(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
19 November 2020 (19.11.2020)

WIPO | PCT

(10) International Publication Number
WO 2020/232255 A1

(51) International Patent Classification:

A61K 31/352 (2006.01)	*A61K 31/519* (2006.01)
A61K 31/426 (2006.01)	*C07D 215/00* (2006.01)
A61K 31/437 (2006.01)	*C07D 277/00* (2006.01)
A61K 31/4709 (2006.01)	*A61P 3/00* (2006.01)
A61K 31/473 (2006.01)	*A61P 25/28* (2006.01)
A61K 31/502 (2006.01)	*A61P 43/00* (2006.01)
A61K 31/5025 (2006.01)	

(21) International Application Number:
PCT/US2020/032903

(22) International Filing Date:
14 May 2020 (14.05.2020)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/847,600 14 May 2019 (14.05.2019) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report (Art. 21(3))*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

WO 2020/232255 A1

(54) Title: COMPOUNDS FOR THE TREATMENT OF NEURODEGENERATIVE AND METABOLIC DISORDERS

(57) Abstract: Compounds described herein may be used for the treatment of neurodegenerative diseases linked to protein misfolding, including prion diseases, Alzheimers' disease, Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS), and also other neurodegenerative, degenerative, metabolic and ischemic conditions. Indeed, NAD metabolism impairment is also a critical feature in brain ischemia/reperfusion injury, Wallerian degeneration, kidney failure, multiple sclerosis, aging, and metabolic disorders such as diabetes mellitus. Therapies that elevate or stabilize NAD levels may thus have broad potential for treating many severely debilitating neurological and metabolic conditions. Evidence is provided herein with compounds from 8 lead series for NAD restoring properties and for therapeutic efficacy in cellular and/or animal models of prion disease, PD and ALS.

COMPOUNDS FOR THE TREATMENT OF NEURODEGENERATIVE AND METABOLIC DISORDERS

CROSS-REFERENCES TO RELATED APPLICATIONS

This application claims the benefit of priority of U.S. Provisional Application No. 62/847,600 filed on May 14, 2019, which is incorporated herein by reference in its entirety and for all purposes.

STATEMENT OF GOVERNMENT SUPPORT

This invention was made with government support under grant numbers 5R01NS085223 and R21NS093488 awarded by the National Institutes of Health. The government has certain rights in the invention.

BACKGROUND

A number of fatal neurodegenerative diseases, including prion diseases such as Creutzfeldt-Jakob disease (CJD), Alzheimer's (AD), Parkinson's (PD), frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS), are characterized by toxicity resulting from protein misfolding, and are called protein misfolding neurodegenerative diseases (PMNDs). Proteins involved in these diseases misfold and form aggregates of various sizes. Some of these aggregates are highly toxic for neurons, a phenomenon also referred to as proteotoxicity. Protein aggregates can also exhibit "prion-like" properties, in the sense that they propagate from cell to cell and act as seeds to amplify the misfolding and aggregation process within a cell. Such toxic misfolded proteins include the prion protein PrP in CJD, Aβ and tau in AD; α-synuclein and tau in PD; tau, TDP-43 and C9ORF72 in FTD; SOD1, TDP43, FUS and C9ORF72 in ALS. PD belongs to a broader group of diseases called synucleinopathies, characterized by the accumulation of misfolded α-synuclein aggregates. Lewy body dementia is also a synucleinopathy. FTD belongs to another group of PMNDs termed tauopathies, a group that also includes chronic traumatic encephalopathy (CTE) and progressive supranuclear palsy (PSP). There are also non-neurological diseases involving protein misfolding, such as diabetes mellitus where the proteins IAPP and proinsulin form protein aggregates that are toxic for pancreatic beta-cells.

Poor knowledge of the mechanisms of neurotoxicity has hampered the development of effective therapies for PMNDs. To study such mechanisms, a model that uses misfolded and toxic prion protein (TPrP) has been developed, and in particular TPrP reproducibly

induces neuronal death in cell culture and after intracerebral injection[1]. TPrP induces death of more than 60% of cultured neurons at nanomolar concentration, whereas the natively folded counterpart of the prion protein, NTPrP, does not. Therefore, this model provides a highly efficient system to study mechanisms of neuronal death that follow exposure to a misfolded protein. Certain mechanisms for prion-induced toxicity, and the knowledge of how to thwart them, were thought to be more broadly applicable to other PMNDs. Thus, as demonstrated herein, TPrP-based studies spurred the development of new neuroprotective approaches for treating devastating PMNDs.

SUMMARY

There are no disease-modifying treatments currently available for any protein misfolding neurodegenerative disease (PMND). Current treatments, when they exist at all, alleviate certain disease symptoms but neither slow down the progression of the underlying pathogenic mechanisms nor halt neuronal loss. The compounds described herein, in contrast, are capable of interfering with fundamental mechanisms of neurotoxicity linked to alterations in NAD metabolism, thereby sparing neurons from further injury. The approach described herein may therefore provide first-in-kind disease-modifying treatments for PMNDs and other diseases associated with an impairment of NAD metabolism.

Provided is, in various embodiments, a method for inhibiting NAD consumption and/or increasing NAD synthesis in a patient, comprising administering to the patient an effective amount of a compound comprising any of the species, or a member of any of the genera, of chemical structures disclosed and claimed herein for the purpose.

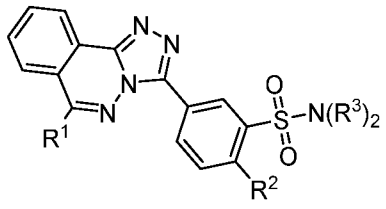
Provided is, in various embodiments, a method for preventing or inhibiting NAD depletion in a patient, or a method for improving a condition linked to alterations of NAD metabolism in a patient , comprising administering to the patient an effective amount of a compound comprising any of the species, or a member of any of the genera, of chemical structures disclosed and claimed herein for the purpose. The condition can comprise a metabolic disorder, diabetes, aging, a neurodegenerative disease, neuronal degeneration associated with multiple sclerosis, hearing loss or retinal damage, brain or cardiac ischemia, kidney failure, traumatic brain injury, or an axonopathy.

Provided is, in various embodiments, a method for providing protection from toxicity of misfolded proteins in a patient, comprising administering to the patient an effective amount of a compound comprising any of the species, or a member of any of the genera, of chemical structures disclosed and claimed herein for the purpose.

Provided is, in various embodiments, a method for preventing or treating a protein misfolding neurodegenerative disease in a patient, comprising administering to the patient an effective amount of a compound comprising any of the species, or a member of any of the genera, of chemical structures disclosed and claimed herein for the purpose. The disease can be a prion disease such as Creutzfeldt-Jakob disease (CJD), Parkinson's disease (PD) or other synucleinopathies, Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), or tauopathies such as frontotemporal dementia (FTD), chronic traumatic encephalopathy (CTE), and progressive supranuclear palsy (PSP).

Further provided are novel compounds that may be useful for the methods described herein.

Provided is, in various embodiments, a compound having a Formula (I),



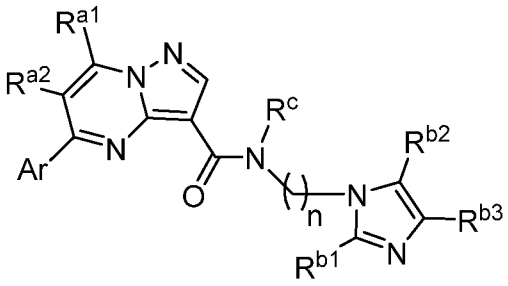
(I), or a pharmaceutically acceptable salt thereof.

In Formula (I):

Each R^1 and R^2 are independently H, (C_1-C_4)alkyl, or (C_1-C_4)alkoxy; and

Each R^3 is independently selected H, (C_1-C_4)alkyl optionally substituted with OH, (C_1-C_4)alkoxy, or heteroaryl, and provided that both R^3 are not H; or, both R^3 together with the nitrogen atom to which they are bonded form a 5- to 7-membered heterocyclyl ring comprising at least on additional heteroatom selected from O, S, S=O, S(=O)=O, or NR, wherein R is (C_1-C_4)alkyl optionally substituted with -OH or (C_1-C_4)alkoxyl.

Provided is, in various embodiments, a compound having a Formula (II).



(II), or a pharmaceutically acceptable salt thereof.

In Formula (II):

Each R^{a1} and R^{a2} is independently hydrogen, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$haloalkyl, $(C_1\text{-}C_4)$alkoxyl, $(C_1\text{-}C_4)$haloalkoxyl, 2 to 4 membered heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

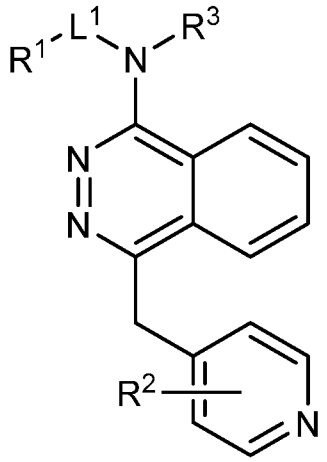
Each R^{b1}, R^{b2}, and R^{b3} is independently hydrogen, halo, $(C_1\text{-}C_4)$alkyl, $-S(O)_2R^d$, $-S(O)_2OR^d$, or $(C_1\text{-}C_4)$haloalkyl; or R^{b2} and R^{b3} are joined together to form an aryl or heteroaryl;

Each R^c and R^d is independently hydrogen or $(C_1\text{-}C_4)$alkyl;

Ar is mono- or bi-cyclic aryl or heteroaryl, optionally substituted with one or more halo, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$haloalkyl, $(C_1\text{-}C_4)$alkoxyl, $(C_1\text{-}C_4)$haloalkoxyl, or heteroaryl; and

n = 2, 3, 4, or 5.

Provided is, in various embodiments, a compound having a Formula (III),



(III), or a pharmaceutically acceptable salt thereof.

In Formula (III):

L^1 is a bond, $C_1\text{-}C_4$ alkylene, or 2 to 4-membered heteroalkylene;

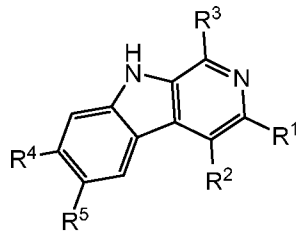
R^1 is mono- or bi-cyclic cycloalkyl, heterocycloalkyl, aryl, alkylaryl, or heteroaryl, wherein the cycloalkyl, heterocycloalkyl, aryl, alkylaryl or heteroaryl is optionally substituted with one or more selected from halo, $(C_1\text{-}C_4)$alkyl, hydroxy$(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxyl, $-C(=O)(C_1\text{-}C_4)$alkyl, $-C(=O)N(R)_2$, or $-C(=NR)(C_1\text{-}C_4)$alkyl, wherein the $(C_1\text{-}C_4)$alkyl is unsubstituted or substituted with heterocycloalkyl ;

Each R is independently H, -OH, $(C_1\text{-}C_4)$alkyl, or $(C_1\text{-}C_4)$alkoxyl, or two R together with the nitrogen atom to which it is bonded form a heterocycloalkyl, optionally further comprising an O atom in the heterocyclyl ring;

R^2 occurs 0, 1, or 2 times, and is $(C_1\text{-}C_4)$ alkyl, $(C_1\text{-}C_4)$ haloalkyl, or $SO_2N(R^4)_2$; and

each R^3 and R^4 is independently H, or $(C_1\text{-}C_4)$alkyl.

Provided is, in various embodiments, a compound having a Formula (IV).



(IV), or a pharmaceutically acceptable salt thereof.

In Formula (IV):

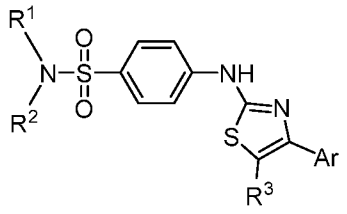
R^1 is hydrogen, (C_1-C_4)alkyl, -C(O)OH, –C(O)O-(C_1-C_4)alkyl, -C(O)NHNHR^6, -C(O)NR^6-((C_1-C_4)alkylene)-NHR^6, -C(O)NR^6(C_1-C_4)alkyl, or –C(O)NR^6-cycloalkylene-NHR^6;

R^3 is hydrogen or (C_1-C_4)alkyl;

Each R^2, R^4, R^5 is independently hydrogen, halo, (C_1-C_4)alkyl, –C(O)O-(C_1-C_4)alkyl, (C_1-C_4)alkoxyl, (C_1-C_4)haloalkyl, or CN; and

Each R^6 is hydrogen or (C_1-C_4)alkyl.

Provided is, in various embodiments, a compound having a Formula (V).



(V), or a pharmaceutically acceptable salt thereof.

In Formula (V):

Ar is mono- or bi-cyclic aryl or heteroaryl, optionally substituted one or more with halo, (C_1-C_4)alkyl, (C_1-C_4)haloalkyl, CN, -S(O)$_2$NH$_2$, oxo, -NH$_2$, (C_1-C_4)alkoxyl, or –NHC(O)(C_1-C_4)alkyl;

Each R^1 and R^2 is independently hydrogen, (C_1-C_4)alkyl, aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted with halo or (C_1-C_4)alkyl, or R^1 and R^2 attached to nitrogen join together to form a 5 to 6 membered heterocycloalkyl; and

R^3 is hydrogen, or hydroxy-(C_1-C_4)alkyl.

Other aspects of the inventions are disclosed *infra*.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 shows the primary neuroprotection assay and confirmatory NAD quantification assay in the 384 well plate format. PK1 neuroblastoma cells (2000 cells/well) were treated with 2.5 μg/ml TPrP for 3 days as indicated in the presence or absence of either NAD or the screening hit DMCM at the doses indicated (doses in μM). TPrP was prepared as

described in Zhou, et. al., *Proc Natl Acad Sci U S A* **109**, 3113-3118 (2012)[1]. DMSO was 0.3%. Quintuplicates and SDs are shown. Upper panel: luminescent cell viability assay using CellTiter-Glo® (Promega). Lower panel: NAD quantification assay using NAD+/NADH-Glo™ (Promega).

Figures 2A, 2B, 2C, 2D, 2E, 2F, 2G, 2H show structures and dose-response curves of 8 series of lead compounds (cell viability in the presence of TPrP, red; NAD quantification in the presence of TPrP, black; cell viability counterscreen in naïve cells, green; NAD quantification counterscreen in naïve cells, blue): Figure 2A carbazoles; Figure 2B pyrazolopyrimidines; Figure 2C aminothiazoles; Figure 2D triazolophthalazines; Figure 2E aminophthalazines; Figure 2F flavonoids (nobiletin); Figure 2G alkaloids (palmatine); Figure 2H 3-heteroarylquinolines (DMPQ).

The cell viability assay was performed in 1536-well plates. PK1 neuroblastoma cells (80 cells/well) were treated with 4 μg/ml TPrP for 3 days in 5 μl volume total. TPrP was prepared as described in Zhou, et. al., *Proc Natl Acad Sci U S A* **109**, 3113-3118 (2012)[1]. Compounds were added in 0.6% DMSO in a 30 nl volume in a 10-point, 4 logs titration at the doses indicated. Cell viability was measured using CellTiter-Glo® (Promega). NAD was quantified using NAD+/NADH-Glo™ (Promega).

Figure 3 shows the absence of neuroprotection by a $GABA_A$ R inhibitor structurally unrelated to DMCM. PK1 cells (1500 cells/well, 96-well plates) were treated with flumazenil (50 nM) for 24 h prior to exposure to TPrP (3 μg/ml) with or without DMCM (0.5 or 5 μM) for 4 days. TPrP was prepared as described in Zhou, et. al., *Proc Natl Acad Sci U S A* **109**, 3113-3118 (2012)[1]. Cell viability was measured using CellTiter-Glo® (Promega). The absence of protection of flumazenil against TPrP toxicity was repeated in a 10-point dose response experiment (0.3-164 nM, not shown). Flumazenil was used in this experiment at 100 times its IC_{50} for $GABA_A$ R inhibition.

Figure 4 shows that a $GABA_A$ R-inactive DMCM analog (DMCM-10049) and the aminoamide DMCM-8137 are neuroprotective. DMCM-8137 and DMCM-10049 show nearly identical dose-response profiles in the TPrP neuroprotection assay. Cells (1500 cells/well, 96-well plates) were exposed to TPrP at 5 μg/ml and to compounds at the doses indicated for 4 days. TPrP was prepared as described in Zhou, et. al., *Proc Natl Acad Sci U S A* **109**, 3113-3118 (2012)[1]. Cell viability was measured using CellTiter-Glo® (Promega).

Figure 5 shows that DMCM rescues TPrP-induced toxicity in primary neurons. Primary mouse cortical neurons (Life Technologies) were exposed to TPrP at 12 μg/ml for 5

days, and treated with DMCM or NAD where indicated. The assay was performed in the 96-well plate format. TPrP was prepared as described in Zhou, et. al., *Proc Natl Acad Sci U S A* **109**, 3113-3118 (2012)[1]. Shown is triplicate data ± SDs. Cell viability was measured using CellTiter-Glo® (Promega). DMCM and NAD treatments also suppressed neuritic breakdown and neuronal vacuolation induced by TPrP exposure (not shown).

Figure 6 shows that DMCM mitigates excessive protein ADP ribosylation induced by a misfolded protein. PK1 cells were treated with 5 µg/ml TPrP in the presence of 9 nM FK866 (to inhibit NAD synthesis from nicotinamide present in the medium) and 40 µM biotin-NAD (Trevigen). Cells were harvested after 2 or 3 days of treatment. Cell lysates were analyzed by SDS-PAGE, and ADP-ribosylated, biotinylated proteins were revealed using streptavidin-HRP. Bands corresponding to TPrP-specific ADP-ribosylation at ~80 and 130 kD are reduced in the presence of DMCM (compare lanes 1&2 of each time point). DMCM has no effect in the absence of TPrP (lanes 3&4 of each time point). 10 µg of protein was loaded per lane.

Figure 7 shows that DMCM-10049 preserves dendritic spines and reduces pα-syn* levels in a cellular PD model. Human stem cell-derived neurons (30 days post-differentiation) were seeded with 50 µg/ml preformed α-synuclein fibrils (PFFs), treated with DMCM-10049 at 2 µM or vehicle, and fixed 17 days later for analysis. Control cells were not PFFs-seeded. A: Dendritic spines were labeled with the marker F-actin using Phalloidin-iFluor 488 (Abcam). B: pα-syn* (red, antibody GTX50222, GeneTex) + DAPI (blue) staining. Quantification was done using ImageJ (NIH), statistical analysis with one way ANOVA (Prism7). Mean values and SDs of 8 images (A) or 6 images (B) per each condition are shown. ****P<0.0001; ***P<0.001; ns = non significant.

Figure 8 shows therapeutic effects of DMCM-10049 in a murine model of Parkinson's disease. Tg(SNCA*A53T) mice were treated from 9 months of age with 50 mg/kg/day DMCM-10049 in drinking water. Sugar-free strawberry flavored gelatin (Royal®) was used for taste-masking and 4% DMSO for compound solubilization. Vehicle controls received the same mixture without compound. Median survival was 411 days in the control group (n=48), 488 days in the treatment group (n=16). Prolongation of survival was significant (p=0.01 in the Log-rank test, Prism 7).

Figure 9 shows therapeutic effects of DMCM-10049 in a murine model of ALS.

Tg(SOD1*G93A) mice were treated from 70 days of age with 50 mg/kg/day DMCM-10049 in drinking water. Sugar-free strawberry flavored gelatin (Royal®) was used for taste-

masking and 4% DMSO for compound solubilization. Vehicle controls received the same mixture without compound. Median survival was 165 days in the control group (n=7), 177 days in the treatment group (n=11). Prolongation of survival was significant (p=0.0007 in the Log-rank test, Prism 7).

Figure 10 shows that oral vatalanib (SR5-1457) treatment delays impairment of motor function in a mouse model of ALS. Mice (all female) received 50 mg/kg vatalanib daily in their drinking water from day 47 of age. Sugar-free strawberry flavored gelatin (Royal®) is used for taste-masking and 4% DMSO for compound solubilization. Vehicle controls received the same mixture without compound. Rotarod and hanging-wire tests were performed as described[2,3]. Average ± SEM are shown. Statistical analysis was performed with 2-way Anova, n=12; *p<0.05; **p<0.01; ***p<0.001.

Figure 11 that the SAR for neuroprotective/NAD restoring effects does not correlate with the SAR for VEGFR inhibition in vatalanib analogs. VEGFR active and inactive compounds related to vatalanib (SR5-1457), including the methyl ketone SR1-134005, were prepared and tested in our assays. Dose-response curves are shown for neuroprotection (red) and NAD levels (black), as well as the counterscreen, which is aimed at detecting compounds increasing luminescence/cell viability nonspecifically in the absence of TPrP (green). The assays were performed in the 1536-well plate format as described in the legend of Figure 2.

Figure 12 shows that therapeutic effects of the much less $GABA_AR$-active 3-methyl ketone analog of vatalanib (SR1-134005) in a murine model of ALS. Tg(SOD1*G93A) mice were treated from 100 days of age with 6 mg/kg/day of SR1-134005 in drinking water. Sugar-free strawberry flavored gelatin (Royal®) was used for taste-masking and 4% DMSO for compound solubilization. Vehicle controls received the same mixture without compound. Hanging wire test was performed to measure muscle strength. Average ± SEM are shown. The difference between the treated (n=14) and the control group (n =19) was significant (p<0.001 for all but the 145 day time point, multiple unpaired t-test, Prism 7).

Figure 13 shows therapeutic effects of the much less $GABA_AR$-active 3-methyl ketone analog of vatalanib (SR1-134005) in a murine model of Parkinson's disease. Tg(SNCA*A53T) mice were treated from 8 months of age with 25 mg/kg/day of SR1-134005 in drinking water. Sugar-free strawberry flavored gelatin (Royal®) was used for taste-masking and 4% DMSO for compound solubilization. Vehicle controls received the same mixture without compound. Median survival was 411 days in the control group (n=58), 462

days in the treatment group (n=16). Prolongation of survival was significant (p=0.03 in the Log-rank test, Prism 7).

Figure 14 shows neuroprotection in a cellular PD/synucleinopathy model. Murine stem-cell derived neurons (8 days post-differentiation) were seeded with PFFs (A, B: 4 μg/ml; C, D: 3 μg/ml) and treated with the test compounds at the dose indicated, or with the vehicle DMSO, during the last 2 days of differentiation. Control cells were not PFFs-seeded. Cells were photographed by phase contrast microscopy. Neurite length was quantified using the NeuronJ plugin of ImageJ (NIH), statistical analysis was done in pairs by comparing compound-treated cells with the DMSO control (student's t-test, Prism8). Mean values and SEMs of 4 fields per each condition are shown. Each field contained approximately 50 to 100 neurons. Images shown correspond to a representative area of one field. ****P<0.0001; ***P<0.001; **P<0.01; *P<0.05; ns = not significant.

Figure 15 shows absence of PARP-1 inhibition by a carbazole (DMCM-10049), an aminophthalazine (SR1-134005, aka SR-005), a pyrazolopyrimidine (SR1-293229, aka SR-229), a triazolophthalazine (SR5-22843, aka SR-843), and a flavonoid (nobiletin). ABT-888 is a known PARP1 inhibitor serving as pharmacological control for the assay. "Control" indicates that the assay was performed in the absence of compound. The assay was performed using the BPS Bioscience PARP1 chemiluminescent assay kit according to the manufacturer's instructions.

Figure 16 shows that the aminophthalazines vatalanib and SR1-134005 (aka SR-005) are NAMPT activators. Compounds were tested in a colorimetric NAMPT activity assay (Abcam, ab221819). Each data point represents a duplicate sample. A, B: Activation of NAMPT by SR-005, but not by DMCM, SR-229, SR-259, SR-186 or nobiletin. Compounds were tested at 5 μM (A) or 20 μM (B). C, D: Dose-dependent activation of NAMPT by SR-005 (C, 0.5 and 2.5 μM; D, 5 and 20 μM). E: Dose-dependent activation of NAMPT by vatalanib. Pazopanib, a potent inhibitor of VEGFR-1, -2 and -3, does not activate NAMPT at 10 μM. This data adds to the previous demonstration that the NAD-restoring effect of vatalanib and SR-005 is not linked to its VEGFR activity.

DETAILED DESCRIPTION

The misfolded toxic prion protein TPrP induces a profound depletion of neuronal NAD that is responsible for cell death, since NAD replenishment leads to full recovery of cells exposed to TPrP injury *in vitro* and *in vivo,* despite continued exposure to TPrP[2]. Intranasal NAD treatment improved motor function and activity in murine prion disease.

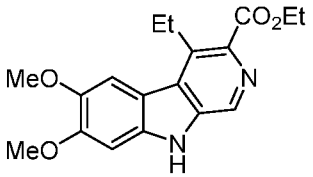
Further it was discovered that NAD depletion in neurons exposed to TPrP was due, at least in part, to overconsumption of cellular NAD during metabolic reactions called mono-ADP ribosylations[2]. Inhibitors of poly-ADP-ribosylations, called PARP inhibitors, have previously been developed as anticancer agents. Available selective PARP inhibitors did not alleviate NAD depletion and neuronal death caused by TPrP, demonstrating the need to identify new compounds capable of interfering with the mechanisms at play in misfolded protein-induced toxicity. Such mechanisms could also be operating in the case of other disorders associated with an imbalance in NAD metabolism, as described herein.

Using TPrP as a prototypic amyloidogenic misfolded protein exhibiting high neurotoxicity, a high-throughput screening (HTS) assay has been developed to identify compounds effective at a) preventing neuronal death; and b) preventing NAD depletion induced by TPrP (Figure 1).

The HTS campaign was performed at Scripps Florida using a subset of the Scripps Drug Discovery Library (SDDL). Several potent, novel and chemically tractable small molecules are identified that can provide complete neuroprotection and preservation of NAD levels when used at doses ranging from low nanomolar to low micromolar levels. Among the highly active compounds were DMCM, an allosteric $GABA_A$ receptor ($GABA_A$ R) modulator, and vatalanib, a VEGF receptor (VEGFR) tyrosine kinase inhibitor that has been studied in clinical trials for the treatment of cancer. Six other classes of neuroprotective molecules were also identified in this effort.

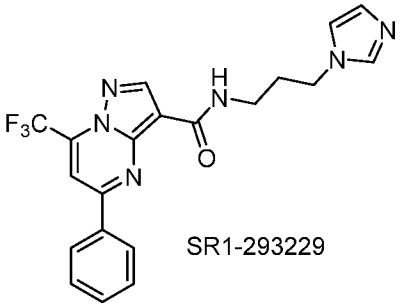
Exemplary active compounds are provided below:

1) carbazoles (example: SR1-75869, aka DMCM);



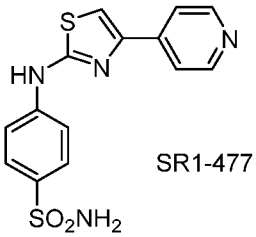
DMCM, aka SR1-75869

2) pyrazolopyrimidines (example: SR1-293229);



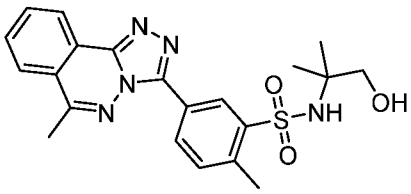
SR1-293229

3) aminothiazoles (example: SR1-477186);



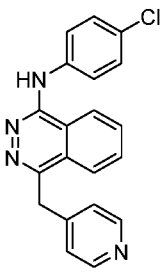
SR1-477186

4) triazolophthalazines (example: SR1-115259);

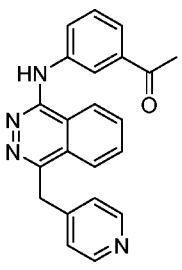


SR1-115259

5) aminophthalazines (examples: SR5-1457, aka vatalanib, aka CGP79787, and also SR1-134005, a much less $GABA_AR$-active analog of vatalanib);

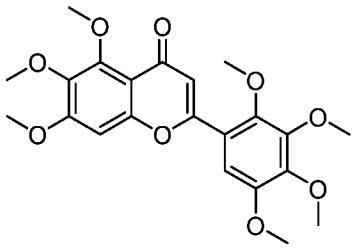


SR5-1457
aka vatalanib
aka CGP79787



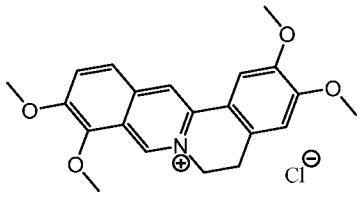
SR1-134005

6) flavonoids (example: nobiletin, aka SR1-712262);



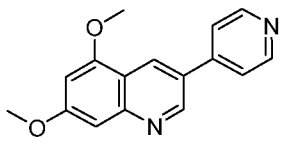
nobiletin, aka SR1-712262

7) alkaloids, including isoquinoline, aporphine, and ergot alkaloids (example shown is an isoquinoline alkaloid, named palmatine chloride, aka SR1-841226);



palmatine chloride
aka SR1-841226

8) 3-heteroarylquinolines (example: DMPQ, aka SR1-597975)



DMPQ
SR1-597975

Activities of the above compound series are characterized in detail in Figures 2A - 2H. Members of each series are highly potent in neuroprotection assays designed to reflect the potential for the successful treatment of several neurodegenerative diseases as described herein. Further, many have favorable properties for lead development (e.g., they are *PAINS-free*[4] and compliant with Lipinski and Veber rules for *drug-likeness*[5,6]).

Definitions

The abbreviations used herein have their conventional meaning within the chemical and biological arts. The chemical structures and formulae set forth herein are constructed according to the standard rules of chemical valency known in the chemical arts.

Where substituent groups are specified by their conventional chemical formulae, written from left to right, they equally encompass the chemically identical substituents that

would result from writing the structure from right to left, e.g., $-CH_2O-$ is equivalent to $-OCH_2-$.

The term "alkyl," by itself or as part of another substituent, means, unless otherwise stated, a straight (i.e., unbranched) or branched carbon chain (or carbon), or combination thereof, which may be fully saturated, mono- or polyunsaturated and can include mono-, di- and multivalent radicals. The alkyl may include a designated number of carbons (e.g., C_1-C_{10} means one to ten carbons). Alkyl is an uncyclized chain. Examples of saturated hydrocarbon radicals include, but are not limited to, groups such as methyl ("Me"), ethyl ("Et"), n-propyl ("Pr"), isopropyl ("iPr"), n-butyl ("Bu"), t-butyl ("t-Bu"), isobutyl, sec-butyl, methyl, homologs and isomers of, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. An unsaturated alkyl group is one having one or more double bonds or triple bonds. Examples of unsaturated alkyl groups include, but are not limited to, vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), ethynyl, 1- and 3-propynyl, 3-butynyl, and the higher homologs and isomers. An alkoxy is an alkyl attached to the remainder of the molecule via an oxygen linker (-O-). An alkyl moiety may be an alkenyl moiety. An alkyl moiety may be an alkynyl moiety. An alkyl moiety may be fully saturated. An alkenyl may include more than one double bond and/or one or more triple bonds in addition to the one or more double bonds. An alkynyl may include more than one triple bond and/or one or more double bonds in addition to the one or more triple bonds.

The term "alkylene," by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from an alkyl, as exemplified, but not limited by, $-CH_2CH_2CH_2CH_2-$. Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms being preferred herein. A "lower alkyl" or "lower alkylene" is a shorter chain alkyl or alkylene group, generally having eight or fewer carbon atoms. The term "alkenylene," by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from an alkene.

The term "heteroalkyl," by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain, or combinations thereof, including at least one carbon atom and at least one heteroatom (e.g., O, N, P, Si, and S), and wherein the nitrogen and sulfur atoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) (e.g., O, N, S, Si, or P) may be placed at any interior position of the heteroalkyl group or at the position at which the alkyl group is attached to the remainder of the molecule. Heteroalkyl is an uncyclized chain. Examples

include, but are not limited to: $-CH_2-CH_2-O-CH_3$, $-CH_2-CH_2-NH-CH_3$, $-CH_2-CH_2-N(CH_3)-CH_3$, $-CH_2-S-CH_2-CH_3$, $-CH_2-S-CH_2$, $-S(O)-CH_3$, $-CH_2-CH_2-S(O)_2-CH_3$, $-CH=CH-O-CH_3$, $-Si(CH_3)_3$, $-CH_2-CH=N-OCH_3$, $-CH=CH-N(CH_3)-CH_3$, $-O-CH_3$, $-O-CH_2-CH_3$, and -CN. Up to two or three heteroatoms may be consecutive, such as, for example, $-CH_2-NH-OCH_3$ and $-CH_2-O-Si(CH_3)_3$. A heteroalkyl moiety may include one heteroatom (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include two optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include three optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include four optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include five optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include up to 8 optionally different heteroatoms (e.g., O, N, S, Si, or P). The term "heteroalkenyl," by itself or in combination with another term, means, unless otherwise stated, a heteroalkyl including at least one double bond. A heteroalkenyl may optionally include more than one double bond and/or one or more triple bonds in additional to the one or more double bonds. The term "heteroalkynyl," by itself or in combination with another term, means, unless otherwise stated, a heteroalkyl including at least one triple bond. A heteroalkynyl may optionally include more than one triple bond and/or one or more double bonds in additional to the one or more triple bonds.

Similarly, the term "heteroalkylene," by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from heteroalkyl, as exemplified, but not limited by, $-CH_2-CH_2-S-CH_2-CH_2-$ and $-CH_2-S-CH_2-CH_2-NH-CH_2-$. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (e.g., alkyleneoxy, alkylenedioxy, alkyleneamino, alkylenediamino, and the like). Still further, for alkylene and heteroalkylene linking groups, no orientation of the linking group is implied by the direction in which the formula of the linking group is written. For example, the formula $-C(O)_2R'-$ represents both $-C(O)_2R'-$ and $-R'C(O)_2-$. As described above, heteroalkyl groups, as used herein, include those groups that are attached to the remainder of the molecule through a heteroatom, such as -C(O)R', -C(O)NR', -NR'R", -OR', -SR', and/or $-SO_2R'$. Where "heteroalkyl" is recited, followed by recitations of specific heteroalkyl groups, such as -NR'R" or the like, it will be understood that the terms heteroalkyl and -NR'R" are not redundant or mutually exclusive. Rather, the specific heteroalkyl groups are recited to add clarity. Thus, the term "heteroalkyl" should not be interpreted herein as excluding specific heteroalkyl groups, such as -NR'R" or the like.

The terms "cycloalkyl" and "heterocycloalkyl," by themselves or in combination with other terms, mean, unless otherwise stated, cyclic versions of "alkyl" and "heteroalkyl," respectively. Cycloalkyl and heterocycloalkyl are not aromatic. Additionally, for heterocycloalkyl, a heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule. Examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, and the like. Examples of heterocycloalkyl include, but are not limited to, 1-(1,2,5,6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1-piperazinyl, 2-piperazinyl, and the like. A "cycloalkylene" and a "heterocycloalkylene," alone or as part of another substituent, means a divalent radical derived from a cycloalkyl and heterocycloalkyl, respectively.

In embodiments, a heterocycloalkyl is a heterocyclyl. The term "heterocyclyl" as used herein, means a monocyclic, bicyclic, or multicyclic heterocycle. The heterocyclyl monocyclic heterocycle is a 3, 4, 5, 6 or 7 membered ring containing at least one heteroatom independently selected from the group consisting of O, N, and S where the ring is saturated or unsaturated, but not aromatic. The 3 or 4 membered ring contains 1 heteroatom selected from the group consisting of O, N and S. The 5 membered ring can contain zero or one double bond and one, two or three heteroatoms selected from the group consisting of O, N and S. The 6 or 7 membered ring contains zero, one or two double bonds and one, two or three heteroatoms selected from the group consisting of O, N and S. The heterocyclyl monocyclic heterocycle is connected to the parent molecular moiety through any carbon atom or any nitrogen atom contained within the heterocyclyl monocyclic heterocycle. Representative examples of heterocyclyl monocyclic heterocycles include, but are not limited to, azetidinyl, azepanyl, aziridinyl, diazepanyl, 1,3-dioxanyl, 1,3-dioxolanyl, 1,3-dithiolanyl, 1,3-dithianyl, imidazolinyl, imidazolidinyl, isothiazolinyl, isothiazolidinyl, isoxazolinyl, isoxazolidinyl, morpholinyl, oxadiazolinyl, oxadiazolidinyl, oxazolinyl, oxazolidinyl, piperazinyl, piperidinyl, pyranyl, pyrazolinyl, pyrazolidinyl, pyrrolinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothienyl, thiadiazolinyl, thiadiazolidinyl, thiazolinyl, thiazolidinyl, thiomorpholinyl, 1,1-dioxidothiomorpholinyl (thiomorpholine sulfone), thiopyranyl, and trithianyl. The heterocyclyl bicyclic heterocycle is a monocyclic heterocycle fused to either a phenyl, a monocyclic cycloalkyl, a monocyclic cycloalkenyl, a monocyclic heterocycle, or a monocyclic heteroaryl. The heterocyclyl bicyclic heterocycle is connected to the parent

molecular moiety through any carbon atom or any nitrogen atom contained within the monocyclic heterocycle portion of the bicyclic ring system. Representative examples of bicyclic heterocyclyls include, but are not limited to, 2,3-dihydrobenzofuran-2-yl, 2,3-dihydrobenzofuran-3-yl, indolin-1-yl, indolin-2-yl, indolin-3-yl, 2,3-dihydrobenzothien-2-yl, decahydroquinolinyl, decahydroisoquinolinyl, octahydro-1H-indolyl, and octahydrobenzofuranyl. In embodiments, heterocyclyl groups are optionally substituted with one or two groups which are independently oxo or thia. In certain embodiments, the bicyclic heterocyclyl is a 5 or 6 membered monocyclic heterocyclyl ring fused to a phenyl ring, a 5 or 6 membered monocyclic cycloalkyl, a 5 or 6 membered monocyclic cycloalkenyl, a 5 or 6 membered monocyclic heterocyclyl, or a 5 or 6 membered monocyclic heteroaryl, wherein the bicyclic heterocyclyl is optionally substituted by one or two groups which are independently oxo or thia. Multicyclic heterocyclyl ring systems are a monocyclic heterocyclyl ring (base ring) fused to either (i) one ring system selected from the group consisting of a bicyclic aryl, a bicyclic heteroaryl, a bicyclic cycloalkyl, a bicyclic cycloalkenyl, and a bicyclic heterocyclyl; or (ii) two other ring systems independently selected from the group consisting of a phenyl, a bicyclic aryl, a monocyclic or bicyclic heteroaryl, a monocyclic or bicyclic cycloalkyl, a monocyclic or bicyclic cycloalkenyl, and a monocyclic or bicyclic heterocyclyl. The multicyclic heterocyclyl is attached to the parent molecular moiety through any carbon atom or nitrogen atom contained within the base ring. In embodiments, multicyclic heterocyclyl ring systems are a monocyclic heterocyclyl ring (base ring) fused to either (i) one ring system selected from the group consisting of a bicyclic aryl, a bicyclic heteroaryl, a bicyclic cycloalkyl, a bicyclic cycloalkenyl, and a bicyclic heterocyclyl; or (ii) two other ring systems independently selected from the group consisting of a phenyl, a monocyclic heteroaryl, a monocyclic cycloalkyl, a monocyclic cycloalkenyl, and a monocyclic heterocyclyl. Examples of multicyclic heterocyclyl groups include, but are not limited to 10H-phenothiazin-10-yl, 9,10-dihydroacridin-9-yl, 9,10-dihydroacridin-10-yl, 10H-phenoxazin-10-yl, 10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl, 1,2,3,4-tetrahydropyrido[4,3-g]isoquinolin-2-yl, 12H-benzo[b]phenoxazin-12-yl, and dodecahydro-1H-carbazol-9-yl.

The terms “halo” or “halogen,” by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Additionally, terms such as “haloalkyl” are meant to include monohaloalkyl and polyhaloalkyl. For example, the

term "halo(C_1-C_4)alkyl" includes, but is not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like.

The term "aryl" means, unless otherwise stated, a polyunsaturated, aromatic, hydrocarbon substituent, which can be a single ring or multiple rings (preferably from 1 to 3 rings) that are fused together (i.e., a fused ring aryl) or linked covalently. A fused ring aryl refers to multiple rings fused together wherein at least one of the fused rings is an aryl ring. The term "heteroaryl" refers to aryl groups (or rings) that contain at least one heteroatom such as N, O, or S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. Thus, the term "heteroaryl" includes fused ring heteroaryl groups (i.e., multiple rings fused together wherein at least one of the fused rings is a heteroaromatic ring). A 5,6-fused ring heteroarylene refers to two rings fused together, wherein one ring has 5 members and the other ring has 6 members, and wherein at least one ring is a heteroaryl ring. Likewise, a 6,6-fused ring heteroarylene refers to two rings fused together, wherein one ring has 6 members and the other ring has 6 members, and wherein at least one ring is a heteroaryl ring. And a 6,5-fused ring heteroarylene refers to two rings fused together, wherein one ring has 6 members and the other ring has 5 members, and wherein at least one ring is a heteroaryl ring. A heteroaryl group can be attached to the remainder of the molecule through a carbon or heteroatom. Non-limiting examples of aryl and heteroaryl groups include phenyl, naphthyl, pyrrolyl, pyrazolyl, pyridazinyl, triazinyl, pyrimidinyl, imidazolyl, pyrazinyl, purinyl, oxazolyl, isoxazolyl, thiazolyl, furyl, thienyl, pyridyl, pyrimidyl, benzothiazolyl, benzoxazoyl benzimidazolyl, benzofuran, isobenzofuranyl, indolyl, isoindolyl, benzothiophenyl, isoquinolyl, quinoxalinyl, quinolyl, 1-naphthyl, 2-naphthyl, 4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 2-phenyl-4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxalinyl, 5-quinoxalinyl, 3-quinolyl, and 6-quinolyl. Substituents for each of the above noted aryl and heteroaryl ring systems are selected from the group of acceptable substituents described below. An "arylene" and a "heteroarylene," alone or as part of another substituent, mean a divalent radical derived from an aryl and heteroaryl, respectively. A heteroaryl group substituent may be -O- bonded to a ring heteroatom nitrogen.

The symbol "~~" denotes the point of attachment of a chemical moiety to the remainder of a molecule or chemical formula.

The term "pharmaceutically acceptable salts" is meant to include salts of the active compounds that are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds of the present disclosure contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds of the present disclosure contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, oxalic, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (*see*, for example, Berge *et al.*, "Pharmaceutical Salts", *Journal of Pharmaceutical Science*, **1977**, *66*, 1-19). Certain specific compounds of the present disclosure contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

The term "EC_{50}" or "half maximal effective concentration" as used herein refers to the concentration of a molecule (e.g., small molecule, drug, antibody, chimeric antigen receptor or bispecific antibody) capable of inducing a response which is halfway between the baseline response and the maximum response after a specified exposure time. In embodiments, the EC_{50} is the concentration of a molecule (e.g., small molecule, drug, antibody, chimeric antigen receptor or bispecific antibody) that produces 50% of the maximal possible effect of that molecule.

As used herein, the term "neurodegenerative disorder" refers to a disease or condition in which the function of a subject's nervous system becomes impaired. Examples

of neurodegenerative diseases that may be treated with a compound, pharmaceutical composition, or method described herein include Alexander's disease, Alper's disease, Alzheimer's disease, Amyotrophic lateral sclerosis, Ataxia telangiectasia, Batten disease (also known as Spielmeyer-Vogt-Sjogren-Batten disease), Bovine spongiform encephalopathy (BSE), Canavan disease, chronic fatigue syndrome, Chronic Traumatic Encephalopathy, Cockayne syndrome, Corticobasal degeneration, Creutzfeldt-Jakob disease, frontotemporal dementia, Gerstmann-Sträussler-Scheinker syndrome, Huntington's disease, HIV-associated dementia, Kennedy's disease, Krabbe's disease, Kuru, Lewy body dementia, Machado-Joseph disease (Spinocerebellar ataxia type 3), Multiple sclerosis, Multiple System Atrophy, myalgic encephalomyelitis, Narcolepsy, Neuroborreliosis, Parkinson's disease, Pelizaeus-Merzbacher Disease, Pick's disease, Primary lateral sclerosis, Prion diseases, Refsum's disease, Sandhoff's disease, Schilder's disease, Subacute combined degeneration of spinal cord secondary to Pernicious Anaemia, Schizophrenia, Spinocerebellar ataxia (multiple types with varying characteristics), Spinal muscular atrophy, Steele-Richardson-Olszewski disease , progressive supranuclear palsy, or Tabes dorsalis.

The terms “treating”, or “treatment” refers to any indicia of success in the therapy or amelioration of an injury, disease, pathology or condition, including any objective or subjective parameter such as abatement; remission; diminishing of symptoms or making the injury, pathology or condition more tolerable to the patient; slowing in the rate of degeneration or decline; making the final point of degeneration less debilitating; improving a patient’s physical or mental well-being. The treatment or amelioration of symptoms can be based on objective or subjective parameters; including the results of a physical examination, neuropsychiatric exams, and/or a psychiatric evaluation. The term "treating" and conjugations thereof, may include prevention of an injury, pathology, condition, or disease. In embodiments, treating is preventing. In embodiments, treating does not include preventing.

“Treating” or “treatment” as used herein (and as well-understood in the art) also broadly includes any approach for obtaining beneficial or desired results in a subject’s condition, including clinical results. Beneficial or desired clinical results can include, but are not limited to, alleviation or amelioration of one or more symptoms or conditions, diminishment of the extent of a disease, stabilizing (*i.e.*, not worsening) the state of disease, prevention of a disease’s transmission or spread, delay or slowing of disease progression, amelioration or palliation of the disease state, diminishment of the reoccurrence of disease, and remission, whether partial or total and whether detectable or undetectable. In other

words, "treatment" as used herein includes any cure, amelioration, or prevention of a disease. Treatment may prevent the disease from occurring; inhibit the disease's spread; relieve the disease's symptoms, fully or partially remove the disease's underlying cause, shorten a disease's duration, or do a combination of these things.

The term "prevent" refers to a decrease in the occurrence of disease symptoms in a patient. As indicated above, the prevention may be complete (no detectable symptoms) or partial, such that fewer symptoms are observed than would likely occur absent treatment.

"Patient" or "subject in need thereof" refers to a living organism suffering from or prone to a disease or condition that can be treated by administration of a pharmaceutical composition as provided herein. Non-limiting examples include humans, other mammals, bovines, rats, mice, dogs, monkeys, goat, sheep, cows, deer, and other non-mammalian animals. In some embodiments, a patient is human.

A "effective amount" is an amount sufficient for a compound to accomplish a stated purpose relative to the absence of the compound (e.g. achieve the effect for which it is administered, treat a disease, reduce enzyme activity, increase enzyme activity, reduce a signaling pathway, or reduce one or more symptoms of a disease or condition). An example of an "effective amount" is an amount sufficient to contribute to the treatment, prevention, or reduction of a symptom or symptoms of a disease, which could also be referred to as a "therapeutically effective amount." A "reduction" of a symptom or symptoms (and grammatical equivalents of this phrase) means decreasing of the severity or frequency of the symptom(s), or elimination of the symptom(s). A "prophylactically effective amount" of a drug is an amount of a drug that, when administered to a subject, will have the intended prophylactic effect, e.g., preventing or delaying the onset (or reoccurrence) of an injury, disease, pathology or condition, or reducing the likelihood of the onset (or reoccurrence) of an injury, disease, pathology, or condition, or their symptoms. The full prophylactic effect does not necessarily occur by administration of one dose, and may occur only after administration of a series of doses. Thus, a prophylactically effective amount may be administered in one or more administrations. An "activity decreasing amount," as used herein, refers to an amount of antagonist required to decrease the activity of an enzyme relative to the absence of the antagonist. A "function disrupting amount," as used herein, refers to the amount of antagonist required to disrupt the function of an enzyme or protein relative to the absence of the antagonist. The exact amounts will depend on the purpose of the treatment, and will be ascertainable by one skilled in the art using known techniques (*see*,

e.g., Lieberman, *Pharmaceutical Dosage Forms* (vols. 1-3, 1992); Lloyd, *The Art, Science and Technology of Pharmaceutical Compounding* (1999); Pickar, *Dosage Calculations* (1999); and *Remington: The Science and Practice of Pharmacy*, 20th Edition, 2003, Gennaro, Ed., Lippincott, Williams & Wilkins).

For any compound described herein, the therapeutically effective amount can be initially determined from cell culture assays. Target concentrations will be those concentrations of active compound(s) that are capable of achieving the methods described herein, as measured using the methods described herein or known in the art.

As is well known in the art, therapeutically effective amounts for use in humans can also be determined from animal models. For example, a dose for humans can be formulated to achieve a concentration that has been found to be effective in animals. The dosage in humans can be adjusted by monitoring compounds effectiveness and adjusting the dosage upwards or downwards, as described above. Adjusting the dose to achieve maximal efficacy in humans based on the methods described above and other methods is well within the capabilities of the ordinarily skilled artisan.

The term "therapeutically effective amount," as used herein, refers to that amount of the therapeutic agent sufficient to ameliorate the disorder, as described above. For example, for the given parameter, a therapeutically effective amount will show an increase or decrease of at least 5%, 10%, 15%, 20%, 25%, 40%, 50%, 60%, 75%, 80%, 90%, or at least 100%. Therapeutic efficacy can also be expressed as "-fold" increase or decrease. For example, a therapeutically effective amount can have at least a 1.2-fold, 1.5-fold, 2-fold, 5-fold, or more effect over a control.

Dosages may be varied depending upon the requirements of the patient and the compound being employed. The dose administered to a patient, in the context of the present disclosure, should be sufficient to effect a beneficial therapeutic response in the patient over time. The size of the dose also will be determined by the existence, nature, and extent of any adverse side-effects. Determination of the proper dosage for a particular situation is within the skill of the practitioner. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under circumstances is reached. Dosage amounts and intervals can be adjusted individually to provide levels of the administered compound effective for the particular clinical indication being treated. This will provide a therapeutic regimen that is commensurate with the severity of the individual's disease state.

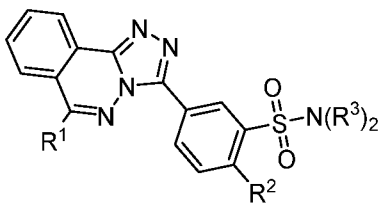
As used herein, the term "administering" means oral administration, administration as a suppository, topical contact, intravenous, parenteral, intraperitoneal, intramuscular, intralesional, intrathecal, intranasal or subcutaneous administration, or the implantation of a slow-release device, *e.g.*, a mini-osmotic pump, to a subject. Administration is by any route, including parenteral and transmucosal (*e.g.*, buccal, sublingual, palatal, gingival, nasal, vaginal, rectal, or transdermal). Parenteral administration includes, *e.g.*, intravenous, intramuscular, intra-arteriole, intradermal, subcutaneous, intraperitoneal, intraventricular, and intracranial. Other modes of delivery include, but are not limited to, the use of liposomal formulations, intravenous infusion, transdermal patches, *etc.* In embodiments, the administering does not include administration of any active agent other than the recited active agent.

A "cell" as used herein, refers to a cell carrying out metabolic or other function sufficient to preserve or replicate its genomic DNA. A cell can be identified by well-known methods in the art including, for example, presence of an intact membrane, staining by a particular dye, ability to produce progeny or, in the case of a gamete, ability to combine with a second gamete to produce a viable offspring. Cells may include prokaryotic and eukaroytic cells. Prokaryotic cells include but are not limited to bacteria. Eukaryotic cells include but are not limited to yeast cells and cells derived from plants and animals, for example mammalian, insect (e.g., spodoptera) and human cells. Cells may be useful when they are naturally nonadherent or have been treated not to adhere to surfaces, for example by trypsinization.

Compounds

In an aspect, provided herein are compounds that may provide complete neuroprotection and protection of cell types other than neurons, and preservation of NAD levels. The compounds may be highly potent in a) preventing neuronal and/or cellular death; and b) preventing NAD depletion induced by TPrP, for example, as identified by neuroprotection assays when used at doses ranging from low nanomolar to low micromolar levels.

In an aspect, a compound has a Formula (I),



(I).

In Formula (I),

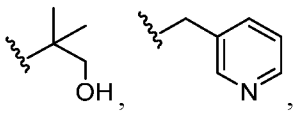
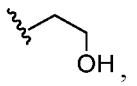
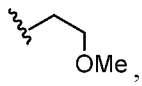
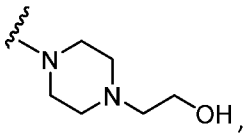
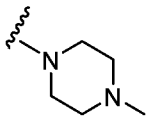
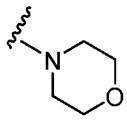
Each R^1 and R2 are independently hydrogen, (C_1-C_4)alkyl, or (C_1-C_4)alkoxy; and

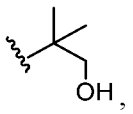
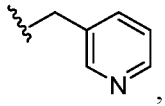
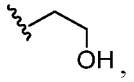
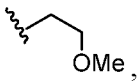
Each R^3 is independently selected hydrogen, (C_1-C_4)alkyl optionally substituted with OH, (C_1-C_4)alkoxy, or heteroaryl, and provided that both R^3 are not H; or both R^3 together with the nitrogen atom to which they are bonded form a 5- to 7-membered heterocyclyl ring comprising at least on additional heteroatom selected from O, S, S=O, S(=O)=O, or NR, wherein R is (C_1-C_4)alkyl optionally substituted with -OH or (C_1-C_4)alkoxyl.

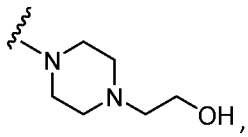
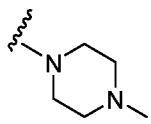
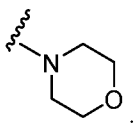
The compound of Formula (I) includes all pharmaceutically acceptable salt forms.

In embodiments, R^1 is methyl.

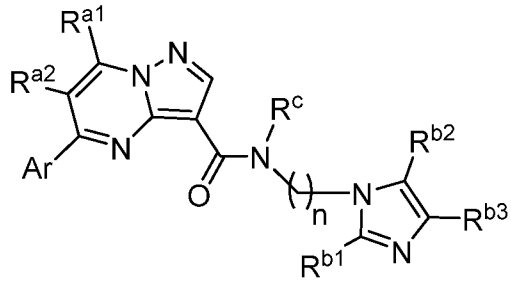
In embodiments, R^2 is methyl.

In embodiments, one of R^3 is hydrogen and the other R^3 is , , , methyl, , , or .

In some compounds of Formula (I), when R^1 and R^2 are methyl, one of R^3 is hydrogen, then the other R^3 is not , , , , or methyl.

In some compounds of Formula (I), when R^1 and R^2 are methyl, two R^3 attached to the nitrogen atom does not form , , or .

In an aspect, a compound has a Formula (II),



(II).

In Formula (II):

Each R^{a1} and R^{a2} is independently hydrogen, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$haloalkyl, $(C_1\text{-}C_4)$alkoxyl, $(C_1\text{-}C_4)$haloalkoxyl, 2 to 4 membered heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

Each R^{b1}, R^{b2}, and R^{b3} is independently hydrogen, halo, $(C_1\text{-}C_4)$alkyl, $-S(O)_2R^d$, $-S(O)_2OR^d$, or $(C_1\text{-}C_4)$haloalkyl; or R^{b2} and R^{b3} are joined together to form an aryl or heteroaryl;

Each R^c and R^d is independently hydrogen or $(C_1\text{-}C_4)$alkyl;

Ar is mono- or bi-cyclic aryl or heteroaryl, optionally substituted with one or more halo, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$haloalkyl, $(C_1\text{-}C_4)$alkoxyl, $(C_1\text{-}C_4)$haloalkoxyl, or heteroaryl; and

n = 2, 3, 4, or 5.

The compound of Formula (II) includes all pharmaceutically acceptable salt forms.

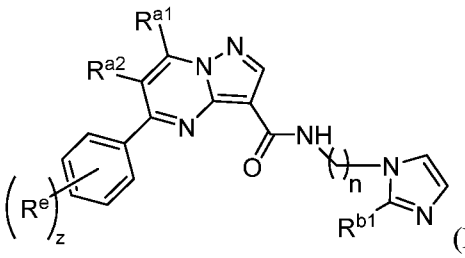
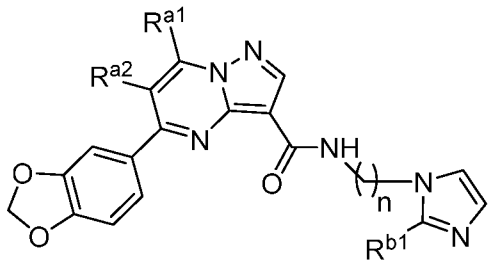
In embodiments, R^{b1} is hydrogen. In embodiments, R^{b1} is $C_1\text{-}C_4$ alkyl. In embodiments, R^{b1} is methyl. In embodiments, R^{b1} is ethyl. In embodiments, R^{b1} is halo. In embodiments, R^{b1} is -F. In embodiments, R^{b1} is $(C_1\text{-}C_4)$ haloalkyl. In embodiments, R^{b1} is $-CF_3$. In embodiments, R^{b1} is $-S(O)_2R^c$. In embodiments, R^{b1} is $-S(O)_2CH_3$.

In embodiments, R^{b2} is hydrogen. In embodiments, R^{b2} is methyl. In embodiments, R^{b3} is hydrogen. In embodiments, R^{b3} is methyl. In embodiments, R^c is hydrogen. In embodiments, R^c is methyl. In embodiments, R^d is hydrogen. In embodiments, R^d is methyl.

In embodiments, R^{b2} and R^{b3} are joined together to form a phenyl.

In embodiments, R^{a2} is hydrogen. In embodiments, R^{a2} is $(C_1\text{-}C_4)$alkyl. In embodiments, R^{a2} is methyl.

In embodiments, the compound has the following formula:


(II-a) or

(II-b)

R^{a1} and R^{b1} are as described herein. R^e is independently halo, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$haloalkyl, $(C_1\text{-}C_4)$alkoxyl, $(C_1\text{-}C_4)$haloalkoxyl, or heteroaryl, and z is 0, 1, 2, 3, 4, or 5.

In embodiments, z is 0, 1, 2, or 3.

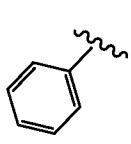
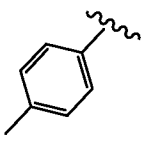
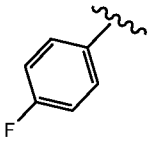
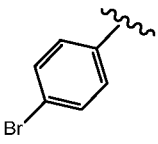
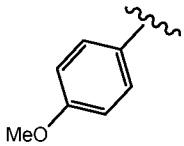
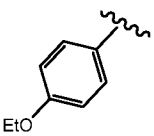
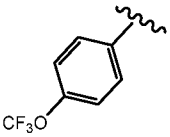
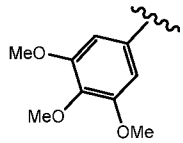
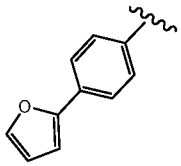
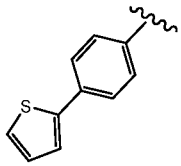
In embodiments, R^{b1} is hydrogen, methyl, ethyl, -F, $-CF_3$, or $-S(O)_2Me$.

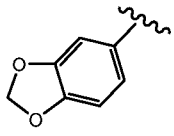
In embodiments, R^{a2} is hydrogen or methyl.

In embodiments, n is 2. In embodiments, n is 3. In embodiments, n is 4.

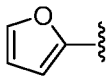
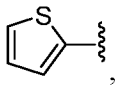
In embodiments, R^{a1} is $(C_1\text{-}C_4)$alkyl. In embodiments, R^{a1} is methyl. In embodiments, R^{a1} is ethyl. In embodiments, R^{a1} is isopropyl. In embodiments, R^{a1} is t-butyl. In embodiments, R^{a1} is $(C_1\text{-}C_4)$haloalkyl. In embodiments, R^{a1} is $-CF_3$. In embodiments, R^{a1} is heterocycloalkyl. In embodiments, R^{a1} is . In embodiments, R^{a1} is $-CH_2\text{-}O\text{-}CH_3$. In embodiments, R^{a1} is phenyl.

In embodiments, Ar is phenyl optionally substituted with one or more of halo, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$haloalkyl, $(C_1\text{-}C_4)$alkoxyl, $(C_1\text{-}C_4)$haloalkoxyl, or heteroaryl

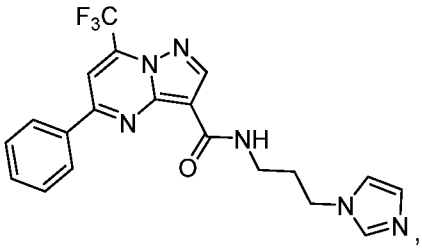
In embodiments, Ar is , , , , , , , or . In embodiments, Ar is , or .

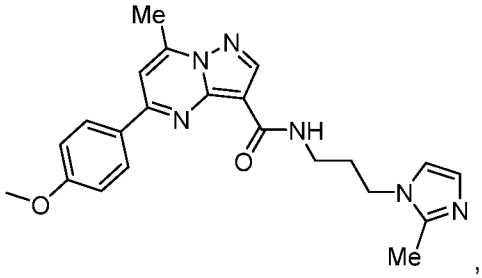
In embodiments, Ar is .

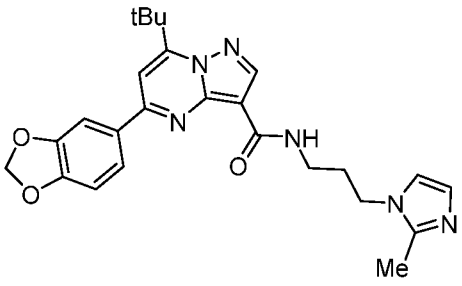
In some compounds of Formula (II), when R^{a2}, R^{b1}, R^{b2}, R^{b3}, and R^c are hydrogen, n is 3, Ar is phenyl which is unsubstituted or substituted with $-CH_3$ or -OMe, then R^{a1} is not difluoromethyl or trifluoromethyl.

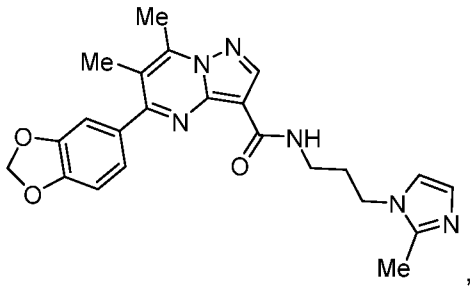
In some compounds of Formula (II), when R^{a2}, R^{b1}, R^{b2}, R^{b3}, and R^c are hydrogen, n is 3, Ar is phenyl substituted with -F, Br, , or , then R^{a1} is not trifluoromethyl.

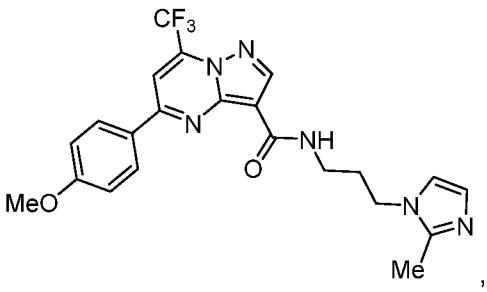
In embodiments, the compounds of Formula (II) include:

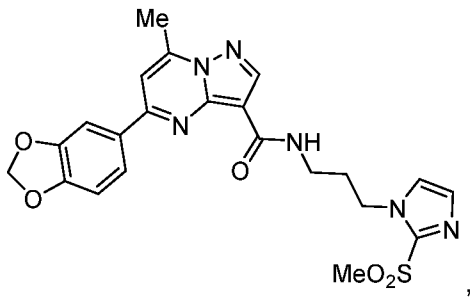


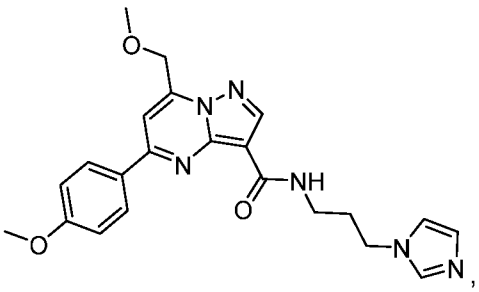


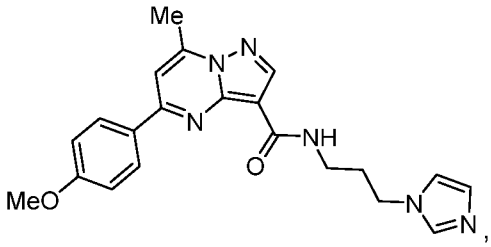


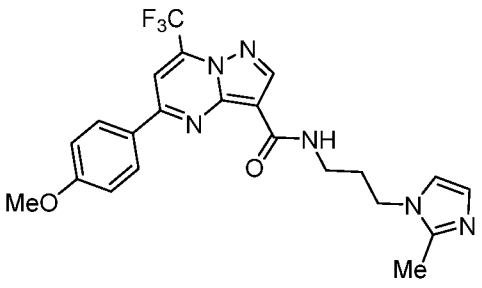


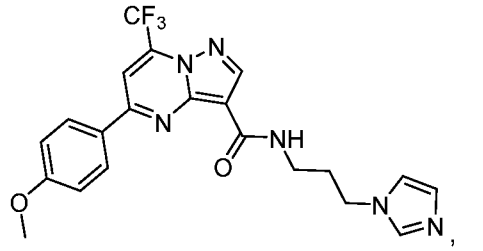


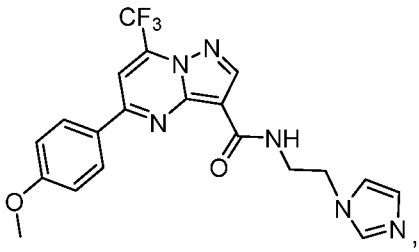


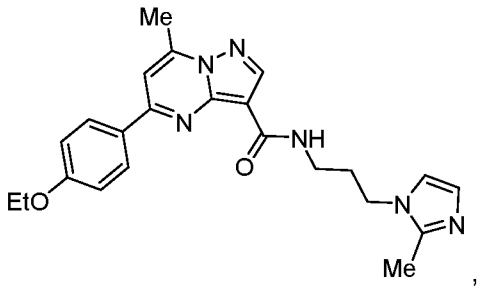


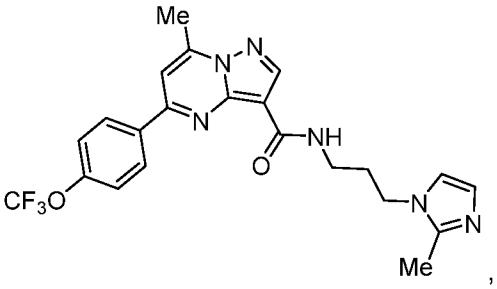


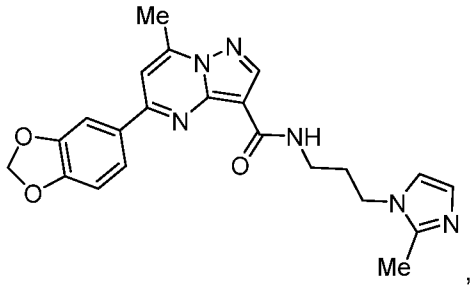


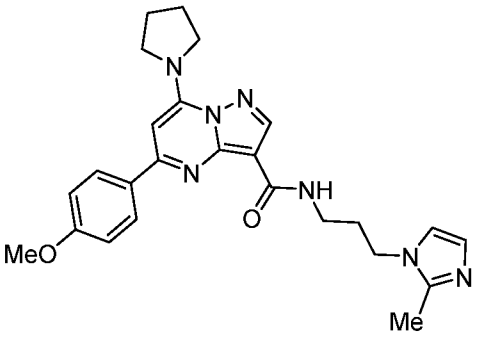


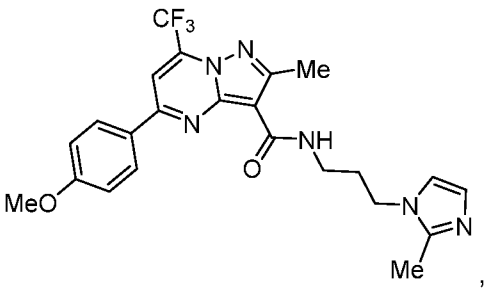


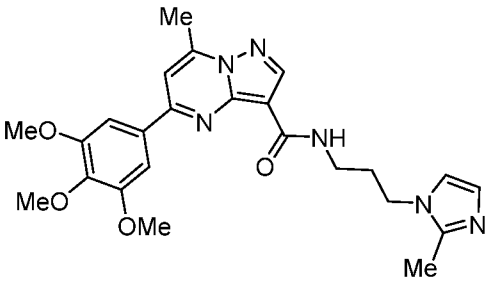


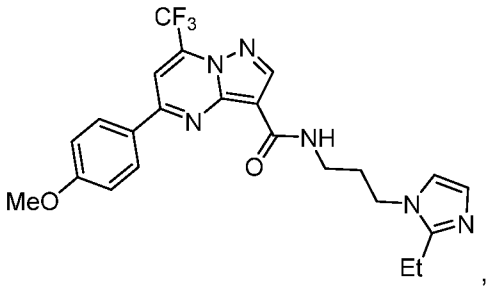


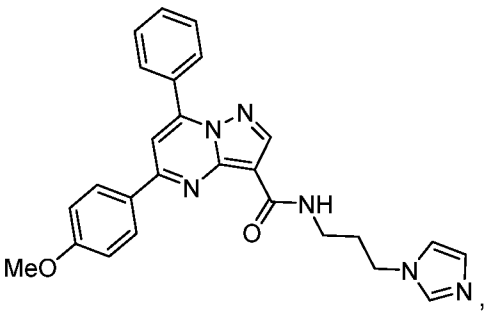


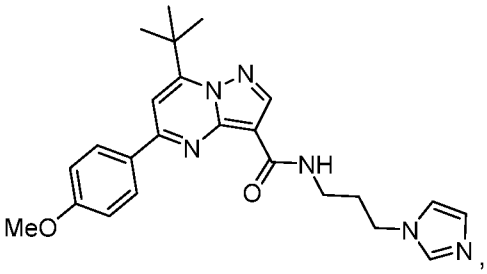


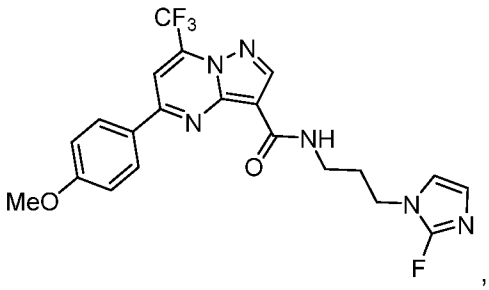


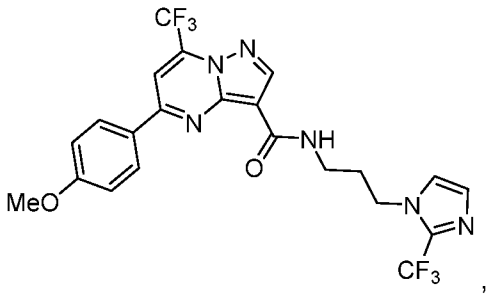


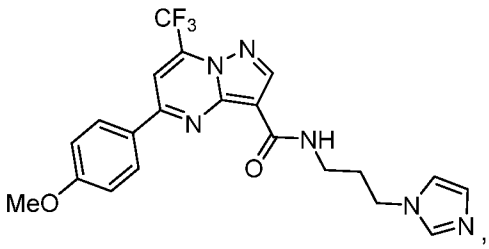


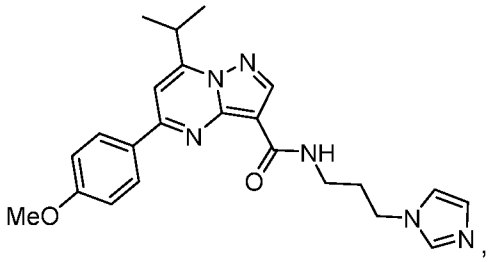


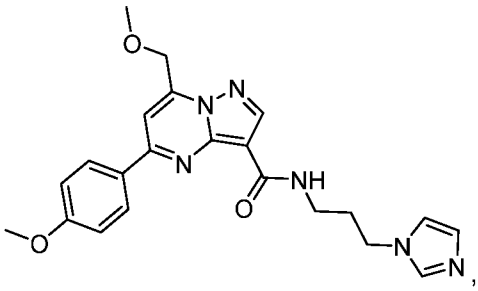


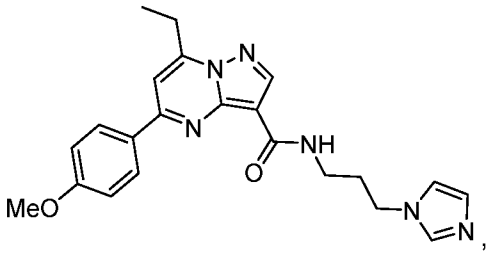


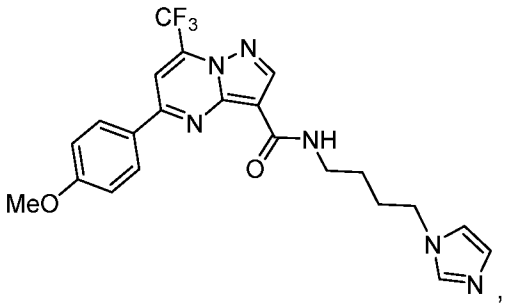


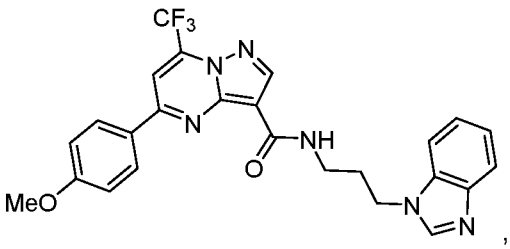


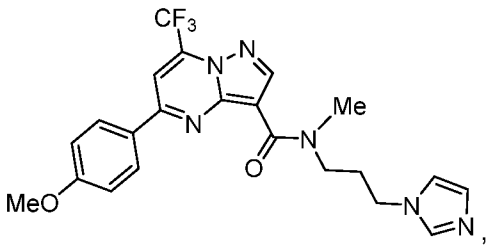


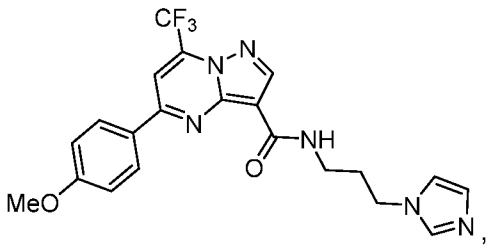


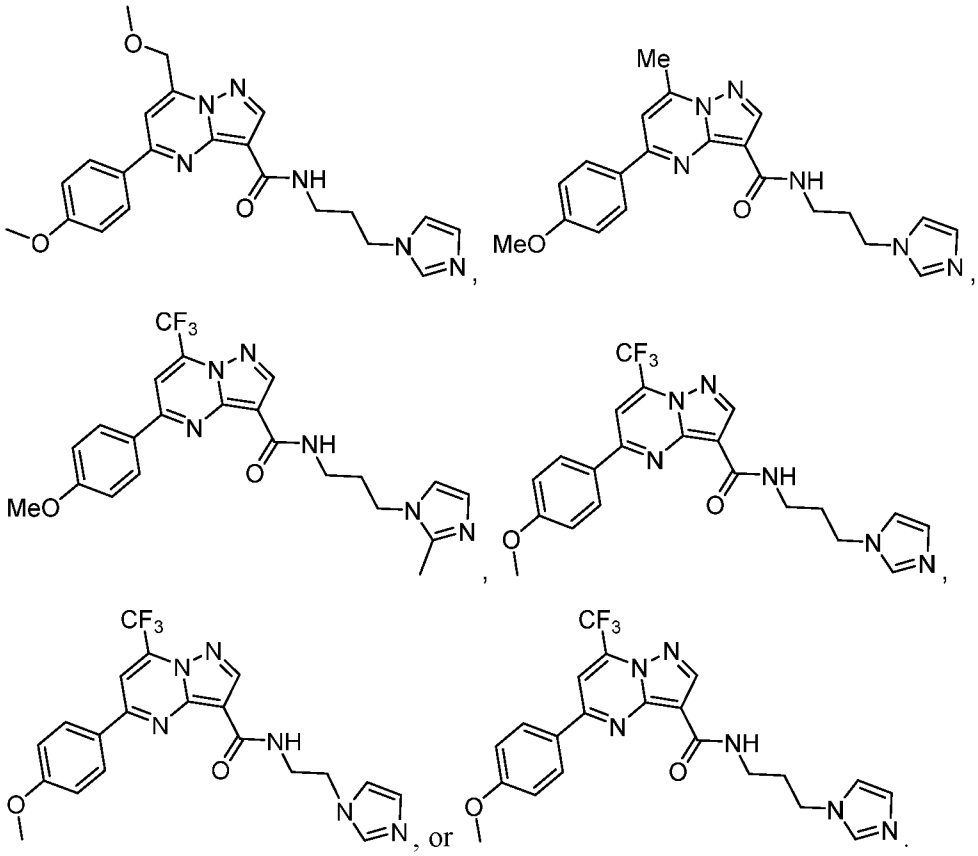




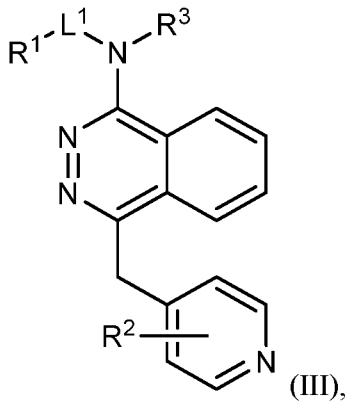








In an aspect, a compound has a Formula (III),



In Formula (III),

L^1 is a bond, C_1-C_4 alkylene, or 2 to 4-membered heteroalkylene;

R^1 is mono- or bi-cyclic cycloalkyl, heterocycloalkyl, aryl, alkylaryl, or heteroaryl, wherein the cycloalkyl, heterocycloalkyl, aryl, alkylaryl or heteroaryl is optionally substituted with one or more selected from halo, (C_1-C_4)alkyl, hydroxy(C_1-C_4)alkyl, (C_1-C_4)alkoxyl, -C(=O)(C_1-C_4)alkyl, -C(=O)N(R)$_2$, or -C(=NR)(C_1-C_4)alkyl, wherein the (C_1-C_4)alkyl is unsubstituted or substituted with heterocycloalkyl;

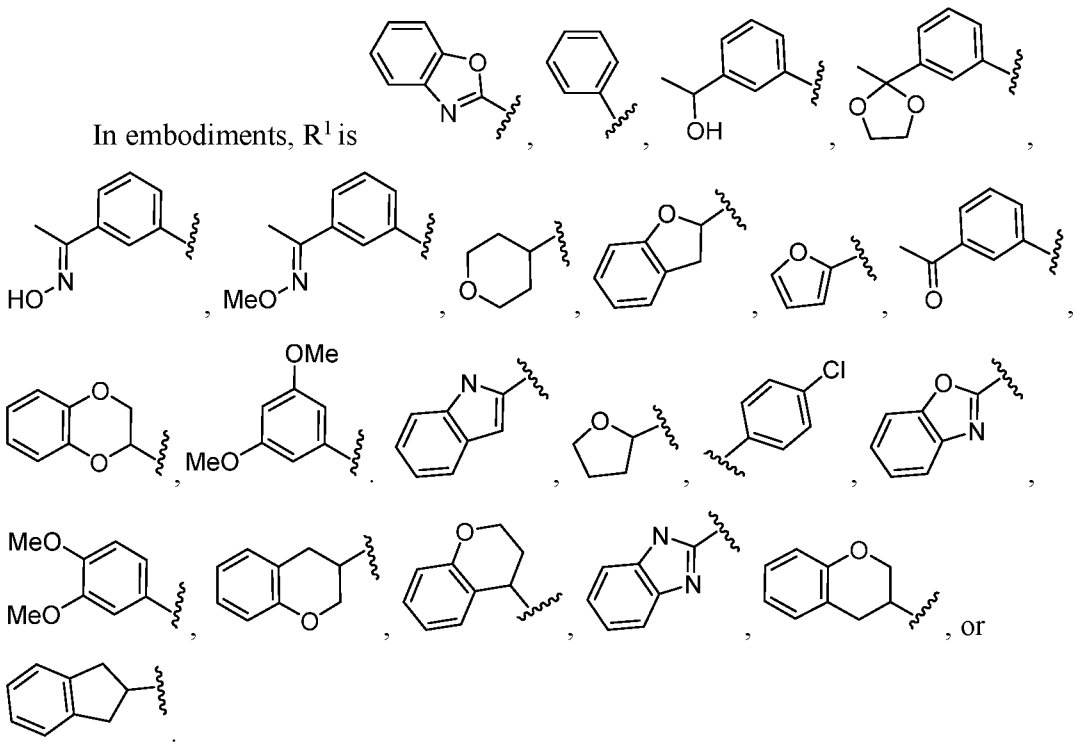
each R is independently hydrogen, -OH, (C_1-C_4)alkyl, or (C_1-C_4)alkoxyl, or two R together with the nitrogen atom to which it is bonded form a heterocycloalkyl, optionally further comprising an O atom in the heterocyclyl ring;

R^2 occurs 0, 1, or 2 times, and is (C_1-C_4) alkyl, (C_1-C_4) haloalkyl, or $SO_2N(R^4)_2$;

each R^3 and R^4 is independently H, or (C_1-C_4)alkyl.

The compound of Formula (III) includes all pharmaceutically acceptable salt forms.

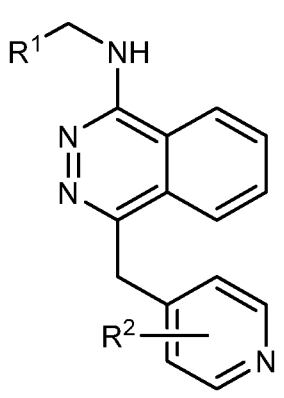
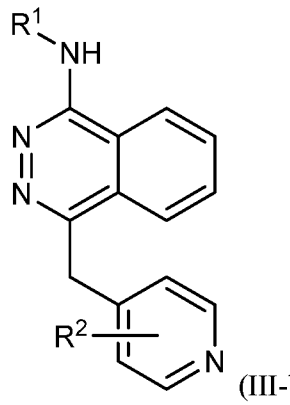
In embodiments, L^1 is a bond. In embodiments, L^1 is methylene. In embodiments, L^1 is $–CH_2CH_2-O-$.

In embodiments, R^1 is .

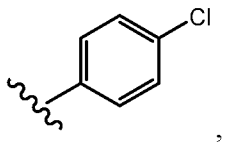
In embodiments, R^2 does not occur. In embodiment, R^2 occurs once.

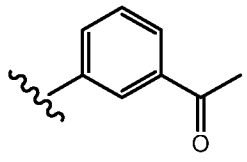
In embodiments, R^3 is hydrogen. In embodiment, R^3 is methyl.

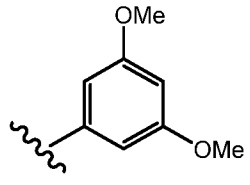
In embodiments, the compound has the following formula:

 (III-a), or  (III-b).

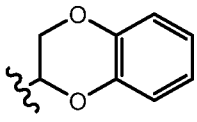
R^1 and R^2 are described herein.

In some compounds of Formula (III), when L^1 is a bond, R^2 does not occur, and R^3 is hydrogen, then R^1 is not 

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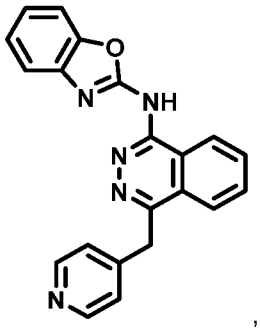
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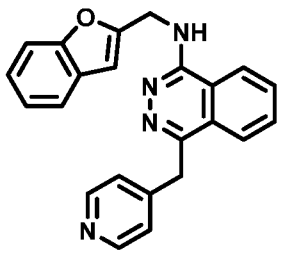
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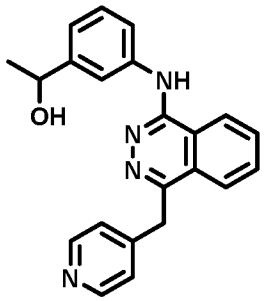
In some compounds of Formula (III), when L^1 is methylene, R^2 does not occur, and R^3 is hydrogen, then R^1 is not 

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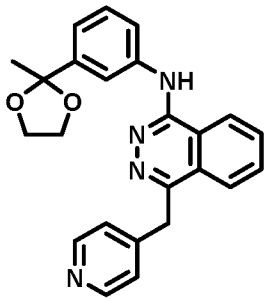
In embodiments, the compounds of Formula (III) include:

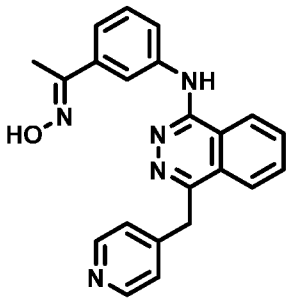


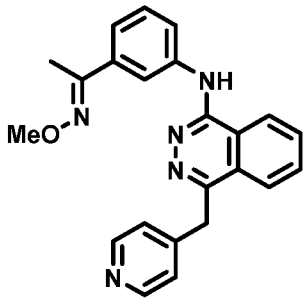
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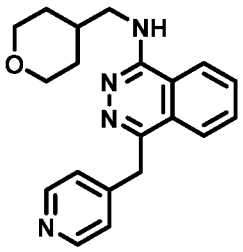
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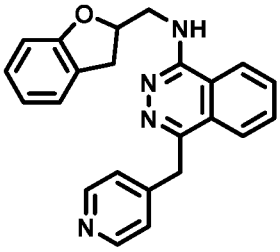


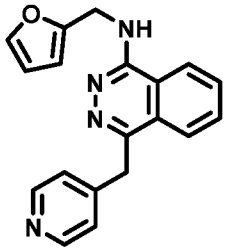
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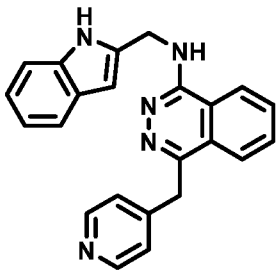
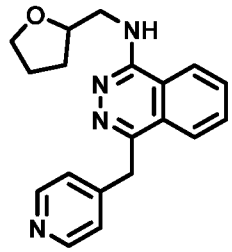
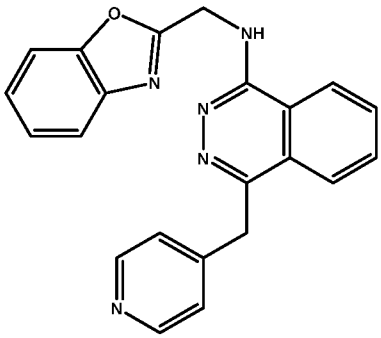
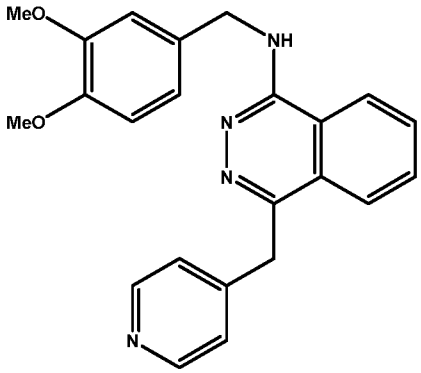
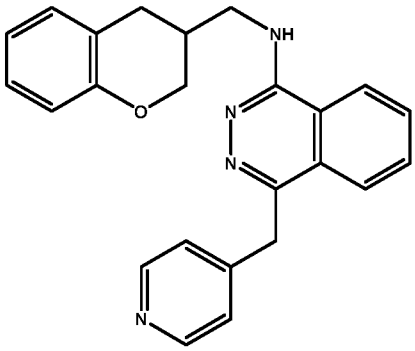
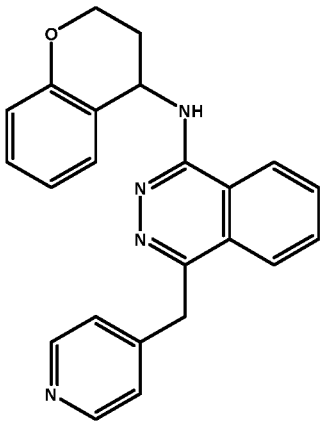
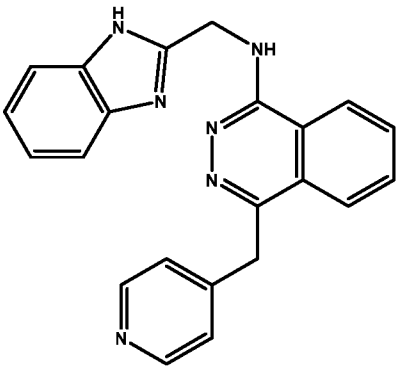
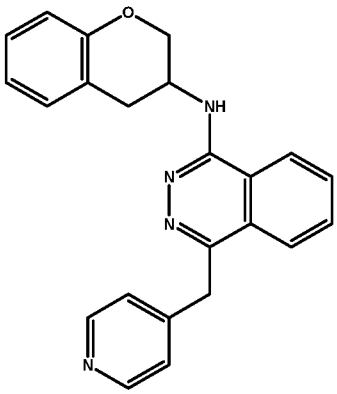
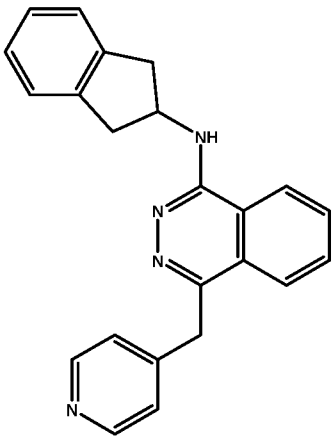
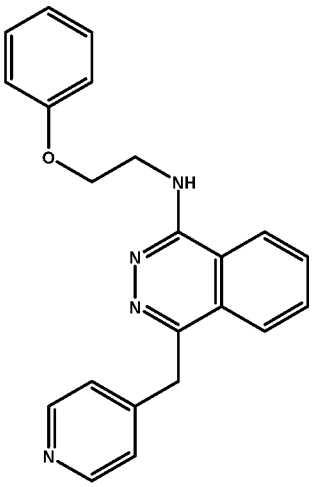
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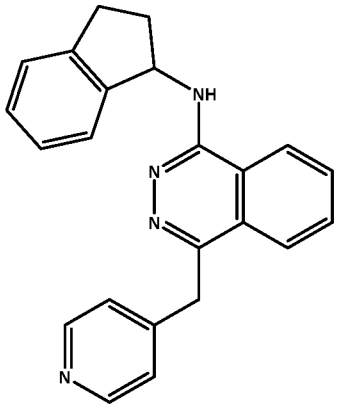


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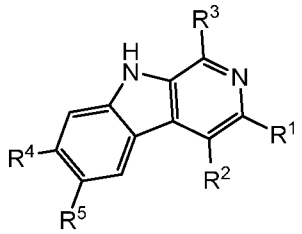
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In embodiments, a compound has a Formula (IV),



(IV).

In Formula (IV),

R^1 is hydrogen, (C_1-C_4)alkyl, -C(O)OH, –C(O)O-(C_1-C_4)alkyl, -C(O)NHNHR^6, -C(O)NR^6-((C_1-C_4)alkylene)-NHR^6, -C(O)NR^6 (C_1-C_4)alkyl, or –C(O)NR^6-cycloalkylene-NHR^6;

R^3 is hydrogen or (C_1-C_4)alkyl; and

each R^2, R^4, R^5 is independently hydrogen, halo, (C_1-C_4)alkyl, –C(O)O-(C_1-C_4)alkyl, (C_1-C_4)alkoxyl, (C_1-C_4)haloalkyl, or CN; and

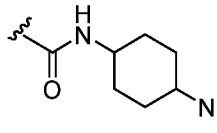
Each R^6 is hydrogen or (C_1-C_4)alkyl.

The compound of Formula (IV) includes all pharmaceutically acceptable salt forms.

In embodiments, each R^4 and R^5 is independently hydrogen or (C_1-C_4)alkoxyl. In embodiments, each R^4 and R^5 are –OMe. In embodiments, R^4 is hydrogen and R^5 is –OMe. In embodiments, R^5 is hydrogen and R^4 is –OMe.

In embodiments, R^1 is hydrogen, (C_1-C_4)alkyl. In embodiments, R^1 is methyl. In embodiments, R^1 is ethyl. In embodiments, R^1 is -C(O)OH, or –C(O)OCH_3. In embodiments, R^1 is –C(O)NH(C_1-C_4)alkyl. In embodiments, R^1 is –C(O)NHCH_3.

In embodiments, R^1 is -C(O)NH-((C_1-C_4)alkylene)-NH_2 or –C(O)NH-cycloalkylene-NH_2. In embodiments, R^1 is - -C(O)NH-CH_2CH_2-NH_2, -C(O)NCH_3-CH_2CH_2-$NHCH_3$,



, or -C(O)$NHNH_2$.

In embodiments, R^3 is hydrogen or methyl.

In embodiments, R^2 is hydrogen, (C_1-C_4)alkyl, or –C(O)O-(C_1-C_4)alkyl. In embodiments, R^2 is hydrogen. In embodiments, R^2 is ethyl. In embodiments, R^2 is methyl. In embodiments, R^2 is –C(O)OCH_3. In embodiments, R^2 is –C(O)OCH_2CH_3.

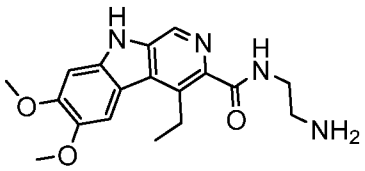
In embodiments, R^6 is independently hydrogen. In embodiments, R^6 is independently methyl.

In some compounds of Formula (IV), when R^4 and R^5 are –OMe, R^3 is hydrogen, and R^2 is ethyl, then R^1 is not –COOMe.

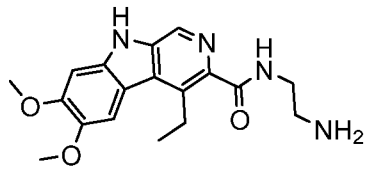
In some compounds of Formula (IV), when R^4 is –OMe, R^5 is hydrogen, and R^1 and R^2 are hydrogen, then R^3 is not methyl.

In some compounds of Formula (IV), when R^2, R^3, R^4, and R^5 are hydrogen, and then R^1 is not –C(O)$NHCH_3$.

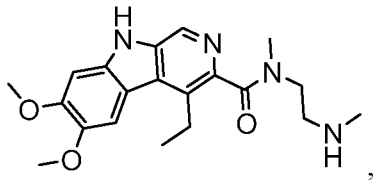
In embodiments, the compounds of Formula (IV) include:



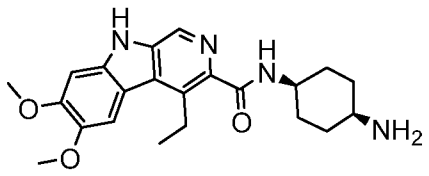
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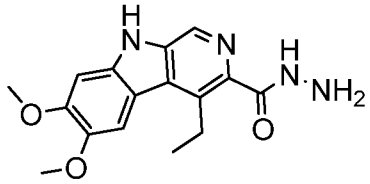
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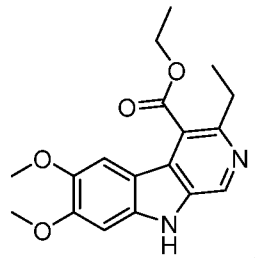
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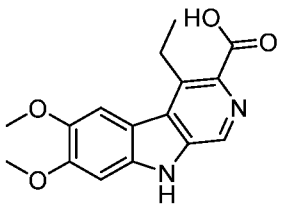
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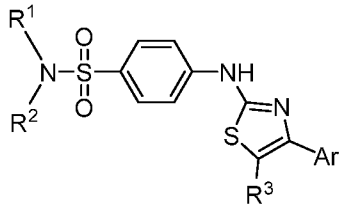


, or



.

In embodiments, a compound has a Formula (V),



(V).

In Formula (V):

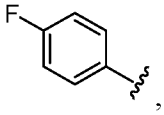
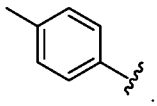
Ar is mono- or bi-cyclic aryl or heteroaryl, optionally substituted one or more with halo, (C_1-C_4)alkyl, (C_1-C_4)haloalkyl, CN, -S(O)$_2$NH$_2$, oxo, -NH$_2$, (C_1-C_4)alkoxyl, or –NHC(O)(C_1-C_4)alkyl;

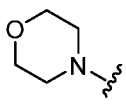
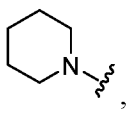
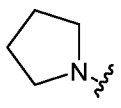
Each R^1 and R^2 is independently hydrogen, (C_1-C_4)alkyl, aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted with halo or (C_1-C_4)alkyl, or R^1 and R^2 attached to nitrogen join together to form a 5 to 6 membered heterocycloalkyl; and

R^3 is hydrogen, or hydroxy-(C_1-C_4)alkyl.

The compound of Formula (V) includes all pharmaceutically acceptable salt forms.

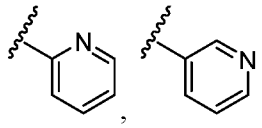
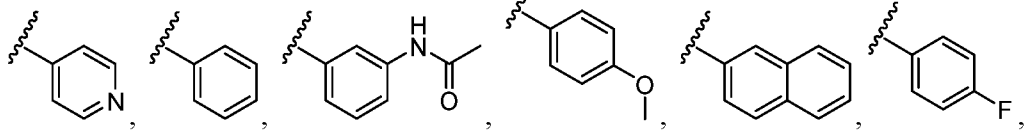
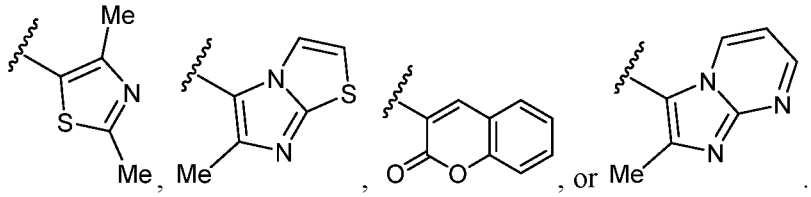
In embodiments, R^1 and R^2 are hydrogen. In embodiments, one of R^1 and R^2 is hydrogen and the other is (C_1-C_4)alkyl such as methyl, ethyl, propyl, isopropyl, n-butyl or t-butyl. In embodiments, R^1 and R^2 are independently (C_1-C_4)alkyl. For example, R^1 and R^2 are independently selected from methyl, ethyl, propyl, isopropyl, n-butyl or t-butyl. In embodiments, R^1 and R^2 are methyl.

In embodiments, one of R^1 and R^2 is hydrogen and the other is phenyl, which may be optionally substituted with F, Cl, Br, or (C_1-C_4)alkyl. In embodiments, one of R^1 and R^2 is hydrogen and the other is phenyl, , or .

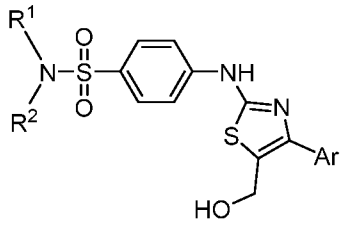
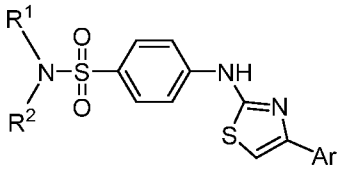
In embodiments, R^1 and R^2 attached to nitrogen join together to form a 5 to 6 membered heterocycloalkyl such as , , or .

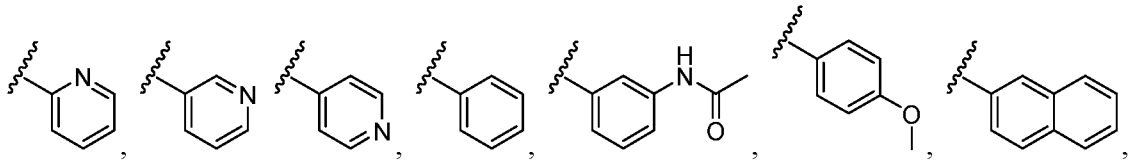
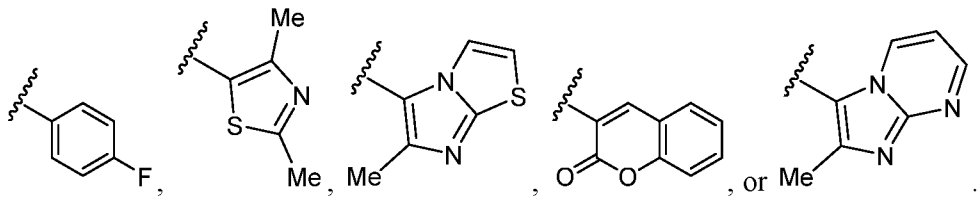
In embodiments, R^3 is hydrogen. In embodiments, R^3 is hydroxy-(C_1-C_4)alkyl. In embodiments, R^3 is –CH$_2$-OH.

In embodiments, Ar is pyridyl, phenyl, naphthyl, or thiazolyl, which is optionally substituted with one or more with halo, (C_1-C_4)alkyl, (C_1-C_4)haloalkyl, -CN, -S(O)$_2$-NH$_2$, -

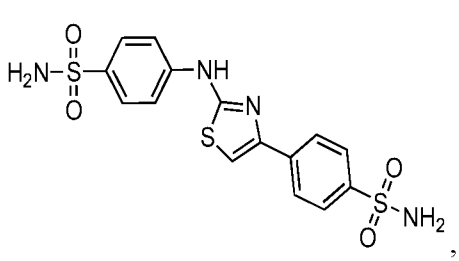
NH_2, (C_1-C_4)alkoxyl, or-NHC(O)alkyl. In embodiments, Ar is , , , or .

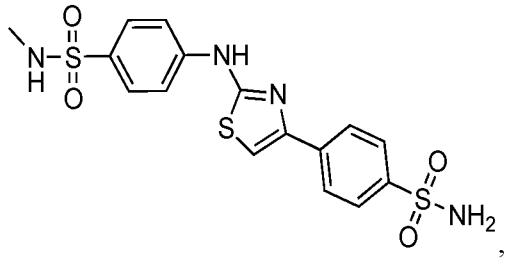
In embodiments, the compound has the following formula:

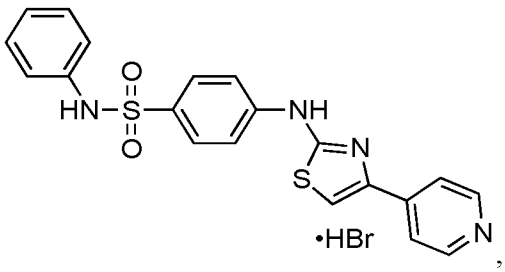
 (V-a) or  (V-b). R^1, R^2 and Ar are as described herein.

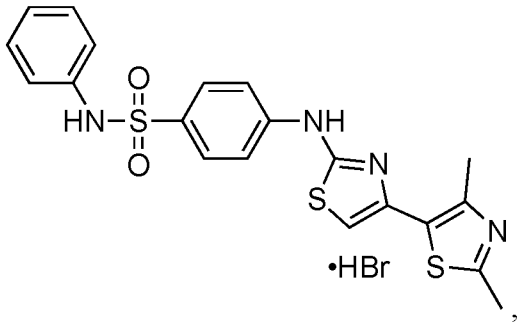
In some compounds of Formula (V), when R^1, R^2 and R^3 are hydrogen, then Ar is not , , or .

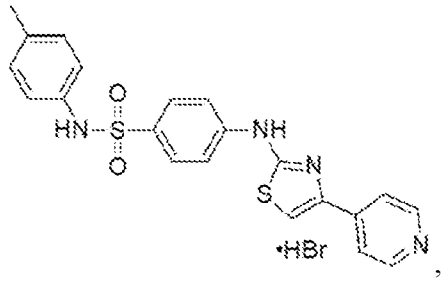
In embodiments, the compounds of Formula (V) include:

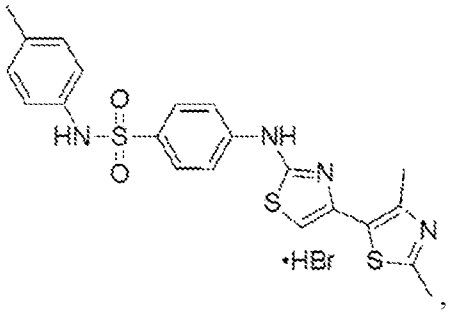


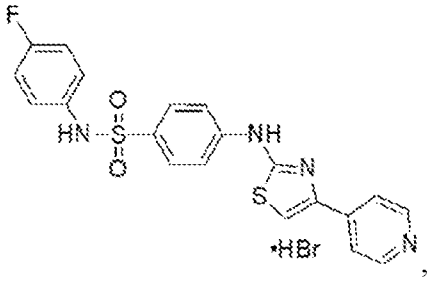


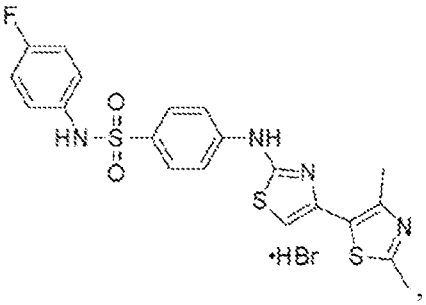


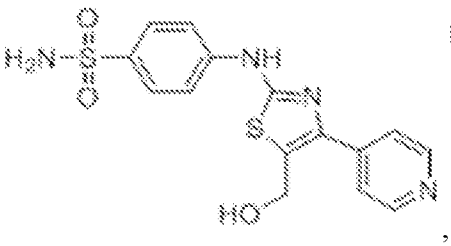


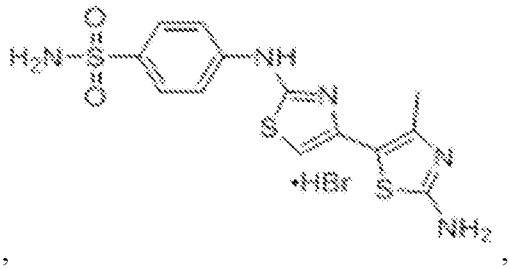


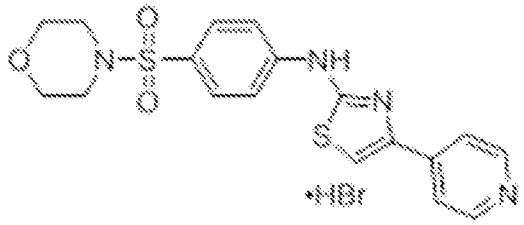
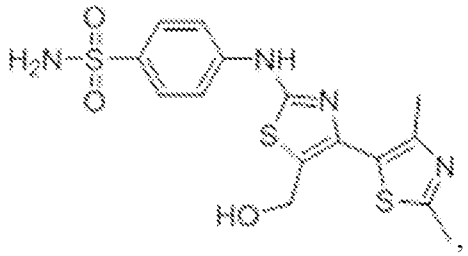
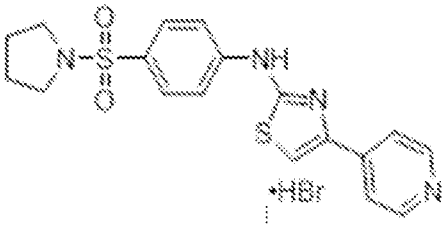
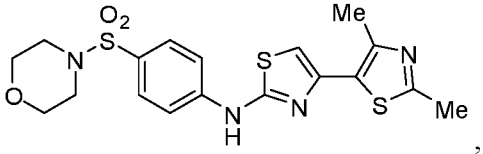
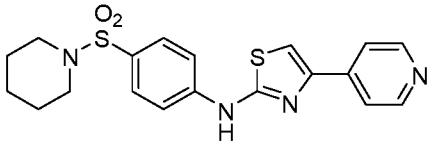
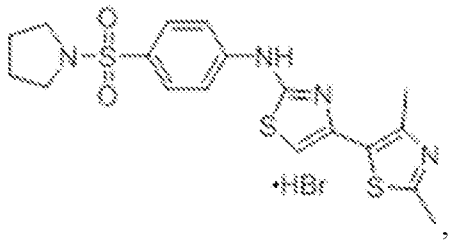
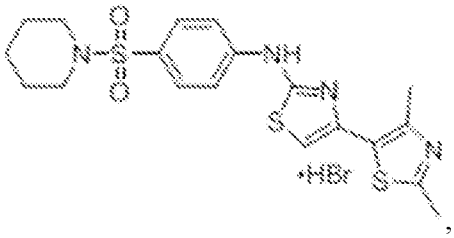
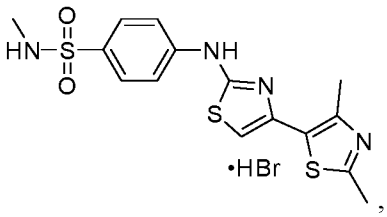
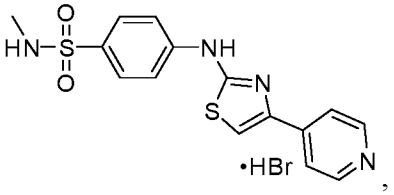
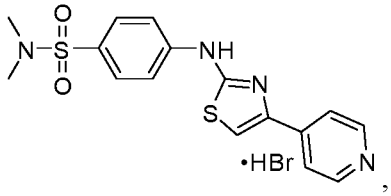
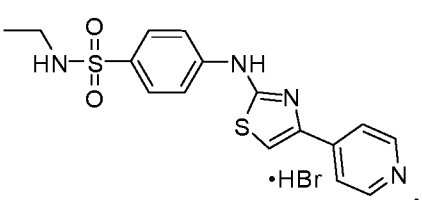
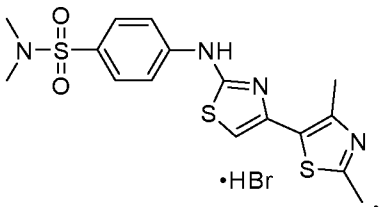
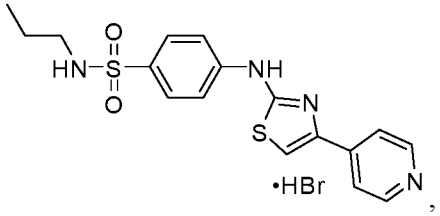
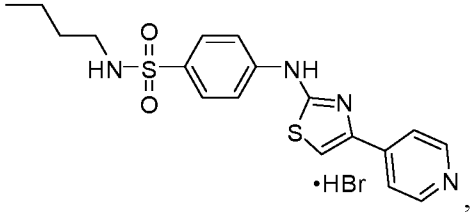


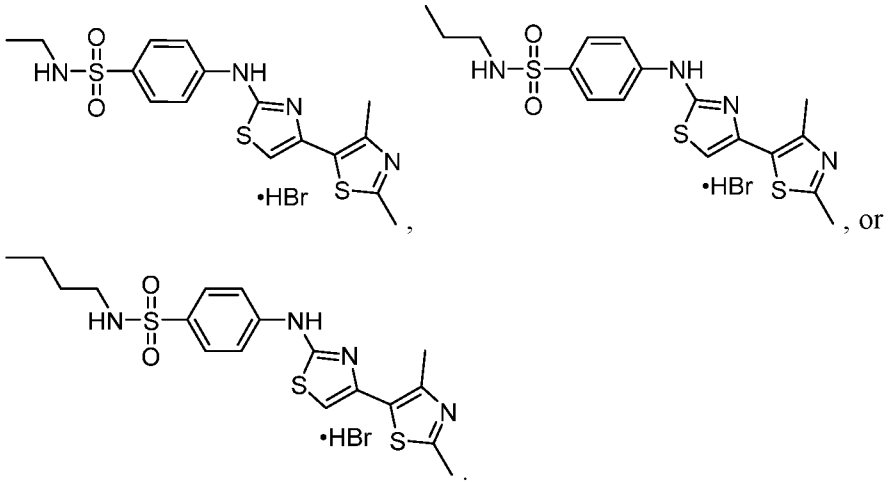










Methods

In an aspect, provided is a method for inhibiting NAD consumption and/or increasing NAD synthesis in a patient, and the method includes administering to the patient an effective dose of the compound described herein.

The compound can inhibit protein ADP-ribosylation reactions. The compound can inhibit NAD cleavage by protein deacetylases or glycohydrolases. The compound can increase NAD synthesis. The patient is afflicted with, or at risk for, a protein misfolding neurodegenerative disease or another protein misfolding disease.

The protein misfolding neurodegenerative disease includes a prion disease, Parkinson's disease or other synucleinopathies, Alzheimer's disease, amyotrophic lateral sclerosis, or a tauopathy and the protein misfolding disease includes diabetes mellitus.

In an aspect, provided is a method for preventing or inhibiting NAD depletion in a patient. In another aspect, provided is a method for improving a condition linked to alterations of NAD metabolism in a patient. The method includes administering to the patient an effective dose of the compound described herein.

The condition includes a metabolic disorder, aging, a degenerative disease, a neurodegenerative disease, neuronal degeneration associated with multiple sclerosis, hearing loss, retinal damage or multiple sclerosis, brain or cardiac ischemia, kidney failure, kidney disease, traumatic brain injury, or an axonopathy.

In an aspect, provided is a method for providing protection from toxicity of misfolded proteins in a patient. The method includes administering to the patient an effective dose of the compound described herein. The patient is afflicted with a prion disease, Parkinson's

disease or other synucleinopathy, Alzheimer's disease, amyotrophic lateral sclerosis, a tauopathy or diabetes mellitus.

In an aspect, provided is a method for preventing or treating a protein misfolding neurodegenerative disease in a patient. The method includes administering to the patient an effective dose of the compound described herein. The protein misfolding neurodegenerative disease includes a prion disease, Parkinson's disease or other synucleinopathy, Alzheimer's disease, amyotrophic lateral sclerosis, or a tauopathy.

Neuroprotection and $GABA_A$ R inhibition are two distinct activities of DMCM.

DMCM, a member of the carbazole series (structure shown earlier, and in Examples), has a known mode of action: it is an inverse agonist of all subtypes of $GABA_A$ R[7], binding to its benzodiazepine (BZ) site. It is therefore a convulsant *in vivo*. Because convulsive activity is intolerable in a neuroprotectant, it cannot be directly repurposed[8].Another pharmacological modulator binding to the BZ site, flumazenil (Ro 15-1788)[9,10] has been tested. It neither rescued TPrP-induced toxicity nor competed with the effect of DMCM (Figure 3), suggesting that neuroprotection is likely unrelated to intrinsic activity at $GABA_A$ R.

A pilot SAR study has been conducted to further test the conclusion that DMCM's activities, neuroprotection vs. $GABA_A$ R binding, are distinct. Figure 4 shows the hydrazine amide **1,** a close analog of DMCM (DMCM-10049), which is reported to be devoid of $GABA_A$ R activity (over 100x reduced potency for most $GABA_A$ R subtypes[11]). It showed, however, neuroprotective activity very close to that of DMCM (Figure 4). Treatment of DMCM with diamines, including 1,4-cis-diaminocyclohexane, gave aminoamides such as compound **2** (DMCM-8137). This compound was also neuroprotective (Figure 4). Moreover, it is designed to have a handle to permit conjugation for target identification (Figure 4).

Taken together, these studies show that DMCM acts on a target other than $GABA_A$ R to confer neuroprotection, a finding enabling the optimization of DMCM analogs as neuroprotectants that are devoid of the activity for which the parent compound has been used. DMCM is neuroprotective in primary neurons (See Figure 5).

DMCM prevents excessive mono-ADP ribosylation induced by TPrP.

It has been demonstrated that TPrP induces NAD depletion at least in part by excessive protein mono-ADP ribosylation[2], an NAD-consuming reaction. Figure 6 shows that DMCM prevents this excessive protein ADP-ribosylation.

DMCM is neuroprotective in a cellular model of Parkinson's disease (PD).

Parkinson's disease, similar to prion diseases, arises from the misfolding and aggregation of a protein, α-synuclein in this case. Therefore, the neuroprotective properties of compounds from HTS were investigated in cellular models of PD-induced neurodegeneration (Figs. 7 and 14). In these models, neuronal cells exposed to preformed alpha-synuclein fibrils (PFFs) undergo loss of synapses and dendritic spines, as well as a shortening and loss of neurites (Figure 7, see PFFs-exposed neurons vs control neurons). PFFs-seeded neurons accumulate α-synuclein fibrils and a particular type of α-synuclein aggregates that is toxic to the cells (called pα-syn*[12]). Figure 7 shows that the hydrazine amide of DMCM, named DMCM-10049, preserves dendritic spines in PFFs-exposed neurons and reduces the amounts of toxic pα-syn*.

Therapeutic effect of DMCM-10049 in a murine model of Parkinson's disease.

Moreover, DMCM has been used *in vivo* as a tool compound, with favorable PK properties[5,7-9,13,14]. Therefore, DMCM-10049 was tested in a murine model of PD (the Tg(SNCA*A53T) mice, harboring an α-synuclein mutation responsible for familial PD in humans). Treatment with DMCM-10049 significantly prolonged the survival of these mice (Figure 8).

Therapeutic effect of DMCM-10049 in a murine model of ALS.

DMCM-10049 was tested in a murine model of ALS (the Tg(SOD1*G93A) mice, harboring an SOD1 mutation[15]). Mutant SOD1 accounts for 15-20% of familial ALS and 1-2% of apparently sporadic ALS cases, and misfolded SOD1 is found in ALS patients not carrying a mutation[16]. Treatment with DMCM-10049 significantly prolonged the survival of these mice (Figure 9).

Detailed study of the Vatalanib series (aminophthalazine series).

Vatalanib, aka SR5-1457, has recently been in late-stage clinical development as an orally administered antitumor agent[17-21]. It is a receptor tyrosine kinase inhibitor, specifically a potent VEGFR inhibitor, is highly cell-permeable and has overall excellent PK properties in humans and in rodents[22-24]. This compound was highly neuroprotective with an EC_{50} = 39.9 nM (TPrP toxicity rescue) and EC_{50} = 195 nM (NAD assay). Because of its high potency and

excellent PK properties (including high brain penetration and high oral bioavailability), we opted to advance this compound rapidly to *in vivo* neuroprotection studies.

As shown in Figure 10, vatalanib treatment of ALS mice significantly improved their motor function and muscle strength, assessed using the rotarod and hanging-wire tests. However, a prolongation in survival times (160±2 d survival in treated animals vs 157±2 d for the control group) was not observed.

While using vatalanib for this early proof-of-concept study, this specific compound is ill-suited for direct repurposing due to its ability to strongly inhibit VEGFR, which confers the antiangiogenic effects that are thought to be responsible for its antitumor properties, which may be reasoned that the neuroprotective mode of action for this compound is unrelated to its known activity vs. VEGFR, because VEGF/VEGFR-2 signaling is known to be neuroprotective (thus blocking VEGFR would be expected to confer mild neurotoxicity rather than neuroprotection)[25]. VEGFR-2 overexpression is known to delay neurodegeneration of spinal motor neurons in Tg(SOD1*G93A) mice and VEGF administration has been shown to delay muscle weakness in ALS models[26-28] and to be neuroprotective in PD models[29,30]. Therefore, the VEGFR inhibitory activity of vatalanib should *oppose* the objective of neuroprotection and thus vatalanib would be a poor choice for repurposing to treat ALS or, more generally, any neurodegenerative disease that requires chronic treatment. The NAD-preserving activity identified herein likely opposes (and prevails) over the intrinsic VEGFR effects. Analogs lacking VEGFR activity should be better candidates for neuroprotective drug leads.

Analogs of vatalanib that are known to be inactive at VEGFR, or at least to have very low affinity for VEGFR, are shown in Figure 11. Note: Flt-1 and KDR are subtypes of VEGFR, also known as VEGFR-1 and VEGFR-2, respectively. As shown, the activity of these compounds with respect to their neuroprotective/NAD-restoring effects does not correlate with their activity for VEGFR inhibition[24]. For example, a methyl ketone-containing structural analog of vatalanib, SR1-134005 (2nd structure, Figure 11), is more than 6-fold more potent than is vatalanib as a neuroprotective agent (6.3 nM vs. 39.9 nM), though this same compound is 13-fold less potent than vatalanib as a VEGFR-1 inhibitor (1 μM vs. 77 nM). Similarly, the analog SR1-151915 (3rd structure) retains about half of vatalanib's neuroprotective activity (EC_{50} = 71.4 nM) but this same compound is also a poor VEGFR inhibitor (IC_{50} > 1 μM). Conversely, analog SR1-151911 (4th structure) is far less neuroprotective (only 44% neuroprotection @ 6.4 μM) though it has modest VEGFR activity

(IC_{50} = 793 nM vs. VEGFR-1, only ~20-fold less than vatalanib and more potent at VEGFR than are SR1-134005 and SR1-151915).

Further, other commercially available potent VEGFR inhibitors structurally unrelated to vatalanib (lenvatinib, pazopanib, tivozanib & sorafenib) entirely lacked neuroprotective activity in the TPrP assay at concentrations up to 10 μM (data not shown).

Clearly the two activities (neuroprotection and antitumor effects through VEGFR inhibition) can be differentiated, and this unambiguous result prompted us to test the vatalanib analog SR1-134005, having low VEGF-R activity, in an ALS mouse model.

Therapeutic effect of SR1-134005 in a murine model of ALS.

The methyl ketone analog of vatalanib SR1-134005 (exhibiting ~13-fold reduced VEGFR-1 activity relative to vatalanib, Figure 11) provides the same overall *in vivo* benefit as does vatalanib, and moreover it is efficacious at an 8-fold lower dose (Figure 12). This *in vivo* result supports our *in vitro* findings that SR1-134005 is a more potent neuroprotectant than is vatalanib and further that neuroprotection is dissociated from VEGFR inhibition, which is presumed to be responsible for the antitumor effects seen for this class of compounds.

Therapeutic effect of SR1-134005 in a murine model of Parkinson's disease.

Treatment with the methyl ketone analog of vatalanib SR1-134005 significantly prolonged the survival of Tg(SNCA*A53T) mice (Figure 13).

Neuroprotective effect of pyrazolopyrimidines (SR1-293229), aminothiazoles (SR1-477186), triazolophthalazines (SR1-115259), aminophthalazines (vatalanib) and flavonoids (nobiletin, apigenin) in a cellular model of PD, a synucleinopathy.

Similar to our observations with the carbazole series, compounds of other leads series protected against neurodegeneration induced by α-synuclein PFFs in cultured neurons. These include the pyrazolopyrimidines (SR1-293229), aminothiazoles (SR1-477186), triazolophthalazines (SR1-115259), aminophthalazines (vatalanib) and flavonoids (nobiletin, apigenin). Figure 14 illustrates the protective effect and shows that the lead compounds prevent loss of neurites induced by PFFs exposure.

NAD rescue by the carbazole, aminophthalazine, pyrazolopyrimidine, triazolophtalazine and flavonoid series is not due to PARP-1 inhibition.

Figure 15 shows that at least five of the lead series described herein are not PARP-1 inhibitors.

Aminophthalazines (vatalanib and SR1-134005) are NAMPT activators.

It has been demonstrated that TPrP induces excessive ADP-ribosylation and designed the compound screening strategy to capture compounds able to restore physiological NAD levels. Figure 6 shows that this can be achieved by preventing excessive ADP-ribosylation. Figure 16 shows that it can also be achieved by enhancing NAD synthesis since one of our lead series, the aminophthalazines vatalanib and "SR-005" acts by activating NAMPT, the rate-limiting enzyme in NAD synthesis.

For the first time, it has been shown that failure of NAD metabolism is a fundamental mechanism of neurotoxicity induced by a misfolded amyloidogenic protein (TPrP), and that NAD replenishment is neuroprotective[2]. Therefore, NAD-restorative compounds were screened for rescue from proteotoxicity, with the hypothesis that other conditions may be successfully treated using compounds that can restore healthy NAD levels, by any mechanism. Indeed, NAD dysregulation is now also recognized as being involved in AD[31,32], aging[33-36], neuronal degeneration associated with multiple sclerosis[37], hearing loss[38], retinal damage[39], traumatic brain injury[40], and axonopathy[41]. Substantial decreases in NAD levels are found in degenerative renal conditions[42]. NAD augmentation such as NAD administration or increased NAD synthesis by enzyme overexpression has been shown to mitigate brain ischemia [43], cardiac ischemia/reperfusion injury[44,45] and acute kidney injury[42].

NAD metabolism has also been shown to be altered in murine models of type 2 diabetes (T2D)[46,47]. Alterations of NAD metabolism in diabetes can be explained by our findings that misfolded proteins induce NAD dysregulation. Indeed, diabetes has been shown to be a protein misfolding disease, characterized by pancreatic beta-cell dysfunction and death, concomitant with the deposition of aggregated islet amyloid polypeptide (IAPP), a protein co-expressed and secreted with insulin by pancreatic beta-cells[48]. Amyloid IAPP deposition is a common feature of diabetes of different etiologies[49]. Similarly to proteins involved in other protein misfolding diseases, IAPP forms toxic oligomers[48]. Moreover, proinsulin, the precursor of insulin, is also prone to misfold in beta-cells. Misfolding of

proinsulin has been linked to type 2, type 1 and some monogenic forms of diabetes progression[48,50,51]. Finally, pancreatic beta cells harbor some common physiological properties with neurons[52]. The compounds described herein will therefore also be used to mitigate dysfunction and death of pancreatic cells in cellular models of diabetes, and to achieve therapeutic benefits in animal models of diabetes, as a demonstration of their potential for the treatment of diabetes mellitus in humans. To this end, we will use rodent derived insulin-secreting cell lines such as MIN-6 and INS-1 cells[52,53]; we expect alterations of their beta cell function, NAD levels and viability upon exposure to misfolded and/or aggregated forms of IAPP and/or proinsulin. Further, we expect that such alterations will be corrected by treatment with the compounds described herein. Therapeutic benefits of the compounds will be assessed in rodent models such as, for example, high fat fed mice, ob/ob mice and db/db mice (leptin deficient and resistant, respectively) for T2D[54], and streptozotoxin-treated mice, non-obese diabetic (NOD) mice, BioBreeding diabetes-prone (BB) rat for type 1 diabetes[55,56].

NAD, as used here, designates both the oxidized (NAD+) and the reduced (NADH) forms of the cofactor. NAD is critical, *inter alia*, as a co-enzyme for the regulation of energy metabolism pathways such as glycolysis, TCA cycle and oxidative phosphorylation leading to ATP production. In addition, NAD serves as a substrate for signal transduction and post-translational protein modifications called ADP-ribosylations.

Physiological cellular NAD levels result from the balance of activity of NAD synthesis enzymes and NAD consuming enzymes, which may be reasoned that the NAD imbalance induced by misfolded proteins (and that is assessed in our phenotypic assays) could therefore result from either impaired NAD biosynthesis or from increased NAD consumption.

In mammalian cells, NAD is mainly synthesized *via* the salvage pathway using the precursor nicotinamide (NAM). The rate-limiting enzyme for NAD synthesis in the salvage pathway is nicotinamide phosphoribosyltransferase (NAMPT). Other NAD synthesis pathways are the *de novo* pathway utilizing the precursor tryptophan and the Preiss-Handler pathway utilizing the precursor nicotinic acid (NA).

On the other hand, NAD is consumed during the following cellular reactions: 1) the production of calcium-releasing second messengers cyclic ADP-ribose (cADPR) and ADP-ribose (ADPR) from NAD by enzymes called NAD hydrolases or ADP-ribosyl cyclases (CD38 and CD157); 2) sirtuin-mediated protein deacetylations, and 3) protein ADP-

ribosylations, in which one or several ADP-ribose moiety of NAD is transferred unto proteins by mono/oligo-ADP-ribose transferases (mARTs) or poly-ADP ribose transferases (called PARPs).

It has been showed that TPrP induced excessive ADP-ribosylation of cellular proteins, and further that toxicity was not alleviated by selective PARP1 inhibitors. Therefore, these studies unveiled a new mechanism of neurotoxicity linked to an imbalance in NAD metabolism due, at least in part, to excessive mono or oligo ADP-ribosylation reactions. As mentioned above, the HTS campaign and follow-up assays that led to the identification of the 8 compound series presented herein rely upon phenotypic readouts, and the study was thus purposefully agnostic of the mechanism underlying preservation of NAD levels and viability in cells exposed to proteotoxicity. This design was intended to identify compounds regulating NAD levels by any mechanism of action such as enhancing NAD synthesis or preventing excessive NAD degradation/consumption, and to include non-PARP1 inhibitors. Our data show that: 1) all the protective compounds presented herein are neuroprotective and preserve cellular NAD levels; 2) at least 5 of these compounds are not PARP-1 inhibitors (Figure 15); 3) as proof-of-concept, at least one test compound prevents excessive ADP-ribosylation induced by a misfolded protein (Figure 6), and at least one test compound is a NAMPT activator (Figure 16).

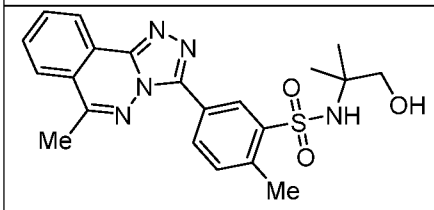
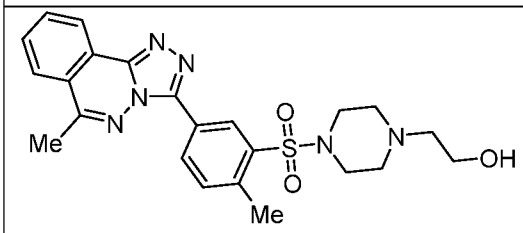
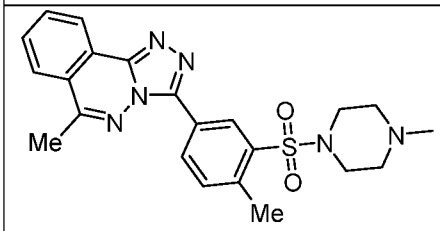
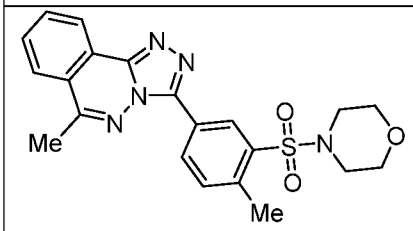
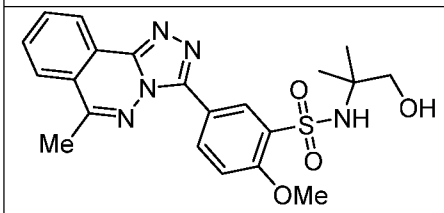
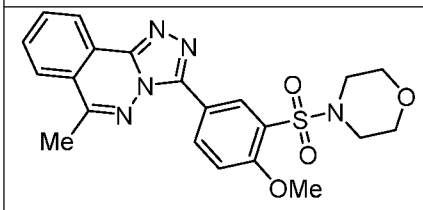
EXAMPLES

Example 1: cell viability assays and NAD quantification assays

The tables below show the structures of specific examples of compounds useful for practice of methods of the invention, associated with corresponding data such as compound identifier, molecular weight, compound properties, and biological results.

The biological activity of test compounds was quantified in two assays: a cell viability assay (CellTiter-Glo®) assessing the ability of compounds to prevent neuronal death induced by the misfolded protein TPrP, and a NAD quantification assay (NAD+/NADH-Glo™) assessing the ability of compounds to prevent NAD depletion induced by the misfolded protein TPrP. Efficacious concentrations (EC_{50} values) are shown. The procedures were as described in Figure 2 (1536 well-plate format) for those compounds where both viability EC_{50} and NAD EC_{50} are indicated (Tables 1-8), as described in Figure 4 (96 well-plate format) for those compounds where only viability EC_{50} is indicated (Tables 9-12).

Table 1 Triazolophthalazines: SR1-115259 series

Structure	identifier, properties	Viability EC_{50}	NAD EC_{50}
	SR1-115259 Mol. Wt. = 425 HBD = 2 HBA = 5 tPSA = 107	5.1 nM	167 nM
	SR1-626887 Mol. Wt. = 467 HBD = 1 HBA = 6 tPSA = 101	<3 nM	9.1 nM
	SR1-115275 Mol. Wt. = 437 HBD = 0 HBA = 6 tPSA = 81	839 nM	2.6 μM
	SR5-22843 Mol. Wt. = 423 HBD = 0 HBA = 6 tPSA = 87	30 nM	219 nM
	SR1-87819 Mol. Wt. = 442 HBD = 2 HBA = 6 tPSA = 116	98 nM	682 nM
	SR5-22837 Mol. Wt. = 439 HBD = 0 HBA = 7 tPSA = 96	29 nM	89 nM

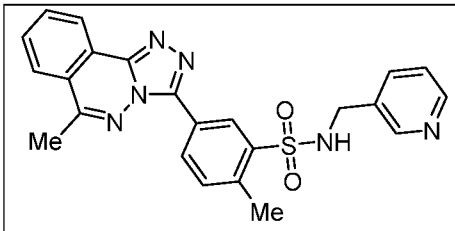
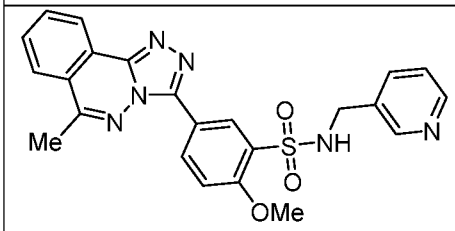
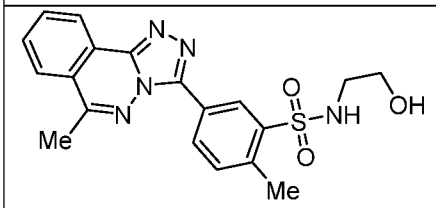
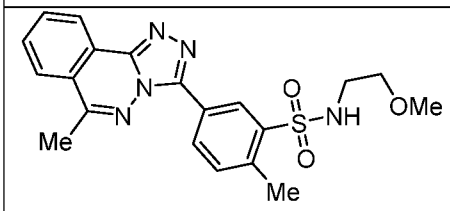
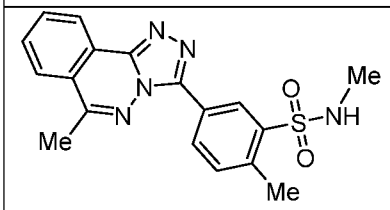
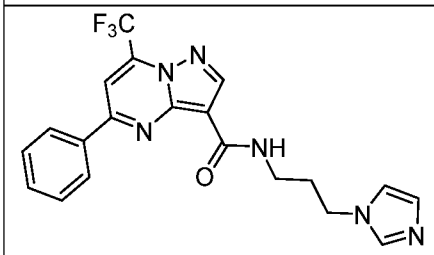
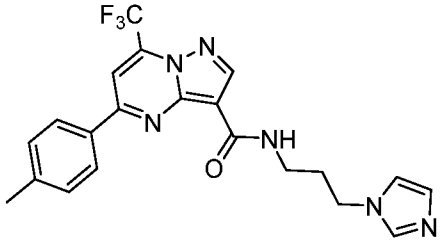
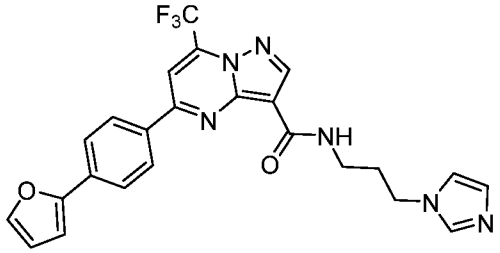
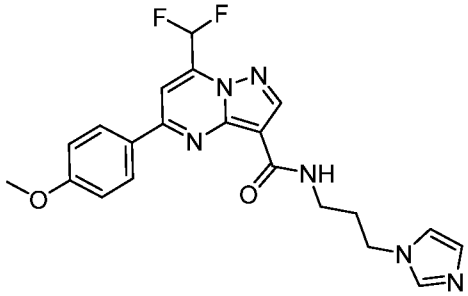
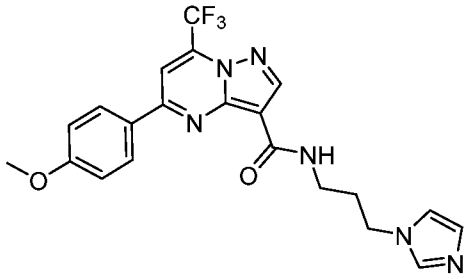
	SR5-22839 Mol. Wt. = 445 HBD = 1 HBA = 6 tPSA = 99	28 nM	92 nM
	SR5-22838 Mol. Wt. = 461 HBD = 1 HBA = 7 tPSA = 108	90 nM	380 nM
	SR1-87813 Mol. Wt. = 397 HBD = 2 HBA = 5 tPSA = 107	156 nM	733 nM
	SR5-22841 Mol. Wt. = 411 HBD = 1 HBA = 6 tPSA = 96	130 nM	688 nM
	SR1-115255 Mol. Wt. = 367 HBD = 1 HBA = 5 tPSA = 86	196 nM	1.2 μM

Table 2 Pyrazolopyrimidines: SR1-293229 and related compounds

Structure	Data	Viability EC_{50}	NAD EC_{50}
	SR1-293229 Mol. Wt: 414 cLog P: 3.0 HBD = 1 HBA = 4 tPSA = 73	1.9 nM	6.8 nM
	SR1-527764 Mol. Wt: 428 cLog P: 3.5 HBD = 1 HBA = 4 tPSA = 73	1.9 nM	7.1 nM
	SR1-550907 Mol. Wt: 480 cLog P: 4.2 HBD = 1 HBA = 5 tPSA = 82	2.9 nM	9.7 nM
	SR0-24089 Mol. Wt: 426 cLog P: 2.2 HBD = 1 HBA = 5 tPSA = 82	fully effective at 1 nM, partially effective at 0.2 nM	nt
	SR0-24081 Mol. Wt: 444 cLog P: 3.0 HBD = 1 HBA = 5 tPSA = 82	fully effective at 1 nM	nt

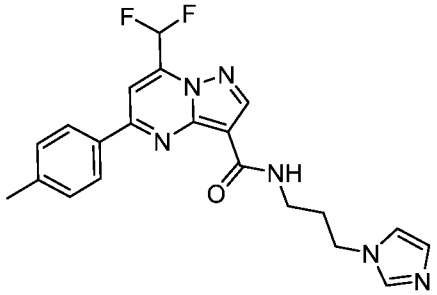
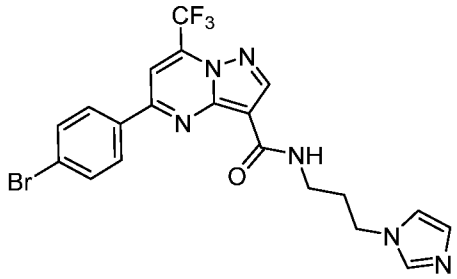
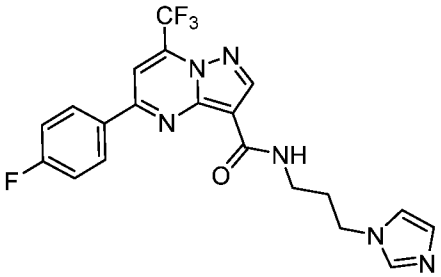
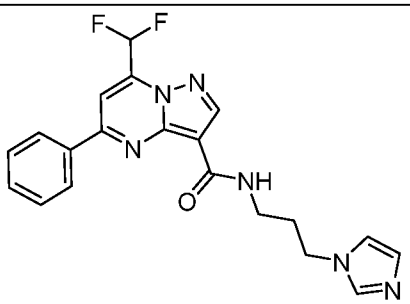
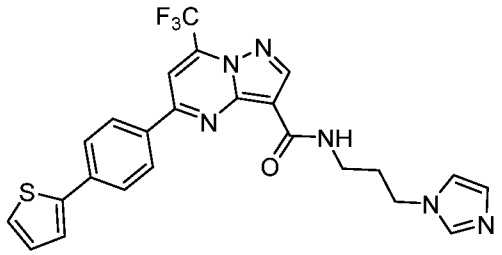
	SR-024088 Mol. Wt: 410 cLog P: 2.7 HBD = 1 HBA = 4 tPSA = 73	>80% effective at 1 nM	nt
	SR0-24082 Mol. Wt: 493 cLog P: 3.8 HBD = 1 HBA = 4 tPSA = 73	~40% effective at 1 nM, fully effective at 10 nM	nt
	SR0-24083 Mol. Wt: 432 cLog P: 3.1 HBD = 1 HBA = 4 tPSA = 73	~40% effective at 1 nM, fully effective at 10 nM	nt
	SR0-24084 Mol. Wt: 396 cLog P: 2.2 HBD = 1 HBA = 4 tPSA = 73	~40% effective at 1 nM, fully effective at 10 nM	nt
	SR1-221674 Mol. Wt: 497 cLog P: 4.7 HBD = 1 HBA = 4 tPSA = 73	fully effective at 10 nM, ineffective at 1 nM	nt

Table 3. Aminophthalazines: Vatalanib and related compounds

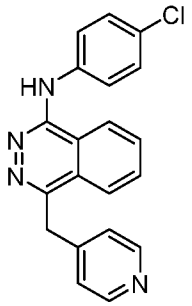
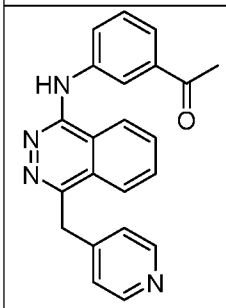
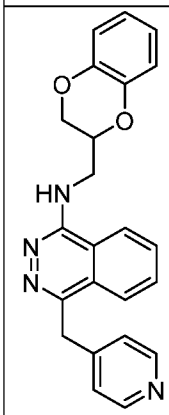
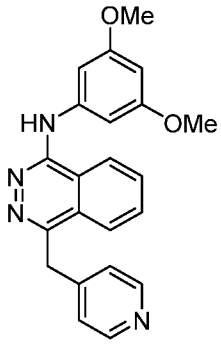
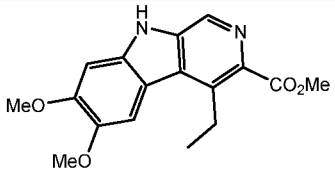
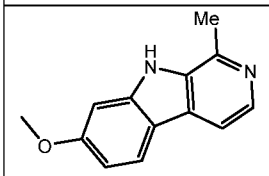
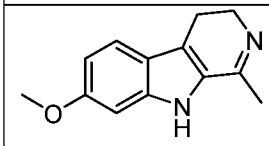
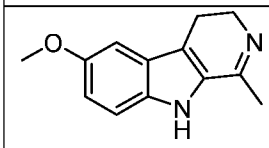
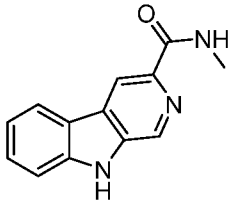
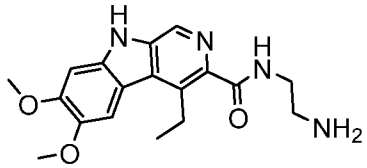
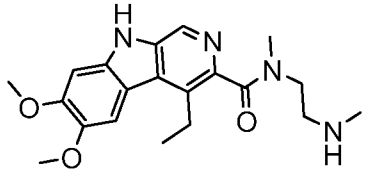
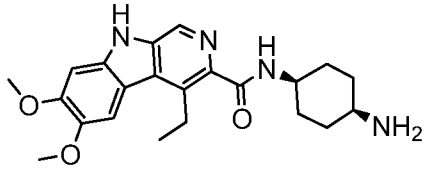
Structure	identifier	Viability EC_{50}	NAD EC_{50}
	Vatalanib SR5-1457	40 nM	195 nM
	SR1-134005	6.3 nM	105 nM
	SR1-134003	200 nM	1.2 μM
	SR1-151915	71.4 nM	280 nM

Table 4. Carbazoles: DMCM and related compounds

Structure	identifier	Viability EC_{50}	NAD EC_{50}
	SR1-75869, aka DMCM	120 nM	749 nM
	SR5-1527, aka methoxy harman	1.8 μM	14 μM
	SR1-721899, aka harmaline	3.8 μM	14 μM
	SR1-841225, aka 6-methoxy harmaline	3.3 μM	>15 μM
	SR1-75632, aka N-methyl-9H-pyrido[3,4-b]indole-3-carboxamide	3.2 μM	>15 μM
	DMCM-8124	~1.8 μM	nt
	DMCM-8130	~600 nM	nt
	DMCM-8137	~500 nM	nt

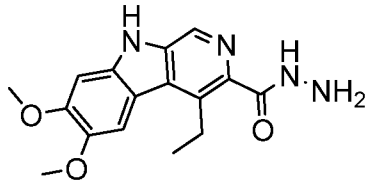
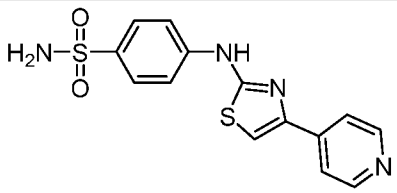
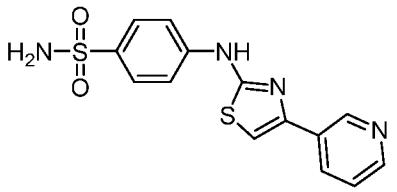
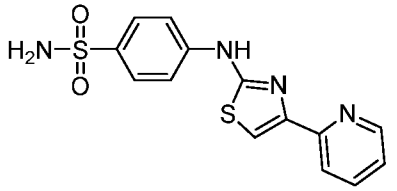
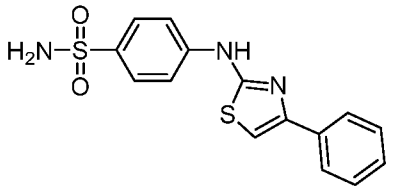
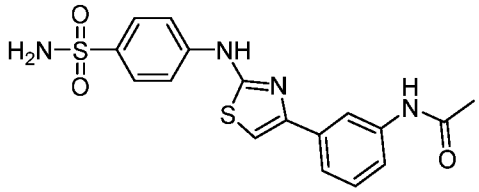
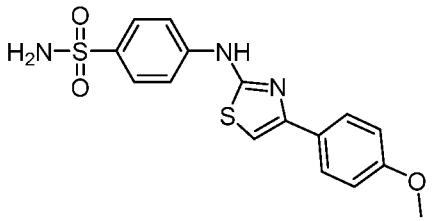
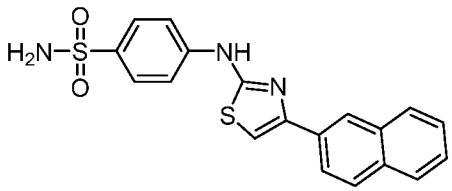
	DMCM-10049	~500 nM	nt

Table 5. Aminothiazoles: SR1-477186 and related compounds

Structure	identifier	Viability EC_{50}	NAD EC_{50}
	SR1-477186	26 nM	365 nM
	SR1-809850	88 nM	337 nM
	SR1-477176	227 nM	891 nM
	SR1-492469	311 nM	859 nM
	SR1-364643	53 nM	263 nM
	SR1-223735	87 nM	360 nM
	SR1-281377	192 nM	1.2 μM

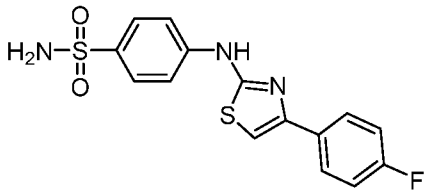
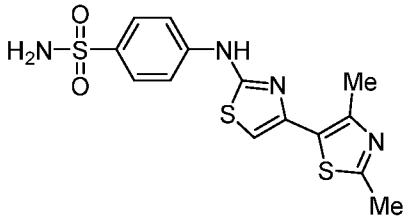
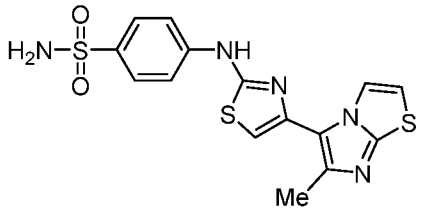
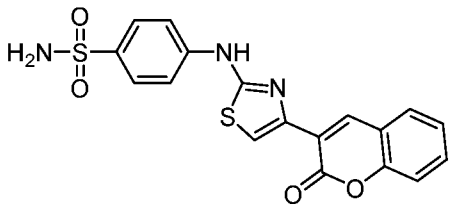
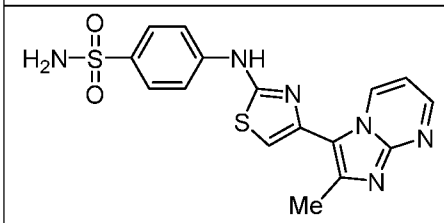
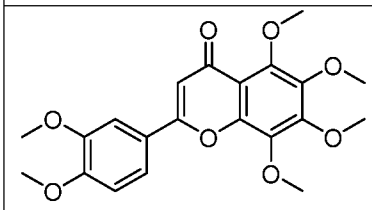
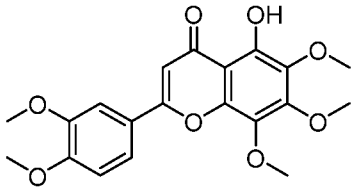
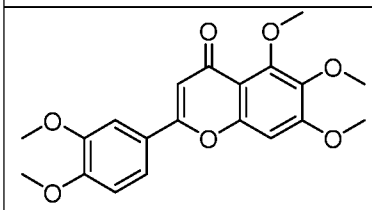
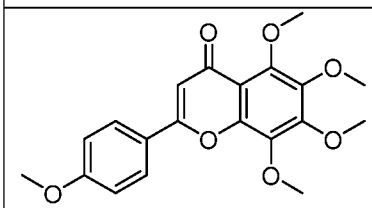
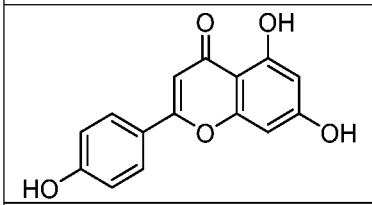
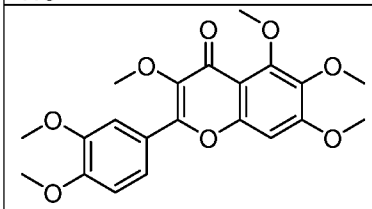
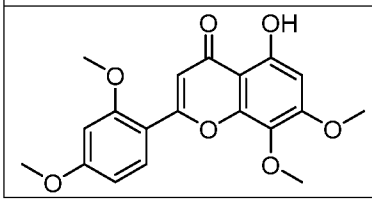
	SR1-742242	197 nM	946 nM
	SR1-477302	14 nM	103 nM
	SR1-477230	47 nM	204 nM
	SR1-22833	57 nM	245 nM
	SR1-477264	155 nM	597 nM

Table 6. Flavonoids Nobiletin and related compounds

Structure	Data	Viability EC_{50}	NAD EC_{50}
	SR-01000712262, aka nobiletin, aka 2-(3,4-dimethoxy phenyl)-5,6,7,8-tetramethoxy-4H-chromen-4-one	580 nM	664 nM
	SR-05000002635, aka 5-demethyl nobiletin, aka 2-(3,4-dimethoxy phenyl)-5-hydroxy-6,7,8-trimethoxy-4H-chromen-4-one	81 nM	609 nM
	SR-05000002257, aka sinensetin, aka 2-(3,4-dimethoxy phenyl)-5,6,7-trimethoxy-4H-chromen-4-one	323 nM	3.6 µM
	SR-05000002625, aka tangeretin, aka 5,6,7,8-tetramethoxy-2-(4-methoxyphenyl)-4H-chromen-4-one	1.9 µM	6.0 µM
	SR1-75663, aka apigenin, aka 5,7-dihydroxy-2-(4-hydroxyphenyl)-4H-chromen-4-one	1.7 µM	>10 µM
	SR5-2644, aka quercetagetin hexamethyl ether, aka 2-(3,4-dimethoxyphenyl)-3,5,6,7-tetramethoxy-4H-chromen-4-one	620 nM	1.2 µM
	SR5-2616, aka 2-(2,4-dimethoxy phenyl)-5-hydroxy-7,8-dimethoxy-4H-chromen-4-one	1.6 µM	2.1 µM

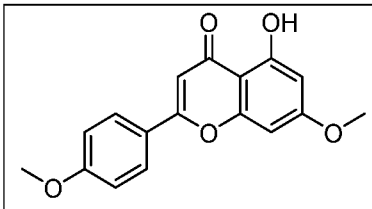
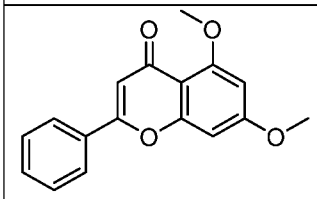
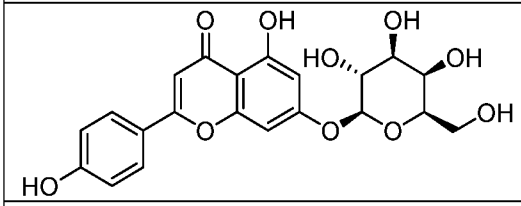
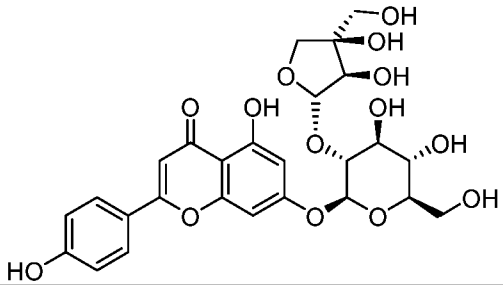
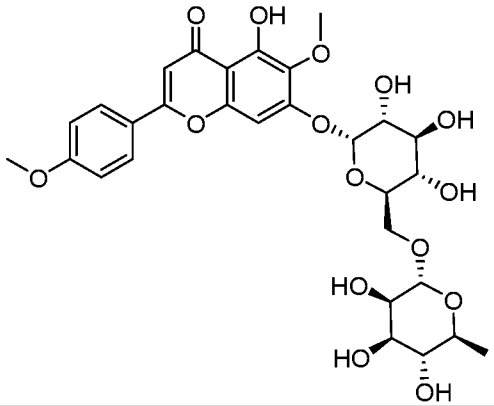
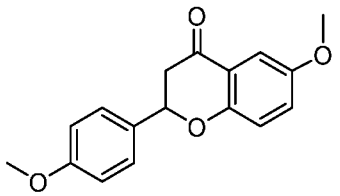
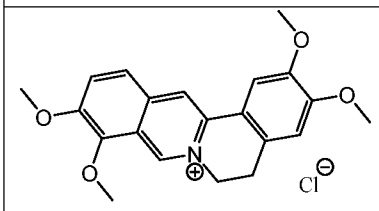
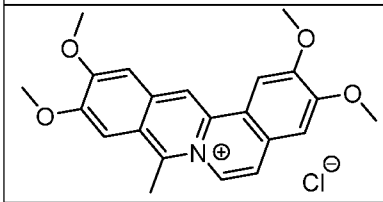
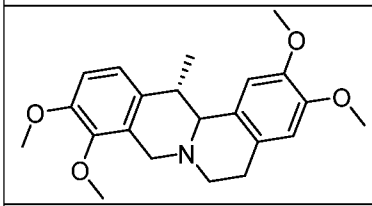
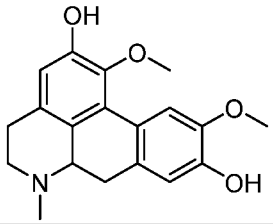
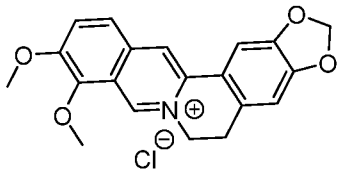
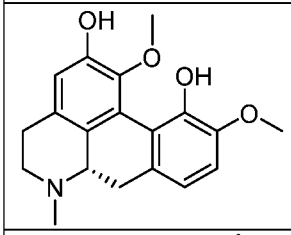
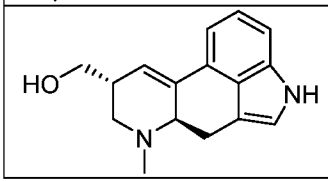
	SR5-2549, aka 7,4'-di-O-methylapigenin, aka 5-hydroxy-7-methoxy-2-(4-methoxyphenyl)-4H-chromen-4-one	2.0 μM	7.3 μM
	SR1-758978, aka chrysin dimethyl ether, aka 5,7-dimethoxy-2-phenyl-4H-chromen-4-one	1.7 μM	>10 μM
	SR5-2196, aka apigenin 7-(β-D-galactopyranosyl) ether	4.6 μM	>10 μM
	SR1-712126, aka apigenin 7-[(2-O-D-apio-β-D-furanosyl-β-D-glucopyranosyl ether	4.6 μM	10.7 μM
	SR5-2766, aka pectolinargenin 7-[6-O-(6-deoxy-α-L-manno pyranosyl)-β-D-glucopyranosyl] ether	2.1 μM	4.0 μM
	SR5-2542, aka 6-methoxy-2-(4-methoxyphenyl) chroman-4-one	2.1 μM	>10 μM

Table 7. Alkaloids, including selected members of isoquinoline, aporphine, and ergot alkaloid families:

Structure	Data	Viability EC_{50}	NAD EC_{50}
	SR1-841226 aka palmatine chloride, an isoquinoline alkaloid	1.1 μM	2.0 μM
	SR5-2641, aka coralyne chloride, an isoquinoline alkaloid	507 nM	671 nM
	SR5-2225, aka corydaline, an isoquinoline alkaloid	1.3 μM	2.0 μM
	SR1-758928, aka boldine, an isoquinoline alkaloid	2.0 μM	7.6 μM
	SR1-711827, aka berberine chloride	3.1 μM	13.2 μM
	SR1-841246, aka N-Methyl lindcarpine, an aporphine alkaloid	4.4 μM	>15 μM
	SR1-758923, aka lysergol, an ergot alkaloid	1.9 μM	>15 μM

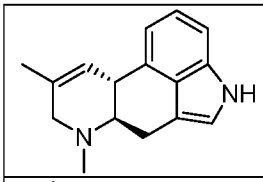
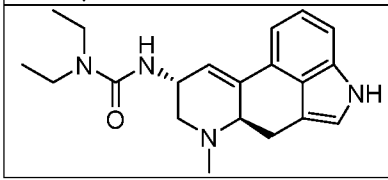
	SR1-75354, aka agroclavine, an ergot alkaloid	1.6 μM	2.0 μM
	SR1-75971, aka lisuride, an ergot alkaloid	4.1 μM	>15 μM

Table 8. 3-heteroarylquinolines (DMPQ)

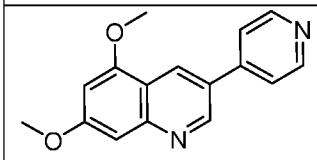
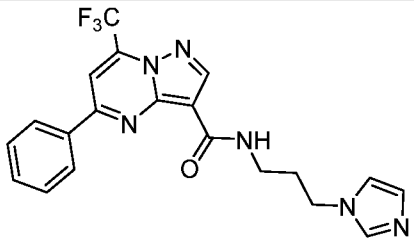
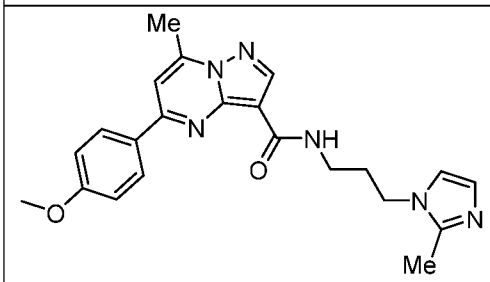
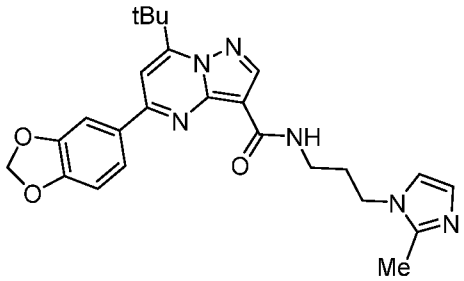
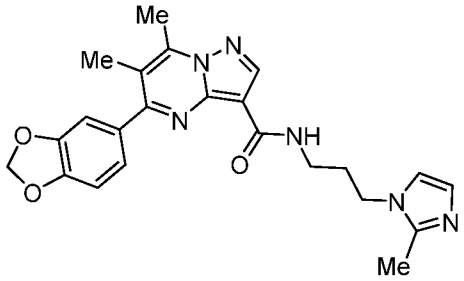
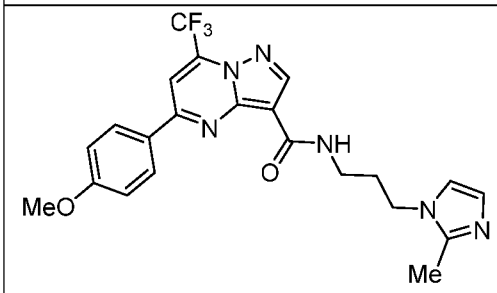
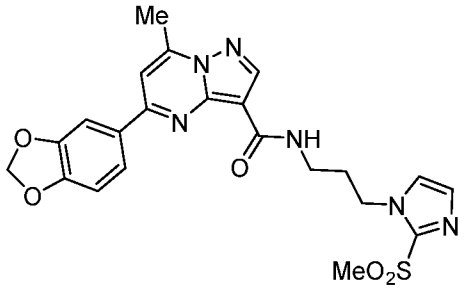
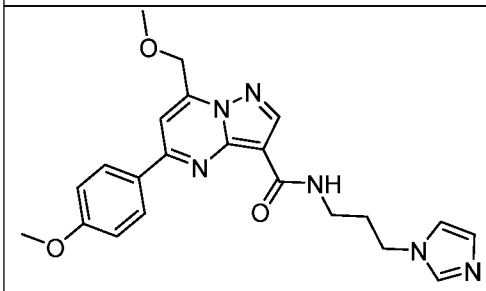
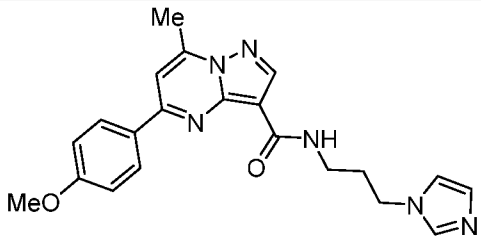
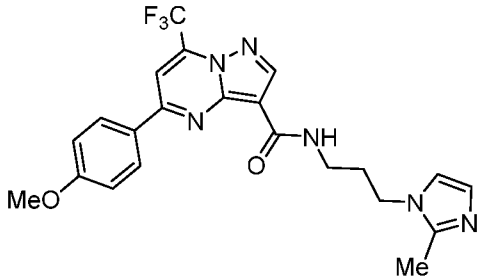
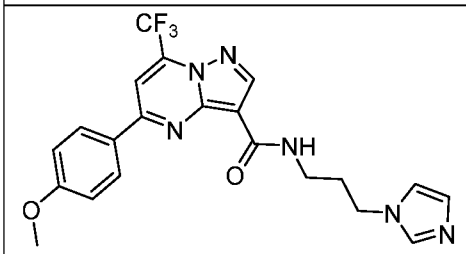
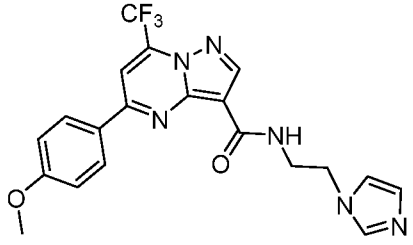
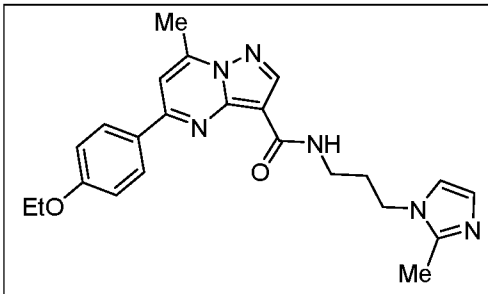
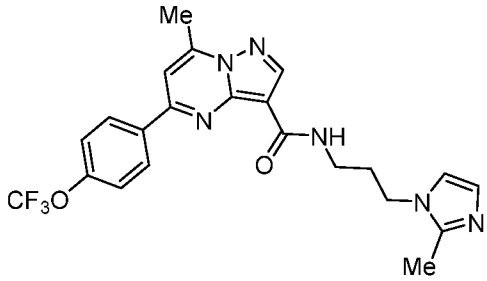
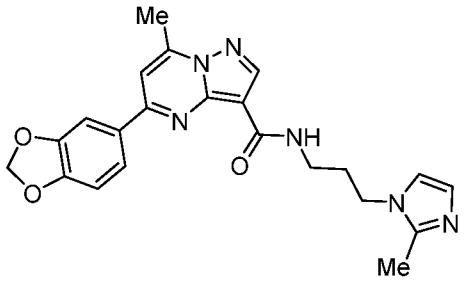
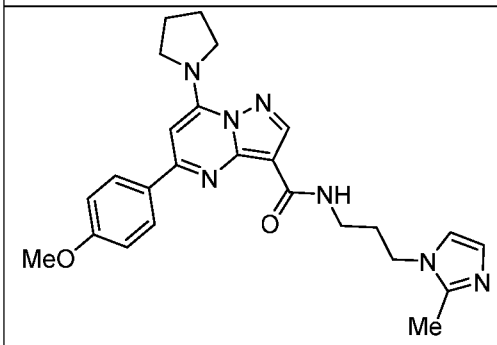
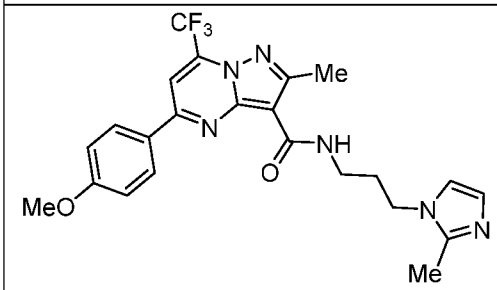
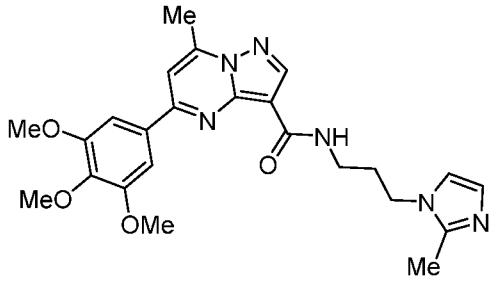
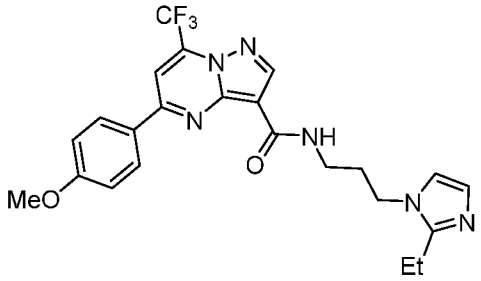
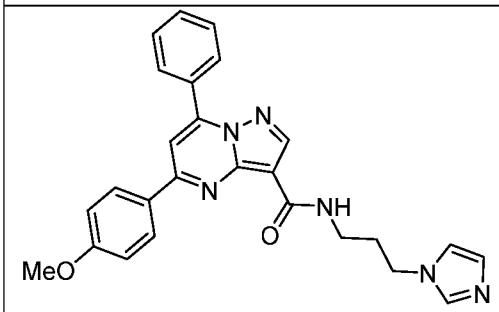
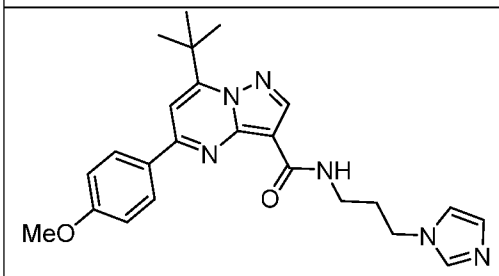
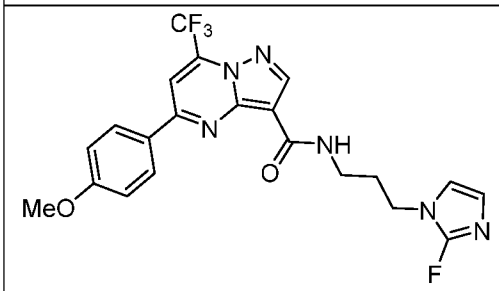
Structure	Data	Viability EC_{50}	NAD EC_{50}
	DMPQ SR-01000597975	505 nM	5.5 μM

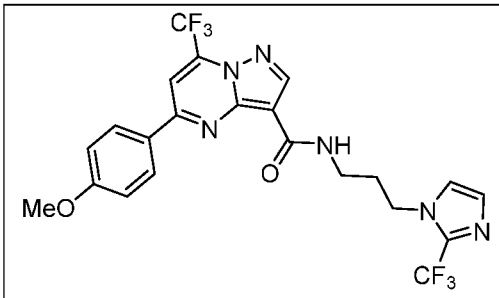
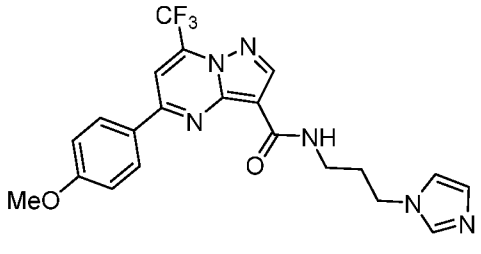
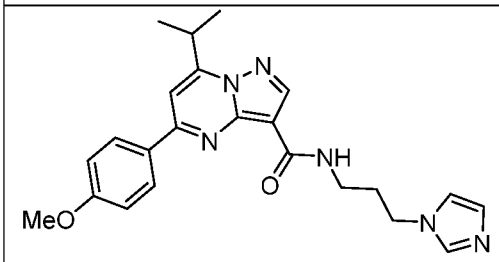
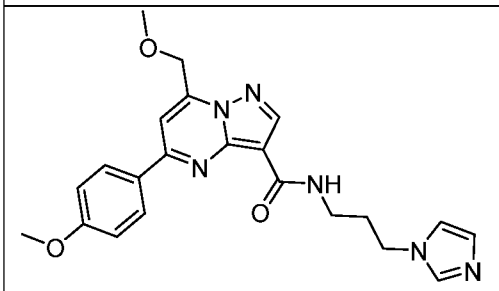
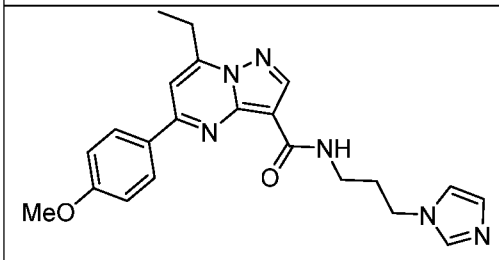
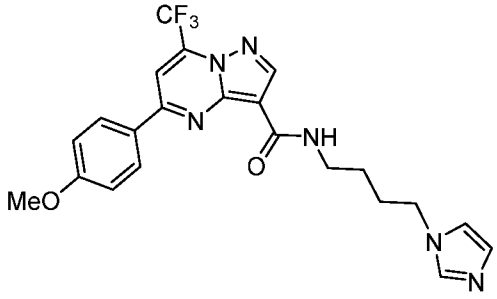
Table 9. Compounds of Formula (II)

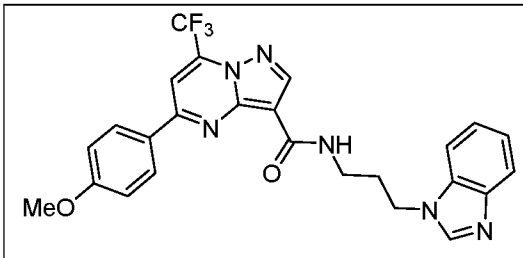
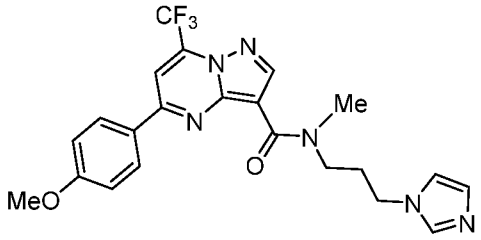
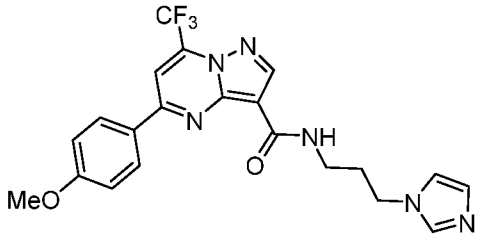
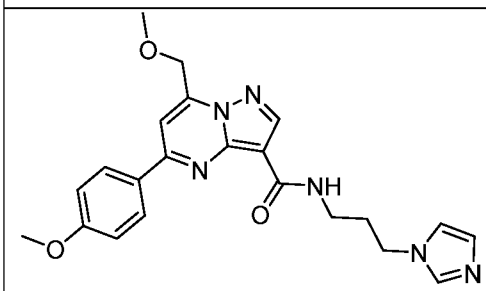
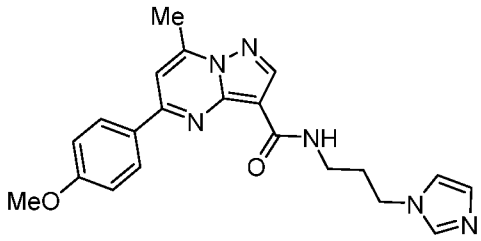
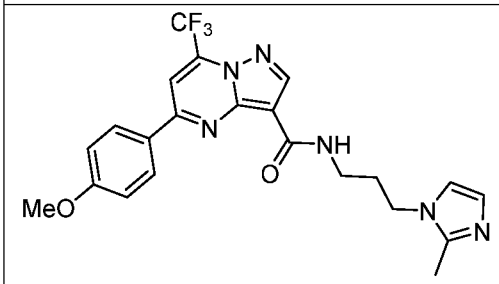
Structure	identifier	Viability EC_{50}
	SR1-293229	1.5 nM, 2 nM
	SR0-31107	2 nM
	SR0-31104	10 nM
	SR0-31106	30 nM
	SR0-31108	> 50 nM

	SR0-31110	> 50 nM
	SR3-5250	0.5 nM
	SR3-5170	1nM
	SR3-5210	2.7 nM
	SR3-5230	> 32 nM
	SR3-5290	> 32 nM

	SR0-29245	1.2 nM
	SR0-29246	2 nM
	SR0-29247	2.2 nM
	SR0-29249	2.2 nM
	SR0-29250	3.6 nM

	SR0-29248	4 nM
	SR0-29244	25 nM
	SR0-28465	1 nM
	SR0-28464	1.2 nM
	SR0-28467	16 nM

	SR0-28466	20 nM
	SR0-28468	> 50 nM
	SR3-5311	0.4 nM
	SR3-5250	0.5 nM
	SR3-5310	0.6 nM
	SR3-5312	6 nM

	SR3-5313	>16 nM
	SR3-5314	>16 nM
	SR3-5315	>16 nM
	SR3-5250	0.5 nM
	SR3-5170	1 nM
	SR3-5210	2.7 nM

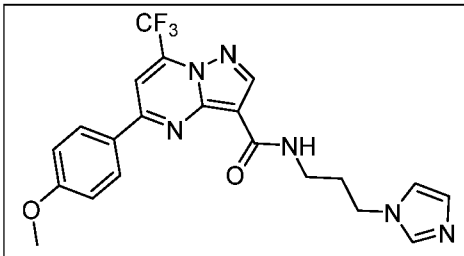
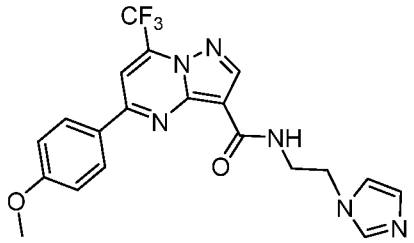
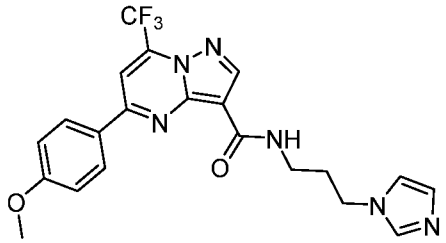
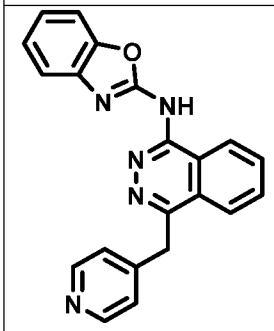
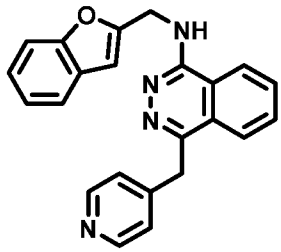
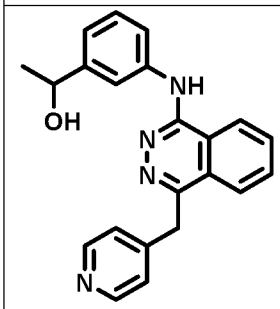
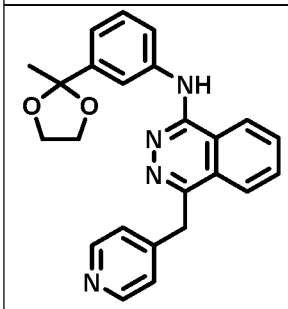
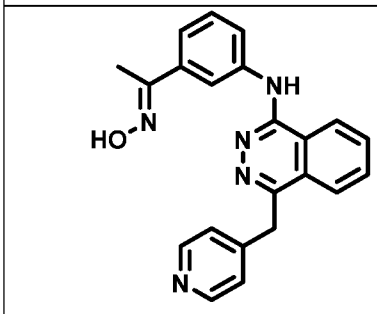
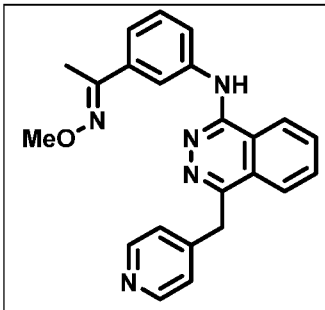
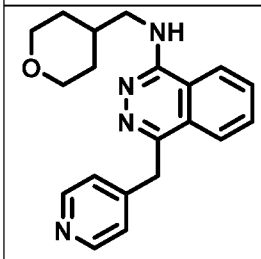
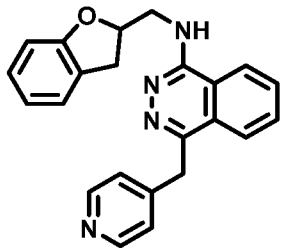
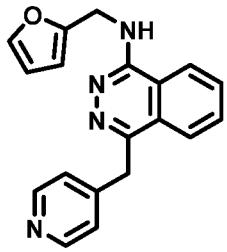
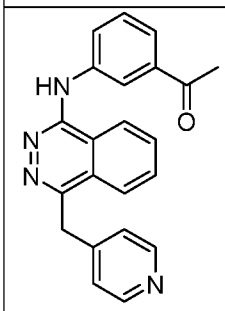
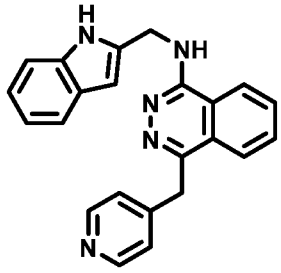
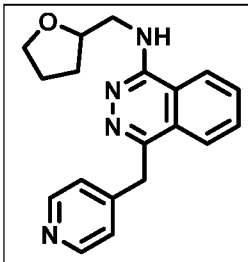
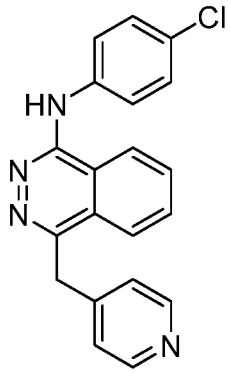
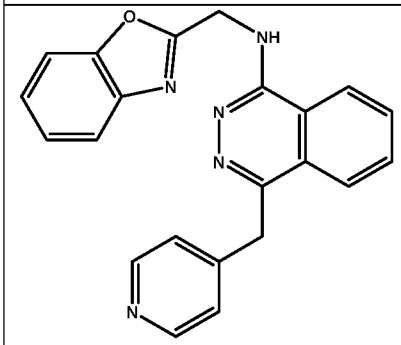
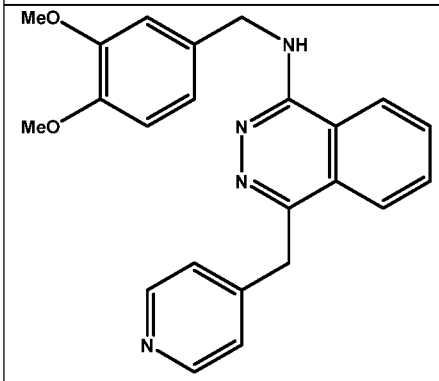
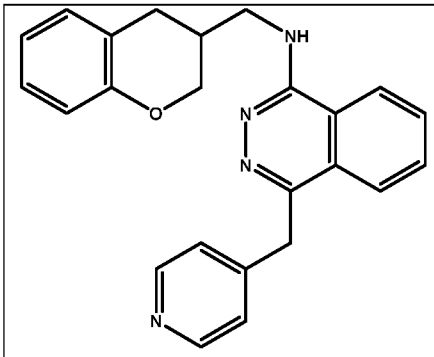
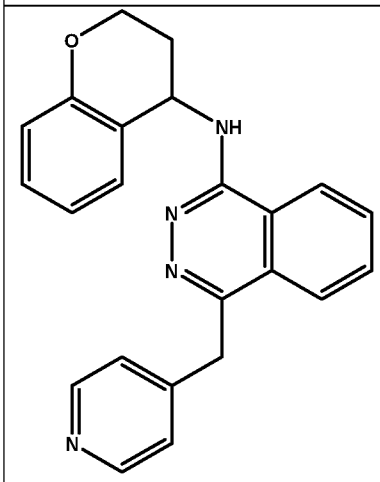
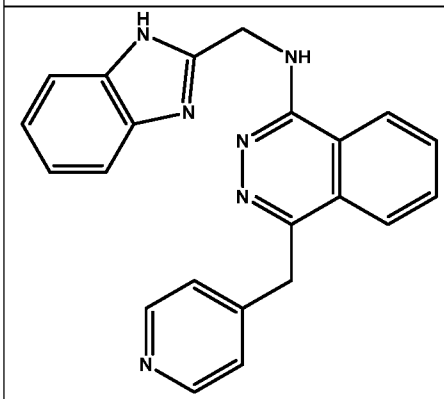
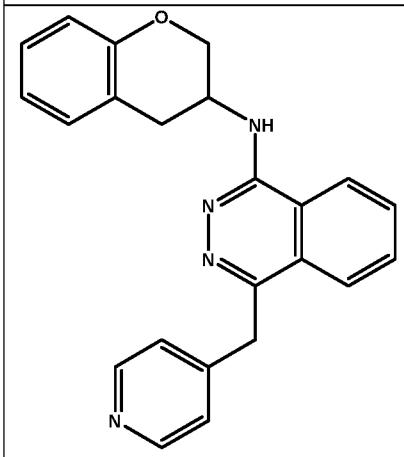
	SR3-5230	> 32 nM
	SR3-5290	> 32 nM
	SR0-24081	0.5 nM

Table 10. Compounds of Formula (III)

Structure	identifier	Viability EC_{50}
	SR-30010	2 nM
	SR-30011	2 nM
	SR-29684	2 nM
	SR-30012	2 nM
	SR-30013	2 nM

	SR-30014	2 nM (lower EC_{100})
	SR-30008	8 nM
	SR-30024	8 nM
	SR-30005	15 nM
	SR1-134005	20 nM
	SR-30006	30 nM

	SR-30004	45nM
	vatalanib	45 nM
	SR-27888	45 nM
	SR-27886	140 nM

	SR-27890	140 nM (toxic at >400 nM)
	SR-27891	200 nM
	SR-27887	200 nM
	SR-27889	200 nM

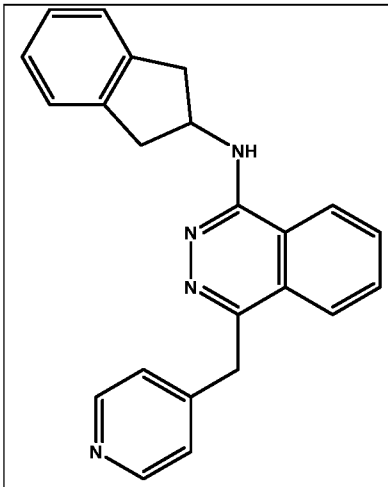
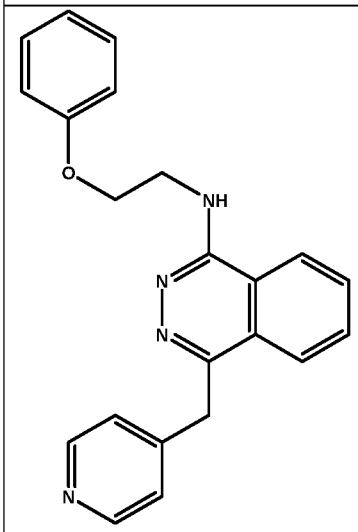
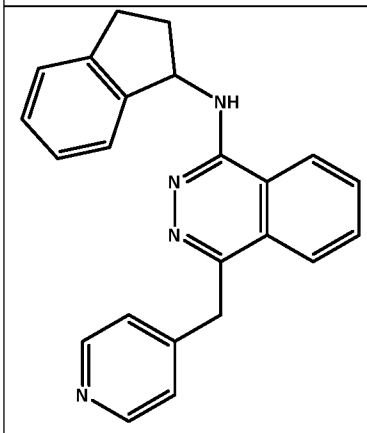
	SR-27885	200 nM
	SR-27892	500 nM
	SR-27884	500 nM

Table 11. Compounds of Formula (IV)

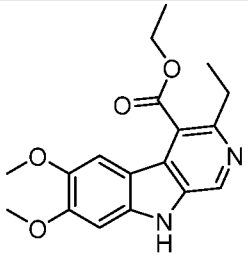
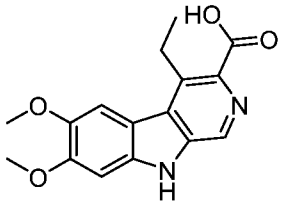
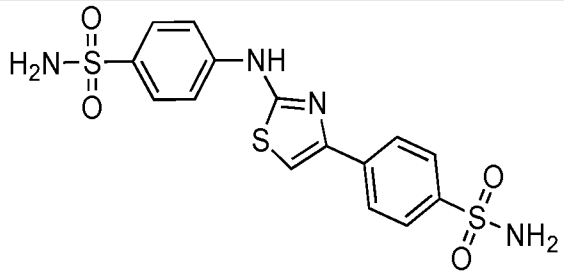
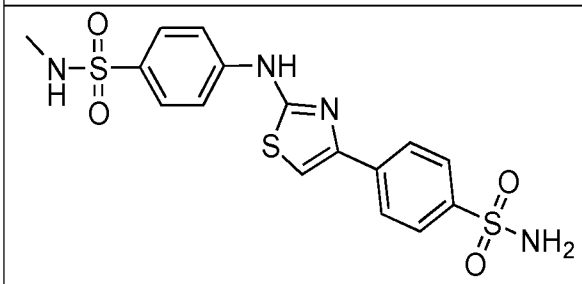
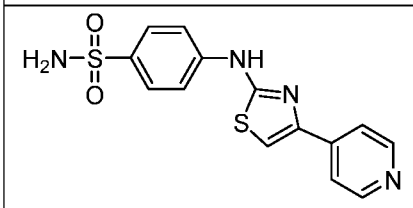
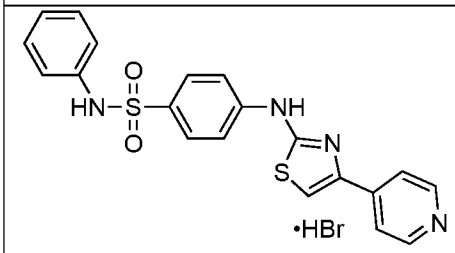
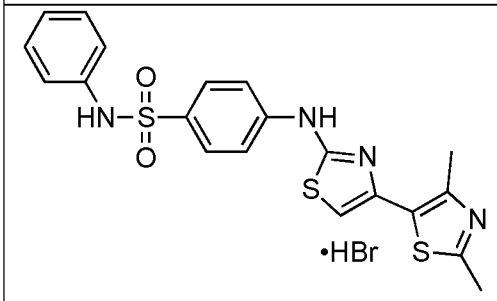
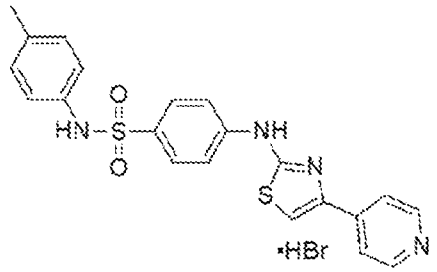
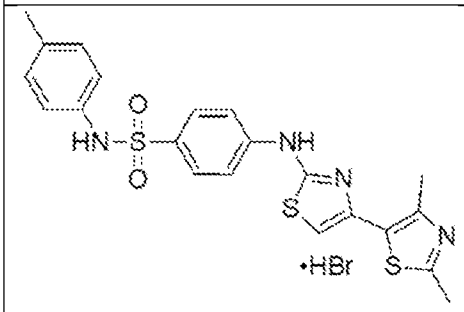
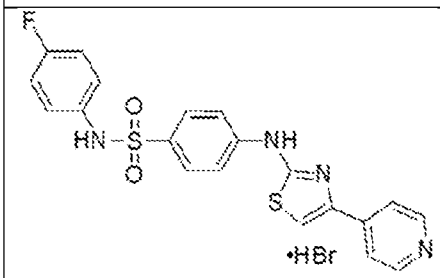
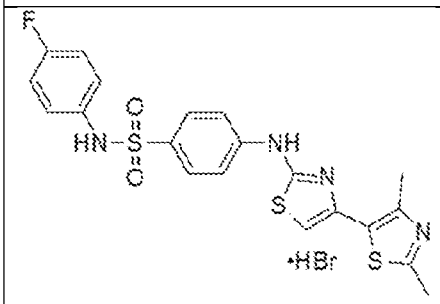
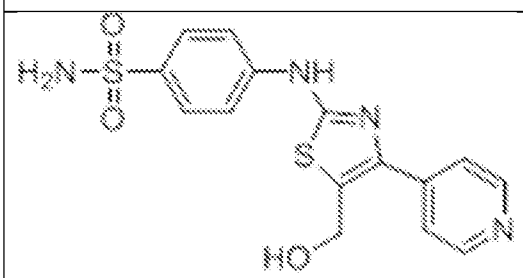
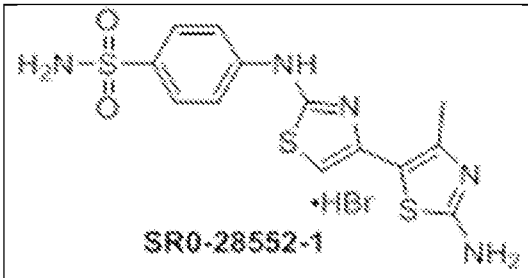
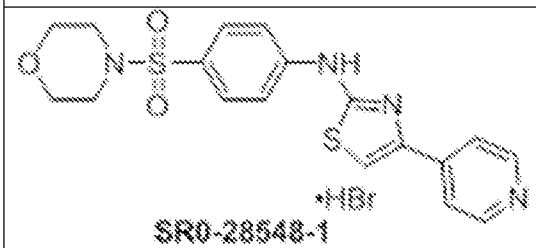
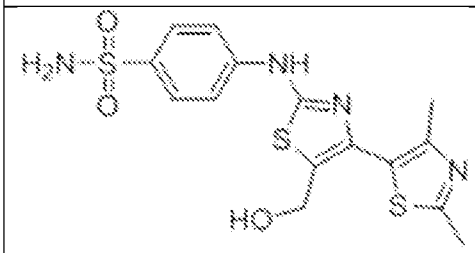
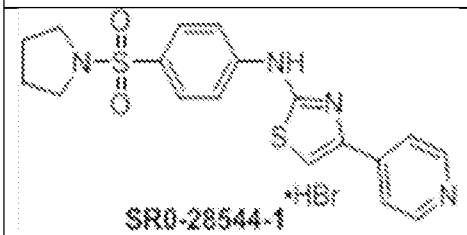
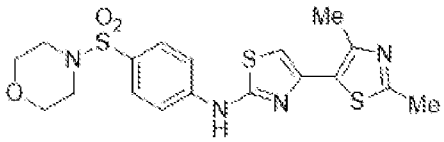
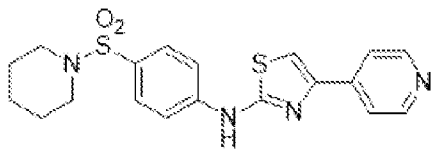
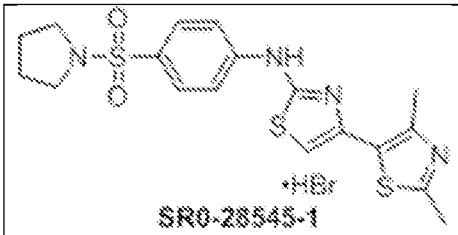
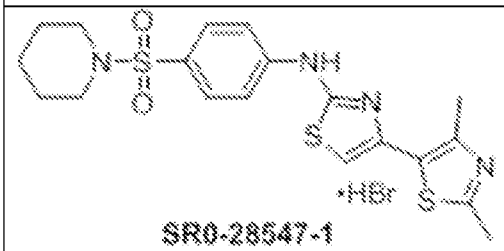
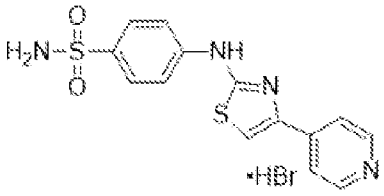
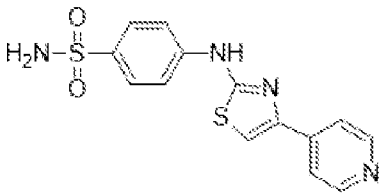
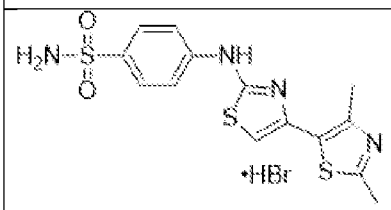
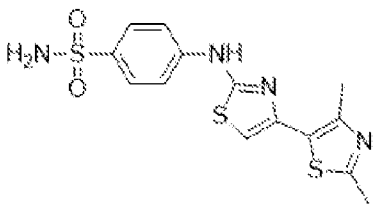
Structure	identifier	Viability EC_{50}
	SR26084	~ 10 μM (30% protection at 4 μM)
	SR26266	> 4 μM

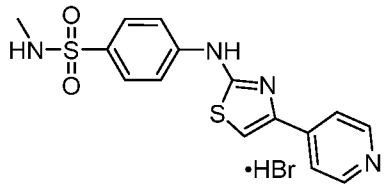
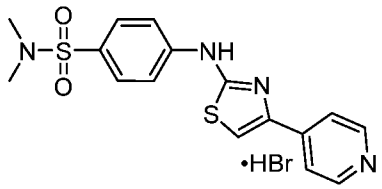
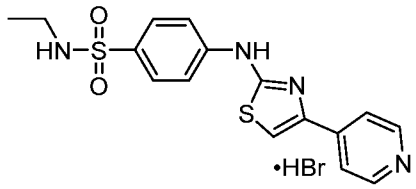
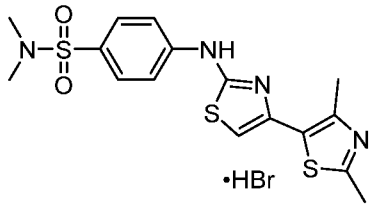
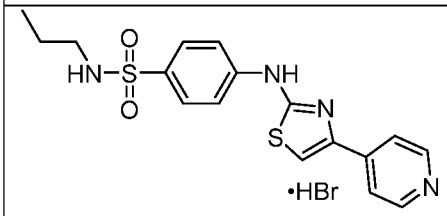
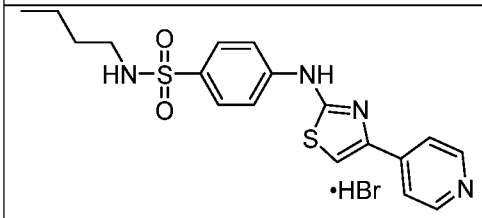
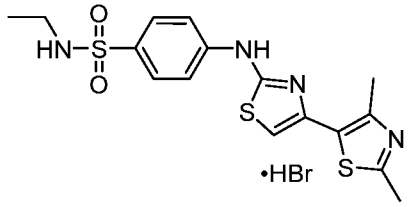
Table 12. Compounds of Formula (V)

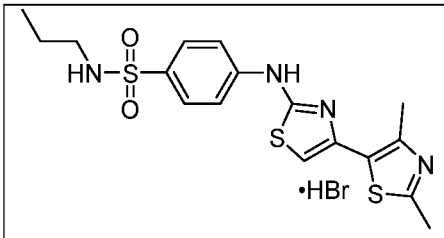
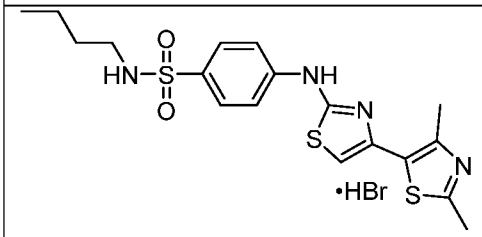
Structure	identifier	Viability EC_{50}
	SR-29450	15 nM
	SR-29451	20 nM
	SR1-477186	40 nM 50 nM
	SR-29444	> 500 nM
	SR-29445	> 500 nM

	SR-29446	> 500 nM
	SR-29447	> 500 nM
	SR-29448	> 500 nM
	SR-29449	> 500 nM
 SR0-28550-1	SR-28550	60 nM

 SR0-28552-1	SR-28552	160 nM
 SR0-28548-1	SR-28548	170 nM
 SR0-28551-1	SR-28551	300 nM
 SR0-28544-1	SR-28544	350 nM
	SR-28549	400 nM
	SR-28546	400 nM
	SR-28545	> 500 nM

 SR0-28545-1		
 SR0-28547-1	SR-28547	> 500 nM
 	SR477186	20,30,35 nM
 	SR477302	18,30 nM
	SR-27807	50 nM

	SR-27806	60 nM
	SR-27744	60 nM
	SR-27784	60 nM
	SR-27764	70 nM
	SR-27804	170 nM
	SR-27808	170 nM
	SR-27785	500 nM

	SR-27805	> 500 nM
	SR-27809	> 500 nM

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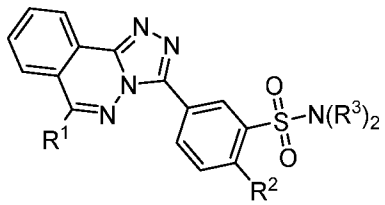
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CLAIMS

What is claimed is:

1. A method for inhibiting NAD consumption and/or increasing NAD synthesis in a patient, comprising administering to the patient an effective dose of a triazolophthalazine compound of Formula (I)



(I), or a pharmaceutically acceptable salt thereof,

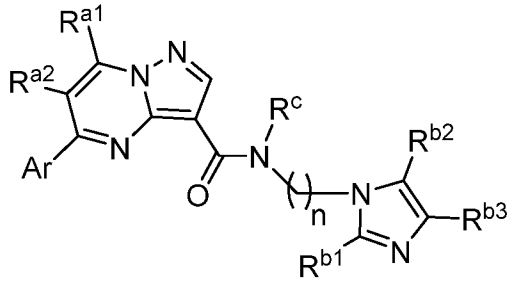
wherein in Formula (I):

Each R^1 and R2 are independently hydrogen (C_1-C_4)alkyl, or (C_1-C_4)alkoxy; and

Each R^3 is independently selected hydrogen, (C_1-C_4)alkyl optionally substituted with OH, (C_1-C_4)alkoxy, or heteroaryl, and provided that both R^3 are not hydrogen; or, both R^3 together with the nitrogen atom to which they are bonded form a 5- to 7-membered heterocyclyl ring comprising at least on additional heteroatom selected from O, S, S=O, S(=O)=O, or NR, wherein R is (C_1-C_4)alkyl optionally substituted with -OH or (C_1-C_4)alkoxyl,

or,

an effective dose of a pyrazolopyrimidine compound of Formula (II)



(II),

or a pharmaceutically acceptable salt thereof,

wherein in Formula (II):

Each R^{a1} and R^{a2} is independently hydrogen, (C_1-C_4)alkyl, (C_1-C_4)haloalkyl, (C_1-C_4)alkoxyl, (C_1-C_4)haloalkoxyl, 2 to 4 membered heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

Each R^{b1}, R^{b2}, and R^{b3} is independently hydrogen, halo, $(C_1\text{-}C_4)$alkyl, $-S(O)_2R^d$, $-S(O)_2OR^d$, or $(C_1\text{-}C_4)$haloalkyl; or R^{b2} and R^{b3} are joined together to form an aryl or heteroaryl;

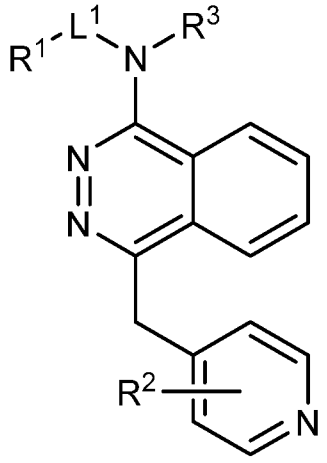
Each R^c and R^d is independently hydrogen or $(C_1\text{-}C_4)$alkyl;

Ar is mono- or bi-cyclic aryl or heteroaryl, optionally substituted with one or more halo, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$haloalkyl, $(C_1\text{-}C_4)$alkoxyl, $(C_1\text{-}C_4)$haloalkoxyl, or heteroaryl; and

n = 2, 3, 4, or 5,

or,

an effective dose of a compound of Formula (III)



(III), or a pharmaceutically acceptable salt thereof,

wherein in Formula (III):

L^1 is a bond, $C_1\text{-}C_4$ alkylene, or 2 to 4-membered heteroalkylene;

R^1 is mono- or bi-cyclic cycloalkyl, heterocycloalkyl, aryl, alkylaryl, or heteroaryl, wherein the cycloalkyl, heterocycloalkyl, aryl, alkylaryl or heteroaryl is optionally substituted with one or more selected from halo, $(C_1\text{-}C_4)$alkyl, hydroxy$(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxyl, $-C(=O)(C_1\text{-}C_4)$alkyl, $-C(=O)N(R)_2$, or $-C(=NR)(C_1\text{-}C_4)$alkyl, wherein the $(C_1\text{-}C_4)$alkyl is unsubstituted or substituted with heterocycloalkyl;

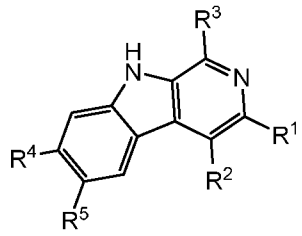
Each R is independently H, -OH, $(C_1\text{-}C_4)$alkyl, or $(C_1\text{-}C_4)$alkoxyl, or two R together with the nitrogen atom to which it is bonded form a heterocycloalkyl, optionally further comprising an O atom in the heterocyclyl ring;

R^2 occurs 0, 1, or 2 times, and is $(C_1\text{-}C_4)$ alkyl, $(C_1\text{-}C_4)$ haloalkyl, or $SO_2N(R^4)_2$; and

Each R^3 and R^4 is independently H, or $(C_1\text{-}C_4)$alkyl,

or,

an effective dose of a compound of Formula (IV)



(IV), or a pharmaceutically acceptable salt thereof.

wherein in Formula (IV):

R^1 is hydrogen, (C_1-C_4)alkyl, -C(O)OH, –C(O)O-(C_1-C_4)alkyl, -C(O)NHNHR^6, -C(O)NR^6-((C_1-C_4)alkylene)-NHR^6, -C(O)NR^6 (C_1-C_4)alkyl, or –C(O)NR^6-cycloalkylene-NHR^6;

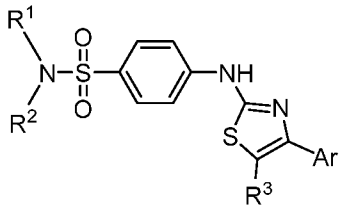
R^3 is hydrogen or (C_1-C_4)alkyl;

Each R^2, R^4, R^5 is independently hydrogen, halo, (C_1-C_4)alkyl, –C(O)O-(C_1-C_4)alkyl, (C_1-C_4)alkoxyl, (C_1-C_4)haloalkyl, or CN; and

Each R^6 is hydrogen or (C_1-C_4)alkyl.

or,

an effective dose of a compound of Formula (V)



(V), or a pharmaceutically acceptable salt thereof,

wherein in Formula (V):

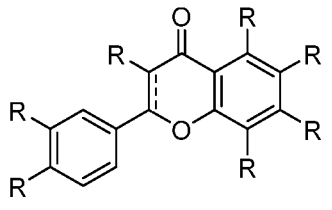
Ar is mono- or bi-cyclic aryl or heteroaryl, optionally substituted one or more with halo, (C_1-C_4)alkyl, (C_1-C_4)haloalkyl, CN, -S(O)$_2$NH$_2$, oxo, -NH$_2$, (C_1-C_4)alkoxyl, or –NHC(O)(C_1-C_4)alkyl;

Each R^1 and R^2 is independently hydrogen, (C_1-C_4)alkyl, aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted with halo or (C_1-C_4)alkyl, or R^1 and R^2 attached to nitrogen join together to form a 5 to 6 membered heterocycloalkyl; and

R^3 is hydrogen, or hydroxy-(C_1-C_4)alkyl,

or,

an effective dose of a compound of formula (VI)

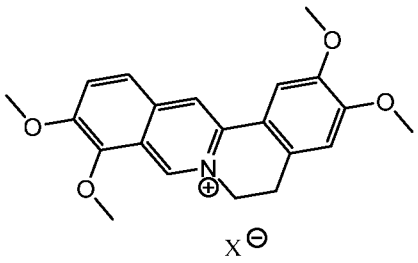


(VI),

wherein in formula (VI), the indicated dashed double bond is optionally present, each R is independently selected from H, OH, or (C1-C4)alkoxyl, or O-glycosyl, provided that at least two R groups are non-hydrogen,

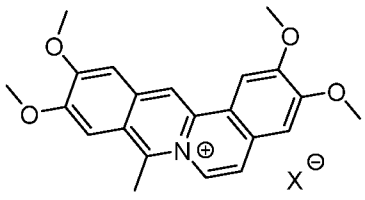
or,

an effective dose of a compound of formulas (VII)-(XV), or demethylated derivatives (phenolic analogs) thereof, or methyl ethers thereof, in the case of phenols or other alcohols:



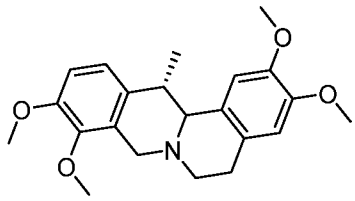
(VII),

wherein in formula (VII), X is a pharmaceutically acceptable salt;



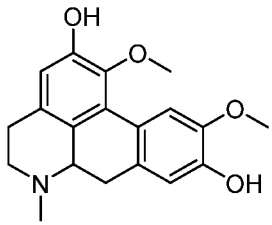
(VIII),

wherein in formula (VIII), X is a pharmaceutically acceptable salt;



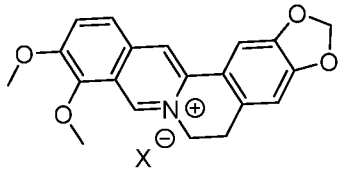
(IX),

and including all pharmaceutically acceptable salt forms,



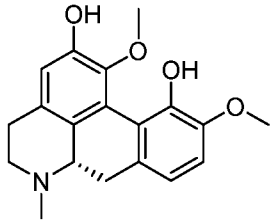
(X),

and including all pharmaceutically acceptable salt forms,



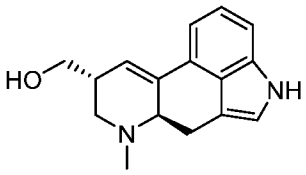
(XI),

wherein in formula (XI), X is a pharmaceutically acceptable salt;



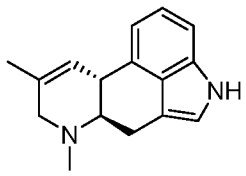
(XII),

and including all pharmaceutically acceptable salt forms,

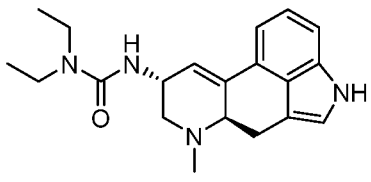


(XIII),

and including all pharmaceutically acceptable salt forms,



(XIV),

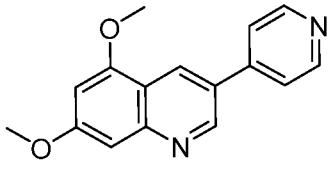


(XV),

and including all pharmaceutically acceptable salt forms,

or,

an effective dose of a compound of formula (XVI)



(XVI),

and including all pharmaceutically acceptable salt forms.

2. The method of claim 1, wherein compounds of Formula (I) to (XVI) inhibit protein ADP-ribosylation reactions.

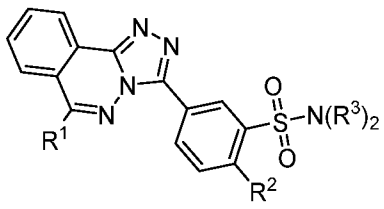
3. The method of claim 1, wherein compounds of Formula (I) to (XVI) inhibit NAD cleavage by protein deacetylases or glycohydrolases.

4. The method of claim 1, wherein compounds of Formula (I) to (XVI) increase NAD synthesis.

5. The method of claim 1, wherein the patient is afflicted with, or at risk for, a protein misfolding neurodegenerative disease or another protein misfolding disease.

6. The method of claim 5 wherein the protein misfolding neurodegenerative disease comprises a prion disease, Parkinson's disease or other synucleinopathies, Alzheimer's disease, amyotrophic lateral sclerosis, or a tauopathy and the protein misfolding disease comprises diabetes mellitus.

7. A method for preventing or inhibiting NAD depletion in a patient, or a method for improving a condition linked to alterations of NAD metabolism in a patient, comprising administering to the patient an effective dose of a triazolophthalazine compound of Formula (I)



(I), or a pharmaceutically acceptable salt thereof,

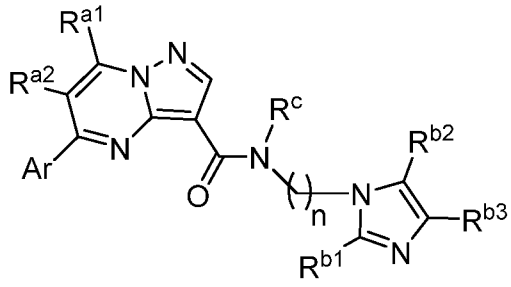
wherein in Formula (I):

Each R^1 and R^2 are independently H, (C_1-C_4)alkyl, or (C_1-C_4)alkoxy; and

Each R^3 is independently selected H, (C_1-C_4)alkyl optionally substituted with OH, (C_1-C_4)alkoxy, or heteroaryl, and provided that both R^3 are not H; or, both R^3 together with the nitrogen atom to which they are bonded form a 5- to 7-membered heterocyclyl ring comprising at least on additional heteroatom selected from O, S, S=O, S(=O)=O, or NR, wherein R is (C_1-C_4)alkyl optionally substituted with -OH or (C_1-C_4)alkoxyl,

or,

an effective dose of a pyrazolopyrimidine compound of Formula (II)



(II),

or a pharmaceutically acceptable salt thereof,

wherein in Formula (II):

Each R^{a1} and R^{a2} is independently hydrogen, (C_1-C_4)alkyl, (C_1-C_4)haloalkyl, (C_1-C_4)alkoxyl, (C_1-C_4)haloalkoxyl, 2 to 4 membered heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

Each R^{b1}, R^{b2}, and R^{b3} is independently hydrogen, halo, (C_1-C_4)alkyl, -$S(O)_2R^d$, -$S(O)_2OR^d$, or (C_1-C_4)haloalkyl; or R^{b2} and R^{b3} are joined together to form an aryl or heteroaryl;

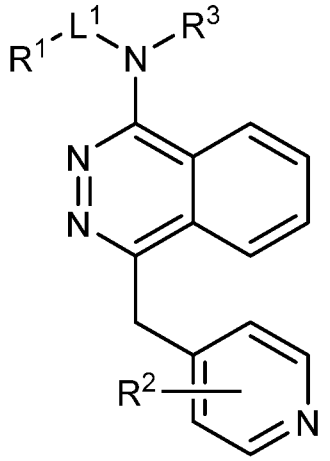
Each R^c and R^d is independently hydrogen or (C_1-C_4)alkyl;

Ar is mono- or bi-cyclic aryl or heteroaryl, optionally substituted with one or more halo, (C_1-C_4)alkyl, (C_1-C_4)haloalkyl, (C_1-C_4)alkoxyl, (C_1-C_4)haloalkoxyl, or heteroaryl; and

n = 2, 3, 4, or 5,

or,

an effective dose of a compound of Formula (III),



(III), or a pharmaceutically acceptable salt thereof,

wherein in Formula (III):

L^1 is a bond, C_1-C_4 alkylene, or 2 to 4-membered heteroalkylene;

R^1 is mono- or bi-cyclic cycloalkyl, heterocycloalkyl, aryl, alkylaryl, or heteroaryl, wherein the cycloalkyl, heterocycloalkyl, aryl, alkylaryl or heteroaryl is optionally substituted with one or more selected from halo, (C_1-C_4)alkyl, hydroxy(C_1-C_4)alkyl, (C_1-C_4)alkoxyl, -C(=O)(C_1-C_4)alkyl, -C(=O)N(R)$_2$, or -C(=NR)(C_1-C_4)alkyl, wherein the (C_1-C_4)alkyl is unsubstituted or substituted with heterocycloalkyl;

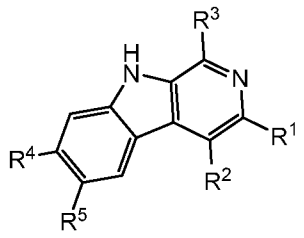
Each R is independently H, -OH, (C_1-C_4)alkyl, or (C_1-C_4)alkoxyl, or two R together with the nitrogen atom to which it is bonded form a heterocycloalkyl, optionally further comprising an O atom in the heterocyclyl ring;

R^2 occurs 0, 1, or 2 times, and is (C_1-C_4) alkyl, (C_1-C_4) haloalkyl, or $SO_2N(R^4)_2$; and

each R^3 and R^4 is independently H, or (C_1-C_4)alkyl,

or,

an effective dose of a compound of Formula (IV)



(IV), or a pharmaceutically acceptable salt thereof.

wherein in Formula (IV):

R^1 is hydrogen, (C_1-C_4)alkyl, -C(O)OH, –C(O)O-(C_1-C_4)alkyl, -C(O)NHNHR^6, -C(O)NR^6-((C_1-C_4)alkylene)-NHR^6, -C(O)NR^6 (C_1-C_4)alkyl, or –C(O)NR^6-cycloalkylene-NHR^6;

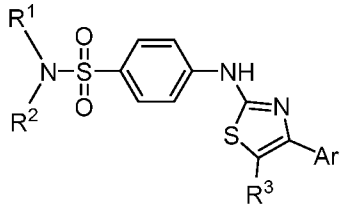
R^3 is hydrogen or (C_1-C_4)alkyl; and

each R^2, R^4, R^5 is independently hydrogen, halo, (C_1-C_4)alkyl, –C(O)O-(C_1-C_4)alkyl, (C_1-C_4)alkoxyl, (C_1-C_4)haloalkyl, or CN; and

Each R^6 is hydrogen or (C_1-C_4)alkyl.

or,

an effective dose of a compound of Formula (V)



(V), or a pharmaceutically acceptable salt thereof,

wherein in Formula (V):

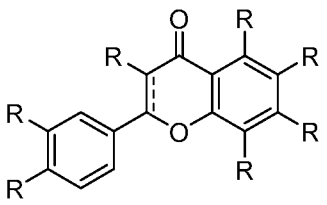
Ar is mono- or bi-cyclic aryl or heteroaryl, optionally substituted one or more with halo, (C_1-C_4)alkyl, (C_1-C_4)haloalkyl, CN, -S(O)$_2$NH$_2$, oxo, -NH$_2$, (C_1-C_4)alkoxyl, or –NHC(O)(C_1-C_4)alkyl;

Each R^1 and R^2 is independently hydrogen, (C_1-C_4)alkyl, aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted with halo or (C_1-C_4)alkyl, or R^1 and R^2 attached to nitrogen join together to form a 5 to 6 membered heterocycloalkyl; and

R^3 is hydrogen, or hydroxy-(C_1-C_4)alkyl,

or,

an effective dose of a compound of formula (VI)

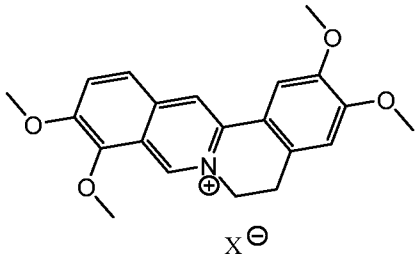


(VI),

wherein in formula (VI), the indicated dashed double bond is optionally present, each R is independently selected from H, OH, or (C1-C4)alkoxyl, or O-glycosyl, provided that at least two R groups are non-hydrogen,

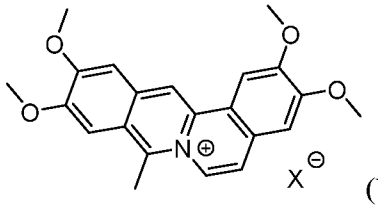
or,

an effective dose of a compound of formulas (VII)-(XV), or demethylated derivatives (phenolic analogs) thereof, or methyl ethers thereof, in the case of phenols or other alcohols:



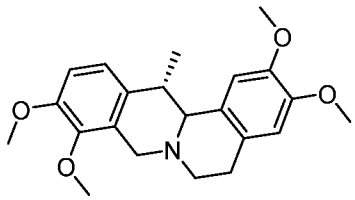
(VII),

wherein in formula (VII), X is a pharmaceutically acceptable salt;



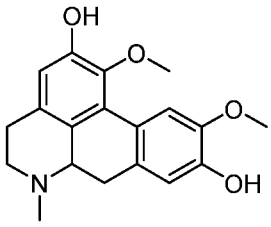
(VIII),

wherein in formula (VIII), X is a pharmaceutically acceptable salt;



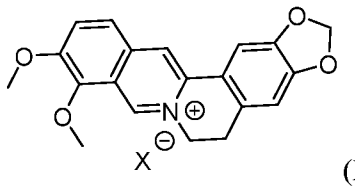
(IX),

and including all pharmaceutically acceptable salt forms,



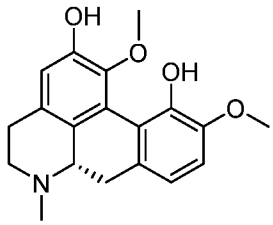
(X),

and including all pharmaceutically acceptable salt forms,



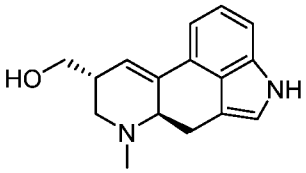
(XI),

wherein in formula (XI), X is a pharmaceutically acceptable salt;



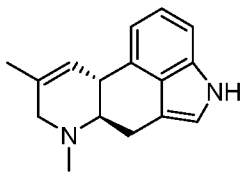
(XII),

and including all pharmaceutically acceptable salt forms,



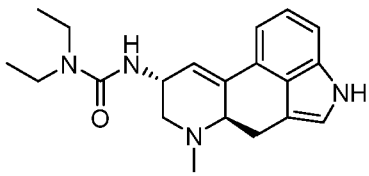
(XIII),

and including all pharmaceutically acceptable salt forms,



(XIV),

and including all pharmaceutically acceptable salt forms,

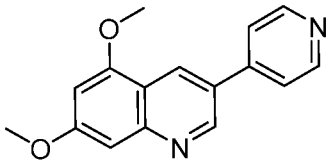


(XV),

and including all pharmaceutically acceptable salt forms,

or,

an effective dose of a compound of formula (XVI)



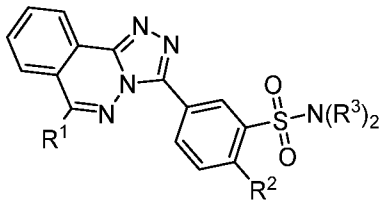
(XVI),

and including all pharmaceutically acceptable salt forms.

8. The method of claim 7 wherein the condition comprises a metabolic disorder, aging, a degenerative disease, a neurodegenerative disease, neuronal degeneration associated with

multiple sclerosis, hearing loss, retinal damage or multiple sclerosis, brain or cardiac ischemia, kidney failure, kidney disease, traumatic brain injury, or an axonopathy.

9. A method for providing protection from toxicity of misfolded proteins in a patient, comprising administering to the patient an effective dose of a triazolophthalazine compound of Formula (I)



(I), or a pharmaceutically acceptable salt thereof,

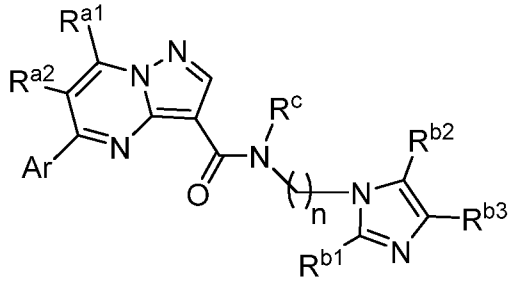
wherein in Formula (I):

Each R^1 and R^2 are independently H, (C_1-C_4)alkyl, or (C_1-C_4)alkoxy; and

Each R^3 is independently selected H, (C_1-C_4)alkyl optionally substituted with OH, (C_1-C_4)alkoxy, or heteroaryl, and provided that both R^3 are not H; or, both R^3 together with the nitrogen atom to which they are bonded form a 5- to 7-membered heterocyclyl ring comprising at least on additional heteroatom selected from O, S, S=O, S(=O)=O, or NR, wherein R is (C_1-C_4)alkyl optionally substituted with -OH or (C_1-C_4)alkoxyl,

or,

an effective dose of a pyrazolopyrimidine compound of Formula (II)



(II),

or a pharmaceutically acceptable salt thereof,

wherein in Formula (II):

Each R^{a1} and R^{a2} is independently hydrogen, (C_1-C_4)alkyl, (C_1-C_4)haloalkyl, (C_1-C_4)alkoxyl, (C_1-C_4)haloalkoxyl, 2 to 4 membered heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

Each R^{b1}, R^{b2}, and R^{b3} is independently hydrogen, halo, $(C_1\text{-}C_4)$alkyl, $-S(O)_2R^d$, $-S(O)_2OR^d$, or $(C_1\text{-}C_4)$haloalkyl; or R^{b2} and R^{b3} are joined together to form an aryl or heteroaryl;

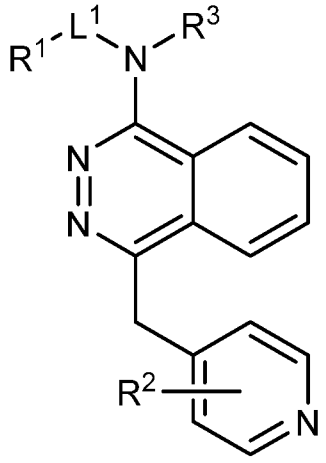
Each R^c and R^d is independently hydrogen or $(C_1\text{-}C_4)$alkyl;

Ar is mono- or bi-cyclic aryl or heteroaryl, optionally substituted with one or more halo, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$haloalkyl, $(C_1\text{-}C_4)$alkoxyl, $(C_1\text{-}C_4)$haloalkoxyl, or heteroaryl; and

n = 2, 3, 4, or 5,

or,

an effective dose of a compound of Formula (III)



(III), or a pharmaceutically acceptable salt thereof,

wherein in Formula (III):

L^1 is a bond, $C_1\text{-}C_4$ alkylene, or 2 to 4-membered heteroalkylene;

R^1 is mono- or bi-cyclic cycloalkyl, heterocycloalkyl, aryl, alkylaryl, or heteroaryl, wherein the cycloalkyl, heterocycloalkyl, aryl, alkylaryl or heteroaryl is optionally substituted with one or more selected from halo, $(C_1\text{-}C_4)$alkyl, hydroxy$(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxyl, $-C(=O)(C_1\text{-}C_4)$alkyl, $-C(=O)N(R)_2$, or $-C(=NR)(C_1\text{-}C_4)$alkyl, wherein the $(C_1\text{-}C_4)$alkyl is unsubstituted or substituted with heterocycloalkyl ;

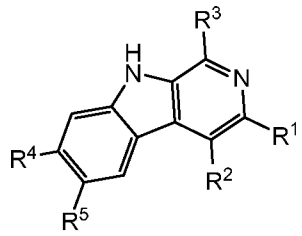
Each R is independently H, -OH, $(C_1\text{-}C_4)$alkyl, or $(C_1\text{-}C_4)$alkoxyl, or two R together with the nitrogen atom to which it is bonded form a heterocycloalkyl, optionally further comprising an O atom in the heterocyclyl ring;

R^2 occurs 0, 1, or 2 times, and is $(C_1\text{-}C_4)$ alkyl, $(C_1\text{-}C_4)$ haloalkyl, or $SO_2N(R^4)_2$; and

Each R^3 and R^4 is independently H, or $(C_1\text{-}C_4)$alkyl,

or,

an effective dose of a compound of Formula (IV)



(IV), or a pharmaceutically acceptable salt thereof.

wherein in Formula (IV):

R^1 is hydrogen, (C_1-C_4)alkyl, -C(O)OH, –C(O)O-(C_1-C_4)alkyl, -C(O)NHNHR^6, -C(O)NR^6-((C_1-C_4)alkylene)-NHR^6, -C(O)NR^6 (C_1-C_4)alkyl, or –C(O)NR^6-cycloalkylene-NHR^6;

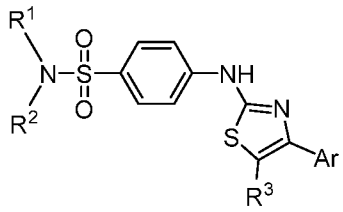
R^3 is hydrogen or (C_1-C_4)alkyl;

Each R^2, R^4, R^5 is independently hydrogen, halo, (C_1-C_4)alkyl, –C(O)O-(C_1-C_4)alkyl, (C_1-C_4)alkoxyl, (C_1-C_4)haloalkyl, or CN; and

Each R^6 is hydrogen or (C_1-C_4)alkyl.

or,

an effective dose of a compound of Formula (V)



(V), or a pharmaceutically acceptable salt thereof,

wherein in Formula (V):

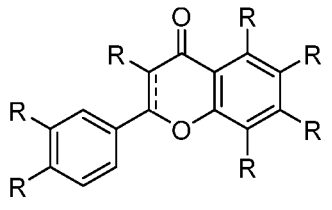
Ar is mono- or bi-cyclic aryl or heteroaryl, optionally substituted one or more with halo, (C_1-C_4)alkyl, (C_1-C_4)haloalkyl, CN, -S(O)$_2$NH$_2$, oxo, -NH$_2$, (C_1-C_4)alkoxyl, or –NHC(O)(C_1-C_4)alkyl;

Each R^1 and R^2 is independently hydrogen, (C_1-C_4)alkyl, aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted with halo or (C_1-C_4)alkyl, or R^1 and R^2 attached to nitrogen join together to form a 5 to 6 membered heterocycloalkyl; and

R^3 is hydrogen, or hydroxy-(C_1-C_4)alkyl,

or,

an effective dose of a compound of formula (VI),

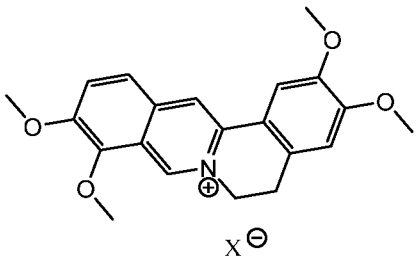


(VI),

wherein in formula (VI), the indicated dashed double bond is optionally present, each R is independently selected from H, OH, or (C1-C4)alkoxyl, or O-glycosyl, provided that at least two R groups are non-hydrogen,

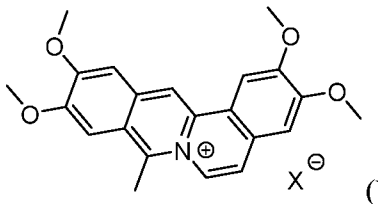
or,

an effective dose of a compound of formulas (VII)-(XV), or demethylated derivatives (phenolic analogs) thereof, or methyl ethers thereof, in the case of phenols or other alcohols:



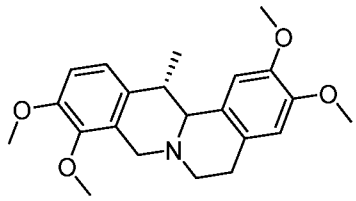
(VII),

wherein in formula (VII), X is a pharmaceutically acceptable salt;



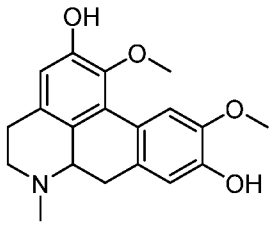
(VIII),

wherein in formula (VIII), X is a pharmaceutically acceptable salt;



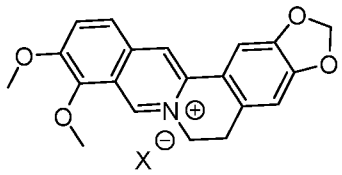
(IX),

and including all pharmaceutically acceptable salt forms,



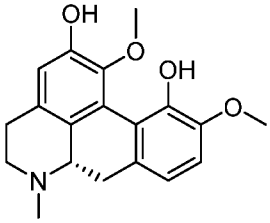
(X),

and including all pharmaceutically acceptable salt forms,



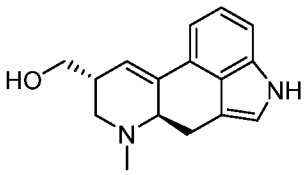
(XI),

wherein in formula (XI), X is a pharmaceutically acceptable salt;

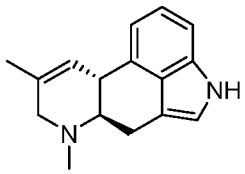


(XII),

and including all pharmaceutically acceptable salt forms,

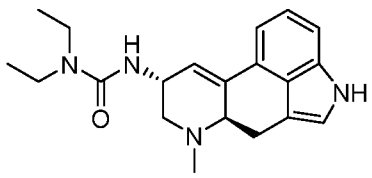


(XIII),



(XIV),

and including all pharmaceutically acceptable salt forms,

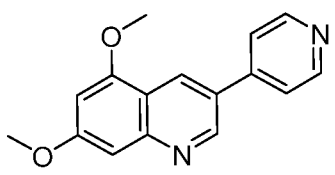


(XV),

and including all pharmaceutically acceptable salt forms,

or,

an effective dose of a compound of formula (XVI)

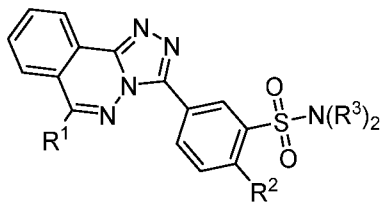


(XVI),

and including all pharmaceutically acceptable salt forms

10. The method of claim 9 wherein the patient is afflicted with a prion disease, Parkinson's disease or other synucleinopathy, Alzheimer's disease, amyotrophic lateral sclerosis, a tauopathy or diabetes mellitus.

11. A method for preventing or treating a protein misfolding neurodegenerative disease in a patient, comprising administering to the patient an effective dose of a triazolophthalazine compound of Formula (I)



(I), or a pharmaceutically acceptable salt thereof,

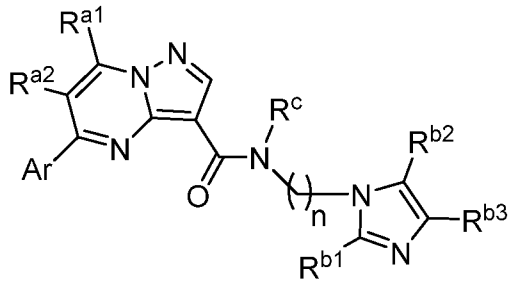
wherein in Formula (I):

Each R^1 and R^2 are independently H, (C_1-C_4)alkyl, or (C_1-C_4)alkoxy; and

Each R^3 is independently selected H, (C_1-C_4)alkyl optionally substituted with OH, (C_1-C_4)alkoxy, or heteroaryl, and provided that both R^3 are not H; or, both R^3 together with the nitrogen atom to which they are bonded form a 5- to 7-membered heterocyclyl ring comprising at least on additional heteroatom selected from O, S, S=O, S(=O)=O, or NR, wherein R is (C_1-C_4)alkyl optionally substituted with -OH or (C_1-C_4)alkoxyl,

or,

an effective dose of a pyrazolopyrimidine compound of Formula (II)



(II),

or a pharmaceutically acceptable salt thereof,

wherein in Formula (II):

Each R^{a1} and R^{a2} is independently hydrogen, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$haloalkyl, $(C_1\text{-}C_4)$alkoxyl, $(C_1\text{-}C_4)$haloalkoxyl, 2 to 4 membered heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

Each R^{b1}, R^{b2}, and R^{b3} is independently hydrogen, halo, $(C_1\text{-}C_4)$alkyl, $-S(O)_2R^d$, $-S(O)_2OR^d$, or $(C_1\text{-}C_4)$haloalkyl; or R^{b2} and R^{b3} are joined together to form an aryl or heteroaryl;

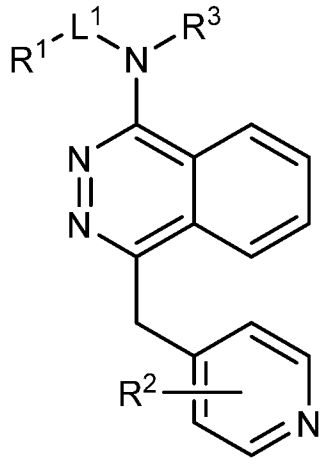
Each R^c and R^d is independently hydrogen or $(C_1\text{-}C_4)$alkyl;

Ar is mono- or bi-cyclic aryl or heteroaryl, optionally substituted with one or more halo, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$haloalkyl, $(C_1\text{-}C_4)$alkoxyl, $(C_1\text{-}C_4)$haloalkoxyl, or heteroaryl; and

n = 2, 3, 4, or 5,

or,

an effective dose of a compound of Formula (III)



(III),

or a pharmaceutically acceptable salt thereof,

wherein in Formula (III):

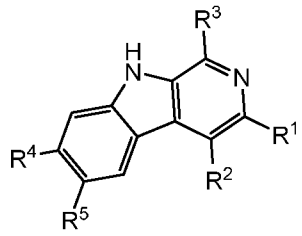
R^1 is mono- or bi-cyclic aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted with halo, (C1-C4)C(=O)-, $C(=O)N(R)_2$ wherein each R is independently selected H or (C1-C4)alkyl, or where two R together with the nitrogen atom to which it is bonded form a heterocyclyl, optionally further comprising an O atom in the heterocyclyl ring

R^2 occurs 0, 1, or 2 times, and is (C1-C4) alkyl or $SO_2N(R^3)_2$;

and including all pharmaceutically acceptable salt forms,

or,

an effective dose of a compound of Formula (IV)



(IV), or a pharmaceutically acceptable salt thereof.

wherein in Formula (IV):

R^1 is hydrogen, (C_1-C_4)alkyl, -C(O)OH, –C(O)O-(C_1-C_4)alkyl, -C(O)NHNHR^6, -C(O)NR^6-((C_1-C_4)alkylene)-NHR^6, -C(O)NR^6 (C_1-C_4)alkyl, or –C(O)NR^6-cycloalkylene-NHR^6;

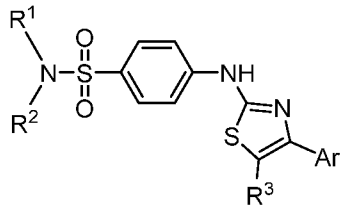
R^3 is hydrogen or (C_1-C_4)alkyl; and

each R^2, R^4, R^5 is independently hydrogen, halo, (C_1-C_4)alkyl, –C(O)O-(C_1-C_4)alkyl, (C_1-C_4)alkoxyl, (C_1-C_4)haloalkyl, or CN; and

Each R^6 is hydrogen or (C_1-C_4)alkyl.

or,

an effective dose of a compound of Formula (V)



(V), or a pharmaceutically acceptable salt thereof.

wherein in Formula (V):

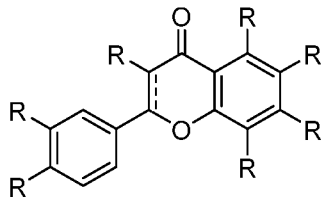
Ar is mono- or bi-cyclic aryl or heteroaryl, optionally substituted one or more with halo, (C_1-C_4)alkyl, (C_1-C_4)haloalkyl, CN, -S(O)$_2$NH$_2$, oxo, -NH$_2$, (C_1-C_4)alkoxyl, or –NHC(O)(C_1-C_4)alkyl;

Each R^1 and R^2 is independently hydrogen, (C_1-C_4)alkyl, aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted with halo or (C_1-C_4)alkyl, or R^1 and R^2 attached to nitrogen join together to form a 5 to 6 membered heterocycloalkyl; and

R^3 is hydrogen, or hydroxy-(C_1-C_4)alkyl,

or,

an effective dose of a compound of formula (VI)

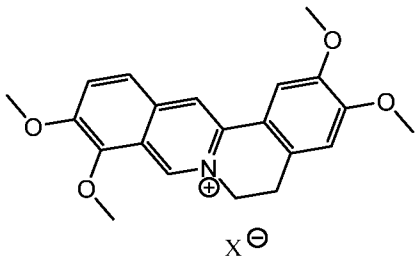


(VI),

wherein in formula (VI), the indicated dashed double bond is optionally present, each R is independently selected from H, OH, or (C1-C4)alkoxyl, or O-glycosyl, provided that at least two R groups are non-hydrogen,

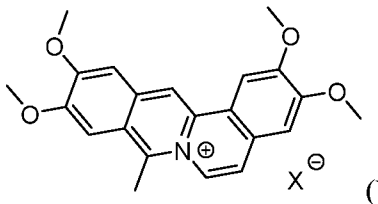
or,

an effective dose of a compound of formulas (VII)-(XV), or demethylated derivatives (phenolic analogs) thereof, or methyl ethers thereof, in the case of phenols or other alcohols:



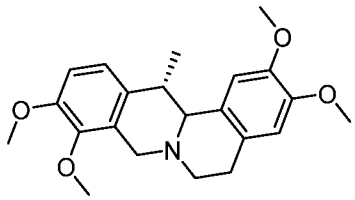
(VII),

wherein in formula (VII), X is a pharmaceutically acceptable salt;



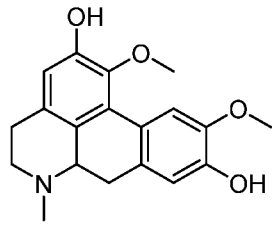
(VIII),

wherein in formula (VIII), X is a pharmaceutically acceptable salt;



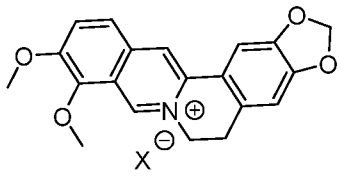
(IX),

and including all pharmaceutically acceptable salt forms,



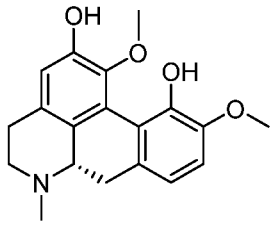
(X),

and including all pharmaceutically acceptable salt forms,



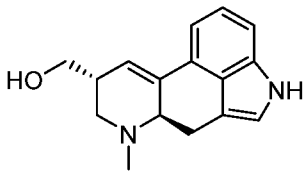
(XI),

wherein in formula (XI), X is a pharmaceutically acceptable salt;



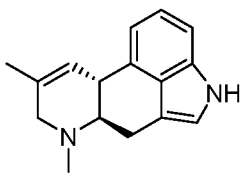
(XII),

and including all pharmaceutically acceptable salt forms,



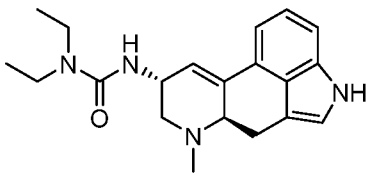
(XIII),

and including all pharmaceutically acceptable salt forms,



(XIV),

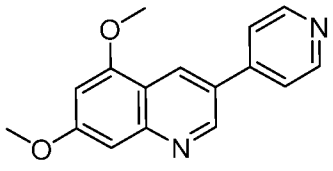
and including all pharmaceutically acceptable salt forms,



(XV),

or,

an effective dose of a compound of formula (XVI)

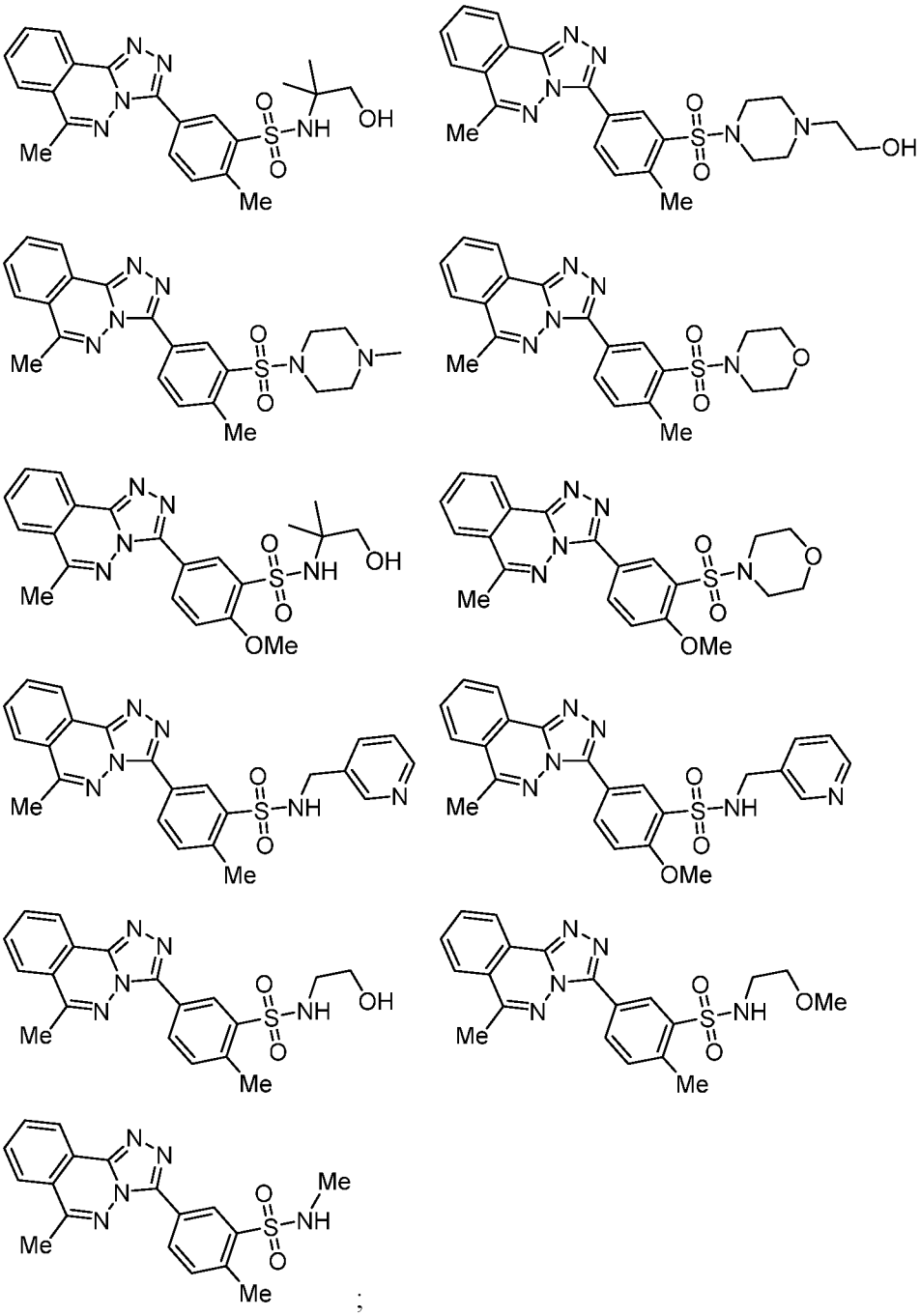


(XVI),

and including all pharmaceutically acceptable salt forms.

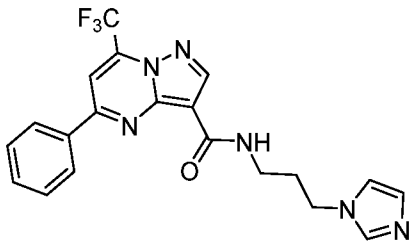
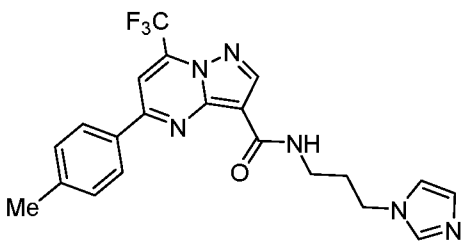
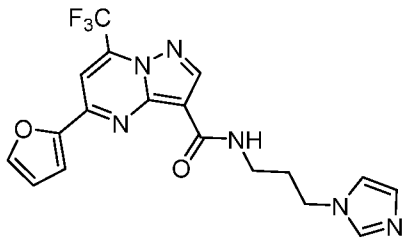
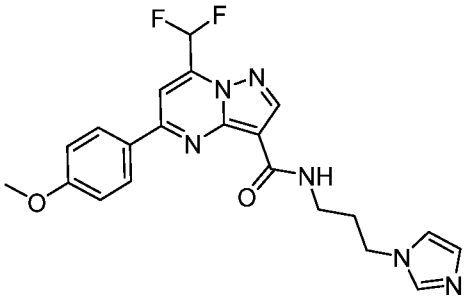
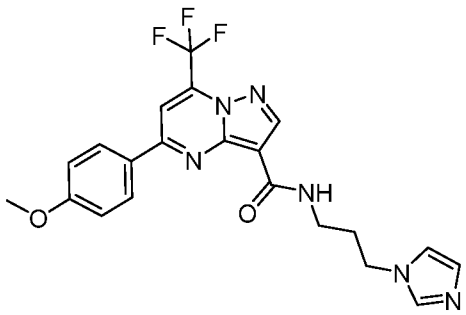
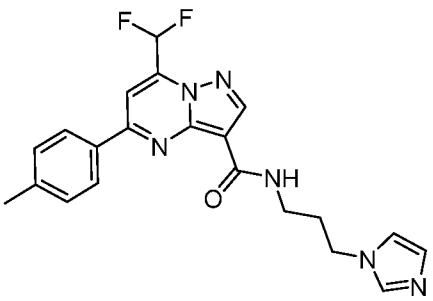
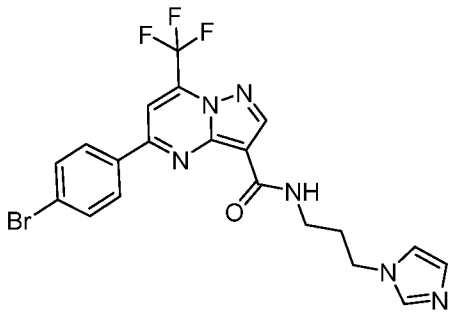
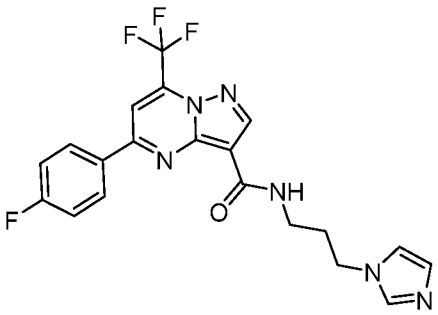
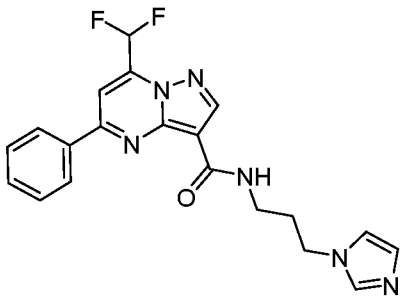
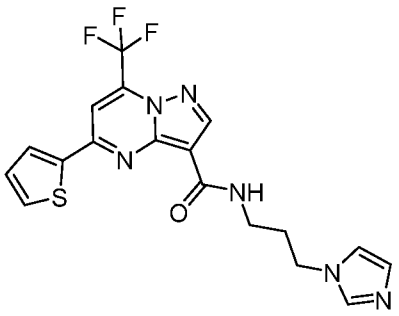
12. The method of claim 11 wherein the protein misfolding neurodegenerative disease comprises a prion disease, Parkinson's disease or other synucleinopathy, Alzheimer's disease, amyotrophic lateral sclerosis, or a tauopathy.

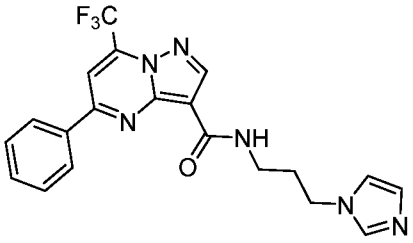
13. The method of any one of claims 1-12 wherein the compound of Formula (I) is any one of these structures, including their pharmaceutically acceptable salt forms:

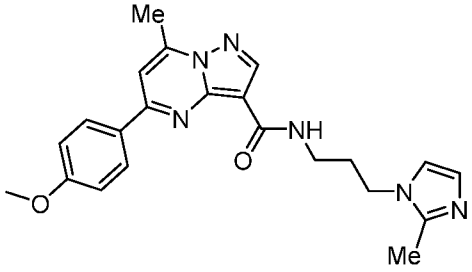


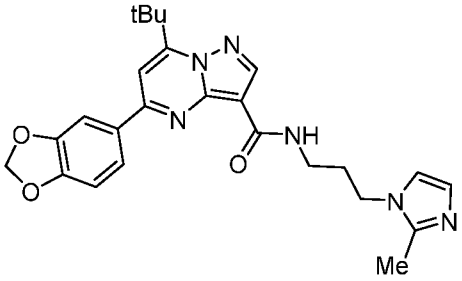
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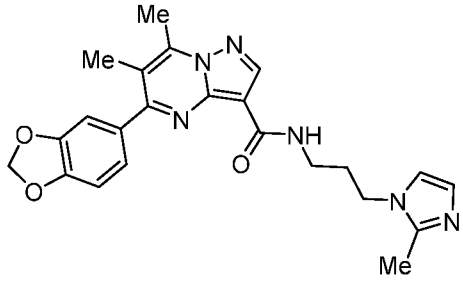
or, the compound of Formula (II) is any one these structures, including their pharmaceutically acceptable salt forms:

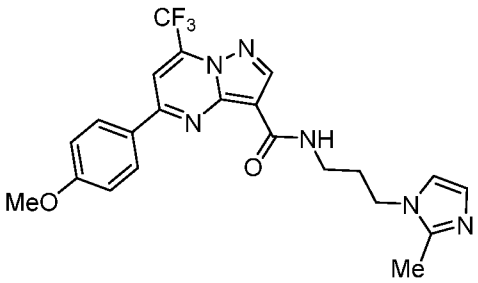











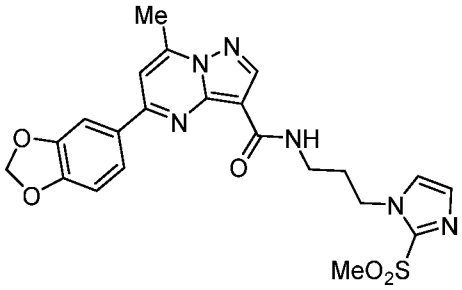


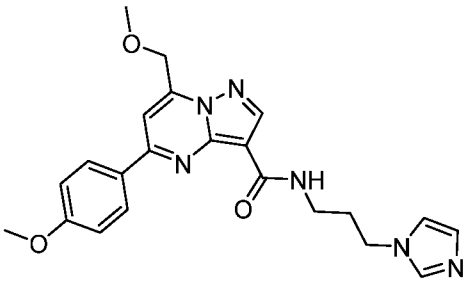


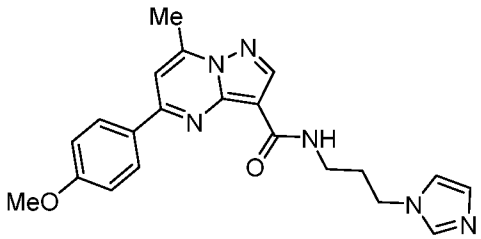


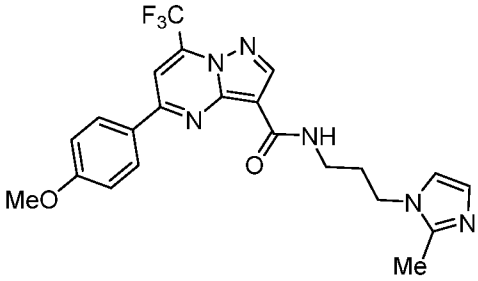


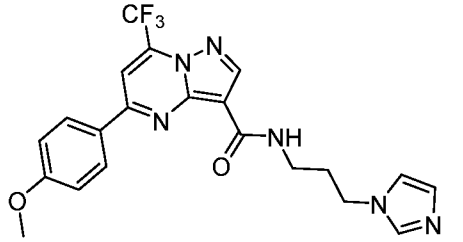


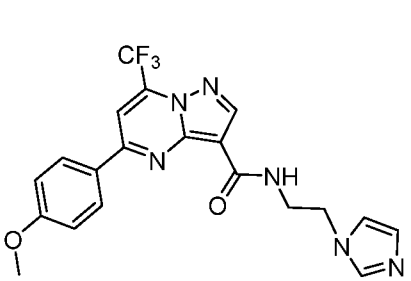


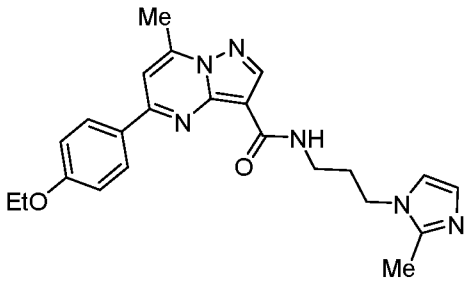


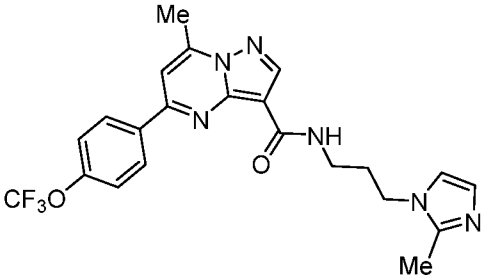


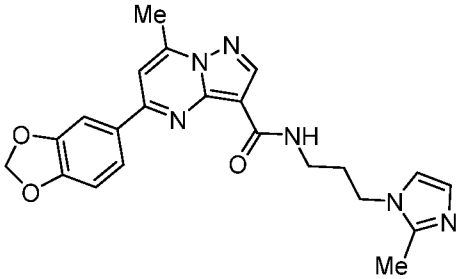


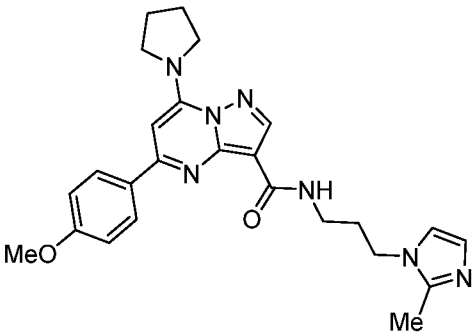


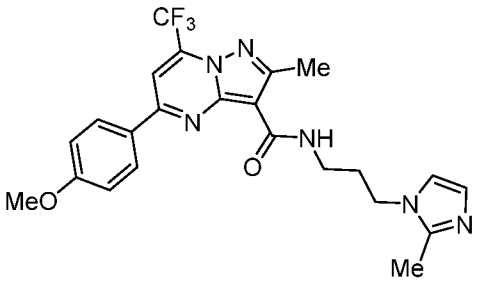


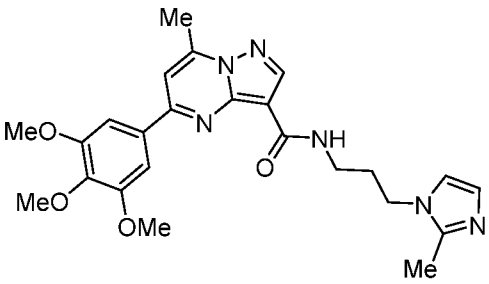


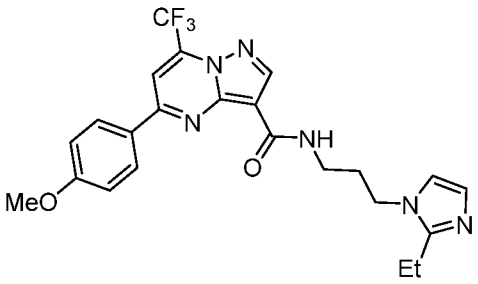


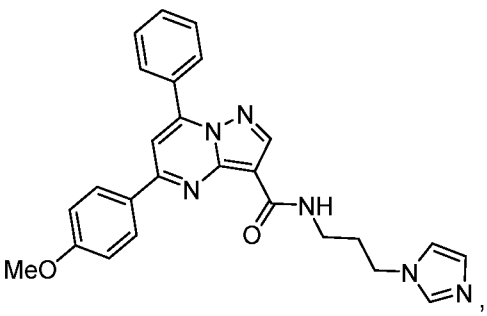


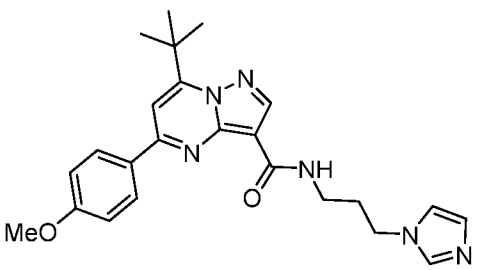


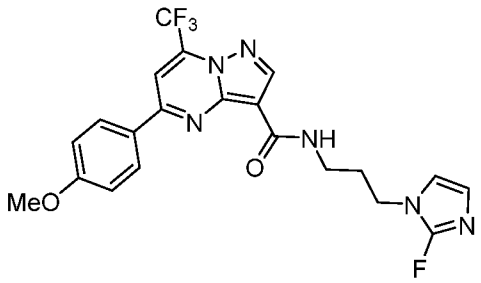


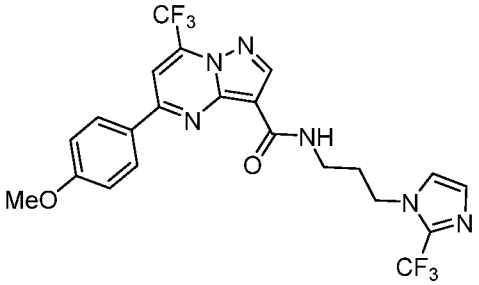


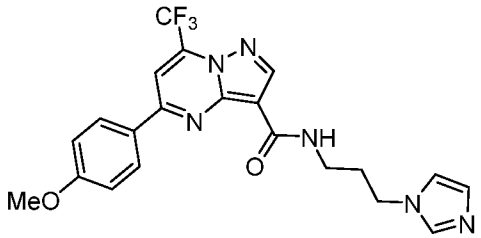


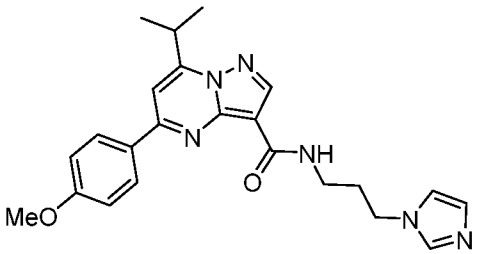


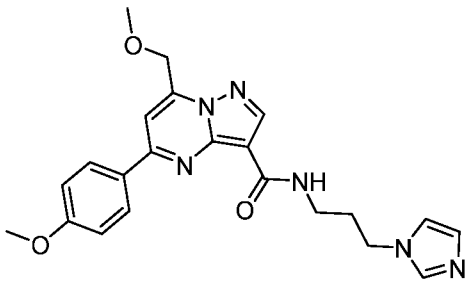


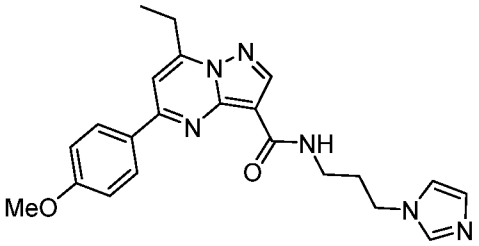


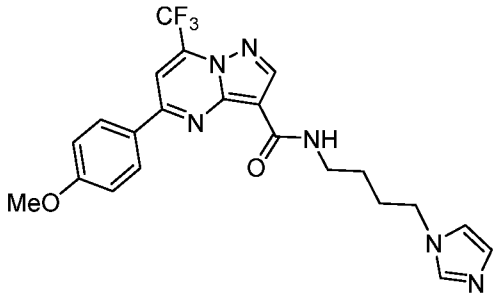


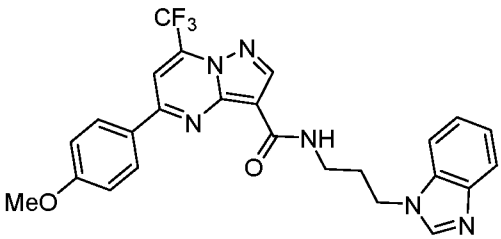


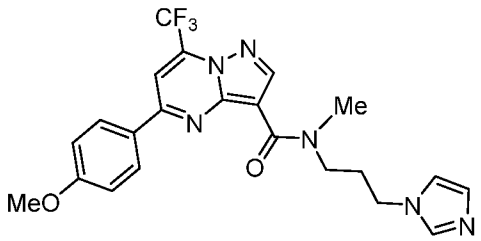


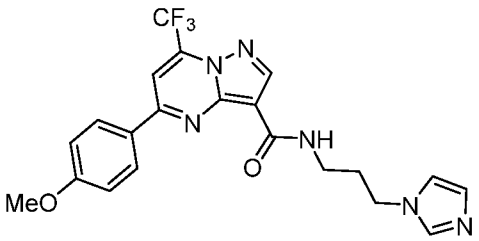


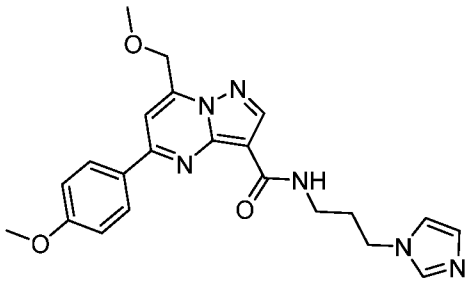


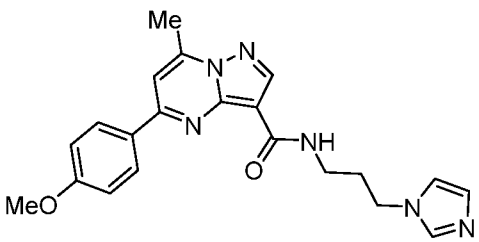


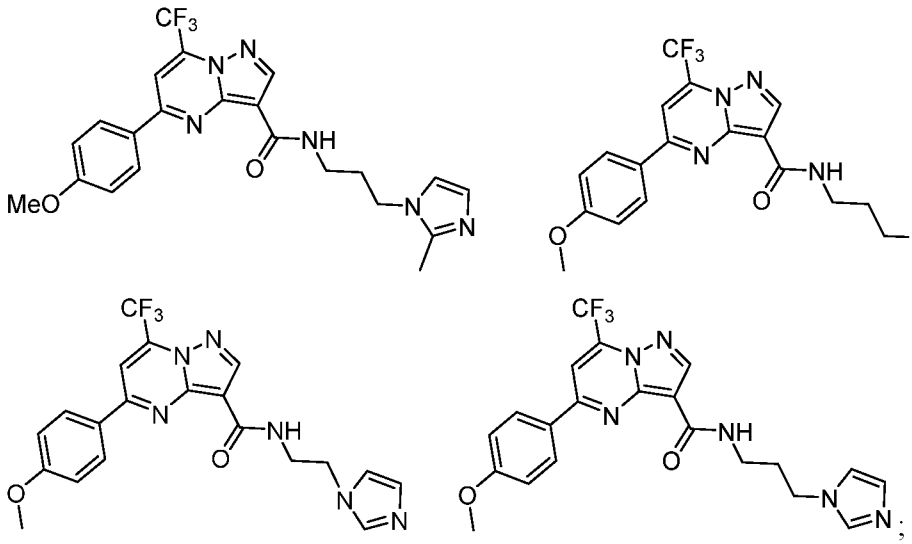




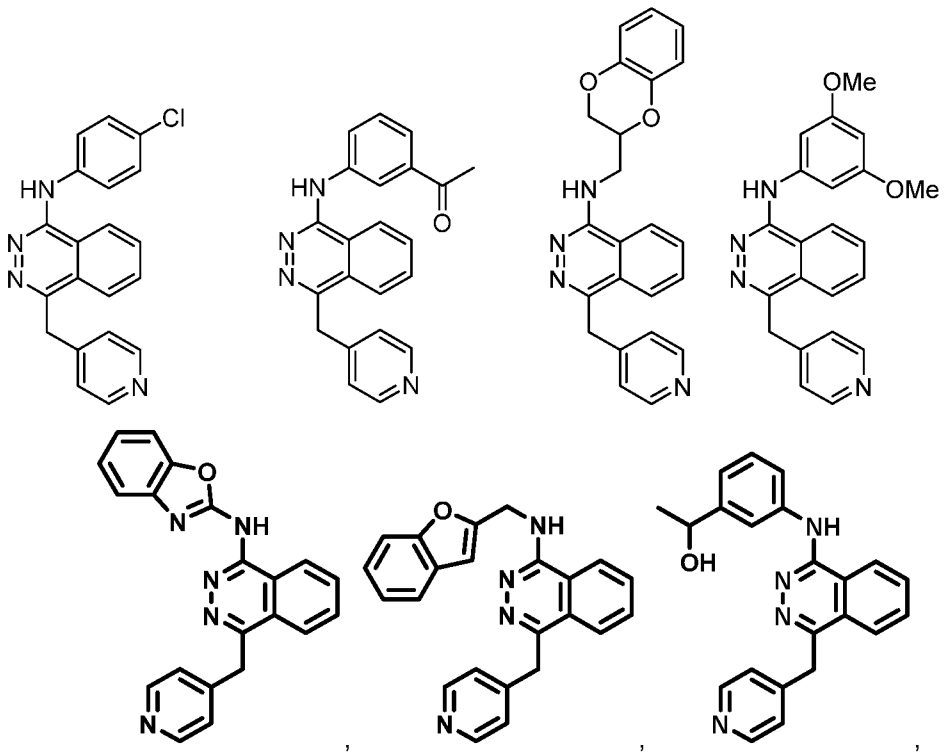


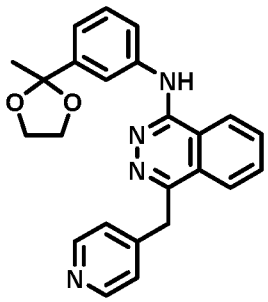
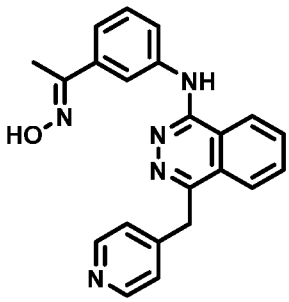
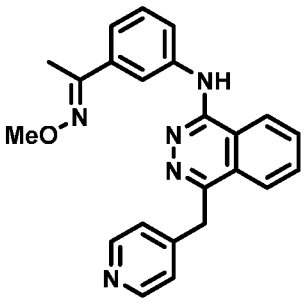
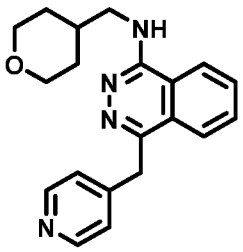
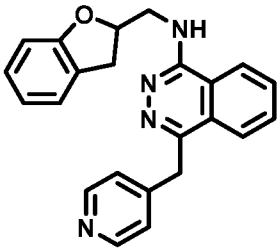
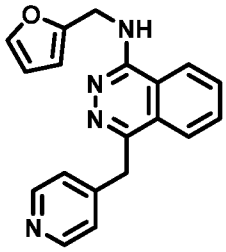
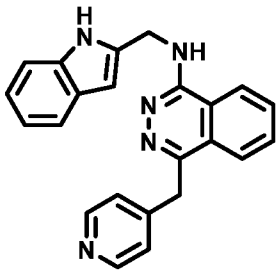
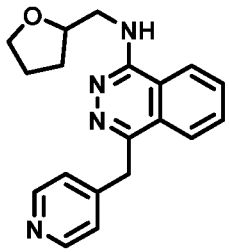
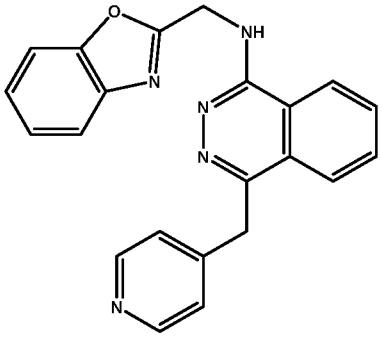


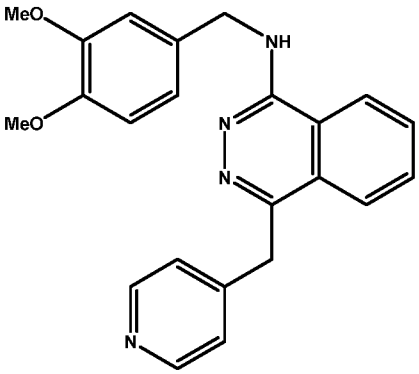




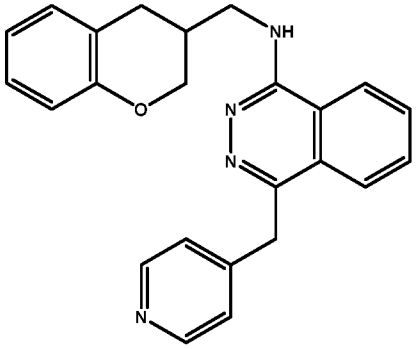
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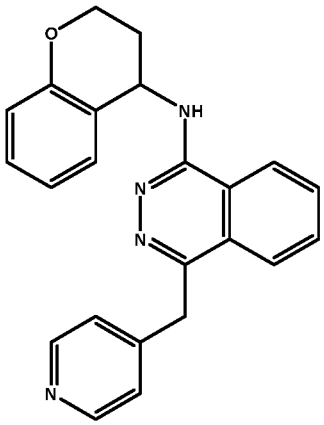











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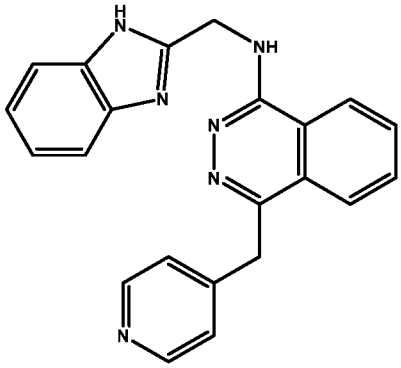
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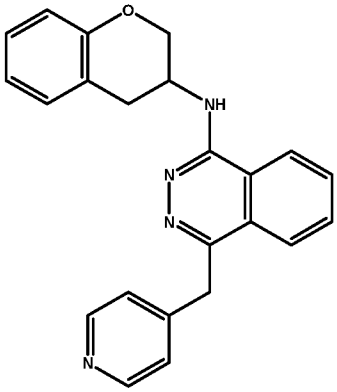
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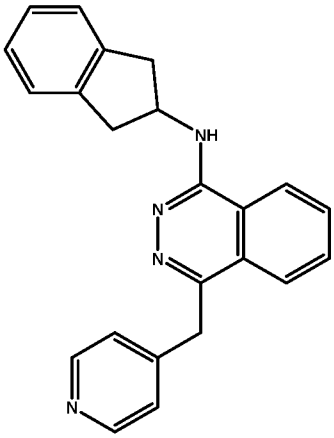
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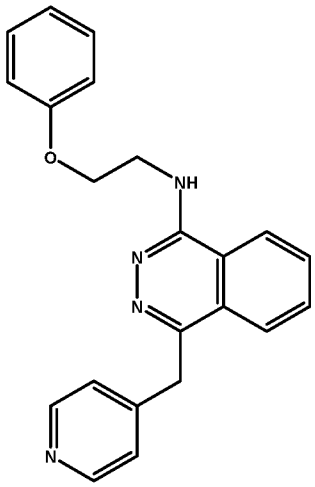
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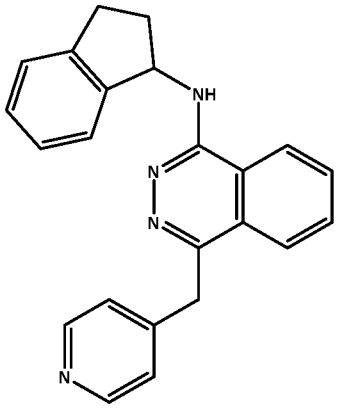
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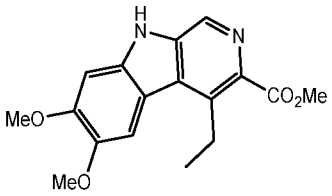

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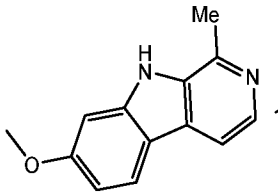
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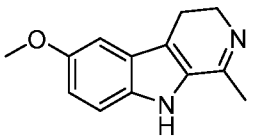


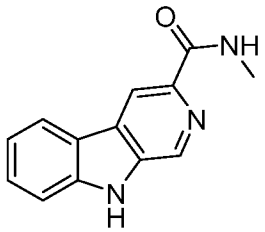
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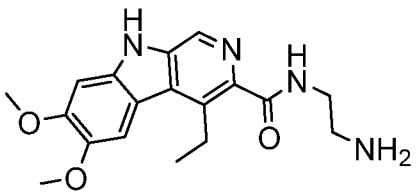
or, the compound of Formula (IV) is any one of these structures, including their pharmaceutically acceptable salt forms:

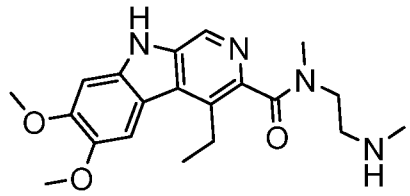


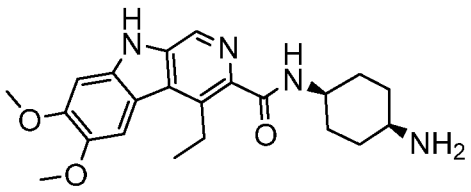


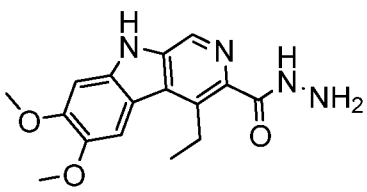


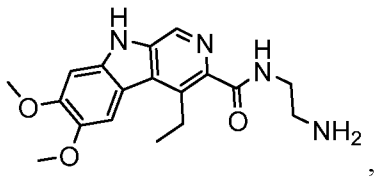


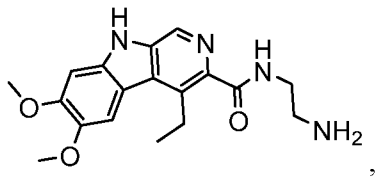


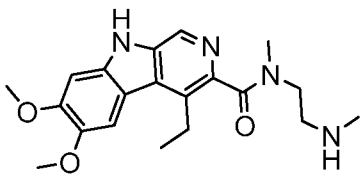


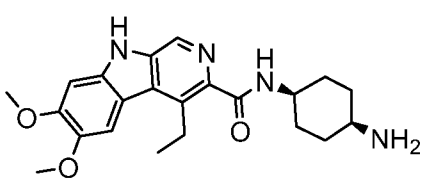
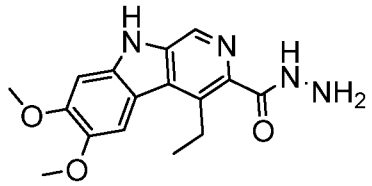


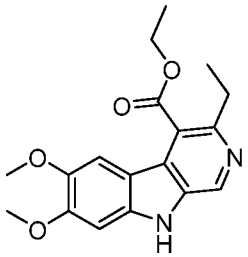
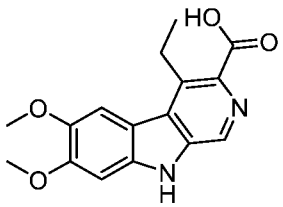


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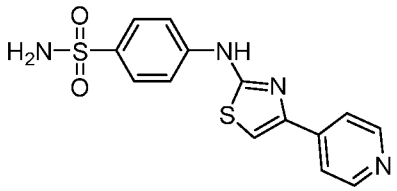
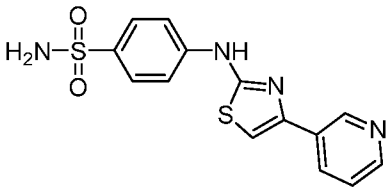
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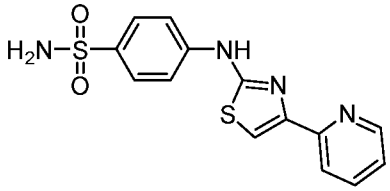
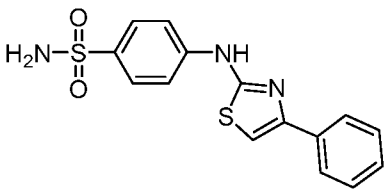


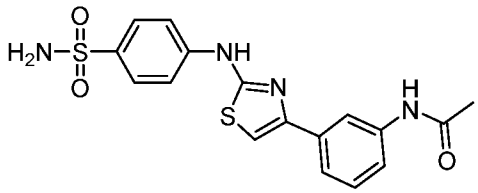
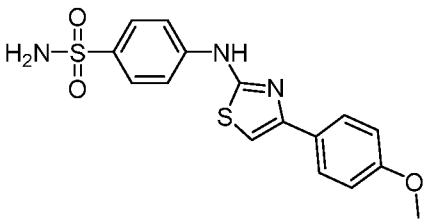

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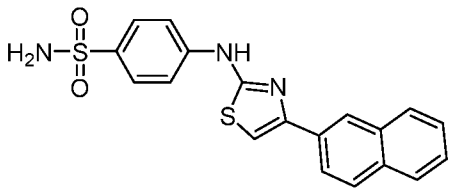
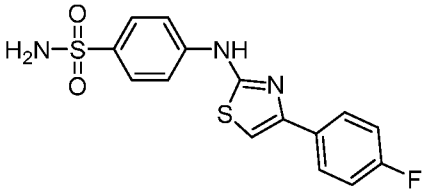


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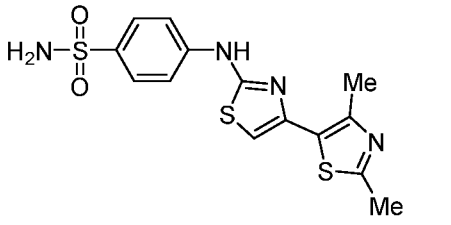
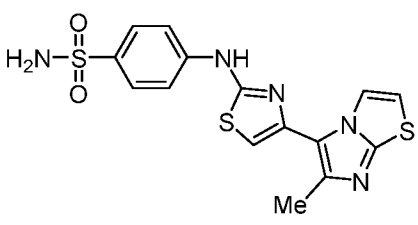
or, the compound of Formula (V) is any one of:

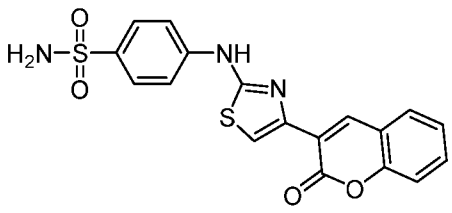



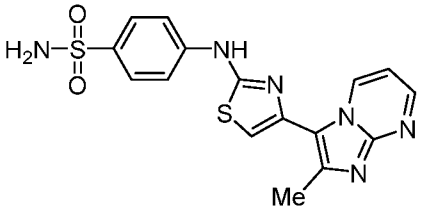



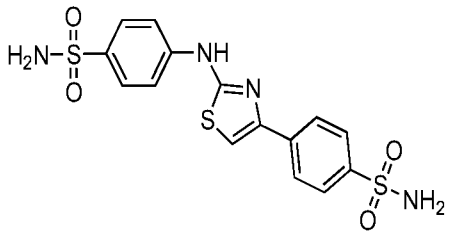



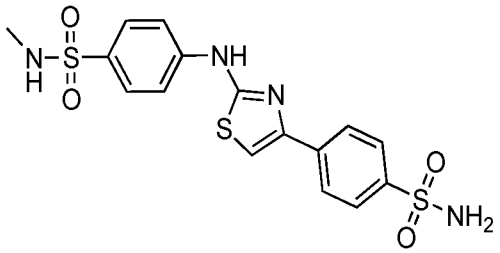



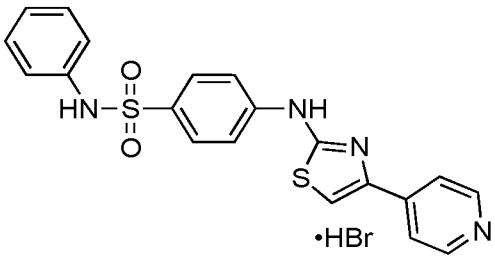



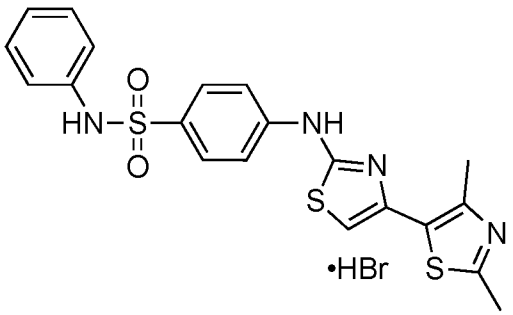


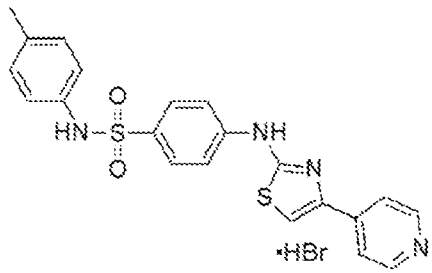


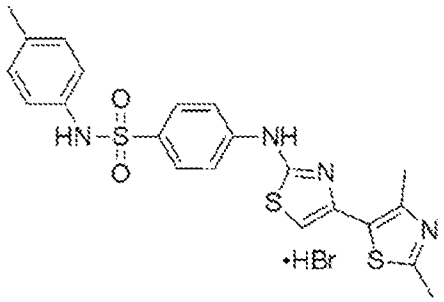


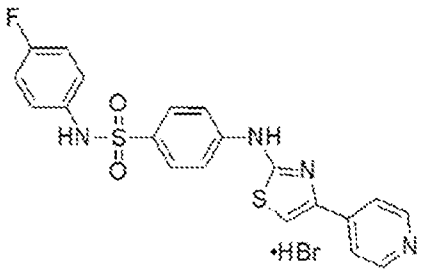


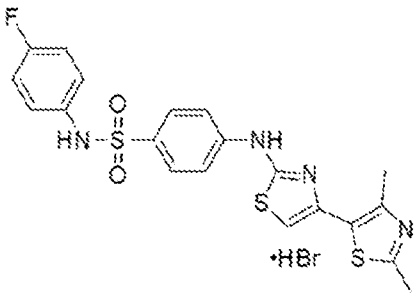


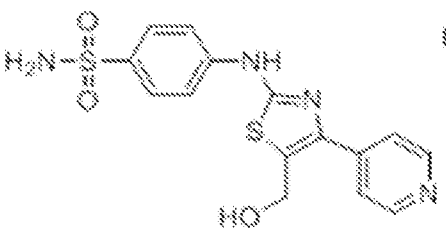


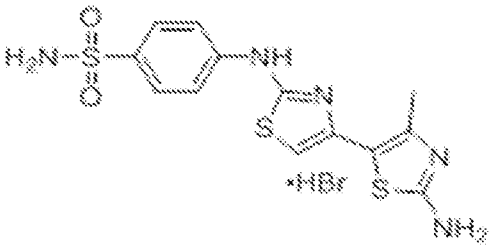


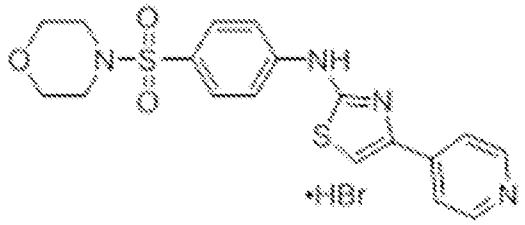


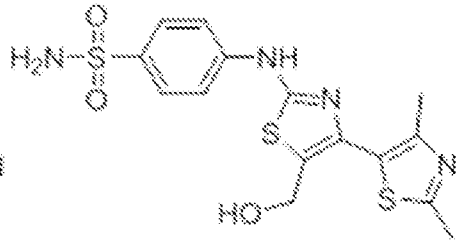


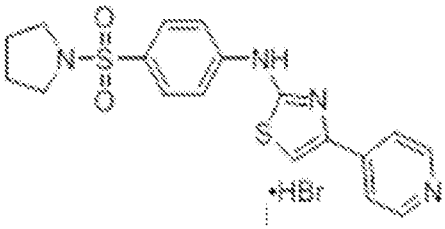


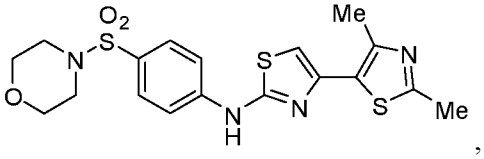


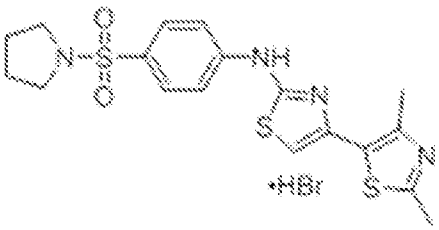


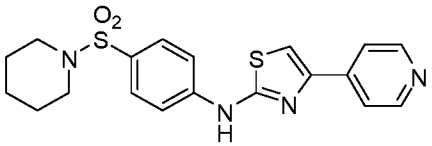


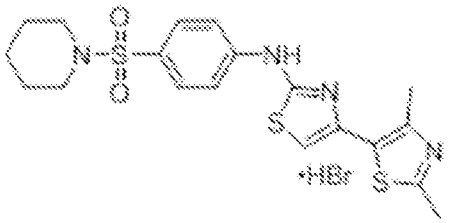


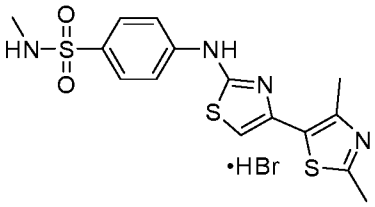


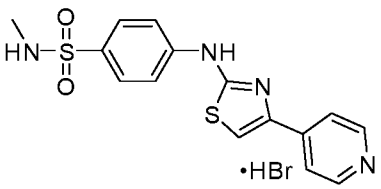


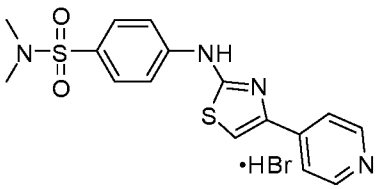


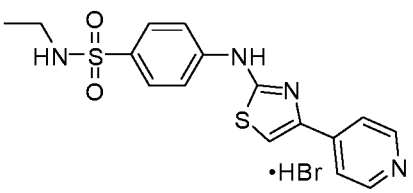


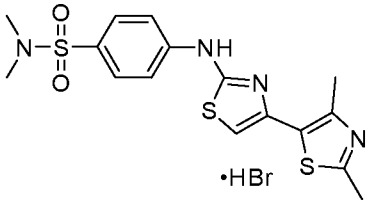


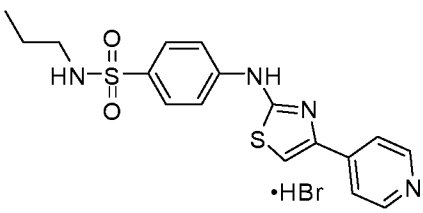


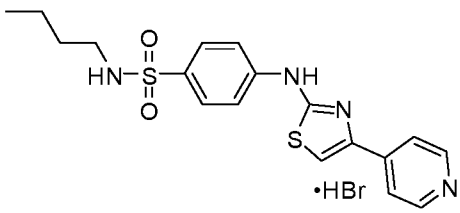


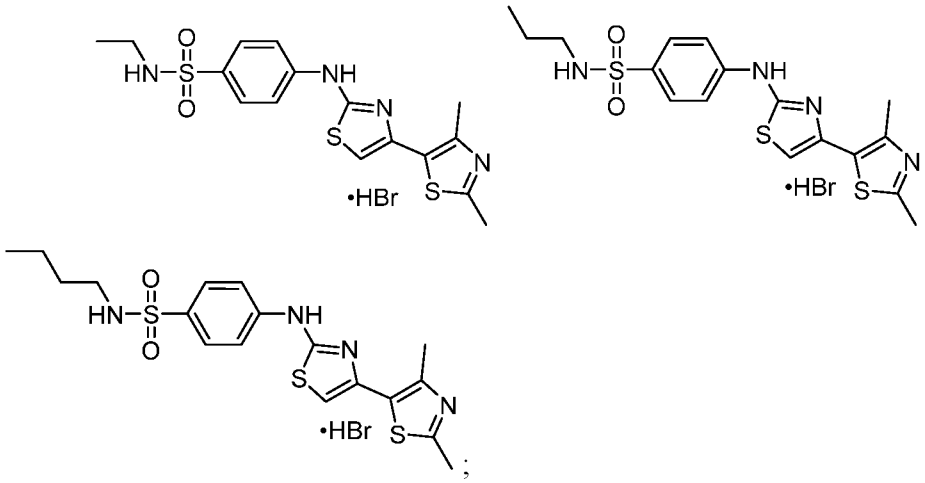




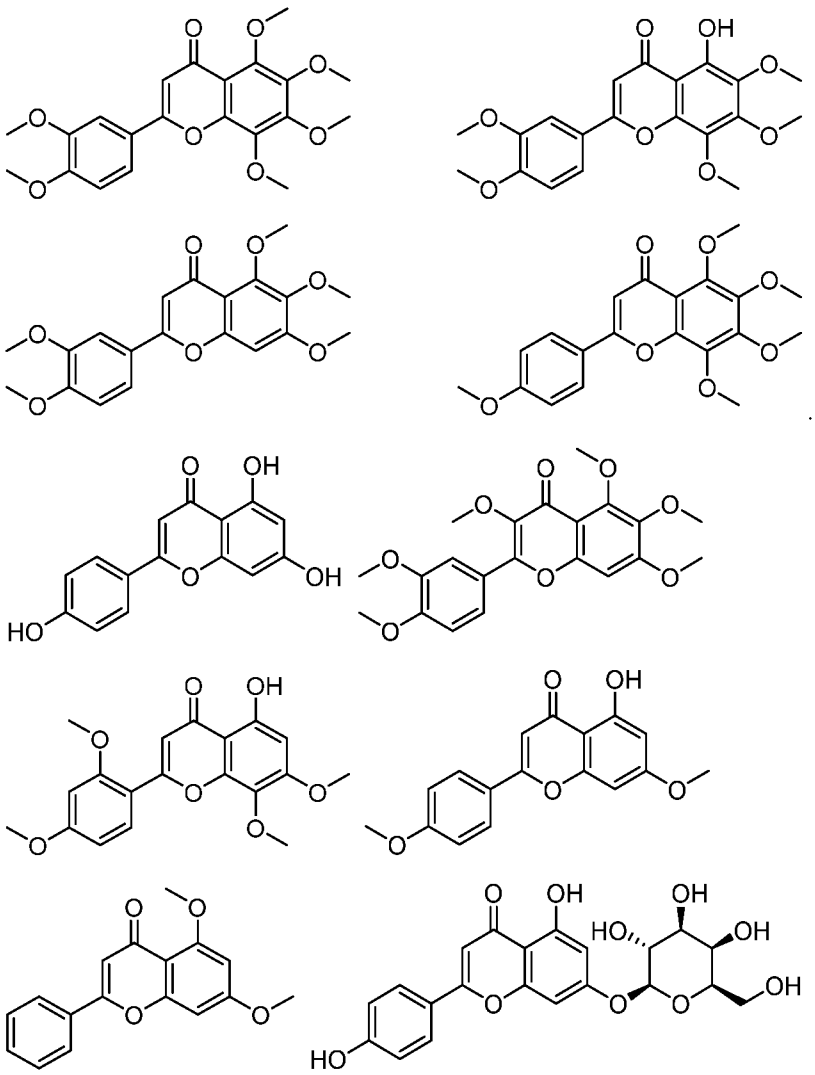


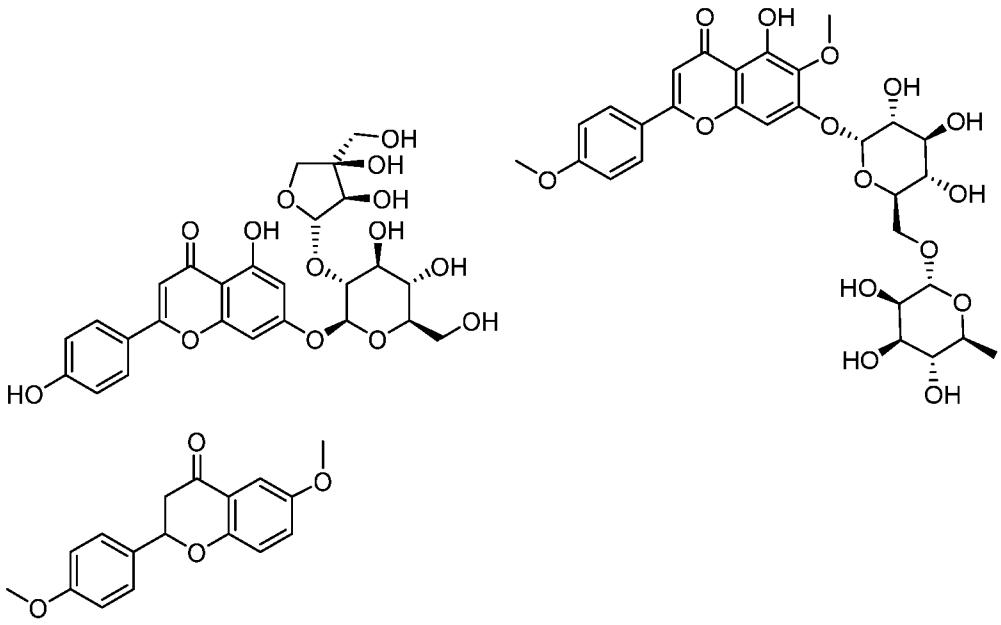




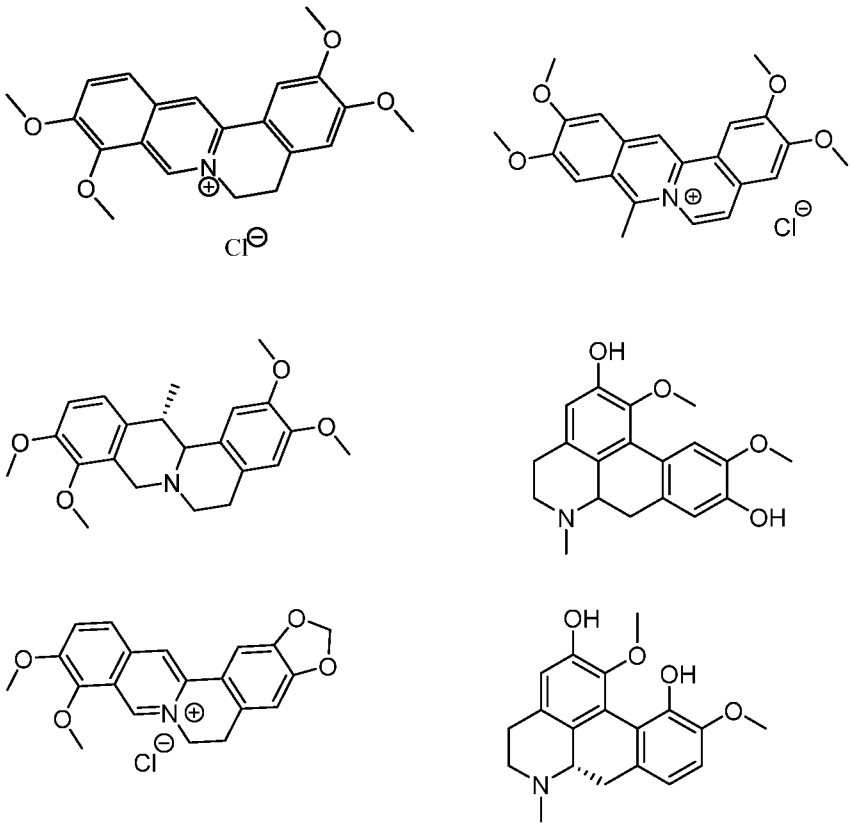


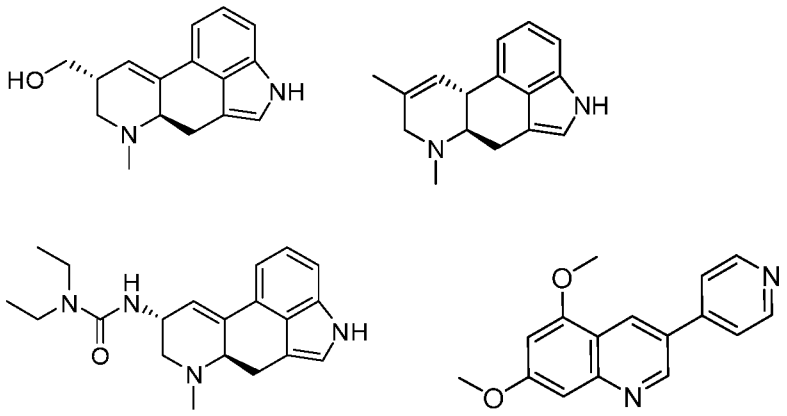
or, the compound of formula (VI) is any one of:



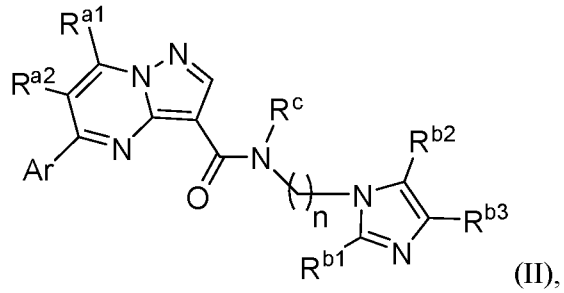


or, the compound of formulas (VII)-(XVI) is any one of these structures, including their pharmaceutically acceptable salt forms:





14. A compound having a Formula (II),



(II),

or a pharmaceutically acceptable salt thereof,

wherein:

Each R^{a1} and R^{a2} is independently hydrogen, (C_1-C_4)alkyl, (C_1-C_4)haloalkyl, (C_1-C_4)alkoxyl, (C_1-C_4)haloalkoxyl, 2 to 4 membered heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

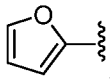
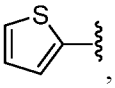
Each R^{b1}, R^{b2}, and R^{b3} is independently hydrogen, halo, (C_1-C_4)alkyl, -$S(O)_2R^d$, -$S(O)_2OR^d$, or (C_1-C_4)haloalkyl; or R^{b2} and R^{b3} are joined together to form an aryl or heteroaryl;

Each R^c and R^d is independently hydrogen or (C_1-C_4)alkyl;

Ar is mono- or bi-cyclic aryl or heteroaryl, optionally substituted with one or more halo, (C_1-C_4)alkyl, (C_1-C_4)haloalkyl, (C_1-C_4)alkoxyl, (C_1-C_4)haloalkoxyl, or heteroaryl; and

n = 2, 3, 4, or 5,

provided that when R^{a2}, R^{b1}, R^{b2}, R^{b3}, and R^c are hydrogen, n is 3, Ar is phenyl which is unsubstituted or substituted with –CH_3 or -OMe, then R^{a1} is not difluoromethyl or trifluoromethyl, and

provided that when R^{a2}, R^{b1}, R^{b2}, R^{b3}, and R^{c} are hydrogen, n is 3, Ar is phenyl substituted with -F, Br, , or , then R^{a1} is not trifluoromethyl.

15. The compound of claim 14, wherein R^{b1} is hydrogen, halo, C_1-C_4 alkyl, (C_1-C_4) haloalkyl, or -$S(O)_2R^c$.

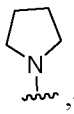
16. The compound of claim 15, wherein R^{b1} is methyl, ethyl, -F, -CF_3., or -$S(O)_2CH_3$.

17. The compound of claim 14, wherein each R^{b2}, R^{b3}, R^{c}, and R^{d} is independently hydrogen or methyl.

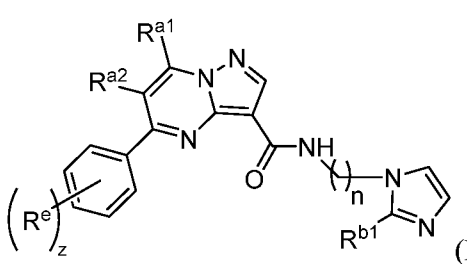
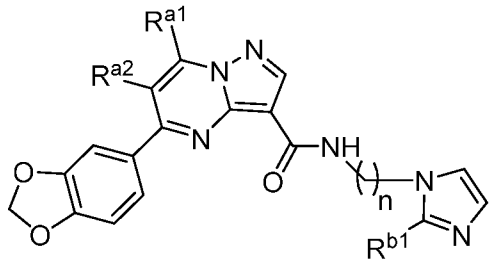
18. The compound of claim 14, wherein R^{b2} and R^{b3} are joined together to form a phenyl.

19. The compound of claim 14, wherein n is 2, 3, or 4.

20. The compound of any one of claims 14-19, wherein R^{a1} is (C_1-C_4)alkyl, (C_1-C_4)haloalkyl, heterocycloalkyl, 2 to 4 membered heteroalkyl, or aryl.

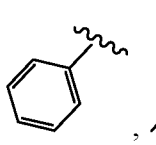
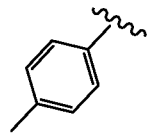
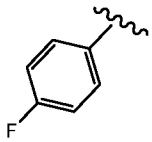
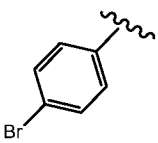
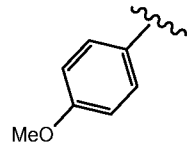
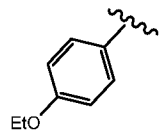
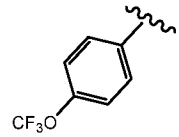
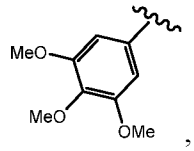
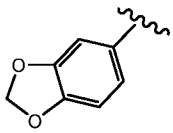
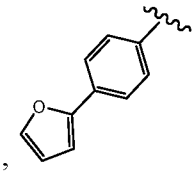
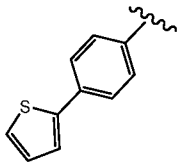
21. The compound of claim 20, wherein R^{a1} is methyl, ethyl, isopropyl, t-butyl,–CF_3, ,–CH_2-O-CH_3, or phenyl.

22. The compound of any one of claims 14-21, wherein the compound has the formula of:

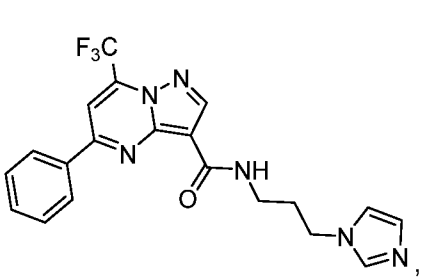
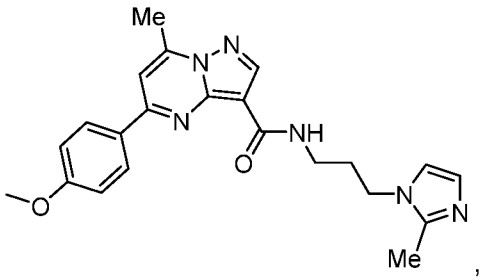
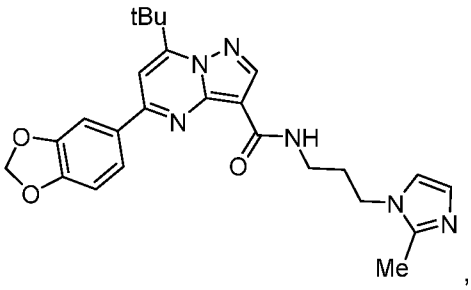
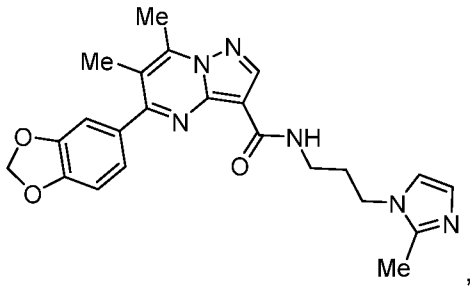
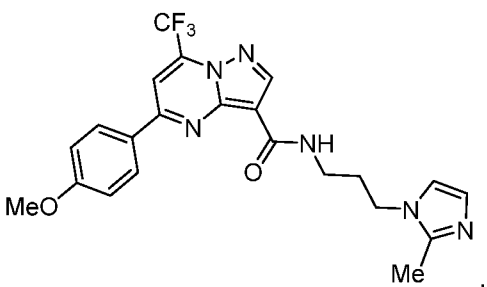
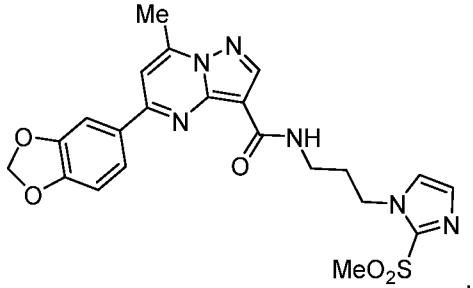

(II-a) or

(II-b)

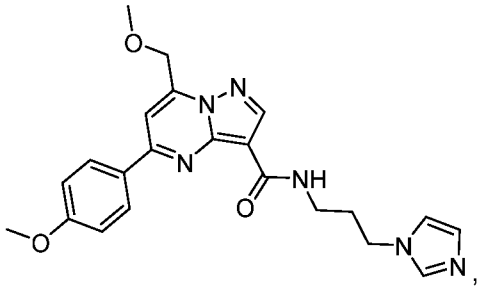
wherein R^{b1} is hydrogen, methyl, ethyl, -F, -CF_3, or –$S(O)_2$Me; and R^{2a} is hydrogen or methyl.

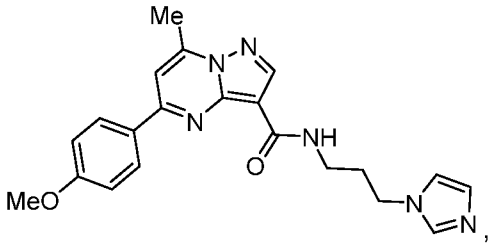
23. The compound of any one of claims 14-22, wherein Ar is phenyl optionally substituted with one or more of halo, (C_1-C_4)alkyl, (C_1-C_4)haloalkyl, (C_1-C_4)alkoxyl, (C_1-C_4)haloalkoxyl, or heteroaryl.

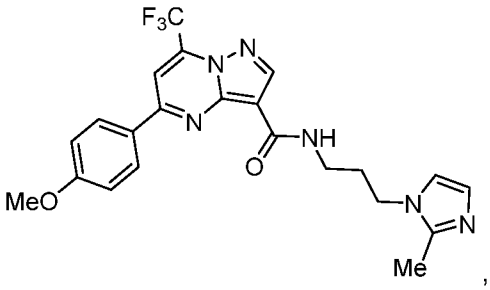
24. The compound of any one of claims 14-23, wherein Ar is , , , , , , , , , , or .

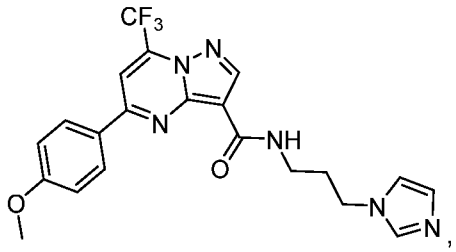
25. The compound of claim 14, wherein the compound is selected from:

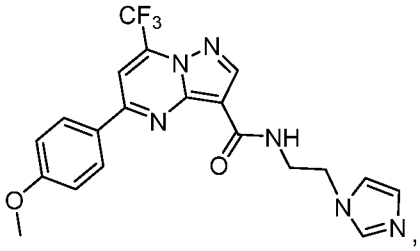
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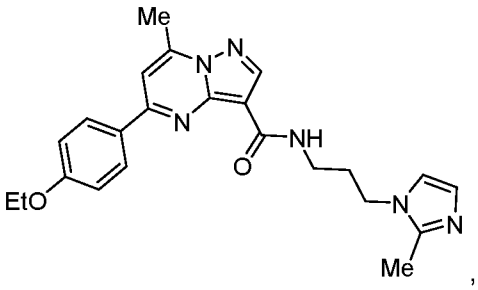


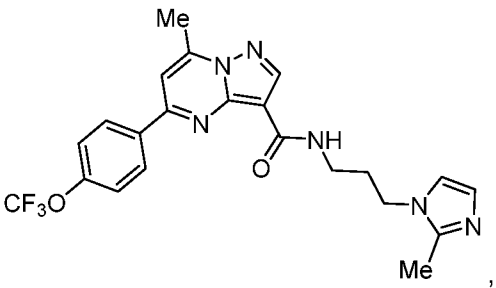


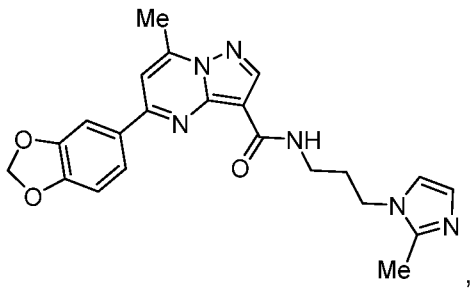


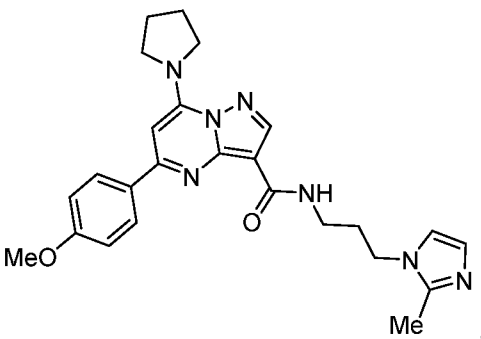


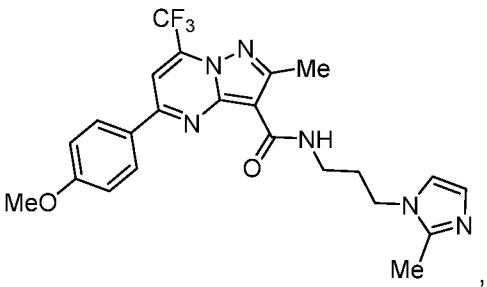


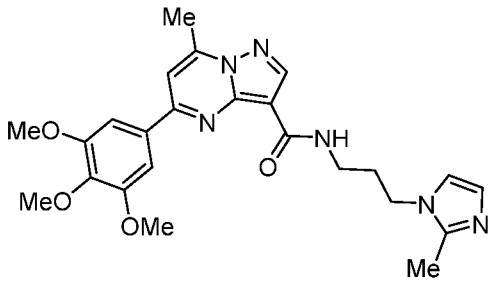
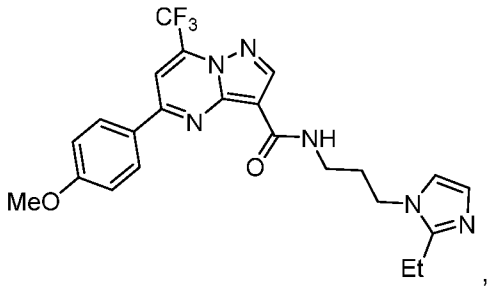
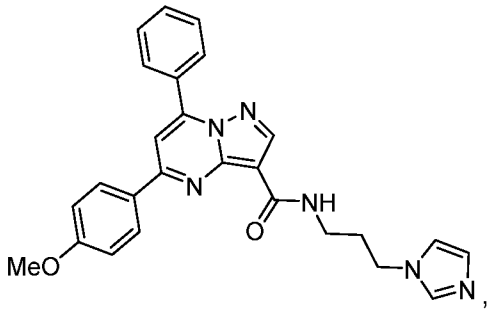
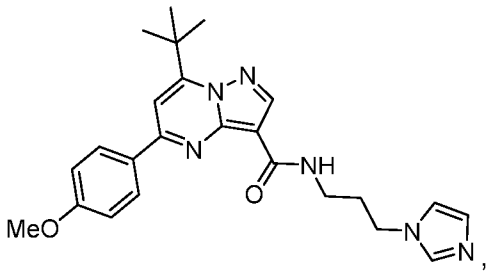
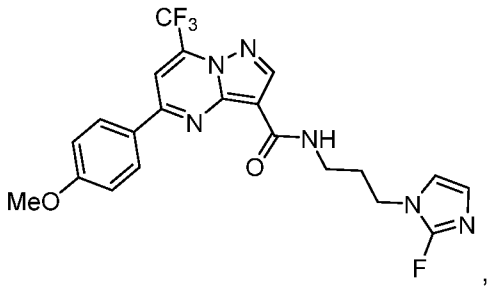
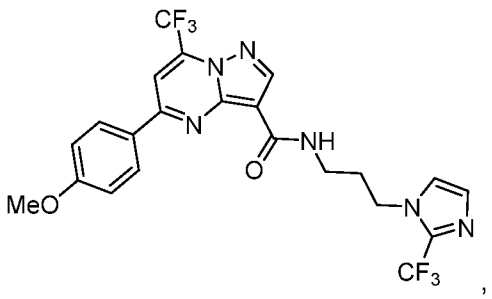
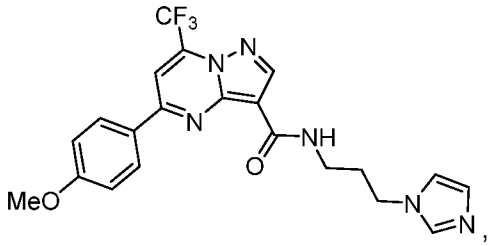
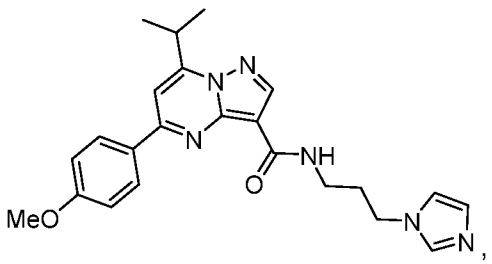
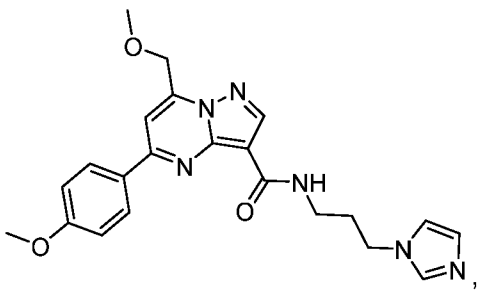
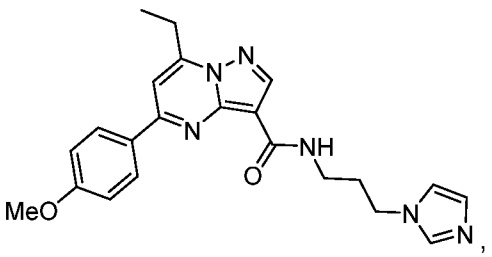


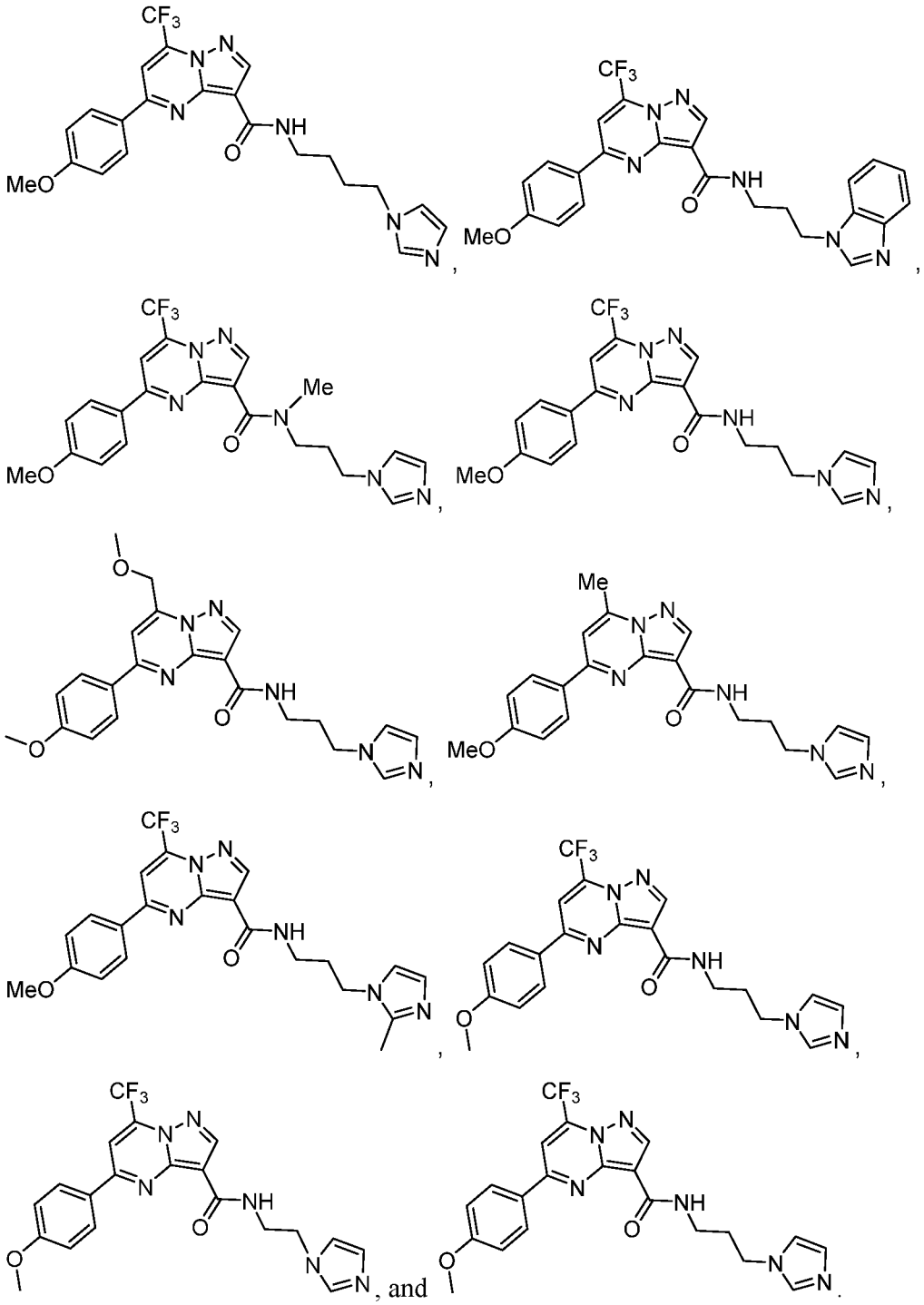




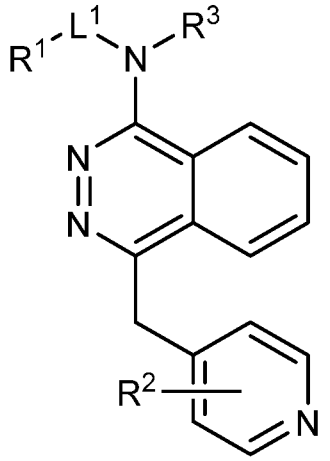






26. A compound having a Formula (III),



(III), or a pharmaceutically acceptable salt thereof,

wherein:

L^1 is a bond, C_1-C_4 alkylene, or 2 to 4-membered heteroalkylene;

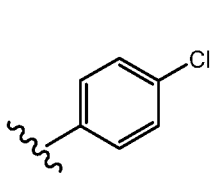
R^1 is mono- or bi-cyclic cycloalkyl, heterocycloalkyl, aryl, alkylaryl, or heteroaryl, wherein the cycloalkyl, heterocycloalkyl, aryl, alkylaryl or heteroaryl is optionally substituted with one or more selected from halo, (C_1-C_4)alkyl, hydroxy(C_1-C_4)alkyl, (C_1-C_4)alkoxyl, -C(=O)(C_1-C_4)alkyl, -C(=O)N(R)$_2$, or -C(=NR)(C_1-C_4)alkyl, wherein the (C_1-C_4)alkyl is unsubstituted or substituted with heterocycloalkyl ;

Each R is independently H, -OH, (C_1-C_4)alkyl, or (C_1-C_4)alkoxyl, or two R together with the nitrogen atom to which it is bonded form a heterocycloalkyl, optionally further comprising an O atom in the heterocyclyl ring;

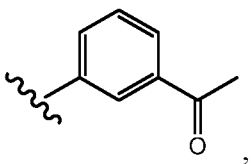
R^2 occurs 0, 1, or 2 times, and is (C_1-C_4) alkyl, (C_1-C_4) haloalkyl, or $SO_2N(R^4)_2$; and

Each R^3 and R^4 is independently H, or (C_1-C_4)alkyl,

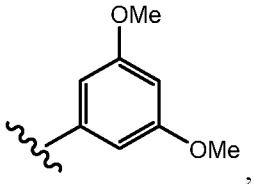
provided that when L^1 is a bond, R^2 does not occur, and R^3 is hydrogen, then R^1 is not



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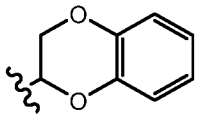


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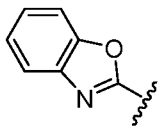
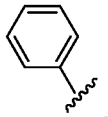
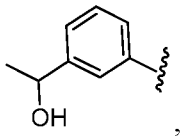
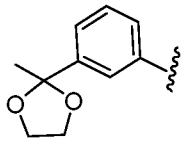
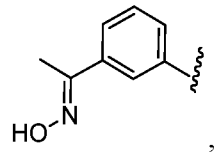
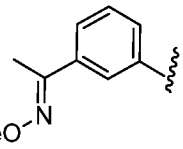
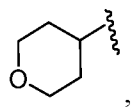
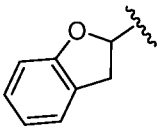
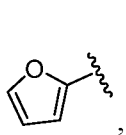
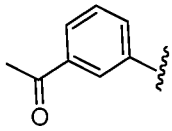
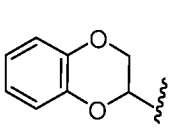
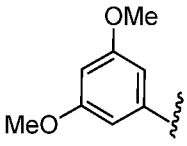
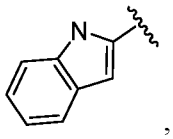
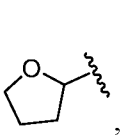
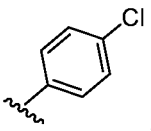
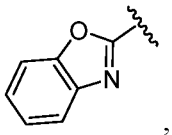
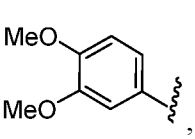
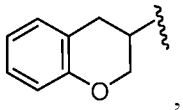
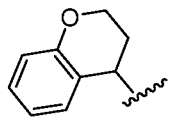
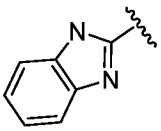
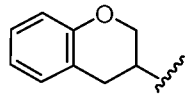
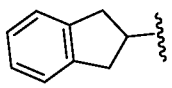
, and

provided that when L^1 is methylene, R^2 does not occur, and R^3 is hydrogen, then R^1 is not



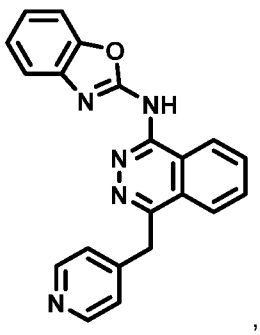
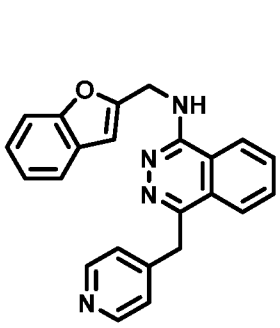
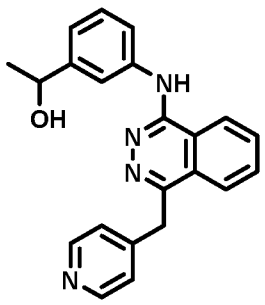
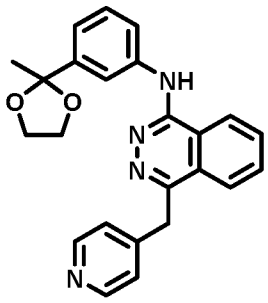
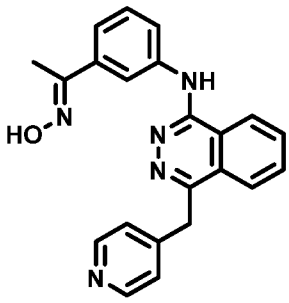
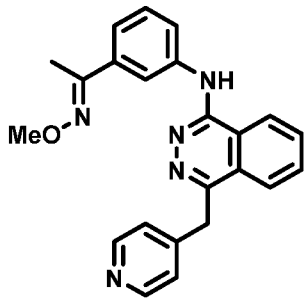
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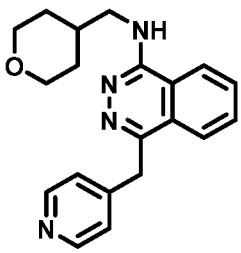
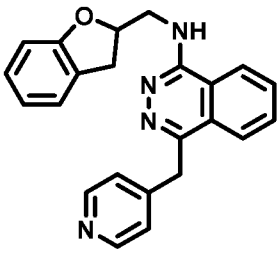
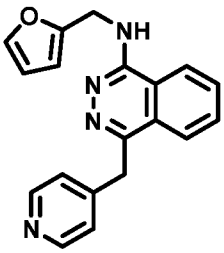
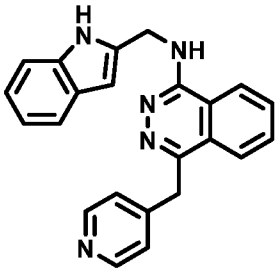
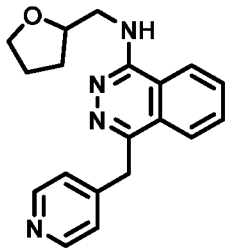
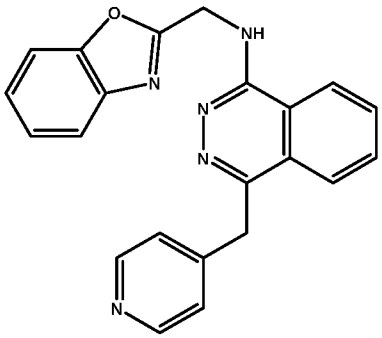
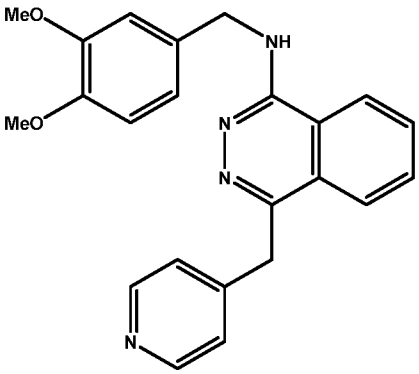
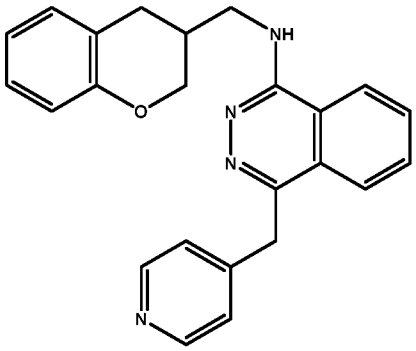
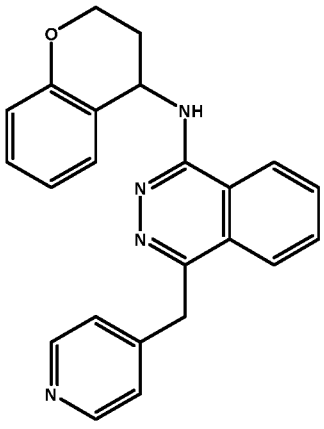
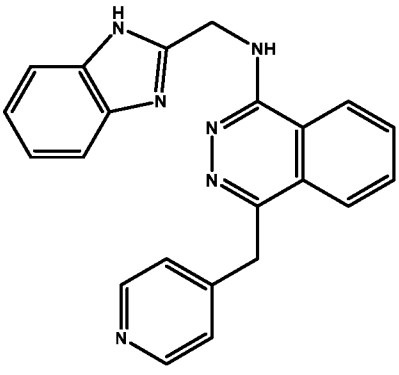
27. The compound of claim 26, wherein L^1 is a bond, methylene, or –CH_2CH_2-O-.

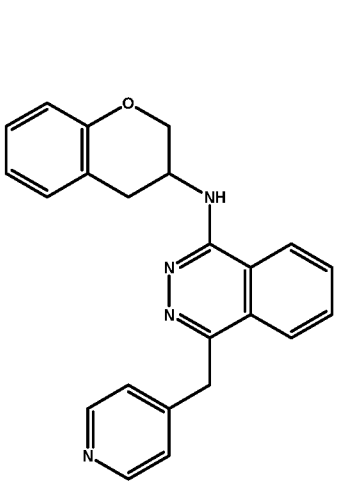
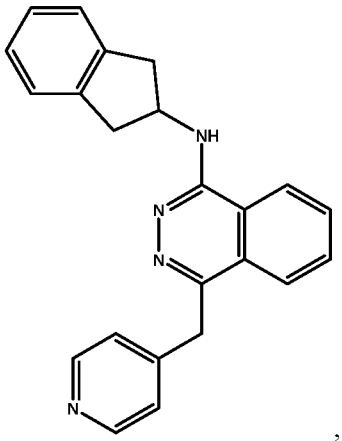
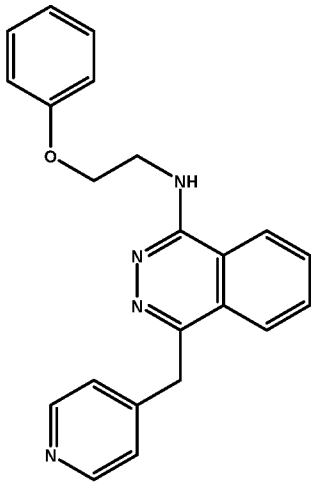
28. The compound of any one of claims 26-27, wherein R^1 is , , , , , , , , , , , , , , , , , , , , , or .

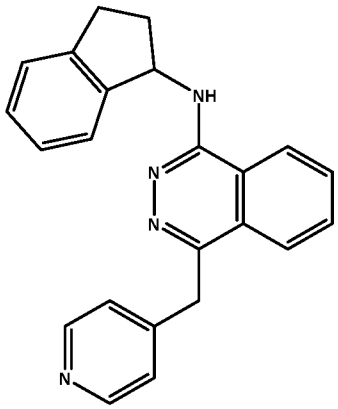
29. The compound of any one of claims 26-28, wherein R^3 is hydrogen or methyl.

30. The compound of claim 26, wherein the compound is selected from:

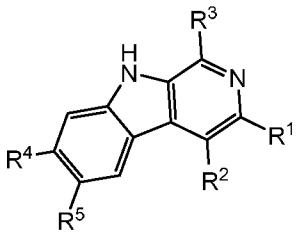
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31. A compound having a Formula (IV),


(IV), or a pharmaceutically acceptable salt thereof,

wherein:

R^1 is hydrogen, (C_1-C_4)alkyl, -C(O)OH, –C(O)O-(C_1-C_4)alkyl, -C(O)$NHNH_2$, -C(O)NH-((C_1-C_4)alkylene)-NH_2, -C(O)NH(C_1-C_4)alkyl, or –C(O)NH-cycloalkylene-NH_2;

R^3 is hydrogen or (C_1-C_4)alkyl; and

each R^2, R^4, and R^5 is independently hydrogen, halo, (C_1-C_4)alkyl, –C(O)O-(C_1-C_4)alkyl, (C_1-C_4)alkoxyl, (C_1-C_4)haloalkyl, or CN,

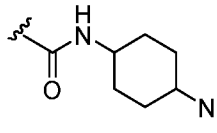
provided that when R^4 and R^5 are –OMe, R^3 is hydrogen, and R^2 is ethyl, then R^1 is not –COOMe,

provided that when R^4 is –OMe, R^5 is hydrogen, and R^1 and R^2 are hydrogen, then R^3 is not methyl, and

provided that when R^2, R^3, R^4, and R^5 are hydrogen, and then R^1 is not $-C(O)NHCH_3$.

32. The compound of claim 31, wherein each R^4 and R^5 is independently hydrogen or -OMe.

33. The compound of any one of claims 31-32, R^1 is hydrogen, $(C_1\text{-}C_4)$alkyl, -C(O)OH, $-C(O)O(C_1\text{-}C_4)$alkyl, $-C(O)NH\text{-}CH_2CH_2\text{-}NH_2$, $-C(O)NCH_3\text{-}CH_2CH_2\text{-}NHCH_3$,

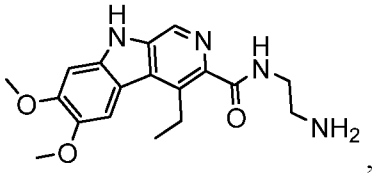


, or $-C(O)NHNH_2$.

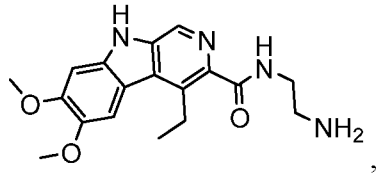
34. The compound of any one of claims 31-33, wherein R^3 is hydrogen or methyl.

35. The compound of any one of claims 31-34, wherein R^2 is hydrogen, $(C_1\text{-}C_4)$alkyl, or $-C(O)O\text{-}(C_1\text{-}C_4)$alkyl.

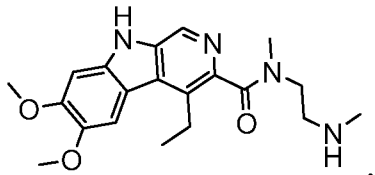
36. The compound of claim 31, wherein the compound is selected from:



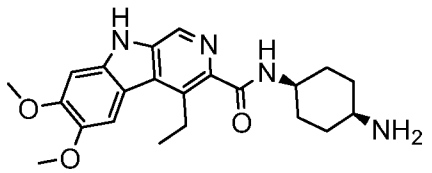
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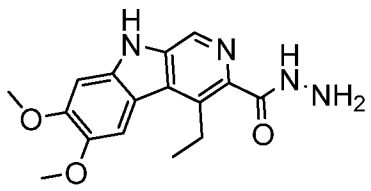
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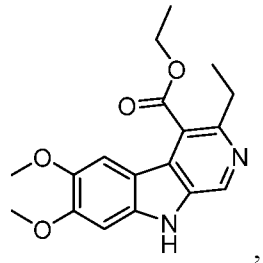
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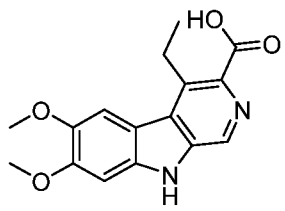
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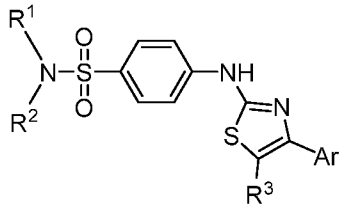


, and



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37. A compound having a Formula (V),



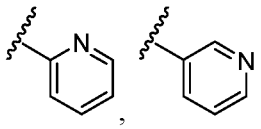
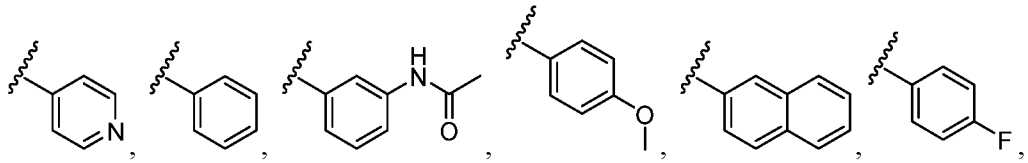
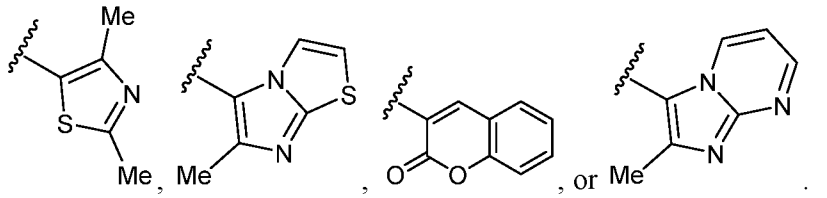
(V), or a pharmaceutically acceptable salt thereof,

wherein:

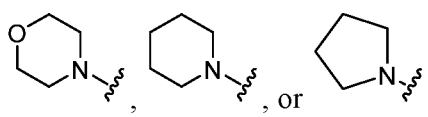
Ar is mono- or bi-cyclic aryl or heteroaryl, optionally substituted one or more with halo, (C_1-C_4)alkyl, (C_1-C_4)haloalkyl, CN, -$S(O)_2NH_2$, oxo, -NH_2, (C_1-C_4)alkoxyl, or –NHC(O)(C_1-C_4)alkyl;

Each R^1 and R^2 is independently hydrogen, (C_1-C_4)alkyl, aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted with halo or (C_1-C_4)alkyl, or R^1 and R^2 attached to nitrogen join together to form a 5 to 6 membered heterocycloalkyl; and

R^3 is hydrogen, or hydroxy-(C_1-C_4)alkyl,

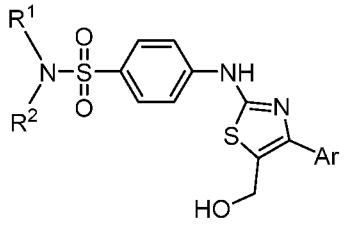
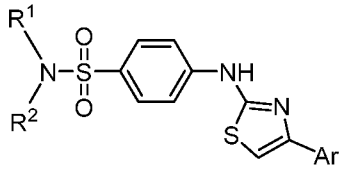
provided that when R^1, R^2 and R^3 are hydrogen, then Ar is not , , , or .

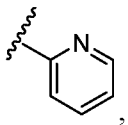
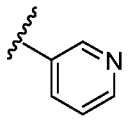
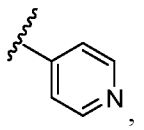
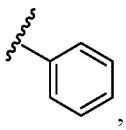
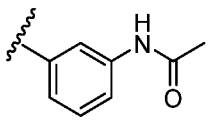
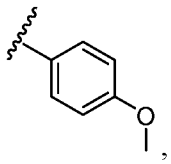
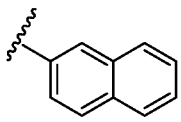
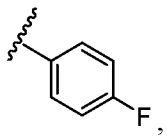
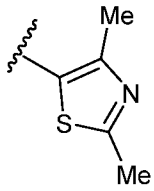
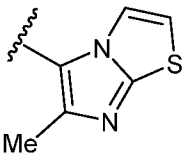
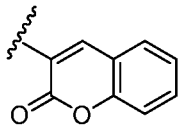
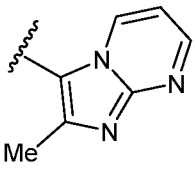
38. The compound of claim 37, herein R^1 and R^2 are independently hydrogen, (C_1-C_4)alkyl, or phenyl which is optionally substituted with F, Cl, Br, or (C_1-C_4)alkyl.

39. The compound of claim 37, wherein R^1 and R^2 attached to nitrogen join together to form .

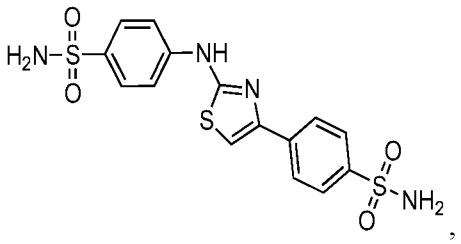
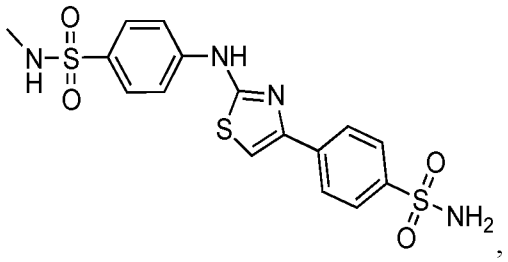
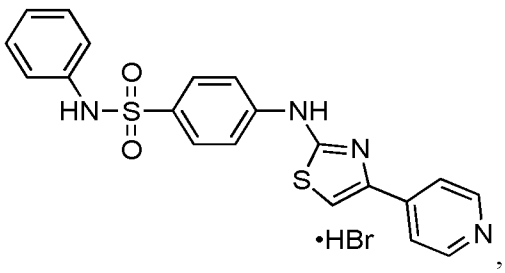
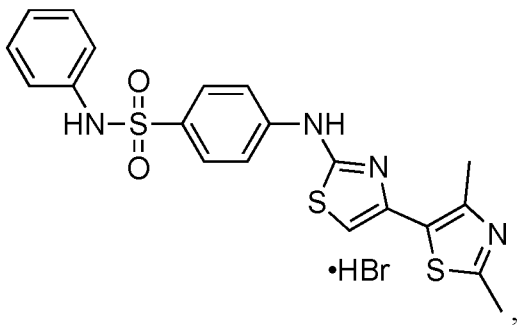
40. The compound of any one of claims 37-39, wherein R^3 is hydrogen, or –CH_2-OH.

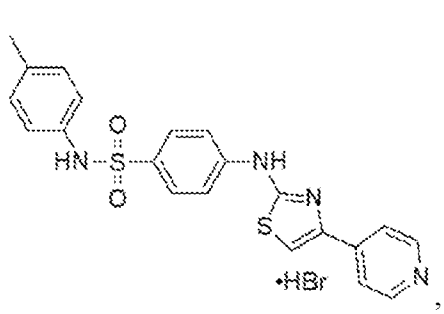
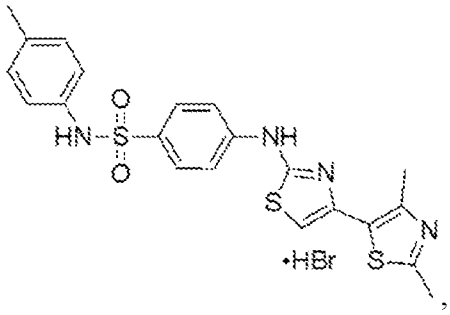
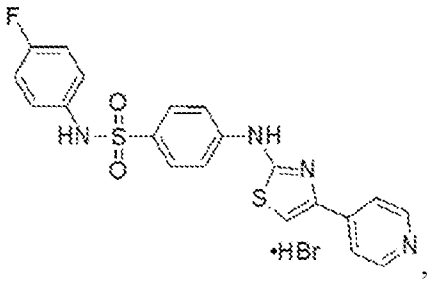
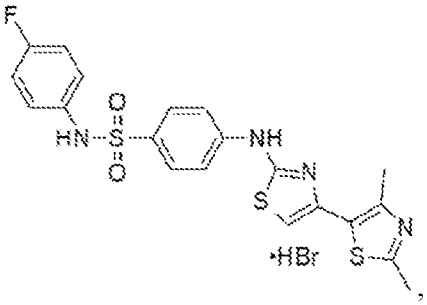
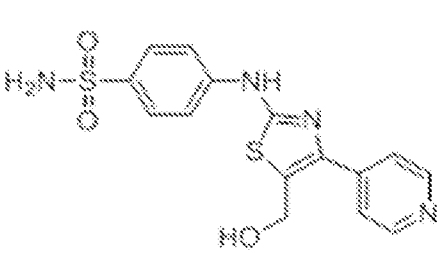
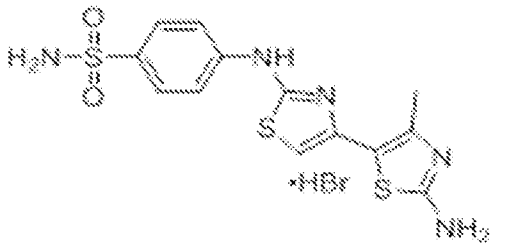
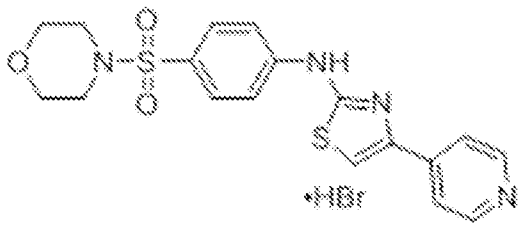
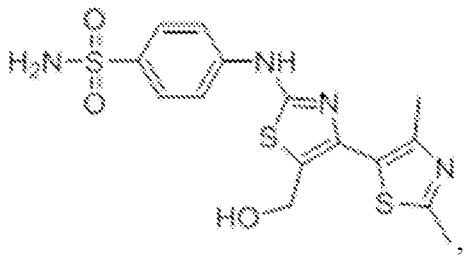
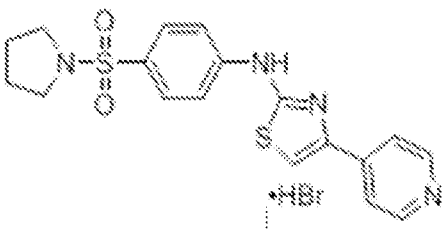
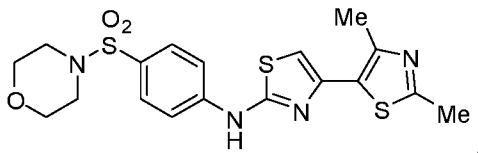
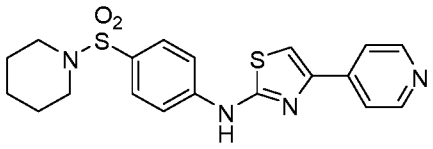
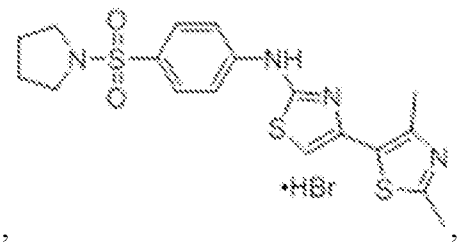
41. The compound of any one of claims 37-40, wherein the compound has the formula of:

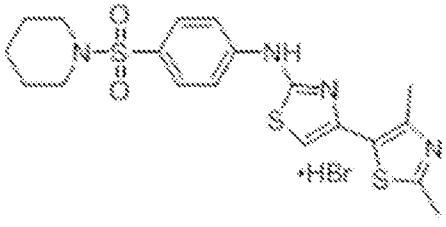
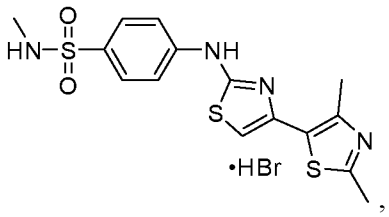
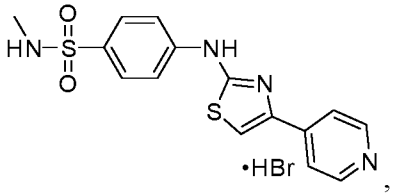
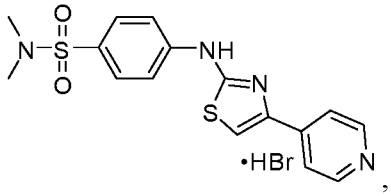
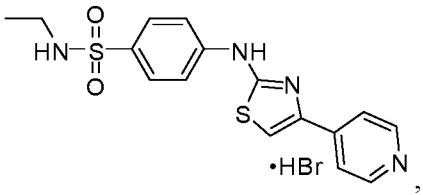
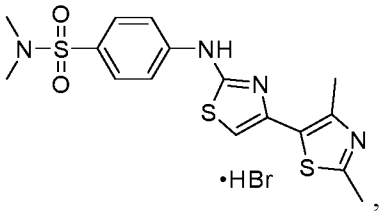
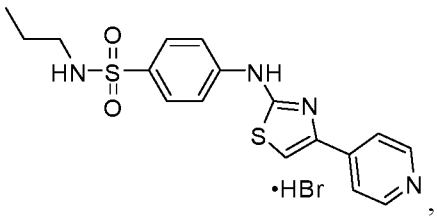
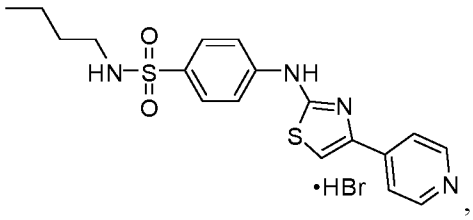
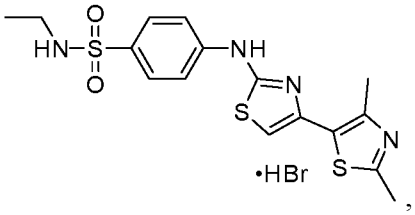
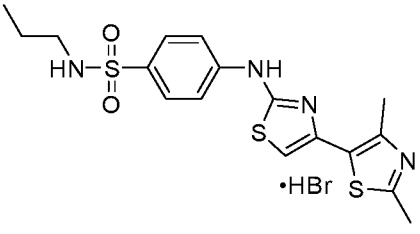
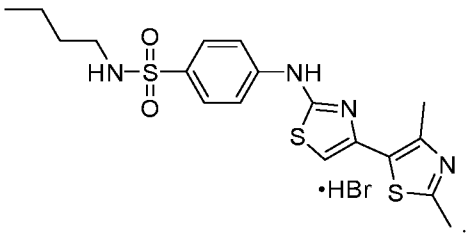

(V-a) or

(V-b).

42. The compounds of any one of claims 37-41, wherein Ar is , , , , , , , , , , , or .

43. The compound of claim 37, wherein the compound is selected from:

,
,
,
,


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, and

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44. A pharmaceutical composition comprising a compound of any one of claims 14 to 43.

Figure 1

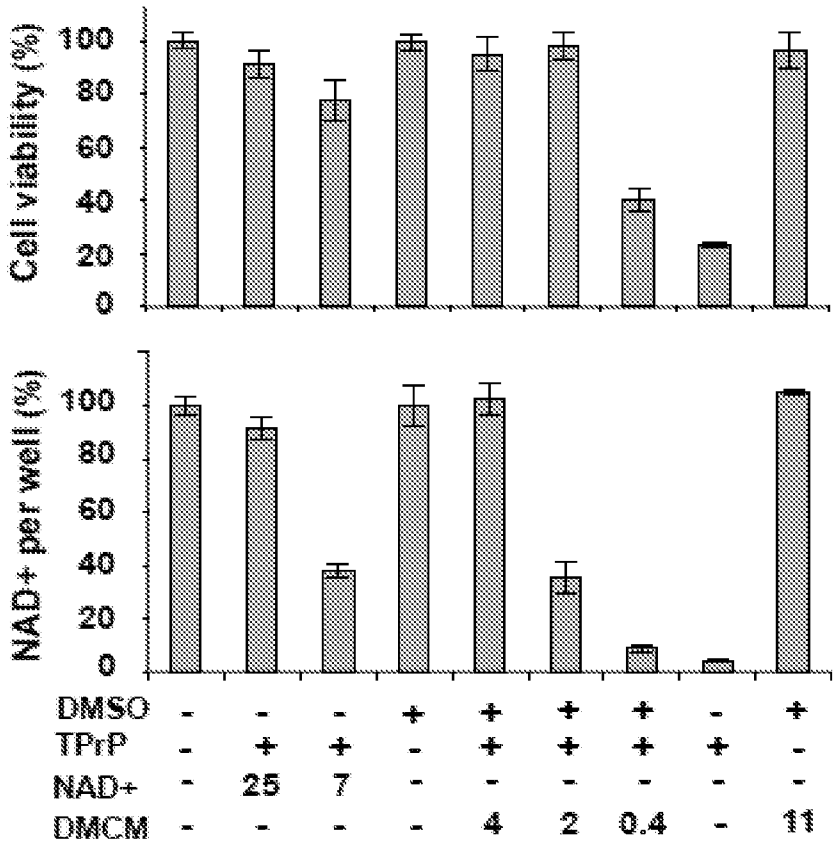
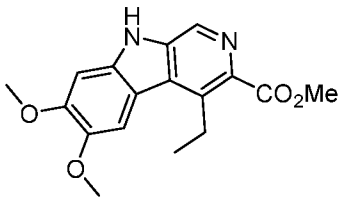

Cell viability (%)
100
80
60
40
20
0
NAD+ per well (%)
100
80
60
40
20
0
DMSO - - - + + + + - +
TPrP - + + - + + + + -
NAD+ - 25 7 - - - - - -
DMCM - - - - 4 2 0.4 - 11

Figure 2A

carbazoles (e.g., DMCM)



SR1-75869
Mol Wt. = 314
cLogP = 2.2
HBD = 1
HBA = 4
tPSA = 69

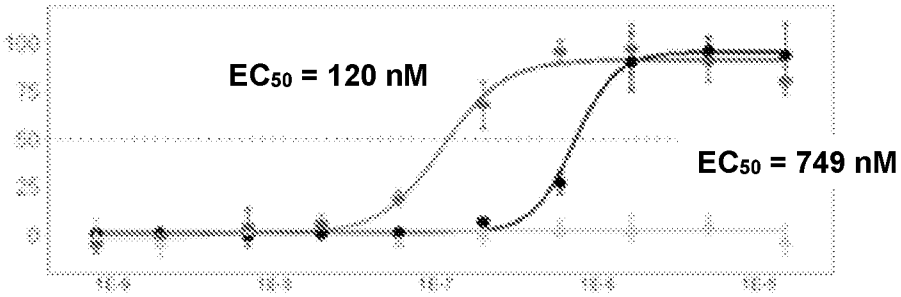
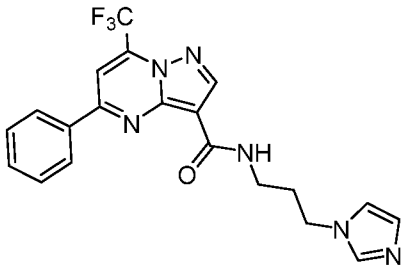


Figure 2B

pyrazolopyrimidines



SR1-293229
Mol Wt. = 414
cLogP = 3.0
HBD = 1
HBA = 4
tPSA = 73

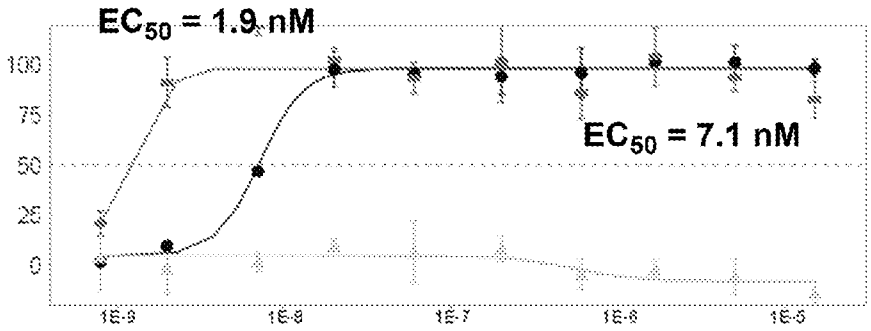
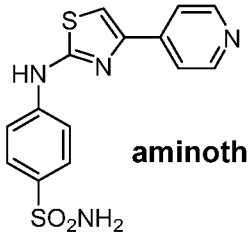


Figure 2C



SR1-477186
Mol Wt. = 332
cLogP = 2.7
HBD = 3
HBA = 4
tPSA = 97

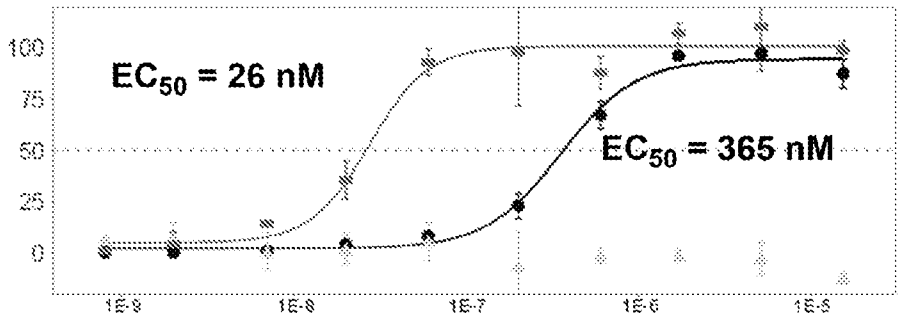


Figure 2D



SR1-115259
Mol Wt. = 426
cLogP = 2.9
HBD = 2
HBA = 6
tPSA = 107

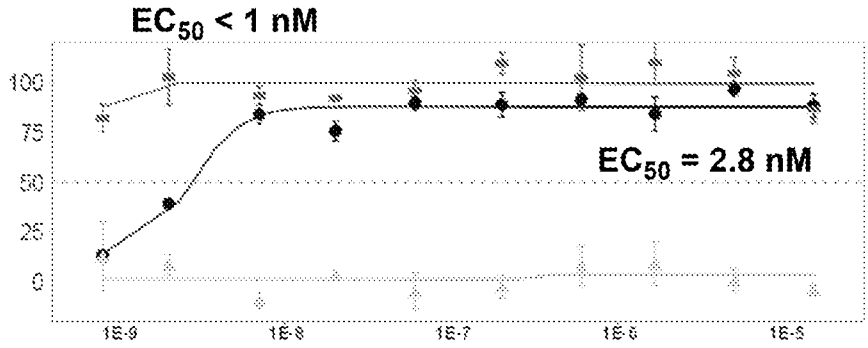
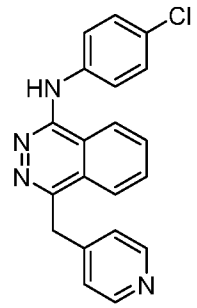


Figure 2E

aminophthalazines (e.g., vatalanib)



SR5-1457
aka vatalanib
Mol Wt. = 347
cLogP = 4.7
HBD = 1
HBA = 3
tPSA = 49

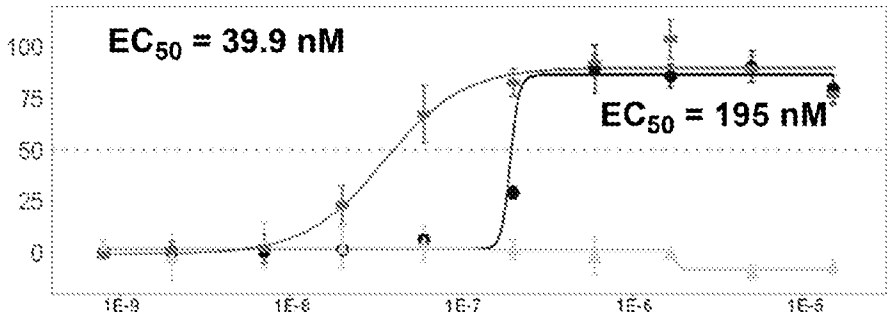
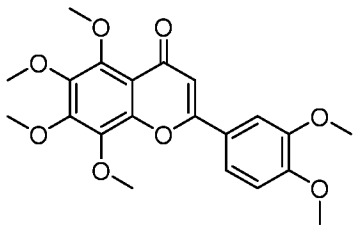


Figure 2F

flavonoids
(e.g., nobiletin)



SR1-712262
aka nobiletin
Mol Wt. = 402
cLogP = 2.1
HBD = 0
HBA = 8
tPSA = 82

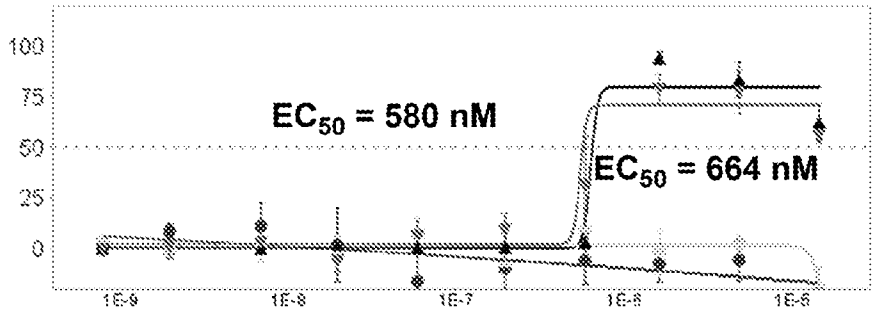


Figure 2G

Alkaloids (e.g., palmatine chloride)

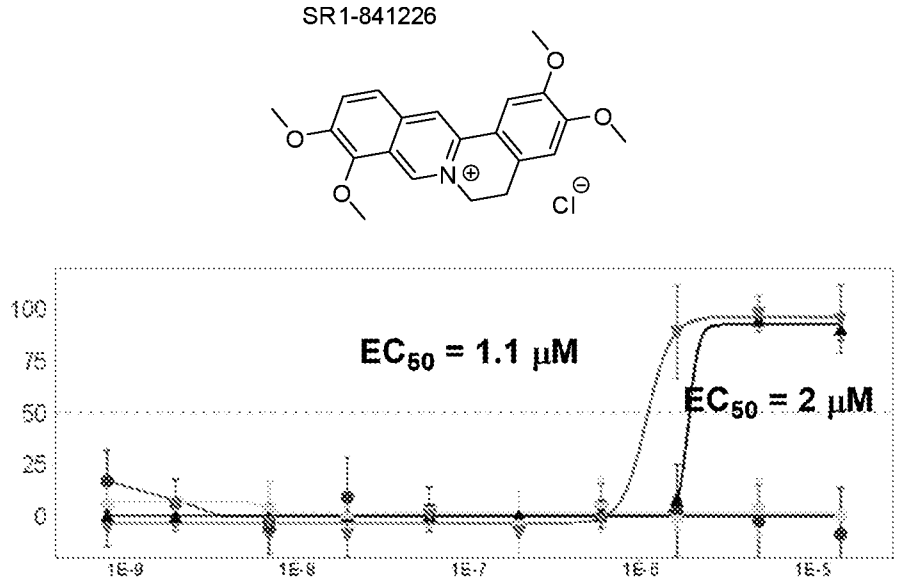
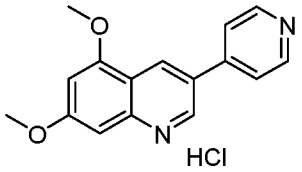


Figure 2H

3-heteroaryl quinolines (e.g. DMPQ)



SR1-597957
aka DMPQ HCl
Mol Wt. = 266 (free base)
cLogP = 3.1
HBD = 0
HBA = 4
tPSA = 43

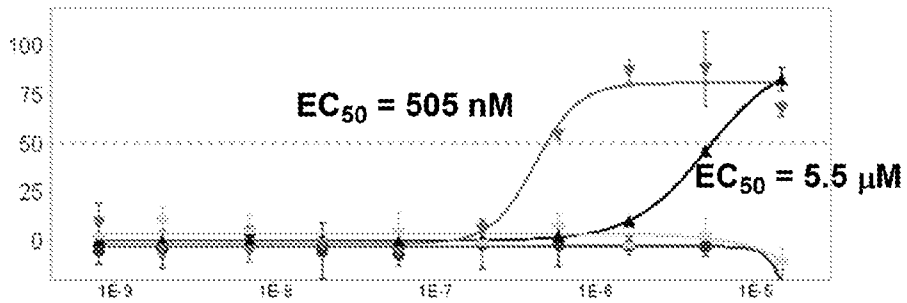


Figure 3

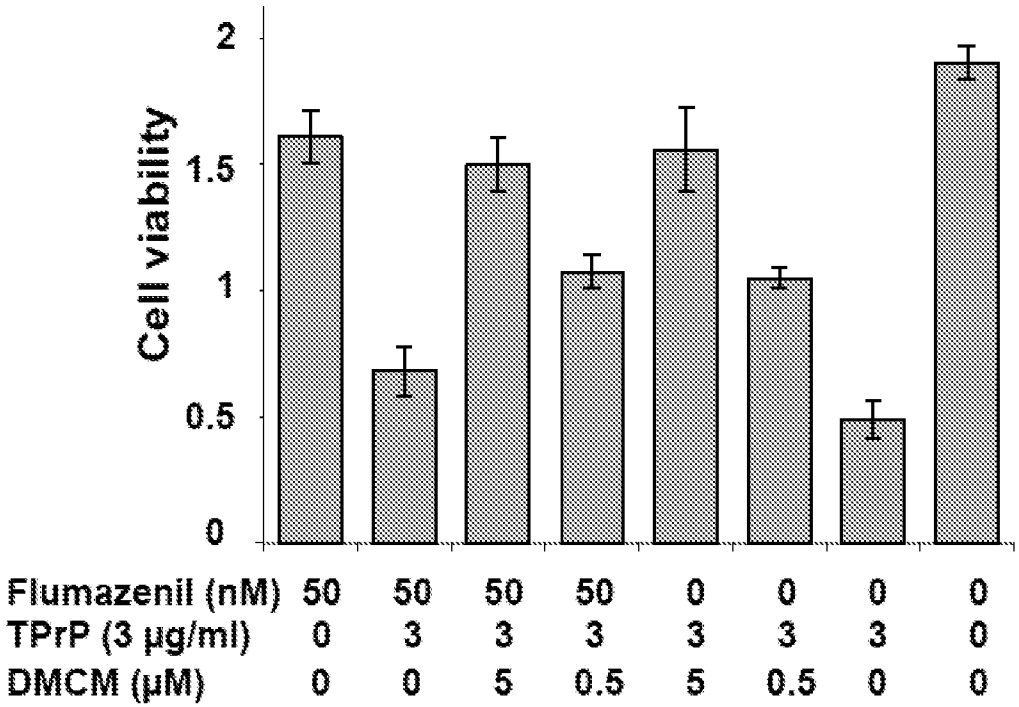
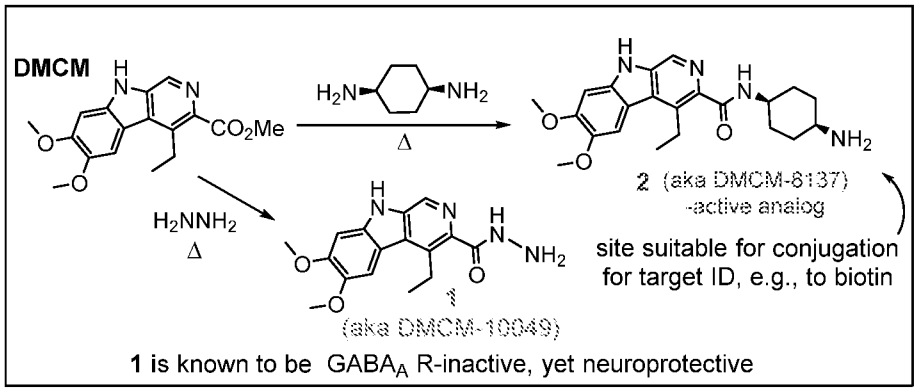

Cell viability
2
1.5
1
0.5
0
Flumazenil (nM) 50 50 50 50 0 0 0 0
TPrP (3 µg/ml) 0 3 3 3 3 3 3 0
DMCM (µM) 0 0 5 0.5 5 0.5 0 0

Figure 4


DMCM
CO_2Me
H_2N
NH_2
Δ
2 (aka DMCM-8137)
-active analog
H_2NNH_2
Δ
site suitable for conjugation
for target ID, e.g., to biotin
1
(aka DMCM-10049)
1 is known to be $GABA_A$ R-inactive, yet neuroprotective

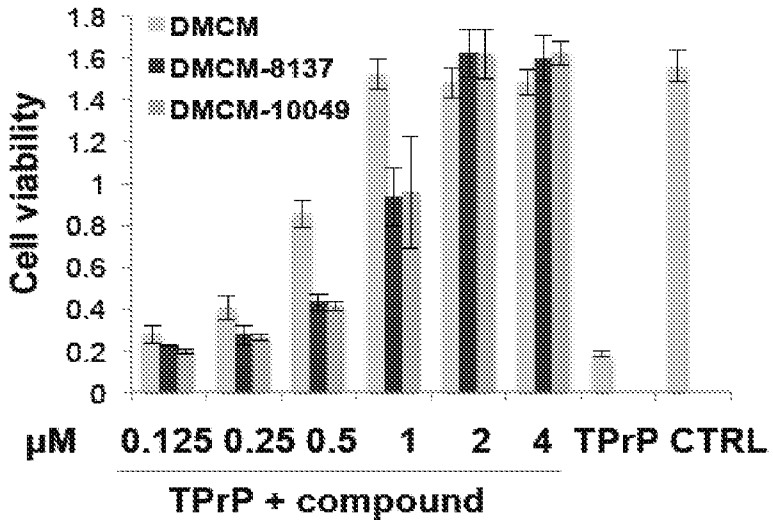

DMCM
DMCM-8137
DMCM-10049
Cell viability
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
μM 0.125 0.25 0.5 1 2 4 TPrP CTRL
TPrP + compound

Figure 5

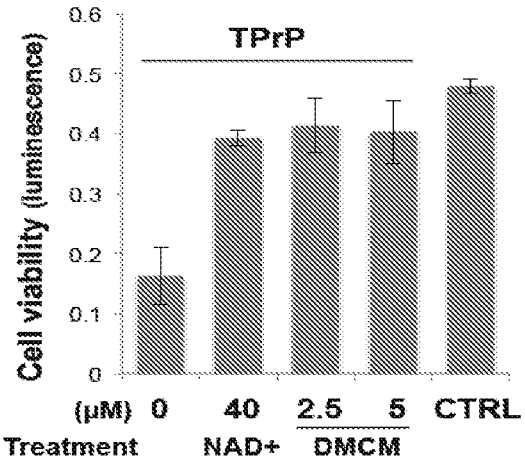


Figure 6

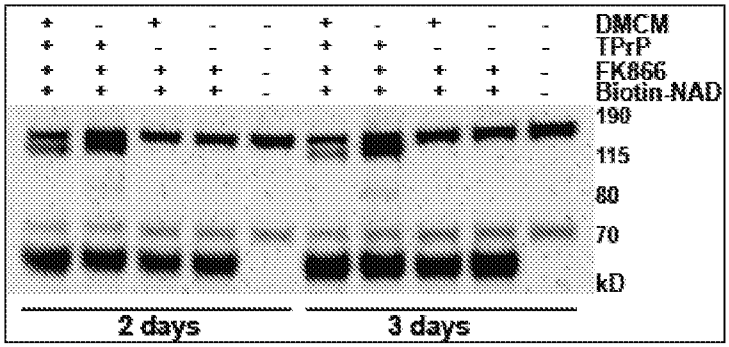


Figure 7

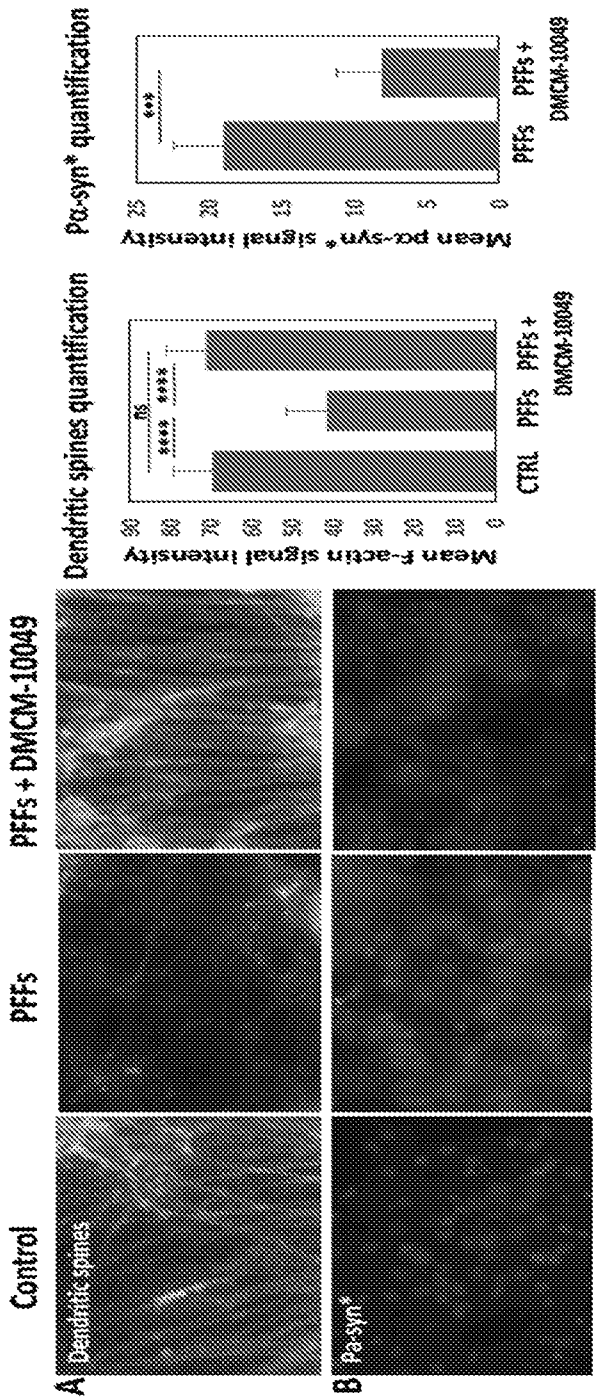

Control
PFFs
PFFs + DMCM-10049
A
Dendritic spines
B
Pα-syn*
Dendritic spines quantification
Mean f-actin signal intensity
ns
****
****
CTRL
PFFs
PFFs + DMCM-10049
Pα-syn* quantification
Mean pα-syn* signal intensity
***
PFFs
PFFs + DMCM-10049

Figure 8

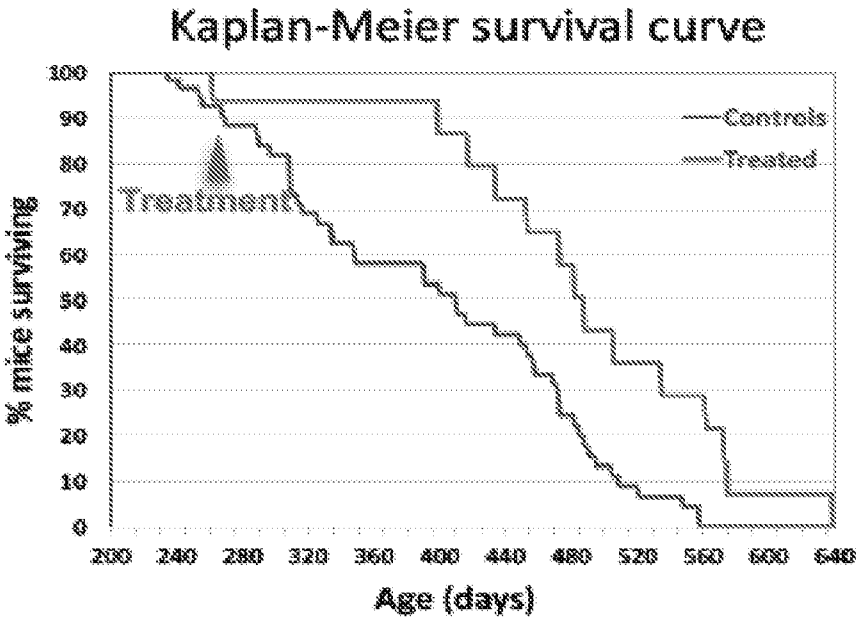


Figure 9

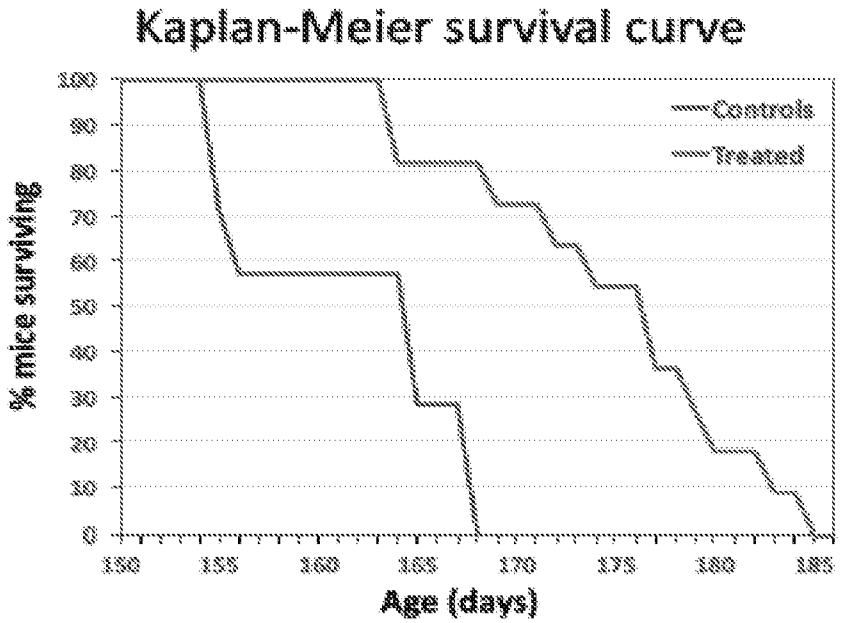


Figure 10

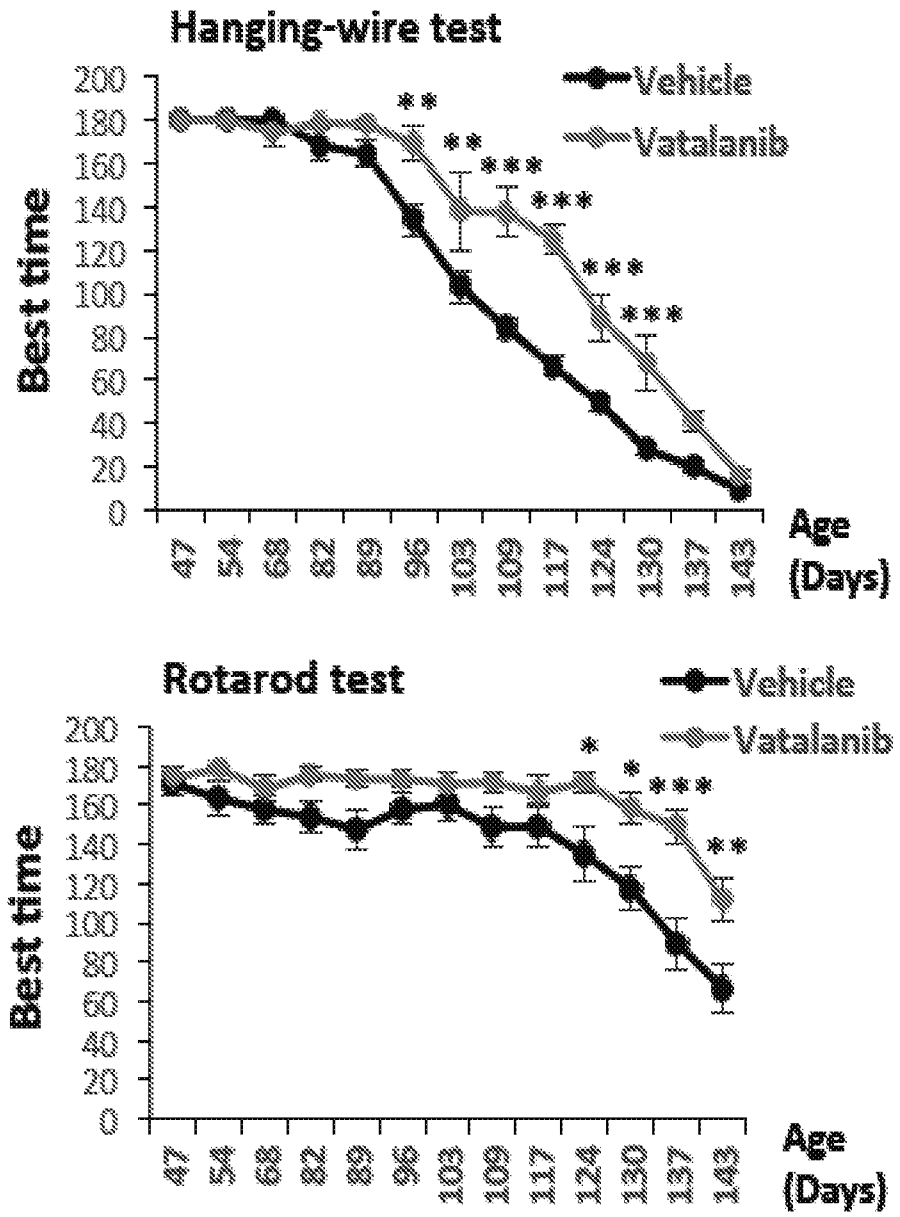
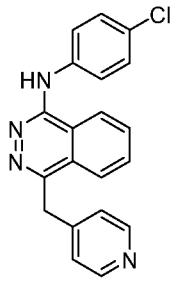
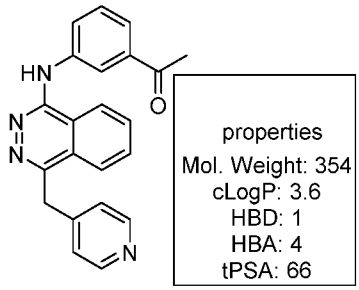

Hanging-wire test
Vehicle
Vatalanib
Best time
Age (Days)
Rotarod test
Vehicle
Vatalanib
Best time
Age (Days)

Figure 11

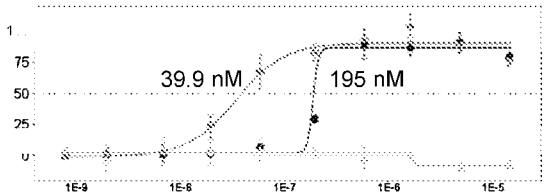


CGP 79787 / vatalanib
VEGF-R activity:
IC_{50} = 77 nM (Flt-1), 37 nM (KDR)

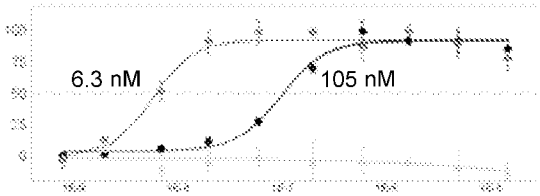


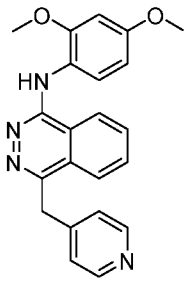
example 70A in WO9835958A1
VEGF-R activity
IC_{50} = 1.0 μM (Flt-1)

SR5-1457
neuroprotective activity IC_{50} = 39.9 nM
NAD restoration IC_{50} = 195 nM

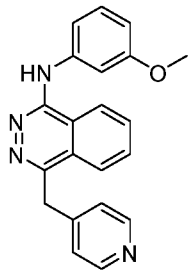


SR1-134005
neuroprotective activity IC_{50} = 6.3 nM
NAD restoration IC_{50} = 105 nM



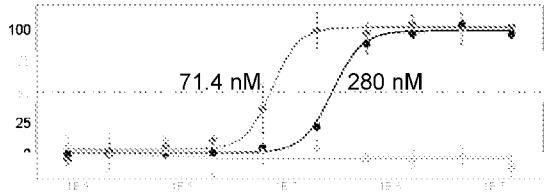


example 67T in WO9835958A1
VEGF-R activity
IC_{50} >1 μM (Flt-1)



example 32F in WO9835958A1
VEGF-R activity
IC_{50} = 793 nM (Flt-1)

SR1-151915
neuroprotective activity IC_{50} = 71.4 nM
NAD restoration IC_{50} = 280 nM



SR1-151911
neuroprotective activity
44% @ 6.4 μM

Figure 12

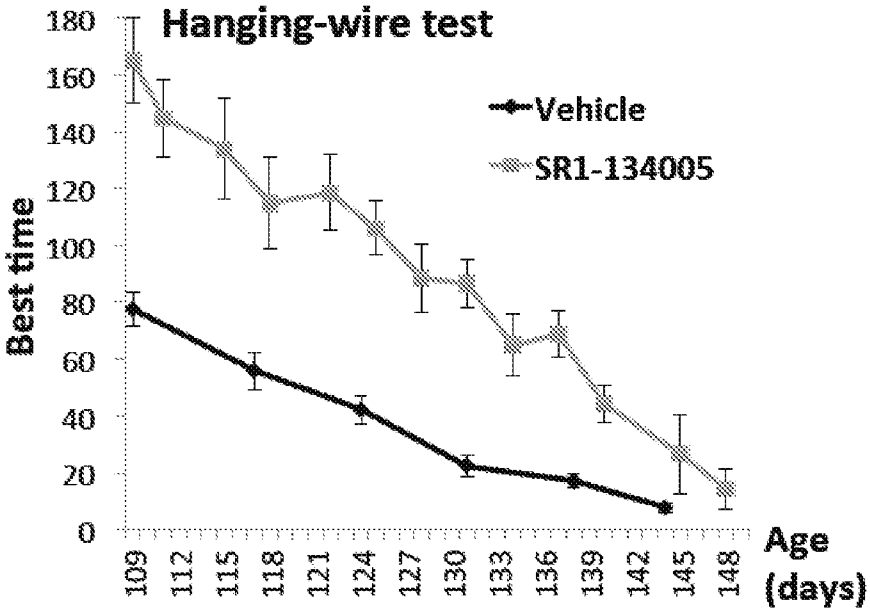


Figure 13

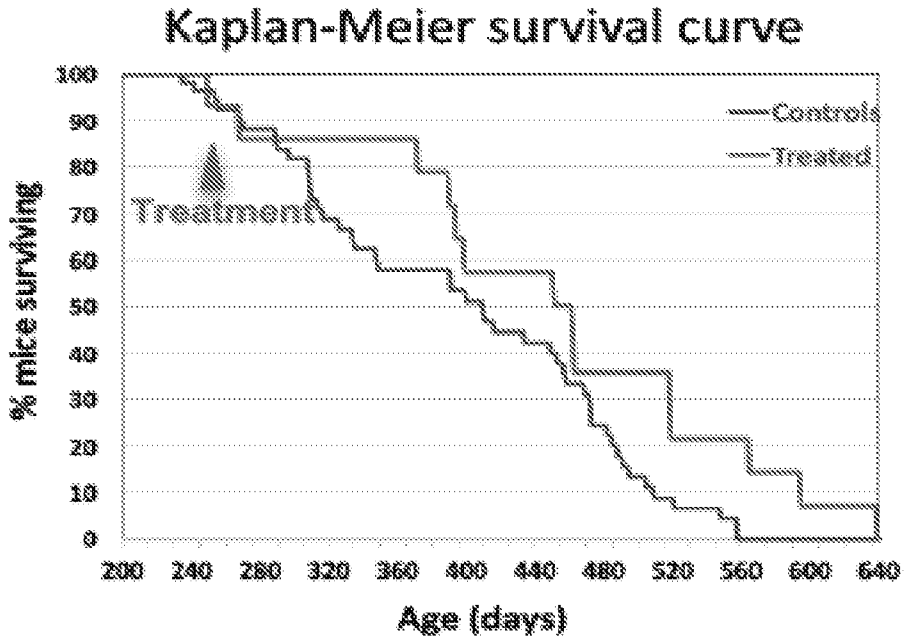


Figure 14

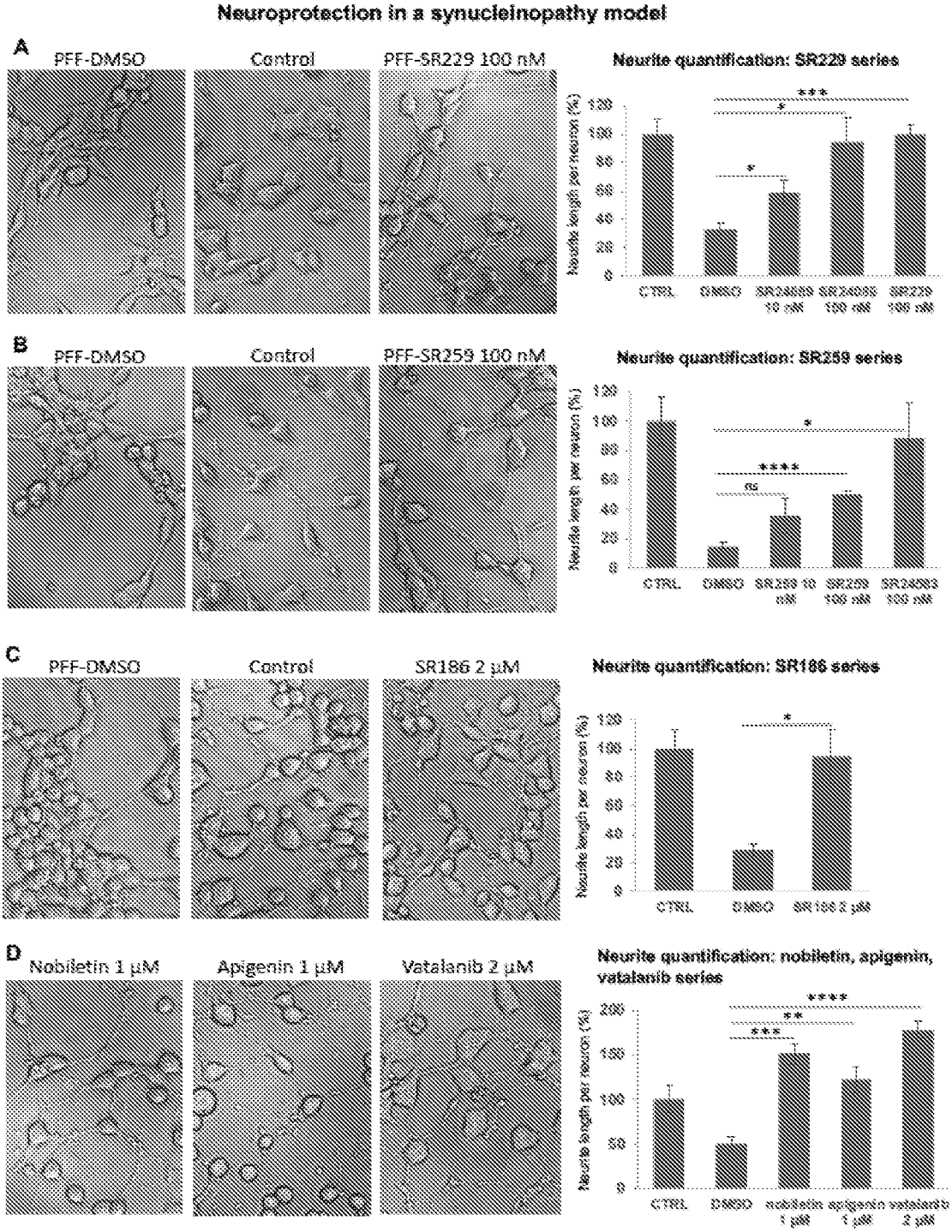

Neuroprotection in a synucleinopathy model
A
PFF-DMSO
Control
PFF-SR229 100 nM
Neurite quantification: SR229 series
Neurite length per neuron (%)
CTRL
DMSO
B
PFF-DMSO
Control
PFF-SR259 100 nM
Neurite quantification: SR259 series
Neurite length per neuron (%)
CTRL
DMSO
C
PFF-DMSO
Control
SR186 2 µM
Neurite quantification: SR186 series
Neurite length per neuron (%)
CTRL
DMSO
SR186 2 µM
D
Nobiletin 1 µM
Apigenin 1 µM
Vatalanib 2 µM
Neurite quantification: nobiletin, apigenin, vatalanib series
Neurite length per neuron (%)
CTRL
DMSO

Figure 15

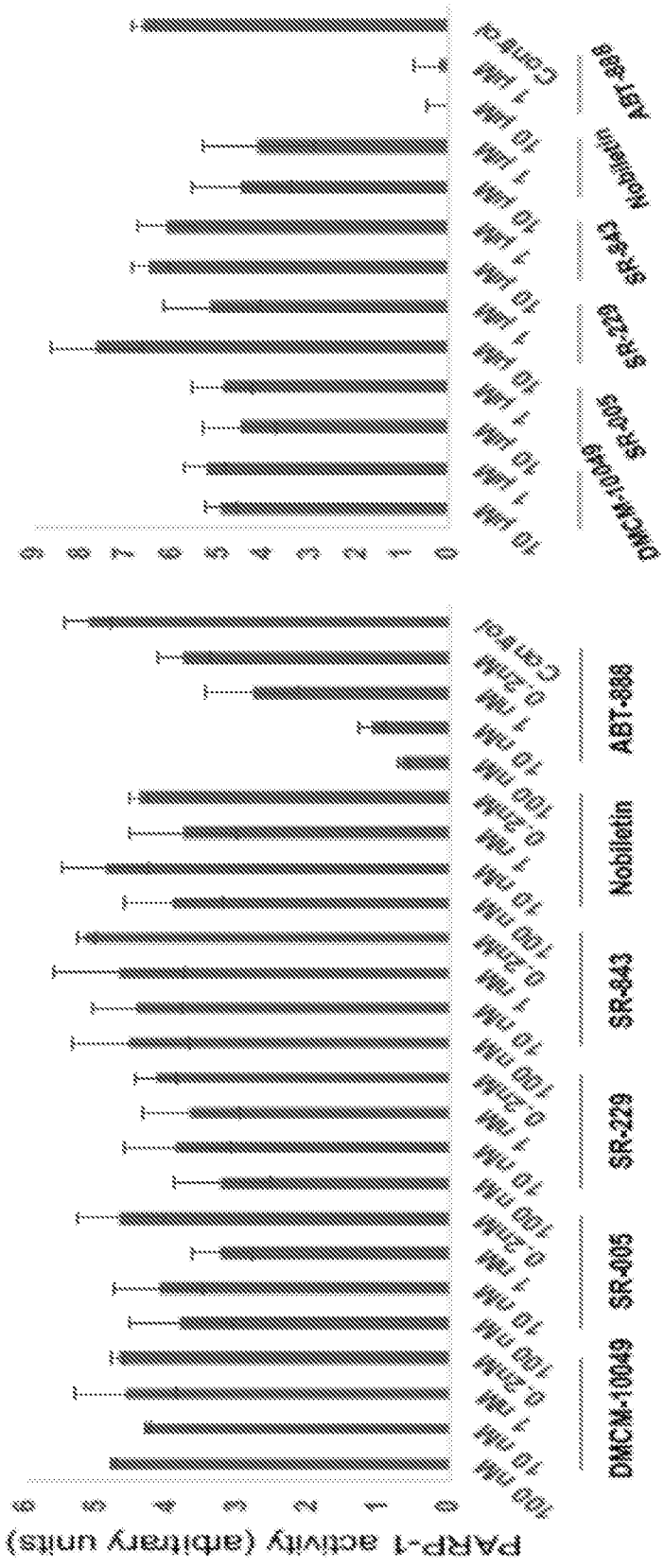
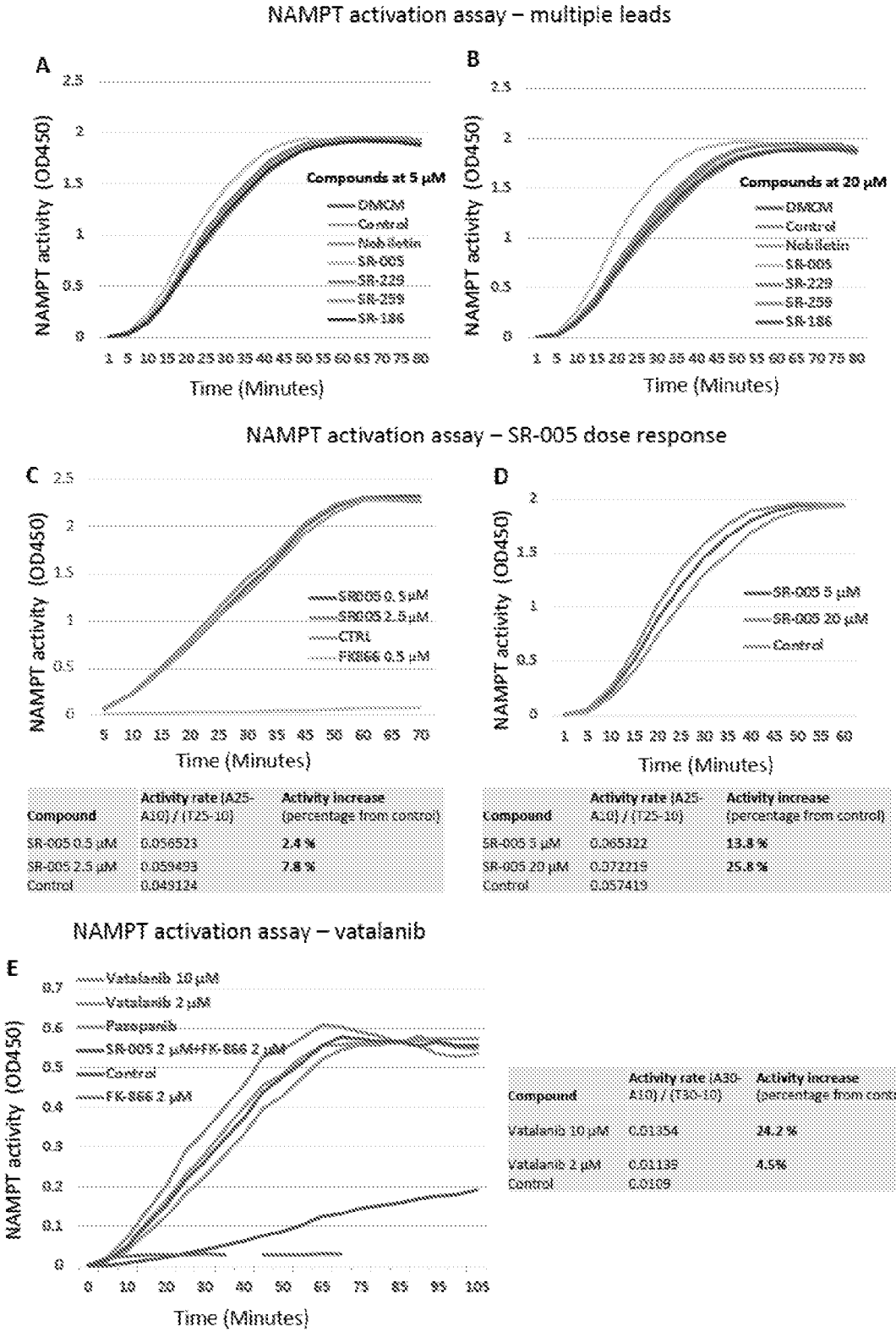

PARP-1 activity (arbitrary units)
0
1
2
3
4
5
6
7
8
9
DMCM-10049
SR-405
SR-229
SR-843
Nobiletin
ABT-888
100 nM
10 nM
1 nM
0.25nM
100 nM
10 nM
1 nM
0.25nM
100 nM
10 nM
1 nM
0.25nM
100 nM
10 nM
1 nM
0.25nM
100 nM
10 nM
1 nM
0.25nM
Control
DMCM-10049
SR-405
SR-229
SR-843
Nobiletin
ABT-888
10 nM
1 nM
10 nM
1 nM
10 nM
1 nM
10 nM
1 nM
10 nM
1 nM
10 nM
1 nM
Control

Figure 16



Compound	Activity rate (A25-A10) / (T25-10)	Activity increase (percentage from control)
SR-005 0.5 µM	0.056523	2.4 %
SR-005 2.5 µM	0.059493	7.8 %
Control	0.049134	

Compound	Activity rate (A25-A10) / (T25-10)	Activity increase (percentage from control)
SR-005 5 µM	0.065322	13.8 %
SR-005 20 µM	0.072219	25.8 %
Control	0.057419	

Compound	Activity rate (A30-A10) / (T30-10)	Activity increase (percentage from control)
Vatalanib 10 µM	0.01354	24.2 %
Vatalanib 2 µM	0.01139	4.5%
Control	0.0109	

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2020/032903

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/352 A61K31/426 A61K31/437 A61K31/4709 A61K31/473
A61K31/502 A61K31/5025 A61K31/519 C07D215/00 C07D277/00
A61P3/00 A61P25/28 A61P43/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K C07D A61P

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2017/160864 A1 (UNIV TEXAS [US]) 21 September 2017 (2017-09-21) page 1, lines 5-7 page 2, lines 1-25 claims 1, 3, 5, 16, 18, 19	1-13
A	WO 2006/003147 A1 (JANSSEN PHARMACEUTICA NV [BE]; MEVELLEC LAURENCE ANNE [FR] ET AL.) 12 January 2006 (2006-01-12) page 6, line 29 - page 8, line 20	1-13
A	WO 2017/015660 A1 (SALK INST FOR BIOLOGICAL STUDI [US]) 26 January 2017 (2017-01-26) claim 11	1-13

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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

"E" earlier application or patent but published on or after the international filing date

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 August 2020	26/10/2020

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Collins, Sally

1

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2020/032903

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	LUNDIN A ET AL: "Two novel fusion inhibitors of human respiratory syncytial virus", ANTIVIRAL RESEARCH, ELSEVIER BV, NL, vol. 88, no. 3, 1 December 2010 (2010-12-01), pages 317-324, XP027509945, ISSN: 0166-3542, DOI: 10.1016/J.ANTIVIRAL.2010.10.004 [retrieved on 2010-11-20] page 320; table 1 -----	1-13

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2020/032903

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

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

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-13(partially)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-13(partially)

   Compounds of formula (I) for use in the prevention or treatment of diseases influenced by NAD synthesis, consumption, depletion or metabolism.

   ---

2. claims: 14-25(completely); 1-13, 44(partially)

   Compounds of formula (II) and their use in the prevention or treatment of diseases influenced by NAD synthesis, consumption, depletion or metabolism.

   ---

3. claims: 26-30(completely); 1-13, 44(partially)

   Compounds of formula (III) and their use in the prevention or treatment of diseases influenced by NAD synthesis, consumption, depletion or metabolism.

   ---

4. claims: 31-36(completely); 1-13, 44(partially)

   Compounds of formula (IV) and their use in the prevention or treatment of diseases influenced by NAD synthesis, consumption, depletion or metabolism.

   ---

5. claims: 37-43(completely); 1-13, 44(partially)

   Compounds of formula (V) and their use in the prevention or treatment of diseases influenced by NAD synthesis, consumption, depletion or metabolism.

   ---

6. claims: 1-13(partially)

   Compounds of formula (VI) for use in the prevention or treatment of diseases influenced by NAD synthesis, consumption, depletion or metabolism.

   ---

7. claims: 1-13(partially)

   Compounds of formula (VII), (VIII), (IX) or (XI) for use in the prevention or treatment of diseases influenced by NAD synthesis, consumption, depletion or metabolism.

   ---

8. claims: 1-13(partially)

   Compounds of formula (X) or (XII) for use in the prevention

or treatment of diseases influenced by NAD synthesis, consumption, depletion or metabolism.

---

9. claims: 1-13(partially)

Compounds of formula (XIII), (XIV) or (XV) for use in the prevention or treatment of diseases influenced by NAD synthesis, consumption, depletion or metabolism.

---

10. claims: 1-13(partially)

Compounds of formula (XVI)) for use in the prevention or treatment of diseases influenced by NAD synthesis, consumption, depletion or metabolism.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2020/032903

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2017160864 A1	21-09-2017	US 2019298717 A1	03-10-2019
		WO 2017160864 A1	21-09-2017
WO 2006003147 A1	12-01-2006	AR 049951 A1	20-09-2006
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		US 2015072972 A1	12-03-2015
		WO 2006003147 A1	12-01-2006
		ZA 200610774 B	25-06-2008
WO 2017015660 A1	26-01-2017	NONE	