells. Compounds, and compositions of the present invention inhibit the activity of a protein involved in the assembly and maintenance of the mitotic spindle. One class of proteins which acts on the mitotic spindle is the family of mitotic kinesins, a subset of the kinesin superfamily.

[0011] In one aspect, the present invention provides a compound having the formula (I):



and pharmaceutically acceptable derivatives thereof; as described generally and in subclasses herein, which compounds are useful as kinesin inhibitors (*e.g.*, Eg5 inhibitors), and thus are useful, for example, for the treatment of cancer.

[0012] In certain other embodiments, the invention provides pharmaceutical compositions comprising an inventive compound, wherein the compound is present in an amount effective to inhibit Eg5 activity. In certain other embodiments, the

invention provides pharmaceutical compositions comprising an inventive compound and optionally further comprising an additional therapeutic and/or palliative agent. In yet other embodiments, the additional therapeutic agent is an anticancer agent.

[0013] In yet another aspect, the present invention provides methods for inhibiting Eg5 activity in a patient or a biological sample, comprising administering to said patient, or contacting said biological sample with an effective inhibitory amount of a compound of the invention. In still another aspect, the present invention provides methods for treating any disorder involving Eg5 activity, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of the invention. In yet other embodiments, the present invention provides a method for treating cancer comprising administering to a subject in need thereof a therapeutically effective amount of a compound of the invention.

BRIEF DESCRIPTION OF DRAWINGS

[0014] Figure 1 depicts results of semi-empirical quantum mechanic calculation (PM3) on conformations of Monastrol.

[0015] Figure 2 depicts data from an experiment examining the inhibition of Eg5 ATPase activity by inventive compounds.

DEFINITIONS

[0016] Certain compounds of the present invention, and definitions of specific functional groups are described in more detail below. For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in "Organic Chemistry", Thomas Sorrell, University Science Books, Sausalito: 1999, the entire contents of which are incorporated herein by reference. Furthermore, it will be appreciated by one of ordinary skill in the art that the synthetic methods, as described herein, utilize a variety of protecting groups. By the term "protecting group", as used herein, it is meant that a particular functional moiety, *e.g.*, O, S, or N, is temporarily blocked so that a reaction can be carried out selectively at another reactive site in a multifunctional compound. In preferred embodiments, a protecting group reacts selectively in good yield to give a protected substrate that is stable to the projected

reactions; the protecting group must be selectively removed in good yield by readily available, preferably nontoxic reagents that do not attack the other functional groups; the protecting group may form an easily separable derivative (more preferably without the generation of new stereogenic centers); and the protecting group has a minimum of additional functionality to avoid further sites of reaction. As detailed herein, oxygen, sulfur, nitrogen and carbon protecting groups may be utilized. For example, in certain embodiments, as detailed herein, certain exemplary oxygen protecting groups are utilized. These oxygen protecting groups include, but are not limited to methyl ethers, substituted methyl ethers (*e.g.*, MOM (methoxymethyl ether), MTM (methylthiomethyl ether), BOM (benzyloxymethyl ether), PMBM (p-methoxybenzyloxymethyl ether), to name a few), substituted ethyl ethers, substituted benzyl ethers, silyl ethers (*e.g.*, TMS (trimethylsilyl ether), TES (triethylsilyl ether), TIPS (triisopropylsilyl ether), TBDMS (t-butyldimethylsilyl ether), tribenzyl silyl ether, TBDPS (t-butyldiphenyl silyl ether), to name a few), esters (*e.g.*, formate, acetate, benzoate (Bz), trifluoroacetate, dichloroacetate, to name a few), carbonates, cyclic acetals and ketals. In certain other exemplary embodiments, nitrogen protecting groups are utilized. These nitrogen protecting groups include, but are not limited to, carbamates (including methyl, ethyl and substituted ethyl carbamates (*e.g.*, Troc), to name a few) amides, cyclic imide derivatives, N-Alkyl and N-Aryl amines, imine derivatives, and enamine derivatives, to name a few. Certain other exemplary protecting groups are detailed herein, however, it will be appreciated that the present invention is not intended to be limited to these protecting groups; rather, a variety of additional equivalent protecting groups can be readily identified using the above criteria and utilized in the present invention. Additionally, a variety of protecting groups are described in "Protective Groups in Organic Synthesis" Third Ed. Greene, T.W. and Wuts, P.G., Eds., John Wiley & Sons, New York: 1999, the entire contents of which are hereby incorporated by reference

[0017] It will be appreciated that the compounds, as described herein, may be substituted with any number of substituents or functional moieties. In general, the term "substituted" whether preceded by the term "optionally" or not, and substituents contained in formulas of this invention, refer to the replacement of hydrogen radicals in a given structure with the radical of a specified substituent. When more than one position in any given structure may be substituted with more than one substituent

selected from a specified group, the substituent may be either the same or different at every position. As used herein, the term "substituted" is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and non-aromatic substituents of organic compounds. For purposes of this invention, heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valencies of the heteroatoms. Furthermore, this invention is not intended to be limited in any manner by the permissible substituents of organic compounds. Combinations of substituents and variables envisioned by this invention are preferably those that result in the formation of stable compounds useful in the treatment and prevention, for example of disorders, as described generally above. The term "stable", as used herein, preferably refers to compounds which possess stability sufficient to allow manufacture and which maintain the integrity of the compound for a sufficient period of time to be detected and preferably for a sufficient period of time to be useful for the purposes detailed herein.

[0018] The term "aliphatic", as used herein, includes both saturated and unsaturated, straight chain (*i.e.*, unbranched), branched, cyclic, or polycyclic aliphatic hydrocarbons, which are optionally substituted with one or more functional groups. As will be appreciated by one of ordinary skill in the art, "aliphatic" is intended herein to include, but is not limited to, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, and cycloalkynyl moieties. Thus, as used herein, the term "alkyl" includes straight, branched and cyclic alkyl groups. An analogous convention applies to other generic terms such as "alkenyl", "alkynyl" and the like. Furthermore, as used herein, the terms "alkyl", "alkenyl", "alkynyl" and the like encompass both substituted and unsubstituted groups. In certain embodiments, as used herein, "lower alkyl" is used to indicate those alkyl groups (cyclic, acyclic, substituted, unsubstituted, branched or unbranched) having 1-6 carbon atoms.

[0019] In certain embodiments, the alkyl, alkenyl and alkynyl groups employed in the invention contain 1-20 aliphatic carbon atoms. In certain other embodiments, the alkyl, alkenyl, and alkynyl groups employed in the invention contain 1-10 aliphatic carbon atoms. In yet other embodiments, the alkyl, alkenyl, and alkynyl groups employed in the invention contain 1-8 aliphatic carbon atoms. In still other

embodiments, the alkyl, alkenyl, and alkynyl groups employed in the invention contain 1-6 aliphatic carbon atoms. In yet other embodiments, the alkyl, alkenyl, and alkynyl groups employed in the invention contain 1-4 aliphatic carbon atoms. Illustrative aliphatic groups thus include, but are not limited to, for example, methyl, ethyl, n-propyl, isopropyl, cyclopropyl, -CH₂-cyclopropyl, allyl, n-butyl, sec-butyl, isobutyl, tert-butyl, cyclobutyl, -CH₂-cyclobutyl, n-pentyl, sec-pentyl, isopentyl, tert-pentyl, cyclopentyl, -CH₂-cyclopentyl-n, hexyl, sec-hexyl, cyclohexyl, -CH₂-cyclohexyl moieties and the like, which again, may bear one or more substituents. Alkenyl groups include, but are not limited to, for example, ethenyl, propenyl, butenyl, 1-methyl-2-buten-1-yl, and the like. Representative alkynyl groups include, but are not limited to, ethynyl, 2-propynyl (propargyl), 1-propynyl and the like.

[0020] The term “alkoxy” (or “alkyloxy”), or “thioalkyl” as used herein refers to an alkyl group, as previously defined, attached to the parent molecular moiety through an oxygen atom or through a sulfur atom. In certain embodiments, the alkyl group contains 1-20 aliphatic carbon atoms. In certain other embodiments, the alkyl group contains 1-10 aliphatic carbon atoms. In yet other embodiments, the alkyl, alkenyl, and alkynyl groups employed in the invention contain 1-8 aliphatic carbon atoms. In still other embodiments, the alkyl group contains 1-6 aliphatic carbon atoms. In yet other embodiments, the alkyl group contains 1-4 aliphatic carbon atoms. Examples of alkoxy, include but are not limited to, methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, tert-butoxy, neopentoxo and n-hexoxy. Examples of thioalkyl include, but are not limited to, methylthio, ethylthio, propylthio, isopropylthio, n-butylthio, and the like.

[0021] The term “alkylamino” refers to a group having the structure -NHR' wherein R' is alkyl, as defined herein. The term “dialkylamino” refers to a group having the structure -N(R')₂, wherein R' is alkyl, as defined herein. The term “aminoalkyl” refers to a group having the structure NH₂R'-, wherein R' is alkyl, as defined herein. In certain embodiments, the alkyl group contains 1-20 aliphatic carbon atoms. In certain other embodiments, the alkyl group contains 1-10 aliphatic carbon atoms. In yet other embodiments, the alkyl, alkenyl, and alkynyl groups employed in the invention contain 1-8 aliphatic carbon atoms. In still other embodiments, the alkyl group contains 1-6 aliphatic carbon atoms. In yet other embodiments, the alkyl group

contains 1-4 aliphatic carbon atoms. Examples of alkylamino include, but are not limited to, methylamino, ethylamino, iso-propylamino and the like.

[0022] Some examples of substituents of the above-described aliphatic (and other) moieties of compounds of the invention include, but are not limited to aliphatic; heteroaliphatic; aryl; heteroaryl; alkylaryl; alkylheteroaryl; alkoxy; aryloxy; heteroalkoxy; heteroaryloxy; alkylthio; arylthio; heteroalkylthio; heteroarylthio; F; Cl; Br; I; -OH; -NO₂; -CN; -CF₃; -CH₂CF₃; -CHCl₂; -CH₂OH; -CH₂CH₂OH; -CH₂NH₂; -CH₂SO₂CH₃; -C(O)R_x; -CO₂(R_x); -CON(R_x)₂; -OC(O)R_x; -OCO₂R_x; -OCON(R_x)₂; -N(R_x)₂; -S(O)R_x; -S(O)₂R_x; -NR_x(CO)R_x; -N(R_x)CO₂R_x; -N(R_x)S(O)₂R_x; -N(R_x)C(=O)N(R_x)₂; -S(O)₂N(R_x)₂; wherein each occurrence of R_x independently includes, but is not limited to, aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl, wherein any of the aliphatic, heteroaliphatic, alkylaryl, or alkylheteroaryl substituents described above and herein may be substituted or unsubstituted, branched or unbranched, cyclic or acyclic, and wherein any of the aryl, heteroaryl, -(alkyl)aryl or -(alkyl)heteroaryl substituents described above and herein may be substituted or unsubstituted. Additional examples of generally applicable substituents are illustrated by the specific embodiments shown in the Examples that are described herein.

[0023] In general, the terms “aromatic moiety” and “heteroaromatic moiety”, as used herein, refer to stable mono- or polycyclic, heterocyclic, polycyclic, and polyheterocyclic unsaturated moieties having preferably 3-14 carbon atoms, each of which may be substituted or unsubstituted. It will also be appreciated that aromatic and heteroaromatic moieties, as defined herein may be attached via an alkyl or heteroalkyl moiety and thus also include -(alkyl)aromatic, -(heteroalkyl)aromatic, -(heteroalkyl)heteroaromatic, and -(heteroalkyl)heteroaromatic moieties. Thus, as used herein, the phrases “aromatic or heteroaromatic moieties” and “aromatic, heteroaromatic, -(alkyl)aromatic, -(heteroalkyl)aromatic, -(heteroalkyl)heteroaromatic, and -(heteroalkyl)heteroaromatic” are interchangeable. Substituents include, but are not limited to, any of the previously mentioned substituents, *i.e.*, the substituents recited for aliphatic moieties, or for other moieties as disclosed herein, resulting in the formation of a stable compound.

[0024] The term “aryl”, as used herein, does not differ significantly from the common meaning of the term in the art, and refers to a mono- or bicyclic carbocyclic ring

system having one or two aromatic rings including, but not limited to, phenyl, naphthyl, tetrahydronaphthyl, indanyl, indenyl and the like.

[0025] The term “heteroaryl”, as used herein, does not differ significantly from the common meaning of the term in the art, and refers to a cyclic aromatic radical having from five to ten ring atoms of which one ring atom is selected from S, O and N; zero, one or two ring atoms are additional heteroatoms independently selected from S, O and N; and the remaining ring atoms are carbon, the radical being joined to the rest of the molecule via any of the ring atoms, such as, for example, pyridyl, pyrazinyl, pyrimidinyl, pyrrolyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, isooxazolyl, thiadiazolyl, oxadiazolyl, thiophenyl, furanyl, quinoliny, isoquinoliny, and the like.

[0026] It will be appreciated that aryl and heteroaryl groups (including bicyclic aryl groups) can be unsubstituted or substituted, wherein substitution includes replacement of one or more of the hydrogen atoms thereon independently with any one or more of the following moieties including, but not limited to: aliphatic; heteroaliphatic; aryl; heteroaryl; alkylaryl; alkylheteroaryl; alkoxy; aryloxy; heteroalkoxy; heteroaryloxy; alkylthio; arylthio; heteroalkylthio; heteroarylthio; F; Cl; Br; I; -OH; -NO₂; -CN; -CF₃; -CH₂CF₃; -CHCl₂; -CH₂OH; -CH₂CH₂OH; -CH₂NH₂; -CH₂SO₂CH₃; -C(O)R_x; -CO₂(R_x); -CON(R_x)₂; -OC(O)R_x; -OCO₂R_x; -OCON(R_x)₂; -N(R_x)₂; -S(O)R_x; -S(O)₂R_x; -NR_x(CO)R_x; -N(R_x)CO₂R_x; -N(R_x)S(O)₂R_x; -N(R_x)C(=O)N(R_x)₂; -S(O)₂N(R_x)₂; wherein each occurrence of R_x independently includes, but is not limited to, aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl, wherein any of the aliphatic, heteroaliphatic, alkylaryl, or alkylheteroaryl substituents described above and herein may be substituted or unsubstituted, branched or unbranched, cyclic or acyclic, and wherein any of the aryl, heteroaryl, -(alkyl)aryl or -(alkyl)heteroaryl substituents described above and herein may be substituted or unsubstituted. Additionally, it will be appreciated, that any two adjacent groups taken together may represent a 4, 5, 6, or 7-membered cyclic, substituted or unsubstituted aliphatic or heteroaliphatic moiety. Additional examples of generally applicable substituents are illustrated by the specific embodiments shown in the Examples that are described herein.

[0027] The term “cycloalkyl”, as used herein, refers specifically to cyclic moieties having three to seven, preferably three to ten carbon atoms. Suitable cycloalkyls include, but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl,

cycloheptyl and the like, which, as in the case of other aliphatic, heteroaliphatic or heterocyclic moieties, may optionally be substituted with substituents including, but not limited to aliphatic; heteroaliphatic; aryl; heteroaryl; alkylaryl; alkylheteroaryl; alkoxy; aryloxy; heteroalkoxy; heteroaryloxy; alkylthio; arylthio; heteroalkylthio; heteroarylthio; F; Cl; Br; I; -OH; -NO₂; -CN; -CF₃; -CH₂CF₃; -CHCl₂; -CH₂OH; -CH₂CH₂OH; -CH₂NH₂; -CH₂SO₂CH₃; -C(O)R_x; -CO₂(R_x); -CON(R_x)₂; -OC(O)R_x; -OCO₂R_x; -OCON(R_x)₂; -N(R_x)₂; -S(O)R_x; -S(O)₂R_x; -NR_x(CO)R_x; -N(R_x)CO₂R_x; -N(R_x)S(O)₂R_x; -N(R_x)C(=O)N(R_x)₂; -S(O)₂N(R_x)₂; wherein each occurrence of R_x independently includes, but is not limited to, aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl, wherein any of the aliphatic, heteroaliphatic, alkylaryl, or alkylheteroaryl substituents described above and herein may be substituted or unsubstituted, branched or unbranched, cyclic or acyclic, and wherein any of the aryl, heteroaryl, -(alkyl)aryl or -(alkyl)heteroaryl substituents described above and herein may be substituted or unsubstituted. Additionally, it will be appreciated that any of the cycloaliphatic or cycloheteroaliphatic moieties described above and herein may comprise an aryl, heteroaryl, -(alkyl)aryl or -(alkyl)heteroaryl moiety fused thereto. Additional examples of generally applicable substituents are illustrated by the specific embodiments shown in the Examples that are described herein.

[0028] The term “heteroaliphatic”, as used herein, refers to aliphatic moieties in which one or more carbon atoms in the main chain have been substituted with a heteroatom. Thus, a heteroaliphatic group refers to an aliphatic chain which contains one or more oxygen sulfur, nitrogen, phosphorus or silicon atoms, *e.g.*, in place of carbon atoms. Heteroaliphatic moieties may be branched, unbranched, cyclic or acyclic and include saturated and unsaturated heterocycles such as morpholino, pyrrolidinyl, etc. In certain embodiments, heteroaliphatic moieties are substituted by independent replacement of one or more of the hydrogen atoms thereon with one or more moieties including, but not limited to aliphatic; heteroaliphatic; aryl; heteroaryl; alkylaryl; alkylheteroaryl; alkoxy; aryloxy; heteroalkoxy; heteroaryloxy; alkylthio; arylthio; heteroalkylthio; heteroarylthio; F; Cl; Br; I; -OH; -NO₂; -CN; -CF₃; -CH₂CF₃; -CHCl₂; -CH₂OH; -CH₂CH₂OH; -CH₂NH₂; -CH₂SO₂CH₃; -C(O)R_x; -CO₂(R_x); -CON(R_x)₂; -OC(O)R_x; -OCO₂R_x; -OCON(R_x)₂; -N(R_x)₂; -S(O)R_x; -S(O)₂R_x; -NR_x(CO)R_x; -N(R_x)CO₂R_x; -N(R_x)S(O)₂R_x; -N(R_x)C(=O)N(R_x)₂; -

$S(O)_2N(R_x)_2$; wherein each occurrence of R_x independently includes, but is not limited to, aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl, wherein any of the aliphatic, heteroaliphatic, alkylaryl, or alkylheteroaryl substituents described above and herein may be substituted or unsubstituted, branched or unbranched, cyclic or acyclic, and wherein any of the aryl, heteroaryl, -(alkyl)aryl or -(alkyl)heteroaryl substituents described above and herein may be substituted or unsubstituted.

[0029] In general, the term “cycloaliphatic”, as used herein, refer to a cyclic aliphatic moiety, wherein the term *aliphatic* is as defined above. A cycloaliphatic moiety may be substituted or unsubstituted and saturated or unsaturated. Substituents include, but are not limited to, any of the previously mentioned substituents, *i.e.*, the substituents recited for aliphatic moieties, or for other moieties as disclosed herein, resulting in the formation of a stable compound. In certain embodiments, cycloaliphatic compounds include but are not limited to monocyclic, or polycyclic aliphatic hydrocarbons and bridged cycloalkyl compounds, which are optionally substituted with one or more functional groups. As will be appreciated by one of ordinary skill in the art, “cycloaliphatic” is intended herein to include, but is not limited to, cycloalkyl, cycloalkenyl, and cycloalkynyl moieties, which are optionally substituted with one or more functional groups. Illustrative cycloaliphatic groups thus include, but are not limited to, for example, cyclopropyl, -CH₂-cyclopropyl, cyclobutyl, -CH₂-cyclobutyl, cyclopentyl, -CH₂-cyclopentyl, cyclohexyl, -CH₂-cyclohexyl, cyclohexenylethyl, cyclohexanylethyl, norborbyl moieties and the like, which again, may bear one or more substituents.

[0030] The terms “halo” and “halogen” as used herein refer to an atom selected from fluorine, chlorine, bromine and iodine.

[0031] The term “haloalkyl” denotes an alkyl group, as defined above, having one, two, or three halogen atoms attached thereto and is exemplified by such groups as chloromethyl, bromoethyl, trifluoromethyl, and the like.

[0032] The term “acyl”, as used herein, refers to a group having the general formula -C(=O)R, where R is an aliphatic, heteroaliphatic, heterocycle, aromatic or heteroaromatic moiety, as defined herein.

[0033] The term “heterocycloalkyl”, “heterocycle” or “heterocyclic”, as used herein, refers to compounds which combine the properties of heteroaliphatic and cyclic

compounds and include, but are not limited to, saturated and unsaturated mono- or polycyclic cyclic ring systems having 5-16 atoms wherein at least one ring atom is a heteroatom selected from O, S and N (wherein the nitrogen and sulfur heteroatoms may be optionally be oxidized), wherein the ring systems are optionally substituted with one or more functional groups, as defined herein. In certain embodiments, the term "heterocycloalkyl", "heterocycle" or "heterocyclic" refers to a non-aromatic 5-, 6- or 7- membered ring or a polycyclic group wherein at least one ring atom is a heteroatom selected from O, S and N (wherein the nitrogen and sulfur heteroatoms may be optionally be oxidized), including, but not limited to, a bi- or tri-cyclic group, comprising fused six-membered rings having between one and three heteroatoms independently selected from oxygen, sulfur and nitrogen, wherein (i) each 5-membered ring has 0 to 2 double bonds, each 6-membered ring has 0 to 2 double bonds and each 7-membered ring has 0 to 3 double bonds, (ii) the nitrogen and sulfur heteroatoms may be optionally be oxidized, (iii) the nitrogen heteroatom may optionally be quaternized, and (iv) any of the above heterocyclic rings may be fused to an aryl or heteroaryl ring. Representative heterocycles include, but are not limited to, heterocycles such as furanyl, thiofuranyl, pyranal, pyrrolal, thienal, pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, oxazolyl, oxazolidinyl, isooxazolyl, isoxazolidinyl, dioxazolyl, thiadiazolyl, oxadiazolyl, tetrazolyl, triazolyl, thiatriazolyl, oxatriazolyl, thiadiazolyl, oxadiazolyl, morpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, dithiazolyl, dithiazolidinyl, tetrahydrofuryl, and benzofused derivatives thereof. In certain embodiments, a "substituted heterocycle, or heterocycloalkyl or heterocyclic" group is utilized and as used herein, refers to a heterocycle, or heterocycloalkyl or heterocyclic group, as defined above, substituted by the independent replacement of one, two or three of the hydrogen atoms thereon with but are not limited to aliphatic; cycloaliphatic; heteroaliphatic; heterocyclic; aromatic; heteroaromatic; aryl; heteroaryl; alkylaryl; heteroalkylaryl; alkylheteroaryl; heteroalkylheteroaryl; alkoxy; aryloxy; heteroalkoxy; heteroaryloxy; alkylthio; arylthio; heteroalkylthio; heteroarylthio; F; Cl; Br; I; - OH; -NO₂; -CN; -CF₃; -CH₂CF₃; -CHCl₂; -CH₂OH; -CH₂CH₂OH; -CH₂NH₂; -CH₂SO₂CH₃; -C(O)R_x; -CO₂(R_x); -CON(R_x)₂; -OC(O)R_x; -OCO₂R_x; -OCON(R_x)₂; -N(R_x)₂; -S(O)₂R_x; -NR_x(CO)R_x; -N(R_x)CO₂R_x; -N(R_x)S(O)₂R_x; -N(R_x)C(=O)N(R_x)₂; -S(O)₂N(R_x)₂; wherein each occurrence of R_x

independently includes, but is not limited to, aliphatic, cycloaliphatic, heteroaliphatic, heterocyclic, aromatic, heteroaromatic, aryl, heteroaryl, alkylaryl, alkylheteroaryl, heteroalkylaryl or heteroalkylheteroaryl, wherein any of the aliphatic, cycloaliphatic, heteroaliphatic, heterocyclic, alkylaryl, or alkylheteroaryl substituents described above and herein may be substituted or unsubstituted, branched or unbranched, saturated or unsaturated, and wherein any of the aromatic, heteroaromatic, aryl or heteroaryl substituents described above and herein may be substituted or unsubstituted. Additional examples or generally applicable substituents are illustrated by the specific embodiments shown in the Examples, which are described herein.

[0034] Additionally, it will be appreciated that any of the cycloaliphatic or cycloheteroaliphatic moieties described above and herein may comprise an aryl, heteroaryl, -(alkyl)aryl or -(alkyl)heteroaryl moiety fused thereto. Additional examples of generally applicable substituents are illustrated by the specific embodiments shown in the Examples that are described herein.

[0035] As used herein, the terms "aliphatic", "heteroaliphatic", "alkyl", "alkenyl", "alkynyl", "heteroalkyl", "heteroalkenyl", "heteroalkynyl", and the like encompass substituted and unsubstituted, saturated and unsaturated, and linear and branched groups. Similarly, the terms "alicyclic", "heterocyclic", "heterocycloalkyl", "heterocycle" and the like encompass substituted and unsubstituted, and saturated and unsaturated groups. Additionally, the terms "cycloalkyl", "cycloalkenyl", "cycloalkynyl", "heterocycloalkyl", "heterocycloalkenyl", "heterocycloalkynyl", "aromatic", "heteroaromatic", "aryl", "heteroaryl" and the like encompass both substituted and unsubstituted groups.

[0036] As used herein, the term "isolated", when applied to the compounds of the present invention, refers to such compounds that are (i) separated from at least some components with which they are associated in nature or when they are made and/or (ii) produced, prepared or manufactured by the hand of man.

[0037] The phrase, "pharmaceutically acceptable derivative", as used herein, denotes any pharmaceutically acceptable salt, ester, or salt of such ester, of such compound, or any other adduct or derivative which, upon administration to a patient, is capable of providing (directly or indirectly) a compound as otherwise described herein, or a metabolite or residue thereof. Pharmaceutically acceptable derivatives thus include among others pro-drugs. A pro-drug is a derivative of a compound, usually with

significantly reduced pharmacological activity, which contains an additional moiety that is susceptible to removal *in vivo* yielding the parent molecule as the pharmacologically active species. An example of a pro-drug is an ester which is cleaved *in vivo* to yield a compound of interest. Pro-drugs of a variety of compounds, and materials and methods for derivatizing the parent compounds to create the pro-drugs, are known and may be adapted to the present invention. Certain exemplary pharmaceutical compositions and pharmaceutically acceptable derivatives will be discussed in more detail herein below.

[0038] The term “treating”, as used herein generally means that the compounds of the invention can be used in humans or animals with at least a tentative diagnosis of disease. The compounds of the invention will delay or slow the progression of the disease thereby giving the individual a more useful life span.

[0039] The term “preventing” or “prevention” as used herein means that the compounds of the present invention are useful when administered to a patient who has not been diagnosed as possibly having the disease at the time of administration, but who would normally be expected to develop the disease or be at increased risk for the disease. The compounds of the invention will slow the development of disease symptoms, delay the onset of disease, or prevent the individual from developing the disease at all.

[0040] As used herein the term “*biological sample*” includes, without limitation, cell cultures or extracts thereof; biopsied material obtained from an animal (*e.g.*, mammal) or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof. For example, the term “biological sample” refers to any solid or fluid sample obtained from, excreted by or secreted by any living organism, including single-celled micro-organisms (such as bacteria and yeasts) and multicellular organisms (such as plants and animals, for instance a vertebrate or a mammal, and in particular a healthy or apparently healthy human subject or a human patient affected by a condition or disease to be diagnosed or investigated). The biological sample can be in any form, including a solid material such as a tissue, cells, a cell pellet, a cell extract, cell homogenates, or cell fractions; or a biopsy, or a biological fluid. The biological fluid may be obtained from any site (*e.g.* blood, saliva (or a mouth wash containing buccal cells), tears, plasma, serum, urine, bile, cerebrospinal fluid, amniotic fluid, peritoneal fluid, and pleural fluid, or cells therefrom, aqueous or

vitreous humor, or any bodily secretion), a transudate, an exudate (*e.g.* fluid obtained from an abscess or any other site of infection or inflammation), or fluid obtained from a joint (*e.g.* a normal joint or a joint affected by disease such as rheumatoid arthritis, osteoarthritis, gout or septic arthritis). The biological sample can be obtained from any organ or tissue (including a biopsy or autopsy specimen) or may comprise cells (whether primary cells or cultured cells) or medium conditioned by any cell, tissue or organ. Biological samples may also include sections of tissues such as frozen sections taken for histological purposes. Biological samples also include mixtures of biological molecules including proteins, lipids, carbohydrates and nucleic acids generated by partial or complete fractionation of cell or tissue homogenates. Although the sample is preferably taken from a human subject, biological samples may be from any animal, plant, bacteria, virus, yeast, etc. The term *animal*, as used herein, refers to humans as well as non-human animals, at any stage of development, including, for example, mammals, birds, reptiles, amphibians, fish, worms and single cells. Cell cultures and live tissue samples are considered to be pluralities of animals. In certain exemplary embodiments, the non-human animal is a mammal (*e.g.*, a rodent, a mouse, a rat, a rabbit, a monkey, a dog, a cat, a sheep, cattle, a primate, or a pig). An animal may be a transgenic animal or a human clone. If desired, the biological sample may be subjected to preliminary processing, including preliminary separation techniques.

[0041] As used herein, the phrase "radiation therapy" includes, but is not limited to, x-rays or gamma rays which are delivered from either an externally applied source such as a beam or by implantation of small radioactive sources.

[0042] As used herein, the phrase "antineoplastic agent" refers to compounds which prevent cancer cells from multiplying. In general, the antineoplastic agents of this invention prevent cancer cells from multiplying by: (1) interfering with the cell's ability to replicate DNA, or (2) inducing apoptosis in the cancerous cells.

[0043] As used herein, the term "subject" encompasses all animal species. In certain embodiments, the subject is a mammal. In certain other embodiments, the subject is a human.

[0044] "Therapeutically effective": As used herein, the term "therapeutically effective" is defined as an amount of a compound or composition comprising the compound which is administered to an individual in need thereof to slow or cease uncontrolled or abnormal growth of cells in the individual without toxicity.

[0045] "Cancer or cancerous growth": As used herein, the term "cancer" or "cancerous growth" means the uncontrolled, abnormal growth of cells and includes within its scope all the well known diseases that are caused by the uncontrolled and abnormal growth of cells. Non-limiting examples of common cancers include bladder cancer, breast cancer, colon cancer, endometrial cancer, head and neck cancer, lung cancer, melanoma, non-hodgkin's lymphoma, prostate cancer, and rectal cancer. A complete list of cancers is available from the National Cancer Institute (Bethesda, MD).

DESCRIPTION OF CERTAIN PREFERRED EMBODIMENTS OF THE INVENTION

[0046] As noted above, there remains a need for small molecule activators or inhibitors that are specific for one member of the kinesin family. Such compounds, having specificity for a particular member of a kinesin class, would be useful as an anti-mitotic and also as an anti-cancer, anti-tumorigenic compound. In certain embodiments, the present invention provides compounds, compositions, methods and systems for inhibiting cell growth. In certain exemplary embodiments, the present invention provides for methods, compounds and compositions which are capable of inhibiting mitosis in metabolically active cells. In certain embodiments, compounds, compositions and methods of the present invention inhibit the activity of a protein involved in the assembly and maintenance of the mitotic spindle. One class of proteins which acts on the mitotic spindle is the family of mitotic kinesins, a subset of the kinesin superfamily. In certain exemplary embodiments, the invention provides a new class of bicyclic dihydropyrimidines exhibiting Eg5 inhibitory activity. Thus, in certain exemplary embodiments, the present invention provides novel bicyclic dihydropyrimidine compounds useful for the treatment of cancer.

[0047] Additionally, the present invention provides pharmaceutically acceptable derivatives of the inventive compounds, and methods of treating a subject using these compounds, pharmaceutical compositions thereof, or either of these in combination with one or more additional therapeutic agents.

[0048] *Monastrol*

[0049] Mitchison and coworkers have demonstrated that the dihydropyrimidine-based compound monastrol is capable of arresting mammalian cells in mitosis with monopolar spindles (Mayer *et al. Science* 286:971-974, 1999; incorporated herein by reference). *In vitro*, monastrol specifically inhibited the motility of the mitotic kinesin

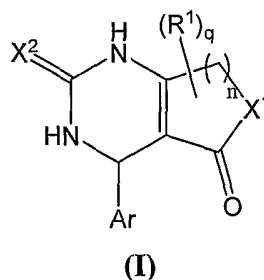
Eg5, a motor protein required for spindle bipolarity. Monastrol was identified as causing monoastrol spindles in mitotic cells in a multistep screen. See U.S. Patent Application 09/791,339 filed 2/23/01, which is hereby incorporated by reference in its entirety.

[0050] In addition, by studying the effects of monastrol and a related compound DHP2 on microtubule motility, Mayer *et al.* (*Science* 286:971-974, 1999) determined that the inhibition of monastrol on the Eg5 kinesin is specific to monastrol. Furthermore, monastrol's inhibiting effect on motility is specific for the Eg5 kinesin. Monastrol did not inhibit microtubule motility driven by conventional kinesin (Mayer *et al.* *Science* 286:971-974, 1999.)

[0051] In certain embodiments, the present invention provides constrained analogs of Monastrol having Eg5 inhibitory activity.

[0052] **1) General Description of Compounds of the Invention**

[0053] In certain embodiments, the compounds of the invention include compounds of the general formula (I) as further defined below:



and pharmaceutically acceptable derivatives thereof;

wherein **Ar** is an aromatic or heteroaromatic moiety;

X¹ is O or NR^{X¹}, wherein R^{X¹} is hydrogen or an aliphatic, heteroaliphatic, aromatic or heteroaromatic moiety;

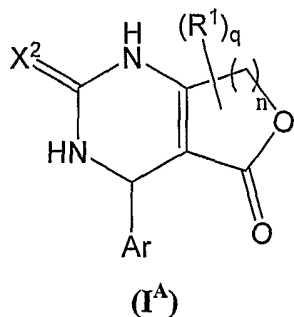
X² is O or S;

n is 1 or 2;

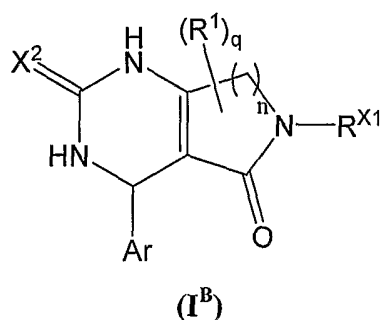
q is an integer from 0-4; and

each occurrence of **R₁** is independently hydrogen, halogen, hydroxy, or an aliphatic, heteroaliphatic, aromatic or heteroaromatic moiety.

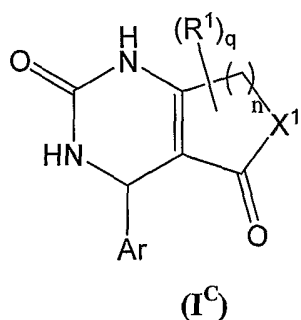
[0054] In certain embodiments, the present invention defines particular classes of compounds which are of special interest. For example, one class of compounds of special interest includes those compounds of formula (I) wherein, X¹ is O and the compound has the structure (I^A):



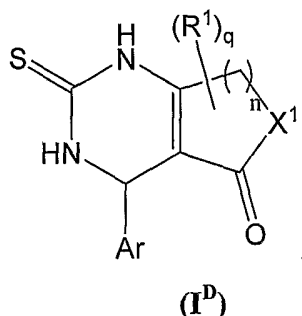
[0055] Another class of compounds of special interest includes those compounds of formula **(I)** wherein, X^1 is NR^{X1} and the compound has the Formula **(I^B)**:



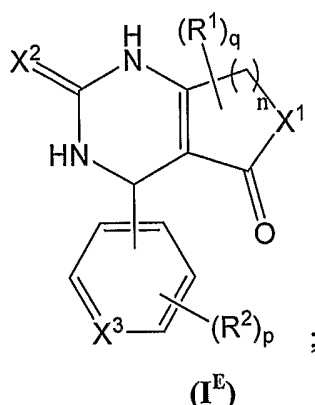
[0056] Another class of compounds of special interest includes those compounds of formula **(I)** wherein, X^2 is O and the compound has the Formula **(I^C)**:



[0057] Another class of compounds of special interest includes those compounds of formula **(I)** wherein, X^2 is S and the compound has the Formula **(I^D)**:



[0058] Another class of compounds of special interest includes those compounds of formula **(I)** wherein, Ar is a phenyl or pyridyl moiety and the compound has the Formula **(I^E)**:



wherein X^3 is N or CR^2 ; p is 0-5; and each occurrence of R^2 is independently hydrogen, halogen, CN, NO_2 , alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, heterocycle, aryl, heteroaryl, -(alkyl)cycloalkyl, -(alkyl)heterocycle, -(heteroalkyl)cycloalkyl, -(heteroalkyl)heterocycle, -(alkyl)aryl, -(heteroalkyl)aryl, -(alkyl)heteroaryl, -(heteroalkyl)heteroaryl, $-OR^{2A}$, $-S(=O)_xR^{2A}$, $-N(R^{2A})_2$, $-SO_2N(R^{2A})_2$, $-C(=O)R^{2A}$, $-C(=O)N(R^{2A})_2$, $-C(=O)OR^{2A}$, $-N(R^{2A})C(=O)R^{2B}$ or $-N(R^{2A})SO_2R^{2B}$, wherein x is 0, 1 or 2; and each occurrence of R^{2A} and R^{2B} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl or -(alkyl)heteroaryl; or R^{2A} and R^{2B} , taken together with the atoms to which they are attached, form a substituted or unsubstituted 5-8 membered heterocyclic moiety.

[0059] In certain embodiments, the following groups do not occur simultaneously as defined: X^1 and X^2 are each O, n is 1 and q is 0.

[0060] In certain embodiments, the following groups do not occur simultaneously as defined: X^2 is O, n is 1, q is 0 and X^1 is NR^{X1} , wherein R^{X1} is H, methyl or $-CH_2Ph$.

[0061] A number of important subclasses of each of the foregoing classes deserve separate mention; these subclasses include subclasses of the foregoing classes in which:

[0062] i) X^1 is O;

[0063] ii) X^1 is NR^{X1} , wherein R^{X1} is hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, heterocycle, acyl, aryl, heteroaryl, -(alkyl)cycloalkyl, -(alkyl)heterocycle, -(heteroalkyl)cycloalkyl, -(heteroalkyl)heterocycle, -(alkyl)aryl, -(heteroalkyl)aryl, -(alkyl)heteroaryl or -(heteroalkyl)heteroaryl;

[0064] iii) X^1 is NR^{X1} , wherein R^{X1} is hydrogen, lower alkyl, lower heteroalkyl, cycloalkyl, heterocycle, lower acyl, aryl, heteroaryl, -(alkyl)cycloalkyl, -(alkyl)heterocycle, -(alkyl)aryl, -(heteroalkyl)aryl or -(alkyl)heteroaryl;

[0065] iv) X^1 is NR^{X1} , wherein R^{X1} is hydrogen, lower alkyl, lower acyl, aryl or heteroaryl;

[0066] v) X^1 is NR^{X1} , wherein R^{X1} is hydrogen, lower alkyl or lower acyl;

[0067] vi) X^1 is NH;

[0068] vii) X^1 is NAc;

[0069] viii) X^1 is NR^{X1} , wherein R^{X1} is methyl, ethyl, propyl or iso-propyl;

[0070] ix) X^2 is O;

[0071] x) X^2 is S;

[0072] xi) n is 1;

[0073] xii) n is 2;

[0074] xiii) p is 0;

[0075] xiv) p is 1;

[0076] xv) p is 2;

[0077] xvi) p is 3;

[0078] xvii) q is 0;

[0079] xviii) q is 1;

[0080] xix) q is 2;

[0081] xx) q is 3;

[0082] xxi) q is 4;

[0083] xxii) n is 1 and q is 0;

[0084] xxiii) n is 2 and q is 0;

[0085] xxiv) each occurrence of R^1 is independently hydrogen, halogen, hydroxy, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, heterocycle, aryl, heteroaryl, -(alkyl)cycloalkyl, -(alkyl)heterocycle, -(heteroalkyl)cycloalkyl, -(heteroalkyl)heterocycle, -(alkyl)aryl, -(heteroalkyl)aryl, -(alkyl)heteroaryl, -(heteroalkyl)heteroaryl, $-OR^{1A}$, $-SR^{1A}$, $-N(R^{1A})_2$, $-SO_2N(R^{1A})_2$, $-C(=O)N(R^{1A})_2$, halogen, -CN, $-NO_2$, $-C(=O)R^{1A}$, $-C(=O)OR^{1A}$, $-N(R^{1A})C(=O)R^{1B}$ or $-N(R^{1A})SO_2R^{1B}$, wherein each occurrence of R^{1A} and R^{1B} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl or -(alkyl)heteroaryl; or

R^{1A} and R^{1B} , taken together with the atoms to which they are attached, form a substituted or unsubstituted 5-8 membered heterocyclic moiety;

[0086] xxv) each occurrence of R^1 is independently hydrogen, halogen, hydroxy, lower alkyl, lower heteroalkyl, 3-6 membered cycloalkyl, 3-6 membered heterocycle, aryl, heteroaryl, -(lower alkyl)cycloalkyl, -(lower alkyl)heterocycle, -(lower alkyl)aryl or -(lower alkyl)heteroaryl;

[0087] xxvi) each occurrence of R^1 is independently lower alkyl;

[0088] xxvii) each occurrence of R^1 is independently methyl, ethyl, propyl, i-propyl, butyl or t-butyl;

[0089] xxviii) q is 1 and R^1 is methyl;

[0090] xxix) q is 2 and each occurrence of R^1 is lower alkyl;

[0091] xxx) q is 2 and each occurrence of R^1 is methyl;

[0092] xxxi) R^1 , for each occurrence, is hydrogen;

[0093] xxxii) each occurrence of R^2 is independently hydrogen, halogen, CN, NO₂, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, heterocycle, aryl, heteroaryl, -(alkyl)cycloalkyl, -(alkyl)heterocycle, -(heteroalkyl)cycloalkyl, -(heteroalkyl)heterocycle, -(alkyl)aryl, -(heteroalkyl)aryl, -(alkyl)heteroaryl, -(heteroalkyl)heteroaryl, -OR^{2A}, -S(=O)_xR^{2A}, -N(R^{2A})₂, -SO₂N(R^{2A})₂, -C(=O)R^{2A}, -C(=O)N(R^{2A})₂, -C(=O)OR^{2A}, -N(R^{2A})C(=O)R^{2B} or -N(R^{2A})SO₂R^{2B}, wherein x is 0, 1 or 2; and each occurrence of R^{2A} and R^{2B} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl or -(alkyl)heteroaryl; or R^{2A} and R^{2B} , taken together with the atoms to which they are attached, form a substituted or unsubstituted 5-8 membered heterocyclic moiety;

[0094] xxxiii) each occurrence of R^2 is independently hydrogen, halogen, CN, NO₂, lower alkyl, lower heteroalkyl, 3-6 membered cycloalkyl, 3-8 membered heterocycle, aryl, heteroaryl, -(lower alkyl)cycloalkyl, -(lower alkyl)heterocycle, -(lower heteroalkyl)cycloalkyl, -(lower heteroalkyl)heterocycle, -(lower alkyl)aryl, -(lower heteroalkyl)aryl, -(lower alkyl)heteroaryl, -(lower heteroalkyl)heteroaryl, -OR^{2A}, -SR^{2A}, -N(R^{2A})₂, -C(=O)R^{2A}, -C(=O)N(R^{2A})₂, -C(=O)OR^{2A}, -N(R^{2A})C(=O)R^{2B} or -N(R^{2A})SO₂R^{2B}, wherein each occurrence of R^{2A} and R^{2B} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(lower alkyl)aryl or -(lower alkyl)heteroaryl; or R^{2A} and R^{2B} , taken together with the atoms to which they are attached, form a substituted or unsubstituted 5-8 membered heterocyclic moiety;

[0095] xxxiv) each occurrence of R^2 is independently hydrogen, halogen, lower alkyl, lower heteroalkyl, $-OR^{2A}$, $-SR^{2A}$, $-N(R^{2A})_2$, $-C(=O)R^{2A}$, $-C(=O)N(R^{2A})_2$, $-C(=O)OR^{2A}$, $-N(R^{2A})C(=O)R^{2B}$ or $-N(R^{2A})SO_2R^{2B}$, wherein each occurrence of R^{2A} and R^{2B} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, $-(\text{lower alkyl})\text{aryl}$ or $-(\text{lower alkyl})\text{heteroaryl}$; or R^{2A} and R^{2B} , taken together with the atoms to which they are attached, form a substituted or unsubstituted 5-8 membered heterocyclic moiety;

[0096] xxxv) each occurrence of R^2 is independently hydrogen, halogen, lower alkyl or $-OR^{2A}$; wherein R^{2A} is hydrogen, lower alkyl, aryl, heteroaryl, $-(\text{lower alkyl})\text{aryl}$ or $-(\text{lower alkyl})\text{heteroaryl}$;

[0097] xxxvi) each occurrence of R^2 is independently hydrogen, halogen, lower alkyl or $-OR^{2A}$; wherein R^{2A} is hydrogen, or lower alkyl;

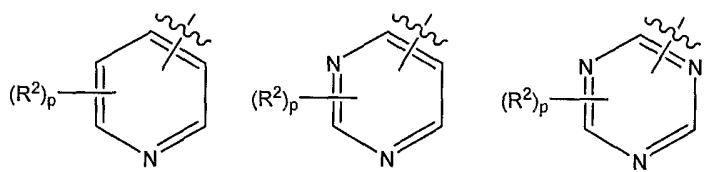
[0098] xxxvii) each occurrence of R^2 is independently hydrogen, hydroxyl or lower alkoxy;

[0099] xxxviii) p is 1 and R^2 is hydroxyl or lower alkoxy;

[0100] xxxix) p is 1 and R^2 is *meta*-hydroxyl or *meta*-lower alkoxy;

[0101] xl) p is 1 and R^2 is *meta*-hydroxyl;

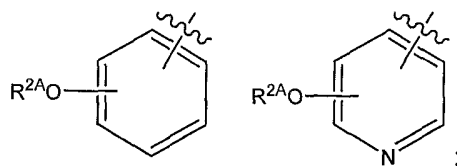
[0102] xli) Ar is substituted or unsubstituted phenyl or naphthyl, or a moiety having one of the following structures:



wherein p is 0-5 and R^2 takes the definition given in any one of subsets xxxii)-xl);

[0103] xlii) Ar is substituted or unsubstituted phenyl or pyridyl;

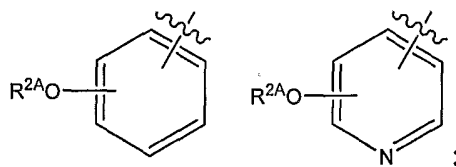
[0104] xliii) Ar has one of the following structures:



wherein R^{2A} is hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, heterocycle, acyl, aryl, heteroaryl, $-(\text{alkyl})\text{cycloalkyl}$, $-(\text{alkyl})\text{heterocycle}$, $-(\text{heteroalkyl})\text{cycloalkyl}$, $-(\text{heteroalkyl})\text{heterocycle}$, $-(\text{alkyl})\text{aryl}$, -

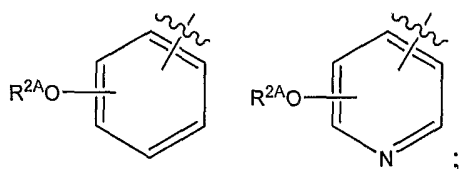
(heteroalkyl)aryl, -(alkyl)heteroaryl, -(heteroalkyl)heteroaryl or an oxygen protecting group;

[0105] xlv) Ar has one of the following structures:



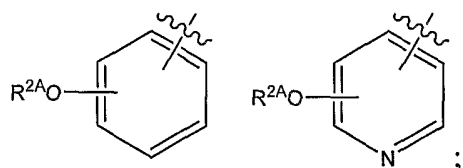
wherein R^{2A} is hydrogen, lower alkyl, lower heteroalkyl, cycloalkyl, heterocycle, lower acyl, aryl, heteroaryl, -(alkyl)cycloalkyl, -(alkyl)heterocycle, -(alkyl)aryl, -(heteroalkyl)aryl, -(alkyl)heteroaryl or an oxygen protecting group;

[0106] xlv) Ar has one of the following structures:



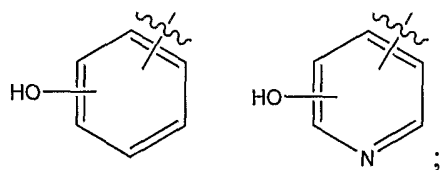
wherein R^{2A} is hydrogen, lower alkyl, lower acyl, aryl, heteroaryl or an oxygen protecting group;

[0107] xlv) Ar has one of the following structures:

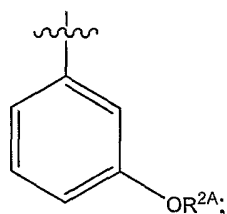


wherein R^{2A} is hydrogen, lower alkyl, lower acyl or an oxygen protecting group;

[0108] xlvii) Ar has one of the following structures:



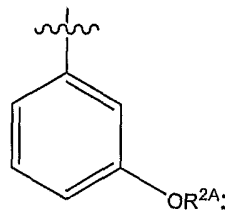
[0109] xlviii) Ar has the structure:



wherein R^{2A} is hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, heterocycle, acyl, aryl, heteroaryl, -(alkyl)cycloalkyl, -

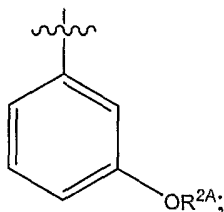
(alkyl)heterocycle, -(heteroalkyl)cycloalkyl, -(heteroalkyl)heterocycle, -(alkyl)aryl, -(heteroalkyl)aryl, -(alkyl)heteroaryl, -(heteroalkyl)heteroaryl or an oxygen protecting group;

[0110] xlix) Ar has the structure:



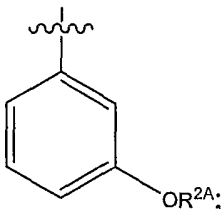
wherein R^{2A} is hydrogen, lower alkyl, lower heteroalkyl, cycloalkyl, heterocycle, lower acyl, aryl, heteroaryl, -(alkyl)cycloalkyl, -(alkyl)heterocycle, -(alkyl)aryl, -(heteroalkyl)aryl, -(alkyl)heteroaryl or an oxygen protecting group;

[0111] l) Ar has the structure:



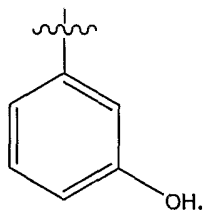
wherein R^{2A} is hydrogen, lower alkyl, lower acyl, aryl, heteroaryl or an oxygen protecting group;

[0112] li) Ar has the structure:



wherein R^{2A} is hydrogen, lower alkyl, lower acyl or an oxygen protecting group; and/or

[0113] lii) Ar has the structure:



[0114] It will be appreciated that for each of the classes and subclasses described above and herein, any one or more occurrences of aliphatic or heteroaliphatic may independently be substituted or unsubstituted, cyclic or acyclic, linear or branched, saturated or unsaturated and any one or more occurrences of aryl, heteroaryl, cycloaliphatic, cycloheteroaliphatic may be substituted or unsubstituted.

[0115] The reader will also appreciate that all possible combinations of the variables described in i)- through lii) above (e.g., R^1 , R^2 , X^1 , X^2 , n , p and q , among others) are considered part of the invention. Thus, the invention encompasses any and all compounds of formula **I** generated by taking any possible permutation of variables R^1 , R^2 , X^1 , X^2 , n , p and q , and other variables/substituents (e.g., R^{X1} , R^{1A} , R^{1BA} , R^{2A} , etc.) as further defined for R^1 , R^2 , X^1 , described in i)- through lii) above.

[0116] For example, an exemplary combination of variables described in i)- through lii) above includes those compounds of Formula **I** wherein:

X^1 is O;

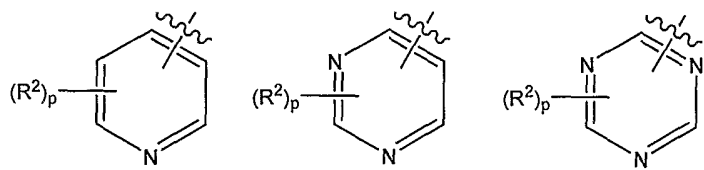
X^2 is S;

each occurrence of R^1 is independently hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, heterocycle, aryl, heteroaryl, -(alkyl)cycloalkyl, -(alkyl)heterocycle, -(heteroalkyl)cycloalkyl, -(heteroalkyl)heterocycle, -(alkyl)aryl, -(heteroalkyl)aryl, -(alkyl)heteroaryl, -(heteroalkyl)heteroaryl, $-OR^{1A}$, $-S(=O)_xR^{1A}$, $-N(R^{1A})_2$, $-SO_2N(R^{1A})_2$, $-C(=O)R^{1A}$, $-C(=O)N(R^{1A})_2$, halogen, $-CN$, $-NO_2$, $-C(=O)OR^{1A}$, $-N(R^{1A})C(=O)R^{1B}$ or $-N(R^{1A})SO_2R^{1B}$, wherein x is 0, 1 or 2; and each occurrence of R^{1A} and R^{1B} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl or -(alkyl)heteroaryl; or R^{1A} and R^{1B} , taken together with the atoms to which they are attached, form a substituted or unsubstituted 5-8 membered heterocyclic moiety;

n is 1 or 2;

q is 0;

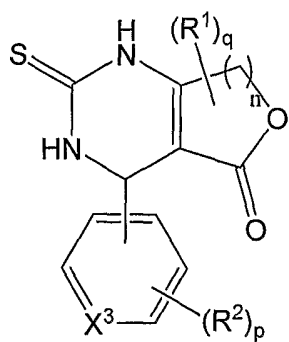
Ar is substituted or unsubstituted phenyl or naphthyl, or a moiety having one of the following structures:



wherein p is 1; and each occurrence of R^2 is independently hydrogen, halogen, CN, NO_2 , alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, heterocycle, aryl, heteroaryl, -(alkyl)cycloalkyl, -(alkyl)heterocycle, -(heteroalkyl)cycloalkyl, -(heteroalkyl)heterocycle, -(alkyl)aryl, -(heteroalkyl)aryl, -(alkyl)heteroaryl, -(heteroalkyl)heteroaryl, $-OR^{2A}$, $-S(=O)_xR^{2A}$, $-N(R^{2A})_2$, $-SO_2N(R^{2A})_2$, $-C(=O)R^{1A}$, $-C(=O)N(R^{2A})_2$, $-C(=O)OR^{2A}$, $-N(R^{2A})C(=O)R^{2B}$ or $-N(R^{2A})SO_2R^{2B}$, wherein x is 0, 1 or 2; and each occurrence of R^{2A} and R^{2B} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl or -(alkyl)heteroaryl; or R^{2A} and R^{2B} , taken together with the atoms to which they are attached, form a substituted or unsubstituted 5-8 membered heterocyclic moiety.

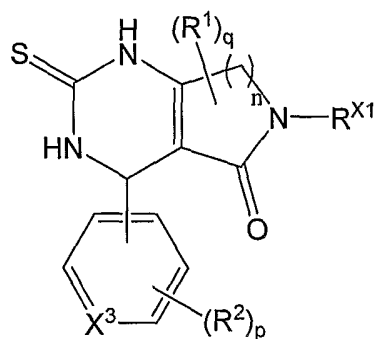
[0117] Other exemplary combinations are illustrated by compounds of the following subgroups I-XII:

[0118] I. Compounds having the structure (and pharmaceutically acceptable derivatives thereof):



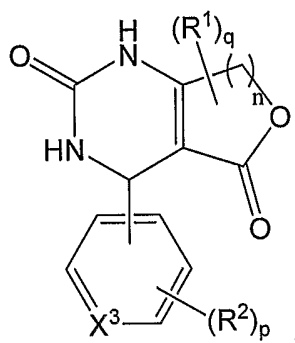
wherein n, p, q, R^1 , R^2 , and X^3 are as defined generally and in classes and subclasses herein.

[0119] II. Compounds having the structure (and pharmaceutically acceptable derivatives thereof):



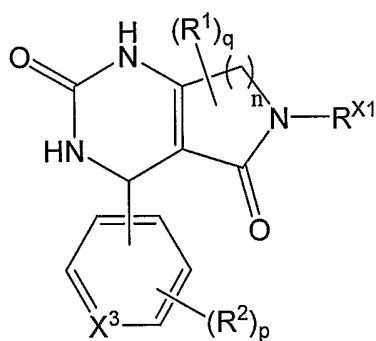
wherein n , p , q , R^1 , R^2 , and X^3 are as defined generally and in classes and subclasses herein; and R^{X1} is hydrogen, lower alkyl, acyl or a nitrogen protecting group.

[0120] III. Compounds having the structure (and pharmaceutically acceptable derivatives thereof):



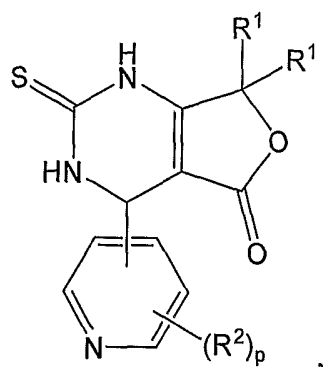
wherein n , p , q , R^1 , R^2 , and X^3 are as defined generally and in classes and subclasses herein.

[0121] IV. Compounds having the structure (and pharmaceutically acceptable derivatives thereof):



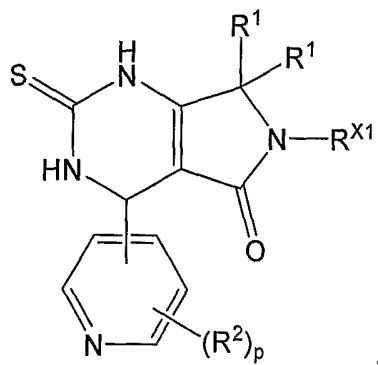
wherein n , p , q , R^1 , R^2 , and X^3 are as defined generally and in classes and subclasses herein; and R^{X1} is hydrogen, lower alkyl, acyl or a nitrogen protecting group.

[0122] V. Compounds having the structure (and pharmaceutically acceptable derivatives thereof):



wherein p and R^2 are as defined generally and in classes and subclasses herein and each occurrence of R^1 is independently hydrogen, halogen, lower alkyl or lower haloalkyl. In certain embodiments, each occurrence of R^1 is hydrogen. In certain embodiments, each occurrence of R^1 is independently halogen, lower alkyl or lower haloalkyl. In certain embodiments, each occurrence of R^1 is independently lower alkyl. In certain embodiments, each occurrence of R^1 is methyl. In certain embodiments, p is 0. In certain other embodiments, p is 1. In yet other embodiments, p is 1 and R^2 is halogen, lower alkyl, hydroxy or lower alkoxy. In certain other embodiments, p is 1 and R^2 is *meta*-hydroxyl.

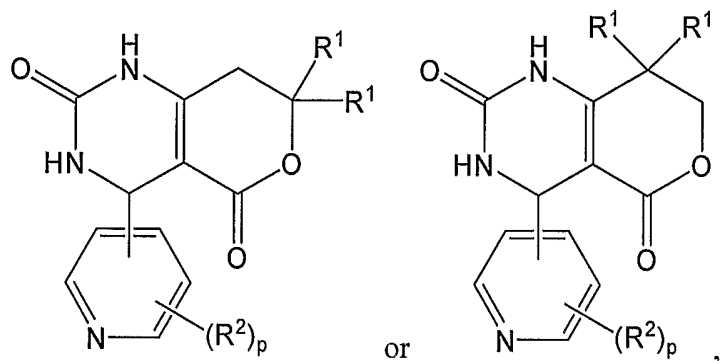
[0123] VI. Compounds having the structure (and pharmaceutically acceptable derivatives thereof):



wherein p and R^2 are as defined generally and in classes and subclasses herein; each occurrence of R^1 is independently hydrogen, halogen, lower alkyl or lower haloalkyl and R^{X1} is hydrogen, lower alkyl, acyl or a nitrogen protecting group. In certain embodiments, each occurrence of R^1 is hydrogen. In certain embodiments, each occurrence of R^1 is independently halogen, lower alkyl or lower haloalkyl. In certain embodiments, each occurrence of R^1 is independently lower alkyl. In certain embodiments, each occurrence of R^1 is methyl. In certain embodiments, p is 0. In certain other embodiments, p is 1. In yet other embodiments, p is 1 and R^2 is halogen,

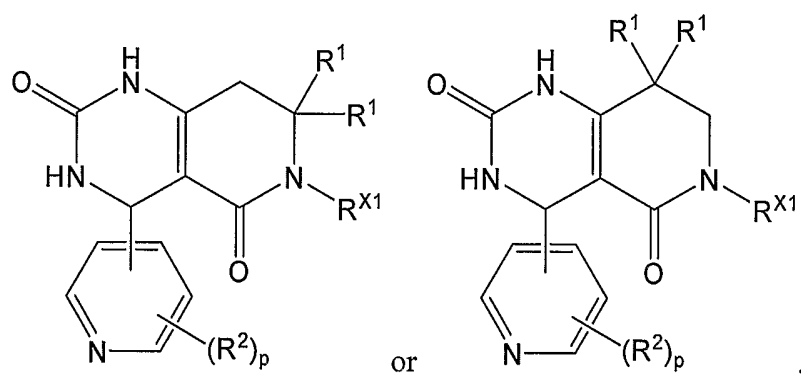
lower alkyl, hydroxy or lower alkoxy. In certain other embodiments, p is 1 and R² is *meta*-hydroxyl.

[0124] VII. Compounds having the structure (and pharmaceutically acceptable derivatives thereof):



wherein p and R² are as defined generally and in classes and subclasses herein and each occurrence of R¹ is independently hydrogen, halogen, lower alkyl or lower haloalkyl. In certain embodiments, each occurrence of R¹ is hydrogen. In certain embodiments, each occurrence of R¹ is independently halogen, lower alkyl or lower haloalkyl. In certain embodiments, each occurrence of R¹ is independently lower alkyl. In certain embodiments, each occurrence of R¹ is methyl. In certain embodiments, p is 0. In certain other embodiments, p is 1. In yet other embodiments, p is 1 and R² is halogen, lower alkyl, hydroxy or lower alkoxy. In certain other embodiments, p is 1 and R² is *meta*-hydroxyl. In certain exemplary embodiments, R^{X1} is hydrogen.

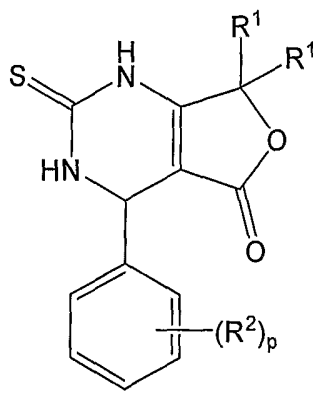
[0125] VIII. Compounds having the structure (and pharmaceutically acceptable derivatives thereof):



wherein p and R² are as defined generally and in classes and subclasses herein; each occurrence of R¹ is independently hydrogen, halogen, lower alkyl or lower haloalkyl and R^{X1} is hydrogen, lower alkyl, acyl or a nitrogen protecting group. In

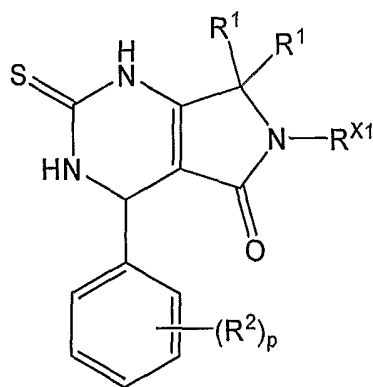
certain embodiments, each occurrence of R^1 is hydrogen. In certain embodiments, each occurrence of R^1 is independently halogen, lower alkyl or lower haloalkyl. In certain embodiments, each occurrence of R^1 is independently lower alkyl. In certain embodiments, each occurrence of R^1 is methyl. In certain embodiments, p is 0. In certain other embodiments, p is 1. In yet other embodiments, p is 1 and R^2 is halogen, lower alkyl, hydroxy or lower alkoxy. In certain other embodiments, p is 1 and R^2 is *meta*-hydroxyl. In certain exemplary embodiments, R^{X1} is hydrogen. In certain exemplary embodiments, R^{X1} is hydrogen.

[0126] IX. Compounds having the structure (and pharmaceutically acceptable derivatives thereof):



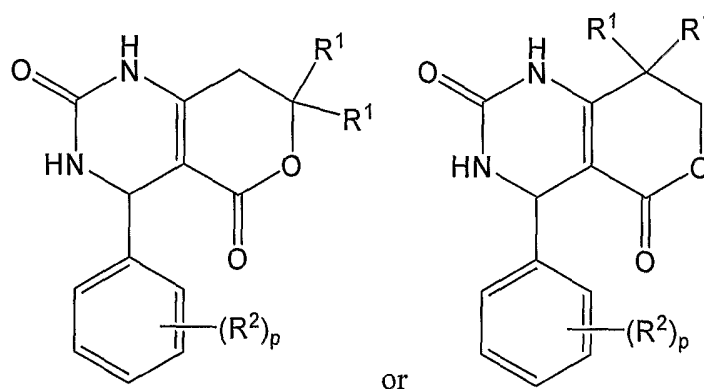
wherein p and R^2 are as defined generally and in classes and subclasses herein and each occurrence of R^1 is independently hydrogen, halogen, lower alkyl or lower haloalkyl. In certain embodiments, each occurrence of R^1 is hydrogen. In certain embodiments, each occurrence of R^1 is independently halogen, lower alkyl or lower haloalkyl. In certain embodiments, each occurrence of R^1 is independently lower alkyl. In certain embodiments, each occurrence of R^1 is methyl. In certain embodiments, p is 0. In certain other embodiments, p is 1. In yet other embodiments, p is 1 and R^2 is halogen, lower alkyl, hydroxy or lower alkoxy. In certain other embodiments, p is 1 and R^2 is *meta*-hydroxyl

[0127] X. Compounds having the structure (and pharmaceutically acceptable derivatives thereof):



wherein p and R^2 are as defined generally and in classes and subclasses herein; each occurrence of R^1 is independently hydrogen, halogen, lower alkyl or lower haloalkyl and R^{X1} is hydrogen, lower alkyl, acyl or a nitrogen protecting group. In certain embodiments, each occurrence of R^1 is hydrogen. In certain embodiments, each occurrence of R^1 is independently halogen, lower alkyl or lower haloalkyl. In certain embodiments, each occurrence of R^1 is independently lower alkyl. In certain embodiments, each occurrence of R^1 is methyl. In certain embodiments, p is 0. In certain other embodiments, p is 1. In yet other embodiments, p is 1 and R^2 is halogen, lower alkyl, hydroxy or lower alkoxy. In certain exemplary embodiments, p is 1 and R^2 is *meta*-hydroxyl.

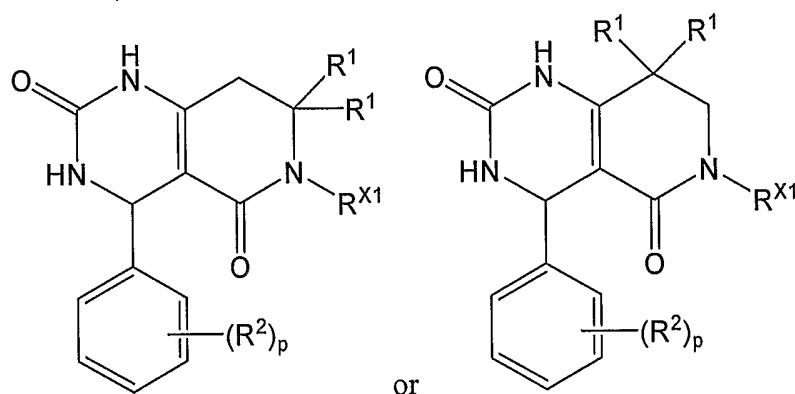
[0128] XI. Compounds having the structure (and pharmaceutically acceptable derivatives thereof):



wherein p and R^2 are as defined generally and in classes and subclasses herein and each occurrence of R^1 is independently hydrogen, halogen, lower alkyl or lower haloalkyl. In certain embodiments, each occurrence of R^1 is hydrogen. In certain embodiments, each occurrence of R^1 is independently halogen, lower alkyl or lower haloalkyl. In certain embodiments, each occurrence of R^1 is independently lower alkyl. In certain embodiments, each occurrence of R^1 is methyl. In certain

embodiments, p is 0. In certain other embodiments, p is 1. In yet other embodiments, p is 1 and R² is halogen, lower alkyl, hydroxy or lower alkoxy. In certain exemplary embodiments, p is 1 and R² is *meta*-hydroxyl. In certain exemplary embodiments, R^{X1} is hydrogen.

[0129] XII. Compounds having the structure (and pharmaceutically acceptable derivatives thereof):

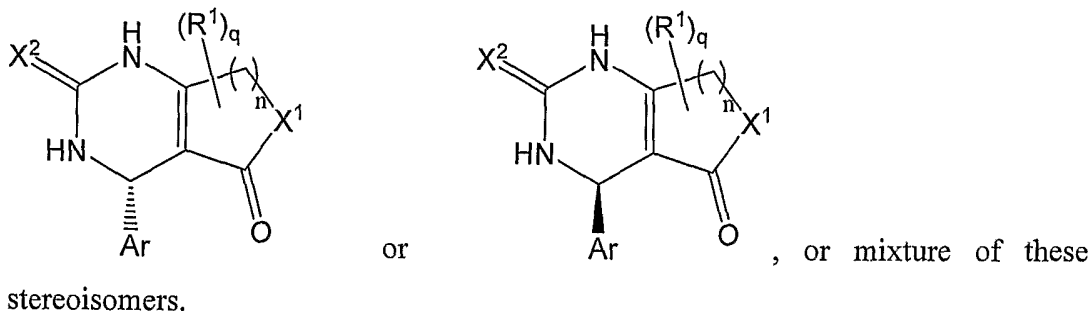


wherein p and R² are as defined generally and in classes and subclasses herein; each occurrence of R¹ is independently hydrogen, halogen, lower alkyl or lower haloalkyl and R^{X1} is hydrogen, lower alkyl, acyl or a nitrogen protecting group. In certain embodiments, each occurrence of R¹ is hydrogen. In certain embodiments, each occurrence of R¹ is independently halogen, lower alkyl or lower haloalkyl. In certain embodiments, each occurrence of R¹ is independently lower alkyl. In certain embodiments, each occurrence of R¹ is methyl. In certain embodiments, p is 0. In certain other embodiments, p is 1. In yet other embodiments, p is 1 and R² is halogen, lower alkyl, hydroxy or lower alkoxy. In certain exemplary embodiments, p is 1 and R² is *meta*-hydroxyl. In certain exemplary embodiments, R^{X1} is hydrogen.

[0130] It will also be appreciated that for each of the subgroups **I-XII** described above, a variety of other subclasses are of special interest, including, but not limited to those classes described above i)- lii) and classes, subclasses and species of compounds described above and in the examples herein.

[0131] Some of the foregoing compounds can comprise one or more asymmetric centers, and thus can exist in various isomeric forms, *e.g.*, stereoisomers and/or diastereomers. Thus, inventive compounds and pharmaceutical compositions thereof may be in the form of an individual enantiomer, diastereomer or geometric isomer, or may be in the form of a mixture of stereoisomers. In certain embodiments, the compounds of the invention are enantiopure compounds. In certain other

embodiments, mixtures of stereoisomers or diastereomers are provided. For example, compounds having the following stereochemistry are provided:



[0132] Furthermore, certain compounds, as described herein may have one or more double bonds that can exist as either the Z or E isomer, unless otherwise indicated. The invention additionally encompasses the compounds as individual isomers substantially free of other isomers and alternatively, as mixtures of various isomers, *e.g.*, racemic mixtures of stereoisomers. In addition to the above-mentioned compounds *per se*, this invention also encompasses pharmaceutically acceptable derivatives of these compounds and compositions comprising one or more compounds of the invention and one or more pharmaceutically acceptable excipients or additives.

[0133] Compounds of the invention may be prepared by crystallization of compound of formula (I) under different conditions and may exist as one or a combination of polymorphs of compound of general formula (I) forming part of this invention. For example, different polymorphs may be identified and/or prepared using different solvents, or different mixtures of solvents for recrystallization; by performing crystallizations at different temperatures; or by using various modes of cooling, ranging from very fast to very slow cooling during crystallizations. Polymorphs may also be obtained by heating or melting the compound followed by gradual or fast cooling. The presence of polymorphs may be determined by solid probe NMR spectroscopy, IR spectroscopy, differential scanning calorimetry, powder X-ray diffractogram and/or other techniques. Thus, the present invention encompasses inventive compounds, their derivatives, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts their pharmaceutically acceptable solvates and pharmaceutically acceptable compositions containing them.

[0134] 2) *Synthetic Overview:*

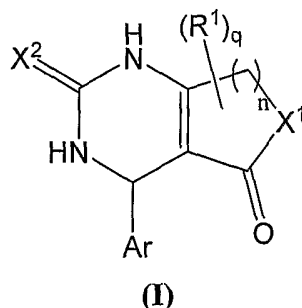
[0135] The practitioner has a well-established literature of heterocycle chemistry to draw upon, in combination with the information contained herein, for guidance on

synthetic strategies, protecting groups, and other materials and methods useful for the synthesis of the compounds of this invention, including compounds containing the various R^1 , R^2 and Ar substituents and X^1 , X^2 and X^3 moieties.

[0136] The various references cited herein provide helpful background information on preparing compounds similar to the inventive compounds described herein or relevant intermediates, as well as information on formulation, uses, and administration of such compounds which may be of interest.

[0137] Moreover, the practitioner is directed to the specific guidance and examples provided in this document relating to various exemplary compounds and intermediates thereof.

[0138] As described above, the present invention provides novel compounds, specifically compounds having the following general structure:

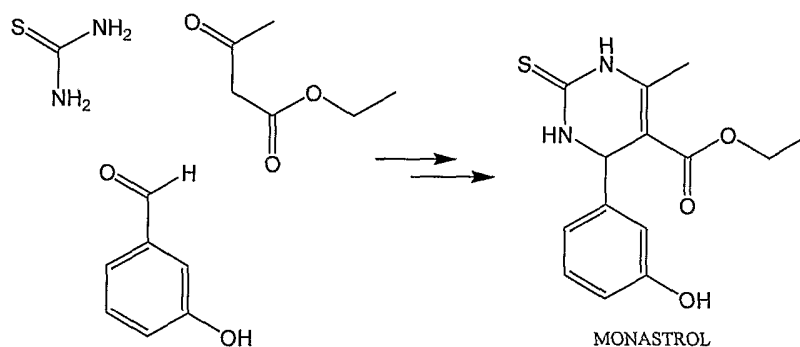


and pharmaceutically acceptable derivatives thereof;

wherein n, p, Ar, R^1 , X^1 and X^2 are as defined generally above and in classes and subclasses herein.

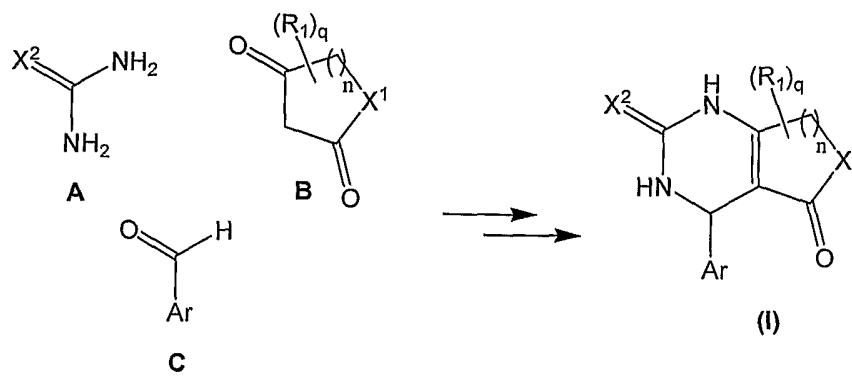
[0139] A synthesis of Monastrol, previously reported by Biginelli and co-workers, is depicted in Scheme 1 (see, C. O. Kappe, *Tetrahedron* **1993**, 49, 6937-6963).

[0140] **Scheme 1**



[0141] In analogy to Biginelli's three-component synthesis of Monastrol, it is proposed that compounds of the invention may be accessible via a similar approach, as depicted in Scheme 2.

[0142] Scheme 2



wherein **Ar** is an aromatic or heteroaromatic moiety;

X¹ is O or NR^{X¹}, wherein R^{X¹} is hydrogen or an aliphatic, heteroaliphatic, aromatic or heteroaromatic moiety;

X² is O or S;

n is 1 or 2;

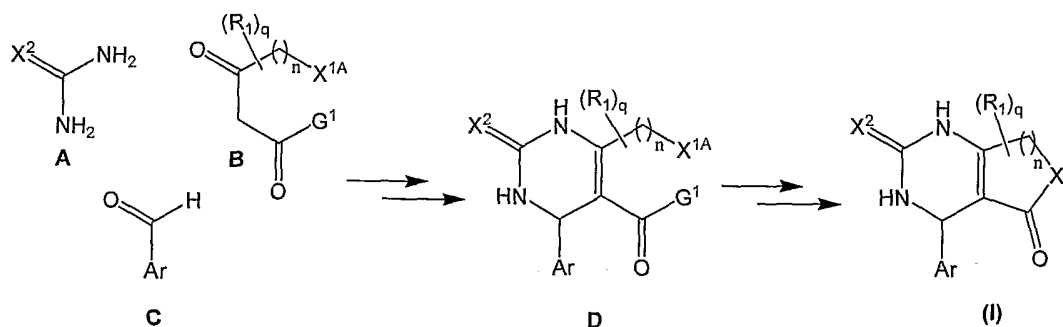
q is an integer from 0-4; and

each occurrence of **R₁** is independently hydrogen, or an aliphatic, heteroaliphatic, aromatic or heteroaromatic moiety.

[0143] However, published reports indicate that subjecting 5-membered esters (*i.e.*, component **B** where **n** is 1 and **X¹** is O) to Biginelli reaction conditions did not yield the desired products (See, for example, G. Byk, H. E. Gottlieb, J. Herscovici, F. Mirkin, *J Comb Chem* **2000**, 2, 732-735).

[0144] An alternative approach comprises effecting Biginelli's reaction with an open-chain component **B**, as depicted in Scheme 3. Ring closure of dihydropyrimidine intermediate **D** may then be effected to yield compounds of general formula (**I**).

[0145] Scheme 3



wherein n is 1 or 2; Ar is an aromatic or heteroaromatic moiety; X^{1A} is $-OR^{X1B}$ or $-NR^{X1C}R^{X1}$, where R^{X1B} is hydrogen or an oxygen protecting group, R^{X1C} is hydrogen or a nitrogen protecting group and R^{X1} is hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, heterocycle, acyl, aryl, heteroaryl, $-(alkyl)cycloalkyl$, $-(alkyl)heterocycle$, $-(heteroalkyl)cycloalkyl$, $-(heteroalkyl)heterocycle$, $-(alkyl)aryl$, $-(heteroalkyl)aryl$, $-(alkyl)heteroaryl$ or $-(heteroalkyl)heteroaryl$; and G^1 is a leaving group.

[0146] In certain embodiments, R^{X1} is hydrogen, lower alkyl, lower heteroalkyl, cycloalkyl, heterocycle, lower acyl, aryl, heteroaryl, $-(alkyl)cycloalkyl$, $-(alkyl)heterocycle$, $-(alkyl)aryl$, $-(heteroalkyl)aryl$ or $-(alkyl)heteroaryl$. In certain other embodiments, R^{X1} is hydrogen, lower alkyl, lower acyl, aryl or heteroaryl. In certain other embodiments, R^{X1} is hydrogen, lower alkyl or lower acyl. In certain exemplary embodiments, R^{X1} is hydrogen.

[0147] In certain other embodiments, G^1 is halogen or $-OR^{G1A}$, wherein R^{G1A} is alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, heterocycle, aryl, heteroaryl, $-(alkyl)cycloalkyl$, $-(alkyl)heterocycle$, $-(heteroalkyl)cycloalkyl$, $-(heteroalkyl)heterocycle$, $-(alkyl)aryl$, $-(heteroalkyl)aryl$, $-(alkyl)heteroaryl$ or $-(heteroalkyl)heteroaryl$. In certain other embodiments, G^1 is halogen or $-OR^{G1A}$, wherein R^{G1A} is lower alkyl, lower heteroalkyl, cycloalkyl, heterocycle, aryl, heteroaryl, $-(alkyl)cycloalkyl$, $-(alkyl)heterocycle$, $-(alkyl)aryl$, $-(heteroalkyl)aryl$ or $-(alkyl)heteroaryl$. In certain other embodiments, G^1 is halogen or $-OR^{G1A}$, wherein R^{G1A} is lower alkyl, aryl or heteroaryl. In certain other embodiments, G^1 is $-OR^{G1A}$, wherein R^{G1A} is lower alkyl.

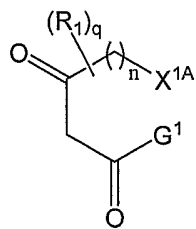
[0148] In certain embodiments, R^{X1B} is alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heteroaryl, silyl, $-C(=O)R^x$, $-C(=S)R^x$, $-C(=NR^x)R^y$, $-SO_2R^x$, wherein R^x and R^y are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocycloalkyl, heterocycloalkenyl, heterocycloalkynyl, heteroaliphatic, heteroalicyclic, aryl, heteroaryl, $-C(=O)R^A$ or $-ZR^A$, wherein Z is $-O-$, $-S-$, $-NR^B$, wherein each occurrence of R^A and R^B is independently hydrogen, or an alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocycloalkyl, heterocycloalkenyl, heterocycloalkynyl, heteroaliphatic, heteroalicyclic, aryl or heteroaryl moiety. In

certain exemplary embodiments, R^{X1B} is a silyl protecting group. In certain exemplary embodiments, R^{X1B} is a trialkylsilyl protecting group. In certain exemplary embodiments, R^{X1B} is triisopropylsilyl.

[0149] In certain embodiments, R^{X1C} is alkyl, alkenyl, $-C(=O)R^x$, $-C(=O)OR^x$, $-SR^x$, SO_2R^x , or R^{X1} and R^{X1C} , taken together form a moiety having the structure $=CR^xR^y$, wherein R^{X1} and R^{X1C} are not simultaneously hydrogen and R^x and R^y are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocycloalkyl, heterocycloalkenyl, heterocycloalkynyl, heteroaliphatic, heteroalicyclic, aryl, heteroaryl, $-C(=O)R^A$ or $-ZR^A$, wherein Z is $-O-$, $-S-$, $-NR^B$, wherein each occurrence of R^A and R^B is independently hydrogen, or an alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocycloalkyl, heterocycloalkenyl, heterocycloalkynyl, heteroaliphatic, heteroalicyclic, aryl or heteroaryl moiety. In certain exemplary embodiments, R^{X1} is hydrogen and R^{X1C} is $-C(=O)R^x$, wherein R^x is substituted or unsubstituted lower alkyl or lower alkoxy. In certain exemplary embodiments, R^{X1} is hydrogen and R^{X1C} is $-C(=O)R^x$, wherein R^x is tert-Butoxy.

[0150] Thus, in certain embodiments, the inventive method comprises

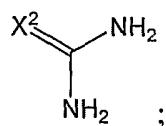
i) reacting a compound having the structure:



wherein n, q and R^1 are as defined generally above and in classes and subclasses herein,

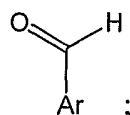
X^{1A} is $-OR^{X1B}$ or $-NR^{X1C}R^{X1}$, where R^{X1B} is hydrogen or an oxygen protecting group, R^{X1C} is hydrogen or a nitrogen protecting group and R^{X1} is hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, heterocycle, acyl, aryl, heteroaryl, $-(\text{alkyl})\text{cycloalkyl}$, $-(\text{alkyl})\text{heterocycle}$, $-(\text{heteroalkyl})\text{cycloalkyl}$, $-(\text{heteroalkyl})\text{heterocycle}$, $-(\text{alkyl})\text{aryl}$, $-(\text{heteroalkyl})\text{aryl}$, $-(\text{alkyl})\text{heteroaryl}$ or $-(\text{heteroalkyl})\text{heteroaryl}$; and G^1 is a leaving group;

with a compound having the structure:



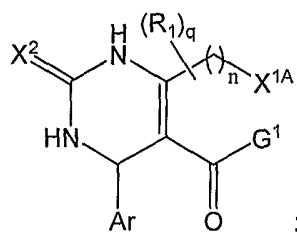
wherein X^2 is O or S;

and a compound having the structure:

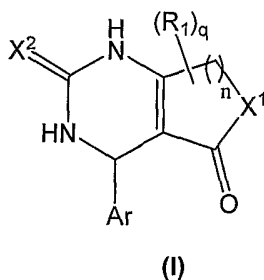


wherein Ar is an aromatic or heteroaromatic moiety;

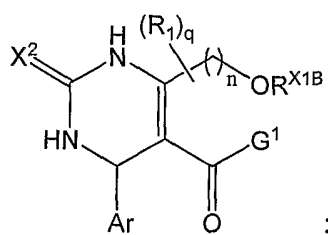
under suitable conditions to give an intermediate having the structure:



ii) reacting the intermediate of step i) under suitable conditions to give a compound of formula (I):

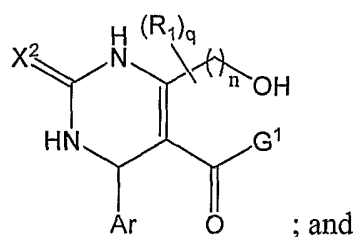


[0151] In certain embodiments, the intermediate of step i) has the structure:



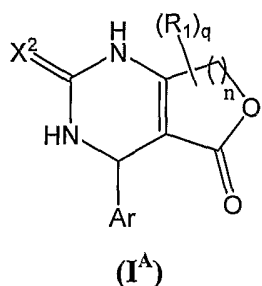
wherein R^{X1B} is an oxygen protecting group, and step ii) comprises steps of:

a) deprotecting the intermediate of step i) under suitable conditions to give an alcohol having the structure:



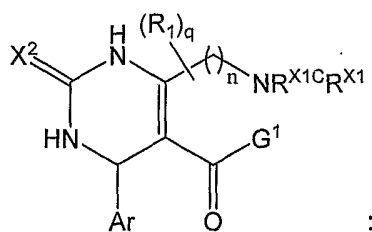
; and

b) reacting the alcohol of step (a) under suitable conditions to give the compound of formula (I^A):



[0152] In certain embodiments, R^{X1B} is alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heteroaryl, silyl, $-C(=O)R^x$, $-C(=S)R^x$, $-C(=NR^x)R^y$, $-SO_2R^x$, wherein R^x and R^y are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocycloalkyl, heterocycloalkenyl, heterocycloalkynyl, heteroaliphatic, heteroalicyclic, aryl, heteroaryl, $-C(=O)R^A$ or $-ZR^A$, wherein Z is $-O-$, $-S-$, $-NR^B$, wherein each occurrence of R^A and R^B is independently hydrogen, or an alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocycloalkyl, heterocycloalkenyl, heterocycloalkynyl, heteroaliphatic, heteroalicyclic, aryl or heteroaryl moiety. In certain exemplary embodiments, R^{X1B} is a silyl protecting group. In certain exemplary embodiments, R^{X1B} is a trialkylsilyl protecting group. In certain exemplary embodiments, R^{X1B} is triisopropylsilyl.

[0153] In certain other embodiments, the intermediate of step i) has the structure:



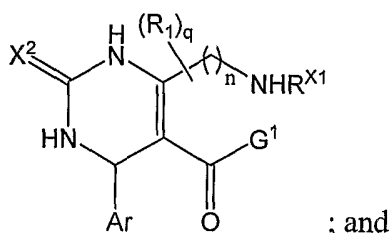
;

wherein R^{X1C} is hydrogen or a nitrogen protecting group and R^{X1} is hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, heterocycle, acyl, aryl, heteroaryl, $-(alkyl)cycloalkyl$, $-(alkyl)heterocycle$, -

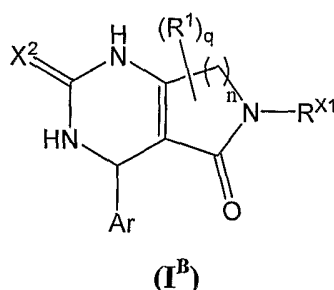
(heteroalkyl)cycloalkyl, -(heteroalkyl)heterocycle, -(alkyl)aryl, -(heteroalkyl)aryl, -(alkyl)heteroaryl or -(heteroalkyl)heteroaryl;

and step ii) comprises steps of:

a) deprotecting the intermediate of step i) under suitable conditions to give an amino compound having the structure:



b) reacting the amino compound of step (a) under suitable conditions to give the compound of formula (I^B):



[0154] In certain embodiments, R^{X1C} is alkyl, alkenyl, -C(=O)R^x, -C(=O)OR^x, -SR^x, SO₂R^x, or R^{X1} and R^{X1C}, taken together form a moiety having the structure =CR^xR^y, wherein R^{X1} and R^{X1C} are not simultaneously hydrogen and R^x and R^y are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocycloalkyl, heterocycloalkenyl, heterocycloalkynyl, heteroaliphatic, heteroalicyclic, aryl, heteroaryl, -C(=O)R^A or -ZR^A, wherein Z is -O-, -S-, -NR^B, wherein each occurrence of R^A and R^B is independently hydrogen, or an alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocycloalkyl, heterocycloalkenyl, heterocycloalkynyl, heteroaliphatic, heteroalicyclic, aryl or heteroaryl moiety. In certain exemplary embodiments, R^{X1} is hydrogen and R^{X1C} is -C(=O)R^x, wherein R^x is substituted or unsubstituted lower alkyl or lower alkoxy. In certain exemplary embodiments, R^{X1} is hydrogen and R^{X1C} is -C(=O)R^x, wherein R^x is tert-Butoxy.

[0155] Diversification:

[0156] It will also be appreciated that each of the components used in the synthesis of inventive compounds can be diversified either before synthesis or alternatively after the construction of the core structure of formula (I). As used herein, the term "diversifying" or "diversify" means reacting an inventive compound (I) or any of the precursor fragments (or any classes or subclasses thereof) at one or more reactive sites to modify a functional moiety or to add a functional moiety (*e.g.*, nucleophilic addition of a substrate). Described generally herein are a variety of schemes to assist the reader in the synthesis of a variety of compounds, either by diversification of the intermediate components or by diversification of the core structures as described herein, and classes and subclasses thereof. It will be appreciated that a variety of diversification reactions can be employed to generate compounds other than those described in the Exemplification herein. As but a few examples, where a double bond is present in the compound structure, epoxidation and aziridation can be conducted to generate epoxide and aziridine derivatives of compounds described herein. For additional guidance available in the art, the practitioner is directed to "Advanced Organic Chemistry", March, J. John Wiley & Sons, 2001, 5th ed., the entire contents of which are hereby incorporated by reference.

[0157] **3) Pharmaceutical Compositions**

[0158] As discussed above, the present invention provides novel compounds having Eg5 inhibitory activity, and thus the inventive compounds have antitumor and antiproliferative activity and are useful for the treatment of cancer.

[0159] Accordingly, in another aspect of the present invention, pharmaceutical compositions are provided, which comprise any one or more of the compounds described herein (or a prodrug, pharmaceutically acceptable salt or other pharmaceutically acceptable derivative thereof), and optionally comprise a pharmaceutically acceptable carrier. In certain embodiments, these compositions optionally further comprise one or more additional therapeutic agents. Alternatively, a compound of this invention may be administered to a patient in need thereof in combination with the administration of one or more other therapeutic agents. For example, additional therapeutic agents for conjoint administration or inclusion in a pharmaceutical composition with a compound of this invention may be an approved chemotherapeutic agent, or it may be any one of a number of agents undergoing approval in the Food and Drug Administration that ultimately obtain approval for the

treatment of cancer. In certain other embodiments, the additional therapeutic agent is an anticancer agent, as discussed in more detail herein. In certain other embodiments, the compositions of the invention are useful for the treatment of cancer.

[0160] It will also be appreciated that certain of the compounds of present invention can exist in free form for treatment, or where appropriate, as a pharmaceutically acceptable derivative thereof. According to the present invention, a pharmaceutically acceptable derivative includes, but is not limited to, pharmaceutically acceptable salts, esters, salts of such esters, or a pro-drug or other adduct or derivative of a compound of this invention which upon administration to a patient in need is capable of providing, directly or indirectly, a compound as otherwise described herein, or a metabolite or residue thereof.

[0161] As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts of amines, carboxylic acids, and other types of compounds, are well known in the art. For example, S.M. Berge, *et al.* describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences*, 66: 1-19 (1977), incorporated herein by reference. The salts can be prepared *in situ* during the final isolation and purification of the compounds of the invention, or separately by reacting a free base or free acid function with a suitable reagent, as described generally below. For example, a free base function can be reacted with a suitable acid. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include metal salts such as alkali metal salts, *e.g.* sodium or potassium salts; and alkaline earth metal salts, *e.g.* calcium or magnesium salts. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate,

dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, harnisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pantoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, loweralkyl sulfonate and aryl sulfonate.

[0162] Additionally, as used herein, the term “pharmaceutically acceptable ester” refers to esters that hydrolyze *in vivo* and include those that break down readily in the human body to leave the parent compound or a salt thereof. Suitable ester groups include, for example, those derived from pharmaceutically acceptable aliphatic carboxylic acids, particularly alkanoic, alkenoic, cycloalkanoic and alkanedioic acids, in which each alkyl or alkenyl moiety advantageously has not more than 6 carbon atoms. Examples of particular esters include formates, acetates, propionates, butyrates, acrylates and ethylsuccinates.

[0163] Furthermore, the term “pharmaceutically acceptable prodrugs” as used herein refers to those prodrugs of the compounds of the present invention which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals with undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the invention. The term “prodrug” refers to compounds that are rapidly transformed *in vivo* to yield the parent compound of the above formula, for example by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series, and in Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference.

[0164] As described above, the pharmaceutical compositions of the present invention additionally comprise a pharmaceutically acceptable carrier, which, as used herein, includes any and all solvents, diluents, or other liquid vehicle, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, lubricants and the like, as suited to the particular dosage form desired. Remington's Pharmaceutical Sciences, Sixteenth Edition, E. W. Martin (Mack Publishing Co., Easton, Pa., 1980) discloses various carriers used in formulating pharmaceutical compositions and known techniques for the preparation thereof. Except insofar as any conventional carrier medium is incompatible with the compounds of the invention, such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutical composition, its use is contemplated to be within the scope of this invention. Some examples of materials which can serve as pharmaceutically acceptable carriers include, but are not limited to, sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatine; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil; safflower oil, sesame oil; olive oil; corn oil and soybean oil; glycols; such as propylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogenfree water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator.

[0165] Liquid dosage forms for oral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn,

germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

[0166] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[0167] The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[0168] In order to prolong the effect of a drug, it is often desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension or crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution that, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle. Injectable depot forms are made by forming microcapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include (poly(orthoesters) and poly(anhydrides)). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissues.

[0169] Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

[0170] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

[0171] Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

[0172] The active compounds can also be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose and starch. Such dosage forms may also comprise, as in normal practice, additional substances other than inert diluents, *e.g.*, tableting lubricants and other tableting aids such as magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes.

[0173] The present invention encompasses pharmaceutically acceptable topical formulations of inventive compounds. The term "pharmaceutically acceptable topical formulation", as used herein, means any formulation which is pharmaceutically acceptable for intradermal administration of a compound of the invention by application of the formulation to the epidermis. In certain embodiments of the invention, the topical formulation comprises a carrier system. Pharmaceutically effective carriers include, but are not limited to, solvents (*e.g.*, alcohols, poly alcohols, water), creams, lotions, ointments, oils, plasters, liposomes, powders, emulsions, microemulsions, and buffered solutions (*e.g.*, hypotonic or buffered saline) or any other carrier known in the art for topically administering pharmaceuticals. A more complete listing of art-known carriers is provided by reference texts that are standard in the art, for example, Remington's Pharmaceutical Sciences, 16th Edition, 1980 and 17th Edition, 1985, both published by Mack Publishing Company, Easton, Pa., the disclosures of which are incorporated herein by reference in their entireties. In certain other embodiments, the topical formulations of the invention may comprise excipients. Any pharmaceutically acceptable excipient known in the art may be used to prepare the inventive pharmaceutically acceptable topical formulations. Examples of excipients that can be included in the topical formulations of the invention include, but are not limited to, preservatives, antioxidants, moisturizers, emollients, buffering

agents, solubilizing agents, other penetration agents, skin protectants, surfactants, and propellants, and/or additional therapeutic agents used in combination to the inventive compound. Suitable preservatives include, but are not limited to, alcohols, quaternary amines, organic acids, parabens, and phenols. Suitable antioxidants include, but are not limited to, ascorbic acid and its esters, sodium bisulfite, butylated hydroxytoluene, butylated hydroxyanisole, tocopherols, and chelating agents like EDTA and citric acid. Suitable moisturizers include, but are not limited to, glycerine, sorbitol, polyethylene glycols, urea, and propylene glycol. Suitable buffering agents for use with the invention include, but are not limited to, citric, hydrochloric, and lactic acid buffers. Suitable solubilizing agents include, but are not limited to, quaternary ammonium chlorides, cyclodextrins, benzyl benzoate, lecithin, and polysorbates. Suitable skin protectants that can be used in the topical formulations of the invention include, but are not limited to, vitamin E oil, allantoin, dimethicone, glycerin, petrolatum, and zinc oxide.

[0174] In certain embodiments, the pharmaceutically acceptable topical formulations of the invention comprise at least a compound of the invention and a penetration enhancing agent. The choice of topical formulation will depend on several factors, including the condition to be treated, the physicochemical characteristics of the inventive compound and other excipients present, their stability in the formulation, available manufacturing equipment, and costs constraints. As used herein the term "penetration enhancing agent" means an agent capable of transporting a pharmacologically active compound through the stratum corneum and into the epidermis or dermis, preferably, with little or no systemic absorption. A wide variety of compounds have been evaluated as to their effectiveness in enhancing the rate of penetration of drugs through the skin. See, for example, *Percutaneous Penetration Enhancers*, Maibach H. I. and Smith H. E. (eds.), CRC Press, Inc., Boca Raton, Fla. (1995), which surveys the use and testing of various skin penetration enhancers, and Buyuktimkin *et al.*, *Chemical Means of Transdermal Drug Permeation Enhancement in Transdermal and Topical Drug Delivery Systems*, Gosh T. K., Pfister W. R., Yum S. I. (Eds.), Interpharm Press Inc., Buffalo Grove, Ill. (1997). In certain exemplary embodiments, penetration agents for use with the invention include, but are not limited to, triglycerides (*e.g.*, soybean oil), aloe compositions (*e.g.*, aloe-vera gel), ethyl alcohol, isopropyl alcohol, octyloxyphenylpolyethylene glycol, oleic acid,

polyethylene glycol 400, propylene glycol, N-decylmethysulfoxide, fatty acid esters (*e.g.*, isopropyl myristate, methyl laurate, glycerol monooleate, and propylene glycol monooleate) and N-methyl pyrrolidone.

[0175] In certain embodiments, the compositions may be in the form of ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. In certain exemplary embodiments, formulations of the compositions according to the invention are creams, which may further contain saturated or unsaturated fatty acids such as stearic acid, palmitic acid, oleic acid, palmito-oleic acid, cetyl or oleyl alcohols, stearic acid being particularly preferred. Creams of the invention may also contain a non-ionic surfactant, for example, polyoxy-40-stearate. In certain embodiments, the active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, eardrops, and eye drops are also contemplated as being within the scope of this invention. Additionally, the present invention contemplates the use of transdermal patches, which have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms are made by dissolving or dispensing the compound in the proper medium. As discussed above, penetration enhancing agents can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

[0176] It will also be appreciated that the compounds and pharmaceutical compositions of the present invention can be formulated and employed in combination therapies, that is, the compounds and pharmaceutical compositions can be formulated with or administered concurrently with, prior to, or subsequent to, one or more other desired therapeutics or medical procedures. The particular combination of therapies (therapeutics or procedures) to employ in a combination regimen will take into account compatibility of the desired therapeutics and/or procedures and the desired therapeutic effect to be achieved. It will also be appreciated that the therapies employed may achieve a desired effect for the same disorder (for example, an inventive compound may be administered concurrently with another anticancer agent), or they may achieve different effects (*e.g.*, control of any adverse effects).

[0177] For example, other therapies or anticancer agents that may be used in combination with the inventive compounds of the present invention include surgery,

radiotherapy (in but a few examples, γ -radiation, neutron beam radiotherapy, electron beam radiotherapy, proton therapy, brachytherapy, and systemic radioactive isotopes, to name a few), endocrine therapy, biologic response modifiers (interferons, interleukins, and tumor necrosis factor (TNF) to name a few), hyperthermia and cryotherapy, agents to attenuate any adverse effects (*e.g.*, antiemetics), and other approved chemotherapeutic drugs, including, but not limited to, alkylating drugs (mechlorethamine, chlorambucil, Cyclophosphamide, Melphalan, Ifosfamide), antimetabolites (Methotrexate), purine antagonists and pyrimidine antagonists (6-Mercaptopurine, 5-Fluorouracil, Cytarabine, Gemcitabine), spindle poisons (Vinblastine, Vincristine, Vinorelbine, Paclitaxel), podophyllotoxins (Etoposide, Irinotecan, Topotecan), antibiotics (Doxorubicin, Bleomycin, Mitomycin), nitrosoureas (Carmustine, Lomustine), inorganic ions (Cisplatin, Carboplatin), enzymes (Asparaginase), and hormones (Tamoxifen, Leuprolide, Flutamide, and Megestrol), to name a few. For a more comprehensive discussion of updated cancer therapies see, The Merck Manual, Seventeenth Ed. 1999, the entire contents of which are hereby incorporated by reference. See also the National Cancer Institute (CNI) website (www.nci.nih.gov) and the Food and Drug Administration (FDA) website for a list of the FDA approved oncology drugs (www.fda.gov/cder/cancer/druglistframe.htm – See Appendix A).

[0178] In certain embodiments, the pharmaceutical compositions of the present invention further comprise one or more additional therapeutically active ingredients (*e.g.*, chemotherapeutic and/or palliative). For purposes of the invention, the term “*Palliative*” refers to treatment that is focused on the relief of symptoms of a disease and/or side effects of a therapeutic regimen, but is not curative. For example, palliative treatment encompasses painkillers, antinausea medications and anti-sickness drugs. In addition, chemotherapy, radiotherapy and surgery can all be used palliatively (that is, to reduce symptoms without going for cure; *e.g.*, for shrinking tumors and reducing pressure, bleeding, pain and other symptoms of cancer).

[0179] Additionally, the present invention provides pharmaceutically acceptable derivatives of the inventive compounds, and methods of treating a subject using these compounds, pharmaceutical compositions thereof, or either of these in combination with one or more additional therapeutic agents.

[0180] It will also be appreciated that certain of the compounds of present invention can exist in free form for treatment, or where appropriate, as a pharmaceutically acceptable derivative thereof. According to the present invention, a pharmaceutically acceptable derivative includes, but is not limited to, pharmaceutically acceptable salts, esters, salts of such esters, or a prodrug or other adduct or derivative of a compound of this invention which upon administration to a patient in need is capable of providing, directly or indirectly, a compound as otherwise described herein, or a metabolite or residue thereof.

[0181] 4) Research Uses, Pharmaceutical Uses and Methods of Treatment

[0182] *Research Uses*

[0183] According to the present invention, the inventive compounds may be assayed in any of the available assays known in the art for identifying compounds having Eg5 inhibitory and/or antiproliferative activity. For example, the assay may be cellular or non-cellular, *in vivo* or *in vitro*, high- or low-throughput format, etc.

[0184] Thus, in one aspect, compounds of this invention which are of particular interest include those which:

- exhibit Eg5-inhibitory activity;
- exhibit cytotoxic or growth inhibitory effect on cancer cell lines maintained *in vitro* or in animal studies using a scientifically acceptable cancer cell xenograft model; and/or
- exhibit a therapeutic profile (*e.g.*, optimum safety and curative effect) that is superior to existing chemotherapeutic agents.

[0185] As detailed in the exemplification herein, in assays to determine the ability of compounds to inhibit Eg5 activity in purified protein assays, certain inventive compounds exhibited IC_{50} values $\leq$ about 100 μ M. In certain embodiments, certain inventive compounds exhibited IC_{50} values $\leq$ about 50 μ M. In certain embodiments, certain inventive compounds exhibited IC_{50} values $\leq$ about 40 μ M. In certain embodiments, certain inventive compounds exhibited IC_{50} values $\leq$ about 30 μ M. In certain embodiments, certain inventive compounds exhibited IC_{50} values $\leq$ about 20 μ M. In certain embodiments, certain inventive compounds exhibited IC_{50} values $\leq$ about 10 μ M. In certain embodiments, certain inventive compounds exhibited IC_{50} values $\leq$ about 5 μ M. In certain embodiments, certain inventive compounds exhibited IC_{50} values $\leq$ about 4 μ M. In certain embodiments, certain inventive compounds

exhibited IC_{50} values $\leq$ about 3 μ M. In certain embodiments, certain inventive compounds exhibited IC_{50} values $\leq$ about 2.5 μ M. In certain embodiments, certain inventive compounds exhibited IC_{50} values $\leq$ about 2 μ M. In certain embodiments, certain inventive compounds exhibited IC_{50} values $\leq$ about 1.5 μ M. In certain embodiments, certain inventive compounds exhibited IC_{50} values $\leq$ about 1 μ M. In certain embodiments, certain inventive compounds exhibit IC_{50} values $\leq$ about 500 nM. In certain embodiments, certain inventive compounds exhibit IC_{50} values $\leq$ about 250 nM. In certain embodiments, certain inventive compounds exhibit IC_{50} values $\leq$ about 100 nM. In certain embodiments, certain inventive compounds exhibit IC_{50} values $\leq$ about 50 nM.

[0186] As detailed in the exemplification herein, in assays to determine the ability of compounds to inhibit Eg5 activity in cells, certain inventive compounds exhibited IC_{50} values $\leq$ about 500 μ M. In certain embodiments, certain inventive compounds exhibited IC_{50} values $\leq$ about 400 μ M. In certain embodiments, certain inventive compounds exhibited IC_{50} values $\leq$ about 350 μ M. In certain embodiments, certain inventive compounds exhibited IC_{50} values $\leq$ about 300 μ M. In certain embodiments, certain inventive compounds exhibited IC_{50} values $\leq$ about 250 μ M. In certain embodiments, certain inventive compounds exhibited IC_{50} values $\leq$ about 200 μ M. In certain embodiments, certain inventive compounds exhibited IC_{50} values $\leq$ about 150 μ M. In certain embodiments, certain inventive compounds exhibited IC_{50} values $\leq$ about 100 μ M. In certain embodiments, certain inventive compounds exhibited IC_{50} values $\leq$ about 75 μ M. In certain embodiments, certain inventive compounds exhibited IC_{50} values $\leq$ about 50 μ M. In certain embodiments, certain inventive compounds exhibited IC_{50} values $\leq$ about 40 μ M. In certain embodiments, certain inventive compounds exhibited IC_{50} values $\leq$ about 30 μ M. In certain embodiments, certain inventive compounds exhibit IC_{50} values $\leq$ about 25 μ M. In certain embodiments, certain inventive compounds exhibit IC_{50} values $\leq$ about 20 μ M. In certain embodiments, certain inventive compounds exhibit IC_{50} values $\leq$ about 15 μ M. In certain embodiments, certain inventive compounds exhibit IC_{50} values $\leq$ about 10 μ M. In certain embodiments, certain inventive compounds exhibit IC_{50} values $\leq$ about 5 μ M. In certain embodiments, certain inventive compounds exhibit IC_{50} values $\leq$ about 2.5 μ M. In certain embodiments, certain inventive compounds exhibit IC_{50} values $\leq$ about 1 μ M.

[0187] *Pharmaceutical Uses and Methods of Treatment*

[0188] In general, methods of using the compounds of the present invention comprise administering to a subject in need thereof a therapeutically effective amount of a compound of the present invention. As discussed above, compounds of the invention are inhibitors of Eg5 and, as such, are useful in the treatment of disorders in which Eg5 is involved. For example, compounds of the invention may be useful in the treatment of cancer. Accordingly, in yet another aspect, according to the methods of treatment of the present invention, tumor cells are killed, or their growth is inhibited by contacting said tumor cells with an inventive compound or composition, as described herein.

[0189] Thus, in another aspect of the invention, methods for the treatment of cancer are provided comprising administering a therapeutically effective amount of a compound of formula (I), as described herein, to a subject in need thereof. In certain embodiments, a method for the treatment of cancer is provided comprising administering a therapeutically effective amount of an inventive compound, or a pharmaceutical composition comprising an inventive compound to a subject in need thereof, in such amounts and for such time as is necessary to achieve the desired result. In certain embodiments of the present invention a "therapeutically effective amount" of the inventive compound or pharmaceutical composition is that amount effective for killing or inhibiting the growth of tumor cells. The compounds and compositions, according to the method of the present invention, may be administered using any amount and any route of administration effective for killing or inhibiting the growth of tumor cells. Thus, the expression "amount effective to kill or inhibit the growth of tumor cells", as used herein, refers to a sufficient amount of agent to kill or inhibit the growth of tumor cells. The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the infection, the particular anticancer agent, its mode of administration, and the like.

[0190] In certain embodiments, any system where the control of cellular growth and cell division is desired may utilize compounds in the bicyclic dihydropyrimidine class to regulate mitosis. More specifically, inventive compounds may be used to inhibit cell growth. One non-limiting example of an application of compounds of the invention to a cellular system is their use as anti-mitotic anti-cancer drugs. Other

examples include controlling cell division and the immune system in diseases such as rheumatoid arthritis

[0191] In certain embodiments, a method of treating an individual with uncontrolled or abnormal cell growth is provided. Compositions comprising one or more inventive compounds or derivatives thereof with similar biological activity are useful for treating individuals with cells that having become cancerous tumors. Such compositions may be administered to an individual in need thereof at therapeutically effective amounts to slow or cease the abnormal cell growth. Generally, abnormal cell growth is associated with cancerous cells. However, other diseases resulting from uncontrolled cell growth (*e.g.* cardiovascular diseases, rheumatoid arthritis etc.) may be treated with compositions and methods of the present invention.

[0192] In certain embodiments, the method involves the administration of a therapeutically effective amount of the compound or a pharmaceutically acceptable derivative thereof to a subject (including, but not limited to a human or animal) in need of it.

[0193] As discussed above, the compounds of the present invention are useful as anticancer agents, and thus may be useful in the treatment of cancer, by effecting tumor cell death or inhibiting the growth of tumor cells. In certain embodiments, the inventive compounds as useful for the treatment of cancer (including, but not limited to, glioblastoma, retinoblastoma, breast cancer, cervical cancer, colon and rectal cancer, leukemia, lymphoma, lung cancer (including, but not limited to small cell lung cancer), melanoma and/or skin cancer, multiple myeloma, non-Hodgkin's lymphoma, ovarian cancer, pancreatic cancer, prostate cancer and gastric cancer, bladder cancer, uterine cancer, kidney cancer, testicular cancer, stomach cancer, brain cancer, liver cancer, or esophageal cancer). In certain embodiments, the inventive anticancer agents are active against leukemia cells and melanoma cells, and thus are useful for the treatment of leukemias (*e.g.*, myeloid, lymphocytic, myelocytic and lymphoblastic leukemias) and malignant melanomas. In still other embodiments, the inventive anticancer agents kill and/or inhibit the growth of multidrug resistant cells (MDR cells). In still other embodiments, the inventive anticancer agents are active against solid tumors.

[0194] Additionally, the present invention provides pharmaceutically acceptable derivatives of the inventive compounds, and methods of treating a subject using these

compounds, pharmaceutical compositions thereof, or either of these in combination with one or more additional therapeutic agents.

[0195] Another aspect of the invention relates to a method of treating or lessening the severity of a disease or condition associated with a proliferation disorder in a patient, said method comprising a step of administering to said patient, a compound of formula **I** or a composition comprising said compound.

[0196] It will be appreciated that the compounds and compositions, according to the method of the present invention, may be administered using any amount and any route of administration effective for the treatment of cancer and/or disorders associated with cell hyperproliferation. For example, when using the inventive compounds for the treatment of cancer, the expression "effective amount" as used herein, refers to a sufficient amount of agent to inhibit cell proliferation, or refers to a sufficient amount to reduce the effects of cancer. The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the diseases, the particular anticancer agent, its mode of administration, and the like.

[0197] The compounds of the invention are preferably formulated in dosage unit form for ease of administration and uniformity of dosage. The expression "dosage unit form" as used herein refers to a physically discrete unit of therapeutic agent appropriate for the patient to be treated. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically effective dose level for any particular patient or organism will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and like factors well known in the medical arts (see, for example, Goodman and Gilman's, "The Pharmacological Basis of Therapeutics", Tenth Edition, A. Gilman, J. Hardman and L. Limbird, eds., McGraw-Hill Press, 155-173, 2001, which is incorporated herein by reference in its entirety).

[0198] Another aspect of the invention relates to a method for inhibiting Eg5 activity in a biological sample or a patient, which method comprises administering to the patient, or contacting said biological sample with at least one compound of formula I or a composition comprising said compound.

[0199] Furthermore, after formulation with an appropriate pharmaceutically acceptable carrier in a desired dosage, the pharmaceutical compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, creams or drops), buccally, as an oral or nasal spray, or the like, depending on the severity of the infection being treated. In certain embodiments, the compounds of the invention may be administered at dosage levels of about 0.001 mg/kg to about 50 mg/kg, from about 0.01 mg/kg to about 25 mg/kg, or from about 0.1 mg/kg to about 10 mg/kg of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect. It will also be appreciated that dosages smaller than 0.001 mg/kg or greater than 50 mg/kg (for example 50-100 mg/kg) can be administered to a subject. In certain embodiments, compounds are administered orally or parenterally.

[0200] As discussed above, the present invention provides a method of treating a condition via modulation of the Eg5 protein activity comprising administering to a subject in need thereof an effective amount at least one compound of the invention. The invention also provides a method for treating a condition via modulation of the Eg5 protein activity comprising administering to a subject in need thereof a combination (simultaneous or sequential) of at least one antineoplastic agent and at least one compound of the invention. In a preferred embodiment, the condition treated is a proliferative disease such as cancer. Any compounds that act as antineoplastic agents and any small molecule which modulates the Eg5 protein sufficiently to induce mitotic arrest and apoptosis can be used in the instant invention. Monastrol has not been shown to induce apoptosis and is not included within the scope of this invention.

[0201] When combination therapy is employed, it is anticipated that the therapeutic effect of the instant invention may be achieved with smaller amounts of the antineoplastic agents and Eg5 protein inhibitors than would be required if such antineoplastic agents and Eg5 inhibitors were administered alone, thereby avoiding or minimizing adverse toxicity effects.

[0202] Antineoplastic agents which are suitable for use in the methods and compositions of this invention include, but are not limited to, microtubule-stabilizing agents such as paclitaxel (also known as Taxol®), docetaxel (also known as Taxotere®), 7-O-methylthiomethylpaclitaxel (disclosed in U.S. Pat. No. 5,646,176, herein incorporated by reference), 3'-tert-butyl-3'-N-tert-butyloxycarbonyl-4-deacetyl-3'-dephenyl-3'-N-debenzoyl-4-O-methoxycarbonyl-paclitaxel, C-4 methyl carbonate paclitaxel (disclosed in WO 94/14787, herein incorporated by reference), epothilone A, epothilone B, epothilone C, epothilone D, desoxyepothilone A, desoxyepothilone B, [1S-[1R*, 3R*(E), 7R*, 10S*, 11R*, 12R*, 16S*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione (disclosed in WO 99/02514, herein incorporated by reference), [1S-[1R*, 3R*(E), 7R*, 10S*, 11R*, 12R*, 16S*]]-3-[2-[2-(aminomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4-17-dioxabicyclo-[14.1.0]-heptadecane-5,9-dione, and derivatives thereof; microtubule-disruptor agents; inhibitors of cyclin dependent kinases (including those disclosed in U.S. Pat. No. 6,040,321, herein incorporated by reference); inhibitors of farnesyltransferase; alkylating agents; anti-metabolites; epidophyllotoxin; an antineoplastic enzyme; a topoisomerase inhibitor; procarbazine; mitoxantrone; platinum coordination complexes; biological response modifiers; growth factor inhibitors; hormonal/antihormonal therapeutic agents; and haematopoietic growth factors.

[0203] Classes of antineoplastic agents suitable for use in the present invention include, but are not limited to, the anthracycline family of drugs, the vinca drugs, the mitomycins, the bleomycins, the cytotoxic nucleosides, the taxanes, the epothilones, discodermolide, the pteridine family of drugs, diynenes, aromatase inhibitors, and the podophyllotoxins. Particularly useful members of those classes include, for example, paclitaxel, docetaxel, 7-O-methylthiomethylpaclitaxel, 3'-tert-butyl-3'-N-tert-butyloxycarbonyl-4-deacetyl-3'-dephenyl-3'-N-debenzoyl-4-O-methoxycarbonyl-paclitaxel, C-4 methyl carbonate paclitaxel, epothilone A, epothilone B, epothilone C, epothilone D, desoxyepothilone A, desoxyepothilone B, [1S-[1R*, 3R*(E), 7R*, 10S*, 11R*, 12R*, 16S*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione, [1S-[1R*, 3R*(E), 7R*, 10S*, 11R*, 12R*, 16S*]]-3-[2-[2-(aminomethyl)-4-

thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione, doxorubicin, carminomycin, daunorubicin, aminopterin, methotrexate, methopterin, dichloro-methotrexate, mitomycin C, porfiromycin, 5-fluorouracil, 6-mercaptopurine, gemcitabine, cytosine arabinoside, podophyllotoxin or podophyllotoxin derivatives such as etoposide, etoposide phosphate or teniposide, melphalan, vinblastine, vincristine, leurosine, vindesine, leurosine, and the like. Other useful antineoplastic agents include estramustine, cisplatin, carboplatin, cyclophosphamide, bleomycin, tamoxifen, ifosamide, melphalan, hexamethyl melamine, thiotepa, cytarabin, idatrexate, trimetrexate, dacarbazine, L-asparaginase, camptothecin, CPT-11, topotecan, ara-C, bicalutamide, flutamide, leuprolide, pyridobenzoindole derivatives, interferons, interleukins, and inhibitors of cyclin dependent kinases including, but not limited to, those in U.S. Pat. No. 6,040,321, herein incorporated by reference; and inhibitors of farnesyltransferase including, but not limited to, those in U.S. Pat. No. 6,011,029 herein incorporated by reference.

[0204] Preferred classes of antineoplastic agents are the taxanes and the epothilones, and the preferred antineoplastic agents are paclitaxel, docetaxel, 7-O-methylthiomethylpaclitaxel, 3'-tert-butyl-3'-N-tert-butyl-oxycarbonyl-4-deacetyl-3'-dephenyl-3'-N-debenzoyl-4-O-methoxycarbonyl-paclitaxel, C-4 methyl carbonate paclitaxel, epothilone A, epothilone B, epothilone C, epothilone D, desoxyepothilone A, desoxyepothilone B, [1S-[1R*, 3R*(E), 7R*, 10S*, 11R*, 12R*, 16S*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione, and [1S-[1R*, 3R*(E), 7R*, 10S*, 11R*, 12R*, 16S*]]-3-[2-[2-(aminomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione, the cyclin dependent kinase exemplified in U.S. Pat. No. 6,040,321; the farnesyltransferase inhibitors exemplified in U.S. Pat. No. 6,011,029 as well as (R)-7-cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-(2-thienylsulfonyl)-1H-1,4-benzodiazepine, mesylate salt.

TREATMENT KIT

[0205] In other embodiments, the present invention relates to a kit for conveniently and effectively carrying out the methods in accordance with the present invention. In general, the pharmaceutical pack or kit comprises one or more containers filled with

one or more of the ingredients of the pharmaceutical compositions of the invention. Such kits are especially suited for the delivery of solid oral forms such as tablets or capsules. Such a kit preferably includes a number of unit dosages, and may also include a card having the dosages oriented in the order of their intended use. If desired, a memory aid can be provided, for example in the form of numbers, letters, or other markings or with a calendar insert, designating the days in the treatment schedule in which the dosages can be administered. Alternatively, placebo dosages, or calcium dietary supplements, either in a form similar to or distinct from the dosages of the pharmaceutical compositions, can be included to provide a kit in which a dosage is taken every day. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceutical products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

EQUIVALENTS

[0206] The representative examples which follow are intended to help illustrate the invention, and are not intended to, nor should they be construed to, limit the scope of the invention. Indeed, various modifications of the invention and many further embodiments thereof, in addition to those shown and described herein, will become apparent to those skilled in the art from the full contents of this document, including the examples which follow and the references to the scientific and patent literature cited herein. It should further be appreciated that, unless otherwise indicated, the entire contents of each of the references cited herein are incorporated herein by reference to help illustrate the state of the art. The following examples contain important additional information, exemplification and guidance which can be adapted to the practice of this invention in its various embodiments and the equivalents thereof.

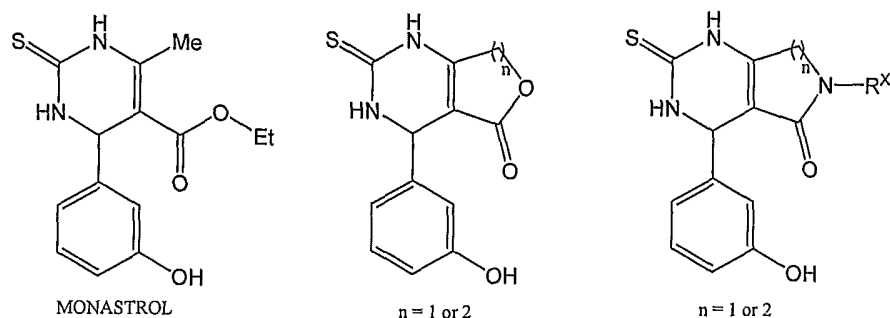
[0207] These and other aspects of the present invention will be further appreciated upon consideration of the following Examples, which are intended to illustrate certain particular embodiments of the invention but are not intended to limit its scope, as defined by the claims.

EXEMPLIFICATION

[0208] The compounds of this invention and their preparation can be understood further by the examples that illustrate some of the processes by which these

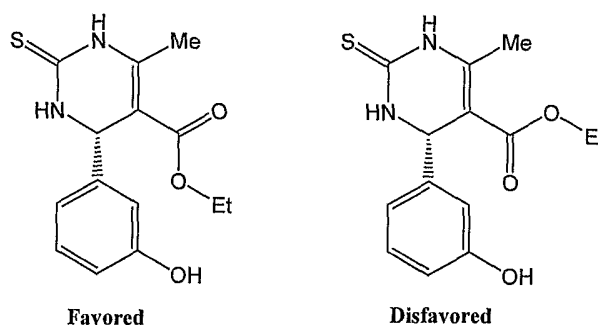
compounds are prepared or used. It will be appreciated, however, that these examples do not limit the invention. Variations of the invention, now known or further developed, are considered to fall within the scope of the present invention as described herein and as hereinafter claimed.

[0209] Two novel classes of constrained analogs of S-Monastrol – a known Eg5 inhibitor – were conceived, species of which are depicted below:



[0210] The assumption that this class of compounds could be more potent Eg5 inhibitors than Monastrol itself was made based on semi-empirical quantum mechanics calculation (PM3). These calculations were performed in order to get insight in the potential energies of individual conformations of Monastrol. Only the rotatable bonds of the phenyl substituent and the ethyl ester side chain were selected as search parameters. Results are shown in Figure 1.

[0211] We found that the energies between the s-cis and the s-trans conformations of the ester side chain differ by 2.4 to 2.9 kcal/mol in favor of the s-trans conformation.



[0212] This results in a population ratio of 1:40 to 1:100 for the two individual conformers. Assuming that the disfavored conformation is the biologically active species, an increase of the potency by up to two orders of magnitude seemed feasible if the molecule was arrested in this state.

[0213] Compounds were tested and showed a highly improved activity towards the isolated Eg5 protein. The IC₅₀ values were more than one order of magnitude lower than that of Monastrol (See Figure 2).

[0214] Furthermore, it was shown that all tested compounds retained their activity in cell based assays. Additionally, the tested compounds showed an improved solubility profile as compared to Monastrol.

[0215] *1) General Description of Synthetic Methods:*

[0216] Additional synthetic guidance is provided elsewhere in this document.

[0217] The compounds of this invention and their preparation can be understood further by the examples that illustrate some of the processes by which these compounds are prepared or used. It will be appreciated, however, that these examples do not limit the invention. Variations of the invention, now known or further developed, are considered to fall within the scope of the present invention as described herein and as hereinafter claimed.

[0218] According to the present invention, any available techniques can be used to make or prepare the inventive compounds or compositions including them. For example, a variety of solution phase synthetic methods such as those discussed in detail below may be used. Alternatively or additionally, the inventive compounds may be prepared using any of a variety of combinatorial techniques, parallel synthesis and/or solid phase synthetic methods known in the art.

[0219] It will be appreciated as described below, that a variety of inventive compounds can be synthesized according to the methods described herein. The starting materials and reagents used in preparing these compounds are either available from commercial suppliers such as Aldrich Chemical Company (Milwaukee, WI), Bachem (Torrance, CA), Sigma (St. Louis, MO), or are prepared by methods well known to a person of ordinary skill in the art following procedures described in such references as Fieser and Fieser 1991, "Reagents for Organic Synthesis", vols 1-17, John Wiley and Sons, New York, NY, 1991; Rodd 1989 "Chemistry of Carbon Compounds", vols. 1-5 and supps, Elsevier Science Publishers, 1989; "Organic Reactions", vols 1-40, John Wiley and Sons, New York, NY, 1991; March 2001, "Advanced Organic Chemistry", 5th ed. John Wiley and Sons, New York, NY; and Larock 1990, "Comprehensive Organic Transformations: A Guide to Functional Group Preparations", 2nd ed. VCH Publishers. These schemes are merely illustrative of some methods by which the compounds of this invention can be synthesized, and various modifications to these schemes can be made and will be suggested to a person of ordinary skill in the art having regard to this disclosure.

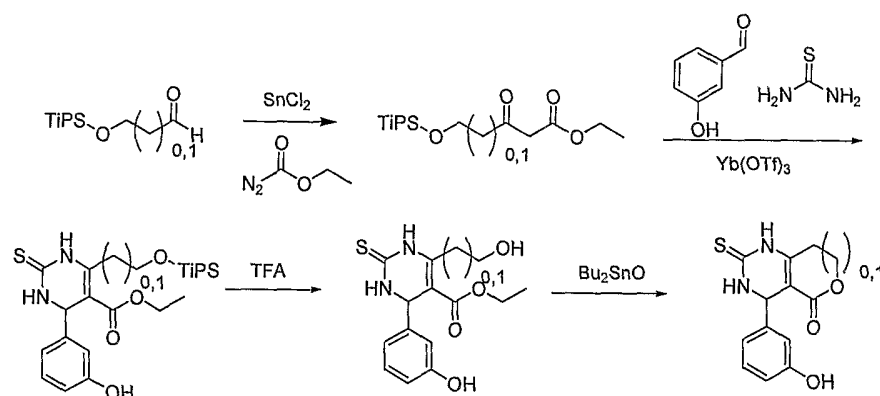
[0220] The starting materials, intermediates, and compounds of this invention may be isolated and purified using conventional techniques, including filtration, distillation, crystallization, chromatography, and the like. They may be characterized using conventional methods, including physical constants and spectral data.

[0221] *1-a) Synthesis of Exemplary Compounds:*

[0222] Unless otherwise indicated, starting materials are either commercially available or readily accessible through laboratory synthesis by anyone reasonably familiar with the art. Described generally below, are procedures and general guidance for the synthesis of compounds as described generally and in subclasses and species herein. Unless mentioned specifically, reaction mixtures were stirred using a magnetically driven stirrer bar. An inert atmosphere refers to either dry argon or dry nitrogen. Reactions were monitored either by thin layer chromatography, by proton nuclear magnetic resonance or by high-pressure liquid chromatography (HPLC), of a suitably worked up sample of the reaction mixture.

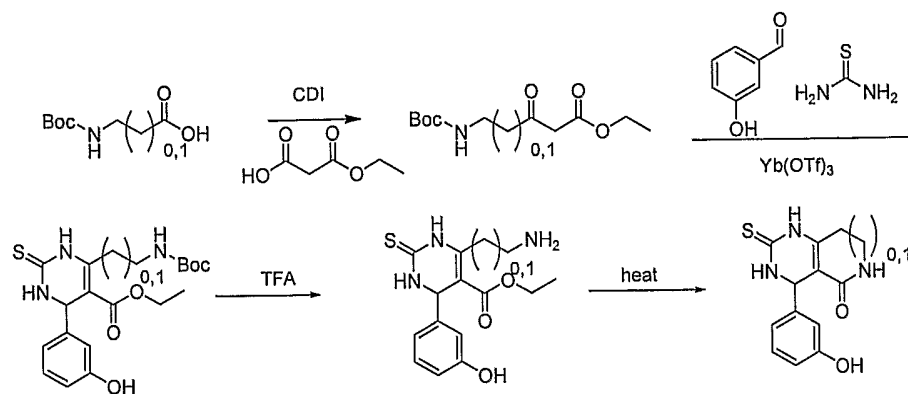
[0223] An exemplary synthetic approach to Cyclic-Monastrol derivatives O-series is depicted in Scheme 4.

[0224] **Scheme 4**

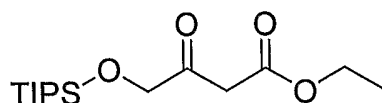


[0225] An exemplary synthetic approach to Cyclic-Monastrol derivatives N-series is depicted in Scheme 5.

[0226] **Scheme 5**



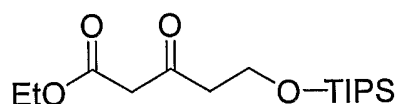
[0227] **Example 1:** 3-Oxo-4-triisopropylsilyloxy-butyric acid ethyl ester



[0228] 3.24g (15mmol) TIPS-protected Hydroxy-acetaldehyde and 284mg (1.5mmol) powdered tin (II) chloride were suspended in 40ml Methylene Chloride and placed in a 30°C water bath. 2.56g (22.5mmol) Ethyl diazoacetate were added via syringe over 5min and the yellow suspension was stirred for 30min. Water and 1M HCl were added to the solution and the aqueous layer was extracted three times with ether. The combined organic layers were dried over Na₂SO₄. The solvent was removed under reduced pressure and the crude product was purified on silica (Ether/Hexanes 4:1) to yield the desired ketoester (3.69g, 82%) as a colorless oil.

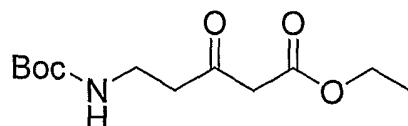
[0229] ¹H-NMR (500 MHz, CDCl₃); 4.29 (s, 2H); 4.18 (q, 2H, J=7.1Hz); 3.61 (s, 2H); 1.27 (t, 3H, J=7.1Hz); 1.14 (m, 3H); 1.06 (m, 18H)

[0230] **Example 2:** 3-Oxo-5-triisopropylsilyloxy-pentanoic acid ethyl ester



[0231] Prepared according to literature reference (D. J. Kopecky and S. D. Rychnovsky, *J. Am. Chem. Soc.* 2001, 123, 8240-8421)

[0232] **Example 3:** 5-tert-Butoxycarbonylamino-3-oxo-pentanoic acid ethyl ester

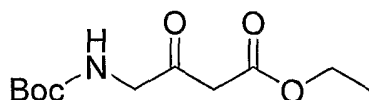


[0233] 1,1'-carbonyldiimidazole (12.15, 76mmol) was added to a solution N-Boc beta-Alanine (14.3g 76mmol) in dry THF (100ml) and stirred under nitrogen for 2h to form the acid imidazolide.

[0234] To ethyl hydrogen malonate (10g, 76 mmol) in dry THF (100ml) at 0°C was added 100ml freshly prepared propan-2-ylmagnesium bromide in THF (144mmol) over 10min. After stirring at room temperature for 30min and warming to 40°C for 30min, the solution was cooled to 0°C and the imidazolide solution added. The resultant gummy precipitate was stirred vigorously at room temperature for 4h and cooled to 0°C. Saturated bicarbonate solution was added to the solution. The aqueous layer was extracted three times with EtOAc. 20ml of sat. CuSO₄ were added to the organic layer, whereby the organic layer turned green. Subsequently 1M HCl was added in small portions until the blue color remained in the aqueous layer. The organic layer was dried over Na₂SO₄. After evaporation of the solvent under reduced pressure, the crude product was purified on silica (Hexanes/Ethyl Acetate 2:1) to yield the Ketoester as a colorless oil (13.2g, 51mmol, 68%).

[0235] ¹H-NMR (500 MHz, CDCl₃); 4.96 (s, 1H) ; 4.19 (q, 2H, J=7.1Hz); 3.44 (s, 2H) ; 3.38 (dd, 2H, J=5.0Hz, J=10.8Hz); 2.78 (t, 2H, J=5.7Hz); 1.42 (s, 9H) ; 1.28 (t, 3H, J=7.1Hz)

[0236] **Example 4:** 4-tert-Butoxycarbonylamino-3-oxo-butyric acid ethyl ester



[0237] To N-Boc Glycine (6.65g 38mmol) in dry THF (50ml) was added 1,1'-carbonyldiimidazole (6.16g, 38mmol) and the reaction was stirred under nitrogen for 2h to form the acid imidazolide.

[0238] To ethyl hydrogen malonate (5g, 38 mmol) in dry THF (50ml) at 0°C was added 50ml over 10min freshly prepared propan-2-ylmagnesium bromide in THF (72mmol). After stirring at room temperature for 30min and warming to 40°C for 30min, the solution was cooled to 0°C and the imidazolide solution added. The

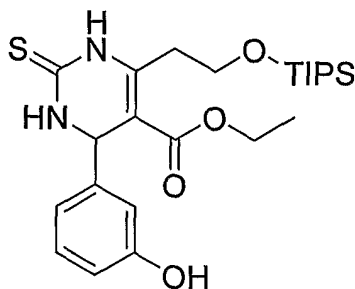
resultant gummy precipitate was stirred vigorously at room temperature for 4 h, saturated bicarbonate solution was added after cooling to 0°C. The aqueous layer was extracted three times with EtOAc. 20ml of sat. CuSO₄ were added to the organic layer, whereby the organic layer turned green. Subsequently 1M HCl was added in small portions until the blue color remained in the aqueous layer. The organic layer was dried over Na₂SO₄. After evaporation of the solvent under reduced pressure the crude product was purified on silica (Hexanes/Ethyl acetate 2:1) to yield the Ketoester as a colorless oil (5.7g, 23.2mmol, 61%).

[0239] ¹H-NMR (500 MHz, CDCl₃); 5.18 (s, 1H) ; 4.19 (q, 2H, J=7.1Hz); 4.12 (d, 2H, J=4.6Hz); 3.47 (s, 2H) ; 1.44 (s, 9H) ; 1.27 (t, 3H, J=7.2Hz)

[0240] **Example 5:** General Procedure for the Biginelli Reaction

[0241] The Ketoester (2mmol), 3-Hydroxybenzaldehyde (2mmol), Thiourea (3mmol, 1.5eq) and Yb(OTf)₃ (0.2mmol, 0.1eq.) were dissolved in 4ml Acetonitrile and stirred under inert conditions for 2-24h at 90°C. After cooling to room temperature, the crude reaction was poured into water and extracted three times with Methylene Chloride. The combined organic layers were dried over Na₂SO₄. After evaporation of the solvent, the crude product was purified on silica.

[0242] **Example 6:** 4-(3-Hydroxy-phenyl)-2-thioxo-6-(2-triisopropylsilyloxy-ethyl)-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester

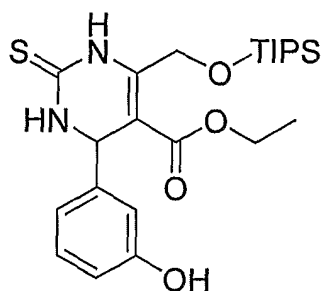


[0243] yellow oil (yield 44%), purification with 10-50% Ethyl acetate in Hexanes

[0244] ¹H-NMR (500 MHz, CDCl₃); 8.84 (s, 1H) ; 7.75 (s, 1H) ; 7.08 (t, 1H, J=7.8Hz); 6.80 (d, 1H, J=7.8Hz); 6.7 (br, 1H); 6.75 (m, 1H); 6.72 (dd, 1H, J=2.6Hz, J=7.6Hz); 5.29 (d, 1H, J=3.1Hz); 4.08 (m, 2H); 4.00 (m, 2H); 3.19 (ddd, 1H, J=3.6Hz, J=6.2Hz, J=14.9Hz); 3.02 (ddd, 1H, J=3.9Hz, J=7.3Hz, J=15.1Hz); 1.14 (m, 24H)

[0245] HRMS (M+H⁺, calc. 479.2400, found 479.2397)

[0246] **Example 7:** 4-(3-Hydroxy-phenyl)-2-thioxo-6-triisopropylsilyloxymethyl-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester

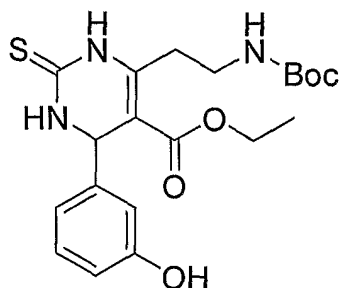


[0247] yellow oil (yield 34%), purification with 20-50% Ethyl acetate in Hexanes

[0248] $^1\text{H-NMR}$ (500 MHz, CDCl_3); 8.71 (s, 1H) ; 7.84 (s, 1H) ; 7.06 (t, 1H, $J=7.8\text{Hz}$); 6.73 (m, 4H); 5.27 (d, 1H, $J=2.4\text{Hz}$); 4.91 (q, 2H, $J=17.1\text{Hz}$); 4.06 (m, 2H); 1.08 (m, 24H).

[0249] HRMS ($\text{M}+\text{H}^+$, calc. 465.2243, found 465.2242)

[0250] **Example 8:** 6-(2-tert-Butoxycarbonylamino-ethyl)-4-(3-hydroxy-phenyl)-2-thioxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester

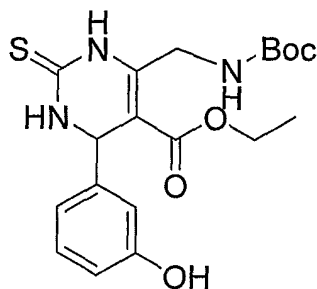


[0251] yellow oil (yield 48%), purification with 10-70% Ethyl acetate in Hexanes

[0252] $^1\text{H-NMR}$ (500 MHz, CD_3OD); 7.11 (t, 1H, $J=7.8\text{Hz}$); 6.75 (ddd, 1H, $J=1.0\text{Hz}$, $J=1.5\text{Hz}$, $J=7.5\text{Hz}$); 6.73 (t, 1H, $J=2.2\text{Hz}$); 6.69 (ddd, 1H, $J=0.9\text{Hz}$, $J=2.5\text{Hz}$, $J=8.1\text{Hz}$); 5.25 (s, 1H); 4.06 (dq, 2H, $J=1.7\text{Hz}$, $J=7.1\text{Hz}$); 3.32 (m, 2H); 2.88 (m, 2H); 1.42 (s, 9H) ; 1.15 (t, 3H, $J=7.1\text{Hz}$)

[0253] HRMS ($\text{M}+\text{H}^+$, calc. 422.1749, found 422.1754)

[0254] **Example 9:** 6-(tert-Butoxycarbonylamino-methyl)-4-(3-hydroxy-phenyl)-2-thioxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester



[0255] yellow oil (yield 16%), purification with 10-70% Ethyl acetate in Hexanes

[0256] $^1\text{H-NMR}$ (500 MHz, CDCl_3); 8.80 (s, 1H); 8.10 (s, 1H); 7.20 (s, 1H) ; 7.07

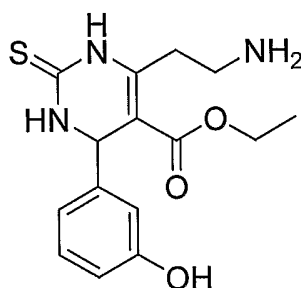
(t, 1H, J=7.9Hz); 6.80 (br, 1H) ; 6.73 (m, 3H); 5.24 (s, 1H) ; 4.38 (m, 2H) ; 4.06 (q, 2H, J=7.0Hz); 1.44 (s, 9H) ; 1.14 (t, 3H, J=7.1Hz)

[0257] HRMS ($M+H^+$, calc. 408.1593 found 408.1583)

[0258] **Example 10:** General Procedure: Boc-deprotection

[0259] The Boc-protected amine was dissolved in Methylene Chloride (0.2M). After cooling to 0°C Trifluoroacetic acid (5% v/v) was added. The reaction was warmed to room temperature and stirred for additional 4h, before the solvent was evaporated under reduced pressure and the amine was used for the following cyclization without further purification.

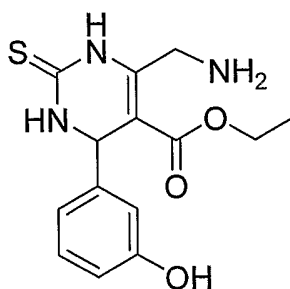
[0260] **Example 11:** 6-(2-Amino-ethyl)-4-(3-hydroxy-phenyl)-2-thioxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester



[0261] 1H -NMR (500 MHz, CD_3OD); 7.14 (t, 1H, J=8.0Hz); 6.78 (d, 1H, J=7.7Hz); 6.75 (m, 1H) ; 6.71 (ddd, 1H, J=0.9Hz, J=2.2Hz, J=8.0Hz); 5.27 (s, 1H) ; 4.11 (dd, 2H, J=7.0Hz, J=14.0Hz); 3.22 (m 3H) ; 2.94 (td, 1H, J=6.5Hz, J=7.7Hz); 1.16 (t, 3H, J=7.1Hz)

[0262] HRMS ($M+H^+$, calc. 322.1225, found 322.1232)

[0263] **Example 12:** 6-Aminomethyl-4-(3-hydroxy-phenyl)-2-thioxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester



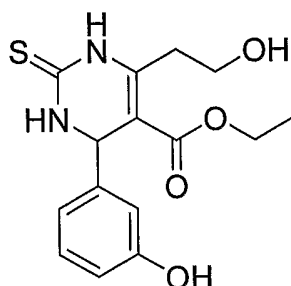
[0264] 1H -NMR (500 MHz, CD_3OD); 7.16 (t, 1H, J=7.9Hz); 6.82 (d, 1H, J=7.7Hz); 6.78 (t, 1H, J=2Hz); 6.73 (ddd, 1H, J=0.9Hz, J=2.4Hz, J=8.1Hz); 5.32 (s, 1H); 4.19 (m, 2H); 4.14 (d, 1H, J=13.5Hz); 4.07 (d, 1H, J=13.4Hz); 1.22 (t, 3H, J=7.1Hz)

[0265] HRMS ($M+H^+$, calc. 308.1069, found 308.1075)

[0266] Example 13: General Procedure: TIPS-deprotection

[0267] The TIPS-protected alcohol was dissolved in THF (0.2M). After addition of 15% HF/Pyridine (v/v) the reaction was stirred at room temperature. After 3h excess HF was quenched by addition of 2 eq. of TMSOEt. The solvent is removed under reduced pressure and the crude product was purified on silica (0-10% Methanol in Methylene Chloride) to yield the desired alcohol as a yellow oil.

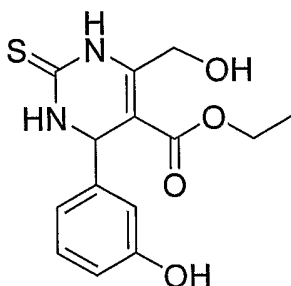
[0268] Example 14: 6-(2-Hydroxy-ethyl)-4-(3-hydroxy-phenyl)-2-thioxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester



[0269] ¹H-NMR (500 MHz, CD₃OD); 7.13 (t, 1H, J=7.8Hz); 6.78 (dm, 1H, J=7.7Hz); 6.74 (t, 1H, J=7.8Hz); 6.68 (dd, 1H, J=0.9Hz, J=2.5Hz); 5.26 (s, 1H); 4.08 (dq, 2H, J=1.9Hz, J=7.1Hz); 3.80 (t, 1H, J=6.7Hz); 3.34 (s, 1H); 3.02 (m, 2H); 1.17 (t, 3H, J=7.1Hz)

[0270] HRMS (M+H⁺, calc. 323.1065, found 323.1066)

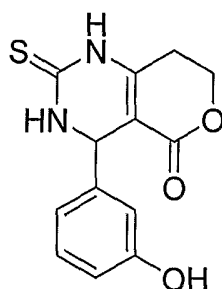
[0271] Example 14: 6-Hydroxymethyl-4-(3-hydroxy-phenyl)-2-thioxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester



[0272] ¹H-NMR (500 MHz, CD₃OD); 7.13 (t, 1H, J=7.8Hz); 6.79 (m, 2H); 6.70 (ddd, 1H, J=1.0Hz, J=2.3Hz, J=8.1Hz); 5.28 (s, 1H); 4.77 (d, 1H, J=16.9Hz); 4.70 (d, 1H, J=16.9Hz); 4.10 (m, 2H); 1.18 (t, 3H, J=6.9Hz)

[0273] HRMS (M+H⁺, calc. 309.0909, found 309.0903)

[0274] Example 15: 4-(3-Hydroxy-phenyl)-2-thioxo-1,2,3,4,7,8-hexahydro-pyrano[4,3-d]pyrimidin-5-one

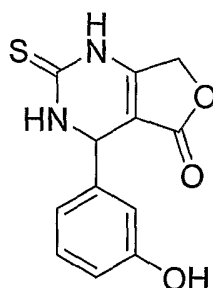


[0275] 20mg of the deprotected alcohol and 20mg Dibutyltin oxide were dissolved in 2ml Methanol. The reaction mixture was stirred for 16h at 70°C. The solvent was removed under reduced pressure and the crude product was purified by reversed phase HPLC (AtlantisAQ) to yield 14mg of the desired product as a white solid (82%).

[0276] ¹H-NMR (500 MHz, CD₃OD); 7.14 (t, 1H, J=7.9Hz); 6.80 (d, 1H, J=7.6Hz); 6.69 (ddd, 1H, J=0.9Hz, J=2.5Hz, J=8.1Hz); 5.25 (d, 1H, J=1.1Hz); 4.41 (ddd, 1H, J=3.3Hz, J=5.7Hz, J=11.2Hz); 4.28 (dt, 1H, J=4.2Hz, J=11.6Hz); 2.80 (dddd, 1H, J=1.3Hz, J=5.7Hz, J=11.8Hz, J=17.6Hz); 2.55 (td, 1H, J=3.8Hz, J=17.7Hz)

[0277] HRMS (M+H⁺, calc. 277.0647, found 277.0648)

[0278] **Example 16:** 4-(3-Hydroxy-phenyl)-2-thioxo-2,3,4,7-tetrahydro-1H-furo[3,4-d]pyrimidin-5-one

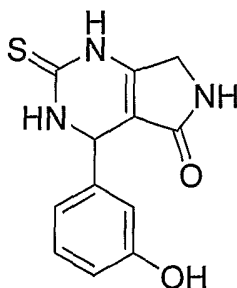


[0279] 5 mg of the deprotected alcohol and 10mg Dibutyltin oxide were dissolved in 2ml Methanol. The reaction mixture was heated for 15min at 160°C in a microwave reactor. The solvent was removed under reduced pressure and the crude product was purified by reversed phase HPLC (AtlantisAQ) to yield 3mg of the desired product as a white solid (71%).

[0280] ¹H-NMR (500 MHz, CD₃OD) 7.19 (t, 1H, J=7.9Hz); 6.82 (d, 1H, J=8.1Hz); 6.78 (t, 1H, J=2.0Hz); 6.74 (ddd, 1H, J=0.8Hz, J=2.4Hz, J=8.1Hz); 5.27 (s, 1H); 4.85 (m, 2H)

[0281] HRMS (M+H⁺, calc. 263.0490, found 263.0493)

[0282] **Example 17:** 4-(3-Hydroxy-phenyl)-2-thioxo-1,2,3,4,6,7-hexahydro-pyrrolo[3,4-d]pyrimidin-5-one

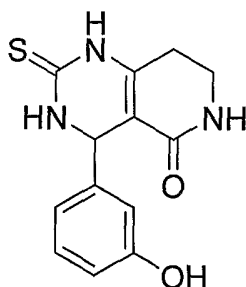


[0283] 12 mg of the deprotected amine were dissolved in 2ml Methanol. The reaction mixture was heated for 15min at 160°C in a microwave reactor. The solvent was removed under reduced pressure and the crude product was purified by reversed phase HPLC (AtlantisAQ) to yield 8mg of the desired product as a colorless oil (77%).

[0284] ¹H-NMR (500 MHz, CD₃OD); 7.16 (t, 1H, J=7.9Hz); 6.82 (d, 1H, J=7.1Hz); 6.78 (m, 1H); 6.71 (ddd, 1H, J=0.8Hz, J=2.4Hz, J=8.1Hz); 5.27 (s, 1H); 4.08 (d, 1H, J=19.1Hz); 4.02 (d, 1H, J=19.1Hz)

[0285] HRMS (M+H⁺, calc. 262.0650, found 262.0653)

[0286] **Example 18:** 4-(3-Hydroxy-phenyl)-2-thioxo-2,3,4,6,7,8-hexahydro-1H-pyrido[4,3-d]pyrimidin-5-one



[0287] 12 mg of the deprotected amine and 10ul Triethylamine were dissolved in 500ul Methanol. The reaction mixture was heated for 16h at 60°C. The solvent was removed under reduced pressure and the crude product was purified on silica (10-30% Methanol in Methylene Chloride) to yield 8mg of a white solid (80%).

[0288] ¹H-NMR (500 MHz, d₆-DMSO); 10.34 (s, 1H); 9.41 (s, 2H); 7.19 (s, 1H); 7.11 (t, 1H, J=7.7Hz); 6.68 (m, 2H); 6.63 (ddd, 1H, J=0.9Hz, J=2.4Hz, J=8.1Hz); 5.12 (d, 1H, J=3.1Hz); 3.18 (m, 2H); 2.51 (m, 1H); 2.42 (td, 1H, J=4.6Hz, J=17.2Hz)

[0289] HRMS (M+H⁺, calc. 276.0806, found 276.0808)

[0290] *1-b) PM3 calculations*

[0291] The PM3 calculations were performed with CAChe 6.1.1 (Fujitsu - <http://www.cachesoftware.com>) using default PM3 settings.

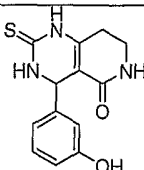
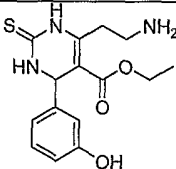
[0292] *1-c) Biological data*

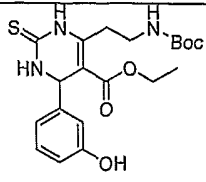
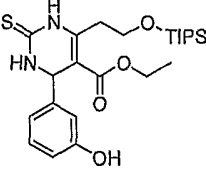
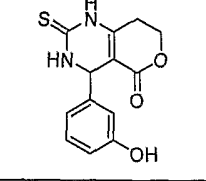
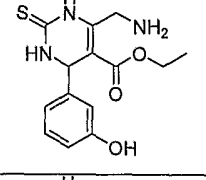
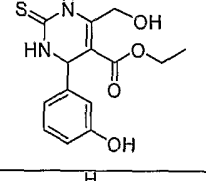
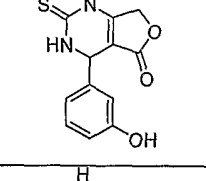
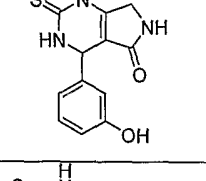
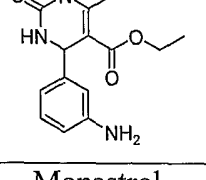
[0293] Example 19: Measuring activity of Eg5 inhibitors in pure protein assay:

[0294] We utilized a colorimetric phosphate detection assay (Funk, 2004) to measure microtubule-stimulated ATP hydrolysis by the Eg5 motor domain construct Eg5-367H (Maliga, 2002) as a function of drug concentration. Stocks solutions of each compound were prepared by serial dilution into DMSO and 0.1 microliters was added by pin transfer into KC25 buffer (20 mM PIPES-KOH, pH 6.9, 25 mM KCl, 2 mM MgCl₂) supplemented with 1 mM ATP-KOH, pH 6.9. KC25 supplemented with 10 micromolar taxol, 50 nanomolar Eg5-367H, and 1 micromolar taxol-polymerized microtubules was then added and the reaction incubated at 25 degrees for 2 hours. Malachite green assay solution (7 % (w/v) perchloric acid, .0075 % (w/v) malachite green oxalate, 0.2% (w/v) sodium molybdate dihydrate) was added to each reaction and the optical absorbance at 640 nm (640) was measured after a 30 minute incubation using a Wallac II automated plate reader. A₆₄₀ as a function of drug concentration (C) was fit to the equation $A_{640} = A_0 + B/(1 + C/IC_{50})$ using Kaleidegraph 3.0, A₀ is the basal A₆₄₀, B is the maximum increase in A₆₄₀, and IC₅₀ is the drug concentration that inhibits half the Eg5 activity. We divided the IC₅₀ of each drug by that of monastrol to obtain the relative potency.

[0295] Certain inventive compounds, and related acyclic intermediates, were tested. In general, compounds falling within the scope of the invention showed activity, while acyclic intermediates were inactive. Table 1 below summarizes assay results for certain compounds of the invention:

[0296] Table 1

Entry	Compound	IC ₅₀ (μM)
1		1.5
2		-

3		-
4		-
5		0.5
6		12
7		30
8		20
9		12
10		-
11	Monastrol	12

Legend: in Table I above, “-” means that the compound was inactive under the assay conditions used.

[0297] Example 20: NCI Screen

[0298] Compounds of the invention were screened against NCI’s 60 cancer cell line pannel. Experimental details may be found at

dtp.nci.nih.gov/branches/btb/ivclsp.html (See also Appendix B).

[0299] The two compounds tested against NCI's 60 cancer cell line pannel (MAZ1202 and MAZ1193) did not show very dominant selectivity for a specific cancer cell line. In general IC₅₀ values were in the order of 10 μ M.

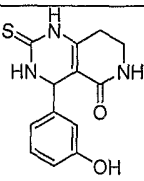
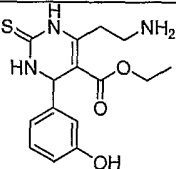
[0300] CNS cancer cell lines seem to be the most sensitive with IC₅₀ values in the range of 1-10 μ M whereas leukemia cell lines exhibited the lowest sensitivity. All cell lines but one (NCI-H226) responded to the treatment.

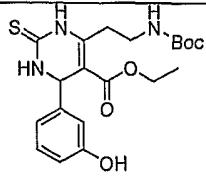
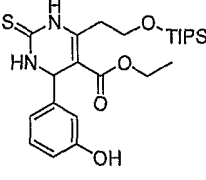
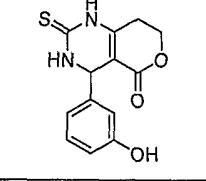
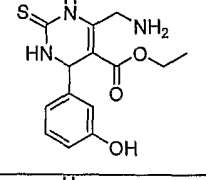
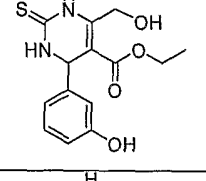
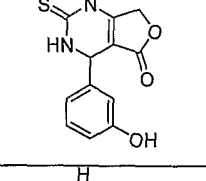
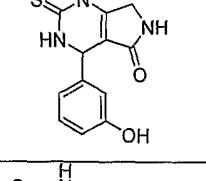
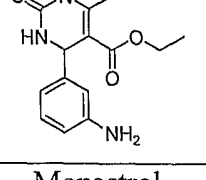
[0301] Example 21: Tissue culture cell assay

[0302] Hela cells were grown (Maliga, et. al. 2001) to 20 % confluence in 384-well, clear-bottomed, black-walled NUNC plates and serial dilutions of prospective Eg5 inhibitors were added by pin transfer, as above [0277], incubated at 37°C for 20 hours, fixed with TBS-0.1% Triton X100 supplemented with 4% formaldehyde, and stained stained for DNA, phosphorylated Ser10-Histone 3, and alpha-tubulin. Each drug concentration was inspected for the characteristic monoaster phenotype: condensed phospho-S10 positive chromosomes arranged in a rosette pattern around a circularly symmetric array of microtubules, and the absence of bi-polar mitotic spindles.

[0303] Certain inventive compounds, and related acyclic intermediates, were tested. In general, compounds falling within the scope of the invention showed activity, while acyclic intermediates were inactive. Table 2 below summarizes assay results for certain compounds of the invention:

[0304] Table 2

Entry	Compound	IC ₅₀ (μ M)
1		50
2		-

3		-
4		-
5		30
6		200
7		300
8		300
9		-
10		-
11	Monastrol	300

Legend: in Table 2 above, “-” means that the compound was inactive under the assay conditions used.

[0305] Example 22: Further biological characterization

[0306] Pharmacological properties of the Eg5 inhibitors of this invention may be evaluated in a number of pharmacological assays, such as those described below.

[0307] *Cell Culture*

[0308] Cell lines are maintained in RPMI-1640 plus 10% fetal bovine serum. Human cell lines used in one or more of the following assays described below include but are not limited to A2780 ovarian carcinoma, HCT1 16, colorectal carcinoma; HT-29, colorectal adenocarcinoma; SK-BR-3, mammary adenocarcinoma; Saos-2, osteosarcoma; PC-3, prostate adenocarcinoma; and LX-1, lung carcinoma. The kangaroo rat kidney epithelial cell line, PTK2, may also be used.

[0309] *72-Hour Proliferation Assay*

[0310] Cells are plated at a density of about 3,000-6,000 cells/well, depending upon the cell line used, in a 96-well plate. The cultures are grown overnight. Cells are then treated in triplicate with a seven concentration dose-response curve. The maximum concentration of DMSO may not exceed 0.5%. Cells are exposed to compound for about 72 hours. Proliferation is measured using XTT or MTS from Promega.

[0311] *Clonogenic Growth Assay*

[0312] Colony growth inhibition is measured using a standard clonogenic assay. Briefly, about 200 cells/well are seeded into 6-well tissue culture plates (Falcon, Franklin Lakes, N.J.) and allowed to attach for 18 hours. Assay medium consists of RPMI-1640 plus 10% fetal bovine serum. Cells are then treated in duplicate with a six concentration dose-response curve. The maximum concentration of DMSO may not exceed 0.25%. Cells are exposed to compound for about 4 to 24 hours. Compound is then removed and the cells are washed with 2 volumes of PBS. The normal growth medium is then replaced. Colonies are fed with fresh media every third day. Colony number is scored on day 10-14 using a Optimax imaging station. The compound concentration required to inhibit 50% or 90% of colony formation (IC₅₀ or IC₉₀, respectively) is determined by non-linear regression analysis.

[0313] *Combination Studies--Clonogenic Growth Assays*

[0314] Combination studies to examine the use of the Eg5 inhibitors of the present invention in combination with other antineoplastic agents may be conducted essentially in a similar fashion as standard colony growth assay with the exception of compound treatment. In the combination studies, the cells are treated with both a compound of formula I and another antineoplastic agent. The compounds are administered simultaneously or sequentially; both the order of sequence and length of treatment (about 1 to 24 hours) are varied. Data evaluation is based upon the

isobologram analysis and the envelope of additivity, using the line of multiplicity which compares the survival fractions of combination treatments with those of single drug treatments.

[0315] *Cell Cycle Analysis*

[0316] The cell cycle profile of cells treated with compounds of the present invention may be monitored by flow cytometry. Briefly, cells are seeded at a density of about 2×10^5 per well in standard 6 well culture plates and permitted to grow for about 17 hours. Cells are then exposed to compounds of the present invention at varying concentrations for about 2 to 24 hours. Following exposure, cell populations are harvested, stained with propidium iodide to determine DNA content and also stained with the appropriate immunological reagent for protein biomarkers of mitosis and apoptosis, including, but not limited to, for example, anti-phospho-ThreonineProline, anti-M Phase Phosphoprotein 2 (MMP2), and anti-p85 PARP.

[0317] *Immunocytochemistry Assays*

[0318] Cells are plated at a density of 200 to 2000 cells per well in 4 chamber glass slides and allowed to attach overnight. Cells are then treated with compounds of the present invention at concentrations of 100 nM to 50 μ M for about 4 to 30 hours, fixed and permeabilized for subsequent staining. Stain reagents included, for example, propidium iodide, DAPI, rhodamine phalloidin, anti- α tubulin, anti- β tubulin, anti- γ tubulin, and the appropriate fluorescent-tagged secondary antibodies. Cells are imaged by fluorescent and confocal fluorescent microscopy.

[0319] *Preparation of Recombinant human Eg5 kinesin (Eg5-405)*

[0320] DNA encoding full length human Eg5 kinesin is amplified by the polymerase chain reaction (PCR) using Vent DNA polymerase (NE Biolabs, Beverly, MA) and subcloned into an expression plasmid (pRSETa). For the PCR reaction, the template used is a pBluescript vector containing the full length coding sequence for human Eg5 (a gift from Anne Blangy). The 5' primer (5'-GCA ACG ATT AAT ATG GCG TCG CAG CCA AAT TCG TCT GCG AAG) contains an *Ase* I cleavage site upstream of the Eg5 start codon. The 3' primer (5'-GCA ACG CTC GAG TCA GTG ATG ATG GTG GTG ATG CAT GAC TCT AAA ATT TTC TTC AGA AAT) is complimentary to amino acid 405 and adds a downstream six histidine tag (6-HIS) followed by a UGA stop codon, and *Xho* I cleavage site.

[0321] The resulting PCR DNA amplification product and also the target plasmid to be used as the expression plasmid (pRSETa) are double digested with *Ase* I/*Xho* I and *Nde* I/*Xho* I respectively (New England Biolabs). Both products of the two restriction enzyme double digests are resolved and purified by agarose gel electrophoresis. The bands on the agarose gel corresponding to the desired DNA fragments, more than 2kb for pRSETa and 1.2kb for Eg5-405 are excised and purified (Qiagen Gel Purification Kit). The cleaved and purified DNA fragments are ligated together using T4 DNA ligase (New England Biolabs). The ligation products are transformed into *E. coli* DH5 α chemically competent cells (Life Technologies), and selected by overnight growth on LB ampicillin plates. Transformants are amplified by growth of *E. coli* in LB ampicillin. Plasmids are purified (Qiagen Midiprep), and sequenced (Harvard Medical School Biopolymer Facilities).

[0322] *Purification of Eg5-405 and K560 (560 amino acid kinesin construct):*

[0323] BL21 pLysS (DE3) bacteria are transfected with the expression plasmid described in the preceding section and grown overnight at 37° C on LB plates containing 100ug/ml ampicillin (LB-amp). Several colonies are picked and grown at 37° C in 1 ml LB-amp, pooled and used to inoculate each of six 1.5 L of LB-amp. These 1 L cultures are incubated at 37° C on a shaker (200 RPM) until the optical density (O.D.) of the culture reached an absorbance of approximately $A_{600\text{ nm}}=0.5$ O.D. The cultures are cooled to 20° C, induced with 24 mg/ml of isopropyl beta-D-thiogalactopyranoside (IPTG; Boehringer Mannheim) and incubated at room temperature for approximately 3 hours. Cells are pelleted by centrifugation (4000x g), rinsed in phosphate buffered saline (PBS) and repelleted at 10,000 x g). The bacterial pellets are flash frozen in liquid nitrogen and stored at -80° C.

[0324] The bacterial pellets are thawed on ice and resuspended in a solution containing 50 mM potassium phosphate (pH 8.0), 250 mM KCl, 0.1% Tween-20, 10 mM imidazole, 0.5 mM magnesium adenosine triphosphate (Mg-ATP), 1 mM phenylmethanesulfonyl fluoride (PMSF), and 2 mM benzimidazole-HCl. To lyse the bacteria, lysozyme (1 mg/ml) and 2-mercaptoethanol (5 mM) are added to the solution to result in the indicated final concentration, incubated and sonicated (3 times 20 seconds, repeated 3 times incubating for 1 minute on ice between each triple sonication) to break up the DNA and guarantee bacterial lysis.

[0325] The lysate is spun at 40,000 x g for approximately 35 minutes at 4° C with the resulting supernatant separated from the pellet by decanting and then incubated with a nickel-nitrilotriacetic acid resin (Ni-NTA; QIAGEN). The remaining pellet is washed three times with a wash buffer (lysis buffer supplemented with 10 mM 2-mercaptoethanol, no PMSF, and 0.1 mM Mg-ATP) to extract any remaining protein. These washes are then followed by a final wash using a low pH buffer (pH 6.0). The wash solutions are then also added to the Ni-NTA resin. The resin containing the desired tagged protein is poured into a column (Biorad, 0.8 x 4 cm PolyPrep Chromatography Column) and allowed to settle. The HIS-tagged proteins are eluted with a solution containing 250 mM imidazole and 150 mM KCl (pH 7.0). Protein-containing fractions of the eluate are loaded onto a Superose 6 size-exclusion column (Pharmacia) and equilibrated with a solution containing 80 mM potassium HEPES (pH 6.8), 200 mM KCl, 10 uM Mg-ATP, 1 mM dithiothreitol (DTT). Fractions containing homogeneous proteins as determined by molecular weight and mobility on SDS-PAGE are used for further enzymology experiments.

[0326] *Polymerization of Microtubules:*

[0327] A solution containing 1 mg/ml tubulin, 1 mM DTT, 1 mM guanosine triphosphate (GTP), 1 mM MgCl₂, 80 mM potassium HEPES (pH 6.8), and 1 mM ethylene glycol-bis(beta-aminoethyl ether)-N,N,N',N'-tetraacetic acid (EGTA) is spun at 90,000 x g for 5 minutes. The solution is then warmed to 37° C for 2 minutes. Taxol is added in stepwise as 0.01, 0.1, and 1 equivalents. The polymerization solution is placed onto a solution containing 40% glycerol, 80 mM potassium HEPES (pH 6.8), 1 mM MgCl₂, and 1 mM EGTA, and centrifuged at 90,000 x g for approximately 50 minutes. The resulting microtubule pellet is washed extensively with and resuspended in resuspension buffer containing 80 mM potassium HEPES (pH 6.8), 1 mM MgCl₂, and 1 mM EGTA.

[0328] *In vitro NADH Enzyme Coupled ATPase:* (variation on methods described in Crevel, Lockhart, and Cross. *J. Mol. Biol.* (1997) **273**, 160-170.)

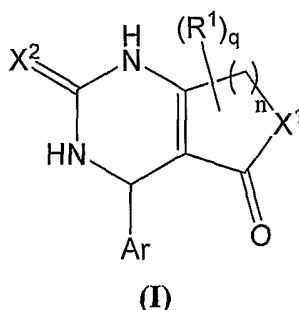
[0329] A solution containing the microtubule resuspension buffer is supplemented with 1 mM Mg-ATP, 100 uM nicotinamide adenine dinucleotide (NADH), 1 mM phosphoenol pyruvate, 5 µg/ml pyruvate kinase, 7.5 µg/ml lactate dehydrogenase, 0.7 µM resuspended microtubules, and 0.5% dimethylsulfoxide (DMSO).

[0330] Next, serial dilutions of the test compound are prepared in the supplemented microtubule resuspension buffer. Purified recombinant human Eg5 protein is added resulting in a final concentration of 50 μ M. The subsequent fluorescent reaction is measured in NUNC black walled 384 well plates at 340nm using a Wallac plate reader.

CLAIMS

We claim:

1. An isolated compound having the structure:



or pharmaceutically acceptable derivative thereof;

wherein **Ar** is an aromatic or heteroaromatic moiety;

X¹ is O or NR^{X1}, wherein R^{X1} is hydrogen or an aliphatic, heteroaliphatic, aromatic or heteroaromatic moiety;

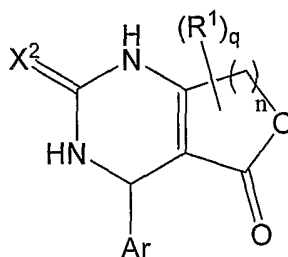
X² is O or S;

n is 1 or 2;

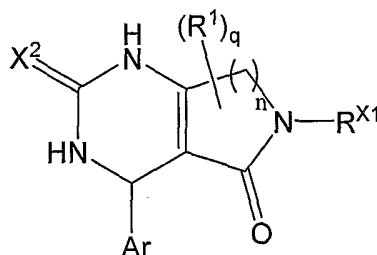
q is an integer from 0-4; and

each occurrence of **R₁** is independently hydrogen, halogen, hydroxyl, or an aliphatic, heteroaliphatic, aromatic or heteroaromatic moiety.

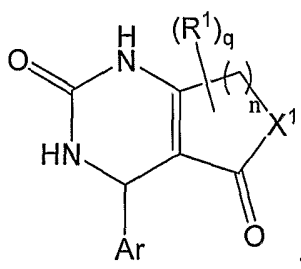
2. The compound of claim 1 having the structure:



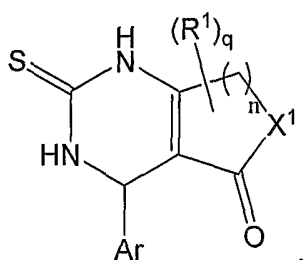
3. The compound of claim 1 having the structure:



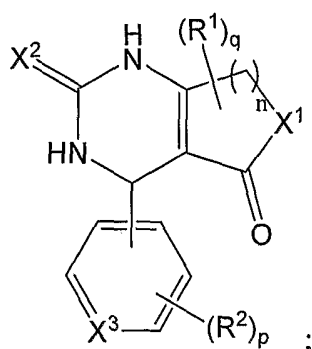
4. The compound of claim 1 having the structure:



5. The compound of claim 1 having the structure:

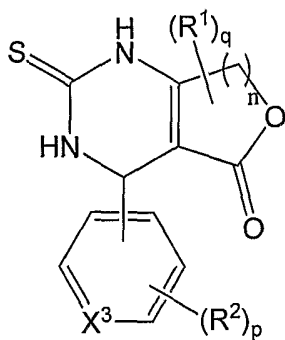


6. The compound of claim 1 having the structure:



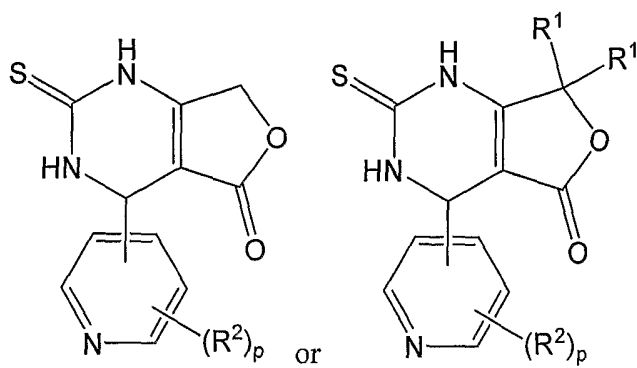
wherein X^3 is N or CR^2 ; p is 0-5; and each occurrence of R^2 is independently hydrogen, halogen, CN, NO_2 , alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, heterocycle, aryl, heteroaryl, -(alkyl)cycloalkyl, -(alkyl)heterocycle, -(heteroalkyl)cycloalkyl, -(heteroalkyl)heterocycle, -(alkyl)aryl, -(heteroalkyl)aryl, -(alkyl)heteroaryl, -(heteroalkyl)heteroaryl, $-OR^{2A}$, $-S(=O)_xR^{2A}$, $-N(R^{2A})_2$, $-SO_2N(R^{2A})_2$, $-C(=O)R^{2A}$, $-C(=O)N(R^{2A})_2$, $-C(=O)OR^{2A}$, $-N(R^{2A})C(=O)R^{2B}$ or $-N(R^{2A})SO_2R^{2B}$, wherein x is 0, 1 or 2; and each occurrence of R^{2A} and R^{2B} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl or -(alkyl)heteroaryl; or R^{2A} and R^{2B} , taken together with the atoms to which they are attached, form a substituted or unsubstituted 5-8 membered heterocyclic moiety.

7. The compound of claim 1 having the structure:



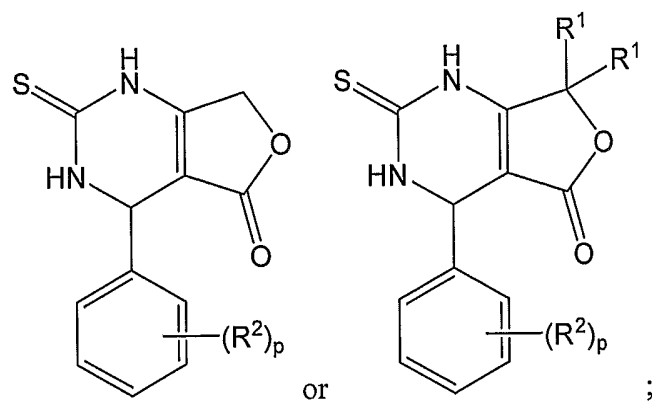
wherein p is 0-5; and each occurrence of R^2 is independently hydrogen, halogen, CN, NO₂, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, heterocycle, aryl, heteroaryl, -(alkyl)cycloalkyl, -(alkyl)heterocycle, -(heteroalkyl)cycloalkyl, -(heteroalkyl)heterocycle, -(alkyl)aryl, -(heteroalkyl)aryl, -(alkyl)heteroaryl, -(heteroalkyl)heteroaryl, -OR^{2A}, -S(=O)_xR^{2A}, -N(R^{2A})₂, -SO₂N(R^{2A})₂, -C(=O)R^{2A}, -C(=O)N(R^{2A})₂, -C(=O)OR^{2A}, -N(R^{2A})C(=O)R^{2B} or -N(R^{2A})SO₂R^{2B}, wherein x is 0, 1 or 2; and each occurrence of R^{2A} and R^{2B} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl or -(alkyl)heteroaryl; or R^{2A} and R^{2B}, taken together with the atoms to which they are attached, form a substituted or unsubstituted 5-8 membered heterocyclic moiety.

8. The compound of claim 7 having the structure:



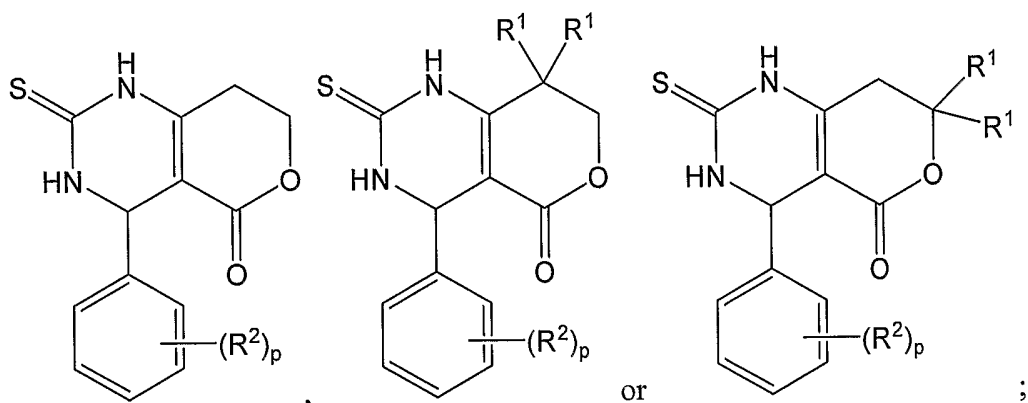
wherein each occurrence of R¹ is independently halogen or lower alkyl.

9. The compound of claim 7 having the structure:



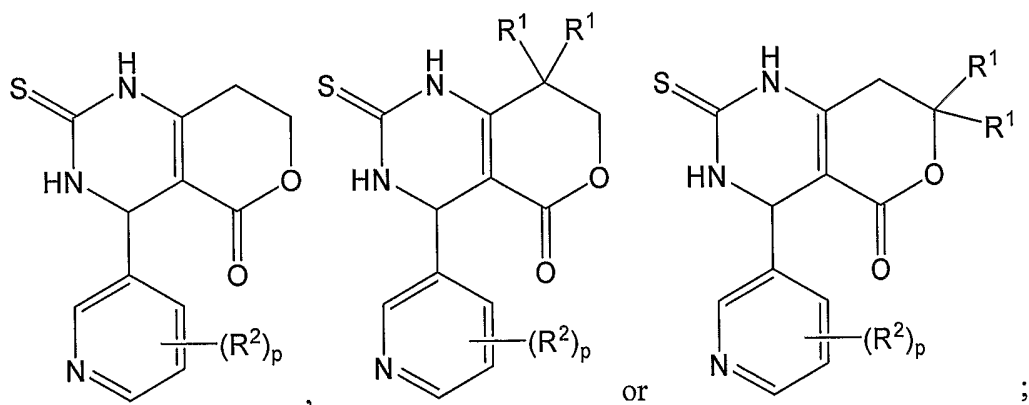
wherein each occurrence of R^1 is independently halogen or lower alkyl.

10. The compound of claim 7 having the structure:



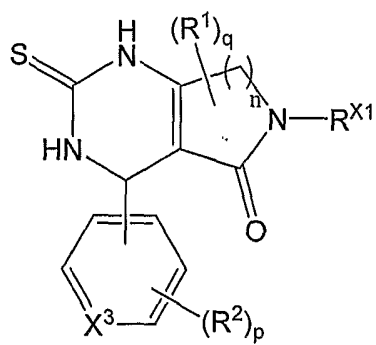
wherein each occurrence of R^1 is independently halogen or lower alkyl.

11. The compound of claim 7 having the structure:



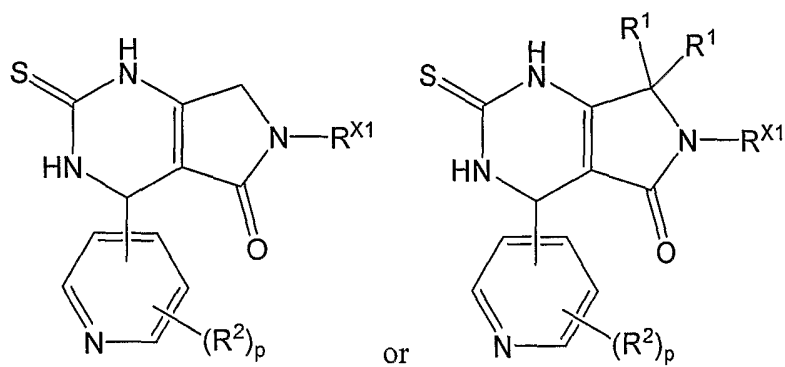
wherein each occurrence of R^1 is independently halogen or lower alkyl.

12. The compound of claim 1 having the structure:



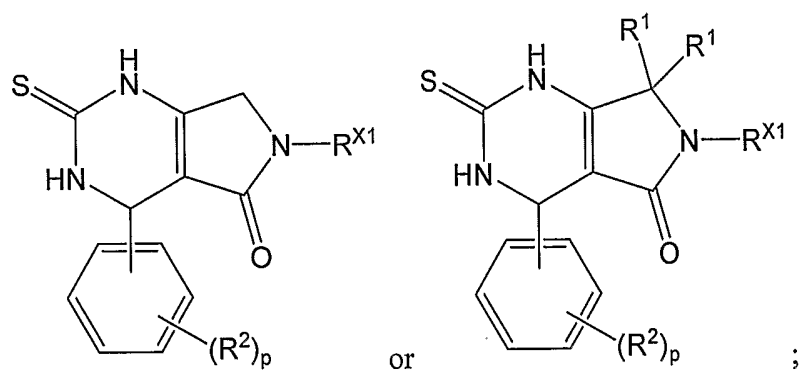
wherein R^{X1} is hydrogen, lower alkyl, acyl or a nitrogen protecting group; p is 0-5; and each occurrence of R^2 is independently hydrogen, halogen, CN, NO_2 , alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, heterocycle, aryl, heteroaryl, -(alkyl)cycloalkyl, -(alkyl)heterocycle, -(heteroalkyl)cycloalkyl, -(heteroalkyl)heterocycle, -(alkyl)aryl, -(heteroalkyl)aryl, -(alkyl)heteroaryl, -(heteroalkyl)heteroaryl, $-OR^{2A}$, $-S(=O)_xR^{2A}$, $-N(R^{2A})_2$, $-SO_2N(R^{2A})_2$, $-C(=O)R^{2A}$, $-C(=O)N(R^{2A})_2$, $-C(=O)OR^{2A}$, $-N(R^{2A})C(=O)R^{2B}$ or $-N(R^{2A})SO_2R^{2B}$, wherein x is 0, 1 or 2; and each occurrence of R^{2A} and R^{2B} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl or -(alkyl)heteroaryl; or R^{2A} and R^{2B} , taken together with the atoms to which they are attached, form a substituted or unsubstituted 5-8 membered heterocyclic moiety.

13. The compound of claim 12 having the structure:



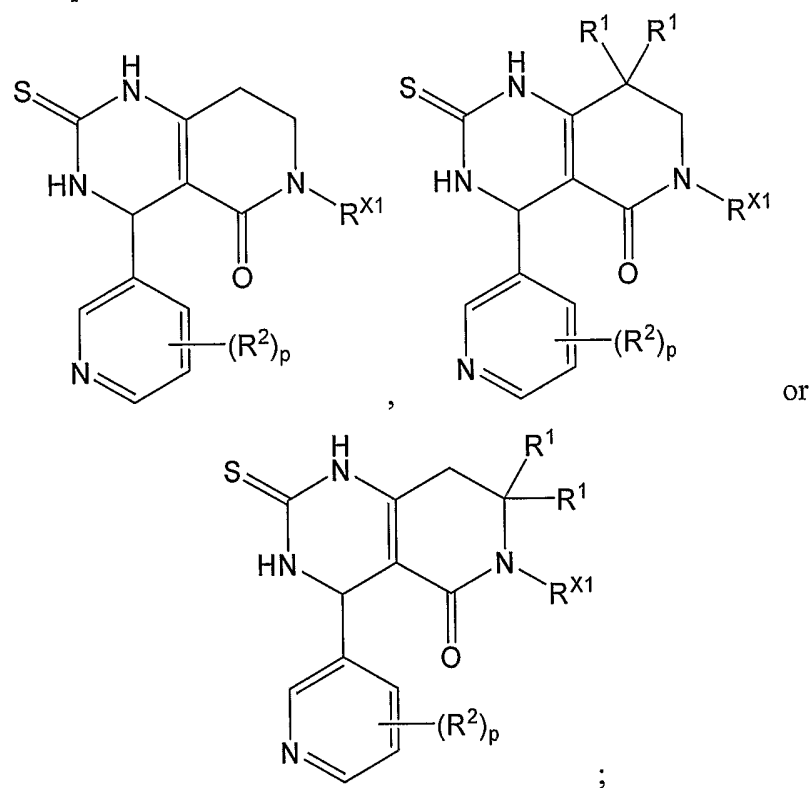
wherein each occurrence of R^1 is independently halogen or lower alkyl.

14. The compound of claim 12 having the structure:



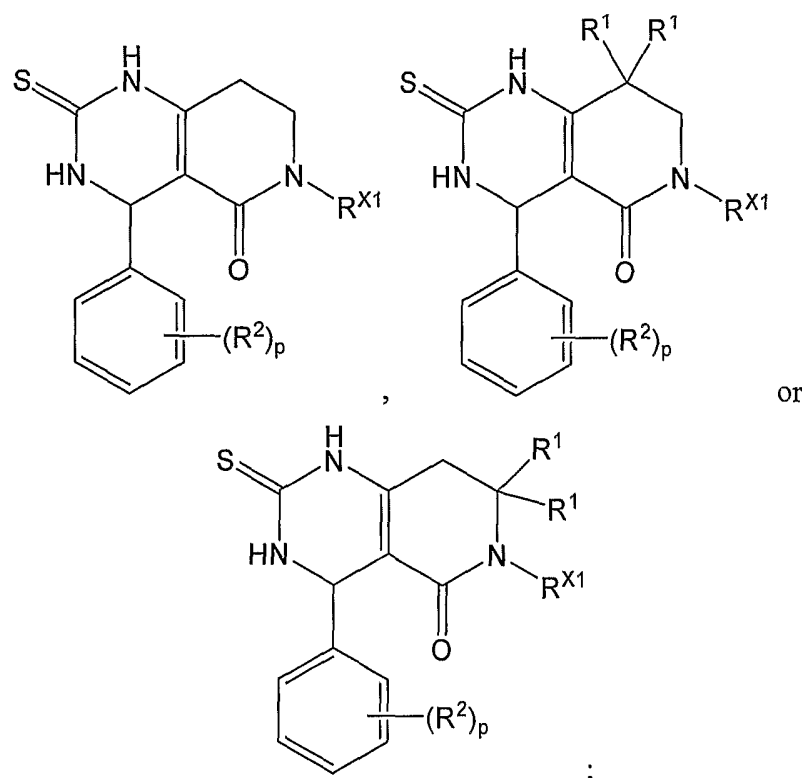
wherein each occurrence of R^1 is independently halogen or lower alkyl.

15. The compound of claim 12 having the structure:



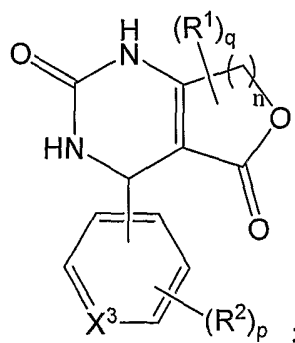
wherein each occurrence of R^1 is independently halogen or lower alkyl.

16. The compound of claim 12 having the structure:



wherein each occurrence of R^1 is independently halogen or lower alkyl.

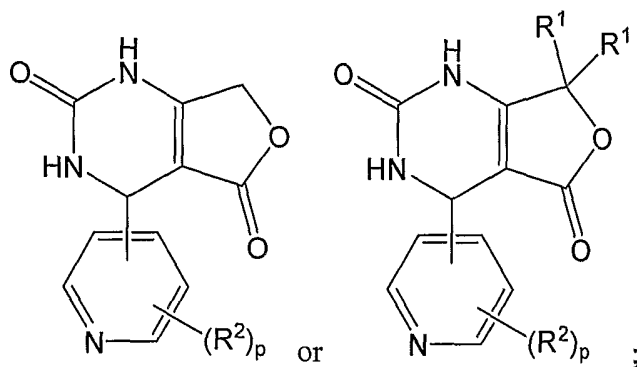
17. The compound of claim 1 having the structure:



wherein p is 0-5; and each occurrence of R^2 is independently hydrogen, halogen, CN, NO₂, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, heterocycle, aryl, heteroaryl, -(alkyl)cycloalkyl, -(alkyl)heterocycle, -(heteroalkyl)cycloalkyl, -(heteroalkyl)heterocycle, -(alkyl)aryl, -(heteroalkyl)aryl, -(alkyl)heteroaryl, -(heteroalkyl)heteroaryl, -OR^{2A}, -S(=O)_xR^{2A}, -N(R^{2A})₂, -SO₂N(R^{2A})₂, -C(=O)R^{2A}, -C(=O)N(R^{2A})₂, -C(=O)OR^{2A}, -N(R^{2A})C(=O)R^{2B} or -N(R^{2A})SO₂R^{2B}, wherein x is 0, 1 or 2; and each occurrence of R^{2A} and R^{2B} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl

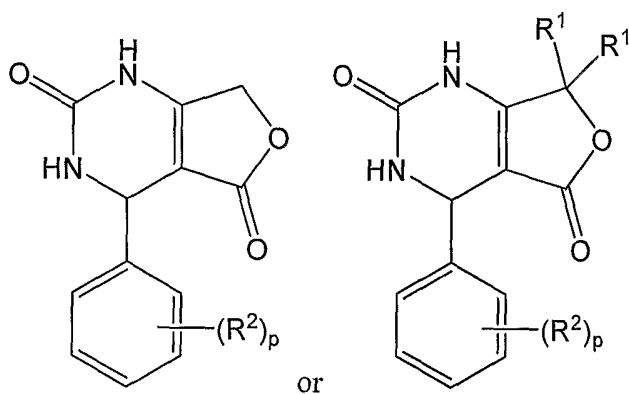
or -(alkyl)heteroaryl; or R^{2A} and R^{2B} , taken together with the atoms to which they are attached, form a substituted or unsubstituted 5-8 membered heterocyclic moiety.

18. The compound of claim 17 having the structure:



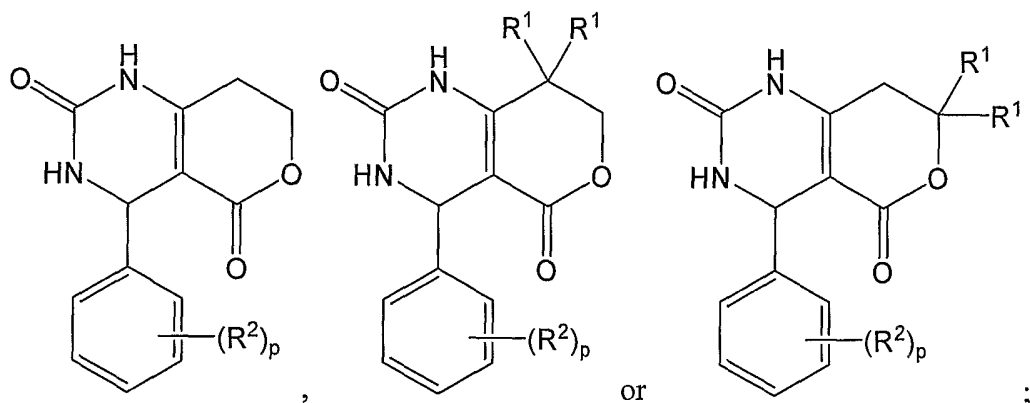
wherein each occurrence of R^1 is independently halogen or lower alkyl.

19. The compound of claim 17 having the structure:



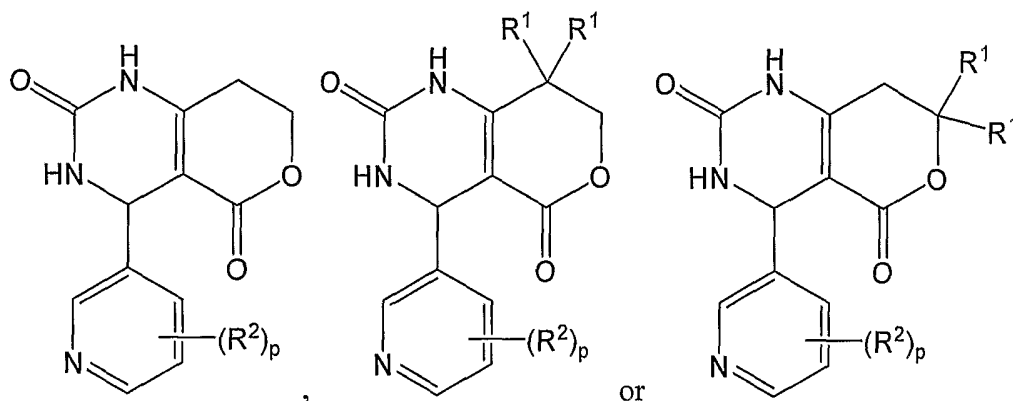
wherein each occurrence of R^1 is independently halogen or lower alkyl.

20. The compound of claim 17 having the structure:



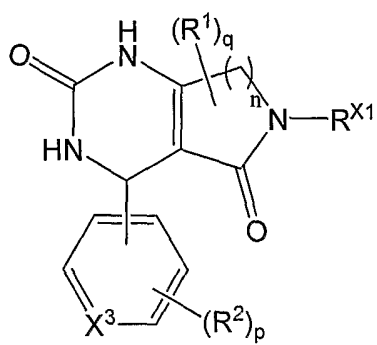
wherein each occurrence of R^1 is independently halogen or lower alkyl.

21. The compound of claim 17 having the structure:



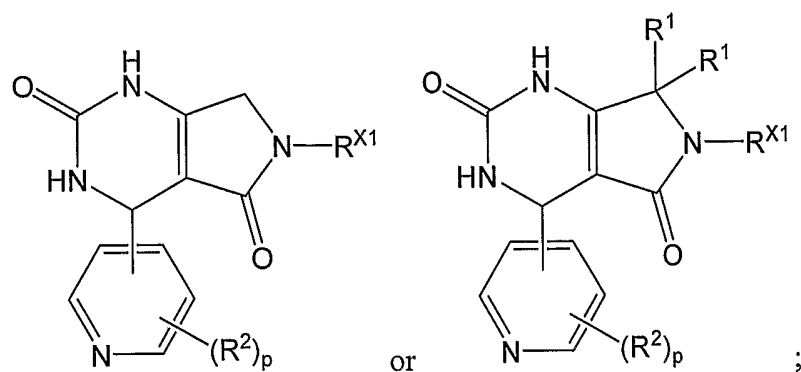
wherein each occurrence of R^1 is independently halogen or lower alkyl.

22. The compound of claim 1 having the structure:



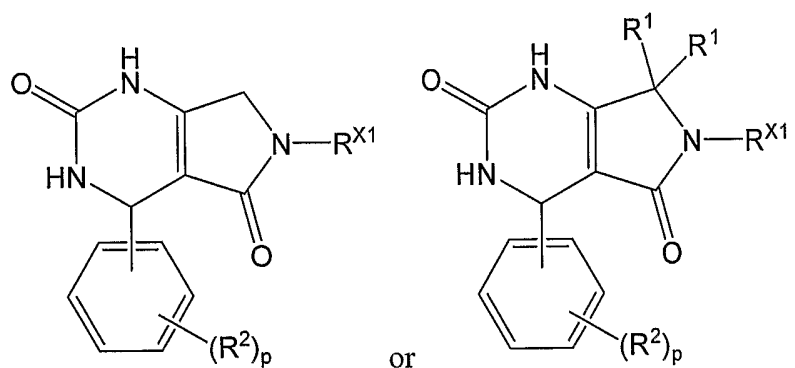
wherein R^{X1} is hydrogen, lower alkyl, acyl or a nitrogen protecting group; p is 0-5; and each occurrence of R^2 is independently hydrogen, halogen, CN, NO_2 , alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, heterocycle, aryl, heteroaryl, -(alkyl)cycloalkyl, -(alkyl)heterocycle, -(heteroalkyl)cycloalkyl, -(heteroalkyl)heterocycle, -(alkyl)aryl, -(heteroalkyl)aryl, -(alkyl)heteroaryl, -(heteroalkyl)heteroaryl, $-OR^{2A}$, $-S(=O)_xR^{2A}$, $-N(R^{2A})_2$, $-SO_2N(R^{2A})_2$, $-C(=O)R^{2A}$, $-C(=O)N(R^{2A})_2$, $-C(=O)OR^{2A}$, $-N(R^{2A})C(=O)R^{2B}$ or $-N(R^{2A})SO_2R^{2B}$, wherein x is 0, 1 or 2; and each occurrence of R^{2A} and R^{2B} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl or -(alkyl)heteroaryl; or R^{2A} and R^{2B} , taken together with the atoms to which they are attached, form a substituted or unsubstituted 5-8 membered heterocyclic moiety.

23. The compound of claim 22 having the structure:



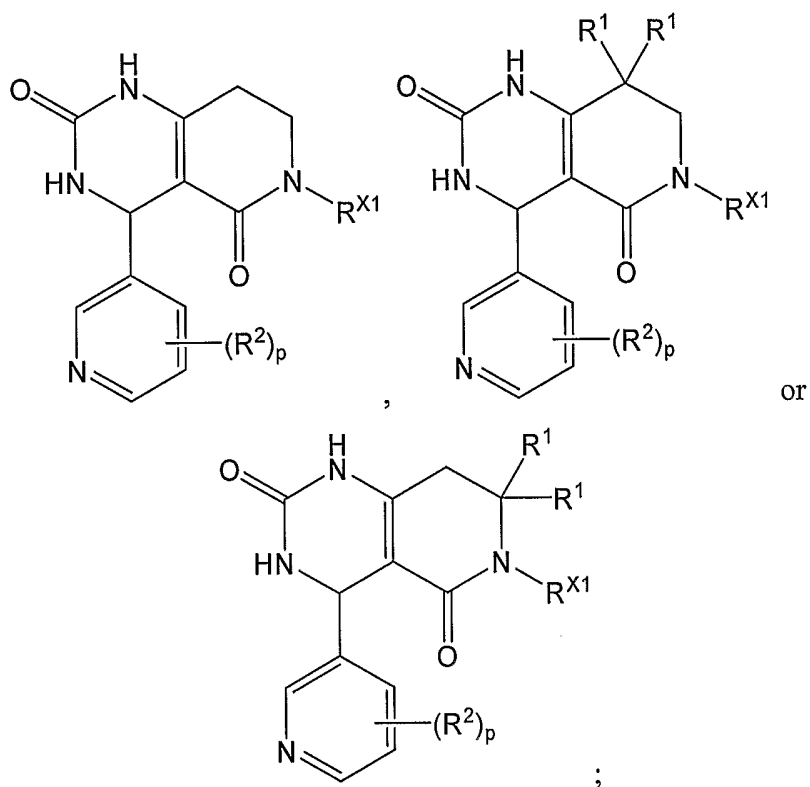
wherein each occurrence of R^1 is independently halogen or lower alkyl.

24. The compound of claim 22 having the structure:



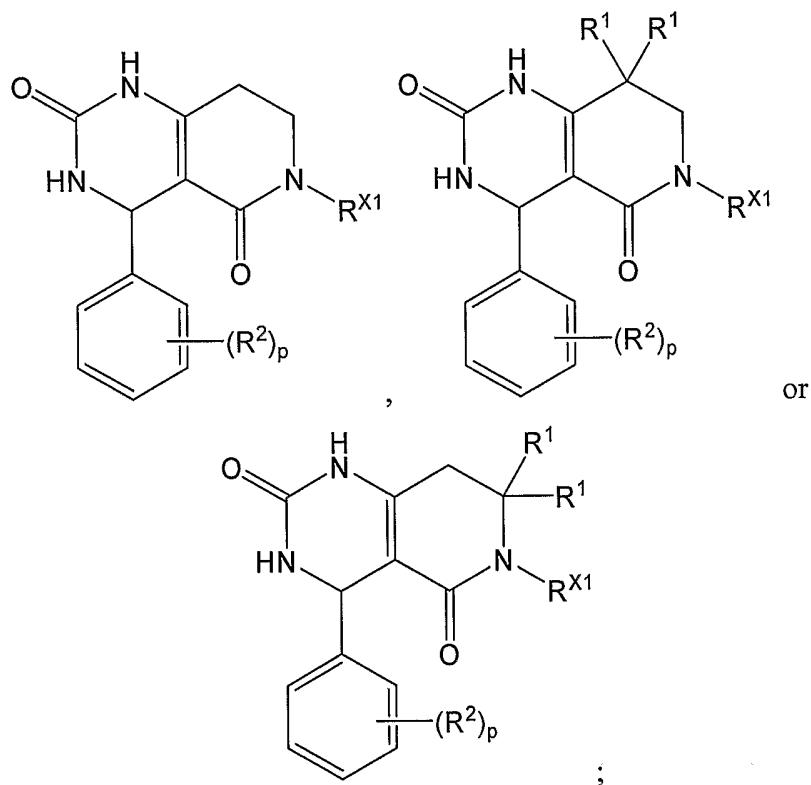
wherein each occurrence of R^1 is independently halogen or lower alkyl.

25. The compound of claim 22 having the structure:



wherein each occurrence of R^1 is independently halogen or lower alkyl.

26. The compound of claim 22 having the structure:



wherein each occurrence of R^1 is independently halogen or lower alkyl.

27. The compound of claim 1, 4, 5 or 6 wherein X^1 is O.
28. The compound of claim 1, 4, 5 or 6 wherein X^1 is NR^{X1} , wherein R^{X1} is hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, heterocycle, acyl, aryl, heteroaryl, -(alkyl)cycloalkyl, -(alkyl)heterocycle, -(heteroalkyl)cycloalkyl, -(heteroalkyl)heterocycle, -(alkyl)aryl, -(heteroalkyl)aryl, -(alkyl)heteroaryl or -(heteroalkyl)heteroaryl.
29. The compound of claim 1, 4, 5 or 6 wherein X^1 is NR^{X1} , wherein R^{X1} is hydrogen, lower alkyl, lower heteroalkyl, cycloalkyl, heterocycle, lower acyl, aryl, heteroaryl, -(alkyl)cycloalkyl, -(alkyl)heterocycle, -(alkyl)aryl, -(heteroalkyl)aryl or -(alkyl)heteroaryl.
30. The compound of claim 1, 4, 5 or 6 wherein X^1 is NR^{X1} , wherein R^{X1} is hydrogen, lower alkyl, lower acyl, aryl or heteroaryl.
31. The compound of claim 1, 4, 5 or 6 wherein X^1 is NR^{X1} , wherein R^{X1} is hydrogen, lower alkyl or lower acyl.
32. The compound of claim 1, 2, 3 or 6 wherein X^2 is O.
33. The compound of claim 1, 2, 3 or 6 wherein X^2 is S.
34. The compound of any one of claims 1-7, 12, 17 and 22 wherein n is 1.
35. The compound of any one of claims 1-7, 12, 17 and 22 wherein n is 2.
36. The compound of any one of claims 6-26 wherein p is 1.
37. The compound of any one of claims 1-7, 12, 17 and 22 wherein q is 0.
38. The compound of any one of claims 1-7, 12, 17 and 22 wherein q is 1.

39. The compound of any one of claims 1-7, 12, 17 and 22 wherein n is 1 and q is 0.

40. The compound of any one of claims 1-7, 12, 17 and 22 wherein n is 2 and q is 0.

41. The compound of any one of claims 1-7, 12, 17 and 22 wherein each occurrence of R^1 is independently hydrogen, halogen, hydroxy, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, heterocycle, aryl, heteroaryl, -(alkyl)cycloalkyl, -(alkyl)heterocycle, -(heteroalkyl)cycloalkyl, -(heteroalkyl)heterocycle, -(alkyl)aryl, -(heteroalkyl)aryl, -(alkyl)heteroaryl, -(heteroalkyl)heteroaryl, $-OR^{1A}$, $-SR^{1A}$, $-N(R^{1A})_2$, $-SO_2N(R^{1A})_2$, $-C(=O)N(R^{1A})_2$, halogen, $-CN$, $-NO_2$, $-C(=O)R^{1A}$, $-C(=O)OR^{1A}$, $-N(R^{1A})C(=O)R^{1B}$ or $-N(R^{1A})SO_2R^{1B}$, wherein each occurrence of R^{1A} and R^{1B} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl or -(alkyl)heteroaryl; or R^{1A} and R^{1B} , taken together with the atoms to which they are attached, form a substituted or unsubstituted 5-8 membered heterocyclic moiety.

42. The compound of any one of claims 1-7, 12, 17 and 22 wherein each occurrence of R^1 is independently hydrogen, halogen, hydroxy, lower alkyl, lower heteroalkyl, 3-6 membered cycloalkyl, 3-6 membered heterocycle, aryl, heteroaryl, -(lower alkyl)cycloalkyl, -(lower alkyl)heterocycle, -(lower alkyl)aryl or -(lower alkyl)heteroaryl.

43. The compound of any one of claims 1-7, 12, 17 and 22 wherein R^1 , for each occurrence, is hydrogen.

44. The compound of any one of claims 6-26 wherein each occurrence of R^2 is independently hydrogen, halogen, CN, NO_2 , alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, heterocycle, aryl, heteroaryl, -(alkyl)cycloalkyl, -(alkyl)heterocycle, -(heteroalkyl)cycloalkyl, -(heteroalkyl)heterocycle, -(alkyl)aryl, -(heteroalkyl)aryl, -(alkyl)heteroaryl, -(heteroalkyl)heteroaryl, $-OR^{2A}$, $-SR^{2A}$, $-N(R^{2A})_2$, $-SO_2N(R^{2A})_2$, $-C(=O)N(R^{2A})_2$, halogen, $-CN$, $-NO_2$, $-C(=O)R^{2A}$, $-C(=O)OR^{2A}$, $-N(R^{2A})C(=O)R^{2B}$ or $-N(R^{2A})SO_2R^{2B}$, wherein each occurrence of R^{2A} and R^{2B} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl or -(alkyl)heteroaryl; or R^{2A} and R^{2B} , taken together with the atoms to which they are attached, form a substituted or unsubstituted 5-8 membered heterocyclic moiety.

(heteroalkyl)heteroaryl, $-OR^{2A}$, $-S(=O)_xR^{2A}$, $-N(R^{2A})_2$, $-SO_2N(R^{2A})_2$, $-C(=O)R^{2A}$, $-C(=O)N(R^{2A})_2$, $-C(=O)OR^{2A}$, $-N(R^{2A})C(=O)R^{2B}$ or $-N(R^{2A})SO_2R^{2B}$, wherein x is 0, 1 or 2; and each occurrence of R^{2A} and R^{2B} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, $-(alkyl)aryl$ or $-(alkyl)heteroaryl$; or R^{2A} and R^{2B} , taken together with the atoms to which they are attached, form a substituted or unsubstituted 5-8 membered heterocyclic moiety.

45. The compound of any one of claims 6-26 wherein each occurrence of R^2 is independently hydrogen, halogen, CN, NO_2 , lower alkyl, lower heteroalkyl, 3-6 membered cycloalkyl, 3-8 membered heterocycle, aryl, heteroaryl, $-(lower\ alkyl)cycloalkyl$, $-(lower\ alkyl)heterocycle$, $-(lower\ heteroalkyl)cycloalkyl$, $-(lower\ heteroalkyl)heterocycle$, $-(lower\ alkyl)aryl$, $-(lower\ heteroalkyl)aryl$, $-(lower\ alkyl)heteroaryl$, $-(lower\ heteroalkyl)heteroaryl$, $-OR^{2A}$, $-SR^{2A}$, $-N(R^{2A})_2$, $-C(=O)R^{2A}$, $-C(=O)N(R^{2A})_2$, $-C(=O)OR^{2A}$, $-N(R^{2A})C(=O)R^{2B}$ or $-N(R^{2A})SO_2R^{2B}$, wherein each occurrence of R^{2A} and R^{2B} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, $-(lower\ alkyl)aryl$ or $-(lower\ alkyl)heteroaryl$; or R^{2A} and R^{2B} , taken together with the atoms to which they are attached, form a substituted or unsubstituted 5-8 membered heterocyclic moiety.

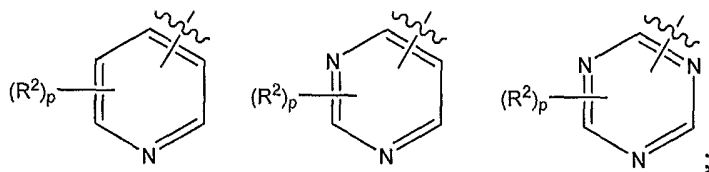
46. The compound of any one of claims 6-26 wherein each occurrence of R^2 is independently hydrogen, halogen, lower alkyl, lower heteroalkyl, $-OR^{2A}$, $-SR^{2A}$, $-N(R^{2A})_2$, $-C(=O)R^{2A}$, $-C(=O)N(R^{2A})_2$, $-C(=O)OR^{2A}$, $-N(R^{2A})C(=O)R^{2B}$ or $-N(R^{2A})SO_2R^{2B}$, wherein each occurrence of R^{2A} and R^{2B} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, $-(lower\ alkyl)aryl$ or $-(lower\ alkyl)heteroaryl$; or R^{2A} and R^{2B} , taken together with the atoms to which they are attached, form a substituted or unsubstituted 5-8 membered heterocyclic moiety.

47. The compound of any one of claims 6-26 wherein each occurrence of R^2 is independently hydrogen, halogen, lower alkyl or $-OR^{2A}$; wherein R^{2A} is hydrogen, lower alkyl, aryl, heteroaryl, $-(lower\ alkyl)aryl$ or $-(lower\ alkyl)heteroaryl$.

48. The compound of any one of claims 6-26 wherein each occurrence of R^2 is independently hydrogen, halogen, lower alkyl or $-OR^{2A}$; wherein R^{2A} is hydrogen, or lower alkyl.

49. The compound of any one of claims 6-26 wherein each occurrence of R^2 is independently hydrogen, hydroxyl or lower alkoxy.

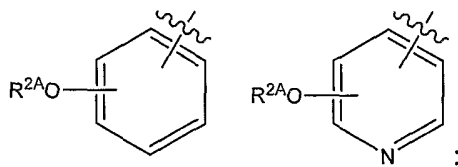
50. The compound of any one of claims 1-5 wherein Ar is substituted or unsubstituted phenyl or naphthyl, or a moiety having one of the following structures:



wherein p is 0-5; and each occurrence of R^2 is independently hydrogen, halogen, CN, NO_2 , alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, heterocycle, aryl, heteroaryl, $-(alkyl)cycloalkyl$, $-(alkyl)heterocycle$, $-(heteroalkyl)cycloalkyl$, $-(heteroalkyl)heterocycle$, $-(alkyl)aryl$, $-(heteroalkyl)aryl$, $-(alkyl)heteroaryl$, $-(heteroalkyl)heteroaryl$, $-OR^{2A}$, $-S(=O)_xR^{2A}$, $-N(R^{2A})_2$, $-SO_2N(R^{2A})_2$, $-C(=O)R^{2A}$, $-C(=O)N(R^{2A})_2$, $-C(=O)OR^{2A}$, $-N(R^{2A})C(=O)R^{2B}$ or $-N(R^{2A})SO_2R^{2B}$, wherein x is 0, 1 or 2; and each occurrence of R^{2A} and R^{2B} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, $-(alkyl)aryl$ or $-(alkyl)heteroaryl$; or R^{2A} and R^{2B} , taken together with the atoms to which they are attached, form a substituted or unsubstituted 5-8 membered heterocyclic moiety.

51. The compound of claim 50 wherein Ar is substituted or unsubstituted phenyl or pyridyl.

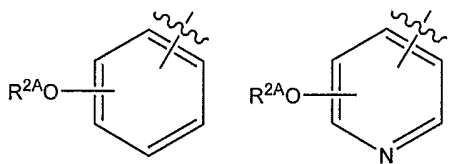
52. The compound of claim 50 wherein Ar has one of the following structures:



wherein R^{2A} is hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, heterocycle, acyl, aryl, heteroaryl, $-(alkyl)cycloalkyl$, $-$

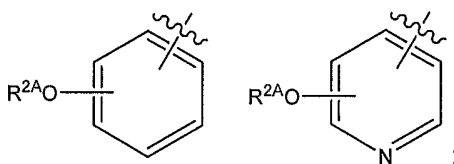
(alkyl)heterocycle, -(heteroalkyl)cycloalkyl, -(heteroalkyl)heterocycle, -(alkyl)aryl, -(heteroalkyl)aryl, -(alkyl)heteroaryl, -(heteroalkyl)heteroaryl or an oxygen protecting group.

53. The compound of claim 50 wherein Ar has one of the following structures:



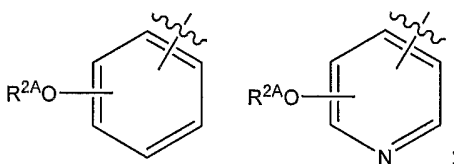
wherein R^{2A} is hydrogen, lower alkyl, lower heteroalkyl, cycloalkyl, heterocycle, lower acyl, aryl, heteroaryl, -(alkyl)cycloalkyl, -(alkyl)heterocycle, -(alkyl)aryl, -(heteroalkyl)aryl, -(alkyl)heteroaryl or an oxygen protecting group.

54. The compound of claim 50 wherein Ar has one of the following structures:



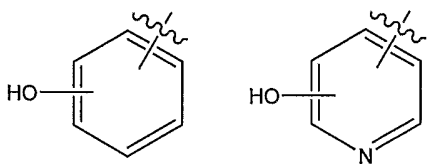
wherein R^{2A} is hydrogen, lower alkyl, lower acyl, aryl, heteroaryl or an oxygen protecting group.

55. The compound of claim 50 wherein Ar has one of the following structures:

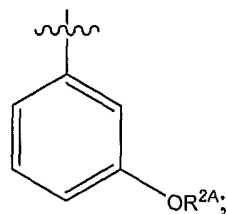


wherein R^{2A} is hydrogen, lower alkyl, lower acyl or an oxygen protecting group.

56. The compound of claim 50 wherein Ar has one of the following structures:

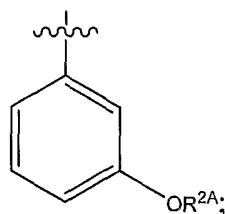


57. The compound of claim 50 wherein Ar has the structure:



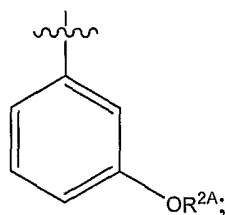
wherein R^{2A} is hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, heterocycle, acyl, aryl, heteroaryl, -(alkyl)cycloalkyl, -(alkyl)heterocycle, -(heteroalkyl)cycloalkyl, -(heteroalkyl)heterocycle, -(alkyl)aryl, -(heteroalkyl)aryl, -(alkyl)heteroaryl, -(heteroalkyl)heteroaryl or an oxygen protecting group.

58. The compound of claim 50 wherein Ar has the structure:



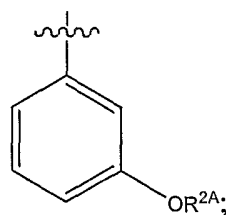
wherein R^{2A} is hydrogen, lower alkyl, lower heteroalkyl, cycloalkyl, heterocycle, lower acyl, aryl, heteroaryl, -(alkyl)cycloalkyl, -(alkyl)heterocycle, -(alkyl)aryl, -(heteroalkyl)aryl, -(alkyl)heteroaryl or an oxygen protecting group.

59. The compound of claim 50 wherein Ar has the structure:



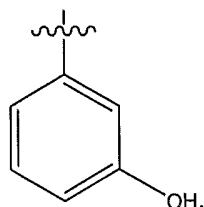
wherein R^{2A} is hydrogen, lower alkyl, lower acyl, aryl, heteroaryl or an oxygen protecting group.

60. The compound of claim 50 wherein Ar has the structure:



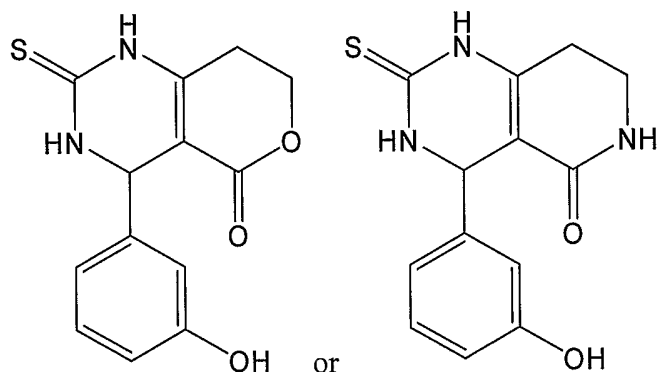
wherein R^{2A} is hydrogen, lower alkyl, lower acyl or an oxygen protecting group.

61. The compound of claim 50 wherein Ar has the structure:



62. The compound of any one of claims 8-11, 13-16, 18-21 and 23-26 wherein each occurrence of R^1 is methyl.

63. The compound of claim 1 having the structure:



64. A pharmaceutical composition comprising at least one compound of any one of claims 1-62 and further comprising a pharmaceutically acceptable carrier.

65. A method for treating or lessening the severity of a condition via modulation of Eg5 protein activity comprising administering to a subject in need thereof an effective amount of at least one compound of any one of claims 1-62 and a pharmaceutically acceptable carrier.

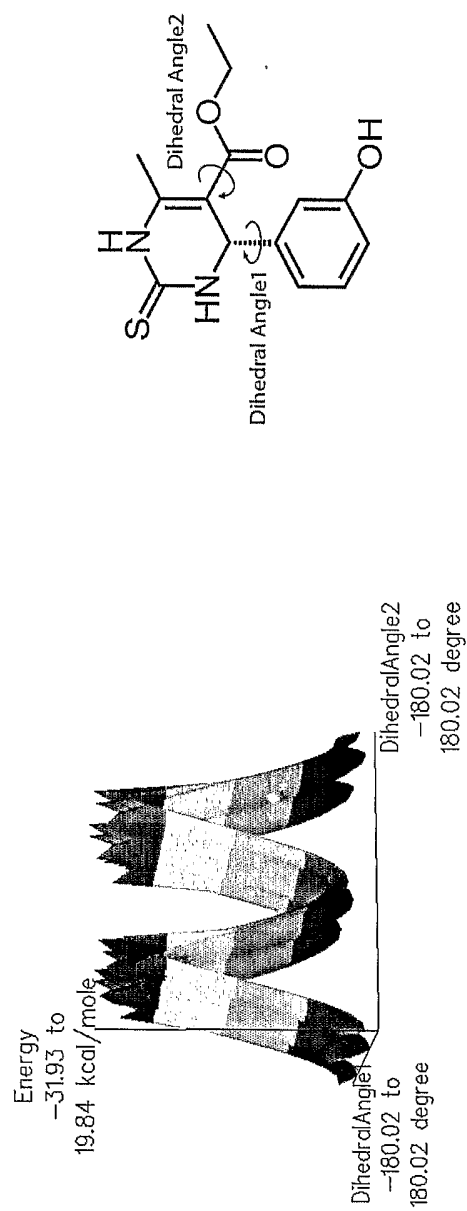
66. The method of claim 65 wherein the condition is cancer.

67. A method for inducing mitotic arrest in cells comprising contacting the cells with an effective amount of at least one compound of any one of claims 1-62 and optionally a pharmaceutically acceptable carrier.

68. A method for inducing apoptosis in cells comprising contacting the cells with an effective amount of at least one compound of any one of claims 1-62 and optionally a pharmaceutically acceptable carrier.

1/2

FIG. 1



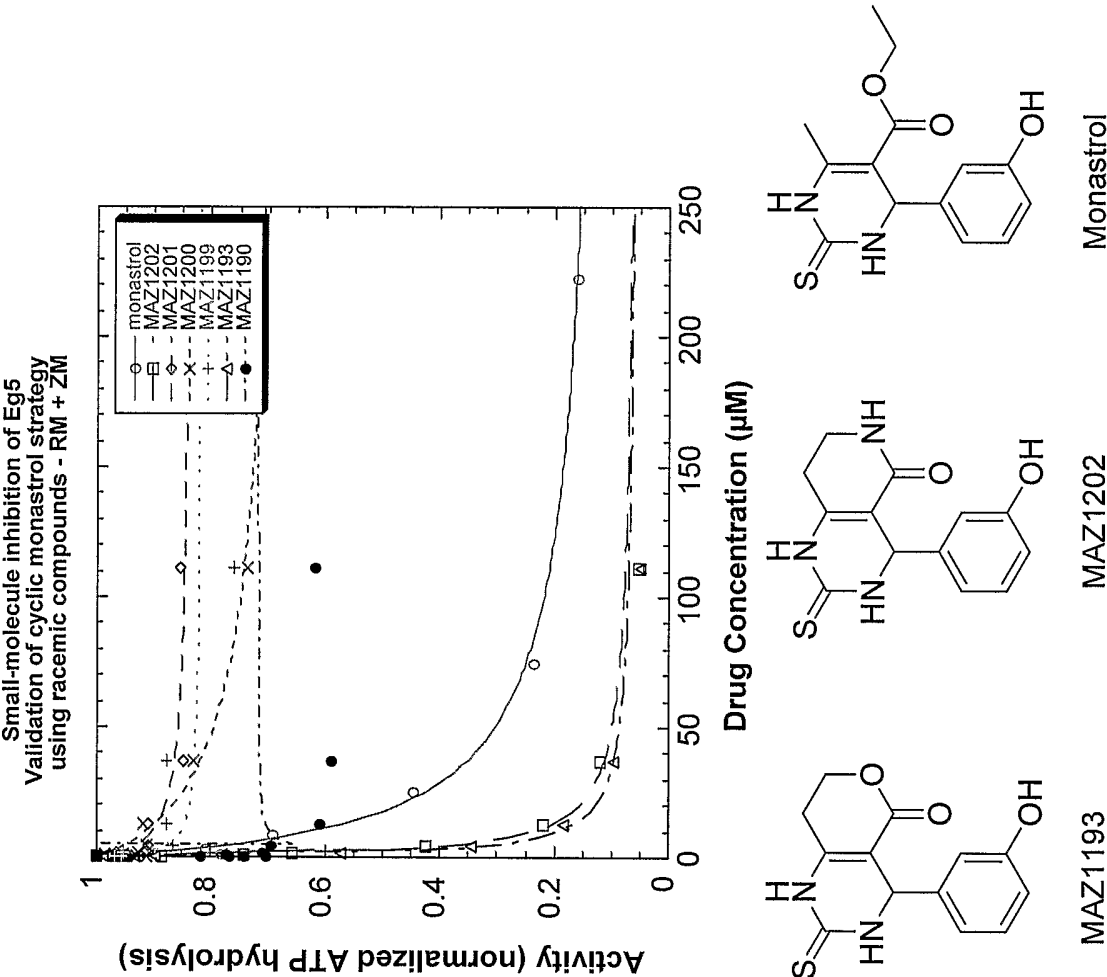


FIG. 2

APPENDIX A

FDA Approved Oncology Drugs

List of Approved Oncology Drugs with Approved Indications

Page 1 of 10

Aldesleukin	Proleukin		Chiron Corp	May 05 1992
Alemtuzumab	Campath	Accel. Approv. (clinical benefit not established) Campath is indicated for the treatment of B-cell chronic lymphocytic leukemia (B-CLL) in patients who have been treated with alkylating agents and who have failed fludarabine therapy.	Millennium and ILEX Partners, LP	May 07 2001
alitretinoin	Panretin	Topical treatment of cutaneous lesions in patients with AIDS-related Kaposi's sarcoma.	Ligand Pharmaceuticals	Feb 02 1999
allopurinol	Zyloprim	Patients with leukemia, lymphoma and solid tumor malignancies who are receiving cancer therapy which causes elevations of serum and urinary uric acid levels and who cannot tolerate oral therapy.	GlaxoSmithKline	May 17 1996
altretamine	Hexalen	Single agent palliative treatment of patients with persistent or recurrent ovarian cancer following first-line therapy with a cisplatin and/or alkylating agent based combination.	US Bioscience	Dec 26 1990
amifostine	Ethvol	To reduce the cumulative renal toxicity associated with repeated administration of cisplatin in patients with advanced ovarian cancer	US Bioscience	Dec 08 1995
amifostine	Ethvol	Accel. Approv. (clinical benefit not established) Reduction of platinum toxicity in non-small cell lung cancer	US Bioscience	Mar 15 1996
amifostine	Ethvol	To reduce post-radiation xerostomia for head and neck cancer where the radiation port includes a substantial portion of the parotid glands.	US Bioscience	Jun 24 1999
anastrozole	Arimidex	Accel. Approv. (clinical benefit not established) for the adjuvant treatment of postmenopausal women with hormone receptor positive early breast cancer	AstraZeneca	Sep 05 2002
anastrozole	Arimidex	Treatment of advanced breast cancer in postmenopausal women with disease progression following tamoxifen therapy.	AstraZeneca Pharmaceuticals	Dec 27 1995
anastrozole	Arimidex	For first-line treatment of postmenopausal women with hormone receptor positive or hormone receptor unknown locally advanced or metastatic breast cancer.	AstraZeneca Pharmaceuticals	Sep 01 2000
arsenic trioxide	Trisenox	Second line treatment of relapsed or refractory APL following ATRA plus an anthracycline.	Cell Therapeutic	Sep 25 2000
Asparaginase	Elspar	ELSPAR is indicated in the therapy of patients with acute lymphocytic leukemia. This agent is useful primarily in combination with other chemotherapeutic agents in the induction of remissions of the disease in pediatric patients.	Merck & Co, Inc	Aug 01 2002
BCG Live	TICE BCG		Organon Teknika Corp	Aug 21 1998
bexarotene capsules	Targretin	For the treatment by oral capsule of cutaneous manifestations of cutaneous T-cell lymphoma in patients who are refractory to at least one prior systemic therapy.	Ligand Pharmaceuticals	Dec 29 1999
bexarotene gel	Targretin	For the topical treatment of cutaneous manifestations of cutaneous T-cell lymphoma in patients who are refractory to at least one prior systemic therapy.	Ligand Pharmaceuticals	Jun 28 2000
bleomycin	Blenoxane		Bristol-Myers Squibb	Jul 31 1973
bleomycin	Blenoxane	Sclerosing agent for the treatment of malignant pleural effusion (MPE) and prevention of recurrent pleural effusions.	Bristol-Myers Squibb	Feb 20 1996
busulfan intravenous	Busulfex	Use in combination with cyclophosphamide as conditioning regimen prior to allogeneic hematopoietic progenitor cell transplantation for chronic myelogenous leukemia.	Orphan Medical, Inc	Feb 04 1999
busulfan oral	Myleran	Chronic Myelogenous Leukemia- palliative therapy	GlaxoSmithKline	Jun 26 1954
calusterone	Methosarb		Pharmacia & Upjohn Company	Feb 20 1973
capecitabine	Xeloda	Accel. Approv. (clinical benefit subsequently established) Treatment of metastatic breast cancer resistant to both paclitaxel and an anthracycline containing chemotherapy regimen or resistant to paclitaxel and for whom further anthracycline therapy may be contraindicated, e.g., patients who have received cumulative doses of 400 mg/m ² of doxorubicin or doxorubicin equivalents	Roche	Apr 30 1998
capecitabine	Xeloda	Initial therapy of patients with metastatic colorectal carcinoma when treatment with fluoropyrimidine therapy alone is preferred. Combination chemotherapy has shown a survival benefit compared to 5-FU/LV alone. A survival benefit over 5-FU/LV has not been demonstrated with Xeloda monotherapy.	Roche	Apr 30 2001

List of Approved Oncology Drugs with Approved Indications

<u>capecitabine</u>	<u>Xeloda</u>	Treatment in combination with docetaxel of patients with metastatic breast cancer after failure of prior anthracycline containing chemotherapy	<u>Roche</u>	Sep 07 2001
<u>carboplatin</u>	<u>Paraplatin</u>	Palliative treatment of patients with ovarian carcinoma recurrent after prior chemotherapy, including patients who have been previously treated with cisplatin.	<u>Bristol-Myers Squibb</u>	Mar 03 1989
<u>carboplatin</u>	<u>Paraplatin</u>	Initial chemotherapy of advanced ovarian carcinoma in combination with other approved chemotherapeutic agents.	<u>Bristol-Myers Squibb</u>	Jul 05 1991
<u>carmustine</u>	<u>BCNU, BICNU</u>		<u>Bristol-Myers Squibb</u>	Mar 07 1977
<u>carmustine with Polifeprosan 20 Implant</u>	<u>Gliadel Wafer</u>	For use in addition to surgery to prolong survival in patients with recurrent glioblastoma multiforme who qualify for surgery.	<u>Gulford Pharmaceuticals Inc.</u>	Sep 23 1986
<u>celecoxib</u>	<u>Celebrex</u>	Accel. Approv. (clinical benefit not established) Reduction of polyp number in patients with the rare genetic disorder of familial adenomatous polyposis.	<u>Searle</u>	Dec 23 1999
<u>chlorambucil</u>	<u>Leukeran</u>	Chronic Lymphocytic Leukemia- palliative therapy	<u>GlaxoSmithKline</u>	
<u>chlorambucil</u>	<u>Leukeran</u>		<u>GlaxoSmithKline</u>	Mar 18 1957
<u>cisplatin</u>	<u>Platinol</u>	Metastatic testicular-in established combination therapy with other approved chemotherapeutic agents in patients with metastatic testicular tumors who have already received appropriate surgical and/or radiotherapeutic procedures. An established combination therapy consists of Platinol, Blenoxane and Velbam.	<u>Bristol-Myers Squibb</u>	Dec 19 1978
<u>cisplatin</u>	<u>Platinol</u>	Metastatic ovarian tumors - in established combination therapy with other approved chemotherapeutic agents: Ovarian-in established combination therapy with other approved chemotherapeutic agents in patients with metastatic ovarian tumors who have already received appropriate surgical and/or radiotherapeutic procedures. An established combination consists of Platinol and Adriamycin. Platinol, as a single agent, is indicated as secondary therapy in patients with metastatic ovarian tumors refractory to standard chemotherapy who have not previously received Platinol therapy.	<u>Bristol-Myers Squibb</u>	Dec 19 1978
<u>cisplatin</u>	<u>Platinol</u>	as a single agent for patients with transitional cell bladder cancer which is no longer amenable to local treatments such as surgery and/or radiotherapy.	<u>Bristol-Myers Squibb</u>	Apr 22 1993
<u>cladribine</u>	<u>Leustatin, 2-CdA</u>	Treatment of active hairy cell leukemia.	<u>R.W. Johnson Pharmaceutical Research Institute</u>	Feb 26 1983
<u>cyclophosphamide</u>	<u>Cytoxan, Neosar</u>		<u>Bristol-Myers Squibb</u>	Nov 16 1959
<u>cyclophosphamide</u>	<u>Cytoxan Injection</u>		<u>Bristol-Myers Squibb</u>	Nov 16 1959
<u>cyclophosphamide</u>	<u>Cytoxan Injection</u>		<u>Bristol-Myers Squibb</u>	Apr 29 1987
<u>cyclophosphamide</u>	<u>Cytoxan Tablet</u>		<u>Bristol-Myers Squibb</u>	Apr 29 1987
<u>cytarabine</u>	<u>Cytosar-U</u>		<u>Pharmacia & Upjohn Company</u>	Jun 17 1969
<u>cytarabine liposomal</u>	<u>DepoCyt</u>	Accel. Approv. (clinical benefit not established) Intrathecal therapy of lymphomatous meningitis	<u>Skye Pharmaceuticals</u>	Apr 01 1999
<u>dacarbazine</u>	<u>DTIC-Dome</u>		<u>Bayer</u>	May 27 1975
<u>dactinomycin, actinomycin D</u>	<u>Cosmegen</u>		<u>Merck</u>	Feb 04 1964
<u>dactinomycin, actinomycin D</u>	<u>Cosmegen</u>		<u>Merck</u>	Dec 10 1964
<u>Darbepoetin alfa</u>	<u>Aranesp</u>	Treatment of anemia associated with chronic renal failure.	<u>Amgen, Inc</u>	Sep 17 2001
<u>Darbepoetin alfa</u>	<u>Aranesp</u>	Aranesp is indicated for the treatment of anemia in patients with non- myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy.	<u>Amgen, Inc</u>	Jul 19 2002

List of Approved Oncology Drugs with Approved Indications

<u>daunorubicin liposomal</u>	<u>DanuoXome</u>	First line cytotoxic therapy for advanced, HIV related Kaposi's sarcoma.	<u>Nexstar, Inc.</u>	Apr 08 1996
<u>daunorubicin, daunomycin</u>	<u>Daunorubicin</u>	Leukemia/myelogenous/monocytic/erythroid of adults/remission induction in acute lymphocytic leukemia of children and adults.	<u>Bedford Labs</u>	Jan 30 1998
<u>daunorubicin, daunomycin</u>	<u>Cerubidine</u>	In combination with approved anticancer drugs for induction of remission in adult ALL.	<u>Wyeth Averst</u>	Mar 11 1987
<u>Denileukin difitox</u>	<u>Ontak</u>	Accel. Approv. (clinical benefit not established) treatment of patients with persistent or recurrent cutaneous T-cell lymphoma whose malignant cells express the CD25 component of the IL-2 receptor	<u>Seragen, Inc</u>	Feb 05 1999
<u>dexrazoxane</u>	<u>Zinecard</u>	Accel. Approv. (clinical benefit subsequently established) Prevention of cardiomyopathy associated with doxorubicin administration	<u>Pharmacia & Upjohn Company</u>	May 26 1995
<u>dexrazoxane</u>	<u>Zinecard</u>	reducing the incidence and severity of cardiomyopathy associated with doxorubicin administration in women with metastatic breast cancer who have received a cumulative doxorubicin dose of 300 mg/m2 and who will continue to receive doxorubicin therapy to maintain tumor control. It is not recommended for use with the initiation of doxorubicin therapy.	<u>Pharmacia & Upjohn Company</u>	Oct 31 2002
<u>docetaxel</u>	<u>Taxotere</u>	Accel. Approv. (clinical benefit subsequently established) Treatment of patients with locally advanced or metastatic breast cancer who have progressed during anthracycline-based therapy or have relapsed during anthracycline-based adjuvant therapy.	<u>Aventis Pharmaceutical</u>	May 14 1996
<u>docetaxel</u>	<u>Taxotere</u>	For the treatment of locally advanced or metastatic breast cancer which has progressed during anthracycline-based treatment or relapsed during anthracycline-based adjuvant therapy.	<u>Aventis Pharmaceutical</u>	Jun 22 1998
<u>docetaxel</u>	<u>Taxotere</u>	For locally advanced or metastatic non-small cell lung cancer after failure of prior platinum-based chemotherapy.	<u>Aventis Pharmaceutical</u>	Dec 23 1999
<u>docetaxel</u>	<u>Taxotere</u>		<u>Aventis Pharmaceutical</u>	Nov 27 2002
<u>docetaxel</u>	<u>Taxotere</u>	in combination with cisplatin for the treatment of patients with unresectable, locally advanced or metastatic non-small cell lung cancer who have not previously received chemotherapy for this condition.	<u>Aventis Pharmaceutical</u>	Nov 27 2002
<u>doxorubicin</u>	<u>Adriamycin, Rubex</u>		<u>Pharmacia & Upjohn Company</u>	Aug 07 1974
<u>doxorubicin</u>	<u>Adriamycin PFS injection/intravenous injection</u>	Antibiotic, antitumor agent.	<u>Pharmacia & Upjohn Company</u>	Dec 23 1987
<u>doxorubicin liposomal</u>	<u>Doxil</u>	Accel. Approv. (clinical benefit not established) Treatment of AIDS-related Kaposi's sarcoma in patients with disease that has progressed on prior combination chemotherapy or in patients who are intolerant to such therapy.	<u>Sequus Pharmaceuticals, Inc.</u>	Nov 17 1995
<u>doxorubicin liposomal</u>	<u>Doxil</u>	Accel. Approv. (clinical benefit not established) Treatment of metastatic carcinoma of the ovary in patient with disease that is refractory to both paclitaxel and platinum based regimens	<u>Sequus Pharmaceuticals, Inc.</u>	Jun 28 1999
<u>DROMOSTANOLONE PROPIONATE</u>	<u>DROMOSTANOLONE</u>		<u>Eli Lilly</u>	Oct 26 1961
<u>DROMOSTANOLONE PROPIONATE</u>	<u>MASTERONE INJECTION</u>		<u>SYNTEX</u>	Oct 08 1964
<u>Elliott's B Solution</u>	<u>Elliott's B Solution</u>	Diluent for the intrathecal administration of methotrexate sodium and cytarabine for the prevention or treatment of meningeal leukemia or lymphocytic lymphoma.	<u>Orphan Medical, Inc</u>	Sep 27 1996
<u>epirubicin</u>	<u>Ellence</u>	A component of adjuvant therapy in patients with evidence of axillary node tumor involvement following resection of primary breast cancer.	<u>Pharmacia & Upjohn Company</u>	Sep 15 1999
<u>Epoetin alfa</u>	<u>epogen</u>	EPOGENB is indicated for the treatment of anemia related to therapy with zidovudine in HIV- infected patients. EPOGENB is indicated to elevate or maintain the red blood cell level (as manifested by the hematocrit or hemoglobin determinations) and to decrease the need for transfusions in these patients. EPOGENB is not indicated for the treatment of anemia in HIV-infected patients due to other factors such as iron or folate deficiencies, hemolysis or gastrointestinal bleeding, which should be managed appropriately.	<u>Amgen, Inc</u>	Jul 26 1999
<u>Epoetin alfa</u>	<u>epogen</u>	EPOGENB is indicated for the treatment of anemic patients (hemoglobin > 10 to < 13 g/dL) scheduled to undergo elective, noncardiac, nonvascular surgery to reduce the need for allogeneic blood transfusions.	<u>Amgen, Inc</u>	Jul 26 1999
<u>Epoetin alfa</u>	<u>epogen</u>	EPOGENB is indicated for the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy. EPOGENB is indicated to decrease the need for transfusions in patients who will be receiving concomitant chemotherapy for a minimum of 2 months. EPOGENB is not indicated for the treatment of anemia in cancer patients due to other factors such as	<u>Amgen, Inc</u>	Jul 26 1999

		iron or folate deficiencies, hemolysis or gastrointestinal bleeding, which should be managed appropriately.		
<u>Epoetin alfa</u>	<u>epogen</u>	EPOGEN is indicated for the treatment of anemia associated with CRF, including patients on dialysis (ESRD) and patients not on dialysis.	<u>Amgen, Inc</u>	Jul 26 1999
<u>estramustine</u>	<u>Emcyt</u>	palliation of prostate cancer	<u>Pharmacia & Upjohn Company</u>	Dec 24 1981
<u>etoposide phosphate</u>	<u>Etopophos</u>	Management of refractory testicular tumors, in combination with other approved chemotherapeutic agents.	<u>Bristol-Myers Squibb</u>	May 17 1996
<u>etoposide phosphate</u>	<u>Etopophos</u>	Management of small cell lung cancer, first-line, in combination with other approved chemotherapeutic agents.	<u>Bristol-Myers Squibb</u>	May 17 1996
<u>etoposide phosphate</u>	<u>Etopophos</u>	Management of refractory testicular tumors and small cell lung cancer.	<u>Bristol-Myers Squibb</u>	Feb 27 1998
<u>etoposide, VP-16</u>	<u>Vepesid</u>	Refractory testicular tumors-in combination therapy with other approved chemotherapeutic agents in patients with refractory testicular tumors who have already received appropriate surgical, chemotherapeutic and radiotherapeutic therapy.	<u>Bristol-Myers Squibb</u>	Nov 10 1983
<u>etoposide, VP-16</u>	<u>VePesid</u>	In combination with other approved chemotherapeutic agents as first line treatment in patients with small cell lung cancer.	<u>Bristol-Myers Squibb</u>	Dec 30 1986
<u>etoposide, VP-16</u>	<u>Vepesid</u>	In combination with other approved chemotherapeutic agents as first line treatment in patients with small cell lung cancer.	<u>Bristol-Myers Squibb</u>	Dec 30 1986
<u>exemestane</u>	<u>Aromasin</u>	Treatment of advance breast cancer in postmenopausal women whose disease has progressed following tamoxifen therapy.	<u>Pharmacia & Upjohn Company</u>	Oct 21 1999
<u>Filgrastim</u>	<u>Neupogen</u>		<u>Amgen, Inc</u>	Feb 20 1991
<u>Filgrastim</u>	<u>Neupogen</u>	NEUPOGEN is indicated to reduce the duration of neutropenia and neutropenia-related clinical sequelae, eg, febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by marrow transplantation.	<u>Amgen, Inc</u>	Apr 02 1998
<u>Filgrastim</u>	<u>Neupogen</u>	NEUPOGEN is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a significant incidence of severe neutropenia with fever.	<u>Amgen, Inc</u>	Apr 02 1998
<u>Filgrastim</u>	<u>Neupogen</u>	NEUPOGEN is indicated for reducing the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of adults with AML.	<u>Amgen, Inc</u>	Apr 02 1998
<u>floxuridine (intraarterial)</u>	<u>FUDR</u>		<u>Roche</u>	Dec 18 1970
<u>fludarabine</u>	<u>Fludara</u>	Palliative treatment of patients with B-cell lymphocytic leukemia (CLL) who have not responded or have progressed during treatment with at least one standard alkylating agent containing regimen.	<u>Berlex Laboratories Inc.</u>	Apr 18 1991
<u>fluorouracil, 5-FU</u>	<u>Adrucil</u>	prolong survival in combination with leucovorin	<u>ICN Puerto Rico</u>	Apr 25 1962
<u>fulvestrant</u>	<u>Faslodex</u>	the treatment of hormone receptor-positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy	<u>IPR</u>	Apr 25 2002
<u>gemcitabine</u>	<u>Gemzar</u>	Treatment of patients with locally advanced (nonresectable stage II or III) or metastatic (stage IV) adenocarcinoma of the pancreas. Indicated for first-line treatment and for patients previously treated with a 5-fluorouracil-containing regimen.	<u>Eli Lilly</u>	May 15 1996
<u>gemcitabine</u>	<u>Gemzar</u>	For use in combination with cisplatin for the first-line treatment of patients with inoperable, locally advanced (Stage IIIA or IIIB) or metastatic (Stage IV) non-small cell lung cancer.	<u>Eli Lilly</u>	Aug 25 1998
<u>gemtuzumab ozogamicin</u>	<u>Mylotarg</u>	Accel. Approv. (clinical benefit not established) Treatment of CD33 positive acute myeloid leukemia in patients in first relapse who are 60 years of age or older and who are not considered candidates for cytotoxic chemotherapy.	<u>Wyeth Ayerst</u>	May 17 2000
<u>goserelin acetate</u>	<u>Zoladex Implant</u>	Palliative treatment of advanced breast cancer in pre- and perimenopausal women.	<u>AstraZeneca Pharmaceuticals</u>	Dec 18 1995
<u>goserelin acetate</u>	<u>Zoladex</u>		<u>AstraZeneca Pharmaceuticals</u>	Dec 18 1995
<u>hydroxyurea</u>	<u>Hydrea</u>		<u>Bristol-Myers Squibb</u>	Dec 07 1967
				Feb

hydroxyurea	Hydrea	Decrease need for transfusions in sickle cell anemia	Bristol-Myers Squibb	25 1998
Ibritumomab Tiuxetan	Zevalin	Accel. Approv. (clinical benefit not established) treatment of patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma, including patients with Rituximab refractory follicular non-Hodgkin's lymphoma.	IDEC Pharmaceuticals Corp	Feb 19 2002
idarubicin	Idamycin	For use in combination with other approved antileukemic drugs for the treatment of acute myeloid leukemia (AML) in adults.	Adria Laboratories	Sep 27 1990
idarubicin	Idamycin	In combination with other approved antileukemic drugs for the treatment of acute non-lymphocytic leukemia in adults.	Pharmacia & Upjohn Company	Feb 17 1997
ifosfamide	IFEX	Third line chemotherapy of germ cell testicular cancer when used in combination with certain other approved antineoplastic agents.	Bristol-Myers Squibb	Dec 30 1988
imatinib mesylate	Gleevec	Accel. Approv. (clinical benefit not established) Initial therapy of chronic myelogenous leukemia	Novartis	May 10 2001
imatinib mesylate	Gleevec	Accel. Approv. (clinical benefit not established) metastatic or unresectable malignant gastrointestinal stromal tumors	Novartis	Feb 01 2002
imatinib mesylate	Gleevec	Accel. Approv. (clinical benefit not established) Initial treatment of newly diagnosed Ph+ chronic myelogenous leukemia (CML).	Novartis	Dec 20 2002
Interferon alfa-2a	Roferon-A		Hoffmann-La Roche Inc	Nov 01 1996
Interferon alfa-2b	Intron A	Interferon alfa-2b, recombinant for injection is indicated as adjuvant to surgical treatment in patients 18 years of age or older with malignant melanoma who are free of disease but at high risk for systemic recurrence within 56 days of surgery.	Schering Corp	Nov 06 1997
Interferon alfa-2b	Intron A	Interferon alfa-2b, recombinant for injection is indicated for the initial treatment of clinically aggressive follicular Non-Hodgkin's Lymphoma in conjunction with anthracycline-containing combination chemotherapy in patients 18 years of age or older.	Schering Corp	Nov 06 1997
Interferon alfa-2b	Intron A	Interferon alfa-2b, recombinant for injection is indicated for intralesional treatment of selected patients 18 years of age or older with condylomata acuminata involving external surfaces of the genital and perianal areas.	Schering Corp	Nov 06 1997
Interferon alfa-2b	Intron A	Interferon alfa-2b, recombinant for injection is indicated for the treatment of chronic hepatitis C in patients 18 years of age or older with compensated liver disease who have a history of blood or blood-product exposure and/or are HCV antibody positive.	Schering Corp	Nov 06 1997
Interferon alfa-2b	Intron A	Interferon alfa-2b, recombinant for injection is indicated for the treatment of chronic hepatitis B in patients 18 years of age or older with compensated liver disease and HBV replication.	Schering Corp	Nov 06 1997
Interferon alfa-2b	Intron A	Interferon alfa-2b, recombinant for injection is indicated for the treatment of patients 18 years of age or older with hairy cell leukemia.	Schering Corp	Nov 06 1997
Interferon alfa-2b	Intron A	Interferon alfa-2b, recombinant for injection is indicated for the treatment of selected patients 18 years of age or older with AIDS-Related Kaposi's Sarcoma. The likelihood of response to INTRON A therapy is greater in patients who are without systemic symptoms, who have limited lymphadenopathy and who have a relatively intact immune system as indicated by total CD4 count.	Schering Corp	Nov 06 1997
Interferon alfa-2b	Intron A		Schering Corp	Jun 21 2002
Interferon alfa-2b	Intron A		Schering Corp	Jun 21 2002
Interferon alfa-2b	Intron A Intron A		Schering Corp	Jun 21 2002
irinotecan	Camptosar	Accel. Approv. (clinical benefit subsequently established) Treatment of patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following 5-FU-based therapy.	Pharmacia & Upjohn Company	Jun 14 1996
irinotecan	Camptosar	Follow up of treatment of metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following 5-FU-based therapy.	Pharmacia & Upjohn Company	Oct 22 1998
irinotecan	Camptosar	For first line treatment in combination with 5-FU/leucovorin of metastatic carcinoma of the colon or rectum.	Pharmacia & Upjohn Company	Apr 20 2000
letrozole	Femara	Treatment of advanced breast cancer in postmenopausal women.	Novartis	Jul 25 1997
letrozole	Femara	First-line treatment of postmenopausal women with hormone receptor positive or hormone	Novartis	Jan 10

		receptor unknown locally advanced or metastatic breast cancer.		2001
<u>letrozole</u>	<u>Femara</u>		<u>Novartis</u>	Jan 17 2003
<u>leucovorin</u>	<u>Wellcovorin, Leucovorin</u>	Leucovorin calcium is indicated for use in combination with 5-fluorouracil to prolong survival in the palliative treatment of patients with advanced colorectal cancer.	<u>Immunex Corporation</u>	Jun 20 1952
<u>leucovorin</u>	<u>Leucovorin</u>		<u>Immunex Corporation</u>	Jan 30 1987
<u>leucovorin</u>	<u>Leucovorin</u>		<u>Immunex Corporation</u>	Jan 30 1987
<u>leucovorin</u>	<u>Leucovorin</u>		<u>Immunex Corporation</u>	Aug 31 1988
<u>leucovorin</u>	<u>Leucovorin</u>	In combination with fluorouracil to prolong survival in the palliative treatment of patients with advanced colorectal cancer.	<u>Lederle Laboratories</u>	Dec 12 1991
<u>levamisole</u>	<u>Ergamisol</u>	Adjuvant treatment in combination with 5-fluorouracil after surgical resection in patients with Dukes' Stage C colon cancer.	<u>Janssen Research Foundation</u>	Jun 18 1990
<u>lomustine, CCNU</u>	<u>CeeBU</u>		<u>Bristol-Myers Squibb</u>	Aug 04 1976
<u>meclorothamine, nitrogen mustard</u>	<u>Mustargen</u>		<u>Merck</u>	Mar 15 1949
<u>megestrol acetate</u>	<u>Megace</u>		<u>Bristol-Myers Squibb</u>	Aug 18 1971
<u>melphalan, L-PAM</u>	<u>Alkeran</u>		<u>GlaxoSmithKline</u>	Jan 17 1964
<u>melphalan, L-PAM</u>	<u>Alkeran</u>	Systemic administration for palliative treatment of patients with multiple myeloma for whom oral therapy is not appropriate.	<u>GlaxoSmithKline</u>	Nov 18 1992
<u>mercaptopurine, 6-MP</u>	<u>Purinethol</u>		<u>GlaxoSmithKline</u>	Sep 11 1953
<u>mesna</u>	<u>Mesnex</u>	Prevention of ifosfamide-induced hemorrhagic cystitis	<u>Asta Medica</u>	Dec 30 1988
<u>methotrexate</u>	<u>Methotrexate</u>		<u>Lederle Laboratories</u>	Dec 07 1953
<u>methotrexate</u>	<u>Methotrexate</u>		<u>Lederle Laboratories</u>	Aug 10 1959
<u>methotrexate</u>	<u>Methotrexate</u>		<u>Lederle Laboratories</u>	Nov 01 1971
<u>methotrexate</u>	<u>Methotrexate</u>		<u>Lederle Laboratories</u>	Nov 01 1971
<u>methotrexate</u>	<u>Methotrexate</u>	osteosarcoma	<u>Lederle Laboratories</u>	Apr 07 1988
<u>methotrexate</u>	<u>Methotrexate</u>		<u>Lederle Laboratories</u>	Oct 31 1988
<u>methoxsalen</u>	<u>Uvadex</u>	For the use of UVADEX with the UVAR Photopheresis System in the palliative treatment of the skin manifestations of cutaneous T-cell lymphoma (CTCL) that is unresponsive to other forms of treatment.	<u>Therakos</u>	Feb 25 1999
<u>mitomycin C</u>	<u>Mitomycin</u>		<u>Bristol-Myers Squibb</u>	May 28 1974
<u>mitomycin C</u>	<u>Mitozytrex</u>	therapy of disseminated adenocarcinoma of the stomach or pancreas in proven combinations with other approved chemotherapeutic agents and as palliative treatment when other modalities have failed.	<u>Supergen</u>	Nov 14 2002
<u>mitofane</u>	<u>Lysodren</u>		<u>Bristol-Myers Squibb</u>	Jul 08

<u>mitoxantrone</u>	<u>Novantrone</u>	For use in combination with corticosteroids as initial chemotherapy for the treatment of patients with pain related to advanced hormone-refractory prostate cancer.	<u>Immunex Corporation</u>	Nov 13 1996
<u>mitoxantrone</u>	<u>Novantrone</u>	For use with other approved drugs in the initial therapy for acute nonlymphocytic leukemia (ANLL) in adults.	<u>Lederle Laboratories</u>	Dec 23 1987
<u>nandrolone phenpropionate</u>	<u>Durabolin-50</u>		<u>Organon</u>	Oct 30 1959
<u>Nofetumomab</u>	<u>Verluma</u>		<u>Boehringer Ingelheim Pharma KG (formerly Dr. Karl Thomae GmbH)</u>	Aug 20 1996
<u>Oprelvekin</u>	<u>Neumega</u>		<u>Genetics Institute, Inc</u>	Nov 25 1997
<u>Oprelvekin</u>	<u>Neumega</u>		<u>Genetics Institute, Inc</u>	Sep 18 2002
<u>Oprelvekin</u>	<u>Neumega</u>	Neumega is indicated for the prevention of severe thrombocytopenia and the reduction of the need for platelet transfusions following myelosuppressive chemotherapy in adult patients with nonmyeloid malignancies who are at high risk of severe thrombocytopenia.	<u>Genetics Institute, Inc</u>	Sep 18 2002
<u>oxaliplatin</u>	<u>Eloxatin</u>	Accel. Approv. (clinical benefit not established) in combination with infusional 5-FU/LV, is indicated for the treatment of patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed during or within 6 months of completion of first line therapy with the combination of bolus 5-FU/LV and irinotecan.	<u>Sanofi Synthelabo</u>	Aug 09 2002
<u>paclitaxel</u>	<u>Paxene</u>	treatment of advanced AIDS-related Kaposi's sarcoma after failure of first line or subsequent systemic chemotherapy	<u>Baker Norton Pharmaceuticals, Inc</u>	Dec 24 1997
<u>paclitaxel</u>	<u>Taxol</u>	Treatment of patients with metastatic carcinoma of the ovary after failure of first-line or subsequent chemotherapy.	<u>Bristol-Myers Squibb</u>	Dec 29 1992
<u>paclitaxel</u>	<u>Taxol</u>	Treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.	<u>Bristol-Myers Squibb</u>	Apr 13 1994
<u>paclitaxel</u>	<u>Taxol</u>	New dosing regimen for patients who have failed initial or subsequent chemotherapy for metastatic carcinoma of the ovary	<u>Bristol-Myers Squibb</u>	Jun 22 1994
<u>paclitaxel</u>	<u>Taxol</u>	second line therapy for AIDS related Kaposi's sarcoma.	<u>Bristol-Myers Squibb</u>	Aug 04 1997
<u>paclitaxel</u>	<u>Taxol</u>	For first-line therapy for the treatment of advanced carcinoma of the ovary in combination with cisplatin.	<u>Bristol-Myers Squibb</u>	Apr 09 1998
<u>paclitaxel</u>	<u>Taxol</u>	for use in combination with cisplatin, for the first-line treatment of non-small cell lung cancer in patients who are not candidates for potentially curative surgery and/or radiation therapy.	<u>Bristol-Myers Squibb</u>	Jun 30 1998
<u>paclitaxel</u>	<u>Taxol</u>	For the adjuvant treatment of node-positive breast cancer administered sequentially to standard doxorubicin-containing combination therapy.	<u>Bristol-Myers Squibb</u>	Oct 25 1999
<u>paclitaxel</u>	<u>Taxol</u>	First line ovarian cancer with 3 hour infusion.	<u>Bristol-Myers Squibb</u>	Jun 20 2000
<u>pamidronate</u>	<u>Aredia</u>	Treatment of osteolytic bone metastases of breast cancer in conjunction with standard antineoplastic therapy.	<u>Novartis</u>	Sep 22 1998
<u>pegademase</u>	<u>Adagen (Pegademase Bovine)</u>	Enzyme replacement therapy for patients with severe combined immunodeficiency as a result of adenosine deaminase deficiency.	<u>Enzon</u>	Mar 21 1990
<u>Pegaspargase</u>	<u>Oncaspar</u>		<u>Enzon, Inc</u>	Feb 01 1994
<u>Pegfilgrastim</u>	<u>Neulasta</u>	Neulasta is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.	<u>Amgen, Inc</u>	Jan 31 2002
<u>pentostatin</u>	<u>Nipent</u>	Single agent treatment for adult patients with alpha interferon refractory hairy cell leukemia.	<u>Parke-Davis Pharmaceutical Co.</u>	Oct 11 1991
<u>pentostatin</u>	<u>Nipent</u>	Single-agent treatment for untreated hairy cell leukemia patients with active disease as defined by clinically significant anemia, neutropenia, thrombocytopenia, or disease-related symptoms. (Supplement for front-line therapy.)	<u>Parke-Davis Pharmaceutical Co.</u>	Sep 29 1993

<u>pipobroman</u>	<u>Vercyte</u>		<u>Abbott Labs</u>	Jul 01 1966
<u>plicamycin, mithramycin</u>	<u>Mithracin</u>		<u>Pfizer Labs</u>	May 05 1970
<u>porfimer sodium</u>	<u>Photofrin</u>	For use in photodynamic therapy (PDT) for palliation of patients with completely obstructing esophageal cancer, or patients with partially obstructing esophageal cancer who cannot be satisfactorily treated with ND-YAG laser therapy.	<u>QLT Phototherapeutics Inc.</u>	Dec 27 1995
<u>porfimer sodium</u>	<u>Photofrin</u>	For use in photodynamic therapy for treatment of microinvasive endobronchial nonsmall cell lung cancer in patients for whom surgery and radiotherapy are not indicated.	<u>QLT Phototherapeutics Inc.</u>	Jan 09 1998
<u>porfimer sodium</u>	<u>Photofrin</u>	For use in photodynamic therapy (PDT) for reduction of obstruction and palliation of symptoms in patients with completely or partially obstructing endobronchial nonsmall cell lung cancer (NSCLC).	<u>QLT Phototherapeutics Inc.</u>	Dec 22 1998
<u>procarbazine</u>	<u>Matulane</u>		<u>Sigma Tau Pharms</u>	Jul 22 1969
<u>quinacrine</u>	<u>Atabrine</u>		<u>Abbott Labs</u>	Dec 07 1964
<u>Rasburicase</u>	<u>Elitek</u>	ELITEK is indicated for the initial management of plasma uric acid levels in pediatric patients with leukemia, lymphoma, and solid tumor malignancies who are receiving anti-cancer therapy expected to result in tumor lysis and subsequent elevation of plasma uric acid.	<u>Sanofi-Synthelabo, Inc</u>	Jul 12 2002
<u>Rituximab</u>	<u>Rituxan</u>		<u>Genentech, Inc</u>	Nov 26 1997
<u>Sargramostim</u>	<u>Prokine</u>		<u>Immunex Corp</u>	Nov 07 1996
<u>streptozocin</u>	<u>Zanosar</u>	Antineoplastic agent.	<u>Pharmacia & Upjohn Company</u>	May 07 1982
<u>talc</u>	<u>Sclerosol</u>	For the prevention of the recurrence of malignant pleural effusion in symptomatic patients.	<u>Bryan</u>	Dec 24 1997
<u>tamoxifen</u>	<u>Nolvadex</u>		<u>AstraZeneca Pharmaceuticals</u>	Dec 30 1977
<u>tamoxifen</u>	<u>Nolvadex</u>	As a single agent to delay breast cancer recurrence following total mastectomy and axillary dissection in postmenopausal women with breast cancer (T1-3, N1, M0)	<u>AstraZeneca Pharmaceuticals</u>	Dec 03 1986
<u>tamoxifen</u>	<u>Nolvadex</u>	For use in premenopausal women with metastatic breast cancer as an alternative to oophorectomy or ovarian irradiation	<u>AstraZeneca Pharmaceuticals</u>	Mar 16 1989
<u>tamoxifen</u>	<u>Nolvadex</u>	For use in women with axillary node-negative breast cancer adjuvant therapy.	<u>AstraZeneca Pharmaceuticals</u>	Jun 21 1990
<u>tamoxifen</u>	<u>Nolvadex</u>	Metastatic breast cancer in men.	<u>AstraZeneca Pharmaceuticals</u>	Apr 01 1993
<u>tamoxifen</u>	<u>Nolvadex</u>	Equal bioavailability of a 20 mg Nolvadex tablet taken once a day to a 10 mg Nolvadex tablet taken twice a day.	<u>AstraZeneca Pharmaceuticals</u>	Mar 21 1994
<u>tamoxifen</u>	<u>Nolvadex</u>	to reduce the incidence of breast cancer in women at high risk for breast cancer	<u>AstraZeneca Pharmaceuticals</u>	Oct 29 1998
<u>tamoxifen</u>	<u>Nolvadex</u>	In women with DCIS, following breast surgery and radiation, Nolvadex is indicated to reduce the risk of invasive breast cancer.	<u>AstraZeneca Pharmaceuticals</u>	Jun 29 2000
<u>temozolomide</u>	<u>Temodar</u>	Accel. Approv. (clinical benefit not established) Treatment of adult patients with refractory anaplastic astrocytoma, i.e., patients at first relapse with disease progression on a nitrosourea and procarbazine containing regimen	<u>Schering</u>	Aug 11 1999
<u>teniposide, VM-26</u>	<u>Vumon</u>	In combination with other approved anticancer agents for induction therapy in patients with refractory childhood acute lymphoblastic leukemia (all).	<u>Bristol-Myers Squibb</u>	Jul 14 1992
<u>testolactone</u>	<u>Teslac</u>		<u>Bristol-Myers Squibb</u>	Jun 03 1969
<u>testolactone</u>	<u>Teslac</u>		<u>Bristol-Myers Squibb</u>	May 27

List of Approved Oncology Drugs with Approved Indications

				1970
<u>thioguanine, 6-TG</u>	<u>Thioguanine</u>		<u>GlaxoSmithKline</u>	Jan 18 1966
<u>thiotepa</u>	<u>Thioplex</u>		<u>Immunex Corporation</u>	Mar 09 1959
<u>thiotepa</u>	<u>Thioplex</u>		<u>Immunex Corporation</u>	Dec 22 1994
<u>thiotepa</u>	<u>Thioplex</u>		<u>Lederle Laboratories</u>	Aug 15 1990
<u>topotecan</u>	<u>Hycamtin</u>	Treatment of patients with metastatic carcinoma of the ovary after failure of initial or subsequent chemotherapy.	<u>GlaxoSmithKline</u>	May 28 1996
<u>topotecan</u>	<u>Hycamtin</u>	Treatment of small cell lung cancer sensitive disease after failure of first-line chemotherapy. In clinical studies submitted to support approval, sensitive disease was defined as disease responding to chemotherapy but subsequently progressing at least 60 days (in the phase 3 study) or at least 90 days (in the phase 2 studies) after chemotherapy	<u>GlaxoSmithKline</u>	Nov 30 1998
<u>toremifene</u>	<u>Fareston</u>	Treatment of advanced breast cancer in postmenopausal women.	<u>Orion Corp.</u>	May 29 1997
<u>Tositumomab</u>	<u>Bexxar</u>	Accel. Approv. (clinical benefit not established) Treatment of patients with CD20 positive, follicular, non-Hodgkin's lymphoma, with and without transformation, whose disease is refractory to Rituximab and has relapsed following chemotherapy	<u>Corixa Corporation</u>	Jun 27 2003
<u>Trastuzumab</u>	<u>Herceptin</u>	HERCEPTIN as a single agent is indicated for the treatment of patients with metastatic breast cancer whose tumors overexpress the HER2 protein and who have received one or more chemotherapy regimens for their metastatic disease.	<u>Genentech, Inc</u>	Sep 25 1998
<u>Trastuzumab</u>	<u>Herceptin</u>	Herceptin in combination with paclitaxel is indicated for treatment of patients with metastatic breast cancer whose tumors overexpress the HER-2 protein and had not received chemotherapy for their metastatic disease	<u>Genentech, Inc</u>	Feb 09 2000
<u>Trastuzumab</u>	<u>Herceptin</u>		<u>Genentech, Inc</u>	Dec 11 2001
<u>Trastuzumab</u>	<u>Herceptin</u>		<u>Genentech, Inc</u>	Aug 28 2002
<u>Trastuzumab</u>	<u>Herceptin</u>		<u>Genentech, Inc</u>	Aug 28 2002
<u>tretinoin, ATRA</u>	<u>Vesanoid</u>	Induction of remission in patients with acute promyelocytic leukemia (APL) who are refractory to or unable to tolerate anthracycline based cytotoxic chemotherapeutic regimens.	<u>Roche</u>	Nov 22 1995
<u>Uracil Mustard</u>	<u>Uracil Mustard Capsules</u>		<u>Roberts Labs</u>	Sep 13 1962
<u>valrubicin</u>	<u>Valstar</u>	For intravesical therapy of BCG-refractory carcinoma in situ (CIS) of the urinary bladder in patients for whom immediate cystectomy would be associated with unacceptable morbidity or mortality.	<u>Anthra --> Medeva</u>	Sep 25 1998
<u>vinblastine</u>	<u>Velban</u>		<u>Eli Lilly</u>	Nov 05 1965
<u>vincristine</u>	<u>Oncovin</u>		<u>Eli Lilly</u>	Jul 10 1963
<u>vincristine</u>	<u>Oncovin</u>		<u>Eli Lilly</u>	Jul 10 1963
<u>vincristine</u>	<u>Oncovin</u>		<u>Eli Lilly</u>	Jul 10 1963
<u>vincristine</u>	<u>Oncovin</u>		<u>Eli Lilly</u>	Jul 10 1963
<u>vincristine</u>	<u>Oncovin</u>		<u>Eli Lilly</u>	Jul 10 1963
<u>vincristine</u>	<u>Oncovin</u>		<u>Eli Lilly</u>	Jul 10 1963
				Jul

<u>vincristine</u>	<u>Oncovin</u>		<u>Eli Lilly</u>	10 1963
<u>vinorelbine</u>	<u>Navelbine</u>	Single agent or in combination with cisplatin for the first-line treatment of ambulatory patients with unresectable, advanced non-small cell lung cancer (NSCLC).	<u>GlaxoSmithKline</u>	Dec 23 1994
<u>vinorelbine</u>	<u>Navelbine</u>	Navelbine is indicated as a single agent or in combination with cisplatin for the first-line treatment of ambulatory patients with unresectable, advanced non-small cell lung cancer (NSCLC). In patients with Stage IV NSCLC, Navelbine is indicated as a single agent or in combination with cisplatin. In Stage III NSCLC, Navelbine is indicated in combination with cisplatin.	<u>GlaxoSmithKline</u>	Nov 05 2002
<u>zoledronate</u>	<u>Zometa</u>	the treatment of patients with multiple myeloma and patients with documented bone metastases from solid tumors, in conjunction with standard antineoplastic therapy. Prostate cancer should have progressed after treatment with at least one hormonal therapy	<u>Novartis</u>	Feb 22 2002

APPENDIX B

NCI Screen Protocol

- APPENDIX B -

Adapted from Developmental Therapeutics Program NCI/NIH

<http://dtp.nci.nih.gov/branches/btb/ivclsp.html>

Screening Services

DTP Human Tumor Cell Line Screen

Process

The In Vitro Cell Line Screening Project (IVCLSP) is a dedicated service providing direct support to the DTP anticancer drug discovery program. The in vitro cell line screen was implemented in fully operational form in April of 1990. It required approximately five years (1985 - 1990) to develop, and persistence in the effort reflected dissatisfaction with the performance of prior in vivo primary screens. This project is designed to screen up to 20,000 compounds per year for potential anticancer activity. The operation of this screen utilizes 60 different human tumor cell lines, representing leukemia, melanoma and cancers of the lung, colon, brain, ovary, breast, prostate, and kidney. The aim is to prioritize for further evaluation, synthetic compounds or natural product samples showing selective growth inhibition or cell killing of particular tumor cell lines. This screen is unique in that the complexity of a 60 cell line dose response produced by a given compound results in a biological response pattern which can be utilized in pattern recognition algorithms. Using these algorithms, it is possible to assign a putative mechanism of action to a test compound, or to determine that the response pattern is unique and not similar to that of any of the standard prototype compounds included in the NCI database (see DTP Overview tab). In addition, following characterization of various cellular molecular targets in the 60 cell lines, it may be possible to select compounds most likely to interact with a specific molecular target.

Methodology Of The In Vitro Cancer Screen

The human tumor cell lines of the cancer screening panel are grown in RPMI 1640 medium containing 5% fetal bovine serum and 2 mM L-glutamine. For a typical screening experiment, cells are inoculated into 96 well microtiter plates in 100 μ L at plating densities ranging from 5,000 to 40,000 cells/well depending on the doubling time of individual cell lines. After cell inoculation, the microtiter plates are incubated at 37° C, 5 % CO₂, 95 % air and 100 % relative humidity for 24 h prior to addition of experimental drugs.

After 24 h, two plates of each cell line are fixed *in situ* with TCA, to represent a measurement of the cell population for each cell line at the time of drug addition (Tz). Experimental drugs are solubilized in dimethyl sulfoxide at 400-fold the desired final maximum test concentration and stored frozen prior to use. At the time of drug addition, an aliquot of frozen concentrate is thawed and diluted to twice the desired final maximum test concentration with complete medium containing 50 µg/ml gentamicin. Additional four, 10-fold or ½ log serial dilutions are made to provide a total of five drug concentrations plus control. Aliquots of 100 µl of these different drug dilutions are added to the appropriate microtiter wells already containing 100 µl of medium, resulting in the required final drug concentrations.

Following drug addition, the plates are incubated for an additional 48 h at 37°C, 5 % CO₂, 95 % air, and 100 % relative humidity. For adherent cells, the assay is terminated by the addition of cold TCA. Cells are fixed *in situ* by the gentle addition of 50 µl of cold 50 % (w/v) TCA (final concentration, 10 % TCA) and incubated for 60 minutes at 4°C. The supernatant is discarded, and the plates are washed five times with tap water and air dried. Sulforhodamine B (SRB) solution (100 µl) at 0.4 % (w/v) in 1 % acetic acid is added to each well, and plates are incubated for 10 minutes at room temperature. After staining, unbound dye is removed by washing five times with 1 % acetic acid and the plates are air dried. Bound stain is subsequently solubilized with 10 mM trizma base, and the absorbance is read on an automated plate reader at a wavelength of 515 nm. For suspension cells, the methodology is the same except that the assay is terminated by fixing settled cells at the bottom of the wells by gently adding 50 µl of 80 % TCA (final concentration, 16 % TCA). Using the seven absorbance measurements [time zero, (Tz), control growth, (C), and test growth in the presence of drug at the five concentration levels (Ti)], the percentage growth is calculated at each of the drug concentrations levels. Percentage growth inhibition is calculated as:

$$[(Ti - Tz)/(C - Tz)] \times 100 \text{ for concentrations for which } Ti \geq Tz$$

$$[(Ti - Tz)/Tz] \times 100 \text{ for concentrations for which } Ti < Tz.$$

Three dose response parameters are calculated for each experimental agent. Growth inhibition of 50 % (GI50) is calculated from $[(Ti - Tz)/(C - Tz)] \times 100 = 50$, which is the drug concentration resulting in a 50% reduction in the net protein increase (as measured by SRB staining) in control cells during the drug incubation. The drug concentration resulting in total growth inhibition (TGI) is calculated from $Ti = Tz$. The LC50 (concentration of drug

resulting in a 50% reduction in the measured protein at the end of the drug treatment as compared to that at the beginning) indicating a net loss of cells following treatment is calculated from $[(Ti-Tz)/Tz] \times 100 = -50$. Values are calculated for each of these three parameters if the level of activity is reached; however, if the effect is not reached or is exceeded, the value for that parameter is expressed as greater or less than the maximum or minimum concentration tested.

Publications

Alley, M.C., Scudiero, D.A., Monks, P.A., Hursey, M. L., Czerwinski, M.J., Fine, D.L., Abbott, B.J., Mayo, J.G., Shoemaker, R.H., and Boyd, M.R. Feasibility of Drug Screening with Panels of Human Tumor Cell Lines Using a Microculture Tetrazolium Assay. *Cancer Research* 48: 589-601, 1988.

Grever, M.R., Schepartz, S.A., and Chabner, B.A. The National Cancer Institute: Cancer Drug Discovery and Development Program. *Seminars in Oncology*, Vol. 19, No. 6, pp 622-638, 1992.

Boyd, M.R., and Paull, K.D. Some Practical Considerations and Applications of the National Cancer Institute In Vitro Anticancer Drug Discovery Screen. *Drug Development Research* 34: 91-109, 1995.

Three Cell Line Prescreen

The three cell line, one-dose prescreen identifies a large proportion of the compounds that would be inactive in multi-dose 60 cell line screening. Computer modeling indicates that approximately 50% of compounds can be eliminated by this prescreen without a significant decrease in the ability to identify active agents, while increasing the throughput and efficiency of the main cancer screen with limited loss of information. The current assay utilizes a 384 well plate format and fluorescent staining technologies resulting in greater screening capacity for testing of synthetic samples.

Cell Lines

The cell lines are grown in the same manner as for the 60 cell line screen (see above). The cells are plated a densities of 5000 cells/well (MCF7), 1000 cells/well (NCI-H460), and 7500

cells/well (SF-268) to allow for varying doubling time of the cell lines. Each plate contains all three cell lines, a series of dilutions of standard agents, total kill wells and appropriate controls. Plates are incubated under standard conditions for 24 hours prior to addition of experimental compounds or extracts.

Addition of Experimental Agents (Pure Compounds)

Experimental compounds are solubilized in dimethyl sulfoxide (DMSO) at 400-times the desired maximum test concentration (maximum final DMSO concentration of 0.25%) and stored frozen. Compounds are then diluted with complete media with 0.1% gentamicin sulfate (5 μ l of test sample in 100% DMSO is added to 565 μ l of complete medium). 20 μ l of this solution is then dispensed into test wells containing 50 μ l of cell suspension to yield a test concentration of 1.00E-04M.

Two standard drugs, meaning that their activities against the cell lines are well documented, are tested against each cell line: NSC 19893 (5-FU) and NSC 123127 (Adriamycin).

Endpoint Measurement

After compound addition, plates are incubated at standard conditions for 48 hours, 10 μ l/well Alamar Blue is added and the plates are incubated for an additional 4 hours. Fluorescence is measured using an excitation wavelength of 530 nm and an emission wavelength of 590 nm.

Calculation of Percent Test Cell Growth/Control (untreated) Cell Growth (T/C)

Percent growth is calculated on a plate-by-plate basis for test wells relative to control wells. Percent Growth is expressed as the ratio of fluorescence of the test well to the average fluorescence of the control wells * 100.

Criteria for Activity

Compounds which inhibit the growth of any of the 3 cell lines to 32% or less than control growth are automatically forwarded for testing in the 60 cell line assay. To validate the selection of 32% as the cutoff point for activity, 208 compounds that produced T/Cs of 32% to 50% in any one cell line in the 3 cell line assay were forwarded to the 60 cell line assay. Of those 208, 17% were considered sufficiently active to warrant a confirmatory 60 cell line experiment. Six percent of the 208 demonstrated confirmed activity upon retest in the 60 cell

line screen and were reviewed for possible in vivo testing. Less than 1% of the original 208 were actually selected for follow-up in vivo hollow fiber testing.

Modifications to Screen for Natural Product Extracts

Cell Lines

Cells are harvested as above and plated onto a 96-Well flat-bottom, polystyrene plate in 180 μ l standard RPMI -1640 media, at densities of 10,000 cells/well (MCF7), 7500 cells/well (NCI-H460), and 15,000 cells/well (SF-268). Each cell line is plated on duplicate plates: one time-zero plate, and one drug background plate is made with media only added.

Addition of Extracts

Extracts are prepared in DMSO at 400-times the desired maximum test concentration and stored frozen. Extracts are diluted in complete media with 0.1% Gentamicin sulfate and dispensed into wells in a volume of 20 μ l to yield a test concentration of 100 μ g/ml. NSC 123127 (Adriamycin) is used as the standard and is included on each plate.

Endpoint Measurement

Cells are fixed in situ by the addition of cold TCA (final concentration 10 % TCA) and incubated for 60 minutes at 4°C. The supernatant is discarded, plates washed five times with tap water and air-dried. SRB at a 0.4 % (w/v) in 1 % acetic acid is added to each well and the plates are incubated for 10 minutes at room temperature. Unbound dye is removed by washing six times with 1 % acetic acid and the plates are air-dried. Bound SRB is solubilized with 10mM trizma base and the absorbance is measured at a wavelength of 515 nm.

Calculation of Percent T/C

Percent growth is calculated from six control wells, time zero wells and one test well for each cell line. % Growth is calculated by the same method used in the 60- cell line primary screen.

<u>Cell Line</u>	<u>Tumor Type</u>
MCF7	Breast

NCI-H460	Lung
SF-268	CNS

Cell Lines In The Screen (http://dtp.nci.nih.gov/docs/misc/common_files/cell_list.html)

Cell Lines In The *In Vitro* Screen

Note: This is a list of the 60 human cancer cell lines used in the screen and maintained at NCI-Frederick. Additional lines evaluated for use in the screen and currently available are listed separately at the bottom of the page.

Cell Line Name	Panel Name	Doubling Time	Inoculation Density
CCRF-CEM	Leukemia	26.7	40000
HL-60(TB)	Leukemia	28.6	40000
K-562	Leukemia	19.6	5000
MOLT-4	Leukemia	27.9	30000
RPMI-8226	Leukemia	33.5	20000
SR	Leukemia	28.7	20000
A549/ATCC	Non-Small Cell Lung	22.9	7500
EKVX	Non-Small Cell Lung	43.6	20000
HOP-62	Non-Small Cell Lung	39	10000
HOP-92	Non-Small Cell Lung	79.5	20000
NCI-H226	Non-Small Cell Lung	61	20000
NCI-H23	Non-Small Cell Lung	33.4	20000
NCI-H322M	Non-Small Cell Lung	35.3	20000
NCI-H460	Non-Small Cell Lung	17.8	7500
NCI-H522	Non-Small Cell Lung	38.2	20000
COLO 205	Colon	23.8	15000

HCC-2998	Colon	31.5	15000
HCT-116	Colon	17.4	5000
HCT-15	Colon	20.6	10000
HT29	Colon	19.5	5000
KM12	Colon	23.7	15000
SW-620	Colon	20.4	10000
SF-268	CNS	33.1	15000
SF-295	CNS	29.5	10000
SF-539	CNS	35.4	15000
SNB-19	CNS	34.6	15000
SNB-75	CNS	62.8	20000
U251	CNS	23.8	7500
LOX IMVI	Melanoma	20.5	7500
MALME-3M	Melanoma	46.2	20000
M14	Melanoma	26.3	15000
SK-MEL-2	Melanoma	45.5	20000
SK-MEL-28	Melanoma	35.1	10000
SK-MEL-5	Melanoma	25.2	10000
UACC-257	Melanoma	38.5	20000
UACC-62	Melanoma	31.3	10000
IGR-OV1 Restricted Use	Ovarian	31	10000
OVCAR-3	Ovarian	34.7	10000
OVCAR-4	Ovarian	41.4	15000
OVCAR-5	Ovarian	48.8	20000
OVCAR-8	Ovarian	26.1	10000

SK-OV-3	Ovarian	48.7	20000
786-0	Renal	22.4	10000
A498	Renal	66.8	25000
ACHN	Renal	27.5	10000
CAKI-1	Renal	39	10000
RXF 393 Restricted Use	Renal	62.9	15000
SN12C	Renal	29.5	15000
TK-10 Restricted Use	Renal	51.3	15000
UO-31	Renal	41.7	15000
PC-3	Prostate	27.1	7500
DU-145	Prostate	32.3	10000
MCF7	Breast	25.4	10000
NCI/ADR-RES	Breast	34	15000
MDA-MB-231/ATCC	Breast	41.9	20000
HS 578T	Breast	53.8	20000
MDA-MB-435	Breast (For more information)	25.8	15000
MDA-N Not Available	Breast	22.5	15000
BT-549	Breast	53.9	20000
T-47D Restricted Use	Breast	45.5	20000

Additional Lines

Cell Line Name	Panel Name	Doubling Time	Inoculation Density
LXFL 529	Non-Small Cell Lung		10000

Restricted Use			
DMS 114	Small Cell Lung		20000
SHP-77	Small Cell Lung		40000
DLD-1	Colon		50000
KM20L2	Colon		10000
SNB-78	CNS		20000
XF 498	CNS		20000
Restricted Use			
RPMT-7951	Melanoma		20000
M19-MEL	Melanoma		10000
RXF-631	Renal		10000
Restricted Use			
SN12K1	Renal		10000
MDA-MB-468	Breast		20000
P388	Leukemia		50000
P388/ADR	Leukemia		50000

Standard AntiCancer Agent Database

The list of compounds designated standard agents was originally determined by Boyd (2). He chose 175 drugs with cancer treatment New Drug Applications or Investigational New Drug Applications as well as compounds that had reached a particular high stage of interest at the NCI in recent years for the list. A database, which will be referred to as the standard agent database, was created by averaging the results of multiple tests with each of 171 of these agents. NSC numbers and common names for the standard agents are provided in the table below.

Compound	NSC Number	2D Structure	3D Structure	Full Information
methotrexate	740	<u>2D</u>	<u>3D</u>	<u>Full</u>

busulfan	750	<u>2D</u>	<u>3D</u>	<u>Full</u>
thioguanine	752	<u>2D</u>	<u>3D</u>	<u>Full</u>
6-mercaptopurine	755	<u>2D</u>	<u>3D</u>	<u>Full</u>
nitrogen mustard	762	<u>2D</u>	<u>3D</u>	<u>Full</u>
guanazole	1895	<u>2D</u>	<u>3D</u>	<u>Full</u>
R-methylformamide	3051	<u>2D</u>	<u>3D</u>	<u>Full</u>
actinomycin D	3053	<u>2D</u>	<u>3D</u>	<u>Full</u>
chlorambucil	3088	<u>2D</u>	<u>3D</u>	<u>Full</u>
thiadiazole	4728	<u>2D</u>	<u>3D</u>	<u>Full</u>
thio-tepa	6396	<u>2D</u>	<u>3D</u>	<u>Full</u>
DON	7365	<u>2D</u>	<u>3D</u>	<u>Full</u>
melphalan	8806	<u>2D</u>	<u>3D</u>	<u>Full</u>
triethylenemelamine	9706	<u>2D</u>	<u>3D</u>	<u>Full</u>
hexamethylenemelamine	13875	<u>2D</u>	<u>3D</u>	<u>Full</u>
gallium nitrate	15200	<u>2D</u>	<u>3D</u>	<u>Full</u>
5-fluorouracil	19893	<u>2D</u>	<u>3D</u>	<u>Full</u>
thymidine	21548	<u>2D</u>	<u>3D</u>	<u>Full</u>
delta-1-testololactone	23759	<u>2D</u>	<u>3D</u>	<u>Full</u>
mitramycin	24559	<u>2D</u>	<u>3D</u>	<u>Full</u>
pipobroman	25154	<u>2D</u>	<u>3D</u>	<u>Full</u>
cyclophosphamide	26271	<u>2D</u>	<u>3D</u>	<u>Full</u>
mitomycin C	26980	<u>2D</u>	<u>3D</u>	<u>Full</u>
5-FUDR	27640	<u>2D</u>	<u>3D</u>	<u>Full</u>
hydroxyurea	32065	<u>2D</u>	<u>3D</u>	<u>Full</u>

methyl-GAG	32946	<u>2D</u>	<u>3D</u>	<u>Full</u>
uracil nitrogen mustard	34462	<u>2D</u>	<u>3D</u>	<u>Full</u>
O6-methylguanine	37364	<u>2D</u>	<u>3D</u>	<u>Full</u>
<i>o,p'</i> -DDD	38721	<u>2D</u>	<u>3D</u>	<u>Full</u>
DTIC	45388	<u>2D</u>	<u>3D</u>	<u>Full</u>
vinblastine sulfate	49842	<u>2D</u>	<u>3D</u>	<u>Full</u>
IMPY	51143	<u>2D</u>	<u>3D</u>	<u>Full</u>
porfiromycin	56410	<u>2D</u>	<u>3D</u>	<u>Full</u>
chromomycin A3	58514	<u>2D</u>	<u>3D</u>	<u>Full</u>
cytosine arabinoside	63878	<u>2D</u>	<u>3D</u>	<u>Full</u>
vincristine sulfate	67574	<u>2D</u>	<u>3D</u>	<u>Full</u>
thalicarpine	68075	<u>2D</u>	<u>3D</u>	<u>Full</u>
B-TGDR	71261	<u>2D</u>	<u>3D</u>	<u>Full</u>
A-TGDR	71851	<u>2D</u>	<u>3D</u>	<u>Full</u>
fluorodopan	73754	<u>2D</u>	<u>3D</u>	<u>Full</u>
D-tetrandrine	77037	<u>2D</u>	<u>3D</u>	<u>Full</u>
procarbazine	77213	<u>2D</u>	<u>3D</u>	<u>Full</u>
CCNU	79037	<u>2D</u>	<u>3D</u>	<u>Full</u>
daunorubicin (daunomycin)	82151	<u>2D</u>	<u>3D</u>	<u>Full</u>
S-trityl-L-cysteine	83265	<u>2D</u>	<u>3D</u>	<u>Full</u>
streptozotacin	85998	<u>2D</u>	<u>3D</u>	<u>Full</u>
methyl-CCNU	95441	<u>2D</u>	<u>3D</u>	<u>Full</u>
PCNU	95466	<u>2D</u>	<u>3D</u>	<u>Full</u>
hexamethylenebisacetamide	95580	<u>2D</u>	<u>3D</u>	<u>Full</u>

3HP	95678	<u>2D</u>	<u>3D</u>	<u>Full</u>
Yoshi-864	102627	<u>2D</u>	<u>3D</u>	<u>Full</u>
5-azacytidine	102816	<u>2D</u>	<u>3D</u>	<u>Full</u>
cytembena	104801	<u>2D</u>	<u>3D</u>	<u>Full</u>
5HP	107392	<u>2D</u>	<u>3D</u>	<u>Full</u>
L-asparaginase	109229	<u>2D</u>	<u>3D</u>	<u>Full</u>
iphosphamide	109724	<u>2D</u>	<u>3D</u>	<u>Full</u>
pentamethylmelamine	118742	<u>2D</u>	<u>3D</u>	<u>Full</u>
diglycoaldehyde	118994	<u>2D</u>	<u>3D</u>	<u>Full</u>
cisplatin	119875	<u>2D</u>	<u>3D</u>	<u>Full</u>
VM-26 (teniposide)	122819	<u>2D</u>	<u>3D</u>	<u>Full</u>
doxorubicin (Adriamycin)	123127	<u>2D</u>	<u>3D</u>	<u>Full</u>
bleomycin	125066	<u>2D</u>	<u>3D</u>	<u>Full</u>
paclitaxel (Taxol)	125973	<u>2D</u>	<u>3D</u>	<u>Full</u>
dichloroallyl lawsone	126771	<u>2D</u>	<u>3D</u>	<u>Full</u>
3-deazauridine	126849	<u>2D</u>	<u>3D</u>	<u>Full</u>
5-azadeoxycytidine	127716	<u>2D</u>	<u>3D</u>	<u>Full</u>
triazinate	127755	<u>2D</u>	<u>3D</u>	<u>Full</u>
ICRF-159	129943	<u>2D</u>	<u>3D</u>	<u>Full</u>
dianhydrogalatitol	132313	<u>2D</u>	<u>3D</u>	<u>Full</u>
indicine N-oxide	132319	<u>2D</u>	<u>3D</u>	<u>Full</u>
rifamycin SV	133100	<u>2D</u>	<u>3D</u>	<u>Full</u>
piperazinedione	135758	<u>2D</u>	<u>3D</u>	<u>Full</u>
soluble Baker's Antifol	139105	<u>2D</u>	<u>3D</u>	<u>Full</u>

emofolin sodium	139490	<u>2D</u>	<u>3D</u>	<u>Full</u>
anguidine	141537	<u>2D</u>	<u>3D</u>	<u>Full</u>
VP-16 (etoposide)	141540	<u>2D</u>	<u>3D</u>	<u>Full</u>
homoharringtonine	141633	<u>2D</u>	<u>3D</u>	<u>Full</u>
hycanthone	142982	<u>2D</u>	<u>3D</u>	<u>Full</u>
pyrazofurin	143095	<u>2D</u>	<u>3D</u>	<u>Full</u>
cyclocytidine	145668	<u>2D</u>	<u>3D</u>	<u>Full</u>
ftorafur	148958	<u>2D</u>	<u>3D</u>	<u>Full</u>
hydrazine sulfate	150014	<u>2D</u>	<u>3D</u>	<u>Full</u>
L-alanosine	153353	<u>2D</u>	<u>3D</u>	<u>Full</u>
maytansine	153858	<u>2D</u>	<u>3D</u>	<u>Full</u>
neocarzinostatin	157365	<u>2D</u>	<u>3D</u>	<u>Full</u>
AT-125 (acivicin)	163501	<u>2D</u>	<u>3D</u>	<u>Full</u>
rubidazone	164011	<u>2D</u>	<u>3D</u>	<u>Full</u>
bruceantin	165563	<u>2D</u>	<u>3D</u>	<u>Full</u>
asaley	167780	<u>2D</u>	<u>3D</u>	<u>Full</u>
ICRF-187	169780	<u>2D</u>	<u>3D</u>	<u>Full</u>
spirohydantoin mustard	172112	<u>2D</u>	<u>3D</u>	<u>Full</u>
chlorozotocin	178248	<u>2D</u>	<u>3D</u>	<u>Full</u>
tamoxifen	180973	<u>2D</u>	<u>3D</u>	<u>Full</u>
AZQ	182986	<u>2D</u>	<u>3D</u>	<u>Full</u>
spirogermanium	192965	<u>2D</u>	<u>3D</u>	<u>Full</u>
aclacinomycin A	208734	<u>2D</u>	<u>3D</u>	<u>Full</u>
2'-deoxycoformycin	218321	<u>2D</u>	<u>3D</u>	<u>Full</u>

PALA	224131	<u>2D</u>	<u>3D</u>	<u>Full</u>
rapamycin	226080	<u>2D</u>	<u>3D</u>	<u>Full</u>
largomycin	237020	<u>2D</u>	<u>3D</u>	<u>Full</u>
CBDCA (carboplatin)	241240	<u>2D</u>	<u>3D</u>	<u>Full</u>
m-AMSA (amsacrine)	249992	<u>2D</u>	<u>3D</u>	<u>Full</u>
caracemide	253272	<u>2D</u>	<u>3D</u>	<u>Full</u>
CHIP	256927	<u>2D</u>	<u>3D</u>	<u>Full</u>
3-deazaguanine	261726	<u>2D</u>	<u>3D</u>	<u>Full</u>
dihydro-5-azacytidine	264880	<u>2D</u>	<u>3D</u>	<u>Full</u>
glyoxalic acid	267213	<u>2D</u>	<u>3D</u>	<u>Full</u>
deoxydoxorubicin	267469	<u>2D</u>	<u>3D</u>	<u>Full</u>
N,N-dibenzyl daunomycin	268242	<u>2D</u>	<u>3D</u>	<u>Full</u>
menogaril	269148	<u>2D</u>	<u>3D</u>	<u>Full</u>
(carboxyphthalato)platinum	271674	<u>2D</u>	<u>3D</u>	<u>Full</u>
pyrrolizine dicarbamate	278214	<u>2D</u>	<u>3D</u>	<u>Full</u>
tricitabine phosphate	280594	<u>2D</u>	<u>3D</u>	<u>Full</u>
ARA AC	281272	<u>2D</u>	<u>3D</u>	<u>Full</u>
trimethyltrimethylolmelamine	283162	<u>2D</u>	<u>3D</u>	<u>Full</u>
mitindomide	284356	<u>2D</u>	<u>3D</u>	<u>Full</u>
8Cl-cyc-AMP	284751	<u>2D</u>	<u>3D</u>	<u>Full</u>
tiazofurin	286193	<u>2D</u>	<u>3D</u>	<u>Full</u>
pyrimidine-5-glycodialdehyde	291643	<u>2D</u>	<u>3D</u>	<u>Full</u>
flavoneacetic acid ester	293015	<u>2D</u>	<u>3D</u>	<u>Full</u>
teroxirone	296934	<u>2D</u>	<u>3D</u>	<u>Full</u>

DHAD (mitoxantrone)	301739	<u>2D</u>	<u>3D</u>	<u>Full</u>
aphidicolin glycinate	303812	<u>2D</u>	<u>3D</u>	<u>Full</u>
L-cysteine analogue	303861	<u>2D</u>	<u>3D</u>	<u>Full</u>
acodazole hydrochloride	305884	<u>2D</u>	<u>3D</u>	<u>Full</u>
amonafide	308847	<u>2D</u>	<u>3D</u>	<u>Full</u>
fludarabine phosphate	312887	<u>2D</u>	<u>3D</u>	<u>Full</u>
SR2555 (nitroimidazole)	314055	<u>2D</u>	<u>3D</u>	<u>Full</u>
batracylin	320846	<u>2D</u>	<u>3D</u>	<u>Full</u>
nitroestrone	321803	<u>2D</u>	<u>3D</u>	<u>Full</u>
pibenzimol hydrochloride	322921	<u>2D</u>	<u>3D</u>	<u>Full</u>
bactobolin	325014	<u>2D</u>	<u>3D</u>	<u>Full</u>
didemnin B	325319	<u>2D</u>	<u>3D</u>	<u>Full</u>
L-buthionine sulfoximine	326231	<u>2D</u>	<u>3D</u>	<u>Full</u>
phyllanthoside	328426	<u>2D</u>	<u>3D</u>	<u>Full</u>
hepsulfam	329680	<u>2D</u>	<u>3D</u>	<u>Full</u>
macbecin II	330500	<u>2D</u>	<u>3D</u>	<u>Full</u>
rhizoxin	332598	<u>2D</u>	<u>3D</u>	<u>Full</u>
tetrocarcin A sodium salt	333856	<u>2D</u>	<u>3D</u>	<u>Full</u>
merbarone	336628	<u>2D</u>	<u>3D</u>	<u>Full</u>
bisantrene hydrochloride	337766	<u>2D</u>	<u>3D</u>	<u>Full</u>
penclomedine	338720	<u>2D</u>	<u>3D</u>	<u>Full</u>
clomesone	338947	<u>2D</u>	<u>3D</u>	<u>Full</u>
chloroquinoxaline sulfonamide	339004	<u>2D</u>	<u>3D</u>	<u>Full</u>
bryostatin 1	339555	<u>2D</u>	<u>3D</u>	<u>Full</u>

fostriecin	339638	<u>2D</u>	<u>3D</u>	<u>Full</u>
dihydrolenperone	343513	<u>2D</u>	<u>3D</u>	<u>Full</u>
piperazine alkylator	344007	<u>2D</u>	<u>3D</u>	<u>Full</u>
flavoneacetic acid	347512	<u>2D</u>	<u>3D</u>	<u>Full</u>
cyclodisone	348948	<u>2D</u>	<u>3D</u>	<u>Full</u>
pancratiastatin	349156	<u>2D</u>	<u>3D</u>	<u>Full</u>
oxanthrazole	349174	<u>2D</u>	<u>3D</u>	<u>Full</u>
4-ipomeanol	349438	<u>2D</u>	<u>3D</u>	<u>Full</u>
trimetrexate	352122	<u>2D</u>	<u>3D</u>	<u>Full</u>
mitozolamide	353451	<u>2D</u>	<u>3D</u>	<u>Full</u>
morpholino-ADR	354646	<u>2D</u>	<u>3D</u>	<u>Full</u>
anthrapyrazole	355644	<u>2D</u>	<u>3D</u>	<u>Full</u>
deoxyspergualin	356894	<u>2D</u>	<u>3D</u>	<u>Full</u>
cyanomorpholino-ADR	357704	<u>2D</u>	<u>3D</u>	<u>Full</u>
pyrazine diazohydroxide	361456	<u>2D</u>	<u>3D</u>	<u>Full</u>
tetraplatin	363812	<u>2D</u>	<u>3D</u>	<u>Full</u>
pyrazoloacridine	366140	<u>2D</u>	<u>3D</u>	<u>Full</u>
bispyridocarbazolium DMS	366241	<u>2D</u>	<u>3D</u>	<u>Full</u>
DUP785 (brequinar)	368390	<u>2D</u>	<u>3D</u>	<u>Full</u>
cyclopentenylcytosine	375575	<u>2D</u>	<u>3D</u>	<u>Full</u>
ARA-6-MP	406021	<u>2D</u>	<u>3D</u>	<u>Full</u>
BCNU	409962	<u>2D</u>	<u>3D</u>	<u>Full</u>
echinomycin	526417	<u>2D</u>	<u>3D</u>	<u>Full</u>
carmethizole	602668	<u>2D</u>	<u>3D</u>	<u>Full</u>

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topotecan	609699	<u>2D</u>	<u>3D</u>	<u>Full</u>
MX2 HCl	619003	<u>2D</u>	<u>3D</u>	<u>Full</u>

- **AntiCancer Agent Mechanism Database**

Description

The Anti-cancer Agent Mechanism Database is a set of 122 compounds with anti-cancer activity and reasonably well known mechanism of action. The list of compounds was assembled as a training set for neural network analysis of drug mechanism of action (Weinstein, et. al. *Science* **258**:447, 1992; van Osdol, et. al, *J Natl Cancer Inst* **86**:1853, 1994). It was based on the Standard Anti-cancer Agent Database described above.

Preliminary Set Up

This page makes use of Chemical MIME types to serve some information. In order to take advantage of Chemical MIME types, your browser needs to have several helper programs installed. For information on where to get these helper programs and how to install them refer to the browser setup page.

3D Database Build

Building of the 3D database followed generally the procedure already described. The main difference is that this database was small enough to allow each structure to be checked for proper stereochemistry and then each structure was geometry optimized using a molecular mechanics energy calculation. There were no conformational searches performed, so the given conformation is not necessarily a global minimum, nor is it necessarily the conformation responsible for activity. The 3D coordinates are available in the MDL SDfile format.

In Vitro Cancer Screening Results

The NCI has a drug screen that measures ability to inhibit growth of a panel of 60 human tumor lines (Monks, et. al., *J. Natl. Cancer Inst.* **83**:757, 1990). The mean graph display

format used here is described in Paull, et. al. *J. Natl. Cancer Inst.* 81:1088, 1989. A single file with the screening results is available.

Anti-cancer Agents

Compounds grouped by mechanism of action.

- Alkylating Agents

<u>Asaley</u>	NSC 167780
<u>AZQ</u>	NSC 182986
<u>BCNU</u>	NSC 409962
<u>Busulfan</u>	NSC 750
<u>carboxyphthalatoplatinum</u>	NSC 271674
<u>CBDCA</u>	NSC 241240
<u>CCNU</u>	NSC 79037
<u>CHIP</u>	NSC 256927
<u>chlorambucil</u>	NSC 3088
<u>chlorozotocin</u>	NSC 178248
<u>cis-platinum</u>	NSC 119875
<u>clomesone</u>	NSC 338947
<u>cyanomorpholinodoxorubicin</u>	NSC 357704
<u>cyclodisone</u>	NSC 348948
<u>dianhydrogalactitol</u>	NSC 132313
<u>fluorodopan</u>	NSC 73754
<u>hepsulfam</u>	NSC 329680
<u>hycanthone</u>	NSC 142982
<u>melphalan</u>	NSC 8806
<u>methyl CCNU</u>	NSC 95441
<u>mitomycin C</u>	NSC 26980

11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100 101 102 103 104 105 106 107 108 109 110 111 112 113 114 115 116 117 118 119 120 121 122 123 124 125 126 127 128 129 130 131 132 133 134 135 136 137 138 139 140 141 142 143 144 145 146 147 148 149 150 151 152 153 154 155 156 157 158 159 160 161 162 163 164 165 166 167 168 169 170 171 172 173 174 175 176 177 178 179 180 181 182 183 184 185 186 187 188 189 190 191 192 193 194 195 196 197 198 199 200 201 202 203 204 205 206 207 208 209 210 211 212 213 214 215 216 217 218 219 220 221 222 223 224 225 226 227 228 229 230 231 232 233 234 235 236 237 238 239 240 241 242 243 244 245 246 247 248 249 250 251 252 253 254 255 256 257 258 259 260 261 262 263 264 265 266 267 268 269 270 271 272 273 274 275 276 277 278 279 280 281 282 283 284 285 286 287 288 289 290 291 292 293 294 295 296 297 298 299 300 301 302 303 304 305 306 307 308 309 310 311 312 313 314 315 316 317 318 319 320 321 322 323 324 325 326 327 328 329 330 331 332 333 334 335 336 337 338 339 340 341 342 343 344 345 346 347 348 349 350 351 352 353 354 355 356 357 358 359 360 361 362 363 364 365 366 367 368 369 370 371 372 373 374 375 376 377 378 379 380 381 382 383 384 385 386 387 388 389 390 391 392 393 394 395 396 397 398 399 400 401 402 403 404 405 406 407 408 409 410 411 412 413 414 415 416 417 418 419 420 421 422 423 424 425 426 427 428 429 430 431 432 433 434 435 436 437 438 439 440 441 442 443 444 445 446 447 448 449 450 451 452 453 454 455 456 457 458 459 460 461 462 463 464 465 466 467 468 469 470 471 472 473 474 475 476 477 478 479 480 481 482 483 484 485 486 487 488 489 490 491 492 493 494 495 496 497 498 499 500 501 502 503 504 505 506 507 508 509 510 511 512 513 514 515 516 517 518 519 520 521 522 523 524 525 526 527 528 529 530 531 532 533 534 535 536 537 538 539 540 541 542 543 544 545 546 547 548 549 550 551 552 553 554 555 556 557 558 559 560 561 562 563 564 565 566 567 568 569 570 571 572 573 574 575 576 577 578 579 580 581 582 583 584 585 586 587 588 589 590 591 592 593 594 595 596 597 598 599 600 601 602 603 604 605 606 607 608 609 610 611 612 613 614 615 616 617 618 619 620 621 622 623 624 625 626 627 628 629 630 631 632 633 634 635 636 637 638 639 640 641 642 643 644 645 646 647 648 649 650 651 652 653 654 655 656 657 658 659 660 661 662 663 664 665 666 667 668 669 670 671 672 673 674 675 676 677 678 679 680 681 682 683 684 685 686 687 688 689 690 691 692 693 694 695 696 697 698 699 700 701 702 703 704 705 706 707 708 709 710 711 712 713 714 715 716 717 718 719 720 721 722 723 724 725 726 727 728 729 730 731 732 733 734 735 736 737 738 739 740 741 742 743 744 745 746 747 748 749 750 751 752 753 754 755 756 757 758 759 760 761 762 763 764 765 766 767 768 769 770 771 772 773 774 775 776 777 778 779 780 781 782 783 784 785 786 787 788 789 790 791 792 793 794 795 796 797 798 799 800 801 802 803 804 805 806 807 808 809 810 811 812 813 814 815 816 817 818 819 820 821 822 823 824 825 826 827 828 829 830 831 832 833 834 835 836 837 838 839 840 841 842 843 844 845 846 847 848 849 850 851 852 853 854 855 856 857 858 859 860 861 862 863 864 865 866 867 868 869 870 871 872 873 874 875 876 877 878 879 880 881 882 883 884 885 886 887 888 889 890 891 892 893 894 895 896 897 898 899 900 901 902 903 904 905 906 907 908 909 910 911 912 913 914 915 916 917 918 919 920 921 922 923 924 925 926 927 928 929 930 931 932 933 934 935 936 937 938 939 940 941 942 943 944 945 946 947 948 949 950 951 952 953 954 955 956 957 958 959 960 961 962 963 964 965 966 967 968 969 970 971 972 973 974 975 976 977 978 979 980 981 982 983 984 985 986 987 988 989 990 991 992 993 994 995 996 997 998 999 1000

<u>mitozolamide</u>	NSC 353451
<u>nitrogen mustard</u>	NSC 762
<u>PCNU</u>	NSC 95466
<u>piperazine ../drugs/mainator</u>	NSC 344007
<u>piperazinedione</u>	NSC 135758
<u>pipobroman</u>	NSC 25154
<u>porfiromycin</u>	NSC 56410
<u>spirohydantoin mustard</u>	NSC 172112
<u>teroxirone</u>	NSC 296934
<u>tetraplatin</u>	NSC 363812
<u>thio-tepa</u>	NSC 6396
<u>triethylenemelamine</u>	NSC 9706
<u>uracil nitrogen mustard</u>	NSC 34462
<u>Yoshi-864</u>	NSC 102627

- Topoisomerase I inhibitors

<u>camptothecin</u>	NSC 94600
<u>camptothecin, Na salt</u>	NSC 100880
<u>aminocamptothecin</u>	NSC 603071
<u>camptothecin derivative</u>	NSC 95382
<u>camptothecin derivative</u>	NSC 107124
<u>camptothecin derivative</u>	NSC 643833
<u>camptothecin derivative</u>	NSC 629971
<u>camptothecin derivative</u>	NSC 295500
<u>camptothecin derivative</u>	NSC 249910
<u>camptothecin derivative</u>	NSC 606985
<u>camptothecin derivative</u>	NSC 374028

camptothecin derivative	NSC 176323
camptothecin derivative	NSC 295501
camptothecin derivative	NSC 606172
camptothecin derivative	NSC 606173
camptothecin derivative	NSC 610458
camptothecin derivative	NSC 618939
camptothecin derivative	NSC 610457
camptothecin derivative	NSC 610459
camptothecin derivative	NSC 606499
camptothecin derivative	NSC 610456
camptothecin derivative	NSC 364830
camptothecin derivative	NSC 606497
morpholinodoxorubicin	NSC 354646

- Topoisomerase II inhibitors

doxorubicin	NSC 123127
amonafide	NSC 308847
m-AMSA	NSC 249992
anthrapyrazole derivative	NSC 355644
pyrazoloacridine	NSC 366140
bisantrone HCL	NSC 337766
daunorubicin	NSC 82151
deoxydoxorubicin	NSC 267469
mitoxantrone	NSC 301739
menogaril	NSC 269148
N,N-dibenzyl daunomycin	NSC 268242
oxanthrazole	NSC 349174

<u>rubidazone</u>	NSC 164011
<u>VM-26</u>	NSC 122819
<u>VP-16</u>	NSC 141540

- RNA/DNA antimetabolites

<u>L-alanosine</u>	NSC 153353
<u>5-azacytidine</u>	NSC 102816
<u>5-fluorouracil</u>	NSC 19893
<u>acivicin</u>	NSC 163501
<u>aminopterin derivative</u>	NSC 132483
<u>aminopterin derivative</u>	NSC 184692
<u>aminopterin derivative</u>	NSC 134033
<u>an antifol</u>	NSC 633713
<u>an antifol</u>	NSC 623017
<u>Baker's soluble antifol</u>	NSC 139105
<u>dichlorallyl lawsone</u>	NSC 126771
<u>brequinar</u>	NSC 368390
<u>ftorafur (pro-drug)</u>	NSC 148958
<u>5,6-dihydro-5-azacytidine</u>	NSC 264880
<u>methotrexate</u>	NSC 740
<u>methotrexate derivative</u>	NSC 174121
<u>N-(phosphonoacetyl)-L-aspartate (PALA)</u>	NSC 224131
<u>pyrazofurin</u>	NSC 143095
<u>trimetrexate</u>	NSC 352122

- DNA antimetabolites

<u>3-HP</u>	NSC 95678
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15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100 105 110 115 120 125 130 135 140 145 150 155 160 165 170 175 180 185 190 195 200 205 210 215 220 225 230 235 240 245 250 255 260 265 270 275 280 285 290 295 300 305 310 315 320 325 330 335 340 345 350 355 360 365 370 375 380 385 390 395 400 405 410 415 420 425 430 435 440 445 450 455 460 465 470 475 480 485 490 495 500 505 510 515 520 525 530 535 540 545 550 555 560 565 570 575 580 585 590 595 600 605 610 615 620 625 630 635 640 645 650 655 660 665 670 675 680 685 690 695 700 705 710 715 720 725 730 735 740 745 750 755 760 765 770 775 780 785 790 795 800 805 810 815 820 825 830 835 840 845 850 855 860 865 870 875 880 885 890 895 900 905 910 915 920 925 930 935 940 945 950 955 960 965 970 975 980 985 990 995

<u>2'-deoxy-5-fluorouridine</u>	NSC 27640
<u>5-HP</u>	NSC 107392
<u>alpha-TGDR</u>	NSC 71851
<u>aphidicolin glycinate</u>	NSC 303812
<u>ara-C</u>	NSC 63878
<u>5-aza-2'-deoxycytidine</u>	NSC 127716
<u>beta-TGDR</u>	NSC 71261
<u>cyclocytidine</u>	NSC 145668
<u>guanazole</u>	NSC 1895
<u>hydroxyurea</u>	NSC 32065
<u>inosine glycodialdehyde</u>	NSC 118994
<u>macbecin II</u>	NSC 330500
<u>pyrazoloimidazole</u>	NSC 51143
<u>thioguanine</u>	NSC 752
<u>thiopurine</u>	NSC 755

- Antimitotic Agents

<u>allicolchicine</u>	NSC 406042
<u>Halichondrin B</u>	NSC 609395
<u>colchicine</u>	NSC 757
<u>colchicine derivative</u>	NSC 33410
<u>dolastatin 10</u>	NSC 376128
<u>maytansine</u>	NSC 153858
<u>rhizoxin</u>	NSC 332598
<u>taxol</u>	NSC 125973
<u>taxol derivative</u>	NSC 608832
<u>thiocolchicine</u>	NSC 361792

<u>trityl cysteine</u>	NSC 83265
<u>vinblastine sulfate</u>	NSC 49842
<u>vincristine sulfate</u>	NSC 67574