



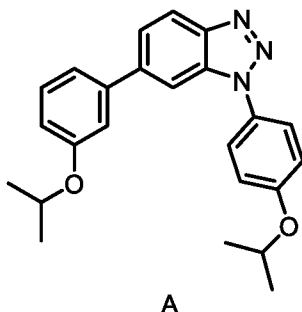
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(71) Demandeur/Applicant:
ARISAN THERAPEUTICS, INC., US
(72) Inventeurs/Inventors:
BROWN, ERIC, US;
GANTLA, VIDYASAGAR REDDY, US;
SOKOLOVA, NADEZDA, US;
PLEWE, MICHAEL BRUNO, US;
HENKEL, GREGORY, US;
MCCORMACK, KENNETH, US
(74) Agent: ROBIC

(54) Titre : COMPOSES POUR LE TRAITEMENT D'UNE INFECTION A ARENAVIRUS
(54) Title: COMPOUNDS FOR THE TREATMENT OF ARENAVIRUS INFECTION



(57) Abrégé/Abstract:

Compounds as exemplified by compound A are useful in the treatment of arenavirus infections and viral infections mediated by arenavirus glycoproteins.

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(71) Applicant: **ARISAN THERAPEUTICS, INC.** [US/US];
11189 Sorrento Valley Road Suite 104, San Diego, California 92121 (US).

(72) Inventors: **BROWN, Eric**; 8803 Pebble Beach Court, Santee, California 92071 (US). **GANTLA, Vidyasagar Reddy**; 6783 Monterra Trail, San Diego, California 92130 (US). **SOKOLOVA, Nadezda**; 12635 El Camino Real Apt 4106, San Diego, California 92130 (US). **PLEWE, Michael Bruno**; 5036 Pearlman Way, San Diego, California 92130 (US). **HENKEL, Gregory**; 3445 Circulo Adorno, Carlsbad, California 92009 (US). **MCCORMACK, Kenneth**; 218 South Freeman Street, Oceanside, California 92054 (US).

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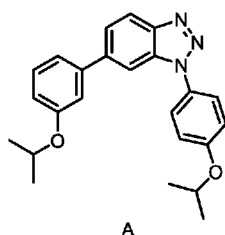
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WO 2020/117794 A1

COMPOUNDS FOR THE TREATMENT OF ARENAVIRUS INFECTION

CROSS REFERENCES TO RELATED APPLICATIONS

This patent application is a continuation in part of and claims the benefit of priority to United States

5 Provisional Patent Application serial number 62/776,390, filed December 6, 2018 herein incorporated by reference in its entirety for all purposes.

STATEMENT AS TO RIGHTS TO INVENTIONS MADE UNDER FEDERALLY 10 SPONSORED RESEARCH AND DEVELOPMENT

This invention was made with government support under **R44 AI112097** awarded by U.S. National Institutes of Health. The government has certain rights in the invention.

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

NOT APPLICABLE

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FIELD OF THE INVENTION

The present invention relates to the use of heterocyclic compounds for inhibiting arenavirus infection in humans, other mammals, or in cell culture, to methods of treating arenavirus infection such as Lassa, Bolivian, Argentine, Venezuelan, Brazilian, Chapare and Lujo hemorrhagic fevers, to methods of inhibiting the replication of arenaviruses, to methods of reducing the amount of arenaviruses, and to compositions that can be employed for such methods.

BACKGROUND OF THE INVENTION

Arenaviridae comprise a diverse family of 29 (and growing) negative stranded enveloped RNA viruses. Arenaviruses are divided into two groups, Old and New World, based on serological, genetic and geographical data. Old World viruses are found primarily throughout South and West Africa and include the prototypic lymphocytic choriomeningitis virus (LCMV), along with Lassa (LASV), Lujo (LUJV), Mopeia (MOPV), Ippy and Mobala (MOBV) viruses. Both LASV and LUJV can cause lethal hemorrhagic fever (HF), while LCMV infection is associated with aseptic meningitis. Lassa (LASV) alone is estimated to cause over 300,000 disease cases each year in West Africa, of which 15-20% of hospitalized patients die and survivors often suffer sequelae, including permanent bilateral hearing damage. The larger New World complex primarily located in the South American continent, is divided into 3 clades, A, B, and C, with clade B being important as many of the viruses in this group can cause lethal HF. Clade B HF viruses include, Junin (JUNV), Machupo (MACV), Guanarito (GTOV), Sabia (SABV) and Chapare, along with non-HF viruses such as Tacaribe (TCRV) and Amapari (AMPV). Human infection occurs through contact with the excretions of an infected rodent or by inhalation of tiny particles soiled with rodent urine or saliva (aerosol transmission). There is also evidence of human-to-human spread primarily in nosocomial settings (e.g. hospitals). The incubation period of virus is 1-2 weeks followed by fever, general malaise, weakness, sore throat, headache, cough, diarrhea, and vomiting. These general symptoms make it difficult to differentially diagnose arenavirus infection. Poor prognosis is indicated as symptoms worsen to include pleural effusions, facial edema, neurological complications and bleeding from mucosal surfaces. Current arenavirus treatment is limited to the use of ribavirin, which is only partially effective if given early and associated with significant side effects. Although a vaccine has been developed for Junin virus its usage is primarily restricted to the most at risk populations of farm workers in Argentina and there are no approved vaccines for any other arenaviruses. Although highly desirable, prophylactic vaccines may not always be effective countermeasures against rapidly emerging, antigenically distinct new virus strains and the existing vaccine development and production strategies cannot adequately respond to the diverse family of current or emergent arenaviruses. Novel broad-spectrum antiviral drugs could therefore, provide a first line therapy and/or prophylactic not only for endemic regions of arenavirus infection but also as a safeguard against potential biological warfare agents.

Arenaviruses consist of a nucleocapsid (NP) surrounded by an envelope membrane, and the NP

contains two ambisense RNA genome segments L and S that direct the synthesis of two polypeptides. The L segment encodes the RNA-dependent-RNA polymerase (RdRp) and a small Ring Finger protein Z. The S segment encodes for nucleoprotein and a glycoprotein precursor GPC that is cleaved by host proteases and undergoes post-translational modification into a mature complex composed of glycoproteins GP1 (binds host protein at the cell surface), GP2 (directs pH dependent membrane fusion and release of genomic material in the cytoplasm) and a stable signal peptide (SSP1). The mature glycoprotein complex (GP, or referred to as glycoprotein) is formed in the viral envelope and is responsible for mediating viral entry. The Old World arenaviruses bind to host α -dystroglycan while New World arenaviruses bind to transferrin receptor 1 for entry/endocytosis into cells. Upon binding to cell surface receptors, the virus is endocytosed and directed to acidic late endosomes whereby, GP2 mediates pH dependent membrane fusion and release of genomic material into the cytoplasm for viral replication and transcription. Therefore, viral entry inhibitors (e.g. small molecules) that target virus GP complex or host factors are a potential therapeutic/prophylactic approach in treating patients infected with arenavirus infection. Because the HF arenavirus species are classified as BSL-4, alternative approaches are needed to identify viral entry inhibitors. To facilitate the identification of arenavirus entry inhibitors one may express arenavirus GP complex in nonpathogenic BSL-2 envelope viruses to produce single round infectious pseudoviruses whose viral entry functions are determined by the heterogeneous glycoprotein of interest. One viral expression system that may be utilized is the vesicular stomatitis virus (VSV) system, whereby the envelope protein of VSV is substituted with an envelope glycoprotein from another virus, e.g., LASV, to mediate entry of the pseudotype virion. The cell entry and infectivity properties of GP pseudotype VSV viruses have been shown for multiple viruses including HIV, Hepatitis B and C, Ebola, Lassa, Hanta and others [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]. The above papers are herein incorporated by reference in their entirety for all purposes. To monitor pseudovirus infection, a reporter gene such as green fluorescent protein (GFP) or luciferase can be engineered into the pseudovirus genome, and virus infectivity in mammalian cell lines (e.g. Vero or Hek293) can be monitored using optical detection methods (e.g. plate reader) [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, 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]. The above papers are herein incorporated by reference in their entirety for all

purposes. The “pseudoviruses” may therefore be used to screen chemical compound libraries to identify inhibitors of arenavirus cell entry while avoiding the complications of working with highly pathogenic BSL-4 agents.

The introduction of deuterium (D) into drug molecules is an attractive strategy that might help improving drug's metabolism, pharmacokinetic and toxicity profiles. Deuterium is a stable, nontoxic, nonradioactive isotope of hydrogen. Due to the greater atomic mass, deuterium forms a stronger bond with carbon than hydrogen, making the carbon-deuterium bond much harder to break. In cases where the breaking of a carbon-hydrogen bond is partially or wholly rate-limiting step in the cytochrome P450-mediated drug metabolism, replacing hydrogen atom(s) with deuterium may slow the rate of metabolism, resulting in improved half-life, greater tolerability, improved efficacy and dosing regimen, lower side effects, and decreased toxicity [Foster, A. B. *Deuterium isotope effects in studies of drug metabolism*. Trends in Pharmacological Sciences (1984) 5:524-527; Anderson, K.E.; Stamler, D.; Davis, M.D., et al. *Deutetrabenazine for treatment of involuntary movements in patients with tardive dyskinesia (AIM-TD): a double-blind, randomised, placebo-controlled, phase 3 trial*. Lancet Psychiatry (2017) 4:595-604; Harbeson, S.; Morgan, A.; Liu, J., et al. *Altering metabolic profiles of drugs by precision deuteration 2: discovery of a deuterated analog of ivacaftor with differentiated pharmacokinetics for clinical development*. J. Pharmacol. Exp. Ther. (2017) 362:359-367; Malmlöf, T.; Feltmann, K.; Konradsson-Geuken, Å., et al. *Deuterium-substituted L-DOPA displays increased behavioral potency and dopamine output in an animal model of Parkinson's disease: comparison with the effects produced by L-DOPA and an MAO-B inhibitor*. J. Neural. Transm. (Vienna) (2015) 122:259-272; Mutlib, A. E.; Gerson, R. J.; Meunier, P. C., et al. *The Species-Dependent Metabolism of Efavirenz Produces a Nephrotoxic Glutathione Conjugate in Rats*. Toxicol. Appl. Pharmacol. (2000) 169:102-113]. The above papers are herein incorporated by reference in their entirety for all purposes. However, in some cases, hydrogen-deuterium exchange may lead to redirecting sites of metabolism (“metabolic switching”) [Homing, M. G., et al. *Metabolic switching of drug pathways as a consequence of drug substitution*. Proceedings of the Second International Conference on Stable Isotopes (Klein. E. R. and Klein. P. D. eds) (1976) 41-54; Miwa, G. T.; Lu, A. Y. H. *Kinetic isotope effects and 'metabolic switching' in cytochrome P450-catalyzed reactions*. Bioessays (1987) 7:215–219]. The above papers are herein incorporated by reference in their entirety for all purposes. At the same time, deuterium and hydrogen are essentially the same size, and in most cases, deuteration of a drug would not be expected to affect the biochemical potency or selectivity of the deuterated drug for a biological target as compared to its non-deuterated analog. The effects of deuterium modification on a drug's metabolic and pharmacokinetic properties are not predictable even when deuterium atoms are incorporated at known sites of metabolism. One can determine the effect of deuterium incorporation on the absorption, distribution, metabolism, excretion and/or toxicity (ADMET) properties only by preparing and testing the actual deuterated compound.

In the present invention, entry inhibitors described were identified using an arenavirus GP

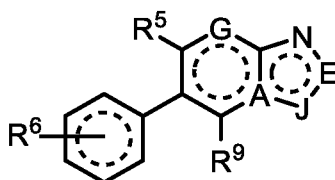
pseudovirus screen and selected compounds were tested against native non-HF virus TCRV to confirm activity against replicative arenavirus. Selected top compounds were then tested against native LASV to confirm activity against the native highly pathogenic human (HF) arenaviruses, and initial drug-like properties were assessed.

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BRIEF SUMMARY OF THE INVENTION

The present invention relates to the use of heterocyclic compounds for inhibiting arenavirus infection in humans, other mammals, or in cell culture, to methods of treating arenavirus infection such as Lassa, Bolivian, Argentine, Venezuelan, Brazilian, Chapare and Lujo hemorrhagic fevers, to methods of inhibiting the replication of arenaviruses, to methods of reducing the amount of arenaviruses, and to compositions that can be employed for such methods.

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



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I

or a pharmaceutically acceptable salt and a pharmaceutically acceptable carrier, dilutant or vehicle thereof wherein

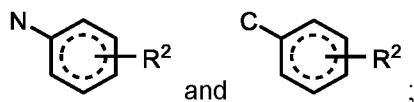
A is independently selected from C and N;

G is independently selected from CH, CD, and N;

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E is independently selected from CH, CD, and N;

J is independently selected from



R² is independently selected from H, D, -OR³, -R⁴, -NHR¹⁰, -CONHR¹⁰;

R³ is independently selected from H, D, C₁ to C₆ alkyl, C₂ to C₆ alkenyl, (C₃ to C₁₀) cycloalkyl, (C₂ to C₉) cycloheteroalkyl, -NHC(O)R⁴, -C(O)NHR¹⁰, and -C(O)R¹⁰, wherein each C₁ to C₆ alkyl is optionally substituted with D, halogen, -OH, -OR⁴, -NHR¹⁰;

R⁴ is independently selected from C₁ to C₆ alkyl and (C₂ to C₉) cycloheteroalkyl optionally substituted with D, halogen, -OH, -OR¹⁰, and NHR¹⁰;

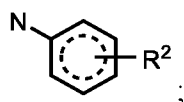
R^5 is independently selected from H, D, C_1 to C_6 alkyl, C_2 to C_6 alkenyl, C_2 to C_6 alkynyl, halogen, $-OR^3$, $-CO_2R^{10}$, $-NHC(O)R^4$, $-C(O)NHR^{10}$, $-NHR^{10}$, $-CHNHR^{10}$, $-CN$, $-CR^4$, and $-C(O)R^{10}$, wherein each C_1 to C_6 alkyl is optionally substituted with D;

R^6 is independently selected from H, D, halogen, $-OR^3$, and R^4 ;

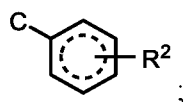
5 R^9 is independently selected from H, D, halogen, C_1 to C_6 alkyl, and $-OR^{10}$;

R^{10} is independently selected from H, D, $-OH$, C_1 to C_6 alkyl and C_2 to C_6 alkenyl;

and when E is N, CH or CD then A is C, G is CH or CD, and J is

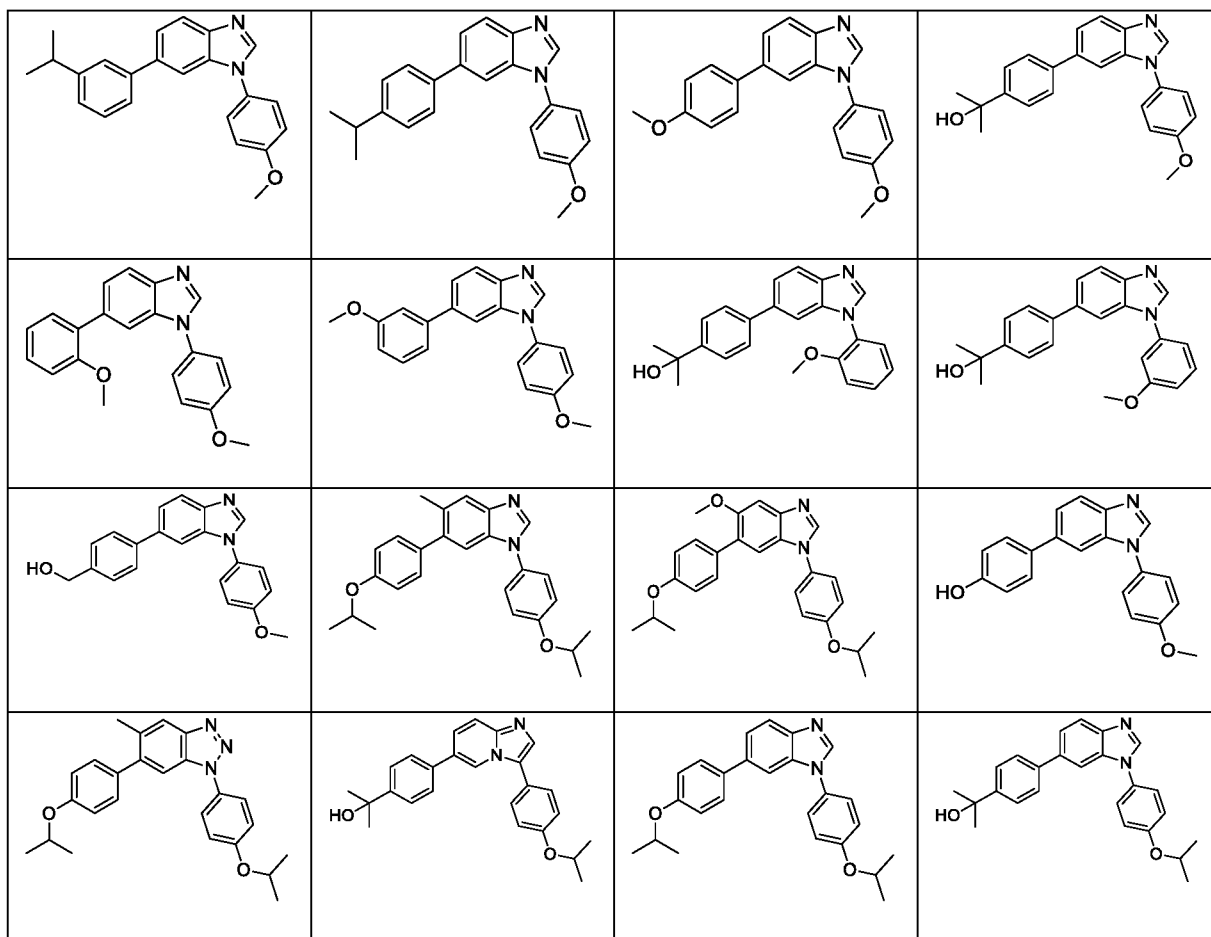


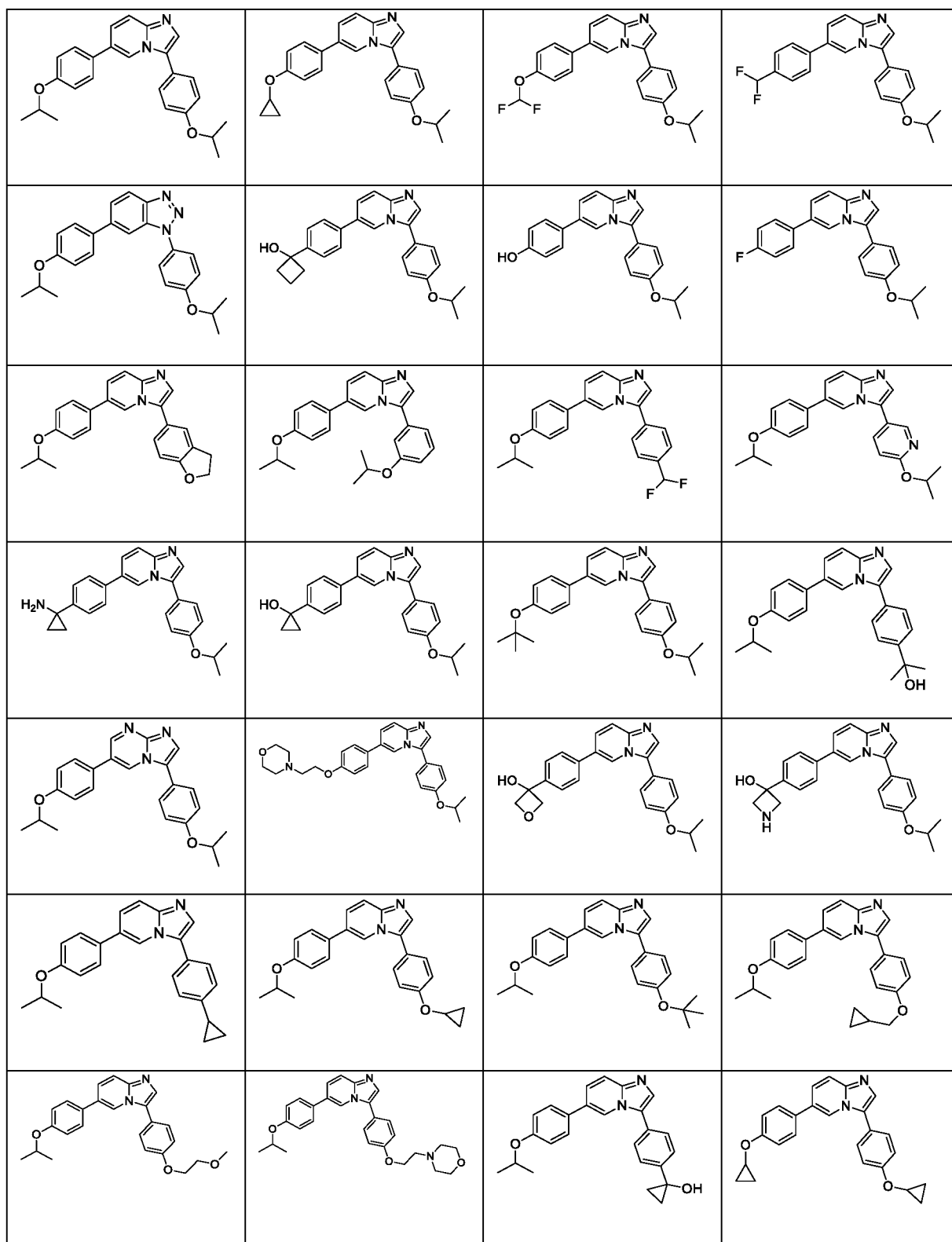
and when A is N then J is

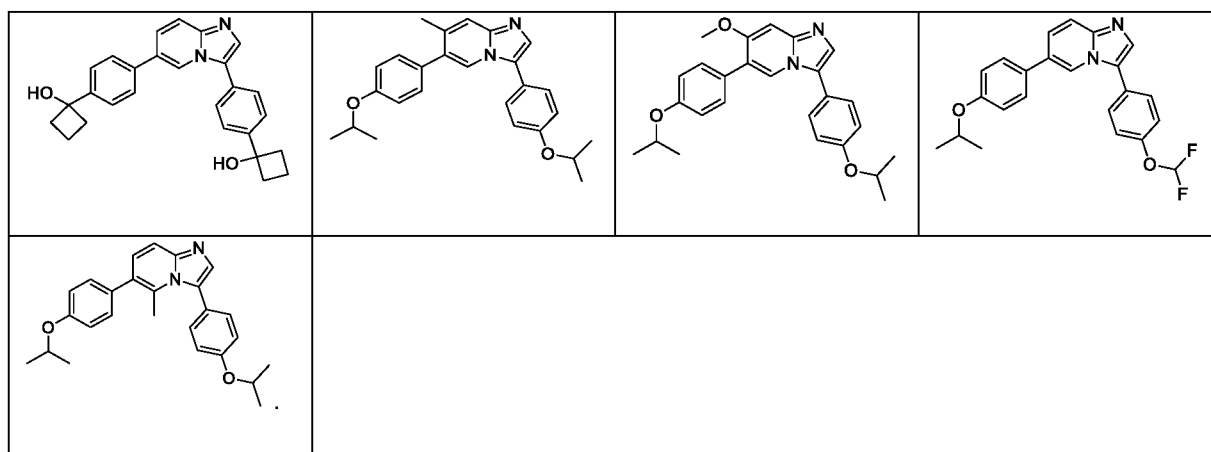


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with the proviso that the following compounds are excluded:

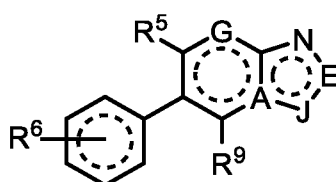






DETAILED DESCRIPTION OF THE INVENTION

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



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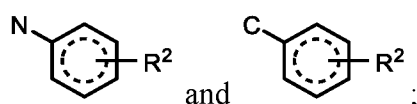
or a pharmaceutically acceptable salt and a pharmaceutically acceptable carrier, dilutant or vehicle thereof wherein

A is independently selected from C and N;

G is independently selected from CH, CD, and N;

E is independently selected from CH, CD, and N;

J is independently selected from



R² is independently selected from H, D, -OR³, -R⁴, -NHR¹⁰, -CONHR¹⁰;

R³ is independently selected from H, D, C₁ to C₆ alkyl, C₂ to C₆ alkenyl, (C₃ to C₁₀) cycloalkyl, (C₂ to C₉) cycloheteroalkyl, -NHC(O)R⁴, -C(O)NHR¹⁰, and -C(O)R¹⁰, wherein each C₁ to C₆ alkyl is optionally substituted with D, halogen, -OH, -OR⁴, -NHR¹⁰;

R⁴ is independently selected from C₁ to C₆ alkyl and (C₂ to C₉) cycloheteroalkyl optionally substituted with D, halogen, -OH, -OR¹⁰, and NHR¹⁰;

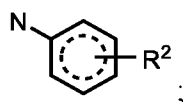
R^5 is independently selected from H, D, C_1 to C_6 alkyl, C_2 to C_6 alkenyl, C_2 to C_6 alkynyl, halogen, $-OR^3$, $-CO_2R^{10}$, $-NHC(O)R^4$, $-C(O)NHR^{10}$, $-NHR^{10}$, $-CHNHR^{10}$, $-CN$, $-CR^4$, and $-C(O)R^{10}$, wherein each C_1 to C_6 alkyl is optionally substituted with D;

R^6 is independently selected from H, D, halogen, $-OR^3$, and R^4 ;

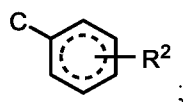
5 R^9 is independently selected from H, D, halogen, $-OR^{10}$, and C_1 to C_6 alkyl;

R^{10} is independently selected from H, D, $-OH$, C_1 to C_6 alkyl, and C_2 to C_6 alkenyl;

and when E is N, CH or CD then A is C, G is CH or CD, and J is

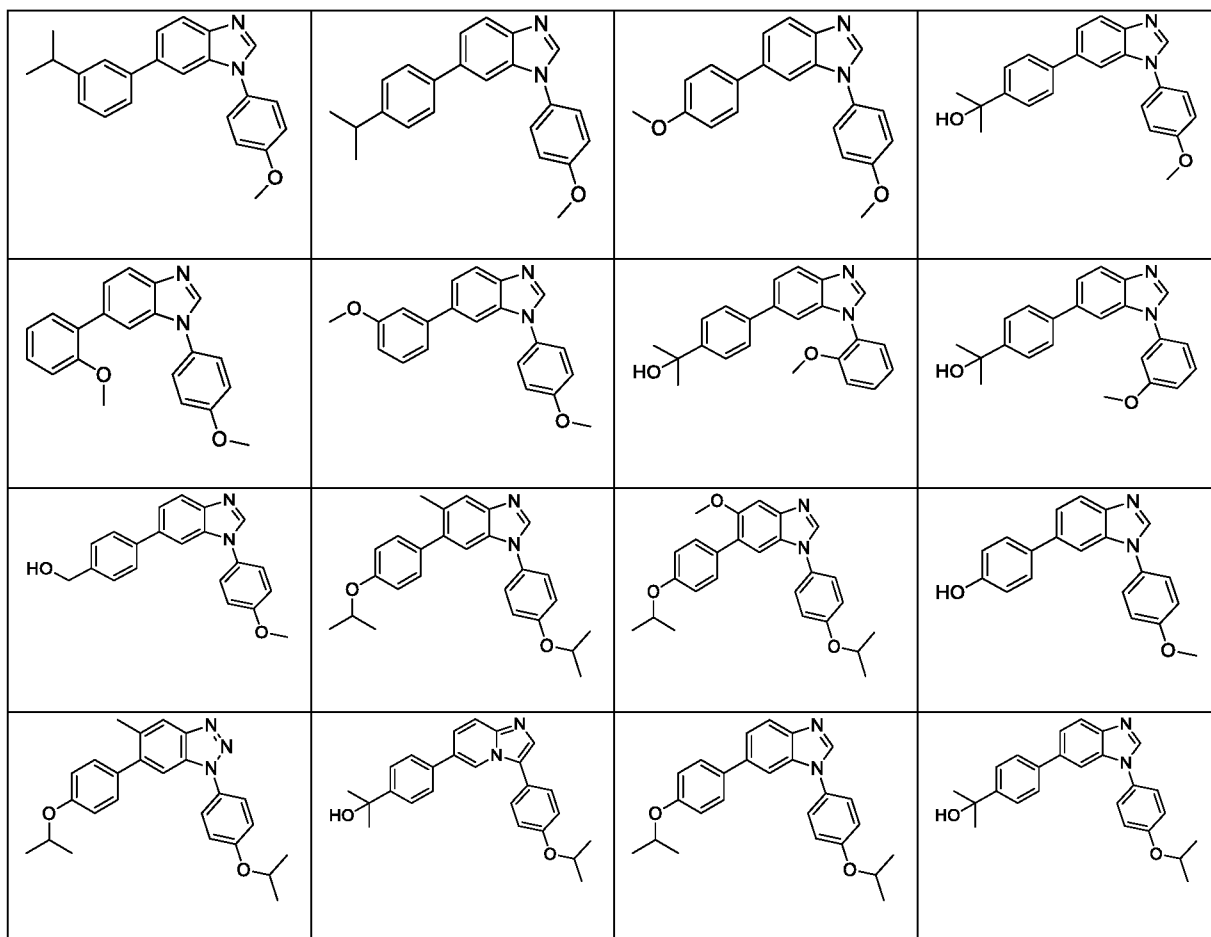


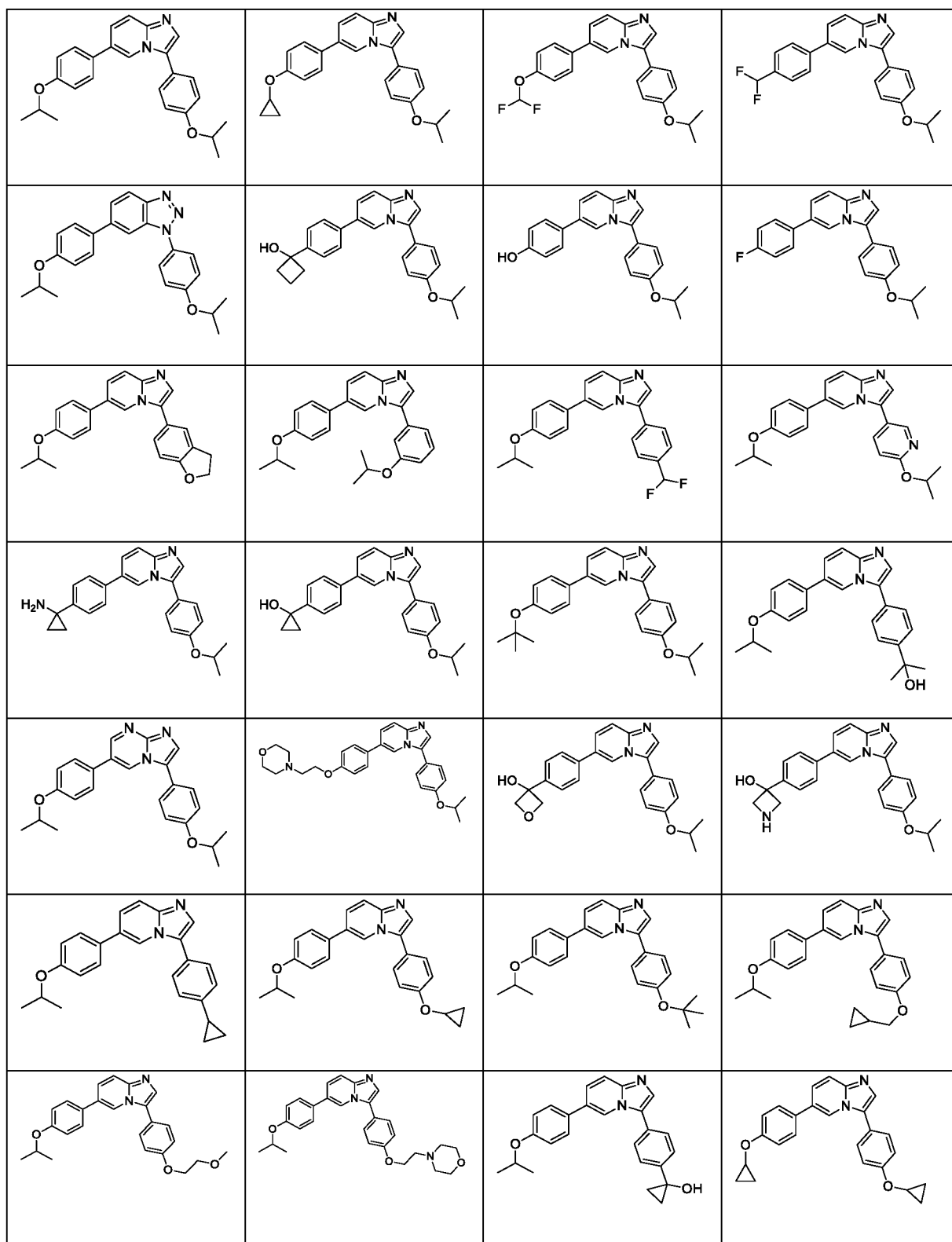
and when A is N then J is

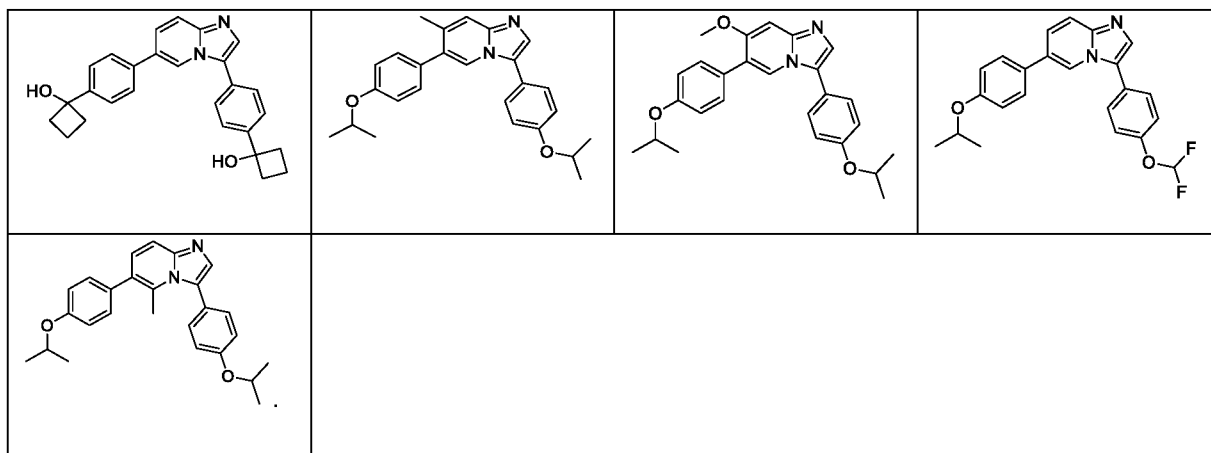


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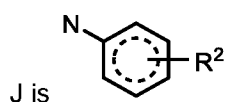
with the proviso that the following compounds are excluded:



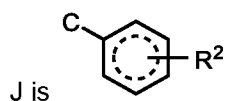




In another embodiment, the method comprises administering to humans, other mammals, cell culture, or biological sample an effective amount of a compound represented by Structural Formula I, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein A, G, E, R², R³, R⁴, R⁵, R⁶, R⁹, and R¹⁰ are defined as above and wherein



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, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein A, G, E, R², R³, R⁴, R⁵, R⁶, R⁹, and R¹⁰ are defined as above and wherein



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, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein A, G, J, R², R³, R⁴, R⁵, R⁶, R⁹, and R¹⁰ are defined as above and wherein

E is CH or CD.

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, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein E, G, J, R², R³, R⁴, R⁵, R⁶, R⁹, and R¹⁰ are defined as above and wherein

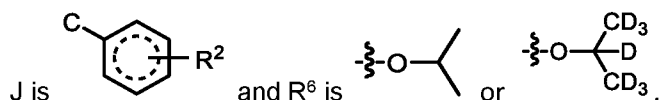
A is C.

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, or a

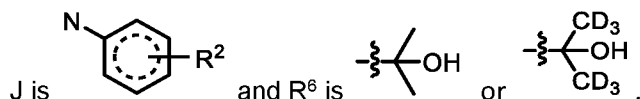
pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein E, G, J, R², R³, R⁴, R⁵, R⁶, R⁹, and R¹⁰ are defined as above and wherein

A is N.

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, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein A, G, E, R², R³, R⁴, R⁵, R⁹, and R¹⁰ are defined as above and wherein



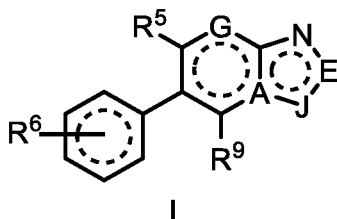
In another embodiment, the method comprises administering to humans, other mammals, cell culture, or biological sample an effective amount of a compound represented by Structural Formula I, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein A, G, E, R², R³, R⁴, R⁵, R⁹, and R¹⁰ are defined as above and wherein



In another embodiment, the method comprises of administering to humans, other mammals, cell culture, or biological sample a pharmaceutically effective amount of a pharmaceutical composition comprising a compound selected from the group of compounds described as Examples A1 to A3, B4 to B9, C10 to C26, D27 to D29, and E30 with a pharmaceutically acceptable carrier, dilutant, or vehicle.

In another embodiment the method comprises of administering a pharmaceutically effective amount of a pharmaceutical composition comprising a compound selected of Structural Formula I or a compound as shown above with a pharmaceutically acceptable carrier, dilutant, or vehicle, with an additional therapeutically effective amount of a therapeutic agent selected from the group consisting of Ribavirin, polymerase inhibitors, Favipiravir, Triazavirin, small interfering RNAs (siRNAs), vaccines, monoclonal antibodies, immunomodulators, and other arenavirus inhibitors.

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



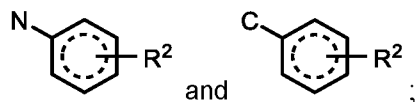
or a pharmaceutically acceptable salt and a pharmaceutically acceptable carrier, dilutant or vehicle thereof wherein

A is independently selected from C and N;

G is independently selected from CH, CD, and N;

E is independently selected from CH, CD, and N;

J is independently selected from



R^2 is independently selected from H, D, $-OR^3$, $-R^4$, $-NHR^{10}$, $-CONHR^{10}$;

5 R^3 is independently selected from H, D, C_1 to C_6 alkyl, C_2 to C_6 alkenyl, $(C_3$ to $C_{10})$ cycloalkyl, $(C_2$ to $C_9)$ cycloheteroalkyl, $-NHC(O)R^4$, $-C(O)NHR^{10}$, and $-C(O)R^{10}$, wherein each C_1 to C_6 alkyl is optionally substituted with D, halogen, $-OH$, $-OR^4$, $-NHR^{10}$;

R^4 is independently selected from C_1 to C_6 alkyl and $(C_2$ to $C_9)$ cycloheteroalkyl optionally substituted with D, halogen, $-OH$, $-OR^{10}$, and NHR^{10} ;

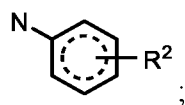
10 R^5 is independently selected from H, D, C_1 to C_6 alkyl, C_2 to C_6 alkenyl, C_2 to C_6 alkynyl, halogen, $-OR^3$, $-CO_2R^{10}$, $-NHC(O)R^4$, $-C(O)NHR^{10}$, $-NHR^{10}$, $-CHNHR^{10}$, $-CN$, $-CR^4$, and $-C(O)R^{10}$, wherein each C_1 to C_6 alkyl is optionally substituted with D;

R^6 is independently selected from H, D, halogen, $-OR^3$, and R^4 ;

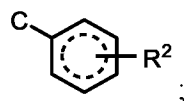
R^9 is independently selected from H, D, halogen, $-OR^{10}$, and C_1 to C_6 alkyl;

15 R^{10} is independently selected from H, D, $-OH$, C_1 to C_6 alkyl and C_2 to C_6 alkenyl;

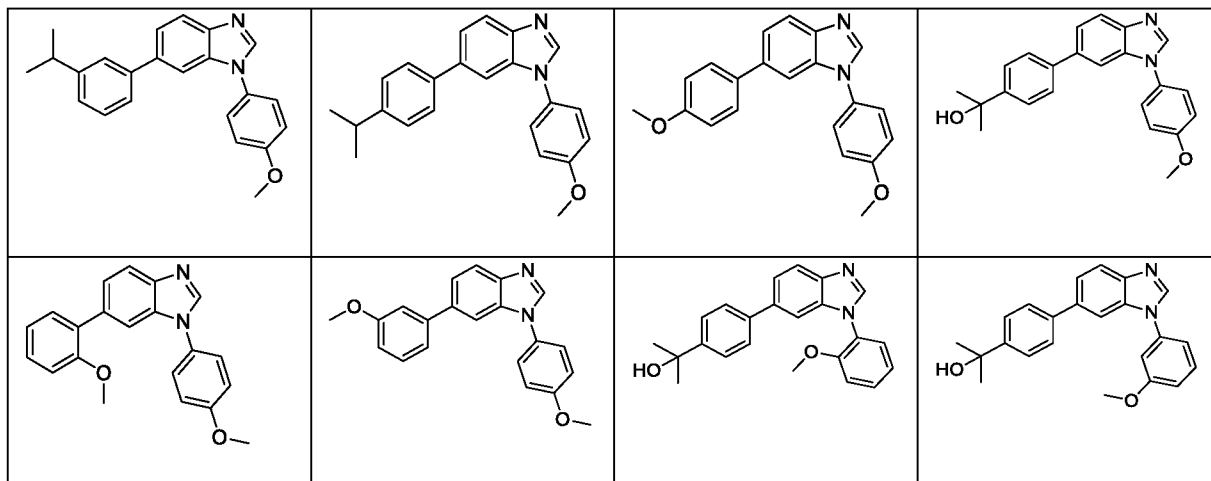
and when E is N, CH or CD then A is C, G is CH or CD, and J is

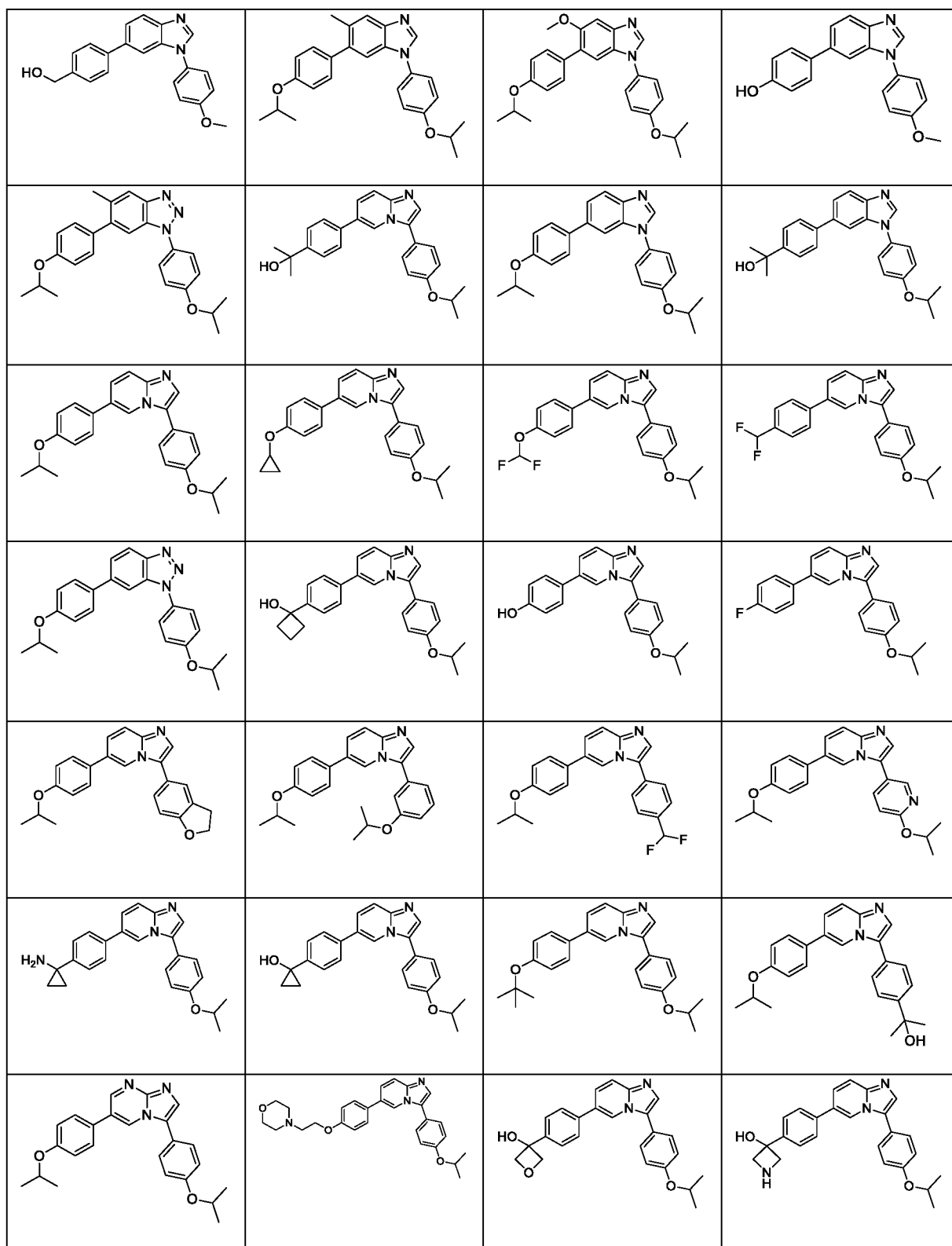


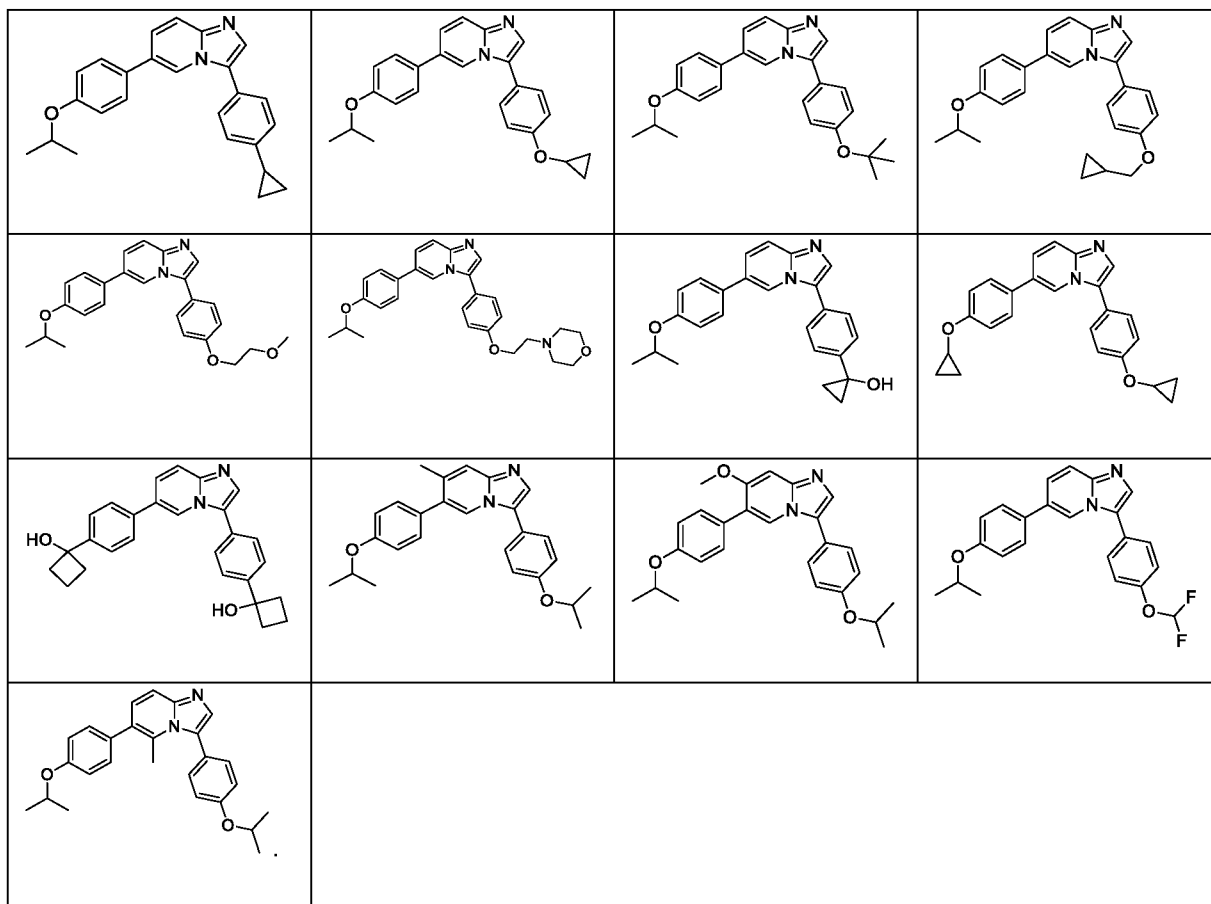
and when A is N then J is



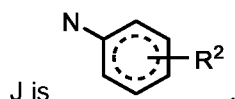
20 with the proviso that the following compounds are excluded:



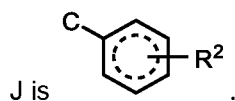




In another embodiment, the invention relates to compounds of Structural Formula I or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein A, G, E, R², R³, R⁴, R⁵, R⁶, R⁹, and R¹⁰ are defined as above and wherein



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 A, G, E, R², R³, R⁴, R⁵, R⁶, R⁹, and R¹⁰ are defined as above and wherein



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 A, G, J, R², R³, R⁴, R⁵, R⁶, R⁹, and R¹⁰ are defined as above and wherein

E is CH or CD.

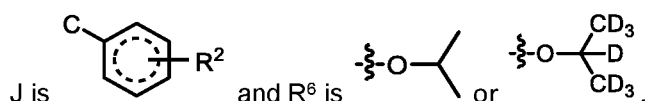
In another embodiment, the invention relates to compounds of Structural Formula I or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein E, G, J, R², R³, R⁴, R⁵, R⁶, R⁹, and R¹⁰ are defined as above and wherein

A is C.

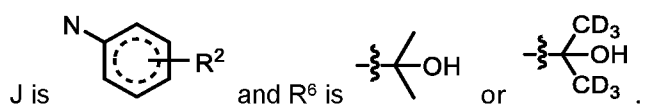
5 In another embodiment, the invention relates to compounds of Structural Formula I or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein E, G, J, R², R³, R⁴, R⁵, R⁶, R⁹, and R¹⁰ are defined as above and wherein

A is N.

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 A, G, E, R², R³, R⁴, R⁵, R⁹, and R¹⁰ are defined as above and wherein

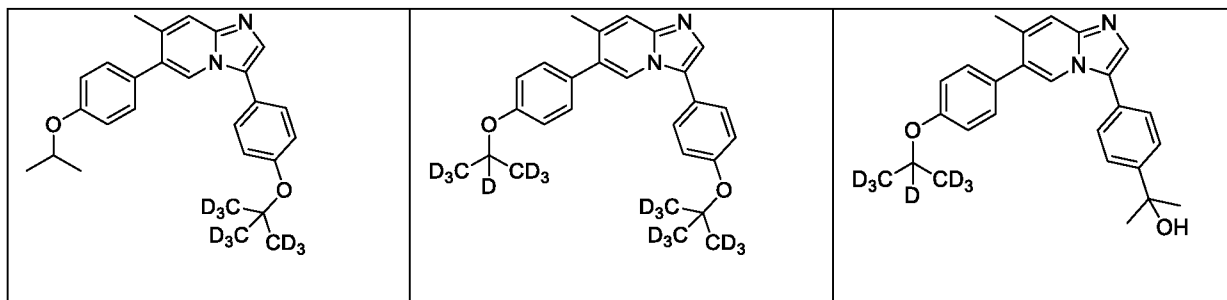


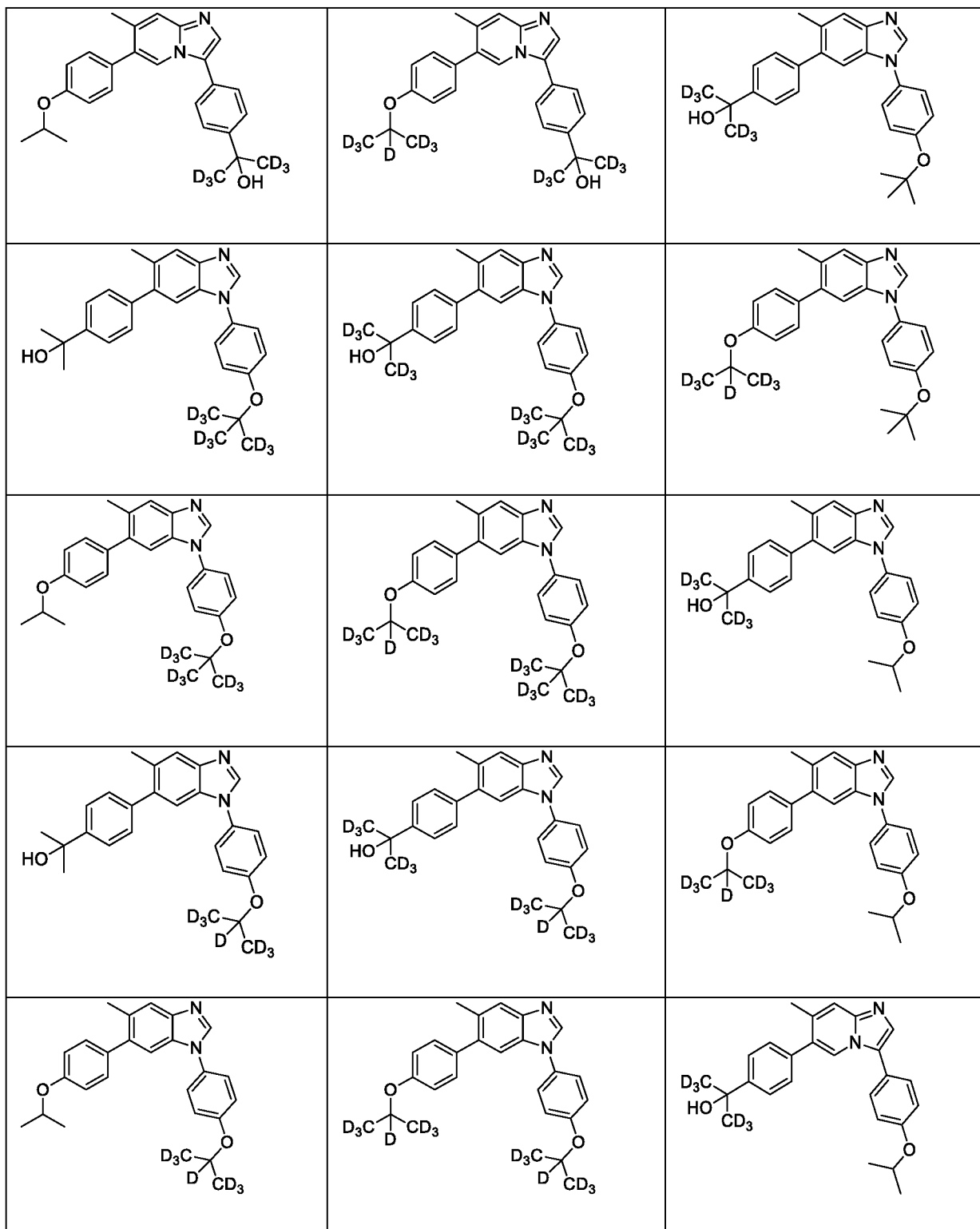
15 In another embodiment, the invention relates to compounds of Structural Formula I or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, wherein A, G, E, R², R³, R⁴, R⁵, R⁹, and R¹⁰ are defined as above and wherein

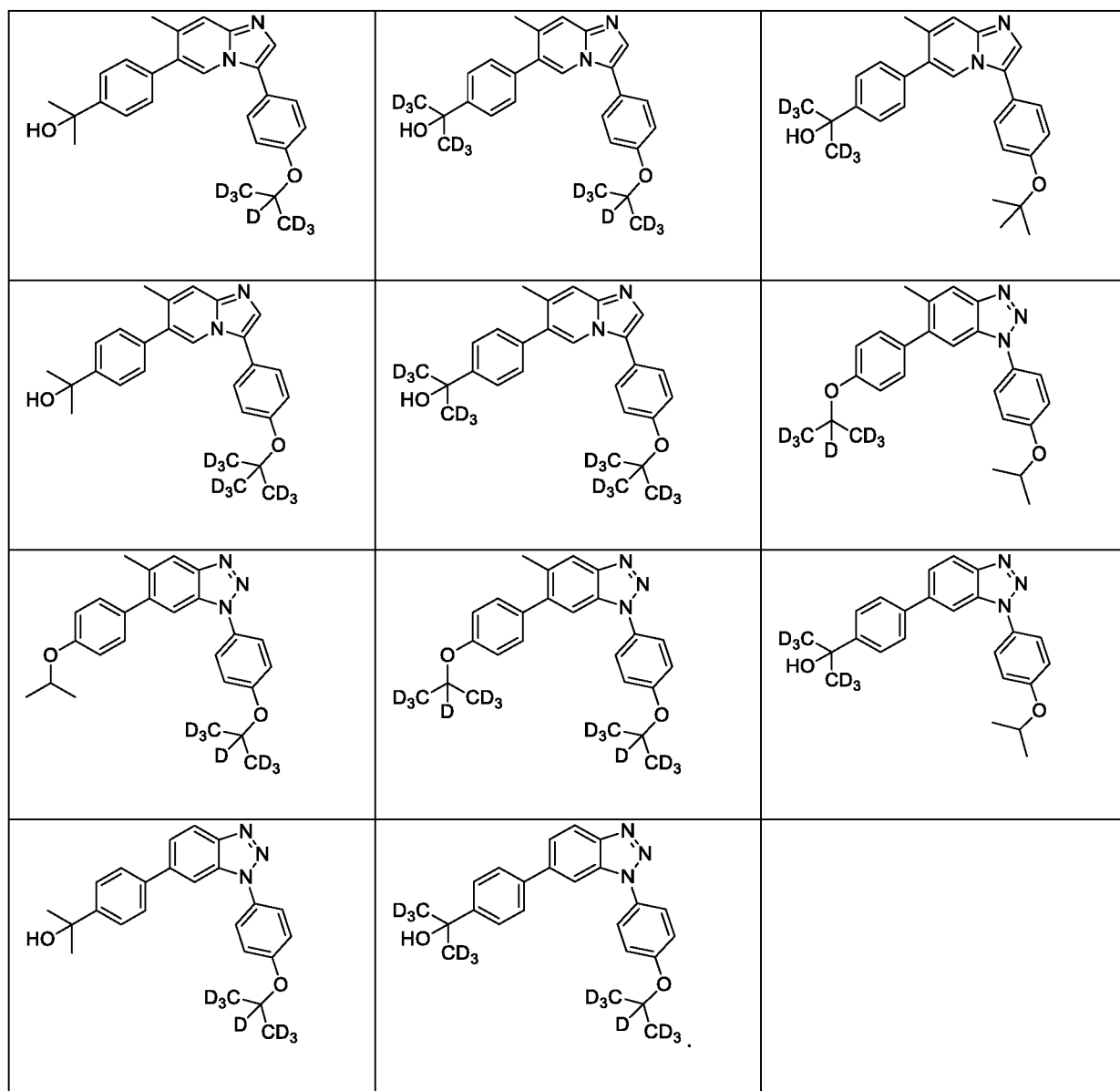


20 In another embodiment, the invention relates to compounds, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier, diluent, or vehicle thereof, selected from the group consisting of the compounds described as examples A1 to A3, B4 to B9, C10 to C26, D27 to D29, and E30.

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 of:







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 C₆)” alkyl refers to a saturated aliphatic hydrocarbon radical including straight chain and branched chain groups of 1 to 6 carbon atoms. Examples of (C₁ to C₆) 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 C₈) alkenyl", as used herein, means an alkyl moiety comprising 2 to 8 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 8 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, ethenyl, propenyl, butenyl, allyl, and pentenyl. The term "allyl," as used herein, means a -CH₂CH=CH₂ group. The term, "C(R)=C(R)," as used herein, represents a carbon-carbon double bond in which each carbon is substituted by an R group, and includes both the E and Z isomers.

As used herein, the term "(C₂ to C₈) 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 8 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 C₈) 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, *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.

"(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, indolizynyl, 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).

"(C₂ to C₉) 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 9 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 C₉ 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 C₉ 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 pyrrolidiny. An example of a 6 membered cycloheteroalkyl group is piperidiny. An example of a 9 membered cycloheteroalkyl group is indoliny. An example of a 10 membered cycloheteroalkyl group is 4*H*-quinoliziny. Further examples of such C₂ to C₉ 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, 2*H*-pyranyl, 4*H* pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazoliny, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidiny, imidazoliny, imidazolidiny, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, 3*H*-indolyl quinoliziny, 3-oxopiperaziny, 4-methylpiperaziny, 4-ethylpiperaziny, and 1-oxo-2,8,diazaspiro[4.5]dec-8-yl.

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 "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 are not limited to, cyclopentenyl, cyclohexenyl.

An "aldehyde" group refers to a carbonyl group, -C(O)R, 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 refer to a -SO₂ alkyl.

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

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

5 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)O aryl.

An "arylsulfonyl" group refers to a -SO₂ aryl.

10 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.

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

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

20 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.

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

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

25 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.

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

30 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.

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

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

35 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.

A "trihalomethanecarbonyl" group refers to a $Z_3CC(O)$ group, where Z is halogen.

A "trihalomethanesulfonamido" group refers to a $Z_3CS(O)_2NR-$ group, where Z is halogen.

A "trihalomethanesulfonyl" group refers to a $Z_3CS(O)_2$ group, where Z is halogen.

5 A "trihalomethyl" group refers to a $-CZ_3$ group, where Z is halogen.

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

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 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 C_6 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 C_6 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 C_6 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 C_6 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.

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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 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.

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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.

35

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.

5 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
10 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.

15 Final pharmaceutical forms may be pills, tablets, powders, lozenges, sachets, cachets, dragees, 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
20 of the present invention and one or more additional agents that inhibit arenavirus.

The term "Arenavirus GP-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 Arenaviruses *in vivo*, such as in a mammal, birds 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
25 known to those of ordinary skill in the art.

The term "therapeutically effective amount," as used herein, means an amount of a compound of the present invention, or a salt thereof, that, when administered to a mammal in need of such treatment, is sufficient to effect treatment, as defined herein. Thus, a therapeutically effective amount of a compound of the present invention, or a salt thereof, is a quantity sufficient to modulate or inhibit the activity of the
30 Arenavirus GP protein such that cell entry and replication of arenaviruses that is mediated by activity of the Arenavirus GP protein is reduced or alleviated.

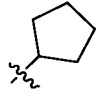
The terms "treat", "treating", and "treatment" with reference to arenavirus infection, in mammals, particularly a human, include: (i) preventing the disease or condition from occurring in a subject which may be predisposed to the condition, such that the treatment constitutes prophylactic treatment for the
35 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.

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 about 10% 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 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.

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) may be 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 compounds 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 entireties. 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
5 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,
10 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,
15 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
20 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
25 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
30 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
35 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 , ^{35}Cl , and ^{37}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 Tomography (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 term “deuterated” refers to the replacement of one or more hydrogen atoms with a corresponding number of deuterium atoms. Unless otherwise stated, when a particular position in a compound of this invention is designated specifically as “D”, “deuterium”, being “deuterated”, or “having deuterium” (the element deuterium is represented by the letter “D” in chemical structures and formulas and indicated with a lower case “d” in chemical names), the position is understood to have deuterium at an abundance that is at least 3000 times greater than the natural abundance of deuterium, which is 0.015% (i.e., the term “D”, “d” or “deuterium” indicates at least 45% incorporation of deuterium).

The term “isotopic enrichment factor”, as used herein, means the ratio between the isotopic abundance and the natural abundance of a specified isotope.

In some embodiments, a compound of this invention has an isotopic enrichment factor for each deuterium present at a site designated as a potential site of deuteration on the compound of at least 3500 (52.5% deuterium incorporation), at least 4000 (60% deuterium incorporation), at least 4500 (67.5% deuterium incorporation), at least 5000 (75% deuterium incorporation), at least 5500 (82.5% deuterium incorporation), at least 6000 (90% deuterium incorporation), at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation), at least 6600 (99% deuterium incorporation), or at least 6633.3 (99.5% deuterium incorporation).

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 arenavirus infection or viruses expressing the arenavirus glycoprotein, a pharmaceutical composition of the invention is administered in a suitable formulation prepared by combining a therapeutically effective amount (i.e., an arenavirus GP 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. 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.

5 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
10 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 co-solvent 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
15 benzyl alcohol, 8% w/v of the non-polar surfactant polysorbate 80, and 65% w/v polyethylene glycol 300, 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 co-solvent system may be suitably varied without destroying its solubility and toxicity characteristics. Furthermore, the identity of the
20 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
25 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
30 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
35 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 a mammal, such as a human, suffering from a condition or disease mediated by arenavirus or any virus expressing arenavirus glycoprotein, either alone or in combination with one or more compounds selected from Ribavirin, polymerase inhibitors, Favipiravir, Triazavirin, small interfering RNAs (siRNAs), vaccines, monoclonal antibodies, immunomodulators, and other arenavirus inhibitors 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 a mammal, such as a human, suffering from a condition or disease mediated by arenavirus in combination with at least one other agent used for treatment of arenavirus selected from the group consisting of Ribavirin, viral RNA-dependent-RNA-polymerase inhibitors as shown by Ng KK, Arnold JJ and Cameron CE, *Structure-Function Relationships Among RNA-Dependent RNA Polymerases*, Curr Top Microbiol Immunol, 2008; **320**: 137-156, incorporated herein by reference in its entirety, Favipiravir, a broad-spectrum inhibitor of viral RNA-Dependent RNA Polymerases, Triazavirin, a broad-spectrum inhibitor of

viral RNA-Dependent RNA Polymerases, small interfering RNAs (siRNAs) and microRNAs as shown by Carthew RW and Sontheimer EJ, *Origins and Mechanisms of miRNAs and siRNAs*, Nature, 2009; **136**: 642-655, incorporated herein by reference in its entirety, vaccines as shown by Nabel GJ, *Designing Tomorrow's Vaccines*, NEJM, 2013; **368**: 551-560, incorporated herein by reference in its entirety, and immunomodulators as shown by Patil US, Jaydeokar AV and Bandawane DD, *Immunomodulators: A Pharmacological Review*, Internatl J Pharmacy and Pharmaceutical Sci, 2012; **4**: 30-36, incorporated herein by reference in its entirety], alone or as part of a pharmaceutically acceptable formulation containing other arenavirus inhibitors, 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 a mammal requiring such treatment, are all choices within the knowledge of one of ordinary skill in the art and can be determined without undue experimentation.

The compounds of the present invention are useful for modulating or inhibiting arenavirus glycoprotein (GP) both *in vitro* and *in vivo*.

Accordingly, these compounds are useful for the prevention and/or treatment of disease states associated with arenavirus infection or treating viruses expressing the arenavirus glycoprotein.

This invention also relates to a method for the treatment of arenavirus infection in mammals including a human comprising administering to said mammal an amount of a compound of the Formula I, as defined above, or a salt or solvate thereof, that is effective in treating disease states associated with Arenavirus infection or viruses expressing the arenavirus glycoprotein.

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, "DCM" (CH₂Cl₂) means dichloromethane or methylene chloride, "dba" means dibenzylideneacetone, "DCE" means dichloroethane or ethylene chloride, "D" or "d" means deuterium, "DIAD" means diisopropylazadicarboxylate, "DIPEA" or "DIEA" means diisopropyl ethyl amine, "DMA" means N,N-dimethylacetamide, "DMF" means N,N-dimethyl formamide, "DMSO" means dimethylsulfoxide, "DPPP" means 1,3-bis(diphenylphosphino)propane, "HOAc" means acetic acid, "IPA" means isopropyl alcohol, "NMP" means 1-methyl 2-pyrrolidinone, "TEA" means triethyl amine, "TFA" means trifluoroacetic acid, "DCM" means dichloromethane, "EtOAc" means ethyl acetate, "MgSO₄" means magnesium sulphate, "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, "LiHMDS" or "LHMDS" means lithium hexamethyldisilazide, "TBME" or "MTBE" means *tert*-butyl methyl ether, "LDA" means lithium diisopropylamide, "NBS" means N-bromosuccinimide, "NIS" means N-iodosuccinimide, "Xanthphos"

means 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene; "P(Ph₃)" means triphenylphosphine, "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,

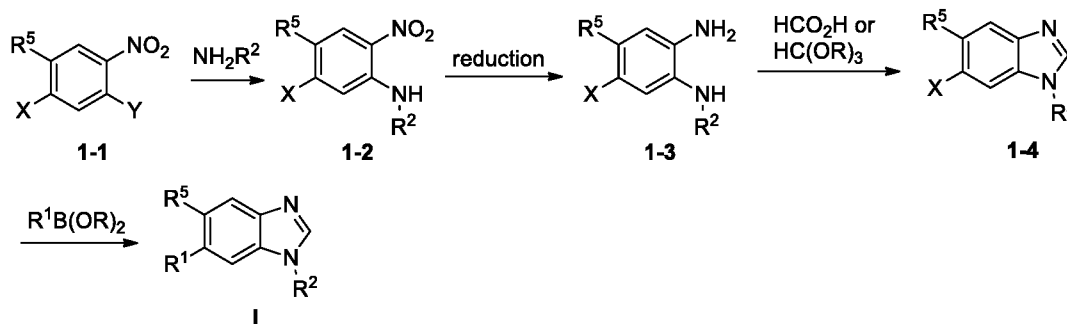
5 Methods of Preparation.

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
10 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
15 adaptability for preparing other compounds of the invention.

Scheme 1 shows a method useful for the synthesis of compounds of structural Formula I wherein G is CH, J is N, E is CH, and A is C. Compound **1-1** (X = Cl, Br, or I, and Y is F, Cl, Br, or I) can be reacted with amine R²NH₂ in the presence of a base such as NaH or Cs₂CO₃ in a solvent such as THF or DMF to form compound **1-2**. Reduction of the nitro group using a reducing agent such as Fe or SnCl₂ in a
20 solvent such as THF or methanol can provide aniline **1-3** which can be reacted with formic acid HCO₂H or orthoester HC(OR)₃ to form **1-4**. Coupling of **1-4** with a boronic acid or boronic ester R¹B(OR)₂ using a catalyst such as [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride in the presence of a base such as K₂CO₃ in a solvent such as dimethoxyethane can provide compound of structural Formula I.

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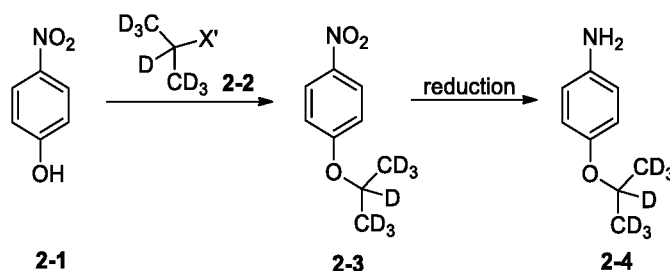
Scheme 1



Scheme 2 depicts a method of synthesis of deuterated aniline **2-4** useful in preparing deuterated intermediates **1-2** for the synthesis of deuterated compounds of the invention as described in Scheme 1 above. Reaction of phenol **2-1** with deuterated alkyl halide **2-2** (X' = Br or I) in the presence of a base
30 such as K₂CO₃ in a solvent such as N,N-dimethylformamide can afford compound **2-3**. Reduction of the

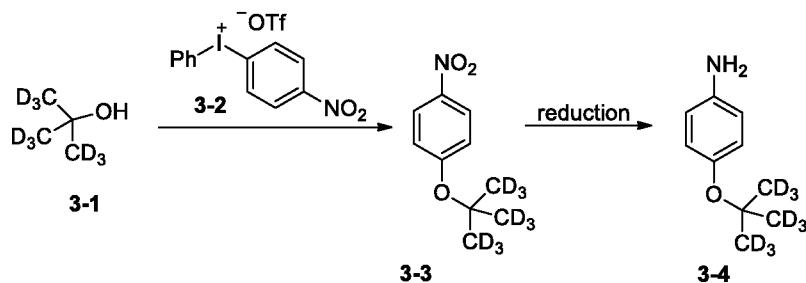
nitro group using a reducing agent such as hydrogen gas in the presence of a catalyst such as palladium on carbon in a solvent such as methanol can provide aniline **2-4**.

Scheme 2



Scheme 3 depicts a method of synthesis of deuterated aniline **3-4** useful in preparing deuterated intermediates **1-2** for the synthesis of deuterated compounds of the invention as described in Scheme 1 above. Arylation of alcohol **3-1** with diaryliodonium salt **3-2** in the presence of a base such as NaHMDS in a solvent such as pentane can provide compound **3-3** [Lindstedt, E.; Stridfelt, E.; Olofsson, B. *Mild synthesis of sterically congested alkyl aryl ethers*. Org. Lett. (2016) 18: 4234-4237]. The above paper is herein incorporated by reference in its entirety for all purposes. Reduction of the nitro group using a reducing agent such as hydrogen gas in the presence of a catalyst such as palladium on carbon in a solvent such as methanol can provide aniline **3-4**.

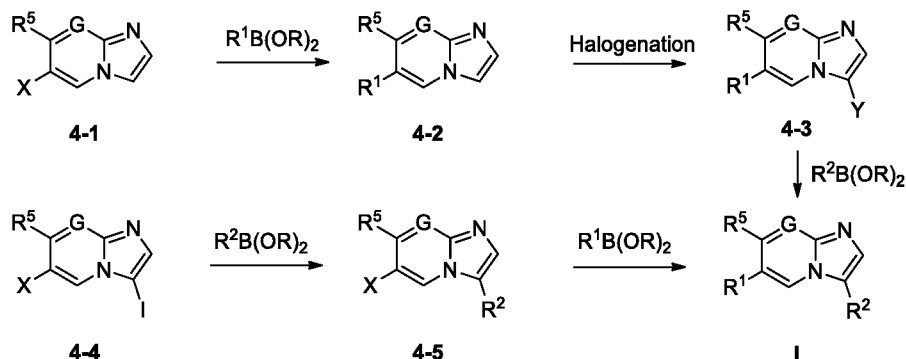
Scheme 3



Scheme 4 depicts a method useful for the synthesis of compounds of structural Formula I wherein A is N, E is CH, and J is C. Compound **4-1** (X = Cl, Br) can be coupled with a boronic acid or boronic ester R¹B(OR)₂ using a catalyst such as [1,1'-bis(diphenylphosphino)ferrocene] palladium(II) dichloride in the presence of a base such as K₂CO₃ in a solvent such as dimethoxyethane to form **4-2** which can be treated with a halogenation reagent such as bromine or *N*-bromosuccinimide (NBS), or iodine or *N*-iodosuccinimide (NIS) to form compound **4-3** (Y = Br, I). Treatment of **4-3** with a boronic acid or boronic ester R²B(OR)₂ using a catalyst such as tetrakis(triphenylphosphine)palladium in the presence of a base such as K₂CO₃ in a solvent such as dioxane can provide a compound of Structural Formula I. Alternatively, compound **4-4** (X = Cl, Br) can react with boronic acid or boronic ester R²B(OR)₂ using a

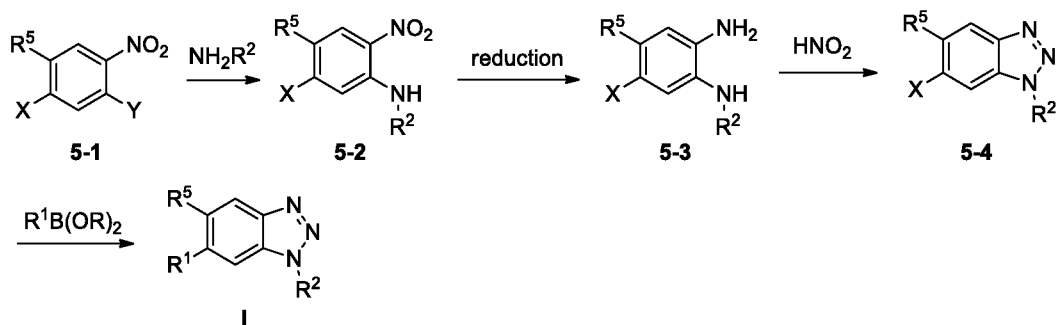
catalyst such as tetrakis(triphenylphosphine) palladium in the presence of a base such as K_2CO_3 in a solvent such as dioxane to provide compound **4-5** which can react with a second boronic acid or boronic ester $R^1B(OR)_2$ using a catalyst such as [1,1'-bis(diphenylphosphino)ferrocene] palladium(II) dichloride in the presence of a base such as K_2CO_3 in a solvent such as dimethoxyethane to provide a compound of structural Formula I.

Scheme 4



Scheme 5 depicts a method useful for the synthesis of compounds of structural Formula I wherein G is CH , A is C , J is N , and E is N . Compound **5-1** ($X = Cl, Br, \text{ or } I$, and Y is $F, Cl, Br, \text{ or } I$) can be reacted with amine R^2NH_2 in the presence of a base such as NaH or K_2CO_3 in a solvent such as THF or DMF to form compound **5-2**. Reduction of the nitro groups using a reducing agent such as Fe or $SnCl_2$ in a solvent such as THF or methanol can provide aniline **5-3** which can be reacted with nitrous acid to form **5-4**. Coupling of **5-4** with a boronic acid or boronic ester $R^1B(OR)_2$ using a catalyst such as [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride in the presence of a base such as K_2CO_3 in a solvent such as dimethoxyethane can provide compound of structural Formula I.

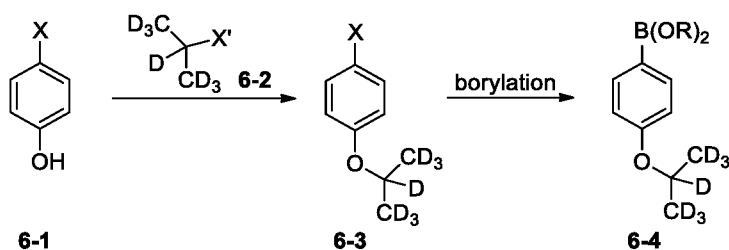
Scheme 5



Reaction Schemes 6-8 illustrate methods of synthesis of borane reagents **6-4**, **7-4**, and **8-4** useful in preparing deuterated intermediates and final compounds of the invention as described in Schemes 1, 4, and 5 above, to introduce R^1 and/or R^2 substituents.

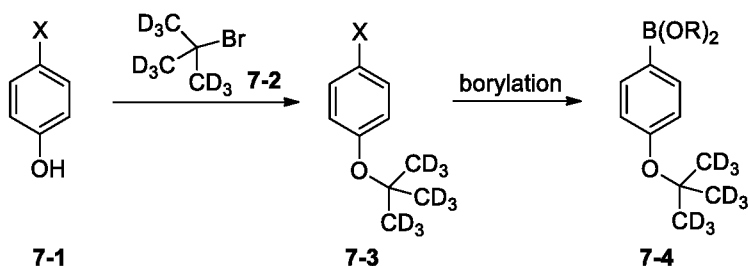
Scheme 6 depicts a method useful for the synthesis of deuterated boronic acid or ester **6-4**. Reaction of phenol **6-1** (X = Br or I) with deuterated alkyl halide **6-2** (X' = Br or I) in the presence of a base such as K₂CO₃ in a solvent such as N,N-dimethylformamide can afford compound **6-3**. Compound **6-3** can be converted to a boronic acid or ester **6-4** using standard borylation reaction conditions well known to those skilled in the art. For example, metal-halogen exchange of compound **6-3** with organolithium reagent such as *n*-Butyllithium followed by treatment with trialkyl borate B(OR)₃ can provide boronic ester **6-4**, which can be hydrolyzed to afford free boronic acid **6-4** (R = H).

Scheme 6



Scheme 7 depicts a method useful for the synthesis of deuterated boronic acid or ester **7-4**. Reaction of phenol **7-1** (X = Br or I) with deuterated alkyl bromide **7-2** using catalyst such as nickel(II) acetylacetonate in the presence of a base such as NaHCO₃ in a solvent such as toluene can afford compound **7-3** [Hodous, B. L. US patent application, publication number US2016/0031892, 4 Feb 2016]. The above patent is herein incorporated by reference in its entirety for all purposes. Compound **7-3** can be converted to a boronic acid or ester **7-4** using standard borylation reaction conditions well known to those skilled in the art. For example, metal-halogen exchange of compound **7-3** with organolithium reagent such as *n*-Butyllithium followed by treatment with trialkyl borate B(OR)₃ can provide boronic ester **7-4**, which can be hydrolyzed to afford free boronic acid **7-4** (R = H).

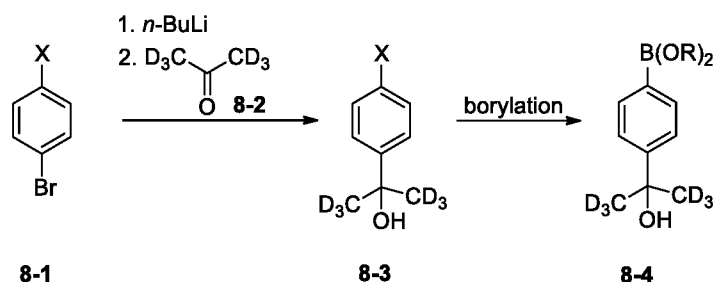
Scheme 7



Scheme 8 depicts a method useful for the synthesis of deuterated boronic acid or ester **8-4**. Metal-halogen exchange of compound **8-1** (X = Br or I) with organolithium reagent such as *n*-Butyllithium followed by treatment with compound **8-2** in a solvent such as tetrahydrofuran can provide compound **8-3**. Compound **8-3** can be converted to a boronic acid or ester **8-4** using standard borylation reaction

conditions well known to those skilled in the art. For example, coupling of compound **8-3** with diboronyl reagent such as bis(pinacolato)diboron using a catalyst such as [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride in the presence of a base such as potassium acetate in a solvent such as dioxane can provide boronic ester **8-4**.

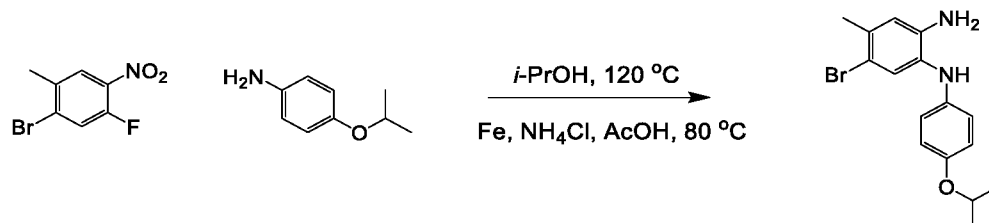
Scheme 8



Examples

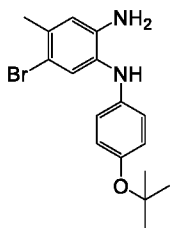
10 Preparation of intermediates for Examples A1 to A3.

5-Bromo-*N*'-(4-isopropoxyphenyl)-4-methylbenzene-1,2-diamine

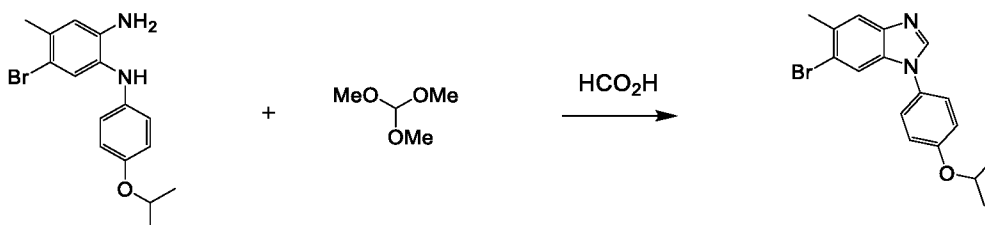


To a solution of 1-bromo-5-fluoro-2-methyl-4-nitrobenzene (200 mg, 0.85 mmol) in *i*-propanol (2 mL), was added 4-isopropoxyaniline (129 mg, 0.85 mmol). The resulting mixture was stirred at 120 °C for 30 min under microwave irradiation. After cooling to room temperature, the reaction was concentrated under reduced pressure and the residue was dissolved in ethanol (0.6 mL), dioxane (0.6 mL), and water (0.3 mL). To the solution was added iron (476 mg, 8.5 mmol) and NH₄Cl (457 mg, 8.5 mmol). The reaction was stirred at 80 °C for 2 hr. After cooling to room temperature, the reaction was filtered through a celite pad. The filtrate was concentrated under reduced pressure and the residue was poured into water and extracted with ethyl acetate. The organic phase was dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by SiO₂ column chromatography (hexane/EtOAc = 3:1) to give 198 mg (69.2 %) of the product as a white solid. LC/MS *m/z*: 335.13 (⁷⁹Br, M+H)⁺, 337.19 (⁸¹Br, M+H)⁺, 376.28 (⁷⁹Br, M+H+CH₃CN)⁺, 378.25 (⁸¹Br, M+H+CH₃CN)⁺.

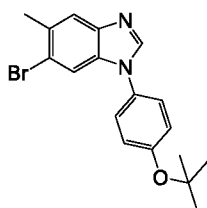
5-bromo-N1-(4-(tert-butoxy)phenyl)-4-methylbenzene-1,2-diamine



The title compound was prepared from 1-bromo-5-fluoro-2-methyl-4-nitrobenzene and 4-(*tert*-butoxy)aniline in the same manner as described for 5-Bromo-*N*¹-(4-isopropoxyphenyl)-4-methylbenzene-1,2-diamine. LC/MS *m/z*: 351.24 (⁷⁹Br, M+H+CH₃CN)⁺

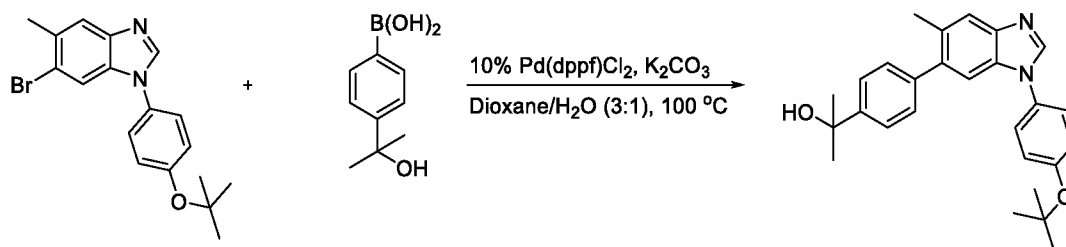
6-Bromo-5-methyl-1-[4-(propan-2-yloxy)phenyl]-1*H*-1,3-benzodiazole

To a solution of 5-bromo-*N*¹-(4-isopropoxyphenyl)-4-methylbenzene-1,2-diamine (50.1 mg, 0.15 mmol) in THF (1 mL), was added trimethoxymethane (18.9 mg, 0.18 mmol) followed by formic acid (100 uL). The resulting mixture was stirred at 80 °C for 2 hr. After cooling to room temperature, the reaction was poured into water and extracted with ethyl acetate. The organic phase was dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by SiO₂ column chromatography (hexane/EtOAc = 1:1) to give 42.1 mg (81.7 %) of the product as a white solid. LC/MS *m/z*: 345.15 (⁷⁹Br, M+H)⁺, 347.21 (⁸¹Br, M+H)⁺, 386.28 (⁷⁹Br, M+H+CH₃CN)⁺, 388.20 (⁸¹Br, M+H+CH₃CN)⁺.

6-bromo-1-(4-(tert-butoxy)phenyl)-5-methyl-1*H*-benzo[d]imidazole

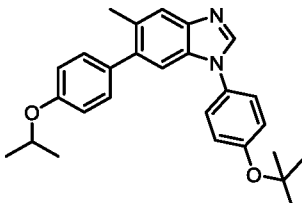
The title compound was prepared from 5-bromo-*N*¹-(4-(tert-butoxy)phenyl)-4-methylbenzene-1,2-diamine in the same manner as described for 6-Bromo-5-methyl-1-[4-(propan-2-yloxy)phenyl]-1*H*-1,3-benzodiazole. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.51 (s, 1H), 7.77 (s, 1H), 7.74 (s, 1H), 7.57 (d, 2H), 7.21 (d, 2H), 2.47 (s, 3H), 1.37 (s, 9H). LC/MS *m/z*: 359.16 (⁷⁹Br, M+H+CH₃CN)⁺, 361.17 (⁸¹Br, M+H+CH₃CN)⁺.

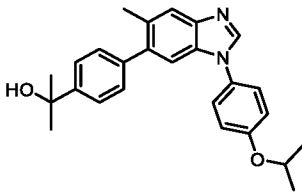
Example A1: 2-(4-(1-(4-(tert-butoxy)phenyl)-5-methyl-1H-benzo[d]imidazol-6-yl)phenyl)propan-2-ol



To a solution of 6-bromo-1-(4-(tert-butoxy)phenyl)-5-methyl-1H-benzo[d]imidazole (1 g, 2.79 mmol) in 1,4-dioxane (15 mL) were added 4-(2-hydroxypropan-2-yl)phenylboronic acid (0.502 g, 2.79 mmol), [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride (230 mg, 0.279 mmol), potassium carbonate (1.15 g, 8.4 mmol) and water (5 mL). The resulting reaction mixture was degassed with nitrogen for 10 min, then heated to 100°C overnight. Then the reaction mixture was diluted with ethyl acetate 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 7:3 to 1:4) to give 826 mg of the product as a colorless oil. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.48 (s, 1H), 7.67 (s, 1H), 7.58 (d, 2H), 7.52 (d, 2H), 7.31 (s, 1H), 7.29 (d, 2H), 7.17 (d, 2H), 5.01 (s, 1H), 2.32 (s, 3H), 1.46 (s, 6H), 1.34 (d, 9H). LC/MS *m/z*: 415.32 (M+H)⁺

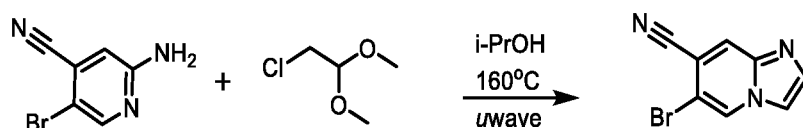
Examples A2 to A3 were prepared in the same manner as described above for 2-(4-(1-(4-(tert-butoxy)phenyl)-5-methyl-1H-benzo[d]imidazol-6-yl)phenyl)propan-2-ol (Example A1), using the appropriate aryl halide described above and the appropriate commercially available boronic acid.

Ex.	Starting materials	Product/Name	Analytical Data
A2	6-bromo-1-(4-(tert-butoxy)phenyl)-5-methyl-1H-benzo[d]imidazole	 1-(4-(tert-butoxy)phenyl)-6-(4-isopropoxyphenyl)-5-methyl-1H-benzo[d]imidazole	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.56 (s, 1H), 7.67 (s, 1H), 7.60 (d, 2H), 7.30 (s, 1H), 7.27 (d, 2H), 7.19 (d, 2H), 6.95 (d, 2H), 4.61-4.66 (m, 1H), 2.32 (s, 3H), 1.34 (s, 9H), 1.28 (d, 6H). LC/MS <i>m/z</i> : 415.40 (M+H) ⁺
	4-isopropoxyphenylboronic acid		
A3	6-Bromo-5-methyl-1-[4-(propan-2-yloxy)phenyl]-1,3-benzodiazole		¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.57 (s, 1H), 7.69 (s, 1H), 7.56 (d, 2H), 7.50 (d, 2H), 7.31 (s, 1H), 7.29 (d, 2H), 7.10 (d, 2H), 4.65-

	(4-(2-hydroxypropan-2-yl)phenyl)boronic acid	 2-(4-(1-(4-isopropoxyphenyl)-5-methyl-1H-benzo[d]imidazol-6-yl)phenyl)propan-2-ol	4.70 (m, 1H), 2.34 (s, 3H), 1.46 (s, 6H), 1.28 (d, 6H). LC/MS <i>m/z</i> : 401.31 (M+H) ⁺
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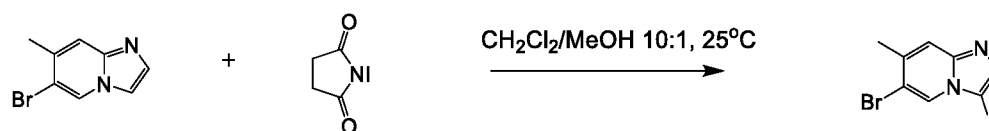
Preparation of intermediates for Examples B4 to B9

6-bromoimidazo[1,2-a]pyridine-7-carbonitrile



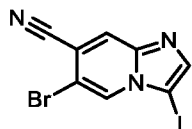
- 5 To a solution of 2-amino-5-bromoisonicotinonitrile (150 mg, 0.76 mmol) in i-PrOH (2 mL) is added 0.6 mL (1.5 eq) of 2-chloro-1,1-dimethoxyethane. The solution is capped tightly and heated in a microwave reactor to 160°C for 30 minutes. The mixture is cooled and evaporated *in vacuo*, the residue dissolved in ethyl acetate, washed with saturated aq. NaHCO₃, and evaporated *in vacuo* to give 0.47 g of the title compound, pure enough for further use. LC/MS *m/z*: 221.10 (M+H)⁺

- 10 6-bromo-3-iodo-7-methylimidazo[1,2-a]pyridine



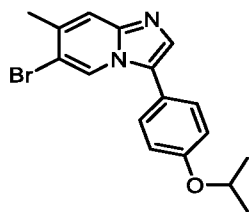
- To a solution of 6-bromo-7-methylimidazo[1,2-a]pyridine (100 mg, 0.47 mmol) in CH₂Cl₂ (1 mL), was added 1-iodopyrrolidine-2,5-dione (84 mg, 0.47 mmol) and MeOH (0.1 mL). The resulting mixture was stirred at room temperature for 2 h. The reaction was poured into water and extracted with ethyl acetate.
- 15 The organic phase was dried over Na₂SO₄, filtered, and concentrated in vacuo. The residue was purified by SiO₂ column chromatography (hexane/EtOAc = 1:1) to give 122 mg (77 %) of the product as a white solid. LC/MS *m/z*: 337.00 (M+H)⁺.

6-bromo-3-iodoimidazo[1,2-a]pyridine-7-carbonitrile



The title compound was prepared from 6-bromoimidazo[1,2-a]pyridine-7-carbonitrile and NIS in the same manner as described for 6-bromo-3-iodo-7-methylimidazo[1,2-a]pyridine. LC/MS *m/z*: 348.01 (M+H)⁺.

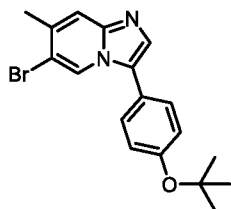
6-bromo-3-(4-isopropoxyphenyl)-7-methylimidazo[1,2-a]pyridine



5

The title compound was prepared from 6-bromo-3-iodo-7-methylimidazo[1,2-a]pyridine and 4-isopropoxyboronic acid in the same manner as described for 2-(4-(1-(4-(tert-butoxy)phenyl)-5-methyl-1H-benzo[d]imidazol-6-yl)phenyl)propan-2-ol (Example A1). LC/MS *m/z*: 345.20 (M+H)⁺

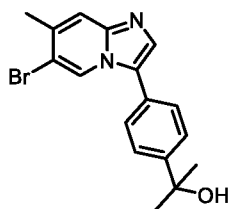
6-bromo-3-(4-(tert-butoxy)phenyl)-7-methylimidazo[1,2-a]pyridine



10

The title compound was prepared from 6-bromo-3-iodo-7-methylimidazo[1,2-a]pyridine and (4-(tert-butoxy)phenyl)boronic acid in the same manner as described for 2-(4-(1-(4-(tert-butoxy)phenyl)-5-methyl-1H-benzo[d]imidazol-6-yl)phenyl)propan-2-ol (Example A1). LC/MS *m/z*: 359.22 (M+H)⁺

2-(4-(6-bromo-7-methylimidazo[1,2-a]pyridin-3-yl)phenyl)propan-2-ol

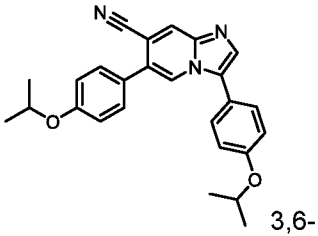
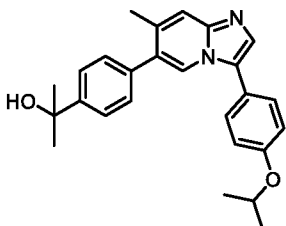
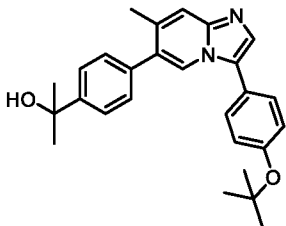


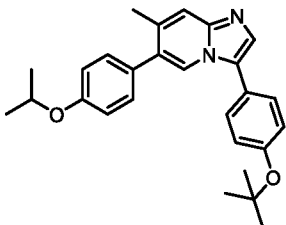
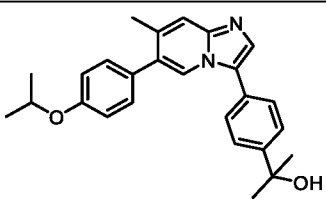
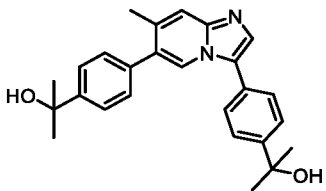
15

The title compound was prepared from 6-bromo-3-iodo-7-methylimidazo[1,2-a]pyridine and (4-(2-hydroxypropan-2-yl)phenyl)boronic acid in the same manner as described for 2-(4-(1-(4-(tert-

butoxy)phenyl)-5-methyl-1H-benzo[d]imidazol-6-yl)phenyl)propan-2-ol (Example A1). LC/MS *m/z*: 345.10 (M+H)⁺

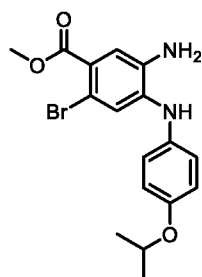
Examples B4 to B9 were prepared in the same manner as described above for 2-(4-(1-(4-(tert-butoxy)phenyl)-5-methyl-1H-benzo[d]imidazol-6-yl)phenyl)propan-2-ol (Example A1) using the appropriate aryl halide and commercially available boronic acids. In the case of compounds which have identical substitutions of the aryl halide, 2 equivalents of the boronic acid are used.

Ex.	Starting materials	Product/Name	Analytical Data
B4	6-bromo-3-iodoimidazo[1,2-a]pyridine-7-carbonitrile	 3,6-bis(4-isopropoxyphenyl)imidazo[1,2-a]pyridine-7-carbonitrile	LC/MS <i>m/z</i> : 412.29 (M+H) ⁺
	4-isopropoxyphenylboronic acid (2 Equivalents)		
B5	6-bromo-3-(4-isopropoxyphenyl)-7-methylimidazo[1,2-a]pyridine	 2-(4-(3-(4-isopropoxyphenyl)-7-methylimidazo[1,2-a]pyridin-6-yl)phenyl)propan-2-ol	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.11 (s, 1H), 7.62 (s, 1H), 7.58 (s, 1H), 7.56 (d, 2H), 7.55 (d, 2H), 7.42 (d, 2H), 7.05 (d, 2H), 4.63-4.68 (m, 1H), 2.26 (s, 3H), 1.46 (s, 6H), 1.27 (d, 6H). LC/MS <i>m/z</i> : 401.31 (M+H) ⁺
	(4-(2-hydroxypropan-2-yl)phenyl)boronic acid		
B6	6-bromo-3-(4-(tert-butoxy)phenyl)-7-methylimidazo[1,2-a]pyridine	 2-(4-(3-(4-(tert-butoxy)phenyl)-7-methylimidazo[1,2-a]pyridin-6-yl)phenyl)propan-2-ol	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.17 (s, 1H), 7.67 (s, 1H), 7.58 (d, 2H), 7.56 (s, 1H), 7.54 (d, 2H), 7.37 (d, 2H), 7.10 (d, 2H), 2.26 (s, 3H), 1.46 (s, 6H), 1.33 (s, 9H). LC/MS <i>m/z</i> : 415.34 (M+H) ⁺
	(4-(2-hydroxypropan-2-yl)phenyl)boronic acid		

B7	6-bromo-3-(4-(tert-butoxy)phenyl)-7-methylimidazo[1,2-a]pyridine		¹ H NMR (500 MHz, DMSO- <i>d</i> 6) δ 8.13 (s, 1H), 7.65 (s, 1H), 7.57 (d, 2H), 7.54 (s, 1H), 7.33 (d, 2H), 7.11 (d, 2H), 6.97 (d, 2H), 4.62-4.67 (m, 1H), 2.24 (s, 3H), 1.33 (s, 9H), 1.28 (d, 6H). LC/MS <i>m/z</i> : 415.36 (M+H) ⁺
	4-isopropoxyphenylboronic acid		
B8	2-(4-(6-bromo-7-methylimidazo[1,2-a]pyridin-3-yl)phenyl)propan-2-ol		¹ H NMR (500 MHz, DMSO- <i>d</i> 6) δ 8.29 (s, 1H), 8.15 (s, 1H), 7.88 (s, 1H), 7.38 (d, 2H), 7.34 (d, 2H), 7.13 (d, 2H), 7.01 (d, 2H), 4.64-4.69 (m, 1H), 2.38 (s, 3H), 1.46 (s, 6H), 1.28 (d, 6H). LC/MS <i>m/z</i> : 401.36 (M+H) ⁺
	4-isopropoxyphenylboronic acid		
B9	2-(4-(6-bromo-7-methylimidazo[1,2-a]pyridin-3-yl)phenyl)propan-2-ol		LC/MS <i>m/z</i> : 401.37 (M+H) ⁺
	(4-(2-hydroxypropan-2-yl)phenyl)boronic acid		

Preparation of intermediates for Examples C10 to C26

methyl 2-bromo-4-((4-isopropoxyphenyl)amino)-5-nitrobenzoate

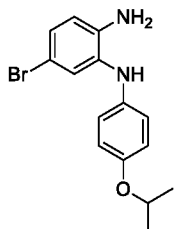


The title compound was prepared from methyl 2-bromo-4-fluoro-5-nitrobenzoate and 4-isopropoxyaniline

in the same manner as described for 5-Bromo-*N*'-(4-isopropoxyphenyl)-4-methylbenzene-1,2-diamine.

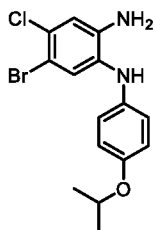
LC/MS *m/z*: 381.01 ($M+H$)⁺, 421.97 ($M+H+CH_3CN$)⁺

5-bromo-*N*'-(4-isopropoxyphenyl)benzene-1,2-diamine



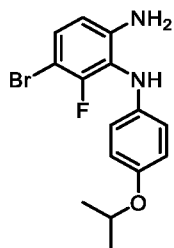
- 5 The title compound was prepared from 4-bromo-2-fluoro-1-nitrobenzene and 4-isopropoxyaniline in the same manner as described for 5-bromo-*N*'-(4-isopropoxyphenyl)-4-methylbenzene-1,2-diamine. LCMS *m/z*: 321.20 (^{79}Br , $M+H$)⁺, 323.19 (^{81}Br , $M+H$)⁺, 362.20 (^{79}Br , $M+H+CH_3CN$)⁺, 364.24 (^{81}Br , $M+H+CH_3CN$)⁺.

5-bromo-4-chloro-*N*'-(4-isopropoxyphenyl)benzene-1,2-diamine

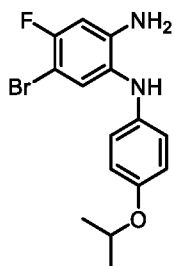


- 10 The title compound was prepared from 1-bromo-2-chloro-5-fluoro-4-nitrobenzene and 4-isopropoxyaniline in the same manner as described for 5-bromo-*N*'-(4-isopropoxyphenyl)-4-methylbenzene-1,2-diamine. LC/MS *m/z*: 355.05 (^{79}Br , $M+H$)⁺, 357.12 (^{81}Br , $M+H$)⁺

5-bromo-6-fluoro-*N*'-(4-isopropoxyphenyl)benzene-1,2-diamine

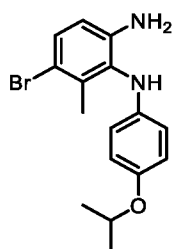


- 15 The title compound was prepared from 1-bromo-2,3-difluoro-4-nitrobenzene and 4-isopropoxyaniline in the same manner as described for 5-bromo-*N*'-(4-isopropoxyphenyl)-4-methylbenzene-1,2-diamine. LC/MS *m/z*: 339.13 (^{79}Br , $M+H$)⁺, 341.27 (^{81}Br , $M+H$)⁺

5-bromo-4-fluoro-N¹-(4-isopropoxyphenyl)benzene-1,2-diamine

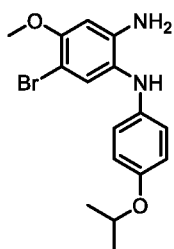
The title compound was prepared from 1-bromo-2,5-difluoro-4-nitrobenzene and 4-isopropoxyaniline in the same manner as described for 5-bromo-*N*¹-(4-isopropoxyphenyl)-4-methylbenzene-1,2-diamine.

5 LC/MS *m/z*: 339.13 (⁷⁹Br, M+H)⁺, 341.22 (⁸¹Br, M+H)⁺

5-bromo-N¹-(4-isopropoxyphenyl)-6-methylbenzene-1,2-diamine

The title compound was prepared from 1-bromo-3-fluoro-2-methyl-4-nitrobenzene and 4-isopropoxyaniline in the same manner as described for 5-bromo-*N*¹-(4-isopropoxyphenyl)-4-methylbenzene-1,2-diamine. LC/MS *m/z*: 335.19 (M+H)⁺

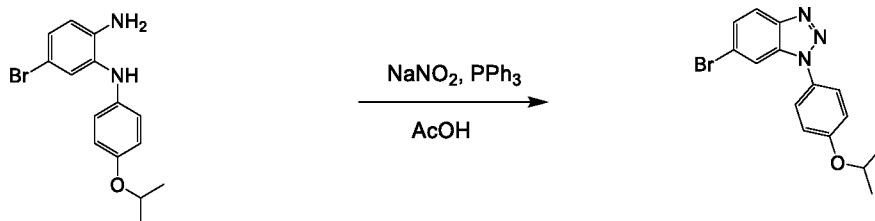
10

5-bromo-N¹-(4-isopropoxyphenyl)-4-methoxybenzene-1,2-diamine

The title compound was prepared from 1-bromo-5-fluoro-2-methoxy-4-nitrobenzene and 4-isopropoxyaniline in the same manner as described for 5-bromo-*N*¹-(4-isopropoxyphenyl)-4-methylbenzene-1,2-diamine. LC/MS *m/z*: 418.30 (M+H)⁺

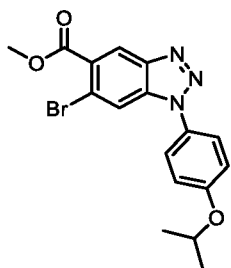
15

6-bromo-1-[4-(propan-2-yloxy)phenyl]-1*H*-1,2,3-benzotriazole



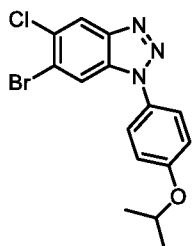
To a solution of 5-bromo-N'-(4-isopropoxyphenyl)benzene-1,2-diamine (100 mg, 0.3 mmol) in acetic acid (3 mL), was added PPh₃ (81.6 mg, 0.3 mmol) followed by addition of sodium nitrite (25.8 mg, 0.36 mmol) at 0 °C. The reaction was warmed to room temperature and stirred for 1 h. The reaction was poured into water and extracted with ethyl acetate. The organic phase was dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by SiO₂ column chromatography (hexane/EtOAc = 2:1) to give 98 mg (95%) of the product as a white solid. LC/MS *m/z*: 332.07 (⁷⁹Br, M+H)⁺, 334.08 (⁸¹Br, M+H)⁺, 373.15 (⁷⁹Br, M+H+CH₃CN)⁺, 375.14 (⁸¹Br, M+H+CH₃CN)⁺.

methyl 6-bromo-1-(4-isopropoxyphenyl)-1H-benzo[d][1,2,3]triazole-5-carboxylate



The title compound was prepared from methyl 2-bromo-4-((4-isopropoxyphenyl)amino)-5-nitrobenzoate, sodium nitrite, and triphenylphosphine in the same manner as described for 6-bromo-1-[4-(propan-2-yloxy)phenyl]-1H-1,2,3-benzotriazole. LC/MS *m/z*: 390.17 (⁷⁹Br, M+H+CH₃CN)⁺, 392.16 (⁸¹Br, M+H+CH₃CN)⁺.

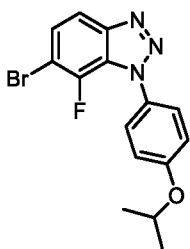
6-bromo-5-chloro-1-(4-isopropoxyphenyl)-1H-benzo[d][1,2,3]triazole



The title compound was prepared from 5-bromo-4-chloro-N1-(4-isopropoxyphenyl)benzene-1,2-diamine in the same manner as described for 6-bromo-1-[4-(propan-2-yloxy)phenyl]-1*H*-1,2,3-benzotriazole.

LC/MS *m/z*: 368.13 (*M*+*H*)⁺, 408.91 (*M*+*H*+CH₃CN)⁺

6-bromo-7-fluoro-1-(4-isopropoxyphenyl)-1*H*-benzo[d][1,2,3]triazole

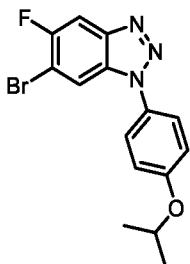


5

The title compound was prepared from 5-bromo-6-fluoro-N1-(4-isopropoxyphenyl)benzene-1,2-diamine in the same manner as described for 6-bromo-1-[4-(propan-2-yloxy)phenyl]-1*H*-1,2,3-benzotriazole. ¹H NMR (500 MHz, DMSO-*d*₆) δ 7.98 (d, 1H), 7.73-7.68 (m, 3H), 7.16 (d, 2H), 4.78-4.73 (m, 1H), 1.34 (d, 6H).

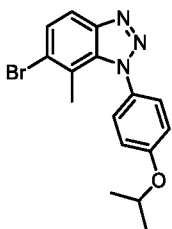
LC/MS *m/z*: 351.93 (*M*+*H*)⁺

10 6-bromo-5-fluoro-1-(4-isopropoxyphenyl)-1*H*-benzo[d][1,2,3]triazole



The title compound was prepared from 5-bromo-4-fluoro-N1-(4-isopropoxyphenyl)benzene-1,2-diamine in the same manner as described for 6-bromo-1-[4-(propan-2-yloxy)phenyl]-1*H*-1,2,3-benzotriazole. LC/MS *m/z*: 352.20 (*M*+*H*)⁺, 393.19 (*M*+*H*+CH₃CN)⁺

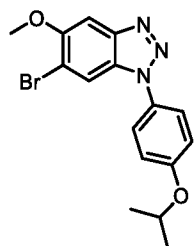
15 6-bromo-1-(4-isopropoxyphenyl)-7-methyl-1*H*-benzo[d][1,2,3]triazole



The title compound was prepared from 5-bromo-N1-(4-isopropoxyphenyl)-6-methylbenzene-1,2-diamine in the same manner as described for 6-bromo-1-[4-(propan-2-yloxy)phenyl]-1*H*-1,2,3-benzotriazole.

LC/MS *m/z*: 346.03 (*M*+*H*)⁺

6-bromo-1-(4-isopropoxyphenyl)-5-methoxy-1*H*-benzo[d][1,2,3]triazole



5

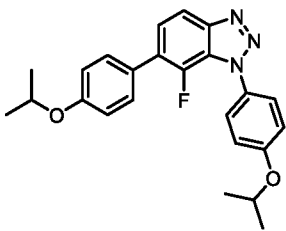
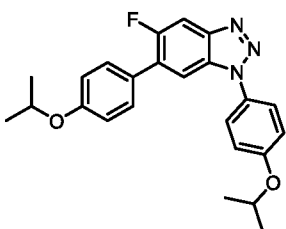
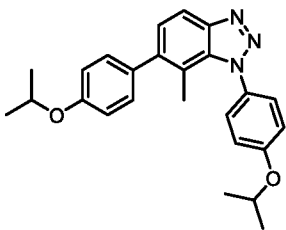
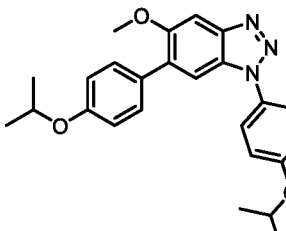
The title compound was prepared from 5-bromo-N1-(4-isopropoxyphenyl)-4-methoxybenzene-1,2-diamine in the same manner as described for 6-bromo-1-[4-(propan-2-yloxy)phenyl]-1*H*-1,2,3-benzotriazole.

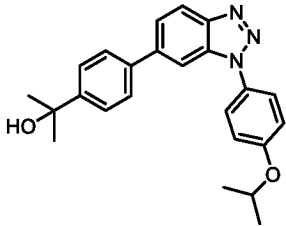
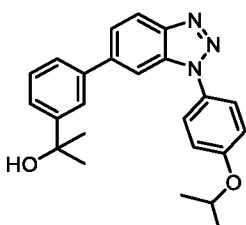
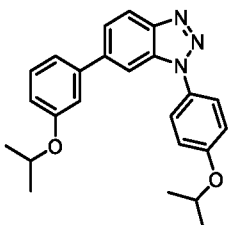
LC/MS *m/z*: 362.13 (*M*+*H*)⁺

Examples C10 to C18 were prepared in the same manner as described above for 2-(4-(1-(4-(tert-butoxy)phenyl)-5-methyl-1*H*-benzo[d]imidazol-6-yl)phenyl)propan-2-ol (Example A1), using the appropriate aryl halide described above and the appropriate commercially available boronic acid.

10

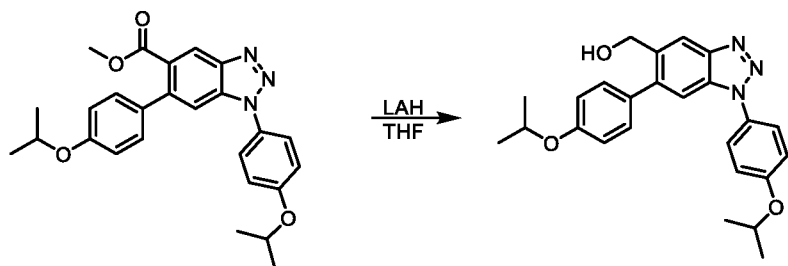
Ex.	Starting materials	Product/Name	Analytical Data
C10	methyl 6-bromo-1-(4-isopropoxyphenyl)-1 <i>H</i> -benzo[d][1,2,3]triazole-5-carboxylate		LC/MS <i>m/z</i> : 446.34 (<i>M</i> + <i>H</i>) ⁺
	4-isopropoxyboronic acid		
C11	6-bromo-5-chloro-1-(4-isopropoxyphenyl)-1 <i>H</i> -benzo[d][1,2,3]triazole		¹ H NMR (500 MHz, DMSO- <i>d</i> 6) δ 8.44 (s, 1H), 7.77 (d, 2H), 7.72 (s, 1H), 7.42 (d, 2H), 7.17 (d, 2H), 7.01 (d, 2H), 4.74-4.67 (m, 2H), 1.32 (d, 6H), 1.30 (d, 6H). LC/MS <i>m/z</i> : 422.15 (<i>M</i> + <i>H</i>) ⁺
	4-isopropoxyboronic acid		

		5-chloro-1,6-bis(4-isopropoxyphenyl)-1H-benzo[d][1,2,3]triazole	
C12	6-bromo-7-fluoro-1-(4-isopropoxyphenyl)-1H-benzo[d][1,2,3]triazole	 7-fluoro-1,6-bis(4-isopropoxyphenyl)-1H-benzo[d][1,2,3]triazole	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.02 (d, 1H), 7.71 (d, 2H), 7.59-7.54 (m, 3H), 7.14 (d, 2H), 7.04 (d, 2H), 4.77-4.66 (m, 2H), 1.33 (d, 6H), 1.30 (d, 6H). LC/MS <i>m/z</i> : 406.35 (M+H) ⁺
	4-isopropoxyboronic acid		
C13	6-bromo-5-fluoro-1-(4-isopropoxyphenyl)-1H-benzo[d][1,2,3]triazole	 5-fluoro-1,6-bis(4-isopropoxyphenyl)-1H-benzo[d][1,2,3]triazole	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.11 (d, 1H), 7.82-7.78 (m, 3H), 7.56 (d, 2H), 7.17 (d, 2H), 7.04 (d, 2H), 4.76-4.66 (m, 2H), 1.33 (d, 6H), 1.30 (d, 6H). LC/MS <i>m/z</i> : 406.26 (M+H) ⁺
	4-isopropoxyboronic acid		
C14	6-bromo-1-(4-isopropoxyphenyl)-7-methyl-1H-benzo[d][1,2,3]triazole	 1,6-bis(4-isopropoxyphenyl)-7-methyl-1H-benzo[d][1,2,3]triazole	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 7.98 (d, 1H), 7.58 (d, 2H), 7.30 (d, 1H), 7.26 (d, 2H), 7.13 (d, 2H), 6.98 (d, 2H), 4.73-4.77 (m, 1H), 4.63-4.68 (m, 1H), 2.01 (s, 3H), 1.32 (d, 6H), 1.28 (d, 6H). LC/MS <i>m/z</i> : 402.29 (M+H) ⁺
	4-isopropoxyboronic acid		
C15	6-bromo-1-(4-isopropoxyphenyl)-5-methoxy-1H-benzo[d][1,2,3]triazole		LC/MS <i>m/z</i> : 418.30 (M+H) ⁺ , 459.33 (M+H+CH ₃ CN) ⁺
	4-isopropoxyboronic acid		

		1,6-bis(4-isopropoxyphenyl)-5-methoxy-1H-benzo[d][1,2,3]triazole	
C16	6-bromo-1-(4-isopropoxyphenyl)-1H-benzo[d][1,2,3]triazole	 2-(4-(1-(4-isopropoxyphenyl)-1H-benzo[d][1,2,3]triazol-6-yl)phenyl)propan-2-ol	¹ H NMR (500 MHz, DMSO- <i>d</i> 6) δ 8.22 (d, 1H), 7.93 (s, 1H), 7.82-7.78 (m, 3H), 7.72 (d, 2H), 7.58 (d, 2H), 7.20 (d, 2H), 5.08 (s, 1H), 4.77-4.73 (m, 1H), 1.46 (s, 6H), 1.34 (d, 6H). LC/MS <i>m/z</i> : 388.31 (M+H) ⁺
	(4-(2-hydroxypropan-2-yl)phenyl)boronic acid		
C17	6-bromo-1-(4-isopropoxyphenyl)-1H-benzo[d][1,2,3]triazole	 2-(3-(1-(4-isopropoxyphenyl)-1H-benzo[d][1,2,3]triazol-6-yl)phenyl)propan-2-ol	LC/MS <i>m/z</i> : 388.28 (M+H) ⁺
	(3-(2-hydroxypropan-2-yl)phenyl)boronic acid		
C18	6-bromo-1-(4-isopropoxyphenyl)-1H-benzo[d][1,2,3]triazole	 6-(3-isopropoxyphenyl)-1-(4-isopropoxyphenyl)-1H-benzo[d][1,2,3]triazole	LC/MS <i>m/z</i> : 388.28 (M+H) ⁺
	(3-isopropoxyphenyl)boronic acid		

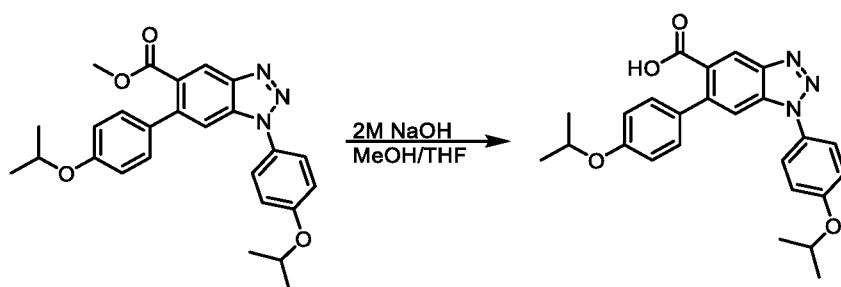
Example C19: (1,6-bis(4-isopropoxyphenyl)-1H-benzo[d][1,2,3]triazol-5-yl)methanol

52



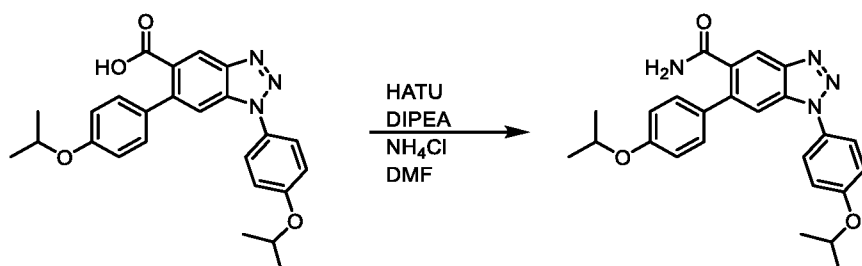
To a solution of methyl 1,6-bis(4-isopropoxyphenyl)-1H-benzo[d][1,2,3]triazole-5-carboxylate (86 mg, 1 Eq) in THF (3 mL), was slowly added 2.6 M lithium aluminum hydride solution in THF (80 μ L, 1 Eq). This mixture was stirred at room temperature for 3 hours, quenched slowly with cold, saturated Na_2SO_4 solution, and filtered through a celite pad. The filtrate was concentrated *in vacuo* and the residue purified by SiO_2 column chromatography (hexane/EtOAc = 7:3 to 6:4) to afford 52 mg of the title compound. LC/MS m/z : 418.31 ($\text{M}+\text{H}$)⁺, 835.60 ($2\text{M}+\text{H}$)⁺

Example C20: 1,6-bis(4-isopropoxyphenyl)-1H-benzo[d][1,2,3]triazole-5-carboxylic acid



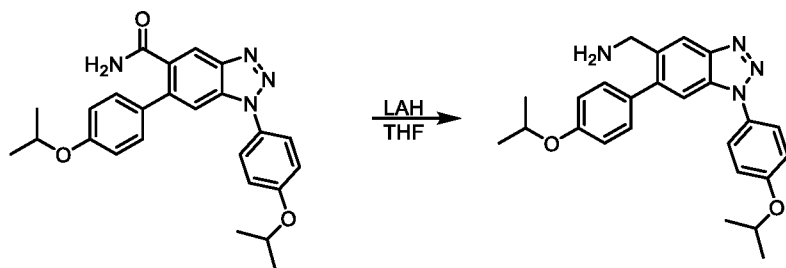
To a solution of methyl 1,6-bis(4-isopropoxyphenyl)-1H-benzo[d][1,2,3]triazole-5-carboxylate (200 mg, 1 Eq), in 1:1 MeOH/THF (8 mL) is added 2 M aq. NaOH (4.25 mL). The mixture is stirred overnight, quenched by addition of 1M aq. HCl, extracted with MTBE, and the organic phase evaporated *in vacuo*. 10 mg of the residue was purified by preparative HPLC to afford 2.3 mg of the title compound. LC/MS m/z : 432.35 ($\text{M}+\text{H}$)⁺, 473.25 ($\text{M}+\text{H}+\text{CH}_3\text{CN}$)⁺

Example C21: 1,6-bis(4-isopropoxyphenyl)-1H-benzo[d][1,2,3]triazole-5-carboxamide



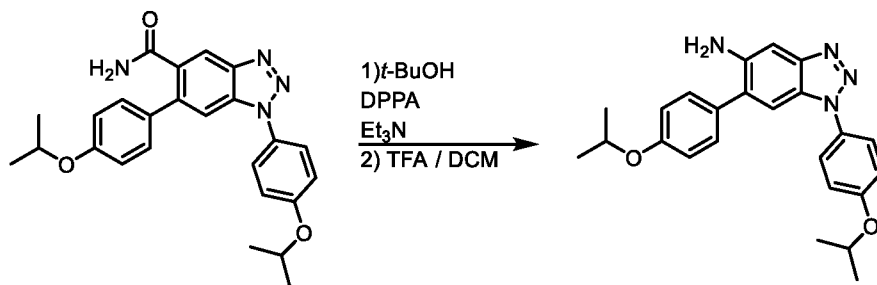
To a solution of 1,6-bis(4-isopropoxyphenyl)-1H-benzo[d][1,2,3]triazole-5-carboxylic acid (9.5 mg, 1 Eq), in DMF (0.5 mL) is added diisopropylethylamine (11 μ L, 3 Eq), and HATU (12 mg, 1.5 Eq). The mixture is stirred for 1 hour, at which time ammonium chloride (5 mg, 4 Eq) is added in one portion. The mixture is stirred overnight, diluted with ethyl acetate, washed twice with 1 M aq. HCl, and evaporated *in vacuo*. The residue is purified by preparative HPLC to afford 5 mg of the title compound as a white solid. LC/MS *m/z*: 431.29 (M+H)⁺, 861.54 (2M+H)⁺

Example C22: (1,6-bis(4-isopropoxyphenyl)-1H-benzo[d][1,2,3]triazol-5-yl)methanamine



The title compound was prepared from 1,6-bis(4-isopropoxyphenyl)-1H-benzo[d][1,2,3]triazole-5-carboxamide in the same manner as described for (1,6-bis(4-isopropoxyphenyl)-1H-benzo[d][1,2,3]triazol-5-yl)methanol (Example C19), stirring at reflux instead of room temperature. LC/MS *m/z*: 417.41 (M+H)⁺

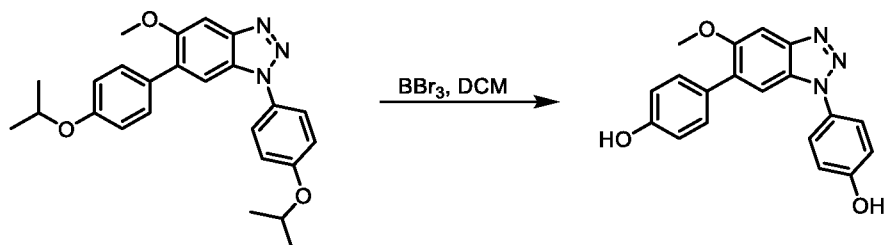
Example C23: 1,6-bis(4-isopropoxyphenyl)-1H-benzo[d][1,2,3]triazol-5-amine



To a solution of 1,6-bis(4-isopropoxyphenyl)-1H-benzo[d][1,2,3]triazole-5-carboxamide (51 mg, 1 Eq) in *t*-BuOH (0.5 mL), is added triethylamine (33 μ L, 2 Eq) and diphenylphosphoryl azide (25 μ L, 1 Eq). The mixture is heated to 85°C and stirred for 6 hours, at which time it is diluted with ethyl acetate, washed with saturated aq. NH₄Cl and water, and evaporated *in vacuo*. The residue is taken up in DCM (1 mL) and TFA (1 mL) is added dropwise. The resulting solution is stirred overnight then diluted with DCM, washed with saturated aq. NaHCO₃, and evaporated *in vacuo*. The residue is purified by SiO₂ column chromatography (hexane/EtOAc = 7:3 to 1:2) to afford 7 mg of the title compound as a colorless oil. LC/MS *m/z*: 403.30 (M+H)⁺, 444.30 (M+H+CH₃CN)⁺

Example C24: 4,4'-(5-methoxy-1H-benzo[d][1,2,3]triazole-1,6-diyl)diphenol

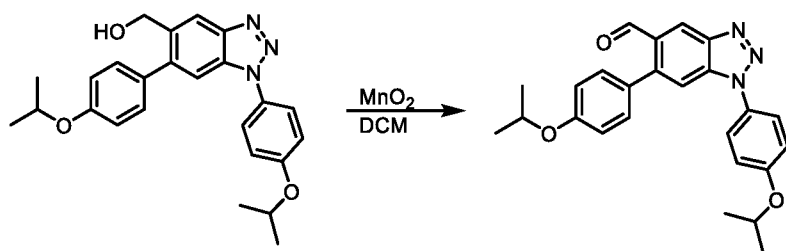
54



To a solution of 1,6-bis(4-isopropoxyphenyl)-5-methoxy-1H-benzo[d][1,2,3]triazole (200 mg, 0.5 mmol) in DCM (4 mL) at 0°C is added a 1M solution of BBr₃ (0.5 mL, 0.5 mmol). The mixture is allowed to warm to room temperature while stirring overnight, at which time it is quenched by pouring over ice, extracted
 5 twice with ethyl acetate, and evaporated *in vacuo*. The residue is purified by preparative HPLC to afford 13 mg of the title compound. LC/MS *m/z*: 334.27 (M+H)⁺

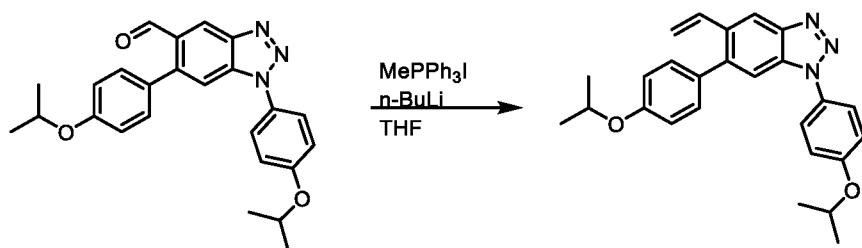
Example C25: 1,6-bis(4-isopropoxyphenyl)-5-vinyl-1H-benzo[d][1,2,3]triazole

Step 1: 1,6-bis(4-isopropoxyphenyl)-1H-benzo[d][1,2,3]triazole-5-carbaldehyde



10 To a solution of (1,6-bis(4-isopropoxyphenyl)-1H-benzo[d][1,2,3]triazol-5-yl)methanol (30 mg, 0.072 mmol) is added DCM (0.5 mL) and MnO₂ (12 mg, 0.14 mmol). The mixture is stirred overnight, filtered through a celite pad, and the filtrate evaporated to afford 24 mg of the title compound, which is not purified further. LC/MS *m/z*: 416.27 (M+H)⁺

Step 2: 1,6-bis(4-isopropoxyphenyl)-5-vinyl-1H-benzo[d][1,2,3]triazole

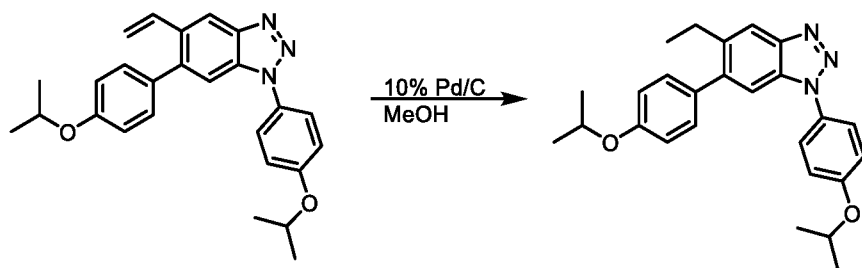


15

To a suspension of methyltriphenylphosphonium iodide (40 mg, 0.1 mmol) in THF (1 mL) at 0°C is added a 1.6 M solution of *n*-butyllithium (0.06 mL, 0.1 mmol). The mixture is stirred for 30 minutes at 0°C, at

which time a solution of 1,6-bis(4-isopropoxyphenyl)-1H-benzo[d][1,2,3]triazole-5-carbaldehyde (24 mg, 0.057 mmol) in THF (0.5 mL) is added, and stirring is continued for 3 hours at room temperature. The mixture is quenched with aq. NH_4Cl , extracted with ethyl acetate, and the organics evaporated *in vacuo*. The residue is purified by preparative HPLC to afford 12.9 mg of the title compound. LC/MS m/z : 414.29 (M+H)⁺

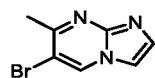
Example C26: 5-ethyl-1,6-bis(4-isopropoxyphenyl)-1H-benzo[d][1,2,3]triazole



A solution of 1,6-bis(4-isopropoxyphenyl)-5-vinyl-1H-benzo[d][1,2,3]triazole (11.5 mg, 0.028 mmol) in MeOH (0.5 mL) is purged of air by drawing a vacuum and backfilling with nitrogen twice. 10% palladium on carbon (5 mg) is then added, and the atmosphere replaced with hydrogen by drawing a vacuum and backfilling twice with a hydrogen balloon. The mixture is stirred overnight, diluted with ethyl acetate, filtered through a celite pad, and the filtrate evaporated *in vacuo* to afford 10 mg of the title compound, pure enough for use without further purification. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.05 (s, 1H), 7.74 (d, 2H), 7.49 (s, 1H), 7.29 (d, 2H), 7.15 (d, 2H), 6.98 (d, 2H), 4.70-4.72 (m, 1H), 4.65-4.67 (m, 1H), 2.69-2.74 (m, 2H), 1.31 (d, 6H), 1.29 (d, 6H), 1.08 (t, 3H). LC/MS m/z : 416.33 (M+H)⁺

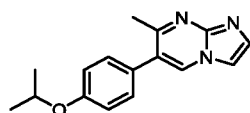
Example D27: 3,6-bis(4-isopropoxyphenyl)-7-methylimidazo[1,2-a]pyrimidine

Step 1: 6-bromo-7-methylimidazo[1,2-a]pyrimidine



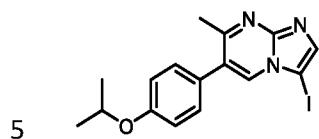
The title compound was prepared from 5-bromo-4-methylpyrimidin-2-amine in the same manner as described for 6-bromoimidazo[1,2-a]pyridine-7-carbonitrile. ¹H NMR (500 MHz, CDCl₃) δ 8.57 (s, 1H), 7.85 (s, 1H), 7.49 (s, 1H), 2.79 (s, 3H). LC/MS m/z : 214.25 (M+H)⁺

Step 2: 6-(4-isopropoxyphenyl)-7-methylimidazo[1,2-a]pyrimidine



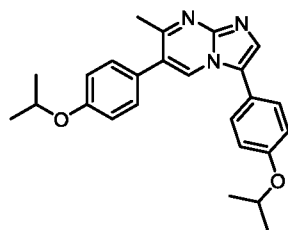
The title compound was prepared from 6-bromo-7-methylimidazo[1,2-a]pyrimidine and 4-isopropoxyphenylboronic acid in the same manner as described for 2-(4-(1-(4-(tert-butoxy)phenyl)-5-methyl-1H-benzo[d]imidazol-6-yl)phenyl)propan-2-ol (Example A1). LC/MS m/z : 268.25 (M+H)⁺

Step 3: 3-iodo-6-(4-isopropoxyphenyl)-7-methylimidazo[1,2-a]pyrimidine



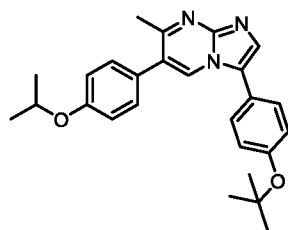
The title compound was prepared from 6-(4-isopropoxyphenyl)-7-methylimidazo[1,2-a]pyrimidine and NIS in the same manner as described for 6-bromo-3-iodo-7-methylimidazo[1,2-a]pyridine. LC/MS m/z : 394.23

Step 4: 3,6-bis(4-isopropoxyphenyl)-7-methylimidazo[1,2-a]pyrimidine



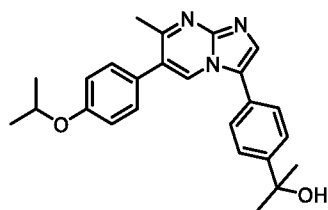
- 10 The title compound was prepared from 3-iodo-6-(4-isopropoxyphenyl)-7-methylimidazo[1,2-a]pyrimidine and 4-isopropoxyphenylboronic acid in the same manner as described for 2-(4-(1-(4-(tert-butoxy)phenyl)-5-methyl-1H-benzo[d]imidazol-6-yl)phenyl)propan-2-ol (Example A1). ¹H NMR (500 MHz, CDCl₃) δ 8.31 (s, 1H), 7.74 (s, 1H), 7.40 (d, 2H), 7.22 (d, 2H), 6.98 (d, 2H), 6.96 (d, 2H), 4.66-4.56 (m, 2H), 2.55 (s, 3H), 1.38 (d, 6H), 1.36 (d, 6H). LC/MS m/z : 402.36 (M+H)⁺

- 15 Example D28: 3-(4-(tert-butoxy)phenyl)-6-(4-isopropoxyphenyl)-7-methylimidazo[1,2-a]pyrimidine



The title compound was prepared from 3-iodo-6-(4-isopropoxyphenyl)-7-methylimidazo[1,2-a]pyrimidine and 4-*tert*-butoxyphenylboronic acid in the same manner as described for 2-(4-(1-(4-(tert-butoxy)phenyl)-5-methyl-1H-benzo[d]imidazol-6-yl)phenyl)propan-2-ol (Example A1). LC/MS m/z : 416.35 (M+H)⁺

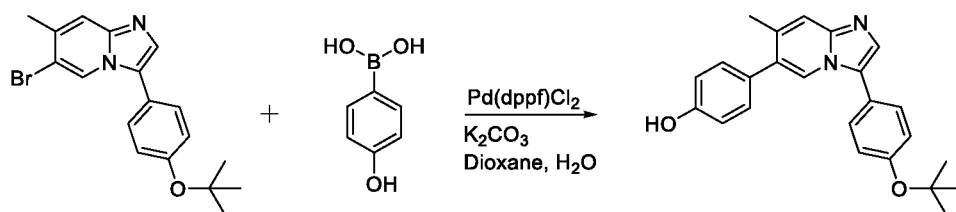
Example D29: 2-(4-(6-(4-isopropoxyphenyl)-7-methylimidazo[1,2-a]pyrimidin-3-yl)phenyl)propan-2-ol



The title compound was prepared from 3-iodo-6-(4-isopropoxyphenyl)-7-methylimidazo[1,2-a]pyrimidine and (4-(2-hydroxypropan-2-yl)phenyl)boronic acid in the same manner as described for 2-(4-(1-(4-(tert-butoxy)phenyl)-5-methyl-1H-benzo[d]imidazol-6-yl)phenyl)propan-2-ol (Example A1). LC/MS m/z : 402.39 (M+H)⁺

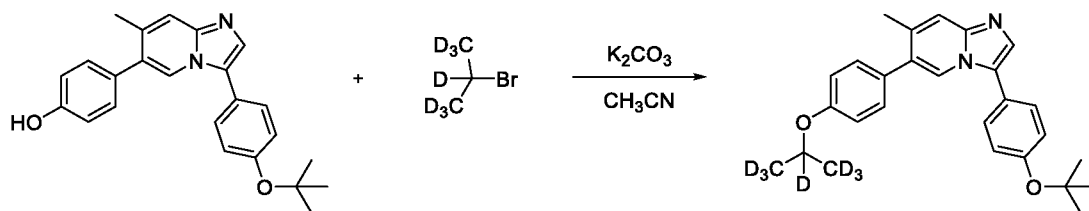
Example E30: 3-(4-(tert-butoxy)phenyl)-6-(4-(isopropoxy-d₇)phenyl)-7-methylimidazo[1,2-a]pyridine

Step 1: 4-(3-(4-(tert-butoxy)phenyl)-7-methylimidazo[1,2-a]pyridin-6-yl)phenol



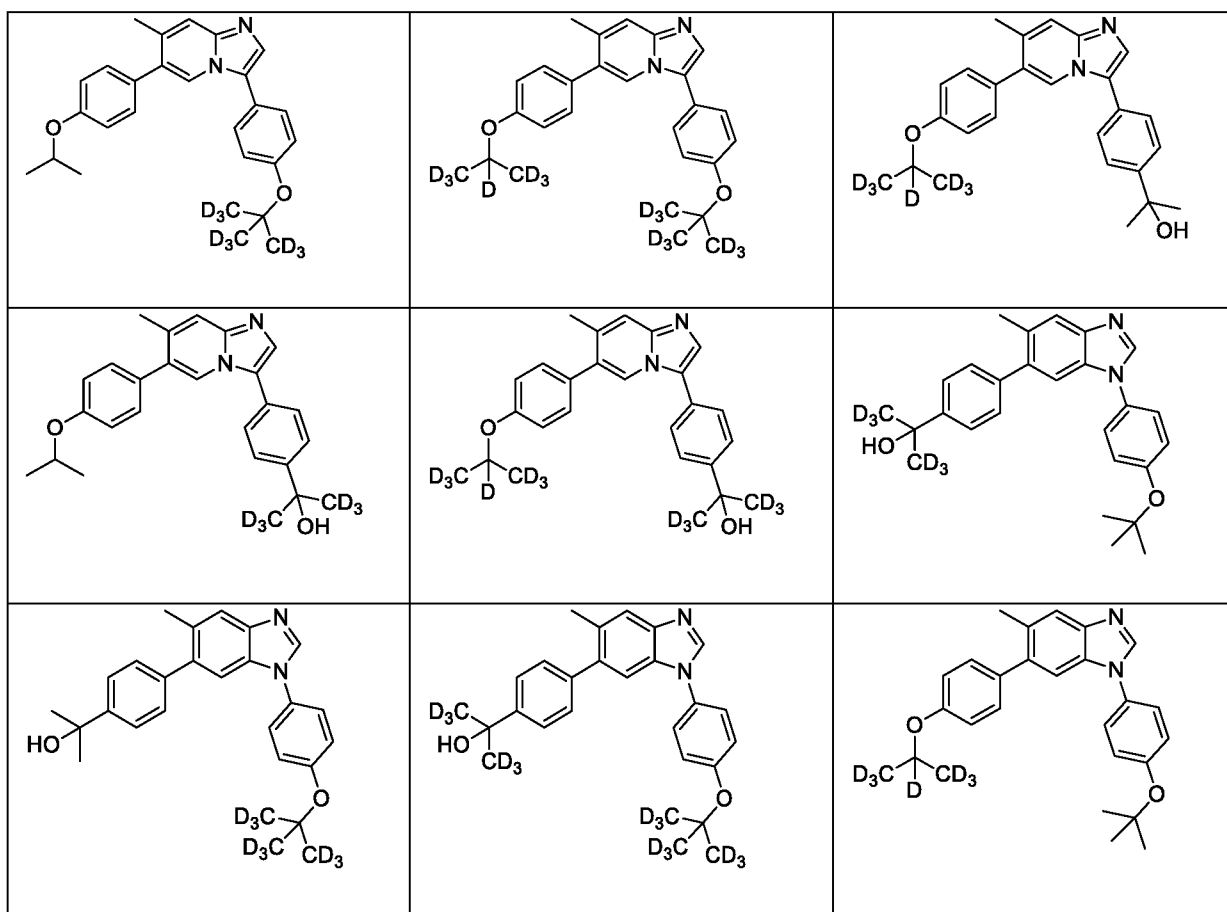
To a microwave reactor vial is added 6-bromo-3-(4-(tert-butoxy)phenyl)-7-methylimidazo[1,2-a]pyridine (25 mg, 0.07 mmol), 4-hydroxyphenylboronic acid (11 mg, .083 mmol, 1.2 Eq), Pd(dppf)Cl₂ (6 mg, 10 mol %), and potassium carbonate (30 mg, .210 mmol, 3 Eq). 1.5 mL 1,4-dioxane and 0.5 mL water are then added, and the mixture degassed by bubbling nitrogen for 5 minutes. The vial is then tightly capped and subjected to microwave irradiation at 80 °C for 1 hour. The resulting mixture is diluted with ethyl acetate and the aqueous layer extracted 3X with ethyl acetate, followed by drying over Na₂SO₄ and evaporation to yield the crude product. The crude material is purified using silica gel flash chromatography with 100% ethyl acetate as eluent to give 20 mg of the title compound as a light brown oil. LC/MS m/z : 373.35 (M+H)⁺

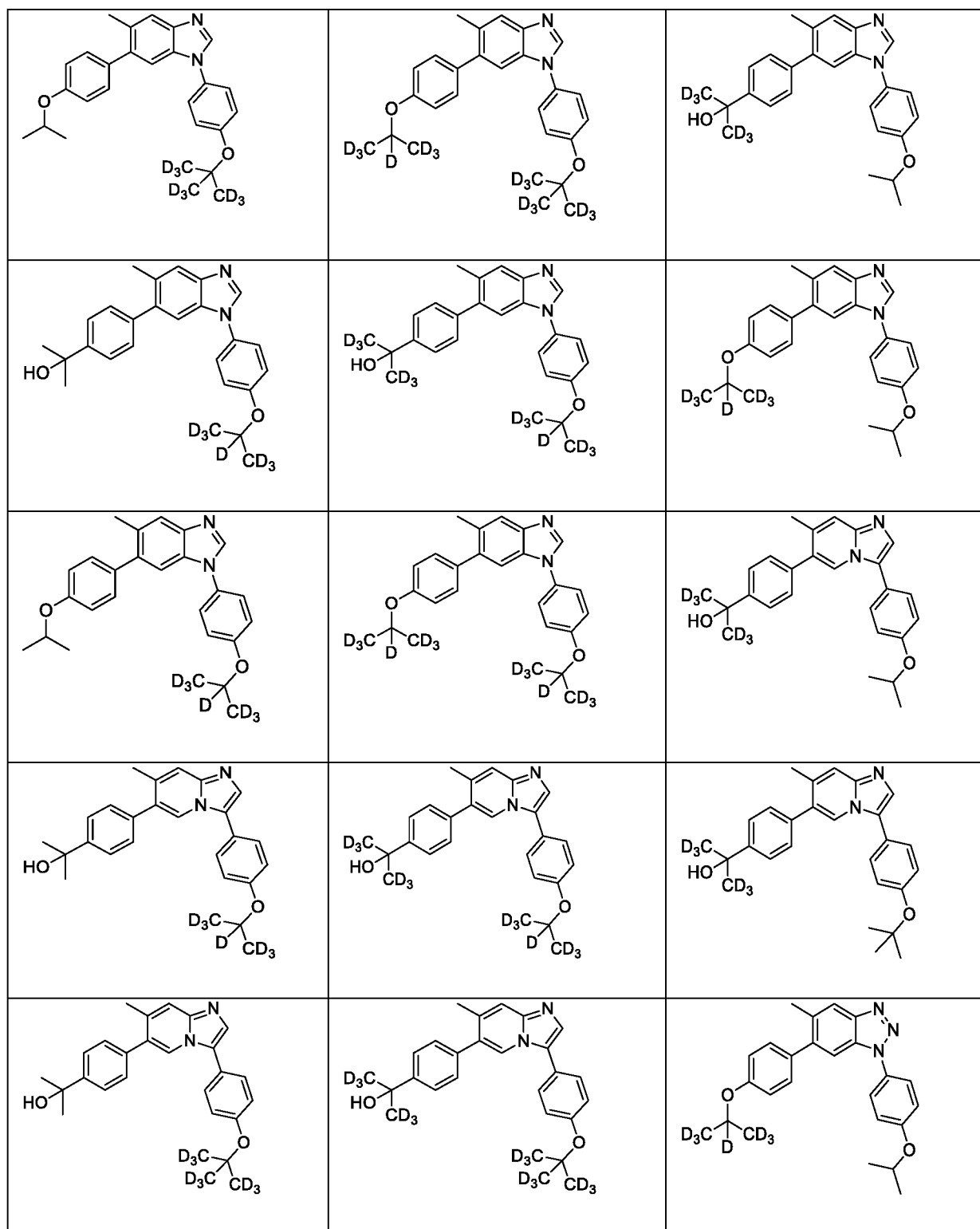
Step 2: 3-(4-(tert-butoxy)phenyl)-6-(4-(isopropoxy-d₇)phenyl)-7-methylimidazo[1,2-a]pyridine

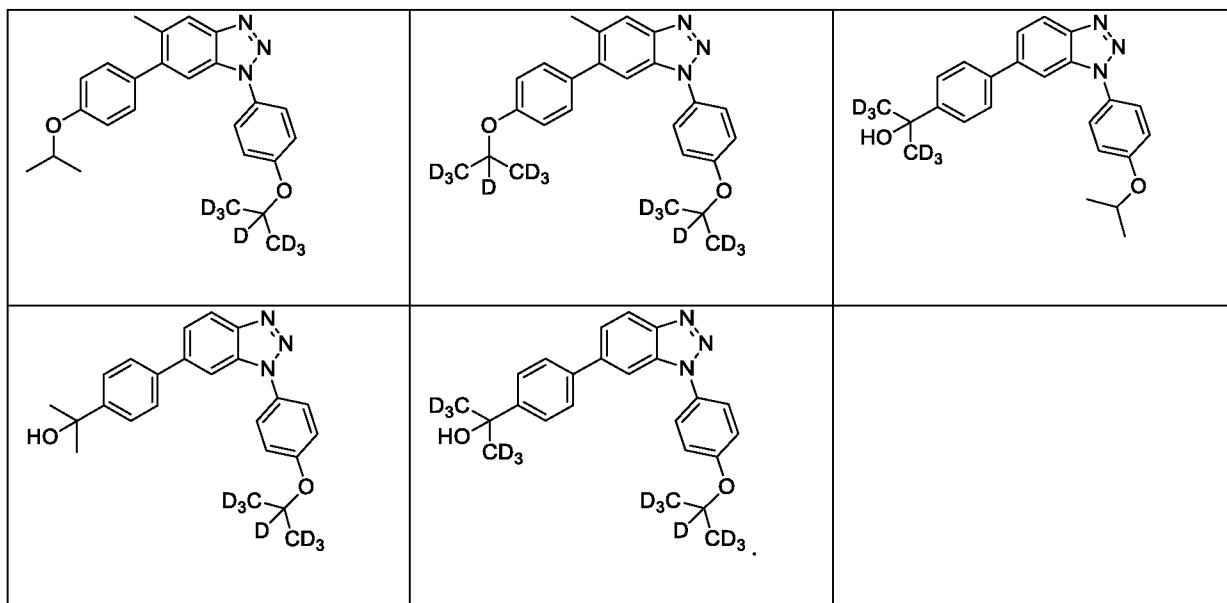


To a solution of 4-(3-(4-(tert-butoxy)phenyl)-7-methylimidazo[1,2-a]pyridin-6-yl)phenol (142 mg, 0.38 mmol) in acetonitrile is added potassium carbonate (0.105 g, 0.76 mmol, 2 Eq). The mixture is stirred at reflux for 30 minutes, at which time *d*7-isopropyl bromide (57 μ L, 1.5 Eq) is added in one portion. The mixture is stirred at reflux overnight, then evaporated to dryness. The residue is dissolved in ethyl acetate, washed twice with water, dried over Na₂SO₄ and evaporated to give the crude solid, which is purified using silica gel flash chromatography with 3:7 hexanes : ethyl acetate as eluent to give 42 mg of the title compound. LC/MS *m/z*: 422.33 (M+H)⁺

Following schemes 2, 3, 6-8, and procedures above using the appropriate starting materials, the following examples can be made.







Arenavirus GP Pseudotype Assay.

Utilizing a VSV pseudotype system expressing arenavirus glycoproteins (pseudotyped viruses here to referred to as LASV-p, MACV-p, JUNV-p, GTOV-p and TCRV-p) and the *Renilla* luciferase reporter gene heterocyclic compounds were screened to identify individual compounds that inhibit infectivity of the pseudotyped viruses but not the native VSV virus expressing the VSV glycoprotein. VSV viruses expressing the VSV glycoprotein or pseudotyped with LASV, MACV, JUNV, GTOV and TCRV glycoproteins (LASV-p, MACV-p, JUNV-p, GTOV-p and TCRV-p) were generated in cultured HEK-293T cells (ATCC CRL-3216), which were grown in 10 cm dishes in DMEM supplemented with 10% FBS, 1X Pen-Strep, non-essential amino acids and L-glutamine. When cells reached approximately 80% confluency, they were transfected with a mixture of 15 μ g of the pCAGGS plasmid encoding the desired glycoprotein and 45 μ l of PEI (polyethylenimine) transfection reagent (PEI MAX, Polysciences Inc., #24765). The cells were incubated with the solution for 5 hours at 37°C at 5% CO₂ 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 μ l of VSV reporter virus whereby the VSV glycoprotein was replaced with a luciferase reporter gene. The cells were infected for 1 hour, then washed 1X with PBS and incubated in supplemented media. 24 hours post-infection, supernatant was collected, clarified by centrifugation and filtration through a 0.45 μ m filter, aliquoted and stored at -80°C. Both VSV-Luciferase and arenavirus glycoproteins pseudotypes were titrated for luminescence activity in Vero cells as described in the Luciferase assay protocol (below). Vero cells (ATCC: CCL-81) were grown in clear 384 well plates (3000 cells/well) in supplemented DMEM media. After incubating overnight at 37°C and 5% CO₂, cells were treated with compounds at desired concentrations and pseudotyped virus in assay media. Assay media consisted of 50% Opti-MEM, 50% DMEM, with 1% FBS, Pen-Strep, non-

essential amino acids and L-glutamine. Each of the viral supernatants generated was diluted (from 1:100 to 1:2000) to give similar luminescence signal / background values of ≥ 200 . 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 then lysed using 20 μ l of lysis buffer from a Luciferase kit diluted according to manufacturer's instructions. After incubating for approximately 20 minutes, 5 μ l of cell lysate was transferred to an opaque white plate, and mixed with 12.5 μ l 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.

Cytotoxicity Screening

Active compounds in the pseudotype assays were also evaluated for cytotoxicity over a period of 3 days. 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 1% FBS. The plates were incubated at 37 °C for 3 days, and then dead cells were removed by washing with Phosphate buffered saline (PBS). CPE was assessed by staining cells with neutral red dye for 1 hour and then de-staining with a solution of 50% ethanol/ 1% acetic acid solution. Absorbances were 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 survival.

Replicative LASV inhibitory activity plaque assays

Confluent or near-confluent cell culture monolayers in 12-well disposable cell culture plates were prepared. Cells were maintained in MEM or DMEM supplemented with 10% FBS. For antiviral assays the same medium was used but with FBS reduced to 2% or less and supplemented with 1% penicillin/streptomycin. The test compounds were prepared at seven half log₁₀ final concentrations, (0.1-10 μ M) in 2X MEM or 2X DMEM. Test compounds and positive control compounds (favipiravir or ribavirin) were run in parallel in biological triplicates. The assay was initiated by first removing growth media from the 12-well plates of cells, which was challenged with compound at a given concentration and 0.01 MOI of virus or about 50 to 100 plaque forming units (pfu). Cells were incubated for 60 min: 100 μ L inoculum/ well, at 37°C, 5% CO₂ with constant gentle rocking. Virus inoculum was 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 along with the corresponding drug concentration. Cells were incubated at 37°C with 5% CO₂ for 5 days. The overlay was then removed and plates stained with 0.05% crystal

violet in 10% buffered formalin for approximately twenty minutes at room temperature. The plates were washed, dried and the number of plaques counted. The number of plaques in each set of compound dilution was converted to a percentage relative to the untreated virus control. The 50% effective (EC_{50} , virus-inhibitory) concentrations were then calculated by linear regression analysis.

5 The quotient of CC_{50} divided by EC_{50} gives the selectivity index (SI) value. Compounds showing SI values ≥ 10 were considered active.

Replicative LASV Viral Yield Reduction Assay

The VYR test is a direct determination of the concentration of the test compound that inhibits virus replication. Compound and virus were added to Vero cells for 3-4 days at which point
10 the supernatant was removed and tested for infectious particles. The supernatant was titrated log₁₀ dilutions of virus using 3 or 4 microwells per dilution on fresh monolayers of Vero cells in 96-well plates. Wells were scored for presence or absence of virus after distinct CPE is observed. Plotting the inhibitor concentration versus log₁₀ of virus produced at each concentration allows calculation of the 90% effective concentration by linear regression. In addition, compounds were
15 run at different concentrations in parallel on Vero cells without virus to determine cytotoxic CC_{50} value. The selectivity index (SI) was calculated as a ratio of CC_{50}/EC_{90} .

Replicative Tacaribe virus testing

Selected compounds were tested against native replicating Tacaribe (TCRV) virus (TRVL-11573, BEI Resources) using an ELISA-based assay. Vero cells (ATCC: CCL-81) were grown in a 96-well format
20 (5000 cells/well) in supplemented DMEM media. After overnight incubation, cells were treated with TCRV and compounds at desired concentrations, in MEM media with 1% FBS and supplements. Final DMSO concentration in the compound testing wells was kept $\leq 1\%$ and control wells were treated with TCRV or media and 1% DMSO. After 5 days of incubation at 37°C in 5% CO₂, cells were fixed with 2% paraformaldehyde for 45 minutes and then washed with PBS. Subsequently the cells were permeabilized
25 with 0.25% triton-X, then TCRV was detected using ELISA with the following protocol. Monoclonal Anti-Junin Virus antibody (BEI #NR 41860), which cross reacts with TCRV nucleoprotein, was used to stain cells. After washing, cells were treated with biotin conjugated secondary antibody and subsequently, streptavidin conjugated horseradish peroxidase. TMB substrate was added to the wells, and the reaction was stopped using 2M sulfuric acid. The absorbance was read using a plate reader (Beckman Coulter
30 DTX 880 multimode detector with an emission of 450 nm). OD readings were obtained for compound containing and control wells to determine % activity for each compound.

Microsomal Assays

In addition to the ability of compounds to demonstrate broad inhibitory activity against arenaviruses *in vitro*, compounds must also have certain drug-like properties for them to be used to

inhibit arenaviruses and provide methods of treatment for arenavirus infection in mammals *in vivo*. Such compounds may exhibit drug-like properties including but not limited to chemical stability against metabolic degradation by 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]. The above publication is herein incorporated by reference for all purposes. To characterize drug-like properties of the chemical series example compounds were evaluated for metabolic stability in human, mouse, guinea pig, monkey, rat, mouse, or dog liver microsome assays (**Table 4**), and for inhibition of the hERG ion channel (**Table 5**). Compounds exhibiting > 60% remaining of parent 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.

A reaction premixture was set up, containing 1 μ M compound of interest, 1 mg/mL liver microsomes of desired species, 2.1 mM $MgCl_2$ and 0.1 M sodium phosphate buffer, pH 7.4. This premixture was incubated at 37°C for 30 minutes with gentle agitation to allow the compound to be completely dissolved in the mixture. Then freshly made NADPH solution in 0.1M sodium phosphate buffer was added at a concentration of 2mM to start the reaction. A 'Time 0' sample (30 μ L) was taken out immediately after addition of NADPH and added to 140 μ L cold acetonitrile containing 1 μ M of pre-decided internal standard. The rest of the reaction mixture was incubated at 37°C for the remaining time period. Test compounds were left in the reaction mixture for 60 minutes before 'Time 60' sample was added to acetonitrile with internal standard. The control compound (Verapamil for human, monkey and dog LM, Lidocaine for Guinea pig LM, and diphenhydramine for rat and mouse LM) was incubated in reaction mixture for 15 minutes before 'Time 15' samples were collected and added to cold acetonitrile with internal standard. The samples were then spun in a centrifuge for 10 minutes at 4000 rpm, supernatant was collected and mixed with equal parts distilled water. These were then analyzed on a Varian 500-MS.

hERG Channel Assay

Drugs belonging to different classes have been shown to be associated with QT prolongation and in some cases serious ventricular arrhythmias. The most common mechanism for these adverse events is the inhibition of one or more cardiac potassium channels, in particular hERG. This current is important for cardiac myocyte repolarization and is a common target for drugs that prolong the QT interval. Test articles in this study were therefore, characterized to determine their ability to inhibit the hERG channel. Ion channel activity was measured using a stably transfected Chinese Hamster Ovary (CHO) cell line expressing the hERG mRNA. The pharmacology of this cloned channel expressed in the CHO cell line is very similar to that observed in native tissue. Cells were cultured in DMEM/F12 containing 10% FBS, 1%

penicillin/streptomycin and 500 µg/ml G418. Before testing, cells were harvested using Accumax (Innovative Cell Technologies). For electrophysiological recordings, the following solutions were used: External solution: 2 mM CaCl₂; 2 mM MgCl₂; 4 mM KCl; 150 mM NaCl; 10 mM Glucose; 10 mM HEPES; 305-315 mOsm; pH 7.4 (adjusted with 5M NaOH); Internal solution: 140 mM KCl; 10 mM MgCl₂; 6 mM EGTA; 5 mM HEPES-Na; 5 mM ATP-Mg; 295-305 mOsm; pH 7.25 (adjusted with 1M KOH). Whole cell recordings were performed using PX 7000A (Axon Instruments) with AVIVA's SealChip™ technology. Cells were voltage clamped at a holding potential of -80 mV. The hERG current was then activated by a depolarizing step to -50 mV for 300 ms. This first step at -50 mV was used as a baseline for measuring peak amplitude of the tail current. Next, a voltage step to +20 mV was applied for 5 s to activate the channels. Finally, a step back to -50 mV for 5 s removed activation and the deactivating tail current was recorded. External solution containing 0.1% DMSO (vehicle) was applied to the cells to establish a baseline. After allowing the current to stabilize for 3 to 10 min, test articles were applied. Test article solutions were added to cells in 4 separate additions. Cells were kept in test solution until effect of the test article reached steady state, to a maximum of 12 min. Next, 1 µM cisapride (positive control) was added. Finally, washout with External Solution was performed until the recovery current reached steady state. Data analysis was performed using DataXpress (Axon Instruments), Clampfit (Axon Instruments) and Origin (OriginLab Corporation) software.

Table 1. Pseudotyped Virus Activity. Example compounds and their observed inhibitory activities are shown as EC₅₀ values for LASV-p, MACV-p, JUNV-p, TCRV-p and GTOV-p (VSV-p EC₅₀ values were all > 10 µM) and CC₅₀ for cytotoxicity; nd: not determined.

Ex.	LASV-p EC ₅₀ (nM)	MACV-p EC ₅₀ (nM)	JUNV-p EC ₅₀ (nM)	TCRV-p EC ₅₀ (nM)	GTOV-p EC ₅₀ (nM)	VSV-p EC ₅₀ (nM)	CC ₅₀ (µM)
A1	0.83	0.12	0.87	0.29	nd	>10,000	37.71
A2	0.38	0.14	0.15	0.15	0.05	>10,000	7.3
A3	0.75	0.17	.40	0.24	nd	>10,000	4.5
B4	1.32	0.25	0.21	0.12	0.31	>10,000	6.71
B5	0.53	0.16	0.18	0.16	nd	>10,000	3.87
B6	0.7	0.13	0.22	0.16	0.11	>10,000	4.32
B7	0.9	0.42	0.31	0.16	0.12	>10,000	8.14
B8	2.91	0.61	0.76	0.32	0.94	>10,000	27.76

B9	>25	>25	>25	16.15	nd	>10,000	nd
C10	20.6	4.05	11.02	12.27	nd	>10,000	>100
C11	2.29	0.19	0.10	0.77	nd	>10,000	>100
C12	1.31	0.55	0.15	15	nd	>10,000	>100
C13	4.0	0.66	0.27	1.53	nd	>10,000	>100
C14	2.44	0.28	0.17	4.70	nd	>10,000	>100
C15	23.42	7.09	3.06	11.37	nd	>10,000	98.44
C16	3.02	1.72	0.45	3.67	nd	>10,000	4.12
C17	15.77	>25	12.18	>25	nd	>10,000	10.46
C18	>25	>25	>25	>25	nd	>10,000	nd
C19	22.5	3.82	0.75	8.0	nd	>10,000	81.71
C20	>25	>25	>25	>25	nd	>10,000	nd
C21	>25	>25	>25	>25	nd	>10,000	nd
C22	>25	>25	>25	>25	nd	>10,000	nd
C23	6.72	0.53	0.29	0.96	nd	>10,000	42.99
C24	4.62	>25	18.97	18.40	nd	>10,000	32.21
C25	6.78	0.3	1.47	8.01	nd	>10,000	3.87
C26	3.9	0.04	0.1	5.92	nd	>10,000	3.59
D27	0.75	0.85	0.78	0.20	nd	>10,000	2.18
D28	0.30	0.31	0.40	0.15	nd	>10,000	12.32
D29	1.84	0.87	1.03	1.27	nd	>10,000	42.10
E30	0.39	0.09	0.09	nd	nd	nd	3.8

Table 2. Comparison of Pseudotyped Versus Replicative TCRV Inhibitory Activities.

Example compounds and their observed inhibitory activities (EC₅₀) against pseudotyped or replicative TCRV.

Example	TCRV-p EC ₅₀ (nM)	TCRV EC ₅₀ (nM)
A1	0.24	0.89
A2	0.12	0.33
A3	0.21	0.87
B4	0.16	0.74
B5	0.10	0.88
B6	0.10	0.95
B7	0.20	0.74
B8	0.32	2.16
C11	0.61	0.84
E30	0.2	nd

A very close correlation was surprisingly discovered between the pseudotyped and replicative virus inhibitory activities by the compounds of the invention.

Table 3. Inhibition of Native Lassa Virus. Example compounds and their observed inhibitory activities and selectivity indices (SI) in both replicative LASV plaque and viral yield reduction (VYR) assays.

Example	Plaque Assay EC ₅₀ (uM)	VYR Assay EC ₉₀ (uM)	SI ₉₀
B8	<.003	<0.003	>9,000
B7	<.003	<0.001	>11,000
A1	<.003	<0.001	>33,000
A2	<.003	<0.001	>13,000
E30	nd	<0.014	>1,510

All five compounds demonstrated very potent EC₅₀ and EC₉₀ of less than 1-3 nM for compounds A1, A2, B7, and B8 in the plaque and VYR assay formats and EC₉₀ of less than 14 nM for compound E30 in the VYR assay format. SI₉₀ values (obtained from the VYR assay data) were >1510 clearly indicating compound efficacy was due to antiviral activity and not cytotoxic effects. The results shown in tables 1-3 confirm the activity of the compounds against arenaviruses including the replicative LASV and also strongly validates the approach for identifying *bona fide* HF arenavirus inhibitors through the utilization of pseudotyped virus assays.

Table 4. Multi-species Microsomal Stability. Percent parent compound remaining at 60 minutes in liver microsomes

Ex.	Mouse	Monkey	Dog	Human	Guinea	Rat
A1	82.7	8.6	>95	68.3	>95	93.8
A2	93.9	53	>95	95	>95	>95

A3	25.4	nd	nd	89.9	67.6	nd
B4	37.5	4.9	83.3	88.1	55.45	70.6
B5	16.4	nd	nd	86.7	7.4	nd
B6	81.7	nd	nd	81.5	61.5	nd
B7	92.9	22.9	>95	>95	>95	>95
B8	77.5	33.7	77.57	87.6	67.7	93
C11	>95	nd	nd	>95	>95	nd
C12	90.3	nd	nd	>95	>95	nd
C13	nd	nd	nd	79.5	nd	nd
C14	>95	nd	nd	>95	>95	nd
C16	57.4	nd	nd	72.3	61.9	nd
E30	>95	74.4	>95	>95	>95	>95

The results of multi-species microsomal stability studies (Table 4) showed that deuterated compound E30 demonstrated improved metabolic stability in monkey liver microsome assay as compared to its non-deuterated analog B7, thus showing good microsomal stability in both human and nonhuman species.

5 Table 5: hERG Channel Assay

Example	% Inhibition at 3 uM
A1	<10
B7	<10
B8	<10
C11	<10

These data indicate lack of hERG channel inhibition suggesting good potential for cardiac safety.

Table 6: Mouse Pharmacokinetic Parameters

Example	Clearance (mL/min/kg)	Oral half-life (hr)	Oral C-Max (ug/mL)	Oral T-Max (hr)	Oral AUC _{t-0} (ug/mL*h)	Vd (L/kg)	% Oral Bioavailability
B7	13.7	13.2	5.5	2	70.4	35.7	30
A1	0.8	17	20.4	0.5	182.6	17.6	35

- 10 Compounds were dosed in mice by intravenous (3 mg/kg) and oral (30 mg/kg) routes to determine pharmacokinetic parameters. IV time points included 0.083, 0.25, 0.5, 1, 2, 6 and 24h and oral time points included 0.5, 1, 2, 4, 6, 8 and 24h. Blood was drawn from 3 mice per time point. Plasma was isolated and measured by LC/MS/MS on a Varian 500-LC/MS. Both compounds demonstrated low first pass liver clearance which is in agreement with high levels of compound remaining after 1 hour in mouse liver
- 15 microsome (Table 4). Both compounds demonstrate reasonable oral bioavailability and long half-lives suitable for once a day dosing. Finally, the volume of distribution (Vd) values indicate compound is being taken up into tissue that further supports good oral biodistribution for targeting arenavirus infection.

Mice were able to tolerate both compounds dosed orally daily for 3 days up to at least (the highest dose tested) 100 mg/kg once a day. There were no clinical signs of overt toxicity as determined by daily monitoring of weight, temperature and behavior. On day 4 (24hrs after last dose) plasma and liver samples were collected from dosed animals to measure compound levels. Livers were homogenized in a 1:1 w/v of phosphate buffered saline. Both plasma and liver extracts were measured by LC/MS/MS on a Varian 500-MS (Table 7).

Table 7: Compound Concentrations 24 Hours Post Final Administration

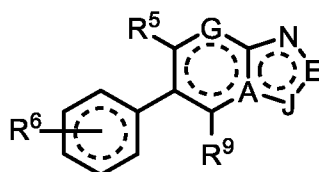
Example	24hr plasma concentration (ug/mL)	24hr liver concentration (ug/g liver)
B7	9.1	63.4
A1	8.8	240.3

Taken together the results show that the compounds of the invention exhibit potent, broad-spectrum inhibition of HF arenaviruses and attractive drug-like properties for utilization as treatments for viral infections that are mediated by arenavirus glycoproteins.

AMENDED CLAIMS
received by the International Bureau on 30 April 2020 (30.04.2020)

WHAT IS CLAIMED IS:

1. A method of treating infections associated with viruses of the *Arenaviridae* enveloped virus family, or any virus expressing Arenavirus glycoproteins to mediate cell entry comprising administering a pharmaceutically effective dose of a compound of structural formula I:



I

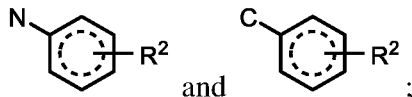
or a pharmaceutically acceptable salt and a pharmaceutically acceptable carrier, dilutant or vehicle thereof wherein

A is independently selected from C and N;

G is independently selected from CH, CD, and N;

E is independently selected from CH, CD, and N;

J is independently selected from



R² is independently selected from -OR³, -R⁴, -NHR¹⁰, -CONHR¹⁰;

R³ is independently selected from H, D, C₁ to C₆ alkyl, C₂ to C₆ alkenyl, -NHC(O)R⁴ -C(O)NHR¹⁰, and -C(O)R¹⁰, wherein each C₁ to C₆ alkyl is optionally substituted with D, halogen, -OH, -OR⁴, -NHR¹⁰;

R⁴ is independently selected from C₁ to C₆ alkyl and (C₂ to C₉) cycloheteroalkyl optionally substituted with D, halogen, -OH, -OR¹⁰, and NHR¹⁰;

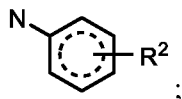
R⁵ is independently selected from H, D, C₁ to C₆ alkyl, C₂ to C₆ alkenyl, C₂ to C₆ alkynyl, halogen, -OR³, -CO₂R¹⁰, -NHC(O)R⁴, -C(O)NHR¹⁰, -NHR¹⁰, -CHNHR¹⁰, -CN, -CR⁴, and -C(O)R¹⁰, wherein each C₁ to C₆ alkyl is optionally substituted with D;

R⁶ is independently selected from halogen, -OR³, and R⁴;

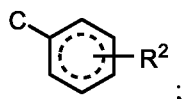
R⁹ is independently selected from H, D, halogen, -OR¹⁰, and C₁ to C₆ alkyl;

R¹⁰ is independently selected from H, D, -OH, C₁ to C₆ alkyl and C₂ to C₆ alkenyl;

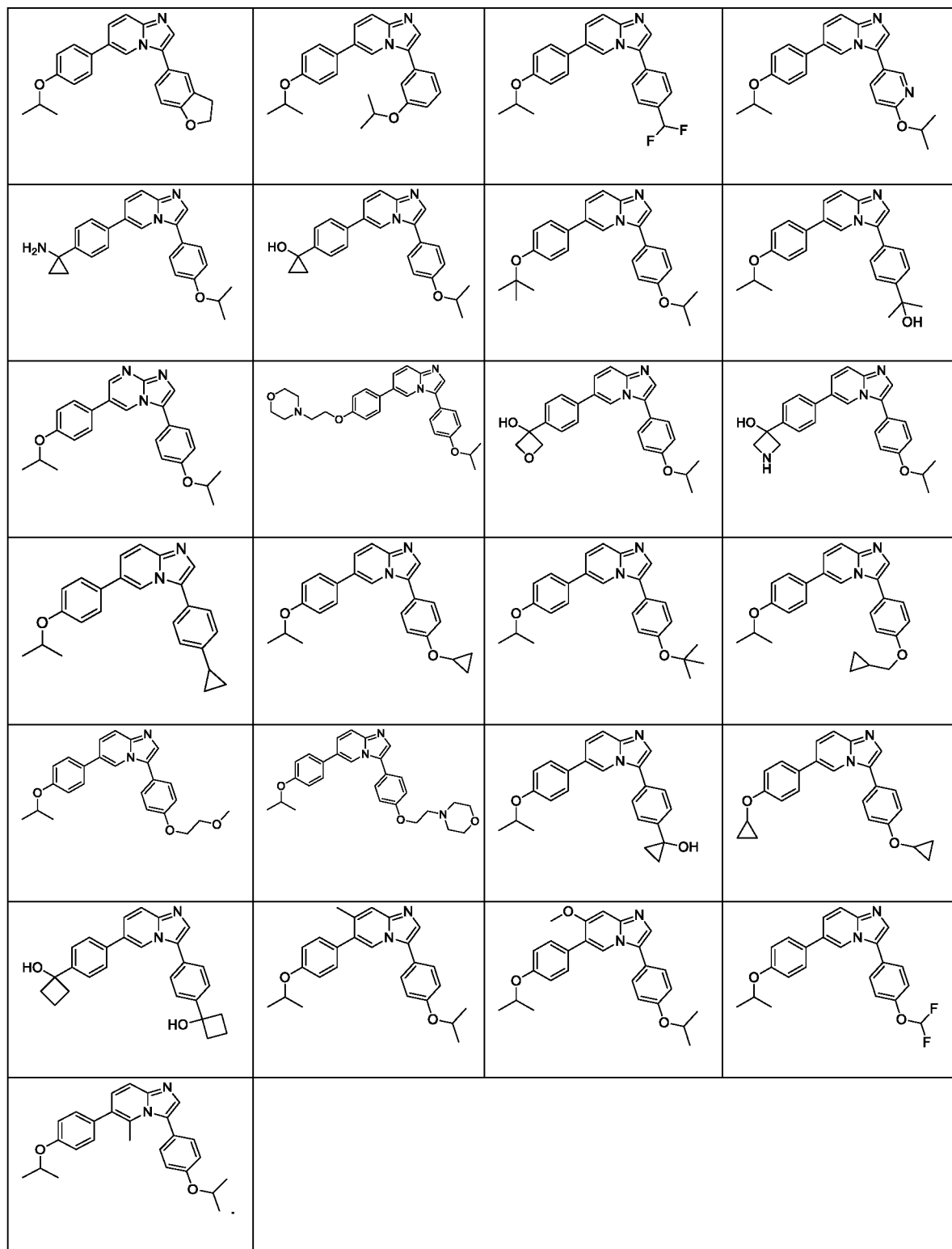
and when E is N, CH or CD then A is C, G is CH or CD, and J is



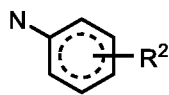
and when A is N then J is



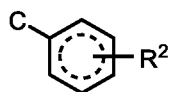
with the proviso that the following compounds are excluded:



2. The method of claim 1 wherein J is



3. The method of claim 1 wherein J is

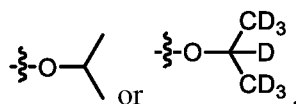


4. The method of claim 1 wherein E is CH or CD.

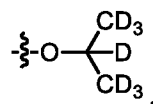
5. The method of claim 1 wherein A is C.

6. The method of claim 1 wherein A is N.

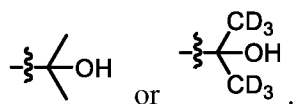
7. The method of claim 3 wherein R⁶ is



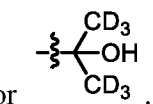
or



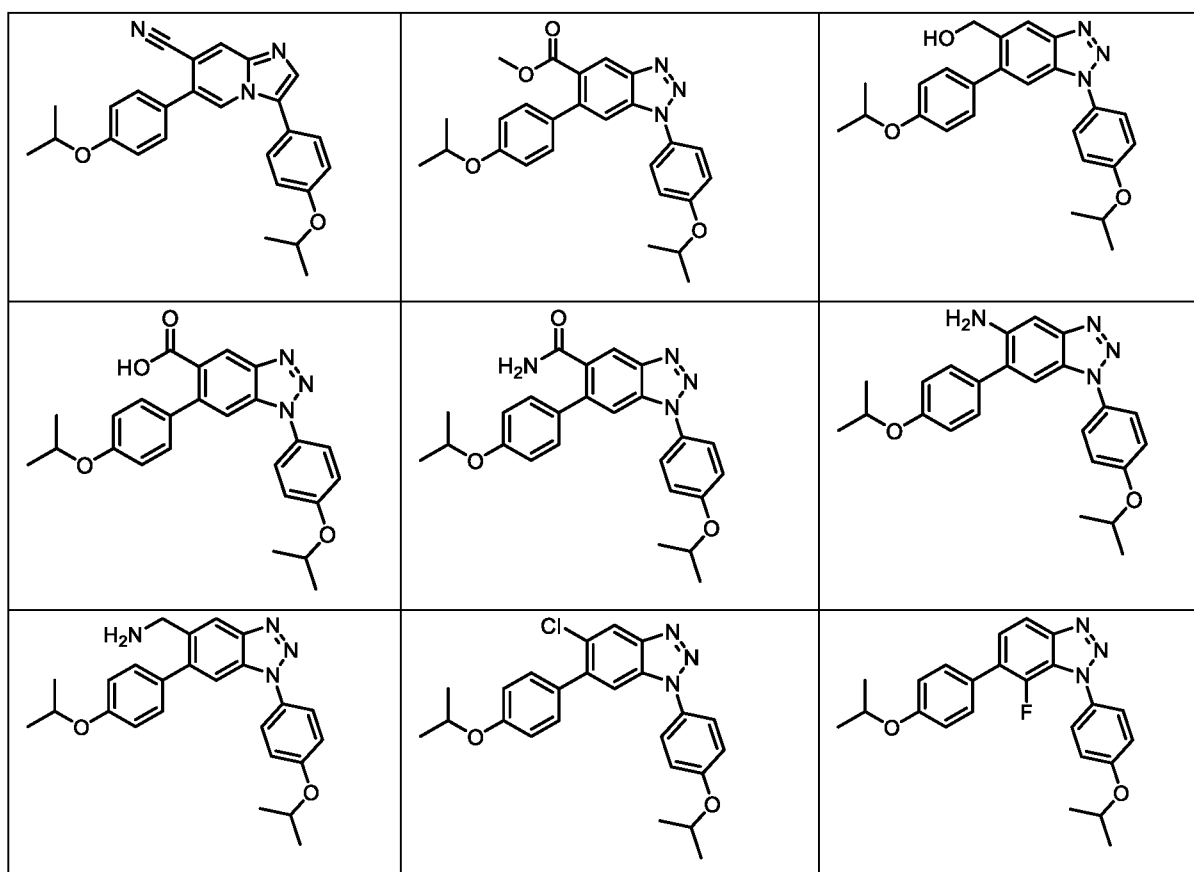
8. The method of claim 2 wherein R⁶ is

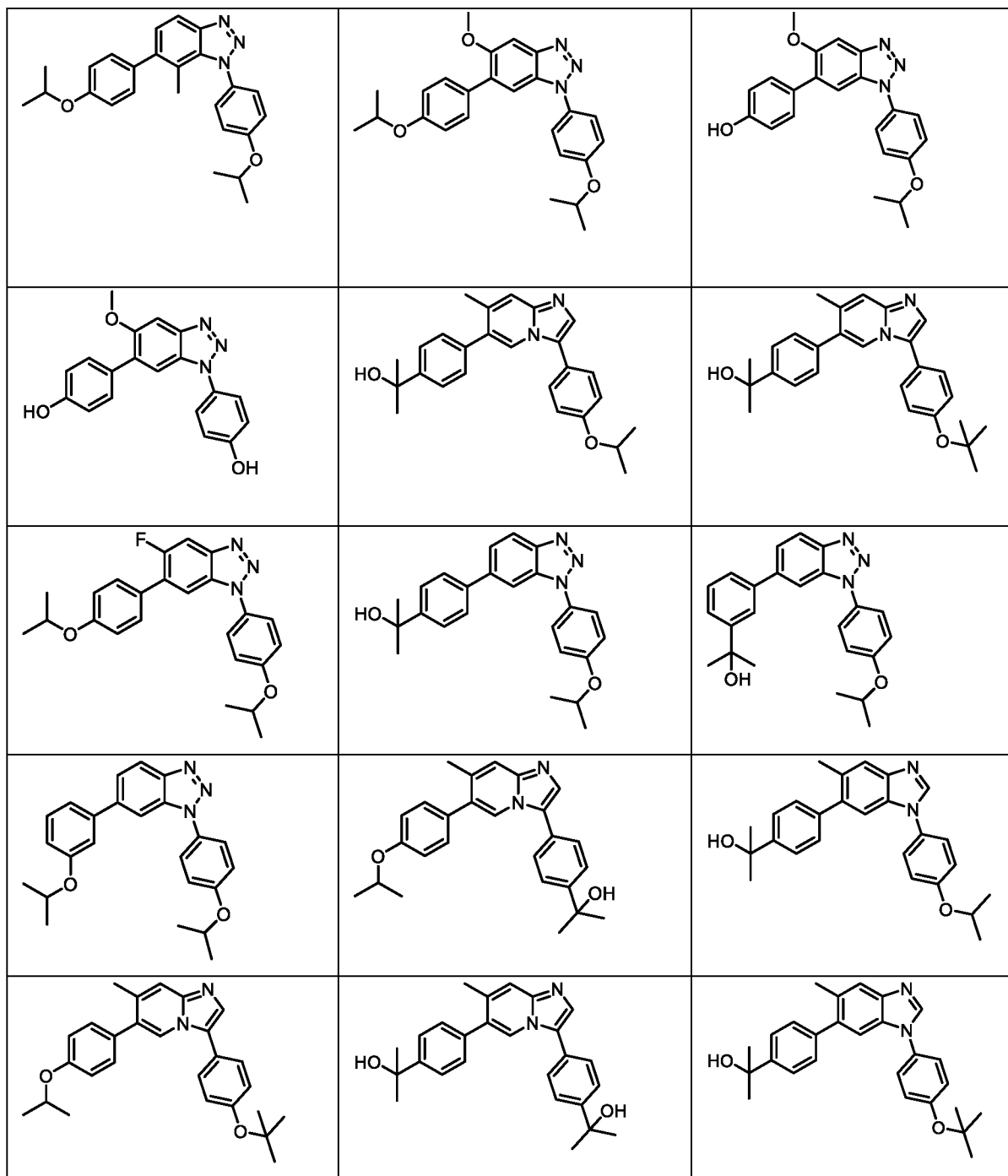


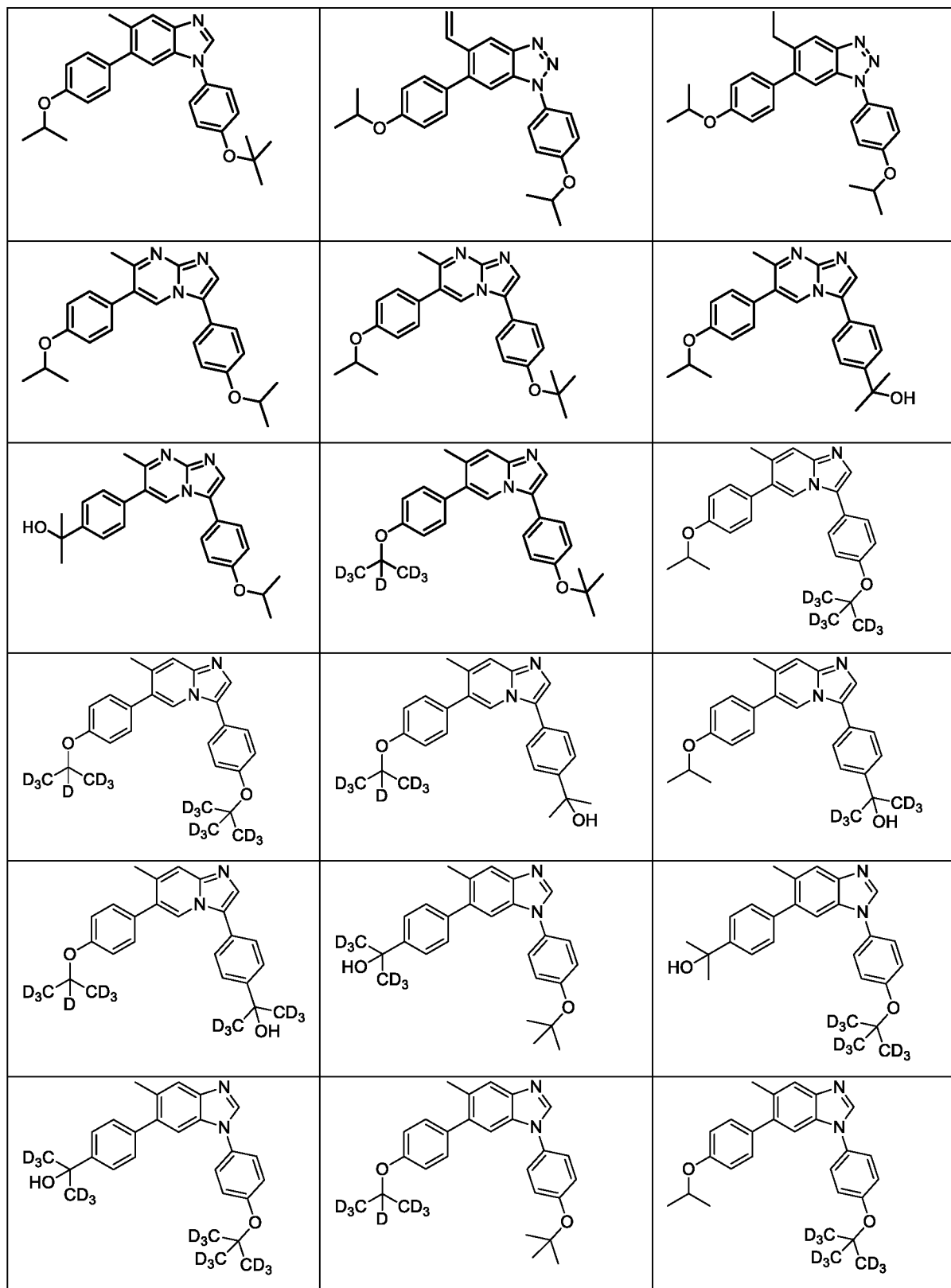
or

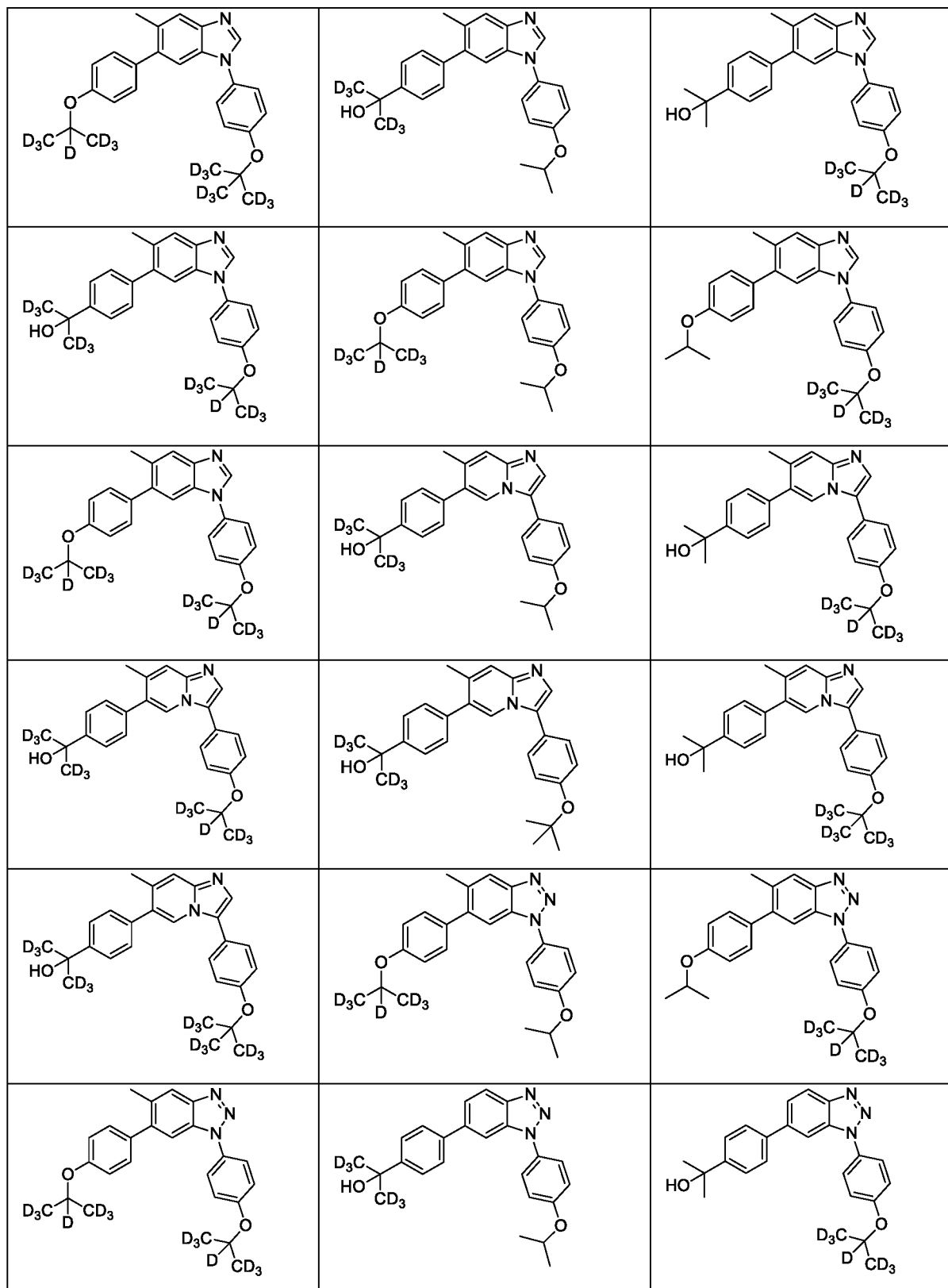


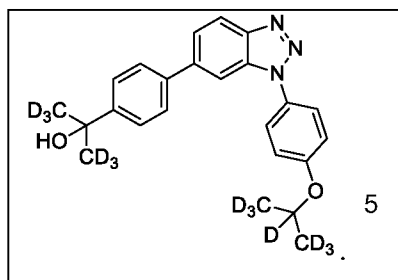
9. A method of treating infections associated with viruses of the *Arenaviridae* enveloped virus family, or any virus expressing Arenavirus glycoproteins to mediate cell entry, comprising administration of a therapeutically effective amount of a compound selected from the group consisting of:



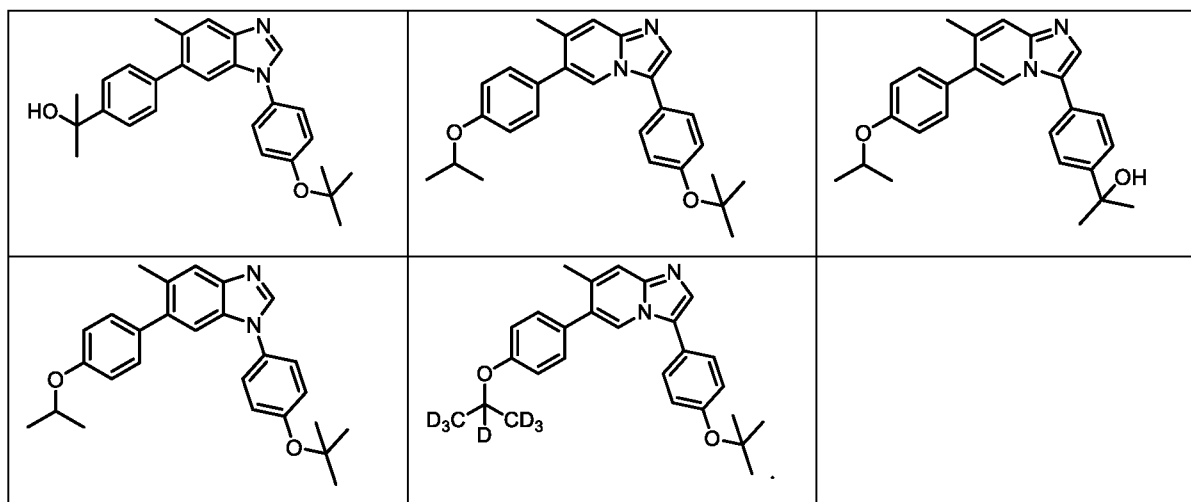




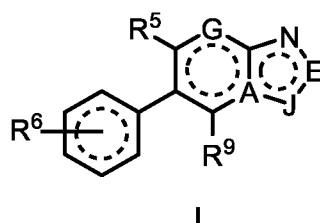




10. The method of claim 9, wherein the compound is selected from the group consisting of

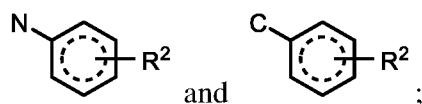


10 11. A compound of structural formula I:



or a pharmaceutically acceptable salt and a pharmaceutically acceptable carrier, dilutant or vehicle there of wherein

- 15 A is independently selected from C and N;
 G is independently selected from CH, CD, and N;
 E is independently selected from CH, CD, and N;
 J is independently selected from



20 R² is independently selected from -OR³, -R⁴, -NHR¹⁰, -CONHR¹⁰;

R^3 is independently selected from H, D, C_1 to C_6 alkyl, C_2 to C_6 alkenyl, $-NHC(O)R^4 -C(O)NHR^{10}$, and $-C(O)R^{10}$, wherein each C_1 to C_6 alkyl is optionally substituted with D, halogen, $-OH$, $-OR^4$, $-NHR^{10}$;

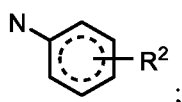
R^4 is independently selected from C_1 to C_6 alkyl and (C_2 to C_9) cycloheteroalkyl optionally substituted with D, halogen, $-OH$, $-OR^{10}$, and NHR^{10} ;

5 R^5 is independently selected from H, D, C_1 to C_6 alkyl, C_2 to C_6 alkenyl, C_2 to C_6 alkynyl, halogen, $-OR^3$, $-CO_2R^{10}$, $-NHC(O)R^4$, $-C(O)NHR^{10}$, $-NHR^{10}$, $-CHNHR^{10}$, $-CN$, $-CR^4$, and $-C(O)R^{10}$, wherein each C_1 to C_6 alkyl is optionally substituted with D;

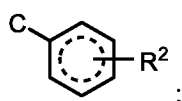
R^6 is independently selected from halogen, $-OR^3$, and R^4 ;

R^9 is independently selected from H, D, halogen, $-OR^{10}$, and C_1 to C_6 alkyl;

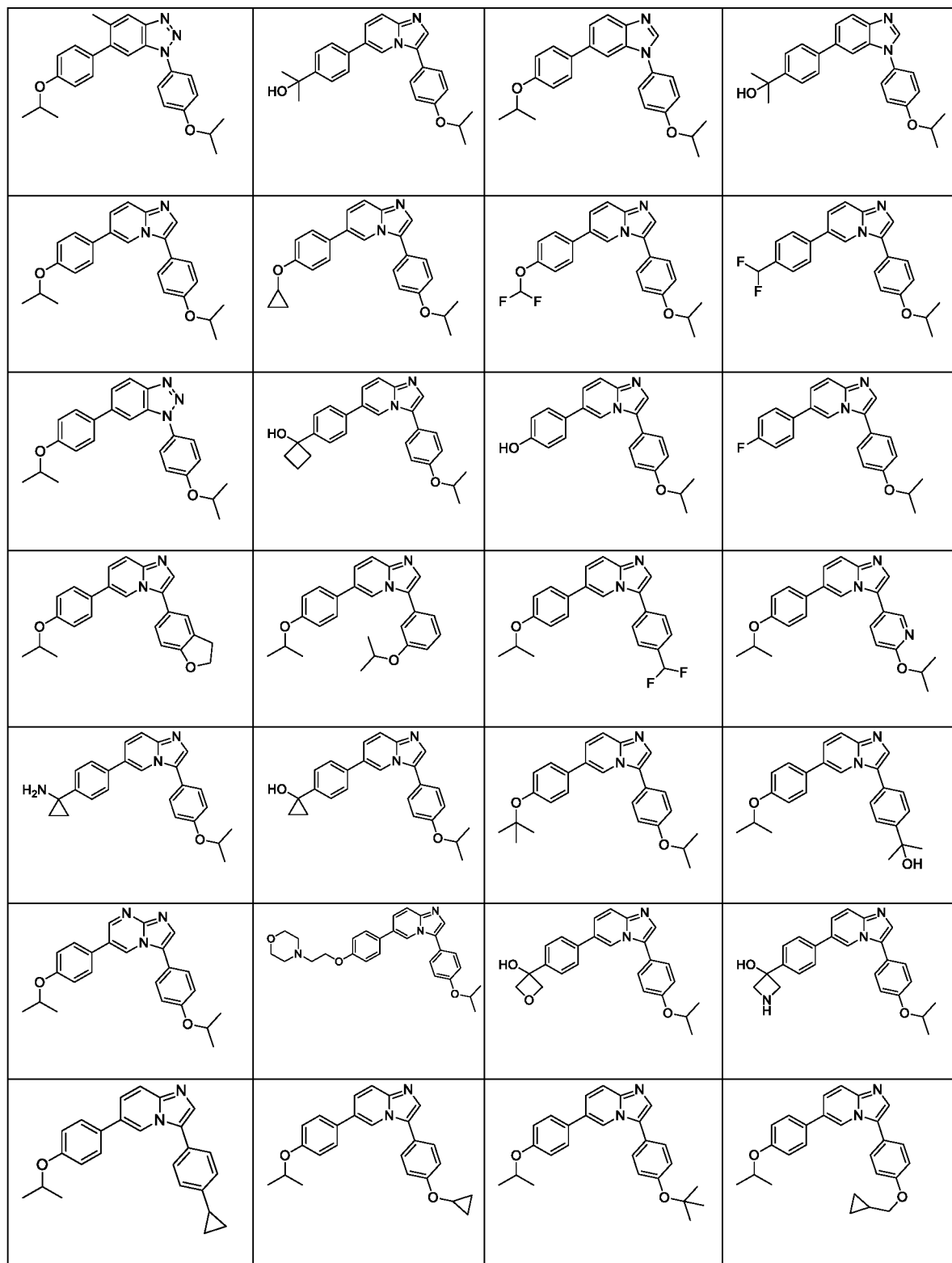
10 R^{10} is independently selected from H, D, $-OH$, C_1 to C_6 alkyl and C_2 to C_6 alkenyl;
and when E is N, CH or CD then A is C, G is CH or CD, and J is

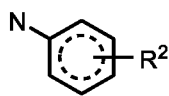
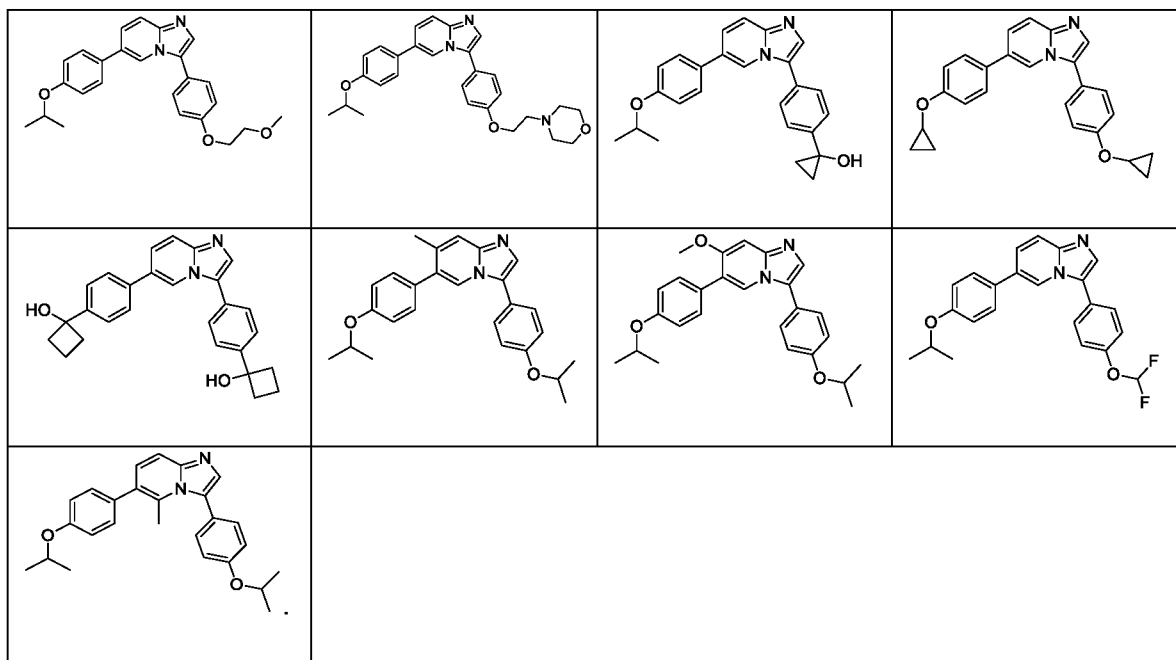


and when A is N then J is

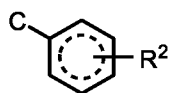


15 with the proviso that the following compounds are excluded:





12. The compound of claim 11 wherein J is



13. The compound of claim 11 wherein J is

14. The compound of claim 11 wherein E is CH or CD.

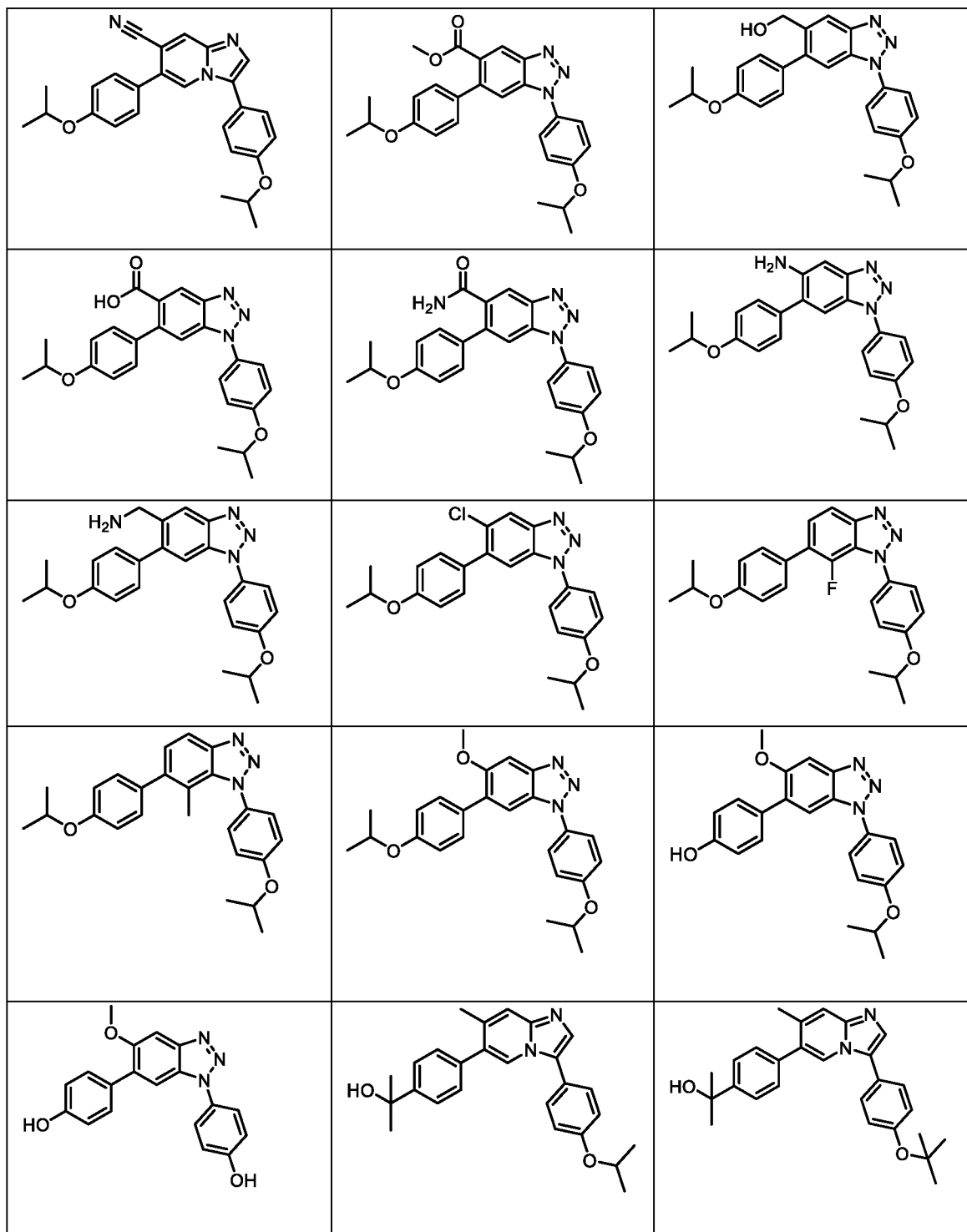
5 15. The compound of claim 11 wherein A is C.

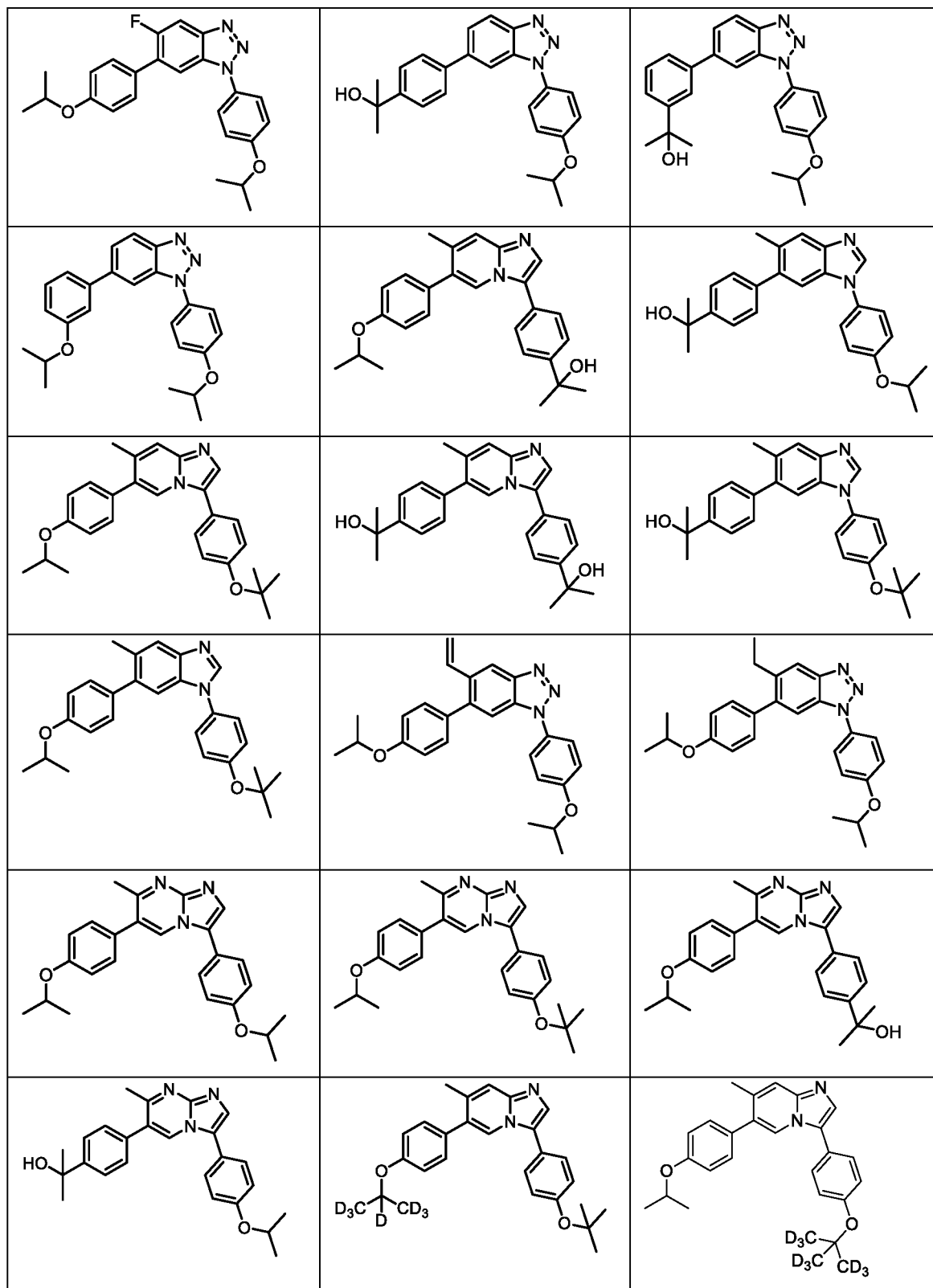
16. The compound of claim 11 wherein A is N.

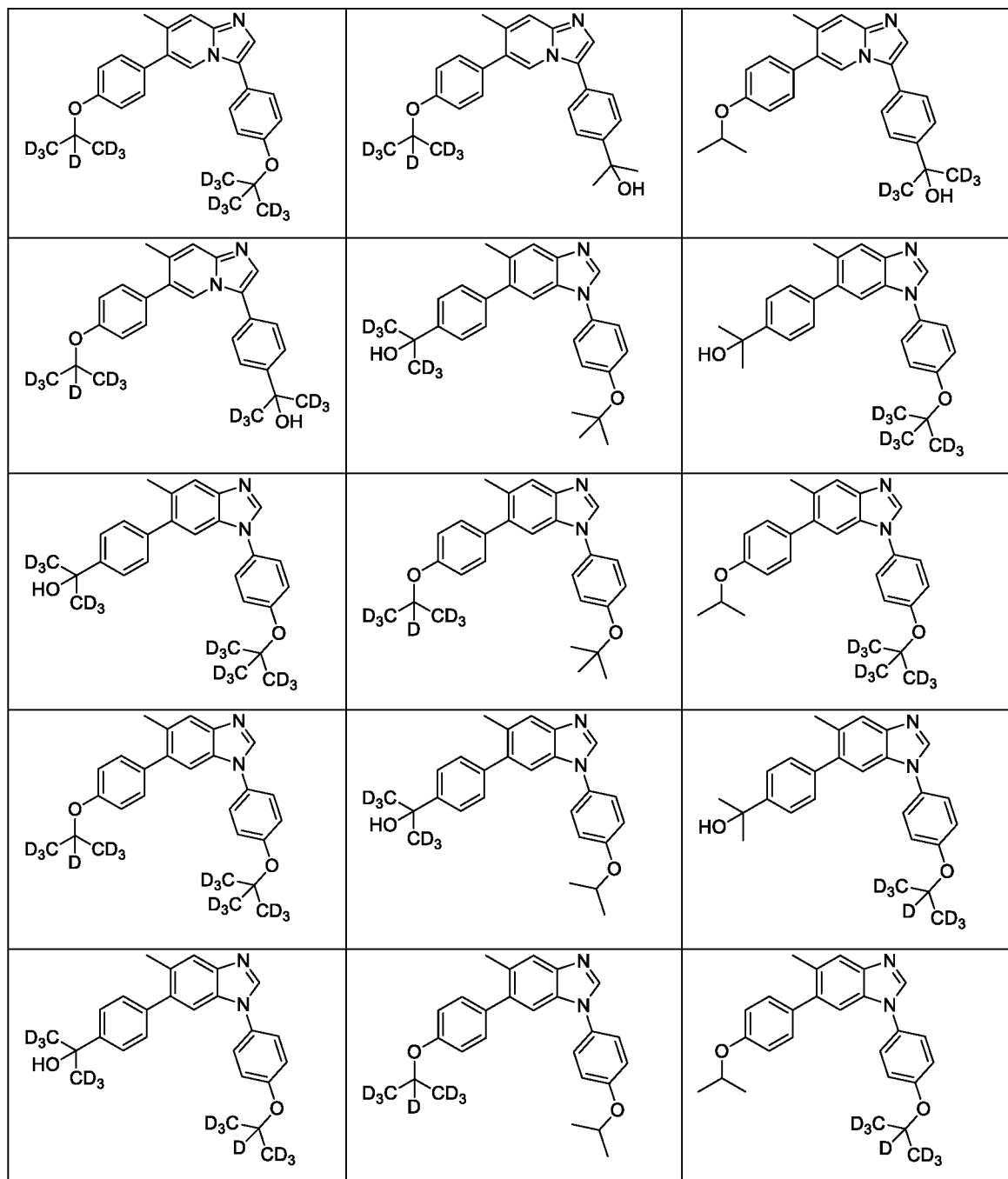
17. The compound of claim 13 wherein R⁶ is or .

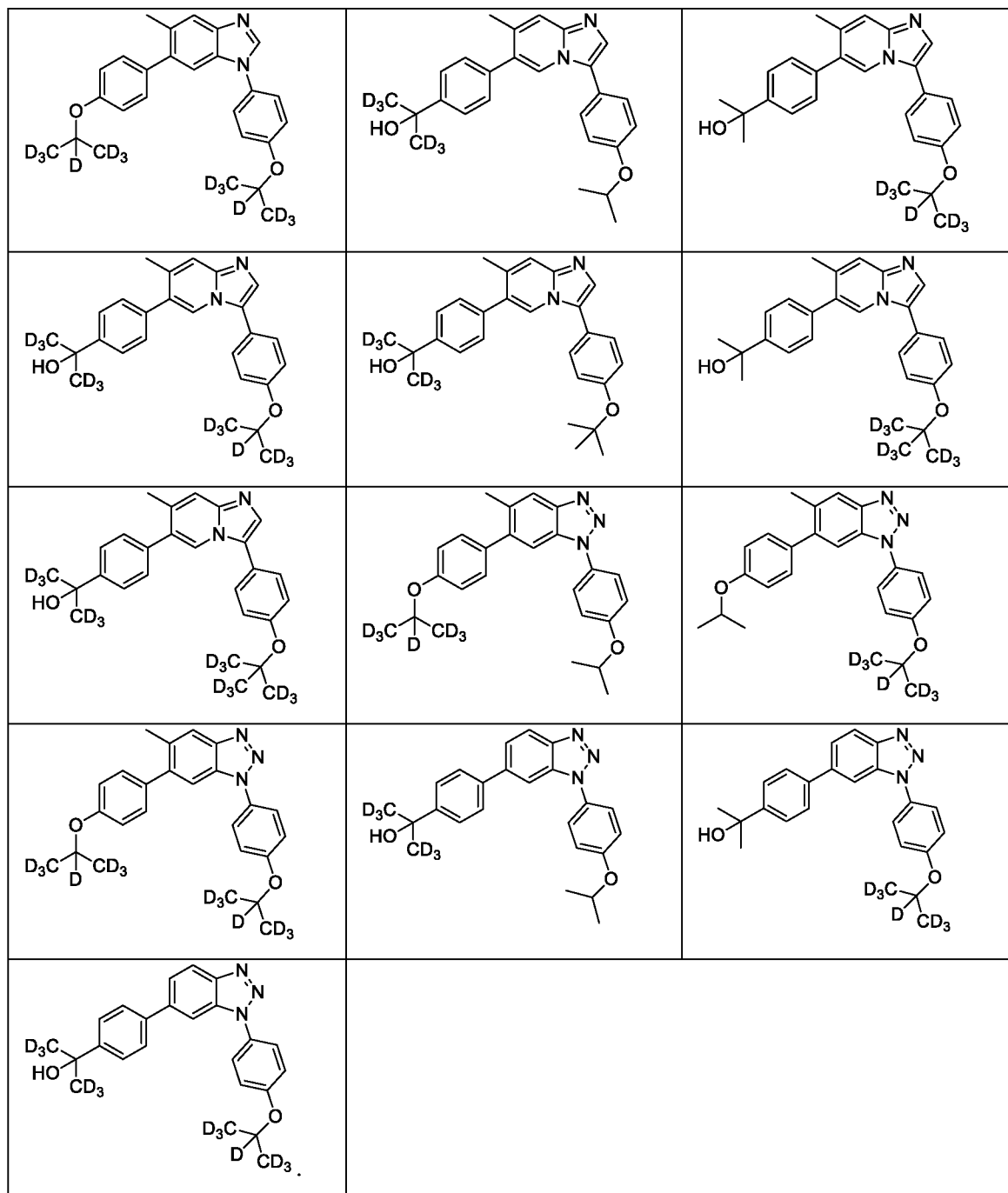
18. The compound of claim 12 wherein R⁶ is or .

19. A compound selected from the group consisting of:

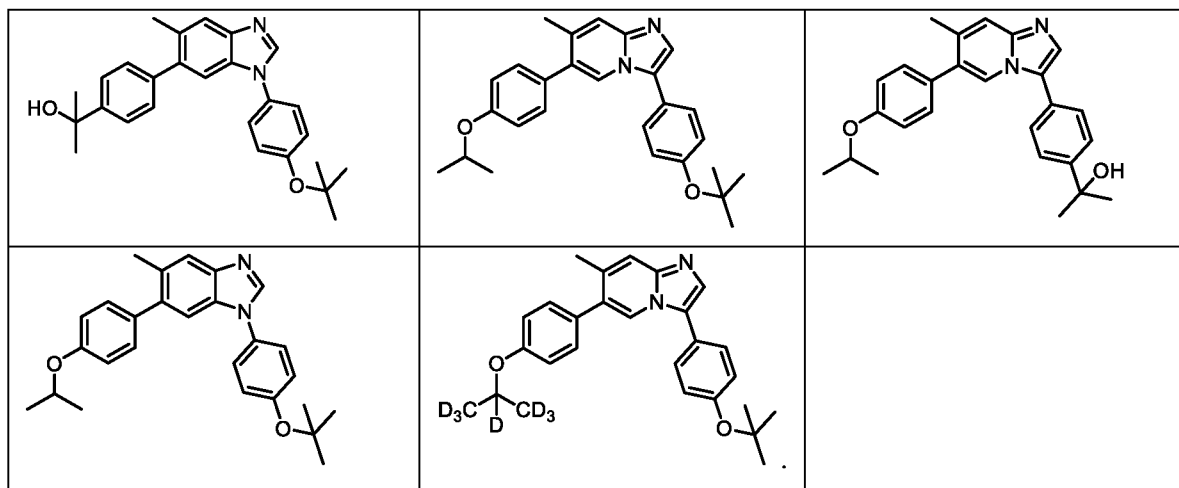








20. The compound of claim 19, wherein the compound is selected from the group consisting of



21. The method of claim 1 wherein a pharmaceutically acceptable dose of the compound of claim 1 is administered with a pharmaceutically acceptable dose of at least one of the compounds selected from Ribavirin, polymerase inhibitors, Favipiravir, Triazavirin, small interfering RNAs (siRNAs), vaccines, monoclonal antibodies, and immunomodulators.