



(51) International Patent Classification:

A61K 31/18 (2006.01) A61K 45/06 (2006.01)
A61K 31/277 (2006.01)

(21) International Application Number:

PCT/US2016/024179

(22) International Filing Date:

25 March 2016 (25.03.2016)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/138,704 26 March 2015 (26.03.2015) US

(71) Applicant: EMORY UNIVERSITY [US/US]; Office of Technology Transfer, 1599 Clifton Road NE, 4th Floor, Atlanta, Georgia 30322 (US).

(72) Inventors: SNYDER, James P.; 1086 Rosedale Drive, Atlanta, Georgia 30329 (US). SHI, Qi; 1646 Clairmont Way NE, Atlanta, Georgia 30329 (US). KAISER, Thomas M.; 1901 N Crossing Way, Decatur, Georgia 30033 (US). DENTMON, Zackery W.; 2451 Springdale Rd SW, Atlanta, Georgia 30315 (US). LIOTTA, Dennis C.; 3344 Peachtree Road NE, Suite 4702, Atlanta, Georgia 30326 (US).

(74) Agents: MASON, James C. et al.; Emory University, Office of Technology Transfer, 1599 Clifton Road NE, 4th Floor, Atlanta, Georgia 30322 (US).

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

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

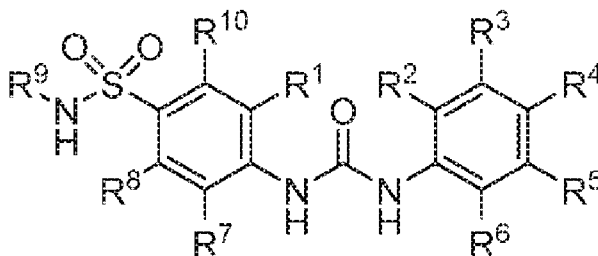
Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- of inventorship (Rule 4.17(iv))

Published:

- with international search report (Art. 21(3))

(54) Title: CARBONIC ANHYDRASE INHIBITORS AND USES RELATED THERETO



Formula I

(57) Abstract: In certain embodiments, this disclosure relates to carbonic anhydrase inhibitors that are phenylureidobenzenesulfonamide derivatives and uses related thereto. In certain embodiments, the phenylureidobenzenesulfonamide derivatives are of Formula I, wherein the substituents are defined herein. In certain embodiments, the disclosure relates to pharmaceutical compositions comprising compounds disclosed herein and a pharmaceutically acceptable excipient.

CARBONIC ANHYDRASE INHIBITORS AND USES RELATED THERETO

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 62/138,704 filed
5 March 26, 2015. The entirety of this application is hereby incorporated by reference for all purposes.

BACKGROUND

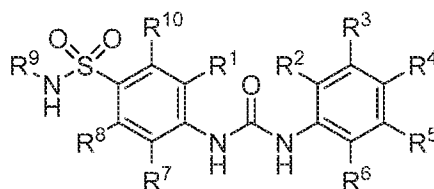
Carbonic anhydrase (CA) is a metalloenzyme that catalyzes the reversible reaction
10 involving the hydration of carbon dioxide and the dehydration of carbonic acid. In humans, carbonic anhydrase exists as a number of isoenzymes, the most active being carbonic anhydrase II (CA-II), found primarily in red blood cells (RBCs). CA inhibitors (CAIs) are useful as diuretics, anti-glaucoma and anti-obesity agents. See Supuran, Medicinal Research Reviews, 2003, 23(2):146–189. Acetazolamide is a carbonic anhydrase inhibitor effective in the control of
15 fluid secretion (e.g., glaucoma), in the treatment of certain convulsive disorders (e.g., epilepsy), and in the promotion of diuresis in instances of abnormal fluid retention (e.g., cardiac edema). Topiramate is a CA-II and -IV inhibitor that has anti-convulsant and migraine prophylaxis effects. It has also been shown to be effective in the treatment of seizures. Ben-Menachem et al., report weight loss in adults treated for epilepsy with topiramate. Obes Res 2003, 11:556–62.
20 A combination of phentermine and topiramate is approved by the FDA as an adjunct therapy for chronic weight management. CA-II inhibitors such as brinzolamide and dorzolamide are also approved for the use of treating elevated intraocular pressure.

Pacchiano et al., report ureido-substituted benzenesulfonamides potently inhibit carbonic anhydrase IX and show antimetastatic activity in a model of breast cancer metastasis. J Med
25 Chem. 2011, 54(6):1896-902. See also US 2013/0190396 and US 2011/0071142.

References cited herein are not an admission of prior art.

SUMMARY

In certain embodiments, this disclosure relates to carbonic anhydrase inhibitors that are
30 phenylureidobenzenesulfonamide derivatives and uses related thereto. In certain embodiments, the phenylureidobenzenesulfonamide derivatives are of Formula I,



Formula I

wherein the substituents are reported herein. In certain embodiments, the disclosure relates to pharmaceutical compositions comprising compounds disclosed herein and a pharmaceutically acceptable excipient.

In certain embodiments, the disclosure relates to methods of treating or preventing conditions associated with carbonic anhydrase inhibition such as obesity, cancer, glaucoma, ocular hypertension, altitude sickness, or neurological disorders such as epilepsy, Lennox-Gastaut syndrome, and migraine headaches by administering compounds disclosed herein to a subject in need thereof. In certain embodiments, the disclosure relates to methods of increasing urinary excretion comprising administering an effective amount of a compound disclosed herein to a subject in need thereof, e.g., wherein the subject is diagnosed with, at risk of, or exhibiting symptoms of heart failure, liver cirrhosis, hypertension, water poisoning, or kidney disease.

DETAILED DISCUSSION

Before the present disclosure is described in greater detail, it is to be understood that this disclosure is not limited to particular embodiments described, and as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present disclosure will be limited only by the appended claims.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Although any methods and materials similar or equivalent to those described herein can also be used in the practice or testing of the present disclosure, the preferred methods and materials are now described.

All publications and patents cited in this specification are herein incorporated by reference as if each individual publication or patent were specifically and individually indicated to be incorporated by reference and are incorporated herein by reference to disclose and describe

the methods and/or materials in connection with which the publications are cited. The citation of any publication is for its disclosure prior to the filing date and should not be construed as an admission that the present disclosure is not entitled to antedate such publication by virtue of prior disclosure. Further, the dates of publication provided could be different from the actual publication dates that may need to be independently confirmed.

As will be apparent to those of skill in the art upon reading this disclosure, each of the individual embodiments described and illustrated herein has discrete components and features which may be readily separated from or combined with the features of any of the other several embodiments without departing from the scope or spirit of the present disclosure. Any recited method can be carried out in the order of events recited or in any other order that is logically possible.

Embodiments of the present disclosure will employ, unless otherwise indicated, techniques of medicine, organic chemistry, biochemistry, molecular biology, pharmacology, and the like, which are within the skill of the art. Such techniques are explained fully in the literature.

It must be noted that, as used in the specification and the appended claims, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. In this specification and in the claims that follow, reference will be made to a number of terms that shall be defined to have the following meanings unless a contrary intention is apparent.

Prior to describing the various embodiments, the following definitions are provided and should be used unless otherwise indicated.

As used herein, "alkyl" means a noncyclic straight chain or branched, unsaturated or saturated hydrocarbon such as those containing from 1 to 22 carbon atoms, while the term "lower alkyl" or "C₁₋₄alkyl" has the same meaning as alkyl but contains from 1 to 4 carbon atoms. The term "higher alkyl" has the same meaning as alkyl but contains from 8 to 22 carbon atoms. Representative saturated straight chain alkyls include methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, n-septyl, n-octyl, n-nonyl, and the like; while saturated branched alkyls include isopropyl, sec-butyl, isobutyl, tert-butyl, isopentyl, and the like. Unsaturated alkyls contain at least one double or triple bond between adjacent carbon atoms (referred to as an "alkenyl" or "alkynyl", respectively). Representative straight chain and branched alkenyls include ethylenyl, propylenyl, 1-butenyl, 2-butenyl, isobutylenyl, 1-pentenyl, 2-pentenyl, 3-methyl-1-butenyl, 2-

methyl-2-butenyl, 2,3- dimethyl-2-butenyl, and the like; while representative straight chain and branched alkynyls include acetylenyl, propynyl, 1-butyne, 2-butyne, 1-pentyne, 2-pentyne, 3-methyl-1-butyne, and the like.

Non-aromatic mono or polycyclic alkyls are referred to herein as "carbocycles" or "carbocyclyl" groups. Representative saturated carbocycles include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like; while unsaturated carbocycles include cyclopentenyl and cyclohexenyl, and the like.

"Heterocarbocycles" or heterocarbocyclyl" groups are carbocycles which contain from 1 to 4 heteroatoms independently selected from nitrogen, oxygen and sulfur which may be saturated or unsaturated (but not aromatic), monocyclic or polycyclic, and wherein the nitrogen and sulfur heteroatoms may be optionally oxidized, and the nitrogen heteroatom may be optionally quaternized. Heterocarbocycles include morpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydropyridinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, and the like.

"Aryl" means an aromatic carbocyclic monocyclic or polycyclic ring such as phenyl or naphthyl. Polycyclic ring systems may, but are not required to, contain one or more non-aromatic rings, as long as one of the rings is aromatic.

As used herein, "heteroaryl" refers an aromatic heterocarbocycle having 1 to 4 heteroatoms selected from nitrogen, oxygen and sulfur, and containing at least 1 carbon atom, including both mono- and polycyclic ring systems. Polycyclic ring systems may, but are not required to, contain one or more non-aromatic rings, as long as one of the rings is aromatic. Representative heteroaryls are furyl, benzofuranyl, thiophenyl, benzothiophenyl, pyrrolyl, indolyl, isoindolyl, azaindolyl, pyridyl, quinolinyl, isoquinolinyl, oxazolyl, isooxazolyl, benzoxazolyl, pyrazolyl, imidazolyl, benzimidazolyl, thiazolyl, benzothiazolyl, isothiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, cinnolinyl, phthalazinyl, and quinazolinyl. It is contemplated that the use of the term "heteroaryl" includes N-alkylated derivatives such as a 1-methylimidazol-5-yl substituent.

As used herein, "heterocycle" or "heterocyclyl" refers to mono- and polycyclic ring systems having 1 to 4 heteroatoms selected from nitrogen, oxygen and sulfur, and containing at

least 1 carbon atom. The mono- and polycyclic ring systems may be aromatic, non-aromatic or mixtures of aromatic and non-aromatic rings. Heterocycle includes heterocarbocycles, heteroaryls, and the like.

"Alkylthio" refers to an alkyl group as defined above attached through a sulfur bridge. An example of an alkylthio is methylthio, (i.e., -S-CH₃).

"Alkoxy" refers to an alkyl group as defined above attached through an oxygen bridge. Examples of alkoxy include, but are not limited to, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy, t-butoxy, n-pentoxo, and s-pentoxo. Preferred alkoxy groups are methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy, and t-butoxy.

"Alkylamino" refers an alkyl group as defined above attached through an amino bridge. An example of an alkylamino is methylamino, (i.e., -NH-CH₃).

"Alkanoyl" refers to an alkyl as defined above attached through a carbonyl bridge (i.e., -C(=O)alkyl).

"Alkylsulfonyl" refers to an alkyl as defined above attached through a sulfonyl bridge (i.e., -S(=O)₂alkyl) such as mesyl and the like, and "Arylsulfonyl" refers to an aryl attached through a sulfonyl bridge (i.e., -S(=O)₂aryl).

"Alkylsulfinyl" refers to an alkyl as defined above attached through a sulfinyl bridge (i.e., -S(=O)alkyl).

"Aminoalkyl" refers an amino group attached through an alkyl bridge. An example of an aminoalkyl is aminomethyl, (i.e., NH₂-CH₂-).

"Hydroxyalkyl" refers a hydroxy group attached through an alkyl bridge. An example of a hydroxyalkyl is hydroxyethyl, (i.e., HO-CH₂CH₂-).

The term "substituted" refers to a molecule wherein at least one hydrogen atom is replaced with a substituent. When substituted, one or more of the groups are "substituents." The molecule may be multiply substituted. In the case of an oxo substituent ("=O"), two hydrogen atoms are replaced. Example substituents within this context may include halogen, hydroxy, alkyl, alkoxy, nitro, cyano, oxo, carbocyclyl, carbocycloalkyl, heterocarbocyclyl, heterocarbocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, -NRaRb, -NRaC(=O)Rb, -NRaC(=O)NRaNRb, -NRaC(=O)ORb, -NRaSO₂Rb, -C(=O)Ra, -C(=O)ORa, -C(=O)NRaRb, -OC(=O)NRaRb, -ORa, -SRa, -SORa, -S(=O)₂Ra, -OS(=O)₂Ra and -S(=O)₂ORa. Ra and Rb in this context may be the same or different and independently hydrogen, halogen hydroxyl, alkyl,

alkoxy, alkyl, amino, alkylamino, dialkylamino, carbocyclyl, carbocycloalkyl, heterocarbocyclyl, heterocarbocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl.

The term "optionally substituted," as used herein, means that substitution is optional and therefore it is possible for the designated atom to be unsubstituted.

5 As used herein, "salts" refer to derivatives of the disclosed compounds where the parent compound is modified making acid or base salts thereof. Examples of salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines, alkylamines, or dialkylamines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. In typical embodiments, the salts are conventional nontoxic pharmaceutically acceptable salts
10 including the quaternary ammonium salts of the parent compound formed, and non-toxic inorganic or organic acids. Preferred salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pantoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic,
15 salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

"Subject" refers any animal, preferably a human patient, livestock, rodent, monkey or domestic pet.

The term "prodrug" refers to an agent that is converted into a biologically active form in
20 vivo. Prodrugs are often useful because, in some situations, they may be easier to administer than the parent compound. They may, for instance, be bioavailable by oral administration whereas the parent compound is not. The prodrug may also have improved solubility in pharmaceutical compositions over the parent drug. A prodrug may be converted into the parent drug by various mechanisms, including enzymatic processes and metabolic hydrolysis.

25 As used herein, the term "derivative" refers to a structurally similar compound that retains sufficient functional attributes of the identified analogue. The derivative may be structurally similar because it is lacking one or more atoms, substituted with one or more substituents, a salt, in different hydration/oxidation states, e.g., substituting a single or double bond, substituting a hydroxy group for a ketone, or because one or more atoms within the
30 molecule are switched, such as, but not limited to, replacing an oxygen atom with a sulfur or nitrogen atom or replacing an amino group with a hydroxyl group or vice versa. Replacing a

carbon with nitrogen in an aromatic ring is a contemplated derivative. The derivative may be a prodrug. Derivatives may be prepared by any variety of synthetic methods or appropriate adaptations presented in the chemical literature or as in synthetic or organic chemistry text books, such as those provide in March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Wiley, 6th Edition (2007) Michael B. Smith or Domino Reactions in Organic Synthesis, Wiley (2006) Lutz F. Tietze hereby incorporated by reference.

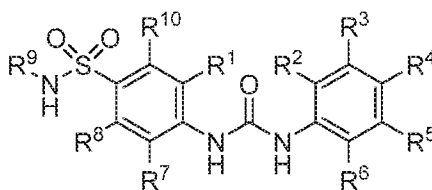
As used herein, the terms "prevent" and "preventing" include the prevention of the recurrence, spread or onset. It is not intended that the present disclosure be limited to complete prevention. In some embodiments, the onset is delayed, or the severity of the disease is reduced.

As used herein, the terms "treat" and "treating" are not limited to the case where the subject (e.g., patient) is cured and the disease is eradicated. Rather, embodiments, of the present disclosure also contemplate treatment that merely reduces symptoms, and/or delays disease progression.

As used herein, the term "combination with" when used to describe administration with an additional treatment means that the agent may be administered prior to, together with, or after the additional treatment, or a combination thereof. Active ingredients may be in separate medicinal compositions (pills, tablets, etc.) or as a single pharmaceutical formulation containing a combination of the active ingredients.

Phenylureidobenzenesulfonamide Derivatives

In certain embodiments, the disclosure contemplates phenylureidobenzenesulfonamide derivatives of Formula I for any of the uses reported herein. Compounds of Formula I may be:



Formula I

or prodrugs, derivatives, or salts thereof wherein,

R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , and R^{10} are each, individually and independently, hydrogen, alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl,

alkoxy, hydroxyalkyl, alkylthio, thioalkyl, alkylamino, aminoalkyl, (alkyl)₂amino, alkanoyl, alkoxy carbonyl, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, and R¹⁰ are optionally substituted with one or more, the same or different, R²⁰;

5 R²⁰ is alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, hydroxyalkyl, alkylthio, thioalkyl, alkylamino, aminoalkyl, (alkyl)₂amino, alkanoyl, alkoxy carbonyl, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein R²⁰ is optionally substituted with one or more, the same or different, R²¹; and

10 R²¹ is halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, isopropoxy, tert-butoxy, hydroxymethyl, hydroxyethyl, thiomethyl, thioethyl, aminomethyl, aminoethyl, acetyl, acetoxymethyl, methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, acetylamino, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-N-ethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl, methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, tert-butoxycarbonyl, N-methylsulfamoyl, N-ethylsulfamoyl, N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N-methyl-N-ethylsulfamoyl, carbocyclyl, aryl, or heterocyclyl.

In certain embodiments, R³ is isopropyl or isopropoxy.

20 In certain embodiments, R³ is halogen and R⁴ is halogen or alkyl

In certain embodiments, R³ is chloro and R⁴ is halogen.

In certain embodiments, R³ is chloro and R⁴ is alkyl.

In certain embodiments, R³ and R⁴ come together with the attached phenyl group to form an aryl, or heterocyclyl bicyclic ring.

25 In certain embodiments, R³ and R⁴ come together with the phenyl group to form naphthalenyl.

In certain embodiments, R⁹ is hydrogen.

In certain embodiments, R¹, R⁷, R⁸, and R¹⁰ are hydrogen.

In certain embodiments, R², R⁵, and R⁶ are hydrogen.

30 In certain embodiments, R⁵, and R⁶ are hydrogen.

In certain embodiments, R² and R⁶ are hydrogen.

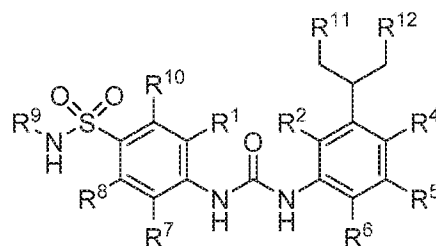
In certain embodiments, R^2 and R^5 are hydrogen.

In certain embodiments, R^2 is hydrogen.

In certain embodiments, R^5 is hydrogen.

In certain embodiments, R^6 is hydrogen.

5 In certain embodiments, compounds of Formula I have Formula IA:



Formula IA

or prodrugs, derivatives, or salts thereof wherein,

10 R^1 , R^2 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , and R^{10} are each, individually and independently, hydrogen, alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, hydroxyalkyl, alkylthio, thioalkyl, alkylamino, aminoalkyl, (alkyl)₂amino, alkanoyl, alkoxycarbonyl, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein R^1 , R^2 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , and R^{10} are optionally substituted with one or more, the same or different, R^{20} ;

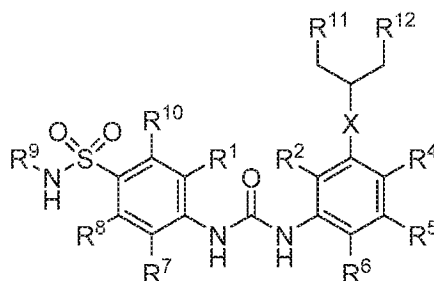
15 R^{11} and R^{12} are each, individually and independently, hydrogen, alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, hydroxyalkyl, alkylthio, thioalkyl, alkylamino, aminoalkyl, (alkyl)₂amino, alkanoyl, alkoxycarbonyl, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein R^{11} and R^{12} are optionally substituted with one or more, the same or different, R^{20} ;

20 R^{20} is alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, hydroxyalkyl, alkylthio, thioalkyl, alkylamino, aminoalkyl, (alkyl)₂amino, alkanoyl, alkoxycarbonyl, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein R^{20} is optionally substituted with one or more, the same or different, R^{21} ; and

25 R^{21} is halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, isopropoxy, tert-butoxy, hydroxymethyl, hydroxyethyl, thiomethyl, thioethyl, aminomethyl, aminoethyl, acetyl,

acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, acetylamino, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-N-ethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl, methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, tert-butoxycarbonyl, N-methylsulfamoyl, N-ethylsulfamoyl, N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N-methyl-N-ethylsulfamoyl, carbocyclyl, aryl, or heterocyclyl.

In certain embodiments, compounds of Formula I have Formula IB:



Formula IB

or prodrugs, derivatives, or salts thereof wherein,

X is O, S, CH₂, or NH;

R¹, R², R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, and R¹⁰ are each, individually and independently, hydrogen, alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, hydroxyalkyl, alkylthio, thioalkyl, alkylamino, aminoalkyl, (alkyl)₂amino, alkanoyl, alkoxycarbonyl, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein R¹, R², R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, and R¹⁰ are optionally substituted with one or more, the same or different, R²⁰;

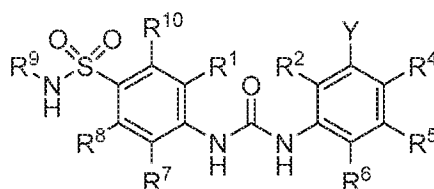
R¹¹ and R¹² are each, individually and independently, hydrogen, alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, hydroxyalkyl, alkylthio, thioalkyl, alkylamino, aminoalkyl, (alkyl)₂amino, alkanoyl, alkoxycarbonyl, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein R¹¹ and R¹² are optionally substituted with one or more, the same or different, R²⁰;

R²⁰ is alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, hydroxyalkyl, alkylthio, thioalkyl, alkylamino, aminoalkyl, (alkyl)₂amino, alkanoyl, alkoxycarbonyl, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or

heterocyclyl, wherein R^{20} is optionally substituted with one or more, the same or different, R^{21} ; and

R^{21} is halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, isopropoxy, tert-butoxy, hydroxymethyl, hydroxyethyl, thiomethyl, thioethyl, aminomethyl, aminoethyl, acetyl, acetoxymethyl, methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, acetylamino, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-N-ethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl, methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, tert-butoxycarbonyl, N-methylsulfamoyl, N-ethylsulfamoyl, N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N-methyl-N-ethylsulfamoyl, carbocyclyl, aryl, or heterocyclyl.

In certain embodiments, compounds of Formula I have Formula IC:



Formula IC

or prodrugs, derivatives, or salts thereof wherein,

Y is halogen such as chloro;

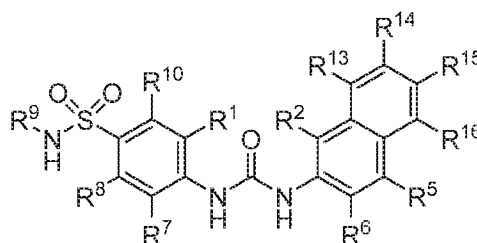
R^1 , R^2 , R^5 , R^6 , R^7 , R^8 , R^9 , and R^{10} are each, individually and independently, hydrogen, alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, hydroxyalkyl, alkylthio, thioalkyl, alkylamino, aminoalkyl, (alkyl)₂amino, alkanoyl, alkoxycarbonyl, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein R^1 , R^2 , R^5 , R^6 , R^7 , R^8 , R^9 , and R^{10} are optionally substituted with one or more, the same or different, R^{20} ;

R^4 is halogen or alkyl optionally substituted with one or more, the same or different, R^{20} ;

R^{20} is alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, hydroxyalkyl, alkylthio, thioalkyl, alkylamino, aminoalkyl, (alkyl)₂amino, alkanoyl, alkoxycarbonyl, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein R^{20} is optionally substituted with one or more, the same or different, R^{21} ; and

R²¹ is halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, isopropoxy, tert-butoxy, hydroxymethyl, hydroxyethyl, thiomethyl, thioethyl, aminomethyl, aminoethyl, acetyl, acetoxymethyl, methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, acetylaminomethyl, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-N-ethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl, methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, tert-butoxycarbonyl, N-methylsulfamoyl, N-ethylsulfamoyl, N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N-methyl-N-ethylsulfamoyl, carbocyclyl, aryl, or heterocyclyl.

In certain embodiments, compounds of Formula I have Formula ID:



Formula ID

or prodrugs, derivatives, or salts thereof wherein,

R¹, R², R⁵, R⁶, R⁷, R⁸, R⁹, and R¹⁰ are each, individually and independently, hydrogen, alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, hydroxyalkyl, alkylthio, thioalkyl, alkylamino, aminoalkyl, (alkyl)₂amino, alkanoyl, alkoxycarbonyl, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein R¹, R², R⁵, R⁶, R⁷, R⁸, R⁹, and R¹⁰ are optionally substituted with one or more, the same or different, R²⁰;

R¹³, R¹⁴, R¹⁵, and R¹⁶ are each, individually and independently, hydrogen, alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, hydroxyalkyl, alkylthio, thioalkyl, alkylamino, aminoalkyl, (alkyl)₂amino, alkanoyl, alkoxycarbonyl, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein R¹³, R¹⁴, R¹⁵, and R¹⁶ are optionally substituted with one or more, the same or different, R²⁰;

R²⁰ is alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, hydroxyalkyl, alkylthio, thioalkyl, alkylamino, aminoalkyl, (alkyl)₂amino, alkanoyl, alkoxycarbonyl, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or

heterocyclyl, wherein R²⁰ is optionally substituted with one or more, the same or different, R²¹; and

R²¹ is halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, isopropoxy, tert-butoxy, hydroxymethyl, hydroxyethyl, thiomethyl, thioethyl, aminomethyl, aminoethyl, acetyl, acetoxymethyl, methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, acetylamino, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-N-ethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl, methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, tert-butoxycarbonyl, N-methylsulfamoyl, N-ethylsulfamoyl, N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N-methyl-N-ethylsulfamoyl, carbocyclyl, aryl, or heterocyclyl.

Methods of Use

In certain embodiments, the disclosure relates to methods of treating or preventing conditions associated with carbonic anhydrase inhibition such as obesity, glaucoma, ocular hypertension, cancer, altitude sickness, or neurological disorders such as epilepsy, Lennox-Gastaut syndrome, and migraine headaches by administering compounds disclosed herein to a subject in need thereof. In certain embodiments, the disclosure relates to methods of increasing urinary excretion comprising administering an effective amount of a compound disclosed herein to a subject in need thereof, e.g., wherein the subject is diagnosed with, at risk of, or exhibiting symptoms of heart failure, liver cirrhosis, hypertension, water poisoning, or kidney disease.

In certain embodiments, the disclosure relates to methods of treating or preventing obesity comprising administering an effective amount of a compound disclosed herein to a subject in need thereof. In certain embodiments, the compound is administered in combination with another therapeutic/anti-obesity medication such as phentermine, orlistat, lorcaserin, phendimetrazine, bupropion, naltrexone, methamphetamine, benzphetamine, sibutramine, topiramate, orlistat, diethylpropion, chorionic gonadotropin (hcg), or combinations thereof.

In certain embodiments, the disclosure relates to methods of treating or preventing glaucoma comprising administering an effective amount of a compound disclosed herein to a subject in need thereof. In certain embodiments, the compound is administered in combination with another therapeutic/anti-glaucoma medication such as prostaglandin analogs, latanoprost,

bimatoprost, travoprost, beta blockers, timolol, alpha agonists, brimonidine, apraclonidine, carbonic anhydrase inhibitors, dorzolamide, brinzolamide, acetazolamide, methazolamide, or combinations thereof.

5 In certain embodiments, the disclosure relates to methods of treating or preventing ocular hypertension comprising administering an effective amount of a compound disclosed herein to a subject in need thereof. In certain embodiments, the compound is administered in combination with another therapeutic/anti-hypertension agent such as latanoprost, bimatoprost, brimonidine, timolol.

10 In certain embodiments, the disclosure relates to methods of treating or preventing epilepsy comprising administering an effective amount of a compound disclosed herein to a subject in need thereof. In certain embodiments, the compound is administered in combination with another therapeutic/anti-epilepsy medication such as acetazolamide, carbamazepine, clobazam, clonazepam, eslicarbazepine, ethosuximide, gabapentin, lacosamide, lamotrigine, levetiracetam, nitrazepam, oxcarbazepine, perampanel, piracetam, phenobarbital, phenytoin, 15 pregabalin, primidone, retigabine, rufinamide, valproate, stiripentol, tiagabine, topiramate, vigabatrin, zonisamide, or combinations thereof.

In certain embodiments, the disclosure relates to methods of treating or preventing altitude sickness comprising administering an effective amount of a compound disclosed herein to a subject in need thereof. In certain embodiments, the compound is administered in 20 combination with another therapeutic/anti-altitude sickness medication such as acetazolamide.

In certain embodiments, the disclosure relates to methods of increasing urinary excretion comprising administering an effective amount of a compound disclosed herein to a subject in need thereof. In certain embodiments, the subject is in need thereof as the subject is diagnosed with, at risk of, or exhibiting symptoms of heart failure, liver cirrhosis, hypertension, water 25 poisoning, or kidney disease.

In certain embodiments, the disclosure relates to methods of treating or preventing cancer comprising administering an effective amount of a compound disclosed herein to a subject in need thereof. In certain embodiments, the cancer is selected from glioblastoma (GBM), breast, pancreatic, colon, metastatic lung cancers, bladder cancer, lung cancer, breast cancer, melanoma, 30 colon and rectal cancer, non-Hodgkin lymphoma, endometrial cancer, pancreatic cancer, kidney cancer, prostate cancer, leukemia, thyroid cancer, and brain cancer.

In certain embodiments, the compositions is administered in combination with a second anti-cancer agent such as temozolomide, bevacizumab, procarbazine, lomustine, vincristine, gefitinib, erlotinib, docetaxel, cisplatin, 5-fluorouracil, gemcitabine, tegafur, raltitrexed, methotrexate, cytosine arabinoside, hydroxyurea, adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin, mithramycin, vinblastine, vindesine, vinorelbine, taxol, docetaxel, etoposide, teniposide, amsacrine, topotecan, camptothecin, bortezomib, anagrelide, tamoxifen, toremifene, raloxifene, droloxifene, iodoxyfene, fulvestrant, bicalutamide, flutamide, nilutamide, cyproterone, goserelin, leuporelin, buserelin, megestrol, anastrozole, letrozole, vorozole, exemestane, finasteride, marimastat, trastuzumab, cetuximab, dasatinib, imatinib, combretastatin, thalidomide, and/or lenalidomide or combinations thereof.

Formulations

Pharmaceutical compositions disclosed herein may be in the form of pharmaceutically acceptable salts, as generally described below. Some preferred, but non-limiting examples of suitable pharmaceutically acceptable organic and/or inorganic acids are hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, acetic acid and citric acid, as well as other pharmaceutically acceptable acids known per se (for which reference is made to the references referred to below).

When the compounds of the disclosure contain an acidic group as well as a basic group, the compounds of the disclosure may also form internal salts, and such compounds are within the scope of the disclosure. When a compound of the disclosure contains a hydrogen-donating heteroatom (e.g., NH), the disclosure also covers salts and/or isomers formed by the transfer of the hydrogen atom to a basic group or atom within the molecule.

Pharmaceutically acceptable salts of the compounds include the acid addition and base salts thereof. Suitable acid addition salts are formed from acids which form non-toxic salts. Examples include the acetate, adipate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulphate/sulphate, borate, camsylate, citrate, cyclamate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, maleate, malonate, mesylate, methylsulphate, naphthylate, 2-napsylate, nicotinate, nitrate, orotate, oxalate,

palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, pyroglutamate, saccharate, stearate, succinate, tannate, tartrate, tosylate, trifluoroacetate and xinofoate salts. Suitable base salts are formed from bases which form non-toxic salts. Examples include the aluminium, arginine, benzathine, calcium, choline, diethylamine, diolamine, glycine, lysine, 5 magnesium, meglumine, olamine, potassium, sodium, tromethamine and zinc salts. Hemisalts of acids and bases may also be formed, for example, hemisulphate and hemicalcium salts. For a review on suitable salts, see Handbook of Pharmaceutical Salts: Properties, Selection, and Use by Stahl and Wermuth (Wiley-VCH, 2002), incorporated herein by reference.

The compounds described herein may be administered in the form of prodrugs. A 10 prodrug can include a covalently bonded carrier which releases the active parent drug when administered to a mammalian subject. Prodrugs can be prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved, either in routine manipulation or in vivo, to the parent compounds. Prodrugs include, for example, compounds wherein a hydroxyl group is bonded to any group that, when administered to a mammalian 15 subject, cleaves to form a free hydroxyl group. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol functional groups in the compounds. Methods of structuring a compound as prodrugs can be found in the book of Testa and Mayer, Hydrolysis in Drug and Prodrug Metabolism, Wiley (2006). Typical prodrugs form the active metabolite by transformation of the prodrug by hydrolytic enzymes, the hydrolysis of 20 amide, lactams, peptides, carboxylic acid esters, epoxides or the cleavage of esters of inorganic acids. It is well within the ordinary skill of the art to make an ester prodrug, e.g., acetyl ester or alkanoyl ester of a free hydroxyl group. It is well known that ester prodrugs are readily degraded in the body to release the corresponding alcohol. See e.g., Imai, Drug Metab Pharmacokinet. (2006) 21(3):173-85, entitled "Human carboxylesterase isozymes: catalytic properties and 25 rational drug design."

Pharmaceutical compositions for use in the present disclosure typically comprise an effective amount of a compound and a suitable pharmaceutical acceptable carrier. The preparations may be prepared in a manner known per se, which usually involves mixing the at least one compound according to the disclosure with the one or more pharmaceutically 30 acceptable carriers, and, if desired, in combination with other pharmaceutical active compounds, when necessary under aseptic conditions. Reference is made to U.S. Pat. No. 6,372,778, U.S.

Pat. No. 6,369,086, U.S. Pat. No. 6,369,087 and U.S. Pat. No. 6,372,733 and the further references mentioned above, as well as to the standard handbooks, such as the latest edition of Remington's Pharmaceutical Sciences.

Generally, for pharmaceutical use, the compounds may be formulated as a pharmaceutical preparation comprising at least one compound and at least one pharmaceutically acceptable carrier, diluent or excipient, and optionally one or more further pharmaceutically active compounds.

The pharmaceutical preparations of the disclosure are preferably in a unit dosage form, and may be suitably packaged, for example in a box, blister, vial, bottle, sachet, ampoule or in any other suitable single-dose or multi-dose holder or container (which may be properly labeled); optionally with one or more leaflets containing product information and/or instructions for use. Generally, such unit dosages will contain between 1 and 1000 mg, and usually between 5 and 500 mg, of the at least one compound of the disclosure, e.g., about 10, 25, 50, 100, 200, 300 or 400 mg per unit dosage.

The compounds can be administered by a variety of routes including the oral, ocular, rectal, transdermal, subcutaneous, intravenous, intramuscular or intranasal routes, depending mainly on the specific preparation used. The compound will generally be administered in an "effective amount", by which is meant any amount of a compound that, upon suitable administration, is sufficient to achieve the desired therapeutic or prophylactic effect in the subject to which it is administered. Usually, depending on the condition to be prevented or treated and the route of administration, such an effective amount will usually be between 0.01 to 1000 mg per kilogram body weight of the patient per day, more often between 0.1 and 500 mg, such as between 1 and 250 mg, for example about 5, 10, 20, 50, 100, 150, 200 or 250 mg, per kilogram body weight of the patient per day, which may be administered as a single daily dose, divided over one or more daily doses. The amount(s) to be administered, the route of administration and the further treatment regimen may be determined by the treating clinician, depending on factors such as the age, gender and general condition of the patient and the nature and severity of the disease/symptoms to be treated. Reference is made to U.S. Pat. No. 6,372,778, U.S. Pat. No. 6,369,086, U.S. Pat. No. 6,369,087 and U.S. Pat. No. 6,372,733 and the further references mentioned above, as well as to the standard handbooks, such as the latest edition of Remington's Pharmaceutical Sciences.

For an oral administration form, the compound can be mixed with suitable additives, such as excipients, stabilizers or inert diluents, and brought by means of the customary methods into the suitable administration forms, such as tablets, coated tablets, hard capsules, aqueous, alcoholic, or oily solutions. Examples of suitable inert carriers are gum arabic, magnesia, magnesium carbonate, potassium phosphate, lactose, glucose, or starch, in particular, corn starch. In this case, the preparation can be carried out both as dry and as moist granules. Suitable oily excipients or solvents are vegetable or animal oils, such as sunflower oil or cod liver oil. Suitable solvents for aqueous or alcoholic solutions are water, ethanol, sugar solutions, or mixtures thereof. Polyethylene glycols and polypropylene glycols are also useful as further auxiliaries for other administration forms. As immediate release tablets, these compositions may contain microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants known in the art.

When administered by nasal aerosol or inhalation, the compositions may be prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art. Suitable pharmaceutical formulations for administration in the form of aerosols or sprays are, for example, solutions, suspensions or emulsions of the compounds of the disclosure or their physiologically tolerable salts in a pharmaceutically acceptable solvent, such as ethanol or water, or a mixture of such solvents. If required, the formulation may additionally contain other pharmaceutical auxiliaries such as surfactants, emulsifiers and stabilizers as well as a propellant.

For subcutaneous or intravenous administration, the compounds, if desired with the substances customary therefore such as solubilizers, emulsifiers or further auxiliaries are brought into solution, suspension, or emulsion. The compounds may also be lyophilized and the lyophilizates obtained used, for example, for the production of injection or infusion preparations. Suitable solvents are, for example, water, physiological saline solution or alcohols, e.g. ethanol, propanol, glycerol, sugar solutions such as glucose or mannitol solutions, or mixtures of the various solvents mentioned. The injectable solutions or suspensions may be formulated according to known art, using suitable non-toxic, parenterally-acceptable diluents or solvents,

such as mannitol, 1,3-butanediol, water, Ringer's solution or isotonic sodium chloride solution, or suitable dispersing or wetting and suspending agents, such as sterile, bland, fixed oils, including synthetic mono- or diglycerides, and fatty acids, including oleic acid.

When rectally administered in the form of suppositories, the formulations may be prepared by mixing the compounds of formula I with a suitable non-irritating excipient, such as cocoa butter, synthetic glyceride esters or polyethylene glycols, which are solid at ordinary temperatures, but liquefy and/or dissolve in the rectal cavity to release the drug.

In certain embodiments, it is contemplated that these compositions can be extended release formulations. Typical extended release formations utilize an enteric coating. Typically, a barrier is applied to oral medication that controls the location in the digestive system where it is absorbed. Enteric coatings prevent release of medication before it reaches the small intestine. Enteric coatings may contain polymers of polysaccharides, such as maltodextrin, xanthan, scleroglucan dextran, starch, alginates, pullulan, hyaluronic acid, chitin, chitosan and the like; other natural polymers, such as proteins (albumin, gelatin etc.), poly-L-lysine; sodium poly(acrylic acid); poly(hydroxyalkylmethacrylates) (for example poly(hydroxyethyl methacrylate)); carboxypolymethylene (for example Carbopol™); carbomer; polyvinyl pyrrolidone; gums, such as guar gum, gum arabic, gum karaya, gum ghatti, locust bean gum, tamarind gum, gellan gum, gum tragacanth, agar, pectin, gluten and the like; poly(vinyl alcohol); ethylene vinyl alcohol; polyethylene glycol (PEG); and cellulose ethers, such as hydroxymethyl cellulose (HMC), hydroxyethylcellulose (HEC), hydroxypropylcellulose (HPC), methylcellulose (MC), ethylcellulose (EC), carboxyethylcellulose (CEC), ethylhydroxy ethylcellulose (EHEC), carboxymethylhydroxyethylcellulose (CMHEC), hydroxypropylmethyl-cellulose (HPMC), hydroxypropylethylcellulose (HPEC) and sodium carboxymethylcellulose (Na CMC); as well as copolymers and/or (simple) mixtures of any of the above polymers.

Certain of the above-mentioned polymers may further be crosslinked by way of standard techniques. The choice of polymer will be determined by the nature of the active ingredient/drug that is employed in the composition of the disclosure as well as the desired rate of release. In particular, it will be appreciated by the skilled person, for example in the case of HPMC, that a higher molecular weight will, in general, provide a slower rate of release of drug from the composition. Furthermore, in the case of HPMC, different degrees of substitution of methoxyl groups and hydroxypropoxyl groups will give rise to changes in the rate of release of drug from

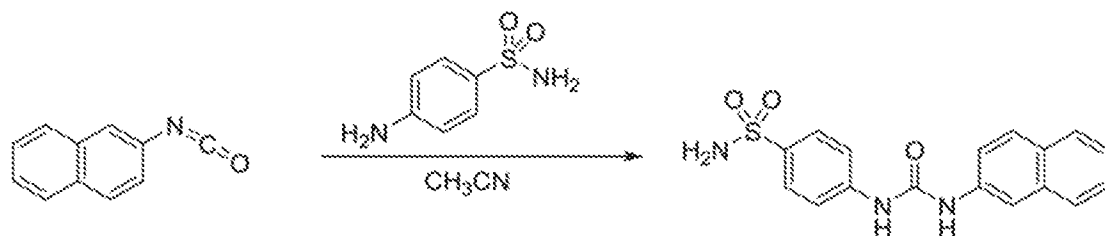
the composition. In this respect, and as stated above, it may be desirable to provide compositions of the disclosure in the form of coatings in which the polymer carrier is provided by way of a blend of two or more polymers of, for example, different molecular weights in order to produce a particular required or desired release profile.

Microspheres of polylactide, polyglycolide, and their copolymers poly(lactide-co-glycolide) may be used to form sustained-release protein delivery systems. Proteins can be entrapped in the poly(lactide-co-glycolide) microsphere depot by a number of methods, including formation of a water-in-oil emulsion with water-borne protein and organic solvent-borne polymer (emulsion method), formation of a solid-in-oil suspension with solid protein dispersed in a solvent-based polymer solution (suspension method), or by dissolving the protein in a solvent-based polymer solution (dissolution method). One can attach poly(ethylene glycol) to proteins (PEGylation) to increase the in vivo half-life of circulating therapeutic proteins and decrease the chance of an immune response.

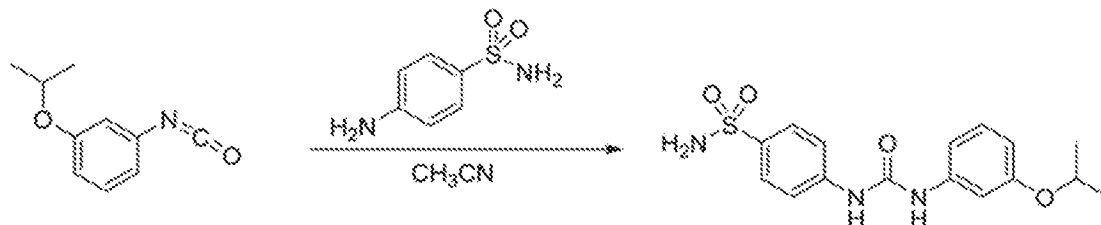
EXPERIMENTAL

Compound synthesis

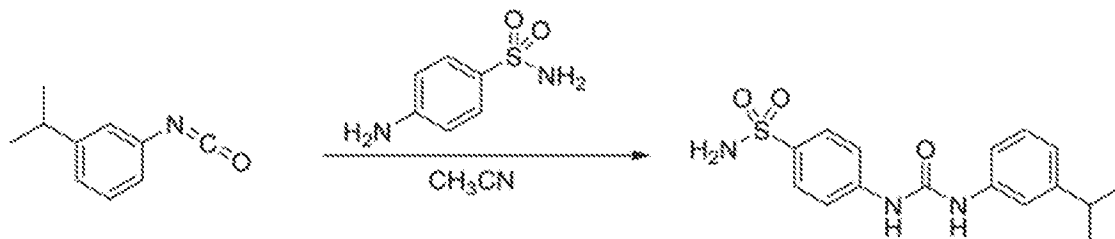
4-(3-(naphthalen-2-yl)ureido)benzenesulfonamide



4-aminobenzenesulfonamide (0.5 g, 2.90 mmol) was dissolved in CH₃CN (25 mL) and 2-isocyanatonaphthalene (0.49 g, 2.9 mmol) was added. The reaction was stirred at r.t. for 19 hours and then the precipitate was filtered off. The precipitate was washed with diethyl ether (100 mL) and dried in vacuo to afford 4-(3-(naphthalen-2-yl)ureido)benzenesulfonamide (282 mg, 28% yield, white solid). ¹H NMR (400 MHz, D₆DMSO) δ 9.16 (s, 1H), 9.03 (s, 1H), 8.13 (s, 1H), 7.87-7.80 (m, 3H), 7.75 (d, *J* = 8.8 Hz, 2H), 7.66 (d, *J* = 8.8 Hz, 2H), 7.51-7.44 (m, 2H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.23 (s, 2H). ¹³C NMR (100 MHz, D₆DMSO) δ 152.4, 142.8, 137.0, 136.9, 133.7, 129.3, 128.5, 127.5, 127.1, 126.9, 126.4, 124.2, 119.7, 117.5, 113.8, 109.8. HRMS (EI⁺) *m/z* calculated for C₁₇H₁₆N₃O₃S [M+H]⁺: 342.0907, found: 342.09154.

4-(3-(3-isopropoxyphenyl)ureido)benzenesulfonamide

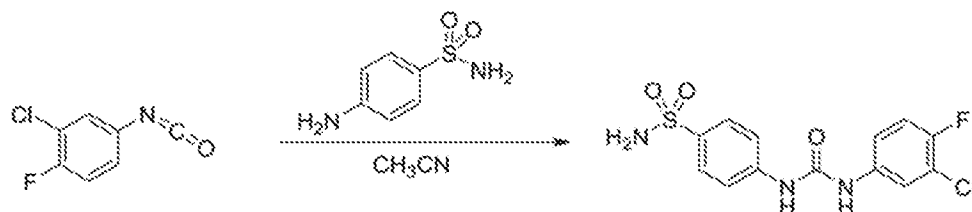
Triphosgene (0.45 g, 1.52 mmol) and sat. aq. NaHCO₃ (20 mL) were added to a stirred solution of 3-isopropoxyaniline (0.674 mL, 4.57 mmol) in DCM (20 mL) at 0 °C. The reaction was warmed to r.t. and stirred for 2 hours. Water (20 mL) was then added. The aqueous layer was extracted with Et₂O (3x 50 mL) and the organics were dried over MgSO₄. The organics were filtered and concentrated and the material was used in the next step without further purification (0.7759 g, >95% yield). 4-aminobenzenesulfonamide (0.716 g, 4.16 mmol) was added to a solution of CH₃CN (36 mL) and 5-isocyanato-2,3-dihydro-1H-indene (0.7366 mL, 4.16 mmol) was added. The reaction was stirred at r.t. overnight and then the precipitate was filtered off. The precipitate was washed with diethyl ether (100 mL) and dried in vacuo to afford the desired compound (97.1 mg, 7% yield, white solid). ¹H NMR (400 MHz, D₆DMSO) δ 9.06 (s, 1H), 8.77 (s, 1H), 7.74 (d, *J* = 8.8, 2H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.23 (s, 2H), 7.18-7.14 (m, 2H), 6.90 (d, *J* = 8.0 Hz, 1H), 6.55 (d, *J* = 8.0 Hz, 1H), 4.57-4.50 (m, 1H), 1.27 (d, *J* = 6.0 Hz, 6H). ¹³C NMR (100 MHz, D₆DMSO) δ 157.9, 152.2, 142.9, 140.6, 136.9, 129.6, 126.9, 117.5, 110.5, 109.4, 105.8, 69.1, 21.9. HRMS (EI⁺) *m/z* calculated for C₃₂H₃₉N₆O₈S₂ [M+H+M]⁺: 699.2265, found: 699.22870.

4-(3-(3-isopropylphenyl)ureido)benzenesulfonamide

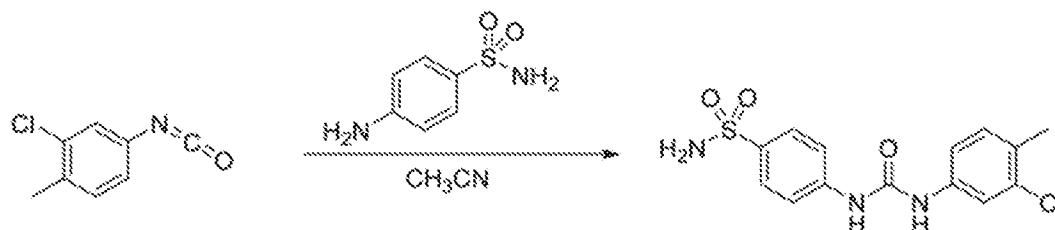
Triphosgene (0.45 g, 1.52 mmol) and sat. aq. NaHCO₃ (20 mL) were added to a stirred solution of 3-isopropylaniline (0.64 mL, 4.57 mmol) in DCM (20 mL) at 0 °C. The reaction was warmed to r.t. and stirred for 2 hours. Water (20 mL) was added then added and the aqueous

layer was extracted with Et₂O (3x 50 mL) and the organics were dried over MgSO₄. The organics were filtered, concentrated and used in the next step without further purification. 4-aminobenzenesulfonamide (0.716 g, 4.16 mmol) was added to a solution of CH₃CN (36 mL) and 5-isocyanato-2,3-dihydro-1H-indene (0.6516 mL, 4.16 mmol) was added. The reaction was stirred at r.t. overnight and then the precipitate was filtered off. The resulting solid was dried in vacuo to afford the desired compound (0.365 g, 27% yield, white solid). ¹H NMR (400 MHz, D₆DMSO) δ 9.03(s, 1H), 8.74 (s, 1H), 7.72 (d, *J* = 8.8 Hz, 2H), 7.61 (d, *J* = 9.2 Hz, 2H), 7.37 (t, *J* = 2.0 Hz, 1H), 7.26-7.18 (m, 4H), 6.88 (d, *J* = 7.2 Hz, 1H), 2.90-2.80 (m, 1H), 1.20 (d, *J* = 6.8 Hz, 6H). ¹³C NMR (100 MHz, D₆DMSO) δ 152.7, 149.5, 143.3, 139.7, 137.2, 129.2, 127.2, 120.7, 117.8, 116.8, 116.4, 33.9, 24.3. HRMS (EI+) *m/z* calculated for C₃₂H₃₉N₆O₆S₂ [M+H+M]⁺: 667.2367, found: 667.24086.

4-(3-(3-chloro-4-fluorophenyl)ureido)benzenesulfonamide



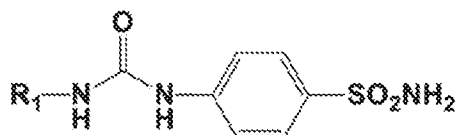
Solid 4-aminobenzenesulfonamide (0.5 g, 2.90 mmol) was dissolved in acetonitrile (25 ml) to give a colorless solution. 2-chloro-1-fluoro-4-isocyanatobenzene (0.362 ml, 2.90 mmol) was drop-wise added with stirring before the solution was heated to 50 °C and allowed to stir for 96 hours. A white precipitate formed, and the mixture was filtered through a fritted funnel. The white solid was washed with diethyl ether before being dried *in vacuo* to afford the desired compound (647 mg, 65% yield, white solid). ¹H NMR (400 MHz, D₆DMSO) δ 9.16 (s, 1H), 9.00 (s, 1H), 7.81 (dd, *J* = 2.4, 7.2 Hz, 1H), 7.74 (d, *J* = 8.8 Hz, 2H), 7.61 (d, *J* = 8.8 Hz, 2H), 7.35-7.30 (m, 2H), 7.22 (s, 2H). ¹³C NMR (100 MHz, D₆DMSO) δ 152.3, 142.6, 137.1, 126.8, 119.8, 118.9, 118.8, 117.7, 117.1, 109.9. HRMS (EI+) *m/z* calculated for C₁₃H₁₁ClFN₃O₃S [M+Na]⁺: 366.0094, found: 366.0079.

4-(3-(3-chloro-4-methylphenyl)ureido)benzenesulfonamide

Solid 4-aminobenzenesulfonamide (0.5 g, 2.90 mmol) was dissolved in acetonitrile (25 ml) to give a colorless solution. 2-chloro-4-isocyanato-1-methylbenzene (0.398 ml, 2.90 mmol) was drop-wise added with stirring before the solution was heated to 50 °C. After ~1.5 hours, a white precipitate formed. The white precipitate was filtered with a fritted funnel, washed with diethyl ether, and dried in vacuo to afford the desired product (103 mg, 10% yield, white solid). ¹H NMR (400 MHz, D₆DMSO) δ 9.10 (s, 1H), 8.89 (s, 1H), 7.73 (d, *J* = 8.4 Hz, 2H), 7.69 (s, 1H), 7.60 (d, *J* = 8.4 Hz, 2H), 7.26-7.19 (m, 4H), 2.26 (s, 3H). ¹³C NMR (100 MHz, D₆DMSO) δ 152.3, 142.7, 138.5, 137.0, 133.2, 131.3, 128.8, 126.9, 118.4, 117.7, 117.3, 18.9. HRMS (EI⁺) *m/z* calculated for C₁₄H₁₄ClN₃O₃S [M+Na]⁺: 362.0344, found: 362.0338.

CA II Assay

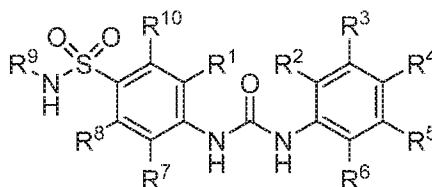
Compounds (>95% pure) were subjected to the CA II potency assay described Pacchiano et al., Chem. Commun, 2010, 46, 8371–8373 and Pacchiano et al., J. Med. Chem. 2011, 54, 1896–1902. The K_i values for the inhibitors in Table 1 are less than 10 nM, with two entries less than 1 nM (Table 1). The K_i for the most potent molecule 9 (0.3 nM) is the lowest among agents for this scaffold (n is 5).



Compd	R ₁ Moiety	K _i , nM
7	2-naphthalenyl	2.6
8	3-isopropoxyphenyl	3.9
9	3-isopropylphenyl	0.3
10	3-chloro-4-fluorophenyl	2.7
11	3-chloro-4-methylphenyl	0.77

CLAIMS

1. A compound having formula I:



Formula I

or prodrugs, derivatives, or salts thereof wherein,

R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , and R^{10} are each, individually and independently, hydrogen, alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, hydroxyalkyl, alkylthio, thioalkyl, alkylamino, aminoalkyl, (alkyl)₂amino, alkanoyl, alkoxycarbonyl, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , and R^{10} are optionally substituted with one or more, the same or different, R^{20} ;

R^{20} is alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, hydroxyalkyl, alkylthio, thioalkyl, alkylamino, aminoalkyl, (alkyl)₂amino, alkanoyl, alkoxycarbonyl, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein R^{20} is optionally substituted with one or more, the same or different, R^{21} ; and

R^{21} is halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, isopropoxy, tert-butoxy, hydroxymethyl, hydroxyethyl, thiomethyl, thioethyl, aminomethyl, aminoethyl, acetyl, acetoxymethyl, methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, acetylamino, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-N-ethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl, methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, tert-butoxycarbonyl, N-methylsulfamoyl, N-ethylsulfamoyl, N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N-methyl-N-ethylsulfamoyl, carbocyclyl, aryl, or heterocyclyl.

2. The compound of Claim 1, wherein R^3 is isopropyl or isopropoxy.
3. The compound of Claim 1, wherein R^3 is halogen and R^4 is halogen or alkyl

4. The compound of Claim 1, wherein R³ is chloro and R⁴ is halogen.
5. The compound of Claim 1, wherein R³ is chloro and R⁴ is alkyl.
6. The compound of Claim 1, wherein R³ and R⁴ come together with the attached phenyl group to form an aryl, or heterocyclcyl bicyclic ring.
7. The compound of Claim 1, wherein R³ and R⁴ come together with the phenyl group to form naphthalenyl.
8. The compound of Claim 1 selected from:
4-(3-(3-isopropylphenyl)ureido)benzenesulfonamide;
4-(3-(3-isopropoxyphenyl)ureido)benzenesulfonamide;
4-(3-(3-chloro-4-fluorophenyl)ureido)benzenesulfonamide;
4-(3-(3-chloro-4-methylphenyl)ureido)benzenesulfonamide; and
4-(3-(naphthalen-2-yl)ureido)benzenesulfonamide.
9. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable excipient.
10. A method of treating obesity comprising administering an effective amount of a compound of Claim 1 to a subject in need thereof.
11. A method of treating glaucoma comprising administering an effective amount of a compound of Claim 1 to a subject in need thereof.
12. A method of treating ocular hypertension comprising administering an effective amount of a compound of Claim 1 to a subject in need thereof.

13. A method of treating epilepsy comprising administering an effective amount of a compound of Claim 1 to a subject in need thereof.
14. A method of treating or preventing cancer comprising administering an effective amount of a compound of Claim 1 to a subject in need thereof.
15. A method of increasing urinary excretion comprising administering an effective amount of a compound of Claim 1 to a subject in need thereof.
16. The method of Claim 15, wherein the subject is in need thereof as the subject is diagnosed with, at risk of, or exhibiting symptoms of heart failure, liver cirrhosis, hypertension, water poisoning, or kidney disease.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US16/24179

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/18, 31/277, 45/06 (2016.01)

CPC - A61K 31/18, 31/277, 45/06

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC(8): A61K 31/18, 31/277, 45/06 (2016.01)

CPC: A61K 31/18, 31/277, 45/06

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PatSeer (US, EP, WO, JP, DE, GB, CN, FR, KR, ES, AU, IN, CA, Other Countries (INPADOC), RU, AT, CH, TH, BR, PH); EBSCO;
 Google/Google Scholar, IP.com: benzenesulfonamide, ureido, carbonic, anhydrase, inhibitor, cancer, epilepsy, obesity, hypertension,
 urinary, glaucoma, ocular

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2013/0190396 A1 (METASIGNAL THERAPEUTICS INC.) 25 July 2013; paragraphs [0008], [0121], [0152], [0169], [0171]; claim 7	1-9, 14
--		-----
Y		10-13, 15-16
Y	(SUPURAN, CT et al.) Carbonic Anhydrases: Novel Therapeutic Applications for Inhibitors and Activators. Nature Reviews Drug Discovery. February 2008, Vol. 7, pages 168-181; page 168, paragraph [3]; page 174, paragraph [3]; DOI: 10.1038/nrd2467	10
Y	(SUPURAN, CT et al.) Carbonic Anhydrase Inhibitors. Medicinal Research Reviews. March 2003, Vol. 23, No. 2, pages 146-189; abstract; page 152, paragraph [2]; page 154, paragraph [1]; page 157, paragraph [3]; page 173, paragraph [2]; DOI: 10.1002/med.10025	11-13, 15-16

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

23 May 2016 (23.05.2016)

Date of mailing of the international search report

17 JUN 2016

Name and mailing address of the ISA/

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-8300

Authorized officer

Shane Thomas

PCT Helpdesk: 571-272-4300

PCT OSP: 571-272-7774