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Triazole compounds that modulate HSP90 activity

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A61K 31/423 (2006.01) **A61K 31/52 (2006.01)**
A61K 31/426 (2006.01) **A61K 31/5377 (2006.01)**
A61K 31/4439 (2006.01) **A61P 35/00 (2006.01)**
A61K 31/4709 (2006.01)

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(54) Title: TRIAZOLE COMPOUNDS THAT MODULATE HSP90 ACTIVITY

(57) Abstract: The present invention relates to substituted triazole compounds and compositions comprising substituted triazole compounds. The invention further relates to methods of treating or inhibiting angiogenesis in a subject in need thereof and methods for blocking, occluding, or otherwise disrupting blood flow in neo vasculature, in a subject in need thereof comprising administering to the subject a substituted triazole compound of the invention, or a composition comprising such a compound.

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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER	INV. A61K31/4196	A61K31/423	A61K31/426	A61K31/4439	A61K31/4709
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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)
A61P A61K

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, CHEM ABS Data, BEILSTEIN Data, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2006/055760 A (SYNTA PHARMACEUTICALS CORP [US]; YING WEIWEI [US]; JAMES DAVID [US]; Z) 26 May 2006 (2006-05-26) the whole document ----- WO 2005/000300 A (VERNALIS CAMBRIDGE LTD [GB]; CANCER REC TECH LTD [GB]; INST OF CANCER) 6 January 2005 (2005-01-06) ----- abstract; examples iii-v page 16, line 24 - page 17, line 21 ----- -/-	1-106
X		1,2,5,8, 9,13-15, 22, 52-55, 58, 60-62, 66-68,75

Further documents are listed in the continuation of Box C.

See patent family 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 doubt 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

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INTERNATIONAL SEARCH REPORT

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C(continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	DE 10 2005 007304 A1 (MERCK PATENT GMBH [DE]) 24 August 2006 (2006-08-24) the whole document -----	1,2,5,8, 9,13,14, 16,18, 20,22, 52-55, 58, 60-62, 66-69, 71,75
P, X	WO 2006/095783 A (NIPPON KAYAKU KK [JP]; KURAMOCHI HIROSHI [JP]; NIITSUMA SETSUZO [JP];) 14 September 2006 (2006-09-14) the whole document & EP 1 857 446 A (NIPPON KAYAKU KK [JP]) 21 November 2007 (2007-11-21) the whole document -----	1,8,9, 13-22, 52-54, 61,62, 66-75
E	WO 2007/139955 A (SYNTA PHARMACEUTICALS CORP [US]; CHAE JUNGHYUN [KR]; DEMKO ZACHARY [US]) 6 December 2007 (2007-12-06) the whole document -----	1-106
E	WO 2007/139967 A (SYNTA PHARMACEUTICALS CORP [US]; YING WEIWEN [US]; PRZEWLOKA TERESA [U]) 6 December 2007 (2007-12-06) the whole document -----	1-106
E	WO 2007/139960 A (SYNTA PHARMACEUTICALS CORP [US]; YING WEIWEN [US]) 6 December 2007 (2007-12-06) the whole document -----	1-106
E	WO 2007/139952 A (SYNTA PHARMACEUTICALS CORP [US]; LEE CHI-WAN [US]; JAMES DAVID [US]; Z) 6 December 2007 (2007-12-06) the whole document -----	1-106
E	WO 2007/139951 A (SYNTA PHARMACEUTICALS CORP [US]; DU ZHENJIAN [US]; FOLEY KEVIN [US]) 6 December 2007 (2007-12-06) the whole document -----	1-106
E	WO 2007/140002 A (SYNTA PHARMACEUTICALS CORP [US]; FOLEY KEVIN [US]) 6 December 2007 (2007-12-06) in particular page 23,24 page 54, 11 21-22 the whole document -----	1-106
		-/-

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/017996

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 2007/134678 A (MERCK PATENT GMBH [DE]; EGGENWEILER HANS-MICHAEL [DE]; WOLF MICHAEL [D] 29 November 2007 (2007-11-29) abstract page 59, line 22 - page 62, line 30; compounds A1-A228 -----	1, 9, 22, 52, 60-62, 66-69, 71
E	WO 2007/094819 A (SYNTA PHARMACEUTICALS CORP [US]; YING WEIWEN [US]; JAMES DAVIS [US]; P) 23 August 2007 (2007-08-23) the whole document -----	1, 8, 9, 13-23, 52, 53, 60-62
X	WO 2004/089367 A (NOVO NORDISK AS [DK]; ANDERSEN HENRIK SUNE [DK]; KAMPEN GITA CAMILLA T) 21 October 2004 (2004-10-21) abstract page 97; compounds 406-408 compounds 421-423 -----	1, 10-12, 52, 63-65
P, X	WO 2006/091246 A (UNIV SOUTHERN CALIFORNIA [US]) 31 August 2006 (2006-08-31) abstract page 84; compounds 245, 246 -----	1, 7-12, 22, 52, 60-65

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2007/017996

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 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 1-106 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:
see FURTHER INFORMATION sheet PCT/ISA/210
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 No. III Observations where unity of invention is lacking (Continuation of item 3 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 allsearchable claims.
2. As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
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 and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Although claims 1-106 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.

Continuation of Box II.2

Claims Nos.: -

Re Claim 24,62,77: these claims contain compounds/substituents not falling under the definition of claim 1,52 respectively because the value of R5 is different from "optionally substituted heteroaryl or an optionally substituted 8 to 14 membered aryl".

Re Claim 1, Claim 52: The compound disclaimed in these claims (3-(2,4-dihydroxy-phenyl) -4-(7-naphthalen-1-yl)-5-mercaptop-triazole) does not satisfy the rules of common organic compounds nomenclature as far as the number 7 is concerned, thereby making said claim unclear.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.2), should the problems which led to the Article 17(2)PCT declaration be overcome.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2007/017996

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
WO 2006055760	A	26-05-2006	AU CA EP KR	2005306484 A1 2586612 A1 1817295 A1 20070086353 A		26-05-2006 26-05-2006 15-08-2007 27-08-2007
WO 2005000300	A	06-01-2005	EP US	1638555 A1 2006235058 A1		29-03-2006 19-10-2006
DE 102005007304	A1	24-08-2006	AR AU CA EP WO	052482 A1 2006215902 A1 2598017 A1 1853570 A2 2006087077 A2		21-03-2007 24-08-2006 24-08-2006 14-11-2007 24-08-2006
WO 2006095783	A	14-09-2006	CA EP	2598899 A1 1857446 A1		14-09-2006 21-11-2007
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WO 2007139967	A	06-12-2007		NONE		
WO 2007139960	A	06-12-2007		NONE		
WO 2007139952	A	06-12-2007		NONE		
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TRIAZOLE COMPOUNDS THAT MODULATE HSP90 ACTIVITY

RELATED APPLICATIONS

The application claims the benefit of U.S. Provisional Application No. 60/838,306, filed August 17, 2006, the entire teachings of which are incorporated herein by reference.

BACKGROUND OF THE INVENTION

Heat shock proteins (HSPs) are a class of chaperone proteins that are up-regulated in response to elevated temperature and other environmental stresses, such as ultraviolet light, nutrient deprivation, and oxygen deprivation. HSPs act as chaperones to other cellular proteins (called client proteins) and facilitate their proper folding and repair, and aid in the refolding of misfolded client proteins. There are several known families of HSPs, each having its own set of client proteins. The Hsp90 family is one of the most abundant HSP families, accounting for about 1-2% of proteins in a cell that is not under stress and increasing to about 4-6% in a cell under stress. Inhibition of Hsp90 results in degradation of its client proteins via the ubiquitin proteasome pathway. Unlike other chaperone proteins, the client proteins of Hsp90 are mostly protein kinases or transcription factors involved in signal transduction, and a number of its client proteins have been shown to be involved in the progression of cancer.

Hsp90 has been shown by mutational analysis to be necessary for the survival of normal eukaryotic cells. However, Hsp90 is over expressed in many tumor types indicating that it may play a significant role in the survival of cancer cells and that cancer cells may be more sensitive to inhibition of Hsp90 than normal cells. For example, cancer cells typically have a large number of mutated and overexpressed oncoproteins that are dependent on Hsp90 for folding. In addition, because the environment of a tumor is typically hostile due to hypoxia, nutrient deprivation, acidosis, etc., tumor cells may be especially dependent on Hsp90 for survival. Moreover, inhibition of Hsp90 causes simultaneous inhibition of a number

of oncoproteins, as well as hormone receptors and transcription factors making it an attractive target for an anti-cancer agent. In fact, benzoquinone ansamycins, a family of natural products that inhibit Hsp90, has shown evidence of therapeutic activity in clinical trials.

5 Angiogenesis is a fundamental process of generating new blood vessels (neovasculature) in tissues or organs. Although angiogenesis is necessary for organ growth and repair, uncontrolled angiogenesis is involved with or associated with many diseases or disorders. (e.g. cancers, macular degeneration, autoimmune diseases, etc.) As such, angiogenesis has become a target for the treatment of these 10 diseases. Ferrara, N., *et al.*, *Nature* 438:15 967-974 (2005).

Angiogenesis is controlled by a number of growth factors and cell-adhesion molecules in endothelial and mural cells. Ferrara, N., *et al.*, *Nature* 438:15 967-974 (2005). Among these, VEGF-A (vascular endothelial growth factor-A) and its receptors have been widely studied and characterized. Ferrara, N., *et al.*, *Nature* 15 438:15 967-974 (2005). It is believed that Hsp90 chaperones a number of proteins in the angiogenic cascade. Sanderson, S., *et al.*, *Mol Cancer Ther* 5(3) 522-32 (2006). Data has shown that VEGFR-2 (VEGF receptor) and other VEGFRs are Hsp90 client proteins. Sanderson, S., *et al.*, *Mol Cancer Ther* 5(3) 522-32 (2006).

A number of VEGF inhibitors are approved or currently in clinical trials. 20 Carmeliet, P., *Nature* 438:15 932-936 (2005). Clinical trials have shown that the current angiogenesis therapies have a number of limitations, including being ineffective as a monotherapy and anti-angiogenic resistance. Carmeliet, *Nature* 438:15 932-936 (2005). Therefore, a need exists for new therapeutics that reduce or overcome the limitations of currently used anti-angiogenic agents.

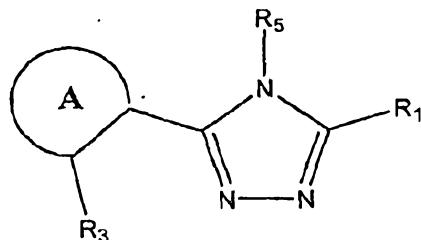
SUMMARY OF THE INVENTION

The present invention provides methods of treating or inhibiting (e.g., reducing) angiogenesis. The present invention also provides methods for reducing, blocking, occluding, or otherwise disrupting blood flow in neovasculature. The 5 present invention also provides new uses for previously disclosed compounds.

Triazole compounds that modulate Hsp90 activity have previously been described in copending U.S. Publication No.20060167070, filed November 17, 2005, which is incorporated by reference herein in its entirety.

The present invention provides compounds having the formula (I):

10



(I)

and tautomers, pharmaceutically acceptable salts, solvates, clathrates, and prodrugs thereof. In formula (I), ring A is an aryl or a heteroaryl, wherein the aryl or the 15 heteroaryl are optionally further substituted with one or more substituents in addition to R₃;

R₁ is -OH, -SH, -NR₇H, -OR₂₆, -SR₂₆, -NHR₂₆, -O(CH₂)_mOH, -O(CH₂)_mSH, -O(CH₂)_mNR₇H, -S(CH₂)_mOH, -S(CH₂)_mSH, -S(CH₂)_mNR₇H, -OC(O)NR₁₀R₁₁, -SC(O)NR₁₀R₁₁, -NR₇C(O)NR₁₀R₁₁, -OC(O)R₇, -SC(O)R₇, 20 -NR₇C(O)R₇, -OC(O)OR₇, -SC(O)OR₇, -NR₇C(O)OR₇, -OCH₂C(O)R₇, -SCH₂C(O)R₇, -NR₇CH₂C(O)R₇, -OCH₂C(O)NR₁₀R₁₁, -SCH₂C(O)NR₁₀R₁₁, -NR₇CH₂C(O)NR₁₀R₁₁, -OS(O)_pR₇, -SS(O)_pR₇, -S(O)_pOR₇, -NR₇S(O)_pR₇, -OS(O)_pNR₁₀R₁₁, -SS(O)_pNR₁₀R₁₁, -NR₇S(O)_pNR₁₀R₁₁, -OS(O)_pOR₇, -SS(O)_pOR₇, 25 -NR₇S(O)_pOR₇, -OC(S)R₇, -SC(S)R₇, -NR₇C(S)R₇, -OC(S)OR₇, -SC(S)OR₇, -NR₇C(S)OR₇, -OC(S)NR₁₀R₁₁, -SC(S)NR₁₀R₁₁, -NR₇C(S)NR₁₀R₁₁, -OC(NR₈)R₇, -SC(NR₈)R₇, -NR₇C(NR₈)R₇, -OC(NR₈)OR₇, -SC(NR₈)OR₇, -NR₇C(NR₈)OR₇, -OC(NR₈)NR₁₀R₁₁, -SC(NR₈)NR₁₀R₁₁, -NR₇C(NR₈)NR₁₀R₁₁, -OP(O)(OR₇)₂, or -SP(O)(OR₇)₂;

R₃ is -OH, -SH, -NR₇H, -OR₂₆, -SR₂₆, -NHR₂₆, -O(CH₂)_mOH,
-O(CH₂)_mSH, -O(CH₂)_mNR₇H, -S(CH₂)_mOH, -S(CH₂)_mSH, -S(CH₂)_mNR₇H,
-OC(O)NR₁₀R₁₁, -SC(O)NR₁₀R₁₁, -NR₇C(O)NR₁₀R₁₁, -OC(O)R₇, -SC(O)R₇,
-NR₇C(O)R₇, -OC(O)OR₇, -SC(O)OR₇, -NR₇C(O)OR₇, -OCH₂C(O)R₇,
5 -SCH₂C(O)R₇, -NR₇CH₂C(O)R₇, -OCH₂C(O)OR₇, -SCH₂C(O)OR₇,
-NR₇CH₂C(O)OR₇, -OCH₂C(O)NR₁₀R₁₁, -SCH₂C(O)NR₁₀R₁₁,
-NR₇CH₂C(O)NR₁₀R₁₁, -OS(O)_pR₇, -SS(O)_pR₇, -S(O)_pOR₇, -NR₇S(O)_pR₇,
-OS(O)_pNR₁₀R₁₁, -SS(O)_pNR₁₀R₁₁, -NR₇S(O)_pNR₁₀R₁₁, -OS(O)_pOR₇, -SS(O)_pOR₇,
-NR₇S(O)_pOR₇, -OC(S)R₇, -SC(S)R₇, -NR₇C(S)R₇, -OC(S)OR₇, -SC(S)OR₇,
10 -NR₇C(S)OR₇, -OC(S)NR₁₀R₁₁, -SC(S)NR₁₀R₁₁, -NR₇C(S)NR₁₀R₁₁, -OC(NR₈)R₇,
-SC(NR₈)R₇, -NR₇C(NR₈)R₇, -OC(NR₈)OR₇, -SC(NR₈)OR₇, -NR₇C(NR₈)OR₇,
-OC(NR₈)NR₁₀R₁₁, -SC(NR₈)NR₁₀R₁₁, -NR₇C(NR₈)NR₁₀R₁₁, -OP(O)(OR₇)₂, or
-SP(O)(OR₇)₂;

15 R₅ is an optionally substituted heteroaryl or an optionally substituted 8 to 14
membered aryl;

R₇ and R₈, for each occurrence, are, independently, -H, an optionally
substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl,
an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an
optionally substituted heterocycl, an optionally substituted aryl, an optionally
20 substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted
heteraralkyl;

25 R₁₀ and R₁₁, for each occurrence, are independently -H, an optionally
substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl,
an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an
optionally substituted heterocycl, an optionally substituted aryl, an optionally
substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted
heteraralkyl; or R₁₀ and R₁₁, taken together with the nitrogen to which they are
attached, form an optionally substituted heterocycl or an optionally substituted
heteroaryl;

30 R₂₆ is a lower alkyl;

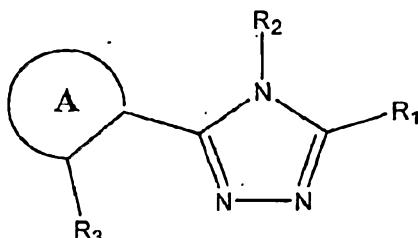
p, for each occurrence, is, independently, 1 or 2; and

m, for each occurrence, is independently, 1, 2, 3, or 4.

In one embodiment, ring A of the the compounds of formula (I) is not a substituted [1,2,3]triazole, and/or compounds represented by formula (I) do not include 3-(2,4-dihydroxy-phenyl)-4-(7-naphthalen-1-yl)-5-mercaptop-triazole.

The present invention also provides compounds having the formula (II):

5



(II)

and tautomers, pharmaceutically acceptable salts, solvates, clathrates, and prodrugs thereof. In formula (II), ring A, R₁, and R₃ are defined as for formula (I); and

10 R₂ is a substituted phenyl, wherein the phenyl group is substituted with:

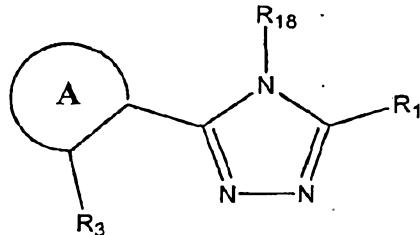
- i) one substituent selected from nitro, cyano, a haloalkoxy, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, hydroxylalkyl, alkoxyalkyl, guanadino, -NR₁₀R₁₁, -O-R₂₀, -C(O)R₇, -C(O)OR₂₀, -OC(O)R₇, -C(O)NR₁₀R₁₁, -NR₈C(O)R₇, -SR₇, -S(O)_pR₇, -OS(O)_pR₇, -S(O)_pOR₇, -NR₈S(O)_pR₇, or -S(O)_pNR₁₀R₁₁, or
- 15 ii) two to five substituents selected from the group consisting of an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted heteraralkyl, hydroxylalkyl, alkoxyalkyl, -F, -Br, -I, cyano, nitro, guanadino, a haloalkyl, a heteroalkyl, -NR₁₀R₁₁, -OR₇, -C(O)R₇, -C(O)OR₇, -OC(O)R₇, -C(O)NR₁₀R₁₁, -NR₈C(O)R₇, -SR₇,
- 20
- 25

-S(O)_pR₇, -OS(O)_pR₇, -S(O)_pOR₇, -NR₈S(O)_pR₇, or -S(O)_pNR₁₀R₁₁;
and

R₂₀, for each occurrence, is independently an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl.

In one embodiment, compounds represented by formula (II) do not include
10 3-(2,4-dihydroxy-phenyl)-4-(7-naphthalen-1-yl)-5-mercaptop-triazole, 3-(2,4-dihydroxyphenyl)-4-(2,5-dimethoxyphenyl)-5-mercaptop-triazole, 3-(1-phenyl-5-amino-pyrazol-4-yl)-4-(2,4-dichlorophenyl)-5-mercaptop-triazole, or 3-(2-hydroxy-phenyl)-4-(2,4-dimethylphenyl)-5-mercaptop-triazole.

The present invention also provides compounds having the formula (III):
15



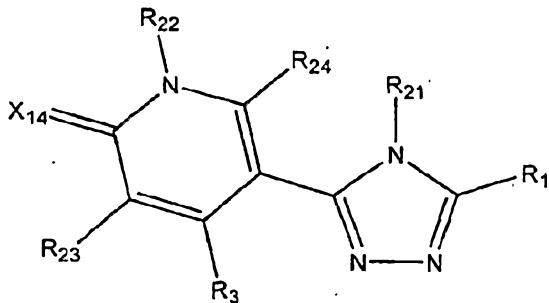
(III)

and tautomers, pharmaceutically acceptable salts, solvates, clathrates, and prodrugs thereof. In formula (III), ring A, R₁, and R₃ are defined as for formula (I); and
20 R₁₈ is an optionally substituted cycloalkyl, and optionally substituted cycloalkenyl, or a substituted alkyl, wherein the alkyl group is substituted with one or more substituents independently selected from the group consisting of an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, halo, cyano, nitro, guanadino, a haloalkyl, -NR₁₀R₁₁, -OR₇, -C(O)R₇, -C(O)OR₇, -OC(O)R₇, -C(O)NR₁₀R₁₁, -NR₈C(O)R₇, -SR₇, -S(O)_pR₇, -OS(O)_pR₇, -S(O)_pOR₇, -NR₈S(O)_pR₇, or -S(O)_pNR₁₀R₁₁, -S(O)_pOR₇, -OP(O)(OR₇)₂, or -SP(O)(OR₇)₂;

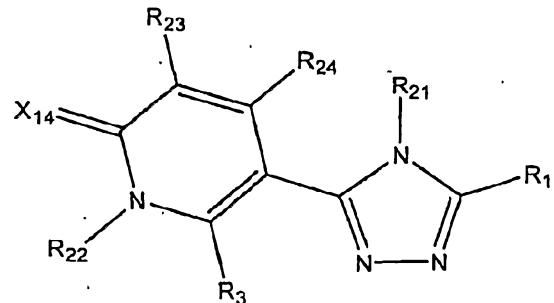
In one embodiment, compounds represented by formula (III) do not include compounds in which R_{18} is not cyclohexyl.

The invention also provides compounds represented by formula (IV) or formula (V):

5



(IV)



(V)

10 and tautomers, pharmaceutically acceptable salts, solvates, clathrates, and prodrugs thereof. In formulas (IV) and (V), R_1 and R_3 are defined as for formula (I); and X_{14} is O, S, or NR_7 ;

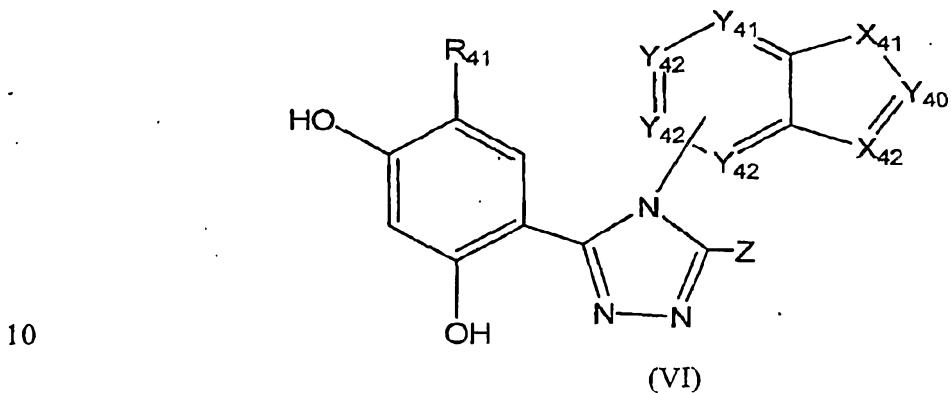
15 R_{21} is an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocycl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl;

20 R_{22} , for each occurrence, is independently -H or is selected from the group consisting of an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocycl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl, a haloalkyl, $-C(O)R_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-C(O)NR_{10}R_{11}$, $-NR_8C(O)R_7$, $-S(O)_pR_7$, $-S(O)_pOR_7$, or $-S(O)_pNR_{10}R_{11}$; and

25 R_{23} and R_{24} , for each occurrence, are independently -H or are selected from the group consisting of an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an

optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl, halo, cyano, nitro, guanadino, a haloalkyl, a heteroalkyl, -NR₁₀R₁₁, -OR₇, -C(O)R₇, -C(O)OR₇, 5 -OC(O)R₇, -C(O)NR₁₀R₁₁, -NR₈C(O)R₇, -SR₇, -S(O)_pR₇, -OS(O)_pR₇, -S(O)_pOR₇, -NR₈S(O)_pR₇, or -S(O)_pNR₁₀R₁₁.

The present invention also provides compounds represented by formula (VI):



and tautomers, pharmaceutically acceptable salts, solvates, clathrates, and prodrugs thereof, wherein:

15 X₄₁ is O, S, or NR₄₂;

 X₄₂ is CR₄₄ or N;

 Y₄₀ is N or CR₄₃;

 Y₄₁ is N or CR₄₅;

 Y₄₂, for each occurrence, is independently N, C or CR₄₆;

 Z is OH, SH, or NHR₇;

20 R₄₁ is -H, -OH, -SH, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl; an optionally substituted heteraralkyl, halo, cyano, nitro, guanadino, a haloalkyl, a heteroalkyl, an alkoxy or cycloalkoxy, a haloalkoxy, -NR₁₀R₁₁, -OR₇, -C(O)R₇, -C(O)OR₇, -C(S)R₇, -C(O)SR₇, -C(S)SR₇, -C(S)OR₇, -C(S)NR₁₀R₁₁, -C(NR₈)OR₇, -C(NR₈)R₇, -C(NR₈)NR₁₀R₁₁, -C(NR₈)SR₇, -OC(O)R₇,

25 -C(NR₈)NR₁₀R₁₁, -C(NR₈)OR₇, -C(NR₈)R₇, -C(NR₈)NR₁₀R₁₁, -C(NR₈)SR₇, -OC(O)R₇,

-OC(O)OR₇, -OC(S)OR₇, -OC(NR₈)OR₇, -SC(O)R₇, -SC(O)OR₇, -SC(NR₈)OR₇,
 -OC(S)R₇, -SC(S)R₇, -SC(S)OR₇, -OC(O)NR₁₀R₁₁, -OC(S)NR₁₀R₁₁,
 -OC(NR₈)NR₁₀R₁₁, -SC(O)NR₁₀R₁₁, -SC(NR₈)NR₁₀R₁₁, -SC(S)NR₁₀R₁₁,
 -OC(NR₈)R₇, -SC(NR₈)R₇, -C(O)NR₁₀R₁₁, -NR₈C(O)R₇, -NR₇C(S)R₇,
 5 -NR₇C(S)OR₇, -NR₇C(NR₈)R₇, -NR₇C(O)OR₇, -NR₇C(NR₈)OR₇,
 -NR₇C(O)NR₁₀R₁₁, -NR₇C(S)NR₁₀R₁₁, -NR₇C(NR₈)NR₁₀R₁₁, -SR₇, -S(O)_pR₇,
 -OS(O)_pR₇, -OS(O)_pOR₇, -OS(O)_pNR₁₀R₁₁, -S(O)_pOR₇, -NR₈S(O)_pR₇,
 -NR₇S(O)_pNR₁₀R₁₁, -NR₇S(O)_pOR₇, -S(O)_pNR₁₀R₁₁, -SS(O)_pR₇, -SS(O)_pOR₇,
 -SS(O)_pNR₁₀R₁₁, -OP(O)(OR₇)₂, or -SP(O)(OR₇)₂;

10 R₄₂ is -H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, hydroxyalkyl, alkoxyalkyl, a haloalkyl, a heteroalkyl, -C(O)R₇, -(CH₂)_mC(O)OR₇, -C(O)OR₇, -OC(O)R₇, -C(O)NR₁₀R₁₁, -S(O)_pR₇, -S(O)_pOR₇, or -S(O)_pNR₁₀R₁₁;

15 R₄₃ and R₄₄ are, independently, -H, -OH, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted heteroalkyl, a heteroalkyl, -C(O)R₇, -C(O)OR₇, -OC(O)R₇, -C(O)NR₁₀R₁₁, -NR₈C(O)R₇, -SR₇, -S(O)_pR₇, -OS(O)_pR₇, -S(O)_pOR₇, -NR₈S(O)_pR₇, -S(O)_pNR₁₀R₁₁, or R₄₃ and R₄₄ taken 20 together with the carbon atoms to which they are attached form an optionally substituted cycloalkenyl, an optionally substituted aryl, an optionally substituted heterocyclyl, or an optionally substituted heteroaryl;

25 R₄₅ is -H, -OH, -SH, -NR₇H, -OR₂₆, -SR₂₆, -NHR₂₆, -O(CH₂)_mOH, -O(CH₂)_mSH, -O(CH₂)_mNR₇H, -S(CH₂)_mOH, -S(CH₂)_mSH, -S(CH₂)_mNR₇H, -OC(O)NR₁₀R₁₁, -SC(O)NR₁₀R₁₁, -NR₇C(O)NR₁₀R₁₁, -OC(O)R₇, -SC(O)R₇, -NR₇C(O)R₇, -OC(O)OR₇, -SC(O)OR₇, -NR₇C(O)OR₇, -OCH₂C(O)R₇, -SCH₂C(O)R₇, -NR₇CH₂C(O)OR₇, -OCH₂C(O)NR₁₀R₁₁, -SCH₂C(O)NR₁₀R₁₁, -NR₇CH₂C(O)NR₁₀R₁₁, -OS(O)_pR₇, -SS(O)_pR₇, -NR₇S(O)_pR₇, -OS(O)_pNR₁₀R₁₁,

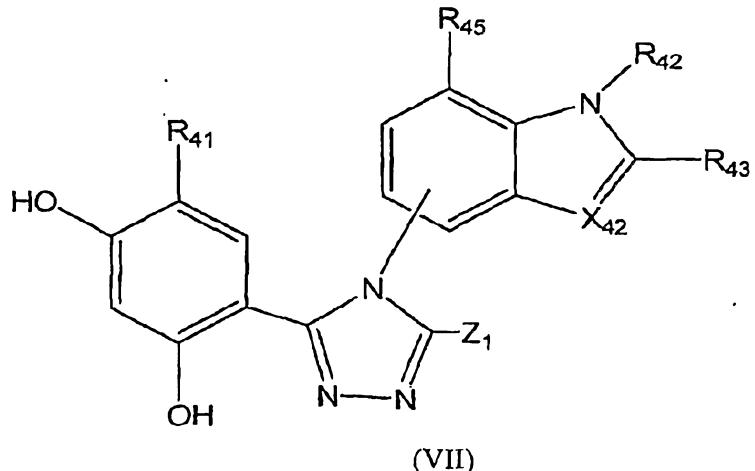
30

-SS(O)_pNR₁₀R₁₁, -NR₇S(O)_pNR₁₀R₁₁, -OS(O)_pOR₇, -SS(O)_pOR₇, -NR₇S(O)_pOR₇,
 -OC(S)R₇, -SC(S)R₇, -NR₇C(S)R₇, -OC(S)OR₇, -SC(S)OR₇, -NR₇C(S)OR₇,
 -OC(S)NR₁₀R₁₁, -SC(S)NR₁₀R₁₁, -NR₇C(S)NR₁₀R₁₁, -OC(NR₈)R₇, -SC(NR₈)R₇,
 -NR₇C(NR₈)R₇, -OC(NR₈)OR₇, -SC(NR₈)OR₇, -NR₇C(NR₈)OR₇,
 5 -OC(NR₈)NR₁₀R₁₁, -SC(NR₈)NR₁₀R₁₁, or -NR₇C(NR₈)NR₁₀R₁₁;

R₄₆, for each occurrence, is independently selected from the group consisting of H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, 10 an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, halo, cyano, nitro, guanadino, a haloalkyl, a heteroalkyl, -NR₁₀R₁₁, -OR₇, -C(O)R₇, -C(O)OR₇, -OC(O)R₇, -C(O)NR₁₀R₁₁, -NR₈C(O)R₇, -SR₇, -S(O)_pR₇, -OS(O)_pR₇, -S(O)_pOR₇, -NR₈S(O)_pR₇, or -S(O)_pNR₁₀R₁₁;
 R₇, R₈, R₁₀, R₁₁, R₂₆, p, and m are defined as above.

15

The present invention also provides compounds represented by formula (VII):



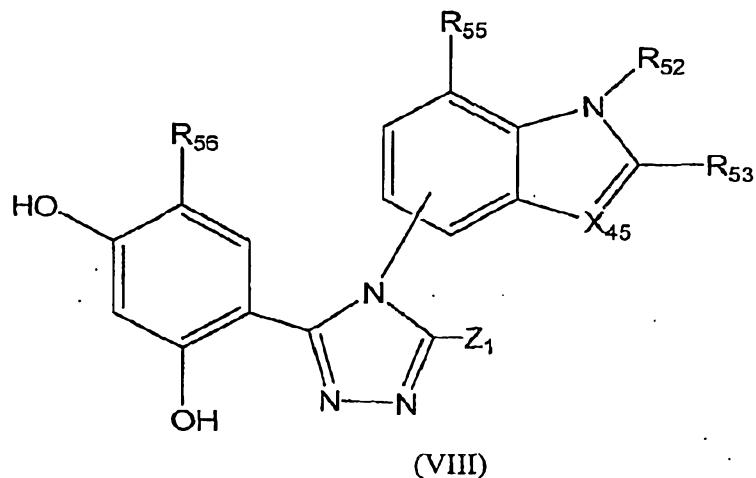
20 and tautomers, pharmaceutically acceptable salts, solvates, clathrates, and prodrugs, wherein:

Z₁ is -OH or -SH; and

X₄₂, R₄₁, R₄₂, R₄₃, and R₄₅ are defined as above.

25

The present invention also provides compounds having the formula (VIII):



and tautomers, pharmaceutically acceptable salts, solvates, clathrates, and prodrugs thereof, wherein:

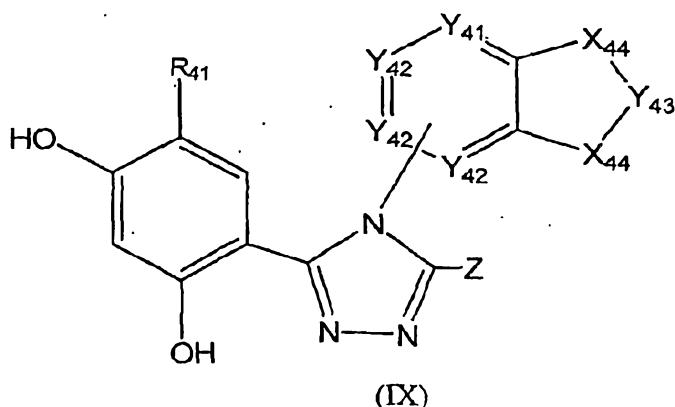
5 X_{45} is CR₅₄ or N;
 Z_1 is -OH or -SH;
 R₅₂ is selected from the group consisting of -H, methyl, ethyl, n-propyl, isopropyl, n-butyl, n-pentyl, n-hexyl, -(CH₂)₂OCH₃, -CH₂C(O)OH, and -C(O)N(CH₃)₂;

10 R₅₃ and R₅₄ are each, independently, -H, methyl, ethyl, or isopropyl; or R₅₃ and R₅₄ taken together with the carbon atoms to which they are attached form a phenyl, cyclohexenyl, or cyclooctenyl ring;

 R₅₅ is selected from the group consisting of -H, -OH, -OCH₃, and -OCH₂CH₃; and

15 R₅₆ is selected from the group consisting of -H, methyl, ethyl, isopropyl, and cyclopropyl.

The present invention also provides compounds having the formula (IX):



and tautomers, pharmaceutically acceptable salts, solvates, clathrates, and prodrugs thereof, wherein,

5 X_{44} , for each occurrence, is independently, O, S, NR_{42} or $C(R_{46})_2$;

Y_{43} is NR_{42} , $C(R_{46})_2$, $C(R_{46})_2-C(R_{46})_2$, $C(O)$, $C(S)$, $C(R_{46})_2C(O)$, or
 $C(R_{46})_2C(S)$;

Y_{41} , Y_{42} , Z , R_{41} , R_{42} , and R_{46} are defined as above.

10 In one embodiment, in formula (IX), R_{41} is selected from the group
 consisting of -H, lower alkyl, lower alkoxy, lower cycloalkyl, and lower
 cycloalkoxy.

 In another embodiment, in formula (IX), R_{41} is selected from the group
 consisting of -H, methyl, ethyl, propyl, isopropyl, cyclopropyl, methoxy, ethoxy,
 propoxy, and cycloprooxy.

15 In another embodiment, in formula (IX), R_{42} is selected from the group
 consisting of -H, methyl, ethyl, n-propyl, isopropyl, cyclopropyl, n-butyl, *sec*-butyl,
 tert-butyl, n-pentyl, n-hexyl, $-C(O)OH$, $-(CH_2)_mC(O)OH$, $-CH_2OCH_3$,
 $-CH_2CH_2OCH_3$, and $-C(O)N(CH_3)_2$.

 In another embodiment, in formula (IX), Y_{41} is CR_{45} . Preferably, R_{45} is H, a
 lower alkoxy, or -OH.

 In another embodiment, in formula (IX), Y_{42} is CH.

 In another embodiment, in formula (IX), Y_{43} is CH_2 .

 In another embodiment, in formula (IX), Y_{43} is NR_{42} , wherein R_{42} is H or a
 lower alkyl.

25 In another embodiment, in formula (IX), one of X_{44} is NR_{42} and the other is
 CH_2 or $C(R_6)_2$. Preferably, one of X_{44} is NR_{42} and the other is CH_2 .

 In another embodiment, in formula (VI), Z is -OH.

In another embodiment, Z is -SH.

In another embodiment, the compound is selected from the group consisting of:

3-(2,4-dihydroxy-5-isopropyl-phenyl)-4-(1,3-benzodioxol-5-yl)-5-mercaptop-[1,2,4] triazole;

3-(2,4-dihydroxy-5-isopropyl-phenyl)-4-(indan-5-yl)-5-mercaptop-[1,2,4] triazole;

4-Ethyl-6-[5-mercaptop-4-(1-methyl-2,3-dihydro-1H-indol-5-yl)-4H-[1,2,4]triazol-3-yl]-benzene-1,3-diol;

5-(3-(5-ethyl-2,4-dihydroxyphenyl)-5-mercaptop-4H-1,2,4-triazol-4-yl)indolin-2-one;

5-(3-(5-ethyl-2,4-dihydroxyphenyl)-5-mercaptop-4H-1,2,4-triazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one;

5-(3-(5-ethyl-2,4-dihydroxyphenyl)-5-mercaptop-4H-1,2,4-triazol-4-yl)-1-methylindolin-2-one;

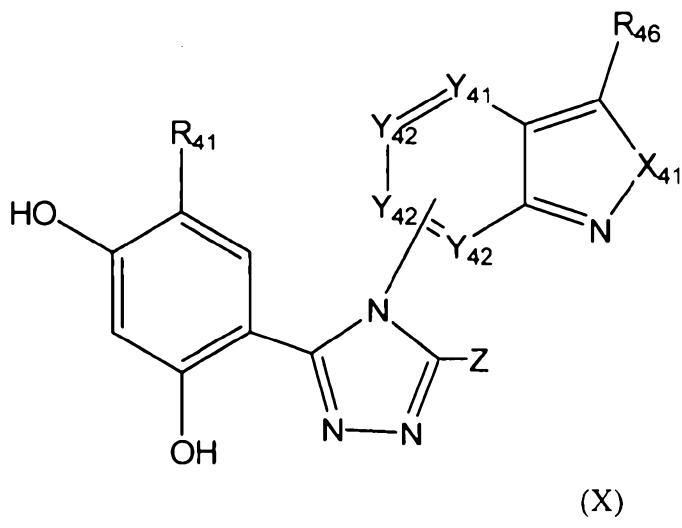
4-isopropyl-6-(5-mercaptop-4-(4-propyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)-4H-1,2,4-triazol-3-yl)benzene-1,3-diol;

6-(3-(5-ethyl-2,4-dihydroxyphenyl)-5-mercaptop-4H-1,2,4-triazol-4-yl)-2H-benzo[b][1,4]oxazin-3(4H)-one;

6-(3-(5-ethyl-2,4-dihydroxyphenyl)-5-mercaptop-4H-1,2,4-triazol-4-yl)-3-methylbenzo[d]thiazol-2(3H)-one;

6-(3-(5-ethyl-2,4-dihydroxyphenyl)-5-mercaptop-4H-1,2,4-triazol-4-yl)benzo[d]thiazol-2(3H)-one; and tautomers, pharmaceutically acceptable salts, solvates, clathrates, and prodrugs thereof.

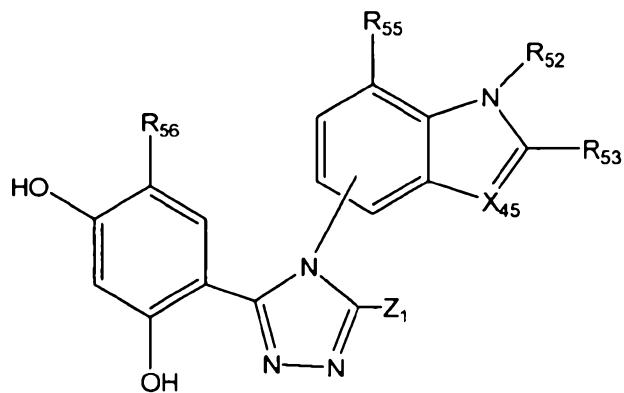
- 14 -



and tautomers, pharmaceutically acceptable salts, solvates, clathrates, and prodrugs thereof, wherein:

X_{41} , Y_{41} , Y_{42} , Z , R_7 , R_8 , R_{10} , R_{11} , R_{41} , R_{46} and p are defined as above.

In one aspect the present invention provides a method of treating, reducing or inhibiting a disease associated with angiogenesis or neovasculature in a subject in need thereof, comprising administering to the subject an effective amount of a compound represented by the following structural formula:



or a tautomer or pharmaceutically acceptable salt thereof, wherein:

X_{45} is CR_{54} ;

Z_1 is $-OH$, or $-SH$;

R_{52} is selected from the group consisting of $-H$, methyl, ethyl, n-propyl, isopropyl, n-butyl, n-pentyl, n-hexyl, $-(CH_2)_2OCH_3$, $-CH_2C(O)OH$, and $-C(O)N(CH_3)_2$;

- 14A -

R_{53} and R_{54} are each, independently, -H, methyl, ethyl, or isopropyl; or R_{53} and R_{54} taken together with the carbon atoms to which they are attached form a phenyl, cyclohexenyl, or cyclooctenyl ring; and

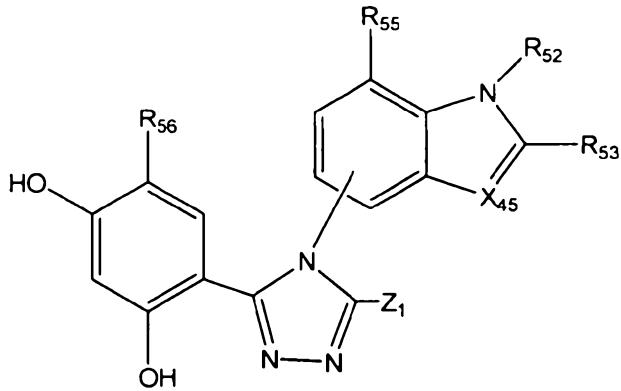
R_{55} is selected from the group consisting of -H, -OH, -OCH₃, and -OCH₂CH₃,

R_{56} is selected from the group consisting of -H, methyl, ethyl, isopropyl, and cyclopropyl;

wherein the disease is selected from the group consisting of an ocular neovascular disease; neovascular glaucoma; retrothalamic fibroplasias; epidemic keratoconjunctivitis; Vitamin A deficiency; contact lens overwear; atopic keratitis; superior limbic keratitis; pterygium keratitis sicca; sjogrens; acne rosacea; warts; eczema; phylectenulosis; syphilis; Mycobacteria infections; lipid degeneration; chemical burns; ulcers (*Helicobacter pylori*); bacterial ulcers; fungal ulcers; Herpes simplex infections; Herpes zoster infections; protozoan infections; Kaposi's sarcoma; Mooren's ulcer; Terrien's marginal degeneration; marginal keratolysis; rheumatoid arthritis; systemic lupus; polyarteritis; trauma; trauma and post-laser complications; scleritis; Stevens-Johnson disease; pemphigoid; radial keratotomy; macular degeneration; sickle cell anemia; sarcoid; pseudoxanthoma elasticum; Paget's disease; carotid obstructive disease; chronic uveitis/vitritis; Lyme's disease; Eales' disease; Behcet's disease; infections causing a retinitis or choroiditis; presumed ocular histoplasmosis; Best's disease; myopia; optic pits; Stargardt's disease; pars planitis; chronic retinal detachment; hyperviscosity syndromes; toxoplasmosis; diseases associated with rubeosis (neovascularization of the angle); osteoarthritis; ulcerative colitis; Bartonellosis; atherosclerosis; Osler-Weber-Rendu disease; telangiectasia; hereditary hemorrhagic telangiectasia; pulmonary hemangiomatosis; pre-eclampsia; endometriosis; fibrosis of the liver and of the kidney; developmental abnormalities (organogenesis); skin discolorations; wound healing; cat scratch disease (*Rochele ninalia quintosa*); gingivitis; periodontal disease; epulis; hepatitis; tonsillitis; obesity; rhinitis; laryngitis; tracheitis; bronchitis; bronchiolitis; pneumonia; pulmonary edema; neurodermitis; thyroiditis; thyroid enlargement; glomerulonephritis; gastritis; inflammatory bone and cartilage

destruction; thromboembolic disease; Buerger's disease, infectious diseases; autoimmune disorders; hemangiomas, acoustic neuromas, neurofibromas, trachomas, pyogenic granulomas; atherosclerotic plaques; corneal graft rejection, retinoblastoma, persistent hyperplastic vitreous syndrome, choroidal neovascularization, plaque neovascularization; uveitis and Pterygia (abnormal blood vessel growth) of the eye; allergic dermatitis; blistering disease; uterine bleeding; ovarian hyperstimulation; vasculogenesis; granulations; wound granulation; hypertrophic scars (keloids); nonunion fractures; vascular adhesions; vascular malformations; DiGeorge syndrome; HHT; transplant arteriopathy; restinosis; myocardial angiogenesis; coronary collaterals; cerebral collaterals; arteriovenous malformations; ischemic limb angiogenesis; primary pulmonary hypertension; nasal polyps; inflammatory bowel disease; ascites; peritoneal adhesions; Osler-Webber Syndrome; hemophiliac joints; synovitis; osteomyelitis; osteophyte formation; angiofibroma; fibromuscular dysplasia; and Crohn's disease.

In one aspect the present invention provides use of a compound represented by the following structural formula:



or a tautomer or pharmaceutically acceptable salt thereof, wherein:

X_{45} is CR $_{54}$;

Z_1 is $-\text{OH}$, or $-\text{SH}$;

R_{52} is selected from the group consisting of -H, methyl, ethyl, n-propyl, isopropyl, n-butyl, n-pentyl, n-hexyl, $-(CH_2)_2OCH_3$, $-CH_2C(O)OH$, and $-C(O)N(CH_3)_2$;

- 14C -

R_{53} and R_{54} are each, independently, -H, methyl, ethyl, or isopropyl; or R_{53} and R_{54} taken together with the carbon atoms to which they are attached form a phenyl, cyclohexenyl, or cyclooctenyl ring; and

R_{55} is selected from the group consisting of -H, -OH, -OCH₃, and -OCH₂CH₃,

R_{56} is selected from the group consisting of -H, methyl, ethyl, isopropyl, and cyclopropyl;

in the manufacture of a medicament for treating, reducing or inhibiting a disease associated with angiogenesis or neovasculature wherein the disease is selected from the group consisting of an ocular neovascular disease; neovascular glaucoma; retrolental fibroplasias; epidemic keratoconjunctivitis; Vitamin A deficiency; contact lens overwear; atopic keratitis; superior limbic keratitis; pterygium keratitis sicca; sjogrens; acne rosacea; warts; eczema; phylectenulosis; syphilis; Mycobacteria infections; lipid degeneration; chemical burns; ulcers (*Helicobacter pylori*); bacterial ulcers; fungal ulcers; Herpes simplex infections; Herpes zoster infections; protozoan infections; Kaposi's sarcoma; Mooren's ulcer; Terrien's marginal degeneration; marginal keratolysis; rheumatoid arthritis; systemic lupus; polyarteritis; trauma; trauma and post-laser complications; scleritis; Stevens-Johnson disease; pemphigoid; radial keratotomy; macular degeneration; sickle cell anemia; sarcoid; pseudoxanthoma elasticum; Paget's disease; carotid obstructive disease; chronic uveitis/vitritis; Lyme's disease; Eales' disease; Behcet's disease; infections causing a retinitis or choroiditis; presumed ocular histoplasmosis; Best's disease; myopia; optic pits; Stargardt's disease; pars planitis; chronic retinal detachment; hyperviscosity syndromes; toxoplasmosis; diseases associated with rubeosis (neovascularization of the angle); osteoarthritis; ulcerative colitis; Bartonellosis; atherosclerosis; Osler-Weber-Rendu disease; telangiectasia; hereditary hemorrhagic telangiectasia; pulmonary hemangiomatosis; pre-eclampsia; endometriosis; fibrosis of the liver and of the kidney; developmental abnormalities (organogenesis); skin discolorations; wound healing; cat scratch disease (Rochelle ninalia quintosa); gingivitis; periodontal disease; epulis; hepatitis; tonsillitis;

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obesity; rhinitis; laryngitis; tracheitis; bronchitis; bronchiolitis; pneumonia; pulmonary edema; neurodermitis; thyroiditis; thyroid enlargement; glomerulonephritis; gastritis; inflammatory bone and cartilage destruction; thromboembolic disease; Buerger's disease, infectious diseases; autoimmune disorders; hemangiomas, acoustic neuromas, neurofibromas, trachomas, pyogenic granulomas; atherosclerotic plaques; corneal graft rejection, retinoblastoma, persistent hyperplastic vitreous syndrome, choroidal neovascularization, plaque neovascularization; uveitis and Pterygia (abnormal blood vessel growth) of the eye; allergic dermatitis; blistering disease; uterine bleeding; ovarian hyperstimulation; vasculogenesis; granulations; wound granulation; hypertrophic scars (keloids); nonunion fractures; vascular adhesions; vascular malformations; DiGeorge syndrome; HHT; transplant arteriopathy; restinosis; myocardial angiogenesis; coronary collaterals; cerebral collaterals; arteriovenous malformations; ischemic limb angiogenesis; primary pulmonary hypertension; nasal polyps; inflammatory bowel disease; ascites; peritoneal adhesions; Osler-Webber Syndrome; hemophiliac joints; synovitis; osteomyelitis; osteophyte formation; angiofibroma; fibromuscular dysplasia; and Crohn's disease.

The compounds shown in Table 1 or compounds of any formula herein, or tautomers, pharmaceutically acceptable salts, solvates, clathrates, hydrates, polymorphs or prodrugs thereof, inhibit the activity of Hsp90 and, thereby facilitates the degradation of Hsp90 client proteins. Hsp90 is necessary for the survival of normal eukaryotic cells. The compounds shown in Table 1 or compounds of any formula herein, or tautomers, pharmaceutically acceptable salts, solvates, clathrates, hydrates, polymorphs or prodrugs thereof, are useful for treating, reducing or inhibiting angiogenesis. The compounds shown in Table 1 or compounds of any formula herein, or tautomers, pharmaceutically acceptable salts, solvates, clathrates, hydrates, polymorphs or prodrugs are also useful for reducing, blocking, occluding, or otherwise disrupting blood flow in neovasculature.

BRIEF DESCRIPTION OF THE DRAWINGS

The foregoing and other objects, features and advantages of the invention will be

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apparent from the following more particular description of preferred embodiments of the invention, as illustrated in the accompanying drawings in which like reference characters refer to the same parts throughout the different views. The drawings are not necessarily to scale, emphasis instead being placed upon illustrating the principles of the invention.

Figure 1 is an image of the effect of Compound 226 on HUVEC migration at different points in time (0, 24, 48, 72, and 106 hours) and at two concentrations (100 nM and 1 μ M) in comparison to DMSO treated cells.

Figure 2 is a quantification of the effect of Compound 226 on HUVEC
5 migration shown if Figure 1.

Figure 3 is a larger magnification of Figure 1 showing the effect of
Compound 226 on HUVEC migration.

Figure 4 is an image showing the effect of Compound 226 (100 nM) on
HUVEC cell morphology (76 hours after treatment) at 2X and 20X magnification
10 compared to DMSO treated cells.

Figure 5 is an image showing the effect of Compound 226 (10 nM, 100 nM,
and 1 μ M) on VE-cadherin junction between HUVEC cells in comparison to DMSO
treated cells.

DETAILED DESCRIPTION OF THE INVENTION

15 A description of preferred embodiments of the invention follows.

The present invention provides compounds and uses of said compounds.
The present invention encompasses the use of the compounds of the invention to
treat or inhibit (e.g., reduce) angiogenesis. The present invention also provides
methods for reducing, blocking, occluding, or otherwise disrupting blood flow in
20 neovasculature.

In certain embodiments, the compounds of the invention can be used in
combination with other therapies. In one aspect, compounds of the invention can be
used in combination with other anti-angiogenic agents.

25 A. Terminology

Unless otherwise specified, the below terms used herein are defined as
follows:

As used herein, the term "alkyl" means a saturated straight chain or branched
non-cyclic hydrocarbon having from 1 to 10 carbon atoms. Representative saturated
30 straight chain alkyls include methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, n-
heptyl, n-octyl, n-nonyl and n-decyl; while saturated branched alkyls include
isopropyl, *sec*-butyl, isobutyl, *tert*-butyl, isopentyl, 2-methylbutyl, 3-methylbutyl, 2-
methylpentyl, 3-methylpentyl, 4-methylpentyl, 2-methylhexyl, 3-methylhexyl, 4-

methylhexyl, 5-methylhexyl, 2,3-dimethylbutyl, 2,3-dimethylpentyl, 2,4-dimethylpentyl, 2,3-dimethylhexyl, 2,4-dimethylhexyl, 2,5-dimethylhexyl, 2,2-dimethylpentyl, 2,2-dimethylhexyl, 3,3-dimethylpentyl, 3,3-dimethylhexyl, 4,4-dimethylhexyl, 2-ethylpentyl, 3-ethylpentyl, 2-ethylhexyl, 3-ethylhexyl, 4-ethylhexyl, 2-methyl-2-ethylpentyl, 2-methyl-3-ethylpentyl, 2-methyl-4-ethylpentyl, 2-methyl-2-ethylhexyl, 2-methyl-3-ethylhexyl, 2-methyl-4-ethylhexyl, 2,2-diethylpentyl, 3,3-diethylhexyl, 2,2-diethylhexyl, 3,3-diethylhexyl and the like. The term “(C₁-C₆)alkyl” means a saturated straight chain or branched non-cyclic hydrocarbon having from 1 to 6 carbon atoms. Representative (C₁-C₆)alkyl groups 5 are those shown above having from 1 to 6 carbon atoms. Alkyl groups included in 10 compounds of this invention may be optionally substituted with one or more 15 substituents.

As used herein, the term “alkenyl” means a saturated straight chain or branched non-cyclic hydrocarbon having from 2 to 10 carbon atoms and having at 15 least one carbon-carbon double bond. Representative straight chain and branched (C₂-C₁₀)alkenyls include vinyl, allyl, 1-butenyl, 2-butenyl, isobutylenyl, 1-pentenyl, 2-pentenyl, 3-methyl-1-butenyl, 2-methyl-2-butenyl, 2,3-dimethyl-2-butenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 1-heptenyl, 2-heptenyl, 3-heptenyl, 1-octenyl, 2-octenyl, 3-octenyl, 1-nonenyl, 2-nonenyl, 3-nonenyl, 1-decenyl, 2-decenyl, 3-decenyl and the like. Alkenyl groups may be optionally substituted with one or 20 more substituents.

As used herein, the term “alkynyl” means a saturated straight chain or branched non-cyclic hydrocarbon having from 2 to 10 carbon atoms and having at 25 least one carbon-carbon triple bond. Representative straight chain and branched alkynyls include acetylenyl, propynyl, 1-butynyl, 2-butynyl, 1-pentynyl, 2-pentynyl, 3-methyl-1-butynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 5-hexynyl, 1-heptynyl, 2-heptynyl, 6-heptynyl, 1-octynyl, 2-octynyl, 7-octynyl, 1-nonyl, 2-nonyl, 8-nonyl, 1-decynyl, 2-decynyl, 9-decynyl, and the like. Alkynyl groups may be optionally substituted with one or more substituents.

As used herein, the term “cycloalkyl” means a saturated, mono- or polycyclic 30 alkyl radical having from 3 to 20 carbon atoms. Representative cycloalkyls include cyclopropyl, 1-methylcyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, -cyclodecyl, octahydro-pentalenyl, and the like. Cycloalkyl groups may be optionally substituted with one or more substituents.

As used herein, the term "cycloalkenyl" means a mono- or poly- cyclic non-aromatic alkyl radical having at least one carbon-carbon double bond in the cyclic system and from 3 to 20 carbon atoms. Representative cycloalkenyls include cyclopentenyl, cyclopentadienyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, 5 cycloheptadienyl, cycloheptatrienyl, cyclooctenyl, cyclooctadienyl, cyclooctatrienyl, cyclooctatetraenyl, cyclononenyl, cyclononadienyl, cyclodecenyl, cyclodecadienyl, 1,2,3,4,5,8-hexahydronaphthalenyl and the like. Cycloalkenyl groups may be optionally substituted with one or more substituents.

As used herein, the term "haloalkyl" means an alkyl group in which one or 10 more (including all) the hydrogen radicals are replaced by a halo group, wherein each halo group is independently selected from -F, -Cl, -Br, and -I. The term "halomethyl" means a methyl in which one to three hydrogen radical(s) have been replaced by a halo group. Representative haloalkyl groups include trifluoromethyl, bromomethyl, 1,2-dichloroethyl, 4-iodobutyl, 2-fluoropentyl, and the like.

15 As used herein, an "alkoxy" is an alkyl group which is attached to another moiety via an oxygen linker.

As used herein, an "haloalkoxy" is an haloalkyl group which is attached to another moiety via an oxygen linker.

As used herein, the term an "aromatic ring" or "aryl" means a hydrocarbon 20 monocyclic or polycyclic radical in which at least one ring is aromatic. Examples of suitable aryl groups include, but are not limited to, phenyl, tolyl, anthracenyl, fluorenyl, indenyl, azulenyl, and naphthyl, as well as benzo-fused carbocyclic moieties such as 5,6,7,8-tetrahydronaphthyl. Aryl groups may be optionally substituted with one or more substituents. In one embodiment, the aryl group is a 25 monocyclic ring, wherein the ring comprises 6 carbon atoms, referred to herein as "(C₆)aryl."

As used herein, the term "aralkyl" means an aryl group that is attached to another group by a (C₁-C₆)alkylene group. Representative aralkyl groups include benzyl, 2-phenyl-ethyl, naphth-3-yl-methyl and the like. Aralkyl groups may be 30 optionally substituted with one or more substituents.

As used herein, the term "alkylene" refers to an alkyl group that has two points of attachment. The term "(C₁-C₆)alkylene" refers to an alkylene group that has from one to six carbon atoms. Straight chain (C₁-C₆)alkylene groups are preferred. Non-limiting examples of alkylene groups include methylene (-CH₂-),

ethylene (-CH₂CH₂-), n-propylene (-CH₂CH₂CH₂-), isopropylene (-CH₂CH(CH₃)-), and the like. Alkylene groups may be optionally substituted with one or more substituents.

As used herein, the term "heterocyclyl" means a monocyclic (typically having 3- to 10-members) or a polycyclic (typically having 7- to 20-members) heterocyclic ring system which is either a saturated ring or a unsaturated non-aromatic ring. A 3- to 10-membered heterocycle can contain up to 5 heteroatoms; and a 7- to 20-membered heterocycle can contain up to 7 heteroatoms. Typically, a heterocycle has at least one carbon atom ring member. Each heteroatom is independently selected from nitrogen, which can be oxidized (e.g., N(O)) or quaternized; oxygen; and sulfur, including sulfoxide and sulfone. The heterocycle may be attached via any heteroatom or carbon atom. Representative heterocycles include morpholinyl, thiomorpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, piperazinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydropyrindinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, and the like. A heteroatom may be substituted with a protecting group known to those of ordinary skill in the art, for example, the hydrogen on a nitrogen may be substituted with a tert-butoxycarbonyl group. Furthermore, the heterocyclyl may be optionally substituted with one or more substituents. Only stable isomers of such substituted heterocyclic groups are contemplated in this definition.

As used herein, the term "heteroaromatic", "heteroaryl" or like terms means a monocyclic or polycyclic heteroaromatic ring comprising carbon atom ring members and one or more heteroatom ring members. Each heteroatom is independently selected from nitrogen, which can be oxidized (e.g., N(O)) or quaternized; oxygen; and sulfur, including sulfoxide and sulfone. Representative heteroaryl groups include pyridyl, 1-oxo-pyridyl, furanyl, benzo[1,3]dioxolyl, benzo[1,4]dioxinyl, thienyl, pyrrolyl, oxazolyl, imidazolyl, thiazolyl, a isoxazolyl, quinolinyl, pyrazolyl, isothiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, a triazinyl, triazolyl, thiadiazolyl, isoquinolinyl, indazolyl, benzoxazolyl, benzofuryl, indolizinyl, imidazopyridyl, tetrazolyl, benzimidazolyl, benzothiazolyl, benzothiadiazolyl, benzoxadiazolyl, indolyl, tetrahydroindolyl, azaindolyl, imidazopyridyl, quinazolinyl, purinyl, pyrrolo[2,3]pyrimidinyl, pyrazolo[3,4]pyrimidinyl, imidazo[1,2-a]pyridyl, and benzothienyl. In one

embodiment, the heteroaromatic ring is selected from 5-8 membered monocyclic heteroaryl rings. The point of attachment of a heteroaromatic or heteroaryl ring to another group may be at either a carbon atom or a heteroatom of the heteroaromatic or heteroaryl rings. Heteroaryl groups may be optionally substituted with one or 5 more substituents.

As used herein, the term “(C₅)heteroaryl” means an aromatic heterocyclic ring of 5 members, wherein at least one carbon atom of the ring is replaced with a heteroatom such as, for example, oxygen, sulfur or nitrogen. Representative (C₅)heteroaryls include furanyl, thienyl, pyrrolyl, oxazolyl, imidazolyl, thiazolyl, 10 isoxazolyl, pyrazolyl, isothiazolyl, pyrazinyl, triazolyl, thiadiazolyl, and the like.

As used herein, the term “(C₆)heteroaryl” means an aromatic heterocyclic ring of 6 members, wherein at least one carbon atom of the ring is replaced with a heteroatom such as, for example, oxygen, nitrogen or sulfur. Representative (C₆)heteroaryls include pyridyl, pyridazinyl, pyrazinyl, triazinyl, tetrazinyl and the 15 like.

As used herein, the term “heteroaralkyl” means a heteroaryl group that is attached to another group by a (C₁-C₆)alkylene. Representative heteroaralkyls include 2-(pyridin-4-yl)-propyl, 2-(thien-3-yl)-ethyl, imidazol-4-yl-methyl and the like. Heteroaralkyl groups may be optionally substituted with one or more 20 substituents.

As used herein, the term “halogen” or “halo” means -F, -Cl, -Br or -I.

Suitable substituents for an alkyl, alkylene, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, aralkyl, heteroaryl, and heteroaralkyl groups include any substituent which will form a stable compound of the invention. 25 Examples of substituents for an alkyl, alkylene, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, aralkyl, heteroaryl, and heteroaralkyl include an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, 30 an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, a haloalkyl, -C(O)NR₂₈R₂₉, -C(S)NR₂₈R₂₉, -C(NR₃₂)NR₂₈R₂₉, -NR₃₀C(O)R₃₁, -NR₃₀C(S)R₃₁, -NR₃₀C(NR₃₂)R₃₁, halo, -OR₃₀, cyano, nitro, haloalkoxy, -C(O)R₃₀, -C(S)R₃₀, -C(NR₃₂)R₃₀, -NR₂₈R₂₉, -C(O)OR₃₀, -C(S)OR₃₀, -C(NR₃₂)OR₃₀, -OC(O)R₃₀, -OC(S)R₃₀, -OC(NR₃₂)R₃₀,

-NR₃₀C(O)NR₂₈R₂₉, -NR₃₀C(S)NR₂₈R₂₉, -NR₃₀C(NR₃₂)NR₂₈R₂₉, -OC(O)NR₂₈R₂₉,
-OC(S)NR₂₈R₂₉, -OC(NR₃₂)NR₂₈R₂₉, -NR₃₀C(O)OR₃₁, -NR₃₀C(S)OR₃₁,
-NR₃₀C(NR₃₂)OR₃₁, -S(O)_hR₃₀, -OS(O)_pR₃₀, -NR₃₀S(O)_pR₃₀, -S(O)_pNR₂₈R₂₉,
-OS(O)_pNR₂₈R₂₉, or -NR₃₀S(O)_pNR₂₈R₂₉, wherein R₂₈ and R₂₉, for each occurrence
5 are, independently, H, an optionally substituted alkyl, an optionally substituted
alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an
optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an
optionally substituted aryl, an optionally substituted heteroaryl, an optionally
substituted aralkyl, or an optionally substituted heteraralkyl; or R₂₈ and R₂₉ taken
10 together with the nitrogen to which they are attached is optionally substituted
heterocyclyl or optionally substituted heteroaryl;
R₃₀ and R₃₁ for each occurrence are, independently, H, an optionally
substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl,
an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an
15 optionally substituted heterocyclyl, an optionally substituted aryl, an optionally
substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted
heteraralkyl; and
R₃₂, for each occurrence is, independently, H, an optionally substituted alkyl,
an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally
20 substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally
substituted heterocyclyl, an optionally substituted aryl, an optionally substituted
heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl,
-C(O)R₃₀, -C(O)NR₂₈R₂₉, -S(O)_pR₃₀, or -S(O)_pNR₂₈R₂₉;
25 p, for each occurrence, is independently, 1 or 2; and
h is 0, 1 or 2.
In addition, alkyl, cycloalkyl, alkylene, a heterocyclyl, and any saturated
portion of a alkenyl, cycloalkenyl, alkynyl, aralkyl, and heteroaralkyl groups, may
also be substituted with =O, =S, =N-R₃₂.
When a heterocyclyl, heteroaryl, or heteroaralkyl group contains a nitrogen
30 atom, it may be substituted or unsubstituted. When a nitrogen atom in the aromatic
ring of a heteroaryl group has a substituent the nitrogen may be a quaternary
nitrogen.
As used herein, the terms "subject", "patient" and "mammal" are used
interchangeably. The terms "subject" and "patient" refer to an animal (e.g., a bird

such as a chicken, quail or turkey, or a mammal), preferably a mammal including a non-primate (e.g., a cow, pig, horse, sheep, rabbit, guinea pig, rat, cat, dog, and mouse) and a primate (e.g., a monkey, chimpanzee and a human), and more preferably a human. In one embodiment, the subject is a non-human animal such as 5 a farm animal (e.g., a horse, cow, pig or sheep), or a pet (e.g., a dog, cat, guinea pig or rabbit). In a preferred embodiment, the subject is a human.

As used herein, the term "lower" refers to a group having up to four atoms. For example, a "lower alkyl" refers to an alkyl radical having from 1 to 4 carbon atoms, "lower alkoxy" refers to " $-O-(C_1-C_4)alkyl$ " and a "lower alkenyl" or "lower 10 alkynyl" refers to an alkenyl or alkynyl radical having from 2 to 4 carbon atoms, respectively.

Unless indicated otherwise, the compounds of the invention containing reactive functional groups (such as (without limitation) carboxy, hydroxy, thiol, and amino moieties) also include protected derivatives thereof. "Protected derivatives" 15 are those compounds in which a reactive site or sites are blocked with one or more protecting groups. Examples of suitable protecting groups for hydroxyl groups include benzyl, methoxymethyl, allyl, trimethylsilyl, tert-butyldimethylsilyl, acetate, and the like. Examples of suitable amine protecting groups include benzyloxycarbonyl, tert-butoxycarbonyl, tert-butyl, benzyl and fluorenylmethoxy- 20 carbonyl (Fmoc). Examples of suitable thiol protecting groups include benzyl, tert-butyl, acetyl, methoxymethyl and the like. Other suitable protecting groups are well known to those of ordinary skill in the art and include those found in T. W. Greene, Protecting Groups in Organic Synthesis, John Wiley & Sons, Inc. 1981.

As used herein, the term "compound(s) of this invention" and similar terms 25 refers to a compound of formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), or Table 1, or a pharmaceutically acceptable salt, solvate, clathrate, hydrate, polymorph or prodrug thereof, and also include protected derivatives thereof.

The compounds of the invention may contain one or more chiral centers and/or double bonds and, therefore, exist as stereoisomers, such as double-bond 30 isomers (*i.e.*, geometric isomers), enantiomers, or diastereomers. According to this invention, the chemical structures depicted herein, including the compounds of this invention, encompass all of the corresponding compounds' enantiomers, diastereomers and geometric isomers, that is, both the stereochemically pure form (*e.g.*, geometrically pure, enantiomerically pure, or diastereomerically pure) and

isomeric mixtures (e.g., enantiomeric, diastereomeric and geometric isomeric mixtures). In some cases, one enantiomer, diastereomer or geometric isomer will possess superior activity or an improved toxicity or kinetic profile compared to other isomers. In those cases, such enantiomers, diastereomers and geometric isomers of 5 compounds of this invention are preferred.

As used herein, the term "polymorph" means solid crystalline forms of a compound of the present invention or complex thereof. Different polymorphs of the same compound can exhibit different physical, chemical and/or spectroscopic properties. Different physical properties include, but are not limited to stability 10 (e.g., to heat or light), compressibility and density (important in formulation and product manufacturing), and dissolution rates (which can affect bioavailability). Differences in stability can result from changes in chemical reactivity (e.g., differential oxidation, such that a dosage form discolors more rapidly when comprised of one polymorph than when comprised of another polymorph) or 15 mechanical characteristics (e.g., tablets crumble on storage as a kinetically favored polymorph converts to thermodynamically more stable polymorph) or both (e.g., tablets of one polymorph are more susceptible to breakdown at high humidity). Different physical properties of polymorphs can affect their processing. For 20 example, one polymorph might be more likely to form solvates or might be more difficult to filter or wash free of impurities than another due to, for example, the shape or size distribution of particles of it.

As used herein, the term "hydrate" means a compound of the present invention or a salt thereof, that further includes a stoichiometric or non-stoichiometric amount of water bound by non-covalent intermolecular forces.

As used herein, the term "clathrate" means a compound of the present invention or a salt thereof in the form of a crystal lattice that contains spaces (e.g., channels) that have a guest molecule (e.g., a solvent or water) trapped within.

As used herein and unless otherwise indicated, the term "prodrug" means a derivative of a compound that can hydrolyze, oxidize, or otherwise react under 30 biological conditions (*in vitro* or *in vivo*) to provide a compound of this invention. Prodrugs may become active upon such reaction under biological conditions, or they may have activity in their unreacted forms. Examples of prodrugs contemplated in this invention include, but are not limited to, analogs or derivatives of compounds of formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), or Table 1 that

comprise biohydrolyzable moieties such as biohydrolyzable amides, biohydrolyzable esters, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, and biohydrolyzable phosphate analogues. Other examples of prodrugs include derivatives of compounds of formula (I), (II), (III), (IV), (V),
5 (VI), (VII), (VIII), (IX), (X), or Table 1 that comprise -NO, -NO₂, -ONO, or -ONO₂ moieties. Prodrugs can typically be prepared using well-known methods, such as those described by 1 BURGER'S MEDICINAL CHEMISTRY AND DRUG DISCOVERY (1995) 172-178, 949-982 (Manfred E. Wolff ed., 5th ed.).

As used herein and unless otherwise indicated, the terms "biohydrolyzable amide", "biohydrolyzable ester", "biohydrolyzable carbamate", "biohydrolyzable carbonate", "biohydrolyzable ureide" and "biohydrolyzable phosphate analogue" mean an amide, ester, carbamate, carbonate, ureide, or phosphate analogue, respectively, that either: 1) does not destroy the biological activity of the compound and confers upon that compound advantageous properties *in vivo*, such as improved
10 water solubility, improved circulating half-life in the blood (e.g., because of reduced metabolism of the prodrug), improved uptake, improved duration of action, or improved onset of action; or 2) is itself biologically inactive but is converted *in vivo* to a biologically active compound. Examples of biohydrolyzable amides include, but are not limited to, lower alkyl amides, α -amino acid amides, alkoxyacyl amides,
15 and alkylaminoalkylcarbonyl amides. Examples of biohydrolyzable esters include, but are not limited to, lower alkyl esters, alkoxyacyloxy esters, alkyl acylamino alkyl esters, and choline esters. Examples of biohydrolyzable carbamates include, but are not limited to, lower alkylamines, substituted ethylenediamines, aminoacids,
20 hydroxyalkylamines, heterocyclic and heteroaromatic amines, and polyether amines.

As used herein, "Hsp90" includes each member of the family of heat shock proteins having a mass of about 90-kiloDaltons. For example, in humans the highly conserved Hsp90 family includes cytosolic Hsp90 α and Hsp90 β isoforms, as well as GRP94, which is found in the endoplasmic reticulum, and HSP75/TRAP1, which is found in the mitochondrial matrix.

As used herein, a "proliferative disorder" or a "hyperproliferative disorder," and other equivalent terms, means a disease or medical condition involving pathological growth of cells. Proliferative disorders include cancer, smooth muscle cell proliferation, systemic sclerosis, cirrhosis of the liver, adult respiratory distress

syndrome, idiopathic cardiomyopathy, lupus erythematosus, retinopathy, e.g., diabetic retinopathy or other retinopathies, cardiac hyperplasia, reproductive system associated disorders such as benign prostatic hyperplasia and ovarian cysts, pulmonary fibrosis, endometriosis, fibromatosis, hamartomas, lymphangiomatosis, 5 sarcoidosis; desmoid tumors,

Smooth muscle cell proliferation includes hyperproliferation of cells in the vasculature, for example, intimal smooth muscle cell hyperplasia; restenosis and vascular occlusion, particularly stenosis following biologically- or mechanically-mediated vascular injury, e.g., vascular injury associated with angioplasty.

10 Moreover, intimal smooth muscle cell hyperplasia can include hyperplasia in smooth muscle other than the vasculature, e.g., bile duct blockage, bronchial airways of the lung in patients with asthma, in the kidneys of patients with renal interstitial fibrosis, and the like.

15 Non-cancerous proliferative disorders also include hyperproliferation of cells in the skin such as psoriasis and its varied clinical forms, Reiter's syndrome, pityriasis rubra pilaris, and hyperproliferative variants of disorders of keratinization (e.g., actinic keratosis, senile keratosis), scleroderma, and the like.

20 Cancers that can be treated or prevented by the methods of the present invention include, but are not limited to human sarcomas and carcinomas, e.g., fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, 25 craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendrogioma, meningioma, melanoma, neuroblastoma, retinoblastoma; leukemias, e.g., acute lymphocytic leukemia and acute myelocytic leukemia (myeloblastic, promyelocytic, myelomonocytic, monocytic and

erythroleukemia); chronic leukemia (chronic myelocytic (granulocytic) leukemia and chronic lymphocytic leukemia); and polycythemia vera, lymphoma (Hodgkin's disease and non-Hodgkin's disease), multiple myeloma, Waldenstrom's macroglobulinemia, and heavy chain disease.

5 Other examples of leukemias include acute and/or chronic leukemias, e.g., lymphocytic leukemia (e.g., as exemplified by the p388 (murine) cell line), large granular lymphocytic leukemia, and lymphoblastic leukemia; T-cell leukemias, e.g., T-cell leukemia (e.g., as exemplified by the CEM, Jurkat, and HSB-2 (acute), YAC-1 (murine) cell lines), T-lymphocytic leukemia, and T-lymphoblastic leukemia; B 10 cell leukemia (e.g., as exemplified by the SB (acute) cell line), and B-lymphocytic leukemia; mixed cell leukemias, e.g., B and T cell leukemia and B and T lymphocytic leukemia; myeloid leukemias, e.g., granulocytic leukemia, myelocytic leukemia (e.g., as exemplified by the HL-60 (promyelocyte) cell line), and myelogenous leukemia (e.g., as exemplified by the K562(chronic)cell line); 15 neutrophilic leukemia; eosinophilic leukemia; monocytic leukemia (e.g., as exemplified by the THP-1(acute) cell line); myelomonocytic leukemia; Naegeli-type myeloid leukemia; and nonlymphocytic leukemia. Other examples of leukemias are described in Chapter 60 of *The Chemotherapy Sourcebook*, Michael C. Perry Ed., Williams & Williams (1992) and Section 36 of *Holland Frie Cancer Medicine* 5th 20 Ed., Bast et al. Eds., B.C. Decker Inc. (2000). The entire teachings of the preceding references are incorporated herein by reference.

As used herein the term "multi-drug resistant cancer" refers to a cancer which initially responded to an anti-cancer drug becomes resistant to the anti-cancer drug when the anti-cancer drug is no longer effective in treating the subject with the 25 cancer. For example, many tumors will initially respond to treatment with an anti-cancer drug by decreasing in size or even going into remission, only to develop resistance to the drug. Drug resistant tumors are characterized by a resumption of their growth and/or reappearance after having seemingly gone into remission, despite the administration of increased dosages of the anti-cancer drug. Cancers that 30 have developed resistance to two or more anti-cancer drugs are said to be "multi-drug resistant". For example, it is common for cancers to become resistant to three or more anti-cancer agents, often five or more anti-cancer agents and at times ten or more anti-cancer agents.

As used herein, the term “pharmaceutically acceptable salt,” is a salt formed from, for example, an acid and a basic group of one of the compounds of formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), or Table 1. Illustrative salts include, but are not limited, to sulfate, citrate, acetate, oxalate, chloride, bromide, 5 iodide, nitrate, bisulfate, phosphate, acid phosphate, isonicotinate, lactate, salicylate, acid citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, besylate, gentisinate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, *p*-toluenesulfonate, and pamoate (*i.e.*, 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)) 10 salts. The term “pharmaceutically acceptable salt” also refers to a salt prepared from a compound of formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), or Table 1 having an acidic functional group, such as a carboxylic acid functional group, and a pharmaceutically acceptable inorganic or organic base. Suitable bases include, but are not limited to, hydroxides of alkali metals such as sodium, 15 potassium, and lithium; hydroxides of alkaline earth metal such as calcium and magnesium; hydroxides of other metals, such as aluminum and zinc; ammonia, and organic amines, such as unsubstituted or hydroxy-substituted mono-, di-, or trialkylamines; dicyclohexylamine; tributyl amine; pyridine; N-methyl,N-ethylamine; diethylamine; triethylamine; mono-, bis-, or tris-(2-hydroxy-lower alkyl 20 amines), such as mono-, bis-, or tris-(2-hydroxyethyl)amine, 2-hydroxy-tert-butylamine, or tris-(hydroxymethyl)methylamine, N,N-di-lower alkyl-N-(hydroxy lower alkyl)-amines, such as N,N-dimethyl-N-(2-hydroxyethyl)amine, or tri-(2-hydroxyethyl)amine; N-methyl-D-glucamine; and amino acids such as arginine, 25 lysine, and the like. The term “pharmaceutically acceptable salt” also refers to a salt prepared from a compound of formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), or Table 1 having a basic functional group, such as an amine functional group, and a pharmaceutically acceptable inorganic or organic acid.. Suitable acids include, but are not limited to, hydrogen sulfate, citric acid, acetic acid, oxalic acid, hydrochloric acid (HCl), hydrogen bromide (HBr), hydrogen iodide (HI), nitric acid, 30 hydrogen bisulfide, phosphoric acid, lactic acid, salicylic acid, tartaric acid, bitartratic acid, ascorbic acid, succinic acid, maleic acid, besylic acid, fumaric acid, gluconic acid, glucaronic acid, formic acid, benzoic acid, glutamic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, and *p*-toluenesulfonic acid.

In one embodiment, compounds of the invention are vascular targeting agents. In one aspect, compounds of the invention are effective for reducing, blocking, occluding, or otherwise disrupting blood flow in "neovasculature." In one aspect, the invention provides a novel treatment for diseases involving the growth of new blood vessels ("neovasculature"), including, but not limited to: cancer; infectious diseases; autoimmune disorders; benign tumors, *e.g.* hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas; arteriosclerotic plaques; ocular angiogenic diseases, *e.g.*, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, 5 neovascular glaucoma, retrolental fibroplasia, rubeosis, retinoblastoma, persistent hyperplastic vitreous syndrome, choroidal neovascularization, uveitis and Pterygia (abnormal blood vessel growth) of the eye; rheumatoid arthritis; psoriasis; warts; allergic dermatitis; blistering disease; Karposi sarcoma; delayed wound healing; 10 endometriosis; uterine bleeding; ovarian cysts; ovarian hyperstimulation; vasculogenesis; granulations; hypertrophic scars (keloids); nonunion fractures; 15 scleroderma; trachoma; vascular adhesions; vascular malformations; DiGeorge syndrome; HHT; transplant arteriopathy; restinosis; obesity; myocardial angiogenesis; coronary collaterals; cerebral collaterals; arteriovenous malformations; ischemic limb angiogenesis; primary pulmonary hypertension; 20 pulmonary edema; asthma; nasal polyps; inflammatory bowel disease; periodontal disease; ascites; peritoneal adhesions; Osler-Webber Syndrome; plaque neovascularization; telangiectasia; hemophiliac joints; synovitis; osteomyelitis; osteophyte formation; angiofibroma; fibromuscular dysplasia; wound granulation; Crohn's disease; and atherosclerosis.

25 Vascular targeting can be demonstrated by any method known to those skilled in the art, such as the method described herein in Examples 170 and 171.

As used herein, the term "angiogenesis" refers to a fundamental process of generating new blood vessels in tissues or organs. Angiogenesis is involved with or associated with many diseases or conditions, including, but not limited to: cancer; 30 ocular neovascular disease; age-related macular degeneration; diabetic retinopathy, retinopathy of prematurity; corneal graft rejection; neovascular glaucoma; retrolental fibroplasias; epidemic keratoconjunctivitis; Vitamin A deficiency; contact lens overwear; atopic keratitis; superior limbic keratitis; pterygium keratitis sicca;

sjogrens; acne rosacea; warts; eczema; phylectenulosis; syphilis; Mycobacteria infections; lipid degeneration; chemical burns; bacterial ulcers; fungal ulcers; Herpes simplex infections; Herpes zoster infections; protozoan infections; Kaposi's sarcoma; Mooren's ulcer; Terrien's marginal degeneration; marginal keratolysis; 5 rheumatoid arthritis; systemic lupus; polyarteritis; trauma; Wegener's sarcoidosis; scleritis; Stevens-Johnson disease; pemphigoid; radial keratotomy; corneal graft rejection; diabetic retinopathy; macular degeneration; sickle cell anemia; sarcoid; syphilis; pseudoxanthoma elasticum; Paget's disease; vein occlusion; artery occlusion; carotid obstructive disease; chronic uveitis/vitritis; mycobacterial infections; Lyme's disease; systemic lupus erythematosis; retinopathy of 10 prematurity; Eales' disease; Behcet's disease; infections causing a retinitis or choroiditis; presumed ocular histoplasmosis; Best's disease; myopia; optic pits; Stargardt's disease; pars planitis; chronic retinal detachment; hyperviscosity syndromes; toxoplasmosis; trauma and post-laser complications; diseases associated 15 with rubeosis (neovascularization of the angle); diseases caused by the abnormal proliferation of fibrovascular or fibrous tissue including all forms of proliferative vitreoretinopathy; rheumatoid arthritis; osteoarthritis; ulcerative colitis; Crohn's disease; Bartonellosis; atherosclerosis; Osler-Weber-Rendu disease; hereditary hemorrhagic telangiectasia; pulmonary hemangiomatosis; pre-eclampsia; 20 endometriosis; fibrosis of the liver and of the kidney; developmental abnormalities (organogenesis); skin discolorations (e.g., hemangioma, nevus flammeus, or nevus simplex); wound healing; hypertrophic scars, i.e., keloids; wound granulation; vascular adhesions; cat scratch disease (Rochele ninalia quintosa); ulcers (Helicobacter pylori); keratoconjunctivitis; gingivitis; periodontal disease; epulis; 25 hepatitis; tonsillitis; obesity; rhinitis; laryngitis; tracheitis; bronchitis; bronchiolitis; pneumonia; interstitial pulmonary fibrosis; pulmonary edema; neurodermitis; thyroiditis; thyroid enlargement; endometriosis; glomerulonephritis; gastritis; inflammatory bone and cartilage destruction; thromboembolic disease; and Buerger's disease.

30 As used herein, the term "pharmaceutically acceptable solvate," is a solvate formed from the association of one or more pharmaceutically acceptable solvent molecules to one of the compounds of formula (I), (II), (III), (IV), (V), (VI), (VII),

(VIII), (IX), (X), or Table 1. The term solvate includes hydrates (e.g., hemihydrate, monohydrate, dihydrate, trihydrate, tetrahydrate, and the like).

A pharmaceutically acceptable carrier may contain inert ingredients which do not unduly inhibit the biological activity of the compounds. The 5 pharmaceutically acceptable carriers should be biocompatible, i.e., non-toxic, non-inflammatory, non-immunogenic and devoid of other undesired reactions upon the administration to a subject. Standard pharmaceutical formulation techniques can be employed, such as those described in Remington's Pharmaceutical Sciences, *ibid*. Suitable pharmaceutical carriers for parenteral administration include, for example, 10 sterile water, physiological saline, bacteriostatic saline (saline containing about 0.9% mg/ml benzyl alcohol), phosphate-buffered saline, Hank's solution, Ringer's-lactate and the like. Methods for encapsulating compositions (such as in a coating of hard gelatin or cyclodextran) are known in the art (Baker, *et al.*, "Controlled Release of Biological Active Agents", John Wiley and Sons, 1986).

15 As used herein, the term "effective amount" refers to an amount of a compound of this invention which is sufficient to reduce or ameliorate the severity, duration, progression, or onset of an angiogenesis related disorder, prevent the advancement of a an angiogenesis related disorder, cause the regression of an angiogenesis related disorder, prevent the recurrence, development, onset or 20 progression of a symptom associated with an angiogenesis related disorder, or enhance or improve the prophylactic or therapeutic effect(s) of another therapy. In one embodiment, the term refers to the amount of the compound needed to reduce, block, occlude, or otherwise disrupt blood flow in neovasculature. The precise amount of compound administered to a subject will depend on the mode of 25 administration, the type and severity of the disease or condition and on the characteristics of the subject, such as general health, age, sex, body weight and tolerance to drugs. It will also depend on the degree, severity and type of the angiogenesis related, and the mode of administration. The skilled artisan will be able to determine appropriate dosages depending on these and other factors. When 30 co-administered with other agents, e.g., when co-administered with a chemotherapeutic agent, an "effective amount" of the second agent will depend on the type of drug used. Suitable dosages are known for approved agents and can be adjusted by the skilled artisan according to the condition of the subject, the type of condition(s) being treated and the amount of a compound of the invention being

used. In cases where no amount is expressly noted, an effective amount should be assumed.

Non-limiting examples of an effective amount of a compound of the invention are provided herein below. In a specific embodiment, the invention 5 provides a method of preventing, treating, managing, or ameliorating an angiogenesis related disorder or one or more symptoms thereof, said methods comprising administering to a subject in need thereof a dose of at least 150 μ g/kg, preferably at least 250 μ g/kg, at least 500 μ g/kg, at least 1 mg/kg, at least 5 mg/kg, at least 10 mg/kg, at least 25 mg/kg, at least 50 mg/kg, at least 75 mg/kg, at least 100 10 mg/kg, at least 125 mg/kg, at least 150 mg/kg, or at least 200 mg/kg or more of one or more compounds of the invention once every day, preferably, once every 2 days, once every 3 days, once every 4 days, once every 5 days, once every 6 days, once every 7 days, once every 8 days, once every 10 days, once every two weeks, once every three weeks, or once a month.

15 The dosages of a chemotherapeutic agents other than compounds of the invention, which have been or are currently being used to prevent, treat, manage, or ameliorate a proliferative disorder, or one or more symptoms thereof, can be used in the combination therapies of the invention. Preferably, dosages lower than those which have been or are currently being used to prevent, treat, manage, or ameliorate 20 a proliferative disorder, or one or more symptoms thereof, are used in the combination therapies of the invention. The recommended dosages of agents currently used for the prevention, treatment, management, or amelioration of a proliferative disorder, or one or more symptoms thereof, can be obtained from any reference in the art including, but not limited to, Hardman *et al.*, eds., 1996,

25 Goodman & Gilman's The Pharmacological Basis Of Basis Of Therapeutics 9th Ed, Mc-Graw-Hill, New York; Physician's Desk Reference (PDR) 57th Ed., 2003, Medical Economics Co., Inc., Montvale, NJ, which are incorporated herein by reference in its entirety.

As used herein, the terms "treat", "treatment" and "treating" refer to the 30 reduction or amelioration of the progression, severity and/or duration of a disease or disorder, or the amelioration of one or more symptoms (preferably, one or more discernible symptoms) of a disease or disorder resulting from the administration of one or more therapies (e.g., one or more therapeutic agents such as a compound of the invention). In specific embodiments, the terms "treat", "treatment" and

“treating” refer to the amelioration of at least one measurable physical parameter of an angiogenesis related disorder, not necessarily discernible by the patient. In other embodiments the terms “treat”, “treatment” and “treating” refer to the inhibition (e.g., reduction) of the progression of an angiogenesis related disorder, either 5 physically by, *e.g.*, stabilization of a discernible symptom, physiologically by, *e.g.*, stabilization of a physical parameter, or both. In other embodiments the terms “treat”, “treatment” and “treating” refers to reduce, blocking, occluding, or otherwise disrupting blood flow in neovasculature.

As used herein, the terms “prevent”, “prevention” and “preventing” refer to 10 the reduction in the risk of acquiring or developing a disease or disorder, or the reduction or inhibition of the recurrence or a disease or disorder. In one embodiment, a compound of the invention is administered as a preventative measure to a patient, preferably a human, having a genetic predisposition to any of the disorders described herein.

15 As used herein, the terms “therapeutic agent” and “therapeutic agents” refer to any agent(s) which can be used in the treatment, management, or amelioration of a disease or disorder or one or more symptoms thereof. In certain embodiments, the term “therapeutic agent” refers to a compound of the invention. In certain other embodiments, the term “therapeutic agent” refers does not refer to a compound of 20 the invention. Preferably, a therapeutic agent is an agent which is known to be useful for, or has been or is currently being used for the treatment, management, prevention, or amelioration of an angiogenesis related disorder or one or more symptoms thereof.

As used herein, the term “synergistic” refers to a combination of a compound 25 of the invention and another therapy (*e.g.*, a prophylactic or therapeutic agent), which is more effective than the additive effects of the therapies. A synergistic effect of a combination of therapies (*e.g.*, a combination of prophylactic or therapeutic agents) permits the use of lower dosages of one or more of the therapies and/or less frequent administration of said therapies to a subject with a proliferative 30 disorder. The ability to utilize lower dosages of a therapy (*e.g.*, a prophylactic or therapeutic agent) and/or to administer said therapy less frequently reduces the toxicity associated with the administration of said therapy to a subject without reducing the efficacy of said therapy in the prevention, management or treatment of a proliferative disorder. In addition, a synergistic effect can result in improved

efficacy of agents in the prevention, management or treatment of an angiogenesis related disorder. Finally, a synergistic effect of a combination of therapies (e.g., a combination of prophylactic or therapeutic agents) may avoid or reduce adverse or unwanted side effects associated with the use of either therapy alone.

5 As used herein, the phrase "side effects" encompasses unwanted and adverse effects of a therapy (e.g., a prophylactic or therapeutic agent). Side effects are always unwanted, but unwanted effects are not necessarily adverse. An adverse effect from a therapy (e.g., prophylactic or therapeutic agent) might be harmful or uncomfortable or risky. Side effects include, but are not limited to fever, chills, 10 lethargy, gastrointestinal toxicities (including gastric and intestinal ulcerations and erosions), nausea, vomiting, neurotoxicities, nephrotoxicities, renal toxicities (including such conditions as papillary necrosis and chronic interstitial nephritis), hepatic toxicities (including elevated serum liver enzyme levels), myelotoxicities (including leukopenia, myelosuppression, thrombocytopenia and anemia), dry 15 mouth, metallic taste, prolongation of gestation, weakness, somnolence, pain (including muscle pain, bone pain and headache), hair loss, asthenia, dizziness, extra-pyramidal symptoms, akathisia, cardiovascular disturbances and sexual dysfunction.

As used herein, the term "in combination" refers to the use of more than one 20 therapies (e.g., one or more prophylactic and/or therapeutic agents). The use of the term "in combination" does not restrict the order in which therapies (e.g., prophylactic and/or therapeutic agents) are administered to a subject with a disease or disorder. A first therapy (e.g., a prophylactic or therapeutic agent such as a compound of the invention) can be administered prior to (e.g., 5 minutes, 15 25 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks before), concomitantly with, or subsequent to (e.g., 5 30 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks after) the administration of a second therapy (e.g., a prophylactic or therapeutic agent such as an anti-cancer agent) to a subject with an angiogenesis related disorder, such as macular degeneration.

As used herein, the terms "therapies" and "therapy" can refer to any protocol(s), method(s), and/or agent(s) that can be used in the prevention, treatment,

management, or amelioration of an angiogenesis related disorder or one or more symptoms thereof.

A used herein, a "protocol" includes dosing schedules and dosing regimens. The protocols herein are methods of use and include prophylactic and therapeutic 5 protocols.

As used herein, the terms "manage," "managing," and "management" refer to the beneficial effects that a subject derives from a therapy (e.g., a prophylactic or therapeutic agent), which does not result in a cure of the disease. In certain 10 embodiments, a subject is administered one or more therapies (e.g., one or more prophylactic or therapeutic agents) to "manage" a disease so as to prevent the progression or worsening of the disease.

As used herein, a composition that "substantially" comprises a compound means that the composition contains more than about 80% by weight, more 15 preferably more than about 90% by weight, even more preferably more than about 95% by weight, and most preferably more than about 97% by weight of the compound.

As used herein, a reaction that is "substantially complete" means that the 20 reaction contains more than about 80% by weight of the desired product, more preferably more than about 90% by weight of the desired product, even more preferably more than about 95% by weight of the desired product, and most preferably more than about 97% by weight of the desired product.

As used herein, a racemic mixture means about 50% of one enantiomer and about 50% of its corresponding enantiomer relative to a chiral center in the molecule. The invention encompasses all enantiomerically-pure, enantiomerically-enriched, 25 diastereomerically pure, diastereomerically enriched, and racemic mixtures of the compounds of the invention.

Enantiomeric and diastereomeric mixtures can be resolved into their component enantiomers or diastereomers by well known methods, such as chiral-phase gas chromatography, chiral-phase high performance liquid chromatography, 30 crystallizing the compound as a chiral salt complex, or crystallizing the compound in a chiral solvent. Enantiomers and diastereomers can also be obtained from diastereomerically- or enantiomerically-pure intermediates, reagents, and catalysts by well known asymmetric synthetic methods.

The compounds of the invention are defined herein by their chemical structures and/or chemical names. Where a compound is referred to by both a chemical structure and a chemical name, and the chemical structure and chemical name conflict, the chemical structure is determinative of the compound's identity.

5 When administered to a patient, *e.g.*, to a non-human animal for veterinary use or for improvement of livestock, or to a human for clinical use, the compounds of the invention are administered in isolated form or as the isolated form in a pharmaceutical composition. As used herein, "isolated" means that the compounds of the invention are separated from other components of either (a) a natural source, 10 such as a plant or cell, preferably bacterial culture, or (b) a synthetic organic chemical reaction mixture. Preferably, the compounds of the invention are purified via conventional techniques. As used herein, "purified" means that when isolated, the isolate contains at least 95%, preferably at least 98%, of a compound of the invention by weight of the isolate either as a mixture of stereoisomers or as a 15 diastereomeric or enantiomeric pure isolate.

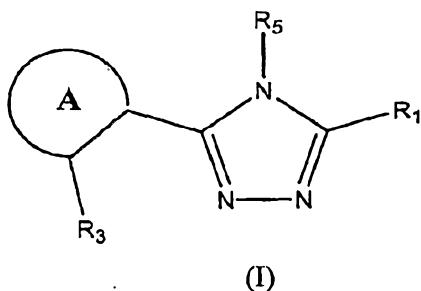
As used herein, a composition that is "substantially free" of a compound means that the composition contains less than about 20% by weight, more preferably less than about 10% by weight, even more preferably less than about 5% by weight, and most preferably less than about 3% by weight of the compound.

20 Only those choices and combinations of substituents that result in a stable structure are contemplated. Such choices and combinations will be apparent to those of ordinary skill in the art and may be determined without undue experimentation.

25 The invention can be understood more fully by reference to the following detailed description and illustrative examples, which are intended to exemplify non-limiting embodiments of the invention.

B. The Compounds of the Invention

The present invention encompasses compounds having Formulas (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), and those set forth in Table 1 and 30 tautomers, pharmaceutically acceptable salts, solvates, clathrates, hydrates, polymorphs and prodrugs thereof. In one aspect, the invention provides compounds of formula (I) as set forth below:

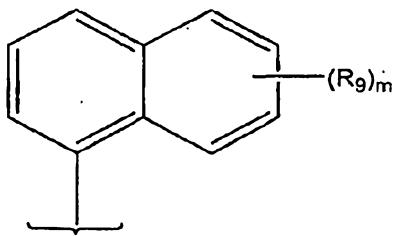


and tautomers, pharmaceutically acceptable salts, solvates, clathrates, and prodrugs thereof, wherein ring A, R₁, R₃ and R₅ are defined as above.

5 Compounds of formula (I) inhibit the activity of Hsp90 and are particularly useful for treating or preventing (e.g., reduce the likelihood of developing) angiogenesis related disorders, such as macular degeneration. In addition, compounds of formula (I) are particularly useful in reducing, blocking, occluding, or otherwise disrupting blood flow in neovasculature.

10 In one embodiment, in the compounds of formula (I), R₅ is an optionally substituted naphthyl.

In another embodiment, in the compounds of formula (I), R₅ is represented by the following formula:



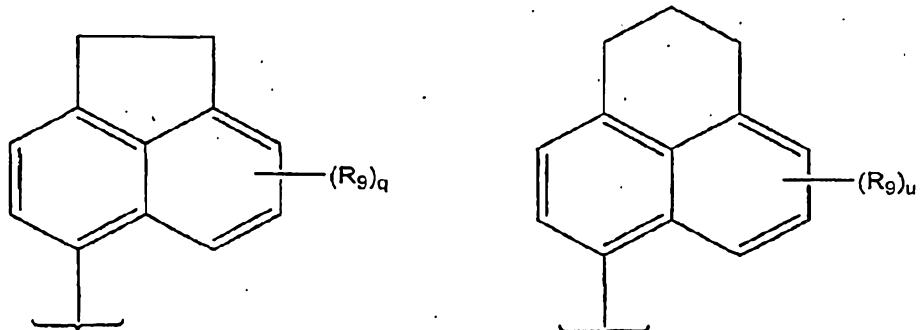
15 wherein:

R₉, for each occurrence, is independently a substituent selected from the group consisting of an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, hydroxyalkyl, alkoxyalkyl, halo, cyano, nitro, guanadino, a haloalkyl, a heteroalkyl, -NR₁₀R₁₁, -OR₇, -C(O)R₇, -C(O)OR₇, -OC(O)R₇, -C(O)NR₁₀R₁₁, -NR₈C(O)R₇, -SR₇, -S(O)_pR₇, -OS(O)_pR₇, -S(O)_pOR₇, -NR₈S(O)_pR₇, or -S(O)_pNR₁₀R₁₁, -S(O)_pOR₇, -OP(O)(OR₇)₂, or 25 -SP(O)(OR₇)₂;

or two R_9 groups taken together with the carbon atoms to which they are attached form a fused ring; and

m is zero or an integer from 1 to 7, wherein R_7 , R_8 , R_{10} , R_{11} , and p are defined as above.

5 In another embodiment, in the compounds represented by formula (I), R_5 is represented by one of the following formulas:

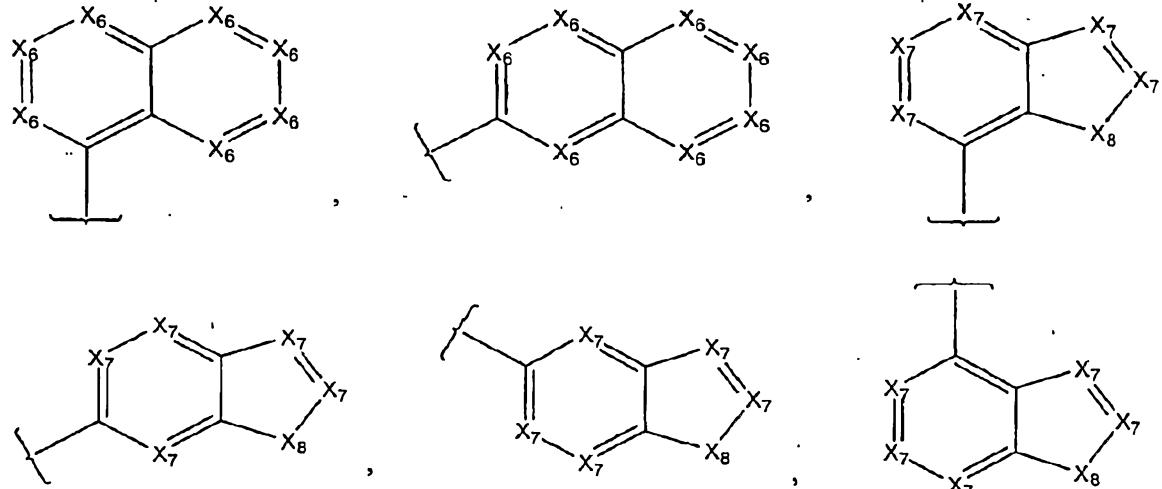


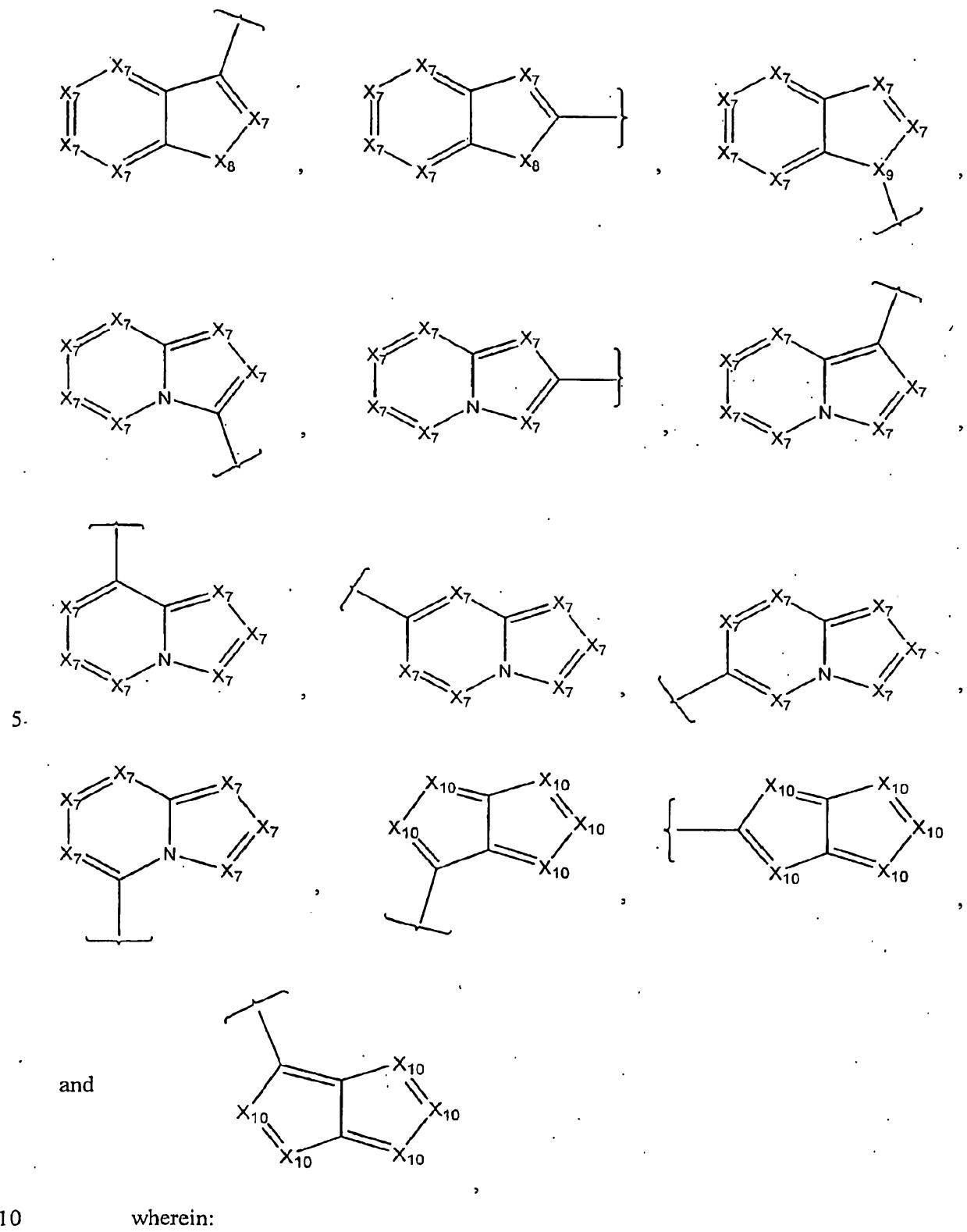
wherein R_9 is defined as above;

q is zero or an integer from 1 to 7; and

10 u is zero or an integer from 1 to 8.

In another embodiment, in the compounds represented by formula (I), R_5 is selected from the group consisting of:





X₆, for each occurrence, is independently CH, CR₉, N, N(O), N⁺(R₁₇), provided that at least three X₆ groups are independently selected from CH and CR₉;

X₇, for each occurrence, is independently CH, CR₉, N, N(O), N⁺(R₁₇), provided that at least three X₇ groups are independently selected from CH and CR₉;

5 X₈, for each occurrence, is independently CH₂, CHR₉, CR₉R₉, O, S, S(O)p, NR₇, or NR₁₇;

X₉, for each occurrence, is independently N or CH;

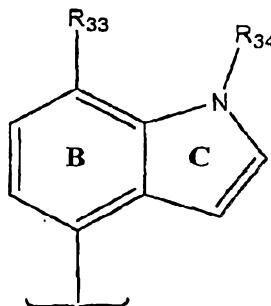
X₁₀, for each occurrence, is independently CH, CR₉, N, N(O), N⁺(R₁₇), provided that at least one X₁₀ is selected from CH and CR₉;

10 R₁₇, for each occurrence, is independently -H, an alkyl, an aralkyl, -C(O)R₇, -C(O)OR₇, or -C(O)NR₁₀R₁₁; wherein R₇, R₉, R₁₀, R₁₁ and p are defined as above.

In another embodiment, in the compounds represented by formula (I), R₅ is an optionally substituted indolyl, an optionally substituted benzoimidazolyl, an optionally substituted indazolyl, an optionally substituted 3*H*-indazolyl, an 15 optionally substituted indolizinyl, an optionally substituted quinolinyl, an optionally substituted isoquinolinyl, an optionally substituted benzoxazolyl, an optionally substituted benzo[1,3]dioxolyl, an optionally substituted benzofuryl, an optionally substituted benzothiazolyl, an optionally substituted benzo[d]isoxazolyl, an optionally substituted benzo[d]isothiazolyl, an optionally substituted thiazolo[4,5-c]pyridinyl, an optionally substituted thiazolo[5,4-c]pyridinyl, an optionally substituted thiazolo[4,5-b]pyridinyl, an optionally substituted thiazolo[5,4-b]pyridinyl, an optionally substituted oxazolo[4,5-c]pyridinyl, an optionally substituted oxazolo[4,5-b]pyridinyl, an optionally substituted oxazolo[5,4-c]pyridinyl, an optionally substituted oxazolo[5,4-b]pyridinyl, an optionally substituted imidazopyridinyl, an optionally substituted benzothiadiazolyl, 20 benzoxadiazolyl, an optionally substituted benzotriazolyl, an optionally substituted tetrahydroindolyl, an optionally substituted azaindolyl, an optionally substituted quinazolinyl, an optionally substituted purinyl, an optionally substituted imidazo[4,5-a]pyridinyl, an optionally substituted imidazo[1,2-a]pyridinyl, an 25 optionally substituted 3*H*-imidazo[4,5-b]pyridinyl, an optionally substituted 1*H*-imidazo[4,5-b]pyridinyl, an optionally substituted 1*H*-imidazo[4,5-c]pyridinyl, an optionally substituted 3*H*-imidazo[4,5-c]pyridinyl, an optionally substituted pyridopyrdazinyl, and optionally substituted pyridopyrimidinyl, an optionally 30 substituted pyrrolo[2,3]pyrimidyl, an optionally substituted pyrazolo[3,4]pyrimidyl

an optionally substituted cyclopentaimidazolyl, an optionally substituted cyclopentatriazolyl, an optionally substituted pyrrolopyrazolyl, an optionally substituted pyrroloimidazolyl, an optionally substituted pyrrolotriazolyl, or an optionally substituted benzo(b)thienyl.

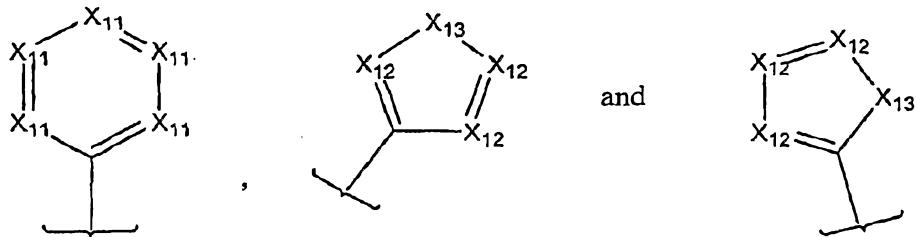
5 In another embodiment, in the compounds represented by formula (I), R_5 is an optionally substituted indolyl. Preferably, R_5 is an indolyl represented by the following structural formula:



wherein:

10 R_{33} is a halo, lower alkyl, a lower alkoxy, a lower haloalkyl, a lower haloalkoxy, and lower alkyl sulfanyl;
 R_{34} is H, a lower alkyl, or a lower alkylcarbonyl; and
Ring B and Ring C are optionally substituted with one or more substituents.

In another embodiment, in the compounds represented by formula (I), R_5 is
15 selected from the group consisting of:

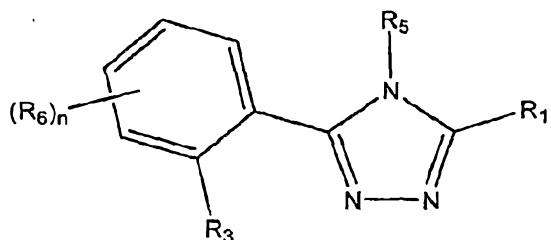


wherein:

X_{11} , for each occurrence, is independently CH, CR₉, N, N(O), or N⁺(R₁₇), provided that at least one X_{11} is N, N(O), or N⁺(R₁₇) and at least two X_{11} groups are independently selected from CH and CR₉;
 X_{12} , for each occurrence, is independently CH, CR₉, N, N(O), N⁺(R₁₇), provided that at least one X_{12} group is independently selected from CH and CR₉;
 X_{13} , for each occurrence, is independently O, S, S(O)p, NR₇, or NR₁₇;
wherein R₇, R₉ and R₁₇ are defined as above.

In another embodiment, in compounds represented by formula (I), or any of the embodiments of formula (I) in which particular groups are disclosed, the compound is represented by the following structural formula:

5

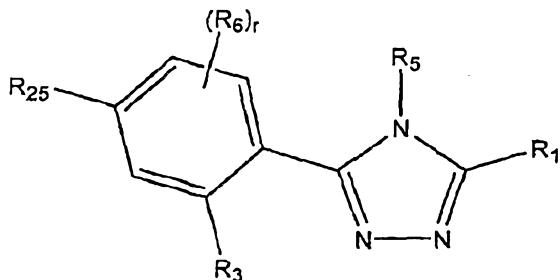


wherein R₁, R₃, and R₅ are defined as above; and

R₆, for each occurrence, is independently an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteroaralkyl, halo, cyano, nitro, guanadino, a haloalkyl, a heteroalkyl, alkoxy, haloalkoxy, -NR₁₀R₁₁, -OR₇, -C(O)R₇, -C(O)OR₇, -C(S)R₇, -C(O)SR₇, -C(S)SR₇, -C(S)OR₇, -C(S)NR₁₀R₁₁, -C(NR₈)OR₇, -C(NR₈)R₇, -C(NR₈)NR₁₀R₁₁, -C(NR₈)SR₇, -OC(O)R₇, -OC(O)OR₇, -OC(S)OR₇, -OC(NR₈)OR₇, -SC(O)R₇, -SC(O)OR₇, -SC(NR₈)OR₇, -OC(S)R₇, -SC(S)R₇, -SC(S)OR₇, -OC(O)NR₁₀R₁₁, -OC(S)NR₁₀R₁₁, -OC(NR₈)NR₁₀R₁₁, -SC(O)NR₁₀R₁₁, -SC(NR₈)NR₁₀R₁₁, -SC(S)NR₁₀R₁₁, -OC(NR₈)R₇, -SC(NR₈)R₇, -C(O)NR₁₀R₁₁, -NR₈C(O)R₇, -NR₇C(S)R₇, -NR₇C(S)OR₇, -NR₇C(NR₈)R₇, -NR₇C(O)OR₇, -NR₇C(NR₈)OR₇, -NR₇C(O)NR₁₀R₁₁, -NR₇C(S)NR₁₀R₁₁, -NR₇C(NR₈)NR₁₀R₁₁, -SR₇, -S(O)_pR₇, -OS(O)_pR₇, -OS(O)_pOR₇, -OS(O)_pNR₁₀R₁₁, -S(O)_pOR₇, -NR₈S(O)_pR₇, -NR₇S(O)_pNR₁₀R₁₁, -NR₇S(O)_pOR₇, -S(O)_pNR₁₀R₁₁, -SS(O)_pR₇, -SS(O)_pOR₇, -SS(O)_pNR₁₀R₁₁, -OP(O)(OR₇)₂, or -SP(O)(OR₇)₂; and

n is zero or an integer from 1 to 4, wherein R₇, R₈, R₁₀, R₁₁, and p are defined as above.

In another embodiment, in compounds represented by formula (I), or any of the embodiments of formula (I) in which particular groups are disclosed, the compound is represented by the following structural formula:



wherein R₁, R₃, R₅, and R₆ are defined as above; and

R₂₅ is an optionally substituted alkyl, an optionally substituted alkenyl, an
 5 optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteroaralkyl, halo, cyano, nitro, guanadino, a
 haloalkyl, a heteroalkyl, alkoxy, haloalkoxy, -NR₁₀R₁₁, -OR₇, -C(O)R₇, -C(O)OR₇,
 10 -C(S)R₇, -C(O)SR₇, -C(S)SR₇, -C(S)OR₇, -C(S)NR₁₀R₁₁, -C(NR₈)OR₇, -C(NR₈)R₇,
 -C(NR₈)NR₁₀R₁₁, -C(NR₈)SR₇, -OC(O)R₇, -OC(O)OR₇, -OC(S)OR₇, -OC(NR₈)OR₇,
 -SC(O)R₇, -SC(O)OR₇, -SC(NR₈)OR₇, -OC(S)R₇, -SC(S)R₇, -SC(S)OR₇,
 -OC(O)NR₁₀R₁₁, -OC(S)NR₁₀R₁₁, -OC(NR₈)NR₁₀R₁₁, -SC(O)NR₁₀R₁₁,
 15 -SC(NR₈)NR₁₀R₁₁, -SC(S)NR₁₀R₁₁, -OC(NR₈)R₇, -SC(NR₈)R₇, -C(O)NR₁₀R₁₁,
 -NR₈C(O)R₇, -NR₇C(S)R₇, -NR₇C(S)OR₇, -NR₇C(NR₈)R₇, -NR₇C(O)OR₇,
 -NR₇C(NR₈)OR₇, -NR₇C(O)NR₁₀R₁₁, -NR₇C(S)NR₁₀R₁₁, -NR₇C(NR₈)NR₁₀R₁₁,
 -SR₇, -S(O)_pR₇, -OS(O)_pR₇, -OS(O)_pOR₇, -OS(O)_pNR₁₀R₁₁, -S(O)_pOR₇,
 -NR₈S(O)_pR₇, -NR₇S(O)_pNR₁₀R₁₁, -NR₇S(O)_pOR₇, -S(O)_pNR₁₀R₁₁, -SS(O)_pR₇,
 -SS(O)_pOR₇, -SS(O)_pNR₁₀R₁₁, -OP(O)(OR₇)₂, or -SP(O)(OR₇)₂;

20 k is 1, 2, 3, or 4; and

r is zero or an integer from 1 to 3, wherein R₇, R₈, R₁₀, R₁₁, and p are defined as above.

In another embodiment of the compound represented by the above formula, R₁, R₃ and R₂₅ are each independently -OH, -SH, -NHR₇, -OC(O)NR₁₀R₁₁,
 25 -SC(O)NR₁₀R₁₁, -OC(O)R₇, -SC(O)R₇, -OC(O)OR₇, -SC(O)OR₇, -OS(O)_pR₇,
 -S(O)_pOR₇, -SS(O)_pR₇, -OS(O)_pOR₇, -SS(O)_pOR₇, -OC(S)R₇, -SC(S)R₇, -OC(S)OR₇,
 -SC(S)OR₇, -OC(S)NR₁₀R₁₁, -SC(S)NR₁₀R₁₁, -OC(NR₈)R₇, -SC(NR₈)R₇,
 -OC(NR₈)OR₇, -SC(NR₈)OR₇, -OP(O)(OR₇)₂ or -SP(O)(OR₇)₂.

In another embodiment of the compound represented by the above formula, R₁ and R₃ are each, independently, -OH, -SH, or -NHR₇. In this case, R₆ can be an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, cyano, halo, nitro, an optionally substituted cycloalkyl, haloalkyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteroaralkyl, -OR₇, -SR₇, -NR₁₀R₁₁, -OC(O)NR₁₀R₁₁, -SC(O)NR₁₀R₁₁, -NR₇C(O)NR₁₀R₁₁, -OC(O)R₇, -SC(O)R₇, -NR₇C(O)R₇, -OC(O)OR₇, -SC(O)OR₇, -NR₇C(O)OR₇, -OCH₂C(O)R₇, -SCH₂C(O)R₇,

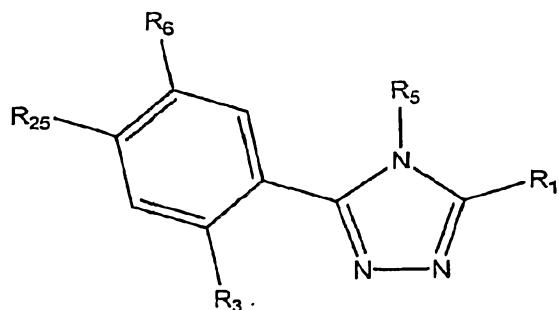
5 10 -NR₇CH₂C(O)R₇, -OCH₂C(O)OR₇, -SCH₂C(O)OR₇, -NR₇CH₂C(O)OR₇, -OCH₂C(O)NR₁₀R₁₁, -SCH₂C(O)NR₁₀R₁₁, -NR₇CH₂C(O)NR₁₀R₁₁, -OS(O)_pR₇, -SS(O)_pR₇, -NR₇S(O)_pR₇, -OS(O)_pNR₁₀R₁₁, -SS(O)_pNR₁₀R₁₁, -NR₇S(O)_pNR₁₀R₁₁, -OS(O)_pOR₇, -SS(O)_pOR₇, -NR₇S(O)_pOR₇, -OC(S)R₇, -SC(S)R₇, -NR₇C(S)R₇, -OC(S)OR₇, -SC(S)OR₇, -NR₇C(S)OR₇, -OC(S)NR₁₀R₁₁, -SC(S)NR₁₀R₁₁,

15 20 -NR₇C(S)NR₁₀R₁₁, -OC(NR₈)R₇, -SC(NR₈)R₇, -NR₇C(NR₈)R₇, -OC(NR₈)OR₇, -SC(NR₈)OR₇, -NR₇C(NR₈)OR₇, -OC(NR₈)NR₁₀R₁₁, -SC(NR₈)NR₁₀R₁₁, -NR₇C(NR₈)NR₁₀R₁₁, -C(O)R₇, -C(O)OR₇, -C(O)NR₁₀R₁₁, -C(O)SR₇, -C(S)R₇, -C(S)OR₇, -C(S)NR₁₀R₁₁, -C(S)SR₇, -C(NR₈)OR₇, -C(NR₈)R₇, -C(NR₈)NR₁₀R₁₁, -C(NR₈)SR₇, -S(O)_pOR₇, -S(O)_pNR₁₀R₁₁, or -S(O)_pR₇.

In another embodiment of the above compound, R₁ is -SH or -OH; R₃ and R₂₅ are -OH; R₆ is a lower alkyl, C3-C6 cycloalkyl, lower alkoxy, a lower alkyl sulfanyl, or -NR₁₀R₁₁; and R₉, for each occurrence, is independently selected from the group consisting of -OH, -SH, halo, a lower haloalkyl, cyano, a lower alkyl, a lower alkoxy, and a lower alkyl sulfanyl.

25 30 In another embodiment, in compounds represented by formula (I), or any of the embodiments of formula (I) in which particular groups are disclosed, R₁ and R₃ are each, independently, -OH, -SH, or -NHR₇.

In another embodiment, in compounds represented by formula (I), or any of the embodiments of formula (I) in which particular groups are disclosed, the compound is represented by the following structural formula:

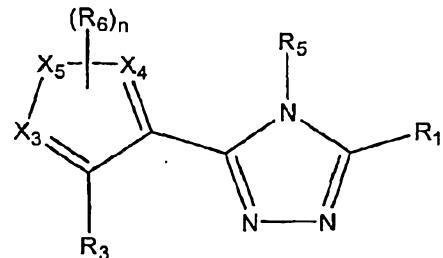
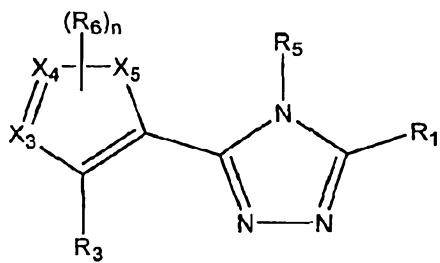


wherein R₁, R₃, R₅, and R₂₅ are defined as above; and

R₆ is an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, cyano, halo, nitro, an optionally substituted cycloalkyl, haloalkyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteroaralkyl, -OR₇, -SR₇, -NR₁₀R₁₁, -OC(O)NR₁₀R₁₁, -SC(O)NR₁₀R₁₁, -NR₇C(O)NR₁₀R₁₁, -OC(O)R₇, -SC(O)R₇, -NR₇C(O)R₇, -OC(O)OR₇, -SC(O)OR₇, -NR₇C(O)OR₇, -OCH₂C(O)R₇, -SCH₂C(O)R₇, -NR₇CH₂C(O)R₇, -OCH₂C(O)OR₇, -SCH₂C(O)OR₇, -NR₇CH₂C(O)OR₇, -OCH₂C(O)NR₁₀R₁₁, -SCH₂C(O)NR₁₀R₁₁, -NR₇CH₂C(O)NR₁₀R₁₁, -OS(O)_pR₇, -SS(O)_pR₇, -NR₇S(O)_pR₇, -OS(O)_pNR₁₀R₁₁, -SS(O)_pNR₁₀R₁₁, -NR₇S(O)_pNR₁₀R₁₁, -OS(O)_pOR₇, -SS(O)_pOR₇, -NR₇S(O)_pOR₇, -OC(S)R₇, -SC(S)R₇, -NR₇C(S)R₇, -OC(S)OR₇, -SC(S)OR₇, -NR₇C(S)OR₇, -OC(S)NR₁₀R₁₁, -SC(S)NR₁₀R₁₁, -NR₇C(S)NR₁₀R₁₁, -OC(NR₈)R₇, -SC(NR₈)R₇, -NR₇C(NR₈)R₇, -OC(NR₈)OR₇, -SC(NR₈)OR₇, -NR₇C(NR₈)OR₇, -OC(NR₈)NR₁₀R₁₁, -SC(NR₈)NR₁₀R₁₁, -NR₇C(NR₈)NR₁₀R₁₁, -C(O)R₇, -C(O)OR₇, -C(O)NR₁₀R₁₁, -C(O)SR₇, -C(S)R₇, -C(S)OR₇, -C(S)NR₁₀R₁₁, -C(S)SR₇, -C(NR₈)R₇, -C(NR₈)NR₁₀R₁₁, -C(NR₈)SR₇, -S(O)_pOR₇, -S(O)_pNR₁₀R₁₁, or -S(O)_pR₇, wherein R₇, R₈, R₁₀, R₁₁, and p are defined as above.

In a preferred embodiment, R₁ is -SH or -OH; R₃ and R₂₅ are -OH; R₁₂ is a lower alkyl, lower alkoxy, a lower alkyl sulfanyl, or -NR₁₀R₁₁; and R₉, for each occurrence, is independently selected from the group consisting of -OH, -SH, halo, a lower haloalkyl, cyano, a lower alkyl, a lower alkoxy, and a lower alkyl sulfanyl.

25 In another embodiment, in compounds represented by formula (I), or any of the embodiments of formula (I) in which particular groups are disclosed, the compound is represented by one of the following structural formulas:

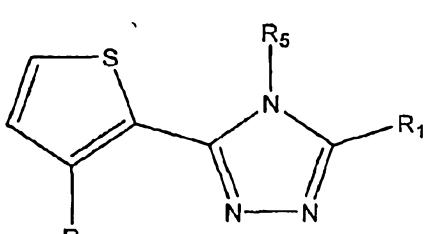
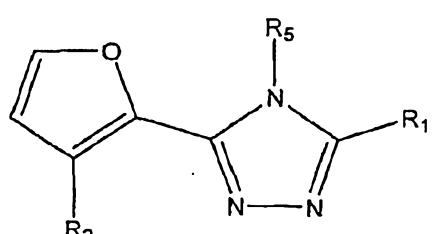
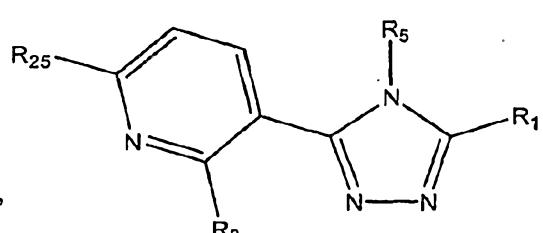
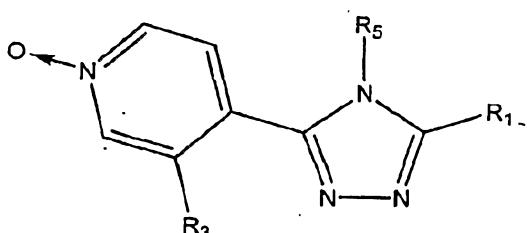
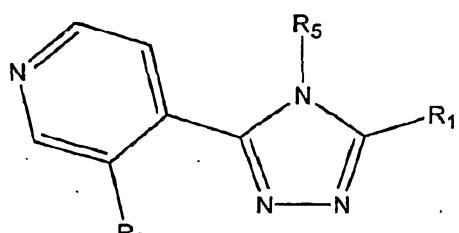
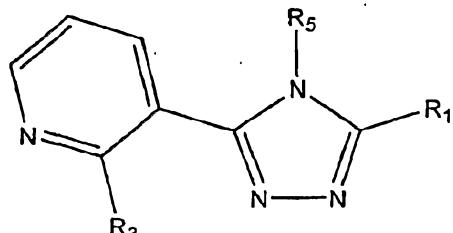


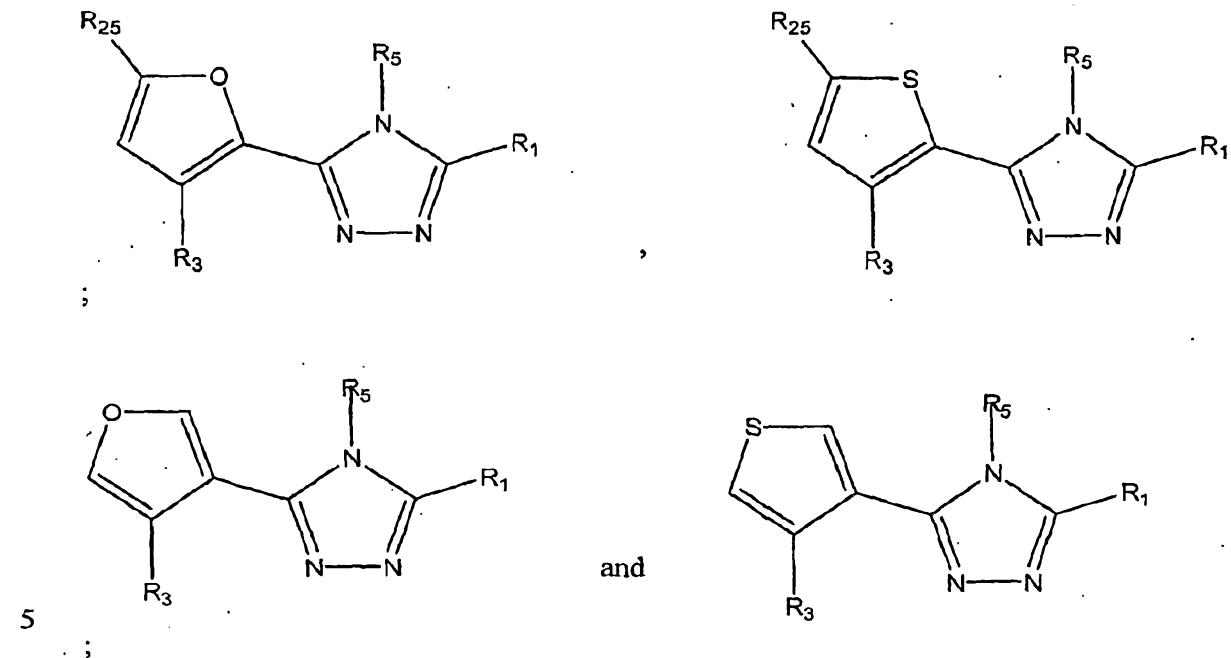
wherein R₁, R₃, R₅, R₆ and n are as defined above; and

X₃ and X₄ are each, independently, N, N(O), N⁺(R₁₇), CH or CR₆; and

5 X₅ is O, S, NR₁₇, CH=CH, CH=CR₆, CR₆=CH, CR₆=CR₆, CH=N, CR₆=N, CH=N(O), CR₆=N(O), N=CH, N=CR₆, N(O)=CH, N(O)=CR₆, N⁺(R₁₇)=CH, N⁺(R₁₇)=CR₆, CH=N⁺(R₁₇), CR₆=N⁺(R₁₇), or N=N; wherein R₁₇ is defined as above.

10 In another embodiment, in compounds represented by formula (I), or any of the embodiments of formula (I) in which particular groups are disclosed, the compound is selected from the group consisting of:

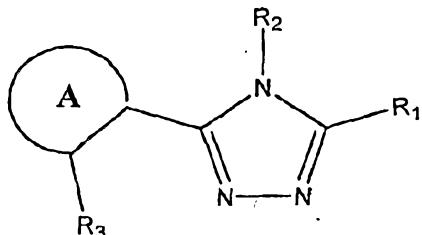




wherein R_1 , R_3 , R_5 , and R_{25} are defined as above.

In another aspect, the invention provides compounds of formula (II) as set forth below:

10



and tautomers, pharmaceutically acceptable salts, solvates, clathrates, and prodrugs thereof, wherein ring A, R_1 and R_3 are defined as above; and

15

R_2 is a substituted phenyl, wherein the phenyl group is substituted with:

- i) one substituent selected from nitro, cyano, a haloalkoxy, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclol, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteroaralkyl,

20

hydroxylalkyl, alkoxyalkyl, guanadino, $-NR_{10}R_{11}$, $-O-R_{20}$, $-C(O)R_7$,
 $-C(O)OR_{20}$, $-OC(O)R_7$, $-C(O)NR_{10}R_{11}$, $-NR_8C(O)R_7$, $-SR_7$,
 $-S(O)_pR_7$, $-OS(O)_pR_7$, $-S(O)_pOR_7$, $-NR_8S(O)_pR_7$, or $-S(O)_pNR_{10}R_{11}$,
or

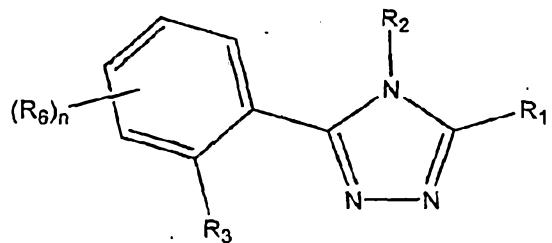
5 ii) two to five substituents selected from the group consisting of an
optionally substituted alkyl, an optionally substituted alkenyl, an
optionally substituted alkynyl, an optionally substituted cycloalkyl,
an optionally substituted cycloalkenyl, an optionally substituted
heterocyclyl, an optionally substituted aryl, an optionally substituted
heteroaryl, an optionally substituted aralkyl, an optionally substituted
10 heteraralkyl, hydroxylalkyl, alkoxyalkyl, $-F$, $-Br$, $-I$, cyano, nitro,
guanadino, a haloalkyl, a heteroalkyl, $-NR_{10}R_{11}$, $-OR_7$, $-C(O)R_7$,
 $-C(O)OR_7$, $-OC(O)R_7$, $-C(O)NR_{10}R_{11}$, $-NR_8C(O)R_7$, $-SR_7$,
 $-S(O)_pR_7$, $-OS(O)_pR_7$, $-S(O)_pOR_7$, $-NR_8S(O)_pR_7$, or $-S(O)_pNR_{10}R_{11}$;
15 R_{20} , for each occurrence, is independently an optionally substituted alkyl, an
optionally substituted alkenyl, an optionally substituted alkynyl, an optionally
substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally
substituted heterocyclyl, an optionally substituted aryl, an optionally substituted
heteroaryl, an optionally substituted aralkyl, or an optionally substituted
heteroaryl, an optionally substituted aralkyl, or an optionally substituted
20 heteraralkyl;

 p, for each occurrence, is, independently, 1 or 2.

Compounds of formula (II) inhibit the activity of Hsp90 and are particularly useful for treating or preventing (e.g., reducing the likelihood of developing) angiogenesis related disorders, such as macular degeneration. In addition, 25 compounds of formula (II) are particularly useful in reducing, blocking, occluding, or otherwise disrupting blood flow in neovasculature.

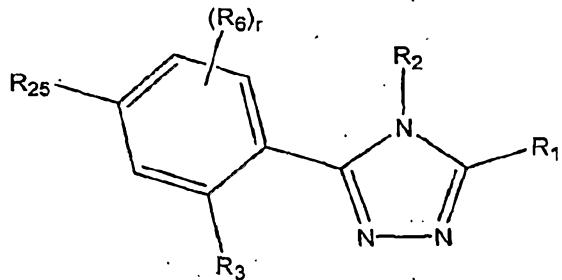
In one embodiment, the compounds represented by formula (II) do not include 3-(2,4-dihydroxy-phenyl)-4-(7-naphthalen-1-yl)-5-mercaptop-triazole, 3-(2,4-dihydroxyphenyl)-4-(2,5-dimethoxyphenyl)-5-mercaptop-triazole, 3-(1-phenyl-5-30 amino-pyrazol-4-yl)-4-(2,4-dichlorophenyl)-5-mercaptop-triazole, and 3-(2-hydroxy-phenyl)4-(2,4-dimethylphenyl)-5-mercaptop-triazole.

In another embodiment, in compounds represented by formula (II), or any of the embodiments of formula (II) in which particular groups are disclosed, the compound is represented by the following structural formula:



wherein R₁, R₂, R₃, R₆, and n are defined as above.

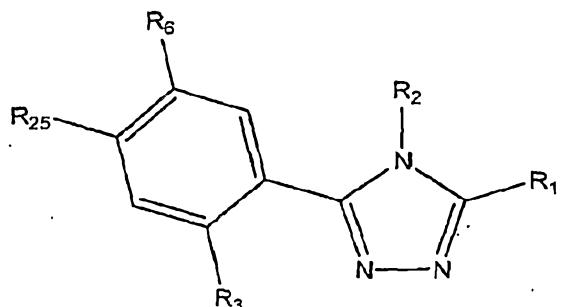
5 In another embodiment, in compounds represented by formula (II), or any of the embodiments of formula (II) in which particular groups are disclosed, the compound is represented by the following structural formula:



wherein R₁, R₂, R₃, R₆, R₂₅ and r are defined as above.

10 In another embodiment, in compounds represented by formula (II), or any of the embodiments of formula (II) in which particular groups are disclosed, R₁ and R₃ are each, independently, -OH, -SH, or -NHR₇.

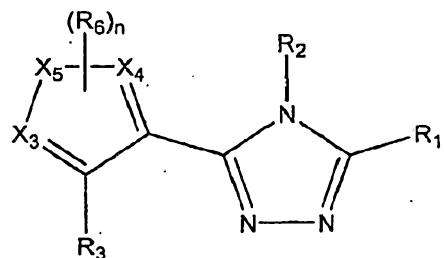
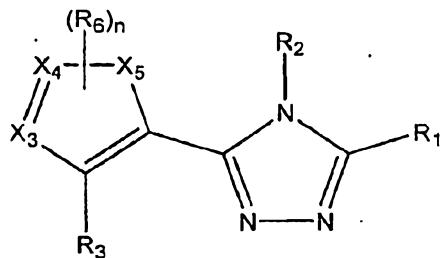
15 In another embodiment, in compounds represented by formula (II), or any of the embodiments of formula (II) in which particular groups are disclosed, the compound is represented by the following structural formula:



wherein R₁, R₂, R₃, R₆ and R₂₅ are defined as above. In a preferred embodiment, R₁ is -SH or -OH; R₃ and R₂₅ are -OH; R₁₂ is a lower alkyl, lower alkoxy, a lower alkyl sulfanyl, or -NR₁₀R₁₁; and R₉, for each occurrence, is

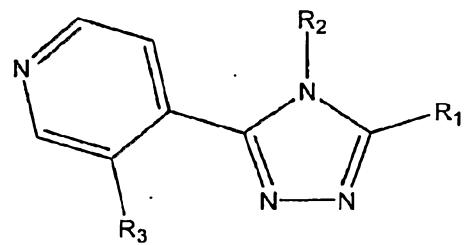
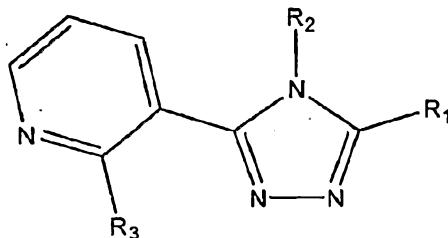
independently selected from the group consisting of -OH, -SH, halo, a lower haloalkyl, cyano, a lower alkyl, a lower alkoxy, and a lower alkyl sulfanyl.

In another embodiment, in compounds represented by formula (II), or any of the embodiments of formula (II) in which particular groups are disclosed, the 5 compound is represented by one of the following structural formulas:

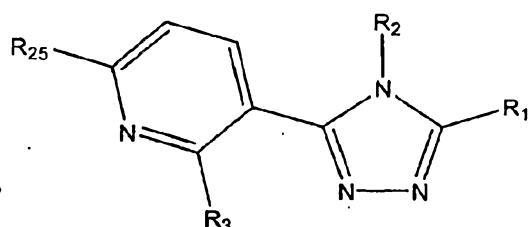
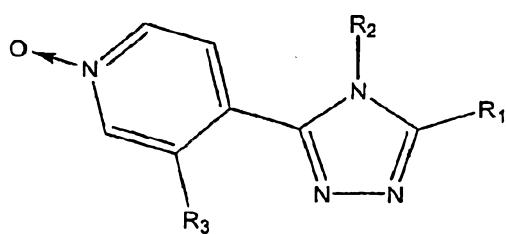


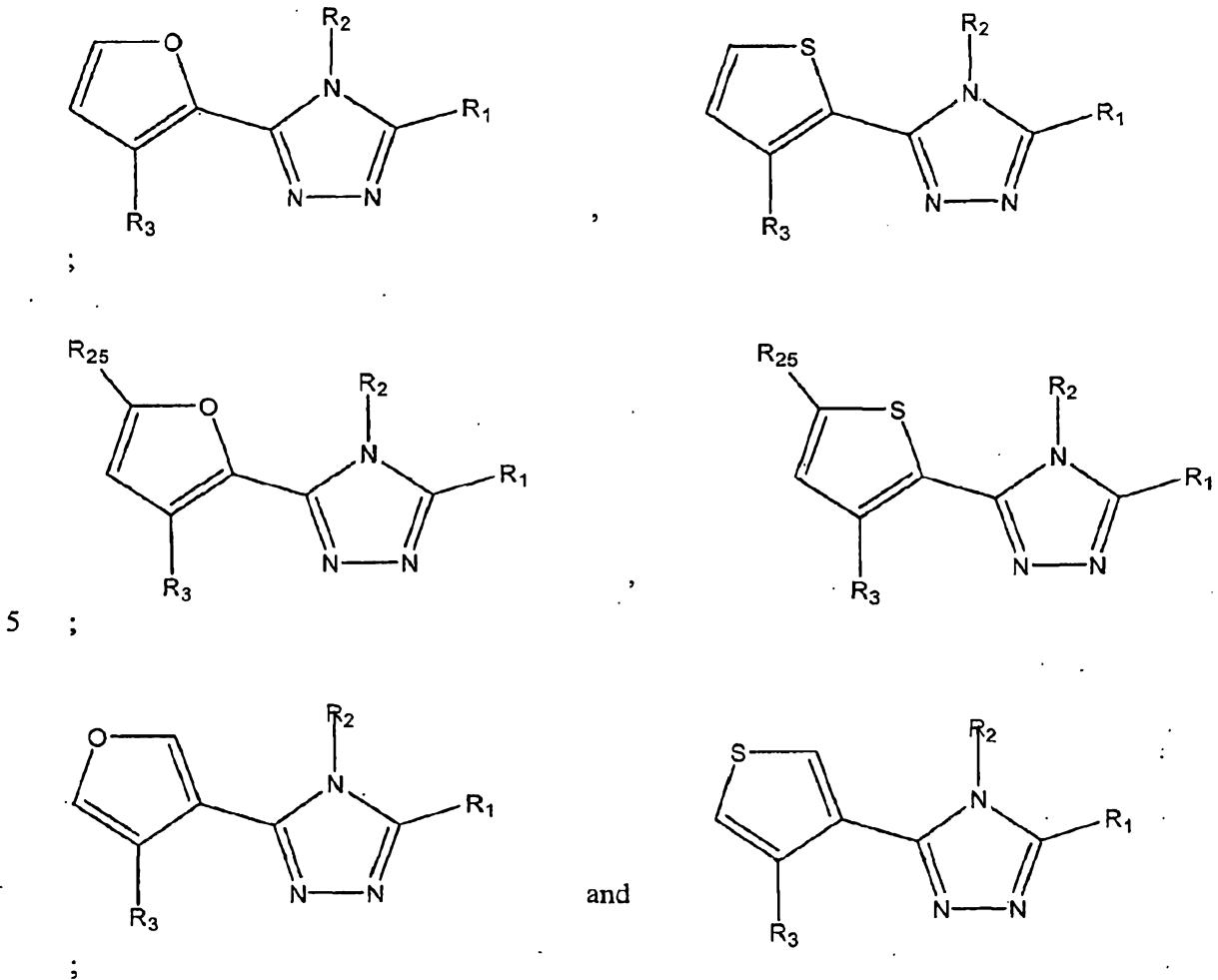
wherein R₁, R₂, R₃, R₆, X₃, X₄, X₅ and n are defined as above.

10 In another embodiment, in compounds represented by formula (II), or any of the embodiments of formula (II) in which particular groups are disclosed, the compound is selected from the group consisting of:



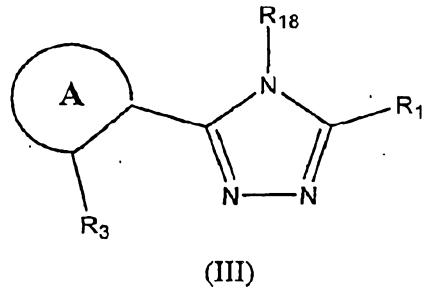
15





wherein R_1 , R_2 , R_3 , and R_{25} are defined as above.

10 In another aspect, the invention provides compounds of formula (III) as set forth below:



15 and tautomers, pharmaceutically acceptable salts, solvates, clathrates, and prodrugs. In formula (III), ring A, R₁, and R₃ are defined as above; and

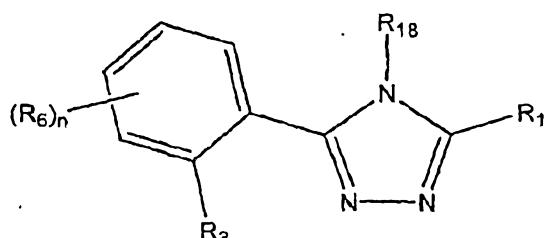
R₁₈ is an optionally substituted cycloalkyl, and optionally substituted cycloalkenyl, or a substituted alkyl, wherein the alkyl group is substituted with one or more substituents independently selected from the group consisting of an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, halo, cyano, nitro, guanadino, a haloalkyl, -NR₁₀R₁₁, -OR₇, -C(O)R₇, -C(O)OR₇, -OC(O)R₇, -C(O)NR₁₀R₁₁, -NR₈C(O)R₇, -SR₇, -S(O)_pR₇, -OS(O)_pR₇, -S(O)_pOR₇, -NR₈S(O)_pR₇, or -S(O)_pNR₁₀R₁₁, wherein R₇, R₈, R₁₀, R₁₁, and p are defined as above.

Compounds of formula (III) inhibit the activity of Hsp90 and are particularly useful for treating or preventing (e.g., reducing the likelihood of developing) angiogenesis related disorders, such as macular degeneration. In addition, compounds of formula (III) are particularly useful in reducing, blocking, occluding, or otherwise disrupting blood flow in neovasculature. In one embodiment, in formula (III) R₁₈ is not cyclohexyl.

In another embodiment, in formula (III) R₁₈ is an optionally substituted cycloalkyl or an optionally substituted cycloalkenyl.

In another embodiment, in formula (III) R₁₈ is a substituted alkyl.

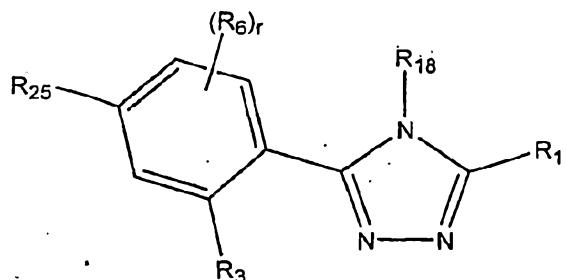
In another embodiment, in compounds represented by formula (III), or any of the embodiments of formula (III) in which particular groups are disclosed, the compound is represented by the following structural formula:



25

wherein R₁, R₃, R₆, R₁₈, and n are defined as above.

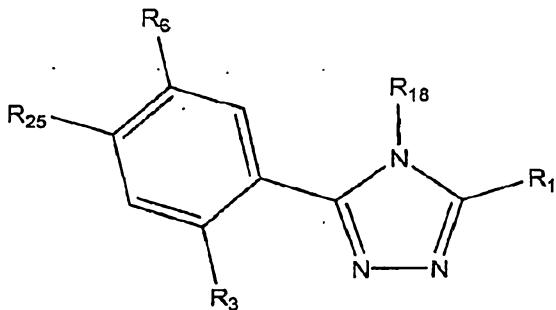
In another embodiment, in compounds represented by formula (III), or any of the embodiments of formula (III) in which particular groups are disclosed, the compound is represented by the following structural formula:



wherein R₁, R₃, R₆, R₁₈, R₂₅ and r are defined as above.

In another embodiment, in compounds represented by formula (III), or any of 5 the embodiments of formula (III) in which particular groups are disclosed, R₁ and R₃ are each, independently, -OH, -SH, or -NHR₇.

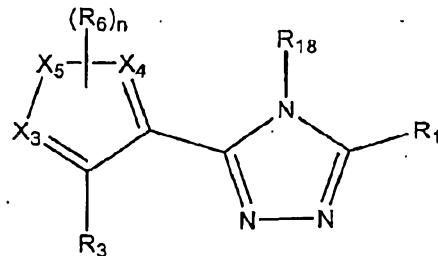
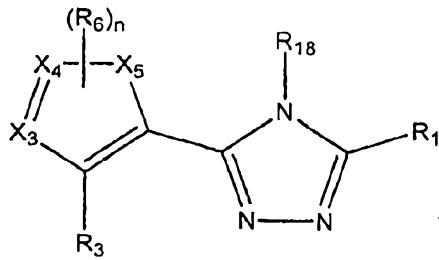
In another embodiment, in compounds represented by formula (III), or any of the embodiments of formula (III) in which particular groups are disclosed, the compound is represented by the following structural formula:



10

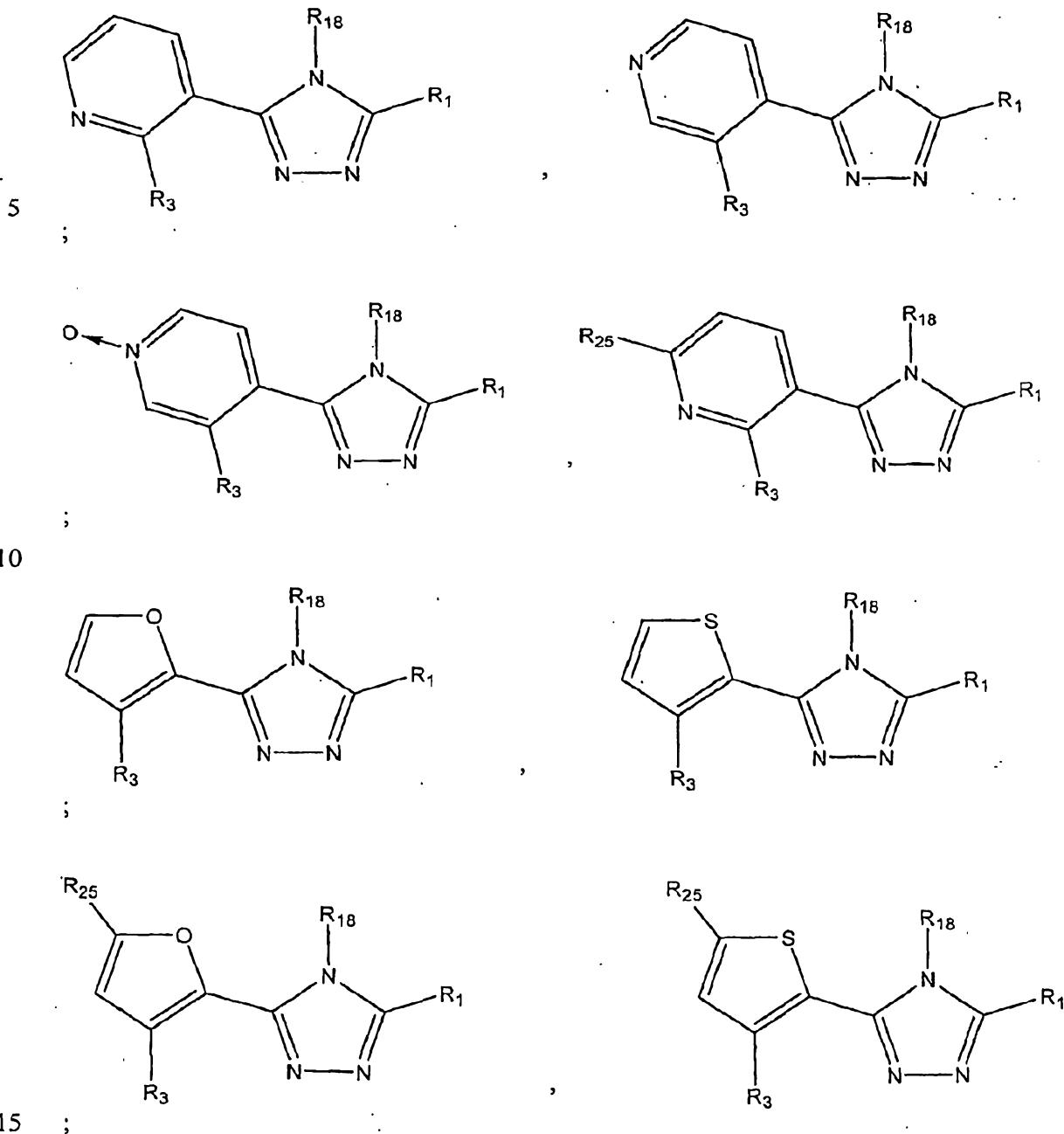
wherein R₁, R₃, R₆, R₁₈, and R₂₅ are defined as above. In a preferred embodiment, R₁ is -SH or -OH; R₃ and R₂₅ are -OH; and R₁₂ is a lower alkyl, lower alkoxy, a lower alkyl sulfanyl, or -NR₁₀R₁₁.

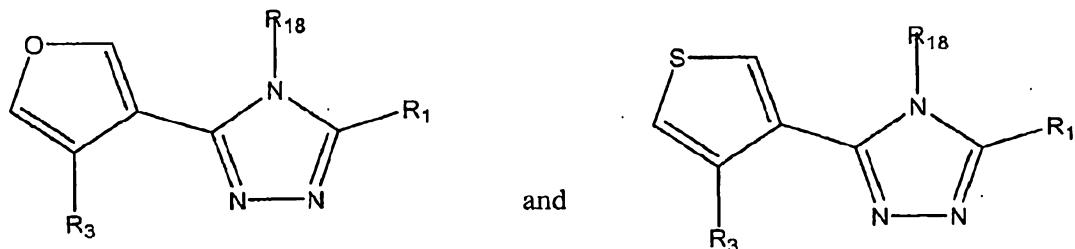
In another embodiment, in compounds represented by formula (III), or any of 15 the embodiments of formula (III) in which particular groups are disclosed, the compound is represented by one of the following structural formulas:



wherein R₁, R₃, R₆, R₁₈, X₃, X₄, X₅, and n are defined as above.

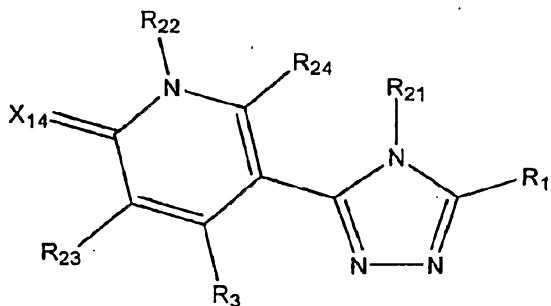
In another embodiment, in compounds represented by formula (III), or any of the embodiments of formula (III) in which particular groups are disclosed, the compound is selected from the group consisting of:



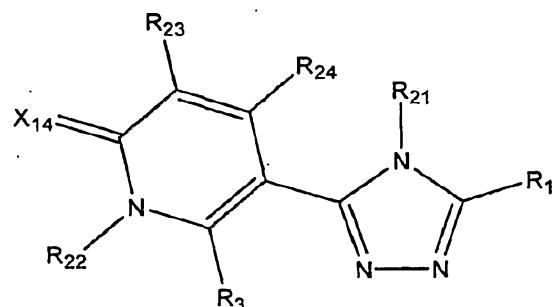


wherein R₁, R₃, R₁₈, and R₂₅ are defined as above.

In another aspect, the invention provides compounds of formula (IV) or (V)
5 as set forth below:



(IV)



(V)

10 and tautomers, pharmaceutically acceptable salts, solvates, clathrates, and prodrugs thereof. In formulas (IV) and (V), R₁ and R₃ are as defined above; and

X₁₄ is O, S, or NR₇;

15 R₂₁ is an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl; an optionally substituted cycloalkenyl, an optionally substituted heterocycl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl;

20 R₂₂, for each occurrence, is independently an -H or is selected from the group consisting of an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocycl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl, a haloalkyl, -C(O)R₇, -C(O)OR₇,

-OC(O)R₇, -C(O)NR₁₀R₁₁, -NR₈C(O)R₇, -S(O)_pR₇, -S(O)_pOR₇, or -S(O)_pNR₁₀R₁₁; and

R₂₃ and R₂₄, for each occurrence, are independently -H or are selected from the group consisting of an optionally substituted alkyl, an optionally substituted

5 alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocycl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl, halo, cyano, nitro, guanadino, a haloalkyl, a heteroalkyl, -NR₁₀R₁₁, -OR₇, -C(O)R₇, -C(O)OR₇,
10 -OC(O)R₇, -C(O)NR₁₀R₁₁, -NR₈C(O)R₇, -SR₇, -S(O)_pR₇, -OS(O)_pR₇, -S(O)_pOR₇, -NR₈S(O)_pR₇, or -S(O)_pNR₁₀R₁₁;

wherein R₇, R₈, R₁₀, R₁₁ and p are defined as above.

In one embodiment, in formulas (IV) and (V), R₂₁ is an optionally substituted alkyl, an optionally substituted cycloalkyl, an optionally substituted aryl or an 15 optionally substituted heteroaryl.

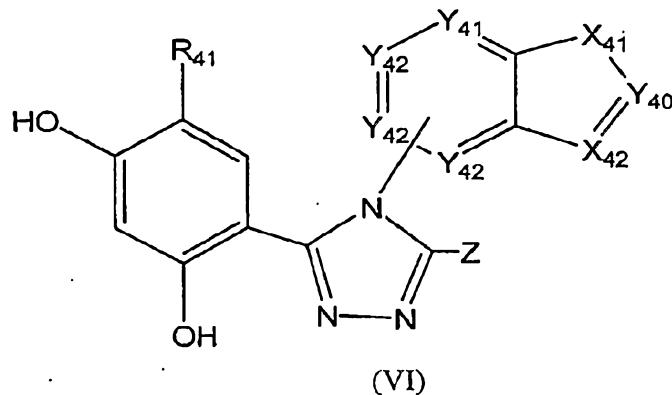
In another embodiment, in the formulas (IV) and (V), R₁ is -OH, -SH, or -NHR₇.

In another embodiment, in the formulas (IV) and (V), R₂₂ is -H, an alkyl, an aralkyl, -C(O)R₇, -C(O)OR₇, or -C(O)NR₁₀R₁₁.

20 In another embodiment, in the formulas (IV) and (V), X₁₄ is O.

Compounds of formula (IV) or (V) inhibit the activity of Hsp90 and are particularly useful for treating or preventing (e.g., reducing the likelihood of developing) angiogenesis related disorders, such as macular degeneration. In addition, compounds of formula (IV) or (V) are particularly useful in reducing, 25 blocking, occluding, or otherwise disrupting blood flow in neovasculature:

In another aspect, the invention provides compounds represented by formula (VI):



and tautomers, pharmaceutically acceptable salts, solvates, clathrates, and prodrugs thereof, wherein:

5 X_{41} is O, S, or NR_{42} ;

X_{42} is CR_{44} or N;

Y_{40} is N or CR_{43} ;

Y_{41} is N or CR_{45} ;

Y_{42} , for each occurrence, is independently N, C or CR_{46} ;

10 Z is OH, SH, or NHR_7 ;

R_{41} is -H, -OH, -SH, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally 15 substituted aralkyl, an optionally substituted heteraralkyl, halo, cyano, nitro, guanadino, a haloalkyl, a heteroalkyl, an alkoxy or cycloalkoxy, a haloalkoxy, - $NR_{10}R_{11}$, - OR_7 , - $C(O)R_7$, - $C(O)OR_7$, - $C(S)R_7$, - $C(O)SR_7$, - $C(S)SR_7$, - $C(S)OR_7$, - $C(S)NR_{10}R_{11}$, - $C(NR_8)OR_7$, - $C(NR_8)R_7$, - $C(NR_8)NR_{10}R_{11}$, - $C(NR_8)SR_7$, - $OC(O)R_7$, - $OC(O)OR_7$, - $OC(NR_8)OR_7$, - $SC(O)R_7$, - $SC(O)OR_7$, - $SC(NR_8)OR_7$, 20 - $OC(S)R_7$, - $SC(S)R_7$, - $SC(S)OR_7$, - $OC(O)NR_{10}R_{11}$, - $OC(S)NR_{10}R_{11}$, - $OC(NR_8)NR_{10}R_{11}$, - $SC(O)NR_{10}R_{11}$, - $SC(NR_8)NR_{10}R_{11}$, - $SC(S)NR_{10}R_{11}$, - $OC(NR_8)R_7$, - $SC(NR_8)R_7$, - $C(O)NR_{10}R_{11}$, - $NR_8C(O)R_7$, - $NR_7C(S)R_7$, - $NR_7C(S)OR_7$, - $NR_7C(NR_8)R_7$, - $NR_7C(O)OR_7$, - $NR_7C(NR_8)OR_7$, - $NR_7C(O)NR_{10}R_{11}$, - $NR_7C(S)NR_{10}R_{11}$, - $NR_7C(NR_8)NR_{10}R_{11}$, - SR_7 , - $S(O)_pR_7$, 25 - $OS(O)_pR_7$, - $OS(O)_pOR_7$, - $OS(O)_pNR_{10}R_{11}$, - $S(O)_pOR_7$, - $NR_8S(O)_pR_7$, - $NR_7S(O)_pNR_{10}R_{11}$, - $NR_7S(O)_pOR_7$, - $S(O)_pNR_{10}R_{11}$, - $SS(O)_pR_7$, - $SS(O)_pOR_7$, - $SS(O)_pNR_{10}R_{11}$, - $OP(O)(OR_7)_2$, or - $SP(O)(OR_7)_2$;

R_{42} is -H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, hydroxyalkyl, alkoxyalkyl, a haloalkyl, a heteroalkyl, $-C(O)R_7$, $-(CH_2)_mC(O)OR_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-C(O)NR_{10}R_{11}$, $-S(O)_pR_7$, $-S(O)_pOR_7$, or $-S(O)_pNR_{10}R_{11}$;

R_{43} and R_{44} are, independently, -H, -OH, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, hydroxyalkyl, alkoxyalkyl, halo, cyano, nitro, guanadino, a haloalkyl, a heteroalkyl, $-C(O)R_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-C(O)NR_{10}R_{11}$, $-NR_8C(O)R_7$, $-SR_7$, $-S(O)_pR_7$, $-OS(O)_pR_7$, $-S(O)_pOR_7$, $-NR_8S(O)_pR_7$, $-S(O)_pNR_{10}R_{11}$, or R_{43} and R_{44} taken together with the carbon atoms to which they are attached form an optionally substituted cycloalkenyl, an optionally substituted aryl, an optionally substituted heterocyclyl, or an optionally substituted heteroaryl;

R_{45} is -H, -OH, -SH, $-NR_7H$, $-OR_{26}$, $-SR_{26}$, $-NHR_{26}$, $-O(CH_2)_mOH$, $-O(CH_2)_mSH$, $-O(CH_2)_mNR_7H$, $-S(CH_2)_mOH$, $-S(CH_2)_mSH$, $-S(CH_2)_mNR_7H$, $-OC(O)NR_{10}R_{11}$, $-SC(O)NR_{10}R_{11}$, $-NR_7C(O)NR_{10}R_{11}$, $-OC(O)R_7$, $-SC(O)R_7$, $-NR_7C(O)R_7$, $-OC(O)OR_7$, $-SC(O)OR_7$, $-NR_7C(O)OR_7$, $-OCH_2C(O)R_7$, $-SCH_2C(O)R_7$, $-NR_7CH_2C(O)R_7$, $-OCH_2C(O)OR_7$, $-SCH_2C(O)OR_7$, $-NR_7CH_2C(O)OR_7$, $-OCH_2C(O)NR_{10}R_{11}$, $-SCH_2C(O)NR_{10}R_{11}$, $-NR_7CH_2C(O)NR_{10}R_{11}$, $-OS(O)_pR_7$, $-SS(O)_pR_7$, $-NR_7S(O)_pR_7$, $-OS(O)_pNR_{10}R_{11}$, $-SS(O)_pNR_{10}R_{11}$, $-NR_7S(O)_pNR_{10}R_{11}$, $-OS(O)_pOR_7$, $-SS(O)_pOR_7$, $-NR_7S(O)_pOR_7$, $-OC(S)R_7$, $-SC(S)R_7$, $-NR_7C(S)R_7$, $-OC(S)OR_7$, $-SC(S)OR_7$, $-NR_7C(S)OR_7$, $-OC(S)NR_{10}R_{11}$, $-SC(S)NR_{10}R_{11}$, $-NR_7C(S)NR_{10}R_{11}$, $-OC(NR_8)R_7$, $-SC(NR_8)R_7$, $-NR_7C(NR_8)R_7$, $-OC(NR_8)OR_7$, $-SC(NR_8)OR_7$, $-NR_7C(NR_8)OR_7$, $-OC(NR_8)NR_{10}R_{11}$, $-SC(NR_8)NR_{10}R_{11}$, or $-NR_7C(NR_8)NR_{10}R_{11}$;

R_{46} , for each occurrence, is independently selected from the group consisting of H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl,

an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, halo, cyano, nitro, guanadino, a haloalkyl, a heteroalkyl, -NR₁₀R₁₁, -OR₇, -C(O)R₇, -C(O)OR₇, -OC(O)R₇, -C(O)NR₁₀R₁₁, -NR₈C(O)R₇, -SR₇, -S(O)_pR₇, -OS(O)_pR₇, -S(O)_pOR₇, -NR₈S(O)_pR₇, or -S(O)_pNR₁₀R₁₁;

5 R₇, R₈, R₁₀, R₁₁, R₂₆, p, and m are defined as above.

In one embodiment, in formula (VI), X₄₁ is NR₄₂ and X₄₂ is CR₄₄.

In another embodiment, in formula (VI), X₄₁ is NR₄₂ and X₄₂ is N.

In another embodiment, in formula (VI), R₄₁ is selected from the group consisting of -H, lower alkyl, lower alkoxy, lower cycloalkyl, and lower 10 cycloalkoxy.

In another embodiment, in formula (VI), R₄₁ is selected from the group consisting of -H, methyl, ethyl, propyl, isopropyl, cyclopropyl, methoxy, ethoxy, propoxy, and cyclopropoxy.

In another embodiment, in formula (VI), X₄₁ is NR₄₂, and R₄₂ is selected 15 from the group consisting of -H, a lower alkyl, a lower cycloalkyl, -C(O)N(R₂₇)₂, and -C(O)OH, wherein R₂₇ is -H or a lower alkyl.

In another embodiment, in formula (VI), X₄₁ is NR₄₂, and R₄₂ is selected 20 from the group consisting of -H, methyl, ethyl, n-propyl, isopropyl, cyclopropyl, n-butyl, *sec*-butyl, *tert*-butyl, n-pentyl, n-hexyl, -C(O)OH, -(CH₂)_mC(O)OH, -CH₂OCH₃, -CH₂CH₂OCH₃, and -C(O)N(CH₃)₂.

In one embodiment, Y₄₀ is CR₄₃. Preferably, Y₄₀ is CR₄₃ and R₄₃ is H or a lower alkyl.

In another embodiment, in formula (VI), R₄₃ and R₄₄ are, independently, selected from the group consisting of -H, methyl, ethyl, propyl, isopropyl, 25 cyclopropyl, methoxy, ethoxy, propoxy, and cyclopropoxy.

In another embodiment, in formula (VI), X₄₂ is CR₄₄; Y is CR₄₃; and R₄₃ and R₄₄ together with the carbon atoms to which they are attached form a cycloalkenyl, an aryl, heterocyclyl, or heteroaryl ring. In one aspect of this embodiment, R₄₃ and R₄₄ together with the carbon atoms to which they are attached form a C₅-C₈ 30 cycloalkenyl or a C₅-C₈ aryl.

In another embodiment, in formula (VI), R₄₅ is selected from the group consisting of -H, -OH, -SH, -NH₂, a lower alkoxy, a lower alkyl amino, and a lower dialkyl amino.

In another embodiment, in formula (VI), R₄₅ is selected from the group consisting of -H, -OH, methoxy and ethoxy.

In another embodiment, in formula (VI), X₄₁ is O.

5 In another embodiment, the compound is selected from the group consisting of:

3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(2-methyl-7-methoxy-benzofuran-4-yl)-5-mercaptop-[1,2,4]triazole,

10 3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(benzofuran-5-yl)-5-mercaptop-[1,2,4]triazole,

3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(2-methyl-1,3-benzoxaz-5-yl)-5-mercaptop-[1,2,4]triazole, and

tautomers, pharmaceutically acceptable salts, solvates, clathrates, and prodrugs thereof.

In another embodiment, in formula (VI), Z is -OH.

15 In another embodiment, the compound is selected from the group consisting of:

3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1,3-dimethyl-indol-5-yl)-5-hydroxy-[1,2,4]triazole,

20 3-(2,4-dihydroxy-5-isopropyl-phenyl)-4-(1,3-dimethyl-indol-5-yl)-5-hydroxy-[1,2,4]triazole,

3-(2,4-dihydroxy-5-isopropyl-phenyl)-4-(1-methyl-indol-5-yl)-5-hydroxy-[1,2,4]triazole,

25 3-(2,4-dihydroxy-5-isopropyl-phenyl)-4-(1-isopropyl-indol-4-yl)-5-hydroxy-[1,2,4]triazole, and

tautomers, pharmaceutically acceptable salts, solvates, clathrates, and prodrugs thereof.

In another embodiment, Z is -SH.

In another embodiment, the compound is selected from the group consisting of:

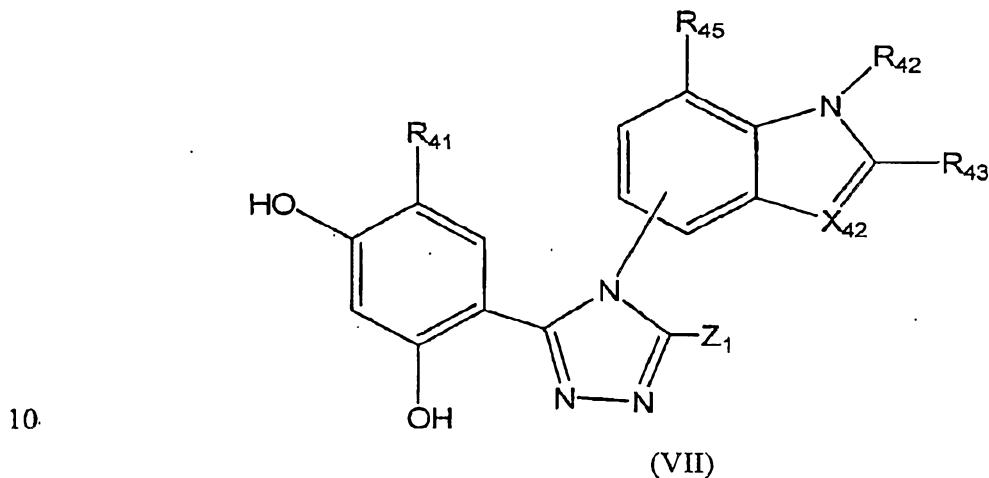
30 3-(2,4-dihydroxy-5-isopropyl-phenyl)-4-(1-methyl-indazol-5-yl)-5-mercaptop-[1,2,4]triazole,

3-(2,4-dihydroxy-5-isopropyl-phenyl)-4-(1-methyl-indazol-6-yl)-5-mercaptop-[1,2,4]triazole, and

tautomers, pharmaceutically acceptable salts, solvates, clathrates, and prodrugs thereof.

Compounds of formula (VI) inhibit the activity of Hsp90 and are particularly useful for treating or preventing (e.g., reducing the likelihood of developing) 5 angiogenesis related disorders, such as macular degeneration. In addition, compounds of formula (VI) are particularly useful in reducing, blocking, occluding, or otherwise disrupting blood flow in neovasculature.

In another aspect, the invention provides compounds represented by formula (VII):



and tautomers, pharmaceutically acceptable salts, solvates, clathrates, and prodrugs thereof, wherein:

15. Z_1 is $-\text{OH}$ or $-\text{SH}$;
 X_{42} , R_{41} , R_{42} , R_{43} , and R_{45} are defined as above.
 In one embodiment, in formula (VII), Z_1 is $-\text{OH}$.
 In another embodiment, in formula (VII), Z_1 is $-\text{SH}$.
 In another embodiment, in formula (VII), R_{41} is selected from the group consisting of $-\text{H}$, lower alkyl, lower alkoxy, lower cycloalkyl, and lower 20 cycloalkoxy.
 In another embodiment, in formula (VII), R_{41} is selected from the group consisting of $-\text{H}$, methyl, ethyl, propyl, isopropyl, cyclopropyl, methoxy, ethoxy, propoxy, and cyclopropoxy.
 In another embodiment, in formula (VII), R_{42} is selected from the group 25 consisting of lower alkyl, lower cycloalkyl, $-\text{C}(\text{O})\text{N}(\text{R}_{27})_2$, or $-\text{C}(\text{O})\text{OH}$, wherein R_{27} is $-\text{H}$ or a lower alkyl.

In another embodiment, in formula (VII), R₄₂ is selected from the group consisting of -H, methyl, ethyl, n-propyl, isopropyl, cyclopropyl, n-butyl, *sec*-butyl, *tert*-butyl, n-pentyl, n-hexyl, -C(O)OH, -(CH₂)_mC(O)OH, -CH₂OCH₃, -CH₂CH₂OCH₃, and -C(O)N(CH₃)₂.

5 In another embodiment, R₄₃ is H or a lower alkyl.

In another embodiment, in formula (VII), X₄₂ is CR₄₄, and R₄₃ and R₄₄ are, independently, selected from the group consisting of -H, methyl, ethyl, propyl, isopropyl, cyclopropyl, methoxy, ethoxy, propoxy, and cyclopropoxy.

In another embodiment, in formula (VII), X₄₂ is CR₄₄, and R₄₃ and R₄₄, taken together with the carbon atoms to which they are attached, form a cycloalkenyl, aryl, heterocyclyl, or heteroaryl ring. Preferably, in this embodiment, R₄₃ and R₄₄, taken together with the carbon atoms to which they are attached, form a C₅-C₈ cycloalkenyl or a C₅-C₈ aryl.

15 In another embodiment, in formula (VII), R₄₅ is selected from the group consisting of -H, -OH, -SH, -NH₂, a lower alkoxy, a lower alkyl amino, and a lower dialkyl amino.

In another embodiment, in formula (VII), R₄₅ is selected from the group consisting of -H, -OH, methoxy, and ethoxy.

In another embodiment, in formula (VII), X₄₃ is CR₄₄.

20 In another embodiment, the compound is selected from the group consisting of:

3-(2,4-dihydroxyphenyl)-4-(1-ethyl-indol-4-yl)-5-mercpto-[1,2,4]triazole,

3-(2,4-dihydroxyphenyl)-4-(1-isopropyl-indol-4-yl)-5-mercpto-

[1,2,4]triazole,

25 3-(2,4-dihydroxyphenyl)-4-(indol-4-yl)-5-mercpto-[1,2,4]triazole,

3-(2,4-dihydroxyphenyl)-4-(1-methoxyethyl-indol-4-yl)-5-mercpto-

[1,2,4]triazole,

3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1-isopropyl-indol-4-yl)-5-mercpto-[1,2,4]triazole,

30 3-(2,4-dihydroxyphenyl)-4-(1-dimethylcarbamoyl-indol-4-yl)-5-mercpto-[1,2,4]triazole,

3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1-propyl-indol-4-yl)-5-mercpto-[1,2,4]triazole,

3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1,2,3-trimethyl-indol-5-yl)-5-mercaptop-[1,2,4]triazole,

3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(2,3-dimethyl-indol-5-yl)-5-mercaptop-[1,2,4]triazole,

5 3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1-acetyl-2,3-dimethyl-indol-5-yl)-5-mercaptop-[1,2,4]triazole,

3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1-isopropyl-7-methoxy-indol-4-yl)-5-mercaptop-[1,2,4]triazole,

10 3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1-propyl-2,3-dimethyl-indol-5-yl)-5-mercaptop-[1,2,4]triazole,

3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(N-methyl-tetrahydrocarbozol-7-yl)-5-mercaptop-[1,2,4]triazole,

3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(N-methyl-cyclononan[a]indol-5-yl)-5-mercaptop-[1,2,4]triazole,

15 3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1-n-butyl-indol-4-yl)-5-mercaptop-[1,2,4]triazole,

3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1-n-pentyl-indol-4-yl)-5-mercaptop-[1,2,4]triazole,

3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1-n-hexyl-indol-4-yl)-5-mercaptop-[1,2,4]triazole,

20 3-(2,4-dihydroxy-5-cyclopropyl-phenyl)-4-(1-(1-methylcyclopropyl)-indol-4-yl)-5-mercaptop-[1,2,4]triazole,

3-(2,4-dihydroxy-5-cyclopropyl-phenyl)-4-(1-isopropyl-7-methoxy-indol-4-yl)-5-mercaptop-[1,2,4]triazole,

25 3-(2,4-dihydroxy-5-cyclopropyl-phenyl)-4-(1,2,3-trimethyl-indol-5-yl)-5-mercaptop-[1,2,4]triazole,

3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1-isopropyl-7-methoxy-indol-4-yl)-5-mercaptop-[1,2,4]triazole disodium salt,

30 3-(2,4-dihydroxy-5-*tert*-butyl-phenyl)-4-(1-isopropyl-7-methoxy-indol-4-yl)-5-mercaptop-[1,2,4]triazole,

3-(2,4-dihydroxy-5-cyclopropyl-phenyl)-4-(1-propyl-7-methoxy-indol-4-yl)-5-mercaptop-[1,2,4]triazole,

3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1-methyl-3-ethyl-indol-5-yl)-5-mercaptop-[1,2,4]triazole,

3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1,3-dimethyl-indol-5-yl)-5-mercaptop-[1,2,4]triazole,

3-(2,4-dihydroxy-5-isopropyl-phenyl)-4-(1-isopropyl-7-methoxy-indol-4-yl)-5-mercaptop-[1,2,4]triazole,

5 3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1-methyl-3-isopropyl-indol-5-yl)-5-mercaptop-[1,2,4]triazole,

3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(N-ethyl-carbozol-7-yl)-5-mercaptop-[1,2,4]triazole,

10 3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1-isopropyl-7-hydroxy-indol-4-yl)-5-mercaptop-[1,2,4]triazole,

3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1-isopropyl-7-ethoxy-indol-4-yl)-5-mercaptop-[1,2,4]triazole,

3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1,2-dimethyl-indol-5-yl)-5-mercaptop-[1,2,4]triazole,

15 3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(N-methyl-indol-5-yl)-5-mercaptop-[1,2,4]triazole,

3-(2,4-dihydroxy-5-isopropyl-phenyl)-4-(1,3-dimethyl-indol-5-yl)-5-mercaptop-[1,2,4]triazole,

3-(2,4-dihydroxy-5-cyclopropyl-phenyl)-4-(1,3-dimethyl-indol-5-yl)-5-mercaptop-[1,2,4]triazole,

20 3-(2,4-dihydroxy-5-isopropyl-phenyl)-4-(1H-indol-5-yl)-5-mercaptop-[1,2,4]triazole,

3-(2,4-dihydroxy-5-cyclopropyl-phenyl)-4-(1-methyl-indol-5-yl)-5-mercaptop-[1,2,4]triazole,

3-(2,4-dihydroxy-5-isopropyl-phenyl)-4-(1H-indol-5-yl)-5-mercaptop-[1,2,4]triazole,

25 3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1,2-dimethyl-indol-5-yl)-5-mercaptop-[1,2,4]triazole,

3-(2,4-dihydroxy-5-isopropyl-phenyl)-4-(1-ethyl-indol-5-yl)-5-mercaptop-[1,2,4]triazole,

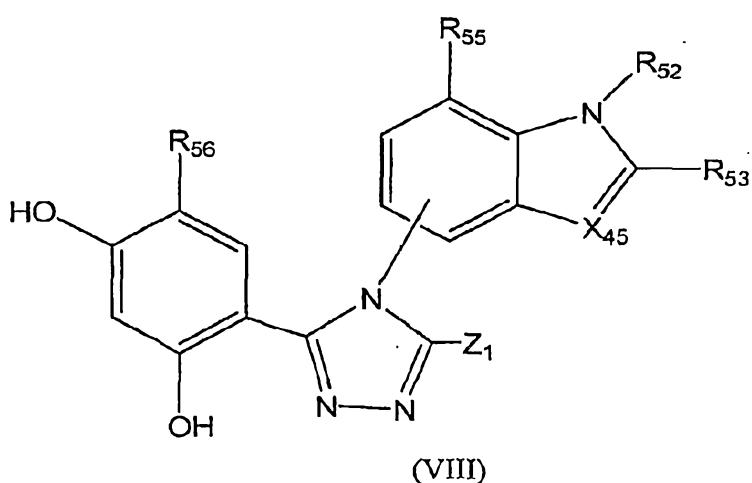
3-(2,4-dihydroxy-5-isopropyl-phenyl)-4-(1-propyl-indol-5-yl)-5-mercaptop-[1,2,4]triazole, and

30 tautomers, pharmaceutically acceptable salts, solvates, clathrates, and prodrugs thereof.

In another embodiment, in formula (VII), X₄₂ is N.

In another embodiment, the compound is selected from the group consisting of

3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1-ethyl-benzimidazol-4-yl)-5-mercaptop-[1,2,4]triazole,
 5 3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1-ethyl-benzimidazol -4-yl)-5-mercaptop-[1,2,4]triazole HCL salt,
 3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(2-methyl-3-ethyl-benzimidazol-5-yl)-5-mercaptop-[1,2,4]triazole,
 10 3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1-ethyl-2-methyl-benzimidazol-5-yl)-5-mercaptop-[1,2,4]triazole,
 3-(2,4-dihydroxy-5-isopropyl-phenyl)-4-(1-methyl-2-trifluoromethyl-benzimidazol-5-yl)-5-mercaptop-[1,2,4]triazole, and
 tautomers, pharmaceutically acceptable salts, solvates, clathrates, and prodrugs thereof.
 15 Compounds of formula (VII) inhibit the activity of Hsp90 and are particularly useful for treating or preventing (e.g., reducing the likelihood of developing) angiogenesis related disorders, such as macular degeneration. In addition, compounds of formula (VII) are particularly useful in reducing, blocking, occluding, or otherwise disrupting blood flow in neovasculature.
 20 In another aspect, the invention provides compounds represented by formula (VIII):



and tautomers, pharmaceutically acceptable salts, solvates, clathrates, and prodrugs thereof, wherein:

X_{45} is CR_{54} or N;

Z_1 is $-\text{OH}$ or $-\text{SH}$;

R_{52} is selected from the group consisting of $-\text{H}$, methyl, ethyl, n-propyl, isopropyl, n-butyl, n-pentyl, n-hexyl, $-(\text{CH}_2)_2\text{OCH}_3$, $-\text{CH}_2\text{C}(\text{O})\text{OH}$, and $-\text{C}(\text{O})\text{N}(\text{CH}_3)_2$;

5 R_{53} and R_{54} are each, independently, $-\text{H}$, methyl, ethyl, or isopropyl; or R_{53} and R_{54} taken together with the carbon atoms to which they are attached form a phenyl, cyclohexenyl, or cyclooctenyl ring;

R_{55} is selected from the group consisting of $-\text{H}$, $-\text{OH}$, $-\text{OCH}_3$, and $-\text{OCH}_2\text{CH}_3$; and

10 R_{56} is selected from the group consisting of $-\text{H}$, methyl, ethyl, isopropyl, and cyclopropyl.

In one embodiment, in formula (VIII), Z_1 is $-\text{OH}$.

In another embodiment, in formula (VIII), Z_1 is $-\text{SH}$.

In another embodiment, in formula (VIII), R_{53} is H or a lower alkyl.

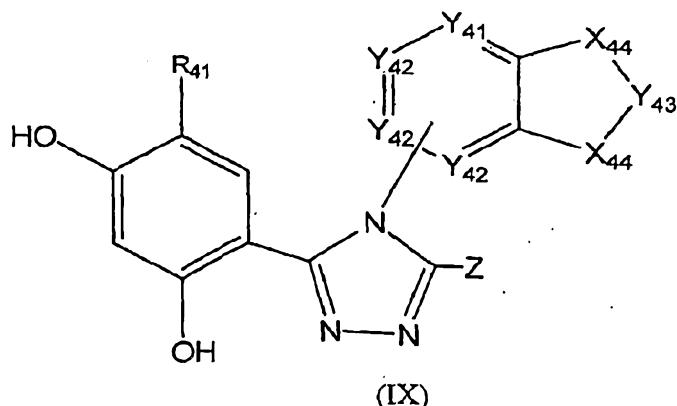
15 In another embodiment, in formula (VIII), X_{45} is CR_{54} . Preferably, R_{54} is H or a lower alkyl.

In another embodiment, X_{45} is N .

20 In another embodiment, the compound is 3-(2,4-dihydroxy-5-isopropyl-phenyl)-4-(N-methyl-indol-5-yl)-5-mercaptop-[1,2,4]triazole.

Compounds of formula (VIII) inhibit the activity of Hsp90 and are particularly useful for treating or preventing (e.g., reducing the likelihood of developing) angiogenesis related disorders, such as macular degeneration. In addition, compounds of formula (VIII) are particularly useful in reducing, blocking, 25 occluding, or otherwise disrupting blood flow in neovasculature.

In another aspect, the invention provides compounds represented by formula (IX):



and tautomers, pharmaceutically acceptable salts, solvates, clathrates, and prodrugs thereof, wherein,

5 X_{44} , for each occurrence, is independently, O, NR_{42} or $C(R_{46})_2$;
 Y_{43} is NR_{42} or $C(R_{46})_2$;
 Y_{41} , Y_{42} , Z , R_{41} , R_{42} , and R_{46} are defined as above.

In one embodiment, in formula (IX), R_{41} is selected from the group consisting of -H, lower alkyl, lower alkoxy, lower cycloalkyl, and lower cycloalkoxy.

In another embodiment, in formula (IX), R_{41} is selected from the group consisting of -H, methyl, ethyl, propyl, isopropyl, cyclopropyl, methoxy, ethoxy, propoxy, and cycloprooxy.

15 In another embodiment, in formula (IX), R_{42} is selected from the group consisting of -H, methyl, ethyl, n-propyl, isopropyl, cyclopropyl, n-butyl, *sec*-butyl, *tert*-butyl, n-pentyl, n-hexyl, $-C(O)OH$, $-(CH_2)_mC(O)OH$, $-CH_2OCH_3$, $-CH_2CH_2OCH_3$, and $-C(O)N(CH_3)_2$.

In another embodiment, in formula (IX), Y_{41} is CR_{45} . Preferably, R_{45} is H, a lower alkoxy, or -OH.

20 In another embodiment, in formula (IX), Y_{42} is CH.

In another embodiment, in formula (IX), Y_{43} is CH_2 .

In another embodiment, in formula (IX), Y_{43} is NR_{42} , wherein R_{42} is H or a lower alkyl.

In another embodiment, in formula (IX), one of X_{44} is NR_{42} and the other is CH_2 or $C(R_6)_2$. Preferably, one of X_{44} is NR_{42} and the other is CH_2 .

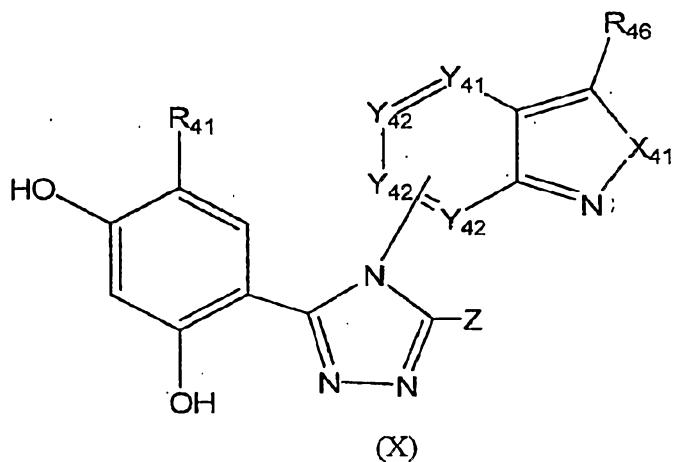
In another embodiment, in formula (VI), Z is -OH.

In another embodiment, Z is -SH.

Compounds of formula (IX) inhibit the activity of Hsp90 and are particularly useful for treating or preventing (e.g., reducing the likelihood of developing) angiogenesis related disorders, such as macular degeneration. In addition, compounds of formula (IX) are particularly useful in reducing, blocking, occluding, 5 or otherwise disrupting blood flow in neovasculature.

In another aspect, the invention provides compounds represented by formula (X):

10



and tautomers, pharmaceutically acceptable salts, solvates, clathrates, and prodrugs thereof, wherein:

X₄₁, Y₄₁, Y₄₂, Z, R₇, R₈, R₁₀, R₁₁, R₄₁, R₄₆, and p are defined as above.

15 In one embodiment, in formula (X), R₄₁ is selected from the group consisting of -H, lower alkyl, lower alkoxy, lower cycloalkyl, and lower cycloalkoxy.

In another embodiment, in formula (X), R₄₁ is selected from the group consisting of -H, methyl, ethyl, propyl, isopropyl, cyclopropyl, methoxy, ethoxy, propoxy, and cyclopropoxy.

20 In another embodiment, in formula (X), X₄₁ is NR₄₂. Preferably, R₄₂ is selected from the group consisting of -H, methyl, ethyl, n-propyl, isopropyl, cyclopropyl, n-butyl, *sec*-butyl, *tert*-butyl, n-pentyl, n-hexyl, -C(O)OH, -(CH₂)_mC(O)OH, -CH₂OCH₃, -CH₂CH₂OCH₃, and -C(O)N(CH₃)₂. More preferably, R₄₂ is H or a lower alkyl.

25 In another embodiment, in formula (X), X₄₁ is O.

In another embodiment, in formula (X), X₄₁ is S.

In another embodiment, in formula (X), Y_{41} is CR_{45} . Preferably, R_{45} is H, a lower alkoxy, or -OH.

In another embodiment, in formula (X), Y_{42} is CH.

In another embodiment, in formula (X), R_{46} is H or a lower alkyl.

5 In one embodiment, the compound is 3-(2,4-dihydroxy-5-isopropyl-phenyl)-4-(2-methyl-indazol-6-yl)-5-mercaptop-[1,2,4]triazole.

Compounds of formula (X) inhibit the activity of Hsp90 and are particularly useful for treating or preventing (e.g., reducing the likelihood of developing) angiogenesis related disorders, such as macular degeneration. In addition,

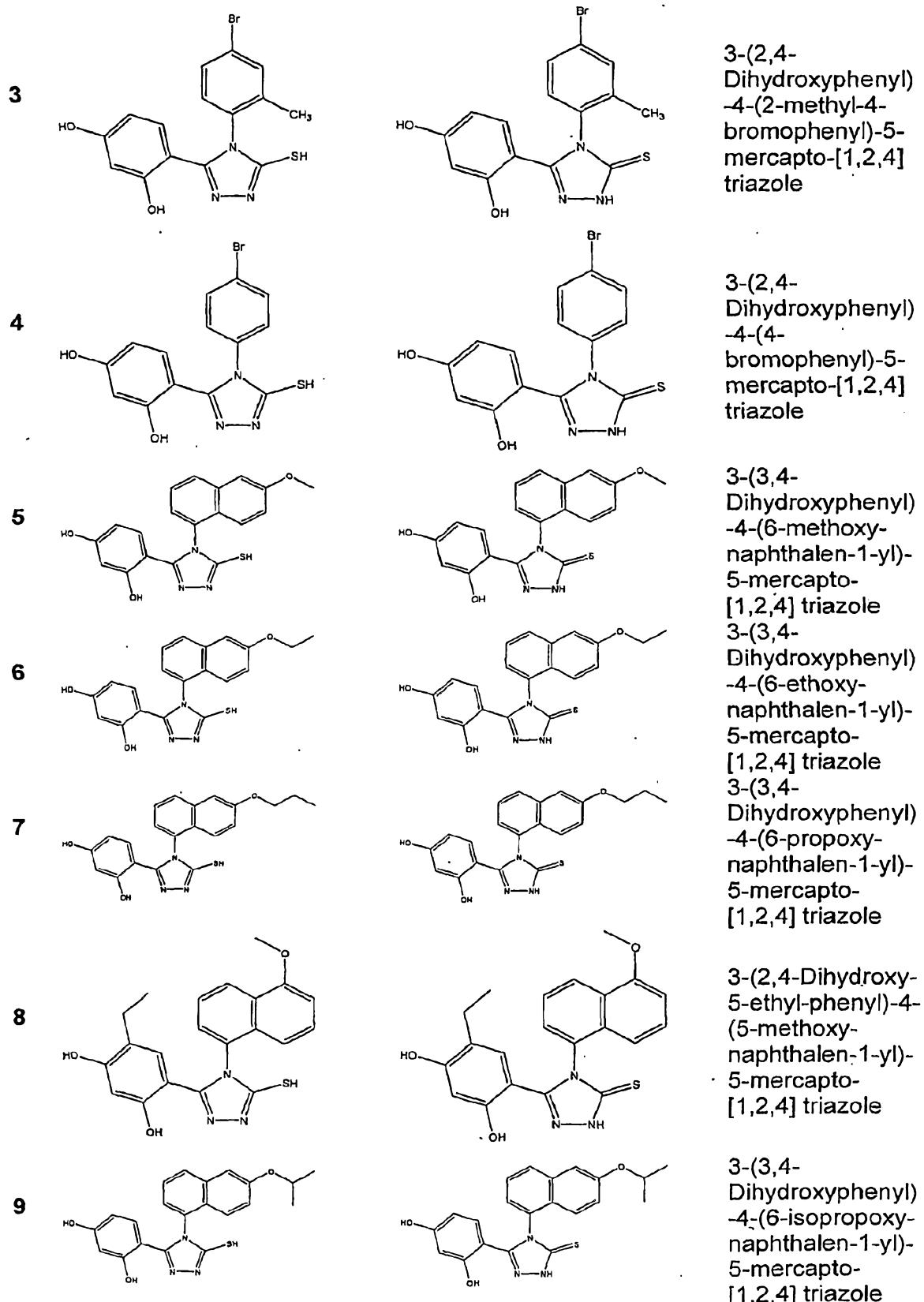
10 compounds of formula (X) are particularly useful in reducing, blocking, occluding, or otherwise disrupting blood flow in neovasculature.

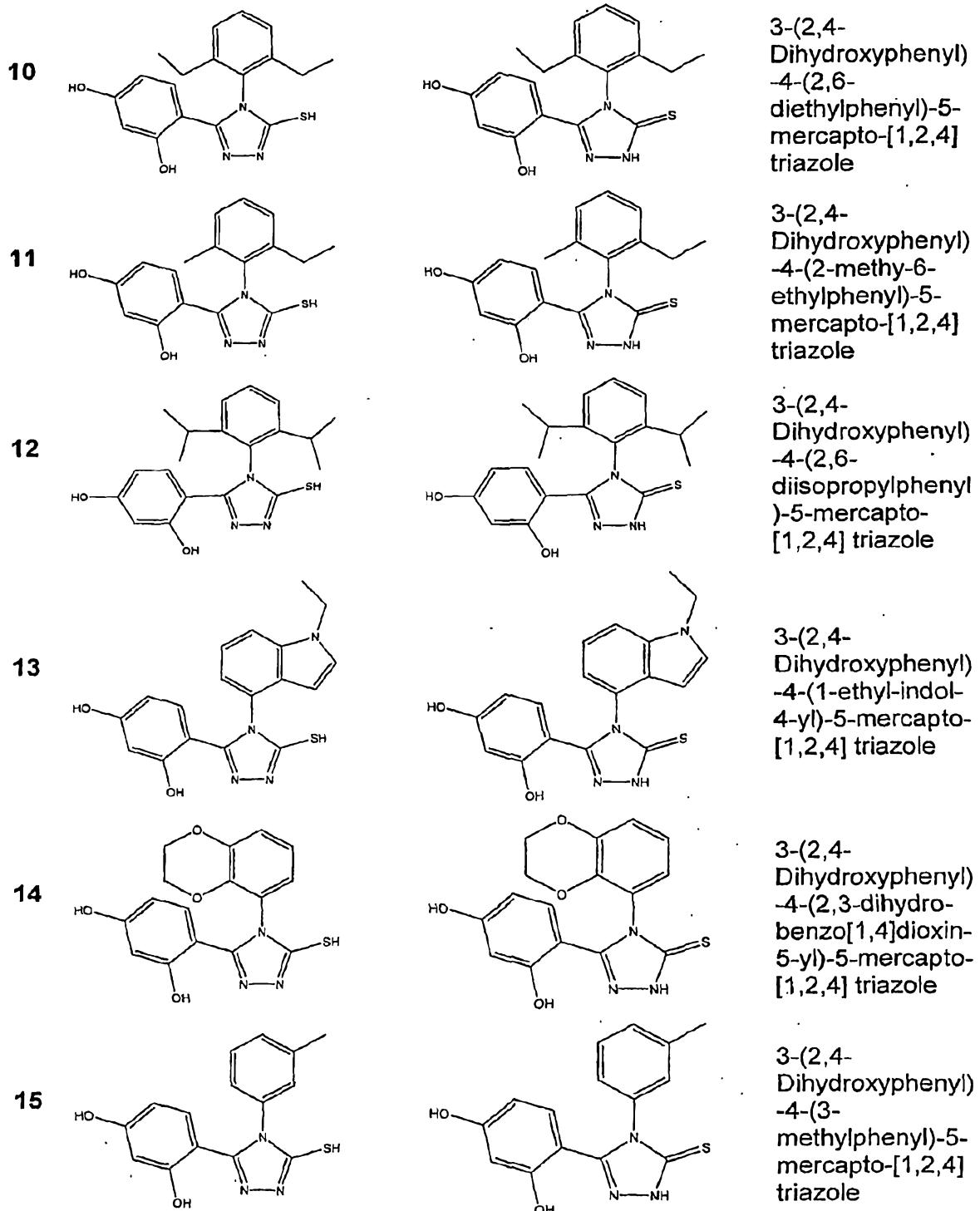
i) Exemplary Compounds of the Invention

Exemplary compounds of the invention are depicted in Table 1 below, 15 including tautomers, pharmaceutically acceptable salts, solvates, clathrates, hydrates, polymorphs or prodrugs thereof.

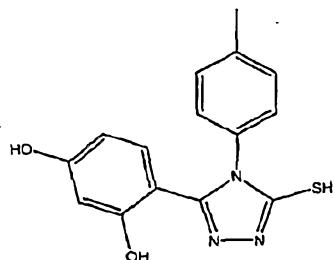
Table 1

No.	Structure	Tautomeric Structure	Name
1			3-(2-Hydroxyphenyl)-4-(naphthalen-1-yl)-5-mercaptop-[1,2,4]triazole
2			3-(2,4-Dihydroxyphenyl)-4-[4-(2-methoxyethoxy)-naphthalen-1-yl]-5-mercaptop-[1,2,4]triazole



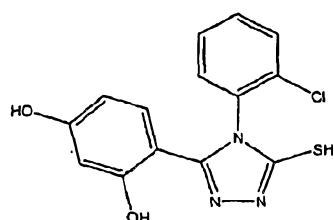


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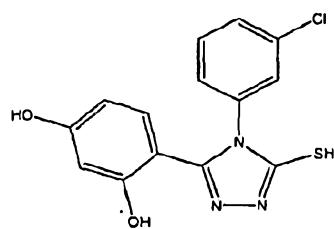
3-(2,4-Dihydroxyphenyl)-4-(4-methylphenyl)-5-mercaptop-[1,2,4]triazole

17



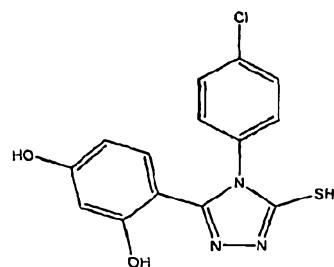
3-(2,4-Dihydroxyphenyl)-4-(2-chlorophenyl)-5-mercaptop-[1,2,4]triazole

18



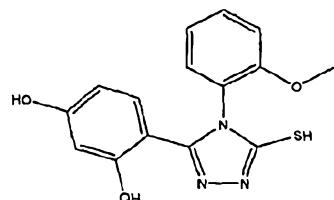
3-(2,4-Dihydroxyphenyl)-4-(3-chlorophenyl)-5-mercaptop-[1,2,4]triazole

19



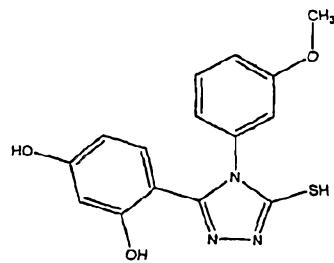
3-(2,4-Dihydroxyphenyl)-4-(4-chlorophenyl)-5-mercaptop-[1,2,4]triazole

20

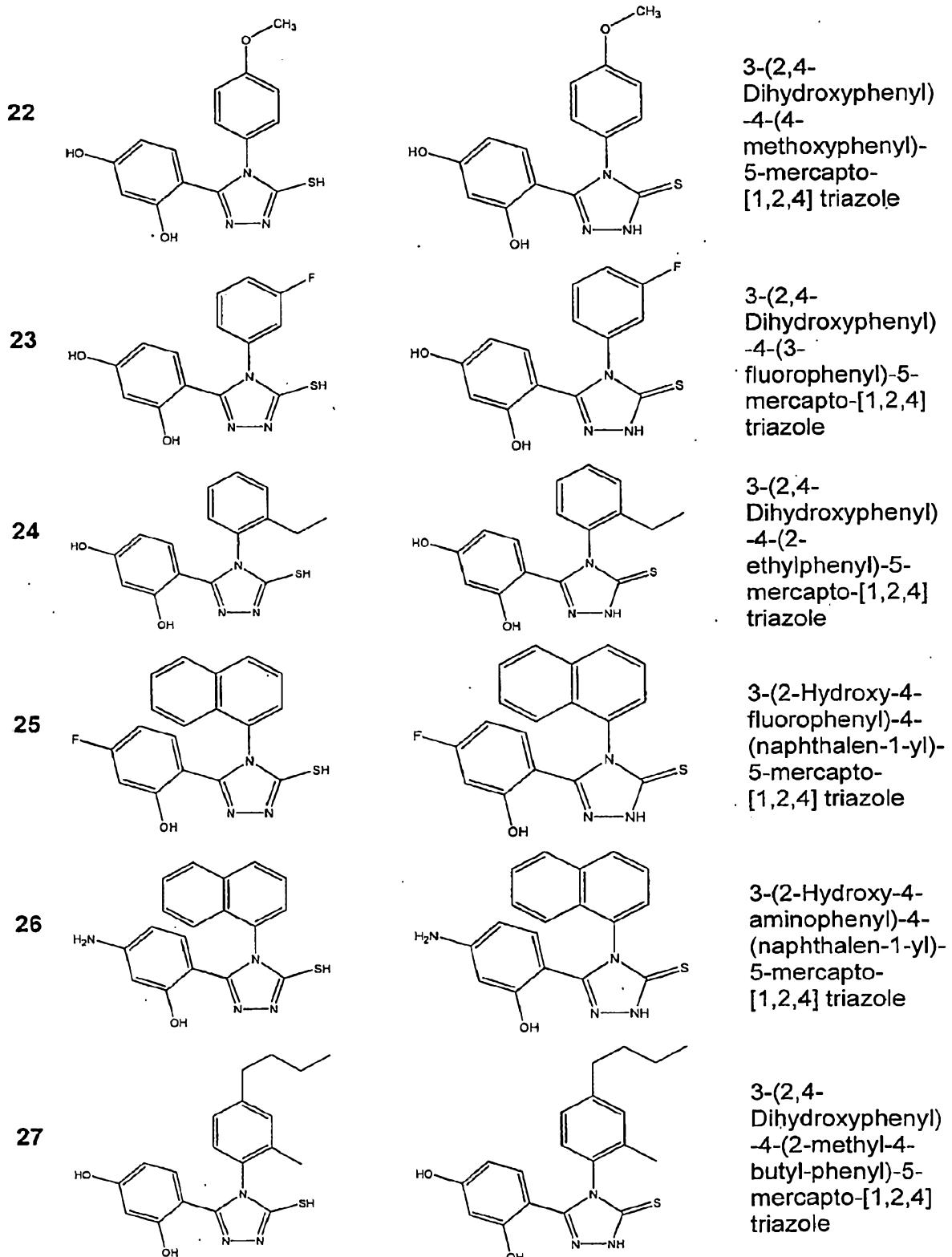


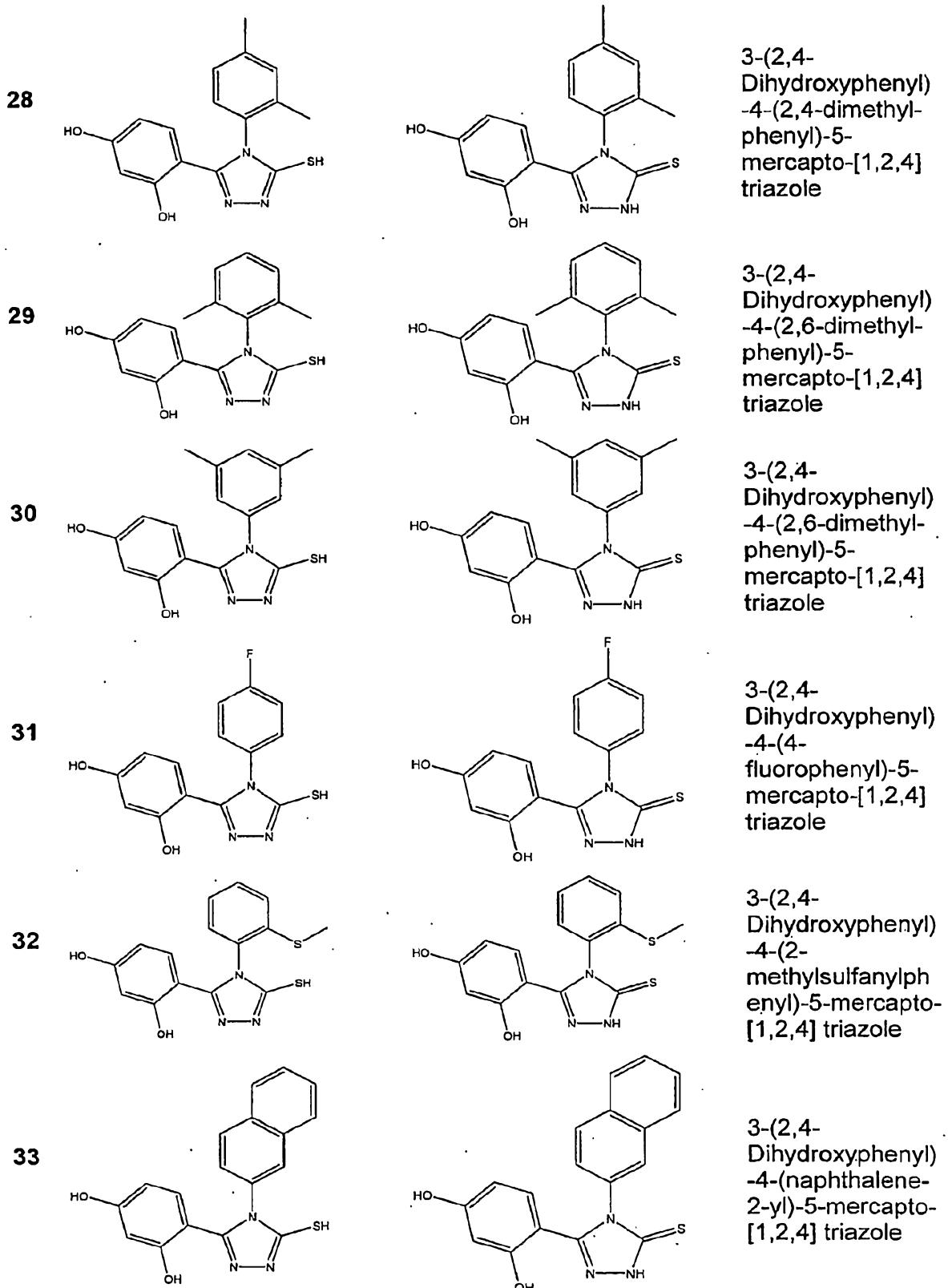
3-(2,4-Dihydroxyphenyl)-4-(2-methoxyphenyl)-5-mercaptop-[1,2,4]triazole

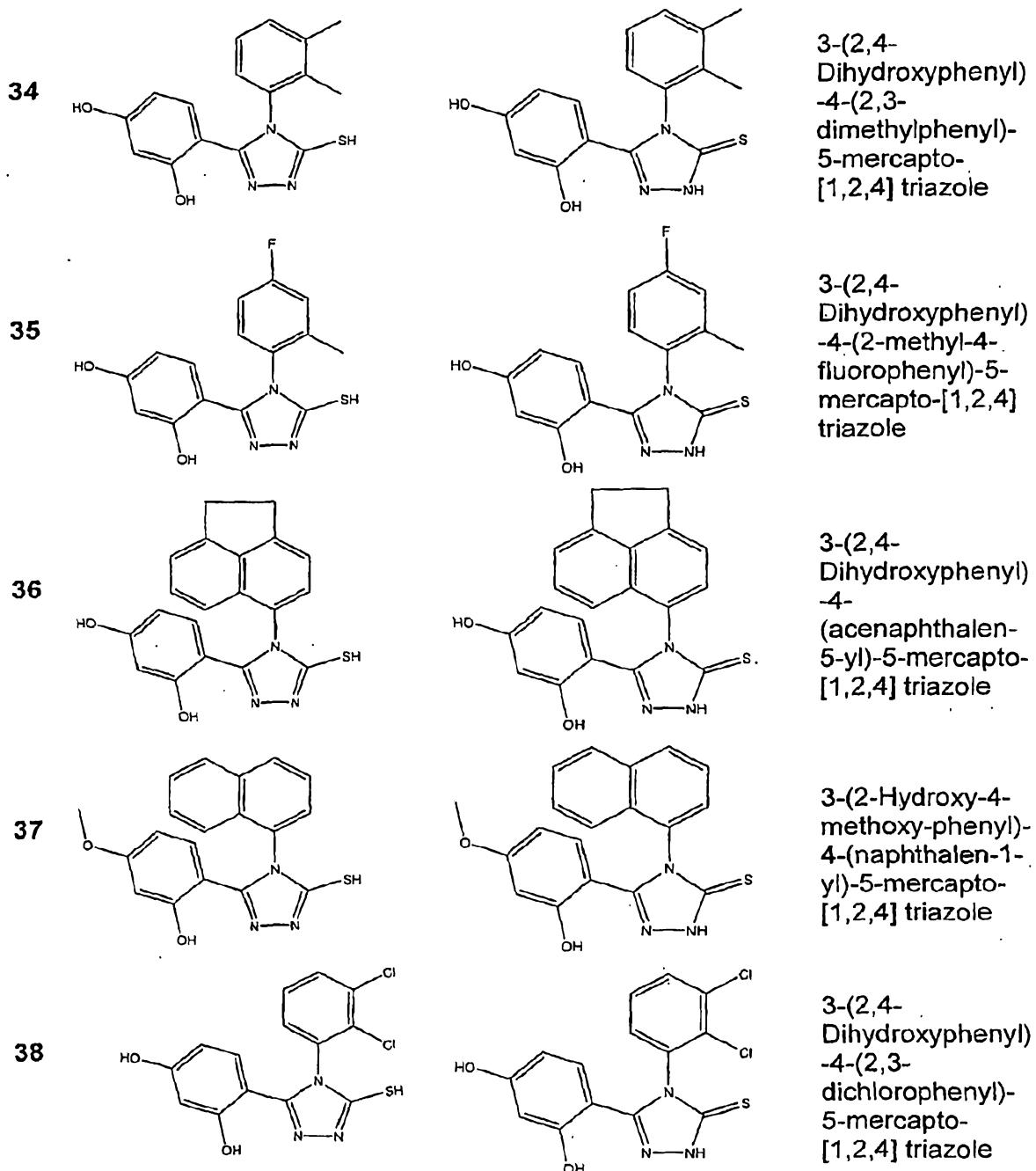
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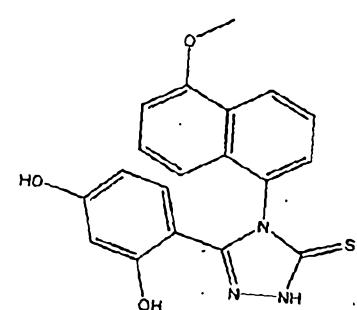
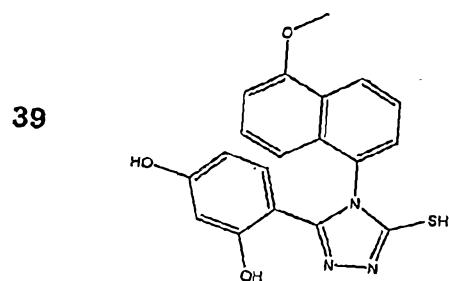


3-(2,4-Dihydroxyphenyl)-4-(3-methoxyphenyl)-5-mercaptop-[1,2,4]triazole

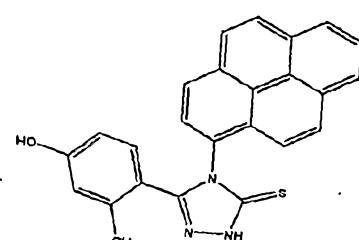
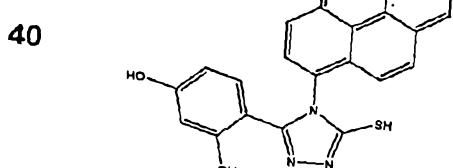




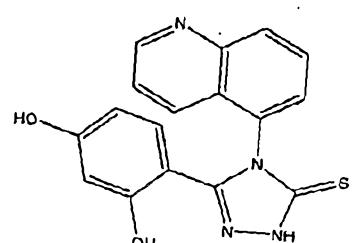
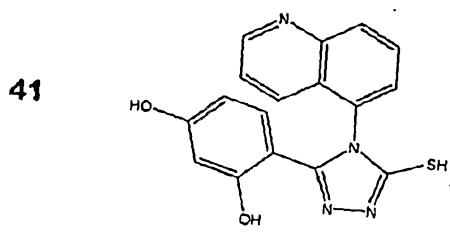




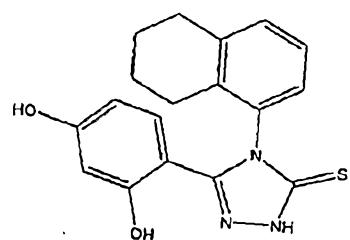
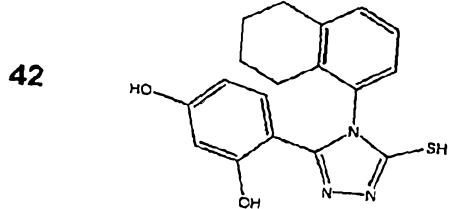
3-(2,4-Dihydroxyphenyl)-4-(5-methoxynaphthalen-1-yl)-5-mercaptop-[1,2,4]triazole



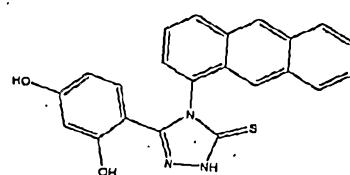
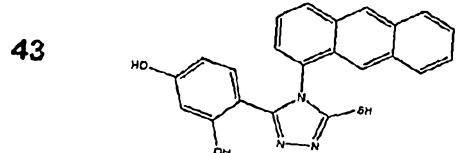
3-(2,4-Dihydroxyphenyl)-4-(pyren-1-yl)-5-mercaptop-[1,2,4]triazole



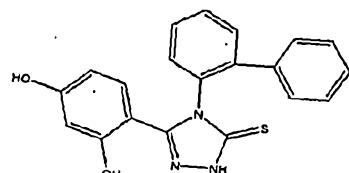
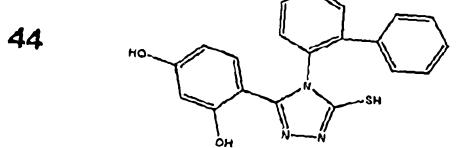
3-(2,4-Dihydroxyphenyl)-4-(quinolin-5-yl)-5-mercaptop-[1,2,4]triazole



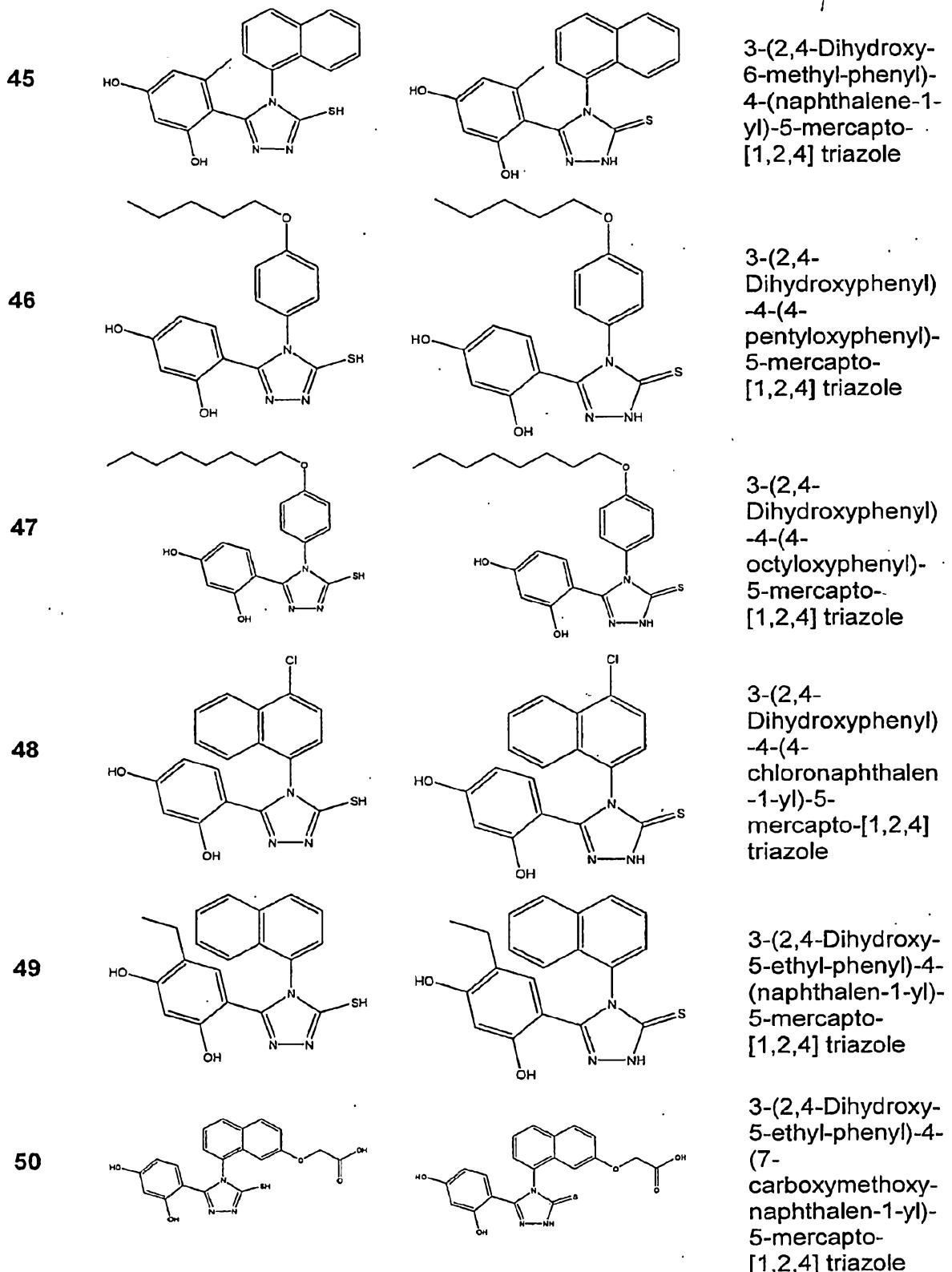
3-(2,4-Dihydroxyphenyl)-4-(1,2,3,4-tetrahydronaphthalen-5-yl)-5-mercaptop-[1,2,4]triazole

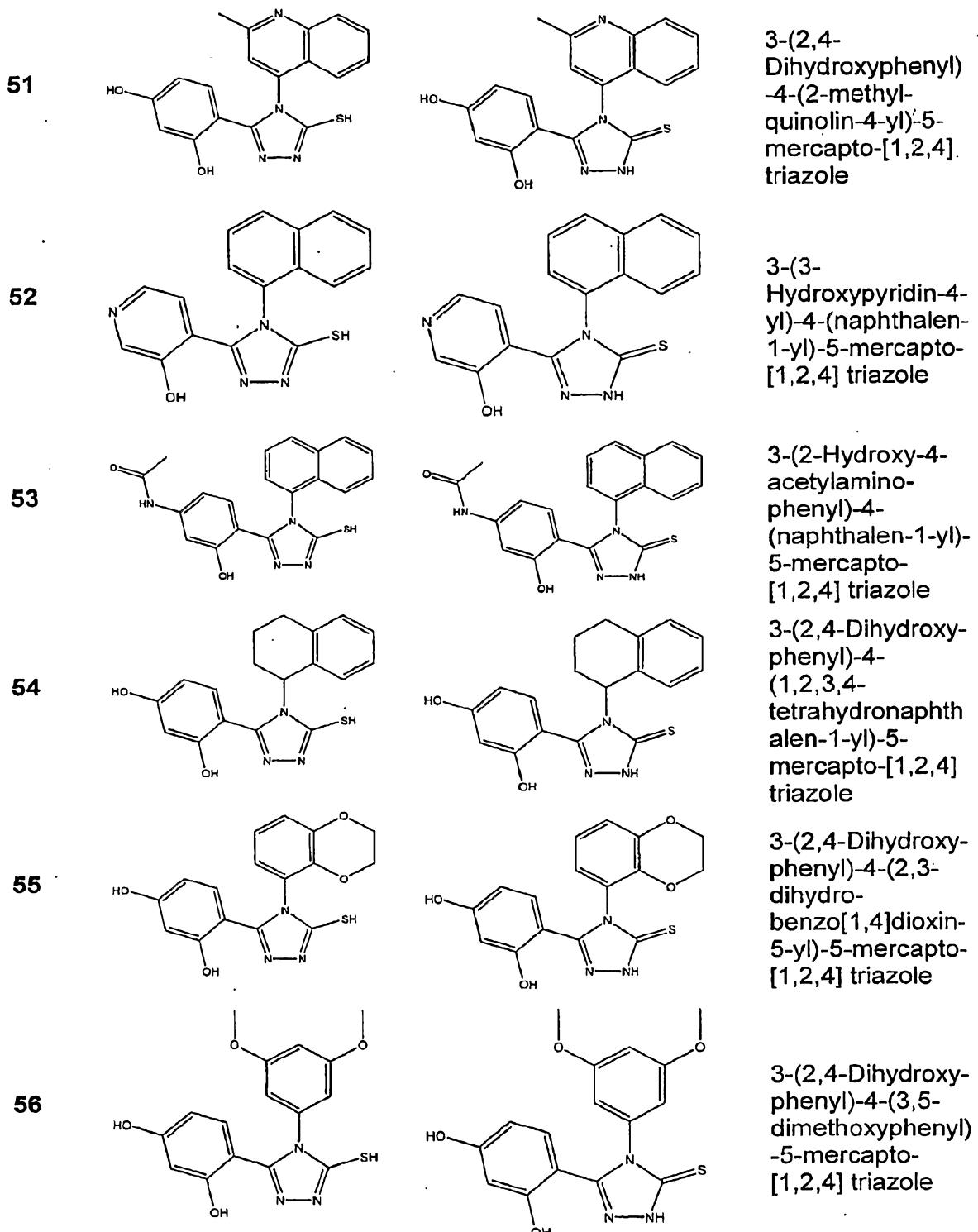


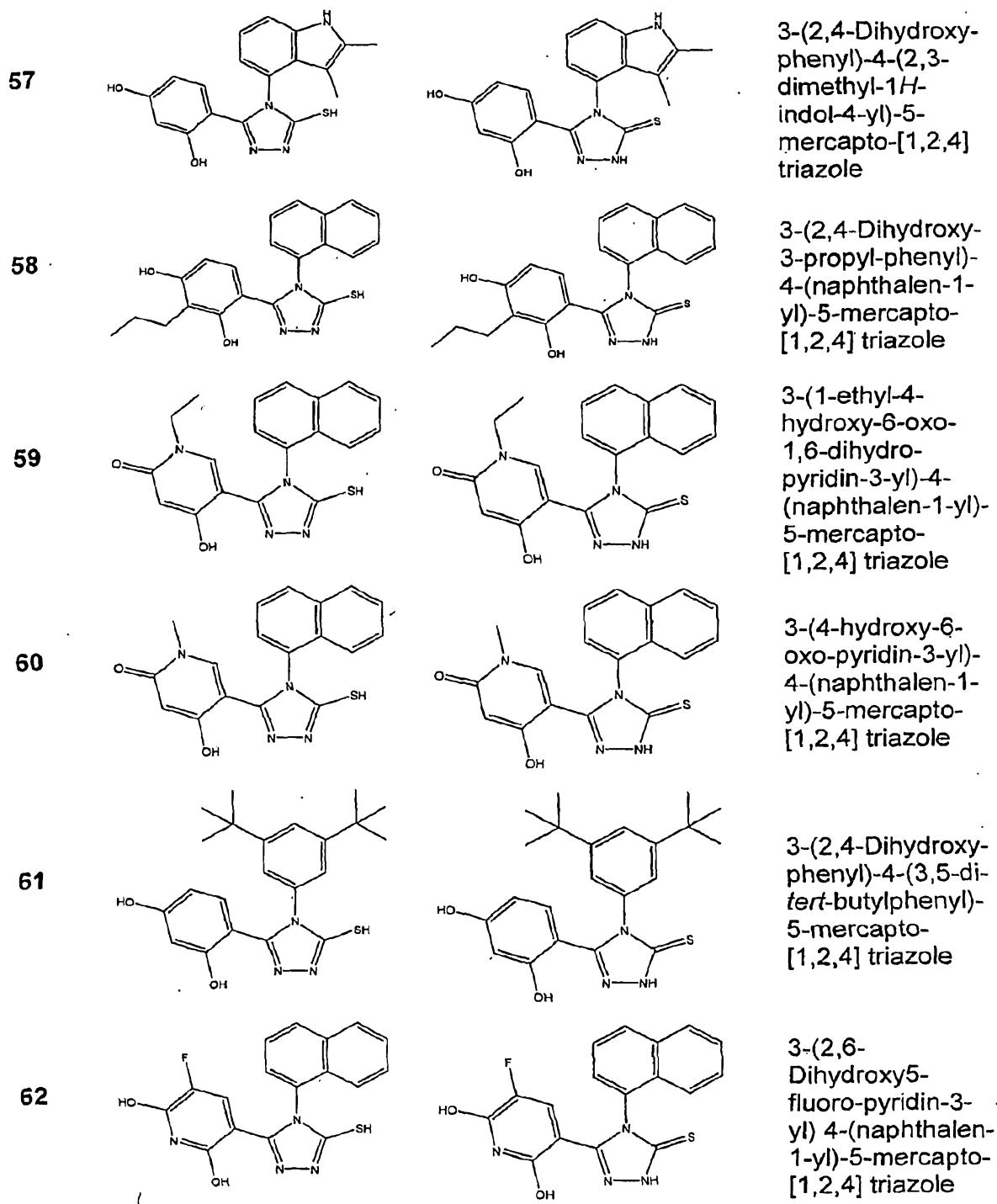
3-(2,4-Dihydroxyphenyl)-4-(anthracen-1-yl)-5-mercaptop-[1,2,4]triazole

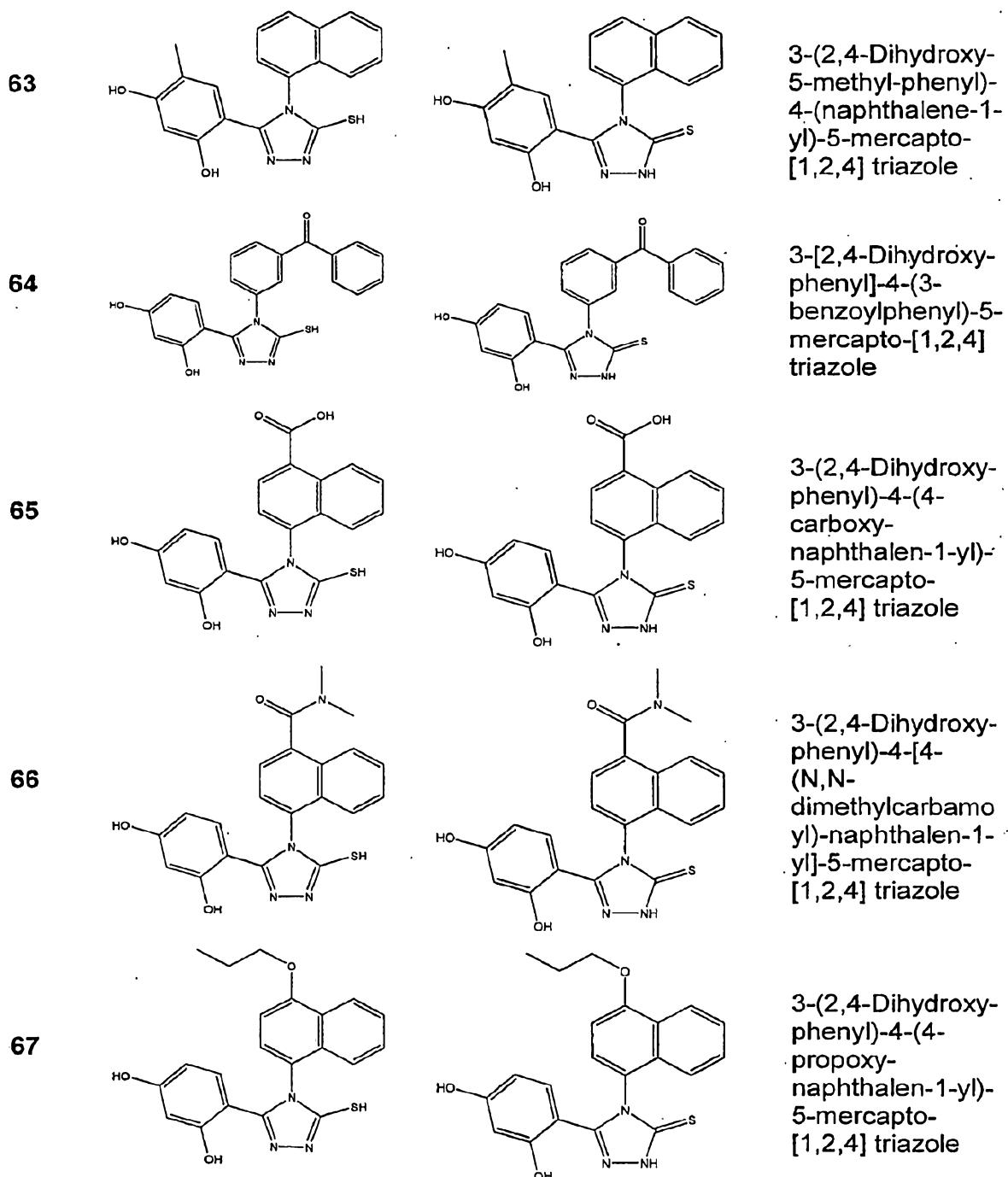


3-(2,4-Dihydroxyphenyl)-4-(biphenyl-2-yl)-5-mercaptop-[1,2,4]triazole

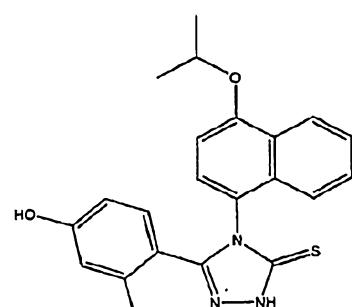
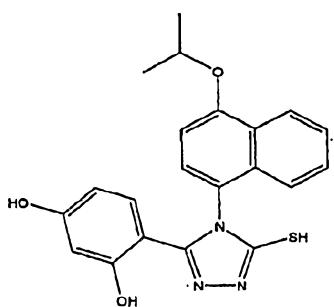






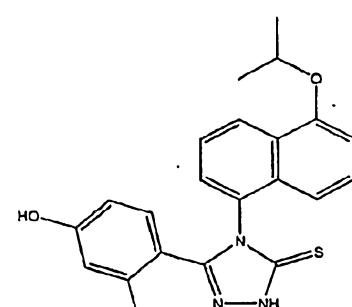
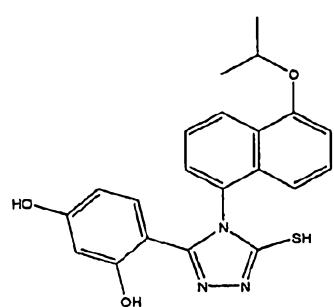


68



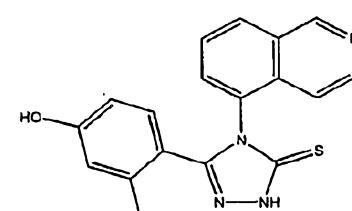
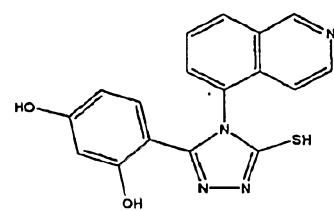
3-(2,4-Dihydroxy-phenyl)-4-(4-isopropoxy-naphthalen-1-yl)-5-mercaptop-[1,2,4] triazole

69



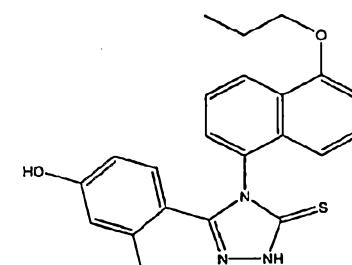
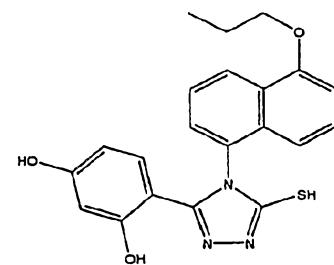
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70



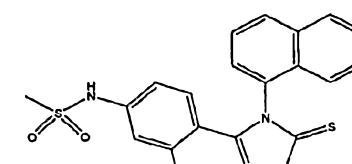
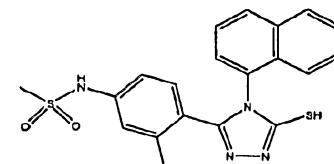
3-(2,4-Dihydroxy-phenyl)-4-(isoquinolin-5-yl)-5-mercaptop-[1,2,4] triazole

71



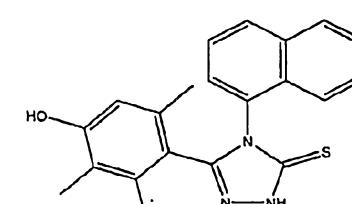
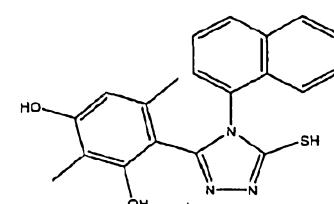
3-(2,4-Dihydroxy-phenyl)-4-(5-propoxy-naphthalen-1-yl)-5-mercaptop-[1,2,4] triazole

72

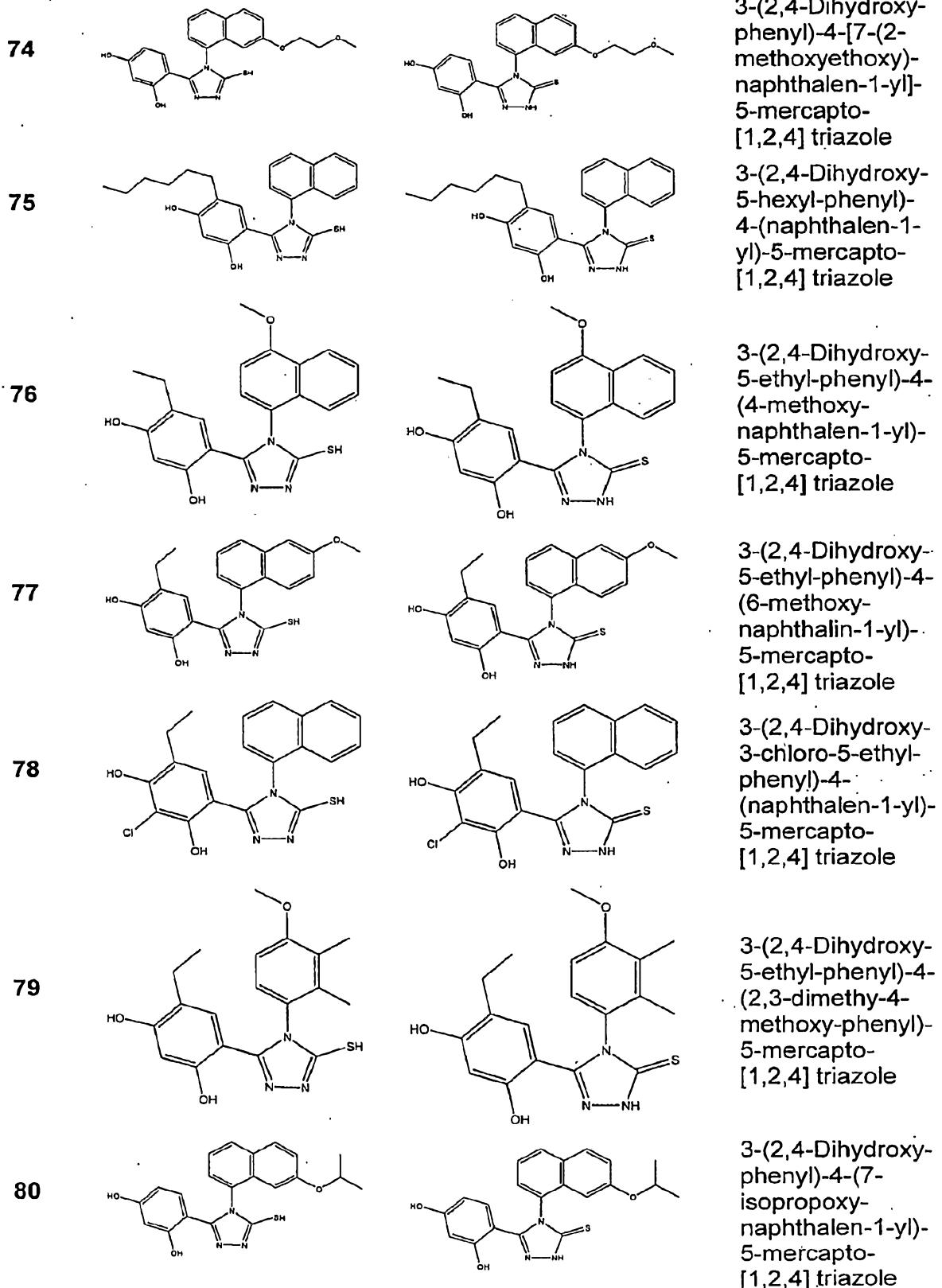


3-(2-Hydroxy-4-methanesulfamino-phenyl)-4-(naphthalen-1-yl)-5-mercaptop-[1,2,4] triazole

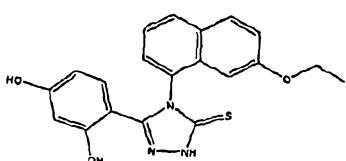
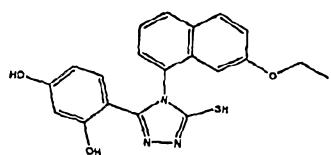
73



3-(2,4-Dihydroxy-3,6-dimethyl-phenyl)-4-(naphthalen-1-yl)-5-mercaptop-[1,2,4] triazole

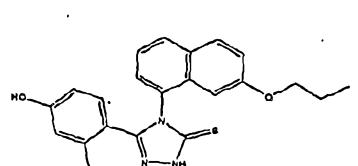
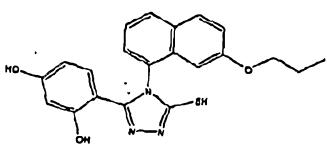


81

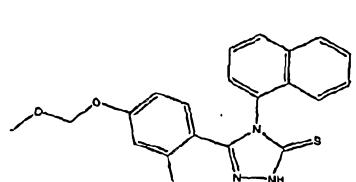
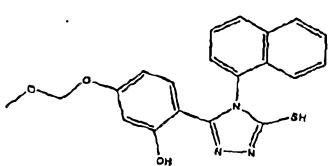


3-(2,4-Dihydroxy-phenyl)-4-(7-ethoxy-naphthalen-1-yl)-5-mercaptop-[1,2,4]triazole

82

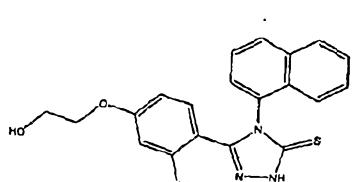
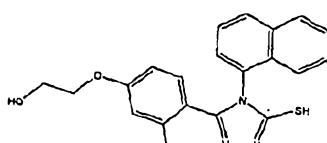


83



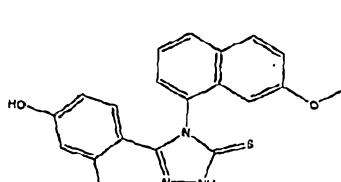
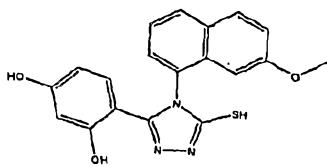
3-(2-Hydroxy-4-methoxymethoxy-phenyl)-4-(naphthalen-1-yl)-5-mercaptop-[1,2,4]triazole

84



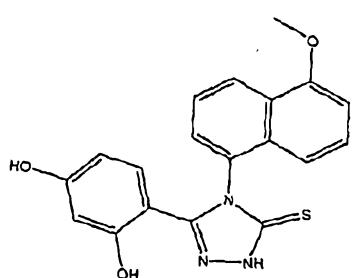
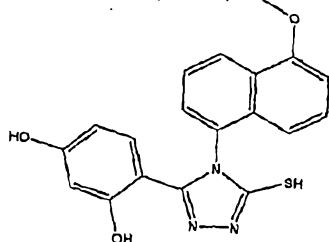
3-[2-Hydroxy-4-(2-hydroxyethoxy)-phenyl]-4-(naphthalen-1-yl)-5-mercaptop-[1,2,4]triazole

85



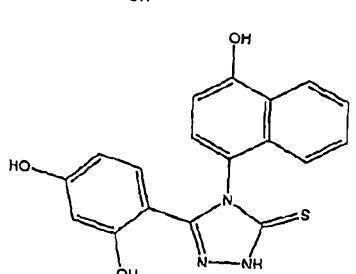
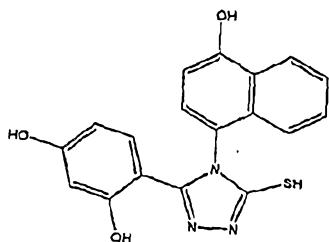
3-(2,4-Dihydroxyphenyl)-4-(7-methoxy-naphthalen-1-yl)-5-mercaptop-[1,2,4]triazole

86

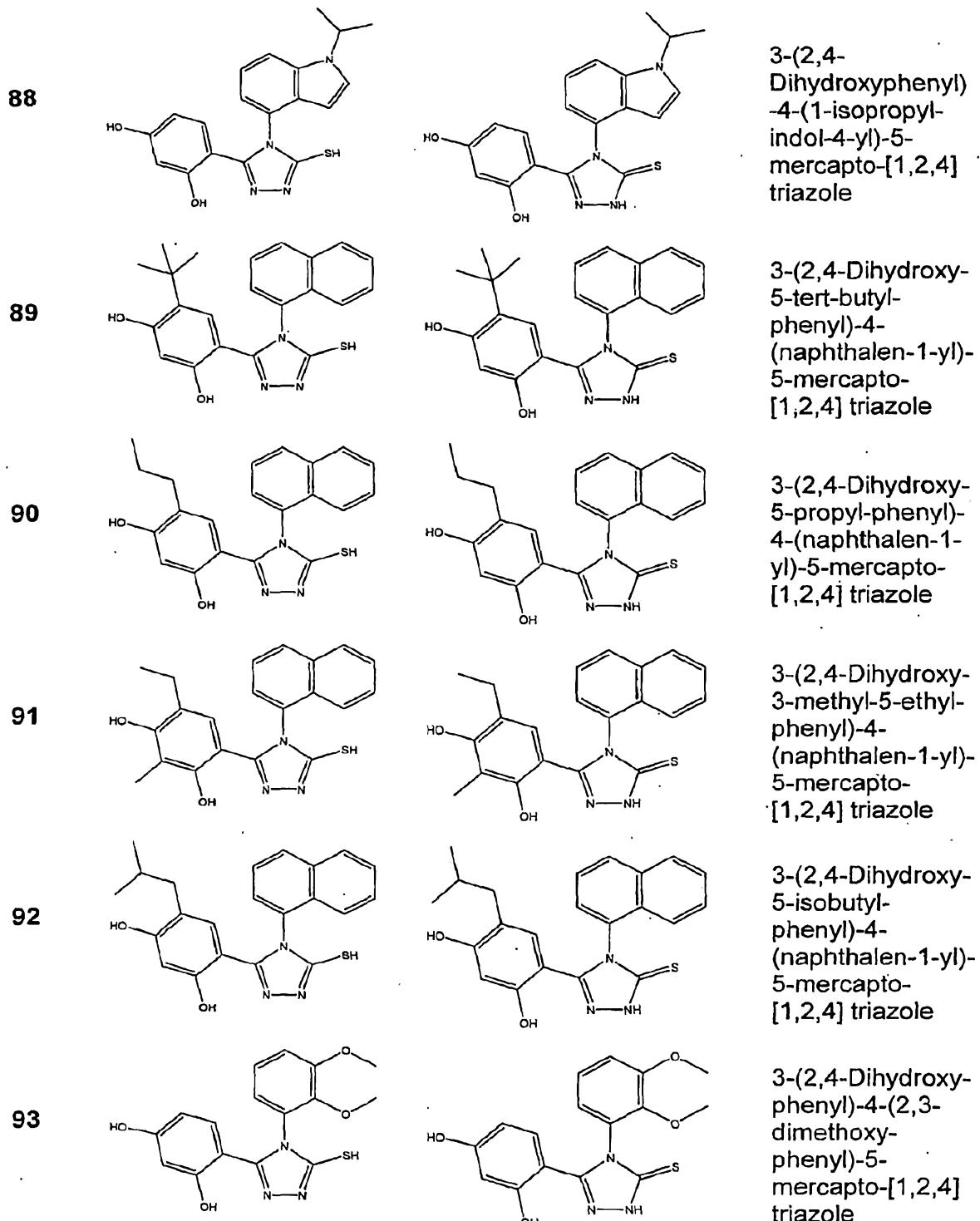


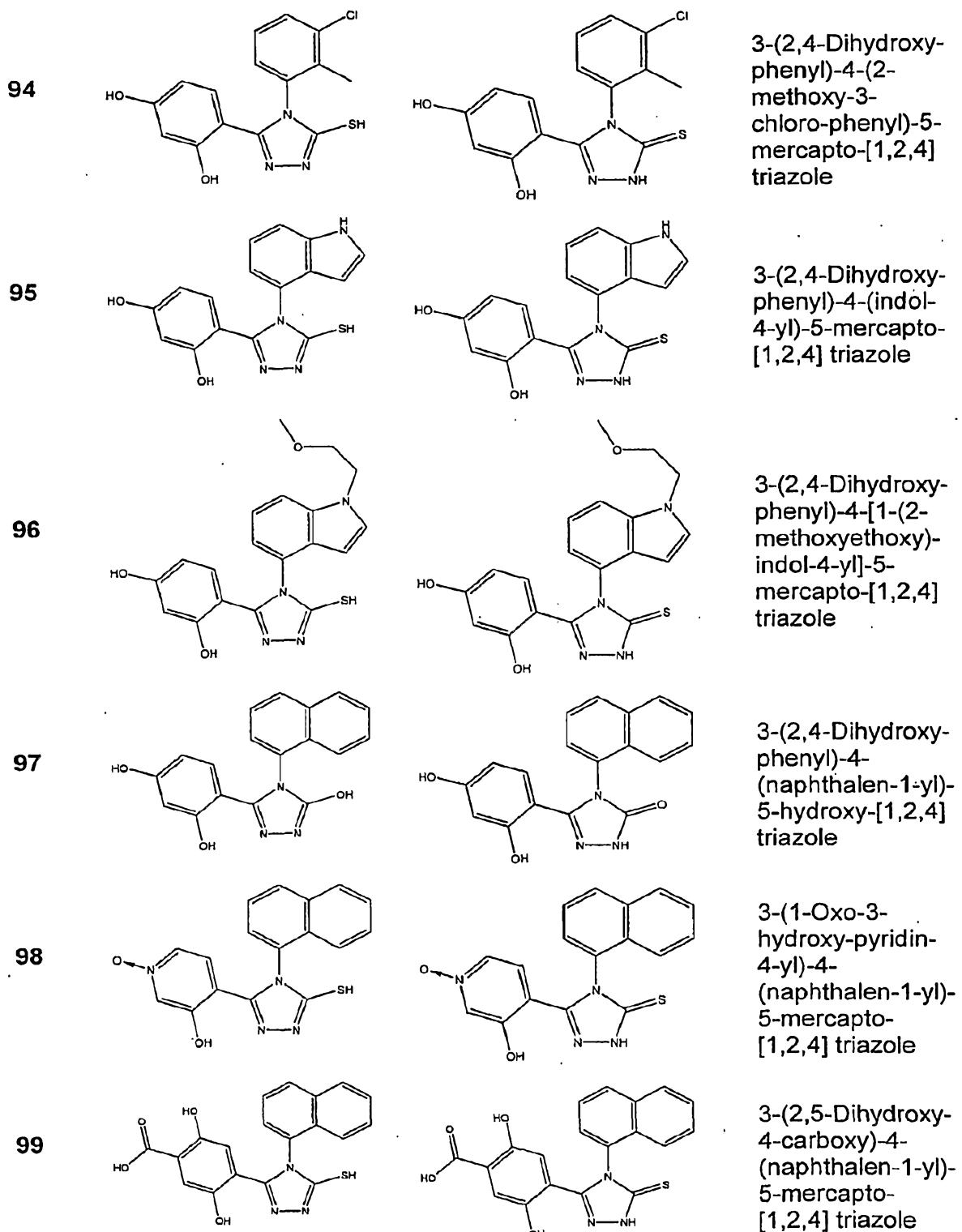
3-(2,4-Dihydroxyphenyl)-4-(5-methoxy-naphthalen-1-yl)-5-mercaptop-[1,2,4]triazole

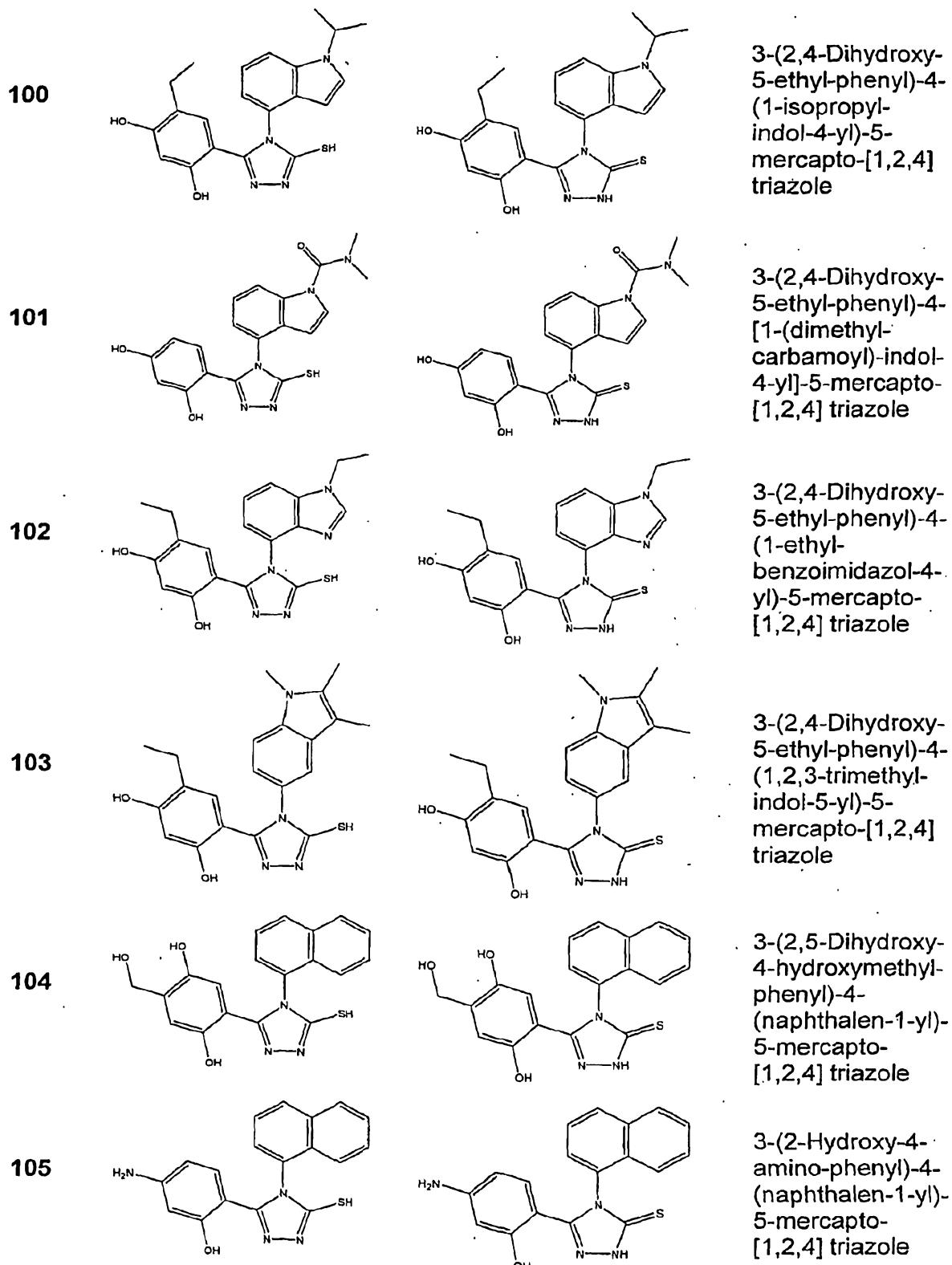
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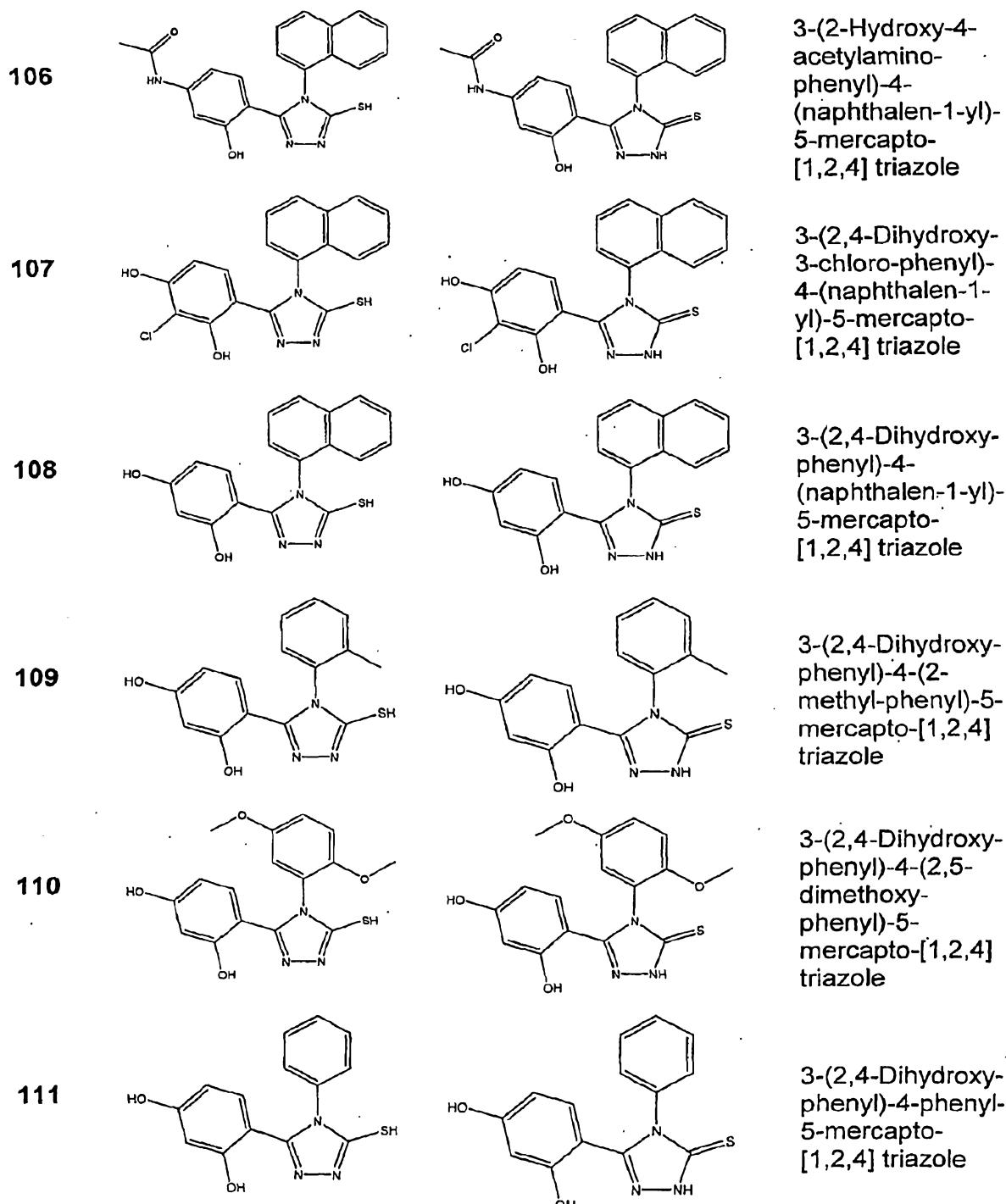


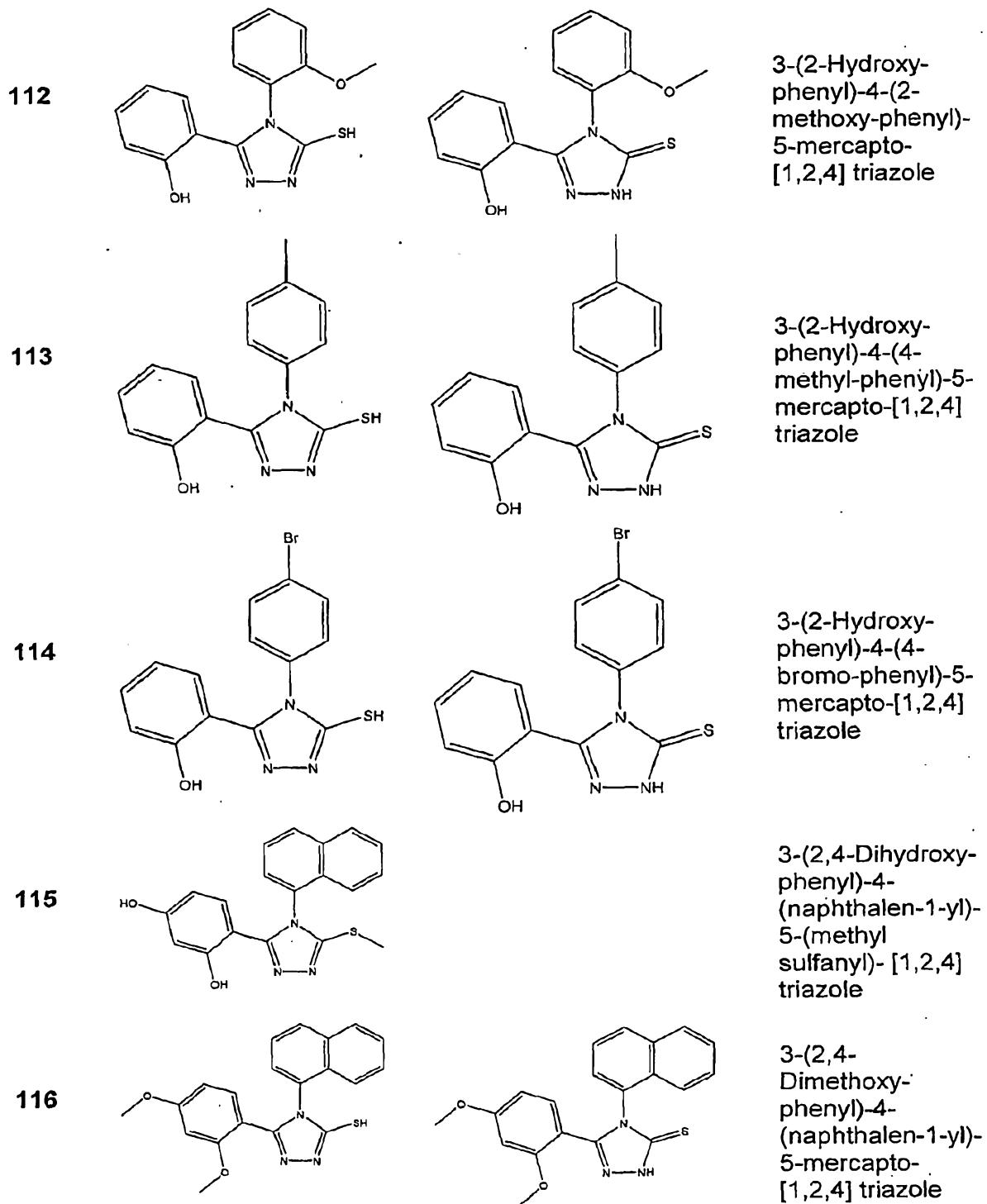
3-(2,4-Dihydroxyphenyl)-4-(4-hydroxy-naphthalen-1-yl)-5-mercaptop-[1,2,4]triazole



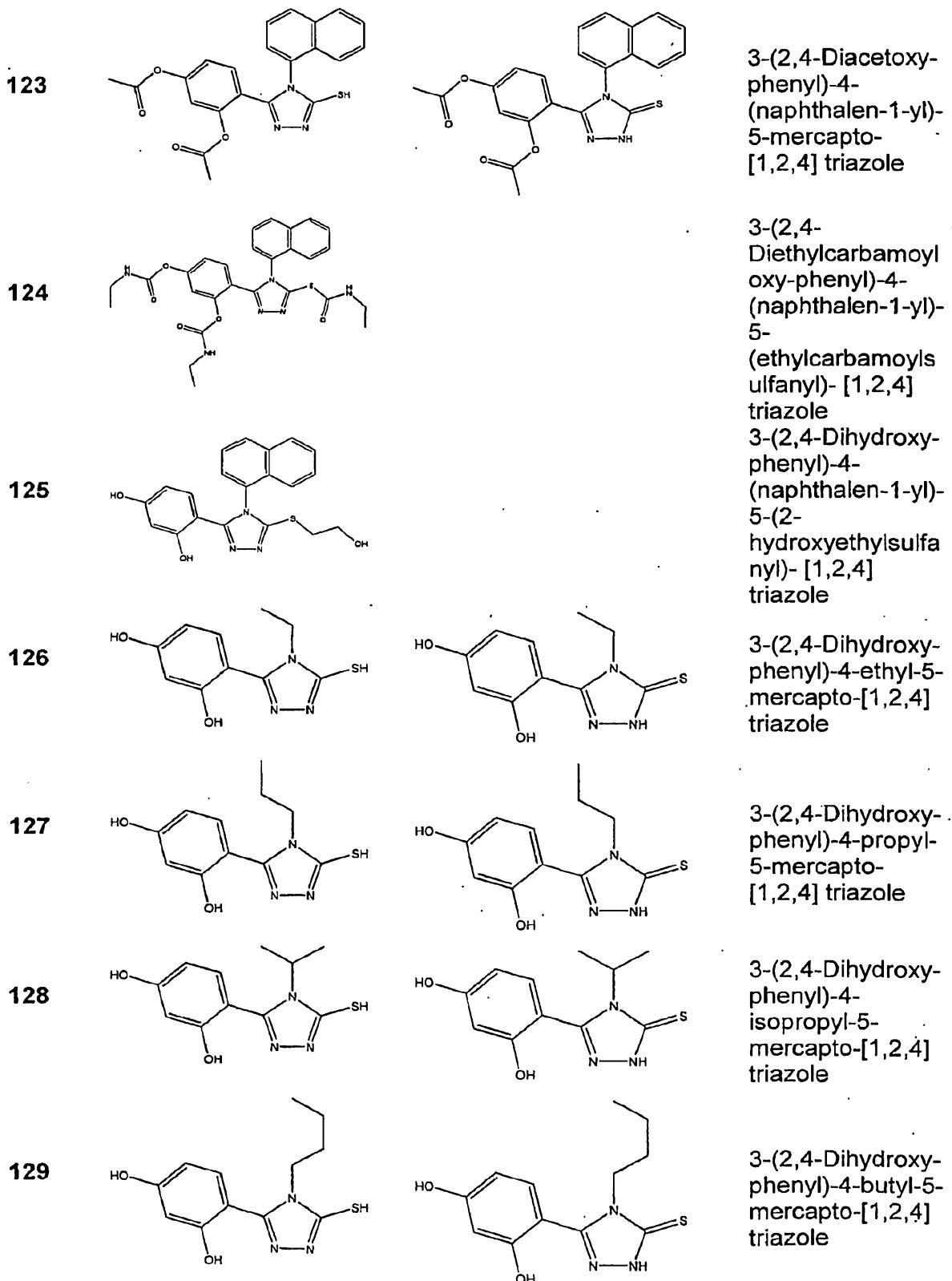


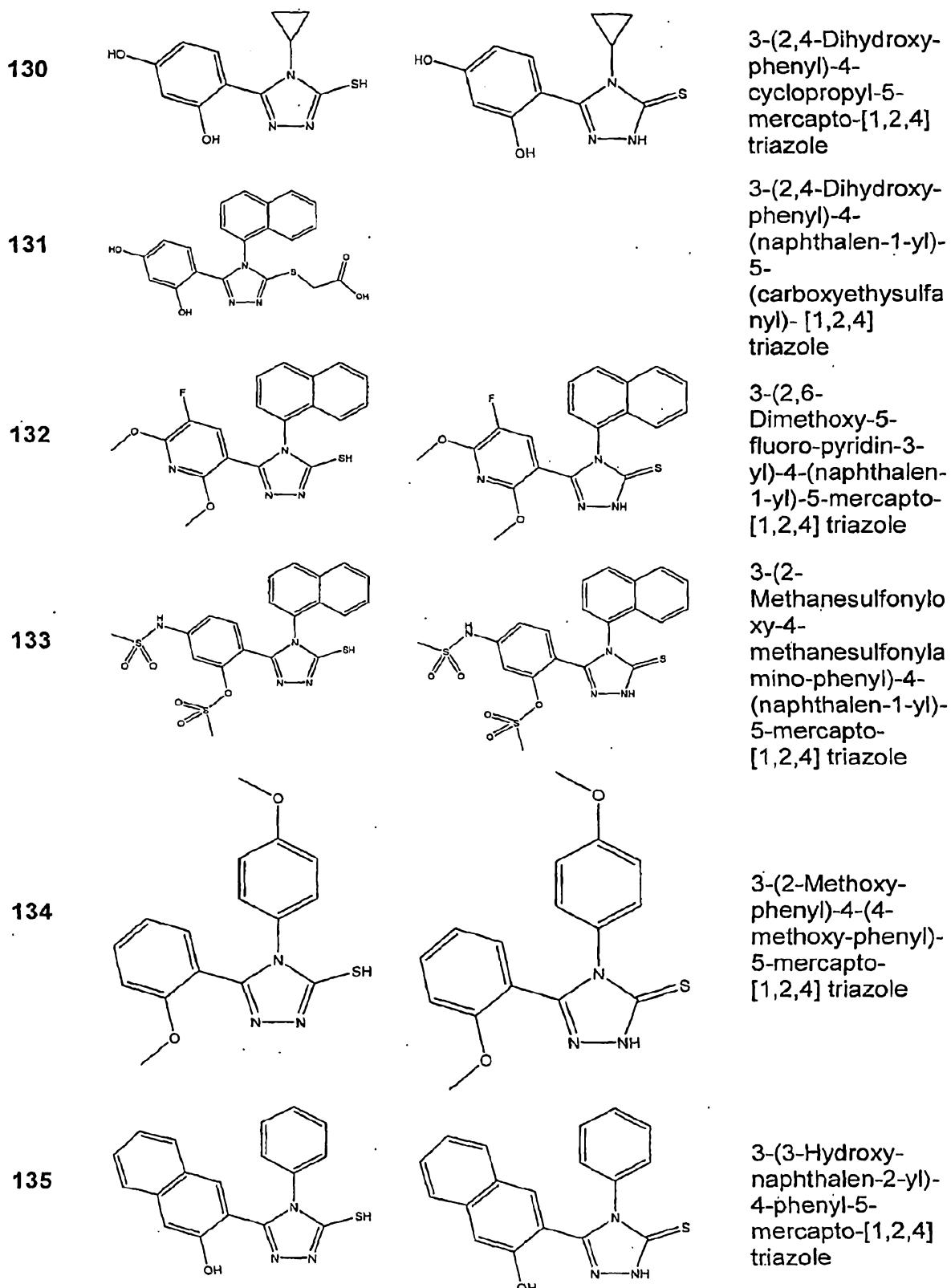


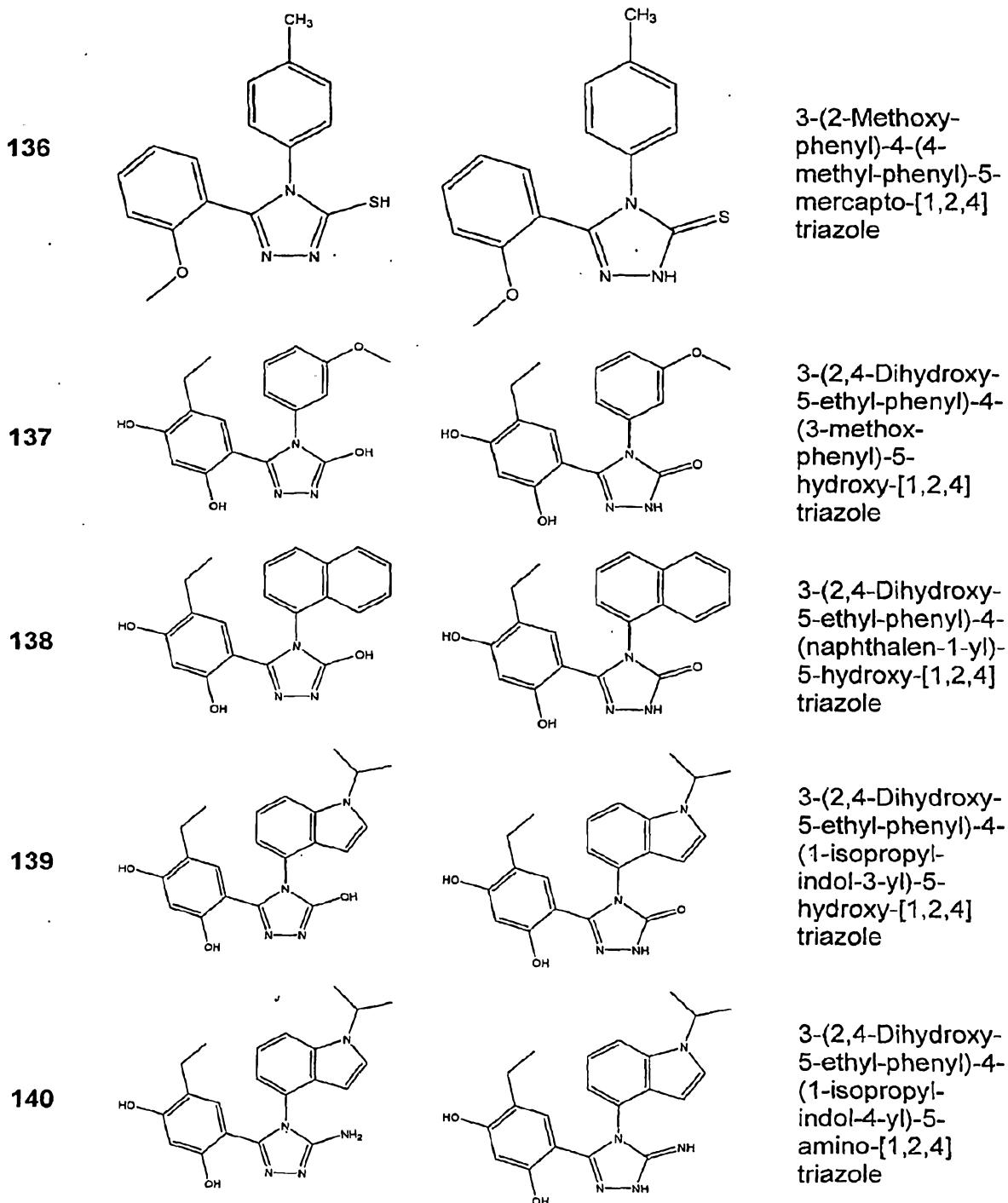


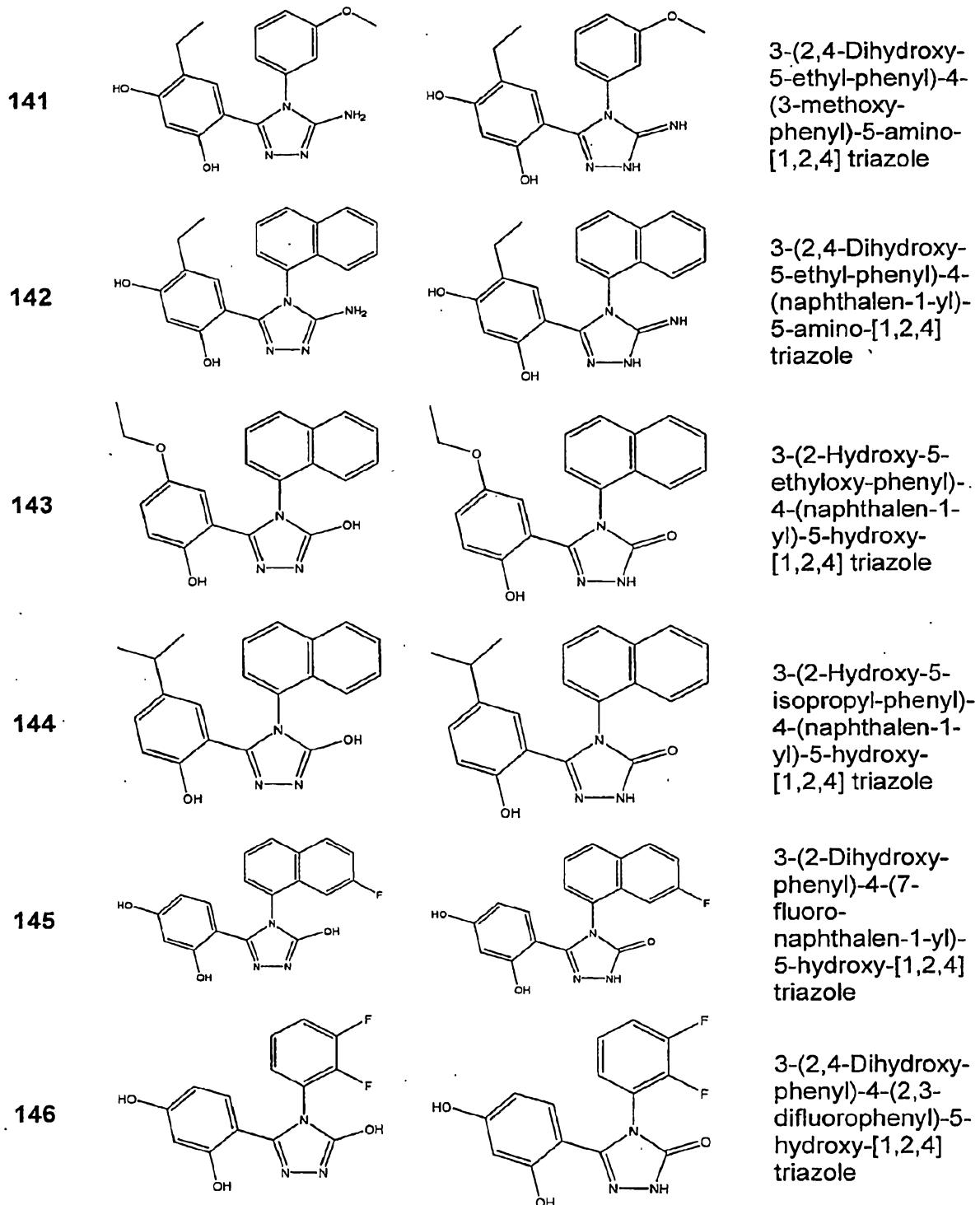


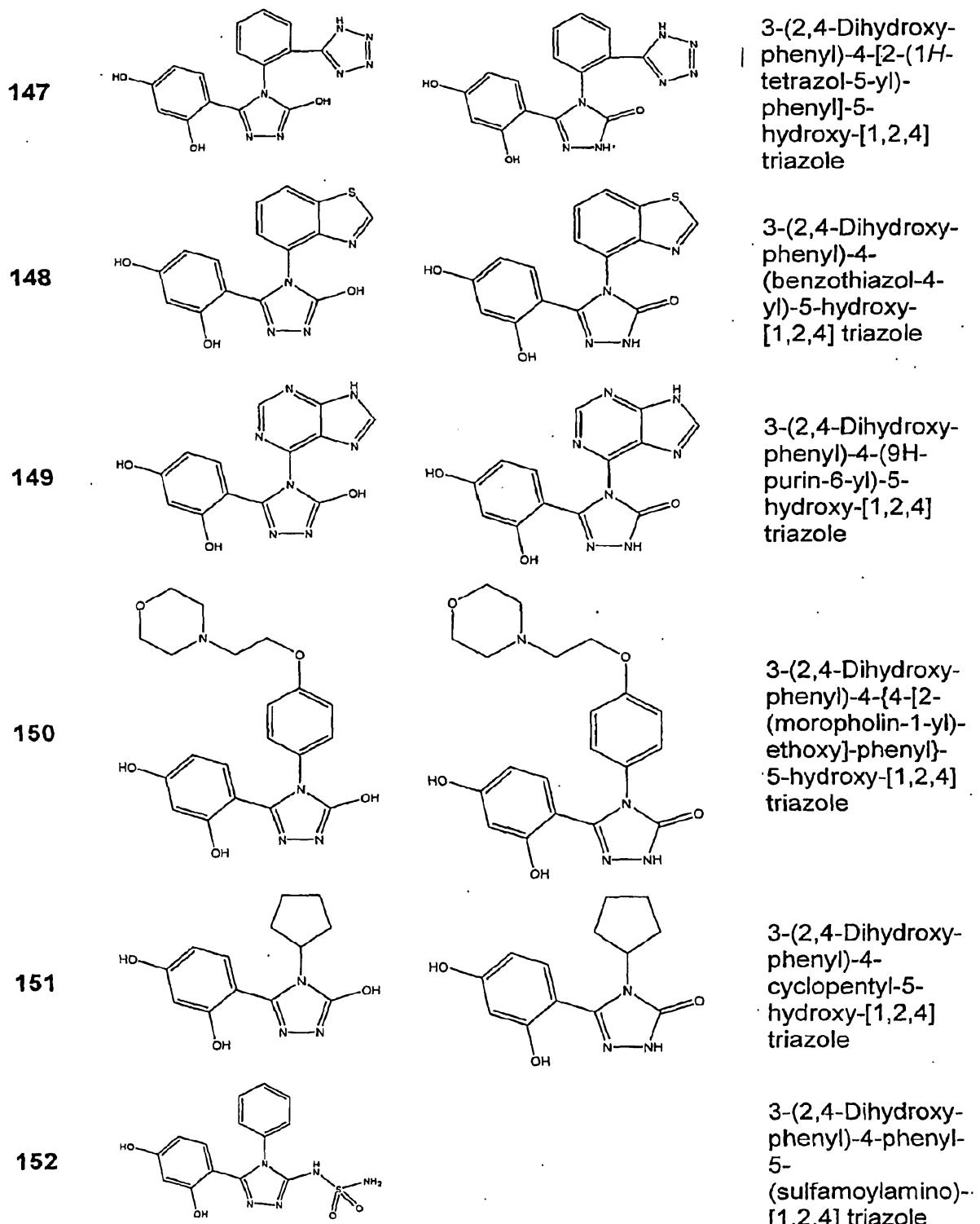
117		3-[2,4-Di-(dimethylcarbamoyloxy)-phenyl]-4-(naphthalen-1-yl)-5-(dimethylcarbamoylsulfanyl)-[1,2,4]triazole
118		3-(2,4-Dihydroxy-phenyl)-4-(naphthalen-1-yl)-5-(dimethylcarbamoylsulfanyl)-[1,2,4]triazole
119		3-(2,4-Diethoxycarbonyloxy-phenyl)-4-(naphthalen-1-yl)-5-(ethoxycarbonylsulfanyl)-[1,2,4]triazole
120		3-(2,4-Diisobutyryloxy-phenyl)-4-(naphthalen-1-yl)-5-(isobutyrylsulfanyl)-[1,2,4]triazole
121		3-[2,4-Di-(dimethylcarbamoyloxy)-phenyl]-4-(quinolin-5-yl)-5-(dimethylcarbamoylsulfanyl)-[1,2,4]triazole
122		3-(2,4-Diacetoxy-phenyl)-4-(naphthalen-1-yl)-5-(acetylulfanyl)-[1,2,4]triazole





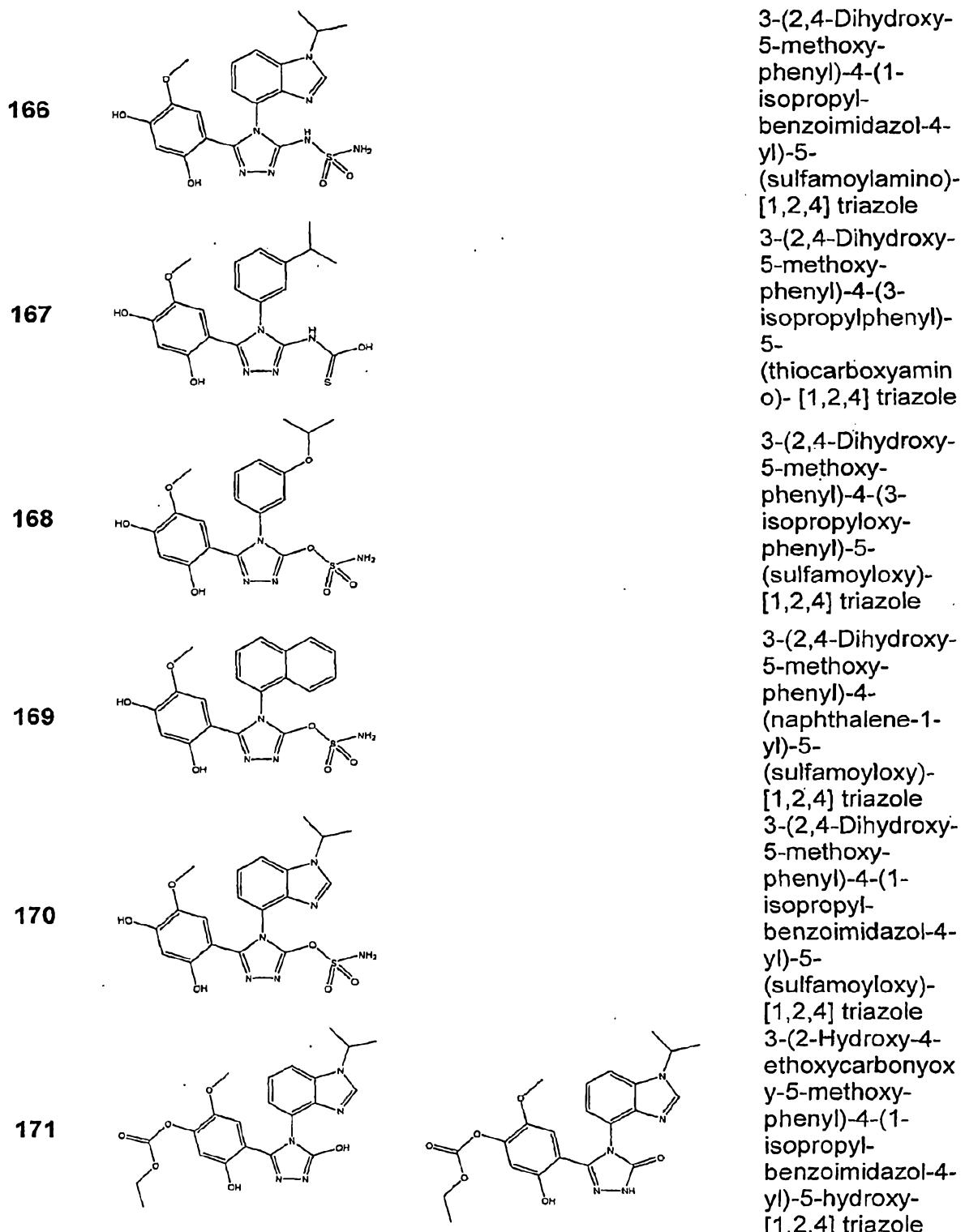


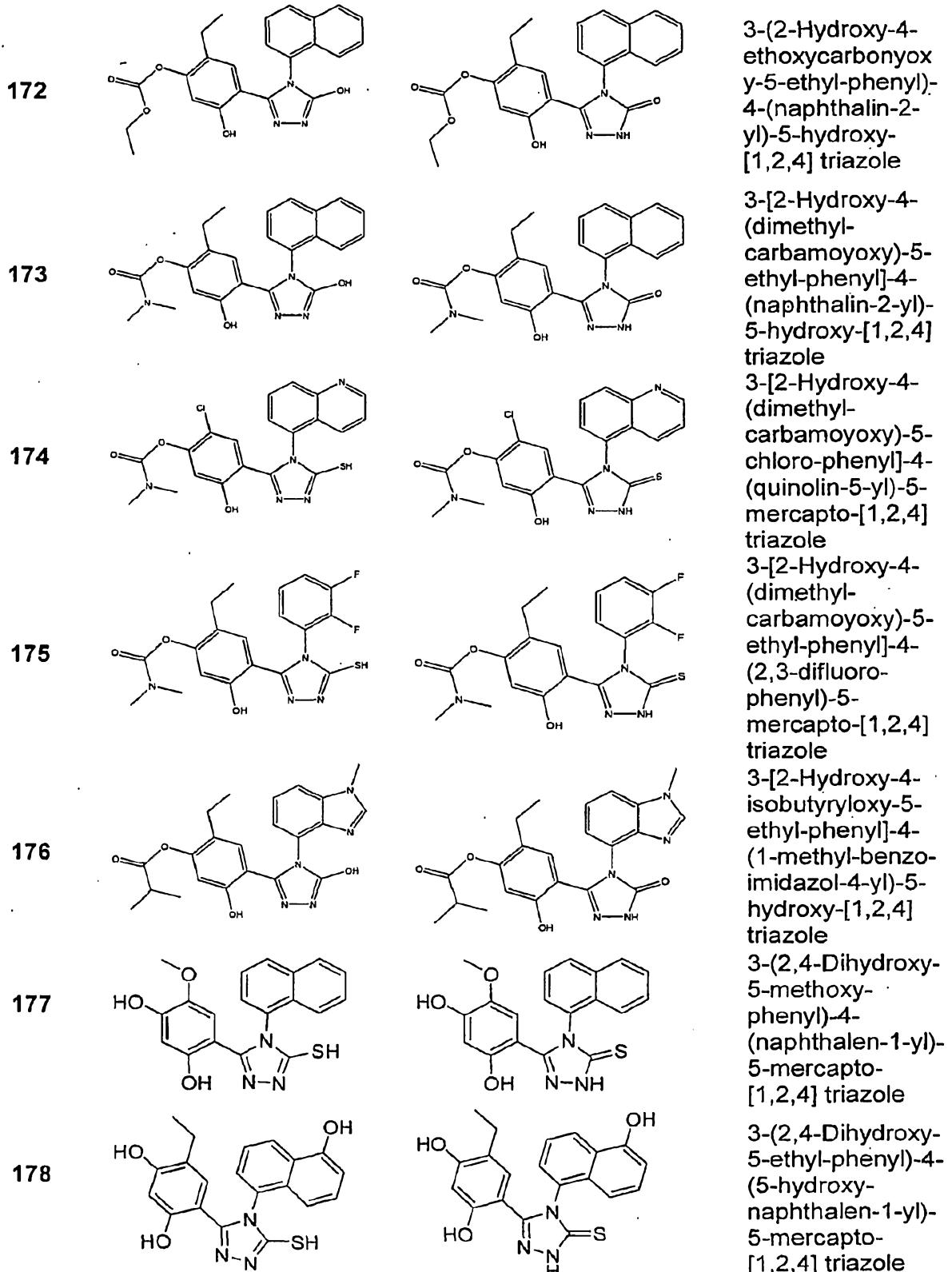


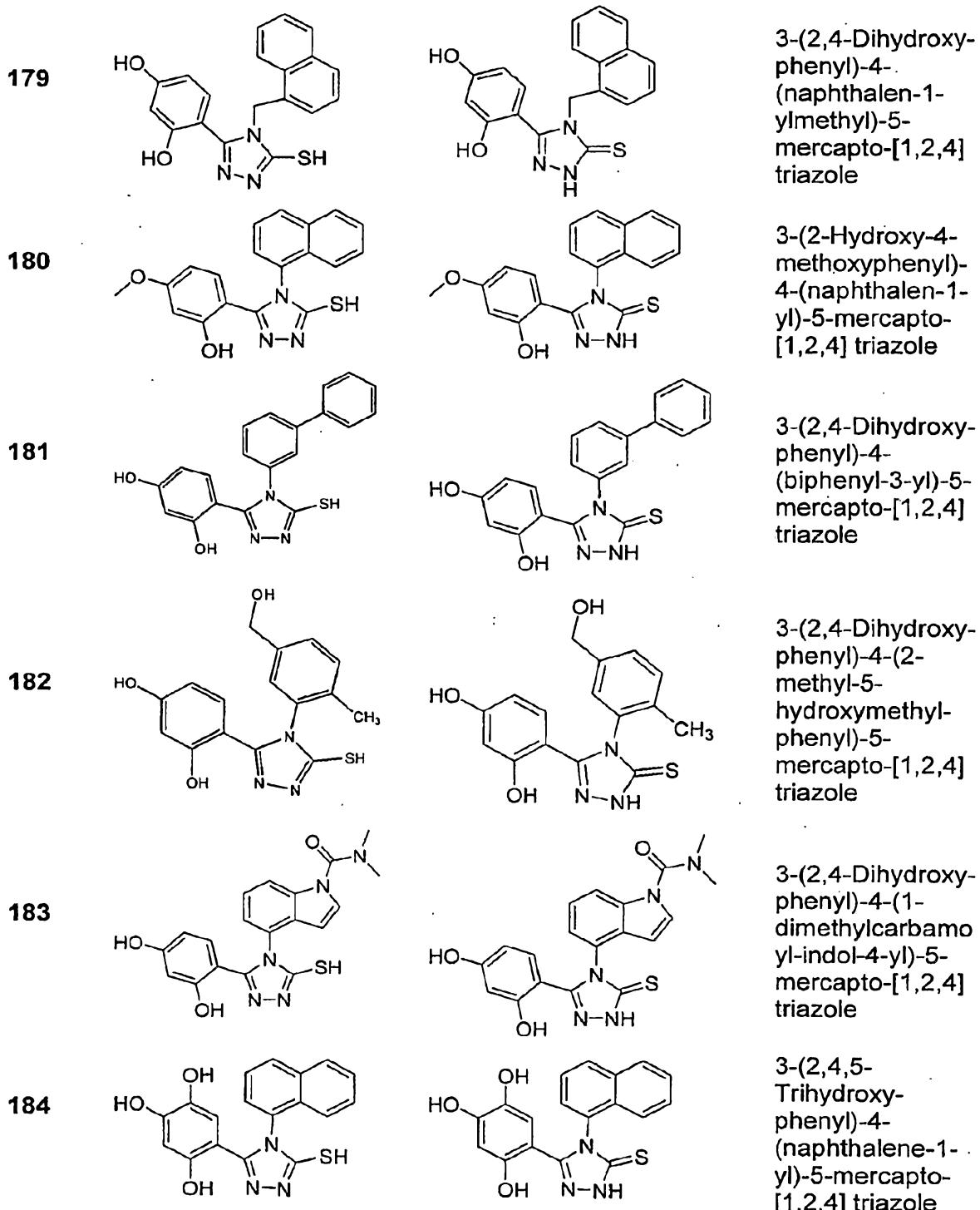


153		3-(2,4-Dihydroxy-5-methoxy-phenyl)-4-(naphthalene-1-yl)-5-ureido-[1,2,4] triazole
154		3-(2,4-Dihydroxy-5-methoxy-phenyl)-4-(2,3-difluorophenyl)-5-ureido-[1,2,4] triazole
155		3-(2,4-Dihydroxy-5-ethyl-phenyl)-4-(1-isopropyl-indol-4-yl)-5-ureido-[1,2,4] triazole
156		3-(2,4-Dihydroxy-5-ethyl-phenyl)-4-(quinolin-5-yl)-5-ureido-[1,2,4] triazole
157		3-(2,4-Dihydroxy-5-methoxy-phenyl)-4-(naphthalene-1-yl)-5-carbamoyloxy-[1,2,4] triazole
158		3-(2,4-Dihydroxy-5-ethyl-phenyl)-4-(3-trifluoromethyl-phenyl)-5-carbamoyloxy-[1,2,4] triazole
159		3-(2,4-Dihydroxy-5-ethyl-phenyl)-4-(1-methyl-indol-4-yl)-5-carbamoyloxy-[1,2,4] triazole

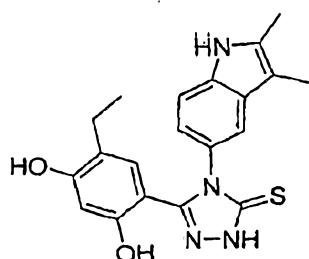
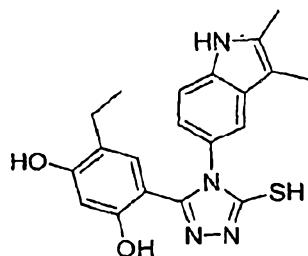
160		3-(2,4-Dihydroxy-5-methoxy-phenyl)-4-(8-methoxy-quinolin-5-yl)-5-carbamoyloxy-[1,2,4] triazole
161		3-(2,4-Dihydroxy-5-isopropyl-phenyl)-4-(3-methyl-quinolin-5-yl)-5-carboxyamino-[1,2,4] triazole
162		3-(2,4-Dihydroxy-phenyl)-4-(1-methyl-2-chloro-indol-4-yl)-5-carbamoyloxy-[1,2,4] triazole
163		3-(2,4-Dihydroxy-5-methoxy-phenyl)-4-[3,5-di(trifluoromethyl)-phenyl]-5-carbamoyloxy-[1,2,4] triazole
164		3-(2,4-Dihydroxy-5-methoxy-phenyl)-4-(3-trifluoromethyl-phenyl)-5-(sulfamoylamino)-[1,2,4] triazole
165		3-(2,4-Dihydroxy-5-methoxy-phenyl)-4-(naphthalene-1-yl)-5-(sulfamoylamino)-[1,2,4] triazole





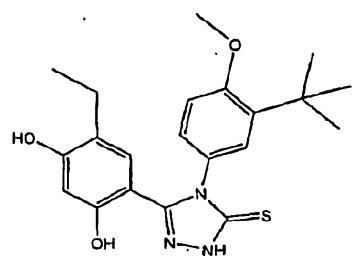
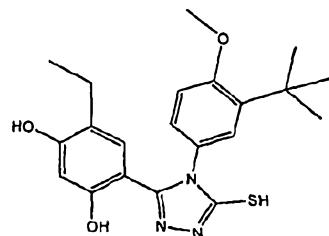


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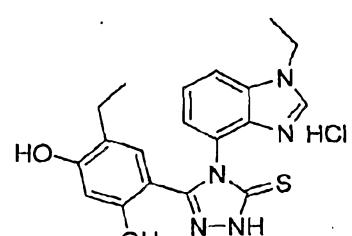
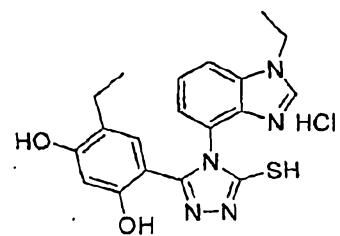
3-(2,4-Dihydroxy-5-ethyl-phenyl)-4-(2,3-dimethyl-indol-5-yl)-5-mercaptop-[1,2,4]triazole

186



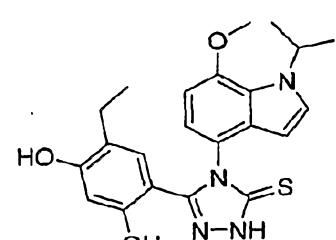
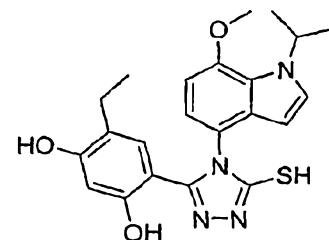
3-(2,4-Dihydroxy-5-ethyl-phenyl)-4-(3-t-butyl-4-methoxy-phenyl)-5-mercaptop-[1,2,4]triazole

187



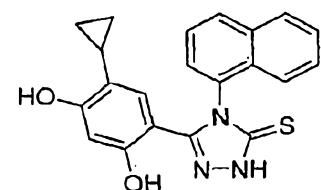
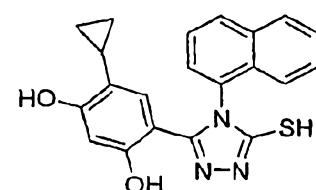
3-(2,4-Dihydroxy-5-ethyl-phenyl)-4-(1-ethyl-1H-benzoimidazol-4-yl)-5-mercaptop-[1,2,4]triazole, HCl salt

188



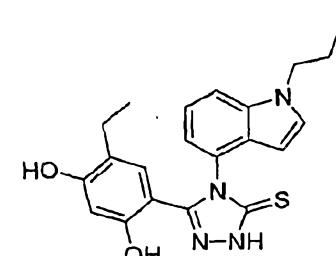
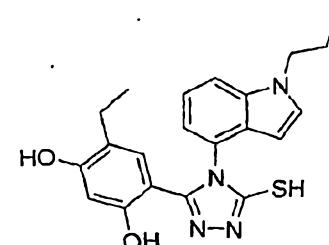
3-(2,4-Dihydroxy-5-ethyl-phenyl)-4-(1-isopropyl-7-methoxy-indol-4-yl)-5-mercaptop-[1,2,4]triazole

189

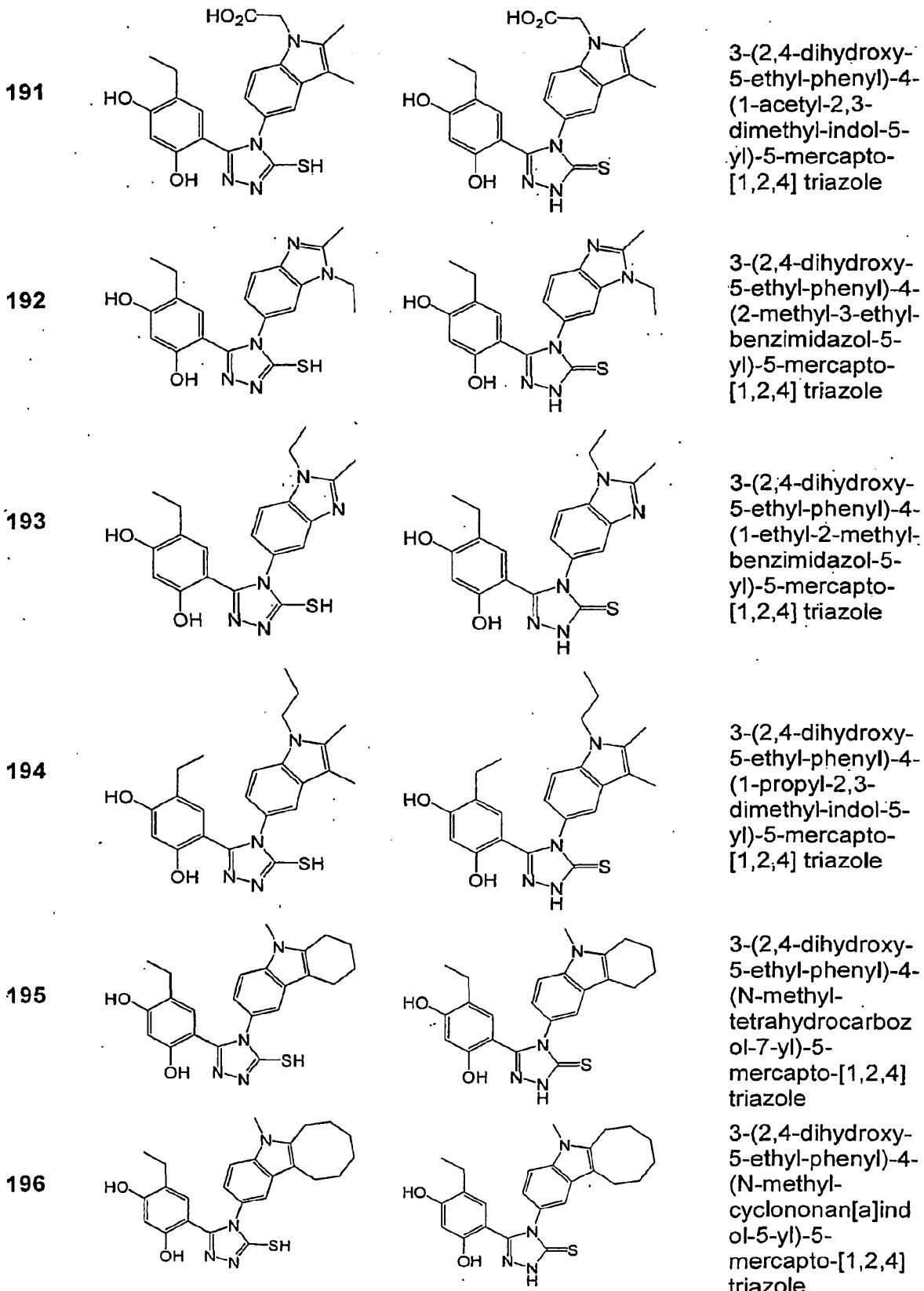


3-(2,4-Dihydroxy-5-cyclopropyl-phenyl)-4-(naphthalene-1-yl)-5-mercaptop-[1,2,4]triazole

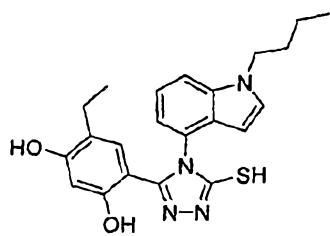
190



3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1-propyl-indol-4-yl)-5-mercaptop-[1,2,4]triazole

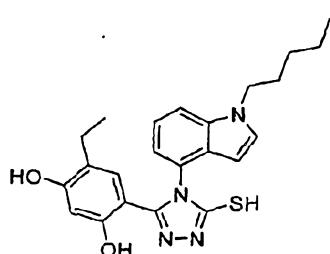


197



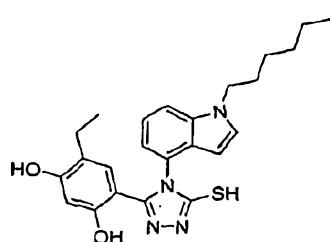
3-(2,4-dihydroxy-
5-ethyl-phenyl)-4-
(1-n-butyl-indol-4-
yl)-5-mercaptop-
[1,2,4] triazole

198



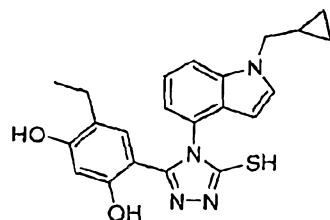
3-(2,4-dihydroxy-
5-ethyl-phenyl)-4-
(1-n-pentyl-indol-
4-yl)-5-mercaptop-
[1,2,4] triazole

199



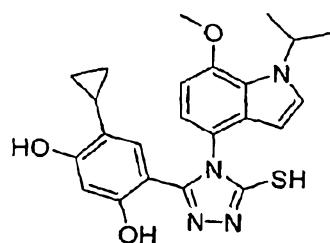
3-(2,4-dihydroxy-
5-ethyl-phenyl)-4-
(1-n-hexyl-indol-
4-yl)-5-mercaptop-
[1,2,4] triazole

200



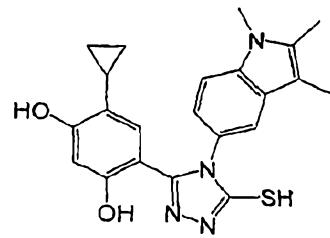
3-(2,4-dihydroxy-
5-cyclopropyl-
phenyl)-4-(1-(1-
methylcyclopropyl)-
indol-4-yl)-5-
mercaptop-[1,2,4]
triazole

201

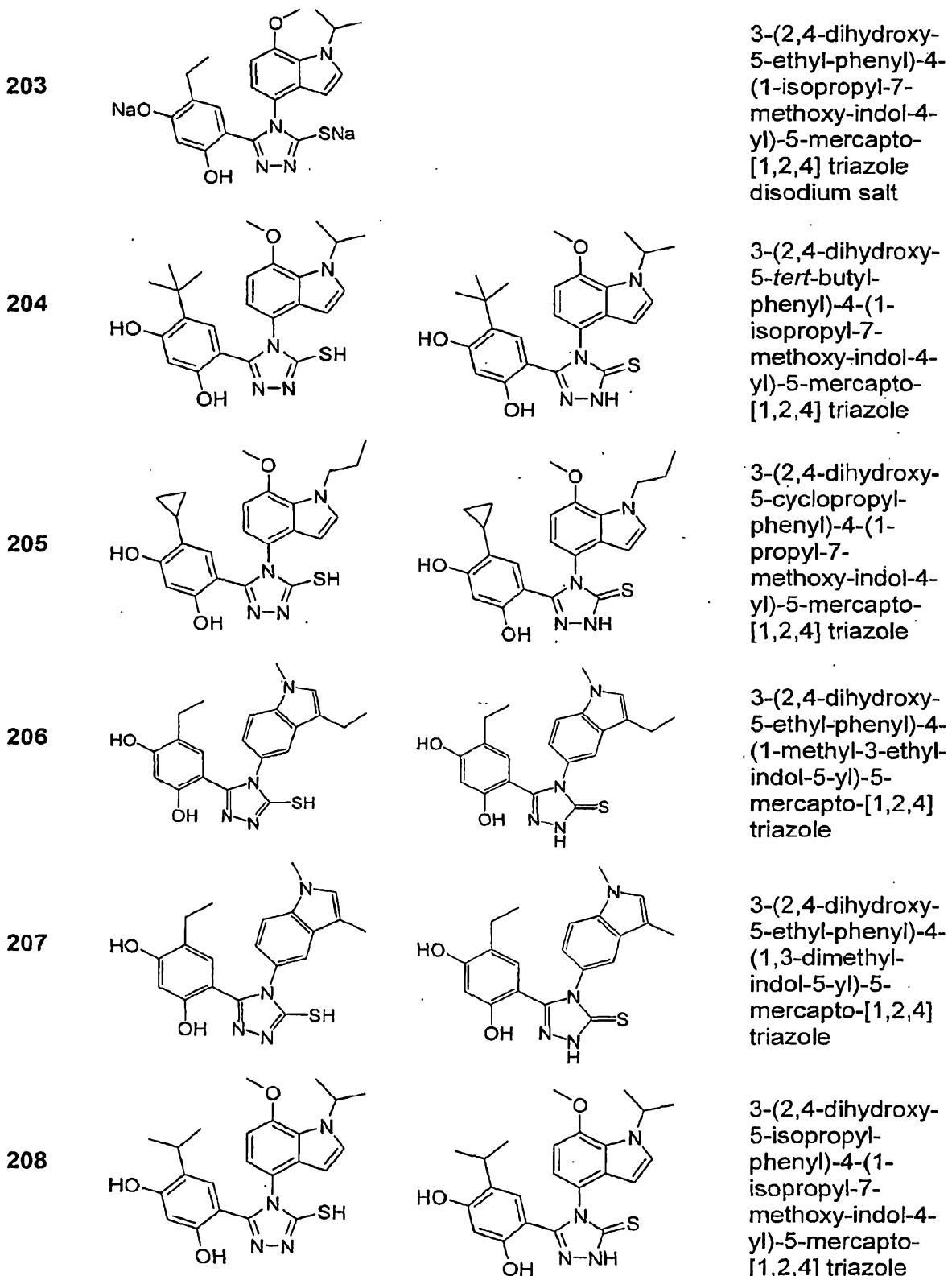


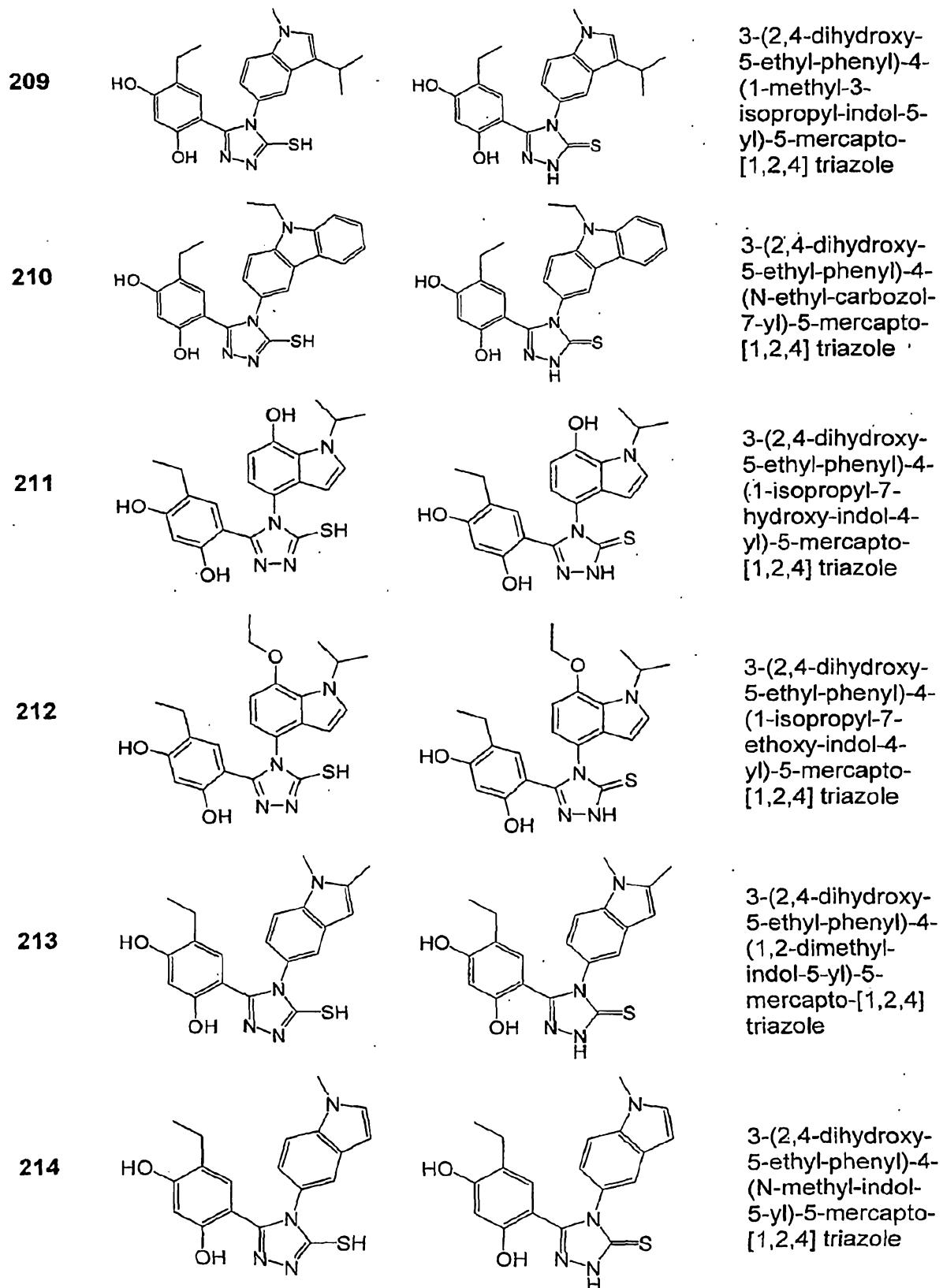
3-(2,4-dihydroxy-
5-cyclopropyl-
phenyl)-4-(1-
isopropyl-7-
methoxy-indol-4-
yl)-5-mercaptop-
[1,2,4] triazole

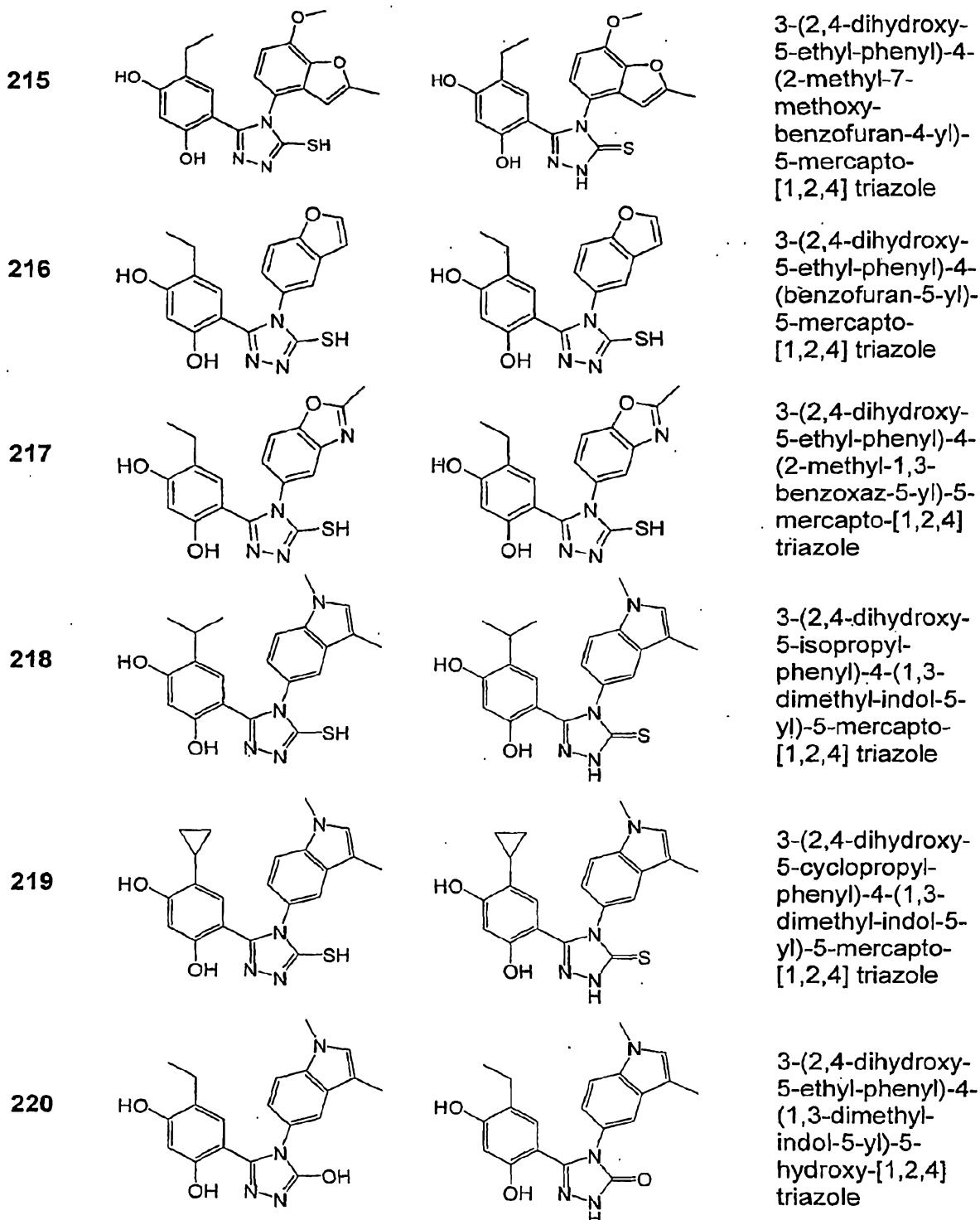
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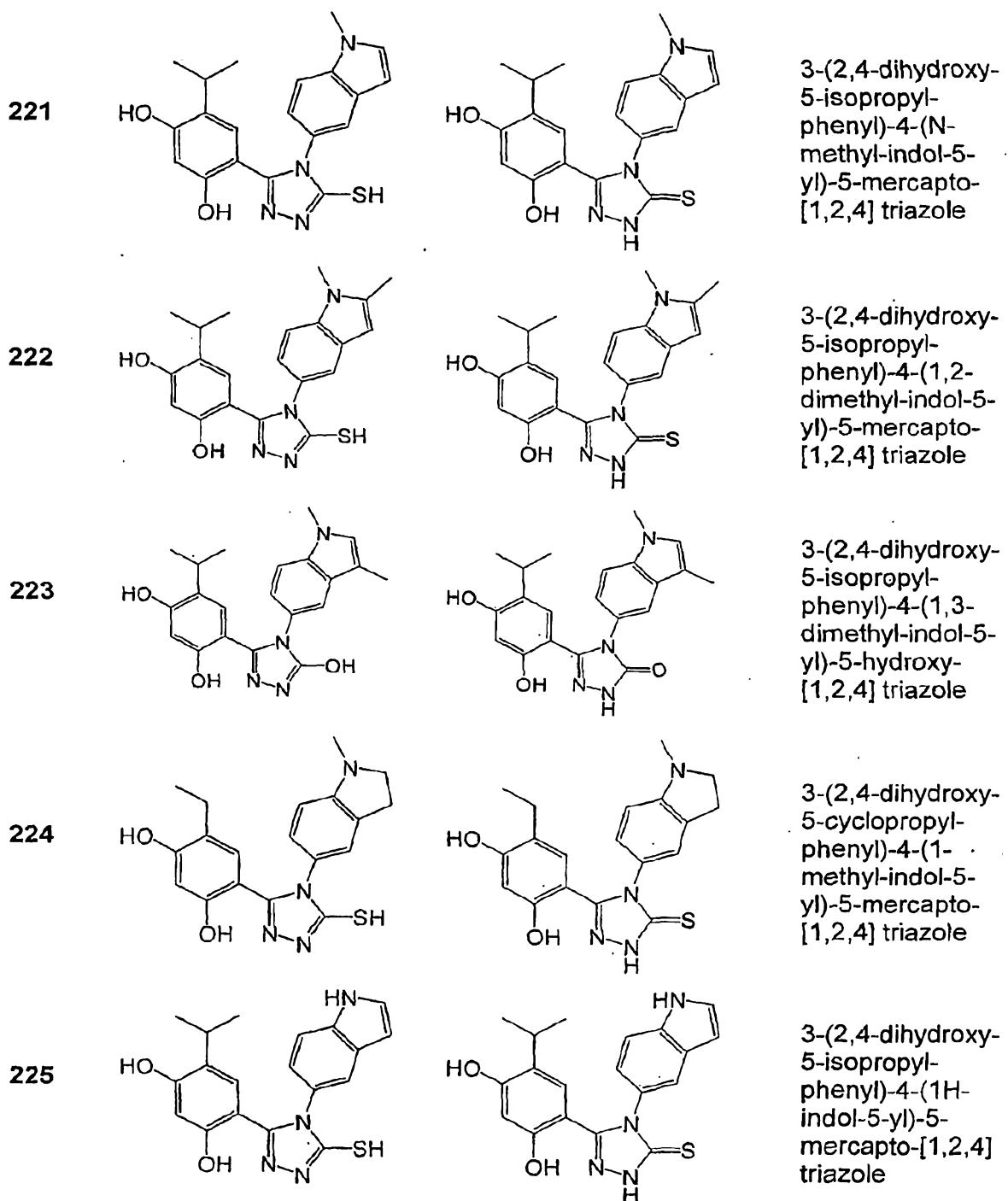


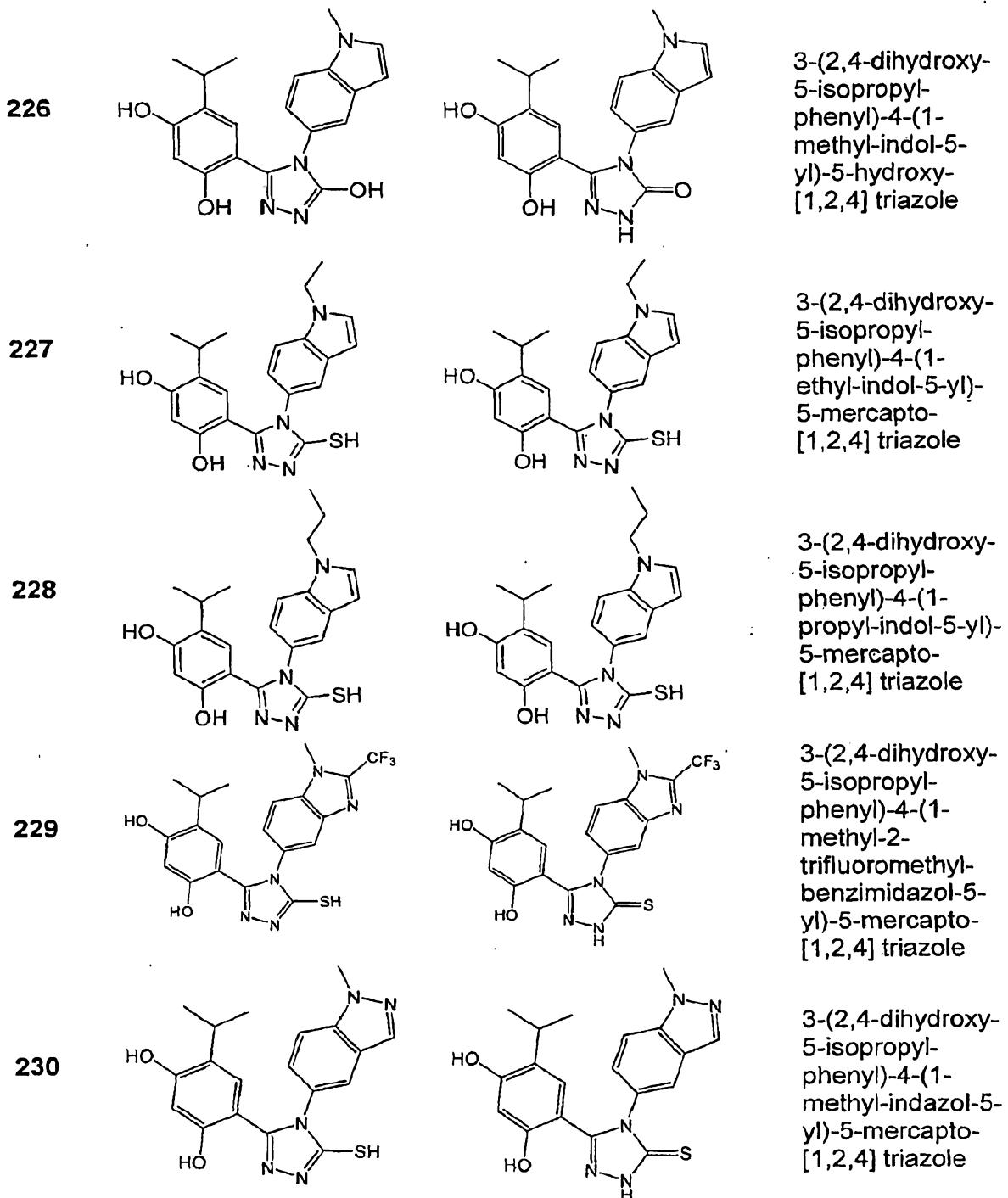
3-(2,4-dihydroxy-
5-cyclopropyl-
phenyl)-4-(1,2,3-
trimethyl-indol-5-
yl)-5-mercaptop-
[1,2,4] triazole

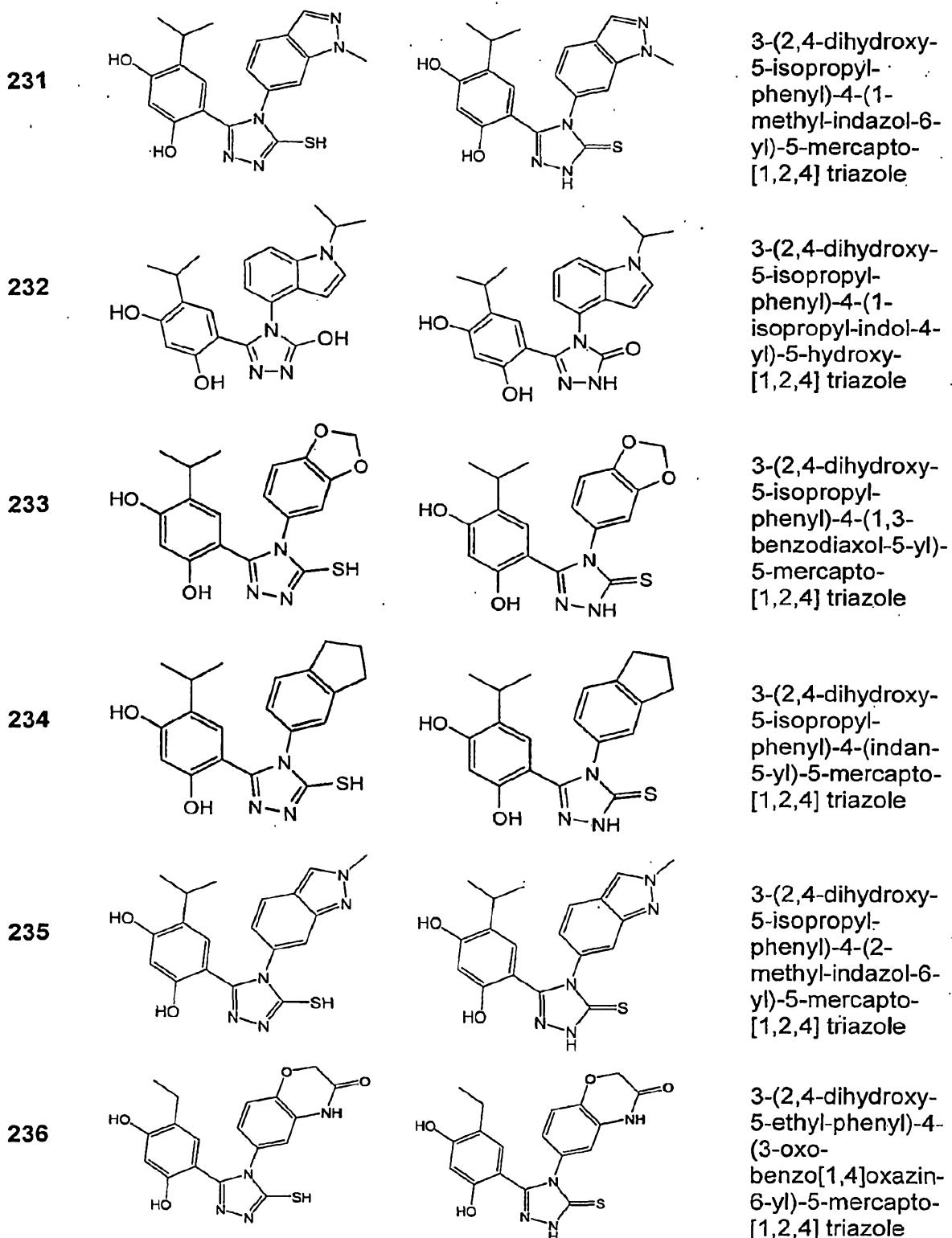


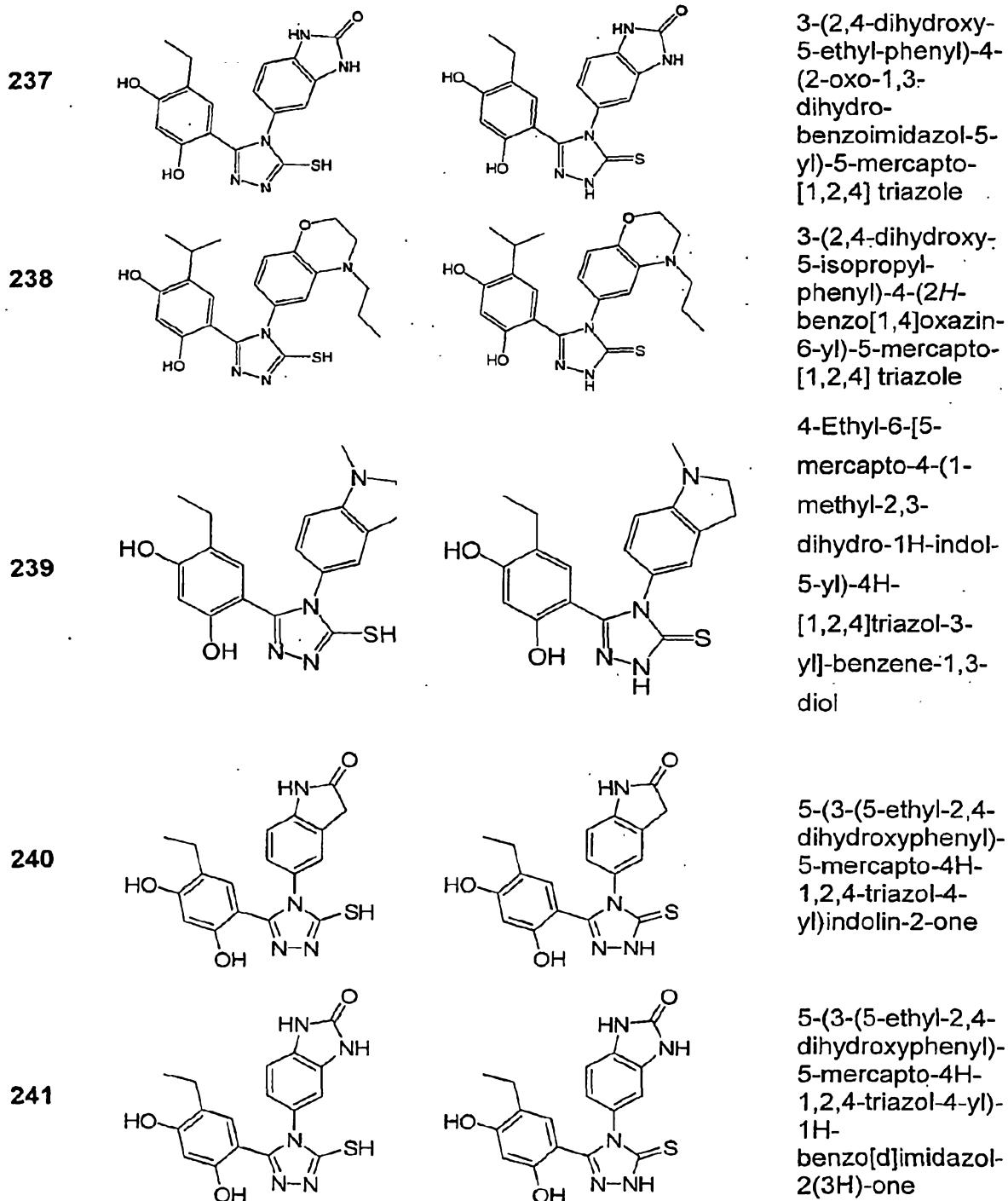


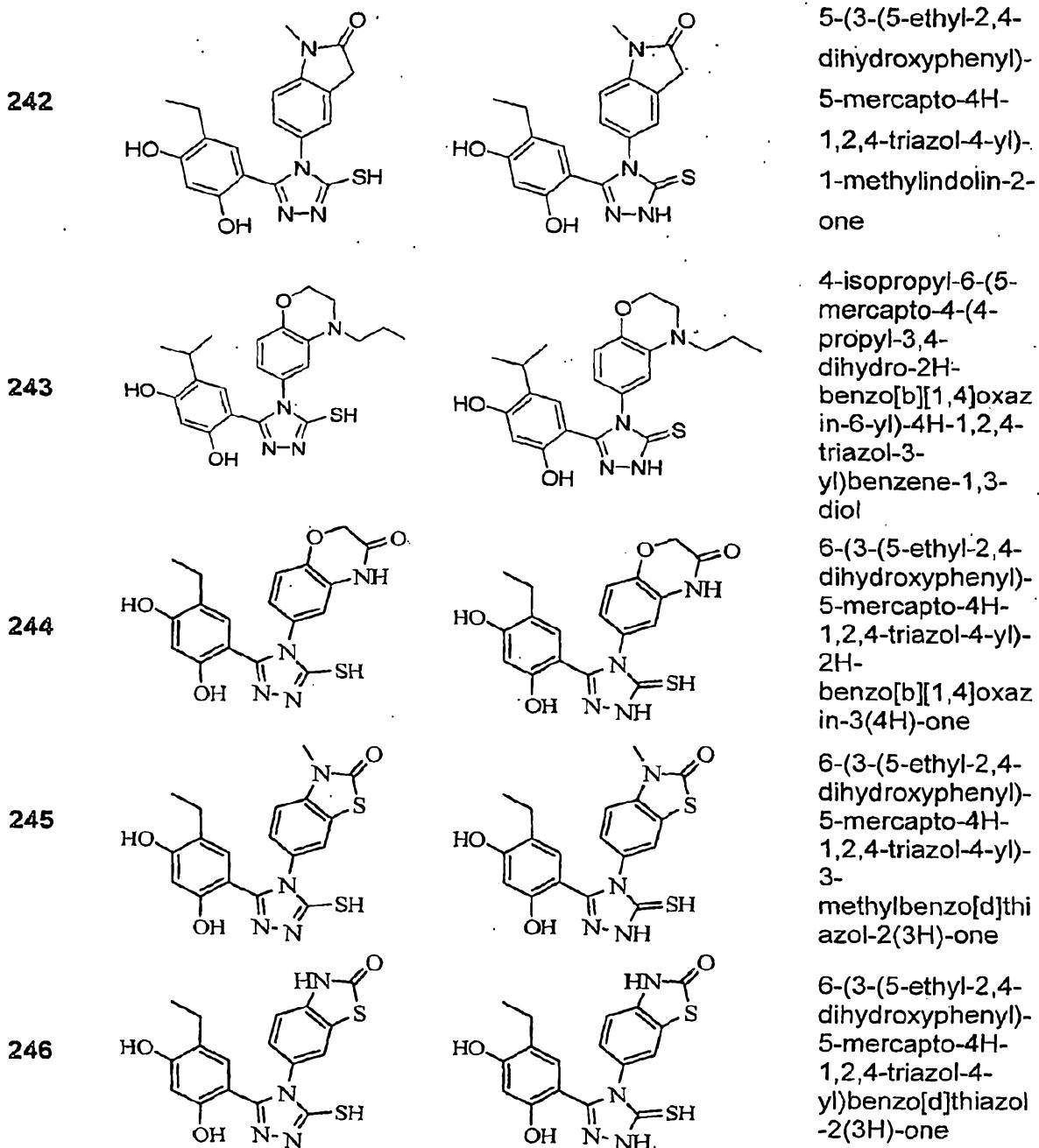




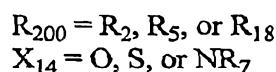
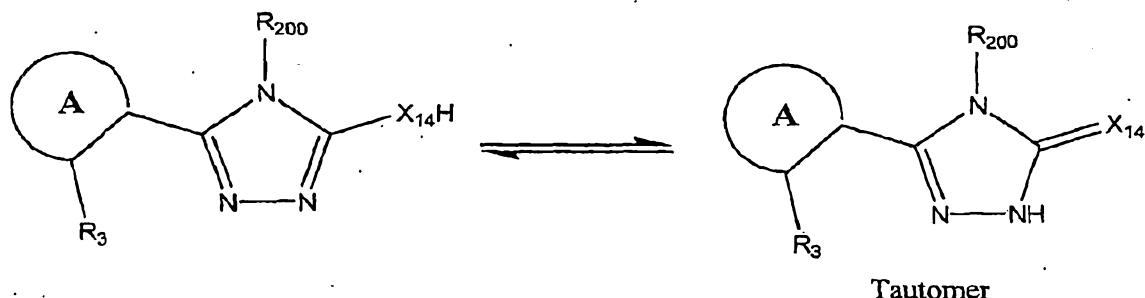




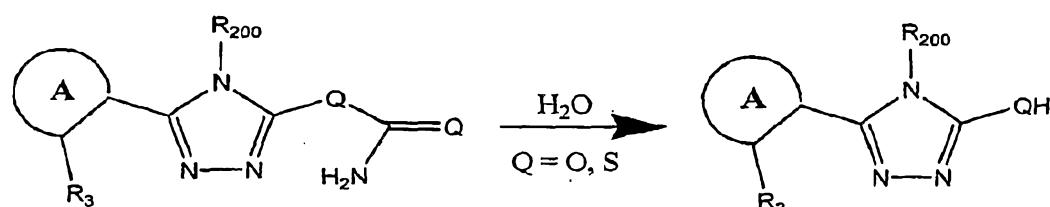
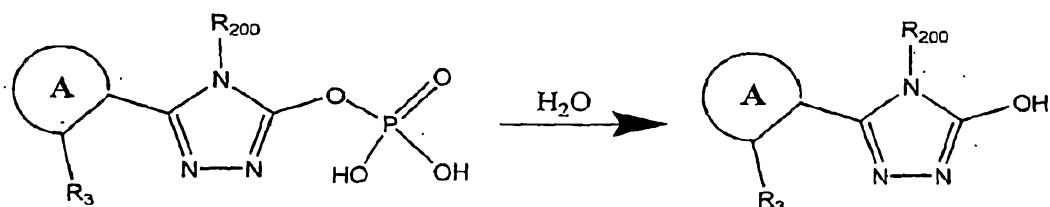




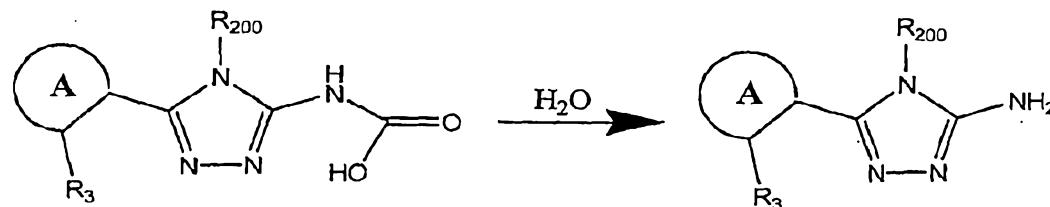
Preferred compounds of the invention are those compounds that can form a tautomeric structure as shown below and as exemplified by the tautomeric structures shown in Table 1:

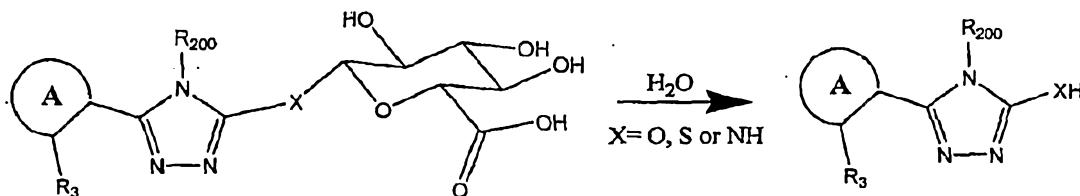


Similarly, prodrugs, *i.e.* compounds which can be metabolized or hydrolyzed *in vivo* to a compound of the present invention are encompassed by the present description. For example, the following embodiments of a compound of the present invention can be produced *in vivo* in the following reaction:



10





where R_{200} is R_2 , R_5 or R_{18} .

One skilled in the art will understand that other hydrolyzable protecting groups can be employed with the compounds of the present invention to obtain prodrugs encompassed by the present description.

Without wishing to be bound by any theory, it is believed that the compounds of the invention preferentially bind to Hsp90 in the tautomeric form shown above, and thereby inhibit the activity of Hsp90.

10

C. Methods for Making Compounds of the Invention

Compounds of the invention can be obtained via standard, well-known synthetic methodology, see e.g., March, J. Advanced Organic Chemistry; Reactions Mechanisms, and Structure, 4th ed., 1992.

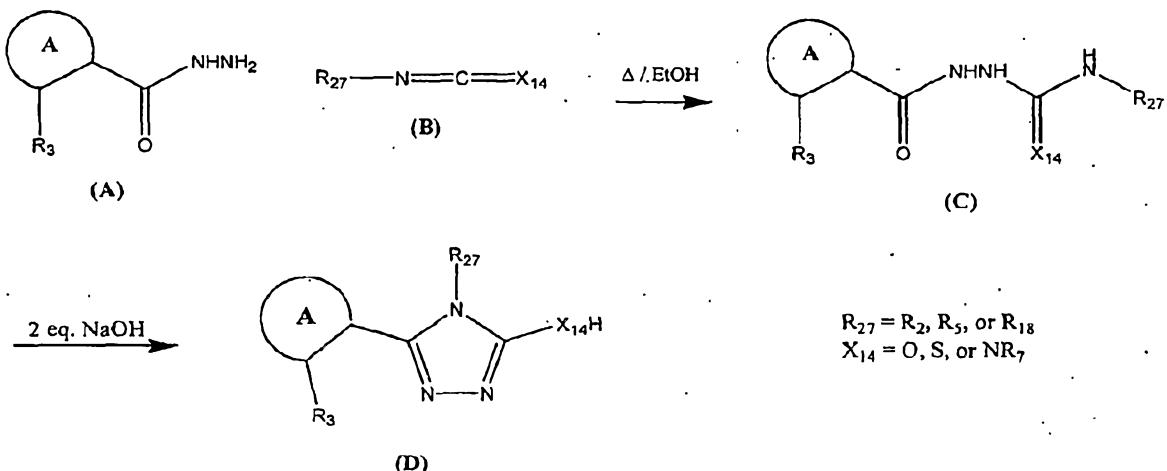
15 Compounds of the invention can also be made as in the following provisional applications: 60/808,376, filed May 25, 2006; 60/808,342, filed May 25, 2006; and 60/808,375, filed May 25, 2006, which are incorporated by reference herein in their entirety.

20 In particular, compounds of the invention can be obtained by heating a hydrazide (A) with an isocyanate ($X_{14} = O$), isothiocyanate, ($X_{14} = S$) or carbodiimide ($X_{14} = NR_7$) (B) in an alcohol to form intermediate (C). Intermediate (C) can be cyclized to form a triazole core (D) by heating it in an aqueous solution which includes about 2 molar equivalents of NaOH (see Scheme I below). Starting materials useful for preparing compounds of the invention and intermediates 25 therefore, are commercially available or can be prepared from commercially available materials using known synthetic methods and reagents. For example, a hydrazide can be prepared by reacting an ester (such as 2,4-dihydroxybenzoic acid methyl ester) or acid chloride with hydrazine. Isocyanates and isothiocyanates (X_{14} is O or S, respectively) can be formed in a number of ways from compounds that 30 have a primary amine group. For example, a primary amine can be reacted with

phosgene or thiophosgene to form an isocyanate or an isothiocyanate, respectively. Alternatively, a cyanate or thiocyanate ion can be reacted with an alkyl halide to form an alkyl isocyanate or an alkyl isothiocyanate. In addition, a isothiocyanate can be prepared by reacting a diazonium salt with a thiocyanate ion. Carbodiimides (X₁₄ is NR₇) can be prepared by dehydration of ureas using a dehydration agent such as tosyl chloride in pyridine, POCl₃, PCl₅, P₂O₅-pyridine, and Ph₃PBr₂-Et₃N. Other methods of preparing isocyanates, thioisocyanates, and carbodiimides can be found in March, J. Advanced Organic Chemistry; Reactions Mechanisms, and Structure, 4th ed., 1992, the entire teachings of which are incorporated by reference.

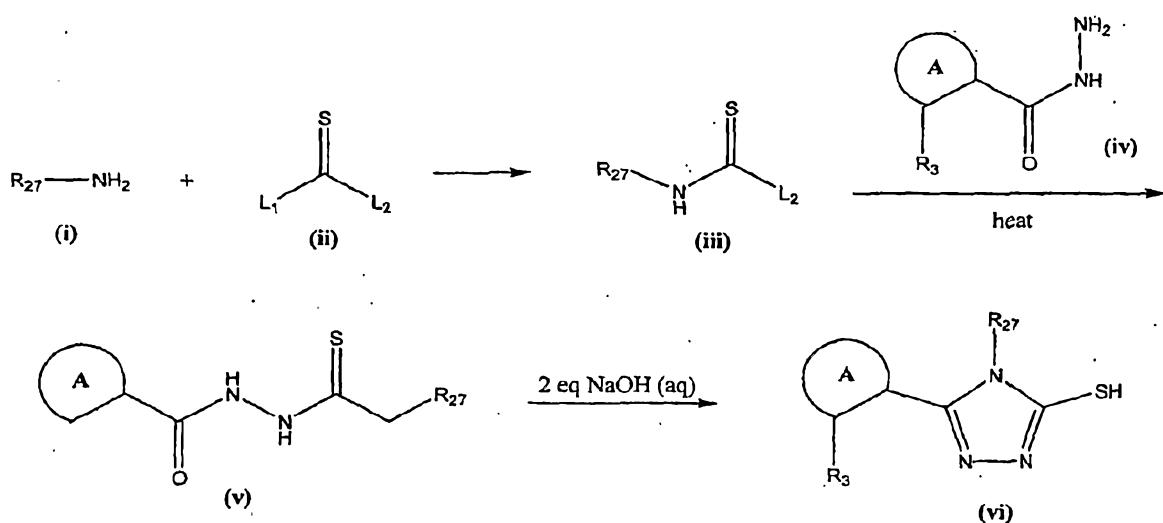
10 Compounds represented by formulas (IV) and (V) can be made in an analogous fashion as compounds depicted in Scheme I. Reactive functional groups can be protected during one or more reaction step, then deprotected to restore the original functionality. Examples of suitable protecting groups for hydroxyl groups include benzyl, methoxymethyl, allyl, trimethylsilyl, tert-butyldimethylsilyl, acetate, and the like. Examples of suitable amine protecting groups include benzyloxycarbonyl, tert-butoxycarbonyl, tert-butyl, benzyl and fluorenylmethoxy-carbonyl (Fmoc). Examples of suitable thiol protecting groups include benzyl, tert-butyl, acetyl, methoxymethyl and the like. Other suitable protecting groups are well known to those of ordinary skill in the art and include those found in T. W. Greene, Protecting Groups in Organic Synthesis, John Wiley & Sons, Inc. 1981.

Scheme I: Synthesis of triazole compounds of the invention



An alternative method of preparing the compounds of the invention is shown in Scheme II. In this method, an aryl, heteroaryl, cycloalkyl, or alkyl amine compound (i) is stirred at about room temperature with a thiocarbonyl (ii) which has two leaving groups, L_1 and L_2 , such as imidazole-1-yl groups, to form compound (iii). Typically, the thiocarbonyl compound is present in a slight molar excess of about 1.05 eq. to about 1.3 eq. compared with compound (i). Compound (iii) is then combined with a hydrazide compound (iv) in a solvent and heated to about 50°C to about 100°C for about 0.5 to 5 hrs to form compound (v). Typically, compound (iii) and compound (iv) can be present in about equal molar ratio or a slight excess of compound (iii), such as about 1.01 to about 1.1 molar eq. of compound (iii) compare to compound (iv). Compound (v) can then be cyclized to form a triazole compound of the invention (vi) by suspending it in aqueous solution containing about 2 molar eq. of NaOH and heating the solution to about 75°C to about 110°C for about 0.5 hr to about 2 hrs. Typically, the NaOH solution containing compound (v) is degassed before heating by bubbling an inert gas, such as nitrogen or argon, through it.

Scheme II: Alternative synthesis of triazole compounds of the invention

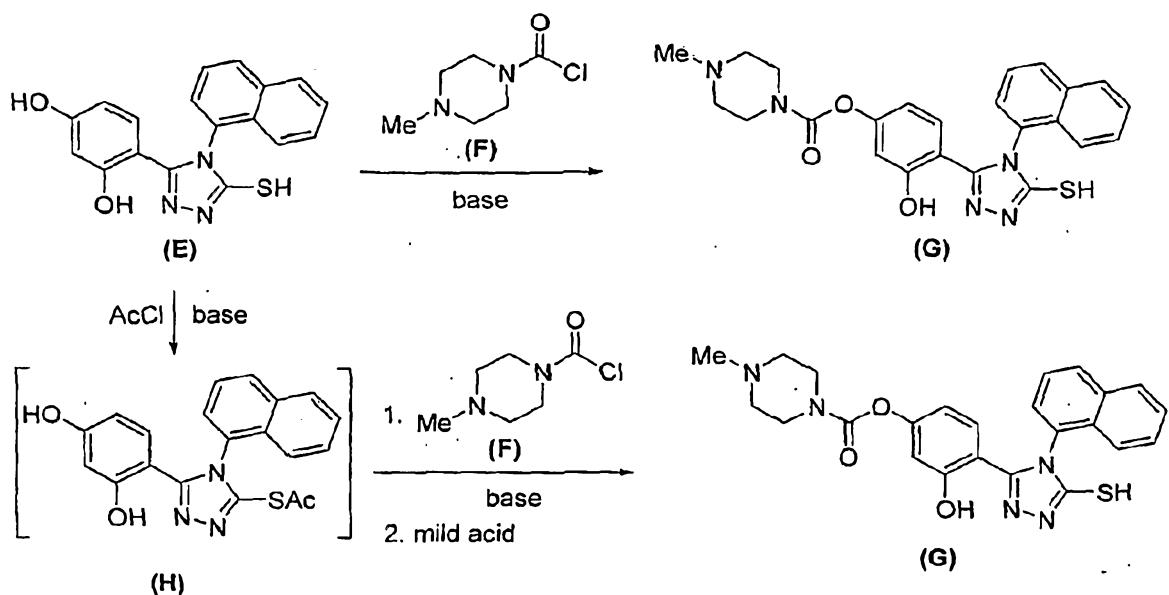


In one embodiment, ring A of the compounds of the invention is a 2,4-

5 dihydroxyphenyl group. In this embodiment, it is sometimes desirable to prepare a prodrug by protecting the 4-hydroxy group with a moiety that can be hydrolyzed in vivo. Protection of the 4-hydroxy group is expected to improve the circulating half-life of compound compounds of the invention. In addition, it is desirable that a group added to the 4-hydroxy group increase the water solubility of the compounds
10 of the invention. In one embodiment, 4-methyl-piperazine-1-carbamoyl group is used to protect the 4-hydroxy group (see Scheme III). In this embodiment, a compound of the invention, such as compound (E), is treated with about one molar equivalents of 4-methyl-piperazine-1-carbonyl chloride (F) in the presence of a base to form compound (G) in which the 4-hydroxy group is protected. Alternatively, the
15 metcapto group can be protected first by reacting compound (E) with about one molar equivalent of acyl chloride in the presence of a base to form intermediate (H). Intermediate (H) can then be reacted with about one molar equivalent of 4-methyl-piperazine-1-carbonyl chloride (F) in the presence of a base, then the acetyl group can be removed by treatment with a mild acid to form compound (G).

20

Scheme III: Preparation of prodrugs in which the 4-hydroxy group of compounds of the invention is protected with 4-methyl-piperazine-1-carbamoyl.

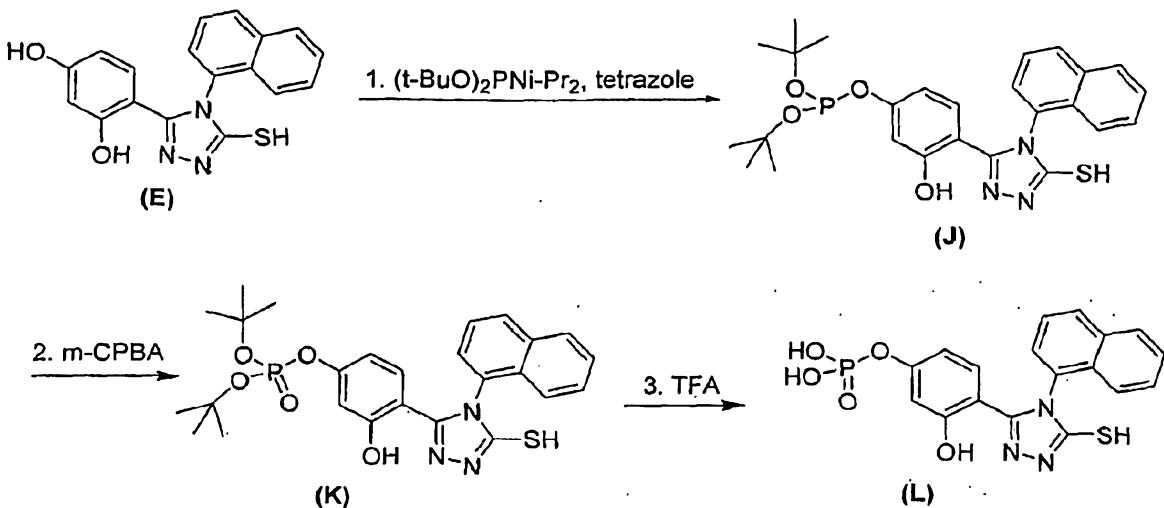


Another prodrug of compounds of the the invention can be formed by :

5 addition of a phosphate group to the 4-hydroxy group (Scheme IV). In this embodiment, a compound of the invention, such as compound (E), is treated with about one molar equivalent of diisopropyl phosphoramidous acid di-t-butyl ester in the presence of tetrazole to yield compound (J). The phosphorous group is then oxidized with m-CPBA to form a phosphoric acid di-t-butyl ester group of

10 compound K. The t-butyl groups are then hydrolyzed with trifluoroacetic acid (TFA) to yield a phosphoric acid group or compound L.

Scheme IV: Preparation of prodrugs in which the 4-hydroxy group of compounds of the invention is protected with a phosphate group.



D. Uses of Compounds of the Invention

5 The present invention provides methods for treating, reducing or inhibiting angiogenesis in a subject in need thereof, comprising administering to the subject an effective amount of a compound represented by formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), or any embodiment thereof, or a compound shown in Table 1.

10 In one aspect, compounds of the invention are used in combination with one or more other therapeutic agents. In one aspect, compounds of the invention are used in combination with one or more other anti-angiogenic agents.

15 In another aspect, the invention provides methods of reducing, blocking, occluding, or otherwise disrupting blood flow in neovasculature, comprising contacting the neovasculature with an effective amount of a compound represented by formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), or any embodiment thereof, or a compound shown in Table 1. In one aspect, the neovasculature is in a subject and blood flow in the neovasculature is reduced, blocked, occluded, or otherwise disrupted in the subject by administering to the subject an effective 20 amount of a compound represented by formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), or any embodiment thereof, or a compound shown in Table 1. In one aspect, the subject is human.

2. Agents Useful In Combination With the Compounds of the Invention

Anti-angiogenesis agents that can be co-administered with the compounds of the invention include Dalteparin, Suramin, ABT-510, Combretastatin A4 Phosphate, Lenalidomide, LY317615 (Enzastaurin), Soy Isoflavone (Genistein; Soy Protein Isolate), Thalidomide, AMG-706, Anti-VEGF Antibody (Bevacizumab; AvastinTM), AZD2171, Bay 43-9006 (Sorafenib tosylate), PI-88, PTK787/ZK 222584 (Vatalanib), SU11248 (Sunitinib malate), VEGF-Trap, XL184, ZD6474, ATN-161, EMD 121974 (Cilenigotide), Celecoxib, Angiostatin, Endostatin, Regranex, Apligraf, Paclitaxel, tetracyclines, clarithromycin, lasix, captopril, aspirin, Vitamin D3 analogs, retinoids, Imiquomod, Interferon alfa2a, Minocycline, copper peptide containing dressings, LucentisTM, ATG002, Pegaptanib Sodium, Tryptophanyl-tRNA synthetase, squalamine lactate, anecortave acetate, AdPEDF, AG-013958, JSM6427, TG100801, Veglin, ascorbic acid ethers (and their analogs), and Pamidronate.

Anti-cancer agents that can be employed in combination with the compounds of the invention include TaxolTM, also referred to as "paclitaxel", is a well-known anti-cancer drug which acts by enhancing and stabilizing microtubule formation, and analogs of TaxolTM, such as TaxotereTM. Compounds that have the basic taxane skeleton as a common structure feature, have also been shown to have the ability to arrest cells in the G2-M phases due to stabilization or inhibition of microtubules. Other anti-cancer agents that can be employed in combination with compounds of the invention include Avastin, Adriamycin, Dactinomycin, Bleomycin, Vinblastine, Cisplatin, acivicin; aclarubicin; acodazole hydrochloride; acronine; adozelesin; aldesleukin; altretamine; ambomycin; ametantrone acetate; aminoglutethimide; amsacrine; anastrozole; anthramycin; asparaginase; asperlin; azacitidine; azetepa; azotomycin; batimastat; benzodepa; bicalutamide; bisantrene hydrochloride; bisnafide dimesylate; bizelesin; bleomycin sulfate; brequinar sodium; bropirimine; busulfan; cactinomycin; calusterone; caracemide; carbetimer; carboplatin; carmustine; carubicin hydrochloride; carzelesin; cedefingol; chlorambucil; cirolemycin; cladribine; crisnatol mesylate; cyclophosphamide; cytarabine; dacarbazine; daunorubicin hydrochloride; decitabine; dexormaplatin; dezaguanine; dezaguanine mesylate; diaziquone; doxorubicin; doxorubicin hydrochloride; droloxitene; droloxitene citrate; dromostanolone propionate; dūazomycin; edatrexate; eflornithine hydrochloride; elsamitracin; enloplatin; enpromate;

epipropidine; epirubicin hydrochloride; erbulozole; esorubicin hydrochloride; estramustine; estramustine phosphate sodium; etanidazole; etoposide; etoposide phosphate; etoprine; fadrozole hydrochloride; fazarabine; fenretinide; floxuridine; fludarabine phosphate; fluorouracil; flurocitabine; fosquidone; fostriecin sodium; 5 gemcitabine; gemcitabine hydrochloride; hydroxyurea; idarubicin hydrochloride; ifosfamide; ilmofosine; interleukin II (including recombinant interleukin II, or rIL2), interferon alfa-2a; interferon alfa-2b; interferon alfa-n1 ; interferon alfa-n3; interferon beta-I a; interferon gamma-I b; iproplatin; irinotecan hydrochloride; lanreotide acetate; letrozole; leuprolide acetate; liarozole hydrochloride; lometrexol 10 sodium; lomustine; losoxantrone hydrochloride; masoprocol; maytansine; mechlorethamine hydrochloride; megestrol acetate; melengestrol acetate; melphalan; menogaril; mercaptopurine; methotrexate; methotrexate sodium; metoprine; meturedepa; mitindomide; mitocarcin; mitocromin; mitogillin; mitomalcin; mitomycin; mitosper; mitotane; mitoxantrone hydrochloride; mycophenolic acid; 15 nocodażole; nogalamycin; ormaplatin; oxisuran; pegaspargase; peliomycin; pentamustine; peplomycin sulfate; perfosfamide; pipobroman; piposulfan; piroxantrone hydrochloride; plicamycin; plomestane; porfimer sodium; porfiromycin; prednimustine; procarbazine hydrochloride; puromycin; puromycin hydrochloride; pyrazofurin; riboprine; rogletimide; safingol; safingol hydrochloride; 20 semustine; simtrazene; sparfosate sodium; sparsomycin; spirogermanium hydrochloride; spiromustine; spiroplatin; streptonigrin; streptozocin; sulofenur; talisomycin; tecogalan sodium; tegafur; teloxantrone hydrochloride; temoporfin; teniposide; teroxirone; testolactone; thiamiprime; thioguanine; thiotepla; tiazofurin; tirapazamine; toremifene citrate; trestolone acetate; triciribine phosphate; 25 trimetrexate; trimetrexate glucuronate; triptorelin; tubulozole hydrochloride; uracil mustard; uredepa; vapreotide; verteporfin; vinblastine sulfate; vincristine sulfate; vindesine; vindesine sulfate; vinepidine sulfate; vinglycinate sulfate; vinleurosine sulfate; vinorelbine tartrate; vinrosidine sulfate; vinzolidine sulfate; vorozole; zeniplatin; zinostatin; zorubicin hydrochloride.

30 Other anti-cancer drugs that can be employed in combination with the compounds of the invention include: 20-epi-1,25 dihydroxyvitamin D3; 5-ethynyluracil; abiraterone; aclarubicin; acylfulvene; adecyepenol; adozelesin; aldesleukin; ALL-TK antagonists; altretamine; ambamustine; amidox; amifostine; aminolevulinic acid; amrubicin; amsacrine; anagrelide; anastrozole;

andrographolide; angiogenesis inhibitors; antagonist D; antagonist G; antarelix; anti-dorsalizing morphogenetic protein-1; antiandrogen, prostatic carcinoma; antiestrogen; antineoplaston; antisense oligonucleotides; aphidicolin glycinate; apoptosis gene modulators; apoptosis regulators; apurinic acid; ara-CDP-DL-PTBA; 5 arginine deaminase; asulacrine; atamestane; atrimustine; axinastatin 1; axinastatin 2; axinastatin 3; azasetron; azatoxin; azatyrosine; baccatin III derivatives; balanol; batimastat; BCR/ABL antagonists; benzochlorins; benzoylstauroporine; beta lactam derivatives; beta-alethine; betaclamycin B; betulinic acid; bFGF inhibitor; bicalutamide; bisantrene; bisaziridinylspermine; bisnafide; bistratene A; bizelesin; 10 breflate; bropirimine; budotitane; buthionine sulfoximine; calcipotriol; calphostin C; camptothecin derivatives; canarypox IL-2; capecitabine; carboxamide-amino-triazole; carboxyamidotriazole; CaRest M3; CARN 700; cartilage derived inhibitor; carzelesin; casein kinase inhibitors (ICOS); castanospermine; cecropin B; cetrorelix; chlorlins; chloroquinoxaline sulfonamide; cicaprost; cis-porphyrin; cladribine; 15 clomifene analogues; clotrimazole; collismycin A; collismycin B; combretastatin A4; combretastatin analogue; conagenin; crambescidin 816; crisnatol; cryptophycin 8; cryptophycin A derivatives; curacin A; cyclopentanthraquinones; cycloplatam; cypemycin; cytarabine ocfosfate; cytolytic factor; cytostatin; dacliximab; decitabine; dehydrodidemnin B; deslorelin; dexamethasone; dexifosfamide; dexrazoxane; 20 dexverapamil; diaziquone; didemnin B; didox; diethylnorspermine; dihydro-5-azacytidine; 9-dioxamycin; diphenyl spiomustine; docosanol; dolasetron; doxifluridine; droloxitene; dronabinol; duocarmycin SA; ebselen; ecomustine; edelfosine; edrecolomab; eflornithine; elemene; emitefur; epirubicin; epristeride; estramustine analogue; estrogen agonists; estrogen antagonists; étanidazole; 25 etoposide phosphate; exemestane; fadrozole; fazarabine; fenretinide; filgrastim; finasteride; flavopiridol; flezelastine; fluasterone; fludarabine; fluorodaunorubicin hydrochloride; forfenimex; formestane; fostriecin; fotemustine; gadolinium texaphyrin; gallium nitrate; galocitabine; ganirelix; gelatinase inhibitors; gemcitabine; glutathione inhibitors; hepsulfam; heregulin; hexamethylene 30 bisacetamide; hypericin; ibandronic acid; idarubicin; idoxifene; idramantone; ilmofosine; ilomastat; imidazoacridones; imiquimod; immunostimulant peptides; insulin-like growth factor-1 receptor inhibitor; interferon agonists; interferons; interleukins; iobenguane; iododoxorubicin; ipomeanol, 4-; iroplact; irsogladine; isobengazole; isohomohalicondrin B; itasetron; jasplakinolide; kahalalide F;

lamellarin-N triacetate; lanreotide; leinamycin; lenograstim; lentinan sulfate; leptolstatin; letrozole; leukemia inhibiting factor; leukocyte alpha interferon; leuprolide+estrogen+progesterone; leuprorelin; levamisole; liarozole; linear polyamine analogue; lipophilic disaccharide peptide; lipophilic platinum compounds; lissoclinamide 7; lobaplatin; lombricine; lometrexol; lonidamine; losoxantrone; lovastatin; loxoribine; lurtotecan; lutetium texaphyrin; lysofylline; lytic peptides; maitansine; mannostatin A; marimastat; masoprolol; maspin; matrilysin inhibitors; matrix metalloproteinase inhibitors; menogaril; merbarone; metevelin; methioninase; metoclopramide; MIF inhibitor; mifepristone; miltefosine; mirimostim; mismatched double stranded RNA; mitoguazone; mitolactol; mitomycin analogues; mitonafide; mitotoxin fibroblast growth factor-saporin; mitoxantrone; mofarotene; molgramostim; monoclonal antibody, human chorionic gonadotrophin; monophosphoryl lipid A+myobacterium cell wall sk; molidamol; multiple drug resistance gene inhibitor; multiple tumor suppressor 1-based therapy; mustard anticancer agent; mycaperoxide B; mycobacterial cell wall extract; myriaporone; N-acetyldinaline; N-substituted benzamides; nafarelin; nagrestip; naloxone+pentazocine; napavin; naphterpin; nartograstim; nedaplatin; nemorubicin; neridronic acid; neutral endopeptidase; nilutamide; nisamycin; nitric oxide modulators; nitroxide antioxidant; nitrullyn; O6-benzylguanine; octreotide; okicenone; oligonucleotides; onapristone; ondansetron; ondansetron; oracin; oral cytokine inducer; ormaplatin; osaterone; oxaliplatin; oxaunomycin; palauamine; palmitoylrhizoxin; pamidronic acid; panaxytriol; panomifene; parabactin; pazelliptine; pegaspargase; peldesine; pentosan polysulfate sodium; pentostatin; pentozole; perflubron; perfosfamide; perillyl alcohol; phenazinomycin; phenylacetate; phosphatase inhibitors; picibanil; pilocarpine hydrochloride; pirarubicin; piritrexim; placetin A; placetin B; plasminogen activator inhibitor; platinum complex; platinum compounds; platinum-triamine complex; porfimer sodium; porfiromycin; prednisone; propyl bis-acridone; prostaglandin J2; proteasome inhibitors; protein A-based immune modulator; protein kinase C inhibitor; protein kinase C inhibitors, microalgal; protein tyrosine phosphatase inhibitors; purine nucleoside phosphorylase inhibitors; purpurins; pyrazoloacridine; pyridoxylated hemoglobin polyoxyethylene conjugate; raf antagonists; raltitrexed; ramosetron; ras farnesyl protein transferase inhibitors; ras inhibitors; ras-GAP inhibitor; retelliptine demethylated; rhenium Re 186 etidronate; rhizoxin; ribozymes;

RII retinamide; rogletimide; rohitukine; romurtide; roquinimex; rubiginone B1; ruboxyl; safingol; saintopin; SarCNU; sarcophytol A; sargramostim; Sdi 1 mimetics; semustine; senescence derived inhibitor 1; sense oligonucleotides; signal transduction inhibitors; signal transduction modulators; single chain antigen-binding protein; sizofiran; sobuzoxane; sodium borocaptate; sodium phenylacetate; sоловол; somatomedin binding protein; sonermin; sparfosic acid; spicamycin D; spiromustine; splenopentin; spongistatin 1; squalamine; stem cell inhibitor; stem-cell division inhibitors; stipiamide; stromelysin inhibitors; sulfinosine; superactive vasoactive intestinal peptide antagonist; suradista; suramin; swainsonine; synthetic glycosaminoglycans; tallimustine; tamoxifen methiodide; tauromustine; tazarotene; tecogalan sodium; tegafur; tellurapyrylium; telomerase inhibitors; temoporfin; temozolamide; teniposide; tetrachlorodecaoxide; tetrazomine; thaliblastine; thiocoraline; thrombopoietin; thrombopoietin mimetic; thymalfasin; thymopoietin receptor agonist; thymotrinan; thyroid stimulating hormone; tin ethyl etiopurpurin; tirapazamine; titanocene bichloride; topsentin; toremifene; totipotent stem cell factor; translation inhibitors; tretinoin; triacetyluridine; triciribine; trimetrexate; triptorelin; tropisetron; turosteride; tyrosine kinase inhibitors; tyrophostins; UBC inhibitors; ubenimex; urogenital sinus-derived growth inhibitory factor; urokinase receptor antagonists; vapreotide; variolin B; vector system, erythrocyte gene therapy; velaresol; veramine; verdins; verteporfin; vinorelbine; vinxaltine; vitaxin; vorozole; zanoterone; zeniplatin; zilascorb; and zinostatin stimalamer. Preferred anti-cancer drugs are 5-fluorouracil and leucovorin.

Other chemotherapeutic agents that can be employed in combination with the compounds of the invention include but are not limited to alkylating agents, antimetabolites, natural products, or hormones. Examples of alkylating agents useful for the treatment or prevention of T-cell malignancies in the methods and compositions of the invention include but are not limited to, nitrogen mustards (e.g., mechloroethamine, cyclophosphamide, chlorambucil, *etc.*), alkyl sulfonates (e.g., busulfan), nitrosoureas (e.g., carmustine, lomustine, *etc.*), or triazenes (decarbazepine, *etc.*). Examples of antimetabolites useful for the treatment or prevention of T-cell malignancies in the methods and compositions of the invention include but are not limited to folic acid analog (e.g., methotrexate), or pyrimidine analogs (e.g., Cytarabine), purine analogs (e.g., mercaptopurine, thioguanine, pentostatin). Examples of natural products useful for the treatment or prevention of T-cell

malignancies in the methods and compositions of the invention include but are not limited to vinca alkaloids (e.g., vinblastin, vincristine), epipodophyllotoxins (e.g., etoposide), antibiotics (e.g., daunorubicin, doxorubicin, bleomycin), enzymes (e.g., L-asparaginase), or biological response modifiers (e.g., interferon alpha).

5 Examples of alkylating agents that can be employed in combination with the compounds of the invention include but are not limited to, nitrogen mustards (e.g., mechloroethamine, cyclophosphamide, chlorambucil, melphalan, *etc.*), ethylenimine and methylmelamines (e.g., hexamethylmelamine, thiotepa), alkyl sulfonates (e.g., busulfan), nitrosoureas (e.g., carmustine, lomustine, semustine, streptozocin, *etc.*), or 10 triazenes (decarbazine, *etc.*). Examples of antimetabolites useful for the treatment or prevention of cancer in the methods and compositions of the invention include but are not limited to folic acid analog (e.g., methotrexate), or pyrimidine analogs (e.g., fluorouracil, floxouridine, Cytarabine), purine analogs (e.g., mercaptopurine, thioguanine, pentostatin). Examples of natural products useful for the treatment or 15 prevention of cancer in the methods and compositions of the invention include but are not limited to vinca alkaloids (e.g., vinblastin, vincristine), epipodophyllotoxins (e.g., etoposide, teniposide), antibiotics (e.g., actinomycin D, daunorubicin, doxorubicin, bleomycin, plicamycin, mitomycin), enzymes (e.g., L-asparaginase), or biological response modifiers (e.g., interferon alpha). Examples of hormones and 20 antagonists useful for the treatment or prevention of cancer in the methods and compositions of the invention include but are not limited to adrenocorticosteroids (e.g., prednisone), progestins (e.g., hydroxyprogesterone caproate, megestrol acetate, medroxyprogesterone acetate), estrogens (e.g., diethylstilbestrol, ethinyl estradiol), antiestrogen (e.g., tamoxifen), androgens (e.g., testosterone propionate, 25 fluoxymesterone), antiandrogen (e.g., flutamide), gonadotropin releasing hormone analog (e.g., leuprolide). Other agents that can be used in the methods and compositions of the invention for the treatment or prevention of cancer include platinum coordination complexes (e.g., cisplatin, carboblatin), anthracenedione (e.g., mitoxantrone), substituted urea (e.g., hydroxyurea), methyl hydrazine derivative 30 (e.g., procarbazine), adrenocortical suppressant (e.g., mitotane, aminoglutethimide).

Examples of anti-cancer agents which act by arresting cells in the G2-M phases due to stabilization or inhibition of microtubules and which can be used in combination with the compounds of the invention include without limitation the following marketed drugs and drugs in development: Erbulozole (also known as R-

55104), Dolastatin 10 (also known as DLS-10 and NSC-376128), Mivobulin isethionate (also known as CI-980), Vincristine, NSC-639829, Discodermolide (also known as NVP-XX-A-296), ABT-751 (Abbott, also known as E-7010), Altorhyrtins (such as Altorhyrtin A and Altorhyrtin C), Spongistatins (such as Spongistatin 1, 5 Spongistatin 2, Spongistatin 3, Spongistatin 4, Spongistatin 5, Spongistatin 6, Spongistatin 7, Spongistatin 8, and Spongistatin 9), Cemadotin hydrochloride (also known as LU-103793 and NSC-D-669356), Epothilones (such as Epothilone A, Epothilone B, Epothilone C (also known as desoxyepothilone A or dEpoA), Epothilone D (also referred to as KOS-862, dEpoB, and desoxyepothilone B), 10 Epothilone E, Epothilone F, Epothilone B N-oxide, Epothilone A N-oxide, 16-aza-epothilone B, 21-aminoepothilone B (also known as BMS-310705), 21-hydroxyepothilone D (also known as Desoxyepothilone F and dEpoF), 26-fluoroepothilone), Auristatin PE (also known as NSC-654663), Soblidotin (also known as TZT-1027), LS-4559-P (Pharmacia, also known as LS-4577), LS-4578 (Pharmacia, also known as LS-477-P), LS-4477 (Pharmacia), LS-4559 (Pharmacia), RPR-112378 (Aventis), Vincristine sulfate, DZ-3358 (Daiichi), FR-182877 (Fujisawa, also known as WS-9885B), GS-164 (Takeda), GS-198 (Takeda), KAR-2 (Hungarian Academy of Sciences), BSF-223651 (BASF, also known as ILX-651 and LU-223651), SAH-49960 (Lilly/Novartis), SDZ-268970 (Lilly/Novartis), AM- 15 97 (Armad/Kyowa Hakko), AM-132 (Armad), AM-138 (Armad/Kyowa Hakko), IDN-5005 (Indena), Cryptophycin 52 (also known as LY-355703), AC-7739 (Ajinomoto, also known as AVE-8063A and CS-39.HCl), AC-7700 (Ajinomoto, also known as AVE-8062, AVE-8062A, CS-39-L-Ser.HCl, and RPR-258062A), Vitilevuamide, Tubulysin A, Canadensol, Centaureidin (also known as NSC- 20 106969), T-138067 (Tularik, also known as T-67, TL-138067 and TI-138067), COBRA-1 (Parker Hughes Institute, also known as DDE-261 and WHI-261), H10 (Kansas State University), H16 (Kansas State University), Oncocidin A1 (also known as BTO-956 and DIME), DDE-313 (Parker Hughes Institute), Fijianolide B, Laulimalide, SPA-2 (Parker Hughes Institute), SPA-1 (Parker Hughes Institute, also known as SPIKET-P), 3-IAABU (Cytoskeleton/Mt. Sinai School of Medicine, also known as MF-569), Narcosine (also known as NSC-5366), Nascapine, D-24851 (Asta Medica), A-105972 (Abbott), Hemiasterlin, 3-BAABU (Cytoskeleton/Mt. Sinai School of Medicine, also known as MF-191), TMPN (Arizona State 25 University), Vanadocene acetylacetone, T-138026 (Tularik), Monsatrol, Inanocine 30

(also known as NSC-698666), 3-IAABE (Cytoskeleton/Mt. Sinai School of Medicine), A-204197 (Abbott), T-607 (Tularik, also known as T-900607), RPR-115781 (Aventis), Eleutherobins (such as Desmethylleleutherobin, Desaetyleleutherobin, Isoeleutherobin A, and Z-Eleutherobin), Caribaeoside, 5 Caribaeolin, Halichondrin B, D-64131 (Asta Medica), D-68144 (Asta Medica), Diazonamide A, A-293620 (Abbott), NPI-2350 (Nereus), Taccalonolide A, TUB-245 (Aventis), A-259754 (Abbott), Diozostatin, (-)-Phenylahistin (also known as NSCL-96F037), D-68838 (Asta Medica), D-68836 (Asta Medica), Myoseverin B, D-43411 (Zentaris, also known as D-81862), A-289099 (Abbott), A-318315 10 (Abbott), HTI-286 (also known as SPA-110, trifluoroacetate salt) (Wyeth), D-82317 (Zentaris), D-82318 (Zentaris), SC-12983 (NCI), Resverastatin phosphate sodium, BPR-0Y-007 (National Health Research Institutes), and SSR-250411 (Sanofi).

E. Compositions and Methods for Administering Therapies

15 The present invention provides compositions for the treatment or prevention of angiogenesis related disorders, such as macular degeneration. In a specific embodiment, a composition comprises one or more compounds of the invention, or a pharmaceutically acceptable salt, solvate, clathrate, hydrate or prodrug thereof. In another embodiment, a composition of the invention comprises one or more 20 prophylactic or therapeutic agents other than a compound of the invention, or a pharmaceutically acceptable salt, solvate, clathrate, hydrate, prodrug thereof. In another embodiment, a composition of the invention comprises one or more compounds of the invention, or a pharmaceutically acceptable salt, solvate, clathrate, hydrate or prodrug thereof, and one or more other prophylactic or therapeutic agents. 25 In another embodiment, the composition comprises a compound of the invention, or a pharmaceutically acceptable salt, solvate, clathrate, hydrate, or prodrug thereof, and a pharmaceutically acceptable carrier, diluent or excipient.

In a preferred embodiment, a composition of the invention is a pharmaceutical composition or a single unit dosage form. Pharmaceutical 30 compositions and dosage forms of the invention comprise one or more active ingredients in relative amounts and formulated in such a way that a given pharmaceutical composition or dosage form can be used to treat or prevent angiogenesis related disorders, such as macular degeneration. Preferred pharmaceutical compositions and dosage forms comprise a compound of formula

(I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), or Table 1, or a pharmaceutically acceptable prodrug, salt, solvate, clathrate, hydrate, or prodrug thereof, optionally in combination with one or more additional active agents.

A pharmaceutical composition of the invention is formulated to be 5 compatible with its intended route of administration. Examples of routes of administration include, but are not limited to, parenteral, e.g., intravenous, intradermal, subcutaneous, oral (e.g., inhalation), intranasal, transdermal (topical), transmucosal, and rectal administration. In a specific embodiment, the composition is formulated in accordance with routine procedures as a pharmaceutical 10 composition adapted for intravenous, subcutaneous, intramuscular, oral, intranasal or topical administration to human beings. In a preferred embodiment, a pharmaceutical composition is formulated in accordance with routine procedures for subcutaneous administration to human beings.

Single unit dosage forms of the invention are suitable for oral, mucosal (e.g., 15 nasal, sublingual, vaginal, buccal, or rectal), parenteral (e.g., subcutaneous, intravenous, bolus injection, intramuscular, or intraarterial), or transdermal administration to a patient. Examples of dosage forms include, but are not limited to: tablets; caplets; capsules, such as soft elastic gelatin capsules; cachets; troches; lozenges; dispersions; suppositories; ointments; cataplasms (poultices); pastes; 20 powders; dressings; creams; plasters; solutions; patches; aerosols (e.g., nasal sprays or inhalers); gels; liquid dosage forms suitable for oral or mucosal administration to a patient, including suspensions (e.g., aqueous or non-aqueous liquid suspensions, oil-in-water emulsions, or a water-in-oil liquid emulsions), solutions, and elixirs; liquid dosage forms suitable for parenteral administration to a patient; and sterile 25 solids (e.g., crystalline or amorphous solids) that can be reconstituted to provide liquid dosage forms suitable for parenteral administration to a patient.

The composition, shape, and type of dosage forms of the invention will typically vary depending on their use. For example, a dosage form suitable for mucosal administration may contain a smaller amount of active ingredient(s) than an 30 oral dosage form used to treat the same indication. This aspect of the invention will be readily apparent to those skilled in the art. *See, e.g., Remington's Pharmaceutical Sciences (1990) 18th ed., Mack Publishing, Easton PA.*

Typical pharmaceutical compositions and dosage forms comprise one or more excipients. Suitable excipients are well known to those skilled in the art of

pharmacy, and non-limiting examples of suitable excipients are provided herein. Whether a particular excipient is suitable for incorporation into a pharmaceutical composition or dosage form depends on a variety of factors well known in the art including, but not limited to, the way in which the dosage form will be administered to a patient. For example, oral dosage forms such as tablets may contain excipients not suited for use in parenteral dosage forms.

The suitability of a particular excipient may also depend on the specific active ingredients in the dosage form. For example, the decomposition of some active ingredients can be accelerated by some excipients such as lactose, or when exposed to water. Active ingredients that comprise primary or secondary amines (e.g., N-desmethylvenlafaxine and N,N-didesmethylvenlafaxine) are particularly susceptible to such accelerated decomposition. Consequently, this invention encompasses pharmaceutical compositions and dosage forms that contain little, if any, lactose. As used herein, the term "lactose-free" means that the amount of lactose present, if any, is insufficient to substantially increase the degradation rate of an active ingredient. Lactose-free compositions of the invention can comprise excipients that are well known in the art and are listed, for example, in the U.S. Pharmacopedia (USP) SP (XXI)/NF (XVI). In general, lactose-free compositions comprise active ingredients, a binder/filler, and a lubricant in pharmaceutically compatible and pharmaceutically acceptable amounts. Preferred lactose-free dosage forms comprise active ingredients, microcrystalline cellulose, pre-gelatinized starch, and magnesium stearate.

This invention further encompasses anhydrous pharmaceutical compositions and dosage forms comprising active ingredients, since water can facilitate the degradation of some compounds. For example, the addition of water (e.g., 5%) is widely accepted in the pharmaceutical arts as a means of simulating long-term storage in order to determine characteristics such as shelf-life or the stability of formulations over time. *See, e.g.,* Jens T. Carstensen (1995) *Drug Stability: Principles & Practice*, 2d. Ed., Marcel Dekker, NY, NY, 379-80. In effect, water and heat accelerate the decomposition of some compounds. Thus, the effect of water on a formulation can be of great significance since moisture and/or humidity are commonly encountered during manufacture, handling, packaging, storage, shipment, and use of formulations.

Anhydrous pharmaceutical compositions and dosage forms of the invention can be prepared using anhydrous or low moisture containing ingredients and low moisture or low humidity conditions. Pharmaceutical compositions and dosage forms that comprise lactose and at least one active ingredient that comprises a primary or secondary amine are preferably anhydrous if substantial contact with moisture and/or humidity during manufacturing, packaging, and/or storage is expected.

An anhydrous pharmaceutical composition should be prepared and stored such that its anhydrous nature is maintained. Accordingly, anhydrous compositions are preferably packaged using materials known to prevent exposure to water such that they can be included in suitable formulary kits. Examples of suitable packaging include, but are not limited to, hermetically sealed foils, plastics, unit dose containers (e.g., vials), blister packs, and strip packs.

The invention further encompasses pharmaceutical compositions and dosage forms that comprise one or more compounds that reduce the rate by which an active ingredient will decompose. Such compounds, which are referred to herein as "stabilizer" include, but are not limited to, antioxidants such as ascorbic acid, pH buffers, or salt buffers.

1) Oral Dosage Forms

Pharmaceutical compositions of the invention that are suitable for oral administration can be presented as discrete dosage forms, such as, but are not limited to, tablets (e.g., chewable tablets), caplets, capsules, and liquids (e.g., flavored syrups). Such dosage forms contain predetermined amounts of active ingredients, and may be prepared by methods of pharmacy well known to those skilled in the art.

See generally, Remington's Pharmaceutical Sciences (1990) 18th ed., Mack Publishing, Easton PA.

Typical oral dosage forms of the invention are prepared by combining the active ingredient(s) in an admixture with at least one excipient according to conventional pharmaceutical compounding techniques. Excipients can take a wide variety of forms depending on the form of preparation desired for administration. For example, excipients suitable for use in oral liquid or aerosol dosage forms include, but are not limited to, water, glycols, oils, alcohols, flavoring agents, preservatives, and coloring agents. Examples of excipients suitable for use in solid

oral dosage forms (e.g., powders, tablets, capsules, and caplets) include, but are not limited to, starches, sugars, micro-crystalline cellulose, diluents, granulating agents, lubricants, binders, and disintegrating agents.

Because of their ease of administration, tablets and capsules represent the 5 most advantageous oral dosage unit forms, in which case solid excipients are employed. If desired, tablets can be coated by standard aqueous or nonaqueous techniques. Such dosage forms can be prepared by any of the methods of pharmacy. In general, pharmaceutical compositions and dosage forms are prepared by uniformly and intimately admixing the active ingredients with liquid carriers, finely 10 divided solid carriers, or both, and then shaping the product into the desired presentation if necessary.

For example, a tablet can be prepared by compression or molding. Compressed tablets can be prepared by compressing in a suitable machine the active 15 ingredients in a free-flowing form such as powder or granules, optionally mixed with an excipient. Molded tablets can be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

Examples of excipients that can be used in oral dosage forms of the invention include, but are not limited to, binders, fillers, disintegrants, and lubricants. Binders suitable for use in pharmaceutical compositions and dosage forms include, but are 20 not limited to, corn starch, potato starch, or other starches, gelatin, natural and synthetic gums such as acacia, sodium alginate, alginic acid, other alginates, powdered tragacanth, guar gum, cellulose and its derivatives (e.g., ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), polyvinyl pyrrolidone, methyl cellulose, pre-gelatinized starch, 25 hydroxypropyl methyl cellulose, (e.g., Nos. 2208, 2906, 2910), microcrystalline cellulose, and mixtures thereof.

Suitable forms of microcrystalline cellulose include, but are not limited to, the materials sold as AVICEL-PH-101, AVICEL-PH-103 AVICEL RC-581, AVICEL-PH-105 (available from FMC Corporation, American Viscose Division, 30 Avicel Sales, Marcus Hook, PA), and mixtures thereof. One specific binder is a mixture of microcrystalline cellulose and sodium carboxymethyl cellulose sold as AVICEL RC-581. Suitable anhydrous or low moisture excipients or additives include AVICEL-PH-103J and Starch 1500 LM.

Examples of fillers suitable for use in the pharmaceutical compositions and dosage forms disclosed herein include, but are not limited to, talc, calcium carbonate (e.g., granules or powder), microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof.

5 The binder or filler in pharmaceutical compositions of the invention is typically present in from about 50 to about 99 weight percent of the pharmaceutical composition or dosage form.

Disintegrants are used in the compositions of the invention to provide tablets that disintegrate when exposed to an aqueous environment. Tablets that contain too 10 much disintegrant may disintegrate in storage, while those that contain too little may not disintegrate at a desired rate or under the desired conditions. Thus, a sufficient amount of disintegrant that is neither too much nor too little to detrimentally alter the release of the active ingredients should be used to form solid oral dosage forms of the invention. The amount of disintegrant used varies based upon the type of 15 formulation, and is readily discernible to those of ordinary skill in the art. Typical pharmaceutical compositions comprise from about 0.5 to about 15 weight percent of disintegrant, preferably from about 1 to about 5 weight percent of disintegrant.

Disintegrants that can be used in pharmaceutical compositions and dosage forms of the invention include, but are not limited to, agar-agar, alginic acid, 20 calcium carbonate, microcrystalline cellulose, croscarmellose sodium, crospovidone, polacrilin potassium, sodium starch glycolate, potato or tapioca starch, other starches, pre-gelatinized starch, other starches, clays, other algins, other celluloses, gums, and mixtures thereof.

Lubricants that can be used in pharmaceutical compositions and dosage 25 forms of the invention include, but are not limited to, calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil (e.g., peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil), zinc stearate, ethyl oleate, ethyl laurate, agar, and 30 mixtures thereof. Additional lubricants include, for example, a syloid silica gel (AEROSIL 200, manufactured by W.R. Grace Co. of Baltimore, MD), a coagulated aerosol of synthetic silica (marketed by Degussa Co. of Plano, TX), CAB-O-SIL (a pyrogenic silicon dioxide product sold by Cabot Co. of Boston, MA), and mixtures thereof. If used at all, lubricants are typically used in an amount of less than about 1

weight percent of the pharmaceutical compositions or dosage forms into which they are incorporated.

2) Controlled Release Dosage Forms

Active ingredients of the invention can be administered by controlled release means or by delivery devices that are well known to those of ordinary skill in the art. Examples include, but are not limited to, those described in U.S. Patent Nos.: 5,845,770; 3,916,899; 3,536,809; 3,598,123; and 4,008,719, 5,674,533, 5,059,595, 5,591,767, 5,120,548, 5,073,543, 5,639,476, 5,354,556, and 5,733,566, each of which is incorporated herein by reference. Such dosage forms can be used to provide slow or controlled-release of one or more active ingredients using, for example, hydropropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, liposomes, microspheres, or a combination thereof to provide the desired release profile in varying proportions. Suitable controlled-release formulations known to those of ordinary skill in the art, including those described herein, can be readily selected for use with the active ingredients of the invention. The invention thus encompasses single unit dosage forms suitable for oral administration such as, but not limited to, tablets, capsules, gelcaps, and caplets that are adapted for controlled-release.

All controlled-release pharmaceutical products have a common goal of improving drug therapy over that achieved by their non-controlled counterparts. Ideally, the use of an optimally designed controlled-release preparation in medical treatment is characterized by a minimum of drug substance being employed to cure or control the condition in a minimum amount of time. Advantages of controlled-release formulations include extended activity of the drug, reduced dosage frequency, and increased patient compliance.

Most controlled-release formulations are designed to initially release an amount of drug (active ingredient) that promptly produces the desired therapeutic effect, and gradually and continually release of other amounts of drug to maintain this level of therapeutic or prophylactic effect over an extended period of time. In order to maintain this constant level of drug in the body, the drug must be released from the dosage form at a rate that will replace the amount of drug being metabolized and excreted from the body. Controlled-release of an active ingredient

can be stimulated by various conditions including, but not limited to, pH, temperature, enzymes, water, or other physiological conditions or compounds.

A particular extended release formulation of this invention comprises a therapeutically or prophylactically effective amount of a compound of formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), or Table 1, or a pharmaceutically acceptable salt, solvate, hydrate, clathrate, or prodrug thereof, in spheroids which further comprise microcrystalline cellulose and, optionally, hydroxypropylmethylcellulose coated with a mixture of ethyl cellulose and hydroxypropylmethylcellulose. Such extended release formulations can be prepared according to U.S. Patent No. 6,274,171, the entirety of which is incorporated herein by reference.

A specific controlled-release formulation of this invention comprises from about 6% to about 40% a compound of formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), or Table 1, or a pharmaceutically acceptable salt, solvate, hydrate, clathrate, or prodrug thereof, by weight, about 50% to about 94% microcrystalline cellulose, NF, by weight, and optionally from about 0.25% to about 1% by weight of hydroxypropyl-methylcellulose, USP, wherein the spheroids are coated with a film coating composition comprised of ethyl cellulose and hydroxypropylmethylcellulose.

20 3) Parenteral Dosage Forms

Parenteral dosage forms can be administered to patients by various routes including, but not limited to, subcutaneous, intravenous (including bolus injection), intramuscular, and intraarterial. Because their administration typically bypasses patients' natural defenses against contaminants, parenteral dosage forms are preferably sterile or capable of being sterilized prior to administration to a patient. Examples of parenteral dosage forms include, but are not limited to, solutions ready for injection, dry products ready to be dissolved or suspended in a pharmaceutically acceptable vehicle for injection, suspensions ready for injection, and emulsions.

Suitable vehicles that can be used to provide parenteral dosage forms of the invention are well known to those skilled in the art. Examples include, but are not limited to: Water for Injection USP; aqueous vehicles such as, but not limited to, Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer's Injection; water-miscible vehicles

such as, but not limited to, ethyl alcohol, polyethylene glycol, and polypropylene glycol; and non-aqueous vehicles such as, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate.

Compounds that increase the solubility of one or more of the active 5 ingredients disclosed herein can also be incorporated into the parenteral dosage forms of the invention.

4) Transdermal, Topical, and Mucosal Dosage Forms

Transdermal, topical, and mucosal dosage forms of the invention include, but are not limited to, ophthalmic solutions, sprays, aerosols, creams, lotions, ointments, 10 gels, solutions, emulsions, suspensions, or other forms known to one of skill in the art. *See, e.g.*, Remington's Pharmaceutical Sciences (1980 & 1990) 16th and 18th eds., Mack Publishing, Easton PA and Introduction to Pharmaceutical Dosage Forms (1985) 4th ed., Lea & Febiger, Philadelphia. Dosage forms suitable for treating mucosal tissues within the oral cavity can be formulated as mouthwashes or 15 as oral gels. Further, transdermal dosage forms include "reservoir type" or "matrix type" patches, which can be applied to the skin and worn for a specific period of time to permit the penetration of a desired amount of active ingredients.

Suitable excipients (*e.g.*, carriers and diluents) and other materials that can be used to provide transdermal, topical, and mucosal dosage forms encompassed by 20 this invention are well known to those skilled in the pharmaceutical arts, and depend on the particular tissue to which a given pharmaceutical composition or dosage form will be applied. With that fact in mind, typical excipients include, but are not limited to, water, acetone, ethanol, ethylene glycol, propylene glycol, butane-1,3-diol, isopropyl myristate, isopropyl palmitate, mineral oil, and mixtures thereof to 25 form lotions, tinctures, creams, emulsions, gels or ointments, which are non-toxic and pharmaceutically acceptable. Moisturizers or humectants can also be added to pharmaceutical compositions and dosage forms if desired. Examples of such additional ingredients are well known in the art. *See, e.g.*, Remington's Pharmaceutical Sciences (1980 & 1990) 16th and 18th eds., Mack Publishing, 30 Easton PA.

Depending on the specific tissue to be treated, additional components may be used prior to, in conjunction with, or subsequent to treatment with active ingredients of the invention. For example, penetration enhancers can be used to assist in

delivering the active ingredients to the tissue. Suitable penetration enhancers include, but are not limited to: acetone; various alcohols such as ethanol, oleyl, and tetrahydrofuryl; alkyl sulfoxides such as dimethyl sulfoxide; dimethyl acetamide; dimethyl formamide; polyethylene glycol; pyrrolidones such as

5 polyvinylpyrrolidone; Kollidon grades (Povidone, Polyvidone); urea; and various water-soluble or insoluble sugar esters such as Tween 80 (polysorbate 80) and Span 60 (sorbitan monostearate).

The pH of a pharmaceutical composition or dosage form, or of the tissue to which the pharmaceutical composition or dosage form is applied, may also be 10 adjusted to improve delivery of one or more active ingredients. Similarly, the polarity of a solvent carrier, its ionic strength, or tonicity can be adjusted to improve delivery. Compounds such as stearates can also be added to pharmaceutical compositions or dosage forms to advantageously alter the hydrophilicity or 15 lipophilicity of one or more active ingredients so as to improve delivery. In this regard, stearates can serve as a lipid vehicle for the formulation, as an emulsifying agent or surfactant, and as a delivery-enhancing or penetration-enhancing agent. Different salts, hydrates or solvates of the active ingredients can be used to further 20 adjust the properties of the resulting composition.

5) Dosage & Frequency of Administration

20 The amount of the compound or composition of the invention which will be effective in the prevention, treatment, management, or amelioration of an angiogenesis related disorder, such as macular degeneration, or one or more symptoms thereof, will vary with the nature and severity of the disease or condition, and the route by which the active ingredient is administered. The frequency and 25 dosage will also vary according to factors specific for each patient depending on the specific therapy (e.g., therapeutic or prophylactic agents) administered, the severity of the disorder, disease, or condition, the route of administration, as well as age, body, weight, response, and the past medical history of the patient. Effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal 30 model test systems. Suitable regiments can be selected by one skilled in the art by considering such factors and by following, for example, dosages reported in the literature and recommended in the *Physician's Desk Reference* (57th ed., 2003).

Exemplary doses of a small molecule include milligram or microgram amounts of the small molecule per kilogram of subject or sample weight (e.g., about 1 microgram per kilogram to about 500 milligrams per kilogram, about 100 micrograms per kilogram to about 5 milligrams per kilogram, or about 1 microgram per kilogram to about 50 micrograms per kilogram).

In general, the recommended daily dose range of a compound of the invention for the conditions described herein lie within the range of from about 0.01 mg to about 1000 mg per day, given as a single once-a-day dose preferably as divided doses throughout a day. In one embodiment, the daily dose is administered twice daily in equally divided doses. Specifically, a daily dose range should be from about 5 mg to about 500 mg per day, more specifically, between about 10 mg and about 200 mg per day. In managing the patient, the therapy should be initiated at a lower dose, perhaps about 1 mg to about 25 mg, and increased if necessary up-to about 200 mg to about 1000 mg per day as either a single dose or divided doses, depending on the patient's global response. It may be necessary to use dosages of the active ingredient outside the ranges disclosed herein in some cases, as will be apparent to those of ordinary skill in the art. Furthermore, it is noted that the clinician or treating physician will know how and when to interrupt, adjust, or terminate therapy in conjunction with individual patient response.

Different therapeutically effective amounts may be applicable for different diseases or disorders, as will be readily known by those of ordinary skill in the art. Similarly, amounts sufficient to prevent, manage, treat or ameliorate angiogenesis related disorders, but insufficient to cause, or sufficient to reduce, adverse effects associated with the compounds of the invention are also encompassed by the above described dosage amounts and dose frequency schedules. Further, when a patient is administered multiple dosages of a compound of the invention, not all of the dosages need be the same. For example, the dosage administered to the patient may be increased to improve the prophylactic or therapeutic effect of the compound or it may be decreased to reduce one or more side effects that a particular patient is experiencing.

In a specific embodiment, the dosage of the composition of the invention or a compound of the invention administered to prevent, treat, manage, or ameliorate angiogenesis related disorders, such as macular degeneration, or one or more symptoms thereof in a patient is 150 μ g/kg, preferably 250 μ g/kg, 500 μ g/kg, 1

mg/kg, 5 mg/kg, 10 mg/kg, 25 mg/kg, 50 mg/kg, 75 mg/kg, 100 mg/kg, 125 mg/kg, 150 mg/kg, or 200 mg/kg or more of a patient's body weight. In another embodiment, the dosage of the composition of the invention or a compound of the invention administered to prevent, treat, manage, or ameliorate angiogenesis related disorders, such as macular degeneration, or one or more symptoms thereof in a patient is a unit dose of 0.1 mg to 20 mg, 0.1 mg to 15 mg, 0.1 mg to 12 mg, 0.1 mg to 10 mg, 0.1 mg to 8 mg, 0.1 mg to 7 mg, 0.1 mg to 5 mg, 0.1 to 2.5 mg, 0.25 mg to 20 mg, 0.25 to 15 mg, 0.25 to 12 mg, 0.25 to 10 mg, 0.25 to 8 mg, 0.25 mg to 7 mg, 0.25 mg to 5 mg, 0.5 mg to 2.5 mg, 1 mg to 20 mg, 1 mg to 15 mg, 1 mg to 12 mg, 1 mg to 10 mg, 1 mg to 8 mg, 1 mg to 7 mg, 1 mg to 5 mg, or 1 mg to 2.5 mg.

The dosages of prophylactic or therapeutic agents other than compounds of the invention, which have been or are currently being used to prevent, treat, manage, or proliferative disorders, such as cancer, or one or more symptoms thereof can be used in the combination therapies of the invention. Preferably, dosages lower than those which have been or are currently being used to prevent, treat, manage, or ameliorate a proliferative disorders, or one or more symptoms thereof, are used in the combination therapies of the invention. The recommended dosages of agents currently used for the prevention, treatment, management, or amelioration of a proliferative disorders, such as cancer, or one or more symptoms thereof, can obtained from any reference in the art including, but not limited to, Hardman *et al.*, eds., 1996, Goodman & Gilman's The Pharmacological Basis Of Basis Of Therapeutics 9th Ed, Mc-Graw-Hill, New York; Physician's Desk Reference (PDR) 57th Ed., 2003, Medical Economics Co., Inc., Montvale, NJ, which are incorporated herein by reference in its entirety.

In certain embodiments, when the compounds of the invention are administered in combination with another therapy, the therapies (e.g., prophylactic or therapeutic agents) are administered less than 5 minutes apart, less than 30 minutes apart, 1 hour apart, at about 1 hour apart, at about 1 to about 2 hours apart, at about 2 hours to about 3 hours apart, at about 3 hours to about 4 hours apart, at about 4 hours to about 5 hours apart, at about 5 hours to about 6 hours apart, at about 6 hours to about 7 hours apart, at about 7 hours to about 8 hours apart, at about 8 hours to about 9 hours apart, at about 9 hours to about 10 hours apart, at about 10 hours to about 11 hours apart, at about 11 hours to about 12 hours apart, at about 12 hours to 18 hours apart, 18 hours to 24 hours apart, 24 hours to 36 hours apart, 36

hours to 48 hours apart, 48 hours to 52 hours apart, 52 hours to 60 hours apart, 60 hours to 72 hours apart, 72 hours to 84 hours apart, 84 hours to 96 hours apart, or 96 hours to 120 hours part. In one embodiment, two or more therapies (e.g., prophylactic or therapeutic agents) are administered within the same patent visit.

5 In certain embodiments, one or more compounds of the invention and one or more other the therapies (e.g., prophylactic or therapeutic agents) are cyclically administered. Cycling therapy involves the administration of a first therapy (e.g., a first prophylactic or therapeutic agents) for a period of time, followed by the administration of a second therapy (e.g., a second prophylactic or therapeutic agents)

10 10 for a period of time, followed by the administration of a third therapy (e.g., a third prophylactic or therapeutic agents) for a period of time and so forth, and repeating this sequential administration, *i.e.*, the cycle in order to reduce the development of resistance to one of the agents, to avoid or reduce the side effects of one of the agents, and/or to improve the efficacy of the treatment.

15 In certain embodiments, administration of the same compound of the invention may be repeated and the administrations may be separated by at least 1 day, 2 days, 3 days, 5 days, 10 days, 15 days, 30 days, 45 days, 2 months, 75 days, 3 months, or 6 months. In other embodiments, administration of the same prophylactic or therapeutic agent may be repeated and the administration may be

20 20 separated by at least at least 1 day, 2 days, 3 days, 5 days, 10 days, 15 days, 30 days, 45 days, 2 months, 75 days, 3 months, or 6 months.

In a specific embodiment, the invention provides a method of preventing, treating, managing, or ameliorating a proliferative disorders, such as cancer, or one or more symptoms thereof, said methods comprising administering to a subject in need thereof a dose of at least 150 $\mu\text{g}/\text{kg}$, preferably at least 250 $\mu\text{g}/\text{kg}$, at least 500 $\mu\text{g}/\text{kg}$, at least 1 mg/kg, at least 5 mg/kg, at least 10 mg/kg, at least 25 mg/kg, at least 50 mg/kg, at least 75 mg/kg, at least 100 mg/kg, at least 125 mg/kg, at least 150 mg/kg, or at least 200 mg/kg or more of one or more compounds of the invention once every day, preferably, once every 2 days, once every 3 days, once every 4 days, once every 5 days, once every 6 days, once every 7 days, once every 8 days, once every 10 days, once every two weeks, once every three weeks, or once a month.

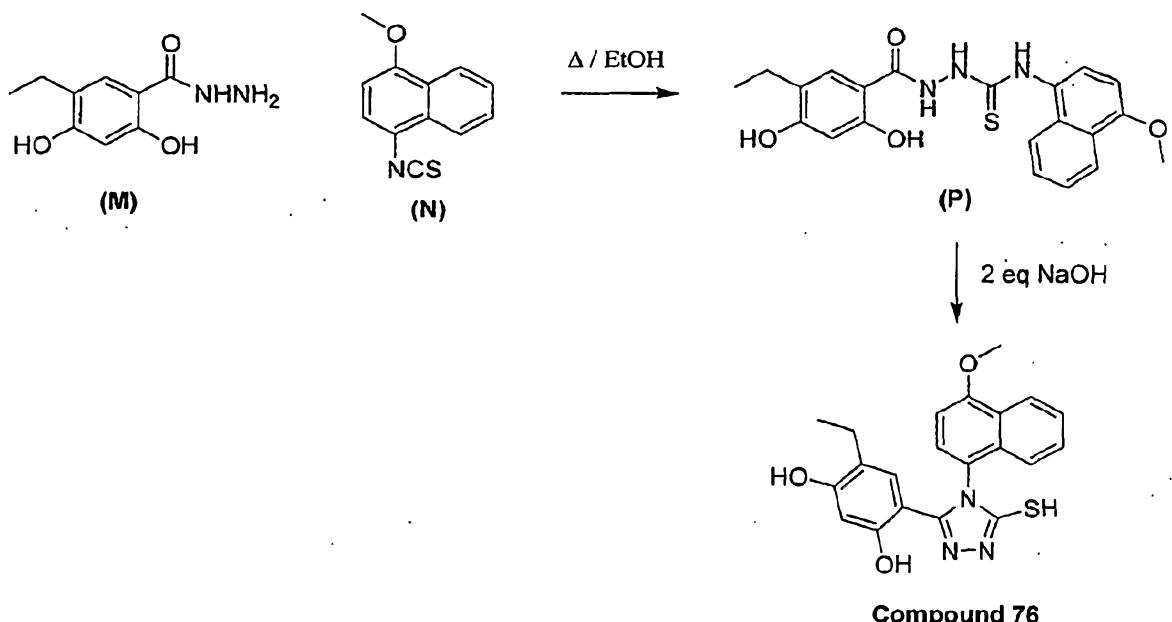
F. Other Embodiments

The compounds of the invention may be used as research tools (for example, to evaluate the mechanism of action of new drug agents, to isolate new drug discovery targets using affinity chromatography, as antigens in an ELISA or ELISA-like assay, or as standards in *in vitro* or *in vivo* assays). These and other uses and 5 embodiments of the compounds and compositions of this invention will be apparent to those of ordinary skill in the art.

The invention is further defined by reference to the following examples describing in detail the preparation of compounds of the invention. It will be 10 apparent to those skilled in the art that many modifications, both to materials and methods, may be practiced without departing from the purpose and interest of this invention. The following examples are set forth to assist in understanding the invention and should not be construed as specifically limiting the invention described and claimed herein. Such variations of the invention, including the 15 substitution of all equivalents now known or later developed, which would be within the purview of those skilled in the art, and changes in formulation or minor changes in experimental design, are to be considered to fall within the scope of the invention incorporated herein.

20 EXAMPLES

Reagents and solvents used below can be obtained from commercial sources such as Aldrich Chemical Co. (Milwaukee, Wisconsin, USA). ¹H-NMR and ¹³C-NMR spectra were recorded on a Varian 300MHz NMR spectrometer. Significant peaks are tabulated in the order: δ (ppm): chemical shift, multiplicity (s, singlet; d, 25 doublet; t, triplet; q, quartet; m, multiplet; br s, broad singlet), coupling constant(s) in Hertz (Hz) and number of protons.

Example 1: Synthesis of Compound 76

5 The hydrazide (M) (1.45 g, 7.39 mmol) and the isothiocyanate (N) (1.59 g, 7.39 mmol) were dissolved in ethanol (20 ml) with heating. When the starting materials were dissolved the solution was allowed to cool to room temperature and a precipitate formed. This precipitate was filtered then washed with ether to provide the intermediate (P) as a white solid (2.85 g, 97%). The intermediate (VII) (1.89 g,

10 4.77 mmol) was heated in a solution of sodium hydroxide (0.38 g, 9.54 mmol) in water (20 mL) at 110°C for 2 hours. The solution was allowed to cool to room temperature then acidified with conc. HCl. The resulting precipitate was filtered then washed with water (100 mL) and dried. The crude product was recrystallized from ethanol to produce compound 76 as a white solid (1.4 g, 75%).

15 ¹H NMR (DMSO-d₆) δ 9.43-9.53 (bs, 2H), 8.11-8.16 (m, 1H), 7.47-7.55 (m, 2H), 7.38 (d, *J*=8.1 Hz, 1H), 7.31-7.36 (m, 1H), 6.98 (d, *J*=8.1 Hz, 1H), 6.71 (s, 1H), 6.17 (s, 1H), 3.98 (s, 3H), 2.17 (q, *J*=7.5 Hz, 2H), 0.73 (t, *J*=7.5 Hz, 3H);
ESMS calculated for (C₂₁H₁₉N₃O₃S) 393.11; Found 394.1(M+1)⁺.

20 Example 2: Synthesis of Compound 124

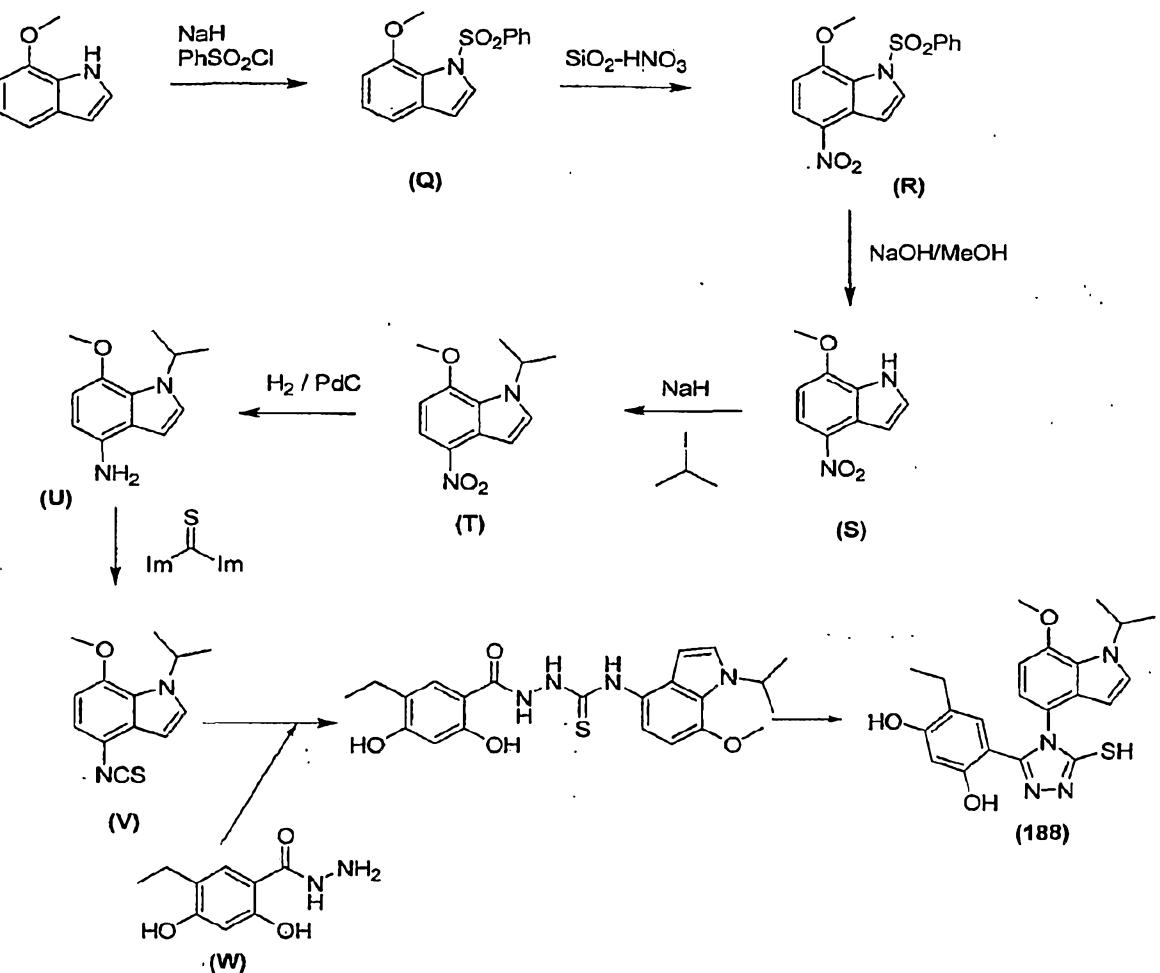
3-(2,4-Dihydroxy-phenyl)-4-(naphthalen-1-yl)-5-mercaptop-triazole (505 mg, 1.5 mmol), which is commercially available from Scientific Exchange, Inc., Center

Ossipee, NH 03814, and Et₃N (0.84ml, 6.0 mmol) in 15ml CH₂Cl₂ were treated dropwise with ethyl isocyanate (360mg, 5.0 mmol) at 0°C. The mixture was then warmed to room temperature and stirred for 3h. The reaction mixture was diluted with CH₂Cl₂, washed with H₂O and saturated brine, dried with Na₂SO₄, and 5 concentrated *in vacuo*. The residue was chromatographed (Hexane/ EtOAc 3:1) to give Compound 124 as a white solid (480 mg, 58%).

10 ¹H-NMR (CDCl₃) δ 10.13 (s, 1H), 7.96 (d, *J*=9.0 Hz, 2H), 7.61-7.57 (m, 3H), 7.49-7.36(m, 2H), 7.01(s, 1H), 6.88 (d, *J*=8.4Hz, 1H), 6.70 (d, *J*=8.4Hz, 1H), 4.98-4.96(m, 2H), 3.56(q, *J*=7.2 Hz, *J*=12.6 Hz, 2H), 3.28-3.10(m, 4H), 1.33(t, *J*=7.2 Hz, 3H), 1.13 (q, *J*=15.0 Hz, *J*=7.2Hz, 6H);

ESMS calculated for C₂₇H₂₈N₆O₅S: 548.18; Found: 549.1 (M+1)⁺.

Example 3: Synthesis of Compound 188



1-Benzene sulfonyl-7-methoxy-1H-indole (Q)

5 To a solution of 7-methoxyindole (1 eq) in DMF cooled in an ice bath was added NaH (60% dispersion in oil, 1.2 eq). The reaction was stirred for 1 hr at room temperature then recooled in an ice bath. Benzenesulfonyl chloride (1.1 eq) was added then the reaction was stirred for 2 hrs at room temperature. Water/ethyl acetate were added and the ethyl acetate layer was washed repeatedly (3x) with 10 water. The ethyl acetate layer was concentrated and evaporated to dryness.

1-Benzene sulfonyl-7-methoxy-4-nitro-1H-indole (R)

15 To a solution of 1-benzenesulfonyl-7-methoxy-1H-indole (Q) (1eq) in dichloromethane cooled in an ice bath was added SiO₂-HNO₃ (2 wt eq) in small portions. The reaction was stirred for 1 hr at room temperature. Activated carbon (2

wt eq) was added then the entire mixture was stirred for 1 hr. The mixture was then filtered and evaporated to dryness. Separation of the isomers was achieved by column chromatography.

5 **7-Methoxy-4-nitro-1H-indole (S)**

To a solution of 1-benzenesulfonyl-7-methoxy-4-nitro-1H-indole (R) (1 eq) in methanol was added a solution of sodium hydroxide (5 eq) in water. The solution was heated to reflux for 3 hrs. Methanol was removed under reduced pressure then water and ethyl acetate were added. The ethyl acetate layer separated and washed 10 repeatedly (3x) with water. The ethyl acetate layer was concentrated and evaporated to dryness to produce the desired product.

1-Isopropyl-7-methoxy-4-nitro-1H-indole (T)

To a solution of 7-methoxy-4-nitro-1H-indole (S) (1 eq) in DMF cooled in 15 an ice bath was added NaH (60% dispersion in oil, 1.2 eq). The reaction was stirred for 1 hr at room temperature then recooled in an ice bath. 2-Iodopropane (1.1 eq) was added then the reaction was stirred for 2 hrs at room temperature. Water and ethyl acetate were added. The ethyl acetate layer was separated and washed repeatedly (3x) with water. The ethyl acetate layer was concentrated then 20 evaporated to dryness. Further purification by column chromatography produced the pure desired product.

1-Isopropyl-7-methoxy-1H-indol-4-ylamine (U)

A solution of 1-isopropyl-7-methoxy-4-nitro-1H-indole (T) (1 eq) and 25 palladium 10% on activated carbon (0.1 wt eq) in methanol/ethyl acetate (1:1) was shaken on a Parr hydrogenation apparatus under hydrogen for 1 hr. The reaction was then filtered through Celite and evaporated to dryness to produce the desired product.

30 **1-Isopropyl-4-isothiocyanato-7-methoxy-1H-indole (V)**

To a solution of 1-isopropyl-7-methoxy-1H-indol-4-ylamine (U) (1 eq) in dichloromethane was added 1,1'-thiocarbonyldiimidazole (1.2 eq). The reaction was stirred for 2 hrs at room temperature then evaporated to dryness. Further purification by column chromatography produced the pure desired product.

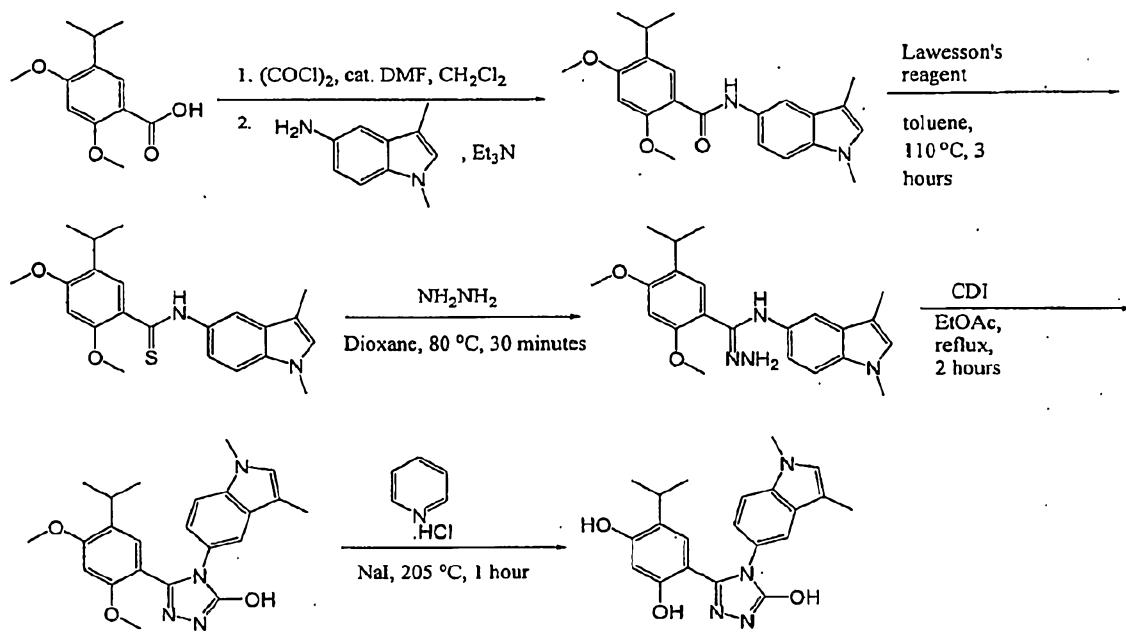
3-(2,4-Dihydroxy-5-ethyl-phenyl)-4-(1-isopropyl-7-methoxy-indol-4-yl)-5-mercapto-[1,2,4] triazole (Compound 188)

5-Ethyl-2,4-dihydroxy-benzoic acid hydrazide (W) (1 eq) and 1-isopropyl-4-
5 isothiocyanato-7-methoxy-1H-indole (V) (1.01 eq) were heated in ethanol (0.02 M
based on isothiocyanate) at 80°C for 1 hr. The solution was allowed to cool to room
temperature overnight. The resulting precipitate was filtered, washed with ether,
dried and used without further purification (yield 80%). The precipitate was
suspended in aqueous NaOH solution (2 eq NaOH) and nitrogen was bubbled
10 through this suspension for 10 min. The reaction was then heated to 110°C for 1 hr
under a nitrogen atmosphere then allowed to cool to room temperature.
Neutralisation with conc. HCl produced a white precipitate which was filtered and
washed with water. Repeated recrystallisation from EtOH/water produced the
desired product (purity >95%, yield 50-70%)

15

¹H-NMR (DMSO-d₆) δ (ppm), 9.52 (s, 1H), 9.42 (s, 1H), 7.40 (d, *J*=3.3 Hz,
1H), 6.82 (d, *J*=8.4 Hz, 1H), 6.61 (s, 1H), 6.20 (s, 1H), 6.05 (d, *J*=3.3 Hz, 1H), 5.30
(qn, *J*=6.6 Hz, 1H), 3.89 (s, 3H), 2.14 (q, *J*=7.5 Hz, 2H), 1.41-1.47 (m, 6H), 0.68 (t,
J=7.5 Hz, 3H);

20 **ESMS CALCULATED. FOR C₂₂H₂₄N₄O₃S: 424.16; FOUND: 425.1 (M+1)⁺.**

Example 4: Synthesis of Compound 223**Compound 223 :**

5 2,4-Dimethoxy-5-isopropylbenzoic acid (2.24 g, 10.0 mmol, 1.00 equiv.) in 50 mL CH_2Cl_2 at room temperature was treated with $(\text{COCl})_2$ (1.40 g, 11.0 mmol, 1.10 equiv.) and catalytic amount of DMF (0.1 mL) for 1 hour. Solvent and excess $(\text{COCl})_2$ were removed *in vacuo*. The residue was dissolved in 100 mL CH_2Cl_2 , and treated with 1,3-dimethyl-5-aminoindole (1.60 g, 10.0 mmol, 1.00 equiv.) and 10 triethylamine (1.55 g, 15.0 mmol, 1.50 equiv.) at 0°C for one hour. Aqueous workup and removal of solvent gave a light brown solid which was washed with ether to yield off-white solid (2.28g, 6.22 mmol, 62%).

15 ^1H NMR (CDCl_3) δ (ppm) 9.78 (br s, 1H), 8.21 (s, 1H), 8.09 (d, $J = 2.1$ Hz, 1H), 7.31 (dd, $J = 8.7$ Hz, 2.1 Hz, 1H), 7.22 (d, $J = 8.7$ Hz, 1H), 6.82 (s, 1H), 6.50 (s, 1H), 4.09 (s, 3H), 3.92 (s, 3H), 3.73 (s, 3H), 3.26 (hept, $J = 6.9$ Hz, 1H), 2.32 (s, 3H), 1.24 (d, $J = 6.9$ Hz, 6H).

20 The off-white solid obtained above was treated with Lawesson's reagent (1.51 g, 3.74 mmol, 0.6 equiv.) in 50 mL toluene at 110°C for three hours. Toluene was removed on rotary evaporator and vacuum pump, and the residue was treated with hydrazine (anhydrous, 3.0 g, 94 mmol, 15.0 equiv.) in 20 mL dioxane at 80°C

for 30 minutes. The reaction mixture was extracted with ethyl acetate and water to remove excess hydrazine. The organic layer was dried over MgSO_4 , and filtered to remove drying agent. Carbodiimidazole (CDI)(3.02 g, 18.7 mmol, 3.00 equiv.) was added to the solution, and the solution was refluxed (65°C) for 2 hours. Solvent was removed, and the residue was treated with 20 mL THF and 10 mL NaOH (2M) to destroy excess CDI. Extraction with ethyl acetate (EtOAc) and water, followed by chromatography purification gave the desired product 3-(2,4-methoxy-5-isopropyl-phenyl)-4-(1,3-dimethyl-indol-5-yl)-5-hydroxy-[1,2,4] triazole as light brown solid (2.20 g, 5.42 mmol, 87%).

10

^1H NMR (CDCl_3), δ (ppm) 9.63 (br s, 1H), 7.34 (d, $J = 2.1$ Hz, 1H), 7.20 (s, 1H), 7.18 (d, $J = 8.4$ Hz, 1H), 7.00 (dd, $J = 8.4$ Hz, 2.1 Hz, 1H), 6.80 (s, 1H), 6.19 (s, 1H), 3.76 (s, 3H), 3.69 (s, 3H), 3.40 (s, 3H), 3.15 (hept, $J = 6.9$ Hz, 1H), 2.20 (s, 3H), 1.10 (d, $J = 6.9$ Hz, 6H).

15

3-(2,4-methoxy-5-isopropyl-phenyl)-4-(1,3-dimethyl-indol-5-yl)-5-hydroxy-[1,2,4] triazole obtained above was treated with pyridine hydrochloride (12.53 g, 108.3 mmol, 20.0 equiv.), NaI (0.812 g, 5.42 mmol, 1.0 equiv.) and 0.5 mL water at 205°C under nitrogen protection for 1 hour. The reaction mixture was treated with 200 mL water. The solid was collected by filtration, washed with 3 x 20 mL water, and dissolved in 50 mL 2M NaOH solution. The aqueous solution was extracted with 100 mL EtOAc, and the EtOAc layer was extracted with 2 x 20 mL 0.5M NaOH. EtOAc layer was discarded. The aqueous layer were combined, neutralized with HCl to PH around 5, and extracted with 3 x 100 mL EtOAc. The combined EtOAc layer was diluted with 50 mL THF, dried over MgSO_4 , and filtered through silica gel plug. Most of solvents were removed to form a slurry with around 2 mL of solvent left. Solid was collected by filtration, washed with 2 mL EtOAc, and dried. The desired product 3-(2,4-dihydroxy-5-isopropyl-phenyl)-4-(1,3-dimethyl-indol-5-yl)-5-hydroxy-[1,2,4] triazole (**Compound 223**) was obtained as an off-white solid (1.75g, 4.63mmol, 85%).

¹H NMR (CD₃OD), δ (ppm) 7.46 (d, J = 1.8 Hz, 1H), 7.41 (d, J = 8.4 Hz, 1H), 7.04 (dd, J = 8.4 Hz, 1.8 Hz, 1H), 7.02 (s, 1H), 6.53 (s, 1H), 6.26 (s, 1H), 3.74 (s, 3H), 2.88 (sept, J = 6.9 Hz, 1H), 2.24 (s, 3H), 0.62 (d, J = 6.9 Hz, 6H);

5 ESMS calculated for C₂₁H₂₃N₄O₃: 378.1; Found: 379.1 (M + 1)⁺.

10 The following compounds were prepared as described above in the section entitled "Methods of Making the Compounds of the Invention" and as exemplified in Examples 1 through 4.

Example 5: Compound 1

ESMS calcd for C₁₈H₁₃N₃OS: 319.1; Found: 320.0 (M+1)⁺.

15

Example 6: Compound 2

ESMS calcd for C₂₁H₁₉N₃O₄S: 409.11; Found: 410.0 (M+H)⁺.

Example 7: Compound 5

20 ESMS calcd for C₁₉H₁₅N₃O₂S: 365.08; Found: 266.0 (M+H)⁺.

Example 8: Compound 6

ESMS calcd for C₂₀H₁₇N₃O₂S: 379.10; Found: 380.0 (M+H)⁺.

25 **Example 9: Compound 7**

ESMS calcd for C₂₁H₁₉N₃O₂S: 393.11; Found: 394.0 (M+H)⁺.

Example 10: Compound 8

ESMS calcd for C₂₁H₁₉N₃O₃S: 393.11; Found: 394.0(M+H)⁺.

30

Example 11: Compound 9

ESMS calcd for C₂₁H₁₉N₃O₂S: 393.11; Found: 394.0 (M+H)⁺.

Example 12: Compound 13

5 $^1\text{H-NMR}$ (DMSO-d₆) δ 9.65 (s, 1H), 9.57 (s, 1H), 7.50 (d, $J=8.1\text{Hz}$, 1H),
1.36 (t, $J=7.2\text{Hz}$, 3H);

ESMS calcd for C₁₈H₁₆N₄O₂S: 352.10; Found: 353.1 (M+1)⁺.

Example 13: Compound 14

10 $^1\text{H NMR}$ (DMSO-d₆) δ 9.72(s, 1H), 9.67(s, 1H), 7.04-7.01(m, 1H), 6.83-
6.78(m, 2H), 6.66-6.63(m, 1H), 6.20-6.19(m, 2H), 4.22(s, 4H);

ESMS calcd for C₁₆H₁₃N₃O₄S: 343.06; Found: 344.0 (M+1)⁺.

Example 14: Compound 15

15 ESMS calcd for C₁₅H₁₃N₃O₂S: 299.07; Found: 300.0 (M+H)⁺.

Example 15: Compound 16

ESMS calcd for C₁₅H₁₃N₃O₂S: 299.07; Found: 300.0 (M+H)⁺.

Example 16: Compound 17

20 ESMS calcd for C₁₄H₁₀ClN₃O₂S: 319.02; Found: 320.0 (M+H)⁺.

Example 17: Compound 18

ESMS calcd for C₁₄H₁₀ClN₃O₂S: 319.02; Found: 320.0 (M+H)⁺.

25 **Example 18: Compound 19**

ESMS calcd for C₁₄H₁₀ClN₃O₂S: 319.02; Found: 320.1 (M+H)⁺.

Example 19: Compound 20

ESMS calcd for C₁₅H₁₃N₃O₃S: 315.07; Found: 316.0 (M+H)⁺.

30

Example 20: Compound 21

ESMS calcd for C₁₅H₁₃N₃O₃S: 315.07; Found: 316.0 (M+H)⁺.

Example 21: Compound 22

ESMS calcd for C₁₅H₁₃N₃O₃S: 315.07; Found: 316.0 (M+H)⁺.

Example 22: Compound 23

5 ESMS calcd for C₁₄H₁₀FN₃O₂S: 303.05; Found: 304.0 (M+H)⁺.

Example 23: Compound 23

10 ¹H NMR (DMSO-d₆) δ 9.69 (s, 1H), 9.65 (s, 1H), 7.16 (d, J=7.2Hz, 1H),
7.05 (t, J=7.2Hz, 1H), 6.93 (d, J=8.1Hz, 2H), 6.11-6.16 (m, 2H), 2.21 (s, 3H), 1.89
(s, 3H);

ESMS Calcd C₁₆H₁₅N₃O₂S: 313.09, Found 314.1(M+1)⁺.

Example 24: Compound 24

15 ESMS calcd for C₁₆H₁₅N₃O₂S: 313.09; Found: 314.0 (M+H)⁺.

Example 25: Compound 25

16 ¹H NMR (DMSO-d₆) δ 10.44 (m, 1H), 8.00-7.95 (m, 2H), 7.55-7.37 (m, 5H),
6.61 (d, J = 7.8 and 1.8 Hz, 1H), 6.51 (t, J = 8.6 Hz, 1H), 6.41(d, J = 10.8 Hz, 1H);
ESMS calcd for C₁₈H₁₂FN₃OS: 337.07; Found: 338.0 (M+1)⁺.

20 **Example 26: Compound 26**
¹H NMR (DMSO-d₆) δ 9.57 (s, 1H), 7.99 (d, J = 8.4 Hz, 1H), 7.96 (d, J = 6.9
Hz, 1H), 7.55-7.37 (m, 5H), 6.61 (d, J = 8.1 Hz, 1H), 5.83 (d, J = 2.1 Hz, 1H),
5.73(dd, J = 8.1 and 1.8 Hz, 1H), 5.24 (s, 2H);
25 ESMS calcd for C₁₈H₁₄N₄OS: 334.09; Found: 335.0 (M+1)⁺.

Example 27: Compound 27

ESMS calcd for C₁₈H₁₉N₃O₂S: 341.12; Found: 342.0 (M+H)⁺.

30 **Example 28: Compound 28**

ESMS calcd for C₁₆H₁₅N₃O₂S: 313.09; Found: 314.0 (M+H)⁺.

Example 29: Compound 29

ESMS calcd for $C_{16}H_{15}N_3O_2S$: 313.09; Found: 314.0 ($M+H$)⁺.

Example 30: Compound 30

ESMS calcd for $C_{16}H_{15}N_3O_2S$: 313.09; Found: 314.0 ($M+H$)⁺.

5

Example 31: Compound 31

ESMS calcd for $C_{14}H_{10}FN_3O_2S$: 303.05; Found: 304.0 ($M+H$)⁺.

Example 32: Compound 32

10 ESMS calcd for $C_{15}H_{13}N_3O_2S$: 331.04; Found: 332.0 ($M+H$)⁺.

Example 33: Compound 33

ESMS calcd for $C_{18}H_{13}N_3O_2S$: 335.07; Found: 336.0 ($M+H$)⁺.

15 **Example 34: Compound 34**

ESMS calcd for $C_{16}H_{15}N_3O_2S$: 313.09; Found: 314.0 ($M+H$)⁺.

Example 35: Compound 35

ESMS calcd for $C_{15}H_{12}FN_3O_2S$: 317.06; Found: 317.0 ($M+H$)⁺.

20

Example 36: Compound 36

ESMS calcd for $C_{20}H_{15}N_3O_2S$: 361.1; Found: 362.0 ($M+1$)⁺.

Example 37: Compound 37

25 1H NMR (DMSO-d₆) δ 10.03 (s, 1H), 8.00-7.96 (m, 2H), 7.55-7.37 (m, 5H), 7.00 (d, J = 8.1 Hz, 1H), 6.20 (m, 2H), 3.57 (s, 3H);

ESMS calcd for $C_{19}H_{15}N_3O_2S$: 349.09; Found: 350.0 ($M+1$)⁺.

Example 38: Compound 38

30 ESMS calcd for $C_{14}H_9Cl_2N_3O_2S$: 352.98; Found: 353.9 ($M+H$)⁺.

Example 39: Compound 39

¹H NMR (DMSO-d₆) δ 9.74 (s, 1H), 9.63 (s, 1H), 8.14 (m, 1H), 7.52-7.48 (m, 2H), 7.37 (d, *J* = 8.4 Hz, 1H), 7.32 (m, 1H), 6.96 (d, *J* = 8.1 Hz, 1H), 6.90 (d, *J* = 8.4 Hz, 1H), 6.08 (d, *J* = 1.9 Hz, 1H), 6.01 (d, *J* = 8.4 Hz, 1H), 3.98 (s, 3H);
ESMS calcd for C₁₉H₁₅N₃O₃S: 365.08; Found: 366.0 (M+1)⁺.

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Example 40: Compound 40

ESMS calcd for C₂₅H₁₆N₃O₂S: 409.09; Found: 410.0 (M+1)⁺.

Example 41: Compound 42

10 ¹H NMR (DMSO-d₆) δ 9.75(s, 1H), 9.67(s, 1H), 7.08(s, 2H), 6.96-6.94(m, 2H), 6.18-6.13(m, 2H), 2.72-2.50(m, 3H), 2.35-2.28(m, 1H), 1.64-1.60(m, 4H);
ESMS calcd for C₁₈H₁₇N₃O₂S: 339.10; Found: 340.0 (M+1)⁺.

Example 42: Compound 43

15 ESMS calcd for C₂₂H₁₅N₃O₂S: 385.09; Found: 386.0 (M+1)⁺.

Example 43: Compound 44

ESMS calcd for C₂₀H₁₅N₃O₂S: 361.09; Found: 362.0 (M+1)⁺.

20 **Example 44: Compound 45**

ESMS calcd for C₁₉H₁₅N₃O₂S: 349.09; Found: 350.0 (M+1)⁺.

Example 45: Compound 46

ESMS calcd for C₁₉H₂₁N₃O₃S: 371.13; Found: 372.0 (M+1)⁺.

25

Example 46: Compound 47

ESMS calcd for C₂₂H₂₇N₃O₃S: 413.18; Found: 414.1 (M+1)⁺.

Example 47: Compound 48

30 ESMS calcd for C₁₈H₁₂ClN₃O₂S: 369.03; Found: 370.0 (M+H)⁺.

Example 48: Compound 49

¹H NMR (DMSO-d₆) δ 9.49 (s, 1H), 9.40 (s, 1H), 7.94-7.99 (m, 2H), 7.38-7.56 (m, 5H), 6.70 (s, 1H), 6.13 (s, 1H), 2.12 (q, *J*=7.2 Hz, 2H), 0.71 (t, *J*=7.2 Hz, 3H);

ESMS Calcd for $C_{20}H_{17}N_3O_2S$: 363.10, Found 364.1(M+1)⁺.

5

Example 49: Compound 50

ESMS calcd for $C_{20}H_{15}N_3O_5S$: 409.07; Found: 410.0 ($M+H$)⁺.

Example 50: Compound 51

10 ESMS calcd for $C_{18}H_{14}N_4O_2S$: 350.08; Found: 351.0 ($M+H$)⁺.

Example 51: Compound 52

ESMS calcd for $C_{17}H_{12}N_4OS$: 320.07; Found: 320.9 ($M + H$)⁺.

15 Example 52: Compound 53

¹H NMR (CDCl₃) δ 12.0 (br s, 1H), 9.87 (br s, 1H), 9.83 (br s, 1H), 7.97 (d, *J* = 8.1 Hz, 2H), 7.41-7.56 (m, 5H), 7.13 (d, *J* = 1.5 Hz, 1H), 7.07 (d, *J* = 8.7 Hz, 1H), 6.71 (dd, *J* = 1.8 Hz, 8.1 Hz, 1H), 1.93 (s, 3H);

ESMS calcd for $C_{20}H_{17}N_4O_2S$: 376.1; Found: 377.0(M+1)⁺.

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Example 53: Compound 56

ESMS calcd for $C_{16}H_{15}N_3O_4S$: 345.08; Found: 346.0 ($M+1$)⁺.

Example 54: Compound 57

25

ESMS calcd for $C_{18}H_{16}N_4O_2S$: 352.10; Found: 353.0 ($M+1$)⁺.

Example 55: Compound 61

¹H NMR (DMSO-d₆) δ 9.66(s, 1H), 9.60(s, 1H), 7.29-7.27(m, 1H), 7.12-7-10(m, 2H), 7.03-7.00(m, 1H), 6.19-6.17(m, 2H), 1.18(s, 18H);

30

ESMS calcd for $C_{22}H_{27}N_3O_2S$: 397.18; Found: 398.1 ($M+1$)⁺.

Example 56: Compound 64

ESMS calcd for $C_{21}H_{15}N_3O_3S$: 389.08; Found: 390.0 ($M+H$)⁺.

Example 57: Compound 65

ESMS calcd for C₁₉H₁₃N₃O₄S: 379.06; Found: 380.0 (M+1)⁺.

5 **Example 58: Compound 66**

ESMS calcd for C₂₁H₁₈N₄O₃S: 406.11; Found: 407.0 (M+1)⁺.

Example 59: Compound 67

ESMS calcd for C₂₁H₁₉N₃O₃S: 393.11; Found: 394.0 (M+1)⁺.

10

Example 60: Compound 68

ESMS calcd for C₂₁H₁₉N₃O₃S: 393.11; Found: 394.0 (M+1)⁺.

Example 61: Compound 69

15

ESMS calcd for C₂₁H₁₉N₃O₃S: 393.11; Found: 394.0 (M+1)⁺.

Example 62: Compound 70

ESMS calcd for C₁₇H₁₂N₄O₂S: 336.07; Found: 337.0 (M+H)⁺.

20

Example 63: Compound 71

ESMS calcd for C₂₁H₁₉N₃O₃S: 393.11; Found: 394.0 (M+1)⁺.

Example 64: Compound 72

25 ¹H NMR (DMSO-d₆) δ 10.3 (br s, 1H), 7.95-8.19 (m, 2H), 7.48-7.72 (m, 5H), 7.17 (d, J = 8.4 Hz, 1H), 6.44 (d, J = 8.4 Hz, 1H), 5.95 (d, J = 2.1 Hz, 1H), 5.73 (dd, J = 2.1 Hz, 8.4 Hz, 1H), 5.47 (br s, 1H), 3.62 (s, 3H);

ESMS calcd for C₁₉H₁₇N₄O₂S₂: 412.1; Found: 413.0(M+1)⁺.

Example 65: Compound 73

30 ¹H NMR (DMSO-d₆) δ 9.37 (s, 1H), 8.94 (s, 1H), 7.94-7.98 (m, 2H), 7.43-7.60 (m, 5H), 5.97 (s, 1H), 1.85 (s, 3H), 1.81 (s, 3H);

ESMS calcd for C₂₀H₁₈N₃O₂S: 363.1; Found: 364.0(M+1)⁺.

Example 66: Compound 74

ESMS calcd for $C_{21}H_{19}N_3O_4S$: 409.11; Found: 410.0 $(M+H)^+$.

Example 67: Compound 75

5 1H NMR (DMSO-d₆) δ 9.46 (s, 1H), 9.45 (s, 1H), 7.95-8.00 (m, 2H), 7.38-7.56 (m, 5H), 6.65 (s, 1H), 6.15 (s, 1H), 2.07-2.14 (m, 2H), 0.81-1.18 (m, 11H);
ESMS calcd for $C_{24}H_{26}N_3O_2S$: 419.1; Found: 420.1 $(M+1)^+$.

Example 68: Compound 76

10 ESMS calcd for $C_{21}H_{19}N_3O_3S$: 393.11; Found: 394.0 $(M+H)^+$.

Example 69: Compound 77

ESMS calcd for $C_{21}H_{19}N_3O_3S$: 393.11; Found: 394.0 $(M+H)^+$.

15 **Example 70: Compound 78**

1H NMR (DMSO-d₆) δ 9.71 (s, 1H), 9.35 (s, 1H), 7.98-8.04 (m, 2H), 7.50-7.62 (m, 5H), 6.58 (s, 1H), 2.15 (q, $J = 7.5$ Hz, 2H), 0.58 (t, $J = 7.5$ Hz, 3H);
ESMS calcd for $C_{20}H_{17}ClN_3O_2S$: 397.0; Found: 398.0 $(M+1)^+$.

20 **Example 71: Compound 79**

ESMS calcd for $C_{19}H_{21}N_3O_3S$: 371.13; Found: 372.0 $(M+H)^+$.

Example 72: Compound 80

ESMS calcd for $C_{21}H_{19}N_3O_2S$: 393.11; Found: 394.0 $(M+H)^+$.

25

Example 73: Compound 81

ESMS calcd for $C_{20}H_{17}N_3O_2S$: 379.10; Found: 380.0 $(M+H)^+$.

Example 74: Compound 82

30 ESMS calcd for $C_{21}H_{19}N_3O_3S$: 393.11; Found: 394.0 $(M+H)^+$.

Example 75: Compound 83

ESMS calcd for $C_{20}H_{17}N_3O_3S$: 379.10; Found: 380.0 $(M+H)^+$.

Example 76: Compound 84

ESMS calcd for C₂₀H₁₇N₃O₃S: 379.10; Found: 380.0 (M+H)⁺.

5 Example 77: Compound 85

ESMS calcd for C₁₉H₁₅N₃O₂S: 365.08; Found: 266.0 (M+H)⁺.

Example 78: Compound 86

10 ¹H NMR (DMSO-d₆) δ 9.68 (s, 1H), 9.58 (s, 1H), 8.2 (dd, *J* = 7.0 and 2.4 Hz, 1H), 7.50 (m, 2H), 7.40 (tr, *J* = 8.1 Hz, 1H), 7.32 (m, 1H), 6.97 (d, *J* = 7.5 Hz, 1H), 6.95 (m, 1H), 6.89 (d, *J* = 8.4 Hz, 1H), 6.08 (d, *J* = 2.1 Hz, 1H), 6.0 (dd, *J* = 7.4 and 2.1 Hz, 1H), 3.96 (s, 3H);

ESMS calcd for C₁₉H₁₅N₃O₃S: 365.08; Found: 366.0 (M+1)⁺.

15 Example 79: Compound 87

15 ¹H NMR (MeOH-d₄) δ 8.25 (m, 1H), 7.96 (s, 1H), 7.46-7.44 (m, 2H), 7.26 (d, *J* = 8.4 Hz, 1H), 6.83 (d, *J* = 8.1 Hz, 1H), 6.70 (d, *J* = 8.7 Hz, 1H), 6.17 (d, *J* = 2.1 Hz, 1H), 5.98 (dd, *J* = 8.4 and 2.4 Hz, 1H);

ESMS calcd for C₁₈H₁₃N₃O₃S: 351.07; Found: 352.0 (M+1)⁺.

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Example 80: Compound 88

20 ¹H-NMR (DMSO-d₆) δ 9.69 (s, 1H), 9.59 (s, 1H), 7.54 (d, *J*=8.1Hz, 1H), 7.46 (d, *J*=3Hz, 1H), 7.14 (t, *J*=7.8 Hz, 1H), 6.97 (d, *J*=7.2 Hz, 1H), 6.89 (d, *J*=8.7Hz, 1H), 6.12-6.13 (m, 2H), 6.02 (dd, *J*₁=2.4 Hz, *J*₂=8.4 Hz, 1H), 4.74 (qn, *J*=6.6Hz, 1H), 1.40-1.46 (m, 6H);

ESMS calcd for C₁₉H₁₈N₄O₂S: 366.12; Found: 367.1 (M+1)⁺.

Example 81: Compound 89

ESMS calcd for C₂₂H₂₁N₃O₂S: 391.14; Found: 392.0 (M+H)⁺.

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Example 82: Compound 90

¹H NMR (DMSO-d₆) δ 9.47 (s, 1H), 9.43 (s, 1H), 7.94-8.00 (m, 2H), 7.39-7.57 (m, 5H), 6.68 (s, 1H), 6.15 (s, 1H), 2.05-2.15 (m, 2H), 1.05-1.17 (m, 2H), 0.50 (t, *J* = 7.5 Hz, 3H); ESMS calcd for C₂₁H₂₀N₃O₂S: 377.1; Found: 378.0(M+1)⁺.

5 **Example 83: Compound 91**

¹H NMR (DMSO-d₆) δ 9.15 (s, 1H), 8.50 (s, 1H), 8.00-8.07 (m, 2H), 7.47-7.63 (m, 5H), 6.27 (s, 1H), 2.06 (q, *J* = 7.5 Hz, 2H), 1.93 (s, 3H), 0.45 (t, *J* = 7.5 Hz, 3H);

ESMS calcd for C₂₁H₂₀N₃O₂S: 377.1; Found: 378.0(M+1)⁺.

10

Example 84: Compound 93

ESMS calcd for C₁₆H₁₅N₃O₄S: 345.08; Found: 346.0 (M+H)⁺.

Example 85: Compound 95

15 ESMS calcd for C₁₆H₁₂N₄O₂S: 324.07; Found: 325.0 (M+H)⁺.

Example 86: Compound 96

ESMS calcd for C₁₉H₁₈N₄O₃S: 382.11; Found: 383.0 (M+H)⁺.

20

Example 87: Compound 98

ESMS calcd for C₁₇H₁₂N₄O₂S: 336.07; Found: 337.0 (M+H)⁺.

Example 88: Compound 99

ESMS calcd for C₁₉H₁₃N₃O₄S: 379.06; Found: 379.9 (M+H)⁺.

25

Example 89: Compound 100

¹H-NMR (DMSO-d₆) δ 9.52 (s, 1H), 9.42 (s, 1H), 7.56 (d, *J*=8.7Hz, 1H), 7.49 (d, *J*=3.3Hz, 1H), 7.14 (t, *J*=7.5 Hz, 1H), 6.95 (d, *J*=8.4Hz, 1H), 6.61 (s, 1H), 6.21 (s, 1H), 6.14 (dd, *J*=3.3Hz, 1H), 4.76 (qn, *J*=6.6Hz, 1H), 2.14 (q, *J*=7.5Hz, 2H), 1.41-1.47 (m, 6H), 0.66 (t, *J*=7.5Hz, 3H);

ESMS calcd for C₂₁H₂₂N₄O₂S: 394.15; Found: 395.1 (M+1)⁺.

Example 90: Compound 101

ESMS calcd for $C_{19}H_{17}N_5O_3S$: 395.11; Found: 396.0 $(M+H)^+$.

Example 91: Compound 102

ESMS calcd. for $C_{19}H_{20}N_5O_2S$: 381.1; Found: 382.0 $(M + 1)^+$.

5

Example 92: Compound 103

1H NMR (DMSO-d₆) δ 9.48 (s, 1H), 9.38 (s, 1H), 7.29(d, $J = 8.4$ Hz, 1H), 7.25(d, $J = 1.8$ Hz, 1H), 6.85-6.89 (m, 2H), 6.18 (s, 1H), 3.61 (s, 3H), 2.30 (s, 3H), 2.29 (q, $J = 7.5$ Hz, 2H), 2.09 (s, 3H), 0.94 (t, $J = 7.5$ Hz, 3H);

10 ESMS calcd for $C_{21}H_{23}N_4O_2S$: 394.1; Found: 395.0 $(M+1)^+$.

Example 93: Compound 104

ESMS calcd for $C_{19}H_{15}N_3O_3S$: 365.08; Found: 366.0 $(M+H)^+$.

15 **Example 94: Compound 106**

ESMS calcd for $C_{20}H_{17}N_4O_2S$: 377.1; Found: 378.0 $(M+H)^+$.

Example 95: Compound 107

ESMS calcd for $C_{18}H_{13}ClN_3O_2S$: 369.0; Found: 370.0 $(M+H)^+$.

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Example 96: Compound 116

1H NMR (DMSO-d₆) δ 7.98-7.56 (m, 2H), 7.55-7.30 (m, 6H), 6.43 (dd, $J = 8.1$ and 1.8 Hz, 1H), 6.29 (m, 1H), 3.65 (s, 3H), 3.16 (s, 3H);

ESMS calcd for $C_{20}H_{17}N_3O_2S$: 363.10; Found: 364.0 $(M+1)^+$.

25

Example 97: Compound 117

1H -NMR (CDCl₃) δ 7.83(d, $J=8.1$ Hz, 2H), 7.48-7.34(m, 4H), 7.28-7.20(m, 1H), 6.99 (d, $J=1.8$ Hz, 1H), 6.80(d, $J=8.7$ Hz, 1H), 6.62-6.58(m, 1H), 2.94(s, 3H), 2.89(s, 3H), 2.84(s, 3H), 2.81(s, 3H), 2.75-2.69(m, 6H);

30 ESMS calcd for $C_{27}H_{28}N_6O_5S$: 548.18; Found: 549.2 $(M+1)^+$.

Example 98: Compound 122

¹H-NMR (CDCl₃) δ 7.98(m, 2H), 7.60-7.55(m, 3H), 7.51-7.45(m, 1H), 7.36-7.33(m, 1H), 6.98-6.97(m, 1H), 6.86(d, J=9.9Hz, 1H), 6.70-6.67(m, 1H), 2.86(s, 3H), 2.26(s, 3H), 2.21(s, 3H);

ESMS calcd for C₂₄H₁₉N₃O₅S: 461.10; Found: 462.0 (M+1)⁺.

5

Example 99: Compound 125

ESMS calcd for C₂₀H₁₇N₃O₃S: 379.10; Found: 380.0 (M+H)⁺.

Example 100: Compound 126

10 ESMS calcd for C₁₀H₁₁N₃O₂S: 237.06; Found: 238.0 (M+H)⁺.

Example 101: Compound 127

ESMS calcd for C₁₁H₁₃N₃O₂S: 251.07; Found: 252.0 (M+H)⁺.

15 **Example 102: Compound 128**

ESMS calcd for C₁₁H₁₃N₃O₂S: 251.07; Found: 252.0 (M+H)⁺.

Example 103: Compound 129

ESMS calcd for C₁₁H₁₁N₃O₂S: 249.06; Found: 250.0 (M+H)⁺.

20

Example 104: Compound 130

ESMS calcd for C₁₂H₁₅N₃O₂S: 265.09; Found: 266.0 (M+H)⁺.

Example 105: Compound 131

25 ESMS calcd for C₂₀H₁₅N₃O₄S: 393.08; Found: 394.1 (M+H)⁺.

Example 106: Compound 177

¹H NMR (DMSO-d₆) δ 9.34(s, 1H), 9.22 (s, 1H), 8.01-7.96 (m, 2H), 7.58-7.44 (m, 5H), 6.56 (s, 1H), 6.14 (s, 1H), 3.29 (s, 3H);

30 ESMS calcd for C₁₉H₁₅N₃O₃S: 365.08; Found: 366.0(M+1)⁺.

Example 107: Compound 178

¹H NMR (DMSO-d₆) δ 10.29 (s, 1H), 9.49 (s, 1H), 9.42 (s, 1H), 8.16 (t, *J* = 5.1 Hz, 1H), 7.45-7.43 (m, 2H), 7.26 (t, *J* = 8.0 Hz, 1H), 6.84 (d, *J* = 7.8 Hz, 1H), 6.75 (d, *J* = 8.7 Hz, 1H), 6.66 (s, 1H), 6.14 (s, 1H), 2.12 (q, *J* = 7.5 Hz, 2H), 0.70 (t, *J* = 7.2 Hz, 3H);

5 ESMS calcd for C₂₀H₁₇N₃O₃S: 379.10; Found: 379.9 (M+1)⁺.

Example 108: Compound 179

ESMS calcd for C₁₉H₁₅N₃O₂S: 349.09; Found: 350.0 (M+1)⁺.

10 **Example 109: Compound 180**

ESMS calcd for C₁₉H₁₅N₃O₂S: 349.09; Found: 350.0 (M+H)⁺.

Example 110: Compound 181

ESMS calcd for C₂₀H₁₅N₃O₂S: 361.09; Found: 362.0 (M+H)⁺.

15

Example 111: Compound 182

ESMS calcd for C₁₆H₁₅N₃O₃S: 329.08; Found: 330.0 (M+H)⁺.

Example 112: Compound 183

20 ESMS calcd for C₂₀H₁₇N₃O₂S: 363.10; Found: 364.0 (M+H)⁺.

Example 113: Compound 184

ESMS calcd for C₁₈H₁₃N₃O₃S: 350.38; Found: 351.9(M+H)⁺.

25 **Example 114: Compound 185**

ESMS calcd. for C₂₀H₂₁N₄O₂S: 380.1; Found: 381.0 (M + 1)⁺.

Example 115: Compound 187

ESMS calcd. for C₁₉H₂₀N₅O₂S: 381.1; Found: 382.0 (M + 1)⁺.

30

Example 116: Compound 190

ESMS CALCD. FOR C₂₁H₂₂N₄O₂S: 394.15; FOUND: 395.0 (M+1)⁺.

Example 117: Compound 191

ESMS calcd. for $C_{22}H_{23}N_4O_4S$: 438.1; Found: 439.0 $(M + 1)^+$.

Example 118: Compound 192

ESMS calcd. for $C_{20}H_{22}N_5O_2S$: 395.1; Found: 396.0 $(M + 1)^+$.

5

Example 119: Compound 193

ESMS calcd. for $C_{20}H_{22}N_5O_2S$: 395.1; Found: 396.0 $(M + 1)^+$.

Example 120: Compound 194

10 ESMS calcd. for $C_{23}H_{27}N_4O_2S$: 422.1; Found: 423.0 $(M + 1)^+$.

Example 121: Compound 195

ESMS calcd. for $C_{23}H_{25}N_4O_2S$: 420.1; Found: 421.0 $(M + 1)^+$.

15 **Example 122: Compound 196**

ESMS calcd. for $C_{25}H_{29}N_4O_2S$: 448.1; Found: 449.3 $(M + 1)^+$.

Example 123: Compound 197

ESMS calcd. for $C_{22}H_{24}N_4O_2S$: 408.16; Found: 409.2 $(M + 1)^+$.

20

Example 124: Compound 198

ESMS calcd. for $C_{23}H_{26}N_4O_2S$: 422.18; Found: 423.3 $(M + 1)^+$.

Example 125: Compound 199

25 ESMS calcd. for $C_{24}H_{28}N_4O_2S$: 436.19; Found: 437.3 $(M + 1)^+$.

Example 126: Compound 200

ESMS calcd. for $C_{22}H_{22}N_4O_2S$: 406.15; Found: 407.2 $(M + 1)^+$.

30 **Example 127: Compound 201**

ESMS calcd. for $C_{23}H_{24}N_4O_3S$: 436.16; Found: 437.3 $(M + 1)^+$.

Example 128: Compound 202

ESMS calcd. for $C_{22}H_{23}N_4O_2S$: 406.1; Found: 407.0 $(M + H)^+$.

Example 129: Compound 204

ESMS calcd. for $C_{24}H_{28}N_4O_3S$: 452.19; Found: 453.2 $(M+1)^+$.

5 **Example 130: Compound 205**

ESMS calcd. for $C_{23}H_{24}N_4O_3S$: 436.16; Found: 437.1 $(M+1)^+$.

Example 131: Compound 206

ESMS calcd. for $C_{21}H_{23}N_4O_2S$: 394.1; Found: 395.1 $(M + 1)^+$.

10

Example 132: Compound 207

ESMS calcd. for $C_{20}H_{21}N_4O_2S$: 380.1; Found: 381.1 $(M + 1)^+$.

Example 133: Compound 208

15

ESMS calcd. for $C_{23}H_{26}N_4O_3S$: 438.17; Found: 439.1 $(M+1)^+$.

Example 134: Compound 209

ESMS calcd. for $C_{22}H_{24}N_4O_2S$: 408.1; Found: 409.1 $(M + 1)^+$.

20

Example 135: Compound 210

ESMS calcd. for $C_{24}H_{23}N_4O_2S$: 430.1; Found: 431.1 $(M + 1)^+$.

Example 136: Compound 211

25

ESMS calcd. for $C_{21}H_{22}N_4O_3S$: 410.14; Found: 411.1 $(M+1)^+$.

Example 137: Compound 212

ESMS calcd. for $C_{23}H_{26}N_4O_3S$: 438.17; Found: 439.1 $(M+1)^+$.

Example 138: Compound 213

30

ESMS calcd. for $C_{20}H_{21}N_4O_2S$: 380.1; Found: 381.1 $(M + 1)^+$.

Example 139: Compound 214

ESMS calcd. for $C_{19}H_{19}N_4O_2S$: 366.1; Found: 367.1 $(M + 1)^+$.

Example 140: Compound 215

ESMS calcd. for $C_{20}H_{19}N_3O_4S$: 397.1; Found: 398.1 ($M+1$)⁺.

Example 141: Compound 216

5 1H NMR (DMSO-d₆): δ (ppm) 9.56 (s, 1H), 9.40 (s, 1H), 8.03 (d, J = 2.4 Hz, 1H), 7.58 (d, J = 8.4 Hz, 1H), 7.54 (d, J = 2.1 Hz, 1H), 7.11 (dd, J = 8.4, 2.1 Hz, 1H), 6.97 (d, J = 2.4 Hz, 1H), 6.89 (s, 1H), 6.17 (s, 1H), 2.23 (q, J = 7.2 Hz, 2H), 0.93 (t, J = 7.2 Hz, 3H);

10 ESMS calcd. for $C_{18}H_{15}N_3O_3S$: 353.08; Found: 354.0 ($M+1$)⁺.

10

Example 142: Compound 217

15 1H NMR (DMSO-d₆): δ (ppm) 9.59 (s, 1H), 9.43 (s, 1H), 7.67 (d, J = 8.7 Hz, 1H), 7.54 (d, J = 2.1 Hz, 1H), 7.20 (dd, J = 8.4, 2.1 Hz, 1H), 6.96 (s, 1H), 6.18 (s, 1H), 2.60 (s, 3H), 2.34 (q, J = 7.2 Hz, 2H), 0.98 (t, J = 7.2 Hz, 3H);

15

ESMS calcd. for $C_{18}H_{16}N_4O_3S$: 368.09; Found: 369.0 ($M+1$)⁺.

Example 143: Compound 218

ESMS calcd. for $C_{21}H_{23}N_4O_2S$: 394.1; Found: 395.1 ($M + 1$)⁺.

20

Example 144: Compound 219

ESMS calcd. for $C_{21}H_{21}N_4O_2S$: 392.1; Found: 393.1 ($M + 1$)⁺.

Example 145: Compound 220

25 ESMS calcd. for $C_{20}H_{21}N_4O_3$: 364.1; Found: 365.1 ($M + 1$)⁺.

25

Example 146: Compound 221

ESMS calcd. for $C_{20}H_{21}N_4O_2S$: 379.1; Found: 381.1 ($M + 1$)⁺.

Example 147: Compound 222

30

ESMS calcd. for $C_{21}H_{23}N_4O_2S$: 394.1; Found: 395.1 ($M + 1$)⁺.

Example 148: Compound 224

ESMS calcd. for $C_{19}H_{21}N_4O_2S$: 368.1; Found: 369.1 ($M + 1$)⁺.

Example 149: Compound 225

ESMS calcd. for $C_{19}H_{19}N_4O_2S$: 366.1; Found: 367.1 ($M + 1$)⁺.

5 Example 150: Compound 226

ESMS calcd. for $C_{20}H_{21}N_4O_3$: 364.1; Found: 365.1 ($M + 1$)⁺.

Example 151: Compound 227

ESMS calcd. for $C_{21}H_{22}N_4O_2S$: 394.15; Found: 395.1 ($M + 1$)⁺.

10

Example 152: Compound 228

ESMS calcd. for $C_{22}H_{24}N_4O_2S$: 408.16; Found: 409.1 ($M + 1$)⁺.

15

Example 153: Compound 229

ESMS calcd. for $C_{20}H_{18}F_3N_5O_2S$: 449.11; Found: 450.1 ($M + 1$)⁺.

20

Example 154: Compound 230

ESMS calcd. for $C_{19}H_{19}N_5O_2S$: 381.13; Found: 382.1 ($M + 1$)⁺.

25

Example 155: Compound 231

ESMS calcd. for $C_{19}H_{19}N_5O_2S$: 381.13; Found: 382.1 ($M + 1$)⁺.

25

Example 156: Compound 232

ESMS calcd. for $C_{22}H_{24}N_4O_3S$: 392.18; Found: 393.1 ($M + 1$)⁺.

25

Example 157: Compound 233

ESMS calcd. for $C_{18}H_{17}N_3O_4S$: 371.09; Found: 372.1 ($M + 1$)⁺.

30

Example 158: Compound 234

ESMS calcd. for $C_{20}H_{21}N_3O_2S$: 367.14; Found: 368.1 ($M + 1$)⁺.

Example 159: Compound 235

ESMS calcd. for $C_{19}H_{19}N_5O_2S$: 381.13; Found: 382.1 ($M + 1$)⁺.

Example 160: Compound 239

ESMS clcd for $C_{19}H_{21}N_4O_2S$: 368.1; Found: 369.1 ($M + H$)⁺.

Example 161: Compound 240

5 ESMS clcd for $C_{18}H_{16}N_4O_3S$: 368.09.10; Found: 369.1 ($M + H$)⁺.

Example 162: Compound 241

ESMS clcd for $C_{17}H_{15}N_5O_3S$: 369.09; Found: 370.1 ($M + H$)⁺.

10 **Example 163: Compound 242**

ESMS clcd for $C_{19}H_{18}N_4O_3S$: 382.11; Found: 383.1 ($M + H$)⁺.

Example 164: Compound 243

ESMS clcd for $C_{22}H_{26}N_4O_3S$: 426.17; Found: 427.1 ($M + H$)⁺.

15

Example 165: Compound 244

ESMS clcd for $C_{18}H_{16}N_4O_4S$: 384.09; Found: 385.1 ($M + H$)⁺

Example 166: Compound 245

20 ESMS clcd for $C_{18}H_{16}N_4O_3S_2$: 400.07; Found: 401.1 ($M + H$)⁺

Example 167: Compound 245

ESMS clcd for $C_{17}H_{14}N_4O_3S_2$: 386.05; Found: 387.0 ($M + H$)⁺.

25 **Example 168: Inhibition of HUVEC cell migration**

To examine if the compounds of the invention affect endothelial cell function, an *in vitro* human umbilical vein endothelial cell (HUVEC) migration assay was performed in the presence of Compound 226. HUVEC cells (ATCC, VA) (passage number 4) were cultured in EGM2 medium (Cambrex, MA) on 12-well plates and performed time-lapse imaging with the live cell imaging system on an inverted microscope supplied with 6-7% CO₂. The temperature was kept at 37°C. Images were taken every 30 minutes using the 2X objective for up to 106 hr (results in Fig. 1, 2 and 3), or, every 60 seconds using the 20X objective for 30 min (for Fig. 4). Confluent HUVEC cultures were scraped similarly to make a blank area,

followed by culturing in HUVEC medium for 15 hr without treatment. The migration areas, which were imaged as time-lapse sequences for each well, were used as a basis to standardize/correct migration rates. Then, migration of cells under different treatments was imaged at the same time to generate time-lapse image sequences for each well. Time-lapse movies were further analyzed by measuring areas that were covered by migrating cells. Fig. 1 shows cell migration during compound treatment in different time points (0, 24, 48, 72 and 106 hrs). The red lines indicate the front lines of migrating cells. DMSO (1:100) treated cells migrated rapidly and covered the entire blank (wounded) area at 106 hr. However, compared to DMSO, Compound 226 (100 nM and 1 μ M) completely blocked migration of HUVEC cells to the blank area. The quantitative analysis of Fig. 1 is shown in Fig. 2. This demonstrates that covered areas were similar between Compound 226, 100 nM and 1 μ M treatment, indicating that the IC₅₀ of the inhibition should be below 100 nM. As a reference, a separate experiment was performed and showed that the IC₅₀ of Compound 226 for HUVEC killing was around 800 nM. Images with larger magnification (Fig. 3) showed that no significant cell death was seen at 24 hr, suggesting that the observed migration inhibition was due to the limited motility of HUVEC cells and not due to cell death. During experiments, HUVEC cells were activated by the presence of VEGF (Cambrex, MA) and basic FGF (Cambrex, MA). Compound 226 possesses potent inhibitory effect on the migration of activated HUVEC cell *in vitro* induced by VEGF and basic FGF.

In addition to the analysis of HUVEC cell migration, HUVEC behavior was also tracked during above treatments. We found HUVEC cells began to shrink after 24 hr treatment with 100nM and 1 μ M Compound 226. The green arrows in Fig. 2 show that at 48 hr HUVEC cells retracted due to the shrinking of the entire population. However, despite of cell shrinkage, the majority of cells were alive at 48 hr even under 1 μ M Compound 226 treatment (see Fig. 3). Careful examination under larger magnification of microscopy (Fig. 4) reveals that HUVEC cells treated with Compound 226 at 100nM or above appeared to contact to each other tightly. Cell-cell contact lines disappeared in 100nM Compound 226 treated population in both magnifications in Fig. 4. In time-lapse videos captured with larger magnification objective (20x), significantly reduced movement of HUVEC cells was observed when treated with 100nM Compound 226, which was distinct from that of

DMSO treated cells that moved in rapid speed. These changes of HUVEC cell behavior and morphology suggested that Compound 226 may affect HUVEC cell-cell junction (see Example 169).

5 **Example 169: Compound 226 enhanced VE-cadherin junctions of HUVEC cells**

An immunofluorescence study was performed by using anti-VE-cadherin antibodies (1:1 mixed, obtained from Amersham Biosciences, NJ, and Santa Cruz Biotechnology, CA) to examine VE-cadherin junctions between HUVEC cells.

HUVEC cells were treated with DMSO or Compound 226 (10, 100 and 1000nM)

10 for 24 hrs and fixed for immunostaining. DMSO concentration was 1:100 for all treatments. To boost the immunofluorescence signal, cells were stained with a mixture of 2 polyclonal anti-human VE-cadherin Abs followed by staining with a mixture of fluorescent secondary antibodies. Fig. 5 shows that VE-cadherin was stained strongly at the cell-cell junctions (red arrows in DMSO), but not the non-contacted regions of cells (green arrows), in the DMSO control. Non-DMSO treated cells gave a similar result to those with DMSO treatment (data not shown).

15 Surprisingly, with 10nM Compound 226 treatment, VE-cadherin staining was extremely strong in cell-cell junction regions, but not the non-contacted regions (red arrow in Compound 226 10nM) compared to that in DMSO treated cultures.

20 Increasing the Compound 226 concentration to 100nM seemed to further increase the VE-cadherin staining areas (red arrows in Compound 226 100nM). Aggregations of VE-cadherin molecules appeared in wells treated with higher concentration (1 μ M). These results strongly suggest that Compound 226 enhances the assembly of cell-cell junctions of activated human endothelial cells, likely through induction of 25 the accumulation of VE-cadherin molecules at the junctions. This effect could result in limited motility of the cells and reducing permeability of the endothelium, thus contributing to the cell migration inhibition and the potential anti-angiogenesis effect of Compound 226.

30 **Example 170: Necrosis in a *nude* Mouse Tumor Model**

The mouse mammary carcinoma cell line, EMT6 (ATCC #CRL-2755), is obtained from the American Type Culture Collection (ATCC; Manassas, Virginia, USA). The cell line is cultured in growth media prepared from 50% Dulbecco's

Modified Eagle Medium (high glucose), 50% RPMI Media 1640, 10% fetal bovine serum (FBS), 1% 100X L-glutamine, 1% 100X Penicillin-Streptomycin, 1% 100X sodium pyruvate and 1% 100X MEM non-essential amino acids. FBS is obtained from ATCC and all other reagents are obtained from Invitrogen Corp. (Carlsbad, California, USA). Approximately 4-5 x 10(6) cells that have been cryopreserved in liquid nitrogen are rapidly thawed at 37 °C and transferred to a 175 cm² tissue culture flask containing 50 ml of growth media and then incubated at 37°C in a 5% CO₂ incubator. The growth media is replaced every 2-3 days until the flask became 90% confluent, typically in 5-7 days. To passage and expand the cell line, a 90% confluent flask is washed with 10 ml of room temperature phosphate buffered saline (PBS) and the cells are disassociated by adding 5 ml 1X Trypsin-EDTA (Invitrogen) and incubating at 37 °C until the cells detach from the surface of the flask. To inactivate the trypsin, 5 ml of growth media is added and then the contents of the flask are centrifuged to pellet the cells. The supernatant is aspirated and the cell pellet is resuspended in 10 ml of growth media and the cell number determined using a hemocytometer. Approximately 1-3 x 10(6) cells per flask are seeded into 175 cm² flasks containing 50 ml of growth media and incubated at 37 °C in a 5% CO₂ incubator. When the flasks reach 90% confluence, the above passaging process is repeated until sufficient cells have been obtained for implantation into mice.

Seven to eight week old, female Crl:CD-1-*nude* mice are obtained from Charles River Laboratories (Wilmington, Massachusetts, USA). Animals are housed 4-5/cage in micro-isolators, with a 12hr/12hr light/dark cycle, acclimated for at least 1 week prior to use and fed normal laboratory chow *ad libitum*. Studies are conducted on animals between 8 and 10 weeks of age at implantation. To implant EMT6 tumor cells into *nude* mice, the cells are trypsinized as above, washed in PBS and resuspended at a concentration of 10 x 10(6) cells/ml in PBS. Using a 27 gauge needle and 1 cc syringe, 0.1 ml of the cell suspension is injected subcutaneously into the flank of each *nude* mouse.

Tumors are then permitted to develop *in vivo* until the majority reached 75-125 mm³ in tumor volume, which typically requires 1 week following implantation. Animals with oblong, very small or large tumors are discarded, and only animals carrying tumors that display consistent growth rates are selected for studies. Tumor

volumes (V) are calculated by caliper measurement of the width (W), length (L) and thickness (T) of tumors using the following formula: $V = 0.5236 \times (L \times W \times T)$. Animals are randomized into treatment groups so that each group had median tumor volumes of ~ 100 mm³ at the start of dosing.

5 To formulate a compound of the invention in DRD, a stock solution of the test article is prepared by dissolving an appropriate amount of the compound in dimethyl sulfoxide (DMSO) by sonication in an ultrasonic water bath. A solution of 20% Cremophore RH40 (polyoxyl 40 hydrogenated castor oil; BASF Corp., Aktiengesellschaft, Ludwigshafen, Germany) in 5% dextrose in water (Abbott

10 Laboratories, North Chicago, Illinois, USA) is also prepared by first heating 100% Cremophore RH40 at 50-60°C until liquefied and clear, diluting 1:5 with 100% D5W, reheating again until clear and then mixing well. This solution is stored at room temperature for up to 3 months prior to use. To prepare a DRD formulation for dosing, the DMSO stock solution is diluted 1:10 with 20% Cremophore RH40.

15 The final DRD formulation for dosing contains 10% DMSO, 18% Cremophore RH40, 3.6% dextrose, 68.4% water and the appropriate amount of test article.

Tumor-bearing animals are given a single intravenous (i.v.) bolus injections of either DRD vehicle or a compound of the invention formulated in DRD, both at 10 mL per kg body weight. Then, 4-24 hr after drug treatment, tumors are excised, 20 cut in half and fixed overnight in 10% neutral-buffered formalin. Each tumor is embedded in paraffin with the cut surfaces placed downwards in the block, and rough cut until a complete section is obtained. From each tumor, 5 μ M serial sections are prepared and stained with hematoxylin and eosin. Slides are evaluated manually using light microscopy with a 10 x 10 square gridded reticle. The 25 percentage of necrosis in a tumor is quantified at 200X magnification by scoring the total number of grid squares containing necrosis and the total number of grid squares containing viable tumor cells.

It is expected that compounds of the invention will result in an increase in necrotic tissue in the center of EMT6 tumors relative to the baseline necrosis 30 observed in vehicle treated tumors. As would be expected for a vascular targeting mechanism of action, rapid onset of necrosis is consistent with there being a loss of blood flow to tumors resulting in hypoxia and tumor cell death.

Example 171: Vascular Disrupting Activities in a *nude* Mouse Tumor Model

The mouse mammary carcinoma cell line, EMT6 (ATCC #CRL-2755), is obtained from the American Type Culture Collection (ATCC; Manassas, Virginia, USA). The cell line is cultured in growth media prepared from 50% Dulbecco's 5 Modified Eagle Medium (high glucose), 50% RPMI Media 1640, 10% fetal bovine serum (FBS), 1% 100X L-glutamine, 1% 100X Penicillin-Streptomycin, 1% 100X sodium pyruvate and 1% 100X MEM non-essential amino acids. FBS is obtained from ATCC and all other reagents are obtained from Invitrogen Corp. (Carlsbad, California, USA). Approximately $4-5 \times 10^6$ cells that have been cryopreserved in 10 liquid nitrogen are rapidly thawed at 37°C and transferred to a 175 cm² tissue culture flask containing 50 mL of growth media and then incubated at 37°C in a 5% CO₂ incubator. The growth media is replaced every 2-3 days until the flask became 90% confluent, typically in 5-7 days. To passage and expand the cell line, a 90% confluent flask is washed with 10 mL of room temperature phosphate buffered 15 saline (PBS) and the cells are disassociated by adding 5 mL 1X Trypsin-EDTA (Invitrogen) and incubating at 37°C until the cells detach from the surface of the flask. To inactivate the trypsin, 5 mL of growth media is added and then the contents of the flask are centrifuged to pellet the cells. The supernatant is aspirated and the cell pellet is resuspended in 10 mL of growth media and the cell number 20 determined using a hemocytometer. Approximately $1-3 \times 10^6$ cells per flask are seeded into 175 cm² flasks containing 50 mL of growth media and incubated at 37°C in a 5% CO₂ incubator. When the flasks reach 90% confluence, the above passaging process is repeated until sufficient cells have been obtained for 25 implantation into mice.

Seven to eight week old, female Crl:CD-1-*nuBR* (*nude*) mice are obtained from Charles River Laboratories (Wilmington, Massachusetts, USA). Animals are housed 4-5/cage in micro-isolators, with a 12hr/12hr light/dark cycle, acclimated for at least 1 week prior to use and fed normal laboratory chow *ad libitum*. Studies are conducted on animals between 8 and 10 weeks of age at implantation. To 30 implant EMT6 tumor cells into *nude* mice, the cells are trypsinized as above, washed in PBS and resuspended at a concentration of 10×10^6 cells/mL in PBS. Using a 27 gauge needle and 1 cc syringe, 0.1 mL of the cell suspension is injected subcutaneously into the flank of each *nude* mouse.

For the Evans Blue dye assay, tumors are permitted to develop *in vivo* until the majority reach 40-90 mm³ in tumor volume (to minimize the extent of tumor necrosis), which typically require 4-6 days following implantation. Animals with visibly necrotic, oblong, very small or very large tumors are discarded and only 5 animals carrying tumors that display consistent growth rates are selected for use. Tumor volumes (V) are calculated by caliper measurement of the width (W), length (L) and thickness (T) of tumors using the following formula: $V = 0.5236 \times (L \times W \times T)$. Animals are randomized into treatment groups so that at the start of dosing each group have median tumor volumes of ~125 mm³ or ~55 mm³ for the Evans 10 Blue dye assay.

To formulate compounds of the invention for dosing, the appropriate amount of compound is dissolved in 5% dextrose in water (D5W; Abbott Laboratories, North Chicago, Illinois, USA). Vehicle-treated animals are dosed with D5W.

15 To conduct the Evans Blue dye assay, tumor-bearing animals are dosed with vehicle or test article at 0 hr, and then i.v. injected with 100 µL of a 1% (w/v) Evan's Blue dye (Sigma #E-2129; St. Louis, Missouri, USA) solution in 0.9% NaCl at +1 hr. Tumors are excised at + 4 hr, weighed and the tissue disassociated by incubation in 50 µL 1 N KOH at 60 °C for 16 hr. To extract the dye, 125 µL of 20 a 0.6 N phosphoric acid and 325 µL acetone are added, and the samples vigorously vortexed and then microcentrifuged at 3000 RPM for 15 min to pellet cell debris. The optical absorbance of 200 µL of supernatant is then measured at 620 nM in a Triad spectrophotometer (Dynex Technologies, Chantilly, Virginia, USA). Background OD₆₂₀ values from similarly sized groups of vehicle or test article-treated animals that have not been injected with dye are subtracted as background. 25 OD₆₂₀ values are then normalized for tumor weight and dye uptake is calculated relative to vehicle-treated tumors.

To examine the vascular disrupting activity of a compound of the invention, the Evans Blue dye assay is employed as a measurement of tumor blood volume 30 (Graff *et al.*, Eur J Cancer 36:1433-1440, 2000). Evans Blue dye makes a complex with serum albumin by electrostatic interaction between the sulphonic acid group of the dye and the terminal cationic nitrogens of the lysine residues in albumin. The dye leaves the circulation very slowly, principally by diffusion into extravascular

tissues while still bound to albumin. Albumin-dye complex taken up by tumors is located in the extracellular space of non-necrotic tissue, and intracellular uptake and uptake in necrotic regions is negligible. The amount of dye present in a tumor is a measurement of the tumor blood volume and microvessel permeability. Compounds of the invention are expected to result in substantially decreased tumor dye uptake relative to vehicle-treated animals. Such a decrease in dye penetration into the tumor is consistent with there being a loss of blood flow to tumors due to blockage of tumor vasculature, consistent with a vascular disrupting mechanism of action.

All publications, patent applications, patents, and other documents cited herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

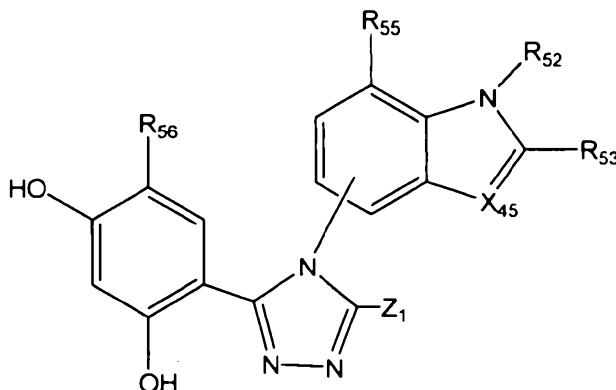
While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as an acknowledgment or admission or any form of suggestion that that prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A method of treating, reducing or inhibiting a disease associated with angiogenesis or neovasculature in a subject in need thereof, comprising administering to the subject an effective amount of a compound represented by the following structural formula:



or a tautomer or pharmaceutically acceptable salt thereof, wherein:

X_{45} is CR_{54} ;

Z_1 is $-OH$, or $-SH$;

R_{52} is selected from the group consisting of $-H$, methyl, ethyl, n-propyl, isopropyl, n-butyl, n-pentyl, n-hexyl, $-(CH_2)_2OCH_3$, $-CH_2C(O)OH$, and $-C(O)N(CH_3)_2$;

R_{53} and R_{54} are each, independently, $-H$, methyl, ethyl, or isopropyl; or R_{53} and R_{54} taken together with the carbon atoms to which they are attached form a phenyl, cyclohexenyl, or cyclooctenyl ring; and

R_{55} is selected from the group consisting of $-H$, $-OH$, $-OCH_3$, and $-OCH_2CH_3$,

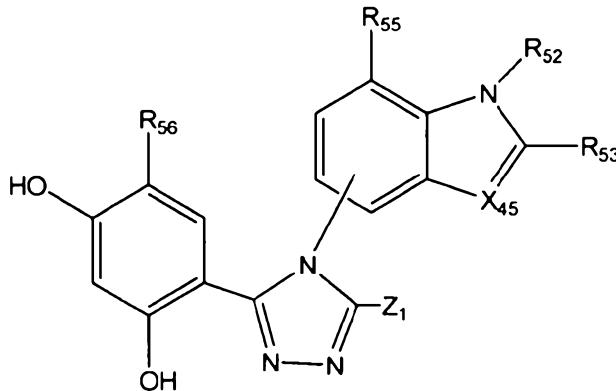
R_{56} is selected from the group consisting of $-H$, methyl, ethyl, isopropyl, and cyclopropyl;

wherein the disease is selected from the group consisting of an ocular neovascular disease; neovascular glaucoma; retrothalamic fibroplasias; epidemic keratoconjunctivitis; Vitamin A deficiency; contact lens overwear; atopic keratitis; superior limbic keratitis; pterygium keratitis sicca; sjogrens; acne rosacea; warts; eczema; phylectenulosis; syphilis; Mycobacteria infections; lipid degeneration;

chemical burns; ulcers (*Helicobacter pylori*); bacterial ulcers; fungal ulcers; Herpes simplex infections; Herpes zoster infections; protozoan infections; Kaposi's sarcoma; Mooren's ulcer; Terrien's marginal degeneration; marginal keratolysis; rheumatoid arthritis; systemic lupus; polyarteritis; trauma; trauma and post-laser complications; scleritis; Stevens-Johnson disease; pemphigoid; radial keratotomy; macular degeneration; sickle cell anemia; sarcoid; pseudoxanthoma elasticum; Paget's disease; carotid obstructive disease; chronic uveitis/vitritis; Lyme's disease; Eales' disease; Behcet's disease; infections causing a retinitis or choroiditis; presumed ocular histoplasmosis; Best's disease; myopia; optic pits; Stargardt's disease; pars planitis; chronic retinal detachment; hyperviscosity syndromes; toxoplasmosis; diseases associated with rubeosis (neovascularization of the angle); osteoarthritis; ulcerative colitis; Bartonellosis; atherosclerosis; Osler-Weber-Rendu disease; telangiectasia; hereditary hemorrhagic telangiectasia; pulmonary hemangiomatosis; pre-eclampsia; endometriosis; fibrosis of the liver and of the kidney; developmental abnormalities (organogenesis); skin discolorations; wound healing; cat scratch disease (*Rochele ninalia quintosa*); gingivitis; periodontal disease; epulis; hepatitis; tonsillitis; obesity; rhinitis; laryngitis; tracheitis; bronchitis; bronchiolitis; pneumonia; pulmonary edema; neurodermitis; thyroiditis; thyroid enlargement; glomerulonephritis; gastritis; inflammatory bone and cartilage destruction; thromboembolic disease; Buerger's disease, infectious diseases; autoimmune disorders; hemangiomas, acoustic neuromas, neurofibromas, trachomas, pyogenic granulomas; arteriosclerotic plaques; corneal graft rejection, retinoblastoma, persistent hyperplastic vitreous syndrome, choroidal neovascularization, plaque neovascularization; uveitis and Pterygia (abnormal blood vessel growth) of the eye; allergic dermatitis; blistering disease; uterine bleeding; ovarian hyperstimulation; vasculogenesis; granulations; wound granulation; hypertrophic scars (keloids); nonunion fractures; vascular adhesions; vascular malformations; DiGeorge syndrome; HHT; transplant arteriopathy; restinosis; myocardial angiogenesis; coronary collaterals; cerebral collaterals; arteriovenous malformations; ischemic limb angiogenesis; primary pulmonary hypertension; nasal polyps; inflammatory bowel disease; ascites; peritoneal

adhesions; Osler-Webber Syndrome; hemophiliac joints; synovitis; osteomyelitis; osteophyte formation; angiosfibroma; fibromuscular dysplasia; and Crohn's disease.

2. Use of a compound represented by the following structural formula:



or a tautomer or pharmaceutically acceptable salt thereof, wherein:

X_{45} is CR_{54} ;

Z_1 is $-OH$, or $-SH$;

R_{52} is selected from the group consisting of $-H$, methyl, ethyl, n-propyl, isopropyl, n-butyl, n-pentyl, n-hexyl, $-(CH_2)_2OCH_3$, $-CH_2C(O)OH$, and $-C(O)N(CH_3)_2$;

R_{53} and R_{54} are each, independently, $-H$, methyl, ethyl, or isopropyl; or R_{53} and R_{54} taken together with the carbon atoms to which they are attached form a phenyl, cyclohexenyl, or cyclooctenyl ring; and

R_{55} is selected from the group consisting of $-H$, $-OH$, $-OCH_3$, and $-OCH_2CH_3$,

R_{56} is selected from the group consisting of $-H$, methyl, ethyl, isopropyl, and cyclopropyl;

in the manufacture of a medicament for treating, reducing or inhibiting a disease associated with angiogenesis or neovasculature wherein the disease is selected from the group consisting of an ocular neovascular disease; neovascular glaucoma; retrolental fibroplasias; epidemic keratoconjunctivitis; Vitamin A deficiency; contact lens overwear; atopic keratitis; superior limbic keratitis; pterygium keratitis sicca; sjogrens; acne rosacea; warts; eczema; phylectenulosis;

syphilis; Mycobacteria infections; lipid degeneration; chemical burns; ulcers (Helicobacter pylori); bacterial ulcers; fungal ulcers; Herpes simplex infections; Herpes zoster infections; protozoan infections; Kaposi's sarcoma; Mooren's ulcer; Terrien's marginal degeneration; marginal keratolysis; rheumatoid arthritis; systemic lupus; polyarteritis; trauma; trauma and post-laser complications; scleritis; Stevens-Johnson disease; pemphigoid; radial keratotomy; macular degeneration; sickle cell anemia; sarcoid; pseudoxanthoma elasticum; Paget's disease; carotid obstructive disease; chronic uveitis/vitritis; Lyme's disease; Eales' disease; Behcet's disease; infections causing a retinitis or choroiditis; presumed ocular histoplasmosis; Best's disease; myopia; optic pits; Stargardt's disease; pars planitis; chronic retinal detachment; hyperviscosity syndromes; toxoplasmosis; diseases associated with rubeosis (neovascularization of the angle); osteoarthritis; ulcerative colitis; Bartonellosis; atherosclerosis; Osler-Weber-Rendu disease; telangiectasia; hereditary hemorrhagic telangiectasia; pulmonary hemangiomatosis; pre-eclampsia; endometriosis; fibrosis of the liver and of the kidney; developmental abnormalities (organogenesis); skin discolorations; wound healing; cat scratch disease (Rochelle ninalia quintosa); gingivitis; periodontal disease; epulis; hepatitis; tonsillitis; obesity; rhinitis; laryngitis; tracheitis; bronchitis; bronchiolitis; pneumonia; pulmonary edema; neurodermitis; thyroiditis; thyroid enlargement; glomerulonephritis; gastritis; inflammatory bone and cartilage destruction; thromboembolic disease; Buerger's disease, infectious diseases; autoimmune disorders; hemangiomas, acoustic neuromas, neurofibromas, trachomas, pyogenic granulomas; arteriosclerotic plaques; corneal graft rejection, retinoblastoma, persistent hyperplastic vitreous syndrome, choroidal neovascularization, plaque neovascularization; uveitis and Pterygia (abnormal blood vessel growth) of the eye; allergic dermatitis; blistering disease; uterine bleeding; ovarian hyperstimulation; vasculogenesis; granulations; wound granulation; hypertrophic scars (keloids); nonunion fractures; vascular adhesions; vascular malformations; DiGeorge syndrome; HHT; transplant arteriopathy; restinosis; myocardial angiogenesis; coronary collaterals; cerebral collaterals; arteriovenous

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malformations; ischemic limb angiogenesis; primary pulmonary hypertension; nasal polyps; inflammatory bowel disease; ascites; peritoneal adhesions; Osler-Webber Syndrome; hemophiliac joints; synovitis; osteomyelitis; osteophyte formation; angiofibroma; fibromuscular dysplasia; and Crohn's disease.

3. The method of claim 1 or use of claim 2, wherein Z_1 is $-\text{OH}$.
4. The method of claim 1 or use of claim 2, wherein Z_1 is $-\text{SH}$.
5. The method of claim 1 or use of claim 2, whercin the compound is selected from the group consisting of:
3-(2,4-dihydroxyphenyl)-4-(1-ethyl-indol-4-yl)-5-mercaptop-[1,2,4]triazole,
3-(2,4-dihydroxyphenyl)-4-(1-isopropyl-indol-4-yl)-5-mercaptop-[1,2,4]triazole,
3-(2,4-dihydroxyphenyl)-4-(indol-4-yl)-5-mercaptop-[1,2,4]triazole,
3-(2,4-dihydroxyphenyl)-4-(1-methoxyethyl-indol-4-yl)-5-mercaptop-[1,2,4]triazole,
3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1-isopropyl-indol-4-yl)-5-mercaptop-[1,2,4]triazole,
3-(2,4-dihydroxyphenyl)-4-(1-dimethylcarbamoyl-indol-4-yl)-5-mercaptop-[1,2,4]triazole,
3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1-propyl-indol-4-yl)-5-mercaptop-[1,2,4]triazole,
3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1,2,3-trimethyl-indol-5-yl)-5-mercaptop-[1,2,4]triazole,
3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1-acetyl-2,3-dimethyl-indol-5-yl)-5-mercaptop-[1,2,4]triazole,
3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(2,3-dimethyl-indol-5-yl)-5-mercaptop-[1,2,4]triazole,
3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1-isopropyl-7-methoxy-indol-4-yl)-5-mercaptop-[1,2,4]triazole,
3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1-propyl-2,3-dimethyl-indol-5-yl)-5-mercaptop-[1,2,4]triazole,

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3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(N-methyl-tetrahydrocarbozol-7-yl)-5-mercaptop-[1,2,4]triazole,

3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(N-methyl-cyclononan[a]indol-5-yl)-5-mercaptop-[1,2,4]triazole,

3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1-n-butyl-indol-4-yl)-5-mercaptop-[1,2,4]triazole,

3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1-n-pentyl-indol-4-yl)-5-mercaptop-[1,2,4]triazole,

3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1-n-hexyl-indol-4-yl)-5-mercaptop-[1,2,4]triazole,

3-(2,4-dihydroxy-5-cyclopropyl-phenyl)-4-(1-isopropyl-7-methoxy-indol-4-yl)-5-mercaptop-[1,2,4]triazole,

3-(2,4-dihydroxy-5-cyclopropyl-phenyl)-4-(1,2,3-trimethyl-indol-5-yl)-5-mercaptop-[1,2,4]triazole,

3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1-isopropyl-7-methoxy-indol-4-yl)-5-mercaptop-[1,2,4]triazole disodium salt,

3-(2,4-dihydroxy-5-*tert*-butyl-phenyl)-4-(1-isopropyl-7-methoxy-indol-4-yl)-5-mercaptop-[1,2,4]triazole,

3-(2,4-dihydroxy-5-cyclopropyl-phenyl)-4-(1-propyl-7-methoxy-indol-4-yl)-5-mercaptop-[1,2,4]triazole,

3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1-methyl-3-ethyl-indol-5-yl)-5-mercaptop-[1,2,4]triazole,

3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1,3-dimethyl-indol-5-yl)-5-mercaptop-[1,2,4]triazole,

3-(2,4-dihydroxy-5-isopropyl-phenyl)-4-(1-isopropyl-7-methoxy-indol-4-yl)-5-mercaptop-[1,2,4]triazole,

3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1-methyl-3-isopropyl-indol-5-yl)-5-mercaptop-[1,2,4]triazole,

3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(N-ethyl-carbozol-7-yl)-5-mercaptop-[1,2,4]triazole,

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3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1-isopropyl-7-hydroxy-indol-4-yl)-5-mercaptop-[1,2,4]triazole,

3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1-isopropyl-7-ethoxy-indol-4-yl)-5-mercaptop-[1,2,4]triazole,

3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1,2-dimethyl-indol-5-yl)-5-mercaptop-[1,2,4]triazole,

3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(N-methyl-indol-5-yl)-5-mercaptop-[1,2,4]triazole,

3-(2,4-dihydroxy-5-isopropyl-phenyl)-4-(1,3-dimethyl-indol-5-yl)-5-mercaptop-[1,2,4]triazole,

3-(2,4-dihydroxy-5-cyclopropyl-phenyl)-4-(1,3-dimethyl-indol-5-yl)-5-mercaptop-[1,2,4]triazole,

3-(2,4-dihydroxy-5-cyclopropyl-phenyl)-4-(1-methyl-indol-5-yl)-5-mercaptop-[1,2,4]triazole,

3-(2,4-dihydroxy-5-isopropyl-phenyl)-4-(1H-indol-5-yl)-5-mercaptop-[1,2,4]triazole,

3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1,2-dimethyl-indol-5-yl)-5-mercaptop-[1,2,4]triazole,

3-(2,4-dihydroxy-5-isopropyl-phenyl)-4-(1-ethyl-indol-5-yl)-5-mercaptop-[1,2,4]triazole,

3-(2,4-dihydroxy-5-isopropyl-phenyl)-4-(1-propyl-indol-5-yl)-5-mercaptop-[1,2,4]triazole,

3-(2,4-dihydroxy-phenyl)-4-(2,3-dimethyl-1H-indol-4-yl)-5-mercaptop-triazole,

3-(2,4-dihydroxy-phenyl)-4-(1-dimethylcarbamoyl-indol-4-yl)-5-mercaptop-triazole,

3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(2,3-dimethyl-indol-5-yl)-5-mercaptop-triazole,

3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1-isopropyl-7-methoxy-indol-4-yl)-5-mercaptop-triazole, and

3-(2,4-dihydroxy-5-isopropyl-phenyl)-4-(1,2-dimethyl-indol-5-yl)-5-mercaptop-[1,2,4]triazole,

or a tautomer or pharmaceutically acceptable salt thereof.

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6. The method of claim 1 or use of claim 2, wherein the compound is selected from the group consisting of 3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1-isopropyl-indol-3-yl)-5-hydroxy-[1,2,4]triazole; 3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1,3-dimethyl-indol-5-yl)-5-hydroxy-[1,2,4]triazole, 3-(2,4-dihydroxy-5-isopropyl-phenyl)-4-(1,3-dimethyl-indol-5-yl)-5-hydroxy-[1,2,4]triazole, 3-(2,4-dihydroxy-5-isopropyl-phenyl)-4-(1-methyl-indol-5-yl)-5-hydroxy-[1,2,4]triazole, and 3-(2,4-dihydroxy-5-isopropyl-phenyl)-4-(1-isopropyl-indol-4-yl)-5-hydroxy-[1,2,4]triazole; or a tautomer or pharmaceutically acceptable salt thereof.
7. The method of claim 1 or use of claim 2, wherein the compound is selected from the group consisting of 3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1-isopropyl-indol-3-yl)-5-hydroxy-[1,2,4]triazole, or a tautomer or pharmaceutically acceptable salt thereof.
8. The method of claim 1 or use of claim 2, wherein the compound is 3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1,3-dimethyl-indol-5-yl)-5-hydroxy-[1,2,4]triazole, or a tautomer or pharmaceutically acceptable salt thereof.
9. The method of claim 1 or use of claim 2, wherein the compound is 3-(2,4-dihydroxy-5-isopropyl-phenyl)-4-(1,3-dimethyl-indol-5-yl)-5-hydroxy-[1,2,4]triazole, or a tautomer or pharmaceutically acceptable salt thereof.
10. The method of claim 1 or use of claim 2, wherein the compound is 3-(2,4-dihydroxy-5-isopropyl-phenyl)-4-(1-methyl-indol-5-yl)-5-hydroxy-[1,2,4]triazole, or a tautomer or pharmaceutically acceptable salt thereof.

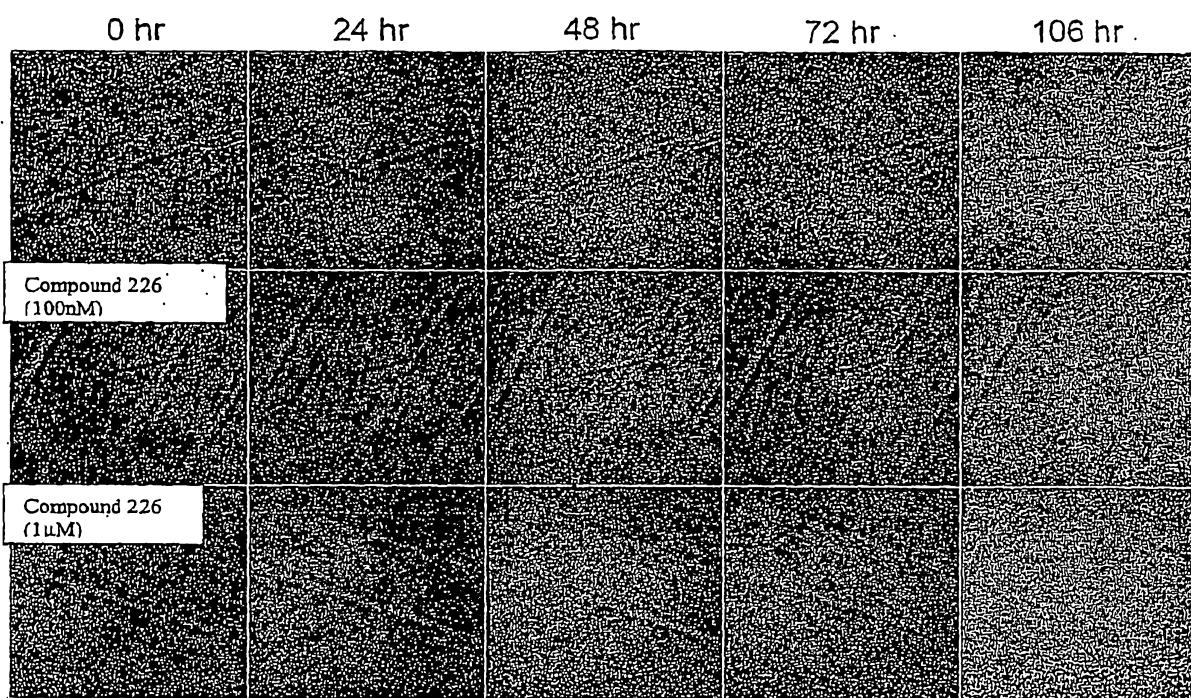
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11. The method of claim 1 or use of claim 2, wherein the compound is 3-(2,4-dihydroxy-5-isopropyl-phenyl)-4-(1-isopropyl-indol-4-yl)-5-hydroxy-[1,2,4]triazole, or a tautomer or pharmaceutically acceptable salt thereof.
12. The method of claim 1 or claim 2, wherein the compound is 3-(2,4-dihydroxy-5-isopropyl-phenyl)-4-(N-methyl-indol-5-yl)-5-mercaptop-[1,2,4]triazole, or a tautomer or pharmaceutically acceptable salt thereof.
13. The method of claim 1 or use of claim 2 substantially as hereinbefore described with reference to any one of the examples.

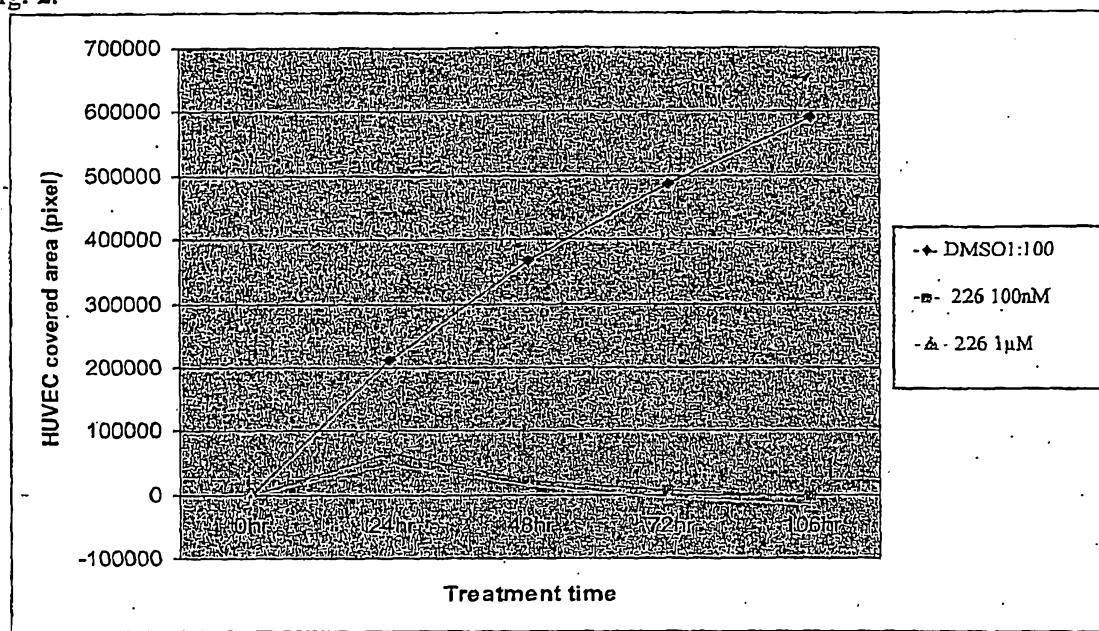
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Fig. 1.



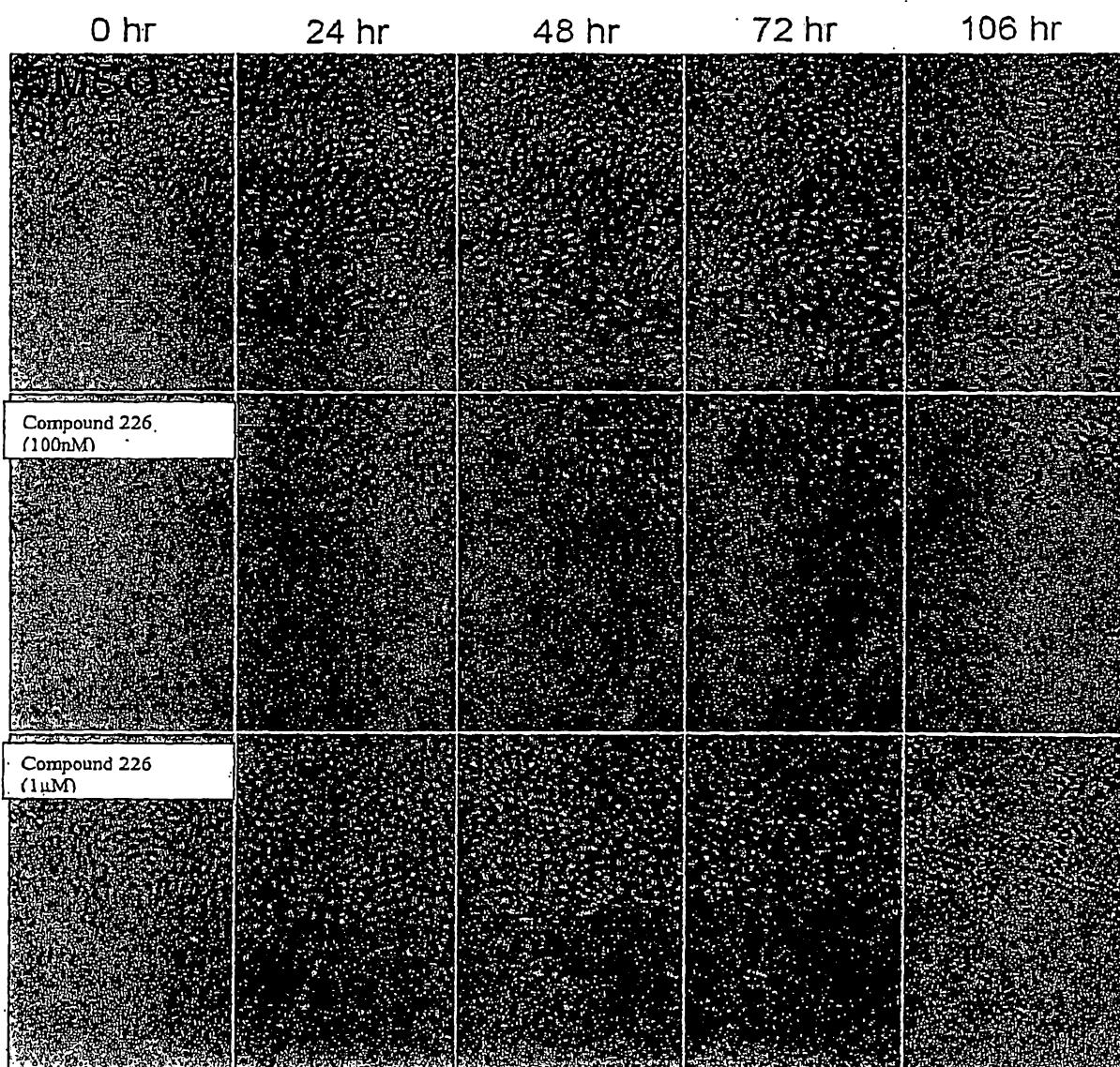
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Fig. 2.



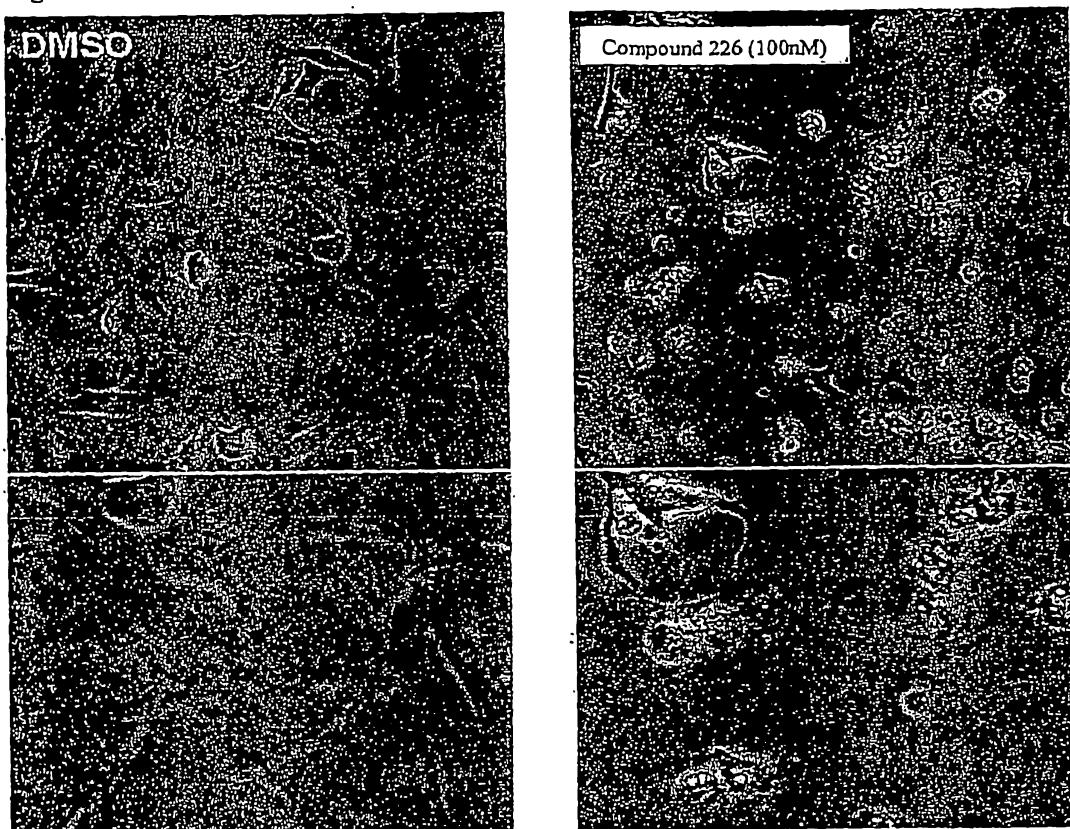
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Fig. 3.



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Fig. 4.



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Fig. 5.

