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International application number: PCT/US2009/067197

International filing date: 08 December 2009 (08.12.2009)

Document type: Certified copy of priority document

Document details: Country/Office: US
Number: 61/120,827
Filing date: 08 December 2008 (08.12.2008)

Date of receipt at the International Bureau: 14 December 2009 (14.12.2009)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)

220953

THE UNITED STATES OF AMERICA

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UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

December 13, 2009

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APPLICATION NUMBER: *61/120,827*
FILING DATE: *December 08, 2008*
RELATED PCT APPLICATION NUMBER: *PCT/US09/67197*

THE COUNTRY CODE AND NUMBER OF YOUR PRIORITY APPLICATION, TO BE USED FOR FILING ABROAD UNDER THE PARIS CONVENTION, IS *US61/120,827*

Certified by

Under Secretary of Commerce
for Intellectual Property
and Director of the United States
Patent and Trademark Office

Doc Code: **TR.PROV**
Document Description: Provisional Cover Sheet (SB16)

PTO/SB/16 (04-07)
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Provisional Application for Patent Cover Sheet

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c)

Inventor(s)

Inventor 1 — Remove

Given Name	Middle Name	Family Name	City	State	Country
Jay	Jie-Qiang	Wu	Fremont	CA	US

Inventor 2 — Remove

Given Name	Middle Name	Family Name	City	State	Country
Luat	T.	Nguyen	San Jose	CA	US

Inventor 3 — Remove

Given Name	Middle Name	Family Name	City	State	Country
Ling		Wang	Union City	CA	

All Inventors Must Be Listed – Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. — Add

Title of Invention	COMPOSITIONS OF PROTEIN RECEPTOR TYROSINE KINASE INHIBITORS
Attorney Docket Number (if applicable)	VMDI-010/00US

Correspondence Address

Direct all correspondence to (select one):

◉ The address corresponding to Customer Number	○ Firm or Individual Name
Customer Number	58249

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

◉ No.

○ Yes, the name of the U.S. Government agency and the Government contract number are:

Doc Code: **TR.PROV**
Document Description: Provisional Cover Sheet (SB16)

PTO/SB/16 (04-07)
Approved for use through 06/30/2010 OMB 0651-0032
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Entity Status

Applicant claims small entity status under 37 CFR 1.27

(•) Yes, applicant qualifies for small entity status under 37 CFR 1.27

( ) No

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Signature

Please see 37 CFR 1.4(d) for the form of the signature.

Signature	/Yong Lu/			Date (YYYY-MM-DD)	2008-12-08
First Name	Yong	Last Name	Lu	Registration Number (If appropriate)	56038

This collection of information is required by 37 CFR 1.51. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 8 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **This form can only be used when in conjunction with EFS-Web. If this form is mailed to the USPTO, it may cause delays in handling the provisional application.**

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2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
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7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
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PTO/SB/14 (07-07)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	VMDI-010/00US
	Application Number	
Title of Invention	COMPOSITIONS OF PROTEIN RECEPTOR TYROSINE KINASE INHIBITORS	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

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☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Applicant Information:

Applicant 1 Remove

Applicant Authority	◉ Inventor	○ Legal Representative under 35 U.S.C. 117	○ Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
	Jay	Jie-Qiang	Wu	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Fremont	State/Province	CA	Country of Residence [i]	US

Citizenship under 37 CFR 1.41(b) [i] US

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Address 1	Frederick Lane
Address 2	

City	Fremont	State/Province	CA
Postal Code	94555	Country [i]	US

Applicant 2 Remove

Applicant Authority	◉ Inventor	○ Legal Representative under 35 U.S.C. 117	○ Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
	Luat	T.	Nguyen	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

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Citizenship under 37 CFR 1.41(b) [i] US

Mailing Address of Applicant:

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Address 2	Apt. # 158

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Postal Code	95134	Country [i]	US

Applicant 3 Remove

Applicant Authority	◉ Inventor	○ Legal Representative under 35 U.S.C. 117	○ Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
	Ling		Wang	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Union City	State/Province	CA	Country of Residence [i]	

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	VMDI-010/00US
	Application Number	
Title of Invention	COMPOSITIONS OF PROTEIN RECEPTOR TYROSINE KINASE INHIBITORS	

Citizenship under 37 CFR 1.41(b) [i]	CN		
Mailing Address of Applicant:			
Address 1	31404 San Ardo Court		
Address 2			
City	Union City	**State/Province**	CA
Postal Code		**Country**[i]	US

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	58249		
Email Address	ylu@cooley.com	Add Email	Remove Email

Application Information:

Title of the Invention	COMPOSITIONS OF PROTEIN RECEPTOR TYROSINE KINASE INHIBITORS		
Attorney Docket Number	VMDI-010/00US	**Small Entity Status Claimed**	☒
Application Type	Provisional		
Subject Matter	Utility		
Suggested Class (if any)		**Sub Class (if any)**	
Suggested Technology Center (if any)			
Total Number of Drawing Sheets (if any)	4	**Suggested Figure for Publication (if any)**	

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S. C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	VMDI-010/00US
	Application Number	
Title of Invention	COMPOSITIONS OF PROTEIN RECEPTOR TYROSINE KINASE INHIBITORS	

Customer Number	58249

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This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, or 365(c) or indicate National Stage entry from a PCT application. Providing this information in the application data sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78(a)(2) or CFR 1.78(a)(4), and need not otherwise be made part of the specification.

Prior Application Status			Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button. Add

Foreign Priority Information:

This section allows for the applicant to claim benefit of foreign priority and to identify any prior foreign application for which priority is not claimed. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55(a).

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Application Number	Country [i]	Parent Filing Date (YYYY-MM-DD)	Priority Claimed
			◉ Yes ○ No

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Assignee Information:

Providing this information in the application data sheet does not substitute for compliance with any requirement of part 3 of Title 37 of the CFR to have an assignment recorded in the Office.

Assignee 1 Remove

If the Assignee is an Organization check here. ☒

Organization Name	VM DISCOVERY INC.		
Mailing Address Information:			
Address 1	45535 Northport Loop East 2nd Floor FREMONT , CA		
Address 2	2nd Floor		
City	Fremont	**State/Province**	CA
Country [i] US		Postal Code	94538
Phone Number		Fax Number	
Email Address			

Additional Assignee Data may be generated within this form by selecting the **Add** button. Add

Signature:

A signature of the applicant or representative is required in accordance with 37 CFR 1.33 and 10.18. Please see 37 CFR 1.4(d) for the form of the signature.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	VMDI-010/00US
	Application Number	
Title of Invention	COMPOSITIONS OF PROTEIN RECEPTOR TYROSINE KINASE INHIBITORS	

Signature	/Yong Lu/			Date (YYYY-MM-DD)	2008-12-08
First Name	Yong	Last Name	Lu	Registration Number	56038

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The information provided by you in this form will be subject to the following routine uses:

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2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

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COMPOSITIONS OF PROTEIN RECEPTOR TYROSINE KINASE INHIBITORS

1. Field of the Invention

The present invention relates to synthetic substituted heterocyclic compounds and pharmaceutical compositions containing the same that are capable of inhibiting or antagonizing a family of receptor tyrosine kinases, Tropomysosin Related Kinases (Trk), in particular the nerve growth factor (NGF) receptor, TrkA. The invention further concerns the use of such compounds in the treatment and/or prevention of pain, cancer, restenosis, atherosclerosis, psoriasis, thrombosis, or a disease, disorder or injury relating to dysmyelination or demyelination.

2. Background of the Invention

Trk family proteins are receptor tyrosine kinases composed of three family members, TrkA, TrkB and TrkC. They bind with high affinity to, and mediate the signal transduction induced by the Neurotrophin family of ligands whose prototype members are Nerve Growth Factor (NGF), Brain-Derived Neurotrophic Factor (BDNF) and Neurotrophin 3-5 (NT 3-5). In addition, a co-receptor lacking enzymatic activity, p75, has been identified which binds all neurotrophines (NTs) with low affinity and regulates neurotrophin signaling. A critical role of the Trks and their ligands during the development of the central and peripheral nervous systems have been established through gene disruption studies in mice. In particular, TrkA-NGF interaction was shown as a requirement for the survival of certain peripheral neuron populations involved in mediating pain signaling. It has been shown that increased expression of TrkA also correlates with an increased level of pain in the case of pancreatic cancer (Zhu, et al, Journal of clinical oncology, 17:2419-2428 (1999)). Increased expression of NGF and TrkA was also observed in human osteoarthritis chondrocytes (Iannone et al, Rheumatology 41:1413-1418 (2002)).

TrkA (Troponyosin-receptor kinase A) is a cell surface receptor kinase containing an extracellular, a transmembrane, and a cytoplasmic kinase domain. The binding of a neurotrophin triggers oligomerization of the receptors, phosphorylation of tyrosine residues in the kinase domain, and activation of intercellular signaling pathways, including Ras/MAPK cascade, PI3K/AKT, and IP3-dependent Ca2+ release. Tyrosine kinase activity is an absolute requirement for signal transduction through this class of receptor. NGF receptors have been also found on a variety of cell types outside of the nervous system. For example, TrkA has been also found on human monocytes, T- and B-lymphocytes and mast cells.

There are several examples of either ant-TrkA antibodies or anti-NGF antibodies known in the art. For example, PCT Publication Nos. WO 2006/131952, WO 2005/061540 and EP 1181318 disclose use of anti-TrkA antibodies as effective analgesics in in-vivo animal models of inflammatory and neuropathic pain. PCT Application Nos. WO 01/78698, WO 2004/058184 and WO 2005/019266 disclose the use of an NGF antagonist for preventing or treating pain. PCT Application WO 2004/096122 describes a method for the treatment or the prevention of pain with co-administration of an anti-NGF antibody and an opioid analgesic. PCT Application WO 2006/137106 discloses a method for the treatment or the prevention of pain with co-administration of an anti-TrkA antibody and an opioid analgesic. In addition, profound or significantly attenuated reduction of bone pain caused by prostate cancer metastasis has been achieved by utilization of an anti-NGF antibody (Sevik, MA, et al, Pain 115:128-141 (2005)).

Besides antibodies, however, few TrkA inhibitors are known and very few (if any) show high TrkA kinase selectivity (including staurosporine derived TrkA inhibitors, CEP-751 and CEP-701). It has been rarely (if any) known in the art that a synthetic organic molecule or compound had been used as either direct TrkA or NGF inhibitor or antagonist for treatment or prevention of pain in particular. It may due mainly to the facts of difficulty in identifying potent and particularly selective anti-TrkA or anti-NGF small

organic compounds, though the crystal structure of NGF in complex with the TrkA receptor has been determined (Nature 401:184-188 (1996) & 254:411(1991)).

The therapeutic implications of an effective Trk inhibitor may well go beyond pain therapy. The subversion of this receptor and its signaling pathway in certain malignancies has also been documented. The tyrosine kinase activity of Trk is believed to promote the unregulated activation of cell proliferation machinery. It is believed that inhibitors of either TrkA, TrkB, or TrkC kinases, individually or in combination, have utility against some of the most common cancers such as brain, melanoma, multiple myeloma, squamous cell, bladder, gastric, pancreatic, breast, head, neck, esophageal, prostate, colorectal, lung, renal, ovarian, gynecological, thyroid cancer, and certain type of hematological malignancies. Lestaurtinib (CEP-701, Cephalon), an indolocarbazole inhibitor of several tyrosine kinases, including Flt-3 and TrkA, and CEP-751, a pan Trk inhibitor have been entered Phase II clinical trails for the treatment of acute myelogenous leukaemia (AML), pancreatic cancer and multiple myeloma (MM) and/or prostate cancer.

Of particular note are reports of aberrant expression of NGF and TrkA receptor kinase are implicated in the development and progression of human prostatic carcinoma and pancreatic ductal adrenocarcinoma and activating chromosomal rearrangements of Trks in acute myelogenous leukemia (AML), thyroid and breast cancers and receptor point mutations predicted to be constitutively activating in colon tumors. In addition to these activation mechanisms, elevated Trk receptor and ligand have also been reported in a variety of tumor types including multiple myeloma, melanoma, neuroblastoma, ovarian and pancreatic carcinoma. The neurotrophins and their corresponding Trk receptor subtypes have been shown to exert a variety of pleiotropic responses on malignant cells, including enhanced tumor invasiveness and chemotaxis, activation of apoptosis, stimulation of clonal growth, and altered cell morphology. These effects have been observed in carcinomas of the prostate, breast, thyroid, colon, malignant melanomas, lung carcinomas, glioblastomas, pancreatic carcinoids and a wide variety of pediatric and neuroectodermal-derived tumors including Wilm's tumor, neuroblastomas and medulloblastomas. Neurotrophins and their receptor subtypes have been implicated in

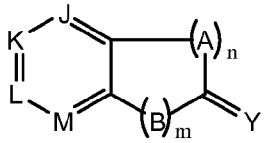
these cancers either through autocrine or paracrine mechanisms involving carcinoma cells and the surrounding parenchymal and stromal tissues. Overall, the oncogenic properties of Trk signaling in multiple tumor types makes the modulation of the Trk receptor signaling a potentially attractive therapeutic intervention point in different malignancies.

Due to the therapeutic promise associated with inhibiting TrkA, and the relative lack of potent and selective inhibitors, it is great need to discover the potent and particular selective TrkA inhibitors, especially of orally active small synthetic molecules for possible treatment or prevention of the disease associated with inhibiting TrkA.

3. Summary of the Invention

The object of the present invention is the use of a small synthetic molecule as NGF receptor TrkA inhibitor and/or antagonist for the preparation of a medicament for the treatment and/or prevention of diseases associated with inhibiting TrkA, which including pain, cancer, restenosis, atherosclerosis, psoriasis, thrombosis, or a disease, disorder or injury relating to dysmyelination or demyelination.

In one aspect, the present invention provides compounds having structural Formula (I):



(I)

or a salt, solvate, ester, and/or prodrug thereof;

wherein:

n is 1, 2, or 3;

m is 0, 1, or 2;

A is C, N, O, S, NR^1, $C=CR^1$ (E and Z isomers), $C=NR^1$ (E and Z isomers), or $C(R^1R^2)$;

B is C, N, O, S, NR^3, or $C(R^3R^4)$;

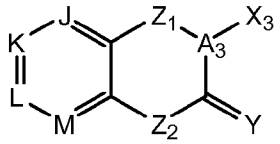
J, K, L, and M are independently N or CR^5;

Y is O, S, NR^6, or $C(R^6R^7)$;

R^1, R^2, R^3, R^4, R^5, R^6, and R^7 are independently hydrogen, halogen, acyl, substituted acyl, alkoxycarbonyl, substituted alkoxycarbonyl, aryloxycarbonyl, substituted aryloxycarbonyl, $-CONR^8R^9$, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyl;

R^8 and R^9 are independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyl or substituted heteroalkyl or alternatively, R^8 and R^9, taken together with the nitrogen atom to which they are attached, form a 4-, 5-, 6-, or 7-membered cycloheteroalkyl ring, provided that both R^8 and R^9 are not hydrogen;

In another aspect, the present invention provides compounds having structural Formula (IV):



(IV)

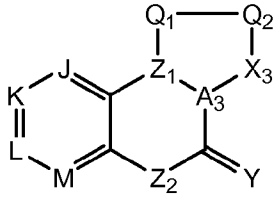
or a salt, solvate, ester, and/or prodrug thereof;

wherein:

A_3-X_3 is NR^1, $C{=}CR^1$ (E and Z isomers), $C{=}NR^1$ (E and Z isomers), or $C(R^1R^2)$;

Z_1 and Z_2 are O, S, CR^3, NR^3, $C(R^3R^4)$;

In another aspect, the present invention provides compounds having structural Formula (IVb.0):



(IVb.0)

or a salt, solvate, ester, and/or prodrug thereof;

wherein:

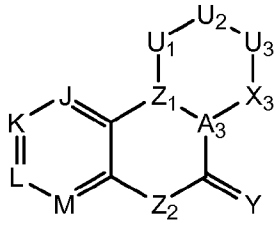
Z_1-Q_1, Q_1-Q_2, Q_2-X_3, A_3-X_3, Z_1-A_3 are independently single or double bond;

Q_1, Q_2, and X_3 are independently S, O, N, N(R^{10}), C(R^{10}), C($R^{10}R^{11}$);

Z_1 and A_3 are independently N, C, or CR^{12};

R^{10}, R^{11}, and R^{12} are independently hydrogen, halogen, acyl, substituted acyl, alkoxycarbonyl, substituted alkoxycarbonyl, aryloxycarbonyl, substituted aryloxycarbonyl, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyl;

In another aspect, the present invention provides compounds having structural Formula (IVc):



(IVc)

or a salt, solvate, ester, and/or prodrug thereof;

wherein:

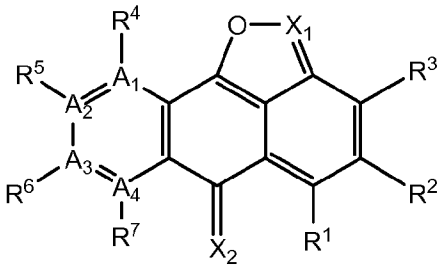
Z_1-U_1, U_1-U_2, U_2-U_3, U_3-X_3, A_3-X_3, Z_1-A_3 are independently single or double bond;

U_1, U_2, U_3, and X_3 are independently S, O, N, N(R^{13}), C(R^{13}), C($R^{13}R^{14}$);

Z_1 and A_3 are independently N, C, or CR^{15};

R^{13}, R^{14}, and R^{15} are independently hydrogen, halogen, acyl, substituted acyl, alkoxycarbonyl, substituted alkoxycarbonyl, aryloxycarbonyl, substituted aryloxycarbonyl, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyl;

In another aspect, the present invention provides compounds having structural Formula (VI):



(VI)

or a salt, solvate, ester, and/or prodrug thereof;

wherein:

X_1 is N, or CR^8;

X_2 is S, O, or NR^9;

A_1, A_2, A_3 and A_4 are independently C or N;

R^1, R^2, R^3, R^4, R^5, R^6, R^7, and R^8 are independently hydrogen, halogen, cyano, nitro, amino, substituted amino, sulfonyl, substituted sulfonyl, acyl, substituted acyl, alkoxycarbonyl, substituted alkoxycarbonyl, aryloxycarbonyl, substituted aryloxycarbonyl, $-CONR^{10}R^{11}$, $S(O)_2NR^{10}R^{11}$, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyl or substituted heteroalkyl or alternatively, R^1 and R^2, R^2 and R^3, R^4 and R^5, R^5 and R^6, or R^6 and R^7 taken together with the atoms to which they are bonded, form an aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroaryl or substituted heteroaryl ring;

With the proviso that when X_1 is N, or X_1 is CR^8 and R^8 is hydrogen or alkyl, R^1, R^2, R^3, R^4, R^5, R^6 and R^7 are not hydrogen, halogen, cyano, nitro, amino, substituted amino, sulfonyl, substituted sulfonyl, alkyl, substituted alkyl, acyl, substituted acyl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyl, or substituted heteroalkyl;

R^9, R^{10} and R^{11} are independently hydrogen alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyl, substituted heteroalkyl or alternatively R^{10} and R^{11} taken together to with the atoms to which they are bonded, form an aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroaryl or substituted heteroaryl ring.

In another aspect, the present invention provides pharmaceutical compositions comprising one or more compounds as described above or a salt, solvate, ester, and/or prodrug thereof, and a pharmaceutically acceptable vehicle.

In still another aspect, the present invention provides methods for selectively inhibiting or antagonizing NGF receptor TrkA for treatment and/or prevention of pain, cancer, restenosis, atherosclerosis, psoriasis, thrombosis, or a disease, disorder or injury relating to dysmyelination or demyelination, with therapeutic effective amount of the compound as described above, or a salt, solvate, ester, and/or prodrug thereof.

In still another aspect, the present invention provides methods for treatment and/or prevention of pain, cancer, restenosis, atherosclerosis, psoriasis, thrombosis, or a disease, disorder or injury relating to dysmyelination or demyelination, with combination of (a) therapeutic effective amount of the compound as described above, or a salt, solvate, ester, and/or prodrug thereof, and (b) an opioid analgesic.

4. Brief Description of the Drawings

FIGURES 1-6 provide examples of compounds of present invention in inhibiting in certain *in vitro* assays.

FIGURE-1. Dose-dependent inhibition of recombinant TrkA phosphorylation by the Compound 201 with measured IC50 = 85 nM, in a radiometric based (^{33}P) assay

(Staurosporine was used as control. Substrate: PolyEY(4:1), 0.2 mg/ml & 2nM MnCl2; ATP: 10 uM; TrkA 30nM; Buffer: 20 mM HEPES (pH 7.5), 10 mM MgCl2, 1 mM EGTA, 0.02% Brij 35, 0.02 mg/ml BSA, 0.1 mM Na3VO4, 2 mM DTT, 1% DMSO).

FIGURE-2. Selectivity screening of Compound 201 at 10 uM against 21 related kinases/proteins in radiometric based (^{33}P) assays (% Activity (DMSO control as 100% activity). Except TrkA, there is no activity (inhibition < 30%) of Compound 201 against these kinases/proteins at 10 uM.

FIGURE-3. Dose-dependent inhibition of recombinant TrkA, TrkB and TrkC phosphorylation by the Compound 701 with measured IC50 = 7, 33,100, 26,500 nM for TrkA, TrkB and TrkC, respectively (radiometric based (^{33}P) assay, for assay condition, ref Figure-1 legend).

FIGURE-4. Selectivity screening of Compound 701 at 10 uM against 15 related kinases/proteins in radiometric based (^{33}P) assays (% Activity (DMSO control as 100% activity). Except TrkA, there is no activity (inhibition < 40%) of Compound 701 against these kinases/proteins at 10 uM.

FIGURE-5. ATP competition evaluation for TrkA/Compound 701. Michaelis-Menten plot (A) and double-reciprocal plot (B), and secondary plot (C) for TRKA with Compound 701, with measured Ki = 0.05 uM and Ki' = 0.26 (alpha = 5), which suggest that Compound 701 is a mixed (not a pure ATP) competitive inhibitor.

FIGURE-6. Substare (PloyEY(4:1)) competition evaluation for TrkA/Compound 701. Michaelis-Menten plot (A) and double-reciprocal plot (B) for TRKA with Compound 701, with measured Ki = 46 uM and Ki' = 30 uM (alpha = 0.65), which suggest that Compound 701 is noncompetitive inhibitor for TrkA with respect to PloyEY peptide substrate.

5. Detailed Description of the Invention

The present invention relates to novel synthetic small molecules that act as inhibitors and/or antagonists of the members of Trk family protein kinases, in particularly the NGF receptor, TrkA.

5.1 Definitions

Terms used in the claims and specification are defined as set forth below unless otherwise specified.

The term "a compound of the present invention", "the compound of the present invention", "compounds of the present invention", or "the present compounds" refers to one or more compounds encompassed by the structural formulae and/or any subgeneric formulae disclosed herein and includes any specific compounds within these generic formula whose structure is disclosed herein. Compounds of the invention may contain one or more chiral centers and/or double bonds and therefore, may exist as stereoisomers, such as double-bond isomers (*i.e.*, geometric isomers), the racemic mixtures, enantiomers or diastereomers. Accordingly, the chemical structures depicted herein encompass all possible enantiomers and stereoisomers of the illustrated compounds including the stereoisomerically pure form (*e.g.*, geometrically pure, enantiomerically pure or diastereomerically pure) and enantiomeric and stereoisomeric mixtures. The compounds of the invention may also exist in several tautomeric forms. Accordingly, the chemical structures depicted herein encompass all possible tautomeric forms of the illustrated compounds. Compounds also include isotopically labeled compounds where one or more atoms have an atomic mass different from the atomic mass conventionally found in nature. Examples of isotopes that may be incorporated into the compounds include, but are not limited to, ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{17}O, ^{18}O, *etc.* Compounds may exist in unsolvated forms as well as solvated forms, including hydrated forms and as N-oxides. In general, the salt, hydrated, solvated, and N-oxide forms are within the scope of the present invention. Certain compounds of the present invention may exist in multiple crystalline forms or an amorphous form. In general, all physical forms are equivalent for

the uses contemplated by the present invention and are intended to be within the scope of the present invention.

"Identity" or "percent identity" in the context of two polypeptide sequences, refer to two or more sequences or subsequences that are the same or have a specified percentage of amino acid residues hat are the same, when compared and aligned for maximum correspondence, as measured using either a PILEUP or BLAST sequence comparison algorithm (*see, e.g., J. Mol. Evol.* 35:351-360, 1987; Higgins and Sharp, *CABIOS* 5:151-153, 1989; Altschul *et al., J. Mol. Biol.* 215:403-410, 1990; Zhang *et al., Nucleic Acid Res.* 26:3986-3990, 1998; Altschul *et al., Nucleic Acid Res.* 25:3389-33402, 1997). Optimal alignment of sequences for comparison can be conducted, *e.g.*, by the local homology algorithm of Smith and Waterman, *Adv. Appl. Math.* 2:482, 1981, by the homology alignment algorithm of Needleman and Wunsch, *J. Mol. Biol.* 48:443, 1970, by the search for similarity method of Pearson and Lipman, *Proc. Nat. Acad. Sci. USA* 85:2444, 1988, by computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group, 575 Science Dr., Madison, WI), or by visual inspection (*see, generally*, Ausubel *et al., supra*).

"Alkyl" by itself or as part of another substituent, refers to a saturated or unsaturated, branched, straight-chain or cyclic monovalent hydrocarbon radical derived by the removal of one hydrogen atom from a single carbon atom of a parent alkane, alkene or alkyne. Typical alkyl groups include, but are not limited to, methyl; ethyls such as ethanyl, ethenyl, ethynyl; propyls such as propan-1-yl, propan-2-yl, cyclopropan-1-yl, prop-1-en-1-yl, prop-1-en-2-yl, prop-2-en-1-yl (allyl), cycloprop-1-en-1-yl; cycloprop-2-en-1-yl, prop-1-yn-1-yl, prop-2-yn-1-yl, *etc.*; butyls such as butan-1-yl, butan-2-yl, 2-methyl-propan-1-yl, 2-methyl-propan-2-yl, cyclobutan-1-yl, but-1-en-1-yl, but-1-en-2-yl, 2-methyl-prop-1-en-1-yl, but-2-en-1-yl, but-2-en-2-yl, buta-1,3-dien-1-yl, buta-1,3-dien-2-yl, cyclobut-1-en-1-yl, cyclobut-1-en-3-yl, cyclobuta-1,3-dien-1-yl, but-1-yn-1-yl, but-1-yn-3-yl, but-3-yn-1-yl, *etc.*; and the like.

The term "alkyl" is specifically intended to include groups having any degree or level of saturation, *i.e.*, groups having exclusively single carbon-carbon bonds, groups having one or more double carbon-carbon bonds, groups having one or more triple

carbon-carbon bonds and groups having mixtures of single, double and triple carbon-carbon bonds. Where a specific level of saturation is intended, the expressions "alkanyl," "alkenyl," and "alkynyl" are used. In some embodiments, an alkyl group comprises from 1 to 20 carbon atoms (C_1-C_{20} alkyl). In other embodiments, an alkyl group comprises from 1 to 10 carbon atoms (C_1-C_{10} alkyl). In still other embodiments, an alkyl group comprises from 1 to 6 carbon atoms (C_1-C_6 alkyl).

"Alkanyl," by itself or as part of another substituent, refers to a saturated branched, straight-chain or cyclic alkyl radical derived by the removal of one hydrogen atom from a single carbon atom of a parent alkane. Typical alkanyl groups include, but are not limited to, methanyl; ethanyl; propanyls such as propan-1-yl, propan-2-yl (isopropyl), cyclopropan-1-yl, *etc.*; butanyls such as butan-1-yl, butan-2-yl (*sec*-butyl), 2-methyl-propan-1-yl (isobutyl), 2-methyl-propan-2-yl (*t*-butyl), cyclobutan-1-yl, *etc.*; and the like.

"Alkenyl," by itself or as part of another substituent, refers to an unsaturated branched, straight-chain or cyclic alkyl radical having at least one carbon-carbon double bond derived by the removal of one hydrogen atom from a single carbon atom of a parent alkene. The group may be in either the *cis* or *trans* conformation about the double bond(s). Typical alkenyl groups include, but are not limited to, ethenyl; propenyls such as prop-1-en-1-yl, prop-1-en-2-yl, prop-2-en-1-yl (allyl), prop-2-en-2-yl, cycloprop-1-en-1-yl; cycloprop-2-en-1-yl; butenyls such as but-1-en-1-yl, but-1-en-2-yl, 2-methyl-prop-1-en-1-yl, but-2-en-1-yl , but-2-en-1-yl, but-2-en-2-yl, buta-1,3-dien-1-yl, buta-1,3-dien-2-yl, cyclobut-1-en-1-yl, cyclobut-1-en-3-yl, cyclobuta-1,3-dien-1-yl, *etc.*; and the like.

"Alkynyl," by itself or as part of another substituent refers to an unsaturated branched, straight-chain or cyclic alkyl radical having at least one carbon-carbon triple bond derived by the removal of one hydrogen atom from a single carbon atom of a parent alkyne. Typical alkynyl groups include, but are not limited to, ethynyl; propynyls such as prop-1-yn-1-yl, prop-2-yn-1-yl, *etc.*; butynyls such as but-1-yn-1-yl, but-1-yn-3-yl, but-3-yn-1-yl, *etc.*; and the like.

"Alkyldiyl" by itself or as part of another substituent, refers to a saturated or unsaturated, branched, straight-chain or cyclic divalent hydrocarbon group derived by the

removal of one hydrogen atom from each of two different carbon atoms of a parent alkane, alkene or alkyne, or by the removal of two hydrogen atoms from a single carbon atom of a parent alkane, alkene or alkyne. The two monovalent radical centers or each valency of the divalent radical center can form bonds with the same or different atoms. Typical alkyldiyl groups include, but are not limited to methandiyl; ethyldiyls such as ethan-1,1-diyl, ethan-1,2-diyl, ethen-1,1-diyl, ethen-1,2-diyl; propyldiyls such as propan-1,1-diyl, propan-1,2-diyl, propan-2,2-diyl, propan-1,3-diyl, cyclopropan-1,1-diyl, cyclopropan-1,2-diyl, prop-1-en-1,1-diyl, prop-1-en-1,2-diyl, prop-2-en-1,2-diyl, prop-1-en-1,3-diyl, cycloprop-1-en-1,2-diyl, cycloprop-2-en-1,2-diyl, cycloprop-2-en-1,1-diyl, prop-1-yn-1,3-diyl, *etc.*; butyldiyls such as, butan-1,1-diyl, butan-1,2-diyl, butan-1,3-diyl, butan-1,4-diyl, butan-2,2-diyl, 2-methyl-propan-1,1-diyl, 2-methyl-propan-1,2-diyl, cyclobutan-1,1-diyl; cyclobutan-1,2-diyl, cyclobutan-1,3-diyl, but-1-en-1,1-diyl, but-1-en-1,2-diyl, but-1-en-1,3-diyl, but-1-en-1,4-diyl, 2-methyl-prop-1-en-1,1-diyl, 2-methanylidene-propan-1,1-diyl, buta-1,3-dien-1,1-diyl, buta-1,3-dien-1,2-diyl, buta-1,3-dien-1,3-diyl, buta-1,3-dien-1,4-diyl, cyclobut-1-en-1,2-diyl, cyclobut-1-en-1,3-diyl, cyclobut-2-en-1,2-diyl, cyclobuta-1,3-dien-1,2-diyl, cyclobuta-1,3-dien-1,3-diyl, but-1-yn-1,3-diyl, but-1-yn-1,4-diyl, buta-1,3-diyn-1,4-diyl, *etc.*; and the like. Where specific levels of saturation are intended, the nomenclature alkanyldiyl, alkenyldiyl and/or alkynyldiyl is used. In some embodiments, the alkyldiyl group is (C_1-C_{20}) alkyldiyl, more preferably, (C_1-C_{10}) alkyldiyl, most preferably, (C_1-C_6) alkyldiyl.

"Alkyleno" by itself or as part of another substituent, refers to a straight-chain alkyldiyl group having two terminal monovalent radical centers derived by the removal of one hydrogen atom from each of the two terminal carbon atoms of straight-chain parent alkane, alkene or alkyne. Typical alkyleno groups include, but are not limited to, methano; ethylenos such as ethano, etheno, ethyno; propylenos such as propano, prop[1]eno, propa[1,2]dieno, prop[1]yno, etc.; butylenos such as butano, but[1]eno, but[2]eno, buta[1,3]dieno, but[1]yno, but[2]yno, but[1,3]diyno, *etc.*; and the like. Where specific levels of saturation are intended, the nomenclature alkano, alkeno and/or alkyno is used.

"Acyl" by itself or as part of another substituent refers to a radical $-C(O)R^{200}$, where R^{200} is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl,

substituted arylalkyl, heteroalkyl, substituted heteroalkyl, heteroarylalkyl or substituted heteroarylalkyl as defined herein. Representative examples include, but are not limited to formyl, acetyl, cyclohexylcarbonyl, cyclohexylmethylcarbonyl, benzoyl, benzylcarbonyl and the like.

"Amino" by itself or as part of another substituent refers to a radical $-NR^aR^b$, where R^a and R^b are independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroalkyl, substituted heteroalkyl, heteroarylalkyl or substituted heteroarylalkyl as defined herein, or alternatively R^a and R^b, taken together with the atoms to which they are bonded, form a cycloheteroalkyl ring. Representative examples include, but are not limited to $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, -NH-phenyl, $-NH-CH_2$-phenyl, pyrrolidine, and the like.

"Aryl," by itself or as part of another substituent, refers to a monovalent aromatic hydrocarbon group derived by the removal of one hydrogen atom from a single carbon atom of a parent aromatic ring system, as defined herein. Typical aryl groups include, but are not limited to, groups derived from aceanthrylene, acenaphthylene, acephenanthrylene, anthracene, azulene, benzene, chrysene, coronene, fluoranthene, fluorene, hexacene, hexaphene, hexalene, *as*-indacene, *s*-indacene, indane, indene, naphthalene, octacene, octaphene, octalene, ovalene, penta-2,4-diene, pentacene, pentalene, pentaphene, perylene, phenalene, phenanthrene, picene, pleiadene, pyrene, pyranthrene, rubicene, triphenylene, trinaphthalene and the like. In some embodiments, an aryl group comprises from 6 to 20 carbon atoms (C_6-C_{20} aryl). In other embodiments, an aryl group comprises from 6 to 15 carbon atoms (C_6-C_{15} aryl). In still other embodiments, an aryl group comprises from 6 to 10 carbon atoms (C_6-C_{10} aryl).

"Arylalkyl," by itself or as part of another substituent, refers to an acyclic alkyl group in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, is replaced with an aryl group as, as defined herein. Typical arylalkyl groups include, but are not limited to, benzyl, 2-phenylethan-1-yl, 2-phenylethen-1-yl, naphthylmethyl, 2-naphthylethan-1-yl, 2-naphthylethen-1-yl, naphthobenzyl, 2-naphthophenylethan-1-yl and the like. Where specific alkyl moieties are intended, the nomenclature arylalkanyl, arylalkenyl and/or arylalkynyl is used. In some embodiments, an arylalkyl group is (C_6-C_{30}) arylalkyl, *e.g.*, the alkanyl, alkenyl or alkynyl moiety of the

arylalkyl group is (C_1-C_{10}) alkyl and the aryl moiety is (C_6-C_{20}) aryl. In other embodiments, an arylalkyl group is (C_6-C_{20}) arylalkyl, *e.g.*, the alkanyl, alkenyl or alkynyl moiety of the arylalkyl group is (C_1-C_8) alkyl and the aryl moiety is (C_6-C_{12}) aryl. In still other embodiments, an arylalkyl group is (C_6-C_{15}) arylalkyl, *e.g.*, the alkanyl, alkenyl or alkynyl moiety of the arylalkyl group is (C_1-C_5) alkyl and the aryl moiety is (C_6-C_{10}) aryl.

"Aryloxy," by itself or as part of another substituent, refers to a radical of the formula -O-R^{201}, where R^{201} is aryl, substituted aryl, arylalkyl, or substituted arylalkyl.

"Aryloxycarbonyl," by itself or as part of another substituent, refers to a radical of the formula -C(O)-O-R^{201}, where R^{201} is aryl, substituted aryl, arylalkyl, or substituted arylalkyl.

"Cycloalkyl" or "carbocyclyl" by itself or as part of another substituent, refers to a saturated or unsaturated cyclic alkyl radical, as defined herein. Where a specific level of saturation is intended, the nomenclature "cycloalkanyl" or "cycloalkenyl" is used. Typical cycloalkyl groups include, but are not limited to, groups derived from cyclopropane, cyclobutane, cyclopentane, cyclohexane, and the like. In some embodiments, a cycloalkyl group comprises from 3 to 10 ring atoms (C_3-C_{10} cycloalkyl). In other embodiments, a cycloalkyl group comprises from 3 to 7 ring atoms (C_3-C_7 cycloalkyl).

"Cycloheteroalkyl" or "heterocyclyl" by itself or as part of another substituent, refers to a saturated or unsaturated cyclic alkyl radical in which one or more carbon atoms (and optionally any associated hydrogen atoms) are independently replaced with the same or different heteroatom. Typical heteroatoms to replace the carbon atom(s) include, but are not limited to, B, N, P, O, S, Si, *etc.* Where a specific level of saturation is intended, the nomenclature "cycloheteroalkanyl" or "cycloheteroalkenyl" is used. Typical cycloheteroalkyl groups include, but are not limited to, groups derived from epoxides, azirines, thiiranes, imidazolidine, morpholine, piperazine, piperidine, pyrazolidine, pyrrolidone, quinuclidine, borolane, dioxaborolane, and the like. In some embodiments, the cycloheteroalkyl group comprises from 3 to 10 ring atoms (3-10 membered cycloheteroalkyl). In other embodiments, the cycloalkyl group comprise from 5 to 7 ring atoms (5-7 membered cycloheteroalkyl).

A cycloheteroalkyl group may be substituted at a heteroatom, for example, a nitrogen atom, with a (C_1-C_6) alkyl group. As specific examples, N-methyl-imidazolidinyl, N-methyl-morpholinyl, N-methyl-piperazinyl, N-methyl-piperidinyl, N-methyl-pyrazolidinyl and N-methyl-pyrrolidinyl are included within the definition of "cycloheteroalkyl." A cycloheteroalkyl group may be attached to the remainder of the molecule *via* a ring carbon atom or a ring heteroatom.

"Heteroalkyl, Heteroalkanyl, Heteroalkenyl, Heteroalkanyl, Heteroalkyldiyl and Heteroalkyleno" by themselves or as part of another substituent, refer to alkyl, alkanyl, alkenyl, alkynyl, alkyldiyl and alkyleno groups, respectively, in which one or more of the carbon atoms (and any associated hydrogen atoms) are each independently replaced with the same or different heteroatomic groups. Typical heteroatomic groups which can be included in these groups include, but are not limited to, -O-, -S-, -O-O-, -S-S-, -O-S-, $-NR^{203}R^{204}-$, =N-N=, -N=N-, $-N=N-NR^{205}R^{206}$, $-PR^{207}-$, $-P(O)_2-$, $-POR^{208}-$, $-O-P(O)_2-$, -SO-, $-SO_2-$, $-SnR^{209}R^{210}-$, $-BR^{211}R^{212}$, $BOR^{213}OR^{214}$ and the like, where R^{203}, R^{204}, R^{205}, R^{206}, R^{207}, R^{208}, R^{209}, R^{210}, R^{211}, R^{212}, R^{213} and R^{214} are independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl.

"Heteroaryl," by itself or as part of another substituent, refers to a monovalent heteroaromatic radical derived by the removal of one hydrogen atom from a single atom of a parent heteroaromatic ring systems, as defined herein. Typical heteroaryl groups include, but are not limited to, groups derived from acridine, □-carboline, chromane, chromene, cinnoline, furan, imidazole, indazole, indole, indoline, indolizine, isobenzofuran, isochromene, isoindole, isoindoline, isoquinoline, isothiazole, isoxazole, naphthyridine, oxadiazole, oxazole, perimidine, phenanthridine, phenanthroline, phenazine, phthalazine, pteridine, purine, pyran, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolizine, quinazoline, quinoline, quinolizine, quinoxaline, tetrazole, thiadiazole, thiazole, thiophene, triazole, xanthene, furopyridine, and the like. In some embodiments, the heteroaryl group comprises from 5 to 20 ring atoms (5-20 membered heteroaryl). In other embodiments, the heteroaryl group comprises from 5 to

10 ring atoms (5-10 membered heteroaryl). Exemplary heteroaryl groups include those derived from furan, thiophene, pyrrole, benzothiophene, benzofuran, benzimidazole, indole, pyridine, pyrazole, quinoline, imidazole, oxazole, isoxazole and pyrazine.

"Heteroarylalkyl" by itself or as part of another substituent refers to an acyclic alkyl group in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, is replaced with a heteroaryl group. Where specific alkyl moieties are intended, the nomenclature heteroarylalkanyl, heteroarylakenyl and/or heteroarylalkynyl is used. In some embodiments, the heteroarylalkyl group is a 6-21 membered heteroarylalkyl, *e.g.*, the alkanyl, alkenyl or alkynyl moiety of the heteroarylalkyl is (C_1-C_6) alkyl and the heteroaryl moiety is a 5-15-membered heteroaryl. In other embodiments, the heteroarylalkyl is a 6-13 membered heteroarylalkyl, *e.g.*, the alkanyl, alkenyl or alkynyl moiety is (C_1-C_3) alkyl and the heteroaryl moiety is a 5-10 membered heteroaryl.

"Heteroaryloxy," by itself or as part of another substituent, refers to a radical of the formula -O-R^{201}, where R^{201} is heteroaryl, substituted heteroaryl, heteroarylalkyl, or substituted heteroarylalkyl.

"Heteroaryloxycarbonyl," by itself or as part of another substituent, refers to a radical of the formula -C(O)-O-R^{201}, where R^{201} is heteroaryl, substituted heteroaryl, heteroarylalkyl, or substituted heteroarylalkyl.

"Modulating" refers to adjusting, varying, or changing. As used herein, modulation of calcium ion channel includes antagonizing, agonizing, or partially antagonizing. That is, the compounds of the present invention may act as antagonists, agonists, or partial antagonists of the calcium ion channel activity.

"Parent Aromatic Ring System" refers to an unsaturated cyclic or polycyclic ring system having a conjugated π electron system. Specifically included within the definition of "parent aromatic ring system" are fused ring systems in which one or more of the rings are aromatic and one or more of the rings are saturated or unsaturated, such as, for example, fluorene, indane, indene, phenalene, *etc.* Typical parent aromatic ring systems include, but are not limited to, aceanthrylene, acenaphthylene, acephenanthrylene, anthracene, azulene, benzene, chrysene, coronene, fluoranthene, fluorene, hexacene, hexaphene, hexalene, *as*-indacene, *s*-indacene, indane, indene,

naphthalene, octacene, octaphene, octalene, ovalene, penta-2,4-diene, pentacene, pentalene, pentaphene, perylene, phenalene, phenanthrene, picene, pleiadene, pyrene, pyranthrene, rubicene, triphenylene, trinaphthalene and the like.

"Parent Heteroaromatic Ring System" refers to a parent aromatic ring system in which one or more carbon atoms (and optionally any associated hydrogen atoms) are each independently replaced with the same or different heteroatom. Typical heteroatoms to replace the carbon atoms include, but are not limited to, B, N, P, O, S, Si, *etc.* Specifically included within the definition of "parent heteroaromatic ring system" are fused ring systems in which one or more of the rings are aromatic and one or more of the rings are saturated or unsaturated, such as, for example, benzodioxan, benzofuran, chromane, chromene, indole, indoline, xanthene, *etc.* Typical parent heteroaromatic ring systems include, but are not limited to, arsindole, carbazole, β-carboline, chromane, chromene, cinnoline, furan, imidazole, indazole, indole, indoline, indolizine, isobenzofuran, isochromene, isoindole, isoindoline, isoquinoline, isothiazole, isoxazole, naphthyridine, oxadiazole, oxazole, perimidine, phenanthridine, phenanthroline, phenazine, phthalazine, pteridine, purine, pyran, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolizine, quinazoline, quinoline, quinolizine, quinoxaline, tetrazole, thiadiazole, thiazole, thiophene, triazole, xanthene and the like.

"Patient" or "subject" includes, but is not limited to animals such as, for example, mammals. Preferably, the patient is a human.

"Preventing" or "prevention" refers to a reduction in risk of acquiring a disease or disorder (*i.e.*, causing at least one of the clinical symptoms of the disease not to develop in a patient that may be exposed to or predisposed to the disease but does not yet experience or display symptoms of the disease).

"Protecting group" refers to a grouping of atoms that when attached to a reactive functional group in a molecule masks, reduces or prevents reactivity of the functional group. Examples of protecting groups can be found in Green *et al.*, "Protective Groups in Organic Chemistry", (Wiley, 2nd ed. 1991) and Harrison *et al.*, "Compendium of Synthetic Organic Methods", Vols. 1-8 (John Wiley and Sons, 1971-1996). Representative amino protecting groups include, but are not limited to, formyl, acetyl, trifluoroacetyl, benzyl, benzyloxycarbonyl ("CBZ"), *tert*-butoxycarbonyl ("Boc"),

trimethylsilyl ("TMS"), 2-trimethylsilyl-ethanesulfonyl ("SES"), trityl and substituted trityl groups, allyloxycarbonyl, 9-fluorenylmethyloxycarbonyl ("FMOC"), nitro-veratryloxycarbonyl ("NVOC") and the like. Representative hydroxy protecting groups include, but are not limited to, those where the hydroxy group is either acylated or alkylated such as benzyl, and trityl ethers as well as alkyl ethers, tetrahydropyranyl ethers, trialkylsilyl ethers and allyl ethers.

"Salt" refers to a salt of a compound, which possesses the desired pharmacological activity of the parent compound. Such salts include: (1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl) benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethane-disulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]-oct-2-ene-1-carboxylic acid, glucoheptonic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like; or (2) salts formed when an acidic proton present in the parent compound is replaced by a metal ion, *e.g.*, an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, N-methylglucamine and the like.

"Solvate" means a compound formed by solvation (the combination of solvent molecules with molecules or ions of the solute, i.e., a compound of the present invention), or an aggregate that consists of a solute ion or molecule (the compound of the present invention) with one or more solvent molecules.

"Pharmaceutically acceptable" means suitable for use in contact with the tissues of humans and animals without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use within the scope of sound medical judgment.

"Prodrug or softdrug" refers to a precursor of a pharmaceutically active compound wherein the precursor itself may or may not be pharmaceutically active but, upon administration, will be converted, either metabolically or otherwise, into the pharmaceutically active compound or drug of interest. For example, prodrug or softdrug is an ester or an ether form of a pharmaceutically active compound. Several prodrugs have been prepared and disclosed for a variety of pharmaceuticals. See, for example, Bundgaard, H. and Moss, J., J. Pharm. Sci. 78: 122-126 (1989). Thus, one of ordinary skill in the art knows how to prepare these precursors, prodrugs or softdrugs with commonly employed techniques of organic synthesis.

"Substituted," when used to modify a specified group or radical, means that one or more hydrogen atoms of the specified group or radical are each, independently of one another, replaced with the same or different substituent(s). Substituent groups useful for substituting saturated carbon atoms in the specified group or radical include, but are not limited to $-R^a$, halo, $-O^-$, =O, $-OR^b$, $-SR^b$, $-S^-$, =S, $-NR^cR^c$, $=NR^b$, $=N-OR^b$, trihalomethyl, $-CF_3$, -CN, -OCN, -SCN, -NO, $-NO_2$, $=N_2$, $-N_3$, $-S(O)_2R^b$, $-S(O)_2NR^b$, $-S(O)_2O^-$, $-S(O)_2OR^b$, $-OS(O)_2R^b$, $-OS(O)_2O^-$, $-OS(O)_2OR^b$, $-P(O)(O^-)_2$, $-P(O)(OR^b)(O^-)$, $-P(O)(OR^b)(OR^b)$, $-C(O)R^b$, $-C(S)R^b$, $-C(NR^b)R^b$, $-C(O)O^-$, $-C(O)OR^b$, $-C(S)OR^b$, $-C(O)NR^cR^c$, $-C(NR^b)NR^cR^c$, $-OC(O)R^b$, $-OC(S)R^b$, $-OC(O)O^-$, $-OC(O)OR^b$, $-OC(S)OR^b$, $-NR^bC(O)R^b$, $-NR^bC(S)R^b$, $-NR^bC(O)O^-$, $-NR^bC(O)OR^b$, $-NR^bC(S)OR^b$, $-NR^bC(O)NR^cR^c$, $-NR^bC(NR^b)R^b$ and $-NR^bC(NR^b)NR^cR^c$, where R^a is selected from the group consisting of alkyl, substituted alkyl, arylalkyl, alkyldiyl, substituted alkyldiyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroalkyl, substituted heteroalkyl, heteroalkyldiyl, substituted heteroalkyldiyl, heteroaryl, substituted heteroaryl, heteroarylalkyl substituted heteroarylalkyl; each R^b is independently hydrogen or R^a; and each R^c is independently R^b or alternatively, the two R^cs are taken together with the nitrogen atom to which they are bonded form a cycloheteroalkyl ring which may optionally include from 1 to 4 of the same or different additional heteroatoms selected from the group consisting of O, N and S. As specific examples, $-NR^cR^c$ is meant to include $-NH_2$, -NH-alkyl, N-pyrrolidinyl and N-morpholinyl.

Similarly, substituent groups useful for substituting unsaturated carbon atoms in the specified group or radical include, but are not limited to, $-R^a$, halo, $-O^-$, $-OR^b$, $-SR^b$,

$-S^-$, $-NR^cR^c$, trihalomethyl, $-CF_3$, -CN, -OCN, -SCN, -NO, $-NO_2$, $-N_3$, $-S(O)_2R^b$, $-S(O)_2O^-$, $-S(O)_2OR^b$, $-OS(O)_2R^b$, $-OS(O)_2O^-$, $-OS(O)_2OR^b$, $-P(O)(O^-)_2$, $-P(O)(OR^b)(O^-)$, $-P(O)(OR^b)(OR^b)$, $-C(O)R^b$, $-C(S)R^b$, $-C(NR^b)R^b$, $-C(O)O^-$, $-C(O)OR^b$, $-C(S)OR^b$, $-C(O)NR^cR^c$, $-C(NR^b)NR^cR^c$, $-OC(O)R^b$, $-OC(S)R^b$, $-OC(O)O^-$, $-OC(O)OR^b$, $-OC(S)OR^b$, $-NR^bC(O)R^b$, $-NR^bC(S)R^b$, $-NR^bC(O)O^-$, $-NR^bC(O)OR^b$, $-NR^bC(S)OR^b$, $-NR^bC(O)NR^cR^c$, $-NR^bC(NR^b)R^b$ and $-NR^bC(NR^b)NR^cR^c$, where R^a, R^b and R^c are as previously defined.

Substituent groups useful for substituting nitrogen atoms in heteroalkyl and cycloheteroalkyl groups include, but are not limited to, $-R^a$, $-O^-$, $-OR^b$, $-SR^b$, $-S^-$, $-NR^cR^c$, trihalomethyl, $-CF_3$, -CN, -NO, $-NO_2$, $-S(O)_2R^b$, $-S(O)_2O^-$, $-S(O)_2OR^b$, $-OS(O)_2R^b$, $-OS(O)_2O^-$, $-OS(O)_2OR^b$, $-P(O)(O^-)_2$, $-P(O)(OR^b)(O^-)$, $-P(O)(OR^b)(OR^b)$, $-C(O)R^b$, $-C(S)R^b$, $-C(NR^b)R^b$, $-C(O)OR^b$, $-C(S)OR^b$, $-C(O)NR^cR^c$, $-C(NR^b)NR^cR^c$, $-OC(O)R^b$, $-OC(S)R^b$, $-OC(O)OR^b$, $-OC(S)OR^b$, $-NR^bC(O)R^b$, $-NR^bC(S)R^b$, $-NR^bC(O)OR^b$, $-NR^bC(S)OR^b$, $-NR^bC(O)NR^cR^c$, $-NR^bC(NR^b)R^b$ and $-NR^bC(NR^b)NR^cR^c$, where R^a, R^b and R^c are as previously defined.

Substituent groups from the above lists useful for substituting other specified groups or atoms will be apparent to those of skill in the art.

The substituents used to substitute a specified group can be further substituted, typically with one or more of the same or different groups selected from the various groups specified above.

"Treating" or "treatment" of any disease or disorder refers, in some embodiments, to ameliorating or preventing the disease or disorder (*i.e.*, arresting or reducing the development of the disease or at least one of the clinical symptoms thereof). In other embodiments "treating" or "treatment" refers to ameliorating at least one physical parameter, which may not be discernible by the patient. In yet other embodiments, "treating" or "treatment" refers to inhibiting the disease or disorder, either physically, (*e.*g., stabilization of a discernible symptom), physiologically, (*e.g.*, stabilization of a physical parameter) or both. In yet other embodiments, "treating" or "treatment" refers to delaying the onset of the disease or disorder.

"Therapeutically effective amount" means the amount of a compound that, when administered to a patient for treating a disease, is sufficient to effect such treatment for

the disease. The "therapeutically effective amount" will vary depending on the compound, the disease and its severity and the age, weight, *etc.*, of the patient to be treated.

"Vehicle" refers to a diluent, adjuvant, excipient or carrier with which a compound is administered.

Reference will now be made in detail to preferred embodiments of the invention. While the invention will be described in conjunction with the preferred embodiments, it will be understood that it is not intended to limit the invention to those preferred embodiments. To the contrary, it is intended to cover alternatives, modifications, and equivalents as may be included within the spirit and scope of the invention as defined by the appended claims.

The term "receptor" refers to a molecule or complex of molecules, typically (although not necessarily) a protein(s), that is specifically bound by one or more particular ligands. The receptor is said to be a receptor for such ligand(s). Ligand-receptor binding, in many instances, induces one or more biological responses.

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A "modulator" of a polypeptide is either an inhibitor or an enhancer of an action or function of the polypeptide. Similarly, a "modulator" of a signaling pathway is an inhibitor or enhancer of at least one function mediated by the signaling pathway. Aspects of modulators are defined below with respect to polypeptides; however, those of skill in the art readily appreciate that these definitions also apply to signaling pathways.

A "non-selective" modulator of a polypeptide is an agent that modulates other members of the same family of polypeptides at the concentrations typically employed for modulation of the particular polypeptide.

A "selective" modulator of a polypeptide significantly modulates the particular polypeptide at a concentration at which other members of the same family of polypeptides are not significantly modulated.

A modulator "acts directly on" a polypeptide when the modulator exerts its action by interacting directly with the polypeptide.

A modulator "acts indirectly on" a polypeptide when the modulator exerts its action by interacting with a molecule other than the polypeptide, which interaction results in modulation of an action or function of the polypeptide.

An "inhibitor" or "antagonist" of a polypeptide is an agent that reduces, by any mechanism, any action or function of the polypeptide, as compared to that observed in the absence (or presence of a smaller amount) of the agent. An inhibitor of a polypeptide can affect: (1) the expression, mRNA stability, protein trafficking, modification (e.g., phosphorylation), or degradation of a polypeptide, or (2) one or more of the normal action or functions of the polypeptide. An inhibitor of a polypeptide can be non-selective or selective. Preferred inhibitors (antagonists) are generally small molecules that act directly on, and are selective for, the target polypeptide.

A "reversible" inhibitor is one whose effects can be reversed (i.e., one that does not irreversibly inactivate the target polypeptide).

A "competitive" inhibitor of a polypeptide is one that competes for binding to the polypeptide with another component required for polypeptide function. For example, TrkA function requires the binding of ATP and substrate. Accordingly, a competitive inhibitor of TrkA can act, for example, by binding at the ATP or substrate binding sites. This inhibition is generally reversible by increasing the concentration of ATP or substrate to the reaction mixture. Such an inhibitor is said to inhibit TrkA competitively with respect to ATP or substrate, respectively.

A "non-competitive" inhibitor of a polypeptide generally binds the polypeptide at a site other than the binding site of another component required for polypeptide function. This inhibition cannot be reversed by increasing the concentration of component(s) required for polypeptide function.

An "enhancer" or "activator" or "agonist" is an agent that increases, by any mechanism, any polypeptide action or function, as compared to that observed in the absence (or presence of a smaller amount) of the agent. An enhancer of a polypeptide can affect: (1) the expression, mRNA stability, protein trafficking, modification (e.g., phosphorylation), or degradation of a polypeptide, or (2) one or more of the normal

actions or functions of the polypeptide. An enhancer of a polypeptide can be non-selective or selective. Preferred enhancers (agonists) are generally small molecules that act directly on, and are selective for, the target polypeptide.

As used herein, an "allosteric modulator" of an polypeptide, typically an enzyme or receptor, is a modulator that binds at a location other than the active site of the target polypeptide, altering activity by inducing an allosteric change in the shape of the target polypeptide.

The terms "polypeptide" and "protein" are used interchangeably herein to refer a polymer of amino acids, and unless otherwise limited, include atypical amino acids that can function in a similar manner to naturally occurring amino acids.

The terms "amino acid" or "amino acid residue," include naturally occurring L-amino acids or residues, unless otherwise specifically indicated. The commonly used one- and three-letter abbreviations for amino acids are used herein (Lehninger, A. L. (1975) Biochemistry, 2d ed., pp. 71-92, Worth Publishers, N. Y.). The terms "amino acid" and "amino acid residue" include D-amino acids as well as chemically modified amino acids, such as amino acid analogs, naturally occurring amino acids that arc not usually incorporated into proteins, and chemically synthesized compounds having the characteristic properties of amino acids (collectively, "atypical" amino acids). For example, analogs or mimetics of phenylalanine or proline, which allow the same conformational restriction of the peptide compounds as natural Phe or Pro are included within the definition of "amino acid."

Exemplary atypical amino acids, include, for example, those described in International Publication No. WO 90/01940 as well as 2-amino adipic acid (Aad) which can be substituted for Glu and Asp; 2-aminopimelic acid (Apm), for Glu and Asp; 2-aminobutyric acid (Abu), for Met, Leu, and other aliphatic amino acids; 2-aminoheptanoic acid (Ahe), for Met, Leu, and other aliphatic amino acids; 2-aminoisobutyric acid (Aib), for Gly; cyclohexylalanine (Cha), for Val, Leu, and Ile; homoarginine (Har), for Arg and Lys; 2, 3-diaminopropionic acid (Dpr), for Lys, Arg, and His; N-ethylglycine (EtGly) for Gly, Pro, and Ala; N-ethylasparagine (EtAsn), for Asn and Gln; hydroxyllysine (Hyl), for Lys; allohydroxyllysine (Ahyl), for Lys; 3- (and 4-) hydoxyproline (3Hyp, 4Hyp), for Pro, Ser, and Thr; allo-isoleucine (Aile), for Ile,

Leu, and Val; amidinophenylalanine, for Ala; N-methylglycine (MeGly, sarcosine), for Gly, Pro, and Ala; N-methylisoleucine (MeIle), for Ile; norvaline (Nva), for Met and other aliphatic amino acids; norleucine (Nle), for Met and other aliphatic amino acids; ornithine (Orn), for Lys, Arg, and His; citrulline (Cit) and methionine sulfoxide (MSO) for Thr, Asn, and Gln; N-methylphenylalanine (MePhe), trimethylphenylalanine, halo (F, Cl, Br, and I) phenylalanine, and trifluorylphenylalanine, for Phe.

The term "specific binding" is defined herein as the preferential binding of binding partners to another (e.g., two polypeptides, a polypeptide and nucleic acid molecule, or two nucleic acid molecules) at specific sites. The term "specifically binds" indicates that the binding preference (e.g., affinity) for the target molecule/sequence is at least 2-fold, more preferably at least 5-fold, and most preferably at least 10- or 20-fold over a non-specific target molecule (e.g. a randomly generated molecule lacking the specifically recognized site(s)).

The phrases "an effective amount" and "an amount sufficient to" refer to amounts of a biologically active agent that produce an intended biological activity.

The term "polynucleotide" refers to a deoxyribonucleotide or ribonucleotide polymer, and unless otherwise limited, includes known analogs of natural nucleotides that can function in a similar manner to naturally occurring nucleotides. The term "polynucleotide" refers any form of DNA or RNA, including, for example, genomic DNA; complementary DNA (cDNA), which is a DNA representation of mRNA, usually obtained by reverse transcription of messenger RNA (mRNA) or amplification; DNA molecules produced synthetically or by amplification; and mRNA. The term "polynucleotide" encompasses double-stranded nucleic acid molecules, as well as single-stranded molecules. In double-stranded polynucleotides, the polynucleotide strands need not be coextensive (i.e., a double-stranded polynucleotide need not be double-stranded along the entire length of both strands).

The term "co-administer" or "co-administering" when used in reference to the administration of Trk (i.e., TrkA) antagonists and other agents indicates that the antagonist and other agent(s) are administered so that there is at least some chronological overlap in their physiological activity on the subject. Thus, a TrkA antagonist can be administered simultaneously and/or sequentially with another agent. In sequential

administration, there may even be some substantial delay (e.g., minutes or even hours or days) before administration of the second agent as long as the first administered agent is exerting some physiological effect on the organism when the second administered agent is administered or becomes active in the subject.

The term "reducing pain," as used herein, refers to decreasing the level of pain a subject perceives relative to the level of pain the subject would have perceived were it not for the intervention. Where the subject is a person, the level of pain the person perceives can be assessed by asking him or her to describe the pain or compare it to other painful experiences. Alternatively, pain levels can be determined by measuring the subject's physical responses to the pain, such as the release of stress-related factors or the activity of pain-transducing nerves in the peripheral nervous system or the CNS. One can also determine pain levels by measuring the amount of a well-characterized analgesic required for a person to report that no pain is present or for a subject to stop exhibiting symptoms of pain. A reduction in pain can also be measured as an increase in the threshold at which a subject experiences a given stimulus as painful. In certain embodiments, a reduction in pain is achieved by decreasing "hyperalgesia," the heightened sensitivity to a noxious stimulus, and such inhibition can occur without impairing "nociception," the subject's normal sensitivity to a "noxious" stimulus.

As used with reference to pain reduction, "a subject in need thereof" refers to an animal or person, preferably a person, expected to experience pain in the near future. Such animal or person may have an ongoing condition that is causing pain currently and is likely to continue to cause pain. Alternatively, the animal or person has been, is, or will be enduring a procedure or event that usually has painful consequences. Chronic painful conditions such as diabetic neuropathic hyperalgesia and collagen vascular diseases are examples of the first type; dental work, particularly that accompanied by inflammation or nerve damage, and toxin exposure (including exposure to chemotherapeutic agents) are examples of the latter type.

"Inflammatory pain" refers to pain arising from inflammation. Inflammatory pain often manifests as increased sensitivity to mechanical stimuli (mechanical hyperalgesia or tenderness). For examples, inflammatory pain is due to a condition selected from the group consisting of: burn, sunburn, arthritis, colitis, carditis, dermatitis, myositis,

neuritis, mucositis, urethritis, cystitis, gastritis, pneumonitis, and collagen vascular disease.

"Neuropathic pain" refers to pain arising from conditions or events that result in nerve damage. "Neuropathy" refers to a disease process resulting in damage to nerves. "Causalgia" denotes a state of chronic pain following nerve injury. "Allodynia" refers to a condition in which a person experiences pain in response to a normally nonpainful stimulus, such as a gentle touch. For examples, neuropathic pain is due to a condition selected from the group consisting of: causalgia, diabetes, collagen vascular disease, trigeminal neuralgia, spinal cord injury, brain stem injury, thalamic pain syndrome, complex regional pain syndrome type I/reflex sympathetic dystrophy, Fabry's syndrome, small fiber neuropathy, cancer, cancer chemotherapy, chronic alcoholism, stroke, abscess, demyelinating disease, viral infection, anti-viral therapy, AIDS, and AIDS therapy. Neuropathic pain is due to an agent selected from the group consisting of: trauma, surgery, amputation, toxin, and chemotherapy.

As used herein, the term "generalized pain disorder" refers to a group of idiopathic pain syndromes (e.g., fibromyalgia, irritable bowel syndrome, and temporomandibular disorders), for which the pathogenic mechanism is currently unknown, characterized by diffuse or generalized pain, and for which a diagnosis of inflammation or neuropathy as the direct cause of pain is excluded.

An "analgesic agent" refers to a molecule or combination of molecules that causes a reduction in pain.

A "neuroleptic" refers to a class of tranquilizing drugs, used to treat psychotic conditions, that modulate neurotransmitter activity in the central nervous system and can act by modulating acetylcholine, dopamine, norepinephrine, serotonin, or γ-aminobutyric acid (GABA) transmission.

The term "neurosteroid" refers to a class of steroids, the natural forms of which are produced by cells of the central or peripheral nervous systems, independently of the steroidogenic activity of the endocrine glands. Neurosteroids are derived from cholesterol, and examples of neurosteroids include 3□,5□-tetrahydroprogesterone, 3□,5□-tetrahydroprogesterone, and 3□,5□-tetrahydrodeoxycorticosterone. For examples, ganaxalone and alphaxalone.

The difference between "acute" and "chronic" pain is one of timing: acute pain is experienced soon (e.g., generally within about 48 hours, more typically within about 24 hours, and most typically within about 12 hours) after the occurrence of the event (such as inflammation or nerve injury) that led to such pain. By contrast, there is a significant time lag between the experience of chronic pain and the occurrence of the event that led to such pain. Such time lag is generally at least about 48 hours after such event, more typically at least about 96 hours after such event, and most typically at least about one week after such event.

The term "maladaptive substance use" refers to the use of any substance that results in adverse consequences for the user that outweigh any benefits derived from the substance. Substances that are used in a maladaptive manner are generally consumed or administered (usually self-administered) to the body, by any route of administration, to produce an effect on the body that the user generally experiences as pleasurable. The substance can be a single substance (cocaine, for example) or a type of substance (e.g., food, in general). The adverse consequences can include, for example, adverse effects on health, the ability to care for oneself, the ability to form and maintain human relationships, and/or the ability to work. The adverse consequences are generally significant enough that the user would like to control, reduce, or end substance use or, alternatively, the user's family members and/or friends would like to see the user control, reduce, or end substance use. Maladaptive substance use can include uncontrollable craving for the substance; substance dependence, including psychological and/or physical dependence; and maladaptive substance use; as well as any of the individual symptoms of substance dependence and/or abuse listed below.

A "symptom of maladaptive substance use" includes any symptom arising from maladaptive substance use. Thus, a symptom of maladaptive substance use arises from the previous, and/or ongoing, use of a substance. Examples include, but are not limited to, elevated drug reward, incentive salience for the drug, drug craving, drug preference, drug seeking, and drug consumption, as compared to that in a normal population (i.e., one that is not using the substance in a maladaptive manner), as well as any of the individual symptoms of substance dependence and/or abuse listed below.

"Substance dependence" includes a maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following symptoms, occurring at any time in the same 12-month period:

(1) Tolerance, as defined by either of the following: (a) a need for markedly increased amounts of the substance to achieve intoxication or desired effect, or (b) markedly diminished effect with continued use of the same amount of the substance;

(2) Withdrawal, as manifested by either of the following: (a) the characteristic withdrawal syndrome for the substance, or (b) the same (or closely related) substance is taken to relieve or avoid withdrawal symptoms;

(3) The substance is often taken in larger amounts or over a longer period than was intended;

(4) There is a persistent desire or unsuccessful efforts to cut down or control substance use;

(5) A great deal of time is spent in activities necessary to obtain the substance (e.g., visiting multiple doctors or driving long distances), use the substance (e.g., chain-smoking), or recover from its effects;

(6) Important social, occupational, or recreational activities are given up or reduced because of substance use; and

(7) The substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance (e.g., current cocaine use despite recognition of cocaine-induced depression, or continued drinking despite recognition that an ulcer was made worse by alcohol consumption). (See American Psychiatric Association, Diagnostic Criteria for DSM-IV, Washington DC, APA, 1994.)

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(5) A great deal of time is spent in activities necessary to obtain the substance (e.g., visiting multiple doctors or driving long distances), use the substance (e.g., chain-smoking), or recover from its effects;

(6) Important social, occupational, or recreational activities are given up or reduced because of substance use; and

(7) The substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance (e.g., current cocaine use despite recognition of cocaine-induced depression, or continued drinking despite recognition that an ulcer was made worse by alcohol consumption). (See American Psychiatric Association, Diagnostic Criteria for DSM-IV, Washington DC, APA, 1994.)

A person is "dependent upon a substance" if such person is determined by a licensed physician or other appropriate accredited medical personnel to meet the criteria for substance dependence with respect to such substance.

"Substance abuse" includes a maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by one (or more) of the following, occurring within a 12-month period:

(1) recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home (e.g., repeated absences or poor work performance related to substance use; substance-related absences, suspensions, or expulsions from school; neglect of children or household);

(2) recurrent substance use in situations in which it is physically hazardous (e.g., driving an automobile or operating a machine when impaired by substance use);

(3) recurrent substance-related legal problems (e.g., arrests for substance-related disorderly conduct); and

(4) continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance (e.g., arguments with spouse about consequences of intoxication, physical fights). (See American Psychiatric Association, Diagnostic Criteria for DSM-IV, Washington DC, APA, 1994.)

A person is "an abuser of a substance" or "abusive of a substance" if such person is determined by a licensed physician or other appropriate accredited medical personnel to meet the criteria for substance abuse with respect to such substance.

The terms drug reward, incentive salience for the drug, drug craving, drug preference, drug seeking, and drug consumption refer to "drugs" because these concepts have generally been used in the drug dependence/abuse context. However, it should be understood that these terms, as used herein, also encompass reward, incentive salience, craving, preference, seeking and consumption of any substance that is used in a maladaptive manner.

The term "drug reward" refers to the tendency of a drug or substance to cause pleasurable effects that induce a subject to alter their behavior to obtain more of the drug or substance.

The phrase "incentive salience for the drug" refers to a particular form of motivation to consume a previously experienced drug or substance that results from a hypersensitive neural state thought to be mediated by dopaminergic systems.

The term "drug craving" refers to the desire to experience the effects of a previously experienced drug or substance or to ameliorate the negative symptoms of drug or substance withdrawal by taking more of a previously experienced drug or substance.

The term "drug preference" refers to the tendency to consume a drug or substance that produces pleasurable effects, a opposed than a control substance that does not produce such effects.

The term "drug seeking" refers to behavior aimed at obtaining a drug or substance, even in the face of negative health and social consequences. Drug seeking is often uncontrollable and compulsive.

"Drug consumption" refers to the amount of drug or substance consumed by a subject over a selected period of time.

A "drug of abuse" includes any substance, the excessive consumption or administration of which can result in a diagnosis of substance dependence or abuse as defined herein or as defined by the current DSM Criteria promulgated by the American Psychiatric Association or equivalent criteria. Drugs of abuse include, without limitation, an opioid, a psychostimulant, a cannabinoid, an empathogen, a dissociative drug, and ethanol. Thus, for example, heroin, cocaine, methamphetamines, cannabis, 3-4 methylenedioxy-methamphetamine (MDMA), barbiturates, phencyclidine (PCP), ketamine, and ethanol are all drugs of abuse, as defined herein.

The phrase "a drug-related effect" refers to an in vivo effect that occurs in response to a drug. Exemplary effects include stimulant, sedative, hypnotic, and ataxic effects.

A "sedative effect" refers to a decrease in activity and/or excitement in a subject.

A "hypnotic effect" includes an increase in drowsiness and/or a facilitation of the onset and/or maintenance of sleep.

An "ataxic effect" refers to a decrease in motor coordination.

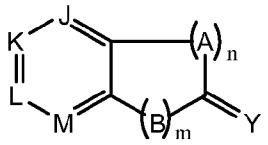
An agent is said to "mitigate" a symptom of maladaptive substance use or a drug-related effect if the agent inhibits (i.e., reduces or prevents) the symptom or effect.

A "benzodiazepine" is referred to a agent selected from the group consisting of: alprazolam, chlordiazepoxide, chlordiazepoxide hydrochloride, chlormezanone, clobazam, clonazepam, clorazepate dipotassium, diazepam, droperidol, estazolam, fentanyl citrate, flurazepam hydrochloride, halazepam, lorazepam, midazolam hydrochloride, oxazepam, prazepam, quazepam, temazepam, and triazolam.

A "barbiturate" referred to a agent selected from the group consisting of: amobarbital, amobarbital sodium, aprobarbital, butabarbital sodium, hexobarbital sodium, mephobarbital, metharbital, methohexital sodium, pentobarbital, pentobarbital sodium, phenobarbital, phenobarbital sodium, secobarbital, secobarbital sodium, talbutal, thiamylal sodium, and thiopental sodium.

5.2 Compounds

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



(I)

or a salt, solvate, ester, and/or prodrug thereof;

wherein:

n is 1, 2, or 3;

m is 0, 1, or 2;

A is C, N, O, S, NR^1, $C=CR^1$ (E and Z isomers), $C=NR^1$ (E and Z isomers), or $C(R^1R^2)$;

B is C, N, O, S, NR^3, or $C(R^3R^4)$;

J, K, L, and M are independently N or CR^5;

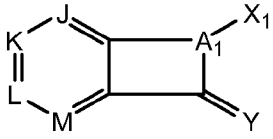
Y is O, S, NR^6, or $C(R^6R^7)$;

R^1, R^2, R^3, R^4, R^5, R^6, and R^7 are independently hydrogen, halogen, acyl, substituted acyl, alkoxycarbonyl, substituted alkoxycarbonyl, aryloxycarbonyl, substituted aryloxycarbonyl, $-CONR^8R^9$, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyl;

R^8 and R^9 are independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyl or substituted heteroalkyl or alternatively, R^8 and R^9, taken together with the nitrogen atom to which they are attached, form a 4-, 5-, 6-, or 7-membered cycloheteroalkyl ring, provided that both R^8 and R^9 are not hydrogen;

In one embodiment of formula (I), wherein m = 0, n = 1, and $A = A_1\text{-}X_1$;

In one embodiment of formula (I), the compound having structural formula (II):



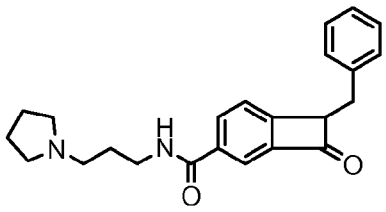
(II)

or a salt, solvate, ester, and/or prodrug thereof;

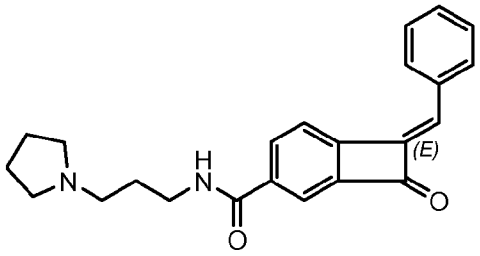
wherein:

A_1-X_1 is NR^1, $C{=}CR^1$ (E and Z isomers), $C{=}NR^1$ (E and Z isomers), or $C(R^1R^2)$;

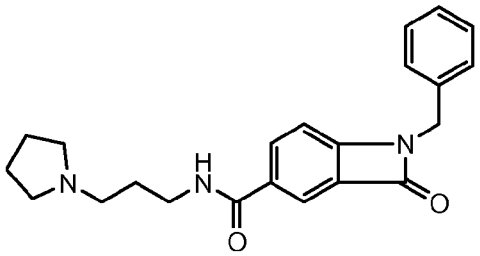
In one embodiment of formula (II), the compound having a structure selected from the group consisting of:



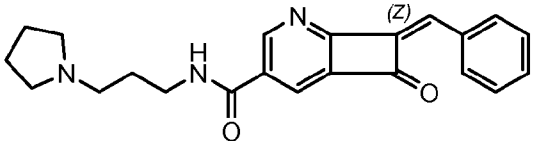
(101)



(103)



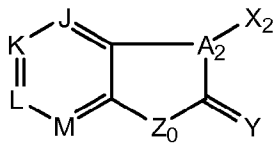
(105)



(107)

In one embodiment of formula (I), wherein m = 1, n = 1, A = A_2-X_2, B = Z_0;

In one embodiment of formula (I), the compound having a structural formula (III):



(III)

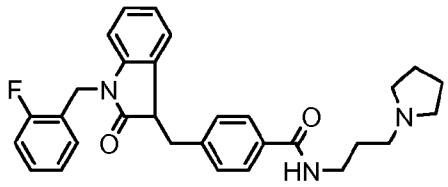
or a salt, solvate, ester, and/or prodrug thereof;

where in:

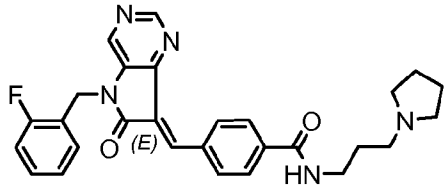
Z_0 is O, S, NR^3, or $C(R^3R^4)$;

A_2-X_2 is NR^1, $C{=}CR^1$ (E and Z isomers), $C{=}NR^1$ (E and Z isomers), or $C(R^1R^2)$;

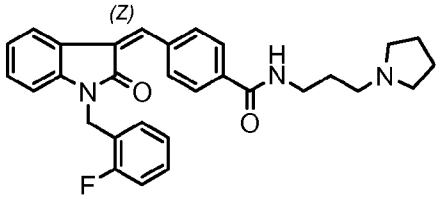
In one embodiment of formula (III), the compound having a structure selected from the group consisting of:



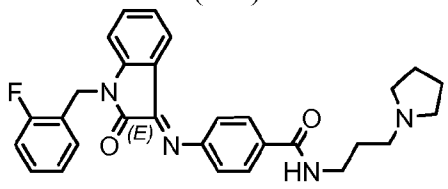
(109)



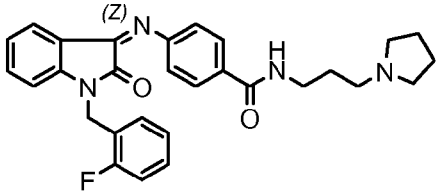
(111)



(113)



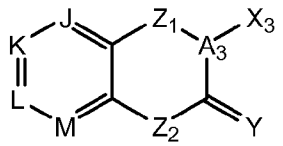
(115)



(117)

In one embodiment of formula (I), wherein m = 1, n = 2, A = Z_1 and A_3-X_3, and B = Z_2;

In one embodiment of formula (I), the compound having a structural formula (IV):



(IV)

or a salt, solvate, ester, and/or prodrug thereof;

wherein:

A_3-X_3 is NR^1, $C{=}CR^1$ (E and Z isomers), $C{=}NR^1$ (E and Z isomers), or $C(R^1R^2)$;
Z_1 and Z_2 are O, S, CR^3, NR^3, $C(R^3R^4)$;

In one embodiment, wherein the compound of formula (IV) does not include the compound selected from the group consisting of:

ID	IUPAC
201	N-{3-[4-(5-chloro-2-methylphenyl)piperazin-1-yl]propyl}-6-oxo-6,6a,7,8,9,10-hexahydro-5H-pyrido[1,2-a]quinoxaline-3-carboxamide
203	(2Z)-N-[3-(4-benzylpiperidin-1-yl)propyl]-4-(4-fluorobenzyl)-3-oxo-2-(phenylmethylidene)-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide
205	N-[3-(4-benzylpiperidin-1-yl)propyl]-2-{(2E)-2-[(3-bromo-4-methoxyphenyl)methylidene]-3-oxo-2,3-dihydro-4H-1,4-benzothiazin-4-yl}acetamide
207	4-{(E)-[4-(3-chlorobenzyl)-3-oxo-3,4-dihydro-2H-1,4-benzothiazin-2-ylidene]methyl}-N-[2-(dibutylamino)ethyl]benzamide
209	N-[3-(4-benzylpiperidin-1-yl)propyl]-2-{(2Z)-2-[(3-chlorophenyl)methylidene]-3-oxo-2,3-dihydro-4H-1,4-benzothiazin-4-yl}acetamide
211	(2Z)-N-{3-[cyclohexyl(methyl)amino]propyl}-4-(4-fluorobenzyl)-3-oxo-2-(phenylmethylidene)-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide
213	(2Z)-N-[3-(4-benzylpiperidin-1-yl)propyl]-4-(3-methylbenzyl)-3-oxo-2-(phenylmethylidene)-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide
215	(2Z)-N-{3-[cyclohexyl(methyl)amino]propyl}-4-(3-methylbenzyl)-3-oxo-2-(phenylmethylidene)-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide
217	N-[3-(4-benzylpiperidin-1-yl)propyl]-2-{(2E)-2-[(3-bromophenyl)methylidene]-3-oxo-2,3-dihydro-4H-1,4-benzothiazin-4-yl}acetamide
219	(2Z)-N-(2-azepan-1-ylethyl)-4-(3-methylbenzyl)-3-oxo-2-(phenylmethylidene)-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide
221	N-[2-(4-benzylpiperidin-1-yl)ethyl]-4-{(E)-[4-(2,5-dimethylbenzyl)-3-oxo-3,4-dihydro-2H-1,4-benzothiazin-2-ylidene]methyl}benzamide
223	(2Z)-N-[3-(2-ethylpiperidin-1-yl)propyl]-4-(4-fluorobenzyl)-3-oxo-2-(phenylmethylidene)-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide
225	4-{(E)-[4-(3-chlorobenzyl)-3-oxo-3,4-dihydro-2H-1,4-benzothiazin-2-ylidene]methyl}-N-{3-[cyclohexyl(methyl)amino]propyl}benzamide
227	(2Z)-N-(3-azepan-1-ylpropyl)-4-(3-methylbenzyl)-3-oxo-2-(phenylmethylidene)-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide
229	(2Z)-4-(4-fluorobenzyl)-N-[3-(3-methylpiperidin-1-yl)propyl]-3-oxo-2-(phenylmethylidene)-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide
231	N-(2-azepan-1-ylethyl)-4-{(E)-[4-(3-methylbenzyl)-3-oxo-3,4-dihydro-2H-1,4-benzothiazin-2-ylidene]methyl}benzamide
233	N-{3-[cyclohexyl(methyl)amino]propyl}-4-{(E)-[4-(3-methylbenzyl)-3-oxo-3,4-dihydro-2H-1,4-benzothiazin-2-ylidene]methyl}benzamide
235	N-(2-azepan-1-ylethyl)-4-{(E)-[4-(3-chlorobenzyl)-3-oxo-3,4-dihydro-2H-1,4-benzothiazin-2-ylidene]methyl}benzamide
237	(2Z)-N-{2-[4-(2-fluorophenyl)piperazin-1-yl]ethyl}-2-[2-(4-methoxyphenyl)-2-oxoethylidene]-3-oxo-1,2,3,4-tetrahydroquinoxaline-6-carboxamide
239	2-{(2Z)-2-[(3-chlorophenyl)methylidene]-3-oxo-2,3-dihydro-4H-1,4-benzothiazin-4-yl}-N-{3-[4-(4-methoxyphenyl)piperazin-1-yl]propyl}acetamide
241	(2Z)-N-{3-[4-(2,5-dimethylphenyl)piperazin-1-yl]propyl}-4-(3-methylbenzyl)-3-oxo-2-(phenylmethylidene)-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide
243	4-{(E)-[4-(3-chlorobenzyl)-3-oxo-3,4-dihydro-2H-1,4-benzothiazin-2-ylidene]methyl}-N-[(1-ethylpyrrolidin-2-yl)methyl]benzamide
245	N-{3-[cyclohexyl(methyl)amino]propyl}-4-{(E)-[4-(2-methylbenzyl)-3-oxo-3,4-dihydro-2H-

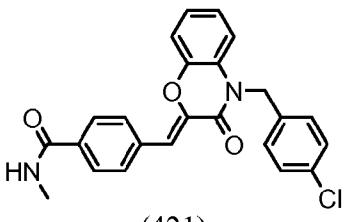
	1,4-benzothiazin-2-ylidene]methyl}benzamide
247	(2Z)-N-[3-(3,5-dimethylpiperidin-1-yl)propyl]-4-(3-methylbenzyl)-3-oxo-2-(phenylmethylidene)-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide
249	(2Z)-N-[3-(3,5-dimethylpiperidin-1-yl)propyl]-4-(4-fluorobenzyl)-3-oxo-2-(phenylmethylidene)-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide
251	N-{3-[benzyl(methyl)amino]propyl}-4-{(E)-[4-(3-methylbenzyl)-3-oxo-3,4-dihydro-2H-1,4-benzothiazin-2-ylidene]methyl}benzamide
253	N-(2-azepan-1-ylethyl)-2-{(2E)-2-[(3-chlorophenyl)methylidene]-3-oxo-2,3-dihydro-4H-1,4-benzothiazin-4-yl}acetamide
255	2-{(2E)-2-[(3-bromo-4-methoxyphenyl)methylidene]-3-oxo-2,3-dihydro-4H-1,4-benzothiazin-4-yl}-N-{3-[4-(2-fluorophenyl)piperazin-1-yl]propyl}acetamide
257	N-{3-[benzyl(methyl)amino]propyl}-2-{(2Z)-2-[(3-chlorophenyl)methylidene]-3-oxo-2,3-dihydro-4H-1,4-benzothiazin-4-yl}acetamide
259	2-{(2Z)-2-[(3-chlorophenyl)methylidene]-3-oxo-2,3-dihydro-4H-1,4-benzothiazin-4-yl}-N-{3-[4-(2-fluorophenyl)piperazin-1-yl]propyl}acetamide
261	N-{2-[cyclohexyl(1-methylpropyl)amino]ethyl}-4-{(E)-[4-(2-fluorobenzyl)-3-oxo-3,4-dihydro-2H-1,4-benzothiazin-2-ylidene]methyl}benzamide
263	N-{2-[cyclohexyl(methyl)amino]ethyl}-4-{(E)-[4-(3-methylbenzyl)-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-ylidene]methyl}benzamide
265	2-{(2E)-2-[(3-bromophenyl)methylidene]-3-oxo-2,3-dihydro-4H-1,4-benzothiazin-4-yl}-N-[3-(3,5-dimethylpiperidin-1-yl)propyl]acetamide
267	N-{3-[benzyl(butyl)amino]propyl}-4-{(E)-[4-(3-chlorobenzyl)-3-oxo-3,4-dihydro-2H-1,4-benzothiazin-2-ylidene]methyl}benzamide
269	N-(2-azepan-1-ylethyl)-2-{(2E)-2-[(3-bromo-4-methoxyphenyl)methylidene]-3-oxo-2,3-dihydro-4H-1,4-benzothiazin-4-yl}acetamide
271	2-{(2Z)-2-[(3-chlorophenyl)methylidene]-3-oxo-2,3-dihydro-4H-1,4-benzothiazin-4-yl}-N-{3-[4-(4-fluorophenyl)piperazin-1-yl]propyl}acetamide
273	2-{(2E)-2-[(3-bromophenyl)methylidene]-3-oxo-2,3-dihydro-4H-1,4-benzothiazin-4-yl}-N-[3-(2-ethylpiperidin-1-yl)propyl]acetamide
275	N-{3-[4-(5-chloro-2-methylphenyl)piperazin-1-yl]propyl}-4-{(E)-[4-(2-fluorobenzyl)-3-oxo-3,4-dihydro-2H-1,4-benzothiazin-2-ylidene]methyl}benzamide
277	N-[2-(dipropylamino)ethyl]-4-{(E)-[4-(3-methylbenzyl)-3-oxo-3,4-dihydro-2H-1,4-benzothiazin-2-ylidene]methyl}benzamide
279	(2Z)-N-(2-azepan-1-ylethyl)-4-(4-fluorobenzyl)-3-oxo-2-(phenylmethylidene)-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide
281	4-{(E)-[4-(3-chlorobenzyl)-3-oxo-3,4-dihydro-2H-1,4-benzothiazin-2-ylidene]methyl}-N-{3-[4-(2-fluorophenyl)piperazin-1-yl]propyl}benzamide
283	2-{(2Z)-2-[(3-chlorophenyl)methylidene]-3-oxo-2,3-dihydro-4H-1,4-benzothiazin-4-yl}-N-{3-[4-(3-chlorophenyl)piperazin-1-yl]propyl}acetamide
285	2-{(2E)-2-[(3-chlorophenyl)methylidene]-3-oxo-2,3-dihydro-4H-1,4-benzothiazin-4-yl}-N-[3-(2-ethylpiperidin-1-yl)propyl]acetamide
287	N-{3-[4-(5-chloro-2-methylphenyl)piperazin-1-yl]propyl}-4-{(E)-[4-(3-methylbenzyl)-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-ylidene]methyl}benzamide
289	N-{3-[4-(3-chlorophenyl)piperazin-1-yl]propyl}-6-oxo-6,6a,7,8,9,10-hexahydro-5H-pyrido[1,2-a]quinoxaline-3-carboxamide
291	(2Z)-N-[3-(3,4-dihydroisoquinolin-2(1H)-yl)propyl]-4-(3-methylbenzyl)-3-oxo-2-(phenylmethylidene)-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide
293	2-{(2E)-2-[(3-bromo-4-methoxyphenyl)methylidene]-3-oxo-2,3-dihydro-4H-1,4-benzothiazin-4-yl}-N-{3-[4-(4-fluorophenyl)piperazin-1-yl]propyl}acetamide
295	4-{(E)-[4-(3-chlorobenzyl)-3-oxo-3,4-dihydro-2H-1,4-benzothiazin-2-ylidene]methyl}-N-(2-pyrrolidin-1-ylethyl)benzamide
297	2-{(2E)-2-[(3-bromophenyl)methylidene]-3-oxo-2,3-dihydro-4H-1,4-benzothiazin-4-yl}-N-{2-[methyl(2-phenylethyl)amino]ethyl}acetamide
299	4-{(E)-[4-(3-chlorobenzyl)-3-oxo-3,4-dihydro-2H-1,4-benzothiazin-2-ylidene]methyl}-N-

	[3-(3-methylpiperidin-1-yl)propyl]benzamide
301	(2Z)-N-{3-[4-(4-methoxyphenyl)piperazin-1-yl]propyl}-4-(3-methylbenzyl)-3-oxo-2-(phenylmethylidene)-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide
303	(2Z)-N-(3-azepan-1-ylpropyl)-4-(4-fluorobenzyl)-3-oxo-2-(phenylmethylidene)-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide
305	N-{3-[4-(2-fluorophenyl)piperazin-1-yl]propyl}-4-{(E)-[4-(3-methylbenzyl)-3-oxo-3,4-dihydro-2H-1,4-benzothiazin-2-ylidene]methyl}benzamide
307	N-{3-[4-(2-fluorophenyl)piperazin-1-yl]propyl}-4-{(E)-[4-(2-methylbenzyl)-3-oxo-3,4-dihydro-2H-1,4-benzothiazin-2-ylidene]methyl}benzamide
309	N-{3-[4-(4-methoxyphenyl)piperazin-1-yl]propyl}-4-{(E)-[4-(4-methylbenzyl)-3-oxo-3,4-dihydro-2H-1,4-benzothiazin-2-ylidene]methyl}benzamide
311	2-{(2E)-2-[(3-chlorophenyl)methylidene]-3-oxo-2,3-dihydro-4H-1,4-benzothiazin-4-yl}-N-[3-(3-methylpiperidin-1-yl)propyl]acetamide
313	(2E)-2-[(4-ethoxy-3-methoxyphenyl)methylidene]-N-{3-[4-(2-fluorophenyl)piperazin-1-yl]propyl}-4-methyl-3-oxo-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide
315	2-{(2E)-2-[(2-chlorophenyl)methylidene]-3-oxo-2,3-dihydro-4H-1,4-benzothiazin-4-yl}-N-{3-[4-(4-fluorophenyl)piperazin-1-yl]propyl}acetamide
317	(2Z)-N-{3-[4-(2-fluorophenyl)piperazin-1-yl]propyl}-4-methyl-2-[(3-methylphenyl)methylidene]-3-oxo-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide
319	2-{(2E)-2-[(3-chlorophenyl)methylidene]-3-oxo-2,3-dihydro-4H-1,4-benzothiazin-4-yl}-N-[3-(3,5-dimethylpiperidin-1-yl)propyl]acetamide
321	(2E)-N-{3-[4-(2-fluorophenyl)piperazin-1-yl]propyl}-2-[(2-methoxyphenyl)methylidene]-4-methyl-3-oxo-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide
323	(2Z)-N-{3-[4-(4-fluorophenyl)piperazin-1-yl]propyl}-4-methyl-2-[(2-methylphenyl)methylidene]-3-oxo-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide

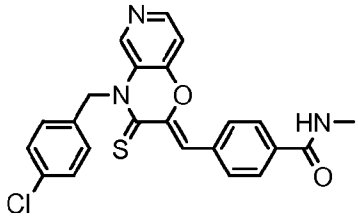
In one embodiment of formula (IV), wherein R^1 and R^2 are not hydrogen;

In one embodiment of formula (IV), wherein at least two of R^1, R^2, and R^3 are not hydrogen;

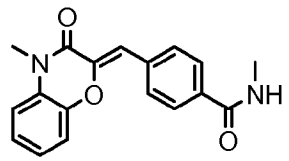
In one embodiment, wherein the compound having a structural formula (IV) is selected from the group consisting of:



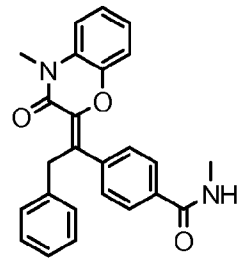
(421)



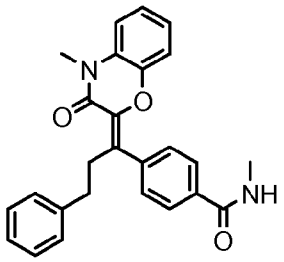
(423)



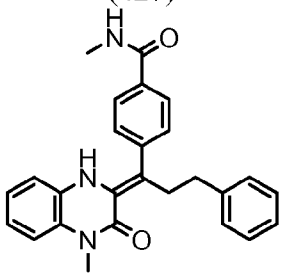
(425)



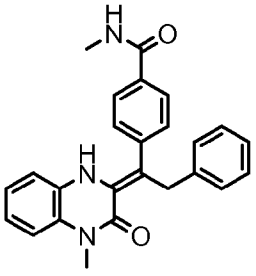
(427)



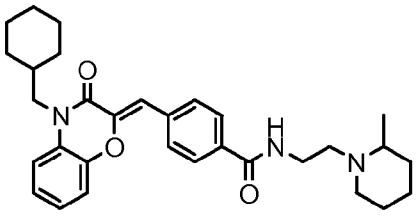
(429)



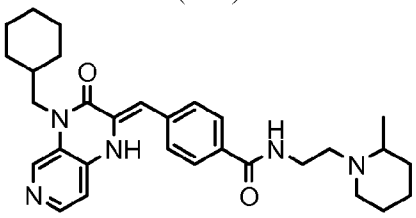
(431)



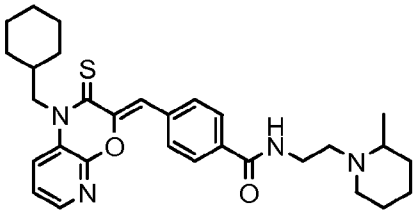
(433)



(435)



(437)



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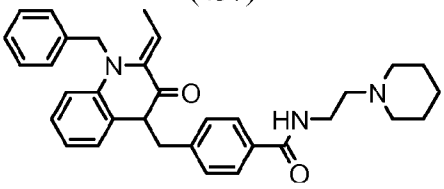
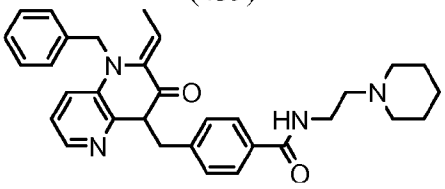
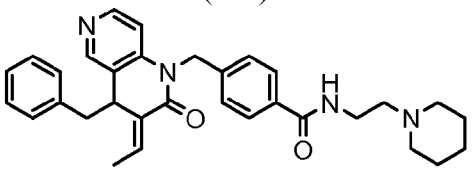


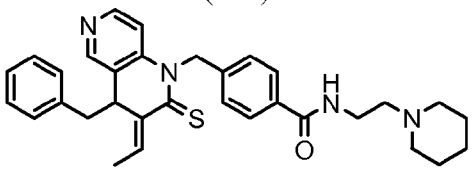
(441)



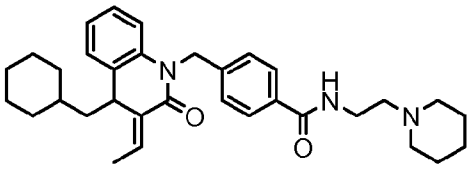
(443)



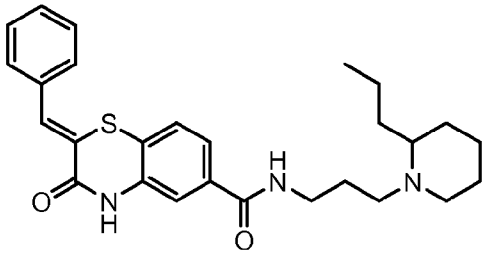
(445)



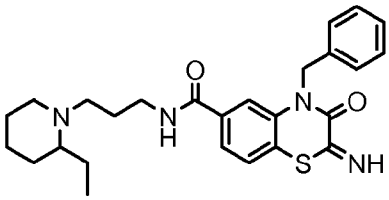
(447)



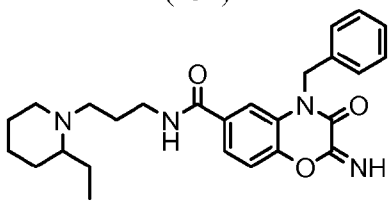
(449)



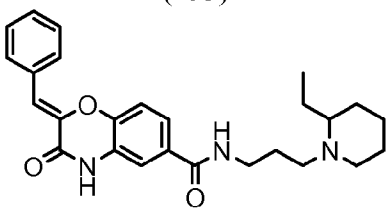
(451)



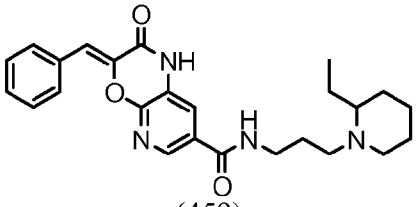
(453)



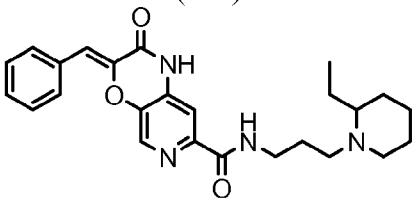
(455)



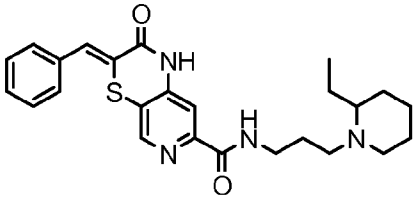
(457)



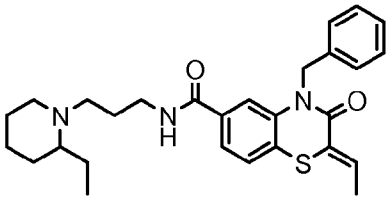
(459)



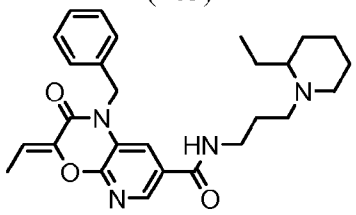
(461)



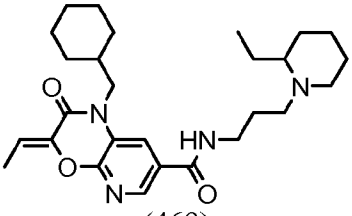
(463)



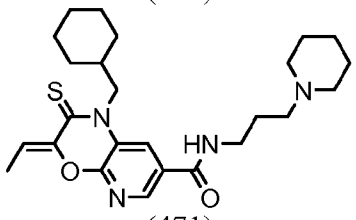
(465)



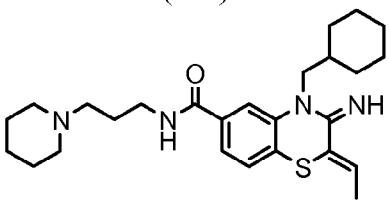
(467)

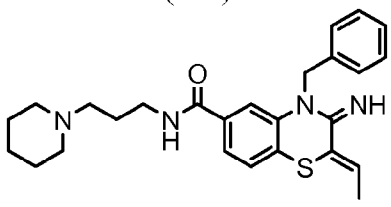


(469)

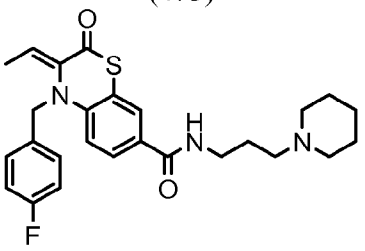


(471)

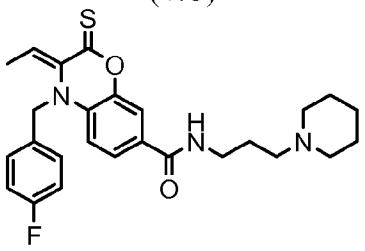




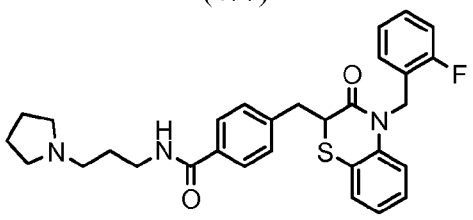
(473)



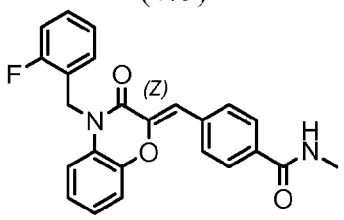
(475)



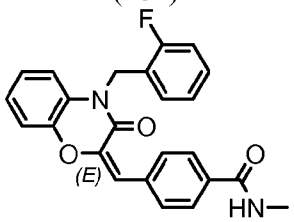
(477)



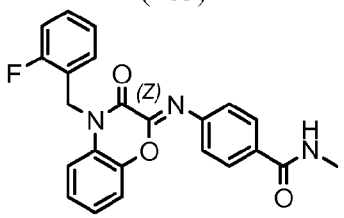
(479)



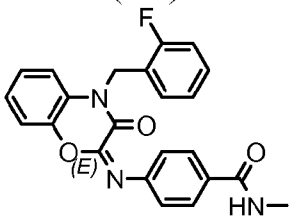
(481)



(483)



(485)

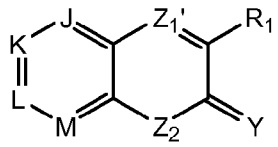


(487)

(489)

In one embodiment of formula (IV), wherein Z_1-A_3 is a double bond, A_3-X_3 is CR^1;

In one embodiment of formula (IV), the compound having a structural formula (IVa):



(IVa)

or salt, solvate, ester, and/or prodrug thereof;

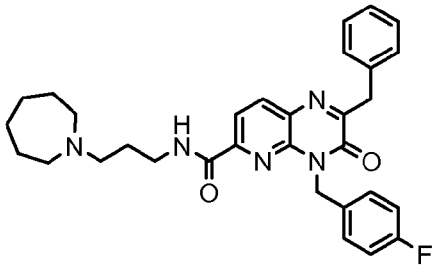
wherein:

Z_1' is either N or CR^3;

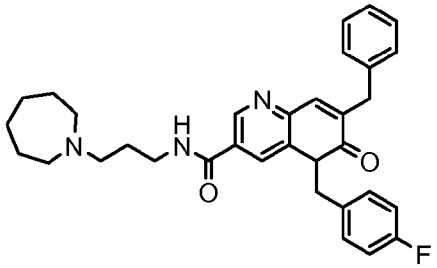
In one embodiment of formula (IVa), wherein at least one of J, K, L, and M is independently N;

In one embodiment of formula (IVa), wherein at least one of J, K, L, and M is independently CR^5;

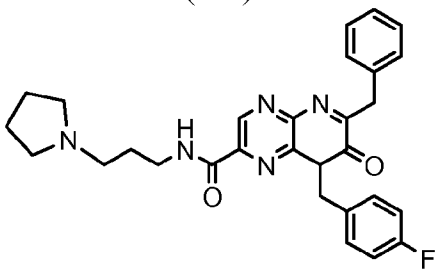
In one embodiment of formula (IVa), the compound having a structure selected from the group consisting of:



(491)



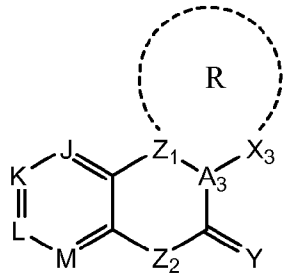
(493)



(495)

In one embodiment of formula (IV), wherein Z1 and X3 form a ring system;

In one embodiment of formula (IV), the compound having the structural formula (IVb):



(IVb)

or a salt, solvate, ester, and/or prodrug thereof;

wherein:

A3 is N or CR1

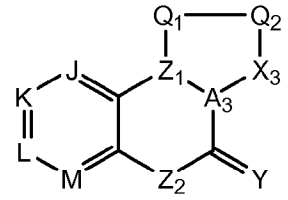
Z1 is N or CR3;

X3 is independently S, O, N, N(R^1), C(R^1), C(R^1R^2);

R ring is an aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroaryl or substituted heteroaryl ring;

In one embodiment of formula (IVb), wherein R is a 5-member ring system;

In one embodiment of formula (IVb), the compound having the structural formula (IVb.0):



(IVb.0)

or a salt, solvate, ester, and/or prodrug thereof;

wherein:

Z_1-Q_1, Q_1-Q_2, Q_2-X_3, A_3-X_3, Z_1-A_3 are independently single or double bond;

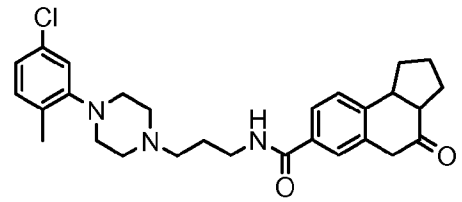
Q_1, Q_2, and X_3 are independently S, O, N, N(R^{10}), C(R^{10}), C($R^{10}R^{11}$);

Z_1 and A_3 are independently N, C, or CR^{12};

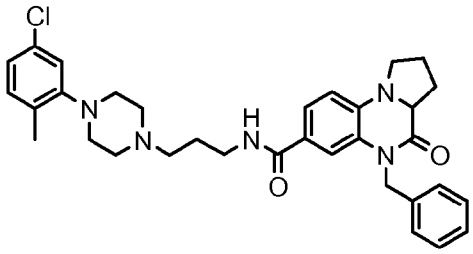
R^{10}, R^{11}, and R^{12} are independently hydrogen, halogen, acyl, substituted acyl, alkoxycarbonyl, substituted alkoxycarbonyl, aryloxycarbonyl, substituted aryloxycarbonyl, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted

arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyl;

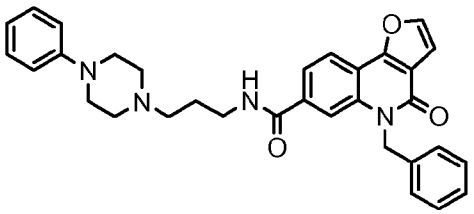
In one embodiment of formula (IVb.0), the compound having a structure selected from the group consisting of:



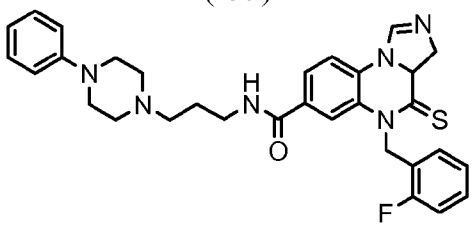
(497)



(499)



(501)

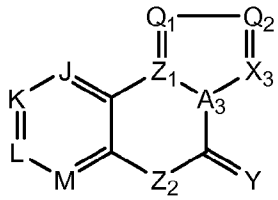


(503)

In one embodiment of formula (IVb.0), wherein Z_1-Q_1 and Q_2-X_3 are double bond;

In one embodiment of formula (IVb.0), wherein Q_1-Q_2, A_3-X_3, and Z_1-A_3 are single bond;

In one embodiment of formula (IVb.0), the compound having the structural formula (IVb.1):



(IVb.1)

or a salt, solvate, ester, and/or prodrug thereof;

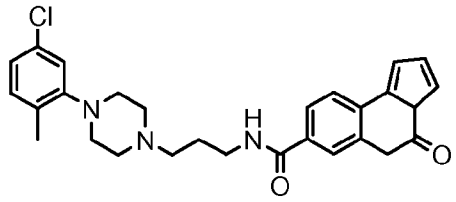
wherein:

Z_1 is C;

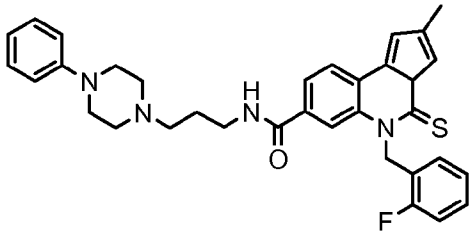
A_3 is N or CR^{12};

X_3, Q_1 and Q_2 are independently N or CR^{10};

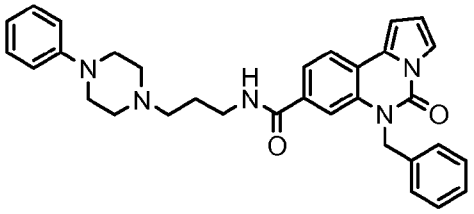
In one embodiment of formula (IVb.1), the compound having a structure selected from the group consisting of:



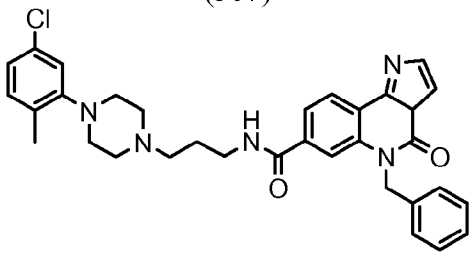
(505)



(507)



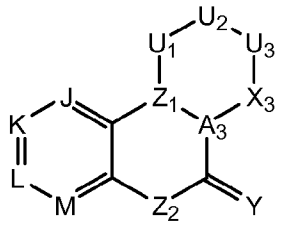
(509)



(511)

In one embodiment of formula (IV), wherein R^3 forms a 6-member-ring system with A_3-X_3;

In one embodiment of formula (IV), the compound having the structural formula (IVc):



(IVc)

or a salt, solvate, ester, and/or prodrug thereof;

wherein:

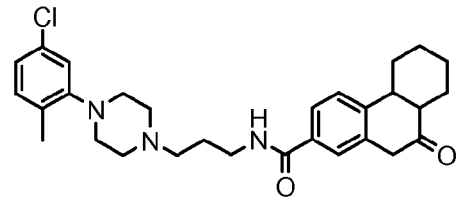
Z_1-U_1, U_1-U_2, U_2-U_3, U_3-X_3, A_3-X_3, Z_1-A_3 are independently single or double bond;

U_1, U_2, U_3, and X_3 are independently S, O, N, $N(R^{13})$, $C(R^{13})$, $C(R^{13}R^{14})$;

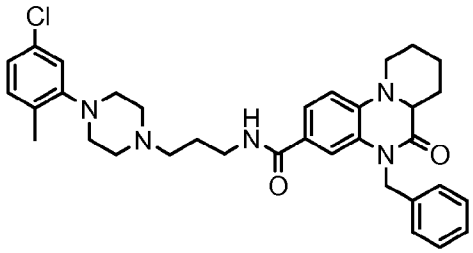
Z_1 and A_3 are independently N, C, or CR^{15};

R^{13}, R^{14}, and R^{15} are independently hydrogen, halogen, acyl, substituted acyl, alkoxycarbonyl, substituted alkoxycarbonyl, aryloxycarbonyl, substituted aryloxycarbonyl, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyl;

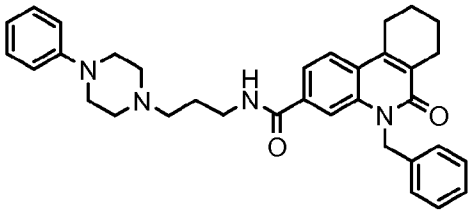
In one embodiment of formula (IVc), the compound having a structure selected from the group consisting of:



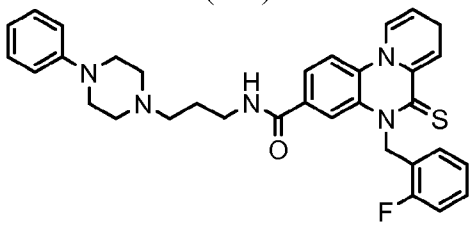
(515)



(517)



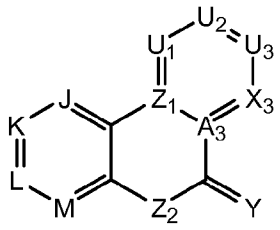
(519)



(521)

In one embodiment of formula (IVc), wherein Z_1-U_1, U_1-U_2, U_2-U_3, U_3-X_3, A_3-X_3, Z_1-A_3 is an aromatic system;

In one embodiment of formula (IVc), the compound having the structural formula (IVc.1):



(IVc.1)

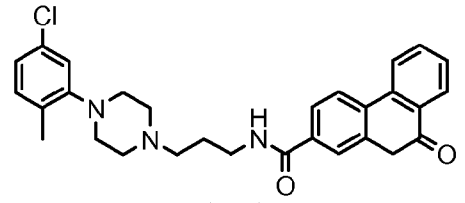
or a salt, solvate, ester, and/or prodrug thereof;

wherein:

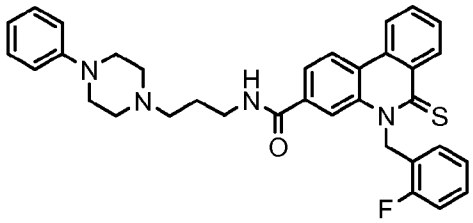
U_1, U_2, U_3 and X_3 are independently N or CR^{13};

Z_1 and A_3 are C;

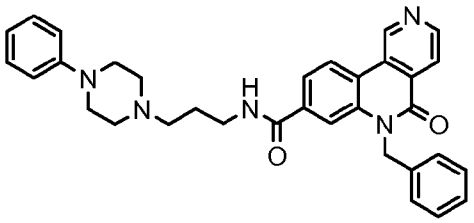
In one embodiment of formula (IVc.1),The compound of Claim 34 having a structure selected from the group consisting of:



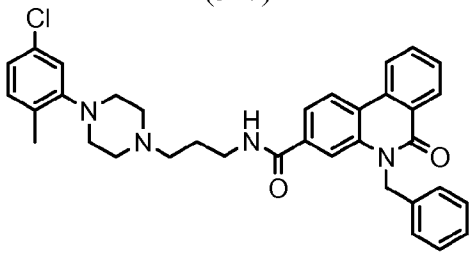
(525)



(527)



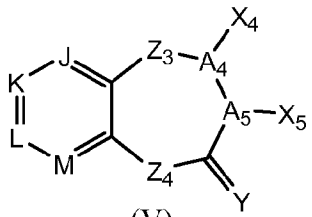
(529)



(531)

In one embodiment of formula (I), wherein m = 1, n = 3, A is Z_3, A_4-X_4, A_5-X_5, B is Z_4;

In one embodiment of formula (I), the compound having the structural of formula (V):



(V)

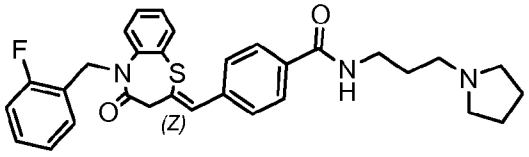
or a salt, solvate, ester, and/or prodrug thereof;

wherein:

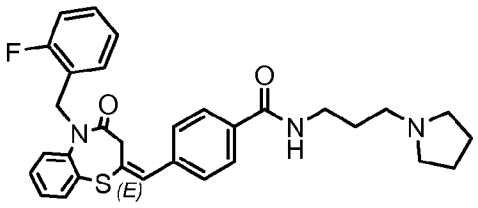
A_4-X_4, A_5-X_5 are independently NR^1, $C{=}CR^1$ (E and Z isomers), $C{=}NR^1$, or $C(R^1R^2)$;

Z_3 and Z_4 are independently O, S, NR^3, or $C(R^3R^4)$;

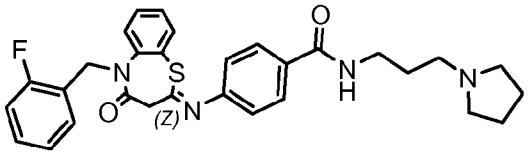
In one embodiment of formula (V), the compound having a structure selected from the group consisting of:



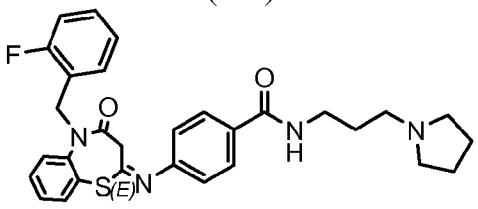
(801)



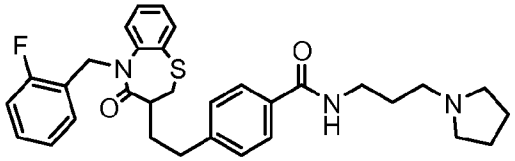
(803)



(805)



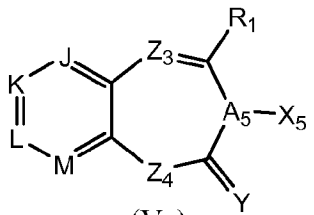
(807)



(809)

In one embodiment of formula (V), wherein Z_3-A_4 is double bond, $A_4(X_4)$ is CR^1, A_5-X_5 is $C(R^1R^2)$, NR^1, $C{=}CR^1$ (E and Z isomers), or $C{=}NR^1$ (E and Z isomers);

In one embodiment of formula (V), the compound having the structural formula (Va):



(Va)

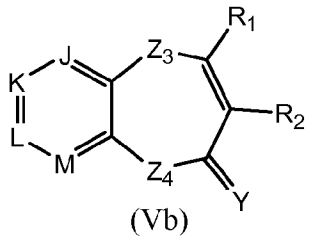
or a salt, solvate, ester, and/or prodrug thereof;

wherein:

Z_3 and Z_4 are independently O, N, S, $N(R^3)$, or $C(R^3R^4)$;

In one embodiment of formula (V), wherein A_4-A_5 is double bond, $A_4(X_4)$ is CR^1, and $A_5(X_5)$ is CR^2;

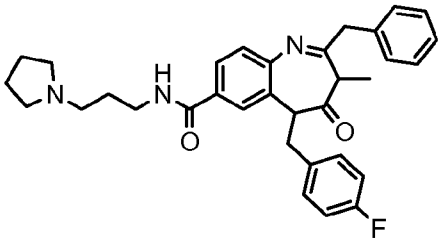
In one embodiment of formula (V), the compound having the structural formula (Vb):



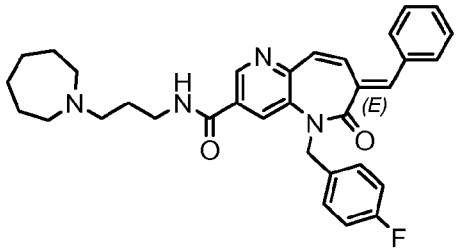
(Vb)

or a salt, solvate, ester, and/or prodrug thereof;

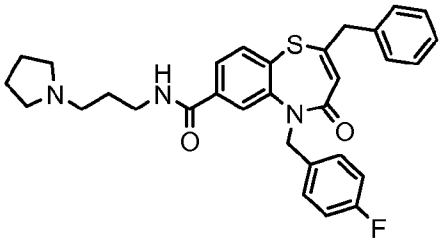
In one embodiment of formula (V), the compounds having a structure selected from the group consisting of:



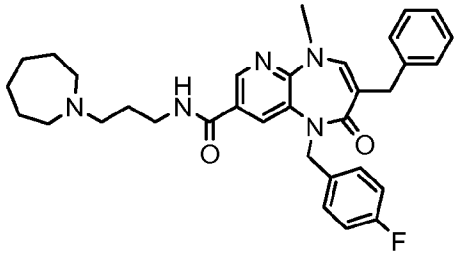
(811)



(813)



(815)

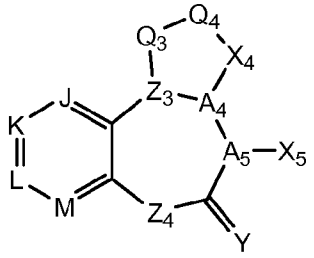


(817)

In one embodiment of formula (V), wherein Z3 is NR^3, or $C(R^3R^4)$;

In one embodiment of formula (V), wherein R^3 forms a 5-member ring system with A4-X4;

In one embodiment of formula (V), the compound having the structural formula (Vc):



(Vc)

or a salt, solvate, ester, and/or prodrug thereof;

wherein:

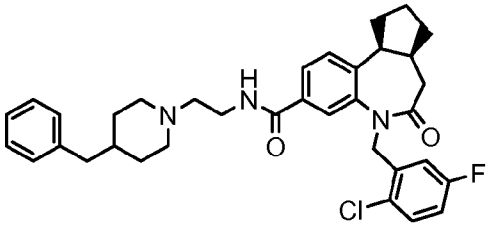
Z_3-Q_3, Q_3-Q_4, Q_4-X_4, A_4-X_4, Z_3-A_4 are independently single or double bond;

Q_3, Q_4, and X_4 are independently S, O, N, N(R^{16}), C(R^{16}), C($R^{16}R^{17}$);

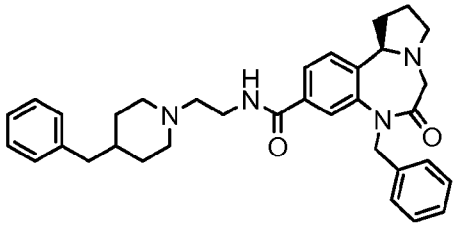
Z_3 and A_4 are independently N, C, or CR^{18};

R^{16}, R^{17}, and R^{18} are independently hydrogen, halogen, acyl, substituted acyl, alkoxycarbonyl, substituted alkoxycarbonyl, aryloxycarbonyl, substituted aryloxycarbonyl, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyl;

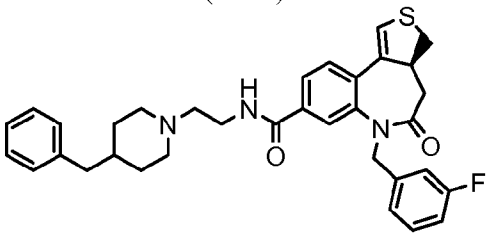
In one embodiment of formula (Vc), the compound having a structure selected from the group consisting of:



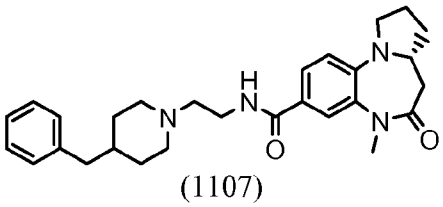
(1101)



(1103)



(1105)

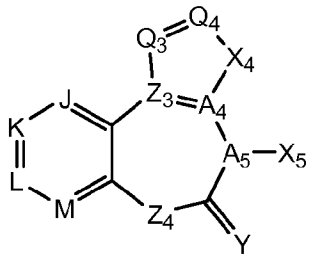


(1107)

In one embodiment of formula (Vc), wherein Z3-Q3 and Q4-X4 are double bond;

In one embodiment of formula (Vc), wherein Z3-A4, Q3-Q4, and A4-X4 are single bond;

In one embodiment of formula (Vc), the compound having the structural formula (Vc.1):



(Vc.1)

or a salt, solvate, ester, and/or prodrug thereof;

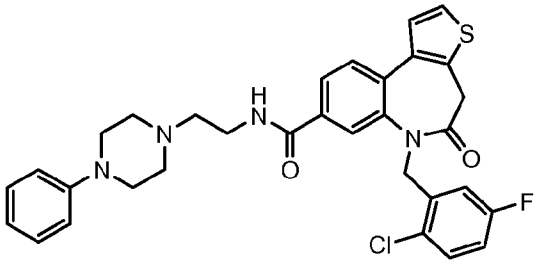
wherein:

Z_3 is C;

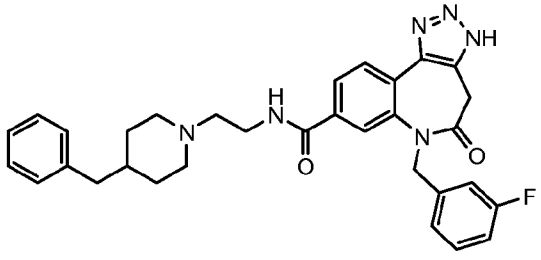
A_4 is N or CR^{18};

X_4, Q_3 and Q_4 are independently N or CR^{16};

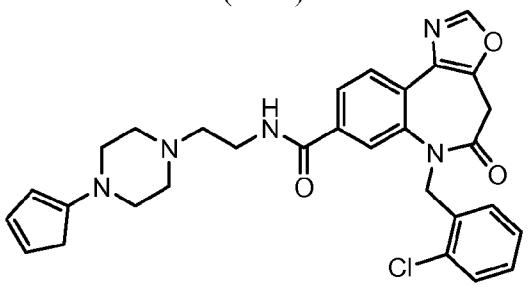
In one embodiment of formula (Vc.1), the compound having a structure selected from the group consisting of:



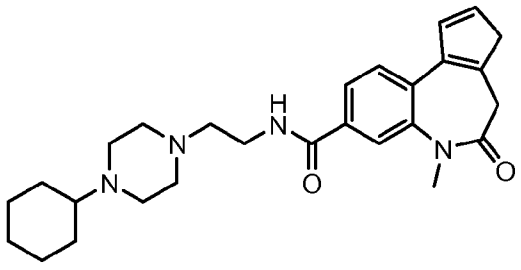
(1121)



(1123)



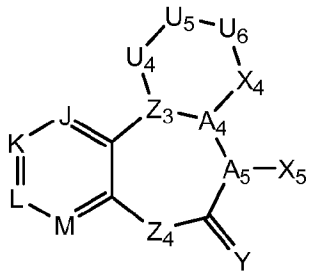
(1125)



(1127)

In one embodiment of formula (V), wherein R^3 forms a 6-member ring system with A_4-X_4;

In one embodiment of formula (V), the compound having the structural formula (Vd):



(Vd)

o a salt, solvate, ester, and/or prodrug thereof;

wherein:

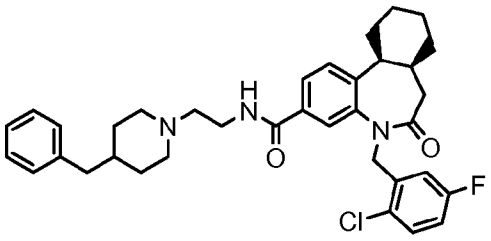
Z_3-U_4 U_4-U_5, U_5-U_6, U_6-X_4, A_4-X_4, Z_3-A_4 are independently single or double bond;

U_4, U_5, U_6, and X_4 are independently S, O, N, $N(R^{19})$, $C(R^{19})$, $C(R^{19}R^{20})$;

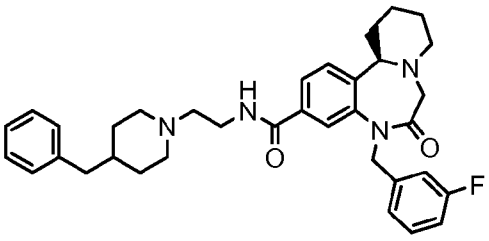
Z_3 and A_4 are independently N, C, or CR^{21};

R^{19}, R^{20}, and R^{21} are independently hydrogen, halogen, acyl, substituted acyl, alkoxycarbonyl, substituted alkoxycarbonyl, aryloxycarbonyl, substituted aryloxycarbonyl, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyl;

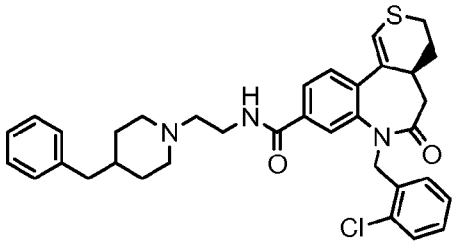
In one embodiment of formula (Vd), the compound having a structure selected from the group consisting of:



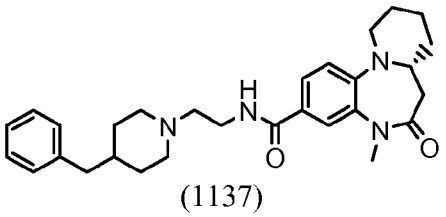
(1131)



(1133)



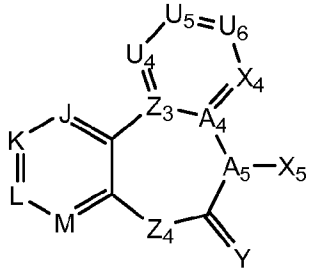
(1135)



(1137)

In one embodiment of formula (Vd), wherein Z_3-U_4 U_4-U_5, U_5-U_6, U_6-X_4, A_4-X_4, Z_3-A_4 together form an aromatic system;

In one embodiment of formula (Vd), the compound having the structural formula (Vd.1):



(Vd.1)

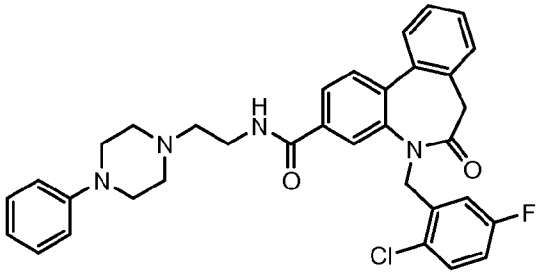
or a salt, solvate, ester, and/or prodrug thereof;

wherein:

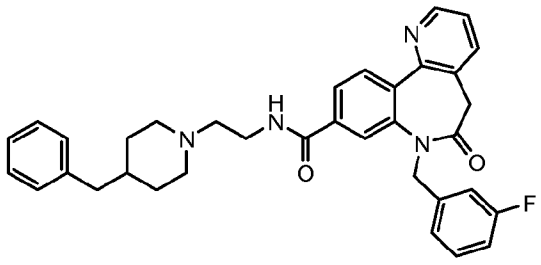
Z_3 and A_4 are C;

U_4, U_5, U_6, and X_4 are independently N or CR^{19}

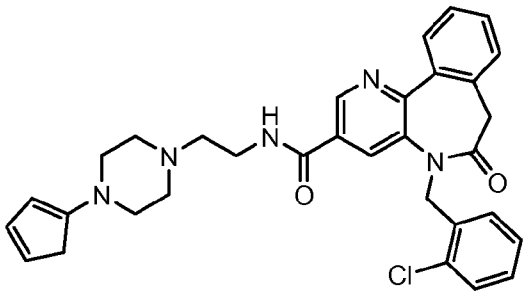
In one embodiment of formula (Vd.1), the compound having a structure selected from the group consisting of:



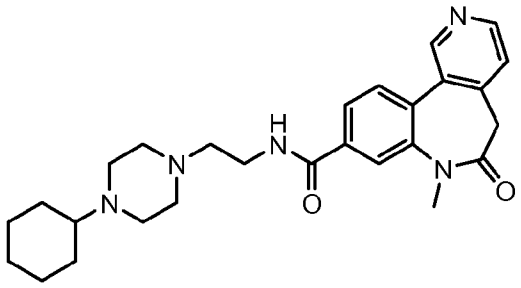
(1141)



(1143)



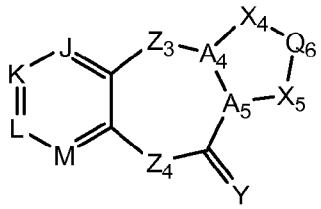
(1145)



(1147)

In one embodiment of formula (V), wherein A_4-X_4 and A_5-X_5 form a 5-member ring system;

In one embodiment of formula (V), the compound having the structural formula (Ve):



(Ve)

or a salt, solvate, ester, and/or prodrug thereof;

wherein:

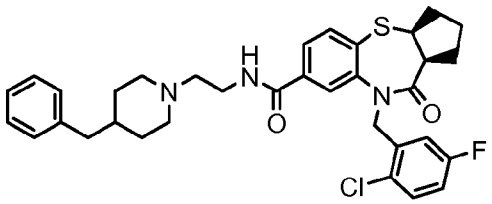
A_4-X_4, X_4-Q_6, Q_6-X_5, A_5-X_5, A_4-A_5 are independently single or double bond;

X_4, X_5, and Q_6 are indpenedently S, O, N, N(R^{22}), C(R^{22}), or C($R^{22}R^{23}$);

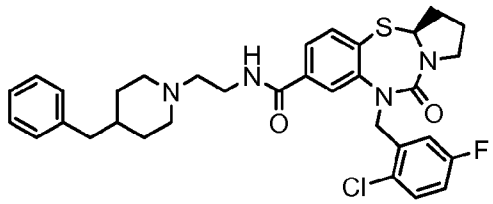
A_4 and A_5 are independently N, C, or CR^{24};

R^{22}, R^{23}, and R^{24} are independently hydrogen, halogen, acyl, substituted acyl, alkoxycarbonyl, substituted alkoxycarbonyl, aryloxycarbonyl, substituted aryloxycarbonyl, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyl;

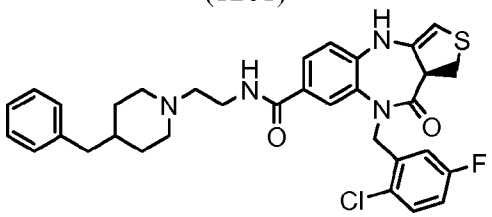
In one embodiment of formula (Ve), the compound having a structure selected from the group consisting of:



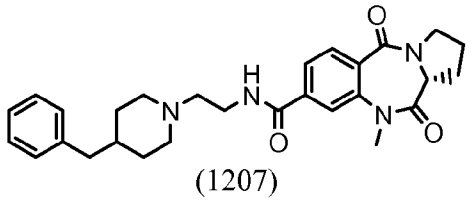
(1201)



(1203)



(1205)

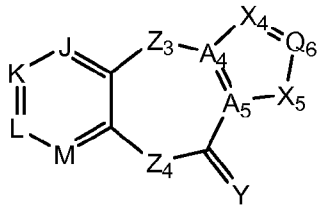


(1207)

In one embodiment of formula (Ve), wherein A4-X4 and Q6-X5 are double bond;

In one embodiment of formula (Ve), the compound wherein A4-A5, X4-Q6, and A5-X5 are single bond;

In one embodiment of formula (Ve), the compound having the structural formula (Ve.1):



(Ve.1)

or a salt, solvate, ester, and/or prodrug thereof;

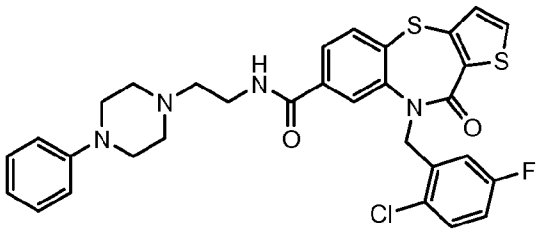
wherein:

A4 and A5 are C;

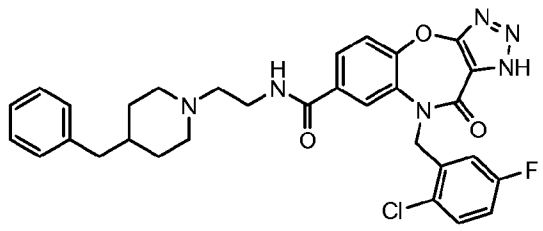
X5 is S, O, N, NR24, or CR24;

X4, and Q6 are independently N or CR20;

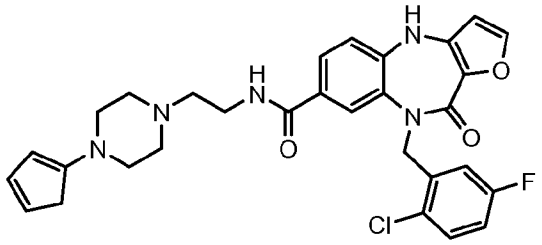
In one embodiment of formula (Ve.1), the compound having a structure selected from the group consisting of:



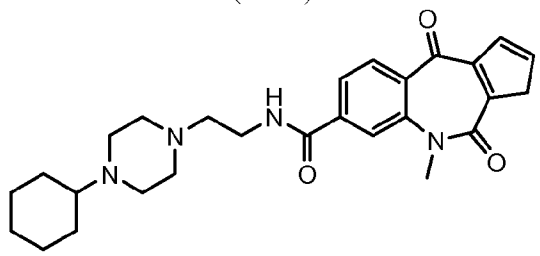
(1215)



(1217)



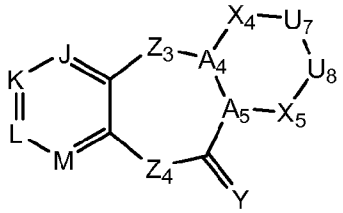
(1219)



(1221)

In one embodiment of formula (V), wherein A_4-X_4 and A_5-X_5 form a 6-member ring system;

In one embodiment of formula (V), the compound having the structural formula (Vf):



(Vf)

or a salt, solvate, ester, and/or prodrug thereof;

wherein:

A4-X4, X4-U7, U7-U8, U8-X5, A5-X5, and A4-A5 are independently single or double bond;

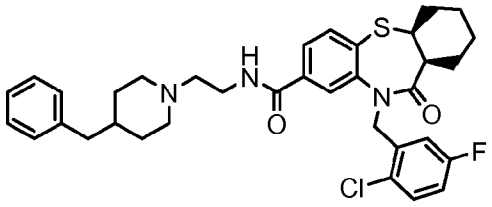
X4, U7, U8, and X5 are independently S, O, N, N(R25), C(R25), or C(R25R26);

A4 and A5 are independently N, C, or CR27;

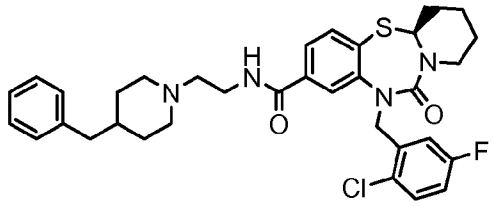
R^{25}, R^{26}, and R^{27} are independently hydrogen, halogen, acyl, substituted acyl, alkoxycarbonyl, substituted alkoxycarbonyl, aryloxycarbonyl, substituted aryloxycarbonyl, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted

arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyl;

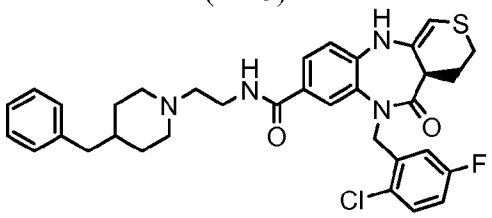
In one embodiment of formula (Vf), the compound of having a structure selected from the group consisting of:



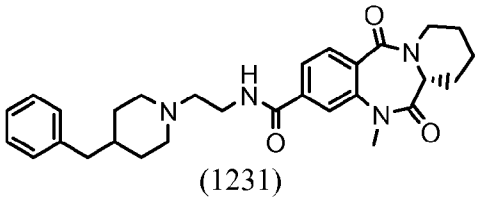
(1225)



(1227)



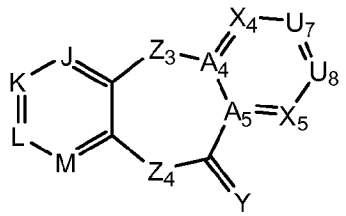
(1229)



(1231)

In one embodiment of formula (Vf), wherein A4-X4, X4-U7, U7-U8, U8-X5, A5-X5, and A4-A5 together form an aromatic system;

In one embodiment of formula (Vf), the compound having the structural formula (Vf.1):



(Vf.1)

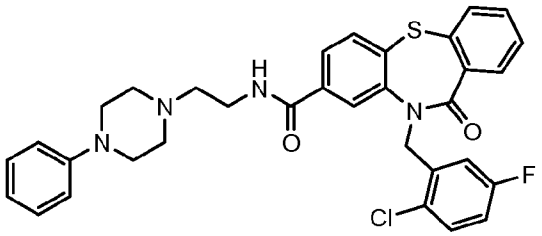
or a salt, solvate, ester, and/or prodrug thereof;

wherein:

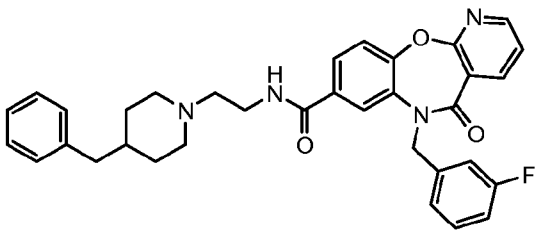
A4 and A5 are C;

X4, U7, U8, and X5 are independently N or CR25;

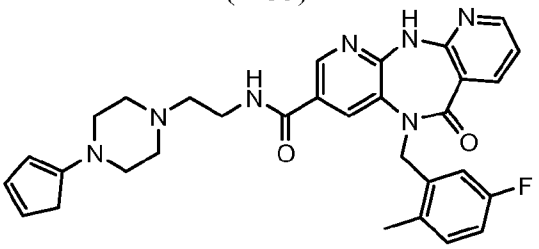
In one embodiment of formula (Vf.1), the compound having a structure selected from the group consisting of:



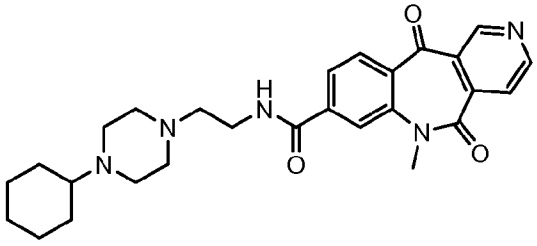
(1235)



(1237)



(1239)



(1241)

In another embodiment, a pharmaceutical composition comprising a compound having a structural formula (I) selected from the group consisting of:

ID	IUPAC
101	7-Benzyl-8-oxo-bicyclo[4.2.0]octa-1,3,5-triene-3-carboxylic acid (3-pyrrolidin-1-yl-propyl)-amide
103	(E) 7-Benzylidene-8-oxo-bicyclo[4.2.0]octa-1,3,5-triene-3-carboxylic acid (3-pyrrolidin-1-yl-propyl)-amide
105	7-Benzyl-8-oxo-7-aza-bicyclo[4.2.0]octa-1,3,5-triene-3-carboxylic acid (3-pyrrolidin-1-yl-propyl)-amide
107	(Z) 8-Benzylidene-7-oxo-2-aza-bicyclo[4.2.0]octa-1,3,5-triene-4-carboxylic acid (3-pyrrolidin-1-yl-propyl)-amide

ID	IUPAC
109	4-[1-(2-Fluoro-benzyl)-2-oxo-2,3-dihydro-1H-indol-3-ylmethyl]-N-(3-pyrrolidin-1-yl-propyl)-benzamide
111	(E) 4-[5-(2-Fluoro-benzyl)-6-oxo-5,6-dihydro-pyrrolo[3,2-d]pyrimidin-7-ylidenemethyl]-N-(3-pyrrolidin-1-yl-propyl)-benzamide
113	(Z) 4-[1-(2-Fluoro-benzyl)-2-oxo-1,2-dihydro-indol-3-ylidenemethyl]-N-(3-pyrrolidin-1-yl-propyl)-benzamide
115	(E) 4-[1-(2-Fluoro-benzyl)-2-oxo-1,2-dihydro-indol-3-ylideneamino]-N-(3-pyrrolidin-1-yl-propyl)-benzamide
117	(Z) 4-[1-(2-Fluoro-benzyl)-2-oxo-1,2-dihydro-indol-3-ylideneamino]-N-(3-pyrrolidin-1-yl-propyl)-benzamide

In another embodiment, a pharmaceutical composition comprising a compound having a structural formula (IV) selected from the group consisting of:

ID	IUPAC
201	N-{3-[4-(5-chloro-2-methylphenyl)piperazin-1-yl]propyl}-6-oxo-6,6a,7,8,9,10-hexahydro-5H-pyrido[1,2-a]quinoxaline-3-carboxamide
203	(2Z)-N-[3-(4-benzylpiperidin-1-yl)propyl]-4-(4-fluorobenzyl)-3-oxo-2-(phenylmethylidene)-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide
205	N-[3-(4-benzylpiperidin-1-yl)propyl]-2-{(2E)-2-[(3-bromo-4-methoxyphenyl)methylidene]-3-oxo-2,3-dihydro-4H-1,4-benzothiazin-4-yl}acetamide
207	4-{(E)-[4-(3-chlorobenzyl)-3-oxo-3,4-dihydro-2H-1,4-benzothiazin-2-ylidene]methyl}-N-[2-(dibutylamino)ethyl]benzamide
209	N-[3-(4-benzylpiperidin-1-yl)propyl]-2-{(2Z)-2-[(3-chlorophenyl)methylidene]-3-oxo-2,3-dihydro-4H-1,4-benzothiazin-4-yl}acetamide
211	(2Z)-N-{3-[cyclohexyl(methyl)amino]propyl}-4-(4-fluorobenzyl)-3-oxo-2-(phenylmethylidene)-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide
213	(2Z)-N-[3-(4-benzylpiperidin-1-yl)propyl]-4-(3-methylbenzyl)-3-oxo-2-(phenylmethylidene)-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide
215	(2Z)-N-{3-[cyclohexyl(methyl)amino]propyl}-4-(3-methylbenzyl)-3-oxo-2-(phenylmethylidene)-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide
217	N-[3-(4-benzylpiperidin-1-yl)propyl]-2-{(2E)-2-[(3-bromophenyl)methylidene]-3-oxo-2,3-dihydro-4H-1,4-benzothiazin-4-yl}acetamide
219	(2Z)-N-(2-azepan-1-ylethyl)-4-(3-methylbenzyl)-3-oxo-2-(phenylmethylidene)-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide
221	N-[2-(4-benzylpiperidin-1-yl)ethyl]-4-{(E)-[4-(2,5-dimethylbenzyl)-3-oxo-3,4-dihydro-2H-1,4-benzothiazin-2-ylidene]methyl}benzamide
223	(2Z)-N-[3-(2-ethylpiperidin-1-yl)propyl]-4-(4-fluorobenzyl)-3-oxo-2-(phenylmethylidene)-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide
225	4-{(E)-[4-(3-chlorobenzyl)-3-oxo-3,4-dihydro-2H-1,4-benzothiazin-2-ylidene]methyl}-N-{3-[cyclohexyl(methyl)amino]propyl}benzamide
227	(2Z)-N-(3-azepan-1-ylpropyl)-4-(3-methylbenzyl)-3-oxo-2-(phenylmethylidene)-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide
229	(2Z)-4-(4-fluorobenzyl)-N-[3-(3-methylpiperidin-1-yl)propyl]-3-oxo-2-(phenylmethylidene)-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide
231	N-(2-azepan-1-ylethyl)-4-{(E)-[4-(3-methylbenzyl)-3-oxo-3,4-dihydro-2H-1,4-benzothiazin-2-ylidene]methyl}benzamide
233	N-{3-[cyclohexyl(methyl)amino]propyl}-4-{(E)-[4-(3-methylbenzyl)-3-oxo-3,4-dihydro-2H-1,4-benzothiazin-2-ylidene]methyl}benzamide
235	N-(2-azepan-1-ylethyl)-4-{(E)-[4-(3-chlorobenzyl)-3-oxo-3,4-dihydro-2H-1,4-benzothiazin-2-ylidene]methyl}benzamide
237	(2Z)-N-{2-[4-(2-fluorophenyl)piperazin-1-yl]ethyl}-2-[2-(4-methoxyphenyl)-2-oxoethylidene]-3-oxo-1,2,3,4-tetrahydroquinoxaline-6-carboxamide
239	2-{(2Z)-2-[(3-chlorophenyl)methylidene]-3-oxo-2,3-dihydro-4H-1,4-benzothiazin-4-yl}-N-{3-[4-(4-methoxyphenyl)piperazin-1-yl]propyl}acetamide
241	(2Z)-N-{3-[4-(2,5-dimethylphenyl)piperazin-1-yl]propyl}-4-(3-methylbenzyl)-3-oxo-2-(phenylmethylidene)-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide
243	4-{(E)-[4-(3-chlorobenzyl)-3-oxo-3,4-dihydro-2H-1,4-benzothiazin-2-ylidene]methyl}-N-[(1-ethylpyrrolidin-2-yl)methyl]benzamide
245	N-{3-[cyclohexyl(methyl)amino]propyl}-4-{(E)-[4-(2-methylbenzyl)-3-oxo-3,4-dihydro-2H-1,4-benzothiazin-2-ylidene]methyl}benzamide
247	(2Z)-N-[3-(3,5-dimethylpiperidin-1-yl)propyl]-4-(3-methylbenzyl)-3-oxo-2-(phenylmethylidene)-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide
249	(2Z)-N-[3-(3,5-dimethylpiperidin-1-yl)propyl]-4-(4-fluorobenzyl)-3-oxo-2-(phenylmethylidene)-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide
251	N-{3-[benzyl(methyl)amino]propyl}-4-{(E)-[4-(3-methylbenzyl)-3-oxo-3,4-dihydro-2H-1,4-benzothiazin-2-ylidene]methyl}benzamide

253	N-(2-azepan-1-ylethyl)-2-{(2E)-2-[(3-chlorophenyl)methylidene]-3-oxo-2,3-dihydro-4H-1,4-benzothiazin-4-yl}acetamide
255	2-{(2E)-2-[(3-bromo-4-methoxyphenyl)methylidene]-3-oxo-2,3-dihydro-4H-1,4-benzothiazin-4-yl}-N-{3-[4-(2-fluorophenyl)piperazin-1-yl]propyl}acetamide
257	N-{3-[benzyl(methyl)amino]propyl}-2-{(2Z)-2-[(3-chlorophenyl)methylidene]-3-oxo-2,3-dihydro-4H-1,4-benzothiazin-4-yl}acetamide
259	2-{(2Z)-2-[(3-chlorophenyl)methylidene]-3-oxo-2,3-dihydro-4H-1,4-benzothiazin-4-yl}-N-{3-[4-(2-fluorophenyl)piperazin-1-yl]propyl}acetamide
261	N-{2-[cyclohexyl(1-methylpropyl)amino]ethyl}-4-{(E)-[4-(2-fluorobenzyl)-3-oxo-3,4-dihydro-2H-1,4-benzothiazin-2-ylidene]methyl}benzamide
263	N-{2-[cyclohexyl(methyl)amino]ethyl}-4-{(E)-[4-(3-methylbenzyl)-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-ylidene]methyl}benzamide
265	2-{(2E)-2-[(3-bromophenyl)methylidene]-3-oxo-2,3-dihydro-4H-1,4-benzothiazin-4-yl}-N-[3-(3,5-dimethylpiperidin-1-yl)propyl]acetamide
267	N-{3-[benzyl(butyl)amino]propyl}-4-{(E)-[4-(3-chlorobenzyl)-3-oxo-3,4-dihydro-2H-1,4-benzothiazin-2-ylidene]methyl}benzamide
269	N-(2-azepan-1-ylethyl)-2-{(2E)-2-[(3-bromo-4-methoxyphenyl)methylidene]-3-oxo-2,3-dihydro-4H-1,4-benzothiazin-4-yl}acetamide
271	2-{(2Z)-2-[(3-chlorophenyl)methylidene]-3-oxo-2,3-dihydro-4H-1,4-benzothiazin-4-yl}-N-{3-[4-(4-fluorophenyl)piperazin-1-yl]propyl}acetamide
273	2-{(2E)-2-[(3-bromophenyl)methylidene]-3-oxo-2,3-dihydro-4H-1,4-benzothiazin-4-yl}-N-[3-(2-ethylpiperidin-1-yl)propyl]acetamide
275	N-{3-[4-(5-chloro-2-methylphenyl)piperazin-1-yl]propyl}-4-{(E)-[4-(2-fluorobenzyl)-3-oxo-3,4-dihydro-2H-1,4-benzothiazin-2-ylidene]methyl}benzamide
277	N-[2-(dipropylamino)ethyl]-4-{(E)-[4-(3-methylbenzyl)-3-oxo-3,4-dihydro-2H-1,4-benzothiazin-2-ylidene]methyl}benzamide
279	(2Z)-N-(2-azepan-1-ylethyl)-4-(4-fluorobenzyl)-3-oxo-2-(phenylmethylidene)-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide
281	4-{(E)-[4-(3-chlorobenzyl)-3-oxo-3,4-dihydro-2H-1,4-benzothiazin-2-ylidene]methyl}-N-{3-[4-(2-fluorophenyl)piperazin-1-yl]propyl}benzamide
283	2-{(2Z)-2-[(3-chlorophenyl)methylidene]-3-oxo-2,3-dihydro-4H-1,4-benzothiazin-4-yl}-N-{3-[4-(3-chlorophenyl)piperazin-1-yl]propyl}acetamide
285	2-{(2E)-2-[(3-chlorophenyl)methylidene]-3-oxo-2,3-dihydro-4H-1,4-benzothiazin-4-yl}-N-[3-(2-ethylpiperidin-1-yl)propyl]acetamide
287	N-{3-[4-(5-chloro-2-methylphenyl)piperazin-1-yl]propyl}-4-{(E)-[4-(3-methylbenzyl)-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-ylidene]methyl}benzamide
289	N-{3-[4-(3-chlorophenyl)piperazin-1-yl]propyl}-6-oxo-6,6a,7,8,9,10-hexahydro-5H-pyrido[1,2-a]quinoxaline-3-carboxamide
291	(2Z)-N-[3-(3,4-dihydroisoquinolin-2(1H)-yl)propyl]-4-(3-methylbenzyl)-3-oxo-2-(phenylmethylidene)-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide
293	2-{(2E)-2-[(3-bromo-4-methoxyphenyl)methylidene]-3-oxo-2,3-dihydro-4H-1,4-benzothiazin-4-yl}-N-{3-[4-(4-fluorophenyl)piperazin-1-yl]propyl}acetamide
295	4-{(E)-[4-(3-chlorobenzyl)-3-oxo-3,4-dihydro-2H-1,4-benzothiazin-2-ylidene]methyl}-N-(2-pyrrolidin-1-ylethyl)benzamide
297	2-{(2E)-2-[(3-bromophenyl)methylidene]-3-oxo-2,3-dihydro-4H-1,4-benzothiazin-4-yl}-N-{2-[methyl(2-phenylethyl)amino]ethyl}acetamide
299	4-{(E)-[4-(3-chlorobenzyl)-3-oxo-3,4-dihydro-2H-1,4-benzothiazin-2-ylidene]methyl}-N-[3-(3-methylpiperidin-1-yl)propyl]benzamide
301	(2Z)-N-{3-[4-(4-methoxyphenyl)piperazin-1-yl]propyl}-4-(3-methylbenzyl)-3-oxo-2-(phenylmethylidene)-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide
303	(2Z)-N-(3-azepan-1-ylpropyl)-4-(4-fluorobenzyl)-3-oxo-2-(phenylmethylidene)-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide
305	N-{3-[4-(2-fluorophenyl)piperazin-1-yl]propyl}-4-{(E)-[4-(3-methylbenzyl)-3-oxo-3,4-dihydro-2H-1,4-benzothiazin-2-ylidene]methyl}benzamide

307	N-{3-[4-(2-fluorophenyl)piperazin-1-yl]propyl}-4-{(E)-[4-(2-methylbenzyl)-3-oxo-3,4-dihydro-2H-1,4-benzothiazin-2-ylidene]methyl}benzamide
309	N-{3-[4-(4-methoxyphenyl)piperazin-1-yl]propyl}-4-{(E)-[4-(4-methylbenzyl)-3-oxo-3,4-dihydro-2H-1,4-benzothiazin-2-ylidene]methyl}benzamide
311	2-{(2E)-2-[(3-chlorophenyl)methylidene]-3-oxo-2,3-dihydro-4H-1,4-benzothiazin-4-yl}-N-[3-(3-methylpiperidin-1-yl)propyl]acetamide
313	(2E)-2-[(4-ethoxy-3-methoxyphenyl)methylidene]-N-{3-[4-(2-fluorophenyl)piperazin-1-yl]propyl}-4-methyl-3-oxo-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide
315	2-{(2E)-2-[(2-chlorophenyl)methylidene]-3-oxo-2,3-dihydro-4H-1,4-benzothiazin-4-yl}-N-{3-[4-(4-fluorophenyl)piperazin-1-yl]propyl}acetamide
317	(2Z)-N-{3-[4-(2-fluorophenyl)piperazin-1-yl]propyl}-4-methyl-2-[(3-methylphenyl)methylidene]-3-oxo-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide
319	2-{(2E)-2-[(3-chlorophenyl)methylidene]-3-oxo-2,3-dihydro-4H-1,4-benzothiazin-4-yl}-N-[3-(3,5-dimethylpiperidin-1-yl)propyl]acetamide
321	(2E)-N-{3-[4-(2-fluorophenyl)piperazin-1-yl]propyl}-2-[(2-methoxyphenyl)methylidene]-4-methyl-3-oxo-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide
323	(2Z)-N-{3-[4-(4-fluorophenyl)piperazin-1-yl]propyl}-4-methyl-2-[(2-methylphenyl)methylidene]-3-oxo-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide

ID	IUPAC
421	4-{(Z)-[4-(4-chlorobenzyl)-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-ylidene]methyl}-N-methylbenzamide
423	4-{(Z)-[4-(4-chlorobenzyl)-3-thioxo-3,4-dihydro-2H-pyrido[4,3-b][1,4]oxazin-2-ylidene]methyl}-N-methylbenzamide
425	N-methyl-4-[(Z)-(4-methyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-ylidene)methyl]benzamide
427	N-methyl-4-[(1Z)-1-(4-methyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-ylidene)-2-phenylethyl]benzamide
429	N-methyl-4-[(1Z)-1-(4-methyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-ylidene)-3-phenylpropyl]benzamide
431	N-methyl-4-[(1Z)-1-(4-methyl-3-oxo-3,4-dihydroquinoxalin-2(1H)-ylidene)-3-phenylpropyl]benzamide
433	N-methyl-4-[(1Z)-1-(4-methyl-3-oxo-3,4-dihydroquinoxalin-2(1H)-ylidene)-2-phenylethyl]benzamide
435	4-{(Z)-[4-(cyclohexylmethyl)-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-ylidene]methyl}-N-[2-(2-methylpiperidin-1-yl)ethyl]benzamide
437	4-{(Z)-[4-(cyclohexylmethyl)-3-oxo-3,4-dihydropyrido[3,4-b]pyrazin-2(1H)-ylidene]methyl}-N-[2-(2-methylpiperidin-1-yl)ethyl]benzamide
439	4-{(Z)-[1-(cyclohexylmethyl)-2-thioxo-1,2-dihydro-3H-pyrido[2,3-b][1,4]oxazin-3-ylidene]methyl}-N-[2-(2-methylpiperidin-1-yl)ethyl]benzamide
441	4-{[(2Z)-1-benzyl-2-ethylidene-3-oxo-1,2,3,4-tetrahydroquinolin-4-yl]methyl}-N-(2-piperidin-1-ylethyl)benzamide
443	4-{[(2Z)-1-benzyl-2-ethylidene-3-oxo-1,2,3,4-tetrahydro-1,5-naphthyridin-4-yl]methyl}-N-(2-piperidin-1-ylethyl)benzamide
445	4-{[(3E)-4-benzyl-3-ethylidene-2-oxo-3,4-dihydro-1,6-naphthyridin-1(2H)-yl]methyl}-N-(2-piperidin-1-ylethyl)benzamide
447	4-{[(3E)-4-benzyl-3-ethylidene-2-thioxo-3,4-dihydro-1,6-naphthyridin-1(2H)-yl]methyl}-N-(2-piperidin-1-ylethyl)benzamide
449	4-{[(3E)-4-(cyclohexylmethyl)-3-ethylidene-2-oxo-3,4-dihydroquinolin-1(2H)-yl]methyl}-N-(2-piperidin-1-ylethyl)benzamide
451	(2Z)-3-Oxo-2-(phenylmethylidene)-*N*-[3-(2-propylpiperidin-1-yl)propyl]-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxamide

453	4-benzyl-N-[3-(2-ethylpiperidin-1-yl)propyl]-2-imino-3-oxo-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide
455	4-benzyl-N-[3-(2-ethylpiperidin-1-yl)propyl]-2-imino-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-6-carboxamide
457	(2Z)-N-[3-(2-ethylpiperidin-1-yl)propyl]-3-oxo-2-(phenylmethylidene)-3,4-dihydro-2H-1,4-benzoxazine-6-carboxamide
459	(3Z)-N-[3-(2-ethylpiperidin-1-yl)propyl]-2-oxo-3-(phenylmethylidene)-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazine-7-carboxamide
461	(3Z)-N-[3-(2-ethylpiperidin-1-yl)propyl]-2-oxo-3-(phenylmethylidene)-2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazine-7-carboxamide
463	(3Z)-N-[3-(2-ethylpiperidin-1-yl)propyl]-2-oxo-3-(phenylmethylidene)-2,3-dihydro-1H-pyrido[3,4-b][1,4]thiazine-7-carboxamide
465	(2Z)-4-benzyl-2-ethylidene-N-[3-(2-ethylpiperidin-1-yl)propyl]-3-oxo-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide
467	(3Z)-1-benzyl-3-ethylidene-N-[3-(2-ethylpiperidin-1-yl)propyl]-2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazine-7-carboxamide
469	(3Z)-1-(cyclohexylmethyl)-3-ethylidene-N-[3-(2-ethylpiperidin-1-yl)propyl]-2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazine-7-carboxamide
471	(3Z)-1-(cyclohexylmethyl)-3-ethylidene-N-(3-piperidin-1-ylpropyl)-2-thioxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazine-7-carboxamide
473	(2Z)-4-(cyclohexylmethyl)-2-ethylidene-3-imino-N-(3-piperidin-1-ylpropyl)-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide
475	(2Z)-4-benzyl-2-ethylidene-3-imino-N-(3-piperidin-1-ylpropyl)-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide
477	(3Z)-3-ethylidene-4-(4-fluorobenzyl)-2-oxo-N-(3-piperidin-1-ylpropyl)-3,4-dihydro-2H-1,4-benzothiazine-7-carboxamide
479	(3Z)-3-ethylidene-4-(4-fluorobenzyl)-N-(3-piperidin-1-ylpropyl)-2-thioxo-3,4-dihydro-2H-1,4-benzoxazine-7-carboxamide
481	4-[4-(2-Fluoro-benzyl)-3-oxo-3,4-dihydro-2H-benzo[1,4]thiazin-2-ylmethyl]-N-(3-pyrrolidin-1-yl-propyl)-benzamide
483	(Z) 4-[4-(2-Fluoro-benzyl)-3-oxo-3,4-dihydro-benzo[1,4]oxazin-2-ylidenemethyl]-N-methyl-benzamide
485	(E) 4-[4-(2-Fluoro-benzyl)-3-oxo-3,4-dihydro-benzo[1,4]oxazin-2-ylidenemethyl]-N-methyl-benzamide
487	(Z) 4-[4-(2-Fluoro-benzyl)-3-oxo-3,4-dihydro-benzo[1,4]oxazin-2-ylideneamino]-N-methyl-benzamide
489	(E) 4-[4-(2-Fluoro-benzyl)-3-oxo-3,4-dihydro-benzo[1,4]oxazin-2-ylideneamino]-N-methyl-benzamide

ID	IUPAC
491	2-Benzyl-4-(4-fluoro-benzyl)-3-oxo-3,4-dihydro-pyrido[2,3-b]pyrazine-6-carboxylic acid (3-azepan-1-yl-propyl)-amide
493	7-Benzyl-5-(4-fluoro-benzyl)-6-oxo-5,6-dihydro-quinoline-3-carboxylic acid (3-azepan-1-yl-propyl)-amide
495	6-Benzyl-8-(4-fluoro-benzyl)-7-oxo-7,8-dihydro-pyrido[2,3-b]pyrazine-2-carboxylic acid (3-pyrrolidin-1-yl-propyl)-amide

ID	IUPAC
497	4-Oxo-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[a]naphthalene-7-carboxylic acid {3-[4-(5-chloro-2-methyl-phenyl)-piperazin-1-yl]-propyl}-amide
499	5-Benzyl-4-oxo-1,2,3,3a,4,5-hexahydro-pyrrolo[1,2-a]quinoxaline-7-carboxylic acid {3-

	[4-(5-chloro-2-methyl-phenyl)-piperazin-1-yl]-propyl}-amide
501	5-Benzyl-4-oxo-4,5-dihydro-furo[3,2-c]quinoline-7-carboxylic acid [3-(4-phenyl-piperazin-1-yl)-propyl]-amide
503	5-(2-Fluoro-benzyl)-4-thioxo-3,3a,4,5-tetrahydro-imidazo[1,5-a]quinoxaline-7-carboxylic acid [3-(4-phenyl-piperazin-1-yl)-propyl]-amide

ID	IUPAC
505	4-Oxo-4,5-dihydro-3aH-cyclopenta[a]naphthalene-7-carboxylic acid {3-[4-(5-chloro-2-methyl-phenyl)-piperazin-1-yl]-propyl}-amide
507	5-(2-Fluoro-benzyl)-2-methyl-4-thioxo-4,5-dihydro-3aH-cyclopenta[c]quinoline-7-carboxylic acid [3-(4-phenyl-piperazin-1-yl)-propyl]-amide
509	6-Benzyl-5-oxo-5,6-dihydro-pyrrolo[1,2-c]quinazoline-8-carboxylic acid [3-(4-phenyl-piperazin-1-yl)-propyl]-amide
511	5-Benzyl-4-oxo-4,5-dihydro-3aH-pyrrolo[3,2-c]quinoline-7-carboxylic acid {3-[4-(5-chloro-2-methyl-phenyl)-piperazin-1-yl]-propyl}-amide

ID	IUPAC
515	9-Oxo-4b,5,6,7,8,8a,9,10-octahydro-phenanthrene-2-carboxylic acid {3-[4-(5-chloro-2-methyl-phenyl)-piperazin-1-yl]-propyl}-amide
517	5-Benzyl-6-oxo-6,6a,7,8,9,10-hexahydro-5H-pyrido[1,2-a]quinoxaline-3-carboxylic acid {3-[4-(5-chloro-2-methyl-phenyl)-piperazin-1-yl]-propyl}-amide
519	5-Benzyl-6-oxo-5,6,7,8,9,10-hexahydro-phenanthridine-3-carboxylic acid [3-(4-phenyl-piperazin-1-yl)-propyl]-amide
521	5-(2-Fluoro-benzyl)-6-thioxo-6,8-dihydro-5H-pyrido[1,2-a]quinoxaline-3-carboxylic acid [3-(4-phenyl-piperazin-1-yl)-propyl]-amide

ID	IUPAC
525	9-Oxo-9,10-dihydro-phenanthrene-2-carboxylic acid {3-[4-(5-chloro-2-methyl-phenyl)-piperazin-1-yl]-propyl}-amide
527	5-(2-Fluoro-benzyl)-6-thioxo-5,6-dihydro-phenanthridine-3-carboxylic acid [3-(4-phenyl-piperazin-1-yl)-propyl]-amide
529	6-Benzyl-5-oxo-5,6-dihydro-benzo[c][2,6]naphthyridine-8-carboxylic acid [3-(4-phenyl-piperazin-1-yl)-propyl]-amide
531	5-Benzyl-6-oxo-5,6-dihydro-phenanthridine-3-carboxylic acid {3-[4-(5-chloro-2-methyl-phenyl)-piperazin-1-yl]-propyl}-amide

In another embodiment, a pharmaceutical composition comprising a compound having a structural formula (V) selected from the group consisting of:

ID	IUPAC
801	(Z) 4-[5-(2-Fluoro-benzyl)-4-oxo-4,5-dihydro-3H-benzo[b][1,4]thiazepin-2-ylidenemethyl]-N-(3-pyrrolidin-1-yl-propyl)-benzamide
803	(E) 4-[5-(2-Fluoro-benzyl)-4-oxo-4,5-dihydro-3H-benzo[b][1,4]thiazepin-2-ylidenemethyl]-N-(3-pyrrolidin-1-yl-propyl)-benzamide
805	(Z) 4-[5-(2-Fluoro-benzyl)-4-oxo-4,5-dihydro-3H-benzo[b][1,4]thiazepin-2-ylideneamino]-N-(3-pyrrolidin-1-yl-propyl)-benzamide
807	(E) 4-[5-(2-Fluoro-benzyl)-4-oxo-4,5-dihydro-3H-benzo[b][1,4]thiazepin-2-ylideneamino]-N-(3-pyrrolidin-1-yl-propyl)-benzamide

809	4-{2-[5-(2-Fluoro-benzyl)-4-oxo-2,3,4,5-tetrahydro-benzo[b][1,4]thiazepin-3-yl]-ethyl}-N-(3-pyrrolidin-1-yl-propyl)-benzamide

ID	IUPAC
811	2-Benzyl-5-(4-fluoro-benzyl)-3-methyl-4-oxo-4,5-dihydro-3H-benzo[b]azepine-7-carboxylic acid (3-pyrrolidin-1-yl-propyl)-amide
813	(E) 7-Benzylidene-5-(4-fluoro-benzyl)-6-oxo-6,7-dihydro-5H-pyrido[3,2-b]azepine-3-carboxylic acid (3-azepan-1-yl-propyl)-amide
815	2-Benzyl-5-(4-fluoro-benzyl)-4-oxo-4,5-dihydro-benzo[b][1,4]thiazepine-7-carboxylic acid (3-pyrrolidin-1-yl-propyl)-amide
817	3-Benzyl-1-(4-fluoro-benzyl)-5-methyl-2-oxo-2,5-dihydro-1H-pyrido[3,4-b][1,4]diazepine-8-carboxylic acid (3-azepan-1-yl-propyl)-amide

ID	IUPAC
1101	(7aS,10aS)-N-[2-(4-Benzylpiperidin-1-yl)ethyl]-5-(2-chloro-5-fluorobenzyl)-6-oxo-5,6,7,7a,8,9,10,10a-octahydrobenzo[b]cyclopenta[d]azepine-3-carboxamide
1103	(11bR)-7-Benzyl-N-[2-(4-benzylpiperidin-1-yl)ethyl]-6-oxo-2,3,5,6,7,11b-hexahydro-1H-pyrrolo[1,2-d][1,4]benzodiazepine-9-carboxamide
1105	(3aS)-N-[2-(4-Benzylpiperidin-1-yl)ethyl]-6-(3-fluorobenzyl)-5-oxo-3a,4,5,6-tetrahydro-3H-thieno[3,4-d][1]benzazepine-8-carboxamide
1107	(7aR)-N-[2-(4-Benzylpiperidin-1-yl)ethyl]-5-methyl-6-oxo-6,7,7a,8,9,10-hexahydro-5H-pyrrolo[1,2-a][1,5]benzodiazepine-3-carboxamide

ID	IUPAC
1121	6-(2-Chloro-5-fluorobenzyl)-5-oxo-N-[2-(4-phenylpiperazin-1-yl)ethyl]-5,6-dihydro-4H-thieno[2,3-d][1]benzazepine-8-carboxamide
1123	N-[2-(4-Benzylpiperidin-1-yl)ethyl]-6-(3-fluorobenzyl)-5-oxo-3,4,5,6-tetrahydro[1,2,3]triazolo[4,5-d][1]benzazepine-8-carboxamide
1125	6-(2-Chlorobenzyl)-N-[2-(4-cyclopenta-1,3-dien-1-ylpiperazin-1-yl)ethyl]-5-oxo-5,6-dihydro-4H-[1,3]oxazolo[5,4-d][1]benzazepine-8-carboxamide
1127	N-[2-(4-Cyclohexylpiperazin-1-yl)ethyl]-5-methyl-6-oxo-5,6,7,8-tetrahydrobenzo[b]cyclopenta[d]azepine-3-carboxamide

ID	IUPAC
1131	(7aS,11aS)-N-[2-(4-Benzylpiperidin-1-yl)ethyl]-5-(2-chloro-5-fluorobenzyl)-6-oxo-6,7,7a,8,9,10,11,11a-octahydro-5H-dibenzo[b,d]azepine-3-carboxamide
1133	(12aR)-N-[2-(4-Benzylpiperidin-1-yl)ethyl]-5-(3-fluorobenzyl)-6-oxo-5,6,7,9,10,11,12,12a-octahydropyrido[1,2-d][1,4]benzodiazepine-3-carboxamide
1135	(4aR)-N-[2-(4-Benzylpiperidin-1-yl)ethyl]-7-(2-chlorobenzyl)-6-oxo-3,4,4a,5,6,7-hexahydrothiopyrano[4,3-d][1]benzazepine-9-carboxamide
1137	(7aR)-N-[2-(4-Benzylpiperidin-1-yl)ethyl]-5-methyl-6-oxo-5,6,7,7a,8,9,10,11-octahydropyrido[1,2-a][1,5]benzodiazepine-3-carboxamide

ID	IUPAC
1141	5-(2-Chloro-5-fluorobenzyl)-6-oxo-N-[2-(4-phenylpiperazin-1-yl)ethyl]-6,7-dihydro-5H-dibenzo[b,d]azepine-3-carboxamide
1143	N-[2-(4-Benzylpiperidin-1-yl)ethyl]-7-(3-fluorobenzyl)-6-oxo-6,7-dihydro-5H-pyrido[3,2-d][1]benzazepine-9-carboxamide
1145	5-(2-Chlorobenzyl)-N-[2-(4-cyclopenta-1,3-dien-1-ylpiperazin-1-yl)ethyl]-6-oxo-6,7-dihydro-5H-pyrido[2,3-a][3]benzazepine-3-carboxamide

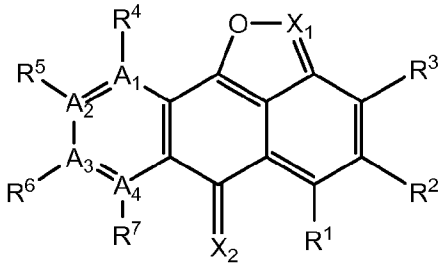
1147	N-[2-(4-Cyclohexylpiperazin-1-yl)ethyl]-7-methyl-6-oxo-6,7-dihydro-5H-pyrido[4,3-d][1]benzazepine-9-carboxamide

ID	IUPAC
1201	(3aS,10aS)-N-[2-(4-Benzylpiperidin-1-yl)ethyl]-9-(2-chloro-5-fluorobenzyl)-10-oxo-2,3,3a,9,10,10a-hexahydro-1H-benzo[b]cyclopenta[f][1,4]thiazepine-7-carboxamide
1203	(11aS)-N-[2-(4-Benzylpiperidin-1-yl)ethyl]-6-(2-chloro-5-fluorobenzyl)-5-oxo-1,2,3,5,6,11a-hexahydropyrrolo[2,1-b][1,3,5]benzothiadiazepine-8-carboxamide
1205	(10aR)-N-[2-(4-Benzylpiperidin-1-yl)ethyl]-9-(2-chloro-5-fluorobenzyl)-10-oxo-4,9,10,10a-tetrahydro-1H-thieno[3,4-b][1,5]benzodiazepine-7-carboxamide
1207	(11aR)-N-[2-(4-Benzylpiperidin-1-yl)ethyl]-10-methyl-5,11-dioxo-2,3,5,10,11,11a-hexahydro-1H-pyrrolo[2,1-c][1,4]benzodiazepine-8-carboxamide

ID	IUPAC
1215	9-(2-Chloro-5-fluorobenzyl)-10-oxo-N-[2-(4-phenylpiperazin-1-yl)ethyl]-9,10-dihydrothieno[3,2-b][1,5]benzothiazepine-7-carboxamide
1217	N-[2-(4-Benzylpiperidin-1-yl)ethyl]-9-(2-chloro-5-fluorobenzyl)-10-oxo-9,10-dihydro-1H-[1,2,3]triazolo[4,5-b][1,5]benzoxazepine-7-carboxamide
1219	9-(2-Chloro-5-fluorobenzyl)-N-[2-(4-cyclopenta-1,3-dien-1-ylpiperazin-1-yl)ethyl]-10-oxo-9,10-dihydro-4H-furo[3,2-b][1,5]benzodiazepine-7-carboxamide
1221	N-[2-(4-Cyclohexylpiperazin-1-yl)ethyl]-5-methyl-4,10-dioxo-3,4,5,10-tetrahydrobenzo[b]cyclopenta[e]azepine-7-carboxamide

ID	IUPAC
1225	(4aS,11aS)-N-[2-(4-Benzylpiperidin-1-yl)ethyl]-10-(2-chloro-5-fluorobenzyl)-11-oxo-1,2,3,4,4a,10,11,11a-octahydrodibenzo[b,f][1,4]thiazepine-8-carboxamide
1227	(11aS)-N-[2-(4-Benzylpiperidin-1-yl)ethyl]-5-(2-chloro-5-fluorobenzyl)-6-oxo-5,6,9,10,11,11a-hexahydro-8H-pyrido[2,1-b][1,3,5]benzothiadiazepine-3-carboxamide
1229	(4aR)-N-[2-(4-Benzylpiperidin-1-yl)ethyl]-6-(2-chloro-5-fluorobenzyl)-5-oxo-3,4,4a,5,6,11-hexahydrothiopyrano[3,4-b][1,5]benzodiazepine-8-carboxamide
1231	(6aR)-N-[2-(4-Benzylpiperidin-1-yl)ethyl]-5-methyl-6,12-dioxo-5,6,6a,7,8,9,10,12-octahydropyrido[2,1-c][1,4]benzodiazepine-3-carboxamide

In another aspect, the present invention provides a compound having a structural formula (VI):



(VI)

or a salt, solvate, ester, and/or prodrug thereof;
wherein:
X_1 is N, or CR^8;

X_2 is S, O, or NR^9;

A_1, A_2, A_3 and A_4 are independently C or N;

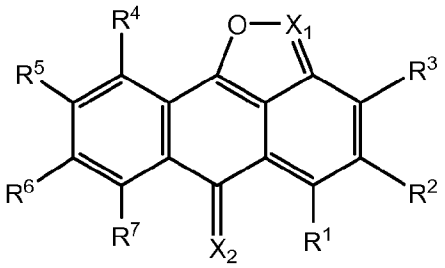
R^1, R^2, R^3, R^4, R^5, R^6, R^7, and R^8 are independently hydrogen, halogen, cyano, nitro, amino, substituted amino, sulfonyl, substituted sulfonyl, acyl, substituted acyl, alkoxycarbonyl, substituted alkoxycarbonyl, aryloxycarbonyl, substituted aryloxycarbonyl, $-CONR^{10}R^{11}$, $S(O)_2NR^{10}R^{11}$, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyl or substituted heteroalkyl or alternatively, R^1 and R^2, R^2 and R^3, R^4 and R^5, R^5 and R^6, or R^6 and R^7 taken together with the atoms to which they are bonded, form an aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroaryl or substituted heteroaryl ring;

With the proviso that when X_1 is N, or X_1 is CR^8 and R^8 is hydrogen or alkyl, R^1, R^2, R^3, R^4, R^5, R^6 and R^7 are not hydrogen, halogen, cyano, nitro, amino, substituted amino, sulfonyl, substituted sulfonyl, alkyl, substituted alkyl, acyl, substituted acyl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyl, or substituted heteroalkyl;

R^9, R^{10} and R^{11} are independently hydrogen alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyl, substituted heteroalkyl or alternatively R^{10} and R^{11} taken together to with the atoms to which they are bonded, form an aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroaryl or substituted heteroaryl ring.

In one embodiment of formula (VI), wherein A_1, A_2, A_3 and A_4 are C.

In one embodiment of formula (VI), the compound having a structure formula (VII):



(VII)

or a salt, solvate, ester, and/or prodrug thereof;

X_1 is N, or CR^8;

X_2 is S, O, or NR^9;

R^1, R^2, R^3, R^4, R^5, R^6, R^7, and R^8 are independently hydrogen, halogen, cyano, nitro, amino, substituted amino, sulfonyl, substituted sulfonyl, acyl, substituted acyl, alkoxycarbonyl, substituted alkoxycarbonyl, aryloxycarbonyl, substituted aryloxycarbonyl, $-CONR^{10}R^{11}$, $S(O)_2NR^{10}R^{11}$, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyl or substituted heteroalkyl or alternatively, R^1 and R^2, R^2 and R^3, R^4 and R^5, R^5 and R^6, or R^6 and R^7 taken together with the atoms to which they are bonded, form an aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroaryl or substituted heteroaryl ring;

With the proviso that when X_1 is N, or X_1 is CR^8 and R^8 is hydrogen or alkyl, R^1, R^2, R^3, R^4, R^5, R^6 and R^7 are not hydrogen, halogen, cyano, nitro, amino, substituted amino, sulfonyl, substituted sulfonyl, alkyl, substituted alkyl, acyl, substituted acyl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyl, or substituted heteroalkyl;

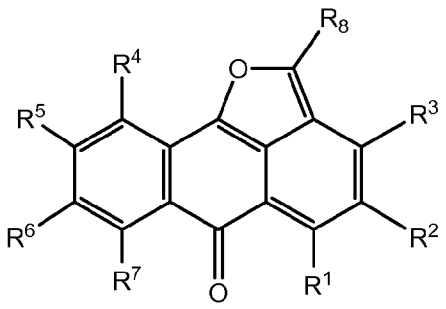
R^9, R^{10} and R^{11} are independently hydrogen alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyl, substituted heteroalkyl or alternatively R^{10} and R^{11} taken together to with the atoms to which they are bonded, form an aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroaryl or substituted heteroaryl ring.

In one embodiment of formula (VII), wherein X_2 is O.

In one embodiment of formula (VII), wherein X_1 is CR^8.

In one embodiment of formula (VII), wherein X_2 is O and X_1 is CR^8.

In one embodiment of formula (VII), the compound having a structure formula (VIII):



(VIII)

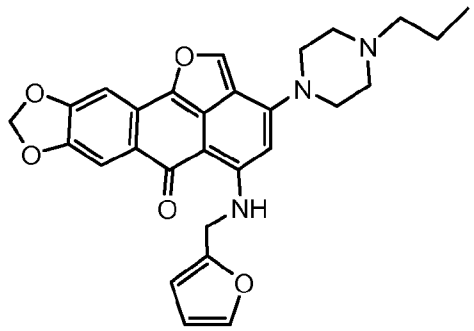
or a salt, solvate, ester, and/or prodrug thereof;

R^1, R^2, R^3, R^4, R^5, R^6, R^7, and R^8 are independently hydrogen, halogen, cyano, nitro, amino, substituted amino, sulfonyl, substituted sulfonyl, acyl, substituted acyl, alkoxycarbonyl, substituted alkoxycarbonyl, aryloxycarbonyl, substituted aryloxycarbonyl, $-CONR^{10}R^{11}$, $S(O)_2NR^{10}R^{11}$, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyl or substituted heteroalkyl or alternatively, R^1 and R^2, R^2 and R^3, R^4 and R^5, R^5 and R^6, or R^6 and R^7 taken together with the atoms to which they are bonded, form an aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroaryl or substituted heteroaryl ring;

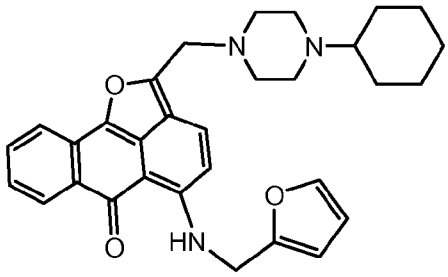
With the proviso that when R^8 is hydrogen or alkyl, R^1, R^2, R^3, R^4, R^5, R^6 and R^7 are not hydrogen, halogen, cyano, nitro, amino, sulfonyl, substituted sulfonyl, alkyl, substituted alkyl, acyl, substituted acyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyl, substituted heteroalkyl;

R^9, R^{10} and R^{11} are independently hydrogen alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyl, substituted heteroalkyl or alternatively R^{10} and R^{11} taken together to with the atoms to which they are bonded, form an aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroaryl or substituted heteroaryl ring.

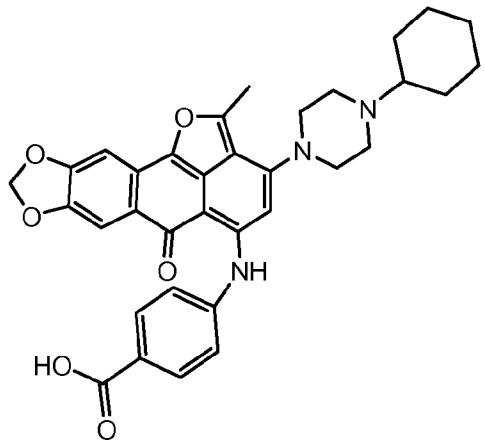
In one embodiment of formula (VIII), the compounds having the following structures:



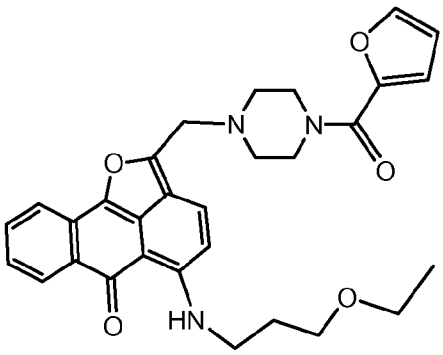
(11)



(13)



(15)

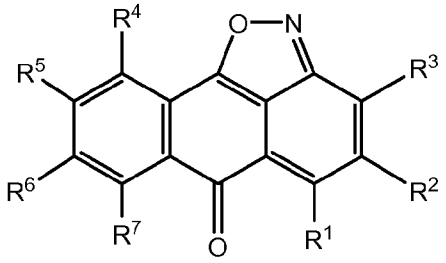


(17)

In one embodiment of formula (VII), wherein X_1 is N.

In one embodiment of formula (VII), wherein X_1 is N, X_2 is O.

In one embodiment of formula (VII), the compound having a structure formula (IX):



(IX)

or a salt, solvate, ester, and/or prodrug thereof;

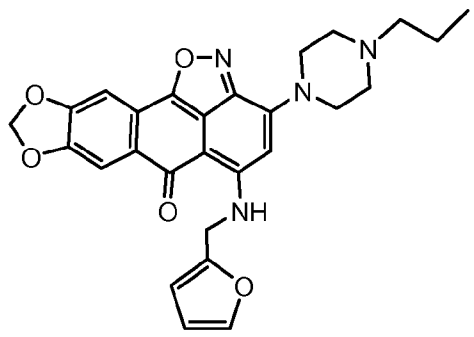
R^1, R^2, R^3, R^4, R^5, R^6, and R^7 are independently substituted amino, substituted sulfonyl, acyl, substituted acyl, alkoxycarbonyl, substituted alkoxycarbonyl, aryloxycarbonyl, substituted aryloxycarbonyl, -$CONR^{10}R^{11}$, -$SO_2NR^{10}R^{11}$, alkyl, substituted alkyl, aryl, substituted aryl, substituted heteroaryl, substituted heteroarylalkyl, heteroalkyl or substituted heteroalkyl or alternatively, R^1 and R^2, R^2 and R^3, R^4 and R^5, R^5 and R^6, or R^6 and R^7 taken together with the atoms to which they are bonded, form an aryl, substituted

aryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroaryl or substituted heteroaryl ring;

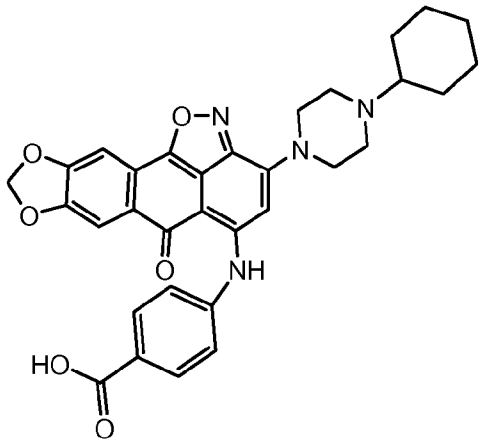
With the proviso that R^1, R^2, R^3, R^4, R^5, R^6 and R^7 are not hydrogen, halogen, cyano, nitro, amino, sulfonyl, acyl, substituted acyl, arylalkyl, substituted arylalkyl, heteroaryl, or heteroarylalkyl;

R^9, R^{10} and R^{11} are independently hydrogen alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyl, substituted heteroalkyl or alternatively R^{10} and R^{11} taken together to with the atoms to which they are bonded, form an aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroaryl or substituted heteroaryl ring.

In one embodiment of formula (IX), the compounds having the following structures:

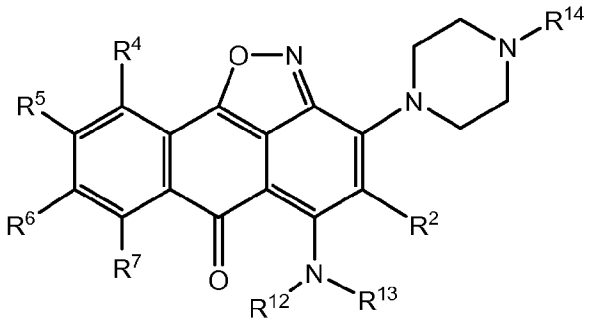


(41)



(43)

In one embodiment of formula (IX), the compound having a structure formula (X):



(X)

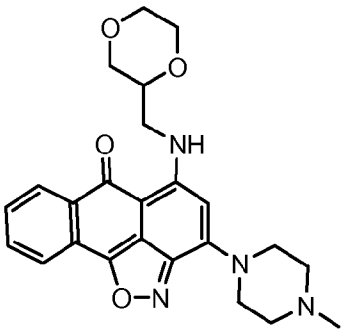
or a salt, solvate, ester, and/or prodrug thereof;

R^2, R^4, R^5, R^6, R^7, R^8, R^{12}, R^{13}, and R^{14} are independently hydrogen, halogen, cyano, nitro, amino, substituted amino, sulfonyl, substituted sulfonyl, acyl, substituted acyl, alkoxycarbonyl, substituted alkoxycarbonyl, aryloxycarbonyl, substituted aryloxycarbonyl, -$CONR^{10}R^{11}$, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyl or substituted heteroalkyl or alternatively, R^{12} and R^{13}, R^4 and R^5, R^5 and R^6, or R^6 and R^7 taken together with the atoms to which they are bonded, form an aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroaryl or substituted heteroaryl ring;

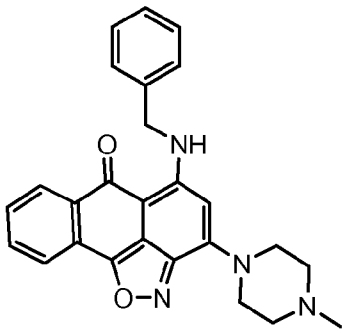
With the proviso that R^1, R^2, R^3, R^4, R^5, R^6 and R^7 are not hydrogen, halogen, cyano, nitro, amino, sulfonyl, substituted sulfonyl, alkyl, substituted alkyl, acyl, substituted acyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyl, substituted heteroalkyl, -$C(O)NR^{10}R^{11}$ or -$S(O)_2NR^{10}R^{11}$;

R^9, R^{10} and R^{11} are independently hydrogen alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyl, substituted heteroalkyl or alternatively R^{10} and R^{11} taken together to with the atoms to which they are bonded, form an aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroaryl or substituted heteroaryl ring.

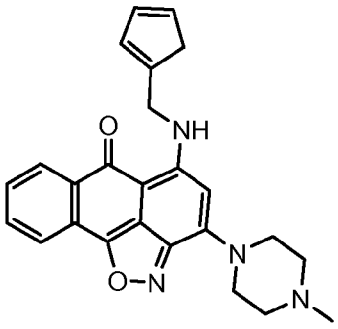
In one embodiment of formula (X), the compound o having the following structures:



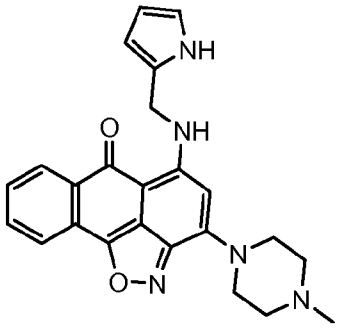
(1001)



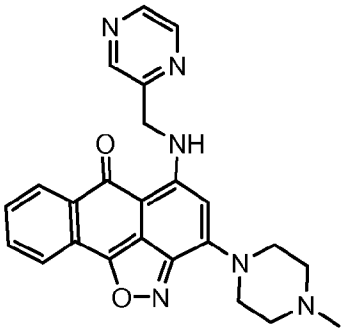
(1003)



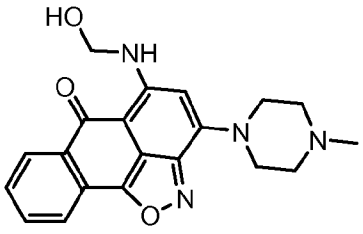
(1005)



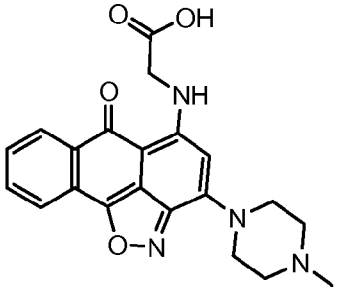
(1007)



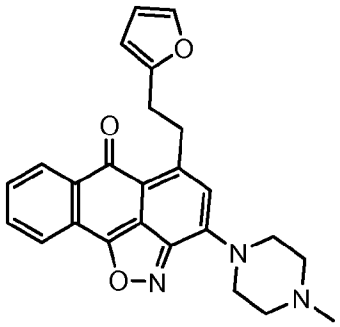
(1009)



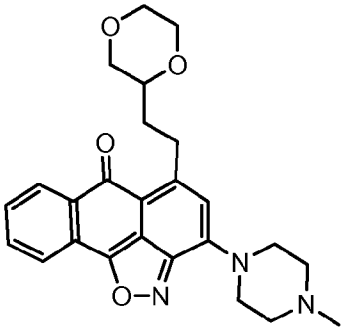
(1011)



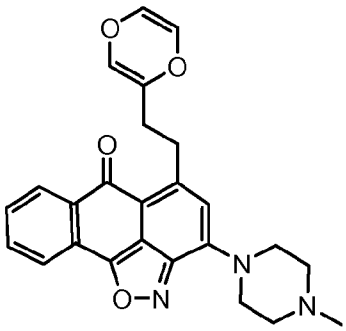
(1013)



(1015)

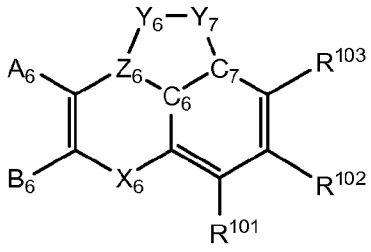


(1017)



(1019)

In another aspect, a pharmaceutical composition comprising a compound having a structural formula (XI):



(XI)

or a salt, solvate, ester, and/or prodrug thereof;

wherein:

R^{101}, R^{102} and R^{103} are independently hydrogen, halogen, cyano, nitro, amino, substituted amino, sulfonyl, substituted sulfonyl, acyl, substituted acyl, alkoxycarbonyl, substituted alkoxycarbonyl, aryloxycarbonyl, substituted aryloxycarbonyl, -$CONR^{104}R^{105}$, $S(O)_2NR^{104}R^{105}$, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyl or substituted heteroalkyl or alternatively, R^{101} and R^{102}, or R^{102} and R^{103} taken together with the atoms to which they are bonded, form an aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroaryl or substituted heteroaryl ring;

A_6 and B_6 are independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyl or substituted heteroalkyl or alternatively, A_6 and B_6, taken together with the atoms to which they are bonded, form an aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroaryl or substituted heteroaryl ring;

C_6, C_7 and Z_6 are independently C or N;

X_6, Y_6 and Y_7 are independently $N(R^{104})$, $C(R^{105}R^{106})$, CR^{107}, $C(=NR^{108})$, $NR^{109}R^{110}$, O, S, SO_2, C(=O), or C(=S);

R^{106}, R^{107} and R^{108} are independently hydrogen, alkyl, substituted alkyl, acyl, substituted acyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyl, substituted heteroalkyl, -$C(O)NR^{104}R^{105}$ or -$S(O)_2NR^{104}R^{105}$;

R^{104}, R^{105}, R^{109}, and R^{110} are independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyl or substituted heteroalkyl or

alternatively, R^{104} and R^{105}, or R^{109}, and R^{110} taken together with the atoms to which they are bonded, form a cycloheteroalkyl or substituted cycloheteroalkyl ring;

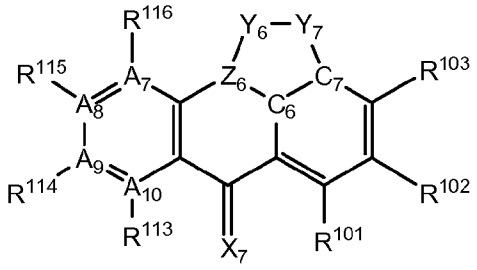
The bond between C_6 and C_7, C_7 and Y_6, Y_7 and Y_6, Y_6 and Z_6, or Z_6 and C_6 are independently selected to be a single bond or a double bond.

In one embodiment of formula (XI), wherein X_6 is $C(=X_7)$ and X_7 is S, O, or NR^{117}.

In one embodiment of formula (XI), wherein A_6 and B_6 form a substituted aryl ring or substituted heteroaryl ring.

In one embodiment of formula (XI), wherein X_6 is $C(=X_7)$ and A_6 and B_6 form a substituted aryl ring or substituted heteroaryl ring.

In one embodiment, a pharmaceutical composition comprising the compound of Formula (VI) having a structural Formula (XII):



(XII)

or a salt, solvate, ester, and/or prodrug thereof;

wherein:

X_7 is S, O, or NR^{117};

A_7, A_8, A_9 and A_{10} are independently C or N; and

R^{113}, R^{114}, R^{115}, R^{116} and R^{117} are independently hydrogen, halogen, cyano, nitro, amino, substituted amino, sulfonyl, substituted sulfonyl, alkyl, substituted alkyl, acyl, substituted acyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyl, substituted heteroalkyl, $-C(O)NR^{104}R^{105}$ or $-S(O)_2NR^{104}R^{105}$ or alternatively, R^{113} and R^{114}, R^{114} and R^{115}, or R^{115} and R^{116} taken together with the atoms to which they are bonded, form an

aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroaryl or substituted heteroaryl ring.

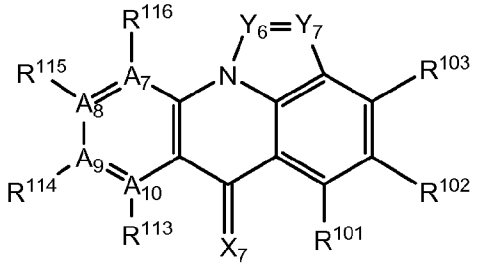
In one embodiment of formula (XII), wherein C_6 and C_7 are C.

In one embodiment of formula (XII), wherein Z_6 is N.

In one embodiment of formula (XII), wherein Y_7 is CR^7 or N.

In one embodiment of formula (XII), wherein C_6 and C_7 are C, Z_6 is N, the bond between C_6 and C_7 is a double bond, the bond between Y_6 and Y_7 is also a double bond.

In one embodiment of formula (XII), a pharmaceutical composition comprising the compound having a structural Formula (XIII):



(XIII)

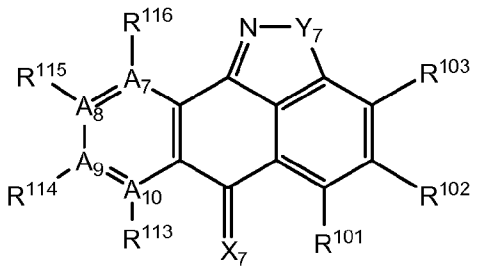
or a salt, solvate, ester, and/or prodrug thereof.

In one embodiment of formula (XIII), wherein Z_6 is C.

In one embodiment of formula (XIII), wherein Y_6 is N.

In one embodiment of formula (XIII), wherein C_6, C_7 and Z_6 are C, Y_6 is N, the bond between C_6 and C_7 is a double bond, the bond between Y_6 and Z_6 is also a double bond.

In one embodiment of formula (XIII), a pharmaceutical composition comprising the compound having a structural Formula (XIV):

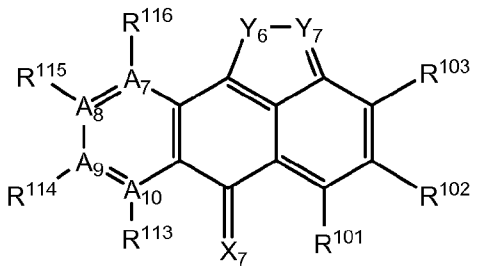


(XIV)

or a salt, solvate, ester, and/or prodrug thereof.

In one embodiment of formula (XIV), wherein C_6, C_7 and Z_6 are C, the bond between C_6 and Z_6 is a double bond, the bond between Y_7 and C_7 is also a double bond.

In one embodiment of formula (XIV), a pharmaceutical composition comprising the compound having a structural Formula (XV):



(XV)

or a salt, solvate, ester, and/or prodrug thereof.

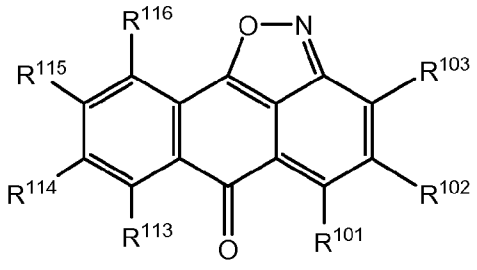
In one embodiment of formula (XV), wherein X_7 is O.

In one embodiment of formula (XV), wherein Y_6 is O and Y_7 is N.

In one embodiment of formula (XV), wherein X_7 is O, Y_6 is O and Y_7 is N.

In one embodiment of formula (XV), wherein A_6, A_7, A_8 and A_9 are C.

In one embodiment of formula (XV), a pharmaceutical composition comprising the compound having a structural Formula (XVI):



(XVI)

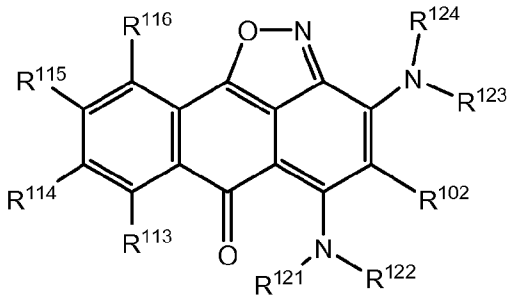
or a salt, solvate, ester, and/or prodrug thereof.

In one embodiment of formula (XVI), wherein R^{101} is $NR^{121}R^{122}$.

In one embodiment of formula (XVI), wherein R^{103} is $NR^{123}R^{124}$.

In one embodiment of formula (XVI), wherein R^{101} is $NR^{121}R^{122}$ and R^{103} is $NR^{123}R^{124}$.

In one embodiment of formula (XVI), a pharmaceutical composition comprising the compound having a structural Formula (XVII):



(XVII)

or a salt, solvate, ester, and/or prodrug thereof;

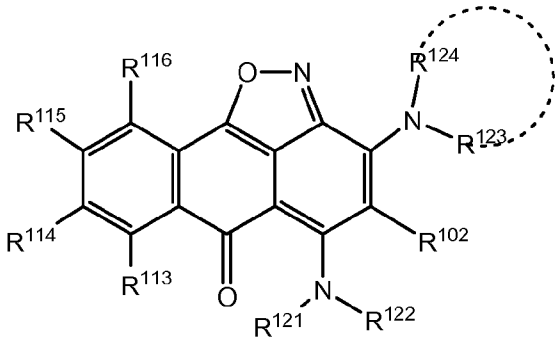
R^{121}, R^{122}, R^{123} and R^{124} are independently hydrogen, sulfonyl, substituted sulfonyl, acyl, substituted acyl, alkoxycarbonyl, substituted alkoxycarbonyl, aryloxycarbonyl, substituted aryloxycarbonyl, -$CONR^{104}R^{105}$, -$S(O)_2NR^{104}R^{105}$, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyl or substituted heteroalkyl or alternatively, R^{121} and R^{122}, or R^{123} and R^{124} taken together with the atoms to which they are bonded, form a cycloheteroalkyl, substituted cycloheteroalkyl, heteroaryl or substituted heteroaryl ring.

In one embodiment of formula (XVII), wherein R^{123} and R^{124} taken together with the atoms to which they are bonded, form a cycloheteroalkyl.

In one embodiment of formula (XVII), wherein R^{121} is hydrogen.

In one embodiment of formula (XVII), wherein R^{121} is hydrogen and R^{123} and R^{124} taken together with the atoms to which they are bonded, form a cycloheteroalkyl ring or substituted cycloheteroalkyl ring.

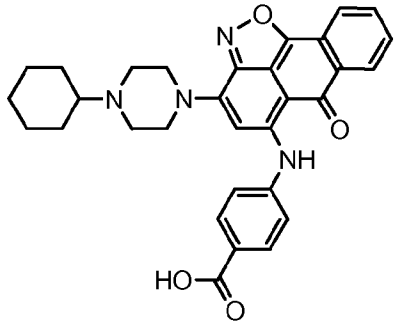
In one embodiment of formula (XVII), a pharmaceutical composition comprising the compound having a structural Formula (XVIII):



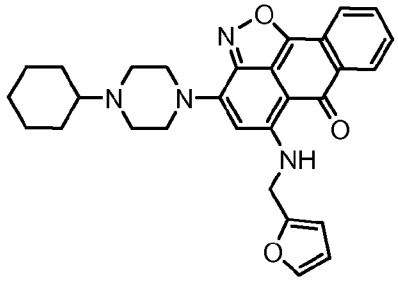
(XVIII)

or a salt, solvate, ester, and/or prodrug thereof.

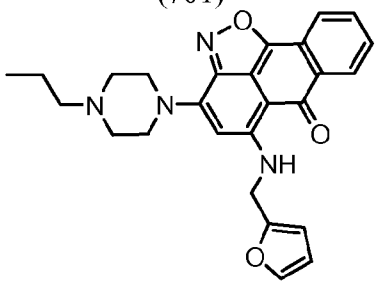
In one embodiment of formula (XVII), the compound having a structure selected from the group consisting of:



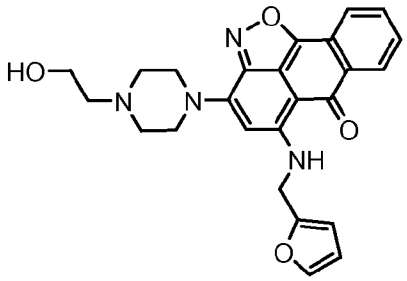
(701)



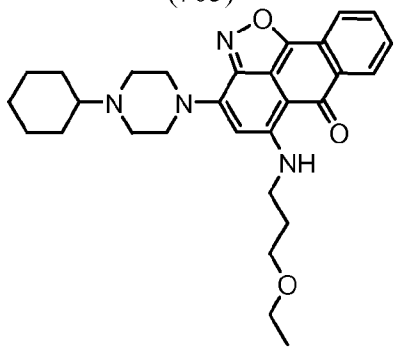
(703)



(705)



(707)



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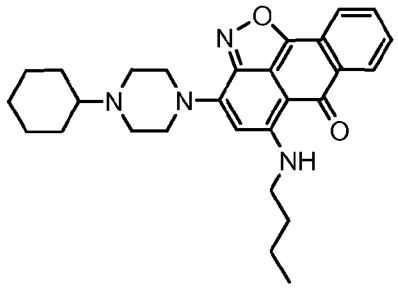
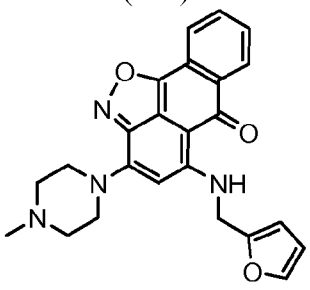
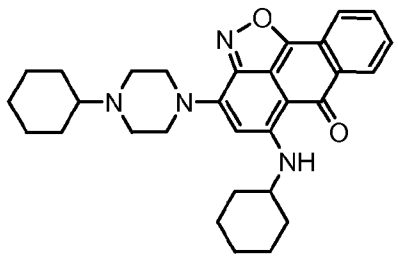


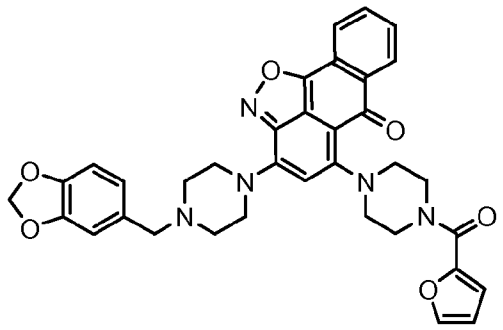
(711)



(713)



(715)



(717)

5.3 Synthesis of the Compounds

Several methods for preparing the compounds of this invention are illustrated in the following Schemes and Examples. Starting materials are made according to procedures known in the art or as illustrated herein. The following abbreviations are used herein: Me: methyl; Et: ethyl; t-Bu: tert-butyl; Ar: aryl; Ph: phenyl; Bn: benzyl; BuLi: butyllithium; Piv: pivaloyl; Ac: acetyl; THF: tetrahydrofuran; DMSO: dimethylsulfoxide; EDC: N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide; Boc: tert-butyloxy carbonyl; Et_3N: triethylamine; DCM: dichloromethane; DCE: dichloroethane; DME: dimethoxyethane; DBA: diethylamine; DAST: diethylaminosulfur trifluoride; EtMgBr: ethylamgnesium bromide; BSA: bovine serum albumin; TFA: trifluoracetic acid; DMF: N,N-dimethylformamide; $SOCl_2$: thionyl chloride; CDI: carbonyl diirnidazole; rt: room temperature; HPLC: high performance liquid chromatography; TLC: thin-layer chromatography. The compounds described herein may be prepared in a variety of ways known to one skilled in the art.

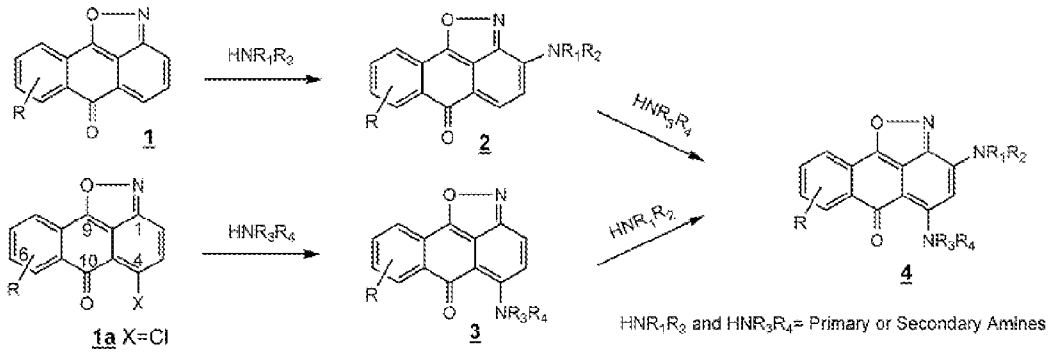
Some of the compounds described herein as pharmaceutical composition can be obtained from commercial sources, such as Aldrich Chemical Co. (Milwaukee, Wis.), Sigma Chemical Co. (St. Louis, Mo.), Maybridge (Cornwall, England), Asinex (Winston-Salem, NC), ChemBridge (San Diego, CA), ChemDiv (San Diego, CA), SPECS (Delft, The Netherlands), Timtec (Newark, DE) or can be synthesized. The compounds described herein and other related compounds having different substituents identified by

any of the methods described above can be synthesized using techniques and materials known to those of skill in the art, such as described, for example, in March, ADVANCED ORGANIC CHEMISTRY 4.sup.th Ed., (Wiley 1992); Carey and Sundberg, ADVANCED ORGANIC CHEMISTY 3.sup.rd Ed., Vols. A and B (Plenum 1992), and Green and Wuts, PROTECTIVE GROUPS IN ORGANIC SYNTHESIS 2.sup.nd Ed. (Wiley 1991). Starting materials useful for preparing compounds described herein or intermediates thereof are commercially available or can be prepared by well-known synthetic methods (see, e.g., Harrison et al., "Compendium of Synthetic Organic Methods", Vols. 1-8 (John Wiley and Sons, 1971-1996); "Beilstein Handbook of Organic Chemistry," Beilstein Institute of Organic Chemistry, Frankfurt, Germany; Feiser et al., "Reagents for Organic Synthesis," Volumes 1-21, Wiley Interscience; Trost et al., "Comprehensive Organic Synthesis," Pergamon Press, 1991; "Theilheimer's Synthetic Methods of Organic Chemistry," Volumes 1-45, Karger, 1991; March, "Advanced Organic Chemistry," Wiley Interscience, 1991; Larock "Comprehensive Organic Transformations," VCH Publishers, 1989; Paquette, "Encyclopedia of Reagents for Organic Synthesis," 3d Edition, John Wiley & Sons, 1995). Other methods for synthesis of the compounds described herein and/or starting materials are either described in the art or will be readily apparent to the skilled artisan. Alternatives to the reagents and/or protecting groups may be found in the references provided above and in other compendiums well known to the skilled artisan. Guidance for selecting suitable protecting groups can be found, for example, in Greene & Wuts, "Protective Groups in Organic Synthesis," Wiley Interscience, 1999. Accordingly, the synthetic methods and strategy presented herein are illustrative rather than comprehensive.

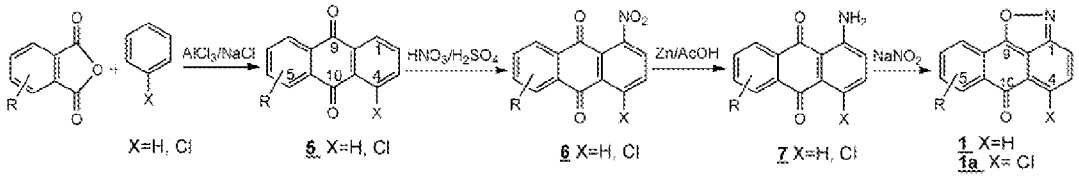
The procedures described herein for synthesizing the present compounds may include one or more steps of protection and deprotection (*e.g.*, the formation and removal of acetal groups). In addition, the synthetic procedures disclosed below can include various purifications, such as column chromatography, flash chromatography, thin-layer chromatography (TLC), recrystallization, distillation, high-pressure liquid chromatography (HPLC) and the like. Also, various techniques well known in the chemical arts for the identification and quantification of chemical reaction products, such as proton and carbon-13 nuclear magnetic resonance (^{1}H and ^{13}C NMR), infrared and

ultraviolet spectroscopy (IR and UV), X-ray crystallography, elemental analysis (EA), HPLC and mass spectroscopy (MS) can be used as well. Methods of protection and deprotection, purification and identification and quantification are well known in the chemical arts.

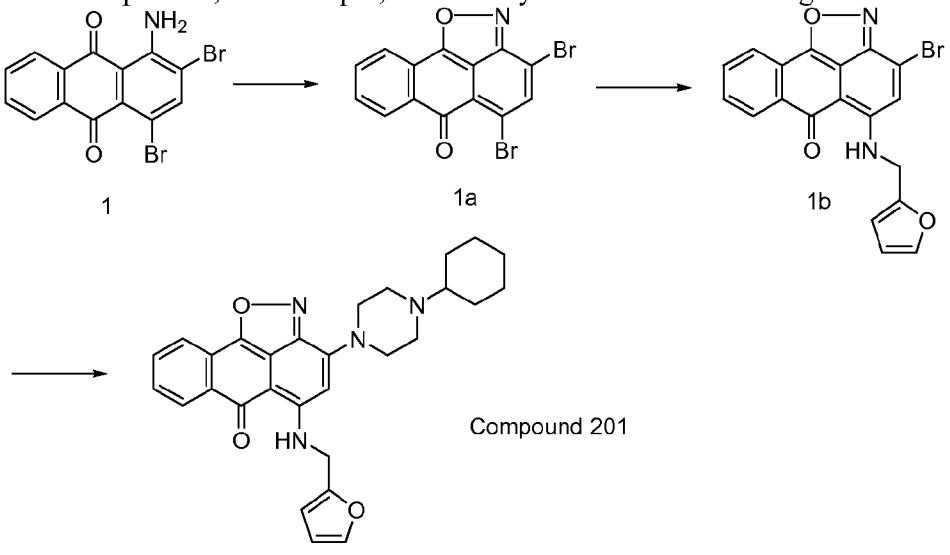
Examples of General Reaction Scheme for a compound having Formula of IX or X or XVI or XVII,

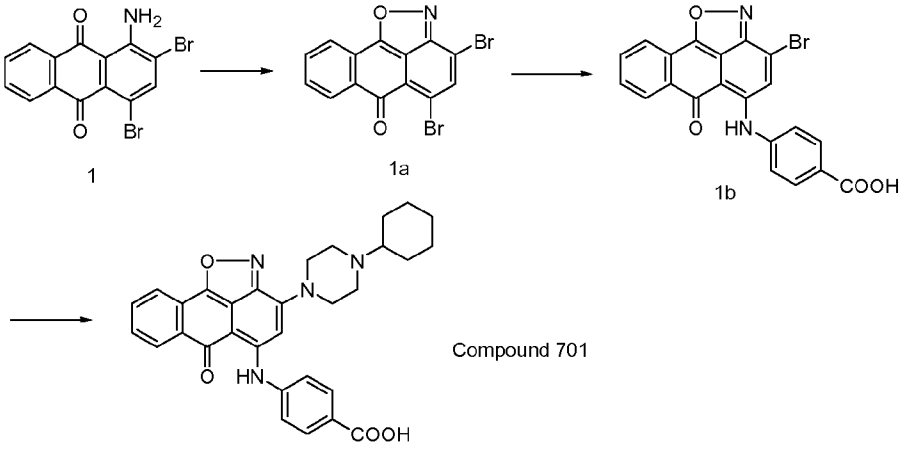


Synthesis of key intermediates, **1 and Ia.**



For specific compounds, for example, it can be synthesized as following scheme.





For the compound 201, the sythesis was carried out as: $NaNO_2$ (0.57 g, 8.3 mmol) was added to 5.2 mL concentrated H_2SO_4 at 30-40℃ over 20 minutes. The mixture was stirred for 30 minutes. Then 2.9 g compound 1 was added to the solution and the solution was stirred for 4 hours at 50-55℃. The resulting solution was poured into ice (50 g) and the yellow precipitate was filtered, washed with 50 mL ice-water, followed by 150 mL 1:1 mixture of ethanol-ether. The wet filter cake was added to a solution of NaN_3 (0.78 g, 12 mmol) in 100 mL of water and stirred for 30 minutes. The product was filtered, washed with 100 mL water, followed by 50 mL of a mixture (9:1) of acetone and water. The product was suspended in 30 mL toluene and heated to 70℃ for 8 hours. Then the suspension was filtered, washed with 50 mL of methanol and dried to give yellow solid. It was further purified and then confirmed by 1HNMR, MS and HPLC.

5.3 Biological Experiments

Also refer to drawing and drawing legends for examples of biological data.

Compound inhibition in a radiometric based assay: In a final reaction volume of 25 µL, TrkA (h) (3 nM) is incubated with the buffer (20 mM HEPES (pH 7.5), 10 mM MgCl2, 1 mM EGTA, 0.02% Brij 35, 0.02 mg/ml BSA, 0.1 mM Na3VO4, 2 mM DTT, 1% DMSO), 0.2 mg/ml substarte PolyEY(4:1) and 2 nM MnCl2, and [33P-ATP] (specific

activity approx. 500 cpm/pmol, concentration as required). The reaction is initiated by the addition of the MgATP mix. After incubation for at least 40 minutes at room temperature, the reaction is stopped by the addition of 5 μL of a 3% phosphoric acid solution. 10 μL of the reaction is then spotted onto a P30 filtermat and washed three times for 5 minutes in 75 mM phosphoric acid and once in methanol prior to drying and scintillation counting.

Kinase reaction buffer: 20 mM HEPES-HCl, pH 7.5, 10 mM $MgCl_2$, 1 mM EGTA, 0.02% Brij35, 0.1 mM Na_3VO_4, 0.02 mg/ml BSA, 2 mM DTT, and 1% DMSO.

Kinases: TRKA; Recombinant Human Cytoplasmic Domain (amino acids 441-796), Histidine-tagged, expressed in insect cells. Activated *in vitro* via auto-phosphorylation. Mw=42.8 kDa.

Substrates for kinases: poly(EY) for TRKA; poly(EY)(4:1) with 2 mM $MnCl_2$, average Mw=16 kDa

Standard conditions (unless otherwise specified): 30 nM TRKA, 0.2 mg/ml poly(EY) + 2 mM $MnCl_2$, and 10 μM ATP

Experimental Procedures:

A. Mode of inhibition (MOI) with respect to ATP

The kinase assays were performed at room temperature. Various concentrations of compounds (as below) were added into Enzyme/substrate mixture using acoustic technology, and incubated for 40 min to ensure all compounds were equilibrated and bound to the enzyme. Then various concentrations of ATP were added to initiate the reaction. The activity was monitored every 5-15 min for time course. ATP and compound concentrations tested were as follows:

ATP competition evaluation for TRKA

ATP concentrations tested: 10, 100, 200, 350, and 500 μM ATP with 0.2 mg/ml poly(EY)

Compound 701 concentrations tested: 0.037, 0.11, and 0.33 μM

Compound 201 concentrations tested: 0.11, and 0.33, and 1 μM

The "Mixed-Model Inhibition" equation for global fit:

$$v = \frac{V_{max}.[S]}{K_m\left(1+\frac{[I]}{K_i}\right)+\left(1+\frac{[I]}{K_i'}\right)[S]} \quad (1)$$

Where v is velocity, [S] is substrate (ATP) concentration, [I] is inhibitor concentration, Ki is inhibitor affinity for enzyme, and Ki' (=alpha*Ki) is inhibitor affinity for enzyme/ATP complex. When Ki = Ki', i.e. alpha = 1, the inhibitor doses not alter binding of substrate to the enzyme, it is identical to noncompetitive inhibition. When alpha is very large, binding of inhibitor prevents binding of the substarte and it is competitive inhibition. When alpha is very small, binding of the inhibitor enhances substarte binding to the enzyme, and it is uncompetitive model.

See FIGURE-5, as an example for Compound 701 mode of inhibition with respect to ATP, where alphas = 5, suggests Compound 701 is not a pure ATP competitive inhibitor for TrkA.

B. Mode of inhibition (MOI) with respect to substrate

The kinase assays were performed similar manner to ATP study. Various concentrations of compounds (same as ATP study) were added into Enzyme/substrate mixture using acoustic technology, and incubated for 40 min to ensure all compounds were equilibrated and bound to the enzyme. Then 10 μM ATP was added to initiate the reaction. The activity was monitored every 5-15 min for time course. Substrate and compound concentrations tested were as follows:

Substrate competition evaluation for TRKA

Substrate concentrations tested: 0.02, 0.05, 0.1, 0.2, and 0.5 mg/ml poly(EY) with 10 μM ATP.

Compound 701 concentrations tested: 0.037, 0.11, and 0.33 μM

Compound 201 concentrations tested: 0.11, and 0.33, and 1 μM

See FIGURE-6, as an example for Compound 701 mode of inhibition with respect to substare PolyEY pepetive, where alphas = 065, suggests Compound 701 is noncompetitive inhibitor for TrkA with respect to PolyEY pepetite substrate.

C. Determination of whether the enzyme inhibition is caused by compound aggregation.

To test the possibility whether the enzyme inhibition is caused by compound aggregation, two concentrations of two detergents (TX-100 and Nrij35) in the reaction were tested.

Triton X-100 increased TRKA control activity; 1.5-fold in the presence of 0.02% TX-100 (Table-2A). Table-2B shows % Enzyme activities relative to corresponding DMSO controls. Both compounds showed comparable inhibition in the presence of Triton X-100 and Brij35. These results suggest the inhibition was not caused by aggregation of compounds:

Table -2A. Detergent effects on TRKA activity

Raw data were obtained at 10 μM ATP and 0.2 mg/ml polyEY peptide substrate

	0.02% Brij35	0.02% TX-100
Average DMSO Ctrl	3584708	5454507

Table-2B. Detergent effects on compound inhibition of TRKA activity

The data were expressed as % enzyme activity using above activity (Table-2A) in each condition as 100% activity. Each compound concentration was in duplicate.

701 (M)	**0.02% Brij35**	**0.02% TX-100**
1.60E-07	32.43	29.77
1.60E-07	35.64	28.63
4.00E-08	75.08	75.75
4.00E-08	75.83	75.00
1.00E-08	94.73	90.44
1.00E-08	91.54	88.15
201 (M)	**0.02% Brij35**	**0.02% TX-100**
1.00E-06	42.17	36.02
1.00E-06	40.25	37.25
3.33E-07	65.59	61.71
3.33E-07	70.34	63.65

1.11E-07	85.65	82.20
1.11E-07	84.40	81.33

Rat Formalin Paw Test (in Vivo Assay):

Compounds were assessed for their ability to inhibit the behavioral response evoked by an injection of formalin (50µl of 5% formalin). A metal band was affixed to the left hind paw of male Holtzman rats (225-250 g, Harlan Industries, Indianapolis IN) and each rat was conditioned to the band for 60 min within a plastic cylinder (15 cm diameter). Rats were dosed with either vehicle, positive control compound or a test compound either before (local) or after (systemic) formalin challenge. For local administration, compounds were prepared in either a 10:7.5 vehicle of saline (in mL) and (D)- or (L)-Tartaric acid (in mg), or a 1:1:6 vehicle of DMA (N,N-Dimethylacetamide), Tween 80 and saline, and injected intraperitoneally into the dorsal surface of the right hind paw of the rat 60 min prior to formalin. The number of flinches was counted continuously for 60 min using an automated nociception analyzer (UCSD Anesthesiology Research, San Diego, Calif.). Statistical significance was determined by comparing the total flinches detected in the early (0-10 min, Phase I) and late (11-60 min) phase with an unpaired t-test. Here the drug Ethosiximide, a known weak T-type calcium ion channels antagonist, was used as a positive control compound (Gogas. K. R., et al. "Effects of the T-type calcium channel blocker, Elhosuximide in rodent models of acute and chronic pain", Abstract. IASP 10th World Congress on Pain. San Diego. CA 2002).

5.4 Therapeutic Uses

In accordance with the present invention, a compound of the present invention, or a salt, solvate, ester, and/or a prodrug thereof, or a pharmaceutical composition containing the compound, or a salt, solvate, ester, and/or a prodrug thereof, is administered to a patient, preferably a human, suffering from a variety of disorders. These include cancers, anxiety, generalized pain disorder, acute pain, chronic pain, inflammatory pain and neuropathic pain.

While the invention has been described and illustrated with reference to certain preferred embodiments, those skilled in the art will appreciate that various changes, modifications and substitutions can be made therein without departing from the spirit and scope of the invention.

5.5 Therapeutic/Prophylactic Administration

The present compounds, or salts, solvates, esters, and/or prodrugs thereof, or pharmaceutical compositions containing the present compounds, or salts, solvates, esters, and/or prodrugs thereof, may be advantageously used in human medicine. As previously described in Section 6.4 above, the present compounds are useful for the treatment or prevention of various diseases.

When used to treat or prevent the above-mentioned diseases or disorders, the present compounds may be administered or applied solely, or in combination with other active agents (*e.g.*, other pain agents).

The present invention provides methods of treatment and prophylaxis by administration to a patient in need of such treatment a therapeutically effective amount of one or more compounds of the present invention, or salts, solvates, esters, and/or prodrugs thereof. The patient may be an animal, more preferably, a mammal and most preferably, a human.

The present compounds, or salts, solvates, esters, and/or prodrugs thereof, may be administered orally. The present compounds, or salts, solvates, esters, and/or prodrugs thereof, may also be administered by any other convenient route, for example, by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (*e.g.*, oral mucosa, rectal and intestinal mucosa, *etc.*). Administration can be systemic or local. Various delivery systems are known, (*e.g.*, encapsulation in liposomes, microparticles, microcapsules, capsules, *etc.*) that can be used to administer a compound and/or pharmaceutical composition thereof. Methods of administration include, but are not limited to, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, oral, sublingual, intranasal, intracerebral, intravaginal, transdermal, rectally, by inhalation, or topically, particularly to the ears, nose, eyes, or skin. The preferred mode of administration is left to the discretion of the practitioner and will

depend in-part upon the site of the medical condition. In most instances, administration will result in the release of the present compounds, or salts, solvates, esters, and/or prodrugs thereof, into the bloodstream of a patient.

In specific embodiments, it may be desirable to administer one or more of the present compounds, or salts, solvates, esters, and/or prodrugs thereof, locally to the area in need of treatment. This may be achieved, for example, and not by way of limitation, by local infusion during surgery, topical application, *e.g.*, in conjunction with a wound dressing after surgery, by injection, by means of a catheter, by means of a suppository, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers. In some embodiments, administration can be accomplished by direct injection at the site (or former site) of cancer or arthritis.

In certain embodiments, it may be desirable to introduce one or more the present compounds, or salts, solvates, esters, and/or prodrugs thereof, into the central nervous system of a patient by any suitable route, including intraventricular, intrathecal and epidural injection. Intraventricular injection may be facilitated by an intraventricular catheter, for example, attached to a reservoir, such as an Ommaya reservoir.

The present compounds, or salts, solvates, esters, and/or prodrugs thereof, may also be administered directly to the lung by inhalation. For administration by inhalation, the present compounds, or salts, solvates, esters, and/or prodrugs thereof, may be conveniently delivered to the lung by a number of different devices. For example, a Metered Dose Inhaler ("MDI"), which utilizes canisters that contain a suitable low boiling propellant, (*e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or any other suitable gas), may be used to deliver compounds of the invention directly to the lung.

Alternatively, a Dry Powder Inhaler ("DPI") device may be used to administer the present compounds, or salts, solvates, esters, and/or prodrugs thereof, to the lung. DPI devices typically use a mechanism such as a burst of gas to create a cloud of dry powder inside a container, which may then be inhaled by the patient. DPI devices are also well known in the art. A popular variation is the multiple dose DPI ("MDDPI") system, which allows for the delivery of more than one therapeutic dose. For example, capsules

and cartridges of gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch for these systems.

Another type of device that may be used to deliver the present compounds, or salts, solvates, esters, and/or prodrugs thereof, to the lung is a liquid spray device supplied, for example, by Aradigm Corporation, Hayward, CA. Liquid spray systems use extremely small nozzle holes to aerosolize liquid drug formulations that may then be directly inhaled into the lung.

In some embodiments, a nebulizer is used to deliver the present compounds, or salts, solvates, esters, and/or prodrugs thereof, to the lung. Nebulizers create aerosols from liquid drug formulations by using, for example, ultrasonic energy to form fine particles that may be readily inhaled (see *e.g.*, Verschoyle *et al.*, *British J. Cancer*, 1999, 80, Suppl. 2, 96. Nebulizers are available from a number of commericial sources such as Sheffield/Systemic Pulmonary Delivery Ltd. Aventis and Batelle Pulmonary Therapeutics.

In other embodimenst, an electrohydrodynamic ("EHD") aerosol device is used to deliver the present compounds, or salts, solvates, esters, and/or prodrugs thereof, to the lung. EHD aerosol devices use electrical energy to aerosolize liquid drug solutions or suspensions (see *e.g.*, Noakes *et al.*, United States Patent No. 4,765,539). The electrochemical properties of the formulation may be important parameters to optimize when delivering the present compounds, or salts, solvates, esters, and/or prodrugs thereof, to the lung with an EHD aerosol device and such optimization is routinely performed by one of skill in the art. EHD aerosol devices may more efficiently deliver drugs to the lung than existing pulmonary delivery technologies.

In other embodiments, the present compounds, or salts, solvates, esters, and/or prodrugs thereof, can be delivered in a vesicle, in particular a liposome (See, Langer, **1990**, *Science*, 249:1527-1533; Treat *et al.*, in "Liposomes in the Therapy of Infectious Disease and Cancer," Lopez-Berestein and Fidler (eds.), Liss, New York, pp.353-365 (1989); *see* generally "Liposomes in the Therapy of Infectious Disease and Cancer," Lopez-Berestein and Fidler (eds.), Liss, New York, pp.353-365 (1989)).

In other embodiments, the present compounds, or salts, solvates, esters, and/or prodrugs thereof, can be delivered *via* sustained release systems. In still other embodiments, the sustained release system is an oral sustained release systems. In still other embodiments, a pump may be used (See, Langer, *supra*; Sefton, **1987**, *CRC Crit Ref Biomed Eng.* 14:201; Saudek *et al.*, **1989**, *N. Engl. J Med.* 321:574).

In still other embodiments, polymeric materials can be used in the pharmaceutical compositions containing the present compounds, or salts, solvates, esters, and/or prodrugs thereof. (for exemplary polymeric materials, *see* "Medical Applications of Controlled Release," Langer and Wise (eds.), CRC Pres., Boca Raton, Florida (1974); "Controlled Drug Bioavailability," Drug Product Design and Performance, Smolen and Ball (eds.), Wiley, New York (1984); Ranger and Peppas, **1983**, *J Macromol. Sci. Rev. Macromol Chem.* 23:61; *see also* Levy *et al.*, **1985**, *Science* 228: 190; During *et al.*, **1989**, *Ann. Neurol.* 25:351; Howard *et al.*, **1989**, *J. Neurosurg.* 71:105). In still other embodiments, polymeric materials are used for sustained release delivery of oral pharmaceutical compositions. Exemplary polymers include, but are not limited to, sodium carboxymethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose and hydroxyethylcellulose (most preferred, hydroxypropyl methylcellulose). Other cellulose ethers have been described (Alderman, *Int. J. Pharm. Tech. & Prod. Mfr.*, **1984**, 5(3) 1-9). Factors affecting drug release are well known to the skilled artisan and have been described in the art (Bamba *et al.*, *Int. J. Pharm.*, **1979**, 2, 307).

In other embodiments, enteric-coated preparations can be used for oral sustained release administration. Coating materials include, but are not limited to, polymers with a pH-dependent solubility (*i.e.*, pH-controlled release), polymers with a slow or pH-dependent rate of swelling, dissolution or erosion (*i.e.*, time-controlled release), polymers that are degraded by enzymes (*i.e.*, enzyme-controlled release) and polymers that form firm layers that are destroyed by an increase in pressure (*i.e.*, pressure-controlled release).

In still other embodiments, osmotic delivery systems are used for oral sustained release administration (Verma *et al.*, *Drug Dev. Ind. Pharm.*, **2000**, 26:695-708). In still other embodiments, OROS^{TM} osmotic devices are used for oral sustained release delivery devices (Theeuwes *et al.*, United States Patent No. 3,845,770; Theeuwes *et al.*, United States Patent No. 3,916,899).

In still other embodiments, a controlled-release system can be placed in proximity of the target of the present compounds, or salts, solvates, esters, and/or prodrugs thereof, thus requiring only a fraction of the systemic dose (See, *e.g.*, Goodson, in "Medical Applications of Controlled Release," *supra,* vol. 2, pp. 115-138 (1984)). Other controlled-release systems discussed in Langer, **1990**, *Science* 249:1527-1533 may also be used.

5.6 Pharmaceutical Compositions of the Invention

In one aspect, the present invention provides pharmaceutical compositions comprising one or more compounds of the present invention including the compound having structural formula (I) to (XVIII) and any of their subgeneric groups and specific embodiments described above in Section 5.2.

The present pharmaceutical compositions contain a therapeutically effective amount of one or more compounds of the present invention, or salts, solvates, esters, and/or prodrugs thereof, preferably in purified form, together with a suitable amount of a pharmaceutically acceptable vehicle, so as to provide a form for proper administration to a patient. When administered to a patient, the present compounds and the pharmaceutically acceptable vehicles are preferably sterile. Water is a preferred vehicle when a compound is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid vehicles, particularly for injectable solutions. Suitable pharmaceutical vehicles also include excipients such as starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The present pharmaceutical compositions, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. In addition, auxiliary, stabilizing, thickening, lubricating and coloring agents may be used.

Pharmaceutical compositions may be manufactured by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes. Pharmaceutical compositions may be formulated in conventional manner using one or more physiologically acceptable carriers, diluents,

excipients or auxiliaries, which facilitate processing of compounds of the invention into preparations that can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen.

The present pharmaceutical compositions can take the form of solutions, suspensions, emulsion, tablets, pills, pellets, capsules, capsules containing liquids, powders, sustained-release formulations, suppositories, emulsions, aerosols, sprays, suspensions, or any other form suitable for use. In some embodiments, the pharmaceutically acceptable vehicle is a capsule (see *e.g.*, Grosswald *et al.*, United States Patent No. 5,698,155). Other examples of suitable pharmaceutical vehicles have been described in the art (see Remington: The Science and Practice of Pharmacy, Philadelphia College of Pharmacy and Science, 20th Edition, 2000).

For topical administration a compound may be formulated as solutions, gels, ointments, creams, suspensions, *etc.* as is well-known in the art.

Systemic formulations include those designed for administration by injection, *e.g.*, subcutaneous, intravenous, intramuscular, intrathecal or intraperitoneal injection, as well as those designed for transdermal, transmucosal, oral or pulmonary administration. Systemic formulations may be made in combination with a further active agent such as another anti-cancer agent.

In some embodiments, the present compounds, or salts, solvates, esters, and/or prodrugs thereof, are formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous administration to human beings. Typically, compounds for intravenous administration are solutions in sterile isotonic aqueous buffer. For injection, the present compounds, or salts, solvates, esters, and/or prodrugs thereof, may be formulated in aqueous solutions, preferably, in physiologically compatible buffers such as Hanks' solution, Ringer's solution, or physiological saline buffer. The solution may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. When necessary, the pharmaceutical compositions may also include a solubilizing agent. Pharmaceutical compositions for intravenous administration may optionally include a local anesthetic such as lignocaine to ease pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a lyophilized powder or water free concentrate in a

hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. When the present compounds, or salts, solvates, esters, and/or prodrugs thereof, are administered by infusion, it can be dispensed, for example, with an infusion bottle containing sterile pharmaceutical grade water or saline. When the present compounds, or salts, solvates, esters, and/or prodrugs thereof, are administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

Pharmaceutical compositions for oral delivery may be in the form of tablets, lozenges, aqueous or oily suspensions, granules, powders, emulsions, capsules, syrups, or elixirs, for example. Orally administered pharmaceutical compositions may contain one or more optional agents, for example, sweetening agents such as fructose, aspartame or saccharin; flavoring agents such as peppermint, oil of wintergreen, or cherry coloring agents and preserving agents, to provide a pharmaceutically palatable preparation. Moreover, in tablet or pill form, the compositions may be coated to delay disintegration and absorption in the gastrointestinal tract, thereby providing a sustained action over an extended period of time. Selectively permeable membranes surrounding an osmotically active driving compound are also suitable for orally administered compounds of the invention. In these later platforms, fluid from the environment surrounding the capsule is imbibed by the driving compound, which swells to displace the agent or agent composition through an aperture. These delivery platforms can provide an essentially zero order delivery profile as opposed to the spiked profiles of immediate release formulations. A time delay material such as glycerol monostearate or glycerol stearate may also be used. Oral compositions can include standard vehicles such as mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, *etc.* Such vehicles are preferably of pharmaceutical grade.

For oral liquid preparations such as, for example, suspensions, elixirs and solutions, suitable carriers, excipients or diluents include water, saline, alkyleneglycols (*e.g.*, propylene glycol), polyalkylene glycols (*e.g.*, polyethylene glycol) oils, alcohols, slightly acidic buffers between pH 4 and pH 6 (*e.g.*, acetate, citrate, ascorbate at between

about 5.0 mM to about 50.0 mM) *etc.* Additionally, flavoring agents, preservatives, coloring agents, bile salts, acylcarnitines and the like may be added.

For buccal administration, the pharmaceutical compositions may take the form of tablets, lozenges, *etc.* formulated in conventional manner.

Liquid drug formulations suitable for use with nebulizers and liquid spray devices and EHD aerosol devices will typically include a compound of the invention with a pharmaceutically acceptable vehicle. In some embodiments, the pharmaceutically acceptable vehicle is a liquid such as alcohol, water, polyethylene glycol or a perfluorocarbon. Optionally, another material may be added to alter the aerosol properties of the solution or suspension of compounds disclosed herein. Preferably, this material is liquid such as an alcohol, glycol, polyglycol or a fatty acid. Other methods of formulating liquid drug solutions or suspension suitable for use in aerosol devices are known to those of skill in the art (see, *e.g.*, Biesalski, United States Patent No. 5,112,598; Biesalski, United States Patent No. 5,556,611).

The present compounds, or salts, solvates, esters, and/or prodrugs thereof, may also be formulated in rectal or vaginal pharmaceutical compositions such as suppositories or retention enemas, *e.g.*, containing conventional suppository bases such as cocoa butter or other glycerides.

In addition to the formulations described previously, the present compounds, or salts, solvates, esters, and/or prodrugs thereof, may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example, subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the present compounds, or salts, solvates, esters, and/or prodrugs thereof, may be formulated with suitable polymeric or hydrophobic materials (for example, as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

5.7 Therapeutic Doses

The present compounds, or a salt, prodrug or softdrug, salt of prodrug or softdrug, solvate or hydrate thereof and a pharmaceutically acceptable vehicle is provided, will

generally be used in an amount effective to achieve the intended purpose. For use to treat or prevent diseases or disorders characterized by down regulated apoptosis the compounds and/or pharmaceutical compositions thereof, are administered or applied in a therapeutically effective amount.

The amount of the present compounds, or salts, solvates, esters, and/or prodrugs thereof, that will be effective in the treatment of a particular disorder or condition disclosed herein will depend on the nature of the disorder or condition, and can be determined by standard clinical techniques known in the art. In addition, *in vitro* or *in vivo* assays may optionally be employed to help identify optimal dosage ranges. The amount of the present compounds, or salts, solvates, esters, and/or prodrugs thereof, administered will, of course, be dependent on, among other factors, the subject being treated, the weight of the subject, the severity of the affliction, the manner of administration and the judgment of the prescribing physician.

For example, the dosage may be delivered in a pharmaceutical composition by a single administration, by multiple applications or controlled release. In some embodiment, the present compounds, or salts, solvates, esters, and/or prodrugs thereof, are delivered by oral sustained release administration. Dosing may be repeated intermittently, may be provided alone or in combination with other drugs and may continue as long as required for effective treatment of the disease state or disorder. Suitable dosage ranges for oral administration depend on the potency of the present compounds, but are generally between about 0.001 mg to about 200 mg of a compound of the invention per kilogram body weight. Dosage ranges may be readily determined by methods known to the artisan of ordinary skill.

Suitable dosage ranges for intravenous (i.v.) administration are about 0.01 mg to about 100 mg per kilogram body weight. Suitable dosage ranges for intranasal administration are generally about 0.01 mg/kg body weight to about 1 mg/kg body weight. Suppositories generally contain about 0.01 milligram to about 50 milligrams of a compound of the invention per kilogram body weight and comprise active ingredient in the range of about 0.5% to about 10% by weight. Recommended dosages for intradermal, intramuscular, intraperitoneal, subcutaneous, epidural, sublingual or intracerebral administration are in the range of about 0.001 mg to about 200 mg per

kilogram of body weight. Effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal model test systems. Such animal models and systems are well-known in the art.

The present compounds, or salts, solvates, esters, and/or prodrugs thereof, are preferably assayed *in vitro* and *in vivo,* for the desired therapeutic or prophylactic activity, prior to use in humans. For example, *in vitro* assays can be used to determine whether administration of a specific compound of the invention or a combination of compounds is preferred for inducing apoptosis in cells which over-express bcl-2 proteins. The present compounds, or salts, solvates, esters, and/or prodrugs thereof, may also be demonstrated to be effective and safe using animal model systems.

Preferably, a therapeutically effective dose of the present compounds, or salts, solvates, esters, and/or prodrugs thereof, will provide therapeutic benefit without causing substantial toxicity. Toxicity of the present compounds, or salts, solvates, esters, and/or prodrugs thereof, may be determined using standard pharmaceutical procedures and may be readily ascertained by the skilled artisan. The dose ratio between toxic and therapeutic effect is the therapeutic index. The present compounds, or salts, solvates, esters, and/or prodrugs thereof, generally exhibit particularly high therapeutic indices in treating apoptosis associated disease and disorders. The dosage of the present compounds, or salts, solvates, esters, and/or prodrugs thereof, will preferably be within a range of circulating concentrations that include an effective dose with little or no toxicity.

5.8 Combination Therapy

In certain embodiments of the present invention, the present compounds, or salts, solvates, esters, and/or prodrugs thereof, can be used in combination therapy with at least one additional active or therapeutic agent. The present compounds, or salts, solvates, esters, and/or prodrugs thereof, and the at least one additional active or therapeutic agent can act additively or, more preferably, synergistically. In some embodiments, the present compounds, or salts, solvates, esters, and/or prodrugs thereof are administered concurrently, sequentially, or separately with the administration of another therapeutic agent. Exemplary active or chemotherapeutic agents include, but are not limited to, aceglatone, aclarubicin, altretamine, aminoglutethimide; 5-aminogleavulinic acid,

amsacrine, anastrozole, ancitabine hydrochloride, 17-1a antibody, antilymphocyte immunoglobulins, antineoplaston a10, asparaginase, pegaspargase, azacitidine, azathioprine, batimastat, benzoporphyrin derivative, bicalutamide, bisantrene hydrochloride, bleomycin sulphate, brequinar sodium, broxuridine, busulphan, campath-ih, caracemide, carbetimer, carboplatin, carboquone, carmofur, carmustine, chlorambucil, chlorozotocin, chromomycin, cisplatin, cladribine, corynebacterium parvum, cyclophosphamide, cyclosporin, cytarabine, dacarbazine, dactinomycin, daunorubicin hydrochloride, decitabine, diaziquone, dichlorodiethylsulphide, didemnin b., docetaxel, doxifluridine, doxorubicin hychloride, droloxifene, echinomycin, edatrexate, elliptinium, elmustine, enloplatin, enocitabine, epirubicin hydrochloride, estramustine sodium phosphate, etanidazole, ethoglucid, etoposide, fadrozole hydrochloride, fazarabine, fenretinide, floxuridine, fludarabine phosphate, fluorouracil, flutamide, formestane, fotemustine, gallium nitrate, gencitabine, gusperimus, homoharringtonine, hydroxyurea, idarubicin hydrochloride, ifosfamide, ilmofosine, improsulfan tosylate, inolimomab, interleukin-2; irinotecan, jm-216, letrozole, lithium gamolenate, lobaplatin, lomustine, lonidamine, mafosfamide, melphalan, menogaril, mercaptopurine, methotrexate, methotrexate sodium, miboplatin, miltefosine, misonidazole, mitobronitol, mitoguazone dihydrochioride, mitolactol, mitomycin, mitotane, mitozanetrone hydrochloride, mizoribine, mopidamol, muitlaichilpeptide, muromonab-cd3, mustine hydrochloride, mycophenolic acid, mycophenolate mofetil, nedaplatin, nilutamide, nimustine hydrochloride, oxaliplatin, paclitaxel, pcnu, penostatin, peplomycin sulphate, pipobroman, pirarubicin, piritrexim isethionate, piroxantrone hydrochloride, plicamycin, porfimer sodium, prednimustine, procarbazine hydrochloride, raltitrexed, ranimustine, razoxane, rogletimide, roquinimex, sebriplatin, semustine, sirolimus, sizofiran, sobuzoxane, sodium bromebrate, sparfosic acid, sparfosate sodium, sreptozocin, sulofenur, tacrolimus, tamoxifen, tegafur, teloxantrone hydrochloride, temozolomide, teniposide, testolactone, tetrasodium mesotetraphenylporphine-sulphonate, thioguanine, thioinosine, thiotepa, topotecan, toremifene, treosulfan, trimetrexate, trofosfamide, tumor necrosis factor, ubenimex, uramustine, vinblastine sulphate, vincristine sulphate, vindesine sulphate, vinorelbine tartrate, vorozole, zinostatin, zolimomab aritox, and zorubicin hydrochloride, and the like, either individually or in any combination, an

inhibitor of protein kinase A (PKA), an inhibitor of cAMP signaling, a nonsteroidal anti-inflammatory drug, a prostaglandin synthesis inhibitor, a local anesthetic, an anticonvulsant, an antidepressant, an opioid receptor agonist, and a neuroleptic, a benzodiazepine, a barbiturate, a neurosteroid and a inhalation anesthetic, a anesthetic and another pain killer.

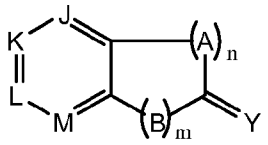
Abstract

COMPOSITIONS OF PROTEIN RECEPTOR TYROSINE KINASE INHIBITORS

The present invention relates to novel synthetic substituted heterocyclic compounds and pharmaceutical compositions containing the same that are capable of inhibiting or antagonizing a family of receptor tyrosine kinases, Tropomysosin Related Kinases (Trk), in particular the nerve growth factor (NGF) receptor, TrkA. The invention further concerns the use of such compounds in the treatment and/or prevention of pain, cancer, restenosis, atherosclerosis, psoriasis, thrombosis, or a disease, disorder or injury relating to dysmyelination or demyelination.

We claim:

1. A compound having a structural formula (I):



(I)

or a salt, solvate, ester, and/or prodrug thereof;

wherein:

n is 1, 2, or 3;

m is 0, 1, or 2;

A is C, N, O, S, NR^1, $C=CR^1$ (E and Z isomers), $C=NR^1$ (E and Z isomers), or $C(R^1R^2)$;

B is C, N, O, S, NR^3, or $C(R^3R^4)$;

J, K, L, and M are independently N or CR^5;

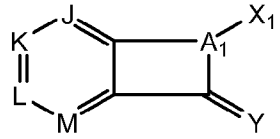
Y is O, S, NR^6, or $C(R^6R^7)$;

R^1, R^2, R^3, R^4, R^5, R^6, and R^7 are independently hydrogen, halogen, acyl, substituted acyl, alkoxycarbonyl, substituted alkoxycarbonyl, aryloxycarbonyl, substituted aryloxycarbonyl, $-CONR^8R^9$, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyl;

R^8 and R^9 are independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyl or substituted heteroalkyl or alternatively, R^8 and R^9, taken together with the nitrogen atom to which they are attached, form a 4-, 5-, 6-, or 7-membered cycloheteroalkyl ring, provided that both R^8 and R^9 are not hydrogen.

2. The compound of Claim 1, wherein m = 0, n = 1, and $A = A_1\text{-}X_1$.

3. The compound of Claim 2, having structural formula (II):



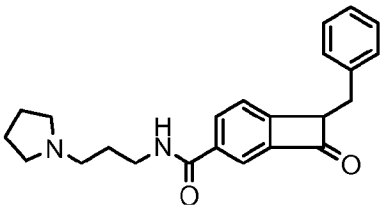
(II)

or a salt, solvate, ester, and/or prodrug thereof;

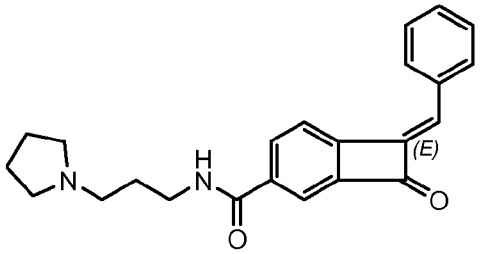
wherein:

A_1-X_1 is NR^1, $C{=}CR^1$ (E and Z isomers), $C{=}NR^1$ (E and Z isomers), or $C(R^1R^2)$.

4. The compound of Claim 3 having a structure selected from the group consisting of:



(101)



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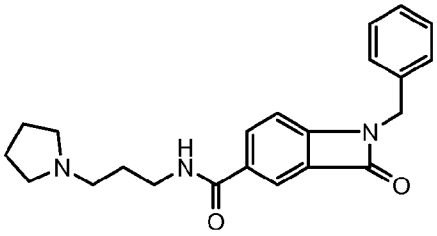

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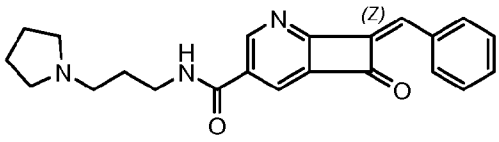
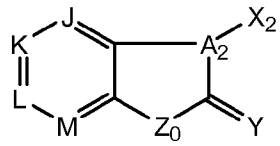


(107).

5. The compound of Claim 1, wherein m = 1, n = 1, A = A_2-X_2, B = Z_0.

6. The compound of Claim 5 having a structural formula (III):



(III)

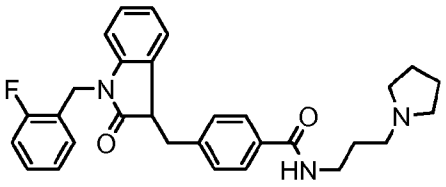
or a salt, solvate, ester, and/or prodrug thereof;

where in:

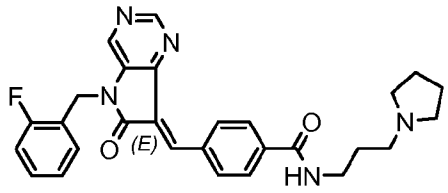
Z_0 is O, S, NR^3, or $C(R^3R^4)$;

A_2-X_2 is NR^1, $C{=}CR^1$ (E and Z isomers), $C{=}NR^1$ (E and Z isomers), or $C(R^1R^2)$.

7. The compound of Claim 6 having a structure selected from the group consisting of:



(109)



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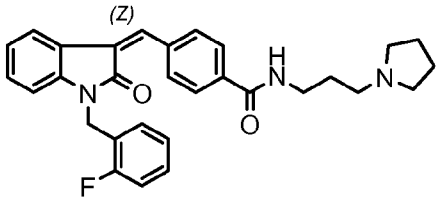
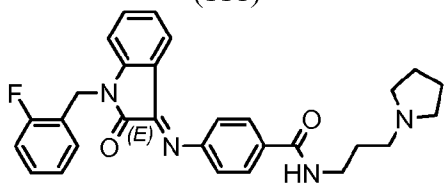


(113)



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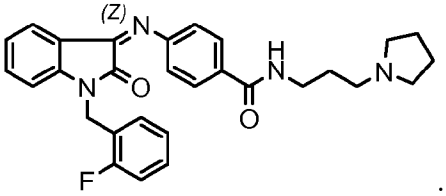
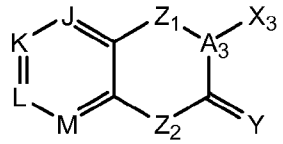


(117)

8. The compound of Claim 1, wherein m = 1, n = 2, A = Z_1 and A_3-X_3, and B = Z_2.

9. The compound of Claim 8 having a structural formula (IV):



(IV)

or a salt, solvate, ester, and/or prodrug thereof;

wherein:

A_3-X_3 is NR^1, $C{=}CR^1$ (E and Z isomers), $C{=}NR^1$ (E and Z isomers), or $C(R^1R^2)$;

Z_1 and Z_2 are O, S, CR^3, NR^3, $C(R^3R^4)$.

10. The compound of Claim 9, wherein the compound of formula (IV) does not include the compound selected from the group consisting of:

ID	IUPAC
201	N-{3-[4-(5-chloro-2-methylphenyl)piperazin-1-yl]propyl}-6-oxo-6,6a,7,8,9,10-hexahydro-5H-pyrido[1,2-a]quinoxaline-3-carboxamide
203	(2Z)-N-[3-(4-benzylpiperidin-1-yl)propyl]-4-(4-fluorobenzyl)-3-oxo-2-(phenylmethylidene)-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide
205	N-[3-(4-benzylpiperidin-1-yl)propyl]-2-{(2E)-2-[(3-bromo-4-methoxyphenyl)methylidene]-3-oxo-2,3-dihydro-4H-1,4-benzothiazin-4-yl}acetamide
207	4-{(E)-[4-(3-chlorobenzyl)-3-oxo-3,4-dihydro-2H-1,4-benzothiazin-2-ylidene]methyl}-N-[2-(dibutylamino)ethyl]benzamide
209	N-[3-(4-benzylpiperidin-1-yl)propyl]-2-{(2Z)-2-[(3-chlorophenyl)methylidene]-3-oxo-2,3-dihydro-4H-1,4-benzothiazin-4-yl}acetamide
211	(2Z)-N-{3-[cyclohexyl(methyl)amino]propyl}-4-(4-fluorobenzyl)-3-oxo-2-(phenylmethylidene)-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide
213	(2Z)-N-[3-(4-benzylpiperidin-1-yl)propyl]-4-(3-methylbenzyl)-3-oxo-2-(phenylmethylidene)-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide
215	(2Z)-N-{3-[cyclohexyl(methyl)amino]propyl}-4-(3-methylbenzyl)-3-oxo-2-(phenylmethylidene)-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide
217	N-[3-(4-benzylpiperidin-1-yl)propyl]-2-{(2E)-2-[(3-bromophenyl)methylidene]-3-oxo-2,3-dihydro-4H-1,4-benzothiazin-4-yl}acetamide
219	(2Z)-N-(2-azepan-1-ylethyl)-4-(3-methylbenzyl)-3-oxo-2-(phenylmethylidene)-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide
221	N-[2-(4-benzylpiperidin-1-yl)ethyl]-4-{(E)-[4-(2,5-dimethylbenzyl)-3-oxo-3,4-dihydro-2H-1,4-benzothiazin-2-ylidene]methyl}benzamide
223	(2Z)-N-[3-(2-ethylpiperidin-1-yl)propyl]-4-(4-fluorobenzyl)-3-oxo-2-(phenylmethylidene)-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide
225	4-{(E)-[4-(3-chlorobenzyl)-3-oxo-3,4-dihydro-2H-1,4-benzothiazin-2-ylidene]methyl}-N-{3-[cyclohexyl(methyl)amino]propyl}benzamide
227	(2Z)-N-(3-azepan-1-ylpropyl)-4-(3-methylbenzyl)-3-oxo-2-(phenylmethylidene)-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide
229	(2Z)-4-(4-fluorobenzyl)-N-[3-(3-methylpiperidin-1-yl)propyl]-3-oxo-2-(phenylmethylidene)-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide
231	N-(2-azepan-1-ylethyl)-4-{(E)-[4-(3-methylbenzyl)-3-oxo-3,4-dihydro-2H-1,4-benzothiazin-2-ylidene]methyl}benzamide
233	N-{3-[cyclohexyl(methyl)amino]propyl}-4-{(E)-[4-(3-methylbenzyl)-3-oxo-3,4-dihydro-2H-1,4-benzothiazin-2-ylidene]methyl}benzamide
235	N-(2-azepan-1-ylethyl)-4-{(E)-[4-(3-chlorobenzyl)-3-oxo-3,4-dihydro-2H-1,4-benzothiazin-2-ylidene]methyl}benzamide
237	(2Z)-N-{2-[4-(2-fluorophenyl)piperazin-1-yl]ethyl}-2-[2-(4-methoxyphenyl)-2-oxoethylidene]-3-oxo-1,2,3,4-tetrahydroquinoxaline-6-carboxamide
239	2-{(2Z)-2-[(3-chlorophenyl)methylidene]-3-oxo-2,3-dihydro-4H-1,4-benzothiazin-4-yl}-N-{3-[4-(4-methoxyphenyl)piperazin-1-yl]propyl}acetamide
241	(2Z)-N-{3-[4-(2,5-dimethylphenyl)piperazin-1-yl]propyl}-4-(3-methylbenzyl)-3-oxo-2-(phenylmethylidene)-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide
243	4-{(E)-[4-(3-chlorobenzyl)-3-oxo-3,4-dihydro-2H-1,4-benzothiazin-2-ylidene]methyl}-N-[(1-ethylpyrrolidin-2-yl)methyl]benzamide
245	N-{3-[cyclohexyl(methyl)amino]propyl}-4-{(E)-[4-(2-methylbenzyl)-3-oxo-3,4-dihydro-2H-

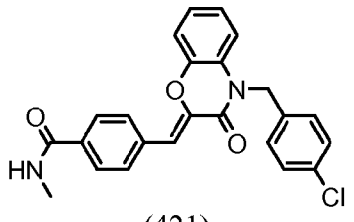
	1,4-benzothiazin-2-ylidene]methyl}benzamide
247	(2Z)-N-[3-(3,5-dimethylpiperidin-1-yl)propyl]-4-(3-methylbenzyl)-3-oxo-2-(phenylmethylidene)-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide
249	(2Z)-N-[3-(3,5-dimethylpiperidin-1-yl)propyl]-4-(4-fluorobenzyl)-3-oxo-2-(phenylmethylidene)-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide
251	N-{3-[benzyl(methyl)amino]propyl}-4-{(E)-[4-(3-methylbenzyl)-3-oxo-3,4-dihydro-2H-1,4-benzothiazin-2-ylidene]methyl}benzamide
253	N-(2-azepan-1-ylethyl)-2-{(2E)-2-[(3-chlorophenyl)methylidene]-3-oxo-2,3-dihydro-4H-1,4-benzothiazin-4-yl}acetamide
255	2-{(2E)-2-[(3-bromo-4-methoxyphenyl)methylidene]-3-oxo-2,3-dihydro-4H-1,4-benzothiazin-4-yl}-N-{3-[4-(2-fluorophenyl)piperazin-1-yl]propyl}acetamide
257	N-{3-[benzyl(methyl)amino]propyl}-2-{(2Z)-2-[(3-chlorophenyl)methylidene]-3-oxo-2,3-dihydro-4H-1,4-benzothiazin-4-yl}acetamide
259	2-{(2Z)-2-[(3-chlorophenyl)methylidene]-3-oxo-2,3-dihydro-4H-1,4-benzothiazin-4-yl}-N-{3-[4-(2-fluorophenyl)piperazin-1-yl]propyl}acetamide
261	N-{2-[cyclohexyl(1-methylpropyl)amino]ethyl}-4-{(E)-[4-(2-fluorobenzyl)-3-oxo-3,4-dihydro-2H-1,4-benzothiazin-2-ylidene]methyl}benzamide
263	N-{2-[cyclohexyl(methyl)amino]ethyl}-4-{(E)-[4-(3-methylbenzyl)-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-ylidene]methyl}benzamide
265	2-{(2E)-2-[(3-bromophenyl)methylidene]-3-oxo-2,3-dihydro-4H-1,4-benzothiazin-4-yl}-N-[3-(3,5-dimethylpiperidin-1-yl)propyl]acetamide
267	N-{3-[benzyl(butyl)amino]propyl}-4-{(E)-[4-(3-chlorobenzyl)-3-oxo-3,4-dihydro-2H-1,4-benzothiazin-2-ylidene]methyl}benzamide
269	N-(2-azepan-1-ylethyl)-2-{(2E)-2-[(3-bromo-4-methoxyphenyl)methylidene]-3-oxo-2,3-dihydro-4H-1,4-benzothiazin-4-yl}acetamide
271	2-{(2Z)-2-[(3-chlorophenyl)methylidene]-3-oxo-2,3-dihydro-4H-1,4-benzothiazin-4-yl}-N-{3-[4-(4-fluorophenyl)piperazin-1-yl]propyl}acetamide
273	2-{(2E)-2-[(3-bromophenyl)methylidene]-3-oxo-2,3-dihydro-4H-1,4-benzothiazin-4-yl}-N-[3-(2-ethylpiperidin-1-yl)propyl]acetamide
275	N-{3-[4-(5-chloro-2-methylphenyl)piperazin-1-yl]propyl}-4-{(E)-[4-(2-fluorobenzyl)-3-oxo-3,4-dihydro-2H-1,4-benzothiazin-2-ylidene]methyl}benzamide
277	N-[2-(dipropylamino)ethyl]-4-{(E)-[4-(3-methylbenzyl)-3-oxo-3,4-dihydro-2H-1,4-benzothiazin-2-ylidene]methyl}benzamide
279	(2Z)-N-(2-azepan-1-ylethyl)-4-(4-fluorobenzyl)-3-oxo-2-(phenylmethylidene)-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide
281	4-{(E)-[4-(3-chlorobenzyl)-3-oxo-3,4-dihydro-2H-1,4-benzothiazin-2-ylidene]methyl}-N-{3-[4-(2-fluorophenyl)piperazin-1-yl]propyl}benzamide
283	2-{(2Z)-2-[(3-chlorophenyl)methylidene]-3-oxo-2,3-dihydro-4H-1,4-benzothiazin-4-yl}-N-{3-[4-(3-chlorophenyl)piperazin-1-yl]propyl}acetamide
285	2-{(2E)-2-[(3-chlorophenyl)methylidene]-3-oxo-2,3-dihydro-4H-1,4-benzothiazin-4-yl}-N-[3-(2-ethylpiperidin-1-yl)propyl]acetamide
287	N-{3-[4-(5-chloro-2-methylphenyl)piperazin-1-yl]propyl}-4-{(E)-[4-(3-methylbenzyl)-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-ylidene]methyl}benzamide
289	N-{3-[4-(3-chlorophenyl)piperazin-1-yl]propyl}-6-oxo-6,6a,7,8,9,10-hexahydro-5H-pyrido[1,2-a]quinoxaline-3-carboxamide
291	(2Z)-N-[3-(3,4-dihydroisoquinolin-2(1H)-yl)propyl]-4-(3-methylbenzyl)-3-oxo-2-(phenylmethylidene)-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide
293	2-{(2E)-2-[(3-bromo-4-methoxyphenyl)methylidene]-3-oxo-2,3-dihydro-4H-1,4-benzothiazin-4-yl}-N-{3-[4-(4-fluorophenyl)piperazin-1-yl]propyl}acetamide
295	4-{(E)-[4-(3-chlorobenzyl)-3-oxo-3,4-dihydro-2H-1,4-benzothiazin-2-ylidene]methyl}-N-(2-pyrrolidin-1-ylethyl)benzamide
297	2-{(2E)-2-[(3-bromophenyl)methylidene]-3-oxo-2,3-dihydro-4H-1,4-benzothiazin-4-yl}-N-{2-[methyl(2-phenylethyl)amino]ethyl}acetamide
299	4-{(E)-[4-(3-chlorobenzyl)-3-oxo-3,4-dihydro-2H-1,4-benzothiazin-2-ylidene]methyl}-N-

	[3-(3-methylpiperidin-1-yl)propyl]benzamide
301	(2Z)-N-{3-[4-(4-methoxyphenyl)piperazin-1-yl]propyl}-4-(3-methylbenzyl)-3-oxo-2-(phenylmethylidene)-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide
303	(2Z)-N-(3-azepan-1-ylpropyl)-4-(4-fluorobenzyl)-3-oxo-2-(phenylmethylidene)-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide
305	N-{3-[4-(2-fluorophenyl)piperazin-1-yl]propyl}-4-{(E)-[4-(3-methylbenzyl)-3-oxo-3,4-dihydro-2H-1,4-benzothiazin-2-ylidene]methyl}benzamide
307	N-{3-[4-(2-fluorophenyl)piperazin-1-yl]propyl}-4-{(E)-[4-(2-methylbenzyl)-3-oxo-3,4-dihydro-2H-1,4-benzothiazin-2-ylidene]methyl}benzamide
309	N-{3-[4-(4-methoxyphenyl)piperazin-1-yl]propyl}-4-{(E)-[4-(4-methylbenzyl)-3-oxo-3,4-dihydro-2H-1,4-benzothiazin-2-ylidene]methyl}benzamide
311	2-{(2E)-2-[(3-chlorophenyl)methylidene]-3-oxo-2,3-dihydro-4H-1,4-benzothiazin-4-yl}-N-[3-(3-methylpiperidin-1-yl)propyl]acetamide
313	(2E)-2-[(4-ethoxy-3-methoxyphenyl)methylidene]-N-{3-[4-(2-fluorophenyl)piperazin-1-yl]propyl}-4-methyl-3-oxo-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide
315	2-{(2E)-2-[(2-chlorophenyl)methylidene]-3-oxo-2,3-dihydro-4H-1,4-benzothiazin-4-yl}-N-{3-[4-(4-fluorophenyl)piperazin-1-yl]propyl}acetamide
317	(2Z)-N-{3-[4-(2-fluorophenyl)piperazin-1-yl]propyl}-4-methyl-2-[(3-methylphenyl)methylidene]-3-oxo-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide
319	2-{(2E)-2-[(3-chlorophenyl)methylidene]-3-oxo-2,3-dihydro-4H-1,4-benzothiazin-4-yl}-N-[3-(3,5-dimethylpiperidin-1-yl)propyl]acetamide
321	(2E)-N-{3-[4-(2-fluorophenyl)piperazin-1-yl]propyl}-2-[(2-methoxyphenyl)methylidene]-4-methyl-3-oxo-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide
323	(2Z)-N-{3-[4-(4-fluorophenyl)piperazin-1-yl]propyl}-4-methyl-2-[(2-methylphenyl)methylidene]-3-oxo-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide.

11. The compound of Claim 9, wherein R^1 and R^2 are not hydrogen.

12. The compound of Claim 9, wherein at least two of R^1, R^2, and R^3 are not hydrogen.

13. The compound of Claim 9, 11, and 12, wherein the compound having a structural formula (IV) is selected from the group consisting of:



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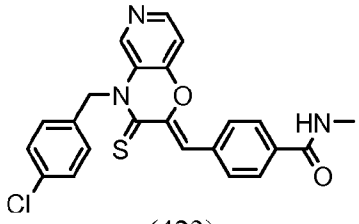

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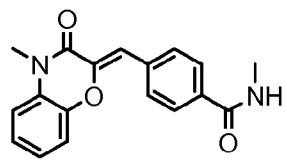

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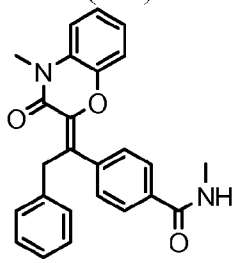

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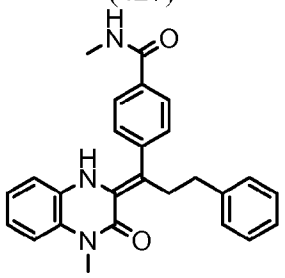

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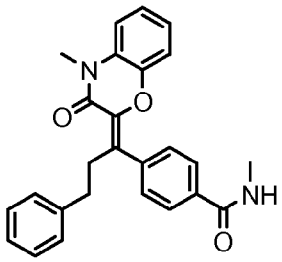

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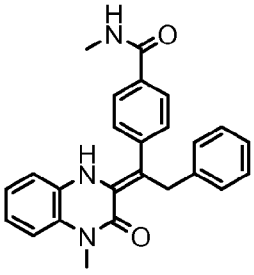

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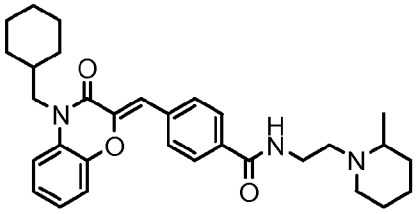

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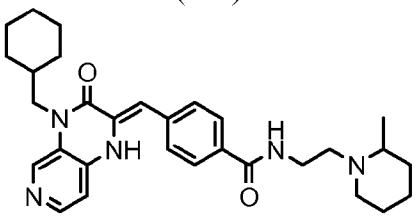

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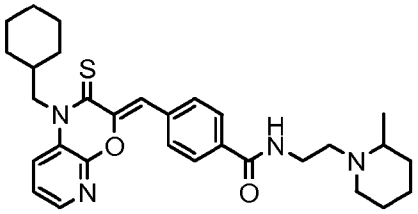

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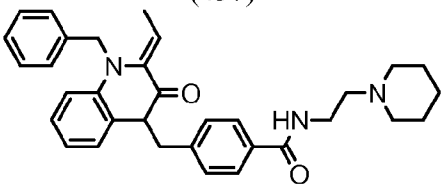

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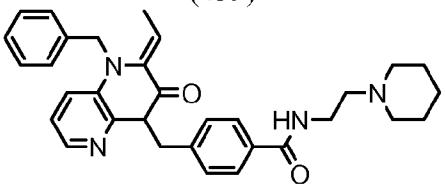

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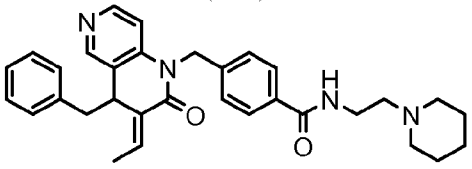

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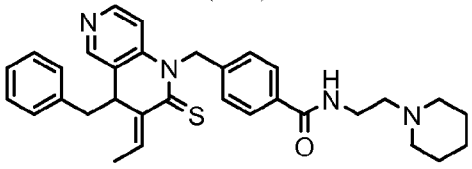

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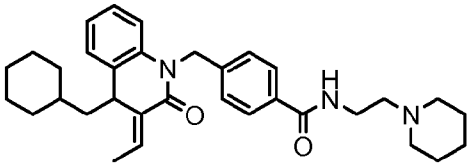

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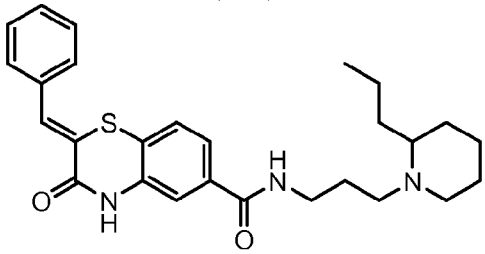

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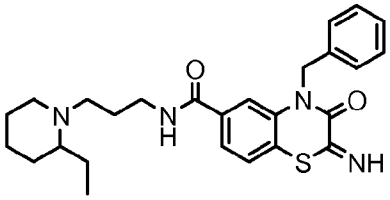

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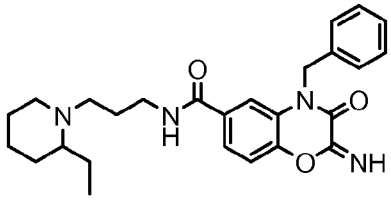

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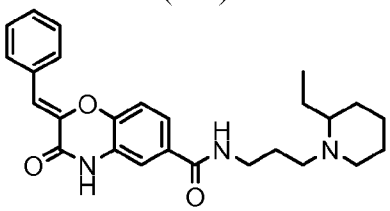

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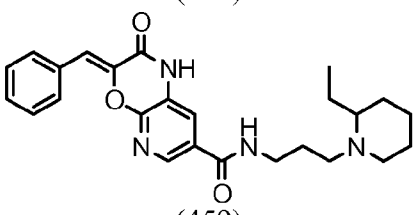

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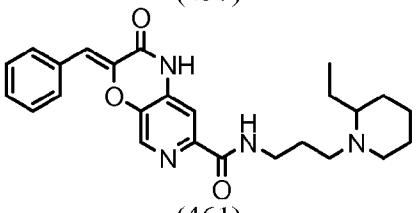

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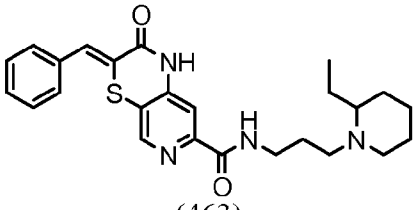

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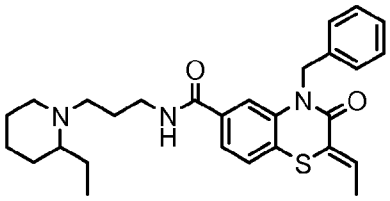

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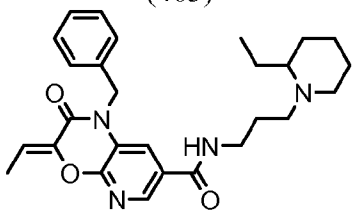

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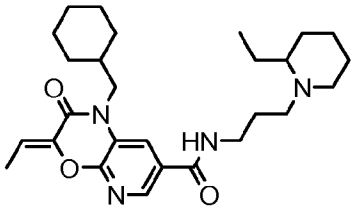

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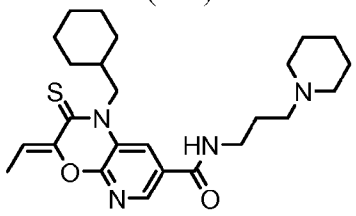

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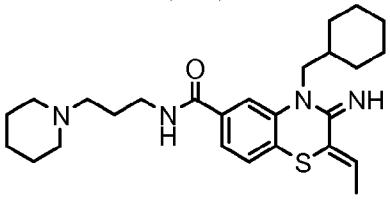

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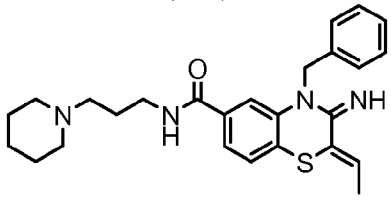

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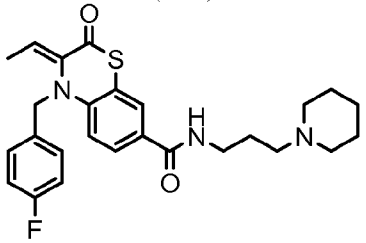

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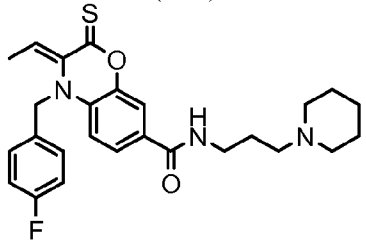

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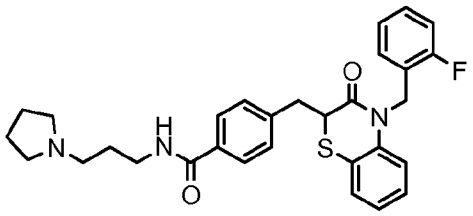

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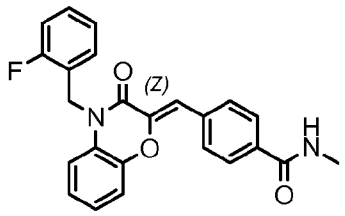

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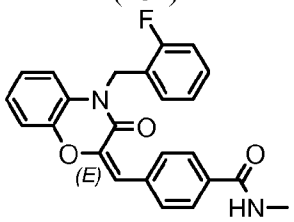

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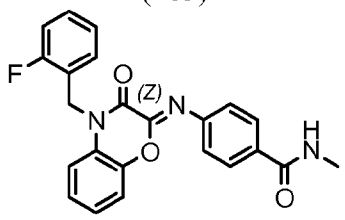

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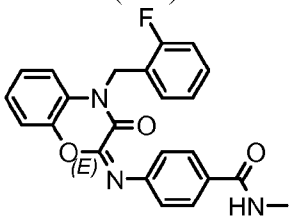
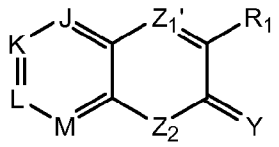


(489)

14. The compound of Claim 9, wherein Z_1-A_3 is a double bond, A_3-X_3 is CR^1.

15. The compound of Claim 14 having a structural formula (IVa):



(IVa)

or salt, solvate, ester, and/or prodrug thereof;

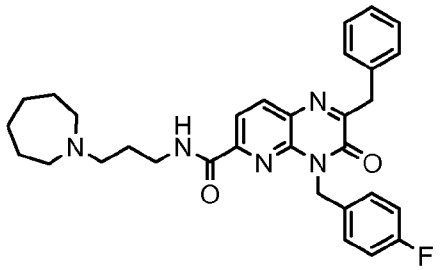
wherein:

Z_1' is either N or CR^3.

16. The compound of Claim 15, wherein at least one of J, K, L, and M is independently N.

17. The compound of Claim 15 and 16, wherein at least one of J, K, L, and M is independently CR^5.

18. The compound of Claim 15 – 17 having a structure selected from the group consisting of:



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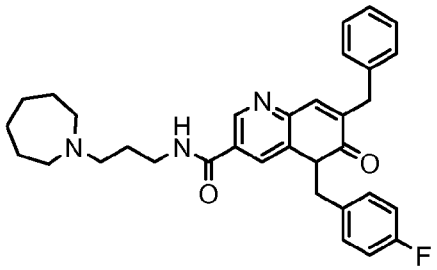

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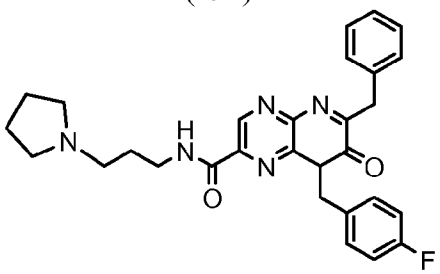
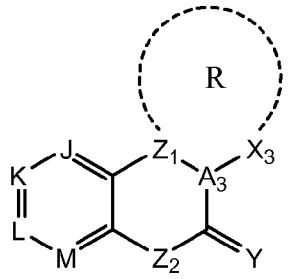


(495)

ID	IUPAC
491	2-Benzyl-4-(4-fluoro-benzyl)-3-oxo-3,4-dihydro-pyrido[2,3-b]pyrazine-6-carboxylic acid (3-azepan-1-yl-propyl)-amide
493	7-Benzyl-5-(4-fluoro-benzyl)-6-oxo-5,6-dihydro-quinoline-3-carboxylic acid (3-azepan-1-yl-propyl)-amide
495	6-Benzyl-8-(4-fluoro-benzyl)-7-oxo-7,8-dihydro-pyrido[2,3-b]pyrazine-2-carboxylic acid (3-pyrrolidin-1-yl-propyl)-amide.

19. The compound of Claim 9, wherein Z1 and X3 form a ring system.

20. The compound of Claim 19 having the structural formula (IVb):



(IVb)

or a salt, solvate, ester, and/or prodrug thereof;

wherein:

A3 is N or CR1

Z1 is N or CR3;

X3 is independently S, O, N, N(R^1), C(R^1), C(R^1R^2);

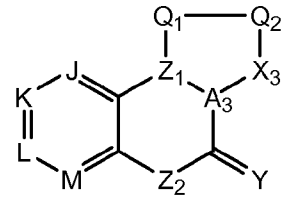
R ring is an aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroaryl or substituted heteroaryl ring.

21. The compound of Claim 9, wherein Z_1 is CR^3 or NR^3.

22. The compound of Claim 9 and 21, wherein R^3 forms a 5-member-ring system with A_3-X_3.

23. The compound of Claim 19, wherein R is a 5-member ring system.

24. The compound of Claim 23 having the structural formula (IVb.0):



(IVb.0)

or a salt, solvate, ester, and/or prodrug thereof;

wherein:

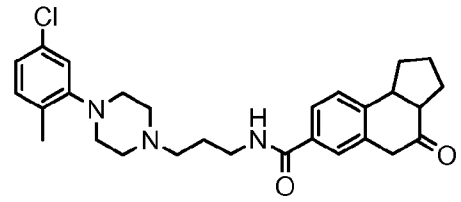
Z_1-Q_1, Q_1-Q_2, Q_2-X_3, A_3-X_3, Z_1-A_3 are independently single or double bond;

Q_1, Q_2, and X_3 are independently S, O, N, N(R^{10}), C(R^{10}), C($R^{10}R^{11}$);

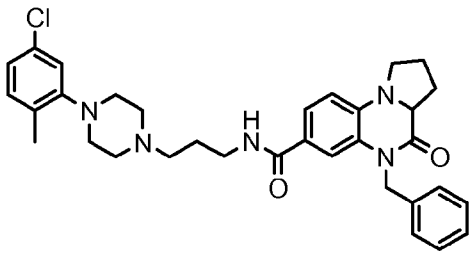
Z_1 and A_3 are independently N, C, or CR^{12};

R^{10}, R^{11}, and R^{12} are independently hydrogen, halogen, acyl, substituted acyl, alkoxycarbonyl, substituted alkoxycarbonyl, aryloxycarbonyl, substituted aryloxycarbonyl, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyl.

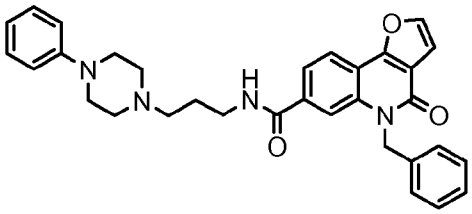
25. The compound of Claim 24 having a structure selected from the group consisting of:



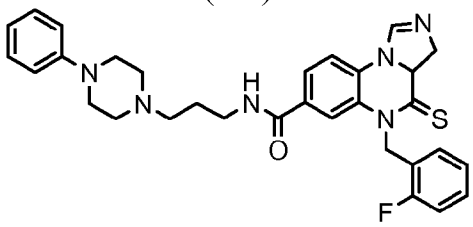
(497)



(499)



(501)

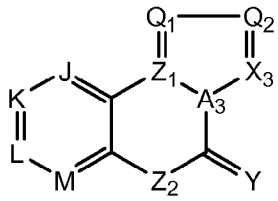


(503).

26. The compound of Claim 24, wherein Z_1-Q_1 and Q_2-X_3 are double bond.

27. The compound of Claim 24, wherein Q_1-Q_2, A_3-X_3, and Z_1-A_3 are single bond.

28. The compound of Claim 24 – 27 having the structural formula (IVb.1):



(IVb.1)

or a salt, solvate, ester, and/or prodrug thereof;

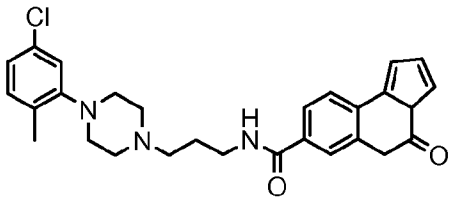
wherein:

Z_1 is C;

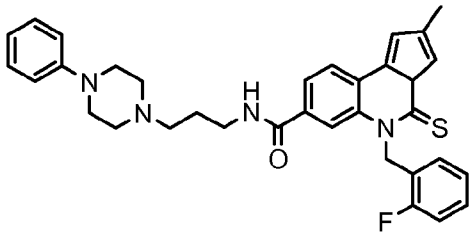
A_3 is N or CR^{12};

X_3, Q_1 and Q_2 are independently N or CR^{10}.

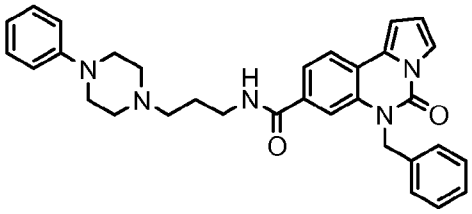
29. The compound of Claim 28 having a structure selected from the group consisting of:



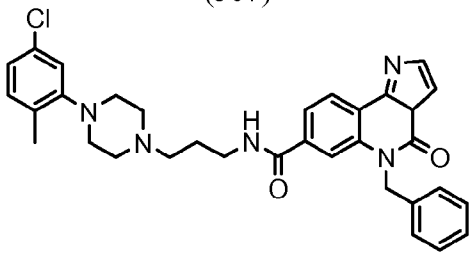
(505)



(507)



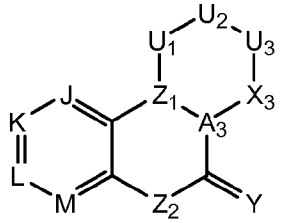
(509)



(511).

30. The compound of Claim 9 and 21, wherein R^3 forms a 6-member-ring system with A_3-X_3.

31. The compound of Claim 30 having the structural formula (IVc):



(IVc)

or a salt, solvate, ester, and/or prodrug thereof;

wherein:

Z_1-U_1, U_1-U_2, U_2-U_3, U_3-X_3, A_3-X_3, Z_1-A_3 are independently single or double bond;

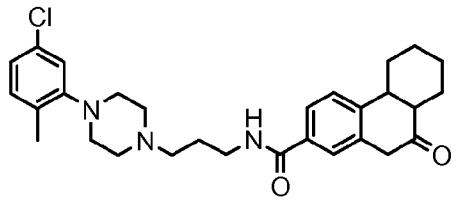
U_1, U_2, U_3, and X_3 are independently S, O, N, $N(R^{13})$, $C(R^{13})$, $C(R^{13}R^{14})$;

Z_1 and A_3 are independently N, C, or CR^{15};

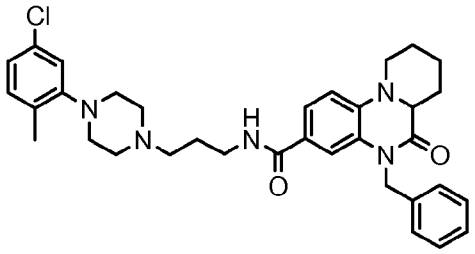
R^{13}, R^{14}, and R^{15} are independently hydrogen, halogen, acyl, substituted acyl, alkoxycarbonyl, substituted alkoxycarbonyl, aryloxycarbonyl, substituted

aryloxycarbonyl, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyl.

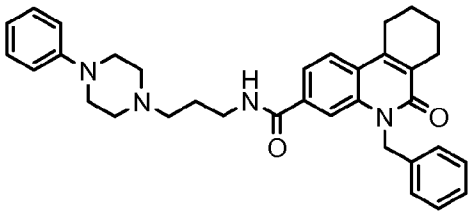
32. The compound of Claim 31 having a structure selected from the group consisting of:



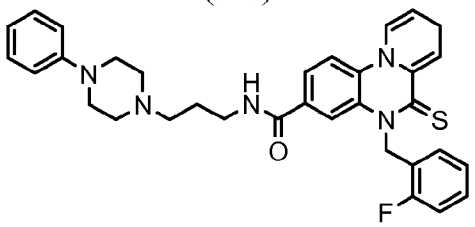
(515)



(517)



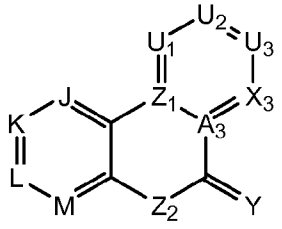
(519)



(521).

33. The compound of Claim 31, wherein Z_1-U_1, U_1-U_2, U_2-U_3, U_3-X_3, A_3-X_3, Z_1-A_3 is an aromatic system.

34. The compound of Claim 31 – 33 having the structural formula (IVc.1):



(IVc.1)

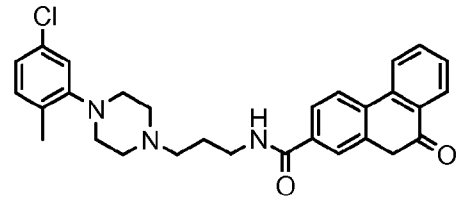
or a salt, solvate, ester, and/or prodrug thereof;

wherein:

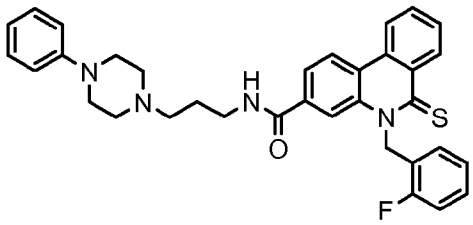
U_1, U_2, U_3 and X_3 are independently N or CR^{13};

Z_1 and A_3 are C.

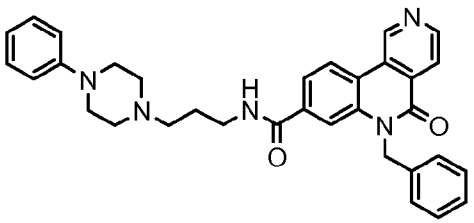
35. The compound of Claim 34 having a structure selected from the group consisting of:



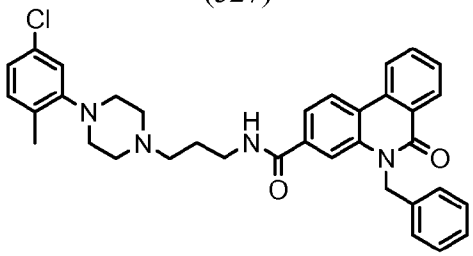
(525)



(527)



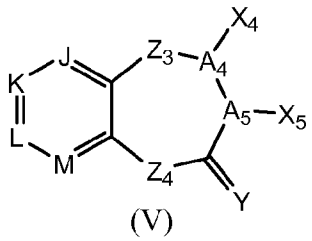
(529)



(531).

36. The compound of Claim 1, wherein m = 1, n = 3, A is Z_3, A_4-X_4, A_5-X_5, B is Z_4.

37. The compound of Claim 36 having the structural of formula (V):



(V)

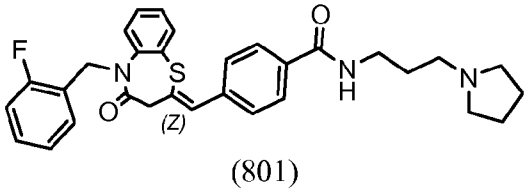
or a salt, solvate, ester, and/or prodrug thereof;

wherein:

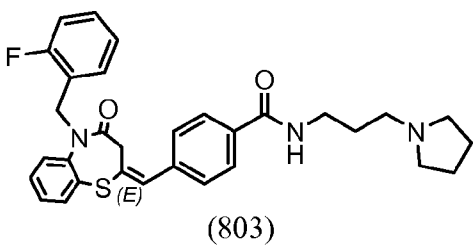
A_4-X_4, A_5-X_5 are independently NR^1, $C{=}CR^1$ (E and Z isomers), $C{=}NR^1$, or $C(R^1R^2)$;

Z_3 and Z_4 are independently O, S, NR^3, or $C(R^3R^4)$.

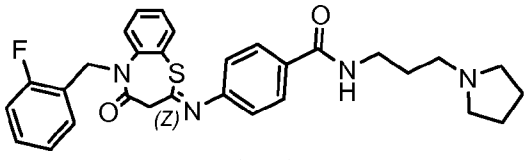
38. The compound of Claim 37 having a structure selected from the group consisting of:



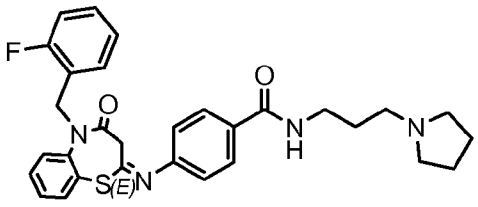
(801)



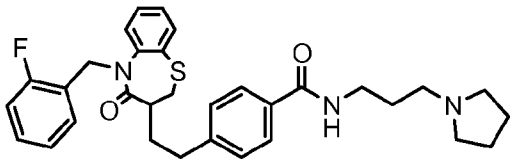
(803)



(805)



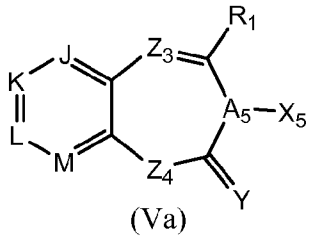
(807)



(809)

39. The compound of Claim 37, wherein Z_3-A_4 is double bond, $A_4(X_4)$ is CR^1, A_5-X_5 is $C(R^1R^2)$, NR^1, $C{=}CR^1$ (E and Z isomers), or $C{=}NR^1$ (E and Z isomers).

40. The compound of Claims 37 & 39 having the structural formula (Va):



(Va)

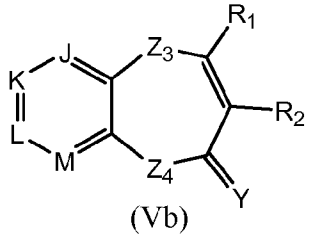
or a salt, solvate, ester, and/or prodrug thereof;

wherein:

Z_3 and Z_4 are independently O, N, S, $N(R^3)$, or $C(R^3R^4)$.

41. The compound of Claim 37, wherein A_4-A_5 is double bond, $A_4(X_4)$ is CR^1, and $A_5(X_5)$ is CR^2.

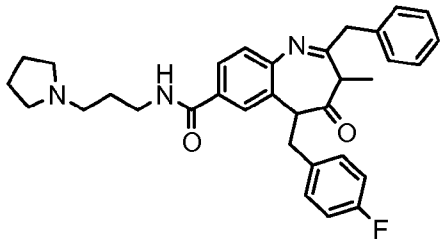
42. The compound of Claim 37 & 41 having the structural formula (Vb):



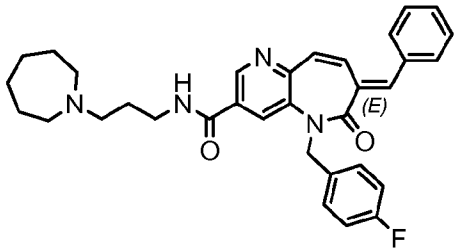
(Vb)

or a salt, solvate, ester, and/or prodrug thereof.

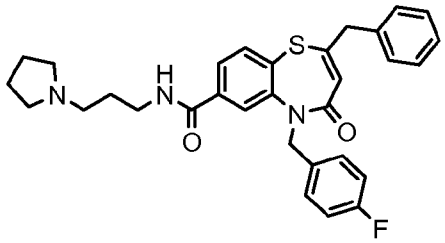
43. The compounds of Claims 40 & 42 having a structure selected from the group consisting of:



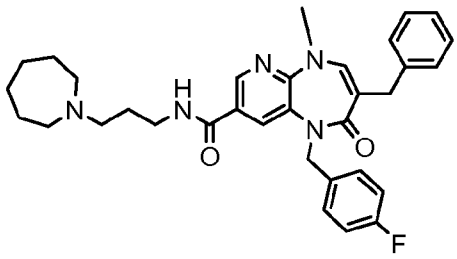
(811)



(813)



(815)

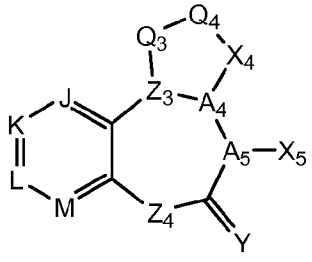


(817).

44. The compound of Claim 37, wherein Z3 is NR^3, or $C(R^3R^4)$.

45. The compound of Claims 37 and 44, wherein R^3 forms a 5-member ring system with A4-X4.

46. The compound of Claims 37, 44 and 45 having the structural formula (Vc):



(Vc)

or a salt, solvate, ester, and/or prodrug thereof;

wherein:

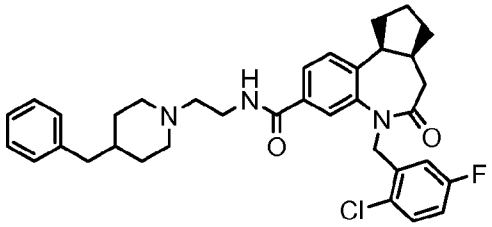
Z_3-Q_3, Q_3-Q_4, Q_4-X_4, A_4-X_4, Z_3-A_4 are independently single or double bond;

Q_3, Q_4, and X_4 are independently S, O, N, $N(R^{16})$, $C(R^{16})$, $C(R^{16}R^{17})$;

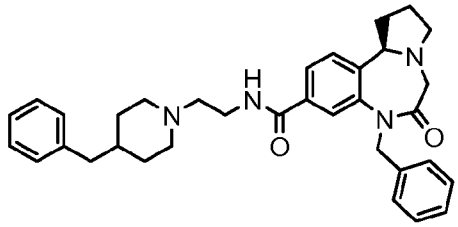
Z_3 and A_4 are independently N, C, or CR^{18};

R^{16}, R^{17}, and R^{18} are independently hydrogen, halogen, acyl, substituted acyl, alkoxycarbonyl, substituted alkoxycarbonyl, aryloxycarbonyl, substituted aryloxycarbonyl, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyl.

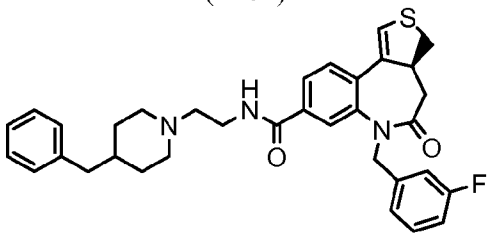
46A. The compounds of Claims 46 having a structure selected from the group consisting of



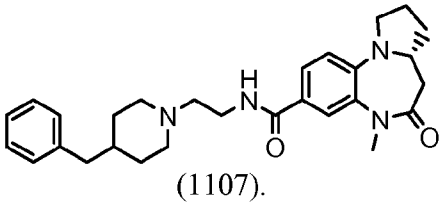
(1101)



(1103)



(1105)

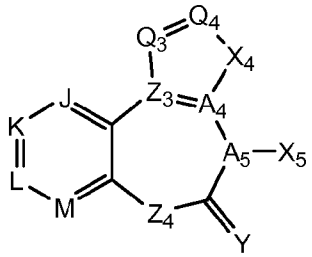


(1107).

47. The compound of Claim 46, wherein Z3-Q3 and Q4-X4 are double bond.

48. The compound of Claim 46, wherein Z3-A4, Q3-Q4, and A4-X4 are single bond.

49. The compound of Claim 46 – 48 having the structural formula (Vc.1):



(Vc.1)

or a salt, solvate, ester, and/or prodrug thereof;

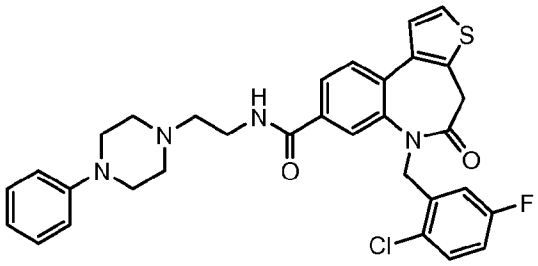
wherein:

Z_3 is C;

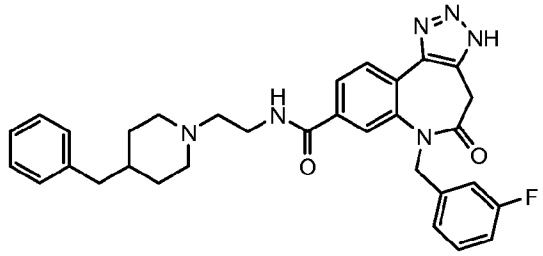
A_4 is N or CR^{18};

X_4, Q_3 and Q_4 are independently N or CR^{16}.

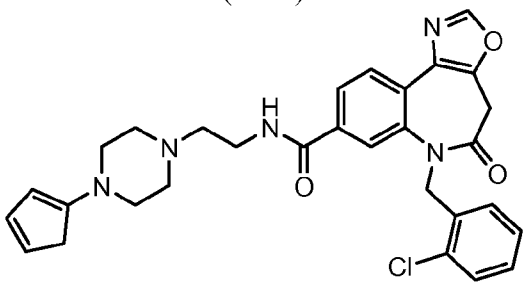
50. The compound of Claim 49 having a structure selected from the group consisting of:



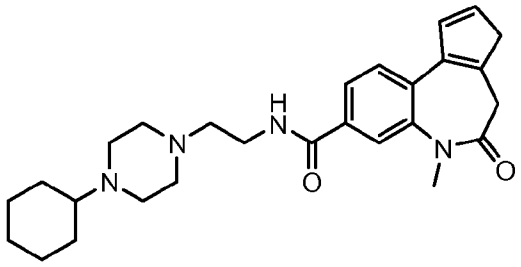
(1121)



(1123)



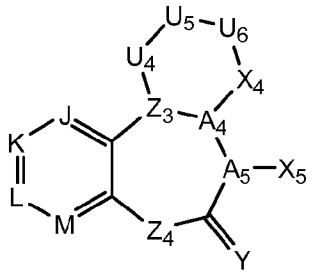
(1125)



(1127).

51. The compound of Claims 37 and 44, wherein R^3 forms a 6-member ring system with A_4-X_4.

52. The compound of Claim 51 having the structural formula (Vd):



(Vd)

o a salt, solvate, ester, and/or prodrug thereof;

wherein:

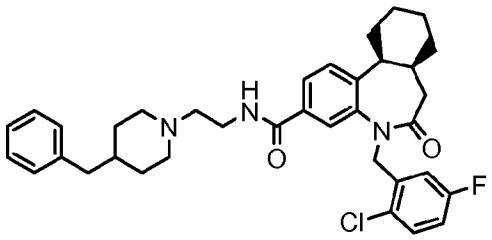
Z_3-U_4 U_4-U_5, U_5-U_6, U_6-X_4, A_4-X_4, Z_3-A_4 are independently single or double bond;

U_4, U_5, U_6, and X_4 are independently S, O, N, $N(R^{19})$, $C(R^{19})$, $C(R^{19}R^{20})$;

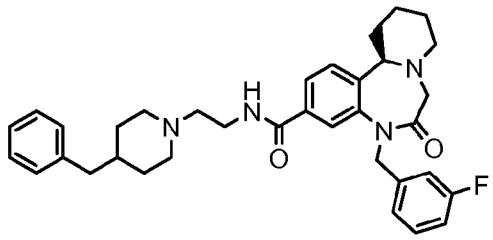
Z_3 and A_4 are independently N, C, or CR^{21};

R^{19}, R^{20}, and R^{21} are independently hydrogen, halogen, acyl, substituted acyl, alkoxycarbonyl, substituted alkoxycarbonyl, aryloxycarbonyl, substituted aryloxycarbonyl, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyl.

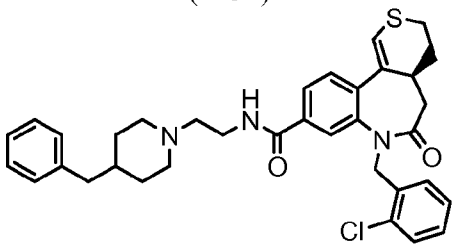
53. The compound of Claim 52 having a structure selected from the group consisting of:



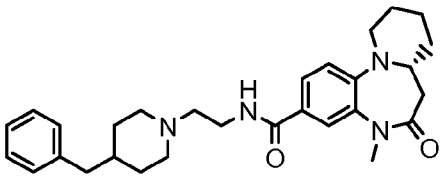
(1131)



(1133)



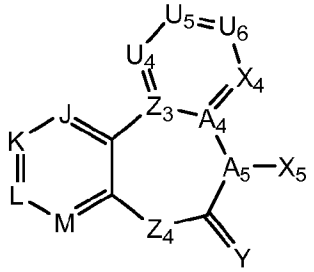
(1135)



(1137).

54. The compound of Claim 52, wherein Z_3-U_4 U_4-U_5, U_5-U_6, U_6-X_4, A_4-X_4, Z_3-A_4 together form an aromatic system.

55. The compound of Claims 52 having the structural formula (Vd.1):



(Vd.1)

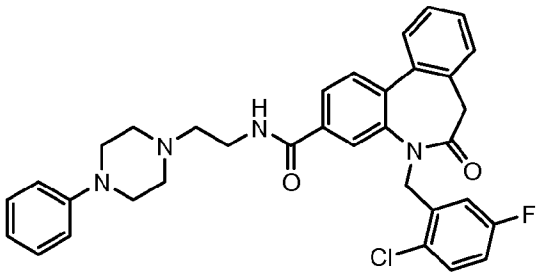
or a salt, solvate, ester, and/or prodrug thereof;

wherein:

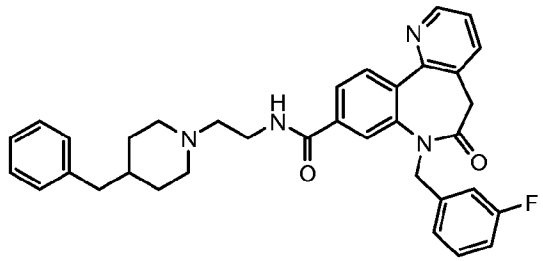
Z_3 and A_4 are C;

U_4, U_5, U_6, and X_4 are independently N or CR^{19}.

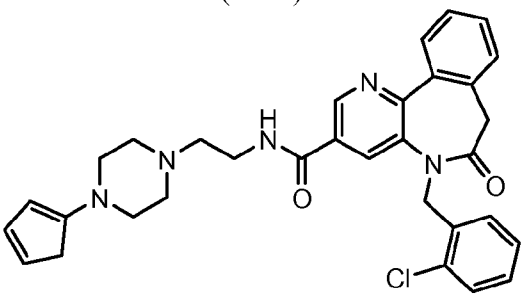
56. The compound of Claim 55 having a structure selected from the group consisting of:



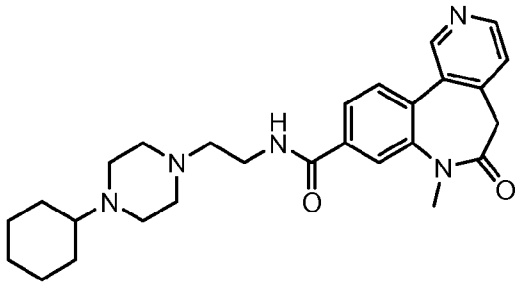
(1141)



(1143)



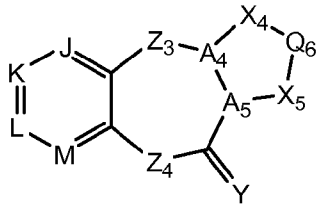
(1145)



(1147).

57. The compound of Claim 37, wherein A_4-X_4 and A_5-X_5 form a 5-member ring system.

58. The compound of Claims 37 and 57 having the structural formula (Ve):



(Ve)

or a salt, solvate, ester, and/or prodrug thereof;

wherein:

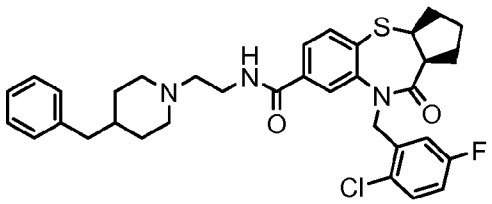
A_4-X_4, X_4-Q_6, Q_6-X_5, A_5-X_5, A_4-A_5 are independently single or double bond;

X_4, X_5, and Q_6 are indpenedently S, O, N, $N(R^{22})$, $C(R^{22})$, or $C(R^{22}R^{23})$;

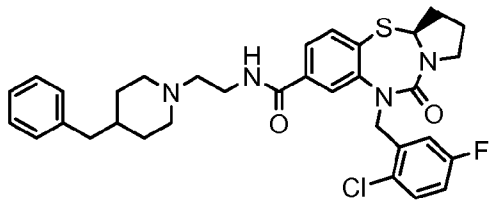
A_4 and A_5 are independently N, C, or CR^{24};

R^{22}, R^{23}, and R^{24} are independently hydrogen, halogen, acyl, substituted acyl, alkoxycarbonyl, substituted alkoxycarbonyl, aryloxycarbonyl, substituted aryloxycarbonyl, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyl.

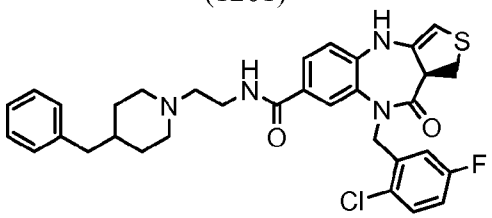
59. The compound of Claim 58 having a structure selected from the group consisting of:



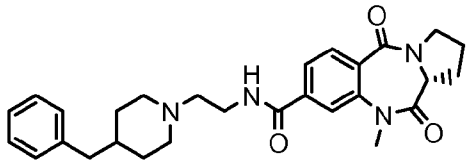
(1201)



(1203)



(1205)

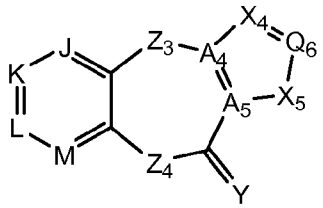


(1207).

60. The compound of Claim 58, wherein A4-X4 and Q6-X5 are double bond.

61. The compound of Claim 58, wherein A4-A5, X4-Q6, and A5-X5 are single bond.

62. The compound of Claims 58, 60 and 61 having the structural formula (Ve.1):



(Ve.1)

or a salt, solvate, ester, and/or prodrug thereof;

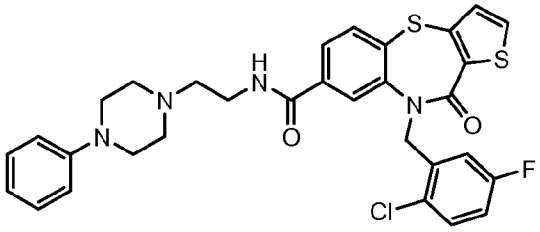
wherein:

A4 and A5 are C;

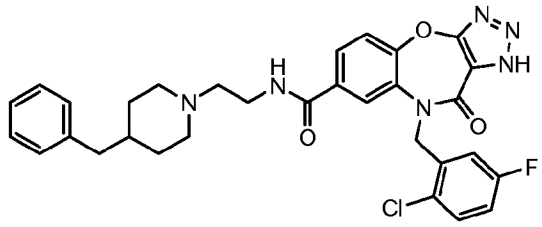
X5 is S, O, N, NR24, or CR24;

X4, and Q6 are independently N or CR20.

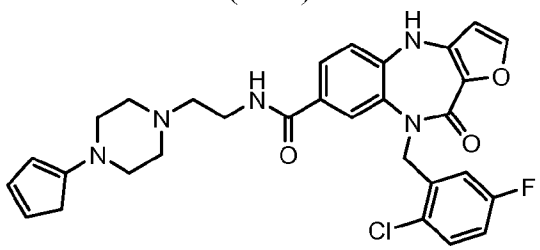
63. The compound of Claim 62 having a structure selected from the group consisting of:



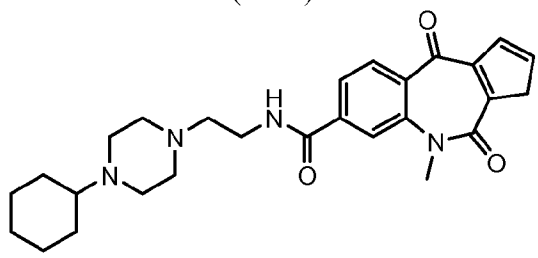
(1215)



(1217)



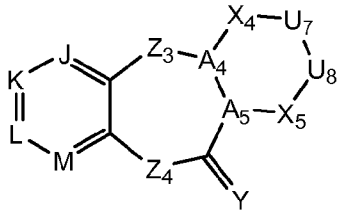
(1219)



(1221).

64. The compound of Claim 37, wherein A_4-X_4 and A_5-X_5 form a 6-member ring system.

65. The compound of Claim 37 and 64 having the structural formula (Vf):



(Vf)

or a salt, solvate, ester, and/or prodrug thereof;

wherein:

A4-X4, X4-U7, U7-U8, U8-X5, A5-X5, and A4-A5 are independently single or double bond;

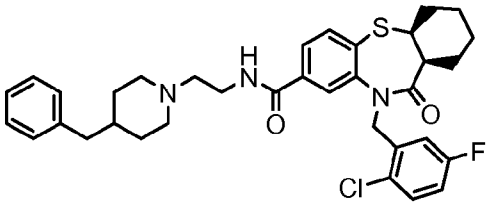
X4, U7, U8, and X5 are independently S, O, N, N(R25), C(R25), or C(R25R26);

A4 and A5 are independently N, C, or CR27;

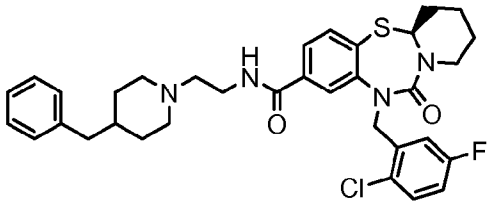
R^{25}, R^{26}, and R^{27} are independently hydrogen, halogen, acyl, substituted acyl, alkoxycarbonyl, substituted alkoxycarbonyl, aryloxycarbonyl, substituted aryloxycarbonyl, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted

arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyl.

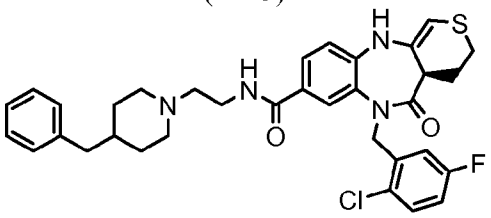
66. The compound of Claim 65 having a structure selected from the group consisting of:



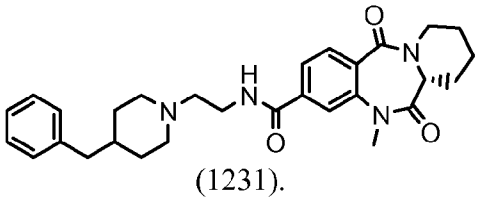
(1225)



(1227)



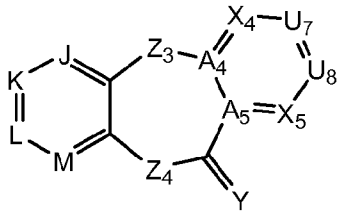
(1229)



(1231).

67. The compound of Claim 65, wherein A4-X4, X4-U7, U7-U8, U8-X5, A5-X5, and A4-A5 together form an aromatic system.

68. The compound of Claim 65 – 67 having the structural formula (Vf.1):



(Vf.1)

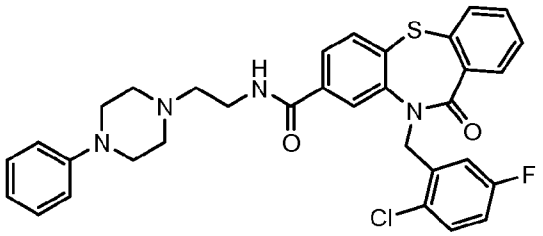
or a salt, solvate, ester, and/or prodrug thereof;

wherein:

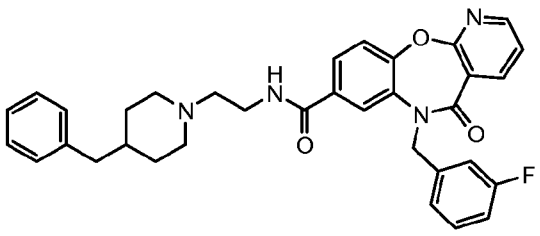
A4 and A5 arc C;

X4, U7, U8, and X5 are independently N or CR25.

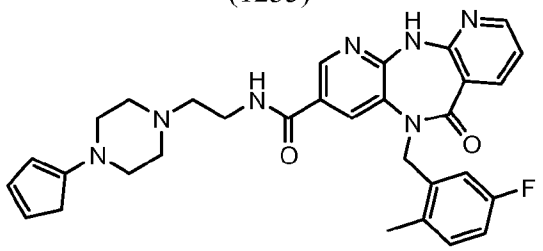
69. The compound of Claim 68 having a structure selected from the group consisting of:



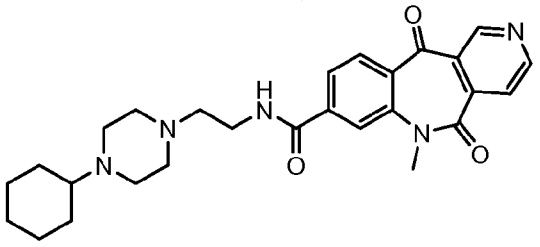
(1235)



(1237)

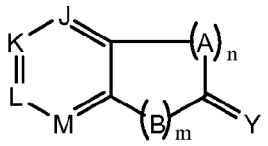


(1239)



(1241).

70. A pharmaceutical composition comprising a compound having a structural formula (I):



(I)

or a salt, solvate, ester, and/or prodrug thereof;

wherein:

n is 1, 2, or 3;

m is 0, 1, or 2;

A is C, N, O, S, $C(R^1R^2)$, NR^1, $C{=}CR^1$ (E and Z isomers), or $C{=}NR^1$ (E and Z isomers);

B is C, N, O, S, $C(R^3R^4)$, or NR^3;

J, K, L, and M are independently N or CR^5;

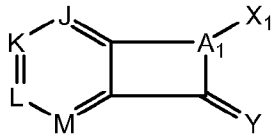
Y is CH_2, NH, O, or S;

R^1, R^2, R^3, R^4, and R^5 are independently hydrogen, halogen, acyl, substituted acyl, alkoxycarbonyl, substituted alkoxycarbonyl, aryloxycarbonyl, substituted aryloxycarbonyl, $-CONR^6R^7$, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyl;

R^6 and R^7 are independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyl or substituted heteroalkyl or alternatively, R^6 and R^7, taken together with the nitrogen atom to which they are attached, form a 4-, 5-, 6-, or 7-membered cycloheteroalkyl ring, provided that both R^6 and R^7 are not hydrogen.

71. The pharmaceutical composition of Claim 70, wherein m = 0, n = 1, and A = A_1-X_1.

72. The pharmaceutical composition of Claim 71, having structural formula (II):



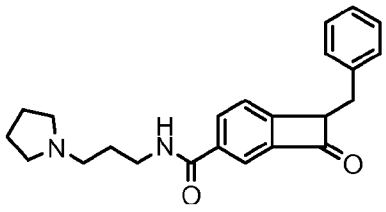
(II)

or a salt, solvate, ester, and/or prodrug thereof;

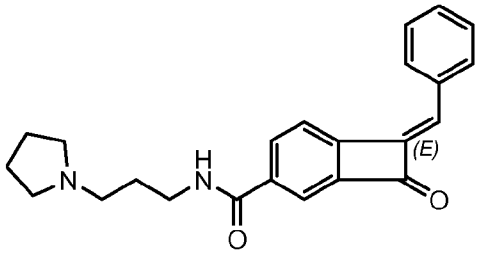
wherein:

A_1-X_1 is $C(R^1R^2)$, NR^1, $C{=}CR^1$ (E and Z isomers), or $C{=}NR^1$ (E and Z isomers).

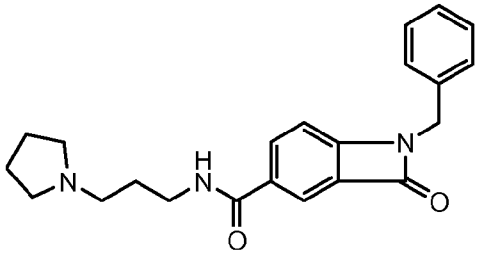
73. The pharmaceutical composition of Claim 72 having a structure selected from the group consisting of:



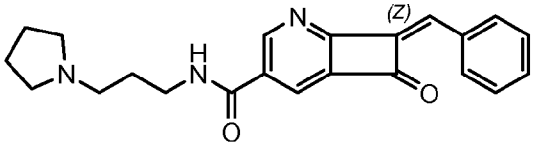
(101)



(103)



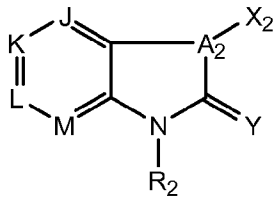
(105)



(107).

74. The pharmaceutical composition of Claim 70, wherein m = 1, n = 1, A = A_2-X_2, B = NR^2.

75. The pharmaceutical composition of Claim 74 having a structural formula (III):



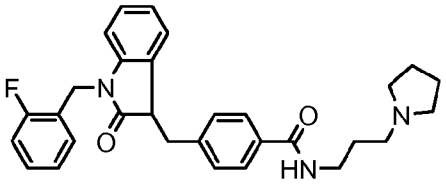
(III)

or a salt, solvate, ester, and/or prodrug thereof;

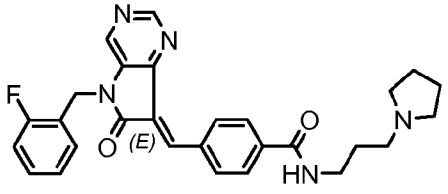
where in:

A_2-X_2 is $C(R^1R^2)$, NR^1, $C{=}CR^1$ (E and Z isomers), or $C{=}NR^1$ (E and Z isomers).

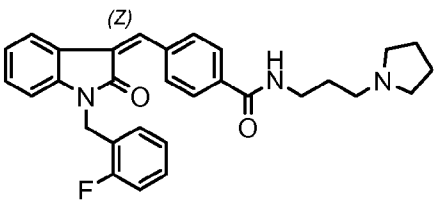
76. The pharmaceutical composition of Claim 75 having a structure selected from the group consisting of:



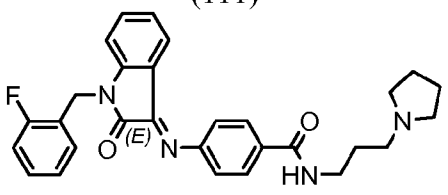
(109)



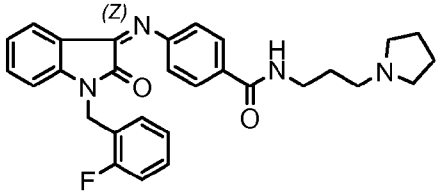
(111)



(113)



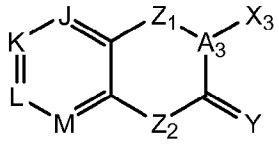
(115)



(117)

77. The pharmaceutical composition of Claim 70, wherein m = 1, n = 2, A = Z_1 and A_3-X_3, and B = Z_2.

78. The pharmaceutical composition of Claim 77 having a structural formula (IV):



(IV)

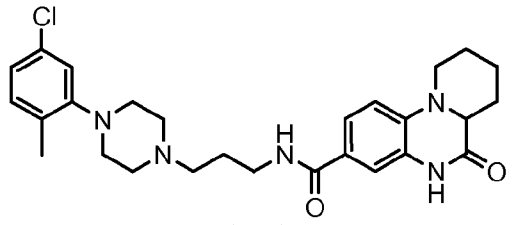
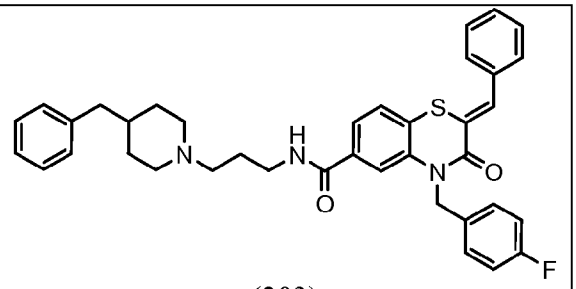
or a salt, solvate, ester, and/or prodrug thereof;

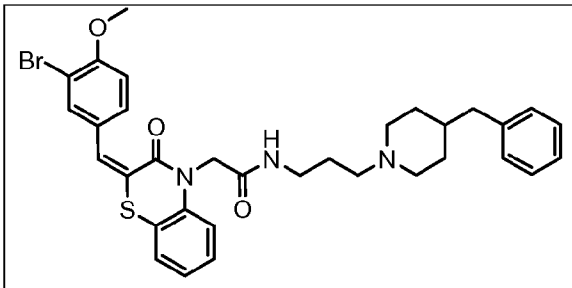
wherein:

A_3-X_3 is $C(R^1R^2)$, NR^1, $C{=}CR^1$ (E and Z isomers), or $C{=}NR^1$ (E and Z isomers);

Z_1 and Z_2 are CH_2, NH, O, S, CR^2, or NR^2.

79. The pharmaceutical composition of Claim 78, wherein the compound of formula (IV) includes the compound selected from the group consisting of:

 (201)	 (203)



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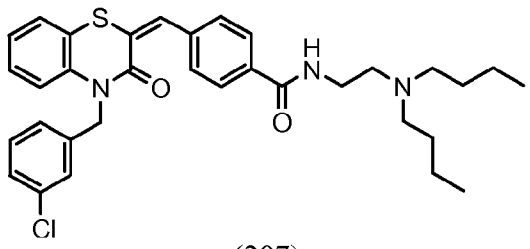

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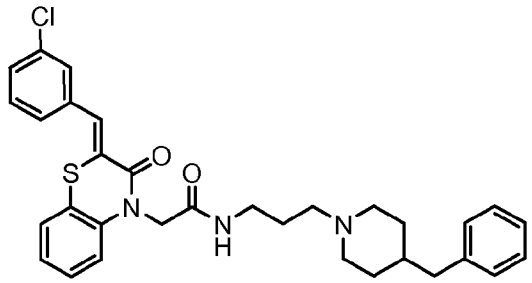

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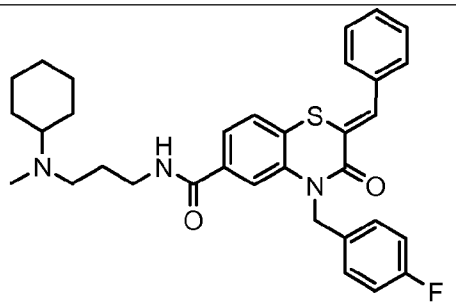

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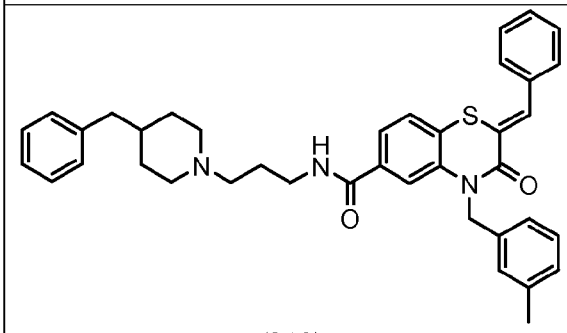

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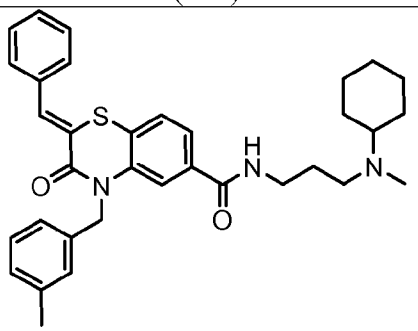

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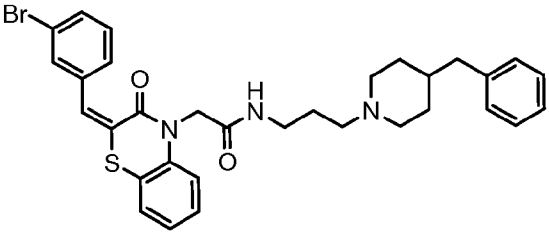

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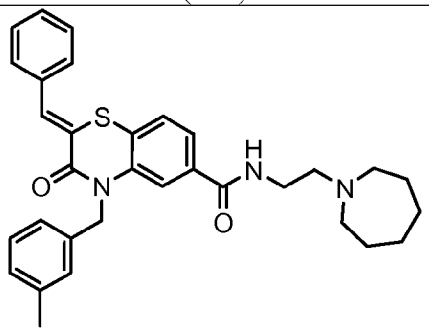

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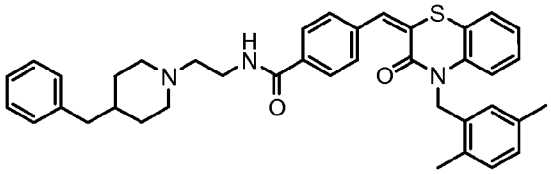
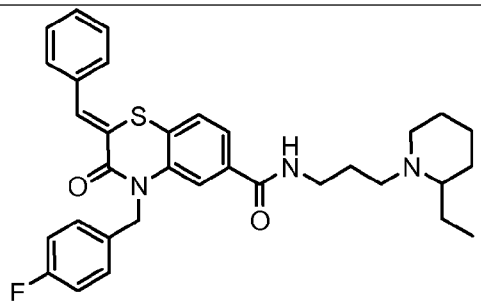
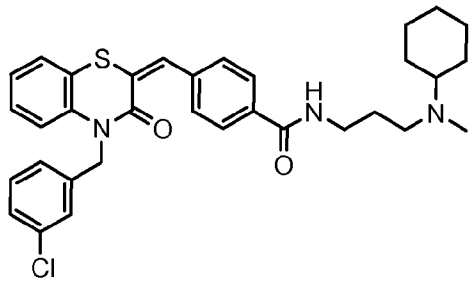
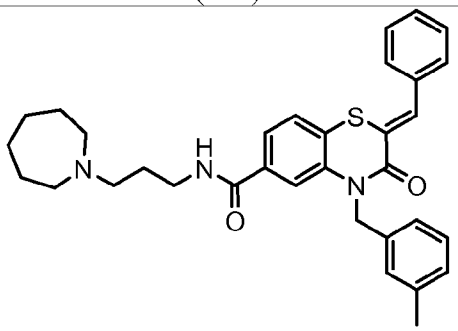
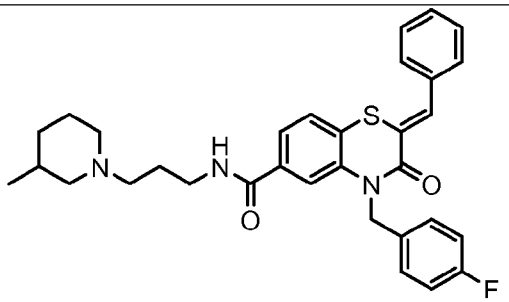
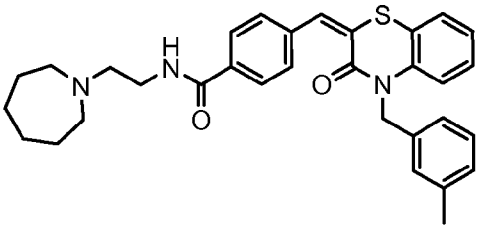
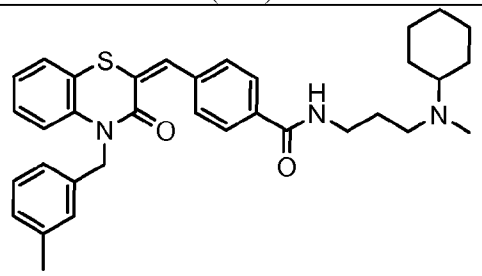
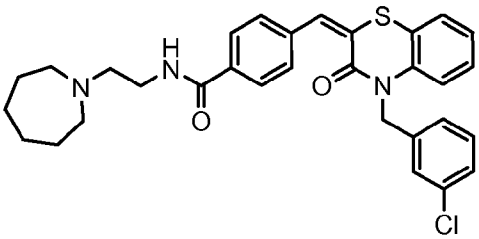
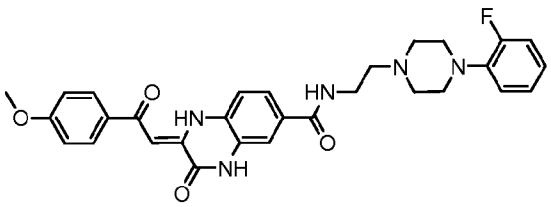
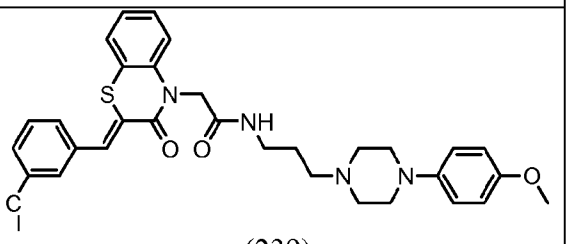
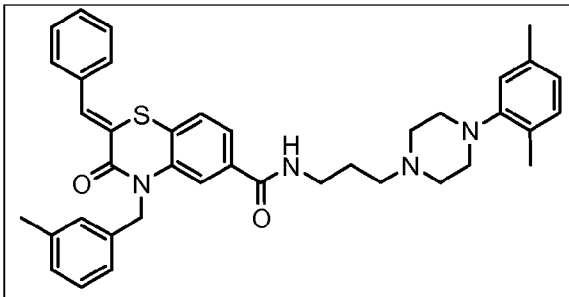
 (221)	 (223)
 (225)	 (227)
 (229)	 (231)
 (233)	 (235)
 (237)	 (239)



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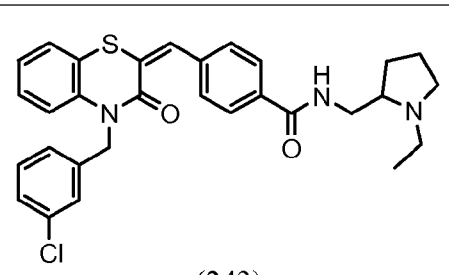

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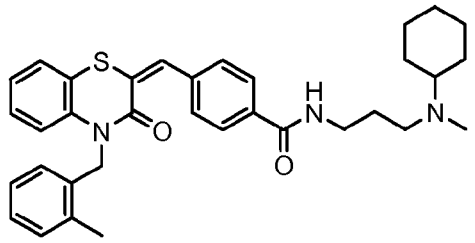

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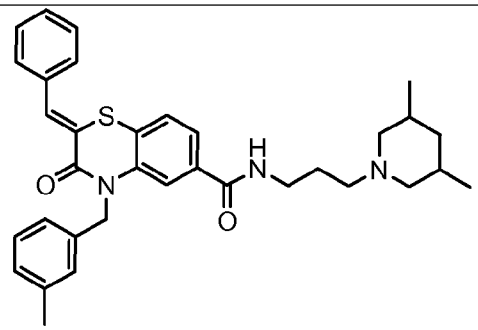

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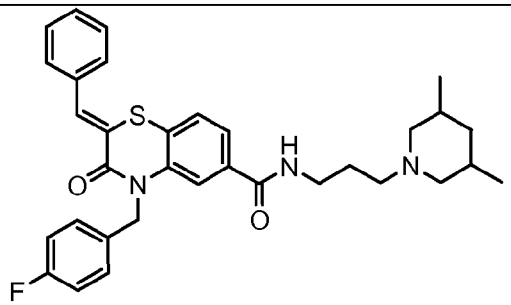

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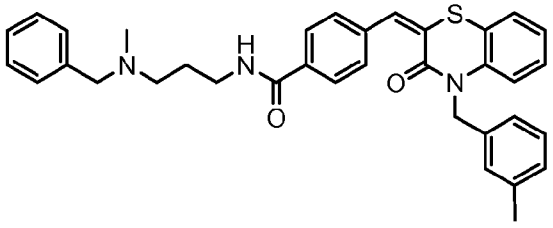

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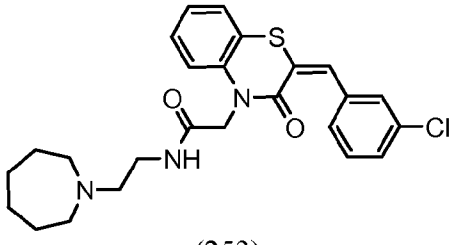

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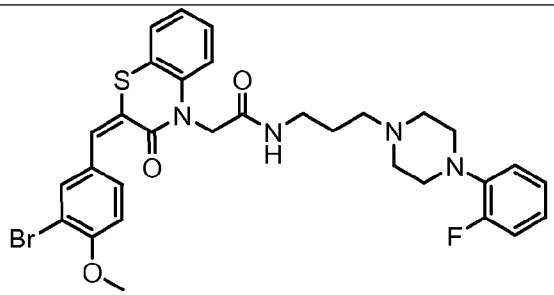

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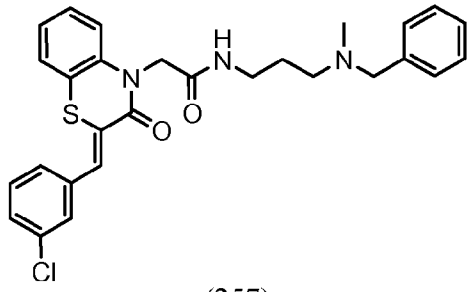
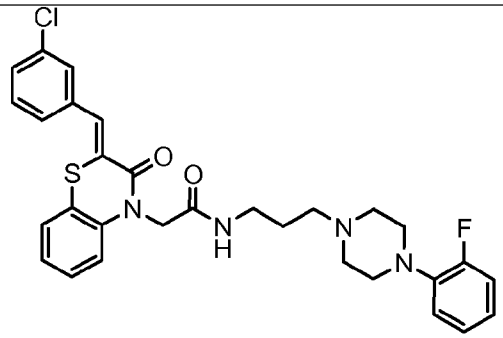
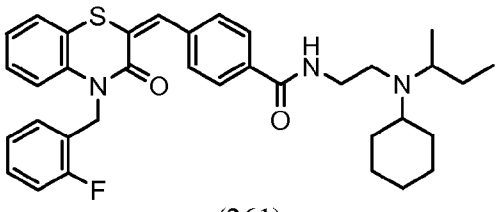
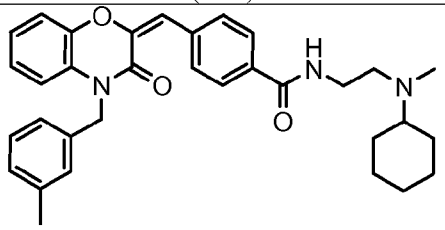
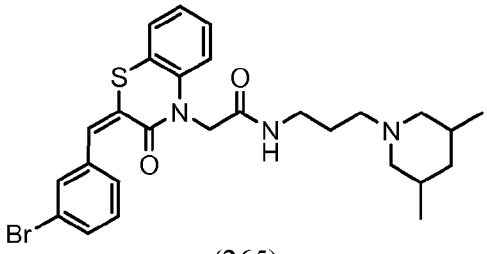
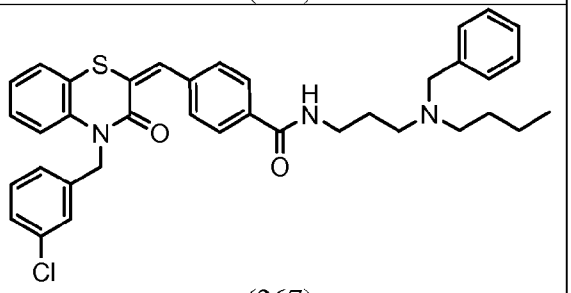
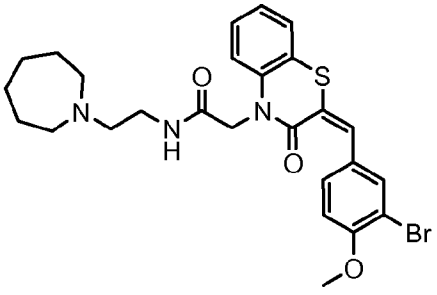
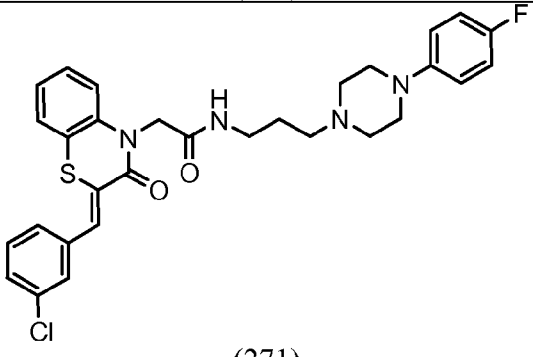
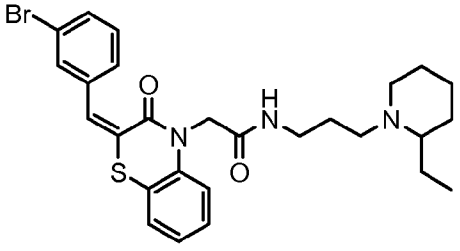
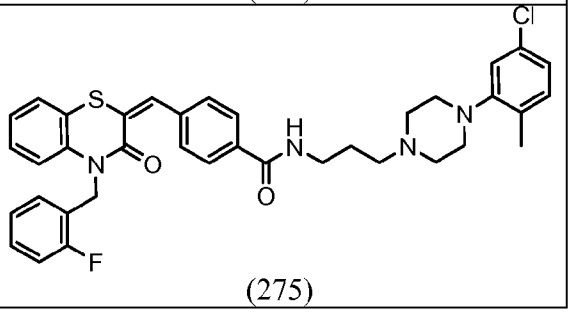
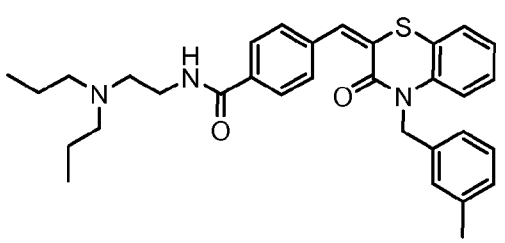
 (257)	 (259)
 (261)	 (263)
 (265)	 (267)
 (269)	 (271)
 (273)	 (275)



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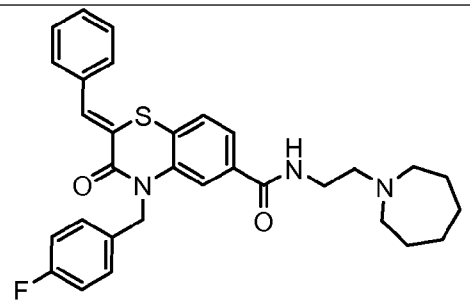

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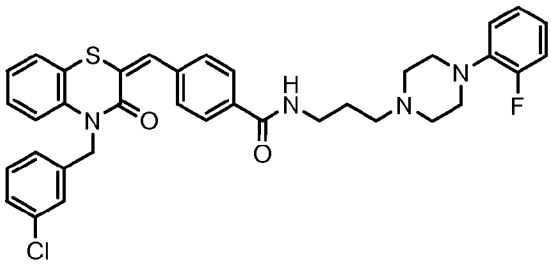

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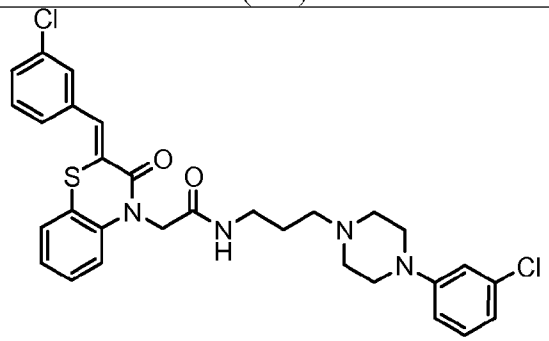

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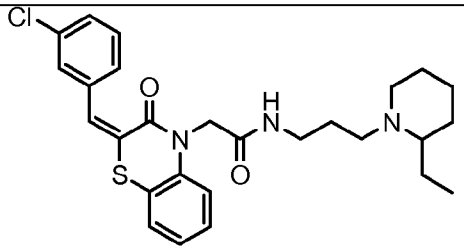
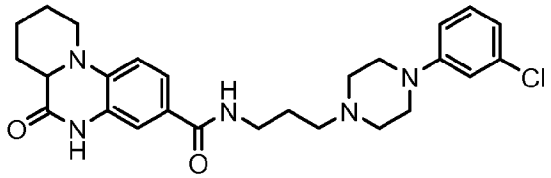


(285)

(287)



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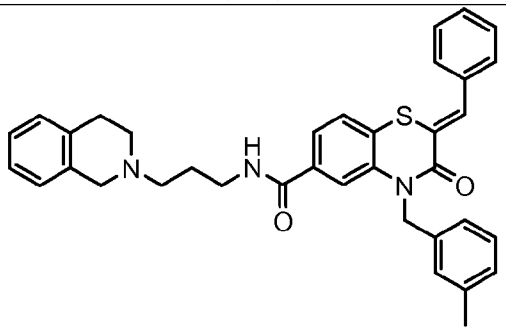

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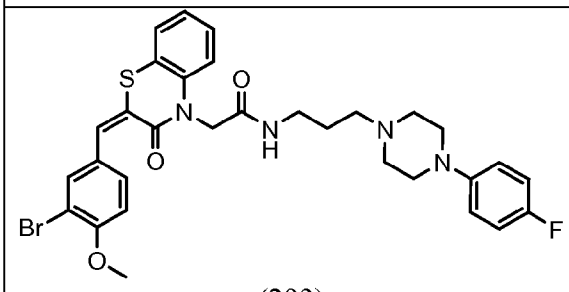

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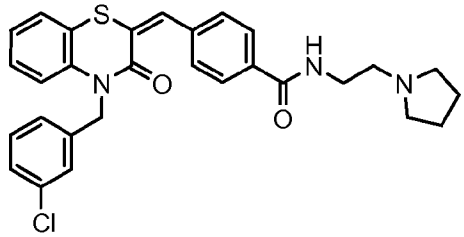

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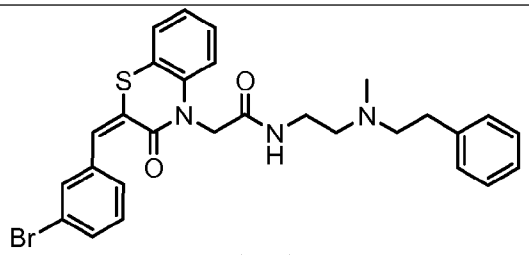
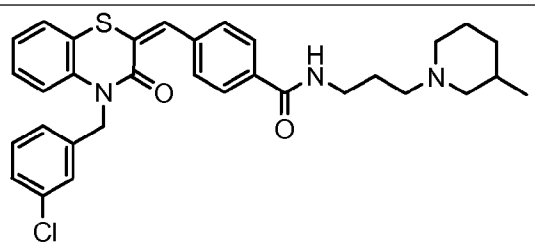
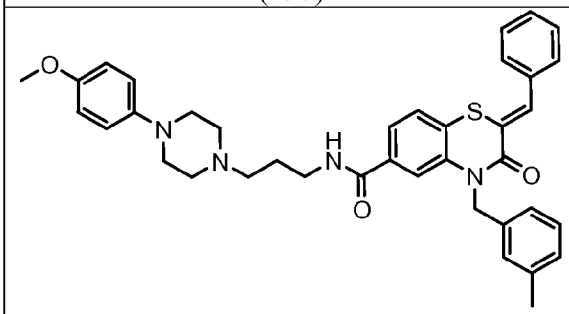
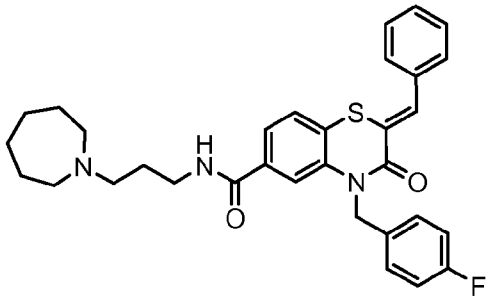
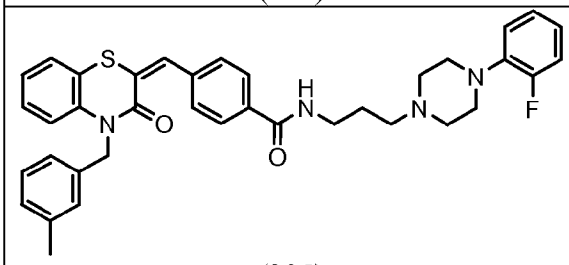
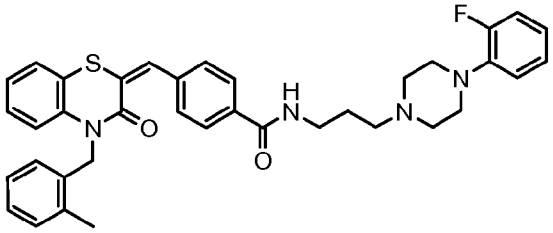
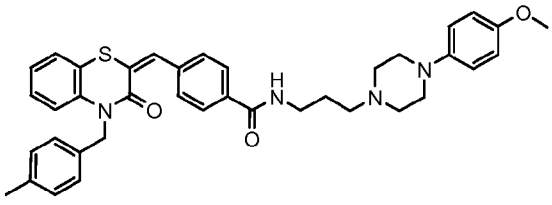
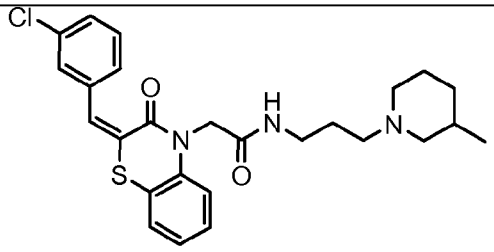
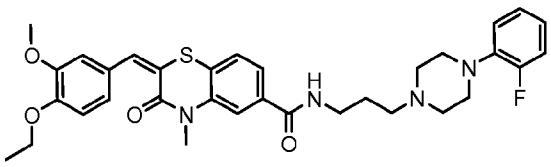
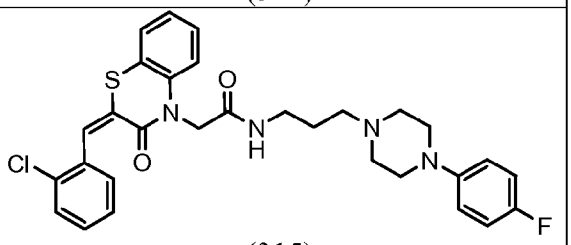
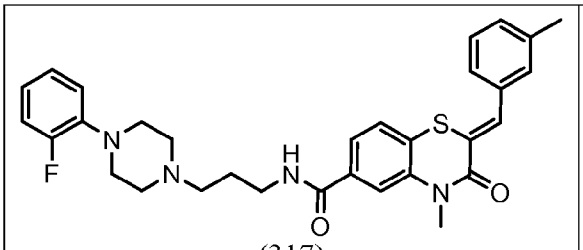
 (297)	 (299)
 (301)	 (303)
 (305)	 (307)
 (309)	 (311)
 (313)	 (315)



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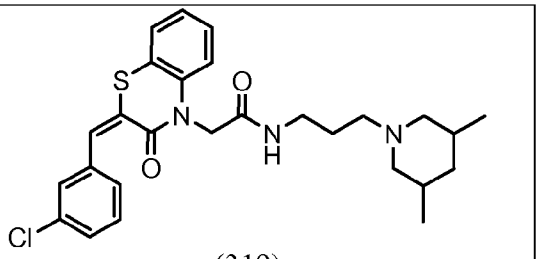

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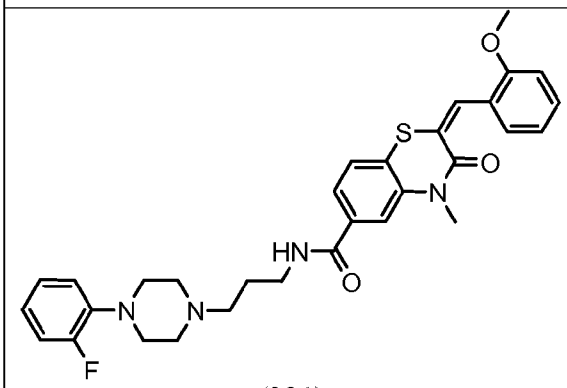
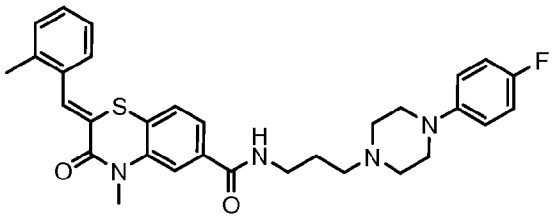


(321)

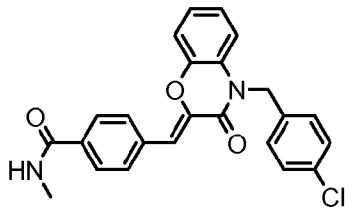


(323).

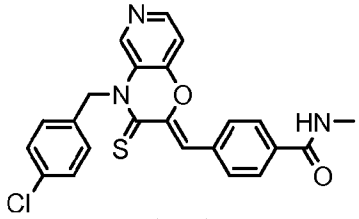
80. The pharmaceutical composition of Claim 78, wherein R^1 and R^2 are not hydrogen.

81. The pharmaceutical composition of Claim 78, wherein at least two of R^1, R^2, and R^3 are not hydrogen.

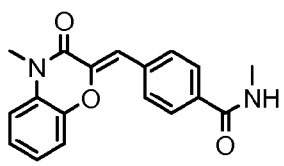
82. The pharmaceutical composition of Claim 78, 80, and 81, wherein the compound having a structural formula (IV) is selected from the group consisting of:



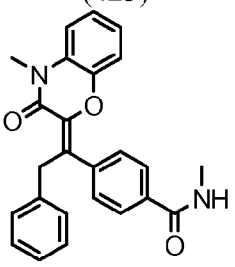
(421)



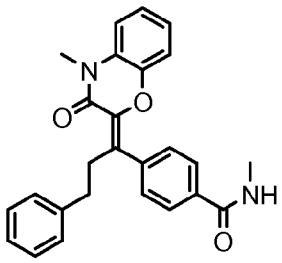
(423)



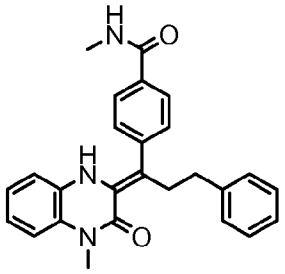
(425)



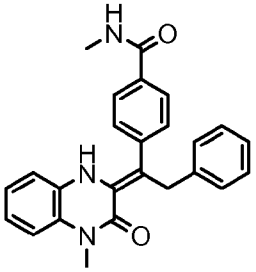
(427)



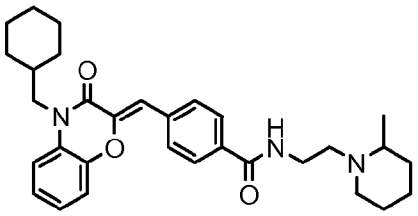
(429)



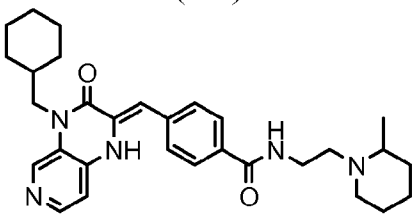
(431)



(433)



(435)



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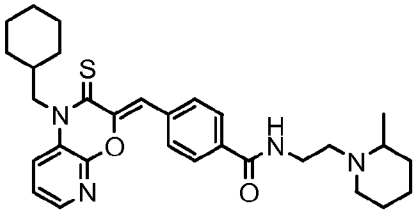

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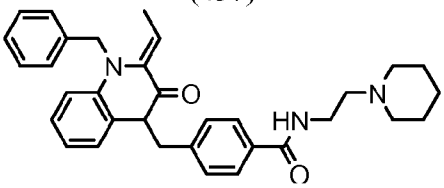

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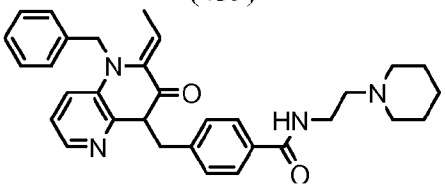

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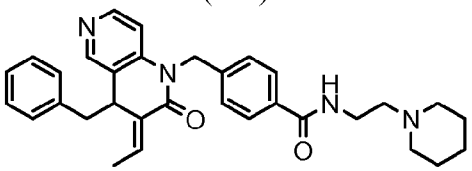
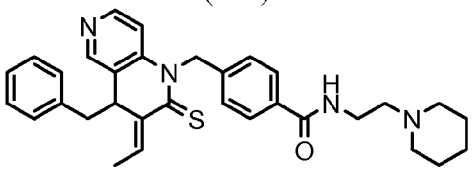
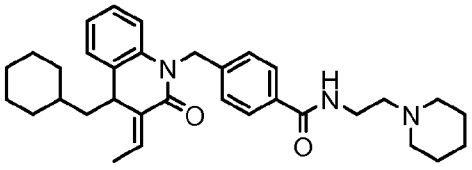


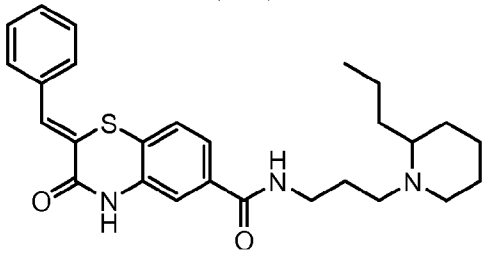
(445)



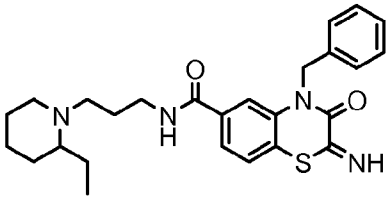
(447)



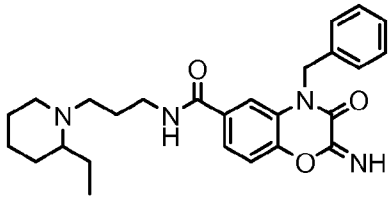
(449)



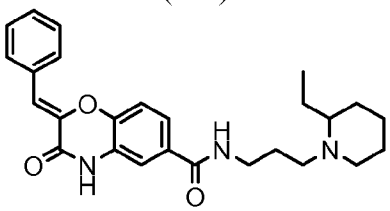
(451)



(453)



(455)



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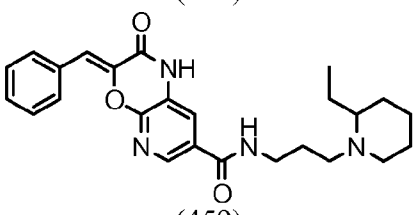

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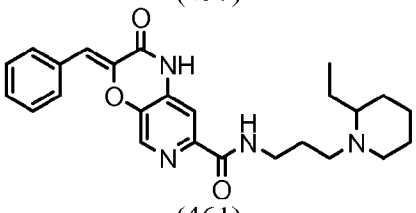

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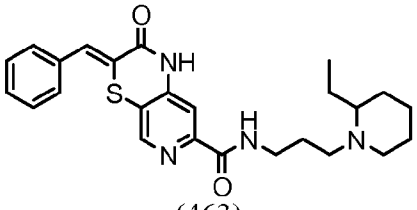
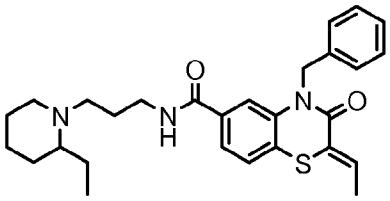


(463)



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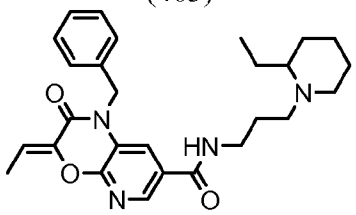
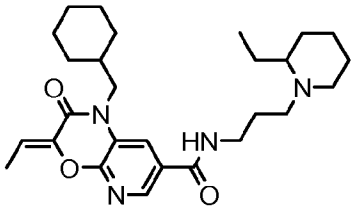


(467)



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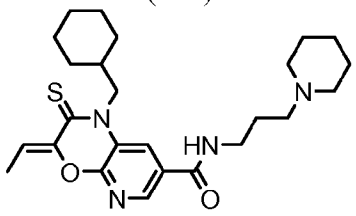
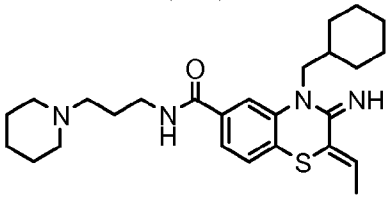


(471)



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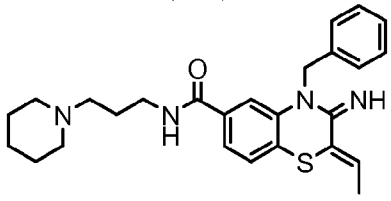

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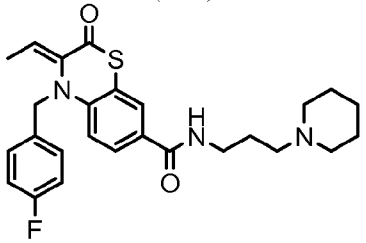

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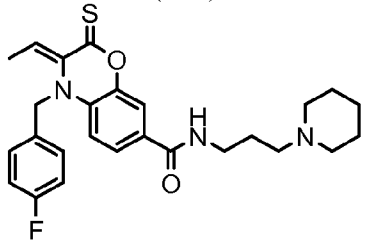
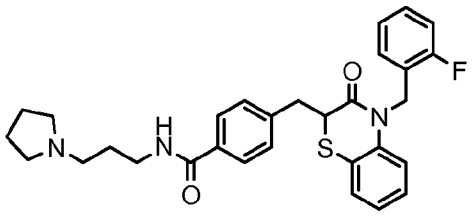
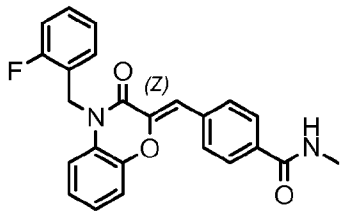


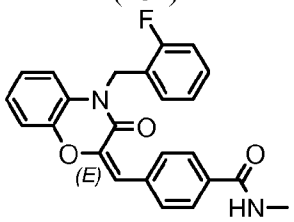
(479)



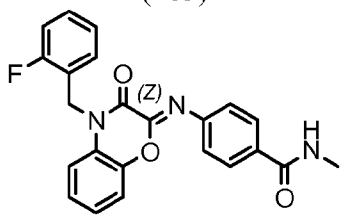
(481)



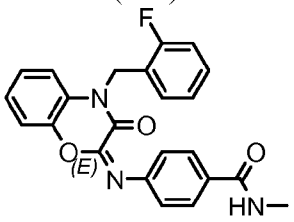
(483)



(485)



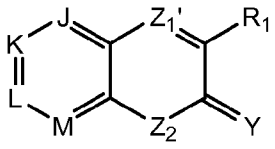
(487)



(489)

83. The pharmaceutical composition of Claim 78, wherein Z_1-A_3 is a double bond, A_3-X_3 is CR^1.

84. The pharmaceutical composition of Claim 83 having a structural formula (IVa):



(IVa)

or salt, solvate, ester, and/or prodrug thereof;

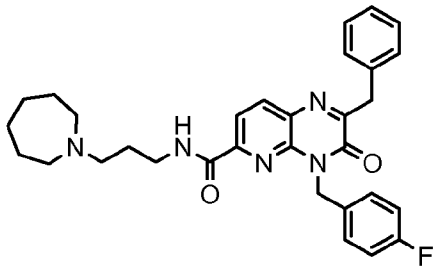
wherein:

Z_1' is either CH or N.

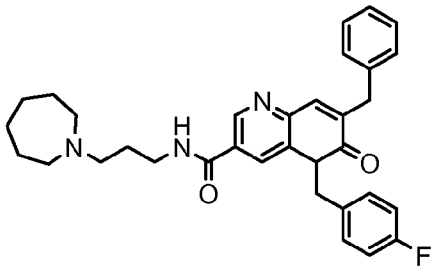
85. The pharmaceutical composition of Claim 84, wherein at least one of J, K, L, and M is independently N.

86. The pharmaceutical composition of Claim 84 and 85, wherein at least one of J, K, L, and M is independently CR^5.

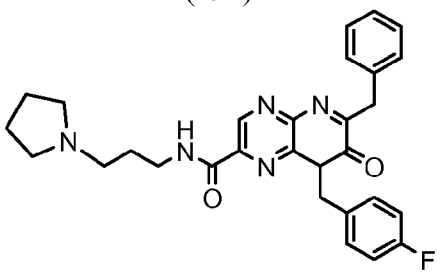
87. The pharmaceutical composition of Claim 84 – 86 having a structure selected from the group consisting of:



(491)



(493)

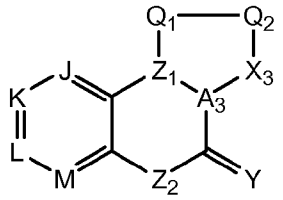


(495)

88. The pharmaceutical composition of Claim 78, wherein Z_1 is CR^3 or NR^3.

89. The pharmaceutical composition of Claim 78 and 88, wherein R^3 forms a 5-member-ring system with A_3-X_3.

90. The pharmaceutical composition of Claim 89 having the structural formula (IVb):



(IVb)

or a salt, solvate, ester, and/or prodrug thereof;

wherein:

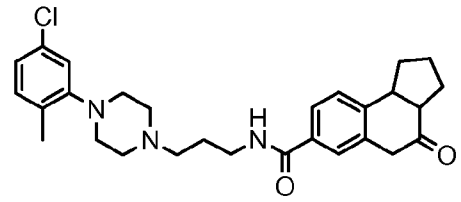
Z_1-Q_1, Q_1-Q_2, Q_2-X_3, A_3-X_3, Z_1-A_3 are independently single or double bond;

Q_1, Q_2, and X_3 are independently S, O, N, N(R^{10}), C(R^{10}), C($R^{10}R^{11}$);

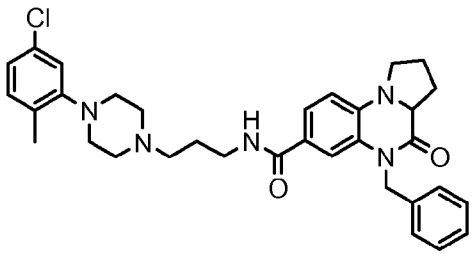
Z_1 and A_3 are independently N, C, or CR^{12};

R^{10}, R^{11}, and R^{12} are independently hydrogen, halogen, acyl, substituted acyl, alkoxycarbonyl, substituted alkoxycarbonyl, aryloxycarbonyl, substituted aryloxycarbonyl, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyl.

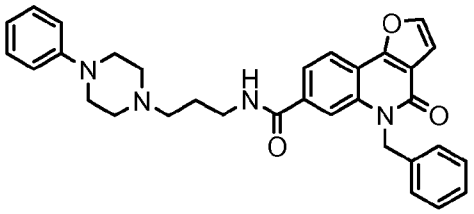
91. The pharmaceutical composition of Claim 90 having a structure selected from the group consisting of:



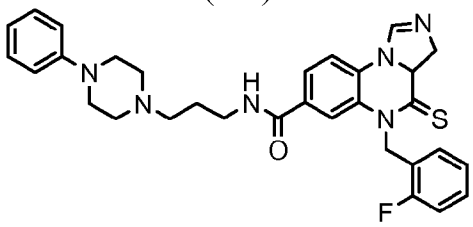
(497)



(499)



(501)

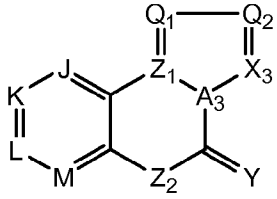


(503).

92. The pharmaceutical composition of Claim 90, wherein Z_1-Q_1 and Q_2-X_3 are double bond.

93. The pharmaceutical composition of Claim 90, wherein Q_1-Q_2, A_3-X_3, and Z_1-A_3 are single bond.

94. The pharmaceutical composition of Claim 90 – 93 having the structural formula (IVb.1):



(IVb.1)

or a salt, solvate, ester, and/or prodrug thereof;

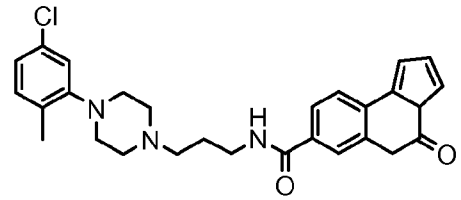
wherein:

Z_1 is C;

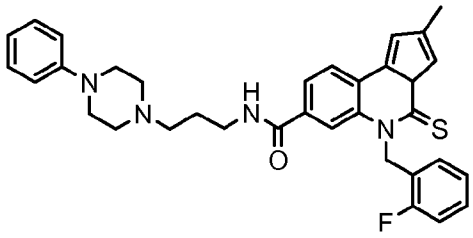
A_3 is N or CR^{12};

X_3, Q_1 and Q_2 are independently N or CR^{10}.

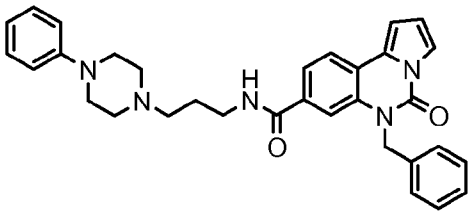
95. The pharmaceutical composition of Claim 94 having a structure selected from the group consisting of:



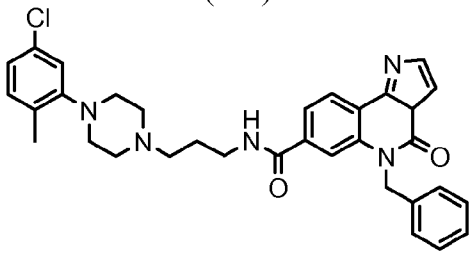
(505)



(507)



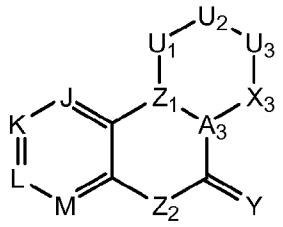
(509)



(511).

96. The pharmaceutical composition of Claim 78 and 88, wherein R^3 forms a 6-member-ring system with A_3-X_3.

97. The pharmaceutical composition of Claim 96 having the structural formula (IVc):



(IVc)

or a salt, solvate, ester, and/or prodrug thereof;

wherein:

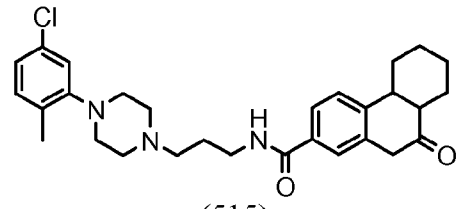
Z_1-U_1, U_1-U_2, U_2-U_3, U_3-X_3, A_3-X_3, Z_1-A_3 are independently single or double bond;

U_1, U_2, U_3, and X_3 are independently S, O, N, $N(R^{13})$, $C(R^{13})$, $C(R^{13}R^{14})$;

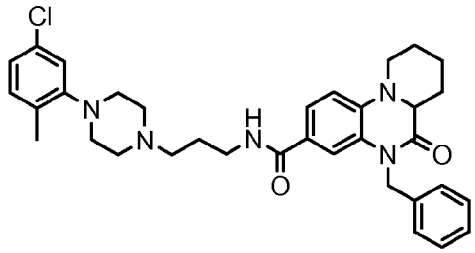
Z_1 and A_3 are independently N, C, or CR^{15};

R^{13}, R^{14}, and R^{15} are independently hydrogen, halogen, acyl, substituted acyl, alkoxycarbonyl, substituted alkoxycarbonyl, aryloxycarbonyl, substituted aryloxycarbonyl, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyl.

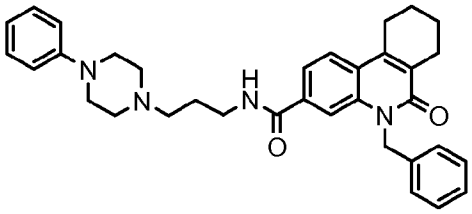
98. The pharmaceutical composition of Claim 97 having a structure selected from the group consisting of:



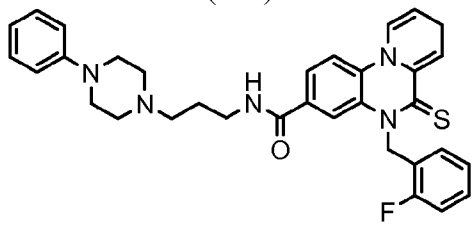
(515)



(517)



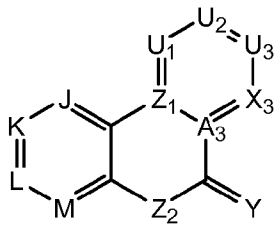
(519)



(521).

99. The pharmaceutical composition of Claim 97, wherein Z_1-U_1, U_1-U_2, U_2-U_3, U_3-X_3, A_3-X_3, Z_1-A_3 is an aromatic system.

100. The pharmaceutical composition of Claim 97 – 99 having the structural formula (IVc.1):



(IVc.1)

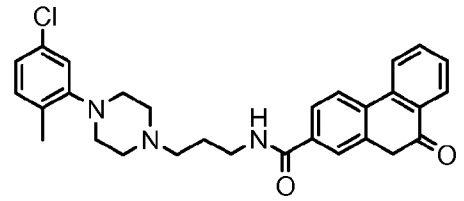
or a salt, solvate, ester, and/or prodrug thereof;

wherein:

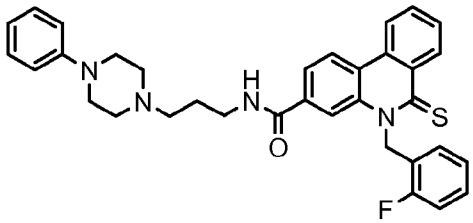
U_1, U_2, U_3 and X_3 are independently N or CR^{13};

Z_1 and A_3 are C.

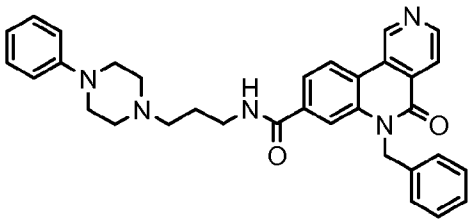
101. The pharmaceutical composition of Claim 100 having a structure selected from the group consisting of:



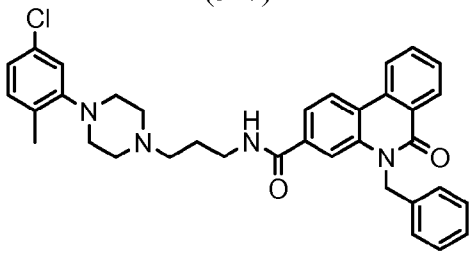
(525)



(527)



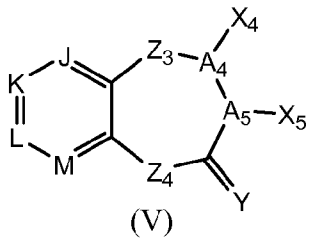
(529)



(531).

102. The pharmaceutical composition of Claim 70, wherein m = 1, n = 3, A is Z_3, A_4-X_4, A_5-X_5, B is Z_4.

103. The pharmaceutical composition of Claim 102 having the structural of formula (V):



(V)

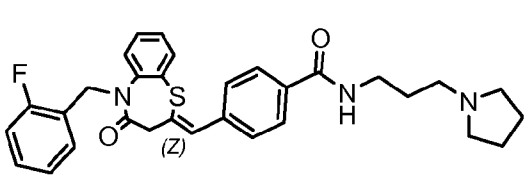
or a salt, solvate, ester, and/or prodrug thereof;

wherein:

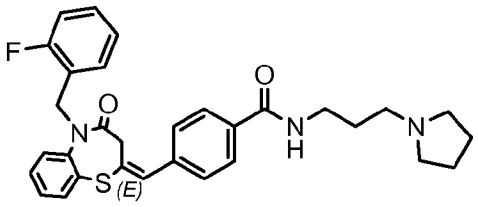
A_4-X_4, A_5-X_5 are independently $C(R^1R^2)$, NR^1, $C{=}CR^1$ (E and Z isomers), or $C{=}NR^1$;

Z_3 and Z_4 are independently O, S, $C(R^1R^2)$, or NR^2.

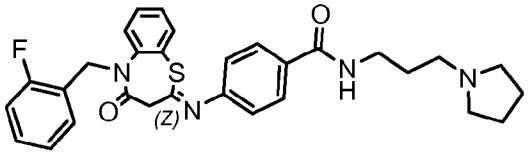
104. The pharmaceutical composition of Claim 103 having a structure selected from the group consisting of:



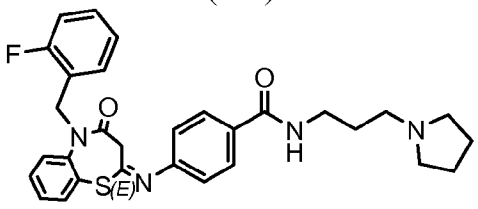
(801)



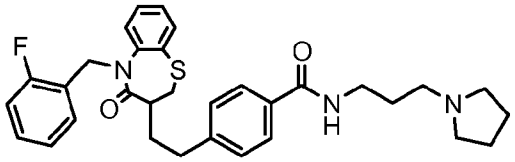
(803)



(805)



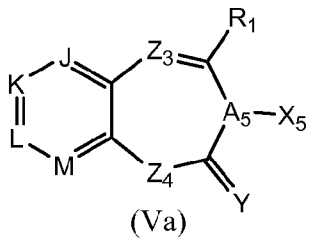
(807)



(809)

105. The pharmaceutical composition of Claim 103, wherein Z_3-A_4 is double bond, $A_4(X_4)$ is CR^1, A_5-X_5 is $C(R^1R^2)$, NR^1, $C{=}CR^1$ (E and Z isomers), or $C{=}NR^1$ (E and Z isomers).

106. The pharmaceutical composition of Claims 103 & 105 having the structural formula (Va):



(Va)

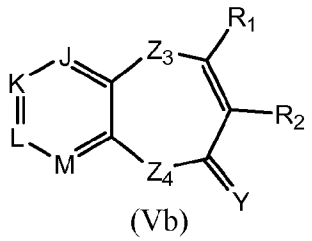
or a salt, solvate, ester, and/or prodrug thereof;

wherein:

Z_3 and Z_4 are independently $C(R^1R^2)$, $N(R^1)$, O, N, or S.

107. The pharmaceutical composition of Claim 103, wherein A_4-A_5 is double bond, $A_4(X_4)$ is CR^1, and $A_5(X_5)$ is CR^2.

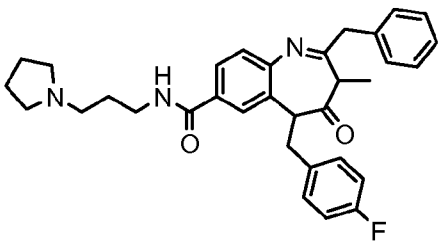
108. The pharmaceutical composition of Claim 103 & 107 having the structural formula (Vb):



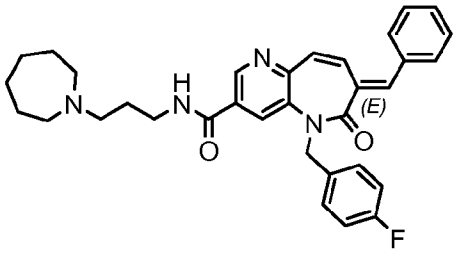
(Vb)

or a salt, solvate, ester, and/or prodrug thereof.

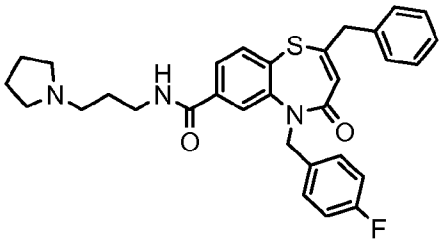
109. The pharmaceutical compositions of Claims 106 & 108 having a structure selected from the group consisting of:



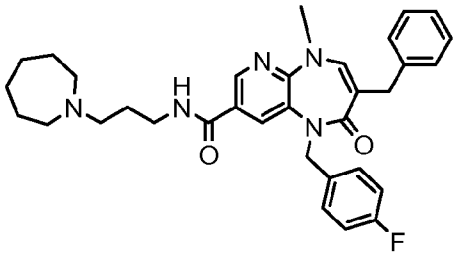
(811)



(813)



(815)

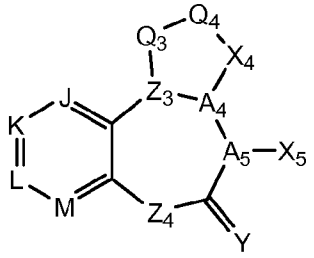


(817).

110. The pharmaceutical composition of Claim 103, wherein Z3 is NR^3, or $C(R^3R^4)$.

111. The pharmaceutical composition of Claims 103 and 110, wherein R^3 forms a 5-member ring system with A4-X4.

112. The pharmaceutical composition of Claims 103, 107 and 111 having the structural formula (Vc):



(Vc)

or a salt, solvate, ester, and/or prodrug thereof;

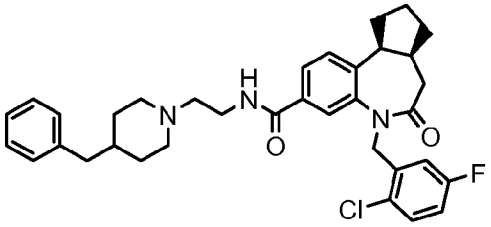
wherein:

Z_3-Q_3, Q_3-Q_4, Q_4-X_4, A_4-X_4, Z_3-A_4 are independently single or double bond;

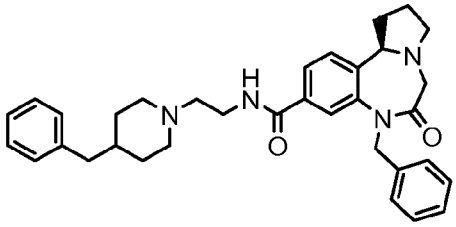
Q_3, Q_4, and X_4 are independently S, O, N, N(R^{16}), C(R^{16}), C($R^{16}R^{17}$);

Z_3 and A_4 are independently N, C, or CR^{18};

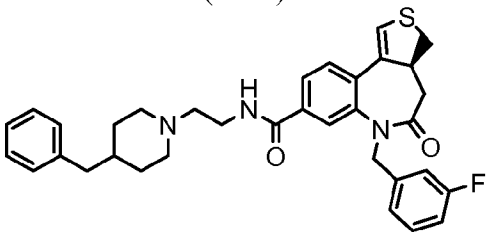
R^{16}, R^{17}, and R^{18} are independently hydrogen, halogen, acyl, substituted acyl, alkoxycarbonyl, substituted alkoxycarbonyl, aryloxycarbonyl, substituted aryloxycarbonyl, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyl;



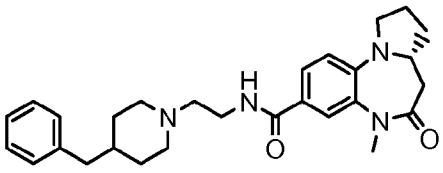
(1101)



(1103)



(1105)

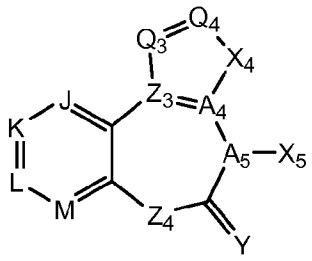


(1107).

113. The pharmaceutical composition of Claim 112, wherein Z3-Q3 and Q4-X4 are double bond.

114. The pharmaceutical composition of Claim 112, wherein Z3-A4, Q3-Q4, and A4-X4 are single bond.

115. The pharmaceutical composition of Claim 112 – 114 having the structural formula (Vc.1):



(Vc.1)

or a salt, solvate, ester, and/or prodrug thereof;

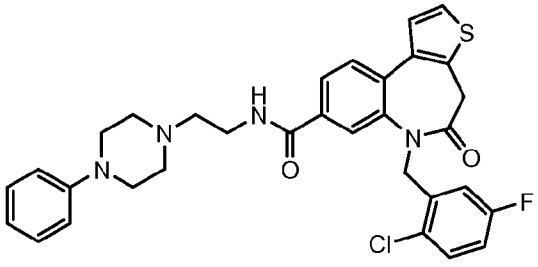
wherein:

Z_3 is C;

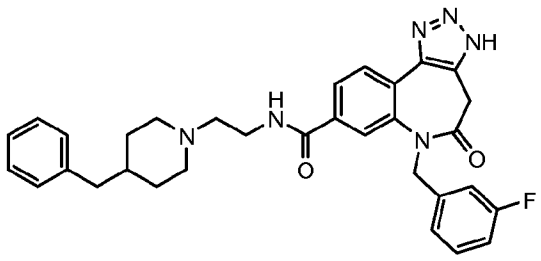
A_4 is N or CR^{18};

X_4, Q_3 and Q_4 are independently N or CR^{16}.

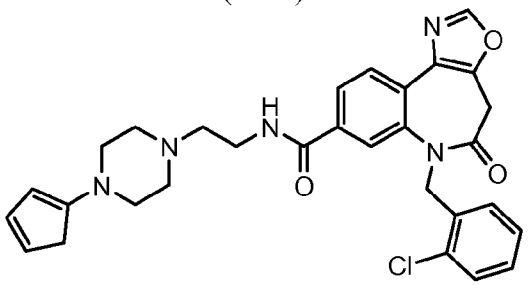
116. The pharmaceutical composition of Claim 115 having a structure selected from the group consisting of:



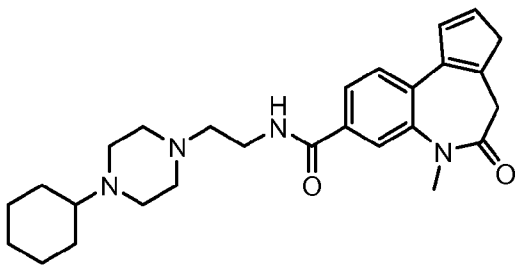
(1121)



(1123)



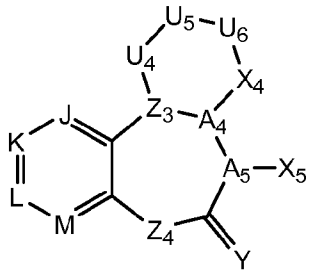
(1125)



(1127).

117. The pharmaceutical composition of Claims 103 and 110, wherein R^3 forms a 6-member ring system with A_4-X_4.

118. The pharmaceutical composition of Claim 117 having the structural formula (Vd):



(Vd)

o a salt, solvate, ester, and/or prodrug thereof;

wherein:

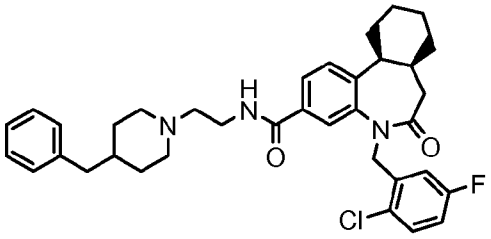
Z_3-U_4 U_4-U_5, U_5-U_6, U_6-X_4, A_4-X_4, Z_3-A_4 are independently single or double bond;

U_4, U_5, U_6, and X_4 are independently S, O, N, $N(R^{19})$, $C(R^{19})$, $C(R^{19}R^{20})$;

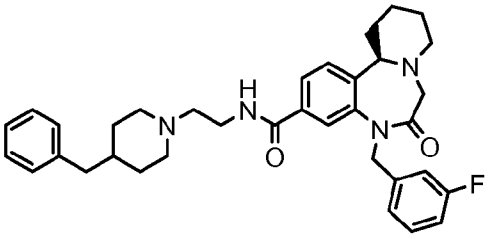
Z_3 and A_4 are independently N, C, or CR^{21};

R^{19}, R^{20}, and R^{21} are independently hydrogen, halogen, acyl, substituted acyl, alkoxycarbonyl, substituted alkoxycarbonyl, aryloxycarbonyl, substituted aryloxycarbonyl, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyl.

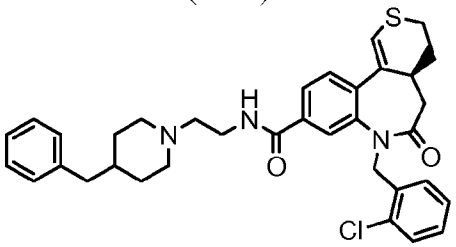
119. The pharmaceutical composition of Claim 118 having a structure selected from the group consisting of:



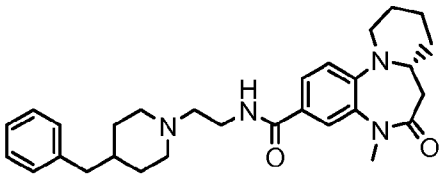
(1131)



(1133)



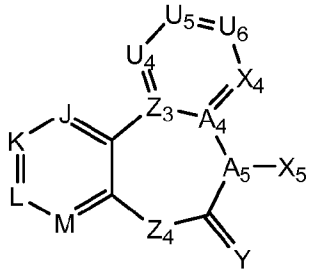
(1135)



(1137).

120. The pharmaceutical composition of Claim 118, wherein Z_3-U_4 U_4-U_5, U_5-U_6, U_6-X_4, A_4-X_4, Z_3-A_4 together form an aromatic system.

121. The pharmaceutical composition of Claims 118 – 120 having the structural formula (Vd.1):



(Vd.1)

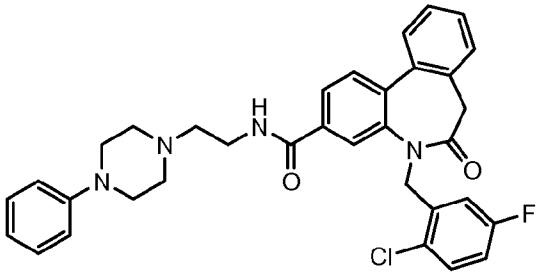
or a salt, solvate, ester, and/or prodrug thereof;

wherein:

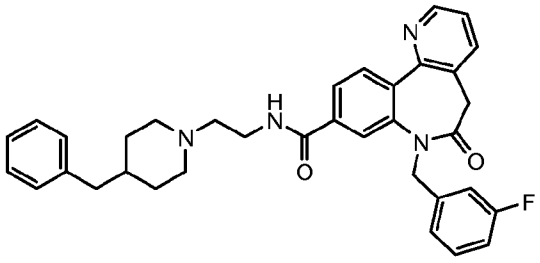
Z_3 and A_4 are C;

U_4, U_5, U_6, and X_4 are independently N or CR^{19}.

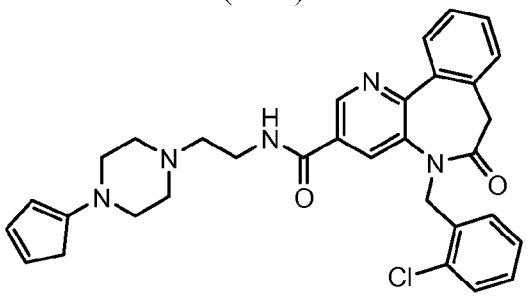
122. The pharmaceutical composition of Claim 121 having a structure selected from the group consisting of:



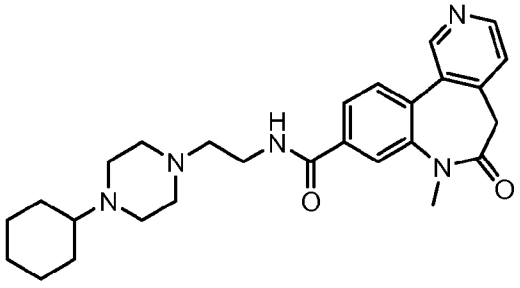
(1141)



(1143)



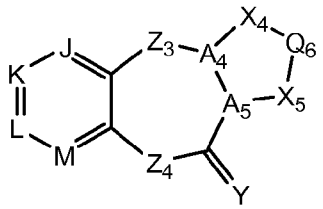
(1145)



(1147).

123. The pharmaceutical composition of Claim 103, wherein A_4-X_4 and A_5-X_5 form a 5-member ring system.

124. The pharmaceutical composition of Claims 103 and 123 having the structural formula (Ve):



(Ve)

or a salt, solvate, ester, and/or prodrug thereof;

wherein:

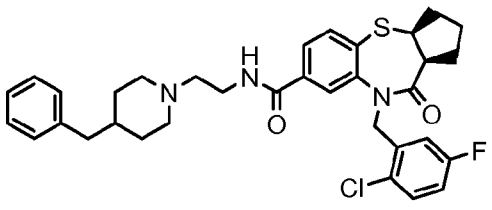
A_4-X_4, X_4-Q_6, Q_6-X_5, A_5-X_5, A_4-A_5 are independently single or double bond;

X_4, X_5, and Q_6 are indpenedently S, O, N, N(R^{22}), C(R^{22}), or C($R^{22}R^{23}$);

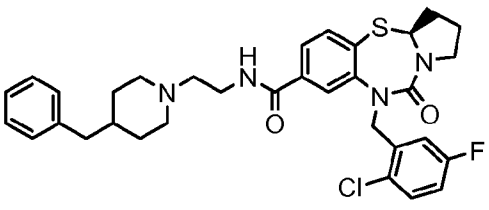
A_4 and A_5 are independently N, C, or CR^{24};

R^{22}, R^{23}, and R^{24} are independently hydrogen, halogen, acyl, substituted acyl, alkoxycarbonyl, substituted alkoxycarbonyl, aryloxycarbonyl, substituted aryloxycarbonyl, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyl.

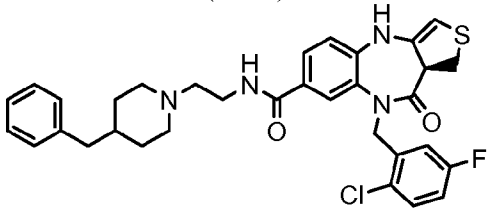
125. The pharmaceutical composition of Claim 124 having a structure selected from the group consisting of:



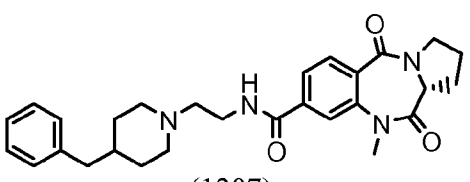
(1201)



(1203)



(1205)

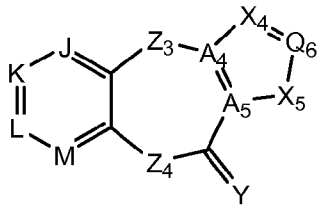


(1207).

126. The pharmaceutical composition of Claim 124, wherein A4-X4 and Q6-X5 are double bond.

127. The pharmaceutical composition of Claim 124, wherein A4-A5, X4-Q6, and A5-X5 are single bond.

128. The pharmaceutical composition of Claims 124 - 127 having the structural formula (Ve.1):



(Ve.1)

or a salt, solvate, ester, and/or prodrug thereof;

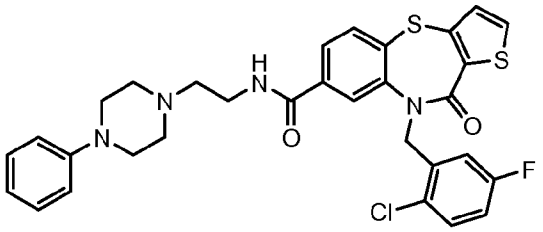
wherein:

A4 and A5 arc C;

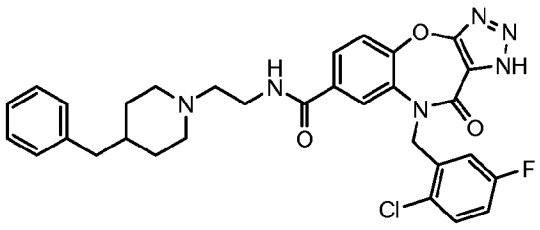
X5 is S, O, N, NR24, or CR24;

X4, and Q6 are independently N or CR20.

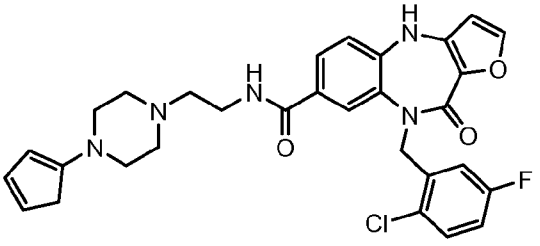
129. The pharmaceutical composition of Claim 128 having a structure selected from thc group consisting of:



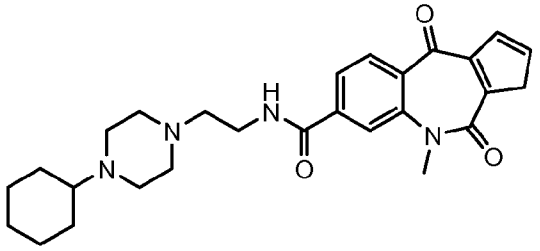
(1215)



(1217)



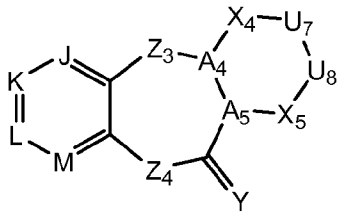
(1219)



(1221).

130. The pharmaceutical composition of Claim 103, wherein A_4-X_4 and A_5-X_5 form a 6-member ring system.

131. The pharmaceutical composition of Claim 103 and 130 having the structural formula (Vf):



(Vf)

or a salt, solvate, ester, and/or prodrug thereof;

wherein:

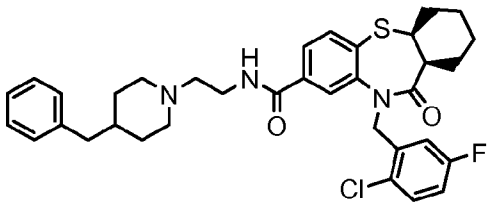
A4-X4, X4-U7, U7-U8, U8-X5, A5-X5, and A4-A5 are independently single or double bond;

X4, U7, U8, and X5 are independently S, O, N, N(R25), C(R25), or C(R25R26);

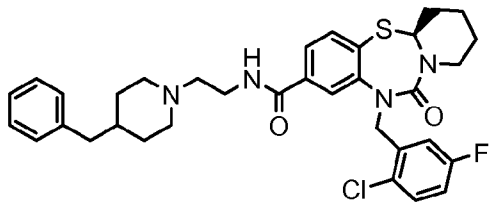
A4 and A5 are independently N, C, or CR27;

R^{25}, R^{26}, and R^{27} are independently hydrogen, halogen, acyl, substituted acyl, alkoxycarbonyl, substituted alkoxycarbonyl, aryloxycarbonyl, substituted aryloxycarbonyl, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyl.

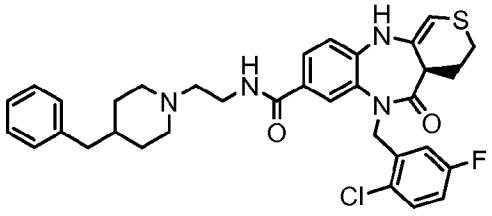
132. The pharmaceutical composition of Claim 131 having a structure selected from the group consisting of:



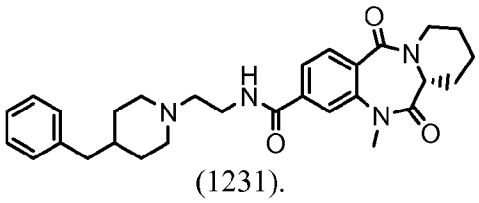
(1225)



(1227)



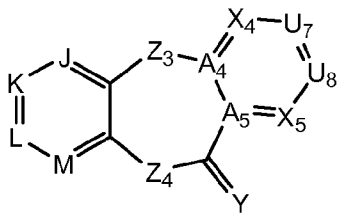
(1229)



(1231).

133. The pharmaceutical composition of Claim 131, wherein A4-X4, X4-U7, U7-U8, U8-X5, A5-X5, and A4-A5 together form an aromatic system.

134. The pharmaceutical composition of Claim 131 – 133 having the structural formula (Vf.1):



(Vf.1)

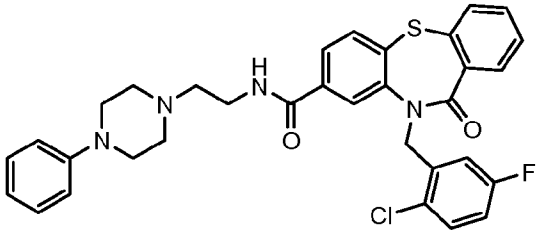
or a salt, solvate, ester, and/or prodrug thereof;

wherein:

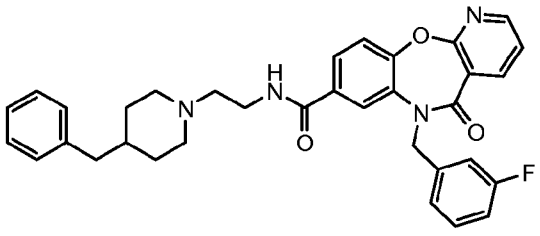
A4 and A5 are C;

X4, U7, U8, and X5 are independently N or CR25.

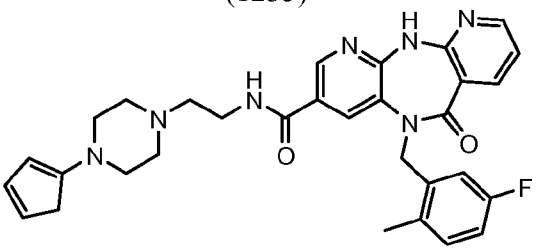
135. The pharmaceutical composition of Claim 134 having a structure selected from the group consisting of:



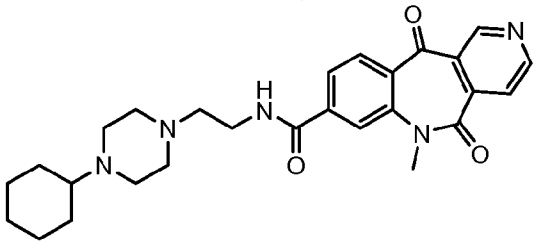
(1235)



(1237)

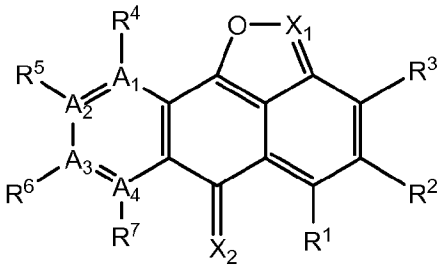


(1239)



(1241).

136. A compounds in the present invention having a structural Formula (VI):



(VI)

or a salt, solvate, ester, and/or prodrug thereof;

wherein:

X_1 is N, or CR^8;

X_2 is S, O, or NR^9;

A_1, A_2, A_3 and A_4 are independently C or N;

R^1, R^2, R^3, R^4, R^5, R^6, R^7, and R^8 are independently hydrogen, halogen, cyano, nitro, amino, substituted amino, sulfonyl, substituted sulfonyl, acyl, substituted acyl, alkoxycarbonyl, substituted alkoxycarbonyl, aryloxycarbonyl, substituted aryloxycarbonyl, $-CONR^{10}R^{11}$, $S(O)_2NR^{10}R^{11}$, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyl or substituted heteroalkyl or alternatively, R^1 and R^2, R^2 and R^3, R^4 and R^5, R^5 and R^6, or R^6 and R^7 taken together with the atoms to which they are bonded, form an aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroaryl or substituted heteroaryl ring;

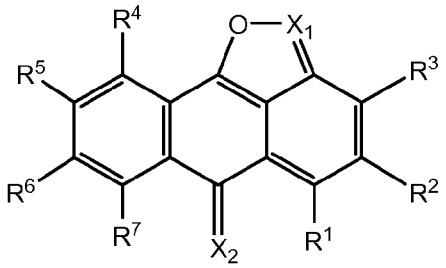
With the proviso that when X_1 is N, or X_1 is CR^8 and R^8 is hydrogen or alkyl, R^1, R^2, R^3, R^4, R^5, R^6 and R^7 are not hydrogen, halogen, cyano, nitro, amino, substituted amino, sulfonyl, substituted sulfonyl, alkyl, substituted alkyl, acyl, substituted acyl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyl, or substituted heteroalkyl;

R^9, R^{10} and R^{11} are independently hydrogen alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl,

substituted heteroarylalkyl, heteroalkyl, substituted heteroalkyl or alternatively R^{10} and R^{11} taken together to with the atoms to which they are bonded, form an aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroaryl or substituted heteroaryl ring.

137. The compound of Claim 136 wherein A_1, A_2, A_3 and A_4 are C.

138. The compound of Claim 137 having a structure formula (VII):



(VII)

or a salt, solvate, ester, and/or prodrug thereof;

X_1 is N, or CR^8;

X_2 is S, O, or NR^9;

R^1, R^2, R^3, R^4, R^5, R^6, R^7, and R^8 are independently hydrogen, halogen, cyano, nitro, amino, substituted amino, sulfonyl, substituted sulfonyl, acyl, substituted acyl, alkoxycarbonyl, substituted alkoxycarbonyl, aryloxycarbonyl, substituted aryloxycarbonyl, $-CONR^{10}R^{11}$, $S(O)_2NR^{10}R^{11}$, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyl or substituted heteroalkyl or alternatively, R^1 and R^2, R^2 and R^3, R^4 and R^5, R^5 and R^6, or R^6 and R^7 taken together with the atoms to which they are bonded, form an aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroaryl or substituted heteroaryl ring;

With the proviso that when X_1 is N, or X_1 is CR^8 and R^8 is hydrogen or alkyl, R^1, R^2, R^3, R^4, R^5, R^6 and R^7 are not hydrogen, halogen, cyano, nitro, amino, substituted amino, sulfonyl, substituted sulfonyl, alkyl, substituted alkyl, acyl, substituted acyl,

arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyl, or substituted heteroalkyl;

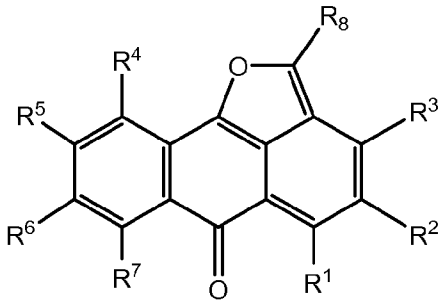
R^9, R^{10} and R^{11} are independently hydrogen alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyl, substituted heteroalkyl or alternatively R^{10} and R^{11} taken together to with the atoms to which they are bonded, form an aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroaryl or substituted heteroaryl ring.

139. The compound of any one of Claims 136 to 138, wherein X_2 is O.

140. The compound of any one of Claims 136 to 138, wherein X_1 is CR^8.

141. The compound of any one of Claims 136 to 138, wherein X_2 is O and X_1 is CR^8.

142. The compound of Claim 141 having a structure formula (VIII):



(VIII)

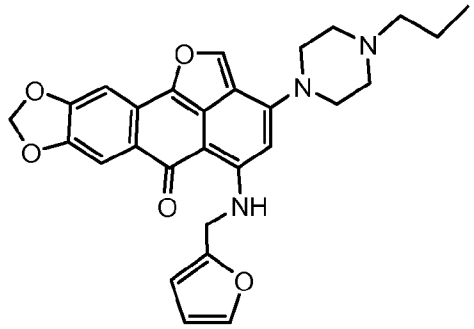
or a salt, solvate, ester, and/or prodrug thereof;

R^1, R^2, R^3, R^4, R^5, R^6, R^7, and R^8 are independently hydrogen, halogen, cyano, nitro, amino, substituted amino, sulfonyl, substituted sulfonyl, acyl, substituted acyl, alkoxycarbonyl, substituted alkoxycarbonyl, aryloxycarbonyl, substituted aryloxycarbonyl, $-CONR^{10}R^{11}$, $S(O)_2NR^{10}R^{11}$, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyl or substituted heteroalkyl or alternatively, R^1 and R^2, R^2 and R^3, R^4 and R^5, R^5 and R^6, or R^6 and R^7 taken together with the atoms to which they are bonded, form an aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroaryl or substituted heteroaryl ring;

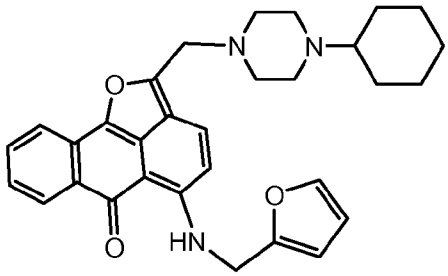
With the proviso that when R^8 is hydrogen or alkyl, R^1, R^2, R^3, R^4, R^5, R^6 and R^7 are not hydrogen, halogen, cyano, nitro, amino, sulfonyl, substituted sulfonyl, alkyl, substituted alkyl, acyl, substituted acyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyl, substituted heteroalkyl;

R^9, R^{10} and R^{11} are independently hydrogen alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyl, substituted heteroalkyl or alternatively R^{10} and R^{11} taken together to with the atoms to which they are bonded, form an aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroaryl or substituted heteroaryl ring.

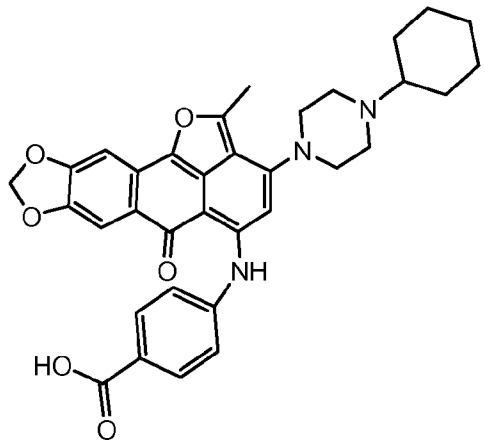
143. The compounds of Claim 142 having the following structures:



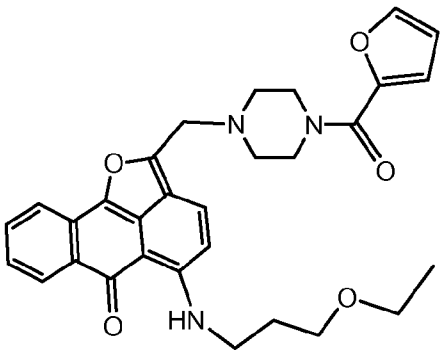
(11)



(13)



(15)

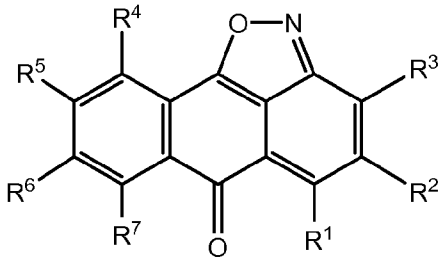


(17).

144. The compound of any one of Claims 136 to 138, wherein X_1 is N.

145. The compound of any one of Claims 136 to 138, wherein X_1 is N, X_2 is O.

146. The compound of Claim 145 having a structure formula (IX):



(IX)

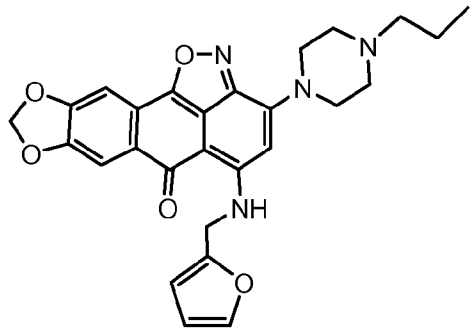
or a salt, solvate, ester, and/or prodrug thereof;

R^1, R^2, R^3, R^4, R^5, R^6, and R^7 are independently substituted amino, substituted sulfonyl, acyl, substituted acyl, alkoxycarbonyl, substituted alkoxycarbonyl, aryloxycarbonyl, substituted aryloxycarbonyl, $-CONR^{10}R^{11}$, $-SO_2NR^{10}R^{11}$, alkyl, substituted alkyl, aryl, substituted aryl, substituted heteroaryl, substituted heteroarylalkyl, heteroalkyl or substituted heteroalkyl or alternatively, R^1 and R^2, R^2 and R^3, R^4 and R^5, R^5 and R^6, or R^6 and R^7 taken together with the atoms to which they are bonded, form an aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroaryl or substituted heteroaryl ring;

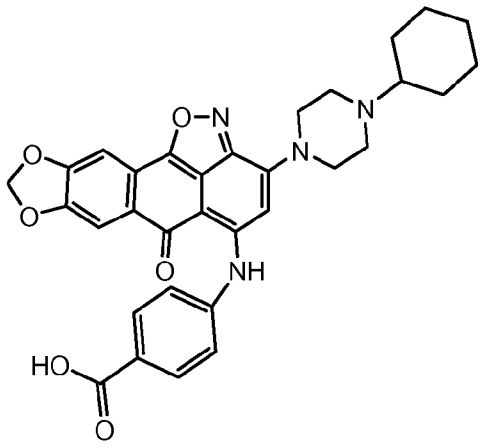
With the proviso that R^1, R^2, R^3, R^4, R^5, R^6 and R^7 are not hydrogen, halogen, cyano, nitro, amino, sulfonyl, acyl, substituted acyl, arylalkyl, substituted arylalkyl, heteroaryl, or heteroarylalkyl;

R^9, R^{10} and R^{11} are independently hydrogen alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyl, substituted heteroalkyl or alternatively R^{10} and R^{11} taken together to with the atoms to which they are bonded, form an aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroaryl or substituted heteroaryl ring.

147. The compounds of Claim 146 having the following structures:

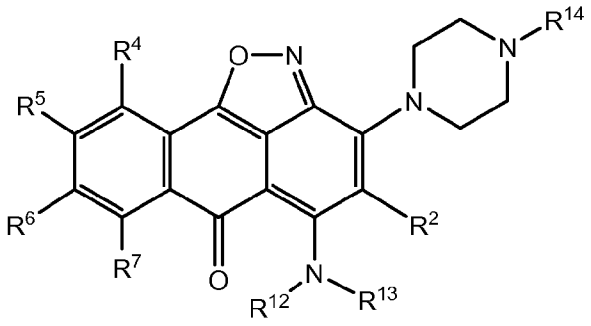


(41)



(43).

148. The compound having a structure formula (X):



(X)

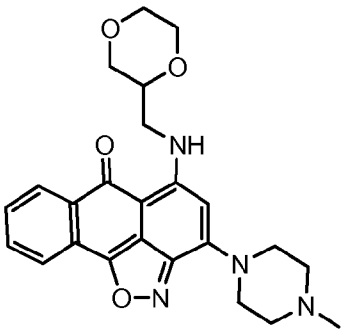
or a salt, solvate, ester, and/or prodrug thereof;

R^2, R^4, R^5, R^6, R^7, R^8, R^{12}, R^{13}, and R^{14} are independently hydrogen, halogen, cyano, nitro, amino, substituted amino, sulfonyl, substituted sulfonyl, acyl, substituted acyl, alkoxycarbonyl, substituted alkoxycarbonyl, aryloxycarbonyl, substituted aryloxycarbonyl, -$CONR^{10}R^{11}$, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyl or substituted heteroalkyl or alternatively, R^{12} and R^{13}, R^4 and R^5, R^5 and R^6, or R^6 and R^7 taken together with the atoms to which they are bonded, form an aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroaryl or substituted heteroaryl ring;

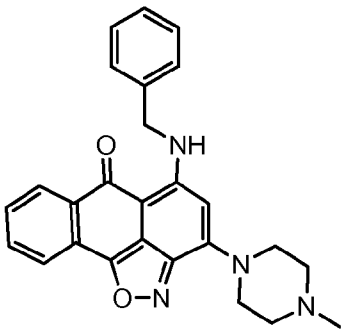
With the proviso that R^1, R^2, R^3, R^4, R^5, R^6 and R^7 are not hydrogen, halogen, cyano, nitro, amino, sulfonyl, substituted sulfonyl, alkyl, substituted alkyl, acyl, substituted acyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyl, substituted heteroalkyl, -$C(O)NR^{10}R^{11}$ or -$S(O)_2NR^{10}R^{11}$;

R^9, R^{10} and R^{11} are independently hydrogen alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyl, substituted heteroalkyl or alternatively R^{10} and R^{11} taken together to with the atoms to which they are bonded, form an aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroaryl or substituted heteroaryl ring.

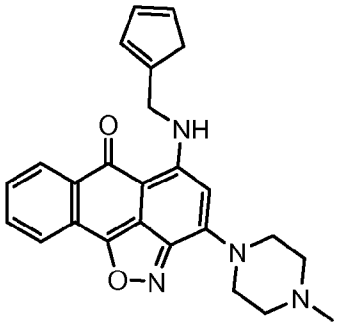
149. The compound of Claim 148 having the following structures:



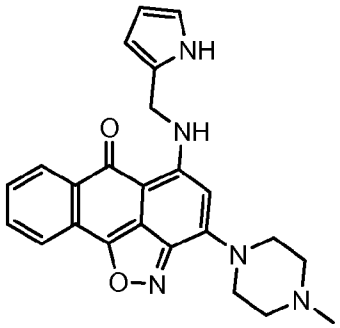
(1001)



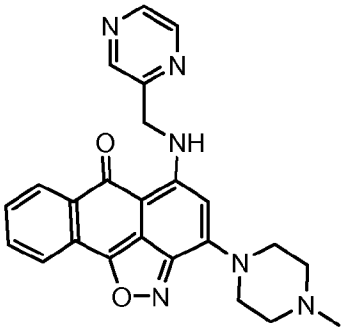
(1003)



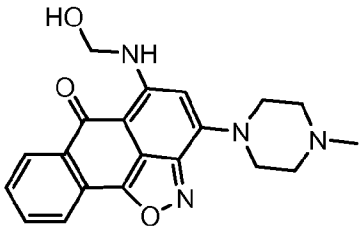
(1005)



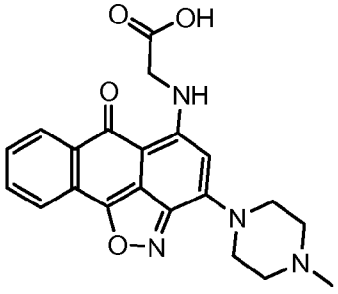
(1007)



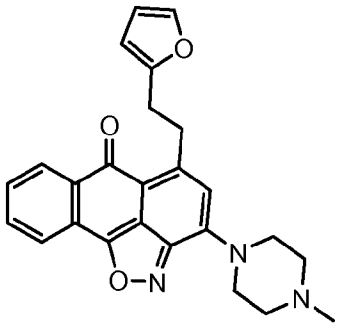
(1009)



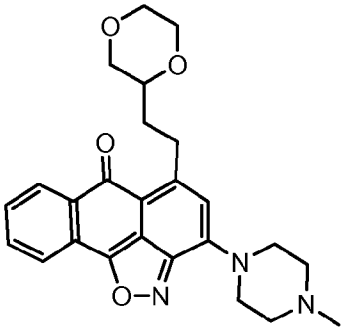
(1011)



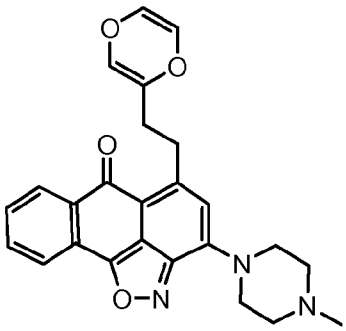
(1013)



(1015)

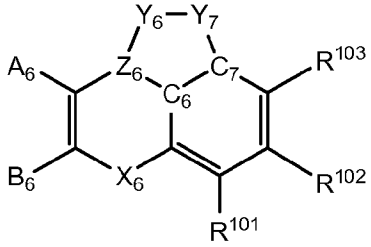


(1017)



(1019).

150. A pharmaceutical composition comprising a compound having a structural formula (XI):



(XI)

or a salt, solvate, ester, and/or prodrug thereof;

wherein:

R^{101}, R^{102} and R^{103} are independently hydrogen, halogen, cyano, nitro, amino, substituted amino, sulfonyl, substituted sulfonyl, acyl, substituted acyl, alkoxycarbonyl, substituted alkoxycarbonyl, aryloxycarbonyl, substituted aryloxycarbonyl, -$CONR^{104}R^{105}$,

$S(O)_2NR^{104}R^{105}$, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyl or substituted heteroalkyl or alternatively, R^{101} and R^{102}, or R^{102} and R^{103} taken together with the atoms to which they are bonded, form an aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroaryl or substituted heteroaryl ring;

A_6 and B_6 are independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyl or substituted heteroalkyl or alternatively, A_6 and B_6, taken together with the atoms to which they are bonded, form an aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroaryl or substituted heteroaryl ring;

C_6, C_7 and Z_6 are independently C or N;

X_6, Y_6 and Y_7 are independently $N(R^{104})$, $C(R^{105}R^{106})$, CR^{107}, $C(=NR^{108})$, $NR^{109}R^{110}$, O, S, SO_2, C(=O), or C(=S);

R^{106}, R^{107} and R^{108} are independently hydrogen, alkyl, substituted alkyl, acyl, substituted acyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyl, substituted heteroalkyl, $-C(O)NR^{104}R^{105}$ or $-S(O)_2NR^{104}R^{105}$;

R^{104}, R^{105}, R^{109}, and R^{110} are independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyl or substituted heteroalkyl or alternatively, R^{104} and R^{105}, or R^{109}, and R^{110} taken together with the atoms to which they are bonded, form a cycloheteroalkyl or substituted cycloheteroalkyl ring;

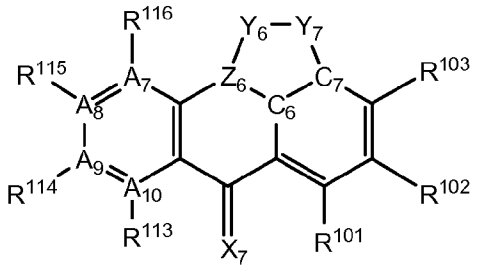
The bond between C_6 and C_7, C_7 and Y_6, Y_7 and Y_6, Y_6 and Z_6, or Z_6 and C_6 are independently selected to be a single bond or a double bond.

151. The compound of any one of Claims 150, wherein X_6 is $C(=X_7)$ and X_7 is S, O, or NR^{117}.

152. The compound of any one of Claims 150, wherein A_6 and B_6 form a substituted aryl ring or substituted heteroaryl ring.

153. The compound of any one of Claims 150, wherein X_6 is $C(=X_7)$ and A_6 and B_6 form a substituted aryl ring or substituted heteroaryl ring.

154. A pharmaceutical composition comprising the compound of Claim 153 having a structural Formula (XII):



(XII)

or a salt, solvate, ester, and/or prodrug thereof;

wherein:

X_7 is S, O, or NR^{117};

A_7, A_8, A_9 and A_{10} are independently C or N; and

R^{113}, R^{114}, R^{115}, R^{116} and R^{117} are independently hydrogen, halogen, cyano, nitro, amino, substituted amino, sulfonyl, substituted sulfonyl, alkyl, substituted alkyl, acyl, substituted acyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyl, substituted heteroalkyl, $-C(O)NR^{104}R^{105}$ or $-S(O)_2NR^{104}R^{105}$ or alternatively, R^{113} and R^{114}, R^{114} and R^{115}, or R^{115} and R^{116} taken together with the atoms to which they are bonded, form an aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroaryl or substituted heteroaryl ring.

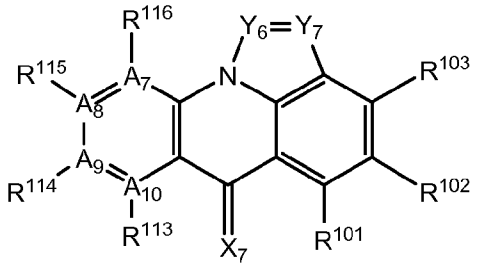
155. The compound of any of Claim 150 to 154, wherein C_6 and C_7 are C.

156. The compound of any of Claim 150 to 154, wherein Z_6 is N.

157. The compound of any of Claim 150 to 154, wherein Y_7 is CR^7 or N.

158. The compound of any of Claim 150 to 154, wherein C_6 and C_7 are C, Z_6 is N, the bond between C_6 and C_7 is a double bond, the bond between Y_6 and Y_7 is also a double bond.

159. A pharmaceutical composition comprising the compound of Claim 158 having a structural Formula (XIII):



(XIII)

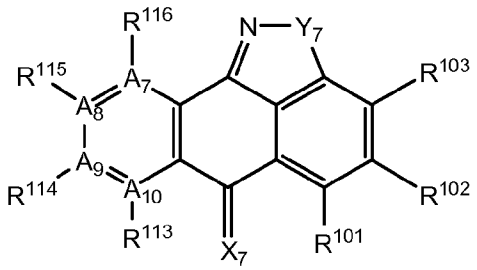
or a salt, solvate, ester, and/or prodrug thereof.

160. The compound of any of Claim 150 to 154, wherein Z_6 is C.

161. The compound of any of Claim 150 to 154, wherein Y_6 is N.

162. The compound of any of Claim 150 to 154, wherein C_6, C_7 and Z_6 are C, Y_6 is N, the bond between C_6 and C_7 is a double bond, the bond between Y_6 and Z_6 is also a double bond.

163. A pharmaceutical composition comprising the compound of Claim 162 having a structural Formula (XIV):

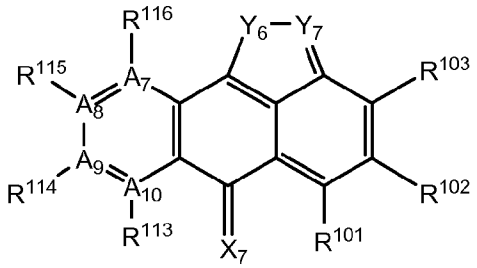


(XIV)

or a salt, solvate, ester, and/or prodrug thereof.

164. The compound of any of Claim 150 to 154, wherein C_6, C_7 and Z_6 are C, the bond between C_6 and Z_6 is a double bond, the bond between Y_7 and C_7 is also a double bond.

165. A pharmaceutical composition comprising the compound of Claim 164 having a structural Formula (XV):



(XV)

or a salt, solvate, ester, and/or prodrug thereof.

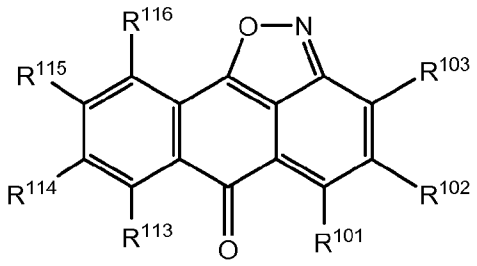
166. The compound of any one of Claims 165, wherein X_7 is O.

167. The compound of any one of Claims 165, wherein Y_6 is O and Y_7 is N.

168. The compound of any one of Claims 165, wherein X_7 is O, Y_6 is O and Y_7 is N.

169. The compound of Claim 168, wherein A_6, A_7, A_8 and A_9 are C.

170. A pharmaceutical composition comprising the compound of Claim 169 having a structural Formula (XVI):



(XVI)

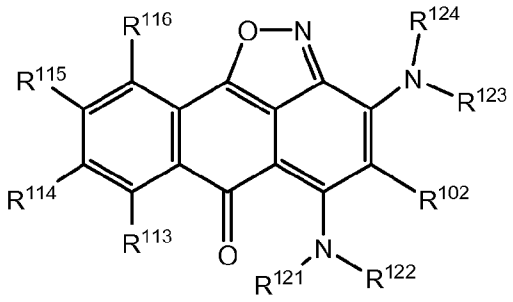
or a salt, solvate, ester, and/or prodrug thereof.

171. The compound of Claim 170, wherein R^{101} is $NR^{121}R^{122}$.

172. The compound of Claim 170, wherein R^{103} is $NR^{123}R^{124}$.

173. The compound of Claim 170, wherein R^{101} is $NR^{121}R^{122}$ and R^{103} is $NR^{123}R^{124}$.

174. A pharmaceutical composition comprising the compound of Claim 173 having a structural Formula (XVII):



(XVII)

or a salt, solvate, ester, and/or prodrug thereof;

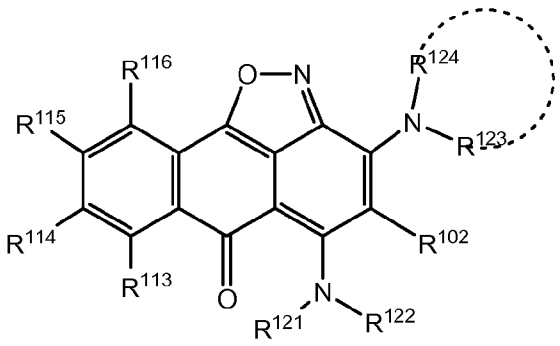
R^{121}, R^{122}, R^{123} and R^{124} are independently hydrogen, sulfonyl, substituted sulfonyl, acyl, substituted acyl, alkoxycarbonyl, substituted alkoxycarbonyl, aryloxycarbonyl, substituted aryloxycarbonyl, $-CONR^{104}R^{105}$, $-S(O)_2NR^{104}R^{105}$, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyl or substituted heteroalkyl or alternatively, R^{121} and R^{122}, or R^{123} and R^{124} taken together with the atoms to which they are bonded, form a cycloheteroalkyl, substituted cycloheteroalkyl, heteroaryl or substituted heteroaryl ring.

175. The compound of Claim 174, wherein R^{123} and R^{124} taken together with the atoms to which they are bonded, form a cycloheteroalkyl.

176. The compound of Claim 174, wherein R^{121} is hydrogen.

177. The compound of Claim 174, wherein R^{121} is hydrogen and R^{123} and R^{124} taken together with the atoms to which they are bonded, form a cycloheteroalkyl ring or substituted cycloheteroalkyl ring.

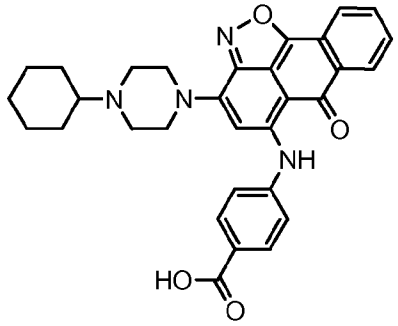
178. A pharmaceutical composition comprising the compound of Claim 177 having a structural Formula (XVIII):



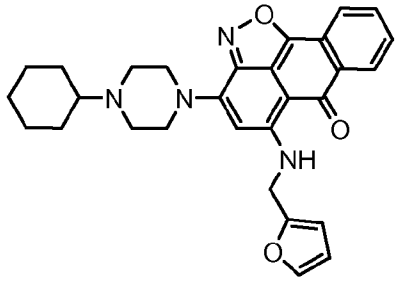
(XVIII)

or a salt, solvate, ester, and/or prodrug thereof.

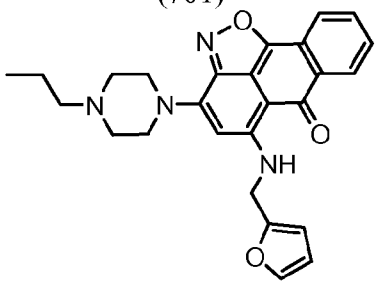
179. The compound of Claim 178 having a structure selected from the group consisting of:



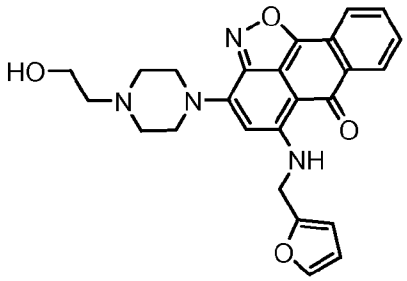
(701)



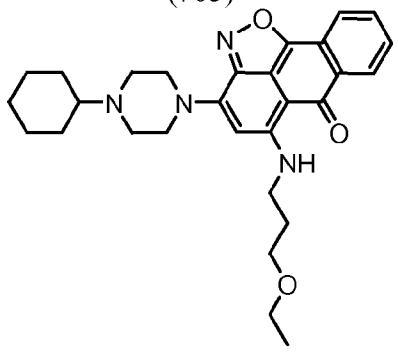
(703)



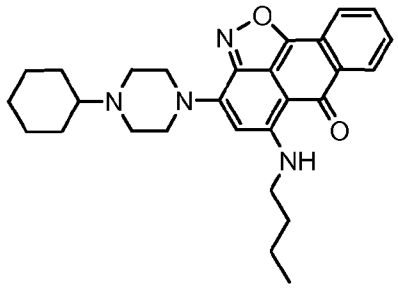
(705)



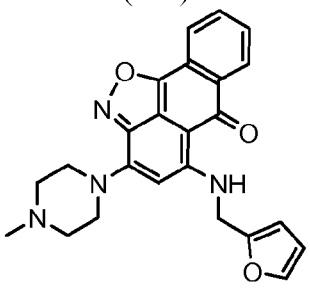
(707)



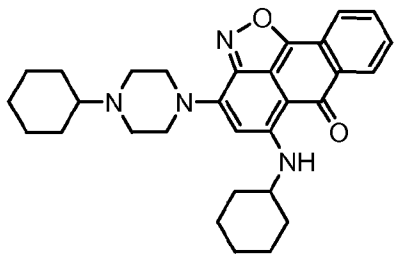
(709)



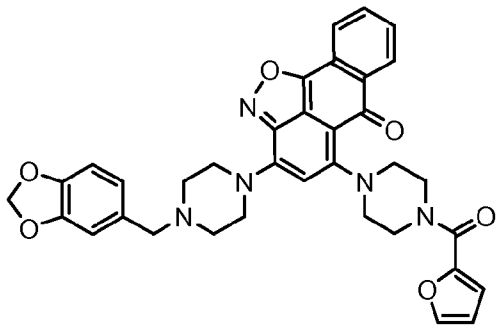
(711)



(713)



(715)



(717)

180. The pharmaceutical composition of Claim 70, 136, or 150, wherein the compound having a structural formula (I), (IV), (XI) is in a therapeutically effective amount.

181. The pharmaceutical composition of Claim 70, 136, or 150, wherein the compound having a structural formula (I), (IV), (XI) inhibits and/or antagonizes NGF receptor TrkA with IC50 value less than 1 uM.

182. The Claim 181, wherein the compound is selectively inhibits and/or antagonizes NGF receptor TrkA.

183. The pharmaceutical composition of Claim 70, 136, or 150, wherein the compound having a structural formula (I), (IV), (XI) reduces pain and/or hyperalgesia.

184. The pharmaceutical composition of Claim 70, 136, or 150, which is used to treat a disease, or symptom or condition selected from the group consisting of: acute pain, chronic pain, inflammatory pain, neuropathic pain, tonic pain, persistent pain, postoperative pain, chemical-induced pain, chemotherapy-induced pain, drug-induced pain, a generalized pain disorder, anxiety, skeletal muscle spasms, convulsive seizures, epilepsy, cancer, restenosis, atherosclerosis, psoriasis, thrombosis, or a disease, disorder or injury relating to dysmyelination or demyelination and a combination thereof.

185. The claim 184, wherein the disease or symptom or condition is due to causalgia, diabetes, collagen vascular disease, trigeminal neuralgia, spinal cord injury, brain stem injury, thalamic pain syndrome, complex regional pain syndrome type I/reflex sympathetic dystrophy, Fabry's syndrome, small fiber neuropathy, cancer, cancer chemotherapy, chronic alcoholism, stroke, abscess, demyelinating disease, viral infection, anti-viral therapy, AIDS, AIDS therapy, burn, sunburn, arthritis, colitis, carditis, dermatitis, myositis, neuritis, mucositis, urethritis, cystitis, gastritis, pneumonitis, collagen vascular disease, trauma, surgery, amputation, toxin, chemotherapy, fibromyalgia, irritable bowel syndrome, a temporomandibular disorder, and a combination thereof.

186. The pharmaceutical composition of Claim 70, 136, or 150, which is incorporated into an oral dose, or an injection, or a transdermal patch or implantation of a depot formulation.

187. A pharmaceutical composition comprising: (a) a compound having a structural formula (I), (IV), (XI) as defined in Claim 70, 136, or 150, and (b) at least one analgesic agent that acts by a mechanism different from a TrkA antagonist.

188. A pharmaceutical composition comprising (a) a compound having a structural formula (I), (IV), (XI) as defined in Claim 70, 136, or 150, and (b) at least one agent selected from the group consisting of: an inhibitor of protein kinase A (PKA), a PKC_epsilon inhibitor, an inhibitor of cAMP signaling, a nonsteroidal anti-inflammatory drug, a prostaglandin synthesis inhibitor, a local anesthetic, an anticonvulsant, an antidepressant, an opioid receptor agonist, a neuroleptic, and a combination thereof.

189. A method of reducing pain, comprising administering to a subject in need thereof an effective amount of a compound having a structural formula (I), (IV), (XI) as defined in Claim 70, 136, or 150.

190. The method of claim 189, wherein the pain is selected from the group consisting of: acute pain, chronic pain, inflammatory pain, neuropathic pain, tonic

pain, persistent pain, postoperative pain, chemical-induced pain, chemotherapy-induced pain, drug-induced pain, a generalized pain disorder, and a combination thereof.

191. The method of claim 189, wherein the pain is associated with a condition selected from the group consisting of: causalgia, diabetes, collagen vascular disease, trigeminal neuralgia, spinal cord injury, brain stem injury, thalamic pain syndrome, complex regional pain syndrome type I/reflex sympathetic dystrophy, Fabry's syndrome, small fiber neuropathy, cancer, cancer chemotherapy, chronic alcoholism, stroke, abscess, demyelinating disease, viral infection, anti-viral therapy, AIDS, AIDS therapy, burn, sunburn, arthritis, colitis, carditis, dermatitis, myositis, neuritis, mucositis, urethritis, cystitis, gastritis, pneumonitis, collagen vascular disease, trauma, surgery, amputation, toxin, chemotherapy, fibromyalgia, irritable bowel syndrome, a temporomandibular disorder, and a combination thereof.

192. The method of claim 189, further comprising co-administering to the subject an analgesic agent that acts by a mechanism different from a TrkA antagonist.

193. The method of claim 189, further comprising co-administering at least one agent selected from the group consisting of: an inhibitor of protein kinase A (PKA), a PKC_epsilon inhibitor, an inhibitor of cAMP signaling, a nonsteroidal anti-inflammatory drug, a prostaglandin synthesis inhibitor, a local anesthetic, an anticonvulsant, an antidepressant, an opioid receptor agonist, a neuroleptic, and a combination thereof.

194. A kit comprising (a) a pharmaceutical composition comprising a compound having a structural formula (I), (IV), (XI) as defined in Claim 70, 136, or 150, and (b) instructions for carrying out the method of claim 189.

195. A pharmaceutical composition comprising (a) a compound having a structural formula (I), (IV), or (XI) as defined in Claim 70, 138, or 150, and (b) at least one agonist of a $GABA_A$ receptor.

196. The composition of claim 195, wherein said agonist is selected from the group consisting of: alprazolam, chlordiazepoxide, chlordiazepoxide hydrochloride, chlormezanone, clobazam, clonazepam, clorazepate dipotassium, diazepam, droperidol, estazolam, fentanyl citrate, flurazepam hydrochloride, halazepam, lorazepam, midazolam hydrochloride, oxazepam, prazepam, quazepam, temazepam, triazolam, amobarbital, amobarbital sodium, aprobarbital, butabarbital sodium, hexobarbital sodium, mephobarbital, metharbital, methohexital sodium, pentobarbital, pentobarbital sodium, phenobarbital, phenobarbital sodium, secobarbital, secobarbital sodium, talbutal, thiamylal sodium, thiopental sodium, ganaxalone, alphaxalone, isoflurane, and a combination thereof.

197. A method of treating a condition amenable to treatment by an modulator of a $GABA_A$ receptor, said method comprising administering to a subject in need thereof, an effective amount of a having a structural formula (I), (IV), or (XI) as defined in Claim 70, 138, or 150.

198. The method of claim 197, wherein said condition is selected from the group consisting of: anxiety, skeletal muscle spasms, convulsive seizures, epilepsy, and a combination thereof.

199. The method of claim 197, further comprising co-administering to said subject, an effective amount of an agonist of a $GABA_A$ receptor.

200. The method of claim 199, wherein said agonist is selected from the group consisting of: alprazolam, chlordiazepoxide, chlordiazepoxide hydrochloride, chlormezanone, clobazam, clonazepam, clorazepate dipotassium, diazepam, droperidol, estazolam, fentanyl citrate, flurazepam hydrochloride, halazepam, lorazepam, midazolam hydrochloride, oxazepam, prazepam, quazepam, temazepam, triazolam, amobarbital, amobarbital sodium, aprobarbital, butabarbital sodium, hexobarbital sodium, mephobarbital, metharbital, methohexital sodium, pentobarbital, pentobarbital sodium, phenobarbital, phenobarbital sodium, secobarbital, secobarbital sodium, talbutal, thiamylal sodium, thiopental sodium, ganaxalone, alphaxalone, isoflurane, and a combination thereof.

201. A kit comprising (a) a pharmaceutical composition comprising compound having a structural formula (I), (IV), or (XI) as defined in Claim 70, 138, or 150, and (b) instructions for carrying out the method of claim 197.

202. A method of mitigating a symptom of maladaptive substance use or drug-related effect, said method comprising administering to a subject having such condition, an effective amount of a compound having a structural formula (I), (IV), or (XI) as defined in Claim 70, 138, or 150.

203. The method of claim 202, wherein the substance comprises a drug selected from the group consisting of an opioid, a psychostimulant, a sedative-hypnotic drug, a cannabinoid, an empathogen, a dissociative drug, alcohol, and a combination thereof.

204. The method of claim 202, wherein the symptom of maladaptive substance use is selected from the group comprising: drug reward, incentive salience for a drug, drug craving, drug preference, drug seeking, drug consumption, drug withdrawal, and a combination thereof.

205. A kit comprising (a) a pharmaceutical composition comprising a compound of the present invention having a structural formula (I), (IV), or (XI) as defined in Claim 70, 138, or 150, and (b) instructions for carrying out the method of claim 202.

Figure-1.

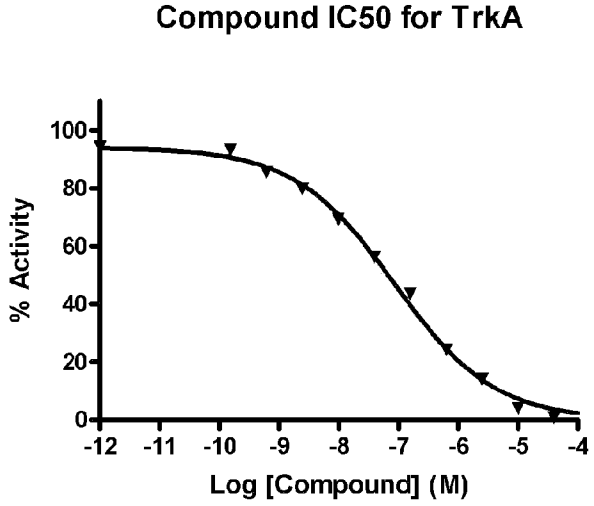


Figure-2.

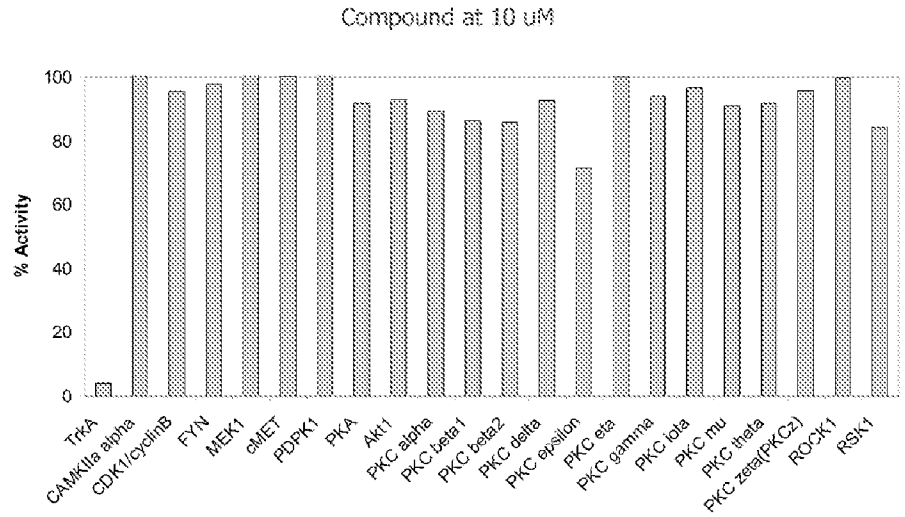


Figure-3.

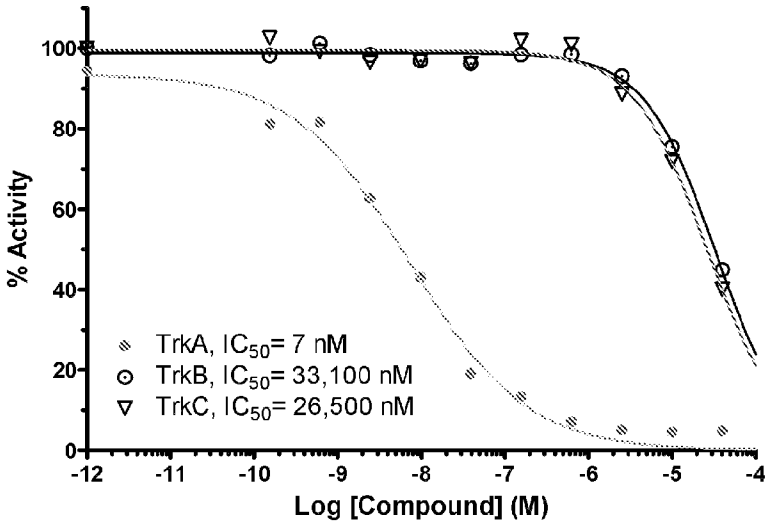


Figure-4.

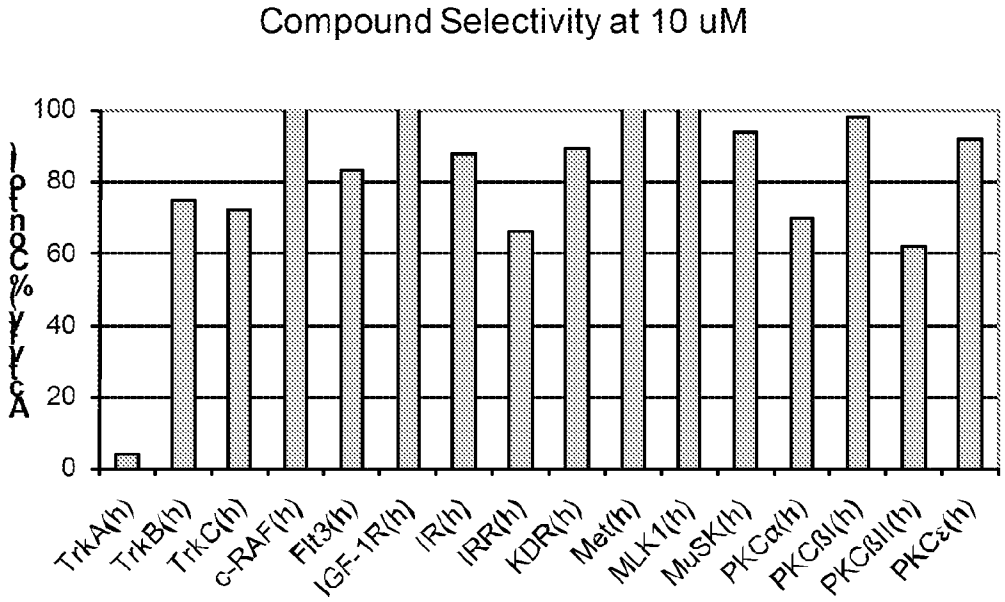
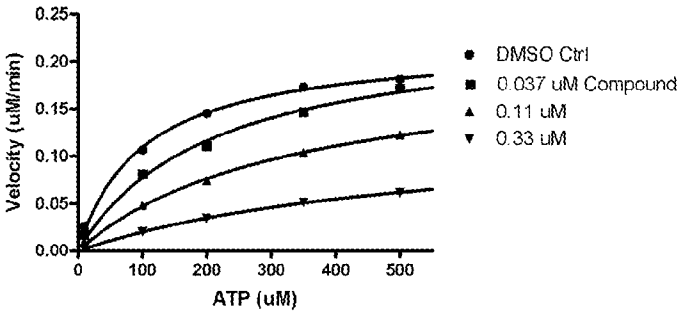


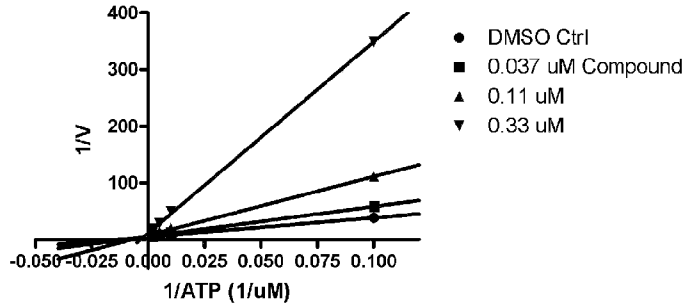
Figure-5.

A



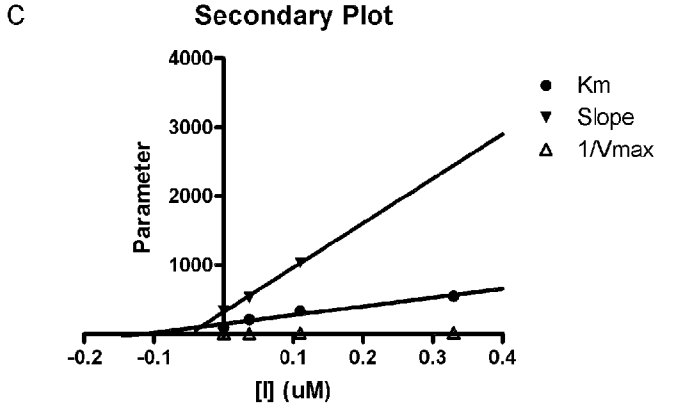
	DMSO Ctrl	0.037 uM Compound	0.11 uM	0.33 uM
Vmax	0.2191	0.2377	0.2033	0.1296
Km	100.5	208.5	333.2	545.2

B



	DMSO Ctrl	0.037 uM Compound	0.11 uM	0.33 uM
Slope	336.5 ?6.670	527.8 ?12.09	1036 ?21.86	3374 ?35.93
Y-intercept when X=0.0	5.213 ?0.3003	5.827 ?0.5443	7.778 ?0.9841	11.84 ?1.618
X-intercept when Y=0.0	-0.01549	-0.01104	-0.007506	-0.003508
1/slope	0.002972	0.001895	0.0009550	0.0002964

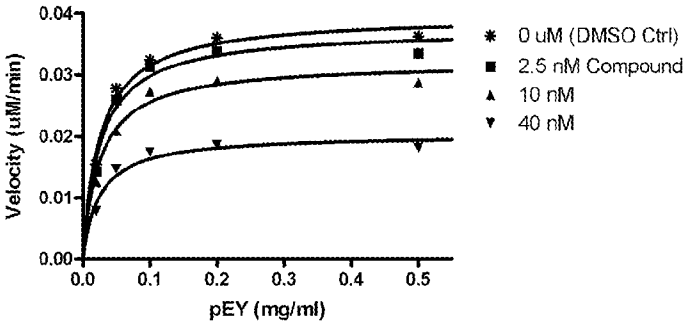
C



	Km	Slope	1/Vmax
Slope	1263 ?194.6	6443 ?445.8	20.19 ?0.9951
Y-intercept when X=0.0	146.3 ?34.03	317.7 ?29.87	5.256 ?0.1740
X-intercept when Y=0.0	-0.1159	-0.04931	-0.2603
1/slope	0.0007920	0.0001552	0.04952

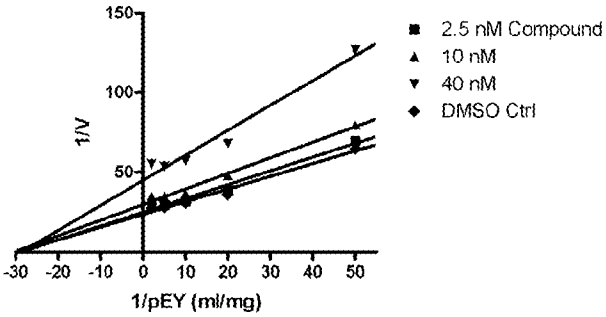
Figure-6.

A



	0 uM (DMSO Ctrl)	2.5 nM Compound	10 nM	40 nM
Vmax	0.03954	0.03954	0.03954	0.03954
I	= 0.0	= 2.500	= 10.00	= 40.00

B



	DMSO Ctrl	2.5 nM Compound	10 nM	40 nM
Slope	0.7949 ?0.08691	0.8838 ?0.08075	0.9764 ?0.06783	1.568 ?0.1774
Y-intercept when X=0.0	23.57 ?1.647	24.89 ?1.988	29.71 ?1.670	44.87 ?4.366
X-intercept when Y=0.0	-29.65	-28.82	-30.43	-28.61
1/slope	1.258	1.158	1.024	0.6378

Electronic Acknowledgement Receipt

EFS ID:	4417441
Application Number:	61120827
International Application Number:	
Confirmation Number:	1934
Title of Invention:	COMPOSITIONS OF PROTEIN RECEPTOR TYROSINE KINASE INHIBITORS
First Named Inventor/Applicant Name:	Jay Jie-Qiang Wu
Customer Number:	58249
Filer:	Yong Lu/Seta Manoukian
Filer Authorized By:	Yong Lu
Attorney Docket Number:	VMDI-010/00US
Receipt Date:	08-DEC-2008
Filing Date:	
Time Stamp:	21:50:30
Application Type:	Provisional

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Application Data Sheet	VMDI-010-00US-ADS.pdf	1165059 87a36081e1d4923759bd64f7beba2334fcaf2bea	no	5

Warnings:	
Information:	

2	Provisional Cover Sheet (SB16)	VMDI-010-00US-ProvCoverSheet.pdf	689968 2fc641bff996e8df047c960080739cd699f99b3e2	no	3
Warnings:					
Information:					
3		VMDI-010-00US-ProvApp.pdf	2102075 887514aa56c932a0f11e436382d7583297552c9d	yes	178

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Specification	1	100
	Claims	101	173
	Abstract	174	174
	Drawings-only black and white line drawings	175	178

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Total Files Size (in bytes):	3957102

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<u>National Stage of an International Application under 35 U.S.C. 371</u>
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

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If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Electronic Acknowledgement Receipt

EFS ID:	4417505
Application Number:	61120827
International Application Number:	
Confirmation Number:	1934
Title of Invention:	COMPOSITIONS OF PROTEIN RECEPTOR TYROSINE KINASE INHIBITORS
First Named Inventor/Applicant Name:	Jay Jie-Qiang Wu
Customer Number:	58249
Filer:	Yong Lu/seta manoukian
Filer Authorized By:	Yong Lu
Attorney Docket Number:	VMDI-010/00US
Receipt Date:	08-DEC-2008
Filing Date:	
Time Stamp:	22:17:52
Application Type:	Provisional

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$110
RAM confirmation Number	5280
Deposit Account	501283
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

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Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

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Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Fee Worksheet (PTO-06)	fee-info.pdf	29971 b0c2b6e34e033b6fc6cacb7db247206bc42f370e	no	2

Warnings:

Information:

Total Files Size (in bytes):	29971

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New Applications Under 35 U.S.C. 111

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