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(54) **METHODS OF MAKING AND USING
THIOXOTHIAZOLIDINE AND RHODANINE
DERIVATIVES AS HIV-1 AND JSP-1
INHIBITORS**

(60) Provisional application No. 61/614,563, filed on Mar.
23, 2012.

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University**, Baltimore, MD (US)

Publication Classification

(51) **Int. Cl.**
A61K 31/427 (2006.01)

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M. Dawson**, Baltimore, MD (US)

(52) **U.S. Cl.**
CPC **A61K 31/427** (2013.01)

(21) Appl. No.: **15/059,018**

(57) **ABSTRACT**

(22) Filed: **Mar. 2, 2016**

Related U.S. Application Data

(62) Division of application No. 13/849,339, filed on Mar.
22, 2013, now Pat. No. 9,309,208.

The present invention provides methods of making and using
5-(2-(indol-3-yl)-2-oxoethylidene)-3-phenyl-2-thioxothia-
zolidin-4-one derivatives having HIV-1 or JSP-1 inhibitory
activity.

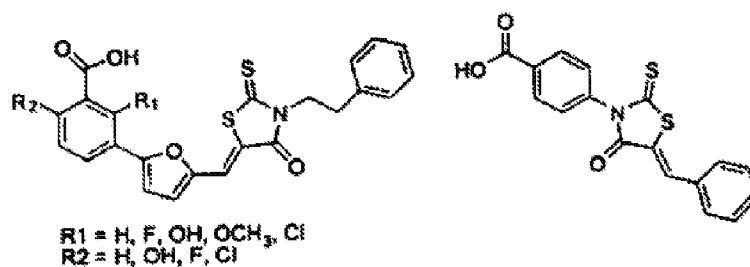


FIGURE 1A

FIGURE 1B

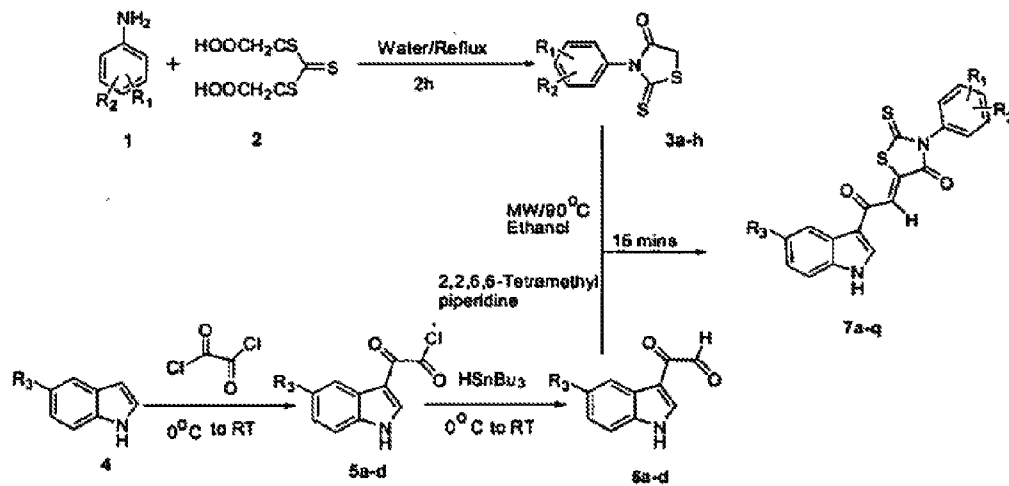


FIGURE 2

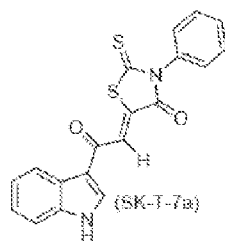


FIGURE 3A

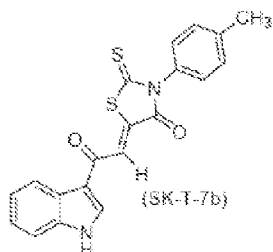


FIGURE 3B

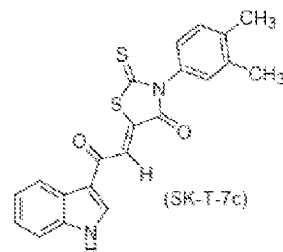


FIGURE 3C

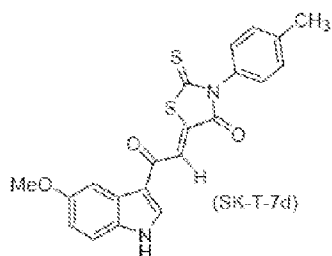


FIGURE 3D

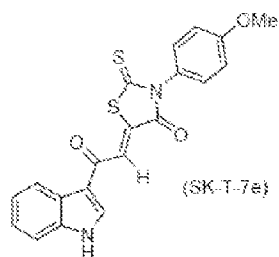


FIGURE 3E

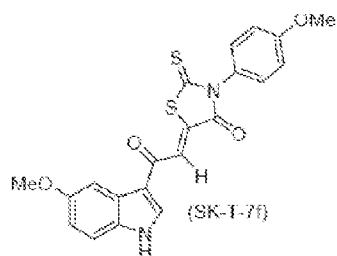


FIGURE 3F

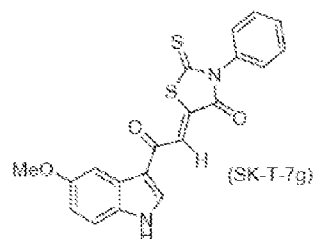


FIGURE 3G

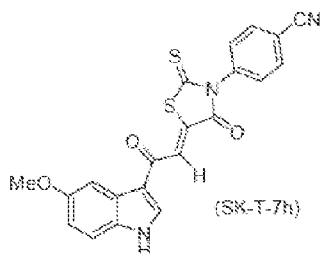


FIGURE 3H

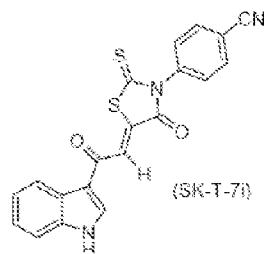


FIGURE 3I

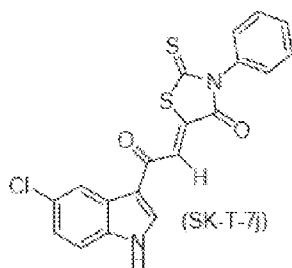


FIGURE 3J

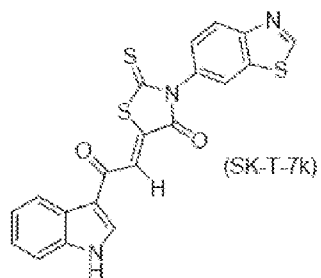


FIGURE 3K

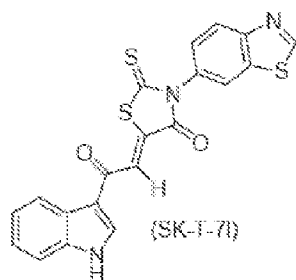


FIGURE 3L

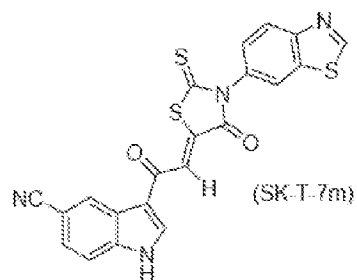


FIGURE 3M

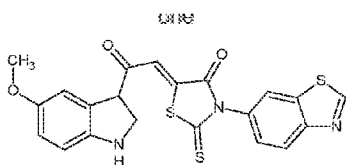


FIGURE 3N

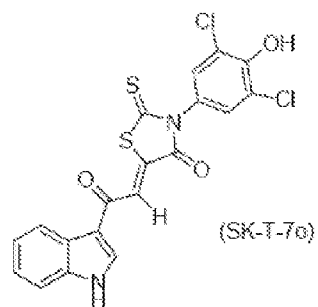


FIGURE 3O

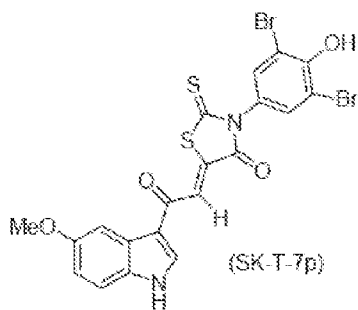


FIGURE 3P

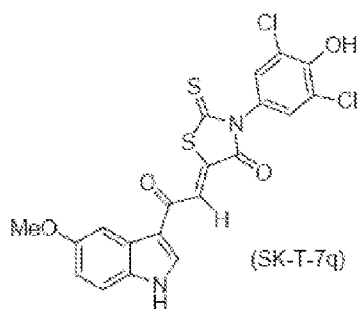


FIGURE 3Q

METHODS OF MAKING AND USING THIOXOTHIAZOLIDINE AND RHODANINE DERIVATIVES AS HIV-1 AND JSP-1 INHIBITORS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a Divisional application and claims priority based on U.S. patent application Ser. No. 13/849,339 filed on Mar. 22, 2013, which is a non-provisional patent application of U.S. Provisional Patent Application No. 61/614,563, filed Mar. 23, 2012. The contents of which is incorporated by reference in its entirety.

STATEMENT OF FEDERALLY FUNDED RESEARCH

[0002] This invention was made with government support NIH, Grant No. 1RC2NS064950. The government has certain rights in this invention.

TECHNICAL FIELD OF THE INVENTION

[0003] The present invention relates in general to the field of thioxothiazolidine and Rhodanine derivatives, specifically to compositions of matter and methods of making and using thioxothiazolidine and Rhodanine derivatives as potential HIV-1 and JNK-stimulating phosphatase-1 (JSP-1) inhibitors.

INCORPORATION-BY-REFERENCE OF MATERIALS FILED ON COMPACT DISC

[0004] None.

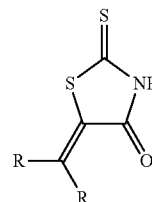
BACKGROUND OF THE INVENTION

[0005] Without limiting the scope of the invention, its background is described in connection with thiazolidine derivatives. United Nations Program on HIV AIDS (UNAIDS) estimates that approximately 35.2 million people worldwide are living with HIV and more than 25 million people have died of AIDS. Most of the anti-HIV drugs licensed by the United States Food and Drug Administration (FDA) belong to two categories: reverse transcriptase inhibitors (RTI) and protease inhibitors (PI). Combined application of these antiretroviral drugs has shown significant synergistic effects. However, an increasing number of patients with HIV infection/AIDS can no longer use such drugs as a result of drug resistance and serious adverse effects.

[0006] U.S. Pat. No. 7,872,027 entitled, "Low molecular weight Myc-max inhibitors" discloses compounds and compositions for interfering with the association of Myc and Max are described herein. These compounds and compositions are useful in methods inhibiting growth or proliferation of a cell. Methods of inhibiting growth or proliferation of a cell are provided, comprising contacting the cell with an amount of a compound that interferes with Myc and Max association effective to inhibit growth or proliferation of the cell.

[0007] U.S. Pat. No. 7,393,869 entitled, "Methods of using thiazolidine derivatives to treat cancer or inflammation" discloses using thiazolidine derivatives to treat cancer, inflammation, or other disorders related to the activities of protein phosphatases PTPN12 or PTPN2 in a mammal.

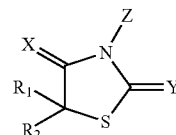
[0008] U.S. Pat. No. 5,116,855, entitled, "Rhodanine derivatives and pharmaceutical compositions" discloses a rhodanine derivative of formula (I)



with inhibitory activity against aldose reductase and useful for the prevention or treatment of complications of diabetes.

[0009] Although, Rhodanine-based molecules have been used as small molecule inhibitors of numerous targets. Rhodanine and its derivatives possessing hydrogen attached to the nitrogen atom have been patented as fungicides while the compounds containing nitrogen atom were patented as pesticides, with mention being made of their usefulness as fungicides.

[0010] For example, U.S. Pat. No. 6,713,629 discloses 5,5-Disubstituted thiazolidine derivative pesticides discloses a fungicidal 5,5-disubstituted thiazolidine derivatives are provided having the formula:



SUMMARY OF THE INVENTION

[0011] The present invention provides (Z)-5-(2-(1H-Indol-3-yl)-2-oxoethylidene)-3-phenyl-2-thioxothiazolidin-4-one (compound 7a-q) derivatives synthesized by the condensation reaction of 3-phenyl-2-thioxothiazolidin-4-ones (3a-h) with suitably substituted 2-(1H-indol-3-yl)-2-oxoacetaldehyde (6a-d) under microwave condition. The thioxothiazolidine-4-ones were prepared from the corresponding aromatic amines (compound 1a-e) and di-(carboxymethyl)-trithiocarbonyl (2). The aldehydes (compound 6a-h) were synthesized from the corresponding acid chlorides (compound 5a-d) using HSnBu_3 .

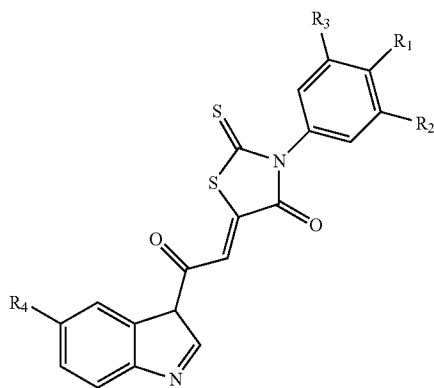
[0012] The present invention provides a method of inhibiting one or more enzymes by contacting the one or more enzymes with a compound having a 5-(2-(indol-3-yl)-2-oxoethylidene)-3-phenyl-2-thioxothiazolidin-4-one skeleton wherein the compound has HIV-1 or JSP-1 inhibitory activity.

[0013] The one or more enzymes may be HIV-1, JNK-stimulating phosphatase-1 (JSP-1) enzyme or both. And more specifically, the one or more enzymes inhibits an HIV-1 enzyme. The compound is a 5-(2-(indol-3-yl)-2-oxoethylidene)-3-phenyl-2-thioxothiazolidin-4-one comprising a 5-substituted 2-(indol-3-yl) and a 3, 4, 5 substituted phenyl. The compound is (Z)-5-(2-(1H-indol-3-yl)-2-oxoethylidene)-3-phenyl-2-thioxothiazolidin-4-one; (Z)-5-(2-(1H-indol-3-yl)-2-oxoethylidene)-2-thioxo-3-p-tolylthiazolidin-4-one; (Z)-5-(2-(1H-indol-3-yl)-2-oxoethylidene)-3-(3,4-

dimethylphenyl)-2-thioxothiazolidin-4-one; (Z)-5-(2-(5-methoxy-1H-indol-3-yl)-2-oxoethylidene)-2-thioxo-3-p-tolylthiazolidin-4-one; (Z)-5-(2-(1H-indol-3-yl)-2-oxoethylidene)-3-(4-methoxyphenyl)-2-thioxothiazolidin-4-one; (Z)-5-(2-(5-methoxy-1H-indol-3-yl)-2-oxoethylidene)-3-(4-methoxyphenyl)-2-thioxothiazolidin-4-one; (Z)-5-(2-(5-methoxy-1H-indol-3-yl)-2-oxoethylidene)-3-phenyl-2-thioxothiazolidin-4-one; (Z)-4-(5-(2-(5-methoxy-1H-indol-3-yl)-2-oxoethylidene)-4-oxo-2-thioxothiazolidin-3-yl)benzonitrile; (Z)-4-(5-(2-(1H-indol-3-yl)-2-oxoethylidene)-4-oxo-2-thioxothiazolidin-3-yl)benzonitrile; (Z)-5-(2-(5-chloro-1H-indol-3-yl)-2-oxoethylidene)-3-phenyl-2-thioxothiazolidin-4-one; (Z)-5-(2-(1H-indol-3-yl)-2-oxoethylidene)-3-(benzo[d]thiazol-6-yl)-2-thioxothiazolidin-4-one; (Z)-5-(2-(1H-indol-3-yl)-2-oxoethylidene)-3-(benzo[d]thiazol-6-yl)-2-thioxothiazolidin-4-one; (Z)-3-(2-(3-(benzo[d]thiazol-6-yl)-4-oxo-2-thioxothiazolidin-5-ylidene)acetyl)-1H-indole-5-carbonitrile; (Z)-5-(2-(1H-indol-3-yl)-2-oxoethylidene)-3-(3,5-dibromo-4-hydroxyphenyl)-2-thioxothiazolidin-4-one; (Z)-5-(2-(1H-indol-3-yl)-2-oxoethylidene)-3-(3,5-dichloro-4-hydroxyphenyl)-2-thioxothiazolidin-4-one; (Z)-3-(3,5-dibromo-4-hydroxyphenyl)-5-(2-(5-methoxy-1H-indol-3-yl)-2-oxoethylidene)-2-thioxothiazolidin-4-one; or (Z)-3-(3,5-dichloro-4-hydroxyphenyl)-5-(2-(5-methoxy-1H-indol-3-yl)-2-oxoethylidene)-2-thioxothiazolidin-4-one.

[0014] The present invention also provides a method of modulating the activity of a HIV-1 or a JSP-1 enzyme by contacting the HIV-1 or JSP-1 enzyme with a compound having a 5-(2-(indol-3-yl)-2-oxoethylidene)-3-phenyl-2-thioxothiazolidin-4-one skeleton wherein the compound has HIV-1 or JSP-1 inhibitory activity.

[0015] The present invention provides a method of inhibiting HIV-1 or JNK-stimulating phosphatase-1 enzyme by contacting the HIV-1 or JNK-stimulating phosphatase-1 enzyme with a compound of formula (I):



wherein R1, R2, R3 and R4 are independently selected from the group consisting of hydrogen, halo, alkyl, aryl, hydroxyl, alkoxy, aryloxy, aralkoxy, cyano, nitro, alkylcarbamido, arylcarbamido, dialkylcarbamido, diarylcarbamido, alkylarylcaramido, alkylthiocaramido, arylthiocaramido, dialkylthiocaramido, diarylthiocaramido, alkylarylthio-

carbamidb, amino, alkylamino, arylamino, dialkylamino, diarylamino, arylalkylamino, aminocarbonyl, alkylaminocarbonyl, arylaminocarbonyl, dialkylaminocarbonyl, diarylaminocarbonyl, arylalkylamino-carbonyl, alkylcarbonyloxy, arylcarbonyloxy, carboxyl, alkoxy, carbonyl, aryloxy, sulfo, alkylsulfonylamido, arylsulfonylamido, alkylsulfonyl, arylsulfonyl, alkylsulfinyl, arylsulfinyl and heteroaryl.

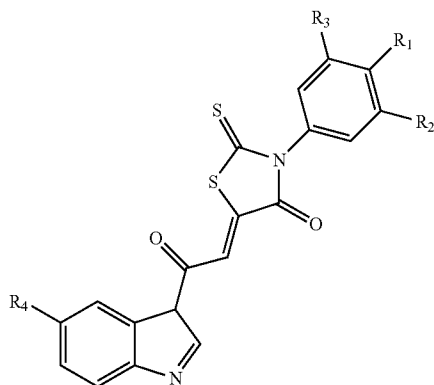
[0016] In one embodiment, the R1, R2, R3 and R4 are independently selected from the group comprising H, CH₃, OCH₃, CN, thiazolidine, OH, Cl, or Br. In another embodiment, the R1 is a H, R2 is a H, R3 is a H, R4 is a H; R1 is a CH₃, R2 is a H, R3 is a H, R4 is a H; R1 is a CH₃, R2 is a CH₃, R3 is a H, R4 is a H; R1 is a CH₃, R2 is a H, R3 is a H, R4 is a OCH₃; R1 is a OCH₃, R2 is a H, R3 is a H, R4 is a H; R1 is a OCH₃, R2 is a H, R3 is a H, R4 is a OCH₃; R1 is a H, R2 is a H, R3 is a H, R4 is a OCH₃; R1 is a CN, R2 is a H, R3 is a H, R4 is a OCH₃; R1 is a CN, R2 is a H, R3 is a H, R4 is a H; R1 is a H, R2 is a H, R3 is a H, R4 is a Cl; R1 is a thiazolidine, R2 is a thiazolidine, R3 is a H, R4 is a H; R1 is a thiazolidine, R2 is a thiazolidine, R3 is a H, R4 is a OCH₃; R1 is a thiazolidine, R2 is a thiazolidine, R3 is a H, R4 is a CN; R1 is a OH, R2 is a Br, R3 is a Br, R4 is a H; R1 is a OH, R2 is a Cl, R3 is a Cl, R4 is a H; R1 is a OH, R2 is a Br, R3 is a Br, R4 is a OCH₃; or R1 is a OH, R2 is a Cl, R3 is a Cl, R4 is a OCH₃.

[0017] The present invention provides a thioxothiazolidin composition for inhibiting an enzyme comprising: a 5-(2-(indol-3-yl)-2-oxoethylidene)-3-phenyl-2-thioxothiazolidin-4-one skeleton having enzyme inhibitory activity. In one embodiment, the enzyme is HIV-1, JNK-stimulating phosphatase-1 (JSP-1) enzyme or both. In one embodiment, the 5-(2-(indol-3-yl)-2-oxoethylidene)-3-phenyl-2-thioxothiazolidin-4-one skeleton comprising a 5-substituted 2-(indol-3-yl) and a 3, 4, 5 substituted phenyl.

[0018] In another embodiment, the 5-(2-(indol-3-yl)-2-oxoethylidene)-3-phenyl-2-thioxothiazolidin-4-one skeleton is selected from (Z)-5-(2-(1H-indol-3-yl)-2-oxoethylidene)-3-phenyl-2-thioxothiazolidin-4-one; (Z)-5-(2-(1H-indol-3-yl)-2-oxoethylidene)-2-thioxo-3-p-tolylthiazolidin-4-one; (Z)-5-(2-(1H-indol-3-yl)-2-oxoethylidene)-3-(3,4-dimethylphenyl)-2-thioxothiazolidin-4-one; (Z)-5-(2-(5-methoxy-1H-indol-3-yl)-2-oxoethylidene)-2-thioxo-3-p-tolylthiazolidin-4-one; (Z)-5-(2-(1H-indol-3-yl)-2-oxoethylidene)-3-(4-methoxyphenyl)-2-thioxothiazolidin-4-one; (Z)-5-(2-(5-methoxy-1H-indol-3-yl)-2-oxoethylidene)-3-(4-methoxyphenyl)-2-thioxothiazolidin-4-one; (Z)-5-(2-(5-methoxy-1H-indol-3-yl)-2-oxoethylidene)-3-phenyl-2-thioxothiazolidin-4-one; (Z)-4-(5-(2-(5-methoxy-1H-indol-3-yl)-2-oxoethylidene)-4-oxo-2-thioxothiazolidin-3-yl)benzonitrile; (Z)-4-(5-(2-(1H-indol-3-yl)-2-oxoethylidene)-4-oxo-2-thioxothiazolidin-3-yl)benzonitrile; (Z)-5-(2-(5-chloro-1H-indol-3-yl)-2-oxoethylidene)-3-phenyl-2-thioxothiazolidin-4-one; (Z)-5-(2-(1H-indol-3-yl)-2-oxoethylidene)-3-(benzo[d]thiazol-6-yl)-2-thioxothiazolidin-4-one; (Z)-5-(2-(1H-indol-3-yl)-2-oxoethylidene)-3-(benzo[d]thiazol-6-yl)-2-thioxothiazolidin-4-one; (Z)-3-(2-(3-(benzo[d]thiazol-6-yl)-4-oxo-2-thioxothiazolidin-5-ylidene)acetyl)-1H-indole-5-

carbonitrile; (Z)-5-(2-(1H-indol-3-yl)-2-oxoethylidene)-3-(3,5-dibromo-4-hydroxyphenyl)-2-thioxothiazolidin-4-one; (Z)-5-(2-(1H-indol-3-yl)-2-oxoethylidene)-3-(3,5-dichloro-4-hydroxyphenyl)-2-thioxothiazolidin-4-one; (Z)-3-(3,5-dibromo-4-hydroxyphenyl)-5-(2-(5-methoxy-1H-indol-3-yl)-2-oxoethylidene)-2-thioxothiazolidin-4-one; or (Z)-3-(3,5-dichloro-4-hydroxyphenyl)-5-(2-(5-methoxy-1H-indol-3-yl)-2-oxoethylidene)-2-thioxothiazolidin-4-one.

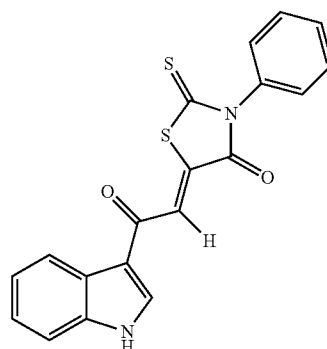
[0019] In one embodiment, the thioxothiazolidin composition of formula (I) for inhibiting an enzyme:



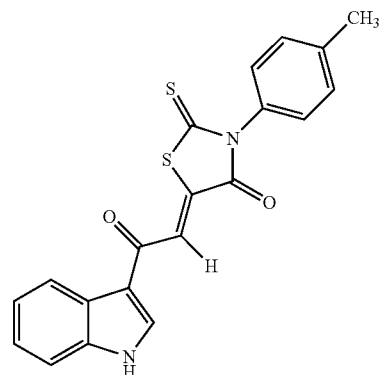
wherein R1, R2, R3 and R4 are independently selected from the group consisting of hydrogen, halo, alkyl, aryl, hydroxyl, alkoxy, aryloxy, aralkoxy, cyano, nitro, alkylcarbamido, arylcarbamido, dialkylcarbamido, diarylcarbamido, alkylarylcarbamido, alkylthiocarbamido, arylthiocarbamido, dialkylthiocarbamido, diarylthiocarbamido, alkylarylthiocarbamidb, amino, alkylamino, arylamino, dialkylamino, diarylamino, arylalkylamino, aminocarbonyl, alkylaminocarbonyl, arylaminocarbonyl, dialkylaminocarbonyl, diarylaminocarbonyl, arylalkylamino-carbonyl, alkylcarbonyloxy, arylcarbonyloxy, carboxyl, alkoxycarbonyl, aryloxy carbonyl, sulfo, alkylsulfonylamido, arylsulfonylamido, alkylsulfonyl, arylsulfonyl, alkylsulfinyl, arylsulfinyl and heteroaryl.

[0020] In another embodiment, the enzyme is HIV-1, JNK-stimulating phosphatase-1 (JSP-1) enzyme or both. In another embodiment, the R1, R2, R3 and R4 are independently selected from the group comprising H, CH₃, OCH₃, CN, thiazolidine, OH, Cl, or Br. In another embodiment, the R1 is a H, R2 is a H, R3 is a H, R4 is a H; R1 is a CH₃, R2 is a H, R3 is a H, R4 is a H; R1 is a CH₃, R2 is a CH₃, R3 is a H, R4 is a H; R1 is a CH₃, R2 is a H, R3 is a H, R4 is a OCH₃; R1 is a OCH₃, R2 is a H, R3 is a H, R4 is a H; R1 is a OCH₃, R2 is a H, R3 is a H, R4 is a OCH₃; R1 is a H, R2 is a H, R3 is a H, R4 is a OCH₃; R1 is a CN, R2 is a H, R3 is a H, R4 is a H; R1 is a H, R2 is a H, R3 is a H, R4 is a Cl; R1 is a thiazolidine, R2 is a thiazolidine, R3 is a H, R4 is a H; R1 is a thiazolidine, R2 is a thiazolidine, R3 is a H, R4 is a OCH₃; R1 is a thiazolidine, R2 is a thiazolidine, R3 is a H, R4 is a CN; R1 is a OH, R2 is a Br, R3 is a Br, R4 is a H; R1 is a OH, R2 is a Cl, R3 is a Cl, R4 is a H; R1 is a OH, R2 is a Br, R3 is a Br, R4 is a OCH₃; or R1 is a OH, R2 is a Cl, R3 is a Cl, R4 is a OCH₃.

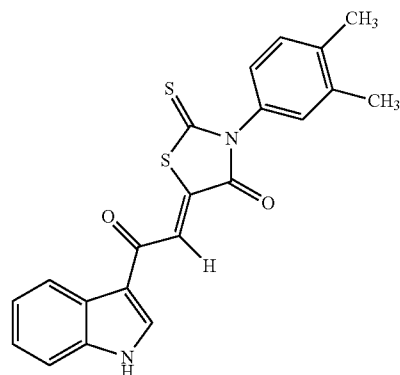
[0021] For example the composition may have the structure:



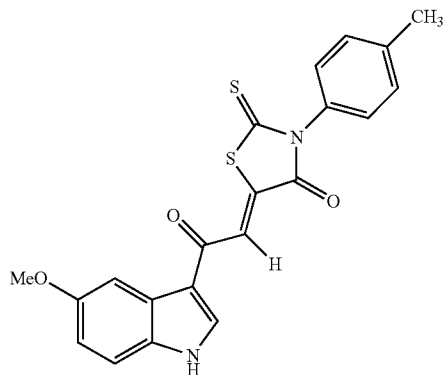
(SK-T-7a)



(SK-T-7b)

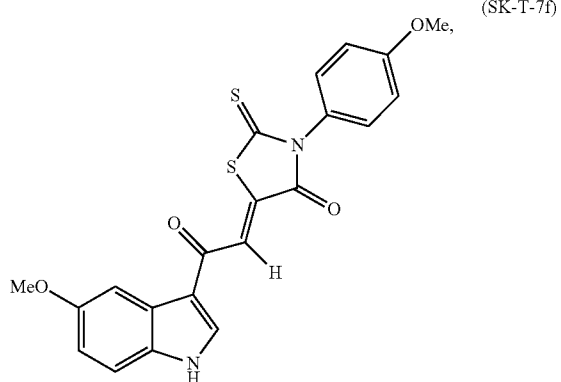


(SK-T-7c)

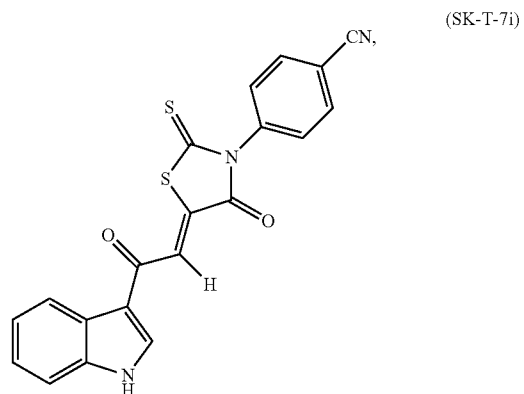


(SK-T-7d)

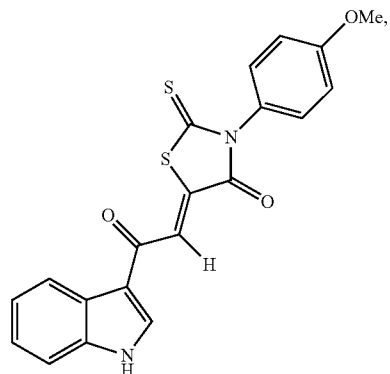
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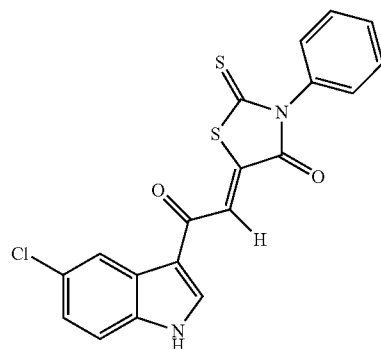
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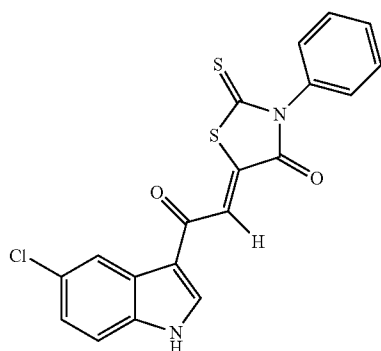
(SK-T-7e)



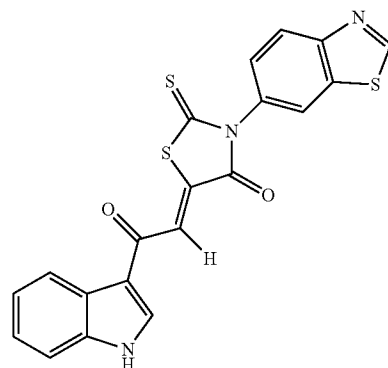
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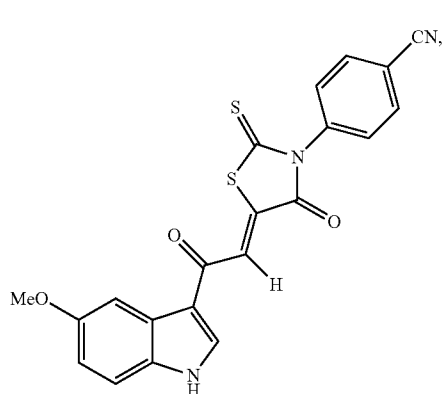
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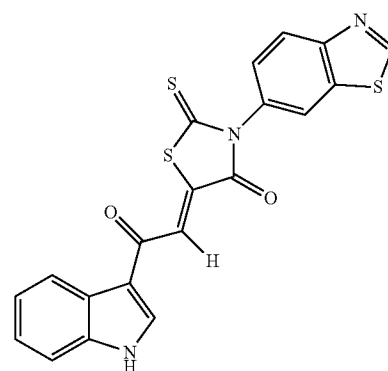
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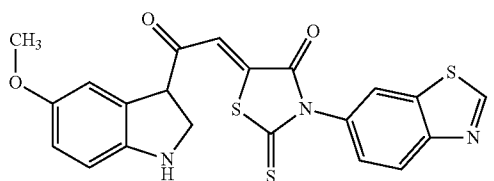
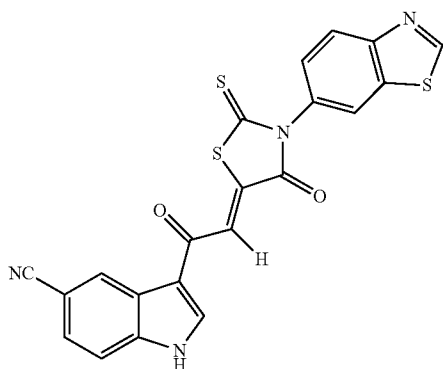


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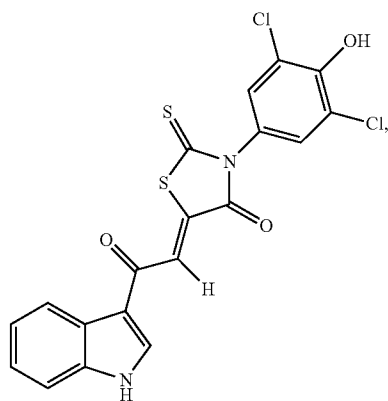


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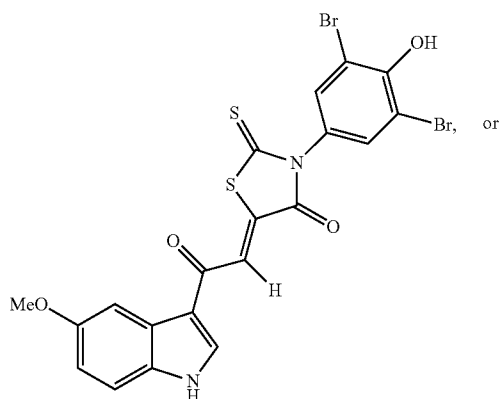
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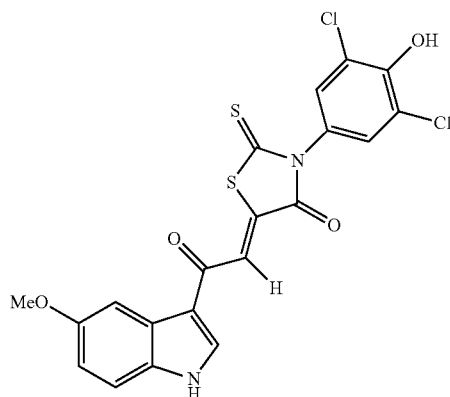


(SK-T-7p)



-continued

(SK-T-7q)



[0022] The present invention provides a thioxothiazolidin composition further comprising a pharmaceutical carrier in contact with the thioxothiazolidin composition to make a composition used in the modulating the activity of HIV-1, JNK-stimulating phosphatase-1 (JSP-1) enzyme or both.

BRIEF DESCRIPTION OF THE DRAWINGS

[0023] For a more complete understanding of the features and advantages of the present invention, reference is now made to the detailed description of the invention along with the accompanying figures and in which:

[0024] FIGS. 1A and 1B are images of competitive inhibitors of HIV-1 and JSP-1;

[0025] FIG. 2 is an image of a reaction scheme of one of the synthesis for 5-(2-(1H-Indol-3-yl)-2-oxoethylidene)-3-phenyl-2-thiox-othiazolidin-4-ones; and

[0026] FIGS. 3A to 3Q are images of 2-thioxothiazolidin-4-ones or Rhodanine compounds of the claimed invention.

DETAILED DESCRIPTION OF THE INVENTION

[0027] While the making and using of various embodiments of the present invention are discussed in detail below, it should be appreciated that the present invention provides many applicable inventive concepts that can be embodied in a wide variety of specific contexts. The specific embodiments discussed herein are merely illustrative of specific ways to make and use the invention and do not delimit the scope of the invention.

[0028] To facilitate the understanding of this invention, a number of terms are defined below. Terms defined herein have meanings as commonly understood by a person of ordinary skill in the areas relevant to the present invention. Terms such as “a”, “an” and “the” are not intended to refer to only a singular entity, but include the general class of which a specific example may be used for illustration. The terminology herein is used to describe specific embodiments of the invention, but their usage does not delimit the invention, except as outlined in the claims.

[0029] As used herein, the term “alkyl” denotes branched or unbranched hydrocarbon chains, preferably having about 1 to about 8 carbons, such as, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, octa-decyl and 2-methylpentyl. These groups can be optionally substituted with one or more functional groups which are attached commonly to such chains, such as, hydroxyl, bromo, fluoro,

chloro, iodo, mercapto or thio, cyano, alkylthio, heterocyclyl, aryl, heteroaryl, carboxyl, carbalkoyl, alkyl, alkenyl, nitro, amino, alkoxy, amido, and the like to form alkyl groups such as trifluoro methyl, 3-hydroxyhexyl, 2-carboxypropyl, 2-fluoroethyl, carboxymethyl, cyanobutyl and the like.

[0030] The term “alkylene” refers to a divalent alkyl group as defined above, such as methylene ($-\text{CH}_2-$), propylene ($-\text{CH}_2\text{CH}_2\text{CH}_2-$), chloroethylene ($-\text{CHClCH}_2-$), 2-thiobutene $-\text{CH}_2\text{CH}(\text{SH})\text{CH}_2\text{CH}_2-$, 1-bromo-3-hydroxy-4-methylpentene ($-\text{CHBrCH}_2\text{CH}(\text{OH})\text{CH}(\text{CH}_3)\text{CH}_2-$), and the like.

[0031] As used herein, the term “alkenyl” denotes branched or unbranched hydrocarbon chains containing one or more carbon-carbon double bonds.

[0032] The term “alkynyl” refers to branched or unbranched hydrocarbon chains containing one or more carbon-carbon triple bonds.

[0033] As used herein, the term “amido” denotes an amide linkage: —C(O)NHR (wherein R is hydrogen or alkyl). The term “amino” denotes an amine linkage: —NR— , wherein R is hydrogen or alkyl.

[0034] As used herein, the term "aryl" denotes a chain of carbon atoms which form at least one aromatic ring having between about 4-14 carbon atoms, such as phenyl, naphthyl, and the like, and which may be substituted with one or more functional groups which are attached commonly to such chains, such as hydroxyl, bromo, fluoro, chloro, iodo, mercapto or thio, cyano, cyanoamido, alkylthio, heterocycle, aryl, heteroaryl, carboxyl, carbalkoyl, alkyl, alkenyl, nitro, amino, alkoxy, amido, and the like to form aryl groups such as biphenyl, iodobiphenyl, methoxybiphenyl, anthryl, bromophenyl, iodophenyl, chlorophenyl, hydroxyphenyl, methoxyphenyl, formylphenyl, acetylphenyl, trifluoromethylthiophenyl, trifluoromethoxyphenyl, alkylthiophenyl, trialkylammoniumphenyl, amidophenyl, thiazolylphenyl, oxazolylphenyl, imidazolylphenyl, imidazolylmethylphenyl, and the like.

[0035] The term “alkoxy” denotes —OR—, wherein R is alkyl.

[0036] The term “alkylcarbonyl” denote an alkyl group as defined above substituted with a C(O) group, for example, CH₃ C(O)—, CH₃ CH₂ C(O)—, etc.

[0037] As used herein, the term “alkylcarboxyl” denote an alkyl group as defined above substituted with a C(O)O group, for example, CH₃ C(O)O—, CH₃ CH₂ C(O)O—, etc.

[0038] As used herein, the term “carboxyl” denotes —C(O)O— , and the term “carbonyl” denotes —C(O)— . The term “cycloalkyl” signifies a saturated, cyclic hydrocarbon group with 3-8, preferably 3-6 carbon atoms, i.e. cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl and the like.

[0039] The term “halogen” includes chlorine, fluorine, bromine, iodine and mixtures thereof.

[0040] The term “heteroaryl” refers to an aromatic mono- or bicyclic radical having 5 to 10, preferably 5 to 6 ring atoms, containing one to three heteroatoms, preferably one heteroatom, e.g. independently selected from nitrogen, oxygen or sulfur. Examples of heteroaryl groups are thiophenyl, isoxazolyl, thiazolyl, piperidinyl, pyridinyl, pyrrolyl, imidazolyl, tetrazolyl, preferably pyridinyl, isoxazolyl or thiazolyl. Optionally, the heteroaryl group can be mono-, di- or trisubstituted, independently, with phenyl, alkyl, alkylcarbonyl, alkoxy carbonyl, hydroxy, amino, alkylamino, dialkylamino, carboxy, alkoxy carbonylalkyl, preferably alkyl.

[0041] The term “heterocycle” means a straight chain or ring system that may contain from zero to four heteroatoms selected from N, O, and S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. These groups can be optionally substituted with one or more functional groups as defined under “alkyl” above.

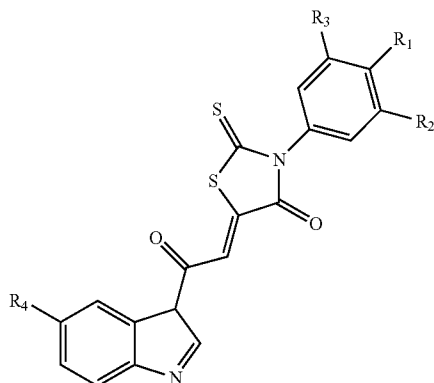
[0042] The present invention provides (Z)-5-(2-(1H-Indol-3-yl)-2-oxoethylidene)-3-phenyl-2-thioxothiazolidin-4-one (compound 7a-q) derivatives synthesized by the condensation reaction of 3-phenyl-2-thioxothiazolidin-4-ones (3a-h) with suitably substituted 2-(1H-indol-3-yl)-2-oxoacetaldehyde (6a-d) under microwave condition. The thioxothiazolidine-4-ones were prepared from the corresponding aromatic amines (compound 1a-e) and di-(carboxymethyl)-trithiocarbonyl (2). The aldehydes (compound 6a-h) were synthesized from the corresponding acid chlorides (compound 5a-d) using HSnBu₃.

[0043] As used herein, "pharmaceutically acceptable," means acceptable for use in humans and animals. Excipients include, without limitation, one or more suitable: vehicle(s), solvent(s), diluent(s), pH modifier(s), buffer(s), salt(s), colorant(s), rheology modifier(s), lubricant(s), filler(s), antifoaming agent(s), erodeable polymer(s), hydrogel(s), surfactant(s), emulsifier(s), adjuvant(s), preservative(s), phospholipid(s), fatty acid(s), mono-, di- and tri-glyceride(s) and derivatives thereof, wax(s), oil(s) and water. The choice of excipient depends on the dosage form in question. Parenteral administration may require at a minimum buffers and salts to match physiological conditions, and thus includes salt and buffer, such as, without limitation, normal saline or phosphate-buffered saline. Depending on the solubility of the compound (active ingredient), the dosage form would be aqueous, micellar (including liposomes) or lipophilic. Formulation of a drug product and choice of suitable excipient(s) with adequate bioavailability is within the average skill of those in the pharmaceutical and formulary arts. The compound may be administered via any useful delivery route, including, without limitation, orally or parenterally, and the drug product/dosage form is tailored to the desired delivery route. For example and without limitation, an HCl salt of a compound described herein may be administered intravenously or intramuscularly in normal saline, or may be administered in tablet or capsule form with appropriate excipients.

[0044] As used herein, “modulate” or “modulation” is used to denote the altering of the activity and can be an increase or a decrease the activity when compared to native or normal activity.

[0045] The present invention provides a method of inhibiting one or more enzymes by contacting the one or more enzymes with a compound having a 5-(2-(indol-3-yl)-2-oxoethylidene)-3-phenyl-2-thioxothiazolidin-4-one skeleton wherein the compound has HIV-1 or JSP-1 inhibitory activity.

[0046] The present invention provides a method of inhibiting HIV-1 or JNK-stimulating phosphatase-1 enzyme by contacting the HIV-1 or JNK-stimulating phosphatase-1 enzyme with a compound of formula (I):



wherein R1, R2, R3 and R4 are independently selected from the group consisting of hydrogen, halo, alkyl, aryl, hydroxyl, alkoxy, aryloxy, aralkoxy, cyano, nitro, alkylcarbamido, arylcarbamido, dialkylcarbamido, diarylcarbamido, alkylarylcarbamido, alkylthiocarbamido, arylthiocarbamido, dialkylthiocarbamido, diarylthiocarbamido, alkylarylthiocarbamido, amino, alkylamino, arylamino, dialkylamino, diarylamino, arylalkylamino, aminocarbonyl, alkylaminocarbonyl, arylaminocarbonyl, dialkylaminocarbonyl, diarylaminocarbonyl, alkylalkylamino-carbonyl, alkylcarbonyloxy, arylcarbonyloxy, carboxyl, alkoxycarbonyl, aryloxy, aryloxy, sulfo, alkylsulfonylamido, arylsulfonylamido, alkylsulfonyl, arylsulfonyl, alkylsulfinyl, arylsulfinyl and heteroaryl.

[0047] FIGS. 1A and 1B are images of competitive inhibitors of HIV-1 and JSP-1. FIG. 1A illustrates 2-aryl-5-(4-oxo-3-phenethyl-2-thioxothiazolidinylidenemethyl)-furans with Rhodanine as a core molecule exhibiting anti-HIV-1 activity. One embodiment of the competitive inhibitor shown in FIG. 1A includes the core structure shown with the R1 group substituted as a H, F, OH, OCH₃, or Cl and the R2 group substituted as a H, OH, F, or Cl. As it is understood, the combinations are derived from the various combinations of R1 substitutions and R2 substitutions. For example, R1 may be a H, and in distinct embodiments R2 may be a H, OH, F, or Cl. Similarly, R1 may be a F and in distinct embodiments R2 may be a H, OH, F, or Cl. R1 may be a OH and in distinct embodiments R2 may be a H, OH, F, or Cl. R1 may be a OCH₃ and in distinct embodiments R2 may be a H, OH, F, or Cl. R1 may be a Cl, and in distinct embodiments R2 may be a H, OH, F, or Cl, thus providing numerous different embodiments of the core composition. FIG. 1B is 5-Benzylidene-3-phenyl-2-thioxothiazolidin-4-one core shown to inhibit the Jun NH₂-terminal kinase (Jnk) stimulatory phosphatase-1 USP-1.

[0048] As stated above, Rhodanine and its derivatives have been used as fungicides and pesticides. However, Rhodanine-based molecules may also be used as small molecule inhibitors of numerous targets such as HCV NS3 protease, aldose reductase, p-lactamase, UDP-N-acetylmuramate/L-alanine UDP-N-acetylmuramate/L-alanine ligase, antidiabetic agents, cathepsin D, and histidine decarboxylase. The present invention includes preparing and evaluating the biological importance of these Rhodanine-based molecules and thioxothiazolidine compounds and derivatives thereof. The present invention provides the synthesis of a novel class of Rhodanine-based small molecule with inhibitory properties against JSP-1 and HIV-1 in the low micro molar range.

[0049] FIG. 2 is the synthesis according to one route for 5-(2-(1H-Indol-3-yl)-2-oxoethylidene)-3-phenyl-2-thioxothiazolidin-4-ones. 5-(2-(1H-Indol-3-yl)-2-oxoethylidene)-3-phenyl-2-thioxothiazolidin-4-ones (7a-q) were synthesized by Knoevenagel condensation of 3-phenyl-2-thioxothiazolidin-4-ones (3a-h) derivatives with suitably substituted 2-(1H-indol-3-yl)-2-oxoacetaldehydes (6a-d) using microwave irradiation and catalytic amounts of 2,2,6,6-tetramethyl piperidine (TMP) in ethanol. Although other bases (Table 1) can be used as catalyst (e.g., piperidine, pyridine, N-methyl piperidine (NMP), DBU), TMP works best.

[0050] FIGS. 3A to 3Q are images of 2-thioxothiazolidin-4-ones or Rhodanine compounds of the claimed invention.

[0051] The optimum temperature and condition for this microwave-assisted reaction were determined by a series of reactions of 3-phenyl-2-thioxothiazolidin-4-one (3b) and 2-(1H-indol-3-yl)-2-oxoacetaldehyde (6a). The results are summarized in Table 1.

TABLE 1

Base	Condition ^a	Temp (° C.)	Time (min)	Yield ^b (%)
—	No solvent	90	15	Trace
—	Ethanol	90	15	Trace
Piperidine	Ethanol	90	15	80
TMP	Ethanol	90	15	96
TMP	No solvent	90	15	Trace
DBU/pyridine	Ethanol	90	20	20
TMP	Acetonitrile	90	15	76
TMP	Acetonitrile	130	15	15
DBU	Acetonitrile	90	30	Trace
TMP	DMF	90	15	45
NMP	DMF	90	30	10
DBU	DMF	120-40	15	Trace
TMP	Water	90	15	Trace
TMP	Water	130	15	Trace
—	Water	130	30	Trace
TMP	Toluene	90	15	Trace
TMP	Isopropanol	90	15	45
TMP	THF	90	15	38
TMP	n-Butanol	90	15	33

^a All the reaction was carried out in equimolar amounts of each compound in 2 ml of solvent at 150 psi pressure.

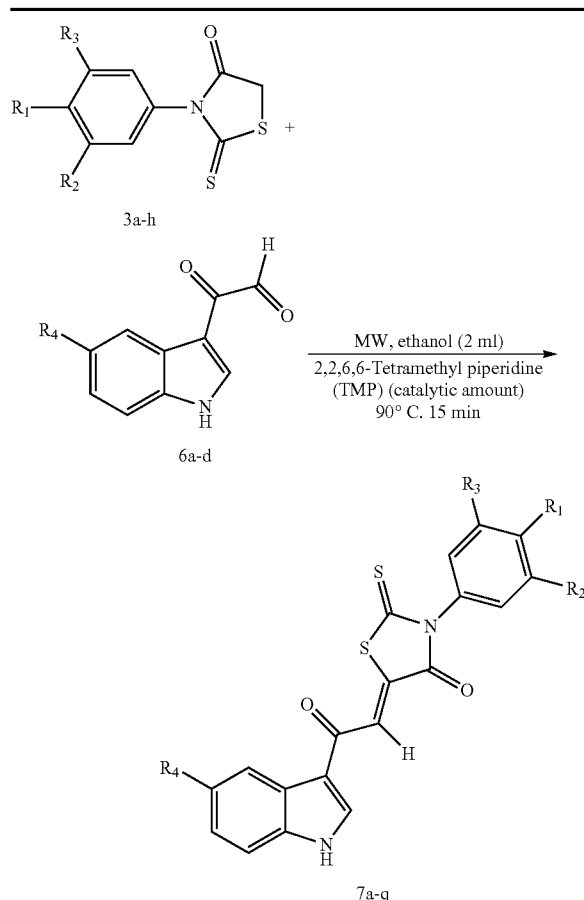
^b Isolated yield.

[0052] The same reaction under a conventional reflux condition using ethanol as solvent gave lower yields of between about 11 to 69% in a longer time of about 5 hours and/or compounds requiring rigorous purification. However, the microwave reaction of the present invention provides cleaner reaction in a shorter time of 15 minutes time, and the products were only required to be washed with cold ethanol. The yields are good to excellent as seen in Table 1.

[0053] As shown in Table 1, it is clear that microwave irradiation at 90° C. for 15 minutes in ethanol is the optimum condition for the synthesis of these molecules.

[0054] All the compounds 7a-q were isolated as a single (Z) isomer and were confirmed by comparing the vinylic proton shift in ¹H NMR with previously reported data which appears around δ 8.00 ppm. The starting materials 3a-h were synthesized, and the structures are listed in Table 2 below:

TABLE 2



Entry	R ₁	R ₂	R ₃	R ₄	Product	Yield ^{a,b} (%)
1	H	H	H	H	7a	95
2	CH ₃	H	H	H	7b	96
3	CH ₃	CH ₃	H	H	7c	90
4	CH ₃	H	H	OCH ₃	7d	93
5	OCH ₃	H	H	H	7e	95
6	OCH ₃	H	H	OCH ₃	7f	92
7	H	H	H	OCH ₃	7g	94
8	CN	H	H	OCH ₃	7h	90
9	CN	H	H	H	7i	91
10	H	H	H	Cl	7j	89
11			H	H	7k	95
12			H	OCH ₃	7l	93

TABLE 2-continued

13			H	CN	7m	91
14	OH	Br	Br	H	7n	90
15	OH	Cl	Cl	H	7o	89
16	OH	Br	Br	OCH ₃	7p	96
17	OH	Cl	Cl	OCH ₃	7q	90

^aIsolated yield.^bAll the compounds were characterized by ¹H NMR, ¹³C NMR, DEPT-135, IR and HRMS analysis.

[0055] Referring now to Table 3, compounds 7a-q were obtained in 89-96% yields with high melting point (>300° C.). They were insoluble in usual organic solvent, water, or hexane. The IR (KBr) spectra of compounds 7a-q exhibit absorption bands due to the stretching vibrations of the NH group of indole cycles (3200 cm⁻¹ range).

TABLE 3

		Water reflux/2 h				
1	2					
3a-h						
Entry	R ₁	R ₂	R ₃	Time (h)	Product	Yield ^a (%)
1	H	H	H	3.0	3a	75
2	CH ₃	H	H	2.5	3b	73
3	CH ₃	CH ₃	H	2.5	3c	76
4	OCH ₃	H	H	2.0	3d	75
5	CN	H	H	4.0	3e	71
6	OH	Br	Br	3.0	3f	78
7	OH	Cl	Cl	3.0	3g	76
8			H	4.0	3h	75

[0056] The spectra of compounds 7a-q display characteristic bands and C=S group (intense bands at 1628-1610 cm⁻¹). The 3-phenyl derivatives due to stretching vibrations of two C=O groups (1720 cm⁻¹ range). -2-thioxothiazolidin-4-ones (3a-b) derivatives were prepared by refluxing equimolar amounts of suitably substituted aromatic amines (1a-e) and di-(carboxymethyl)-trithiocarbonyl (2). The aldehydes 6a-d were

synthesized by treating corresponding acid chlorides with HSnBu_3 . The acid chlorides were prepared by acylation of indole (or substituted indole) with oxalylchloride. All compounds were characterized by ^1H NMR, ^{13}C NMR, DEPT-135, IR and HRMS studies.

[0057] The present invention provides a novel series of (Z)-5-(2-(1H-indol-3-yl)-2-oxoethylidene)-3-phenyl-2-thioxothiazolidin-4-one (7a-q) derivatives. The mild reaction conditions, easy workup, good to excellent yields, and easily available substrate make this reaction an attractive method for the preparation of 3-phenyl-2-thioxothiazolidin-4-ones.

[0058] The present invention provides the synthesis of drug molecules with a Rhodanine moiety by microwave irradiation and includes (Z)-5-(2-(1H-indol-3-yl)-2-oxoethylidene)-3-phenyl-2-thioxothiazolidin-4-one; (Z)-5-(2-(1H-indol-3-yl)-2-oxoethylidene)-2-thioxo-3-p-tolylthiazolidin-4-one; (Z)-5-(2-(1H-indol-3-yl)-2-oxoethylidene)-3-(3,4-dimethylphenyl)-2-thioxothiazolidin-4-one; (Z)-5-(2-(5-methoxy-1H-indol-3-yl)-2-oxoethylidene)-2-thioxo-3-p-tolylthiazolidin-4-one; (Z)-5-(2-(1H-indol-3-yl)-2-oxoethylidene)-3-(4-methoxyphenyl)-2-thioxothiazolidin-4-one; (Z)-5-(2-(5-methoxy-1H-indol-3-yl)-2-oxoethylidene)-3-(4-methoxyphenyl)-2-thioxothiazolidin-4-one; (Z)-5-(2-(5-methoxy-1H-indol-3-yl)-2-oxoethylidene)-3-phenyl-2-thioxothiazolidin-4-one; (Z)-4-(5-(2-(5-methoxy-1H-indol-3-yl)-2-oxoethylidene)-4-oxo-2-thioxothiazolidin-3-yl)benzonitrile; (Z)-4-(5-(2-(1H-indol-3-yl)-2-oxoethylidene)-4-oxo-2-thioxothiazolidin-3-yl)benzonitrile; (Z)-5-(2-(5-chloro-1H-indol-3-yl)-2-oxoethylidene)-3-phenyl-2-thioxothiazolidin-4-one; (Z)-5-(2-(1H-indol-3-yl)-2-oxoethylidene)-3-(benzo[d]thiazol-6-yl)-2-thioxothiazolidin-4-one; (Z)-5-(2-(1H-indol-3-yl)-2-oxoethylidene)-3-(benzo[d]thiazol-6-yl)-2-thioxothiazolidin-4-one; (Z)-3-(2-(3-(benzo[d]thiazol-6-yl)-4-oxo-2-thioxothiazolidin-5-ylidene)acetyl)-1H-indole-5-carbonitrile; (Z)-5-(2-(1H-indol-3-yl)-2-oxoethylidene)-3-(3,5-dibromo-4-hydroxyphenyl)-2-thioxothiazolidin-4-one; (Z)-5-(2-(1H-indol-3-yl)-2-oxoethylidene)-3-(3,5-dichloro-4-hydroxyphenyl)-2-thioxothiazolidin-4-one; (Z)-3-(3,5-dibromo-4-hydroxyphenyl)-5-(2-(5-methoxy-1H-indol-3-yl)-2-oxoethylidene)-2-thioxothiazolidin-4-one; and (Z)-3-(3,5-dichloro-4-hydroxyphenyl)-5-(2-(5-methoxy-1H-indol-3-yl)-2-oxoethylidene)-2-thioxothiazolidin-4-one.

[0059] It is contemplated that any embodiment discussed in this specification can be implemented with respect to any method, kit, reagent, or composition of the invention, and vice versa. Furthermore, compositions of the invention can be used to achieve methods of the invention.

[0060] It will be understood that particular embodiments described herein are shown by way of illustration and not as limitations of the invention. The principal features of this invention can be employed in various embodiments without departing from the scope of the invention. Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, numerous equivalents to the specific procedures described herein. Such equivalents are considered to be within the scope of this invention and are covered by the claims.

[0061] All publications and patent applications mentioned in the specification are indicative of the level of skill of those skilled in the art to which this invention pertains. All publications and patent applications are herein incorporated by reference to the same extent as if each individual publication

or patent application was specifically and individually indicated to be incorporated by reference.

[0062] The use of the word “a” or “an” when used in conjunction with the term “comprising” in the claims and/or the specification may mean “one,” but it is also consistent with the meaning of “one or more,” “at least one,” and “one or more than one.” The use of the term “or” in the claims is used to mean “and/or” unless explicitly indicated to refer to alternatives only or the alternatives are mutually exclusive, although the disclosure supports a definition that refers to only alternatives and “and/or.” Throughout this application, the term “about” is used to indicate that a value includes the inherent variation of error for the device, the method being employed to determine the value, or the variation that exists among the study subjects.

[0063] As used in this specification and claim(s), the words “comprising” (and any form of comprising, such as “comprise” and “comprises”), “having” (and any form of having, such as “have” and “has”), “including” (and any form of including, such as “includes” and “include”) or “containing” (and any form of containing, such as “contains” and “contain”) are inclusive or open-ended and do not exclude additional, unrecited elements or method steps.

[0064] The term “or combinations thereof” as used herein refers to all permutations and combinations of the listed items preceding the term. For example, “A, B, C, or combinations thereof” is intended to include at least one of: A, B, C, AB, AC, BC, or ABC, and if order is important in a particular context, also BA, CA, CB, CBA, BCA, ACB, BAC, or CAB. Continuing with this example, expressly included are combinations that contain repeats of one or more item or term, such as BB, AAA, MB, BBC, AAABCCCC, CBBAAA, CABABB, and so forth. The skilled artisan will understand that typically there is no limit on the number of items or terms in any combination, unless otherwise apparent from the context.

[0065] All of the compositions and/or methods disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure. While the compositions and methods of this invention have been described in terms of preferred embodiments, it will be apparent to those of skill in the art that variations may be applied to the compositions and/or methods and in the steps or in the sequence of steps of the method described herein without departing from the concept, spirit and scope of the invention. All such similar substitutes and modifications apparent to those skilled in the art are deemed to be within the spirit, scope and concept of the invention as defined by the appended claims.

What is claimed is:

1. A method of reducing the activity of one or more enzymes comprising the steps of:

contacting the one or more enzymes with a thioxothiazolidin compound having a 5-(2-(indol-3-yl)-2-oxoethylidene)-3-phenyl-2-thioxothiazolidin-4-one skeleton to reduce the activity of the one or more enzymes, wherein the one or more enzymes are HIV-1 or JNK-stimulating phosphatase-1 (JSP-1) enzymes or both.

2. The method of claim 1, wherein the thioxothiazolidin compound reduces an HIV-1 enzyme activity.

3. The method of claim 1, wherein the thioxothiazolidin compound inhibits the HIV-1 enzyme.

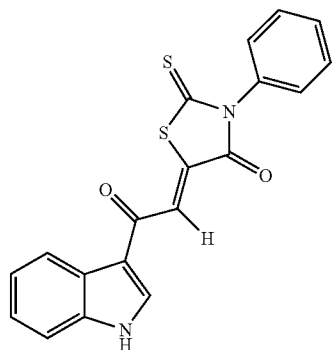
4. The method of claim 1, wherein the thioxothiazolidin compound reduces an JNK-stimulating phosphatase-1 (JSP-1) enzyme activity.

5. The method of claim 1, wherein the thioxothiazolidin compound inhibits an JNK-stimulating phosphatase-1 (JSP-1) enzyme.

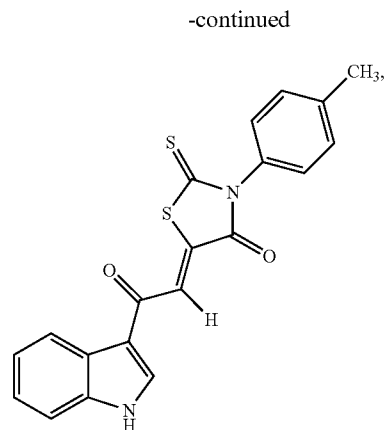
6. The method of claim 1, wherein the thioxothiazolidin compound is a 5-(2-(indol-3-yl)-2-oxoethylidene)-3-phenyl-2-thioxothiazolidin-4-one comprising a 5-substituted 2-(indol-3-yl) and a 3, 4, 5 substituted phenyl.

7. The method of claim 1, wherein the thioxothiazolidin compound is (Z)-5-(2-(1H-indol-3-yl)-2-oxoethylidene)-3-phenyl-2-thioxothiazolidin-4-one; (Z)-5-(2-(1H-indol-3-yl)-2-oxoethylidene)-2-thioxo-3-p-tolylthiazolidin-4-one; (Z)-5-(2-(1H-indol-3-yl)-2-oxoethylidene)-3-(3,4-dimethylphenyl)-2-thioxothiazolidin-4-one; (Z)-5-(2-(5-methoxy-1H-indol-3-yl)-2-oxoethylidene)-2-thioxo-3-p-tolylthiazolidin-4-one; (Z)-5-(2-(1H-indol-3-yl)-2-oxoethylidene)-3-(4-methoxyphenyl)-2-thioxothiazolidin-4-one; (Z)-5-(2-(5-methoxy-1H-indol-3-yl)-2-oxoethylidene)-3-(4-methoxyphenyl)-2-thioxothiazolidin-4-one; (Z)-5-(2-(5-methoxy-1H-indol-3-yl)-2-oxoethylidene)-3-phenyl-2-thioxothiazolidin-4-one; (Z)-4-(5-(2-(5-methoxy-1H-indol-3-yl)-2-oxoethylidene)-4-oxo-2-thioxothiazolidin-3-yl)benzonitrile; (Z)-4-(5-(2-(1H-indol-3-yl)-2-oxoethylidene)-4-oxo-2-thioxothiazolidin-3-yl)benzonitrile; (Z)-5-(2-(5-chloro-1H-indol-3-yl)-2-oxoethylidene)-3-phenyl-2-thioxothiazolidin-4-one; (Z)-5-(2-(1H-indol-3-yl)-2-oxoethylidene)-3-(benzo[d]thiazol-6-yl)-2-thioxothiazolidin-4-one; (Z)-5-(2-(1H-indol-3-yl)-2-oxoethylidene)-3-(benzo[d]thiazol-6-yl)-2-thioxothiazolidin-4-one; (Z)-3-(2-(3-(benzo[d]thiazol-6-yl)-4-oxo-2-thioxothiazolidin-5-ylidene)acetyl)-1H-indole-5-carbonitrile; (Z)-5-(2-(1H-indol-3-yl)-2-oxoethylidene)-3-(3,5-dibromo-4-hydroxyphenyl)-2-thioxothiazolidin-4-one; (Z)-5-(2-(1H-indol-3-yl)-2-oxoethylidene)-3-(3,5-dichloro-4-hydroxyphenyl)-2-thioxothiazolidin-4-one; (Z)-3-(3,5-dibromo-4-hydroxyphenyl)-5-(2-(5-methoxy-1H-indol-3-yl)-2-oxoethylidene)-2-thioxothiazolidin-4-one; or (Z)-3-(3,5-dichloro-4-hydroxyphenyl)-5-(2-(5-methoxy-1H-indol-3-yl)-2-oxoethylidene)-2-thioxothiazolidin-4-one.

8. The method of claim 1, wherein the thioxothiazolidin compound has the structure:

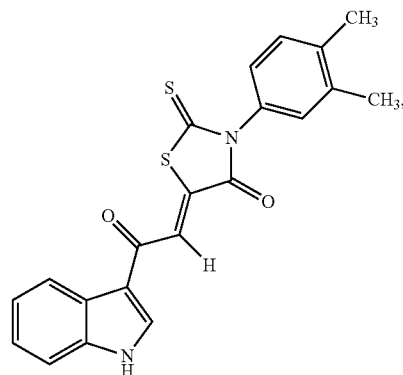


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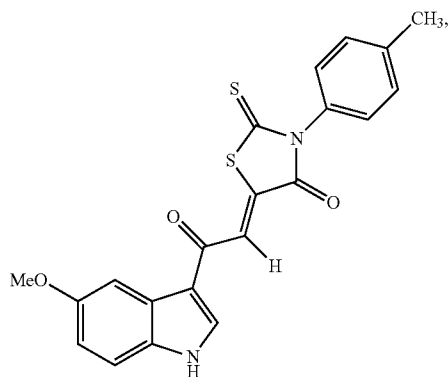


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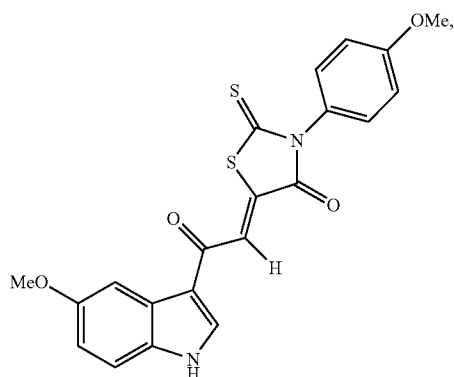
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(SK-T-7c)

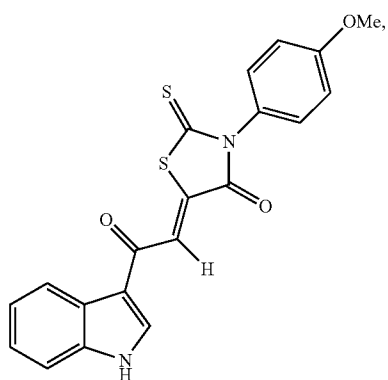


(SK-T-7d)



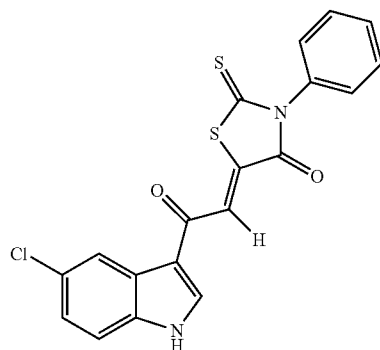
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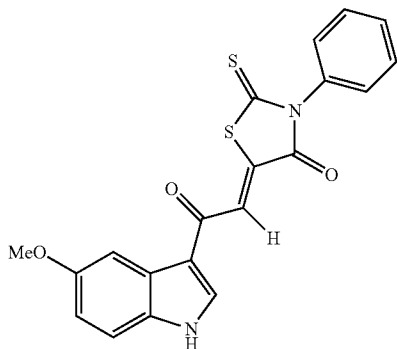
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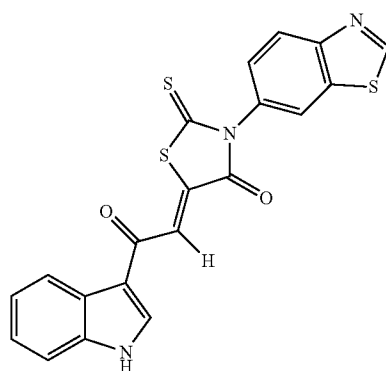


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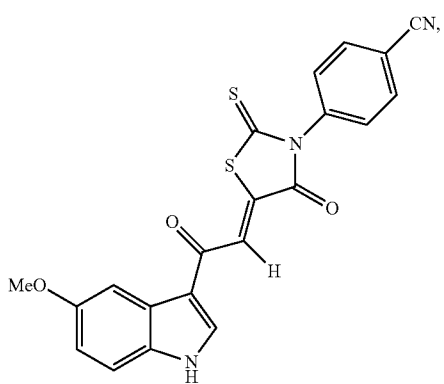
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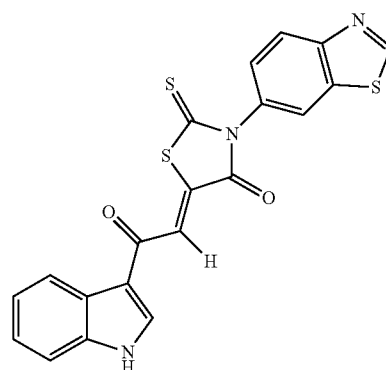
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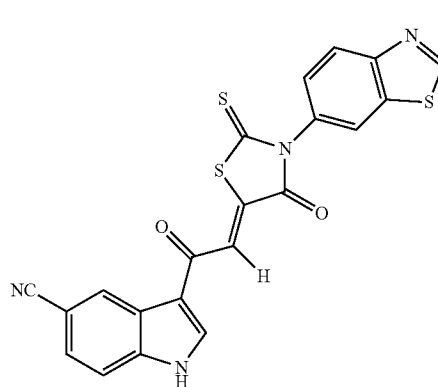
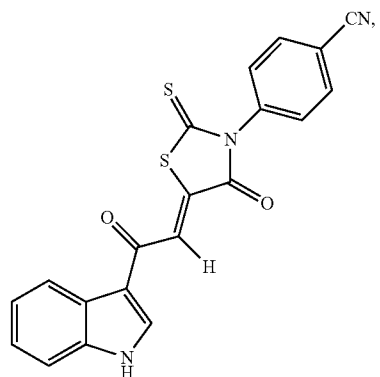
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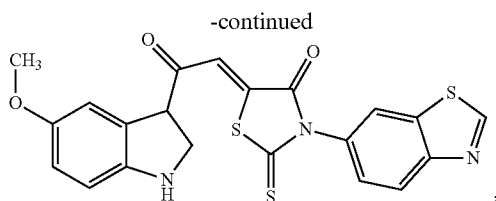
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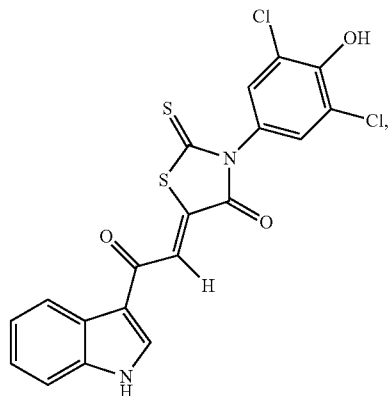
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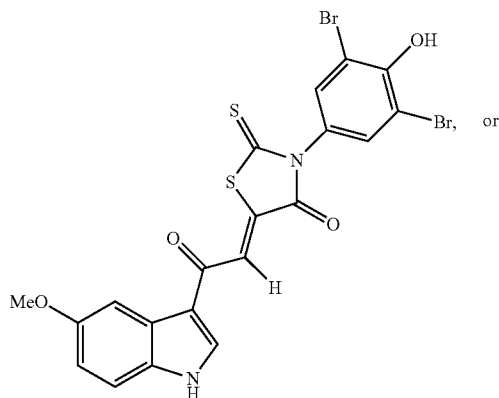
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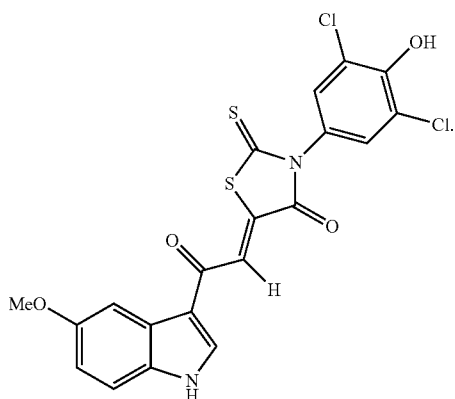
(SK-T-7o)



(SK-T-7p)



(SK-T-7q)



9. A method of treating a subject having an enzyme disorder comprising the steps of:

providing a subject having an enzyme disorder;

wherein the enzyme disorder is an increase in an enzyme activity of an enzyme selected from a HIV-1 enzyme, a JNK-stimulating phosphatase-1 (JSP-1) enzymes or both;

contacting the enzyme with a thioxothiazolidin compound having a 5-(2-(indol-3-yl)-2-oxoethylidene)-3-phenyl-2-thioxothiazolidin-4-one skeleton to reduce the enzyme activity.

10. The method of claim 9, wherein the thioxothiazolidin compound reduces an HIV-1 enzyme activity.

11. The method of claim 9, wherein the thioxothiazolidin compound inhibits the HIV-1 enzyme.

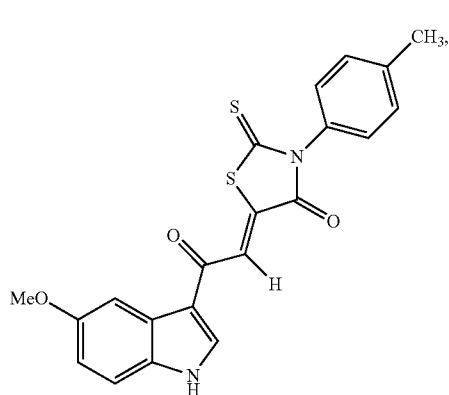
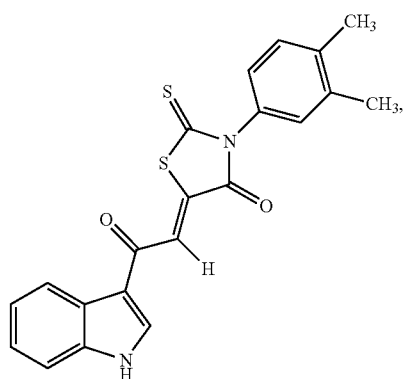
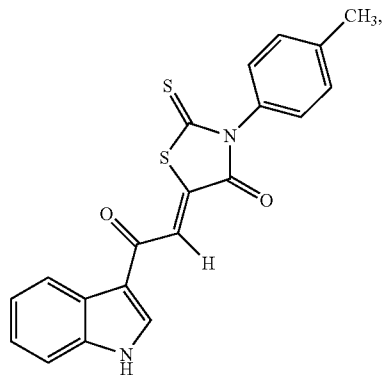
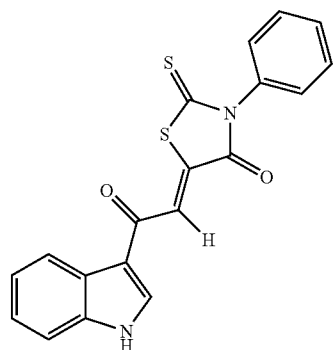
12. The method of claim 9, wherein the thioxothiazolidin compound reduces the JNK-stimulating phosphatase-1 (JSP-1) enzyme activity.

13. The method of claim 9, wherein the thioxothiazolidin compound inhibits the JNK-stimulating phosphatase-1 (JSP-1) enzyme.

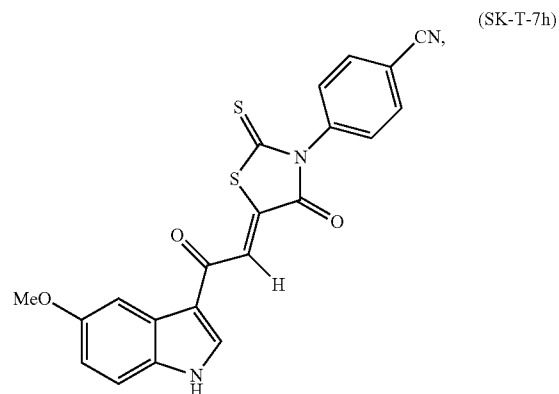
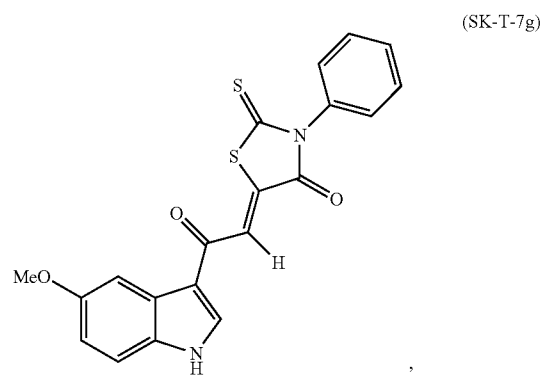
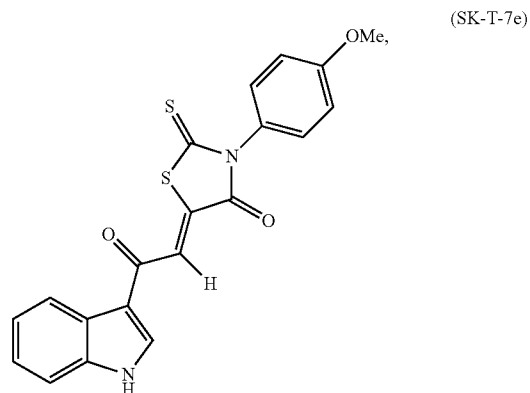
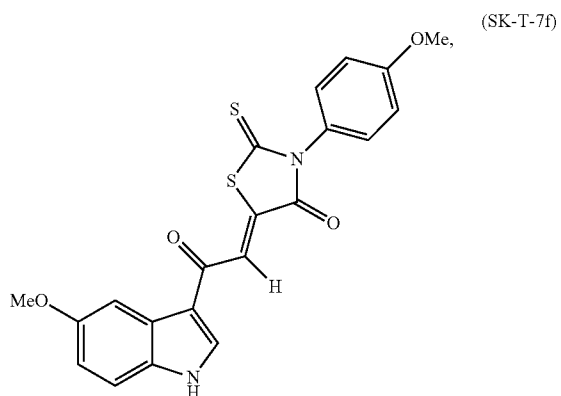
14. The method of claim 9, wherein the thioxothiazolidin compound is a 5-(2-(indol-3-yl)-2-oxoethylidene)-3-phenyl-2-thioxothiazolidin-4-one comprising a 5-substituted 2-(indol-3-yl) and a 3, 4, 5 substituted phenyl.

15. The method of claim 9, wherein the thioxothiazolidin compound is (Z)-5-(2-(1H-indol-3-yl)-2-oxoethylidene)-3-phenyl-2-thioxothiazolidin-4-one; (Z)-5-(2-(1H-indol-3-yl)-2-oxoethylidene)-2-thioxo-3-p-tolylthiazolidin-4-one; (Z)-5-(2-(1H-indol-3-yl)-2-oxoethylidene)-3-(3,4-dimethylphenyl)-2-thioxothiazolidin-4-one; (Z)-5-(2-(5-methoxy-1H-indol-3-yl)-2-oxoethylidene)-2-thioxo-3-p-tolylthiazolidin-4-one; (Z)-5-(2-(1H-indol-3-yl)-2-oxoethylidene)-3-(4-methoxyphenyl)-2-thioxothiazolidin-4-one; (Z)-5-(2-(5-methoxy-1H-indol-3-yl)-2-oxoethylidene)-3-(4-methoxyphenyl)-2-thioxothiazolidin-4-one; (Z)-5-(2-(5-methoxy-1H-indol-3-yl)-2-oxoethylidene)-3-phenyl-2-thioxothiazolidin-4-one; (Z)-4-(5-(2-(5-methoxy-1H-indol-3-yl)-2-oxoethylidene)-4-oxo-2-thioxothiazolidin-3-yl)benzonitrile; (Z)-4-(5-(2-(1H-indol-3-yl)-2-oxoethylidene)-4-oxo-2-thioxothiazolidin-3-yl)benzonitrile; (Z)-5-(2-(5-chloro-1H-indol-3-yl)-2-oxoethylidene)-3-phenyl-2-thioxothiazolidin-4-one; (Z)-5-(2-(1H-indol-3-yl)-2-oxoethylidene)-3-(benzo[d]thiazol-6-yl)-2-thioxothiazolidin-4-one; (Z)-5-(2-(1H-indol-3-yl)-2-oxoethylidene)-3-(benzo[d]thiazol-6-yl)-2-thioxothiazolidin-4-one; (Z)-3-(2-(3-(benzo[d]thiazol-6-yl)-4-oxo-2-thioxothiazolidin-5-ylidene)acetyl)-1H-indole-5-carbonitrile; (Z)-5-(2-(1H-indol-3-yl)-2-oxoethylidene)-3-(3,5-dibromo-4-hydroxyphenyl)-2-thioxothiazolidin-4-one; (Z)-5-(2-(1H-indol-3-yl)-2-oxoethylidene)-3-(3,5-dichloro-4-hydroxyphenyl)-2-thioxothiazolidin-4-one; (Z)-3-(3,5-dibromo-4-hydroxyphenyl)-5-(2-(5-methoxy-1H-indol-3-yl)-2-oxoethylidene)-2-thioxothiazolidin-4-one; or (Z)-3-(3,5-dichloro-4-hydroxyphenyl)-5-(2-(5-methoxy-1H-indol-3-yl)-2-oxoethylidene)-2-thioxothiazolidin-4-one.

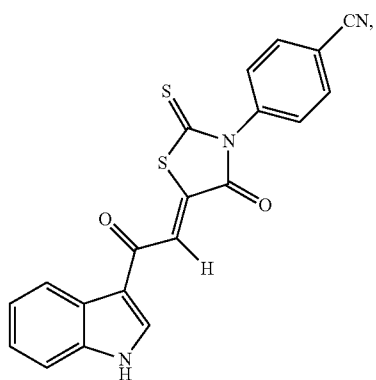
16. The method of claim 9, wherein the thioxothiazolidin compound has the structure:



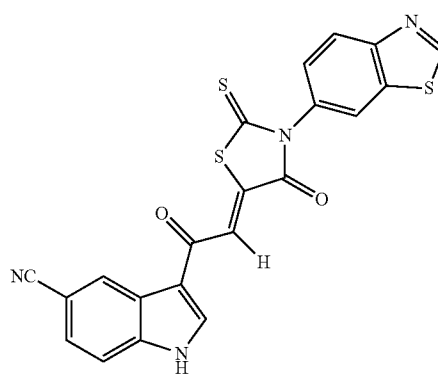
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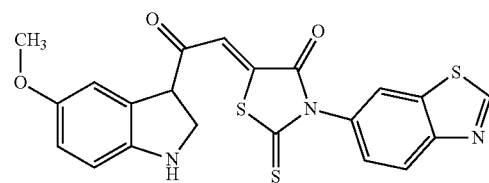
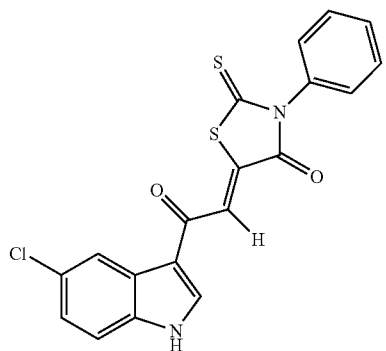
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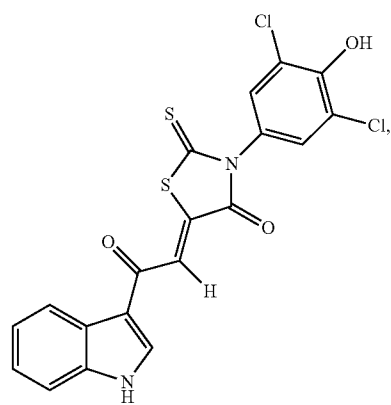
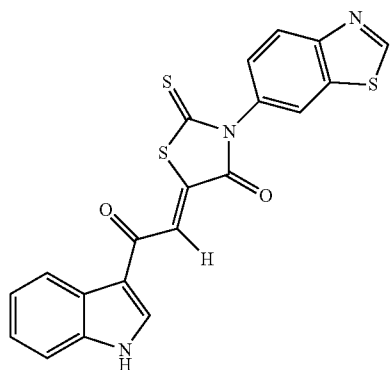
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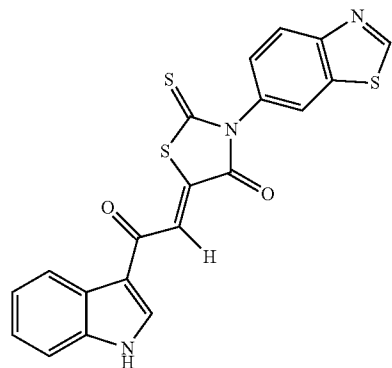
(SK-T-7j)



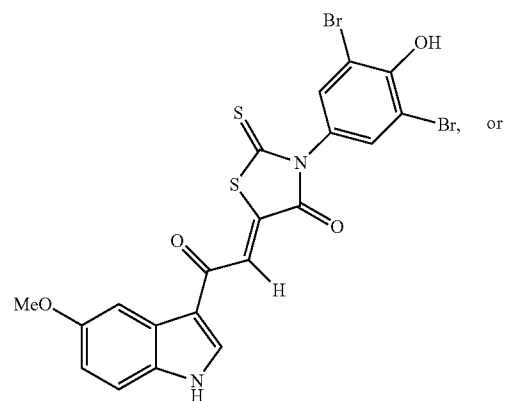
(SK-T-7k)



(SK-T-7l)

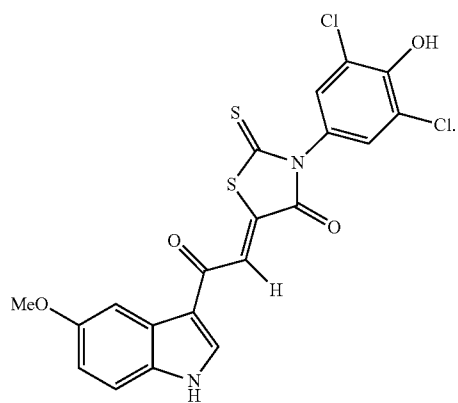


(SK-T-7p)



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(SK-T-7q)



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