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(54) Title: AMINOQUINOLINE DERIVED HEAT SHOCK PROTEIN 90 INHIBITORS, METHODS OF PREPARING SAME,
AND METHODS FOR THEIR USE

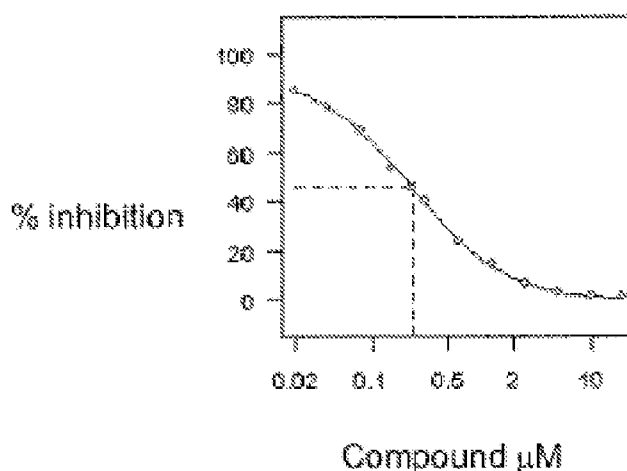


Fig. 1

(57) Abstract: Novel classes of molecular chaperone Heat shock protein 90 (Hsp90) inhibitors and methods for making these classes are provided herein. These compounds are useful in treating and preventing cancer and other Hsp90-related diseases, such as inflammation and neurodegenerative disorders. Also provided herein are methods of treating and preventing cancer and other Hsp90 related disease. The methods include administering to a subject a therapeutically effective amount of an Hsp90 inhibitor.



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upon receipt of that report (Rule 48.2(g))*

Aminoquinoline Derived Heat Shock Protein 90 Inhibitors, Methods of
Preparing Same, and Methods for Their Use

CROSS-REFERENCE TO RELATED APPLICATIONS

- 5 This application claims priority to U.S. Provisional Application No. 61/103,152, filed October 6, 2008, which is incorporated herein by reference in its entirety.

STATEMENT REGARDING FEDERALLY FUNDED RESEARCH

- 10 This invention was made with government support under Grant No. U54 HG003918-02 awarded by the National Institutes of Health. The government has certain rights in the invention.

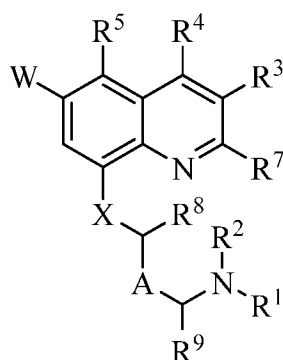
BACKGROUND

- 15 Cancer refers to a class of diseases that arises from the uncontrollable growth and division of normal cells. These malignant tumors are characterized by certain characteristics, including self-sufficiency in growth signaling, insensitivity to anti-growth signaling, evasion of apoptosis, sustained angiogenesis, tissue invasion and metastasis, and limitless potential to replicate (*J. Biosci.* 2007, 32, 517-530). Several
20 of the key signaling proteins of cancer cells are maintained by Heat shock protein 90 (Hsp90), which ranks amongst the most highly expressed cellular proteins. Hsp90 is a molecular chaperone with significant roles in maintaining transformation and in elevating the survival and growth potential of cancer cells. The biological role of Hsp90 is mediated by its ability to interact with client substrates such as Raf-1, Akt,
25 Her2, cdk4 and Bcr-Abl. Hsp90 is required for the ATP-dependent refolding of denatured or “unfolded” proteins and for the conformational maturation of a subset of proteins involved in the response of cells to extracellular signals. Activation of signaling pathways mediated by these Hsp90 clients is necessary for cell proliferation, regulation of cell cycle progression and apoptosis. Additionally, gain-of-function
30 mutations responsible for transformation often require Hsp90 for maintenance of their folded, functionally active conformations. Oncogenic transformation often enhances the tumor cell’s dependency on Hsp90 function.

Hsp90 also has a significant role in the progression of neurodegenerative diseases. Many neurodegenerative diseases, such as Alzheimer's and Parkinson's diseases, are characterized by misfolded and mutated proteins. These pathogenic forms of the proteins depend upon Hsp90 for conformational stability. In addition, neurodegenerative diseases often result from deviant signaling pathways which often rely upon Hsp90 for functioning. The inhibition of this chaperone is a potential mechanism of treating these diseases. Hsp90-interfering drugs represent a class of therapeutic agents that by selective inhibition of the chaperone could exhibit a broad-range of anti-tumor activity by affecting multiple aspects of transformation regulated by Hsp90. In addition, these agents represent a potential class of drugs that promote the survival of neurons and open up a promising approach for the treatment of neurodegenerative diseases.

SUMMARY

Novel methods and compositions for treating and preventing cancer and Hsp90 related diseases or conditions such as, for example, inflammation and neurodegenerative disorders, are provided. The methods comprise administering to a subject a therapeutically effective amount of Hsp90 inhibitor. A first class of Hsp90 inhibitors comprises compounds of the following formula:



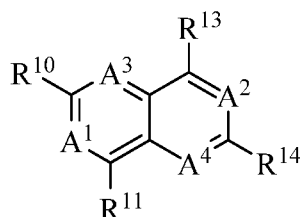
and includes pharmaceutically acceptable salts and prodrugs thereof. In this class of molecules, A is substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, or substituted or unsubstituted C_{2-6} alkynyl; W is NHR^6 , OR^6 , or hydrogen; X is NH, S, or O; R^1 and R^2 are each independently selected from hydrogen, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{1-12} haloalkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted

or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted
 or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or
 unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkylalkyl,
 substituted or unsubstituted acyl, and substituted or unsubstituted sulfonyl, wherein R¹
 5 and R² together are substituted or unsubstituted C₁₋₈ alkyl or substituted or
 unsubstituted C₂₋₈ alkenyl; R³, R⁴, and R⁵ are each independently selected from
 hydrogen, halogen, hydroxyl, nitro, cyano, substituted or unsubstituted amino,
 substituted or unsubstituted thio, substituted or unsubstituted C₁₋₁₂ alkyl, substituted
 or unsubstituted C₂₋₁₂ alkenyl, substituted or unsubstituted C₂₋₁₂ alkynyl, substituted or
 10 unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted
 heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted
 arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted
 cycloalkylalkyl, substituted or unsubstituted heterocycloalkylalkyl, substituted or
 unsubstituted C₁₋₁₂ alkylamine, substituted or unsubstituted C₂₋₁₂ alkenylamine,
 15 substituted or unsubstituted C₂₋₁₂ alkynylamine, substituted or unsubstituted
 arylamine, substituted or unsubstituted acyl, substituted or unsubstituted alkoxy, and
 substituted or unsubstituted aryloxy; R⁶ is hydrogen, substituted or unsubstituted C₁₋₁₂
 alkyl, substituted or unsubstituted C₂₋₁₂ alkenyl, substituted or unsubstituted C₂₋₁₂
 alkynyl, substituted or unsubstituted acyl, substituted or unsubstituted aminoalkyl,
 20 substituted or unsubstituted hydroxyalkyl, or substituted or unsubstituted alkoxyalkyl;
 R⁷ is hydrogen, hydroxyl, substituted or unsubstituted alkoxy, substituted or
 unsubstituted amino, substituted or unsubstituted thio, substituted or unsubstituted C₁₋₁₂
 alkyl, substituted or unsubstituted C₁₋₁₂ haloalkyl, substituted or unsubstituted C₂₋₁₂
 alkenyl, substituted or unsubstituted C₂₋₁₂ alkynyl, substituted or unsubstituted aryl,
 25 substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl,
 substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl,
 substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted
 cycloalkylalkyl, substituted or unsubstituted heterocycloalkylalkyl, substituted or
 unsubstituted acyl, or substituted or unsubstituted sulfonyl; and R⁸ and R⁹ are each
 30 independently selected from hydrogen, substituted or unsubstituted C₁₋₁₂ alkyl,
 substituted or unsubstituted C₂₋₁₂ alkenyl, and substituted or unsubstituted C₂₋₁₂
 alkynyl, wherein if X is NH, W is hydroxyl or methoxyl, and one of R¹ or R² is C₁₋₅
 alkyl, the other of R¹ or R² is not hydrogen or C₁₋₅ alkyl; if X is NH and W is

hydroxyl or methoxyl, R^1 and R^2 are not simultaneously hydrogen; and if X is NH, W is hydroxyl or methoxyl, and R^8 is methyl, R^9 is not hydrogen.

A second class of Hsp90 inhibitors comprises compounds of the following formula:

5



and includes pharmaceutically acceptable salts and prodrugs thereof. In this class of molecules, A^1 , A^2 , A^3 , and A^4 are each independently selected from N and CR^7 , wherein R^7 is hydrogen, substituted or unsubstituted amino, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{1-12} haloalkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkylalkyl, substituted or unsubstituted acyl, or substituted or unsubstituted sulfonyl, wherein at least one of A^1 , A^2 , and A^3 is N; R^{10} is hydrogen, hydroxyl, substituted or unsubstituted alkoxy, substituted or unsubstituted amino, substituted or unsubstituted thiol; R^{11} is substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{1-12} haloalkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkylalkyl, substituted or unsubstituted amino, substituted or unsubstituted alkylsulfonylamino, substituted or unsubstituted arylsulfonylamino, substituted or unsubstituted arylalkylsulfonylamino, substituted or unsubstituted cycloalkylsulfonylamino, substituted or unsubstituted heteroalkylsulfonylamino, substituted or unsubstituted heteroarylulfonylamino, substituted or unsubstituted heterocycloalkylsulfonylamino, substituted or unsubstituted heteroarylalkylsulfonylamino, substituted or unsubstituted

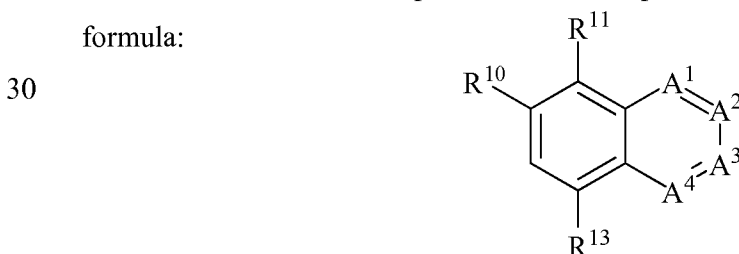
cycloalkylalkylsulfonylamino, or substituted or unsubstituted heterocycloalkylalkylsulfonylamino; and R^{13} and R^{14} are independently hydrogen, halogen, hydroxyl, substituted or unsubstituted amino, substituted or unsubstituted alkoxy, substituted or unsubstituted thiol, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{1-12} haloalkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, and substituted or unsubstituted heterocycloalkylalkyl.

A third class of Hsp90 inhibitors comprises compounds of the following formula:



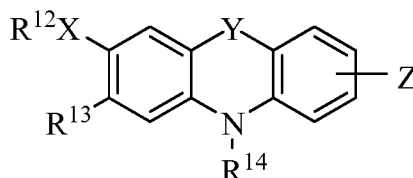
and includes pharmaceutically acceptable salts and prodrugs thereof. In this class of molecules, A^1 is CH or N; X is NH, S, or O; R^{12} is hydrogen or substituted or unsubstituted alkyl; and R^{13} and R^{14} are independently hydrogen, substituted or substituted amino, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{1-12} haloalkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, and substituted or unsubstituted heterocycloalkylalkyl, wherein R^{13} and R^{14} are not both hydrogen.

A fourth class of Hsp90 inhibitors comprises compounds of the following formula:



or a pharmaceutically acceptable salt or prodrug thereof, wherein A^1 , A^2 , A^3 , and A^4 are each independently selected from N and CR^7 , wherein each R^7 is independently hydrogen or substituted or unsubstituted amino; R^{10} is hydrogen, hydroxyl, substituted or unsubstituted alkoxyl, substituted or unsubstituted amino, substituted or unsubstituted carbamate, or substituted or unsubstituted thiol; R^{11} is hydroxyl, substituted or unsubstituted alkoxyl, substituted or unsubstituted amino, substituted or unsubstituted carbamate, substituted or unsubstituted thiol, or substituted or unsubstituted acyl; and R^{13} is substituted or unsubstituted amino.

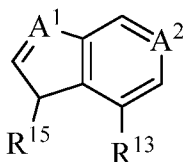
A fifth class of Hsp90 inhibitors comprises compounds of the following formula:



and includes pharmaceutically acceptable salts and prodrugs thereof. In this class of molecules, Y is NR^1 , O, S, CHR^1 , or CHR^1-CHR^2 , wherein R^1 and R^2 are each independently selected from hydrogen, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{1-12} haloalkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkylalkyl, substituted or unsubstituted acyl, and substituted or unsubstituted sulfonyl; Z is hydrogen or halogen; X is NH, S, or O; R^{12} is hydrogen or substituted or unsubstituted alkyl; R^{13} is hydrogen, substituted or unsubstituted amino, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{1-12} haloalkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, or substituted or unsubstituted heterocycloalkylalkyl; and R^{14} is hydrogen, substituted or unsubstituted C_{1-12} alkyl, substituted or

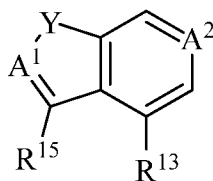
unsubstituted C₁₋₁₂ haloalkyl, substituted or unsubstituted C₂₋₁₂ alkenyl, substituted or unsubstituted C₂₋₁₂ alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, or substituted or unsubstituted heterocycloalkylalkyl, wherein R¹³ and R¹⁴ are not both hydrogen.

A sixth class of Hsp90 inhibitors comprises compounds of the following formula:



and includes pharmaceutically acceptable salts and prodrugs thereof. In this class of molecules, A¹ and A² are each independently selected from CH and N; R¹³ is substituted or unsubstituted amino, substituted or unsubstituted C₁₋₁₂ alkyl, substituted or unsubstituted C₁₋₁₂ haloalkyl, substituted or unsubstituted C₂₋₁₂ alkenyl, substituted or unsubstituted C₂₋₁₂ alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, and substituted or unsubstituted heterocycloalkylalkyl; and R¹⁵ is hydrogen, hydroxyl, or substituted or unsubstituted alkoxy.

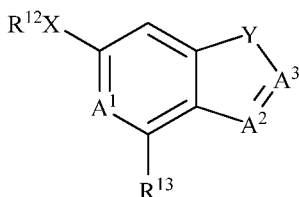
A seventh class of Hsp90 inhibitors comprises compounds of the following formula:



and includes pharmaceutically acceptable salts and prodrugs thereof. In this class of molecules, X is NH, S, or O; Y is NR¹, O, S, and CHR¹, wherein R¹ is hydrogen, substituted or unsubstituted C₁₋₁₂ alkyl, substituted or unsubstituted C₁₋₁₂ haloalkyl, substituted or unsubstituted C₂₋₁₂ alkenyl, substituted or unsubstituted C₂₋₁₂ alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted

or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkylalkyl, substituted or unsubstituted acyl, and substituted or unsubstituted sulfonyl; A¹ and A² are each independently selected from CH and N; R¹³ is substituted or unsubstituted C₁₋₁₂ alkyl, substituted or unsubstituted C₁₋₁₂ haloalkyl, substituted or unsubstituted C₂₋₁₂ alkenyl, substituted or unsubstituted C₂₋₁₂ alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, and substituted or unsubstituted heterocycloalkylalkyl; and R¹⁵ is hydrogen, hydroxyl, or substituted or unsubstituted alkoxy.

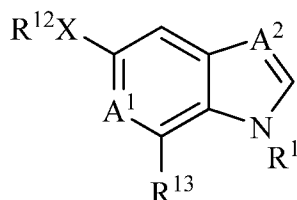
An eighth class of Hsp90 inhibitors comprises compounds of the following formula:



and includes pharmaceutically acceptable salts and prodrugs thereof. In this class of molecules, X is NH, S, or O; Y is NR¹, O, S, and CHR¹, wherein R¹ is hydrogen, substituted or unsubstituted C₁₋₁₂ alkyl, substituted or unsubstituted C₁₋₁₂ haloalkyl, substituted or unsubstituted C₂₋₁₂ alkenyl, substituted or unsubstituted C₂₋₁₂ alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkylalkyl, substituted or unsubstituted acyl, and substituted or unsubstituted sulfonyl; A¹, A², and A³ are each independently selected from CH and N; R¹³ is substituted or unsubstituted amino, substituted or unsubstituted C₁₋₁₂ alkyl, substituted or unsubstituted C₁₋₁₂ haloalkyl, substituted or unsubstituted C₂₋₁₂ alkenyl, substituted or unsubstituted C₂₋₁₂ alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalkyl, substituted or

unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, and substituted or unsubstituted heterocycloalkylalkyl; and R^{12} is hydrogen or substituted or unsubstituted alkyl.

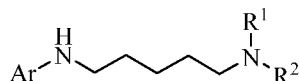
- 5 A ninth class of Hsp90 inhibitors comprises compounds of the following formula:



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- and includes pharmaceutically acceptable salts and prodrugs thereof. In this class of molecules, X is NH, S, or O; A^1 and A^2 are each independently selected from CH and N; R^1 is hydrogen, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{1-12} haloalkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkylalkyl, substituted or unsubstituted acyl, and substituted or unsubstituted sulfonyl; R^{12} is hydrogen or substituted or unsubstituted alkyl; and R^{13} is substituted or unsubstituted amino, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{1-12} haloalkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, and substituted or unsubstituted heterocycloalkylalkyl.

- A tenth class of Hsp90 inhibitors comprises compounds of the following formula:



30

or a pharmaceutically acceptable salt or prodrug thereof, wherein Ar is substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl; and R^1 and R^2 are each independently selected from hydrogen, substituted or unsubstituted C_{1-12} alkyl,

substituted or unsubstituted C₁₋₁₂ haloalkyl, substituted or unsubstituted C₂₋₁₂ alkenyl, substituted or unsubstituted C₂₋₁₂ alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkylalkyl, substituted or unsubstituted acyl, and substituted or unsubstituted sulfonyl.

Also provided is a method of preparing compounds for use as Hsp90

inhibitors. The method of preparing compounds comprises the following steps:

treating 6-methoxy-8-amino-quinoline with excess bromoalkylnitrile in solvent to produce a 4-(6-methoxyquinolin-8-ylamino)alkylnitrile; reducing the 4-(6-methoxyquinolin-8-ylamino) alkylnitrile with a hydride donor to produce a 4-(6-methoxyquinolin-8-ylamino)alkylamine; and alkylating the 4-(6-methoxyquinolin-8-ylamino)alkylamine to produce a N¹,N¹-dialkyl-N⁴-(6-methoxyquinolin-8-yl)alkyldiamine. In some embodiments, the method further comprises the step of treating the N¹,N¹-dialkyl-N⁴-(6-methoxyquinolin-8-yl)alkyldiamine with hydrobromic acid to produce a N¹,N¹-dialkyl-N⁴-(6-hydroxyquinolin-8-yl)alkyldiamine. In some embodiments, the hydride donor in the reducing step is lithium aluminum hydride. In some embodiments, the solvent in the treating step is a mixture of triethylamine and methanol.

The details of one or more embodiments are set forth in the description below. Other features, objects, and advantages will be apparent from the description and from the claims.

DESCRIPTION OF DRAWINGS

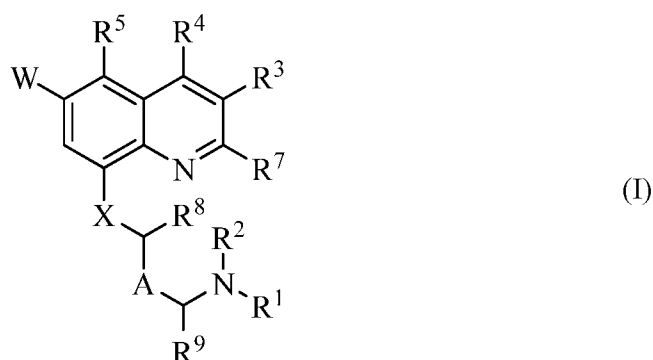
Fig. 1 is a graph showing the dose response binding inhibition of compound 1 in a competitive binding assay.

DETAILED DESCRIPTION

The term “comprising” and variations thereof as used herein are used synonymously with the term “including” and variations thereof and are open, non-limiting terms.

Novel classes of Hsp90 inhibitors are provided herein. These compounds are useful in treating, preventing, and/or ameliorating cancer and other Hsp90 associated diseases or conditions such as, for example, inflammation and neurodegenerative disorders. Specifically, pharmaceutically acceptable salts, prodrugs, and derivatives of aminoquinoline compounds are provided. Methods of their synthesis and use in the treatment of Hsp90 associated conditions are also provided.

A first group of Hsp90 inhibitors comprises compounds represented by Formula I:



or a pharmaceutically acceptable salt or prodrug thereof. In some examples, Formula I is a hydrobromide salt.

In Formula I, A is substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted C₂₋₆ alkenyl, or substituted or unsubstituted C₂₋₆ alkynyl.

Also, in Formula I, W is hydrogen, NHR⁶, or OR⁶ wherein R⁶ is hydrogen, substituted or unsubstituted C₁₋₁₂ alkyl, substituted or unsubstituted C₂₋₁₂ alkenyl, substituted or unsubstituted C₂₋₁₂ alkynyl, substituted or unsubstituted acyl, substituted or unsubstituted aminoalkyl, substituted or unsubstituted hydroxyalkyl, or substituted or unsubstituted alkoxyalkyl.

Additionally, in Formula I, X is NH, S, or O. In some examples, X is NH.

Further, in Formula I, R¹ and R² are each independently selected from hydrogen, substituted or unsubstituted C₁₋₁₂ alkyl, substituted or unsubstituted C₁₋₁₂ haloalkyl, substituted or unsubstituted C₂₋₁₂ alkenyl, substituted or unsubstituted C₂₋₁₂ alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkylalkyl, substituted or unsubstituted acyl, and substituted or

unsubstituted sulfonyl. In some examples, R^1 and R^2 together form substituted or unsubstituted C_{1-8} alkyl or substituted or unsubstituted C_{2-8} alkenyl.

Also, in Formula I, R^3 , R^4 , and R^5 are each independently selected from hydrogen, halogen, hydroxyl, nitro, cyano, substituted or unsubstituted amino, substituted or unsubstituted thio, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkylalkyl, substituted or unsubstituted C_{1-12} alkylamine, substituted or unsubstituted C_{2-12} alkenylamine, substituted or unsubstituted C_{2-12} alkynylamine, substituted or unsubstituted arylamine, substituted or unsubstituted acyl, substituted or unsubstituted alkoxy, and substituted or unsubstituted aryloxy. In some examples, R^5 is substituted or unsubstituted amido.

Further, in Formula I, R^7 is hydrogen, hydroxyl, substituted or unsubstituted alkoxy, substituted or unsubstituted amino, substituted or unsubstituted thio, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{1-12} haloalkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkylalkyl, substituted or unsubstituted acyl, or substituted or unsubstituted sulfonyl. In some examples, R^7 is substituted or unsubstituted amino.

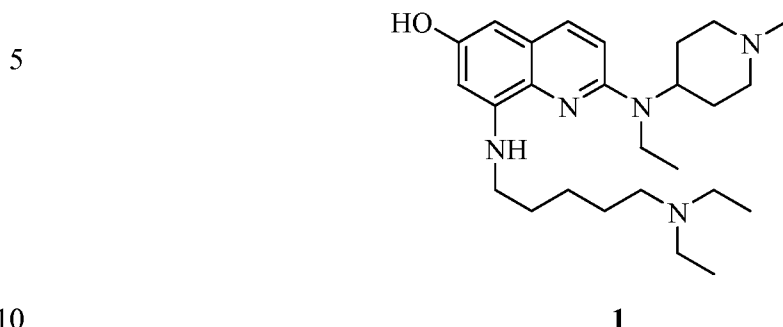
Furthermore, in Formula I, R^8 and R^9 are each independently selected from hydrogen, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{2-12} alkenyl, and substituted or unsubstituted C_{2-12} alkynyl.

In some examples of Formula I, if X is NH, W is hydroxyl or methoxy, and one of R^1 or R^2 is C_{1-5} alkyl, then the other of R^1 or R^2 is not hydrogen or C_{1-5} alkyl.

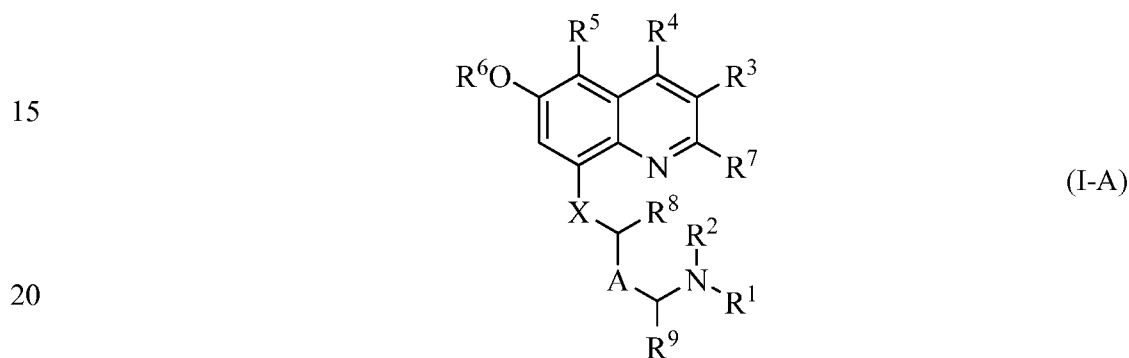
Additionally, in some examples of Formula I, if X is NH and W is hydroxyl or methoxy, then R^1 and R^2 are not simultaneously hydrogen.

Also, in some examples of Formula I, if X is NH, W is hydroxyl or methoxyl, and R⁸ is methyl, then R⁹ is not hydrogen.

An example of Formula I includes the following:



In some examples, Formula I can be Formula I-A:



or a pharmaceutically acceptable salt or prodrug thereof. In some examples, Formula I-A is a hydrobromide salt.

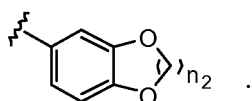
In Formula I-A, A is substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted C₂₋₆ alkenyl, or substituted or unsubstituted C₂₋₆ alkynyl.

Also, in Formula I-A, X is S or O.

Additionally, in Formula I-A, R¹, R², and R⁷ are each independently selected from hydrogen, substituted or unsubstituted C₁₋₁₂ alkyl, substituted or unsubstituted C₁₋₁₂ haloalkyl, substituted or unsubstituted C₂₋₁₂ alkenyl, substituted or unsubstituted C₂₋₁₂ alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkylalkyl, substituted or unsubstituted acyl, and substituted or unsubstituted sulfonyl.

In some examples, R^1 is hydrogen, methyl, ethyl, propyl, butyl, pentyl, isopropyl, *sec*-butyl, isobutyl, benzyl, benzoyl, acetyl, or substituted or unsubstituted sulfonyl (e.g., SO_2R^8). In some examples, R^2 is hydrogen, methyl, ethyl, propyl, butyl, pentyl, isopropyl, *sec*-butyl, isobutyl, benzyl, benzoyl, acetyl, or

5



In some examples, R^1 and R^2 together form substituted or unsubstituted C_{1-8} alkyl or substituted or unsubstituted C_{2-8} alkenyl. For example, R^1-N-R^2 can combine to form aziridine, azetidine, pyrrolidine, or piperidine. In some examples, R^7 is

10 hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *t*-butyl, acetyl, or propanoyl.

Further, in Formula I-A, R^3 , R^4 , and R^5 are each independently selected from hydrogen, halogen, hydroxyl, nitro, substituted or unsubstituted amino, cyano, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkylalkyl, substituted or unsubstituted C_{1-12} alkylamine, substituted or unsubstituted C_{2-12} alkenylamine, substituted or unsubstituted C_{2-12} alkynylamine, substituted or unsubstituted arylamine, substituted or unsubstituted alkoxy, and substituted or unsubstituted aryloxy.

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In some examples, R^3 is hydrogen, methyl, ethyl, propyl, or NH-ethyl. In some examples, R^4 is hydrogen, methyl, ethyl, propyl, NH-ethyl, NH-phenyl, chloro, hydroxyl, methoxyl, or phenoxy. In some examples, R^5 is hydrogen, hydroxyl, chloro, nitro, amino, NH-phenyl, *p*-chlorophenyl, or *p*-methoxyphenyl.

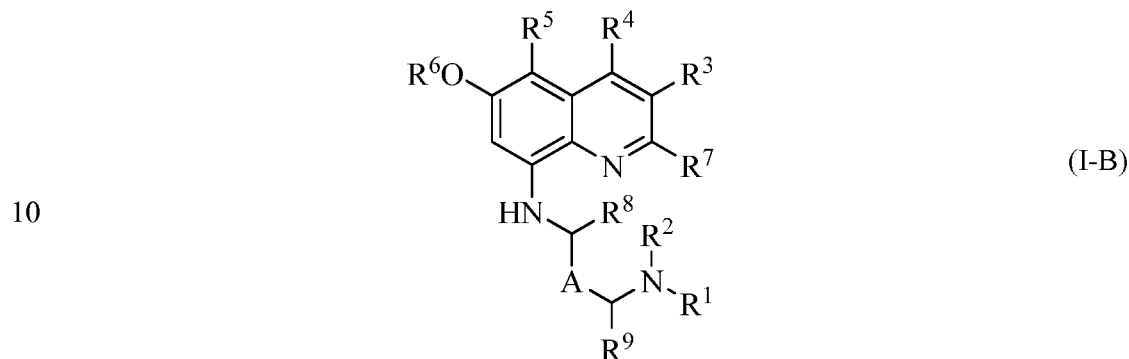
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Additionally, in Formula I-A, R^6 is hydrogen, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted acyl, substituted or unsubstituted aminoalkyl, substituted or unsubstituted hydroxyalkyl, or substituted or unsubstituted alkoxyalkyl. In some examples, R^6 is hydrogen, methyl, ethyl, allyl, acetyl, or $-(CH_2)_{n_1}T$, wherein n_1 is 1-5 and T is hydrogen, hydroxyl, amino, or alkoxy.

30

Furthermore, in Formula I-A, R^8 and R^9 are each independently selected from hydrogen, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{2-12} alkenyl, and substituted or unsubstituted C_{2-12} alkynyl. In some examples, one or both of R^8 and R^9 is hydrogen, methyl, or ethyl.

5 In some examples, Formula I can be Formula I-B:



or a pharmaceutically acceptable salt or prodrug thereof. In some examples, Formula I-B is a hydrobromide salt.

In Formula I-B, A is substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, or substituted or unsubstituted C_{2-6} alkynyl.

Also, in Formula I-B, R^1 and R^2 are each independently selected from hydrogen, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{1-12} haloalkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkylalkyl, substituted or unsubstituted acyl, and substituted or unsubstituted sulfonyl. In some examples, R^1 and R^2 are not C_{1-12} alkyl. In some examples, R^1 is hydrogen, benzyl, benzoyl, acetyl, or substituted or unsubstituted sulfonyl (e.g., SO_2R^8). In some examples, R^2 is hydrogen, benzyl, benzoyl, acetyl, or



In some examples, R^1 and R^2 together form substituted or unsubstituted C_{1-8} alkyl or substituted or unsubstituted C_{2-8} alkenyl. For example, R^1 -N- R^2 can combine to form aziridine, azetidine, pyrrolidine, or piperidine.

Additionally, in Formula I-B, R^3 , R^4 , and R^5 are each independently selected from hydrogen, halogen, hydroxyl, nitro, substituted or unsubstituted amino, cyano, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkylalkyl, substituted or unsubstituted C_{1-12} alkylamine, substituted or unsubstituted C_{2-12} alkenylamine, substituted or unsubstituted C_{2-12} alkynylamine, substituted or unsubstituted arylamine, substituted or unsubstituted alkoxy, and substituted or unsubstituted aryloxy.

In some examples, R^3 is hydrogen, methyl, ethyl, propyl, or NH-ethyl. In some examples, R^4 is hydrogen, methyl, ethyl, propyl, NH-ethyl, NH-phenyl, chloro, hydroxyl, methoxy, or phenoxy. In some examples, R^5 is hydrogen, hydroxyl, chloro, nitro, amino, NH-phenyl, *p*-chlorophenyl, or *p*-methoxyphenyl.

Further, in Formula I-B, R^6 is hydrogen, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted acyl, substituted or unsubstituted aminoalkyl, substituted or unsubstituted hydroxyalkyl, or substituted or unsubstituted alkoxyalkyl. In some examples, R^6 is hydrogen, methyl, ethyl, allyl, acetyl, or $-(CH_2)_{n_1}T$, wherein n_1 is 1-5 and T is hydrogen, hydroxyl, amino, or alkoxy.

Also, in Formula I, R^7 is hydrogen, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{1-12} haloalkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkylalkyl, substituted or unsubstituted acyl, or substituted or unsubstituted sulfonyl. In some examples, R^7 is hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *t*-butyl, acetyl, or propanoyl.

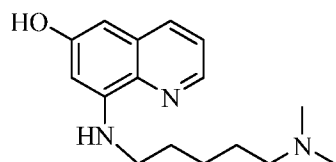
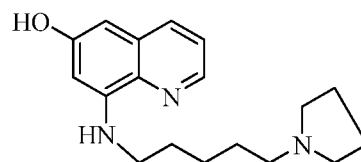
Further, in Formula I-B, R^8 and R^9 are each independently selected from hydrogen, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{2-12}

alkenyl, and substituted or unsubstituted C₂₋₁₂ alkynyl. In some examples, one or both of R⁸ and R⁹ is hydrogen, methyl, or ethyl.

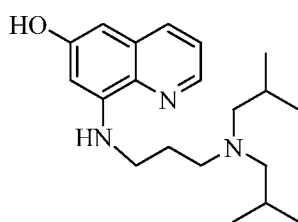
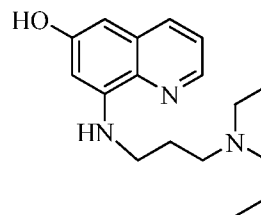
In some examples of Formula I-B, if R⁶ is hydrogen or methyl and one of R¹ or R² is C₁₋₅ alkyl, then the other of R¹ or R² is not hydrogen or C₁₋₅ alkyl. In some examples of Formula I, if R⁶ is hydrogen or methyl, then R¹ and R² are not simultaneously hydrogen. Also, in some examples of Formula I-B, if R⁶ is hydrogen or methyl and R⁸ is methyl, then R⁹ is not hydrogen.

Examples of Formula I include the following:

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**2****3**

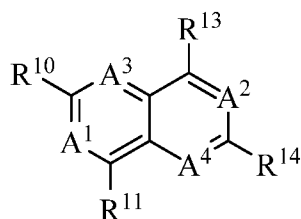
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**4****5**

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A second group of Hsp90 inhibitors comprises compounds represented by Formula II:

25



(II)

or a pharmaceutically acceptable salt or prodrug thereof.

In Formula II, A¹, A², A³, and A⁴ are each independently selected from N and CR⁷, wherein at least one of A¹, A², and A³ is N. In some examples, A³ is N.

30

Also, in Formula II, R⁷ is hydrogen, substituted or unsubstituted amino, substituted or unsubstituted C₁₋₁₂ alkyl, substituted or unsubstituted C₁₋₁₂ haloalkyl, substituted or unsubstituted C₂₋₁₂ alkenyl, substituted or unsubstituted C₂₋₁₂ alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted

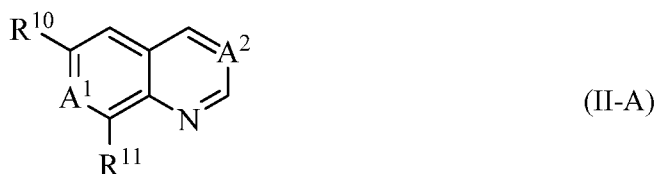
or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkylalkyl, substituted or unsubstituted acyl, or substituted or unsubstituted sulfonyl.

5 Additionally, in Formula II, R¹⁰ is hydrogen, hydroxyl, substituted or unsubstituted alkoxy, substituted or unsubstituted amino, or substituted or unsubstituted thiol.

 Further, in Formula II, R¹¹ is substituted or unsubstituted C₁₋₁₂ alkyl, substituted or unsubstituted C₁₋₁₂ haloalkyl, substituted or unsubstituted C₂₋₁₂ alkenyl, substituted or unsubstituted C₂₋₁₂ alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkylalkyl, substituted or unsubstituted amino, substituted or unsubstituted alkylsulfonylamino, substituted or unsubstituted arylsulfonylamino, substituted or unsubstituted arylalkylsulfonylamino, substituted or unsubstituted cycloalkylsulfonylamino, substituted or unsubstituted heteroalkylsulfonylamino, substituted or unsubstituted heteroarylsulfonylamino, substituted or unsubstituted heterocycloalkylsulfonylamino, substituted or unsubstituted heteroarylalkylsulfonylamino, substituted or unsubstituted cycloalkylalkylsulfonylamino, or substituted or unsubstituted heterocycloalkylalkylsulfonylamino.

 Further, in Formula II, R¹³ and R¹⁴ are independently hydrogen, halogen, hydroxyl, substituted or substituted amino, substituted or unsubstituted alkoxy, substituted or unsubstituted thiol, substituted or unsubstituted C₁₋₁₂ alkyl, substituted or unsubstituted C₁₋₁₂ haloalkyl, substituted or unsubstituted C₂₋₁₂ alkenyl, substituted or unsubstituted C₂₋₁₂ alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, and substituted or unsubstituted heterocycloalkylalkyl.

 In some examples, Formula II can be Formula II-A:



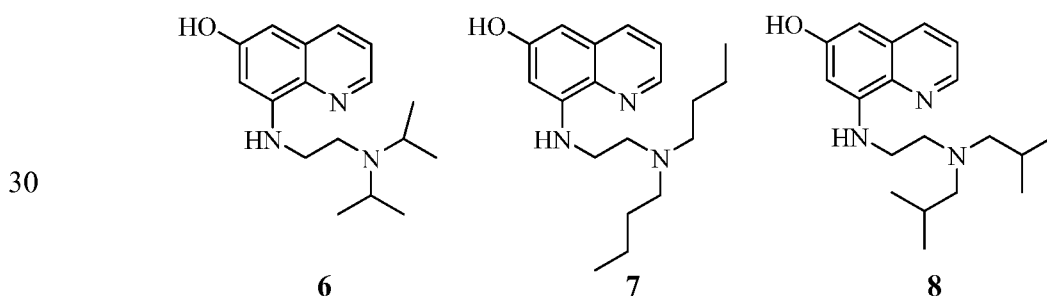
or a pharmaceutically acceptable salt or prodrug thereof.

5 In Formula II-A, A¹ and A² are each independently selected from CH and N.

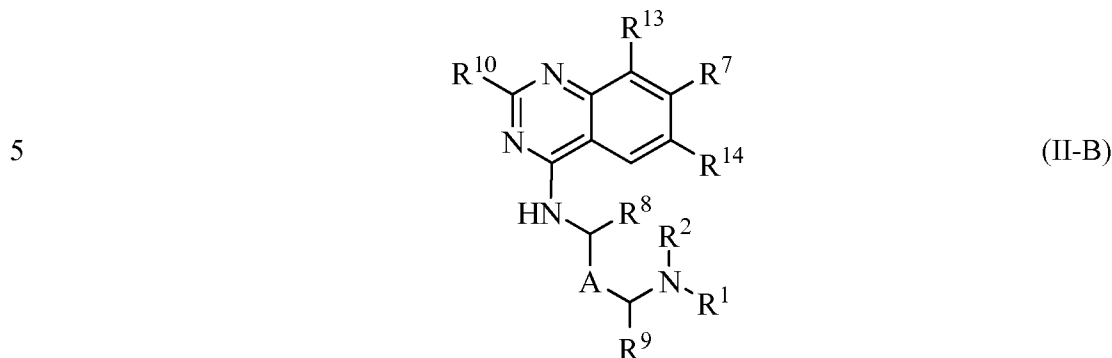
Also, in Formula II-A, R¹⁰ is hydrogen, hydroxyl, substituted or unsubstituted alkoxy, substituted or unsubstituted amino, or substituted or unsubstituted thiol. In some examples, R¹⁰ is substituted or unsubstituted amino.

10 Additionally, in Formula II-A, R¹¹ is substituted or unsubstituted C₁₋₁₂ alkyl, substituted or unsubstituted C₁₋₁₂ haloalkyl, substituted or unsubstituted C₂₋₁₂ alkenyl, substituted or unsubstituted C₂₋₁₂ alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or
 15 unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkylalkyl, substituted or unsubstituted amino, substituted or unsubstituted alkylsulfonylamino, substituted or unsubstituted arylsulfonylamino, substituted or unsubstituted arylalkylsulfonylamino, substituted or unsubstituted cycloalkylsulfonylamino, substituted or unsubstituted heteroalkylsulfonylamino, substituted or unsubstituted
 20 heteroarylulfonylamino, substituted or unsubstituted heterocycloalkylsulfonylamino, substituted or unsubstituted heteroarylalkylsulfonylamino, substituted or unsubstituted cycloalkylalkylsulfonylamino, or substituted or unsubstituted heterocycloalkylalkylsulfonylamino. In some examples, R¹¹ is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, or unsubstituted or unsubstituted amino.

25 Examples of Formula II-A include the following:



In some examples, Formula II can be Formula II-B:



10 or a pharmaceutically acceptable salt or prodrug thereof.

In Formula II-B, R¹ and R² are each independently selected from hydrogen, substituted or unsubstituted C₁₋₁₂ alkyl, substituted or unsubstituted C₁₋₁₂ haloalkyl, substituted or unsubstituted C₂₋₁₂ alkenyl, substituted or unsubstituted C₂₋₁₂ alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkylalkyl, substituted or unsubstituted acyl, and substituted or unsubstituted sulfonyl. In some examples, R¹ and R² together form substituted or unsubstituted C₁₋₈ alkyl or substituted or unsubstituted C₂₋₈ alkenyl.

15

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Also, in Formula II-B, R⁷ is hydrogen, substituted or unsubstituted amino, substituted or unsubstituted C₁₋₁₂ alkyl, substituted or unsubstituted C₁₋₁₂ haloalkyl, substituted or unsubstituted C₂₋₁₂ alkenyl, substituted or unsubstituted C₂₋₁₂ alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkylalkyl, substituted or unsubstituted acyl, or substituted or unsubstituted sulfonyl.

25

Additionally, in Formula II-B, R⁸ and R⁹ are each independently selected from hydrogen, substituted or unsubstituted C₁₋₁₂ alkyl, substituted or unsubstituted C₂₋₁₂ alkenyl, and substituted or unsubstituted C₂₋₁₂ alkynyl.

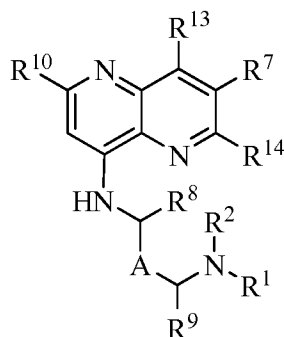
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Further, in Formula II-B, R¹⁰ is hydrogen, hydroxyl, substituted or unsubstituted alkoxy, substituted or unsubstituted amino, or substituted or unsubstituted thiol.

Also, in Formula II-B, R¹¹ is substituted or unsubstituted C₁₋₁₂ alkyl, substituted or unsubstituted C₁₋₁₂ haloalkyl, substituted or unsubstituted C₂₋₁₂ alkenyl, substituted or unsubstituted C₂₋₁₂ alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkylalkyl, substituted or unsubstituted amino, substituted or unsubstituted alkylsulfonylamino, substituted or unsubstituted arylsulfonylamino, substituted or unsubstituted arylalkylsulfonylamino, substituted or unsubstituted cycloalkylsulfonylamino, substituted or unsubstituted heteroalkylsulfonylamino, substituted or unsubstituted heteroaryl sulfonylamino, substituted or unsubstituted heterocycloalkylsulfonylamino, substituted or unsubstituted heteroarylalkylsulfonylamino, substituted or unsubstituted cycloalkylalkylsulfonylamino, or substituted or unsubstituted heterocycloalkylalkylsulfonylamino.

Further, in Formula II-B, R¹³ and R¹⁴ are each independently hydrogen, halogen, substituted or substituted amino, substituted or unsubstituted C₁₋₁₂ alkyl, substituted or unsubstituted C₁₋₁₂ haloalkyl, substituted or unsubstituted C₂₋₁₂ alkenyl, substituted or unsubstituted C₂₋₁₂ alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, and substituted or unsubstituted heterocycloalkylalkyl.

In some examples, Formula II can be Formula II-C:



(II-C)

or a pharmaceutically acceptable salt or prodrug thereof.

In Formula II-C, R¹ and R² are each independently selected from hydrogen, substituted or unsubstituted C₁₋₁₂ alkyl, substituted or unsubstituted C₁₋₁₂ haloalkyl, substituted or unsubstituted C₂₋₁₂ alkenyl, substituted or unsubstituted C₂₋₁₂ alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkylalkyl, substituted or unsubstituted acyl, and substituted or unsubstituted sulfonyl. In some examples, R¹ and R² together form substituted or unsubstituted C₁₋₈ alkyl or substituted or unsubstituted C₂₋₈ alkenyl.

Also, in Formula II-C, R⁷ is hydrogen, substituted or unsubstituted amino, substituted or unsubstituted C₁₋₁₂ alkyl, substituted or unsubstituted C₁₋₁₂ haloalkyl, substituted or unsubstituted C₂₋₁₂ alkenyl, substituted or unsubstituted C₂₋₁₂ alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkylalkyl, substituted or unsubstituted acyl, or substituted or unsubstituted sulfonyl.

Additionally, in Formula II-C, R⁸ and R⁹ are each independently selected from hydrogen, substituted or unsubstituted C₁₋₁₂ alkyl, substituted or unsubstituted C₂₋₁₂ alkenyl, and substituted or unsubstituted C₂₋₁₂ alkynyl.

Further, in Formula II-C, R¹⁰ is hydrogen, hydroxyl, substituted or unsubstituted alkoxyl, substituted or unsubstituted amino, or substituted or unsubstituted thiol. In some examples, R¹⁰ is substituted or unsubstituted amino.

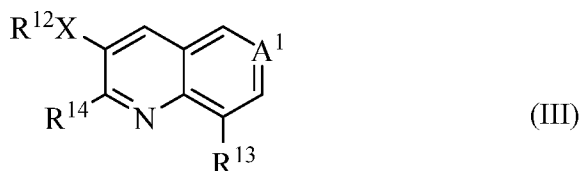
Also, in Formula II-C, R¹¹ is substituted or unsubstituted C₁₋₁₂ alkyl, substituted or unsubstituted C₁₋₁₂ haloalkyl, substituted or unsubstituted C₂₋₁₂ alkenyl, substituted or unsubstituted C₂₋₁₂ alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkylalkyl, substituted or unsubstituted amino, substituted or unsubstituted alkylsulfonylamino,

substituted or unsubstituted arylsulfonylamino, substituted or unsubstituted arylalkylsulfonylamino, substituted or unsubstituted cycloalkylsulfonylamino, substituted or unsubstituted heteroalkylsulfonylamino, substituted or unsubstituted heteroarylsulfonylamino, substituted or unsubstituted heterocycloalkylsulfonylamino, substituted or unsubstituted heteroarylalkylsulfonylamino, substituted or unsubstituted cycloalkylalkylsulfonylamino, or substituted or unsubstituted heterocycloalkylalkylsulfonylamino.

Further, in Formula II-C, R^{13} and R^{14} are independently hydrogen, halogen, substituted or unsubstituted amino, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{1-12} haloalkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, and substituted or unsubstituted heterocycloalkylalkyl.

In some examples of Formula II-C, A is $(CH_2)_3$, R^8 is hydrogen, and R^9 is hydrogen.

A third group of Hsp90 inhibitors comprises compounds represented by Formula III:



or pharmaceutically acceptable salts or prodrugs thereof.

In Formula III, A^1 is CH and N.

Also, in Formula III, X is NH, S, or O.

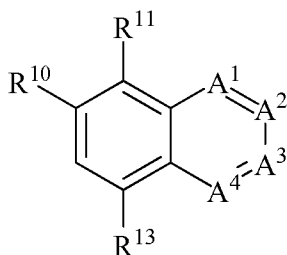
Additionally, in Formula III, R^{12} is hydrogen or substituted or unsubstituted C_{1-12} alkyl. In some examples, $R^{12}X$ is substituted or unsubstituted amino.

Further, in Formula III, R^{13} and R^{14} are independently hydrogen, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{1-12} haloalkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloalkylalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted

heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, and substituted or unsubstituted heterocycloalkylalkyl, wherein R^{13} and R^{14} are not both hydrogen. In some examples, R^{13} or R^{14} is substituted or unsubstituted amino.

A fourth group of Hsp90 inhibitors comprises compounds represented by

5 Formula IV:



10 or a pharmaceutically acceptable salt or prodrug thereof.

In Formula IV, A^1 , A^2 , A^3 , and A^4 are each independently selected from N and CR^7 . If one or more of R^7 is present in Formula IV, each R^7 is independently hydrogen, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-8} alkenyl, or substituted or unsubstituted amino. In some examples, R^7 is hydrogen.

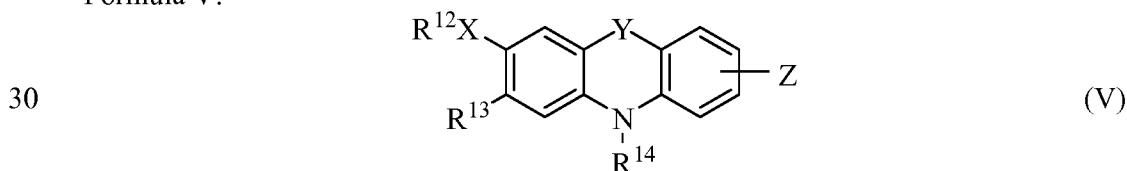
15 In some examples, A^3 is CR^7 . In some examples, A^1 , A^2 , A^3 , and A^4 are CR^7 . Adjacent R^7 groups can combine to form a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl.

Also, in Formula IV, R^{10} is hydrogen, hydroxyl, substituted or unsubstituted alkoxy, substituted or unsubstituted amino, substituted or unsubstituted carbamate, or substituted or unsubstituted thiol.

25 Additionally, in Formula IV, R^{11} is hydroxyl, substituted or unsubstituted alkoxy, substituted or unsubstituted amino, substituted or unsubstituted carbamate, substituted or unsubstituted thiol, or substituted or unsubstituted acyl. In some examples, R^{11} is amido.

Further, in Formula IV, R^{13} is substituted or unsubstituted amino.

A fifth group of Hsp90 inhibitors comprises compounds represented by Formula V:



or pharmaceutically acceptable salts or prodrugs thereof.

In Formula V, Y is NR^1 , O, S, CHR^1 , or $\text{CHR}^1\text{-CHR}^2$, wherein R^1 and R^2 are each independently selected from hydrogen, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{1-12} haloalkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkylalkyl, substituted or unsubstituted acyl, and substituted or unsubstituted sulfonyl. In some examples, Y is NR^1 , O, S, or CHR^1 .

Also, in Formula V, Z is hydrogen or a halogen.

Additionally, in Formula V, X is NH, S, or O.

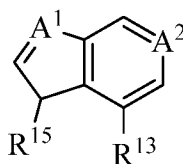
Also, in Formula V, R^{12} is hydrogen or substituted or unsubstituted alkyl.

Further, in Formula V, R^{13} is hydrogen, substituted or unsubstituted amino, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{1-12} haloalkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, or substituted or unsubstituted heterocycloalkylalkyl.

Furthermore, in Formula V, R^{14} is hydrogen, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{1-12} haloalkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, or substituted or unsubstituted heterocycloalkylalkyl. R^{13} and R^{14} are not both hydrogen.

A sixth group of Hsp90 inhibitors comprises compounds represented by

Formula VI:



(VI)

or pharmaceutically acceptable salts or prodrugs thereof.

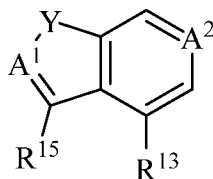
In Formula VI, A¹ and A² are each independently selected from CH and N.

Also, in Formula VI, R¹³ is substituted or unsubstituted amino, substituted or unsubstituted C₁₋₁₂ alkyl, substituted or unsubstituted C₁₋₁₂ haloalkyl, substituted or unsubstituted C₂₋₁₂ alkenyl, substituted or unsubstituted C₂₋₁₂ alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, and substituted or unsubstituted heterocycloalkylalkyl.

Additionally, in Formula VI, R¹⁵ is hydrogen, hydroxyl, or substituted or unsubstituted alkoxyl.

A seventh group of Hsp90 inhibitors comprises compounds represented by Formula VII:

15



(VII)

or pharmaceutically acceptable salts or prodrugs thereof.

20 In Formula VII, X is NH, S, or O.

Also, in Formula VII, Y is NR¹, O, S, or CHR¹, wherein R¹ is hydrogen, substituted or unsubstituted C₁₋₁₂ alkyl, substituted or unsubstituted C₁₋₁₂ haloalkyl, substituted or unsubstituted C₂₋₁₂ alkenyl, substituted or unsubstituted C₂₋₁₂ alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkylalkyl, substituted or unsubstituted acyl, or substituted or unsubstituted sulfonyl.

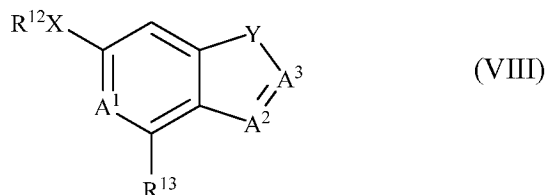
30 Additionally, in Formula VII, A¹ and A² are each independently selected from CH and N.

Also, in Formula VII, R¹³ is substituted or unsubstituted amino, substituted or unsubstituted C₁₋₁₂ alkyl, substituted or unsubstituted C₁₋₁₂ haloalkyl, substituted or unsubstituted C₂₋₁₂ alkenyl, substituted or unsubstituted C₂₋₁₂ alkynyl, substituted or

unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, or substituted or unsubstituted heterocycloalkylalkyl.

Further, in Formula VII, R^{15} is hydrogen, hydroxyl, or substituted or unsubstituted alkoxy.

An eighth group of Hsp90 inhibitors comprises compounds represented by Formula VIII:



or pharmaceutically acceptable salts or prodrugs thereof.

In Formula VIII, X is NH, S, or O.

Also, in Formula VIII, Y is NR^1 , O, S, or CHR^1 , wherein R^1 is hydrogen, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{1-12} haloalkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkylalkyl, substituted or unsubstituted acyl, and substituted or unsubstituted sulfonyl.

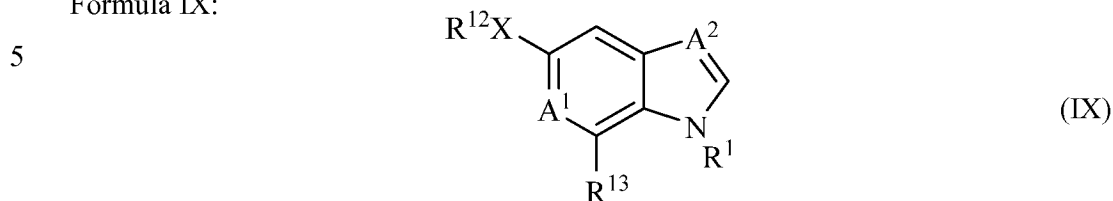
Additionally, in Formula VIII, A^1 , A^2 , and A^3 are each independently selected from CH and N.

Also, in Formula VIII, R^{12} is hydrogen or substituted or unsubstituted alkyl.

Further, in Formula VIII, R^{13} is substituted or unsubstituted amino, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{1-12} haloalkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted

heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, and substituted or unsubstituted heterocycloalkylalkyl.

A ninth group of Hsp90 inhibitors comprises compounds represented by Formula IX:



10 or pharmaceutically acceptable salts or prodrugs thereof.

In Formula IX, X is NH, S, or O.

Also, in Formula IX, A¹ and A² are each independently selected from CH and N.

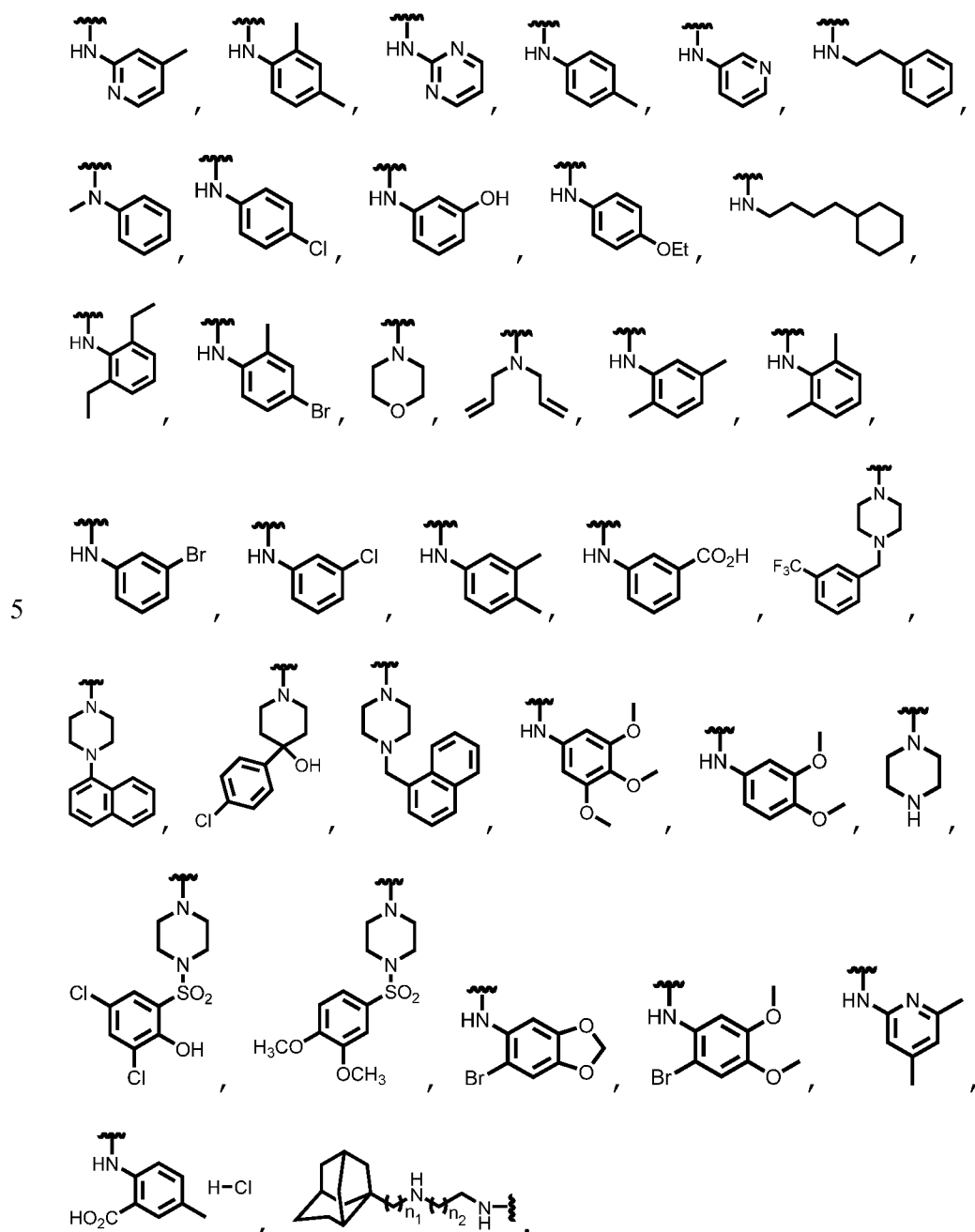
15 Additionally, in Formula IX, R¹ is hydrogen, substituted or unsubstituted C₁₋₁₂ alkyl, substituted or unsubstituted C₁₋₁₂ haloalkyl, substituted or unsubstituted C₂₋₁₂ alkenyl, substituted or unsubstituted C₂₋₁₂ alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkylalkyl, substituted or unsubstituted acyl, and substituted or unsubstituted sulfonyl.

Also, in Formula IX, R¹² is hydrogen or substituted or unsubstituted alkyl.

25 Further, in Formula IX, R¹³ is substituted or unsubstituted amino, substituted or unsubstituted C₁₋₁₂ alkyl, substituted or unsubstituted C₁₋₁₂ haloalkyl, substituted or unsubstituted C₂₋₁₂ alkenyl, substituted or unsubstituted C₂₋₁₂ alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, and substituted or unsubstituted heterocycloalkylalkyl.

In some examples of Formulas III – IX, R¹¹ or R¹³ can independently be alkyl, alkenyl, alkynyl, cycloalkyl, or aryl. In some examples of Formulas III – IX, R¹³ is substituted or unsubstituted amino.

In other examples of Formulas III – IX, R¹¹ or R¹³ can independently be



10 A tenth group of Hsp90 inhibitors comprises compounds represented by Formula X:



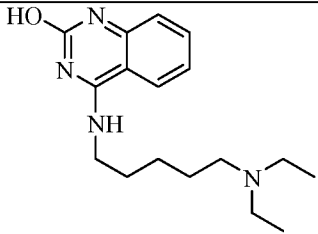
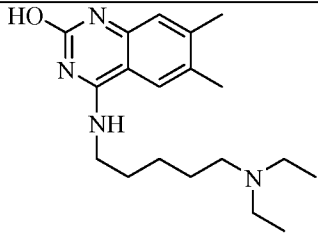
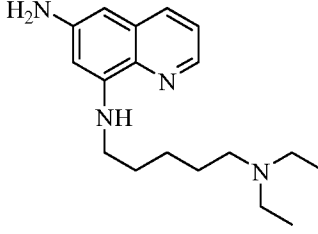
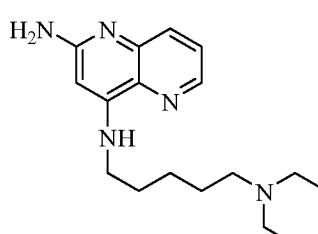
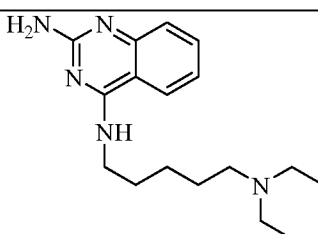
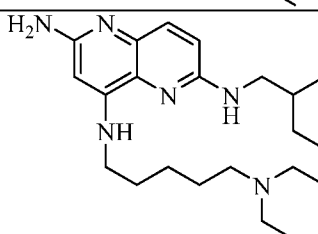
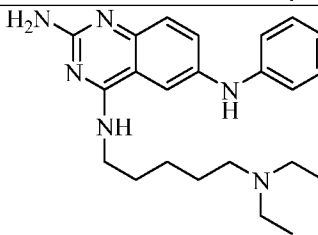
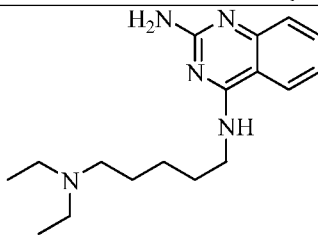
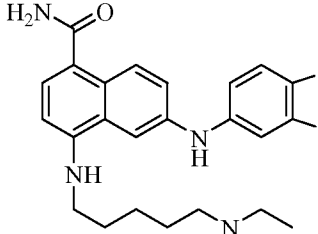
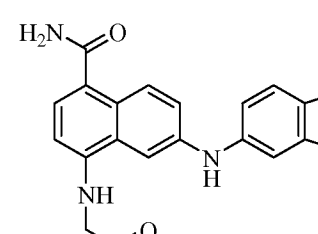
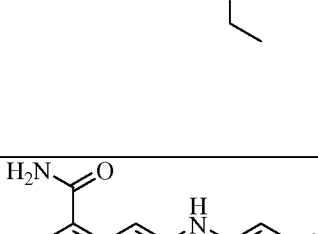
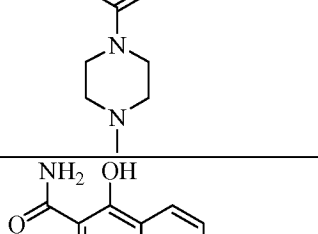
or a pharmaceutically acceptable salt or prodrug thereof.

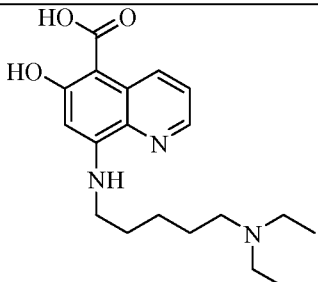
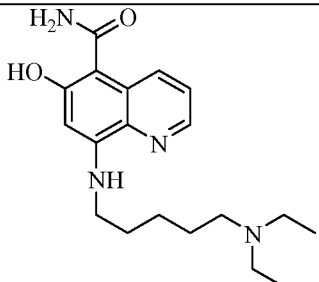
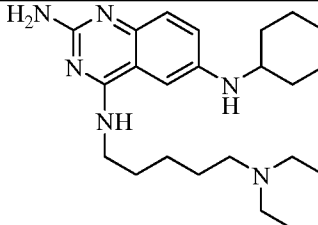
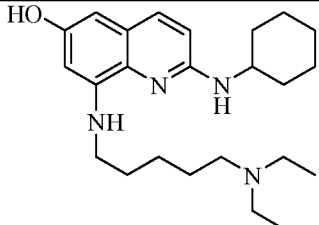
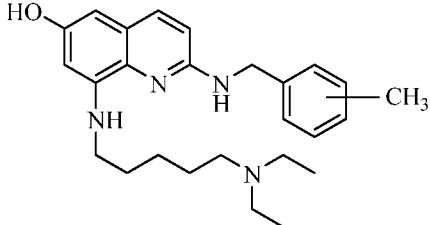
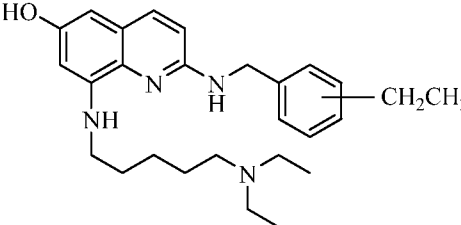
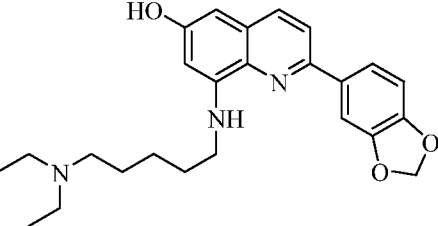
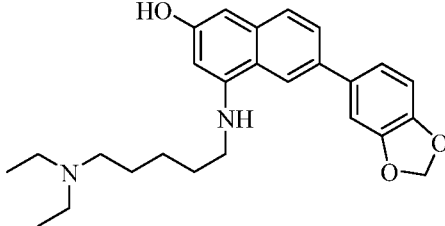
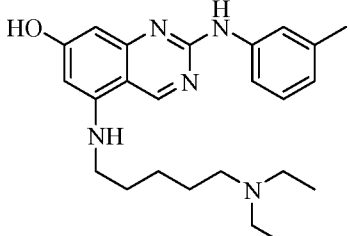
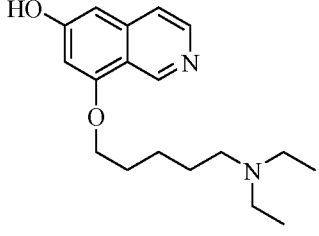
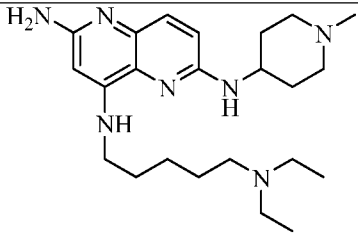
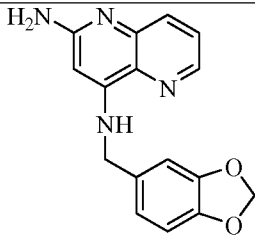
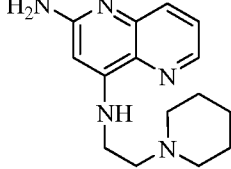
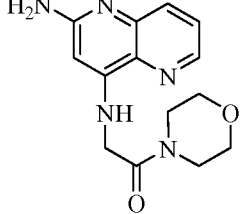
In Formula X, Ar is substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl. In some examples, Ar is substituted or unsubstituted naphthalene, substituted or unsubstituted quinoline, substituted or unsubstituted quinazoline, or substituted or unsubstituted naphthyridine.

- 5 Also, in Formula X, R¹ and R² are each independently selected from hydrogen, substituted or unsubstituted C₁₋₁₂ alkyl, substituted or unsubstituted C₁₋₁₂ haloalkyl, substituted or unsubstituted C₂₋₁₂ alkenyl, substituted or unsubstituted C₂₋₁₂ alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkylalkyl, substituted or unsubstituted acyl, and substituted or unsubstituted sulfonyl. In some examples, R¹ and R² is substituted or unsubstituted C₁₋₆ alkyl.

- 15 Examples of Hsp90 inhibitors represented by Formulas I, II, III, IV, V, VI, VII, VIII, IX, and X are provided below:

No	Compound	No	Compound
9		10	
11		12	
13		14	

15	 <chem>CCN(CC)CCCCCNc1nc2ccccc2n1C(=O)O</chem>	16	 <chem>CCN(CC)CCCCCNc1nc2cc(C)c(C)cc2n1C(=O)O</chem>
17	 <chem>CCN(CC)CCCCCNc1nc2cc(N)ccc2n1</chem>	18	 <chem>CCN(CC)CCCCCNc1nc2cc(N)ccn2</chem>
19	 <chem>CCN(CC)CCCCCNc1nc2cc(N)ccc2n1</chem>	20	 <chem>CCN(CC)CCCCCNc1nc2cc(N)ccc2n1CNc3ccccc3</chem>
21	 <chem>CCN(CC)CCCCCNc1nc2cc(N)ccc2n1CNc3cc4ccccc4o3</chem>	22	 <chem>CCN(CC)CCCCCNc1nc2cc(N)ccc2n1CNc3cc4ccccc4o3</chem>
23	 <chem>CCN(CC)CCCCCNc1nc2cc(N)ccc2n1C(=O)N</chem>	24	 <chem>CCN(CC)CCCCCNc1nc2cc(N)ccc2n1C(=O)N</chem>
25	 <chem>CCN(CC)CCCCCNc1nc2cc(N)ccc2n1C(=O)N</chem>	26	 <chem>CCN(CC)CCCCCNc1nc2cc(N)ccc2n1C(=O)N</chem>

27		28	
29		30	
31		32	
33		34	
35		36	
37		38	
39		40	

41		42	
43		44	
45		46	
47		48	

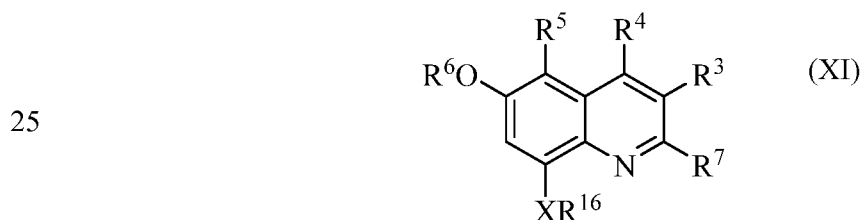
Variations on Formulas I, II, III, IV, V, VI, VII, VIII, IX, and X include the addition, subtraction, or movement of the various constituents as described for each compound. Similarly, when one or more chiral centers are present in a molecule, the chirality of the molecule can be changed. Additionally, compound synthesis can involve the protection and deprotection of various chemical groups. The use of protection and deprotection, and the selection of appropriate protecting groups can be determined by one skilled in the art. The chemistry of protecting groups can be found, for example, in Greene, et al., *Protective Groups in Organic Synthesis*, 2d. Ed., Wiley & Sons, 1991, which is incorporated herein by reference in its entirety. The synthesis and subsequent testing of various compounds as described for Formulas I, II, III, IV, V, VI, VII, VIII, IX, and X to determine efficacy is contemplated.

As used herein, the terms “alkyl”, “alkenyl”, “alkynyl”, and “cycloalkyl” can include straight-chain and branched monovalent substituents. Examples include methyl, ethyl, isobutyl, cyclohexyl, cyclopentylethyl, 2-propenyl, 3-butenyl, and the

like. "Heteroalkyl", "heteroalkenyl", "heteroalkynyl", and "heterocycloalkyl" refer to compounds that are similar to "alkyl", "alkenyl", "alkynyl", and "cycloalkyl" but that further contain a hetero atom such as O, S, or N or combinations thereof. The terms "cycloalkylalkyl" and "heterocycloalkylalkyl" refer to cycloalkyl and

5 heterocycloalkyl groups that are bonded to alkyl. The term "aryl" can include monocyclic or fused bicyclic moieties such as phenyl or naphthyl and the term "heteroaryl" can include monocyclic or fused bicyclic ring systems containing one or more heteroatoms selected from O, S, and N. Heteroaryls can include, for example, 5-, 6-, 7-, and 8-membered rings. Thus, aryl and heteroaryl systems can include
 10 pyridyl, pyrimidyl, indolyl, benzimidazolyl, benzotriazolyl, isoquinolyl, quinolyl, benzothiazolyl, benzofuranyl, thienyl, furyl, pyrrolyl, thiazolyl, oxazolyl, imidazolyl and the like. Similarly, the terms "arylalkyl" and "heteroarylalkyl" refer to aryl and heteroaryl groups bonded to alkyl groups, including substituted or unsubstituted, saturated or unsaturated, carbon chains. The term "substituted" indicates the main
 15 substituent has attached to it one or more additional components, such as, for example, OH, halogen, or one of the other substituents listed above. Substituted aryls can include, for example, monosubstituted, disubstituted, or trisubstituted aryls. As used herein, the term "acyl" indicated a substituted carbonyl. Acyls can include, for example, ketones, aldehydes, amides, carboxylic acids, esters, acyl halides, acid
 20 anhydrides, and the like.

A general method of preparing a compound of Formula I includes treating a compound of Formula XI:

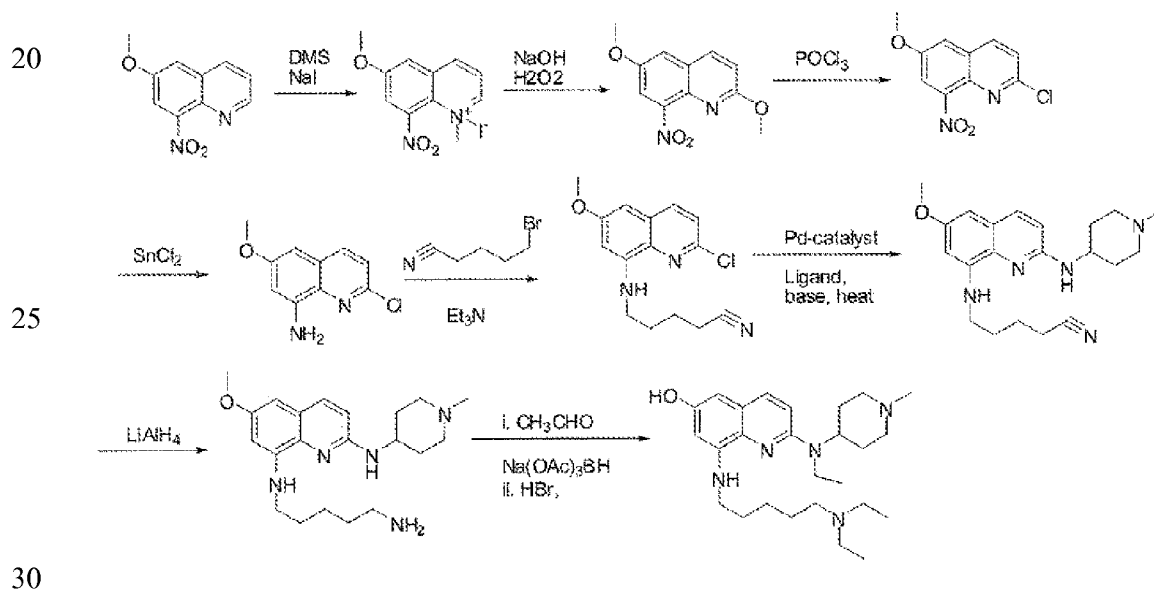


wherein X is NH, S, or O and R¹⁶ is H, with excess bromoalkylnitrile in solvent to produce the compound of formula XI, wherein R¹⁶ is alkyl nitrile. The compounds of
 30 formula XI, wherein R¹⁶ is alkyl nitrile, can then be reduced with a hydride donor to produce the compound of formula XI, wherein R¹⁶ is alkylamine. An example of a hydride donor that can be used in the reduction step is lithium aluminum hydride. The compound of formula XI, wherein R¹⁶ is alkylamine can then be alkylated to

produce the compound of formula XI, wherein R^{16} is N^1, N^1 -dialkylamine. This compound can then be treated with hydrobromic acid in solvent to produce the compound of formula XI, wherein R^{16} is N^1, N^1 -dialkylamine and R^6 is H. The solvent used in the treatment step can be, for example, a mixture of triethylamine and methanol.

The aminoquinoline compounds, for example, can be prepared by refluxing 6-methoxy-8-amino-quinoline and 4-bromobutanenitrile in a mixture of triethylamine and methanol. The mixture can then be concentrated and purified by chromatography to afford the desired nitrile. A solution of nitrile in THF can then be reacted with lithium aluminum hydride. The reaction can be quenched by the addition of $NaHCO_3$ and worked up under normal conditions. The crude product can then be dissolved in dichloromethane and acetaldehyde added. Then, $NaBH(OAc)_3$ can be added and the product can be stirred to allow the reaction to occur. After the reaction is complete, silica gel chromatography provides the desired, purified diamine. A solution of the diamine in HBr can be reacted in a microwave initiator. The resulting product can then be purified by chromatography to give the desired aminoquinoline.

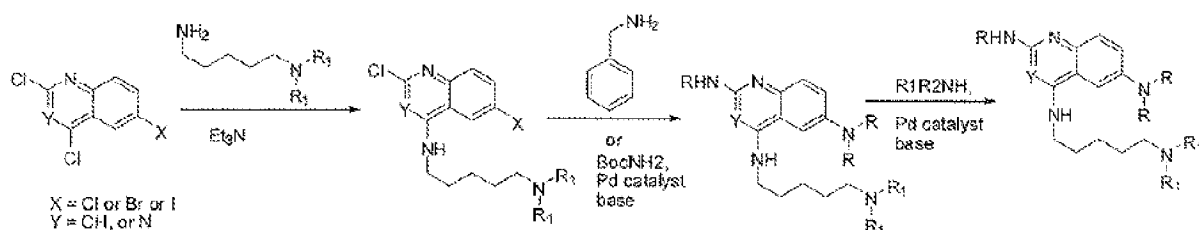
Compound 1 can be synthesized according to the method shown in the following scheme:



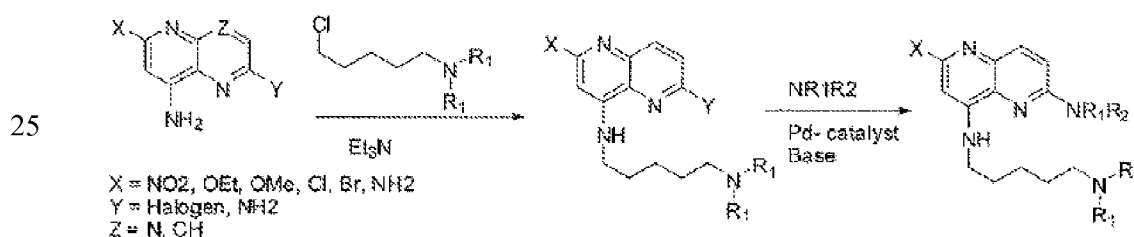
A general method of preparing a compound of Formulas II and III includes, for example, treating 6-alkoxy-8-quinazolinamine in pyridine with an alkyl halide. The reaction mixture can be heated to refluxing temperatures until there is no

remaining starting material as evidenced by chromatography (e.g., TLC). The compound can then be purified by column chromatography to obtain 6-alkoxy-*N*-alkylquinazolin-8-amine, which can then undergo demethylation by treatment with HBr (48% aq) in a microwave initiator at 120°C for 2-2.5 h. The reaction mixture can then be cooled to room temperature and the solvent can be evaporated using a Genevac DD-4X evaporator. The resulting residue can then be purified by silica gel chromatography to provide 6-alkoxy-*N*-alkylquinazolin-8-amine hydrobromide salt. The hydrobromide salt can be treated with a variety of halides in the presence of K₂CO₃ to provide the final 6,8-substituted quinazoline derivatives.

- 10 Compounds of Formula II can be prepared according to the method shown in the following scheme. In this example, A¹ is represented by Y, A² and A⁴ are CH, and A³ is N. Also in this example, A is (CH₂)₃, R⁸ and R⁹ are hydrogen, and R¹⁰ is substituted or unsubstituted amino. A compound of Formula X wherein Ar is substituted quinazoline can also be synthesized according to this method.



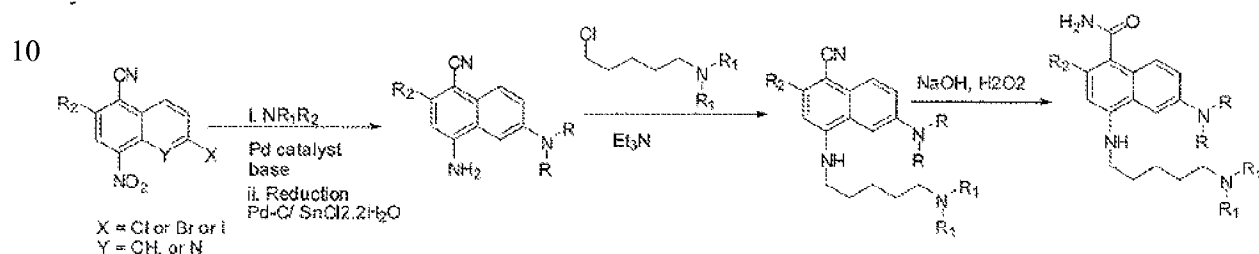
- 20 Compounds of Formula II-C can be prepared according to the method shown in the following scheme. In this example, A is (CH₂)₃, R⁸ and R⁹ are hydrogen, and R¹⁰ is substituted or unsubstituted amino. A compound of Formula X wherein Ar is substituted naphthyridine can also be synthesized according to this method.



- 30 A general method of preparing a compound of Formula IV includes, for example, treating a 6-halo-4-nitro-1-naphthionitrile with an amine, a palladium

catalyst, and a base and then reducing the product using palladium on carbon. The resulting product can then be treated with an alkyl halide in triethylamine.

Subsequent treatment with base and hydrogen peroxide results in the desired compound. For example, a compound of Formula IV wherein A^1 , A^2 , and A^4 are CH, A^3 is CR^7 , R^7 is substituted amino, R^8 and R^9 are hydrogen, R^{11} is amido, and A is $(CH_2)_3$ can be synthesized according to the method shown below. A compound of Formula X wherein Ar is substituted naphthalene can also be synthesized according to this method.



15

A general method of preparing a compound of Formula V includes, for example, stirring a mixture of 3,5-dinitropyridin-2-amine, 2-chlorophenol, and sodium acetate in a solvent mixture (e.g., EtOH and H₂O) under refluxing conditions. The solvent can be evaporated to provide a residue, which can be dissolved in H₂O and then extracted with an organic solvent (e.g., EtOAc). The organic layers can be combined and washed with H₂O and brine, dried over MgSO₄, and then concentrated in vacuo. Purification by column chromatography can provide 2-(3,5-dinitropyridin-2-ylamino)phenol. A mixture of the phenol compound and K₂CO₃ in solvent (e.g., DMF) can be stirred under refluxing conditions. The compound can be extracted with solvent (e.g., CH₂Cl₂), dried over MgSO₄, and purified by column chromatography to obtain 3-nitro-10H-benzo[e]pyrido[3,2-b][1,4]oxazine. The 3-nitro-oxazine can be treated with LHMDs in solvent (e.g., toluene). An alkyl halide can then be added and the reaction mixture heated (e.g., to 80°C) until there is no remaining starting material as evidenced by chromatography (e.g., TLC). The crude compound can be purified by column chromatography to obtain 10-alkyl-3-nitro-10H-benzo[e]pyrido[3,2-b][1,4]oxazine, which can be subjected to hydrogenation to obtain amino-oxazine derivative. The amino-oxazine compound can then be treated with a variety of

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halides in the presence of pyridine or other bases to obtain substituted amines as the final products.

A general method of preparing a compound of Formulas VI, VII, VIII, and IX includes, for example, treating 7-chloro-5-nitro-1H-benzo[d]imidazole with an amine and K_2CO_3 under refluxing conditions in solvent, for example, CH_3CN . The reaction can then be quenched and the crude product can be purified by column chromatography to obtain N-alkyl-5-nitro-1H-benzo[d]imidazol-7-amine. The N-alkyl-5-nitro-1H-benzo[d]imidazol-7-amine can then be treated with a variety of halides in the presence of K_2CO_3 in solvent, for example, CH_3CN , to provide a 5-nitro-substituted imidazole. The imidazole can then be subjected to hydrogenation to afford a 5-amino-7-amine-substituted imidazole. Further treatment of the amine with alkyl halides can provide the final substituted amine.

Reactions to produce the compounds described herein can be carried out using the described or different solvents, which can be selected by one of skill in the art of organic synthesis. Solvents can be substantially nonreactive with the starting materials (reactants), the intermediates, or products under the conditions at which the reactions are carried out, i.e., temperature and pressure. Reactions can be carried out in one solvent or a mixture of more than one solvent. Product or intermediate formation can be monitored according to any suitable method known in the art. For example, product formation can be monitored by spectroscopic means, such as nuclear magnetic resonance spectroscopy (e.g., 1H or ^{13}C) infrared spectroscopy, spectrophotometry (e.g., UV-visible), or mass spectrometry, or by chromatography such as high performance liquid chromatography (HPLC) or thin layer chromatography.

The compounds described herein can be prepared using other methods known to one skilled in the art of organic synthesis or variations thereon as appreciated by those skilled in the art. The compounds described herein can be prepared from readily available starting materials. Optimum reaction conditions may vary with the particular reactants or solvents used, but such conditions can be determined by one skilled in the art.

The compounds described herein or derivatives thereof can be provided in a pharmaceutical composition. Depending on the intended mode of administration, the pharmaceutical composition can be in the form of solid, semi-solid or liquid dosage

forms, such as, for example, tablets, suppositories, pills, capsules, powders, liquids, or suspensions, preferably in unit dosage form suitable for single administration of a precise dosage. The compositions will include a therapeutically effective amount of the compound described herein or derivatives thereof in combination with a
5 pharmaceutically acceptable carrier and, in addition, may include other medicinal agents, pharmaceutical agents, carriers, or diluents. By pharmaceutically acceptable is meant a material that is not biologically or otherwise undesirable, which can be administered to an individual along with the selected compound without causing unacceptable biological effects or interacting in a deleterious manner with the other
10 components of the pharmaceutical composition in which it is contained.

As used herein, the term carrier encompasses any excipient, diluent, filler, salt, buffer, stabilizer, solubilizer, lipid, stabilizer, or other material well known in the art for use in pharmaceutical formulations. The choice of a carrier for use in a composition will depend upon the intended route of administration for the
15 composition. The preparation of pharmaceutically acceptable carriers and formulations containing these materials is described in, *e.g.*, Remington's Pharmaceutical Sciences, 21st Edition, ed. University of the Sciences in Philadelphia, Lippincott, Williams & Wilkins, Philadelphia Pa., 2005. Examples of physiologically acceptable carriers include buffers such as phosphate buffers, citrate buffer, and
20 buffers with other organic acids; antioxidants including ascorbic acid; low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, arginine or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose,
25 or dextrans; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; salt-forming counterions such as sodium; and/or nonionic surfactants such as TWEEN[®] (ICI, Inc.; Bridgewater, New Jersey), polyethylene glycol (PEG), and PLURONICS[™] (BASF; Florham Park, NJ).

Compositions containing the compound described herein or derivatives thereof
30 suitable for parenteral injection may comprise physiologically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include

water, ethanol, polyols (propyleneglycol, polyethyleneglycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the
5 case of dispersions and by the use of surfactants.

These compositions may also contain adjuvants such as preserving, wetting, emulsifying, and dispensing agents. Prevention of the action of microorganisms can be promoted by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. Isotonic agents, for example, sugars,
10 sodium chloride, and the like may also be included. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, for example, aluminum monostearate and gelatin.

Solid dosage forms for oral administration of the compounds described herein or derivatives thereof include capsules, tablets, pills, powders, and granules. In such
15 solid dosage forms, the compounds described herein or derivatives thereof is admixed with at least one inert customary excipient (or carrier) such as sodium citrate or dicalcium phosphate or (a) fillers or extenders, as for example, starches, lactose, sucrose, glucose, mannitol, and silicic acid, (b) binders, as for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia,
20 (c) humectants, as for example, glycerol, (d) disintegrating agents, as for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain complex silicates, and sodium carbonate, (e) solution retarders, as for example, paraffin, (f) absorption accelerators, as for example, quaternary ammonium compounds, (g) wetting agents, as for example, cetyl alcohol, and glycerol monostearate, (h)
25 adsorbents, as for example, kaolin and bentonite, and (i) lubricants, as for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft
30 and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethyleneglycols, and the like.

Solid dosage forms such as tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells, such as enteric coatings and others known in the

art. They may contain opacifying agents and can also be of such composition that they release the active compound or compounds in a certain part of the intestinal tract in a delayed manner. Examples of embedding compositions that can be used are polymeric substances and waxes. The active compounds can also be in micro-
5 encapsulated form, if appropriate, with one or more of the above-mentioned excipients.

Liquid dosage forms for oral administration of the compounds described herein or derivatives thereof include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. In addition to the active compounds, the
10 liquid dosage forms may contain inert diluents commonly used in the art, such as water or other solvents, solubilizing agents, and emulsifiers, as for example, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propyleneglycol, 1,3-butyleneglycol, dimethylformamide, oils, in particular, cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil, sesame oil, glycerol,
15 tetrahydrofurfuryl alcohol, polyethyleneglycols, and fatty acid esters of sorbitan, or mixtures of these substances, and the like.

Besides such inert diluents, the composition can also include additional agents, such as wetting, emulsifying, suspending, sweetening, flavoring, or perfuming agents.

Suspensions, in addition to the active compounds, may contain additional
20 agents, as for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, or mixtures of these substances, and the like.

Compositions of the compounds described herein or derivatives thereof for rectal administrations are preferably suppositories, which can be prepared by mixing
25 the compounds with suitable non-irritating excipients or carriers such as cocoa butter, polyethyleneglycol or a suppository wax, which are solid at ordinary temperatures but liquid at body temperature and therefore, melt in the rectum or vaginal cavity and release the active component.

Dosage forms for topical administration of the compounds described herein or
30 derivatives thereof include ointments, powders, sprays, and inhalants. The compounds described herein or derivatives thereof are admixed under sterile conditions with a physiologically acceptable carrier and any preservatives, buffers, or

propellants as may be required. Ophthalmic formulations, ointments, powders, and solutions are also contemplated as being within the scope of the compositions.

The term pharmaceutically acceptable salt as used herein refers to those salts of the compound described herein or derivatives thereof that are, within the scope of sound medical judgment, suitable for use in contact with the tissues of subjects without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds described herein. The term salts refers to the relatively non-toxic, inorganic and organic acid addition salts of the compounds described herein. These salts can be prepared *in situ* during the isolation and purification of the compounds or by separately reacting the purified compound in its free base form with a suitable organic or inorganic acid and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, nitrate, acetate, oxalate, valerate, oleate, palmitate, stearate, laurate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate mesylate, glucoheptonate, lactobionate, methane sulphonate, and laurylsulphonate salts, and the like. These may include cations based on the alkali and alkaline earth metals, such as sodium, lithium, potassium, calcium, magnesium, and the like, as well as non-toxic ammonium, quaternary ammonium, and amine cations including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like. (See S.M. Barge et al., *J. Pharm. Sci.* (1977) 66, 1, which is incorporated herein by reference in its entirety, at least, for compositions taught herein.)

The compounds described above or derivatives thereof are useful in treating cancer and other Hsp90 related diseases and conditions, such as inflammation and neurodegenerative disorders in humans, e.g., including pediatric and geriatric populations, and animals, e.g., veterinary applications. The methods described herein comprise administering to a subject a therapeutically effective amount of the compounds described herein or a pharmaceutically acceptable salt or prodrug thereof. Examples of Hsp90 related diseases include cancer and neurodegenerative disorders. The compounds described herein are also useful in treating inflammation associated with Hsp90 related diseases. As used herein, the terms promoting, treating, and

treatment includes prevention; delay in onset; diminution, eradication, or delay in exacerbation of one or more signs or symptoms after onset; and prevention of relapse.

The methods and compounds as described herein are useful for both prophylactic and therapeutic treatment. For prophylactic use, a therapeutically effective amount of the compounds described herein or derivatives thereof are administered to a subject prior to onset (e.g., before obvious signs of an Hsp90 related disease), during early onset (e.g., upon initial signs and symptoms of an Hsp90 related disease), or an established Hsp90 related disease. Prophylactic administration can occur for several days to years prior to the manifestation of symptoms of the Hsp90 related disease. Prophylactic administration can be used, for example, in the preventative treatment of subjects diagnosed with genetic Hsp90 related disease. Therapeutic treatment involves administering to a subject a therapeutically effective amount of the compounds described herein or derivatives thereof after an Hsp90 related disease is diagnosed.

Administration of compounds described herein or derivatives thereof can be carried out using therapeutically effective amounts of the compounds described herein or derivatives thereof for periods of time effective to treat Hsp90 related diseases. The effective amount of the compounds described herein or derivatives thereof may be determined by one of ordinary skill in the art and includes exemplary dosage amounts for a mammal of from about 0.5 to about 200mg/kg of body weight of active compound per day, which may be administered in a single dose or in the form of individual divided doses, such as from 1 to 4 times per day. Alternatively, the dosage amount can be from about 0.5 to about 150mg/kg of body weight of active compound per day, about 0.5 to 100mg/kg of body weight of active compound per day, about 0.5 to about 75mg/kg of body weight of active compound per day, about 0.5 to about 50mg/kg of body weight of active compound per day, about 0.5 to about 25mg/kg of body weight of active compound per day, about 1 to about 20mg/kg of body weight of active compound per day, about 1 to about 10mg/kg of body weight of active compound per day, about 20mg/kg of body weight of active compound per day, about 10mg/kg of body weight of active compound per day, or about 5mg/kg of body weight of active compound per day. Those of skill in the art will understand that the specific dose level and frequency of dosage for any particular subject may be varied and will depend upon a variety of factors, including the activity of the specific

compound employed, the metabolic stability and length of action of that compound, the species, age, body weight, general health, sex and diet of the subject, the mode and time of administration, rate of excretion, drug combination, and severity of the particular condition.

5 In these methods, an Hsp90 related disease, for example, can be further treated with one or more additional agents. The one or more additional agents and the compounds described herein or derivatives thereof can be administered in any order, including simultaneous administration, as well as temporally spaced order of up to several days apart. The methods may also include more than a single administration
10 of the one or more additional agents and/or the compounds described herein or derivatives thereof. The administration of the one or more additional agents and the compounds described herein or derivatives thereof may be by the same or different routes and concurrently or sequentially.

 The examples below are intended to further illustrate certain aspects of the
15 methods and compounds described herein, and are not intended to limit the scope of the claims.

EXAMPLES

20 **Example 1: Activity characterization**

 Compound 1 was evaluated in a competitive binding assay (Du, Moulick et al. *J. Biomol. Screen*, 2007, 12, 915-24). The assay protocol and other assay protocols useful for the methods described herein are briefly described below.

25 **Hsp90 binding FP assay**

 To measure a therapeutically significant state of Hsp90, an FP assay that uses human cancer cell lysates (Du, Moulick et al. *J. Biomol. Screen*, 2007, 12, 915-24) was utilized. It probes the interaction of small molecules with tumor-specific Hsp90 and can therefore lead to inhibitors that are not only selective for cancer cells but also
30 specific for a particular malignancy.

 The dose-response effect of Compound 1 was tested in Hsp90 binding FP competition assays to obtain the IC₅₀ of the compound. The Hsp90 FP competition assay was performed in a 384-well black plate using the small-cell lung carcinoma

(SCLC) cell line NCI-N417 as a source of tumor specific Hsp90 and the Cy3B-labeled geldanamycin (GM-cy3B) as the FP ligand. The compound was dissolved in DMSO and added at several concentrations to the reaction buffer containing both GM-cy3B (5 nM) and NCI-N417 cell lysate (1 µg/well) in a final volume of 50 µL. Free GM-cy3B (5 nM) and bound GM-cy3B with NCI-N417 cell lysate (5 nM GM-cy3B and 1 µg/well of NCI-N417 cell lysate) were included as controls in each plate. After incubating at room temperature for 2 to 16 hours, the polarization values were measured and expressed as millipolarization (mP) units using an Analyst HT plate reader (Molecular Devices). The competitive efficiency of Compound 1 was expressed as a percentage of control and calculated according to the following equation: % of control = $((mP_c - mP_f)/(mP_b - mP_f)) \times 100$, where mP_c is the recorded mP from wells containing compound, mP_f is the average recorded mP from wells containing GM-cy3B-only, and mP_b is the average recorded mP from wells containing both GM-cy3B and NCI-N417 lysate. IC₅₀ values were determined using a nonlinear regression analysis as implemented in Prism 4.0 (Graphpad Software).

Fig. 1 is a graph showing the inhibition activity of compound 1 in a FP assay. The IC₅₀ of Compound 1 was determined as 200 nM.

Cell-based Her2 degradation assay by Western Blot

Hsp90 uniquely stabilizes the Her2/Hsp90 association (Xu, Mimnaugh et al. *J. Biol. Chem.* 2001, 276, 3702-3708). Addition of Hsp90 inhibitors to cancer cells induces the proteasomal degradation of a subset of proteins involved in signal transduction such as Raf1 kinase, Akt, and certain transmembrane tyrosine kinases such as Her2. Thus, Her2 degradation in cells is a functional read-out of Hsp90 inhibition. A correlation between Hsp90 binding and Her2 degradation in cancer cells is indicative of a selective biological effect in these cells via Hsp90.

A Western blot-based assay is used to measure the cellular level of Her2 protein in MCF-7 breast cancer cell lysates collected after 24 hours of compound treatment. MCF-7 cells are grown in RPMI-1640 medium supplemented with 10% fetal bovine serum (FBS). Then, 2×10^5 cells are seeded in 24 well plates in 500 µL PRMI1640 medium and allowed to attach overnight. The compounds are dissolved in DMSO, added to the wells, and incubated for 24 hours. The cells are washed using ice-cold phosphate-buffered saline (PBS) and lysed in 1% NP40 lysis buffer (10 mM

HEPES, pH 7.4, 150 mM NaCl, 1% Nonident P-40, 5 mM Pyrophosphate, 5 mM NaF, 2 mM Orthovanadate, 10 ug/ml Aprotinin, 10 ug/ml Leupeptin, 1 mM PMSF). After boiling with 6 X SDS sample buffer, the cell lysates are separated by SDS-PAGE and transferred to nitrocellulose membrane. The membranes are blocked with 5% milk in tris-buffered saline buffer. The Her2 status is revealed by Western blotting with anti-Her2 antibody (Santa Cruz Biotechnology).

Cell-based Her2 degradation assay by Cytoblot

The cellular Her2 level after compound treatment is monitored by a microtiter-based Her2 degradation assay, which is the Cytoblot assay (Huezo, Vilenchik et al. *Chem. Biol.*, 2003, 10, 629-634). This is a cell-based assay that enables the quantitative analysis of intracellular levels of Her2 protein.

The human breast cancer cell lines SKBr3 are maintained in RPMI1640 medium supplemented with 10% FBS. 3000 cells in 100 μ L of growth medium are plated per well in black, clear-bottom microtiter plates (Corning) and allowed to attach for at least 24 hours at 37°C and 5% CO₂. Compounds at different doses or the vehicle (DMSO) are carefully added to the wells and incubated for 24 hours. The cells are washed twice with ice-cold Tris buffer saline (TBS) containing 0.1% Tween 20 (TBST) and fixed with ice-cold methanol. After washing with TBST, the plate is incubated at RT for 1 hour with SuperBlock (Pierce 37535) and overnight at 4°C with the anti-Her-2 antibody (Santa Cruz Biotechnology). The plate is then washed with TBST and incubated at RT for 2 hours with an anti-rabbit HRP-linked antibody (Sigma A0545). The chemiluminescent substrate solution (Pierce 38040) is added and the plate is read 5 minutes later in an Analyst HT plate reader (Molecular Devices). Luminescence readings resulting from compound-treated cells versus untreated cells (vehicle treated) are quantified and plotted against compound concentrations to give the IC₅₀ values (concentration of compound required to degrade 50% of total Her2).

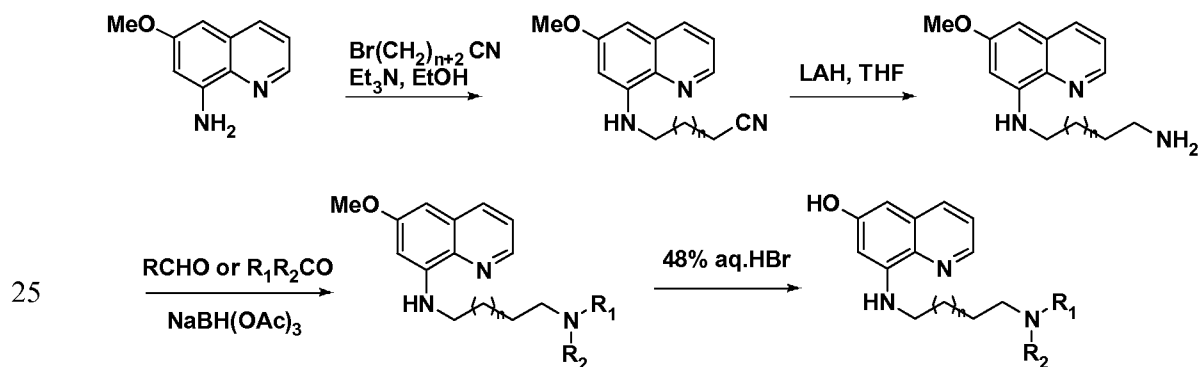
Cancer cell growth inhibition assay

The effects of the compounds on cancer cell growth are determined using the CellTiter-Blue cell viability assay (Promega). CellTiter-Blue[®] Cell Viability is based on the ability of living cells to convert a redox dye (resazurin) into a fluorescent end

product (resorufin). Nonviable cells rapidly lose metabolic capacity and thus do not generate a fluorescent signal.

The SKBR3 breast cancer cells are plated in 384-well microtiter plates (Costar) and allowed to attach overnight. After treatment with either the compounds or the vehicle (DMSO) for 96 hours, the cells are measured for their viability by CellTiter-Blue. Briefly, 10 μ L of CellTiter-Blue are added to each well in 384-well plates and incubated at 37°C for 4 hours. The fluorescence intensity (FI) is measured using the Analyst HT plate reader (Molecular Devices) with an excitation at 545 nm and an emission at 595 nm. The IC₅₀ is calculated as the compound concentration that inhibits cell viability by 50% compared with vehicle control wells.

Example 2: Synthesis of aminoquinoline derivatives

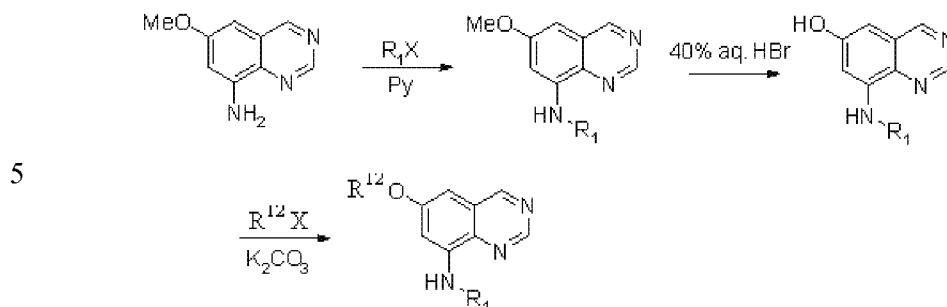


6-Methoxy-8-amino-quinoline (1.5 mmol, 261.3 mg) and 4-bromobutanenitrile (2.25 mmol, 333.0 mg) were refluxed in a mixture of Et_3N (2 ml) and MeOH (1 ml) for 24 hours. Additional 4-bromobutanenitrile (2.25 mmol, 333.0 mg) was added and the mixture was refluxed for another 48 hours. The mixture was concentrated to give a dark oily residue which was purified by chromatography using hexane/ EtOAc (2:1) as the eluent to afford 4-(6-methoxyquinolin-8-ylamino)butanenitrile (148 mg, 40%). ¹H NMR (400 MHz, CDCl_3): δ 8.54 (dd, J = 1.6 Hz, 4.0 Hz, 1H), 7.95 (dd, J = 1.6 Hz, 8.4 Hz, 1H), 7.33 (dd, J = 8.0 Hz, 4.4 Hz, 1H), 6.40 (d, J = 2.8 Hz, 1H), 6.32 (d, J = 2.8 Hz, 1H), 6.20 (m, 1H), 3.90 (s, 3H), 3.49 (q, J = 6.4 Hz, 2H), 2.53 (t, J = 7.2 Hz, 2H), 2.11 (quintet, J = 6.8 Hz, 2H).

To a solution of 4-(6-methoxyquinolin-8-ylamino)butanenitrile (1.0 mmol, 1 equiv, 255.31 mg) in THF (5 ml) was added LAH (2.0 mmol, 2 equiv, 1.0 M in THF) dropwise at -78 °C. The reaction mixture was kept at this temperature for an

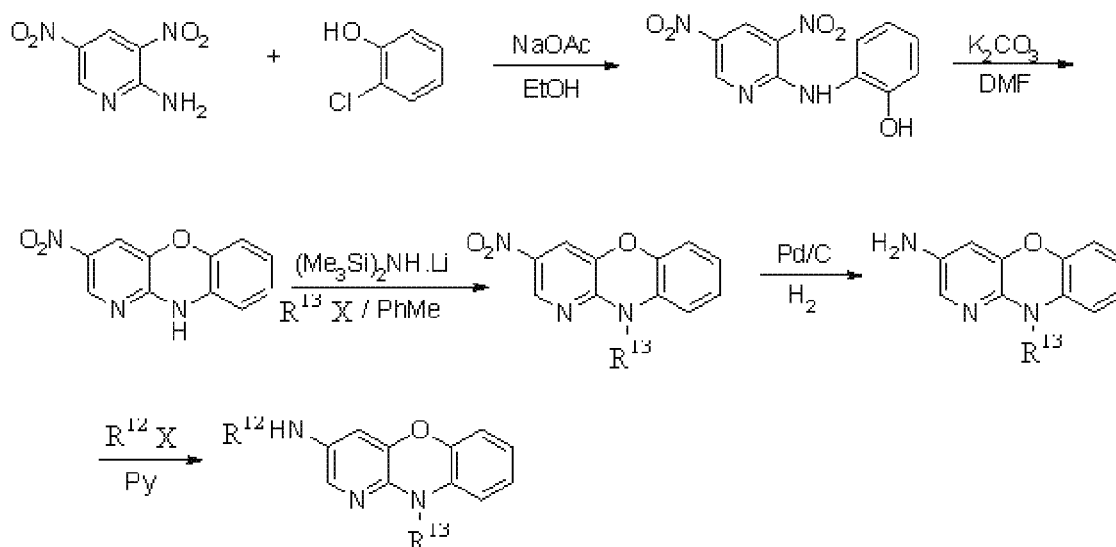
additional 2 hours, which was then allowed to slowly warm up to room temperature. The reaction was quenched by the addition of NaHCO_3 (satd aq) and extracted with EtOAc (3 x 5 ml). The combined organic layers were washed with brine and the resulting product was dried over Na_2SO_4 . The solvent was evaporated to obtain the crude amine as an oily residue, which was subjected to the next step without further purification. To a solution of crude amine in 5 ml of CH_2Cl_2 at 0°C was added acetaldehyde (85 μL , 1.52 mmol). The reaction mixture was kept at 0°C for about 30 minutes, and then $\text{NaBH}(\text{OAc})_3$ (350 mg, 1.65 mmol) was added to the above mixture. The resulting solution was allowed to warm to room temperature for another 3 hours. The mixture was diluted with CH_2Cl_2 (30 ml) and sequentially washed with 10% NaHCO_3 and brine. Drying the organic layers over sodium sulfate followed by filtration and concentration provided a residue that was purified by silica gel chromatography to obtain N^1,N^1 -diethyl- N^4 -(6-methoxyquinolin-8-yl)butane-1,4-diamine (90 mg, 43%). ^1H NMR (400 MHz, $\text{MeOH}-d_4$): δ 8.61 (dd, $J = 3.9, 1.6$ Hz, 1H), 8.13 (dd, $J = 8.6, 1.6$ Hz, 1H), 7.36 (dd, $J = 8.6, 3.9$ Hz, 1H), 6.86 (d, $J = 2.3$ Hz, 1H), 6.83 (d, $J = 2.3$ Hz, 1H), 3.88 (s, 3H), 3.37 (quartet, $J = 7.0$ Hz, 2H), 2.47 (quartet, $J = 7.0$ Hz, 4H), 2.35 (t, $J = 7.8$ Hz, 2H), 1.55–1.48 (m, 2H), 1.41–1.33 (m, 2H), 1.26–1.21 (m, 2H), 0.96 (t, $J = 7.0$ Hz, 6H). MS, m/z ($\text{C}_{19}\text{H}_{29}\text{N}_3\text{O}$): calcd, 315.2; found, 316.4 (MH).

A solution of N^1,N^1 -Diethyl- N^4 -(6-methoxyquinolin-8-yl)butane-1,4-diamine (10 mg, 0.031 mmol) in HBr (1 ml, 48% aq) was heated to 120°C in a microwave initiator for 2.5 h. The reaction mixture was cooled and the solvent was then evaporated using a Genevac DD-4X evaporator. The resulting dark brown residue was purified by silica gel chromatography to provide 8-(5-(diethylamino)pentylamino)quinolin-6-ol (8 mg, 55%) as a pale brown solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 9.12 (br s, 1H), 8.60 (d, $J = 3.9$ Hz, 1H), 8.30 (d, $J = 7.8$ Hz, 1H), 7.56 (dd, $J = 7.8, 4.6$ Hz, 1H), 6.50 (s, 1H), 6.43 (s, 1H), 3.21 (t, $J = 7.0$ Hz, 2H), 3.08 (quintet, $J = 7.0$ Hz, 4H), 3.03–2.98 (m, 2H), 1.74–1.62 (m, 4H), 1.47–1.39 (m, 2H), 1.16 (t, $J = 7.0$ Hz, 6H). ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ 158.5, 143.9, 142.0, 133.0, 132.9, 130.7, 122.5, 100.4, 92.4, 54.5, 51.3, 46.8, 28.1, 24.4, 23.5, 9.2, 9.1. EI, m/z ($\text{C}_{18}\text{H}_{27}\text{N}_3\text{O}$): calcd, 301.4; found: 302.3 (M+H). Anal. Calcd for $\text{C}_{18}\text{H}_{29}\text{Br}_2\text{N}_3\text{O}\cdot\text{H}_2\text{O}$: C, 44.92; H, 6.49; N, 8.73; observed: C, 45.50; H, 6.26; N, 8.59.

Example 3: Synthesis of quinazoline derivatives

6-Methoxy-8-quinazolinamine (1.0 mmol) in pyridine (5 ml) was treated with R_1X (1.1 mmol). The reaction mixture was heated to refluxing temperatures until there was no remaining starting material as evidenced by chromatography (e.g., TLC). The compound was purified by column chromatography to obtain 6-methoxy-*N*-alkylquinazolin-8-amine, which was then de-methylated by treatment with HBr (1 ml, 48%aq) in a microwave initiator at 120 °C for 2-2.5 h. The reaction mixture was cooled to room temperature and the solvent was then evaporated using a Genevac DD-4X evaporator. The resulting dark brown residue was purified by silica gel chromatography to provide 6-hydroxy-*N*-alkylquinazolin-8-amine hydrobromide salt. The hydrobromide salt was then treated with a variety of halides in the presence of K_2CO_3 to provide the final 6,8-substituted quinazoline derivatives.

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Example 4: Synthesis of amino-oxazine derivatives

A mixture of 3,5-dinitropyridin-2-amine (1.0 mmol), 2-chlorophenol (1.0 mmol) and sodium acetate (4.0 mmol) in EtOH (4 ml) and H₂O (1 ml) was stirred under refluxing conditions for 24 h. The solvent was evaporated to provide a residue, which was dissolved in H₂O and extracted with EtOAc. The organic layers were
 5 combined and washed with H₂O and brine, dried over MgSO₄, and then concentrated in vacuo. Purification by column chromatography provided 2-(3,5-dinitropyridin-2-ylamino)phenol.

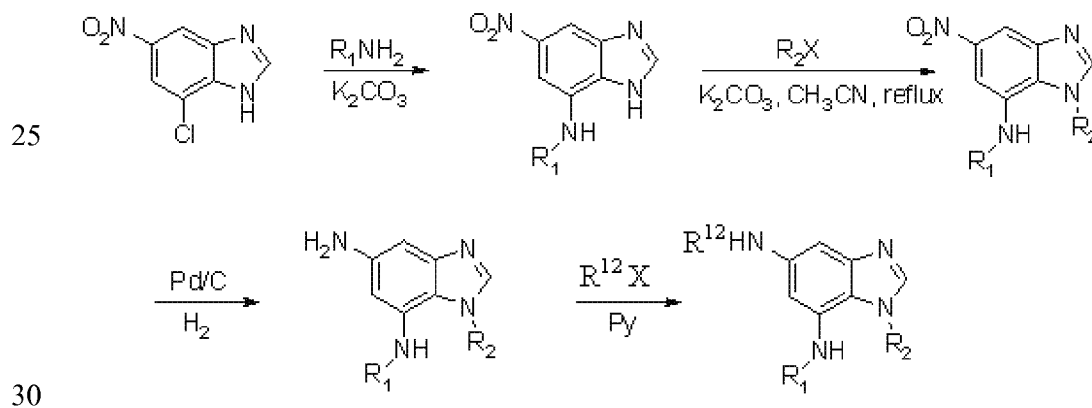
A mixture of the phenol compound (0.5 mmol) and K₂CO₃ (0.6 mmol) in DMF was stirred under reflux for 12h. The compound was extracted with CH₂Cl₂ (3
 10 x 8 ml), dried over MgSO₄, and purified by column chromatography to obtain 3-nitro-10H-benzo[e]pyrido[3,2-b][1,4]oxazine.

The 3-nitro-oxazine (0.1 mmol) was treated with LHMDS (1M in hexanes) in toluene for 20 min. An alkyl halide was then added and the reaction mixture was kept at 80 °C until there was no remaining starting material as evidenced by

15 chromatography (e.g., TLC). The crude compound was purified by column chromatography to obtain 10-alkyl-3-nitro-10H-benzo[e]pyrido[3,2-b][1,4]oxazine, which was subjected to hydrogenation to obtain amino-oxazine derivative.

The amino-oxazine compound was then treated with a variety of halides in the presence of pyridine or other bases to obtain substituted amines as the final products.

20 Example 5: Synthesis of amino-imidazole derivatives



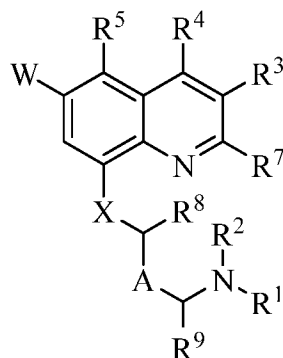
7-Chloro-5-nitro-1H-benzimidazole (1.0 mmol), an amine (1.1 mmol) and K₂CO₃ were refluxed in CH₃CN (5 mL) for 12 h. The reaction was quenched and the

product was purified by column chromatography to obtain N-alkyl-5-nitro-1H-benzo[d]imidazol-7-amine. N-alkyl-5-nitro-1H-benzo[d]imidazol-7-amine was then treated with a variety of halides in the presence of K_2CO_3 in CH_3CN to provide 5-nitro-substituted imidazole. The imidazole was then subjected to hydrogenation to afford 5-amino-7-amine-substituted imidazole. Further treatment of the amine with alkyl halides provided the final substituted amine.

A number of embodiments have been described. Nevertheless, it will be understood to one skilled in the art that various modifications may be made. Further, while only certain representative combinations of the formulations, methods, or products are disclosed herein are specifically described, other combinations of the method steps or combinations of elements of a composition or product are intended to fall within the scope of the appended claims. Thus a combination of steps, elements, or components may be explicitly mentioned herein; however, all other combinations of steps, elements, and components are included, even though not explicitly stated.

WHAT IS CLAIMED IS:

1. A compound of the following formula:



or a pharmaceutically acceptable salt or prodrug thereof, wherein:

A is substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted C₂₋₆ alkenyl, or substituted or unsubstituted C₂₋₆ alkynyl;

W is NHR⁶, OR⁶, or hydrogen;

X is NH, S, or O;

R¹ and R² are each independently selected from hydrogen, substituted or unsubstituted C₁₋₁₂ alkyl, substituted or unsubstituted C₁₋₁₂ haloalkyl, substituted or unsubstituted C₂₋₁₂ alkenyl, substituted or unsubstituted C₂₋₁₂ alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkylalkyl, substituted or unsubstituted acyl, and substituted or unsubstituted sulfonyl, wherein R¹ and R² together are substituted or unsubstituted C₁₋₈ alkyl or substituted or unsubstituted C₂₋₈ alkenyl;

R³, R⁴, and R⁵ are each independently selected from hydrogen, halogen, hydroxyl, nitro, cyano, substituted or unsubstituted amino, substituted or unsubstituted thio, substituted or unsubstituted C₁₋₁₂ alkyl, substituted or unsubstituted C₂₋₁₂ alkenyl, substituted or unsubstituted C₂₋₁₂ alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted

arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkylalkyl, substituted or unsubstituted C₁₋₁₂ alkylamine, substituted or unsubstituted C₂₋₁₂ alkenylamine, substituted or unsubstituted C₂₋₁₂ alkynylamine, substituted or unsubstituted arylamine, substituted or unsubstituted acyl, substituted or unsubstituted alkoxy, and substituted or unsubstituted aryloxy;

R⁶ is hydrogen, substituted or unsubstituted C₁₋₁₂ alkyl, substituted or unsubstituted C₂₋₁₂ alkenyl, substituted or unsubstituted C₂₋₁₂ alkynyl, substituted or unsubstituted acyl, substituted or unsubstituted aminoalkyl, substituted or unsubstituted hydroxyalkyl, or substituted or unsubstituted alkoxyalkyl;

R⁷ is hydrogen, hydroxyl, substituted or unsubstituted alkoxy, substituted or unsubstituted amino, substituted or unsubstituted thio, substituted or unsubstituted C₁₋₁₂ alkyl, substituted or unsubstituted C₁₋₁₂ haloalkyl, substituted or unsubstituted C₂₋₁₂ alkenyl, substituted or unsubstituted C₂₋₁₂ alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkylalkyl, substituted or unsubstituted acyl, or substituted or unsubstituted sulfonyl; and

R⁸ and R⁹ are each independently selected from hydrogen, substituted or unsubstituted C₁₋₁₂ alkyl, substituted or unsubstituted C₂₋₁₂ alkenyl, and substituted or unsubstituted C₂₋₁₂ alkynyl,

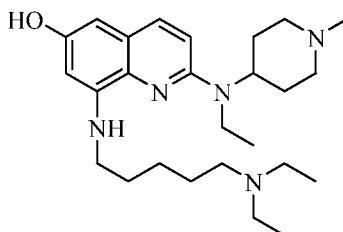
wherein if X is NH, W is hydroxyl or methoxy, and one of R¹ or R² is C₁₋₅ alkyl, the other of R¹ or R² is not hydrogen or C₁₋₅ alkyl;

if X is NH and W is hydroxyl or methoxy, R¹ and R² are not simultaneously hydrogen; and

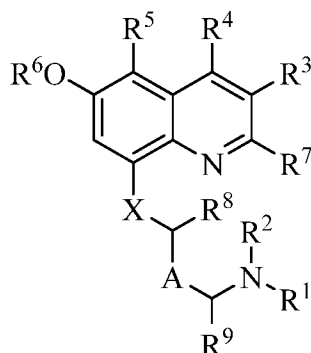
if X is NH, W is hydroxyl or methoxy, and R⁸ is methyl, R⁹ is not hydrogen.

2. The compound of claim 1, wherein X is NH.
3. The compound of claim 1 or 2, wherein R⁵ is substituted or unsubstituted amido.

4. The compound of any of claims 1-3, wherein R^7 is substituted or unsubstituted amino.
5. The compound of claim 1, 2, or 4, wherein the compound is



6. The compound of claim 1, wherein the compound has the following formula:



or a pharmaceutically acceptable salt or prodrug thereof, wherein:

A is substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, or substituted or unsubstituted C_{2-6} alkynyl;

X is S or O;

R^1 , R^2 , and R^7 are each independently selected from hydrogen, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{1-12} haloalkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkylalkyl, substituted or unsubstituted acyl, and substituted or unsubstituted sulfonyl, wherein R^1 and R^2 together are substituted or unsubstituted C_{1-8} alkyl or substituted or unsubstituted C_{2-8} alkenyl;

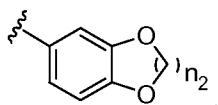
R^3 , R^4 , and R^5 are each independently selected from hydrogen, halogen, hydroxyl, nitro, substituted or unsubstituted amino, cyano, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkylalkyl, substituted or unsubstituted C_{1-12} alkylamine, substituted or unsubstituted C_{2-12} alkenylamine, substituted or unsubstituted C_{2-12} alkynylamine, substituted or unsubstituted arylamine, substituted or unsubstituted alkoxy, and substituted or unsubstituted aryloxy;

R^6 is hydrogen, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted acyl, substituted or unsubstituted aminoalkyl, substituted or unsubstituted hydroxyalkyl, or substituted or unsubstituted alkoxyalkyl; and

R^8 and R^9 are each independently selected from hydrogen, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{2-12} alkenyl, and substituted or unsubstituted C_{2-12} alkynyl.

7. The compound of claim 6, wherein R^1 is hydrogen, methyl, ethyl, propyl, butyl, pentyl, isopropyl, *sec*-butyl, isobutyl, benzyl, benzoyl, acetyl, or substituted or unsubstituted sulfonyl.

8. The compound of claim 6 or 7, wherein R^2 is hydrogen, methyl, ethyl, propyl, butyl, pentyl, isopropyl, *sec*-butyl, isobutyl, benzyl, benzoyl, acetyl, or

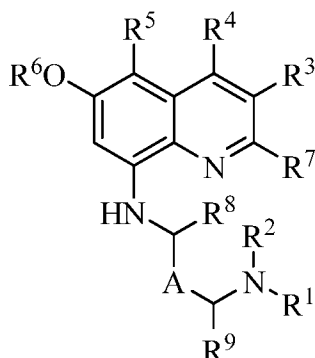


9. The compound of claim 6, wherein R^1 -N- R^2 combine to form aziridine, azetidine, pyrrolidine, or piperidine.

10. The compound of any of claims 6-9, wherein R^3 is hydrogen, methyl, ethyl, propyl, or NH-ethyl.

11. The compound of any of claims 6-10, wherein R^4 is hydrogen, methyl, ethyl, propyl, NH-ethyl, NH-phenyl, chloro, hydroxyl, methoxyl, or phenoxy.

12. The compound of any of claims 6-11, wherein R^5 is hydrogen, hydroxyl, chloro, nitro, amino, NH-phenyl, *p*-chlorophenyl, or *p*-methoxyphenyl.
13. The compound of any of claims 6-12, wherein R^6 is hydrogen, methyl, ethyl, allyl, acetyl, or $-(CH_2)_{n_1}T$, wherein n_1 is 1-5 and T is hydrogen, hydroxyl, amino, or alkoxy.
14. The compound of any of claims 6-13, wherein R^7 is hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *t*-butyl, acetyl, or propanoyl.
15. The compound of any of claims 6-14, wherein R^8 is hydrogen, methyl, or ethyl.
16. The compound of any of claims 6-15, wherein R^9 is hydrogen, methyl, or ethyl.
17. The compound of claim 1, wherein the compound has the following formula:



or a pharmaceutically acceptable salt or prodrug thereof, wherein:

A is substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, or substituted or unsubstituted C_{2-6} alkynyl;

R^1 and R^2 are each independently selected from hydrogen, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{1-12} haloalkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkylalkyl, substituted or unsubstituted acyl, and substituted or unsubstituted sulfonyl, wherein R^1 and R^2

together are substituted or unsubstituted C₁₋₈ alkyl or substituted or unsubstituted C₂₋₈ alkenyl;

R³, R⁴, and R⁵ are each independently selected from hydrogen, halogen, hydroxyl, nitro, substituted or unsubstituted amino, cyano, substituted or unsubstituted C₁₋₁₂ alkyl, substituted or unsubstituted C₂₋₁₂ alkenyl, substituted or unsubstituted C₂₋₁₂ alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkylalkyl, substituted or unsubstituted C₁₋₁₂ alkylamine, substituted or unsubstituted C₂₋₁₂ alkenylamine, substituted or unsubstituted C₂₋₁₂ alkynylamine, substituted or unsubstituted arylamine, substituted or unsubstituted alkoxy, and substituted or unsubstituted aryloxy;

R⁶ is hydrogen, substituted or unsubstituted C₁₋₁₂ alkyl, substituted or unsubstituted C₂₋₁₂ alkenyl, substituted or unsubstituted C₂₋₁₂ alkynyl, substituted or unsubstituted acyl, substituted or unsubstituted aminoalkyl, substituted or unsubstituted hydroxyalkyl, or substituted or unsubstituted alkoxyalkyl;

R⁷ is hydrogen, substituted or unsubstituted C₁₋₁₂ alkyl, substituted or unsubstituted C₁₋₁₂ haloalkyl, substituted or unsubstituted C₂₋₁₂ alkenyl, substituted or unsubstituted C₂₋₁₂ alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkylalkyl, substituted or unsubstituted acyl, or substituted or unsubstituted sulfonyl; and

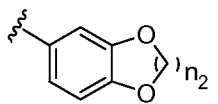
R⁸ and R⁹ are each independently selected from hydrogen, substituted or unsubstituted C₁₋₁₂ alkyl, substituted or unsubstituted C₂₋₁₂ alkenyl, and substituted or unsubstituted C₂₋₁₂ alkynyl,

wherein if R⁶ is hydrogen or methyl and one of R¹ or R² is C₁₋₅ alkyl, the other of R¹ or R² is not hydrogen or C₁₋₅ alkyl;

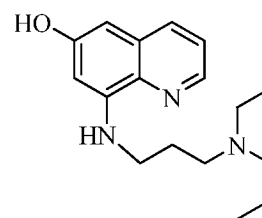
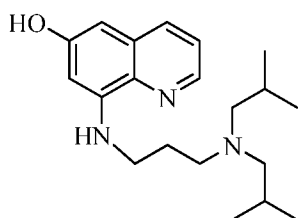
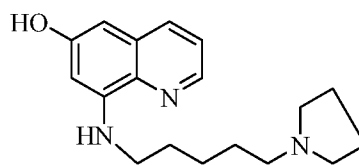
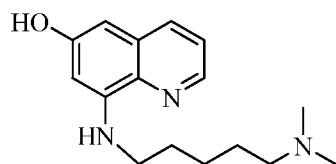
if R⁶ is hydrogen or methyl, R¹ and R² are not simultaneously hydrogen; and

if R⁶ is hydrogen or methyl and R⁸ is methyl, R⁹ is not hydrogen.

18. The compound of claim 17, wherein R¹ and R² are not C₁₋₁₂ alkyl.
19. The compound of claim 17 or 18, wherein R¹ is hydrogen, benzyl, benzoyl, acetyl, or substituted or unsubstituted sulfonyl.
20. The compound of any of claims 17-19, wherein R² is hydrogen, benzyl, benzoyl, acetyl, or

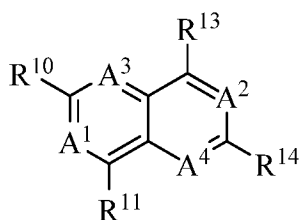


21. The compound of claim 17, wherein R¹-N-R² combine to form aziridine, azetidine, pyrrolidine, or piperidine.
22. The compound of any of claims 17-21, wherein R³ is hydrogen, methyl, ethyl, propyl, or NH-ethyl.
23. The compound of any of claims 17-22, wherein R⁴ is hydrogen, methyl, ethyl, propyl, NH-ethyl, NH-phenyl, chloro, hydroxyl, methoxyl, or phenoxy.
24. The compound of any of claims 17-23, wherein R⁵ is hydrogen, hydroxyl, chloro, nitro, amino, NH-phenyl, *p*-chlorophenyl, or *p*-methoxyphenyl.
25. The compound of any of claims 17-24, wherein R⁶ is hydrogen, methyl, ethyl, allyl, acetyl, or -(CH₂)_{n₁}T, wherein n₁ is 1-5 and T is hydrogen, hydroxyl, amino, or alkoxy.
26. The compound of any of claims 17-25, wherein R⁷ is hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *t*-butyl, acetyl, or propanoyl.
27. The compound of any of claims 17-26, wherein R⁸ is hydrogen, methyl, or ethyl.
28. The compound of any of claims 17-27, wherein R⁹ is hydrogen, methyl, or ethyl.
29. The compound of claim 17, wherein the compound is selected from the following:



30. The compound of any of claims 1-29, wherein the compound is a hydrobromide salt.

31. A compound of the following formula:



or a pharmaceutically acceptable salt or prodrug thereof, wherein:

A^1 , A^2 , A^3 , and A^4 are each independently selected from N and CR^7 , wherein R^7 is hydrogen, substituted or unsubstituted amino, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{1-12} haloalkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkylalkyl, substituted or unsubstituted acyl, or substituted or unsubstituted sulfonyl, wherein at least one of A^1 , A^2 , and A^3 is N;

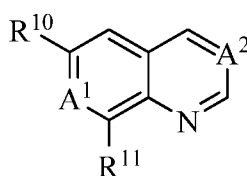
R^{10} is hydrogen, hydroxyl, substituted or unsubstituted alkoxy, substituted or unsubstituted amino, or substituted or unsubstituted thiol;

R^{11} is substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{1-12} haloalkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkylalkyl, substituted or unsubstituted amino, substituted or unsubstituted alkylsulfonylamino, substituted or unsubstituted arylsulfonylamino, substituted or unsubstituted arylalkylsulfonylamino, substituted or unsubstituted cycloalkylsulfonylamino, substituted or unsubstituted heteroalkylsulfonylamino, substituted or unsubstituted heteroarylsulfonylamino, substituted or unsubstituted heterocycloalkylsulfonylamino, substituted or unsubstituted heteroarylalkylsulfonylamino, substituted or unsubstituted cycloalkylalkylsulfonylamino, or substituted or unsubstituted heterocycloalkylalkylsulfonylamino; and

R^{13} and R^{14} are independently hydrogen, halogen, hydroxyl, substituted or substituted amino, substituted or unsubstituted alkoxy, substituted or unsubstituted thiol, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{1-12} haloalkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, and substituted or unsubstituted heterocycloalkylalkyl.

32. The compound of claim 31, wherein A^3 is N.

33. The compound of claim 31, wherein the compound has the following formula:



or a pharmaceutically acceptable salt or prodrug thereof, wherein:

A^1 and A^2 are each independently selected from CH and N;

R^{10} is hydrogen, hydroxyl, substituted or unsubstituted alkoxy, substituted or unsubstituted amino, or substituted or unsubstituted thiol; and

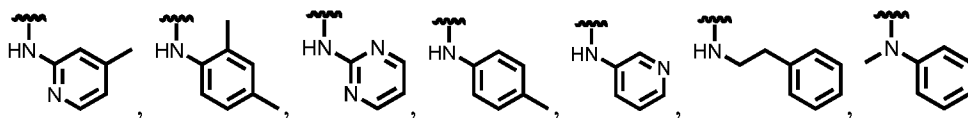
R^{11} is substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{1-12} haloalkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkylalkyl, substituted or unsubstituted amino, substituted or unsubstituted alkylsulfonylamino, substituted or unsubstituted arylsulfonylamino, substituted or unsubstituted arylalkylsulfonylamino, substituted or unsubstituted cycloalkylsulfonylamino, substituted or unsubstituted heteroalkylsulfonylamino, substituted or unsubstituted heteroarylsulfonylamino, substituted or unsubstituted heterocycloalkylsulfonylamino, substituted or unsubstituted heteroarylalkylsulfonylamino, substituted or unsubstituted cycloalkylalkylsulfonylamino, or substituted or unsubstituted heterocycloalkylalkylsulfonylamino.

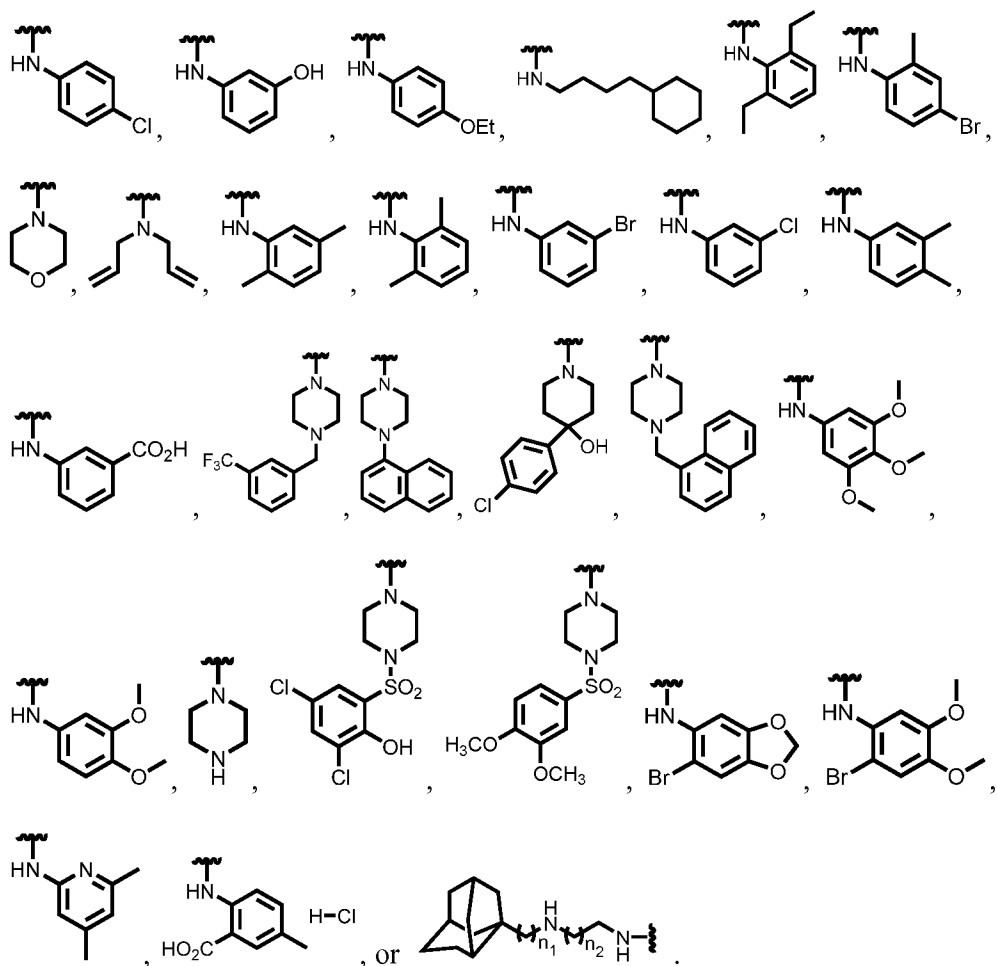
34. The compound of claim 33, wherein R^{10} is substituted or unsubstituted amino.

35. The compound of claim 33 or 34, wherein R^{11} is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, or substituted or unsubstituted amino.

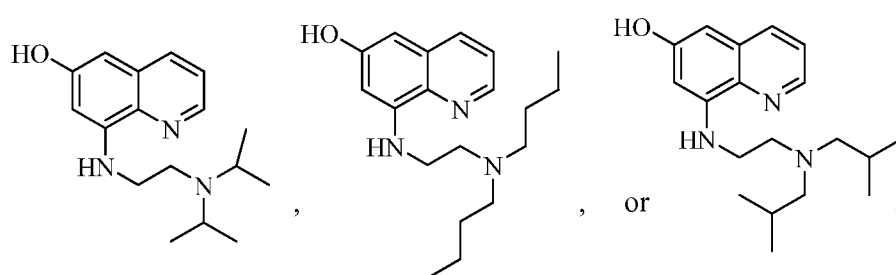
36. The compound of claim 33 or 34, wherein R^{11} is substituted or unsubstituted amino.

37. The compound of claim 33 or 34, wherein R^{11} is

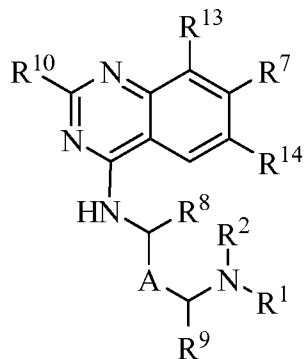




38. The compound of claim 33, wherein the compound is selected from:



39. The compound of claim 31, wherein the compound has the following formula:



or a pharmaceutically acceptable salt or prodrug thereof, wherein:

R^1 and R^2 are each independently selected from hydrogen, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{1-12} haloalkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkylalkyl, substituted or unsubstituted acyl, and substituted or unsubstituted sulfonyl, wherein R^1 and R^2 together are substituted or unsubstituted C_{1-8} alkyl or substituted or unsubstituted C_{2-8} alkenyl;

R^7 is hydrogen, substituted or unsubstituted amino, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{1-12} haloalkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkylalkyl, substituted or unsubstituted acyl, or substituted or unsubstituted sulfonyl;

R^8 and R^9 are each independently selected from hydrogen, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{2-12} alkenyl, and substituted or unsubstituted C_{2-12} alkynyl;

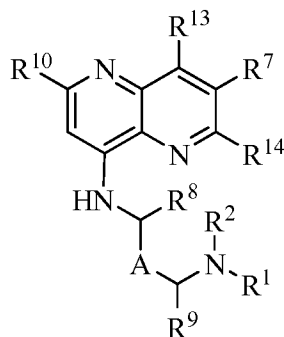
R^{10} is hydrogen, hydroxyl, substituted or unsubstituted alkoxyl, substituted or unsubstituted amino, or substituted or unsubstituted thiol;

R^{11} is substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{1-12} haloalkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkylalkyl, substituted or unsubstituted amino, substituted or unsubstituted alkylsulfonylamino, substituted or

unsubstituted arylsulfonylamino, substituted or unsubstituted arylalkylsulfonylamino, substituted or unsubstituted cycloalkylsulfonylamino, substituted or unsubstituted heteroalkylsulfonylamino, substituted or unsubstituted heteroarylsulfonylamino, substituted or unsubstituted heterocycloalkylsulfonylamino, substituted or unsubstituted heteroarylalkylsulfonylamino, substituted or unsubstituted cycloalkylalkylsulfonylamino, or substituted or unsubstituted heterocycloalkylalkylsulfonylamino; and

R^{13} and R^{14} are each independently hydrogen, halogen, substituted or substituted amino, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{1-12} haloalkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, and substituted or unsubstituted heterocycloalkylalkyl.

40. The compound of claim 31, wherein the compound has the following formula:



or a pharmaceutically acceptable salt or prodrug thereof, wherein:

R^1 and R^2 are each independently selected from hydrogen, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{1-12} haloalkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkylalkyl, substituted or unsubstituted acyl, and substituted or unsubstituted sulfonyl, wherein R^1 and R^2

together are substituted or unsubstituted C₁₋₈ alkyl or substituted or unsubstituted C₂₋₈ alkenyl;

R⁷ is hydrogen, substituted or unsubstituted amino, substituted or unsubstituted C₁₋₁₂ alkyl, substituted or unsubstituted C₁₋₁₂ haloalkyl, substituted or unsubstituted C₂₋₁₂ alkenyl, substituted or unsubstituted C₂₋₁₂ alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkylalkyl, substituted or unsubstituted acyl, or substituted or unsubstituted sulfonyl;

R⁸ and R⁹ are each independently selected from hydrogen, substituted or unsubstituted C₁₋₁₂ alkyl, substituted or unsubstituted C₂₋₁₂ alkenyl, and substituted or unsubstituted C₂₋₁₂ alkynyl;

R¹⁰ is hydrogen, hydroxyl, substituted or unsubstituted alkoxy, substituted or unsubstituted amino, or substituted or unsubstituted thiol;

R¹¹ is substituted or unsubstituted C₁₋₁₂ alkyl, substituted or unsubstituted C₁₋₁₂ haloalkyl, substituted or unsubstituted C₂₋₁₂ alkenyl, substituted or unsubstituted C₂₋₁₂ alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkylalkyl, substituted or unsubstituted amino, substituted or unsubstituted alkylsulfonylamino, substituted or unsubstituted arylsulfonylamino, substituted or unsubstituted arylalkylsulfonylamino, substituted or unsubstituted cycloalkylsulfonylamino, substituted or unsubstituted heteroalkylsulfonylamino, substituted or unsubstituted heteroarylalkylsulfonylamino, substituted or unsubstituted heterocycloalkylsulfonylamino, substituted or unsubstituted heteroarylalkylsulfonylamino, substituted or unsubstituted cycloalkylalkylsulfonylamino, or substituted or unsubstituted heterocycloalkylalkylsulfonylamino; and

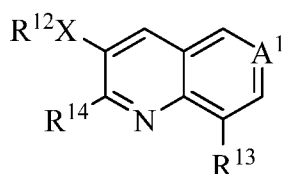
R¹³ and R¹⁴ are independently hydrogen, halogen, substituted or substituted amino, substituted or unsubstituted C₁₋₁₂ alkyl, substituted or unsubstituted C₁₋₁₂

haloalkyl, substituted or unsubstituted C₂₋₁₂ alkenyl, substituted or unsubstituted C₂₋₁₂ alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, and substituted or unsubstituted heterocycloalkylalkyl.

41. The compound of claim 39 or 40, wherein R¹⁰ is substituted or unsubstituted amino.

42. The compound of any of claims 39-41, wherein A is (CH₂)₃, R⁸ is hydrogen, and R⁹ is hydrogen.

43. A compound of the following formula:



or a pharmaceutically acceptable salt or prodrug thereof, wherein:

A¹ is CH or N;

X is NH, S, or O;

R¹² is hydrogen or substituted or unsubstituted C₁₋₁₂ alkyl; and

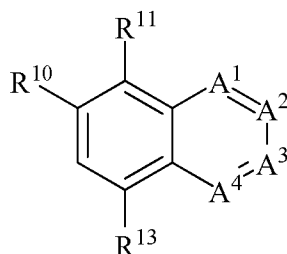
R¹³ and R¹⁴ are independently hydrogen, substituted or substituted amino, substituted or unsubstituted C₁₋₁₂ alkyl, substituted or unsubstituted C₁₋₁₂ haloalkyl, substituted or unsubstituted C₂₋₁₂ alkenyl, substituted or unsubstituted C₂₋₁₂ alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, and substituted or unsubstituted heterocycloalkylalkyl, wherein R¹³ and R¹⁴ are not both hydrogen.

44. The compound of claim 43, wherein R¹²X is substituted or unsubstituted amino.

45. The compound of claim 43 or 44, wherein R^{13} is substituted or unsubstituted amino.

46. The compound of any of claims 43-45, wherein R^{14} is substituted or unsubstituted amino.

47. A compound of the following formula:



or a pharmaceutically acceptable salt or prodrug thereof, wherein:

A^1 , A^2 , A^3 , and A^4 are each independently selected from N and CR^7 , wherein each R^7 is independently hydrogen, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-8} alkenyl, or substituted or unsubstituted amino;

R^{10} is hydrogen, hydroxyl, substituted or unsubstituted alkoxy, substituted or unsubstituted amino, substituted or unsubstituted carbamate, or substituted or unsubstituted thiol;

R^{11} is hydroxyl, substituted or unsubstituted alkoxy, substituted or unsubstituted amino, substituted or unsubstituted carbamate, substituted or unsubstituted thiol, or substituted or unsubstituted acyl; and

R^{13} is substituted or unsubstituted amino.

48. The compound of claim 47, wherein R^{11} is amido.

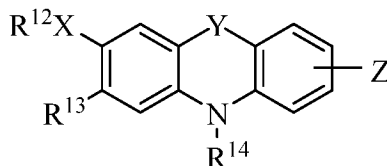
49. The compound of claim 47 or 48, wherein A^3 is CR^7 .

50. The compound of any of claims 47-49, wherein A^1 , A^2 , A^3 , and A^4 are CR^7 .

51. The compound of any of claims 47-50, wherein adjacent R^7 groups combine to form a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl.

52. The compound of any of claims 47-51, wherein R^7 is hydrogen.

53. A compound of the following formula:



or a pharmaceutically acceptable salt or prodrug thereof, wherein:

Y is NR^1 , O, S, CHR^1 , or $\text{CHR}^1\text{-CHR}^2$, wherein R^1 and R^2 are each independently selected from hydrogen, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{1-12} haloalkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkylalkyl, substituted or unsubstituted acyl, and substituted or unsubstituted sulfonyl;

Z is hydrogen or halogen;

X is NH, S, or O;

R^{12} is hydrogen or substituted or unsubstituted alkyl; and

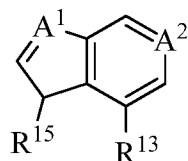
R^{13} is hydrogen, substituted or unsubstituted amino, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{1-12} haloalkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, or substituted or unsubstituted heterocycloalkylalkyl; and

R^{14} is hydrogen, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{1-12} haloalkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or

unsubstituted cycloalkylalkyl, or substituted or unsubstituted heterocycloalkylalkyl, wherein R^{13} and R^{14} are not both hydrogen.

54. The compound of claim 53, wherein Y is NR^1 , O, S, or CHR^1 .

55. A compound of the following formula:



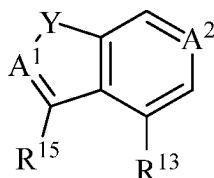
or a pharmaceutically acceptable salt or prodrug thereof, wherein:

A^1 and A^2 are each independently selected from CH and N;

R^{15} is hydrogen, hydroxyl, or substituted or unsubstituted alkoxyl; and

R^{13} is substituted or unsubstituted amino, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{1-12} haloalkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, or substituted or unsubstituted heterocycloalkylalkyl.

56. A compound of the following formula:



or a pharmaceutically acceptable salt or prodrug thereof, wherein:

X is NH, S, or O;

Y is NR^1 , O, S, or CHR^1 , wherein R^1 is hydrogen, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{1-12} haloalkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl,

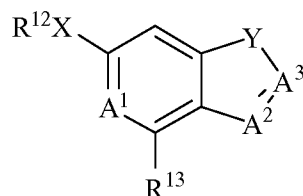
substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkylalkyl, substituted or unsubstituted acyl, and substituted or unsubstituted sulfonyl;

A^1 and A^2 are each independently selected from CH and N;

R^{13} is substituted or unsubstituted amino, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{1-12} haloalkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, or substituted or unsubstituted heterocycloalkylalkyl; and

R^{15} is hydrogen, hydroxyl, or substituted or unsubstituted alkoxy.

57. A compound of the following formula:



or a pharmaceutically acceptable salt or prodrug thereof, wherein:

X is NH, S, or O;

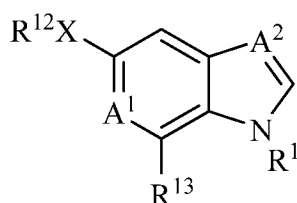
Y is NR^1 , O, S, or CHR^1 , wherein R^1 is hydrogen, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{1-12} haloalkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkylalkyl, substituted or unsubstituted acyl, and substituted or unsubstituted sulfonyl;

A^1 , A^2 , and A^3 are each independently selected from CH and N;

R^{12} is hydrogen or substituted or unsubstituted alkyl; and

R^{13} is substituted or unsubstituted amino, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{1-12} haloalkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, or substituted or unsubstituted heterocycloalkylalkyl.

58. A compound of the following formula:



or a pharmaceutically acceptable salt or prodrug thereof, wherein:

X is NH, S, or O;

A^1 and A^2 are each independently selected from CH and N;

R^1 is hydrogen, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{1-12} haloalkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkylalkyl, substituted or unsubstituted acyl, or substituted or unsubstituted sulfonyl;

R^{12} is hydrogen or substituted or unsubstituted alkyl; and

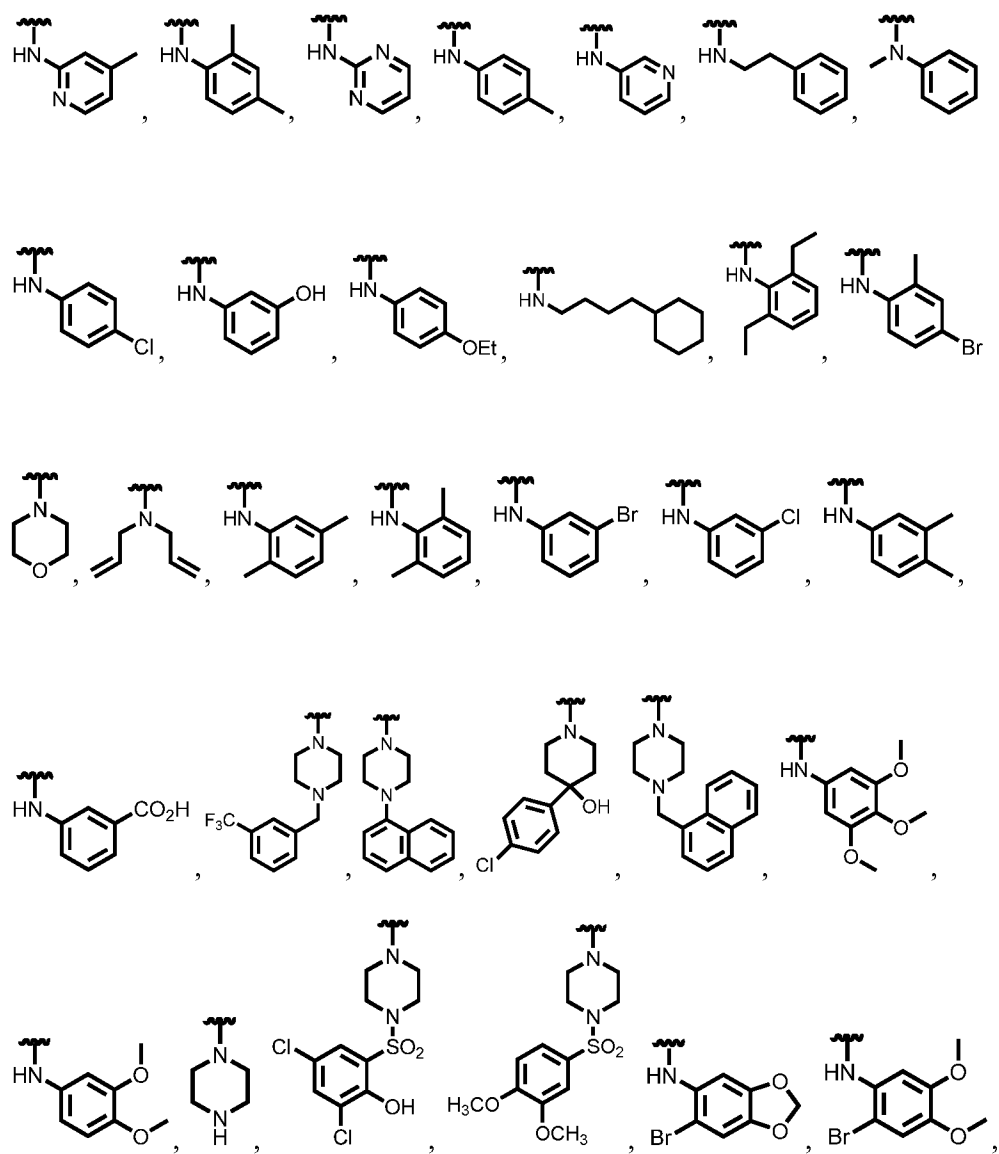
R^{13} is substituted or unsubstituted amino, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{1-12} haloalkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl,

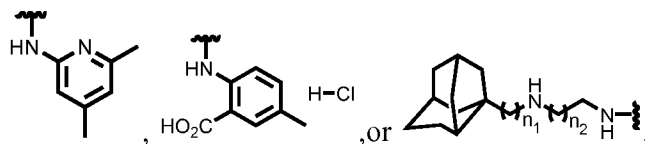
substituted or unsubstituted cycloalkylalkyl, or substituted or unsubstituted heterocycloalkylalkyl.

59. The compound of any of claims 47-58, wherein R^{13} is alkyl, alkenyl, alkynyl, cycloalkyl, or aryl.

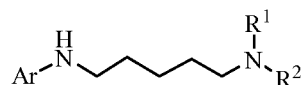
60. The compound of any of claims 47-58, wherein R^{13} is substituted or unsubstituted amino.

61. The compound of any of claims 47-58, wherein R^{13} is





62. A compound of the following formula:



or a pharmaceutically acceptable salt or prodrug thereof, wherein:

Ar is substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl; and

R¹ and R² are each independently selected from hydrogen, substituted or unsubstituted C₁₋₁₂ alkyl, substituted or unsubstituted C₁₋₁₂ haloalkyl, substituted or unsubstituted C₂₋₁₂ alkenyl, substituted or unsubstituted C₂₋₁₂ alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkylalkyl, substituted or unsubstituted acyl, and substituted or unsubstituted sulfonyl.

63. The compound of claim 62, wherein R¹ and R² are substituted or unsubstituted C₁₋₆ alkyl.

64. The compound of claim 62 or 63, wherein Ar is substituted or unsubstituted naphthalene.

65. The compound of claim 62 or 63, wherein Ar is substituted or unsubstituted quinoline.

66. The compound of claim 62 or 63, wherein Ar is substituted or unsubstituted quinazoline.

67. The compound of claim 62 or 63, wherein Ar is substituted or unsubstituted naphthyridine.

68. A composition comprising a compound of any of claims 1-67 and a pharmaceutically acceptable carrier.

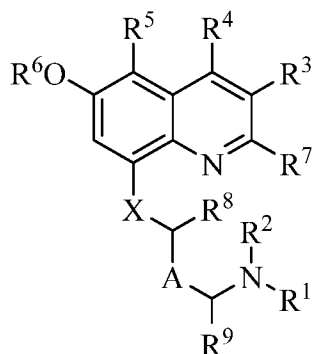
69. A method preventing or treating cancer in a subject comprising administering to the subject a therapeutically effective amount of the compound or compositions of any of claims 1-68.

70. A method of preventing or treating Hsp90 related diseases in a subject comprising administering to the subject a therapeutically effective amount of the compound or compositions of any of claims 1-68.

71. The method of claim 70, wherein the Hsp90 related disease causes inflammation and the compound treats inflammation.

72. The method of claim 70, wherein the Hsp90 related disease is a neurodegenerative disorder.

73. A method of preventing or treating Hsp90 related diseases in a subject comprising selecting a subject with a Hsp90 related disease and administering to the subject a therapeutically effective amount of the compound or compositions of the following formula:



or a pharmaceutically acceptable salt or prodrug thereof, wherein:

A is substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted C₁₋₆ haloalkyl, substituted or unsubstituted C₂₋₆ alkenyl, or substituted or unsubstituted C₂₋₆ alkynyl;

X is NH, S, or O;

R¹, R², and R⁷ are each independently selected from hydrogen, substituted or unsubstituted C₁₋₁₂ alkyl, substituted or unsubstituted C₁₋₁₂ haloalkyl, substituted or unsubstituted C₂₋₁₂ alkenyl, substituted or unsubstituted C₂₋₁₂ alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkylalkyl, substituted or

unsubstituted acyl, and substituted or unsubstituted sulfonyl, wherein R^1 and R^2 together are substituted or unsubstituted C_{1-8} alkyl or substituted or unsubstituted C_{2-8} alkenyl;

R^3 , R^4 , and R^5 are each independently selected from hydrogen, halogen, nitro, substituted or unsubstituted amino, cyano, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkylalkyl, substituted or unsubstituted C_{1-12} alkylamine, substituted or unsubstituted C_{2-12} alkenylamine, substituted or unsubstituted C_{2-12} alkynylamine, substituted or unsubstituted arylamine, substituted or unsubstituted alkoxy, and substituted or unsubstituted aryloxy;

R^6 is hydrogen, halogen, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{2-12} alkenyl, and substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted acyl, substituted or unsubstituted aminoalkyl, hydroxyalkyl, or substituted or unsubstituted alkoxyalkyl; and

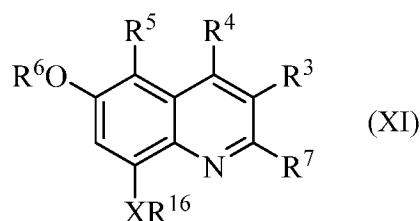
R^8 and R^9 are each independently selected from hydrogen, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{2-12} alkenyl, and substituted or unsubstituted C_{2-12} alkynyl,

wherein if X is NH, R^6 is hydrogen or methyl, and one of R^1 or R^2 is C_{1-5} alkyl, the other of R^1 or R^2 is not hydrogen or C_{1-5} alkyl;

if X is NH and R^6 is hydrogen or methyl, R^1 and R^2 are not simultaneously hydrogen; and

if X is NH, R^6 is hydrogen or methyl, and R^8 is methyl, R^9 is not hydrogen.

74. A method of making a compound of claim 1, comprising:
treating



wherein X is NH, S, or O and R¹⁶ is H, with excess bromoalkylnitrile in solvent to produce the compound of formula XI, wherein R¹⁶ is alkylnitrile;

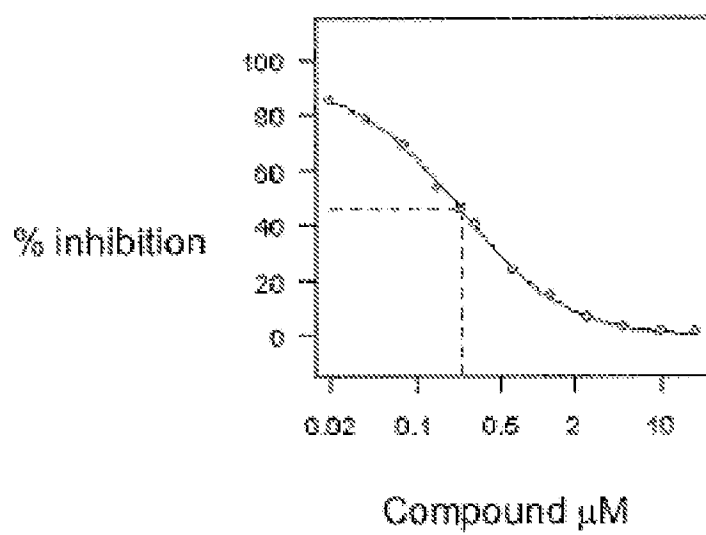
reducing the compound of formula XI, wherein R¹⁶ is alkylnitrile with a hydride donor to produce the compound of formula XI, wherein R¹⁶ is alkylamine; and

alkylating the compound of formula XI, wherein R¹⁶ is alkylamine to produce the compound of formula XI, wherein R¹⁶ is N¹,N¹-dialkylamine.

75. The method of claim 74, further comprising the step of treating the compound of formula IX, wherein R¹⁶ is N¹, N¹-dialkylamine with hydrobromic acid to produce the compound of formula IX, wherein R¹⁶ is N¹, N¹-dialkylamine and R⁶ is H.

76. The method of claim 74 or 75, wherein the hydride donor in the reducing step is lithium aluminum hydride.

77. The method of any of claims 74-76, wherein the solvent in the treating step is a mixture of triethylamine and methanol.

**Fig. 1**