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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
13 June 2013 (13.06.2013)

W I P O | P C T

(10) International Publication Number
WO 2013/086131 Al

(51) International Patent Classification:
C07H 15/00 (2006.01)

(21) International Application Number:
PCT/US20 12/068 163

(22) International Filing Date:
6 December 2012 (06.12.2012)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/567,328 6 December 201 1 (06. 12.201 1) US

(71) Applicant: **THE TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA** [US/US]; 3160 Chestnut Street, Suite 200, Philadelphia, PA 19104 (US).

(72) Inventors: **DeGRADO, William, F.;** 934 Carolina Street, #1, San Francisco, CA 94107 (US). **WANG, Jizhou;** 1716 Osprey Drive, Eagleville, PA 19403 (US). **WANG, Jun;** 3925 Pine Street, #3R, Philadelphia, PA 19104 (US). **JO, Hyunil;** 1000 Conestoga Road, C-151, Bryn Mawr, PA 19010 (US). **CANTURK, Belgin;** 12 Fawn Hollow Road, Burlington, NJ 0801 6 (US).

(74) Agents: **CALDWELL, John W.** et al; Woodcock Washburn LLP, Cira Centre, 12th Floor, 2929 Arch Street, Philadelphia, PA 19104-289 1 (US).

(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, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, 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, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, 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, 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, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

WO 2013/086131 A1

(54) Title: INHIBITORS TARGETING DRUG-RESISTANT INFLUENZA A

(57) Abstract: Provided are compounds according to formula (la) or (lb) as described herein, that are capable of modulating the activity of influenza viruses *(e.g.,* influenza A virus), for example, via interaction with the M2 transmembrane protein, and other similar viroporins. Also provided are methods for treating an influenza A-affected disease state or infection comprising administering a composition comprising one or more compounds according to according to formulas (la') or (lb), as described herein.

INHIBITORS TARGETING DRUG-RESISTANT INFLUENZA A

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] The present application claims the benefit of U.S. Provisional App. No. 61/567,328, filed December 6, 2011 and U.S. Provisional App. No. 61/705,310, filed September 25, 2012, the entire contents of both of which are hereby incorporated by reference.

GOVERNMENT RIGHTS

[0002] Research leading to the disclosed invention was funded, in part, by the U.S. National Institutes of Health, Bethesda, Maryland, GM56423 **and** AI74571 (both to William F. DeGrado). Accordingly, the United States Government may have rights in the invention described herein.

TECHNICAL FIELD

[0003] The present invention relates, in part, to methods of treatment, prevention, and inhibition of viral disorders. In one aspect, the present invention relates to inhibition of the M2 proton channel of influenza viruses (e.g., influenza A virus and/or influenza B virus) and other similar viroporins *(e.g.,* VP24 of Ebola and Marburg viruses; and NS3 protein of Bluetongue). The present invention further relates to compounds which have been shown to possess antiviral activity, in particular, inhibiting the M2 proton channel *(e.g.,* wild type and/or drug resistant influenza such as S31N or V27A influenza or other drug-resistant influenza strains) of influenza viruses and other similar viroporins.

BACKGROUND

[0004] Viroporins are a growing class of membrane proteins that are important for viral replication and packaging. These proteins also affect cellular functions, including the cell vesicle system, glycoprotein trafficking and membrane permeability *(Gonzalez et al., FEBS Lett., 2003, 552, 28-34).* The M2 proton channel is a prototype for this class of proteins that is essential

to the survival of the virus *{Lamb et al., Wimmer E, editor, Receptor-Mediated Virus Entry into Cells, Cold Spring Harbor, N.Y., Cold Spring Harbor Press, 1994, p. 303-321).*

[0005] Viroporins are essential components of a variety of viruses including Ebola, Marburg, Bluetongue, African horse sickness, foot and mouth disease, and Japanese encephalitis viruses. In particular, Ebola and Marburg viruses pose a particularly serious threat to human health and are classified as category A biowarfare agents by the Center for Disease Control (CDC) *(Khan et al., MMWR, 2000, 49, RR-4, 1-14).* VP24 from Ebola and Marburg viruses is an integral membrane protein that possesses viroporin activity similar to the M2 protein *(Han et al., J. Virology, 2003, 77(3), 793-800).* NS3 protein of Bluetongue is a viroporin that is critical for virus release *(Han et al., J. Biol. Chem., 2004, 279, 41, 43092-43097).* In addition, picronaviruses *(Gonzalez et al, FEBS Lett., 2003, 552, 28-34),* African horse sickness, and Japanese encephalitis encode proteins with viroporin activity that play central roles in viral pathogenesis *(Van Niekerk et al., Virology, 2001, 279, 499-508; Chang et al., J. Virol., 1999, 73(8), 6257-6264).*

[0006] Influenza viruses infect the upper and lower respiratory tracts and cause substantial morbidity and mortality annually. Influenza A viruses, which also infect a wide number of avian and mammalian species, pose a considerable public health burden with epidemic and pandemic potential. Influenza together with complications of the virus is consistently among the top 10 common causes of death, ranking higher than some other much more widely publicized killers, such as the HIV virus that causes AIDS. It is estimated that in annual influenza epidemics, 5-15% of the world's population contracts influenza, resulting in an estimated 3-5 million cases of severe illness and 250,000 to 500,000 deaths around the world from influenza-associated complications. In the U.S., 10%-20% of the population is infected with the flu every year, with an average 0.1% mortality. The flu causes 36,000 deaths each year in the U.S., and 114,000 hospitalizations. The cost of influenza epidemics to the U.S. economy is estimated at $3-15 billion. Approximately 20% to 40% of the world's population became ill during the catastrophic "Spanish" flu pandemic in 1918, which killed an estimated 40 to 50 million people worldwide and 675,000 people in the United States. The "Asian" flu pandemic of 1957 resulted in the deaths of approximately 69,800 people in the United States and 2.0 to 7.4 million worldwide. The H1N1 swine flu pandemic in 2009 has caused about 3,000 deaths worldwide to date.

[0007] Tamiflu (oseltamivir), which targets neuraminidase protein, is the only remaining orally administered anti-flu drug on the market and resistance to the drug is increasing with oseltamivir-resistant viruses arising during clinical use of the drug in children *(Kiso et al., Lancet, 2004, 364, 759-65).* Oseltamivir has been used for treatment of infected individuals and although it is FDA-approved for prophylaxis its usefulness for prophylactic treatment has been questioned in a recent systematic analysis of data from 51 controlled trials *(Jefferson et al., Lancet, 2006, 367, 303-13).* Thus, there is an immediate need to develop additional agents that inhibit the M2 proton channel and its drug-resistant forms, and in particular the most prevalent mutant form, S31N, but also in others including L26, V27, A30, and G34.

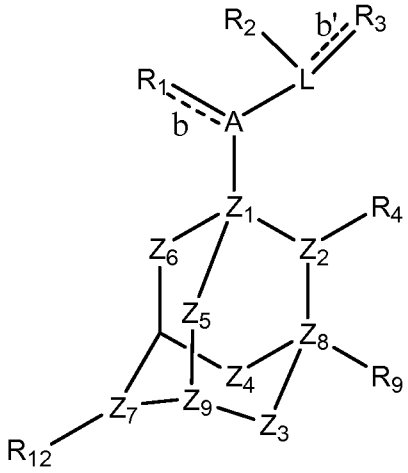
[0008] Influenza A and B viruses each encode a small oligomeric integral membrane protein, M2 of influenza A virus and BM2 of influenza B virus, each of which is a proton-selective ion channel. The M2 protein plays an important role during the early and late stages of the viral life cycle. Early in the cycle, the virus enters cells by receptor-mediated endocytosis, which places the virus into endosomal vesicles. Proton-pumping ATP-ases in the endosomal membrane lower the internal pH, which triggers the fusion of the viral envelope with the endosomal membrane and the release of the viral RNA into the cytoplasm. However, unless the inside of the virus is acidified prior to fusion, the RNA remains encapsulated by a matrix protein known as M1 *(Ito et al., J. Virol., 1981, 65, 5491-8).* The M2 protein provides a conduit for passage of protons into the interior of the virus, thereby promoting the dissociation of RNA from its matrix protein. This is a crucial step in uncoating of the virus and exposing its content to the cytoplasm of the host cell. In some strains of influenza A virus, the M2 protein is also important for equilibrating the pH of the lumen of the Golgi apparatus with the cytoplasm, thus preventing a premature conformational change in the viral hemagglutinin at the wrong time and in the wrong place *(Ciampor et al., Acta Virologica, 1995, 39, 171-181).* Inhibition of M2 at this later stage of the viral life cycle prevents viral maturation and release from the host cell.

[0009] Several features make M2 an excellent target for an anti-influenza drug. It is essential and present in all known isolates of influenza A virus, and it is already validated as a drug target. Although a variety of mutations occur naturally and can be isolated in cell culture, one mutant in particular, S31N, predominates in more than 98% of the transmissible resistant viral strains isolated from patients in the last decade *(Bright et al, Lancet, 2005, 366, 1175-1181).*

[0010] Thus, there is a great need for additional compositions and methods of treatment based on the use of antiviral compounds against key viral pathogens and, optionally, less prone to the development of resistance by those pathogens. Moreover, there is a great need for additional compositions and methods of treatment based on the use of antiviral compounds that are effective in the treatment of viral pathogens that have already developed resistance to existing antiviral agents. In particular, there is a great need for effective compositions and methods for the treatment of viral infections such as influenza, Ebola, Marburg, bluetongue, foot and mouth disease, African horse sickness, and Japanese encephalitis (including the strains that have already developed resistance to existing antiviral agents). The present invention is directed to these and other important ends

SUMMARY

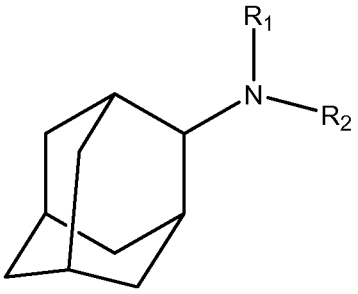
[0011] The present invention provides, in part, compounds according to formula (la):



(Ia)

or a stereoisomer, isotopically substituted analogue, or pharmaceutically acceptable salt thereof, wherein each of the variable groups are as defined herein.

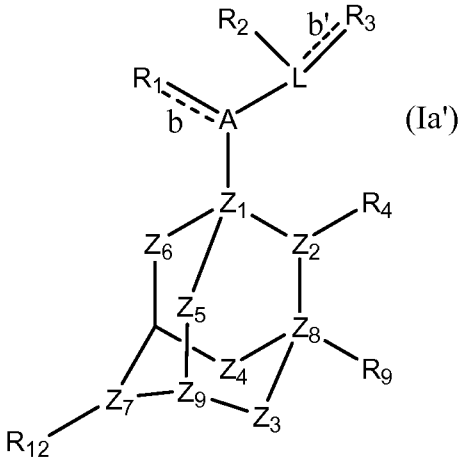
[0012] The present disclosure also pertains to compounds according to formula (lb):



(Ib)

or a stereoisomer, isotopically substituted analogue, or pharmaceutically acceptable salt thereof, wherein Ri and R_2 are as defined herein.

[0013] Also disclosed are compounds according to formula (la'):



or a stereoisomer, isotopically substituted analogue, or pharmaceutically acceptable salt thereof, wherein each of the variable groups are as defined herein.

[0014] The present invention is also directed to methods for treating a viral infection, such as influenza (e.g., wild-type influenza, such as wild-type influenza A or B, or one or more mutant varieties of influenza such as S3IN influenza), Ebola, Marburg, bluetongue, foot and mouth disease, African horse sickness, and Japanese encephalitis, in a patient (including a human or an animal) comprising administering to a subject in need thereof a composition comprising a compound of Formula (la), (la'), or (lb) as defined herein.

[0015] Also provided are compositions comprising a compound according to Formula (la), (la'), or (lb) or a pharmaceutically acceptable salt, isotopically substituted analogue, or stereoisomer thereof, and a pharmaceutically acceptable carrier, diluent, or excipient.

DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

[0016] The present invention may be understood more readily by reference to the following detailed description taken in connection with the accompanying figures and examples, which form a part this disclosure. It is to be understood that this invention is not limited to the specific products, methods, conditions or parameters described and/or shown herein, and that the terminology used herein is for the purpose of describing particular embodiments by way of example only and is not intended to be limiting of the claimed invention.

[0017] The disclosures of each patent, patent application, and publication cited or described in this document are hereby incorporated herein by reference, in their entirety.

[0018] As employed above and throughout the disclosure, the following terms and abbreviations, unless otherwise indicated, shall be understood to have the following meanings.

[0019] In the present disclosure the singular forms "a," "an," and "the" include the plural reference, and reference to a particular numerical value includes at least that particular value, unless the context clearly indicates otherwise. Thus, for example, a reference to "a compound" is a reference to one or more of such compounds and equivalents thereof known to those skilled in the art, and so forth. Furthermore, when indicating that a certain chemical moiety "may be" X, Y, or Z, it is not intended by such usage to exclude in all instances other choices for the moiety; for example, a statement to the effect that R_i "may be alkyl, aryl, or amino" does not necessarily exclude other choices for R_1, such as halo, aralkyl, and the like.

[0020] When values are expressed as approximations, by use of the antecedent "about," it will be understood that the particular value forms another embodiment. As used herein, "about X" (where X is a numerical value) preferably refers to ±10% of the recited value, inclusive. For example, the phrase "about 8" refers to a value of 7.2 to 8.8, inclusive; as another example, the phrase " about 8%" refers to a value of 7.2% to 8.8%, inclusive. Where present, all ranges are inclusive and combinable. For example, when a range of " 1 to 5" is recited, the recited range should be construed as including ranges " 1 to 4", " 1 to 3", "1-2", "1-2 & 4-5", "1-3 & 5", and the like. In addition, when a list of alternatives is positively provided, such listing can be interpreted to mean that any of the alternatives may be excluded, *e.g.,* by a negative limitation in the claims. For example, when a range of " 1 to 5" is recited, the recited range may be construed as including situations whereby any of 1, 2, 3, 4, or 5 are negatively excluded; thus, a recitation of " 1 to 5" may be construed as " 1 and 3-5, but not 2", or simply "wherein 2 is not included." In another example, when a listing of possible substituents including "hydrogen, alkyl, and aryl" is provided, the recited listing may be construed as including situations whereby any of "hydrogen, alkyl, and aryl" is negatively excluded; thus, a recitation of "hydrogen, alkyl, and aryl" may be construed as "hydrogen and aryl, but not alkyl", or simply "wherein the substituent is not alkyl".

[0021] As used herein, the terms "component," "composition of compounds," "compound," "drug," "pharmacologically active agent," "active agent," "therapeutic," "therapy," "treatment," or "medicament" are used interchangeably herein to refer to a compound or

compounds or composition of matter which, when administered to a subject (human or animal) induces a desired pharmacological and/or physiologic effect by local and/or systemic action.

[0022] The abbreviations in the specification correspond to units of measure, techniques, properties, or compounds as follows: "min" means minute(s), "g" means gram(s), "mg" means milligram(s), '^g" means microgram(s), "eq" means equivalent(s), "h" means hour(s), "μL" means microliter(s), "mL" means milliliter(s), "mM" means millimolar, "M" means molar, "mmol" or "mmole" means millimole(s), "cm" means centimeters, "SEM" means standard error of the mean, and "IU" means International Units. "IC_{50} value" or "IC_{50}" means dose of the compound which results in 50% alleviation or inhibition of the observed condition or effect.

[0023] As used herein, "alkyl" refers to an optionally substituted, saturated straight, or branched, hydrocarbon radical having from about 1 to about 20 carbon atoms (and all combinations and subcombinations of ranges and specific numbers of carbon atoms therein). Where appropriate, "alkyl" can mean "alkylene"; for example, if X is -R_1R_2, and Ri is said to be "alkyl", then "alkyl" may correctly be interpreted to mean "alkylene".

[0024] "Amino" refers to -NH_2 and may include one or more substituents that replace hydrogen. "Amino" is used interchangeably with amine and is also intended to include any pharmaceutically acceptable amine salts. For example, amino may refer to -$NH^+(X)(Y)C1^-$, wherein X and Y are preferably and independently hydrogen or alkyl, wherein alkyl may include one or more halo substitutions.

[0025] As used herein, "aryl", "arene", and "aromatic" each refer to an optionally substituted, saturated or unsaturated, monocyclic, polycyclic, or other homo-, carbo- or heterocyclic aromatic ring system having from about 3 to about 50 ring members (and all combinations and subcombinations of ranges and specific numbers of carbon atoms therein), with from about 5 to about 10 ring atom members being preferred. Such moieties encompass (include) "heteroaryl" and "heteroarene" as defined *infra*. Where appropriate, "aryl" can mean "arene"; for example, if X is -RiR_2, and Ri is said to be "aryl", then "aryl" may correctly be interpreted to mean "arene".

[0026] As used herein, "alkenyl" refers to an alkyl radical having from about 2 to about 20 carbon atoms and one or more double bonds (and all combinations and subcombinations of ranges and specific numbers of carbon atoms therein), wherein alkyl is as previously defined. In

some embodiments, it is preferred that the alkenyl groups have from about 2 to about 6 carbon atoms. Alkenyl groups may be optionally substituted.

[0027] As used herein, "aralkyl" refers to alkyl radicals bearing one or more aryl substituents and having from about 4 to about 50 carbon atoms (and all combinations and subcombinations of ranges and specific numbers of carbon atoms therein), wherein aryl and alkyl are as previously defined. In some preferred embodiments, the alkyl moieties of the aralkyl groups have from about 1 to about 4 carbon atoms. In other preferred embodiments, the alkyl moieties have from about 1 to about 3 carbon atoms. Aralkyl groups may be optionally substituted.

[0028] "Alkylamino" signifies alkyl-(NH)-, wherein alkyl is as previously described and NH is defined in accordance with the provided definition of amino. "Arylamino" represents aryl-(NH)-, wherein aryl is as defined herein and NH is defined in accordance with the provided definition of amino. Likewise, "aralkylamino" is used to denote aralkyl-(NH)-, wherein aralkyl is as previously defined and NH is defined in accordance with the provided definition of amino. "Alkylamido" refers to alkyl-CH(=0)NH-, wherein alkyl is as previously described. "Alkoxy" as used herein refers to the group R-O- where R is an alkyl group, and alkyl is as previously described. "Aralkoxy" stands for R-O-, wherein R is an aralkyl group as previously defined. "Alkylsulfonyl" means alkyl-$S0_2$-, wherein alkyl is as previously defined. "Aminooxy" as used herein refers to the group amino-(O)-, wherein amino is defined as above. "Aralkylaminooxy" as used herein is used to denote aryl-akyl-aminooxy-, wherein aryl, alkyl, and aminooxy are respectively defined as provided previously.

[0029] As used herein, "alkylene" refers to an optionally branched or substituted bivalent alkyl radical having the general formula $-(CH_2)_n-$, where n is 1 to 10. Non-limiting examples include methylene, trimethylene, pentamethylene, and hexamethylene.

[0030] "Alkyleneamino" refers to $-(CH_2)_n$-NH-, where n is 1 to 10 and wherein the bivalent alkyl radical may be optionally branched or substituted, and the amino group may include one or more substituents that replace hydrogen.

[0031] As used herein, "heteroaryl" or "heteroarene" refers to an aryl radical wherein in at least one of the rings, one or more of the carbon atom ring members is independently replaced by a heteroatom group selected from the group consisting of S, O, N, and NH, wherein aryl is as previously defined. Heteroaryl / heteroarene groups having a total of from about 3 to about 14

carbon atom ring members and heteroatom ring members are preferred. Likewise, a "heterocyclic ring" is an aryl radical wherein one or more of the carbon atom ring members may be (but are not necessarily) independently replaced by a heteroatom group selected from the group consisting of S, O, N, and NH. Heterocyclic rings having a total from about 3 to 14 ring members and heteroatom ring members are preferred, but not necessarily present; for example, "heterocyclohexyl" may be a six-membered aryl radical with or without a heteroatom group.

[0032] "Halo" and "halogen" each refers to a fluoro, chloro, bromo, or iodo moiety, with fluoro, chloro, or bromo being preferred.

[0033] "Haloalkyl" signifies halo-alkyl- wherein alkyl and halo, respectively, are as previously described.

[0034] The phrase reading "[moiety] is absent" may mean that the substituents to which the moiety is attached are directly attached to each other.

[0035] Typically, substituted chemical moieties include one or more substituents that replace hydrogen. Exemplary substituents include, for example, halo *(e.g.,* F, CI, Br, I), alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, aralkyl, aryl, heteroaryl, heteroaralkyl, spiroalkyl, heterocycloalkyl, hydroxyl (-OH), nitro (-N0 $_2$), cyano (-CN), amino (-NH_2), -N-substituted amino (-NHR"), -N ,N -disubstituted amino (-N(R")R"), oxo (=0), carboxy (-COOH), -0-C(=0)R", -C(=0)R", -OR", -C(=0)OR", -(alkylene)-C(=0)-OR", -NHC(=0)R", aminocarbonyl (-C(=0)NH $_2$), -N-substituted aminocarbonyl (-C(=0)NHR"), -N,N-disubstituted aminocarbonyl (-C(=0)N(R")R"), thiol, thiolato (-SR"), sulfonic acid (-S0 $_3$H), phosphonic acid (-PO_3H), -P(=0)(OR")OR", -S(=0)R", -S(=0) $_2$R", -S(=0) $_2$$NH_2$, -S(=0) $_2$ NHR", -S(=0) $_2$NR"R", -NHS(=0) $_2$R", -NR"S(=0) $_2$R", -CF_3, -CF_2CF_3, -NHC(=0)NHR", -NHC(=0)NR"R", -NR"C(=0)NHR", -NR"C(=0)NR"R", -NR"C(=0)R" and the like. In relation to the aforementioned substituents, each moiety R" can be, independently, any of H, alkyl, cycloalkyl, alkenyl, aryl, aralkyl, heteroaryl, or heterocycloalkyl, for example.

[0036] As used herein, the terms "treatment" or "therapy" (as well as different word forms thereof) includes preventative *(e.g.,* prophylactic), curative or palliative treatment.

[0037] As employed above and throughout the disclosure the term "effective amount" refers to an amount effective, at dosages, and for periods of time necessary, to achieve the desired result with respect to the treatment of the relevant disorder, condition, or side effect. It will be appreciated that the effective amount of components of the present invention will vary

from patient to patient not only with the particular compound, component or composition selected, the route of administration, and the ability of the components to elicit a desired response in the individual, but also with factors such as the disease state or severity of the condition to be alleviated, hormone levels, age, sex, weight of the individual, the state of being of the patient, and the severity of the pathological condition being treated, concurrent medication or special diets then being followed by the particular patient, and other factors which those skilled in the art will recognize, with the appropriate dosage ultimately being at the discretion of the attendant physician. Dosage regimens may be adjusted to provide the improved therapeutic response. An effective amount is also one in which any toxic or detrimental effects of the components are outweighed by the therapeutically beneficial effects. As an example, the compounds useful in the methods of the present invention are administered at a dosage and for a time such that the level of activation and adhesion activity of platelets is reduced as compared to the level of activity before the start of treatment.

[0038] "Pharmaceutically acceptable" refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem complications commensurate with a reasonable benefit/risk ratio.

[0039] Within the present invention, the disclosed compounds may be prepared in the form of pharmaceutically acceptable salts. "Pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic,

and the like. These physiologically acceptable salts are prepared by methods known in the art, *e.g.,* by dissolving the free amine bases with an excess of the acid in aqueous alcohol, or neutralizing a free carboxylic acid with an alkali metal base such as a hydroxide, or with an amine.

[0040] Compounds described herein throughout, can be used or prepared in alternate forms. For example, many amino-containing compounds can be used or prepared as an acid addition salt. Often such salts improve isolation and handling properties of the compound. For example, depending on the reagents, reaction conditions and the like, compounds as described herein can be used or prepared, for example, as their hydrochloride or tosylate salts. Isomorphic crystalline forms, all chiral and racemic forms, N-oxide, hydrates, solvates, and acid salt hydrates, are also contemplated to be within the scope of the present invention.

[0041] Certain acidic or basic compounds of the present invention may exist as zwitterions. All forms of the compounds, including free acid, free base and zwitterions, are contemplated to be within the scope of the present invention. It is well known in art that compounds containing both amino and carboxy groups often exist in equilibrium with their zwitterionic forms. Thus, any of the compounds described herein throughout that contain, for example, both amino and carboxy groups, also include reference to their corresponding zwitterions.

[0042] "Hydrate" refers to a compound of the present invention which is associated with water in the molecular form, i.e., in which the H-OH bond is not split, and may be represented, for example, by the formula $R \cdot H_2 0$, where R is a compound of the invention. A given compound may form more than one hydrate including, for example, monohydrates ($R \cdot H_2 0$) or polyhydrates ($R \cdot nH_2 0$ wherein n is an integer > 1) including, for example, dihydrates ($R\text{-}2H_2 0$), trihydrates ($R \cdot 3H_2 0$), and the like, or hemihydrates, such as, for example, $R\text{-}n/_2 H_2 0$, $R\text{-}n/3H_2 0$, $R \cdot n_{/4} H_2 O$ and the like wherein n is an integer.

[0043] "Solvate" refers to a compound of the present invention which is associated with solvent in the molecular form, i.e., in which the solvent is coordinatively bound, and may be represented, for example, by the formula R-(solvent), where R is a compound of the invention. A given compound may form more than one solvate including, for example, monosolvates (R-(solvent)) or polysolvates (R-n(solvent)) wherein n is an integer > 1) including, for example, disolvates (R-2(solvent)), trisolvates (R-3(solvent)), and the like, or hemisolvates, such as, for

example, R-$n_{/2}$(solvent), R-$n_{/3}$(solvent), R-$n_{/4}$(solvent) and the like wherein n is an integer. Solvents herein include mixed solvents, for example, methanol/water, and as such, the solvates may incorporate one or more solvents within the solvate.

[0044] "Acid hydrate" refers to a complex that may be formed through association of a compound having one or more base moieties with at least one compound having one or more acid moieties or through association of a compound having one or more acid moieties with at least one compound having one or more base moieties, said complex being further associated with water molecules so as to form a hydrate, wherein said hydrate is as previously defined and R represents the complex herein described above.

[0045] The term "stereoisomers" refers to compounds that have identical chemical constitution, but differ as regards the arrangement of the atoms or groups in space.

[0046] "Racemic" means having the capacity for resolution into forms of opposed optical activity.

[0047] As used herein, the term "partial stereoisomer" refers to stereoisomers having two or more chiral centers wherein at least one of the chiral centers has defined stereochemistry (i.e., *R* or *S)* and at least one has undefined stereochemistry (i.e., *R* or *S).* When the term "partial stereoisomers thereof is used herein, it refers to any compound within the described genus whose configuration at chiral centers with defined stereochemistry centers is maintained and the configuration of each undefined chiral center is independently selected from *R* or *S*. For example, if a stereoisomer has three chiral centers and the stereochemical configuration of the first center is defined as having *"S"* stereochemistry, the term "or partial stereoisomer thereof refers to stereoisomers having *SRR, SRS, SSR,* or *SSS* configurations at the three chiral centers, and mixtures thereof.

[0048] An "isotopically substituted analogue" is a compound of the present disclosure in which one or more atoms have been replaced with an isotope of that atom. For example, hydrogen (protium) may be substituted with deuterium or tritium. Other atoms that may be replaced with an isotope thereof in order to form an isotopically substituted analogue thereof include, for example, carbon (replaced with C^{13}), nitrogen (replaced with N^{15}), iodine (replaced with I^{131}), fluorine (replaced with F^{18}), or sulfur (replaced with S^{31}). Any available isotope may be used to form an isotopically substituted analogue thereof, and those of ordinary skill in the art will recognize available techniques for forming such analogues from a given compound.

[0049] "Prodrug" refers to compounds which are themselves inactive or minimally active for the activity desired, but through biotransformation can be converted into biologically active metabolites. For example, a prodrug of the present invention would include, *inter alia,* any compound which is convertible *in vivo* by metabolic means to a compound claimed or described in the present disclosure.

[0050] "N-oxide" refers to compounds wherein the basic nitrogen atom of either a heteroaromatic ring or tertiary amine is oxidized to give a quaternary nitrogen bearing a positive formal charge and an attached oxygen atom bearing a negative formal charge.

[0051] When any variable occurs more than one time in any constituent or in any formula, its definition in each occurrence is independent of its definition at every other occurrence. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

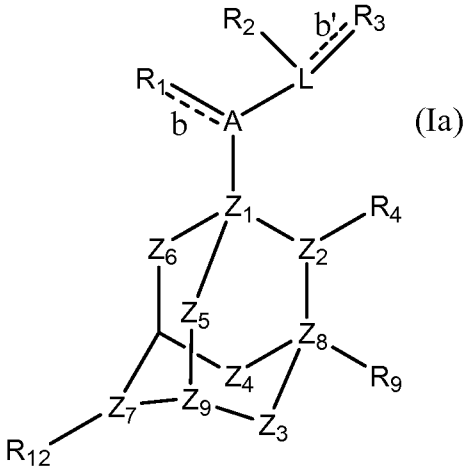
[0052] The term "administering" means either directly administering a compound or composition of the present invention, or administering a prodrug, derivative or analog which will form an equivalent amount of the active compound or substance within the body.

[0053] "Dosage unit" refers to physically discrete units suited as unitary dosages for the particular individual to be treated. Each unit may contain a predetermined quantity of active compound(s) calculated to produce the desired therapeutic effect(s) in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention may be dictated by (a) the unique characteristics of the active compound(s) and the particular therapeutic effect(s) to be achieved, and (b) the limitations inherent in the art of compounding such active compound(s).

[0054] "Subject" or "patient" refers to an embryonic, immature, or adult animal, including the human species, that is treatable with the compositions, and/or methods of the present invention.

[0055] It has presently been discovered that certain adamantane variants are effective for inhibiting the respective viroporins of various virus species, including virus species in which a mutation of the viroporin and/or associated structures is present. As used herein, "inhibition" of a viroporin refers to the reduction of the viroporin' s ability to function in a manner that is most consistent with the vitality of the virus of which the viroporin is a component.

[0056] Accordingly, in one aspect, the present invention provides compounds according to Formula la:



(Ia)

wherein

A is Ci_3 alkylene or a bond between L and the atom at position Zi;

L is nitrogen;

R i is NH, NH_2, alkyl, or, if A is a bond, is absent;

dashed lines b and b' may independently represent a double bond;

R_2 is H, alkyl, -(D)(E), or is absent;

R_3 is -(X)(Y);

R_4 is -(R_5)(R6), halo, or is absent;

R_5 is nitrogen or oxygen;

Re is hydrogen or -(R_7)(R_8)

R_7 is alkylene, -CH(R_{7a})-, -(CH_2)$_{0-6}$CH(OH)-, or represents a bond between R_5 and Rg;

R_{7a} is alkyl;

Rg is optionally substituted mono-, di-, or tricyclic ring system that optionally includes one or more heteroatoms;

R_9 is -(Rio)(Rii) or is absent;

Rio is oxygen, nitrogen, alkyl, -CF_3, or alkylene;

R_{11} is hydrogen, halo, or is absent;

Ri_2 is alkyl, alkoxy, halo, oxo, or hydroxyl;

D is alkylene, alkenylene, alkynylene, -CH(Q)-, carbonyl, or a bond;

E is an optionally substituted mono-, di-, or tricyclic ring system that optionally includes

one or more heteroatoms;

X is alkylene, alkenylene, alkynylene, -CH(Q)-, carbonyl, or a bond;

Q is alkyl, -C(=0)0(CH $_{2}$)i$_{-3}$CH$_{3}$, or -(CH$_{2}$)$_{0-3}$OH;

Y is an optionally substituted mono-, di-, or tricyclic ring system that optionally includes one or more heteroatoms;

Z_2 is optionally substituted alkylene of which one or more carbon atoms is optionally replaced with N, O, or S, or represents a bond between Zi and Z_8;

Z_3 is optionally substituted alkylene of which one or more carbon atoms is optionally replaced with N, O, or S, or represents a bond between Z_8 and Z_9;

Z_4, Z_5, and Z_6 are independently alkylene, N, O, or S;

Z_7 is optionally substituted alkylene of which one or more carbon atoms is optionally replaced with N, O, or S;

or a stereoisomer, isotopically substituted analogue, or pharmaceutically acceptable salt thereof,

with the proviso that

(i) if A is a bond and R_2 is H or absent, except if X is alkynyl, then:

Y is not unsubstituted phenyl, pyridinyl, furanyl, thiopheneyl, pyrrolyl, or benzodioxolyl;

if Y is mono-substituted furanyl, then the substituent on Y is not methyl, hydroxyl, methanolyl, alkoxy, acetylamino, nitro, bromo, chloro, or fluoro;

if Y is mono-substituted phenyl, then the substituent on Y is not methyl, hydroxyl, methanolyl, alkoxy, unsubstituted phenyl, methoxybenzyloxy, acetylamino, nitro, bromo, chloro, or fluoro;

if Y is mono-substituted thiopheneyl, then the substituent on Y is not methyl, ethyl, chloro, or bromo;

if Y is mono-substituted oxadiazolyl, then the substituent on Y is not methoxyphenyl;

if Y is mono-substituted thiazolyl, then the substituent on Y is not methyl;

if Y is mono-substituted naphthyl, then the substituent on Y is not 1-hydroxyl; and,

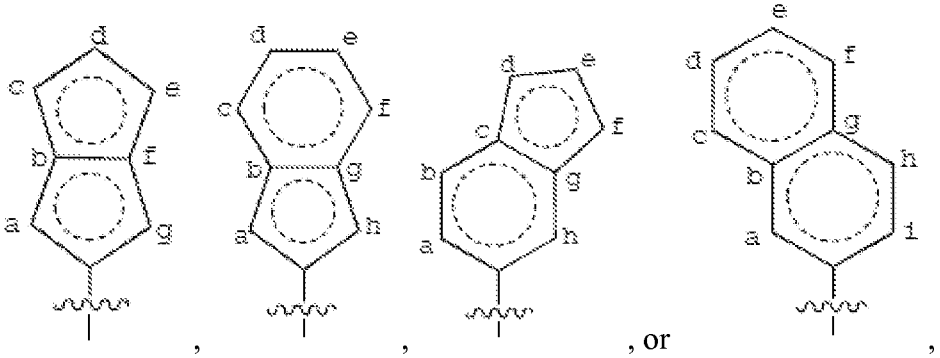
if Y is di-substituted phenyl, then the substituents on Y may not both be alkoxy,

and,

(ii) if A is Ci alkyl, Ri is NH, and Y is mono-substituted phenyl, then the substituent is not hydroxyl.

[0057] In certain embodiments, A is a bond, Ri is absent, X is alkylene or -CH(Q)-, and Y is a carbocyclic ring optionally substituted with one or more substituents independently selected from alkoxy, halo, alkyl, cycloalkyl, hydroxyl, aryl, trifluoromethoxy, trifluoromethyl, alkylsilanyl, alkylsulfanyl, aryloxy, aralkoxy, and hydroxyalkyl. For example, Y may be substituted with aryl, aryloxy, or aralkoxy, in which the aryl moiety of the aryl, aryloxy, or aralkoxy is optionally substituted phenyl, pyrrolidinyl, furanyl, thiopheneyl, oxazolyl, imidazolyl, pyridinyl, naphthyl. isoxazolyl, isoxazolinyl, isothiazolyl, isothiazolinyl, oxadiazolyl, thiadiazolyl, thiazolyl, triazolyl, tetrazolyl, morpholinyl, pyrimidinyl, pyridazinyl, pyrazinyl, pyrrolyl, cyclopropyl, cyclopentyl, or cyclohexyl.

[0058] In certain other embodiments, A is a bond, Ri is absent, X is alkylene or -CH(Q)-, and Y is an unsubstituted mono-, di-, or tricyclic ring system that optionally includes one or more heteroatoms independently selected from oxygen, nitrogen, and sulfur. In such instances, Y may be, for example, Y is a six-membered carbocyclic ring that is ortho-fused with a six-membered heterocyclic ring; a six membered heterocyclic ring that is ortho-fused with a six-membered heterocyclic ring; a six membered heterocyclic ring that is ortho-fused with a five-membered heterocyclic ring; a six membered heterocyclic ring that is ortho-fused with a five-membered carbocyclic ring; a six-membered carbocyclic ring that is ortho-fused with a five-membered heterocyclic ring; a pair of ortho-fused five-membered heterocyclic rings; a pair of ortho-fused five-membered carbocyclic rings; or, a single three- to seven-membered carbo- or heterocyclic ring. For example, Y may be represented by the structure

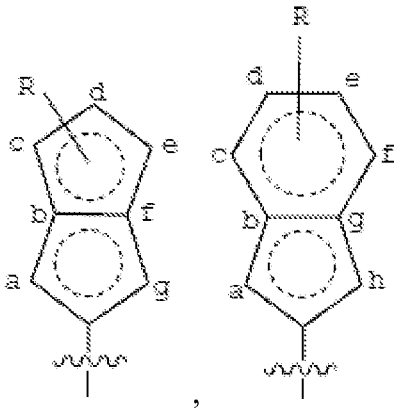


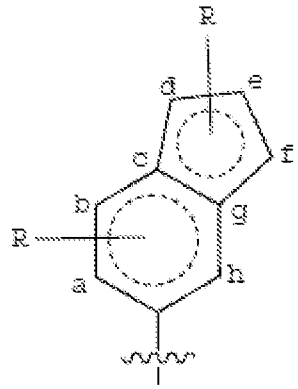
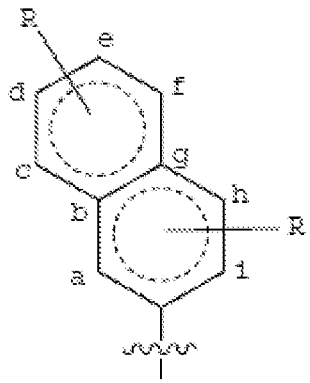
, , , or ,

or any heterocyclic analog of which that includes one or more heteroatoms independently selected from oxygen, nitrogen, and sulfur at any of the positions labeled a, b, c, d, e, f, g, h, and i in the structures above. In some examples, Y is a single unsaturated, partially saturated, or fully saturated six-membered carbo- or heterocyclic ring; a single unsaturated, partially saturated, or fully saturated five-membered carbo- or heterocyclic ring; an unsaturated, partly-saturated, or fully-saturated thiophene ring that is ortho-fused to an unsaturated, partly-saturated, or fully-saturated thiophene, pyrrole, furan, imidazole, thiazole, or oxazole ring, an unsaturated, partly-saturated, or fully-saturated furan ring that is ortho-fused to an unsaturated, partly-saturated, or fully-saturated thiazole or oxazole ring; an unsaturated, partly-saturated, or fully-saturated pyrrole ring that is ortho-fused to an unsaturated, partly-saturated, or fully-saturated thiazole or oxazole ring; or, a phenyl ring that is ortho-fused to an unsaturated, partly-saturated, or fully-saturated thiophene, pyridine, imidazole, or furan ring. In such embodiments, when Y is a single unsaturated, partially saturated, or fully saturated six-membered carbo- or heterocyclic ring, or is a single unsaturated, partially saturated, or fully saturated five-membered carbo- or heterocyclic ring, Y may be, for example, isoxazolyl, isoxazolinyl, isothiazolyl, isothiazolinyl, oxadiazolyl, thiadiazolyl, oxazolyl, thiazolyl, triazolyl, tetrazolyl, imidazolyl, phenyl, morpholinyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, thiopheneyl, furanyl, pyrrolyl, cyclopropyl, cyclopentyl, or cyclohexyl.

[0059] In other embodiments of compounds according to formula (la), A is a bond, Ri is absent, X is alkylene or -CH(Q)-, and Y is a substituted mono-, di-, or tricyclic ring system that includes one or more heteroatoms independently selected from oxygen, nitrogen, and sulfur. In such embodiments, Y may be, for example, a single three- to seven-membered heterocyclic ring; a single unsaturated, partially saturated, or fully saturated six-membered carbo- or heterocyclic ring; a single unsaturated, partially saturated, or fully saturated five-membered carbo- or heterocyclic ring; a pair of ortho-fused five-membered heterocyclic rings, wherein at least one of said rings is substituted; a pair of ortho-fused six-membered heterocyclic rings, wherein at least one of said rings is substituted; a six-membered heterocyclic ring that is ortho-fused with a six-membered carbocyclic ring, wherein at least one of said rings is substituted; a five-membered heterocyclic ring that is ortho-fused with a five-membered carbocyclic ring, wherein at least one of said rings is substituted; a five-membered heterocyclic ring that is ortho-fused with a six-membered carbocyclic ring, wherein at least one of said rings is substituted; or,

a five-membered carbocyclic ring that is ortho-fused with a six-membered heterocyclic ring, wherein at least one of said rings is substituted. The substituents may independently be, for example, oxo, hydroxyl, halo, nitro, alkyl, trifluoromethyl, trifluoromethoxy, cycloalkyl, alkoxy, alkoxyalkyl, alkylsulfanyl, alkylsulfanylalkyl, trifluoromethylsulfanyl, cyano, amino, alkylamino, di-alkylamino, alkoxycarbonylalkyl(alkyl)amino, aryl, or aralkyl. In certain embodiments, Y may be represented by the structure


,

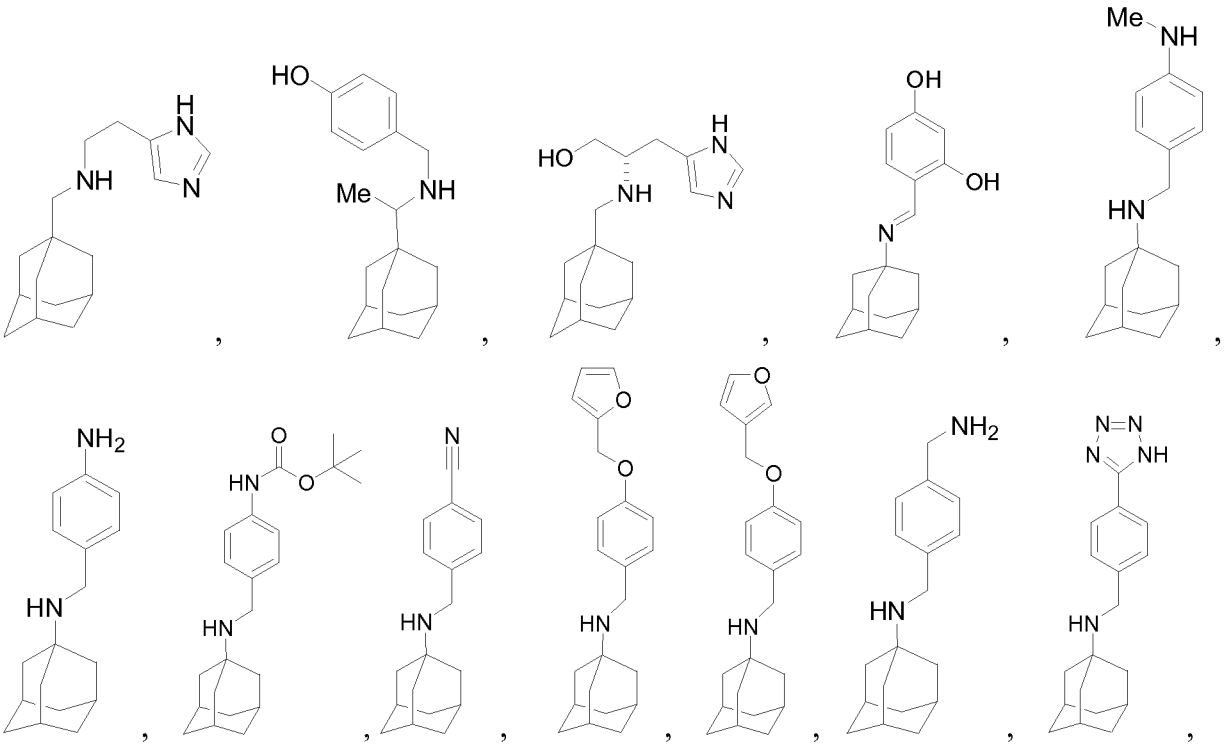
,

, or

,

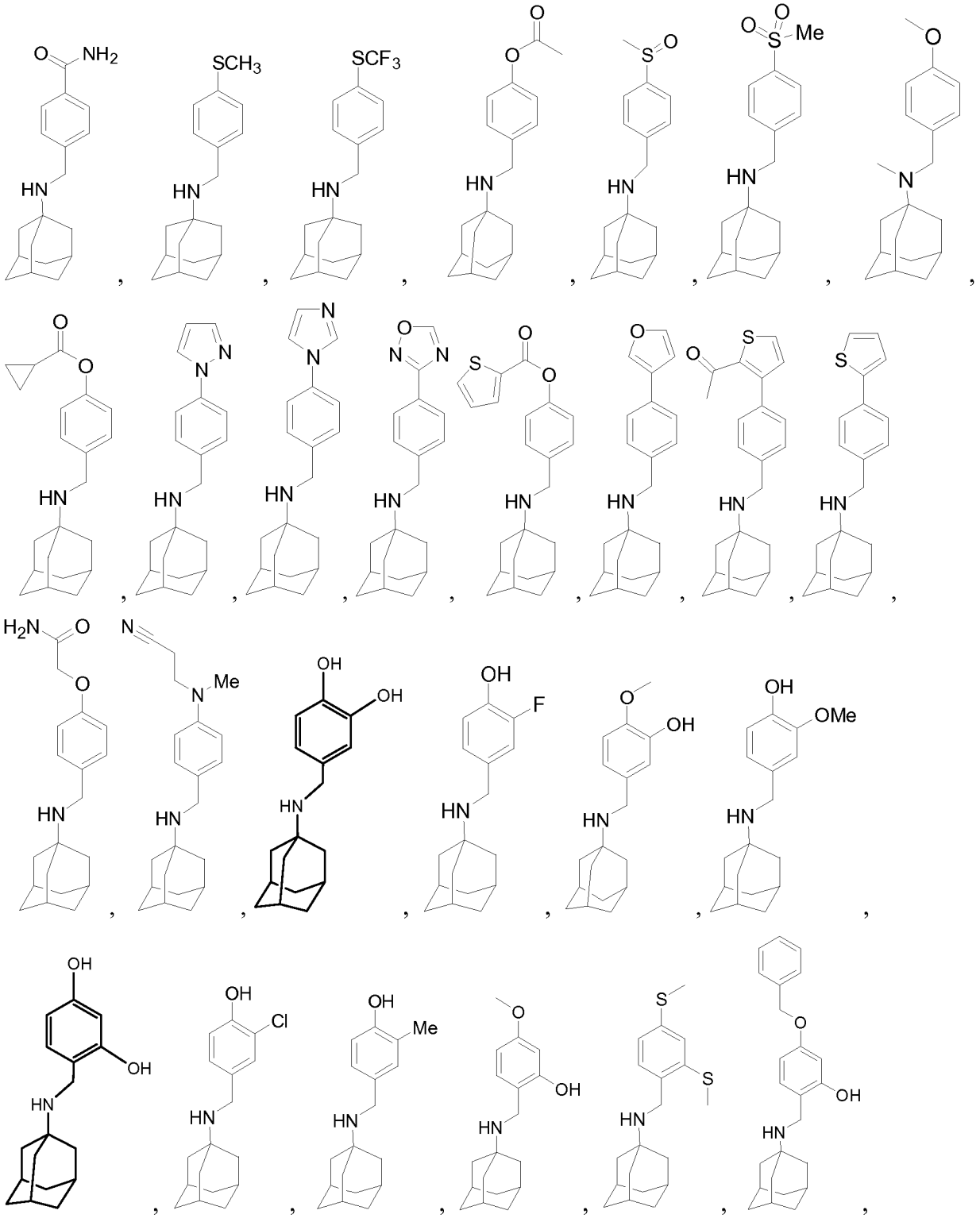
wherein R represents a substitution, or any heterocyclic analog of which that includes one or more heteroatoms independently selected from oxygen, nitrogen, and sulfur at any of the positions labeled a, b, c, d, e, f, g, h, and i in the structures above. In the structures above, each R may independently be oxo, hydroxyl, halo, nitro, alkyl, trifluoromethyl, trifluoromethoxy, cycloalkyl, alkoxy, alkylsulfanyl, trifluoromethylsulfanyl, cyano, amino, or aryl. When Y represents a single ring, Y may be, for example, isoxazolyl, isoxazolinyl, isothiazolyl, isothiazolinyl, oxadiazolyl, thiadiazolyl, oxazolyl, thiazolyl, triazolyl, tetrazolyl, imidazolyl, phenyl, morpholinyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, thiopheneyl, furanyl, pyrrolyl, cyclopropyl, cyclopentyl, or cyclohexyl, each with at least one substitution. The substitutions on Y when it is a single ring may be, for example, halo, thiopheneyl, alkylthiopheneyl, alkoxythiopheneyl, imidazolyl, imidazolyl substituted with one or both of methyl and trifluoromethyl, tetrahydrofuranyl, furanyl, alkylfuranyl, phenyl, pyridinyl, morpholinomethyl, cyclopropyl, cyclopentyl, cyclohexyl, alkoxy, alkoxyalkyl, alkyl, alkylsulfanyl, alkylsulfanylalkyl, alkylsilanyl, cyano, amino, alkylamino, di-alkylamino, alkoxycarbonylalkyl(alkyl)amino, nitro, alkoxyphenyl, alkylsulfanylphenyl, halophenyl, trifluoromethyl, trifluoromethylphenyl, trifluoromethoxyphenyl, thiazolyl substituted with one or both of methyl and trifluoromethyl, isoxazolyl optionally substituted with methyl, isoxazolinyl,

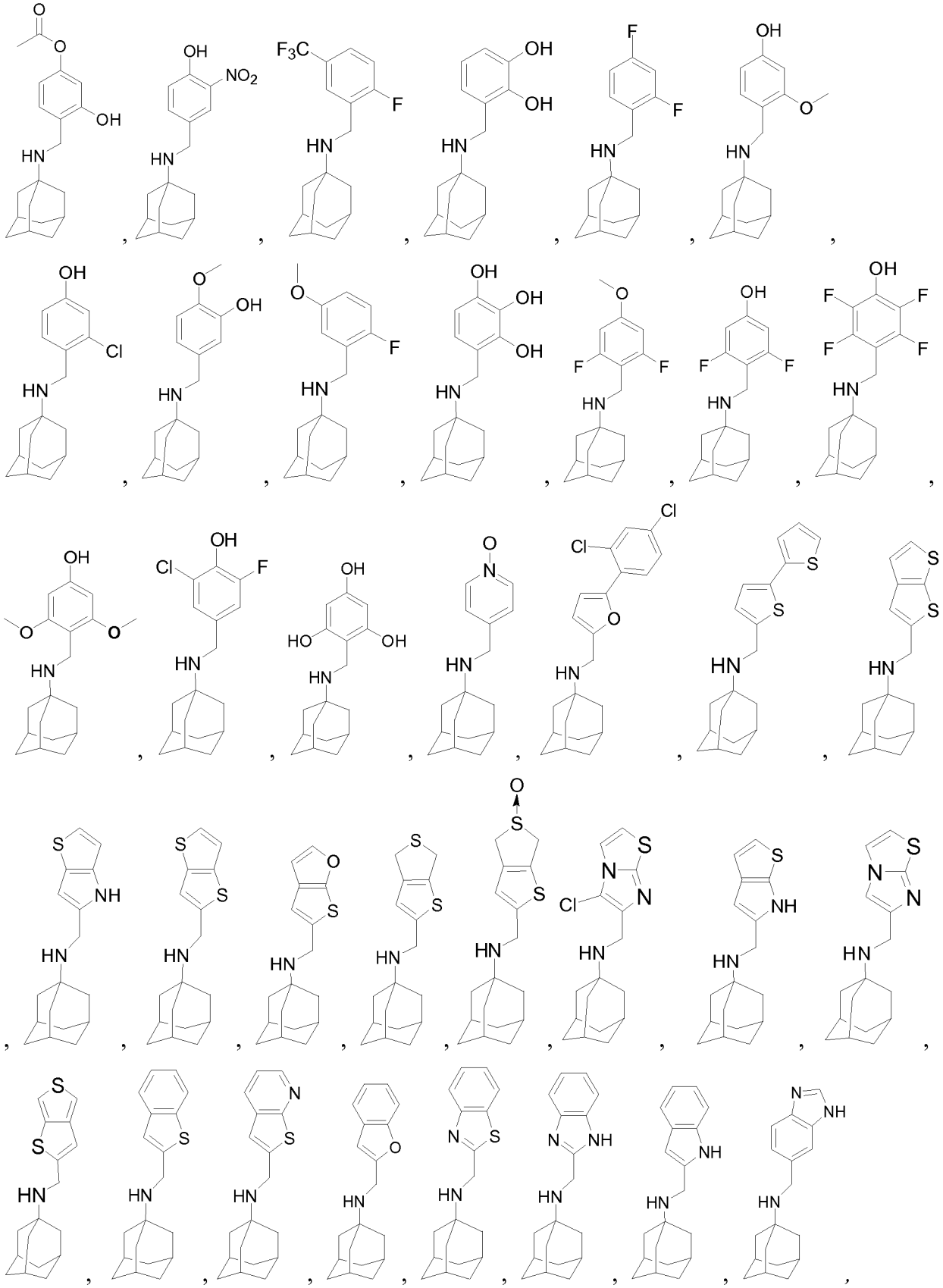
isothiazolyl, isothiazolinyl, oxadiazolyl, thiadiazolyl, oxazolyl, thiazolyl, triazolyl, tetrazolyl, morpholinyl, pyrimidinyl, pyridazinyl, pyrrolidinyl, piperadinyl, pyrazinyl, or pyrrolyl. Any of the substitutions on Y may themselves be substituted.

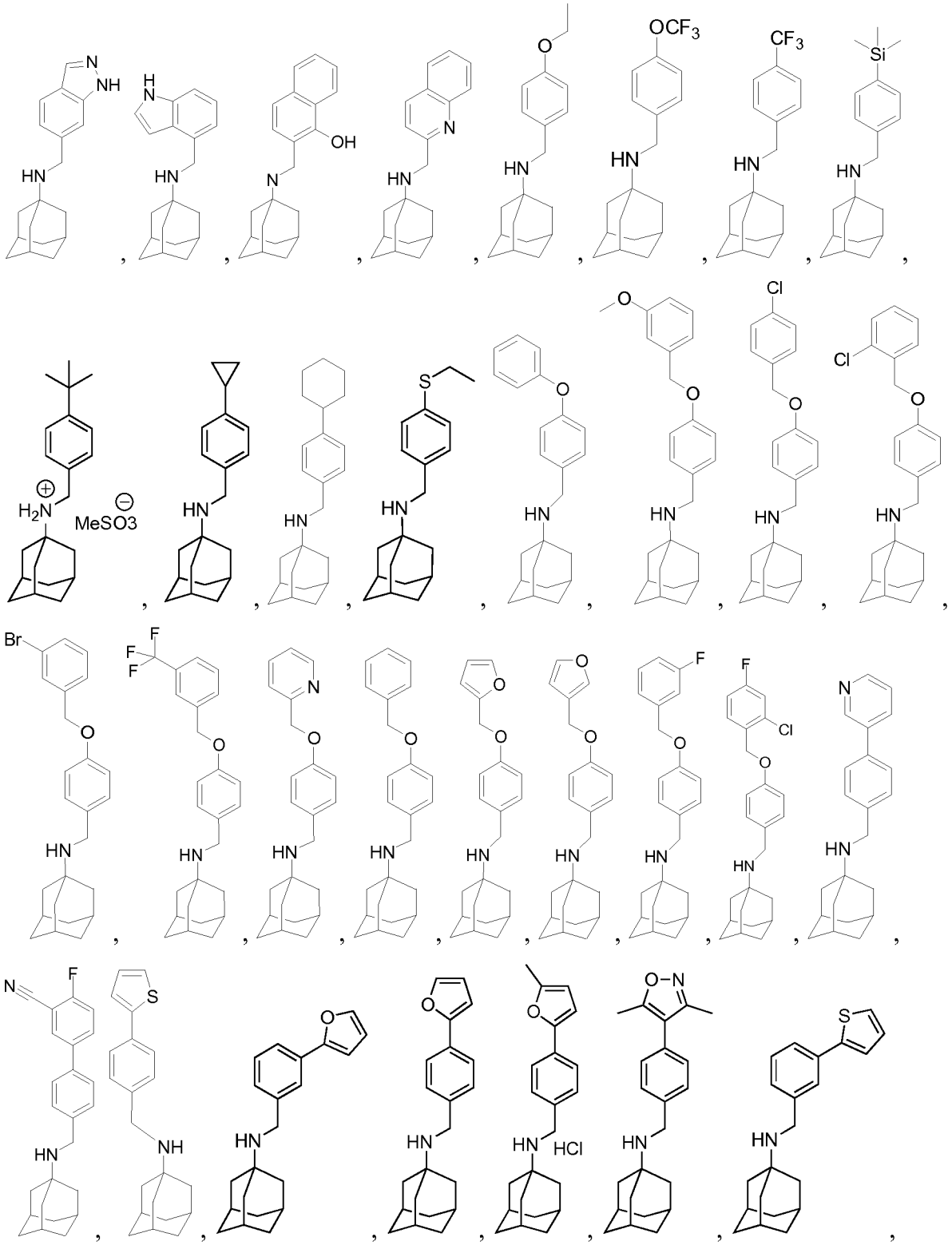
[0060] In other embodiments of the compounds of formula (la), A is a bond, **Ri** is absent, X is alkylene or -CH(Q)-, and R_9 is **-(Rio)(Rn).** In still other embodiments, A is a bond, **Ri** is absent, X is alkylene or -CH(Q)-, and $\mathbf{R_4}$ is **-(R** $_5$)(R_6). In yet other embodiments, A is a bond, **Ri** is absent, X is alkylene or -CH(Q)-, and $\mathbf{R_2}$ is **-(D**)(E). Other embodiments are such that A is a bond, **Ri** is absent, X is alkylene or -CH(Q)-, and Z_7 is alkylene that is substituted with alkyl, hydroxyl, or halo. Still other embodiments are such that A is a bond, **Ri** is absent, X is alkylene or -CH(Q)-, and Z_7 is alkylene of which one or more carbon atoms is replaced with N, O, or S. In other embodiments, A is a bond, **Ri** is absent, X is alkylene or -CH(Q)-, and one or more of Z_2-Z_7 is N, O, or S. In yet other embodiments, A is a bond, **Ri** is absent, X is alkenylene or alkynylene, and Y is optionally substituted aryl.

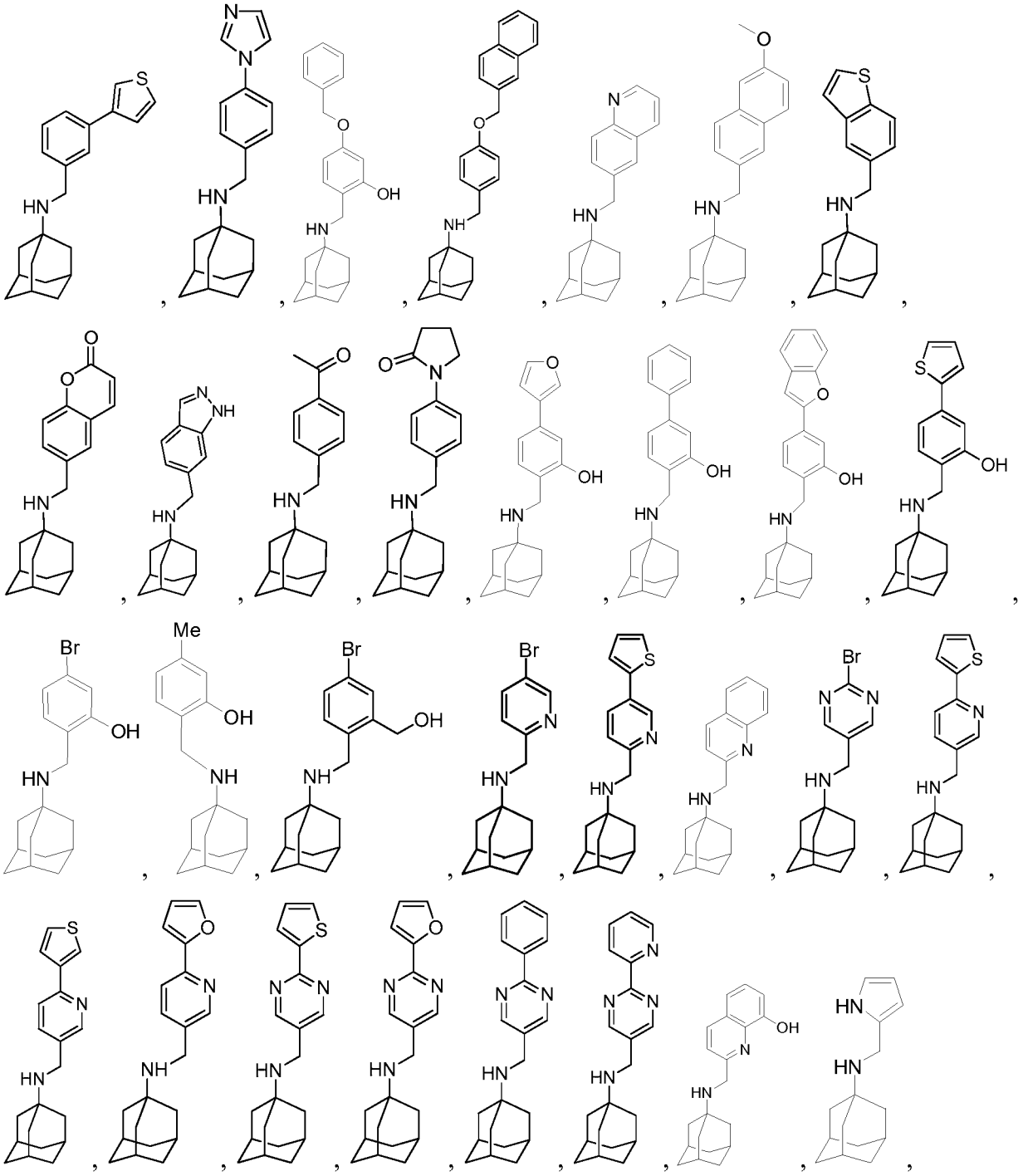
[0061] Exemplary compounds according to formula (la) include:

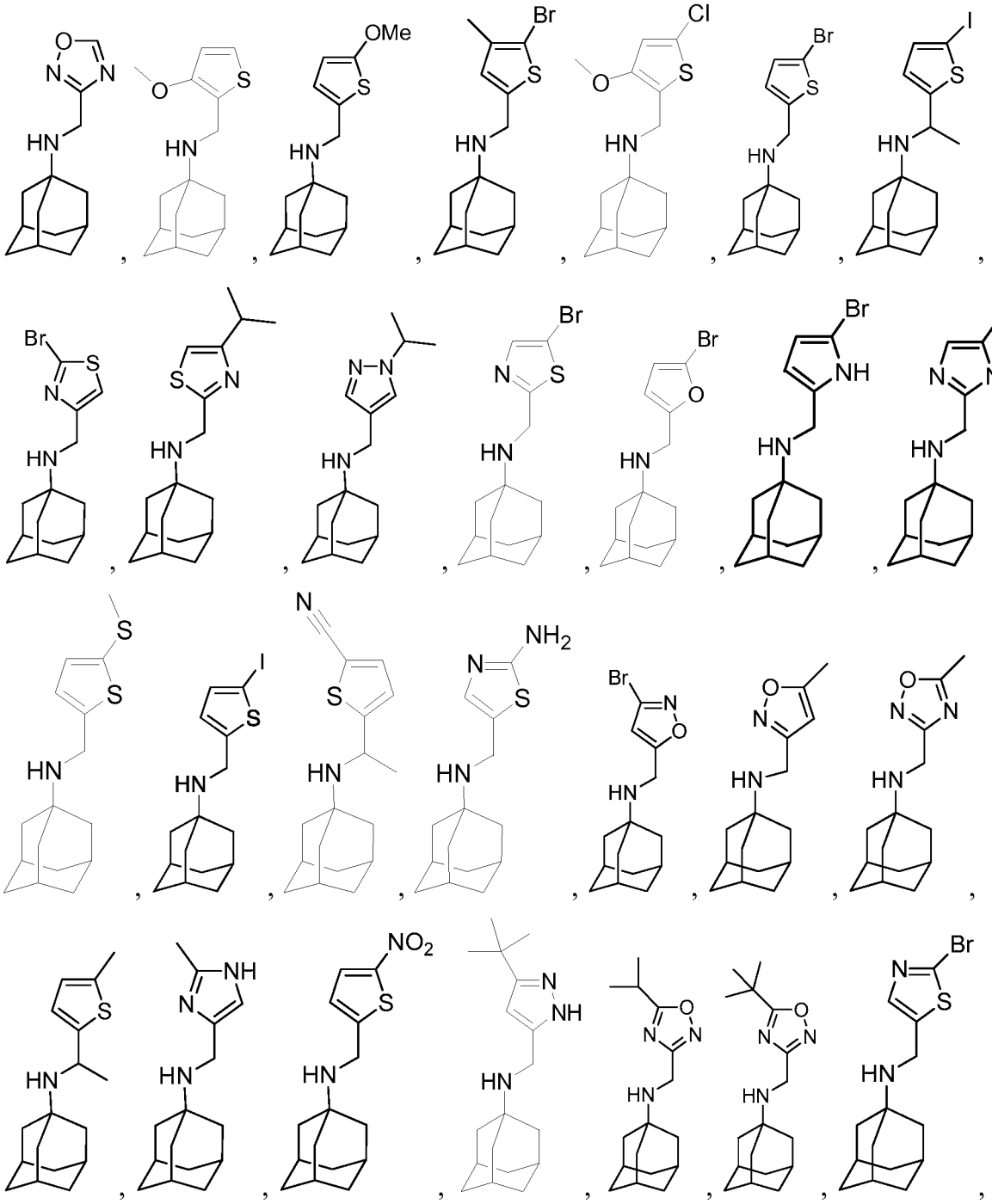


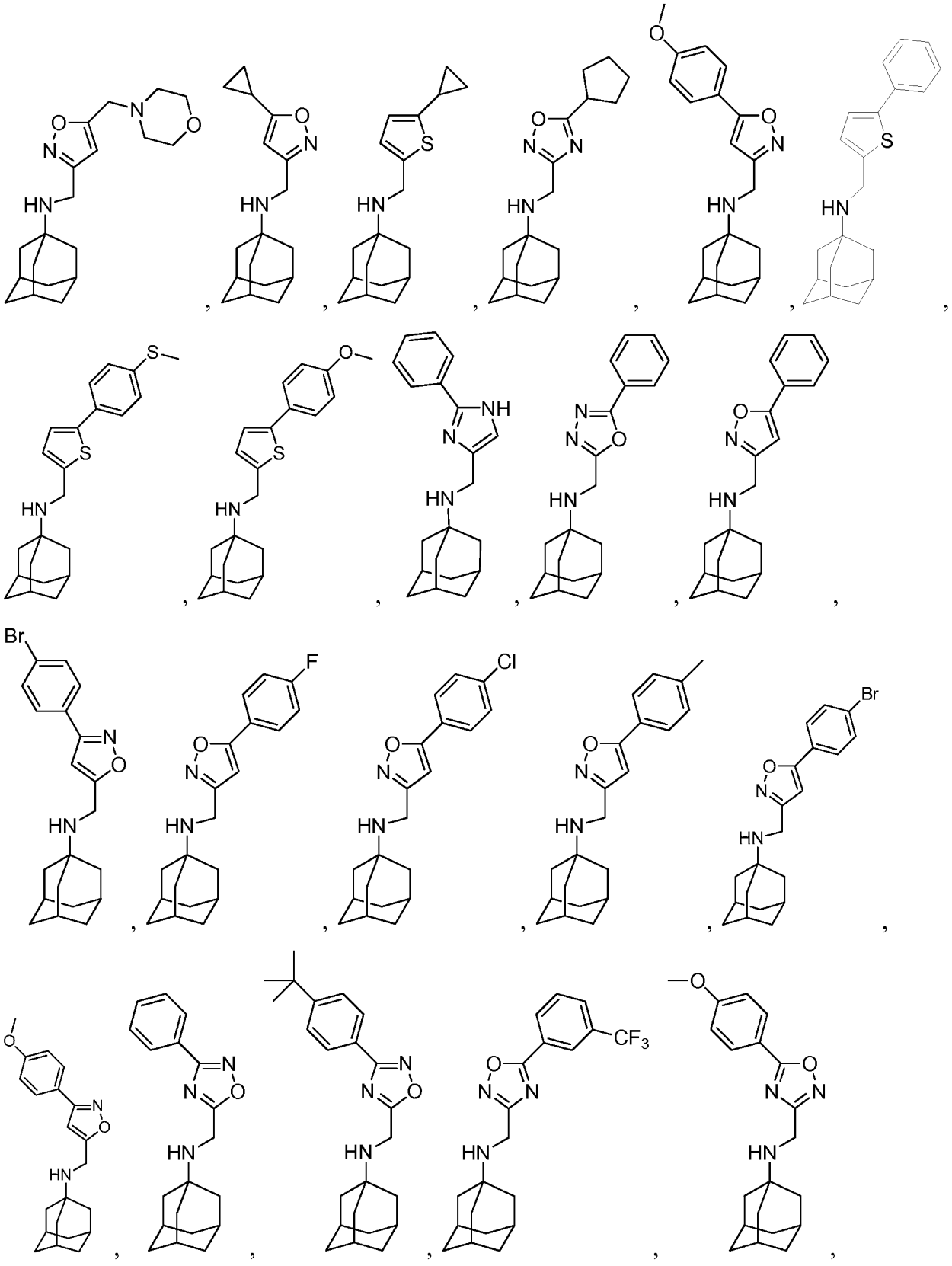


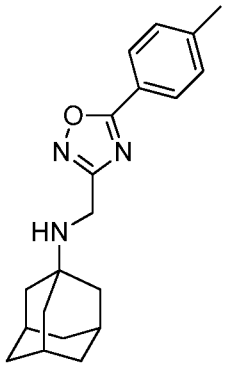
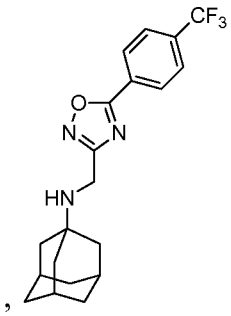
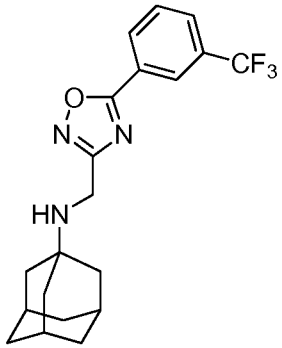
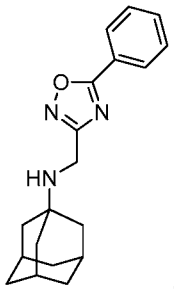
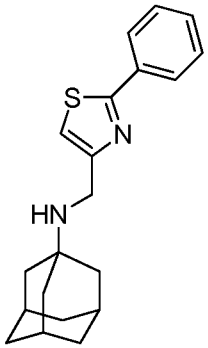
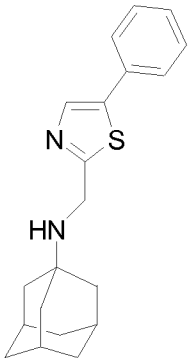
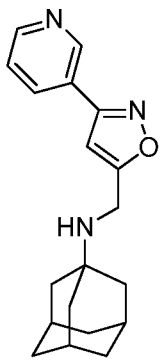
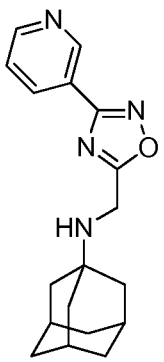
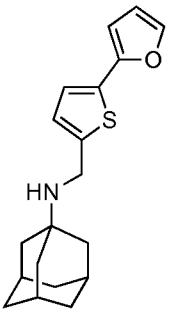
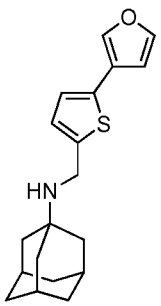
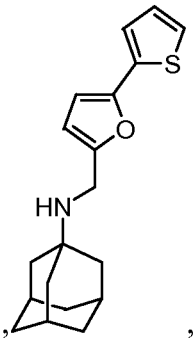
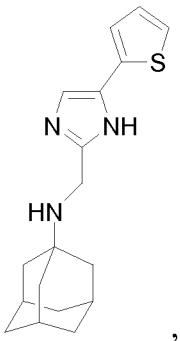
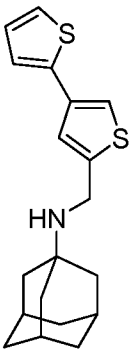
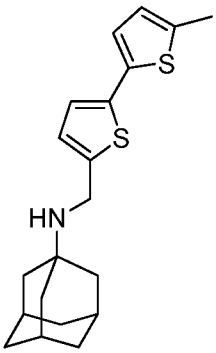
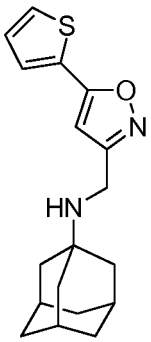
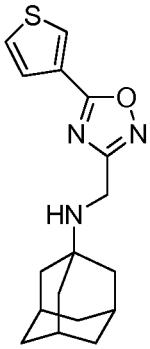
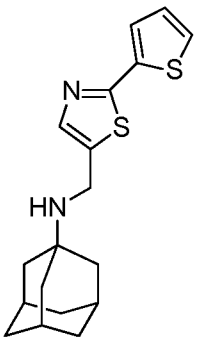
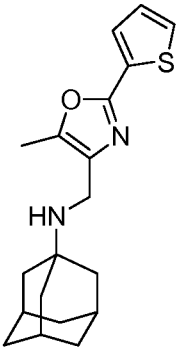
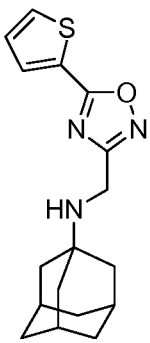
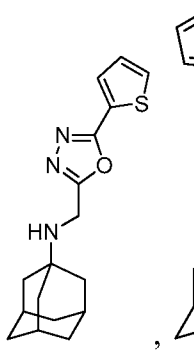
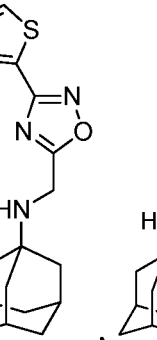
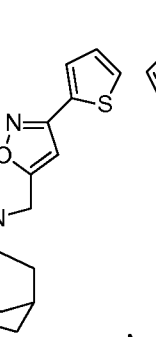
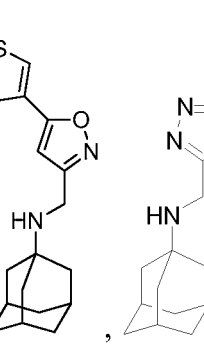


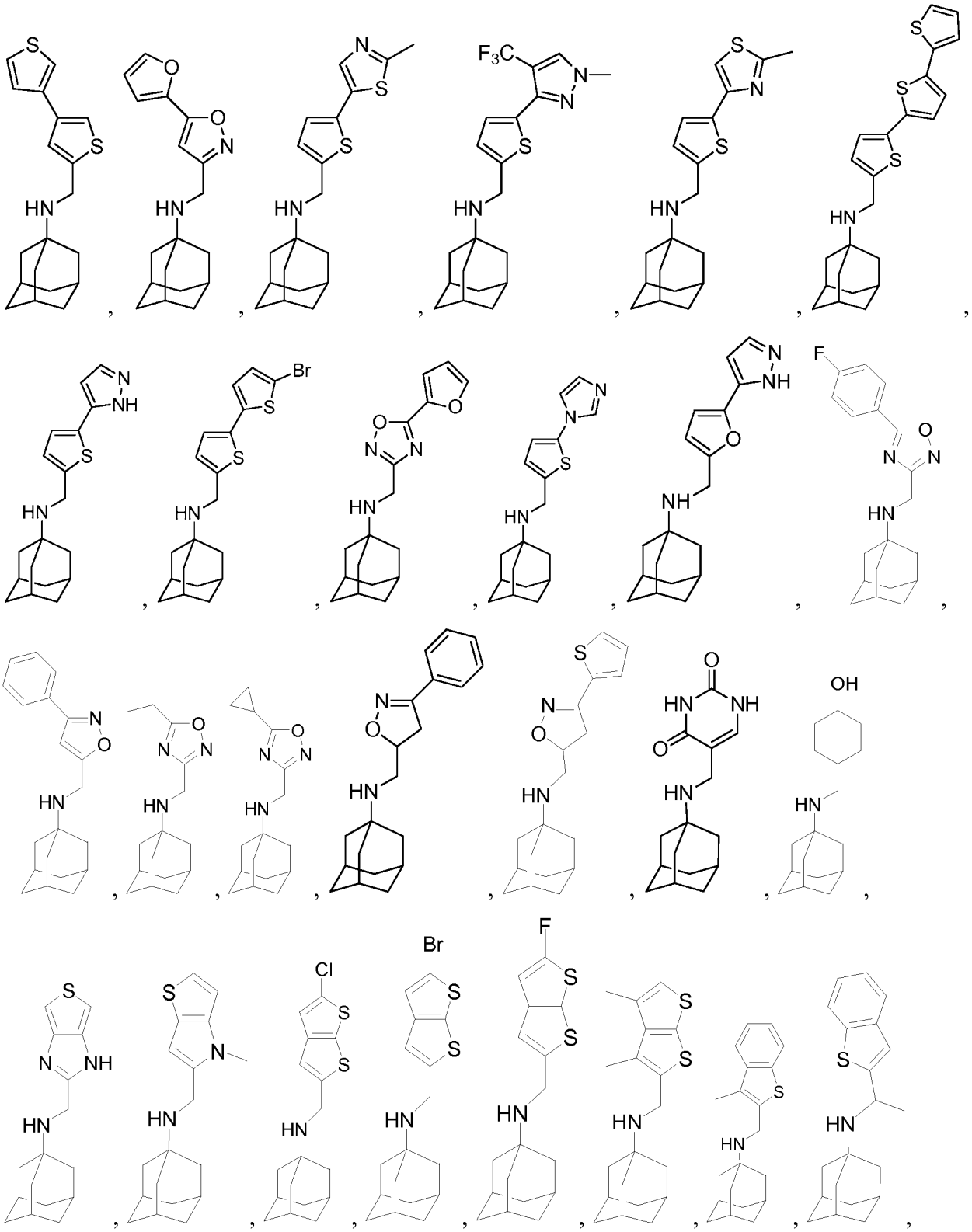


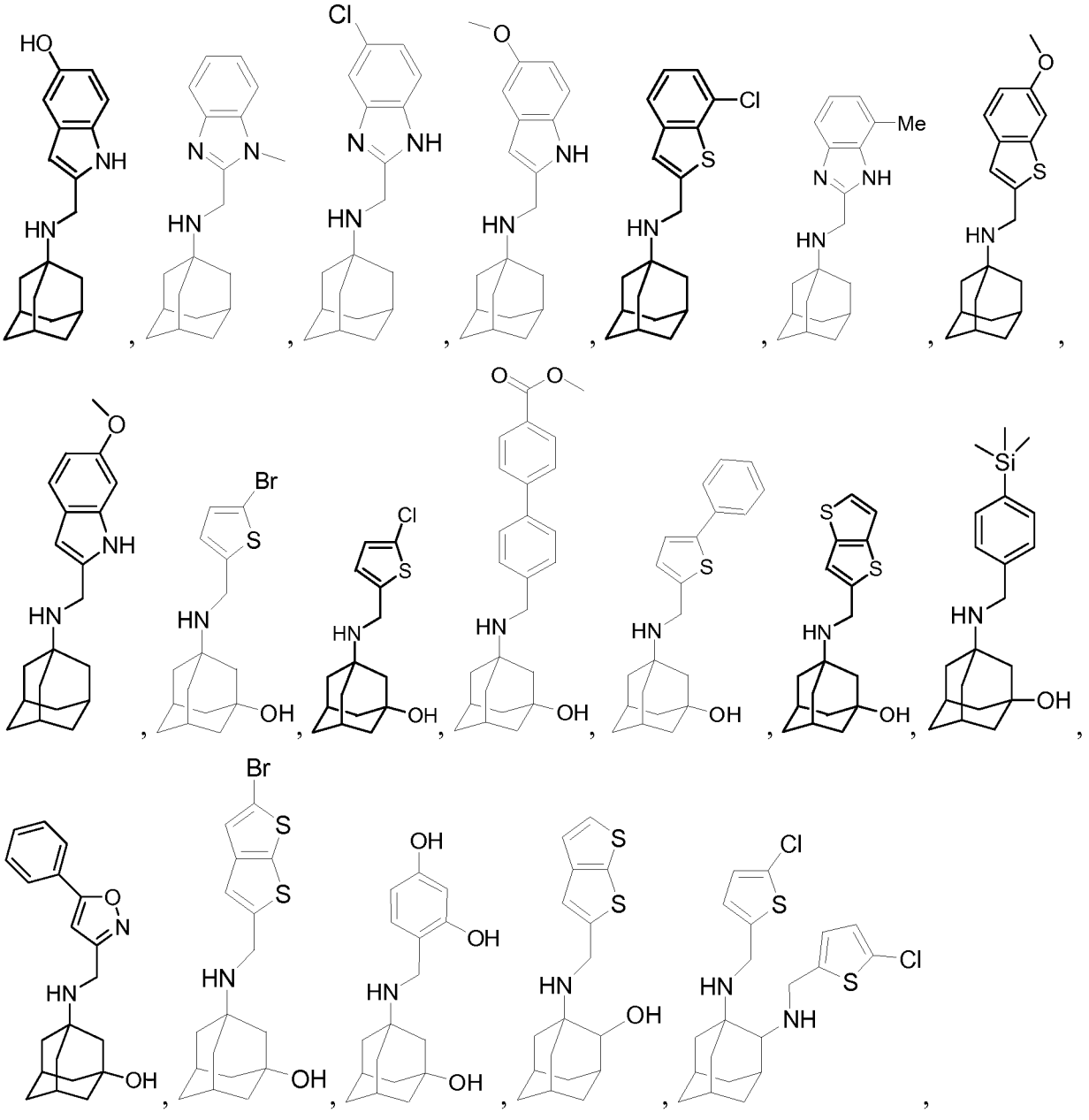




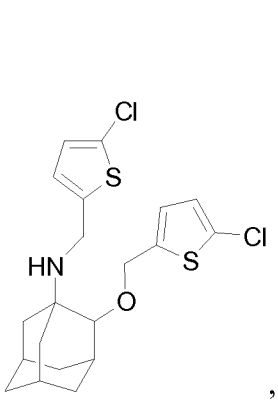
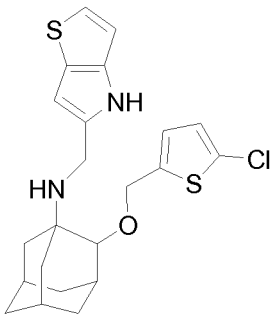
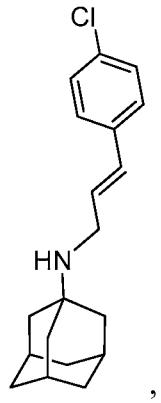
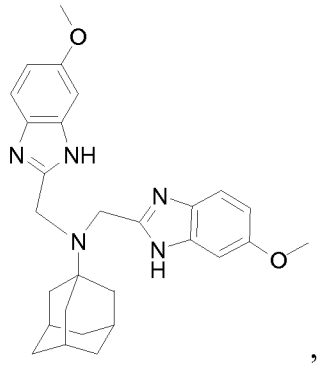
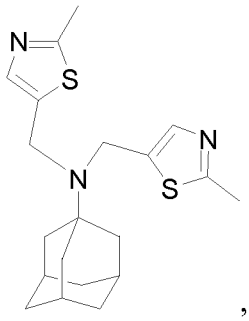
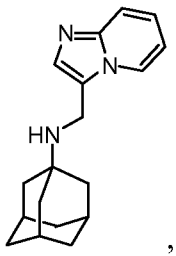
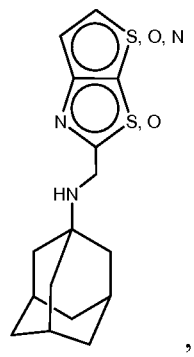
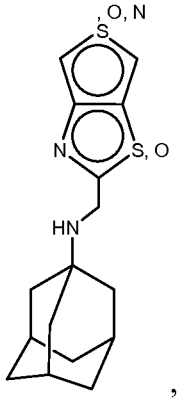
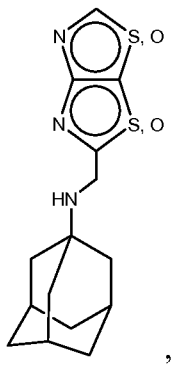
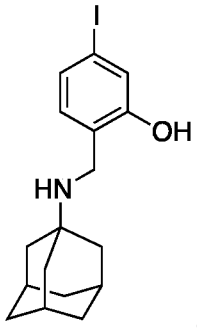
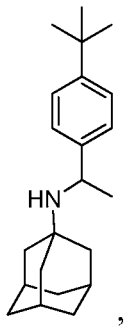
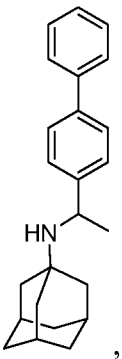
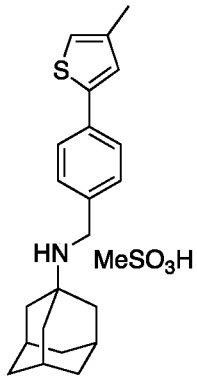
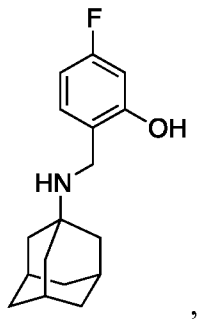
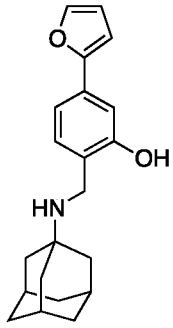
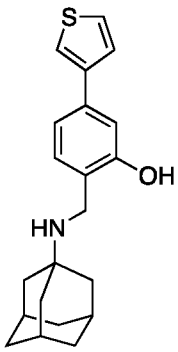
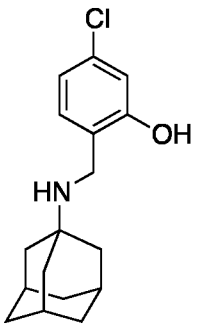
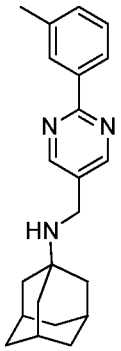
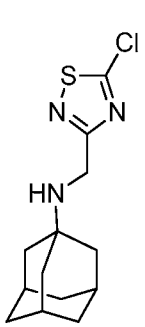
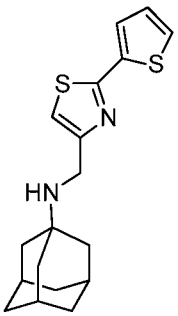
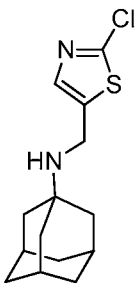
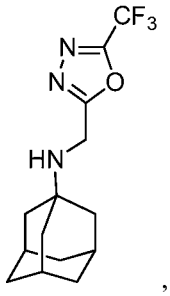


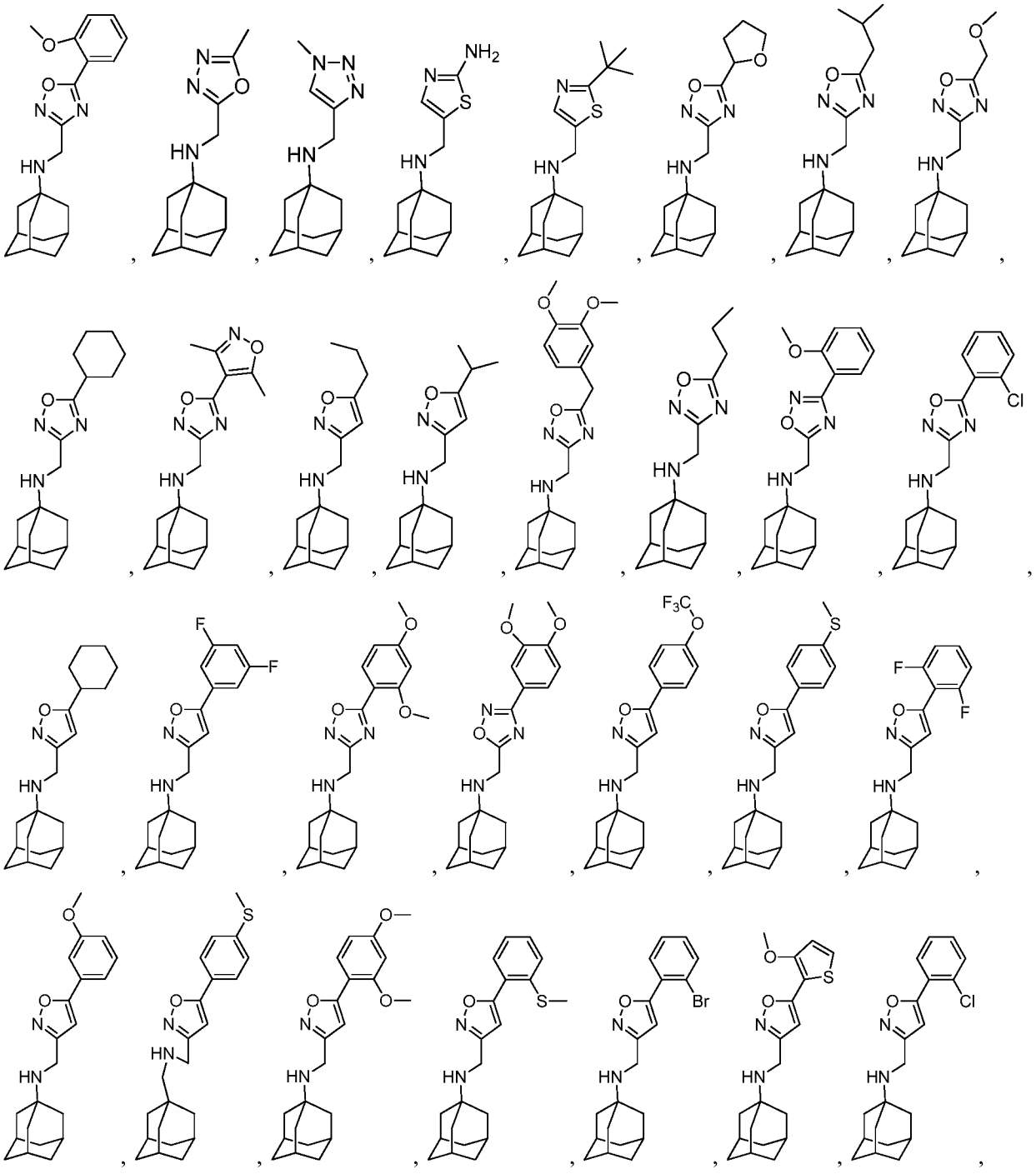
























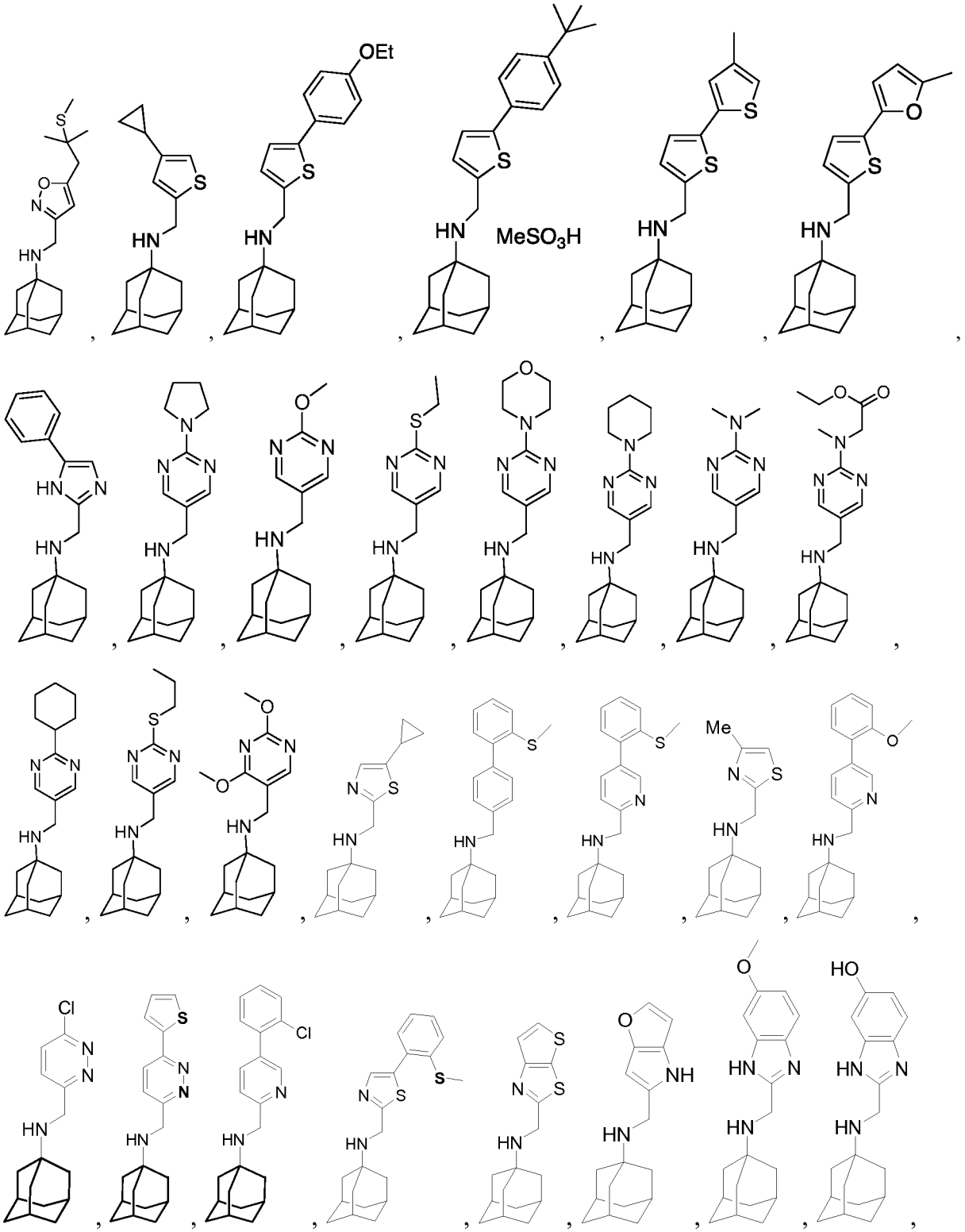


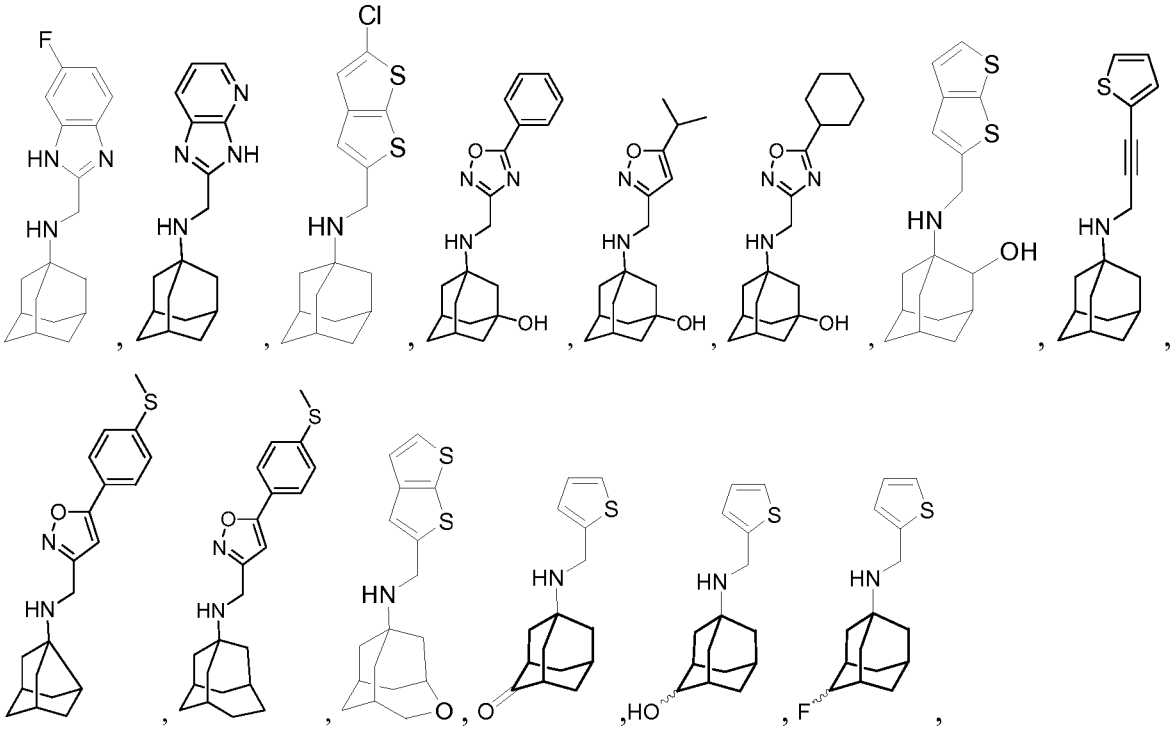


,


,

,

,

,

,

,

,

,

,

,

,

,

MeSO3H
,

,

,

,

,

,

,

,

,

,

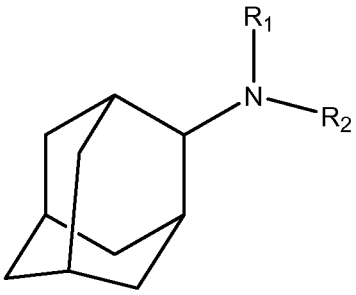



OEt
MeSO3H
Me
Cl
HO



and stereoisomers, isotopically substituted analogues, or pharmaceutically acceptable salts thereof.

[0062] Also disclosed are compounds according to formula lb



(Ib)

wherein

Ri is hydrogen; and,

R_2 is $-(R_3)(R_4)$;

$\mathbf{R_3}$ is alkyl; and,

R_4 is a substituted mono-, di-, or tricyclic ring system,

or,

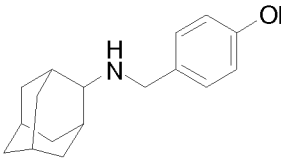
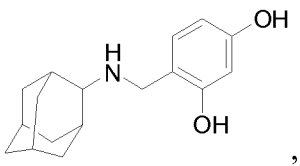
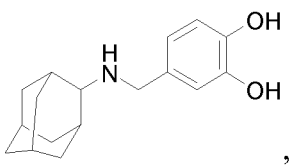
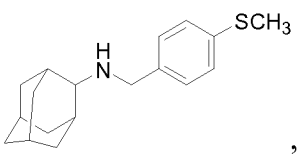
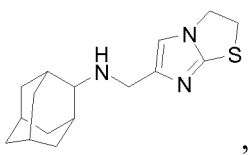
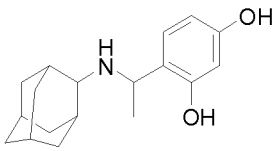
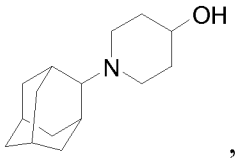
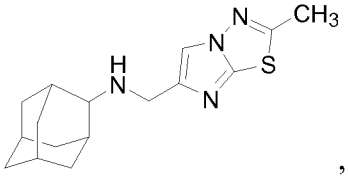
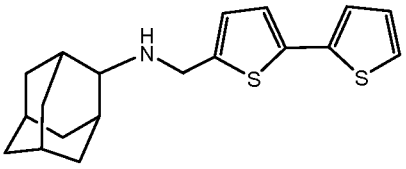
Ri together with $\mathbf{R_2}$ and the atom to which they are both attached form an optionally substituted mono-, di-, or tricyclic ring system,

or a stereoisomer, partial stereoisomer, isotopically substituted analogue, prodrug, pharmaceutically acceptable salt, hydrate, solvate, acid hydrate, or N-oxide thereof.

[0063] In some embodiments of the compounds according to formula lb, R_4 is a substituted monocyclic ring. For example, R_4 may be a five- or six-membered carbocyclic or heterocyclic ring bearing one or more substituents independently selected from hydroxyl, halo, alkyl, alkoxy, trifluoromethyl, trifluoromethoxy, alkylsulfanyl, cycloalkyl, and aryl. In one example, R_4 is a five-membered heterocyclic ring bearing one or more aryl substituents.

[0064] In other embodiments of the compounds according to formula lb, R_4 is a substituted dicyclic ring system that optionally includes one or more heteroatoms. For example, R_4 may be a a pair of ortho-fused heterocyclic rings.

[0065] Exemplary compounds according to formula lb include


,

,

,

,

,

,

,

,

,

or a stereoisomer, isotopically substituted analogue, or pharmaceutically acceptable salt thereof.

[0066] The compounds employed in the present invention may exist in prodrug form. As used herein, "prodrug" is intended to include any covalently bonded carriers which release the active parent drug, for example, as according to the formulas or compounds employed in the methods of the present invention *in vivo* when such prodrug is administered to a subject. Since prodrugs are known to enhance numerous desirable qualities of pharmaceuticals *{e.g.,* solubility, bioavailability, manufacturing, etc.) the compounds of the present invention may, if desired, be delivered in prodrug form. Thus, the present invention contemplates methods of delivering prodrugs. Prodrugs of the compounds employed in the present invention, for example, according to formula (la), (la') (described more fully *infra),* or (lb) may be prepared by modifying

functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo,* to the parent compound.

[0067] Accordingly, prodrugs include, for example, compounds described herein in which a hydroxy, amino, or carboxy group is bonded to any group that, when the prodrug is administered to a mammalian subject, cleaves to form a free hydroxyl, free amino, or carboxylic acid, respectively. Examples include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups; and alkyl, carbocyclic, aryl, and alkylaryl esters such as methyl, ethyl, propyl, ż so-propyl, butyl, isobutyl, *sec*-butyl, *tert-hvXyl,* cyclopropyl, phenyl, benzyl, and phenethyl esters, and the like.

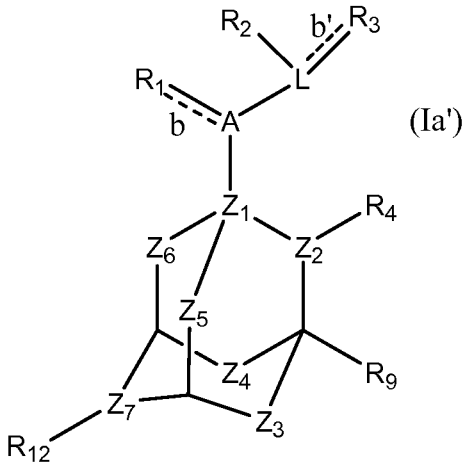
[0068] As will be readily understood, functional groups present may contain protecting groups during the course of synthesis. Protecting groups are known *per se* as chemical functional groups that can be selectively appended to and removed from functionalities, such as hydroxyl groups and carboxyl groups. These groups are present in a chemical compound to render such functionality ineroom temperatureto chemical reaction conditions to which the compound is exposed. Any of a variety of protecting groups may be employed with the present invention. Protecting groups that may be employed in accordance with the present invention may be described in *Greene, T.W. and Wuts, P.G.M., Protective Groups in Organic Synthesis 2d. Ed., Wiley & Sons, 1991.*

[0069] In a further aspect, the present disclosure relates to pharmaceutical compositions comprising a compound according to formula (la), (lb), or a pharmaceutically acceptable salt, isotopically substituted analogue, or stereoisomer thereof and a pharmaceutically acceptable carrier, diluent, or excipient. The applicable carrier, diluent, or excipient may be selected on the basis of the chosen route of administration and standard pharmaceutical practice as described, for example, in *Remington 's Pharmaceutical Sciences (Mack Pub. Co., Easton, PA, 1985),* the disclosure of which is hereby incorporated by reference in its entirety. The pharmaceutical compositions may further comprise a therapeutically effective amount of a further agent that modulates an influenza virus. With respect to certain embodiments, the present compositions may further comprise a therapeutically effective amount of a further agent that modulates Influenza A virus, Influenza B virus, or another Viroporin-type virus. For example, the further agent that modulates virus may be a known anti-viral agents, such as Tamiflu®, Relenza®, or peramivir. In certain embodiments, the present compositions comprise a therapeutically

effective amount of a compound according to formula (la) or (lb) which is administered in combination with immunizations or vaccines that are effective in preventing or lessening the symptoms of influenza. Examples include antibodies, immune suppressants, anti-inflammatory agents, and the like.

[0070] The present disclosure also pertains to methods for treating an influenza A virus-affected disease state or infection comprising the step of administering to a subject in need thereof a composition comprising

a compound according to formula (la')



(Ia')

wherein

A is Ci_3 alkylene or a bond between L and the atom at position Z_1;

L is nitrogen;

Ri is NH, NH_2, alkyl, or, if A is a bond, is absent;

dashed lines b and b' may independently represent a double bond;

R_2 is H, alkyl, -(D)(E), or is absent;

R_3 is -(X)(Y);

R_4 is -(R_5)(R6), halo, or is absent;

R_5 is nitrogen or oxygen;

Re is hydrogen or -(R_7)(R_8)

R_7 is alkylene, -CH(R_{7a})-, -$(CH_2)_{0-6}$CH(OH)-, or represents a bond between R_5 and Rg;

R_{7a} is alkyl;

Rg is optionally substituted mono-, di-, or tricyclic ring system that optionally includes one or more heteroatoms;

R_9 is -(Rio)(Ri i) or is absent;

Rio is oxygen, nitrogen, alkyl, $-CF_3$, or alkylene;

R_{11} is hydrogen, halo, or is absent;

R12 is alkyl, alkoxy, halo, oxo, or hydroxyl;

D is alkylene, alkenylene, alkynylene, -CH(Q)-, carbonyl, or a bond;

E is an optionally substituted mono-, di-, or tricyclic ring system that optionally includes one or more heteroatoms;

X is alkylene, alkenylene, alkynylene, -CH(Q)-, carbonyl, or a bond;

Q is alkyl, -C(=0)0(CH $_2)_{1-3}CH_3$, $-(CH_2)_{0-3}OH$, or -C(=0)-;

Y is an optionally substituted mono-, di-, or tricyclic ring system that optionally includes one or more heteroatoms;

Z_2 is optionally substituted alkylene of which one or more carbon atoms is optionally replaced with N, O, or S, or represents a bond between Z i and Z_8;

Z_3 is optionally substituted alkylene of which one or more carbon atoms is optionally replaced with N, O, or S, or represents a bond between Z_8 and Z_9;

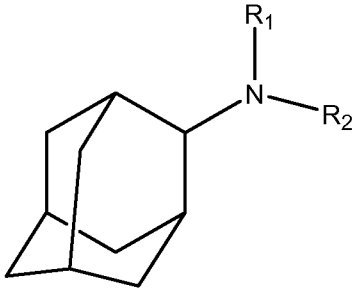
Z_4, Z_5, and Z_6 are independently alkylene, N, O, or S;

Z_7 is optionally substituted alkylene of which one or more carbon atoms is optionally replaced with N, O, or S;

or a stereoisomer, partial stereoisomer, isotopically substituted analogue, prodrug, pharmaceutically acceptable salt, hydrate, solvate, acid hydrate, or N-oxide thereof, wherein each of the variable groups may be defined according to any of the embodiments described above in connection with the inventive compounds according to formula (la), albeit without the limiting provisos that are recited with respect to the compounds according to formula (la);

or,

a compound according to formula (lb)



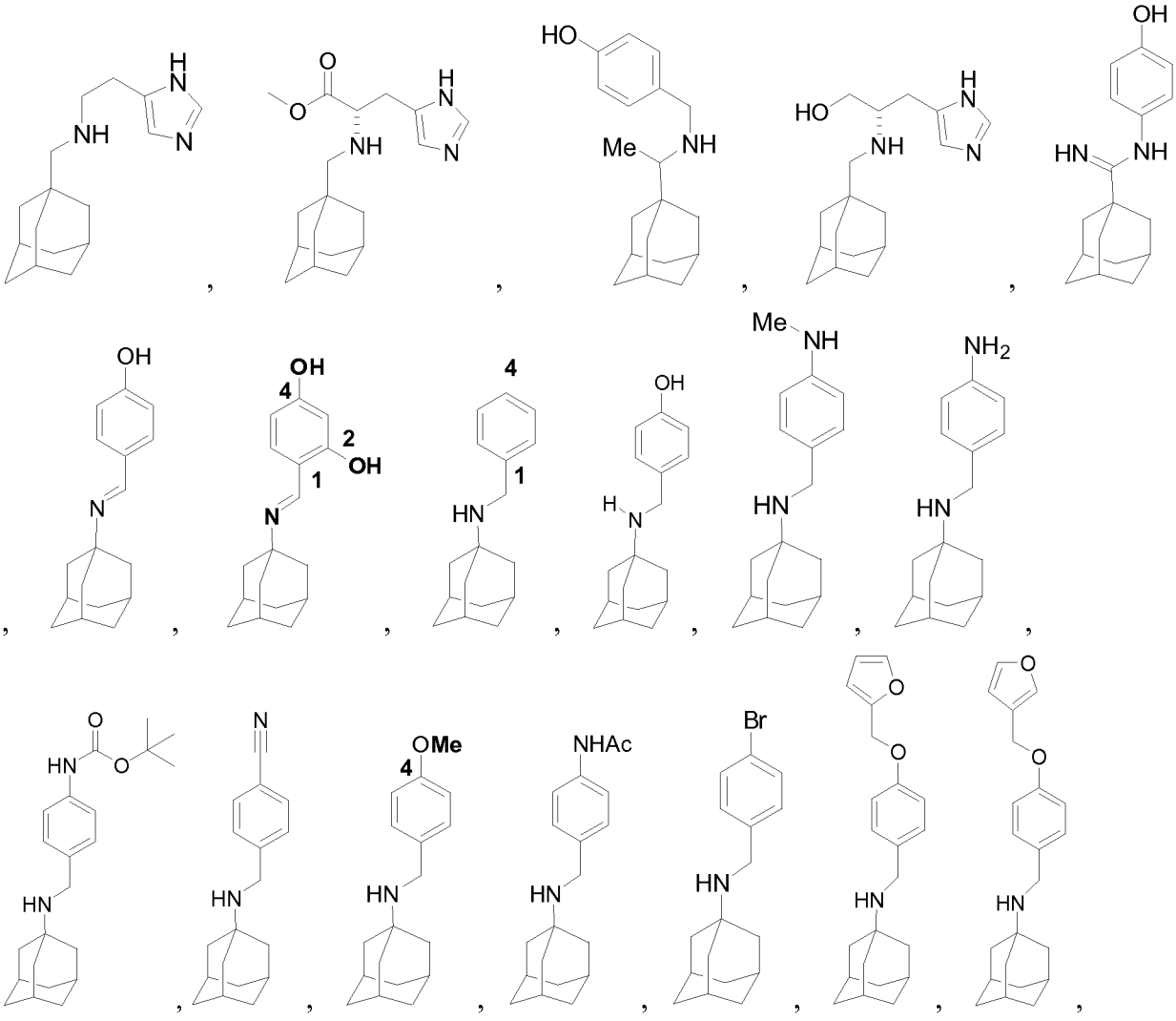
(Ib)

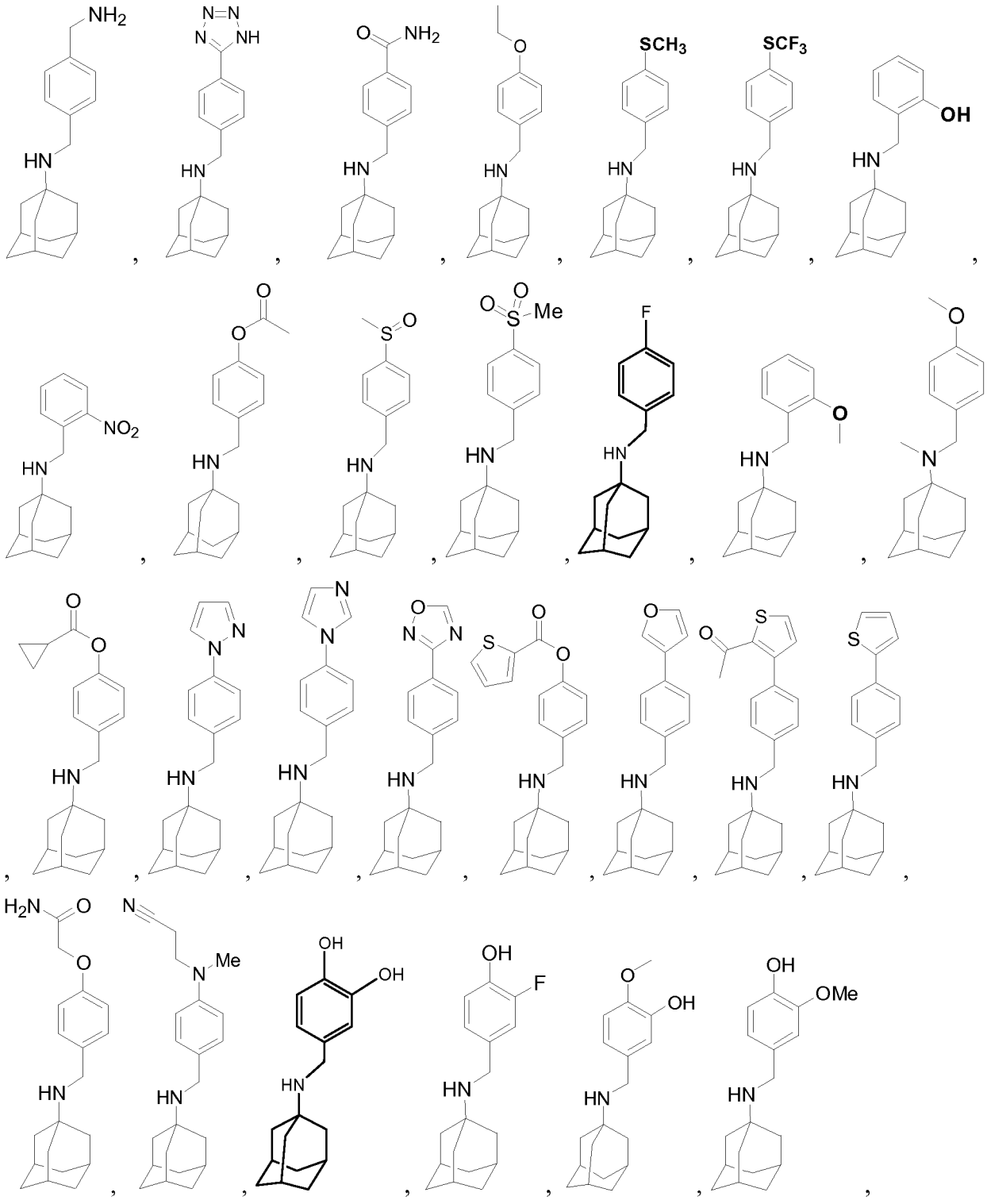
or a stereoisomer, partial stereoisomer, isotopically substituted analogue, prodrug, pharmaceutically acceptable salt, hydrate, solvate, acid hydrate, or N-oxide thereof, wherein Ri and R_2 may be defined according to any of the embodiments described above in connection with the inventive compounds according to formula (lb),

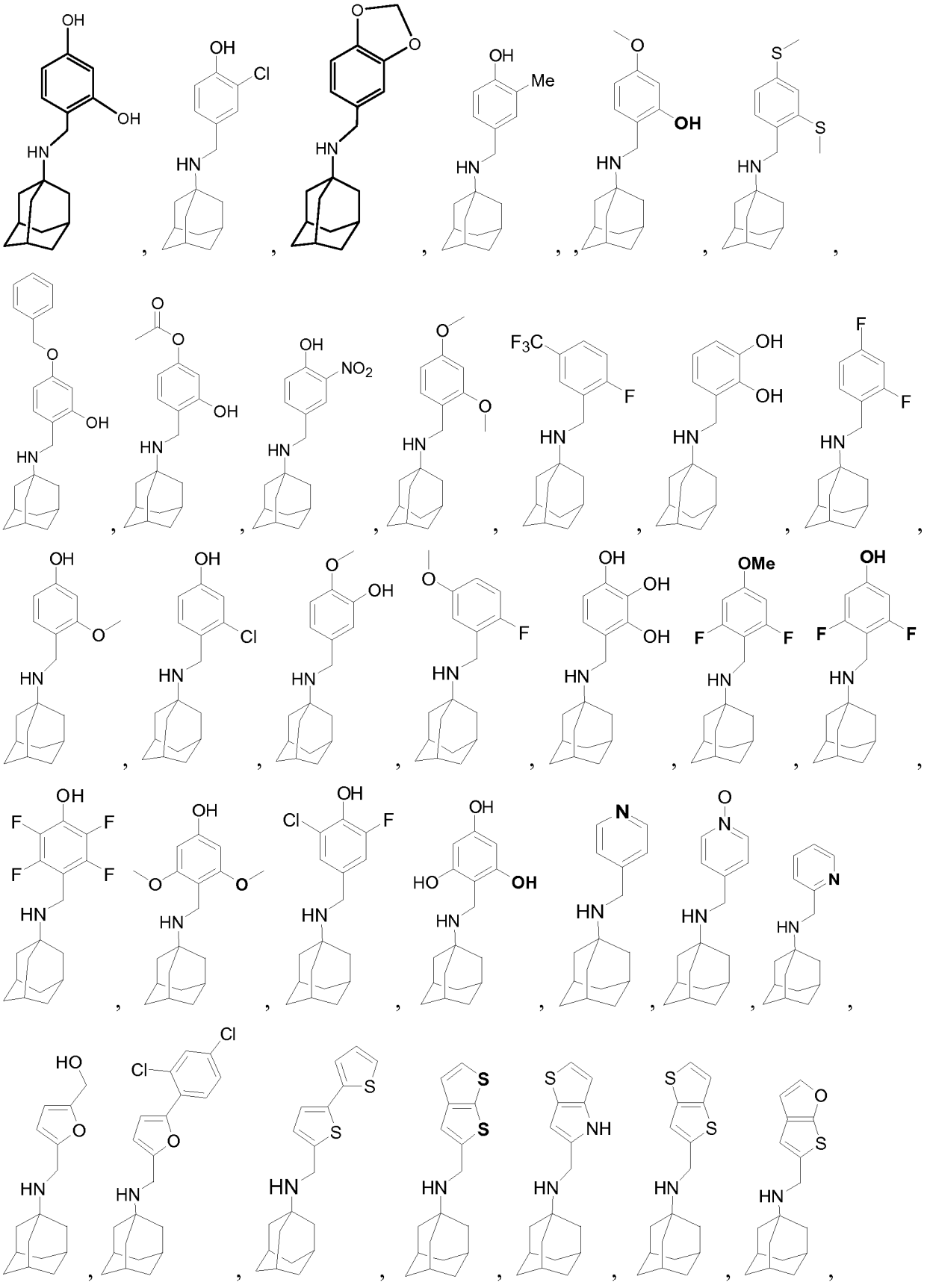
or,

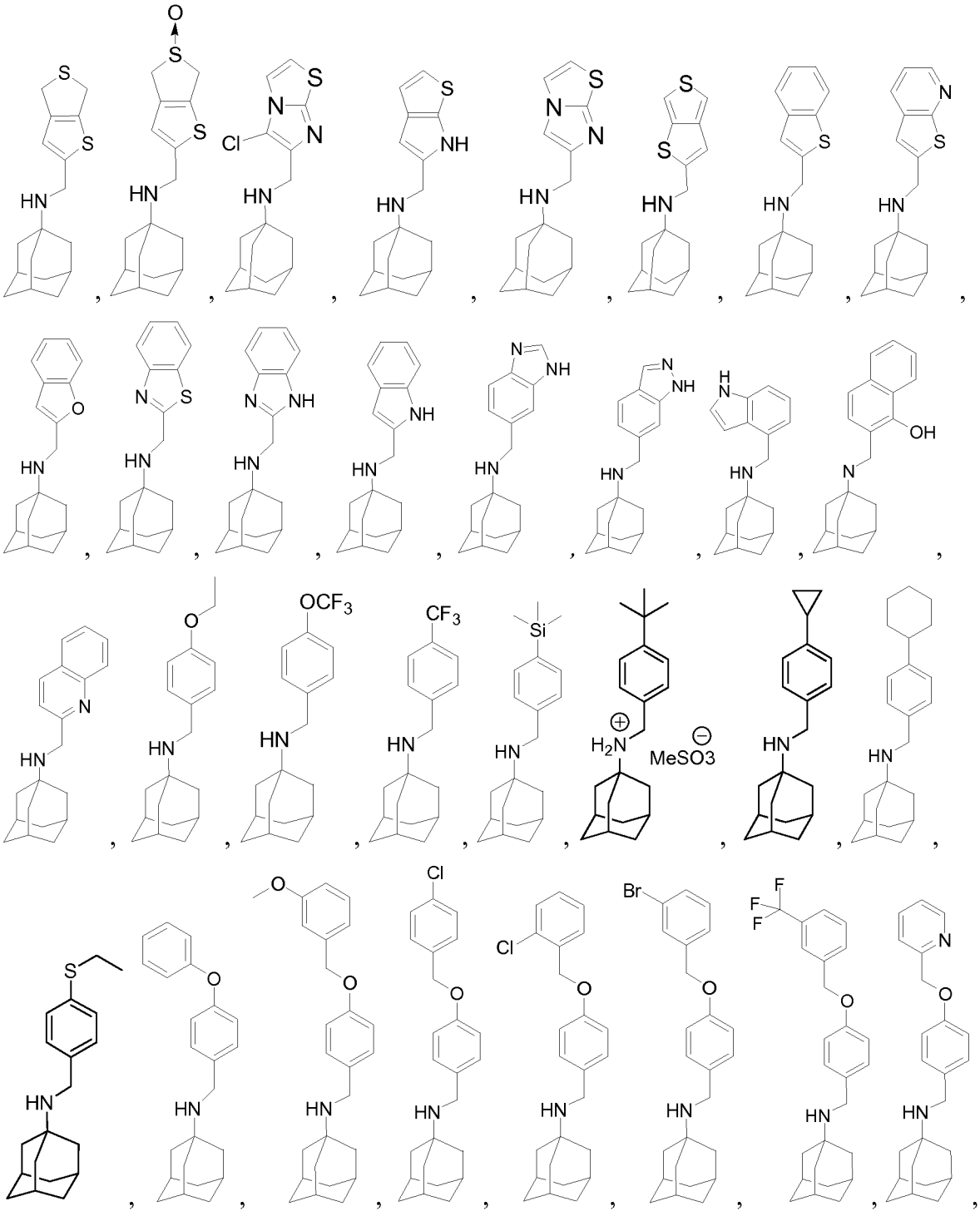
a combination of two more compounds according to any of formula (la') and (lb), and a pharmaceutically acceptable carrier, diluent, or excipient.

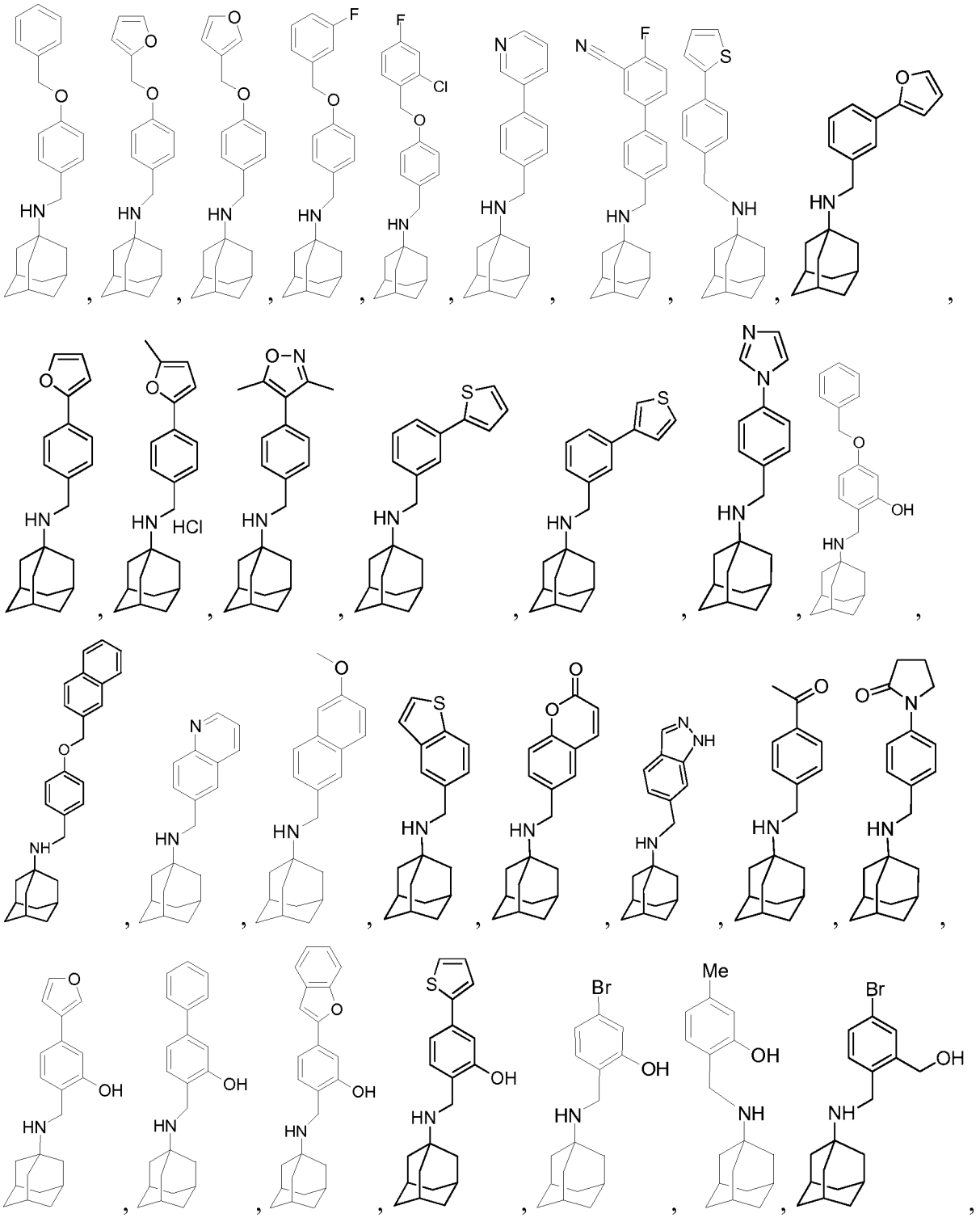
[0071] Exemplary compounds according to formula (la') include

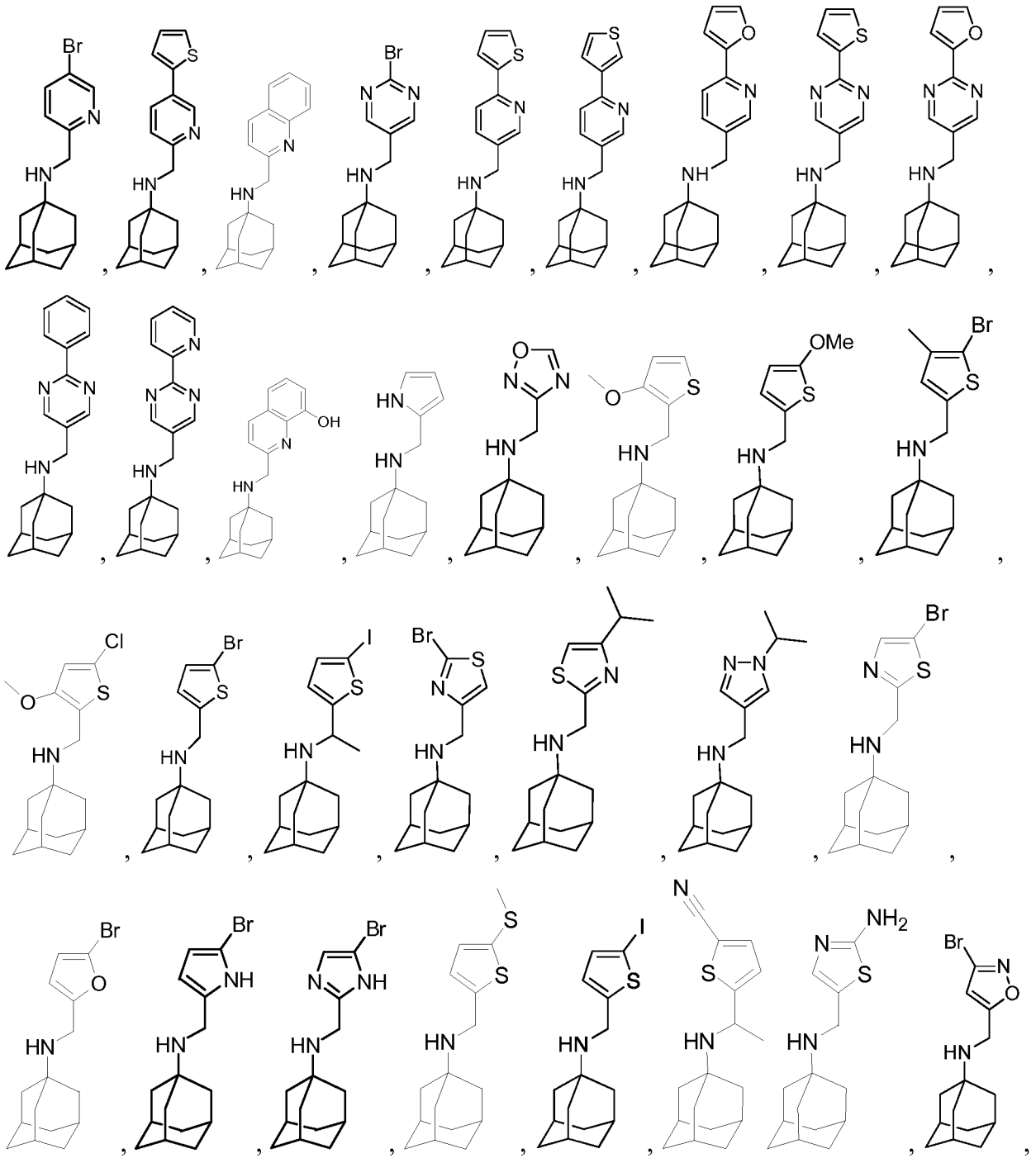


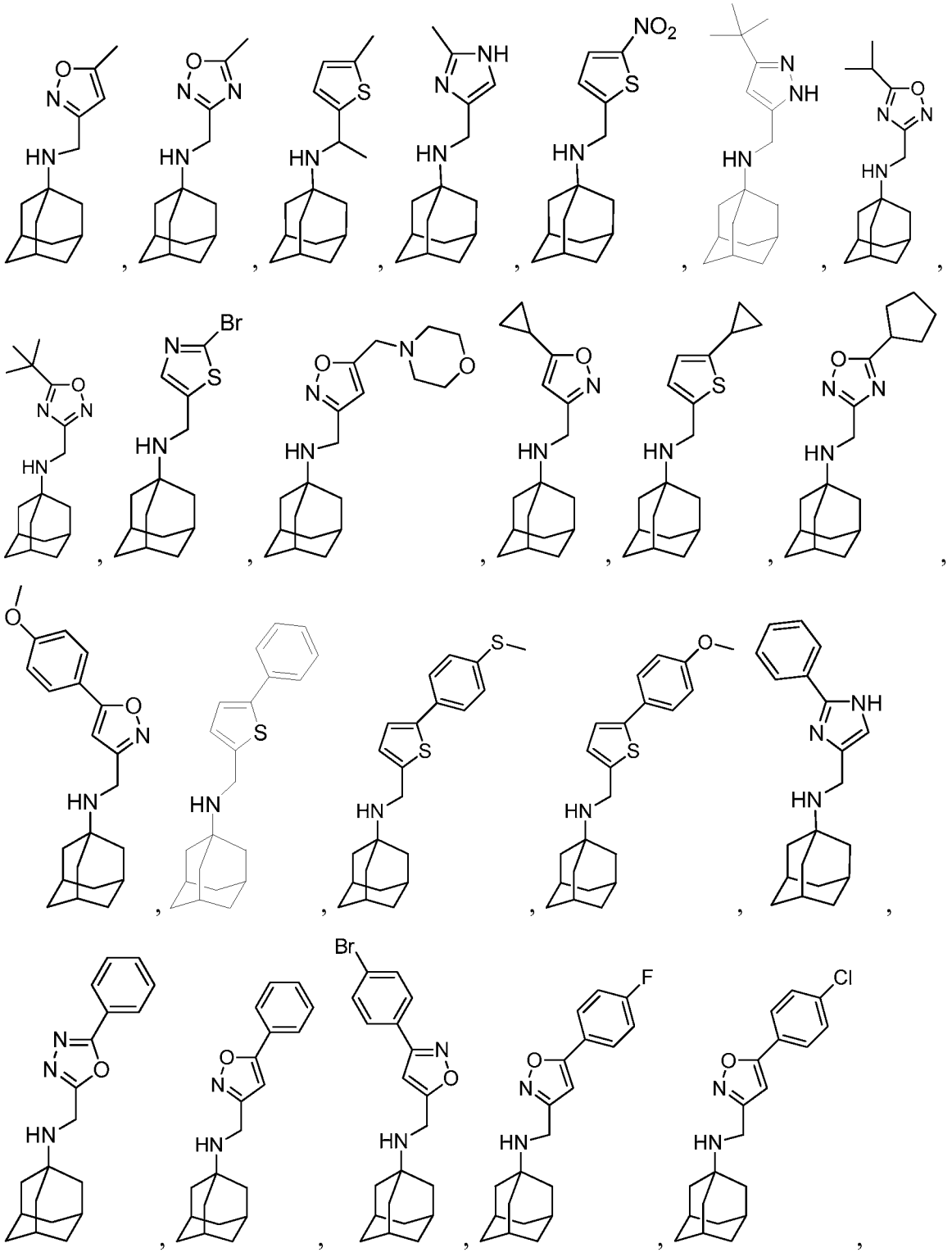


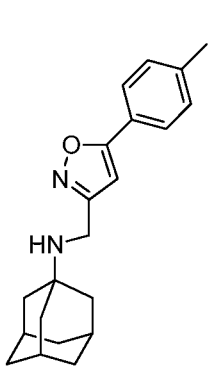
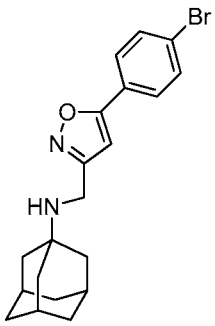
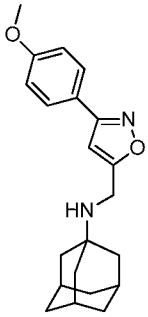
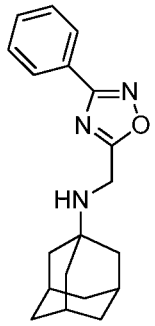
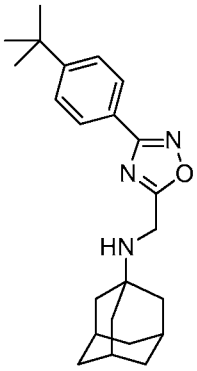
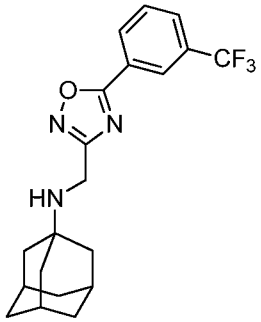
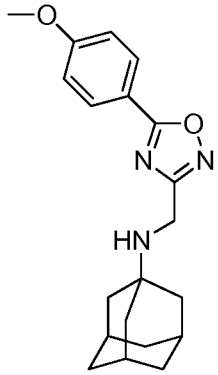
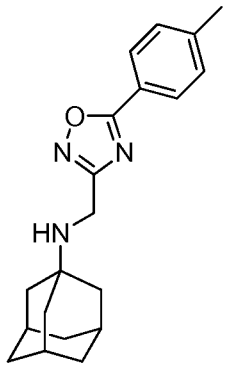
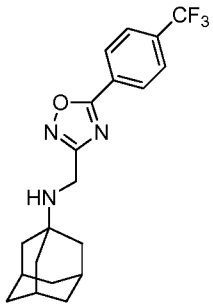
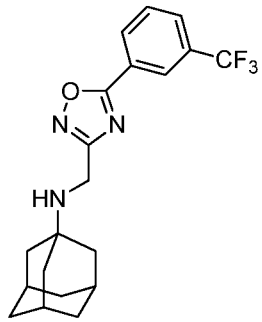
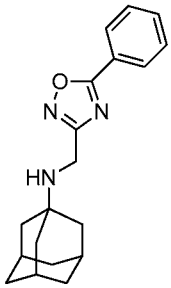
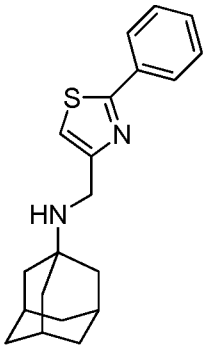
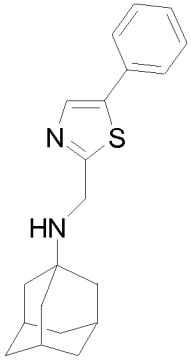
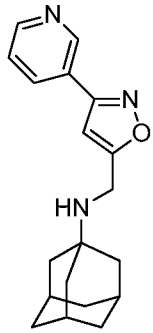
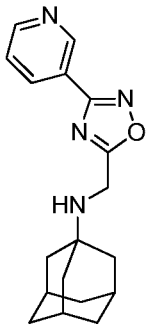
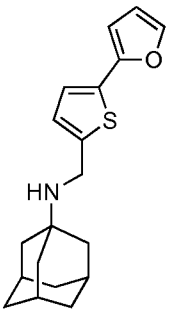
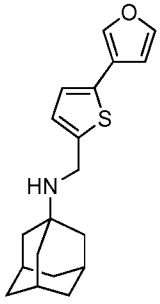
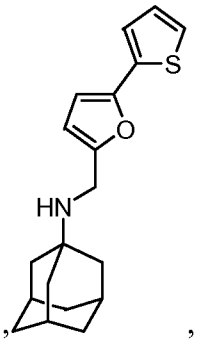
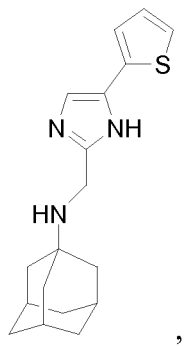
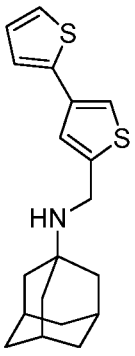
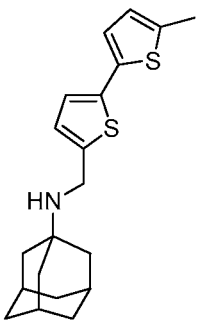
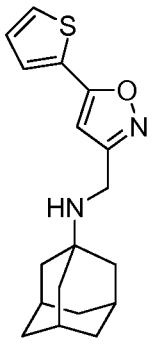
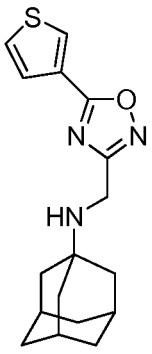


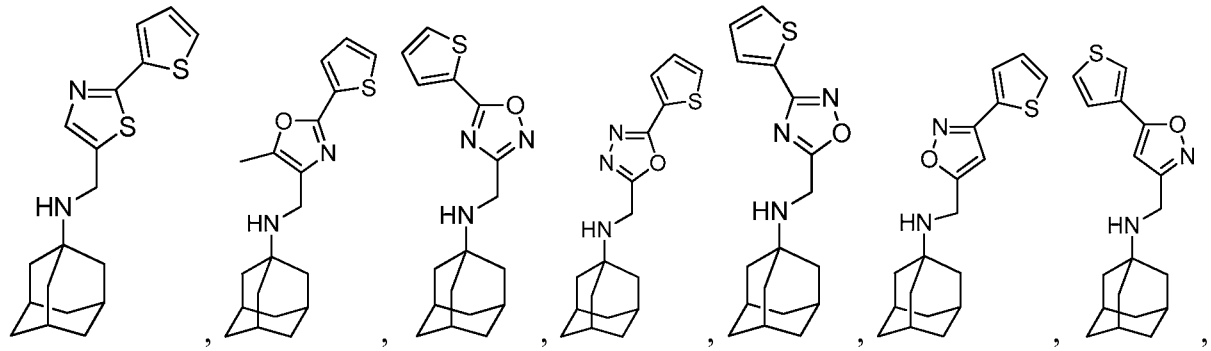


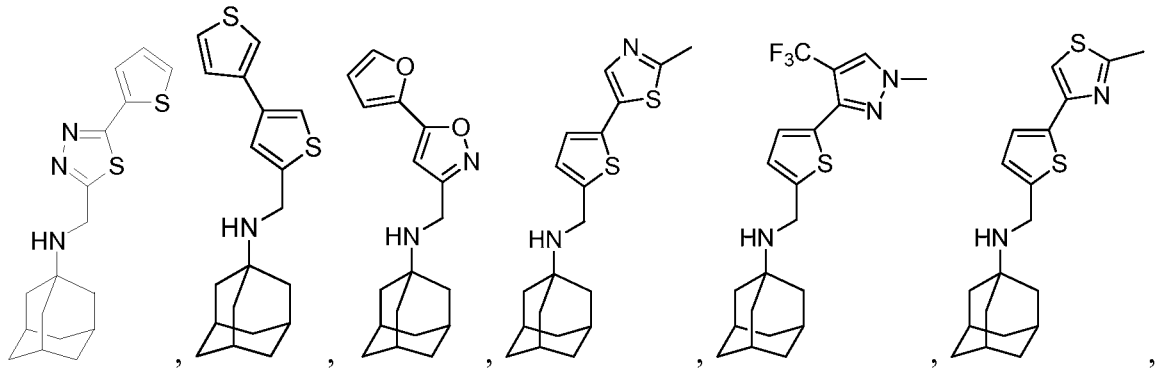


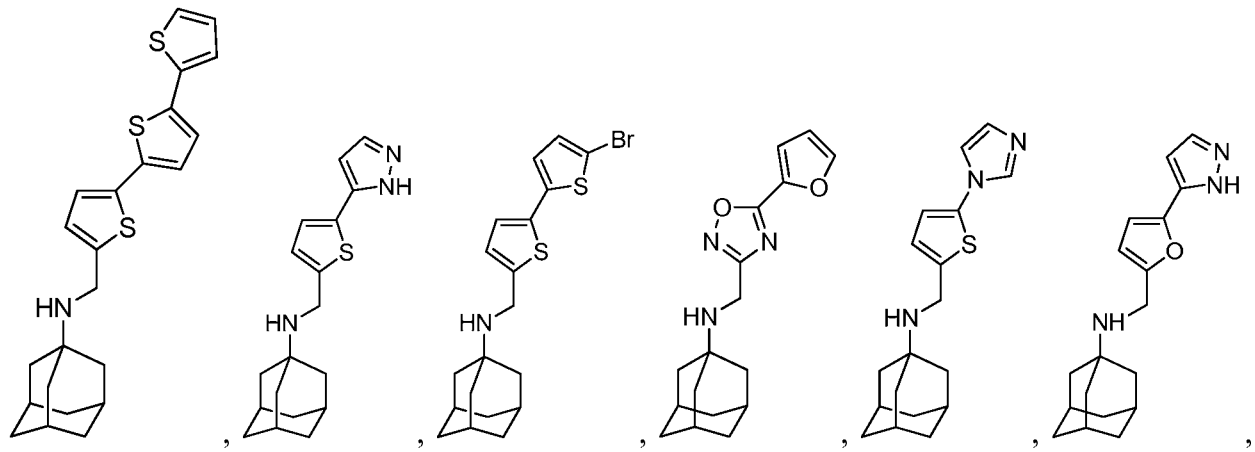


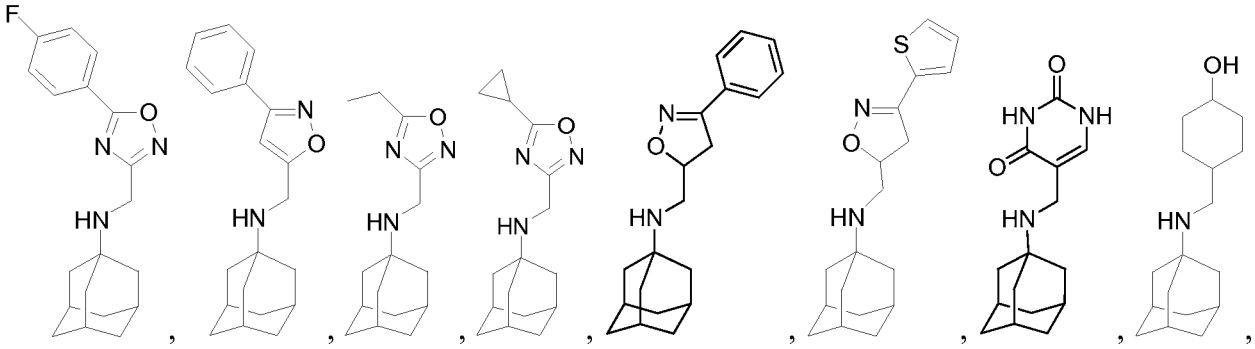


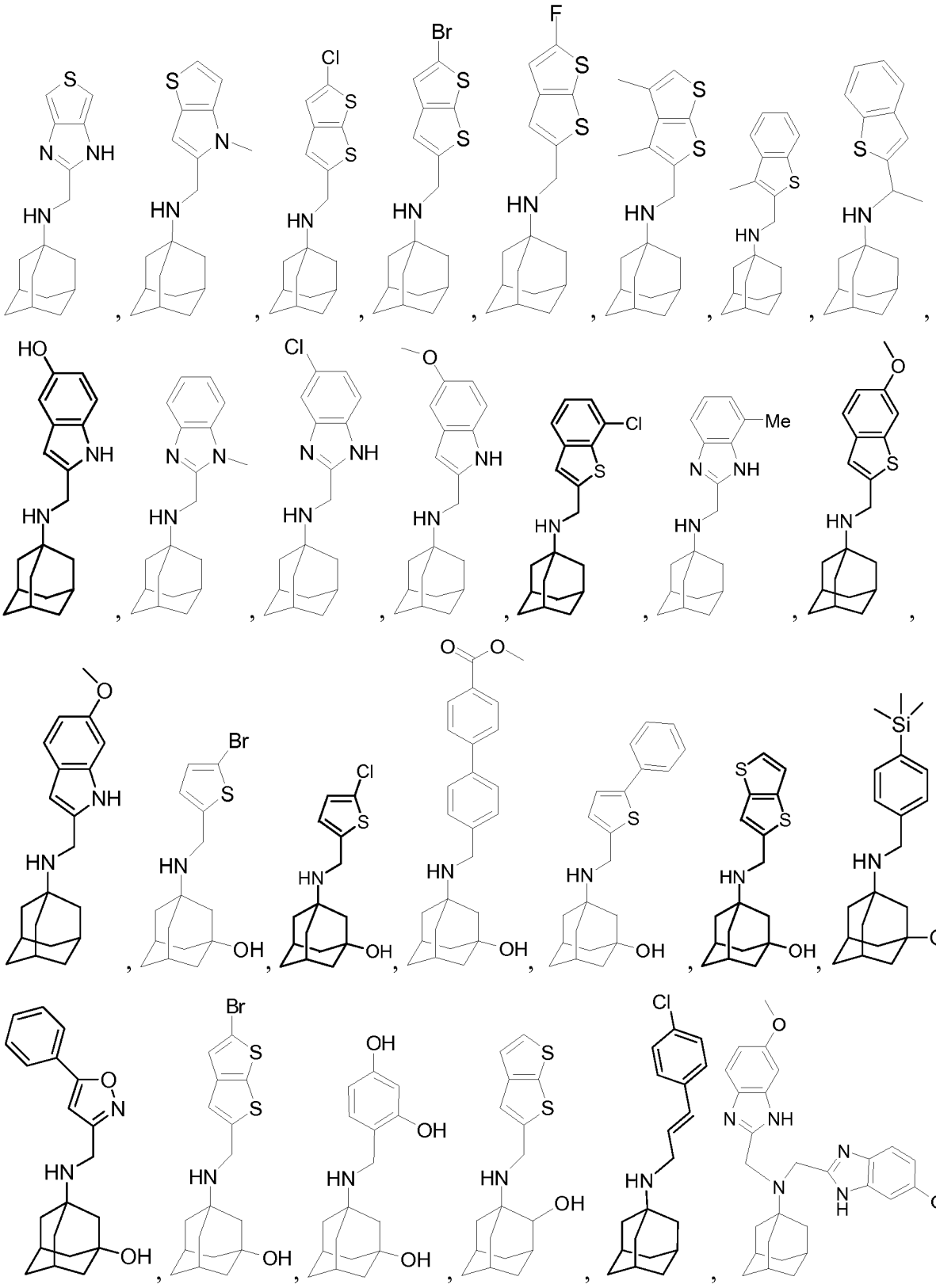
























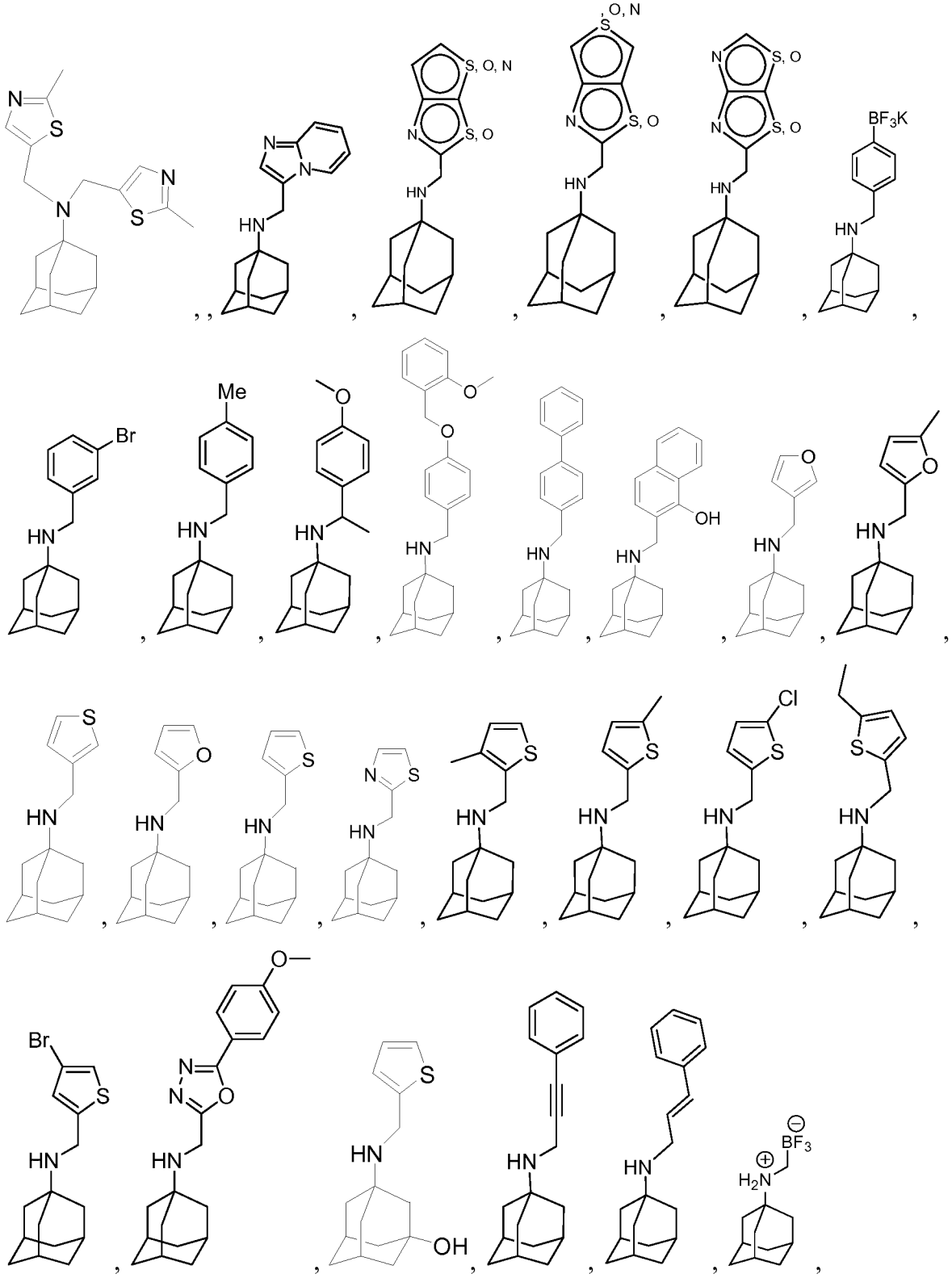


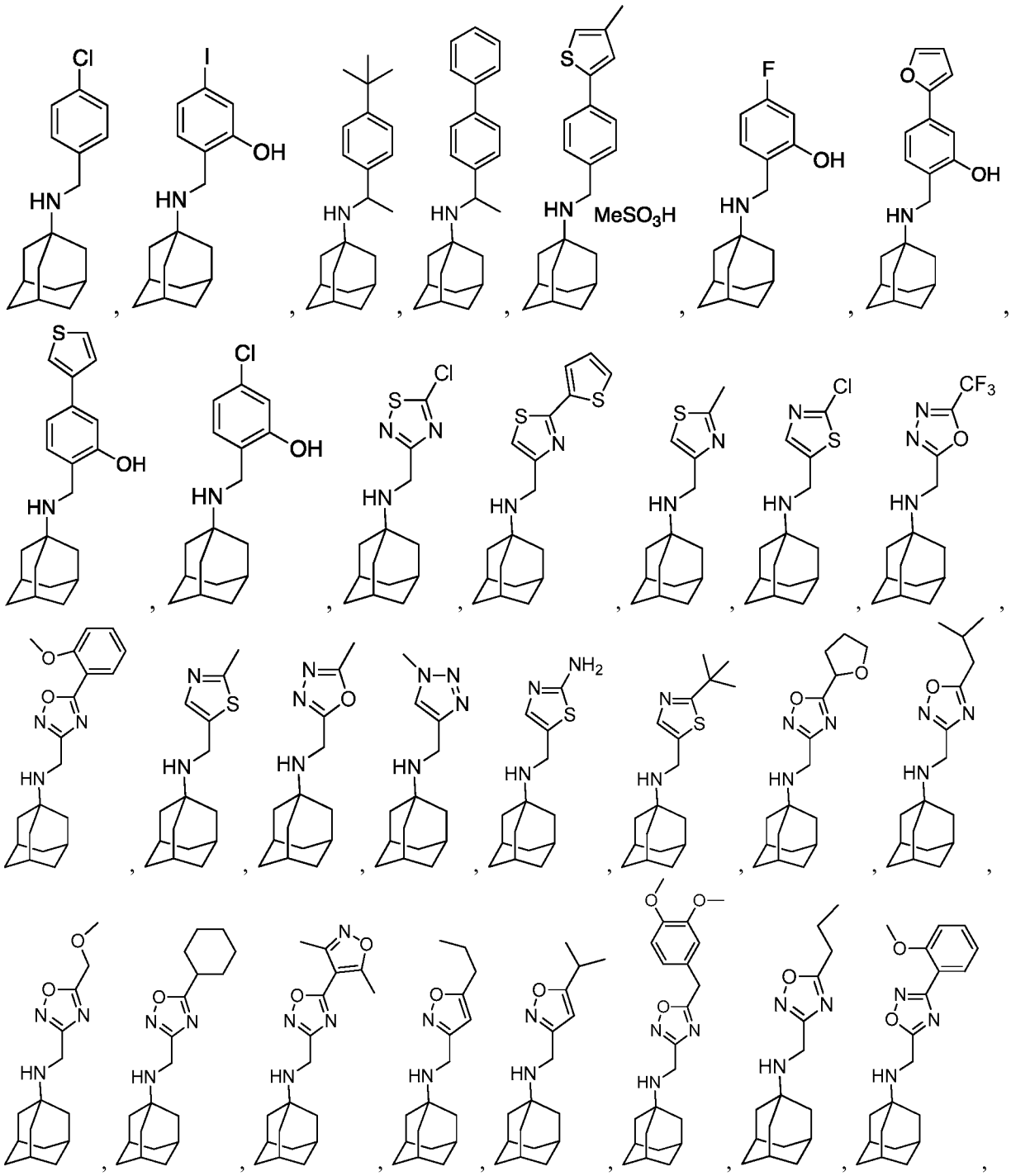


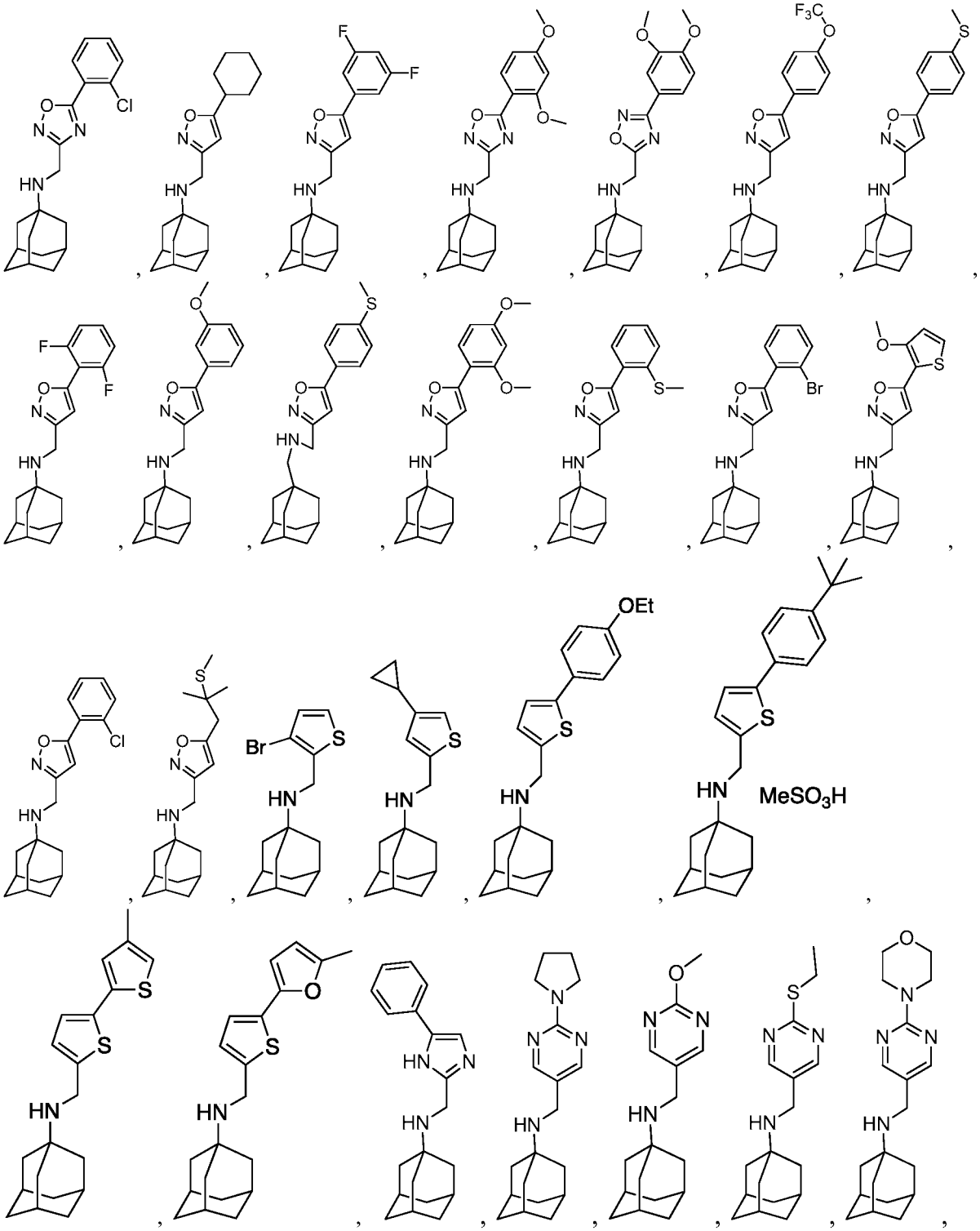


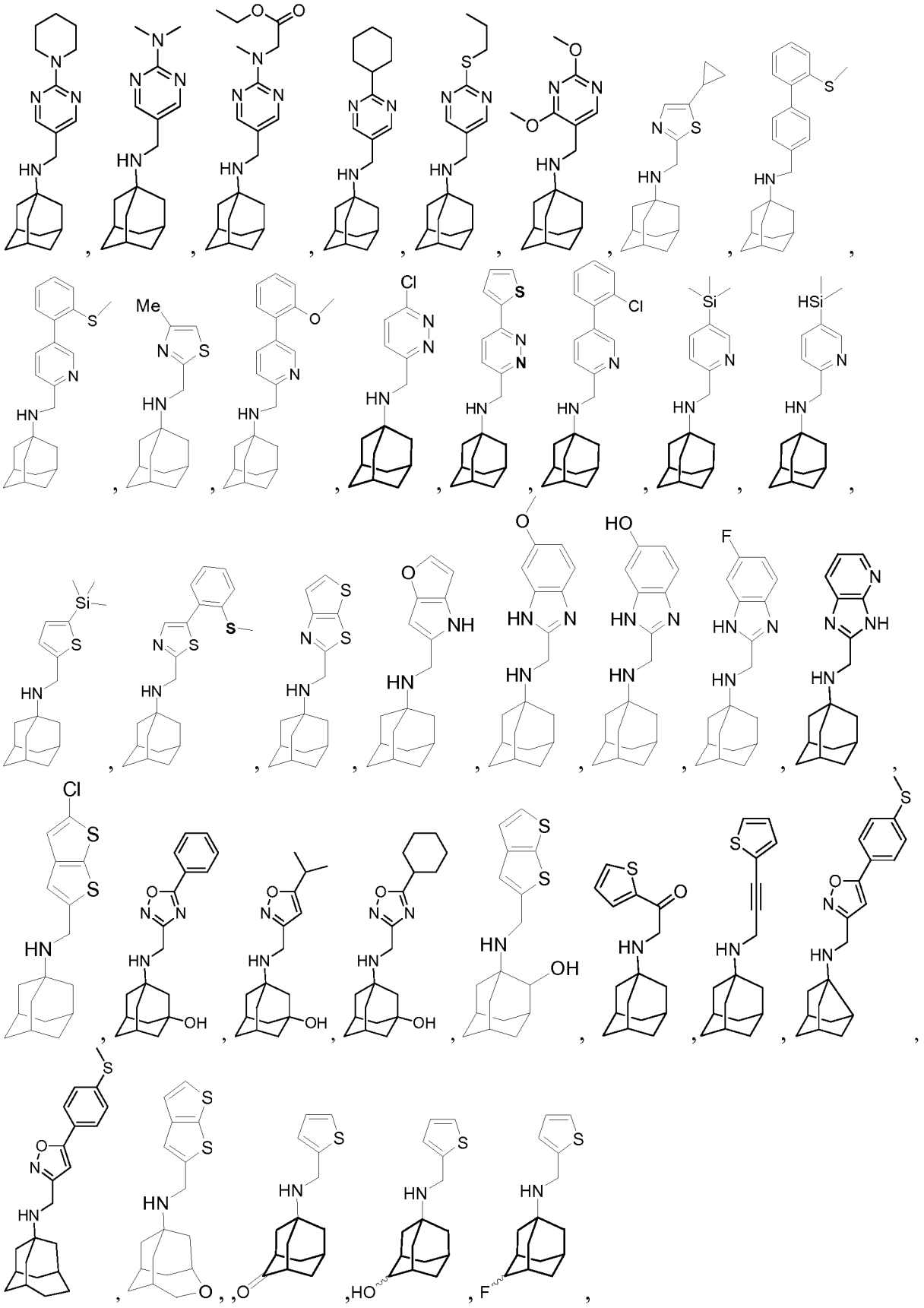












or a stereoisomer, partial stereoisomer, isotopically substituted analogue, prodrug, pharmaceutically acceptable salt, hydrate, solvate, acid hydrate, or N-oxide thereof.

[0072] In some embodiments, the methods provided herein inhibit an M2 proton channel *(i.e.,* M2 protein or M2) of an influenza virus (including M2 of an influenza A virus and/or BM2 of an influenza B virus). In some embodiments, the M2 belongs to a wild type influenza virus. In some embodiments, the M2 belongs to an influenza virus strain that is resistant to the existing anti-influenza drugs (such as amantadine and/or rimantadine), for example, a S31N mutant. The mutant virus may comprise an influenza virus having the L26F mutation; may comprise an influenza virus having the V27G mutation, the V27I mutation, the V27T mutation, the V27S mutation, or the V27A mutation; may comprise an influenza virus having the A30T mutation; may comprise an influenza virus having the S31A mutation or the S31N mutation; may an influenza virus having the G34E mutation or the G34A mutation; may comprise an influenza virus having the L38F mutation; may comprise an influenza virus having the W41L mutation or the W41Y mutation; may comprise an influenza virus having the D44N mutation or the D44H mutation; and/or may comprise an influenza virus having the R45K mutation or the R45H mutation.

[0073] In some embodiments, the methods provided herein inhibit VP24 of an Ebola or a Marburg virus.

[0074] In some embodiments, the methods provided herein inhibit NS3 protein of a Bluetongue virus.

[0075] In some embodiments, the methods provided herein inhibit a viroporin of a picomavirus, foot and mouth disease virus, African horse sickness virus, or Japanese encephalitis virus.

[0076] In some embodiments, the compounds and/or salts provided herein can inhibit (i.e., decrease activity of) an M2 proton channel of an influenza virus (including M2 of an influenza A virus; BM2 of an influenza B virus, M2 of a wild type influenza virus, and/or M2 of a drug resistant influenza such as S31N influenza or other drug-resistant strains) by, for example, binding to the transmembrane region of M2 and interfering with proton conduction inside the virus and ultimately preventing the replication of the virus. In some embodiments, the compounds and/or salts provided herein can inhibit M2 and prevent viral maturation and release

from the host cell. Accordingly, in some embodiments, the present invention provides a method for treating influenza (including wild type influenza and/or drug resistant influenza such as S3IN influenza or other drug-resistant strains) in a patient (including a human or another animal) comprising contacting the patient with a therapeutically effective amount of a compound of formula (la'), (lb), or (II) as defined herein. In some embodiments, the method is a method for treating influenza that is a wild type. In some embodiments, the method is for treating influenza that is resistant to one or more of the existing anti-influenza drugs. In some embodiments, the method is a method for treating influenza that is resistant to amantadine and/or rimantadine.

[0077] In some embodiments, the compounds and/or salts provided herein can inhibit other integral membrane proteins that possess viroporin activity similar to the M2 protein (for example, VP24 of Ebola and Marburg viruses, NS3 protein of a Bluetongue virus, and a viroporin of a picomavirus, foot and mouth disease virus, African horse sickness virus, or Japanese encephalitis virus). Accordingly, in some embodiments, the present invention provides methods for treating Ebola, Marburg, bluetongue, foot and mouth disease, African horse sickness, and Japanese encephalitis in a patient (including a human or another animal) comprising contacting the patient with a therapeutically effective amount of the compound of formula (la'), (lb), or (II) as defined herein. In some embodiments, the method is a method for treating Ebola or Marburg in a patient. In some embodiments, the method is a method for treating Bluetongue in a patient. In some embodiments, the method is a method of treating a picomavirus infection, foot and mouth disease, African horse sickness, or Japanese encephalitis in a patient.

[0078] Methods of measuring inhibition of M2 protein of an influenza vims (or other integral membrane proteins that possess viroporin activity similar to the M2 protein (for example, VP24 of Ebola and Marburg vimses, NS3 protein of a Bluetongue vims, and a viroporin of a picomavims, foot and mouth disease, African horse sickness, or Japanese encephalitis vims) are routine in the art.

[0079] The present invention further provides methods for treating viral infections such as influenza, Ebola, Marburg, bluetongue, foot and mouth disease, African horse sickness, and Japanese encephalitis in an individual *(e.g.,* patient) by administering to the individual in need of such treatment a therapeutically effective amount or dose of a compound of formula (la'), (lb), or (II) as defined herein or a pharmaceutical composition thereof.

[0080] As used herein, the term "cell" is meant to refer to a cell that is *in vitro, ex vivo* or *in vivo.* In some embodiments, an *ex vivo* cell can be paroom temperatureof a tissue sample excised from an organism such as a mammal. In some embodiments, an *in vitro* cell can be a cell in a cell culture. In some embodiments, an *in vivo* cell is a cell living in an organism such as a mammal.

[0081] As used herein, the term "contacting" refers to the bringing together of indicated moieties in an *in vitro* system or an *in vivo* system. For example, "contacting" the M2 protein *(i.e.,* the M2 proton channel) of an influenza virus with a compound in the invention may include the administration of a compound in the present invention to an individual or patient, such as a human, having an influenza infection, as well as, for example, introducing a compound of the invention into a sample containing a cellular or purified preparation containing the M2 protein.

[0082] As used herein, the term "individual" or "patient," used interchangeably, refers to any animal, including mammals, such as mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, such as humans.

[0083] As used herein, the phrase "therapeutically effective amount" refers to the amount of active compound or pharmaceutical agent that elicits the biological or medicinal response that is being sought in a tissue, system, animal, individual or human by a researcher, veterinarian, medical doctor or other clinician, which includes one or more of the following:

(1) preventing the disease; for example, preventing a disease, condition or disorder in an individual who may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease;

(2) inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., including arresting further development of the pathology and/or symptomatology); and

(3) ameliorating the disease; for example, ameliorating a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., including reversing the pathology and/or symptomatology).

[0084] A subject or patient in whom administration of the therapeutic compound is an effective therapeutic regimen for a disease or disorder is preferably a human, but can be any

animal, including a laboratory animal in the context of a clinical trial or screening or activity experiment. Thus, as can be readily appreciated by one of ordinary skill in the art, the methods, compounds and compositions of the present invention are particularly suited to administration to any animal, particularly a mammal, and including, but by no means limited to, humans, domestic animals, such as feline or canine subjects, farm animals, such as but not limited to bovine, equine, caprine, ovine, and porcine subjects, wild animals (whether in the wild or in a zoological garden), research animals, such as mice, rats, rabbits, goats, sheep, pigs, dogs, cats, and the like, avian species, such as chickens, turkeys, songbirds, and the like, *i.e.,* for veterinary medical use.

[0085] The compounds of this invention may be administered orally or parenterally, neat or in combination with conventional pharmaceutical carriers, diluents, or excipients, which may be liquid or solid. The applicable solid carrier, diluent, or excipient may function as, among other things, a binder, disintegrant, filler, lubricant, glidant, compression aid, processing aid, color, sweetener, preservative, suspensing/dispersing agent, tablet-disintegrating agent, encapsulating material, film former or coating, flavors, or printing ink. Of course, any material used in preparing any dosage unit form is preferably pharmaceutically pure and substantially non-toxic in the amounts employed. In addition, the active compound may be incorporated into sustained-release preparations and formulations. Parenteral administration in this respect includes administration by, *inter alia*, the following routes: intravenous, intramuscular, subcutaneous, intraocular, intrasynovial, transepithelial including transdermal, ophthalmic, sublingual and buccal; topically including ophthalmic, dermal, ocular, rectal and nasal inhalation via insufflation, aerosol, and rectal systemic.

[0086] In powders, the carrier, diluent, or excipient may be a finely divided solid that is in admixture with the finely divided active ingredient. In tablets, the active ingredient is mixed with a carrier, diluent or excipient having the necessary compression properties in suitable proportions and compacted in the shape and size desired. For oral therapeutic administration, the active compound may be incorporated with the carrier, diluent, or excipient and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. The amount of active compound(s) in such therapeutically useful compositions is preferably such that a suitable dosage will be obtained. The therapeutic compositions preferably contain up to about 99% of the active ingredient.

[0087] Liquid carriers, diluents, or excipients may be used in preparing solutions, suspensions, emulsions, syrups, elixirs, and the like. The active ingredient of this invention can be dissolved or suspended in a pharmaceutically acceptable liquid such as water, an organic solvent, a mixture of both, or pharmaceutically acceptable oils or fat. The liquid carrier, excipient, or diluent can contain other suitable pharmaceutical additives such as solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilizers, or osmo-regulators.

[0088] Suitable solid carriers, diluents, and excipients may include, for example, calcium phosphate, silicon dioxide, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, ethylcellulose, sodium carboxymethyl cellulose, microcrystalline cellulose, polyvinylpyrrolidine, low melting waxes, ion exchange resins, croscarmellose carbon, acacia, pregelatinized starch, crospovidone, HPMC, povidone, titanium dioxide, polycrystalline cellulose, aluminum methahydroxide, agar-agar, tragacanth, or mixtures thereof.

[0089] Suitable examples of liquid carriers, diluents and excipients for oral and parenteral administration include water (particularly containing additives as above, *e.g.* cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols, *e.g.* glycols) and their derivatives, and oils *(e.g.* fractionated coconut oil and arachis oil), or mixtures thereof.

[0090] For parenteral administration, the carrier, diluent, or excipient can also be an oily ester such as ethyl oleate and isopropyl myristate. Also contemplated are sterile liquid carriers, diluents, or excipients, which are used in sterile liquid form compositions for parenteral administration. Solutions of the active compounds as free bases or pharmacologically acceptable salts can be prepared in water suitably mixed with a surfactant, such as hydroxypropylcellulose. A dispersion can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations may contain a preservative to prevent the growth of microorganisms.

[0091] The pharmaceutical forms suitable for injectable use include, for example, sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form is preferably sterile and fluid to provide easy syringability. It is preferably stable under the conditions of manufacture and

storage and is preferably preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier, diluent, or excipient may be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, liquid polyethylene glycol and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating, such as lecithin, by the maintenance of the required particle size in the case of a dispersion, and by the use of surfactants. The prevention of the action of microorganisms may be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions may be achieved by the use of agents delaying absorption, for example, aluminum monostearate and gelatin.

[0092] Sterile injectable solutions may be prepared by incorporating the active compounds in the required amounts, in the appropriate solvent, with various of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions may be prepared by incorporating the sterilized active ingredient into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation may include vacuum drying and the freeze drying technique that yields a powder of the active ingredient or ingredients, plus any additional desired ingredient from the previously sterile-filtered solution thereof.

[0093] The compounds of the invention may be administered in an effective amount by any of the conventional techniques well-established in the medical field. The compounds employed in the methods of the present invention including the compounds of formula (la'), (lb), or (II), may be administered by any means that results in the contact of the active agents with the agents' site or sites of action in the body of a patient. The compounds may be administered by any conventional means available.

[0094] Preferably the pharmaceutical composition is in unit dosage form, *e.g.* as tablets, buccal tablets, troches, capsules, elixirs, powders, solutions, suspensions, emulsions, syrups, wafers, granules, suppositories, or the like. In such form, the composition is sub-divided in unit dose containing appropriate quantities of the active ingredient; the unit dosage forms can be

packaged compositions, for example packeted powders, vials, ampoules, prefilled syringes or sachets containing liquids. The unit dosage form can be, for example, a capsule or tablet itself, or it can be the appropriate number of any such compositions in package form. In addition, dosage forms of the present invention can be in the form of capsules wherein one active ingredient is compressed into a tablet or in the form of a plurality of microtablets, particles, granules or non-perils. These microtablets, particles, granules or non-perils are then placed into a capsule or compressed into a capsule, possibly along with a granulation of the another active ingredient.

[0095] The dosage of the compounds of the present invention that will be most suitable for prophylaxis or treatment will vary with the form of administration, the particular compound chosen and the physiological characteristics of the particular patient under treatment. Generally, small dosages may be used initially and, if necessary, increased by small increments until the desired effect under the circumstances is reached. Generally speaking, oral administration may require higher dosages.

[0096] The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per day. The sub-dose itself may be further divided, *e.g.*, into a number of discrete loosely spaced administrations. The dose may also be provided by controlled release of the compound, by techniques well known to those in the art.

[0097] Additional information regarding the preparation of the present compounds for administration and the formulation of compositions according to the present invention is provided *infra.*

[0098] The compounds useful in the methods of the present invention may be prepared in a number of ways well known to those skilled in the art. The compounds can be synthesized, for example, by the methods as described below, or variations thereon as appreciated by the skilled artisan. The reagents used in the preparation of the compounds of this invention can be either commercially obtained or can be prepared by standard procedures described in the literature. All processes disclosed in association with the present invention are contemplated to be practiced on any scale, including milligram, gram, multigram, kilogram, multikilogram or commercial industrial scale.

[0099] For compounds herein in which a variable appears more than once, each variable can be a different moiety selected from the Markush group defining the variable. For example, where a structure is described having two R groups that are simultaneously present on the same compound, the two R groups can represent different moieties selected from the Markush group defined for R.

[0100] It is further appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, can also be provided in combination in a single embodiment. Conversely, various features of the invention which are, for brevity, described in the context of a single embodiment, can also be provided separately or in any suitable subcombination.

[0101] The present invention is further defined in the following Examples. It should be understood that these examples, while indicating preferred embodiments of the invention, are given by way of illustration only, and should not be construed as limiting the appended claims From the above discussion and these examples, one skilled in the art can ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

EXAMPLES

[0102] ***General Synthesis.*** The compounds of this invention can be prepared from readily available starting materials using the following general methods and procedures. It will be appreciated that where typical or suitable process conditions (i.e., reaction temperatures, times, mole ratios of reactants, solvents, pressures, etc.) are given, other process conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvent used, but such conditions can be determined by one skilled in the art by routine optimization procedures.

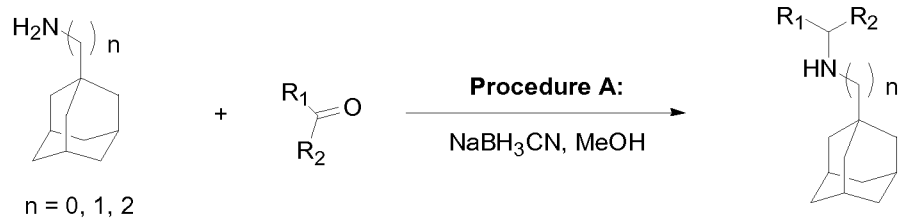
[0103] The processes described herein can be monitored according to any suitable method known in the art. For example, product formation can be monitored by spectroscopic means, such as nuclear magnetic resonance spectroscopy (e.g., ^{1}H or ^{13}C NMR), infrared spectroscopy (IR), spectrophotometry ***{e.g.,*** UV-visible), or mass spectrometry, or by chromatography such as high performance liquid chromatography (HPLC) or thin layer chromatography.

[0104] Preparation of compounds can involve the protection and deprotection of various chemical groups. The need for protection and deprotection, and the selection of appropriate protecting groups can be readily determined by one skilled in the art. The chemistry of protecting groups can be found, for example, in P. G. M. Wuts and T. Greene, *Greene's Protective Groups in Organic Synthesis*, 4th. Ed., Wiley & Sons, 2006, which is incorporated herein by reference in its entirety.

[0105] The reactions of the processes described herein can be carried out in suitable solvents which can be readily selected by one of skill in the art of organic synthesis. Suitable solvents can be substantially nonreactive with the starting materials (reactants), the intermediates, or products at the temperatures at which the reactions are carried out, *i.e.*, temperatures which can range from the solvent's freezing temperature to the solvent's boiling temperature. A given reaction can be carried out in one solvent or a mixture of more than one solvent. Depending on the particular reaction step, suitable solvents for a particular reaction step can be selected. The compounds of the invention can be prepared, for example, using the reaction pathways and techniques as described below.

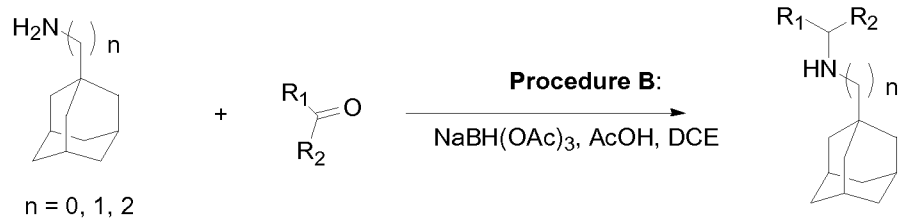
Generalprocedures

[0106] **Procedure** A: Amine (1.2 equiv) and aldehyde/ketone (1.0 equiv) were mixed in methanol and then treated with sodium cyanoborohydride (3.0eq). The mixture was stirred at room temperature under a N_2 atmosphere overnight. The reaction mixture was quenched by adding water, and the product was extracted with butanol. The combined organic layer was dried over $Na_2SC"4$, and concentrated under reduced pressure. The crude product was separated by flash column chromatography (1-10% CH_30H/CH_2C1_2).

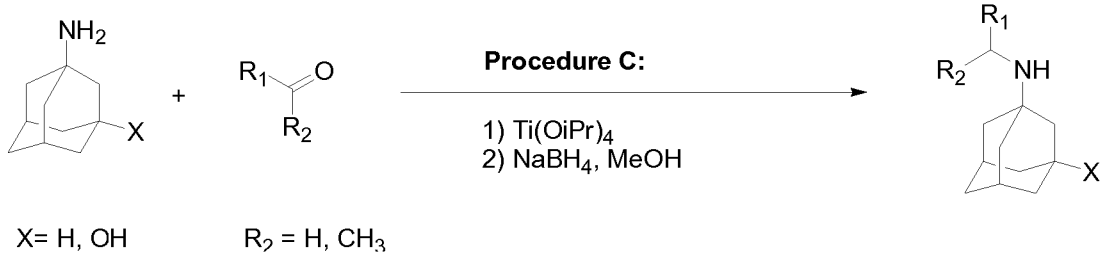


[0107] **Procedure B:** Amine (1equiv) and aldehyde/ketone (leq) were mixed in 1,2-dichloroethane and then treated with sodium triacetoxyborohydride (1.4eq) and AcOH (leq). The mixture was stirred at room temperature under a N_2 atmosphere overnight. The reaction

mixture was quenched by adding 1 N NaOH, and the product was extracted with DCM. The combined organic layer was dried over $MgS0_4$, and concentrated under reduced pressure after filtration. The crude product was separated by flash column chromatography (1-10% CH_30H/CH_2C1_2).

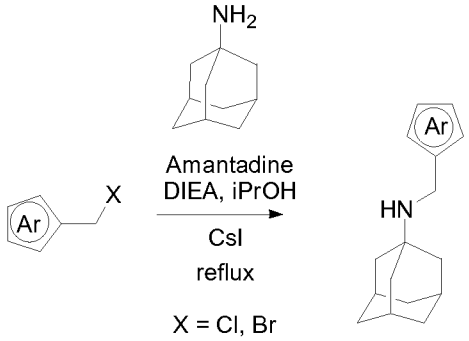


[0108] Procedure C: Adamantane (1 eq) and aldehyde (1 eq) were mixed, and 2 ml of titanium (IV) isopropoxide was added. The resulting slurry was heated to 100 °C and stirred overnight. Then the solution was cooled down to 0 °C in ice bath, methanol was added and sodium boronhydride (4 eq) was added portionwise in 10 mins. The solution was warmed to room temperature and stirred overnight. The solvent was removed under reduced pressure, and the resulting residue was extracted with ethyl acetate and water. The organic layer was separated, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The mixture was then purified by silica gel flash column chromatography to give the final product (5-10% CH_3OH/CH_2Cl_2).



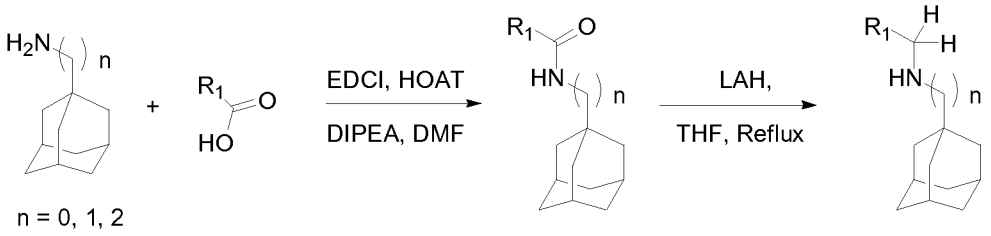
[0109] Procedure D: The chloride/bromide (1 eq), amantadine (1.5 eq) was dissolved in isopropanol, Csl (0.1 eq) and triethyl amine (2 eq) were then added. The reaction mixture was heated to reflux overnight. The solvent was removed under reduced pressure, and the resulting residue was extracted with dichloromethane and water. The organic layer was separated, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The

mixture was then purified by silica gel flash column chromatography to give the final product (5-10% CH_30H/CH_2C1_2).



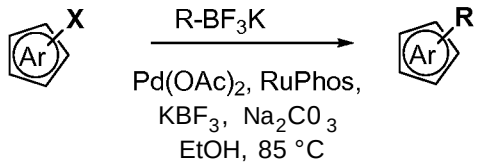
[0110] **Procedure** E: Acid (1.0 equiv) was added to a solution (0.5 M) of HOAT (1.5 equiv) and EDCI (1.5 equiv) in anhydrous DMF and stirring was continued for 1 h. Then, amine (1.5 equiv) was added and the reaction mixture was stirred at room temperature overnight. After the solvent was removed under reduced pressure, the residue was purified by flash column chromatography (1-10% CH_30H/CH_2C1_2) to give the tile amid.

[0111] To a solution of above amide (1.0 equiv) in anhydrous THF was added dropwise of $L1AIH_4$ solution (2.0 M in THF) (4 equiv) at 0 °C. The resulting solution was stirred for 10 h at reflux. The solution was then cooled to 0 °C and quenched by H_20/1N NaOH/H_20 protocol. After the mixture was stirred for 1 h, the solid was removed by filtration. The resulting solution was evaporated to dryness and purified by flash column chromatography (1-10% CH_30H/CH_2C1_2).

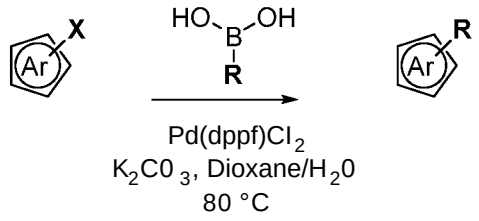


[0112] **Procedure** F: A Biotage microwave vial was charged with $Pd(OAc)_2$ (3 mol %), RuPhos (6 mol %), halide (1 equiv), potassium trifluoroborate (1.3 equiv), and Na_2C0_3 (2 equiv). The test tube was sealed with a cap lined with a disposable Teflon septum, evacuated and purged (x 3). Degassed ethanol (0.18 M) was added via syringe and the reaction was heated at 85

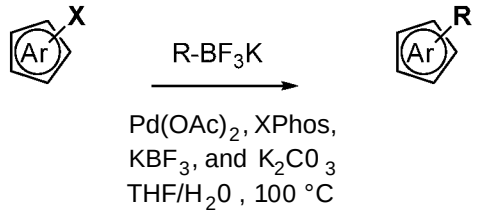
°C for 12 h. The reaction mixture was allowed to cool to room temperature and filtered through a thin pad of celite (elution with EtOAc). The solvent was removed *in vacuo* and the crude product was purified by flash column chromatography (0-10% MeOH/CH_2Cl_2).



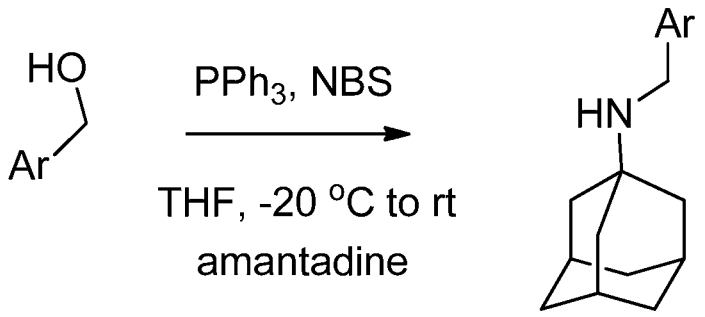
[0113] Procedure G: A mixture of aryl halide (1.0 equiv), boronic acid (1.2 equiv), K_2C0_3 (2.0 equiv), and $Pd(dppf)Cl_2$ (10% mol) in dioxane/H_20 (v/v 5:1) was heated at 80 °C under inert environment for 2 h. The solution was evaporated to dryness and purified by flash column chromatography (1-10% CH_3OH/CH_2CI_2) to give the title compound.



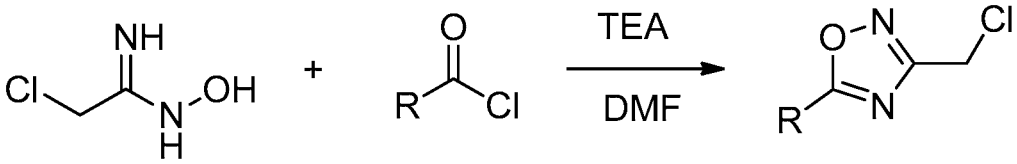
[0114] Procedure H: A Biotage microwave vial was charged with $Pd(OAc)_2$ (3 mol %>), XPhos (6 mol %>), halide (1 equiv), potassium trifluoroborate (1.3 equiv), and K_2C0_3 (3 equiv). The vial was sealed with a cap lined with a disposable Teflon septum, evacuated and purged (x 3). Degassed THF (3.8 mL) and H_20 (0.38 mL) were added via syringe, and the reaction was heated at 100 °C for 24 h. The reaction mixture was allowed to cool to rt and extracted with CH_2C1_2 (x 3) and dried over $MgS0_4$, filtered, and concentrated in vacuo. Unless otherwise specified, the crude product was purified by HPLC.



[0115] Procedure I: The corresponding alcohol was dissolved in THF and triphenylphosphine(leq) was added. After cooling to -20 oC using 50% iPrOH/dry ice bath, NBS (leq) was added to the mixture. After 5 min stirring at the same temperature, adamantan-1-ylamine (2eq) was added and the temperature was raised to rt and stirred for 2h. The crude mixture was diluted with diethyl ether and filtered to remove triphenylphosphine oxide.The filtrated was concentrated and the product was isolated by RP-HPLC.



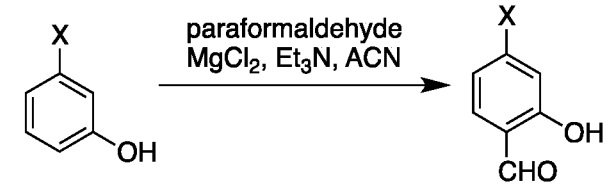
[0116] Procedure j: 2-chloro-N-hydroxyacetimidamide (leq) and acid chloride (leq) in DMF was cooled to 0°C in ice bath, TEA (leq) was added dropwise. After addition, the mixture was heated to 135°C for 4hrs. Solvent was removed under reduced pressure, extracted with ethyl acetate and water. The combined organic phases was dried over $MgS0_4$, filtered and concentrated under reduced pressure. The intermediate chloride was used for the next step alkylation without further purification.



[0117] Procedure K: A KO^tBu (1.2 eq) was added dropwise to a stirred solution of dimethyl oxalate (1.1 eq) and ketone (1 eq) in toluene. The reaction was stirred at room temperature overnight. The reaction was quenched by IN HCl, followed by concentration under reduced pressure. The resulting aqueous slurry was extracted with DCM. The combined organic phase was dried over $MgS0_4$, filtered and concentrated under reduced pressure. The crude ester (leq) was dissolved in MeOH, hydroxylamine hydrochloride (2eq) was added, and the solution was heated to 50°C for 4 hrs. The resulting isoxazole carboxylate was purified by flash column chromatography (60-100% DCM/Hexane). The ester was subsequently reduced by $NaBH_4$ (3eq)

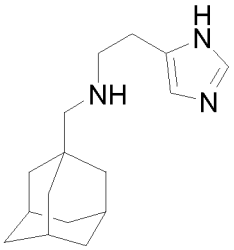
in MeOH for 2 hrs at room temperature. The alcohol intermediate was used for the next step bromination without further purification. For bromination, the alcohol (leq) and CBr_4 (1.5eq) in DCM was cooled to 0°C, PPh_3 (1.5 eq) was added and the solution was stirred at the same temperature for 2 hrs. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography to give the desired bromide intermediate. Final alkylation was performed by following general procedure E.

[01 18] General Procedure L. A mixture of halophenol (1 eq), anhydrous magnesium dichloride (1.5 eq), and triethylamine (3.75 eq) in acetonitrile (0.32 M) was stirred at rt under N_2. Dry (P_2O_5) paraformaldehyde (6.8 eq) was added to the mixture dropwise and after the addition was complete, the mixture was refluxed for 72 h. Then the mixture was acidified with 5% HCl and extracted with diethyl ether (x 3). The ethereal solution was washed with H_20 (x 2) and brine and then dried over MgS04, filtered, and concentrated *in vacuo.* The crude product was purified by column chromatography (0-10% ethyl acetate/hexane) to give the title compound.



X = F, CI, Br, I

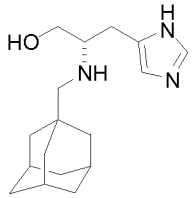
[0119]Example 1/IMX559



Adamantan-l-ylmethyl-[2-(3H-imidazol-4-yl)-ethyl]-amine

Based on general procedure A, from adamantane-l-carbaldehyde and 2-(3H-Imidazol-4-yl)-ethylamine, a white solid (70%) is obtained. Data: LC/MS (ESR) *mlz 260* $[M+H]^+$.

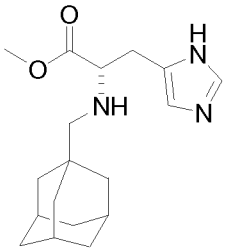
[0120] Example 2/IMX563



2-[(adamantan-l-ylmethyl)-amino]-3-(3H-imidazol-4-yl)-propan-l-ol

Based on general procedure A, from adamantane-l-carbaldehyde and 2-Amino-3-(3H-imidazol-4-yl)-propionic acid methyl ester, 2-[(Adamantan-l-ylmethyl)-amino]-3-(3H-imidazol-4-yl)-propionic acid methyl ester. Reduction of the ester with LAH gave the title compound. Data: LC/MS (ESR) *mlz* 290 $[M+H]^+$.

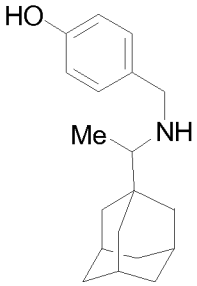
[0121] Example 3/ IMX558



2-[(Adamantan-l-ylmethyl)-amino]-3-(3H-imidazol-4-yl)-propionic acid methyl ester

Based on general procedure A, from adamantane-l-carbaldehyde and 2-Amino-3-(3H-imidazol-4-yl)-propionic acid methyl ester, a white solid (75%) is obtained. Data: LC/MS (ESR) *mlz* 318 $[M+H]^+$.

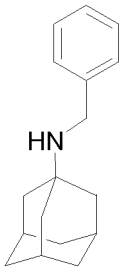
[0122] Example 4/ IMX574



4-[(l-Adamantan-l-yl-ethylamino)-methyl]-phenol

Based on general procedure A, from 1-adamantan-l-yl-ethylamine and 4-Hydroxy-benzaldehyde, a white solid (71%) is obtained. Data: LC/MS (ESR) *mlz 286* $[M+H]^+$.

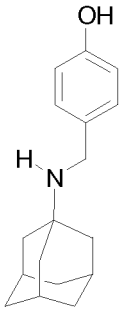
[0123] Example 8/ IMX583



Adamantan-l-yl-benzyl-amine

Based on general procedure A, from adamantan-l-ylamine and benzaldehyde, a white solid (80%) is obtained. Data: LC/MS (ESR) *mlz 242* $[M+H]^+$.

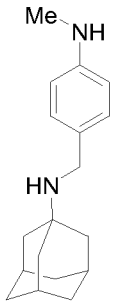
[0124] Example *91* IMX 557



4-(Adamantan-l-ylaminomethyl)-phenol

Based on general procedure A, from adamantan-l-ylamine and 4-hydroxy-benzaldehyde, an off-white solid (71%) is obtained. Data: LC/MS (ESR) *mlz* 258 $[M+H]^+$.

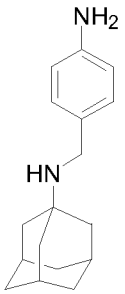
[0125] Example 10/ IMX576



Adamantan-l-yl-(4-methylamino-benzyl)-amine

Based on general procedure A, from adamantan-l-ylamine and (4-Formyl-phenyl)-methyl-carbamic acid tert-butyl ester, followed with deprotection with HC1, a white solid (75%) is obtained. Data: LC/MS (ESR) *mlz 271* $[M+H]^+$

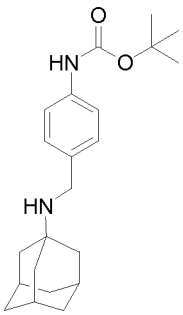
[0126] Example 11/ IMX 569



Adamantan-l-yl-(4-amino-benzyl)-amine

Based on general procedure A, from adamantan-l-ylamine and (4-Formyl-phenyl)-carbamic acid tert-butyl ester, followed with deprotection with HC1, an off-white solid (83%) is obtained. Data: LC/MS (ESR) *mlz 257* $[M+H]^+$.

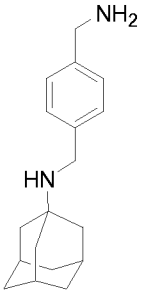
[0127] Example 12/ IMX579



[4-(Adamantan-l-ylaminomethyl)-phenyl]-carbamic acid tert-butyl ester

Based on general procedure A, from adamantan-l-ylamine and (4-Formyl-phenyl)-carbamic acid tert-butyl ester, an off-white solid (81%) is obtained. Data: LC/MS (ESR) *mlz 357* $[M+H]^+$.

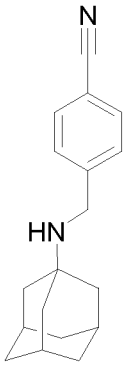
[0128] Example 13/ IMX572



Adamantan-l-yl-(4-aminomethyl-benzyl)-amine

Based on general procedure A, from adamantan-l-ylamine and (4-Formyl-benzyl)-carbamic acid tert-butyl ester, followed with deprotection with HC1, an of-white solid (72%) is obtained. Data: LC/MS (ESR) *mlz 271* $[M+H]^+$.

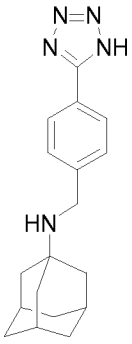
[0129] Example 14/ IMX571



4-(Adamantan-l-ylaminomethyl)-benzonitrile

Based on general procedure A, from adamantan-l-ylamine and 4-Formyl-benzonitrile, a white solid (78%) is obtained. Data: LC/MS (ESR) *mlz 267* $[M+H]^+$.

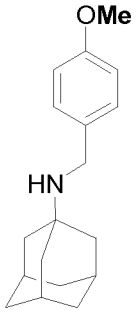
[0130] Example 15/ IMX570



Adamantan-l-yl-[4-(lH-tetrazol-5-yl)-benzyl]-amine

Based on general procedure A, from 4-(adamantan-l-ylaminomethyl)-benzonitrile (IMX571) withNaN3, an off-white solid (69%) is obtained. Data: LC/MS (ESR) *mlz 310* $[M+H]^+$.

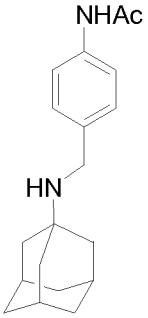
[0131] Example 16/ IMX586



Adamantan-l-yl-(4-methoxy-benzyl)-amine

Based on general procedure A, from adamantan-l-ylamine and 4-Methoxy-benzaldehyde, a white solid (90%) is obtained. Data: LC/MS (ESR) *mlz 272* $[M+H]^+$.

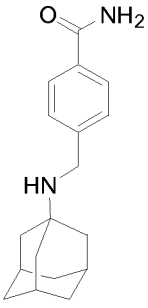
[0132] Example 17/ IMX584



N-[4-(Adamantan-l-ylaminomethyl)-phenyl] -acetamide

Based on general procedure A, from adamantan-l-ylamine andN-(4-Formyl-phenyl)-acetamide, a white solid (65%) is obtained. Data: LC/MS (ESR) *mlz 242* $[M+H]^+$.

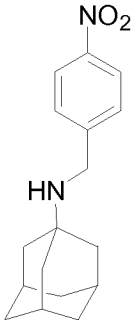
[0133] Example 18/ IMX585



4-(Adamantan-l-ylaminomethyl)-benzamide

Based on general procedure A, from adamantan-l-ylamine andN-(4-Formyl-phenyl)-acetamide, a white solid (65%) is obtained. Data: LC/MS (ESR) *mlz 285* $[M+H]^+$.

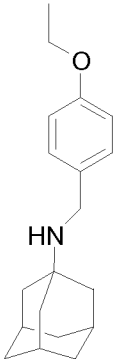
[0134] Example 19/ IMX590/ M2WJ261



Adamantan-l-yl-(4-nitro-benzyl)-amine

Based on general procedure A, from adamantan-l-ylamine and 4-Nitro-benzaldehyde, an off-white solid (89%) is obtained. Data: LC/MS (ESR) *mlz 287* $[M+H]^+$.

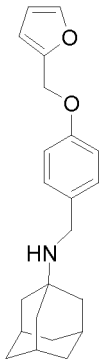
[0135] Example 20/ IMX627



Adamantan-l-yl-(4-ethoxy-benzyl)-amine

Based on general procedure A, from adamantan-l-ylamine and 4-ethoxy-benzaldehyde, a white solid (83%) is obtained. Data: LC/MS (ESR) *mlz 286* $[M+H]^+$.

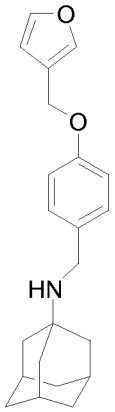
[0136] Example 21/ IMX629



Adamantan-l-yl-[4-(furan-2-ylmethoxy)-benzyl]-amine

Based on general procedure A, from adamantan-l-ylamine and 4-(Furan-2-ylmetfioxy)-benzaldehyde, a white solid (83%) is obtained. Data: LC/MS (ESR) *mlz 338* $[M+H]^+$.

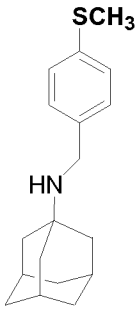
[0137] Example 22/ IMX630



Adamantan-l-yl-[4-(furan-3-ylmethoxy)-benzyl]-amine

Based on general procedure A, from adamantan-l-ylamine and 4-(furan-3-ylmetfioxy)-benzaldehyde, a white solid (83%) is obtained. Data: LC/MS (ESR) *mlz 338* $[M+H]^+$.

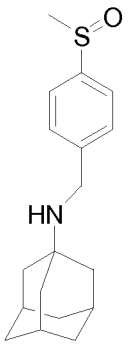
[0138] Example 23/ IMX613/ M2WJ275



Adamantan-l-yl-(4-methylsulfanyl-benzyl)-amine

Based on general procedure A, from adamantan-l-ylamine and 4-methylsulfanyl-benzaldehyde, a white solid (72%) is obtained. Data: LC/MS (ESR) *mlz 288[M+H]*$^+$.

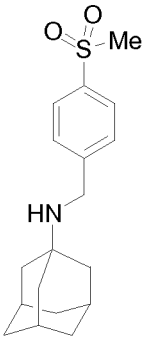
[0139] Example 24/ IMX614



Adamantan-l-yl-(4-methanesulfinyl-benzyl)-amine

Treating adamantan-l-yl-(4-methylsulfanyl-benzyl)-amine (based on general procedure A, from adamantan-l-ylamine and 4-methylsulfanyl-benzaldehyde) with mCPBA (1.1 equiv) at room temperature gave adamantan-l-yl-(4-methanesulfinyl-benzyl)-amine as a solid (90%). Data: LC/MS (ESR) *mlz 304[M+*H*]*$^{+}$.

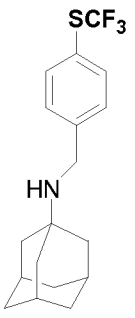
[0140] Example 25/ M2WJ305



Adamantan-l-yl-(4-methanesulfonyl-benzyl)-amine

Treatment of adamantan-l-yl-(4-methylsulfanyl-benzyl)-amine (based on general procedure B, from adamantan-l-ylamine and 4-methylsulfanyl-benzaldehyde) with mCPBA (2.3 equiv) at room temperature gave the title compound as a solid (yield: 82%). Data: LC/MS (ESR) *mlz 320* $[M+H]^{+}$.

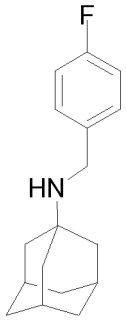
[0141] Example 26/ IMX615/ M2WJ300



Adamantan-l-yl-(4-trifluoromethylsulfanyl-benzyl)-amine

Based on general procedure A, from adamantan-l-ylamine and 4-trifluoromethylsulfanyl-benzaldehyde, a off-white solid (73%) is obtained. Data: LC/MS (ESR) *mlz 342* $[M+H]^+$.

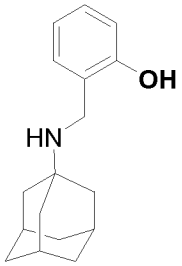
[0142] Example 27/ IMX6 00



Adamantan-l-yl-(4-fluoro-benzyl)-amine

Based on general procedure A, from adamantan-l-ylamine and 4-Fluoro-benzaldehyde, a white solid (82%) is obtained. Data: LC/MS (ESR) *mlz 260* $[M+H]^+$.

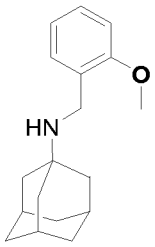
[0143] Example 28/ IMX599



2-(Adamantan-l-ylaminomethyl)-phenol

Based on general procedure A, from adamantan-l-ylamine and 2-hydroxy-benzaldehyde, a white solid (76%) is obtained. Data: LC/MS (ESR) *mlz 258* $[M+H]^+$.

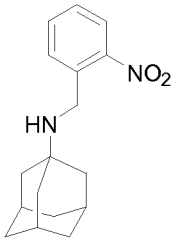
[0144] Example 29/ IMX598



Adamantan-l-yl-(2-methoxy-benzyl)-amine

Based on general procedure A, from adamantan-l-ylamine and 2-methoxy-benzaldehyde, an off-white solid (80%) is obtained. Data: LC/MS (ESR) *mlz 272* $[M+H]^+$.

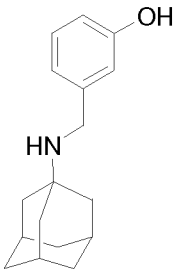
[0145] Example 30/ IMX591



Adamantan-l-yl-(2-nitro-benzyl)-amine

Based on general procedure A, from adamantan-l-ylamine and 2-Nitro-benzaldehyde, an off-white solid (73%) is obtained. Data: LC/MS (ESR) *mlz 287* $[M+H]^+$.

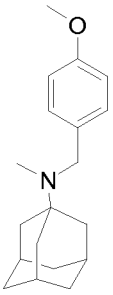
[0146] Example 31/ IMX582



3-(Adamantan-l-ylaminomethyl)-phenol

Based on general procedure A, from adamantan-l-ylamine and 3-Hydroxy-benzaldehyde, an off-white solid (75%) is obtained. Data: LC/MS (ESR) *mlz 258* $[M+H]^+$.

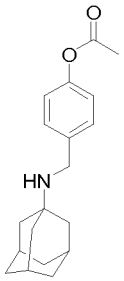
[0147] Example 32/ IMX637



Adamantan-l-yl-(4-methoxy-benzyl)-methyl-amine

Treatment of adamantan-l-yl-(4-methoxy-benzyl)-amine (l.oO equiv) (based on procedure A, from Adamantan-l-ylamine and 4-methoxy-benzaldehyde) with Mel (1.2 equiv) in DMF gave the title compound as a white solid (90%). Data: LC/MS (ESR) *mlz 286[M+*H]$^+$.

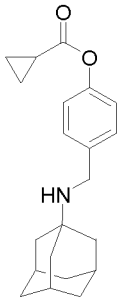
[0148] Example 33/ M2WJ280



Acetic acid 4-(adamantan-l-ylaminomethyl)-phenyl ester

Based on procedure B, from adamantan-l-ylamine and acetic acid 4-formyl-phenyl ester (yield: 64%). Data: MS *mlz 300* $[M+H]^+$.

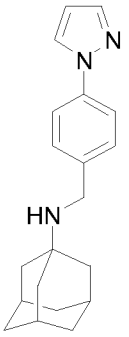
[0149] Example 34/ M2WJ312



Cyclopropanecarboxylic acid 4-(adamantan-l-ylaminomethyl)-phenyl ester

Based on procedure B, from adamantan-l-ylamine and Cyclopropanecarboxylic acid 4-formyl-phenyl ester (yield: 68%). Data: MS *mlz 326* $[M+H]^+$.

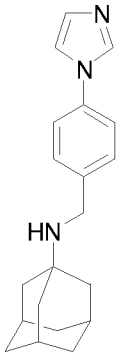
[0150] Example 35/ M2WJ308



Adamantan-l-yl-(4-pyrazol-l-yl-benzyl)-amine

Based on procedure B, from adamantan-l-ylamine and 4-pyrazol-l-yl-benzaldehyde (yield: 82%). Data: MS *mlz 308[M+H]*$^+$.

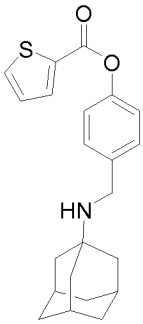
[0151] Example 36/ M2WJ309



Adamantan-l-yl-(4-imidazol-l-yl-benzyl)-amine

Based on procedure B, from adamantan-l-ylamine and 4-Imidazol-l-yl-benzaldehyde (yield: 78%). Data: **MS** *mlz 308[M+H]*$^{+}$.

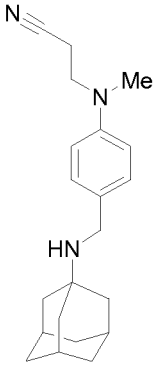
[0152] Example 37 M2WJ313



Thiophene-2-carboxylic acid 4-(adamantan-l-ylaminomethyl)-phenyl ester

Based on procedure B, from adamantan-l-ylamine and Thiophene-2-carboxylic acid 4-formyl-phenyl ester (yield: 74%). Data: **MS** *mlz 368* **[M+H]**$^{+}$**.**

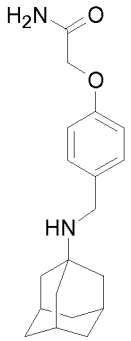
[0153] Example 38/ BCOOl



3-((4-((Adamantan-l-ylamino)methyl)phenyl)(methyl)amino)propanenitrile

Based on general procedure B, from adamantan-l-ylamine and 3-((4-formylphenyl)(methyl)amino)-propanenitrile, a white solid was obtained. Data: LC/MS (ESCi) *mlz* 324.28 $[M+H]^+$.

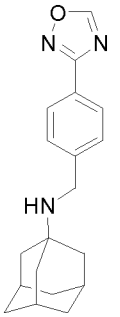
[0154] Example 39/ BC002



2-(4-((Adamantan-l-ylamino)methyl)phenoxy)acetamide

Based on general procedure B, from adamantan-l-ylamine and **2-(4**-formylphenoxy)acetamide, a white solid was obtained. Data: LC/MS (ESCi) *mlz* 315.09 $[M+H]^+$.

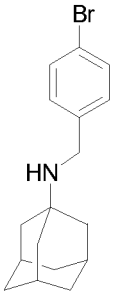
[0155] Example 40/ BC004



Adamantan- l-yl-(4- [1,2,4] oxadiazol-3-yl-benzyl)-amine

Based on general procedure **A,** from adamantan-l-ylamine and 4-(l,2,4-oxadiazol-3-yl)benzaldehyde, a white solid was obtained. Data: LC/MS (ESCi) *mlz* 310.00 $[M+H]^+$.

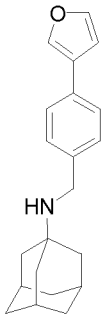
[0156] Example 41/ BC005



N-(4-Bromobenzyl)adamantan-l-amine

Based on general procedure 2, from adamantan-l-ylamine and 4-bromobenzaldehyde, a light yellow solid was obtained. Data: LC/MS (ESCi) *mlz* 320.13 and 322.27 $[M+H]^+$.

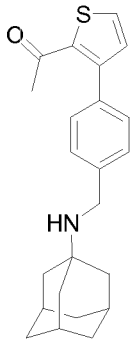
[0157] Example 42/ BC015



N-(4-(Furan-3-yl)benzyl)adamantan-l-amine

Based on general procedure 3, from N-(4-bromobenzyl)adamantan-l -amine and potassium furan-2-yltrifluoroborate, a white solid was obtained. Data: LC/MS (ESCi) *mlz* 308.04 $[M+H]^4$.

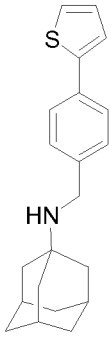
[0158] Example 43/ BC016



l-(3-(4-((Adamantan-l-ylamino)methyl)phenyl)thiophen-2-yl)ethanone

Based on general procedure D, from N-(4-bromobenzyl)adamantan-l -amine and potassium (2-acetylthiophen)-3-yltrifluoroborate, after an HLPC purification a white solid was obtained. Data: LC/MS (ESCi) *mlz* 366.14 $[M+H]^+$.

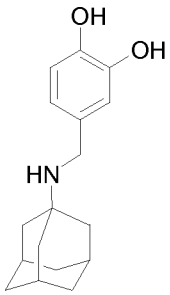
[0159] Example 44/ BC018



N-(4-(Thiophen-2-yl)benzyl)adamantan-l-amine

Based on general procedure D, from N-(4-bromobenzyl)adamantan-l -amine and potassium thiophen-2-yltrifluoroborate, after an HPLC purification a yellow solid was obtained. Data: LC/MS (ESCi) *mlz* 324.16 $[M+H]^+$.

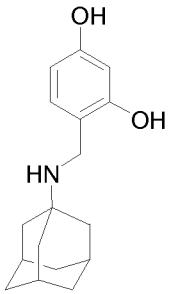
[0160] Example 45/ IMX564



4-(Adamantan-l-ylaminomethyl)-benzene-l,2-diol

Based on general procedure A, from adamantan-l-ylamine and 3,4-Dihydroxy-benzaldehyde, a white solid (82%) is obtained. Data: LC/MS (ESR) *mlz 21*4 $[M+H]^+$.

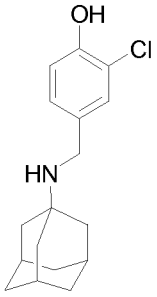
[0161] Example 46/ IMX589



4-(Adamantan-l-ylaminomethyl)-benzene-l,3-diol

Based on general procedure A, from adamantan-l-ylamine and 2,4-Dihydroxy-benzaldehyde, a white solid (70%) is obtained. Data: LC/MS (ESR) *mlz 274* $[M+H]^+$.

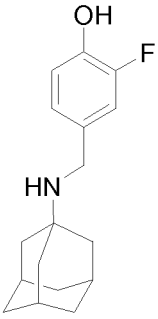
[0162] Example 47/ IMX 566



4-(Adamantan-l-ylaminomethyl)-2-chloro-phenol

Based on general procedure A, from adamantan-l-ylamine and 3-Chloro-4-hydroxy-benzaldehyde, a off-white solid (65%) is obtained. Data: LC/MS (ESR) *mlz 292* $[M+H]^+$.

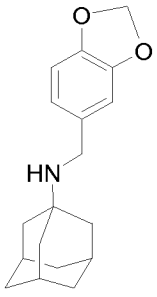
[0163] Example 48/ IMX 573



4-(Adamantan-l-ylaminomethyl)-2-fluoro-phenol

Based on general procedure A, from adamantan-l-ylamine and 3-Fluoro-4-hydroxy-benzaldehyde, a white solid (71%) is obtained. Data: LC/MS (ESR) *mlz 276* $[M+H]^+$.

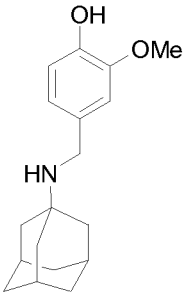
[0164] Example 49/ IMX580



[4-(Adamantan-l-ylaminomethyl)-phenyl]-carbamic acid tert-butyl ester

Based on general procedure A, from adamantan-l-ylamine and Benzo[l,3]dioxole-5-carbaldehyde, a white solid (71%) is obtained. Data: LC/MS (ESR) *mlz 286* $[M+H]^+$.

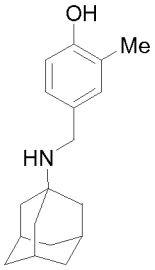
[0165] Example 50/ IMX581



4-(Adamantan-l-ylaminomethyl)-2-methoxy-phenol

Based on general procedure A, from adamantan-l-ylamine and 4-Hydroxy-3-methoxy-benzaldehyde, a white solid (73%) is obtained. Data: LC/MS (ESR) *mlz 288* $[M+H]^+$.

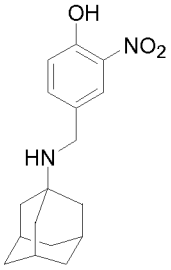
[0166] Example 51/ IMX567



4-(Adamantan-l-ylaminomethyl)-2-methyl-phenol

Based on general procedure A, from adamantan-l-ylamine and 4-Hydroxy-3-methyl-benzaldehyde, a white solid (65%) is obtained. Data: LC/MS (ESR) *mlz 212* $[M+H]^+$.

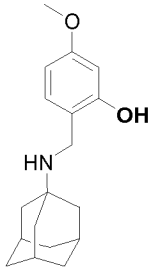
[0167] Example 52/ M2WJ25



4-(Adamantan-l-ylaminomethyl)-2-nitro-phenol

Based on general procedure B, from adamantan-l-ylamine and 4-Hydroxy-3-nitro-benzaldehyde, a white solid (70%) is obtained. Data: MS *mlz 303 [M* +H]$^+$.

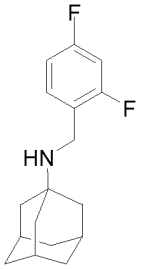
[0168] Example 53/ IMX597



4-(Adamantan-l-ylaminomethyl)-3-methoxy-phenol

Based on general procedure A, from adamantan-l-ylamine and 2-Hydroxy-4-methoxy-benzaldehyde, a white solid (70%) is obtained. Data: LC/MS (ESR) *mlz 288* $[M+H]^+$.

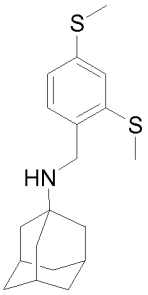
[0169] Example 54/ IMX625



Adamantan-l-yl-(2,4-difluoro-benzyl)-amine

Based on general procedure A, from adamantan-l-ylamine and 2,4-difluoro-benzaldehyde, a white solid (70%) is obtained. Data: LC/MS (ESR) *mlz 278* $[M+H]^+$.

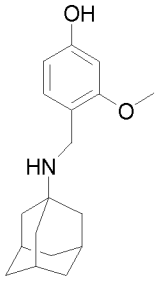
[0170] Example 55/ IMX620



Adamantan-l-yl-(2,4-bis-methylsulfanyl-benzyl)-amine

Treatment of adamantan-l-yl-(2,4-difluoro-benzyl)-amine (1.0 equiv) (based on general procedure A, from adamantan-l-ylamine and 2,4-difluoro-benzaldehyde) with CH_3SNa (3.0 equiv) in DMF at 170°C for 20 h gave the title compound as a yellow solid (38%). Data: LC/MS (ESR) *mlz 334* $[M+H]^+$.

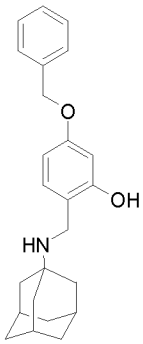
[0171] Example 56/IMX 596



4-(Adamantan-l-ylaminomethyl)-3-methoxy-phenol

Based on general procedure A, from adamantan-l-ylamine and 4-hydroxy-2-methoxy-benzaldehyde, a white solid (72%) is obtained. Data: LC/MS (ESR) *mlz 288* $[M+H]^+$.

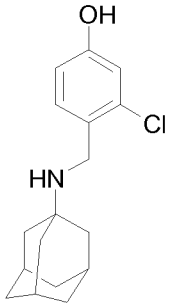
[0172] Example 57/ IMX636



2-(Adamantan-l-ylaminomethyl)-5-benzyloxy-phenol

Based on general procedure A, from adamantan-l-ylamine and 4-benzyloxy-2-hydroxy-benzaldehyde, a white solid (72%) is obtained. Data: LC/MS (ESR) *mlz 364[M+U]*$^+$.

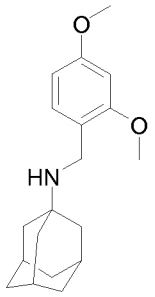
[0173] Example 58/ M2WJ279



4-(Adamantan-l-ylaminomethyl)-3-chloro-phenol

Based on general procedure B, from adamantan-l-ylamine and 2-chloro-4-hydroxy-benzaldehyde (yield: 47%).. Data: MS *mlz 292* $[M+H]^+$.

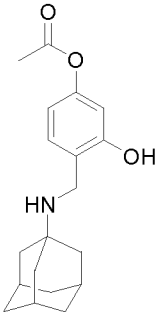
[0174] Example 59/ M2WJ296



Adamantan-l-yl-(2,4-dimethoxy-benzyl)-amine

Based on general procedure B, from adamantan-l-ylamine and 2,4-dimethoxy-benzaldehyde (yield: 74%). Data: **MS** *mlz 302* **$[M+H]^+$.**

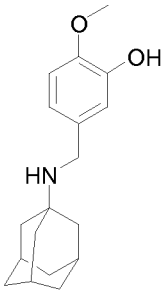
[0175] Example 60/ M2WJ307



Acetic acid 4-(adamantan-l-ylaminomethyl)-3-hydroxy-phenyl ester

Based on general procedure B, from adamantan-l-ylamine and acetic acid 4-formyl-3-hydroxy-phenyl ester (yield: 63%). Data: **MS** *mlz 316* **$[M+H]^+$.**

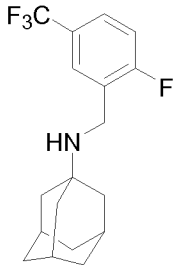
[0176] Example 61 M2WJ290



5-(Adamantan-l-ylaminomethyl)-2-methoxy-phenol

Based on general procedure B, from adamantan-l-ylamine and 3-hydroxy-4-methoxy-benzaldehyde (yield: 55%).. Data: **MS** *mlz 288[M+H]$^+$*.

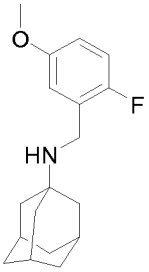
[0177] Example 62/ M2WJ268



Adamantan-l-yl-(2-fluoro-5-trifluoromethyl-benzyl)-amine

Based on general procedure B, from adamantan-l-ylamine and 2-Fluoro-5-trifluoromethyl-benzaldehyde (yield: 89%). Data: **MS** *mlz 328[M+H]*$^+$.

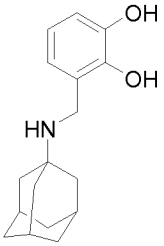
[0178] Example 63/ M2WJ277



Adamantan-l-yl-(2-fluoro-5-methoxy-benzyl)-amine

Based on general procedure B, from adamantan-l-ylamine and 2-Fluoro-5-methoxy-benzaldehyde (yield: 53%). Data: **MS** *mlz 289* **[M+H]$^+$.**

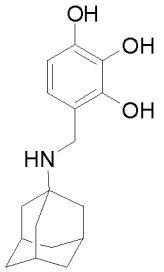
[0179] Example 64/



3-(Adamantan-l-ylaminomethyl)-benzene-l,2-diol

Based on general procedure B, from adamantan-l-ylamine and 2,3-dihydroxy-benzaldehyde (yield: 36%). Data: **MS** *mlz 274* **[M+H]$^+$.**

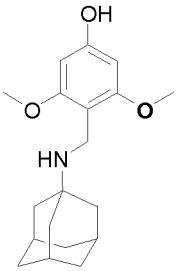
[0180] Example 65/ IMX624



4-(Adamantan- l-ylaminomethyl)-benzene- 1,2,3-triol

Based on general procedure A, from adamantan-l-ylamine and 2,3,4-trihydroxy-benzaldehyde, a white solid (68%) is obtained. Data: LC/MS (ESR) *mlz 290* $[M+H]^+$.

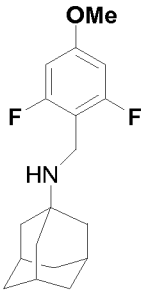
[0181] Example 66/ IMX595



4-(Adamantan-l-ylaminomethyl)-3,5-dimethoxy-phenol

Based on general procedure A, from adamantan-l-ylamine and 4-hydroxy-2,6-dimethoxy-benzaldehyde, a off-white solid (79%) is obtained. Data: LC/MS (ESR) *mlz 318* $[M+H]^+$.

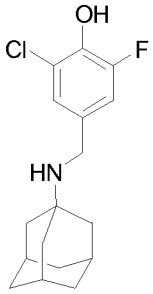
[0182] Example 67/ IMX611



Adamantan-l-yl-(2,6-difluoro-4-methoxy-benzyl)-amine

Based on general procedure A, from adamantan-l-ylamine and 2,6-difluoro-4-methoxy-benzaldehyde, a white solid (71%) is obtained. Data: LC/MS (ESR) *mlz 307[M+U]*$^+$.

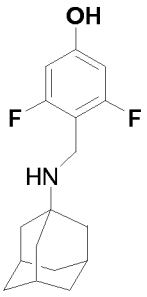
[0183] Example 68/ IMX568



4-(Adamantan-l-ylaminomethyl)-2-chloro-6-fluoro-phenol

Based on general procedure A, from adamantan-l-ylamine and 3-Chloro-5-fluoro-4-hydroxy-benzaldehyde, a white solid (61%) is obtained. Data: LC/MS (ESR) *mlz 310* $[M+H]^+$.

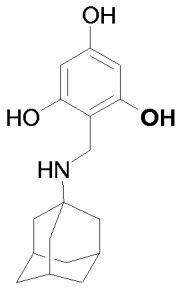
[0184] Example 69/ IMX612



4-(Adamantan-l-ylaminomethyl)-3,5-difluoro-phenol

Treatment of adamantan-l-yl-(2,6-difluoro-4-methoxy-benzyl)-amine (from adamantan-l-ylamine and 3-Chloro-5-fluoro-4-hydroxy-benzaldehyde) with BBr_3 at -78°C gave the title compound as a solid (85%). Data: LC/MS (ESR) *mlz 294* $[M+H]^+$.

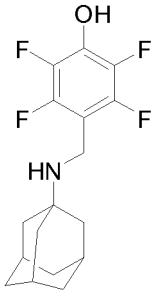
[0185] Example 70/ IMX594



2-(Adamantan-l-ylaminomethyl)-benzene-l,3,5-triol

Based on general procedure A, from adamantan-l-ylamine and 2,4,6-trihydroxy-benzaldehyde, an off-white solid (72%) is obtained. Data: LC/MS (ESR) *mlz 290* $[M+H]^+$.

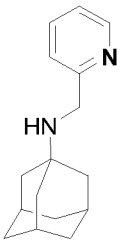
[0186] Example 71/ M2WJ260



4-(Adamantan-l-ylaminomethyl)-2,3,5,6-tetrafluoro-phenol

Based on general procedure B, from adamantan-l-ylamine and 2,3,5,6-tetrafluoro-4-hydroxybenzaldehyde, a solid (yield: 61%) is obtained. Data: MS *mlz 195* $[M+H]^+$.

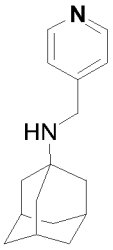
[0187] Example 72/ IMX593



Adamantan-l-yl-pyridin-2-ylmethyl-amine

Based on general procedure **A,** from adamantan-l-ylamine and pyridine-2-carbaldehyde, a white solid (73%) is obtained. Data: LC/MS (ESR) *mlz 243* $[M+H]^+$.

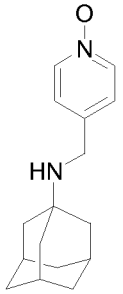
[0188] Example 73/ IMX592



Adamantan-l-yl-pyridin-4-ylmethyl-amine

Based on general procedure **A,** from adamantan-l-ylamine and pyridine-4-carbaldehyde, a white solid (71%) is obtained. Data: LC/MS (ESR) *mlz 243* $[M+H]^+$.

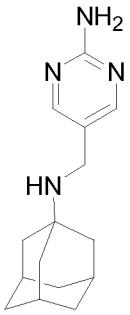
[0189] Example 74/ M2WJ306



Adamantan-l-yl-(l-oxy-pyridin-4-ylmethyl)-amine

Based on general procedure B, from adamantan-l-ylamine and l-Oxy-pyridine-4-carbaldehyde (yield: 79%). MS *mlz 243* $[M+H]^+$.

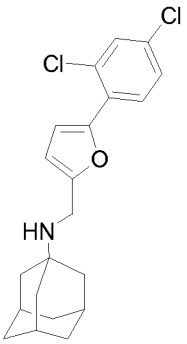
[0190] Example 75/ IMX587



5-(Adamantan-l-ylaminomethyl)-pyrimidin-2-ylamine

Based on general procedure **A,** from adamantan-l-ylamine and 2-amino-pyrimidine-5-carbaldehyde, a white solid (65%) is obtained. Data: LC/MS (ESR) *mlz 259* $[M+H]^+$.

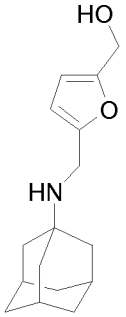
[0191] Example 76/ IMX641



Adamantan- 1-yl- [5-(2,4-dichloro-phenyl)-fur an-2-ylmethyl] -amine

Based on general procedure **A,** from adamantan-l-ylamine and 5-(2,4-dichloro-phenyl)-furan-2-carbaldehyde, a white solid (XX%) is obtained. Data: LC/MS (ESR) *mlz 377* $[M+H]^+$.

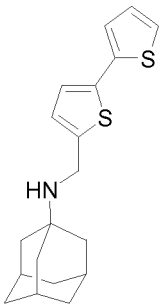
[0192] Example 77/ IMX604



[5-(Adamantan-l-ylaminomethyl)-furan-2-yl]-methanol

From adamantan-l-ylamine and 5-Hydroxymethyl-furan-2-carbaldehyde, a solid (81%) is obtained. Data: LC/MS (ESR) *mlz 262* $[M+H]^+$.

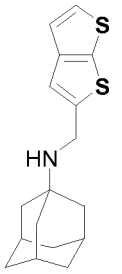
[0193] Example 78/ BC007



N-([2,2'-Bithiophen]-5-ylmethyl)adamantan-l-amine

Based on general procedure A, from adamantan-l-ylamine and [2,2'-bithiophene]-5-carbaldehyde, a yellow solid was obtained. Data: LC/MS (ESCi) *mlz* 330 $[M+H]^+$.

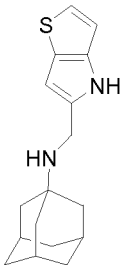
[0194] Example 79/ IMX606



Adamantan-l-yl-thieno[2,3-b]thiophen-2-ylmethyl-amine

Based on general procedure C, from adamantan-l-ylamine and thieno[2,3-b]thiophene-2-carboxylic acid, a yellow solid was obtained. Data: LC/MS (ESR*) mlz* 304 $[M+H]^+$.

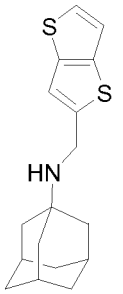
[0195] Example 80/ IMX610



Adamantan-l-yl-(4H-thieno[3,2-b]pyrrol-5-ylmethyl)-amine

Based on general procedure **C**, from adamantan-l-ylamine and **4H**-thieno**[3,2**-b]pyrrole**-5-**carboxylic acid, a yellow solid was obtained. Data: **LC/MS (ESRj** *mlz* **287 [M+H]$^+$.**

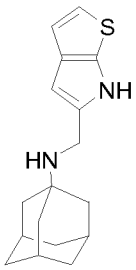
[0196] Example 81/ IMX621



Adamantan-l-yl-thieno[3,2-b]thiophen-2-ylmethyl-amine

Based on general procedure **C**, from adamantan-l-ylamine and thieno**[3,2**-b]thiophene**-2-**carboxylic acid, an off-white solid was obtained. Data: **LC/MS (ESRj** *mlz* **304 [M+H]$^+$.**

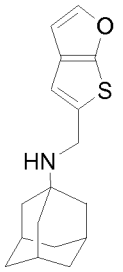
[0197] Example 82/ IMX634



Adamantan-l-yl-(6H-thieno[2,3-b]pyrrol-5-ylmethyl)-amine

Based on general procedure **C**, from adamantan-l-ylamine and **6H**-thieno**[2,3**-b]pyrrole**-5-**carboxylic acid, an off-white solid was obtained. Data: **LC/MS (ESRj** *mlz* **304 [M+H]$^+$.**

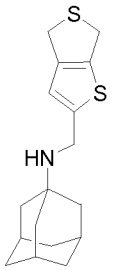
[0198] Example 83/ IMX635



Adamantan-l-yl-thieno[2,3-b]furan-5-ylmethyl-amine

Based on general procedure C, from adamantan-l-ylamine and thieno[2,3-b]furan-5-carboxylic acid, a pink solid was obtained. Data: LC/MS (ESRj *mlz* 288 $[M+H]^+$.

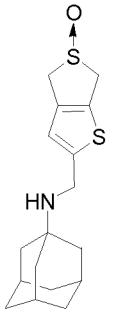
[0199] Example 84/ IMX648



Adamantan-l-yl-(4,6-dihydro-thieno[3,4-b]thiophen-2-ylmethyl)-amine

Based on general procedure C, from adamantan-l-ylamine and 4,6-Dihydro-thieno[3,4-b]thiophene-2-carboxylic acid, a yellow solid was obtained. Data: LC/MS (ESRj *mlz* 306 $[M+H]^+$.

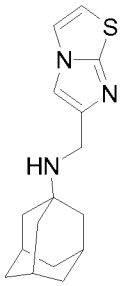
[0200] Example 85/ IMX644



Adamantan-l-yl-(5-oxo-5,6-dihydro-4H-5A4-thieno[3,4-b]thiophen-2-ylmethyl)-amine

Treatment of adamantan-l-yl-(4,6-dihydro-thieno[3,4-b]thiophen-2-ylmethyl)-amine (1.0 equiv) with mCPBA (1.2 equiv) at room temperaturegave the title compound as an off-white solid (72%). Data: LC/MS (ESRj *mlz* 322 $[M+H]^+$.

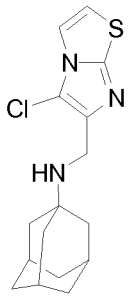
[0201] Example 86/ M2WJ264



Adamantan-l-yl-imidazo[2,l-b]thiazol-6-ylmethyl-amine

Based on procedure B, from adamantan-l-ylamine and imidazo[2,l-b]thiazole-6-carbaldehyde (68%). Data: MS *mlz 288* $[M+H]^+$.

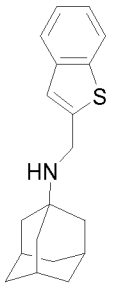
[0202] Example 87/ M2WJ298



Adamantan-l-yl-(5-chloro-imidazo[2,l-b]thiazol-6-ylmethyl)-amine

Based on procedure B, from adamantan-l-ylamine and 5-chloro-imidazo[2,l-b]thiazole-6-carbaldehyde (yield: 58%). Data: MS *mlz 322* $[M+H]^+$.

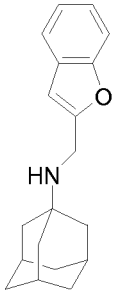
[0203] Example 88/ IMX622



Adamantan-l-yl-benzo[b]thiophen-2-ylmethyl-amine

Based on procedure **A,** from adamantan-l-ylamine and benzo[b]thiophene-2-carbaldehyde, an off-white solid (76%) is obtained. Data: LC/MS (ESR) *mlz 298* $[M+H]^+$.

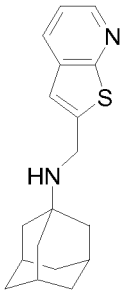
[0204] Example 89/ IMX631



Adamantan-l-yl-benzofuran-2-ylmethyl-amine

Based on procedure A, from adamantan-l-ylamine and benzofuran-2-carbaldehyde, a white solid (71%) is obtained. Data: LC/MS (ESR) *mlz 281* $[M+H]^+$.

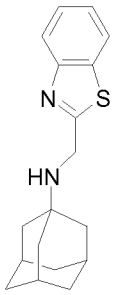
[0205] Example 90/ IMX626



Adamantan-l-yl-thieno [2,3-b] pyridin-2-ylmethyl-amine

Based on procedure A, from adamantan-l-ylamine and thieno[2,3-b]pyridine-2-carbaldehyde, a white solid (70%) is obtained. Data: LC/MS (ESR) *mlz 298* $[M+H]^+$.

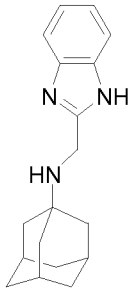
[0206] Example 91/ IMX632



Adamantan-l-yl-benzothiazol-2-ylmethyl-amine

Based on procedure A, from adamantan-l-ylamine and benzothiazole-2-carbaldehyde, an off-white solid (69%) is obtained. Data: LC/MS (ESR) *mlz 299* $[M+H]^+$.

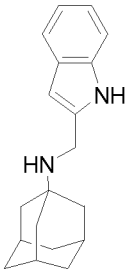
[0207] Example 92/ IMX633



Adamantan-l-yl-(lH-benzoimidazol-2-ylmethyl)-amine

Based on procedure A, from adamantan-l-ylamine and lH-benzoimidazole-2-carbaldehyde, a white solid (76%) is obtained. Data: LC/MS (ESR) *mlz 282* $[M+H]^+$.

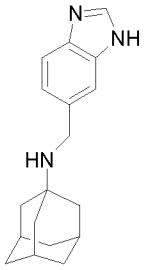
[0208] Example 93/ IMX642



Adamantan-l-yl-(lH-indol-2-ylmethyl)-amine

Based on procedure A, from adamantan-l-ylamine and lH-indole-2-carbaldehyde, an off-white solid (73%) is obtained. Data: LC/MS (ESR) *mlz 281* $[M+H]^+$.

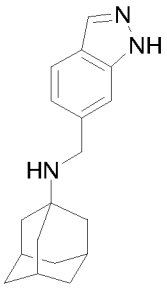
[0209] Example 94/ IMX623



Adamantan-l-yl-(3H-benzoimidazol-5-ylmethyl)-amine

Based on procedure A, from adamantan-l-ylamine and 3H-benzoimidazole-5-carbaldehyde, an off-white solid (75%) is obtained. Data: LC/MS (ESR) *mlz 282* $[M+H]^+$.

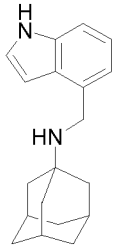
[0210] Example 95/ M2WJ311



Adamantan-l-yl-(lH-indazol-6-ylmethyl)-amine

Based on procedure B, from adamantan-l-ylamine and lH-Indazole-6-carbaldehyde (yield: 63%). Data: MS *mlz 282* $[M+H]^+$.

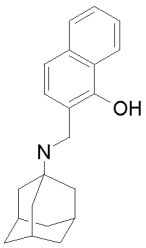
[0211] Example 96/ M2WJ303



Adamantan-l-yl-(lH-indol-4-ylmethyl)-amine

Based on procedure B, from adamantan-l-ylamine and lH-Indole-4-carbaldehyde (yield: 71%).. Data: MS *mlz 281* $[M+H]^+$.

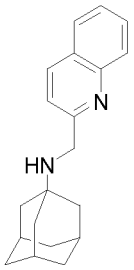
[0212] Example 97/ IMX639



2-(Adamantan-l-ylaminomethyl)-naphthalen-l-ol

Based on procedure **A,** from adamantan-l-ylamine and l-hydroxy-naphthalene-2-carbaldehyde, a white solid (72%) is obtained. Data: LC/MS (ESR) *mlz 308* $[M+H]^+$.

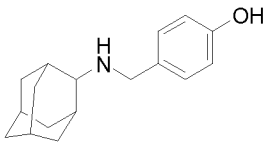
[0213] Example 98/ IMX640



Adamantan-l-yl-quinolin-2-ylmethyl-amine

Based on procedure **A,** from adamantan-l-ylamine and quinoline-2-carbaldehyde, a white solid (80%) is obtained. Data: LC/MS (ESR) *mlz 293* $[M+H]^+$.

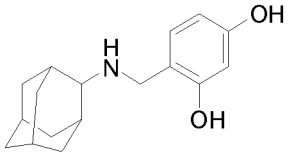
[0214] Example 99/ M2WJ271



4-(Adamantan-2-ylaminomethyl)-phenol

Based on procedure B, from adamantan-2-ylamine and 4-hydroxy-benzaldehyde (yield: 65%). Data: MS *mlz 258* $[M+H]^+$.

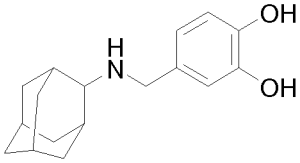
[0215] Example 100/ M2WJ272



4-(Adamantan-2-ylaminomethyl)-benzene-l,3-diol

Based on procedure B, from adamantan-2-ylamine and 2,4-dihydroxy-benzaldehyde (yield: 42%). Data: MS *mlz 274* $[M+H]^+$.

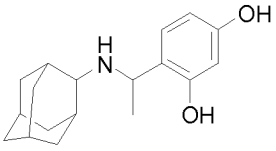
[0216] Example 101/ M2WJ273



4-(Adamantan-2-ylaminomethyl)-benzene-l,2-diol

Based on procedure B, from adamantan-2-ylamine and 3,4-dihydroxy-benzaldehyde (yield: 38%). Data: MS *mlz 274* $[M+H]^+$.

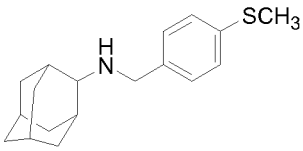
[0217] Example 102/ M2WJ286



4-[l-(Adamantan-2-ylamino)-ethyl] -benzene- 1,3-diol

Based on procedure B, from adamantan-2-ylamine and l-(2,4-dihydroxy-phe nyl)-ethanone. Data: MS *mlz 288* $[M+H]^+$.

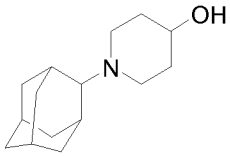
[0218] Example 103/ M2WJ297



Adamantan-2-yl-(4-methylsulfanyl-benzyl)-amine

Based on procedure B, from adamantan-2-ylamine and 4-methylsulfanyl-benzaldehyde (yield: 68%). Data: MS *mlz 288* $[M+H]^+$.

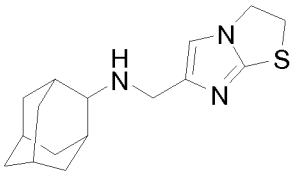
[0219] Example 104/ M2WJ286



l-Adamantan-2-yl-piperidin-4-ol

Based on procedure B, from Adamantan-2-one and Piperidin-4-ol. Data: MS *mlz 236* $[M+H]^+$.

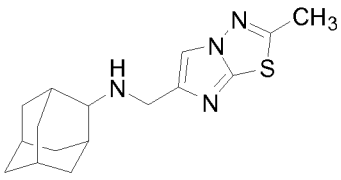
[0220] Example 105/ M2WJ299



Adamantan-2-yl-(2,3-dihydro-imidazo[2,l-b]thiazol-6-ylmethyl)-amine

Based on procedure B, from adamantan-2-ylamine and 2,3-dihydro-imidazo[2,l-b]thiazole-6 -carbaldehyde (yield: 68%). Data: MS *mlz 290* $[M+H]^+$.

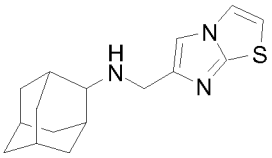
[0221] Example 106/ M2WJ302



Adamantan-2-yl-(2-methyl-imidazo [2,1-b] [1,3,4] thiadiazol-6-ylmethyl)-amine

Based on procedure B, from adamantan-2-ylamine and 2-Methyl-imidazo[2,l-b][l ,3,4]thiadiazole-6-carbaldehyde (yield: 52%). Data: MS *m/z 303* $[M+H]^+$.

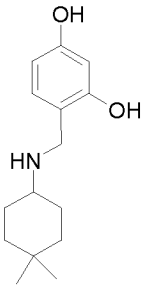
[0222] Example 107/ M2WJ314



Adamantan-2-yl-imidazo[2,l-b]thiazol-6-ylmethyl-amine

Based on procedure B, from adamantan-2-ylamine and Imidazo[2,l-b]thiazole-6-carbaldehyde (yield: 71%). Data: MS *m/z 288* $[M+H]^+$.

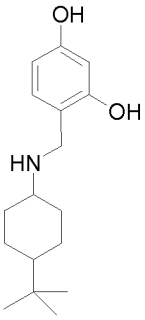
[0223] Example 108/ M2WJ282



4-[(4,4-Dimethyl-cyclohexylamino)-methyl] -benzene- 1,3-diol

Based on procedure B, from 4,4-dimethyl-cyclohexylamine and 2,4-Dihydroxy-benzaldehyde (yield: 43%). Data: MS *m/z 250* $[M+H]^+$.

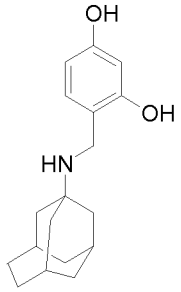
[0224] Example 109/ M2WJ294



4-[(4-tert-Butyl-cyclohexylamino)-methyl] -benzene- 1,3-diol

Based on procedure B, from 4-tert-Butyl-cyclohexylamineand 2,4-dihydroxy-benzaldehyde (yield: 57%). Data: MS *m/z 278* $[M+H]^+$.

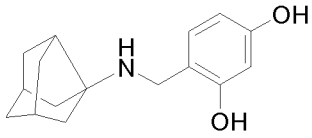
[0225] Example 110/ M2WJ285



4-(Tricyclo[4.3.1.13,8]undec-l-ylaminomethyl)-benzene-l,3-diol

Based on procedure B, from tricyclo[4.3.1.13,8]undec-l-ylamine and 2,4 dihydroxybenzaldehyde (yield: 37%). Data: MS *mlz 288* $[M+H]^+$.

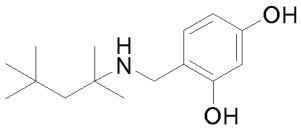
[0226] Example 111/ M2WJ284



4-[(Hexahydro-2,5-methano-pentalen-3a-ylamino)-methyl]-benzene-l,3-diol

Based on procedure B, from hexahydro-2,5-methano-pentalen-3a-ylamine and 2,4-dihydroxy-benzaldehyde (yield: 49%). Data: MS *mlz 260* $[M+H]^+$.

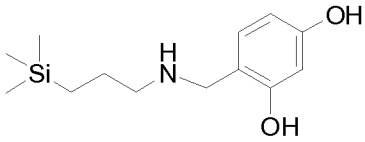
[0227] Example 112/ M2WJ287



4-[(1,1,3,3-Tetramethyl-butylamino)-methyl] -benzene- 1,3-diol

Based on procedure B, from 1,1,3,3-Tetramethyl-butylamine and 2,4-dihydroxy-benzaldehyde (yield: 74%). Data: MS *mlz 252* $[M+H]^+$.

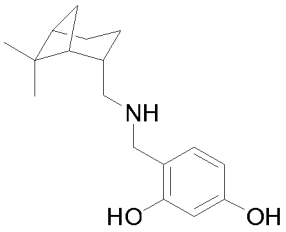
[0228] Example 113/ M2WJ283



4-[(3-Trimethylsilanyl-propylamino)-methyl]-benzene-l,3-diol

Based on procedure B, from 3-Trimethylsilanyl-propylamine and 2,4-dihydroxy-benzaldehyde (yield: 50%). Data: MS *mlz 254* $[M+H]^+$.

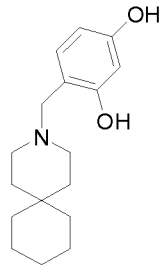
[0229] Example 114/ M2WJ293



4-{[(6,6-Dimethyl-bicyclo [3.1.1] hept-2-ylmethyl)-amino] -methyl}-benzene- 1,3-diol

Based on procedure B, from C-(6,6-Dimethyl-bicyclo[3.1.1]hept-2-yl)-methylamine and 2,4-dihydroxy-benzaldehyde (yield: 65%). Data: MS *mlz 276* $[M+H]^+$.

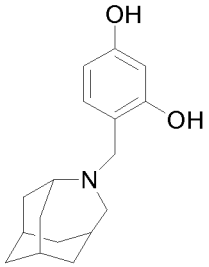
[0230] Example 115/ M2WJ288



4-(3-Aza-spiro[5.5]undec-3-ylmethyl)-benzene-l,3-diol

Based on procedure B, from 3-Aza-spiro[5.5]undecane and 2,4-dihydroxy-benzaldehyde (yield: 61%). Data: MS *mlz 276* $[M+H]^+$.

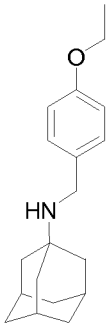
[0231] Example 116/ M2WJ292



4-(4-Aza-tricyclo[4.3.1.13,8]undec-4-ylmethyl)-benzene-l,3-diol

Based on procedure B, from 4-Aza-tricyclo[4.3.1.13,8]undecane and 2,4-dihydroxy-benzaldehyde (yield: 42%). Data: MS *mlz 274* $[M+H]^+$.

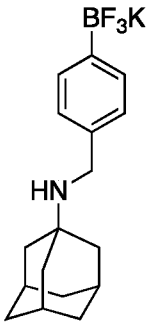
[0232] Example la/IMX627



Adamantan-l-yl-(4-ethoxy-benzyl)-amine

Based on general procedure **A,** from 4-ethoxy-benzaldehyde and adamantan-l-ylamine, a white solid (70%) is obtained. Data: LC/MS (ESR) m/z 286 $[M+H]^+$.

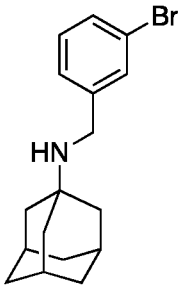
[0233] Example 2a/BC063



Potassium N-(4-adamantan-l-ylamino)methyl)phenyl)trifluoroborate (BC063)

See reference: Molander, G.A.; Trice, S.L.J.; Dreher, S.D. J. Am. Chem. Soc. **2010,** 131, 17701-17703.

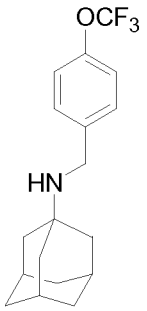
[0234] Example 3a/BC020



N-(3-Bromobenzyl)adamantan-l-amine (BC020)

Based on general procedure A, from adamantan-l-ylamine and 3-bromobenzaldehyde, a light yellow oil was obtained. Data: LC/MS (ESCi) m/z 320.08/322.09 $[M+H]^+$.

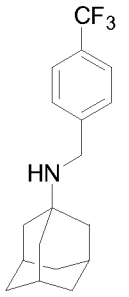
[0235] Example 4a /IMX673



Adamantan-l-yl-(4-trifluoromethoxy-benzyl)-amine

Based on general procedure **A,** from 4-Trifluoromethoxy-benzaldehyde and adamantan-1-ylamine, a white solid (72%) is obtained. Data: LC/MS (ESR) m/z 326 $[M+H]^+$.

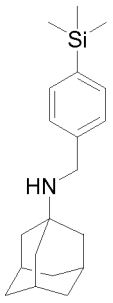
[0236] Example 5a /IMX674



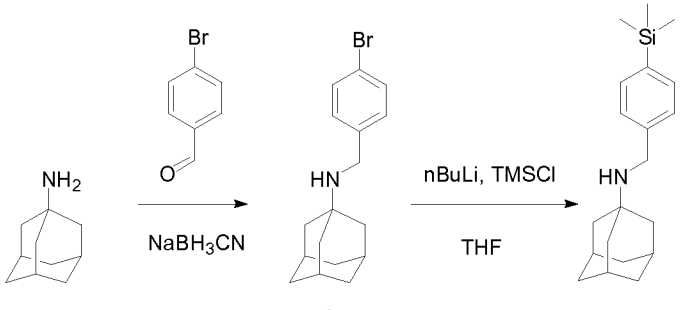
Adamantan-l-yl-(4-trifluoromethyl-benzyl)-amine

Based on general procedure **A,** from 4-trifluoromethyl-benzaldehyde and adamantan-l-ylamine, a white solid (72%) is obtained. Data: LC/MS (ESR) m/z 310 $[M+H]^+$.

[0237] Example 6a /IMX676



Adamantan-l-yl-(4-trimethylsilanyl-benzyl)-amine

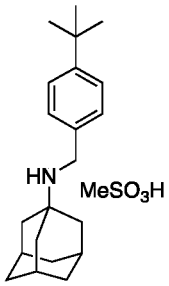


A B

Follow procedure A, from 4-Bromo-benzaldehyde and adamantan-l-ylamine , adamantan-l-yl-(4-bromo-benzyl)-amine (A) was obtained as white solid (81%). Data: LC/MS (ESR) m/z 320 $[M+H]^+$.

To a solution of adamantan-l-yl-(4-bromo-benzyl)-amine (A) (320 mg, 1 mmol) in anhydrous THF (10 mL) at N_2 atmosphere nBuLi (1.5 M in Hex, 1.0 mL, 2.5 mmol) was added dropwise at -78 °C. After the mixture was stirred for 20 min TMSC1 (140 mg, 1.2 mmol) was added. The mixture was stirred for 30 min before it was quenched with NH4C1 (sat'd) (5 mL). and the product was extracted with DCM (10 mL x 3). The combined organic layer was dried over Na_2S0_4, and concentrated under reduced pressure. The crude product was separated by flash column chromatography (1-10% CH_3OH/CH_2CI_2) to give adamantan-l-yl-(4-trimethylsilanyl-benzyl)-amine a white solid (219 mg, 71%). Data: LC/MS (ESR) m/z 314 $[M+H]^+$.

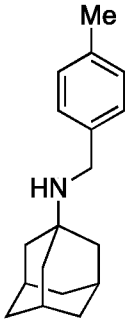
[0238] Example 7a/BC014



N-(4-(tert-Butyl)benzyl)adamantan-l-amine methanesulfonate-(BC014)

Based on general procedure A, from adamantan-l-ylamine and 4-(tert-butyl)benzaldehyde. The pure free amine was dissolved in Et_20 and cooled to 0 °C and $MeS0_3H$ (1 equiv) was added under N_2 and then mixture was stirred at 0 °C for 15 min and filtered to give a white solid. Data: LC/MS (ESCi) m/z 298.25 $[M+H]^+$.

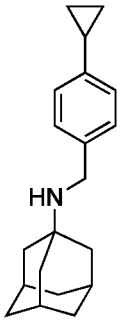
[0239] Example 8a/BC076



N-(4-Methylbenzyl)adamantan-l-amine

Based on general procedure F, from N-(4-bromobenzyl)adamantan-l -amine and potassium methyltrifluoroborate, a yellow solid was obtained. Data: LC/MS (ESCi) m/z 256.00 $[M+H]^+$.

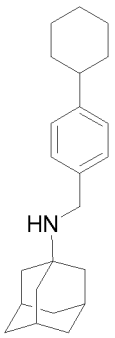
[0240] Example 9a/BC080



N-(4-Cyclopropylbenzyl)adamantan-l-amine (BC080)

Based on general procedure H, from adamantan-l-ylamine, and potassium cyclopropyltrifluoroborate, a white solid was obtained after column chromatography purification (0-10% MeOH/CH_2Cl_2). Data: LC/MS (ESCi) m/z 282.18 $[M+H]^+$.

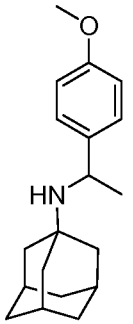
[0241] Example 10a/IMX678



Adamantan-l-yl-(4-cyclohexyl-benzyl)-amine

Based on general procedure **A,** 4-Cyclohexyl-benzaldehyde and Adamantan-l-ylamine, a white solid (70%) is obtained. Data: LC/MS (ESR) m/z 324 $[M+H]^+$.

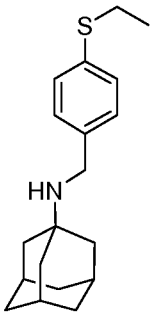
[0242] Example lla/WFD093



N-(l-(4-methoxyphenyl)ethyl)adamantan-l-amine

Based on general procedure **C,** from adamantane-1-amine and l-(4-methoxyphenyl)ethanone, a white solid is obtained. Data: HPLC retention time 7.3 min (77% B, Xterra RP-C18, 4.6 x 250 mm, 5 uM, mobile phase A: lOmM NH4HC03 buffer pH=9, mobile phase B: CH3CN, flow rate: 1.0 ml/min, 254 nm) LC/MS (ESR) m/z 286.3 $[M+H]^+$.

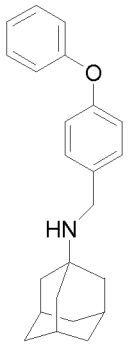
[0243] Example 12a/WFD023



N-(4-(ethylthio)benzyl)adamantan-l-amine

Based on general procedure **C,** from adamantane-1-amine and 4-(ethylthio)benzaldehyde, a white solid is obtained. Data: HPLC retention time : 9.8 min (90% B, Xterra RP-C18, 4.6 x 250 mm, 5 uM, mobile phase A: lOmM NH4HC03 buffer pH=9, mobile phase B: CH3CN, flow rate: 1.0 ml/min, 254 nm) LC/MS (ESR) m/z 302.3 $[M+H]^+$.

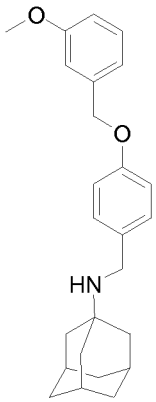
[0244] Example 13a/ IMX00657



Adamantan-l-yl-(4-phenoxy-benzyl)-amine

Based on general procedure **A,** 4-Phenoxy-benzaldehyde and Adamantan-l-ylamine, a white solid (71%) is obtained. Data: LC/MS (ESR) m/z 334 $[M+H]^+$.

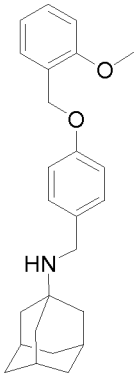
[0245] Example 14a/ IMX00649



Adamantan-l-yl-[4-(3-methoxy-benzyloxy)-benzyl]-amine

Based on general procedure **A,** 4-(3-Methoxy-benzyloxy)-benzaldehyde and Adamantan-l-ylamine, a white solid (71%) is obtained. Data: LC/MS (ESR) m/z 378 $[M+H]^+$.

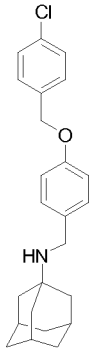
[0246] Example 15a/ IMX00650



Adamantan-l-yl-[4-(2-methoxy-benzyloxy)-benzyl]-amine

Based on general procedure **A,** 4-(2-Methoxy-benzyloxy)-benzaldehyde and Adamantan-1-ylamine, a white solid (68%) is obtained. Data: LC/MS (ESR) m/z 378 $[M+H]^+$.

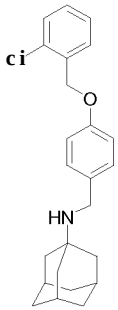
[0247] Example 16a/ IMX00651



Adamantan-l-yl-[4-(4-chloro-benzyloxy)-benzyl]-amine

Based on general procedure **A,** 4-(4-Chloro-benzyloxy)-benzaldehyde and Adamantan-1-ylamine, a white solid (68%) is obtained. Data: LC/MS (ESR) m/z 382 $[M+H]^+$.

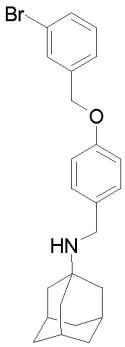
[0248] Example 17a/ IMX00651



Adamantan-l-yl-[4-(2-chloro-benzyloxy)-benzyl]-amine

Based on general procedure **A,** 4-(2-Chloro-benzyloxy)-benzaldehyde and Adamantan-1-ylamine, a white solid (68%) is obtained. Data: LC/MS (ESR) m/z 382 $[M+H]^+$.

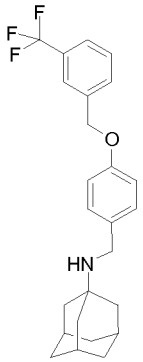
[0249] Example 18a/ IMX00653



Adamantan-l-yl-[4-(3-bromo-benzyloxy)-benzyl]-amine

Based on general procedure **A,** 4-(3-Bromo-benzyloxy)-benzaldehyde and Adamantan-1-ylamine, a white solid (68%) is obtained. Data: LC/MS (ESR) m/z 426 $[M+H]^+$.

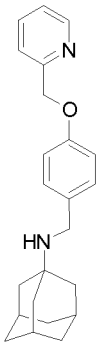
[0250] Example 19a/ IMX00654



Adamantan-l-yl-[4-(3-trifluoromethyl-benzyloxy)-benzyl] -amine

Based on general procedure **A,** 4-(3-Trifluoromethyl-benzyloxy)-benzaldehyde and Adamantan-1-ylamine, a white solid (69%) is obtained. Data: LC/MS (ESR) m/z 416 $[M+H]^+$.

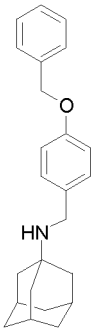
[0251] Example 20a/ IMX00655



Adamantan-l-yl- [4-(pyridin-2-ylmethoxy)-benzyl] -amine

Based on general procedure **A,** 4-(Pyridin-2-ylmethoxy)-benzaldehyde and Adamantan-1-ylamine, a white solid (69%) is obtained. Data: LC/MS (ESR) m/z 349 $[M+H]^+$.

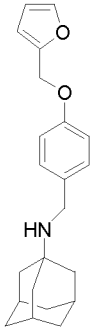
[0252] Example 21a/ IMX00656



Adamantan-l-yl-(4-benzyloxy-benzyl)-amine

Based on general procedure **A,** Adamantan-1-yl-(4-benzyloxy-benzyl)-amine and Adamantan-1-ylamine, a white solid (69%) is obtained. Data: LC/MS (ESR) m/z 348 $[M+H]^+$.

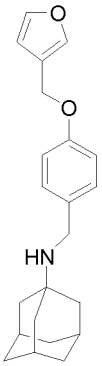
[0253] Example 22a/ IMX00629



Adamantan-l-yl-[4-(furan-2-ylmethoxy)-benzyl]-amine

Based on general procedure **A,** 4-(Furan-2-ylmethoxy)-benzaldehyde and Adamantan-1-ylamine, a white solid (69%) is obtained. Data: LC/MS (ESR) m/z 338 $[M+H]^+$.

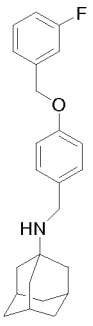
[0254] Example 23a/ IMX00630



Adamantan-l-yl-[4-(furan-3-ylmethoxy)-benzyl]-amine

Based on general procedure **A,** 4-(Furan-3-ylmethoxy)-benzaldehyde and Adamantan-1-ylamine, a white solid (69%) is obtained. Data: LC/MS (ESR) m/z 338 $[M+H]^+$.

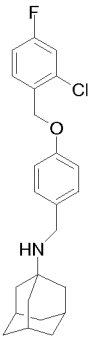
[0255] Example 24a/IMX00658



Adamantan-l-yl-[4-(3-fluoro-benzyloxy)-benzyl] -amine

Based on general procedure **A,** 4-(3-Fluoro-benzyloxy)-benzaldehyde and Adamantan-1-ylamine, a white solid (69%) is obtained. Data: LC/MS (ESR) m/z 366 $[M+H]^+$.

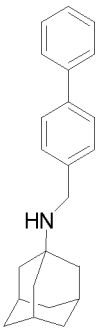
[0256] Example 25a/IMX00659



Adamantan-l-yl-[4-(2-chloro-4-fluoro-benzyloxy)-benzyl]-amine

Based on general procedure **A,** from 4-(2-Chloro-4-fluoro-benzyloxy)-benzaldehyde and Adamantan-l-ylamine, a white solid (69%) is obtained. Data: LC/MS (ESR) m/z 400 $[M+H]^+$.

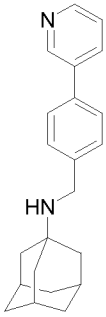
[0257] Example 26a/ WFD097 and IMX00663



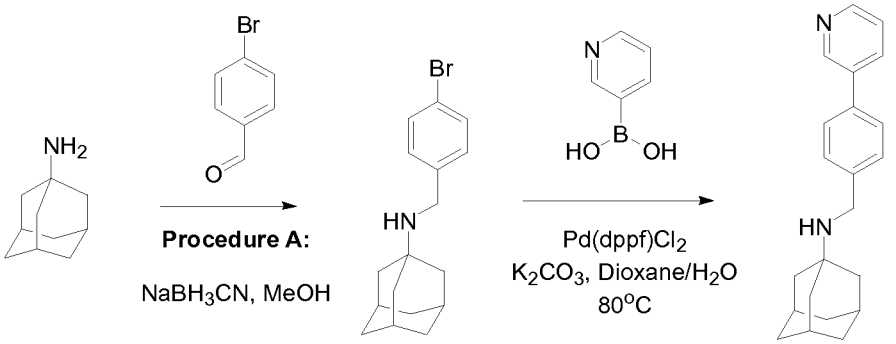
Adamantan-l-yl-biphenyl-4-ylmethyl-amine

Based on general procedure **A,** from Biphenyl-4-carbaldehyde and Adamantan-l-ylamine, a white solid (69%) is obtained. Data: LC/MS (ESR) m/z 318 $[M+H]^+$.

[0258] Example 27a/IMX00694

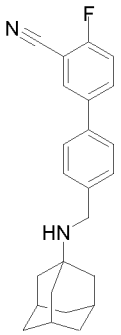


Adamantan-l-yl-[4-(2-chloro-4-fluoro-benzyloxy)-benzyl]-amine



According to Procedure A, adamantan-l-yl-(4-bromo-benzyl)-amine was made from adamantan-l-ylamine and 4-bromo-benzaldehyde (76%). **According to Procedure E,** from adamantan-l-yl-(4-bromo-benzyl)-amine and 3-pyridylboronic acid, adamantan-I-yl-(4-pyridm-3-yl-benzyl)-amine as a white solid (69%) is obtained. Data: LC/MS (ESR) m/z 319 $[M+H]^+$.

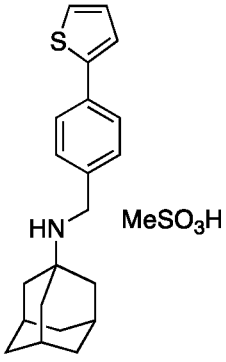
[0259] Example 28a/IMX00695



Adamantan-l-yl-[4-(2-chloro-4-fluoro-benzyloxy)-benzyl]-amine

Following the same sequence as example 27, from adamantan-l-ylamine, 4-bromo-benzaldehyde and (3-cyano-4-fiuorophenyl)boronic acid, adamantan-l-yl-[4-(2-chloro-4-fluoro-benzyloxy)-benzyl]-amine (69%) is obtained as a white solid. Data: LC/MS (ESR) m/z 361$[M+H]^+$.

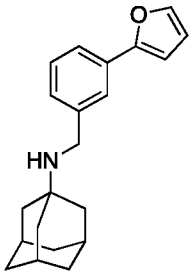
[0260] Example 29a/BC018



N-(4-(Thiophen-2-yl)benzyl)adamantan-l-amine methanesulfonate

Based on general procedure B, from N-(4-bromobenzyl)adamantan-l -amine (M2MJ325) and potassium (thiophen-2-yl)trifuoroborate. The pure free base was dissolved in Et_20 and then cooled to 0 °C, $MeSO_3H$ (1 equiv) was added under N_2. The mixture was stirred at 0 °C for 15 min and then filtered and dried in vacuo to provide a white solid. Data: LC/MS (ESCi) m/z 324.15 $[M+H]^+$.

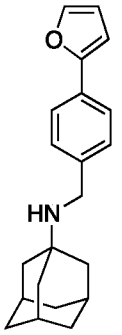
[0261] Example 30a/BC026



N-(3-(Furan-2-yl)benzyl)adamantan-l-amine

Based on general procedure B, from N-(3-bromobenzyl)adamantan-l -amine (BC020) and potassium furan-2-yltrifluoroborate, a brown solid was obtained. Data: LC/MS (ESCi) m/z 308.23 $[M+H]^+$.

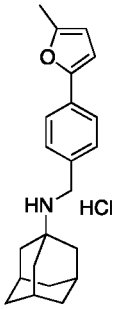
[0262] Example 31a/ BC032



N-(4-(Furan-2-yl)benzyl)adamantan-l-amine (BC032)

Based on general procedure 2, from N-(4-bromobenzyl)adamantan-l -amine (BC005) and potassium furan-2-ylfrifluoroborate, a yellow solid was obtained. Data: LC/MS (ESCi) m/z 308.16 $[M+H]^+$.

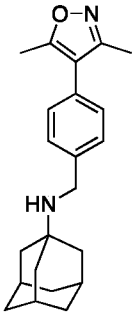
[0263] Example 32a/ BC047



N-(4-(5-Methylfuran-2-yl)benzyl)adamantan-l-amine hydrochloride (BC047)

Based on general procedure B, from N-(4-bromobenzyl)adamantan-l -amine (BC005) and potassium 5-methyl-(furan-2-yl)trifluoroborate. The pure free base was dissolved in Et_20 and then cooled to 0 °C, 2M HCl in ether (5 equiv) was added. The mixture was stirred at 0 °C for 15 min and then concentrated and dried in vacuo to provide a white solid Data: LC/MS (ESCi) m/z 322.14 $[M+H]^+$.

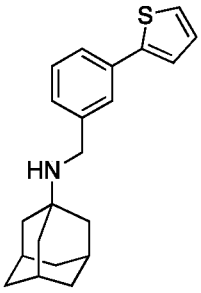
[0264] Example 33a/ BC046



N-(4-(3,5-Dimethylisoxazol-4-yl)benzyl)adamantan-l-amine (BC046)

Based on general procedure B, from 4-(bromobenzyl)adamantan-l -amine (BC005) and potassium (3,5-dimethylisoxazol-4-yl)trifluoroborate, a white solid was obtained. Data: LC/MS (ESCi) m/z 337.19 $[M+H]^+$.

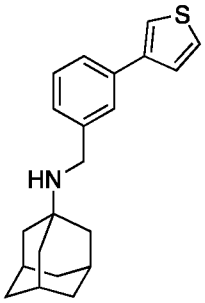
[0265] Example 34a/ BC025



N-(3-(thiophen-2-yl)benzyl)adamantan-l-amine

Based on general procedure B, from 3-bromobenzyl)adamantan-l -amine (BC020) and potassium thiophen-2-yltrifluoroborate, a light yellow oil was obtained. Data: LC/MS (ESCi) m/z 324.16 $[M+H]^+$.

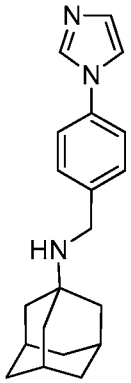
[0266] Example 35a/ BC034



N-(3-(Thiophen-2-yl)benzyl)adamantan-l-amine

Based on general procedure 2, from N-((3-bromobenzyl)adamantan-l -amine (BC020) and potassium thiophen-3-yltrifluoroborate, a yellow solid was obtained. Data: LC/MS (ESCi) m/z 324.16 $[M+H]^+$.

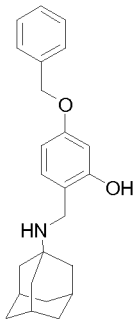
[0267] Example 36a/WFD029



N-(4-(lH-imidazol-l-yl)benzyl)adamantan-l-amine

Based on general procedure **C,** from adamantane-1 -amine and 4-(lH-imidazol-l-yl)benzaldehyde, a white solid is obtained. Data: HPLC retention time : 6.5 min (70% B, Xterra RP-C18, 4.6 x 250 mm, 5 uM, mobile phase A : lOmM NH4HC03 buffer pH=9, mobile phase B : CH3CN, flow rate: 1.0 ml/min, 254 nm) LC/MS (ESR) m/z 308.3 $[M+H]^+$.

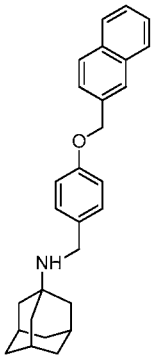
[0268] Example 37a/IMX00636



2-(Adamantan-l-ylaminomethyl)-5-benzyloxy-phenol

Based on general procedure **C,** 4-Benzyloxy-2-hydroxy-benzaldehyde and Adamantan-1-ylamine, a white solid (69%) is obtained. Data: LC/MS (ESR) m/z 364 $[M+H]^+$.

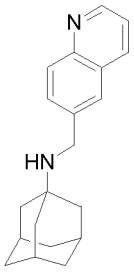
[0269] Example 38a/M2WJ328



N-(4-(naphthalen-2-ylmethoxy)benzyl)adamantan-l-amine

Based on general procedure **A,** from amantadine and 4-(naphthalen-2-ylmethoxy)benzaldehyde, a yellow solid (70%) is obtained. Data: LC/MS (ESR) m/z 398.5 $[M+H]^+$.

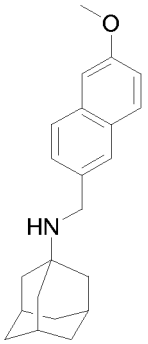
[0270] Example 39a/IMX00681



Adamantan-l-yl-quinolin-6-ylmethyl-amine

Based on general procedure **A,** Quinoline-6-carbaldehyde and Adamantan-l-ylamine, a white solid (74%) is obtained. Data: LC/MS (ESR) m/z 293 $[M+H]^+$.

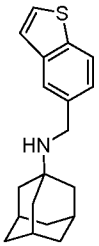
[0271] Example 40a/IMX00682



Adamantan-l-yl-(6-methoxy-naphthalen-2-ylmethyl)-amine

Based on general procedure **A,** 6-Methoxy-naphthalene-2-carbaldehyde and Adamantan-1-ylamine, a white solid (71%) is obtained. Data: LC/MS (ESR) m/z 322 $[M+H]^+$.

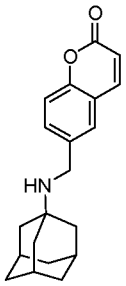
[0272] Example 41a/WFDl 15



N-(benzo[b]thiophen-5-ylmethyl)adamantan-l-amine

Based on general procedure C, from adamantane-1-amine and benzo[b]thiophene-5-carbaldehyde, a white solid is obtained. Data: LC/MS (ES+) m/z 298.2 $[M+H]^+$.

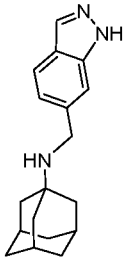
[0273] Example 42a/WFD123



6-((adamantan-l-ylamino)methyl)-2H-chromen-2-one

Based on general procedure C, from adamantane-1-amine and 2-oxo-2H-chromene-6-carbaldehyde, a white solid is obtained. Data: LC/MS (ES+) m/z 310.2 $[M+H]^+$.

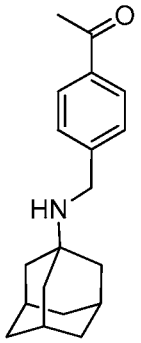
[0274] Example 43a/WFDl 19



N-((lH-indazol-6-yl)methyl)adamantan-l-amine

Based on general procedure **C,** from adamantane-1 -amine and lH-indazole-6-carbaldehyde, a white solid is obtained. Data: HPLC retention time : 5.5 min (70% B, Xterra RP-C18, 4.6 x 250 mm, 5 uM, mobile phase A: lOmM NH4HC03 buffer pH=9, mobile phase B: CH3CN, flow rate: 1.0 ml/min, 254 nm) LC/MS (ES+) m/z 282.3 $[M+H]^+$.

[0275] Example 44a/WFD008



l-(4-(adamantan-l-ylamino)methyl)phenyl)ethanone

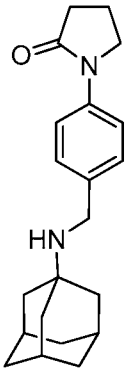
Synthesis of ester precursor

Based on general procedure **C,** from adamantane-1 -amine and methyl 4-formylbenzoate, methyl 4-(((3s,5s,7s)-adamantan-l-ylamino)methyl)benzoate (white solid, 60%>) is obtained . Data: LC/MS (ES+) m/z 300.3 $[M+H]^+$.

Ketone synthesis from the ester precursor

To a solution of methyl 4-formylbenzoate, methyl 4-(((3s,5s,7s)-adamantan-l-ylamino)methyl)benzoate (leq) in toluene was added N.N'-dimethylethylenediamine (DMEDA, 78.7 mg, 1.1 eq) and trimethyi aluminum (12 eq, 2 M in toiuene) dropwise under argon at room temperature. After the mixture was refluxed for 1 hour, it was quenched with water, and the products were extracted with ethyl acetate. The combined organic layers were washed with brine, and dried over Na_2SO_4. The filtered solvents were concentrated in vacuo, and the residue was purified by prep HPLC. . Data: LC/MS (ES+) m/z 284.3 $[M+H]^+$

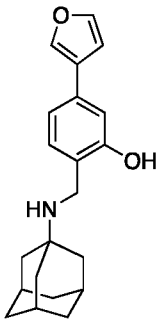
[0276] Example 45a/WFD014



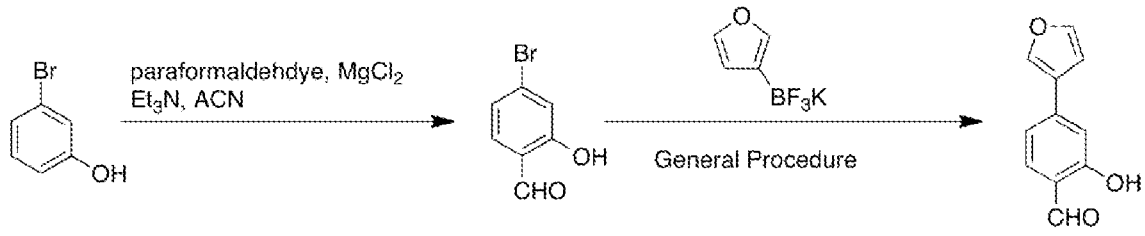
l-(4-((adamantan-l-ylamino)methyl)phenyl)pyrrolidin-2-one

Based on general procedure **C,** from adamantane-1-amine and 4-(2-oxopyrrolidin-l-yl)benzaldehyde, a white solid is obtained. Data: LC/MS (ES+) m/z 325.4 $[M+H]^+$.

[0277] Example 46a/BC090



The preparation of 2-(((-adamantan-l-ylamino)methyl)-5-(furan-3-yl)phenol (BC090)



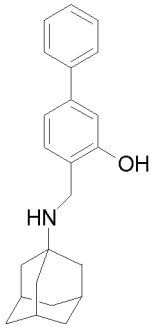
BC087

4-(Furan-3-yl)-2-hydroxybenzaldehyde (BC087). A mixture of 2-bromophenol (58 mmol), anhydrous magnesium dichloride (87 mmol), and triethylamine (218 mmol) in acetonitrile (130 mL) was stirred at rt under N_2. Dry (P_2O_5) paraformaldehyde (235 mmol) was added to the mixture dropwise and after the addition was complete, the mixture was refluxed for 72 h. Then the mixture was acidified with 5% HCl and extracted with Et_20 (x 3). The ethereal solution was washed with H_20 (x 2) and brine and then dried over MgS04, filtered, and concentrated in vacuo. The crude product was purified by column chromatography (0-10% ethyl acetate/hexane)

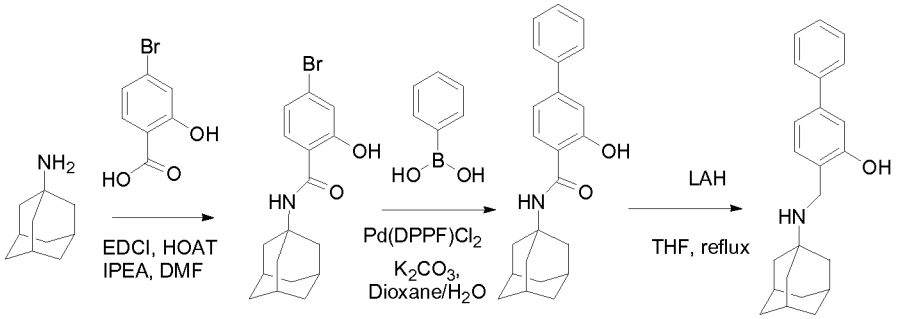
to give 4-bromo-2-hydroxybenzaldehyde as an off-white solid in 42% yield. 4-(Furan-3-yl)-2-hydroxybenzaldehyde (BC087) was prepared based on general procedure 2, from 4-bromo-2-hydroxybenzaldehyde (M2WJ325) and furan-2yltrifluoroborate, a yellow solid in 86%> yield (eluent 0-10% EtOAc/hexane).

2-(((-Adamantan-l-ylamino)methyl)-5-(furan-3-yl)phenol (BC090)-Based on general procedure C, from adamantan-1-amine and 4-(furan-3-yl)-2-hydroxybenzaldehyde (BC087), a light brown solid was obtained. Data: LC/MS (ESCi) m/z 324.22 $[M+H]^+$.

[0278] Example 47a/IMX00661



4-(Adamantan-l-ylaminomethyl)-biphenyl-3-ol



a b

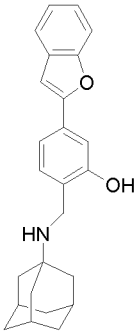
Acid (532 mg, 2 mmol) was added to a solution of HOAT (408 mg, 3 mmol) and EDCI (570 mg, 3 mmol) in anhydrous DMF (10 mL) and stirring was continued for 1 h. Then, amine (5 mL) was added and the reaction mixture was stirred at room temperature overnight. After the solvent was removed under reduced pressure, the residue was purified by flash column chromatography (1-10% CH_30H/CH_2C1_2) to give the tile amid **3** (558 mg, 80%). Data: LC/MS (ESR) m/z 350 $[M+H]^+$.

A mixture of 3 (347 mg), phenylboronic acid (144 mg, 1.2 mmol), K2C03 (278 mg, 2.0 mmol), and Pd(dppf)C12 (73 mg, 10%> mol) in dioxane/H_20 (v/v 5 mL:l mL) was heated at 80

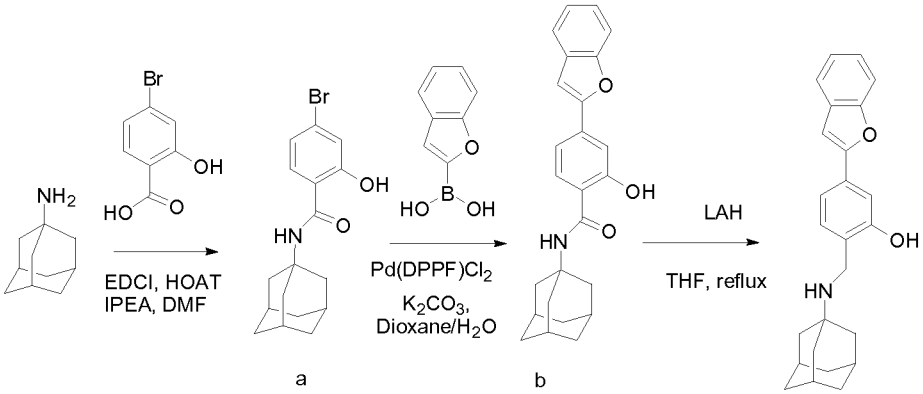
°C under inert environment for 2 h. The solution was evaporated to dryness and purified by flash column chromatography (1-10% CH_3OH/CH_2CI_2) to give the title compound (173 mg, 50%). Data: LC/MS (ESR) m/z 348 $[M+H]^+$.

To a solution of above amide (170 mg, 0.48 mmol) in anhydrous THF (5 mL) was added dropwise of $L1AIH_4$ solution (2.0 M in THF, 1 mL) at 0°C. The resulting solution was stirred for 10 h at reflux. The solution was then cooled to 0°C and quenched by H_20/1N NaOH/H_20 protocol (76uL H_20, 152 uL IN NaOH, 228 uL H_20). After the mixture was stirred for 1 h, the solid was removed by filtration. The resulting solution was evaporated to dryness and purified by flash column chromatography (1-10% CH_3OH/CH_2CI_2) to give 4-(Adamantan-l-ylaminomethyl)-biphenyl-3-ol (73 mg, 46%) as white solid. Data: LC/MS (ESR) m/z 334$[M+H]^+$.

[0279] Example 48a/IMX00660

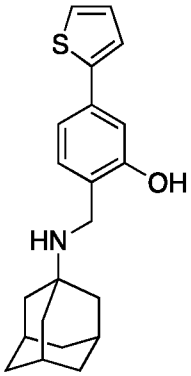


4-(Adamantan-l-ylaminomethyl)-biphenyl-3-ol



Follow the same procedure as example 47. Data: LC/MS (ESR) m/z 374 $[M+H]^+$.

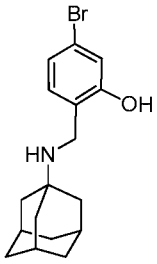
[0280] Example 49a/BC073



2-(-Adamantan-l-ylamino)thiophen-2yl)-5-methylphenol (BC073)

Based on general procedure B, from 2-(-adamantan-l-ylamino)methyl)-5-bromophenol (M2WJ325) and furan-3yltrifluoroborate, an off white solid was obtained. Data: LC/MS (ESCi) m/z 340.08 $[M+H]^+$.

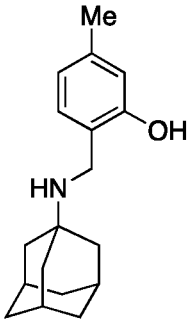
[0281] Example 50a/M2WJ325



2-(((3s,5s,7s)-adamantan-l-ylamino)methyl)-5-bromophenol

Based on general procedure **C,** from amantadine and 4-bromo-2-hydroxybenzaldehyde, a yellow solid (75%) is obtained. Data: LC/MS (ESR) m/z 337.3 $[M+H]^+$.

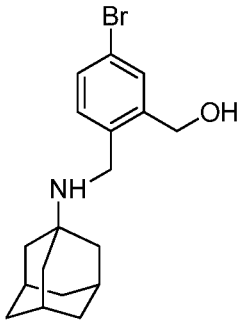
[0282] Example 51a/BC081



Preparation of 2-(-Adamantan-l-ylamino)methyl)-5-methylphenol (BC081)

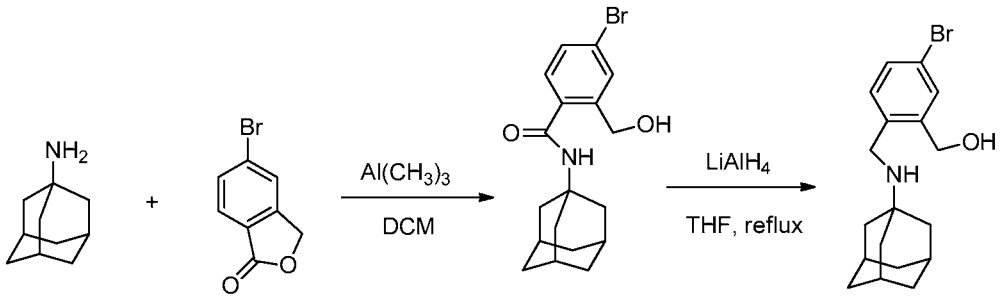
Based on general procedure F, from 2-(-adamantan-l-ylamino)methyl)-5-bromophenol (M2WJ325) and methyltrifluoroborate, an off-white solid was obtained. Data: LC/MS (ESCi) m/z 272.23 $[M+H]^+$.

[0283] Example 52a/M2WJ326

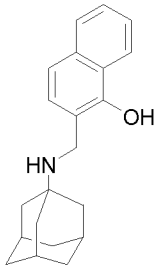


[2-(Adamantan-l-ylaminomethyl)-5-bromo-phenyl]-methanol

To a solution of amantadine (1.5 eq) in DCM was added dropwise a solution of $A1(CH_3)_3$ in hexane (1.5 eq). The mixture was stirred at r.t. for 15 mins, and then 5-bromophthalide (1 eq) was added in one portion. The mixture was then heated at 40°C for 20 hours. After cooling to r.t., diluted HC1 was added and the mixture was extracted with DCM (3×). The combined organic layers were then dried with $MgS0_4$, filtered and concentrated under reduced pressure to give the amide intermediate, which was used in the next step reduction without further purification. Amide (1 eq) was dissolved in anhydrous THF, and the solution was cooled to 0°C using ice-bath, $LiAlH_4$ (4 eq, X gram) was added in small portions in 10 mins. The mixture was warmed to r.t. and stirred for 15 mins, then heated to reflux for 4 hours. After cooling to room temperature, H_20 (X ml), 15% NaOH (X ml) and H_20 (3X ml) were subsequently added, and the slurry was filtered. The filtrate was concentrated under reduced pressure and purified by HPLC.



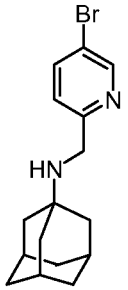
[0294] Example 53a/IMX00639



2-(Adamantan-l-ylaminomethyl)-naphthalen-l-ol

Based on general procedure **A,** l-Hydroxy-naphthalene-2-carbaldehyde and Adamantan-1-ylamine, a white solid (69%) is obtained. Data: LC/MS (ESR) m/z 308 $[M+H]^+$.

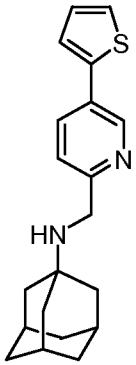
[0295] Example 54a/IMX00710



Adamantan-l-yl-(5-bromo-pyridin-2-ylmethyl)-amine

Based on general procedure A, 5-Bromo-pyridine-2-carbaldehyde and Adamantan-l-ylamine, a white solid (82%) is obtained. Data: LC/MS (ESR) m/z 322 $[M+H]^+$.

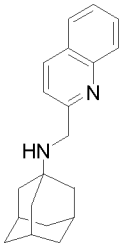
[0296] Example 55a/IMX00711



Adamantan-l-yl-(5-thiophen-2-yl-pyridin-2-ylmethyl)-amine

Based on general procedure **E,** from adamantan-l-yl-(5-bromo-pyridin-2-ylmethyl)-amine (IMX710) and 2-thiopheneboronic acid, Adamantan-l-yl-(5-thiophen-2-yl-pyridin-2-ylmethyl)-amine was obtained (46% two steps) as a white solid. Data: LC/MS (ESR) m/z 325 $[M+H]^+$.

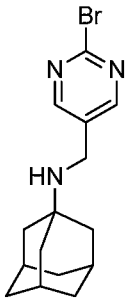
[0297] Example 56a/IMX00640



Adamantan-l-yl-quinolin-2-ylmethyl-amine

Based on general procedure **A,** from Quinoline-2-carbaldehyde and Adamantan-l-ylamine, a white solid (82%) is obtained. Data: LC/MS (ESR) m/z 293 $[M+H]^+$.

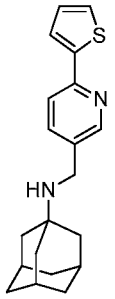
[0298] Example 57a/M2WJ387



N-((2-bromopyrimidin-5-yl)methyl)adamantan-l-amine

Based on general procedure **C** from amantadine and 2-bromopyrimidine-5-carbaldehyde, a brown solid (55%) is obtained. Data: LC/MS (ESR) m/z 323.2 $[M+H]^+$.

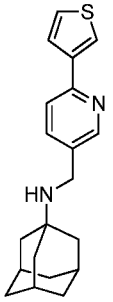
[0299] Example 58a/M2WJ383



N-((6-(thiophen-2-yl)pyridin-3-yl)methyl)adamantan-l-amine

Based on general procedure **C,** from amantadine and 6-(thiophen-2-yl)nicotinaldehyde, a yellow solid (82%) is obtained. Data: LC/MS (ESR) m/z 325.5 $[M+H]^+$.

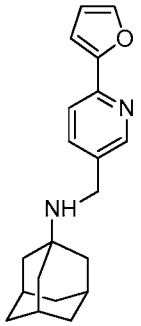
[0300] Example 59a/M2WJ385



N-((6-(thiophen-3-yl)pyridin-3-yl)methyl)adamantan-l-amine

Based on general procedure **C,** from amantadine and 6-(thiophen-3-yl)nicotinaldehyde, a yellow solid (76%) is obtained. Data: LC/MS (ESR) m/z 325.5 $[M+H]^+$.

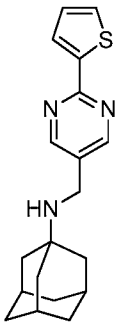
[0301] Example 60a/M2WJ329



N-((6-(furan-2-yl)pyridin-3-yl)methyl)adamantan-l-amine

Based on general procedure **C,** from amantadine and 6-(furan-2-yl)nicotinaldehyde, a yellow solid (80%) is obtained. Data: LC/MS (ESR) m/z 309.4 $[M+H]^+$.

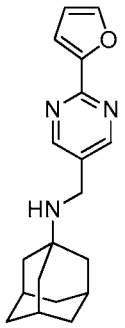
[0302] Example 61a/M2WJ330



N-((2-(thiophen-2-yl)pyrimidin-5-yl)methyl)adamantan-l-amine

Based on general procedure **C,** from amantadine and 2-(thiophen-2-yl)pyrimidine-5-carbaldehyde, a yellow solid (81%) is obtained. Data: LC/MS (ESR) m/z 326.5 $[M+H]^+$.

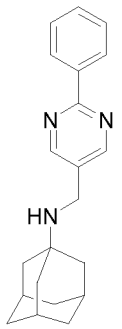
[0303] Example 62a/M2WJ336



N-((2-(furan-2-yl)pyrimidin-5-yl)methyl)adamantan-l-amine

Based on general procedure **C,** from amantadine and 2-(furan-2-yl)pyrimidine-5-carbaldehyde, a yellow solid (72%) is obtained. Data: LC/MS (ESR) m/z 310.4 $[M+H]^+$

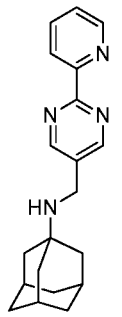
[0304] Example 63a/M2WJ391



N-((2-phenylpyrimidin-5-yl)methyl)adamantan-l-amine

Based on general procedure **C,** from amantadine and 2-phenylpyrimidine-5-carbaldehyde, a yellow solid (85%) is obtained. Data: LC/MS (ESR) m/z 320.4 $[M+H]^+$.

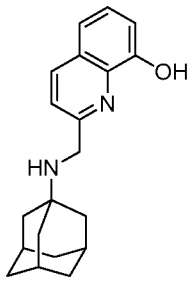
[0305] Example 64a/M2WJ392



N-((2-(pyridin-2-yl)pyrimidin-5-yl)methyl)adamantan-l-amine

Based on general procedure **C,** from amantadine and 2-(pyridin-2-yl)pyrimidine-5-carbaldehyde, a yellow solid (71%) is obtained. Data: LC/MS (ESR) m/z 321.4 $[M+H]^+$.

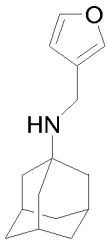
[0306] Example 65a/M2WJ322



2-((adamantan-l-ylamino)methyl)quinolin-8-ol

Based on general procedure **C,** from amantadine and 8-hydroxyquinoline-2-carbaldehyde, a white solid (64%) is obtained. Data: LC/MS (ESR) m/z 309.4 $[M+H]^+$.

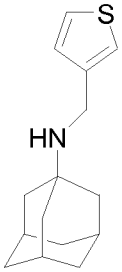
[0307] Example 66a/IMX00616



Adamantan-l-yl-furan-3-ylmethyl-amine

Based on general procedure **A,** From furan-3-carbaldehyde and Adamantan-l-ylamine, a white solid (82%) is obtained. Data: LC/MS (ESR) m/z 232 $[M+H]^+$.

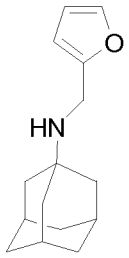
[0308] Example 68a/IMX00617



Adamantan-l-yl-thiophen-3-ylmethyl-amine

Based on general procedure **A,** from thiophene-3-carbaldehyde and adamantan-l-ylamine, a white solid (80%) is obtained. Data: LC/MS (ESR) m/z 248 $[M+H]^+$.

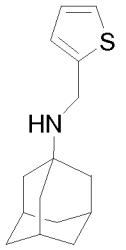
[0309] Example 69a/IMX00667 and WFD046



Adamantan-l-yl-furan-2-ylmethyl-amine

Based on general procedure **A,** from furan-2-carbaldehyde and adamantan-l-ylamine, a white solid (80%) is obtained. Data: LC/MS (ESR) m/z 232 $[M+H]^+$.

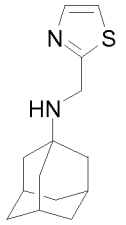
[0310] Example 70a/IMX00668



Adamantan-l-yl-thiophen-2-ylmethyl-amine

Based on general procedure **A,** from thiophene-2-carbaldehyde and adamantan-l-ylamine, a white solid (80%) is obtained. Data: LC/MS (ESR) m/z 248 $[M+H]^+$.

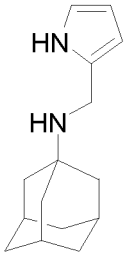
[0311] Example 71a/ WFD079 and IMX00669



Adamantan-l-yl-thiazol-2-ylmethyl-amine

Based on general procedure **C,** from thiazole-2-carbaldehyde and adamantan-l-ylamine, a white solid (70%) is obtained. Data: LC/MS (ESR) m/z 249 $[M+H]^+$.

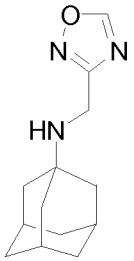
[0312] Example 72a/ IMX00697



Adamantan-l-yl-(lH-pyrrol-2-ylmethyl)-amine

Based on general procedure **A,** ftom lH-Pyrrole-2-carbaldehyde and adamantan-1-ylamine, a white solid (70%) is obtained. Data: LC/MS (ESR) m/z 231 $[M+H]^+$.

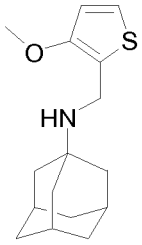
[0313] Example 73a/ M2WJ396



Adamantan-l-yl-[l,2,4]oxadiazol-3-ylmethyl-amine

Based on general procedure **B,** from amantadine and 3-(chloromethyl)-l,2,4-oxadiazole, a white solid (75%) is obtained. Data: ^{1}HNMR (300 MHz, CD_3OD): δ 9.19 (s, 1H), 3.95 (s, 2H), 2.10-2.08 (m, 3H), 1.75-1.72 (m, 12H). EI-MS: *mlz* $(M+H^+)$: 234.3 (calculated), 234.3 (found).

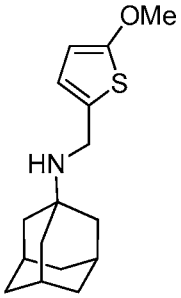
[0314] Example 74a/ IMX00686



Adamantan-l-yl-(3-methoxy-thiophen-2-ylmethyl)-amine

Based on general procedure **A,** from 3-methoxy-thiophene-2-carbaldehyde and adamantan-1-ylamine, a white solid (70%) is obtained. Data: LC/MS (ESR) m/z 278 $[M+H]^+$.

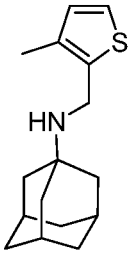
[0315] Example 75a/WFD050



N-((5-methoxythiophen-2-yl)methyl)adamantan-l-amine

Based on general procedure C, from adamantane-1-amine and 5-methoxythiophene-2-carbaldehyde, a white solid is obtained. Data: LC/MS (ES+) m/z 278.2 $[M+H]^+$.

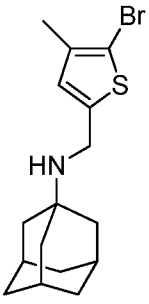
[0316] Example 76a/WFD053



N-((3-methylthiophen-2-yl)methyl)adamantan-l-amine

Based on general procedure C, from adamantane-1-amine and 3-methylthiophene-2-carbaldehyde, a white solid is obtained. Data: LC/MS (ES+) m/z 262.2 $[M+H]^+$.

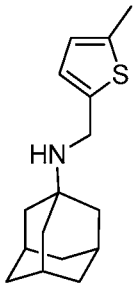
[0317] Example 77a/M2WJ338



N-((5-bromo-4-methylthiophen-2-yl)methyl)adamantan-l-amine

Based on general procedure C, from amantadine and 5-bromo-4-methylthiophene-2-carbaldehyde, a yellow solid (65%) is obtained. Data: LC/MS (ESR) m/z 341.3 $[M+H]^+$.

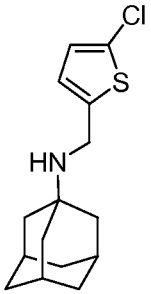
[0318] Example 78a/WFD049



N-((5-methylthiophen-2-yl)methyl)adamantan-l-amine

Based on general procedure **C,** from adamantane-1-amine and 5-methylthiophene-2-carbaldehyde, a white solid is obtained . Data: LC/MS (ES+) m/z 262.1 $[M+H]^+$.

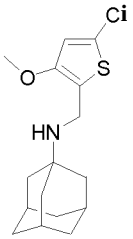
[0319] Example 79a/WFD052



N-((5-chlorothiophen-2-yl)methyl)adamantan-l-amine

Based on general procedure **C,** from adamantane-1-amine and 5-chlorothiophene-2-carbaldehyde, a white solid is obtained . Data: LC/MS (ES+) m/z 282.2 $[M+H]^+$.

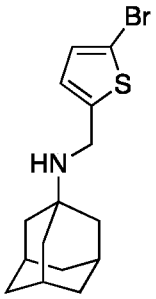
[0320] Example 80a/ IMX00687



Adamantan-l-yl-(3-methoxy-thiophen-2-ylmethyl)-amine

Treatment of adamantan-l-yl-(3-methoxy-thiophen-2-ylmethyl)-amine (278 mg, 1.0 mmol) with NCS (150 mg, 1.2 eq) at 50 °C in DMF for 2h. Solvent was removed under reduced pressure, the residue was purified by flash column chromatography (1-10% **CH_3OH/CH2CI2)** to give the tile compound (215 mg,66%) as a white solid. Data: LC/MS (ESR) m/z 312 $[M+H]^+$.

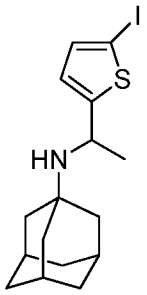
[0321] Example 81a/BC035



N-((5-Bromothiophen-2-yl)methyl)adamantan-l-amine

Based on general procedure A, adamantan-1-amine and 5-bromothiophene-2-carbaldehyde, a light yellow oil was obtained. Data: LC/MS (ESCi) m/z 328.00 $[M+H]^+$.

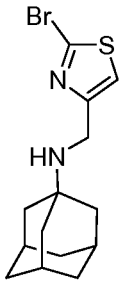
[0322] Example 82a/M2WJ341



N-(l-(5-iodothiophen-2-yl)ethyl)adamantan-l-amine

Based on general procedure **C,** from amantadine and l-(5-iodothiophen-2-yl)ethanone, a white solid (32%) is obtained. Data: LC/MS (ESR) m/z 388.3 $[M+H]^+$.

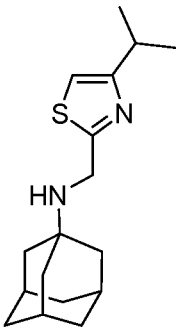
[0323] Example 83a/WFD082



N-((2-bromothiazol-4-yl)methyl)adamantan-l-amine

Based on general procedure **C,** from adamantane-1-amine and 2-bromothiazole-4-carbaldehyde, a white solid is obtained . Data: LC/MS (ES+) m/z 327.09, 329.08 $[M+H]^+$.

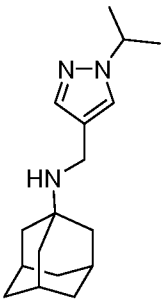
[0324] Example 84a/WFD084



N-((4-isopropylthiazol-2-yl)methyl)adamantan-l-amine

Based on general procedure **C,** from adamantane-1-amine and 4-isopropylthiazole-2-carbaldehyde, a white solid is obtained. Data: LC/MS (ES+) m/z 291.3 $[M+H]^+$.

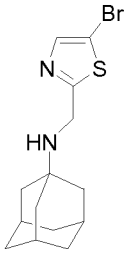
[0325] Example 85a/WFD073



N-((l-isopropyl-lH-pyrazol-4-yl)methyl)adamantan-l-amine

Based on general procedure **C,** from adamantane-1-amine and l-isopropyl-lH-pyrazole-4-carbaldehyde, a white solid is obtained. Data: LC/MS (ES+) m/z 274.4 $[M+H]^+$.

[0326] Example 86a/ IMX00671

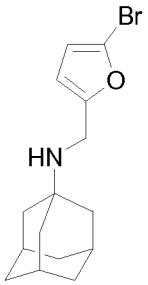


Adamantan-l-yl-(5-bromo-thiazol-2-ylmethyl)-amine

To adamantan-l-yl-thiazol-2-ylmethyl-amine (500 mg, 2.0 mmol) in THF (10 mL) at -78 °C, was added nBuLi (2.5 M, 2.0 mL, 5 mmol). After 30 min, CBr_4 (784 mg, 2.4 mmol) was added. After stirred for 30 min at -10 °C, the reaction was quenched with NH_4C1 (sat'd) (10 mL). The mixture was extracted with DCM (20 mL x3), and the combined organic layers was dried over Na_2S0_4 and solvent was removed under reduced pressure to give a residue, which was purified

by flash column chromatography (1-10% CH_3OH/CH_2CI_2) to give the tile compound (372 mg, 57%) as a white solid. Data: LC/MS (ESR) m/z 328 $[M+H]^+$.

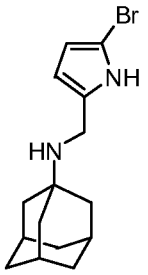
[0327] Example 87a/ IMX00688



Adamantan-l-yl-(5-bromo-furan-2-ylmethyl)-amine

Based on general procedure **A,** 5-Bromo-furan-2-carbaldehyde and adamantan-l-ylamine, a white solid (70%) is obtained. Data: LC/MS (ESR) m/z 311 $[M+H]^+$.

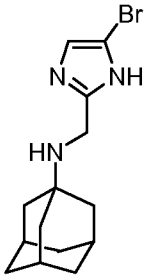
[0328] Example 88a/ IMX00698



Adamantan-l-yl-(5-bromo-lH-pyrrol-2-ylmethyl)-amine

Based on general procedure **A,** 5-bromo-lH-pyrrole-2-carbaldehyde and adamantan-l-ylamine, a white solid (70%) is obtained. Data: LC/MS (ESR) m/z 310 $[M+H]^+$.

[0329] Example 89a/ IMX00701

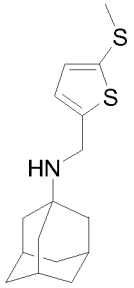


Adamantan-l-yl-(5-bromo-thiazol-2-ylmethyl)-amine

Treatment of Adamantan-l-yl-(lH-imidazol-2-ylmethyl)-amine (231 mg, 1.0 mmol) with NBS (180 mg, 1.1 eq) at 0 °C in DMF for lh. Solvent was removed under reduced pressure, the

residue was purified by flash column chromatography (1-10% CH_3OH/CH_2CI_2) to give the tile compound (71 mg,23%) as a white solid. Data: LC/MS (ESR) m/z 311 $[M+H]^+$.

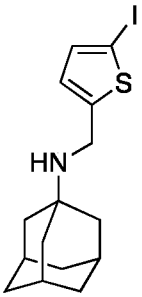
[0330] Example 90a/ M2WJP001 and IMX00689



Adamantan-l-yl-(5-bromo-lH-pyrrol-2-ylmethyl)-amine

Based on general Procedure E, from 5-Methylsulfanyl-thiophene-2-carboxylic acid and adamantan-l-ylamine, a white solid (60%) is obtained. Data: LC/MS (ESR) m/z 294$[M+H]^+$.

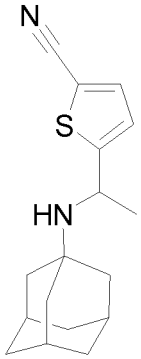
[0331] Example 91a/ BC067



N-((5-Iodothiophen-2-yl)methyl)adamantan-l-amine

A solution of N-((5-bromothiophen-2-yl)methyl)adamantan-l -amine (BC035) (1 mmol) in THF (12 mL) was added n-BuLi in hexane (2.5M 1.8 mL) at -78 °C under N_2. The reaction mixture was stirred for 30 min and then I_2 was added and stirred for 30 min at -78 °C. The mixture was quenched with sodium thiosulfate, and the crude mixture was extracted with Et_20 (x 3). The combined organic layers were dried over $MgS0_4$, filtered, and concentrated in vacuo. A light yellow solid was obtained. Data: LC/MS (ESCi) m/z 374.01 $[M+H]^+$.

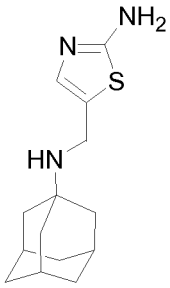
[0332] Example 92a/WFD058



5-(l-(adamantan-l-ylamino)ethyl)thiophene-2-carbonitrile

Based on general procedure **c,** from adamantane-1-amine and 5-acetylthiophene-2-carbonitrile, a white solid is obtained. Data: LC/MS (ES+) m/z 287.2 $[M+H]^+$.

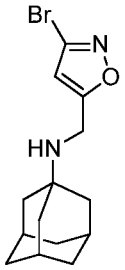
[0333] Example 93a/WFD085



5-((adamantan-l-ylamino)methyl)thiazol-2-amine

Based on general procedure **c,** from adamantane-1-amine and 2-aminothiazole-5-carbaldehyde, a white solid is obtained. Data: LC/MS (ES+) m/z 264.2 $[M+H]^+$.

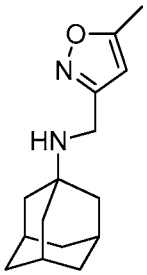
[0334] Example 94a/M2WJ364



N-((3-bromoisoxazol-5-yl)methyl)adamantan-l-amine

Based on general procedure **D,** from amantadine and 3-bromo-5-(chloromethyl)isoxazole, a brown solid (80%) is obtained. Data: LC/MS (ESR) m/z 312.2 $[M+H]^+$.

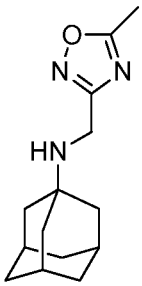
[0335] Example 95a/M2WJ369



N-((5-methylisoxazol-3-yl)methyl)adamantan-l-amine

Based on general procedure C, from amantadine and 5-methylisoxazole-3-carbaldehyde, a yellow solid (83%) is obtained. Data: ^{1}HNMR (300 MHz, CD_3OD): δ 6.19 (s, 1H), 3.77 (s, 2H), 2.40 (s, 3H), 2.09-2.07 (m, 3H), 1.73-1.69 (m, 12H). ^{13}CNMR (75 MHz, CD_3OD): 171.1 1, 164.84, 102.39, 52.28, 42.78, 37.63, 37.08, 30.99, 11.98. EI-MS: m/z ($M+H^+$): 247.4 (calculated), 247.4 (found).

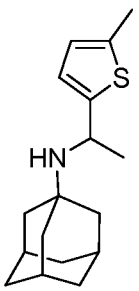
[0336] Example 96a/M2WJ405



N-((5-methyl- 1,2,4-oxadiazol-3-yl)methyl)adamantan- 1-amine

Based on general procedure **D,** from amantadine and 3-(chloromethyl)-5 -methyl- 1,2,4-oxadiazole, a white solid (77%) is obtained. Data: ^{1}HNMR (300 MHz, CD_3OD): δ 3.85 (s, 2H), 2.58 (s, 3H), 2.10-2.08 (m, 3H), 1.76-1.66 (m, 12H). EI-MS: m/z ($M+H^+$): 248.3 (calculated), 248.4 (found).

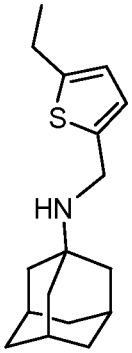
[0337] Example 97a/WFD057



N-(l-(5-methylthiophen-2-yl)ethyl)adamantan-l-amine

Based on general procedure **C,** from adamantane-1-amine and l-(5-methylthiophen-2-yl)ethanone, a white solid is obtained . Data: LC/MS (ES+) m/z 276.3 $[M+H]^+$.

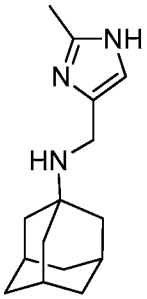
[0338] Example 98a/hij-313



N-((5-ethylthiophen-2-yl)methyl)adamantan-l-amine

Based on general procedure **C,** from adamantane-1-amine and 5-ethylthiophene-2-carbaldehyde, a yellowish liquid is obtained by a silica gel column chromatography . Data: LC/MS (ES+) m/z 276.4 $[M+H]^+$.

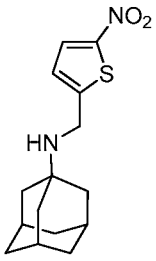
[0339] Example 99a/WFD069



N-((2-methyl-lH-imidazol-4-yl)methyl)adamantan-l-amine

Based on general procedure **C,** from adamantane-1-amine and 2-methyl-lH-imidazole-4-carbaldehyde, a yellowish liquid is obtained by a silica gel column chromatography . Data: LC/MS (ES+) m/z 246.3 $[M+H]^+$.

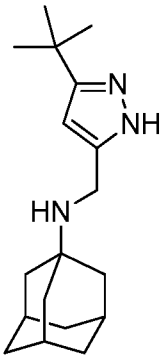
[0340] Example 100a/WFD061



N-((5-nitrothiophen-2-yl)methyl)adamantan-l-amine

Based on general procedure **C,** from adamantane-1 -amine and 5-nitrothiophene-2-carbaldehyde, a white soid is obtained. Data: LC/MS (ES+) m/z 293.2 $[M+H]^+$.

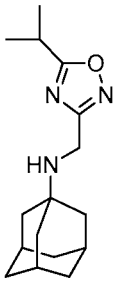
[0341] Example 101a/M2WJ305



N-((3-(tert-butyl)-lH-pyrazol-5-yl)methyl)adamantan-l-amine

Based on general procedure **C,** from amantadine and 3-(tert-butyl)-lH-pyrazole-5-carbaldefiyde, a yellow solid (80%) is obtained. Data: LC/MS (ESR) m/z 288.4 $[M+H]^+$.

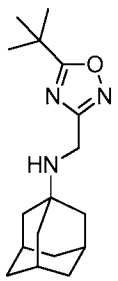
[0342] Example 102a/M2WJ400



N-((5-isopropyl- 1,2,4-oxadiazol-3-yl)methyl)adamantan- 1-amine

Based on general procedure **D,** from amantadine and 3-(chloromethyl)-5-isopropyl-l,2,4-oxadiazole, a yellow solid (83%) is obtained. Data: ^{1}HNMR (300 MHz, CD_3OD): δ 3.24 (q, J = 6.99 Hz, 1H), 2.10-2.08 (m, 3H), 1.76-1.66 (m, 12H), 1.38 (d, J = 6.99 Hz, 6H). EI-MS: m/z ($M+H^+$): 276.4 (calculated), 276.1 (found).

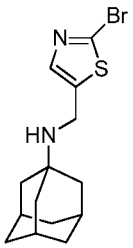
[0343] Example 103a/M2WJ401



N-((5-(tert-butyl)- 1,2,4-oxadiazol-3-yl)methyl)adamantan- 1-amine

Based on general procedure D, from amantadine and 5-(tert-butyl)-3-(chloromethyl)-l,2,4-oxadiazole, a white solid (79%) is obtained. Data: ^{1}HNMR (300 MHz, CD_3OD): δ 3.86 (s, 2H), 2.10-2.08 (m, 3H), 1.76-1.66 (m, 12H), 1.47 (s, 9H). EI-MS: m/z ($M+H^+$): 290.4 (calculated), 290.2 (found).

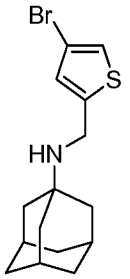
[0344] Example 104a/M2WJ349



N-((2-bromothiazol-5-yl)methyl)adamantan-l-amine

Based on general procedure **C,** from amantadine and 2-(2-bromothiazol-5-yl)acetaldehyde, a white solid (62%) is obtained. Data: LC/MS (ESR) m/z 328.3 $[M+H]^+$.

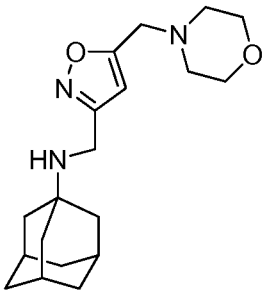
[0345] Example 105a/M2WJ350



N-((4-bromothiophen-2-yl)methyl)adamantan-l-amine

Based on general procedure **C,** from amantadine and 4-bromothiophene-2-carbaldehyde, a white solid (71%) is obtained. Data: LC/MS (ESR) m/z 327.3 $[M+H]^+$.

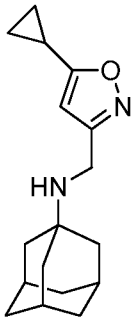
[0346] Example 106a/M2WJ371



N-((5-(morpholinomethyl)isoxazol-3-yl)methyl)adamantan-l-amine

Based on general procedure **D,** from amantadine and 4-((3-(chloromethyl)isoxazol-5-yl)methyl)morpholine, a white solid (86%) is obtained. Data: ^{1}HNMR (300 MHz, CD_3OD-d_4): δ 6.43 (s, 1H), 3.82 (s, 2H), 3.71 (s, 2H), 3.69 (t, J = 4.68 Hz, 4H), 2.53 (t, J = 4.68 Hz, 4H), 2.10-2.07 (m, 3H), 1.74-1.69 (m, 12H). EI-MS: m/z ($M+H^+$): 332.5 (calculated), 332.5 (found).

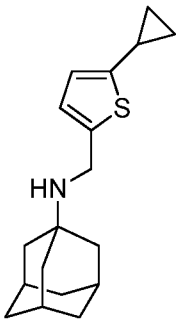
[0347] Example 107a/M2WJ379



N-((5-cyclopropylisoxazol-3-yl)methyl)adamantan-l-amine

Based on general procedure **D,** from amantadine and 3-(chloromethyl)-5-cyclopropylisoxazole, a white solid (86%) is obtained. Data: LC/MS (ESR) m/z 273.4 $[M+H]^+$.

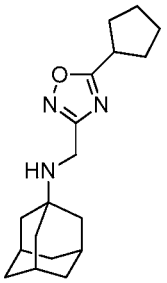
[0348] Example 108a/M2WJ395



N-((5-cyclopropylthiophen-2-yl)methyl)adamantan-l-amine

Based on general procedure **I,** a white solid (77% yield). Data: ^{1}HNMR (300 MHz, CD_3OD): δ 7.03 (d, J = 3.45 Hz, 1H), 6.75 (d, J = 3.45 Hz, 1H), 4.31 (s, 2H), 2.23-2.21 (m, 3H), 2.14-2.09 (m, 1H), 1.98-1.96 (m, 6H), 1.84-1.72 (m, 6H), 1.05-1.02 (m, 2H), 0.71-0.69 (m, 2H). EI-MS: m/z ($M+H^+$): 288.4 (calculated), 288.4 (found).

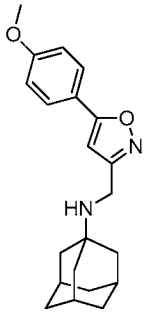
[0349] Example 109a/M2WJ403



N-((5-cyclopentyl-l,2,4-oxadiazol-3-yl)methyl)adamantan-l-amine

Based on general procedure **D,** from amantadine and 3-(chloromethyl)-5-cyclopentyl- 1,2,4-oxadiazole, a white solid (83%) is obtained. Data: ^{1}HNMR (300 MHz, CD_3OD): δ 3.86 (s, 2H), 3.45-3.30 (m, 1H), 2.25-2.02 (m, 5H), 1.98-1.62 (m, 18H). EI-MS: m/z ($M+H^+$): 302.4

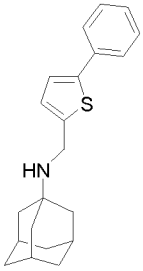
[0350] Example 110a/M2WJ358



N-((5-(4-methoxyphenyl)isoxazol-3-yl)methyl)adamantan-l-amine

Based on general procedure **C,** from amantadine and 5-(4-methoxyphenyl)isoxazole-3-carbaldehyde, a yellow solid (75%) is obtained. Data: ^{1}HNMR (300 MHz, CD_3OD): δ 7.76-7.73 (m, 2H), 7.05-7.02 (m, 2H), 6.67 (s, 1H), 3.84 (s, 2H), 3.83 (s, 2H), 2.09-2.07 (m, 3H), 1.76-1.72 (m, 12H). ^{13}CNMR (75 MHz, CD_3OD): 171.31, 165.34, 162.82, 128.37, 121.39, 115.54, 98.97, 55.89, 52.36, 42.80, 37.63, 37.16, 30.99. EI-MS: m/z ($M+H^+$): 339.4 (calculated), 339.4 (found).

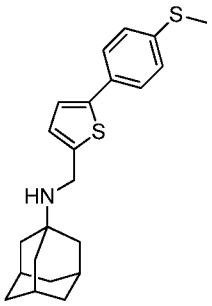
[0351] Example 111a/ WFD060 and IMX00666



Adamantan-l-yl-(5-bromo-thiophen-2-ylmethyl)-amine

Based on general procedure **E,** from Adamantan-l-yl-(5-bromo-thiophen-2-ylmethyl)-amine and pheneboronic acid, adamantan-l-yl-(5-bromo-thiophen-2-ylmethyl)-amine was obtained (66% two steps) as a white solid. Data: LC/MS (ESR) m/z 325 $[M+H]^+$.

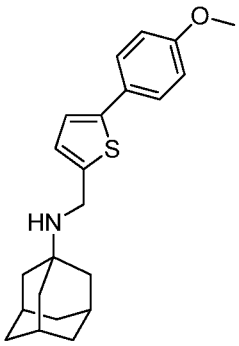
[0352] Example 112a/M2WJ343



N-((5-(4-(methylthio)phenyl)thiophen-2-yl)methyl)adamantan-l-amine

Based on general procedure **C,** from amantadine and 5-(4-(methylthio)phenyl)thiophene-2-carbaldehyde, a white solid (72%) is obtained. Data: LC/MS (ESR) m/z 370.6 [M+H]

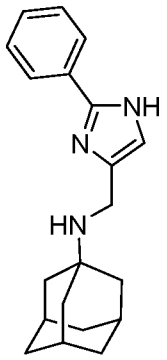
[0353] Example 113a/M2WJ344



N-((5-(4-methoxyphenyl)thiophen-2-yl)methyl)adamantan-l-amine

Based on general procedure **C,** from amantadine and 5-(4-methoxyphenyl)thiophene-2-carbaldehyde, a white solid (71%) is obtained. Data: LC/MS (ESR) m/z 354.5 $[M+H]^+$.

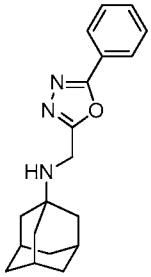
[0354] Example 114a/WFD070



N-((2-phenyl-lH-imidazol-4-yl)methyl)adamantan-l-amine

Based on general procedure **C,** from adamantane-1-amine and 2-phenyl-lH-imidazole-4-carbaldehyde, a white solid is obtained . Data: LC/MS (ES+) m/z 308.3 $[M+H]^+$.

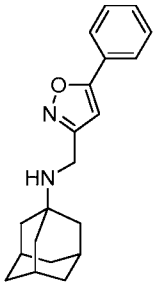
[0355] Example 115a/M2WJ351



N-((5-phenyl-l,3,4-oxadiazol-2-yl)methyl)adamantan-l-amine

Based on general procedure D, from amantadine and 2-(chloromethyl)-5-phenyl-l,3,4-oxadiazole, a yellow solid (78%) is obtained. Data: LC/MS (ESR) m/z 310.4 $[M+H]^+$.

[0356] Example 116a/M2WJ352

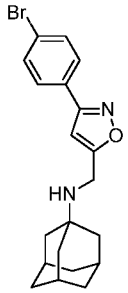


N-((5-phenylisoxazol-3-yl)methyl)adamantan-l-amine

Based on general procedure **C,** from amantadine and 5-phenylisoxazole-3-carbaldehyde, a white solid (89%) is obtained. Data: ^{1}HNMR (300 MHz, DMSO-d_6): δ 7.90-7.87 (m, 2H), 7.56-7.53

(m, 3H), 7.02 (s, 1H), 3.80 (s, 2H), 2.07-2.05 (m, 3H), 1.66-1.64 (m, 12H). EI-MS: m/z ($M+H^+$): 309.4 (calculated), 309.3 (found).

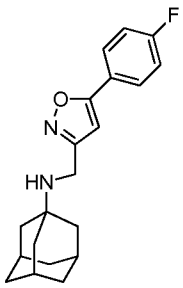
[0357] Example 117a/M2WJ361



N-((3-(4-bromophenyl)isoxazol-5-yl)methyl)adamantan-l-amine

Based on general procedure **C**, from amantadine and 3-(4-bromophenyl)isoxazole-5-carbaldehyde, a brown solid (72%) is obtained. Data: ^{1}HNMR (300 MHz, CD_3OD): δ 7.77-7.73 (m, 2H), 7.66-7.63 (m, 2H), 3.94 (s, 2H), 2.10-2.08 (m, 3H), 1.75-1.70 (m, 12H). EI-MS: m/z ($M+H^+$): 388.3 (calculated), 388.3 (found).

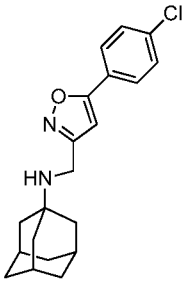
[0358] Example 118a/M2WJ366



N-((5-(4-fluorophenyl)isoxazol-3-yl)methyl)adamantan-l-amine

Based on general procedure **C**, from amantadine and 5-(4-fluorophenyl)isoxazole-3-carbaldehyde, a yellow solid (69%) is obtained. Data: ^{1}HNMR (300 MHz, DMSO-d_6): δ 7.92 (dd, J = 8.21 Hz, 6.27 Hz, 2H), 7.36 (dd, J = 5.79 Hz, 2.73 Hz, 2H), 6.97 (s, 1H), 3.75 (s, 2H), 2.02-2.00 (m, 3H), 1.63-1.61 (m, 12H). EI-MS: m/z ($M+H^+$): 327.4 (calculated), 327.2 (found).

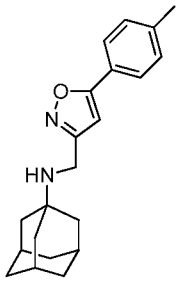
[0359] Example 119a/M2WJ367



N-((5-(4-chlorophenyl)isoxazol-3-yl)methyl)adamantan-l-amine

Based on general procedure **C,** from amantadine and 5-(4-chlorophenyl)isoxazole-3-carbaldehyde, a white solid (80%) is obtained. Data: ^{1}HNMR (300 MHz, CD_3OD): δ 7.82-7.78 (m, 2H), 7.53-7.49 (m, 2H), 6.84 (s, 1H), 3.86 (s, 2H), 2.10-2.08 (m, 3H), 1.75-1.71 (m, 12H). ^{13}CNMR (75 MHz, CD_3OD): 169.98, 165.58, 137.26, 130.43, 128.25, 127.40, 100.97, 52.37, 42.82, 37.62, 37.15, 30.99. EI-MS: m/z ($M+H^+$): 343.9 (calculated), 343.4 (found).

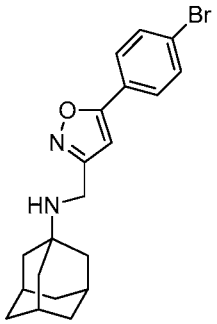
[0360] Example 120a/M2WJ368



N-((5-(p-tolyl)isoxazol-3-yl)methyl)adamantan-l-amine

Based on general procedure **C,** from amantadine and 5-(p-tolyl)isoxazole-3-carbaldehyde, a yellow solid (88%) is obtained. Data: ^{1}HNMR (300 MHz, DMSO-d_6): δ 7.73 (d, J = 8.1 Hz, 2H), 7.33 (d, J = 8.1 Hz, 2H), 6.90 (s, 1H), 3.75 (s, 2H), 2.36 (s, 3H), 2.02-2.00 (m, 3H), 1.63-1.60 (m, 12H). EI-MS: m/z ($M+H^+$): 323.4 (calculated), 323.4 (found).

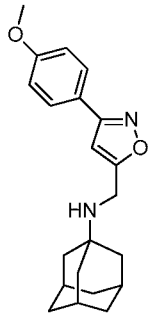
[0361] Example 121a/M2WJ370



N-((5-(4-bromophenyl)isoxazol-3-yl)methyl)adamantan-l-amine

Based on general procedure C, from amantadine and 5-(4-bromophenyl)isoxazole-3-carbaldehyde, a yellow solid (69%) is obtained. Data: ^{1}HNMR (300 MHz, CD_3OD): δ 7.76-7.66 (m, 4H), 6.86 (s, 1H), 3.87 (s, 2H), 2.10-2.08 (m, 2H), 1.77-1.73 (m, 12H). EI-MS: m/z ($M+H^+$): 388 (calculated), 388.1 (found).

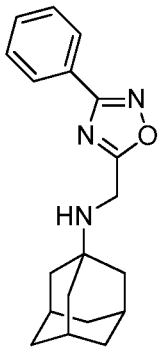
[0362] Example 122a/M2WJ386



N-((3-(4-methoxyphenyl)isoxazol-5-yl)methyl)adamantan-l-amine

Based on general procedure **D,** from amantadine and 5-(chloromethyl)-3-(4-methoxyphenyl)isoxazole, a white solid (80%) is obtained. Data: ^{1}HNMR (300 MHz, DMSO-d_6): δ 7.78 (d, J = 8.73 Hz, 2H), 7.06 (d, J = 8.73 Hz, 2H), 6.82 (s, 1H), 3.81 (s, 3H), 3.73 (s, 2H), 2.10-2.08 (m, 3H), 1.64-1.60 (m, 12H). EI-MS: m/z ($M+H^+$): 339.4 (calculated), 339.2 (found).

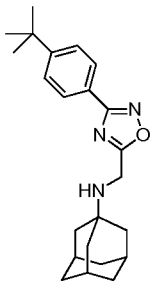
[0363] Example 123a/M2WJ376



N-((3-phenyl-l,2,4-oxadiazol-5-yl)methyl)adamantan-l-amine

Based on general procedure **D,** from amantadine and 5-(chloromethyl)-3-phenyl-l,2,4-oxadiazole, a white solid (74%) is obtained. Data: ^{1}HNMR (300 MHz, DMSO-d_6): δ 8.02-7.99 (m, 2H), 7.58-7.56 (m, 3H), 4.06 (s, 2H), 2.02-2.00 (m, 3H), 1.62-1.55 (m, 12H). EI-MS: m/z ($M+H^+$): 310.4 (calculated), 310.6 (found).

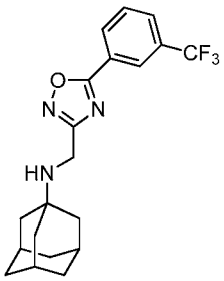
[0364] Example 124a/M2WJ377



N-((3-(4-(tert-butyl)phenyl)-l,2,4-oxadiazol-5-yl)methyl)adamantan-l-amine

Based on general procedure **D,** from amantadine and 3-(4-(tert-butyl)phenyl)-5-(chloromethyl)-1,2,4-oxadiazole, a white solid (89%) is obtained. Data: ^{1}HNMR (300 MHz, DMSO-d $_6$): δ 7.92 (d, J = 8.43 Hz, 2H), 7.57 (d, J = 8.43 Hz, 2H), 4.05 (s, 2H), 2.02-2.00 (m, 3H), 1.59-1.52 (m, 12H), 1.31 (s, 9H). EI-MS: m/z ($M+H^+$): 366.5 (calculated), 366.3 (found).

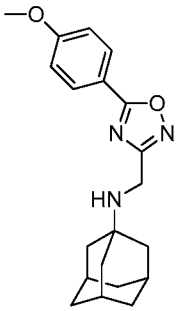
[0365] Example 125a/M2WJ398



N-((5-(3-(trifluoromethyl)phenyl)-l,2,4-oxadiazol-3-yl)methyl)adamantan-l-amine

Based on general procedure **D,** from amantadine and 3-(chloromethyl)-5-(3-(trifluoromethyl)phenyl)-l,2,4-oxadiazole, a yellow solid (91%) is obtained. Data: ^{1}HNMR (300 MHz, CD_3OD): δ 8.43-8.40 (m, 2H), 8.00-7.97 (m, 1H), 7.86-7.80 (m, 1H), 3.99 (s, 2H), 2.11-2.08 (m, 3H), 1.79-1.72 (m, 12H). EI-MS: m/z ($M+H^+$): 378.4 (calculated), 378.4 (found)

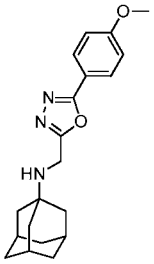
[0366] Example 126a/M2WJ378



N-((5-(4-methoxyphenyl)-l,2,4-oxadiazol-3-yl)methyl)adamantan-l-amine

Based on general procedure **D,** from amantadine and 3-(chloromethyl)-5-(4-methoxyphenyl)-1,2,4-oxadiazole, a yellow solid (88%) is obtained. Data: ^{1}HNMR (300 MHz, DMSO-d$_6$): δ 8.03 (d, J = 8.82 Hz, 2H), 7.15 (d, J = 8.82 Hz, 2H), 3.86 (s, 3H), 3.83 (s, 2H), 2.1 1-2.08 (m, 3H), 1.65-1.58 (m, 12H). EI-MS: m/z (M+H$^+$): 340.4 (calculated), 340.4 (found).

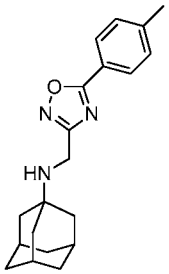
[0367] Example 127a/M2WJ356



N-((5-(4-methoxyphenyl)-l,3,4-oxadiazol-2-yl)methyl)adamantan-l-amine

Based on general procedure **D,** from amantadine and 2-(chloromethyl)-5-(4-methoxyphenyl)-1,3,4-oxadiazole, a white solid (71%) is obtained. Data: LC/MS (ESR) m/z 340.4 [M+H]$^+$.

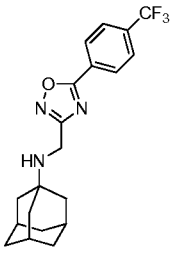
[0368] Example 128a/M2WJ393



N-((5-(p-tolyl)- 1,2,4-oxadiazol-3-yl)methyl)adamantan- 1-amine

Based on general procedure **D,** from amantadine and 3-(chloromethyl)-5-(p-tolyl)-l,2,4-oxadiazole, a white solid (75%) is obtained. Data: ^{1}HNMR (300 MHz, CD$_3$OD): δ 8.03 (d, J = 8.25 Hz, 2H), 7.41 (d, J = 8.25 Hz, 2H), 3.94 (s, 2H), 2.45 (s, 3H), 2.1 1-2.09 (m, 3H), 1.77-1.70 (m, 12H). EI-MS: m/z (M+H$^+$): 324.4 (calculated), 324.3 (found).

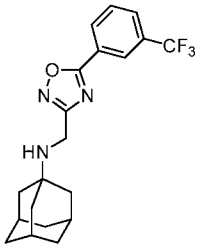
[0369] Example 129a/M2WJ397



N-((5-(4-(trifluoromethyl)phenyl)-l,2,4-oxadiazol-3-yl)methyl)adamantan-l-amine

Based on general procedure **D,** from amantadine and 3-(chloromethyl)-5-(4-(trifluoromethyl)phenyl)-l,2,4-oxadiazole, a white solid (77%) is obtained. Data: ^{1}HNMR (300 MHz, CD_3OD): δ 8.35 (d, J = 8.55 Hz, 2H), 7.93 (d, J = 8.55 Hz, 2H), 3.99 (s, 2H), 2.1 1-2.08 (m, 3H), 1.78-1.71 (m, 12H). EI-MS: m/z ($M+H^+$): 378.4 (calculated), 378.4 (found).

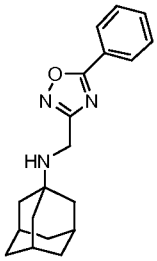
[0370] Example 130a/ M2WJ398



N-((5-(3-(trifluoromethyl)phenyl)-l,2,4-oxadiazol-3-yl)methyl)adamantan-l-amine

Based on general procedure **B,** from amantadine and 3-(chloromethyl)-5-(3-(trifluoromethyl)phenyl)-l,2,4-oxadiazole, a yellow solid (91%) is obtained. Data: ^{1}HNMR (300 MHz, CD_3OD): δ 8.43-8.40 (m, 2H), 8.00-7.97 (m, 1H), 7.86-7.80 (m, 1H), 3.99 (s, 2H), 2.1 1-2.08 (m, 3H), 1.79-1.72 (m, 12H). EI-MS: *mlz* ($M+H^+$): 378.4 (calculated), 378.4 (found).

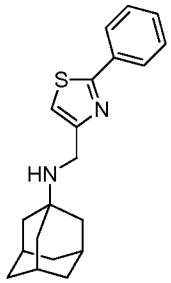
[0371] Example 131a/M2WJ399



N-((5-phenyl-l,2,4-oxadiazol-3-yl)methyl)adamantan-l-amine

Based on general procedure **D,** from amantadine and 3-(chloromethyl)-5-phenyl-l,2,4-oxadiazole, a white solid (84%) is obtained. Data: ^{1}HNMR (300 MHz, CD_3OD): δ 8.17-8.13 (m, 2H), 7.69-7.57 (m, 3H), 3.96 (s, 2H), 2.1 1-2.08 (m, 3H), 1.78-1.70 (m, 12H). EI-MS: m/z ($M+H^+$): 310 (calculated), 310 (found).

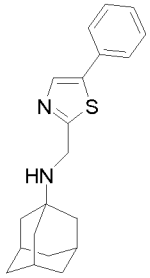
[0372] Example 132a/M2WJ402



N-((2-phenylthiazol-4-yl)methyl)adamantan-l-amine

Based on general procedure **D,** from amantadine and 4-(chloromethyl)-2-phenylthiazole, a yellowsolid (80%) is obtained. Data: LC/MS (ESR) m/z 325.5 $[M+H]^+$.

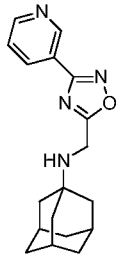
[0373] Example 133a/ IMX00672



Adamantan-l-yl-(5-phenyl-thiazol-2-ylmethyl)-amine

Based on general procedure **E,** from adamantan-l-yl-(5-bromo-thiazol-2-ylmethyl)-amine (example **86)** and pheneboronic acid, adamantan-l-yl-(5-phenyl-thiazol-2-ylmethyl)-aminewas obtained (46% two steps) as a white solid. Data: LC/MS (ESR) m/z 325 $[M+H]^+$.

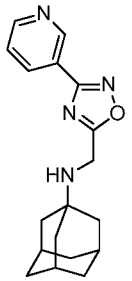
[0374] Example 134a/M2WJ381



N-((3-(pyridin-3-yl)-l,2,4-oxadiazol-5-yl)methyl)adamantan-l-amine

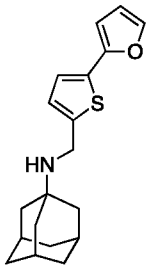
Based on general procedure **D,** from amantadine and 5-(chloromethyl)-3-(pyridin-3-yl)-l,2,4-oxadiazole, a brown solid (73%) is obtained. Data: ^{1}HNMR (300 MHz, DMSO-d_6): δ 9.18-9.16 (m, 1H), 8.79-8.77 (m, 1H), 8.38-8.36 (m, 1H), 7.64-7.62 (m, 1H), 4.09 (s, 2H), 2.07-2.04 (m, 3H), 1.62-1.55 (m, 12H). EI-MS: m/z ($M+H^+$): 311.4 (calculated), 311.5 (found).

[0375] Example 135a/ M2WJ381



Adamantan- l-yl-(3-pyridin-3-yl- [1,2,4] oxadiazol-5-ylmethyl)-amine

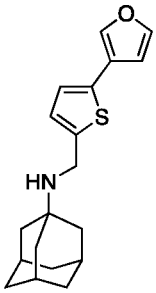
[0376] Example 136a/BC041



N-((5-(Furan-2-yl)thiophen-2-yl)methyl)adamantan-l-amine

Based on general procedure B, from N-((5-bromothiophen-2-yl)methyl)adamantan-l -amine (BC035) and furan-2yl trifluoroborate, a light brown was obtained. Data: LC/MS (ESCi) m/z 314.02 $[M+H]^+$.

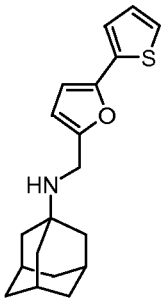
[0377] Example 137a/ BC042



N-((5-(Furan-3-yl)thiophen-2-yl)methyl)adamantan-l-amine

Based on general procedure B, from N-((5-bromothiophen-2-yl)methyl)adamantan-l -amine (BC035) and furan-3yl trifluoroborate, a light yellow solid was obtained. Data: LC/MS (ESCi) m/z 314.15 $[M+H]^+$.

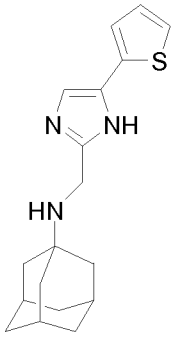
[0378] Example 138a/ IMX00703



Adamantan-l-yl-(5-thiophen-2-yl-furan-2-ylmethyl)-amine

Based on general procedure **F,** from Adamantan-l-yl-(5-bromo-furan-2-ylmethyl)-amine (example **87)** and 2-thiopheneboronic, Adamantan-l-yl-(5-thiophen-2-yl-furan-2-ylmethyl)-aminewas obtained (76% two steps) as a white solid. Data: LC/MS (ESR) m/z 314$[M+H]^+$.

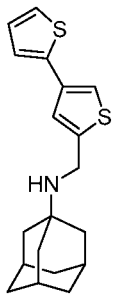
[0379] Example 139a/ IMX00702



Adamantan-l-yl-(5-thiophen-2-yl-lH-imidazol-2-ylmethyl)-amine

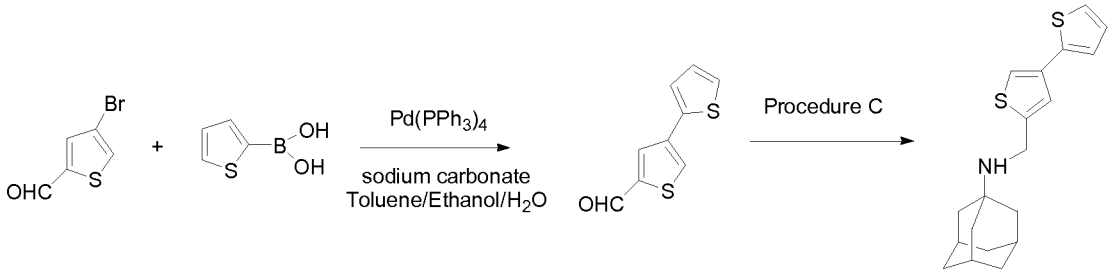
Based on general procedure **G,** from Adamantan-l-yl-(5-bromo-lH-imidazol-2-ylmethyl)-amine (example **89)** and 2-thiopheneboronic, adamantan-l-yl-(5-thiophen-2-yl-lH-imidazol-2-ylmethyl)-amine was obtained (76% two steps) as a white solid. Data: LC/MS (ESR) m/z 314 $[M+H]^+$.

[0380] Example 140a/M2WJ354



Adamantan-l-yl-[2,3']bithiophenyl-5'-ylmethyl-amine

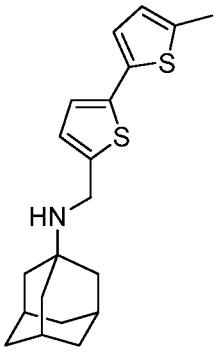
A mixture of 4-bromothiophene-2-carbaldehyde (1 eq), thiophne-2-boronic acid (1.5 eq) and sodium carbonate (2 eq) in toluene, ethanol and water was degassed by bubbling with argon for 30 mins. Then $Pd(Ph_{3})_{4}$ was added and the reaction was heated to reflux for overnight. The mixture was quenched with water, extracted with diethyl ether (3x), dried over MgSC^, and concentrated to give the crude product. Flash column chromatography afforded the intermediate aldehyde as white powder. Subsequent reductive amination with amantadine following procedure A gave the final compound **M2WJ354.**



N-([2,3'-bithiophen]-5'-ylmethyl)adamantan-l-amine

White solid (65% yield). Data: ^{1}HNMR (300 MHz, $CDC1_{3}$): δ 7.51 (s, 1H), 7.46-7.44 (m, 1H), 7.35-7.34 (m, 1H), 7.25 (s, 1H), 7.10-7.07 (m, 1H), 3.92 (s, 2H), 2.07-2.03 (m, 3H), 1.68-1.62 (m, 12H). EI-MS: m/z ($M+H^{+}$): 330.5 (calculated), 330.5 (found)

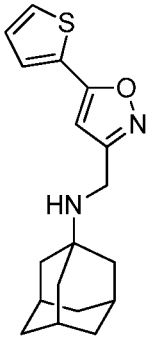
[0381] Example 141a/M2WJ357



N-((5'-methyl-[2,2'-bithiophen]-5-yl)methyl)adamantan-l-amine

Based on general procedure **C,** from amantadine and 5'-methyl-[2,2'-bithiophene]-5-carbaldehyde, a yellow solid (72%) is obtained. Data: LC/MS (ESR) m/z 344.5 $[M+H]^{+}$.

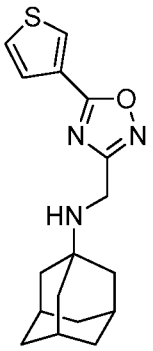
[0382] Example 142a/M2WJ332



N-((5-(thiophen-2-yl)isoxazol-3-yl)methyl)adamantan-l-amine

Based on general procedure **C,** from amantadine and 5-(thiophen-2-yl)isoxazole-3-carbaldehyde, a yellow solid (75%) is obtained. Data: ^{1}HNMR (300 MHz, DMSO-d_6): δ 7.83 (d, J = 4.59 Hz, 1H), 7.72 (d, J = 4.59 Hz, 1H), 7.26 (dd, J = 4.82 Hz, 3.84 Hz, 1H), 6.85 (s, 1H), 3.78 (s, 2H), 2.08-2.05 (m, 3H), 1.65-1.63 (m, 12H). EI-MS: m/z ($M+H^+$): 315.5 (calculated), 315.1 (found).

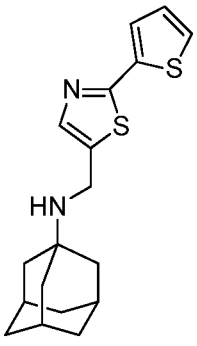
[0383] Example 143a/M2WJ359



N-((5-(thiophen-3-yl)-l,2,4-oxadiazol-3-yl)methyl)adamantan-l-amine

Based on general procedure **D,** from amantadine and 3-(chloromethyl)-5-(thiophen-3-yl)-l,2,4-oxadiazole, a yellow solid (80%) is obtained. Data: LC/MS (ESR) m/z 316.4 $[M+H]^+$.

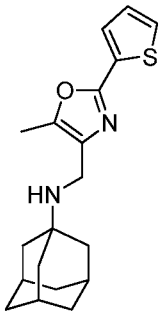
[0384] Example 144a/M2WJ360



N-((2-(thiophen-2-yl)thiazol-5-yl)methyl)adamantan-l-amine

Follow the procedure of example 140/M2WJ354. White solid (88% yield). Data: LC/MS (ESR) m/z 331.5 $[M+H]^+$.

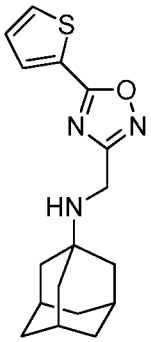
[0385] Example 145a/M2WJ384



N-((5-methyl-2-(thiophen-2-yl)oxazol-4-yl)methyl)adamantan-l-amine

Based on general procedure **C,** from amantadine and 5-methyl-2-(thiophen-2-yl)oxazole-4-carbaldehyde, a yellow solid (84%) is obtained. Data: LC/MS (ESR) m/z 329.5 $[M+H]^+$.

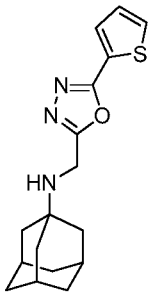
[0386] Example 146a/M2WJ389



N-((5-(thiophen-2-yl)-l,2,4-oxadiazol-3-yl)methyl)adamantan-l-amine

Based on general procedure **D,** from amantadine and 3-(chloromethyl)-5-(thiophen-2-yl)-l,2,4-oxadiazole, a yellow solid (77%) is obtained. Data: ^{1}FiNMR (300 MHz, CD_3OD): δ 7.96 (dd, J = 3.81 Hz, 1.17 Hz, 1H), 7.88 (dd, J = 5.01 Hz, 1.14 Hz, 1H), 7.28 (dd, J = 5.04 Hz, 3.84 Hz, 1H), 3.93 (s, 2H), 2.10-2.08 (m, 3H), 1.76-1.68 (m, 12H). EI-MS: m/z ($M+H^+$): 316.4 (calculated), 316.2 (found).

[0387] Example 147a/M2WJ390



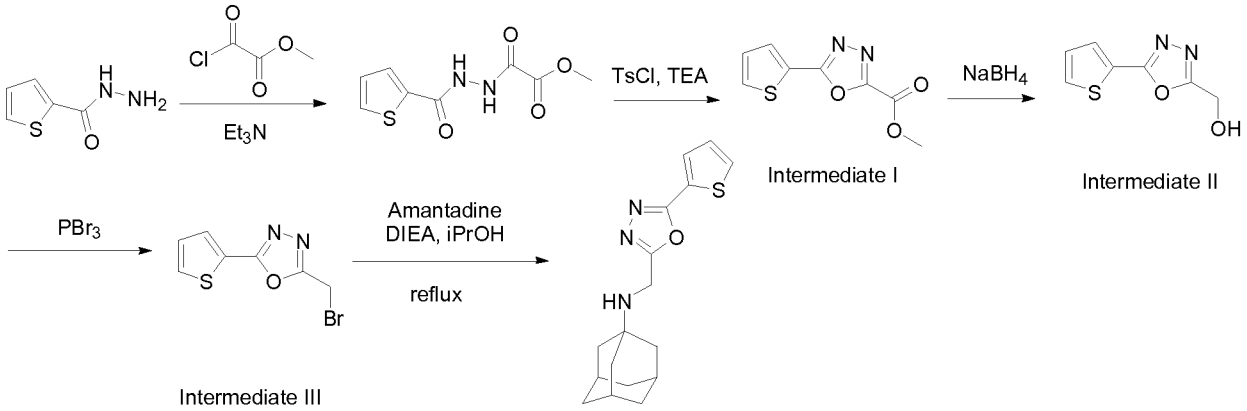
Adamantan-l-yl-(5-thiophen-2-yl-[l,3,4]oxadiazol-2-ylmethyl)-amine

General procedure: 2-thiophenecarboxylic acid hydrazide (leq) and Et_3N (2 eq) were dissolved in CH_2CI_2 at 0°C, methyl oxalate chloride (1 eq) was added dropwise. The reaction mixture was warmed slowly to room temperature and stirred for 6 hours. TsCl (leq) was added and stirred overnight. The mixture was diluted with CH_2CI_2 and was washed with water, and saturated brine. The organic layer was dried over $MgS0_4$ and the solvent was removed under reduced pressure. The crude produce was purified by flash column chromatography to give the ester intermediate I.

General procedure for reduction: Ester (1 eq) was dissolved in methanol and cooled down to 0°C. $NaBH_4$ (4 eq) was added in small portions to the solution over 10 mins. The mixture was warmed slowly to r.t. and stirred for 4 hours. Diluted HC1 was added and the organic solvent was removed under reduced pressure. The resulting aqueous layer was extracted with ethyl acetate (3x), and the organic layers were combined, dried over $MgS0_4$ and the solvent was removed under reduced pressure. This alcohol intermediate II was used for the next step without further purification.

General procedure for brominaiton: Alcohol (1 eq) was dissolved in anhydrous CH_2CI_2 and cooled down to 0°C. PBr_3 (leq) was added dropwise over 5 mins. The mixture was slowly warmed to r.t. and stirred for 2 hrs. Solvent was removed under reduced pressure, and the residue was quenched with water. Ethyl acetate was added and the aqueous layer was extracted for three times. The combined organic layers were combined, dried over $MgS0_4$ and the solvent was removed under reduced pressure. Flash column chromatography gave the bromide intermediate II.

Final alkylation following **procedure D** gave **M2WJ390.**

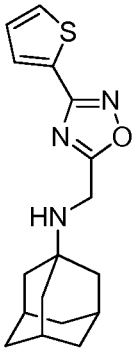


M2WJ390

N-((5-(thiophen-2-yl)-l,3,4-oxadiazol-2-yl)methyl)adamantan-l-amine

White solid (35% yield). Data: ^{1}HNMR (300 MHz, DMSO-d6): δ 7.96-7.91 (m, 1H), 7.82-7.78 (m, 1H), 7.31-7.26 (m, 1H), 3.95 (s, 2H), 2.03-2.00 (m, 3H), 1.60-1.54 (m, 12H). EI-MS: m/z ($M+H^+$): 316.4 (calculated), 316.5 (found).

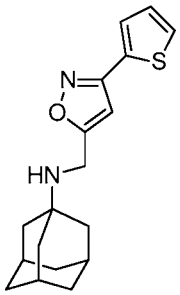
[0388] Example 148a/M2WJ363



N-((3-(thiophen-2-yl)-l,2,4-oxadiazol-5-yl)methyl)adamantan-l-amine

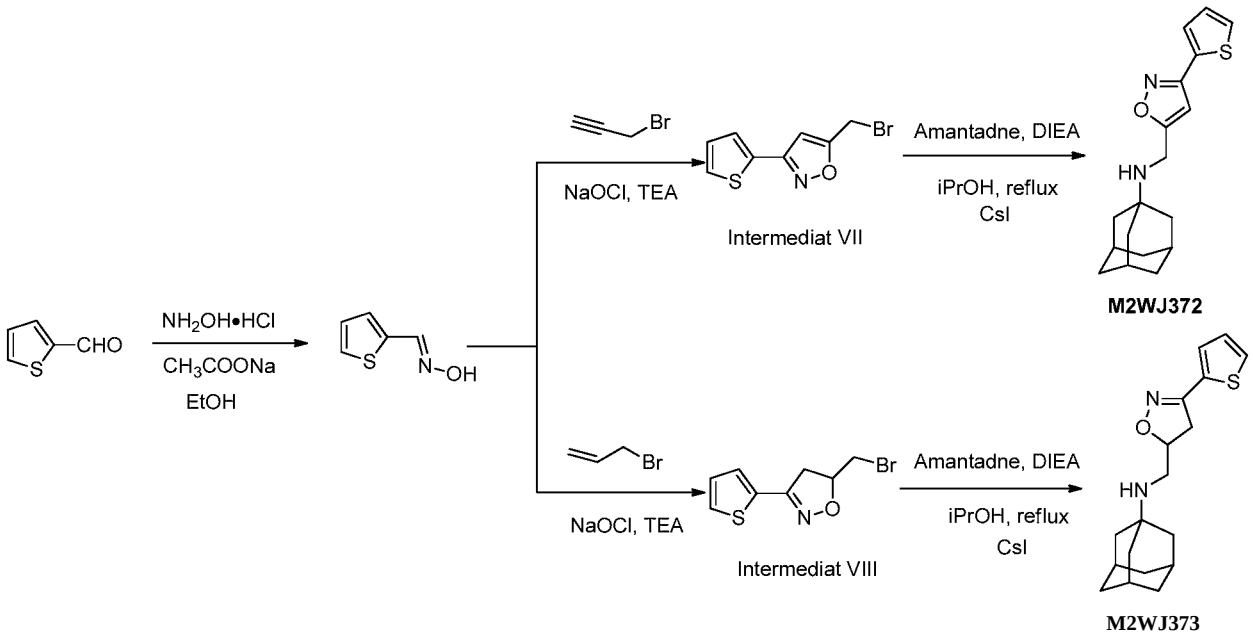
Based on general procedure **D,** from amantadine and 5-(chloromethyl)-3-(thiophen-2-yl)-l,2,4-oxadiazole, a yellow solid (88%) is obtained. Data: ^{1}HNMR (300 MHz, DMSO-d_6): δ 7.90-7.86 (m, 1H), 7.82-7.78 (m, 1H), 7.27-7.24 (m, 1H), 4.03 (s, 2H), 2.02-2.00 (m, 3H), 1.59-1.50 (m, 12H). EI-MS: m/z ($M+H^+$): 316.4 (calculated), 316.4 (found).

[0389] Example 149a/M2WJ372



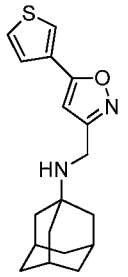
N-((3-(thiophen-2-yl)isoxazol-5-yl)methyl)adamantan-l-amine

Oximes were prepared according to previous published procedure. To a cooled solution (0 °C using ice bath) of oximes (1 eq), propargyl bromide/allyl bromide (1.2 eq), and triethylamine (1 eq) in CH_2CI_2 was dropwise added 8 % aqueous sodium hypochlorite. After addition, the solution was warmed to room temperature and stirred overnight. The mixture was separated, and the aqueous layer was extracted with CH_2CI_2 twice. The organic layers were combined, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The mixture was then purified by silica gel flash column chromatography to give the intermediate isoxazole VII or isoxazoline VIII (10-40% ethyl acetate/hexane). The next step alkylation was performed according to the above general procedure as described in **procedure B.**



Brown solid (43% yield). Data: ^{1}HNMR (300 MHz, DMSO-d6): δ 7.80-7.76 (m, 2H), 7.26-7.23 (m, 1H), 7.16 (s, 1H), 4.48 (s, 2H), 2.17-2.15 (m, 3H), 1.92-1.88 (m, 6H), 1.71-1.59 (m, 6H). EI-MS: m/z ($M+H^+$): 315.5 (calculated), 315.5 (found).

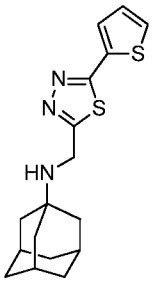
[0390] Example 150a/M2WJ374



Adamantan-l-yl-(5-thiophen-3-yl-isoxazol-3-ylmethyl)-amine

EI-MS: m/z ($M+H^+$): 315

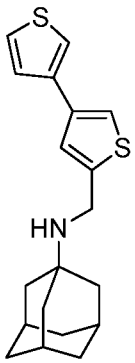
[0391] Example 151a/M2WJ375



N-((5-(thiophen-2-yl)-l,3,4-thiadiazol-2-yl)methyl)adamantan-l-amine

Yellow solid (22% yield). Data: ^{1}HNMR (300 MHz, DMSO-d6): δ 7.78-7.72 (m, 2H), 7.20-7.17 (m, 1H), 4.06 (s, 2H), 2.02-1.99 (m, 3H), 1.62-1.58 (m, 12H). EI-MS: m/z ($M+H^+$): 332.5 (calculated), 332.5 (found).

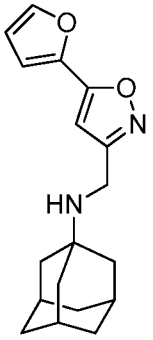
[0392] Example 152a/M2WJ321



N-([3,3'-bithiophen]-5-ylmethyl)adamantan-l-amine

Based on general procedure **A,** from amantadine and [3,3'-bithiophene]-5-carbaldehyde, a white solid (73%) is obtained. Data: LC/MS (ESR) m/z 330.5 $[M+H]^+$.

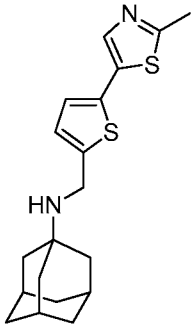
[0393] Example 153a/M2WJ347



N-((5-(furan-2-yl)isoxazol-3-yl)methyl)adamantan-l-amine

Based on general procedure **A,** from amantadine and 5-(furan-2-yl)isoxazole-3-carbaldehyde, a yellow solid (62%) is obtained. Data: LC/MS (ESR) m/z 299.4 $[M+H]^+$.

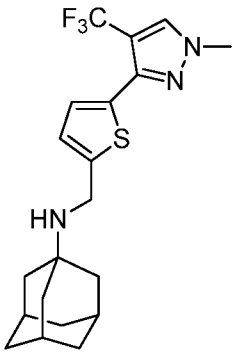
[0394] Example 154a/M2WJ348



N-((5-(2-methylthiazol-5-yl)thiophen-2-yl)methyl)adamantan-l-amine

Based on general procedure **A,** from amantadine and 5-(2-methylthiazol-5-yl)thiophene-2-carbaldehyde, a yellow solid (87%) is obtained. Data: LC/MS (ESR) m/z 345.5 $[M+H]^+$.

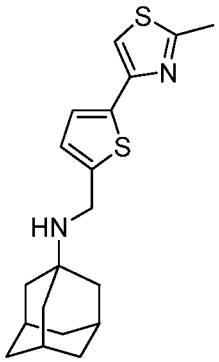
[0395] Example 155a/M2WJ340



N-((5-(l-methyl-4-(trifluoromethyl)-lH-pyrazol-3-yl)thiophen-2-yl)methyl)adamantan-l-amine

Based on general procedure **C,** from amantadine and 5-(l-methyl-4-(trifluoromethyl)-lH-pyrazol-3-yl)thiophene-2-carbaldehyde, a yellow solid (66%) is obtained. Data: LC/MS (ESR) m/z 396.5 $[M+H]^+$.

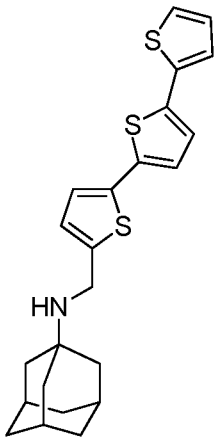
[0396] Example 156a/M2WJ362



N-((5-(2-methylthiazol-4-yl)thiophen-2-yl)methyl)adamantan-l-amine

Based on general procedure **C,** from amantadine and 5-(2-methylthiazol-4-yl)thiophene-2-carbaldehyde, a yellow solid (79%) is obtained. Data: LC/MS (ESR) m/z 345.5 $[M+H]^+$.

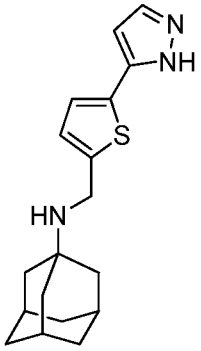
[0397] Example 157a/M2WJ339



N-([2,2':5^2"-terthiophen]-5-ylmethyl)adamantan-l-amine

Based on general procedure **C,** from amantadine and [2,2':5',2"-terthiophene]-5-carbaldehyde, a yellow solid (52%) is obtained. Data: LC/MS (ESR) m/z 412.6 $[M+H]^+$.

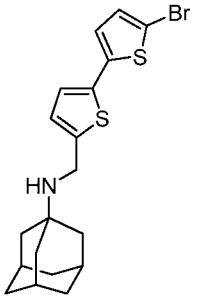
[0398] Example 158a/M2WJ331



N-((5-(lH-pyrazol-5-yl)thiophen-2-yl)methyl)adamantan-l-amine

Based on general procedure **C,** from amantadine and 5-(lH-pyrazol-5-yl)thiophene-2-carbaldehyde, a white solid (68%) is obtained. Data: LC/MS (ESR) m/z 314.4 $[M+H]^+$.

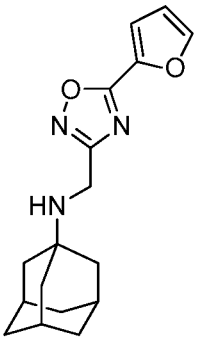
[0399] Example 159a/M2WJ334



N-((5'-bromo-[2,2'-bithiophen]-5-yl)methyl)adamantan-l-amine

Based on general procedure **C,** from amantadine and 5'-bromo-[2,2'-bithiophene]-5-carbaldehyde, a yellow solid (81%) is obtained.

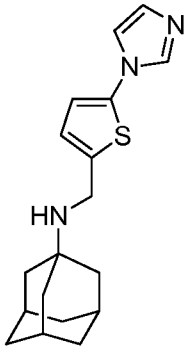
[0400] Example 160a/M2WJ394



N-((5-(furan-2-yl)- 1,2,4-oxadiazol-3-yl)methyl)adamantan- 1-amine

Based on general procedure **D,** from amantadine and 3-(chloromethyl)-5-(furan-2-yl)-l,2,4-oxadiazole, a yellow solid (81%) is obtained. Data: LC/MS (ESR) m/z 300.4 $[M+H]^+$.

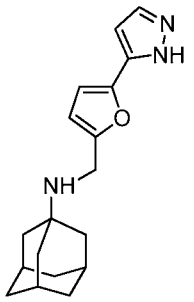
[0401] Example 161a/M2WJ365



N-((5-(lH-imidazol-l-yl)thiophen-2-yl)methyl)adamantan-l-amine

White solid (68% yield). Data: ^{1}HNMR (300 MHz, CD_3OD): δ 9.25 (s, 1H), 7.91 (s, 1H), 7.69 (s, 1H), 7.45 (d, J = 3.93 Hz, 1H), 7.33 (d, J = 3.93 Hz, 1H), 4.50 (s, 2H), 2.26-2.24 (m, 3H), 2.04-2.01 (m, 6H), 1.86-1.74 (m, 6H) . EI-MS: m/z ($M+H^+$): 314.5 (calculated), 314.5 (found).

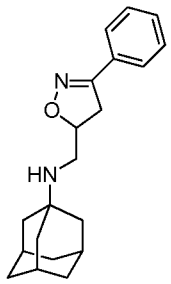
[0402] Example 162a/M2WJ327



N-((5-(lH-pyrazol-5-yl)furan-2-yl)methyl)adamantan-l-amine

Based on general procedure A, from amantadine and 5-(lH-pyrazol-5-yl)furan-2-carbaldehyde, a white solid (81%) is obtained. Data: LC/MS (ESR) m/z 298.4 $[M+H]^+$.

[0403] Example 167a/M2WJ388

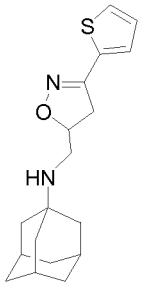


N-((3-phenyl-4,5-dihydroisoxazol-5-yl)methyl)adamantan-l-amine

Based on general procedure **B,** from amantadine and 5-(bromomethyl)-3-phenyl-4,5-dihydroisoxazole, a white solid (80%) is obtained. Data: ^{1}HNMR (300 MHz, CD_3OD): δ 7.70-7.67 (m, 2H), 7.44-7.42 (m, 3H), 4.87-4.76 (m, 1H), 3.51 (dd, J = 17.01 Hz, 10.47 Hz, 1H), 3.18

(dd, J = 17.01 Hz, 7.32 Hz, 1H), 2.80 (ddd, J = 27.93 Hz, 12.00 Hz, 7.83 Hz, 1H), 2.08-2.06 (m, 3H), 1.71-1.68 (m, 12H). EI-MS: m/z ($M+H^+$): 311.4 (calculated), 311.4 (found).

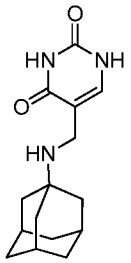
[0404] Example 168a/M2WJ373



N-((3-(thiophen-2-yl)-4,5-dihydroisoxazol-5-yl)methyl)adamantan-l-amine

Follow the same procedure as Example 149/M2WJ372.Brown solid (52% yield). Data: ^{1}HNMR (300 MHz, CD_3OD): δ 7.53 (dd, J = 5.10Hz, 1.08 Hz, 1H), 7.32 (dd, J = 3.66 Hz, 1.08 Hz, 1H), 7.10 (dd, J = 5.10 Hz, 3.66 Hz, 1H), 4.87-4.75 (m, 1H), 3.52 (dd, J = 16.80 Hz, 10.35 Hz, 1H), 3.20 (dd, J =16.80 Hz, 7.29Hz, 1H), 2.80 (ddd, J = 23.64 Hz, 12.09 Hz, 7.80 Hz, 1H), 2.09-2.06 (m, 3H), 1.74-164 (m, 12H). EI-MS: m/z ($M+H^+$): 317.5 (calculated), 317.5 (found).

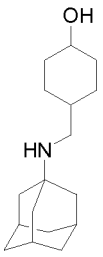
[0405] Example 169a/WFD110



5-((adamantan-l-ylamino)methyl)pyrimidine-2,4(lH,3H)-dione

Based on general procedure C, from adamantane-1 -amine and 2,4-dioxo-l,2,3,4-tetrahydropyrimidine-5-carbaldehyde, a white solid is obtained . Data: LC/MS (ES+) m/z 276.3 $[M+H]^+$.

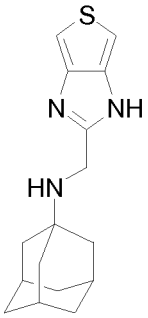
[0406] Example 170a/ IMX00677



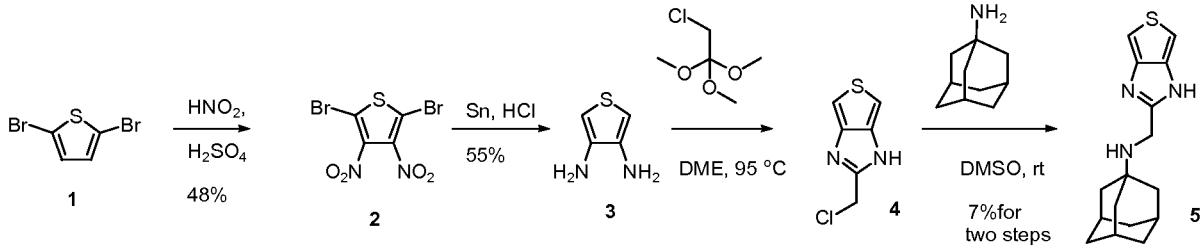
4-(Adamantan-l-ylaminomethyl)-cyclohexanol

Based on general Procedure E, from 4-hydroxy-cyclohexanecarboxylic acid and adamantan-1-ylamine, a white solid (76%) is obtained. Data: LC/MS (ESR) m/z 264[M+H]$^+$.

[0407] Examplel71a/IMX00683



Adamantan-l-yl-(lH-thieno[3,4-d]imidazol-2-ylmethyl)-amine



2,5-Dibromo-3,4-dinitrothiophene (2):

Concentrated sulfuric acid (13 mL), fuming sulfuric acid (20 mL), and fuming nitric acid (110 mL) were combined in a flask and cooled with an ice bath. 2,5- dibromothiophene **(1)** (3.5 mL, 7.5 g, 31.1 mmol) was added dropwise to maintain a temperature of 20-30 °C. The mixture was allowed to react for a total of 3 hours and then poured over 90 g of ice. Upon the melting of the ice, the solid residue was recovered by vacuum filtration and recrystallized via hot methanol to give 5.1 g of product (48%), ^{13}C NMR (300 MHz, $CDC1_3$): δ 113.7, 159.7.

3,4-Diaminothiophene (3):

Concentrated HC1 (46 mL) and compound **2** (1.3 g, 3.8 mmol) were combined in a flask and cooled with an ice bath. Tin metal (3.2 g, 26.9 mmol) was added slowly to maintain a temperature of 25-30 °C. After stabilizing at ~25 °C, the reaction was allowed to continue until all the tin was consumed and then placed in a freezer overnight. The solid precipitate was recovered by vacuum filtration and washed with diethyl ether and acetonitrile until the wash was colorless to give the stable 3·2H+ salt. The 3·2H+ salt was dissolved in 50 mL of water, cooled with an ice bath, and the solution was made basic with 4 N Na_2C0_3. The product was extracted with diethyl ether, dried with anhydrous Na_2S0_4, and concentrated by rotary evaporation without

heating to give 0.29 g (55 %) of a white solid, ^{1}HNMR (300 MHz, $CDC1_3$): δ 3.36 (br s, 4H), 6.16 (s, 2H).

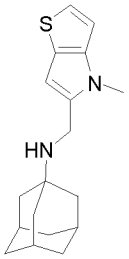
2-Chloromethyl-lH-thieno[3,4-d]imidazole (4)

3,4-Diaminothiophene (0.29 g, 2.54 mmol) and 2-chloro-l,l,l-trimethoxy-ethane (0.5 g, 3.38 mmol) were combined in DME (5 mL) in a sealed tube and heated at 95 °C for overnight and concentrated to give a crude product to go to the next step without purification. LC-MS: m/z 173 $[M+H]^+$.

Adamantan-l-yl-(lH-thieno[3,4-d]imidazol-2-ylmethyl)-amine (5)

To above crude product **(4)** and adamantan-l-ylamine (755 mg, 5 mmol) were combined in DMSO (5 mL) and stirred at 25 °C for 12 h. The reaction was quenched with water (5 mL) and extracted with DCM (20 mL). After organic solvent was removed in vacuo, the residue was purified by flash column chromatography (1-10% CH_3OH/CH_2CI_2) to give the Adamantan-l-yl-(lH-thieno[3,4-d]imidazol-2-ylmethyl)-amine **(5)** (51.1 mg, 7 % over two steps). LC-MS: m/z 288 $[M+H]^+$. ^{1}H NMR (300 MHz, $CDC1_3$) δ 6.75 (s, 2H), 5.74 (brs, 1H), 4.03 (s, 2H), 2.10-1.58 (m, 15H).

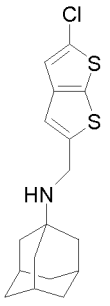
[0408] Example 172a/IMX685



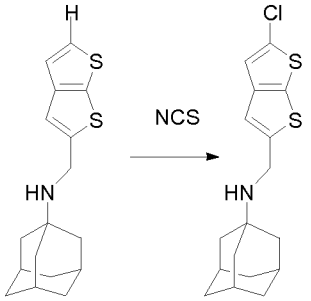
Adamantan-l-yl-(4-methyl-4H-thieno[3,2-b]pyrrol-5-ylmethyl)-amine

Based on general procedure **A,** from 4-Methyl-4H-thieno[3,2-b]pyrrole-5-carbaldehyde and adamantan-l-ylamine, a white solid (71%) is obtained. Data: LC/MS (ESR) m/z 301 $[M+H]^+$.

[0409] Example 173a/IMX00735

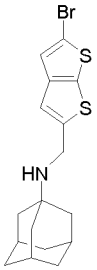


Adamantan-l-yl-(5-chloro-thieno[2,3-b]thiophen-2-ylmethyl)-amine

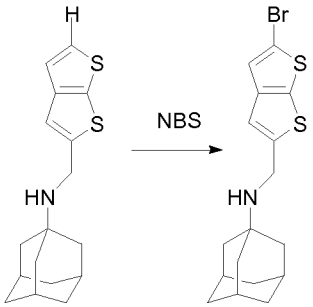


To a solution of Adamantan-l-yl-thieno[2,3-b]thiophen-2-ylmethyl-amine (150 mg, 0.5 mmol) was treated with NCS (67 mg, 0.5 mmol) in DMF (5 mL) at 0 °C for 2h. The solvent was removed concentrated under reduced pressure. The crude product was separated by flash column chromatography (1-10% CH_3OH/CH_2Cl_2) to give the title compound (34 mg, 20%). Data: LC/MS (ESR) m/z 338 $[M+H]^+$.

[0410] Example 174a/IMX00714

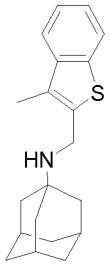


Adamantan-l-yl-(5-bromo-thieno[2,3-b]thiophen-2-ylmethyl)-amine



To a solution of Adamantan-l-yl-thieno[2,3-b]thiophen-2-ylmethyl-amine (150 mg, 0.5 mmol) was treated with NBS (90 mg, 0.5 mmol) in DMF (5 mL) at 0 °C for 2h. The solvent was removed concentrated under reduced pressure. The crude product was separated by flash column chromatography (1-10% CH_3OH/CH_2Cl_2) to give the title compound (36 mg, 20%). Data: LC/MS (ESR) m/z 383 $[M+H]^+$.

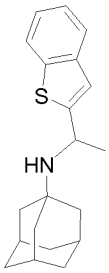
[0411] Example 177a /IMX00643



Adamantan-l-yl-(3-methyl-benzo [b] thiophen-2-ylmethyl)-amine

Based on general procedure **A,** from 3-Methyl-benzo[b]thiophene-2-carbaldehyde and adamantan-1-ylamine, a white solid (71%) is obtained. Data: LC/MS (ESR) m/z 312$[M+H]^+$.

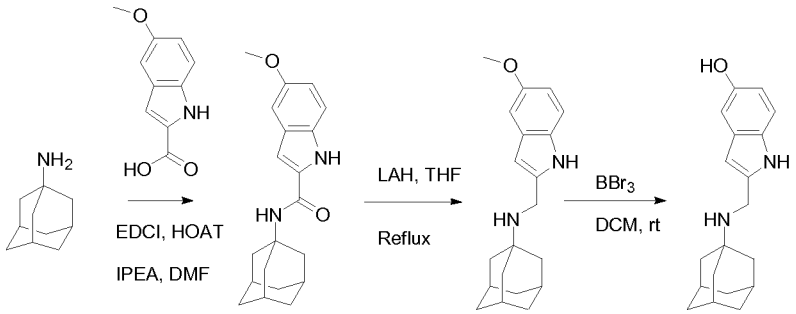
[0412] Example 178a/CMF004



N-(l-(benzo [b] thiophen-2-yl)ethyl)adamantan-l-amine

Based on general procedure **C,** from adamantane-1-amine andl-(benzo[b]thiophen-2-yl)ethanone, a white solid is obtained . Data: LC/MS (ES+) m/z 312.6 $[M+H]^+$.

[0413] Example 179a/ IMX00705/ M2WJ323 & Example 178a/ IMX00696

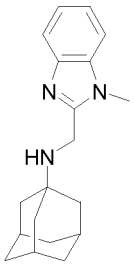


Based on general Procedure E, from 5-Methoxy-lH-indole-2-carboxylic acid and adamantan-1-ylamine, a white solid of example 178 adamantan-1-yl-(5-methoxy-lH-indol-2-ylmethyl)-amine (76%) is obtained. Data: LC/MS (ESR) m/z 311$[M+H]^+$.

Treatment of adamantan-1-yl-(5-methoxy-lH-indol-2-ylmethyl)-amine (110 mg, 1.1 mmol) with BBr_3 (300 mg, 1.2 mmol) in DCM (5 mL) at -78 oC and then warm to rt for 2h. The mixture was

quenched with Na_2C0_3 (sat'd) (5 mL). The mixture was extracted with DCM (10 mL x3), and the combined organic layers was dried over Na_2S0_4 and solvent was removed under reduced pressure to give a residue, which was purified by flash column chromatography (1-10% **CH3OH** /CH_2CI_2) to give the tile compound example 175 (284 mg, 87%) as a white solid. Data: LC/MS (ESR) m/z 297 $[M+H]^+$.

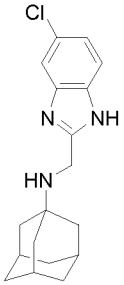
[0414] Example 180a /IMX00692



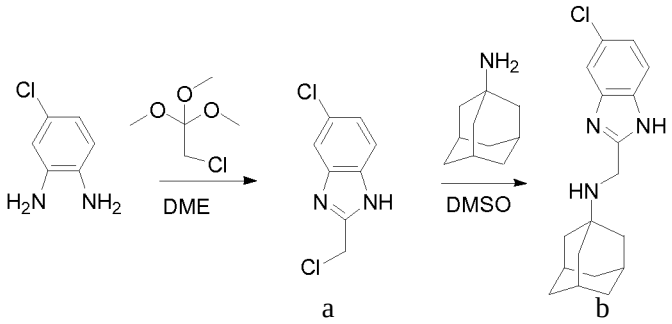
Adamantan-l-yl-(l-methyl-lH-benzoimidazol-2-ylmethyl)-amine

Based on general procedure **A,** from 1-Methyl-lH-benzoimidazole-2-carbaldehyde and adamantan-l-ylamine, a white solid (71%) is obtained. Data: LC/MS (ESR) m/z 296 $[M+H]^+$.

[0415] Example 181a/IMX693

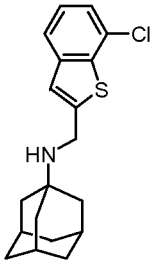


Adamantan-l-yl-(5-chloro-lH-benzoimidazol-2-ylmethyl)-amine

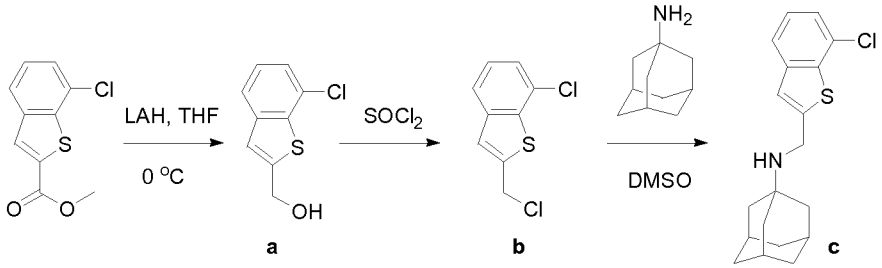


Follow the same procedure of **Examplel67/IMX00683** form 4-Chloro-benzene-l,2-diamine, a white solid (20% two step) is obtained. Data: LC/MS (ESR) m/z 316 $[M+H]^+$.

[0416] Example 183a/IMX713



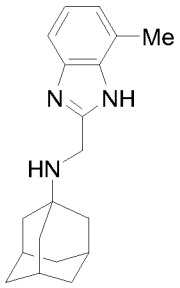
Adamantan-l-yl-(7-chloro-benzo[b]thiophen-2-ylmethyl)-amine



To a solution of 7-chloro-benzo[b]thiophene-2-carboxylic acid methyl ester (225 mg, 1 mmol) in anhydrous THF (5 mL) was added dropwise of $LiAlH_4$ solution (2.0 M in THF, 1 mL) at 0°C. The resulting solution was stirred for 2 h at 0 oC. The solution was quenched by H_20/1N NaOH/H_20 protocol (76uL H_20 , 152 uL IN NaOH, 228 uL H_20). After the mixture was stirred for 1 h, the solid was removed by filtration. The resulting solution was evaporated to dryness and purified by flash column chromatography (1-10% CH_30H/CH_2C1_2) to give (7-Chloro-benzo[b]thiophen-2-yl)-methanol (150 mg, 76%). Data: LC/MS (ESR) m/z 199$[M+H]^+$.

Above alcohol was dissolved in SOC12 (2 mL) and the solution was heat at 80 °C for lh. The solvent was removed under reduced pressure. The residue (7-Chloro-benzo[b]thiophen-2-yl)-methanolwas used directly to the next step without purification. Then the residue was taken to DMSo (5 mL) and Adamantan-l-ylamine (200 mg) was added. The mixture was stirred at rt for overnight and then was quenched with H_20 (5 mL). The mixture was extracted with DCM (10 mL x3), and the combined organic layers was dried over Na_2S0_4 and solvent was removed under reduced pressure to give a residue, which was purified by flash column chromatography (1-10% CH_30H/CH_2C1_2) to give the tile compound example 175 (15 mg, 10%>) as a white solid. Data: LC/MS (ESR) m/z 332 $[M+H]^+$.

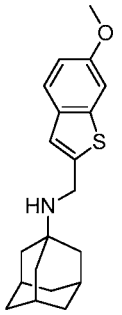
[0417] Example 184a/IMX721



Adamantan-l-yl-(7-methyl-lH-benzoimidazol-2-ylmethyl)-amine

Follow the same procedure as example 179, Adamantan-l-yl-(7-methyl-lH-benzoimidazol-2-ylmethyl)-amine was obtained as a white solid (21%). LC/MS (ESR) m/z 296 $[M+H]^+$.

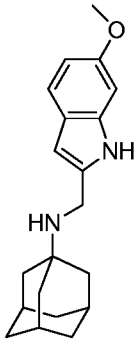
[0418] Example 185a/M2WJ345



N-((6-methoxybenzo[b]thiophen-2-yl)methyl)adamantan-l-amine

Based on general procedure **C,** from amantadine and 6-methoxybenzo[b]thiophene-2-carbaldehyde, a yellow solid (71%) is obtained. Data: LC/MS (ESR) m/z 328.4 $[M+H]^+$.

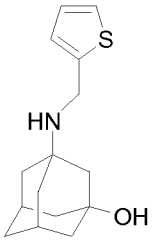
[0419] Example 186a/M2WJ346



N-((6-methoxy-lH-indol-2-yl)methyl)adamantan-l-amine

Based on general procedure **C,** from amantadine and 6-methoxy-lH-indole-2-carbaldehyde, a yellow solid (61%) is obtained. Data: LC/MS (ESR) m/z 311.4 $[M+H]^+$.

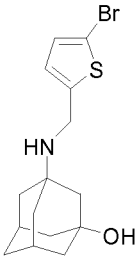
[0420] Example 187a/IMX684



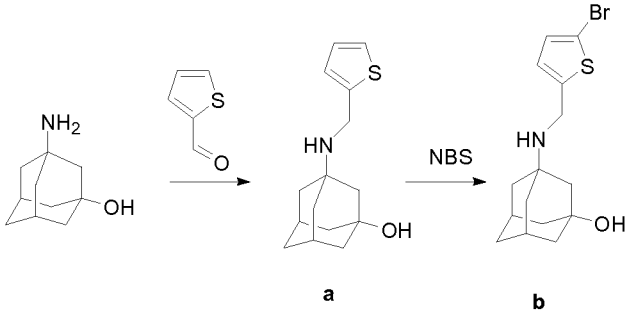
3-[(Thiophen-2-ylmethyl)-amino]-adamantan-l-ol

Follow the procedure A, compound 3-[(Thiophen-2-ylmethyl)-amino]-adamantan-l-ol **(a) (IMX680)** was made from Thiophene-2-carbaldehyde and 3-Amino-adamantan-l-ol as a white solid (70%). LC/MS (ESR) m/z 264 $[M+H]^+$.

[0421] Example 188a/IMX680

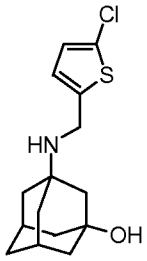


3-[(5-Bromo-thiophen-2-ylmethyl)-amino]-adamantan-l-ol



Treatment of 3-[(Thiophen-2-ylmethyl)-amino]-adamantan-l-ol **(a)** (example 183) (264 mg, 1.0 mmol) with NCS (150 mg, 1.2 eq) at 50 °C in DMF for 2h. Solvent was removed under reduced pressure, the residue was purified by flash column chromatography (1-10% CH_3OH/CH_2CI_2) to give the tile compound 3-[(5-Bromo-thiophen-2-ylmethyl)-amino]-adamantan-l-ol (215 mg, 66%) as a white solid. Data: LC/MS (ESR) m/z 343 $[M+H]^+$.

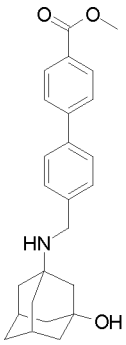
[0422] Example 189a/IMX716



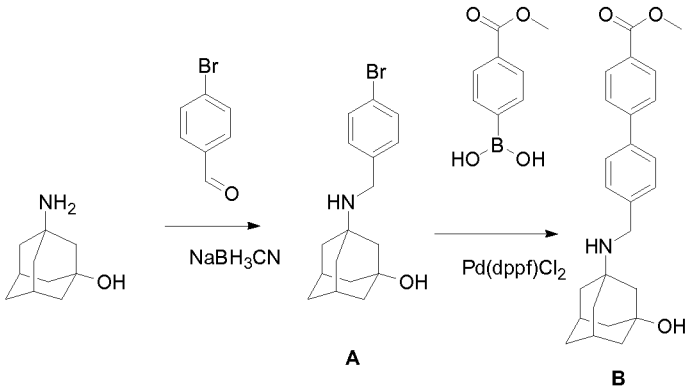
3-[(5-Chloro-thiophen-2-ylmethyl)-amino]-adamantan-l-ol

Follow the same procedure except from NCS in the second step to give 3-[(5-Chloro-thiophen-2-ylmethyl)-amino]-adamantan-l-ol. Data: LC/MS (ESR) m/z 298 $[M+H]^+$.

[0423] Example 190a/ IMX00691



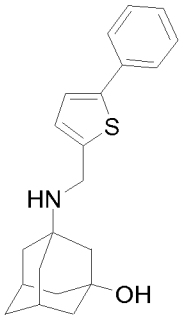
4'-[(3-Hydroxy-adamantan-l-ylamino)-methyl]-biphenyl-4-carboxylic acid methyl ester



Follow the procedure A, compound A 3-(4-Bromo-benzylamino)-adamantan-l-ol was obtained as white solid (70%) from 3-Amino-adamantan-l-ol and 4-Bromo-benzaldehyde. Data: LC/MS (ESR) m/z 337 $[M+H]^+$.

Follow the procedure E, 4'-[(3-Hydroxy-adamantan-l-ylamino)-methyl]-biphenyl-4-carboxylic acid methyl ester (B) was obtained as an off-white solid (60%). LC/MS (ESR) m/z 392 $[M+H]^+$.

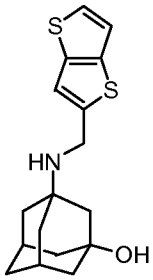
[0424] Example 191a/ IMX00690



3-[(5-Phenyl-thiophen-2-ylmethyl)-amino]-adamantan-l-ol

Follow the procedure A, 3-[(5-Phenyl-thiophen-2-ylmethyl)-amino]-adamantan-l-ol Was obtained as white solid (70%) from 3-Amino-adamantan-l-ol and 5-Phenyl-thiophene-2-carbaldehyde. Data: LC/MS (ESR) m/z 340 $[M+H]^+$.

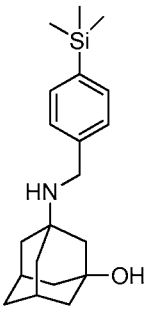
[0425] Example 192a/ IMX00706



3-[(Thieno[3,2-b]thiophen-2-ylmethyl)-amino]-adamantan-l-ol

Follow Procedure E, 3-[(Thieno[3,2-b]thiophen-2-ylmethyl)-amino]-adamantan-l-ol was obtained from Thieno[3,2-b]thiophene-2-carboxylic acid and 3-Amino-adamantan-l-ol as a white solid (40 two steps). Data: LC/MS (ESR) m/z 320 $[M+H]^+$.

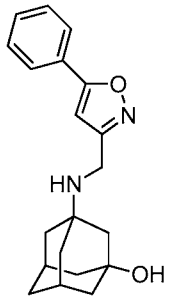
[0426] Example 193a/M2WJ404



(ls,3r,5R,7S)-3-((4-(trimethylsilyl)benzyl)amino)adamantan-l-ol

Based on general procedure C, from 3-amino-l-adamantol and 4-(trimethylsilyl)benzaldehyde, a white solid (83%) is obtained. Data: LC/MS (ESR) m/z 330.6 $[M+H]^+$.

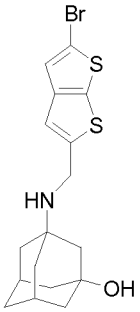
[0427] Example 194a/M2WJ382



(ls,3r,5R,7S)-3-(((5-phenylisoxazol-3-yl)methyl)amino)adamantan-l-ol

Based on general procedure C, from 3-amino-l-adamantol and 5-phenylisoxazole-3-carbaldehyde, a white solid (82%) is obtained. Data: LC/MS (ESR) m/z 325.4 $[M+H]^+$.

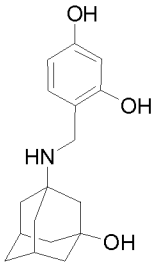
[0428] Example 195a/ IMX00733



3-[(5-Bromo-thieno[2,3-b]thiophen-2-ylmethyl)-amino]-adamantan-l-ol

Based on general procedure A, from 3-amino-l-adamantol and 5-bromo-thieno[2,3-b]thiophene-2-carbaldehyde, a white solid (81%) is obtained. Data: LC/MS (ESR) m/z 398 $[M+H]^+$.

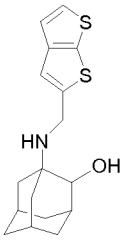
[0429] Example 196a/IM00727



4-[(3-Hydroxy-adamantan- l-ylamino)-methyl] -benzene- 1,3-diol

Based on general procedure A, from 3-amino-l-adamantol and 2,4-dihydroxy-benzaldehyde, a off-white solid (83%) is obtained. Data: LC/MS (ESR) m/z 290 $[M+H]^+$.

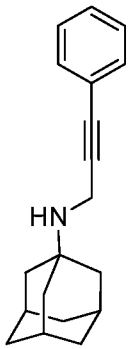
[0430] Example 197a/IMX737



(±)-1-[(Thieno[2,3-b]thiophen-2-ylmethyl)-amino]-adamantan-2-ol

Based on general procedure A, from (±)-l-amino-adamantan-2-ol (Armarego, W. L. F.; Tucker, P. G. Australian Journal of Chemistry, 1979, 32, 1805-17) and thieno[2,3-b]thiophene-2-carbaldehyde, a white solid (30%) is obtained. Data: LC/MS (ESR) m/z 320 $[M+H]^+$.

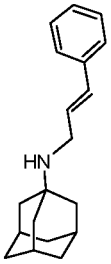
[0431] Example 198a/Hij306



N-(3-phenylprop-2-yn-l-yl)adamantan-l-amine

Based on general procedure **C,** from adamantane-1-amine and 3-phenylpropiolaldehyde, a yellowish liquid was obtained by a silica gel column chromatography. Data: LC/MS (ES+) m/z 312.6 [M+Hf.

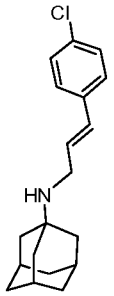
[0432] Example 199a/CFM001



N-cinnamyladamantan-l-amine

Based on general procedure **C,** from adamantane-1-amine and cinnamaldehyde, a yellowish liquid was obtained by a silica gel column chromatography. Data: LC/MS (ES+) m/z 268.3 $[M+H]^+$.

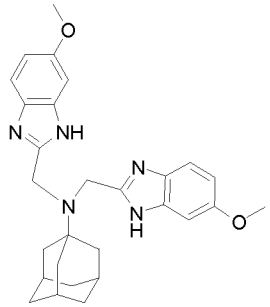
[0433] Example 200a/hij-307



N-((E)-3-(4-chlorophenyl)allyl)adamantan-l-amine

Based on general procedure **C,** from adamantane-1-amine and (E)-3-(4-chlorophenyl)acrylaldehyde, a yellowish liquid was obtained by a silica gel column chromatography. Data: LC/MS (ES+) m/z 302.4 $[M+H]^+$.

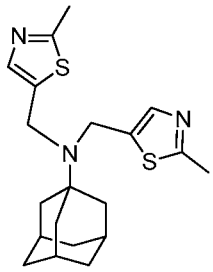
[0434] Example 201a/ IMX00732



Adamantan-l-yl-bis-(6-methoxy-lH-benzoimidazol-2-ylmethyl)-amine

From amantadine (1 eq) and 2-Chloromethyl-6-methoxy-lH-benzo imidazole (3 eq), a white solid (43%) is obtained. Data: LC/MS (ESR) m/z 472 $[M+H]^+$.

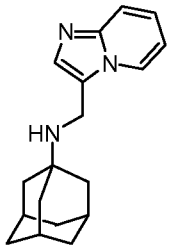
[0435] Example 202a/ M2WJ416



N,N-bis((2-methylthiazol-5-yl)methyl)adamantan-l-amine

Based on general procedure **C,** from amantadine (1 eq) and 5-(chloromethyl)-2-methylthiazole (3 eq), a white solid (80%) is obtained. Data: LC/MS (ESR) m/z 374.6 $[M+H]^+$.

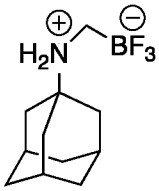
[0436] Example 203a/IMX00709



Adamantan- 1-yl-imidazo [1,2-a] pyridin-3-ylmethyl-amine

Based on general procedure **A,** from imidazo[l,2-a]pyridine-3-carbaldehyde and Adamantan- 1-ylamine, a white solid (69%) is obtained. Data: LC/MS (ESR) m/z 282 $[M+H]^+$.

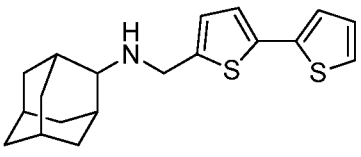
[0437] Example 204a/BC059



N-[(Trifluoro-4-boranyl)methyl]adamantan-l-aminium

See reference: Fleury-Bregeot, N.; Raushel, J.; Sandrock, D. L.; Molander G. A. Chem. Eur. J. **2012,** 18, 9564-9570.

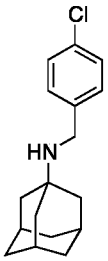
[0438] Example 205a/M2WJ324



N-([2,2'-bithiophen]-5-ylmethyl)adamantan-2-amine

Based on general procedure **C,** from 2-aminoadamantane and [2,2'-bithiophene]-5-carbaldehyde, a yellow solid (84%) is obtained. Data: LC/MS (ESR) m/z 330.5 $[M+H]^+$.

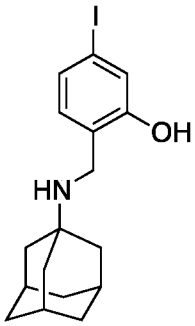
[0439] Example lb/BC085



N-(4-Chlorobenzyl)adamantan-1-amine

Based on general procedure CI, from adamantan-l-ylamine and 4-chlorobenzaldehdye, an off-white solid was obtained. Data: LC/MS (ESCi) *mlz* 276.14 $[M+l]^+$.

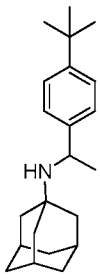
[0440] Example 2b/BC089



2-(-Adamantan-l-ylamino)methyl)-5-iodophenol

Based on general procedure CI, from adamantan-l-ylamine and 2-hydroxy-4-iodobenzaldehyde (General Procedure L), a light brown solid was obtained. Data: LC/MS (ESCi) *mlz* 384.02 $[M+l]^+$.

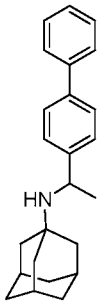
[0441] Example 3b/ Hij339



N-(l-(4-(tert-butyl)phenyl)ethyl)adamantan-l-amine

Based on general procedure C, from adamantan-l-ylamine and t-butylacetophenone, , a white solid (30%) is obtained. Data: LC/MS (ESR) *mlz 312* $[M+H]^+$.

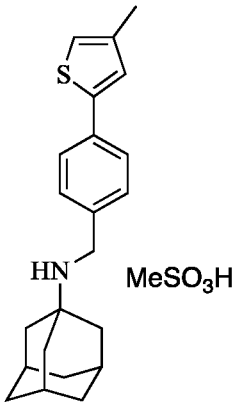
[0442] Example 4b/ Hij339



N-(l-([l,l'-biphenyl]-4-yl)ethyl)adamantan-l-amine

Based on general procedure C, from adamantan-l-ylamine and biphenylketone, a white solid (10%) is obtained. Data: LC/MS (ESR) *mlz 332* $[M+H]^+$.

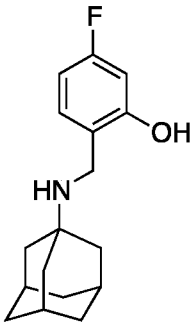
[0443] Example 5b/BC045



***l*v-(4-(4-Methylthiophen-2-yl)benzyl)adamantan-l-amine**

Based on general procedure CI, from N-(4-bromobenzyl)adamantan-l -amine and potassium 4-methyl-(thiophen-2-yl)trifluoroborate. The free amine was dissolved in diethyl ether and cooled to 0 °C and MeSOsH (1 equiv) was added under N_2, and then mixture was stirred at 0 °C for 15 min and filtered to give a white solid. Data: LC/MS (ESCi) *mlz* 338.13 $[M+H]^+$.

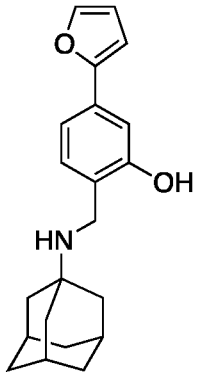
[0444] Example 6b/BC102



2-(-Adamantan-l-ylamino)methyl)-5-fluorophenol

Based on general procedure CI, from adamantan-1-amine and 4-fluoro-2-fiydroxybenzaldehdye (General Procedure L), an off-white solid was obtained Data: LC/MS (ESCi) *mlz* 276.14 $[M+H]^+$.

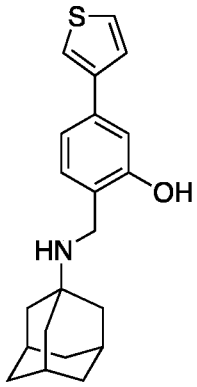
[0445] Example 7b/BC113



2-((-Adamantan-l-ylamino)methyl)-5-(furan-2-yl)phenol

Based on general procedure CI, from adamantan-1-amine and 4-(furan-2-yl)-2-hydroxybenzaldehyde (general procedure F), an off-white solid was obtained Data: LC/MS (ESCi) *mlz* 324.28 $[M+H]^+$.

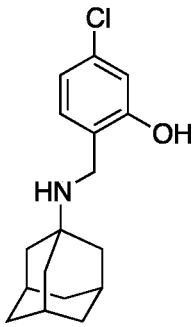
[0445] Example 8b/BC114



2-(((-Adamantan-l-ylamino)methyl)-5-(thiophen-3-yl)phenol

Based on general procedure CI, from adamantan-1-amine and 4-(thiophen-3-yl)-2-hydroxybenzaldehyde (general procedure F), an off-white solid was obtained Data: LC/MS (ESCi) *mlz* 340.21 $[M+H]^+$.

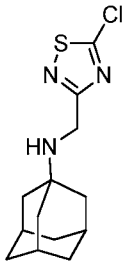
[0446] Example 9b/BC100



2-((-Adamantan-l-ylamino)methyl)-5-chlorophenol

Based on general procedure CI, from adamantan-1-amine and 4-chloro-2-hydroxybenzaldehyde (General Procedure L), an off-white solid was obtained Data: LC/MS (ESCi) *mlz* 292.18 $[M+l]^+$.

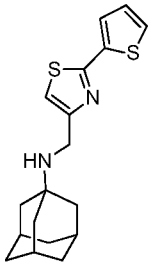
[0447] Example 10b/ M2WJ410



N-((5-chloro-l,2,4-thiadiazol-3-yl)methyl)adamantan-l-amine

Based on general procedure E, from adamantan-1-ylamine and 5-chloro-3-(chloromethyl)- 1,2,4-thiadiazole, a yellow solid (72%) is obtained. Data: LC/MS (ESR) *mlz 284* $[M+H]^+$.

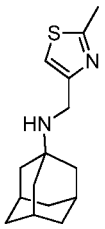
[0448] Example lib/ M2WJ411



N-((2-(thiophen-2-yl)thiazol-4-yl)methyl)adamantan-l-amine

Based on general procedure E, from adamantan-1-ylamine and 4-(chloromethyl)-2-(thiophen-2-yl)thiazole, a yellow solid (78%) is obtained. Data: LC/MS (ESR) *mlz 331* $[M+H]^+$.

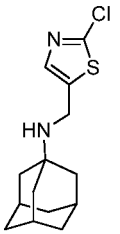
[0449] Example 12b/ M2WJ412



N-((2-methylthiazol-4-yl)methyl)adamantan-l-amine

Based on general procedure E, from adamantan-l-ylamine and 4-(chloromethyl)-2-methylthiazole, a yellow solid (82%) is obtained. Data: LC/MS (ESR) *mlz 263* $[M+H]^+$.

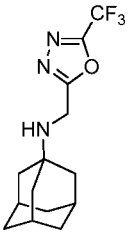
[0450] Example 13b/ M2WJ413



N-((2-chlorothiazol-5-yl)methyl)adamantan-l-amine

Based on general procedure E, from adamantan-l-ylamine and 2-chloro-5-(chloromethyl)thiazole, a yellow solid (75%) is obtained. Data: LC/MS (ESR) *mlz 283* $[M+H]^+$.

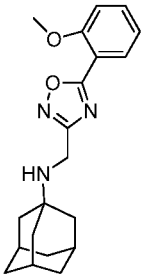
[0451] Example 14b/ M2WJ414



N-((5-(trifluoromethyl)-l,3,4-oxadiazol-2-yl)methyl)adamantan-l-amine

Based on general procedure E, from adamantan-l-ylamine and 2-(chloromethyl)-5-(trifluoromethyl)-l,3,4-oxadiazole, a yellow solid (83%) is obtained. Data: LC/MS (ESR) *mlz 302* $[M+H]^+$.

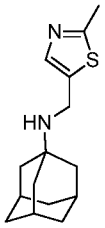
[0452] Example 15b/ M2WJ415



N-((5-(2-methoxyphenyl)-l,2,4-oxadiazol-3-yl)methyl)adamantan-l-amine

Based on general procedure E, from adamantan-l-ylamine and 3-(chloromethyl)-5-(2-methoxyphenyl)-l,2,4-oxadiazole, a yellow solid (78%) is obtained. Data: LC/MS (ESR) *mlz 340* $[M+H]^+$.

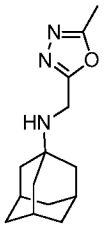
[0453] Example 16b/ M2WJ417



N-((2-methylthiazol-5-yl)methyl)adamantan-l-amine

Based on general procedure E, from adamantan-l-ylamine and 5-(chloromethyl)-2-methylthiazole, a yellow solid (88%) is obtained. Data: LC/MS (ESR) *mlz 263* $[M+H]^+$.

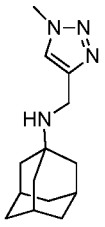
[0454] Example 17b/ M2WJ419



N-((5-methyl-l,3,4-oxadiazol-2-yl)methyl)adamantan-l-amine

Based on general procedure E, from adamantan-l-ylamine and 2-(chloromethyl)-5-methyl-l,3,4-oxadiazole, a yellow solid (72%) is obtained. Data: LC/MS (ESR) *mlz 248* $[M+H]^+$.

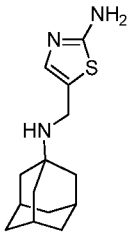
[0455] Example 18b/ M2WJ420



N-((l-methyl-lH-l,2,3-triazol-4-yl)methyl)adamantan-l-amine

Based on general procedure C, from adamantan-l-ylamine and l-methyl-lH-l,2,3-triazole-4-carbaldehyde, a yellow solid (75%) is obtained. Data: LC/MS (ESR) *mlz 247* $[M+H]^+$.

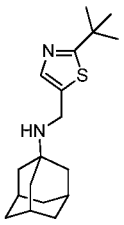
[0456] Example 19b/ M2WJ421



5-(adamantan-l-ylaminomethylthiazol-2-ylamine

Based on general procedure C, from adamantan-l-ylamine and 2-aminothiazole-5-carbaldehyde, a yellow solid (88%) is obtained. Data: LC/MS (ESR) *mlz 264* $[M+H]^+$.

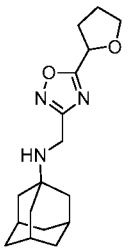
[0457] Example 20b/ M2WJ422



N-((2-(tert-butyl)thiazol-5-yl)methyl)adamantan-l-amine

Based on general procedure C, from adamantan-l-ylamine and 2-(tert-butyl)thiazole-5-carbaldehyde, a yellow solid (70%) is obtained. Data: LC/MS (ESR) *mlz 305* $[M+H]^+$.

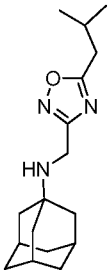
[0458] Example 21b/ M2WJ423



N-((5-(tetrahydrofuran-2-yl)-l,2,4-oxadiazol-3-yl)methyl)adamantan-l-amine

Based on general procedure E, from adamantan-l-ylamine and 3-(chloromethyl)-5-(tetrahydrofuran-2-yl)-l,2,4-oxadiazole, a yellow solid (79%) is obtained. Data: LC/MS (ESR) *mlz 304* $[M+H]^+$.

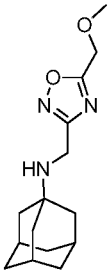
[0459] Example 22b/ M2WJ424



N-((5-isobutyl-l,2,4-oxadiazol-3-yl)methyl)adamantan-l-amine

Based on general procedure E, from adamantan-l-ylamine and 3-(chloromethyl)-5-isobutyl-1,2,4-oxadiazole, a yellow solid (72%) is obtained. Data: LC/MS (ESR) *mlz 290* $[M+H]^+$.

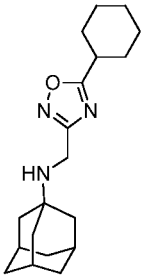
[0460] Example 23b/ M2WJ426



N-((5-(methoxymethyl)-l,2,4-oxadiazol-3-yl)methyl)adamantan-l-amine

Based on general procedure E, from adamantan-l-ylamine and 3-(chloromethyl)-5-(methoxymethyl)-l,2,4-oxadiazole, a yellow solid (81%) is obtained. Data: LC/MS (ESR) *mlz 278* $[M+H]^+$.

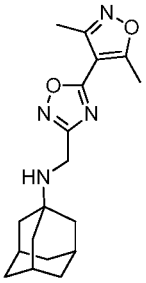
[0461] Example 24b/ M2WJ428



N-((5-(methoxymethyl)-l,2,4-oxadiazol-3-yl)methyl)adamantan-l-amine

Based on general Procedure J, followed by general procedure E, from 2-chloro-N-hydroxyacetimidamide and cyclohexanecarbonyl chloride, a yellow solid (42%) is obtained. Data: LC/MS (ESR) *mlz 316* $[M+H]^+$.

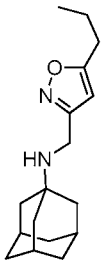
[0462] Example 25b/ M2WJ430



N-((5-(3,5-dimethylisoxazol-4-yl)-l,2,4-oxadiazol-3-yl)methyl)adamantan-l-amine

Based on general procedure E, from adamantan-l-ylamine and 3-(chloromethyl)-5-(3,5-dimethylisoxazol-4-yl)-l,2,4-oxadiazole, a yellow solid (76%) is obtained. Data: LC/MS (ESR) *mlz 329* $[M+H]^+$.

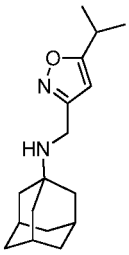
[0463] Example 26b/ M2WJ431



N-((5-propylisoxazol-3-yl)methyl)adamantan-l-amine

Based on general Procedure K, from pentan-2-one, a yellow solid (24%) is obtained. Data: LC/MS (ESR) *mlz 275* $[M+H]^+$.

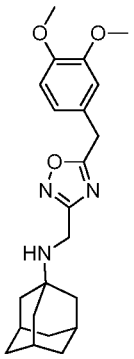
[0464] Example 27b/ M2WJ432



N-((5-isopropylisoxazol-3-yl)methyl)adamantan-l-amine

Based on general Procedure K, from 3-methylbutan-2-one, a yellow solid (23%) is obtained. Data: LC/MS (ESR) *mlz 275* $[M+H]^+$.

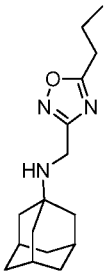
[0465] Example 28b/ M2WJ434



N-((5-(3,4-dimethoxybenzyl)-l,2,4-oxadiazol-3-yl)methyl)adamantan-l-amine

Based on general procedure E, from amantadine and 3-(chloromethyl)-5-(3,4-dimethoxyben zyl)-1,2,4-oxadiazole, a yellow solid (79%) is obtained. Data: LC/MS (ESR) *mlz 384* $[M+H]^+$.

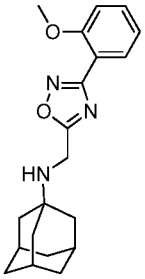
[0466] Example 29b/ M2WJ437



N-((5-propyl- 1,2,4-oxadiazol-3-yl)methyl)adamantan- 1-amine

Based on general procedure E, from amantadine and 3-(chloromethyl)-5-propyl-l,2,4-oxadiazole, a yellow solid (35%) is obtained. Data: LC/MS (ESR) *mlz 276* $[M+H]^+$.

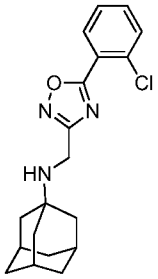
[0467] Example 30b/ M2WJ438



N-((3-(2-methoxyphenyl)-l,2,4-oxadiazol-5-yl)methyl)adamantan-l-amine

Based on general procedure E, from amantadine and 5-(chloromethyl)-3-(2-methoxyphenyl)-1,2,4-oxadiazole, a yellow solid (84%) is obtained. Data: LC/MS (ESR) *mlz 340* $[M+H]^+$.

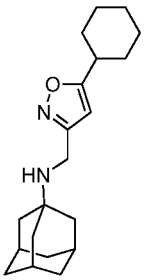
[0468] Example 31b/ M2WJ439



N-((5-(2-chlorophenyl)-l,2,4-oxadiazol-3-yl)methyl)adamantan-l-amine

Based on general procedure E, from amantadine and 3-(chloromethyl)-5-(2-chlorophenyl)- 1,2,4-oxadiazole, a yellow solid (81%) is obtained. Data: LC/MS (ESR) *mlz 344* $[M+H]^+$.

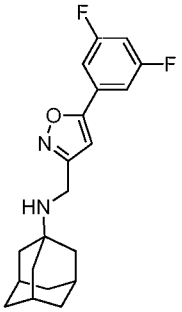
[0469] Example 32b/ M2WJ442



N-((5-cyclohexylisoxazol-3-yl)methyl)adamantan-l-amine

Based on general Procedure K, from 1-cyclohexylethanone, a yellow solid (23%) is obtained. Data: LC/MS (ESR) *mlz 315* $[M+H]^+$.

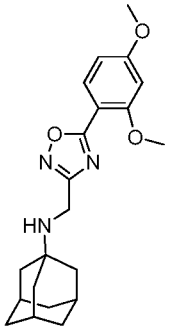
[0470] Example 33b/ M2WJ443



N-((5-(3,5-difluorophenyl)isoxazol-3-yl)methyl)adamantan-l-amine

Based on general Procedure K, from l-(3,5-difluorophenyl)ethanone, a yellow solid (40%>) is obtained. Data: LC/MS (ESR) *mlz 345* $[M+H]^+$.

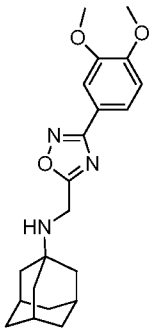
[0471] Example 34b/ M2WJ444



N-((5-(2,4-dimethoxyphenyl)-l,2,4-oxadiazol-3-yl)methyl)adamantan-l-amine

Based on general Procedure J, from 2,4-dimethoxybenzoyl chloride, a yellow solid (41%) is obtained. Data: LC/MS (ESR) *mlz 370* $[M+H]^+$.

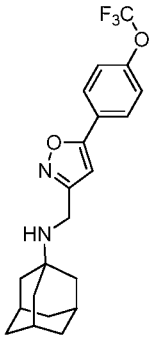
[0472] Example 35b/ M2WJ445



N-((3-(3,4-dimethoxyphenyl)-l,2,4-oxadiazol-5-yl)methyl)adamantan-l-amine

Based on general procedure E, from amantadine and 5-(chloromethyl)-3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazole, a yellow solid (85%) is obtained. Data: LC/MS (ESR) *mlz 370* $[M+H]^+$.

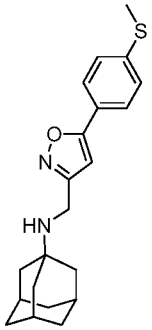
[0473] Example 36b/ M2WJ446



N-((5-(4-(trifluoromethoxy)phenyl)isoxazol-3-yl)methyl)adamantan-l-amine

Based on general Procedure K, from l-(4-(trifluoromethoxy)phenyl)ethanone, a yellow solid (41%) is obtained. Data: LC/MS (ESR) *mlz 393* $[M+H]^+$.

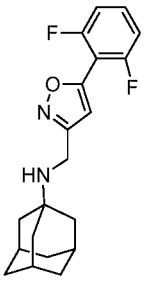
[0474] Example 37b/ M2WJ447



N-((5-(4-(methylthio)phenyl)isoxazol-3-yl)methyl)adamantan-l-amine

Based on general Procedure K, from l-(4-(methylthio)phenyl)ethanone, a yellow solid (38%) is obtained. Data: LC/MS (ESR) *mlz 355* $[M+H]^+$.

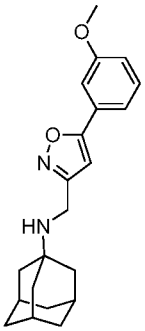
[0474] Example 38b/ M2WJ448



N-((5-(2,6-difluorophenyl)isoxazol-3-yl)methyl)adamantan-l-amine

Based on general Procedure K, from l-(2,6-difluorophenyl)ethanone, a yellow solid (45%) is obtained. Data: LC/MS (ESR) *mlz 345* $[M+H]^+$.

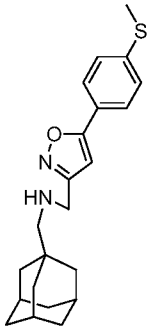
[0475] Example 39b/ M2WJ449



N-((5-(3-methoxyphenyl)isoxazol-3-yl)methyl)adamantan-l-amine

Based on general Procedure K, from l-(3-methoxyphenyl)ethanone, a yellow solid (37%) is obtained. Data: LC/MS (ESR) *mlz 339* $[M+H]^+$.

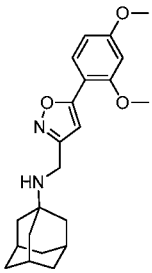
[0476] Example 40b/ M2WJ451



l-((3r,5r,7r)-adamantan-l-yl)-N-((5-(4-(methylthio)phenyl)isoxazol-3-yl)methyl)methanamine

Based on general procedure E, from (3r,5r,7r)-adamantan-l-ylmethanamine and 3-(chloromethyl)-5-(4-(methylthio)phenyl)isoxazole, a yellow solid (82%) is obtained. Data: LC/MS (ESR) *mlz 369* $[M+H]^+$.

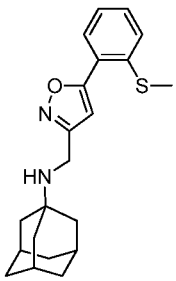
[0477] Example 41b/ M2WJ452



N-((5-(2,4-dimethoxyphenyl)isoxazol-3-yl)methyl)adamantan-l-amine

Based on general Procedure K, from l-(2,4-dimethoxyphenyl)ethanone, a yellow solid (39%) is obtained. Data: LC/MS (ESR) *mlz 369* $[M+H]^+$.

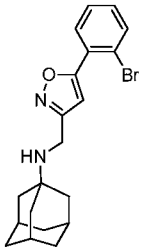
[0478] Example 42b/ M2WJ454



N-((5-(2-(methylthio)phenyl)isoxazol-3-yl)methyl)adamantan-l-amine

Based on general Procedure K, from l-(2-(methylthio)phenyl)ethanone, a yellow solid (41%) is obtained. Data: LC/MS (ESR) *mlz 355* $[M+H]^+$.

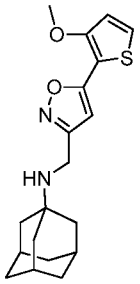
[0479] Example 43b/ M2WJ455



N-((5-(2-bromophenyl)isoxazol-3-yl)methyl)adamantan-l-amine

Based on general Procedure K, from l-(2-bromophenyl)ethanone, a yellow solid (40%) is obtained. Data: LC/MS (ESR) *mlz 388* $[M+H]^+$.

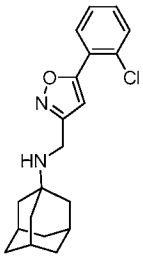
[0480] Example 44b/ M2WJ456



N-((5-(3-methoxythiophen-2-yl)isoxazol-3-yl)methyl)adamantan-l-amine

Based on general Procedure K, from l-(3-methoxythiophen-2-yl)ethanone, a yellow solid (32%) is obtained. Data: LC/MS (ESR) *mlz 345* $[M+H]^+$.

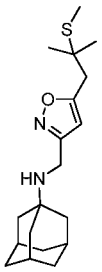
[0481] Example 45b/ M2WJ457



N-((5-(2-chlorophenyl)isoxazol-3-yl)methyl)adamantan-l-amine

Based on general Procedure K, from l-(2-chlorophenyl)ethanone, a yellow solid (42%) is obtained. Data: LC/MS (ESR) *mlz 343* $[M+H]^+$.

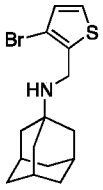
[0482] Example 46b/ M2WJ458



N-((5-(2-methyl-2-(methylthio)propyl)isoxazol-3-yl)methyl)adamantan-l-amine

Based on general Procedure K, from 4-methyl-4-(methylthio)pentan-2-one, a yellow solid (44%) is obtained. Data: LC/MS (ESR) *mlz 335* $[M+H]^+$.

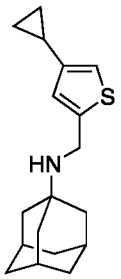
[0483] Example 47b/BC097



***N*-((3-Bromothiophen-2-yl)methyl)adamantan-l-amine**

Based on general procedure CI, from adamantan-1-amine and 3-bromothiophene-2-carbaldehyde, an off-white solid was obtained Data: LC/MS (ESCi) *mlz* 326.05/328.12 $[M+l]^+$.

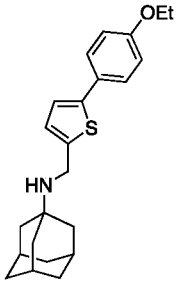
[0484] Example 48/BC119



***N*-((4-Cyclopropylthiophen-2-yl)methyl)adamantan-l-amine**

Based on general procedure C, from adamantan-1-amine and 4-cyclopropylthiophen-2-carbaldehyde (General Procedure H), a light solid was obtained Data: LC/MS (ESCi) *mlz* 288.28 $[M+l]^+$.

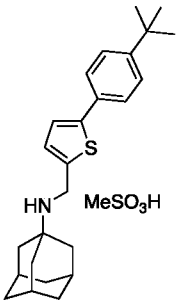
[0485] Example 49b/BC120



7V-((5-(4-Ethoxyphenyl)thiophen-2-yl)methyl)adamantan-l-amine

Based on general procedure CI, from adamantan-1-amine and 5-(4-ethoxyphenyl)thiophene-2-carbaldehyde (general procedure F), a white solid was obtained Data: LC/MS (ESCi) *mlz* 368.16 $[M+l]^+$.

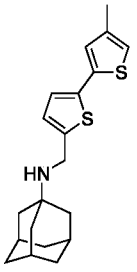
[0486] Example 50b/BC121



7V-((5-(4-(tei"i-Butyl)phenyl)thiophen-2-yl)methyl)adamantan-l-amine

Based on general procedure CI, from adamantan-1-amine and **5**-(4-*(te***r***t*-butyl)phenyl)thiophene-2-carbaldehyde (general procedure F). The free amine was dissolved in diethyl ether and cooled to 0 °C and MeSOsH (1 eq) was added under N_2, and then mixture was stirred at 0 °C for 15 min and filtered to give a white solid was obtained Data: LC/MS (ESCi) *mlz* 380.24 $[M+l]^+$.

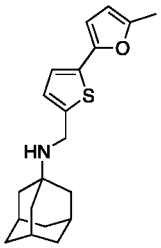
[0487] Example 51b/BC070



7V-((4'-Methyl- [2,2'-bithiophen] -5-yl)methyl)adamantan- 1-amine

Based on general procedure F, from N-((5-bromothiophen-2-yl)methyl)adamantan- 1-amine and potassium 4-methyl(furan-2yl) trifluoroborate, a light brown oil was obtained Data: LC/MS (ESCi) *mlz* 344.24 $[M+l]^+$.

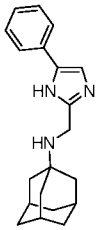
[0488] Example 52b/ BC071



7V-((5-(5-Methylfuran-2-yl)thiophen-2-yl)methyl)adamantan-l-amine

Based on general procedure F, from N-((5-bromothiophen-2-yl)methyl)adamantan-l -amine and potassium 5-methyl(furan-2-yl)trifluoroborate, a brown solid was obtained Data: LC/MS (ESCi) *mlz* 328.12 $[M+l]^+$.

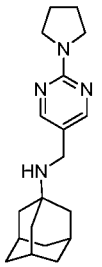
[0489] Example 53b/ Hij411



N-((5-phenyl-lH-imidazol-2-yl)methyl)adamantan-l-amine

4-phenyl-imidazole-2-carbaldehyde (2.7g, 15.6 mmol) in DMF (15mL) was treated with triethylamine (2eq) and trityl chloride (1.3 eq) in DMF (lOmL). After completion of the reaction, the solution was diluted with ethyl acetate and washed with brine, sat. sodium carbonate and water to yield the yellow powder (3.3g) after concentration under reduced pressure. A portion of the crude mixture (828 mg) was dissolved in methanol (lOmL) and sodium borohydride (2eq) was added at room temperature for 3h. The solution was concentrated and diluted with ethyl acetate and water. After washing with brine and concentration under reduced pressure, the crude mixture was concentrated. Based upon the general procedure I, the product was obtained after removal of trityl group 50% TFA/5% TIPS in DCM (lOmL). Data: LC/MS (ESR) *mlz 308* $[M+H]^+$.

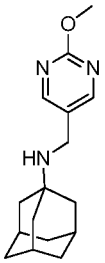
[0490] Example 54b/ Hij372



N-((2-(pyrrolidin-l-yl)pyrimidin-5-yl)methyl)adamantan-l-amine

Based on general procedure I, from adamantan-l-ylamine and 2-(pyrrolidin-l-yl)pyrimidin-5-yl) methanol, a white solid (30%) is obtained. Data: LC/MS (ESR) *m/z 313* $[M+H]^+$.

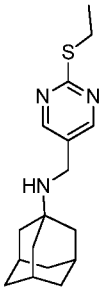
[0491] Example 55b/ Hij374



N-((2-methoxypyrimidin-5-yl)methyl)adamantan-l-amine

Based on general procedure I, from adamantan-l-ylamine and 2-methoxypyrimidin-5-yl)methanol, a white solid (30%) is obtained. Data: LC/MS (ESR) *m/z 274* $[M+H]^+$.

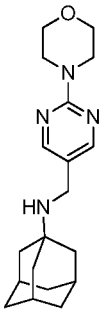
[0492] Example 56b/ Hij381



N-((2-(ethylthio)pyrimidin-5-yl)methyl)adamantan-l-amine

Based on general procedure I, from adamantan-l-ylamine and 2-(ethylthio)pyrimidin-5-yl)methanol, a white solid (20%) is obtained. Data: LC/MS (ESR) *m/z 304* $[M+H]^+$.

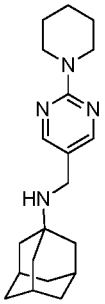
[0493] Example 57b/ Hij405



N-((2-morpholinopyrimidin-5-yl)methyl)adamantan-l-amine

Based on general procedure I, from adamantan-l-ylamine and 2-(morpholino)pyrimidin-5-yl)methanol, a white solid (15%) is obtained. Data: LC/MS (ESR) *mlz 329* $[M+H]^+$.

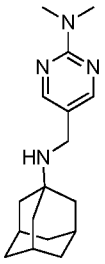
[0494] Example 58b/ Hij382



N-((2-(piperidin-l-yl)pyrimidin-5-yl)methyl)adamantan-l-amine

Based on general procedure I, from adamantan-l-ylamine and 2-(piperidin-l-yl)pyrimidin-5-yl)methanol, a white solid (20%) is obtained. Data: LC/MS (ESR) *mlz 327* $[M+H]^+$.

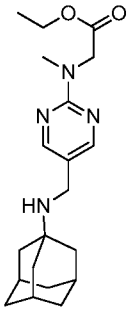
[0495] Example 59b/ WFD108



N-((2-dimethylaminopyrimidin-5-yl)methyl)adamantan-l-amine

Based on general procedure C, from adamantan-l-ylamine and N-((2-dimethylaminopyrimidin-5-yl) carbaldehyde, a white solid (30%) is obtained. Data: LC/MS (ESR) *mlz 287* $[M+H]^+$.

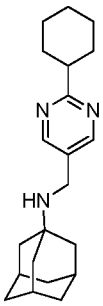
[0496] Example 60b/ Hij415



N-((2-methyl(ethylcarboxymethyl)aminopyrimidin-5-yl)methyl)adamantan-l-amine

Based on general procedure C, from adamantan-l-ylamine and N-((2-methyl(ethylcarboxymethyl)aminopyrimidin-5-yl)methyl) carbaldehyde, a white solid (30%) is obtained. Data: LC/MS (ESR) *mlz 373* $[M+H]^+$.

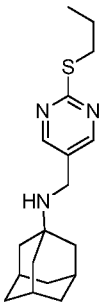
[0497] Example 61b/ Hij414



N-((2-cyclohexylpyrimidin-5-yl)methyl)adamantan-l-amine

Based on general procedure C, from adamantan-l-ylamine and N-((2-cyclohexylpyrimidin-5-yl carbaldehyde, a white solid (15%) is obtained. Data: LC/MS (ESR) *mlz 326* $[M+H]^+$.

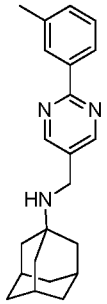
[0498] Example 62b/ Hij416



N-((2-propylthiopyrimidin-5-yl)methyl)adamantan-l-amine

Based on general procedure C, from adamantan-l-ylamine and N-((2-propylthiopyrimidin-5-yl) carbaldehyde, a white solid (60%) is obtained. Data: LC/MS (ESR) *mlz 318* $[M+H]^+$.

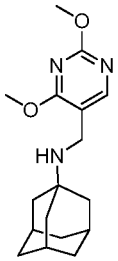
[0499] Example 63b/ Hij417



N-((2-ratolylpyrimidin-5-yl)methyl)adamantan-l-amine

Based on general procedure C, from adamantan-l-ylamine and N-((2-mtolylpyrimidin-5-yl) carbaldehyde, a white solid (10%) is obtained. Data: LC/MS (ESR) *mlz 334* $[M+H]^+$.

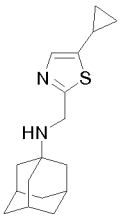
[0500] Example 64b/ Hij406



N-((2,4-dimethoxypyrimidin-5-yl)methyl)adamantan-l-amine

Based on general procedure C, from adamantan-l-ylamine and N-((2,4-dimethoxypyrimidin-5-yl) carbaldehyde, a white solid (10%) is obtained. Data: LC/MS (ESR) *mlz 304* $[M+H]^+$.

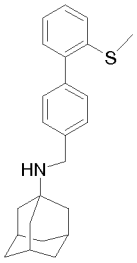
[0501] Example 65MMX769



Adamantan-l-yl-(5-cyclopropyl-thiazol-2-ylmethyl)-amine

Based on general procedure G, form adamantan-l-yl-(5-bromo-thiazol-2-ylmethyl)-amine **(Example 86a)** and cyclopropylboronic acid, an off -white solid was obtained (46%). Data: LC/MS (ESR) m/z 289 $[M+H]^+$.

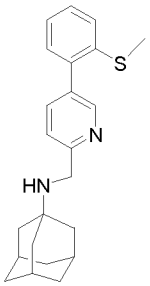
[0502] Example 66MMX747



Adamantan-l-yl-(2'-methylsulfanyl-biphenyl-4-ylmethyl)-amine

Based on general procedure **G,** form adamantan-l-yl-(4-bromo-benzyl)-amine **(Example 41)** and [2-(Methylsulfanyl)phenyl]boronic acid, a white solid was obtained (46%). Data: LC/MS (ESR) m/z 364 $[M+H]^+$.

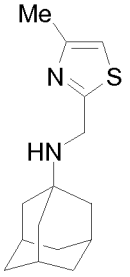
[0503] Example 67MMX745



Adamantan-l-yl-[5-(2-methylsulfanyl-phenyl)-pyridin-2-ylmethyl]-amine

Based on general procedure **G,** form adamantan-l-yl-(5-bromo-pyridin-2-ylmethyl)-amine **(Example 54a)** and [2-(methylsulfanyl)phenyl]boronic acid, a white solid was obtained (56%). Data: LC/MS (ESR) m/z 365 $[M+H]^+$.

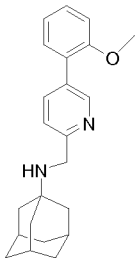
[0504] Example 68MMX746



Adamantan-l-yl-(4-methyl-thiazol-2-ylmethyl)-amine

Based on general procedure **A,** from 4-methyl-thiazole-2-carbaldehyde and adamantan-1-ylamine, a white solid (70%) is obtained. Data: LC/MS (ESR) m/z 263 $[M+H]^+$.

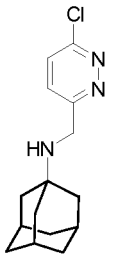
[0505] Example 69MMX744



Adamantan-l-yl-[5-(2-methoxy-phenyl)-pyridin-2-ylmethyl]-amine

Based on general procedure **G,** form adamantan-l-yl-(5-bromo-pyridin-2-ylmethyl)-amine **(Example 54a)** and 2-methoxyphenylboromc acid, a white solid was obtained (66%). Data: LC/MS (ESR) m/z 349 $[M+H]^+$.

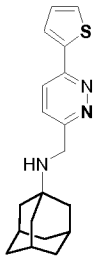
[0506] Example 70MMX747



Adamantan-l-yl-(6-chloro-pyridazin-3-ylmethyl)-amine

Based on general procedure **A,** from 6-Chloro-pyridazine-3-carbaldehyde and adamantan-1-ylamine, an off- white solid (70%) is obtained. Data: LC/MS (ESR) m/z 278 $[M+H]^+$.

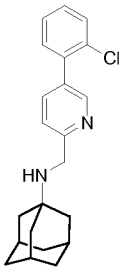
[0507] Example 71MMX748



Adamantan-l-yl-(6-thiophen-2-yl-pyridazin-3-ylmethyl)-amine

Based on general procedure **G,** form adamantan-l-yl-(6-chloro-pyridazin-3-ylmethyl)-amine and 2-thiopheneboronic acid, a yellow solid was obtained (46%>). Data: LC/MS (ESR) m/z 326 $[M+H]^+$.

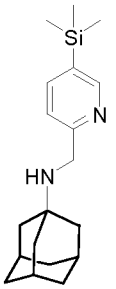
[0508] Example 72MMX755



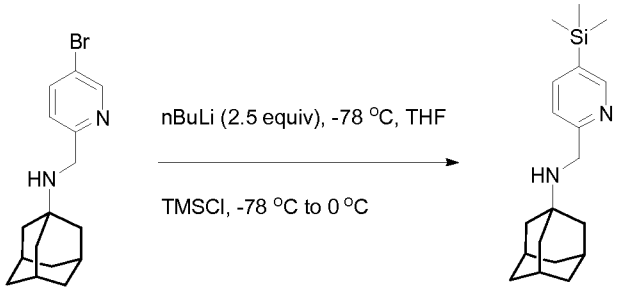
Adamantan-l-yl-[5-(2-chloro-phenyl)-pyridin-2-ylmethyl]-amine

Based on general procedure G, form adamantan-l-yl-(5-bromo-pyridin-2-ylmethyl)-amine **(Example 54a)** and **2-chlorophenylboromc acid,** an off-white solid was obtained (56%). Data: LC/MS (ESR) m/z 353 $[M+H]^+$.

[0509] Example 73MMX756



Adamantan-l-yl-(5-trimethylsilanyl-pyridin-2-ylmethyl)-amine

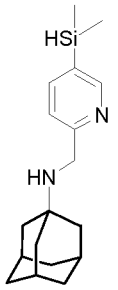


54a **73b**

At -78 °C, to adamantan-l-yl-(5-bromo-pyridin-2-ylmethyl)-amine **54a** (321 mg, 1 mmol) in THF (10 mL) was added dropwise nBuLi (2.5 M in Hexane, 1.0 mL, 2.5 mmol). After the mixture was stirred at the same temperature for 10 min, TMSCI (130 mg, 1.2 mmol) was added dropwise. The resulting mixture was stirred for 30 min and warmed up to 0 °C over 1 h. The mixture was recooled to -78 ° C and was quenched with NH_4C1 (sat'd) (5 ml). After the mixture was wormed to room temperature, it was extracted with DCM (10 mL x3). The organic layer was separated, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The mixture was then purified by silica gel flash column chromatography (1-10%

CH_3OH/CH_2CI_2) to give the title product **73b** (174 mg, 56%) as a white solid. Data: LC/MS (ESR) m/z 315 $[M+H]^+$.

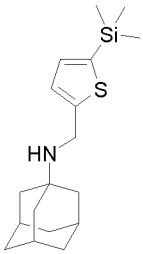
[0510] Example 74b/IMX757



Adamantan-l-yl-(5-dimethylsilanyl-pyridin-2-ylmethyl)-amine

Based on the same procedure of example **73b** excepting using chloro-dimethyl-silane instead of chloro-triimethyl-silane. A white solid (51%) was otained. Data: LC/MS (ESR) m/z 301$[M+H]^+$.

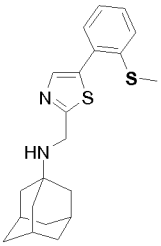
[0511] Example 75b/IMX734



Adamantan-l-yl-(5-trimethylsilanyl-thiophen-2-ylmethyl)-amine

Based on the same procedure of example **73b** excepting using adamantan-l-yl-(5-bromo-thiophen-2-ylmethyl)-amine (Example **81)** instead of adamantan-l-yl-(5-bromo-pyridin-2-ylmethyl)-amine **54a.** A white solid (41%) was obtained. Data: LC/MS (ESR) m/z 320 $[M+H]^4$.

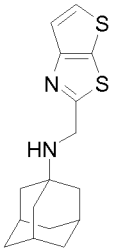
[0512] Example 76b/IMX742



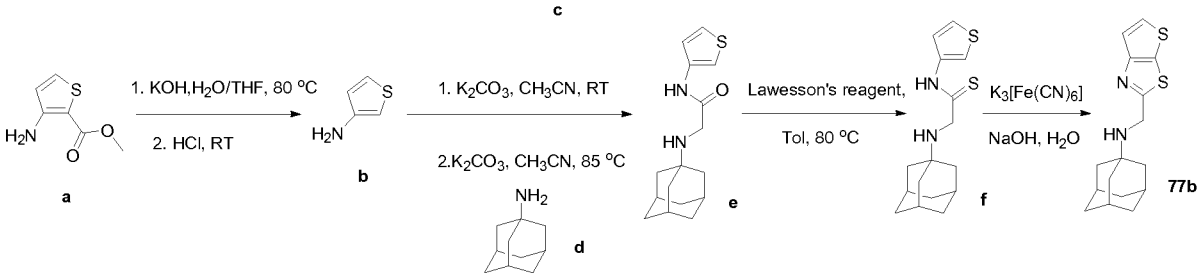
Adamantan-l-yl-[5-(2-methylsulfanyl-phenyl)-thiazol-2-ylmethyl]-amine

Based on general procedure G, form adamantan-l-yl-(5-bromo-thiazol-2-ylmethyl)-amine **(Example 86a)** and [2-(methylsuIfanyl) phenyljboronic acid, an off-white solid was obtained (45%). Data: LC/MS (ESR) m/z 371 $[M+H]^+$.

[0512] Example 77MMX751



Adamantan-l-yl-thieno[3,2-d]thiazol-2-ylmethyl-amine



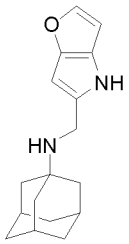
3-Amino-thiophene-2-carboxylic acid methyl ester (a) (1.57 g, 10 mmol), KOH (2.8 g, 50 mml) was dissolved in THF (50 mL) and water (5 mL). The mixture was heated at 80 °C overnight. The volatile was removed under vacuum and resulting mixture was treated with HC1 (5 M, 10 mL, 50 mmol). Then the mixture was extracted with DCM (30 mL x 3). The combined organic layer was dried over $MgS0_4$, and concentrated under reduced pressure after filtration to give a crude product thiophen-3-ylamine **b** (0.55 g, 56%). Data: LC/MS (ESR) m/z 100 $[M+H]^+$. To a mixture of thiophen-3-ylamine **b** (0.5 g, 5.1 mmol) and K_2CO_3 (0.77g, 5.6 mmol) in CH_3CN (10 mL), bromo-acetyl chloride (0.79 g, 5.1 mml) was added dropwise. The mixture was stirred overnight at room temperature. Then K_2CO_3 (0.77g, 5.6 mmol) and adamantan-l-ylamine (0.92 g, 6.1 mmol) were added to the above mixture. After the mixture was heated at 85 °C for overnight, the mixture was filtered and the filter was concentrated. The crude residue was separated by flash column chromatography (1-10% CH_3OH/CH_2CI_2) to give the tile compound 2-(adamantan-l-ylamino)-N-thiophen-3-yl-acetamide **e** (0.75 g, 51%) as a pink solid. Data: LC/MS (ESR) m/z 291 $[M+H]^+$.

Lawesson's reagent (969.6 mg, 2.4 mmol) was added portions to a solution of 2-(adamantan-l-ylamino)-N-thiophen-3-yl-acetamide **e** (580 mg, 2.0 mmol) in toluene (10 mL) at 80 °C. The mixture was heated for 2h before the solvent was removed *in vacuo*. The crude residue was separated by flash column chromatography (1-10% CH_3OH/CH_2CI_2) to give the tile

compound 2-(adamantan-l-ylamino)-N-thiophen-3-yl-thioacetamide **f** (0.53 g, 87%) as a yellow solid. Data: LC/MS (ESR) m/z 307 $[M+H]^+$.

To a solution of 2-(adamantan-l-ylamino)-N-thiophen-3-yl-thioacetamide **f** (0.52 g, 1.7 mmol) in ethanol (1 mL) was added 30% NaOH (1.6 mL, 12 .0 mmol). The mixture was diluted to give 10% NaOH and stirred for 5 min. Portions of this mixture were added at 1 min intervals to a stirred solution of K3[Fe(CN)6] (2.0 g, 6.0 mmol) in H_20 (3 mL) at 85 °C. The resulting mixture was further heated at 85 °C for lh. Solvent was removed in vaccuo and the the residue was extracted with DCM (5 mL x 3). The combined organic layer was dried over $MgS0_4$, concentrated and separated by flash column chromatography (1-10% $CH30H/CH_2C1_2$) to give the tile compound adamantan-l-yl-thieno[3,2-d]thiazol-2-ylmethyl-amine **77b**/IMX751 (0.26 g, 52%) as a pink solid. Data: LC/MS (ESR) m/z 305 $[M+H]^+$.

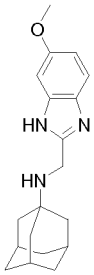
[0513] Example 78b/IMX738



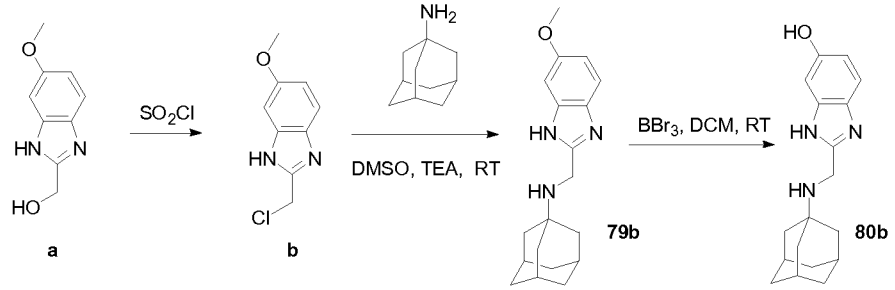
Adamantan-l-yl-(4H-furo[3,2-b]pyrrol-5-ylmethyl)-amine

Based on general procedure **C,** form adamantan-l-ylamine and 4H-Furo[3,2-b]pyrrole-5-carboxylic acid, an pink solid was obtained (26%). Data: LC/MS (ESR) m/z 271 $[M+H]^+$.

[0514] Example 79b/IMX724

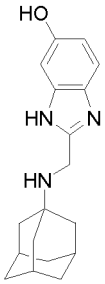


Adamantan-l-yl-(6-methoxy-lH-benzoimidazol-2-ylmethyl)-amine



A solution of (6-methoxy-lH-benzoimidazol-2-yl)-methanol **a** (356 mg, 2.0 mmol) in SO_2Cl_2 (2 mL) was heated at 70 °C for lh. Solvent was removed in vacuo and the resulting 2-chloromethyl-6-methoxy-lH-benzoimidazole **b** was used directly to the next step without further purification. To a solution of 6-methoxy-lH-benzoimidazole **b** in DMSO (5 mL) was added adamantan-1-ylamine (453 mg, 3.0 mmol) and TEA (0.5 mL). The solution was stirred for overnight before it was quenched with H_2O (5 mL). The mixture was extracted with DCM (10 mL x 3). The combined organic layer was dried over $MgSO_4$, concentrated and separated by flash column chromatography (1-10% CH_3OH/CH_2Cl_2) to give the tile compound adamantan-l-yl-(6-methoxy-lH-benzoimidazol-2-ylmethyl)-amine **79b**/IMX724 (0.23 g, 37%) as a white solid. Data: LC/MS (ESR) m/z 312 $[M+H]^+$.

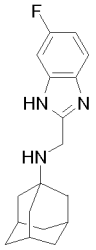
[0515] Example 80b/IMX725



2-(Adamantan-l-ylaminomethyl)-3H-benzoimidazol-5-ol

At -78 °C, BBr_3 (1.0 M in DCM, 0.8 mL, 0.8 mmol) was added dropwise to a solution of adamantan-l-yl-(6-methoxy-lH-benzoimidazol-2-ylmethyl)-amine **79b**/IMX724 (0.15 g, 0.48 mmol). The mixture was stirred at -78 °C for 30 min and warmed to rt. The mixture was quenched with $NaHCO_3$ (sat'd) (5 mL). The mixture was extracted with DCM (10 mL x 3). The combined organic layer was dried over $MgSO_4$, concentrated and separated by flash column chromatography (1-10% CH_3OH/CH_2Cl_2) to give the tile compound 2-(adamantan-l-ylaminomethyl)-3H-benzoimidazol-5-ol **80b**/IMX724 (0.12 g, 86%) as a white solid. Data: LC/MS (ESR) m/z 298 $[M+H]^+$.

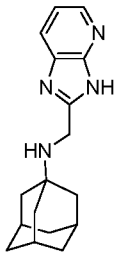
[0516] Example 81MMX722



Adamantan-l-yl-(6-fluoro-lH-benzoimidazol-2-ylmethyl)-amine

Followed the same procedure of **Example 79b/IMX724** except using (6-fluoro-lH-benzoimidazol-2-yl)-methanol to replace (6-methoxy-lH-benzoimidazol-2-yl)-methanol. A white solid (38%). Data: LC/MS (ESR) m/z 300 $[M+H]^+$.

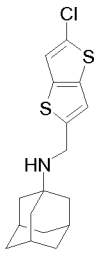
[0517] Example 82b/ M2WJ418



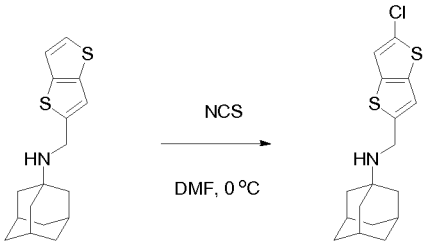
N-((3H-imidazo[4,5-b]pyridin-2-yl)methyl)adamantan-l-amine

Based on general procedure E, from amantadine and 2-(chloromethyl)-3H-imidazo[4,5-b]pyridine, a yellow solid (87%) is obtained. Data: LC/MS (ESR) *mlz 283* $[M+H]^+$.

[0518] Example 83b/IMX715

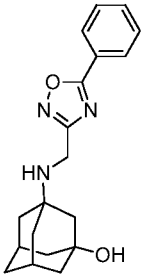


Adamantan-l-yl-(5-chloro-thieno[3,2-b]thiophen-2-ylmethyl)-amine



To a solution of Adamantan-l-yl-thieno[3,2-b]thiophen-2-ylmethyl-amine (150 mg, 0.5 mmol) was treated with NBS (90 mg, 0.5 mmol) in DMF (5 mL) at 0 °C for 2h. The solvent was removed concentrated under reduced pressure. The crude product was separated by flash column chromatography (1-10% CH_30H/CH_2C1_2) to give the title compound (36 mg, 20%). Data: LC/MS (ESR) m/z 338 $[M+l]^+$.

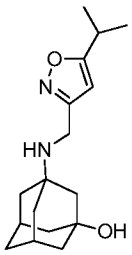
[0519] Example 84b/ M2WJ427



(ls,3r,5R,7S)-3-(((5-phenyl-l,2,4-oxadiazol-3-yl)methyl)amino)adamantan-l-ol

Based on general procedure E, from (ls,3r,5R,7S)-3-aminoadamantan-l-ol and 3-(chloromethyl)-5-phenyl-l,2,4-oxadiazole, a yellow solid (88%) is obtained. Data: LC/MS (ESR) *mlz 326* $[M+H]^+$.

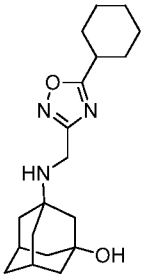
[0520] Example 85b/ M2WJ433



(ls,3r,5R,7S)-3-(((5-isopropylisoxazol-3-yl)methyl)amino)adamantan-l-ol

Based on general procedure E, from (ls,3r,5R,7S)-3-aminoadamantan-l-ol and 3-(bromomethyl)-5-isopropylisoxazole, a yellow solid (72%) is obtained. Data: LC/MS (ESR) *mlz 291* $[M+H]^+$.

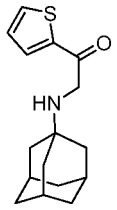
[0521] Example 86b/ M2WJ429



(ls,3r,5R,7S)-3-(((5-cyclohexyl-l,2,4-oxadiazol-3-yl)methyl)amino)adamantan-l-ol

Based on general procedure E, from (ls,3r,5R,7S)-3-aminoadamantan-l-ol and 3-(bromomethyl)-5-cyclohexyl-l,2,4-oxadiazole, a yellow solid (75%) is obtained. Data: LC/MS (ESR) *mlz 332* $[M+H]^+$.

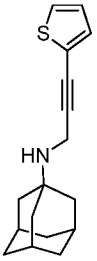
[0522] Example 87b/ Hij341



2-(adamantan-l-ylamino)-l-(thiophen-2-yl)ethanone

A mixture of adamantan-l-ylamine (2mmol) and bromoacetylthiophen(lmmol) in THF(6mL) was stirred for 30 min at room temperature. The voilatiles were removed and the crude mixture was purified by RP-HPLC. Data: LC/MS (ESR) *m/z 276* $[M+H]^+$.

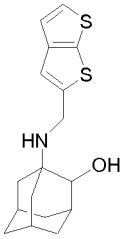
[0523] Example 88b/ Hij350



N-((2,4-dimethoxypyrimidin-5-yl)methyl)adamantan-l-amine

Based on general procedure I, from adamantan-l-ylamine and 3-(thiophen-2-yl)prop-2-yn-l-ol, a white solid (20%) is obtained. Data: LC/MS (ESR) *m/z 272* $[M+H]^+$.

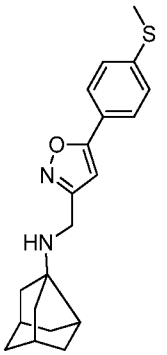
[0524] Example 89MMX737



(±)-l- [(Thieno [2,3-b] thiophen-2-ylmethyl)-amino] -adamantan-2-ol

Based on general procedure **A,** from (±)-l-amino-adamantan-2-ol (Armarego, W. L. F. et al. *Australian Journal of Chemistry,* **1979,** *32,* 1805-17) and thieno[2,3-b]thiophene-2-carbaldehyde, a white solid (30%) is obtained. Data: LC/MS (ESR) m/z 320 $[M+H]^+$.

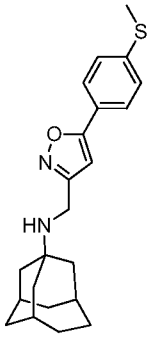
[0525] Example 90b/ M2WJ450



(2R,3as,5S,6as)-N-((5-(4-(methylthio)phenyl)isoxazol-3-yl)methyl)octahydro-2,5-methanopentalen-3a-amine

Based on general procedure E, from (2R,3as,5S,6as)-octahydro-2,5-methanopentalen-3a-amine and 3-(bromomethyl)-5-(4-(methylthio)phenyl)isoxazole, a yellow solid (90%) is obtained. Data: LC/MS (ESR) *m/z 341* $[M+H]^+$.

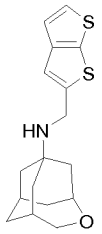
[0526] Example 91b/ M2WJ453



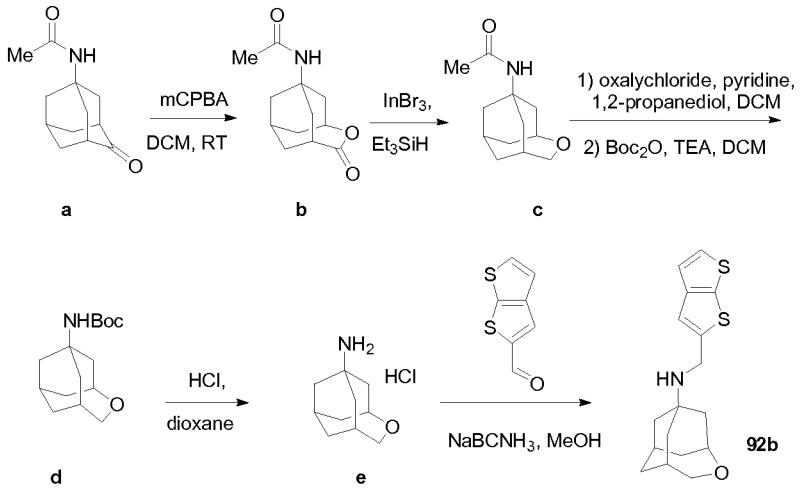
(lS,3R,8S)-N-((5-(4-(methylthio)phenyl)isoxazol-3-yl)methyl)tricyclo[4.3.1.13,8]undecan-l-amine

Based on general procedure E, from (lS,3R,8S)-tricyclo[4.3.1.13,8]undecan-l-amine and 3-(bromomethyl)-5-(4-(methylthio)phenyl)isoxazole, a yellow solid (91%) is obtained. Data: LC/MS (ESR) *mlz 369* $[M+H]^+$.

[0527] Example 92b/IMX800



(4-Oxa-tricyclo[4.3.1.13,8]undec-l-yl)-thieno[2,3-b]thiophen-2-ylmethyl-amine



Solid mCPBA (551 mg, 2.4 mmol, 77% purity) were added to a solution of ketone **a** (414 mg, 2 mmol) in DCM (5 mL) at 0 °C. The reaction mixture was allowed to warm to rt and was maintained for 1 h. The reaction mixture was diluted with a saturated, aqueous solution of sodium bisulfate (10 mL) and was extracted with DCM (3 x 10 mL). The combined organic layers were dried (Na_2S04) and concentrated. The residue was purified by silica gel chromatography (10/90 to 30/70 EtOAc/hexane) to provide lactone **b** in (401 mg, 90%). Data: LC/MS (ESR) *m/z* 224 $[M+H]^+$.

$InBr_3$ (700 mg, 2.0 mmol) and Et_3SiH (1 mL) were successively added to a solution of lactone **16A** (400 mg, 1.79 mmol) in $CHC1_3$ (10 mL) and the reaction mixture was heated at 60 °C for 1 h. The reaction mixture was allowed to cool to rt, was diluted with H_20 (10 mL), and the layers were separated. The aqueous layer was extracted with DCM (3 x 10 mL) and the combined organic layers were dried (Na_2S04) and concentrated. The residue was purified by silica gel chromatography (10/90 to 30/70 EtOAc/hexane) to provide ether **c** (218 mg, 58%). Data: LC/MS (ESR) *m/z* 210 $[M+H]^+$.

A 2.0 M solution of oxalyl chloride in DCM (1.0 ml, 2.0 mmol) was added dropwise to a solution of amide **c** (210 mg, 1.0 mmol) in dry THF (5 mL) and pyridine (0.5 mL) at 0 °C. The reaction mixture was maintained at 0 °C for 30 min when 1,2-propanediol (0.5 mL) was added in

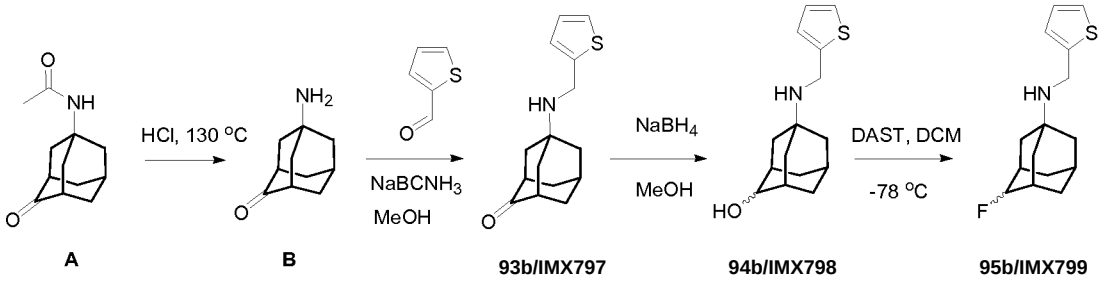
one portion and the reaction was allowed to warm to rt. The reaction mixture was diluted with EtOH (5 mL) and was concentrated. The crude oil was partitioned between 1 M aqueous HC1 (2 mL) and TBME (5 mL) and the layers were separated. The organic phase was extracted with 1.0 M aqueous HC1 solution (2 x 5 mL) and the pH of the combined aqueous layers was adjusted to pH 11 with 4 N aqueous NaOH. The aqueous layer was then extracted with DCM (3 x 5 mL) and the combined organic layers were dried (Na_2S0_4), and concentrated to provide the crude amine. Data: LC/MS (ESR) *mlz* 168 $[M+H]^+$.

Boc-anhydride (654 mg, 3.0 mmol) and TEA (1.0 mL) was added sequentially to a solution of the crude amine in DCM (5 mL) and the reaction mixture was maintained at rt for 2 h. The reaction mixture was diluted with a saturated, aqueous solution of NH_4C1 (1 mL) and the aqueous layer was extracted with DCM (3 x 10 mL). The combined organic layers were dried (Na_2S0_4) and concentrated. The residue was purified by silica gel chromatography (10/90 to 30/70 EtOAc/hexane) to provide the pure carbamate **d** (93.5 mg, 35% yield. Data: LC/MS (ESR) *mlz* 268 $[M+H]^+$.

The carbamate **d** (90 mg, 0.34mmol) in 1,4-dioxane (1 mL) was diluted with a solution of 4 N HC1 in dioxane (1.0 mL, 1.0 mmol) and the reaction mixture was maintained at rt for 2 h. The reaction mixture was concentrated and the residue was dissolved in water (2 mL). The aqueous layer was washed with EtOAc (3 x 5 mL) and concentrated to provide 4-Oxa-tricyclo[4.3.1.13,8]undec-l-ylamine **e** (57.9 mg, 85%) as a hydrochloric acid salt. Data: LC/MS (ESR) *mlz* 168 $[M+H]^+$.

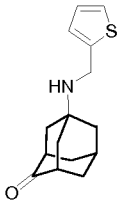
4-Oxa-tricyclo[4.3.1.13,8]undec-l-ylamine **e** (50 mg, 0.25 mmol), TEA (0.2 mL) and thiophene-2-carbaldehyde (84 mg mg, 2.0 mmol) were mixed in methanol (1.0 mL) and then treated with sodium cyanoborohydride (188 mg, 3 mmol). The mixture was stirred at room temperature under a N_2 atmosphere overnight. The reaction mixture was quenched by adding water, and the product was extracted with butanol (5 mL x 3). The combined organic layer was dried over Na_2S0_4, and concentrated under reduced pressure. The crude product was separated by flash column chromatography (1-10% CH_30H/CH_2C1_2) to give the title compound (4-Oxa-tricyclo[4.3.1.13,8]undec-l-yl)-thieno[2,3-b]thiophen-2-ylmethyl-amine **92B/IMX800** (34.2 mg, 43%) as a white solid. Data: LC/MS (ESR) m/z 320 $[M+H]^+$.

[0528] Example 93b /IMX797, example 94MMX798, and example 95MMX799



A solution of *N*-(4-oxoadamantan-l-yl)acetamide **A** (2.07 g, 10 mmol) in 100 mL of concentrated, aqueous HCl (12N) was heated in a sealed pressure tube at 130 °C for 20 h. The solvent was removed under reduced pressure to give 5-aminoadamantan-2-one **B** as an HCl salt (1.45 g, 90%) as an off-white solid. Data: LC/MS (ESR) *mlz* 166 $[M+H]^+$.

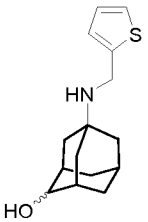
[0529] Example 93b / IMX797,



5-[(Thiophen-2-ylmethyl)-amino] -adamantan-2-one

5-aminoadamantan-2-one **B** (240 mg, 2.2 mmol) and thiophene-2-carbaldehyde (114 mg, 2.0 mmol) were mixed in methanol (5 mL) and then treated with sodium cyanoborohydride (376 mg, 6 mmol). The mixture was stirred at room temperature under a N_2 atmosphere overnight. The reaction mixture was quenched by adding water, and the product was extracted with butanol (10 mL x 3). The combined organic layer was dried over Na_2S0_4, and concentrated under reduced pressure. The crude product was separated by flash column chromatography (1-10% CH_3OH/CH_2CI_2) to give the title compound 5-[(thiophen-2-ylmethyl)-amino]-adamantan-2-one (201 mg, 38%) as a white solid. Data: LC/MS (ESR) *mlz* 262 $[M+H]^+$.

[0530] Example 94MMX798

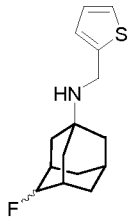


(±)5-[(Thiophen-2-ylmethyl)-amino] -adamantan-2-ol

Sodium borohydride (112 mg, 3.0mmol) was added in one portion to a solution of ketone **93B** (262 mg, 1.0 mmol) in MeOH (5 mL) at 0 °C. The reaction mixture was allowed to warm to

rt and was maintained at rt for 30 min. The solution was diluted with a saturated, aqueous NH_4Cl solution (5 mL) and the mixture was extracted with DCM (3 x 5 mL). The combined organic layers were dried (Na_2SO4) and concentrated. The residue was purified by silica gel chromatography [0/100 to 5/95 MeOH/(50/50 DCM/Hexane)] to give alcohol **94MMX798** (241mg, 92%) white solid. Data: LC/MS (ESR) *mlz* 264 $[M+H]^+$.

[0531] Example 95MMX799



(±) (4-Fluoro-adamantan-l-yl)-thiophen-2-ylmethyl-amine

A solution containing a mixture of alcohol (132 mg, 0.5 mmol) in DCM (1 mL) was added dropwise to a solution of (diethylamino)sulfur trifluoride (DAST) (97 mg, 0.6 mmol) in DCM (5 mL) at -78 °C. The reaction mixture was allowed to warm to rt and was maintained for 1 h. The reaction mixture was diluted with a saturated, aqueous NH_4Cl solution (2 mL) and the mixture was extracted with DCM (3 x 5 mL). The combined organic extracts were dried (Na_2SO4) and concentrated. The residue was purified by silica gel chromatography (0/100 to 30/70 EtOAc/hexane) to give fluoride (±) (4-Fluoro-adamantan-l-yl)-thiophen-2-ylmethyl-amine **95MMX799** (111 mg, 84%) as an off-white solid. Data: LC/MS (ESR) *mlz* 266 $[M+l]^+$.

Bioassay

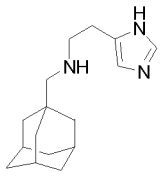
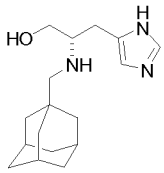
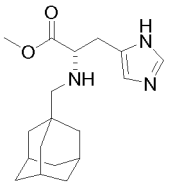
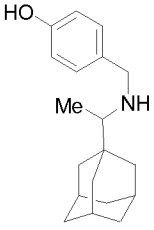
[0532] In Vitro cRNA Transcription, Heterologous Expression, and Electrophysiological Recordings. The cDNA encoding to the influenza virus A/Udorn/72 a.m.2 protein was inserted into pGEMHJ (a gift from N.Dascal Tel-Aviv University, Israel) for expression on Xenopus oocytes. Plasmid was linearized with Hindlll, and capped cRNA was transcribed in Vitro using T7 RNA polymerase (mMessage mMachine; Ambion, Austin, TX). The quality of transcripts was assessed by agarose gel electrophoresis and ethidium bromide staining and analytical UV spectroscopy. Stage V-VI Xenopus laevis oocytes were prepared as described previously (see Shimbo, K.; Brassard, D. L.; Lamb, R. A.; Pinto, L. H. Biophys. J. 1996, 70, 1335-1346). Oocytes were injected with 5-10 ng of cRNA in 50 nL/oocyte and assayed 2-3 days later. Two electrode voltage clamp recordings were carried out using TEV-200 (Dagan, Minneapolis, MN) connected to DIGIDATA 1440A and pCLAMPIO (Axon

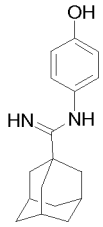
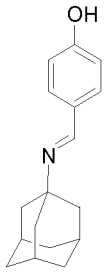
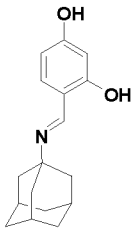
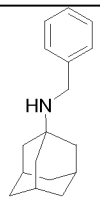
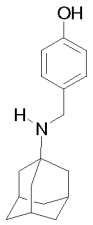
Instruments, Foster City, CA). Oocytes were superfused with Barth's solution containing 88 mM NaCl, 1 mM KCl, 2.4 mM $NaHC0_3$, 0.3 mM $NaN0_3$, 0.71 mM $CaCl_2$, 0.82 mM $MgCl_2$, and 15 mM HEPES for pH 8.5 or 15 mM MES for pH 5.5. Currents were recorded at -20 mV. Dose-inhibition curves were usually constructed by applying 1-3 concentrations per oocyte of antagonist mixed in recording pH 5.5 Barth's solution, and currents were normalized to the steady-state current obtained with pH 5.5 Barth's solution alone. Data were analyzed using the ORIGIN 8.0 software (OriginLab, Northampton, MA).

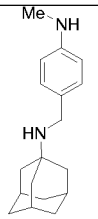
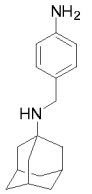
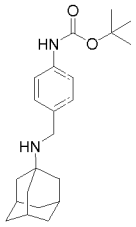
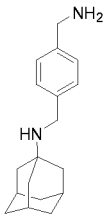
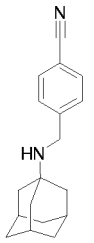
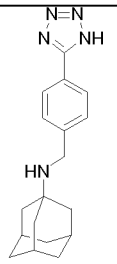
[0533] In Vitro cRNA Transcription, Heterologous Expression, and Electrophysiological Recordings. The cDNA encoding to the influenza virus A/Udorn/72 a.m.2 protein was inserted into pGEMHJ (a gift from N.Dascal Tel-Aviv University, Israel) for expression on Xenopus oocytes. Plasmid was linearized with Hindlll, and capped cRNA was transcribed in Vitro using T7 RNA polymerase (mMessage mMachine; Ambion, Austin, TX). The quality of transcripts was assessed by agarose gel electrophoresis and ethidium bromide staining and analytical UV spectroscopy. Stage V-VI Xenopus laevis oocytes were prepared as described previously (see Shimbo, K.; Brassard, D. L.; Lamb, R. A.; Pinto, L. H. Biophys. J. 1996, 70, 1335-1346). Oocytes were injected with 5-10 ng of cRNA in 50 nL/oocyte and assayed 2-3 days later. Two electrode voltage clamp recordings were carried out using TEV-200 (Dagan, Minneapolis, MN) connected to DIGIDATA 1440A and pCLAMPIO (Axon Instruments, Foster City, CA). Oocytes were superfused with Barth's solution containing 88 mM NaCl, 1 mM KCl, 2.4 mM NaHC03, 0.3 mM NaN03, 0.71 mM CaC12, 0.82 mM MgC12, and 15 mM HEPES for pH 8.5 or 15 mM MES for pH 5.5. Currents were recorded at -20 mV. Dose-inhibition curves were usually constructed by applying 1-3 concentrations per oocyte of antagonist mixed in recording pH 5.5 Barth's solution, and currents were normalized to the steady-state current obtained with pH 5.5 Barth's solution alone. Data were analyzed using the ORIGIN 8.0 software (OriginLab, Northampton, MA).

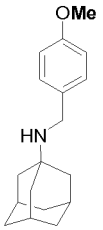
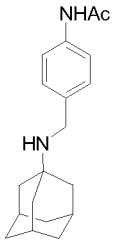
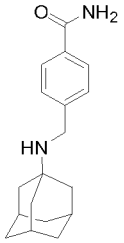
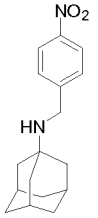
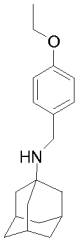
[0534] Representative compounds of the present disclosure were tested for activity using the above protocol with results summarized in Tables 1-3, below. In the tables, S31 refers to AM2 virus that possesses the wild-type serine residue at the 31 position in the M2 protein, S3IN refers to AM2 virus that possesses the serine → asparagine mutation at residue 31 in the M2 protein, and V27A refers to AM2 virus that possesses the valine → alanine mutation at residue 27 in the M2 protein. Activity range: (A) = 31-95%, (B) = 0-30%. ND: not determined.

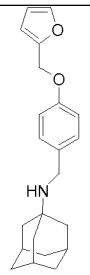
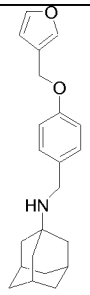
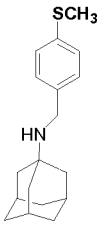
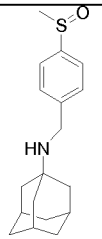
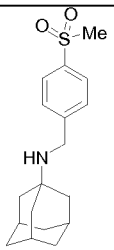
TABLE 1

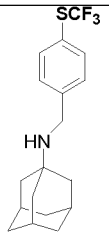
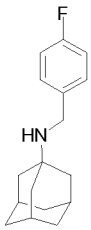
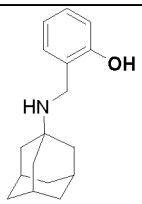
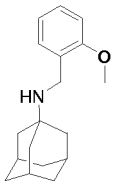
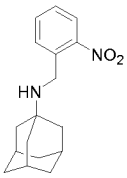
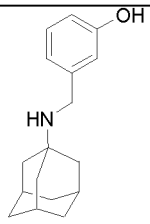
Example Number	Compound Number	Structure	S31 OOcyte Inhibition at 100 uM (%)	S31N OOcyte Inhibition at 100 uM (%)	V27A OOcyte Inhibition at 100 uM (%)
1	IMX559		B	B	B
2	IMX563		B	B	B
3	IMX558		B	B	B
4	IMX574		A	B	B

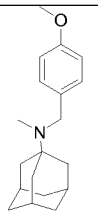
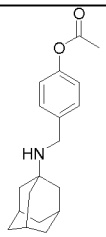
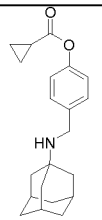
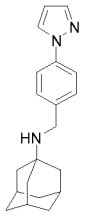
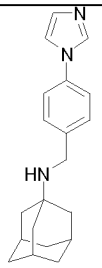
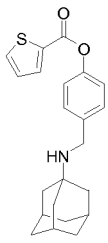
5	IMX603		A	B	B
6	IMX556		A	B	B
7	IMX 588		A	B	A
8	IMX583		A	B	B
9	IMX 557		A	A	B
10	IMX576		ND	ND	ND

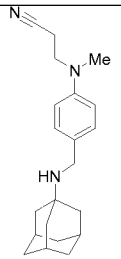
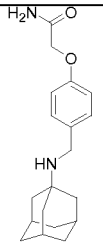
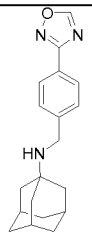
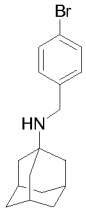
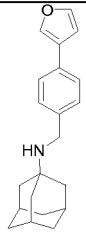
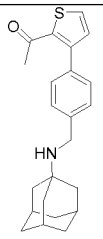
					
11	IMX 569		A	B	B
12	IMX579		B	B	B
13	IMX572		B	B	A
14	IMX571		A	B	B
15	IMX570		B	B	B

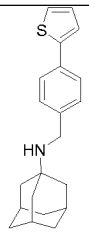
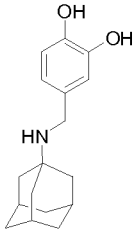
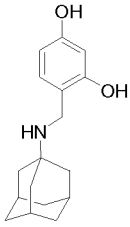
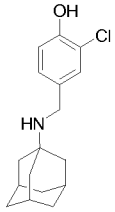
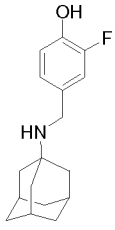
16	IMX586		A	A	A
17	IMX584		B	A	B
18	IMX585		B	B	B
19	IMX590/ M2WJ261		A	B	B
20	IMX627		B	A	B

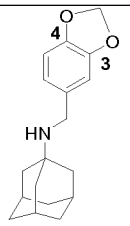
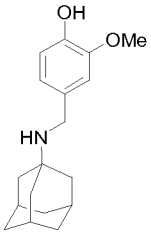
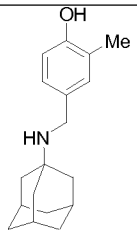
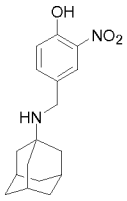
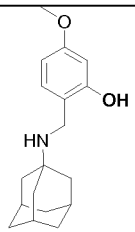
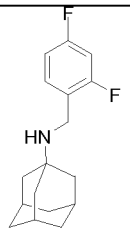
21	IMX629		A	A	A
22	IMX630		A	A	B
23	IMX613/ M2WJ275		B	A	B
24	IMX614		B	B	B
25	M2WJ305		A	B	B
26	IMX615/ M2WJ300		B	A	B

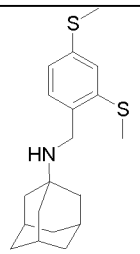
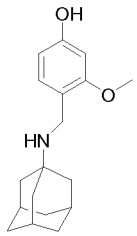
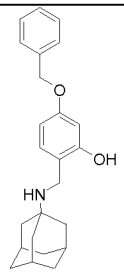
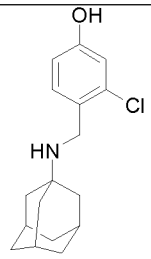
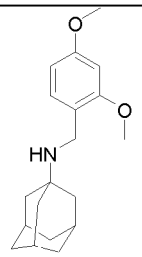
					
27	IMX6 00		A	B	B
28	IMX599		A	B	B
29	IMX598		B	B	B
30	IMX591		A	B	B
31	IMX582		A	B	A

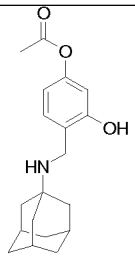
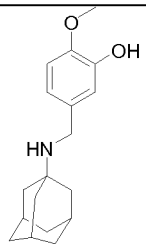
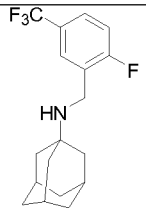
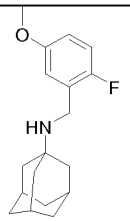
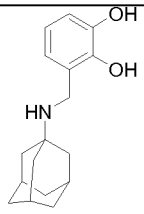
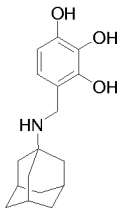
32	IMX637		A	B	B
33	M2WJ280		A	A	B
34	M2WJ312		B	B	B
35	M2WJ308		B	B	B
36	M2WJ309		B	B	B
37	M2WJ313		B	A	B

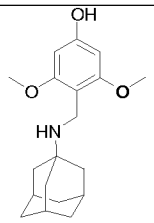
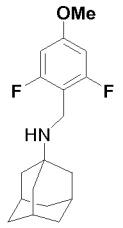
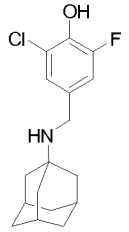
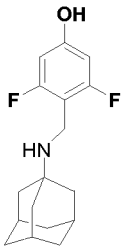
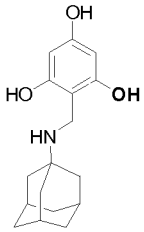
38	BC001		B	A	B
39	BC002		B	B	B
40	BC004		B	A	B
41	BC005		A	A	B
42	BC015		B	A	B
43	BC016		B	A	A

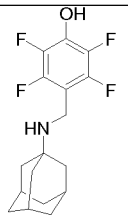
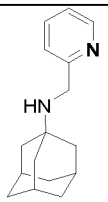
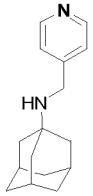
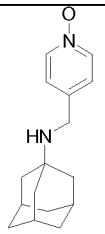
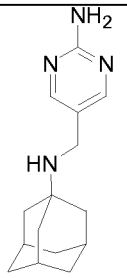
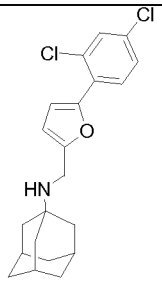
44	BC018		B	A	B
45	IMX564		A	B	A
46	IMX589		A	A	A
47	IMX 566		A	B	A
48	IMX 573		A	A	A

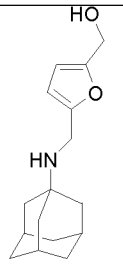
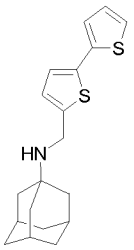
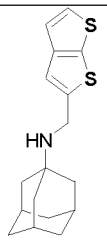
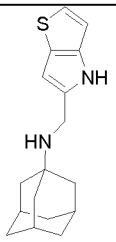
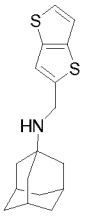
49	IMX580		A	B	B
50	IMX581		A	B	A
51	IMX567		A	B	B
52	M2WJ259		A	B	A
53	IMX597		A	A	B
54	IMX625		A	B	B

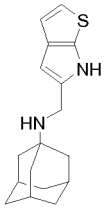
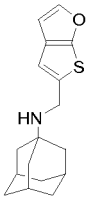
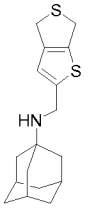
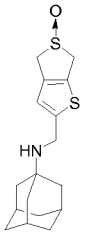
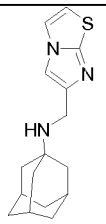
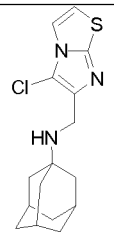
55	IMX620		B	B	B
56	IMX 596		B	B	B
57	IMX636		A	A	B
58	M2WJ279		A	B	A
59	M2WJ296		B	B	B

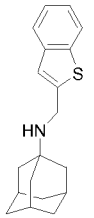
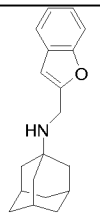
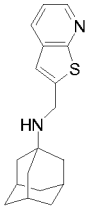
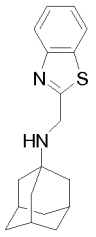
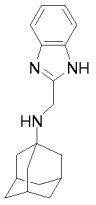
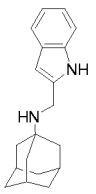
60	M2WJ307		A	A	B
61	M2WJ290		A	B	A
62	M2WJ268		B	B	B
63	M2WJ277		A	B	B
64	M2WJ281		A	B	A
65	IMX624		B	B	A

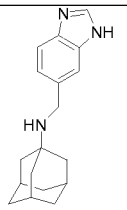
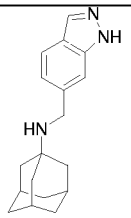
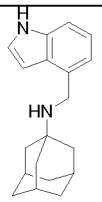
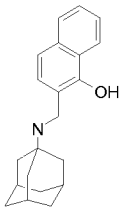
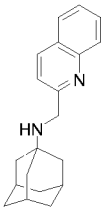
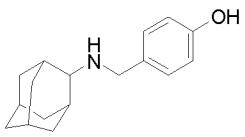
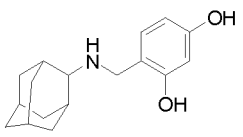
66	IMX595		A	B	B
67	IMX611		A	B	B
68	IMX568		A	B	B
69	IMX612		A	B	A
70	IMX594		B	B	B
71	M2WJ260		B	B	A

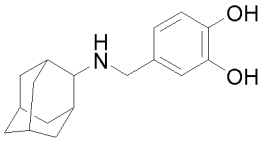
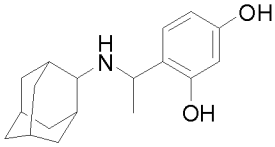
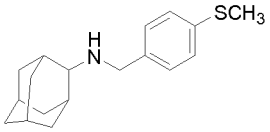
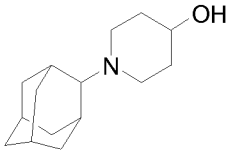
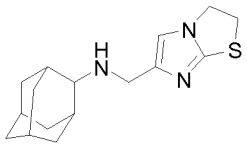
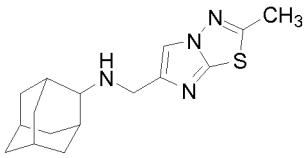
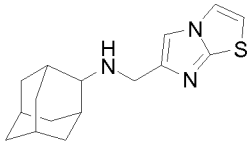
					
72	IMX593		B	B	B
73	IMX592		A	B	B
74	M2WJ306		B	B	B
75	IMX587		A	B	B
76	IMX641		ND	ND	ND

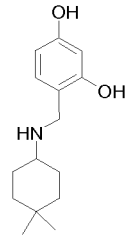
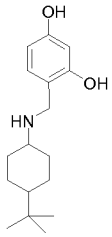
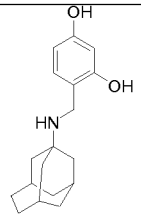
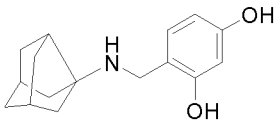
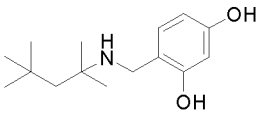
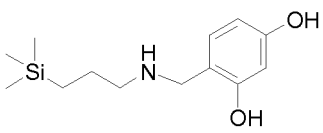
77	IMX604		B	B	B
78	BC007		B	A	B
79	IMX606		A	A	B
80	IMX610		A	A	B
81	IMX621		A	A	B

82	IMX634		A	A	B
83	IMX635		A	A	B
84	IMX648		A	A	B
85	IMX644		B	B	B
86	M2WJ264		A	A	B
87	M2WJ298		B	B	B

88	IMX622		B	A	B
89	IMX631		B	A	B
90	IMX626		B	B	B
91	IMX632		B	A	B
92	IMX633		B	A	B
93	IMX642		B	A	B

94	IMX623		B	B	B
95	M2WJ311		A	B	A
96	M2WJ303		A	B	A
97	IMX639		A	A	B
98	IMX640		A	A	B
99	M2WJ271		A	B	B
100	M2WJ272		A	B	A

101	M2WJ273		A	B	B
102	M2WJ286		A	B	A
103	M2WJ297		B	A	A
104	M2WJ286		B	B	B
105	M2WJ299		A	B	B
106	M2WJ302		B	B	A
107	M2WJ314		A	B	B

108	M2WJ282		A	B	B
109	M2WJ294		A	B	A
110	M2WJ285		A	A	A
111	M2WJ284		A	A	B
112	M2WJ287		A	B	A
113	M2WJ283		A	B	B

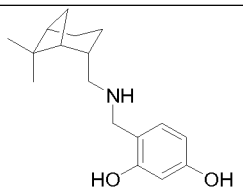
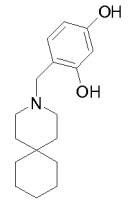
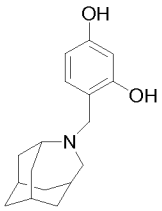
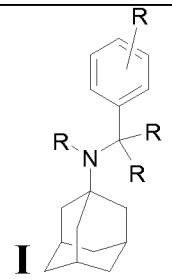
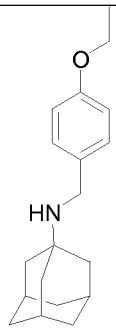
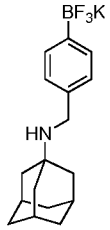
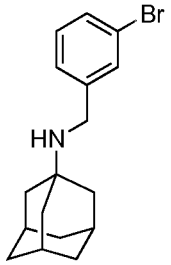
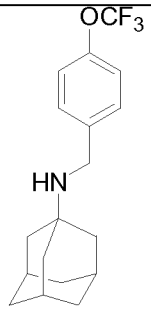
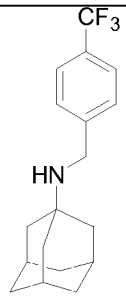
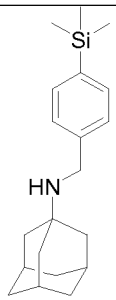
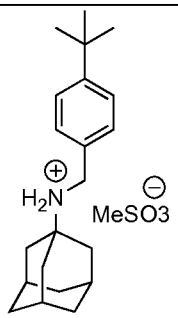
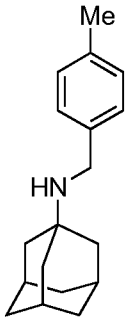
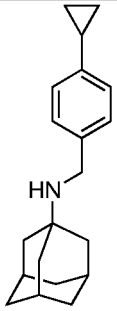
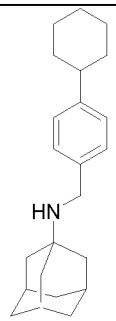
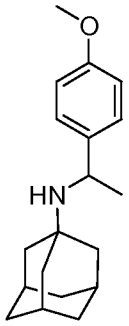
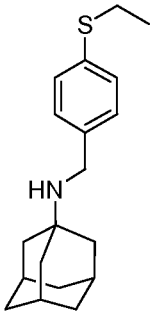
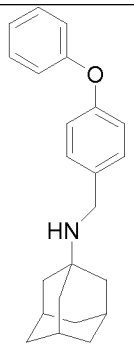
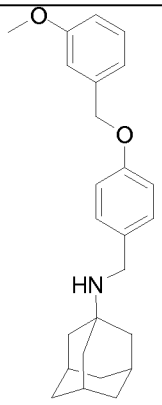
114	M2WJ293		A	B	B
115	M2WJ288		A	B	B
116	M2WJ292		A	B	A

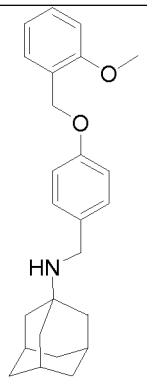
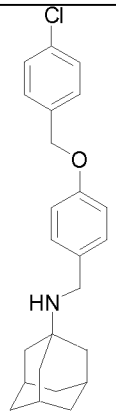
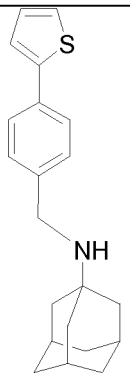
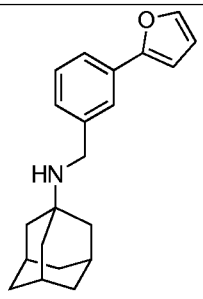
TABLE 2

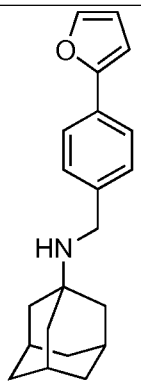
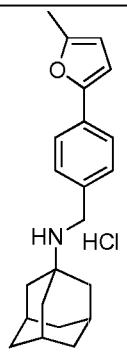
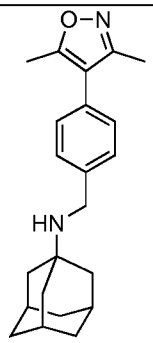
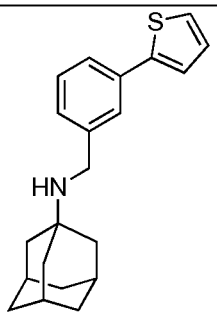
Example #	**Batch External ID**	**Structure**	**S31 OOcyte Inhibition at 100 uM (%)**	**S31N OOcyte Inhibition at 100 uM (%)**	**V27A OOcyte Inhibition at 100 uM (%)**
		 **I**			

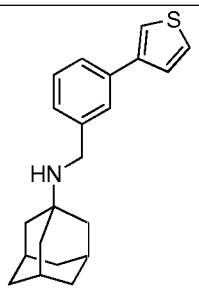
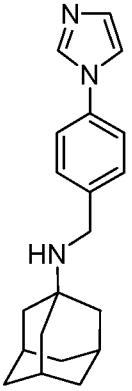
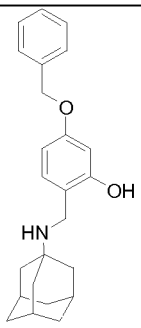
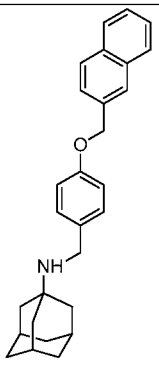
1a	**IMX00627**		B	A	B
2a	BC063		A	B	A
3a	BC020		A	B	B
4a	IMX00673		B	B	B
5a	IMX00674		B	B	B

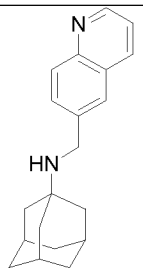
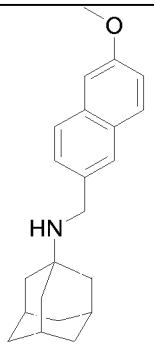
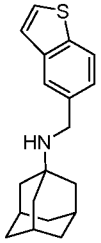
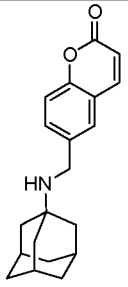
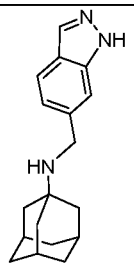
6a	IMX00676		B	A	B
7a	BC014		B	A	B
8a	BC076		A	B	ND
9a	BC080		A	A	ND
10a	IMX00678		B	A	B

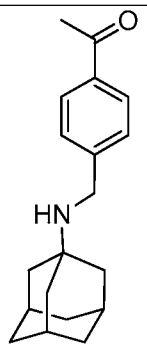
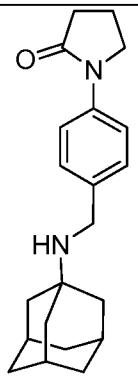
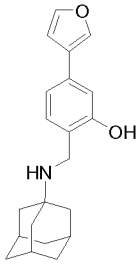
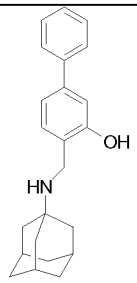
11a	WFD093, hij294		A	A	A
12a	WFD023		B	A	B
13a	IMX00657		A	A	B
14a	IMX00649		B	A	B

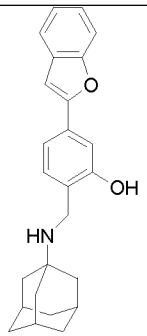
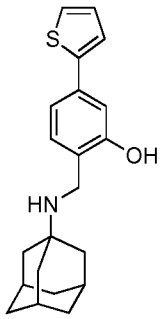
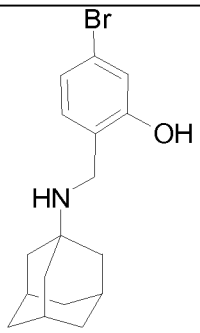
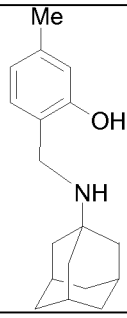
15a	IMX00650		B	A	B
16a	IMX00651		A	A	B
29a	BC018_2		B	A	B
30a	BC026		B	B	A

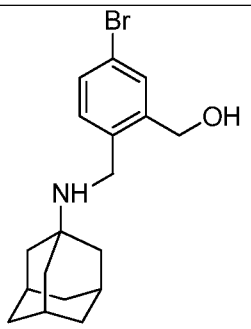
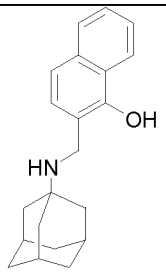
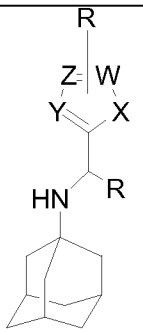
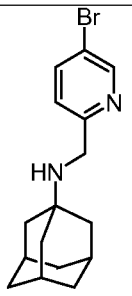
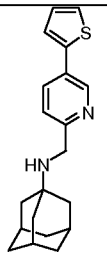
31a	BC032		B	A	B
32a	BC047		B	A	B
33a	BC046		B	B	B
34a	BC025		B	B	A

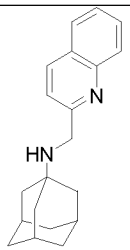
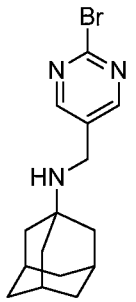
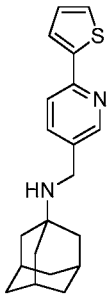
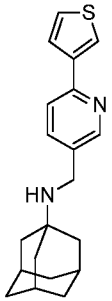
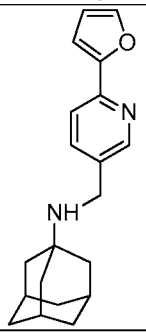
35a	BC034		B	B	A
36a	WFD029		16.1	26.9	ND
37a	IMX00636		A	A	B
38a	M2WJ328		B	B	B

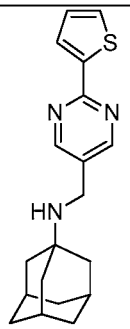
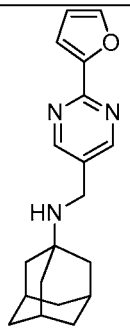
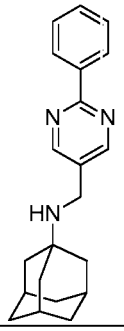
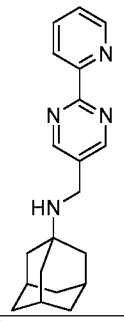
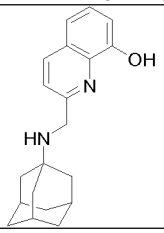
39a	IMX00681		B	A	B
40a	IMX00682		B	B	A
41a	WFD115		A	B	A
42a	M2WJ337, WFD123		B	B	B
43a	WFD119		A	B	ND

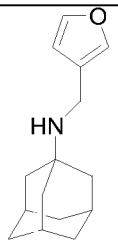
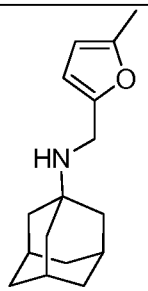
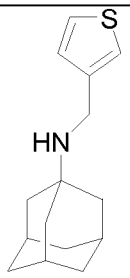
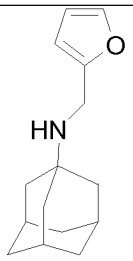
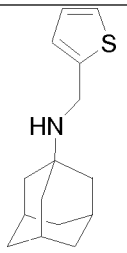
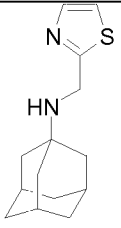
44a	WFD008		B	B	B
45a	WFD014		B	A	B
46a	BC-090		B	A	ND
47a	IMX00661		B	A	B

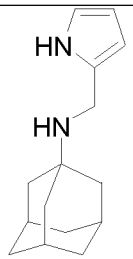
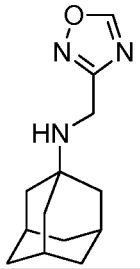
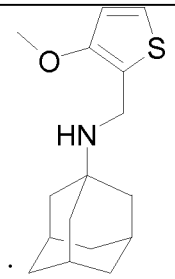
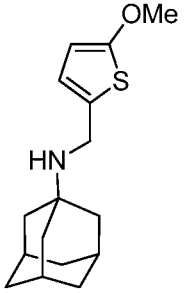
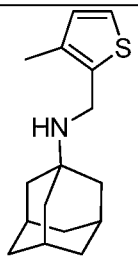
48a	IMX00660		B	B	B
49a	BC073		B	B	ND
50a	M2WJ325		A	A	B
51a	BC081		A	A	ND

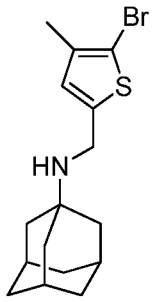
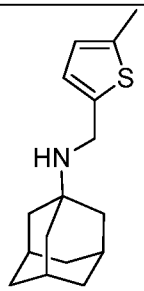
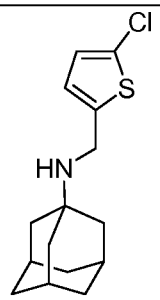
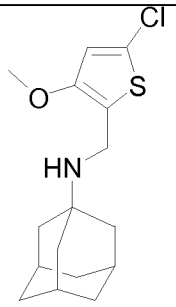
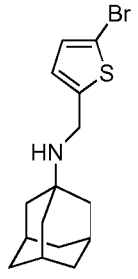
52a	M2WJ326		B	B	B
53a	IMX00639		A	A	B
II.					
54a	IMX00710		A	A	ND
55a	IMX00711		A	A	ND

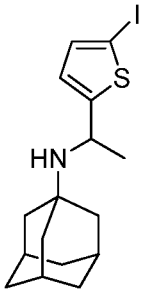
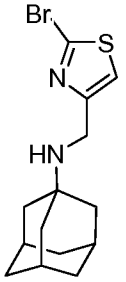
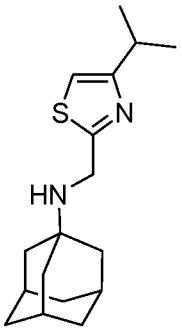
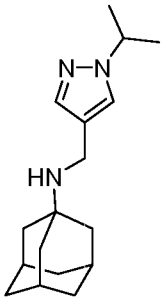
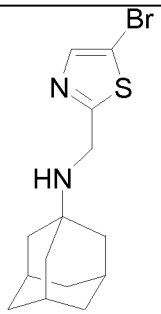
56a	IMX00640		A	A	B
57a	M2WJ387		B	B	ND
58a	M2WJ383		A	A	ND
59a	M2WJ385		B	A	ND
60a	M2WJ329		B	A	B

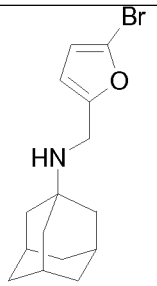
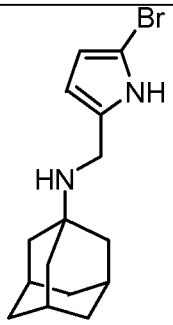
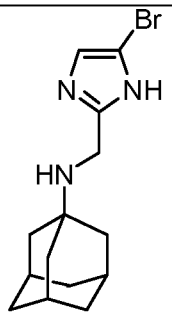
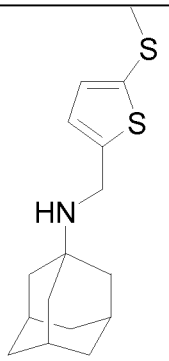
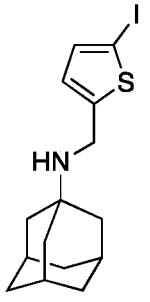
61a	M2WJ330		B	A	B
62a	M2WJ336		B	A	B
63a	M2WJ391		B	A	ND
64a	M2WJ392		B	B	ND
65a	M2WJ322		A	B	B

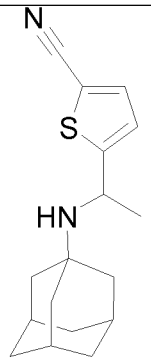
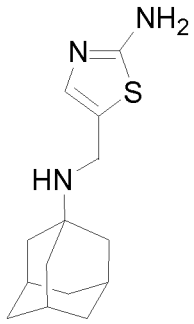
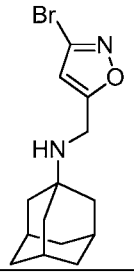
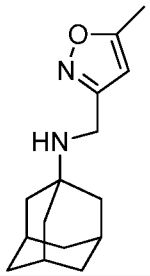
66a	IMX00616		A	B	B
67a	WFD047		A	A	ND
68a	IMX00617		A	B	A
69a	IMX00667 and WFD046		A	B	B
70a	IMX00668		A	B	B
71a	WFD079 and IMX00669		A	A	B

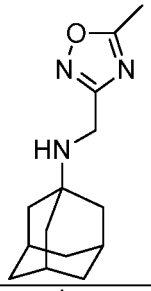
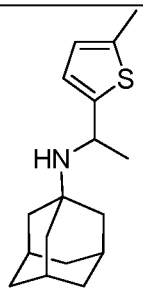
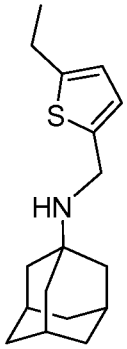
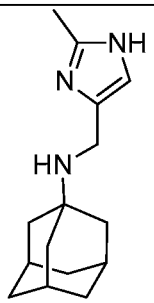
72a	IMX00697		A	B	ND
73a	M2WJ396		A	A	ND
74a	IMX00686		A	A	B
75a	WFD050		A	A	B
76a	WFD053		A	B	B

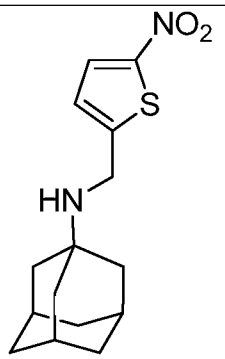
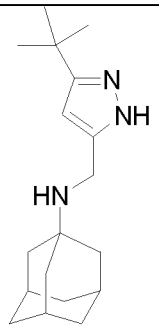
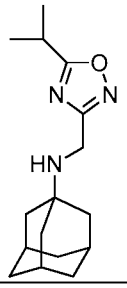
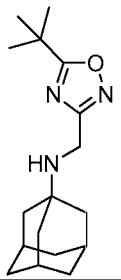
77a	M2WJ338		A	A	A
78a	WFD049		A	A	A
79a	WFD052		A	A	B
80a	IMX00687		A	B	B
81a	BC035		A	A	B

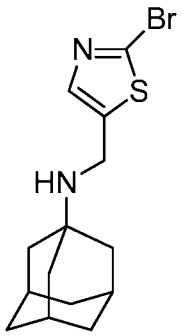
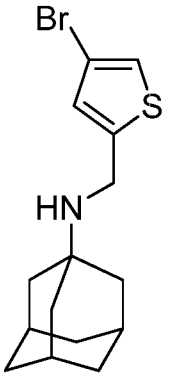
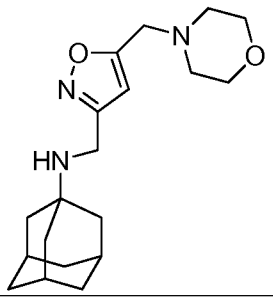
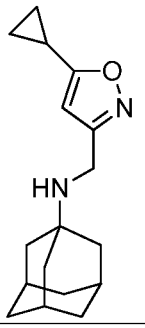
82a	M2WJ341		A	B	A
83a	WFD082		A	A	B
84a	WFD084		B	B	ND
85a	WFD073		B	B	ND
86a	IMX00671		B	A	B

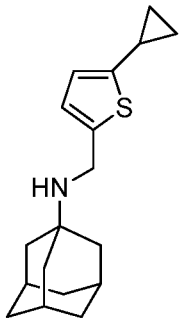
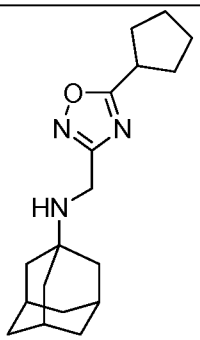
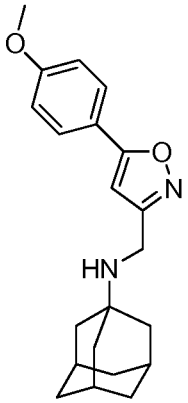
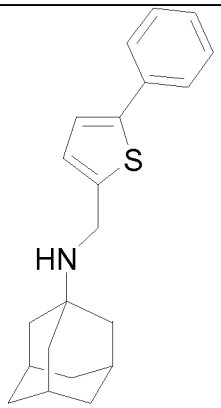
87a	IMX00688		A	B	B
88a	IMX00698		A	A	ND
89a	IMX00701		A	A	ND
90a	M2WJP001 and IMX00689		A	A	ND
91a	BC067		A	A	ND

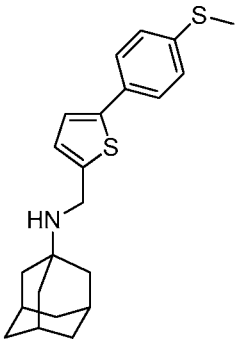
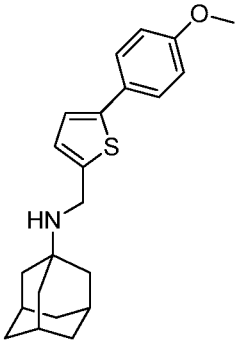
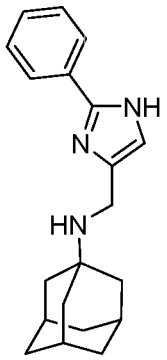
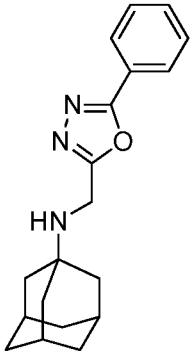
92a	WFD058		A	B	B
93a	WFD085		A	B	ND
94a	M2WJ364		B	A	ND
95a	M2WJ369		A	A	ND
96a	M2WJ405		A	A	ND

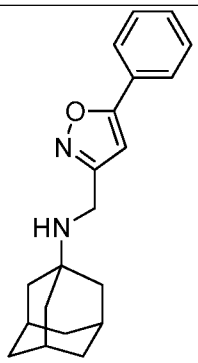
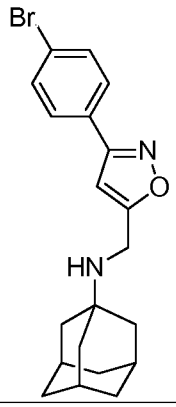
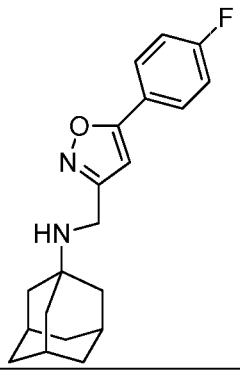
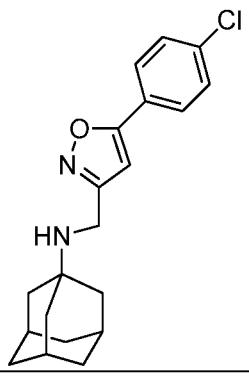
					
97a	WFD057, hij-p011		B	B	B
98a	hij-313		A	A	B
99a	WFD069		B	B	B

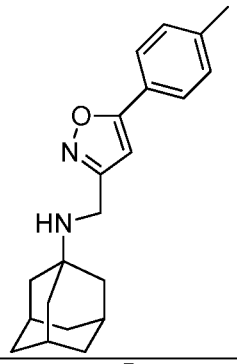
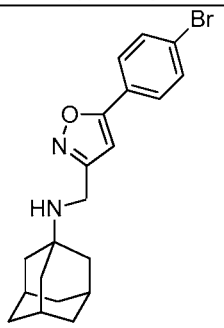
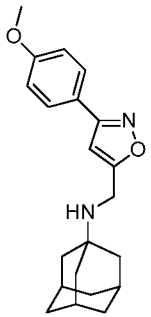
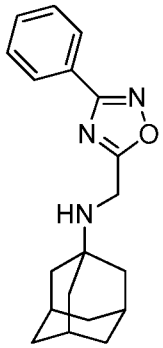
100a	WFD061		A	B	A
101a	M2WJ335		B	B	B
102a	M2WJ400		B	A	ND
103a	M2WJ401		B	A	ND
104a	M2WJ349		B	A	B

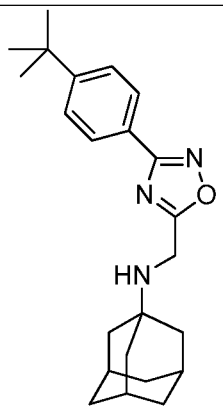
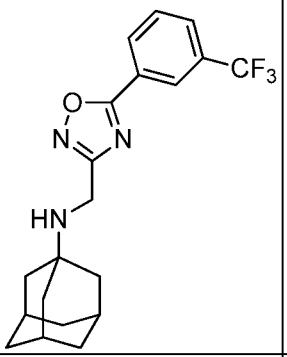
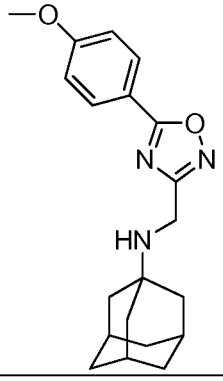
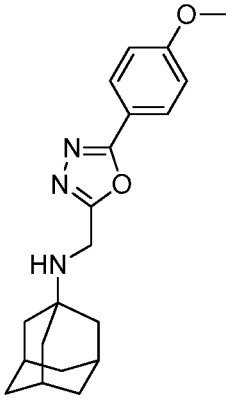
					
105a	M2WJ350		A	A	B
106a	M2WJ371		B	B	ND
107a	M2WJ379		B	A	ND
108a	M2WJ395		B	A	ND

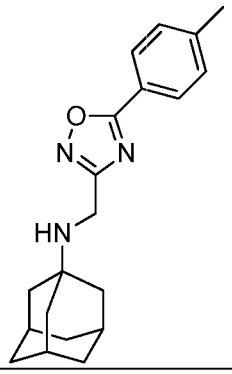
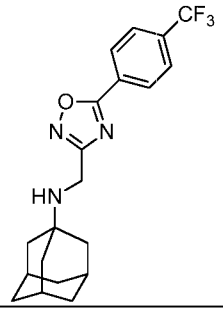
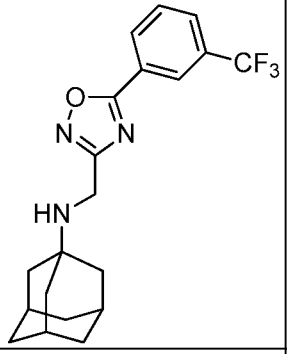
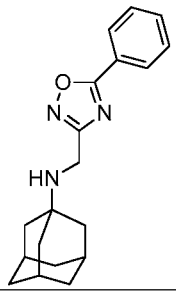
					
109a	M2WJ403		B	A	ND
110a	M2WJ358		B	A	B
111a	WFD060 and IMX00666		B	A	A

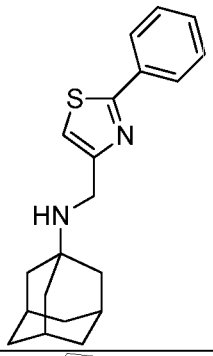
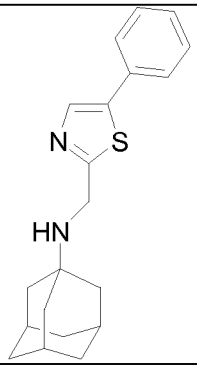
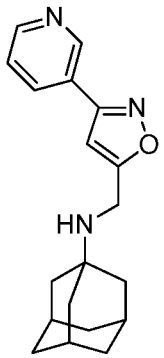
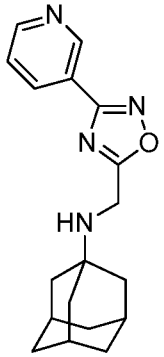
112a	M2WJ343		B	A	B
113a	M2WJ344		B	A	B
114a	WFD070		A	B	ND
115a	M2WJ351		B	A	B

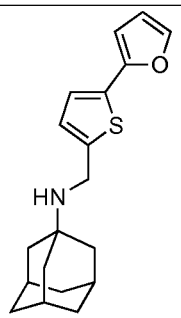
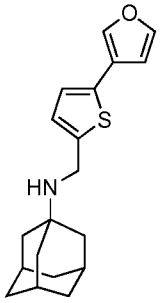
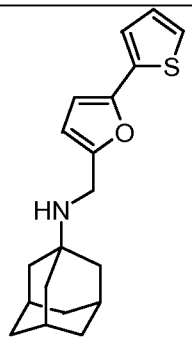
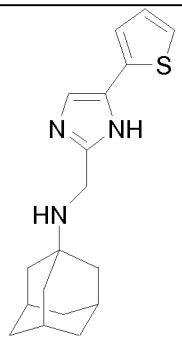
116a	M2WJ352		B	A	B
117a	M2WJ361		B	B	ND
118a	M2WJ366		B	A	ND
119a	M2WJ367		B	A	ND

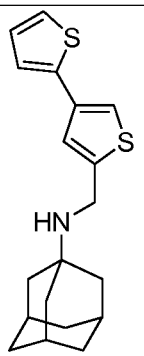
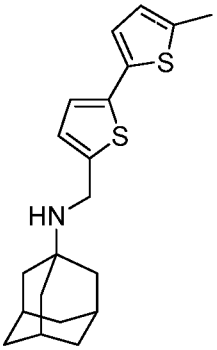
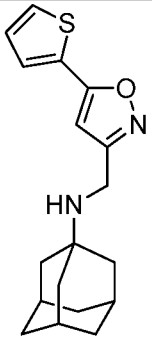
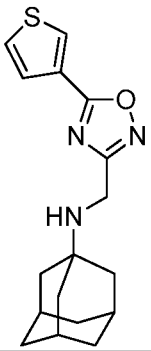
120a	M2WJ368		B	A	ND
121a	M2WJ370		B	A	ND
122a	M2WJ386		B	A	ND
123a	M2WJ376		B	A	ND
124a	M2WJ377		B	B	ND

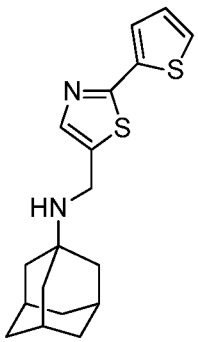
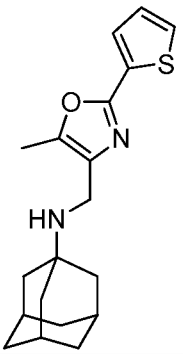
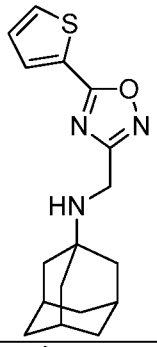
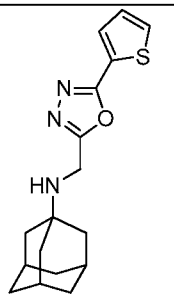
					
125a	M2WJ398		B	A	ND
126a	M2WJ378		B	A	ND
127a	M2WJ356		B	A	B

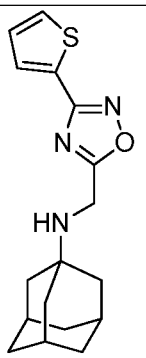
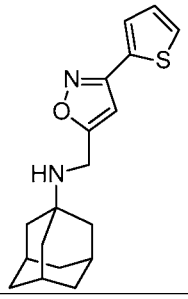
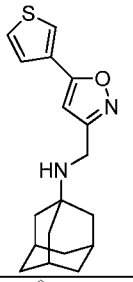
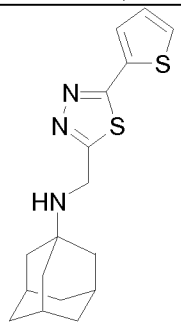
128a	M2WJ393		B	A	ND
129a	M2WJ397		B	A	ND
130a	M2WJ398		B	A	ND
131a	M2WJ399		B	A	ND

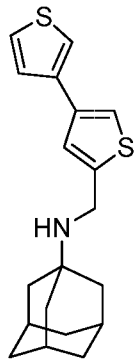
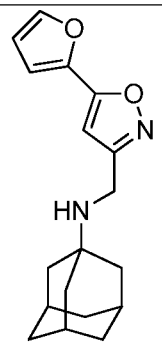
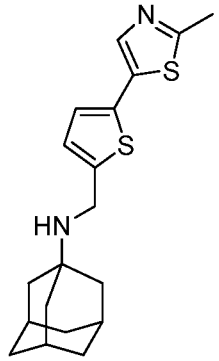
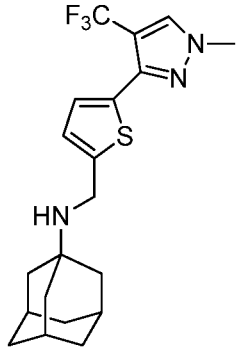
132a	M2WJ402		B	B	ND
133a	IMX00672		ND	ND	ND
134a	M2WJ380		B	A	ND
135a	M2WJ381		B	A	ND
136a					

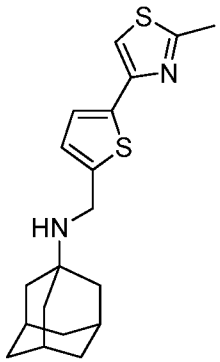
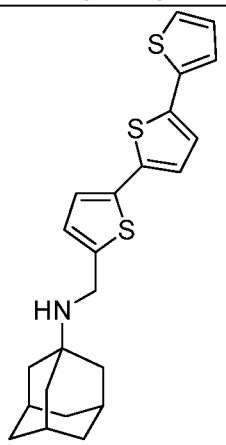
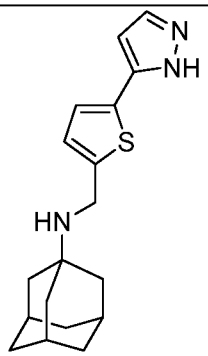
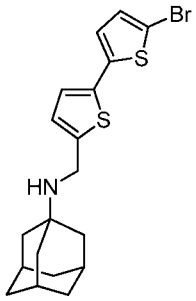
	BC041		B	A	B
137a	BC042		B	A	B
138a	IMX00703		B	A	ND
139a	IMX00702		ND	ND	ND
140a	M2WJ354		B	A	A

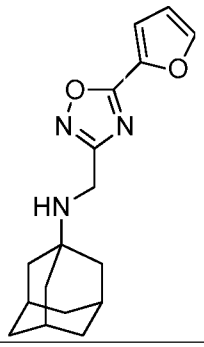
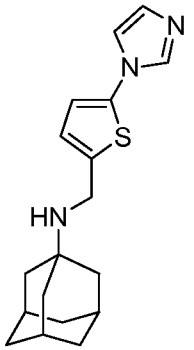
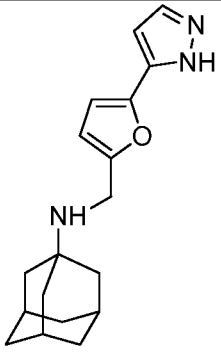
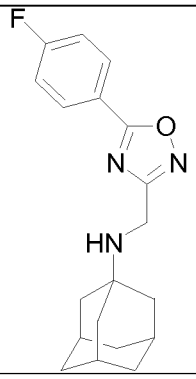
					
141a	M2WJ357		B	A	B
142a	M2WJ332		B	A	B
143a	M2WJ359		B	A	B
144a	M2WJ360		B	A	B

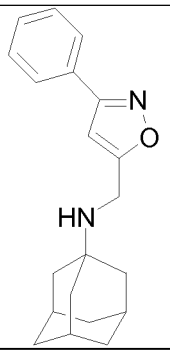
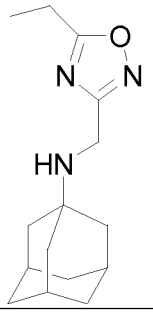
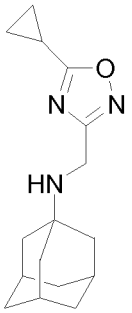
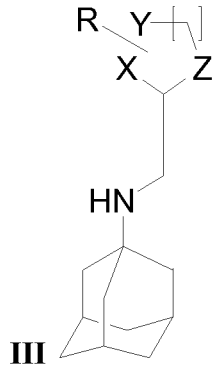
					
145a	M2WJ384		B	B	ND
146a	M2WJ389		B	A	ND
147a	M2WJ390		B	A	
148a	M2WJ363		B	A	ND

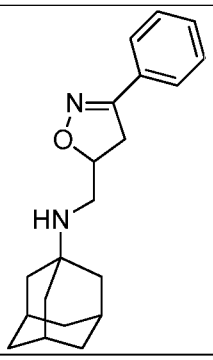
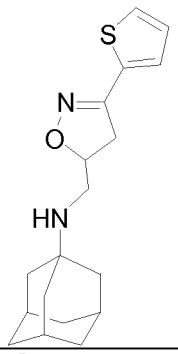
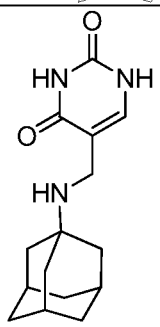
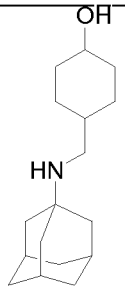
					
149a	M2WJ372		B	A	ND
150a	M2WJ374		B	A	ND
151a	JZW036 and M2WJ375		B	A	ND

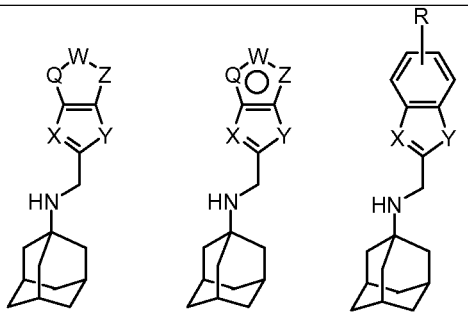
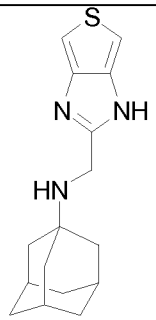
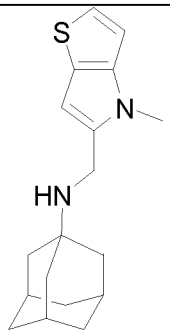
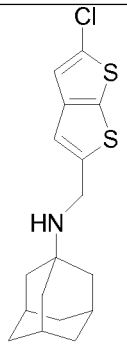
152a	M2WJ321		B	B	A
153a	M2WJ347		B	A	B
154a	M2WJ348		B	A	A
155a	M2WJ340		B	B	B
156a	M2WJ362		B	A	A

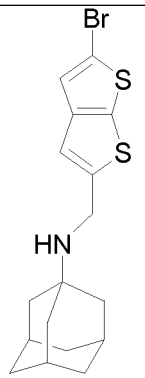
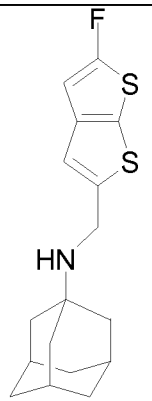
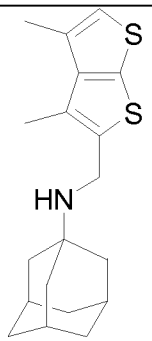
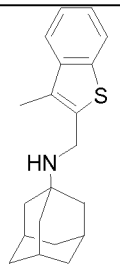
					
157a	M2WJ339		B	B	B
158a	M2WJ331		B	A	A
159a	M2WJ334		B	A	B

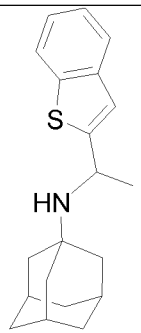
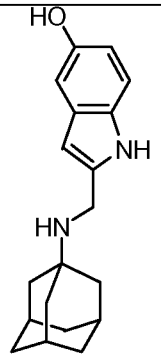
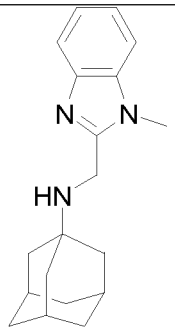
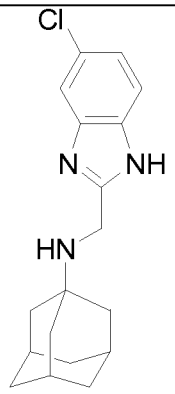
160a	M2WJ394		B	A	ND
161a	M2WJ365		B	B	ND
162a	M2WJ327		B	B	B
163a	M2WJ406		B	A	ND

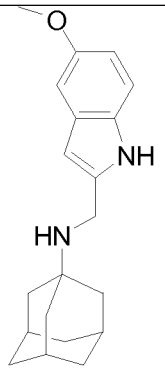
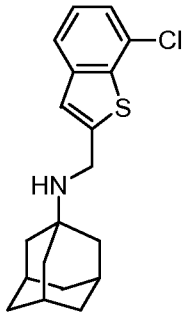
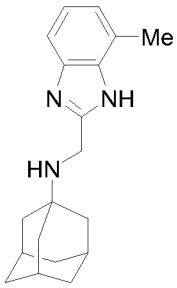
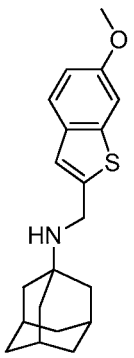
164a	M2WJ353		B	A	ND
165a	M2WJ408		A	A	ND
166a	M2WJ409		B	A	ND
		 **III**			
167a	M2WJ388		B	A	ND

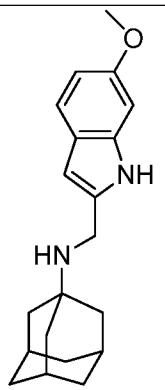
					
168a	M2WJ373		B	A	ND
169a	WFD110		B	B	B
170a	IMX00677		B	B	B

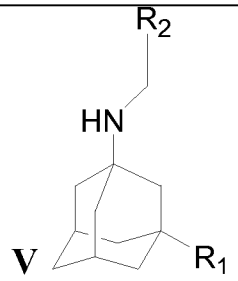
 **IV** X, Y, Z, Q, W, CR, NH, NR, O, S					
171a	IMX00683		B	A	B
172a	IMX00685		B	B	B
173a	IMX00735		A	A	TBD

174a	IMX00714		ND	ND	ND
175a	JZW162		ND	ND	ND
176a	M2WJ333		B	B	B
177a	IMX00643		A	B	B

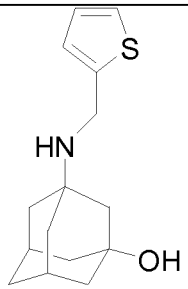
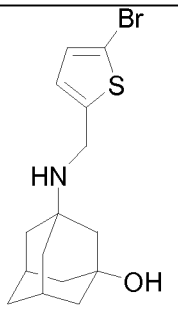
178a	CMF004		A	B	A
179a	IMX00705/ M2WJ323		B	B	B
180a	IMX00692		B	B	ND
181a	IMX00693		B	A	ND

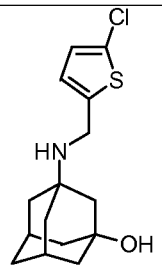
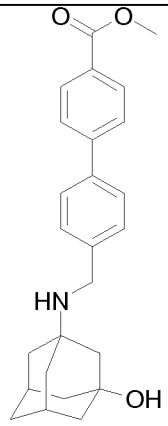
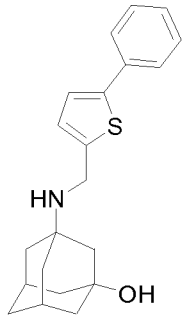
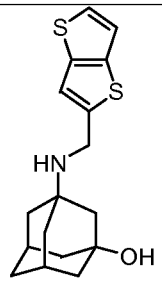
182a	IMX00696		B	A	ND
183a	IMX00713		A	B	ND
184a	IMX00721		B	A	ND
185a	M2WJ345		B	A	B

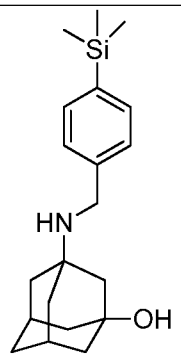
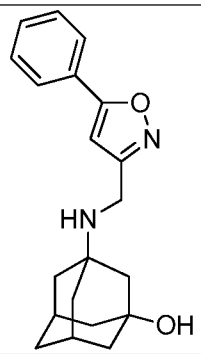
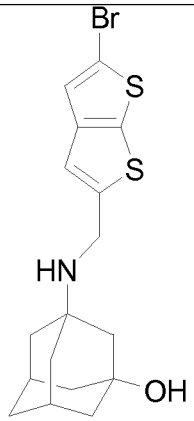
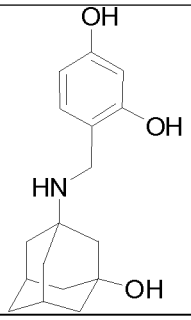
186a	M2WJ346		B	A	B

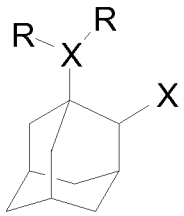
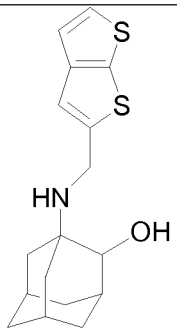
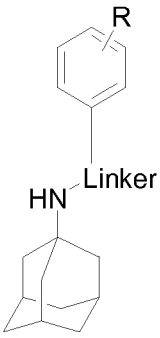
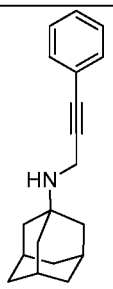


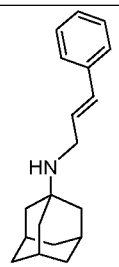
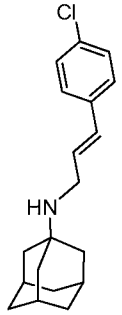
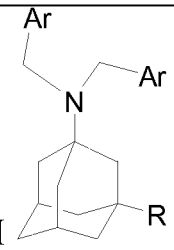
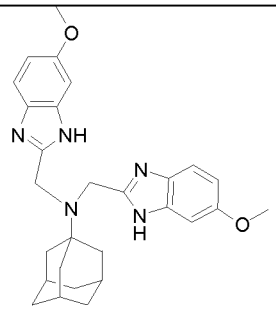
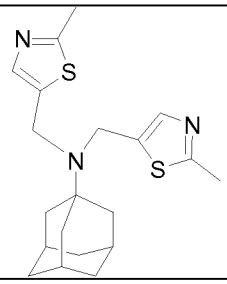
V R1= OH, OR, N, X

187a	IMX00684		B	A	B
188a	IMX00680		B	A	ND

189a	IMX00716		B	B	TBD
190a	IMX00691		B	A	ND
191a	IMX00690		B	A	B
192a	IMX706		B	A	ND

193a	M2WJ404		B	A	ND
194a	M2WJ382		B	A	ND
195a	IMX00733		B	A	ND
196a	Imx00727		B	A	ND

		 **VI:** X = N, O			
197a	IMX00737		ND	ND	ND
		 **VII:**			
198a	hij-306		B	A	B

199a	CFM001		B	A	B
200a	hij-307		B	A	B
		 **VIII**			
201a	IMX00732		B	B	ND
202a	M2WJ416		B	B	ND
Other					

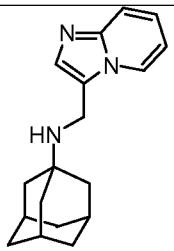
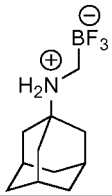
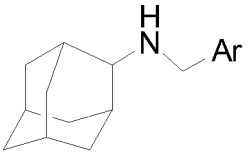
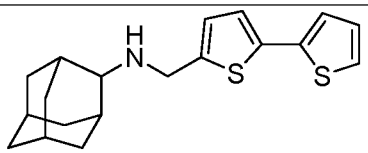
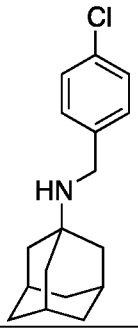
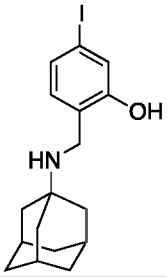
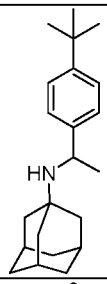
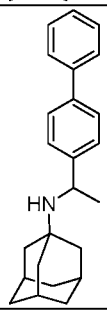
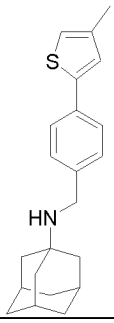
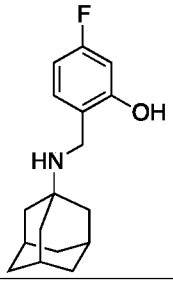
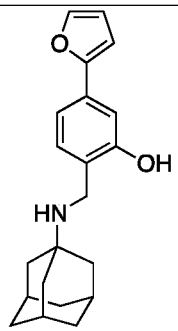
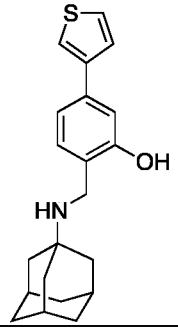
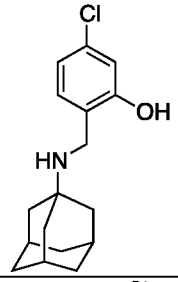
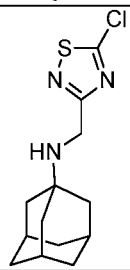
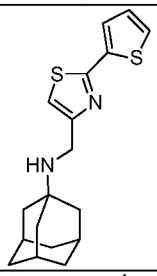
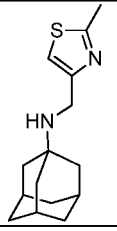
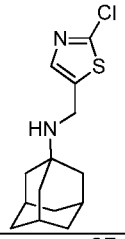
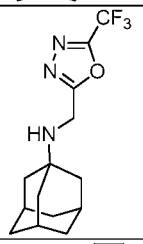
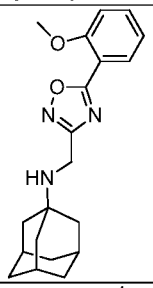
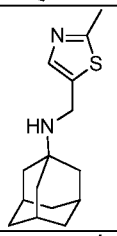
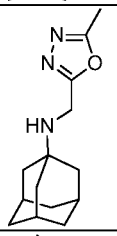
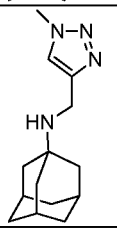
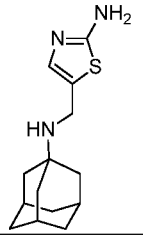
203a	IMX00709		A	B	B
204a	BC059		A	B	B
IX: 					
205a	M2WJ324		B	A	B

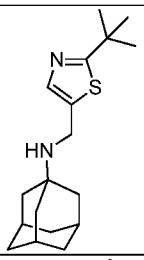
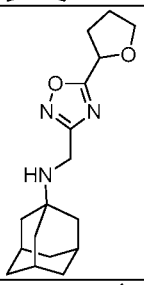
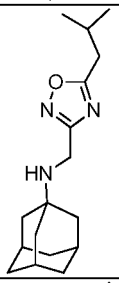
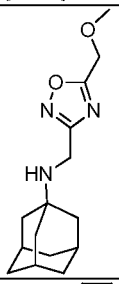
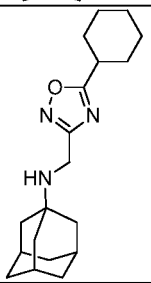
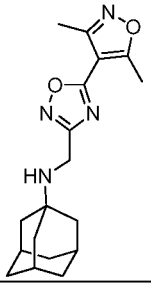
TABLE 3

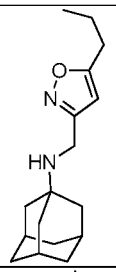
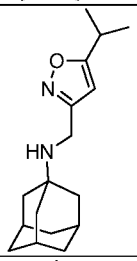
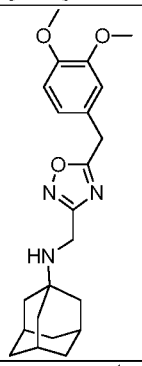
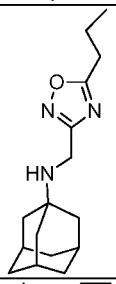
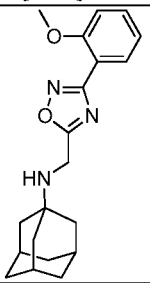
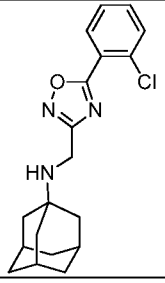
Example #	Batch External ID	Structure	S31 OOcyte Inhibition at 100 uM (%)	S31N OOcyte Inhibition at 100 uM (%)	V27A OOcyte Inhibition at 100 uM (%)
1b	BC085		A	A	ND

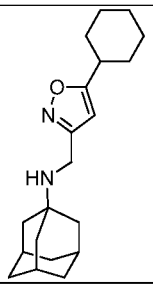
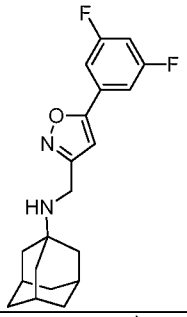
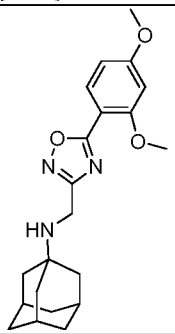
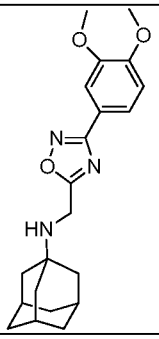
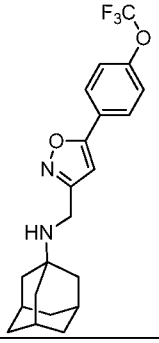
2b	BC089		A	A	ND
3b	Hij339-1		B	B	ND
4b	Hij334-1		A	B	ND
5b	BC045		B	A	ND
6b	BC102		A	A	ND

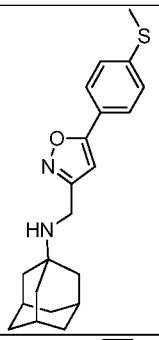
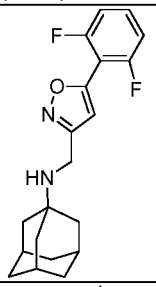
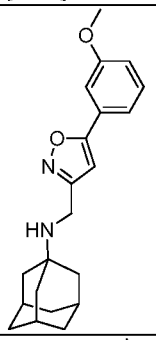
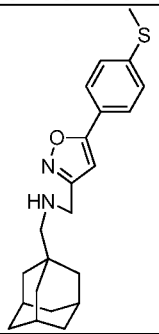
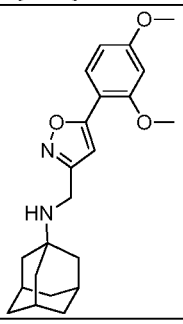
7b	BC113		B	A	ND
8b	BC114		B	A	ND
9b	BC100		A	A	ND
10b	M2WJ410-1		A	A	ND
11b	M2WJ411-1		B	A	ND
12b	M2WJ412-1		A	A	ND

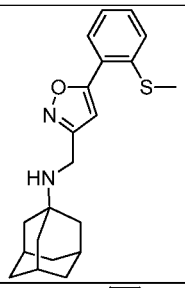
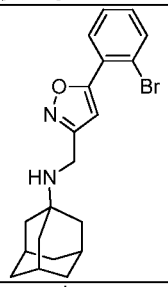
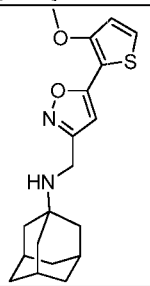
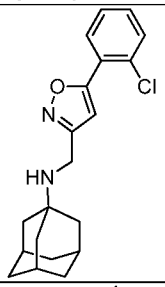
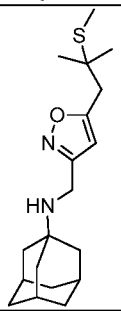
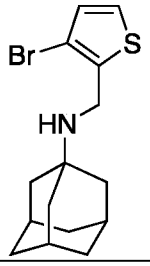
13b	M2WJ413-1		A	B	ND
14b	M2WJ414-1		B	A	ND
15b	M2WJ415-1		B	A	ND
16b	M2WJ417-1		B	B	ND
17b	M2WJ419-1		B	A	ND
18b	M2WJ420-1		B	B	ND
19b	M2WJ421-1		B	B	ND

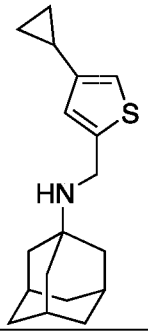
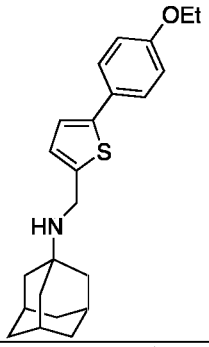
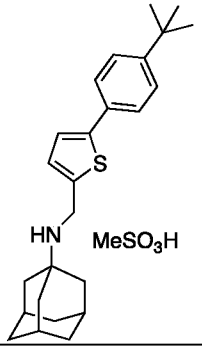
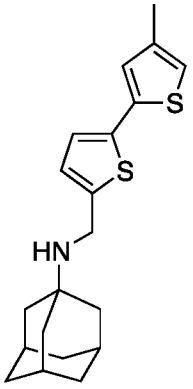
20b	M2WJ422-1		B	A	ND
21b	M2WJ423-1		B	A	ND
22b	M2WJ4241		B	A	ND
23b	M2WJ426-1		B	A	ND
24b	M2WJ428-1		A	A	ND
25b	M2WJ430-1		B	B	ND

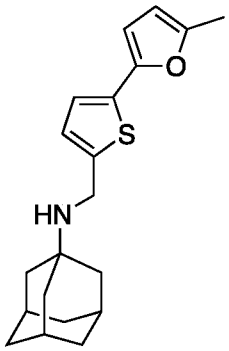
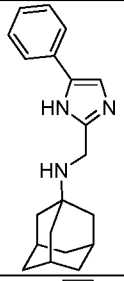
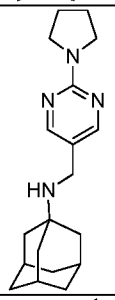
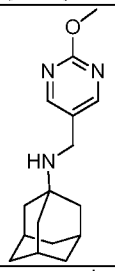
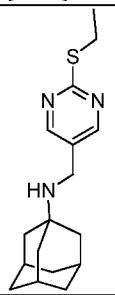
26b	M2WJ431-1		B	A	ND
27b	M2WJ432-1		B	A	ND
28b	M2WJ434-1		B	A	ND
29b	M2WJ437-1		B	A	ND
30b	M2WJ438-1		B	A	ND
31b	M2WJ439-1		B	A	ND

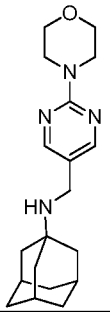
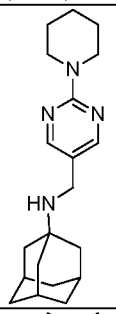
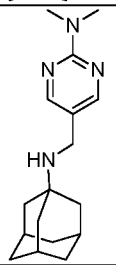
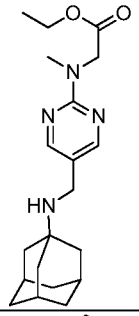
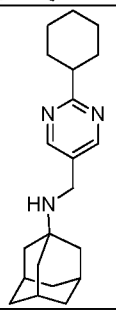
32b	M2WJ442-1		B	A	ND
33b	M2WJ442-1		B	A	ND
34b	M2WJ444-1		B	A	ND
35b	M2WJ445-1		B	A	ND
36b	M2WJ446-1		B	B	ND

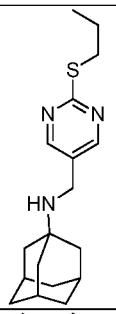
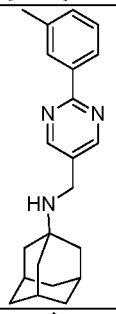
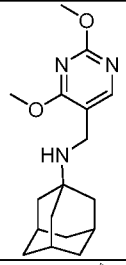
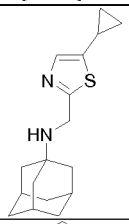
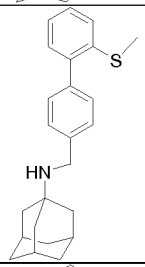
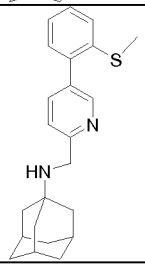
37b	M2WJ447-1		B	A	ND
38b	M2WJ448-1		B	A	ND
39b	M2WJ449-1		B	A	ND
40b	M2WJ451-1		B	A	ND
41b	M2WJ452-1		B	A	ND

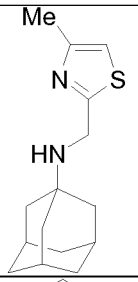
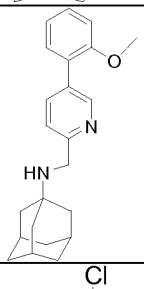
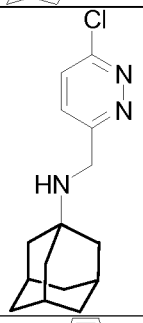
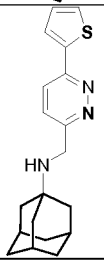
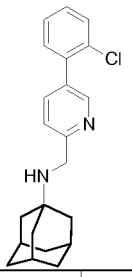
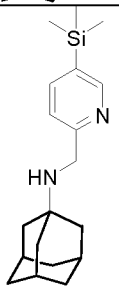
42b	M2WJ454-1		B	A	ND
43b	M2WJ455-1		B	A	ND
44b	M2WJ456-1		B	A	ND
45b	M2WJ457-1		B	A	ND
46b	M2WJ458-1		B	A	ND
47b	BC097		A	B	ND

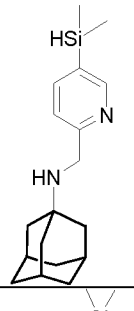
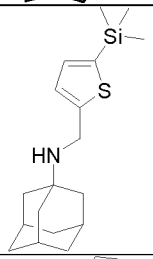
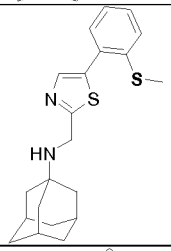
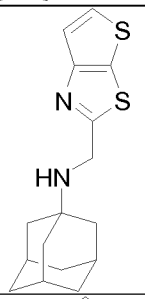
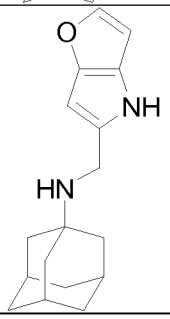
48b	BC119		B	A	ND
49b	BC120		B	A	ND
50b	BC121		B	A	ND
51b	BC070		B	A	ND

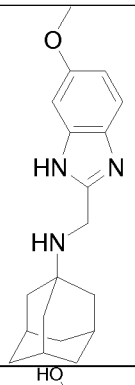
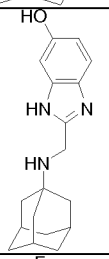
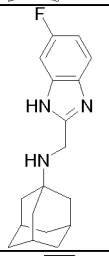
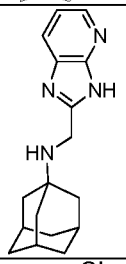
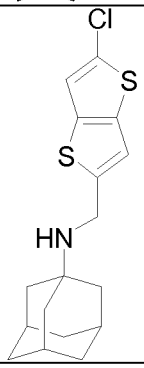
52b	BC071		B	A	ND
53b	Hij411-1/ JZW123		B	A	ND
54b	Hij372-1		B	A	ND
55b	Hij374-1		B	A	ND
56b	Hij381-1		B	A	ND

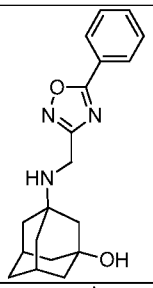
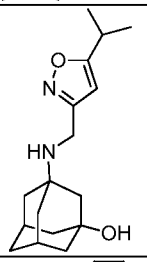
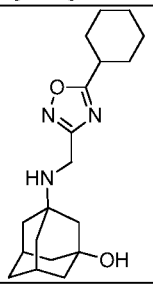
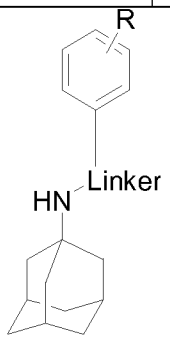
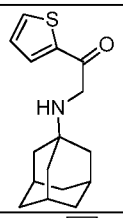
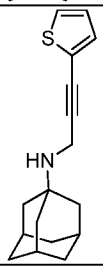
57b	Hij405-1		B	A	ND
58b	Hij382-1		B	A	ND
59b	WFD108-1		B	A	ND
60b	Hij415-1		B	A	ND
61b	Hij414-1		B	A	ND

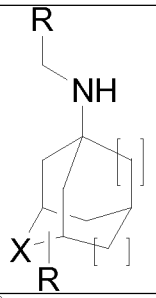
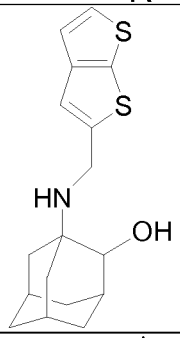
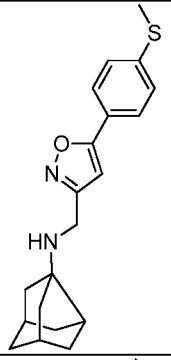
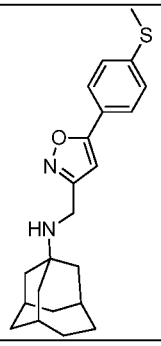
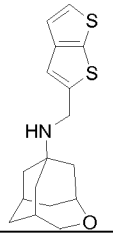
62b	Hij416-1		B	A	ND
63b	Hij417-1		B	A	ND
64b	Hij406-1		B	B	ND
65b	IMX760		B	A	ND
66b	Imx747		B	A	TBD
67b	IMX745		A	A	ND

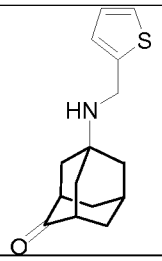
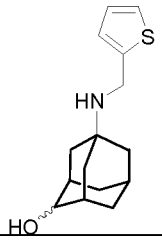
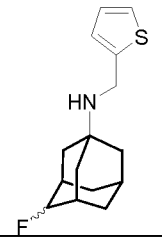
68b	IMX746		A	A	ND
69b	IMX744		B	A	ND
70b	IMX747		A	B	ND
71b	IMX748		B	A	ND
72b	IMX755		B	A	ND
73b	IMX756		ND	ND	ND

74b	IMX757		ND	ND	ND
75b	IMX734		B	A	ND
76b	IMX742		B	A	ND
77b	**IMX00751**		B	A	ND
78b	**IMX738**		A	A	ND

79b	IMX724		B	A	ND
80b	IMX725		ND	ND	ND
81b	IMX722		ND	ND	ND
82b	M2WJ418-1		B	A	ND
83b	IMX715		TBD	TBD	TBD

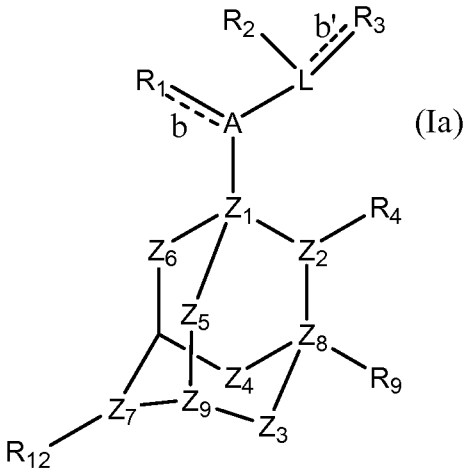
84b	M2WJ427-1		B	A	ND
85b	M2WJ433-1		B	A	ND
86b	M2WJ429-1		B	A	ND
		 **VII:**			
87b	Hij341-1		A	B	ND
88b	Hij350-1		B	A	ND

					
89b	IMX00737				ND
90b	M2WJ450-1		B	A	ND
91b	M2WJ453-1		B	A	ND
92b	IMX800		ND	ND	ND

93b	IMX797		ND	ND	ND
94b	IMX798		ND	ND	ND
95b	IMX799		ND	ND	ND

What is Claimed:

1. A compound according to formula (la):



(Ia)

wherein

A is Ci_3 alkylene or a bond between L and the atom at position Z_1;

L is nitrogen;

R i is NH, NH_2, alkyl, or, if A is a bond, is absent;

dashed lines b and b' may independently represent a double bond;

R_2 is H, alkyl, -(D)(E), or is absent;

R_3 is -(X)(Y);

R_4 is -(R_5)(R_6), halo, or is absent;

R_5 is nitrogen or oxygen;

R_6 is hydrogen or -(R_7)(R_8)

R_7 is alkylene, -CH(R_{7a})-, -(CH_2)o-6CH(OH)-, or represents a bond between R_5 and Rg;

R_{7a} is alkyl;

R_8 is optionally substituted mono-, di-, or tricyclic ring system that optionally includes one or more heteroatoms;

R_9 is -(Rio)(Ri i) or is absent;

Rio is oxygen, nitrogen, alkyl, -CF_3, or alkylene;

R_{11} is hydrogen, halo, or is absent;

R12 is alkyl, alkoxy, halo, oxo, or hydroxyl;

D is alkylene, alkenylene, alkynylene, -CH(Q)-, carbonyl, or a bond;

E is an optionally substituted mono-, di-, or tricyclic ring system that optionally includes

one or more heteroatoms;

X is alkylene, alkenylene, alkynylene, -CH(Q)-, carbonyl, or a bond;

Q is alkyl, -C(=0)0(CH $_{2}$)i$_{-3}$CH$_{3}$, or -(CH$_{2}$)$_{0-3}$OH;

Y is an optionally substituted mono-, di-, or tricyclic ring system that optionally includes one or more heteroatoms;

Z_2 is optionally substituted alkylene of which one or more carbon atoms is optionally replaced with N, O, or S, or represents a bond between Zi and Z_8;

Z_3 is optionally substituted alkylene of which one or more carbon atoms is optionally replaced with N, O, or S, or represents a bond between Z_8 and Z_9;

Z_4, Z_5, and Z_6 are independently alkylene, N, O, or S;

Z_7 is optionally substituted alkylene of which one or more carbon atoms is optionally replaced with N, O, or S;

or a stereoisomer, isotopically substituted analogue, or pharmaceutically acceptable salt thereof,

with the proviso that

(i) if A is a bond and R_2 is H or absent, except if X is alkynyl, then:

Y is not unsubstituted phenyl, pyridinyl, furanyl, thiopheneyl, pyrrolyl, or benzodioxolyl;

if Y is mono-substituted furanyl, then the substituent on Y is not methyl, hydroxyl, methanolyl, alkoxy, acetylamino, nitro, bromo, chloro, or fluoro;

if Y is mono-substituted phenyl, then the substituent on Y is not methyl, hydroxyl, methanolyl, alkoxy, unsubstittued phenyl, methoxybenzloxy, acetylamino, nitro, bromo, chloro, or fluoro

if Y is mono-substituted thiopheneyl, then the substituent on Y is not methyl, ethyl, chloro, or bromo;

if Y is mono-substituted oxadiazolyl, then the substituent on Y is not methoxyphenyl;

if Y is mono-substituted thiazolyl, then the substituent on Y is not methyl;

if Y is mono-substituted naphthyl, then the substituent on Y is not 1-hydroxyl; and,

if Y is di-substituted phenyl, then the substituents on Y may not both be alkoxy,

and,

(ii) if A is C_1 alkyl, R_1 is NH, and Y is mono-substituted phenyl, then the substituent is not hydroxyl.

2. The compound according to claim 1 wherein A is a bond, R_1 is absent, X is alkylene or -CH(Q)-, and Y is a carbocyclic ring optionally substituted with one or more substituents independently selected from alkoxy, halo, alkyl, cycloalkyl, hydroxyl, aryl, trifluoromethoxy, trifluoromethyl, alkylsilanyl, alkylsulfanyl, aryloxy, aralkoxy, and hydroxyalkyl.

3. The compound according to claim 2 wherein Y is substituted with aryl, aryloxy, or aralkoxy in which the aryl moiety thereof is optionally substituted phenyl, pyrrolidinyl, furanyl, thiopheneyl, oxazolyl, imidazolyl, pyridinyl, naphthyl. isoxazolyl, isoxazolinyl, isothiazolyl, isothiazolinyl, oxadiazolyl, thiadiazolyl, thiazolyl, triazolyl, tetrazolyl, morpholinyl, pyrimidinyl, pyridazinyl, pyrazinyl, pyrrolyl, cyclopropyl, cyclopentyl, or cyclohexyl.

4. The compound according to claim 1 wherein A is a bond, R_1 is absent, X is alkylene or -CH(Q)-, and Y is an unsubstituted mono-, di-, or tricyclic ring system that optionally includes one or more heteroatoms independently selected from oxygen, nitrogen, and sulfur.

5. The compound according to claim 4 wherein Y is

a six-membered carbocyclic ring that is ortho-fused with a six-membered heterocyclic ring;

a six membered heterocyclic ring that is ortho-fused with a six-membered heterocyclic ring;

a six membered heterocyclic ring that is ortho-fused with a five-membered heterocyclic ring;

a six membered heterocyclic ring that is ortho-fused with a five-membered carbocyclic ring;

a six-membered carbocyclic ring that is ortho-fused with a five-membered heterocyclic ring;

a pair of ortho-fused five-membered heterocyclic rings;

a pair of ortho-fused five-membered carbocyclic rings; or,

a single three- to seven-membered carbo- or heterocyclic ring.

6. The compound according to claim 5 wherein Y is

a single unsaturated, partially saturated, or fully saturated six-membered carbo- or heterocyclic ring;

a single unsaturated, partially saturated, or fully saturated five-membered carbo- or heterocyclic ring;

an unsaturated, partly-saturated, or fully-saturated thiophene ring that is ortho-fused to an unsaturated, partly-saturated, or fully-saturated thiophene, pyrrole, furan, imidazole, thiazole, or oxazole ring,

an unsaturated, partly-saturated, or fully-saturated furan ring that is ortho-fused to an unsaturated, partly-saturated, or fully-saturated thiazole or oxazole ring;

an unsaturated, partly-saturated, or fully-saturated pyrrole ring that is ortho-fused to an unsaturated, partly-saturated, or fully-saturated thiazole or oxazole ring; or,

a phenyl ring that is ortho-fused to an unsaturated, partly-saturated, or fully-saturated thiophene, pyridine, imidazole, or furan ring.

7. The compound according to claim 1 wherein A is a bond, Ri is absent, X is alkylene or -CH(Q)-, and Y is a substituted mono-, di-, or tricyclic ring system that includes one or more heteroatoms independently selected from oxygen, nitrogen, and sulfur.

8. The compound according to claim 7 wherein Y is

a single three- to seven-membered heterocyclic ring;

a single unsaturated, partially saturated, or fully saturated six-membered carbo- or heterocyclic ring;

a single unsaturated, partially saturated, or fully saturated five-membered carbo- or heterocyclic ring;

a pair of ortho-fused five-membered heterocyclic rings, wherein at least one of said rings is substituted;

a pair of ortho-fused six-membered heterocyclic rings, wherein at least one of said rings is substituted;

a six-membered heterocyclic ring that is ortho-fused with a six-membered carbocyclic ring, wherein at least one of said rings is substituted;

a five-membered heterocyclic ring that is ortho-fused with a five-membered carbocyclic ring, wherein at least one of said rings is substituted;

a five-membered heterocyclic ring that is ortho-fused with a six-membered carbocyclic ring, wherein at least one of said rings is substituted; or,

a five-membered carbocyclic ring that is ortho-fused with a six-membered heterocyclic ring, wherein at least one of said rings is substituted.

9. The compound according to claim 8 wherein said substitutions are independently selected from oxo, hydroxyl, halo, nitro, alkyl, alkoxyalkyl, trifluoromethyl, trifluoromethoxy, cycloalkyl, alkoxy, alkylamino, di-alkylamino, alkoxycarbonylalkyl(alkyl)amino, alkylsulfanyl, alkylsulfanylalkyl, trifluoromethylsulfanyl, cyano, amino, aralkyl, and aryl.

10. The compound according to claim 9 wherein Y is substituted with aryl or cycloalkyl, and the aryl or cycloalkyl is isoxazolyl, isoxazolinyl, isothiazolyl, isothiazolinyl, oxadiazolyl, thiadiazolyl, oxazolyl, thiazolyl, triazolyl, tetrazolyl, imidazolyl, phenyl, morpholinyl, pyridinyl, piperidinyl, pyrimidinyl, pyridazinyl, pyrazinyl, thiopheneyl, furanyl, pyrrolyl, pyrrolidinyl, cyclopropyl, cyclopentyl, or cyclohexyl.

11. The compound according to claim 8 wherein Y is a single 5- or 6-membered ring that includes one or more heteroatoms independently selected from oxygen, nitrogen, and sulfur, and wherein said ring is substituted with one or more of halo, thiopheneyl, alkylthiopheneyl, alkoxythiopheneyl, imidazolyl, imidazolyl substituted with one or both of methyl and trifluoromethyl, tetrahydrofuranyl, furanyl, alkylfuranyl, phenyl, pyridinyl, morpholinomethyl, cyclopropyl, cyclopentyl, cyclohexyl, alkoxy, alkoxyalkyl, alkyl, alkylsulfanyl, alkylsulfanylalkyl, alkylsilanyl, cyano, amino, alkylamino, di-alkylamino, alkoxycarbonylalkyl(alkyl)amino, nitro, alkoxyphenyl, alkylsulfanylphenyl, halophenyl, trifluoromethyl, trifluoromethylphenyl, trifluoromethoxyphenyl, thiazolyl substituted with one or both of methyl and trifluoromethyl, isoxazolyl optionally substituted with methyl, isoxazolinyl, isothiazolyl, isothiazolinyl, oxadiazolyl, thiadiazolyl, oxazolyl, thiazolyl, triazolyl, tetrazolyl, morpholinyl, pyrimidinyl, pyridazinyl, pyrrolidinyl, piperadinyl pyrazinyl, or pyrrolyl.

12. The compound according to claim 1 wherein A is a bond, Ri is absent, X is alkylene or -CH(Q)-, and R_9 is -(R_{10})(Rn).

13. The compound according to claim 1 wherein A is a bond, Ri is absent, X is alkylene or -CH(Q)-, and R_4 is -(R_5)(R_6)

14. The compound according to claim 1 wherein A is a bond, Ri is absent, X is alkylene or -CH(Q)-, and R_2 is -(D)(E).

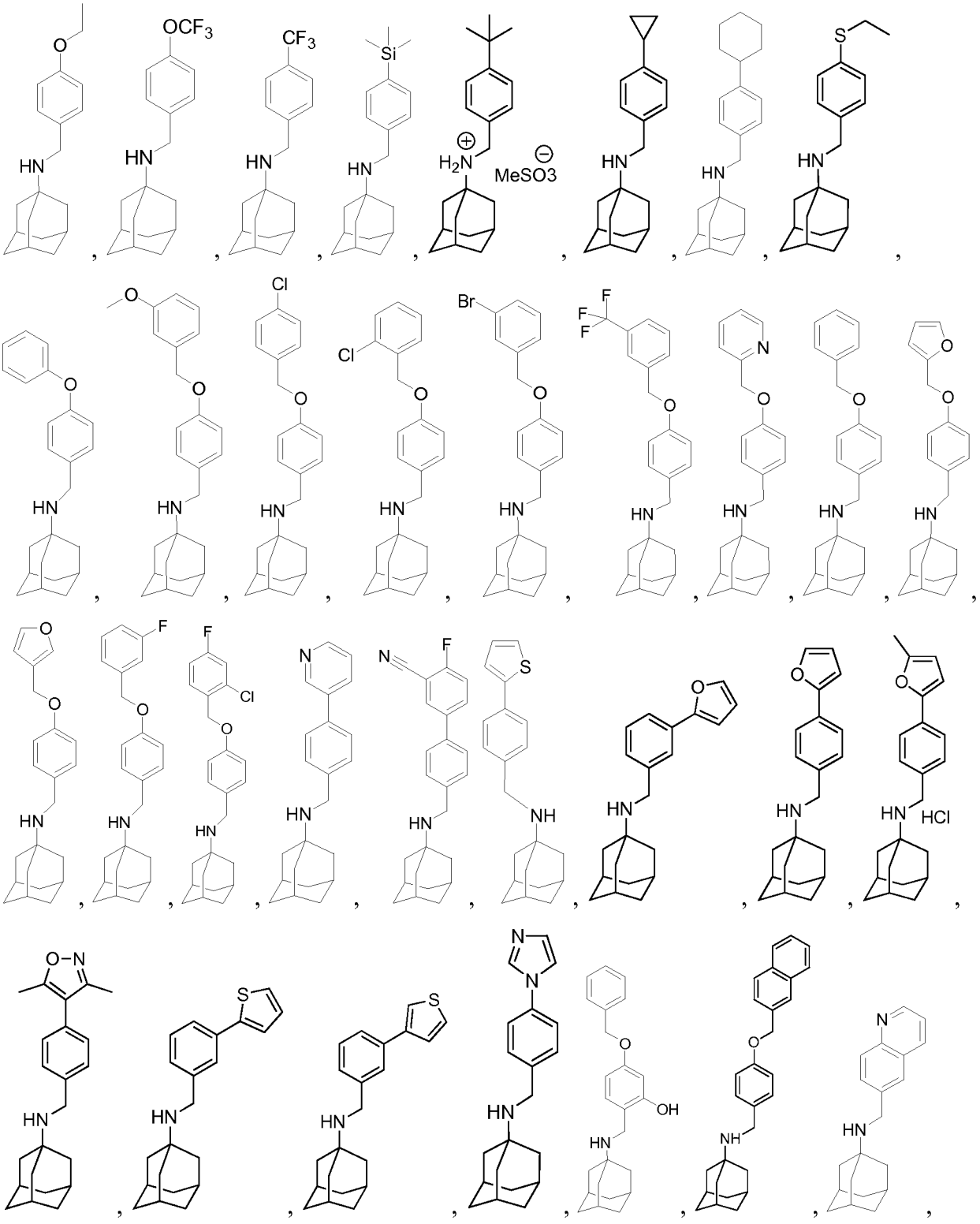
15. The compound according to claim 1 wherein A is a bond, Ri is absent, X is alkylene or -CH(Q)-, and Z_7 is alkylene that is substituted with alkyl, hydroxyl, or halo.

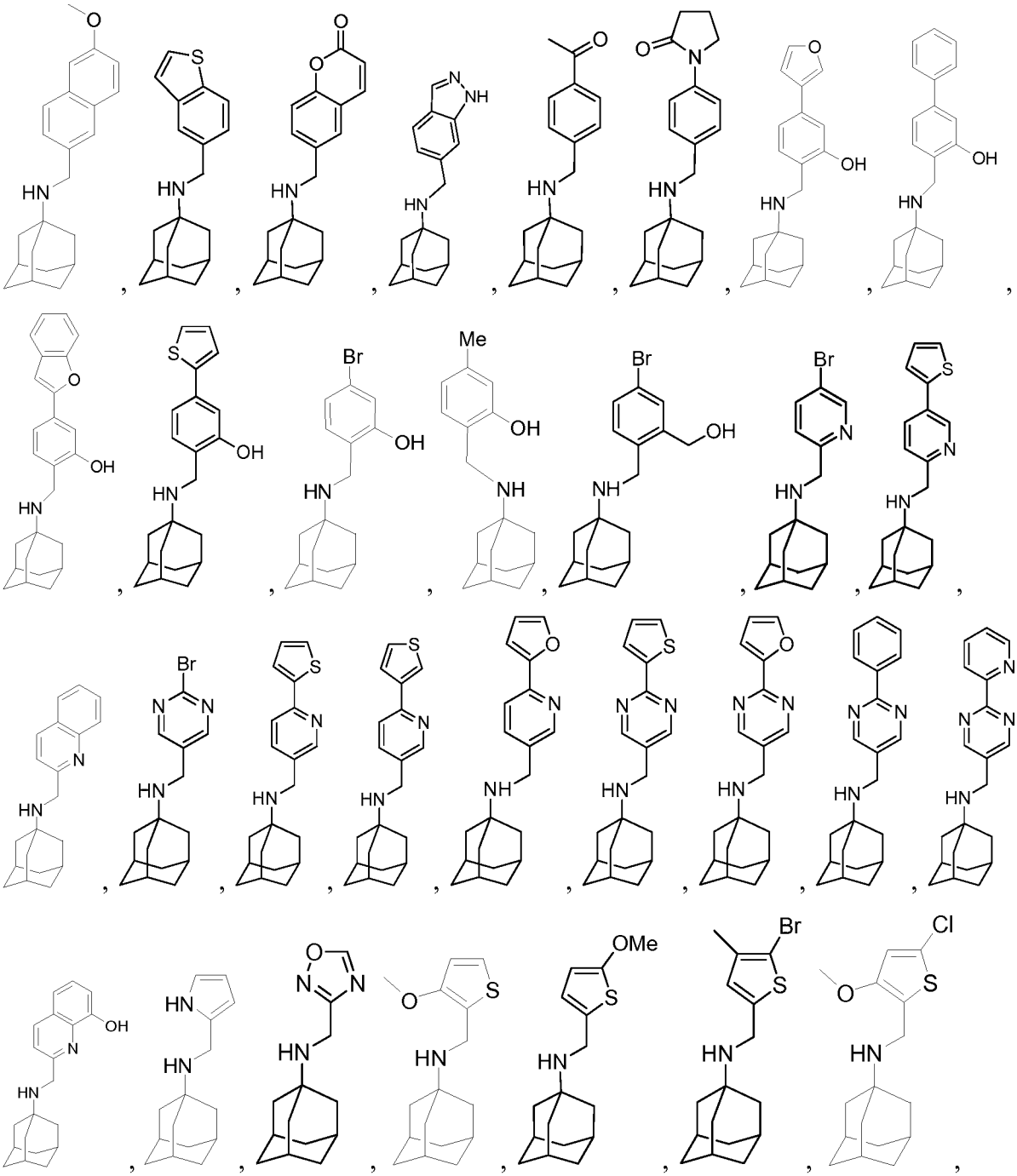
16. The compound according to claim 1 wherein A is a bond, Ri is absent, X is alkylene or -CH(Q)-, and Z_7 is alkylene of which one or more carbon atoms is replaced with N, O, or S.

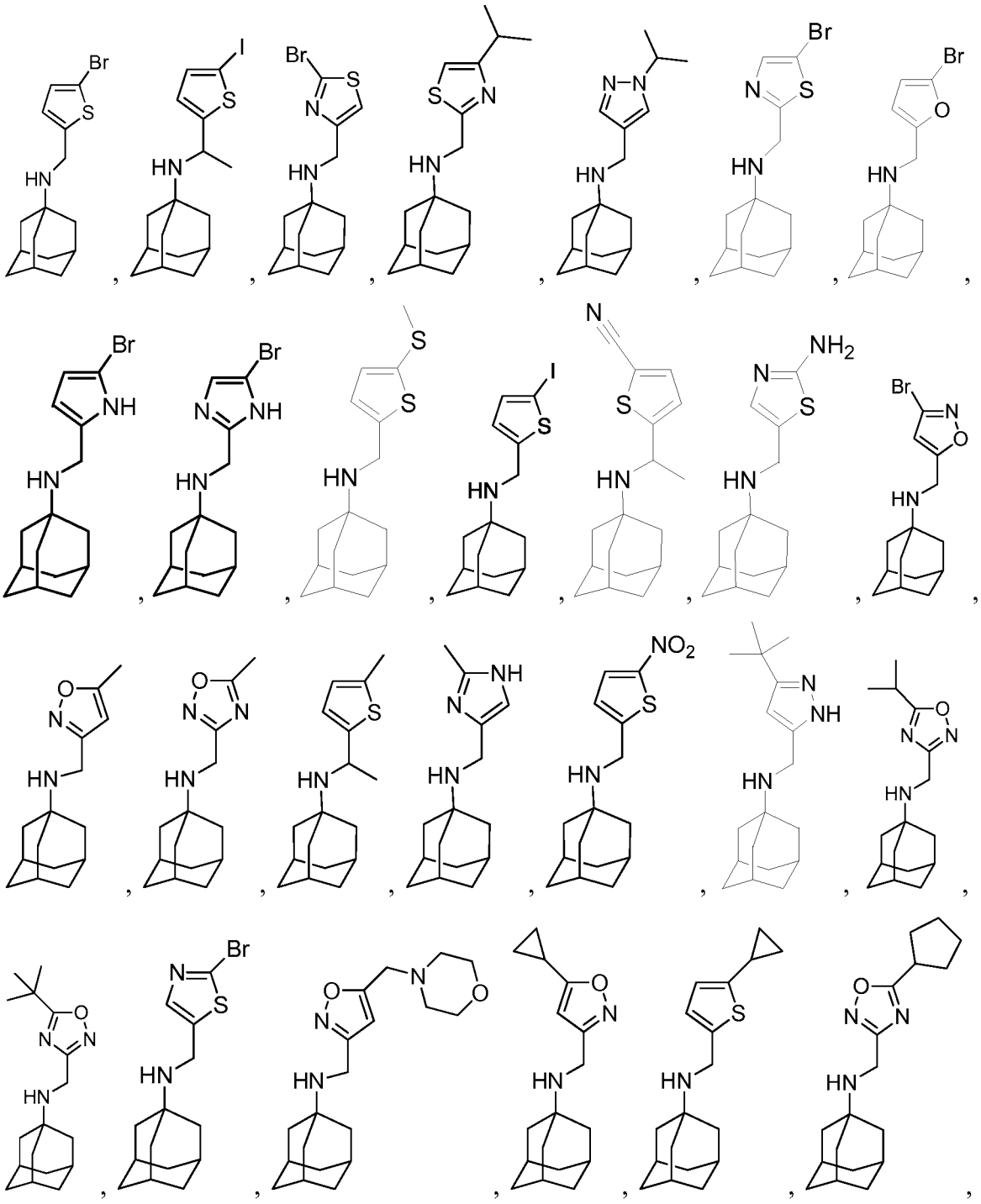
17. The compound according to claim 1 wherein A is a bond, Ri is absent, X is alkylene or -CH(Q)-, and one or more of Z_2-Z_7 is N, O, or S.

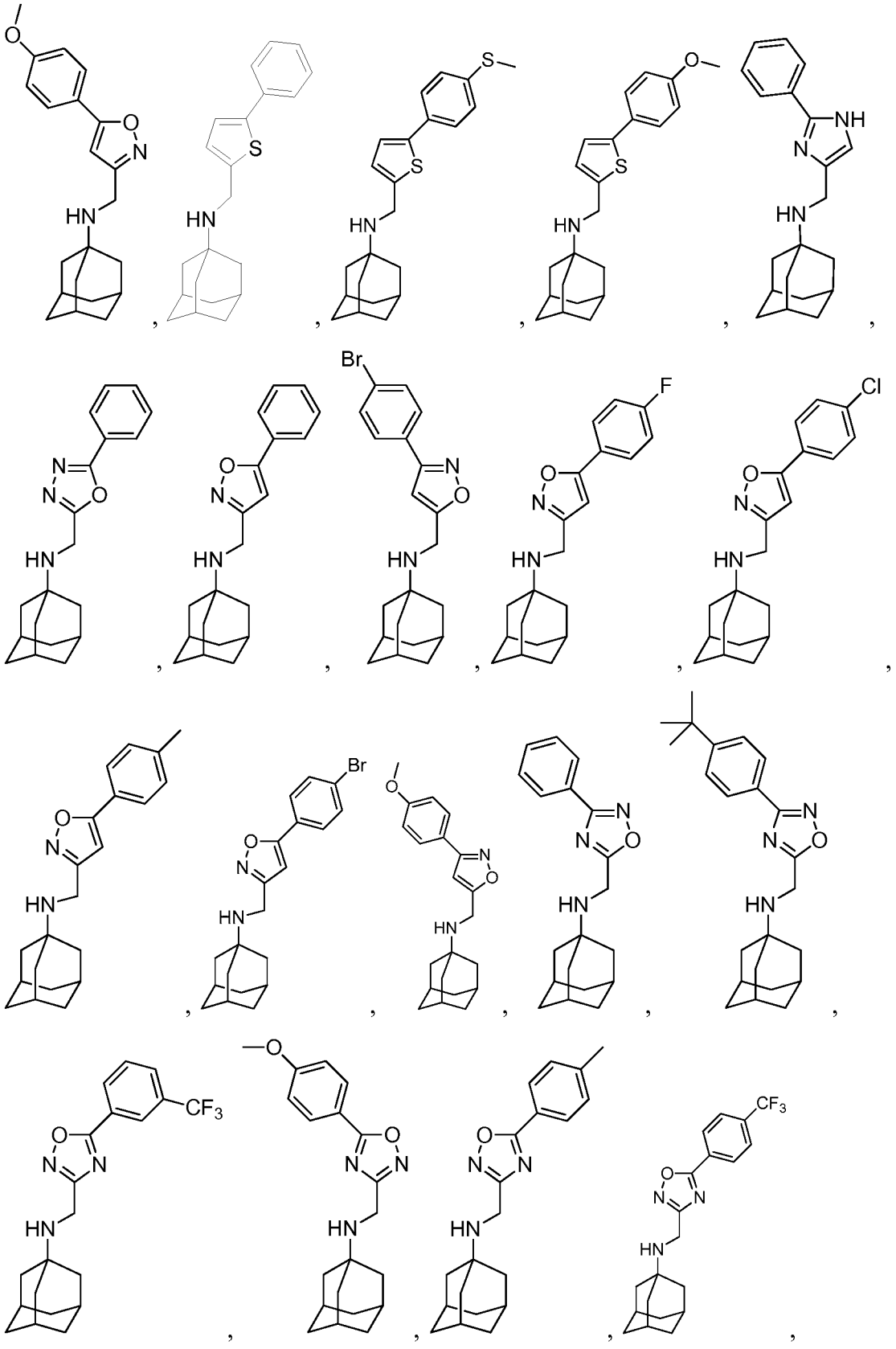
18. The compound according to claim 1 wherein A is a bond, Ri is absent, X is alkenylene or alkynylene, and Y is optionally substituted aryl.

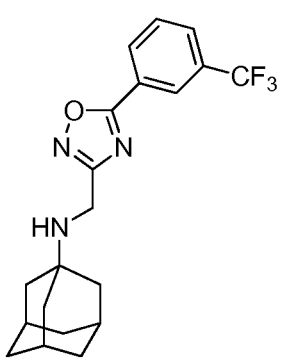
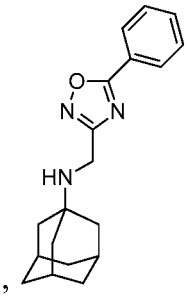
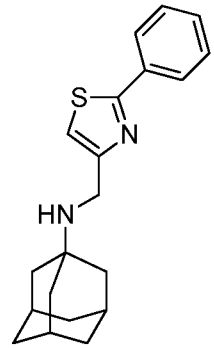
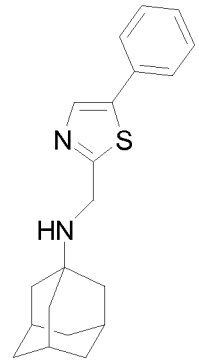
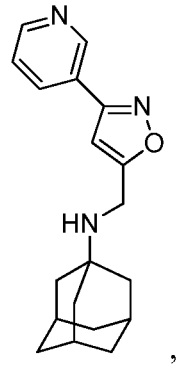
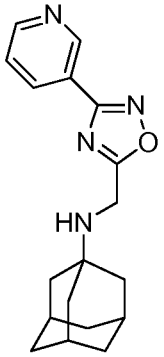
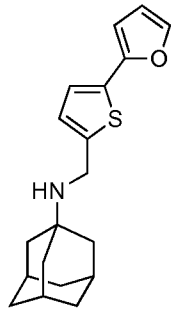
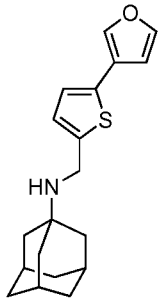
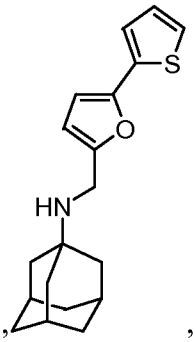
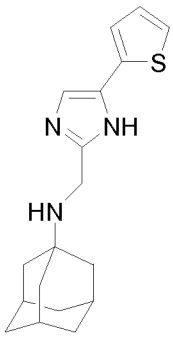
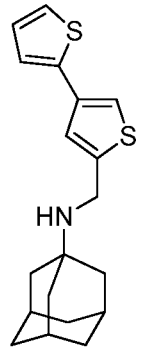
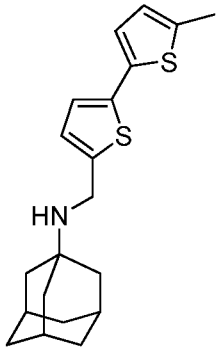
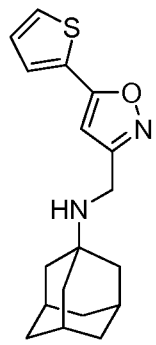
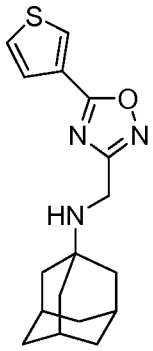
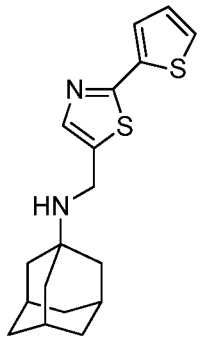
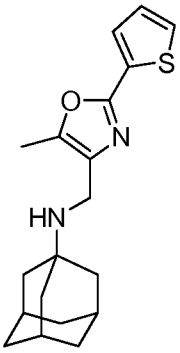
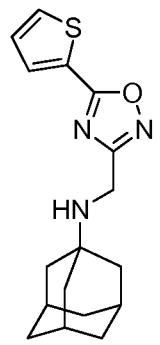
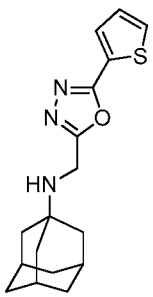
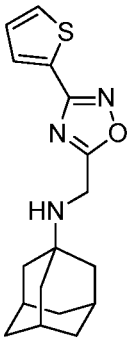
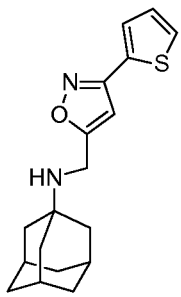
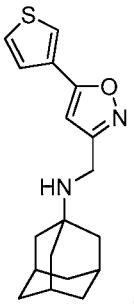
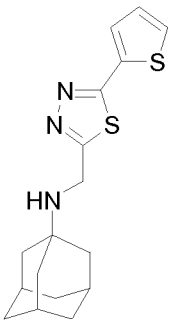
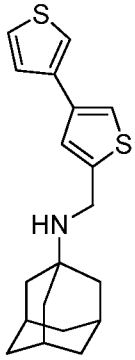
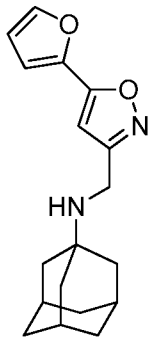
19. The compound according to claim 1 wherein said compound is

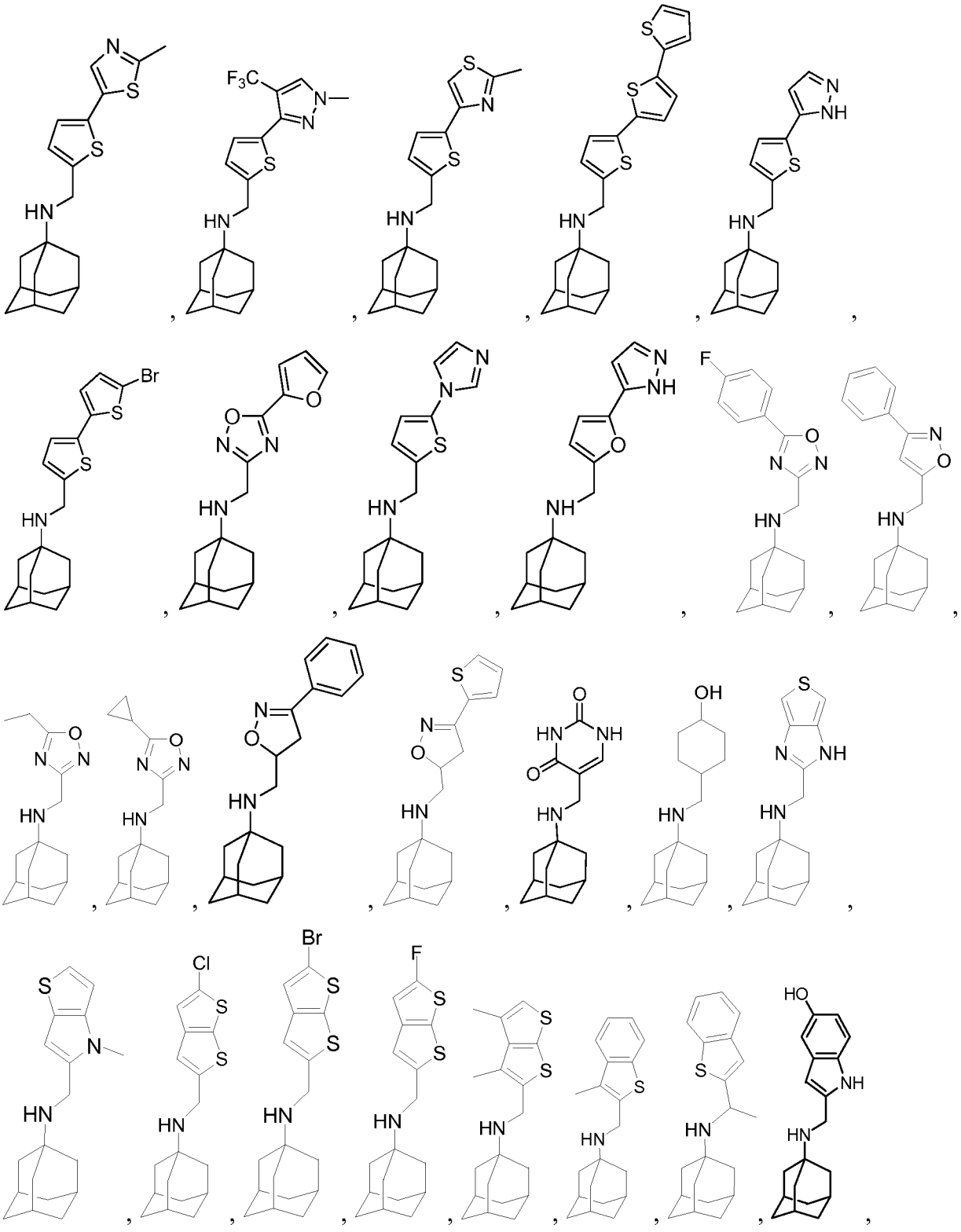


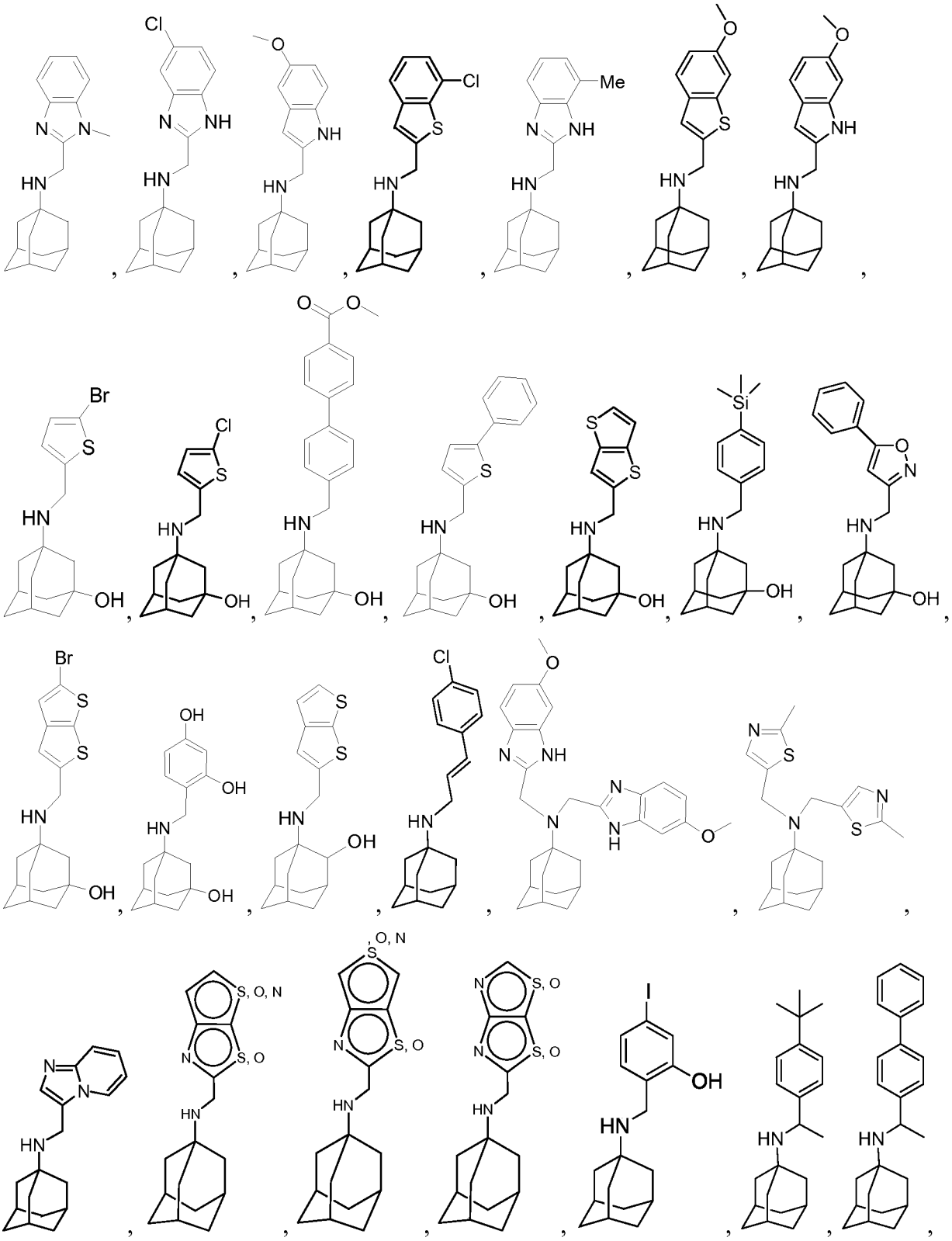


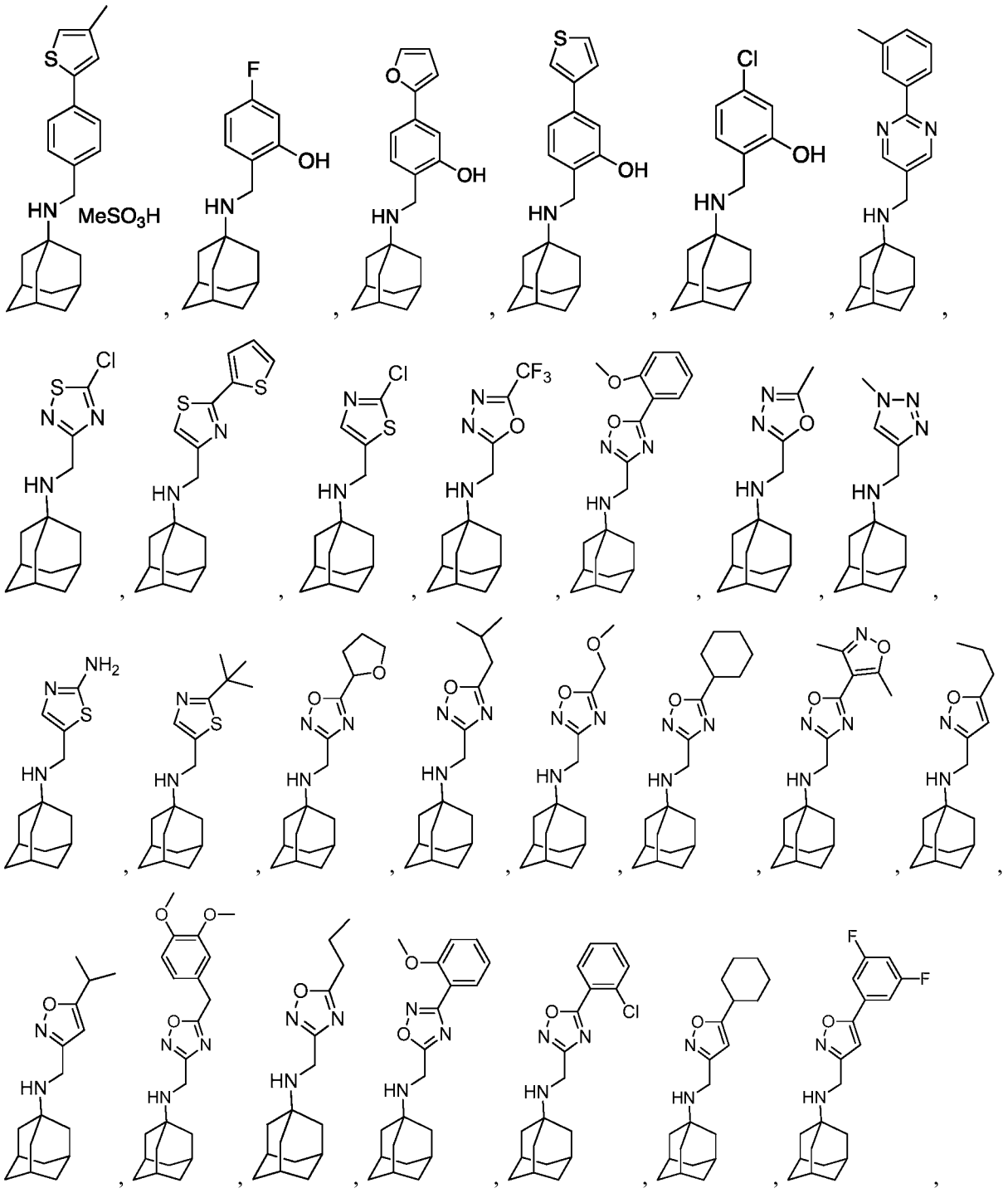


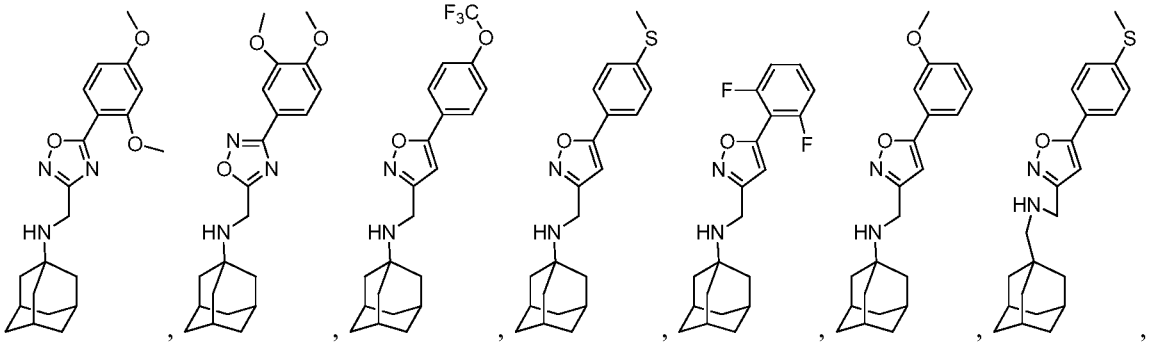


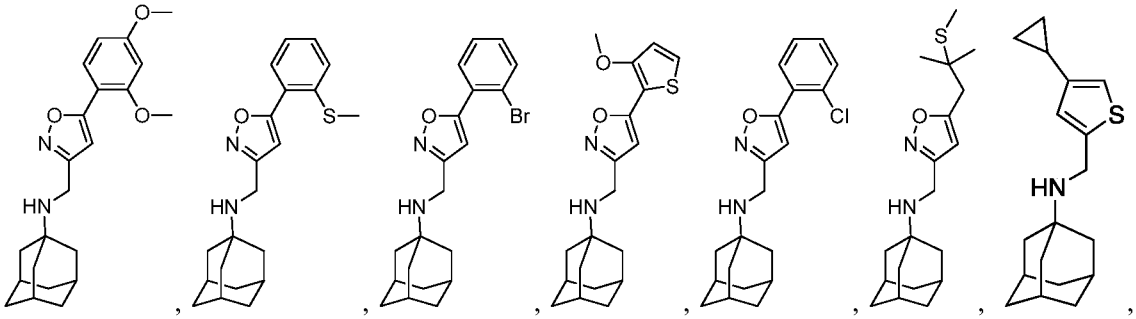

























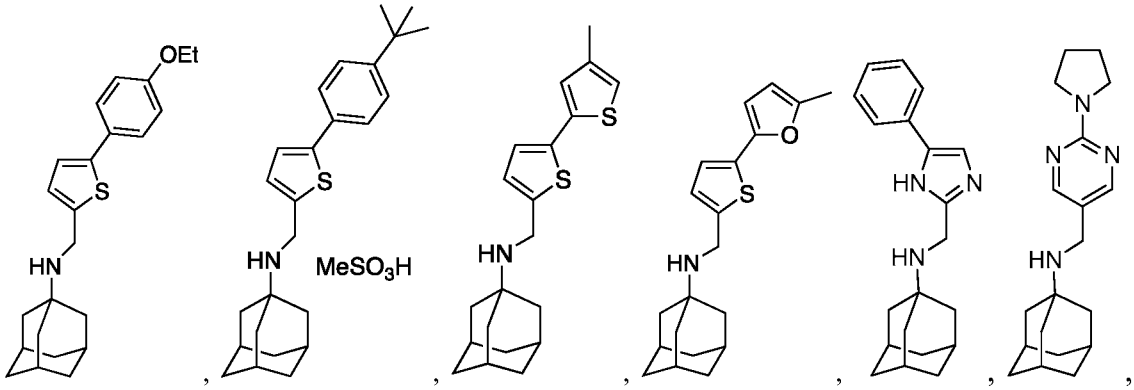


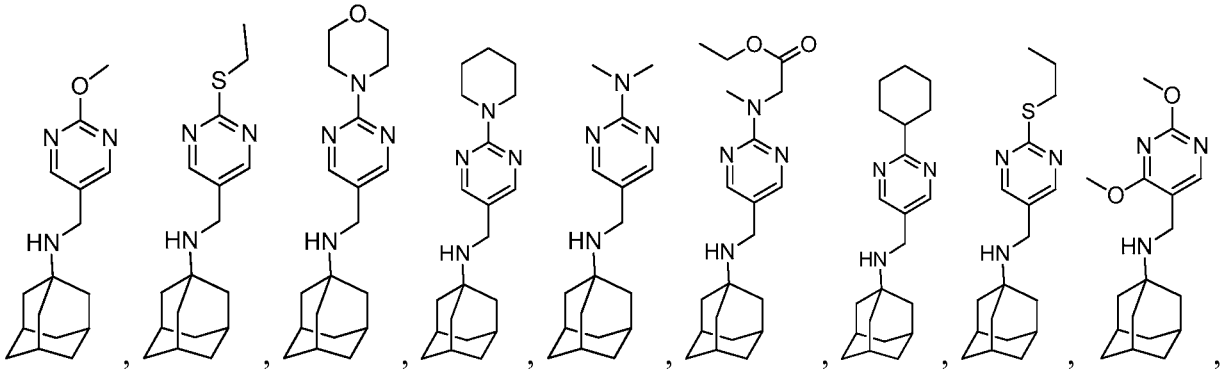


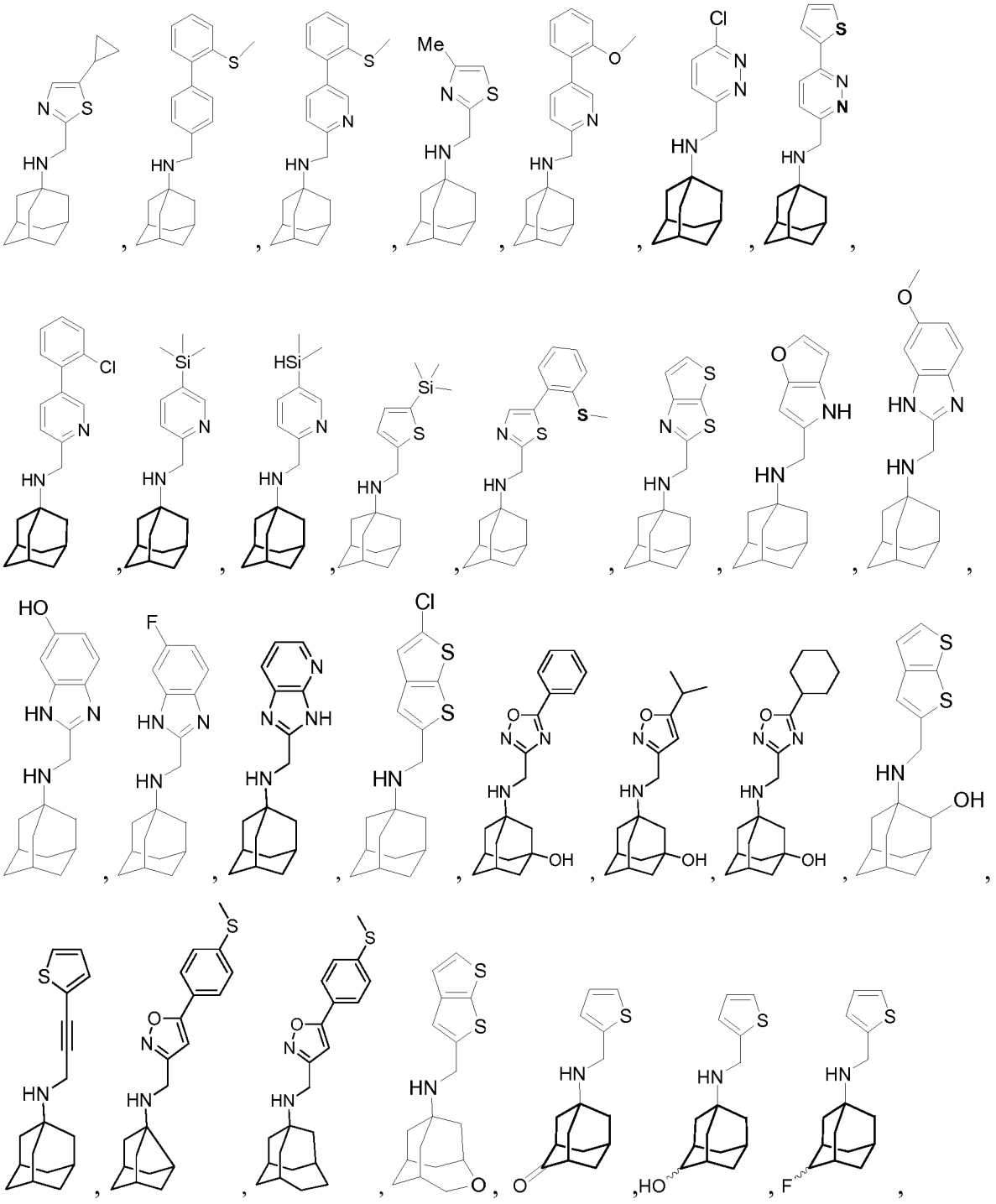






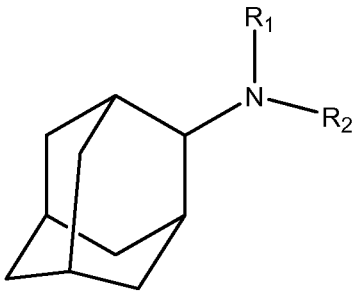

MeSO3H





or a stereoisomer, isotopically substituted analogue, or pharmaceutically acceptable salt thereof.

20. A compound according to formula (lb):



(Ib)

wherein

Ri is hydrogen; and,

R_2 is –(R_3)(R_4);

R_3 is alkyl; and,

R_4 is a substituted mono-, di-, or tricyclic ring system,

or,

Ri together with R_2 and the atom to which they are both attached form an optionally substituted mono-, di-, or tricyclic ring system,

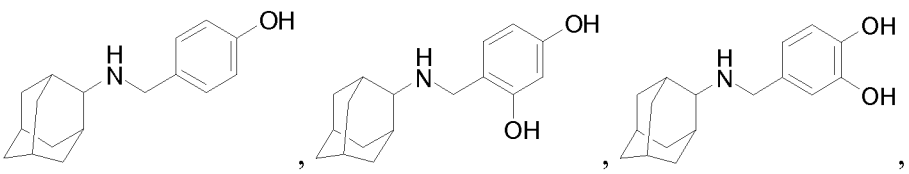
or a stereoisomer, partial stereoisomer, isotopically substituted analogue, prodrug, pharmaceutically acceptable salt, hydrate, solvate, acid hydrate, or N-oxide thereof.

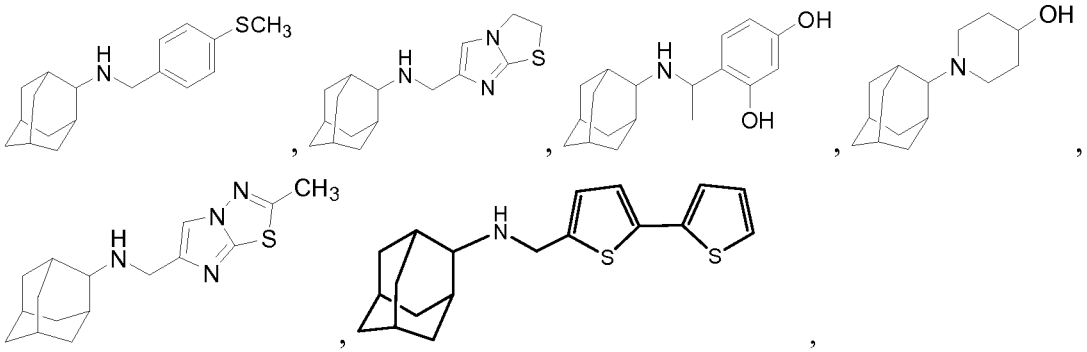
21. The compound according to claim 20 wherein R_4 is a substituted monocyclic ring.

22. The compound according to claim 21 wherein R_4 is a five- or six-membered carbocyclic or heterocyclic ring bearing one or more substituents independently selected from hydroxyl, halo, alkyl, alkoxy, trifluoromethyl, trifluoromethoxy, alkylsulfanyl, and aryl.

23. The compound according to claim 22 wherein R_4 is a five-membered heterocyclic ring bearing one or more aryl substituents.

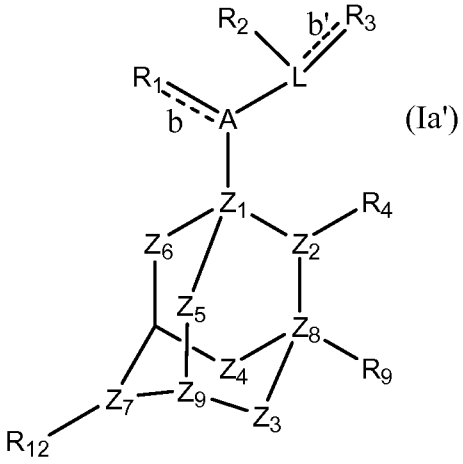
24. The compound according to claim 20, wherein said compound is





or a stereoisomer, isotopically substituted analogue, or pharmaceutically acceptable salt thereof.

25. A method for treating an influenza A virus-affected disease state or infection comprising the step of administering to a subject in need thereof a composition comprising a compound of formula (la'):



(Ia')

wherein

A is C_{i_3} alkylene or a bond between L and the atom at position Zi;

L is nitrogen;

Ri is NH, NH_2, alkyl, or, if A is a bond, is absent;

dashed lines b and b' may independently represent a double bond;

R_2 is H, alkyl, -(D)(E), or is absent;

R_3 is -(X)(Y);

R_4 is -(R_5)(R6), halo, or is absent;

R_5 is nitrogen or oxygen;

Re is hydrogen or -(R_7)(R_8)

R_7 is alkylene, -CH(R_{7a})-, -(CH_2)o-$_6$CH(OH)-, or represents a bond between R_5 and Rg;

R_{7a} is alkyl;

Rg is optionally substituted mono-, di-, or tricyclic ring system that optionally includes one or more heteroatoms;

R_9 is -(Rio)(Rii) or is absent;

Rio is oxygen, nitrogen, alkyl, -CF_3, or alkylene;

R_{11} is hydrogen, halo, or is absent;

Ri_2 is alkyl, alkoxy, halo, oxo, or hydroxyl;

D is alkylene, alkenylene, alkynylene, -CH(Q)-, carbonyl, or a bond;

E is an optionally substituted mono-, di-, or tricyclic ring system that optionally includes one or more heteroatoms;

X is alkylene, alkenylene, alkynylene, -CH(Q)-, carbonyl, or a bond;

Q is alkyl, -C(=0)0(CH_2)$_{1-3}$$CH_3$, -($CH_2$)$_{0-3}$OH, or -C(=0)-;

Y is an optionally substituted mono-, di-, or tricyclic ring system that optionally includes one or more heteroatoms;

Z_2 is optionally substituted alkylene of which one or more carbon atoms is optionally replaced with N, O, or S, or represents a bond between Z_1 and Z_8;

Z_3 is optionally substituted alkylene of which one or more carbon atoms is optionally replaced with N, O, or S, or represents a bond between Z_8 and Z_9;

Z_4, Z_5, and Z_6 are independently alkylene, N, O, or S;

Z_7 is optionally substituted alkylene of which one or more carbon atoms is optionally replaced with N, O, or S;

or a stereoisomer, isotopically substituted analogue, or pharmaceutically acceptable salt thereof.

26. The method according to claim 25 wherein said influenza A virus-affected disease state or infection comprises influenza (flu).

27. The method according to claim 25 wherein said influenza A virus-affected disease state or infection comprises one or more of pneumonia, bronchitis, sinus infection, and ear infection.

28. The method according to claim 25 wherein said composition additionally comprises a pharmaceutically acceptable carrier, diluent, or excipient.

29. The method according to claim 25 wherein said influenza A virus is a wild-type virus.

30. The method according to claim 25 wherein said influenza A virus is a mutant.

31. A composition comprising a compound according to claim 1 or a pharmaceutically acceptable salt, isotopically substituted analogue, or stereoisomer thereof and a pharmaceutically acceptable carrier, diluent, or excipient.

32. The composition according to claim 31 further comprising a therapeutically effective amount of a further agent that modulates an influenza virus.

33. A method for treating an influenza A virus-affected disease state or infection comprising the step of administering to a subject in need thereof a composition comprising a compound according to claim 20.

34. The method according to claim 33 wherein said influenza A virus-affected disease state or infection comprises influenza (flu).

35. The method according to claim 33 wherein said influenza A virus-affected disease state or infection comprises one or more of pneumonia, bronchitis, sinus infection, and ear infection.

36. The method according to claim 33 wherein said composition additionally comprises a pharmaceutically acceptable carrier, diluent, or excipient.

37. The method according to claim 33 wherein said influenza A virus is a wild-type virus.

38. The method according to claim 33 wherein said influenza A virus is a mutant.

39. A composition comprising a compound according to claim 20 or a pharmaceutically acceptable salt, isotopically substituted analogue, or stereoisomer thereof and a pharmaceutically acceptable carrier, diluent, or excipient.

40. The composition according to claim 39 further comprising a therapeutically effective amount of a further agent that modulates an influenza virus.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/68163

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C07H 15/00 (2012.01)
USPC - 536/17.9
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)
USPC - 536/17.9 (see search terms below)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 536/29.1 ; 564/459 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase keywords: methods, treating, influenza viruses, M2 proton channel, influenza A, wild type, drug resistant, adamantane, aralkyi, heteroaralkyi, mutant virus, pharmaceutical composition, affected disease state, pneumonia, spiro-piperidine, inhibitors, three dimensional structure, molecular modeling, adamantine-based drugs, docking, binding si

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2011/0065766 A1 (WANG et al.) 17 March 2011 (17.03.2011), para [0002]; [0012]; [0020] - [0029]; [0035]; [0052]; [0085] - [0086]; [0088]; [0092] - [0093]; [0098].	1-40
Y	DU et al., Designing Inhibitors of M2 Proton Channel against H1N1 Swine Influenza Virus, PLoS ONE 5(2), pp 1-7, 2010, Abstract; pg 3, col 1, para 2 - pg 4, col 1, para 1; pg 4, col 2, para 1; pg 4, col 2, para 3 - pg 6, col 1, para 1. Downloaded at http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjoumal.pone.0009388	1-40
Y	US 2010/0069420 A1 (DEGRADO et al.) 18 March 2010 (18.03.2010), para [0013]; [0052] - [0059]; [0072].	19, 26-27 and 34-35

☐ Further documents are listed in the continuation of Box C.

* 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
18 January 2013 (18.01.2013)	15 FEB 2013

Name and mailing address of the ISA/US	Authorized officer:
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Lee W. Young PCT Helpdesk: 571-272-4300 PCTOSP: 571-272-7774