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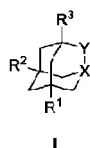
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[Continued on next page]

(54) Title: ADAMATANE DERIVATIVES FOR THE TREATMENT OF FILOVIRUS INFECTION



(57) Abstract: Compounds of structural
Formula (I) were developed for the
treatment of infections by filoviruses
including Ebolavirus and Marburgvir-
us.

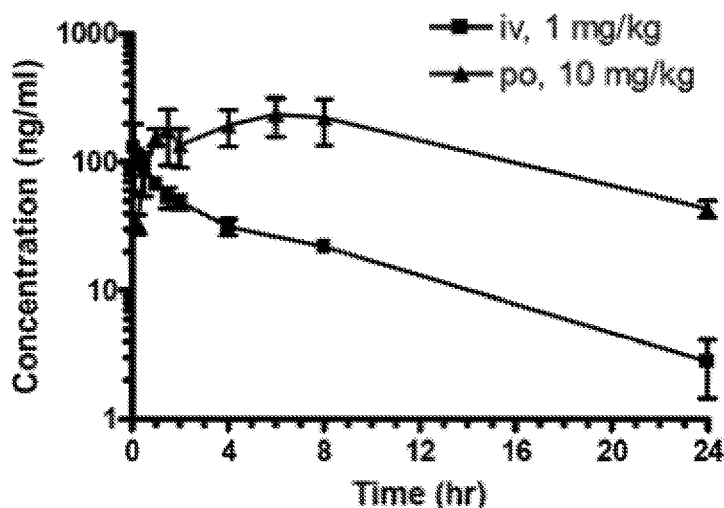


Figure 1



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PATENT APPLICATION

ADAMANTANE DERIVATIVES FOR THE TREATMENT OF FILOVIRUS INFECTION

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ADAMANTANE DERIVATIVES FOR THE TREATMENT OF FILOVIRUS INFECTION

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CROSS REFERENCES TO RELATED APPLICATIONS

This patent application is a continuation in part of and claims the benefit of priority to United States Provisional Patent Applications serial numbers 62/279,917, filed January 18, 2016 and 62/351,839, filed June 17, 2016, both applications are herein incorporated by reference for all purposes.

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This invention was made with government support under 1R43AI118207-01 (Ken McCormack) awarded by U.S. National Institutes of Health. The government has certain rights in the invention.

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REFERENCE TO A "SEQUENCE LISTING, A TABLE, OR A COMPUTER PROGRAM LISTING APPENDIX SUBMITTED ON A COMPACT DISK

NOT APPLICABLE

FIELD OF THE INVENTION

The present invention relates to methods of inhibiting infection by viruses of the *Filoviridae* family (filoviruses) in humans, other mammals, or in cell culture, to treating infection by filoviruses, to methods of inhibiting the replication of filoviruses, to methods of reducing the amount of filoviruses, and to compositions that can be employed for such methods. These methods, applications, and compositions apply not only to *Filoviridae* viruses but also to any virus, whether naturally emerging or engineered, whose cell entry properties are determined by filovirus glycoproteins.

BACKGROUND OF THE INVENTION

The invention relates to the use of compounds for the treatment and/or prophylaxis of infection of humans or other mammals by one or more of a number of enveloped viruses of the *Filoviridae* family (filoviruses) or any other native or engineered enveloped virus utilizing filovirus glycoproteins to mediate cell entry. Enveloped viruses are comprised of an outer host-derived lipid membrane and an inner nucleoprotein core, which contains the viral genetic material (whether RNA or DNA). Virus-cell fusion is the means by which all enveloped viruses enter cells and initiate disease-causing cycles of replication. In all cases virus-cell fusion is executed by one or more viral surface glycoproteins that are anchored within the lipid membrane envelope. One or more glycoproteins from a given virus may form a glycoprotein complex that interacts with a number of different surface and/or intracellular receptors of infected host cells to initiate the association between virus and host cell. However, one glycoprotein is generally denoted as the protein primarily driving the fusion of viral and host cell membranes. At least three distinct classes of viral membrane fusion proteins have been determined (classes I, II, and III) [Weissenhorn, W.; Carfi, A.; Lee, K.H.; Skehel, J.J., and Wiley, D. C. *Crystal structure of the Ebola virus membrane fusion subunit, GP2, from the envelope glycoprotein ectodomain*. Mol. Cell (1998) 2:605-616; White, J.M.; Delos, S.E.; Brecher, M.; Schomberg K. *Structures and mechanisms of viral membrane fusion proteins: multiple variations on a common theme*. Crit. Rev. Biochem. Mol. Biol. (2008) 43:189-219; Ignotz, S.; Vaney, M.C.; Vonnheim, C.; Bricogne, G.; Stura, E.A.; Hengartner H.; Eschli, B.; Rey, F.A. *X-ray structure of the arenavirus glycoprotein GP2 in its postfusion hairpin conformation*, Proc. Natl. Acad. Sci. (2011) 108:19967-19972]. Class I fusion proteins are found in viruses from the Orthomyxoviridae, Retroviridae, Paramyxoviridae, Coronaviridae, Filoviridae, and Arenaviridae families, Class II proteins from Togaviridae, Flaviviridae, and Bunyaviridae while Class III or other types are from Rhadboviridae, Herpesviridae, Poxviridae, and Hepadnaviridae.

Given that viral cell entry is an essential step in the viral replication process the identification of compounds that inhibit virus cell entry could provide attractive antivirals for viruses that are pathogenic to humans and/or other mammals. Chemical compounds that act as inhibitors of one enveloped virus may also act as inhibitors of other enveloped viruses. However, while enveloped

Table 1 Family and Genera of Envelope Viruses and Glycoprotein Classification

Envelope Virus Family	Genera	Examples of pathogenic species	Glycoprotein Class
<i>Orthomyxoviridae</i>	<i>Influenza virus A,B,C</i>	Influenza A virus	I
<i>Filoviridae</i>	<i>Ebolavirus</i>	Zaire virus; Bundibugyo; Sudan; Tai Forest	I
	<i>Marburgvirus</i>	Marburg virus	
<i>Arenaviridae</i>	<i>Mammarenavirus</i>	Lassa virus; Junin; Machupo; Guanarito	I
<i>Coronaviridae</i>	<i>Betacoronaviruses</i>	SARS virus; MERS; HKU-1; OC43	I
<i>Flaviviridae</i>	<i>Flavivirus</i>	Dengue virus; Yellow Fever; West Nile; Japanese encephalitis	II
<i>Bunyaviridae</i>	<i>Hantavirus</i>	Andes virus	II
	<i>Orthobunyavirus</i>	Bunyamwera virus	
	<i>Phlebovirus</i>	Rift Valley fever virus	
	<i>Nairovirus</i>	Crimean-Congo hemorrhagic fever virus	
<i>Togaviridae</i>	<i>Alphavirus</i>	Chikungunya virus; Sindbis virus	II
<i>Paramyxoviridae</i>	<i>Rubulavirus</i>	Mumps virus	I
	<i>Morbillivirus</i>	Measles virus	
	<i>Pneumovirus</i>	Respiratory syncytial virus	
	<i>Henipavirus</i>	Hendra virus; Nipah	
<i>Herpesviridae</i>	<i>Cytomegalovirus</i>	Human CMV	III
	<i>Simplexvirus</i>	HSV-1; HSV-2	
	<i>Varicellovirus</i>	HHV-3 (Varicella zoster virus)	
	<i>Roseolovirus</i>	HHV-6; HHV-7	
	<i>Lymphocryptovirus</i>	Epstein-Barr virus	
	<i>Rhadinovirus</i>	Kaposi's sarcoma-associated herpesvirus	

viruses share some common functional and structural features with regard to glycoprotein-dependent cell entry and fusion the specific host targets and mechanisms of cell entry differ among enveloped viruses: between and even within different virus families as a function of their unique glycoprotein (GP) sequences and structures, and the cellular host proteins that they interact with [White, J.M.; Delos, S.E.; Brecher, M.; Schornberg K. *Structures and mechanisms of viral membrane fusion proteins: multiple variations on a common theme*. Crit. Rev. Biochem. Mol. Biol. (2008) 43:189-219]. The invention described herein relates to the use of compounds for the treatment and/or prophylaxis of infection as mediated by the cell entry and fusion process of filovirus glycoproteins whether native or engineered.

One viral expression system that may be utilized to identify inhibitors of enveloped viruses based on their glycoprotein sequences and functional properties is the vesicular stomatitis virus (VSV) system. This approach uses VSV, a virus in the *Rhabdoviridae* family (expressing Class III fusion proteins), lacking a native VSV glycoprotein. "Pseudotyped" viruses that are infective and functionally replicative in cell culture can be generated by substituting the VSV glycoprotein with a glycoprotein

originating from other enveloped viruses. The cell entry properties and functions of these pseudotyped viruses are determined by the viral glycoprotein that has been introduced. The cell entry and infectivity properties of pseudotyped VSV viruses have been shown to be determined by the introduced glycoprotein from a host of envelope viruses including Ebola, Lassa, Hanta, Hepatitis B, and other viruses [Ogino, M., et al. *Use of vesicular stomatitis virus pseudotypes bearing hantaan or seoul virus envelope proteins in a rapid and safe neutralization test*. Clin. Diagn. Lab. Immunol. (2003) 10(1):154-60; Saha, M.N., et al., *Formation of vesicular stomatitis virus pseudotypes bearing surface proteins of hepatitis B virus*. J. Virol. (2005) 79(19):12566-74; Takada, A., et al., *A system for functional analysis of Ebola virus glycoprotein*, Proc. Natl. Acad. Sci. (1997) 94:14764-69; Garbutt, M., et al., *Properties of replication-competent vesicular stomatitis virus vectors expressing glycoproteins of filoviruses and arenaviruses*. J. Virol. (2004) 78(10):5458-65]. When the pseudotype virion also expresses a reporter gene such as green fluorescent protein (GFP) or *Renilla* luciferase, virion infectivity and replication may be monitored using high-throughput optical methods in cultured mammalian cell lines, including Vero and HEK-293 cells [Cote, M.; Misasi, J.; Ren, T.; Bruchez, A., Lee, K., Filone, C. M.; Hensley, L.; Li, Q.; Ory, D.; Chandran, K.; Cunningham, J., *Small molecule inhibitors reveal Niemann-Pick C1 is essential for Ebola virus infection*, Nature (2011) 477: 344-348]. While VSV does not infect humans and may not be a virus of particular interest for the development of therapeutic antivirals, VSV pseudotyped viruses expressing glycoproteins from other enveloped viruses may be used to screen chemical libraries to identify compounds that inhibit the glycoproteins, cell entry, and infectivity of enveloped viruses associated with significant human health concerns. [Cunningham, J. et al. US patent application, publication number US2013/0231332; WO 2012/031090, 8 Mar 2012; WO2013/022550, 14 Feb 2013; Warren, T. K., et al. *Antiviral activity of a small-molecule inhibitor of Filovirus infection*. Antimicrob. Agents Chemother. (2010) 54: 2152-2159; Yermolina, M., et al. *Discovery, synthesis, and biological evaluation of a novel group of selective inhibitors of filovirus entry*. J. Med. Chem. (2011) 54: 765 – 781; Basu, A., et al. *Identification of a small-molecule entry inhibitor for Filoviruses*. J. Virol. (2011) 85: 3106-3119; Lee, K., et al., *Inhibition of Ebola virus infection: identification of Niemann-Pick as the target by optimization of a chemical probe*. ACS Med. Chem. Lett. (2013) 4: 239-243; Madrid, P. B., et al. *A Systematic screen of FDA-approved drugs for inhibitors of biological threat agents* Plos One (2013) 8: 1-14; Elshabrawy, H. A., et al. *Identification of a broad-spectrum antiviral small molecule against severe acute respiratory syndrome Coronavirus and Ebola, Hendra, and Nipah Viruses by using a novel high-throughput screening assay*. J. Virol. (2014) 88: 4353-4365].

Filovirus infections are associated with hemorrhagic fevers, the clinical manifestations of which may be severe and/or fatal. As described herein, for the current invention, VSV pseudotyped viruses expressing filovirus glycoproteins can be generated and screened with a collection of chemical compounds to identify those compounds that inhibit infectivity. The identification of inhibitors of filovirus glycoprotein-mediated virus cell entry may be utilized to treat infections of filoviruses to provide effective therapeutic regimens for the prophylaxis and/or treatment of filoviruses or any newly emerging virus, whether native or engineered, whose cell entry properties may be determined by filovirus glycoproteins.

The *Filoviridae* virus family is comprised of at least three genera: *Ebolavirus*, which currently includes five species Zaire (EBOV), Sudan (SUDV), Bundibugyo (BDBV), Tai Forest (TAFV) and Reston (RESTV), *Marburgvirus*, which currently includes two species Marburg (MARV) and Ravn (RAVV), and *Cuevavirus*, which currently includes a single species Llovia virus (LLOV). RAVV and LLOV are examples of filoviruses that have been identified only recently and a number of additional new species and genera may continue to emerge.

Table 2: Family *Filoviridae*: currently identified filovirus genera, species, and nomenclature

Genus name	Species name	Virus name (Abbreviation)
<i>Cuevavirus</i>	<i>Lloviu cuevavirus</i>	Lloviu virus (LLOV)
<i>Ebolavirus</i>	<i>Bundibugyo ebolavirus</i>	Bundibugyo virus (BDBV)
	<i>Reston ebolavirus</i>	Reston virus (RESTV)
	<i>Sudan ebolavirus</i>	Sudan virus (SUDV)
	<i>Tai Forest ebolavirus</i>	Tai Forest virus (TAFV)
	<i>Zaire ebolavirus</i>	Ebola virus (EBOV)
<i>Marburgvirus</i>	<i>Marburg marburgvirus</i>	Marburg virus (MARV)
		Ravn virus (RAVV)

Glycoproteins from *Filoviridae* family members can be expressed in pseudotyped viruses (e.g. VSV pseudotype) to identify compounds that inhibit filovirus infection. Based on the structural similarities and/or differences between the viral glycoprotein target and/or host cell targets, the inhibitor compounds may act on only a single filovirus glycoprotein or on a broad spectrum of filoviruses. Furthermore, given the basic functional and structural similarities of glycoproteins among different families of enveloped viruses it is probable that a given compound class may act across a broad range of enveloped viruses.

Alignments of representative filovirus glycoprotein sequences were generated to illustrate the amino acid homology among different filovirus species.

Table 3: Homology of filovirus glycoproteins - created by Clustal2.1

Species/Genbank ID	Zaire	Bundi	T Forest	Reston	Sudan	Marburg
Zaire/AAB81004	100	68.0	66.5	59.9	56.8	32.7
Bundibugyo/AGL73453	68.0	100	73.6	60.4	57.7	33.0
Tai Forest/YP_003815426	66.5	73.6	100	59.5	57.7	33.9
Reston/BAB69006	59.9	60.4	59.5	100	61.4	32.7
Sudan/AAB37096	56.8	57.7	57.7	61.4	100	33.0
Marburg/AAC40460	32.7	33.0	33.9	32.7	33.0	100

A matrix comparison of the amino acid homology (homology is defined as the number of identities between any two sequences, divided by the length of the alignment, and represented as a percentage) as determined from the Clustal2.1 program (<http://www.ebi.ac.uk/Tools/msa/clustalo/>) among and between distinct filovirus genus and species is illustrated in Table 3. Glycoproteins among virus species within the same filovirus genus (e.g., *Ebolavirus*) are more homologous to each other than to those in another genus (Marburgvirus). However, currently available filovirus glycoproteins exhibit significant homology (>30% identity from any one member to another). Given this homology for some chemical series it is possible to identify compounds that exhibit activity against a broad-spectrum of filoviruses.

Similar alignments were subsequently carried out with a number of class I glycoproteins from other enveloped virus families. Each of the glycoproteins from the other enveloped viruses exhibit <20% identity with any of the filovirus glycoproteins. Although there are similarities in functional and structural characteristics among the class I glycoproteins, there are clear distinctions including dependence on low pH, receptor binding, location of the fusion peptide [White, J.M.; Delos, S.E.; Brecher, M.; Schornberg, K. *Structures and mechanisms of viral membrane fusion proteins: multiple variations on a common theme*. Crit. Rev. Biochem. Mol. Biol. (2008) 43:189-219] and given the low amino acid sequence homology across class I virus families it becomes unlikely that a given chemical series that inhibits filovirus cell entry/fusion would also exhibit similar inhibitory activities with other envelope class I glycoprotein virus families.

Table 4: Homology matrix between filoviruses and other class I glycoprotein viruses-created by Clustal2.1

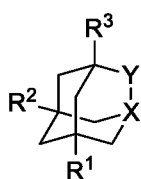
Z AAB81004	100	66.5	68.0	56.8	59.9	32.7	17.0	12.8	13.4	14.2	13.7
T YP_003815426	66.5	100	73.6	57.7	59.5	33.9	17.7	12.0	12.0	13.8	14.2
B AGL73453	68.0	73.6	100	57.7	60.4	33.0	17.9	12.3	12.3	13.4	14.7
S AAB37096	56.8	57.7	57.7	100	61.4	33.0	16.4	12.9	13.0	14.8	12.8
R BAB69006	59.9	59.5	60.4	61.4	100	32.7	19.8	12.9	11.8	14.6	13.5
M AAC40460	32.7	33.9	33.0	33.0	32.7	100	15.7	10.7	8.7	12.2	14.1
INF ACP41105	17.0	17.7	17.9	16.4	19.8	15.7	100	14.5	12.6	11.8	11.2
LASV NP_694870	12.8	12.0	12.3	12.9	12.9	10.7	14.5	100	43.2	18.8	18.3
JUNV AY619641	13.4	12.0	12.3	13.0	11.8	8.7	12.6	43.2	100	15.2	14.3
Nipah AP238467	14.2	13.8	13.4	14.8	14.6	12.2	11.8	18.8	15.2	100	20.8
Measles AF21882	13.7	14.2	14.7	12.8	11.2	14.1	13.5	18.3	14.3	20.8	100

Abbreviations: M: Marburg, Z: Zaire, T: Tai Forest, B: Bundibugyo, S: Sudan, R: Reston, INF: Influenza, LASV: Lassa virus, JUNV: Junin virus; Genbank ID in bold

BRIEF SUMMARY OF THE INVENTION

The present invention relates to methods of inhibiting filoviruses (or any virus whose cell entry is mediated by filovirus glycoproteins) infection in humans, other mammals, or in cell culture, to treating filovirus infection, to methods of inhibiting the replication of filoviruses, to methods of reducing the amount of *filoviruses*, and to compositions that can be employed for such methods. These methods, applications, and compositions apply not only to *Filoviridae* viruses but also to any virus, whether naturally emerging or engineered, whose cell entry properties are determined by filovirus glycoproteins.

In one embodiment, the method comprises administering to humans, other mammals, cell culture, or biological sample an effective amount of a compound represented by Structural Formula I for treatment of filovirus infection



I

or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

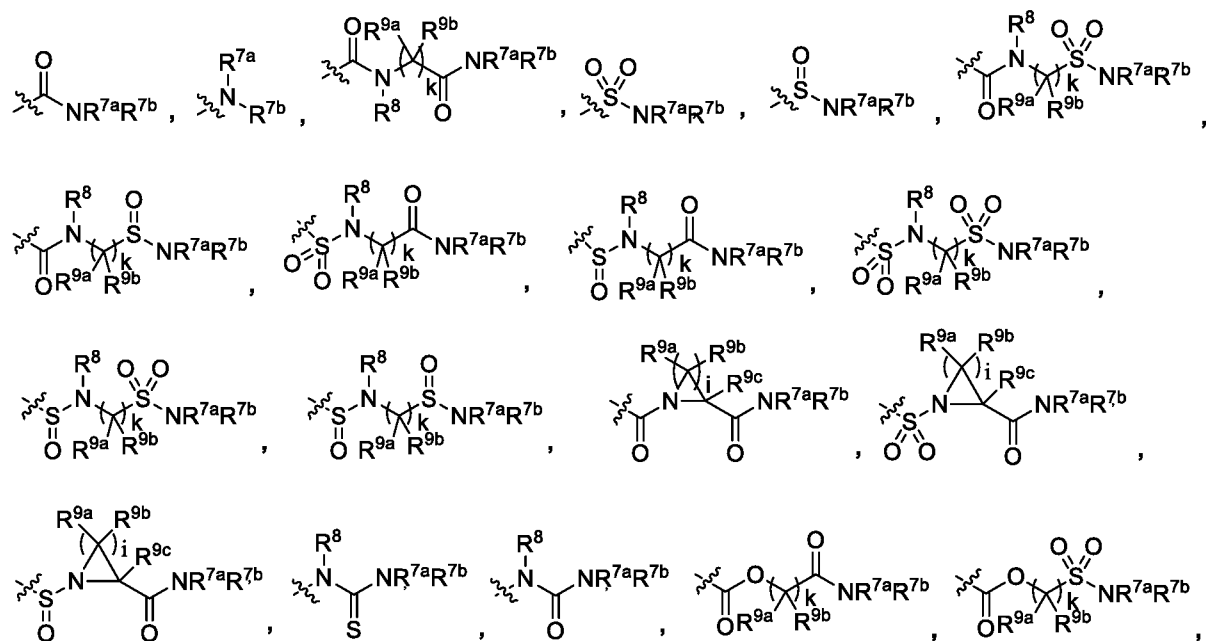
X is C-A-D, and Y is a bond or CR⁴R⁵; or

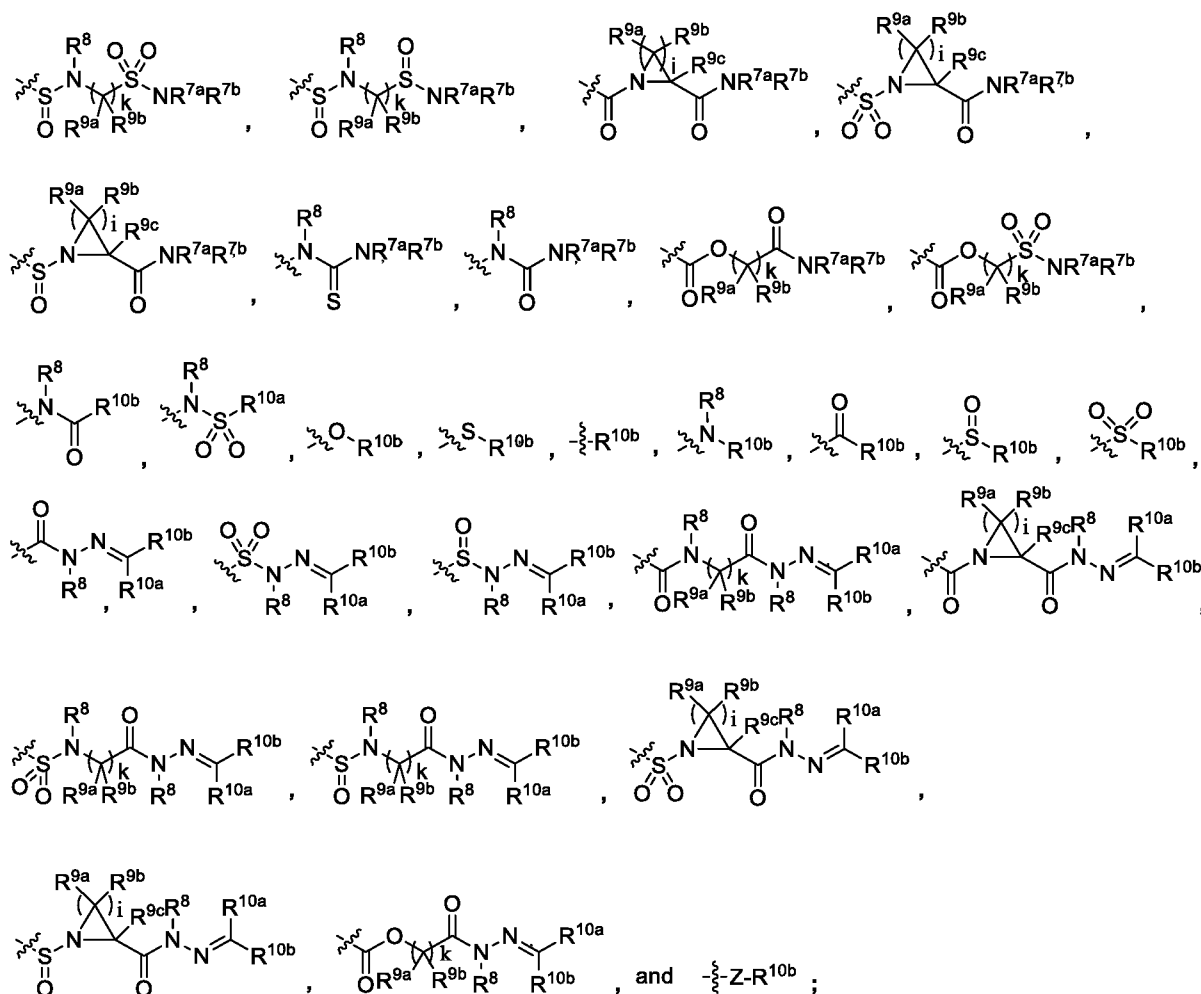
X is CR⁵ and Y is CR⁴-A-D;

A is -C(R^{6a}R^{6b})_i-, (C₆ to C₁₀) arylene, or (C₂ to C₉) heteroarylene, wherein

each of the said (C₆ to C₁₀) arylene or (C₂ to C₉) heteroarylene is optionally substituted with at least one R^{6a} group;

D is selected from the group consisting of





R¹ is selected from hydrogen, halogen, OH, nitro, CF₃, -NR^{11a}R^{11b}, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, cyano, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, -C(O)R¹², -C(O)NR^{11a}R^{11b}, -S(O)_mR¹², -S(O)_mNR^{11a}R^{11b}, -NR^{11a}S(O)_mR¹², -(CH₂)_nC(O)OR¹², -(CH₂)_nCO)N(R^{11a}R^{11b}), -(CH₂)_nN(R^{11a}R^{11b}), -OC(O)R¹², -NR^{11a}C(O)R¹², and -NR^{11a}C(O)N(R^{11a}R^{11b}), wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl is optionally substituted with at least one R¹³ group;

R² is selected from hydrogen, halogen, OH, nitro, CF₃, -NR^{11a}R^{11b}, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, cyano, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, -C(O)R¹², -C(O)NR^{11a}R^{11b}, -S(O)_mR¹², -S(O)_mNR^{11a}R^{11b}, -NR^{11a}S(O)_mR¹², -(CH₂)_nC(O)OR¹², -(CH₂)_nCO)N(R^{11a}R^{11b}), -(CH₂)_nN(R^{11a}R^{11b}), -OC(O)R¹², -NR^{11a}C(O)R¹², and -NR^{11a}C(O)N(R^{11a}R^{11b}), wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl is optionally substituted with at least one R¹³ group;

R³ is selected from hydrogen, halogen, OH, nitro, CF₃, -NR^{11a}R^{11b}, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, cyano, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, -C(O)R¹², -C(O)NR^{11a}R^{11b}, -S(O)_mR¹², -S(O)_mNR^{11a}R^{11b}, -NR^{11a}S(O)_mR¹², -(CH₂)_nC(O)OR¹², -(CH₂)_nC(O)N(R^{11a}R^{11b}), -(CH₂)_nN(R^{11a}R^{11b}), -OC(O)R¹², -NR^{11a}C(O)R¹², and -NR^{11a}C(O)N(R^{11a}R^{11b}), wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl is optionally substituted with at least one R¹³ group;

R⁴ is selected from hydrogen, halogen, OH, nitro, CF₃, -NR^{11a}R^{11b}, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, cyano, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, -C(O)R¹², -C(O)NR^{11a}R^{11b}, -S(O)_mR¹², -S(O)_mNR^{11a}R^{11b}, -NR^{11a}S(O)_mR¹², -(CH₂)_nC(O)OR¹², -(CH₂)_nC(O)N(R^{11a}R^{11b}), -(CH₂)_nN(R^{11a}R^{11b}), -OC(O)R¹², -NR^{11a}C(O)R¹², and -NR^{11a}C(O)N(R^{11a}R^{11b}), wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl is optionally substituted with at least one R¹³ group;

R⁵ is selected from hydrogen, halogen, OH, nitro, CF₃, -NR^{11a}R^{11b}, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, cyano, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, -C(O)R¹², -C(O)NR^{11a}R^{11b}, -S(O)_mR¹², -S(O)_mNR^{11a}R^{11b}, -NR^{11a}S(O)_mR¹², -(CH₂)_nC(O)OR¹², -(CH₂)_nC(O)N(R^{11a}R^{11b}), -(CH₂)_nN(R^{11a}R^{11b}), -OC(O)R¹², -NR^{11a}C(O)R¹², and -NR^{11a}C(O)N(R^{11a}R^{11b}), wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl is optionally substituted with at least one R¹³ group;

each of the R^{6a} and R^{6b} is independently selected from hydrogen, halogen, OH, nitro, CF₃, -NR^{11a}R^{11b}, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, cyano, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, -C(O)R¹², -C(O)NR^{11a}R^{11b}, -S(O)_mR¹², -S(O)_mNR^{11a}R^{11b}, -NR^{11a}S(O)_mR¹², -(CH₂)_nC(O)OR¹², -(CH₂)_nC(O)N(R^{11a}R^{11b}), -(CH₂)_nN(R^{11a}R^{11b}), -OC(O)R¹², -NR^{11a}C(O)R¹², and -NR^{11a}C(O)N(R^{11a}R^{11b}), wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl is optionally substituted with at least one R¹³ group;

each of the R^{7a} and R^{7b} is independently selected from hydrogen, (C_1 to C_{10}) alkyl, (C_1 to C_{10}) alkenyl, (C_1 to C_{10}) alkynyl, (C_1 to C_{10}) alkoxy, aryloxy, $NR^{11a}R^{11b}$, (C_3 to C_{10}) cycloalkyl, (C_5 to C_{10}) cycloalkenyl, (C_2 to C_9) cycloheteroalkyl, (C_6 to C_{10}) aryl, (C_2 to C_9) heteroaryl, (C_6 to C_{10}) arylene, and (C_2 to C_9) heteroarylene, wherein

each of the said (C_1 to C_{10}) alkyl, (C_1 to C_{10}) alkenyl, (C_1 to C_{10}) alkynyl, (C_1 to C_{10}) alkoxy, aryloxy, (C_3 to C_{10}) cycloalkyl, (C_5 to C_{10}) cycloalkenyl, (C_2 to C_9) cycloheteroalkyl, (C_6 to C_{10}) aryl, (C_2 to C_9) heteroaryl, (C_6 to C_{10}) arylene, and (C_2 to C_9) heteroarylene is optionally substituted with at least one R^{13} group,

or R^{7a} and R^{7b} may be taken together with the nitrogen atom to which they are attached to form a (C_2 to C_{10}) cycloheteroalkyl ring, wherein

said (C_2 to C_{10}) membered cycloheteroalkyl ring has 1 to 3 ring heteroatoms selected from the group consisting of N, O, and S, and wherein

the said (C_2 to C_{10}) membered cycloheteroalkyl ring is optionally substituted with at least one R^{13} group;

each R^8 is independently selected from hydrogen, (C_1 to C_{10}) alkyl, (C_1 to C_{10}) alkenyl, (C_1 to C_{10}) alkynyl, (C_1 to C_{10}) alkoxy, aryloxy, (C_3 to C_{10}) cycloalkyl, (C_5 to C_{10}) cycloalkenyl, (C_2 to C_9) cycloheteroalkyl, (C_6 to C_{10}) aryl, (C_2 to C_9) heteroaryl, (C_6 to C_{10}) arylene, and (C_2 to C_9) heteroarylene, wherein

each of the said (C_1 to C_{10}) alkyl, (C_1 to C_{10}) alkenyl, (C_1 to C_{10}) alkynyl, (C_1 to C_{10}) alkoxy, aryloxy, (C_3 to C_{10}) cycloalkyl, (C_5 to C_{10}) cycloalkenyl, (C_2 to C_9) cycloheteroalkyl, (C_6 to C_{10}) aryl, (C_2 to C_9) heteroaryl, (C_6 to C_{10}) arylene, and (C_2 to C_9) heteroarylene is optionally substituted with at least one R^{13} group;

each of the R^{9a} , R^{9b} , and R^{9c} is independently selected from hydrogen, halogen, OH, nitro, CF_3 , $-NR^{11a}R^{11b}$, (C_1 to C_{10}) alkyl, (C_1 to C_{10}) alkenyl, (C_1 to C_{10}) alkynyl, (C_1 to C_{10}) alkoxy, aryloxy, cyano, (C_3 to C_{10}) cycloalkyl, (C_5 to C_{10}) cycloalkenyl, (C_2 to C_9) cycloheteroalkyl, (C_6 to C_{10}) aryl, (C_2 to C_9) heteroaryl, $-C(O)R^{12}$, $-C(O)NR^{11a}R^{11b}$, $-S(O)_mR^{12}$, $-S(O)_mNR^{11a}R^{11b}$, $-NR^{11a}S(O)_mR^{12}$, $-(CH_2)_nC(O)OR^{12}$, $-(CH_2)_nC(O)N(R^{11a}R^{11b})$, $-(CH_2)_nN(R^{11a}R^{11b})$, $-OC(O)R^{12}$, $-NR^{11a}C(O)R^{12}$, and $-NR^{11a}C(O)N(R^{11a}R^{11b})$, wherein

each of the said (C_1 to C_{10}) alkyl, (C_1 to C_{10}) alkenyl, (C_1 to C_{10}) alkynyl, (C_1 to C_{10}) alkoxy, aryloxy, (C_3 to C_{10}) cycloalkyl, (C_5 to C_{10}) cycloalkenyl, (C_2 to C_9) cycloheteroalkyl, (C_6 to C_{10}) aryl, and (C_2 to C_9) heteroaryl is optionally substituted with at least one R^{13} group;

each of the R^{10a} and R^{10b} is independently selected from hydrogen, (C_1 to C_{10}) alkyl, (C_1 to C_{10}) alkenyl, (C_1 to C_{10}) alkynyl, (C_3 to C_{10}) cycloalkyl, (C_5 to C_{10}) cycloalkenyl, (C_2 to C_9) cycloheteroalkyl, (C_6 to C_{10}) aryl, (C_2 to C_9) heteroaryl, wherein

each of the said (C_1 to C_{10}) alkyl, (C_1 to C_{10}) alkenyl, (C_1 to C_{10}) alkynyl, (C_3 to C_{10}) cycloalkyl, (C_5 to C_{10}) cycloalkenyl, (C_2 to C_9) cycloheteroalkyl, (C_6 to C_{10}) aryl, (C_2 to C_9) heteroaryl is optionally substituted with at least one R^{13} group;

each of the R^{11a} and R^{11b} is independently selected from hydrogen, (C_1 to C_{10}) alkyl, (C_1 to C_{10}) alkenyl, (C_1 to C_{10}) alkynyl, (C_1 to C_{10}) alkoxy, aryloxy, (C_3 to C_{10}) cycloalkyl, (C_5 to C_{10})

cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, and (C₂ to C₉) heteroarylene, wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, and (C₂ to C₉) heteroarylene is optionally substituted with at least one R¹³ group,

or R^{11a} and R^{11b} may be taken together with the nitrogen atom to which they are attached to form a (C₂ to C₁₀) cycloheteroalkyl ring, wherein

said (C₂ to C₁₀) cycloheteroalkyl ring has 1 to 3 ring heteroatoms selected from the group consisting of N, O, and S, and wherein

the said (C₂ to C₁₀) cycloheteroalkyl ring is optionally substituted with at least one R¹³ group;

each of the R¹² is independently selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl, wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl is optionally substituted with at least one R¹³ group;

each R¹³ is independently selected from hydrogen, halogen, OH, nitro, CF₃, -NR^{14a}R^{14b}, oxo, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, cyano, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, (C₂ to C₉) heteroarylene, (C₃ to C₁₀) cycloalkylene, (C₂ to C₁₀) cycloheteroalkylene, -C(O)R¹⁵, -C(O)NR^{14a}R^{14b}, -S(O)_mR¹⁵, -S(O)_mNR^{14a}R^{14b}, -NR^{14a}S(O)_mR¹⁵, -(CH₂)_nC(O)OR¹⁵, -(CH₂)_nC(O)N(R^{14a}R^{14b}), -(CH₂)_nN(R^{14a}R^{14b}), -OC(O)R¹⁵, -O(CH₂)_nO-, -NR^{14a}C(O)R¹⁵, and -NR^{14a}C(O)N(R^{14a}R^{14b}), wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, (C₂ to C₉) heteroarylene, (C₃ to C₁₀) cycloalkylene, and (C₂ to C₁₀) cycloheteroalkylene is optionally substituted with at least one R¹⁶ group;

each of the R^{14a} and R^{14b} is independently selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, and (C₂ to C₉) heteroarylene, wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, and (C₂ to C₉) heteroarylene is optionally substituted with at least one R¹⁶ group,

or R^{14a} and R^{14b} may be taken together with the nitrogen atom to which they are attached to form a (C₂ to C₁₀) cycloheteroalkyl ring, wherein

said (C₂ to C₁₀) cycloheteroalkyl ring has 1 to 3 ring heteroatoms selected from the group consisting of N, O, and S, and wherein

the said (C₂ to C₁₀) cycloheteroalkyl ring is optionally substituted with at least one R¹⁶ group;
 each R¹⁵ is independently selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl, wherein

5 each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl is optionally substituted with at least one R¹⁶ group;

each R¹⁶ is independently selected from hydrogen, halogen, OH, nitro, CF₃, -NR^{17a}R^{17b}, oxo, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, cyano, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, (C₂ to C₉) heteroarylene, (C₃ to C₁₀) cycloalkylene, (C₂ to C₁₀) cycloheteroalkylene, -C(O)R¹⁸, -C(O)NR^{17a}R^{17b}, -S(O)_mR¹⁸, -S(O)_mNR^{17a}R^{17b}, -NR^{17a}S(O)_mR¹⁸, -(CH₂)_nC(O)OR¹⁸, -(CH₂)_nC(O)N(R^{17a}R^{17b}), -(CH₂)_nN(R^{17a}R^{17b}), -OC(O)R¹⁸, -NR^{17a}C(O)R¹⁸, and -NR^{17a}C(O)N(R^{17a}R^{17b}), wherein

15 each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) aryl, (C₆ to C₁₀) arylene, (C₂ to C₉) heteroarylene, (C₃ to C₁₀) cycloalkylene, and (C₂ to C₁₀) cycloheteroalkylene is optionally substituted with at least one R¹⁹ group;

each of the R^{17a} and R^{17b} is independently selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, and (C₂ to C₉) heteroarylene, wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, and (C₂ to C₉) heteroarylene is optionally substituted with at least one R¹⁹ group,

or R^{17a} and R^{17b} may be taken together with the nitrogen atom to which they are attached to form a (C₂ to C₁₀) cycloheteroalkyl ring, wherein

30 said (C₂ to C₁₀) cycloheteroalkyl ring has 1 to 3 ring heteroatoms selected from the group consisting of N, O, and S, and wherein

the said (C₂ to C₁₀) cycloheteroalkyl ring is optionally substituted with at least one R¹⁹ group;

each R¹⁸ is independently selected from hydrogen, halogen, OH, nitro, CF₃, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, cyano, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl, wherein

35 each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₂ to C₉) heteroaryl, and (C₆ to C₁₀) aryl is optionally substituted with at least one R¹⁹ group;

each R¹⁹ is independently selected from hydrogen, halogen, OH, nitro, CF₃, -NR^{20a}R^{20b}, oxo, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, cyano, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl,

(C₆ to C₁₀) arylene, (C₂ to C₉) heteroarylene, (C₃ to C₁₀) cycloalkylene, (C₂ to C₁₀) cycloheteroalkylene, -C(O)R²¹, -C(O)NR^{20a}R^{20b}, -S(O)_mR²¹, -S(O)_mNR^{20a}R^{20b}, -NR^{20a}S(O)_mR²¹, -(CH₂)_nC(O)OR²¹, -(CH₂)_nC(O)N(R^{20a}R^{20b}), -(CH₂)_nN(R^{20a}R^{20b}), -OC(O)R²¹, -NR^{20a}C(O)R²¹, and -NR^{20a}C(O)N(R^{20a}R^{20b}), wherein

5 each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, (C₂ to C₉) heteroarylene, (C₃ to C₁₀) cycloalkylene, and (C₂ to C₁₀) cycloheteroalkylene is optionally substituted with at least one R²² group;

10 each of the R^{20a} and R^{20b} is independently selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl, wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl is optionally substituted with at least one R²² group,

15 or R^{20a} and R^{20b} may be taken together with the nitrogen atom to which they are attached to form a (C₂ to C₁₀) cycloheteroalkyl ring, wherein

said (C₂ to C₁₀) cycloheteroalkyl ring has 1 to 3 ring heteroatoms selected from the group consisting of N, O, and S, and wherein

the said (C₂ to C₁₀) cycloheteroalkyl ring is optionally substituted with at least one R²² group;

20 each R²¹ is independently selected from hydrogen, halogen, OH, nitro, CF₃, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, cyano, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl;

25 each R²² is independently selected from hydrogen, halogen, OH, nitro, CF₃, -NR^{23a}R^{23b}, oxo, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, cyano, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, (C₂ to C₉) heteroarylene, (C₃ to C₁₀) cycloalkylene, (C₂ to C₁₀) cycloheteroalkylene, -C(O)R²⁴, -C(O)NR^{23a}R^{23b}, -S(O)_mR²⁴, -S(O)_mNR^{23a}R^{23b}, -NR^{23a}S(O)_mR²⁴, -(CH₂)_nC(O)OR²⁴, -(CH₂)_nC(O)N(R^{23a}R^{23b}), -(CH₂)_nN(R^{23a}R^{23b}), -OC(O)R²⁴, -NR^{23a}C(O)R²⁴, and -NR^{23a}C(O)N(R^{23a}R^{23b}), wherein

30 each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, (C₂ to C₉) heteroarylene, (C₃ to C₁₀) cycloalkylene, and (C₂ to C₁₀) cycloheteroalkylene is optionally substituted with at least one R²⁵ group;

35 each of the R^{23a} and R^{23b} is independently selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₂ to C₉) heteroaryl, and (C₆ to C₁₀) aryl;

each R²⁴ is independently selected from hydrogen, halogen, OH, nitro, CF₃, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, cyano, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl;

each R^{25} is independently selected from hydrogen, halogen, OH, nitro, CF_3 , $-NR^{26a}R^{26b}$, oxo, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, cyano, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, (C₂ to C₉) heteroarylene, (C₃ to C₁₀) cycloalkylene, (C₂ to C₁₀) cycloheteroalkylene, $-C(O)R^{27}$, $-C(O)NR^{26a}R^{26b}$, $-S(O)_mR^{27}$, $-S(O)_mNR^{26a}R^{26b}$, $-NR^{26a}S(O)_mR^{27}$, $-(CH_2)_nC(O)OR^{27}$, $-(CH_2)_nC(O)N(R^{26a}R^{26b})$, $-(CH_2)_nN(R^{26a}R^{26b})$, $-OC(O)R^{27}$, $-NR^{26a}C(O)R^{27}$, and $-NR^{26a}C(O)N(R^{26a}R^{26b})$, wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, (C₂ to C₉) heteroarylene, (C₃ to C₁₀) cycloalkylene, and (C₂ to C₁₀) cycloheteroalkylene is optionally substituted with at least one R^{27} group;

each of the R^{26a} and R^{26b} is independently selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl,

or R^{26a} and R^{26b} may be taken together with the nitrogen atom to which they are attached to form a (C₂ to C₁₀) cycloheteroalkyl ring, wherein

said (C₂ to C₁₀) cycloheteroalkyl ring has 1 to 3 ring heteroatoms selected from the group consisting of N, O, and S;

each R^{27} is independently selected from hydrogen, halogen, OH, nitro, CF_3 , (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, cyano, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl;

h is 1 or 2;

i is 2, 3, 4, 5, or 6;

j is 0, 1, 2, 3, 4, or 5;

k is 1, 2, 3, 4, or 5;

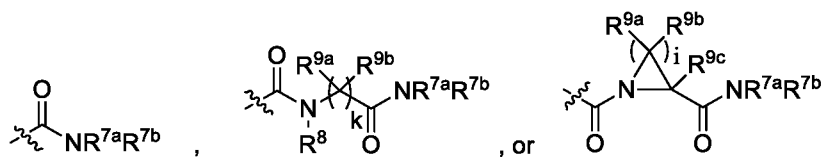
m is 0, 1 or 2;

n is 0, 1, 2, 3, or 4;

Z is selected from the group consisting of -O-, -S-, -S(O)-, and -S(O)₂-;

with the proviso that

when R^1 , R^2 , or R^3 is alkyl or hydrogen, X is $C-C(R^{6a}R^{6b})_i-D$, Y is CH_2 , and D is

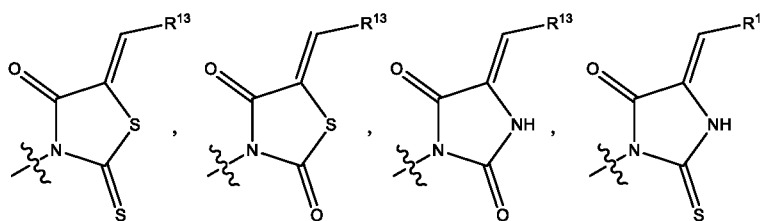


then $NR^{7a}R^{7b}$ cannot be an optionally substituted piperazine or 1,4-diazepane,

and with the proviso that

when X is CR^5 , Y is CR^4-D , D is $-NR^{7a}R^{7b}$, and R^{7a} and R^{7b} are taken together with the nitrogen atom to which they are attached to form a (C₂ to C₁₀) cycloheteroalkyl ring, the said (C₂ to C₁₀) membered cycloheteroalkyl ring cannot be selected from the group consisting of

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DESCRIPTION OF THE DRAWINGS

- 5 Figure 1: Depicts results of a pharmacokinetics (PK) study of compound A78 in male CD-1 mice. Shown are plasma concentrations of A78 after intravenous (iv) administration of 1mg/kg or oral (po) administration at 10 mg/kg dose over a 24 h period.

DETAILED DESCRIPTION OF THE INVENTION

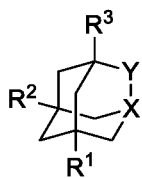
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The present invention relates to methods of inhibiting filoviruses (or any virus whose cell entry is mediated by filovirus glycoproteins) infection in humans, other mammals, or in cell culture, to treating filovirus infection, to methods of inhibiting the replication of filoviruses, to methods of reducing the amount of *filoviruses*, and to compositions that can be employed for such methods. These

15 methods, applications, and compositions apply not only to *Filoviridae* viruses but also to any virus, whether naturally emerging or engineered, whose cell entry properties are determined by filovirus glycoproteins.

In one embodiment, the method comprises administering to humans, other mammals, cell culture, or biological sample an effective amount of a compound represented by Structural Formula I

20 for treatment of filovirus infection



I

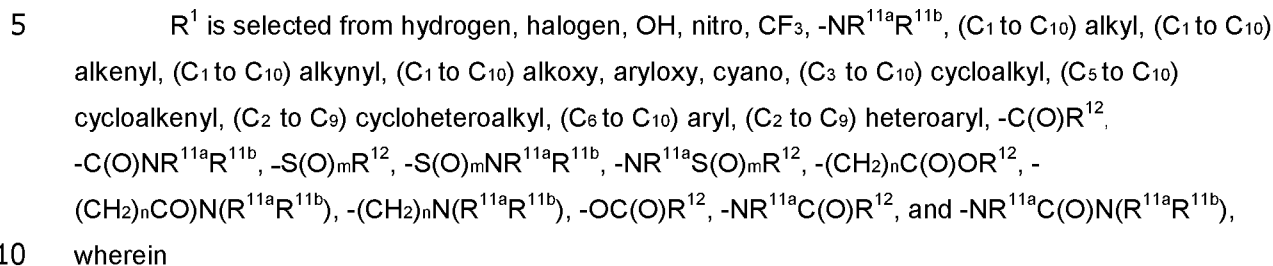
or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

X is C-A-D, and Y is a bond or CR⁴R⁵; or

25 X is CR⁵ and Y is CR⁴-A-D;

A is -C(R^{6a}R^{6b})_n-, (C₆ to C₁₀) arylene, or (C₂ to C₉) heteroarylene, wherein

each of the said (C₆ to C₁₀) arylene or (C₂ to C₉) heteroarylene is optionally substituted with at least one R^{6a} group;



each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl is optionally substituted with at least one R¹³ group;

R^2 is selected from hydrogen, halogen, OH, nitro, CF_3 , $-NR^{11a}R^{11b}$, $(C_1 \text{ to } C_{10})$ alkyl, $(C_1 \text{ to } C_{10})$ alkenyl, $(C_1 \text{ to } C_{10})$ alkynyl, $(C_1 \text{ to } C_{10})$ alkoxy, aryloxy, cyano, $(C_3 \text{ to } C_{10})$ cycloalkyl, $(C_5 \text{ to } C_{10})$ cycloalkenyl, $(C_2 \text{ to } C_9)$ cycloheteroalkyl, $(C_6 \text{ to } C_{10})$ aryl, $(C_2 \text{ to } C_9)$ heteroaryl, $-C(O)R^{12}$, $-C(O)NR^{11a}R^{11b}$, $-S(O)_mR^{12}$, $-S(O)_mNR^{11a}R^{11b}$, $-NR^{11a}S(O)_mR^{12}$, $-(CH_2)_nC(O)OR^{12}$, $-(CH_2)_nC(O)N(R^{11a}R^{11b})$, $-(CH_2)_nN(R^{11a}R^{11b})$, $-OC(O)R^{12}$, $-NR^{11a}C(O)R^{12}$, and $-NR^{11a}C(O)N(R^{11a}R^{11b})$, wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl is optionally substituted with at least one R¹³ group;

R³ is selected from hydrogen, halogen, OH, nitro, CF₃, -NR^{11a}R^{11b}, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, cyano, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, -C(O)R¹², -C(O)NR^{11a}R^{11b}, -S(O)_mR¹², -S(O)_mNR^{11a}R^{11b}, -NR^{11a}S(O)_mR¹², -(CH₂)_nC(O)OR¹², -(CH₂)_nC(O)N(R^{11a}R^{11b}), -(CH₂)_nN(R^{11a}R^{11b}), -OC(O)R¹², -NR^{11a}C(O)R¹², and -NR^{11a}C(O)N(R^{11a}R^{11b}), wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl is optionally substituted with at least one R¹³ group;

R⁴ is selected from hydrogen, halogen, OH, nitro, CF₃, -NR^{11a}R^{11b}, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, cyano, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, -C(O)R¹², -C(O)NR^{11a}R^{11b}, -S(O)_mR¹², -S(O)_mNR^{11a}R^{11b}, -NR^{11a}S(O)_mR¹², -(CH₂)_nC(O)OR¹², -(CH₂)_nC(O)N(R^{11a}R^{11b}), -(CH₂)_nN(R^{11a}R^{11b}), -OC(O)R¹², -NR^{11a}C(O)R¹², and -NR^{11a}C(O)N(R^{11a}R^{11b}), wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl is optionally substituted with at least one R¹³ group;

R⁵ is selected from hydrogen, halogen, OH, nitro, CF₃, -NR^{11a}R^{11b}, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, cyano, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, -C(O)R¹², -C(O)NR^{11a}R^{11b}, -S(O)_mR¹², -S(O)_mNR^{11a}R^{11b}, -NR^{11a}S(O)_mR¹², -(CH₂)_nC(O)OR¹², -(CH₂)_nC(O)N(R^{11a}R^{11b}), -(CH₂)_nN(R^{11a}R^{11b}), -OC(O)R¹², -NR^{11a}C(O)R¹², and -NR^{11a}C(O)N(R^{11a}R^{11b}), wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl is optionally substituted with at least one R¹³ group;

each of the R^{6a} and R^{6b} is independently selected from hydrogen, halogen, OH, nitro, CF₃, -NR^{11a}R^{11b}, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, cyano, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, -C(O)R¹², -C(O)NR^{11a}R^{11b}, -S(O)_mR¹², -S(O)_mNR^{11a}R^{11b}, -NR^{11a}S(O)_mR¹², -(CH₂)_nC(O)OR¹²,

$-(\text{CH}_2)_n\text{C}(\text{O})\text{N}(\text{R}^{11a}\text{R}^{11b})$, $-(\text{CH}_2)_n\text{N}(\text{R}^{11a}\text{R}^{11b})$, $-\text{OC}(\text{O})\text{R}^{12}$, $-\text{NR}^{11a}\text{C}(\text{O})\text{R}^{12}$, and $-\text{NR}^{11a}\text{C}(\text{O})\text{N}(\text{R}^{11a}\text{R}^{11b})$,
wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, and
5 (C₂ to C₉) heteroaryl is optionally substituted with at least one R¹³ group;

each of the R^{7a} and R^{7b} is independently selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, NR^{11a}R^{11b}, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, and
10 (C₂ to C₉) heteroarylene, wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, and (C₂ to C₉) heteroarylene is optionally substituted with at
least one R¹³ group,

or R^{7a} and R^{7b} may be taken together with the nitrogen atom to which they are attached to
15 form a (C₂ to C₁₀) cycloheteroalkyl ring, wherein

said (C₂ to C₁₀) membered cycloheteroalkyl ring has 1 to 3 ring heteroatoms selected from the group consisting of N, O, and S, and wherein

the said (C₂ to C₁₀) membered cycloheteroalkyl ring is optionally substituted with at least one R¹³ group;

each R⁸ is independently selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, and (C₂ to C₉) heteroarylene, wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, and (C₂ to C₉) heteroarylene is optionally substituted with at
25 least one R¹³ group;

each of the R^{9a}, R^{9b}, and R^{9c} is independently selected from hydrogen, halogen, OH, nitro, CF₃, -NR^{11a}R^{11b}, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, cyano, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, -C(O)R¹², -C(O)NR^{11a}R^{11b}, -S(O)_mR¹², -S(O)_mNR^{11a}R^{11b}, -NR^{11a}S(O)_mR¹², -
30 (CH₂)_nC(O)OR¹², -(CH₂)_nC(O)N(R^{11a}R^{11b}), -(CH₂)_nN(R^{11a}R^{11b}), -OC(O)R¹², -NR^{11a}C(O)R¹², and -NR^{11a}C(O)N(R^{11a}R^{11b}), wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, and
35 (C₂ to C₉) heteroaryl is optionally substituted with at least one R¹³ group;

each of the R^{10a} and R^{10b} is independently selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl is optionally substituted with at least one R¹³ group;

each of the R^{11a} and R^{11b} is independently selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, and (C₂ to C₉) heteroarylene, wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, and (C₂ to C₉) heteroarylene is optionally substituted with at least one R¹³ group,

or R^{11a} and R^{11b} may be taken together with the nitrogen atom to which they are attached to form a (C₂ to C₁₀) cycloheteroalkyl ring, wherein

said (C₂ to C₁₀) cycloheteroalkyl ring has 1 to 3 ring heteroatoms selected from the group consisting of N, O, and S, and wherein

the said (C₂ to C₁₀) cycloheteroalkyl ring is optionally substituted with at least one R¹³ group;

each of the R¹² is independently selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl, wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl is optionally substituted with at least one R¹³ group;

each R¹³ is independently selected from hydrogen, halogen, OH, nitro, CF₃, -NR^{14a}R^{14b}, oxo, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, cyano, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, (C₂ to C₉) heteroarylene, (C₃ to C₁₀) cycloalkylene, (C₂ to C₁₀) cycloheteroalkylene, -C(O)R¹⁵, -C(O)NR^{14a}R^{14b}, -S(O)_mR¹⁵, -S(O)_mNR^{14a}R^{14b}, -NR^{14a}S(O)_mR¹⁵, -(CH₂)_nC(O)OR¹⁵, -(CH₂)_nC(O)N(R^{14a}R^{14b}), -(CH₂)_nN(R^{14a}R^{14b}), -OC(O)R¹⁵, -O(CH₂)_nO-, -NR^{14a}C(O)R¹⁵, and -NR^{14a}C(O)N(R^{14a}R^{14b}), wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, (C₂ to C₉) heteroarylene, (C₃ to C₁₀) cycloalkylene, and (C₂ to C₁₀) cycloheteroalkylene is optionally substituted with at least one R¹⁶ group;

each of the R^{14a} and R^{14b} is independently selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, and (C₂ to C₉) heteroarylene, wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂

to C₉) heteroaryl, (C₆ to C₁₀) arylene, and (C₂ to C₉) heteroarylene is optionally substituted with at least one R¹⁶ group,

or R^{14a} and R^{14b} may be taken together with the nitrogen atom to which they are attached to form a (C₂ to C₁₀) cycloheteroalkyl ring, wherein

5 said (C₂ to C₁₀) cycloheteroalkyl ring has 1 to 3 ring heteroatoms selected from the group consisting of N, O, and S, and wherein

the said (C₂ to C₁₀) cycloheteroalkyl ring is optionally substituted with at least one R¹⁶ group;

each R¹⁵ is independently selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl, wherein

10 each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl is optionally substituted with at least one R¹⁶ group;

each R¹⁶ is independently selected from hydrogen, halogen, OH, nitro, CF₃, -NR^{17a}R^{17b}, oxo, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, cyano, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, (C₂ to C₉) heteroarylene, (C₃ to C₁₀) cycloalkylene, (C₂ to C₁₀) cycloheteroalkylene, -C(O)R¹⁸, -C(O)NR^{17a}R^{17b}, -S(O)_mR¹⁸, -S(O)_mNR^{17a}R^{17b}, -NR^{17a}S(O)_mR¹⁸, -(CH₂)_nC(O)OR¹⁸, -(CH₂)_nC(O)N(R^{17a}R^{17b}), -(CH₂)_nN(R^{17a}R^{17b}), -OC(O)R¹⁸, -NR^{17a}C(O)R¹⁸, and -NR^{17a}C(O)N(R^{17a}R^{17b}), wherein

20 each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) aryl, (C₆ to C₁₀) arylene, (C₂ to C₉) heteroarylene, (C₃ to C₁₀) cycloalkylene, and (C₂ to C₁₀) cycloheteroalkylene is optionally substituted with at least one R¹⁹ group;

25 each of the R^{17a} and R^{17b} is independently selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, and (C₂ to C₉) heteroarylene, wherein

30 each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, and (C₂ to C₉) heteroarylene is optionally substituted with at least one R¹⁹ group,

or R^{17a} and R^{17b} may be taken together with the nitrogen atom to which they are attached to form a (C₂ to C₁₀) cycloheteroalkyl ring, wherein

35 said (C₂ to C₁₀) cycloheteroalkyl ring has 1 to 3 ring heteroatoms selected from the group consisting of N, O, and S, and wherein

the said (C₂ to C₁₀) cycloheteroalkyl ring is optionally substituted with at least one R¹⁹ group;

each R¹⁸ is independently selected from hydrogen, halogen, OH, nitro, CF₃, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, cyano, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl, wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₂ to C₉) heteroaryl, and (C₆ to C₁₀) aryl is optionally substituted with at least one R¹⁹ group;

5 each R¹⁹ is independently selected from hydrogen, halogen, OH, nitro, CF₃, -NR^{20a}R^{20b}, oxo, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, cyano, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, (C₂ to C₉) heteroarylene, (C₃ to C₁₀) cycloalkylene, (C₂ to C₁₀) cycloheteroalkylene, -C(O)R²¹, -C(O)NR^{20a}R^{20b}, -S(O)_mR²¹, -S(O)_mNR^{20a}R^{20b}, -NR^{20a}S(O)_mR²¹, -
10 -(CH₂)_nC(O)OR²¹, -(CH₂)_nC(O)N(R^{20a}R^{20b}), -(CH₂)_nN(R^{20a}R^{20b}), -OC(O)R²¹, -NR^{20a}C(O)R²¹, and -NR^{20a}C(O)N(R^{20a}R^{20b}), wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, (C₂ to C₉) heteroarylene, (C₃ to C₁₀) cycloalkylene, and (C₂ to C₁₀) cycloheteroalkylene is optionally substituted with at least one R²² group;

15 each of the R^{20a} and R^{20b} is independently selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl, wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl is optionally substituted with at least one R²² group,

20 or R^{20a} and R^{20b} may be taken together with the nitrogen atom to which they are attached to form a (C₂ to C₁₀) cycloheteroalkyl ring, wherein

said (C₂ to C₁₀) cycloheteroalkyl ring has 1 to 3 ring heteroatoms selected from the group consisting of N, O, and S, and wherein

25 the said (C₂ to C₁₀) cycloheteroalkyl ring is optionally substituted with at least one R²² group;

each R²¹ is independently selected from hydrogen, halogen, OH, nitro, CF₃, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, cyano, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl;

each R²² is independently selected from hydrogen, halogen, OH, nitro, CF₃, -NR^{23a}R^{23b}, oxo, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, cyano, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, (C₂ to C₉) heteroarylene, (C₃ to C₁₀) cycloalkylene, (C₂ to C₁₀) cycloheteroalkylene, -C(O)R²⁴, -C(O)NR^{23a}R^{23b}, -S(O)_mR²⁴, -S(O)_mNR^{23a}R^{23b}, -NR^{23a}S(O)_mR²⁴, -
30 -(CH₂)_nC(O)OR²⁴, -(CH₂)_nC(O)N(R^{23a}R^{23b}), -(CH₂)_nN(R^{23a}R^{23b}), -OC(O)R²⁴, -NR^{23a}C(O)R²⁴, and -NR^{23a}C(O)N(R^{23a}R^{23b}), wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, (C₂ to C₉) heteroarylene, (C₃ to C₁₀) cycloalkylene, and (C₂ to C₁₀) cycloheteroalkylene is optionally substituted with at least one R²⁵ group;

each of the R^{23a} and R^{23b} is independently selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₂ to C₉) heteroaryl, and (C₆ to C₁₀) aryl;

5 each R^{24} is independently selected from hydrogen, halogen, OH, nitro, CF₃, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, cyano, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl;

10 each R^{25} is independently selected from hydrogen, halogen, OH, nitro, CF₃, $-NR^{26a}R^{26b}$, oxo, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, cyano, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, (C₂ to C₉) heteroarylene, (C₃ to C₁₀) cycloalkylene, (C₂ to C₁₀) cycloheteroalkylene, $-C(O)R^{27}$, $-C(O)NR^{26a}R^{26b}$, $-S(O)_mR^{27}$, $-S(O)_mNR^{26a}R^{26b}$, $-NR^{26a}S(O)_mR^{27}$, $-(CH_2)_nC(O)OR^{27}$, $-(CH_2)_nC(O)N(R^{26a}R^{26b})$, $-(CH_2)_nN(R^{26a}R^{26b})$, $-OC(O)R^{27}$, $-NR^{26a}C(O)R^{27}$, and $-NR^{26a}C(O)N(R^{26a}R^{26b})$, wherein

15 each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, (C₂ to C₉) heteroarylene, (C₃ to C₁₀) cycloalkylene, and (C₂ to C₁₀) cycloheteroalkylene is optionally substituted with at least one R^{27} group;

20 each of the R^{26a} and R^{26b} is independently selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl,

or R^{26a} and R^{26b} may be taken together with the nitrogen atom to which they are attached to form a (C₂ to C₁₀) cycloheteroalkyl ring, wherein

said (C₂ to C₁₀) cycloheteroalkyl ring has 1 to 3 ring heteroatoms selected from the group consisting of N, O, and S;

25 each R^{27} is independently selected from hydrogen, halogen, OH, nitro, CF₃, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, cyano, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl;

h is 1 or 2;

i is 2, 3, 4, 5, or 6;

30 j is 0, 1, 2, 3, 4, or 5;

k is 1, 2, 3, 4, or 5;

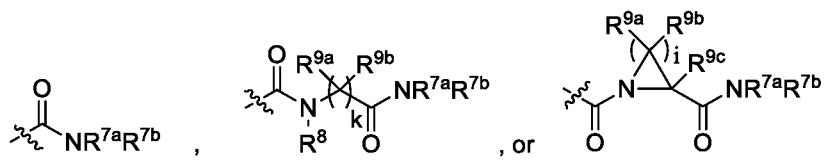
m is 0, 1 or 2;

n is 0, 1, 2, 3, or 4;

Z is selected from the group consisting of -O-, -S-, -S(O)-, and -S(O)₂-;

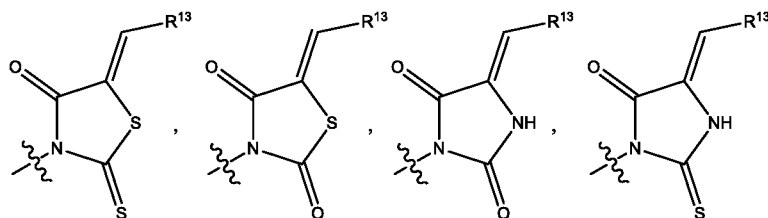
35 with the proviso that

when R^1 , R^2 , or R^3 is alkyl or hydrogen, X is $C-C(R^{6a}R^{6b})_j$ -D, Y is CH₂, and D is



then $\text{NR}^{7a}\text{R}^{7b}$ cannot be an optionally substituted piperazine or 1,4-diazepane, and with the proviso that

when X is CR^5 , Y is $\text{CR}^4\text{-D}$, D is $-\text{NR}^{7a}\text{R}^{7b}$, and R^{7a} and R^{7b} are taken together with the nitrogen atom to which they are attached to form a (C_2 to C_{10}) cycloheteroalkyl ring, the said (C_2 to C_{10}) membered cycloheteroalkyl ring cannot be selected from the group consisting of



In another embodiment, the method comprises administering to humans, other mammals, cell culture, or biological sample an effective amount of a compound represented by Structural Formula I for treatment of *Ebolavirus* infection.

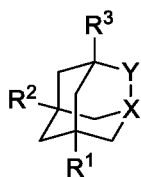
In another embodiment, the method comprises administering to humans, other mammals, cell culture, or biological sample an effective amount of a compound represented by Structural Formula I for treatment of *Marburgvirus* infection.

In another embodiment, the method comprises of inhibiting Ebolavirus.

In another embodiment, the method comprises of including administering a therapeutic amount of a therapeutic agent selected from the group consisting of Ribavirin, viral RNA-dependent-RNA-polymerase inhibitors, Favipiravir, Triazavirin, GS-5734, small interfering RNAs (siRNAs) and microRNAs, vaccines, and immunomodulators.

In another embodiment, the method comprises of inhibiting of Ebolavirus glycoprotein.

In another embodiment, the invention relates to compounds of Structural Formula I,



I

or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

X is C-A-D and Y is CR^4R^5 , wherein A-D is defined as before.

In another embodiment, the invention relates to compounds of Structural Formula I, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

X is C-A-D and Y is a bond, wherein A-D is defined as before.

In another embodiment, the invention relates to compounds of Structural Formula I, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

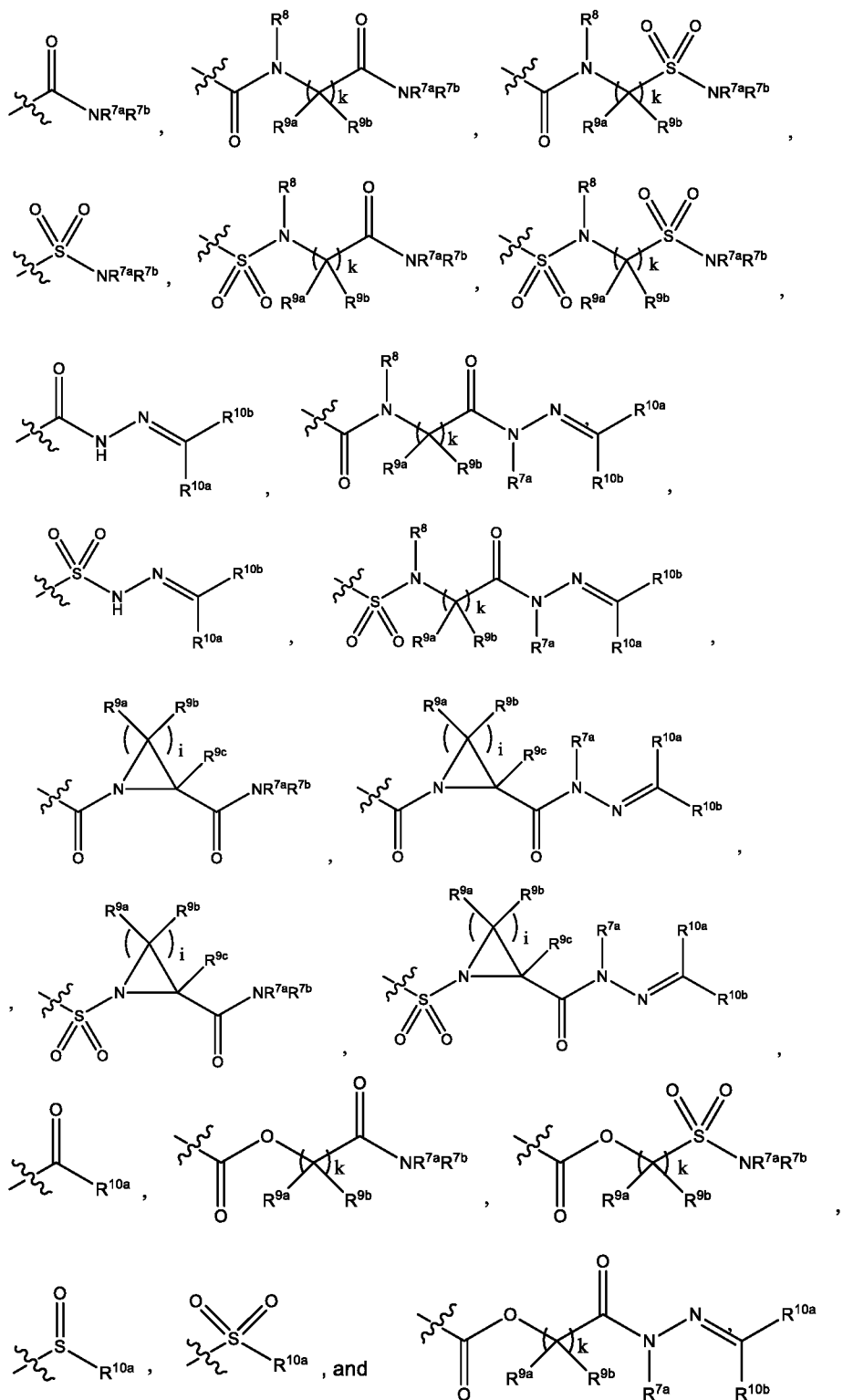
X is CR^5 and Y is $\text{CR}^4\text{-A-D}$, wherein A-D is defined as before.

In another embodiment, the invention relates to compounds of Structural Formula I, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

X is C-A-D and Y is CR^4R^5 ;

5 A is $-C(R^{6a}R^{6b})_i-$; and

D is selected from the group consisting of

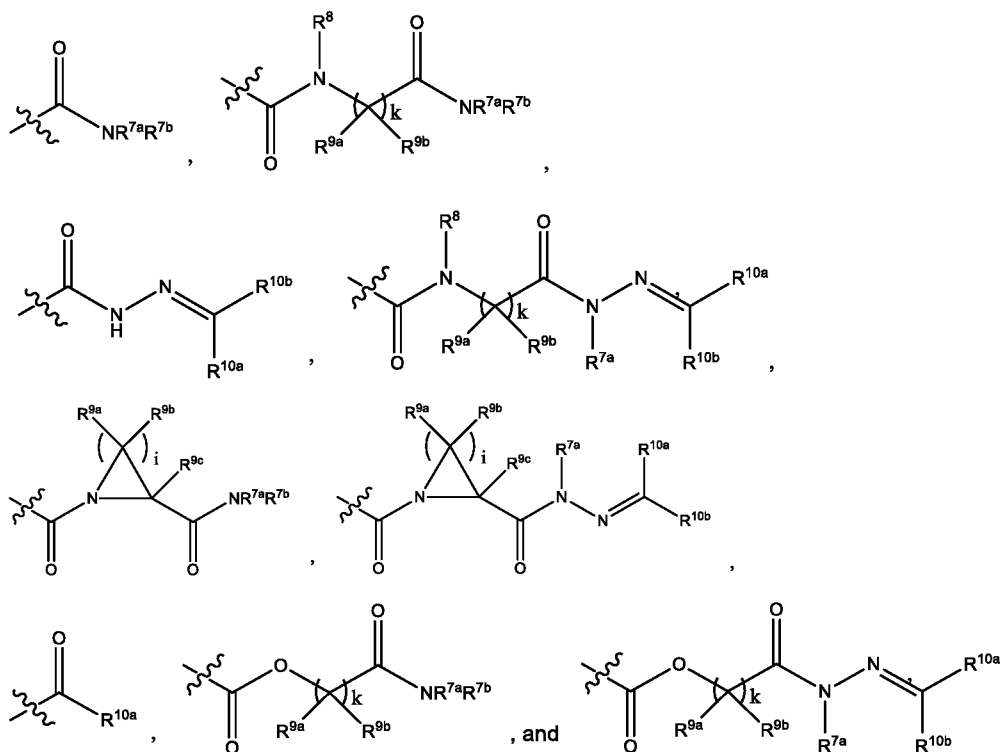


In another embodiment, the invention relates to compounds of Structural Formula I, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

X is C-A-D and Y is CR^4R^5 ;

5 A is $-C(R^{6a}R^{6b})_i-$; and

D is selected from the group consisting of

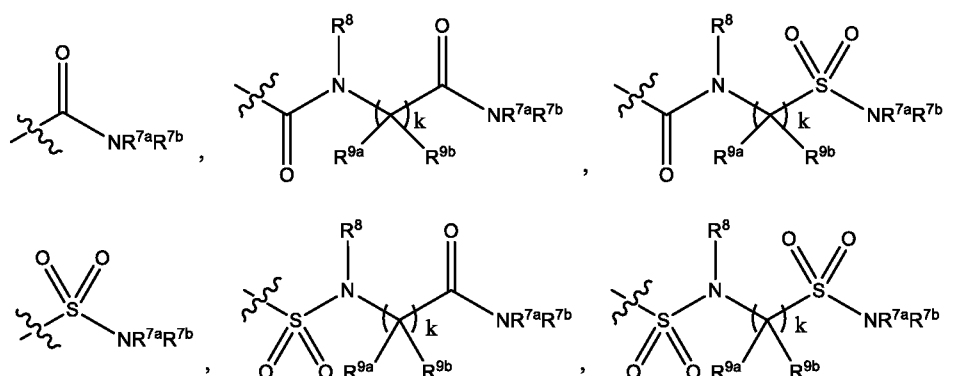


10 In another embodiment, the invention relates to compounds of Structural Formula I, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

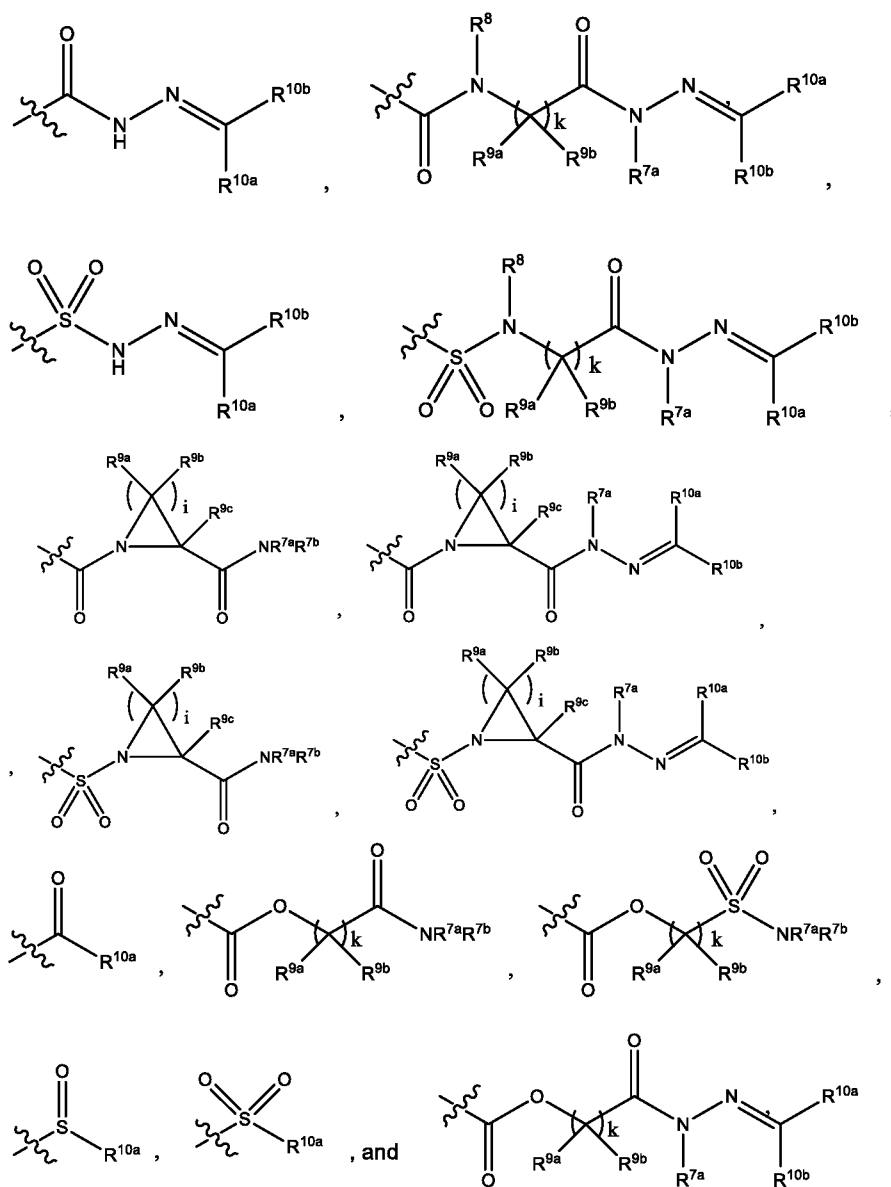
X is C-A-D and Y is a bond;

A is $-\text{C}(\text{R}^{6a}\text{R}^{6b})_i-$; and

15 D is selected from the group consisting of



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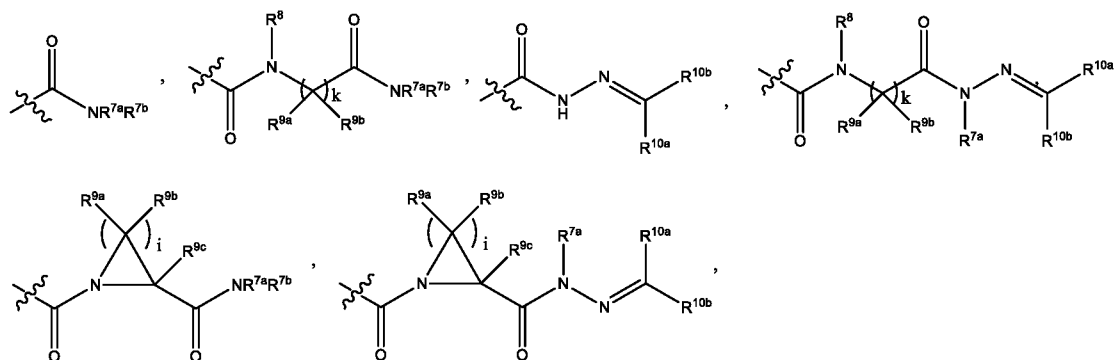


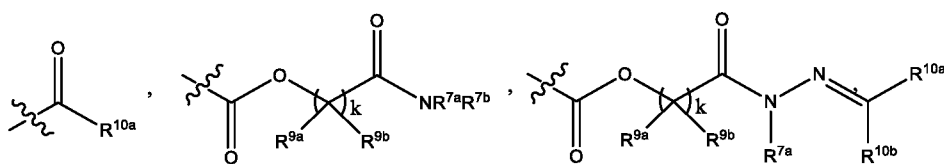
In another embodiment, the invention relates to compounds of Structural Formula I, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

X is C-A-D and Y is a bond;

A is $-\text{C}(\text{R}^{6a}\text{R}^{6b})_j-$; and

D is selected from the group consisting of





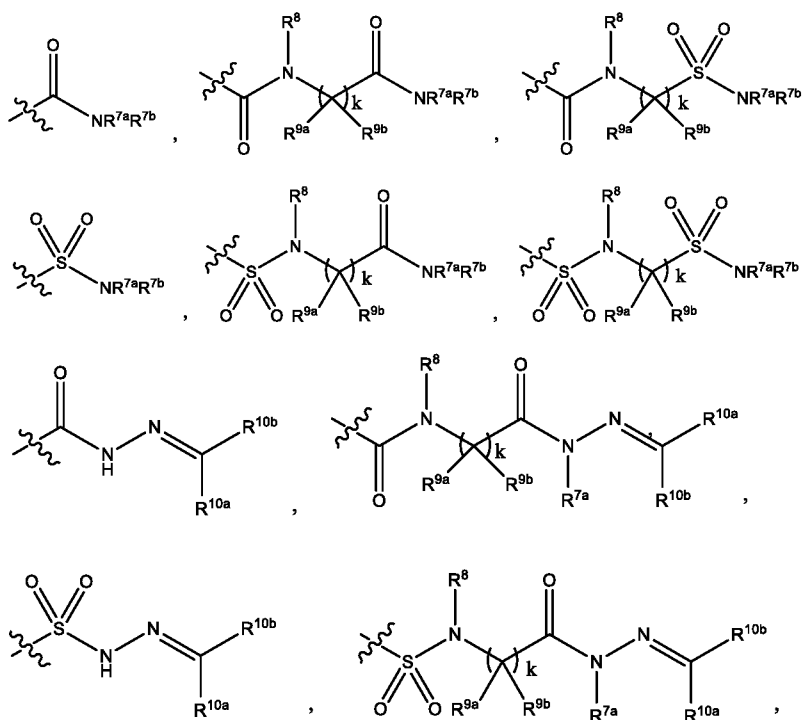
In another embodiment, the invention relates to compounds of Structural Formula I, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

5

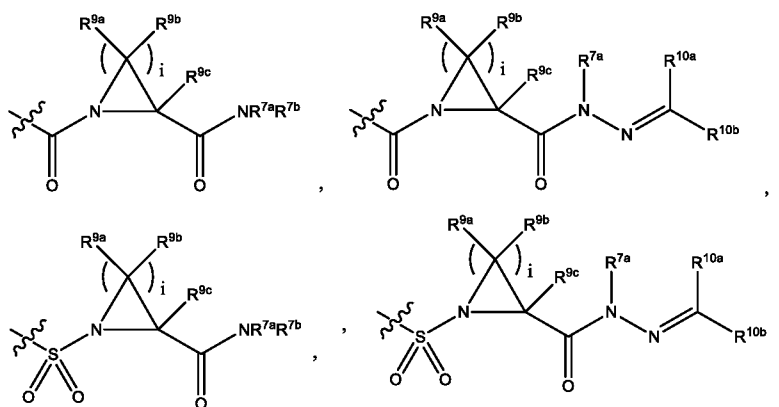
X is CR⁵ and Y is CR⁴-A-D;

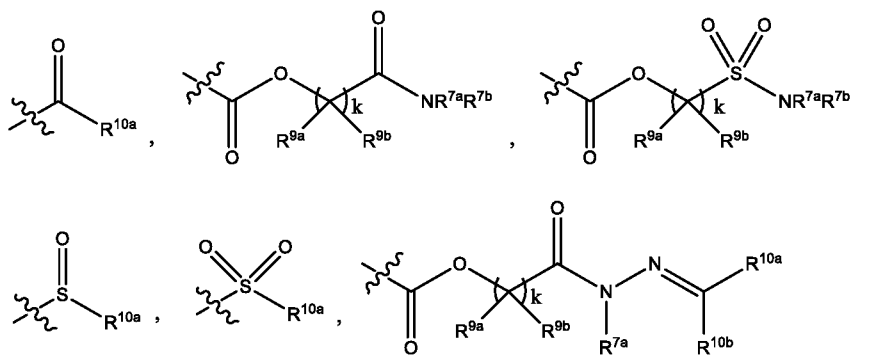
A is $-C(R^{6a}R^{6b})_i-$; and

D is selected from the group consisting of



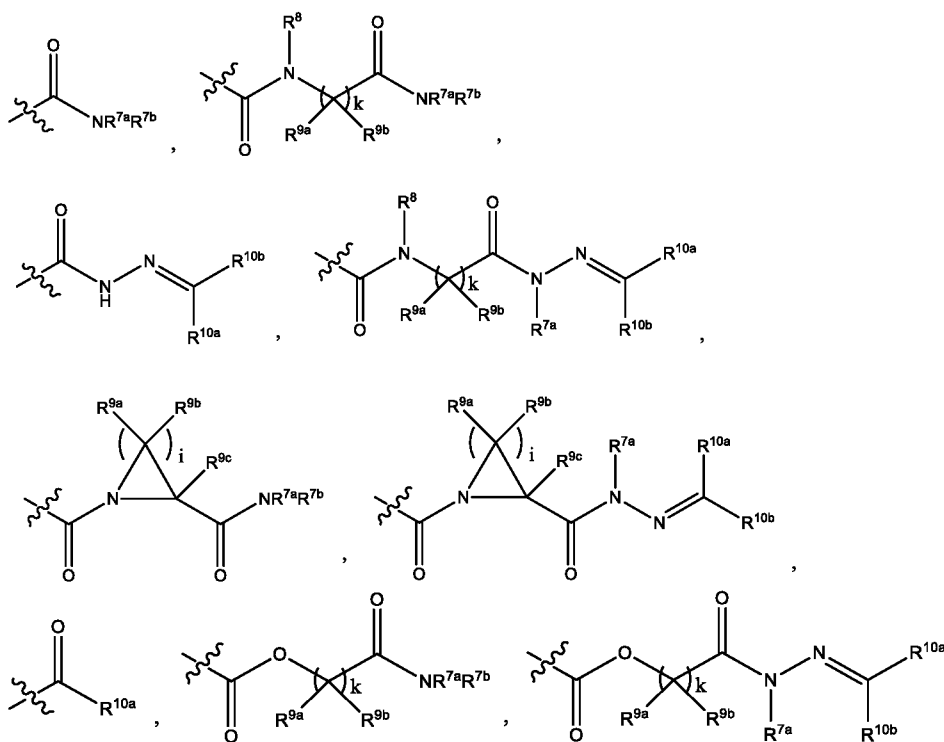
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In another embodiment, the invention relates to compounds of Structural Formula I, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

5 X is CR⁵ and Y is CR⁴-A-D;
A is -C(R^{6a}R^{6b})_J-; and
D is selected from the group consisting of



10 In another embodiment, the invention relates to compounds of Structural Formula I, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

X is C-A-D and Y is CR^4R^5 :

A is $-C(R^{6a}R^{6b})_i-$;

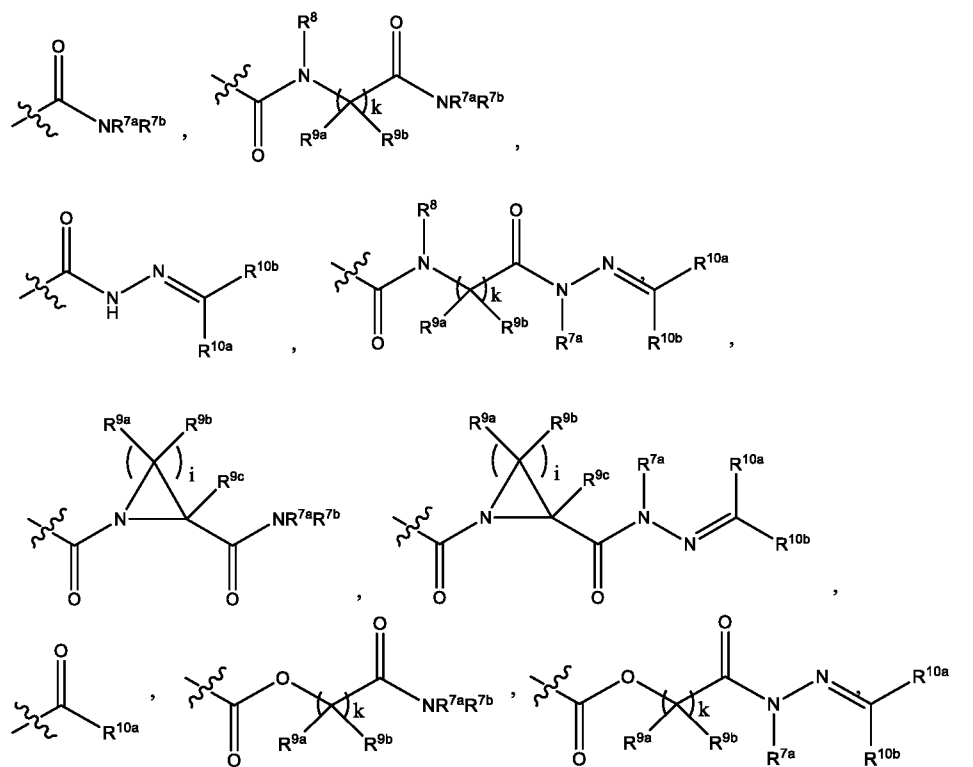
15 R¹ is selected from (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl, wherein
each of the said (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl is optionally substituted with at least
one R¹³ group;
R² is hydrogen;

R^3 is hydrogen;

R^4 is hydrogen;

R^5 is hydrogen; and

D is selected from the group consisting of



In another embodiment, the invention relates to compounds of Structural Formula I, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

10 X is C-A-D and Y is a bond;

A is $-C(R^{6a}R^{6b})_j-$;

R^1 is selected from (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl, wherein

each of the said (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl is optionally substituted with at least one R¹³ group;

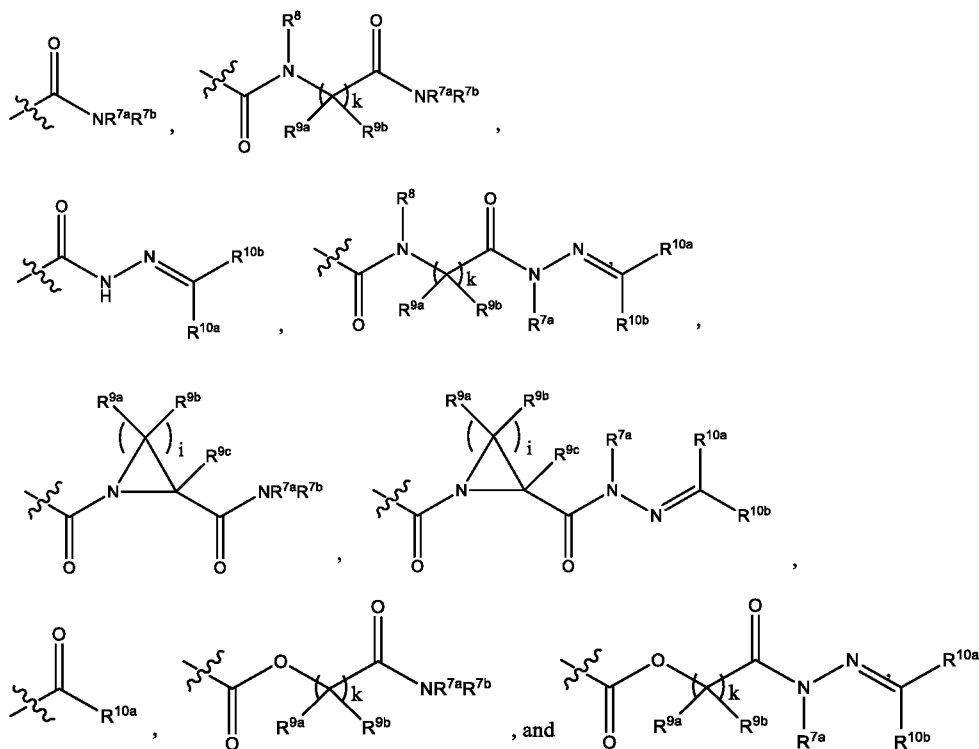
15 R^2 is hydrogen;

R^3 is hydrogen;

R^4 is hydrogen;

R^5 is hydrogen; and

D is selected from the group consisting of



In another embodiment, the invention relates to compounds of Structural Formula I, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

X is CR⁵ and Y is CR⁴-A-D;

A is -C(R^{6a}R^{6b})_j-;

R¹ is selected from (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl, wherein each of the said (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl is optionally substituted with at least one R¹³ group;

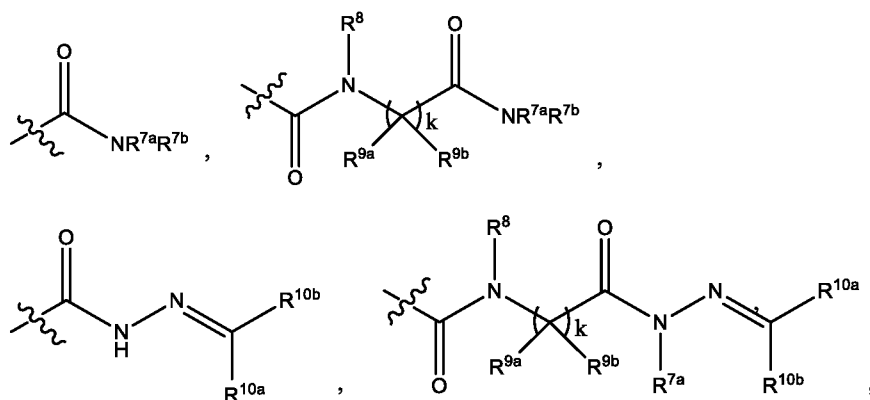
R² is hydrogen;

R³ is hydrogen;

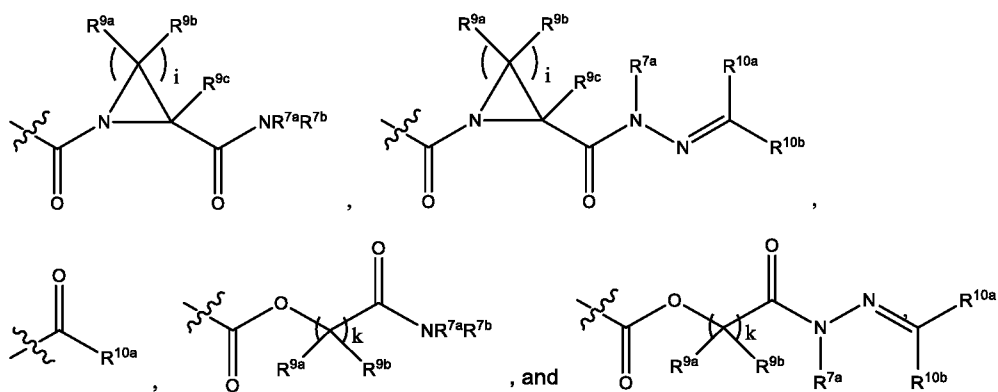
R⁴ is hydrogen;

R⁵ is hydrogen; and

D is selected from the group consisting of



32



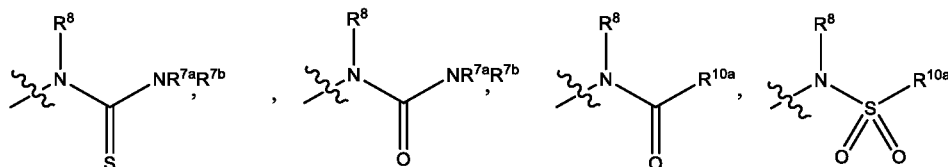
In another embodiment, the invention relates to compounds of Structural Formula I, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

X is C-A-D and Y is a bond or CR⁴R⁵; or

X is CR⁵ and Y is CR⁴-A-D;

A is -C(R^{6a}R^{6b})_j-; and

D is selected from the group consisting of



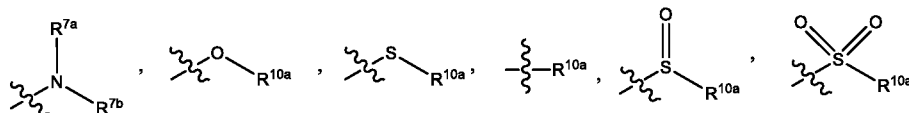
In another embodiment, the invention relates to compounds of Structural Formula I, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

X is C-A-D and Y is a bond or CR⁴R⁵;

A is -C(R^{6a}R^{6b})_j-, (C₆ to C₁₀) arylene, or (C₂ to C₉) heteroarylene, wherein

each of the said (C₆ to C₁₀) arylene or (C₂ to C₉) heteroarylene is optionally substituted with at least one R^{6a} group; and

D is selected from the group consisting of



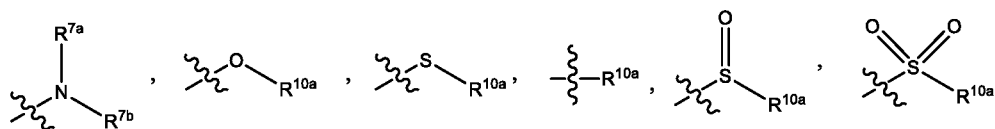
In another embodiment, the invention relates to compounds of Structural Formula I, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

X is C-A-D and Y is a bond or CR⁴R⁵;

A is (C₆ to C₁₀) arylene or (C₂ to C₉) heteroarylene, wherein

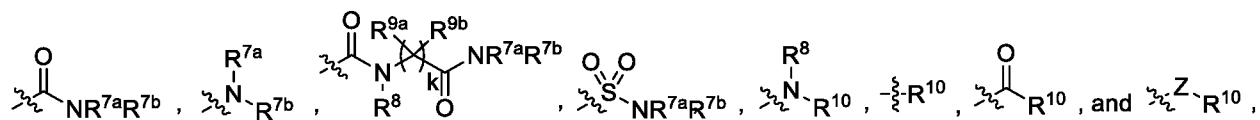
each of the said (C₆ to C₁₀) arylene or (C₂ to C₉) heteroarylene is optionally substituted with at least one R^{6a} group; and

D is selected from the group consisting of

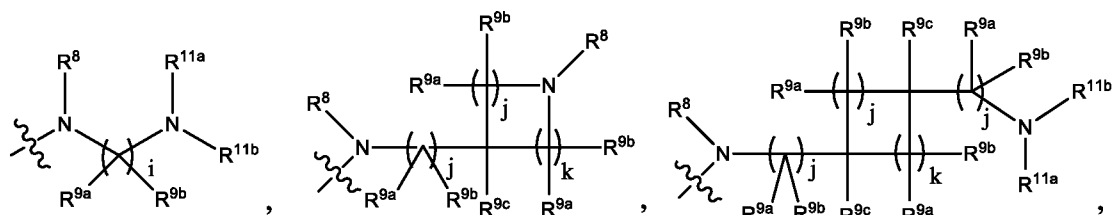


In another embodiment, the invention relates to compounds of Structural Formula I, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

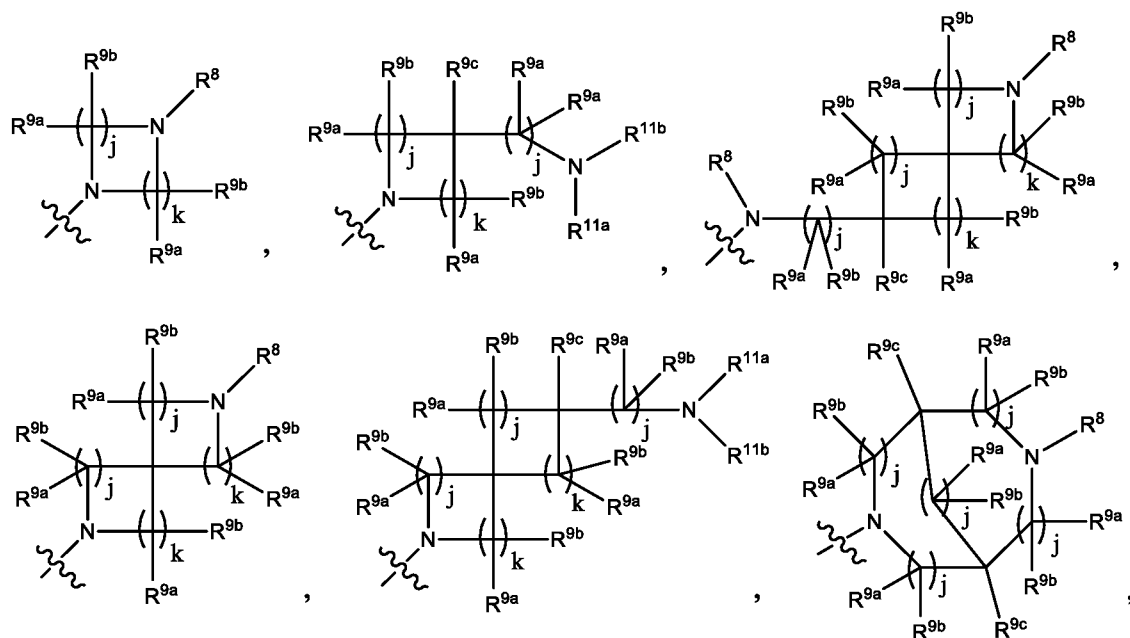
5 D is selected from the group consisting of

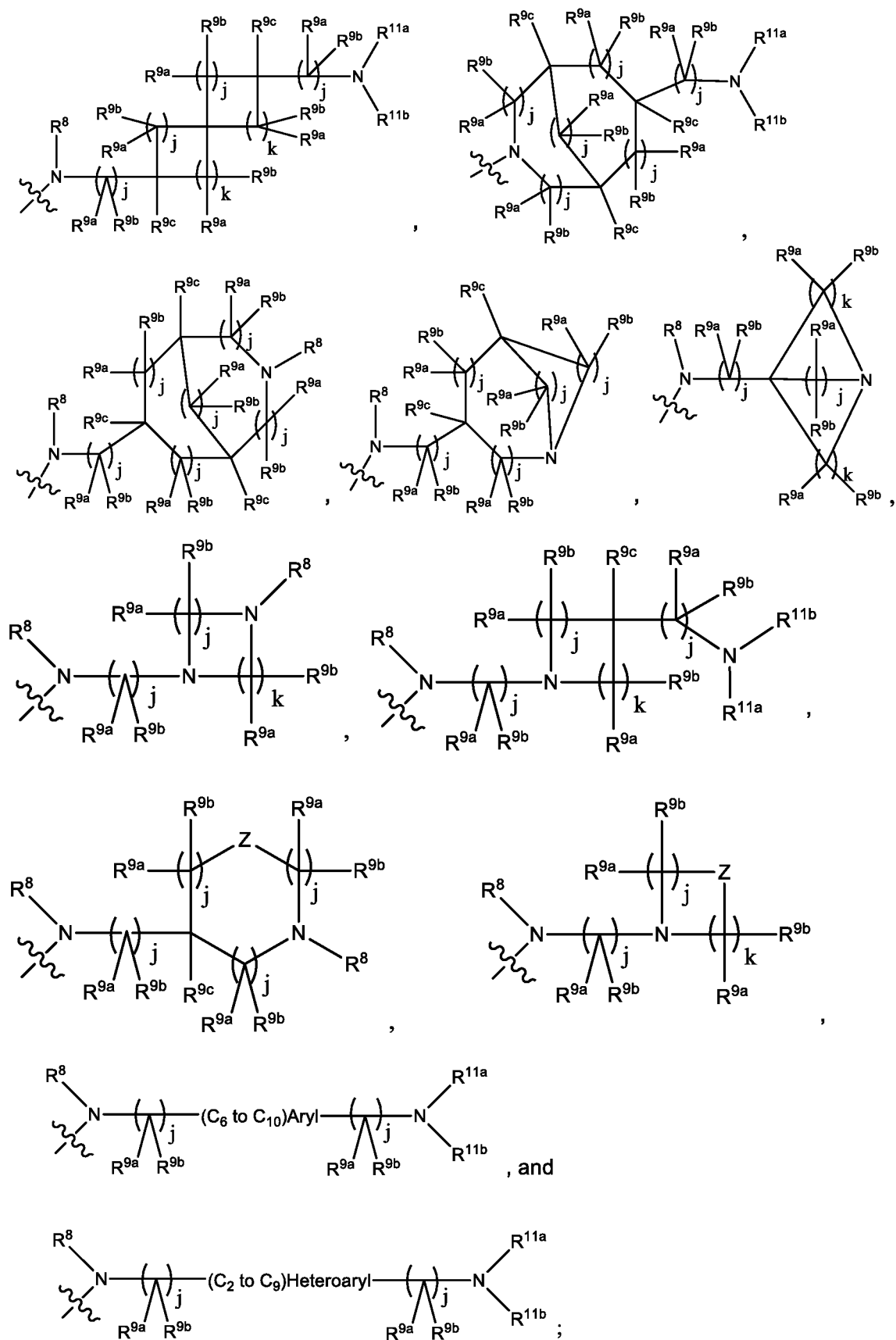


wherein $\text{NR}^{7a}\text{R}^{7b}$ is selected from the group consisting of



10





cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, -C(O)R¹², -C(O)NR^{11a}R^{11b}, -S(O)_mR¹², -S(O)_mNR^{11a}R^{11b}, -NR^{11a}S(O)_mR¹², -(CH₂)_nC(O)OR¹², -(CH₂)_nC(O)N(R^{11a}R^{11b}), -(CH₂)_nN(R^{11a}R^{11b}), -OC(O)R¹², -NR^{11a}C(O)R¹², and -NR^{11a}C(O)N(R^{11a}R^{11b}), wherein

5 each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl is optionally substituted with at least one R¹³ group;

R² is selected from hydrogen, halogen, OH, nitro, CF₃, -NR^{11a}R^{11b}, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, cyano, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, -C(O)R¹², -C(O)NR^{11a}R^{11b}, -S(O)_mR¹², -S(O)_mNR^{11a}R^{11b}, -NR^{11a}S(O)_mR¹², -(CH₂)_nC(O)OR¹², -(CH₂)_nC(O)N(R^{11a}R^{11b}), -(CH₂)_nN(R^{11a}R^{11b}), -OC(O)R¹², -NR^{11a}C(O)R¹², and -NR^{11a}C(O)N(R^{11a}R^{11b}), wherein

15 each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl is optionally substituted with at least one R¹³ group;

R³ is selected from hydrogen, halogen, OH, nitro, CF₃, -NR^{11a}R^{11b}, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, cyano, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, -C(O)R¹², -C(O)NR^{11a}R^{11b}, -S(O)_mR¹², -S(O)_mNR^{11a}R^{11b}, -NR^{11a}S(O)_mR¹², -(CH₂)_nC(O)OR¹², -(CH₂)_nC(O)N(R^{11a}R^{11b}), -(CH₂)_nN(R^{11a}R^{11b}), -OC(O)R¹², -NR^{11a}C(O)R¹², and -NR^{11a}C(O)N(R^{11a}R^{11b}), wherein

25 each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl is optionally substituted with at least one R¹³ group;

R⁴ is selected from hydrogen, halogen, OH, nitro, CF₃, -NR^{11a}R^{11b}, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, cyano, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, -C(O)R¹², -C(O)NR^{11a}R^{11b}, -S(O)_mR¹², -S(O)_mNR^{11a}R^{11b}, -NR^{11a}S(O)_mR¹², -(CH₂)_nC(O)OR¹², -(CH₂)_nC(O)N(R^{11a}R^{11b}), -(CH₂)_nN(R^{11a}R^{11b}), -OC(O)R¹², -NR^{11a}C(O)R¹², and -NR^{11a}C(O)N(R^{11a}R^{11b}), wherein

35 each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl is optionally substituted with at least one R¹³ group;

R⁵ is selected from hydrogen, halogen, OH, nitro, CF₃, -NR^{11a}R^{11b}, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, cyano, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, -C(O)R¹², -C(O)NR^{11a}R^{11b}, -S(O)_mR¹², -S(O)_mNR^{11a}R^{11b}, -NR^{11a}S(O)_mR¹², -(CH₂)_nC(O)OR¹², -(CH₂)_nC(O)N(R^{11a}R^{11b}), -(CH₂)_nN(R^{11a}R^{11b}), -OC(O)R¹², -NR^{11a}C(O)R¹², and -NR^{11a}C(O)N(R^{11a}R^{11b}), wherein

40

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl is optionally substituted with at least one R¹³ group;

each of the R^{6a} and R^{6b} is independently selected from hydrogen, halogen, OH, nitro, CF₃,
 5 -NR^{11a}R^{11b}, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, cyano, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, -C(O)R¹², -C(O)NR^{11a}R^{11b}, -S(O)_mR¹², -S(O)_mNR^{11a}R^{11b}, -NR^{11a}S(O)_mR¹², -(CH₂)_nC(O)OR¹², -(CH₂)_nC(O)N(R^{11a}R^{11b}), -(CH₂)_nN(R^{11a}R^{11b}), -OC(O)R¹², -NR^{11a}C(O)R¹², and -NR^{11a}C(O)N(R^{11a}R^{11b}),
 wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl is optionally substituted with at least one R¹³ group;

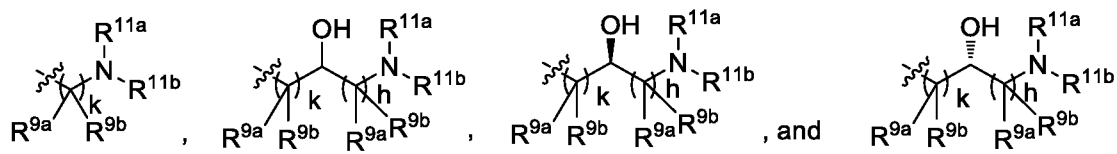
each R⁸ is independently selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉)
 15 cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, and (C₂ to C₉) heteroarylene, wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, and (C₂ to C₉) heteroarylene is optionally substituted with at
 20 least one R¹³ group;

each of the R^{9a}, R^{9b}, and R^{9c} is independently selected from hydrogen, halogen, OH, nitro, CF₃, -NR^{11a}R^{11b}, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, cyano, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, -C(O)R¹², -C(O)NR^{11a}R^{11b}, -S(O)_mR¹², -S(O)_mNR^{11a}R^{11b}, -NR^{11a}S(O)_mR¹², -
 25 (CH₂)_nC(O)OR¹², -(CH₂)_nC(O)N(R^{11a}R^{11b}), -(CH₂)_nN(R^{11a}R^{11b}), -OC(O)R¹², -NR^{11a}C(O)R¹², and -NR^{11a}C(O)N(R^{11a}R^{11b}), wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl is optionally substituted with at least one R¹³ group;

R¹⁰ is selected from the group consisting of



each of the R^{11a} and R^{11b} is independently selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀)
 35 cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, and (C₂ to C₉) heteroarylene, wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, and (C₂ to C₉) heteroarylene is optionally substituted with at least one R¹³ group,

or R^{11a} and R^{11b} may be taken together with the nitrogen atom to which they are attached to form a (C₂ to C₁₀) cycloheteroalkyl ring, wherein

said (C₂ to C₁₀) cycloheteroalkyl ring has 1 to 3 ring heteroatoms selected from the group consisting of N, O, and S, and wherein

the said (C₂ to C₁₀) cycloheteroalkyl ring is optionally substituted with at least one R¹³ group;

each R¹² is independently selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl, wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl is

optionally substituted with at least one R¹³ group;

each R¹³ is independently selected from hydrogen, halogen, OH, nitro, CF₃, -NR^{14a}R^{14b}, oxo, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, cyano, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, (C₂ to C₉) heteroarylene, (C₃ to C₁₀) cycloalkylene, (C₂ to C₁₀) cycloheteroalkylene, -C(O)R¹⁵, -C(O)NR^{14a}R^{14b}, -S(O)_mR¹⁵, -S(O)_mNR^{14a}R^{14b}, -NR^{14a}S(O)_mR¹⁵, -(CH₂)_nC(O)OR¹⁵, -(CH₂)_nC(O)N(R^{14a}R^{14b}), -(CH₂)_nN(R^{14a}R^{14b}), -OC(O)R¹⁵, -O(CH₂)_nO-, -NR^{14a}C(O)R¹⁵, and -NR^{14a}C(O)N(R^{14a}R^{14b}), wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, (C₂ to C₉) heteroarylene, (C₃ to C₁₀) cycloalkylene, and (C₂ to C₁₀) cycloheteroalkylene is optionally substituted with at least one R¹⁶ group;

each of the R^{14a} and R^{14b} is independently selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, and (C₂ to C₉) heteroarylene, wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, and (C₂ to C₉) heteroarylene is optionally substituted with at least one R¹⁶ group,

or R^{14a} and R^{14b} may be taken together with the nitrogen atom to which they are attached to form a (C₂ to C₁₀) cycloheteroalkyl ring, wherein

said (C₂ to C₁₀) cycloheteroalkyl ring has 1 to 3 ring heteroatoms selected from the group consisting of N, O, and S, and wherein

the said (C₂ to C₁₀) cycloheteroalkyl ring is optionally substituted with at least one R¹⁶ group;

each R¹⁵ is independently selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl, wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl is optionally substituted with at least one R¹⁶ group;

each R¹⁶ is independently selected from hydrogen, halogen, OH, nitro, CF₃, -NR^{17a}R^{17b}, oxo, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, cyano, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, (C₂ to C₉) heteroarylene, (C₃ to C₁₀) cycloalkylene, (C₂ to C₁₀) cycloheteroalkylene, -C(O)NR^{17a}R^{17b}, C(O)R¹⁸, S(O)_mR¹⁸, -S(O)_mNR^{17a}R^{17b}, -NR^{17a}S(O)_mR¹⁸, -(CH₂)_nC(O)OR¹⁸, -(CH₂)_nC(O)N(R^{17a}R^{17b}), -(CH₂)_nN(R^{17a}R^{17b}), -OC(O)R¹⁸, -NR^{17a}C(O)R¹⁸, and -NR^{17a}C(O)N(R^{17a}R^{17b}), wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) aryl, (C₆ to C₁₀) arylene, (C₂ to C₉) heteroarylene, (C₃ to C₁₀) cycloalkylene, and (C₂ to C₁₀) cycloheteroalkylene is optionally substituted with at least one R¹⁹ group;

each of the R^{17a} and R^{17b} is independently selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, and (C₂ to C₉) heteroarylene, wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, and (C₂ to C₉) heteroarylene is optionally substituted with at least one R¹⁹ group,

or R^{17a} and R^{17b} may be taken together with the nitrogen atom to which they are attached to form a (C₂ to C₁₀) cycloheteroalkyl ring, wherein

said (C₂ to C₁₀) cycloheteroalkyl ring has 1 to 3 ring heteroatoms selected from the group consisting of N, O, and S, and wherein

the said (C₂ to C₁₀) cycloheteroalkyl ring is optionally substituted with at least one R¹⁹ group;

each R¹⁸ is independently selected from hydrogen, halogen, OH, nitro, CF₃, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, cyano, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl, wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₂ to C₉) heteroaryl, and (C₆ to C₁₀) aryl is optionally substituted with at least one R¹⁹ group;

each R¹⁹ is independently selected from hydrogen, halogen, OH, nitro, CF₃, -NR^{20a}R^{20b}, oxo, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, cyano, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, (C₂ to C₉) heteroarylene, (C₃ to C₁₀) cycloalkylene, (C₂ to C₁₀) cycloheteroalkylene,

$-\text{C}(\text{O})\text{R}^{21}$, $-\text{C}(\text{O})\text{NR}^{20a}\text{R}^{20b}$, $-\text{S}(\text{O})_m\text{R}^{21}$, $-\text{S}(\text{O})_m\text{NR}^{20a}\text{R}^{20b}$, $-\text{NR}^{20a}\text{S}(\text{O})_m\text{R}^{21}$, $-(\text{CH}_2)_n\text{C}(\text{O})\text{OR}^{21}$, $-(\text{CH}_2)_n\text{C}(\text{O})\text{N}(\text{R}^{20a}\text{R}^{20b})$, $-(\text{CH}_2)_n\text{N}(\text{R}^{20a}\text{R}^{20b})$, $-\text{OC}(\text{O})\text{R}^{21}$, $-\text{NR}^{20a}\text{C}(\text{O})\text{R}^{21}$, and $-\text{NR}^{20a}\text{C}(\text{O})\text{N}(\text{R}^{20a}\text{R}^{20b})$, wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, (C₂ to C₉) heteroarylene, (C₃ to C₁₀) cycloalkylene, and (C₂ to C₁₀) cycloheteroalkylene is optionally substituted with at least one R²² group;

each of the R^{20a} and R^{20b} is independently selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl, wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl is optionally substituted with at least one R²² group,

or R^{20a} and R^{20b} may be taken together with the nitrogen atom to which they are attached to form a (C₂ to C₁₀) cycloheteroalkyl ring, wherein

said (C₂ to C₁₀) cycloheteroalkyl ring has 1 to 3 ring heteroatoms selected from the group consisting of N, O, and S, and wherein

the said (C₂ to C₁₀) cycloheteroalkyl ring is optionally substituted with at least one R²² group;

each R²¹ is independently selected from hydrogen, halogen, OH, nitro, CF₃, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, cyano, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl;

each R²² is independently selected from hydrogen, halogen, OH, nitro, CF₃, $-\text{NR}^{23a}\text{R}^{23b}$, oxo, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, cyano, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, (C₂ to C₉) heteroarylene, (C₃ to C₁₀) cycloalkylene, (C₂ to C₁₀) cycloheteroalkylene, $-\text{C}(\text{O})\text{NR}^{23a}\text{R}^{23b}$, $-\text{C}(\text{O})\text{R}^{24}$, $-\text{S}(\text{O})_m\text{R}^{24}$, $-\text{S}(\text{O})_m\text{NR}^{23a}\text{R}^{23b}$, $-\text{NR}^{23a}\text{S}(\text{O})_m\text{R}^{24}$, $-(\text{CH}_2)_n\text{C}(\text{O})\text{OR}^{24}$, $-(\text{CH}_2)_n\text{C}(\text{O})\text{N}(\text{R}^{23a}\text{R}^{23b})$, $-(\text{CH}_2)_n\text{N}(\text{R}^{23a}\text{R}^{23b})$, $-\text{OC}(\text{O})\text{R}^{24}$, $-\text{NR}^{23a}\text{C}(\text{O})\text{R}^{24}$, and $-\text{NR}^{23a}\text{C}(\text{O})\text{N}(\text{R}^{23a}\text{R}^{23b})$, wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, (C₂ to C₉) heteroarylene, (C₃ to C₁₀) cycloalkylene, and (C₂ to C₁₀) cycloheteroalkylene is optionally substituted with at least one R²⁵ group;

each of the R^{23a} and R^{23b} is independently selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₂ to C₉) heteroaryl, and (C₆ to C₁₀) aryl;

each R²⁴ is independently selected from hydrogen, halogen, OH, nitro, CF₃, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, cyano, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl;

R²⁵ is selected from hydrogen, halogen, OH, nitro, CF₃, $-\text{NR}^{26a}\text{R}^{26b}$, oxo, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, cyano, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl;

cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, (C₂ to C₉) heteroarylene, (C₃ to C₁₀) cycloalkylene, (C₂ to C₁₀) cycloheteroalkylene, -C(O)R²⁷, -C(O)NR^{26a}R^{26b}, -S(O)_mR²⁷, -S(O)_mNR^{26a}R^{26b}, -NR^{26a}S(O)_mR²⁷, -(CH₂)_nC(O)OR²⁷, -(CH₂)_nC(O)N(R^{26a}R^{26b}), -(CH₂)_nN(R^{26a}R^{26b}), -OC(O)R²⁷, -NR^{26a}C(O)R²⁷, and -NR^{26a}C(O)N(R^{26a}R^{26b}),

5 wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, (C₂ to C₉) heteroarylene, (C₃ to C₁₀) cycloalkylene, and (C₂ to C₁₀) cycloheteroalkylene is optionally substituted with at least one R²⁷ group;

10 each of the R^{26a} and R^{26b} is independently selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl,

or R^{26a} and R^{26b} may be taken together with the nitrogen atom to which they are attached to form a (C₂ to C₁₀) cycloheteroalkyl ring, wherein

15 said (C₂ to C₁₀) cycloheteroalkyl ring has 1 to 3 ring heteroatoms selected from the group consisting of N, O, and S;

each R²⁷ is independently selected from hydrogen, halogen, OH, nitro, CF₃, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, cyano, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl;

20 h is 1 or 2;

i is 2, 3, 4, 5, or 6;

j is 0, 1, 2, 3, 4, or 5;

k is 1, 2, 3, 4, or 5;

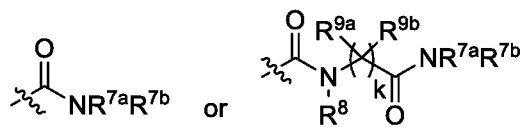
m is 0, 1 or 2;

25 n is 0, 1, 2, 3, or 4;

Z is selected from the group consisting of -O-, -S-, -S(O)-, and -S(O)₂-;

with the proviso that

when R¹, R², or R³ is alkyl or hydrogen, X is C-C(R^{6a}R^{6b})_j-D, Y is CH₂, and D is



30 then NR^{7a}R^{7b} cannot be an optionally substituted piperazine or 1,4-diazepane.

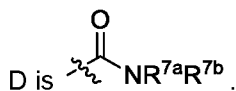
In another embodiment, the invention relates to compounds of Structural Formula I, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

X is C-A-D and Y is CR⁴R⁵, wherein A-D is defined as above.

35 In another embodiment, the invention relates to compounds of Structural Formula I, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

X is C-A-D and Y is CR⁴R⁵;

A is $-C(R^{6a}R^{6b})_j-$; and



In another embodiment, the invention relates to compounds of Structural Formula I, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

X is C-A-D and Y is CR^4R^5 ;

A is $-C(R^{6a}R^{6b})_j-$;

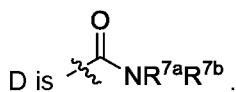
R^1 is selected from (C_6 to C_{10}) aryl and (C_2 to C_9) heteroaryl, wherein

each of the said (C_6 to C_{10}) aryl and (C_2 to C_9) heteroaryl is optionally substituted with at least

one R^{13} group;

R^4 is hydrogen;

R^5 is hydrogen; and



In another embodiment, the invention relates to compounds of Structural Formula I, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

X is C-A-D and Y is CR^4R^5 ;

A is $-C(R^{6a}R^{6b})_j-$;

R^1 is selected from (C_6 to C_{10}) aryl and (C_2 to C_9) heteroaryl, wherein

each of the said (C_6 to C_{10}) aryl and (C_2 to C_9) heteroaryl is optionally substituted with at least one R^{13} group;

R^2 is selected from hydrogen, (C_1 to C_{10}) alkyl, (C_1 to C_{10}) alkenyl, (C_1 to C_{10}) alkynyl, (C_3 to C_{10}) cycloalkyl, and (C_5 to C_{10}) cycloalkenyl, (C_1 to C_{10}) alkoxy, $-(CH_2)_nC(O)N(R^{11a}R^{11b})$, and $-C(O)R^{12}$, wherein

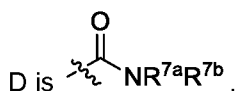
each of the said (C_1 to C_{10}) alkyl, (C_1 to C_{10}) alkenyl, (C_1 to C_{10}) alkynyl, (C_3 to C_{10}) cycloalkyl, (C_5 to C_{10}) cycloalkenyl is optionally substituted with at least one R^{13} group;

R^3 is selected from hydrogen, (C_1 to C_{10}) alkyl, (C_1 to C_{10}) alkenyl, (C_1 to C_{10}) alkynyl, (C_3 to C_{10}) cycloalkyl, and (C_5 to C_{10}) cycloalkenyl, wherein

each of the said (C_1 to C_{10}) alkyl, (C_1 to C_{10}) alkenyl, (C_1 to C_{10}) alkynyl, (C_3 to C_{10}) cycloalkyl, (C_5 to C_{10}) cycloalkenyl is optionally substituted with at least one R^{13} group;

R^4 is hydrogen;

R^5 is hydrogen; and



In another embodiment, the invention relates to compounds of Structural Formula I, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

X is C-A-D and Y is CR⁴R⁵;

A is -C(R^{6a}R^{6b})_j-;

R¹ is selected from (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl, wherein

each of the said (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl is optionally substituted with at least one R¹³ group;

R² is selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, and (C₅ to C₁₀) cycloalkenyl, (C₁ to C₁₀) alkoxy, -(CH₂)_nC(O)N(R^{11a}R^{11b}), and -C(O)R¹², wherein

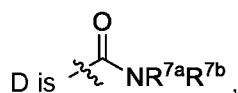
each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl is optionally substituted with at least one R¹³ group;

R³ is selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, and (C₅ to C₁₀) cycloalkenyl, wherein

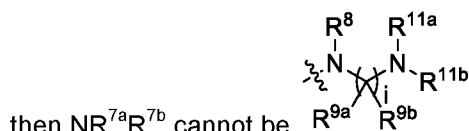
each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl is optionally substituted with at least one R¹³ group;

R⁴ is hydrogen;

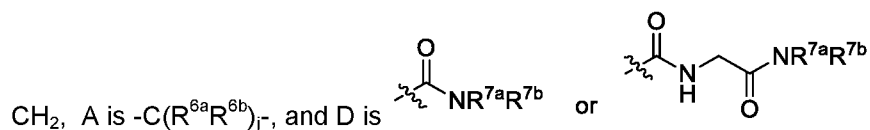
R⁵ is hydrogen; and



except when R¹ is phenyl, R² is hydrogen, and j is 0,



and when R¹ is hydrogen, halogen, or hydroxy, R² is hydrogen, R³ is hydrogen, X is C-A-D, Y is



then j is 2,3,4, or 5, but not 0 or 1.

In another embodiment, the invention relates to compounds of Structural Formula I, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

X is C-A-D and Y is CR⁴R⁵;

A is -C(R^{6a}R^{6b})_j-;

R¹ is selected from (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl, wherein

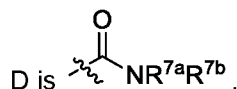
each of the said (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl is optionally substituted with at least one R¹³ group;

R² is (C₁ to C₁₀) alkyl, wherein the said (C₁ to C₁₀) alkyl is optionally substituted with at least one R¹³ group;

R³ is hydrogen;

R⁴ is hydrogen;

R⁵ is hydrogen; and



In another embodiment, the invention relates to compounds of Structural Formula I, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

X is C-A-D and Y is CR⁴R⁵;

A is -C(R^{6a}R^{6b})_j-; and



In another embodiment, the invention relates to compounds of Structural Formula I, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

X is C-A-D and Y is CR⁴R⁵;

A is -C(R^{6a}R^{6b})_j-;

R¹ is selected from (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl, wherein each of the said (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl is optionally substituted with at least one R¹³ group;

R⁴ is hydrogen;

R⁵ is hydrogen; and



In another embodiment, the invention relates to compounds of Structural Formula I, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

X is C-A-D and Y is CR⁴R⁵;

A is -C(R^{6a}R^{6b})_j-;

R¹ is selected from (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl, wherein each of the said (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl is optionally substituted with at least one R¹³ group;

R² is selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, and (C₅ to C₁₀) cycloalkenyl, (C₁ to C₁₀) alkoxy, -(CH₂)_nC(O)N(R^{11a}R^{11b}), and -C(O)R¹², wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl is optionally substituted with at least one R¹³ group;

R³ is selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, and (C₅ to C₁₀) cycloalkenyl, wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl is optionally substituted with at least one R¹³ group;

R⁴ is hydrogen;

R⁵ is hydrogen; and



In another embodiment, the invention relates to compounds of Structural Formula I, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

X is C-A-D and Y is CR⁴R⁵;

10 A is -C(R^{6a}R^{6b})_j-;

R¹ is selected from (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl, wherein

each of the said (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl is optionally substituted with at least one R¹³ group;

R² is selected from hydrogen and (C₁ to C₁₀) alkyl, wherein the said (C₁ to C₁₀) alkyl is

15 optionally substituted with at least one R¹³ group;

R³ is hydrogen;

R⁴ is hydrogen;

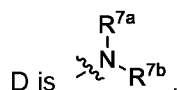
R⁵ is hydrogen; and



In another embodiment, the invention relates to compounds of Structural Formula I, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

X is C-A-D and Y is CR⁴R⁵;

A is -C(R^{6a}R^{6b})_j-; and



In another embodiment, the invention relates to compounds of Structural Formula I, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

X is C-A-D and Y is CR⁴R⁵;

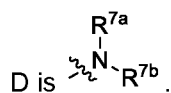
30 A is -C(R^{6a}R^{6b})_j-;

R¹ is selected from (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl, wherein

each of the said (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl is optionally substituted with at least one R¹³ group;

R⁴ is hydrogen;

R⁵ is hydrogen; and



In another embodiment, the invention relates to compounds of Structural Formula I, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

X is C-A-D and Y is CR⁴R⁵;

A is -C(R^{6a}R^{6b})_j-;

R¹ is selected from (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl, wherein

each of the said (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl is optionally substituted with at least one R¹³ group;

R² is selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, and (C₅ to C₁₀) cycloalkenyl, (C₁ to C₁₀) alkoxy, -(CH₂)_nC(O)N(R^{11a}R^{11b}), and -C(O)R¹², wherein

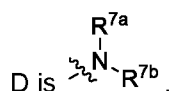
each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl is optionally substituted with at least one R¹³ group;

R³ is selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, and (C₅ to C₁₀) cycloalkenyl, wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl is optionally substituted with at least one R¹³ group;

R⁴ is hydrogen;

R⁵ is hydrogen; and



In another embodiment, the invention relates to compounds of Structural Formula I, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

X is C-A-D and Y is CR⁴R⁵;

A is -C(R^{6a}R^{6b})_j-;

R¹ is selected from (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl, wherein

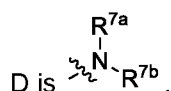
each of the said (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl is optionally substituted with at least one R¹³ group;

R² is selected from hydrogen and (C₁ to C₁₀) alkyl, wherein the said (C₁ to C₁₀) alkyl is optionally substituted with at least one R¹³ group;

R³ is hydrogen;

R⁴ is hydrogen;

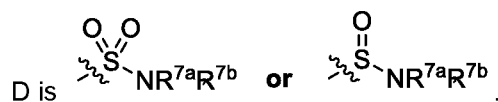
R⁵ is hydrogen; and



In another embodiment, the invention relates to compounds of Structural Formula I, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

X is C-A-D and Y is CR⁴R⁵;

5 A is -C(R^{6a}R^{6b})_j-; and



In another embodiment, the invention relates to compounds of Structural Formula I, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

10 X is C-A-D and Y is CR⁴R⁵;

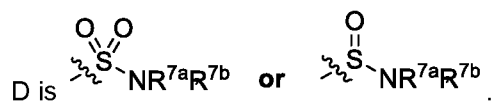
A is -C(R^{6a}R^{6b})_j-;

R¹ is selected from (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl, wherein

each of the said (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl is optionally substituted with at least one R¹³ group;

15 R⁴ is hydrogen;

R⁵ is hydrogen; and



In another embodiment, the invention relates to compounds of Structural Formula I, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

20 X is C-A-D and Y is CR⁴R⁵;

A is -C(R^{6a}R^{6b})_j-;

R¹ is selected from (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl, wherein

each of the said (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl is optionally substituted with at least one R¹³ group;

R² is selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, and (C₅ to C₁₀) cycloalkenyl, (C₁ to C₁₀) alkoxy, -(CH₂)_nC(O)N(R^{11a}R^{11b}), and -C(O)R¹², wherein

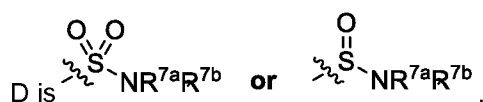
each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl is optionally substituted with at least one R¹³ group;

R³ is selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, and (C₅ to C₁₀) cycloalkenyl, wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl is optionally substituted with at least one R¹³ group;

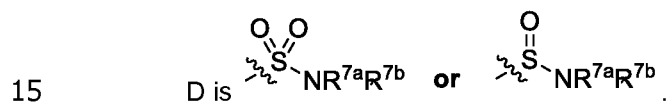
35 R⁴ is hydrogen;

R⁵ is hydrogen; and



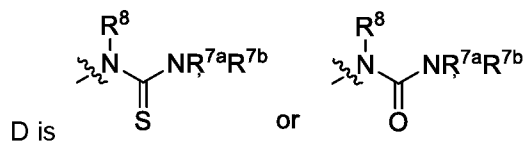
In another embodiment, the invention relates to compounds of Structural Formula I, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

- 5 X is C-A-D and Y is CR⁴R⁵;
 A is -C(R^{6a}R^{6b})_j-;
 R¹ is selected from (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl, wherein
 each of the said (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl is optionally substituted with at least
 one R¹³ group;
 10 R² is selected from hydrogen and (C₁ to C₁₀) alkyl, wherein the said (C₁ to C₁₀) alkyl is
 optionally substituted with at least one R¹³ group;
 R³ is hydrogen;
 R⁴ is hydrogen;
 R⁵ is hydrogen; and



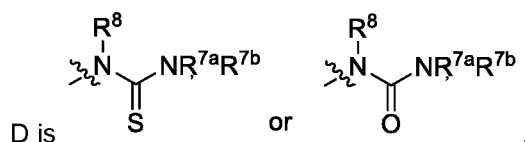
In another embodiment, the invention relates to compounds of Structural Formula I, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

- 20 X is C-A-D and Y is CR⁴R⁵;
 A is -C(R^{6a}R^{6b})_j-;



In another embodiment, the invention relates to compounds of Structural Formula I, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

- 25 X is C-A-D and Y is CR⁴R⁵;
 A is -C(R^{6a}R^{6b})_j-;
 R¹ is selected from (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl, wherein
 each of the said (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl is optionally substituted with at least
 one R¹³ group;
 30 R⁴ is hydrogen;
 R⁵ is hydrogen; and



In another embodiment, the invention relates to compounds of Structural Formula I, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

X is C-A-D and Y is CR^4R^5 ;

5 A is $-C(R^{6a}R^{6b})_j-$;

R^1 is selected from (C_6 to C_{10}) aryl and (C_2 to C_9) heteroaryl, wherein

each of the said (C_6 to C_{10}) aryl and (C_2 to C_9) heteroaryl is optionally substituted with at least one R^{13} group;

10 R^2 is selected from hydrogen, (C_1 to C_{10}) alkyl, (C_1 to C_{10}) alkenyl, (C_1 to C_{10}) alkynyl, (C_3 to C_{10}) cycloalkyl, and (C_5 to C_{10}) cycloalkenyl, (C_1 to C_{10}) alkoxy, $-(CH_2)_nC(O)N(R^{11a}R^{11b})$, and $-C(O)R^{12}$, wherein

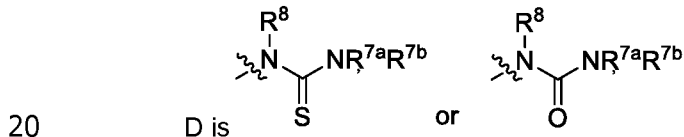
each of the said (C_1 to C_{10}) alkyl, (C_1 to C_{10}) alkenyl, (C_1 to C_{10}) alkynyl, (C_3 to C_{10}) cycloalkyl, (C_5 to C_{10}) cycloalkenyl is optionally substituted with at least one R^{13} group;

15 R^3 is selected from hydrogen, (C_1 to C_{10}) alkyl, (C_1 to C_{10}) alkenyl, (C_1 to C_{10}) alkynyl, (C_3 to C_{10}) cycloalkyl, and (C_5 to C_{10}) cycloalkenyl, wherein

each of the said (C_1 to C_{10}) alkyl, (C_1 to C_{10}) alkenyl, (C_1 to C_{10}) alkynyl, (C_3 to C_{10}) cycloalkyl, (C_5 to C_{10}) cycloalkenyl is optionally substituted with at least one R^{13} group;

R^4 is hydrogen;

R^5 is hydrogen; and



In another embodiment, the invention relates to compounds of Structural Formula I, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

X is C-A-D and Y is CR^4R^5 ;

25 A is $-C(R^{6a}R^{6b})_j-$;

R^1 is selected from (C_6 to C_{10}) aryl and (C_2 to C_9) heteroaryl, wherein

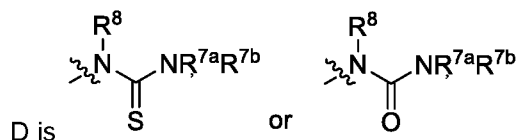
each of the said (C_6 to C_{10}) aryl and (C_2 to C_9) heteroaryl is optionally substituted with at least one R^{13} group;

30 R^2 is selected from hydrogen and (C_1 to C_{10}) alkyl, wherein the said (C_1 to C_{10}) alkyl is optionally substituted with at least one R^{13} group;

R^3 is hydrogen;

R^4 is hydrogen;

R^5 is hydrogen; and

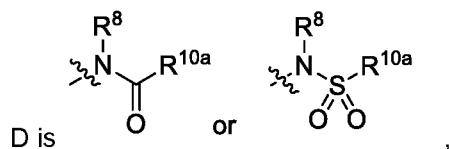


In another embodiment, the invention relates to compounds of Structural Formula I, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

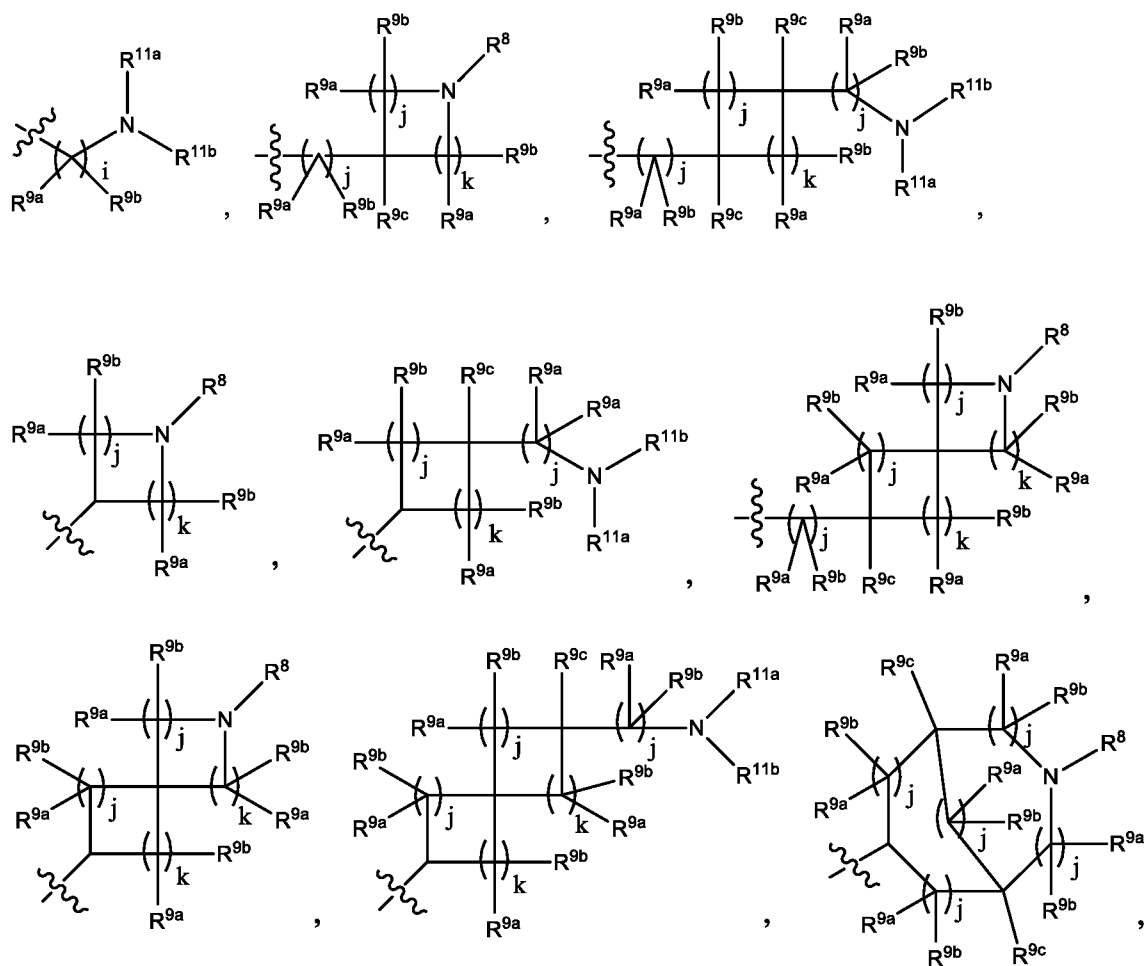
X is C-A-D, and Y is a bond or CR⁴R⁵; or

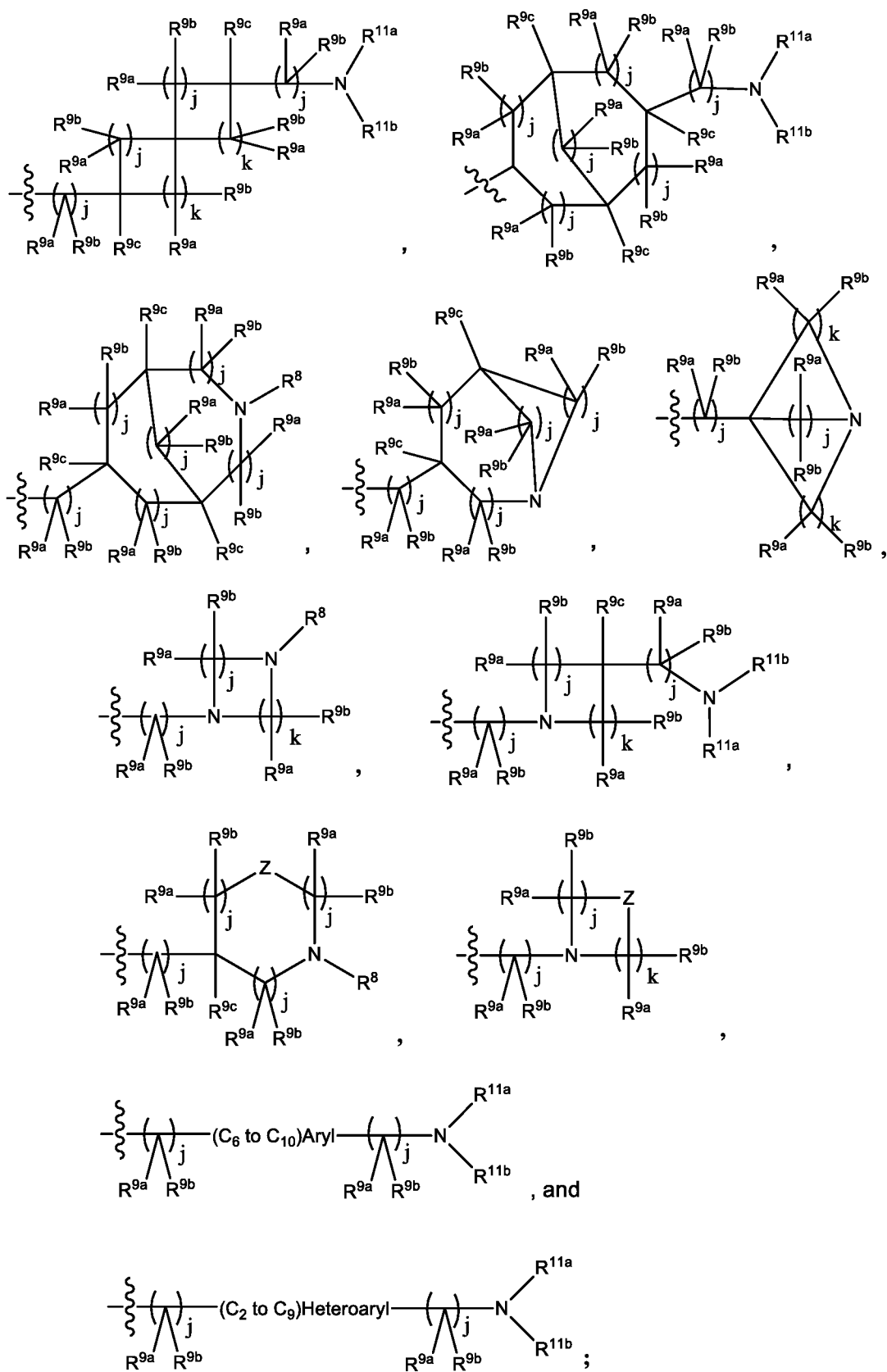
5 X is CR⁵ and Y is CR⁴-A-D;

A is -C(R^{6a}R^{6b})_j-; and



wherein R^{10a} is selected from the group consisting of





R^1 is selected from $(C_6 \text{ to } C_{10})$ aryl and $(C_2 \text{ to } C_9)$ heteroaryl, wherein

each of the said $(C_6 \text{ to } C_{10})$ aryl and $(C_2 \text{ to } C_9)$ heteroaryl is optionally substituted with at least

5 one R^{13} group;

R^2 is selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₁ to C₁₀) alkoxy, $-(CH_2)_nC(O)N(R^{11a}R^{11b})$, and $-C(O)R^{12}$, wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, and (C₁ to C₁₀) alkoxy is optionally substituted with at least one R^{13} group;

R^3 is hydrogen;

R^4 is hydrogen; and

R^5 is hydrogen.

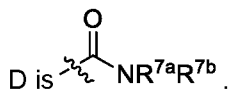
In another embodiment, the invention relates to compounds of Structural Formula I, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

X is C-A-D and Y is a bond.

In another embodiment, the invention relates to compounds of Structural Formula I, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

X is C-A-D and Y is a bond;

A is $-C(R^{6a}R^{6b})_j-$; and



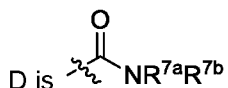
In another embodiment, the invention relates to compounds of Structural Formula I, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

X is C-A-D and Y is a bond;

A is $-C(R^{6a}R^{6b})_j-$;

R^1 is selected from (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl, wherein

each of the said (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl is optionally substituted with at least one R^{13} group;



In another embodiment, the invention relates to compounds of Structural Formula I, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

X is C-A-D and Y is a bond;

A is $-C(R^{6a}R^{6b})_j-$;

R^1 is selected from (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl, wherein

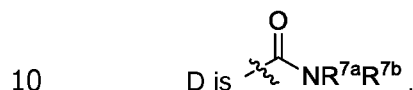
each of the said (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl is optionally substituted with at least one R^{13} group;

R^2 is selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, and (C₅ to C₁₀) cycloalkenyl, (C₁ to C₁₀) alkoxy, $-(CH_2)_n C(O)N(R^{11a}R^{11b})$, and $-C(O)R^{12}$, wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl is optionally substituted with at least one R^{13} group;

R^3 is selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, and (C₅ to C₁₀) cycloalkenyl, wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl is optionally substituted with at least one R^{13} group;



In another embodiment, the invention relates to compounds of Structural Formula I, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

X is C-A-D and Y is a bond;

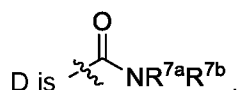
15 A is $-C(R^{6a}R^{6b})_j-$;

R^1 is selected from (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl, wherein

each of the said (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl is optionally substituted with at least one R^{13} group;

R^2 is selected from hydrogen and (C₁ to C₁₀) alkyl, wherein the said (C₁ to C₁₀) alkyl is 20 optionally substituted with at least one R^{13} group;

R^3 is hydrogen; and



In another embodiment, the invention relates to compounds of Structural Formula I, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle 25 thereof, wherein:

X is C-A-D and Y is a bond;

A is $-C(R^{6a}R^{6b})_j-$; and



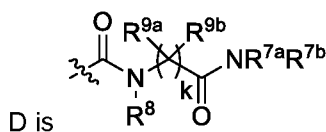
In another embodiment, the invention relates to compounds of Structural Formula I, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle 30 thereof, wherein:

X is C-A-D and Y is a bond;

A is $-C(R^{6a}R^{6b})_j-$;

R^1 is selected from (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl, wherein

each of the said (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl is optionally substituted with at least one R¹³ group; and



In another embodiment, the invention relates to compounds of Structural Formula I, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle wherein:

X is C-A-D and Y is a bond:

A is $-C(R^{6a}R^{6b})_i$;

R¹ is selected from (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl, wherein

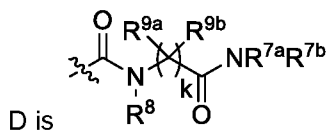
each of the said (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl is optionally substituted with at least one R¹³ group;

R² is selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, and (C₅ to C₁₀) cycloalkenyl, (C₁ to C₁₀) alkoxy, -(CH₂)_nC(O)N(R^{11a}R^{11b}), and -C(O)R¹², wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl is optionally substituted with at least one R¹³ group;

R³ is selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, and (C₅ to C₁₀) cycloalkenyl, wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl is optionally substituted with at least one R¹³ group; and



In another embodiment, the invention relates to compounds of Structural Formula I, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

X is C-A-D and Y is a bond;

A is $-C(R^{6a}R^{6b})_i$;

R¹ is selected from (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl, wherein

each of the said (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl is optionally substituted with at least one R¹³ group:

R² is selected from hydrogen and (C₁ to C₁₀) alkyl, wherein the said (C₁ to C₁₀) alkyl is optionally substituted with at least one R¹³ group;

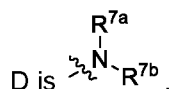
R^3 is hydrogen; and



In another embodiment, the invention relates to compounds of Structural Formula I, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

X is C-A-D and Y is a bond;

5 A is $-\text{C}(\text{R}^{6a}\text{R}^{6b})_j-$; and



In another embodiment, the invention relates to compounds of Structural Formula I, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

10 X is C-A-D and Y is a bond;

A is $-\text{C}(\text{R}^{6a}\text{R}^{6b})_j-$;

R^1 is selected from (C_6 to C_{10}) aryl and (C_2 to C_9) heteroaryl, wherein

each of the said (C_6 to C_{10}) aryl and (C_2 to C_9) heteroaryl is optionally substituted with at least one R^{13} group;



In another embodiment, the invention relates to compounds of Structural Formula I, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

X is C-A-D and Y is a bond;

20 A is $-\text{C}(\text{R}^{6a}\text{R}^{6b})_j-$;

R^1 is selected from (C_6 to C_{10}) aryl and (C_2 to C_9) heteroaryl, wherein

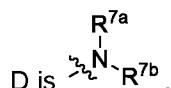
each of the said (C_6 to C_{10}) aryl and (C_2 to C_9) heteroaryl is optionally substituted with at least one R^{13} group;

25 R^2 is selected from hydrogen, (C_1 to C_{10}) alkyl, (C_1 to C_{10}) alkenyl, (C_1 to C_{10}) alkynyl, (C_3 to C_{10}) cycloalkyl, and (C_5 to C_{10}) cycloalkenyl, (C_1 to C_{10}) alkoxy, $-(\text{CH}_2)_n\text{C}(\text{O})\text{N}(\text{R}^{11a}\text{R}^{11b})$, and $-\text{C}(\text{O})\text{R}^{12}$, wherein

each of the said (C_1 to C_{10}) alkyl, (C_1 to C_{10}) alkenyl, (C_1 to C_{10}) alkynyl, (C_3 to C_{10}) cycloalkyl, (C_5 to C_{10}) cycloalkenyl is optionally substituted with at least one R^{13} group;

30 R^3 is selected from hydrogen, (C_1 to C_{10}) alkyl, (C_1 to C_{10}) alkenyl, (C_1 to C_{10}) alkynyl, (C_3 to C_{10}) cycloalkyl, and (C_5 to C_{10}) cycloalkenyl, wherein

each of the said (C_1 to C_{10}) alkyl, (C_1 to C_{10}) alkenyl, (C_1 to C_{10}) alkynyl, (C_3 to C_{10}) cycloalkyl, (C_5 to C_{10}) cycloalkenyl is optionally substituted with at least one R^{13} group; and



35 In another embodiment, the invention relates to compounds of Structural Formula I, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

X is C-A-D and Y is a bond;

A is $-C(R^{6a}R^{6b})_j-$;

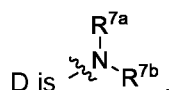
R^1 is selected from (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl, wherein

each of the said (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl is optionally substituted with at least

5 one R^{13} group;

R^2 is selected from hydrogen and (C₁ to C₁₀) alkyl, wherein the said (C₁ to C₁₀) alkyl is optionally substituted with at least one R^{13} group; and

R^3 is hydrogen;



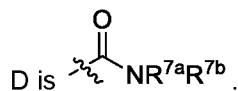
10 In another embodiment, the invention relates to compounds of Structural Formula I, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

X is CR^5 and Y is CR^4 -A-D.

In another embodiment, the invention relates to compounds of Structural Formula I, or a
15 pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

X is CR^5 and Y is CR^4 -A-D;

A is $-C(R^{6a}R^{6b})_j-$; and



20 In another embodiment, the invention relates to compounds of Structural Formula I, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

X is CR^5 and Y is CR^4 -A-D;

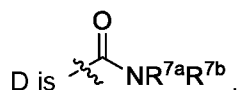
A is $-C(R^{6a}R^{6b})_j-$;

25 R^1 is selected from (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl, wherein

each of the said (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl is optionally substituted with at least one R^{13} group;

R^4 is hydrogen;

R^5 is hydrogen; and



In another embodiment, the invention relates to compounds of Structural Formula I, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

X is CR^5 and Y is CR^4 -A-D;

35 A is $-C(R^{6a}R^{6b})_j-$;

R^1 is selected from (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl, wherein

each of the said (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl is optionally substituted with at least one R¹³ group;

R² is selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, and (C₅ to C₁₀) cycloalkenyl, (C₁ to C₁₀) alkoxy, -(CH₂)_nC(O)N(R^{11a}R^{11b}), and -C(O)R¹²,

5 wherein

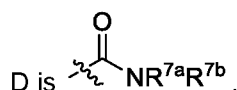
each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl is optionally substituted with at least one R¹³ group;

R³ is selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, and (C₅ to C₁₀) cycloalkenyl, wherein

10 each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl is optionally substituted with at least one R¹³ group;

R⁴ is hydrogen;

R⁵ is hydrogen; and



15 In another embodiment, the invention relates to compounds of Structural Formula I, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

X is CR⁵ and Y is CR⁴-A-D;

A is -C(R^{6a}R^{6b})_j-;

20 R¹ is selected from (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl, wherein

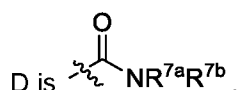
each of the said (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl is optionally substituted with at least one R¹³ group;

R² is selected from hydrogen and (C₁ to C₁₀) alkyl, wherein the said (C₁ to C₁₀) alkyl is optionally substituted with at least one R¹³ group;

25 R³ is hydrogen;

R⁴ is hydrogen;

R⁵ is hydrogen; and



30 In another embodiment, the invention relates to compounds of Structural Formula I, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

X is CR⁵ and Y is CR⁴-A-D;

A is -C(R^{6a}R^{6b})_j-; and



In another embodiment, the invention relates to compounds of Structural Formula I, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

X is CR⁵ and Y is CR⁴-A-D;

A is -C(R^{6a}R^{6b})_j-;

R¹ is selected from (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl, wherein each of the said (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl is optionally substituted with at least one R¹³ group;

R⁴ is hydrogen;

R⁵ is hydrogen; and



In another embodiment, the invention relates to compounds of Structural Formula I, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

X is CR⁵ and Y is CR⁴-A-D;

A is -C(R^{6a}R^{6b})_j-;

R¹ is selected from (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl, wherein each of the said (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl is optionally substituted with at least one R¹³ group;

R² is selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, and (C₅ to C₁₀) cycloalkenyl, (C₁ to C₁₀) alkoxy, -(CH₂)_nC(O)N(R^{11a}R^{11b}), and -C(O)R¹², wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl is optionally substituted with at least one R¹³ group;

R³ is selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, and (C₅ to C₁₀) cycloalkenyl, wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl is optionally substituted with at least one R¹³ group;

R⁴ is hydrogen;

R⁵ is hydrogen; and



In another embodiment, the invention relates to compounds of Structural Formula I, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

X is CR⁵ and Y is CR⁴-A-D;

A is -C(R^{6a}R^{6b})_j-;

R^1 is selected from (C_6 to C_{10}) aryl and (C_2 to C_9) heteroaryl, wherein each of the said (C_6 to C_{10}) aryl and (C_2 to C_9) heteroaryl is optionally substituted with at least one R^{13} group;

R^2 is selected from hydrogen and (C_1 to C_{10}) alkyl, wherein the said (C_1 to C_{10}) alkyl is optionally substituted with at least one R^{13} group;

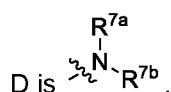
R^3 is hydrogen; and



In another embodiment, the invention relates to compounds of Structural Formula I, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

X is CR^5 and Y is CR^4 -A-D;

A is $-C(R^{6a}R^{6b})_j$; and



In another embodiment, the invention relates to compounds of Structural Formula I, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

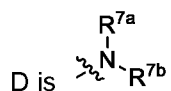
X is CR^5 and Y is CR^4 -A-D;

A is $-C(R^{6a}R^{6b})_j$;

R^1 is selected from (C_6 to C_{10}) aryl and (C_2 to C_9) heteroaryl, wherein each of the said (C_6 to C_{10}) aryl and (C_2 to C_9) heteroaryl is optionally substituted with at least one R^{13} group;

R^4 is hydrogen;

R^5 is hydrogen; and



In another embodiment, the invention relates to compounds of Structural Formula I, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

X is CR^5 and Y is CR^4 -A-D;

A is $-C(R^{6a}R^{6b})_j$;

R^1 is selected from (C_6 to C_{10}) aryl and (C_2 to C_9) heteroaryl, wherein each of the said (C_6 to C_{10}) aryl and (C_2 to C_9) heteroaryl is optionally substituted with at least one R^{13} group;

R^2 is selected from hydrogen, (C_1 to C_{10}) alkyl, (C_1 to C_{10}) alkenyl, (C_1 to C_{10}) alkynyl, (C_3 to C_{10}) cycloalkyl, and (C_5 to C_{10}) cycloalkenyl, (C_1 to C_{10}) alkoxy, $-(CH_2)_nC(O)N(R^{11a}R^{11b})$, and $-C(O)R^{12}$, wherein

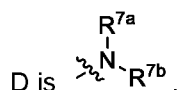
each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl is optionally substituted with at least one R¹³ group;

R³ is selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, and (C₅ to C₁₀) cycloalkenyl, wherein

5 each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl is optionally substituted with at least one R¹³ group;

R⁴ is hydrogen;

R⁵ is hydrogen; and



10 In another embodiment, the invention relates to compounds of Structural Formula I, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

X is CR⁵ and Y is CR⁴-A-D;

A is -C(R^{6a}R^{6b})_j-;

15 R¹ is selected from (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl, wherein

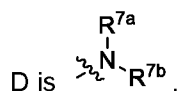
each of the said (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl is optionally substituted with at least one R¹³ group;

R² is selected from hydrogen and (C₁ to C₁₀) alkyl, wherein the said (C₁ to C₁₀) alkyl is optionally substituted with at least one R¹³ group;

20 R³ is hydrogen;

R⁴ is hydrogen;

R⁵ is hydrogen; and

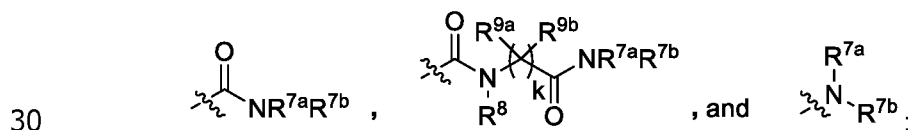


25 In another embodiment, the invention relates to compounds of Structural Formula I, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

X is CR⁵ and Y is CR⁴-A-D;

A is -C(R^{6a}R^{6b})_j-;

D is selected from the group consisting of



R¹ is selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₁ to C₁₀) alkoxy, -(CH₂)_nC(O)N(R^{11a}R^{11b}), and -C(O)R¹², wherein

35 each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, and (C₁ to C₁₀) alkoxy is optionally substituted with at least one R¹³ group;

R^2 is selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₁ to C₁₀) alkoxy, $-(CH_2)_nC(O)N(R^{11a}R^{11b})$, and $-C(O)R^{12}$, wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, and (C₁ to C₁₀) alkoxy is optionally substituted with at least one R^{13} group;

R^3 is selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, and (C₅ to C₁₀) cycloalkenyl, wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl is optionally substituted with at least one R^{13} group.

R^4 is selected from (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl, wherein

each of the said (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl is optionally substituted with at least one R^{13} group;

R^5 is hydrogen.

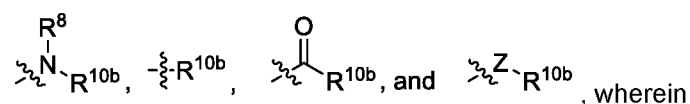
In another embodiment, the invention relates to compounds of Structural Formula I, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

X is C-A-D and Y is CR^4R^5 ;

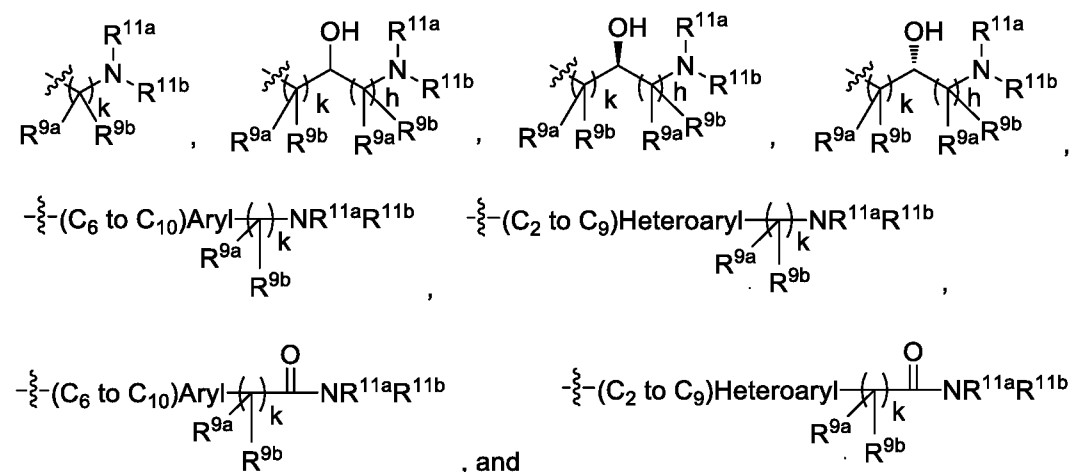
A is $-C(R^{6a}R^{6b})-$, (C₆ to C₁₀) arylene, or (C₂ to C₉) heteroarylene, wherein

each of the said (C₆ to C₁₀) arylene or (C₂ to C₉) heteroarylene is optionally substituted with at least one R^{6a} group; and

D is selected from the group consisting of



R^{10b} is selected from the group consisting of

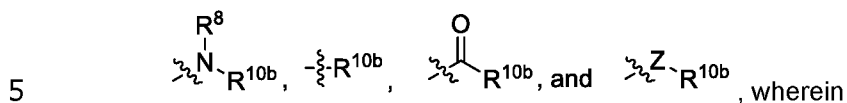


In another embodiment, the invention relates to compounds of Structural Formula I, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

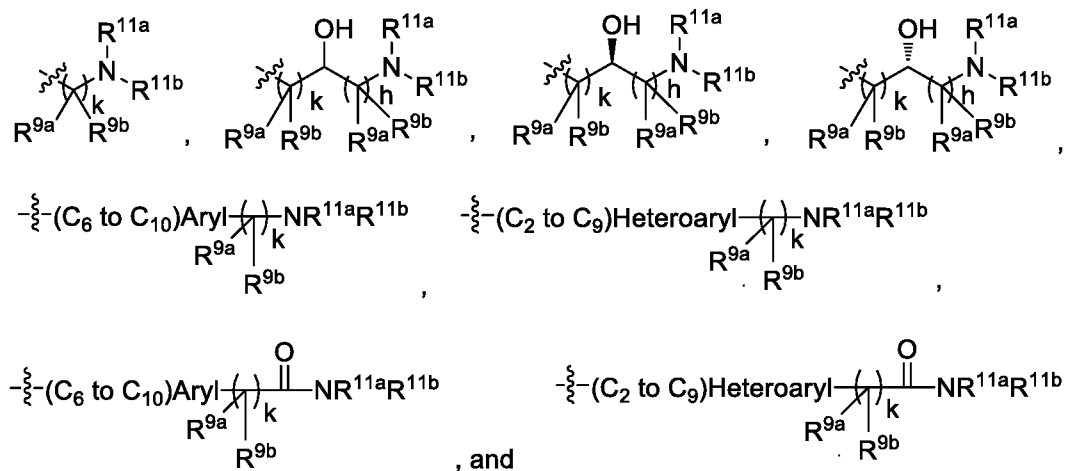
X is C-A-D and Y is a bond;

A is $-C(R^{6a}R^{6b})_j-$, (C_6 to C_{10}) arylene, or (C_2 to C_9) heteroarylene, wherein each of the said (C_6 to C_{10}) arylene or (C_2 to C_9) heteroarylene is optionally substituted with at least one R^{6a} group; and

D is selected from the group consisting of



R^{10b} is selected from the group consisting of

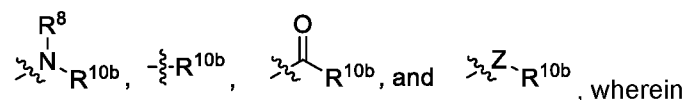


In another embodiment, the invention relates to compounds of Structural Formula I, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

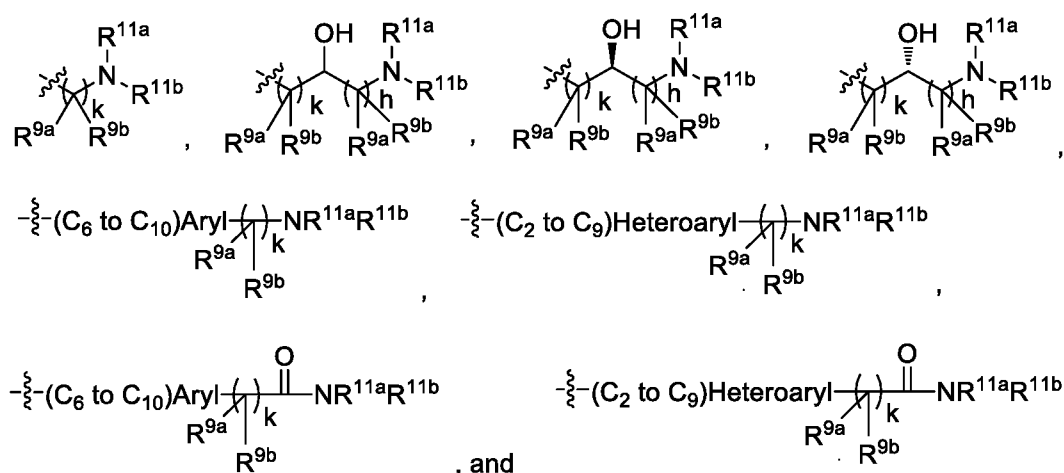
X is CR^5 and Y is CR^4 -A-D;

A is $-C(R^{6a}R^{6b})_j-$, (C_6 to C_{10}) arylene, or (C_2 to C_9) heteroarylene, wherein each of the said (C_6 to C_{10}) arylene or (C_2 to C_9) heteroarylene is optionally substituted with at least one R^{6a} group; and

D is selected from the group consisting of



R^{10b} is selected from the group consisting of



In another embodiment, the invention relates to compounds, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, selected from the group consisting the compounds described as examples A1 to A116, A201 to A205, C1 to C19, E1 to E6 in the method of preparation section, and examples B1 to B19 in table 5 and D1 to D47 in Table 7.

DEFINITIONS

As used herein, the terms "comprising" and "including" are used in their open, non-limiting sense.

The terms "halo" and/or "halogen" refer to fluorine, chlorine, bromine or iodine.

The term "(C₁ to C₁₀) alkyl" refers to a saturated aliphatic hydrocarbon radical including straight chain and branched chain groups of 1 to 8 carbon atoms. Examples of (C₁ to C₁₀) alkyl groups include methyl, ethyl, propyl, 2-propyl, *n*-butyl, *iso*-butyl, *tert*-butyl, pentyl, and the like. The terms "Me" and "methyl," as used herein, mean a -CH₃ group. The terms "Et" and "ethyl," as used herein, mean a -C₂H₅ group.

The term "(C₂ to C₁₀) alkenyl", as used herein, means an alkyl moiety comprising 2 to 10 carbons having at least one carbon-carbon double bond. The carbon-carbon double bond in such a group may be anywhere along the 2 to 10 carbon chain that will result in a stable compound. Such groups include both the E and Z isomers of said alkenyl moiety. Examples of such groups include, but are not limited to, ethene, propene, 1-butene, 2-butene, 1-pentene, 2-pentene, 1-hexene, 2-hexene, and 3-hexene. Examples of such groups include, but are not limited to, ethenyl, propenyl, butenyl, allyl, and pentenyl.

The term "allyl," as used herein, means a -CH₂CH=CH₂ group.

As used herein, the term "(C₂ to C₁₀) alkynyl" means an alkyl moiety comprising from 2 to 8 carbon atoms and having at least one carbon-carbon triple bond. The carbon-carbon triple bond in such a group may be anywhere along the 2 to 10 carbon chain that will result in a stable compound. Examples of such groups include, but are not limited to, ethyne, propyne, 1-butyne, 2-butyne, 1-pentyne, 2-pentyne, 1-hexyne, 2-hexyne, and 3-hexyne.

The term "(C₁ to C₁₀) alkoxy", as used herein, means an O-alkyl group wherein said alkyl group contains from 1 to 8 carbon atoms and is straight, branched, or cyclic. Examples of such groups

include, but are not limited to, methoxy, ethoxy, n-propyloxy, iso-propyloxy, n-butoxy, 5 iso-butoxy, tert-butoxy, cyclopentyloxy, and cyclohexyloxy.

The term “(C₆ to C₁₀) aryl”, as used herein, means a group derived from an aromatic hydrocarbon containing from 6 to 10 carbon atoms. Examples of such groups include, but are not limited to, phenyl or naphthyl. The terms “Ph” and “phenyl,” as used herein, mean a -C₆H₅ group. The term “benzyl,” as used herein, means a -CH₂C₆H₅ group.

The term “(C₆ to C₁₀) arylene” is art-recognized, and as used herein pertains to a bivalent moiety obtained by removing a hydrogen atom from a (C₆ to C₁₀) aryl ring, as defined above.

“(C₂ to C₉) heteroaryl”, as used herein, means an aromatic heterocyclic group having a total of from 5 to 10 atoms in its ring, and containing from 2 to 9 carbon atoms and from one to four heteroatoms each independently selected from O, S and N, and with the proviso that the ring of said group does not contain two adjacent O atoms or two adjacent S atoms. The heterocyclic groups include benzo-fused ring systems. Examples of aromatic heterocyclic groups are pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indoliziny, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, and furopyridinyl. The C₂ to C₉ heteroaryl groups may be C-attached or N-attached where such is possible. For instance, a group derived from pyrrole may be pyrrol-1-yl (N-attached) or pyrrol-3-yl (C-attached). Further, a group derived from imidazole may be imidazol-1-yl (N-attached) or imidazol-3-yl (C-attached).

The term “(C₂ to C₁₀) heteroarylene” is art-recognized, and as used herein pertains to a bivalent moiety obtained by removing a hydrogen atom from a (C₆ to C₁₀) heteroaryl ring, as defined above.

The term “(C₂ to C₁₀) cycloheteroalkyl”, as used herein, means a non-aromatic, monocyclic, bicyclic, tricyclic, spirocyclic, or tetracyclic group having a total of from 4 to 13 atoms in its ring system, and containing from 5 to 10 carbon atoms and from 1 to 4 heteroatoms each independently selected from O, S and N, and with the proviso that the ring of said group does not contain two adjacent O atoms or two adjacent S atoms. Furthermore, such (C₂ to C₁₀) cycloheteroalkyl groups may contain an oxo substituent at any available atom that will result in a stable compound. For example, such a group may contain an oxo atom at an available carbon or nitrogen atom. Such a group may contain more than one oxo substituent if chemically feasible. In addition, it is to be understood that when such a (C₂ to C₁₀) cycloheteroalkyl group contains a sulfur atom, said sulfur atom may be oxidized with one or two oxygen atoms to afford either a sulfoxide or sulfone. An example of a 4 membered cycloheteroalkyl group is azetidiny (derived from azetidine). An example of a 5 membered cycloheteroalkyl group is pyrrolidinyl. An example of a 6 membered cycloheteroalkyl group is piperidinyl. An example of a 9 membered cycloheteroalkyl group is indolinyl. An example of a 10 membered cycloheteroalkyl group is 4H-quinolizinyl. Further examples of such (C₂ to C₁₀) cycloheteroalkyl groups include, but are not limited to, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidino, morpholino,

thiomorpholino, thioxanyl, piperaziny, azetidiny, oxetanyl, thietanyl, homopiperidiny, oxepanyl, thiepanyl, oxazepiny, diazepiny, thiazepiny, 1,2,3,6-tetrahydropyridiny, 2-pyrroliny, 3-pyrroliny, indoliny, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazoliny, dithianyl, dithiolanyl, dihydropyranly, dihydrothienyl, dihydrofuranyl, pyrazolidiny, imidazoliny, imidazolidiny, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, 3H-indolyl, quinoliziny, 3-oxopiperaziny, 4-methylpiperaziny, 4-ethylpiperaziny, and 1-oxo-2,8,diazaspiro[4.5]dec-8-yl. The (C₂ to C₁₀) heteroaryl groups may be C-attached or N-attached where such is possible. For instance, a group derived from piperazine may be piperazin-1-yl (N-attached) or piperazin-2-yl (C-attached).

The term "(C₂ to C₁₀) cycloheteroalkylene" is art-recognized, and as used herein pertains to a bidentate moiety obtained by removing a hydrogen atom from a (C₆ to C₁₀) cycloheteroalkyl ring, as defined above.

The term "(C₃ to C₁₀) cycloalkyl group" means a saturated, monocyclic, fused, spirocyclic, or polycyclic ring structure having a total of from 3 to 10 carbon ring atoms. Examples of such groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cycloheptyl, and adamantyl.

The term "(C₃ to C₁₀) cycloalkylene" is art-recognized, and as used herein pertains to a bidentate moiety obtained by removing a hydrogen atom from a (C₃ to C₁₀) cycloalkyl ring, as defined above.

The term "spirocyclic" as used herein has its conventional meaning, that is, any compound containing two or more rings wherein two of the rings have one ring carbon in common. The rings of a spirocyclic compound, as herein defined, independently have 3 to 20 ring atoms. Preferably, they have 3 to 10 ring atoms. Non-limiting examples of a spirocyclic compound include spiro[3.3]heptane, spiro[3.4]octane, and spiro[4.5]decane.

The term "(C₅ to C₈) cycloalkenyl" means an unsaturated, monocyclic, fused, spirocyclic ring structures having a total of from 5 to 8 carbon ring atoms. Examples of such groups include, but not limited to, cyclopentenyl, cyclohexenyl.

The term "cyano" refers to a -C≡N group.

An "aldehyde" group refers to a carbonyl group where R is hydrogen.

An "alkoxy" group refers to both an -O-alkyl and an -O-cycloalkyl group, as defined herein.

An "alkoxycarbonyl" refers to a -C(O)OR.

An "alkylaminoalkyl" group refers to an -alkyl-NR-alkyl group.

An "alkylsulfonyl" group refers to a -SO₂alkyl.

An "amino" group refers to an -NH₂ or an -NRR' group.

An "aminoalkyl" group refers to an -alkyl-NRR' group.

An "aminocarbonyl" refers to a -C(O)NRR'.

An "arylalkyl" group refers to -alkylaryl, where alkyl and aryl are defined herein.

An "aryloxy" group refers to both an -O-aryl and an -O-heteroaryl group, as defined herein.

An "aryloxycarbonyl" refers to -C(O)Oaryl.

An "arylsulfonyl" group refers to a -SO₂aryl.

A "C-amido" group refers to a -C(O)NRR' group.

A "carbonyl" group refers to a -C(O)R.

A "C-carboxyl" group refers to a -C(O)OR groups.

A "carboxylic acid" group refers to a C-carboxyl group in which R is hydrogen.

A "cyano" group refers to a -CN group.

5 A "dialkylamionalkyl" group refers to an -(alkyl)N(alkyl)₂ group.

A "halo" or "halogen" group refers to fluorine, chlorine, bromine or iodine.

A "haloalkyl" group refers to an alkyl group substituted with one or more halogen atoms.

A "heteroalicycloxy" group refers to a heteroalicyclic-O group with heteroalicyclic as defined herein.

10 A "heteroaryloxy" group refers to a heteroaryl-O group with heteroaryl as defined herein.

A "hydroxy" group refers to an -OH group.

An "N-amido" group refers to a -R'C(O)NR group.

An "N-carbamyl" group refers to a -ROC(O)NR-group.

A "nitro" group refers to a -NO₂ group.

15 An "N-Sulfonamido" group refers to a -NR-S(O)₂R group.

An "N-thiocarbamyl" group refers to a ROC(S)NR' group.

An "O-carbamyl" group refers to a -OC(O)NRR' group.

An "O-carboxyl" group refers to a RC(O)O group.

An "O-thiocarbamyl" group refers to a -OC(S)NRR' group.

20 An "oxo" group refers to a carbonyl moiety such that alkyl substituted by oxo refers to a ketone group.

A "perfluoroalkyl group" refers to an alkyl group where all of the hydrogen atoms have been replaced with fluorine atoms.

A "phosphonyl" group refers to a -P(O)(OR)₂ group.

25 A "silyl" group refers to a -SiR₃ group.

An "S-sulfonamido" group refers to a -S(O)₂NR-group.

A "sulfinyl" group refers to a -S(O)R group.

A "sulfonyl" group refers to a -S(O)₂R group.

A "thiocarbonyl" group refers to a -C(=S)-R group.

30 A "trihalomethanecarbonyl" group refers to a Z₃CC(O) group, where Z is halogen.

A "trihalomethanesulfonamido" group refers to a Z₃CS(O)₂NR-group, where Z is halogen.

A "trihalomethanesulfonyl" group refers to a Z₃CS(O)₂ group, where Z is halogen.

A "trihalomethyl" group refers to a -CZ₃ group.

A "C-carboxyl" group refers to a -C(O)OR groups.

35 The term "substituted," means that the specified group or moiety bears one or more substituents.

The term "unsubstituted," means that the specified group bears no substituents. The term "optionally substituted" means that the specified group is unsubstituted or substituted by one or more substituents. It is to be understood that in the compounds of the present invention when a group is
40 said to be "unsubstituted," or is "substituted" with fewer groups than would fill the valencies of all the

atoms in the compound, the remaining valencies on such a group are filled by hydrogen. For example, if a C₆ aryl group, also called "phenyl" herein, is substituted with one additional substituent, one of ordinary skill in the art would understand that such a group has 4 open positions left on carbon atoms of the C₆ aryl ring (6 initial positions, minus one to which the remainder of the compound of the present invention is bonded, minus an additional substituent, to leave 4). In such cases, the remaining 4 carbon atoms are each bound to one hydrogen atom to fill their valencies. Similarly, if a C₆ aryl group in the present compounds is said to be "disubstituted," one of ordinary skill in the art would understand it to mean that the C₆ aryl has 3 carbon atoms remaining that are unsubstituted. Those three unsubstituted carbon atoms are each bound to one hydrogen atom to fill their valencies.

The term "solvate," is used to describe a molecular complex between compounds of the present invention and solvent molecules. Examples of solvates include, but are not limited to, compounds of the invention in combination with water, isopropanol, ethanol, methanol, dimethylsulfoxide (DMSO), ethyl acetate, acetic acid, ethanolamine, or mixtures thereof.

The term "hydrate" can be used when said solvent is water. It is specifically contemplated that in the present invention one solvent molecule can be associated with one molecule of the compounds of the present invention, such as a hydrate. Furthermore, it is specifically contemplated that in the present invention, more than one solvent molecule may be associated with one molecule of the compounds of the present invention, such as a dihydrate.

Additionally, it is specifically contemplated that in the present invention less than one solvent molecule may be associated with one molecule of the compounds of the present invention, such as a hemihydrate. Furthermore, solvates of the present invention are contemplated as solvates of compounds of the present invention that retain the biological effectiveness of the non-hydrate form of the compounds.

The term "pharmaceutically acceptable salt," as used herein, means a salt of a compound of the present invention that retains the biological effectiveness of the free acids and bases of the specified derivative and that is not biologically or otherwise undesirable.

The term "pharmaceutically acceptable formulation", as used herein, means a combination of a compound of the invention, or a salt or solvate thereof, and a carrier, diluent, and/or excipient(s) that are compatible with a compound of the present invention, and is not deleterious to the recipient thereof. Pharmaceutical formulations can be prepared by procedures known to those of ordinary skill in the art. For example, the compounds of the present invention can be formulated with common excipients, diluents, or carriers, and formed into tablets, capsules, and the like. Examples of excipients, diluents, and carriers that are suitable for such formulations include the following: fillers and extenders such as starch, sugars, mannitol, and silicic derivatives; binding agents such as carboxymethyl cellulose and other cellulose derivatives, alginates, gelatin, and polyvinyl pyrrolidone; moisturizing agents such as glycerol; disintegrating agents such as povidone, sodium starch glycolate, sodium carboxymethylcellulose, agar, calcium carbonate, and sodium bicarbonate; agents for retarding dissolution such as paraffin; resorption accelerators such as quaternary ammonium compounds; surface active agents such as cetyl alcohol, glycerol monostearate; adsorptive carriers such as kaolin and bentonite; and lubricants such as talc, calcium and magnesium stearate and solid polyethylene

glycols. Final pharmaceutical forms may be pills, tablets, powders, lozenges, sachets, cachets, or sterile packaged powders, and the like, depending on the type of excipient used. Additionally, it is specifically contemplated that pharmaceutically acceptable formulations of the present invention can contain more than one active ingredient. For example, such formulations may contain more than one compound according to the present invention. Alternatively, such formulations may contain one or more compounds of the present invention and one or more additional agents that reduce abnormal cell growth.

The term "virus inhibiting amount" as used herein, refers to the amount of a compound of the present invention, or a salt or solvate thereof, required to inhibit the cell entry of an enveloped virus *in vivo*, such as in a mammal, or *in vitro*. The amount of such compounds required to cause such inhibition can be determined without undue experimentation using methods described herein and those known to those of ordinary skill in the art.

The terms "treat", "treating", and "treatment" with reference to enveloped virus infection, in mammals, particularly a human, include: (i) preventing the disease or condition from occurring in a subject which may be predisposed to the condition, such that the treatment constitutes prophylactic treatment for the pathologic condition; (ii) modulating or inhibiting the disease or condition, i.e., arresting its development; (iii) relieving the disease or condition, i.e., causing regression of the disease or condition; or (iv) relieving and/or alleviating the disease or condition or the symptoms resulting from the disease or condition.

The compositions are delivered in effective amounts. The term "effective amount" refers to the amount necessary or sufficient to realize a desired biologic effect and/or reduce the viral load. Combined with the teachings provided herein, by choosing among the various active compounds and weighing factors such as potency, relative bioavailability, patient body weight, severity of adverse side-effects and preferred mode of administration, an effective prophylactic or therapeutic treatment regimen can be planned which does not cause substantial toxicity and yet is effective to treat the particular subject. In addition, based on testing, toxicity of the inhibitor is expected to be low. The effective amount for any particular application can vary depending on such factors as the disease or condition being treated, the particular inhibitor being administered, the size of the subject, or the severity of the disease or condition. One of ordinary skill in the art can empirically determine the effective amount of a particular inhibitor and/or other therapeutic agent without necessitating undue experimentation. It is preferred generally that a maximum dose be used, that is, the highest safe dose according to some medical judgment. Multiple doses per day may be contemplated to achieve appropriate systemic levels of compounds. Appropriate systemic levels can be determined by, for example, measurement of the patient's peak or sustained plasma level of the drug.

"Dose" and "dosage" are used interchangeably herein. For any compound described herein, the therapeutically effective amount can be initially determined from preliminary *in vitro* studies and/or animal models. A therapeutically effective dose can also be determined from human data for inhibitors that have been tested in humans and for compounds, which are known to exhibit similar pharmacological activities, such as other related active agents. The applied dose can be adjusted based on the relative bioavailability and potency of the administered compound. Adjusting the dose to

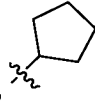
achieve maximal efficacy based on the methods described above and other methods well-known in the art, is well within the capabilities of the ordinarily skilled artisan. In certain embodiments, the methods of the invention are useful for treating infection with enveloped viruses.

Unless indicated otherwise, all references herein to the inventive compounds include references to salts, solvates, and complexes thereof, including polymorphs, stereoisomers, tautomers, and isotopically labeled versions thereof. For example, compounds of the present invention can be pharmaceutically acceptable salts and/or pharmaceutically acceptable solvates.

The term "stereoisomers" refers to compounds that have identical chemical constitution, but differ with regard to the arrangement of their atoms or groups in space. In particular, the term "enantiomers" refers to two stereoisomers of a compound that are non-superimposable mirror images of one another.

A pure enantiomer can be contaminated with up to 2% of the opposite enantiomer.

The terms "racemic" or "racemic mixture," as used herein, refer to a 1:1 mixture of enantiomers of a particular compound. The term "diastereomers", on the other hand, refers to the relationship between a pair of stereoisomers that comprise two or more asymmetric centers and are not mirror images of one another. In accordance with a convention used in the art, the symbol is used in structural formulas herein to depict the bond that is the point of attachment of the moiety or substituent to the core or backbone structure. In accordance with another convention, in some structural formulae herein the carbon atoms and their bound hydrogen atoms are not explicitly

depicted, e.g.,  represents a methyl group,  represents an ethyl group,  represents a cyclopentyl group, etc.

The compounds of the present invention may have asymmetric carbon atoms. The carbon-carbon bonds of the compounds of the present invention may be depicted herein using a solid line (—), a solid wedge (—), or a dotted wedge (.....). The use of a solid line to depict bonds to asymmetric carbon atoms is meant to indicate that all possible stereoisomers (e.g. specific enantiomers, racemic mixtures, etc.) at that carbon atom are included. The use of either a solid or dotted wedge to depict bonds to asymmetric carbon atoms is meant to indicate that only the stereoisomer shown is meant to be included. It is possible that compounds of the invention may contain more than one asymmetric carbon atom. In those compounds, the use of a solid line to depict bonds to asymmetric carbon atoms is meant to indicate that all possible stereoisomers are meant to be included. For example, unless stated otherwise, it is intended that the compounds of the present invention can exist as enantiomers and diastereomers or as racemates and mixtures thereof. The use of a solid line to depict bonds to one or more asymmetric carbon atoms in a compound of the invention and the use of a solid or dotted wedge to depict bonds to other asymmetric carbon atoms in the same compound is meant to indicate that a mixture of diastereomers is present.

(R)_z then, unless otherwise defined, a substituent "R" may reside on any atom of the ring system, assuming replacement of a depicted, implied, or expressly defined hydrogen from one of the ring atoms, so long as a stable structure is formed.

Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate using, for example, chiral high pressure liquid chromatography (HPLC). Alternatively, the racemate (or a racemic precursor) maybe reacted with a suitable optically active compound, for example, an alcohol, or, in the case where the compound contains an acidic or basic moiety, an acid or base such as tartaric acid or 1-phenyl ethyl amine. The resulting diastereomeric mixture may be separated by chromatography and/or fractional crystallization and one or both of the diastereoisomers converted to the corresponding pure enantiomer(s) by means well known to one skilled in the art. Chiral compounds of the invention (and chiral precursors thereof) may be obtained in enantiomerically-enriched form using chromatography, typically HPLC, on an asymmetric resin with a mobile phase consisting of a hydrocarbon, typically heptane or hexane, containing from 0 to 50% isopropanol, typically from 2 to 20%, and from 0 to 5% of an alkylamine, typically 0.1% diethylamine. Concentration of the eluate affords the enriched mixture. Stereoisomeric conglomerates may be separated by conventional techniques known to those skilled in the art. See, e.g. "Stereochemistry of Organic Compounds" by E L Eliel (Wiley, New York, 1994), the disclosure of which is incorporated herein by reference in its entirety.

Where a compound of the invention contains an alkenyl or alkenylene group, geometric *cis/trans* (or *Z/E*) isomers are possible. Where the compound contains, for example, a keto or oxime group or an aromatic moiety, tautomeric isomerism ('tautomerism') can occur. Examples of tautomerism include keto and enol tautomers. A single compound may exhibit more than one type of isomerism. Included within the scope of the invention are all stereoisomers, geometric isomers and tautomeric forms of the inventive compounds, including compounds exhibiting more than one type of isomerism, and mixtures of one or more thereof. *Cis/trans* isomers may be separated by conventional techniques well known to those skilled in the art, for example, chromatography and fractional crystallization.

The compounds of the present invention may be administered as prodrugs. Thus certain derivatives of compounds of Formula I which may have little or no pharmacological activity themselves can, when administered to a mammal, be converted into a compound of Formula I having the desired activity, for example, by hydrolytic cleavage. Such derivatives are referred to as "prodrugs". Prodrugs can, for example, be produced by replacing appropriate functionalities present in the compound of Formula I with certain moieties known to those skilled in the art. See, e.g. "Pro-drugs as Novel Delivery Systems", Vol. 14, ACS Symposium Series (T Higuchi and W Stella) and "Bioreversible Carriers in Drug Design", Pergamon Press, 1987 (ed. E B Roche, American Pharmaceutical Association), the disclosures of which are incorporated herein by reference in their entirety. Some examples of such prodrugs include: an ester moiety in the place of a carboxylic acid functional group; an ether moiety or an amide moiety in place of an alcohol functional group; and an amide moiety in place of a primary or secondary amino functional group. Further examples of replacement groups are known to those of skill in the art. See, e.g. "Design of Prodrugs" by H Bundgaard (Elsevier, 1985), the disclosure of which is incorporated herein by reference in its entirety.

It is also possible that certain compounds of Formula I may themselves act as prodrugs of other compounds of Formula I.

Salts of the present invention can be prepared according to methods known to those of skill in the art. Examples of salts include, but are not limited to, acetate, acrylate, benzenesulfonate, benzoate (such as chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, and methoxybenzoate), bicarbonate, bisulfate, bisulfite, bitartrate, borate, bromide, butyne-1,4-dioate, calcium edetate, camsylate, carbonate, chloride, caproate, caprylate, clavulanate, citrate, decanoate, dihydrochloride, dihydrogenphosphate, edetate, edisylate, estolate, esylate, ethylsuccinate, formate, fumarate, gluceptate, gluconate, glutamate, glycollate, glycollylarsanilate, heptanoate, hexyne-1,6-dioate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, γ -hydroxybutyrate, iodide, isobutyrate, isothionate, lactate, lactobionate, laurate, malate, maleate, malonate, mandelate, mesylate, metaphosphate, methanesulfonate, methylsulfate, monohydrogenphosphate, mucate, napsylate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, nitrate, oleate, oxalate, pamoate (embonate), palmitate, pantothenate, phenylacetates, phenylbutyrate, phenylpropionate, phthalate, phosphate/diphosphate, polygalacturonate, propanesulfonate, propionate, propiolate, pyrophosphate, pyrosulfate, salicylate, stearate, subacetate, suberate, succinate, sulfate, sulfonate, sulfite, tannate, tartrate, teoclate, tosylate, triethiodode, and valerate salts.

The compounds of the present invention that are basic in nature are capable of forming a wide variety of different salts with various inorganic and organic acids. Although such salts must be pharmaceutically acceptable for administration to animals, it is often desirable in practice to initially isolate the compound of the present invention from the reaction mixture as a pharmaceutically unacceptable salt and then simply convert the latter back to the free base compound by treatment with an alkaline reagent and subsequently convert the latter free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of the base compounds of this invention can be prepared by treating the base compound with a substantially equivalent amount of the selected mineral or organic acid in an aqueous solvent medium or in a suitable organic solvent, such as methanol or ethanol. Upon evaporation of the solvent, the desired solid salt is obtained. The desired acid salt can also be precipitated from a solution of the free base in an organic solvent by adding an appropriate mineral or organic acid to the solution.

Those compounds of the present invention that are acidic in nature are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include the alkali metal or alkaline-earth metal salts and particularly, the sodium and potassium salts. These salts are all prepared by conventional techniques. The chemical bases which are used as reagents to prepare the pharmaceutically acceptable base salts of this invention are those which form non-toxic base salts with the acidic compounds of the present invention. Such non-toxic base salts include those derived from such pharmacologically acceptable cations as sodium, potassium calcium and magnesium, etc. These salts can be prepared by treating the corresponding acidic compounds with an aqueous solution containing the desired pharmacologically acceptable cations, and then evaporating the resulting solution to dryness, preferably under reduced pressure. Alternatively, they may also be prepared by mixing lower alkanolic solutions of the acidic compounds and the desired

alkali metal alkoxide together, and then evaporating the resulting solution to dryness in the same manner as before. In either case, stoichiometric quantities of reagents are preferably employed in order to ensure completeness of reaction and maximum yields of the desired final product.

If the inventive compound is a base, the desired salt may be prepared by any suitable method available in the art, for example, treatment of the free base with an inorganic acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, or with an organic acid, such as acetic acid, maleic acid, succinic acid, mandelic acid, fumaric acid, malonic acid, pyruvic acid, oxalic acid, glycolic acid, salicylic acid, a pyranosidyl acid, such as glucuronic acid or galacturonic acid, an alpha-hydroxy acid, such as citric acid or tartaric acid, an amino acid, such as aspartic acid or glutamic acid, an aromatic acid, such as benzoic acid or cinnamic acid, a sulfonic acid, such as p-toluenesulfonic acid or ethanesulfonic acid, or the like.

If the inventive compound is an acid, the desired salt may be prepared by any suitable method, for example, treatment of the free acid with an inorganic or organic base, such as an amine (primary, secondary or tertiary), an alkali metal hydroxide or alkaline earth metal hydroxide, or the like. Illustrative examples of suitable salts include organic salts derived from amino acids, such as glycine and arginine, ammonia, primary, secondary, and tertiary amines, and cyclic amines, such as piperidine, morpholine and piperazine, and inorganic salts derived from sodium, calcium, potassium, magnesium, manganese, iron, copper, zinc, aluminum and lithium.

In the case of agents that are solids, it is understood by those skilled in the art that the inventive compounds, agents and salts may exist in different crystal or polymorphic forms, all of which are intended to be within the scope of the present invention and specified formulas.

The invention also includes isotopically-labeled compounds of the invention, wherein one or more atoms is replaced by an atom having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes suitable for inclusion in the compounds of the invention include isotopes of hydrogen, such as ^2H and ^3H , carbon, such as ^{11}C , ^{13}C and ^{14}C , chlorine, such as ^{36}Cl , fluorine, such as ^{18}F , iodine, such as ^{123}I and ^{125}I , nitrogen, such as ^{13}N and ^{15}N , oxygen, such as ^{15}O , ^{17}O and ^{18}O , phosphorus, such as ^{32}P , and sulfur, such as ^{35}S .

Certain isotopically-labeled compounds of the invention, for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, ^3H , and carbon-14, ^{14}C , are particularly useful for this purpose in view of their ease of incorporation and ready means of detection. Substitution with heavier isotopes such as deuterium, ^2H , may afford certain therapeutic advantages resulting from greater metabolic stability, for example, ^{35}S increased *in vivo* half-life or reduced dosage requirements, and hence may be preferred in some circumstances. Substitution with positron emitting isotopes, such as ^{11}C , ^{18}F , ^{15}O and ^{13}N , can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy.

Isotopically-labeled compounds of the invention can generally be prepared by conventional

techniques known to those skilled in the art or by processes analogous to those described herein, using an appropriate isotopically-labeled reagent in place of the non-labeled reagent otherwise employed.

The compounds of the present invention may be formulated into pharmaceutical compositions as described below in any pharmaceutical form recognizable to the skilled artisan as being suitable. Pharmaceutical compositions of the invention comprise a therapeutically effective amount of at least one compound of the present invention and an inert, pharmaceutically acceptable carrier or diluent.

To treat or prevent diseases or conditions mediated in part or whole by enveloped virus infection, a pharmaceutical composition of the invention is administered in a suitable formulation prepared by combining a therapeutically effective amount (i.e., an enveloped virus GP- or host cell partner- modulating, regulating, or inhibiting amount effective to achieve therapeutic efficacy) of at least one compound of the present invention (as an active ingredient) with one or more pharmaceutically suitable carriers, which may be selected, for example, from diluents, excipients and auxiliaries that facilitate processing of the active compounds into the final pharmaceutical preparations.

The pharmaceutical carriers employed may be either solid or liquid. Exemplary solid carriers are lactose, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like. Exemplary liquid carriers are syrup, peanut oil, olive oil, water and the like. Similarly, the inventive compositions may include time-delay or time-release material known in the art, such as glyceryl monostearate or glyceryl distearate alone or with a wax, ethylcellulose, hydroxypropylmethylcellulose, methylmethacrylate or the like. Further additives or excipients may be added to achieve the desired formulation properties. For example, a bioavailability enhancer, such as Labrasol, Gelucire or the like, or formulator, such as CMC (carboxy-methylcellulose), PG (propyleneglycol), or PEG (polyethyleneglycol), may be added. Gelucire®, a semi-solid vehicle that protects active ingredients from light, moisture and oxidation, may be added, e.g., when preparing a capsule formulation.

If a solid carrier is used, the preparation can be tableted, placed in a hard gelatin capsule in powder or pellet form, or formed into a troche or lozenge. The amount of solid carrier may vary, but generally will be from about 25 mg to about 1 g. If a liquid carrier is used, the preparation may be in the form of syrup, emulsion, soft gelatin capsule, sterile injectable solution or suspension in an ampoule or vial or non-aqueous liquid suspension. If a semi-solid carrier is used, the preparation may be in the form of hard and soft gelatin capsule formulations. The inventive compositions are prepared in unit-dosage form appropriate for the mode of administration, e.g. parenteral or oral administration.

To obtain a stable water-soluble dose form, a salt of a compound of the present invention may be dissolved in an aqueous solution of an organic or inorganic acid, such as a 0.3 M solution of succinic acid or citric acid. If a soluble salt form is not available, the agent may be dissolved in a suitable co-solvent or combinations of co-solvents. Examples of suitable co-solvents include alcohol, propylene glycol, polyethylene glycol 300, polysorbate 80, glycerin and the like in concentrations ranging from 0 to 60% of the total volume. In an exemplary embodiment, a compound of the present invention is dissolved in DMSO and diluted with water. The composition may also be in the form of a

solution of a salt form of the active ingredient in an appropriate aqueous vehicle such as water or isotonic saline or dextrose solution.

Proper formulation is dependent upon the route of administration selected. For injection, the agents of the compounds of the present invention may be formulated into aqueous solutions, preferably in physiologically compatible buffers such as Hanks solution, Ringer's solution, or physiological saline buffer.

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

For oral administration, the compounds can be formulated by combining the active compounds with pharmaceutically acceptable carriers known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a subject to be treated. Pharmaceutical preparations for oral use can be obtained using a solid excipient in admixture with the active ingredient (agent), optionally grinding the resulting mixture, and processing the mixture of granules after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients include: fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; and cellulose preparations, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, or polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as crosslinked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, polyvinyl pyrrolidone, Carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures.

Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active agents.

Pharmaceutical preparations that can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with fillers such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate, and, optionally, stabilizers. In soft capsules, the active agents may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. All formulations for oral administration should be in dosages suitable for such administration. For buccal administration, the compositions may take the form of tablets or lozenges formulated in conventional manner.

For administration intranasally or by inhalation, the compounds for use according to the present invention may be conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebuliser, with the use of a suitable propellant, e.g., dichlorodifluoromethane,

trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount.

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

The compounds may be formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion. Formulations for injection may be presented in unit-dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active agents may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances that increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents that increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

In addition to the formulations described above, the compounds of the present invention may also be formulated as a depot preparation. Such long-acting formulations may be administered by implantation (for example, subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example, as an emulsion in an acceptable oil) or ion-exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt. A pharmaceutical carrier for hydrophobic compounds is a cosolvent system comprising benzyl alcohol, a non-polar surfactant, a water-miscible organic polymer, and an aqueous phase. The co-solvent system may be a VPD co-solvent system. VPD is a solution of 3% w/v benzyl alcohol, 8% w/v of the non-polar surfactant polysorbate 80, and 65% w/v polyethylene glycol300, made up to volume in absolute ethanol. The VPD co-solvent system (VPD: 5W) contains VPD diluted 1:1 with a 5% dextrose in water solution. This co-solvent system dissolves hydrophobic compounds well, and itself produces low toxicity upon systemic administration. The proportions of a cosolvent system may be suitably varied without destroying its solubility and toxicity characteristics. Furthermore, the identity of the co-solvent components may be varied: for example, other low-toxicity nonpolar surfactants may be used instead of polysorbate 80; the fraction size of polyethylene glycol may be varied; other biocompatible polymers may replace polyethylene glycol, e.g. polyvinyl pyrrolidone; and other sugars or polysaccharides may be substituted for dextrose.

Alternatively, other delivery systems for hydrophobic pharmaceutical compounds may be

employed. Liposomes and emulsions are known examples of delivery vehicles or carriers for hydrophobic drugs. Certain organic solvents such as dimethylsulfoxide also may be employed, although usually at the cost of greater toxicity due to the toxic nature of DMSO. Additionally, the compounds may be delivered using a sustained-release system, such as semipermeable matrices of solid hydrophobic polymers containing the therapeutic agent. Various sustained-release materials have been established and are known by those skilled in the art. Sustained-release capsules may, depending on their chemical nature, release the compounds for a few weeks up to over 100 days. Depending on the chemical nature and the biological stability of the therapeutic reagent, additional strategies for protein stabilization may be employed.

The pharmaceutical compositions also may comprise suitable solid- or gel-phase carriers or excipients. These carriers and excipients may provide marked improvement in the bioavailability of poorly soluble drugs. Examples of such carriers or excipients include calcium carbonate, calcium phosphate, sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols. Furthermore, additives or excipients such as Gelucire®, Capryol®, Labrafil®, Labrasol®, Lauroglycol®, Plurol®, Peceol®, Transcutol® and the like may be used.

Further, the pharmaceutical composition may be incorporated into a skin patch for delivery of the drug directly onto the skin.

It will be appreciated that the actual dosages of the agents of this invention will vary according to the particular agent being used, the particular composition formulated, the mode of administration, and the particular site, host, and disease being treated. Those skilled in the art using conventional dosage determination tests in view of the experimental data for a given compound may ascertain optimal dosages for a given set of conditions. For oral administration, an exemplary daily dose generally employed will be from about 0.001 to about 1000 mg/kg of body weight, with courses of treatment repeated at appropriate intervals.

Furthermore, the pharmaceutically acceptable formulations of the present invention may contain a compound of the present invention, or a salt or solvate thereof, in an amount of about 10 mg to about 2000 mg, or from about 10 mg to about 1500 mg, or from about 10 mg to about 1000 mg, or from about 10 mg to about 750 mg, or from about 10 mg to about 500 mg, or from about 25 mg to about 500 mg, or from about 50 to about 500 mg, or from about 100 mg to about 500 mg.

Additionally, the pharmaceutically acceptable formulations of the present invention may contain a compound of the present invention, or a salt or solvate thereof, in an amount from about 0.5 w/w% to about 95 w/w%, or from about 1 w/w% to about 95 w/w%, or from about 1 w/w% to about 75 w/w%, or from about 5 w/w% to about 75 w/w%, or from about 10 w/w% to about 75 w/w%, or from about 10 w/w% to about 50 w/w%.

The compounds of the present invention, or salts or solvates thereof, may be administered to an animal, such as a human, suffering from a condition or disease mediated by an enveloped virus, either alone or as part of a pharmaceutically acceptable formulation, once a day, twice a day, three times a day, four times a day, or even more frequently.

The compounds of the present invention, or salts or solvates thereof, may be administered to humans or mammals suffering from a condition or disease mediated by a filovirus, arenavirus, or

other enveloped virus in combination with at least one other agent used for treatment, alone or as part of a pharmaceutically acceptable formulation, once a day, twice a day, three times a day, four times a day, or even more frequently.

Those of ordinary skill in the art will understand that with respect to the compounds of the present invention, the particular pharmaceutical formulation, the dosage, and the number of doses given per day to humans or mammals requiring such treatment, are all choices within the knowledge of one of ordinary skill in the art and can be determined without undue experimentation.

Combination Therapy

Compounds of Structural Formula I of the invention may be combined with other therapeutic agents. The inhibitor and other therapeutic agent may be administered simultaneously or sequentially. When the other therapeutic agents are administered simultaneously they can be administered in the same or separate formulations, but are administered at the same time. The other therapeutic agents are administered sequentially with one another and with the inhibitors, when the administration of the other therapeutic agents and the inhibitors is temporally separated. The separation in time between the administration of these compounds may be a matter of minutes or it may be longer. Other therapeutic agents include but are not limited to anti-viral vaccines and anti-viral agents. In some instances the inhibitors are administered with multiple therapeutic agents, i.e., 2, 3, 4 or even more different anti-viral agents.

An anti-viral vaccine is a formulation composed of one or more viral antigens and one or more adjuvants. The viral antigens include proteins or fragments thereof as well as whole killed virus. Adjuvants are well known to those of skill in the art.

Antiviral agents are compounds, which prevent infection of cells by viruses or replication of the virus within the cell. There are many fewer antiviral drugs than antibacterial drugs because viruses are more dependent on host cell factors than bacteria. There are several stages within the process of viral infection, which can be blocked or inhibited by antiviral agents. These stages include, attachment of the virus to the host cell (immunoglobulin or binding peptides), membrane penetration inhibitors, e.g. T-20, uncoating of the virus (e.g. amantadine), synthesis or translation of viral mRNA (e.g. interferon), replication of viral RNA or DNA (e.g. nucleotide analogues), maturation of new virus proteins (e.g. protease inhibitors), and budding and release of the virus.

Nucleotide analogues are synthetic compounds which are similar to nucleotides, but which have an incomplete or abnormal deoxyribose or ribose group. Once the nucleotide analogues are in the cell, they are phosphorylated, producing the triphosphate form which competes with normal nucleotides for incorporation into the viral DNA or RNA. Once the triphosphate form of the nucleotide analogue is incorporated into the growing nucleic acid chain, it causes irreversible association with the viral polymerase and thus chain termination. Nucleotide analogues include, but are not limited to, acyclovir (used for the treatment of herpes simplex virus and varicella-zoster virus), gancyclovir (useful for the treatment of cytomegalovirus), idoxuridine, ribavirin (useful for the treatment of respiratory syncytial virus), didoxynosine, dideoxycytidine, zidovudine (azidothymidine), imiquimod, resiquimod, favipiravir, BCX4430, and GS-5374 or their analogues.

The interferons are cytokines which are secreted by virus-infected cells as well as immune cells. The interferons function by binding to specific receptors on cells adjacent to the infected cells, causing the change in the cell which protects it from infection by the virus. α - and β -interferon also induce the expression of Class I and Class II MHC molecules on the surface of infected cells, resulting in increased antigen presentation for host immune cell recognition. α - and β -interferons are available as recombinant proteins and have been used for the treatment of chronic hepatitis B and C infection. At the dosages that are effective for anti-viral therapy, interferons may have severe side effects such as fever, malaise and weight loss.

Anti-viral agents, which may be useful in combination with Structural Formula I of the invention, include but are not limited to immunoglobulins, amantadine, interferons, nucleotide analogues, small interfering RNAs (siRNAs) and other protease inhibitors (other than the papain-like cysteine protease inhibitors-although combinations of papain-like cysteine protease inhibitors are also useful). Specific examples of anti-viral agents include but are not limited to Acemannan; Acyclovir; Acyclovir Sodium; Adefovir; Alovudine; Alvircept Sudotox; Amantadine Hydrochloride; Aranotin; Arildone; Ateviridine Mesylate; AVI-7537; Avridine; Cidofovir; Cipamfylline; Cytarabine Hydrochloride; Delavirdine Mesylate; Desciclovir; Didanosine; Disoxaril; Edoxudine; Enviroxime; Enviroxime; Famciclovir; Famotidine Hydrochloride; Favipiravir; Fiacitabine; Fialuridine; Fosarnet; Fosarnet Sodium; Fosfomate Sodium; Ganciclovir; Ganciclovir Sodium; Idoxuridine; Kethoxal; Lamivudine; Lobucavir; Memotidine Hydrochloride; Methisazone; Nevirapine; Penciclovir; Pirodavir; Ribavirin; Rimantadine Hydrochloride; Saquinavir Mesylate; Somantadine Hydrochloride; Sorivudine; Statolon; Stavudine; Tilorone Hydrochloride; TKM Ebola; Triazavirin; Trifluridine; Valacyclovir Hydrochloride; Vidarabine; Vidarabine Phosphate; Vidarabine Sodium Phosphate; Viroxime; Zalcitabine; Zidovudine; Zidovudine; and ZMapp.

Immunoglobulin therapy is used for the prevention of viral infection. Immunoglobulin therapy for viral infections is different than bacterial infections, because rather than being antigen-specific, the immunoglobulin therapy functions by binding to extracellular virions and preventing them from attaching to and entering cells which are susceptible to the viral infection. The therapy is useful for the prevention of viral infection for the period of time that the antibodies are present in the host. In general there are two types of immunoglobulin therapies, normal immunoglobulin therapy and hyper-immunoglobulin therapy. Normal immune globulin therapy utilizes an antibody product which is prepared from the serum of normal blood donors and pooled. This pooled product contains low titers of antibody to a wide range of human viruses, such as hepatitis A, parvovirus, enterovirus (especially in neonates). Hyper-immune globulin therapy utilizes antibodies which are prepared from the serum of individuals who have high titers of an antibody to a particular virus. Those antibodies are then used against a specific virus. Another type of immunoglobulin therapy is active immunization. This involves the administration of antibodies or antibody fragments to viral surface proteins.

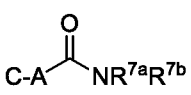
In the following Preparations and Examples, "Ac" means acetyl, "Me" means methyl, "Et" means ethyl, "Ph" means phenyl, "Py" means pyridine, "BOC", "Boc" or "boc" means N-*tert*-butoxycarbonyl, "Ns" means 2-Nitrophenylsulfonyl, "CMMP" means (cyanomethylene) trimethyl phosphorane, "DCM" (CH₂Cl₂) means dichloromethane or methylene chloride, "DCE" means

dichloroethane or ethylene chloride, "DCM" means dichloromethane, "DIAD" means diisopropylazodicarboxylate, "DIPEA" or "DIEA" means diisopropyl ethyl amine, "DMA" means N,N-dimethylacetamide, "DMAP" means 4-dimethylaminopyridine, "DME" means 1,2-dimethoxyethane, "DMF" means N,N-dimethyl formamide, "DMSO" means dimethylsulfoxide, "DPPA" means diphenylphosphorylazide, "DPPP" means 1,3-bis(diphenylphosphino)propane, "EDCI" means 3-(ethyliminomethyleneamino)-N,N-dimethylpropan-1-amine, "EtOAc" means ethyl acetate, "HATU" means 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate, "HOAt" means 1-hydroxy-7 azabenzotriazole, "HOAc" means acetic acid, "IPA" means isopropyl alcohol, "LDA" means lithium diisopropylamide, "NMP" means 1-methyl 2-pyrrolidinone, "TEA" means triethyl amine, "TFA" means trifluoroacetic acid, "TOSMIC" means toluenesulfonylmethyl isocyanide, "MgSO₄" means magnesium sulphate, "NaHMDS" or "NHMDS" means sodium hexamethyldisilazide, "Na₂SO₄" means sodium sulphate, "MeOH" means methanol, "Et₂O" means diethyl ether, "EtOH" means ethanol, "H₂O" means water, "HCl" means hydrochloric acid, "POCl₃" means phosphorus oxychloride, "SOCl₂" means thionylchloride, "K₂CO₃" means potassium carbonate, "THF" means tetrahydrofuran, "DBU" means 1,8-diazabicyclo[5.4.0]undec-7-ene, "LAH" means lithium aluminium hydride, "LiHMDS" or "LHMDS" means lithium hexamethyldisilazide, "TBABr" means tetra butyl ammonium bromide, "TBME" or "MTBE" means *tert*-butyl methyl ether, "TMS" means trimethylsilyl, "PMHS" means polymethylhydrosiloxane, "MCPBA" means 3-chloroperoxy benzoic acid, "N" means Normal, "M" means molar, "mL" means millilitre, "mmol" means millimoles, "μmol" means micromoles, "eq." means equivalent, "°C" means degrees Celsius, "Pa" means pascals, "Xanthphos" means 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene, "rt" means room temperature.

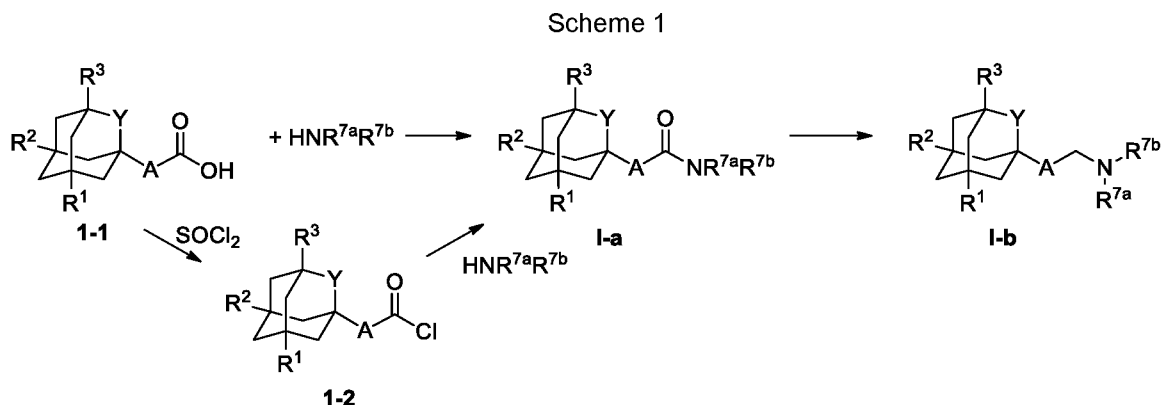
Methods of Preparation.

Compounds of the present invention may be prepared using the reaction routes and synthetic schemes described below, employing the techniques available in the art using starting materials that are readily available. The preparation of certain embodiments of the present invention is described in detail in the following examples, but those of ordinary skill in the art will recognize that the preparations described may be readily adapted to prepare other embodiments of the present invention. For example, the synthesis of non-exemplified compounds according to the invention may be performed by modifications apparent to those skilled in the art, e.g. by appropriately protecting interfering groups, by changing to other suitable reagents known in the art, or by making routine modifications of reaction conditions. Alternatively, other reactions referred to herein or known in the art will be recognized as having adaptability for preparing other compounds of the invention.

In one general synthetic process, compounds of the Structural Formula I where Y is a bond or

CR⁴R⁵ and X is , represented by Formula I-a can be prepared according to Scheme 1 by reacting carboxylic acid 1-1 with amine NHR^{7a}R^{7b} in the presence of a coupling reagent such as EDCI or HATU and a base such as DIEA or triethylamine in a solvent such as DMF or dichloroethane to provide the desired product of Formula I-a. Alternatively, carboxylic acid 1-1 can react with SOCl₂

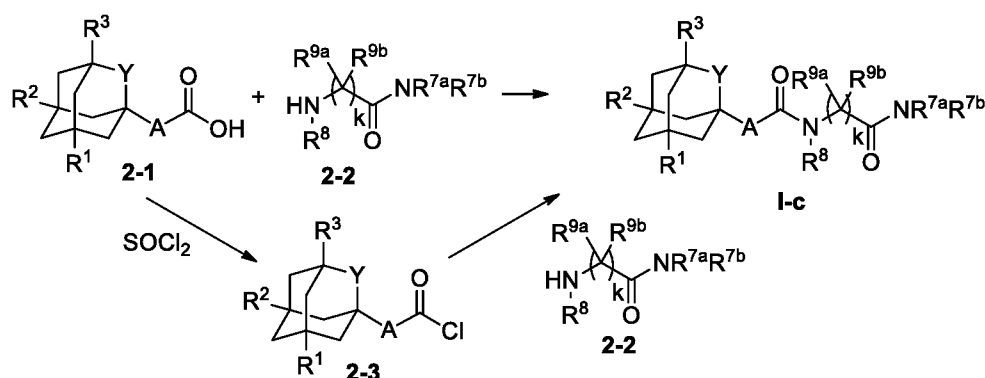
to form acid chloride **1-2** which can react with amine $\text{HNR}^{7a}\text{R}^{7b}$ in presence of a base such as DIEA or triethylamine in a solvent such as DMF or dichloroethane to form amide **I-a**. Reduction of the amide **I-a** with a reducing agent such as lithium aluminum hydride or similar reagents known to those skilled in the arts in a solvent such as THF or diethyl ether can provide a compound of general structure **I** where Y is a bond or CR^4R^5 and X is $-\text{C}-\text{A}-\text{CH}_2\text{NR}^{7a}\text{R}^{7b}$ represented by Formula **I-b**.



In another general synthetic process, compounds of the Structural Formula **I** where Y is a

bond or CR^4R^5 and X is $\text{C}-\text{A}-\text{CH}_2\text{NR}^{7a}\text{R}^{7b}$, represented by Formula **I-c** can be prepared according to Scheme 2 by reacting carboxylic acid **2-1** with amine **2-2** in the presence of a coupling reagent such as EDCI or HATU and a base such as trimethylamine in a solvent such as DMF or dichloromethane to provide the desired product of Formula **I-c**. Alternatively, carboxylic acid **2-1** can react with SOCl_2 to form acid chloride **2-3** which can react with amine **2-2** in presence of a base such as DIEA or triethylamine in a solvent such as DMF or dichloroethane to form amide **I-c**

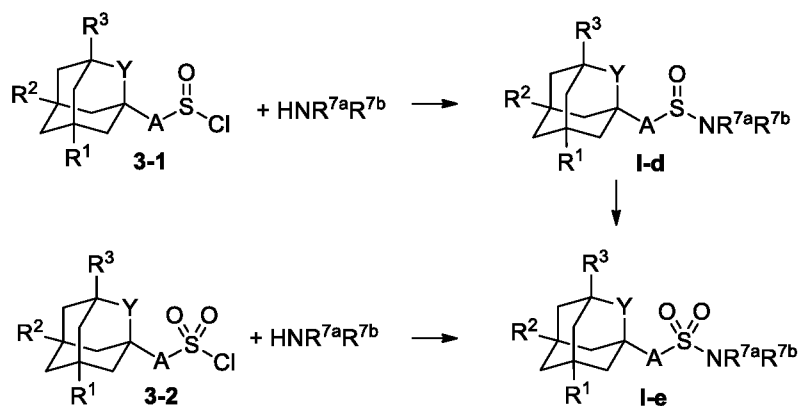
Scheme 2



In another general synthetic process, compounds of the Structural Formula I where Y is a

- 5 bond or CR⁴R⁵ and X is C-A-S(=O)(=O)NR^{7a}R^{7b} or C-A-S(=O)(=O)NR^{7a}R^{7b}, represented by Formula I-d or I-e can be prepared according to Scheme 3 by reacting sulfinyl chloride 3-1 with amine NHR^{7a}R^{7b} in the presence a base such as triethylamine in a solvent such as DMF or dichloromethane to provide the desired product of Formula I-d which can be oxidized with an oxidizing agent such as MCPBA to desired product of formula I-e. Alternatively, sulfonyl chloride 3-2 can be reacted with amine
- 10 NHR^{7a}R^{7b} in the presence of a base such as triethylamine in a solvent such as DMF or dichloromethane to provide the desired product of Formula I-e.

Scheme 3



- 15 In another general synthetic process, compounds of the Structural Formula I where X is CR⁵,

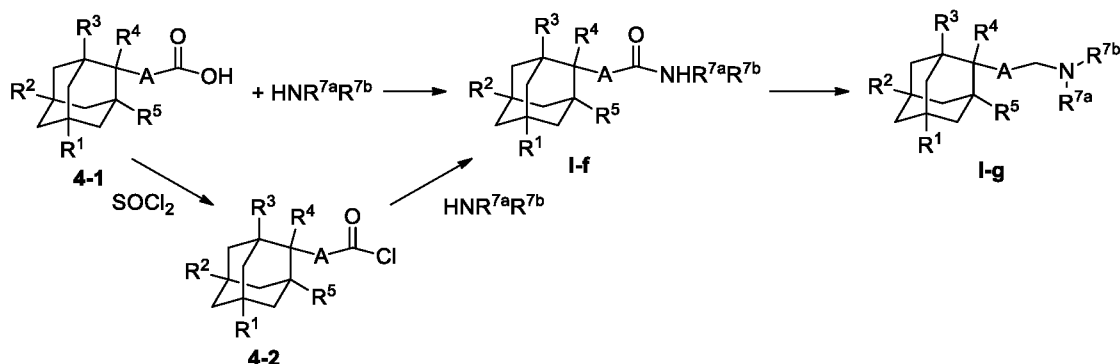
and Y is -CR⁴-A-C(=O)NR^{7a}R^{7b}, represented by Formula I-f can be prepared according to Scheme 4 by reacting carboxylic acid 4-1 with amine NHR^{7a}R^{7b} in the presence of a coupling reagent such as EDCI or HATU and a base such as DIEA or triethylamine in a solvent such as DMF or dichloroethane to provide the desired product of Formula I-f. Alternatively, carboxylic acid 4-1 can react with SOCl₂ to form acid chloride 4-2 which can react with amine NHR^{7a}R^{7b} in presence of a base such as DIEA or triethylamine in a solvent such as DMF or dichloroethane to form amide I-f. Reduction of the amide I-f

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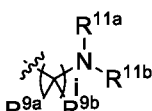
with a reducing agent such as lithium aluminum hydride or similar reagents known to those skilled in the arts in a solvent such as THF or diethyl ether can provide a compound of general structure I where X is CR⁵ and Y is CR⁴-A-CH₂NR^{7a}R^{7b}, represented by Formula I-g.

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Scheme 4

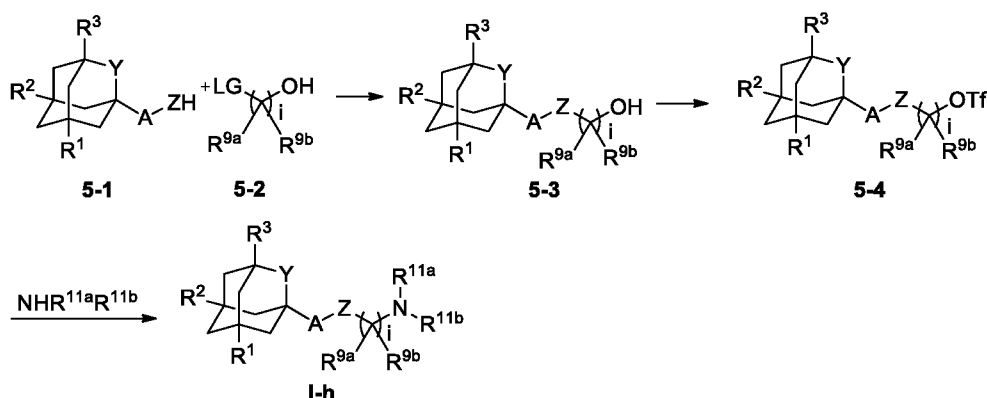


In another general synthetic process, compounds of the Structural Formula I where Y is a

bond or CR⁴R⁵, X is C-A-ZR¹⁰, Z is O, S, or NR⁸, and R¹⁰ is , represented by Formula I-h can be prepared according to Scheme 5 by reacting 5-1 with a suitable hydroxy alkane containing a leaving group (LG) such as a halogen or a sulfonate 5-2 to provide 5-3. Treatment of 5-3 with triflic anhydride in a presence of a base such as triethylamine in a solvent such as THF or DCM can provide triflate 4-5 which can be treated with amine NHR^{11a}R^{11b} in a solvent such as THF or DCM to provide a compound of Formula I-h.

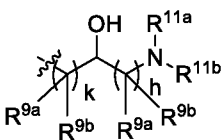
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Scheme 5



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In another general synthetic process, compounds of the Structural Formula I where Y is a

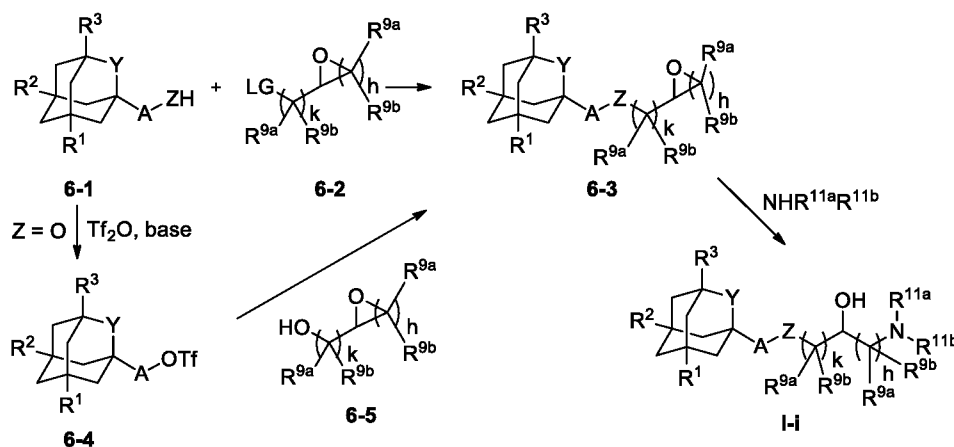
bond or CR⁴R⁵, X is C-A-ZR¹⁰, Z is O, S, or NR⁸, and R¹⁰ is , represented by Formula I-i can be prepared according to Scheme 6 by reacting 6-1 with an alkyl oxirane or oxetane 6-2 containing a leaving group (LG) such as a halogen or a sulfonate in the presence of a base such as K₂CO₃ in a solvent such as DMF to form oxirane or oxetane 6-3. Alternatively, when Z is oxygen,

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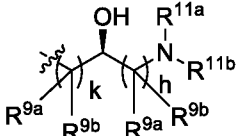
alcohol **6-1** can be treated with triflic anhydride in the presence of a base such as NEt_3 in a solvent such as DCM to form triflate **6-4** which in the presence of a base such sodium hydride in a solvent such as DMF can react with alcohol **6-5** to form **6-3**. Treatment of **6-3** with amine $\text{NHR}^{11a}\text{R}^{11b}$ in a solvent such as isopropanol can provide a compound of Formula I-i.

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Scheme 6



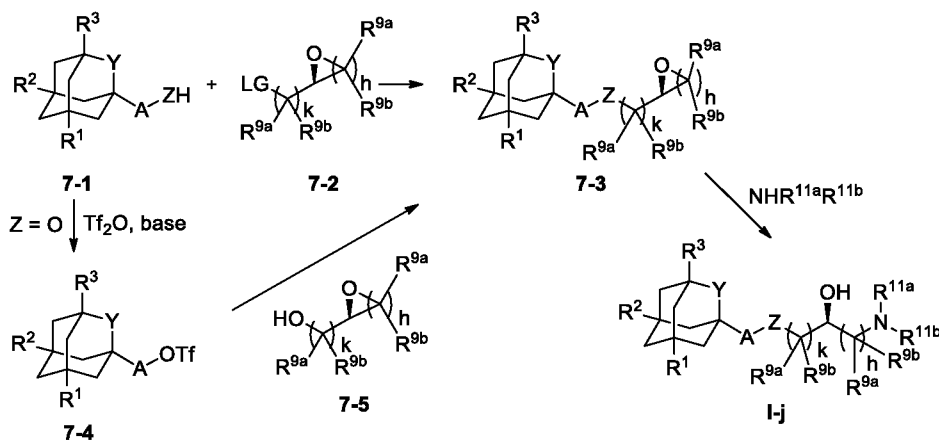
In another general synthetic process, compounds of the Structural Formula I where Y is a

bond or CR^4R^5 , X is C-A-ZR^{10} , Z is O, S, or NR^8 , and R^{10} is , represented by

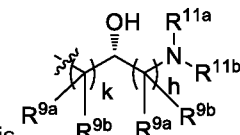
10 Formula I-j can be prepared according to Scheme 7 by reacting **7-1** with an alkyl oxirane or oxetane **7-2** containing a leaving group (LG) such as a halogen or a sulfonate in the presence of a base such K_2CO_3 in a solvent such as DMF to form oxirane or oxetane **7-3**. Alternatively, when Z is oxygen, alcohol **7-1** can be treated with triflic anhydride in the presence of a base such as NEt_3 in a solvent such as DCM to form triflate **7-4** which in the presence of a base such as sodium hydride in a solvent

15 such as DMF can react with alcohol **7-5** to form **7-3**. Treatment of **7-3** with amine $\text{NHR}^{11a}\text{R}^{11b}$ in a solvent such as isopropanol can provide a compound of Formula I-j.

Scheme 7

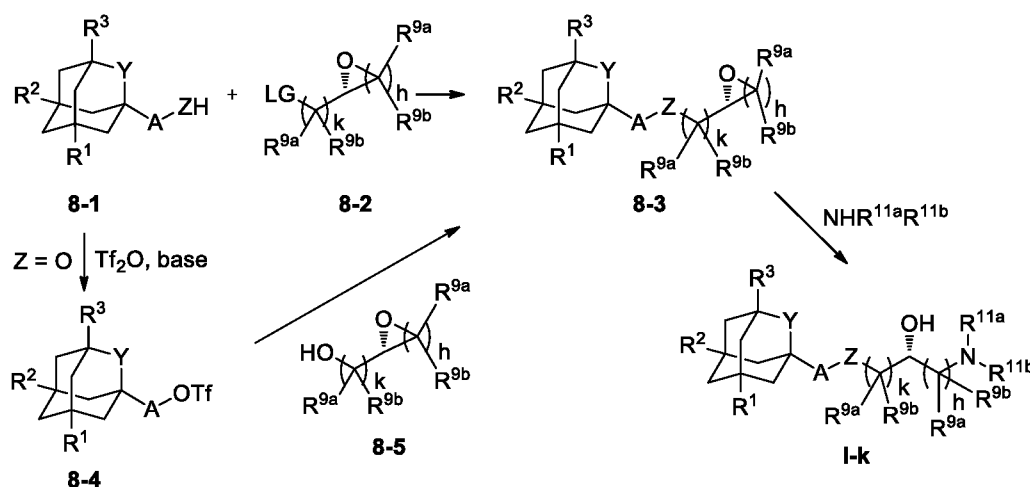


In another general synthetic process, compounds of the Structural Formula I where Y is a

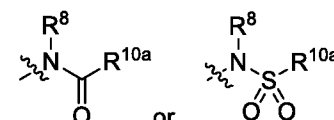
bond or CR^4R^5 , X is C-A-ZR¹⁰, Z is O, S, or NR⁸, and R¹⁰ is , represented by Formula I-k can be prepared according to Scheme 8 by reacting **8-1** with an alkyl oxirane or oxetane **8-2** containing a leaving group (LG) such as a halogen or a sulfonate in the presence of a base such as K₂CO₃ in a solvent such as DMF to form oxirane or oxetane **8-3**. Alternatively, when Z is oxygen, alcohol **8-1** can be treated with triflic anhydride in the presence of a base such as NEt₃ in a solvent such as DCM to form triflate **8-4** which in the presence of a base such as sodium hydride in a solvent such as DMF can react with alcohol **8-5** to form **8-3**. Treatment of **8-3** with amine NHR^{11a}R^{11b} in a solvent such as isopropanol can provide a compound of Formula I-k.

10

Scheme 8



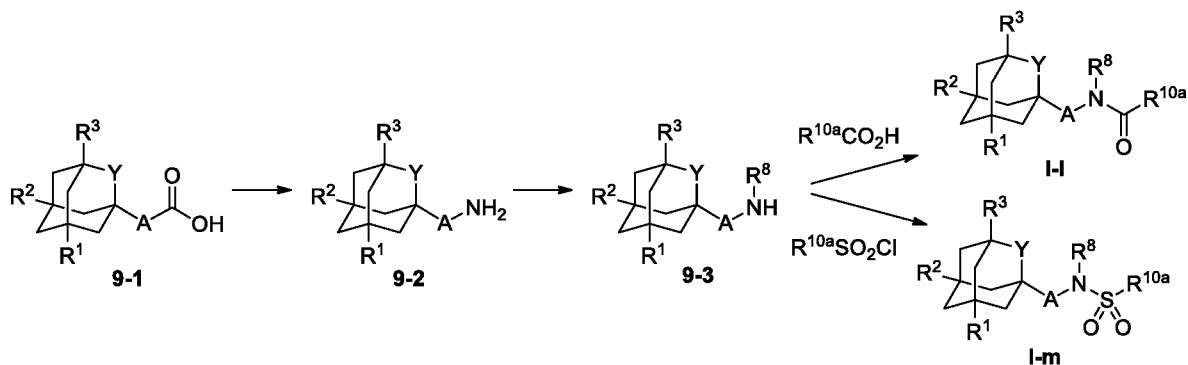
In another general synthetic process, compounds of the Structural Formula I where Y is a

bond or CR^4R^5 , X is C-A-D, A is a bond, and D is , represented by

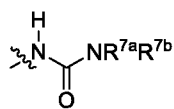
Formula I-l and I-m can be prepared according to Scheme 9 from carboxylic acid **9-1** via a Curtius rearrangement using an azide reagent such as diphenylphosphoryl azide to form amine **9-2** which can react with an aldehyde in the presence of a reducing agent such as NaCNBH₃ in a solvent such as DCM to form amine **9-3**. Reaction of amine with a carboxylic acid R^{10a}CO₂H in the presence of a coupling reagent such as EDCI or HATU and a base such as triethylamine in a solvent such as DMF or dichloromethane can provide the desired product of Formula I-l. Reaction of amine **9-3** with sulfonyl chloride R^{10a}SO₂Cl in the presence of a base such as triethylamine in a solvent such as dichloromethane can provide the desired product of Formula I-m.

25

Scheme 9

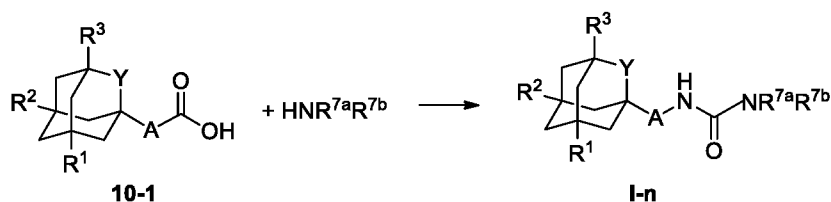


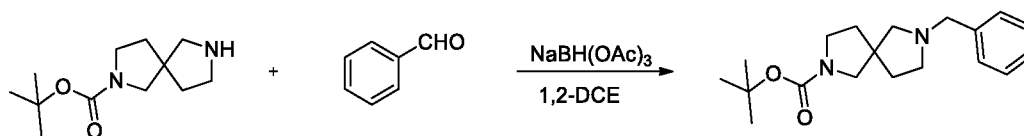
In another general synthetic process, compounds of the Structural Formula I where Y is a



bond or CR^4R^5 , X is C-A-D, A is a bond, and D is $NR^{7a}R^{7b}$, represented by Formula I-n can be prepared according to Scheme 10 from carboxylic acid **10-1** via a Curtius rearrangement using an azide reagent such as diphenylphosphoryl azide to form amine **9-2** and reacting the intermediate isocyanate with an amine $NHR^{7a}R^{7b}$ to form the desired product of Formula I-n.

Scheme 10

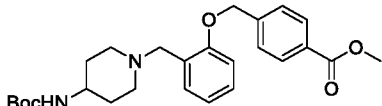
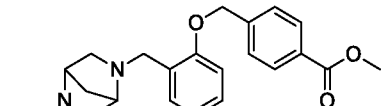
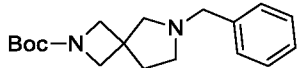


Preparation of Intermediates*tert*-Butyl 7-benzyl-2,7-diazaspiro[4.4]nonane-2-carboxylate

A mixture of *tert*-butyl 2,7-diazaspiro[4.4]nonane-2-carboxylate (0.15 g, 0.66 mmol) and benzaldehyde (0.07 g, 0.66 mmol) in 3 mL 1,2-dichloroethane was stirred at rt for 0.5 h. Sodium triacetoxy borohydride (0.35 g, 1.65 mmol) was then added and the reaction mixture was stirred at rt for 12 h. The reaction mixture was then diluted with CH₂Cl₂ and washed with saturated aq. NaHCO₃ solution. The organic phase was dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by SiO₂ column chromatography (EtOAc, then CH₂Cl₂ / CH₃OH 40:1) to give 0.084 g (40%) of the title compound as a colorless oil. LC/MS *m/z*: 217.28 (M-Boc+H)⁺, 261.29 (M-tBu+H)⁺, 302.31 (M-CH₃+H)⁺, 317.33 (M+H)⁺, 358.31 (M+H+CH₃CN)⁺.

The following intermediates were prepared in the same manner as described above for *tert*-butyl 7-benzyl-2,7-diazaspiro[4.4]nonane-2-carboxylate using the appropriate amine and the appropriate aldehyde as starting materials.

Starting materials	Intermediate/Name	Analytical Data
<i>tert</i> -butyl 2,7-diazaspiro[4.4]nonane-2-carboxylate		LC/MS <i>m/z</i> : 481.36 (M+H) ⁺
methyl 4-(2-formylphenoxy methyl) benzoate	<i>tert</i> -butyl 7-[(2-{[4-(methoxycarbonyl)phenyl] methoxy}phenyl)methyl]-2,7-diazaspiro[4.4]nonane-2-carboxylate	
<i>tert</i> -butyl piperazine-1-carboxylate		LC/MS <i>m/z</i> : 441.24 (M+H) ⁺
methyl 4-(2-formyl phenoxy methyl)benzoate	<i>tert</i> -butyl 4-[(2-{[4-(methoxycarbonyl)phenyl] ethoxy}phenyl)methyl] piperazine-1-carboxylate	

<i>tert</i> -butyl <i>N</i> -(piperidin-4-yl) carbamate	 methyl 4-{2-[(4-{[(<i>tert</i> -butoxy)carbonyl] amino}piperidin-1-yl)methyl]phenoxy methyl]benzoate	LC/MS <i>m/z</i> : 455.28 (M+H) ⁺
methyl 4-(2-formylphenoxy methyl)benzoate		
<i>tert</i> -butyl 2,5-diazabicyclo[2.2.1]heptane-2-carboxylate	 <i>tert</i> -butyl 5-[(2-{[4-(methoxycarbonyl)phenyl] methoxy}phenyl)methyl]-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate	LC/MS <i>m/z</i> : 453.28 (M+H) ⁺
methyl 4-(2-formylphenoxy methyl)benzoate		
<i>tert</i> -butyl 2,6-diazaspiro[3.3]heptane-2-carboxylate	 <i>tert</i> -butyl 6-benzyl-2,6-diazaspiro[3.3]heptane-2-carboxylate	LC/MS <i>m/z</i> : 233.23 (M-tBu+H) ⁺ , 274.23 (M-CH ₃ +H) ⁺ , 289.28 (M+H) ⁺ , 330.32 (M+H+CH ₃ CN) ⁺
benzaldehyde		
<i>tert</i> -butyl 2,6-diazaspiro[3.4]octane-2-carboxylate	 <i>tert</i> -butyl 6-benzyl-2,6-diazaspiro[3.4]octane-2-carboxylate	LC/MS <i>m/z</i> : 247.2 (M-tBu+H) ⁺ , 288.22 (M-CH ₃ +H) ⁺ , 303.33 (M+H) ⁺ , 344.38 (M+H+CH ₃ CN) ⁺
benzaldehyde		

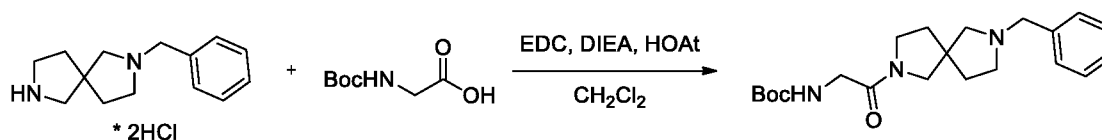
tert-Butyl-*N*-(2-{7-benzyl-2,7-diazaspiro[4.4]nonan-2-yl}-2-oxoethyl)carbamate

Step1: 2-benzyl-2,7-diazaspiro[4.4]nonanedihydrochloride



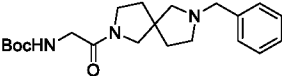
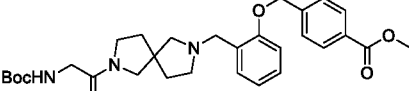
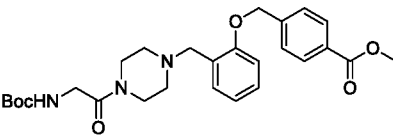
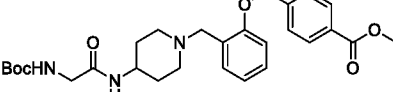
- 5 To a solution of *tert*-butyl 7-benzyl-2,7-diazaspiro[4.4]nonane-2-carboxylate (0.08 g, 0.25 mmol) in 1.5 mL CH₃OH was added 0.75 mL conc. HCl. The reaction mixture was stirred at rt for 12 h, then concentrated *in vacuo* to give 0.073 g (100%) of the product as a viscous oil, which was used in the next step without further purification. LC/MS *m/z*: 258.09 (M+H+CH₃CN)⁺.

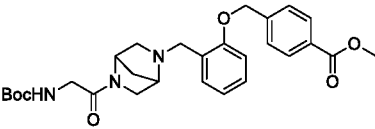
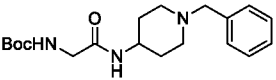
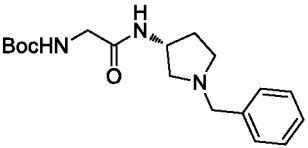
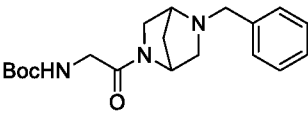
Step 2: *tert*-butyl *N*-(2-{7-benzyl-2,7-diazaspiro[4.4]nonan-2-yl}-2-oxoethyl)carbamate



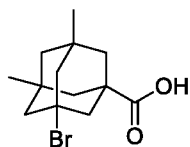
To a mixture of 2-benzyl-2,7-diazaspiro[4.4]nonanedihydrochloride (58 mg, 0.2 mmol) in 2 mL anhydrous CH₂Cl₂ was added *N,N*-diisopropylethylamine (116.6 mg, 0.9 mmol), 2-[(*tert*-butoxy)carbonyl]amino}acetic acid (35 mg, 0.2 mmol), EDC hydrochloride (50 mg, 0.26 mmol), and 1-hydroxy-7-azabenzotriazole (HOAt, 30 mg, 0.22 mmol). The reaction mixture was stirred at rt for 12 h, then diluted with CH₂Cl₂ and washed with saturated aq. NaHCO₃ solution. The organic phase was dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by SiO₂ column chromatography (EtOAc, then CH₂Cl₂ / CH₃OH from 40:1 to 10:1) to give 45 mg (60%) of the product as a colorless oil. LC/MS *m/z*: 274.44 (M-Boc+H)⁺, 318.35 (M-tBu+H)⁺, 374.36 (M+H)⁺.

The following intermediates I-1 to I-8 were prepared in the same manner as described for the preparation of *tert*-butyl *N*-(2-{7-benzyl-2,7-diazaspiro[4.4]nonan-2-yl}-2-oxoethyl)carbamate using the appropriate precursor.

	Starting materials	Product/Name	Analytical data
I-1	<i>tert</i> -butyl 7-benzyl-2,7-diazaspiro[4.4]nonane-2-carboxylate	 <i>tert</i> -butyl <i>N</i> -(2-{7-benzyl-2,7-diazaspiro[4.4]nonan-2-yl}-2-oxoethyl)carbamate	LC/MS <i>m/z</i> : 274.44 (M-Boc+H) ⁺ , 318.35 (M-tBu+H) ⁺ , 374.36 (M+H) ⁺
I-2	<i>tert</i> -butyl 7-[(2-{[4-(methoxycarbonyl)phenyl]methoxy}phenyl)methyl]-2,7-diazaspiro[4.4]nonane-2-carboxylate	 methyl 4-(2-{[7-(2-{[(<i>tert</i> -butoxy)carbonyl]amino}acetyl)-2,7-diazaspiro[4.4]nonan-2-yl]methyl}phenoxy)methyl)benzoate	LC/MS <i>m/z</i> : 538.38 (M+H) ⁺
I-3	<i>tert</i> -butyl 4-[(2-{[4-(methoxycarbonyl)phenyl]methoxy}phenyl)methyl]piperazine-1-carboxylate	 methyl 4-(2-{[4-(2-{[(<i>tert</i> -butoxy)carbonyl]amino}acetyl)piperazin-1-yl]methyl}phenoxy)methyl)benzoate	LC/MS <i>m/z</i> : 398.3 (M-Boc+H) ⁺ , 442.27 (M-tBu+H) ⁺ , 498.28 (M+H) ⁺
I-4	methyl 4-{2-[(4-{[(<i>tert</i> -butoxy)carbonyl]amino}piperidin-1-yl)methyl]phenoxy methyl} benzoate	 methyl 4-(2-{[4-(2-{[(<i>tert</i> -butoxy)carbonyl]amino}acetamido)piperidin-1-yl]methyl}phenoxy)methyl)benzoate	LC/MS <i>m/z</i> : 456.27 (M-tBu+H) ⁺ , 512.35 (M+H) ⁺

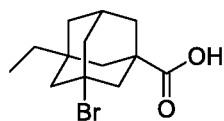
I-5	<i>tert</i> -butyl 5-[(2-[(4-(methoxycarbonyl)phenyl)methoxy]phenyl)methyl]-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate	 methyl 4-(2-[(5-(2-[(<i>tert</i> -butoxy)carbonyl]amino)acetyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)methyl]phenoxy)methyl)benzoate	LC/MS <i>m/z</i> : 510.3 (M+H) ⁺
I-6	1-benzylpiperidin-4-amine	 <i>tert</i> -butyl <i>N</i> -{[(1-benzylpiperidin-4-yl)carbamoyl]methyl}carbamate	LC/MS <i>m/z</i> : 348.34 (M+H) ⁺ , 292.26 (M-tBu+H) ⁺
I-7	(3 <i>R</i>)-1-benzylpyrrolidin-3-amine	 <i>tert</i> -butyl <i>N</i> -{[(3 <i>R</i>)-1-benzylpyrrolidin-3-yl]carbamoyl}methylcarbamate	LC/MS <i>m/z</i> : 334.27(M+H) ⁺ , 278.25(M-tBu+H) ⁺
I-8	2-benzyl-2,5-diazabicyclo[2.2.1]heptane dihydrobromide	 <i>tert</i> -butyl <i>N</i> -(2-{5-benzyl-2,5-diazabicyclo[2.2.1]heptan-2-yl}-2-oxoethyl)carbamate	LC/MS <i>m/z</i> : 246.26 (M-Boc+H) ⁺ , 290.24 (M-tBu+H) ⁺ , 346.32 (M+H) ⁺ , 387.33 (M+H+CH ₃ CN) ⁺

3-Bromo-5,7-dimethyladamantane-1-carboxylic acid.



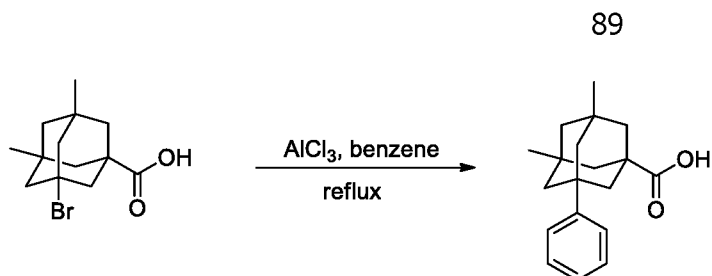
The title compound was obtained by bromination of 3,5-dimethyladamantane-1-carboxylic acid using the procedure described in patent application US 2013/0096120, published April 18, 2013.

3-Bromo-5-ethyladamantane-1-carboxylic acid.



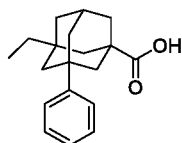
The title compound was prepared from 3-ethyladamantane-1-carboxylic acid in the same manner as described for 3-bromo-5,7-dimethyladamantane-1-carboxylic acid.

10 3,5-Dimethyl-7-phenyladamantane-1-carboxylic acid.



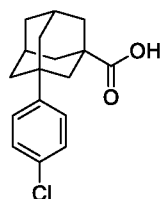
3-Bromo-5,7-dimethyladamantane-1-carboxylic acid (0.033 g, 0.11 mmol) was added to a mixture of AlCl_3 (0.018 g, 0.14 mmol) in 1 mL anhydrous benzene. The reaction mixture was heated to reflux for 6 h, then diluted with EtOAc. The organic phase was washed with 0.5 M aq. HCl and brine, dried over Na_2SO_4 , filtered, and concentrated *in vacuo* to give 0.03 g (91%) of the product as white solid, which was used in the next step without further purification.

3-Ethyl-5-phenyladamantane-1-carboxylic acid.



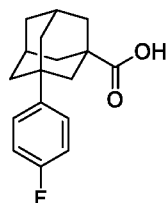
The title compound was prepared from 3-bromo-5-ethyladamantane-1-carboxylic acid and benzene in the same manner as described for 3,5-dimethyl-7-phenyladamantane-1-carboxylic acid.

3-(4-Chlorophenyl)adamantane-1-carboxylic acid.



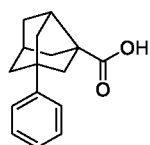
The title compound was prepared from 3-bromoadamantane-1-carboxylic acid and chlorobenzene in the same manner as described for 3,5-dimethyl-7-phenyladamantane-1-carboxylic acid.

3-(4-Fluorophenyl)adamantane-1-carboxylic acid.



The title compound was prepared from 3-bromoadamantane-1-carboxylic acid and fluorobenzene in the same manner as described for 3,5-dimethyl-7-phenyladamantane-1-carboxylic acid.

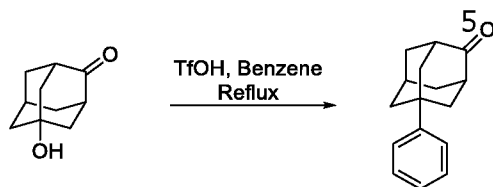
1-Phenyltricyclo[3.3.1.0^{3,7}]nonane-3-carboxylic acid.



The title compound was prepared following the procedure described in patent application US2013/0345127, published Dec 26, 2013.

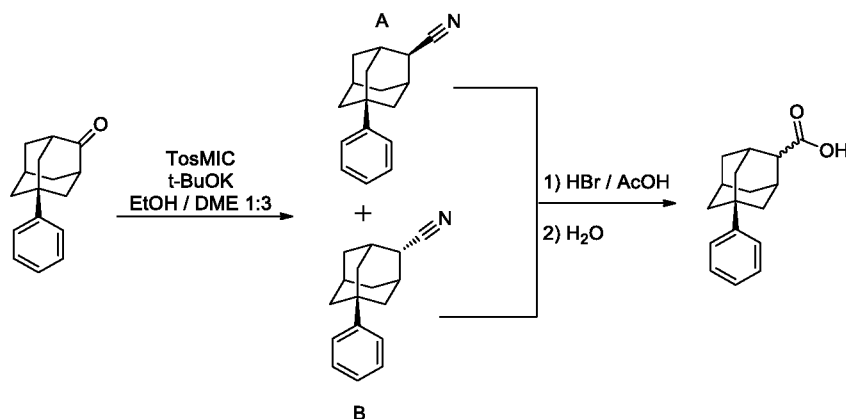
5-Phenyladamantane-2-carboxylic acid.

Step 1: 5-phenyladamantan-2-one



To 5-hydroxyadamantan-2-one (5 g, 150 mmol) was added benzene (20 mL) and triflic acid (3 mL). The heterogenous mixture was heated to reflux, at which time all starting materials dissolved, and reflux was continued overnight. The mixture was cooled to room temperature and partitioned between water and *tert*-butylmethyl ether (50 mL), and the organic phase was washed 3 times with water, followed by saturated NaHCO₃ and brine. The organics were dried over Na₂SO₄ and evaporated to give 4.7g of crude product. Purification with flash chromatography on silica gel using 8:2 hexanes:ethyl acetate eluent gave 3.7 g of pure product as a white solid. ¹H NMR (300MHz, CDCl₃) δ: 7.41-7.32 (m, 4H), 7.27-7.21 (m, 1H), 2.70 (br:s, 2H), 2.37-2.03 (m, 11H).

Step 2: *cis*-5-phenyladamantane-2-carbonitrile and *trans*-5-phenyladamantane-2-carbonitrile



To 5-phenyladamantan-2-one (1.1 g, 4.87 mmol) in a flask with strong stirrer was added dimethoxyethane (20 mL), ethanol (7 mL), and p-toluenesulfonylmethylisocyanide (1.23 g, 6.33 mmol). The mixture was cooled to 0 °C, and potassium *tert*-butoxide (1.31 g, 11.7 mmol) was added in 3 portions (mild exotherm). The reaction mixture was heated to 35 °C overnight and then cooled to room temperature and filtered to remove potassium tosylate. The filtrate was partitioned between water and *tert*-butylmethyl ether and washed three times with water, then brine, dried (Na₂SO₄), and evaporated. The crude residue was purified via flash chromatography on silica gel using 95:5 hexanes:ethyl acetate eluent. Purification gave 200 mg and 234 mg of the less and more polar isomers, respectively, and 410 mg of mixed fractions containing co-eluted meso-isomers **A** and **B**. Top isomer on TLC, configuration unknown: ¹H NMR (500MHz, CDCl₃) δ: 7.38-7.30 (m, 4H), 7.20 (t,

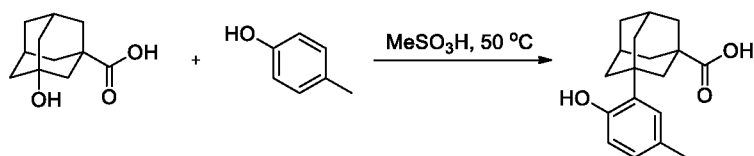
1H), 2.93 (s, 1H), 2.39 (s, 2H), 2.25-2.15 (m, 3H), 2.07 (d, 2H), 1.94 (t, 4H), 1.77 (d, 2H). Bottom isomer on TLC, configuration unknown: ¹H NMR (500MHz, CDCl₃) δ: 7.38-7.31 (m, 4H), 7.20 (t, 1H), 2.94 (s, 1H), 2.39 (s, 2H), 2.35 (d, 2H), 2.15 (s, 1H), 1.97 (s, 1H), 1.90 (d, 4H), 1.78 (d, 2H).

Step 3: 5-phenyladamantane-2-carboxylic acid

- 5 In two separate reactions, 140 mg of the top nitrile on TLC (absolute configuration unknown) and 230 mg of the bottom nitrile on TLC (absolute configuration unknown) were combined with 5 mL of 33% HBr/glacial acetic acid solution. Each reaction was brought to reflux until TLC indicated that the nitriles had hydrolyzed to the primary amide, and the maximum amount of water that does not cause the amide to precipitate was titrated into the reaction mixtures through their condensers. The separate
- 10 reactions were refluxed overnight and then cooled to room temperature. On cooling, both reactions produced precipitates that were filtered off into sintered glass funnels, washed 3 times with 1 M HCl, and dried on a rotary evaporator to yield fine white crystals. The top nitrile on TLC yielded 105 mg, while the bottom nitrile produced 185 mg. ¹³C NMR of both reaction products confirms that both nitriles hydrolyze to identical carboxylic acids, presumably the most thermodynamically stable product.
- 15 The absolute cis / trans configuration of the single carboxylic acid product is unknown. HPLC and TLC also indicate the formation of a single, identical carboxylic acid isomer from both reactions. ¹³C NMR (125 MHz, CDCl₃) δ: 180.35, 150.64, 128.45, 125.96, 125.01, 49.04, 48.76, 43.76, 43.33, 39.16, 37.43, 35.83, 32.96, 30.40, 28.41

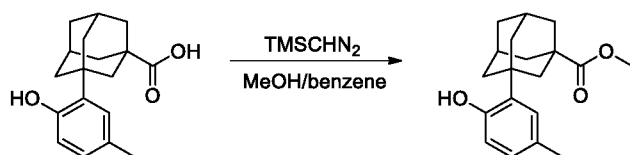
3-(3-Methylphenyl)adamantane-1-carboxylic acid

- 20 Step 1: 3-(2-hydroxy-5-methylphenyl)adamantane-1-carboxylic acid



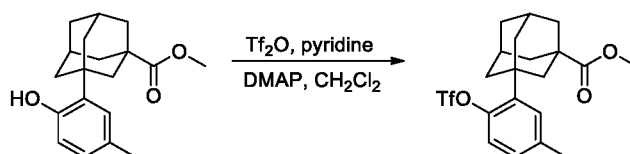
- 4-Methylphenol (0.25 g, 2.3 mmol) was added to a solution of 3-hydroxyadamantane-1-carboxylic acid (0.5 g, 2.55 mmol) in methanesulfonic acid (2.3 mL) heated to 40 °C under N₂ atmosphere (G. Ogawa, M. A. Tius, H. Zhou, S. P. Nikas, A. Halikhedkar, S. Mallipeddi, and A. Makriyannis, *J. Med.*
- 25 *Chem.* **2015**, *58*, 3104 – 3116). The reaction mixture was stirred at 50 °C for 3 h, then cooled to rt, diluted with CH₂Cl₂, poured onto ice-water. The organic layer was separated, and the aqueous layer was extracted with CH₂Cl₂. The organic layers were combined, washed with brine, dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by SiO₂ column chromatography (hexanes / EtOAc from 7:3 to 1:1) to give 0.34 g (47%) of the product as a colorless oil. ¹H NMR (500
- 30 MHz, CDCl₃) δ 6.99 (s, 1H), 6.86 (dd, 1H), 6.53 (d, 1H), 2.28 (br. s, 2H), 2.26 (s, 3H), 2.23 – 2.19 (m, 2H), 2.13 – 2.06 (m, 4H), 1.97 – 1.91 (m, 4H), 1.77 – 1.70 (m, 2H).

Step 2: methyl 3-(2-hydroxy-5-methylphenyl)adamantane-1-carboxylate



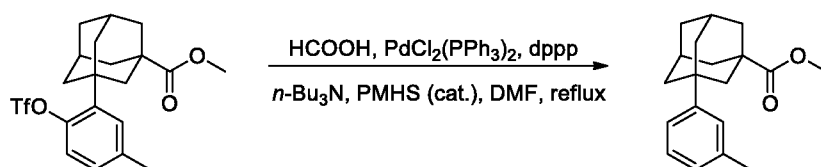
TMSCHN₂ (0.51 mL of 2 M in hexanes, 1.02 mmol) was added to a mixture of 3-(2-hydroxy-5-methylphenyl)adamantane-1-carboxylic acid (0.18 g, 0.63 mmol) in benzene (2.5 mL) and MeOH (0.6 mL) at 10 °C. The reaction mixture was allowed to warm to rt for 1h, then concentrated *in vacuo* to give the product as a colorless oil (0.19g, 100%), which was used in the next step without further purification.

Step 3: methyl 3-{5-methyl-2-[(trifluoromethane)sulfonyloxy]phenyl}adamantane-1-carboxylate



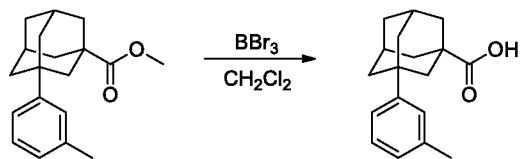
To a mixture of methyl 3-(2-hydroxy-5-methylphenyl)adamantane-1-carboxylate (0.15 g, 0.5 mmol), pyridine (0.12 g, 1.5 mmol) and DMAP (0.6 mg, 0.005 mmol) in CH₂Cl₂ (2 mL) cooled to 0 °C was added Tf₂O (0.17 g, 0.6 mmol) in CH₂Cl₂ (0.12mL) dropwise. The reaction mixture was brought to rt gradually and stirred for 3 h, then diluted with CH₂Cl₂ and washed quickly with water. The organic phase was dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO₂ (hexanes / EtOAc from 8:1 to 7:1) to give 0.11 g (52%) of the title compound as a colorless oil.

Step 4: methyl 3-(3-methylphenyl)adamantane-1-carboxylate



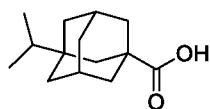
To a solution of methyl 3-{5-methyl-2-[(trifluoromethane)sulfonyloxy]phenyl}adamantane-1-carboxylate (0.11 g, 0.25 mmol) in dry DMF (1 mL) were added PdCl₂(PPh₃)₂ (9 mg, 0.013 mmol), dppp (10 mg, 0.024 mmol), *n*-Bu₃N (0.23 g, 1.27 mmol), HCOOH (0.03 g, 0.63 mmol), and catalytic polymethylhydrosiloxane (PMHS) under N₂ atmosphere. The reaction mixture was stirred at 95 °C overnight, then cooled to rt, diluted with MTBE and 1 N HCl, stirred for 10 min, filtered through a plug of Celite. The organic layer was separated, and the aqueous layer was extracted with MTBE. The organic layers were combined, dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO₂ (hexanes / EtOAc from 9:1 to 8:1) to give 54 mg (75%) of the title compound as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.20 (t, 1H), 7.18 – 7.14 (m, 2H), 7.00 (d, 1H), 3.66 (s, 3H), 2.34 (s, 3H), 2.24 – 2.20 (m, 2H), 2.03 (br. s, 2H), 1.95 – 1.87 (m, 8H), 1.75 – 1.71 (m, 2H).

Step 5: 3-(3-methylphenyl)adamantane-1-carboxylic acid



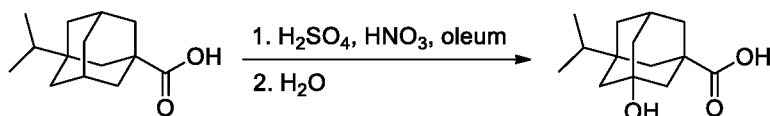
To a solution of methyl 3-(3-methylphenyl)adamantane-1-carboxylate (30 mg, 0.105 mmol) in CH_2Cl_2 (1 mL) cooled to 0°C was added BBr_3 (0.2 mL of 1 M in CH_2Cl_2 , 0.2 mmol) dropwise under N_2 atmosphere. The reaction mixture was gradually warmed to rt over 3 h, diluted with CH_2Cl_2 , then quenched with ice. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The organic layers were combined, dried over Na_2SO_4 , filtered, and concentrated *in vacuo* to give 25 mg (90%) of the title compound as a white solid, which was used in the next step without further purification.

10 3-(Propan-2-yl)adamantane-1-carboxylic acid



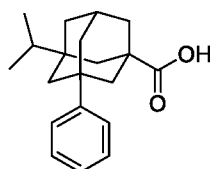
The title compound was prepared by isomerization of 2-(adamantan-1-yl)propan-2-ol into 3-(propan-2-yl)adamantan-1-ol in trifluoroacetic acid, followed by carboxylation of the formed alcohol using Koch-Haaf conditions (V. V. Kovalev, A. K. Rozov, and E. A. Shokova, *Tetrahedron* **1996**, 52, 3983-3990).

15 3-Hydroxy-5-(propan-2-yl)adamantane-1-carboxylic acid



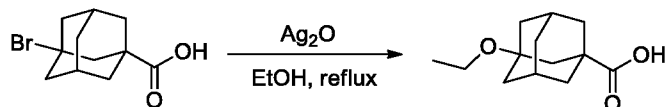
To a suspension of 3-(propan-2-yl)adamantane-1-carboxylic acid (90 mg, 0.4 mmol) in fuming nitric acid (0.25 mL) cooled to 0°C was added sulfuric acid (0.41 mL) (L. Wanka, C. Cabrele, M. Vanejews and P. R. Schreiner, *Eur. J. Org. Chem.* **2007**, 1474-1490). The reaction mixture was stirred at 0°C for 10 min. Then, oleum (0.14 mL, 25% SO_3) was added, and the reaction mixture was stirred for 1 h at 0°C and 3 h at rt, poured onto ice. The aqueous layer was extracted with EtOAc. The organic layer was dried over Na_2SO_4 , filtered, and concentrated *in vacuo* to give 90 mg (94%) of the crude product as a white solid, which was used in the next step without further purification.

3-phenyl-5-(propan-2-yl)adamantane-1-carboxylic acid



The title compound was prepared from 3-hydroxy-5-(propan-2-yl)adamantane-1-carboxylic acid and benzene in the same manner as described above for 5-phenyladamantan-2-one. ¹H NMR (500 MHz, CDCl₃) δ 7.39 – 7.35 (m, 2H), 7.34 – 7.29 (m, 2H), 7.19 (t, 1H), 2.34 – 2.30 (m, 1H), 2.01 (br. s, 2H), 1.89 – 1.81 (m, 4H), 1.72 – 1.65 (m, 2H), 1.63 – 1.58 (m, 2H), 1.54 – 1.48 (m, 2H), 1.39 – 1.34 (m, 1H), 0.86 (d, 6H).

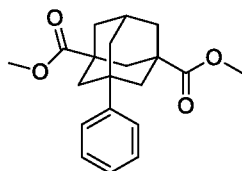
3-Ethoxyadamantane-1-carboxylic acid



To a solution of 3-bromoadamantane-1-carboxylic acid (0.2 g, 0.77 mmol) in dry ethanol (2 mL) was added silver (I) oxide (0.18 g, 0.77 mmol) (H. Stetter and J. Mayer, *Chem. Ber.* **1962**, 95, 667-672).

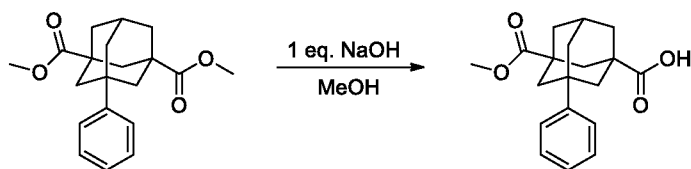
The reaction mixture was refluxed for 3 h, then cooled to rt, diluted with EtOAc. Solids were filtered off and washed with 5% AcOH in EtOAc. Volatiles were concentrated *in vacuo* to give 0.13 g (76%) of the title compound as a colorless oil, which was used in the next step without further purification.

1,3-Dimethyl 5-phenyladamantane-1,3-dicarboxylate



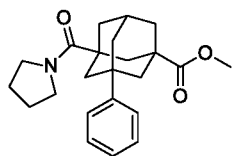
The title compound was prepared from 1,3-dimethyl 5-hydroxyadamantane-1,3-dicarboxylate and benzene in the same manner as described above for 5-phenyladamantan-2-one. ¹H NMR (500 MHz, CDCl₃) δ 7.37 – 7.30 (m, 4H), 7.20 (t, 1H), 3.67 (s, 6H), 2.38 – 2.35 (m, 1H), 2.07 (br. s, 2H), 2.05 – 1.99 (m, 4H), 1.92 – 1.85 (m, 6H).

3-(Methoxycarbonyl)-5-phenyladamantane-1-carboxylic acid



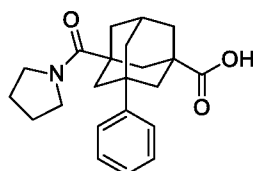
To a solution of 1,3-dimethyl 5-phenyladamantane-1,3-dicarboxylate (0.12 g, 0.37 mmol) in MeOH (1 mL) was added NaOH (15 mg, 0.37 mmol). The reaction mixture was stirred at 50 °C overnight, then concentrated *in vacuo* without heating. The residue was dissolved in water, acidified with 1 N HCl, and extracted with EtOAc. The organic layer was dried over Na₂SO₄, filtered, and concentrated *in vacuo* to give 80mg (68%) of the crude product as a colorless oil, which was used in the next step without further purification.

Methyl 3-phenyl-5-[(pyrrolidin-1-yl)carbonyl]adamantane-1-carboxylate



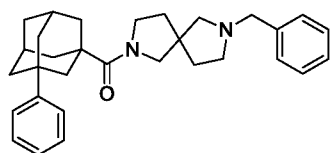
The title compound was prepared from 3-(methoxycarbonyl)-5-phenyladamantane-1-carboxylic acid and pyrrolidine in the same manner as described for 2-benzyl-7-[(3-phenyladamantan-1-yl)carbonyl]-2,7-diazaspiro[4.4]nonane (example A1, Step 2). LC/MS m/z : 368.32 ($M+H$)⁺, 735.54 ($2M+H$)⁺.

3-Phenyl-5-[(pyrrolidin-1-yl)carbonyl]adamantane-1-carboxylic acid.

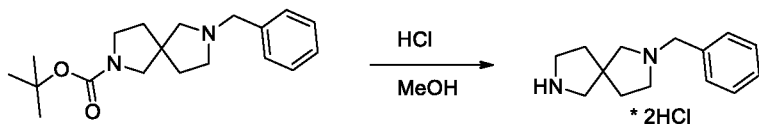


The title compound was prepared from methyl 3-phenyl-5-[(pyrrolidin-1-yl)carbonyl]adamantane-1-carboxylate using excess of NaOH in the same manner as described above for 3-(methoxycarbonyl)-5-phenyladamantane-1-carboxylic acid.

Example A1: 2-benzyl-7-[(3-phenyladamantan-1-yl)carbonyl]-2,7-diazaspiro[4.4]nonane

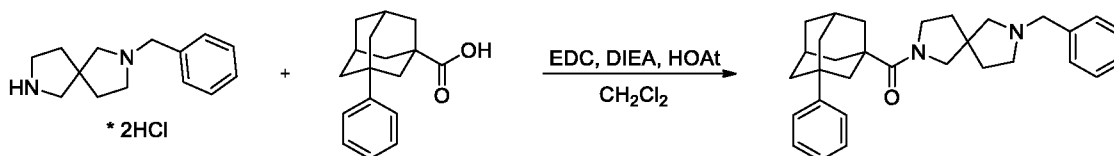


Step1: 2-benzyl-2,7-diazaspiro[4.4]nonanedihydrochloride



To a solution of *tert*-butyl 7-benzyl-2,7-diazaspiro[4.4]nonane-2-carboxylate (0.08 g, 0.25 mmol) in 1.5 mL CH₃OH was added 0.75 mL conc. HCl. The reaction mixture was stirred at rt for 12 h, then concentrated *in vacuo* to give 0.073 g (100%) of the product as a viscous oil, which was used in the next step without further purification. LC/MS m/z : 258.09 ($M+H+CH_3CN$)⁺.

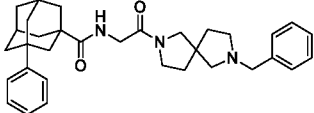
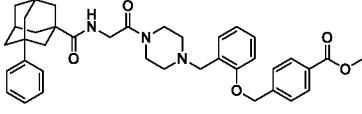
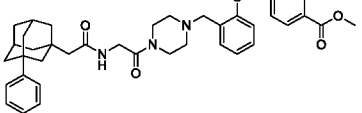
Step 2: 2-benzyl-7-[(3-phenyladamantan-1-yl)carbonyl]-2,7-diazaspiro[4.4]nonane

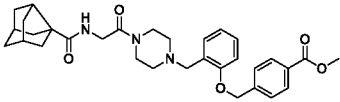
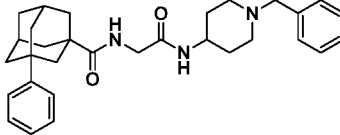
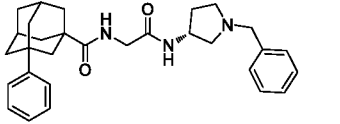
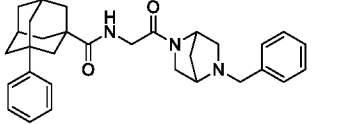
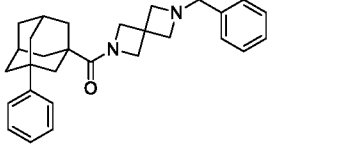


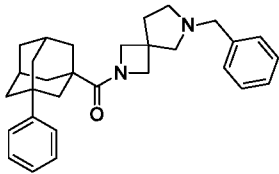
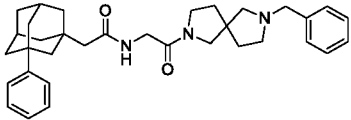
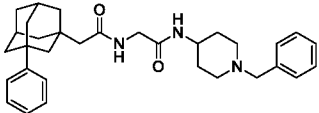
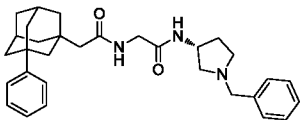
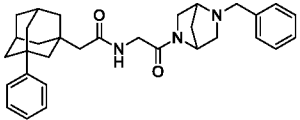
To a mixture of 2-benzyl-2,7-diazaspiro[4.4]nonane dihydrochloride (12.5 mg, 0.043 mmol) in 1 mL anhydrous CH₂Cl₂ was added *N,N*-diisopropylethylamine (25 mg, 0.19 mmol), 3-phenyl-adamantane-1-carboxylic acid (11 mg, 0.043 mmol), EDC hydrochloride (11 mg, 0.057 mmol), and 1-hydroxy-7-azabenzotriazole (HOAt, 6.5 mg, 0.048 mmol). The reaction mixture was stirred at rt for 12 h, then diluted with CH₂Cl₂ and washed with saturated aq. NaHCO₃ solution. The organic phase was dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by SiO₂ column chromatography (EtOAc, then CH₂Cl₂ / CH₃OH from 40:1 to 30:1) to give 10mg (51%) of the product as a colorless oil. LC/MS *m/z*: 455.40 (M+H)⁺, 496.43 (M+H+CH₃CN)⁺.

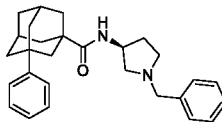
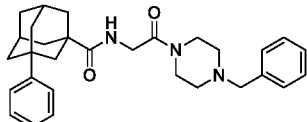
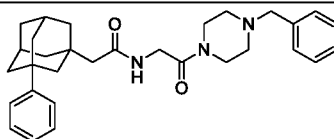
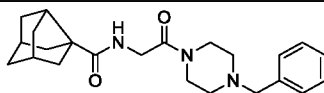
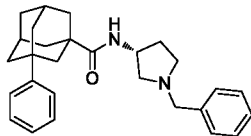
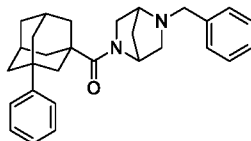
Examples A2 to A14 were prepared in the same manner as described for example A1, Steps 1 and 2 starting from the appropriate Boc-protected amine and the appropriate carboxylic acid.

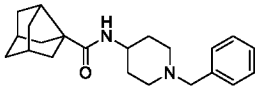
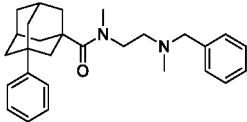
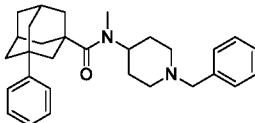
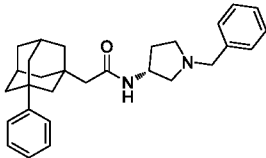
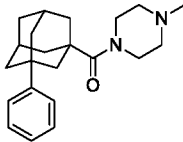
Examples A15 to A48 were prepared in the same manner as described for example A1, Step 2 using the appropriate commercially available amine and carboxylic acid as starting materials.

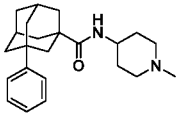
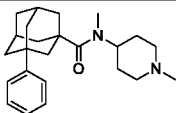
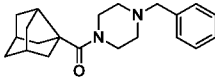
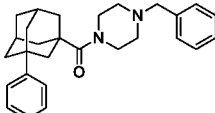
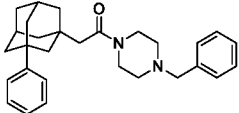
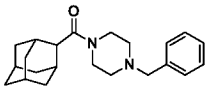
Ex.	Starting materials	Product/Name	Analytical Data
A2	<i>tert</i> -butyl <i>N</i> -(2-{7-benzyl-2,7-diazaspiro [4.4]nonan-2-yl}-2-oxoethyl) carbamate 3-phenyl-adamantane-1-carboxylic acid	 <i>N</i> -(2-{7-benzyl-2,7-diazaspiro [4.4] nonan-2-yl}-2-oxoethyl)-3-phenyladamantane-1-carboxamide	LC/MS <i>m/z</i> : 512.42 (M+H) ⁺ , 553.47 (M+H+CH ₃ CN) ⁺
A3	methyl 4-(2-{[4-(2-{[(<i>tert</i> -butoxy)carbonyl] amino}acetyl)piperazin-1-yl]methyl}phenoxy)methyl}benzoate 3-phenyl-adamantane-1-carboxylic acid	 methyl 4-{2-[(4-{2-[(3-phenyl adamantan-1-yl)formamido] acetyl}piperazin-1-yl)methyl] phenoxy methyl}benzoate	LC/MS <i>m/z</i> : 636.48 (M+H) ⁺
A4	methyl 4-(2-{[4-(2-{[(<i>tert</i> -butoxy)carbonyl] amino}acetyl)piperazin-1-yl]methyl}phenoxy methyl}benzoate 2-(3-phenyladamantan-1-yl)acetic acid	 methyl 4-{2-[(4-{2-[2-(3-phenyl adamantan-1-yl)acetamido] acetyl} piperazin-1-yl)methyl] phenoxy methyl} benzoate	LC/MS <i>m/z</i> : 650.44 (M+H) ⁺

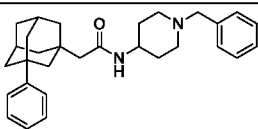
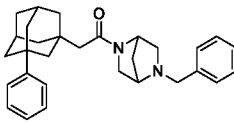
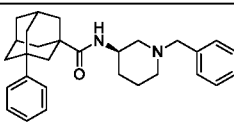
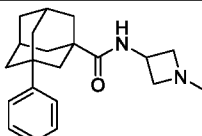
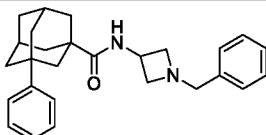
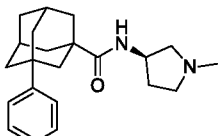
A5	methyl 4-(2-{[4-(2-{[(<i>tert</i> -butoxy) carbonyl] amino}acetyl)piperazin-1-yl]methyl}phenoxy methyl)benzoate		LC/MS <i>m/z</i> : 546.35 (M+H) ⁺
	tricyclo[3.3.1.0 ^{3,7}]nonane-3-carboxylic acid	methyl 4-(2-{[4-(2-{tricyclo[3.3.1.0 ^{3,7}]nonan-3-ylformamido} acetyl)piperazin-1-yl]methyl} phenoxy)methyl) benzoate	
A6	<i>tert</i> -butyl <i>N</i> -{[(1-benzyl piperidin-4-yl)carbamoyl] methyl}carbamate		LC/MS <i>m/z</i> : 486.41 (M+H) ⁺
	3-phenyl-adamantane-1-carboxylic acid	<i>N</i> -(1-benzylpiperidin-4-yl)-2-[(3-phenyl adamantan-1-yl)formamido]acetamide	
A7	<i>tert</i> -butyl <i>N</i> -{[(3 <i>R</i>)-1-benzyl pyrrolidin-3-yl]carbamoyl} methyl}carbamate		LC/MS <i>m/z</i> : 472.40 (M+H) ⁺
	3-phenyl-adamantane-1-carboxylic acid	<i>N</i> -[(3 <i>R</i>)-1-benzylpyrrolidin-3-yl]-2-[(3-phenyladamantan-1-yl)formamido] acetamide	
A8	<i>tert</i> -butyl <i>N</i> -(2-{5-benzyl-2,5-diaza bicyclo[2.2.1]heptan-2-yl}-2-oxoethyl) carbamate		LC/MS <i>m/z</i> : 484.3 (M+H) ⁺
	3-phenyl-adamantane-1-carboxylic acid	<i>N</i> -(2-{5-benzyl-2,5-diazabicyclo [2.2.1] heptan-2-yl}-2-oxoethyl)-3-phenyl adamantane-1-carboxamide	
A9	<i>tert</i> -butyl 6-benzyl-2,6-diazaspiro[3.3]heptane-2-carboxylate		LC/MS <i>m/z</i> : 427.45 (M+H) ⁺ , 468.34 (M+H+CH ₃ CN) ⁺
	3-phenyl-adamantane-1-carboxylic acid	2-benzyl-6-[(3-phenyl adamantan-1-yl)carbonyl]-2,6-diazaspiro [3.3]heptane	

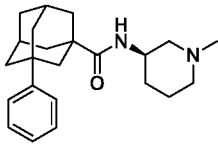
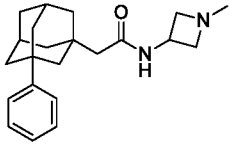
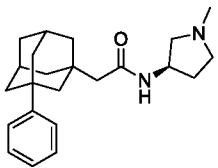
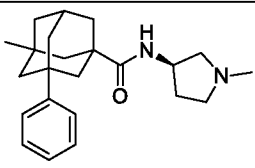
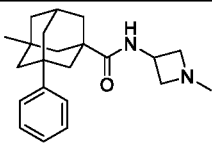
A10	<i>tert</i> -butyl 6-benzyl-2,6-diazaspiro[3.4]octane-2-carboxylate		LC/MS <i>m/z</i> : 441.31 (M+H) ⁺ , 482.36 (M+H+CH ₃ CN) ⁺
	3-phenyl-adamantane-1-carboxylic acid	6-benzyl-2-[(3-phenyladamantan-1-yl)carbonyl]-2,6-diazaspiro [3.4]octane	
A11	<i>tert</i> -butyl <i>N</i> -(2-{7-benzyl-2,7-diazaspiro [4.4] nonan-2-yl}-2-oxoethyl) carbamate		LC/MS <i>m/z</i> : 526.45 (M+H) ⁺
	2-(3-phenyladamantan-1-yl)acetic acid	<i>N</i> -(2-{7-benzyl-2,7-diazaspiro[4.4] nonan-2-yl}-2-oxoethyl)-2-(3-phenyladamantan-1-yl)acetamide	
A12	<i>tert</i> -butyl <i>N</i> -{[(1-benzyl piperidin-4-yl)carbamoyl] methyl}carbamate		LC/MS <i>m/z</i> : 500.46 (M+H) ⁺
	2-(3-phenyladamantan-1-yl)acetic acid	<i>N</i> -{[(1-benzylpiperidin-4-yl)carbamoyl] methyl}-2-(3-phenyladamantan-1-yl)acetamide	
A13	<i>tert</i> -butyl <i>N</i> -{[(3 <i>R</i>)-1-benzyl pyrrolidin-3-yl]carbamoyl} methyl}carbamate		LC/MS <i>m/z</i> : 486.43 (M+H) ⁺
	2-(3-phenyladamantan-1-yl)acetic acid	<i>N</i> -{[(3 <i>R</i>)-1-benzylpyrrolidin-3-yl]carbamoyl}methyl-2-(3-phenyladamantan-1-yl)acetamide	
A14	<i>tert</i> -butyl <i>N</i> -(2-{5-benzyl-2,5-diazabicyclo [2.2.1]heptan-2-yl}-2-oxoethyl)carbamate		LC/MS <i>m/z</i> : 498.39 (M+H) ⁺
	2-(3-phenyladamantan-1-yl)acetic acid	<i>N</i> -(2-{5-benzyl-2,5-diazabicyclo [2.2.1] heptan-2-yl}-2-oxoethyl)-2-(3-phenyladamantan-1-yl)acetamide	

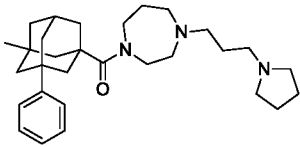
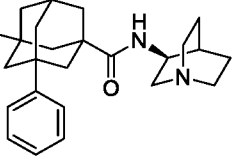
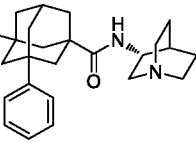
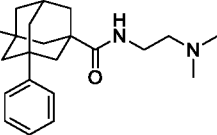
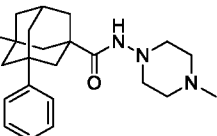
A15	(3 <i>S</i>)-1-benzylpyrrolidin-3-amine		LC/MS <i>m/z</i> : 415.33 (M+H) ⁺ , 456.41 (M+H+CH ₃ CN) ⁺
	3-phenyl-adamantane-1-carboxylic acid	<i>N</i> -[(3 <i>S</i>)-1-benzylpyrrolidin-3-yl]-3-phenyladamantane-1-carboxamide	
A16	2-amino-1-(4-benzyl piperazin-1-yl)ethan-1-one dihydrochloride		LC/MS <i>m/z</i> : 472.33 (M+H) ⁺
	3-phenyl-adamantane-1-carboxylic acid	<i>N</i> -[2-(4-benzylpiperazin-1-yl)-2-oxoethyl]-3-phenyladamantane-1-carboxamide	
A17	2-amino-1-(4-benzyl piperazin-1-yl)ethan-1-one dihydrochloride		LC/MS <i>m/z</i> : 486.33 (M+H) ⁺
	2-(3-phenyladamantan-1-yl)acetic acid	<i>N</i> -[2-(4-benzylpiperazin-1-yl)-2-oxoethyl]-2-(3-phenyladamantan-1-yl)acetamide	
A18	2-amino-1-(4-benzyl piperazin-1-yl)ethan-1-one dihydrochloride		LC/MS <i>m/z</i> : 382.33 (M+H) ⁺
	tricyclo[3.3.1.0 ^{3,7}]nonane-3-carboxylic acid	<i>N</i> -[2-(4-benzylpiperazin-1-yl)-2-oxoethyl]tricyclo [3.3.1.0 ^{3,7}]nonane-3-carboxamide	
A19	(3 <i>R</i>)-1-benzylpyrrolidin-3-amine		LC/MS <i>m/z</i> : 415.44 (M+H) ⁺
	3-phenyl-adamantane-1-carboxylic acid	<i>N</i> -[(3 <i>R</i>)-1-benzylpyrrolidin-3-yl]-3-phenyladamantane-1-carboxamide	
A20	2-benzyl-2,5-diazabicyclo [2.2.1]heptane dihydrobromide		LC/MS <i>m/z</i> : 427.36 (M+H) ⁺ , 468.36 (M+H+CH ₃ CN) ⁺
	3-phenyl-adamantane-1-carboxylic acid	2-benzyl-5-[(3-phenyladamantan-1-yl)carbonyl]-2,5-diazabicyclo [2.2.1]heptane	

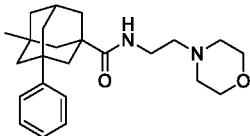
A21	1-benzylpiperidin-4-amine	 <i>N</i> -(1-benzylpiperidin-4-yl) tricyclo [3.3.1.0 ^{3,7}]nonane-3- carboxamide	LC/MS <i>m/z</i> : 339.38 (M+H) ⁺
	tricyclo[3.3.1.0 ^{3,7}]nonane-3-carboxylic acid		
A22	benzyl(methyl)[2-(methylamino)ethyl]amine	 <i>N</i> -{2-[benzyl(methyl)amino] ethyl}- <i>N</i> -methyl-3-phenyl adamantane-1-carboxamide	LC/MS <i>m/z</i> : 417.35 (M+H) ⁺
	3-phenyl-adamantane-1-carboxylic acid		
A23	1-benzyl- <i>N</i> -methylpiperidin-4-amine	 <i>N</i> -(1-benzylpiperidin-4-yl)- <i>N</i> - methyl-3-phenyl adamantane- 1-carboxamide	LC/MS <i>m/z</i> : 443.39 (M+H) ⁺
	3-phenyl-adamantane-1-carboxylic acid		
A24	(3 <i>R</i>)-1-benzylpyrrolidin-3-amine	 <i>N</i> -[(3 <i>R</i>)-1-benzylpyrrolidin-3- yl]-2-(3-phenyladamantan-1-yl) acetamide	LC/MS <i>m/z</i> : 429.26 (M+H) ⁺
	2-(3-phenyladamantan-1-yl)acetic acid		
A25	1-methylpiperazine	 1-methyl-4-[(3-phenyl adamantan-1-yl)carbonyl] piperazine	LC/MS <i>m/z</i> : 339.27 (M+H) ⁺
	3-phenyl-adamantane-1-carboxylic acid		

A26	1-methylpiperidin-4-amine	 <i>N</i> -(1-methylpiperidin-4-yl)-3-phenyladamantane-1-carboxamide	¹ H NMR (300 MHz, CDCl ₃) δ 7.26 - 7.38 (m, 4H) 7.14 - 7.21 (m, 1H) 5.67 (d, 1H) 3.83 - 4.01 (m, 1H) 3.22 (d, 2H) 2.57 (s, 4H) 2.25 (br. s., 2H) 1.98 (br. s., 3H) 1.79 - 1.95 (m, 10H) 1.72 (br. s., 2H); LC/MS <i>m/z</i> : 353.37 (M+H) ⁺
	3-phenyl-adamantane-1-carboxylic acid		
A27	<i>N</i> ,1-dimethylpiperidin-4-amine	 <i>N</i> -methyl- <i>N</i> -(1-methylpiperidin-4-yl)-3-phenyladamantane-1-carboxamide	LC/MS <i>m/z</i> : 367.36 (M+H) ⁺
	3-phenyl-adamantane-1-carboxylic acid		
A28	1-benzylpiperazine	 1-benzyl-4-((tricyclo[3.3.1.0 ^{3,7}]nonan-3-yl)carbonyl)piperazine	LC/MS <i>m/z</i> : 325.35 (M+H) ⁺ , 366.41 (M+H+CH ₃ CN) ⁺
	tricyclo[3.3.1.0 ^{3,7}]nonane-3-carboxylic acid		
A29	1-benzylpiperazine	 1-benzyl-4-[(3-phenyladamantan-1-yl)carbonyl]piperazine	LC/MS <i>m/z</i> : 415.34 (M+H) ⁺
	3-phenyl-adamantane-1-carboxylic acid		
A30	1-benzylpiperazine	 1-(4-benzylpiperazin-1-yl)-2-(3-phenyladamantan-1-yl)ethan-1-one	LC/MS <i>m/z</i> : 429.30 (M+H) ⁺ , 470.49 (M+H+CH ₃ CN) ⁺
	2-(3-phenyladamantan-1-yl)acetic acid		
A31	1-benzylpiperazine	 1-[(adamantan-2-yl)carbonyl]-4-benzylpiperazine	LC/MS <i>m/z</i> : 339.33 (M+H) ⁺ , 380.28
	adamantane-2-carboxylic acid		

A32	1-benzylpiperidin-4-amine	 <i>N</i> -(1-benzylpiperidin-4-yl)-2-(3-phenyladamantan-1-yl)acetamide	LC/MS <i>m/z</i> : 443.42 (M+H) ⁺
	2-(3-phenyladamantan-1-yl)acetic acid		
A33	2-benzyl-2,5-diazabicyclo[2.2.1]heptane dihydrobromide	 1-{5-benzyl-2,5-diazabicyclo[2.2.1]heptan-2-yl}-2-(3-phenyladamantan-1-yl)ethan-1-one	LC/MS <i>m/z</i> : 441.34 (M+H) ⁺ , 482.40 (M+H+CH ₃ CN) ⁺
	2-(3-phenyladamantan-1-yl)acetic acid		
A34	(3 <i>R</i>)-1-benzylpiperidin-3-amine	 <i>N</i> -[(3 <i>R</i>)-1-benzylpiperidin-3-yl]-3-phenyladamantane-1-carboxamide	LC/MS <i>m/z</i> : 429.33 (M+H) ⁺ , 470.56 (M+H+CH ₃ CN) ⁺
	3-phenyl-adamantane-1-carboxylic acid		
A35	1-methylazetidin-3-amine	 <i>N</i> -(1-methylazetidin-3-yl)-3-phenyladamantane-1-carboxamide	LC/MS <i>m/z</i> : 325.35 (M+H) ⁺
	3-phenyl-adamantane-1-carboxylic acid		
A36	1-benzylazetidin-3-amine	 <i>N</i> -(1-benzylazetidin-3-yl)-3-phenyladamantane-1-carboxamide	LC/MS <i>m/z</i> : 401.25 (M+H) ⁺
	3-phenyl-adamantane-1-carboxylic acid		
A37	(3 <i>R</i>)-1-methylpyrrolidin-3-amine	 <i>N</i> -[(3 <i>R</i>)-1-methylpyrrolidin-3-yl]-3-phenyladamantane-1-carboxamide	LC/MS <i>m/z</i> : 339.29 (M+H) ⁺
	3-phenyl-adamantane-1-carboxylic acid		

A38	(3 <i>R</i>)-1-methylpiperidin-3-amine	 <i>N</i> -[(3 <i>R</i>)-1-methylpiperidin-3-yl]-3-phenyladamantane-1-carboxamide	LC/MS <i>m/z</i> : 353.33 (M+H) ⁺
	3-phenyladamantane-1-carboxylic acid		
A39	1-methylazetidin-3-amine	 <i>N</i> -(1-methylazetidin-3-yl)-2-(3-phenyladamantan-1-yl)acetamide	LC/MS <i>m/z</i> : 339.38 (M+H) ⁺
	2-(3-phenyladamantan-1-yl)acetic acid		
A40	(3 <i>R</i>)-1-methylpyrrolidin-3-amine	 <i>N</i> -[(3 <i>R</i>)-1-methylpyrrolidin-3-yl]-2-(3-phenyladamantan-1-yl)acetamide	LC/MS <i>m/z</i> : 353.34 (M+H) ⁺
	2-(3-phenyladamantan-1-yl)acetic acid		
A41	(3 <i>R</i>)-1-methylpyrrolidin-3-amine	 3-methyl- <i>N</i> -[(3 <i>R</i>)-1-methylpyrrolidin-3-yl]-5-phenyladamantane-1-carboxamide	¹ H NMR (300 MHz, CDCl ₃) δ 7.38 – 7.28 (m, 4H), 7.20 – 7.15 (m, 1H), 6.66 – 6.56 (m, 1H), 4.68 – 4.58 (m, 1H), 3.22 – 3.17 (m, 1H), 2.89 (d, 1H), 2.64 (dd, 1H), 2.50 (s, 3H), 2.43 – 2.35 (m, 2H), 2.33 – 2.26 (m, 1H), 1.95 – 1.86 (m, 2H), 1.85 – 1.72 (m, 5H), 1.64 – 1.55 (m, 4H), 1.46 (br. s, 2H), 0.92 (s, 3H). LC/MS <i>m/z</i> : 353.3 (M+H) ⁺ , 394.43(M+H+CH ₃ CN) ⁺
	3-methyl-5-phenyladamantane-1-carboxylic acid		
A42	1-methylazetidin-3-amine	 3-methyl- <i>N</i> -(1-methylazetidin-3-yl)-5-phenyladamantane-1-carboxamide	LC/MS <i>m/z</i> : 339.4 (M+H) ⁺
	3-methyl-5-phenyladamantane-1-carboxylic acid		

A43	1-[3-(pyrrolidin-1-yl)propyl]-1,4-diazepane	 1-[(3-methyl-5-phenyladamantan-1-yl) carbonyl]-4-[3-(pyrrolidin-1-yl)propyl]-1,4-diazepane	LC/MS <i>m/z</i> : 464.43 (M+H) ⁺
	3-methyl-5-phenyladamantane-1-carboxylic acid		
A44	(3 <i>S</i>)-1-azabicyclo[2.2.2]octan-3-amine	 <i>N</i>-[(3<i>S</i>)-1-azabicyclo[2.2.2]octan-3-yl]-3-methyl-5-phenyladamantane-1-carboxamide	¹ H NMR (500 MHz, MeOH- <i>d</i> ₄) δ 7.39 (d, 2H), 7.30 (t, 2H), 7.15 (t, 1H), 4.07 (m, 1H), 3.45 (t, 1H), 3.2-3.12 (m, 1H), 3.12-2.98 (m, 3H), 2.95-2.88 (m, 1H), 2.31-2.29 (m, 1H), 2.1-2.05 (m, 1H), 1.99-1.78 (m, 9H), 1.70-1.58 (m, 5H), 1.53 (br:s, 2H), 0.97 (s, 3H). LC/MS <i>m/z</i> : 379.42 (M+H) ⁺ , 420.30 (M+H+CH ₃ CN)
	3-methyl-5-phenyladamantane-1-carboxylic acid		
A45	(3 <i>R</i>)-1-azabicyclo[2.2.2]octan-3-amine	 <i>N</i>-[(3<i>R</i>)-1-azabicyclo[2.2.2]octan-3-yl]-3-methyl-5-phenyladamantane-1-carboxamide	¹ H NMR (300 MHz, CDCl ₃) δ 7.41 (d, 2H), 7.33 (t, 2H), 7.20 (t, 1H), 4.33 (br:s, 1H), 3.85-3.66 (m, 2H), 3.36 (t, 1H), 3.26-2.88 (m, 4H), 2.31 (br:s, 2H), 2.09-1.40 (m, 15H), 0.95 (s, 3H). LC/MS <i>m/z</i> : 379.33 (M+H) ⁺ , 420.35 (M+H+CH ₃ CN)
	3-methyl-5-phenyladamantane-1-carboxylic acid		
A46	(2-aminoethyl)dimethylamine	 <i>N</i>-[2-(dimethylamino)ethyl]-3-methyl-5-phenyladamantane-1-carboxamide	LC/MS <i>m/z</i> : 341.37 (M+H) ⁺
	3-methyl-5-phenyladamantane-1-carboxylic acid		
A47	4-methylpiperazin-1-amine	 3-methyl-<i>N</i>-(4-methylpiperazin-1-yl)-5-phenyladamantane-1-carboxamide	LC/MS <i>m/z</i> : 368.40 (M+H) ⁺
	3-methyl-5-phenyladamantane-1-carboxylic acid		

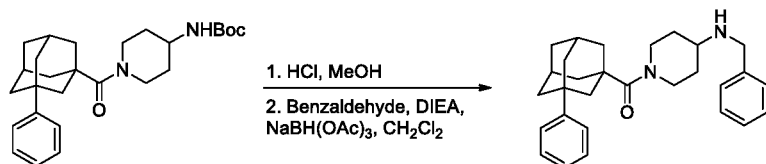
A48	2-(morpholin-4-yl)ethan-1-amine	 3-methyl-N-[2-(morpholin-4-yl)ethyl]-5-phenyladamantane-1-carboxamide	LC/MS m/z : 383.39 (M+H) ⁺
	3-methyl-5-phenyladamantane-1-carboxylic acid		

Example A49: *N*-Benzyl-1-[(3-phenyladamantan-1-yl)carbonyl]piperidin-4-amine

Step 1: *tert*-butyl *N*-{1-[(3-phenyladamantan-1-yl)carbonyl]piperidin-4-yl}carbamate

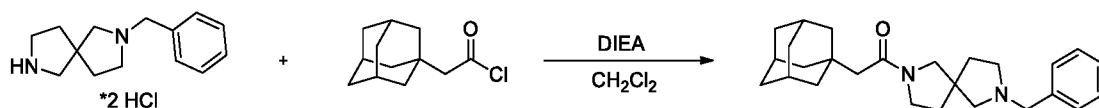
The title compound was prepared in the same manner as described for example A1, Step 2 using *tert*-butyl *N*-(piperidin-4-yl)carbamate instead of 2-benzyl-2,7-diazaspiro[4.4]nonane. LC/MS m/z : 383.31 (M-*t*Bu+H)⁺, 439.34 (M+H)⁺, 877.74 (2M+H)⁺

Step 2: *N*-benzyl-1-[(3-phenyladamantan-1-yl)carbonyl]piperidin-4-amine



To a solution of *tert*-butyl *N*-{1-[(3-phenyladamantan-1-yl)carbonyl]piperidin-4-yl}carbamate (74 mg, 0.17 mmol) in 1 mL CH₃OH was added 0.5 mL conc. HCl. The reaction mixture was stirred at rt for 12 h, then concentrated *in vacuo* to give 64 mg (100%) of HCl salt as a viscous oil. To a mixture of the obtained HCl salt (24 mg, 0.064 mmol) in 1 mL CH₂Cl₂ was added *N,N*-diisopropylethylamine (8.2 mg, 0.064 mmol) followed by benzaldehyde (6.8 mg, 0.064 mmol). The resulting mixture was stirred at rt for 1 h. Sodium triacetoxyborohydride (34 mg, 0.16 mmol) was then added and the reaction mixture was stirred at rt for 12 h. The reaction mixture was then diluted with CH₂Cl₂ and washed with saturated aq. NaHCO₃ solution. The organic phase was dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by SiO₂ column chromatography (EtOAc, then CH₂Cl₂ / CH₃OH from 40:1 to 20:1) to give 6 mg (22%) of the title compound as a colorless oil. LC/MS m/z : 429.28 (M+H)⁺.

Example A50: 2-(Adamantan-1-yl)-1-{7-benzyl-2,7-diazaspiro[4.4]nonan-2-yl}ethan-1-one



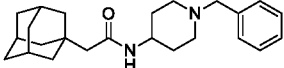
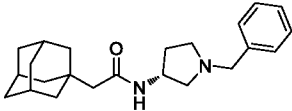
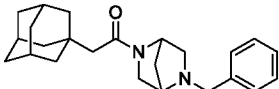
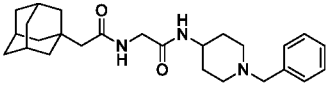
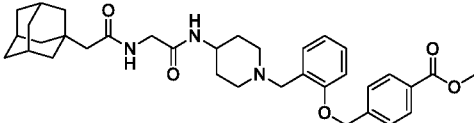
To a mixture of 2-benzyl-2,7-diazaspiro[4.4]nonane dihydrochloride (21 mg, 0.073 mmol) in 0.75 mL CH₂Cl₂ was added *N,N*-diisopropylethylamine (37 mg, 0.29 mmol), followed by 1-adamantanecarbonyl chloride (15 mg, 0.073 mmol). The reaction mixture was stirred at rt for 3 h, then diluted with CH₂Cl₂ and washed with saturated aq. NaHCO₃ solution. The organic phase was dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by preparative HPLC. The obtained TFA salt

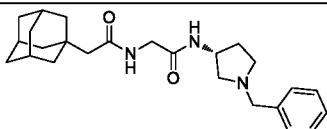
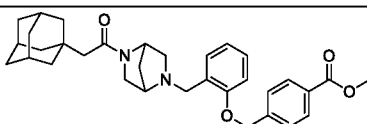
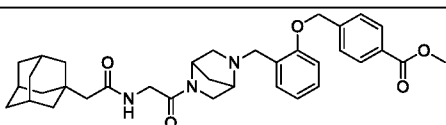
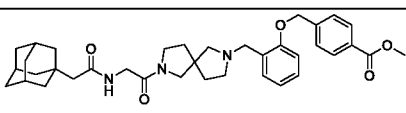
was dissolved in methanol and filtered through an Agilent Stratopheres PL-HCO₃ ion exchange resin. The filtrate was concentrated to afford 16 mg (56%) of the product as a colorless oil. LC/MS *m/z*: 393.42 (M+H)⁺, 434.42 (M+H+CH₃CN)⁺.

Examples A51 to A53 were prepared in the same manner as described above for 2-(adamantan-1-yl)-1-{7-benzyl-2,7-diazaspiro[4.4]nonan-2-yl}ethan-1-one using the appropriate commercially available amine and 1-adamantaneacetyl chloride as starting materials.

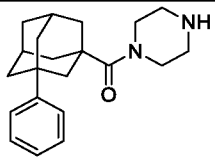
Starting amines in Examples A54 to A59 were prepared from the appropriate Boc-protected amines in the same manner as described above for 2-benzyl-2,7-diazaspiro[4.4]nonane dihydrochloride (Example A1, Step 1), and used in the next step without further purification.

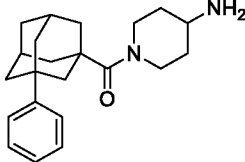
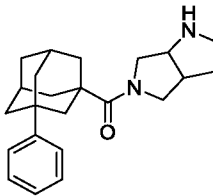
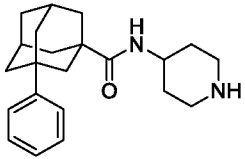
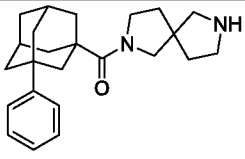
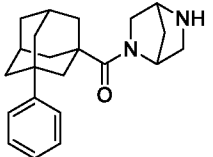
Examples A54 to A59 were prepared in the same manner as described above for 2-(adamantan-1-yl)-1-{7-benzyl-2,7-diazaspiro[4.4]nonan-2-yl}ethan-1-one using the appropriate amine and 1-adamantaneacetyl chloride as starting materials.

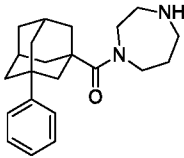
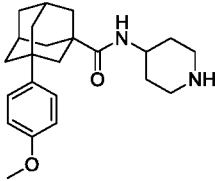
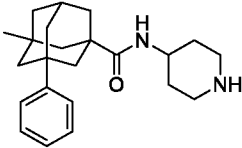
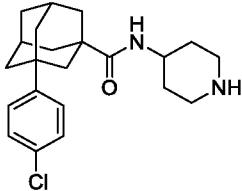
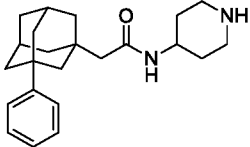
Ex.	Starting amine	Product/Name	Analytical Data
A51	1-benzylpiperidin-4-amine	 2-(adamantan-1-yl)- <i>N</i> -(1-benzylpiperidin-4-yl)acetamide	LC/MS <i>m/z</i> : 367.36 (M+H) ⁺
A52	(3 <i>R</i>)-1-benzylpyrrolidin-3-amine	 2-(adamantan-1-yl)- <i>N</i> -[(3 <i>R</i>)-1-benzylpyrrolidin-3-yl]acetamide	LC/MS <i>m/z</i> : 353.25 (M+H) ⁺
A53	2-benzyl-2,5-diazabicyclo[2.2.1]heptane dihydrobromide	 2-(adamantan-1-yl)-1-{5-benzyl-2,5-diazabicyclo[2.2.1]heptan-2-yl}ethan-1-one	LC/MS <i>m/z</i> : 365.35 (M+H) ⁺ , 406.35 (M+H+CH ₃ CN) ⁺
A54	2-amino- <i>N</i> -(1-benzylpiperidin-4-yl)acetamide dihydrochloride	 2-(adamantan-1-yl)- <i>N</i> -[(1-benzylpiperidin-4-yl)carbamoyl methyl]acetamide	LC/MS <i>m/z</i> : 424.29 (M+H) ⁺
A55	methyl 4-(2-{[4-(2-aminoacetamido)piperidin-1-yl]methyl}phenoxy)methyl)benzoate hydrochloride	 methyl 4-{2-[(4-{2-[2-(adamantan-1-yl)acetamido]acetamido}piperidin-1-yl)methyl]phenoxy)methyl}benzoate	LC/MS <i>m/z</i> : 588.45 (M+H) ⁺

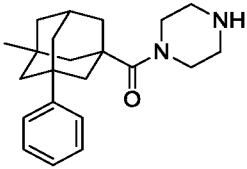
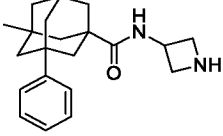
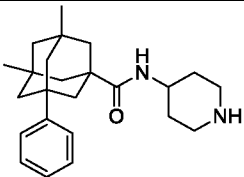
A56	2-amino- <i>N</i> -[(3 <i>R</i>)-1-benzylpyrrolidin-3-yl]acetamide dihydrochloride	 2-(adamantan-1-yl)-<i>N</i>-({[(3<i>R</i>)-1-benzylpyrrolidin-3-yl]carbonyl}methyl)acetamide	LC/MS <i>m/z</i> : 410.31 (M+H) ⁺
A57	methyl 4-(2-{2,5-diazabicyclo[2.2.1]heptan-2-ylmethyl}phenoxy)methyl)benzoate hydrochloride	 methyl 4-[2-({5-[2-(adamantan-1-yl)acetyl]-2,5-diazabicyclo[2.2.1]heptan-2-yl}methyl)phenoxy)methyl]benzoate	LC/MS <i>m/z</i> : 529.36 (M+H) ⁺
A58	methyl 4-(2-{[5-(2-aminoacetyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl]methyl} phenoxy methyl)benzoate dihydrochloride	 methyl 4-{2-[(5-{2-[2-(adamantan-1-yl)acetamido]acetyl}-2,5-diazabicyclo[2.2.1]heptan-2-yl)methyl]phenoxy methyl}benzoate	LC/MS <i>m/z</i> : 586.40 (M+H) ⁺
A59	methyl 4-(2-{[7-(2-aminoacetyl)-2,7-diazaspiro[4.4]nonan-2-yl]methyl}phenoxy)methyl)benzoate hydrochloride	 methyl 4-{2-[(7-{2-[2-(adamantan-1-yl)acetamido]acetyl}-2,7-diazaspiro[4.4]nonan-2-yl)methyl]phenoxy)methyl}benzoate	LC/MS <i>m/z</i> : 614.43 (M+H) ⁺

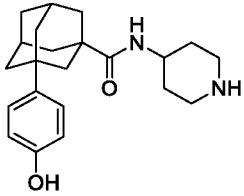
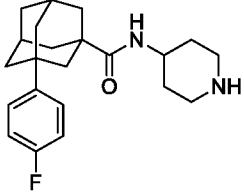
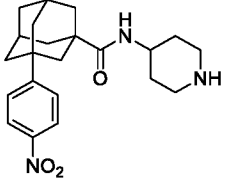
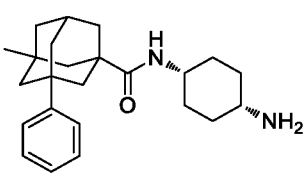
Examples A60 to A115 were prepared in the same manner as described for example A1, Steps 1 and 2 starting from the appropriate Boc-protected amine (Step 2) and the appropriate carboxylic acid followed by Boc-deprotecting as described for Step 1.

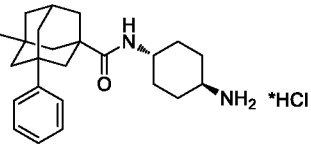
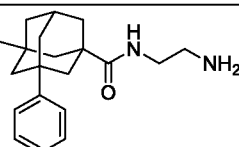
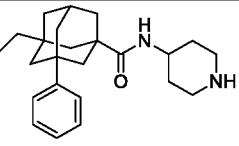
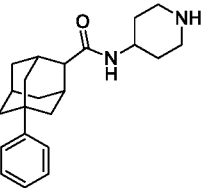
Ex.	Starting materials	Product/Name	Analytical Data
A60	<i>tert</i> -butyl piperazine-1-carboxylate 3-phenyl-adamantane-1-carboxylic acid	 1-[(3-phenyladamantan-1-yl)carbonyl]piperazine	LC/MS <i>m/z</i> : 325.24 (M+H) ⁺

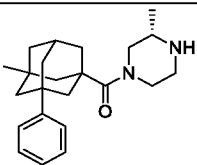
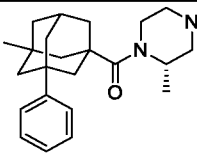
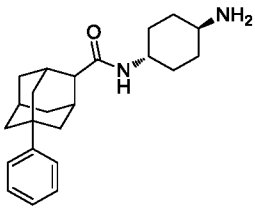
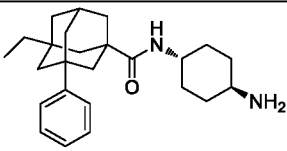
A61	<i>tert</i> -butyl <i>N</i> -(piperidin-4-yl)carbamate	 1-[(3-phenyladamantan-1-yl)carbonyl]piperidin-4-amine	LC/MS <i>m/z</i> : 339.34 (M+H) ⁺
	3-phenyl-adamantane-1-carboxylic acid		
A62	<i>tert</i> -butyl octahydro pyrrolo [3,4- <i>b</i>]pyrrole-1-carboxylate	 5-[(3-phenyladamantan-1-yl)carbonyl]-octahydro pyrrolo [3,4-<i>b</i>]pyrrole	LC/MS <i>m/z</i> : 351.83 (M+H) ⁺ , 392.03 (M+H+CH ₃ CN) ⁺
	3-phenyl-adamantane-1-carboxylic acid		
A63	<i>tert</i> -butyl 4-aminopiperidine-1-carboxylate	 3-phenyl-<i>N</i>-(piperidin-4-yl)adamantane-1-carboxamide	¹ H NMR (300 MHz, CDCl ₃) δ 9.58 (br. s., 1H) 7.28 - 7.37 (m, 4H) 7.15 - 7.22 (m, 1H) 5.66 (d, 0.5 H) 5.46 (d, 0.5H) 4.28 (d, 1H) 4.01 (dd, 1H) 3.49 (d, 1H) 2.84 - 3.11 (m, 2 H) 2.26 (br. s., 2 H) 2.10 (d, 1H) 1.99 (br. s., 1H) 1.78 - 1.95 (m, 10H) 1.72 (br. s., 2H). LC/MS <i>m/z</i> : 339.45(M+H) ⁺
	3-phenyl-adamantane-1-carboxylic acid		
A64	<i>tert</i> -butyl 2,7-diazaspiro [4.4]nonane-2-carboxylate	 2-[(3-phenyladamantan-1-yl)carbonyl]-2,7-diazaspiro [4.4]nonane	LC/MS <i>m/z</i> : 365.32 (M+H) ⁺
	3-phenyl-adamantane-1-carboxylic acid		
A65	2-[1-(<i>tert</i> -butoxy)ethenyl]-2,5-diazabicyclo [2.2.1] heptane	 2-[(3-phenyladamantan-1-yl)carbonyl]-2,5-diazabicyclo[2.2.1]heptane	LC/MS <i>m/z</i> : 337.30 (M+H) ⁺
	3-phenyl-adamantane-1-carboxylic acid		

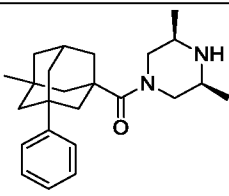
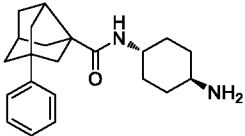
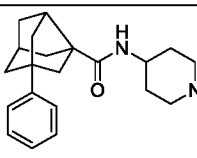
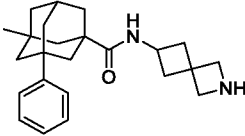
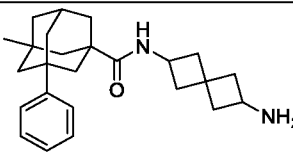
A66	<i>tert</i> -butyl 1,4-diazepane-1-carboxylate		LC/MS <i>m/z</i> : 339.38 (M+H) ⁺
	3-phenyl-adamantane-1-carboxylic acid	1-[(3-phenyladamantan-1-yl)carbonyl]-1,4-diazepane	
A67	<i>tert</i> -butyl 4-aminopiperidine-1-carboxylate		LC/MS <i>m/z</i> : 369.35 (M+H) ⁺ , 410.36(M+H+CH ₃ CN) ⁺
	3-(4-methoxyphenyl)adamantane-1-carboxylic acid	3-(4-methoxyphenyl)- <i>N</i> -(piperidin-4-yl)adamantane-1-carboxamide	
A68	<i>tert</i> -butyl 4-amino piperidine-1-carboxylate		¹ H NMR (300 MHz, CDCl ₃) δ 7.37 – 7.29 (m, 4H), 7.21 – 7.16 (m, 1H), 5.73 (d, 0.6H), 5.50 (dd, 0.4H), 4.28 (d, 0.4H), 4.07 – 3.91 (m, 1H), 3.60 (d, 0.6H), 3.42 (d, 1H), 3.03 – 2.86 (m, 2H), 2.30 (br. s, 1H), 2.23 – 2.00 (m, 2H), 1.91 – 1.71 (m, 8H), 1.61 (br. s, 2H), 1.55 (br. s, 2H), 1.47 (br. s, 2H), 0.93 (s, 3H). LC/MS <i>m/z</i> : 353.39 (M+H) ⁺ , 394.33 (M+H+CH ₃ CN) ⁺
	3-methyl-5-phenyladamantane-1-carboxylic acid	3-methyl-5-phenyl- <i>N</i> -(piperidin-4-yl)adamantane-1-carboxamide	
A69	<i>tert</i> -butyl 4-amino piperidine-1-carboxylate		LC/MS <i>m/z</i> : 373.31 (M+H) ⁺ , 414.31 (M+H+CH ₃ CN) ⁺
	3-(4-chlorophenyl)adamantane-1-carboxylic acid	3-(4-chlorophenyl)- <i>N</i> -(piperidin-4-yl)adamantane-1-carboxamide	
A70	<i>tert</i> -butyl 4-aminopiperidine-1-carboxylate		LC/MS <i>m/z</i> : 353.39 (M+H) ⁺
	2-(3-phenyladamantan-1-yl)acetic acid	2-(3-phenyladamantan-1-yl)- <i>N</i> -(piperidin-4-yl)acetamide	

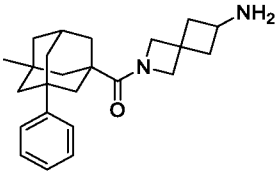
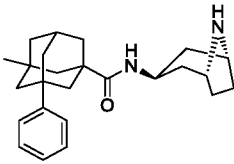
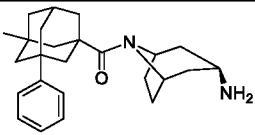
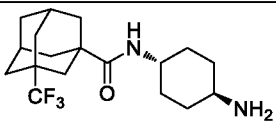
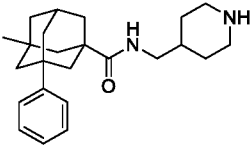
A71	<i>tert</i> -butyl piperazine-1-carboxylate	 1-[(3-methyl-5-phenyladamantan-1-yl)carbonyl]piperazine	LC/MS <i>m/z</i> : 339.42 (M+H) ⁺ , 380.34 (M+H+CH ₃ CN) ⁺ , 677.63 (2M+H) ⁺
	3-methyl-5-phenyladamantane-1-carboxylic acid		
A72	<i>tert</i> -butyl 3-aminoazetidine-1-carboxylate	 <i>N</i>-(azetidin-3-yl)-3-methyl-5-phenyladamantane-1-carboxamide	LC/MS <i>m/z</i> : 325.32(M+H) ⁺ , 366.39 (M+H+CH ₃ CN) ⁺ , 649.59 (2M+H) ⁺
	3-methyl-5-phenyladamantane-1-carboxylic acid		
A73	<i>tert</i> -butyl 4-aminopiperidine-1-carboxylate	 3,5-dimethyl-7-phenyl-<i>N</i>-(piperidin-4-yl)adamantane-1-carboxamide	LC/MS <i>m/z</i> : 367.36 (M+H) ⁺ , 408.35(M+H+CH ₃ CN) ⁺
	3,5-dimethyl-7-phenyladamantane-1-carboxylic acid		

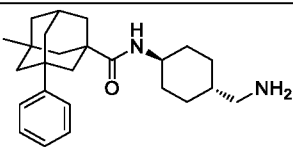
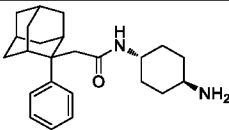
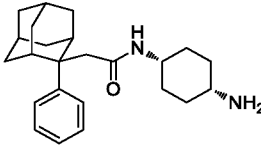
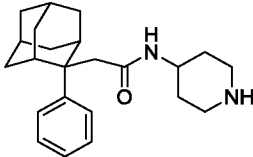
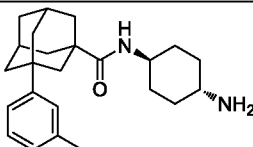
A74	<i>tert</i> -butyl 4-aminopiperidine-1-carboxylate	 3-(4-hydroxyphenyl)-<i>N</i>-(piperidin-4-yl)adamantane-1-carboxamide	LC/MS <i>m/z</i> : 355.31 (M+H) ⁺ , 396.30 (M+H+CH ₃ CN) ⁺
	3-(4-hydroxyphenyl)adamantane-1-carboxylic acid		
A75	<i>tert</i> -butyl 4-aminopiperidine-1-carboxylate	 3-(4-fluorophenyl)-<i>N</i>-(piperidin-4-yl)adamantane-1-carboxamide	LC/MS <i>m/z</i> : 357.29 (M+H) ⁺ , 398.45 (M+H+CH ₃ CN) ⁺
	3-(4-fluorophenyl)adamantane-1-carboxylic acid		
A76	<i>tert</i> -butyl 4-aminopiperidine-1-carboxylate	 3-(4-nitrophenyl)-<i>N</i>-(piperidin-4-yl)adamantane-1-carboxamide	LC/MS <i>m/z</i> : 384.30 (M+H) ⁺ , 425.32 (M+H+CH ₃ CN) ⁺
	3-(4-nitrophenyl)adamantane-1-carboxylic acid		
A77	<i>cis</i> - <i>tert</i> -butyl <i>N</i> -(4-aminocyclohexyl)carbamate	 <i>cis</i>-<i>N</i>-(4-aminocyclohexyl)-3-methyl-5-phenyladamantane-1-carboxamide	¹ H NMR (500 MHz, MeOH- <i>d</i> ₄) δ 7.37 (d, 2H), 7.28 (t, 2H), 7.16 (t, 1H), 3.80 (m, 1H), 3.04 (m, 1H), 2.29 (m 1H), 1.90 (t, 3H), 1.82 (t, 3H), 1.75-1.67 (m, 4H), 1.66-1.58 (m, 8H), 1.51 (br:s, 2H), 0.96 (s, 3H). LC/MS <i>m/z</i> : 367.43 (M+H) ⁺ , 408.30 (M+H+CH ₃ CN) ⁺
	3-methyl-5-phenyladamantane-1-carboxylic acid		

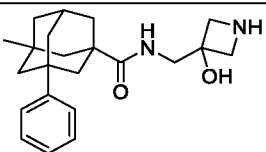
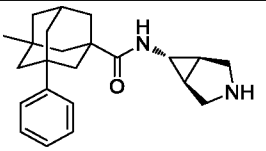
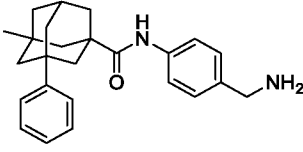
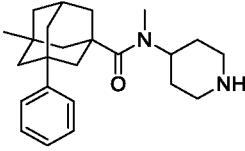
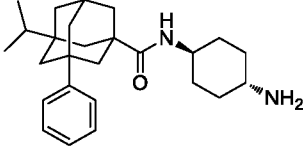
A78	<i>trans-tert-butyl N-(4-aminocyclohexyl)carbamate</i>	 <i>trans-N-(4-aminocyclohexyl)-3-methyl-5-phenyladamantane-1-carboxamide hydrochloride</i>	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.00 (br. s, 3H), 7.36 (d, 2H), 7.30 (t, 2H), 7.20 (d, 1H), 7.16 (t, 1H), 3.54 – 3.47 (m, 1H), 2.91–2.86 (m, 1H), 2.20 – 2.15 (m, 1H), 1.97–1.90 (m, 2H), 1.81 – 1.64 (m, 8H), 1.54 – 1.44 (m, 4H), 1.40 (br. s, 2H), 1.37 – 1.22 (m, 4H), 0.87 (s, 3H). LC/MS <i>m/z</i> : 367.42 (M+H) ⁺ , 408.36 (M+H+CH ₃ CN) ⁺ , 733.73 (2M+H) ⁺
	3-methyl-5-phenyladamantane-1-carboxylic acid		
A79	<i>tert-butyl N-(2-aminoethyl)carbamate</i>	 <i>N-(2-aminoethyl)-3-methyl-5-phenyladamantane-1-carboxamide</i>	LC/MS <i>m/z</i> : 313.47 (M+H) ⁺ , 354.01 (M+H+CH ₃ CN) ⁺
	3-methyl-5-phenyladamantane-1-carboxylic acid		
A80	<i>tert-butyl 4-aminopiperidine-1-carboxylate</i>	 3-ethyl-5-phenyl- <i>N</i> -(piperidin-4-yl)adamantane-1-carboxamide	¹ H NMR (300 MHz, CDCl ₃) δ 7.40 – 7.29 (m, 4H), 7.22 – 7.16 (m, 1H), 5.70 (d, 0.7H), 5.48 (d, 0.3H), 4.29 (d, 0.3H), 4.08 – 3.84 (m, 1H), 3.48 (d, 0.7H), 3.40 – 3.21 (m, 1H), 3.03 – 2.88 (m, 1.4H), 2.68 – 2.53 (m, 0.6H), 2.32 (br. s, 1H), 2.15 – 2.05 (m, 1H), 2.00 – 1.75 (m, 9H), 1.59 (br. s, 2H), 1.56 – 1.52 (m, 2H), 1.46 (br. s, 2H), 1.26 (q, 2H), 0.84 (t, 3H). LC/MS <i>m/z</i> : 367.40 (M+H) ⁺ , 408.51 (M+H+CH ₃ CN) ⁺
	3-ethyl-5-phenyladamantane-1-carboxylic acid		
A81	<i>tert-butyl 4-amino piperidine-1-carboxylate</i>	 5-phenyl- <i>N</i> -(piperidin-4-yl)adamantane-2-carboxamide	¹ H NMR (500 MHz, MeOH- <i>d</i> ₄) δ 7.36 (d, 1H), 7.34–7.23 (m, 3H), 7.13 (q, 1H), 4.04–3.93 (m, 1H), 3.46–3.37 (m, 2H), 3.09 (q, 2H), 2.57 (d, 1H), 2.40 (br. s, 2H), 2.22 (d, 1H), 2.13–1.83 (m, 10H), 1.81–1.67 (m, 3H), 1.63 (d, 1H). LC/MS <i>m/z</i> : 339.34 (M+H) ⁺
	5-phenyladamantane-2-carboxylic acid		

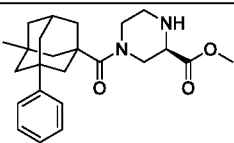
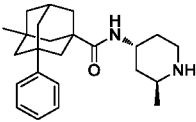
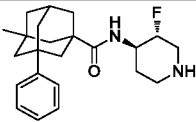
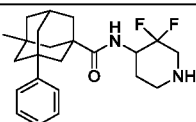
A82	<i>tert</i> -butyl (2 <i>S</i>)-2-methylpiperazine-1-carboxylate	 (3<i>S</i>)-3-methyl-1-[(3-methyl-5-phenyladamantan-1-yl)carbonyl]piperazine	¹ H NMR (300 MHz, CDCl ₃) δ 10.03 (br:s, 1H), 9.53 (br:s, 1H), 7.36 (d, 4H), 7.27-7.20 (m, 1H), 4.52 (d, 2H), 3.50 (d, 2H), 3.45-3.32 (m, 1H), 3.19-3.07 (m, 1H), 3.06-2.88 (m, 1H), 2.35 (br:s, 1H), 2.03 (br:s, 1H), 1.89 (d, 4H), 1.68 (d, 4H), 1.51 (br:s, 2H), 1.39 (d, 3H), 0.97 (s, 3H). LC/MS <i>m/z</i> : 353.41 (M+H) ⁺ , 394.38 (M+H+CH ₃ CN) ⁺
	3-methyl-5-phenyladamantane-1-carboxylic acid		
A83	<i>tert</i> -butyl (3 <i>S</i>)-3-methyl piperazine-1-carboxylate	 (2<i>S</i>)-2-methyl-1-[(3-methyl-5-phenyladamantan-1-yl)carbonyl]piperazine	LC/MS <i>m/z</i> : 353.34 (M+H) ⁺ , 394.38 (M+H+CH ₃ CN) ⁺
	3-methyl-5-phenyladamantane-1-carboxylic acid		
A84	<i>trans-tert</i> -butyl <i>N</i> -(4-amino cyclohexyl)carbamate	 <i>trans-N</i>-(4-aminocyclohexyl)-5-phenyladamantane-2-carboxamide	¹ H NMR (500 MHz, MeOH- <i>d</i> ₄) δ 7.36 (d, 2H), 7.33-7.24 (m, 2H), 7.14 (t, 1H), 3.77-3.67 (m, 1H), 3.13-3.03 (m, 1H), 2.54 (d, 1H), 2.39 (br:s, 2H), 2.13-1.88 (m, 13H), 1.63 (d, 2H), 1.51 (q, 2H), 1.40 (q, 2H). LC/MS <i>m/z</i> : 353.41 (M+H) ⁺ , 394.39 (M+H+CH ₃ CN) ⁺
	5-phenyladamantane-2-carboxylic acid		
A85	<i>trans-tert</i> -butyl <i>N</i> -(4-amino cyclohexyl)carbamate	 <i>trans-N</i>-(4-aminocyclohexyl)-3-ethyl-5-phenyladamantane-1-carboxamide	¹ H NMR (300 MHz, CDCl ₃) δ 8.33 (br. s, 2H), 7.38–7.27 (m, 4H), 7.21–7.15 (m, 1H), 5.73–5.63 (m, 0.6H), 5.40–5.32 (d, 0.4H), 3.79–3.65 (m, 1H), 3.36–3.06 (m, 1H), 2.33–2.21 (m, 2H), 2.02–1.76 (m, 11H), 1.60–1.50 (m, 4H), 1.48–1.40 (m, 2H), 1.30–1.14 (m, 4H), 0.82 (td, 3H). LC/MS <i>m/z</i> : 381.35 (M+H) ⁺ , 422.30 (M+H+CH ₃ CN) ⁺
	3-ethyl-5-phenyladamantane-1-carboxylic acid		

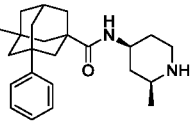
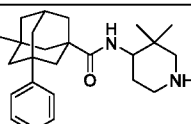
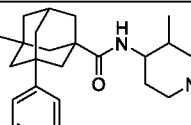
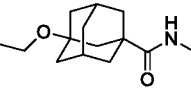
A86	<i>tert</i> -butyl (2 <i>R</i> ,6 <i>S</i>)-2,6-dimethylpiperazine-1-carboxylate		LC/MS <i>m/z</i> : 367.41 (M+H) ⁺ , 408.41 (M+H+CH ₃ CN) ⁺
	3-methyl-5-phenyladamantane-1-carboxylic acid	(3 <i>R</i> ,5 <i>S</i>)-3,5-dimethyl-1-[(3-methyl-5-phenyladamantan-1-yl)carbonyl] piperazine	
A87	<i>trans-tert</i> -butyl <i>N</i> -(4-aminocyclohexyl) carbamate		LC/MS <i>m/z</i> : 339.42 (M+H) ⁺
	1-phenyltricyclo [3.3.1.0 ^{3,7}]nonane-3-carboxylic acid	<i>trans-N</i> -(4-aminocyclohexyl)-1-phenyl tricyclo [3.3.1.0 ^{3,7}] nonane-3-carboxamide	
A88	<i>tert</i> -butyl 4-aminopiperidine-1-carboxylate		LC/MS <i>m/z</i> : 325.32 (M+H) ⁺
	1-phenyltricyclo [3.3.1.0 ^{3,7}]nonane-3-carboxylic acid	1-phenyl- <i>N</i> -(piperidin-4-yl)tricyclo [3.3.1.0 ^{3,7}] nonane-3-carboxamide	
A89	<i>tert</i> -butyl 6-amino-2-azaspiro[3.3]heptane-2-carboxylate		LC/MS <i>m/z</i> : 365.41 (M+H) ⁺
	3-methyl-5-phenyladamantane-1-carboxylic acid	<i>N</i> -{2-azaspiro[3.3]heptan-6-yl}-3-methyl-5-phenyladamantane-1-carboxamide	
A90	<i>tert</i> -butyl <i>N</i> -{6-aminospiro[3.3]heptan-2-yl}carbamate		¹ H NMR (300 MHz, CDCl ₃) δ 8.28 (br. s, 2H), 7.37 – 7.27 (m, 4H), 7.21 – 7.14 (m, 1H), 6.25 – 6.14 (m, 0.6H), 5.76 – 5.69 (m, 0.4H), 4.32 – 4.13 (m, 1H), 3.88 – 3.72 (m, 1H), 2.55 – 2.27 (m, 7H), 1.94 – 1.76 (m, 8H), 1.61 – 1.51 (m, 4H), 1.49 – 1.41 (m, 2H), 0.93 (s, 1.2H), 0.91 (s, 1.8H). LC/MS <i>m/z</i> : 379.31 (M+H) ⁺ , 420.36 (M+H+CH ₃ CN) ⁺
	3-methyl-5-phenyladamantane-1-carboxylic acid	<i>N</i> -{6-aminospiro [3.3] heptan-2-yl}-3-methyl-5-phenyladamantane-1-carboxamide	

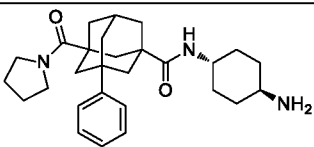
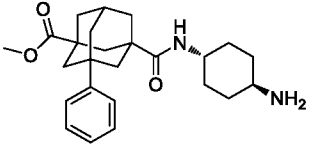
A91	<i>tert</i> -butyl <i>N</i> -{2-azaspiro[3.3]heptan-6-yl}carbamate		¹ H NMR (300 MHz, CDCl ₃) δ 7.36 – 7.27 (m, 4H), 7.21 – 7.12 (m, 1H), 4.46 – 4.19 (m, 2H), 4.11 – 3.86 (m, 2H), 3.78 – 3.64 (m, 1H), 2.70 – 2.48 (m, 3H), 2.29 – 2.20 (m, 1H), 2.04 – 1.71 (m, 7H), 1.61 – 1.51 (m, 4H), 1.43 (br. s, 2H), 0.90 (s, 3H). LC/MS <i>m/z</i> : 365.35 (M+H) ⁺ , 406.41 (M+H+CH ₃ CN) ⁺ , 729.67 (2M+H) ⁺
	3-methyl-5-phenyladamantane-1-carboxylic acid	2-[(3-methyl-5-phenyladamantan-1-yl)carbonyl]-2-azaspiro[3.3]heptan-6-amine	
A92	<i>exo</i> -3-amino-8-Boc-8-azabicyclo[3.2.1]octane		LC/MS <i>m/z</i> : 379.41 (M+H) ⁺
	3-methyl-5-phenyladamantane-1-carboxylic acid	<i>exo</i> - <i>N</i> -8-azabicyclo[3.2.1]octan-3-yl-3-methyl-5-phenyladamantane-1-carboxamide	
A93	<i>exo</i> -3-(Boc-amino)-8-azabicyclo[3.2.1]octane		LC/MS <i>m/z</i> : 379.35 (M+H) ⁺
	3-methyl-5-phenyladamantane-1-carboxylic acid	<i>exo</i> -8-[(3-methyl-5-phenyladamantan-1-yl)carbonyl]-8-azabicyclo[3.2.1]octan-3-amine	
A94	<i>trans</i> - <i>tert</i> -butyl <i>N</i> -(4-aminocyclohexyl)carbamate		LC/MS <i>m/z</i> : 328.31 (M-F+H) ⁺ , 345.25 (M+H) ⁺ , 386.33 (M+H+CH ₃ CN) ⁺ , 689.51 (2M+H) ⁺
	3-(trifluoromethyl)adamantane-1-carboxylic acid	<i>trans</i> - <i>N</i> -(4-aminocyclohexyl)-3-(trifluoromethyl)adamantane-1-carboxamide	
A95	<i>tert</i> -butyl 4-(aminomethyl)piperidine-1-carboxylate		LC/MS <i>m/z</i> : 367.38 (M+H) ⁺ , 733.62 (2M+H) ⁺
	3-methyl-5-phenyladamantane-1-carboxylic acid	3-methyl-5-phenyl- <i>N</i> -(piperidin-4-ylmethyl)adamantane-1-carboxamide	

A96	<i>trans-tert</i> -butyl <i>N</i> -[(4-aminocyclohexyl)methyl] carbamate		¹ H NMR (300 MHz, CDCl ₃) δ 8.17 (br. s, 2H), 7.37 – 7.27 (m, 4H), 7.21 – 7.15 (m, 1H), 5.72 (d, 0.7H), 5.45 (d, 0.3H), 3.78 – 3.61 (m, 1H), 3.00 – 2.91 (m, 2H), 2.90 – 2.80 (m, 1H), 2.33– 2.24 (m, 1H), 2.01 – 1.69 (m, 10H), 1.61 – 1.51 (m, 4H), 1.49 – 1.41 (m, 2H), 1.24 – 1.07 (m, 4H), 0.93 (s, 0.9H), 0.91 (s, 2.1H). LC/MS <i>m/z</i> : 381.39 (M+H) ⁺ , 422.34 (M+H+CH ₃ CN) ⁺
	3-methyl-5-phenyladamantane-1-carboxylic acid	<i>trans-N</i> -[4-(aminomethyl)cyclohexyl]-3-methyl-5-phenyladamantane-1-carboxamide	
A97	<i>trans-tert</i> -butyl <i>N</i> -(4-aminocyclohexyl) carbamate		LC/MS <i>m/z</i> : 367.3 (M+H) ⁺
	2-(2-phenyladamantan-2-yl)acetic acid	<i>trans-N</i> -(4-aminocyclohexyl)-2-(2-phenyladamantan-2-yl)acetamide	
A98	<i>cis-tert</i> -butyl <i>N</i> -(4-aminocyclohexyl)carbamate		LC/MS <i>m/z</i> : 367.38 (M+H) ⁺
	2-(2-phenyladamantan-2-yl)acetic acid	<i>cis-N</i> -(4-aminocyclohexyl)-2-(2-phenyladamantan-2-yl)acetamide	
A99	<i>tert</i> -butyl 4-aminopiperidine-1-carboxylate		LC/MS <i>m/z</i> : 353.34 (M+H) ⁺
	2-(2-phenyladamantan-2-yl)acetic acid	2-(2-phenyladamantan-2-yl)- <i>N</i> -(piperidin-4-yl)acetamide	
A100	<i>trans-tert</i> -butyl <i>N</i> -(4-aminocyclohexyl) carbamate		LC/MS <i>m/z</i> : 367.63 (M+H) ⁺ , 408.41 (M+H+CH ₃ CN) ⁺ , 733.79 (2M+H) ⁺
	3-(3-methylphenyl)adamantane-1-carboxylic acid	<i>trans-N</i> -(4-aminocyclohexyl)-3-(3-methylphenyl)adamantane-1-carboxamide	

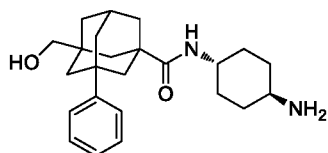
A101	<i>tert</i> -butyl 3-amino-3-hydroxyazetidine-1-carboxylate		LC/MS <i>m/z</i> : 355.36 (M+H) ⁺
	3-methyl-5-phenyladamantane-1-carboxylic acid	<i>N</i> -(3-hydroxyazetidin-3-yl)-3-methyl-5-phenyladamantane-1-carboxamide	
A102	<i>tert</i> -butyl (1 <i>R</i> ,5 <i>S</i> ,6 <i>S</i>)-6-amino-3-azabicyclo[3.1.0]hexane-3-carboxylate		LC/MS <i>m/z</i> : 351.29 (M+H) ⁺ , 392.40 (M+H+CH ₃ CN) ⁺
	3-methyl-5-phenyladamantane-1-carboxylic acid	<i>N</i> -[(1 <i>R</i> ,5 <i>S</i>)-3-azabicyclo[3.1.0]hexan-6-yl]-3-methyl-5-phenyladamantane-1-carboxamide	
A103	<i>tert</i> -butyl <i>N</i> -[(4-aminophenyl)methyl]carbamate		¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.11 (s, 1H), 7.54 (d, 2H), 7.41 (dd, 2H), 7.31 (t, 2H), 7.21 (d, 2H), 7.18 (t, 1H), 3.64 (s, 2H), 2.27 – 2.22 (m, 1H), 1.95 (q, 2H), 1.87 – 1.80 (m, 3H), 1.75 – 1.70 (m, 1H), 1.66 – 1.54 (m, 4H), 1.48 – 1.43 (m, 2H), 0.92 (s, 3H). LC/MS <i>m/z</i> : 416.35 (M+H+CH ₃ CN) ⁺
	3-methyl-5-phenyladamantane-1-carboxylic acid	<i>N</i> -[4-(aminomethyl)phenyl]-3-methyl-5-phenyladamantane-1-carboxamide	
A104	<i>tert</i> -butyl 4-(methylamino)piperidine-1-carboxylate		LC/MS <i>m/z</i> : 367.36 (M+H) ⁺
	3-methyl-5-phenyladamantane-1-carboxylic acid	<i>N</i> ,3-dimethyl-5-phenyl- <i>N</i> -(piperidin-4-yl)adamantane-1-carboxamide	
A105	<i>trans-tert</i> -butyl <i>N</i> -(4-aminocyclohexyl)carbamate		LC/MS <i>m/z</i> : 395.39 (M+H) ⁺ , 436.21 (M+H+CH ₃ CN) ⁺ , 789.67 (2M+H) ⁺
	3-methyl-5-phenyladamantane-1-carboxylic acid	<i>trans-N</i> -(4-aminocyclohexyl)-3-phenyl-5-(propan-2-yl)adamantane-1-carboxamide	

A106	1- <i>tert</i> -butyl 2-methyl (2 <i>R</i>)-piperazine-1,2-dicarboxylate		LC/MS <i>m/z</i> : 397.35 (M+H) ⁺ , 438.37(M+H+CH ₃ CN) ⁺
	3-methyl-5-phenyladamantane-1-carboxylic acid	methyl (2 <i>R</i>)-4-[(3-methyl-5-phenyladamantan-1-yl)carbonyl]piperazine-2-carboxylate	
A107	<i>trans</i> - <i>tert</i> -butyl-4-amino-2-methylpiperidine-1-carboxylate		¹ H NMR (300 MHz, CDCl ₃) δ 7.26 - 7.37 (m, 4H) 7.14 - 7.21 (m, 1H) 5.78 (d, 1H) 4.17 (dt, 1 H) 3.44 (s, 3H) 2.70 - 3.02 (m, 3H) 2.29 (dt, 1H) 2.22 (br. s., 2H) 1.52 - 1.90 (m, 9H) 1.38 - 1.51 (m, 2H) 1.10 (d, 2H) 0.93 (s, 3H). LC/MS <i>m/z</i> : 367.35 (M+H) ⁺
	3-methyl-5-phenyladamantane-1-carboxylic acid	<i>trans</i> -3-methyl- <i>N</i> -[(2 <i>S</i> ,4 <i>R</i>)-2-methylpiperidin-4-yl]-5-phenyladamantane-1-carboxamide	
A108	<i>trans</i> - <i>tert</i> -butyl-4-amino-3-fluoropiperidine-1-carboxylate		¹ H NMR (300 MHz, CDCl ₃) δ 7.26 - 7.39 (m, 4H) 7.13 - 7.22 (m, 1H) 5.62 (d, 1 H) 4.19 - 4.37 (m, 0.5H) 4.05-4.17 (m, 0.5H) 3.98-4.03 (m, 1H) 3.22-3.86 (m, 1H) 2.84 - 2.98 (m, 1H) 2.59 - 2.84 (m, 1H) 2.25 - 2.34 (m, 1H) 1.99 - 2.17 (m, 2H) 1.70 - 1.93 (m, 6H) 1.51 - 1.67 (m, 4H) 1.19 - 1.40 (m, 2H) 0.93 (s, 3H). LC/MS <i>m/z</i> : 371.40 (M+H) ⁺
	3-methyl-5-phenyladamantane-1-carboxylic acid	<i>trans</i> - <i>N</i> -3-fluoropiperidin-4-yl]-3-methyl-5-phenyladamantane-1-carboxamide	
A109	<i>tert</i> -butyl 4-amino-3,3-difluoropiperidine-1-carboxylate		¹ H NMR (300 MHz, CDCl ₃) δ 10.65 (br. s., 0.5H) 10.00 (br. s., 0.5H) 7.27 - 7.38 (m, 4H) 7.14 - 7.22 (m, 1H) 6.04 (d, 0.5H) 5.78 (d, 0.5H) 4.57 - 4.76 (m, 1H) 4.41 (d, 1H) 3.83 (br. s., 1 H) 3.02 - 3.38 (m, 2H) 2.31 (d, 1H) 2.14 (br. s., 1H) 1.71 - 1.97 (m, 3H) 1.51 - 1.70 (m, 6 H) 1.47 (br. s., 2H) 0.93 (s, 3 H). LC/MS <i>m/z</i> : 389.32 (M+H) ⁺
	3-methyl-5-phenyladamantane-1-carboxylic acid	<i>N</i> -(3,3-difluoropiperidin-4-yl)-3-methyl-5-phenyladamantane-1-carboxamide	

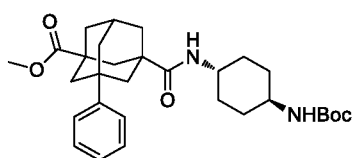
A110	<i>cis-tert</i> -butyl-4-amino-2-methylpiperidine-1-carboxylate		¹ H NMR (300 MHz, CDCl ₃) δ 7.37 – 7.29 (m, 4H), 7.21 – 7.16 (m, 1H), 5.50 (d, 0.8H), 5.38 (d, 0.2H), 4.09 – 3.85 (m, 1H), 3.32 – 2.96 (m, 3H), 2.92 – 2.84 (m, 1H), 2.78 (td, 1H), 2.34 – 2.25 (m, 1H), 2.03 – 1.76 (m, 8H), 1.61 (br. s, 2H), 1.55 (br. s, 2H), 1.50 – 1.44 (m, 2H), 1.34 (d, 0.6H), 1.22 (d, 2.4H), 0.93 (s, 3H). LC/MS <i>m/z</i> : 367.34 (M+H) ⁺
	3-methyl-5-phenyladamantane-1-carboxylic acid	<i>cis</i> -3-methyl- <i>N</i> -(2-methylpiperidin-4-yl)-5-phenyladamantane-1-carboxamide	
A111	<i>tert</i> -butyl 4-amino-3,3-dimethylpiperidine-1-carboxylate		¹ H NMR (300 MHz, CDCl ₃) δ 7.26 – 7.38 (m, 4H) 7.13 – 7.22 (m, 1H) 5.44 (d, 1H) 3.84 (ddd, 1H) 3.45 (s, 2H) 3.08 (d, 1H) 2.61 – 2.75 (m, 2H) 2.47 – 2.57 (m, 1H) 2.29 (dt, 1H) 2.17 (br. s., 3H) 1.95 (br. s., 3H) 1.69 – 1.85 (m, 3H) 1.56 (s, 3H) 1.40 – 1.52 (m, 3H) 0.93 (d, 3H) 0.80 – 0.87 (m, 2H). LC/MS <i>m/z</i> : 381.40 (M+H) ⁺
	3-methyl-5-phenyladamantane-1-carboxylic acid	<i>N</i> -(3,3-dimethylpiperidin-4-yl)-3-methyl-5-phenyladamantane-1-carboxamide	
A112	<i>tert</i> -butyl 4-amino-3-methylpiperidine-1-carboxylate		¹ H NMR (300 MHz, CDCl ₃) δ 7.26 – 7.38 (m, 4H) 7.14 – 7.22 (m, 1H) 5.57 (d, 1H) 4.04 – 4.20 (m, 0.5H) 3.53 – 3.77 (m, 0.5H) 3.45 (s, 3H) 3.13 – 3.28 (m, 1H) 2.61 – 2.99 (m, 2H) 2.35 – 2.53 (m, 4H) 1.64 – 2.00 (m, 8H) 1.51 – 1.63 (m, 2H) 1.41 – 1.51 (m, 2H) 0.93 (s, 3H). LC/MS <i>m/z</i> : 367.43 (M+H) ⁺
	3-methyl-5-phenyladamantane-1-carboxylic acid	<i>N</i> -(3-methylpiperidin-4-yl)-3-methyl-5-phenyladamantane-1-carboxamide	
A113	<i>tert</i> -butyl 4-amino piperidine-1-carboxylate	 3-ethoxy- <i>N</i> -(piperidin-4-yl)adamantane-1-carboxamide	LC/MS <i>m/z</i> : 307.34 (M+H) ⁺ , 613.65 (2M+H) ⁺
	3-ethoxyadamantane-1-carboxylic acid		

A114	<i>trans-tert</i> -butyl <i>N</i> -(4-aminocyclohexyl)carbamate	 <i>trans-N</i> -(4-aminocyclohexyl)-3-phenyl-5-[(pyrrolidin-1-yl)carbonyl]adamantane-1-carboxamide	LC/MS <i>m/z</i> : 450.42 (M+H) ⁺
	3-phenyl-5-[(pyrrolidin-1-yl)carbonyl]adamantane-1-carboxylic acid		
A115	<i>trans-tert</i> -butyl <i>N</i> -(4-aminocyclohexyl)carbamate	 methyl 3-[<i>trans</i> -(4-aminocyclohexyl)carbamoyl]-5-phenyladamantane-1-carboxylate	LC/MS <i>m/z</i> : 411.27 (M+H) ⁺ , 452.2 (M+H+CH ₃ CN) ⁺ , 821.63 (2M+H) ⁺
	3-(methoxycarbonyl)-5-phenyladamantane-1-carboxylic acid		

Example A116: *trans-N*-(4-aminocyclohexyl)-3-(hydroxymethyl)-5-phenyladamantane-1-carboxamide

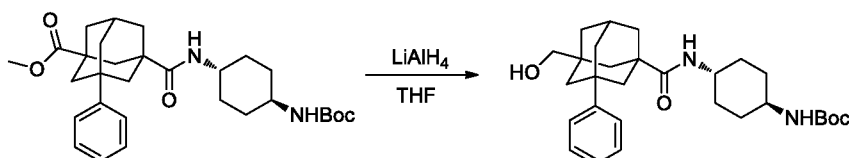


Step 1: methyl 3-[*trans*-(4-[(*tert*-butoxy)carbonyl]amino)cyclohexyl]carbamoyl]-5-phenyladamantane-1-carboxylate



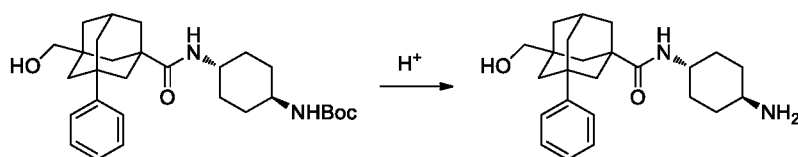
The title compound was prepared from 3-(methoxycarbonyl)-5-phenyladamantane-1-carboxylic acid and *trans-tert*-butyl *N*-(4-aminocyclohexyl)carbamate in the same manner as described above for 2-benzyl-7-[(3-phenyladamantan-1-yl)carbonyl]-2,7-diazaspiro[4.4]nonane (example A1, Step 2). LC/MS *m/z*: 455.32 (M-*t*Bu+H)⁺, 496.35 (M-Me+H)⁺, 511.41 (M+H)⁺, 552.44 (M+H+CH₃CN)⁺.

Step 2: *tert*-butyl *trans-N*-{4-[3-(hydroxymethyl)-5-phenyladamantane-1-amido]cyclohexyl}carbamate



To a solution of methyl 3-[*trans*-(4-[[*tert*-butoxy)carbonyl]amino}cyclohexyl)carbamoyl]-5-phenyladamantane-1-carboxylate (15 mg, 0.03 mmol) in THF (0.5 mL) was added dropwise 2.4 M solution of LiAlH₄ in THF (0.012 mL, 0.03 mmol) at 0 °C. The reaction mixture was stirred at ambient temperature for 2h, then cooled in an ice-bath, and quenched with saturated aqueous Na₂SO₄ solution. After stirring for 0.5 h, the mixture was diluted with THF, filtered through Celite, and concentrated *in vacuo* to give 11 mg (78%) of the title compound as a white solid, which was used in the next step without further purification. LC/MS *m/z*: 427.34 (M-*t*Bu+H)⁺, 483.38 (M+H)⁺, 965.75 (2M+H)⁺.

Step 3: *trans*-N-(4-aminocyclohexyl)-3-(hydroxymethyl)-5-phenyladamantane-1-carboxamide

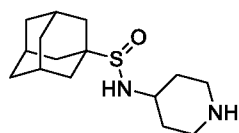


The title compound was prepared from *tert*-butyl *trans*-N-{4-[3-(hydroxymethyl)-5-phenyladamantane-1-amido]cyclohexyl}carbamate in the same manner as described above for 2-benzyl-2,7-diazaspiro[4.4]nonanedihydrochloride (example A1, Step 1). LC/MS *m/z*: 366.35 (M-OH+H)⁺, 383.38 (M+H)⁺, 424.3 (M+H+CH₃CN)⁺.

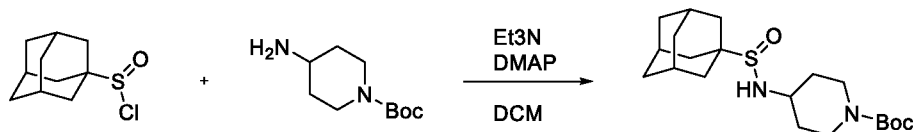
Examples A201 to A203 were prepared in the same manner as described for example A1, Step 2 using the appropriate commercially available amine and carboxylic acid as starting materials.

A201	pyridin-4-amine		LC/MS <i>m/z</i> : 347.36 (M+H) ⁺ , 388.24 (M+H+CH ₃ CN) ⁺
	3-methyl-5-phenyladamantane-1-carboxylic acid		
A202	1 <i>H</i> -imidazol-2-ylmethanamine		LC/MS <i>m/z</i> : 350.24 (M+H) ⁺ , 391.29 (M+H+CH ₃ CN) ⁺
	3-methyl-5-phenyladamantane-1-carboxylic acid		
A203	pyridine-2,4-diamine		LC/MS <i>m/z</i> : 362.28 (M+H) ⁺
	3-methyl-5-phenyladamantane-1-carboxylic acid		

Example A204: *N*-(piperidin-4-yl)adamantane-1-sulfonamide



Step 1: *tert*-butyl 4-(((adamantan-1-yl)sulfonyl)amino)piperidine-1-carboxylate



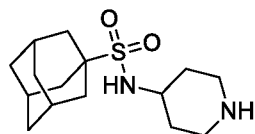
To a solution of adamantane-1-sulfonyl chloride (50 mg, 0.23 mmol) in DCM (1 mL) was added triethylamine (64 μ L, 0.46 mmol) and 4-dimethylaminopyridine (3 mg), followed by *tert*-butyl 4-aminopiperidine-1-carboxylate (56 mg, 0.28 mmol). The mixture was stirred overnight, diluted with DCM, washed 1X with 1 M HCl, dried with brine and sodium sulfate, and evaporated. The crude product was purified via silica gel flash column using 5% MeOH in DCM as eluent to afford 49 mg of the title compound as a clear, viscous oil. LC/MS m/z : 383.35 ($M+H$)⁺, 765.68 ($2M+H$)⁺

Step 2: *N*-(piperidin-4-yl)adamantane-1-sulfonamide

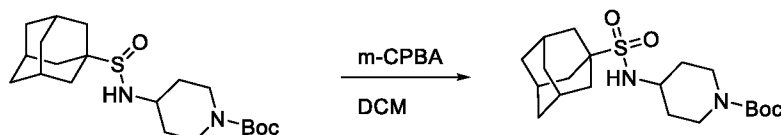


To a solution of *tert*-butyl 4-(((adamantan-1-yl)sulfonyl)amino)piperidine-1-carboxylate (20 mg) in DCM (0.5 mL) was added TFA (0.5 mL), and the mixture was stirred for 2 hours at room temperature. All volatiles were evaporated and the residue dissolved in methanol and passed through an Agilent PL-HCO₃ ion exchange column. The filtrate was evaporated to afford 15 mg of the title compound as a clear oil which requires no further purification. LC/MS m/z : 283.33 ($M+H$)⁺

Example A205: *N*-(piperidin-4-yl)adamantane-1-sulfonamide



Step 1: *tert*-butyl 4-(adamantane-1-sulfonamido)piperidine-1-carboxylate



To a solution of *tert*-butyl 4-(((adamantan-1-yl)sulfonyl)amino)piperidine-1-carboxylate (30 mg, 0.08 mmol) in DCM (1 mL) was added *m*-CPBA (20 mg, 0.1 mmol), and the mixture was stirred at room temperature for 3 hours. After completion, the reaction was diluted with DCM and washed 2X with saturated NaHCO₃, dried over sodium sulfate, and evaporated. The crude product was purified via silica gel flash column using 50:50 hexanes:ethyl acetate as eluent to afford 23 mg of the title compound as a white solid. LC/MS m/z : 399.33 ($M+H$)⁺, 343.27 ($M+H-(t\text{-butyl})$)⁺

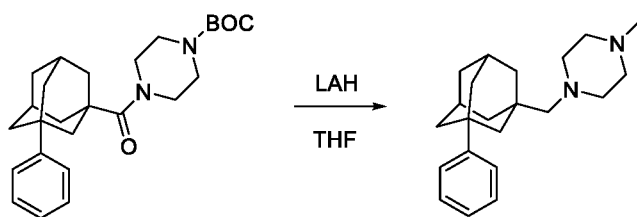
Step 2: N-(piperidin-4-yl)adamantane-1-sulfonamide



The title compound was prepared from tert-butyl 4-(adamantane-1-sulfonamido)piperidine-1-

- 5 carboxylate using the procedure described for example A204, Step 2. LC/MS m/z : 299.26 (M+H)⁺, 597.48 (2M+H)⁺

Example C1: 1-Methyl-4-(3-phenyladamantan-1-yl)methyl)piperazine



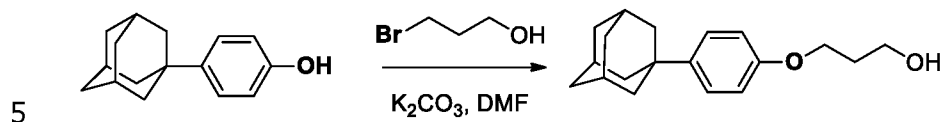
- 10 To a suspension of LAH (0.030 g, 0.78 mmol) in THF (1 mL) cooled to 0 °C was added a solution of (4-*tert*-butoxycarbonylpiperazin-1-yl)(3-phenyladamantan-1-yl)methanone (0.060 g, 0.14 mmol) in THF (1 mL) dropwise. The resulting reaction mixture was brought to room temperature and then refluxed for 6 h, cooled to 0 °C and quenched with sat. aq. Na₂SO₄ solution, filtered and the solvent was evaporated to give a crude residue that was purified using preparative HPLC to give the title compound as pale yellow syrup. Yield : 0.012 g (28%). LC/MS m/z : 325.28 (M+H)⁺ ¹H NMR (300 MHz, CDCl₃) δ 7.26 - 7.38 (m, 4 H) 7.17 (d, 1 H) 2.63 (br. s., 7 H) 2.39 (s, 3 H) 2.14 (br. s., 2 H) 2.06 (s, 2 H) 1.83 (br. s., 4 H) 1.66 (d, 2 H) 1.60 (s, 2 H) 1.45 - 1.52 (m, 3 H)
- 15

The following examples were prepared from the appropriate amide using the same procedure as for example C1.

Ex.	amide	Product/Name	Analytical Data
C2		 <i>N</i> -((3-phenyladamantan-1-yl)methyl)piperidin-4-amine	^1H NMR (300 MHz, CDCl_3) δ 7.26 - 7.38 (m, 4 H) 7.12 - 7.20 (m, 1 H) 3.19 - 3.33 (m, 1 H) 3.13 (s, 1 H) 2.68 - 2.88 (m, 3 H) 2.54 - 2.68 (m, 1 H) 2.25 - 2.37 (m, 2 H) 2.16 (br. s., 2 H) 1.99 (d, 1 H) 1.75 - 1.92 (m, 4 H) 1.38 - 1.75 (m, 10 H). LC/MS m/z : 325.34 ($\text{M}+\text{H}$) $^+$
C3		 <i>N</i> -((3-methyl-5-phenyladamantan-1-yl)methyl)piperidin-4-amine	^1H NMR (300 MHz, CDCl_3) δ 7.25 - 7.38 (m, 4 H) 7.11 - 7.19 (m, 1 H) 3.13 (dt, 2H) 2.57 - 2.71 (m, 2H) 2.41 - 2.55 (m, 1 H) 2.34 (s, 2H) 2.16 - 2.26 (m, 1H) 1.83 - 1.94 (m, 2H) 1.77 (br. s., 2H) 1.47 - 1.63 (m, 4 H) 1.37 - 1.47 (m, 4H) 1.15 - 1.36 (m, 4H) 0.88 (s, 3H). LC/MS m/z : 339.38 ($\text{M}+\text{H}$) $^+$

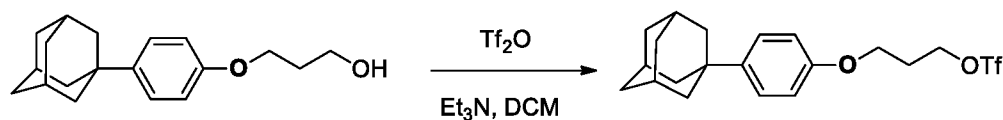
Example C4: 1-(3-(4-(adamantan-1-yl)phenoxy)propyl)-4-methylpiperidine

Step 1: 3-(4-(adamantan-1-yl)phenoxy)propan-1-ol



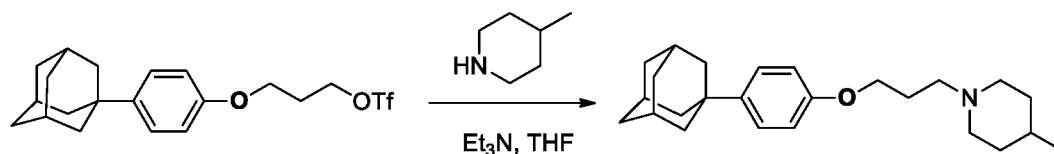
To a solution of 4-(adamantan-1-yl)phenol (0.456 g, 2 mmol) in DMF (2 mL) was added 1-bromopropanol (0.305 g, 2.2 mmol) followed by K_2CO_3 (0.414 g, 3 mmol) and resulting reaction mixture was stirred at 80°C for 6 h. Solvent was evaporated, and residue was extracted with ethyl acetate (2 x 10 mL) and washed with water (1 x 10 mL). Dried (Na_2SO_4), filtered and evaporation of solvent under vacuum gave crude residue, which was purified by SiO_2 column chromatography to give the title compound as a white solid. Yield : 0.253 g (44%).

Step 2: 3-(4-(adamantan-1-yl)phenoxy)propyl trifluoromethanesulfonate



To a solution of 3-(4-(adamantan-1-yl)phenoxy)propan-1-ol (0.143 g, 0.5 mmol) in DCM (5 mL) was added Et_3N (0.101 g, 1 mmol) and cooled to 0°C . Then Tf_2O (0.225 g, 0.8 mmol) was added dropwise. Brought to room temperature gradually and stirred overnight. Reaction mixture was washed quickly with water (2 mL). Dried (Na_2SO_4), filtered and evaporation of solvent gave crude product as syrup, which was used as such in the next step. Yield : 0.208 g (100%).

Step 3: 1-(3-(4-(adamantan-1-yl)phenoxy)propyl)-4-methylpiperidine



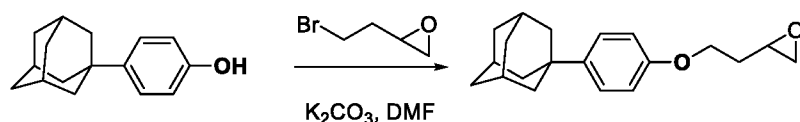
To a solution of 3-(4-(adamantan-1-yl)phenoxy)propyl trifluoromethanesulfonate (0.021 g, 0.05mmol) in THF (0.5 mL) was added 4-methylpiperidine (0.010 g, 1 mmol) followed by Et₃N (0.010 g, 1 mmol) and resulting reaction mixture was stirred at room temperature for 12h. Solvent was evaporated, and residue was purified using preparative HPLC to give the title compound as pale yellow syrup. Yield : 0.007 g (39%). LC/MS m/z: 368.36 (M+H)⁺ ¹H NMR (300 MHz, CDCl₃) δ 7.19 - 7.28 (m, 2 H) 6.78 - 6.85 (m, 2 H) 3.98 (t, 2 H) 3.03 (d, 2 H) 2.62 (t, 2 H) 2.06 (br. s., 6 H) 1.86 (d, 6 H) 1.59 - 1.80 (m, 8 H) 1.39 (br. s., 2 H) 0.93 (d, 3 H).

The following examples were prepared as described for examples C4 using the appropriate amines.

Ex.	Amine	Structure/Name	Analytical Data
C5		 1-(3-(4-(adamantan-1-yl)phenoxy)propyl)piperidine	¹ H NMR (300 MHz, CDCl ₃) δ 7.21 (d, 2 H) 6.81 (d, 2 H) 3.99 (t, 2 H) 2.61 - 2.81 (m, 4 H) 2.10 - 2.23 (m, 2 H) 2.06 (br. s., 3 H) 1.83 - 1.89 (m, 6 H) 1.65 - 1.83 (m, 10 H) 1.52 (br. s., 2 H). LC/MS m/z: 354.41 (M+H) ⁺
C6		 1-(3-(4-(adamantan-1-yl)phenoxy)propyl)-4-methylpiperazine	¹ H NMR (300 MHz, CDCl ₃) δ 7.24 (d, 2 H) 6.81 (d, 2 H) 3.98 (t, 2 H) 2.78 (br. s., 6 H) 2.66 (t, 2 H) 2.49 (s, 3 H) 1.93 - 2.10 (m, 5 H) 1.82 - 1.89 (m, 6 H) 1.73 (br. s., 6 H). LC/MS m/z: 369.37 (M+H) ⁺

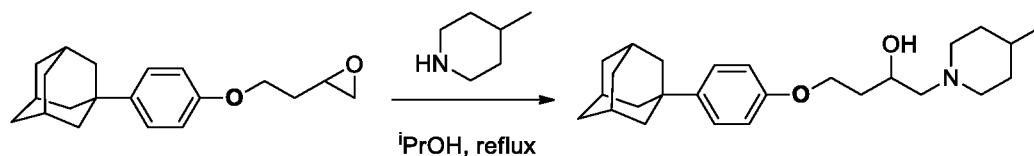
Example C7: 4-(4-(adamantan-1-yl)phenoxy)-1-(4-methylpiperidin-1-yl)butan-2-ol

Step 1: 2-(2-(4-(adamantan-1-yl)phenoxy)ethyl)oxirane



To a solution of 4-(adamantan-1-yl)phenol (0.228 g, 1 mmol) in DMF (2 mL) was added K₂CO₃ (0.276 g, 2 mmol) followed by 2-(2-bromoethyl)oxirane (0.151 g, 1 mmol) and reaction mixture was stirred at 80 °C for 12h. Solvent was evaporated, and residue was extracted with ethyl acetate (2 x 5 mL) and washed with water (1 x 5 mL). Dried (Na₂SO₄), filtered and evaporation of solvent under vacuum gave crude residue, which was purified by SiO₂ column chromatography to give the title compound as a white solid. Yield : 0.224 g (75%).

Step 2: 4-(4-(adamantan-1-yl)phenoxy)-1-(4-methylpiperidin-1-yl)butan-2-ol

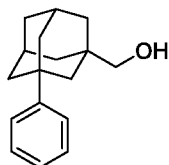


To a solution of 2-(2-(4-(adamantan-1-yl)phenoxy)ethyl)oxirane (0.015 g, 0.05mmol) in iPrOH (0.5 mL) was added 4-methylpiperidine (0.010 g, 1 mmol) and resulting reaction mixture was stirred under
5 reflux for 12h. Solvent was evaporated, and residue was purified using preparative HPLC to give the title compound as an off-white solid. Yield : 0.007 g (36%). LC/MS m/z : 398.43 (M+H)⁺

The following examples were prepared as described for examples C7, step 2 using the appropriate amines.

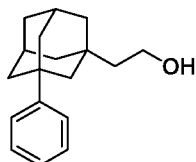
Ex	Amine	Product/Name	Analytical Data
C8		 4-(4-(adamantan-1-yl)phenoxy)-1-(piperidin-1-yl)butan-2-ol	$^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.21 - 7.27 (m, 2 H) 6.80 - 6.87 (m, 2 H) 4.11 (t, 2 H) 3.99 - 4.08 (m, 1 H) 2.75 (d, 2 H) 2.44 - 2.58 (m, 3 H) 2.06 (br. s., 3 H) 1.80 - 1.90 (m, 8 H) 1.61 - 1.80 (m, 10 H) 1.41 - 1.53 (m, 2 H). LC/MS m/z : 384.41 (M+H) ⁺
C9		 4-(4-(adamantan-1-yl)phenoxy)-1-(4-methylpiperazin-1-yl)butan-2-ol	LC/MS m/z : 399.39 (M+H) ⁺

10 (3-Phenyladamantan-1-yl)methanol



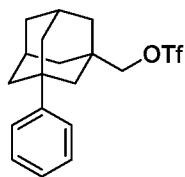
The title compound was prepared by LAH reduction of 3-phenyladamantane-1-carboxylic acid (A. Koperniku, I. Papanastasiou, G. B. Foscolos, A. Tsotinis, M. C. Taylor, and J. M. Kelly, *Med. Chem. Commun.* **2013**, 4, 856-859).

15 2-(3-Phenyladamantan-1-yl)ethan-1-ol



The title compound was prepared from 2-(3-phenyladamantan-1-yl)acetic acid in the same manner as described for (3-phenyladamantan-1-yl)methanol.

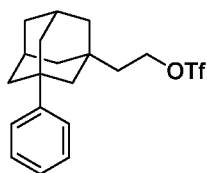
(3-Phenyladamantan-1-yl)methyltrifluoromethanesulfonate



5

The title compound was prepared from (3-phenyladamantan-1-yl)methanol in the same manner as described for Example C4, Step 2.

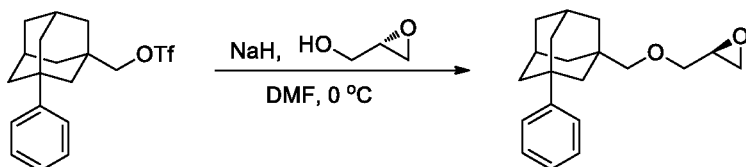
2-(3-Phenyladamantan-1-yl)ethyltrifluoromethanesulfonate



10

The title compound was prepared from 2-(3-phenyladamantan-1-yl)ethan-1-ol in the same manner as described for Example C4, Step 2.

(2S)-2-[(3-phenyladamantan-1-yl)methoxy]methyl}oxirane

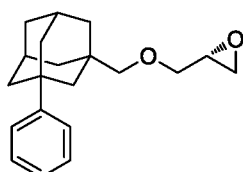


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To a solution of (2S)-oxiran-2-ylmethanol (5.7 mg, 0.061 mmol) in 0.5 mL anhydrous DMF, under N₂ was added NaH (60% w/w in mineral oil, 4 mg, 0.092 mmol) at 0 °C, and the resulting mixture was stirred for 1 h. Then (3-phenyladamantan-1-yl)methyltrifluoromethanesulfonate (23 mg, 0.061 mmol) in 0.3 mL anhydrous DMF was added at 0 °C. The reaction mixture was stirred at 50 °C overnight, then diluted with EtOAc and washed with water. The organic phase was dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by SiO₂ column chromatography (hexanes / EtOAc from 6:1 to 4:1) to give 5 mg (28%) of the product as a colorless oil.

20

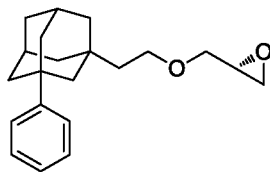
(2R)-2-[(3-phenyladamantan-1-yl)methoxy]methyl}oxirane



The title compound was prepared from (3-phenyladamantan-1-yl)methyltrifluoromethanesulfonate and (2R)-oxiran-2-ylmethanol in the same manner as described above for (2S)-2-[(3-phenyladamantan-1-yl)methoxy]methyl}oxirane.

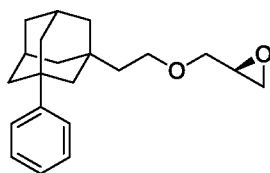
25

(2S)-2-{{2-(3-phenyladamantan-1-yl)ethoxy}methyl}oxirane



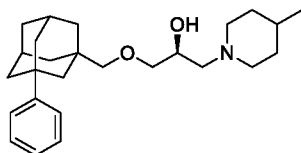
The title compound was prepared from 2-(3-phenyladamantan-1-yl)ethyltrifluoromethanesulfonate and (2S)-oxiran-2-ylmethanol in the same manner as described above for (2S)-2-{{(3-phenyladamantan-1-yl)methoxy}methyl}oxirane.

(2R)-2-{{2-(3-phenyladamantan-1-yl)ethoxy}methyl}oxirane



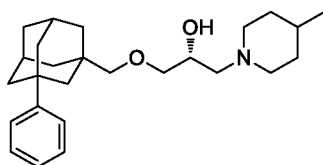
The title compound was prepared from 2-(3-phenyladamantan-1-yl)ethyltrifluoromethanesulfonate and (2R)-oxiran-2-ylmethanol in the same manner as described above for (2S)-2-{{(3-phenyladamantan-1-yl)methoxy}methyl}oxirane.

Example C10: (2S)-1-(4-methylpiperidin-1-yl)-3-[(3-phenyladamantan-1-yl)methoxy]propan-2-ol



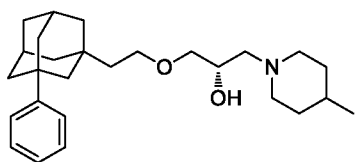
The title compound was prepared from (2S)-2-{{(3-phenyladamantan-1-yl)methoxy}methyl}oxirane and 4-methylpiperidine in the same manner as described for Example C7, Step 2. LC/MS *m/z*: 398.36 (M+H)⁺.

Example C11: (2R)-1-(4-methylpiperidin-1-yl)-3-[(3-phenyladamantan-1-yl)methoxy]propan-2-ol



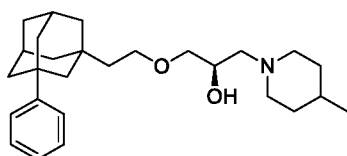
The title compound was prepared from (2R)-2-{{(3-phenyladamantan-1-yl)methoxy}methyl}oxirane and 4-methylpiperidine in the same manner as described for Example C7, Step 2. LC/MS *m/z*: 398.38 (M+H)⁺.

Example C12: (2S)-1-(4-methylpiperidin-1-yl)-3-[2-(3-phenyladamantan-1-yl)ethoxy]propan-2-ol



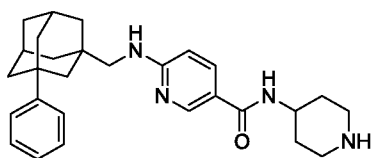
The title compound was prepared from (2*S*)-2-([2-(3-phenyladamantan-1-yl)ethoxy]methyl)oxirane and 4-methylpiperidine in the same manner as described for Example C7, Step 2. LC/MS *m/z*: 412.32 (*M*+*H*)⁺.

5 Example C13: (2*R*)-1-(4-methylpiperidin-1-yl)-3-[2-(3-phenyladamantan-1-yl)ethoxy]propan-2-ol

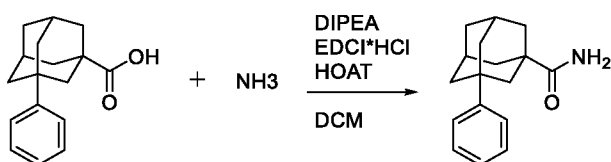


The title compound was prepared from (2*R*)-2-([2-(3-phenyladamantan-1-yl)ethoxy]methyl)oxirane and 4-methylpiperidine in the same manner as described for Example C7, Step 2. LC/MS *m/z*: 412.29 (*M*+*H*)⁺.

10 Example C14: 6-[[3-(3-phenyladamantan-1-yl)methyl]amino]-*N*-(piperidin-4-yl)pyridine-3-carboxamide

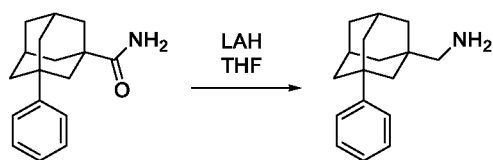


Step 1: 3-phenyladamantane-1-carboxamide



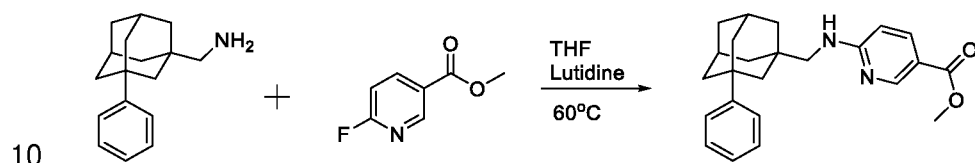
To a solution of 3-phenyladamantane-1-carboxylic acid (300 mg, 1.17 mmol) in dichloromethane (5 mL) is added diisopropylethylamine (610 mg, 3.51 mmol), HOAT (206mg, 1.52 mmol), and EDCI*HCl (290mg, 1.52 mmol). Finally, 2.8 mL of a 0.5 M solution of ammonia (1.4 mmol) in dioxane is added, and the mixture is stirred overnight. The mixture is then diluted with DCM, washed 3X with 1 M HCl, dried over sodium sulfate, and evaporated. The crude product is purified via flash column using ethyl acetate as the eluent to give 180 mg of the title compound as a white solid. LC/MS *m/z*: 256.18 (*M*+*H*)⁺, 297.27 (*M*+*H*+CH₃CN)⁺, 511.39 (2*M*+*H*)⁺

Step 2: (3-phenyladamantan-1-yl)methanamine



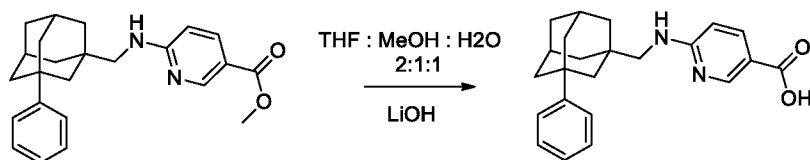
To a solution of 3-phenyladamantan-1-carboxamide (180 mg, 0.71 mmol) in THF (5 mL) was slowly added 0.9 mL of a 2.4M solution of lithium aluminum hydride in THF. The mixture was heated to reflux and stirred overnight. After completion, the reaction was cooled in an ice bath and 80 μ L water, followed by 80 μ L 15% NaOH, and finally 0.24 mL water were added successively, and stirring was continued for one hour at room temperature. The formed precipitate was filtered off and the filtrate was evaporated, giving 165 mg of the title compound as clear oil that was not purified further. LC/MS m/z : 242.22 ($M+H$)⁺, 283.26 ($M+H+CH_3CN$)⁺

Step 3: methyl 6-(((3-phenyladamantan-1-yl)methyl)amino)nicotinate



To a solution of (3-phenyladamantan-1-yl)methanamine (30 mg, 0.12 mmol) in THF (1 mL) was added 23 mg (0.15 mmol) of methyl 6-fluoronicotinate and 0.021 mL (0.18 mmol) of 2,6-lutidine. The mixture was heated to reflux and stirred overnight, then diluted with ethyl acetate and washed 2X with water, dried with brine and sodium sulfate, and evaporated to give the crude product. Purification on flash column using 1:1 hexanes:ethyl acetate eluent gave 41 mg of the title compound as a white solid. LC/MS m/z : 377.33 ($M+H$)⁺, 418.29 ($M+H+CH_3CN$)⁺

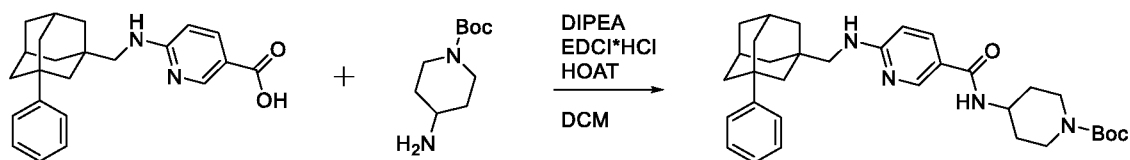
Step 4: 6-(((3-phenyladamantan-1-yl)methyl)amino)nicotinic acid



To 40 mg of methyl 6-(((3-phenyladamantan-1-yl)methyl)amino)nicotinate was added 1 mL of solvent THF:MeOH:water (2:1:1) mixture, followed by 10 mg of LiOH. Stirring was continued for 2 hours and all solvents are then evaporated. The residue was dissolved in 1M HCl and extracted 4X with ethyl acetate. The organics were dried with sodium sulfate and evaporated to give 35 mg of the title compound as a white solid, requiring no further purification. LC/MS m/z : 363.27 ($M+H$)⁺, 404.35 ($M+H+CH_3CN$)⁺

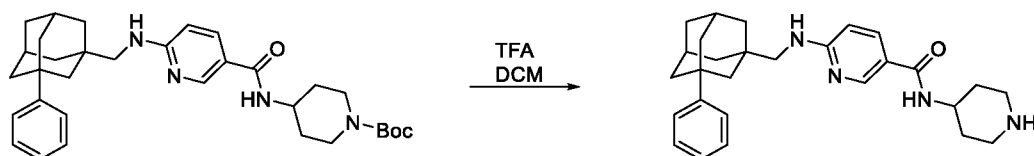
Step 5: *tert*-butyl 4-(6-(((3-phenyladamantan-1-yl)methyl)amino)nicotinamido)piperidine-1-carboxylate

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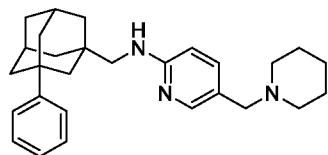
To a solution of 6-((3-phenyladamantan-1-yl)methyl)amino)nicotinic acid (15 mg, 0.04 mmol) in dichloromethane (1 mL) was added diisopropylethylamine (0.022 mL, 0.13 mmol), HOAT (7 mg, 0.052 mmol), and EDCI·HCl (10 mg, 0.052 mmol). Finally, *tert*-butyl 4-aminopiperidine-1-carboxylate (10 mg, 0.052 mmol) was added, and the mixture was stirred overnight. The reaction was then diluted with DCM, washed 2X with water, dried over sodium sulfate, and evaporated. The crude product was purified via flash column using 1:1 hexanes:ethyl acetate as eluent, giving 18 mg of the title compound as a white solid. LC/MS *m/z*: 545.48 (M+H)⁺, 586.47 (M+H+CH₃CN)⁺

Step 6: 6-((3-phenyladamantan-1-yl)methyl)amino)-N-(piperidin-4-yl)nicotinamide

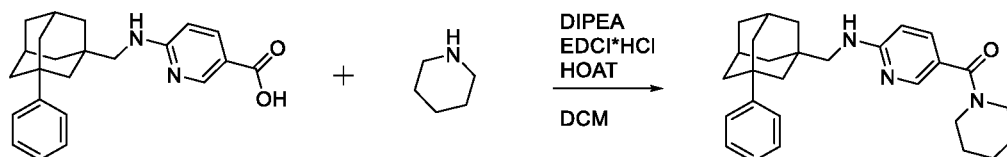


To 18 mg of the protected amine was added 0.25 mL of dichloromethane and 0.25 mL of TFA. The mixture was stirred for 2 h and all volatiles are evaporated. The residue was dissolved in methanol, passed through an Agilent PL-HCO₃ ion exchange column to remove remaining TFA, and evaporated to give 10.5 mg of the title compound requiring no further purification. LC/MS *m/z*: 445.39 (M+H)⁺

Example C15: *N*-[(3-phenyladamantan-1-yl)methyl]-5-(piperidin-1-ylmethyl)pyridin-2-amine



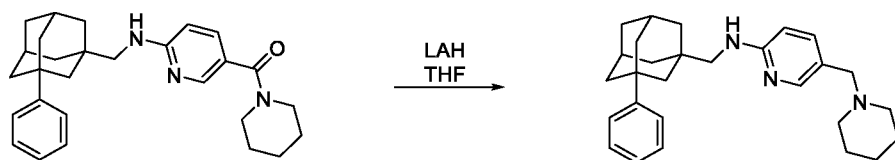
Step 1: (6-((3-phenyladamantan-1-yl)methyl)amino)pyridin-3-yl)(piperidin-1-yl)methanone



The title compound was prepared from 6-((3-phenyladamantan-1-yl)methyl)amino)pyridine-3-carboxylic acid and piperidine using the procedure from example C14, Step 5. LC/MS *m/z*: 430.37 (M+H)⁺, 471.49 (M+H+CH₃CN)⁺, 859.75 (2M+H)⁺

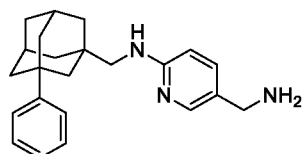
Step 2: *N*-[(3-phenyladamantan-1-yl)methyl]-5-(piperidin-1-ylmethyl)pyridin-2-amine

132

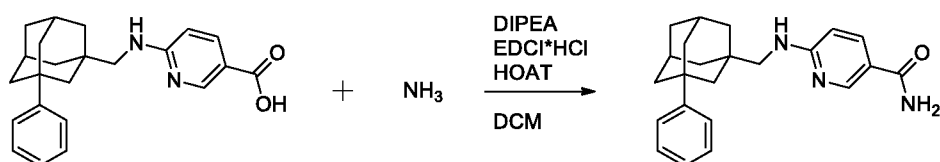


The title compound was prepared from 6-((3-phenyladamantan-1-yl)methyl)amino)pyridin-3-yl)(piperidin-1-yl)methanone using the procedure from example C14, Step 2. LC/MS m/z : 416.31 (M+H)⁺

5 Example C16: 5-(aminomethyl)-N-[(3-phenyladamantan-1-yl)methyl]pyridin-2-amine

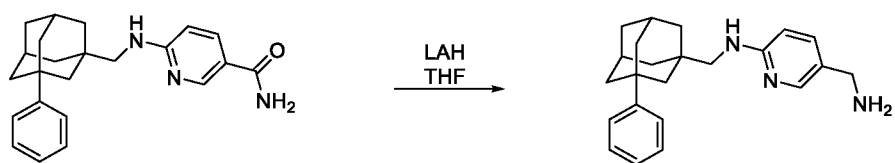


Step 1: 6-((3-phenyladamantan-1-yl)methyl)amino)nicotinamide



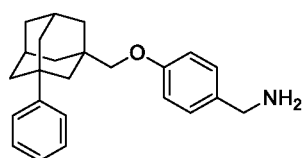
10 The title compound was prepared from 6-((3-phenyladamantan-1-yl)methyl)amino)nicotinic acid and ammonia using the procedure for example C14, Step 1. LC/MS m/z : 362.17 (M+H)⁺, 403.39 (M+H+CH₃CN)⁺,

Step 2: 5-(aminomethyl)-N-((3-phenyladamantan-1-yl)methyl)pyridin-2-amine



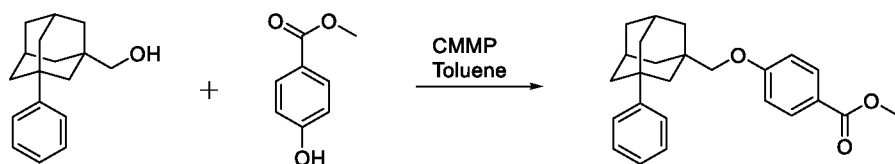
15 The title compound was prepared from 6-((3-phenyladamantan-1-yl)methyl)amino)nicotinamide using the procedure from example C14, Step 2. LC/MS m/z : 348.26 (M+H)⁺

Example C17: {4-[(3-phenyladamantan-1-yl)methoxy]phenyl}methanamine



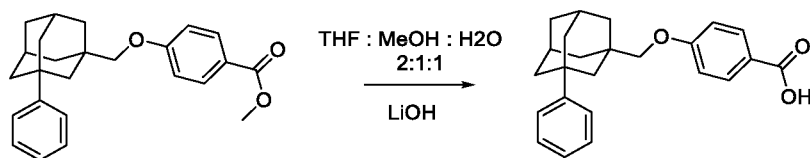
Step 1: methyl 4-((3-phenyladamantan-1-yl)methoxy)benzoate

133



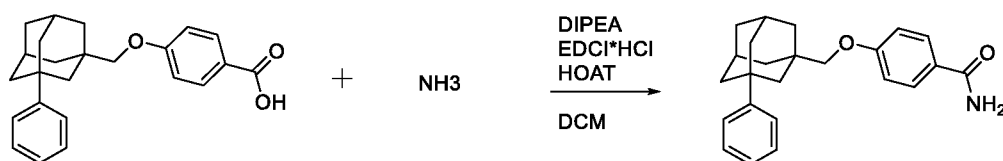
To a flame dried flask was added toluene (1 mL), (3-phenyladamantan-1-yl)methanol (30 mg, 0.12 mmol), methyl-4-hydroxybenzoate (20 mg, 0.12 mmol), and 0.5 mL of a 0.5M (cyanomethylene) trimethyl phosphorane solution in THF. The mixture was brought to reflux and stirred overnight, then diluted with ethyl acetate, washed 2X with water, dried with brine and sodium sulfate, and evaporated. The crude residue was purified by flash column using 9:1 hexanes:ethyl acetate as eluent to give 22 mg of the title compound as a clear oil. ¹H NMR (500MHz, CDCl₃) δ: 7.98 (d, 2H), 7.39 (d, 2H), 7.33 (t, 2H), 7.19 (t, 1H), 6.91 (d, 2H), 3.88 (s, 3H), 3.64 (s, 2H), 2.25 (br:s, 1H), 1.93 (q, 4H), 1.83 (br:s, 2H), 1.76 (d, 5H)

10 Step 3: 4-((3-phenyladamantan-1-yl)methoxy)benzoic acid



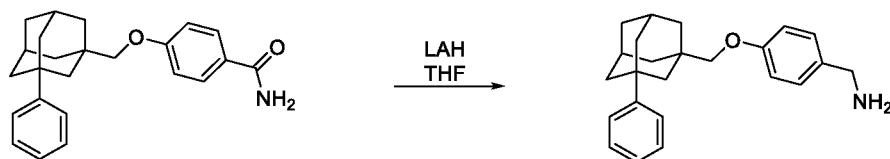
The title compound was prepared from methyl 4-((3-phenyladamantan-1-yl)methoxy)benzoate using the procedure from example C14, Step 4.

Step 4: 4-((3-phenyladamantan-1-yl)methoxy)benzamide



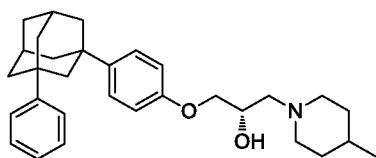
The title compound was prepared from 4-((3-phenyladamantan-1-yl)methoxy)benzoic acid using the procedure from example C14, Step 1. LC/MS *m/z*: 362.07 (M+H)⁺, 403.30 (M+H+CH₃CN)⁺

Step 5: {4-[(3-phenyladamantan-1-yl)methoxy]phenyl}methanamine

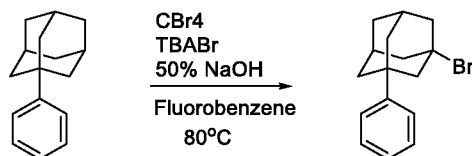


The title compound was prepared from 4-((3-phenyladamantan-1-yl)methoxy)benzamide using the procedure from example C14, Step 2. LC/MS *m/z*: 348.30 (M+H)⁺, 331.31 (M-NH₂)⁺

Example C18: (2S)-1-(4-methylpiperidin-1-yl)-3-[4-(3-phenyladamantan-1-yl)phenoxy]propan-2-ol

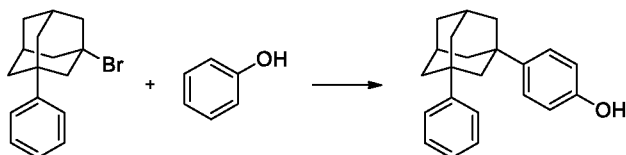


Step 1: 1-bromo-3-phenyladamantane



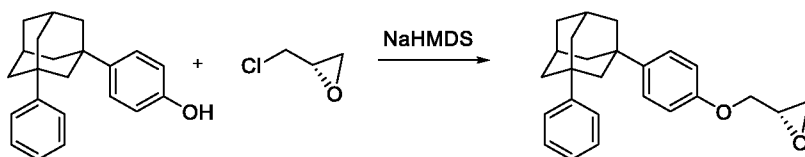
- To a solution of phenyladamantane (100 mg, 0.47 mmol) in fluorobenzene (1.5 mL) was added
 5 carbon tetrabromide (240 mg) and tetrabutylammonium bromide (10 mg). The mixture is stirred until
 homogenous, and 1 mL of a 50% (w/w) aqueous NaOH solution is added. The mixture is heated to
 80°C overnight, cooled to rt, and diluted with water. The mixture is extracted 3X with DCM, and the
 organic layer dried with brine and sodium sulfate. The crude product is purified by flash column with
 pure hexanes as eluent to give 48 mg of the title compound as an off-brown solid. ¹³C NMR (125
 10 MHz, CDCl₃) δ: 148.93, 128.57, 126.37, 124.90, 66.21, 54.57, 48.66, 41.50, 34.96, 32.91

Step 2: 4-(3-phenyladamantan-1-yl)phenol



- To 50 mg (0.17 mmol) of 1-bromo-3-phenyladamantane was added phenol (160 mg, 1.7 mmol). The
 reaction was then heated to 120°C with vigorous stirring for 14 hours and allowed to cool to room
 15 temperature. The solid residue was dissolved in methanol, cooled to 0°C, and water was added until a
 precipitate forms. The formed solid is filtered off, washed with ice cold methanol and water, and dried
 by air suction giving 20 mg of the title compound as an off-brown solid. ¹H NMR (500 MHz, CDCl₃) δ
 7.39 (d, 2H), 7.327 (t, 2H), 7.27 (d, 2H), 7.19 (t, 1H) 6.79 (d, 2H), 4.62 (br:s, 1H), 2.3 (br:s, 2H), 2.0 (s,
 2H), 1.94 (dd, 9H), 1.78 (br:s, 2H)

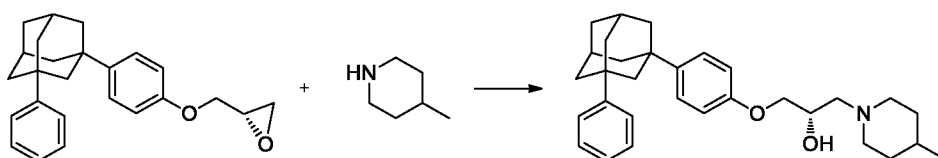
20 Step 3: (2S)-2-[4-(3-phenyladamantan-1-yl)phenoxy]methyloxirane



To a solution of 4-(3-phenyladamantan-1-yl)phenol (32 mg, 0.1 mmol) in THF (1 mL) is added
 NaHMDS (22 mg, 0.12 mmol). The mixture is brought to reflux for 10 minutes, and (S)-epichlorohydrin
 (50 mg, 0.50 mmol) is added in one portion. Reflux is continued overnight, and then all volatiles are

evaporated. The residue was partitioned between ethyl acetate and water, washed 2X with water, then brine, dried over sodium sulfate, and evaporated. The crude product was purified by silica gel flash column with 90:10 hexanes:ethyl acetate as eluent, giving 20 mg of the title compound as a yellow oil. ¹H NMR (500MHz, CDCl₃) δ: 7.40 (d, 2H), 7.32 (t, 4H), 7.19 (t, 1H), 6.88 (d, 2H), 4.18 (dd, 1H), 3.99-3.95 (m, 1H), 3.34 (m, 1H), 2.90 (t, 1H), 2.76-2.74 (m, 1H), 2.31 (br:s, 2H), 2.01 (s, 2H), 1.94 (dd, 9H), 1.78 (br:s, 2H)

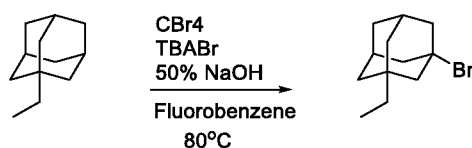
Step 4: (2S)-1-(4-methylpiperidin-1-yl)-3-[4-(3-phenyladamantan-1-yl)phenoxy]propan-2-ol



To a solution of (2S)-2-[4-(3-phenyladamantan-1-yl)phenoxy]methyloxirane (20 mg, 0.056 mmol) in isopropanol (1 mL) is added triethylamine (0.012 mL, 0.083 mmol) and 4-methylpiperidine (10 uL, 0.083 mmol). The mixture was brought to reflux and stirred overnight. After cooling, all volatiles are evaporated and the crude residue is added directly to a small silica flash column using first ethyl acetate and then 95:5 DCM:MeOH as eluents, giving 10.8 mg of the title compound as a viscous oil. LC/MS *m/z*: 460.41 (M+H)⁺

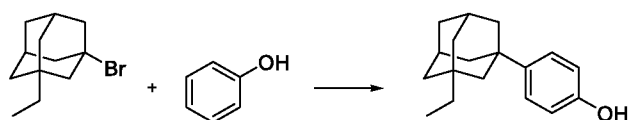
Example C19: (S)-1-(4-(3-ethyladamantan-1-yl)phenoxy)-3-(4-methylpiperidin-1-yl)propan-2-ol

Step 1: 1-bromo-3-ethyladamantane



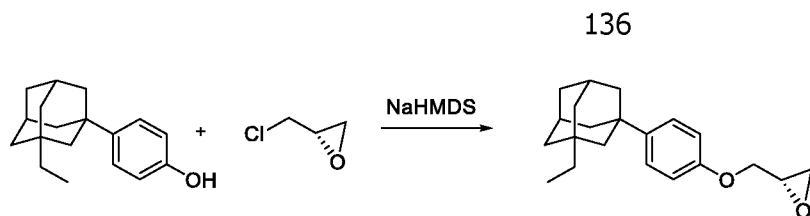
The title compound was prepared from ethyladamantane using the procedure from example C18, Step 1.

Step 2: 4-(3-ethyladamantan-1-yl)phenol



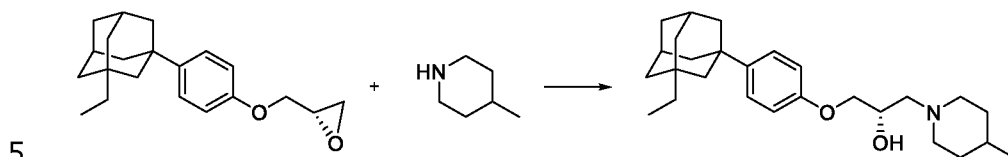
The title compound was prepared from 1-bromo-3-ethyladamantane and phenol using the procedure from example C18, Step 2.

Step 3: (S)-2-((4-(3-ethyladamantan-1-yl)phenoxy)methyl)oxirane



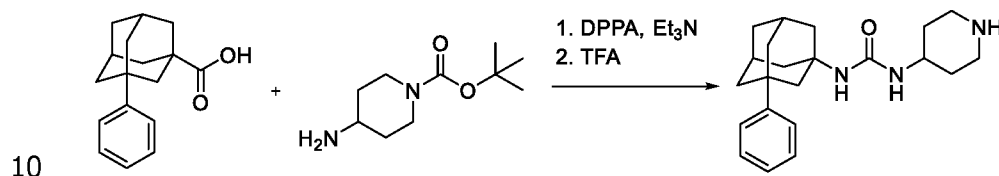
The title compound was prepared from 4-(3-ethyladamantan-1-yl)phenol and (S)-epichlorohydrin using the procedure from example C18, Step 3.

Step 4: (S)-1-(4-((3-ethyladamantan-1-yl)phenoxy)-3-(4-methylpiperidin-1-yl)propan-2-ol



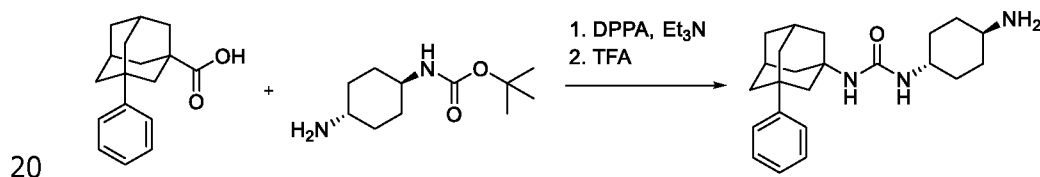
The title compound was prepared from (S)-2-((4-(3-ethyladamantan-1-yl)phenoxy)methyl)oxirane and 4-methylpiperidine using the procedure from example C18, step 4. LC/MS m/z : 412.36 (M+H)⁺

Example E1: 3-(3-phenyladamantan-1-yl)-1-(piperidin-4-yl)urea



To a solution of 3-phenyladamantan-1-carboxylic acid (0.064 g, 0.25 mmol) in toluene (0.75 mL) was added Et₃N (0.04 mL, 0.29 mmol) followed by diphenylphosphorylazide (0.060 mL, 0.28 mmol) and the resulting reaction mixture was stirred at 70°C for 2 h. It was cooled to room temperature, then *tert*-butyl-4-aminopiperidine-1-carboxylate (0.050 g, 0.25 mmol) was added and the mixture was stirred at room temperature overnight. The solvent was evaporated, and the residue was dissolved in DCM (0.5 mL). TFA (0.2 mL) was added and the mixture was stirred for 2 h. The solvent was evaporated and the crude residue was purified by preparative HPLC to give the title compound as an off-white solid. Yield: 9.1 mg (10.3%). LC/MS m/z : 354.36 (M+H)⁺

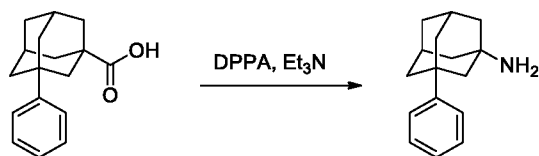
Example E2: 1-(4-aminocyclohexyl)-3-(3-phenyladamantan-1-yl)urea



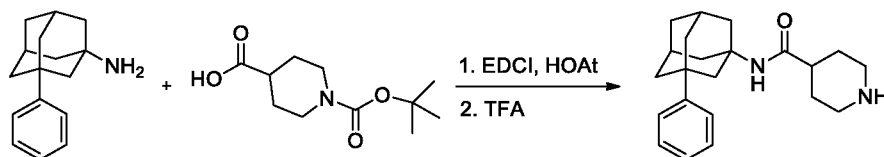
The title compound was prepared following the same procedure as described for example E1, using the appropriate amine. Yield: 10.1 mg (11%). LC/MS m/z : 409.19 (M+H+CH₃CN)⁺

Example E3: *N*-(3-phenyladamantan-1-yl)piperidine-4-carboxamide

Step1: 3-phenyladamantan-1-amine



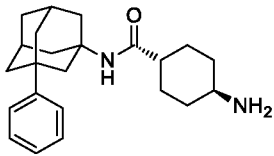
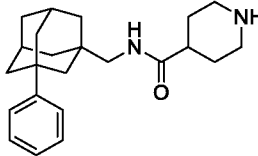
To a solution of 3-phenyladamantan-1-carboxylic acid (0.064 g, 0.25 mmol) in toluene (0.75 mL) was added Et₃N (0.04 ml, 0.29 mmol) followed by diphenylphosphoryl azide (0.060 ml, 0.28 mmol) and the resulting reaction mixture was stirred at 70 °C for 2 h. After cooling to rt, aq. NaHCO₃ solution was added and the mixture was stirred for 0.5 h, and extracted with ethyl acetate (2 mL). The organic extract was dried (Na₂SO₄), filtered and concentrated to give the title compound which was used without purification in the next step.

Step 2: *N*-(3-phenyladamantan-1-yl)piperidine-4-carboxamide

To a solution of *N*-BOC-piperidine-4-carboxylic acid (0.057 g, 0.25 mmol) in DCM (1 mL) was added EDCI.HCl (0.059 g, 0.30 mmol) followed by DIEA (0.06 ml, 0.29 mmol). The mixture was stirred for 0.5 h, then 3-phenyladamantan-1-amine obtained from step 1 was added and the resulting mixture was stirred for 3 h, then TFA was added and stirring was continued for 2 h. The solvent was evaporated and the crude residue was purified by preparative HPLC to give the title compound as a syrup. Yield: 1.5 mg (1.8%). LC/MS *m/z*: 339.40 (M+H)⁺

Examples E4 to E6 were prepared as described for example E3 using the appropriate amine and carboxylic acid.

Ex.	Starting materials	Product	Analytical Data
E4	3-phenyladamantan-1-amine 2-{1-[(<i>tert</i> -butoxy) carbonyl]piperidin-4-yl}acetic acid	 <i>N</i> -(3-phenyladamantan-1-yl)-2-(piperidin-4-yl)acetamide	¹ H NMR (300 MHz, CDCl ₃) δ 7.26 - 7.37 (m, 4 H) 7.13 - 7.21 (m, 1 H) 5.16 (br. s., 1 H) 4.29 (d, 1 H) 3.47 (s, 0.5 H) 3.05 (s, 0.5 H) 2.84 (d, 1 H) 2.27 (br. s., 2 H) 2.13 (s, 2 H) 2.02 (d, 4 H) 1.72 - 1.96 (m, 6 H) 1.68 (br. s., 3 H) 1.59 (s, 4 H). LC/MS <i>m/z</i> : 353.49 (M+H) ⁺

E5	3-phenyladamantan-1-amine	 <i>trans</i> -4-amino- <i>N</i> -(3-phenyladamantan-1-yl)cyclohexane-1-carboxamide	¹ H NMR (300 MHz, CDCl ₃) δ 8.22 (br. s., 2 H) 7.25 - 7.36 (m, 4 H) 7.12 - 7.20 (m, 1 H) 3.05 - 3.41 (m, 1 H) 2.15 - 2.36 (m, 3 H) 1.96 - 2.15 (m, 10 H) 1.71 - 1.96 (m, 3 H) 1.34 - 1.71 (m, 6 H). LC/MS <i>m/z</i> : 394.48 (M+H+CH ₃ CN) ⁺
	<i>trans</i> -4-[[<i>tert</i> -butoxy)carbonyl]amino]cyclohexane-1-carboxylic acid		
E6	(3-phenyladamantan-1-yl)methanamine	 <i>N</i> -[(3-phenyladamantan-1-yl)methyl]piperidine-4-carboxamide	LC/MS <i>m/z</i> : 353.37 (M+H) ⁺
	1-[(<i>tert</i> -butoxy)carbonyl]piperidine-4-carboxylic acid		

In some embodiments, the invention provides for methods of treating infection by members of the *Filoviridae* family, which includes without limitation *Ebolavirus*, *Marburgvirus*, *Cuevavirus*, or any newly emerging filovirus genera. Five species of *Ebolavirus* have been identified: Zaire (EBOV), Bundibugyo (BDBV), Tai Forest (TAFV), Sudan (SUDV), and Reston (RESTV). Two species of Marburgvirus have been identified: (MARV) and Ravn (RAVV). One species of Cuervavirus has currently been identified: Lloviu virus (LLOV).

In some embodiments, the compounds of the invention can selectively inhibit *Ebolavirus* infection. Infection by *Ebolavirus* in humans leads to Ebola Hemorrhagic Fever (EHF), the clinical manifestations of which are severe and/or fatal. The incubation period varies between four and sixteen days. The initial symptoms are generally a severe frontal and temporal headache, generalized aches and pains, malaise, and by the second day the victim will often have a fever. Later symptoms include watery diarrhea, abdominal pain, nausea, vomiting, a dry sore throat, and anorexia. By day seven of the symptoms, the patient will often have a maculopapular (small slightly raised spots) rash. At the same time the person may develop thrombocytopenia and hemorrhagic manifestations, particularly in the gastrointestinal tract, and the lungs, but it can occur from any orifice, mucous membrane or skin site. *Ebolavirus* infections may cause lesions in almost every organ, although the liver and spleen are the most noticeably affected. Both are darkened and enlarged with signs of necrosis. The cause of death (>75% in most outbreaks) is normally shock, associated with fluid and blood loss into the tissues. The hemorrhagic and connective tissue complications of the disease are not well understood, but may be related to onset of disseminated intra-vascular coagulation. Infectious virus may linger in some tissues of some infected individuals for weeks and months after the initial infection.

In some embodiments, the compounds of the invention may inhibit *Marburgvirus* infection. Marburg hemorrhagic fever (MHF) is a severe type of hemorrhagic fever associated with *Marburgvirus*

infection, which affects both humans and non-human primates. The case-fatality rate for MHF was approximately 70% in a recent Angola outbreak. After an incubation period of 5-10 days, the onset of the disease is sudden and is marked by fever, chills, headache, and myalgia. Around the fifth day after the onset of symptoms, a maculopapular rash, most prominent on the trunk (chest, back, stomach), may occur. Nausea, vomiting, chest pain, a sore throat, abdominal pain, and diarrhea then may appear. Symptoms become increasingly severe and may include jaundice, inflammation of the pancreas, severe weight loss, delirium, shock, liver failure, massive hemorrhaging, and multi-organ dysfunction.

In some embodiments, the compounds of the invention may inhibit *Cuervavirus* infection or infections with any newly emerging filovirus.

In some embodiments, the compounds of the invention may inhibit infection by any virus, whether native or engineered, whose cell entry process is mediated by filovirus or hybrid filovirus glycoproteins.

Exemplary kits

The invention also includes kits. The kit has a container housing an inhibitor of the invention and optionally additional containers with other therapeutics such as antiviral agents or viral vaccines. The kit also includes instructions for administering the component(s) to a subject who has or is at risk of having an enveloped viral infection.

In some aspects of the invention, the kit can include a pharmaceutical preparation vial, a pharmaceutical preparation diluent vial, and inhibitor. The vial containing the diluent for the pharmaceutical preparation is optional. The diluent vial contains a diluent such as physiological saline for diluting what could be a concentrated solution or lyophilized powder of inhibitor. The instructions can include instructions for mixing a particular amount of the diluent with a particular amount of the concentrated pharmaceutical preparation, whereby a final formulation for injection or infusion is prepared. The instructions may include instructions for use in an oral formulation, inhaler, intravenous injection or any other device useful according to the invention. The instructions can include instructions for treating a patient with an effective amount of inhibitor. It also will be understood that the containers containing the preparations, whether the container is a bottle, a vial with a septum, an ampoule with a septum, an infusion bag, and the like, can contain indicia such as conventional markings which change color when the preparation has been autoclaved or otherwise sterilized.

INCORPORATION BY REFERENCE

All publications and patents mentioned herein are hereby incorporated by reference in their entirety as if each individual publication or patent was specifically and individually indicated to be incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.

Protocol A for pseudotype inhibitory testing of compounds.

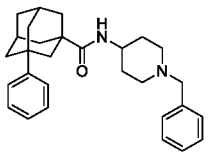
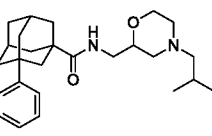
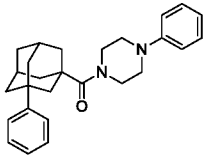
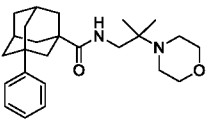
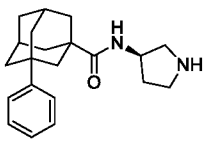
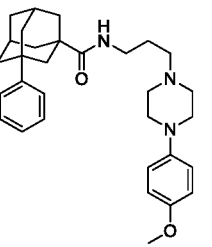
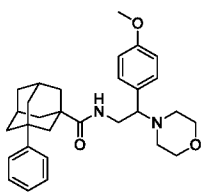
Utilizing a VSV pseudotype system, EBOV or BDBV mucin-domain-deleted glycoproteins were expressed along with the *Renilla* luciferase reporter gene to screen a library collection of small molecule compounds to identify individual compounds that inhibit infectivity of these VSV filovirus-GP pseudotyped viruses and not VSV expressing the native VSV glycoprotein [Cote, M.; Misasi, J.; Ren, T.; Bruchez, A.; Lee, K.; Filone, C. M.; Hensley, L.; Li, Q.; Ory, D.; Chandran, K.; Cunningham, J. T.; Bruchez, A.; Lee, K.; Filone, C. M.; Hensley, L.; Li, Q.; Ory, D.; Chandran, K.; Cunningham, J. *Small molecule inhibitors reveal Niemann-Pick C1 is essential for Ebola virus infection*, Nature (2011) 477: 344-348; Chandran, K.; Sullivan, N. J.; Felbor, U.; Whelan, S.P.; Cunningham, J.M. *Endosomal proteolysis of the Ebola virus glycoprotein is necessary for infection*, Science 2005 308:1643-1645]. For select compounds, similar pseudotyped viruses expressing **full-length** EBOV [Genbank: AAB81004], SUDV [Genbank: YP_138523.1], MARV [Genbank: AAC40460] or Lassa virus [Genbank: NP_694870] (a member of the *Arenaviridae* family of viruses) glycoproteins were also tested to further determine the specificity of action of our compounds against full length glycoproteins within and between different virus families. Vero cells (ATCC: CCL-81) were grown in clear 384 well plates (3000 cells/well) in DMEM media with 10% FBS, 1X Pen-Strep, non-essential amino acids and L-glutamine. After incubating overnight at 37°C and 5% CO₂, cells were treated with compounds at desired concentrations and pseudotyped virus in assay media. VSV viruses expressing the full-length VSV glycoprotein, as well as all pseudotyped VSV viruses expressing the other viral glycoproteins, were generated in cultured HEK-293T cells (ATCC CRL-3216) grown in 10 cm dishes in DMEM supplemented with 10% FBS, 1X Pen-Strep, non-essential amino acids, L-glutamine and 500 µg/mL G418 antibiotic. When cells reached approximately 80% confluency, they were transfected with a mixture of 15 µg of the pCAGGS plasmid encoding one of the desired glycoproteins and 45 µl of PEI (polyethylenimine) transfection reagent. The cells were incubated with the solution for 5 hours at 37°C at 5% CO₂. The cells were then washed and the mixture replaced with supplemented DMEM and incubated at 37°C at 5% CO₂ for approximately 16-18 hours. Subsequently cells were infected with approximately 50 µl of VSV parent pseudotype virus lacking VSV glycoprotein and containing the gene for luciferase. The cells were infected for 1 hour, then washed 1X with PBS and incubated in supplemented media. 24 hours post-infection, supernatant was collected, aliquoted and stored at -80°C. For VSV-Luciferase pseudotypes, one aliquot was thawed and tested in a serial dilution for luminescence activity in Vero cells as described in the Luciferase assay protocol (below). Each of the viral supernatants generated was diluted (from 1:100 to 1:2000) to give similar luminescence signal / background values of ≥ 200 and stored at -80°C as aliquots for later use. Assay media consisted of 50% Opti-MEM, 50% DMEM, with 1% FBS, Pen-Strep, non-essential amino acids and L-glutamine. Final DMSO concentration in the compound testing wells was kept $\leq 1\%$ and control wells were treated with assay media and 1% DMSO. Cells were incubated for 24 hours at 37°C and 5% CO₂. The compound-virus mixture was aspirated off the cells 24 hours post-infection and washed 1X with PBS. Cells were lysed using 20 µl of lysis buffer from a Luciferase kit diluted according to manufacturer's (Thermo Scientific) instructions. After incubating for approximately 20 minutes, 5 µl of cell lysate was transferred to an opaque white plate and mixed with 12.5 µl of Coelenterazine diluted in buffer. This mixture was incubated at room temperature for 10 minutes on a plate shaker, and then the luminescence was read using a plate reader (Beckman Coulter DTX 880 multimode detector with an

emission of 535 nm) Luminescence signals were obtained for compound containing and control wells to determine % activity (inhibition of luciferase signal) for each compound.

To identify filovirus inhibitors a library collection of commercial compounds was initially tested at a 5 or 10 μ M concentration against the EBOV pseudotype virus and selected compounds were tested against BDBV pseudotyped viruses to facilitate identification of broader-spectrum filovirus inhibitors. In order to distinguish between inhibitory activities of the compounds on filovirus cell entry from those potentially resulting from cellular cytotoxicity and/or inhibition of the replication of VSV virus or luciferase reporter, selected compounds were tested in cytotoxicity assays (see cytotoxicity assay methods below) and/or against parent VSV virus, which expresses the native VSV glycoprotein (rather than a filovirus glycoprotein). Compounds exhibiting inhibitory activity against the EBOV and BDBV pseudotype viruses at concentrations ($\geq$ 5-10 fold) below those observed in cytotoxicity and/or parental VSV assays were thereby identified as filovirus cell entry inhibitors. A number of these compounds were selected for prosecution in dose-response experiments and/or additional functional assays (see below) to further characterize their potency and antiviral spectrum of activity.

Tables 5 - 9. Examples. Example (Ex.) compounds from chemical series A, B, C, D, and E including their inhibitory activities (EC_{50} values; the concentration at half-maximal inhibition) are shown against the indicated pseudotyped viruses (EBOV and BDBV) or parental VSV and/or for cytotoxicity, which was evaluated as the % cell viability (% CV) at 3, 5 and/or 10 μ M compound or as the CC_{50} (the concentration inducing half-maximal cell death). Vero cells were infected with dilutions of the viral stocks of the luciferase-expressing EBOV or BDBV pseudotyped viruses, or VSV native viruses (to rule out inhibitors of VSV non-glycoprotein gene products or the luciferase reporter) and incubated for 24 h with or without the example compounds; cells were lysed and luciferase activity read on a Beckman Coulter DTX 880 detector. Compound cytotoxicity was determined to rule out potential false-positive inhibitory activity on filovirus pseudotyped virus cell entry. Compounds exhibiting potential activity against the EBOV and BDBV pseudotyped viruses were more fully characterized in cytotoxicity and/or dose response experiments to confirm activity and determine EC_{50} values. Compounds exhibiting activity against one or more pseudotyped filoviruses without comparable VSV activity or cytotoxicity, indicates they are of potential therapeutic interest to treat filovirus infection. Compounds were serially diluted and added to Vero cells (4000 cells/well) with final DMSO concentration maintained at 1% in growth media consisting of minimal essential media (MEM) with 2% FBS. The plates were incubated at 37 °C for 7 days, and then dead cells were removed by washing with Phosphate buffered saline (PBS). Cells were stained with neutral red vital dye for 1 hour and then de-stained with a solution of 50% ethanol/ 1% acetic acid solution. Absorbance was read at 540 nm and 690 nm on a Spectramax Plus 384 spectrophotometer. Data were analyzed as (540 nm – 690 nm) and then compared to untreated controls to obtain % cell viability.

Table 5

Ex.	Structure	Name	EC ₅₀ (μM)		VSV % inh. at 5 μM	% cell viability at		
			EBOV	BDBV		3 μM	5 μM	10 μM
B1		<i>N</i> -(1-benzylpiperidin-4-yl)-3-phenyladamantane-1-carboxamide	0.44	0.77	<20	ND	62	ND
B2		<i>N</i> -{[4-(2-methylpropyl)morpholin-2-yl]methyl}-3-phenyladamantane-1-carboxamide	0.57	0.93	ND	100	ND	97
B3		1-phenyl-4-[(3-phenyladamantan-1-yl)carbonyl]piperazine	0.61	>5	ND	ND	83	ND
B4		<i>N</i> -[2-methyl-2-(morpholin-4-yl)propyl]-3-phenyladamantane-1-carboxamide	0.69	2.69	ND	100	ND	114
B5		3-phenyl- <i>N</i> -[(3 <i>R</i>)-pyrrolidin-3-yl]adamantane-1-carboxamide	0.79	0.56	<20	ND	97	ND
B6		<i>N</i> -{3-[4-(4-methoxyphenyl)piperazin-1-yl]propyl}-3-phenyladamantane-1-carboxamide	0.92	1.6	ND	75	ND	25
B7		<i>N</i> -[2-(4-methoxyphenyl)-2-(morpholin-4-yl)ethyl]-3-phenyladamantane-1-carboxamide	3.2	3.1	ND	112	ND	95

B8		<i>N</i> -[2-(morpholin-4-yl)-2-(thiophen-2-yl)ethyl]-3-phenyladamantane-1-carboxamide	3.6	4.6	ND	103	ND	90
B9		<i>N</i> -(1-benzylpiperidin-4-yl)-3-chloroadamantane-1-carboxamide	3.8	3.1	ND	112	ND	104
B10		<i>N</i> -cyclopropyl-2-{4-[(3-phenyladamantan-1-yl)carbonyl]piperazin-1-yl}acetamide	<5	ND	<20	ND	ND	ND
B11		<i>N</i> -{1-azabicyclo[2.2.2]octan-3-yl}-3-(4-methylphenyl)adamantane-1-carboxamide	<5	ND	<20	ND	92	ND
B12		3,5-dimethyl- <i>N</i> -[2-(piperidin-1-yl)ethyl]adamantane-1-carboxamide	5.0	ND	<20	ND	90	ND
B13		1-benzyl-4-[(3-(4-methylphenyl)adamantan-1-yl)carbonyl]piperazine	>5	>5	<20	ND	ND	ND
B14		1-methyl-4-[(3-(4-methylphenyl)adamantan-1-yl)carbonyl]piperazine	5.6	ND	<20	ND	95	ND
B15		<i>N</i> -(1-benzylpiperidin-4-yl)adamantane-1-carboxamide	5.9	3.9	ND	99	ND	98
B16		1-ethyl-4-[(3-(4-methylphenyl)adamantan-1-yl)carbonyl]piperazine	1.0	0.9	ND	ND	ND	ND

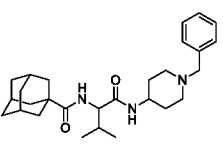
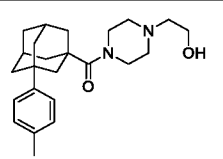
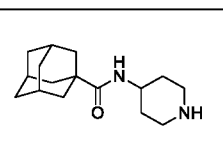
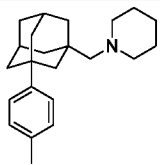
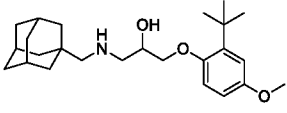
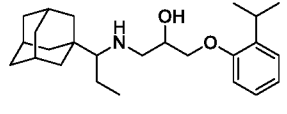
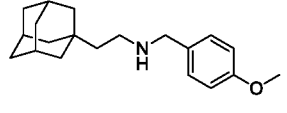
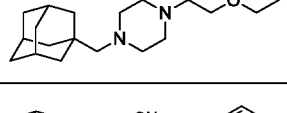
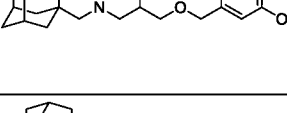
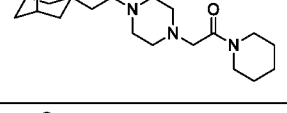
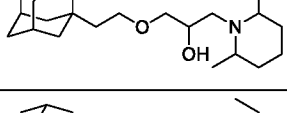
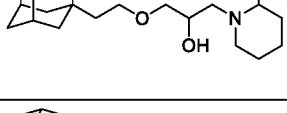
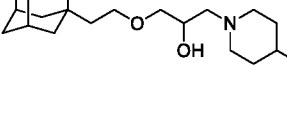
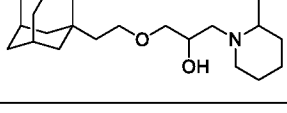
B17		2-(adamantan-1-ylformamido)-N-(1-benzylpiperidin-4-yl)-3-methylbutanamide	>5	<5	ND	ND	ND	ND
B18		2-(4-([3-(4-methylphenyl)adamantan-1-yl]carbonyl)piperazin-1-yl)ethan-1-ol	>5	>5	ND	ND	ND	ND
B19		N-(piperidin-4-yl)adamantane-1-carboxamide	1.1	>1	ND	ND	ND	ND

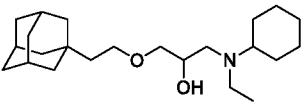
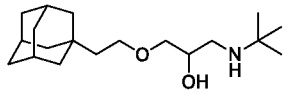
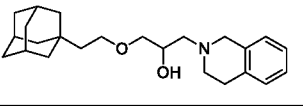
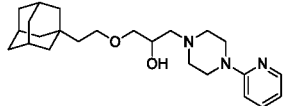
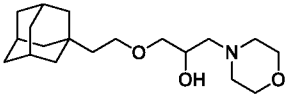
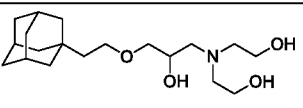
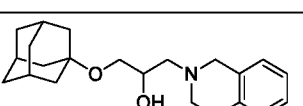
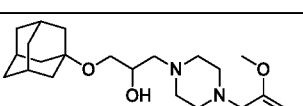
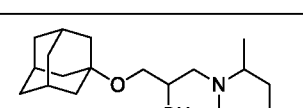
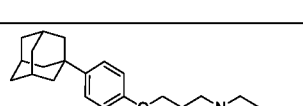
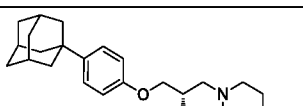
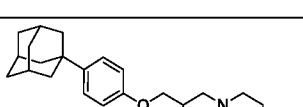
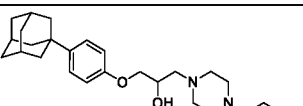
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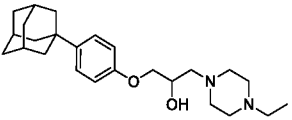
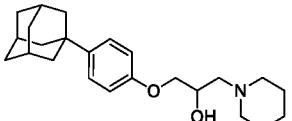
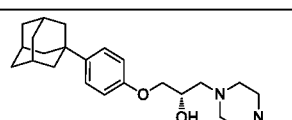
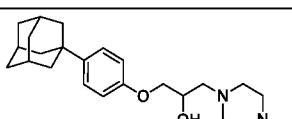
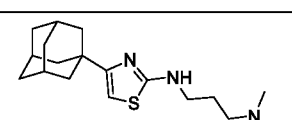
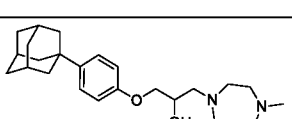
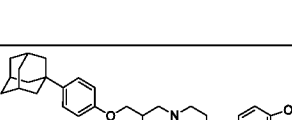
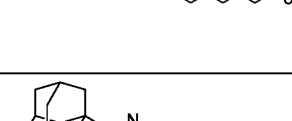
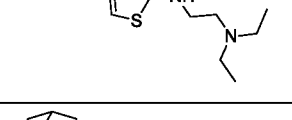
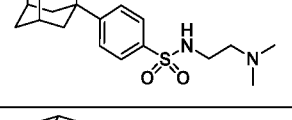
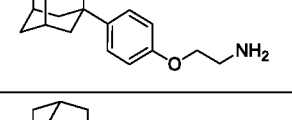
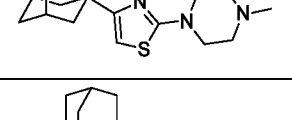
Ex.	EC ₅₀ (μM)		CC ₅₀ (μM)	Ex.	EC ₅₀ (μM)		CC ₅₀ (μM)	Ex.	EC ₅₀ (μM)		CC ₅₀ (μM)
	EBOV	BDBV			EBOV	BDBV			EBOV	BDBV	
A1	0.22	0.25	5.8	A50	2.9	3.3	54.9	A99	0.69	0.19	26.7
A2	0.30	0.39	8.5	A51	9.0	>10	10	A100	0.22	0.18	6.3
A3	0.03	1.24	>3	A52	4.9	4.0	>10	A101	>1	>1	ND
A4	0.19	1.24	>3	A53	9.2	9.0	ND	A102	0.12	0.21	29
A5	1.4	3.9	>3	A54	4.0	10.0	>10	A103	0.07	0.28	7.9
A6	0.21	0.25	16.8	A55	2.9	2.6	>10	A104	0.06	0.22	66
A7	0.48	0.84	>10	A56	3.1	10.0	>10	A105	0.14	1.05	35
A8	0.19	0.22	>10	A57	2.9	>10	ND	A106	>1	>1	ND
A9	0.23	0.29	10.8	A58	0.65	8.0	>10	A107	0.046	0.30	14.7
A10	0.24	0.21	6.9	A59	1.1	1.5	ND	A108	0.025	0.21	16.5
A11	0.2	0.23	ND	A60	0.21	0.17	ND	A109	0.080	0.93	37
A12	0.36	0.43	2.5	A61	0.14	0.08	>10	A110	0.021	0.19	17.5
A13	0.32	0.32	2.3	A62	0.16	0.11	30	A111	0.018	0.15	10.7
A14	0.2	0.23	6.2	A63	0.08	0.08	>10	A112	0.037	0.26	7.2
A15	1.7	2.6	>10	A64	0.71	0.18	>10	A113	>1	>1	ND
A16	0.11	0.35	12.9	A65	0.09	0.09	>10	A114	>1	>1	ND
A17	0.93	0.48	>10	A66	0.16	0.10	>10	A115	0.98	>1	59
A18	>10	>10	ND	A67	0.39	0.41	>10	A116	>1	>1	>100
A19	0.29	0.44	3.9	A68	0.035	0.16	>10	A201	1.1	>1	16.4
A20	0.49	0.41	10.6	A69	0.22	0.24	22.4	A202	0.59	0.96	41.5
A21	>10	>10	ND	A70	0.49	0.19	>50	A203	0.91	1.02	3.9

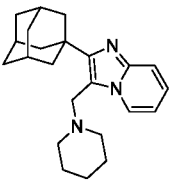
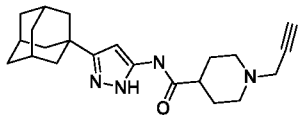
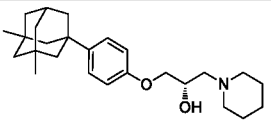
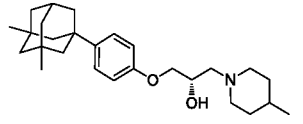
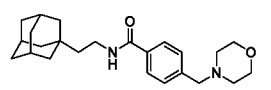
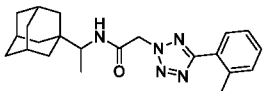
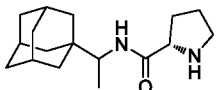
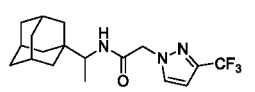
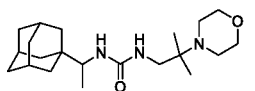
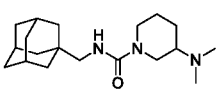
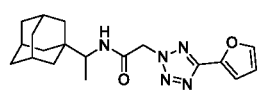
A22	0.26	0.22	ND	A71	0.13	0.13	4.6	A204	>1	>1	>100
A23	0.21	0.17	ND	A72	0.28	0.29	17.4	A205	>1	>1	37
A24	0.29	0.29	7.2	A73	0.32	0.37	13.0	C1	0.18	0.206	5.8
A25	0.45	0.19	>10	A74	1.72	>1	14.0	C2	0.25	0.2	3.6
A26	0.12	0.09	34	A75	0.3	0.3	17.7	C3	0.234	0.21	1.8
A27	0.28	0.14	>10	A76	1.05	1.06	ND	C4	0.14	0.4	7.2
A28	>10	>10	>10	A77	0.12	0.22	8.7	C5	0.14	0.55	14.3
A29	0.34	0.27	5.8	A78	0.02	0.09	ND	C6	0.12	0.64	3.8
A30	0.34	0.22	7.5	A79	0.26	0.29	4.2	C7	0.47	0.77	4.1
A31	>10	>10	>10	A80	0.01	0.05	10.0	C8	0.14	0.29	1.3
A32	0.2	0.26	1.6	A81	0.18	0.11	13.9	C9	0.66	0.99	8.3
A33	0.32	0.3	2.2	A82	0.13	0.16	4.5	C10	0.19	0.17	3.6
A34	0.17	0.22	1.1	A83	0.1	0.18	12.9	C11	0.18	0.11	3.6
A35	0.28	0.22	>10	A84	0.146	0.11	9.0	C12	0.27	0.19	1.2
A36	0.51	0.3	4.3	A85	0.013	0.096	12.1	C13	0.17	0.11	3.6
A37	0.23	0.24	>10	A86	0.155	0.18	3.9	C14	>1	1	3.9
A38	0.25	0.19	>10	A87	0.14	0.19	1.4	C15	>1	0.98	3.9
A39	0.51	0.21	19.1	A88	0.36	0.50	12.5	C16	0.98	0.75	8.0
A40	0.31	0.16	ND	A89	0.25	0.88	40.7	C17	>1	1.2	ND
A41	0.103	0.18	13.6	A90	0.05	0.20	59.0	C18	0.08	0.26	2.7
A42	0.121	0.19	13.9	A91	0.12	0.19	17.4	C19	0.11	0.20	>100
A43	0.14	0.08	1.2	A92	0.19	0.7	10.8	E1	>1	0.77	18.3
A44	0.09	0.19	11.0	A93	0.21	0.36	12.2	E2	0.87	0.61	12.6
A45	0.06	0.14	7.2	A94	1.0	0.88	5.1	E3	>1	0.27	36.3
A46	0.18	0.21	13.5	A95	0.49	0.97	23.1	E4	1.08	0.79	23.1
A47	0.07	0.17	36.2	A96	0.03	0.08	11.6	E5	0.68	0.23	13.3
A48	1.04	2.0	54.9	A97	0.34	0.25	100	E6	0.71	0.20	11.9
A49	0.21	0.29	10	A98	1.16	0.58	11.3				

Table 7

Ex.	Structure	Name	EC ₅₀ (μM)		CC ₅₀ (μM)
			EBOV	BDBV	
D1		1-([3-(4-methylphenyl)adamantan-1-yl]methyl) piperidine	1.3	0.61	>10
D2		(adamantan-1-ylmethyl)[3-(2- <i>tert</i> -butyl-4-methoxyphenoxy)-2-hydroxypropyl]amine	0.68	0.62	ND
D3		[1-(adamantan-1-yl)propyl] ({2-hydroxy-3-[2-(propan-2-yl)phenoxy]propyl})amine	1.29	ND	ND
D4		[2-(adamantan-1-yl)ethyl][(4-methoxyphenyl) methyl]amine	2.19	2.72	>10
D5		1-(adamantan-1-ylmethyl)-4-(2-ethoxyethyl)piperazine	4.6	1.8	>10
D6		(adamantan-1-ylmethyl)({2-hydroxy-3-[(3-methoxyphenyl) methoxy]propyl})amine	3.45	1.5	ND
D7		2-{4-[2-(adamantan-1-yl)ethyl]piperazin-1-yl}-1-(piperidin-1-yl)ethan-1-one	6.0	2.6	ND
D8		1-[2-(adamantan-1-yl)ethoxy]-3-(2,6-dimethylpiperidin-1-yl)propan-2-ol	0.21	0.08	3.8
D9		1-[2-(adamantan-1-yl)ethoxy]-3-(2-ethylpiperidin-1-yl)propan-2-ol hydrochloride	0.25	0.21	ND
D10		1-[2-(adamantan-1-yl)ethoxy]-3-(4-methylpiperidin-1-yl)propan-2-ol	0.32	0.14	15.5
D11		1-[2-(adamantan-1-yl)ethoxy]-3-(2-methyl piperidin-1-yl) propan-2-ol	0.44	0.19	7.5

D12		<i>N</i> -{3-[2-(adamantan-1-yl)ethoxy]-2-hydroxypropyl}- <i>N</i> -ethylcyclohexanamine	0.61	0.49	>3
D13		{3-[2-(adamantan-1-yl)ethoxy]-2-hydroxypropyl}(<i>tert</i> -butyl)amine	0.63	0.67	>10
D14		1-[2-(adamantan-1-yl)ethoxy]-3-(1,2,3,4-tetrahydroisoquinolin-2-yl)propan-2-ol	2.1	2.67	ND
D15		1-[2-(adamantan-1-yl)ethoxy]-3-[4-(pyridin-2-yl) piperazin-1-yl]propan-2-ol	2.9	2.8	ND
D16		1-[2-(adamantan-1-yl)ethoxy]-3-(morpholin-4-yl)propan-2-ol	3.8	3.2	>10
D17		2-({3-[2-(adamantan-1-yl)ethoxy]-2-hydroxypropyl}(2-hydroxyethyl)amino)ethan-1-ol	8.8	0.6	ND
D18		1-(adamantan-1-yloxy)-3-(1,2,3,4-tetrahydroisoquinolin-2-yl)propan-2-ol	>10	ND	ND
D19		1-(adamantan-1-yloxy)-3-[4-(2-methoxyphenyl)piperazin-1-yl]propan-2-ol	>10	ND	ND
D20		1-(adamantan-1-yloxy)-3-(2-methylpiperidin-1-yl)propan-2-ol	>10	ND	ND
D21		1-[4-(adamantan-1-yl)phenoxy]-3-(4-methylpiperidin-1-yl)propan-2-ol	0.05	0.11	1.1
D22		(2 <i>S</i>)-1-[4-(adamantan-1-yl)phenoxy]-3-(4-methylpiperidin-1-yl)propan-2-ol	0.052	0.085	8.5
D23		(2 <i>R</i>)-1-[4-(adamantan-1-yl)phenoxy]-3-(4-methylpiperidin-1-yl)propan-2-ol	0.06	0.077	3.9
D24		1-[4-(adamantan-1-yl)phenoxy]-3-[4-(2-hydroxyethyl)piperazin-1-yl]propan-2-ol	0.08	0.27	4.3

D25		1-[4-(adamantan-1-yl)phenoxy]-3-(4-ethylpiperazin-1-yl)propan-2-ol	0.09	0.24	3.1
D26		1-[4-(adamantan-1-yl)phenoxy]-3-(piperidin-1-yl)propan-2-ol	0.11	0.75	2.3
D27		((2S)-1-[4-(adamantan-1-yl)phenoxy]-3-(4-methylpiperazin-1-yl)propan-2-ol	0.13	0.19	3.5
D28		1-[4-(adamantan-1-yl)phenoxy]-3-(4-methylpiperazin-1-yl)propan-2-ol	0.15	0.21	4.2
D29		(3-[[4-(adamantan-1-yl)-1,3-thiazol-2-yl]amino]propyl) dimethylamine	0.17	0.16	9.4
D30		1-[4-(adamantan-1-yl)phenoxy]-3-(4-methyl-1,4-diazepan-1-yl)propan-2-ol	0.19	0.47	ND
D31		1-[4-(adamantan-1-yl)phenoxy]-3-[4-(2H-1,3-benzodioxol-5-ylmethyl)piperazin-1-yl]propan-2-ol	0.23	1.03	ND
D32		(2-[[4-(adamantan-1-yl)-1,3-thiazol-2-yl]amino]ethyl) diethylamine	0.23	0.17	9.0
D33		4-(adamantan-1-yl)-N-[2-(dimethylamino)ethyl]benzene-1-sulfonamide	0.44	0.42	ND
D34		1-[4-(2-aminoethoxy)phenyl]adamantane	0.43	1.16	3.7
D35		1-[4-(adamantan-1-yl)-1,3-thiazol-2-yl]-4-methylpiperazine	0.44	0.62	ND
D36		4-(adamantan-1-yl)aniline	4.2	6.2	>10

D37		1-[[2-(adamantan-1-yl)imidazo[1,2-a]pyridin-3-yl]methyl]piperidine	8.9	3.2	ND
D38		N-[5-(adamantan-1-yl)-1H-pyrazol-3-yl]-1-(prop-2-yn-1-yl)piperidine-4-carboxamide	3.7	6.8	ND
D39		(2S)-1-[4-(3,5-dimethyladamantan-1-yl)phenoxy]-3-(piperidin-1-yl)propan-2-ol	0.12	0.25	3.2
D40		(2S)-1-[4-(3,5-dimethyladamantan-1-yl)phenoxy]-3-(4-methylpiperidin-1-yl)propan-2-ol	0.19	0.46	2.5
D41		N-[2-(adamantan-1-yl)ethyl]-4-(morpholin-4-ylmethyl)benzamide	2.3	9.7	>3
D42		N-[1-(adamantan-1-yl)ethyl]-2-[5-(2-methylphenyl)-2H-1,2,3,4-tetrazol-2-yl]acetamide	3.2	3.9	>10
D43		(2R)-N-[1-(adamantan-1-yl)ethyl]pyrrolidine-2-carboxamide	4.6	2.5	ND
D44		N-[1-(adamantan-1-yl)ethyl]-2-[3-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide	5.8	2.7	>10
D45		1-[1-(adamantan-1-yl)ethyl]-3-[2-methyl-2-(morpholin-4-yl)propyl]urea	6.5	4.6	>10
D46		N-(adamantan-1-ylmethyl)-3-(dimethylamino)piperidine-1-carboxamide	6.7	4.3	>10
D47		N-[1-(adamantan-1-yl)ethyl]-2-[5-(furan-2-yl)-2H-1,2,3,4-tetrazol-2-yl]acetamide	9.3	5.4	>10

As mentioned above, the EBOV and BDBV glycoproteins expressed in pseudotyped virus assays were missing the mucin domain given that it can contribute to cellular toxicity [Francica, J.R.; Matukonis, M.K.; Bates, P. *Requirements for cell rounding and surface protein down-regulation by Ebola virus glycoprotein*, Virology (2009), 383:237-247]. However, because native *Ebolaviruses*

express glycoproteins that include the mucin domain, we further tested the compounds against native full-length EBOV glycoproteins in pseudotyped viruses (also expressing the Renilla luciferase gene). A representative subset of the compounds exhibiting potent inhibition of the EBOV and BDBV pseudotyped viruses relative to parental VSV (and/or cytotoxicity) were therefore tested against pseudotyped viruses expressing full-length EBOV and SUDV GP to confirm activity against these full length filovirus glycoproteins. In addition, these compounds were also tested against a VSV pseudotyped virus expressing full-length LASV glycoprotein to further define the antiviral activity spectrum of the compounds against both distinct filovirus species as well as other virus families expressing other class I fusion glycoproteins (LASV). As shown in **Table 8**, compounds of the invention exhibited inhibition of *Ebolavirus* glycoprotein pseudotyped viruses but did not exhibit similar inhibition of the parental VSV or pseudotyped LASV viruses (data are a average $\pm$ sd , n = 3 or 4). However, the compound inhibition EC₅₀ values obtained against full-length EBOV and SUDV pseudotyped viruses are comparable to those found for the mucin-deleted EBOV and BDBV pseudotyped viruses. These data further indicate that compounds of the series described herein are inhibitors of filovirus cell entry and as such are inhibitors of filovirus infection.

Table 8

	EC ₅₀ (uM) Pseudotype Assays							Cytotox
Ex.	EBOV	*EBOV _FL	BDBV	SUDV	*MARV	VSV	LASV	CC ₅₀ uM
D8	0.21	0.30	0.08	ND	0.59	3.8	4.9	4
A60	0.26	0.28	0.21	ND	7.9	>10	>10	>10
A68	0.04	0.04	0.17	0.41	2.8	>10	>10	>10
A78	0.02	0.05	0.09	0.21	3.5	>10	>10	>10
A80	0.02	0.04	0.06	0.4	1.1	>10	>10	>10
D32	0.23	0.20	0.17	ND	0.61	>10	>10	>10
D24	0.09	0.08	0.27	2.43	>10	>10	>10	>10
D29	0.17	0.18	0.16	1.44	0.66	>10	>10	>10
A45	0.061	0.12	0.16	ND	0.29	>10	>10	>10
D21	0.05	0.11	0.11	0.41	0.36	3.7	3.0	3.7
A26	0.12	0.16	0.09	ND	2.7	>10	>10	>10
A63	0.08	0.04	0.08	ND	2.8	>10	>10	>10

*EBOV_FL: full-length Ebola Zaire GP, MARV, LASV and VSV are also full-length glycoproteins

As described above, the amino acid homology of full-length MARV and *Ebolavirus* glycoproteins is $\geq 30\%$. To better understand the potential spectrum of activity within the *Filoviridae* family, including the potential activity of compounds against filoviruses more distantly related than EBOV, BDBV and SUDV the compounds listed in **Table 8** were tested against the full-length

Marburgvirus (MARV) pseudotyped virus. In contrast to the nearly equivalent activities and EC₅₀ values observed against EBOV, BDBV and SUDV pseudotyped viruses, most of the compounds exhibited less inhibition against pseudotyped viruses expressing the more distantly related MARV GP. However, at least some compounds inhibited MARV pseudotyped virus with sub-micromolar EC₅₀ concentrations (e.g., compounds D8, D32, D29, A45 and D21). Some compounds such as D8 and D21 appeared to inhibit non-filovirus GP pseudotype viruses including VSV (class III GP) and LASV (class I GP) but only at higher (>10 fold) cytotoxic concentrations. In addition, compounds of the invention, although containing an adamantyl or adamantyl-like group as found in influenza drugs amantadine and rimantidine [Wanka L, Iqbal K and Schreiner PR, *The Lipophilic Bullet Hits the Targets: Medicinal Chemistry of Adamantane Derivatives*, Chem Rev (2013), 113: 3516-3604] did not exhibit any activity against the influenza M2 ion channel or live influenza virus at concentrations of 10 μ M or greater. The results indicate that the compounds and chemical series described herein inhibit the cell entry of a broad range of filoviruses and/or viruses expressing filovirus glycoproteins while exhibiting no similar activity against the glycoproteins from the other enveloped viruses examined.

Protocol B – Native Ebola plaque and viral yield reduction assays. Biosafety Safety Level 2 (BSL2) pseudotyped viruses expressing filovirus GPs were used (above) as surrogates to facilitate the identification of inhibitors of wild-type Biosafety safety level 4 (BSL4) filoviruses, which may only be studied in highly specialized containment facilities. To confirm activity against native BSL4 Ebola virus example compounds were tested against EBOV (Mayinga) in both plaque forming and viral yield reduction (VYR) assay formats (Table 9) under stringent BSL4 testing requirements. In the plaque assay format confluent or near confluent (Vero) cell culture monolayers in 12-well disposable cell culture plates are prepared. Cells are maintained in MEM or DMEM supplemented with 10% FBS. For antiviral assays the same medium is used but with FBS reduced to 2% or less and supplemented with 1% penicillin/streptomycin. The test compound is prepared at four log₁₀ final concentrations in 2X MEM or 2X DMEM. The virus only and cytotoxicity (compound only) controls are run in parallel with each tested compound. Further, a known active drug (favipiravir) is tested as a positive control drug with each test run. Test compounds and positive controls are tested in biological triplicates. The assay is initiated by first removing growth media from the 12-well plates of cells, and infecting cells with 0.01 MOI of virus or about 50 to 100 plaque forming units (pfu). Cells are incubated for 60 min: 100 μ l inoculum/ well, at 37°C, 5% CO₂ with constant gentle rocking. Virus inoculum is removed, cells washed and overlaid with either 1% agarose or 1% methylcellulose diluted 1:1 with 2X MEM and supplemented with 2% FBS and 1% penicillin/streptomycin and supplemented with the corresponding drug concentration. Cells are incubated at 37°C with 5% CO₂ for 10 days. The overlay is removed and plates stained with 0.05% crystal violet in 10% buffered formalin for approximately twenty minutes at room temperature. The plates are washed, dried and the number of plaques counted. The number of plaques in each set of compound dilution is converted to a percentage relative to the untreated virus control. The 50% effective (EC₅₀ virus-inhibitory) concentration is calculated by linear regression analysis. The cytotoxicity assay (In vitro Toxicology Assay Kit, Neutral red based; Sigma) is being performed in parallel in 96-well plates following the manufacturer's instructions. Briefly, growth

medium is removed from confluent cell monolayers and replaced with fresh medium (total of 100 μ l) containing the test compound with the concentrations as indicated for the primary assay. Control wells contain medium with the positive control or medium devoid of compound. A total of up to five replicates are performed for each condition. Plates are incubated for 3, 5, or 10 days at 37°C with 5% CO₂. The plates are stained with 0.033% neutral red for approximately two hours at 37°C in a 5% CO₂ incubator. The neutral red medium is removed by complete aspiration, and the cells rinsed 1X with phosphate buffered solution (PBS) to remove residual dye. The PBS is completely removed and the incorporated neutral red eluted with 1% acetic acid/50% ethanol for at least 30 minutes. Neutral red dye penetrates into living cells: the more intense the red color, the larger the number of viable cells present in the wells. The dye content in each well is quantified using a 96-well spectrophotometer at 540 nm wavelength and 690 nm wavelength (background reading). The 50% cytotoxic (CC₅₀, cell-inhibitory) concentrations are then calculated by linear regression analysis. The quotient of CC₅₀ divided by EC₅₀ gives the selectivity index (SI₅₀) value. The viral yield reduction (VYR) assay format involves similar methodology to that described for the plaque assay format using 12-well plates of cells. Cells are infected and treated with test compound prepared at eight half-log₁₀ final concentration and applied in 1 ml of total volume of liquid media. In parallel compounds are added under similar conditions in the absence of virus for CC₅₀ determination. To quantify virus particles produced tissue culture supernatant (TCS) aliquots are collected at 72 hours, serially diluted in 10-fold increments and added to fresh monolayer of cells overlaid with 1% agarose mixed 1:1 with 2XMEM supplemented with 2% FBS and 1% penicillin, and the number of plaques determined. Test compounds and a positive control (favipiravir) are tested in biological triplicates. Plotting the log₁₀ of the inhibitor concentration versus log₁₀ of virus produced at each concentration allows calculation of the 90% (one log₁₀) effective concentration or EC₉₀ by linear regression. The quotient of CC₅₀ divided by EC₉₀ gives the SI₉₀ selectivity index.

In the plaque assay example compounds showed half-maximal activity (EC₅₀) against the native filovirus (EBOV) at sub (0.89) to low (1.1) micromolar concentrations (Table 9). The SI₅₀ selectivity index (= CC₅₀/EC₅₀) is typically used to determine whether a compound is exhibiting true antiviral inhibitory *in vitro*. Since SI₅₀ values >10 are accepted as confirmation of *bona fide* inhibitory activity against the virus, rather than artifactual activity reflecting cellular cytotoxicity, the data confirm the compounds as inhibitors of live filovirus. As a further test for antifilovirus inhibitory activity the compounds were then tested in a VYR assay where EC₉₀ values (concentration at which 90% virus inhibition is observed) were determined. Compounds exhibiting SI₉₀ (= CC₅₀/EC₉₀) values approaching 10 are thought to represent compounds that are sufficiently active to provide inhibition of viruses in living mammals. As shown in Table 9 the example compounds tested in the VYR assay exhibit 90% of the live BSL4 EBOV (Mayinga) virus at low micromolar (5.6 and 8.9 μ M) concentrations while exhibiting SI₉₀ values approaching 10. By comparison the positive control drug compound favipiravir exhibited EC₉₀ and SI₉₀ values of 333 μ M and 3, respectively. The data from the two independent live virus antiviral assays for the example compounds validate the utilization of pseudotyped virus assays to identify *bona fide* filovirus inhibitors compatible with administration in mammals *in vivo* as a method of treatment for filovirus infection.

Table 9

Example	Assay Format	EC ₅₀ (uM)	SI ₅₀ (CC ₅₀ /EC ₅₀)	EC ₉₀ (uM)	SI ₉₀ (CC ₅₀ /EC ₉₀)
A78	Plaque	1.1	41.5	-	-
	VYR	-	-	5.6	8.2
A80	Plaque	0.89	95.6	-	-
	VYR	-	-	8.9	9.6

Examples 10-12. In addition to the ability of compounds to inhibit live filoviruses *in vitro*, compounds must also have certain drug-like properties for them to be used to inhibit filoviruses and provide methods of treatment for filovirus infection in mammals *in vivo*. Such compounds may exhibit drug-like properties including but not limited to chemical stability against degradation by and lack of inhibition of liver microsomal CYP p450 enzymes, cell permeability and oral bioavailability (if the drug is to delivered orally) and lack of inhibition of the hERG ion channel, which is associated with cardiac safety [Kerns, E.H. Li, D. *Drug-like Properties: Concepts, Structure Design and Methods from ADME to Toxicity Optimization*, (2008) Academic Press, Burlington MA]. To characterize drug-like properties of the chemical series example compounds were evaluated for metabolic stability in human, mouse and monkey liver microsome assays (**Table 10**). Compounds exhibiting half-lives ($T_{1/2}$) > 60 minutes indicate attractive chemical stability. The demonstration of good microsomal stability in human and nonhuman species facilitates the ability to test and optimize compounds in preclinical animal studies. To reduce or prevent serious/life-threatening conditions caused by exposure to lethal or permanently disabling toxic agents where human efficacy trials are not feasible or ethical (such as filovirus infection) the FDA has provided an approach to test and approve drugs using the **Animal Efficacy Rule**; whereby the FDA can rely on evidence from animal studies to provide substantial evidence of product effectiveness. In the absence of an epidemic filovirus outbreak in humans with a sufficiently large patient population efficacy data for new methods of treatment for filovirus infection may only be obtained from relevant animal models (e.g., mouse and monkey efficacy studies). Thus the translation of drug like-properties from one species to another significantly facilitates the testing and development of filovirus inhibitor compounds.

Table 10

Ex.	Microsomal stability $T_{1/2}$ (min)		
	human	Mouse	Monkey
A63	258	>210	237
A68	187	>240	142
A80	103	>120	89
A78	462	267	>120
A85	>120	>120	84

To further characterize compounds of the invention for the inhibition of filoviruses in mammals *in vivo* additional drug-like properties of an example compound (compound **A78**) were determined including solubility, Caco-2 cell permeability, protein binding, Cyp-p450 inhibition and hERG ion channel inhibition (Table 11). The example compound was not an inhibitor of human Cyp-p450 enzymes 1A2, 2B6, 2C9, 2C19, 2D6 while for 3A4 it exhibited an IC₅₀ of ~28 uM for one substrate and > 100 uM for another. The data indicate little if any metabolic liabilities related to Cyp-p450 inhibition (formation of metabolites was measured by LC/MS). In addition, the IC₅₀ for compound A78 against the hERG ion channel was > 10 uM (the highest concentration tested), which indicates attractive cardiac safety properties. Compound **A78** exhibits high protein binding (5 uM test concentration) in PBS, which will factor in for *in vivo* efficacy studies and therapeutic dosing while its solubility at neutral pH is >500 uM, which will facilitate formulation and dissolution *in vivo*. To help determine the potential for oral administration we evaluated the permeability of compound **A78** (5 uM test concentration in PBS in absence or presence of P-gp inhibitor Verapamil) in the Caco-2 *in vitro* model where it demonstrated permeability but was found to be effluxed (ratio of B>A/A>B was 4.32) by P-gP; the addition of verapamil, a known P-gP pump inhibitor, inhibited the efflux to a ratio of less than 1.

Table 11

Turbidimetric solubility (uM)		
Caco-2 Permeability P _{aap} (10 ⁻⁶ cm s ⁻¹)	Mean A>B	3.61
	Mean B>A	15.6
	Efflux ratio	4.32
P-gp substrate ID Caco-2 Permeability (+Verapamil) P _{aap} (10 ⁻⁶ cm s ⁻¹)	Mean A>B	8.47
	Mean B>A	7.45
	Efflux ratio	0.88
PPB fraction bound	Human	97.5%
	Mouse	98.6%
	1A2, 2B6, 2C9, 2C19, 2D9	90 to >100
	3A4 (Testosterone)	28
	3A4 (Midazolam)	>100
hERG IC ₅₀ (uM)		>10

While the P-gP efflux of compound A78 was not ideal, there remained sufficient absorption to justify exploration of an IV/PO PK (intravenous/oral pharmacokinetic) study in mice of compound **A78**. When administered to mice (**Table 12** and **Figure 1**), as either 1 mg/kg IV or 10 mg/kg PO, with analysis of blood plasma samples obtained over a 24 hr period, the example compound was found to demonstrate excellent oral bioavailability (72%), clearance was less than hepatic blood flow and the compound exhibited a half-life of 7.1 hrs and volume of distribution of 14L/kg. These values are consistent with single or twice daily oral dosing.

Table 12

Dose (mg/kg)	t _{1/2} (h)	T _{max} (h)	C _{max} (ng/ml)	AUC _{last} (h·ng/ml)	AUC _{inf} (h·ng/ml)	CI (ml/h·kg)	V _z (ml/kg)	F (%)
1 (IV)	5.4	0.083	129 ± 40	539 ± 23	561	1783	13900	NA ^a
10 (PO)	7.1	6	239 ± 46	3590 ± 576	4040	NC ^b	NC ^b	72

^a NA, not applicable; ^b NC, not calculated.

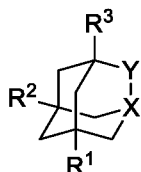
In summary, example compounds of the invention exhibit potencies of i) low nanomolar EC₅₀ activity against pseudotyped viruses expressing a range of filovirus glycoproteins and ii) sub to low uM EC₅₀ and low uM EC₉₀ activities against native BSL4 filovirus with selectivity indices that confirm them as *bona fide* filovirus inhibitors. In addition, drug-like property characterization of example compounds indicate: iii) attractive microsome stability in human, mouse and monkey (potential efficacy models for application of the Animal Efficacy Rule), and other drug-like properties and; iv) mouse PK properties for an example compound were characterized by a long half-life, low clearance and excellent oral bioavailability. These data indicate that the compounds of the invention have sufficient potency and drug-like properties to inhibit filoviruses in mammals *in vivo* as a method of treatment for filovirus infection.

This is further supported by comparisons between favipiravir and compounds of the invention. Favipiravir is a drug that has been evaluated in human clinical trials during the 2014-16 Ebola outbreak with 111 patients in Guinea as a method of treatment for Ebola virus infection. Although this study was not powered to define efficacy and tolerability the results indicated that patients with moderate levels of viremia (below 10⁸ genome copies/mL) responded to the drug (3-4 log drop in viral load) while those with higher levels (>10⁸ genome copies/mL) of viremia did not [Sissoko, D. *Experimental Treatment with Favipiravir for Ebola Virus Disease (the JIKI Trial): A Historically Controlled, Single-Arm Proof-of-Concept Trial in Guinea.* (2016) PLoS Med. 2016 Mar 1;13(3):e1001967]. While efficacy was limited to those in early stages of infection it was likely limited by certain specific properties including potency and chemical stability, i.e., favipiravir's weak potency against EBOV and short half-life in humans (1 - 4 hr). In this context it is useful to compare the potency and dosing characteristics of favipiravir with compounds of the current invention to gauge the potential for their efficacy in inhibiting EBOV infection in mammals including humans. The published EC₅₀ for favipiravir against native EBOV virus has been reported as 67 uM values [Oestereich, L. et al. *Successful treatment of advanced Ebola virus infection with T-705 (favipiravir) in a small animal model.* Antiviral Res. (2014) 105:17-21] whereas EC₅₀ values for example compounds of the invention are ~ 1 uM (67 times more potent than favipiravir). Furthermore, while we have not tested our compounds in humans and cannot yet compare the bioavailability and pharmacokinetic properties of the two compounds in humans to date comparisons of the half-life of favipiravir (1.8 h with 150 mg/kg twice daily oral dosing) [Mentre, F., et al. *Dose regimen of favipiravir for Ebola virus disease.* Lancet Infect. Dis. (2015) 15(2):150-1] versus example compounds of the invention (7 hr half-life with 10 mg/kg single dosing, for compound A78) indicate that compounds of the current invention are significantly more potent than favipiravir and have greater potential to reach higher plasma

concentrations in mammals. These comparisons provide compelling support for the utilization of compounds of the invention to inhibit filoviruses including *in vitro* in mammals and as methods of treatment for filovirus infection in humans.

WHAT IS CLAIMED IS:

1. A method of treating infections associated with viruses of the *Filoviridae* enveloped virus, or any virus expressing filovirus glycoproteins to mediate cell entry comprising administration of a therapeutically effective amount of a compound of Structural Formula I



I

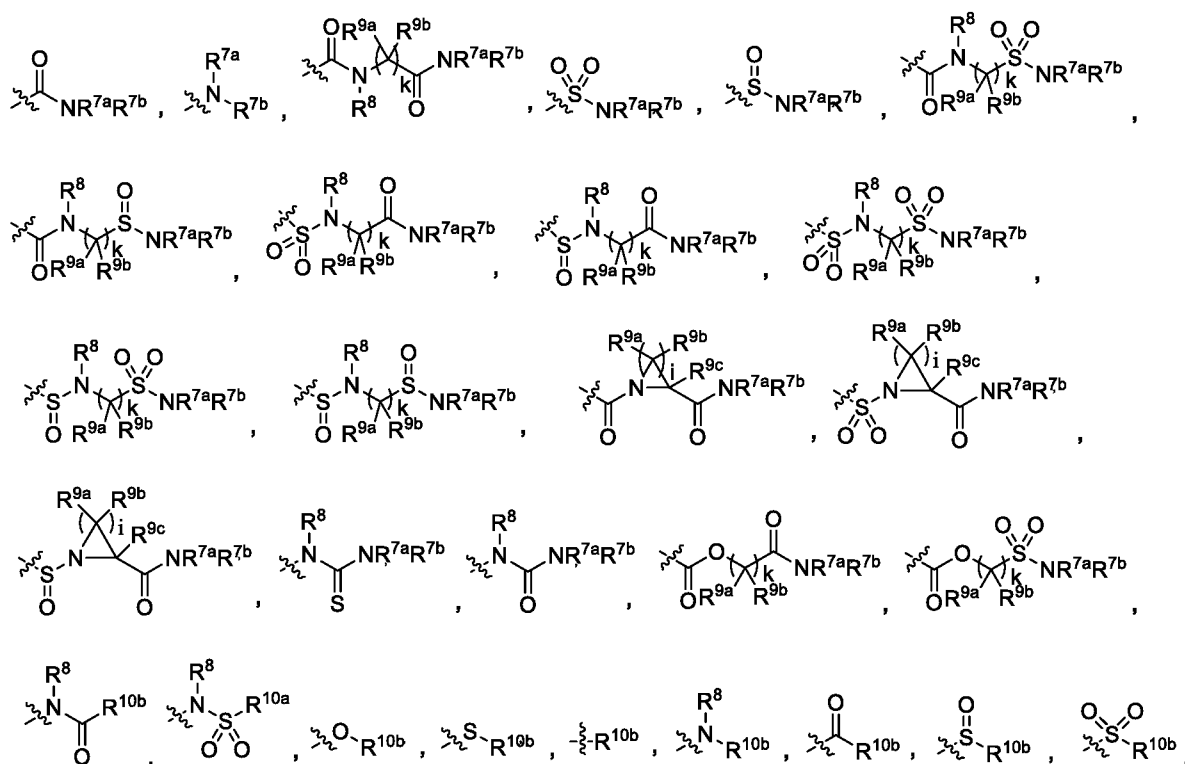
or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

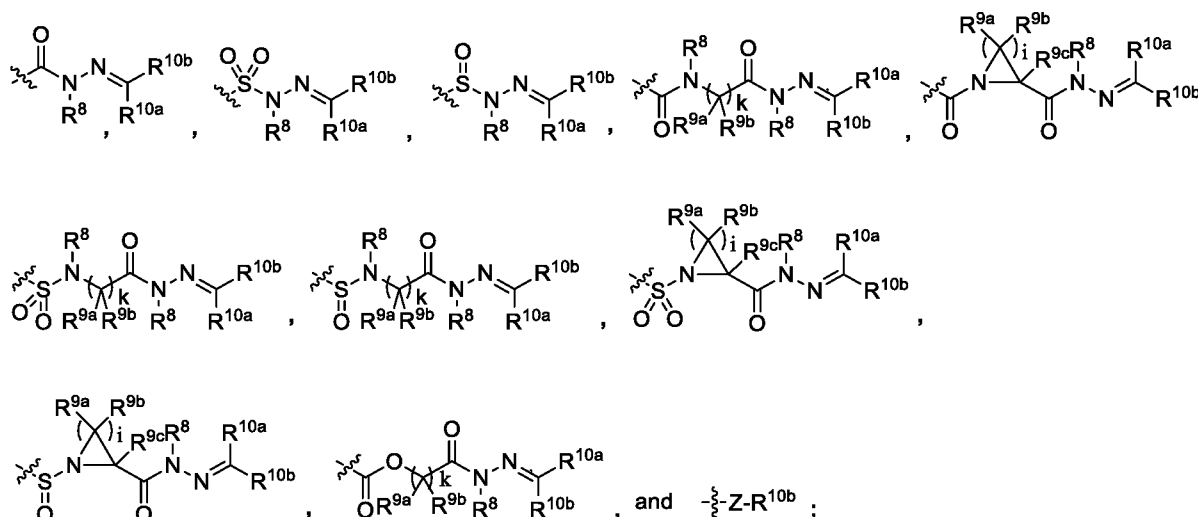
X is C-A-D, and Y is a bond or CR⁴R⁵; or

X is CR⁵ and Y is CR⁴-A-D;

A is -C(R^{6a}R^{6b})_j-, (C₆ to C₁₀) arylene, or (C₂ to C₉) heteroarylene, wherein each of the said (C₆ to C₁₀) arylene or (C₂ to C₉) heteroarylene is optionally substituted with at least one R^{6a} group;

D is selected from the group consisting of





R^1 is selected from hydrogen, halogen, OH, nitro, CF_3 , $-NR^{11a}R^{11b}$, (C_1 to C_{10}) alkyl, (C_1 to C_{10}) alkenyl, (C_1 to C_{10}) alkynyl, (C_1 to C_{10}) alkoxy, aryloxy, cyano, (C_3 to C_{10}) cycloalkyl, (C_5 to C_{10}) cyclo- alkenyl, (C_2 to C_9) cycloheteroalkyl, (C_6 to C_{10}) aryl, (C_2 to C_9) heteroaryl, -
 5 $C(O)R^{12}$, $-C(O)NR^{11a}R^{11b}$, $S(O)_mR^{12}$, $-S(O)_mNR^{11a}R^{11b}$, $-NR^{11a}S(O)_mR^{12}$, $-(CH_2)_nC(O)OR^{12}$, -
 $(CH_2)_nC(O)N(R^{11a}R^{11b})$, $-(CH_2)_nN(R^{11a}R^{11b})$, $-OC(O)R^{12}$, $-NR^{11a}C(O)R^{12}$, and -
 $NR^{11a}C(O)N(R^{11a}R^{11b})$, wherein

each of the said (C_1 to C_{10}) alkyl, (C_1 to C_{10}) alkenyl, (C_1 to C_{10}) alkynyl, (C_1 to C_{10}) alkoxy,
 10 aryloxy, (C_3 to C_{10}) cycloalkyl, (C_5 to C_{10}) cycloalkenyl, (C_2 to C_9) cycloheteroalkyl, (C_6 to C_{10}) aryl,
 and (C_2 to C_9) heteroaryl is optionally substituted with at least one R^{13} group;

R^2 is selected from hydrogen, halogen, OH, nitro, CF_3 , $-NR^{11a}R^{11b}$, (C_1 to C_{10}) alkyl, (C_1 to C_{10}) alkenyl, (C_1 to C_{10}) alkynyl, (C_1 to C_{10}) alkoxy, aryloxy, cyano, (C_3 to C_{10}) cycloalkyl, (C_5 to C_{10}) cyclo- alkenyl, (C_2 to C_9) cycloheteroalkyl, (C_6 to C_{10}) aryl, (C_2 to C_9) heteroaryl, -
 15 $C(O)R^{12}$, $-C(O)NR^{11a}R^{11b}$, $-S(O)_mR^{12}$, $-S(O)_mNR^{11a}R^{11b}$, $-NR^{11a}S(O)_mR^{12}$, $-(CH_2)_nC(O)OR^{12}$, -
 $(CH_2)_nC(O)N(R^{11a}R^{11b})$, $-(CH_2)_nN(R^{11a}R^{11b})$, $-OC(O)R^{12}$, $-NR^{11a}C(O)R^{12}$, and -
 $NR^{11a}C(O)N(R^{11a}R^{11b})$, wherein

each of the said (C_1 to C_{10}) alkyl, (C_1 to C_{10}) alkenyl, (C_1 to C_{10}) alkynyl, (C_1 to C_{10}) alkoxy,
 20 aryloxy, (C_3 to C_{10}) cycloalkyl, (C_5 to C_{10}) cycloalkenyl, (C_2 to C_9) cycloheteroalkyl, (C_6 to C_{10}) aryl,
 and (C_2 to C_9) heteroaryl is optionally substituted with at least one R^{13} group;

R^3 is selected from hydrogen, halogen, OH, nitro, CF_3 , $-NR^{11a}R^{11b}$, (C_1 to C_{10}) alkyl, (C_1 to C_{10}) alkenyl, (C_1 to C_{10}) alkynyl, (C_1 to C_{10}) alkoxy, aryloxy, cyano, (C_3 to C_{10}) cycloalkyl, (C_5 to C_{10}) cycloalkenyl, (C_2 to C_9) cycloheteroalkyl, (C_6 to C_{10}) aryl, (C_2 to C_9) heteroaryl, -
 25 $C(O)R^{12}$, $-C(O)NR^{11a}R^{11b}$, $-S(O)_mR^{12}$, $-S(O)_mNR^{11a}R^{11b}$, $-NR^{11a}S(O)_mR^{12}$, $-(CH_2)_nC(O)OR^{12}$, -
 $(CH_2)_nC(O)N(R^{11a}R^{11b})$, $-(CH_2)_nN(R^{11a}R^{11b})$, $-OC(O)R^{12}$, $-NR^{11a}C(O)R^{12}$, and -
 $NR^{11a}C(O)N(R^{11a}R^{11b})$, wherein

each of the said (C_1 to C_{10}) alkyl, (C_1 to C_{10}) alkenyl, (C_1 to C_{10}) alkynyl, (C_1 to C_{10}) alkoxy,
 aryloxy, (C_3 to C_{10}) cycloalkyl, (C_5 to C_{10}) cycloalkenyl, (C_2 to C_9) cycloheteroalkyl, (C_6 to C_{10}) aryl,
 and (C_2 to C_9) heteroaryl is optionally substituted with at least one R^{13} group;

R^4 is selected from hydrogen, halogen, OH, nitro, CF_3 , $-NR^{11a}R^{11b}$, $(C_1$ to $C_{10})$ alkyl, $(C_1$ to $C_{10})$ alkenyl, $(C_1$ to $C_{10})$ alkynyl, $(C_1$ to $C_{10})$ alkoxy, aryloxy, cyano, $(C_3$ to $C_{10})$ cycloalkyl, $(C_5$ to $C_{10})$ cyclo-alkenyl, $(C_2$ to $C_9)$ cycloheteroalkyl, $(C_6$ to $C_{10})$ aryl, $(C_2$ to $C_9)$ heteroaryl, -
 $C(O)R^{12}$, $-C(O)NR^{11a}R^{11b}$, $-S(O)_mR^{12}$, $-S(O)_mNR^{11a}R^{11b}$, $-NR^{11a}S(O)_mR^{12}$, $-(CH_2)_nC(O)OR^{12}$, -
 5 $(CH_2)_nC(O)N(R^{11a}R^{11b})$, $-(CH_2)_nN(R^{11a}R^{11b})$, $-OC(O)R^{12}$, $-NR^{11a}C(O)R^{12}$, and -
 $NR^{11a}C(O)N(R^{11a}R^{11b})$, wherein

each of the said $(C_1$ to $C_{10})$ alkyl, $(C_1$ to $C_{10})$ alkenyl, $(C_1$ to $C_{10})$ alkynyl, $(C_1$ to $C_{10})$ alkoxy, aryloxy, $(C_3$ to $C_{10})$ cycloalkyl, $(C_5$ to $C_{10})$ cycloalkenyl, $(C_2$ to $C_9)$ cycloheteroalkyl, $(C_6$ to $C_{10})$ aryl, and $(C_2$ to $C_9)$ heteroaryl is optionally substituted with at least one R^{13} group;

10 R^5 is selected from hydrogen, halogen, OH, nitro, CF_3 , $-NR^{11a}R^{11b}$, $(C_1$ to $C_{10})$ alkyl, $(C_1$ to $C_{10})$ alkenyl, $(C_1$ to $C_{10})$ alkynyl, $(C_1$ to $C_{10})$ alkoxy, aryloxy, cyano, $(C_3$ to $C_{10})$ cycloalkyl, $(C_5$ to $C_{10})$ cyclo-alkenyl, $(C_2$ to $C_9)$ cycloheteroalkyl, $(C_6$ to $C_{10})$ aryl, $(C_2$ to $C_9)$ heteroaryl, -
 $C(O)R^{12}$, $-C(O)NR^{11a}R^{11b}$, $-S(O)_mR^{12}$, $-S(O)_mNR^{11a}R^{11b}$, $-NR^{11a}S(O)_mR^{12}$, $-(CH_2)_nC(O)OR^{12}$, -
 15 $(CH_2)_nC(O)N(R^{11a}R^{11b})$, $-(CH_2)_nN(R^{11a}R^{11b})$, $-OC(O)R^{12}$, $-NR^{11a}C(O)R^{12}$, and -
 $NR^{11a}C(O)N(R^{11a}R^{11b})$, wherein

each of the said $(C_1$ to $C_{10})$ alkyl, $(C_1$ to $C_{10})$ alkenyl, $(C_1$ to $C_{10})$ alkynyl, $(C_1$ to $C_{10})$ alkoxy, aryloxy, $(C_3$ to $C_{10})$ cycloalkyl, $(C_5$ to $C_{10})$ cycloalkenyl, $(C_2$ to $C_9)$ cycloheteroalkyl, $(C_6$ to $C_{10})$ aryl, and $(C_2$ to $C_9)$ heteroaryl is optionally substituted with at least one R^{13} group;

20 each of the R^{6a} and R^{6b} is independently selected from hydrogen, halogen, OH, nitro, CF_3 , $-NR^{11a}R^{11b}$, $(C_1$ to $C_{10})$ alkyl, $(C_1$ to $C_{10})$ alkenyl, $(C_1$ to $C_{10})$ alkynyl, $(C_1$ to $C_{10})$ alkoxy, aryloxy, cyano, $(C_3$ to $C_{10})$ cycloalkyl, $(C_5$ to $C_{10})$ cycloalkenyl, $(C_2$ to $C_9)$ cycloheteroalkyl, $(C_6$ to $C_{10})$ aryl, $(C_2$ to $C_9)$ heteroaryl, $-C(O)R^{12}$, $-C(O)NR^{11a}R^{11b}$, $-S(O)_mR^{12}$, $-S(O)_mNR^{11a}R^{11b}$, $-NR^{11a}S(O)_mR^{12}$, -
 $(CH_2)_nC(O)OR^{12}$, $-(CH_2)_nC(O)N(R^{11a}R^{11b})$, $-(CH_2)_nN(R^{11a}R^{11b})$, $-OC(O)R^{12}$, $-NR^{11a}C(O)R^{12}$, and -
 $NR^{11a}C(O)N(R^{11a}R^{11b})$, wherein

25 each of the said $(C_1$ to $C_{10})$ alkyl, $(C_1$ to $C_{10})$ alkenyl, $(C_1$ to $C_{10})$ alkynyl, $(C_1$ to $C_{10})$ alkoxy, aryloxy, $(C_3$ to $C_{10})$ cycloalkyl, $(C_5$ to $C_{10})$ cycloalkenyl, $(C_2$ to $C_9)$ cycloheteroalkyl, $(C_6$ to $C_{10})$ aryl, and $(C_2$ to $C_9)$ heteroaryl is optionally substituted with at least one R^{13} group;

30 each of the R^{7a} and R^{7b} is independently selected from hydrogen, $(C_1$ to $C_{10})$ alkyl, $(C_1$ to $C_{10})$ alkenyl, $(C_1$ to $C_{10})$ alkynyl, $(C_1$ to $C_{10})$ alkoxy, aryloxy, $NR^{11a}R^{11b}$, $(C_3$ to $C_{10})$ cycloalkyl, $(C_5$ to $C_{10})$ cycloalkenyl, $(C_2$ to $C_9)$ cycloheteroalkyl, $(C_6$ to $C_{10})$ aryl, $(C_2$ to $C_9)$ heteroaryl, $(C_6$ to $C_{10})$ arylene, and $(C_2$ to $C_9)$ heteroarylene, wherein

35 each of the said $(C_1$ to $C_{10})$ alkyl, $(C_1$ to $C_{10})$ alkenyl, $(C_1$ to $C_{10})$ alkynyl, $(C_1$ to $C_{10})$ alkoxy, aryloxy, $(C_3$ to $C_{10})$ cycloalkyl, $(C_5$ to $C_{10})$ cycloalkenyl, $(C_2$ to $C_9)$ cycloheteroalkyl, $(C_6$ to $C_{10})$ aryl, $(C_2$ to $C_9)$ heteroaryl, $(C_6$ to $C_{10})$ arylene, and $(C_2$ to $C_9)$ heteroarylene is optionally substituted with at least one R^{13} group,

or R^{7a} and R^{7b} may be taken together with the nitrogen atom to which they are attached to form a $(C_2$ to $C_{10})$ cycloheteroalkyl ring, wherein

said $(C_2$ to $C_{10})$ membered cycloheteroalkyl ring has 1 to 3 ring heteroatoms selected from the group consisting of N, O, and S, and wherein

the said (C₂ to C₁₀) membered cycloheteroalkyl ring is optionally substituted with at least one R¹³ group;

each R⁸ is independently selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, and (C₂ to C₉) heteroarylene, wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, and (C₂ to C₉) heteroarylene is optionally substituted with at least one R¹³ group;

each of the R^{9a}, R^{9b}, and R^{9c} is independently selected from hydrogen, halogen, OH, nitro, CF₃, -NR^{11a}R^{11b}, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, cyano, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, -C(O)R¹², -C(O)NR^{11a}R^{11b}, -S(O)_mR¹², -S(O)_mNR^{11a}R^{11b}, -NR^{11a}S(O)_mR¹², -(CH₂)_nC(O)OR¹², -(CH₂)_nC(O)N(R^{11a}R^{11b}), -(CH₂)_nN(R^{11a}R^{11b}), -OC(O)R¹², -NR^{11a}C(O)R¹², and -NR^{11a}C(O)N(R^{11a}R^{11b}), wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl is optionally substituted with at least one R¹³ group;

each of the R^{10a} and R^{10b} is independently selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl is optionally substituted with at least one R¹³ group;

each of the R^{11a} and R^{11b} is independently selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, and (C₂ to C₉) heteroarylene, wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, and (C₂ to C₉) heteroarylene is optionally substituted with at least one R¹³ group,

or R^{11a} and R^{11b} may be taken together with the nitrogen atom to which they are attached to form a (C₂ to C₁₀) cycloheteroalkyl ring, wherein

said (C₂ to C₁₀) cycloheteroalkyl ring has 1 to 3 ring heteroatoms selected from the group consisting of N, O, and S, and wherein

the said (C₂ to C₁₀) cycloheteroalkyl ring is optionally substituted with at least one R¹³ group;

each of the R^{12} is independently selected from hydrogen, (C_1 to C_{10}) alkyl, (C_1 to C_{10}) alkenyl, (C_1 to C_{10}) alkynyl, (C_3 to C_{10}) cycloalkyl, (C_5 to C_{10}) cycloalkenyl, (C_2 to C_9) cycloheteroalkyl, (C_6 to C_{10}) aryl, and (C_2 to C_9) heteroaryl, wherein

each of the said (C_1 to C_{10}) alkyl, (C_1 to C_{10}) alkenyl, (C_1 to C_{10}) alkynyl, (C_3 to C_{10}) cycloalkyl, (C_5 to C_{10}) cycloalkenyl, (C_2 to C_9) cycloheteroalkyl, (C_6 to C_{10}) aryl, and (C_2 to C_9) heteroaryl is optionally substituted with at least one R^{13} group;

each R^{13} is independently selected from hydrogen, halogen, OH, nitro, CF_3 , $-NR^{14a}R^{14b}$, oxo, (C_1 to C_{10}) alkyl, (C_1 to C_{10}) alkenyl, (C_1 to C_{10}) alkynyl, (C_1 to C_{10}) alkoxy, aryloxy, cyano, (C_3 to C_{10}) cycloalkyl, (C_5 to C_{10}) cycloalkenyl, (C_2 to C_9) cycloheteroalkyl, (C_6 to C_{10}) aryl, (C_2 to C_9) heteroaryl, (C_6 to C_{10}) arylene, (C_2 to C_9) heteroarylene, (C_3 to C_{10}) cycloalkylene, (C_2 to C_{10}) cycloheteroalkylene, $-C(O)R^{15}$, $-C(O)NR^{14a}R^{14b}$, $-S(O)_mR^{15}$, $-S(O)_mNR^{14a}R^{14b}$, $-NR^{14a}S(O)_mR^{15}$, $-(CH_2)_nC(O)OR^{15}$, $-(CH_2)_nC(O)N(R^{14a}R^{14b})$, $-(CH_2)_nN(R^{14a}R^{14b})$, $-OC(O)R^{15}$, $-O(CH_2)_nO-$, $-NR^{14a}C(O)R^{15}$, and $-NR^{14a}C(O)N(R^{14a}R^{14b})$, wherein

each of the said (C_1 to C_{10}) alkyl, (C_1 to C_{10}) alkenyl, (C_1 to C_{10}) alkynyl, (C_1 to C_{10}) alkoxy, aryloxy, (C_3 to C_{10}) cycloalkyl, (C_5 to C_{10}) cycloalkenyl, (C_2 to C_{10}) cycloheteroalkyl, (C_6 to C_{10}) aryl, (C_2 to C_9) heteroaryl, (C_6 to C_{10}) arylene, (C_2 to C_9) heteroarylene, (C_3 to C_{10}) cycloalkylene, and (C_2 to C_{10}) cycloheteroalkylene is optionally substituted with at least one R^{16} group;

each of the R^{14a} and R^{14b} is independently selected from hydrogen, (C_1 to C_{10}) alkyl, (C_1 to C_{10}) alkenyl, (C_1 to C_{10}) alkynyl, (C_1 to C_{10}) alkoxy, aryloxy, (C_3 to C_{10}) cycloalkyl, (C_5 to C_{10}) cycloalkenyl, (C_2 to C_9) cycloheteroalkyl, (C_6 to C_{10}) aryl, (C_2 to C_9) heteroaryl, (C_6 to C_{10}) arylene, and (C_2 to C_9) heteroarylene, wherein

each of the said (C_1 to C_{10}) alkyl, (C_1 to C_{10}) alkenyl, (C_1 to C_{10}) alkynyl, (C_1 to C_{10}) alkoxy, aryloxy, (C_3 to C_{10}) cycloalkyl, (C_5 to C_{10}) cycloalkenyl, (C_2 to C_{10}) cycloheteroalkyl, (C_6 to C_{10}) aryl, (C_2 to C_9) heteroaryl, (C_6 to C_{10}) arylene, and (C_2 to C_9) heteroarylene is optionally substituted with at least one R^{16} group,

or R^{14a} and R^{14b} may be taken together with the nitrogen atom to which they are attached to form a (C_2 to C_{10}) cycloheteroalkyl ring, wherein

said (C_2 to C_{10}) cycloheteroalkyl ring has 1 to 3 ring heteroatoms selected from the group consisting of N, O, and S, and wherein

the said (C_2 to C_{10}) cycloheteroalkyl ring is optionally substituted with at least one R^{16} group;

each R^{15} is independently selected from hydrogen, (C_1 to C_{10}) alkyl, (C_1 to C_{10}) alkenyl, (C_1 to C_{10}) alkynyl, (C_3 to C_{10}) cycloalkyl, (C_5 to C_{10}) cycloalkenyl, (C_2 to C_{10}) cycloheteroalkyl, (C_6 to C_{10}) aryl, and (C_2 to C_9) heteroaryl, wherein

each of the said (C_1 to C_{10}) alkyl, (C_1 to C_{10}) alkenyl, (C_1 to C_{10}) alkynyl, (C_3 to C_{10}) cycloalkyl, (C_5 to C_{10}) cycloalkenyl, (C_2 to C_{10}) cycloheteroalkyl, (C_6 to C_{10}) aryl, and (C_2 to C_9) heteroaryl is optionally substituted with at least one R^{16} group;

each R^{16} is independently selected from hydrogen, halogen, OH, nitro, CF_3 , $-NR^{17a}R^{17b}$, oxo, (C_1 to C_{10}) alkyl, (C_1 to C_{10}) alkenyl, (C_1 to C_{10}) alkynyl, (C_1 to C_{10}) alkoxy, aryloxy, cyano, (C_3 to C_{10}) cycloalkyl, (C_5 to C_{10}) cycloalkenyl, (C_2 to C_{10}) cycloheteroalkyl, (C_6 to C_{10}) aryl, (C_2 to C_9) heteroaryl, (C_6 to C_{10}) arylene, (C_2 to C_9) heteroarylene, (C_3 to C_{10}) cycloalkylene, (C_2 to C_{10})

cycloheteroalkylene, $-C(O)R^{18}$, $-C(O)NR^{17a}R^{17b}$, $-S(O)_mR^{18}$, $-S(O)_mNR^{17a}R^{17b}$, $-NR^{17a}S(O)_mR^{18}$, $-(CH_2)_nC(O)OR^{18}$, $-(CH_2)_nC(O)N(R^{17a}R^{17b})$, $-(CH_2)_nN(R^{17a}R^{17b})$, $-OC(O)R^{18}$, $-NR^{17a}C(O)R^{18}$, and $-NR^{17a}C(O)N(R^{17a}R^{17b})$, wherein

each of the said $(C_1 \text{ to } C_{10})$ alkyl, $(C_1 \text{ to } C_{10})$ alkenyl, $(C_1 \text{ to } C_{10})$ alkynyl, $(C_1 \text{ to } C_{10})$ alkoxy, aryloxy, $(C_3 \text{ to } C_{10})$ cycloalkyl, $(C_5 \text{ to } C_{10})$ cycloalkenyl, $(C_2 \text{ to } C_{10})$ cycloheteroalkyl, $(C_2 \text{ to } C_9)$ heteroaryl, $(C_6 \text{ to } C_{10})$ aryl, $(C_6 \text{ to } C_{10})$ arylene, $(C_2 \text{ to } C_9)$ heteroarylene, $(C_3 \text{ to } C_{10})$ cycloalkylene, and $(C_2 \text{ to } C_{10})$ cycloheteroalkylene is optionally substituted with at least one R^{19} group;

each of the R^{17a} and R^{17b} is independently selected from hydrogen, $(C_1 \text{ to } C_{10})$ alkyl, $(C_1 \text{ to } C_{10})$ alkenyl, $(C_1 \text{ to } C_{10})$ alkynyl, $(C_1 \text{ to } C_{10})$ alkoxy, aryloxy, $(C_3 \text{ to } C_{10})$ cycloalkyl, $(C_5 \text{ to } C_{10})$ cycloalkenyl, $(C_2 \text{ to } C_{10})$ cycloheteroalkyl, $C_6 \text{ to } C_{10})$ aryl, $(C_2 \text{ to } C_9)$ heteroaryl, $(C_6 \text{ to } C_{10})$ arylene, and $(C_2 \text{ to } C_9)$ heteroarylene, wherein

each of the said $(C_1 \text{ to } C_{10})$ alkyl, $(C_1 \text{ to } C_{10})$ alkenyl, $(C_1 \text{ to } C_{10})$ alkynyl, $(C_1 \text{ to } C_{10})$ alkoxy, aryloxy, $(C_3 \text{ to } C_{10})$ cycloalkyl, $(C_5 \text{ to } C_{10})$ cycloalkenyl, $(C_2 \text{ to } C_{10})$ cycloheteroalkyl, $(C_6 \text{ to } C_{10})$ aryl, $(C_2 \text{ to } C_9)$ heteroaryl, $(C_6 \text{ to } C_{10})$ arylene, and $(C_2 \text{ to } C_9)$ heteroarylene is optionally substituted with at least one R^{19} group,

or R^{17a} and R^{17b} may be taken together with the nitrogen atom to which they are attached to form a $(C_2 \text{ to } C_{10})$ cycloheteroalkyl ring, wherein

said $(C_2 \text{ to } C_{10})$ cycloheteroalkyl ring has 1 to 3 ring heteroatoms selected from the group consisting of N, O, and S, and wherein

the said $(C_2 \text{ to } C_{10})$ cycloheteroalkyl ring is optionally substituted with at least one R^{19} group;

each R^{18} is independently selected from hydrogen, halogen, OH, nitro, CF_3 , $(C_1 \text{ to } C_{10})$ alkyl, $(C_1 \text{ to } C_{10})$ alkenyl, $(C_1 \text{ to } C_{10})$ alkynyl, $(C_1 \text{ to } C_{10})$ alkoxy, aryloxy, cyano, $(C_3 \text{ to } C_{10})$ cycloalkyl, $(C_5 \text{ to } C_{10})$ cycloalkenyl, $(C_2 \text{ to } C_{10})$ cycloheteroalkyl, $(C_6 \text{ to } C_{10})$ aryl, and $(C_2 \text{ to } C_9)$ heteroaryl, wherein

each of the said $(C_1 \text{ to } C_{10})$ alkyl, $(C_1 \text{ to } C_{10})$ alkenyl, $(C_1 \text{ to } C_{10})$ alkynyl, $(C_3 \text{ to } C_{10})$ cycloalkyl, $(C_5 \text{ to } C_{10})$ cycloalkenyl, $(C_2 \text{ to } C_{10})$ cycloheteroalkyl, $(C_2 \text{ to } C_9)$ heteroaryl, and $(C_6 \text{ to } C_{10})$ aryl is optionally substituted with at least one R^{19} group;

each R^{19} is independently selected from hydrogen, halogen, OH, nitro, CF_3 , $-NR^{20a}R^{20b}$, oxo, $(C_1 \text{ to } C_{10})$ alkyl, $(C_1 \text{ to } C_{10})$ alkenyl, $(C_1 \text{ to } C_{10})$ alkynyl, $(C_1 \text{ to } C_{10})$ alkoxy, aryloxy, cyano, $(C_3 \text{ to } C_{10})$ cycloalkyl, $(C_5 \text{ to } C_{10})$ cycloalkenyl, $(C_2 \text{ to } C_{10})$ cycloheteroalkyl, $(C_6 \text{ to } C_{10})$ aryl, $(C_2 \text{ to } C_9)$ heteroaryl, $(C_6 \text{ to } C_{10})$ arylene, $(C_2 \text{ to } C_9)$ heteroarylene, $(C_3 \text{ to } C_{10})$ cycloalkylene, $(C_2 \text{ to } C_{10})$ cycloheteroalkylene, $-C(O)R^{21}$, $-C(O)NR^{20a}R^{20b}$, $-S(O)_mR^{21}$, $-S(O)_mNR^{20a}R^{20b}$, $-NR^{20a}S(O)_mR^{21}$, $-(CH_2)_nC(O)OR^{21}$, $-(CH_2)_nC(O)N(R^{20a}R^{20b})$, $-(CH_2)_nN(R^{20a}R^{20b})$, $-OC(O)R^{21}$, $-NR^{20a}C(O)R^{21}$, and $-NR^{20a}C(O)N(R^{20a}R^{20b})$, wherein

each of the said $(C_1 \text{ to } C_{10})$ alkyl, $(C_1 \text{ to } C_{10})$ alkenyl, $(C_1 \text{ to } C_{10})$ alkynyl, $(C_1 \text{ to } C_{10})$ alkoxy, aryloxy, $(C_3 \text{ to } C_{10})$ cycloalkyl, $(C_5 \text{ to } C_{10})$ cycloalkenyl, $(C_2 \text{ to } C_{10})$ cycloheteroalkyl, $(C_6 \text{ to } C_{10})$ aryl, $(C_2 \text{ to } C_9)$ heteroaryl, $(C_6 \text{ to } C_{10})$ arylene, $(C_2 \text{ to } C_9)$ heteroarylene, $(C_3 \text{ to } C_{10})$ cycloalkylene, and $(C_2 \text{ to } C_{10})$ cycloheteroalkylene is optionally substituted with at least one R^{22} group;

each of the R^{20a} and R^{20b} is independently selected from hydrogen, (C_1 to C_{10}) alkyl, (C_1 to C_{10}) alkenyl, (C_1 to C_{10}) alkynyl, (C_1 to C_{10}) alkoxy, aryloxy, (C_3 to C_{10}) cycloalkyl, (C_5 to C_{10}) cycloalkenyl, (C_2 to C_{10}) cycloheteroalkyl, (C_6 to C_{10}) aryl, and (C_2 to C_9) heteroaryl, wherein

each of the said (C_1 to C_{10}) alkyl, (C_1 to C_{10}) alkenyl, (C_1 to C_{10}) alkynyl, (C_1 to C_{10}) alkoxy, aryloxy, (C_3 to C_{10}) cycloalkyl, (C_5 to C_{10}) cycloalkenyl, (C_2 to C_{10}) cycloheteroalkyl, (C_6 to C_{10}) aryl, and (C_2 to C_9) heteroaryl is optionally substituted with at least one R^{22} group,

or R^{20a} and R^{20b} may be taken together with the nitrogen atom to which they are attached to form a (C_2 to C_{10}) cycloheteroalkyl ring, wherein

said (C_2 to C_{10}) cycloheteroalkyl ring has 1 to 3 ring heteroatoms selected from the group consisting of N, O, and S, and wherein

the said (C_2 to C_{10}) cycloheteroalkyl ring is optionally substituted with at least one R^{22} group;

each R^{21} is independently selected from hydrogen, halogen, OH, nitro, CF_3 , (C_1 to C_{10}) alkyl, (C_1 to C_{10}) alkenyl, (C_1 to C_{10}) alkynyl, (C_1 to C_{10}) alkoxy, aryloxy, cyano, (C_3 to C_{10}) cycloalkyl, (C_5 to C_{10}) cycloalkenyl, (C_2 to C_{10}) cycloheteroalkyl, (C_6 to C_{10}) aryl, and (C_2 to C_9) heteroaryl;

each R^{22} is independently selected from hydrogen, halogen, OH, nitro, CF_3 , $-NR^{23a}R^{23b}$, oxo, (C_1 to C_{10}) alkyl, (C_1 to C_{10}) alkenyl, (C_1 to C_{10}) alkynyl, (C_1 to C_{10}) alkoxy, aryloxy, cyano, (C_3 to C_{10}) cycloalkyl, (C_5 to C_{10}) cycloalkenyl, (C_2 to C_{10}) cycloheteroalkyl, (C_6 to C_{10}) aryl, (C_2 to C_9) heteroaryl, (C_6 to C_{10}) arylene, (C_2 to C_9) heteroarylene, (C_3 to C_{10}) cycloalkylene, (C_2 to C_{10}) cycloheteroalkylene, $-C(O)R^{24}$, $-C(O)NR^{23a}R^{23b}$, $-S(O)_mR^{24}$, $-S(O)_mNR^{23a}R^{23b}$, $-NR^{23a}S(O)_mR^{24}$, $-(CH_2)_nC(O)OR^{24}$, $-(CH_2)_nC(O)N(R^{23a}R^{23b})$, $-(CH_2)_nN(R^{23a}R^{23b})$, $-OC(O)R^{24}$, $-NR^{23a}C(O)R^{24}$, and $-NR^{23a}C(O)N(R^{23a}R^{23b})$, wherein

each of the said (C_1 to C_{10}) alkyl, (C_1 to C_{10}) alkenyl, (C_1 to C_{10}) alkynyl, (C_1 to C_{10}) alkoxy, aryloxy, (C_3 to C_{10}) cycloalkyl, (C_5 to C_{10}) cycloalkenyl, (C_2 to C_{10}) cycloheteroalkyl, (C_6 to C_{10}) aryl, (C_2 to C_9) heteroaryl, (C_6 to C_{10}) arylene, (C_2 to C_9) heteroarylene, (C_3 to C_{10}) cycloalkylene, and (C_2 to C_{10}) cycloheteroalkylene is optionally substituted with at least one R^{25} group;

each of the R^{23a} and R^{23b} is independently selected from hydrogen, (C_1 to C_{10}) alkyl, (C_1 to C_{10}) alkenyl, (C_1 to C_{10}) alkynyl, (C_3 to C_{10}) cycloalkyl, (C_5 to C_{10}) cycloalkenyl, (C_2 to C_{10}) cycloheteroalkyl, (C_2 to C_9) heteroaryl, and (C_6 to C_{10}) aryl;

each R^{24} is independently selected from hydrogen, halogen, OH, nitro, CF_3 , (C_1 to C_{10}) alkyl, (C_1 to C_{10}) alkenyl, (C_1 to C_{10}) alkynyl, (C_1 to C_{10}) alkoxy, aryloxy, cyano, (C_3 to C_{10}) cycloalkyl, (C_5 to C_{10}) cycloalkenyl, (C_2 to C_{10}) cycloheteroalkyl, (C_6 to C_{10}) aryl, (C_2 to C_9) heteroaryl;

each R^{25} is independently selected from hydrogen, halogen, OH, nitro, CF_3 , $-NR^{26a}R^{26b}$, oxo, (C_1 to C_{10}) alkyl, (C_1 to C_{10}) alkenyl, (C_1 to C_{10}) alkynyl, (C_1 to C_{10}) alkoxy, aryloxy, cyano, (C_3 to C_{10}) cycloalkyl, (C_5 to C_{10}) cycloalkenyl, (C_2 to C_{10}) cycloheteroalkyl, (C_6 to C_{10}) aryl, (C_2 to C_9) heteroaryl, (C_6 to C_{10}) arylene, (C_2 to C_9) heteroarylene, (C_3 to C_{10}) cycloalkylene, (C_2 to C_{10}) cycloheteroalkylene, $-C(O)R^{27}$, $-C(O)NR^{26a}R^{26b}$, $-S(O)_mR^{27}$, $-S(O)_mNR^{26a}R^{26b}$, $-NR^{26a}S(O)_mR^{27}$, $-(CH_2)_nC(O)OR^{27}$, $-(CH_2)_nC(O)N(R^{26a}R^{26b})$, $-(CH_2)_nN(R^{26a}R^{26b})$, $-OC(O)R^{27}$, $-NR^{26a}C(O)R^{27}$, and $-NR^{26a}C(O)N(R^{26a}R^{26b})$, wherein

each of the said (C_1 to C_{10}) alkyl, (C_1 to C_{10}) alkenyl, (C_1 to C_{10}) alkynyl, (C_1 to C_{10}) alkoxy, aryloxy, (C_3 to C_{10}) cycloalkyl, (C_5 to C_{10}) cycloalkenyl, (C_2 to C_{10}) cycloheteroalkyl, (C_6 to C_{10}) aryl,

(C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, (C₂ to C₉) heteroarylene, (C₃ to C₁₀) cycloalkylene, and (C₂ to C₁₀) cycloheteroalkylene is optionally substituted with at least one R²⁷ group;

each of the R^{26a} and R^{26b} is independently selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl,

or R^{26a} and R^{26b} may be taken together with the nitrogen atom to which they are attached to form a (C₂ to C₁₀) cycloheteroalkyl ring, wherein

said (C₂ to C₁₀) cycloheteroalkyl ring has 1 to 3 ring heteroatoms selected from the group consisting of N, O, and S;

each R²⁷ is independently selected from hydrogen, halogen, OH, nitro, CF₃, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, cyano, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl;

h is 1 or 2;

i is 2, 3, 4, 5, or 6;

j is 0, 1, 2, 3, 4, or 5;

k is 1, 2, 3, 4, or 5;

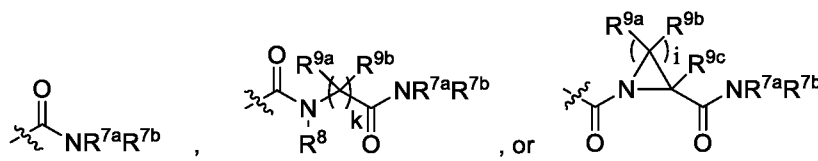
m is 0, 1 or 2;

n is 0, 1, 2, 3, or 4;

Z is selected from the group consisting of -O-, -S-, -S(O)-, and -S(O)₂-;

with the proviso that

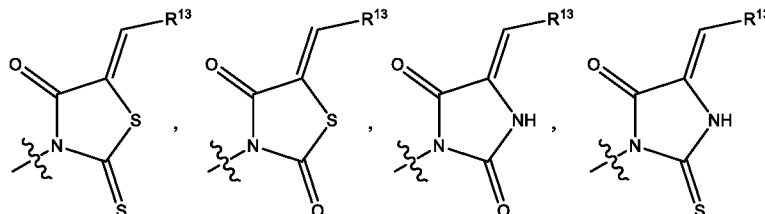
when R¹, R², or R³ is alkyl or hydrogen, X is C-C(R^{6a}R^{6b})_j-D, Y is CH₂, and D is



then NR^{7a}R^{7b} cannot be an optionally substituted piperazine or 1,4-diazepane,

and with the proviso that

when X is CR⁵, Y is CR⁴-D, D is -NR^{7a}R^{7b}, and R^{7a} and R^{7b} are taken together with the nitrogen atom to which they are attached to form a (C₂ to C₁₀) cycloheteroalkyl ring, the said (C₂ to C₁₀) membered cycloheteroalkyl ring cannot be selected from the group consisting of



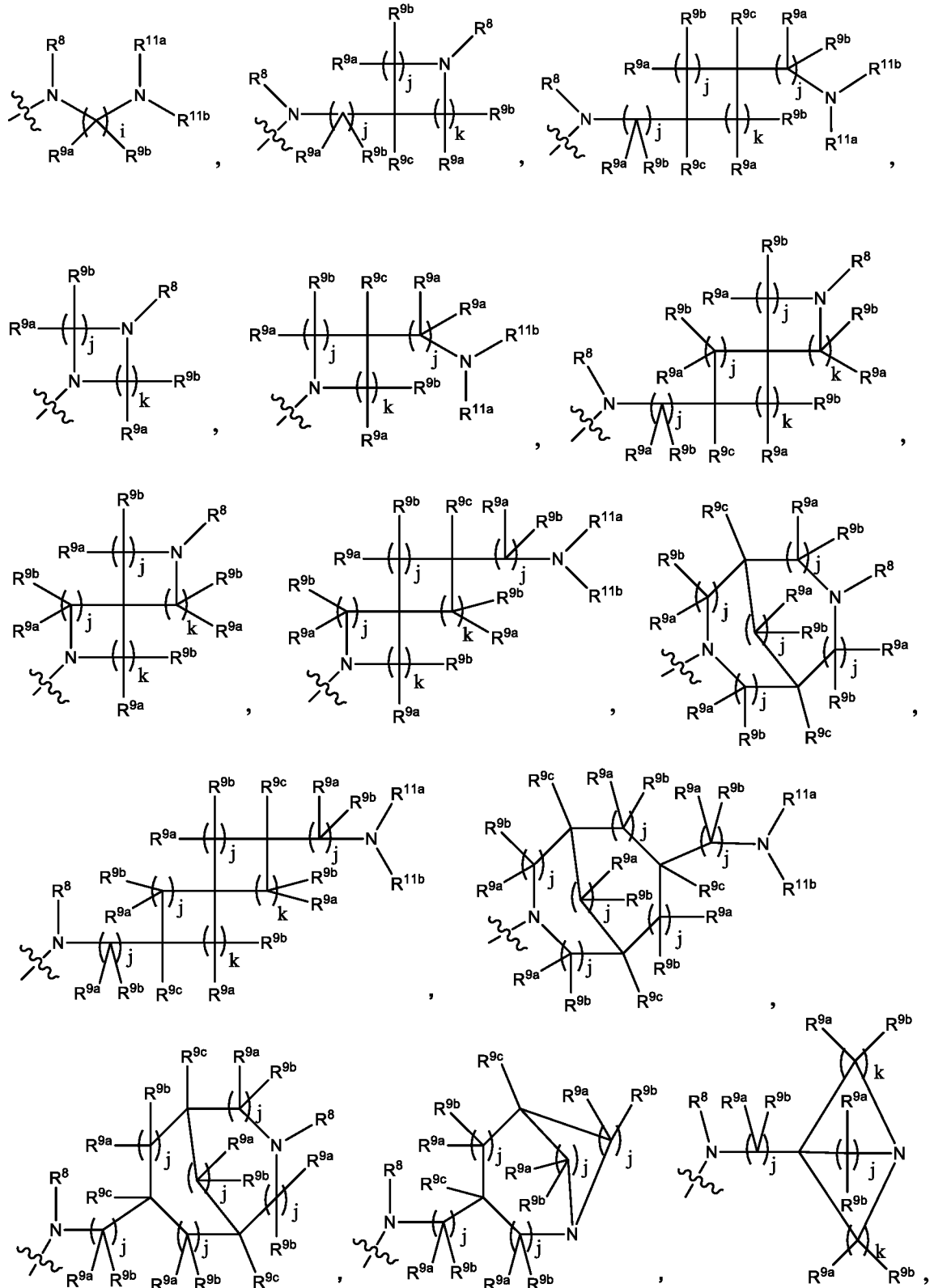
- The method of claim 1, wherein the infection is associated with filovirus selected from the group consisting of Ebolavirus and Marburgvirus.
- The method of claim 2, where the filovirus is Ebolavirus.
- The method of claim 3, including administering a therapeutic amount of a therapeutic agent selected from the group consisting of Ribavirin, viral RNA-dependent-RNA-polymerase inhibitors,

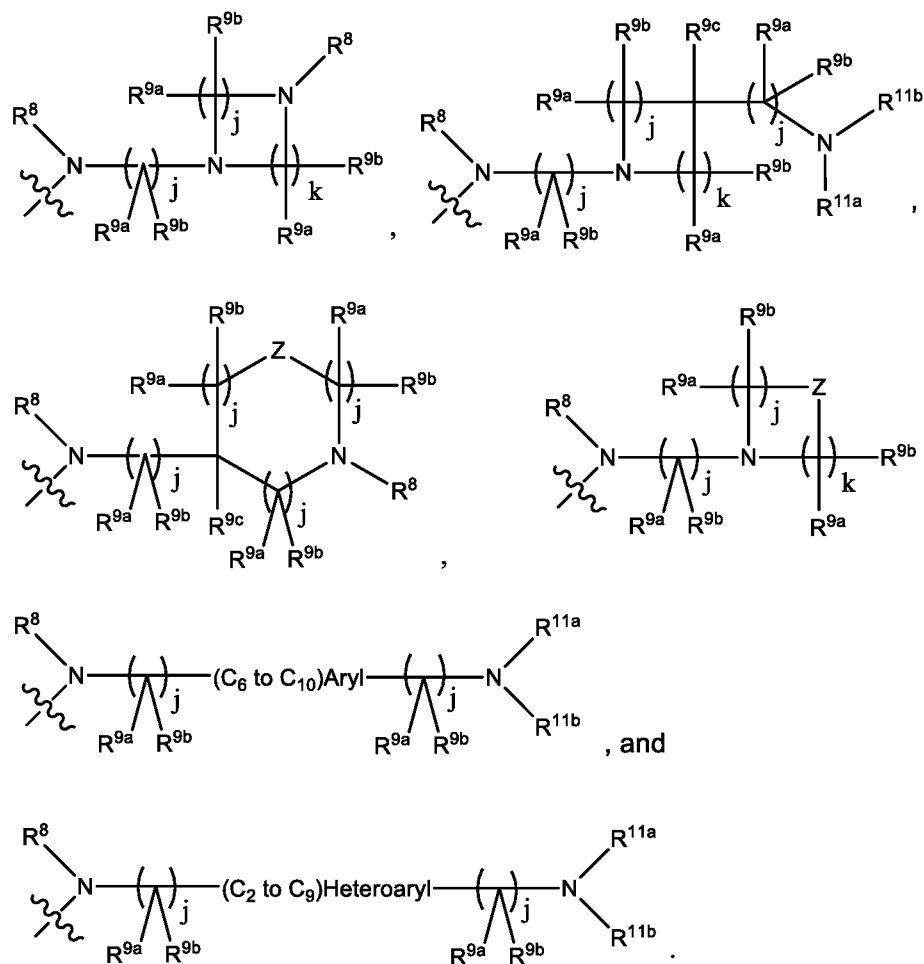
Favipiravir, Triazavirin, GS-5734, small interfering RNAs (siRNAs) and microRNAs, vaccines, and immunomodulators.

5. The method of claim 4, including the inhibition of Ebolavirus glycoprotein.

6. The method of claim 1, wherein

5 $NR^{7a}R^{7b}$ is selected from the group consisting of



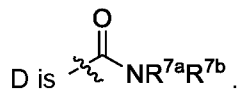


7. The method of claim 6, wherein:

X is C-A-D and Y is CR^4R^5 .

- 5 8. The method of claim 7, wherein:

A is $-C(R^{6a}R^{6b})_j-$;



9. The method of claim 8, wherein:

R^1 is selected from $(C_6 \text{ to } C_{10})$ aryl and $(C_2 \text{ to } C_9)$ heteroaryl, wherein

- 10 each of the said $(C_6 \text{ to } C_{10})$ aryl and $(C_2 \text{ to } C_9)$ heteroaryl is optionally substituted with at least one R^{13} group;

R^2 is selected from hydrogen, $(C_1 \text{ to } C_{10})$ alkyl, $(C_1 \text{ to } C_{10})$ alkenyl, $(C_1 \text{ to } C_{10})$ alkynyl, $(C_3 \text{ to } C_{10})$ cycloalkyl, $(C_5 \text{ to } C_{10})$ cycloalkenyl, $(C_1 \text{ to } C_{10})$ alkoxy, $-(CH_2)_nC(O)N(R^{11a}R^{11b})$, and $-C(O)R^{12}$, wherein

- 15 each of the said $(C_1 \text{ to } C_{10})$ alkyl, $(C_1 \text{ to } C_{10})$ alkenyl, $(C_1 \text{ to } C_{10})$ alkynyl, $(C_3 \text{ to } C_{10})$ cycloalkyl, $(C_5 \text{ to } C_{10})$ cycloalkenyl, and $(C_1 \text{ to } C_{10})$ alkoxy is optionally substituted with at least one R^{13} group;

R^3 is selected from hydrogen, $(C_1 \text{ to } C_{10})$ alkyl, $(C_1 \text{ to } C_{10})$ alkenyl, $(C_1 \text{ to } C_{10})$ alkynyl, $(C_3 \text{ to } C_{10})$ cycloalkyl, and $(C_5 \text{ to } C_{10})$ cycloalkenyl, wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl is optionally substituted with at least one R¹³ group;

R⁴ is hydrogen;

R⁵ is hydrogen.

- 5 10. The method of claim 9, wherein:

R³ is hydrogen.

11. The method of claim 7, wherein:

A is -C(R^{6a}R^{6b})_j-;



- 10 12. The method of claim 11, wherein:

R¹ is selected from (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl, wherein

each of the said (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl is optionally substituted with at least one R¹³ group;

- 15 R² is selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₁ to C₁₀) alkoxy, -(CH₂)_nC(O)N(R^{11a}R^{11b}), and -C(O)R¹², wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, and (C₁ to C₁₀) alkoxy is optionally substituted with at least one R¹³ group;

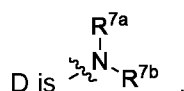
R³ is hydrogen;

- 20 R⁴ is hydrogen;

R⁵ is hydrogen.

13. The method of claim 7, wherein:

A is -C(R^{6a}R^{6b})_j-;



- 25 14. The method of claim 13, wherein:

R¹ is selected from (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl, wherein

each of the said (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl is optionally substituted with at least one R¹³ group;

- 30 R² is selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₁ to C₁₀) alkoxy, -(CH₂)_nC(O)N(R^{11a}R^{11b}), and -C(O)R¹², wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, and (C₁ to C₁₀) alkoxy is optionally substituted with at least one R¹³ group;

R³ is hydrogen;

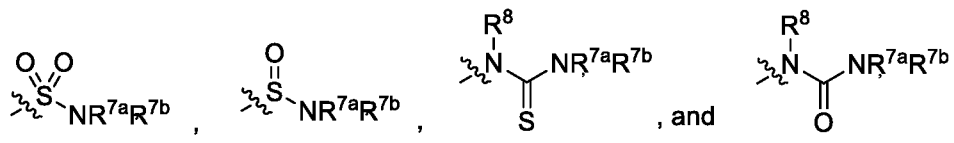
- 35 R⁴ is hydrogen;

R⁵ is hydrogen.

15. The method of claim 7, wherein:

A is $-C(R^{6a}R^{6b})_j-$;

D is selected from the group consisting of



5 16. The method of claim 15, wherein:

R^1 is selected from (C_6 to C_{10}) aryl and (C_2 to C_9) heteroaryl, wherein

each of the said (C_6 to C_{10}) aryl and (C_2 to C_9) heteroaryl is optionally substituted with at least one R^{13} group;

10 R^2 is selected from hydrogen, (C_1 to C_{10}) alkyl, (C_1 to C_{10}) alkenyl, (C_1 to C_{10}) alkynyl, (C_3 to C_{10}) cycloalkyl, (C_5 to C_{10}) cycloalkenyl, (C_1 to C_{10}) alkoxy, $-(CH_2)_nC(O)N(R^{11a}R^{11b})$, and $-C(O)R^{12}$, wherein

each of the said (C_1 to C_{10}) alkyl, (C_1 to C_{10}) alkenyl, (C_1 to C_{10}) alkynyl, (C_3 to C_{10}) cycloalkyl, (C_5 to C_{10}) cycloalkenyl, and (C_1 to C_{10}) alkoxy is optionally substituted with at least one R^{13} group;

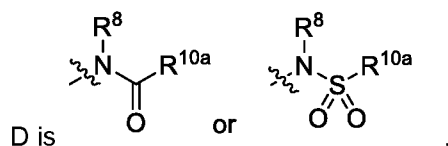
R^3 is hydrogen;

15 R^4 is hydrogen;

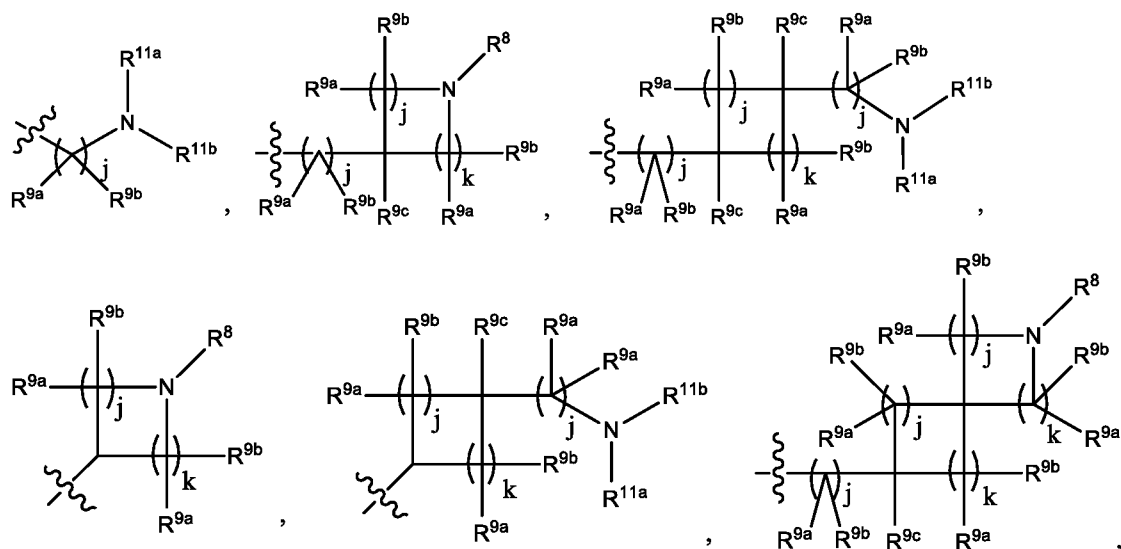
R^5 is hydrogen.

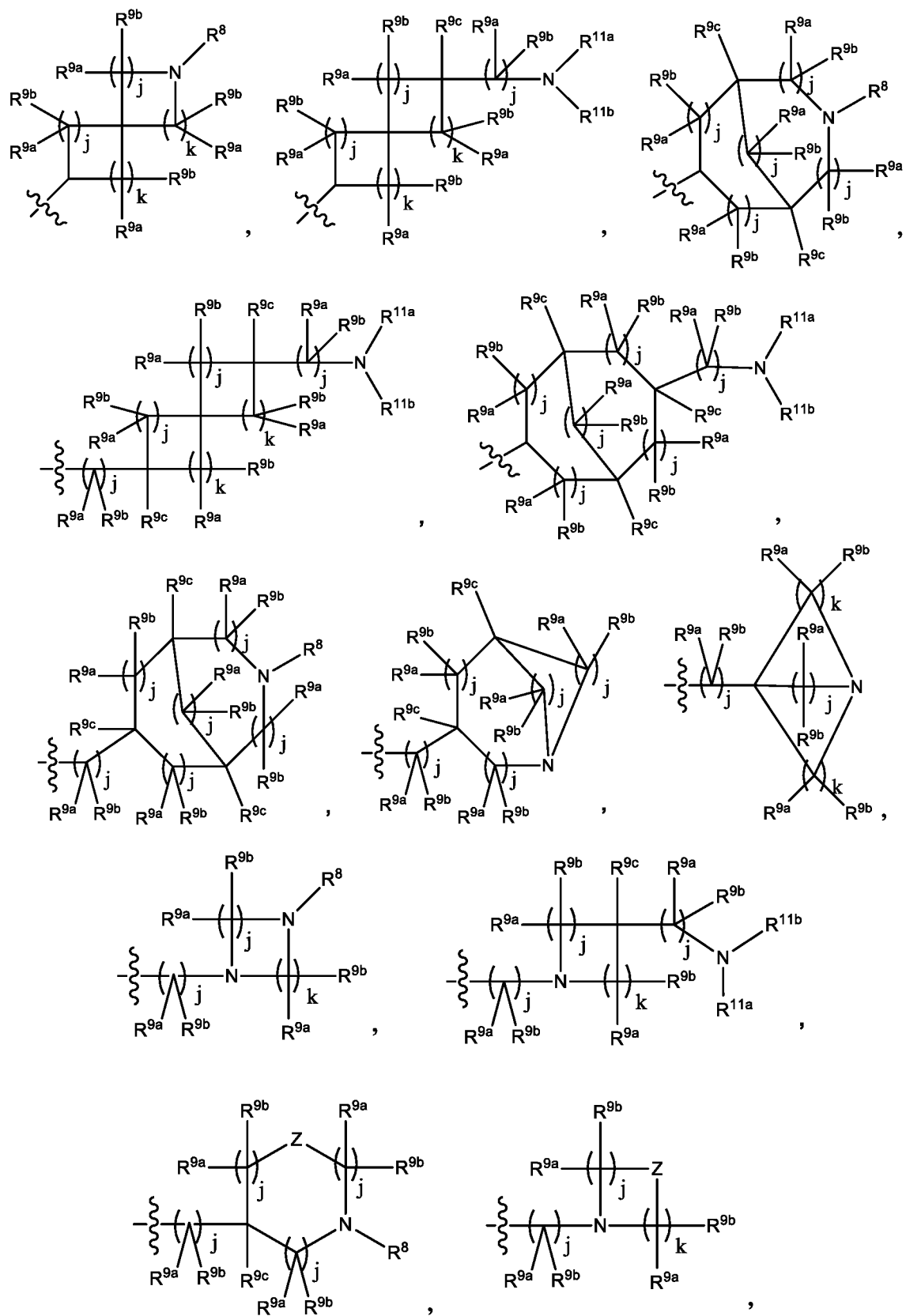
17. The method of claim 1, wherein:

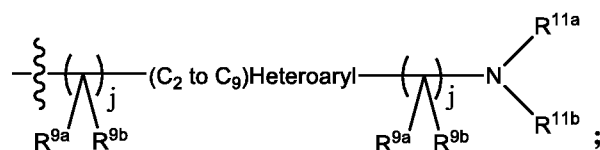
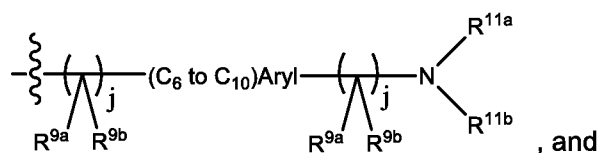
A is $-C(R^{6a}R^{6b})_j-$;



20 wherein R^{10a} is selected from the group consisting of







R¹ is selected from (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl, wherein each of the said (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl is optionally substituted with at least one R¹³ group;

R² is selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₁ to C₁₀) alkoxy, -(CH₂)_nC(O)N(R^{11a}R^{11b}), and -C(O)R¹², wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, and (C₁ to C₁₀) alkoxy is optionally substituted with at least one R¹³ group;

R³ is hydrogen;

R⁴ is hydrogen;

R⁵ is hydrogen.

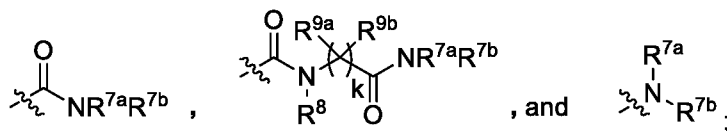
18. The method of claim 6, wherein:

X is C-A-D and Y is a bond.

19. The method of claim 18, wherein:

A is $-C(R^{6a}R^{6b})_i-$;

D is selected from the group consisting of



R¹ is selected from (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl, wherein each of the said (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl is optionally substituted with at least one R¹³ group.

R² is selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₁ to C₁₀) alkoxy, -(CH₂)_nC(O)N(R^{11a}R^{11b}), and -C(O)R¹², wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, and (C₁ to C₁₀) alkoxy is optionally substituted with at least one R¹³ group;

R^3 is hydrogen.

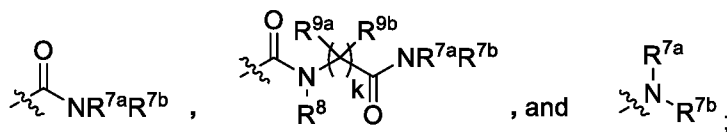
20. The method of claim 6, wherein:

X is CR^5 and Y is CR^4 -A-D.

21. The method of claim 20, wherein:

A is $-\text{C}(\text{R}^{6a}\text{R}^{6b})_j-$;

D is selected from the group consisting of



5

R^1 is selected from (C_6 to C_{10}) aryl and (C_2 to C_9) heteroaryl, wherein

each of the said (C_6 to C_{10}) aryl and (C_2 to C_9) heteroaryl is optionally substituted with at least one R^{13} group;

R^2 is selected from hydrogen, (C_1 to C_{10}) alkyl, (C_1 to C_{10}) alkenyl, (C_1 to C_{10}) alkynyl, (C_3 to C_{10}) cycloalkyl, (C_5 to C_{10}) cycloalkenyl, (C_1 to C_{10}) alkoxy, $-(\text{CH}_2)_n\text{C}(\text{O})\text{N}(\text{R}^{11a}\text{R}^{11b})$, and $-\text{C}(\text{O})\text{R}^{12}$,
10 wherein

each of the said (C_1 to C_{10}) alkyl, (C_1 to C_{10}) alkenyl, (C_1 to C_{10}) alkynyl, (C_3 to C_{10}) cycloalkyl, (C_5 to C_{10}) cycloalkenyl, and (C_1 to C_{10}) alkoxy is optionally substituted with at least one R^{13} group;

R^3 is hydrogen,

R^4 is hydrogen;

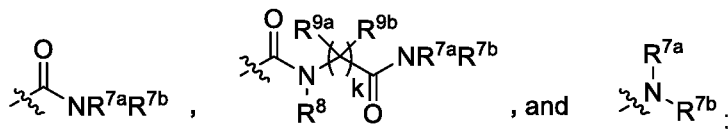
15

R^5 is hydrogen.

22. The method of claim 20, wherein:

A is $-\text{C}(\text{R}^{6a}\text{R}^{6b})_j-$;

D is selected from the group consisting of



20

R^1 is selected from hydrogen, (C_1 to C_{10}) alkyl, (C_1 to C_{10}) alkenyl, (C_1 to C_{10}) alkynyl, (C_3 to C_{10}) cycloalkyl, (C_5 to C_{10}) cycloalkenyl, (C_1 to C_{10}) alkoxy, $-(\text{CH}_2)_n\text{C}(\text{O})\text{N}(\text{R}^{11a}\text{R}^{11b})$, and $-\text{C}(\text{O})\text{R}^{12}$,
wherein

each of the said (C_1 to C_{10}) alkyl, (C_1 to C_{10}) alkenyl, (C_1 to C_{10}) alkynyl, (C_3 to C_{10}) cycloalkyl, (C_5 to C_{10}) cycloalkenyl, and (C_1 to C_{10}) alkoxy is optionally substituted with at least one R^{13} group;

25

R^2 is selected from hydrogen, (C_1 to C_{10}) alkyl, (C_1 to C_{10}) alkenyl, (C_1 to C_{10}) alkynyl, (C_3 to C_{10}) cycloalkyl, (C_5 to C_{10}) cycloalkenyl, (C_1 to C_{10}) alkoxy, $-(\text{CH}_2)_n\text{C}(\text{O})\text{N}(\text{R}^{11a}\text{R}^{11b})$, and $-\text{C}(\text{O})\text{R}^{12}$,
wherein

each of the said (C_1 to C_{10}) alkyl, (C_1 to C_{10}) alkenyl, (C_1 to C_{10}) alkynyl, (C_3 to C_{10}) cycloalkyl, (C_5 to C_{10}) cycloalkenyl, and (C_1 to C_{10}) alkoxy is optionally substituted with at least one R^{13} group;

30

R^3 is selected from hydrogen, (C_1 to C_{10}) alkyl, (C_1 to C_{10}) alkenyl, (C_1 to C_{10}) alkynyl, (C_3 to C_{10}) cycloalkyl, and (C_5 to C_{10}) cycloalkenyl, wherein

each of the said (C_1 to C_{10}) alkyl, (C_1 to C_{10}) alkenyl, (C_1 to C_{10}) alkynyl, (C_3 to C_{10}) cycloalkyl, (C_5 to C_{10}) cycloalkenyl is optionally substituted with at least one R^{13} group.

R^4 is selected from (C_6 to C_{10}) aryl and (C_2 to C_9) heteroaryl, wherein

35

each of the said (C_6 to C_{10}) aryl and (C_2 to C_9) heteroaryl is optionally substituted with at least one R^{13} group;

R^5 is hydrogen.

23. The method of claim 22, wherein:

R^1 is hydrogen;

R^2 is hydrogen;

R^3 is hydrogen.

24. The method of claim 1, wherein:

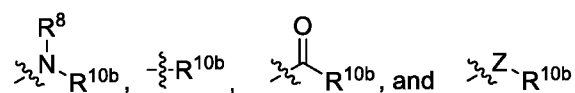
Y is CR^4R^5 ;

X is C-A-D, wherein

A is $-C(R^{6a}R^{6b})_f$, (C_6 to C_{10}) arylene, or (C_2 to C_9) heteroarylene, wherein

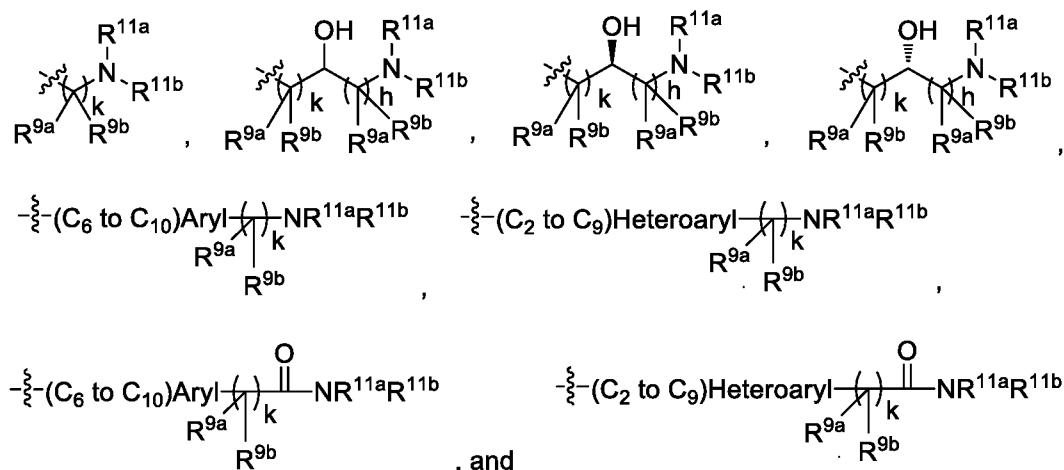
each of the said (C_6 to C_{10}) arylene or (C_2 to C_9) heteroarylene is optionally substituted with at least one R^{6a} group;

D is selected from the group consisting of



25. The method of claim 24, wherein:

R^{10b} is selected from the group consisting of



26. The method of claim 1, wherein:

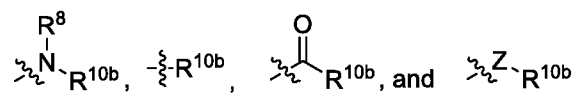
Y is a bond;

X is C-A-D, wherein

A is $-C(R^{6a}R^{6b})_f$, (C_6 to C_{10}) arylene, or (C_2 to C_9) heteroarylene, wherein

each of the said (C_6 to C_{10}) arylene or (C_2 to C_9) heteroarylene is optionally substituted with at least one R^{6a} group;

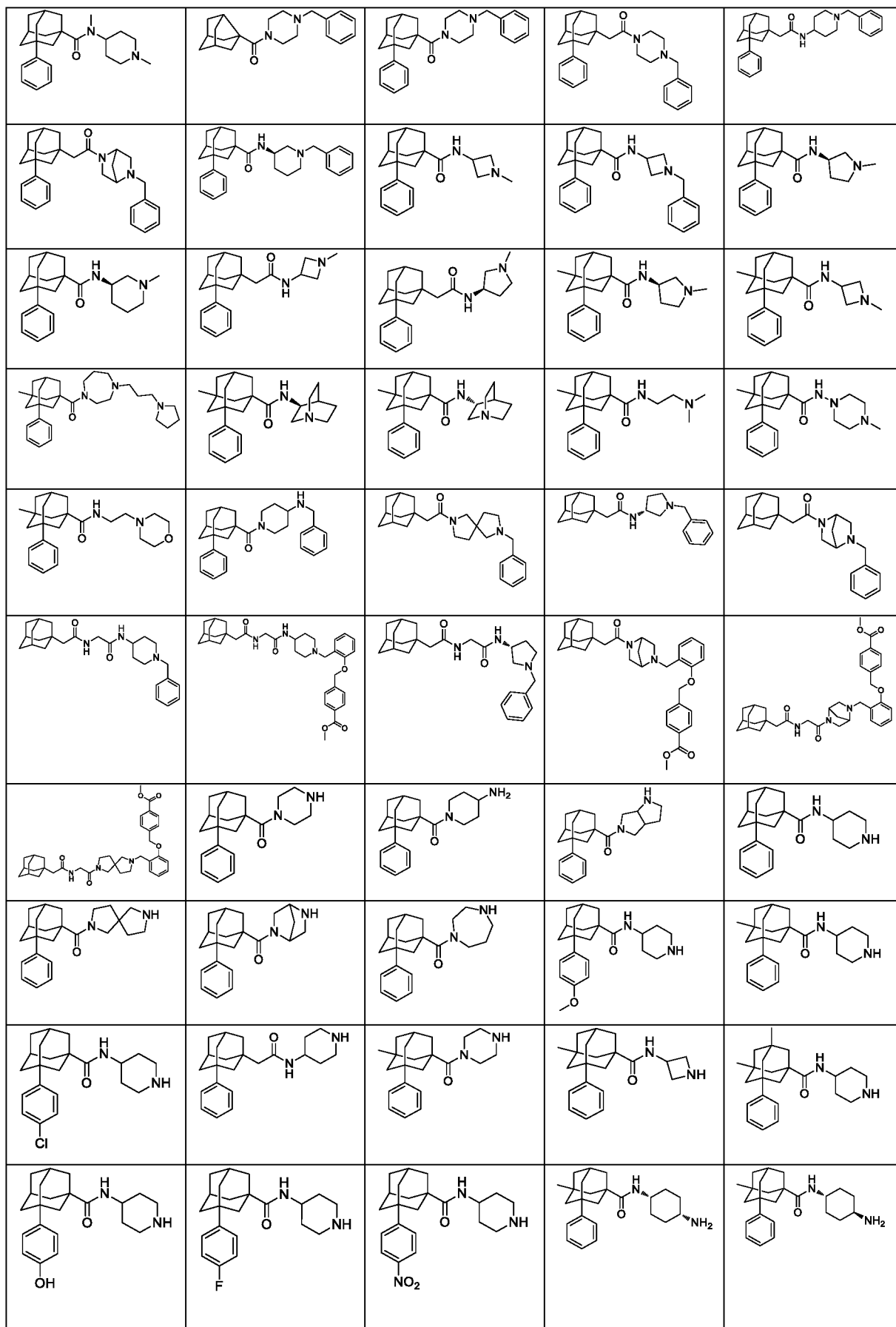
D is selected from the group consisting of

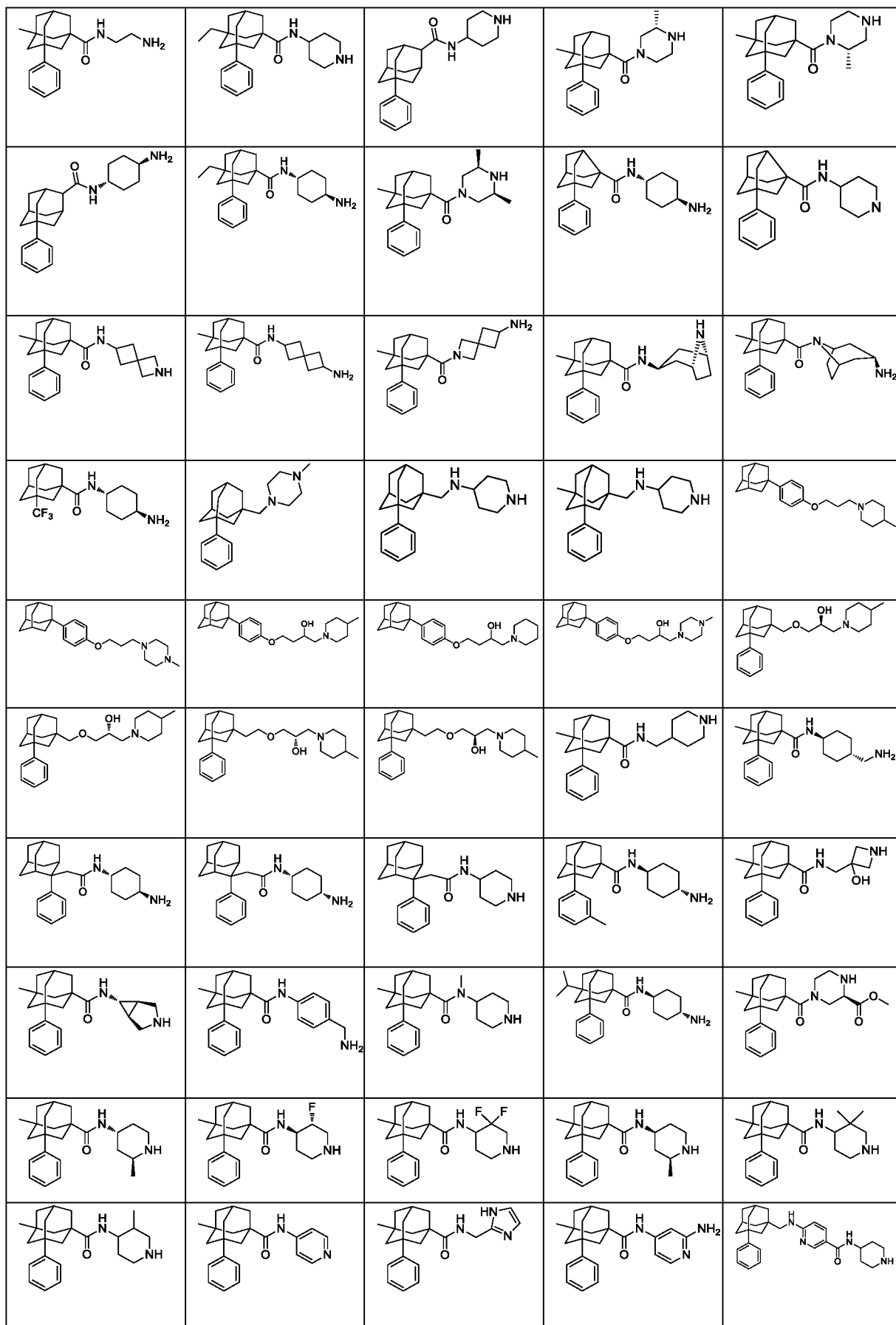


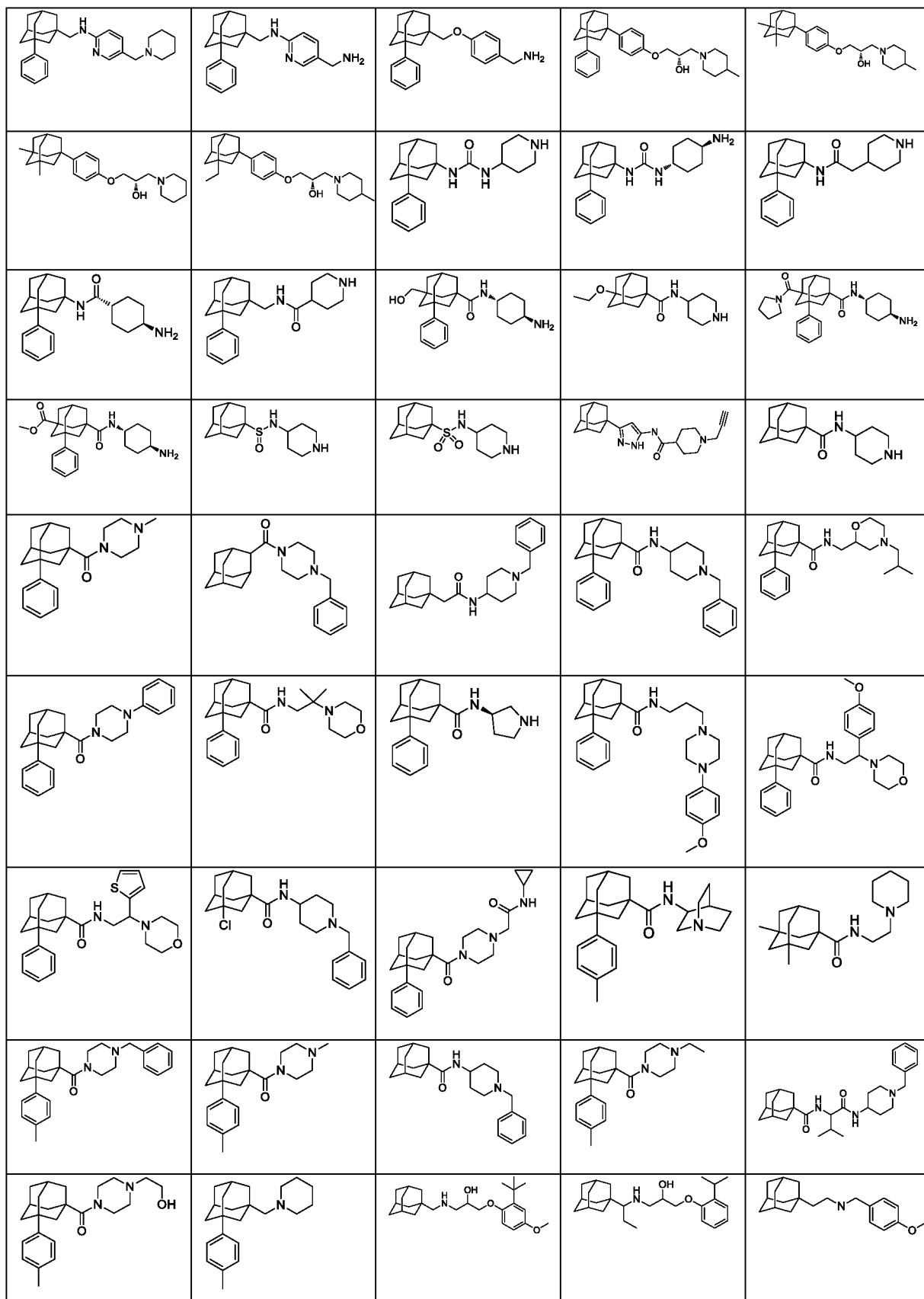
27. The method of claim 26, wherein

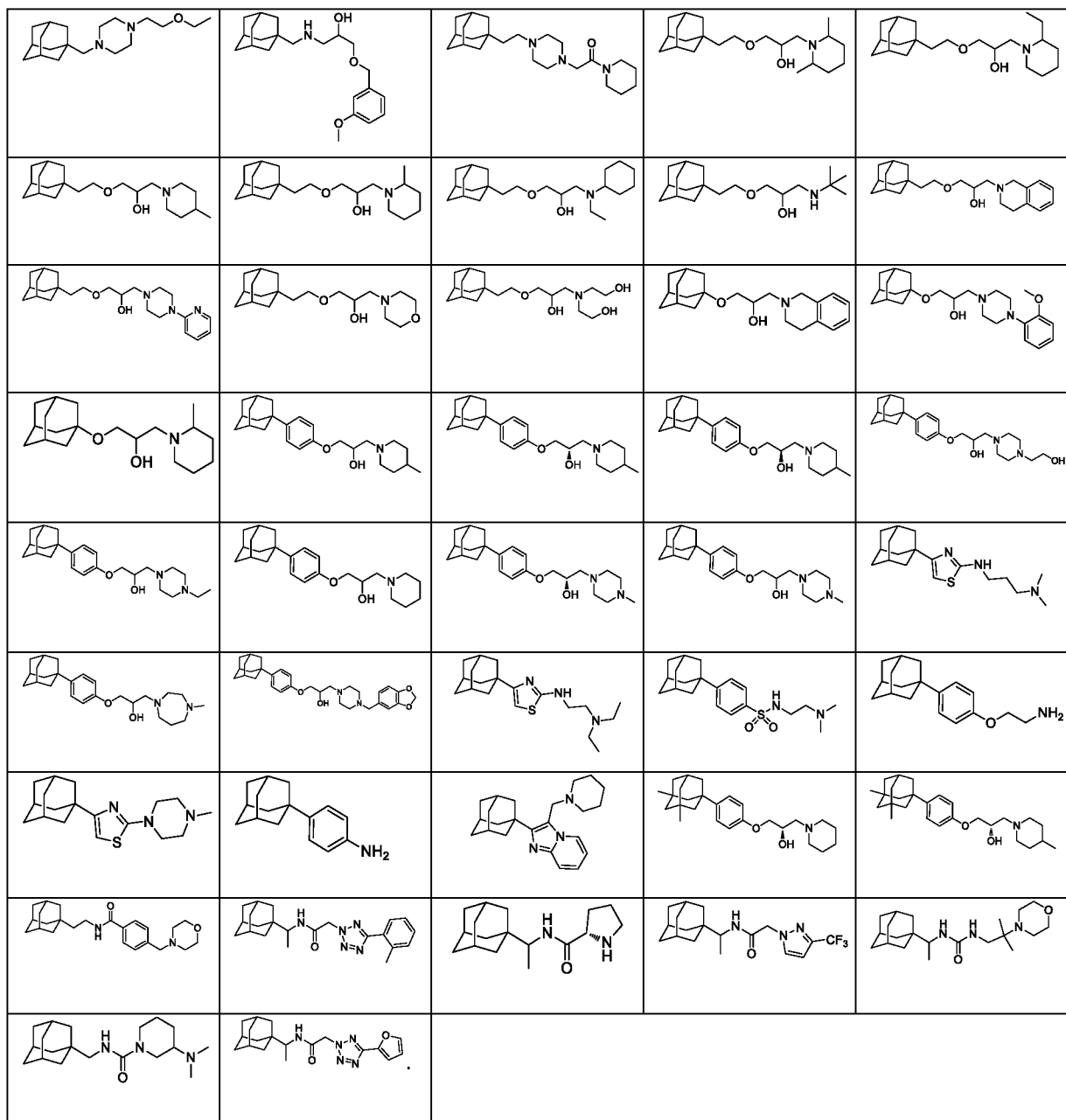
R^{10a} is selected from the group consisting of

5

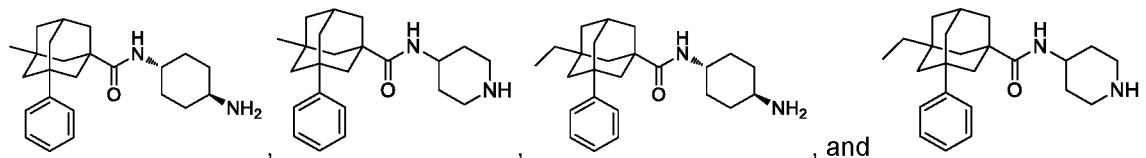








29. The method of claim 28, wherein the compound is selected from the group consisting of:

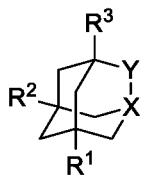


30. The method of claim 28, wherein the infection is associated with filovirus selected from the group consisting of Ebolavirus and Marburgvirus.

31. The method of claim 30, wherein the filovirus is Ebolavirus.

32. The method of claim 31, including administering a therapeutic amount of a therapeutic agent selected from the group consisting of Ribavirin, viral RNA-dependent-RNA-polymerase inhibitors, Favipiravir, Triazavirin, GS-5734, small interfering RNAs (siRNAs) and microRNAs, vaccines, and immunomodulators.

33. The method of claim 29, wherein the infection is associated with filovirus selected from the group consisting of Ebolavirus and Marburgvirus.
34. The method of claim 33, wherein the filovirus is Ebolavirus.
35. The method of claim 34, including administering a therapeutic amount of a therapeutic agent
 5 selected from the group consisting of Ribavirin, viral RNA-dependent-RNA-polymerase inhibitors, Favipiravir, Triazavirin, GS-5734, small interfering RNAs (siRNAs) and microRNAs, vaccines, and immunomodulators.
36. A compound represented by Structural Formula I



I

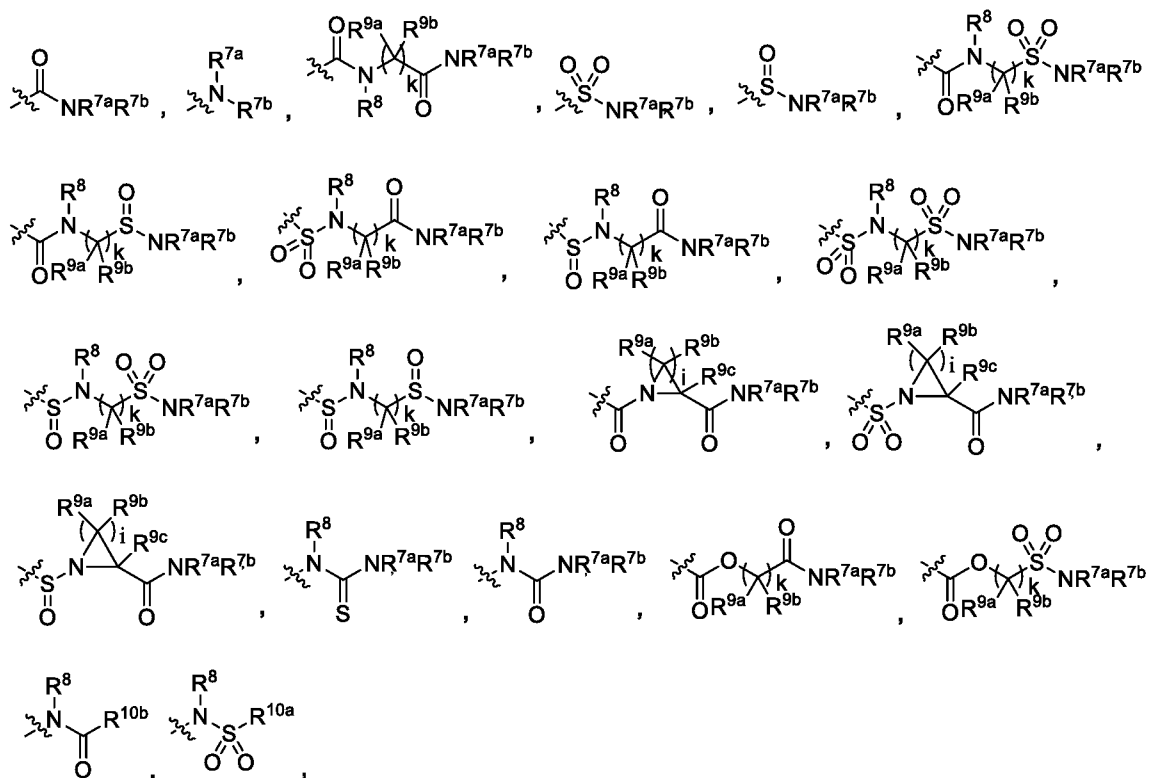
10 or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

X is C-A-D, and Y is a bond or CR⁴R⁵; or

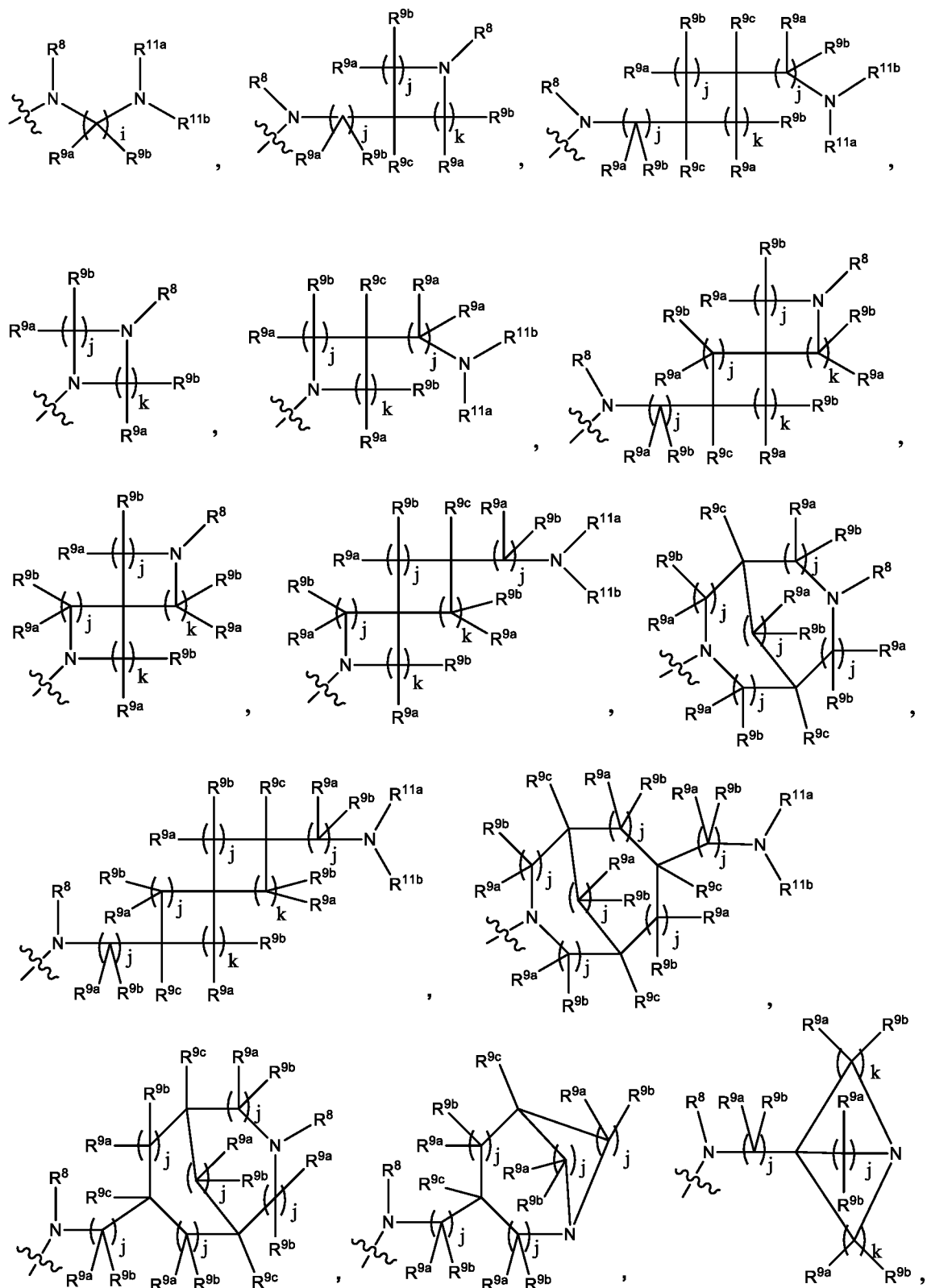
X is CR⁵ and Y is CR⁴-A-D;

A is -C(R^{6a}R^{6b})_j-;

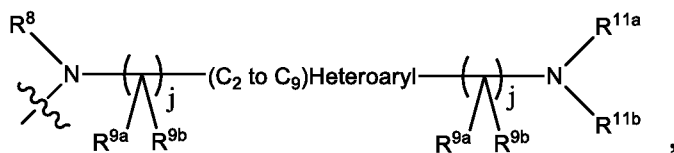
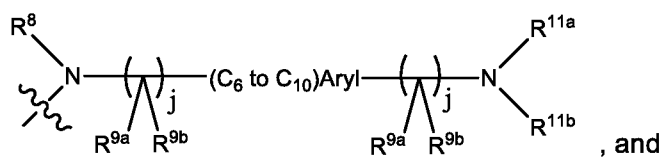
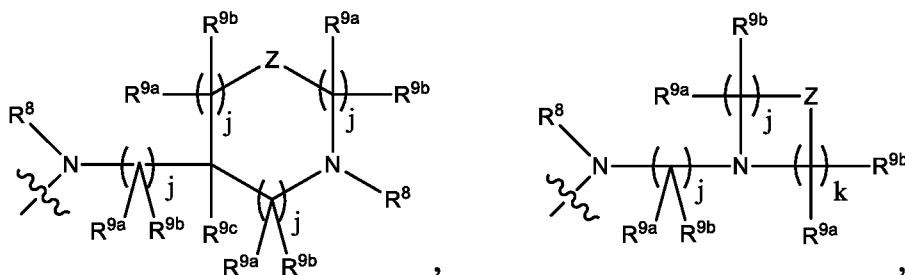
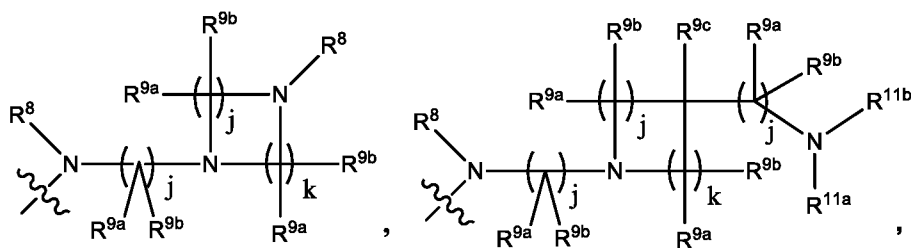
15 D is selected from the group consisting of



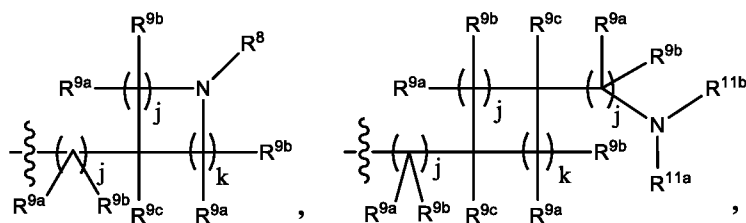
wherein NR^{7a}R^{7b} is selected from the group consisting of

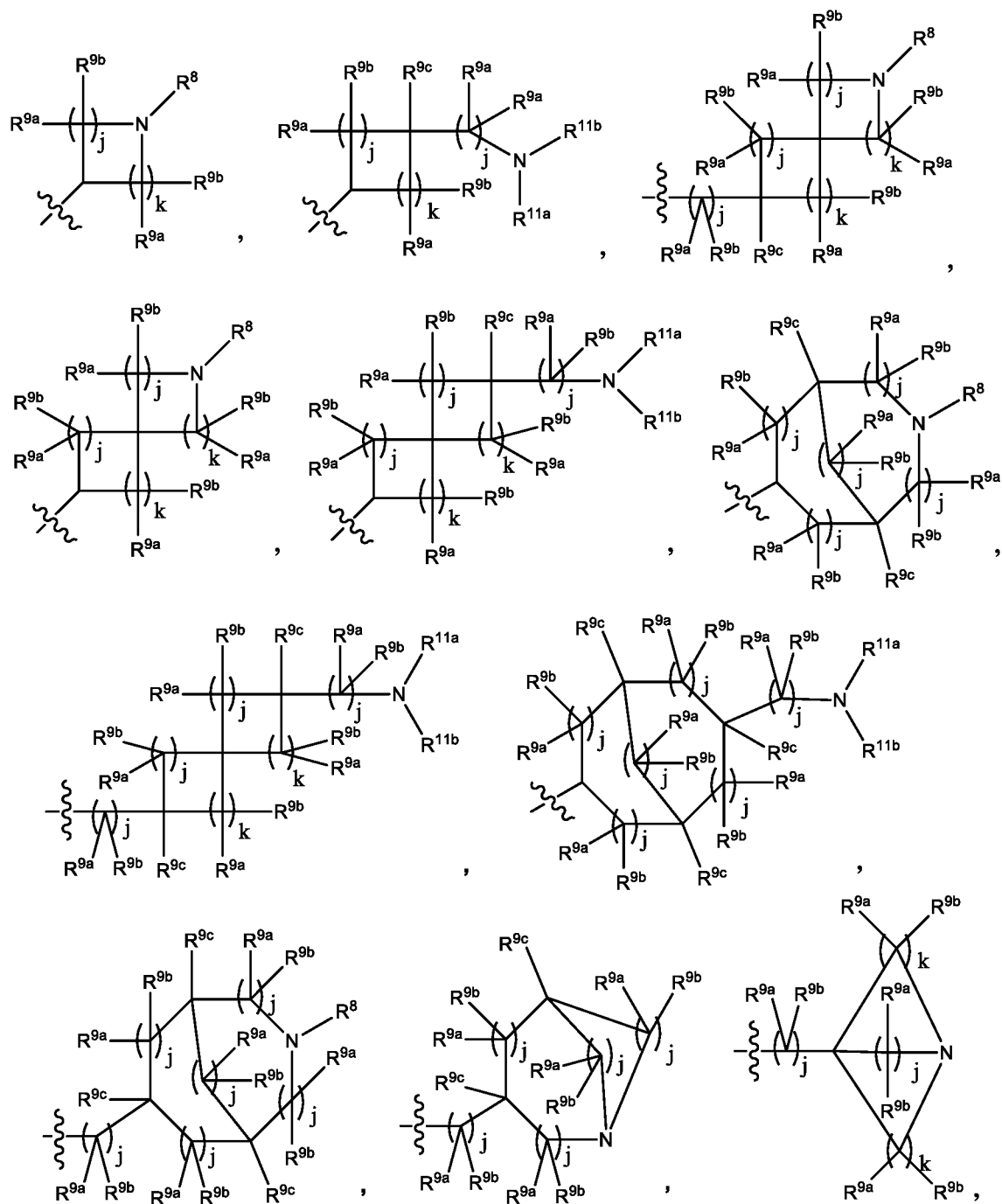


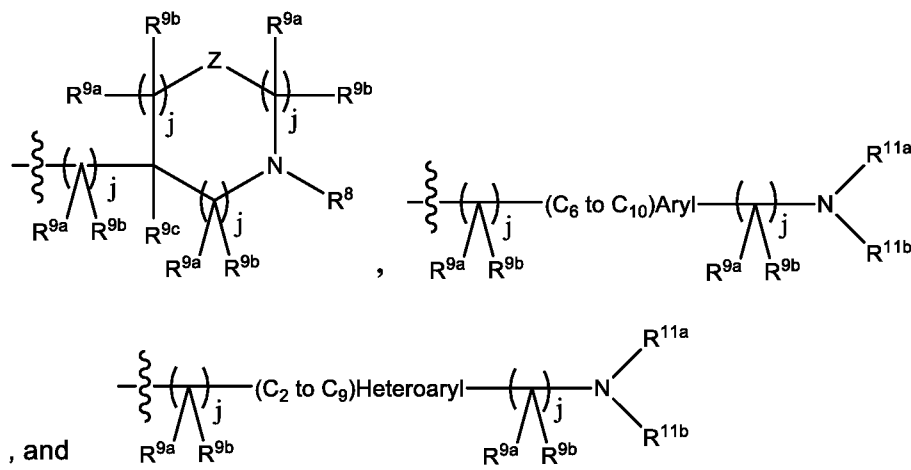
180



and wherein R^{10a} is selected from the group consisting of

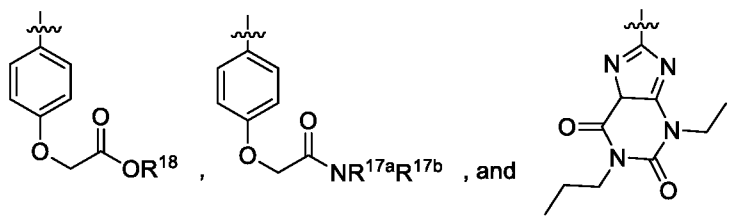






R^1 is selected from (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀), (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl, wherein each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl is optionally substituted with at least one R^{13} group

with the proviso that R^1 is not selected from the group consisting of



R^2 is selected from hydrogen, halogen, OH, nitro, CF₃, -NR^{11a}R^{11b}, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, cyano, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, -C(O)R¹², -C(O)NR^{11a}R^{11b}, -S(O)_mR¹², -S(O)_mNR^{11a}R^{11b}, -NR^{11a}S(O)_mR¹², -(CH₂)_nC(O)OR¹², -(CH₂)_nC(O)N(R^{11a}R^{11b}), -(CH₂)_nN(R^{11a}R^{11b}), -OC(O)R¹², -NR^{11a}C(O)R¹², and -NR^{11a}C(O)N(R^{11a}R^{11b}), wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl is optionally substituted with at least one R^{13} group;

R^3 is selected from hydrogen, halogen, OH, nitro, CF₃, -NR^{11a}R^{11b}, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, cyano, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, -C(O)R¹², -C(O)NR^{11a}R^{11b}, -S(O)_mR¹², -S(O)_mNR^{11a}R^{11b}, -NR^{11a}S(O)_mR¹², -(CH₂)_nC(O)OR¹², -(CH₂)_nC(O)N(R^{11a}R^{11b}), -(CH₂)_nN(R^{11a}R^{11b}), -OC(O)R¹², -NR^{11a}C(O)R¹², and -NR^{11a}C(O)N(R^{11a}R^{11b}), wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl is optionally substituted with at least one R^{13} group;

R^4 is selected from hydrogen, halogen, OH, nitro, CF_3 , $-NR^{11a}R^{11b}$, $(C_1$ to $C_{10})$ alkyl, $(C_1$ to $C_{10})$ alkenyl, $(C_1$ to $C_{10})$ alkynyl, $(C_1$ to $C_{10})$ alkoxy, aryloxy, cyano, $(C_3$ to $C_{10})$ cycloalkyl, $(C_5$ to $C_{10})$ cycloalkenyl, $(C_2$ to $C_9)$ cycloheteroalkyl, $(C_6$ to $C_{10})$ aryl, $(C_2$ to $C_9)$ heteroaryl, -
 $C(O)R^{12}$, $-C(O)NR^{11a}R^{11b}$, $-S(O)_mR^{12}$, $-S(O)_mNR^{11a}R^{11b}$, $-NR^{11a}S(O)_mR^{12}$, $-(CH_2)_nC(O)OR^{12}$, -
 5 $(CH_2)_nC(O)N(R^{11a}R^{11b})$, $-(CH_2)_nN(R^{11a}R^{11b})$, $-OC(O)R^{12}$, $-NR^{11a}C(O)R^{12}$, and -
 $NR^{11a}C(O)N(R^{11a}R^{11b})$, wherein

each of the said $(C_1$ to $C_{10})$ alkyl, $(C_1$ to $C_{10})$ alkenyl, $(C_1$ to $C_{10})$ alkynyl, $(C_1$ to $C_{10})$ alkoxy, aryloxy, $(C_3$ to $C_{10})$ cycloalkyl, $(C_5$ to $C_{10})$ cycloalkenyl, $(C_2$ to $C_9)$ cycloheteroalkyl, $(C_6$ to $C_{10})$ aryl, and $(C_2$ to $C_9)$ heteroaryl is optionally substituted with at least one R^{13} group;

10 R^5 is selected from hydrogen, halogen, OH, nitro, CF_3 , $-NR^{11a}R^{11b}$, $(C_1$ to $C_{10})$ alkyl, $(C_1$ to $C_{10})$ alkenyl, $(C_1$ to $C_{10})$ alkynyl, $(C_1$ to $C_{10})$ alkoxy, aryloxy, cyano, $(C_3$ to $C_{10})$ cycloalkyl, $(C_5$ to $C_{10})$ cycloalkenyl, $(C_2$ to $C_9)$ cycloheteroalkyl, $(C_6$ to $C_{10})$ aryl, $(C_2$ to $C_9)$ heteroaryl, -
 $C(O)R^{12}$, $-C(O)NR^{11a}R^{11b}$, $-S(O)_mR^{12}$, $-S(O)_mNR^{11a}R^{11b}$, $-NR^{11a}S(O)_mR^{12}$, $-(CH_2)_nC(O)OR^{12}$, -
 15 $(CH_2)_nC(O)N(R^{11a}R^{11b})$, $-(CH_2)_nN(R^{11a}R^{11b})$, $-OC(O)R^{12}$, $-NR^{11a}C(O)R^{12}$, and -
 $NR^{11a}C(O)N(R^{11a}R^{11b})$, wherein

each of the said $(C_1$ to $C_{10})$ alkyl, $(C_1$ to $C_{10})$ alkenyl, $(C_1$ to $C_{10})$ alkynyl, $(C_1$ to $C_{10})$ alkoxy, aryloxy, $(C_3$ to $C_{10})$ cycloalkyl, $(C_5$ to $C_{10})$ cycloalkenyl, $(C_2$ to $C_9)$ cycloheteroalkyl, $(C_6$ to $C_{10})$ aryl, and $(C_2$ to $C_9)$ heteroaryl is optionally substituted with at least one R^{13} group;

each of the R^{6a} and R^{6b} is independently selected from hydrogen, halogen, OH, nitro, CF_3 ,
 20 $-NR^{11a}R^{11b}$, $(C_1$ to $C_{10})$ alkyl, $(C_1$ to $C_{10})$ alkenyl, $(C_1$ to $C_{10})$ alkynyl, $(C_1$ to $C_{10})$ alkoxy, aryloxy, cyano, $(C_3$ to $C_{10})$ cycloalkyl, $(C_5$ to $C_{10})$ cycloalkenyl, $(C_2$ to $C_9)$ cycloheteroalkyl, $(C_6$ to $C_{10})$ aryl, $(C_2$ to $C_9)$ heteroaryl, $-C(O)R^{12}$, $-C(O)NR^{11a}R^{11b}$, $-S(O)_mR^{12}$, $-S(O)_mNR^{11a}R^{11b}$, $-NR^{11a}S(O)_mR^{12}$,
 - $(CH_2)_nC(O)OR^{12}$, $-(CH_2)_nC(O)N(R^{11a}R^{11b})$, - $(CH_2)_nN(R^{11a}R^{11b})$, $-OC(O)R^{12}$, - $NR^{11a}C(O)R^{12}$,
 and $-NR^{11a}C(O)N(R^{11a}R^{11b})$, wherein

25 each of the said $(C_1$ to $C_{10})$ alkyl, $(C_1$ to $C_{10})$ alkenyl, $(C_1$ to $C_{10})$ alkynyl, $(C_1$ to $C_{10})$ alkoxy, aryloxy, $(C_3$ to $C_{10})$ cycloalkyl, $(C_5$ to $C_{10})$ cycloalkenyl, $(C_2$ to $C_9)$ cycloheteroalkyl, $(C_6$ to $C_{10})$ aryl, and $(C_2$ to $C_9)$ heteroaryl is optionally substituted with at least one R^{13} group;

each R^8 is independently selected from hydrogen, $(C_1$ to $C_{10})$ alkyl, $(C_1$ to $C_{10})$ alkenyl, $(C_1$ to $C_{10})$ alkynyl, $(C_1$ to $C_{10})$ alkoxy, aryloxy, $(C_3$ to $C_{10})$ cycloalkyl, $(C_5$ to $C_{10})$ cycloalkenyl, $(C_2$ to $C_9)$ cycloheteroalkyl, $(C_6$ to $C_{10})$ aryl, $(C_2$ to $C_9)$ heteroaryl, $(C_6$ to $C_{10})$ arylene, and $(C_2$ to $C_9)$ heteroarylene, wherein

each of the said $(C_1$ to $C_{10})$ alkyl, $(C_1$ to $C_{10})$ alkenyl, $(C_1$ to $C_{10})$ alkynyl, $(C_1$ to $C_{10})$ alkoxy, aryloxy, $(C_3$ to $C_{10})$ cycloalkyl, $(C_5$ to $C_{10})$ cycloalkenyl, $(C_2$ to $C_9)$ cycloheteroalkyl, $(C_6$ to $C_{10})$ aryl, $(C_2$ to $C_9)$ heteroaryl, $(C_6$ to $C_{10})$ arylene, and $(C_2$ to $C_9)$ heteroarylene is optionally substituted
 35 with at least one R^{13} group;

each of the R^{9a} , R^{9b} , and R^{9c} is independently selected from hydrogen, halogen, OH, nitro, CF_3 , $-NR^{11a}R^{11b}$, $(C_1$ to $C_{10})$ alkyl, $(C_1$ to $C_{10})$ alkenyl, $(C_1$ to $C_{10})$ alkynyl, $(C_1$ to $C_{10})$ alkoxy, aryloxy, cyano, $(C_3$ to $C_{10})$ cycloalkyl, $(C_5$ to $C_{10})$ cycloalkenyl, $(C_2$ to $C_9)$ cycloheteroalkyl, $(C_6$ to $C_{10})$ aryl, $(C_2$ to $C_9)$ heteroaryl, $-C(O)R^{12}$, $-C(O)NR^{11a}R^{11b}$, $-S(O)_mR^{12}$, $-S(O)_mNR^{11a}R^{11b}$, $-NR^{11a}S(O)_mR^{12}$, -

$(\text{CH}_2)_n\text{C}(\text{O})\text{OR}^{12}$, $-(\text{CH}_2)_n\text{C}(\text{O})\text{N}(\text{R}^{11a}\text{R}^{11b})$, $-(\text{CH}_2)_n\text{N}(\text{R}^{11a}\text{R}^{11b})$, $-\text{OC}(\text{O})\text{R}^{12}$, $-\text{NR}^{11a}\text{C}(\text{O})\text{R}^{12}$, and $-\text{NR}^{11a}\text{C}(\text{O})\text{N}(\text{R}^{11a}\text{R}^{11b})$, wherein

each of the said $(\text{C}_1$ to C_{10}) alkyl, $(\text{C}_1$ to C_{10}) alkenyl, $(\text{C}_1$ to C_{10}) alkynyl, $(\text{C}_1$ to C_{10}) alkoxy, aryloxy, $(\text{C}_3$ to C_{10}) cycloalkyl, $(\text{C}_5$ to C_{10}) cycloalkenyl, $(\text{C}_2$ to C_9) cycloheteroalkyl, $(\text{C}_6$ to C_{10}) aryl, and $(\text{C}_2$ to C_9) heteroaryl is optionally substituted with at least one R^{13} group;

each of the R^{11a} and R^{11b} is independently selected from hydrogen, $(\text{C}_1$ to C_{10}) alkyl, $(\text{C}_1$ to C_{10}) alkenyl, $(\text{C}_1$ to C_{10}) alkynyl, $(\text{C}_1$ to C_{10}) alkoxy, aryloxy, $(\text{C}_3$ to C_{10}) cycloalkyl, $(\text{C}_5$ to C_{10}) cycloalkenyl, $(\text{C}_2$ to C_9) cycloheteroalkyl, $(\text{C}_6$ to C_{10}) aryl, $(\text{C}_2$ to C_9) heteroaryl, $(\text{C}_6$ to C_{10}) arylene, and $(\text{C}_2$ to C_9) heteroarylene, wherein

each of the said $(\text{C}_1$ to C_{10}) alkyl, $(\text{C}_1$ to C_{10}) alkenyl, $(\text{C}_1$ to C_{10}) alkynyl, $(\text{C}_1$ to C_{10}) alkoxy, aryloxy, $(\text{C}_3$ to C_{10}) cycloalkyl, $(\text{C}_5$ to C_{10}) cycloalkenyl, $(\text{C}_2$ to C_9) cycloheteroalkyl, $(\text{C}_6$ to C_{10}) aryl, $(\text{C}_2$ to C_9) heteroaryl, $(\text{C}_6$ to C_{10}) arylene, and $(\text{C}_2$ to C_9) heteroarylene is optionally substituted with at least one R^{13} group,

or R^{11a} and R^{11b} may be taken together with the nitrogen atom to which they are attached to form a $(\text{C}_2$ to $\text{C}_{10})$ cycloheteroalkyl ring, wherein

said $(\text{C}_2$ to $\text{C}_{10})$ cycloheteroalkyl ring has 1 to 3 ring heteroatoms selected from the group consisting of N, O, and S, and wherein

the said $(\text{C}_2$ to $\text{C}_{10})$ cycloheteroalkyl ring is optionally substituted with at least one R^{13} group;

each of the R^{12} is independently selected from hydrogen, $(\text{C}_1$ to $\text{C}_{10})$ alkyl, $(\text{C}_1$ to $\text{C}_{10})$ alkenyl, $(\text{C}_1$ to $\text{C}_{10})$ alkynyl, $(\text{C}_3$ to $\text{C}_{10})$ cycloalkyl, $(\text{C}_5$ to $\text{C}_{10})$ cycloalkenyl, $(\text{C}_2$ to C_9) cycloheteroalkyl, $(\text{C}_6$ to $\text{C}_{10})$ aryl, and $(\text{C}_2$ to C_9) heteroaryl, wherein

each of the said $(\text{C}_1$ to $\text{C}_{10})$ alkyl, $(\text{C}_1$ to $\text{C}_{10})$ alkenyl, $(\text{C}_1$ to $\text{C}_{10})$ alkynyl, $(\text{C}_3$ to $\text{C}_{10})$ cycloalkyl, $(\text{C}_5$ to $\text{C}_{10})$ cycloalkenyl, $(\text{C}_2$ to C_9) cycloheteroalkyl, $(\text{C}_6$ to $\text{C}_{10})$ aryl, and $(\text{C}_2$ to C_9) heteroaryl is optionally substituted with at least one R^{13} group;

each R^{13} is independently selected from hydrogen, halogen, OH, nitro, CF_3 , $-\text{NR}^{14a}\text{R}^{14b}$, oxo, $(\text{C}_1$ to $\text{C}_{10})$ alkyl, $(\text{C}_1$ to $\text{C}_{10})$ alkenyl, $(\text{C}_1$ to $\text{C}_{10})$ alkynyl, $(\text{C}_1$ to $\text{C}_{10})$ alkoxy, aryloxy, cyano, $(\text{C}_3$ to $\text{C}_{10})$ cycloalkyl, $(\text{C}_5$ to $\text{C}_{10})$ cycloalkenyl, $(\text{C}_2$ to C_9) cycloheteroalkyl, $(\text{C}_6$ to $\text{C}_{10})$ aryl, $(\text{C}_2$ to C_9) heteroaryl, $(\text{C}_6$ to $\text{C}_{10})$ arylene, $(\text{C}_2$ to C_9) heteroarylene, $(\text{C}_3$ to $\text{C}_{10})$ cycloalkylene, $(\text{C}_2$ to $\text{C}_{10})$ cycloheteroalkylene, $-\text{C}(\text{O})\text{R}^{15}$, $-\text{C}(\text{O})\text{NR}^{14a}\text{R}^{14b}$, $-\text{S}(\text{O})_m\text{R}^{15}$, $-\text{S}(\text{O})_m\text{NR}^{14a}\text{R}^{14b}$, $-\text{NR}^{14a}\text{S}(\text{O})_m\text{R}^{15}$, $-(\text{CH}_2)_n\text{C}(\text{O})\text{OR}^{15}$, $-(\text{CH}_2)_n\text{C}(\text{O})\text{N}(\text{R}^{14a}\text{R}^{14b})$, $-(\text{CH}_2)_n\text{N}(\text{R}^{14a}\text{R}^{14b})$, $-\text{OC}(\text{O})\text{R}^{15}$, $-\text{O}(\text{CH}_2)_n\text{O}-$, $-\text{NR}^{14a}\text{C}(\text{O})\text{R}^{15}$, and $-\text{NR}^{14a}\text{C}(\text{O})\text{N}(\text{R}^{14a}\text{R}^{14b})$, wherein

each of the said $(\text{C}_1$ to $\text{C}_{10})$ alkyl, $(\text{C}_1$ to $\text{C}_{10})$ alkenyl, $(\text{C}_1$ to $\text{C}_{10})$ alkynyl, $(\text{C}_1$ to $\text{C}_{10})$ alkoxy, aryloxy, $(\text{C}_3$ to $\text{C}_{10})$ cycloalkyl, $(\text{C}_5$ to $\text{C}_{10})$ cycloalkenyl, $(\text{C}_2$ to $\text{C}_{10})$ cycloheteroalkyl, $(\text{C}_6$ to $\text{C}_{10})$ aryl, $(\text{C}_2$ to C_9) heteroaryl, $(\text{C}_6$ to $\text{C}_{10})$ arylene, $(\text{C}_2$ to C_9) heteroarylene, $(\text{C}_3$ to $\text{C}_{10})$ cycloalkylene, and $(\text{C}_2$ to $\text{C}_{10})$ cycloheteroalkylene is optionally substituted with at least one R^{16} group;

each of the R^{14a} and R^{14b} is independently selected from hydrogen, $(\text{C}_1$ to $\text{C}_{10})$ alkyl, $(\text{C}_1$ to $\text{C}_{10})$ alkenyl, $(\text{C}_1$ to $\text{C}_{10})$ alkynyl, $(\text{C}_1$ to $\text{C}_{10})$ alkoxy, aryloxy, $(\text{C}_3$ to $\text{C}_{10})$ cycloalkyl, $(\text{C}_5$ to $\text{C}_{10})$ cycloalkenyl, $(\text{C}_2$ to C_9) cycloheteroalkyl, $(\text{C}_6$ to $\text{C}_{10})$ aryl, $(\text{C}_2$ to C_9) heteroaryl, $(\text{C}_6$ to $\text{C}_{10})$ arylene, and $(\text{C}_2$ to C_9) heteroarylene, wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, and (C₂ to C₉) heteroarylene is optionally substituted with at least one R¹⁶ group,

or R^{14a} and R^{14b} may be taken together with the nitrogen atom to which they are attached to form a (C₂ to C₁₀) cycloheteroalkyl ring, wherein

said (C₂ to C₁₀) cycloheteroalkyl ring has 1 to 3 ring heteroatoms selected from the group consisting of N, O, and S, and wherein

the said (C₂ to C₁₀) cycloheteroalkyl ring is optionally substituted with at least one R¹⁶ group;

each R¹⁵ is independently selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl, wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl is optionally substituted with at least one R¹⁶ group;

each R¹⁶ is independently selected from hydrogen, halogen, OH, nitro, CF₃, -NR^{17a}R^{17b}, oxo, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, cyano, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, (C₂ to C₉) heteroarylene, (C₃ to C₁₀) cycloalkylene, (C₂ to C₁₀) cycloheteroalkylene, -C(O)R¹⁸, -C(O)NR^{17a}R^{17b}, -S(O)_mR¹⁸, -S(O)_mNR^{17a}R^{17b}, -NR^{17a}S(O)_mR¹⁸, -(CH₂)_nC(O)OR¹⁸, -(CH₂)_nC(O)N(R^{17a}R^{17b}), -(CH₂)_nN(R^{17a}R^{17b}), -OC(O)R¹⁸, -NR^{17a}C(O)R¹⁸, and -NR^{17a}C(O)N(R^{17a}R^{17b}), wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) aryl, (C₆ to C₁₀) arylene, (C₂ to C₉) heteroarylene, (C₃ to C₁₀) cycloalkylene, and (C₂ to C₁₀) cycloheteroalkylene is optionally substituted with at least one R¹⁹ group;

each of the R^{17a} and R^{17b} is independently selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, and (C₂ to C₉) heteroarylene, wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, and (C₂ to C₉) heteroarylene is optionally substituted with at least one R¹⁹ group,

or R^{17a} and R^{17b} may be taken together with the nitrogen atom to which they are attached to form a (C₂ to C₁₀) cycloheteroalkyl ring, wherein

said (C₂ to C₁₀) cycloheteroalkyl ring has 1 to 3 ring heteroatoms selected from the group consisting of N, O, and S, and wherein

the said (C₂ to C₁₀) cycloheteroalkyl ring is optionally substituted with at least one R¹⁹ group;

each R^{18} is independently selected from hydrogen, halogen, OH, nitro, CF_3 , $(C_1 \text{ to } C_{10})$ alkyl, $(C_1 \text{ to } C_{10})$ alkenyl, $(C_1 \text{ to } C_{10})$ alkynyl, $(C_1 \text{ to } C_{10})$ alkoxy, aryloxy, cyano, $(C_3 \text{ to } C_{10})$ cycloalkyl, $(C_5 \text{ to } C_{10})$ cycloalkenyl, $(C_2 \text{ to } C_{10})$ cycloheteroalkyl, $(C_6 \text{ to } C_{10})$ aryl, and $(C_2 \text{ to } C_9)$ heteroaryl, wherein

each of the said $(C_1 \text{ to } C_{10})$ alkyl, $(C_1 \text{ to } C_{10})$ alkenyl, $(C_1 \text{ to } C_{10})$ alkynyl, $(C_3 \text{ to } C_{10})$ cycloalkyl, $(C_5 \text{ to } C_{10})$ cycloalkenyl, $(C_2 \text{ to } C_{10})$ cycloheteroalkyl, $(C_2 \text{ to } C_9)$ heteroaryl, and $(C_6 \text{ to } C_{10})$ aryl is optionally substituted with at least one R^{19} group;

each R^{19} is independently selected from hydrogen, halogen, OH, nitro, CF_3 , $-NR^{20a}R^{20b}$, oxo, $(C_1 \text{ to } C_{10})$ alkyl, $(C_1 \text{ to } C_{10})$ alkenyl, $(C_1 \text{ to } C_{10})$ alkynyl, $(C_1 \text{ to } C_{10})$ alkoxy, aryloxy, cyano, $(C_3 \text{ to } C_{10})$ cycloalkyl, $(C_5 \text{ to } C_{10})$ cycloalkenyl, $(C_2 \text{ to } C_{10})$ cycloheteroalkyl, $(C_6 \text{ to } C_{10})$ aryl, $(C_2 \text{ to } C_9)$ heteroaryl, $(C_6 \text{ to } C_{10})$ arylene, $(C_2 \text{ to } C_9)$ heteroarylene, $(C_3 \text{ to } C_{10})$ cycloalkylene, $(C_2 \text{ to } C_{10})$ cycloheteroalkylene, $-C(O)R^{21}$, $-C(O)NR^{20a}R^{20b}$, $-S(O)_mR^{21}$, $-S(O)_mNR^{20a}R^{20b}$, $-NR^{20a}S(O)_mR^{21}$, $-(CH_2)_nC(O)OR^{21}$, $-(CH_2)_nC(O)N(R^{20a}R^{20b})$, $-(CH_2)_nN(R^{20a}R^{20b})$, $-OC(O)R^{21}$, $-NR^{20a}C(O)R^{21}$, and $-NR^{20a}C(O)N(R^{20a}R^{20b})$, wherein

each of the said $(C_1 \text{ to } C_{10})$ alkyl, $(C_1 \text{ to } C_{10})$ alkenyl, $(C_1 \text{ to } C_{10})$ alkynyl, $(C_1 \text{ to } C_{10})$ alkoxy, aryloxy, $(C_3 \text{ to } C_{10})$ cycloalkyl, $(C_5 \text{ to } C_{10})$ cycloalkenyl, $(C_2 \text{ to } C_{10})$ cycloheteroalkyl, $(C_6 \text{ to } C_{10})$ aryl, $(C_2 \text{ to } C_9)$ heteroaryl, $(C_6 \text{ to } C_{10})$ arylene, $(C_2 \text{ to } C_9)$ heteroarylene, $(C_3 \text{ to } C_{10})$ cycloalkylene, and $(C_2 \text{ to } C_{10})$ cycloheteroalkylene is optionally substituted with at least one R^{22} group;

each of the R^{20a} and R^{20b} is independently selected from hydrogen, $(C_1 \text{ to } C_{10})$ alkyl, $(C_1 \text{ to } C_{10})$ alkenyl, $(C_1 \text{ to } C_{10})$ alkynyl, $(C_1 \text{ to } C_{10})$ alkoxy, aryloxy, $(C_3 \text{ to } C_{10})$ cycloalkyl, $(C_5 \text{ to } C_{10})$ cycloalkenyl, $(C_2 \text{ to } C_{10})$ cycloheteroalkyl, $(C_6 \text{ to } C_{10})$ aryl, and $(C_2 \text{ to } C_9)$ heteroaryl, wherein

each of the said $(C_1 \text{ to } C_{10})$ alkyl, $(C_1 \text{ to } C_{10})$ alkenyl, $(C_1 \text{ to } C_{10})$ alkynyl, $(C_1 \text{ to } C_{10})$ alkoxy, aryloxy, $(C_3 \text{ to } C_{10})$ cycloalkyl, $(C_5 \text{ to } C_{10})$ cycloalkenyl, $(C_2 \text{ to } C_{10})$ cycloheteroalkyl, $(C_6 \text{ to } C_{10})$ aryl, and $(C_2 \text{ to } C_9)$ heteroaryl is optionally substituted with at least one R^{22} group,

or R^{20a} and R^{20b} may be taken together with the nitrogen atom to which they are attached to form a $(C_2 \text{ to } C_{10})$ cycloheteroalkyl ring, wherein

said $(C_2 \text{ to } C_{10})$ cycloheteroalkyl ring has 1 to 3 ring heteroatoms selected from the group consisting of N, O, and S, and wherein

the said $(C_2 \text{ to } C_{10})$ cycloheteroalkyl ring is optionally substituted with at least one R^{22} group;

each R^{21} is independently selected from hydrogen, halogen, OH, nitro, CF_3 , $(C_1 \text{ to } C_{10})$ alkyl, $(C_1 \text{ to } C_{10})$ alkenyl, $(C_1 \text{ to } C_{10})$ alkynyl, $(C_1 \text{ to } C_{10})$ alkoxy, aryloxy, cyano, $(C_3 \text{ to } C_{10})$ cycloalkyl, $(C_5 \text{ to } C_{10})$ cycloalkenyl, $(C_2 \text{ to } C_{10})$ cycloheteroalkyl, $(C_6 \text{ to } C_{10})$ aryl, and $(C_2 \text{ to } C_9)$ heteroaryl;

each R^{22} is independently selected from hydrogen, halogen, OH, nitro, CF_3 , $-NR^{23a}R^{23b}$, oxo, $(C_1 \text{ to } C_{10})$ alkyl, $(C_1 \text{ to } C_{10})$ alkenyl, $(C_1 \text{ to } C_{10})$ alkynyl, $(C_1 \text{ to } C_{10})$ alkoxy, aryloxy, cyano, $(C_3 \text{ to } C_{10})$ cycloalkyl, $(C_5 \text{ to } C_{10})$ cycloalkenyl, $(C_2 \text{ to } C_{10})$ cycloheteroalkyl, $(C_6 \text{ to } C_{10})$ aryl, $(C_2 \text{ to } C_9)$ heteroaryl, $(C_6 \text{ to } C_{10})$ arylene, $(C_2 \text{ to } C_9)$ heteroarylene, $(C_3 \text{ to } C_{10})$ cycloalkylene, $(C_2 \text{ to } C_{10})$ cycloheteroalkylene, $-C(O)R^{24}$, $-C(O)NR^{23a}R^{23b}$, $-S(O)_mR^{24}$, $-S(O)_mNR^{23a}R^{23b}$, $-NR^{23a}S(O)_mR^{24}$, $-(CH_2)_nC(O)OR^{24}$, $-(CH_2)_nC(O)N(R^{23a}R^{23b})$, $-(CH_2)_nN(R^{23a}R^{23b})$, $-OC(O)R^{24}$, $-NR^{23a}C(O)R^{24}$, and $-NR^{23a}C(O)N(R^{23a}R^{23b})$, wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, (C₂ to C₉) heteroarylene, (C₃ to C₁₀) cycloalkylene, and (C₂ to C₁₀) cycloheteroalkylene is optionally substituted with at least one R²⁵ group;

each of the R^{23a} and R^{23b} is independently selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₂ to C₉) heteroaryl, and (C₆ to C₁₀) aryl;

each R²⁴ is independently selected from hydrogen, halogen, OH, nitro, CF₃, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, cyano, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl;

each R²⁵ is independently selected from hydrogen, halogen, OH, nitro, CF₃, -NR^{26a}R^{26b}, oxo, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, cyano, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, (C₂ to C₉) heteroarylene, (C₃ to C₁₀) cycloalkylene, (C₂ to C₁₀) cycloheteroalkylene, -C(O)R²⁷, -C(O)NR^{26a}R^{26b}, -S(O)_mR²⁷, -S(O)_mNR^{26a}R^{26b}, -NR^{26a}S(O)_mR²⁷, -(CH₂)_nC(O)OR²⁷, -(CH₂)_nC(O)N(R^{26a}R^{26b}), -(CH₂)_nN(R^{26a}R^{26b}), -OC(O)R²⁷, -NR^{26a}C(O)R²⁷, and -NR^{26a}C(O)N(R^{26a}R^{26b}), wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, (C₂ to C₉) heteroarylene, (C₃ to C₁₀) cycloalkylene, and (C₂ to C₁₀) cycloheteroalkylene is optionally substituted with at least one R²⁷ group;

each of the R^{26a} and R^{26b} is independently selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl,

or R^{26a} and R^{26b} may be taken together with the nitrogen atom to which they are attached to form a (C₂ to C₁₀) cycloheteroalkyl ring, wherein

said (C₂ to C₁₀) cycloheteroalkyl ring has 1 to 3 ring heteroatoms selected from the group consisting of N, O, and S;

each R²⁷ is independently selected from hydrogen, halogen, OH, nitro, CF₃, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, cyano, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl;

h is 1 or 2;

i is 2, 3, 4, 5, or 6;

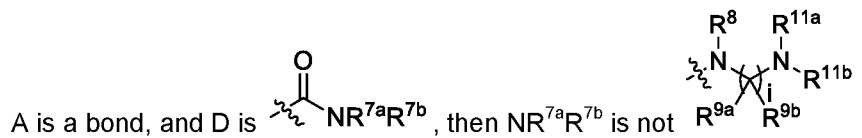
j is 0, 1, 2, 3, 4, or 5;

k is 1, 2, 3, 4, or 5;

m is 0, 1 or 2;

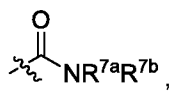
n is 0, 1, 2, 3, or 4;

with the proviso that when R^1 is phenyl, R^2 is hydrogen, R^3 is hydrogen, X is C-A-D, Y is CH_2 ,

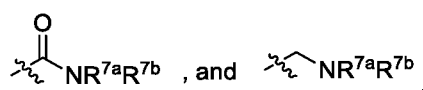


and with the proviso that when R^1 is selected from the group consisting of 4-methylphenyl, 3,4-dimethylphenyl, and 4-methoxyphenyl, R^2 is hydrogen, R^3 is hydrogen, X is C-A-D, Y is CH_2 ,

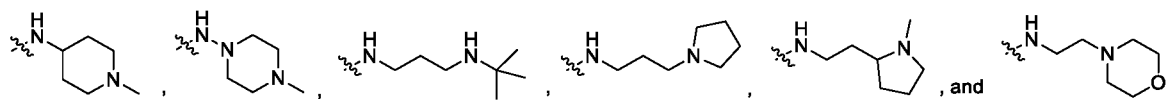
5

A is a bond, then D is not selected from the group consisting of ,

and with the proviso that when R^1 is 4-chlorophenyl, R^2 is hydrogen, R^3 is hydrogen, X is C-A-D, Y is CH_2 , A is a bond, and D is selected from the group consisting of

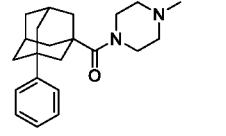
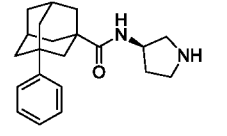
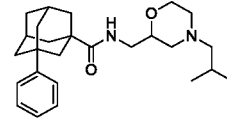
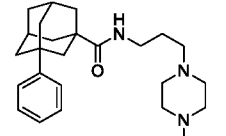
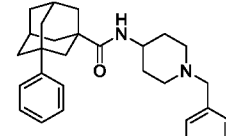
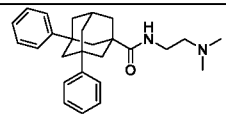
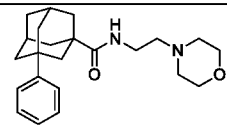
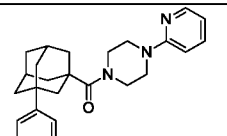
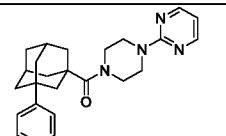
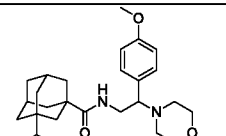
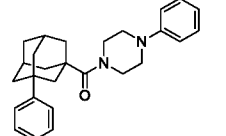
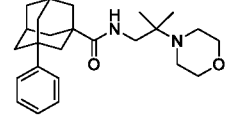
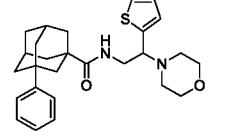
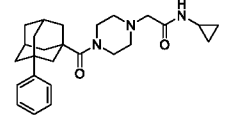
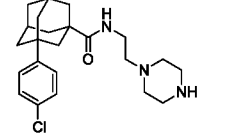
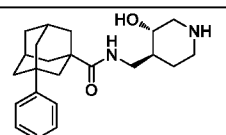
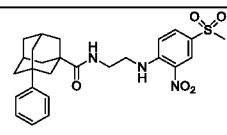
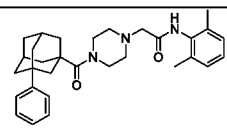
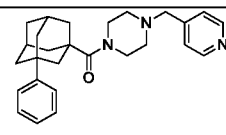
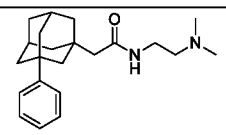
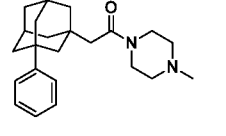
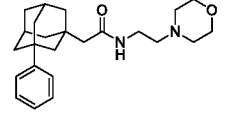
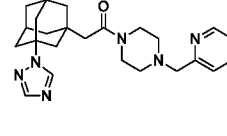
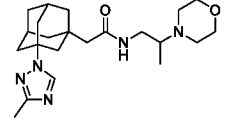
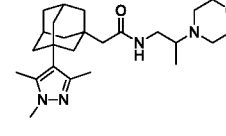


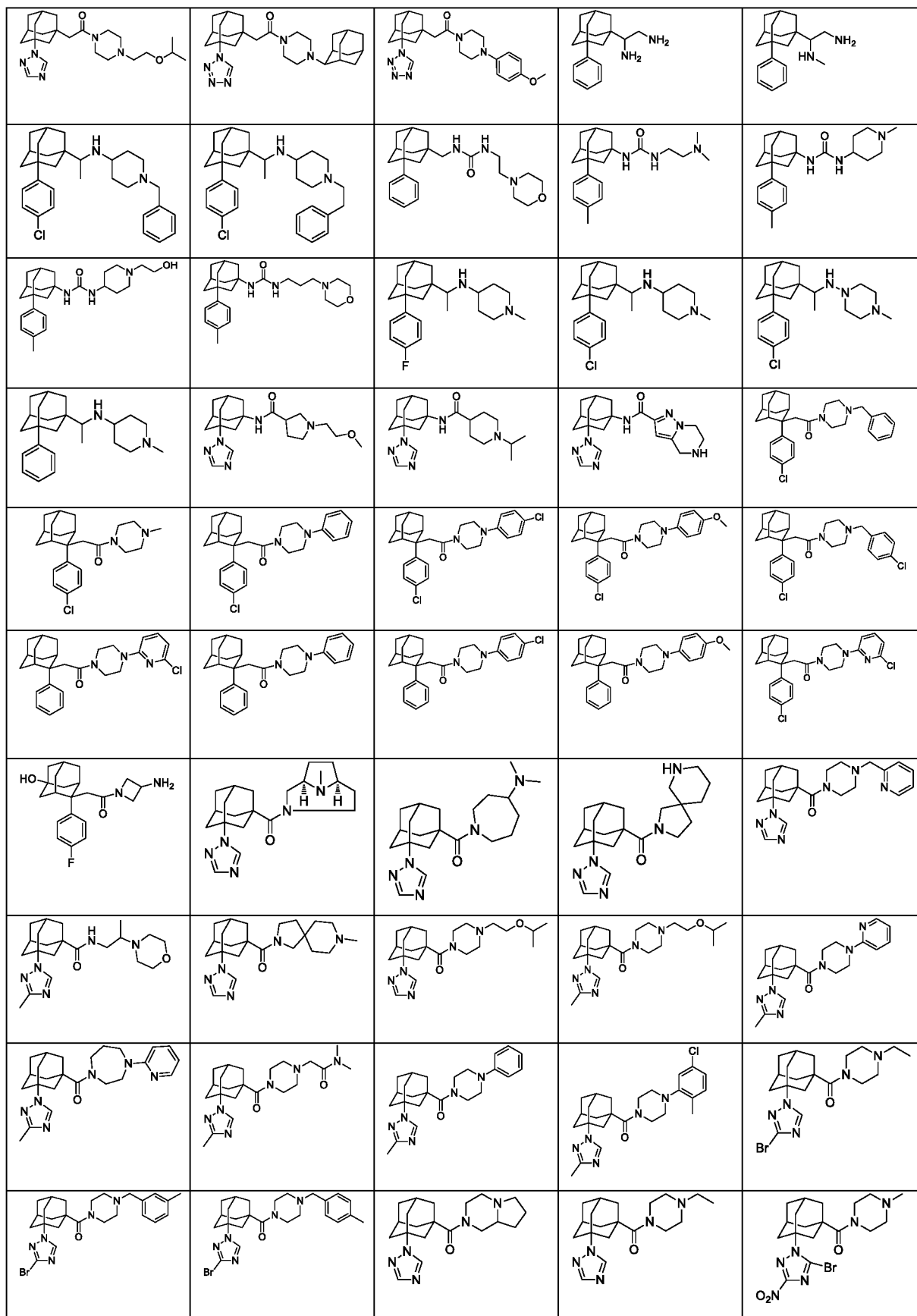
then $NR^{7a}R^{7b}$ is not selected from the group consisting of

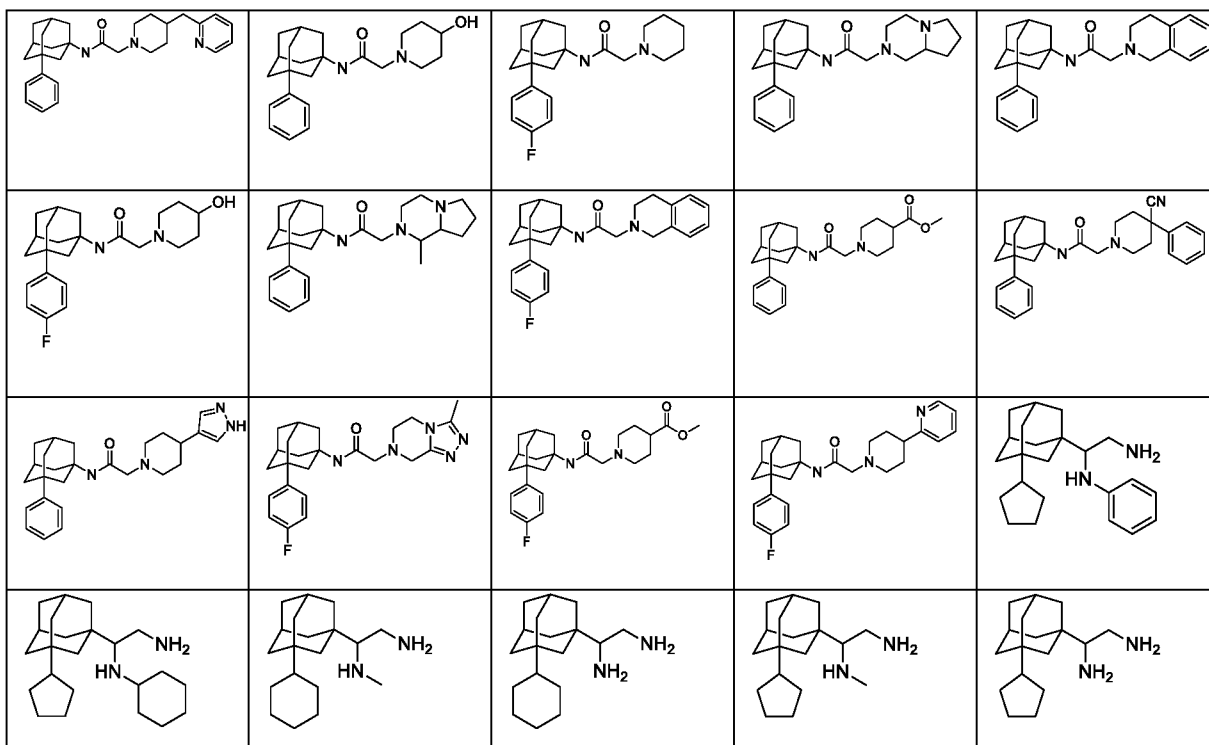


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and with the proviso that the following compounds shall be excluded:





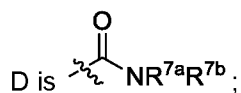
37. The compound of claim 36, wherein:

X is C-A-D and Y is CR⁴R⁵.

38. The compound of claim 37, wherein:

5

A is -C(R^{6a}R^{6b})_j-;



R¹ is selected from (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl, wherein

each of the said (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl is optionally substituted with at least one R¹³ group;

10

R⁴ is hydrogen;

R⁵ is hydrogen.

39. The compound of claim 38, wherein:

R² is selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₁ to C₁₀) alkoxy, -(CH₂)_nC(O)N(R^{11a}R^{11b}), and -C(O)R¹², wherein

15

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, and (C₁ to C₁₀) alkoxy is optionally substituted with at least one R¹³ group;

R³ is selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, and (C₅ to C₁₀) cycloalkenyl, wherein

20

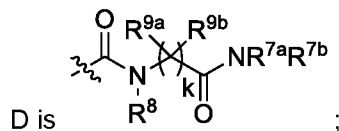
each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl is optionally substituted with at least one R¹³ group.

40. The compound of claim 39, wherein:

R³ is hydrogen.

41. The compound of claim 40, wherein:

A is $-C(R^{6a}R^{6b})_j-$;



R^1 is selected from (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl, wherein

5 each of the said (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl is optionally substituted with at least one R^{13} group;

R^2 is selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₁ to C₁₀) alkoxy, $-(CH_2)_nC(O)N(R^{11a}R^{11b})$, and $-C(O)R^{12}$, wherein

10 each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, and (C₁ to C₁₀) alkoxy is optionally substituted with at least one R^{13} group;

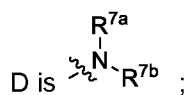
R^3 is hydrogen;

R^4 is hydrogen;

R^5 is hydrogen.

15 42. The compound of claim 37, wherein:

A is $-C(R^{6a}R^{6b})_j-$;



R^1 is selected from (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl, wherein

20 each of the said (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl is optionally substituted with at least one R^{13} group;

R^2 is selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₁ to C₁₀) alkoxy, $-(CH_2)_nC(O)N(R^{11a}R^{11b})$, and $-C(O)R^{12}$, wherein

25 each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, and (C₁ to C₁₀) alkoxy is optionally substituted with at least one R^{13} group;

R^3 is hydrogen;

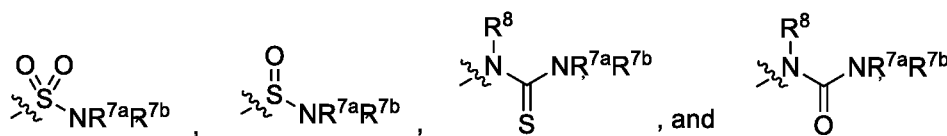
R^4 is hydrogen;

R^5 is hydrogen.

43. The compound of claim 37, wherein:

30 A is $-C(R^{6a}R^{6b})_j-$;

D is selected from the group consisting of



44. The compound of claim 43, wherein:

R^1 is selected from (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl, wherein

each of the said (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl is optionally substituted with at least one R¹³ group;

R² is selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₁ to C₁₀) alkoxy, -(CH₂)_nC(O)N(R^{11a}R^{11b}), and -C(O)R¹²,
 5 wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, and (C₁ to C₁₀) alkoxy is optionally substituted with at least one R¹³ group;

R³ is hydrogen;

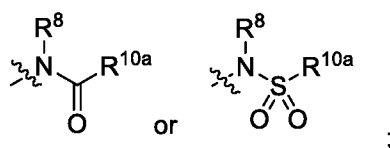
R⁴ is hydrogen;

10 R⁵ is hydrogen.

45. The compound of claim 37, wherein:

A is -C(R^{6a}R^{6b})_j-;

D is selected from the group consisting of



15 R¹ is selected from (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl, wherein

each of the said (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl is optionally substituted with at least one R¹³ group;

R² is selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₁ to C₁₀) alkoxy, -(CH₂)_nC(O)N(R^{11a}R^{11b}), and -C(O)R¹²,
 20 wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, and (C₁ to C₁₀) alkoxy is optionally substituted with at least one R¹³ group;

R³ is hydrogen;

R⁴ is hydrogen;

25 R⁵ is hydrogen.

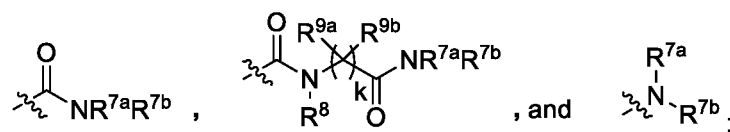
46. The compound of claim 36, wherein:

X is C-A-D and Y is a bond.

47. The compound of claim 46, wherein:

A is -C(R^{6a}R^{6b})_j-;

30 D is selected from the group consisting of



R¹ is selected from (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl, wherein

each of the said (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl is optionally substituted with at least one R¹³ group.

35 R² is selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to

C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₁ to C₁₀) alkoxy, $-(CH_2)_n C(O)N(R^{11a}R^{11b})$, and $-C(O)R^{12}$, wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, and (C₁ to C₁₀) alkoxy is optionally substituted with at least one R¹³ group;

R³ is hydrogen.

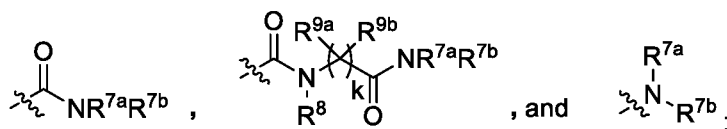
48. The compound of claim 36, wherein:

X is CR⁵ and Y is CR⁴-A-D.

49. The compound of claim 48, wherein:

A is $-C(R^{6a}R^{6b})_j$;

D is selected from the group consisting of



R¹ is selected from (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl, wherein

each of the said (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl is optionally substituted with at least one R¹³ group;

R² is selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₁ to C₁₀) alkoxy, $-(CH_2)_n C(O)N(R^{11a}R^{11b})$, and $-C(O)R^{12}$, wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, and (C₁ to C₁₀) alkoxy is optionally substituted with at least one R¹³ group;

R³ is hydrogen;

R⁴ is hydrogen;

R⁵ is hydrogen.

50. The compound of claim 48, wherein:

A is $-C(R^{6a}R^{6b})_j$;

D is selected from the group consisting of



R¹ is selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₁ to C₁₀) alkoxy, $-(CH_2)_n C(O)N(R^{11a}R^{11b})$, and $-C(O)R^{12}$, wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, and (C₁ to C₁₀) alkoxy is optionally substituted with at least one R¹³ group;

R² is selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₁ to C₁₀) alkoxy, $-(CH_2)_n C(O)N(R^{11a}R^{11b})$, and $-C(O)R^{12}$, wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, and (C₁ to C₁₀) alkoxy is optionally substituted with at least one R¹³ group;

R^3 is selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, and (C₅ to C₁₀) cycloalkenyl, wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl is optionally substituted with at least one R^{13} group;

5 R^4 is selected from (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl, wherein

each of the said (C₆ to C₁₀) aryl and (C₂ to C₉) heteroaryl is optionally substituted with at least one R^{13} group;

R^5 is hydrogen.

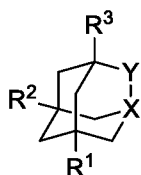
51. The compound of claim 50, wherein:

10 R^1 is hydrogen;

R^2 is hydrogen;

R^3 is hydrogen.

52. A compound represented by Structural Formula I



I

15 or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein:

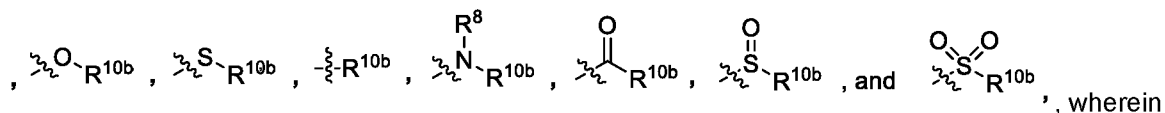
X is C-A-D, and Y is a bond or CR^4R^5 ; or

X is CR^5 and Y is CR^4 -A-D;

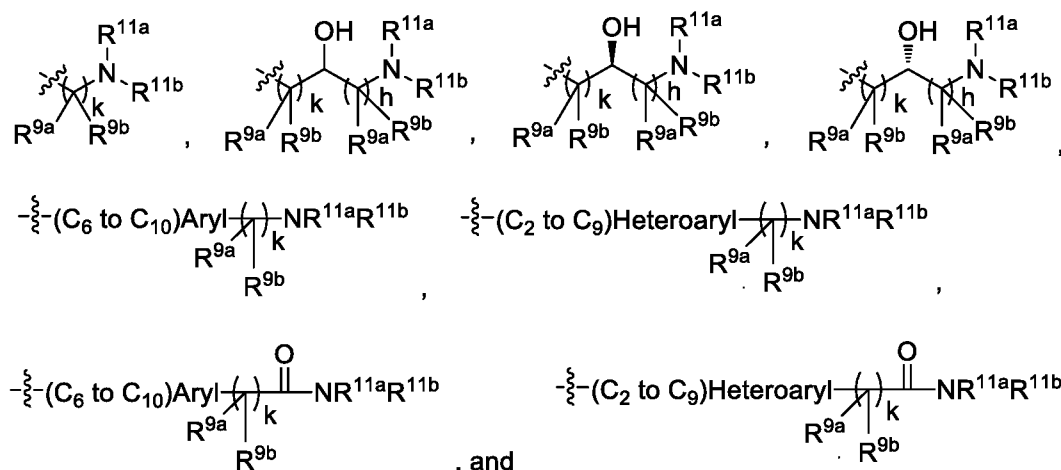
A is $-C(R^{6a}R^{6b})_j$ -, (C₆ to C₁₀) arylene, or (C₂ to C₉) heteroarylene, wherein

20 each of the said (C₆ to C₁₀) arylene or (C₂ to C₉) heteroarylene is optionally substituted with at least one R^{6a} group;

D is selected from the group consisting of



R^{10b} is selected from the group consisting of



R^1 is selected from hydrogen, halogen, OH, nitro, CF_3 , $-\text{NR}^{11a}\text{R}^{11b}$, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, cyano, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, -

5 C(O) R^{12} , -C(O) $\text{NR}^{11a}\text{R}^{11b}$, -S(O) mR^{12} , -S(O) $\text{mNR}^{11a}\text{R}^{11b}$, -NR^{11a}S(O) mR^{12} , -(CH₂)_nC(O)OR¹², - (CH₂)_nCO)N(R^{11a}R^{11b}), -(CH₂)_nN(R^{11a}R^{11b}), -OC(O) R^{12} , -NR^{11a}C(O) R^{12} , and - NR^{11a}C(O)N(R^{11a}R^{11b}), wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl is optionally substituted with at least one R¹³ group;

10

R^2 is selected from hydrogen, halogen, OH, nitro, CF_3 , $-\text{NR}^{11a}\text{R}^{11b}$, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, cyano, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, -

15 C(O) R^{12} , -C(O) $\text{NR}^{11a}\text{R}^{11b}$, -S(O) mR^{12} , -S(O) $\text{mNR}^{11a}\text{R}^{11b}$, -NR^{11a}S(O) mR^{12} , -(CH₂)_nC(O)OR¹², - (CH₂)_nC(O)N(R^{11a}R^{11b}), -(CH₂)_nN(R^{11a}R^{11b}), -OC(O) R^{12} , -NR^{11a}C(O) R^{12} , and - NR^{11a}C(O)N(R^{11a}R^{11b}), wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl is optionally substituted with at least one R¹³ group;

20

R^3 is selected from hydrogen, halogen, OH, nitro, CF_3 , $-\text{NR}^{11a}\text{R}^{11b}$, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, cyano, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, -

25 C(O) R^{12} , -C(O) $\text{NR}^{11a}\text{R}^{11b}$, -S(O) mR^{12} , -S(O) $\text{mNR}^{11a}\text{R}^{11b}$, -NR^{11a}S(O) mR^{12} , -(CH₂)_nC(O)OR¹², - (CH₂)_nC(O)N(R^{11a}R^{11b}), -(CH₂)_nN(R^{11a}R^{11b}), -OC(O) R^{12} , -NR^{11a}C(O) R^{12} , and - NR^{11a}C(O)N(R^{11a}R^{11b}), wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl is optionally substituted with at least one R¹³ group;

30

R^4 is selected from hydrogen, halogen, OH, nitro, CF_3 , $-\text{NR}^{11a}\text{R}^{11b}$, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, cyano, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀)

cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, -C(O)R¹², -C(O)NR^{11a}R^{11b}, -S(O)_mR¹², -S(O)_mNR^{11a}R^{11b}, -NR^{11a}S(O)_mR¹², -(CH₂)_nC(O)OR¹², -(CH₂)_nC(O)N(R^{11a}R^{11b}), -(CH₂)_nN(R^{11a}R^{11b}), -OC(O)R¹², -NR^{11a}C(O)R¹², and -NR^{11a}C(O)N(R^{11a}R^{11b}), wherein

5 each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl is optionally substituted with at least one R¹³ group;

R⁵ is selected from hydrogen, halogen, OH, nitro, CF₃, -NR^{11a}R^{11b}, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, cyano, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, -C(O)R¹², -C(O)NR^{11a}R^{11b}, -S(O)_mR¹², -S(O)_mNR^{11a}R^{11b}, -NR^{11a}S(O)_mR¹², -(CH₂)_nC(O)OR¹², -(CH₂)_nC(O)N(R^{11a}R^{11b}), -(CH₂)_nN(R^{11a}R^{11b}), -OC(O)R¹², -NR^{11a}C(O)R¹², and -NR^{11a}C(O)N(R^{11a}R^{11b}), wherein

10 each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl is optionally substituted with at least one R¹³ group;

each of the R^{6a} and R^{6b} is independently selected from hydrogen, halogen, OH, nitro, CF₃, -NR^{11a}R^{11b}, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, cyano, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, -C(O)R¹², -C(O)NR^{11a}R^{11b}, -S(O)_mR¹², -S(O)_mNR^{11a}R^{11b}, -NR^{11a}S(O)_mR¹², -(CH₂)_nC(O)OR¹², -(CH₂)_nC(O)N(R^{11a}R^{11b}), -(CH₂)_nN(R^{11a}R^{11b}), -OC(O)R¹², -NR^{11a}C(O)R¹², and -NR^{11a}C(O)N(R^{11a}R^{11b}), wherein

20 each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl is optionally substituted with at least one R¹³ group;

each R⁸ is independently selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, and (C₂ to C₉) heteroarylene, wherein

25 each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, and (C₂ to C₉) heteroarylene is optionally substituted with at least one R¹³ group;

each of the R^{9a}, R^{9b}, and R^{9c} is independently selected from hydrogen, halogen, OH, nitro, CF₃, -NR^{11a}R^{11b}, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, cyano, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, -C(O)R¹², -C(O)NR^{11a}R^{11b}, -S(O)_mR¹², -S(O)_mNR^{11a}R^{11b}, -NR^{11a}S(O)_mR¹², -(CH₂)_nC(O)OR¹², -(CH₂)_nC(O)N(R^{11a}R^{11b}), -(CH₂)_nN(R^{11a}R^{11b}), -OC(O)R¹², -NR^{11a}C(O)R¹², and -NR^{11a}C(O)N(R^{11a}R^{11b}), wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl is optionally substituted with at least one R¹³ group;

each of the R^{11a} and R^{11b} is independently selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, and (C₂ to C₉) heteroarylene, wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, and (C₂ to C₉) heteroarylene is optionally substituted with at least one R¹³ group,

or R^{11a} and R^{11b} may be taken together with the nitrogen atom to which they are attached to form a (C₂ to C₁₀) cycloheteroalkyl ring, wherein

said (C₂ to C₁₀) cycloheteroalkyl ring has 1 to 3 ring heteroatoms selected from the group consisting of N, O, and S, and wherein

the said (C₂ to C₁₀) cycloheteroalkyl ring is optionally substituted with at least one R¹³ group;

each of the R¹² is independently selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl, wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl is optionally substituted with at least one R¹³ group;

each R¹³ is independently selected from hydrogen, halogen, OH, nitro, CF₃, -NR^{14a}R^{14b}, oxo, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, cyano, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, (C₂ to C₉) heteroarylene, (C₃ to C₁₀) cycloalkylene, (C₂ to C₁₀) cycloheteroalkylene, -C(O)R¹⁵, -C(O)NR^{14a}R^{14b}, -S(O)_mR¹⁵, -S(O)_mNR^{14a}R^{14b}, -NR^{14a}S(O)_mR¹⁵, -(CH₂)_nC(O)OR¹⁵, -(CH₂)_nC(O)N(R^{14a}R^{14b}), -(CH₂)_nN(R^{14a}R^{14b}), -OC(O)R¹⁵, -O(CH₂)_nO-, -NR^{14a}C(O)R¹⁵, and -NR^{14a}C(O)N(R^{14a}R^{14b}), wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, (C₂ to C₉) heteroarylene, (C₃ to C₁₀) cycloalkylene, and (C₂ to C₁₀) cycloheteroalkylene is optionally substituted with at least one R¹⁶ group;

each of the R^{14a} and R^{14b} is independently selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₉) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, and (C₂ to C₉) heteroarylene, wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl,

(C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, and (C₂ to C₉) heteroarylene is optionally substituted with at least one R¹⁸ group,

or R^{14a} and R^{14b} may be taken together with the nitrogen atom to which they are attached to form a (C₂ to C₁₀) cycloheteroalkyl ring, wherein

5 said (C₂ to C₁₀) cycloheteroalkyl ring has 1 to 3 ring heteroatoms selected from the group consisting of N, O, and S, and wherein

the said (C₂ to C₁₀) cycloheteroalkyl ring is optionally substituted with at least one R¹⁸ group;

each R¹⁵ is independently selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl, wherein

10 each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl is optionally substituted with at least one R¹⁸ group;

each R¹⁶ is independently selected from hydrogen, halogen, OH, nitro, CF₃, -NR^{17a}R^{17b}, oxo, 15 (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, cyano, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, (C₂ to C₉) heteroarylene, (C₃ to C₁₀) cycloalkylene, (C₂ to C₁₀) cycloheteroalkylene, -C(O)R¹⁸, -C(O)NR^{17a}R^{17b}, -S(O)_mR¹⁸, -S(O)_mNR^{17a}R^{17b}, -NR^{17a}S(O)_mR¹⁸, -(CH₂)_nC(O)OR¹⁸, -(CH₂)_nC(O)N(R^{17a}R^{17b}), -(CH₂)_nN(R^{17a}R^{17b}), -OC(O)R¹⁸, -NR^{17a}C(O)R¹⁸, 20 and -NR^{17a}C(O)N(R^{17a}R^{17b}), wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) aryl, (C₆ to C₁₀) arylene, (C₂ to C₉) heteroarylene, (C₃ to C₁₀) cycloalkylene, and (C₂ to C₁₀) cycloheteroalkylene is optionally substituted with at least one R¹⁹ group;

25 each of the R^{17a} and R^{17b} is independently selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, and (C₂ to C₉) heteroarylene, wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, and (C₂ to C₉) heteroarylene is optionally substituted with at least one R¹⁹ group,

or R^{17a} and R^{17b} may be taken together with the nitrogen atom to which they are attached to form a (C₂ to C₁₀) cycloheteroalkyl ring, wherein

35 said (C₂ to C₁₀) cycloheteroalkyl ring has 1 to 3 ring heteroatoms selected from the group consisting of N, O, and S, and wherein

the said (C₂ to C₁₀) cycloheteroalkyl ring is optionally substituted with at least one R¹⁹ group;

each R¹⁸ is independently selected from hydrogen, halogen, OH, nitro, CF₃, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, cyano, (C₃ to C₁₀) cycloalkyl, (C₅

to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl, wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₂ to C₉) heteroaryl, and (C₆ to C₁₀) aryl is optionally substituted with at least one R¹⁹ group;

each R¹⁹ is independently selected from hydrogen, halogen, OH, nitro, CF₃, -NR^{20a}R^{20b}, oxo, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, cyano, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, (C₂ to C₉) heteroarylene, (C₃ to C₁₀) cycloalkylene, (C₂ to C₁₀) cycloheteroalkylene, -C(O)R²¹, -C(O)NR^{20a}R^{20b}, -S(O)_mR²¹, -S(O)_mNR^{20a}R^{20b}, -NR^{20a}S(O)_mR²¹, -(CH₂)_nC(O)OR²¹, -(CH₂)_nC(O)N(R^{20a}R^{20b}), -(CH₂)_nN(R^{20a}R^{20b}), -OC(O)R²¹, -NR^{20a}C(O)R²¹, and -NR^{20a}C(O)N(R^{20a}R^{20b}), wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, (C₂ to C₉) heteroarylene, (C₃ to C₁₀) cycloalkylene, and (C₂ to C₁₀) cycloheteroalkylene is optionally substituted with at least one R²² group;

each of the R^{20a} and R^{20b} is independently selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl, wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl is optionally substituted with at least one R²² group,

or R^{20a} and R^{20b} may be taken together with the nitrogen atom to which they are attached to form a (C₂ to C₁₀) cycloheteroalkyl ring, wherein

said (C₂ to C₁₀) cycloheteroalkyl ring has 1 to 3 ring heteroatoms selected from the group consisting of N, O, and S, and wherein

the said (C₂ to C₁₀) cycloheteroalkyl ring is optionally substituted with at least one R²² group;

each R²¹ is independently selected from hydrogen, halogen, OH, nitro, CF₃, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, cyano, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl;

each R²² is independently selected from hydrogen, halogen, OH, nitro, CF₃, -NR^{23a}R^{23b}, oxo, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, cyano, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, (C₂ to C₉) heteroarylene, (C₃ to C₁₀) cycloalkylene, (C₂ to C₁₀) cycloheteroalkylene, -C(O)R²⁴, -C(O)NR^{23a}R^{23b}, -S(O)_mR²⁴, -S(O)_mNR^{23a}R^{23b}, -NR^{23a}S(O)_mR²⁴, -(CH₂)_nC(O)OR²⁴, -(CH₂)_nC(O)N(R^{23a}R^{23b}), -(CH₂)_nN(R^{23a}R^{23b}), -OC(O)R²⁴, -NR^{23a}C(O)R²⁴, and -NR^{23a}C(O)N(R^{23a}R^{23b}), wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl,

(C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, (C₂ to C₉) heteroarylene, (C₃ to C₁₀) cycloalkylene, and (C₂ to C₁₀) cycloheteroalkylene is optionally substituted with at least one R²⁵ group;

each of the R^{23a} and R^{23b} is independently selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₂ to C₉) heteroaryl, and (C₆ to C₁₀) aryl;

each R²⁴ is independently selected from hydrogen, halogen, OH, nitro, CF₃, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, cyano, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl;

each R²⁵ is independently selected from hydrogen, halogen, OH, nitro, CF₃, -NR^{26a}R^{26b}, oxo, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, cyano, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, (C₂ to C₉) heteroarylene, (C₃ to C₁₀) cycloalkylene, (C₂ to C₁₀) cycloheteroalkylene, -C(O)R²⁷, -C(O)NR^{26a}R^{26b}, -S(O)_mR²⁷, -S(O)_mNR^{26a}R^{26b}, -NR^{26a}S(O)_mR²⁷, -(CH₂)_nC(O)OR²⁷, -(CH₂)_nC(O)N(R^{26a}R^{26b}), -(CH₂)_nN(R^{26a}R^{26b}), -OC(O)R²⁷, -NR^{26a}C(O)R²⁷, and -NR^{26a}C(O)N(R^{26a}R^{26b}), wherein

each of the said (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl, (C₆ to C₁₀) arylene, (C₂ to C₉) heteroarylene, (C₃ to C₁₀) cycloalkylene, and (C₂ to C₁₀) cycloheteroalkylene is optionally substituted with at least one R²⁷ group;

each of the R^{26a} and R^{26b} is independently selected from hydrogen, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, and (C₂ to C₉) heteroaryl,

or R^{26a} and R^{26b} may be taken together with the nitrogen atom to which they are attached to form a (C₂ to C₁₀) cycloheteroalkyl ring, wherein

said (C₂ to C₁₀) cycloheteroalkyl ring has 1 to 3 ring heteroatoms selected from the group consisting of N, O, and S;

each R²⁷ is independently selected from hydrogen, halogen, OH, nitro, CF₃, (C₁ to C₁₀) alkyl, (C₁ to C₁₀) alkenyl, (C₁ to C₁₀) alkynyl, (C₁ to C₁₀) alkoxy, aryloxy, cyano, (C₃ to C₁₀) cycloalkyl, (C₅ to C₁₀) cycloalkenyl, (C₂ to C₁₀) cycloheteroalkyl, (C₆ to C₁₀) aryl, (C₂ to C₉) heteroaryl;

h is 1 or 2;

i is 2, 3, 4, 5, or 6;

j is 0, 1, 2, 3, 4, or 5;

k is 1, 2, 3, 4, or 5;

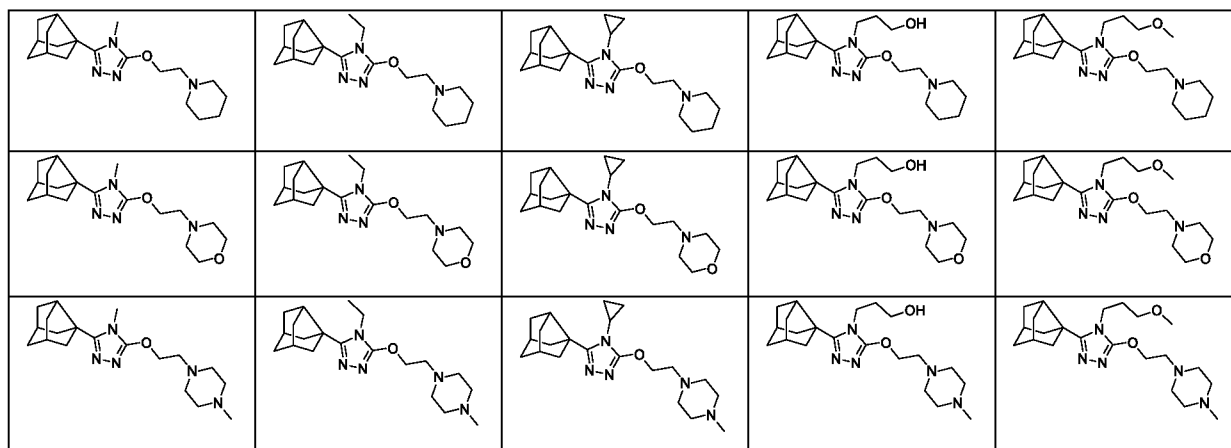
m is 0, 1 or 2;

n is 0, 1, 2, 3, or 4;

with the proviso that when X is C-A-D, and Y is CH₂,

then R¹ is not selected from the group consisting of hydrogen and methyl,

and with the proviso that the following compounds shall be excluded:



53. The compound of claim 52, wherein:

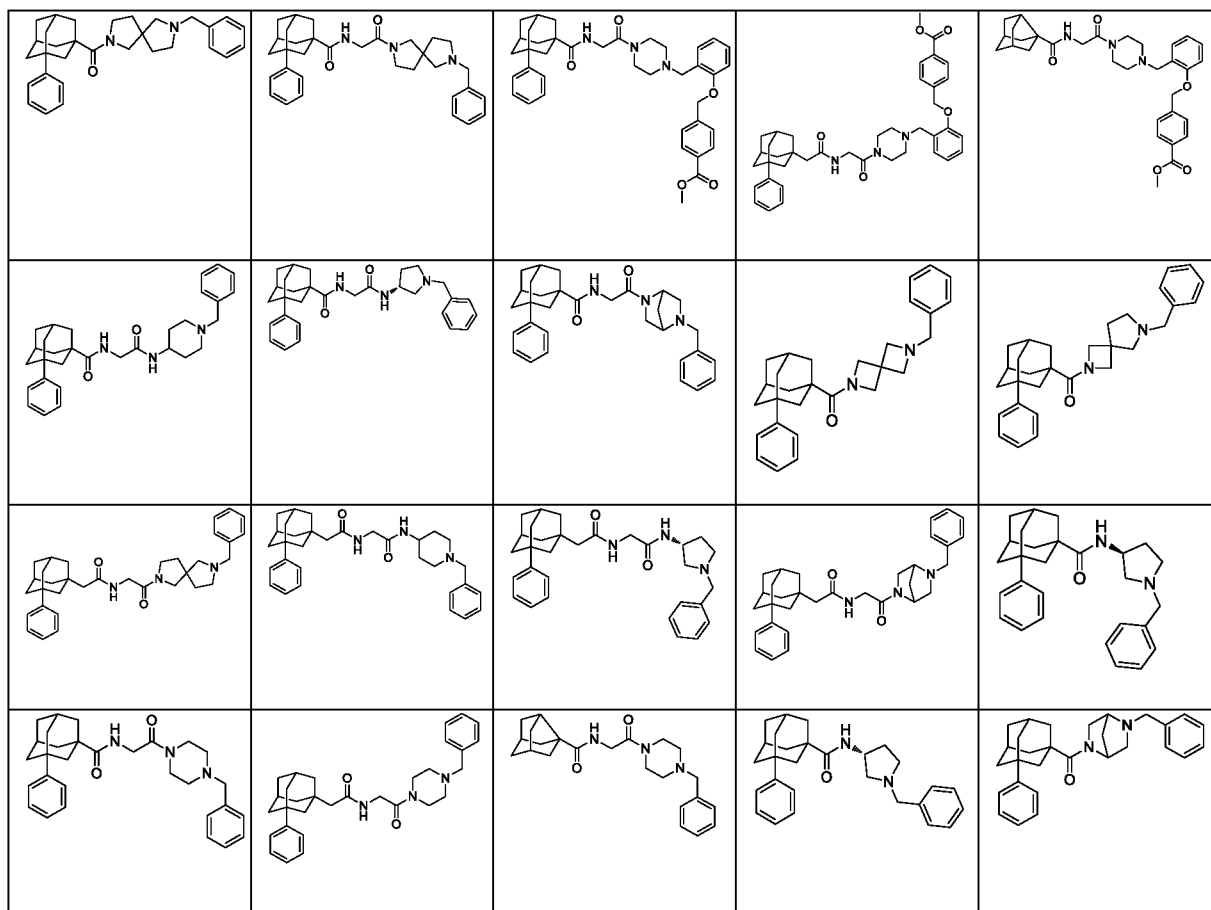
A is $-C(R^{6a}R^{6b})_2-$, (C_6 to C_{10}) arylene, or (C_2 to C_9) heteroarylene, wherein

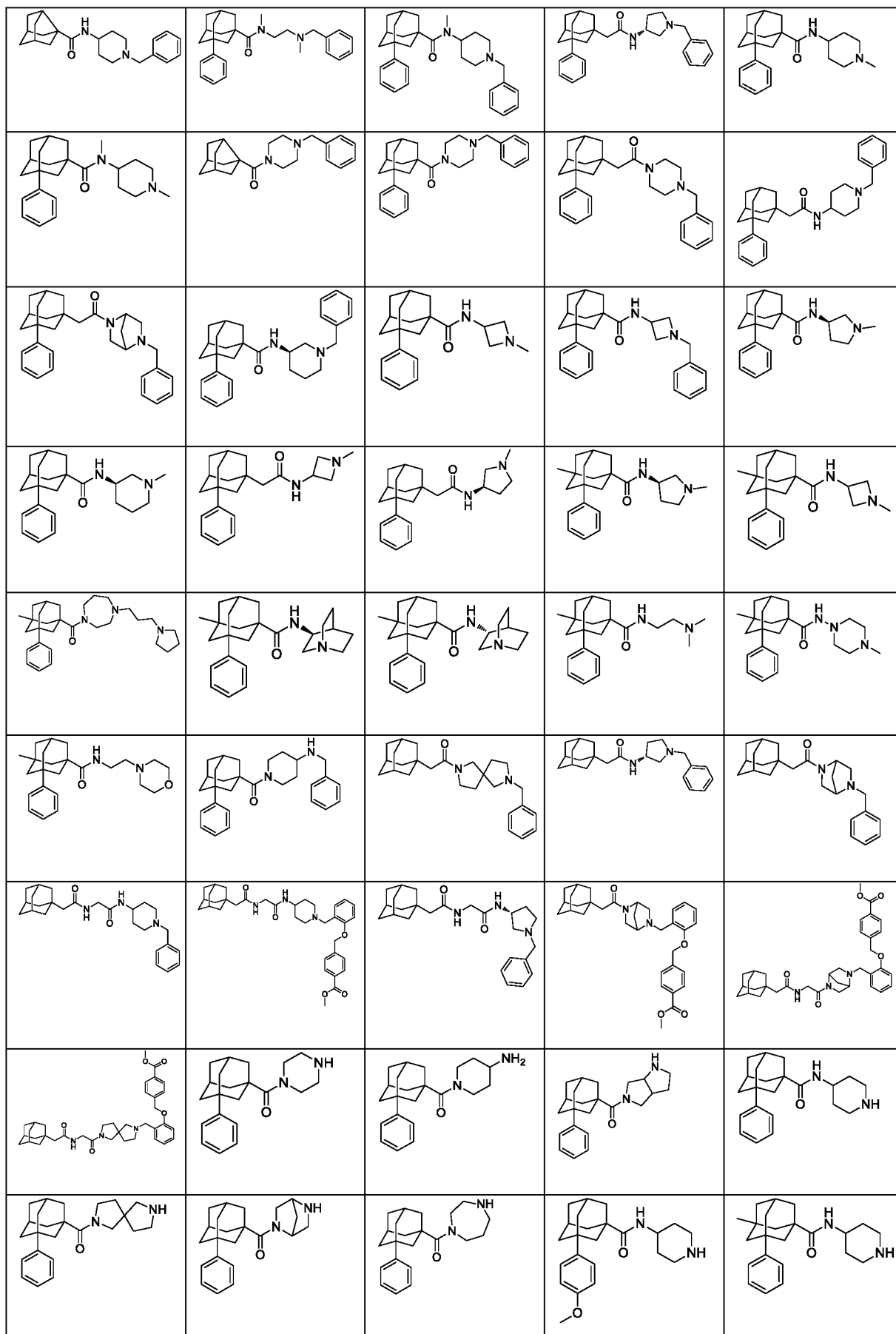
each of the said (C_6 to C_{10}) arylene or (C_2 to C_9) heteroarylene is optionally

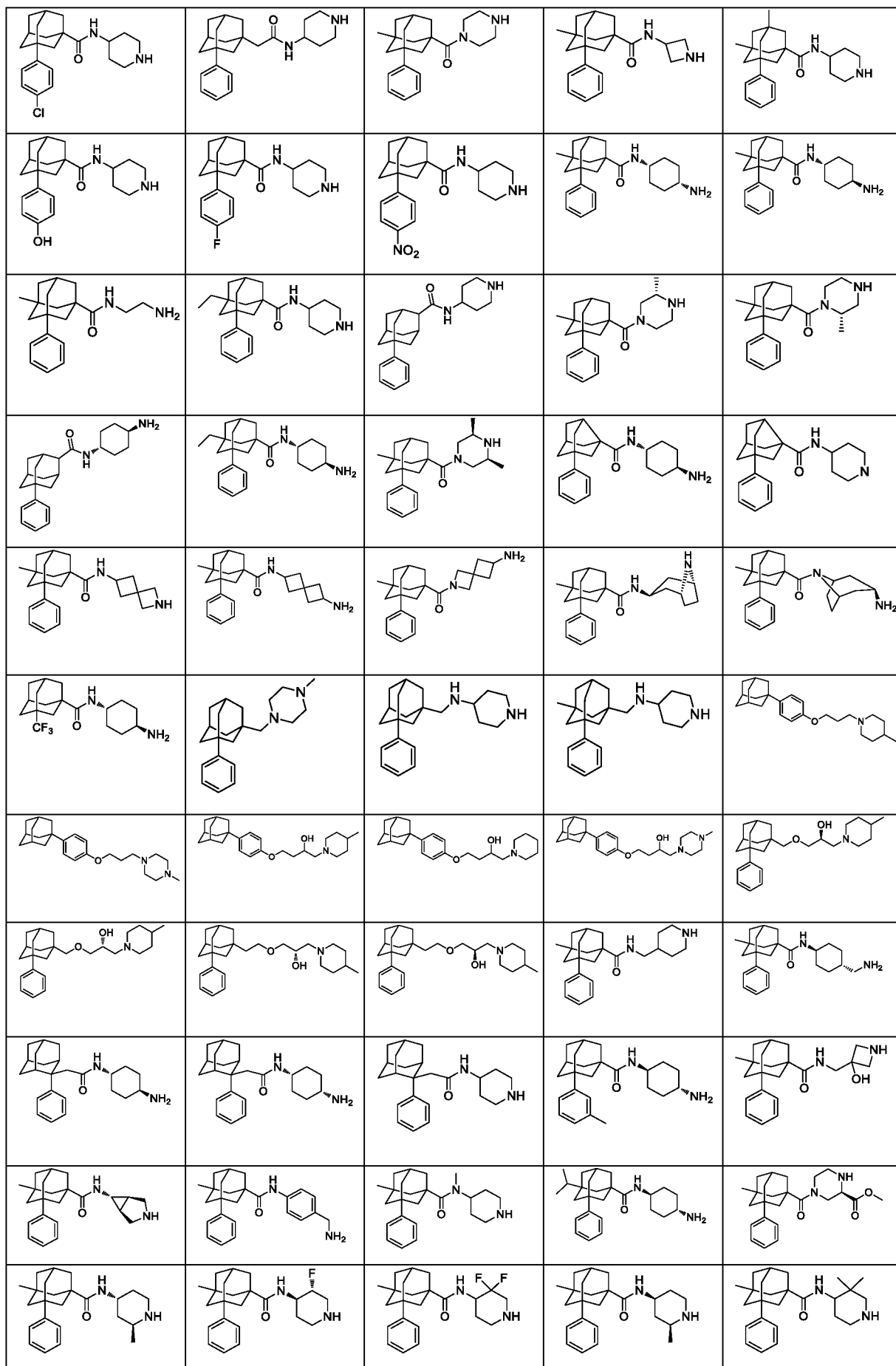
5 substituted with at least one R^{6a} group;

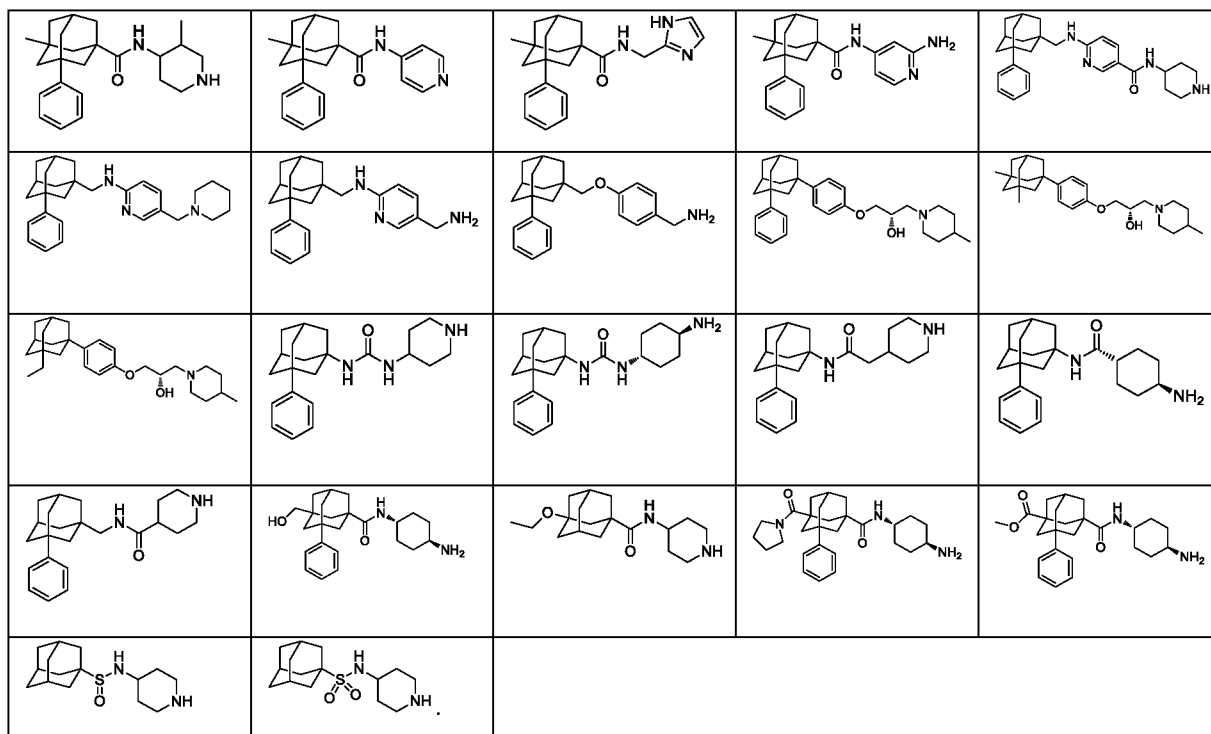
D is of $\text{---}O\text{---}R^{10b}$.

54. A compound selected from the group consisting of:

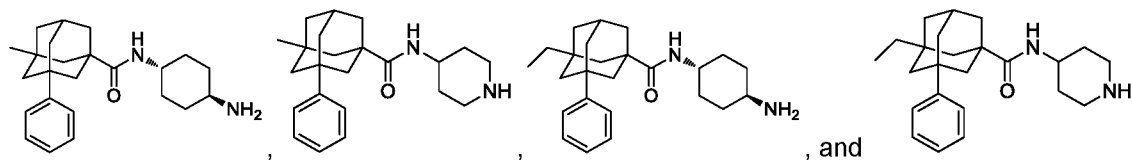








55. The compound of claim 54 selected from the group consisting of



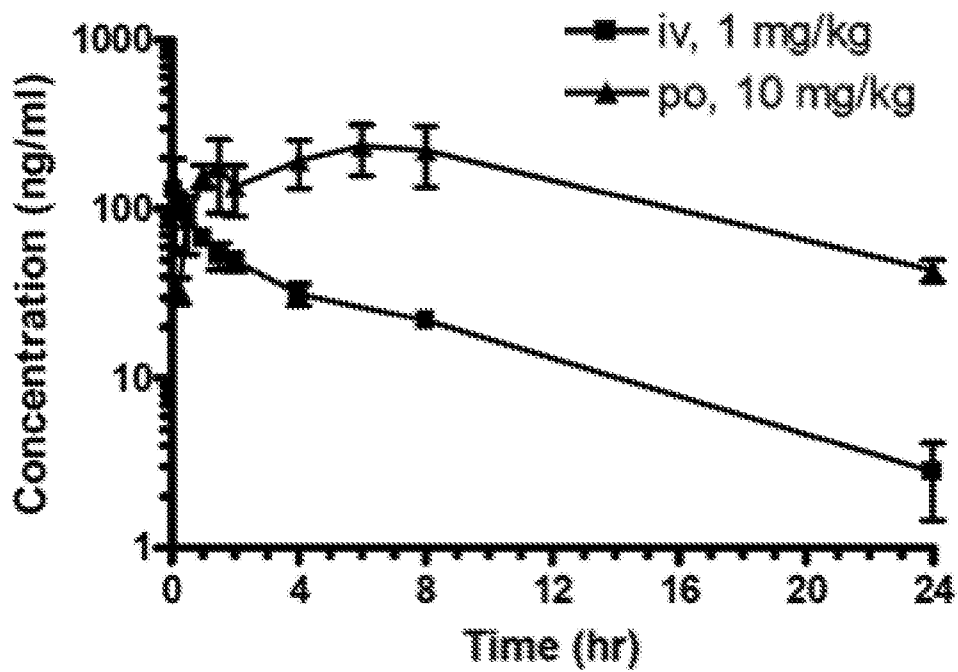


Figure 1

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2017/013560

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/015; A61K 31/135; A61K 31/165; C07C 13/28; C07C 13/54; C07C 13/573 (2017.01)

CPC - A61K 31/015; A61K 31/135; A61K 31/165; C07C 13/28; C07C 13/54; C07C 13/573 (2017.01)

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)

See Search History document

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2004/0209858 A1 (BENNANI et al) 21 October 2004 (21.10.2004) entire document	36, 46, 52
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Y		1-5, 26
Y	WO 2015/057068 A1 (STICHTING VOOR DE TECHNISCHE WETENSCHAPPEN) 23 April 2015 (23.04.2015) entire document	1-5, 26
Y	US 2015/0166532 A1 (PRESIDENT AND FELLOWS OF HARVARD COLLEGE) 18 June 2015 (18.06.2015) entire document	4, 5
A	US 2012/0135954 A1 (SHANG et al) 31 May 2012 (31.05.2012) entire document	1-5, 26, 36-40, 46, 52-55
A	US 2009/0218935 A1 (SOTOYAMA et al) 03 September 2009 (03.09.2009) entire document	1-5, 26, 36-40, 46, 52-55

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

11 May 2017

Date of mailing of the international search report

01 JUN 2017

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, VA 22313-1450

Facsimile No. 571-273-8300

Authorized officer

Blaine R. Copenheaver

PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2017/013560

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

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

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

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

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

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

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

See Extra Sheet

Claims 1-5, 26, 36, 46, and 52 have been analyzed subject to the restriction that the claims read on a method of treating infections associated with viruses of the Filoviridae enveloped virus comprising administration of a therapeutically effective amount of a compound of Structural Formula I or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent or vehicle, wherein: X is C-A-D and Y is a bond; A is -C(R6aR6b)-; D is the first structure shown; R1 is hydrogen; R2 is hydrogen; R3 is hydrogen; each of R6a and R6b is absent; each of the R7a and R7b is independently hydrogen; j is 0.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
1-5, 26, 36-40, 46, 52-55
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☒ No protest accompanied the payment of additional search fees.

Continued from Box No. III Observations where unity of invention is lacking

Claims 36-40 and 52-55 have been analyzed subject to the restriction that the claims read on the Formula I as described in the Response to the Invitation to Pay Additional Fees in the International Application dated 10 April 2017 as further restricted to the variable definitions listed below. The claims are restricted to the compound trans-N-(4-aminocyclohexyl)-3-methyl-5-phenyl adamantane-1-carboxamide.

Claims 36-40 and 52-55 have been analyzed subject to the restriction that the claims read on the Formula I as described in the Response to the Invitation to Pay Additional Fees in the International Application dated 10 April 2017 as further restricted to the variable definitions listed below. The claims are restricted to the compound 3-ethyl-5-phenyl-N-(piperidin-4-yl)adamantane-1-carboxamide.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I+: claims 1-55 are drawn to methods of treating infections associated with viruses and compounds represented by Structural Formula I.

The first invention of Group I+ is restricted based on the proviso that when R1, R2, or R3 is alkyl or hydrogen, X is C-C(R6aR6b)j-D, Y is CH2, and D is one of the structures shown, then NR7aR7b cannot be an optionally substituted piperazine or 1,4-diazepane, and with the proviso that when X is CR5, Y is CR4-D, D is -NR7aR7b, and R7a and R7b are taken together with the nitrogen atom to which they are attached to form a (C2 to C10) cycloheteroalkyl ring, the said (C2 to C10) membered cycloheteroalkyl ring cannot be selected from the group consisting of the structures shown; and is restricted to a method of treating infections associated with viruses of the Filoviridae enveloped virus comprising administration of a therapeutically effective amount of a compound of Structural Formula I or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent or vehicle, wherein: X is C-A-D and Y is a bond; A is -C(R6aR6b)j-; D is the first structure shown; R1 is hydrogen; R2 is hydrogen; R3 is hydrogen; each of R6a and R6b is absent; each of the R7a and R7b is independently hydrogen; j is 0; methods thereof; and compounds thereof. It is believed that claims 1-5, 26, 36, 46, and 52 read on this first named invention and thus these claims will be searched without fee to the extent that they read on the above embodiment.

Applicant is invited to elect additional formula(e) for each additional compound to be searched in a specific combination by paying an additional fee for each set of election. Each additional elected formula(e) requires the selection of a single definition for each compound variable. An exemplary election would be a method of treating infections associated with viruses of the Filoviridae enveloped virus comprising administration of a therapeutically effective amount of a compound of Structural Formula I or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent or vehicle, wherein: X is C-A-D and Y is a bond; A is -C(R6aR6b)j-; D is the first structure shown; R1 is hydrogen; R2 is hydrogen; R3 is hydrogen; each of R6a and R6b is independently hydrogen; each of the R7a and R7b is independently unsubstituted C3 alkyl; j is 5; methods thereof; and compounds thereof. Additional formula(e) will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined.

The inventions listed in Groups I+ do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The Groups I+ formulae do not share a significant structural element requiring the selection of alternatives for the compound variables R1, R2, R3, X, and Y.

'The Groups I+ share the technical features of a method of treating infections associated with viruses of the Filoviridae enveloped virus, or any virus expressing filovirus glycoproteins to mediate cell entry comprising administration of a therapeutically effective amount of a compound of Structural Formula I or a pharmaceutically acceptable salt and species thereof, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof; a compound represented by Structural Formula I or a pharmaceutically acceptable salt and species thereof, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof. However, these shared technical features do not represent a contribution over the prior art.

Specifically, WO 2015/057068 A1 to Stichting Voor De Technische Wetenschappen teaches a method of treating infections associated with viruses of the Filoviridae enveloped virus, or any virus expressing filovirus glycoproteins to mediate cell entry (Claims 1 and 22-24) comprising administration of a therapeutically effective amount of a compound of Structural Formula I or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof (Pg. 26, Lns. 19-21), wherein X is C-A-D and Y is CR4R5; A is -C(R6aR6b)j-; d is -NR7aR7b; R1 is hydrogen; R2 is hydrogen; R3 is hydrogen; R4 is hydrogen; R5 is hydrogen; each of R6a is hydrogen; R6b is C1 alkyl; each of R7a and R7b is independently hydrogen; j is 1 (Claim 30; Pg. 25, Ln. 31 through Pg. 26, Ln. 3, Rimantadine); and a compound represented by Structural Formula I and species thereof or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof (Pg. 26, Lns. 19-21), wherein X is C-A-D and Y is CR4R5; A is -C(R6aR6b)j-; d is -NR7aR7b; R1 is hydrogen; R2 is hydrogen; R3 is hydrogen; R4 is hydrogen; R5 is hydrogen; each of R6a is hydrogen; R6b is C1 alkyl; each of R7a and R7b is independently hydrogen; j is 1 (Claim 30; Pg. 25, Ln. 31 through Pg. 26, Ln. 3, Rimantadine).

The inventions listed in Groups I+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.