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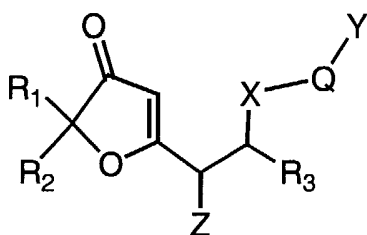
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(54) Title: 5-SUBSTITUTED-3(2H)-FURANONES USEFUL FOR INHIBITION OF FARNESYL-PROTEIN TRANSFERASE



(I)

(57) Abstract: Compounds of Formula (I): wherein R₁, R₂, R₃, X, Y, Z and Q are as defined in the specification which compounds are inhibitors of Ras farnesyl-protein transferase enzyme (FPTase), and useful in treating *ras* onco-gene-dependent tumors, such as cancers of the pancreas, colon, bladder, and thyroid, together with processes for the preparation of such compounds.

5-SUBSTITUTED-3(2H)-FURANONES USEFUL FOR INHIBITION OF FARNESYL- PROTEIN TRANSFERASE

Field of the Invention

The present invention relates to a novel series of 5-substituted-3(2H)-furanones, to pharmaceutical compositions containing them, to their use in cancer therapy and to processes for their preparation. The compounds inhibit *Ras* FPTase, and may be used as an alternative to, or in conjunction with, traditional cancer therapy for treating *ras* oncogene-dependent tumors, such as cancers of the pancreas, colon, bladder, and thyroid. Compounds in the invention may also be useful for controlling metastasis, suppressing angiogenesis, inducing apoptosis, and in treating Ras-associated proliferative diseases other than cancer, such as restenosis, neuro-fibromatosis, endometriosis, and psoriasis. These compounds may also inhibit prenylation of proteins other than Ras, and thus be effective in the treatment of diseases associated with other prenyl modifications of proteins.

BACKGROUND OF THE INVENTION

Mammalian H-, K-, and N-Ras proteins, encoded by H-, K-, and N-*ras* proto-oncogenes, respectively, are 21 kD GTP-binding proteins which possess intrinsic GTPase activity and play a fundamental role in cell proliferation and differentiation (G. L. Bolton, J. S. Sebolt-Leopold, and J. C. Hodges, *Annu. Rep. Med. Chem.*, 1994, 29, 165; R. J. A. Grand in "New Molecular Targets in Cancer Chemotherapy" J. D. Kerr, and P. Workman, Eds., *CRC Press*, Boca Raton, FL, 1994, p. 97). Specific mutations in the *ras* gene impair GTPase activity of Ras, leading to uninterrupted growth signals and to the transformation of normal cells into malignant phenotypes. Mutant *ras* oncogenes are found in approximately 25% of all human cancers, including 90% of pancreatic, 50% of colon, and 50% of thyroid tumors (J. L. Bos, *Cancer Res.*, 1989, 49, 4682). It has been shown that normal cells transfected with mutant *ras* gene become cancerous and that unfarnesylated, cytosolic mutant Ras protein does not anchor in cell membranes and cannot induce

this transformation (J. F. Hancock, H. Paterson, and C. J. Marshall, *Cell*, 1990, 63, 133). Posttranslational modification and plasma membrane association of mutant Ras is essential for this transforming activity. The first and required step in the processing of Ras is farnesylation at the cysteine residue of its carboxyl terminal motif, CAAX (C = Cys-186, A = aliphatic amino acid, X = usually methionine, serine or glutamine). Since its identification, the enzyme farnesyl-protein transferase (FPTase) that catalyzes this first processing step has emerged as a promising target for therapeutic intervention (H.-W. Park, S. R. Boduluri, J. F. Moomaw, P. J. Casey, and L. S. Beese, *Science*, 1997, 275, 1800; P. J. Casey, P. A. Solski, C. J. Der, and J. E. Buss, *Proc. Natl. Acad. Sci. U.S.A.*, 1989, 86, 8323; S. Ayril-Kaloustian and J. S. Skotnicki, *Annu. Rep. Med. Chem.*, 1996, 31, 165, and references therein). Major milestones have been achieved with small molecules, such as mimics of the tetrapeptide CAAX and analogs of farnesyl pyrophosphate, that show efficacy without toxicity *in vitro* as well as in mouse models bearing *ras*-dependent tumors or human xenografts with H-, N-, or K-*ras* mutations (S. Ayril-Kaloustian and J. S. Skotnicki, *Annu. Rep. Med. Chem.*, 1996, 31, 165, and references therein; T. M. Williams, *Exp. Opin. Ther. Patents*, 1998, 8, 553, and references therein). Several low-molecular weight compounds that inhibit FPTase have entered Phase I trials in humans (SCH-66336, *Pharmaprojects*, 1998, No. 5128; R-115777, *Pharmaprojects*, 1998, No. 5532).

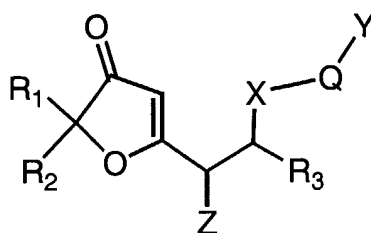
Accordingly, there is still a need for drugs for treating and preventing cancer. In particular, there is a need for drugs which inhibit or treat the growth of tumors expressing an activated Ras oncogene and which include cancers of the pancreas, colon, bladder and thyroid.

The present invention further provides a method of treatment of *ras* oncogene-dependent tumors, such as cancers of the pancreas, colon, bladder, and thyroid; a method of controlling metastasis, suppressing angiogenesis, and inducing apoptosis; a method of treating Ras-associated proliferative diseases other than cancer, such as restenosis, neuro-fibromatosis, endometriosis, and psoriasis. The compounds of the present invention may also inhibit prenylation of proteins other than Ras, and thus provide a method of treatment of diseases associated with other prenyl modifications of proteins.

Brief Summary of the Invention

The present invention discloses compounds represented by Formula (I):

5



Formula (I)

10 wherein:

R₁ is alkyl of 1 to 10 carbon atoms optionally substituted with 1 to 4 substituents independently selected from the group consisting of alkyl of 1 to 10 carbon atoms, -OH, -SH, -NH₂, and halogen, alkenyl of 2 to 12 carbon atoms, optionally substituted
15 aralkyl of 7 to 13 carbon atoms, optionally substituted aryl of 6 to 12 carbon atoms, and optionally substituted heteroaryl;

R₂ is phenyl, substituted phenyl (having from 1 to 3 substituents each independently
20 selected from the group consisting of halogen, alkyl of 1 to 10 carbon atoms, alkylthio of 1 to 10 carbon atoms, alkylamino of 1 to 10 carbon atoms, amino, carboxy, alkylsulfonyl of 1 to 10 carbon atoms, cyano, nitro, perfluoroalkyl of 1 to 10 carbon atoms, and alkoxy of 1 to 10 carbon atoms), or naphthyl;

25 R₃ is optionally substituted aryl and optionally substituted heteroaryl;

X is -O-, -S-, or -NH-;

Y is -OH, -SH, -SR₄, -NH₂, -NHR₅, -CO₂H, -CONHOH, halogen, or heteroaryl;

R₄ is hydrogen, alkyl of 1 to 10 carbon atoms, aryl of 6 to 12 carbon atoms, and aralkyl of 7 to 13 carbon atoms;

- 5 R₅ is alkyl of 1 to 10 carbon atoms, aryl of 6 to 12 carbon atoms, and aralkyl of 7 to 13 carbon atoms;

Z is H or methyl;

- 10 Q is an alkyl chain of 2 to 6 carbon atoms optionally substituted with 1 to 4 substituents independently selected from the group consisting of alkyl of 1 to 10 carbon atoms, -OH, -SH, -NH₂, halogen and alkenyl of 2 to 6 carbon atoms;

or a pharmacologically acceptable salt thereof.

15

In a preferred embodiment of the invention, X is S.

In a further preferred embodiment of the invention, Y is selected from the group consisting of SH, tetrazole and imidazole. More preferably, Y is SH.

20

In another preferred embodiment of the invention, R₃ is thienyl or a pharmaceutically acceptable salt thereof.

- 25 In yet another preferred embodiment of the invention, R₂ is phenyl optionally substituted with one to three substituents each independently selected from the group consisting of halogen, alkyl of 1 to 10 carbon atoms, alkylthio of 1 to 10 carbon atoms, alkylamino of 1 to 10 carbon atoms, amino, carboxy, alkylsulfonyl of 1 to 10 carbon atoms, cyano, nitro, perfluoroalkyl of 1 to 10 carbon atoms, and alkoxy of 1 to 10 carbon atoms.

30

In another preferred embodiment of the invention, R₃ is phenyl optionally substituted with one to three substituents each independently selected from the group consisting of halogen, alkyl of 1 to 10 carbon atoms, alkylthio of 1 to 10 carbon atoms,

alkylamino of 1 to 10 carbon atoms, amino, carboxy, alkylsulfonyl of 1 to 10 carbon atoms, cyano, nitro, perfluoroalkyl of 1 to 10 carbon atoms, and alkoxy of 1 to 10 carbon atoms or a pharmaceutically acceptable salt thereof.

- 5 Among the preferred groups of compounds of Formula (I) of this invention including pharmaceutically acceptable salts thereof are those in the subgroups below, wherein the other variables of Formula (I) in the subgroups are as defined above wherein:

- 10 a.) X is S;
- b.) X is S;
Y is SH;
- 15 c.) X is S;
Y is SH;
R₃ is thienyl;
- d.) X is S;
Y is SH, tetrazole or imidazole;
20 R₃ is thienyl;
- e.) X is S;
Y is SH;
- 25 R₂ is phenyl optionally substituted with one to three substituents each independently selected from the group consisting of halogen, alkyl of 1 to 10 carbon atoms, alkylthio of 1 to 10 carbon atoms, alkylamino of 1 to 10 carbon atoms, amino, carboxy, alkylsulfonyl of 1 to 10 carbon atoms, cyano, nitro, perfluoroalkyl of 1 to 10 carbon atoms, and alkoxy of 1 to 10 carbon atoms;
- 30 R₃ is phenyl optionally substituted with one to three substituents each independently selected from the group consisting of halogen, alkyl of 1 to 10 carbon atoms, alkylthio of 1 to 10 carbon atoms, alkylamino of 1 to 10 carbon atoms, amino, carboxy,

alkylsulfonyl of 1 to 10 carbon atoms, cyano, nitro, perfluoroalkyl of 1 to 10 carbon atoms, and alkoxy of 1 to 10 carbon atoms;

- 5 More preferred aspects of this invention includes compounds of Formula (I) including pharmaceutically acceptable salts thereof are those in the subgroups below, wherein the other variables of Formula (I) in the subgroups are as defined above wherein: X is S; Z is H or methyl; and R₁ is methyl;
- 10 a) R₂ is phenyl optionally substituted with one to three substituents each independently selected from the group consisting of halogen, alkyl of 1 to 10 carbon atoms, alkylthio of 1 to 10 carbon atoms, alkylamino of 1 to 10 carbon atoms, amino, carboxy, alkylsulfonyl of 1 to 10 carbon atoms, cyano, nitro, perfluoroalkyl of 1 to 10 carbon atoms, and alkoxy of 1 to 10 carbon atoms when R₃ is thienyl and Y is SH;
- 15 b) R₂ is phenyl optionally substituted with one to three substituents each independently selected from the group consisting of halogen, alkyl of 1 to 10 carbon atoms, alkylthio of 1 to 10 carbon atoms, alkylamino of 1 to 10 carbon atoms, amino, carboxy, alkylsulfonyl of 1 to 10 carbon atoms, cyano, nitro, perfluoroalkyl of 1 to 10 carbon atoms, and alkoxy of 1 to 10 carbon atoms when R₃ is thienyl and Y is pyrazine;
- 20 c) R₂ is phenyl optionally substituted with one to three substituents each independently selected from the group consisting of halogen, alkyl of 1 to 10 carbon atoms, alkylthio of 1 to 10 carbon atoms, alkylamino of 1 to 10 carbon atoms, amino, carboxy, alkylsulfonyl of 1 to 10 carbon atoms, cyano, nitro, perfluoroalkyl of 1 to 10 carbon atoms, and alkoxy of 1 to 10 carbon atoms;
- 25 R₃ is phenyl optionally substituted with one to three substituents each independently selected from the group consisting of halogen, alkyl of 1 to 10 carbon atoms, alkylthio of 1 to 10 carbon atoms, alkylamino of 1 to 10 carbon atoms, amino, carboxy, alkylsulfonyl of 1 to 10 carbon atoms, cyano, nitro, perfluoroalkyl of 1 to 10 carbon atoms, and alkoxy of 1 to 10 carbon atoms when Y is SH.
- 30

Specifically preferred compounds of this invention according to Formula (I) for treating or controlling ras oncogene-dependent tumors and associated proliferative diseases in warm-blooded animals preferably mammals, most preferably humans in need thereof are the following compounds or a pharmaceutically acceptable salt thereof:

- 5- $\{2-[(2S^*,3S^*)-2,3\text{-dihydroxy-4-mercaptobutyl}]thio\}$ -2-thien-3-ylethyl)-2-methyl-2-phenylfuran-3(2H)-one;
- 10 5- $\{2-[(2R^*,3S^*)-2,3\text{-dihydroxy-4-mercaptobutyl}]thio\}$ -2-thien-3-ylethyl)-2-methyl-2-phenylfuran-3(2H)-one;
- 5-[2- $\{[(2R,3R)-2,3\text{-dihydroxy-4-mercaptobutyl}]thio\}$ -2-(3-thienyl)ethyl]-2-methyl-2-phenylfuran-3(2H)-one;
- 5- $\{2-[(2S^*,3S^*)-2,3\text{-dihydroxy-4-mercaptobutyl}]thio\}$ -2-thien-3-ylethyl)-2-(4-fluorophenyl)-2-methylfuran-3(2H)-one;
- 15 5- $\{2-[(2R^*,3S^*)-2,3\text{-dihydroxy-4-mercaptobutyl}]thio\}$ -2-thien-3-ylethyl)-2-(4-fluorophenyl)-2-methylfuran-3(2H)-one;
- 5- $\{2-[(2R,3R)-2,3\text{-dihydroxy-4-mercaptobutyl}]thio\}$ -2-thien-3-ylethyl)-2-(4-fluorophenyl)-2-methylfuran-3(2H)-one;
- 20 5-[2- $\{[(2S^*,3S^*)-2,3\text{-dihydroxy-4-mercaptobutyl}]thio\}$ -2-(2-nitrophenyl)ethyl]-2-methyl-2-phenylfuran-3(2H)-one;
- 5- $\{2-[(2S^*3S^*)-2,3\text{-dihydroxy-4-mercaptobutyl}]thio\}$ -1-methyl-2-thien-3-ylethyl)-2-methyl-2-phenylfuran-3(2H)-one;
- 5-[2-(4-Mercapto-butylthio)-2-thiophen-3-yl-ethyl]-2-methyl-2-phenylfuran-3-one;
- 25 5-[2-[(4-hydroxybutyl)thio]-2-(3-thienyl)ethyl]-2-methyl-2-phenylfuran-3(2H)-one;
- 5-[2-[(3-mercaptopropyl)thio]-2-(3-thienyl)ethyl]-2-methyl-2-phenylfuran-3(2H)-one;
- 5-[2-[(5-mercaptopentyl)thio]-2-(3-thienyl)ethyl]-2-methyl-2-phenylfuran-3(2H)-one;
- 5-[2-[(2-mercaptoethyl)thio]-2-(3-thienyl)ethyl]-2-methyl-2-phenylfuran-3(2H)-one;
- 5-[2-[(3-hydroxy-2-mercaptopropyl)thio]-2-(3-thienyl)ethyl]-2-methyl-2-phenylfuran-3(2H)-one;
- 30 5-[2-[(3-hydroxypropyl)thio]-2-(3-thienyl)ethyl]-2-methyl-2-phenylfuran-3(2H)-one;
- 5-[2-[(2,3-dihydroxypropyl)thio]-2-(3-thienyl)ethyl]-2-methyl-2-phenylfuran-3(2H)-one;
- 2-methyl-2-phenyl-5-[2-[(2-pyrazin-2-ylethyl)thio]-2-(3-thienyl)ethyl]furan-3(2H)-one;

5-[2-[(2-hydroxyethyl)thio]-2-(3-thienyl)ethyl]-2-methyl-2-phenylfuran-3(2H)-one;
2-(4-fluorophenyl)-5-[2-[(2-hydroxyethyl)thio]-2-(3-thienyl)ethyl]-2-methylfuran-3(2H)-
one; and
(2R)-2-amino-3-[[2-(5-methyl-4-oxo-5-phenyl-4,5-dihydrofuran-2-yl)-1-thien-3-
5 ylethyl]thio]propanoic acid.

It is understood that the definition of compounds of Formula (I) when R₁, R₂, R₃, R₄, or R₅, contain asymmetric carbons, encompass all possible stereoisomers and mixtures thereof which possess the activity discussed below. In particular, the
10 definition encompasses racemic modifications and any optical isomers which possess the indicated activity. Optical isomers may be obtained in pure form by standard separation techniques or enantiomer specific synthesis. It is understood that this invention encompasses all crystalline forms of compounds of Formula (I). The pharmaceutically acceptable salts of the basic compounds of this invention are
15 those derived from such organic and inorganic acids as: lactic, citric, acetic, tartaric, fumaric, succinic, maleic, malonic, hydrochloric, hydrobromic, phosphoric, nitric, sulfuric, methanesulfonic, and similarly known acceptable acids. Where R₁, R₂, R₃, R₄, R₅ or Y contains a carboxyl group, salts of the compounds in this invention may be formed with bases such as alkali metals (Na, K, Li) or alkaline earth metals (Ca or
20 Mg).

For the compounds of Formula (I) defined above and referred to herein, unless otherwise noted, the following terms are defined:

Halogen, as used herein means chloro, fluoro, bromo and iodo.

25

Alkyl as used herein means a branched or straight chain having from 1 to 10 carbon atoms and more preferably from 1 to 6 carbon atoms. Exemplary alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl and hexyl.

30 Alkenyl as used herein means a branched or straight chain having from 2 to 12 carbon atoms and more preferably from 2 to 6 carbon atoms, the chain containing at least one carbon-carbon double bond and all possible configurational isomers. Alkenyl, may be used synonymously with the term olefin and includes alkyldienes.

Exemplary alkenyl groups include ethylene, propylene, isobutylene, ethenyl, 3-hexen-1-yl and the like optionally substituted with phenyl, phenyl optionally substituted with one to three substituents independently selected from the group consisting of halogen, alkyl of 1 to 10 carbon atoms, alkylthio of 1 to 10 carbon atoms, alkylamino of 1 to 10 carbon atoms, amino, carboxy, alkylsulfonyl of 1 to 10 carbon atoms, cyano, nitro, perfluoroalkyl of 1 to 10 carbon atoms, and alkoxy of 1 to 10 carbon atoms.

Aryl as used herein means a mono or bicyclic aromatic radical, having 6 to 12 carbon atoms. Preferred aryl groups include phenyl, alpha-naphthyl and beta-naphthyl and the like optionally substituted with one to three substituents each independently selected from the group consisting of halogen, alkyl of 1 to 10 carbon atoms, alkylthio of 1 to 10 carbon atoms, alkylamino of 1 to 10 carbon atoms, amino, carboxy, alkylsulfonyl of 1 to 10 carbon atoms, cyano, nitro, perfluoroalkyl of 1 to 10 carbon atoms, and alkoxy of 1 to 10 carbon atoms.

Aralkyl as used herein means an aryl-alkyl group in which the aryl and alkyl group are previously defined. Exemplary aralkyl groups include benzyl and phenethyl.

Alkoxy as used herein means an -O-alkyl group in which the alkyl group is as previously described. Exemplary alkoxy groups include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, and t-butoxy.

Heteroaryl denotes an unsubstituted or optionally substituted monocyclic 5 or 6 membered ring, which contains 1 to 4, or particularly 1 or 2 heteroatoms which may be the same or different. Nitrogen, oxygen and sulfur are the preferred heteroatoms, provided that the heteroaryl does not contain O-O, S-S or S-O bonds. Specific examples include 2-thienyl, 3-thienyl, furan, pyrrole, pyrazole, imidazole, 1,2,3-triazole, 1,2,4-triazole, tetrazole, thiazole, isoxazole, 1,3,4-oxadiazole, 1,2,4-oxadiazole, 1,3,4-thiadiazole, pyridine, pyrimidine, pyrazine, pyridazine and 1,3,5-triazine. The heteroaryl ring may be oxidized when a heteroatom is a nitrogen atom to provide the corresponding N-oxide, including pyridine-N-oxide. The heteroaryl ring

may be oxidized on a sulfur atom to provide the corresponding sulfoxide or sulfone, including thiophene-1-oxide.

Phenyl as used herein refers to a 6-membered aromatic ring.

5

A group, eg phenyl, aryl, heteroaryl, described as optionally substituted, unless otherwise provided for, denotes that when substituted has from 1 to 3 substituents said substituents being for example each independently selected from the group consisting of halogen, alkyl of 1 to 10 carbon atoms, alkylthio of 1 to 10 carbon
10 atoms, alkylamino of 1 to 10 carbon atoms, amino, carboxy, alkylsulfonyl of 1 to 10 carbon atoms, cyano, nitro, perfluoroalkyl of 1 to 10 carbon atoms, and alkoxy of 1 to 10 carbon atoms.

Where terms are used in combination, the definition for each individual part of the
15 combination applies unless defined otherwise. For instance, aralkyl refers to an aryl group, and alkyl refers to the alkyl group as defined above.

Additionally, this invention provides a method of treatment, by administration of an effective amount of compounds of Formula (I), of *ras* oncogene-dependent tumors, which include cancers of the pancreas, colon, bladder, and thyroid; a method of
20 controlling metastasis, suppressing angiogenesis, and inducing apoptosis; a method of treating Ras-associated proliferative diseases other than cancer, which include restenosis, neuro-fibromatosis, endometriosis, and psoriasis. The compounds of Formula (I) may also inhibit prenylation of proteins other than Ras, and thus provide a method of treatment of diseases associated with other prenyl modifications of
25 proteins.

The compounds of Formula (I) inhibit farnesyl-protein transferase and the farnesylation of the oncogene protein Ras. Thus, this invention further provides a method of inhibiting farnesyl protein transferase, (e.g., Ras farnesyl protein transferase) in mammals, especially humans, by the administration of an effective
30 amount of the compounds of Formula (I). The administration of the compounds of this invention to patients, to inhibit farnesyl protein transferase, is useful in the treatment of the cancers and other diseases described below.

This invention provides a method for inhibiting or treating the abnormal growth of cells, including transformed cells by administering an effective amount of a compound of Formula (I). Abnormal growth of cells refers to cell growth independent of normal regulatory mechanisms (e.g., loss of contact inhibition). This includes
5 abnormal growth of tumor cells (tumors) expressing an activated Ras oncogene; tumor cells in which the Ras protein is activated as a result of oncogenic mutation in another gene; and benign and malignant cells of other proliferative diseases in which aberrant Ras activation occurs.

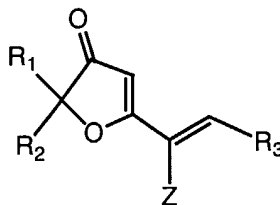
This invention also provides a method for inhibiting or treating tumor growth by
10 administering an effective amount of a compound of Formula (I), described herein, to a mammal (e.g., a human) in need of such treatment. In particular, this invention provides a method for inhibiting or treating the growth of tumors expressing an activated Ras oncogene by administration of an effective amount of a compound of Formula (I). Examples of tumors which may be inhibited or treated include, but are
15 not limited to, lung cancer (e.g., lung adenocarcinoma), pancreatic cancers (e.g., pancreatic carcinoma such as, for example, exocrine pancreatic carcinoma), colon cancers (e.g., colorectal carcinomas, such as, for example, colon adenocarcinoma and colon adenoma), myeloid leukemias (for example, acute myelogenous leukemia (AML)), thyroid follicular cancer, myelodysplastic syndrome (MDS), bladder
20 carcinoma, epidermal carcinoma, breast cancer and prostate cancer.

In another aspect, this invention provides the compounds of the invention for use as a pharmaceutical.

In another aspect, the invention provides the use of a compound of the invention in the preparation of a medicament for treating, inhibiting or controlling a ras-associated
25 disease by inhibiting farnesyl-protein transferase(FPTase) enzyme in a mammal in need thereof.

In another aspect, the invention provides a process for the preparation of a compound of formula (I) as defined above comprising one of the following:

30 (a) reacting a compound of formula



wherein R_1 , R_2 , R_3 and Z are as defined above, with a compound of formula HX-Q-Y wherein X, Q and Y are as defined above;

or

- 5 (b) converting a compound of formula (I) to a pharmaceutically acceptable salt thereof;

or

- (c) resolving an isomeric mixture of compounds of formula (I) to isolate an enantiomer of a compound of formula (I) or a pharmaceutically acceptable salt thereof.
- 10

This invention also provides a method for inhibiting or treating proliferative diseases, both benign and malignant, wherein Ras proteins are aberrantly activated as a result of oncogenic mutation in other genes-i.e., the Ras gene itself is not activated by

15 mutation to an oncogenic form-with said inhibition or treatment being accomplished by the administration of an effective amount of a compound of Formula (I), to a mammal (e.g., a human) in need of such treatment. For example, the benign proliferative disorder neurofibromatosis, or tumors in which Ras is activated due to mutation or overexpression of tyrosine kinase oncogenes (e.g., neu, src, abl, lck, and

20 fyn), may be inhibited or treated by the compounds of Formula (I).

Additionally, this invention provides a method of inhibition or treating the abnormal growth of cells, by administration of an effective amount of compounds of Formula (I), of *ras*-oncogene-dependent tumors, which tumors include cancers of the pancreas, colon, bladder, and thyroid. Without wishing to be bound by theory, these

25 compounds may function through the inhibition of G-protein function, such as ras p21, by blocking G-protein isoprenylation, thus making them useful in the treatment of proliferative diseases such as tumor growth and cancer. Without wishing to be bound by theory, compounds of Formula (I) inhibit Ras farnesyl-protein transferase, and thus antiproliferative activity of *ras*-transformed cells and other prenyl

30 modifications of proteins.

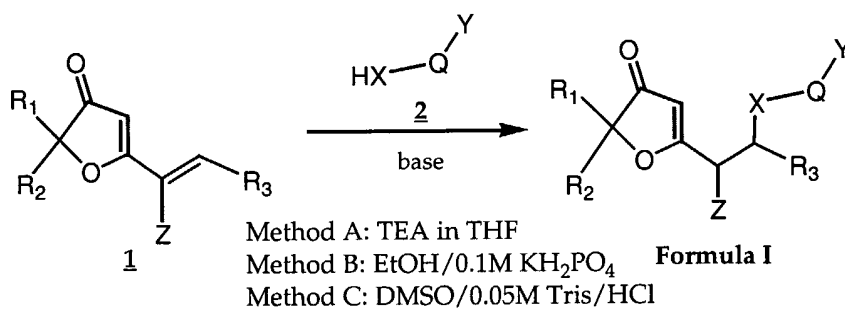
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Detailed Description of the Invention

Compounds of this invention may conveniently be prepared *via* 1,6-conjugate addition reactions, according to Scheme I. Intermediates 1 were synthesized according to the procedures described in U.S. Patents Nos. 5,010,102 and 4,966,905 and 4,169,202 incorporated herein by reference or commercially available. Further procedures for the synthesis of intermediate compounds 1 of the invention are described in Felman, S. W., *et al.*, *J. Med. Chem.* 1992, 35 (7), 1183-89. In addition, intermediates 1 can be synthesized using a combination of procedures described in Smith, A. B., *et al.*, *J. Amer. Chem. Soc.*, 1981, 103, 1501-13, and Baldwin, J. E., *et al.*, *J. Amer. Chem. Soc.*, 1974, 96, 7125-7. Intermediates 2 are commercially available compounds, or may be synthesized by standard literature procedures. Methods A-C may be used to prepare compounds of Formula (I) as described in Scheme I. Referring to Method A, as described in Scheme I, intermediate 1 where R₁, R₂, R₃ and Z are hereinbefore defined was stirred at room temperature for 10 to 24 hours, with intermediate 2 where X, Q and Y are hereinbefore defined in the presence of triethylamine (TEA) in tetrahydrofuran (THF) to afford compounds of Formula (I). Referring to Method B, as described in Scheme I, intermediate 1 where R₁, R₂, R₃ and Z are hereinbefore defined was stirred at room temperature for 10 to 24 hours, with intermediate 2 where X, Q and Y are hereinbefore defined in the presence of aqueous phosphate buffer (pH 7.5) and in the presence of an organic co-solvent such as ethyl alcohol (EtOH) or acetonitrile to afford compounds of Formula (I). Alternatively, using Method C, intermediate 1 where R₁, R₂, R₃ and Z are hereinbefore defined was stirred at room temperature for 10 to 24 hours, with intermediate 2 where X, Q and Y are hereinbefore defined in the presence of 0.05M Tris/HCl (tris(hydroxymethyl)aminomethane hydrochloride) in dimethylsulfoxide (DMSO) for 10 to 24 hours to afford compounds of Formula (I).

5

Scheme I



10

Standard Pharmacological Test Procedures

The ability of the compounds of this invention to inhibit FPTase was evaluated in the standard pharmacological *in vitro* test procedures described below. Data for representative examples is summarized in Table I.

15

Enzyme test procedure: FPTase inhibition *in vitro* assay was performed according to James, G. L., Brown, M. S., and Goldstein, J. L., *Methods in Enzymology*, 1995, 255, 38-46; and Garcia, M. A., *et al.*, *J. Biol. Chem.*, 1993, 268, 18415-18420.

Materials- Purified FPTase (Moomaw, J. F. and Casey, P. J., *J. Biol. Chem.*, 1992, 267, 17438-17443), purified His₆-Ras, inhibitor compounds at 10 mg/ml or 10 mM in 100% DMSO, ³H-FPP (50,000 dpm/pmol) Amersham, TCA/SDS (6%/2%), TCA (6%), Glass fiber filters (0.22 - 0.45 m), vacuum manifold or 96 well filtration plates.

Methods- 1. Dilute FPTase inhibitors from stock solutions to 2.5 X in 2.5 % DMSO, 10 mM DTT, 0.5% octyl-B-glucoside. 2. Solution #1 is added to FPTase reaction in a volume of 20 ml. 3. Standard reaction mix, 50 ml, contains 50 mM Tris (7.5), 10 mM ZnCl₂, 3 mM MgCl₂, 20 mM KCl, 5 mM DTT, 0.2% octyl-B-glucoside, 1% DMSO, 40 mM His₆-Ras, 10 ng FPTase, and various concentrations of FPTase inhibitors. 4. Incubate for 30-90 min at 25° C. 5. Stop reactions with TCA/SDS (6%/2%), hold at 4°

C for 45-60 min. 6. Filter by manifold or 96 well plate, wash filter 3-5 X with TCA (6%). 7. Add scintillant to filters, measure ³H-FPP incorporation into Ras protein.

- 5 Analysis of Results- Percent inhibition by test compounds is determined by the following:

$$\frac{(\text{cpm from precipitated Ras with test compounds}) - (\text{background cpm})}{(\text{cpm from precipitated Ras without test compounds}) - (\text{background cpm})} \times 100$$

= % inhibition.

(cpm from precipitated Ras without test compounds) - (background cpm)

10

Cell-based test procedure: Tumor inhibition *in vitro* assay was performed according to P. Skehan, R. Storeng, D. Scudiero, A. Monks, J. McMohan, D. Vistica, J. Warren, H. Bokesch, S. Kenney, and M. R. Boyd, *J. Natl. Cancer Instit.*, 1990, 82 (13), 1107-1112; L. V. Rubinstein, R. H. Shoemaker, K. D. Paull, R. M. Simon, S. Tosini, P.

- 15 Skehan, D. A. Scudiero, A. Monks, and M. R. Boyd, *J. Natl. Cancer Instit.*, 1990, 82 (13), 1113-1118; A. Monks, *et al.*, *J. Natl. Cancer Instit.*, 1991, 83, 757-766; M. R. Boyd and K. D. Paull, *Drug Development Res.*, 1995, 34, 91-109; and S. P. Fricker and R. G. Buckley, *Anticancer Research*, 1996, 16, 3755-3760.

- 20 Materials- Cell Lines: Human tumor cell lines LS174T, HTB39, LoVo and CaCo2. Cell Media : RPMI 1640 (or DMEM medium and McCoy's medium) with 10% Fetal Bovine Serum supplemented with L-glutamine and Pennicilin/Streptomycin. Compounds: Supplied usually as a 10 mM stock in 100% DMSO. Normal Saline: 150 mM NaCl Trichloroacetic Acid (TCA): 50% (w/v) in water. Sulforhodamine (SRB):
25 0.4% (w/v) in 1% Acetic Acid. Tris Base: 10 mM in water.

- Methods- Cells are plated at 2000 cells per well, per 200 µl media, and allowed to adhere overnight at 37 °C. At 24 h post plating, compounds are added directly at a volume of 0.5 µl. Compound is first diluted in DMSO to generate concentrations of
30 compound or reference standard of: 1, 5, 10 and 25 µM. Dilutions can be made in an identical 96 well plate so that compounds can be added using a multichannel micropipettor set at 0.5 µl. The cells are then incubated for four days after which the media is removed using a 12 well manifold by first tipping the plate forward at a 45

degree angle and then inserting the manifold in an upright orientation to prevent the tips of the manifold from disturbing cells at the bottom of the plate. 200 µl of normal saline is then added to each well using an 8 well multichannel pipettor, followed by the careful addition of 50 µl of 50% TCA. The plates are then incubated for 2 h at 4 °C, after which the supernatant is removed using the same technique as above and the plates washed twice with 200 µl water. The plates are then air dried and 50 µl of SRB stock solution is carefully added so that the entire bottom of each well is covered. This again can be used using an 8 well multichannel pipettor. The SRB is incubated with fixed cells for 15 min at room temperature, after which the SRB is removed with the manifold as described above and the plates washed twice with 350 µl of 1% acetic acid per well each time. The plates are then air dried after which the bound SRB is released from protein by the addition of 200 µl of Tris base. Resolubilizing the SRB is aided by placing the plates on a rotator for 15-30 min. The absorbance of each well is determined at 550 or 562 nm using a microtiter plate reader.

Analysis of Results- Each compound or dilution thereof is performed in triplicate. Outliers are identified by visual inspection of the data. Each plate should have a control (vehicle only). A standard curve is constructed by plotting the concentration of compound against the average absorbance calculated at that concentration. A curve is plotted and the concentration at which the curve passes through the 50% absorbance mark seen in the control well is the IC₅₀ calculated for that compound.

Table I

Example #	<i>in vitro</i> FTase Inhibition	
	Assay	
	IC ₅₀ (vs. H-Ras) μM	IC ₅₀ (vs. K-Ras) μM
1	0.06	0.10
2	0.19	
3	0.18	
6	0.12	0.14
7	0.32	0.09
8	0.50	0.70
9	1.5	3.7
10	5.5	>10
11	0.06	0.15
12	8	
13	0.18	1
14	7.2	4.5
15	8.3	
16	5	
17	>10	>10
18	0.55	
19	>10	
20	>10	

5 *H-Ras or K-Ras used as substrates for farnesylation

Compounds of this invention were tested in cell-based assays against human tumor cell lines LS174T, HTB39 and LoVo, as described under Assays. The range observed for inhibition of cell growth was IC₅₀ = 5 to >25 μM.

Based on the results of these standard pharmacological test procedures, the compounds of this invention are useful as agents for treating, inhibiting or controlling *ras*-associated diseases by inhibiting farnesyl-protein transferase enzyme, when administered in amounts ranging from about 1 to about 200 mg/kg of body weight per day. A preferred regimen for optimum results would be from about 1 mg to about 100 mg/kg of body weight per day and such dosage units are employed that a total of from about 100 mg to about 1000 mg of the active compound for a subject of about 70 kg of body weight are administered in a 24 hour period.

10 The dosage regimen for treating mammals may be adjusted to provide the optimum therapeutic response. For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation. A decidedly practical advantage is that these active compounds may be administered in any convenient manner such as by the oral, 15 intravenous, intramuscular or subcutaneous routes.

The active compounds may be orally administered, for example, with an inert diluent or with an assimilable edible carrier, or they may be enclosed in hard or soft shell gelatin capsules, or they may be compressed into tablets or they may be incorporated directly with the food of the diet. For oral therapeutic administration, 20 these active compounds may be incorporated with excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers and the like. Such compositions and preparations should contain at least 0.1% of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2% to about 60% 25 of the weight of the unit. The amount of active compound in such therapeutically useful compositions is such that a suitable dosage will be obtained. Preferred compositions or preparations according to the present invention are prepared so that an oral dosage unit form contains between 10 and 1000 mg of active compound. The tablets, troches, pills, capsules and the like may also contain the following: a 30 binder such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose, or saccharin may be added or a flavoring agent such

as peppermint, oil of wintergreen or cherry flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills or capsules may be
5 coated with shellac, sugar or both. A syrup or elixir may contain the active compound, sucrose, as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any dosage unit form should be pharmaceutically pure and substantially non-toxic in the amounts used. In addition, these active
10 compounds may be incorporated into sustained-release preparations and formulations.

These active compounds may also be administered parenterally or intraperitoneally. Solutions or suspensions of these active compounds as a free base or pharmacologically acceptable salt can be prepared in water suitably mixed with a
15 surfactant such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous
20 solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be prepared against the contaminating action of microorganisms such as bacteria and fungi. The carrier can
25 be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol and liquid poly-ethylene glycol), suitable mixtures thereof, and vegetable oils.

The present invention accordingly provides a pharmaceutical composition which comprises a compound of Formula (I) of this invention in combination or
30 association with a pharmaceutically acceptable carrier. In particular, the present invention provides a pharmaceutical composition which comprises an effective amount of a compound of this invention and a pharmaceutically acceptable carrier.

As used in accordance with this invention, the term providing an effective amount of a compound means either directly administering such compound, or administering a prodrug, derivative, or analog which will form an effective amount of the compound within the body.

5

The invention will be more fully described in conjunction with the following specific examples which are not to be construed as limiting the scope of the invention.

10

Example 1

5-(2-[[[(2S*,3S*)-2,3-Dihydroxy-4-mercaptobutyl]thio]-2-thien-3-ylethyl]-2-methyl-2-phenylfuran-3(2H)-one

Method A. A solution of (E)-2-methyl-2-phenyl-5-[2-(3-thienyl)ethenyl]-3(2H)-furanone (52 mg, 0.18 mmol) in anhydrous THF (1.5 mL) was treated with 1,4-dithio-DL-threitol (78 mg, 0.50 mmol) and TEA (77.5 μ L, 0.55 mmol), at room temperature, under nitrogen atmosphere. After 24 h at ambient temperature, the mixture was taken up in ether and washed with brine. The organic layer was dried and concentrated to give a crude oil (112 mg), which was purified by flash column chromatography (1:1.5 EtOAc/hexane) and identified as 5-(2-[[[(2S*,3S*)-2,3-dihydroxy-4-mercaptobutyl]thio]-2-thien-3-ylethyl]-2-methyl-2-phenylfuran-3(2H)-one (42.2 mg, 54%) consisting of a mixture of diastereomers: ^1H NMR (CDCl_3) δ 1.43 (m, 1H), 1.66, 1.68 and 1.72 (overlapped singlets, 3H), 2.40-2.70 (m, 4H), 3.10-3.25 (m, 2H), 3.40-3.75 (two broad s, fine structure, 2H), 4.48 (m, 1H), 5.39 and 5.40 (overlapped singlets, 1H), 7.14 (m, 2H), 7.25-7.40 (m, 6H); MS (HR-FAB) m/z 437.0868 (M+H calcd. for $\text{C}_{21}\text{H}_{25}\text{O}_4\text{S}_3$ 437.0915).

Method B. A mixture of (E)-2-methyl-2-phenyl-5-[2-(3-thienyl)ethenyl]-3(2H)-furanone (40 mg, 0.14 mmol) and 1,4-dithio-DL-threitol (1.0 g, 6.4 mmol) in EtOH (4 mL) and aqueous 0.1M KH_2PO_4 pH 7.5 buffer was stirred at room temperature for 20 h. The mixture was extracted with ether and the product was purified as in Method A. or by preparative HPLC.

Method C. A mixture of (E)-2-methyl-2-phenyl-5-[2-(3-thienyl)ethenyl]-3(2H)-furanone (0.5 mg, 1.75 μ mol) and 1,4-dithio-DL-threitol (47 mg, 0.3 mmol, 1M aqueous solution), DMSO (50 μ L), and aqueous 0.05M Tris/HCl pH 7.5 buffer (4 mL) was stirred at room temperature for 4-20 h. After this period, 0.1% TFA in acetonitrile (0.3-0.5 mL) was added to obtain a clear solution. The latter was filtered through polypropylene (LC13 Acrodisc PVDF) and the product was purified by reverse phase HPLC.

Example 2

10 5-(2-[[[(2R*,3S*)-2,3-Dihydroxy-4-mercaptobutyl]thio]-2-thien-3-ylethyl]-2-methyl-2-phenylfuran-3(2H)-one

Following the procedure of Method C, above, (E)-2-methyl-2-phenyl-5-[2-(3-thienyl)ethenyl]-3(2H)-furanone was reacted with 1,4-dithio-DL-erythritol to provide 5-(2-[[[(2R*,3S*)-2,3-dihydroxy-4-mercaptobutyl]thio]-2-thien-3-ylethyl]-2-methyl-2-phenylfuran-3(2H)-one: ^1H NMR (DMSO- d_6) δ 1.53, 1.57 and 1.61 (overlapped singlets, 3H), 2.60-2.90 (m, ~4H), 3.40-3.60 (m overlapped with DMSO, ~2H), 4.60 (m, 1H), 5.52, 5.54 and 5.56 (overlapped singlets, 1H), 7.15-7.60 (m, 8H); MS (LR-ESI) m/z 437 (M+H calcd. for $\text{C}_{21}\text{H}_{25}\text{O}_4\text{S}_3$ 437).

20

Example 3

5-[2-[[[(2R,3R)-2,3-Dihydroxy-4-mercaptobutyl]thio]-2-(3-thienyl)ethyl]-2-methyl-2-phenylfuran-3(2H)-one

25 According to the procedure of Method A, Example 1, (E)-2-methyl-2-phenyl-5-[2-(3-thienyl)ethenyl]-3(2H)-furanone was reacted with 1,4-dithio-L-threitol to provide 5-[2-[[[(2R,3R)-2,3-dihydroxy-4-mercaptobutyl]thio]-2-(3-thienyl)ethyl]-2-methyl-2-phenylfuran-3(2H)-one: ^1H NMR (CDCl_3) δ 1.43 (m, 1H), 1.66 and 1.68 (overlapped singlets, 3H), 2.40-2.70 (m, 4H), 3.10-3.25 (m, 2H), 3.40-3.75 (two broad s, fine structure, 2H), 4.48 (m, 1H), 5.39 and 5.40 (overlapped singlets, 1H), 7.14 (m, 2H), 7.25-7.40 (m, 6H); MS (LR-??) m/z 437 (M+H calcd. for $\text{C}_{21}\text{H}_{25}\text{O}_4\text{S}_3$ 437); MS (HR-FAB) m/z 459.0728 (M+Na calcd. for $\text{C}_{21}\text{H}_{24}\text{NaO}_4\text{S}_3$ 459.0734).

30

Example 45-(2-([(2S*,3S*)-2,3-Dihydroxy-4-mercaptobutyl]thio)-2-thien-3-ylethyl)-2-(4-fluorophenyl)-2-methylfuran-3(2H)-one

- 5 Following the procedure of Method C, Example 1, (E)-2-(4-fluorophenyl)-2-methyl-5-[2-(3-thienyl)ethenyl]-3(2H)-furanone was reacted with 1,4-dithio-DL-threitol to give 5-(2-([(2S*,3S*)-2,3-dihydroxy-4-mercaptobutyl]thio)-2-thien-3-ylethyl)-2-(4-fluorophenyl)-2-methylfuran-3(2H)-one: ¹H NMR (DMSO-d₆) δ 1.53, 1.57 and 1.60 (overlapped singlets, 3H), 4.60 (m, 1H), 5.56 and 5.57 (overlapped singlets, 1H), 7.12-7.60 (m, 7H); MS (LR-ESI) *m/z* 455 (M+H calcd. for C₂₁H₂₄FO₄S₃ 455).

Example 55-(2-([(2R*,3S*)-2,3-Dihydroxy-4-mercaptobutyl]thio)-2-thien-3-ylethyl)-2-(4-fluorophenyl)-2-methylfuran-3(2H)-one

- 15 Following the procedure of Method C, Example 1, (E)-2-(4-fluorophenyl)-2-methyl-5-[2-(3-thienyl)ethenyl]-3(2H)-furanone was reacted with 1,4-dithio-DL-erythritol to provide 5-(2-([(2R*,3S*)-2,3-dihydroxy-4-mercaptobutyl]thio)-2-thien-3-ylethyl)-2-(4-fluorophenyl)-2-methylfuran-3(2H)-one: ¹H NMR (DMSO-d₆) δ 1.53 and 1.56 (overlapped singlets, 3H), 2.65-2.85 (m, 2H), 4.57 (m, 1H), 5.54 and 5.56 (overlapped singlets, 1H), 7.12-7.60 (m, ~7H); MS (LR-ESI) *m/z* 455 (M+H calcd. for C₂₁H₂₄FO₄S₃ 455).

Example 6

- 25 5-(2-([(2R,3R)-2,3-Dihydroxy-4-mercaptobutyl]thio)-2-thien-3-ylethyl)-2-(4-fluorophenyl)-2-methylfuran-3(2H)-one

- According to the procedure of Method A, Example 1, (E)-2-(4-fluorophenyl)-2-methyl-5-[2-(3-thienyl)ethenyl]-3(2H)-furanone was reacted with 1,4-dithio-L-threitol to provide 5-(2-([(2R,3R)-2,3-dihydroxy-4-mercaptobutyl]thio)-2-thien-3-ylethyl)-2-(4-fluorophenyl)-2-methylfuran-3(2H)-one: ¹H NMR (CDCl₃) δ 1.45 (m, 1H), 1.63 and 1.65 (overlapped singlets, 3H), 2.40-2.70 (m, slight xs. of 4H), 3.10-3.25 (m, 2H), 3.40-3.75 (two broad s, fine structure, 2H), 4.49 (m, 1H), 5.40 and 5.41 (overlapped singlets,

1H), 7.01 (m, 2H), 7.15 (m, 2H), 7.33 (m, 3H); MS (HR-FAB) m/z 455.0818 (M+H calcd. for $C_{21}H_{24}FO_4S_3$ 455.0821).

Example 7

5 5-[2-([(2S*,3S*)-2,3-Dihydroxy-4-mercaptobutyl]thio)-2-(2-nitrophenyl)ethyl]-2-methyl-2-phenylfuran-3(2H)-one

According to the procedure of Method A, Example 1, (E)-2-methyl-2-phenyl-5-[2-(3-thienyl)ethenyl]-3(2H)-furanone was reacted with 1,4-dithio-DL-threitol to provide 5-[2-
 10 {[(2S*,3S*)-2,3-dihydroxy-4-mercaptobutyl]thio}-2-(2-nitrophenyl)ethyl]-2-methyl-2-phenylfuran-3(2H)-one as a mixture of diastereomers: 1H NMR ($CDCl_3$) δ 1.40 (m, 1H), 1.62, 1.67 and 1.69 (overlapped singlets, 3H), 2.50-2.75 (m, 4H), 3.17-3.38 (m, 2H), 3.45-3.75 (two broad s, fine structure, 2H), 5.16 (m, 1H), 5.39, 5.40 and 5.50 (singlets, 1H), 7.25-7.50 (m, 6H), 7.65 (m, 1H), 7.82 (m, 2H); MS (LR-ESI) m/z 476
 15 (M+H calcd. for $C_{23}H_{26}NO_6S_2$ 476).

Example 8

5-(2-([(2S*3S*)-2,3-Dihydroxy-4-mercaptobutyl]thio)-1-methyl-2-thien-3-ylethyl)-2-methyl-2-phenylfuran-3(2H)-one

20 According to the procedure of Method A, Example 1, 2-methyl-5-[(E)-1-methyl-2-thien-3-ylethenyl]-2-phenylfuran-3(2H)-one was reacted with 1,4-dithio-DL-threitol to provide 5-(2-([(2S*3S*)-2,3-dihydroxy-4-mercaptobutyl]thio)-1-methyl-2-thien-3-ylethyl)-2-methyl-2-phenylfuran-3(2H)-one as a mixture of diastereomers: 1H NMR
 25 ($CDCl_3$) δ 1.45 (m, 1H), 1.50-1.65 and 1.75-1.80 (overlapped singlets and multiplets, ~8H), 2.40-2.70 (m, ~4H), 3.22 (m, 1H), 3.33-3.65 (m, 2H), 4.33 (m, 1H), 5.25-5.52 (overlapped singlets, 1H), 7.05-7.60 (m, 8H); MS (HR-FAB) m/z 451.1116 (M+H calcd. for $C_{22}H_{27}O_4S_3$ 451.1072).

30

Example 95-[2-[(4-Mercaptobutyl)thio]-2-(3-thienyl)ethyl]-2-methyl-2-phenylfuran-3(2H)-one

According to the procedure of Method A, Example 1, (E)-2-methyl-2-phenyl-5-[2-(3-thienyl)ethenyl]-3(2H)-furanone was reacted with 1,4-butanedithiol to provide 5-[2-[(4-mercaptobutyl)thio]-2-(3-thienyl)ethyl]-2-methyl-2-phenylfuran-3(2H)-one: ¹H NMR (CDCl₃) δ 1.30 (m, 1H), 1.55-1.70 (broad s with fine structure, 4H) and 1.65 and 1.68 (singlets, 3H), 2.33-2.42 (m, 2H), 2.42-2.55 (m, 2H), 3.06-3.25 (m, 2H), 4.40 (m, 1H), 5.37 and 5.39 (singlets, 1H), 7.05-7.18 (m, 2H), 7.25-7.40 (m, 6H); MS (HR- FAB) *m/z* 405.1029 (M+H calcd. for C₂₁H₂₅O₂S₃ 405.1017).

Example 105-[2-[(4-Hydroxybutyl)thio]-2-(3-thienyl)ethyl]-2-methyl-2-phenylfuran-3(2H)-one

According to the procedure of Method A, Example 1, (E)-2-methyl-2-phenyl-5-[2-(3-thienyl)ethenyl]-3(2H)-furanone was reacted with 4-mercapto-1-butanol to provide 5-[2-[(4-hydroxybutyl)thio]-2-(3-thienyl)ethyl]-2-methyl-2-phenylfuran-3(2H)-one: ¹H NMR (CDCl₃) δ 1.52-1.70 (broad s with fine structure, ~5H) and 1.65 and 1.67 (singlets, 3H), 2.41 (m, 2H), 3.08-3.24 (m, 2H), 3.60 (m, 2H), 4.40 (m, 1H), 5.37 and 5.39 (singlets, 1H), 7.05-7.16 (m, 2H), 7.25-7.40 (m, 6H); MS (HR-El) *m/z* 388.1161 (M⁺ calcd. for C₂₁H₂₄O₃S₂ 388.1167).

Example 115-[2-[(3-Mercaptopropyl)thio]-2-(3-thienyl)ethyl]-2-methyl-2-phenylfuran-3(2H)-one

According to the procedure of Method A, Example 1, (E)-2-methyl-2-phenyl-5-[2-(3-thienyl)ethenyl]-3(2H)-furanone was reacted with 1,3-propanedithiol to provide 5-[2-[(3-mercaptopropyl)thio]-2-(3-thienyl)ethyl]-2-methyl-2-phenylfuran-3(2H)-one: ¹H NMR (CDCl₃) δ 1.65 and 1.68 (singlets, 3H), 2.41 (m, 2H), 1.73-2.20 (overlapping multiplets, 3H), 2.45-2.65 (m, ~4H), 3.08-3.27 (m, 2H), 4.40 (m, 1H), 5.37 and 5.39 (singlets, 1H), 7.05-7.18 (m, 2H), 7.27-7.45 (m, 6H); MS (HR-FAB) *m/z* 391.0850 (M+H calcd. for C₂₀H₂₃O₂S₃ 391.0860).

Example 125-[2-[(5-Mercaptopentyl)thio]-2-(3-thienyl)ethyl]-2-methyl-2-phenylfuran-3(2H)-one

According to the procedure of Method A, Example 1, (E)-2-methyl-2-phenyl-5-[2-(3-thienyl)ethenyl]-3(2H)-furanone was reacted with 1,5-pentanedithiol to provide 5-[2-
5 [(5-mercaptopentyl)thio]-2-(3-thienyl)ethyl]-2-methyl-2-phenylfuran-3(2H)-one: ¹H NMR (CDCl₃) δ 1.32 (m, 1H), 1.40-1.75 (m, 6H) and 1.65 and 1.68 (singlets, 3H), 2.33-2.45 (m, 2H), 2.45-2.60 (m, 2H), 3.06-3.25 (m, 2H), 4.40 (m, 1H), 5.37 and 5.39 (singlets, 1H), 7.05-7.18 (m, 2H), 7.25-7.43 (m, 6H); MS (HR-FAB) *m/z* 419.1180 (M+H
10 calcd. for C₂₂H₂₇O₂S₃ 419.1173).

Example 135-[2-[(2-Mercaptoethyl)thio]-2-(3-thienyl)ethyl]-2-methyl-2-phenylfuran-3(2H)-one

According to the procedure of Method A, Example 1, (E)-2-methyl-2-phenyl-5-[2-(3-thienyl)ethenyl]-3(2H)-furanone was reacted with 1,2-ethanedithiol to provide 5-[2-[(2-
15 mercaptoethyl)thio]-2-(3-thienyl)ethyl]-2-methyl-2-phenylfuran-3(2H)-one: ¹H NMR (CDCl₃) δ 1.63 (m, 1H) and overlapping 1.65 and 1.68 (singlets, 3H), 2.47-2.80 (m, 4H), 3.07-3.25 (m, 2H), 4.47 (m, 1H), 5.37 and 5.39 (singlets, 1H), 7.05-7.18 (m, 2H),
20 7.25-7.45 (m, 6H); MS (HR-ESI) *m/z* 376.0605 (M⁺ calcd. for C₁₉H₂₀O₂S₃ 376.0626).

Example 145-[2-[(3-Hydroxy-2-mercaptopropyl)thio]-2-(3-thienyl)ethyl]-2-methyl-2-phenylfuran-3(2H)-one

According to the procedure of Method A, Example 1, (E)-2-methyl-2-phenyl-5-[2-(3-thienyl)ethenyl]-3(2H)-furanone was reacted with 2,3-dimercapto-1-propanol to provide 5-[2-[(3-hydroxy-2-mercaptopropyl)thio]-2-(3-thienyl)ethyl]-2-methyl-2-
25 phenylfuran-3(2H)-one: ¹H NMR (CDCl₃) δ 1.65 (m, 1H) and overlapping 1.65 and 1.68 (singlets, 3H), 1.92 (br s with fine structure, 1H), 2.65-2.80 (m, 2H), 2.89 (br s with fine structure, 1H), 3.10-3.28 (m, 2H), 3.57-3.78 (m, 2H), 4.43-4.60 (m, 1H), 5.38, 5.40 and 5.41 (singlets, 1H), 7.13-7.20 (m, 2H), 7.25-7.43 (m, 6H); MS (LR-ESI) *m/z* 407 (M+H calcd. for C₂₀H₂₃NO₃S₃ 407).
30

Example 155-[2-[(3-Hydroxypropyl)thio]-2-(3-thienyl)ethyl]-2-methyl-2-phenylfuran-3(2H)-one

According to the procedure of Method A, Example 1, (E)-2-methyl-2-phenyl-5-[2-(3-thienyl)ethenyl]-3(2H)-furanone was reacted with 3-mercapto-1-propanol to provide
5-[2-[(3-hydroxypropyl)thio]-2-(3-thienyl)ethyl]-2-methyl-2-phenylfuran-3(2H)-one: ^1H NMR (CDCl_3) δ 1.40 (br s, 1H), 1.65 and 1.68 (singlets, 3H), 1.68-1.82 (m, 2H), 2.42-2.57 (m, 2H), 3.10-3.27 (m, 2H), 3.67 (m, 2H), 4.42 (m, 1H), 5.37 and 5.39 (singlets, 1H), 7.05-7.18 (m, 2H), 7.27-7.40 (m, 6H); MS (HR- FAB) m/z 375.1113 ($\text{M}+\text{H}$ calcd. for $\text{C}_{20}\text{H}_{23}\text{O}_3\text{S}_2$ 375.1089).

Example 165-[2-[(2,3-Dihydroxypropyl)thio]-2-(3-thienyl)ethyl]-2-methyl-2-phenylfuran-3(2H)-one

According to the procedure of Method A, Example 1, (E)-2-methyl-2-phenyl-5-[2-(3-thienyl)ethenyl]-3(2H)-furanone was reacted with 3-mercapto-1,2-propanediol to provide 5-[2-[(2,3-dihydroxypropyl)thio]-2-(3-thienyl)ethyl]-2-methyl-2-phenylfuran-3(2H)-one: ^1H NMR (CDCl_3) δ 1.66 and 1.68 (singlets, 3H), 1.83 (br s, 1H), 2.44 (br s with fine structure, 1H) and overlapping 2.45-2.58 (m, 2H), 3.10-3.28 (m, 2H), 3.47 (br s with fine structure, 1H), 3.55-3.78 (m, 2H), 4.50 (m, 1H), 5.39 and 5.40 (overlapping singlets, 1H), 7.05-7.20 (m, 2H), 7.27-7.43 (m, 6H); MS (HR-EI) m/z 390.0948 (M^+ calcd. for $\text{C}_{20}\text{H}_{22}\text{O}_4\text{S}_2$ 390.0959).

Example 172-Methyl-2-phenyl-5-[2-[(2-pyrazin-2-ylethyl)thio]-2-(3-thienyl)ethyl]furan-3(2H)-one

According to the procedure of Method A, Example 1, (E)-2-methyl-2-phenyl-5-[2-(3-thienyl)ethenyl]-3(2H)-furanone was reacted with 2-(2-mercaptoethyl)pyrazine to provide 2-methyl-2-phenyl-5-[2-[(2-pyrazin-2-ylethyl)thio]-2-(3-thienyl)ethyl]furan-3(2H)-one: ^1H NMR (CDCl_3) δ 1.64 and 1.65 (singlets, 3H), 2.75-2.87 (m, 2H), 2.87-2.98 (m, 2H), 3.07-3.24 (m, 2H), 4.41 (m, 1H), 5.34 and 5.36 (singlets, 1H), 7.03-7.17 (m, 2H), 7.27-7.41 (m, 6H), 8.36 (m, 1H), 8.41 (m, 1H), 8.47 (m, 1H); MS (HR-EI) m/z 422.1118 (M^+ calcd. for $\text{C}_{23}\text{H}_{22}\text{N}_2\text{O}_2\text{S}_2$ 422.1122).

Example 185-[2-[(2-Hydroxyethyl)thio]-2-(3-thienyl)ethyl]-2-methyl-2-phenylfuran-3(2H)-one

Following the procedure of Method C, Example 1, (E)-2-methyl-2-phenyl-5-[2-(3-thienyl)ethenyl]-3(2H)-furanone was reacted with 2-mercapto-1-ethanol to provide 5-[2-[(2-hydroxyethyl)thio]-2-(3-thienyl)ethyl]-2-methyl-2-phenylfuran-3(2H)-one: ¹H NMR (DMSO-d₆) δ 1.54 and 1.57 (singlets, 3H), 3.35-3.60 (m overlapped with DMSO, ~4H), 4.58 (m, 1H), 5.55 and 5.56 (overlapped singlets, 1H), 7.18-7.37 (m, 6H), 7.40-7.57 (m, 2H); MS (LR-ESI) *m/z* 361 (M+H calcd. for C₁₉H₂₁O₃S₂ 361).

Example 192-(4-Fluorophenyl)-5-[2-[(2-hydroxyethyl)thio]-2-(3-thienyl)ethyl]-2-methylfuran-3(2H)-one

Following the procedure of Method C, Example 1, (E)-2-(4-fluorophenyl)-2-methyl-5-[2-(3-thienyl)ethenyl]-3(2H)-furanone was reacted with 2-mercapto-1-ethanol to provide 2-(4-fluorophenyl)-5-[2-[(2-hydroxyethyl)thio]-2-(3-thienyl)ethyl]-2-methylfuran-3(2H)-one: ¹H NMR (DMSO-d₆) δ 1.53 and 1.56 (singlets, 3H), 4.39 (m, 1H), 5.56 (overlapped singlets, 1H), 7.08-7.35 (m, 5H), 7.43-7.60 (m, 2H); MS (HR-Cl) *m/z* 379.0832 (M+H calcd. for C₁₉H₂₀FO₃S₂ 379.0837)

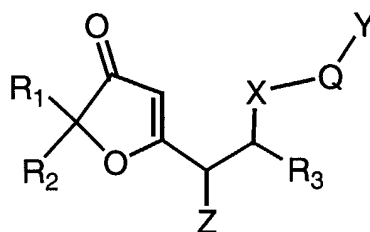
Example 20(2R)-2-Amino-3-[[2-(5-methyl-4-oxo-5-phenyl-4,5-dihydrofuran-2-yl)-1-thien-3-ylethyl]thio]propanoic acid

Following the procedure of Method C, Example 1, (E)-2-methyl-2-phenyl-5-[2-(3-thienyl)ethenyl]-3(2H)-furanone was reacted with L-cysteine to provide (2R)-2-amino-3-[[2-(5-methyl-4-oxo-5-phenyl-4,5-dihydrofuran-2-yl)-1-thien-3-ylethyl]thio]propanoic acid: ¹H NMR (DMSO-d₆) δ 1.50-1.60 (overlapping singlets, 3H), 2.70-3.10 (m, ~2H), 4.00-4.25 (m, 1H), 4.64 (m, 1H), 5.50-5.57 (overlapping singlets, 1H), 7.12-7.38 (m, 6H), 7.52-7.63 (m, 2H), 8.35 (br s, ~ 2H); MS (LR-ESI) *m/z* 402 (M-H calcd. for C₂₀H₂₀NO₄S₂ 402)

CLAIMS:

1. A compound of Formula (I)

5



Formula (I)

10 wherein:

R₁ is alkyl of 1 to 10 carbon atoms optionally substituted with 1 to 4 substituents independently selected from the group consisting of alkyl of 1 to 10 carbon atoms, -OH, -SH, -NH, and halogen, alkenyl of 2 to 12 carbon atoms, optionally substituted
15 aralkyl of 7 to 13 carbon atoms, optionally substituted aryl of 6 to 12 carbon atoms, and optionally substituted heteroaryl;

R₂ is phenyl, substituted phenyl (having from 1 to 3 substituents each independently
20 selected from the group consisting of halogen, alkyl of 1 to 10 carbon atoms, alkylthio of 1 to 10 carbon atoms, alkylamino of 1 to 10 carbon atoms, amino, carboxy, alkylsulfonyl of 1 to 10 carbon atoms, cyano, nitro, perfluoroalkyl of 1 to 10 carbon atoms, and alkoxy of 1 to 10 carbon atoms) or naphthyl;

25 R₃ is optionally substituted aryl and optionally substituted heteroaryl;

X is -O-, -S-, or -NH;

Y is -OH, -SH, -SR₄, -NH₂, -NHR₅, -CO₂H, -CONHOH, halogen, or heteroaryl;

R₄ is hydrogen, alkyl of 1 to 10 carbon atoms, aryl of 6 to 12 carbon atoms, and aralkyl of 7 to 13 carbon atoms;

- 5 R₅ is alkyl of 1 to 10 carbon atoms, aryl of 6 to 12 carbon atoms, and aralkyl of 7 to 13 carbon atoms;

Z is H or methyl ;

- 10 Q is an alkyl chain of 2 to 6 carbon atoms optionally substituted with 1 to 4 substituents independently selected from the group consisting of alkyl of 1 to 10 carbon atoms, -OH, -SH, -NH, halogen and alkenyl of 2 to 6 carbon atoms;

or a pharmacologically acceptable salt thereof.

15

2. A compound according to claim 1 wherein X is S or a pharmaceutically acceptable salt thereof.

- 20 3. A compound according to claim 1 or 2 wherein Y is selected from the group consisting of SH, tetrazole and imidazole or a pharmaceutically acceptable salt thereof.

4. A compound according to any one of claims 1 to 3 wherein Y is SH or a pharmaceutically acceptable salt thereof.

25

5. A compound according to any one of claims 1 to 4 wherein R₃ is thienyl or a pharmaceutically acceptable salt thereof.

- 30 6. A compound according to any one of claims 1 to 4 wherein R₃ is phenyl optionally substituted with one to three substituents each independently selected from the group consisting of halogen, alkyl of 1 to 10 carbon atoms, alkylthio of 1 to 10 carbon atoms, alkylamino of 1 to 10 carbon atoms, amino, carboxy, alkylsulfonyl of 1 to 10

carbon atoms, cyano, nitro, perfluoroalkyl of 1 to 10 carbon atoms, and alkoxy of 1 to 10 carbon atoms or a pharmaceutically acceptable salt thereof.

7. A compound according to any one of claims 1 to 6 wherein R_2 is phenyl optionally substituted with one to three substituents each independently selected from the group consisting of halogen, alkyl of 1 to 10 carbon atoms, alkylthio of 1 to 10 carbon atoms, alkylamino of 1 to 10 carbon atoms, amino, carboxy, alkylsulfonyl of 1 to 10 carbon atoms, cyano, nitro, perfluoroalkyl of 1 to 10 carbon atoms, and alkoxy of 1 to 10 carbon atoms.

10

8. A compound according to claim 1 wherein X is S and Y is SH or a pharmaceutically acceptable salt thereof.

9. A compound according to claim 1 wherein X is S; Y is SH and R_3 is thienyl or a pharmaceutically acceptable salt thereof.

15

10. A compound according to claim 1 wherein X is S; Y is selected from the group consisting of SH, tetrazole and imidazole and R_3 is thienyl or a pharmaceutically acceptable salt thereof.

20

11. A compound according to claim 1 wherein X is S; Y is SH;

R_2 is phenyl optionally substituted with one to three substituents each independently selected from the group consisting of halogen, alkyl of 1 to 10 carbon atoms, alkylthio of 1 to 10 carbon atoms, alkylamino of 1 to 10 carbon atoms, amino, carboxy, alkylsulfonyl of 1 to 10 carbon atoms, cyano, nitro, perfluoroalkyl of 1 to 10 carbon atoms, and alkoxy of 1 to 10 carbon atoms; and

25

R_3 is phenyl optionally substituted with one to three substituents each independently selected from the group consisting of halogen, alkyl of 1 to 10 carbon atoms, alkylthio of 1 to 10 carbon atoms, alkylamino of 1 to 10 carbon atoms, amino, carboxy, alkylsulfonyl of 1 to 10 carbon atoms, cyano, nitro, perfluoroalkyl of 1 to 10 carbon

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atoms, and alkoxy of 1 to 10 carbon atoms or a pharmaceutically acceptable salt thereof.

- 5 12. A compound according to claim 1 wherein X is S;
R₁ is methyl;

R₂ is phenyl optionally substituted with one to three substituents each independently selected from the group consisting of halogen, alkyl of 1 to 10 carbon atoms, alkylthio
10 of 1 to 10 carbon atoms, alkylamino of 1 to 10 carbon atoms, amino, carboxy, alkylsulfonyl of 1 to 10 carbon atoms, cyano, nitro, perfluoroalkyl of 1 to 10 carbon atoms, and alkoxy of 1 to 10 carbon atoms when R₃ is thienyl and Y is SH or a pharmaceutically acceptable salt thereof.

- 15 13. A compound according to claim 1 wherein X is S;
R₁ is methyl;

R₂ is phenyl optionally substituted with one to three substituents each independently selected from the group consisting of halogen, alkyl of 1 to 10 carbon atoms, alkylthio
20 of 1 to 10 carbon atoms, alkylamino of 1 to 10 carbon atoms, amino, carboxy, alkylsulfonyl of 1 to 10 carbon atoms, cyano, nitro, perfluoroalkyl of 1 to 10 carbon atoms, and alkoxy of 1 to 10 carbon atoms when R₃ is thienyl and Y is pyrazine or a pharmaceutically acceptable salt thereof.

- 25 14. A compound according to claim 1 wherein X is S;
R₁ is methyl;

R₂ is phenyl optionally substituted with one to three substituents each independently selected from the group consisting of halogen, alkyl of 1 to 10 carbon atoms, alkylthio
30 of 1 to 10 carbon atoms, alkylamino of 1 to 10 carbon atoms, amino, carboxy, alkylsulfonyl of 1 to 10 carbon atoms, cyano, nitro, perfluoroalkyl of 1 to 10 carbon atoms, and alkoxy of 1 to 10 carbon atoms;

R₃ is phenyl optionally substituted with one to three substituents each independently selected from the group consisting of halogen, alkyl of 1 to 10 carbon atoms, alkylthio of 1 to 10 carbon atoms, alkylamino of 1 to 10 carbon atoms, amino, carboxy, alkylsulfonyl of 1 to 10 carbon atoms, cyano, nitro, perfluoroalkyl of 1 to 10 carbon atoms, and alkoxy of 1 to 10 carbon atoms when Y is SH or a pharmaceutically acceptable salt thereof.

15. The compound of Claim 1, wherein the compound is selected from the group consisting of

10 5-(2-(((2S*,3S*)-2,3-dihydroxy-4-mercaptobutyl]thio)-2-thien-3-ylethyl)-2-methyl-2-phenylfuran-3(2H)-one,

15 5-(2-(((2R*,3S*)-2,3-dihydroxy-4-mercaptobutyl]thio)-2-thien-3-ylethyl)-2-methyl-2-phenylfuran-3(2H)-one,

5-[2-(((2R,3R)-2,3-dihydroxy-4-mercaptobutyl]thio)-2-(3-thienyl)ethyl]-2-methyl-2-phenylfuran-3(2H)-one,

20 5-(2-(((2S*,3S*)-2,3-dihydroxy-4-mercaptobutyl]thio)-2-thien-3-ylethyl)-2-(4-fluorophenyl)-2-methylfuran-3(2H)-one,

5-(2-(((2R*,3S*)-2,3-dihydroxy-4-mercaptobutyl]thio)-2-thien-3-ylethyl)-2-(4-fluorophenyl)-2-methylfuran-3(2H)-one,

25 5-(2-(((2R,3R)-2,3-dihydroxy-4-mercaptobutyl]thio)-2-thien-3-ylethyl)-2-(4-fluorophenyl)-2-methylfuran-3(2H)-one,

30 5-[2-(((2S*,3S*)-2,3-dihydroxy-4-mercaptobutyl]thio)-2-(2-nitrophenyl)ethyl]-2-methyl-2-phenylfuran-3(2H)-one,

5-(2-(((2S*,3S*)-2,3-dihydroxy-4-mercaptobutyl]thio)-1-methyl-2-thien-3-ylethyl)-2-methyl-2-phenylfuran-3(2H)-one,

- 5-[2-(4-Mercapto-butylthio)-2-thiophen-3-yl-ethyl]-2-methyl-2-phenylfuran-3-one,
- 5-[2-[(4-hydroxybutyl)thio]-2-(3-thienyl)ethyl]-2-methyl-2-phenylfuran-3(2H)-one,
- 5
- 5-[2-[(3-mercaptopropyl)thio]-2-(3-thienyl)ethyl]-2-methyl-2-phenylfuran-3(2H)-one,
- 5-[2-[(5-mercaptopentyl)thio]-2-(3-thienyl)ethyl]-2-methyl-2-phenylfuran-3(2H)-one,
- 10 5-[2-[(2-mercaptoethyl)thio]-2-(3-thienyl)ethyl]-2-methyl-2-phenylfuran-3(2H)-one,
- 5-[2-[(3-hydroxy-2-mercaptopropyl)thio]-2-(3-thienyl)ethyl]-2-methyl-2-phenylfuran-3(2H)-one,
- 15 5-[2-[(3-hydroxypropyl)thio]-2-(3-thienyl)ethyl]-2-methyl-2-phenylfuran-3(2H)-one,
- 5-[2-[(2,3-dihydroxypropyl)thio]-2-(3-thienyl)ethyl]-2-methyl-2-phenylfuran-3(2H)-one,
- 2-methyl-2-phenyl-5-[2-[(2-pyrazin-2-ylethyl)thio]-2-(3-thienyl)ethyl]furan-3(2H)-one,
- 20 5-[2-[(2-hydroxyethyl)thio]-2-(3-thienyl)ethyl]-2-methyl-2-phenylfuran-3(2H)-one,
- 2-(4-fluorophenyl)-5-[2-[(2-hydroxyethyl)thio]-2-(3-thienyl)ethyl]-2-methylfuran-3(2H)-one, and
- 25 (2R)-2-amino-3-[[2-(5-methyl-4-oxo-5-phenyl-4,5-dihydrofuran-2-yl)-1-thien-3-ylethyl]thio]propanoic acid or a pharmaceutically acceptable salt thereof.
16. A pharmaceutical composition comprising an effective amount of a compound of
- 30 any one of Claims 1 to 15 in combination with one or more pharmaceutically acceptable carriers.

17. A method of treating, inhibiting or controlling a ras-associated disease by inhibiting farnesyl-protein transferase(FPTase) enzyme in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound of any one of claims 1 to 15.

5

18. The method of Claim 17 wherein the ras-associated disease in mammals is selected from the group consisting of cancers of the pancreas, breast, lung, colon, epidermis, prostate, bladder, thyroid, myelodysplastic tumors and myeloid leukemia.

10 19. The method of Claim 17 wherein the ras-associated disease in mammals is selected from metastasis, suppressing angiogenesis, and inducing apoptosis.

20. The method of Claim 17 wherein the ras-associated proliferative disease in mammals is restenosis, neurofibromatosis, endometriosis, and psoriasis.

15

21. The method of Claim 17 wherein the ras-associated disease in mammals is prenyl modifications or proteins.

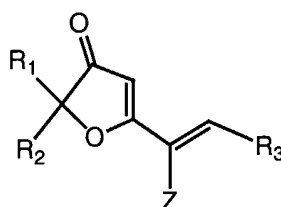
22. A compound of any one of Claims 1 to 15 for use as a pharmaceutical.

20

23. Use of a compound of any one of Claims 1 to 15 in the preparation of a medicament for treating, inhibiting or controlling a ras-associated disease by inhibiting farnesyl-protein transferase(FPTase) enzyme in a mammal in need thereof.

25 24. A process for the preparation of a compound of formula (I) as defined in any one of Claims 1 to 15 comprising

(a) reacting a compound of formula



wherein R₁, R₂, R₃ and Z are as defined in Claim 1, with a compound of formula HX-Q-Y wherein X, Q and Y are as defined in Claim 1;

or

(b) converting a compound of formula (I) to a pharmaceutically acceptable salt

5 thereof;

or

(c) resolving an isomeric mixture of compounds of formula (I) to isolate an enantiomer of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/26674

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D409/06 C07D405/06 A61K31/34 A61K31/38 A61K31/495

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 017 601 A (STEVEN W. FELMAN ET AL.) 21 May 1991 (1991-05-21) column 1 -column 2, line 35 ---	1-24
A	US 4 996 227 A (HANS W. ZIMMER ET AL.) 26 February 1991 (1991-02-26) the whole document --- -/--	1-24



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

13 January 2003

Date of mailing of the international search report

23/01/2003

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/26674

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JOHN S. WAI ET AL.: "Synthesis and biological activity of Ras Farnesyl Protein Transferase Inhibitors. Tetrapeptide Analogs with Amino Methyl and Carbon Linkages" BIOORGANIC & MEDICINAL CHEMISTRY., vol. 2, no. 9, 1994, pages 939-947, XP000565870 ELSEVIER SCIENCE LTD., GB ISSN: 0968-0896 the whole document ---	1-24
A	SAMUEL L. GRAHAM ET AL.: "Pseudopeptide Inhibitors of Ras Farnesyl-Protein Transferase" JOURNAL OF MEDICINAL CHEMISTRY., vol. 37, no. 6, 1994, pages 725-732, XP002037835 AMERICAN CHEMICAL SOCIETY., US ISSN: 0022-2623 the whole document ---	1-24
A	MARTIN SCHLITZER ET AL.: "Non-Peptidic, Non-prenyllic Bisubstrate Farnesyltransferase Inhibitors. Part 3: Structural Requirements of the Central Moiety for Farnesyltransferase Inhibitory Activity" BIOORGANIC & MEDICINAL CHEMISTRY., vol. 8, 2000, pages 2399-2406, XP002225607 ELSEVIER SCIENCE LTD., GB ISSN: 0968-0896 the whole document ---	1-24
A	THERESA M WILLIAMS: "Inhibitors of protein farnesylation 1998" EXPERT OPINION ON THERAPEUTIC PATENTS., 1998, pages 553-569, XP002225608 ASHLEY PUBLICATIONS., GB ISSN: 1354-3776 cited in the application the whole document ---	1-24
A	THERESA M. WILLIAMS ET AL.: "Farnesyl Transferase Inhibitors : Design of a new class of Cancer Chemotherapeutic Agents" ADVANCES IN MEDICINAL CHEMISTRY, vol. 4, 1999, pages 273-314, XP000918622 Jai press US the whole document -----	1-24

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 02/26674

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 17-21 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 02/26674

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 5017601	A	21-05-1991	US 4966905 A	30-10-1990
			US 5001126 A	19-03-1991
			US 5010102 A	23-04-1991
US 4996227	A	26-02-1991	NONE	