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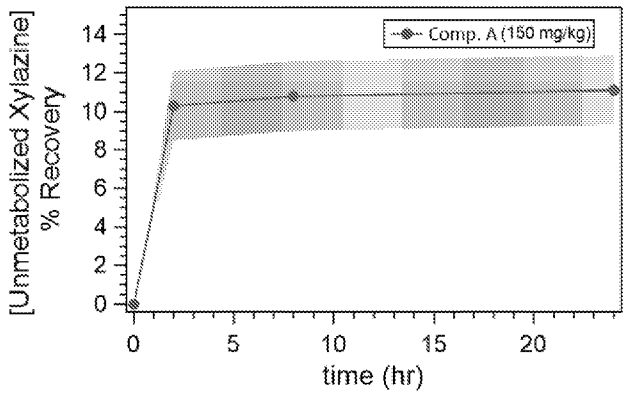
(54) Title: SEQUESTRANT COMPOUNDS FOR ALPHA 2 ADRENERGIC AGONISTS

FIG. 1



(57) Abstract: Provided is a method for reducing the level of an α2 adrenergic receptor agonist in the body of a patient. Also provided is a method to prevent or treat an overdose in a patient from an α2 adrenergic receptor agonist patient, alone or in combination with another drug of abuse.

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SEQUESTRANT COMPOUNDS FOR ALPHA 2 ADRENERGIC AGONISTS

[0001] This invention was made with government support under grant no. R44DA052957 awarded by the National Institute of Health. The government has certain rights in the invention.

FIELD

[0002] The present disclosure provides methods and compositions for reducing an α2 adrenergic receptor agonist in the body of a patient. Also provided are methods and compositions for preventing or treating an overdose from an α2 adrenergic receptor agonist, or from the combination of an α2 adrenergic receptor agonist with another drug of abuse, by administering to the patient a therapeutically effective amount of a sequestration agent.

BACKGROUND

[0003] Drug overdose, intoxication and addiction are major social issues that affects all aspects of society. There is a significant unmet medical for reversal agents for prescription and illicit drugs to treat or prevent abuse and overdose.

[0004] Xylazine is increasingly being found in the US illicit drug supply and linked to overdose deaths. There has been an increase in the number of reports, alerts, and advisories from public health agencies indicating that xylazine is being abused in combination with other drugs of abuse, such as fentanyl, cocaine, and heroin, and is causing significant harm. People who use illicit drugs may not be aware of the presence of xylazine. The DEA has seized xylazine and fentanyl mixtures in 48 of 50 states, and the DEA reported that approximately 23% of fentanyl powder and 7% of fentanyl pills seized by the DEA in 2022 contained xylazine.

[0005] There remains a need for methods and compositions for the treatment of patients suffering from xylazine overdose or intoxication, both for xylazine alone and when xylazine is combined with other drugs of abuse.

SUMMARY

[0006] The present disclosure provides methods and compositions for addressing these and other circumstances wherein it is desirable to reverse the effect of one or more drugs of abuse which comprises an α2 adrenergic receptor agonist.

[0007] In embodiments, the sequestration agent may be administered to the patient orally and/or intravenously. The composition comprising the sequestration agent is administered to the patient, and sequesters the α2 adrenergic receptor agonist and other drug of abuse, if present, and removes the drugs from the patient's body. In embodiments, the α2 adrenergic receptor agonist is xylazine.

[0008] The additional drug may be a pharmaceutical drug and/or a drug of abuse. In particular, the additional drug of abuse may include one or more of amphetamine stimulants, barbiturates, opioids, benzodiazepines and psychedelics. The additional drug of abuse may include one or more of methamphetamine (and e.g., hydroxy methamphetamine, 3,4-methylenedioxy methamphetamine), fentanyl, and cocaine. The additional drug of abuse may comprise fentanyl or a fentanyl analog, such as carfentanil.

[0009] The sequestration agent may be a cucurbituril, a pillararene, a cyclodextrin or a calixarene.

[0010] In one aspect, the disclosure provides a method for rapidly lowering the concentration of an α2 adrenergic receptor agonist in the body of a patient by administering to the patient a sequestration agent in an amount sufficient to reduce the level of drug in the patient's body. The administration of the sequestration agent provides a more rapid drug detoxification for the patient than would occur under metabolic detoxification.

[0011] In some embodiments, the present disclosure provides a method of treating an intoxication, overdose or a symptom thereof due to an α2 adrenergic receptor agonist, or the combination of an α2 adrenergic receptor agonist and another drug of abuse, the method comprising: administering a therapeutically effective amount of a sequestration agent or a pharmaceutically acceptable salt thereof, wherein the administration is effective to reduce the level of α2 adrenergic receptor agonist in the patient. The therapeutically effective amount of a sequestration agent may additionally be simultaneously effective at lowering the level of an additional drug of abuse present in the patient.

[0012] In some embodiments, the present disclosure provides a method of treating a suspected overdose or symptom thereof in a patient, comprising administering a therapeutically effective amount of a sequestration agent or a pharmaceutically acceptable salt thereof, wherein the subject has a suspected overdose from an α2 adrenergic receptor agonist, or from an α2 adrenergic receptor agonist in combination with one or more additional drugs of abuse.

BRIEF DESCRIPTION OF THE FIGURES

[0013] Figure 1 shows the recovery of xylazine in urine from rats given an IV bolus of xylazine followed by Comp. A.

[0014] Figure 2 shows the recovery of fentanyl (Fig. 2a) and xylazine (Fig. 2b) in urine from rats given an IV bolus of fentanyl and xylazine followed by Comp. A.

[0015] Figure 3 shows the recovery of rats after administration of an IV bolus of xylazine followed by Comp. A by the improvement in gait scores over time.

DETAILED DESCRIPTION

[0016] There is an urgent need for pharmacological approaches to treat the abuse and/or overdose of α2 adrenergic receptor agonists, such as xylazine, as no current treatment exists for this public health crisis. A drug that rapidly detoxifies patients from α2 adrenergic receptor agonists, such as xylazine, would be a great benefit to patients and would save lives.

[0017] The present disclosure provides a method for reducing an α2 adrenergic receptor agonist from the body of a patient that has been administered the α2 adrenergic receptor agonist, including self-administration. The disclosure also provides a method to prevent or treat an overdose, or suspected overdose, from an α2 adrenergic receptor agonist that has been administered to a patient. The α2 adrenergic receptor agonist may be present in the patient as the sole toxic agent, or may be present in the patient in combination with another drug of abuse. The method includes at a time after the administration of α2 adrenergic receptor agonist to the patient, administering to the patient a therapeutically effective amount of a sequestration agent. In embodiments, the administration of the sequestration agent may reduce of symptoms associated with α2 adrenergic receptor agonist withdrawal and ease the transition into a medically assisted therapy (MAT) program.

[0018] The sequestration agent tightly binds, inactivates, and clears the α2 adrenergic receptor agonist, and optionally other drugs of abuse that may be present, from the body with high specificity. The sequestration agent may be administered to the patient intravenously and/or orally.

[0019] When the sequestering agent is administered by injection to the patient, the sequestration agent binds to (i.e., sequesters) the α2 adrenergic receptor agonist (and other drug of abuse, if present) in the plasma compartment of blood and removes it from the effect

site. The now 'inactive' drug is eliminated from the body by filtration in the kidney. Alternatively or additionally, the composition comprising the sequestering agent may be administered orally to the patient, and sequesters the α2 adrenergic receptor agonist (and other drug of abuse, if present) in the gastrointestinal tract, reducing and/or preventing absorption into the blood, and removes it from the patient's body by elimination into feces. The administration of the sequestration agent provides a more rapid drug detoxification for the patient than would occur under metabolic detoxification. Metabolic detoxification refers to the elimination of the α2 adrenergic receptor agonist (and other drug of abuse, if present) from the patient's body through the normal routes of drug metabolism as they occur in the absence of the sequestration agent. Rapid sequestration and clearance of the α2 adrenergic receptor agonist (and other drug of abuse, if present) rapidly lower the level of drug in the body and reverses its effects.

[0020] The sequestrants work by strong selective molecular-level binding with the α2 adrenergic receptor agonist (and other drug of abuse, if present), resulting in a more potent, fast-acting, safe, and easy to administer reversal agent. The sequestration agent may include a cucurbituril, a pillararene, or a calixarene, and particularly may include a cucurbituril compound.

[0021] In embodiments, the additional drug of abuse is an opioid drug, such as fentanyl, carfentanil or heroin, which may present in the patient's body in combination with another drug of abuse, such as a stimulant drug (for example, methamphetamine or cocaine). In other embodiments, the additional drug of abuse is a stimulant drug such as methamphetamine (and e.g., hydroxy methamphetamine, 3,4-methylenedioxy methamphetamine) or cocaine.

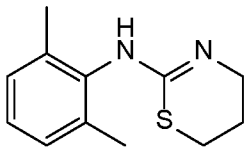
[0022] The terms "subject," "host," "patient," and "individual" are used interchangeably herein to refer to any mammalian subject for whom the therapy provided herein is desired, particularly humans.

α2 adrenergic agonist

[0023] The methods and compositions provided in this disclosure are used for the treatment of patients suffering from the administration of an α2 adrenergic agonist by lowering the concentration of the α2 adrenergic agonist in the body of the patient by binding to the sequestration agent.

[0024] Alpha-adrenergic agonists are a class of sympathomimetic agents that selectively stimulates alpha adrenergic receptors. The alpha-adrenergic receptor has two subclasses, α1 and α2. Alpha 2 receptors are associated with sympatholytic properties, which oppose the downstream effects of postganglionic nerve firing in effector organs innervated by the sympathetic nervous system (SNS).

[0025] Alpha-2 adrenergic agonists may mimic the effects of the hormone norepinephrine. Examples of alpha-2 adrenergic agonists include xylazine, guanabenz, guanfacine, and clonidine. The chemical structure of xylazine is shown below



The IUPAC name is N-(2,6-dimethylphenyl)-5,6-dihydro-4H-1,3-thiazin-2-amine. Following administration, xylazine diffuses extensively and penetrates the blood–brain barrier.

[0026] Xylazine is often used in combination with illicit substances, knowingly or unknowingly, but may also be abused alone. Additionally, published case reports have demonstrated that xylazine has been used in drug-facilitated crimes to induce sleep. Fatalities involving xylazine have been reported. The known doses of xylazine that produce toxicity and fatality in humans vary from 40 to 2400 mg. However, most overdose deaths linked to xylazine involved additional substances such as: fentanyl, heroin, benzodiazepines, alcohol, gabapentin, methadone, prescription opioids, and cocaine. Xylazine and fentanyl drug mixtures place users at a higher risk of suffering a fatal drug poisoning. Because xylazine is not an opioid, naloxone does not reverse its effects.

Additional drugs of abuse

[0027] The compositions and methods provided in this disclosure are additionally suitable for the treatment of patients suffering from the abuse or overdose of a combination of another drug of abuse and an α2 adrenergic agonist, such as xylazine.

[0028] As used herein, the term “drug of abuse” is intended to mean any drug or substance the excessive consumption or administration of which can result in intoxication, overdose, or a diagnosis of substance dependence or substance abuse (e.g., substance use disorder). Drugs of abuse include, without limitation, opioids, stimulants, barbiturates, benzodiazepines, and

psychedelics. Drug of abuse include, but are not limited to, cocaine, amphetamines, methamphetamine (and e.g., hydroxy methamphetamine, 3,4-methylenedioxy methamphetamine), methylphenidate, heroin, codeine, hydrocodone, oxycodone, marijuana (cannabis), methadone, opioids, fentanyl, carfentenil, fentanyl analogs, ayahuasca, CNS depressants, N,N-dimethyltryptamine (DMT), gamma-hydroxybutyrate (GHB), hallucinogens, inhalants, ketamine, khat, kratom, lysergic acid diethylamide (LSD), MDMA (molly/ecstasy), mescaline (peyote), dextromethorphan, loperamide, PCP, psilocybin, rohypnol, salvia, synthetic cannabinoids, synthetic cathinones (bath salts), mephedrone, nicotine, dextroamphetamine, dexmethylphenidate, or any combination thereof. Furthermore, drugs of abuse can include, but are not necessarily limited to those drugs listed by the National Institute of Health (NIH) and the National Institute of Drug Abuse (NIDA).

[0029] In embodiments, the drug of abuse may be a stimulant, including amphetamine, methamphetamine (and e.g., hydroxy methamphetamine, 3,4-methylenedioxy methamphetamine), methylphenidate, cathinone, methcathinone, and the like. In other embodiments, the drug of abuse may be an opioid, such as fentanyl or a fentanyl analog such as carfentanil. In further embodiments, the drug of abuse comprises a combination of one or more stimulants, such as methamphetamine (and e.g., hydroxy methamphetamine, 3,4-methylenedioxy methamphetamine), and one or more opioids, such as fentanyl or a fentanyl analog.

[0030] In embodiments, the drug of abuse is an opioid, such as heroin, fentanyl or carfentanil.

[0031] In embodiments, the methods provided in this disclosure may be particularly suitable for the treatment of patients suffering from abuse, overdose, or suspected overdose of fentanyl and its analogs, in combination with the α2 adrenergic agonist. Fentanyl (N-(1-phenethylpiperidin-4-yl)-N-phenylpropionamide) is a synthetic, lipophilic phenylpiperidine opioid agonist with analgesic and anesthetic properties. Fentanyl has a distinct pharmacological profile as compared to other opioids, including high potency (100x morphine), high lipophilicity, sequestration and gradual release from lipid tissue, and extended elimination half-life. Fentanyl poses an exceptionally high risk for overdose in humans, particular due to its high potency and its unpredictable fatal dosage when mixed with other drugs, such as xylazine.

[0032] The term "fentanyl analog" refers to a molecule that has been designed to mimic the pharmacological effects of fentanyl. Exemplary fentanyl analogs include 3-allylfentanyl, alfentanil, acrylfentanyl, acetylfentanyl, brifentanil, butyrfentanyl, 2,2'-difluorofentanyl, carfentanil, crotonylfentanyl, cyclopentylfentanyl, cyclopropyl fentanyl, (±)-cis-3-methyl fentanyl, furanyl fentanyl, 3-fluorofentanyl, 3-furanylfentanyl, 3-methylbutyrfentanyl, 3-methylfentanyl, 3-methylfuranylfentanyl, 3-methylthiofentanyl, 3-phenylpropanoylfentanyl, 4-fluorobutyrfentanyl, 4-chloroisobutyrylfentanyl, 4-fluoroisobutyrfentanyl, 4-fluorofentanyl, para-fluorofuranylfentanyl, para-chlorofuranylfentanyl, ortho-methylfuranylfentanyl, 4-phenylfentanyl, lofentanil, 4-methoxybutyrfentanyl, para-hydroxy-butyrylfentanyl, 4-methylphenethylacetylfentanyl, α-methylacetylfentanyl, α-methylbutyrfentanyl, α-methylbutyrfentanyl, α-methylthiofentanyl, benzodioxolefentanyl, benzoylfentanyl, butyrfentanyl, isobutyrylfentanyl, isofentanyl, methoxyacetylfentanyl, sufentanil, para-tolylfentanyl, 3-methylfentanyl, α-methylfentanyl, mefentanyl, mirfentanil, remifentanil, phenaridine, ohmefentanyl, trefentanil, and the like.

Sequestering Agents

[0033] Sequestering agents are used in the methods disclosed herein to lower the concentration of the α2 adrenergic agonist, and other drug of abuse, in the body of the patient. The sequestering agent is administered to the patient and binds to (i.e., sequesters) the α2 adrenergic agonist and other drug of abuse in the plasma compartment of blood (for IV administration) and/or in the gastrointestinal tract (for oral administration) and removes it from the body. The now 'inactive' drug is eliminated from the body by filtration in the kidney or by elimination is feces. The administration of the sequestration agent provides a more rapid drug detoxification for the patient than would occur under metabolic detoxification. Metabolic detoxification refers to the elimination of the drug of abuse from the patient's body through the normal routes of drug metabolism as they occur in the absence of the sequestration agent. Rapid sequestration and clearance of the α2 adrenergic agonist and the other drug of abuse, if present, rapidly lower the level of drug(s) in the body and reverses their effects.

[0034] In some embodiments, the sequestration agent can be a cyclodextrin, an acyclic cucurbituril, a cyclic cucurbituril, a pillararene, or a calixarene. In some embodiments, the sequestration agent is a cucurbituril. In some embodiments, the sequestration agent is an acyclic cucurbituril. In some embodiments, the sequestration agent is a cyclic cucurbituril. In

some embodiments, the sequestration agent is a pillararene. In some embodiments, the sequestration agent is a calixarene. In some embodiments, the sequestration agent is a cyclodextrin.

Calixarenes

[0035] In some embodiments, the sequestration agent is a calixarene. In such embodiments, the disclosure provides a method for rapidly lowering the concentration of the α2 adrenergic agonist and the other drug of abuse, if present, in the body of a patient by administering to the patient a calixarene compound in an amount sufficient to reduce the level of the α2 adrenergic agonist and the other drug of abuse, if present, in the patient's body. The administration of the calixarene compound provides a more rapid drug detoxification for the patient than would occur under metabolic detoxification.

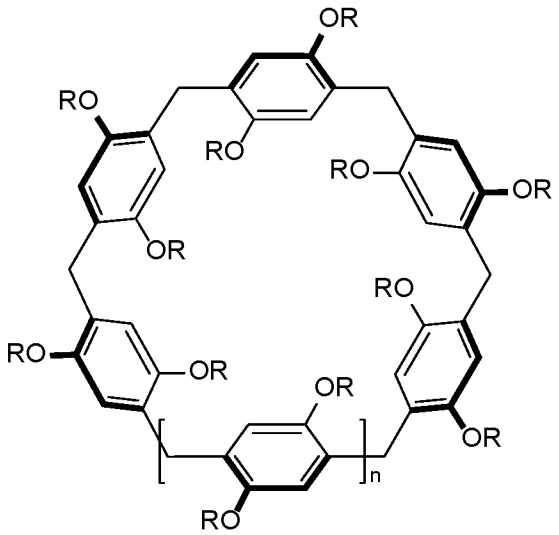
[0036] The calixarenes are a family of cyclic macrocyclic compounds with a variable number of phenol units linked by methylene bridges in ortho position. The number of units of phenol units can be between 4 and 12, with of 4, 5, 6, 7, and 8 being preferred.

Pillararenes

[0037] In some embodiments, the sequestration agent is a pillararene. In such embodiments, the disclosure provides a method for rapidly lowering the concentration of the α2 adrenergic agonist and the other drug of abuse, if present, in the body of a patient by administering to the patient a pillararene compound in an amount sufficient to reduce the level of the α2 adrenergic agonist and the other drug of abuse, if present, in the patient's body. The administration of the pillararene compound provides a more rapid drug detoxification for the patient than would occur under metabolic detoxification.

[0038] Pillararenes are macrocyclic molecules composed of aromatic rings connected by methylene bridges at the para positions, in which the macrocycle comprises is 5, 6, 7 or 8. Small pillararenes bind to narrow n-alkane molecules, whereas larger pillararenes can bind to aromatics, viologens, and alicyclic molecules. Exemplary pillararenes are provided in (Xue et. Al, Angewandte Chemie, 2020), which has been incorporated by reference in its entirety.

[0039] In some embodiments, the sequestration agent is a pillararene of the following structure:



or a pharmaceutically acceptable salt thereof;

wherein n is selected from 0, 1, 2 or 3, and each R is independently selected from $-(CH_2)_aS(O)_bX^1$, $-(CH_2)_aCO_2X^1$, and $-(CH_2)_aPO_bX^1$;

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

b is 2 or 3;

and each X^1 is independently selected from selected from H, -OH, alkali metal cation, and quaternary ammonium cation.

[0040] In embodiments, each R is $-(CH_2)_aSO_3X^{1a}$, $-(CH_2)_aCO_2X^{1a}$, and $-(CH_2)_aPO_3X^{1a}$; wherein a is 0, 1, 2 or 3; and X^{1a} is H, alkali metal cation, and quaternary ammonium cation. In embodiments, R is SO_3H or a salt there (e.g., SO_3Na), or - CH_2COOH or a salt thereof (e.g., CH_2COONa).

[0041] In some embodiments, n=0. In some embodiments, n=1. In some embodiments, n=2. In some embodiments, n=3. In some embodiments, n=1 and R = SO_3H or SO_3Na, and the compound is referred to herein as Compound J.

Cucurbituril compounds

[0042] In some embodiments, the sequestration agent is a cucurbituril compound. In such embodiments, the disclosure provides a method for rapidly lowering the concentration of the α2 adrenergic agonist and the other drug of abuse, if present, in the body of a patient by administering to the patient a cucurbituril compound in an amount sufficient to reduce the level of the α2 adrenergic agonist and the other drug of abuse, if present, in the patient's body. The administration of the cucurbituril compound provides a more rapid drug detoxification for the patient than would occur under metabolic detoxification.

[0043] Cucurbiturils are a class of macrocyclic compounds based on oligomers of glycoluril, its analogues and derivatives. Cucurbiturils can be used to form complexes with other molecules and are useful as sequestering agents. This property makes cucurbiturils an attractive candidate for the entrapment and removal of chemical agents.

[0044] Cucurbituril compounds may be cyclic or acyclic. The molecular structure of cucurbiturils features a central hydrophobic cavity that is guarded by two symmetry equivalent ureidyl carbonyl portals of highly negative electrostatic potential. Thus, cucurbiturils may show a preference to bind molecules that feature a central hydrophobic domain that is flanked by cationic (e.g., ammonium) groups. Binding of molecules are mediated by the hydrophobic effects and ion-dipole interactions.

[0045] Acyclic cucurbiturils may exhibit higher water solubility and may provide a more flexible binding cavity that can accommodate larger molecules. Acyclic cucurbiturils mediate tight binding through interaction of hydrophobic cations but can also be modified synthetically. These molecules generally feature a central glycoluril tetramer to impart a C-shape and hydrophobic cation binding properties, presented by two terminal aromatic side walls to engage in cation -π, CH-π, and π-π interaction with molecules. In embodiments, four sodium sulfonate arms help enhance water solubility and promote secondary electrostatic interactions between the cucurbituril and the bound molecule.

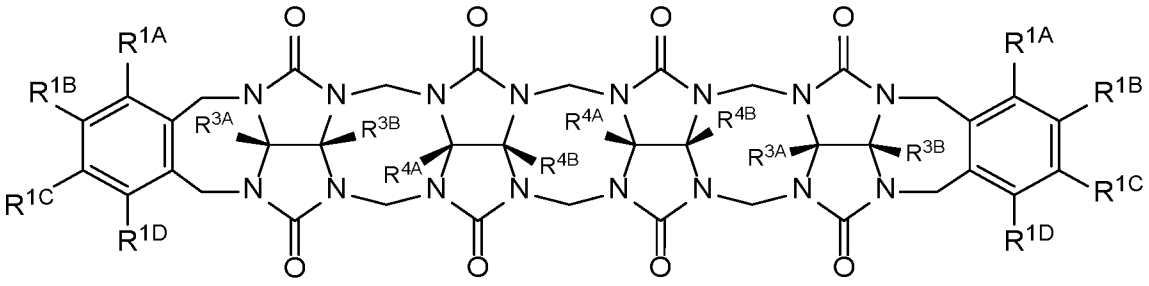
[0046] In embodiments provided herein, one or more cucurbituril compounds is administering to the patient in an amount sufficient to reduce the level of a drug of abuse, and particularly an opioid (fentanyl, carfentanil, etc.), in the patient's body. In some embodiments, the cucurbituril compounds may simultaneously lower the level of amphetamine, methamphetamine (and e.g., hydroxy methamphetamine, 3,4-methylenedioxy methamphetamine), or other stimulants in the patient's body.

[0047] The cucurbituril compound disclosed herein bind to xylazine. In embodiments, this disclosure provides cucurbituril compounds that bind to fentanyl or a fentanyl analog. The cucurbituril compound disclosed herein bind to fentanyl or fentanyl analogs with high affinity. The cucurbituril compound may also bind to amphetamine, methamphetamine (and e.g., hydroxy methamphetamine, 3,4-methylenedioxy methamphetamine), or other stimulants with high affinity.

[0048] In embodiments, the cucurbituril compound may bind to toxic agents having a suitable molecular size. The cucurbituril may show high binding affinity to an opioid

(fentanyl, carfentanyl, etc.), amphetamine, methamphetamine (and e.g., hydroxy methamphetamine, 3,4-methylenedioxy methamphetamine), or other stimulants, and to xylazine.

[0049] In embodiments of the methods provided in this disclosure, the cucurbituril compound has a structure of formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

each R^{1A} and R^{1D} is independently selected from hydrogen, halogen, -OH, C_1-C_6 alkyl, 2 to 6 membered heteroalkyl, C_3-C_6 cycloalkyl, 5 to 6 membered heterocycloalkyl, phenyl, 5 to 6 membered heteroaryl, $-O-(CH_2)_{n1}S(O)_{v1}X^1$, $-O-(CH_2)_{n1}CO_2X^1$, and $-O-(CH_2)_{n1}PO_{v1}X^1$;

each R^{1B} and R^{1C} is independently selected from hydrogen, halogen, -OH, C_1-C_6 alkyl, 2 to 6 membered heteroalkyl, C_3-C_6 cycloalkyl, 5 to 6 membered heterocycloalkyl, phenyl, 5 to 6 membered heteroaryl, $-O-(CH_2)_{n1}S(O)_{v1}X^1$, $-O-(CH_2)_{n1}CO_2X^1$, and $-O-(CH_2)_{n1}PO_{v1}X^1$; or

additionally or alternatively, two R^{1A}, R^{1B}, R^{1C} and R^{1D} attached on the same phenyl ring at adjacent positions, together with atoms to which they are attached, are joined to form a fused C_6-C_{12} aryl, 5 to 12 membered heteroaryl, or 5 to 7 membered heterocycle, which are optionally substituted with 1 to 3 substituents independently selected halogen, -OH, $-NH_2$, substituted or unsubstituted C_1-C_6 alkyl, or substituted or unsubstituted 2 to 6 membered heteroalkyl;

each R^{3A} and R^{3B} is independently selected from hydrogen, halogen, -OH, C_1-C_6 alkyl, phenyl, substituted phenyl and 2 to 6 membered heteroalkyl;

each R^{4A} and R^{4B} is independently selected from hydrogen, halogen, -OH, C_1-C_6 alkyl, phenyl, substituted phenyl and 2 to 6 membered heteroalkyl;

each n1 is independently selected from 0 to 5;

each v1 is independently selected from 2 or 3; and

each X^1 is independently selected from selected from H, -OH, C_1-C_6 alkyl, alkali metal cation, and quaternary ammonium cation.

[0050] In embodiments, R^{1B} is hydrogen, halogen, -OH, C_1-C_6 alkyl, 2 to 6 membered heteroalkyl, C_3-C_6 cycloalkyl, 5 to 6 membered heterocycloalkyl, phenyl, or 5 to 6 membered heteroaryl. In embodiments, R^{1B} is hydrogen, halogen, -OH, or C_1-C_6 alkyl, and particularly R^{1B} is hydrogen or halogen.

[0051] In embodiments, R^{1C} is hydrogen, halogen, -OH, C_1-C_6 alkyl, 2 to 6 membered heteroalkyl, C_3-C_6 cycloalkyl, 5 to 6 membered heterocycloalkyl, phenyl, or 5 to 6 membered heteroaryl. In embodiments, R^{1C} is hydrogen, halogen, -OH or C_1-C_6 alkyl, and particularly, R^{1C} is hydrogen or halogen.

[0052] In embodiments, R^{1B} and R^{1C} are hydrogen.

[0053] Additionally or alternatively, R^{1A} and R^{1B}, attached on the same phenyl ring, together with atoms attached thereto, may be joined to form a C_6-C_{12} aryl, or 5 to 12 membered heteroaryl. In embodiments, R^{1A} and R^{1B}, attached on the same phenyl ring, together with atoms attached thereto, join to form phenyl. In embodiments, R^{1A} and R^{1B}, attached on the same phenyl ring, together with atoms attached thereto, join to form naphthyl. In embodiments, R^{1A} and R^{1B}, attached on the same phenyl ring, together with atoms attached thereto, join to form pyridyl.

[0054] In embodiments, R^{1B} and R^{1C}, attached on the same phenyl ring, together with atoms attached thereto, join to form C_6-C_{12} aryl, or 5 to 12 membered heteroaryl. In embodiments, R^{1B} and R^{1C}, attached on the same phenyl ring, together with atoms attached thereto, join to form phenyl. In embodiments, R^{1B} and R^{1C}, attached on the same phenyl ring, together with atoms attached thereto, join to form naphthyl. In embodiments, R^{1B} and R^{1C}, attached on the same phenyl ring, together with atoms attached thereto, join to form pyridyl.

[0055] In embodiments, R^{1C} and R^{1D}, attached on the same phenyl ring, together with atoms attached thereto, join to form C_6-C_{12} aryl, or 5 to 12 membered heteroaryl. In embodiments, R^{1C} and R^{1D}, attached on the same phenyl ring, together with atoms attached thereto, join to form phenyl. In embodiments, R^{1C} and R^{1D}, attached on the same phenyl ring, together with atoms attached thereto, join to form naphthyl. In embodiments, R^{1C} and R^{1D}, attached on the same phenyl ring, together with atoms attached thereto, join to form pyridyl.

[0056] In embodiments, the C_6-C_{12} aryl or 5 to 12 membered heteroaryl, which are formed by two of R^{1A}, R^{1B}, R^{1C} and R^{1D} attached on the same phenyl ring, may be substituted with one or more substituents, e.g., halogen, -OH, -NH_2, substituted or unsubstituted C_1-C_6 alkyl, or substituted or unsubstituted 2 to 6 membered heteroalkyl.

[0057] In embodiments, R^{3A} is hydrogen or substituted or unsubstituted C_1-C_3 alkyl. In embodiments, R^{3A} is C_1-C_3 alkyl, and particularly methyl.

[0058] In embodiments, R^{3B} is hydrogen or substituted or unsubstituted C_1-C_3 alkyl. In embodiments, R^{3B} is C_1-C_3 alkyl, and particularly methyl.

[0059] In embodiments, R^{3A} and R^{3B} are both hydrogen. Alternatively, R^{3A} and R^{3B} may both be methyl. In embodiments, one of R^{3A} and R^{3B} is hydrogen and the other is methyl.

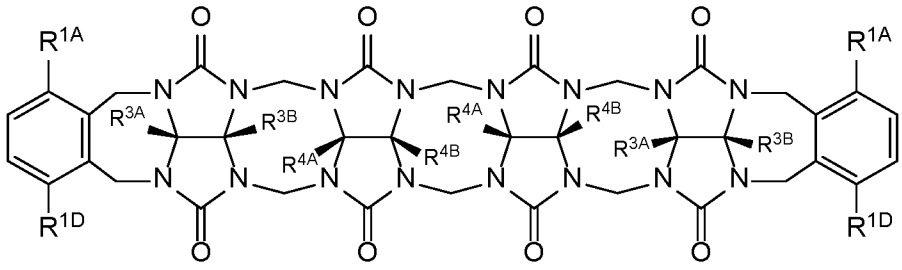
[0060] In embodiments, R^{4A} is hydrogen or substituted or unsubstituted C_1-C_3 alkyl. In embodiments, R^{4A} is C_1-C_3 alkyl, and particularly methyl. In embodiments, R^{4A} is H.

[0061] In embodiments, R^{4B} is hydrogen or substituted or unsubstituted C_1-C_3 alkyl. In embodiments, R^{4B} is C_1-C_3 alkyl, and particularly methyl. In embodiments, R^{4B} is hydrogen.

[0062] In embodiments, each R^{4A} and R^{4B} is hydrogen. Alternatively, each R^{4A} and R^{4B} may be methyl. In embodiments, one of R^{4A} and R^{4B} is hydrogen and the other is methyl.

[0063] In embodiments, each R^{3A} and R^{3B} is independently C_1-C_3 alkyl and R^{4A} and R^{4B} are hydrogen, and particularly, each R^{3A} and R^{3B} are methyl and each R^{4A} and R^{4B} are hydrogen.

[0064] In another aspect, the cucurbituril compounds used in the methods of this disclosure have the structure of formula (I-a):



(I-a)

or a pharmaceutically acceptable salt thereof. R^{1A}, R^{1D}, R^{3A}, R^{3B}, R^{4A}, and R^{4B} are as described herein for formula I.

[0065] In embodiments, R^{3A} is hydrogen or substituted or unsubstituted C_1-C_3 alkyl. In embodiments, R^{3A} is C_1-C_3 alkyl, and particularly methyl.

[0066] In embodiments, R^{3B} is hydrogen or substituted or unsubstituted C_1-C_3 alkyl. In embodiments, R^{3B} is C_1-C_3 alkyl, and particularly methyl.

[0067] In embodiments, R^{3A} and R^{3B} are both hydrogen. Alternatively, R^{3A} and R^{3B} may both be methyl. In embodiments, one of R^{3A} and R^{3B} is hydrogen and the other is methyl.

[0068] In embodiments, R^{4A} is hydrogen or substituted or unsubstituted C_1-C_3 alkyl. In embodiments, R^{4A} is C_1-C_3 alkyl, and particularly methyl. In embodiments, R^{4A} is H.

[0069] In embodiments, R^{4B} is hydrogen or substituted or unsubstituted C_1-C_3 alkyl. In embodiments, R^{4B} is C_1-C_3 alkyl, and particularly methyl. In embodiments, R^{4B} is hydrogen.

[0070] In embodiments, each R^{4A} and R^{4B} is hydrogen. Alternatively, each R^{4A} and R^{4B} may be methyl. In embodiments, one of R^{4A} and R^{4B} is hydrogen and the other is methyl.

[0071] In embodiments, each R^{3A} and R^{3B} is independently C_1-C_3 alkyl and R^{4A} and R^{4B} are hydrogen, and particularly, each R^{3A} and R^{3B} are methyl and each R^{4A} and R^{4B} are hydrogen.

[0072] In embodiments, each R^{1A} and R^{1D} is neutral. In embodiments, each R^{1A} and R^{1D} is in an ionic salt form.

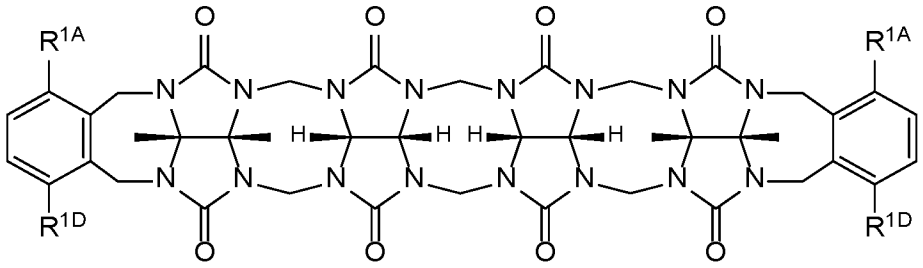
[0073] In embodiments, R^{1A} is -O-$(CH_2)_{n1}S(O)_{v1}X^1$. In embodiments, R^{1A} is -O-$(CH_2)_{n1}CO_2X^1$. In embodiments, R^{1A} is -O-$(CH_2)_{n1}PO_{v1}X^1$. In embodiments, each n1 is 0. In embodiments, each n1 is 1. In embodiments, each n1 is 2. In embodiments, each n1 is 3. In embodiments, each n1 is 4. In embodiments, each n1 is 5. In embodiments, each v1 is 2. In embodiments, each v1 is 3.

[0074] In embodiments, R^{1D} is -O-$(CH_2)_{n1}S(O)_{v1}X^1$. In embodiments, R^{1D} is -O-$(CH_2)_{n1}CO_2X^1$. In embodiments, R^{1D} is -O-$(CH_2)_{n1}PO_{v1}X^1$. In embodiments, each n1 is 0. In embodiments, each n1 is 1. In embodiments, each n1 is 2. In embodiments, each n1 is 3. In embodiments, each n1 is 4. In embodiments, each n1 is 5. In embodiments, each v1 is 2. In embodiments, each v1 is 3.

[0075] In embodiments, R^{1A} and R^{1D} attached to the same phenyl ring may be same or different. In embodiments, R^{1A} and R^{1A} attached to the different phenyl rings may be same or different. In embodiments, R^{1D} and R^{1D} attached to the different phenyl rings may be same or different.

[0076] In embodiments, each R^{1A} and R^{1D} attached to the same phenyl ring is independently -O-$(CH_2)_{n1}S(O)_{v1}X^1$. In embodiments, each R^{1A} and R^{1A} attached to the different phenyl rings is independently -O-$(CH_2)_{n1}S(O)_{v1}X^1$. In embodiments, each R^{1D} and R^{1D} attached to the different phenyl rings is independently -O-$(CH_2)_{n1}S(O)_{v1}X^1$.

[0077] In another aspect, the cucurbituril compounds used in the methods of this disclosure have the structure of formula (I-b):



(I-b)

or a pharmaceutically acceptable salt thereof. R^{1A} and R^{1D} are as described herein for formula I.

[0078] In embodiments, each R^{1A} and R^{1D} is neutral. In embodiments, each R^{1A} and R^{1D} is in an ionic salt form.

[0079] In embodiments, R^{1A} is -O-$(CH_2)_{n1}S(O)_{v1}X^1$. In embodiments, R^{1A} is -O-$(CH_2)_{n1}CO_2X^1$. In embodiments, R^{1A} is -O-$(CH_2)_{n1}PO_{v1}X^1$. In embodiments, each n1 is 0. In embodiments, each n1 is 1. In embodiments, each n1 is 2. In embodiments, each n1 is 3. In embodiments, each n1 is 4. In embodiments, each n1 is 5. In embodiments, each v1 is 2. In embodiments, each v1 is 3.

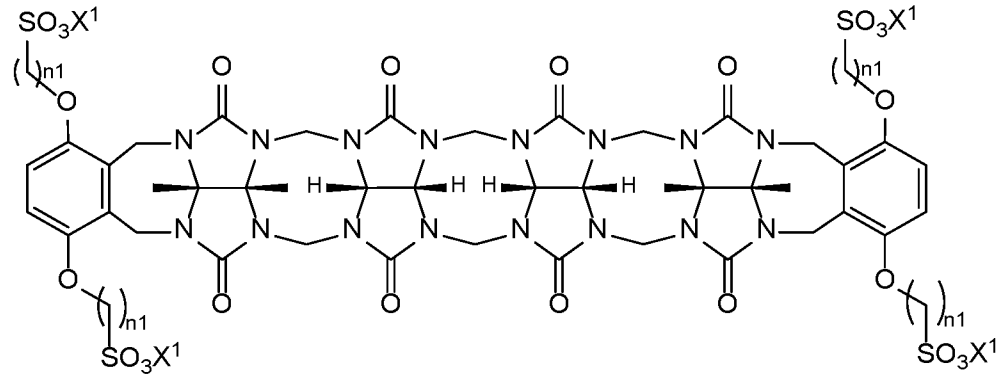
[0080] In embodiments, R^{1D} is -O-$(CH_2)_{n1}S(O)_{v1}X^1$. In embodiments, R^{1D} is -O-$(CH_2)_{n1}CO_2X^1$. In embodiments, R^{1D} is -O-$(CH_2)_{n1}PO_{v1}X^1$. In embodiments, each n1 is 0. In embodiments, each n1 is 1. In embodiments, each n1 is 2. In embodiments, each n1 is 3. In embodiments, each n1 is 4. In embodiments, each n1 is 5. In embodiments, each v1 is 2. In embodiments, each v1 is 3.

[0081] In embodiments, R^{1A} and R^{1D} attached to the same phenyl ring may be same or different. In embodiments, R^{1A} and R^{1A} attached to the different phenyl rings may be same or different. In embodiments, R^{1D} and R^{1D} attached to the different phenyl rings may be same or different.

[0082] In embodiments, each R^{1A} and R^{1D} attached to the same phenyl ring is independently -O-$(CH_2)_{n1}S(O)_{v1}X^1$. In embodiments, each R^{1A} and R^{1A} attached to the

different phenyl rings is independently -O-$(CH_2)_{n1}S(O)_{v1}X^1$. In embodiments, each R^{1D} and R^{1D} attached to the different phenyl rings is independently -O-$(CH_2)_{n1}S(O)_{v1}X^1$.

[0083] In another aspect, the cucurbituril compounds used in the methods of this disclosure have the structure of formula (I-c):

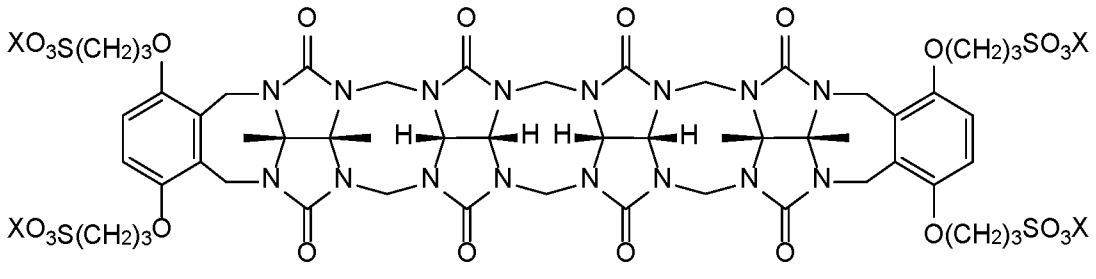


(I-c)

or a pharmaceutically acceptable salt thereof. X^1 and n1 are as described herein for formula I.

[0084] In embodiments, each X^1 are same or different. In embodiments, each X^1 is independently H, -OH, C_1-C_6 alkyl, alkali metal cation, or quaternary ammonium cation. In embodiments, each n1 is 0 to 5. In embodiments, each n1 is 1 to 5. In embodiments, each n1 is 2 to 5. In embodiments, each n1 is 3 to 5. In embodiments, each n1 is 4 to 5.

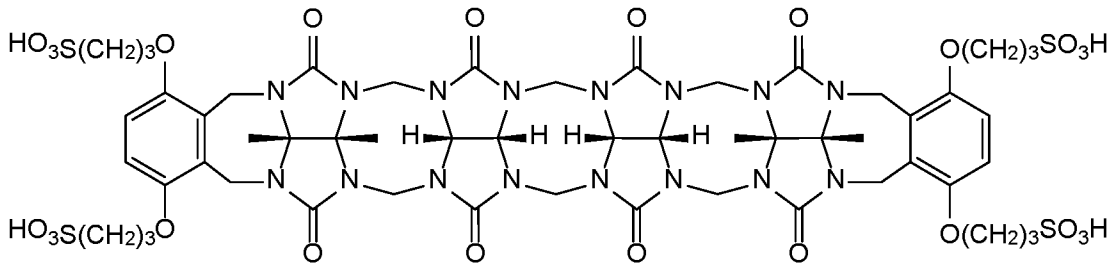
[0085] In another aspect, the cucurbituril compounds used in the methods of this disclosure have the structure of formula (I-A),



(I-A)

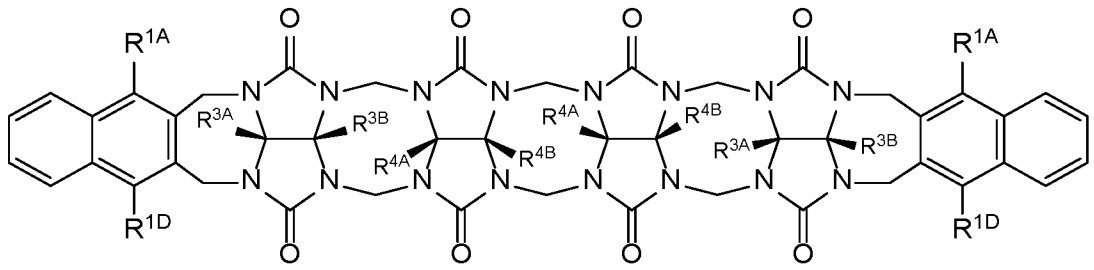
or a pharmaceutically acceptable salt thereof. Each X is independently H, alkali metal cation (e.g., Li^+, Na^+, K^+, or Cs^+), or quaternary ammonium cation.

[0086] In another aspect, the cucurbituril compounds used in the methods of this disclosure is Compound A, having the following structure:



or a pharmaceutically acceptable salt thereof.

[0087] the cucurbituril compounds used in the methods of this disclosure have the structure of formula (I-d),



(I-D)

or a pharmaceutically acceptable salt thereof. R^{1A}, R^{1D}, R^{3A}, R^{3B}, R^{4A}, and R^{4B} are as described herein for formula I.

[0088] In embodiments, R^{3A} is hydrogen or substituted or unsubstituted C_1-C_3 alkyl. In embodiments, R^{3A} is C_1-C_3 alkyl, and particularly methyl.

[0089] In embodiments, R^{3B} is hydrogen or substituted or unsubstituted C_1-C_3 alkyl. In embodiments, R^{3B} is C_1-C_3 alkyl, and particularly methyl.

[0090] In embodiments, R^{3A} and R^{3B} are both hydrogen. Alternatively, R^{3A} and R^{3B} may both be methyl. In embodiments, one of R^{3A} and R^{3B} is hydrogen and the other is methyl.

[0091] In embodiments, R^{4A} is hydrogen or substituted or unsubstituted C_1-C_3 alkyl. In embodiments, R^{4A} is C_1-C_3 alkyl, and particularly methyl. In embodiments, R^{4A} is H.

[0092] In embodiments, R^{4B} is hydrogen or substituted or unsubstituted C_1-C_3 alkyl. In embodiments, R^{4B} is C_1-C_3 alkyl, and particularly methyl. In embodiments, R^{4B} is hydrogen.

[0093] In embodiments, each R^{4A} and R^{4B} is hydrogen. Alternatively, each R^{4A} and R^{4B} may be methyl. In embodiments, one of R^{4A} and R^{4B} is hydrogen and the other is methyl.

[0094] In embodiments, each R^{3A} and R^{3B} is independently C_1-C_3 alkyl and R^{4A} and R^{4B} are hydrogen, and particularly, each R^{3A} and R^{3B} are methyl and each R^{4A} and R^{4B} are hydrogen.

[0095] In embodiments, each R^{1A} and R^{1D} is neutral. In embodiments, each R^{1A} and R^{1D} is in an ionic salt form.

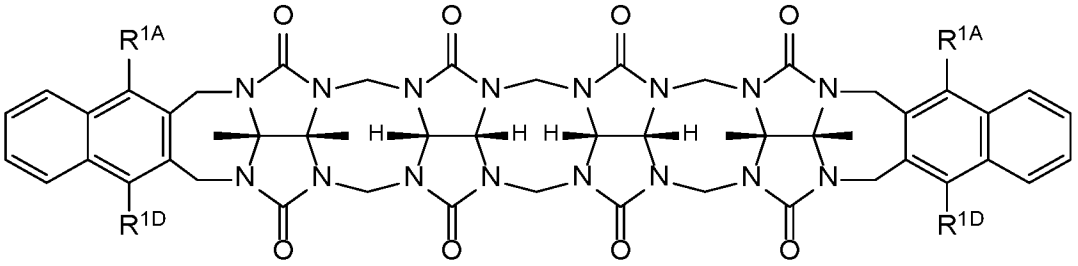
[0096] In embodiments, R^{1A} is $-O-(CH_2)_{n1}S(O)_{v1}X^1$. In embodiments, R^{1A} is $-O-(CH_2)_{n1}CO_2X^1$. In embodiments, R^{1A} is $-O-(CH_2)_{n1}PO_{v1}X^1$. In embodiments, each n1 is 0. In embodiments, each n1 is 1. In embodiments, each n1 is 2. In embodiments, each n1 is 3. In embodiments, each n1 is 4. In embodiments, each n1 is 5. In embodiments, each v1 is 2. In embodiments, each v1 is 3.

[0097] In embodiments, R^{1D} is $-O-(CH_2)_{n1}S(O)_{v1}X^1$. In embodiments, R^{1D} is $-O-(CH_2)_{n1}CO_2X^1$. In embodiments, R^{1D} is $-O-(CH_2)_{n1}PO_{v1}X^1$. In embodiments, each n1 is 0. In embodiments, each n1 is 1. In embodiments, each n1 is 2. In embodiments, each n1 is 3. In embodiments, each n1 is 4. In embodiments, each n1 is 5. In embodiments, each v1 is 2. In embodiments, each v1 is 3.

[0098] In embodiments, R^{1A} and R^{1D} attached to the same phenyl ring may be same or different. In embodiments, R^{1A} and R^{1A} attached to the different phenyl rings may be same or different. In embodiments, R^{1D} and R^{1D} attached to the different phenyl rings may be same or different.

[0099] In embodiments, each R^{1A} and R^{1D} attached to the same phenyl ring is independently $-O-(CH_2)_{n1}S(O)_{v1}X^1$. In embodiments, each R^{1A} and R^{1A} attached to the different phenyl rings is independently $-O-(CH_2)_{n1}S(O)_{v1}X^1$. In embodiments, each R^{1D} and R^{1D} attached to the different phenyl rings is independently $-O-(CH_2)_{n1}S(O)_{v1}X^1$.

[00100] In another aspect, the cucurbituril compounds used in the methods of this disclosure have the structure of formula (X):



(X)

or a pharmaceutically acceptable salt thereof.

[00101] In embodiments, each R^{1A} and R^{1D} is neutral. In embodiments, each R^{1A} and R^{1D} is in an ionic salt form.

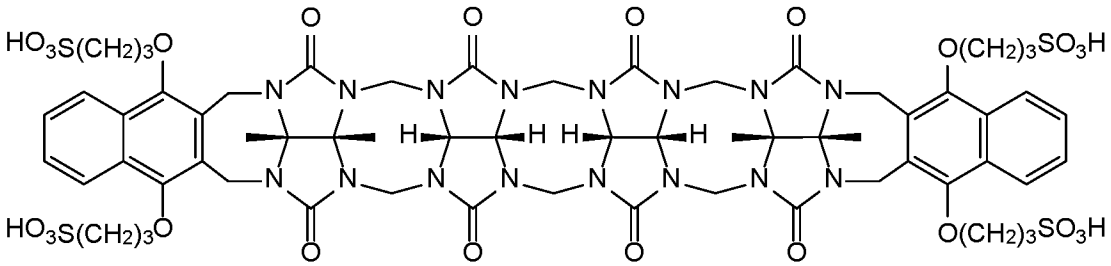
[00102] In embodiments, R^{1A} is -O-$(CH_2)_{n1}S(O)_{v1}X^1$. In embodiments, R^{1A} is -O-$(CH_2)_{n1}CO_2X^1$. In embodiments, R^{1A} is -O-$(CH_2)_{n1}PO_{v1}X^1$. In embodiments, each n1 is 0. In embodiments, each n1 is 1. In embodiments, each n1 is 2. In embodiments, each n1 is 3. In embodiments, each n1 is 4. In embodiments, each n1 is 5. In embodiments, each v1 is 2. In embodiments, each v1 is 3.

[00103] In embodiments, R^{1D} is -O-$(CH_2)_{n1}S(O)_{v1}X^1$. In embodiments, R^{1D} is -O-$(CH_2)_{n1}CO_2X^1$. In embodiments, R^{1D} is -O-$(CH_2)_{n1}PO_{v1}X^1$. In embodiments, each n1 is 0. In embodiments, each n1 is 1. In embodiments, each n1 is 2. In embodiments, each n1 is 3. In embodiments, each n1 is 4. In embodiments, each n1 is 5. In embodiments, each v1 is 2. In embodiments, each v1 is 3.

[00104] In embodiments, R^{1A} and R^{1D} attached to the same phenyl ring may be same or different. In embodiments, R^{1A} and R^{1A} attached to the different phenyl rings may be same or different. In embodiments, R^{1D} and R^{1D} attached to the different phenyl rings may be same or different.

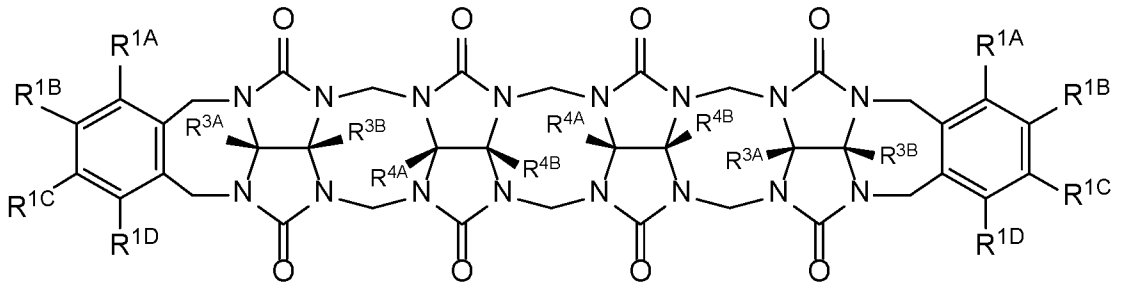
[00105] In embodiments, each R^{1A} and R^{1D} attached to the same phenyl ring is independently -O-$(CH_2)_{n1}S(O)_{v1}X^1$. In embodiments, each R^{1A} and R^{1A} attached to the different phenyl rings is independently -O-$(CH_2)_{n1}S(O)_{v1}X^1$. In embodiments, each R^{1D} and R^{1D} attached to the different phenyl rings is independently -O-$(CH_2)_{n1}S(O)_{v1}X^1$.

[00106] In another aspect, the cucurbituril compounds used in the methods of this disclosure is Compound B, having the following structure:



or a pharmaceutically acceptable salt thereof.

[00107] In an aspect, the cucurbituril compound has a structure of formula XI:



XI

or a pharmaceutically acceptable salt thereof, wherein:

each R^{1A} and R^{1D} is independently selected from -O-L-CO_2X^1 and -O-L-SO_3X^1;

each L is independently selected from a chemical bond (single), C_1 to C_{10} alkylene, C_2 to C_{10} alkenylene, -$(CH_2)_a$-O-$(CH_2)_b$-, -$(CH_2)_c$-N(R)-$(CH_2)_d$-, and -$(CH_2)_a$-$(OCH_2CH_2)_e$-$(Y)_f$-, each of which may be unsubstituted or substituted at any carbon with 1 to 4 substituents selected from halogen, OH, CO_2H, C_{1-3} alkyl, NH_2, NH(C_{1-3} alkyl), N(C_{1-3} alkyl)$_2$, and O-C_{1-3} alkyl;

a is 2 to 8;

b is 0 to 6;

c is 2 to 8;

d is 0 to 6;

e is 1 to 6;

Y is NH, N(C_{1-3} alkyl), or O;

f is 0 or 1;

R is H or C_{1-3} alkyl;

each R^{1B} and R^{1C} is independently selected from hydrogen, halogen, -OH, -CN, CO_2H, SO_3H, C_1-C_6 alkyl, 2 to 6 membered heteroalkyl, C_3-C_6 cycloalkyl, 5 to 6 membered heterocycloalkyl, phenyl, 5 to 6 membered heteroaryl; or

additionally or alternatively, R^{1B} and R^{1C} attached on the same phenyl ring, together with the atoms to which they are attached, are joined to form a fused C_6-C_{12} aryl, 5 to 12 membered heteroaryl, or 5 to 7 membered heterocycle, which are optionally substituted with 1 to 3 substituents independently selected halogen, -OH, -NH_2, substituted or unsubstituted C_1-C_6 alkyl, or substituted or unsubstituted 2 to 6 membered heteroalkyl;

each R^{3A} and R^{3B} is independently selected from hydrogen, halogen, -OH, CO_2H, CO_2R', $CONH_2$, CONHR', CON(R')$_2$, C_1-C_6 alkyl, phenyl, substituted phenyl and 2 to 6 membered heteroalkyl;

additionally or alternatively, R^{3A} and R^{3B} attached to adjacent carbon atoms, together with the carbons to which they are attached, are joined to form a 5- or 6-membered cycloalkyl or heterocycloalkyl ring;

each R^{4A} and R^{4B} is independently selected from hydrogen, halogen, -OH, CO_2H, CO_2R', $CONH_2$, CONHR', $CON(R')_2$, C_1-C_6 alkyl, phenyl, substituted phenyl and 2 to 6 membered heteroalkyl;

each R' is independently selected from C_{1-6} alkyl; and

each X^1 is independently selected from selected from H, C_1-C_6 alkyl, alkali metal cation, and quaternary ammonium cation.

[00108] In embodiments, L is C_1 to C_{10} alkylene, which may be unsubstituted or substituted with 1 to 4 substituents selected from halogen, OH, CO_2H, C_{1-3} alkyl, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl)$_2$, and O-C_{1-3} alkyl. In embodiments, L is C_1 to C_{10} alkylene, C_2 to C_{10} alkylene, C_1 to C_6 alkylene, or C_2 to C_6 alkylene, each of which may be unsubstituted or substituted. L may be $-CH_2-$, $-CH_2CH_2-$, $-CH(CH_3)CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH(CH_3)CH_2-$, $-CH_2CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2CH_2CH_2-$, and the like.

[00109] In other embodiments, L is a C_2 to C_{10} alkenylene chain, which may be unsubstituted or substituted with 1 to 4 substituents selected from halogen, OH, CO_2H, C_{1-3} alkyl, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl)$_2$, and O-C_{1-3} alkyl, and which comprises 1 to 3 carbon-carbon double bonds. In embodiments, L is C_2 to C_6 alkenylene, which may be unsubstituted or substituted. L may be $-CH=CH-$, $-C(CH_3)=CH-$, $-CH_2CH=CH-$, $-CH=C(CH_3)CH_2-$, $-CH=CHCH_2CH_2-$, $-CH_2CH=CHCH_2-$, $-CH=CHCH=CH-$, $-CH_2CH_2CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH=CH-$, $-CH_2CH=CHCH=CH-$, $-CH_2CH_2CH=CHCH_2-$, $-CH_2CH_2CH_2CH_2CH=CH-$, $-CH_2CH_2CH=CHCH=CH-$, and the like.

[00110] In other embodiments, L is $-(CH_2)_a-(OCH_2CH_2)_e-(Y)_f-$, each of which may be unsubstituted or substituted at any carbon with 1 to 4 substituents selected from halogen, OH, CO_2H, C_{1-3} alkyl, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl)$_2$, and O-C_{1-3} alkyl. L may comprise a polyethylene glycol oligomer, i.e., $-(CH_2CH_2O)_x-$, in which x is 2 to 6.

[00111] In other embodiments, L is a chemical bond.

[00112] In embodiments, R^{1B} is hydrogen, halogen, -OH, C_1-C_6 alkyl, 2 to 6 membered heteroalkyl, C_3-C_6 cycloalkyl, 5 to 6 membered heterocycloalkyl, phenyl, or 5 to 6 membered heteroaryl. In embodiments, R^{1B} is hydrogen, halogen, -OH, or C_1-C_6 alkyl, and particularly R^{1B} is hydrogen or halogen.

[00113] In embodiments, R^{1C} is hydrogen, halogen, -OH, C_1-C_6 alkyl, 2 to 6 membered heteroalkyl, C_3-C_6 cycloalkyl, 5 to 6 membered heterocycloalkyl, phenyl, or 5 to 6 membered heteroaryl. In embodiments, R^{1C} is hydrogen, halogen, -OH or C_1-C_6 alkyl, and particularly, R^{1C} is hydrogen or halogen.

[00114] In embodiments, R^{1B} and R^{1C} are hydrogen.

[00115] In embodiments, R^{1B} and R^{1C}, attached on the same phenyl ring, together with atoms attached thereto, join to form C_6-C_{12} aryl, or 5 to 12 membered heteroaryl. In embodiments, R^{1B} and R^{1C}, attached on the same phenyl ring, together with atoms attached thereto, join to form phenyl. In embodiments, R^{1B} and R^{1C}, attached on the same phenyl ring, together with atoms attached thereto, join to form naphthyl or anthracenyl. In embodiments, R^{1B} and R^{1C}, attached on the same phenyl ring, together with atoms attached thereto, join to form pyridyl.

[00116] In embodiments, the C_6-C_{12} aryl or 5 to 12 membered heteroaryl, which are formed by R^{1B} and R^{1C} attached on the same phenyl ring, may be substituted with one or more substituents, e.g., halogen, -OH, $-NH_2$, substituted or unsubstituted C_1-C_6 alkyl, or substituted or unsubstituted 2 to 6 membered heteroalkyl.

[00117] In embodiments, R^{3A} is hydrogen or substituted or unsubstituted C_1-C_3 alkyl. In embodiments, R^{3A} is C_1-C_3 alkyl, and particularly methyl.

[00118] In embodiments, R^{3B} is hydrogen or substituted or unsubstituted C_1-C_3 alkyl. In embodiments, R^{3B} is C_1-C_3 alkyl, and particularly methyl.

[00119] In embodiments, R^{3A} and R^{3B} are both hydrogen. Alternatively, R^{3A} and R^{3B} are both methyl. In embodiments, one of R^{3A} and R^{3B} is hydrogen and the other is methyl.

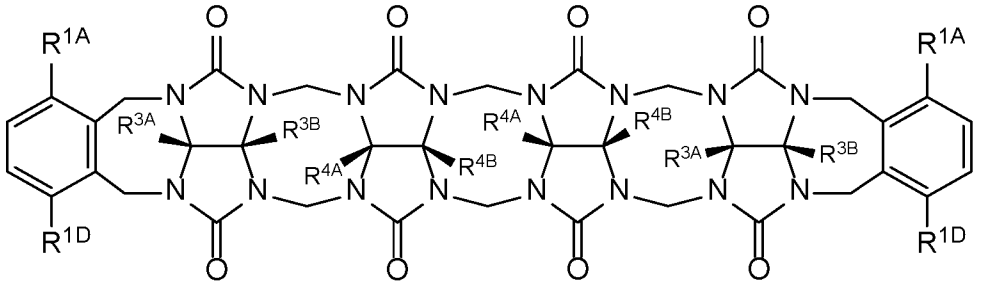
[00120] In embodiments, R^{4A} is hydrogen or substituted or unsubstituted C_1-C_3 alkyl. In embodiments, R^{4A} is C_1-C_3 alkyl, and particularly methyl. In embodiments, R^{4A} is H.

[00121] In embodiments, R^{4B} is hydrogen or substituted or unsubstituted C_1-C_3 alkyl. In embodiments, R^{4B} is C_1-C_3 alkyl, and particularly methyl. In embodiments, R^{4B} is hydrogen.

[00122] In embodiments, each R^{4A} and R^{4B} is hydrogen. Alternatively, each R^{4A} and R^{4B} may be methyl. In embodiments, one of R^{4A} and R^{4B} is hydrogen and the other is methyl.

[00123] In embodiments, each R^{3A} and R^{3B} is independently C_1-C_3 alkyl and R^{4A} and R^{4B} are hydrogen, and particularly, each R^{3A} and R^{3B} are methyl and each R^{4A} and R^{4B} are hydrogen.

[00124] In another aspect, the cucurbituril compound has the structure of formula XII:



(XII)

or a pharmaceutically acceptable salt thereof, wherein:

each R^{1A} and R^{1D} is independently selected from -O-L-CO_2X^1, and -O-L-SO_3X^1;

each L is independently selected from a chemical bond, C_2 to C_{10} alkylene, C_2 to C_{10} alkenylene, -$(CH_2)_a$-O-$(CH_2)_b$, -$(CH_2)_c$-N(R)-$(CH_2)_d$, and -$(CH_2)_a$-$(OCH_2CH_2)_e$-$(Y)_f$-, each of which may be unsubstituted or substituted at any carbon with 1 to 4 substituents selected from halogen, OH, CO_2H, C_{1-3} alkyl, NH_2, NH(C_{1-3} alkyl), N(C_{1-3} alkyl)$_2$, and O-C_{1-3} alkyl;

a is 2 to 8;

b is 0 to 6;

c is 2 to 8;

d is 0 to 6;

e is 1 to 6;

Y is NH, N(C_{1-3} alkyl), or O;

f is 0 or 1;

R is H or C_{1-3} alkyl;

each R^{3A} and R^{3B} is independently selected from hydrogen, halogen, -OH, CO_2H, CO_2R', $CONH_2$, CONHR', CON(R')$_2$, C_1-C_6 alkyl, phenyl, substituted phenyl and 2 to 6 membered heteroalkyl;

additionally or alternatively, R^{3A} and R^{3B} attached to adjacent carbon atoms, together with the carbons to which they are attached, are joined to form a 5- or 6-membered cycloalkyl or heterocycloalkyl ring;

each R^{4A} and R^{4B} is independently selected from hydrogen, halogen, -OH, CO_2H, CO_2R', $CONH_2$, CONHR', CON(R')$_2$, C_1-C_6 alkyl, phenyl, substituted phenyl and 2 to 6 membered heteroalkyl;

each R' is independently selected from C_{1-6} alkyl; and

each X^1 is independently selected from selected from H, C_1-C_6 alkyl, alkali metal cation, and quaternary ammonium cation.

[00125] In embodiments, L is C_1 to C_{10} alkylene, which may be unsubstituted or substituted with 1 to 4 substituents selected from halogen, OH, CO_2H, C_{1-3} alkyl, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl$)_2$, and O-C_{1-3} alkyl. In embodiments, L is C_2 to C_6 alkylene, which may be unsubstituted or substituted. L may be -CH_2-, -CH_2CH_2-, -$CH(CH_3)CH_2$-, -$CH_2CH_2CH_2$-, -$CH_2CH(CH_3)CH_2$-, -$CH_2CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2CH_2CH_2$-, and the like.

[00126] In other embodiments, L is a C_2 to C_{10} alkenylene chain, which may be unsubstituted or substituted with 1 to 4 substituents selected from halogen, OH, CO_2H, C_{1-3} alkyl, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl$)_2$, and O-C_{1-3} alkyl, and which comprises 1 to 3 carbon-carbon double bonds. In embodiments, L is C_2 to C_6 alkenylene, which may be unsubstituted or substituted. L may be -CH=CH-, -$C(CH_3)$=CH-, -CH_2CH=CH-, -CH=$C(CH_3)CH_2$-, -CH=CHCH_2CH_2-, -CH_2CH=CHCH_2-, -CH=CHCH=CH-, -$CH_2CH_2CH_2CH_2CH_2$-, -$CH_2CH_2CH_2$CH=CH-, -CH_2CH=CHCH=CH-, -CH_2CH_2CH=CHCH_2-, -$CH_2CH_2CH_2CH_2$CH=CH-, -CH_2CH_2CH=CHCH=CH-, and the like.

[00127] In other embodiments, L is -$(CH_2)_a$-$(OCH_2CH_2)_e$-$(Y)_f$-, each of which may be unsubstituted or substituted at any carbon with 1 to 4 substituents selected from halogen, OH, CO_2H, C_{1-3} alkyl, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl$)_2$, and O-C_{1-3} alkyl. L may comprise a polyethylene glycol oligomer, i.e., -$(CH_2CH_2O)_x$-, in which x is 2 to 6.

[00128] In other embodiments, L is a single bond.

[00129] In embodiments, R^{3A} is hydrogen or substituted or unsubstituted C_1-C_3 alkyl. In embodiments, R^{3A} is C_1-C_3 alkyl, and particularly methyl.

[00130] In embodiments, R^{3B} is hydrogen or substituted or unsubstituted C_1-C_3 alkyl. In embodiments, R^{3B} is C_1-C_3 alkyl, and particularly methyl.

[00131] In embodiments, R^{3A} and R^{3B} are both hydrogen. Alternatively, R^{3A} and R^{3B} may both be methyl. In embodiments, one of R^{3A} and R^{3B} is hydrogen and the other is methyl.

[00132] In embodiments, R^{4A} is hydrogen or substituted or unsubstituted C_1-C_3 alkyl. In embodiments, R^{4A} is C_1-C_3 alkyl, and particularly methyl. In embodiments, R^{4A} is H.

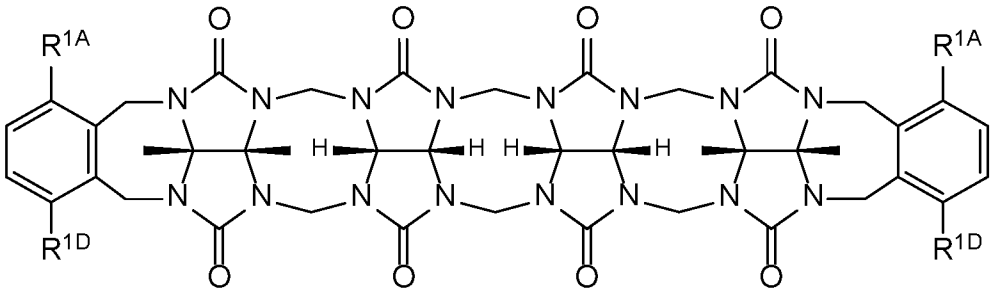
[00133] In embodiments, R^{4B} is hydrogen or substituted or unsubstituted C_1-C_3 alkyl. In embodiments, R^{4B} is C_1-C_3 alkyl, and particularly methyl. In embodiments, R^{4B} is hydrogen.

[00134] In embodiments, each R^{4A} and R^{4B} is hydrogen. Alternatively, each R^{4A} and R^{4B} may be methyl. In embodiments, one of R^{4A} and R^{4B} is hydrogen and the other is methyl.

[00135] In embodiments, each R^{3A} and R^{3B} is independently C_1-C_3 alkyl and R^{4A} and R^{4B} are hydrogen, and particularly, each R^{3A} and R^{3B} are methyl and each R^{4A} and R^{4B} are hydrogen.

[00136] In embodiments, R^{1A} and R^{1D} attached to the same phenyl ring may be same or different. In embodiments, R^{1A} and R^{1A} attached to the different phenyl rings may be same or different. In embodiments, R^{1D} and R^{1D} attached to the different phenyl rings may be same or different. In embodiments, each R^{1A} and R^{1D} is the same.

[00137] In another aspect, the cucurbituril compound has the structure of formula (XIIa):



(XIIa),

or a pharmaceutically acceptable salt thereof, wherein

each R^{1A} and R^{1D} is independently selected from -O-L-CO_2X^1 and -O-L-SO_3X^1;

each L is independently selected from a chemical bond, C_1 to C_{10} alkylene, C_2 to C_{10} alkenylene, $-(CH_2)_a$-O-$(CH_2)_b$-, $-(CH_2)_c$-N(R)-$(CH_2)_d$-, and $-(CH_2)_a$-$(OCH_2CH_2)_e$-$(Y)_f$-, each of which may be unsubstituted or substituted at any carbon with 1 to 4 substituents selected from halogen, OH, CO_2H, C_{1-3} alkyl, NH_2, NH(C_{1-3} alkyl), N(C_{1-3} alkyl)$_2$, and O-C_{1-3} alkyl;

a is 2 to 8;

b is 0 to 6;

c is 2 to 8;

d is 0 to 6;

e is 1 to 6;

Y is NH, N(C_{1-3} alkyl), or O;

f is 0 or 1;

R is H or C_{1-3} alkyl; and

each X^1 is independently selected from selected from H, C_1-C_6 alkyl, alkali metal cation, and quaternary ammonium cation.

[00138] In embodiments, L is C_1 to C_{10} alkylene, which may be unsubstituted or substituted with 1 to 4 substituents selected from halogen, OH, CO_2H, C_{1-3} alkyl, NH_2, NH(C_{1-3} alkyl),

$N(C_{1-3}$ alkyl$)_2$, and O-C_{1-3} alkyl. In embodiments, L is C_2 to C_6 alkylene, which may be unsubstituted or substituted. L may be -CH_2-, -CH_2CH_2-, -$CH(CH_3)CH_2$-, -$CH_2CH_2CH_2$-, -$CH_2CH(CH_3)CH_2$-, -$CH_2CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2CH_2CH_2$-, and the like.

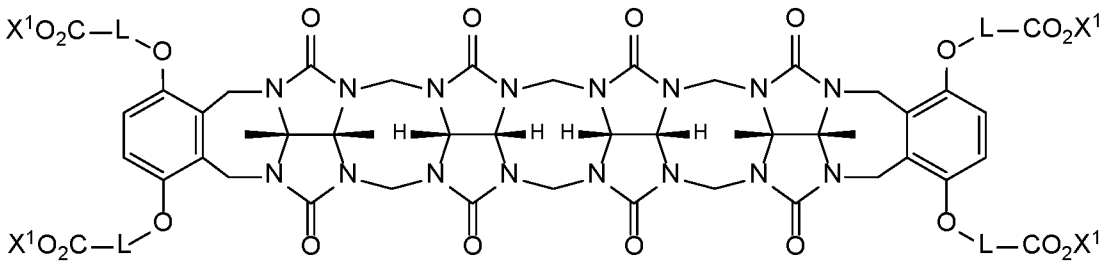
[00139] In other embodiments, L is a C_2 to C_{10} alkenylene chain, which may be unsubstituted or substituted with 1 to 4 substituents selected from halogen, OH, CO_2H, C_{1-3} alkyl, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl$)_2$, and O-C_{1-3} alkyl, and which comprises 1 to 3 carbon-carbon double bonds. In embodiments, L is C_2 to C_6 alkenylene, which may be unsubstituted or substituted. L may be -CH=CH-, -$C(CH_3)$=CH-, -CH_2CH=CH-, -CH=$C(CH_3)CH_2$-, -CH=CHCH_2CH_2-, -CH_2CH=CHCH_2-, -CH=CHCH=CH-, -$CH_2CH_2CH_2CH_2CH_2$-, -$CH_2CH_2CH_2$CH=CH-, -CH_2CH=CHCH=CH-, -CH_2CH_2CH=CHCH_2-, -$CH_2CH_2CH_2CH_2$CH=CH-, -CH_2CH_2CH=CHCH=CH-, and the like.

[00140] In other embodiments, L is -$(CH_2)_a$-$(OCH_2CH_2)_e$-$(Y)_f$-, each of which may be unsubstituted or substituted at any carbon with 1 to 4 substituents selected from halogen, OH, CO_2H, C_{1-3} alkyl, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl$)_2$, and O-C_{1-3} alkyl. L may comprise a polyethylene glycol oligomer, i.e., -$(CH_2CH_2O)_x$-, in which x is 2 to 6.

[00141] In other embodiments, L is a single bond.

[00142] In embodiments, R^{1A} and R^{1D} attached to the same phenyl ring may be same or different. In embodiments, R^{1A} and R^{1A} attached to the different phenyl rings may be same or different. In embodiments, R^{1D} and R^{1D} attached to the different phenyl rings may be same or different. In embodiments, each R^{1A} and R^{1D} is the same.

[00143] In another aspect, the cucurbituril compound has the structure of formula (XIIb):



(XIIb)

or a pharmaceutically acceptable salt thereof, wherein

each L is independently selected from C_1 to C_{10} alkylene, C_2 to C_{10} alkenylene, -$(CH_2)_a$-O-$(CH_2)_b$, -$(CH_2)_c$-N(R)-$(CH_2)_d$, and -$(CH_2)_a$-$(OCH_2CH_2)_e$-$(Y)_f$-, each of which may be unsubstituted or substituted at any carbon with 1 to 4 substituents selected from halogen, OH, CO_2H, C_{1-3} alkyl, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl$)_2$, and O-C_{1-3} alkyl;

a is 2 to 8;

b is 0 to 6;

c is 2 to 8;

d is 0 to 6;

e is 1 to 6;

Y is NH, N(C_{1-3} alkyl), or O;

f is 0 or 1;

R is H or C_{1-3} alkyl; and

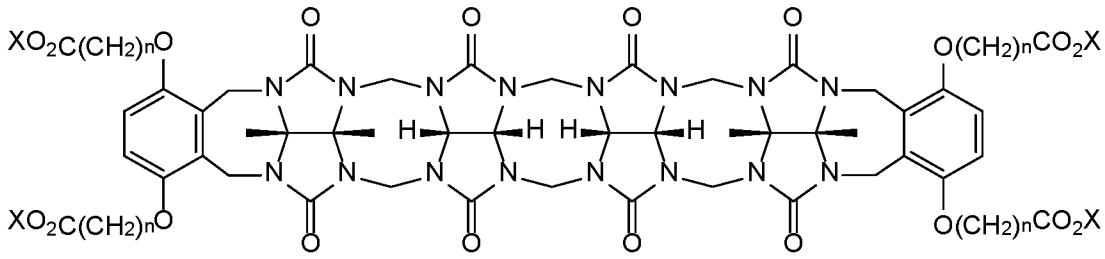
each X^1 is independently selected from selected from H, C_1-C_6 alkyl, alkali metal cation, and quaternary ammonium cation.

[00144] In embodiments, L is C_1 to C_{10} alkylene, which may be unsubstituted or substituted with 1 to 4 substituents selected from halogen, OH, CO_2H, C_{1-3} alkyl, NH_2, NH(C_{1-3} alkyl), N(C_{1-3} alkyl)$_2$, and O-C_{1-3} alkyl. In embodiments, L is C_2 to C_6 alkylene, which may be unsubstituted or substituted. L may be -CH_2-, -CH_2CH_2-, -$CH(CH_3)CH_2$-, -$CH_2CH_2CH_2$-, -$CH_2CH(CH_3)CH_2$-, -$CH_2CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2CH_2CH_2$-, and the like.

[00145] In other embodiments, L is a C_2 to C_{10} alkenylene chain, which may be unsubstituted or substituted with 1 to 4 substituents selected from halogen, OH, CO_2H, C_{1-3} alkyl, NH_2,
NH(C_{1-3} alkyl), N(C_{1-3} alkyl)$_2$, and O-C_{1-3} alkyl, and which comprises 1 to 3 carbon-carbon double bonds. In embodiments, L is C_2 to C_6 alkenylene, which may be unsubstituted or substituted. L may be -CH=CH-, -$C(CH_3)$=CH-, -CH_2CH=CH-, -CH=$C(CH_3)CH_2$-, -CH=CHCH_2CH_2-, -CH_2CH=CHCH_2-, -CH=CHCH=CH-, -$CH_2CH_2CH_2CH_2CH_2$-, -$CH_2CH_2CH_2$CH=CH-, -CH_2CH=CHCH=CH-, -CH_2CH_2CH=CHCH_2-, -$CH_2CH_2CH_2CH_2$CH=CH-, -CH_2CH_2CH=CHCH=CH-, and the like.

[00146] In other embodiments, L is -$(CH_2)_a$-$(OCH_2CH_2)_e$-$(Y)_f$-, each of which may be unsubstituted or substituted at any carbon with 1 to 4 substituents selected from halogen, OH, CO_2H, C_{1-3} alkyl, NH_2, NH(C_{1-3} alkyl), N(C_{1-3} alkyl)$_2$, and O-C_{1-3} alkyl. L may comprise a polyethylene glycol oligomer, i.e., -$(CH_2CH_2O)_x$-, in which *x* is 2 to 6.

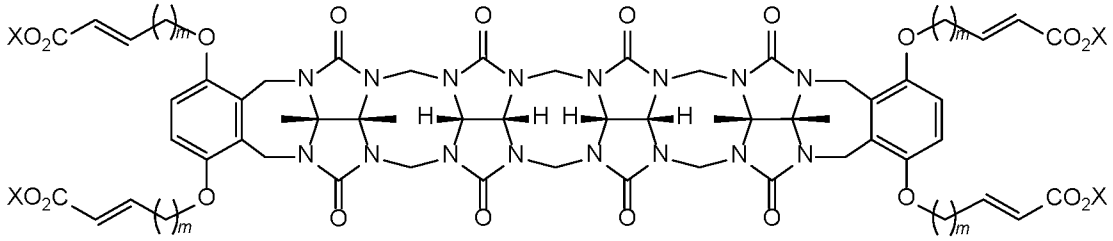
[00147] In another aspect, the cucurbituril compound has the structure of formula (XIIc),



(XIIc)

or a pharmaceutically acceptable salt thereof. Each X is independently H, alkali metal cation (e.g., Li^+, Na^+, K^+, or Cs^+), an ammonium cation, or combination thereof. Each n is independently 1, 2, 3 or 4.

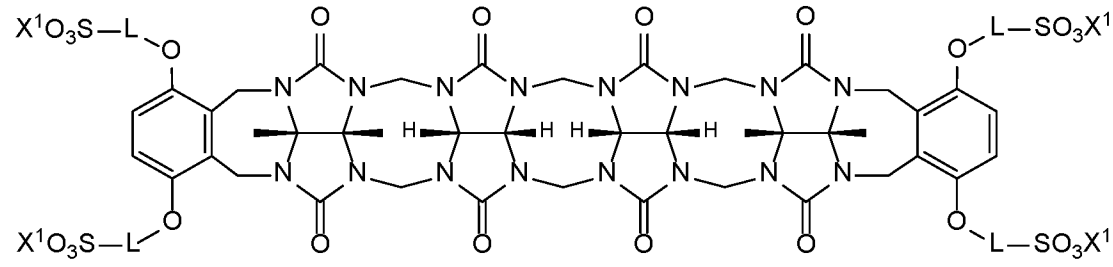
[00148] In another aspect, the cucurbituril compound has the structure of formula (XIId),



(XIId)

or a pharmaceutically acceptable salt thereof. Each X is independently H, alkali metal cation (e.g., Li^+, Na^+, K^+, or Cs^+), an ammonium cation, or combination thereof. Each m is independently 1, 2, 3 or 4.

[00149] In another aspect, the cucurbituril compound has the structure of formula (XIIe):



(XIIe)

or a pharmaceutically acceptable salt thereof, wherein:

each L is independently selected from a chemical bond, C_1 to C_{10} alkylene, C_2 to C_{10} alkenylene, $-(CH_2)_a-O-(CH_2)_b$, $-(CH_2)_c-N(R)-(CH_2)_d$, and $-(CH_2)_a-(OCH_2CH_2)_e-(Y)_f-$, each of which may be unsubstituted or substituted at any carbon with 1 to 4 substituents selected from halogen, OH, CO_2H, C_{1-3} alkyl, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl$)_2$, and O-C_{1-3} alkyl;

a is 2 to 8;

b is 0 to 6;

c is 2 to 8;

d is 0 to 6;

e is 1 to 6;

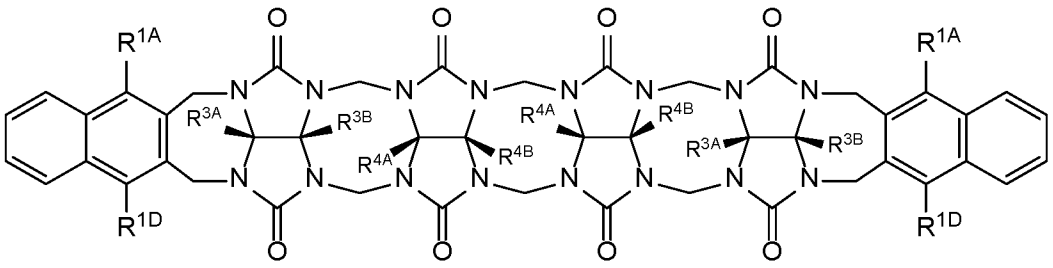
Y is NH, N(C_{1-3} alkyl), or O;

f is 0 or 1;

R is H or C_{1-3} alkyl; and

each X^1 is independently selected from selected from H, C_1-C_6 alkyl, alkali metal cation, and quaternary ammonium cation.

[00150] In another aspect, the cucurbituril compound has the structure of formula (XIII):



(XIII)

or a pharmaceutically acceptable salt thereof, wherein:

each R^{1A} and R^{1D} is independently selected from -O-L-CO_2X^1 and -O-L-SO_3X^1;

each L is independently selected from a chemical bond, C_1 to C_{10} alkylene, C_2 to C_{10} alkenylene, -$(CH_2)_a$-O-$(CH_2)_b$, -$(CH_2)_c$-N(R)-$(CH_2)_d$, and -$(CH_2)_a$-$(OCH_2CH_2)_e$-$(Y)_f$-, each of which may be unsubstituted or substituted at any carbon with 1 to 4 substituents selected from halogen, OH, CO_2H, C_{1-3} alkyl, NH_2, NH(C_{1-3} alkyl), N(C_{1-3} alkyl)$_2$, and

O-C_{1-3} alkyl;

a is 2 to 8;

b is 0 to 6;

c is 2 to 8;

d is 0 to 6;

e is 1 to 6;

Y is NH, N(C_{1-3} alkyl), or O;

f is 0 or 1;

R is H or C_{1-3} alkyl;

each R^{3A} and R^{3B} is independently selected from hydrogen, halogen, CO_2H, CO_2R', $CONH_2$, CONHR', CON(R')$_2$, -OH, C_1-C_6 alkyl, phenyl, substituted phenyl and 2 to 6 membered heteroalkyl;

additionally or alternatively, R^{3A} and R^{3B} attached to adjacent carbon atoms, together with the carbons to which they are attached, are joined to form a 5- or 6-membered cycloalkyl or heterocycloalkyl ring;

each R^{4A} and R^{4B} is independently selected from hydrogen, halogen, -OH, CO_2H, CO_2R', $CONH_2$, CONHR', $CON(R')_2$, C_1-C_6 alkyl, phenyl, substituted phenyl and 2 to 6 membered heteroalkyl;

each R' is independently selected from C_{1-6} alkyl; and

each X^1 is independently selected from selected from H, C_1-C_6 alkyl, alkali metal cation, and quaternary ammonium cation.

[00151] In embodiments, L is C_1 to C_{10} alkylene, which may be unsubstituted or substituted with 1 to 4 substituents selected from halogen, OH, CO_2H, C_{1-3} alkyl, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl)$_2$, and O-C_{1-3} alkyl. In embodiments, L is C_1 to C_{10} alkylene, C_2 to C_{10} alkylene, C_1 to C_6 alkylene, or C_2 to C_6 alkylene, each of which may be unsubstituted or substituted. L may be $-CH_2-$, $-CH_2CH_2-$, $-CH(CH_3)CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH(CH_3)CH_2-$, $-CH_2CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2CH_2CH_2-$, and the like.

[00152] In other embodiments, L is a C_2 to C_{10} alkenylene chain, which may be unsubstituted or substituted with 1 to 4 substituents selected from halogen, OH, CO_2H, C_{1-3} alkyl, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl)$_2$, and O-C_{1-3} alkyl, and which comprises 1 to 3 carbon-carbon double bonds. In embodiments, L is C_2 to C_6 alkenylene, which may be unsubstituted or substituted. L may be $-CH=CH-$, $-C(CH_3)=CH-$, $-CH_2CH=CH-$, $-CH=C(CH_3)CH_2-$, $-CH=CHCH_2CH_2-$, $-CH_2CH=CHCH_2-$, $-CH=CHCH=CH-$, $-CH_2CH_2CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH=CH-$, $-CH_2CH=CHCH=CH-$, $-CH_2CH_2CH=CHCH_2-$, $-CH_2CH_2CH_2CH_2CH=CH-$, $-CH_2CH_2CH=CHCH=CH-$, and the like.

[00153] In other embodiments, L is $-(CH_2)_a-(OCH_2CH_2)_e-(Y)_f-$, each of which may be unsubstituted or substituted at any carbon with 1 to 4 substituents selected from halogen, OH, CO_2H, C_{1-3} alkyl, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl)$_2$, and O-C_{1-3} alkyl. L may comprise a polyethylene glycol oligomer, i.e., $-(CH_2CH_2O)_x-$, in which x is 2 to 6.

[00154] In other embodiments, L is a chemical bond (i.e., a single bond).

[00155] In embodiments, R^{3A} is hydrogen or substituted or unsubstituted C_1-C_3 alkyl. In embodiments, R^{3A} is C_1-C_3 alkyl, and particularly methyl.

[00156] In embodiments, R^{3B} is hydrogen or substituted or unsubstituted C_1-C_3 alkyl. In embodiments, R^{3B} is C_1-C_3 alkyl, and particularly methyl.

[00157] In embodiments, R^{3A} and R^{3B} are both hydrogen. Alternatively, R^{3A} and R^{3B} may both be methyl. In embodiments, one of R^{3A} and R^{3B} is hydrogen and the other is methyl.

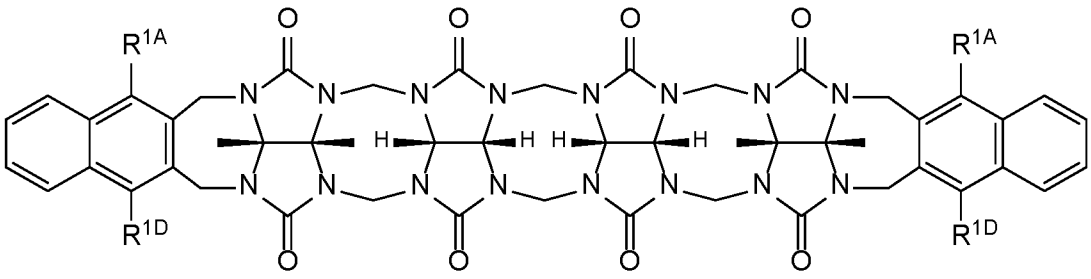
[00158] In embodiments, R^{4A} is hydrogen or substituted or unsubstituted C_1-C_3 alkyl. In embodiments, R^{4A} is C_1-C_3 alkyl, and particularly methyl. In embodiments, R^{4A} is H.

[00159] In embodiments, R^{4B} is hydrogen or substituted or unsubstituted C_1-C_3 alkyl. In embodiments, R^{4B} is C_1-C_3 alkyl, and particularly methyl. In embodiments, R^{4B} is hydrogen.

[00160] In embodiments, each R^{4A} and R^{4B} is hydrogen. Alternatively, each R^{4A} and R^{4B} may be methyl. In embodiments, one of R^{4A} and R^{4B} is hydrogen and the other is methyl.

[00161] In embodiments, each R^{3A} and R^{3B} is independently C_1-C_3 alkyl and R^{4A} and R^{4B} are hydrogen, and particularly, each R^{3A} and R^{3B} are methyl and each R^{4A} and R^{4B} are hydrogen.

[00162] In another aspect, the cucurbituril compound has the structure of formula (XIIIa)



(XIIIa)

or a pharmaceutically acceptable salt thereof, wherein"

each R^{1A} and R^{1D} is independently selected from -O-L-CO_2X^1 and -O-L-SO_3X^1;

each L is independently selected from a chemical bond, C_1 to C_{10} alkylene, C_2 to C_{10} alkenylene, $-(CH_2)_a$-O-$(CH_2)_b$, $-(CH_2)_c$-N(R)-$(CH_2)_d$, and $-(CH_2)_a$-$(OCH_2CH_2)_e$-$(Y)_f$-, each of which may be unsubstituted or substituted at any carbon with 1 to 4 substituents selected from halogen, OH, CO_2H, C_{1-3} alkyl, NH_2, NH(C_{1-3} alkyl), N(C_{1-3} alkyl)$_2$, and

O-C_{1-3} alkyl;

a is 2 to 8;

b is 0 to 6;

c is 2 to 8;

d is 0 to 6;

e is 1 to 6;

Y is NH, N(C_{1-3} alkyl), or O;

f is 0 or 1;

R is H or C_{1-3} alkyl; and

each X^1 is independently selected from selected from H, C_1-C_6 alkyl, alkali metal cation, and quaternary ammonium cation.

[00163] In embodiments, L is C_1 to C_{10} alkylene, which may be unsubstituted or substituted with 1 to 4 substituents selected from halogen, OH, CO_2H, C_{1-3} alkyl, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl)$_2$, and O-C_{1-3} alkyl. In embodiments, L is C_1 to C_{10} alkylene, C_2 to C_{10} alkylene, C_1 to C_6 alkylene, or C_2 to C_6 alkylene, each of which may be unsubstituted or substituted. L may be -CH_2-, -CH_2CH_2-, -$CH(CH_3)CH_2$-, -$CH_2CH_2CH_2$-, -$CH_2CH(CH_3)CH_2$-, -$CH_2CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2CH_2CH_2$-, and the like.

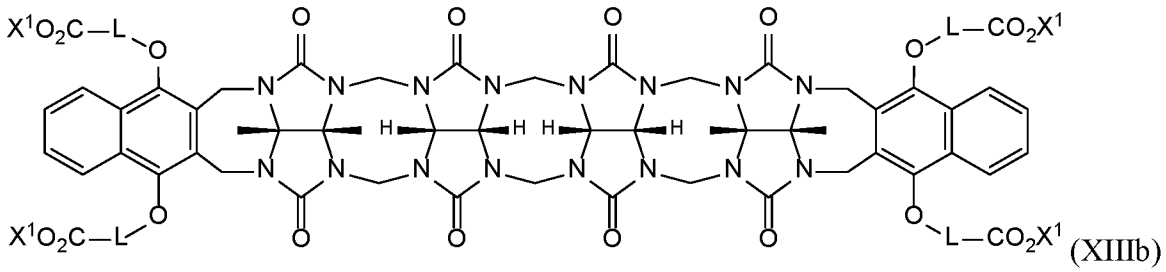
[00164] In other embodiments, L is a C_2 to C_{10} alkenylene chain, which may be unsubstituted or substituted with 1 to 4 substituents selected from halogen, OH, CO_2H, C_{1-3} alkyl, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl)$_2$, and O-C_{1-3} alkyl, and which comprises 1 to 3 carbon-carbon double bonds. In embodiments, L is C_2 to C_6 alkenylene, which may be unsubstituted or substituted. L may be -CH=CH-, -$C(CH_3)$=CH-, -CH_2CH=CH-, -CH=$C(CH_3)CH_2$-, -CH=CHCH_2CH_2-, -CH_2CH=CHCH_2-, -CH=CHCH=CH-, -$CH_2CH_2CH_2CH_2CH_2$-, -$CH_2CH_2CH_2$CH=CH-, -CH_2CH=CHCH=CH-, -CH_2CH_2CH=CHCH_2-, -$CH_2CH_2CH_2CH_2$CH=CH-, -CH_2CH_2CH=CHCH=CH-, and the like.

[00165] In other embodiments, L is -$(CH_2)_a$-$(OCH_2CH_2)_e$-$(Y)_f$-, each of which may be unsubstituted or substituted at any carbon with 1 to 4 substituents selected from halogen, OH, CO_2H, C_{1-3} alkyl, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl)$_2$, and O-C_{1-3} alkyl. L may comprise a polyethylene glycol oligomer, i.e., -$(CH_2CH_2O)_x$-, in which x is 2 to 6.

[00166] In embodiments, L is a chemical bond.

[00167] In embodiments, R^{1A} and R^{1D} attached to the same phenyl ring may be same or different. In embodiments, R^{1A} and R^{1A} attached to the different phenyl rings may be same or different. In embodiments, R^{1D} and R^{1D} attached to the different phenyl rings may be same or different. In embodiments, each R^{1A} and R^{1D} is the same.

[00168] In another aspect, the cucurbituril compound has the structure of formula (XIIIb):



(XIIIb)

or a pharmaceutically acceptable salt thereof, wherein:

each L is independently selected from C_1 to C_{10} alkylene, C_2 to C_{10} alkenylene, $-(CH_2)_a-O-(CH_2)_b-$, $-(CH_2)_c-N(R)-(CH_2)_d-$, and $-(CH_2)_a-(OCH_2CH_2)_e-(Y)_f-$, each of which may be unsubstituted or substituted at any carbon with 1 to 4 substituents selected from halogen, OH, CO_2H, C_{1-3} alkyl, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl$)_2$, and O-C_{1-3} alkyl;

a is 2 to 8;

b is 0 to 6;

c is 2 to 8;

d is 0 to 6;

e is 1 to 6;

Y is NH, $N(C_{1-3}$ alkyl), or O;

f is 0 or 1;

R is H or C_{1-3} alkyl; and

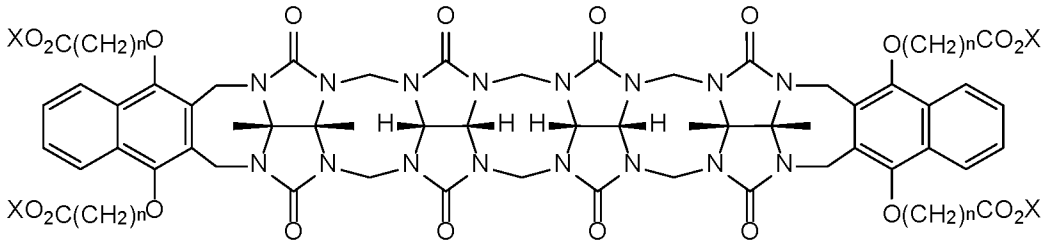
each X^1 is independently selected from selected from H, C_1-C_6 alkyl, alkali metal cation, and quaternary ammonium cation.

[00169] In embodiments, L is C_1 to C_{10} alkylene, which may be unsubstituted or substituted with 1 to 4 substituents selected from halogen, OH, CO_2H, C_{1-3} alkyl, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl$)_2$, and O-C_{1-3} alkyl. In embodiments, L is C_1 to C_{10} alkylene, C_2 to C_{10} alkylene, C_1 to C_6 alkylene, or C_2 to C_6 alkylene, each of which may be unsubstituted or substituted. L may be $-CH_2-$, $-CH_2CH_2-$, $-CH(CH_3)CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH(CH_3)CH_2-$, $-CH_2CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2CH_2CH_2-$, and the like.

[00170] In other embodiments, L is a C_2 to C_{10} alkenylene chain, which may be unsubstituted or substituted with 1 to 4 substituents selected from halogen, OH, CO_2H, C_{1-3} alkyl, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl$)_2$, and O-C_{1-3} alkyl, and which comprises 1 to 3 carbon-carbon double bonds. In embodiments, L is C_2 to C_6 alkenylene, which may be unsubstituted or substituted. L may be $-CH=CH-$, $-C(CH_3)=CH-$, $-CH_2CH=CH-$, $-CH=C(CH_3)CH_2-$, $-CH=CHCH_2CH_2-$, $-CH_2CH=CHCH_2-$, $-CH=CHCH=CH-$, $-CH_2CH_2CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH=CH-$, $-CH_2CH=CHCH=CH-$, $-CH_2CH_2CH=CHCH_2-$, $-CH_2CH_2CH_2CH_2CH=CH-$, $-CH_2CH_2CH=CHCH=CH-$, and the like.

[00171] In other embodiments, L is $-(CH_2)_a-(OCH_2CH_2)_e-(Y)_f-$, each of which may be unsubstituted or substituted at any carbon with 1 to 4 substituents selected from halogen, OH, CO_2H, C_{1-3} alkyl, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl$)_2$, and O-C_{1-3} alkyl. L may comprise a polyethylene glycol oligomer, i.e., $-(CH_2CH_2O)_x-$, in which *x* is 2 to 6.

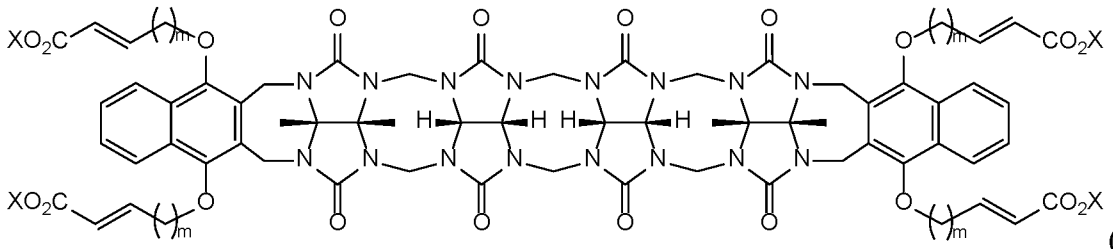
[00172] In another aspect, the cucurbituril compound has the structure of formula (XIIIc):



(XIIIc)

or a pharmaceutically acceptable salt thereof. Each X is independently H, alkali metal cation (e.g., Li^+, Na^+, K^+, or Cs^+), an ammonium cation, or combination thereof. Each n is independently 1, 2, 3 or 4.

[00173] In another aspect, the cucurbituril compound has the structure of formula (XIIId):

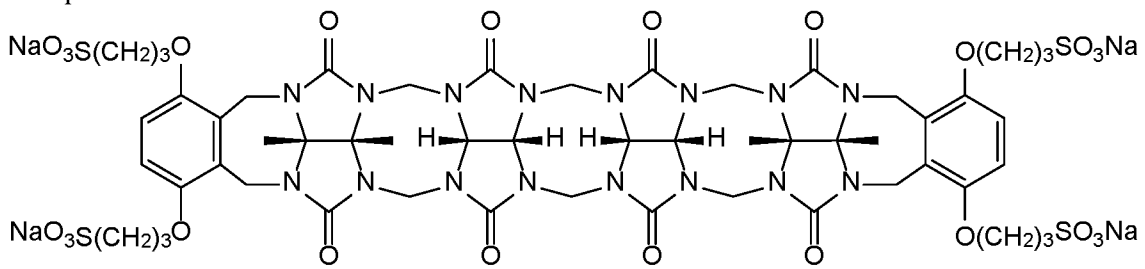


(XIIId)

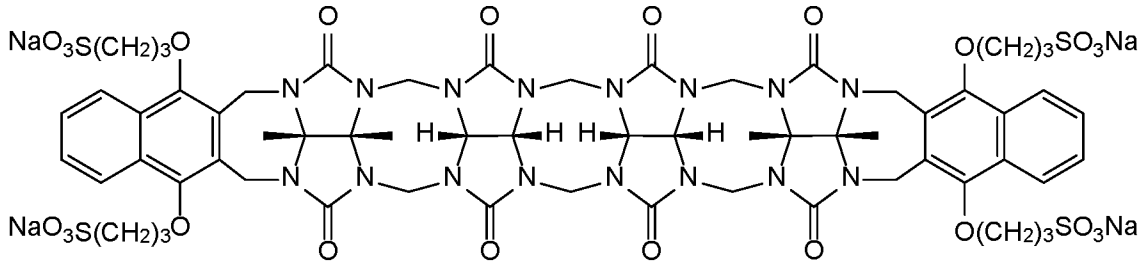
or a pharmaceutically acceptable salt thereof. Each X is independently H, alkali metal cation (e.g., Li^+, Na^+, K^+, or Cs^+), an ammonium cation, or combination thereof. Each m is independently 1, 2, 3 or 4.

[00174] Cucurbituril compounds may have the following chemical structures:

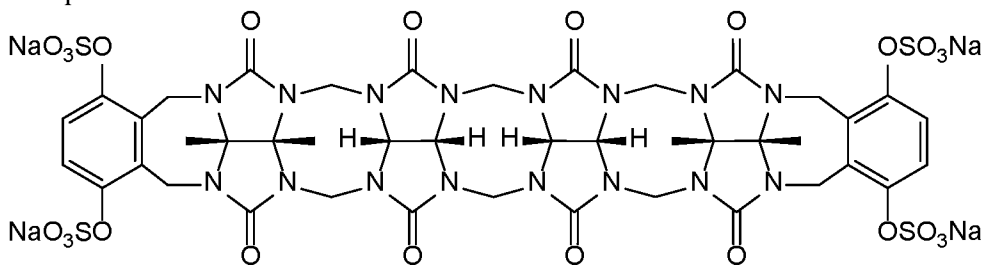
Compound A:



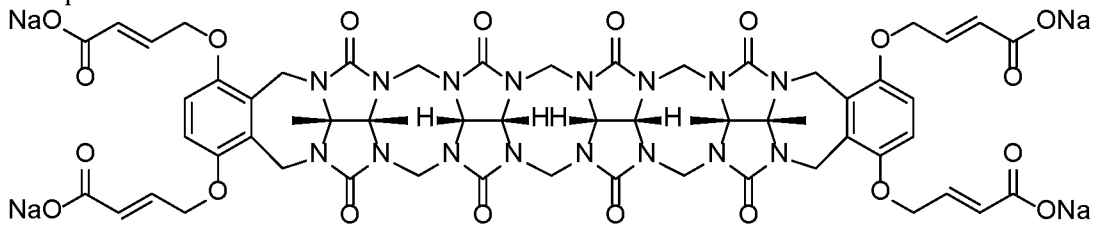
Compound B:



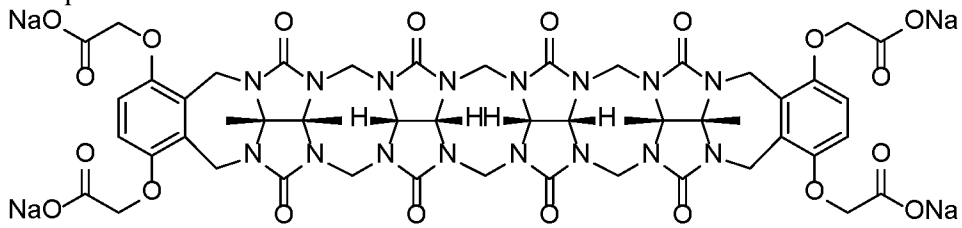
Compound C



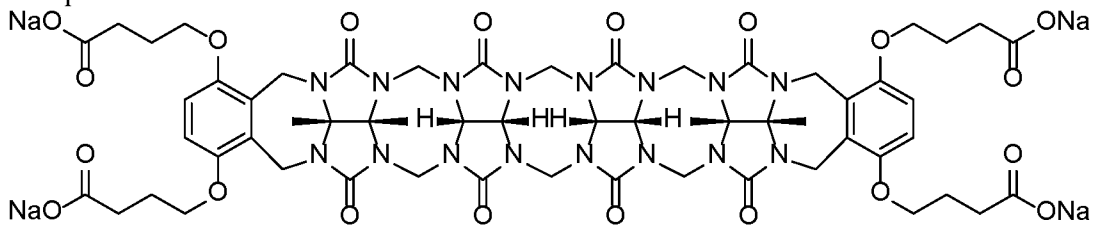
Compound D



Compound E



Compound F



[00175] Cucurbituril compounds may be prepared according to the methods of U.S. App No. 15/417,785 (US 2017/0137431); U.S. provisional application 63/380,318, filed 10/20/2022 and entitled Methods of Synthesis For Cucurbituril Compounds; each of which is incorporated herein by reference in their entirety.

[00176] The abbreviations used herein have their conventional meaning within the chemical and biological arts. The chemical structures and formulae set forth herein are constructed according to the standard rules of chemical valency known in the chemical arts.

[00177] The term "alkyl" refers to the radical of saturated aliphatic groups, including straight-chain alkyl groups and branched-chain alkyl groups. The alkyl may include a designated number of carbons (e.g., C_1-C_{10} means one to ten carbons). Examples of alkyl groups include, but are not limited to, groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like.

[00178] The term "alkenyl" refers to a linear or branched hydrocarbyl having at least one carbon-carbon double bond and including straight-chain and branched-chain alkenyl groups. Examples of alkenyl groups (e.g., "C_2-C_6 alkenyl") includes vinyl, 1-propenyl, 2-propenyl, 2-butenyl, 3-butenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 2-methyl-2-propenyl, 4-methyl-3-pentenyl, and the like. When the compound of the present disclosure contains an alkenyl group, the compound may exist as the E-form, the Z-form, or any mixture thereof.

[00179] The term "alkynyl" refers to a linear or branched hydrocarbyl having at least one carbon-carbon triple bond and including straight-chain and branched-chain alkynyl groups. Examples of alkenyl groups (e.g., "C_2-C_6 alkynyl") includes ethynyl, propynyl, and the like.

[00180] The term "cycloalkyl" refers to saturated, carbocyclic groups having from 3 to 9 carbons in the ring and including a monocyclic, bicyclic, or a multicyclic cycloalkyl ring system. Cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. Examples of monocyclic cycloalkyls include cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, and cyclooctyl. Bicyclic cycloalkyl ring systems are bridged monocyclic rings or fused bicyclic rings. In embodiments, bridged monocyclic rings contain a monocyclic cycloalkyl ring where two non-adjacent carbon atoms of the monocyclic ring are linked by an alkylene bridge of between one and three additional carbon atoms (i.e., a bridging group of the form $(CH_2)_w$, where w is 1, 2, or 3). Representative examples of bicyclic ring systems include, but are not limited to, bicyclo[3.1.1]heptane, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, bicyclo[3.2.2]nonane, bicyclo[3.3.1]nonane, and bicyclo[4.2.1]nonane.

[00181] The term "heteroalkyl," by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain, or combinations thereof, including at least one carbon atom and at least one heteroatom (e.g., O, N, P, Si, and S), and wherein the nitrogen and sulfur atoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) (e.g., N, S, Si, or P) may be

placed at any interior position of the heteroalkyl group or at the position at which the alkyl group is attached to the remainder of the molecule. Examples include, but are not limited to: -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, -O-C_2-C_6 alkynyl, -S-C_1-C_6 alkyl, -S-C_2-C_6 alkenyl, -S-C_2-C_6 alkynyl, -NH-C_1-C_6 alkyl, -NH-C_2-C_6 alkenyl, -NH-C_2-C_6 alkynyl, -N-(C_1-C_6 alkyl)$_2$, -S(O)-C_1-C_6 alkyl, -S(O)-C_2-C_6 alkenyl, -S(O)-C_2-C_6 alkynyl, -S(O)$_2$-C_1-C_6 alkyl, -S(O)$_2$-C_2-C_6 alkenyl, -S(O)$_2$-C_2-C_6 alkynyl, -C_1-C_6 alkyl-O-C_1-C_6 alkyl, -C_1-C_6 alkyl-S-C_1-C_6 alkyl, -C_1-C_6 alkyl-NH-C_1-C_6 alkyl, -C_1-C_6 alkyl-N-(C_1-C_6 alkyl)$_2$, -C_1-C_6 alkyl-S(O)-C_1-C_6 alkyl, -C_1-C_6 alkyl-S(O)$_2$-C_1-C_6 alkyl, and more particularly include, but are not limited to: —CH_2—O—CH_3, —CH_2—NH—CH_3, —CH_2—CH_2—N(CH_3)—CH_3, —CH_2—S—CH_3, —S(O)—CH_3, —CH_2—S(O)$_2$—CH_3, —Si(CH_3)$_3$, —O—CH_3, or —O—CH_2—CH_3. Up to two or three heteroatoms may be consecutive, such as, for example, —CH_2—NH—OCH_3 and —CH_2—O—Si(CH_3)$_3$. The term "heteroalkenyl," by itself or in combination with another term, means, unless otherwise stated, a heteroalkyl including at least one carbon-carbon double bond. The term "heteroalkynyl," by itself or in combination with another term, means, unless otherwise stated, a heteroalkyl including at least one carbon-carbon triple bond.

[00182] The term "cycloalkenyl" as used herein is a monocyclic, bicyclic, or a multicyclic cycloalkenyl ring system. In embodiments, monocyclic cycloalkenyl ring systems are cyclic hydrocarbon groups containing from 3 to 9 carbon atoms, where such groups are unsaturated (i.e., containing at least one annular carbon-carbon double bond), but not aromatic. Examples of monocyclic cycloalkenyl ring systems include cyclopentenyl and cyclohexenyl. In embodiments, bicyclic cycloalkenyl rings are bridged or fused bicyclic rings.

[00183] The term "heterocycle," "heterocyclyl" or "heterocyclic" as used herein, means a monocyclic, bicyclic, or multicyclic heterocycle. The monocyclic heterocycle is a 3, 4, 5, 6, 7 or 8 membered ring containing at least one heteroatom independently selected from the group consisting of O, N, S, Si, and P where the ring is saturated or unsaturated, but not aromatic. Representative examples of monocyclic heterocycles include, but are not limited to, azetidinyl, azepanyl, aziridinyl, diazepanyl, 1,3-dioxanyl, 1,3-dioxolanyl, 1,3-dithiolanyl, 1,3-dithianyl, imidazolinyl, imidazolidinyl, isothiazolinyl, isothiazolidinyl, isoxazolinyl, isoxazolidinyl, morpholinyl, oxadiazolinyl, oxadiazolidinyl, oxazolinyl, oxazolidinyl, piperazinyl, piperidinyl, pyranyl, pyrazolinyl, pyrazolidinyl, pyrrolinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothienyl, thiadiazolinyl, thiadiazolidinyl, thiazolinyl,

thiazolidinyl, thiomorpholinyl, 1,1-dioxidothiomorpholinyl (thiomorpholine sulfone), thiopyranyl, and trithianyl. Representative examples of bicyclic heterocycles include, but are not limited to, 2,3-dihydrobenzofuran-2-yl, 2,3-dihydrobenzofuran-3-yl, indolin-1-yl, indolin-2-yl, indolin-3-yl, 2,3-dihydrobenzothien-2-yl, decahydroquinolinyl, decahydroisoquinolinyl, octahydro-1H-indolyl, and octahydrobenzofuranyl. The heterocycle is connected to the parent molecular moiety through any carbon atom or any nitrogen atom contained within the monocyclic or bicyclic ring system.

[00184] The term "aryl" as used herein includes 5- and 6-membered single-ring aromatic groups that may include from zero to four heteroatoms, for example, benzene, pyrene, pyrrole, furan, thiophene, imidazole, oxazole, thiazole, triazole, pyrazole, pyridine, pyrazine, pyridazine and pyrimidine, and the like. Those aryl groups having heteroatoms in the ring structure may also be referred to as "aryl heterocycles", "heteroaromatics" or "heteroaryl". The term “aryl” also includes 7- to 14-membered polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings (the rings are "fused rings") wherein at least one of the rings is aromatic (including heteroaryl), e.g., the other cyclic rings can be fused cycloalkyls, cycloalkenyls, aryls, heteroaryl and/or heterocyclic groups. Single-ring heteroaryl groups may have from 1 to 3 ring heteroatoms and fused polycyclic heteroaryl groups may have from 1 to 5 ring heteroatoms, wherein the ring heteroatoms are selected from N, O and S.

[00185] The term “alkylene,” by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from an alkyl, as exemplified, but not limited by, —$CH_2CH_2CH_2CH_2$—. Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms being preferred herein. A “lower alkyl” or “lower alkylene” is a shorter chain alkyl or alkylene group, generally having eight or fewer carbon atoms. The term “alkenylene,” by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from an alkene.

[00186] It will be understood that "substituted", "substitution" or "substituted with" includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, e.g., which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc. Exemplary substituents as used herein means a

group selected from oxo, halogen, —CN, —OH, —NH_2, —COOH, —$CONH_2$, —NO_2, —SH, —SCH_3, —SO_3H, —SO_4H, —SO_2NH_2, —$NHNH_2$, —ONH_2, —$NHC(O)NHNH_2$, —$NHC(O)NH_2$, —$NHSO_2H$, —NHC(O)H, —NHC(O)OH, —NHOH, —OCF_3, —$OCCl_3$, —$OCBr_3$, —OCI_3, —$OCHF_2$, —$OCHCl_2$, —$OCHBr_2$, —$OCHI_2$, —OCH_2F, —OCH_2Cl, —OCH_2Br, —OCH_2I, alkyl (e.g., C_1-C_8 alkyl, C_1-C_6 alkyl, or C_1-C_4 alkyl), heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), cycloalkyl (e.g., C_3-C_8 cycloalkyl, C_3-C_6 cycloalkyl, or C_5-C_6 cycloalkyl), heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), aryl (e.g., C_6-C_{10} aryl, C_{10} aryl, or phenyl), or heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl), and these alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl may be optionally substituted with at least one substituents. For example, in the cucurbituril compounds disclosed herein, each alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, phenyl, heteroaryl and heterocycle may be optionally substituted with 1 to 4 substituents selected from the foregoing substituents.

[00187] A quaternary ammonium cation as used herein is has the structure $^{+}N(R)_4$, wherein each R is independently selected from alkyl, cycloalkyl, aryl, aralkyl and heteroaryl, each of which may be optionally substituted. The quaternary ammonium cations, for example, may have the structure $^{+}N(C_{1\text{-}6}$ alkyl$)_4$, wherein each of the $C_{1\text{-}6}$ alkyl group boned to the nitrogen is independently selected.

[00188] The terms “a” or “an” as used in herein means one or more. In addition, the phrase “substituted with a[n],” as used herein, means the specified group may be substituted with one or more of any or all of the named substituents. For example, where a group, such as an alkyl or heteroaryl group, is “substituted with an unsubstituted C_1-C_{20} alkyl, or unsubstituted 2 to 20 membered heteroalkyl,” the group may contain one or more unsubstituted C_1-C_{20} alkyls, and/or one or more unsubstituted 2 to 20 membered heteroalkyls.

[00189] Certain compounds provided in this disclosure may exist in particular geometric or stereoisomeric forms. The disclosure contemplates all such compounds, including *cis*- and *trans*-isomers, *R*- and *S*-enantiomers, diastereomers, the racemic mixtures thereof, and other mixtures thereof, as falling within the scope of the invention. Additional asymmetric carbon atoms may be present in a substituent such as an alkyl group. All such isomers, as well as mixtures thereof, are included in this invention.

[00190] The term "pharmaceutically-acceptable salts" refers to the relatively non-toxic, inorganic and organic acid addition salts of compounds disclosed herein and inorganic and organic basic addition salts of the compounds disclosed herein. When compounds of the present invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds of the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogen-carbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, oxalic, methanesulfonic, and the like.

Administration of the sequestration agent

[00191] Administration refers to the way by which the α2 adrenergic receptor agonist, drug of abuse, or the sequestration agent is taken into the body of the patient. Routes of administration may be classified by the location at which the substance is applied. Common examples include oral and intravenous administration. Routes can also be classified based on where the target of action, such as topical, enteral (system-wide effect, but delivered through the gastrointestinal tract), or parenteral (systemic action, but delivered by routes other than the GI tract). Administration includes self-administration by the patient and administration by a medical professional, or other person. Particularly as applied to the α2 adrenergic receptor agonist or drug of abuse, administration may be purposeful or accidental.

[00192] The pharmaceutical compositions of the sequestration agent as described herein may be formulated for parenteral administration to the patient. In particular, the pharmaceutical compositions of the sequestration agent may be suitable for administration by injection into the patient, including intravenous, intramuscular, subcutaneous, and intraperitoneal administration, and preferably may be suitable for intravenous administration.

[00193] In an embodiment, the dosage form comprising the sequestration agent is an oral dosage form comprising (i) a sequestration agent, and (ii) one or more pharmaceutically acceptable carriers. The oral dosage form may be a capsule or a tablet. Alternatively, the oral dosage form may be an orally administrable solution, suspension, or syrup.

[00194] In another embodiment, the dosage form is an aqueous solution that is suitable for injection into a patient comprising (i) a sequestration agent, (ii) optionally, a buffering agent, and (iv) optionally a tonicity agent. In another embodiment, the dosage form is a solid for reconstitution comprising (i) a sequestration agent, (ii) optionally, a buffering agent, and (iii) optionally a tonicity agent.

[00195] For parenteral administration in an aqueous solution, for example, the liquid dosage form may be suitably buffered if necessary and the liquid diluent rendered isotonic with sufficient saline or glucose. In this connection, sterile aqueous media that can be employed will be known to those of skill in the art in light of the present disclosure. For example, one dosage is dissolved, in certain cases, in 1 mL to 20 mL of isotonic NaCl solution and either added to 100 mL to 1000 mL of a fluid, e.g., sodium-bicarbonate buffered saline, or injected at the proposed site of infusion.

[00196] The pharmaceutical compositions of the sequestration agent as described herein may be formulated for oral administration to the patient. Oral dosage forms for the sequestration agent administration include buccal film, tablets, capsules, oral liquids and syrups.

[00197] The composition comprising a sequestration agent may be included in a pharmaceutical compositions for oral administration to the patient. The pharmaceutical compositions of the disclosure may further include a pharmaceutically acceptable carrier, excipient, or diluent.

[00198] In one aspect, the disclosure provides an oral dosage form. The sequestration agent may be administered to the patient as one or more tablets or capsules. The sequestration agent may be administered to the patient as an aqueous solution or an aqueous suspension. The sequestration agent may be administered to the patient in an amount of from about 5 mg/kg to about 500 mg/kg.

[00199] The oral dosage form may include a cucurbituril compound as an aqueous solution or aqueous suspension comprising from 5 mg to 500 mg of the cucurbituril compound.

[00200] In embodiments, the disclosure provides a fast-disintegrating oral tablet including a cucurbituril compound.

[00201] The term "pharmaceutical composition" as used herein refers to a composition containing a sequestrant, formulated with a pharmaceutically acceptable carrier, and manufactured or sold with the approval of a governmental regulatory agency as part of a therapeutic regimen for the treatment of disorder in a patient. Pharmaceutical compositions can be formulated, for example, for oral administration in unit dosage form (e.g., a tablet, capsule, caplet, gel cap, syrup, or solution).

[00202] The term "pharmaceutically acceptable carrier" as used herein refers to a carrier which is physiologically acceptable to a treated mammal (e.g., a human) while retaining the therapeutic properties of the cucurbituril compound, with which it is administered. One exemplary pharmaceutically acceptable carrier is physiological saline. Other physiologically acceptable carriers and their formulations are known to one skilled in the art and described, for example, in Remington's Pharmaceutical Sciences (18^{th} edition, A. Gennaro, 1990, Mack Publishing Company, Easton, Pa.), incorporated herein by reference.

[00203] Pharmaceutical compositions containing cucurbituril compound and an amino acid or an amino acid derivative are, in some embodiments, prepared as solutions, dispersions in glycerol, liquid polyethylene glycols, and any combinations thereof in oils, in solid dosage forms, as inhalable dosage forms, as intranasal dosage forms, as liposomal formulations, dosage forms comprising nanoparticles, dosage forms comprising microparticles, polymeric dosage forms, or any combinations thereof.

[00204] A pharmaceutically acceptable excipient is, in some examples, an excipient described in the Handbook of Pharmaceutical Excipients, American Pharmaceutical Association (1986). Non-limiting examples of suitable excipients include a buffering agent, a preservative, a stabilizer, a binder, a compaction agent, a lubricant, a chelator, a dispersion enhancer, a disintegration agent, a flavoring agent, a sweetener, and a coloring agent.

[00205] In some embodiments an excipient is a buffering agent. Non-limiting examples of suitable buffering agents include sodium citrate, magnesium carbonate, magnesium bicarbonate, calcium carbonate, and calcium bicarbonate. As a buffering agent, sodium bicarbonate, potassium bicarbonate, magnesium hydroxide, magnesium lactate, magnesium gluconate, aluminum hydroxide, sodium citrate, sodium tartrate, sodium acetate, sodium carbonate, sodium polyphosphate, potassium polyphosphate, sodium pyrophosphate,

potassium pyrophosphate, disodium hydrogen phosphate, dipotassium hydrogen phosphate, trisodium phosphate, tripotassium phosphate, potassium metaphosphate, magnesium oxide, magnesium hydroxide, magnesium carbonate, magnesium silicate, calcium acetate, calcium glycerophosphate, calcium chloride, calcium hydroxide and other calcium salts or combinations thereof is used, in some embodiments, in a pharmaceutical composition of the present disclosure.

[00206] In some embodiments an excipient comprises a preservative. Non-limiting examples of suitable preservatives include antioxidants, such as alpha-tocopherol and ascorbate, and antimicrobials, such as parabens, chlorobutanol, and phenol. In some examples, antioxidants further include but are not limited to EDTA, citric acid, ascorbic acid, butylated hydroxytoluene (BHT), butylated hydroxy anisole (BHA), sodium sulfite, p-amino benzoic acid, glutathione, propyl gallate, cysteine, methionine, ethanol and N-acetyl cysteine. In some instances preservatives include validamycin A, TL-3, sodium ortho vanadate, sodium fluoride, N-a-tosyl-Phe-chloromethylketone, N-a-tosyl-Lys-chloromethylketone, aprotinin, phenylmethylsulfonyl fluoride, diisopropylfluorophosphate, kinase inhibitor, phosphatase inhibitor, caspase inhibitor, granzyme inhibitor, cell adhesion inhibitor, cell division inhibitor, cell cycle inhibitor, lipid signaling inhibitor, protease inhibitor, reducing agent, alkylating agent, antimicrobial agent, oxidase inhibitor, or other inhibitor.

[00207] In some embodiments a pharmaceutical composition as described herein comprises a binder as an excipient. Non-limiting examples of suitable binders include starches, pregelatinized starches, gelatin, polyvinylpyrolidone, cellulose, methylcellulose, sodium carboxymethylcellulose, ethylcellulose, polyacrylamides, polyvinyloxoazolidone, polyvinylalcohols, C12-C18 fatty acid alcohol, polyethylene glycol, polyols, saccharides, oligosaccharides, and combinations thereof. The binders used in a pharmaceutical formulation are, in some examples, selected from starches such as potato starch, corn starch, wheat starch; sugars such as sucrose, glucose, dextrose, lactose, maltodextrin; natural and synthetic gums; gelatine; cellulose derivatives such as microcrystalline cellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropyl methyl cellulose, carboxymethyl cellulose, methyl cellulose, ethyl cellulose; polyvinylpyrrolidone (povidone); polyethylene glycol (PEG); waxes; calcium carbonate; calcium phosphate; alcohols such as sorbitol, xylitol, mannitol and water or any combinations thereof.

[00208] In some embodiments a pharmaceutical composition as described herein comprises a lubricant as an excipient. Non-limiting examples of suitable lubricants include magnesium stearate, calcium stearate, zinc stearate, hydrogenated vegetable oils, sterotex, polyoxyethylene monostearate, talc, polyethyleneglycol, sodium benzoate, sodium lauryl sulfate, magnesium lauryl sulfate, and light mineral oil. The lubricants that are used in a pharmaceutical formulation, in some embodiments, are be selected from metallic stearates (such as magnesium stearate, calcium stearate, aluminum stearate), fatty acid esters (such as sodium stearyl fumarate), fatty acids (such as stearic acid), fatty alcohols, glyceryl behenate, mineral oil, paraffins, hydrogenated vegetable oils, leucine, polyethylene glycols (PEG), metallic lauryl sulphates (such as sodium lauryl sulphate, magnesium lauryl sulphate), sodium chloride, sodium benzoate, sodium acetate and talc or a combination thereof.

[00209] In some embodiments a pharmaceutical formulation comprises a dispersion enhancer as an excipient. Non-limiting examples of suitable dispersants include, in some examples, starch, alginic acid, polyvinylpyrrolidones, guar gum, kaolin, bentonite, purified wood cellulose, sodium starch glycolate, isoamorphous silicate, and microcrystalline cellulose as high HLB emulsifier surfactants.

[00210] In some embodiments a pharmaceutical composition as described herein comprises a disintegrant as an excipient. In some embodiments a disintegrant is a non-effervescent disintegrant. Non-limiting examples of suitable non-effervescent disintegrants include starches such as corn starch, potato starch, pregelatinized and modified starches thereof, sweeteners, clays, such as bentonite, micro-crystalline cellulose, alginates, sodium starch glycolate, gums such as agar, guar, locust bean, karaya, pectin, and tragacanth. In some embodiments a disintegrant is an effervescent disintegrant. Non-limiting examples of suitable effervescent disintegrants include sodium bicarbonate in combination with citric acid, and sodium bicarbonate in combination with tartaric acid.

[00211] In some embodiments an excipient comprises a flavoring agent. Flavoring agents incorporated into an outer layer are, in some examples, chosen from synthetic flavor oils and flavoring aromatics; natural oils; extracts from plants, leaves, flowers, and fruits; and combinations thereof. In some embodiments a flavoring agent can be selected from the group consisting of cinnamon oils; oil of wintergreen; peppermint oils; clover oil; hay oil; anise oil; eucalyptus; vanilla; citrus oil such as lemon oil, orange oil, grape and grapefruit oil;

and fruit essences including apple, peach, pear, strawberry, raspberry, cherry, plum, pineapple, and apricot.

[00212] In some embodiments an excipient comprises a sweetener. Non-limiting examples of suitable sweeteners include glucose (corn syrup), dextrose, invert sugar, fructose, and mixtures thereof (when not used as a carrier); saccharin and its various salts such as a sodium salt; dipeptide sweeteners such as aspartame; dihydrochalcone compounds, glycyrrhizin; Stevia rebaudiana (Stevioside); chloro derivatives of sucrose such as sucralose; and sugar alcohols such as sorbitol, mannitol, sylitol, and the like.

[00213] In some instances, a pharmaceutical composition as described herein comprises a coloring agent. Non-limiting examples of suitable coloring agents include food, drug and cosmetic colors (FD&C), drug and cosmetic colors (D&C), and external drug and cosmetic colors (Ext. D&C). A coloring agents can be used as dyes or their corresponding lakes.

[00214] In some embodiments, the sequestration agent or a pharmaceutically acceptable salt thereof is administered at about 0.05 mg/kg to 500 mg/kg. In some embodiments, sequestering agent is administered at about 0.05 mg/kg - 50 mg/kg, 50 - 60 mg/kg, 50 - 70 mg/kg, 50 - 80 mg/kg, 50 - 90 mg/kg, 50 - 100 mg/kg, 50 - 120 mg/kg, 50 - 140 mg/kg, 50 - 160 mg/kg, 50 - 180 mg/kg, 50 - 200 mg/kg, 50 - 220 mg/kg, 50 - 240 mg/kg, 50 - 260 mg/kg, 50 - 280 mg/kg, 50 - 300 mg/kg, 50 - 350 mg/kg, 50 - 400 mg/kg, 50 - 450 mg/kg, 50 - 500 mg/kg, 60 - 70 mg/kg, 60 - 80 mg/kg, 60 - 90 mg/kg, 60 - 100 mg/kg, 60- 120 mg/kg, 60- 140 mg/kg, 60 - 160 mg/kg, 60 - 180 mg/kg, 60 - 200 mg/kg, 60 - 220 mg/kg, 60 - 240 mg/kg, 60- 260 mg/kg, 60 - 280 mg/kg, 60 - 300 mg/kg, 60 - 350 mg/kg, 60 - 400 mg/kg, 60 - 450 mg/kg, 60- 500 mg/kg, 80 - 90 mg/kg, 80 - 100 mg/kg, 80 - 120 mg/kg, 80 - 140 mg/kg, 80 - 160 mg/kg, 80 - 180 mg/kg, 80 - 200 mg/kg, 80 - 220 mg/kg, 80 - 240 mg/kg, 80 - 260 mg/kg, 80 - 280 mg/kg, 80 - 300 mg/kg, 80 - 350 mg/kg, 80 - 400 mg/kg, 80 - 450 mg/kg, 80 - 500 mg/kg, 100 - 120 mg/kg, 100 - 130 mg/kg, 100 - 140 mg/kg, 100 - 150 mg/kg, 100 - 160 mg/kg, 100 - 180 mg/kg, 100 - 200 mg/kg, 100 -220 mg/kg, 100 - 240 mg/kg, 100 - 260 mg/kg, 100 - 280 mg/kg, 100 - 300 mg/kg, 100 - 350 mg/kg, 100 - 400 mg/kg, 100 - 450 mg/kg, 100 - 500 mg/kg, 140 - 160 mg/kg, 140 - 180 mg/kg, 140 - 200 mg/kg, 140 - 220 mg/kg, 140 - 240 mg/kg, 140 - 260 mg/kg, 140 - 280 mg/kg, 140 - 300 mg/kg, 140 - 350 mg/kg, 140 - 400 mg/kg, 140 - 450 mg/kg, 140 – 500 mg/kg, 160 - 200 mg/kg, 160 - 220 mg/kg, 160 - 240 mg/kg, 160 - 260 mg/kg, 160 - 280 mg/kg, 160 - 300 mg/kg, 160 - 350 mg/kg, 160 - 400 mg/kg, 160 - 450 mg/kg, 160 - 500 mg/kg, 180 - 200 mg/kg, 180 - 220

mg/kg, 180 - 240 mg/kg, 180 - 260 mg/kg, 180 - 280 mg/kg, 180 - 300 mg/kg, 180 - 350 mg/kg, 180 - 400 mg/kg, 180 - 450 mg/kg, 180 - 500 mg/kg, 200 - 220 mg/kg, 200 - 240 mg/kg, 200 - 260 mg/kg, 200 - 280 mg/kg, 200 - 300 mg/kg, 200 - 350 mg/kg, 200 - 400 mg/kg, 200 - 450 mg/kg, 200 - 500 mg/kg, 220 - 240 mg/kg, 220 - 260 mg/kg, 220 - 280 mg/kg, 220 - 300 mg/kg, 240 - 260 mg/kg, 240 - 280 mg/kg, 240 - 300 mg/kg, 240 - 350 mg/kg, 240 - 400 mg/kg, 240 - 450 mg/kg, 240 - 500 mg/kg, 260 - 280 mg/kg, 260 - 300 mg/kg, 280 - 300 mg/kg, 260 - 350 mg/kg, 260 - 400 mg/kg, 260 - 450 mg/kg, 260 - 500 mg/kg, 280 - 350 mg/kg, 280 - 400 mg/kg, 280 - 450 mg/kg, or 280 - 500 mg/kg.

[00215] In some embodiments, sequestration agent or a pharmaceutically acceptable salt thereof is administered at about at least 0.05 mg/kg, 1 mg/kg, 5 mg/kg, 10 mg/kg, 20 mg/kg, 30 mg/kg, 40 mg/kg, 50 mg/kg, 60 mg/kg, 70 mg/kg, 80 mg/kg, 90 mg/kg, 100 mg/kg, 110 mg/kg, 120 mg/kg, 130 mg/kg, 140 mg/kg, 150 mg/kg, 160 mg/kg, 170 mg/kg, 180 mg/kg, 190 mg/kg, 200 mg/kg, 210 mg/kg, 220 mg/kg, 230 mg/kg, 240 mg/kg, 250 mg/kg, 260 mg/kg, 270 mg/kg, 280 mg/kg, 290 mg/kg, 300 mg/kg, 350 mg/kg, 400 mg/kg, 450 mg/kg, or 500 mg/kg. In some embodiments, Compound A or a pharmaceutically acceptable salt thereof is administered at about less than 50 mg/kg, 60 mg/kg, 70 mg/kg, 80 mg/kg, 90 mg/kg, 100 mg/kg, 110 mg/kg, 120 mg/kg, 130 mg/kg, 140 mg/kg, 150 mg/kg, 160 mg/kg, 170 mg/kg, 180 mg/kg, 190 mg/kg, 200 mg/kg, 210 mg/kg, 220 mg/kg, 230 mg/kg, 240 mg/kg, 250 mg/kg, 260 mg/kg, 270 mg/kg, 280 mg/kg, 290 mg/kg, 300 mg/kg, 350 mg/kg, 400 mg/kg, 450 mg/kg, or 500 mg/kg.

[00216] In some embodiments, the sequestration agent or a pharmaceutically acceptable salt thereof can be administered at about 1 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 250 mg, about 300 mg, about 350 mg, about 400 mg, about 450 mg, about 500 mg, about 550 mg, about 600 mg, about 650 mg, about 700 mg, about 750 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg, about 1000 mg, about 1050 mg, about 1100 mg, about 1150 mg, about 1200 mg, about 1250 mg, about 1300 mg, about 1350 mg, about 1400 mg, about 1450 mg, about 1500 mg, about 1550 mg, about 1600 mg, about 1650 mg, about 1700 mg, about 1750 mg, about 1800 mg, about 1850 mg, about 1900 mg, about 1950 mg, or about 2000 mg.

EXAMPLES

EXAMPLE 1. IN-VITRO BINDING STUDIES

[00217] In-vitro binding studies were conducted on sequestrants against drugs of abuse under simulated physiological conditions and are summarized in Table 1.

Table 1. Binding Affinity of the Sequestrants with Drugs of Abuse

Drug of Abuse	Binding Affinity of Comp. A, K_a
Methamphetamine	1.9×10^6
Amphetamine	1.9×10^6
Hydroxy methamphetamine	8.0×10^5
Xylazine	9.1×10^4
Fentanyl	9.6×10^6

[00218] Compound J binds to Methamphetamine with a binding affinity of 8.4×10^6.

[00219] Preparation of host solutions:

[00220] Isothermal Titration Calorimetry – A 1 mM solution of host was prepared volumetrically using 20 mM pH 7.4 phosphate buffer. This solution was diluted to 0.1 mM using the same 20 mM pH 7.4 phosphate buffer.

[00221] Fluorescence – A 1 mM solution of host was prepared volumetrically using 20 mM pH 7.4 phosphate buffer. The solution was diluted to 0.2 mM and 0.02 mM using the same 20 mM pH 7.4 phosphate buffer.

[00222] Preparation of guest solutions:

[00223] Isothermal Titration Calorimetry – A 1 mM solution of each guest molecule was prepared non-volumetrically using 20 mM pH 7.4 phosphate buffer.

[00224] Fluorescence – A 25 mM solution of each guest molecule was prepared non-volumetrically with methanol and diluted to the appropriate concentrations. Studies were conducted with various target molecules to confirm the small amount of residual methanol (<1%) did not interfere with binding.

[00225] Preparation of Rhodamine 6G solutions:

[00226] Fluorescence – A 1 mM solution of Rhodamine 6G was prepared volumetrically using 20 mM pH 7.4 phosphate buffer. That solution was diluted to 0.2 mM using the same 20 mM pH 7.4 phosphate buffer.

[00227] Determination of binding constants

[00228] For each host-guest binding constant determination, the average binding affinity from three measurements was recorded.

[00229] Isothermal Titration Calorimetry – A Malvern Panalytical MicroCal PEAQ-ITC was used to perform isothermal calorimetry titrations. The concentration of each guest was 1 mM and the concentration of host was 0.1 mM. The sample cell was filled with 290 µL of host solution and the syringe was loaded from a vial containing 80 µL of the guest. A 19-injection method was run with the first injection being 0.4 µL followed by 18x 2 µL injections. In the case of weak binding guests, two 19-injection titrations were run. After the first titration was completed, excess liquid from the sample cup was removed and the syringe reloaded with guest solution. The temperature was set to 25 °C, reference power was set to 10 µcal/s, the feedback was set to high, the stir speed set to 750 rpm, the initial delay was set to 60 s, the injection spacing was set to 150 s, and the injection duration was set to 4 s. The data was processed using Malvern software.

Table 2

Compound	Xylazine binding K_a (x 10^5)
Compound A	0.9
Compound B	5.9
Compound J	47
Compound C	1
Compound D	1
Compound E	1.7
Compound F	1.5

Example 3. Capture and Excretion of Unmetabolized Xylazine in Urine

[00230] Rats (Sprague Dawley; N=4) were given a single IV bolus (1 mL/kg) of 3 mg/kg xylazine hydrochloride via a Jugular Vein Catheter (JVC). After 5 minutes, the rats were given a single IV bolus of 150 mg/kg Comp. A (1 mL/kg) via JVC, and then immediately placed into a metabolic cage for collection of urine up to 24 hr. Total urine volumes were collected at 2, 8, and 24 hr, and the total amount of xylazine in each volume was measured using LC-MS/MS. The xylazine recovery is shown in Figure 1.

[00231] The amount of xylazine captured in urine was statistically equivalent to the amount captured in the combinatory xylazine/fentanyl experiments, discussed below.

Example 4. Capture and Excretion of Unmetabolized Xylazine/Fentanyl in Urine

[00232] Rats (Sprague Dawley; N=4) were given a single IV bolus (1 mL/kg) of 3 mg/kg xylazine hydrochloride via a Jugular Vein Catheter (JVC), immediately followed by a single IV bolus (1 mL/kg) of 100 µg/kg of fentanyl citrate. After 5 minutes, rats were given a single IV bolus of either saline (1 mL/kg) or 150 mg/kg Comp. A (1 mL/kg) via JVC, and then immediately placed into a metabolic cage for collection of urine up to 24 hr.

[00233] Total urine volumes were collected at 2, 8, and 24 hr, and the total amount of xylazine and fentanyl in each volume was measured using LC-MS/MS. The fentanyl and xylazine recovery is shown in Figures 2a and 2b, respectively. It was also observed that the rats given Comp. A recovered to normal behavior faster than the rats given placebo.

Example 5. Observational/Behavioral Experiment on Xylazine in Rats

[00234] Rats (Sprague Dawley, N=4) were given a single IV bolus (1 mL/kg) of 3 mg/kg xylazine hydrochloride via the tail vein. After 5 minutes, the rats were given a single IV bolus of saline or either 400 or 200 mg/kg Comp. A via the tail vein. At 15 min post-challenge (10 minutes after the first dose), some rats were given an additional dose of Comp. A (either 400 or 200 mg/kg). The test groups were as follows

Control Group = 3 mg/kg xylazine HCl with 5 min dose of saline.

Test Group 1 = 3 mg/kg xylazine HCl with 5 min dose of 400 mg/kg Comp. A, and 15 min dose of 400 mg/kg Comp. A.

Test Group 2 = 3 mg/kg xylazine HCl with 5 min dose of 200 mg/kg Comp. A, and 15 min dose of 200 mg/kg Comp. A.

Test Group 3 = 3 mg/kg xylazine HCl with 5 min dose of 400 mg/kg Comp. A.

[00235] At specific time intervals post-challenge dosing (2-3 min, 10 min, 20 min, 30 min, 40 min, 60 min, 90 min, and 120 min), rats were taken out of their housing enclosures and placed into a plastic bin test chamber, where their gait was numerically scored by at least 2 observers according to the following criteria:

0 – Normal gait/mobility.

1 – Slightly impaired (any or all of the following can be evident): mild ataxia, rocks or lurches during ambulation; hunched or crouched body position; walks on tiptoe.

2 – Moderately impaired (any or all of the following can be evident): marked ataxia; feet point outwards from the body; hind limbs show exaggerated or overcompensated movements, drag, or are splayed.

3 – Severely impaired (any or all of the following can be evident): forelimbs drag or are unable to support weight; body drags or is flattened against surface.

[00236] In all groups where Comp. A was administered, the rats had improved gait scores (lower score numbers) significantly faster than the control group. The gait scores over time for each group is shown in Figure 3. Test Group 1 (with 2x doses of 400 mg/kg Comp. A, one a 5 min and one at 15 min) shifted the recovery curve of gait by approximately 30 min as compared to controls (similar gait performance at 30 min post-dose with treatment as compared to the same scores observed at 60 min for controls).

We Claim:

1. A method for reducing the level of an α2 adrenergic receptor agonist in the body of a patient that has been administered the α2 adrenergic receptor agonist, the method comprising:

   at a time after administration of the α2 adrenergic receptor agonist, administering to the patient a therapeutically effective amount of a sequestration agent.

2. The method of claim 1, wherein the α2 adrenergic receptor agonist is xylazine.

3. The method of claim 1 or claim 2, wherein the patient has also been administered a pharmaceutical drug and/or an additional drug of abuse.

4. The method of claim 3, wherein the patient has also been administered an additional drug of abuse.

5. The method of claim 4, wherein the additional drug of abuse comprises one or more of amphetamine stimulants, barbiturates, opioids, benzodiazepines and psychedelics.

6. The method of claim 4, wherein the additional drug of abuse comprises one or more of methamphetamine, fentanyl and cocaine.

7. The method of claim 4, wherein the additional drug of abuse comprises fentanyl or a fentanyl analog.

8. The method of claim 7, wherein the fentanyl analog is carfentanil.

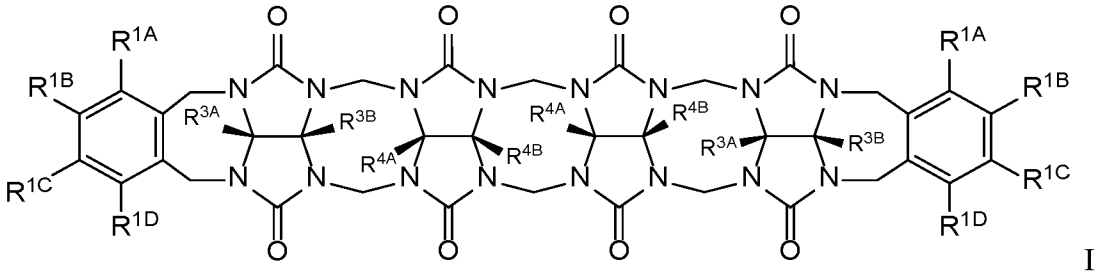
9. The method according to any one of claims 1 to 8, wherein the sequestration agent is orally administered to the patient.

10. The method according to any one of claims 1 to 9, wherein the sequestration agent is administered by injection to the patient.

11. The method according to any one of claims 1 to 10, wherein the sequestration agent comprises a cucurbituril, a pillararene, or a calixarene.

12. The method according to any one of claims 1 to 10, wherein the sequestration agent comprises a cucurbituril compound.

13. The method according to claim 12, wherein the cucurbituril compound has a structure of formula I:



I

or a pharmaceutically acceptable salt thereof,

wherein:

each R^{1A} and R^{1D} is independently selected from hydrogen, halogen, -OH, C_1-C_6 alkyl, 2 to 6 membered heteroalkyl, C_3-C_6 cycloalkyl, 5 to 6 membered heterocycloalkyl, phenyl, 5 to 6 membered heteroaryl, $-O-(CH_2)_{n1}S(O)_{v1}X^1$, $-O-(CH_2)_{n1}CO_2X^1$, and $-O-(CH_2)_{n1}PO_{v1}X^1$;

each R^{1B} and R^{1C} is independently selected from hydrogen, halogen, -OH, C_1-C_6 alkyl, 2 to 6 membered heteroalkyl, C_3-C_6 cycloalkyl, 5 to 6 membered heterocycloalkyl, phenyl, 5 to 6 membered heteroaryl, $-O-(CH_2)_{n1}S(O)_{v1}X^1$, $-O-(CH_2)_{n1}CO_2X^1$, and $-O-(CH_2)_{n1}PO_{v1}X^1$; or

additionally or alternatively, two R^{1A}, R^{1B}, R^{1C} and R^{1D} attached on the same phenyl ring at adjacent positions, together with atoms to which they are attached, are joined to form a fused C_6-C_{12} aryl, 5 to 12 membered heteroaryl, or 5 to 7 membered heterocycle, which are optionally substituted with 1 to 3 substituents independently selected halogen, -OH, $-NH_2$, substituted or unsubstituted C_1-C_6 alkyl, or substituted or unsubstituted 2 to 6 membered heteroalkyl;

each R^{3A} and R^{3B} is independently selected from hydrogen, halogen, -OH, C_1-C_6 alkyl, phenyl, substituted phenyl and 2 to 6 membered heteroalkyl;

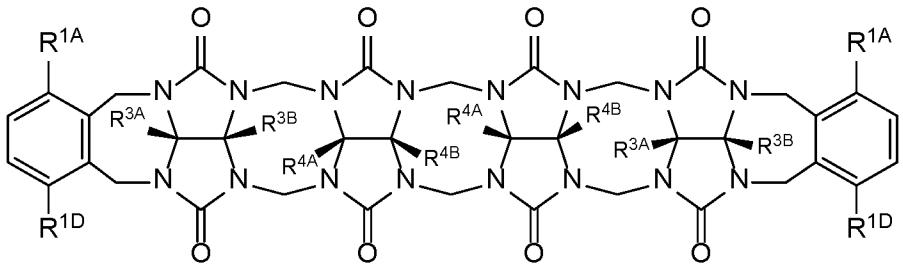
each R^{4A} and R^{4B} is independently selected from hydrogen, halogen, -OH, C_1-C_6 alkyl, phenyl, substituted phenyl and 2 to 6 membered heteroalkyl;

each n1 is independently selected from 0 to 5;

each v1 is independently selected from 2 or 3; and

each X^1 is independently selected from selected from H, -OH, C_1-C_6 alkyl, alkali metal cation, and quaternary ammonium cation.

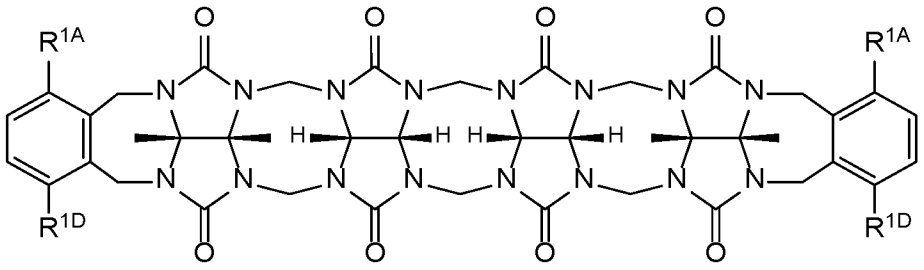
14. The method according to claim 12, wherein the cucurbituril compound has a structure of formula (I-a):



(I-a)

or a pharmaceutically acceptable salt thereof, wherein R^{1A}, R^{1D}, R^{3A}, R^{3B}, R^{4A}, and R^{4B} are defined for formula I.

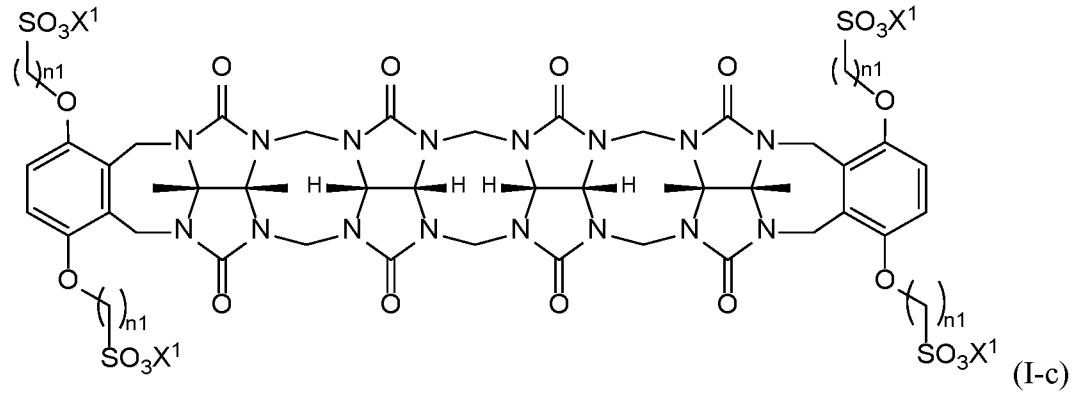
15. The method according to claim 12, wherein the cucurbituril compound has a structure of formula (I-b):



(I-b),

or a pharmaceutically acceptable salt thereof, wherein R^{1A} and R^{1D} are as described for formula I.

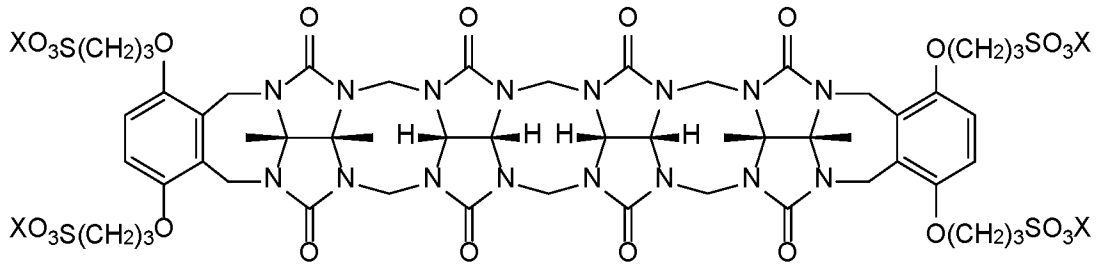
16. The method according to claim 12, wherein the cucurbituril compound has a structure of formula (I-c):



(I-c)

or a pharmaceutically acceptable salt thereof, wherein X^1 and n1 are as described for formula I.

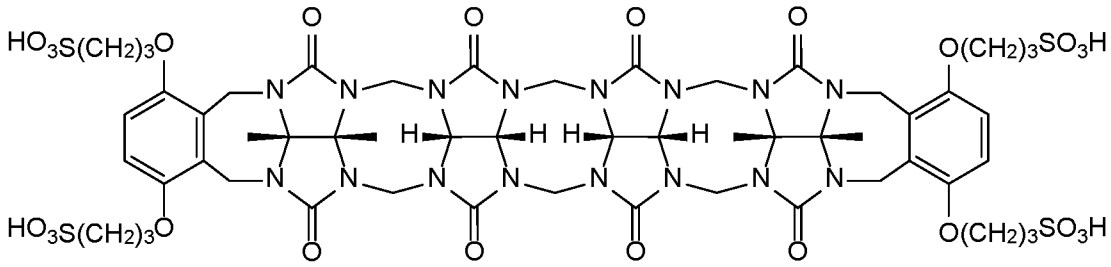
17. The method according claim 12, wherein the cucurbituril compound has a structure of formula (I-A)



(I-A),

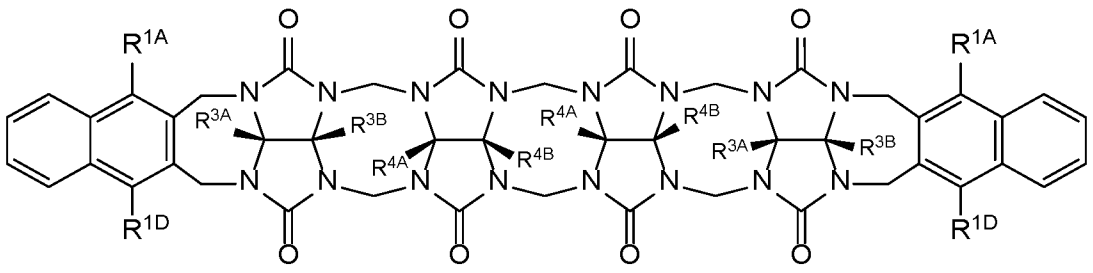
or a pharmaceutically acceptable salt thereof, wherein each X is independently H, alkali metal cation, or quaternary ammonium cation.

18. The method according to claim 12, wherein the cucurbituril compound is Compound A, having the following structure:



or a pharmaceutically acceptable salt thereof.

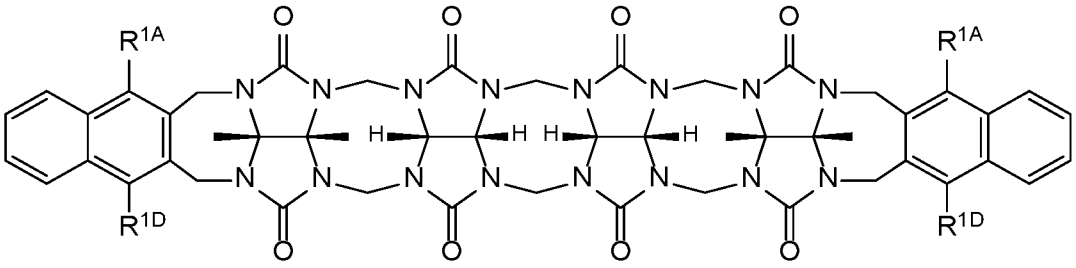
19. The method according to claim 12, wherein the cucurbituril compound has a structure of formula (I-D)



(I-D),

or a pharmaceutically acceptable salt thereof, wherein R^{1A}, R^{1D}, R^{3A}, R^{3B}, R^{4A}, and R^{4B} are as described for formula I.

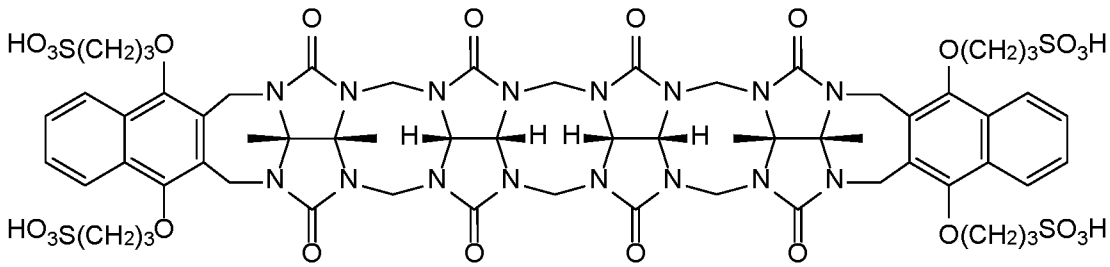
20. The method according to claim 12, wherein the cucurbituril compound has a structure of formula (X):



(X)

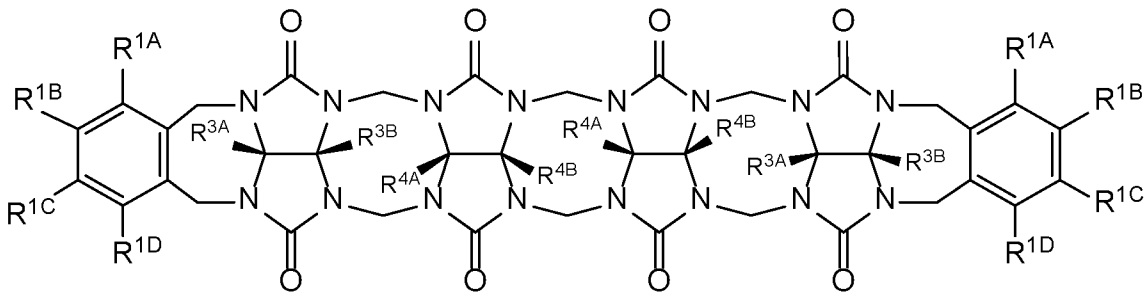
or a pharmaceutically acceptable salt thereof, wherein R^{1A} and R^{1D} are as described for formula I.

21. The method according to claim 12, wherein the cucurbituril compound is Compound B, having the following structure:



or a pharmaceutically acceptable salt thereof.

22. The method according to claim 12, wherein the cucurbituril compound has a structure of formula XI:



XI

or a pharmaceutically acceptable salt thereof, wherein:

each R^{1A} and R^{1D} is independently selected from -O-L-CO_2X^1 and -O-L-SO_3X^1;

each L is independently selected from a chemical bond (single), C_1 to C_{10} alkylene, C_2 to C_{10} alkenylene, -$(CH_2)_a$-O-$(CH_2)_b$, -$(CH_2)_c$-N(R)-$(CH_2)_d$, and -$(CH_2)_a$-$(OCH_2CH_2)_e$-

$(Y)_f$-, each of which may be unsubstituted or substituted at any carbon with 1 to 4 substituents selected from halogen, OH, CO_2H, C_{1-3} alkyl, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl$)_2$, and O-C_{1-3} alkyl;

a is 2 to 8;

b is 0 to 6;

c is 2 to 8;

d is 0 to 6;

e is 1 to 6;

Y is NH, $N(C_{1-3}$ alkyl), or O;

f is 0 or 1;

R is H or C_{1-3} alkyl;

each R^{1B} and R^{1C} is independently selected from hydrogen, halogen, -OH, -CN, CO_2H, SO_3H, C_1-C_6 alkyl, 2 to 6 membered heteroalkyl, C_3-C_6 cycloalkyl, 5 to 6 membered heterocycloalkyl, phenyl, 5 to 6 membered heteroaryl; or

additionally or alternatively, R^{1B} and R^{1C} attached on the same phenyl ring, together with the atoms to which they are attached, are joined to form a fused C_6-C_{12} aryl, 5 to 12 membered heteroaryl, or 5 to 7 membered heterocycle, which are optionally substituted with 1 to 3 substituents independently selected halogen, -OH, $-NH_2$, substituted or unsubstituted C_1-C_6 alkyl, or substituted or unsubstituted 2 to 6 membered heteroalkyl;

each R^{3A} and R^{3B} is independently selected from hydrogen, halogen, -OH, CO_2H, CO_2R', $CONH_2$, CONHR', $CON(R')_2$, C_1-C_6 alkyl, phenyl, substituted phenyl and 2 to 6 membered heteroalkyl;

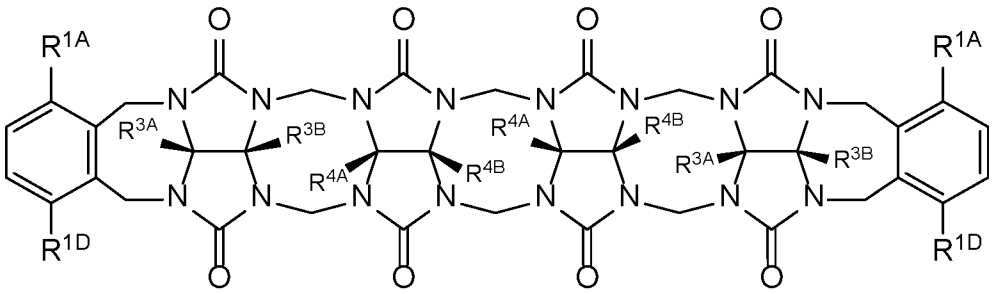
additionally or alternatively, R^{3A} and R^{3B} attached to adjacent carbon atoms, together with the carbons to which they are attached, are joined to form a 5- or 6-membered cycloalkyl or heterocycloalkyl ring;

each R^{4A} and R^{4B} is independently selected from hydrogen, halogen, -OH, CO_2H, CO_2R', $CONH_2$, CONHR', $CON(R')_2$, C_1-C_6 alkyl, phenyl, substituted phenyl and 2 to 6 membered heteroalkyl;

each R' is independently selected from C_{1-6} alkyl; and

each X^1 is independently selected from selected from H, C_1-C_6 alkyl, alkali metal cation, and quaternary ammonium cation.

23. The method according to claim 13, wherein the cucurbituril compound has a structure of formula XII:



(XII)

or a pharmaceutically acceptable salt thereof, wherein:

each R^{1A} and R^{1D} is independently selected from -O-L-CO_2X^1, and -O-L-SO_3X^1;

each L is independently selected from a chemical bond, C_2 to C_{10} alkylene, C_2 to C_{10} alkenylene, -$(CH_2)_a$-O-$(CH_2)_b$, -$(CH_2)_c$-N(R)-$(CH_2)_d$, and -$(CH_2)_a$-$(OCH_2CH_2)_e$-$(Y)_f$-, each of which may be unsubstituted or substituted at any carbon with 1 to 4 substituents selected from halogen, OH, CO_2H, C_{1-3} alkyl, NH_2, NH(C_{1-3} alkyl), N(C_{1-3} alkyl)$_2$, and O-C_{1-3} alkyl;

a is 2 to 8;

b is 0 to 6;

c is 2 to 8;

d is 0 to 6;

e is 1 to 6;

Y is NH, N(C_{1-3} alkyl), or O;

f is 0 or 1;

R is H or C_{1-3} alkyl;

each R^{3A} and R^{3B} is independently selected from hydrogen, halogen, -OH, CO_2H, CO_2R', $CONH_2$, CONHR', CON(R')$_2$, C_1-C_6 alkyl, phenyl, substituted phenyl and 2 to 6 membered heteroalkyl;

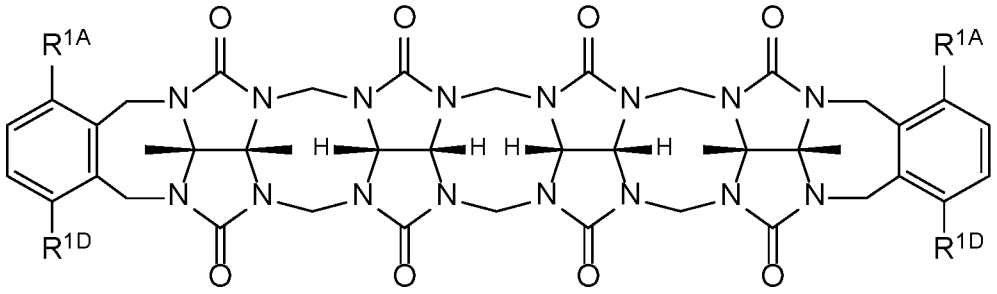
additionally or alternatively, R^{3A} and R^{3B} attached to adjacent carbon atoms, together with the carbons to which they are attached, are joined to form a 5- or 6-membered cycloalkyl or heterocycloalkyl ring;

each R^{4A} and R^{4B} is independently selected from hydrogen, halogen, -OH, CO_2H, CO_2R', $CONH_2$, CONHR', CON(R')$_2$, C_1-C_6 alkyl, phenyl, substituted phenyl and 2 to 6 membered heteroalkyl;

each R' is independently selected from C_{1-6} alkyl; and

each X^1 is independently selected from selected from H, C_1-C_6 alkyl, alkali metal cation, and quaternary ammonium cation.

24. The method according to claim 13, wherein the cucurbituril compound has a structure of formula XIIa:



(XIIa)

or a pharmaceutically acceptable salt thereof, wherein

each R^{1A} and R^{1D} is independently selected from -O-L-CO_2X^1 and -O-L-SO_3X^1;

each L is independently selected from a chemical bond, C_1 to C_{10} alkylene, C_2 to C_{10} alkenylene, -$(CH_2)_a$-O-$(CH_2)_b$, -$(CH_2)_c$-N(R)-$(CH_2)_d$, and -$(CH_2)_a$-$(OCH_2CH_2)_e$-$(Y)_f$-, each of which may be unsubstituted or substituted at any carbon with 1 to 4 substituents selected from halogen, OH, CO_2H, C_{1-3} alkyl, NH_2, NH(C_{1-3} alkyl), N(C_{1-3} alkyl)$_2$, and O-C_{1-3} alkyl;

a is 2 to 8;

b is 0 to 6;

c is 2 to 8;

d is 0 to 6;

e is 1 to 6;

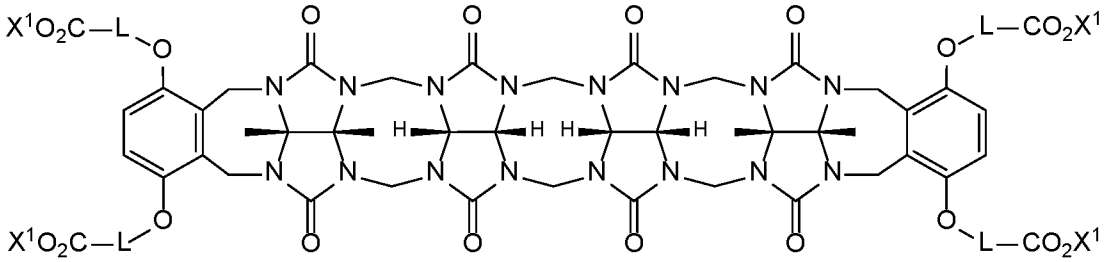
Y is NH, N(C_{1-3} alkyl), or O;

f is 0 or 1;

R is H or C_{1-3} alkyl; and

each X^1 is independently selected from selected from H, C_1-C_6 alkyl, alkali metal cation, and quaternary ammonium cation.

25. The method according to claim 13, wherein the cucurbituril compound has a structure of formula XIIb:



(XIIb)

or a pharmaceutically acceptable salt thereof, wherein

each L is independently selected from C_1 to C_{10} alkylene, C_2 to C_{10} alkenylene, $-(CH_2)_a-O-(CH_2)_b$, $-(CH_2)_c-N(R)-(CH_2)_d$, and $-(CH_2)_a-(OCH_2CH_2)_e-(Y)_f-$, each of which may be unsubstituted or substituted at any carbon with 1 to 4 substituents selected from halogen, OH, CO_2H, C_{1-3} alkyl, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl)$_2$, and O-C_{1-3} alkyl;

a is 2 to 8;

b is 0 to 6;

c is 2 to 8;

d is 0 to 6;

e is 1 to 6;

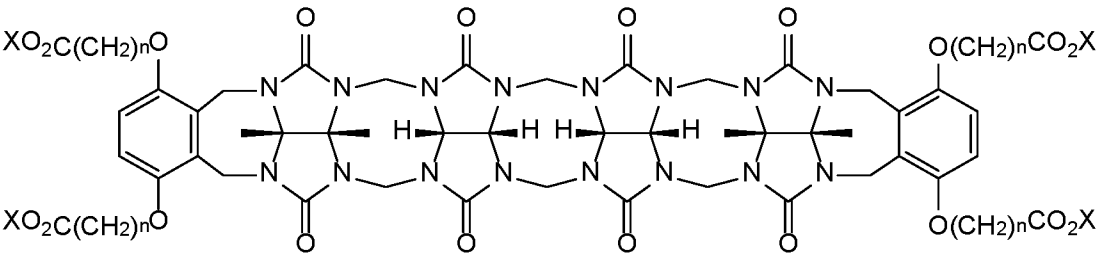
Y is NH, $N(C_{1-3}$ alkyl), or O;

f is 0 or 1;

R is H or C_{1-3} alkyl; and

each X^1 is independently selected from selected from H, C_1-C_6 alkyl, alkali metal cation, and quaternary ammonium cation.

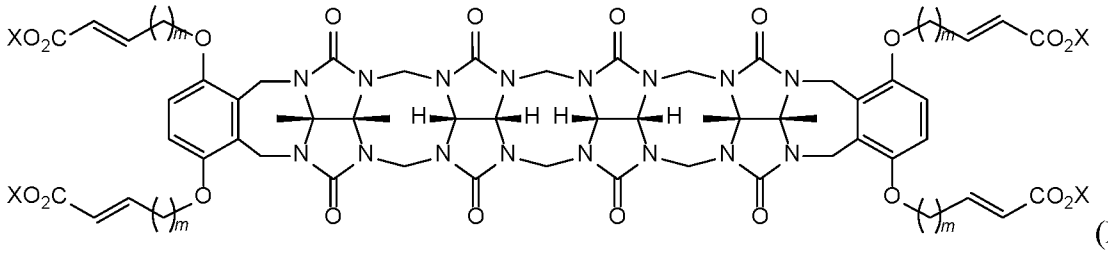
26. The method according to claim 13, wherein the cucurbituril compound has a structure of formula XIIc:



(XIIc)

or a pharmaceutically acceptable salt thereof, wherein each X is independently H, alkali metal cation (e.g., Li^+, Na^+, K^+, or Cs^+), an ammonium cation, or combination thereof; and each n is independently 1, 2, 3 or 4.

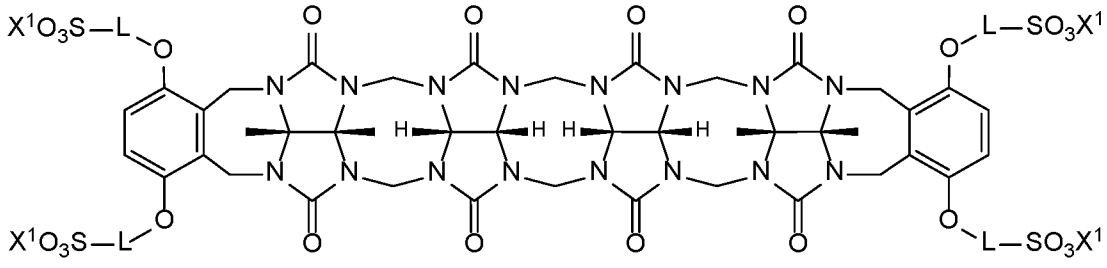
27. The method according to claim 13, wherein the cucurbituril compound has a structure of formula XIId:



(XIId)

or a pharmaceutically acceptable salt thereof, wherein each X is independently H, alkali metal cation, an ammonium cation, or combination thereof; and each m is independently 1, 2, 3 or 4.

28. The method according to claim 13, wherein the cucurbituril compound has a structure of formula XIIe:



(XIIe)

or a pharmaceutically acceptable salt thereof, wherein:

each L is independently selected from a chemical bond, C_1 to C_{10} alkylene, C_2 to C_{10} alkenylene, $-(CH_2)_a-O-(CH_2)_b$, $-(CH_2)_c-N(R)-(CH_2)_d$, and $-(CH_2)_a-(OCH_2CH_2)_e-(Y)_f-$, each of which may be unsubstituted or substituted at any carbon with 1 to 4 substituents selected from halogen, OH, CO_2H, C_{1-3} alkyl, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl$)_2$, and O-C_{1-3} alkyl;

a is 2 to 8;

b is 0 to 6;

c is 2 to 8;

d is 0 to 6;

e is 1 to 6;

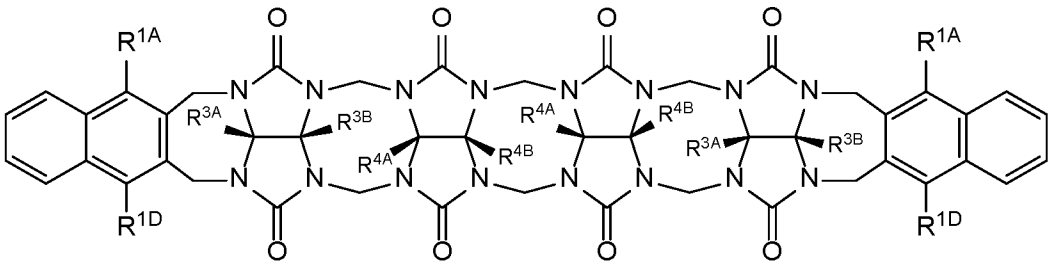
Y is NH, $N(C_{1-3}$ alkyl), or O;

f is 0 or 1;

R is H or C_{1-3} alkyl; and

each X^1 is independently selected from selected from H, C_1-C_6 alkyl, alkali metal cation, and quaternary ammonium cation.

29. The method according to claim 13, wherein the cucurbituril compound has a structure of formula XIII:



(XIII)

or a pharmaceutically acceptable salt thereof, wherein:

each R^{1A} and R^{1D} is independently selected from -O-L-CO_2X^1 and -O-L-SO_3X^1;

each L is independently selected from a chemical bond, C_1 to C_{10} alkylene, C_2 to C_{10} alkenylene, -$(CH_2)_a$-O-$(CH_2)_b$, -$(CH_2)_c$-N(R)-$(CH_2)_d$, and -$(CH_2)_a$-$(OCH_2CH_2)_e$-$(Y)_f$-, each of which may be unsubstituted or substituted at any carbon with 1 to 4 substituents selected from halogen, OH, CO_2H, C_{1-3} alkyl, NH_2, NH(C_{1-3} alkyl), N(C_{1-3} alkyl)$_2$, and

O-C_{1-3} alkyl;

a is 2 to 8;

b is 0 to 6;

c is 2 to 8;

d is 0 to 6;

e is 1 to 6;

Y is NH, N(C_{1-3} alkyl), or O;

f is 0 or 1;

R is H or C_{1-3} alkyl;

each R^{3A} and R^{3B} is independently selected from hydrogen, halogen, CO_2H, CO_2R', $CONH_2$, CONHR', CON(R')$_2$, -OH, C_1-C_6 alkyl, phenyl, substituted phenyl and 2 to 6 membered heteroalkyl;

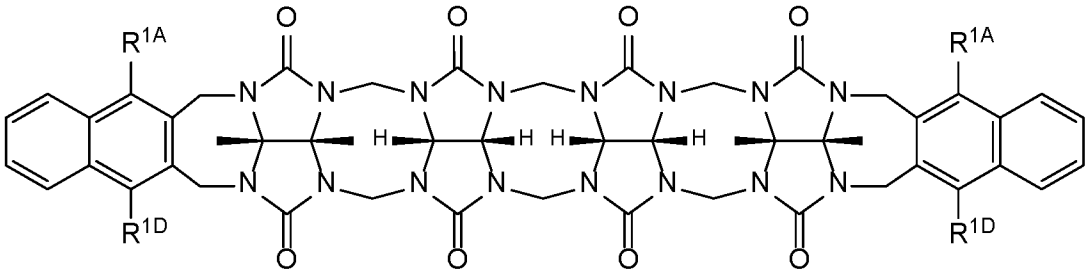
additionally or alternatively, R^{3A} and R^{3B} attached to adjacent carbon atoms, together with the carbons to which they are attached, are joined to form a 5- or 6-membered cycloalkyl or heterocycloalkyl ring;

each R^{4A} and R^{4B} is independently selected from hydrogen, halogen, -OH, CO_2H, CO_2R', $CONH_2$, CONHR', $CON(R')_2$, C_1-C_6 alkyl, phenyl, substituted phenyl and 2 to 6 membered heteroalkyl;

each R' is independently selected from C_{1-6} alkyl; and

each X^1 is independently selected from selected from H, C_1-C_6 alkyl, alkali metal cation, and quaternary ammonium cation.

30. The method according to claim 13, wherein the cucurbituril compound has a structure of formula XIIIa:



(XIIIa)

or a pharmaceutically acceptable salt thereof, wherein

each R^{1A} and R^{1D} is independently selected from -O-L-CO_2X^1 and -O-L-SO_3X^1;

each L is independently selected from a chemical bond, C_1 to C_{10} alkylene, C_2 to C_{10} alkenylene, $-(CH_2)_a$-O-$(CH_2)_b$, $-(CH_2)_c$-N(R)-$(CH_2)_d$, and $-(CH_2)_a$-$(OCH_2CH_2)_e$-$(Y)_f$-, each of which may be unsubstituted or substituted at any carbon with 1 to 4 substituents selected from halogen, OH, CO_2H, C_{1-3} alkyl, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl$)_2$, and

O-C_{1-3} alkyl;

a is 2 to 8;

b is 0 to 6;

c is 2 to 8;

d is 0 to 6;

e is 1 to 6;

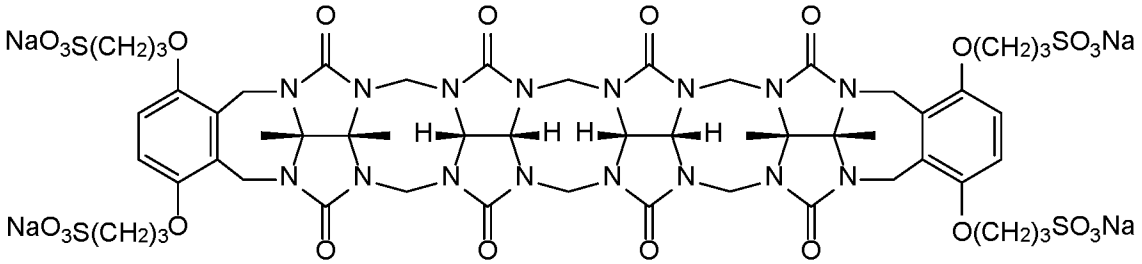
Y is NH, $N(C_{1-3}$ alkyl), or O;

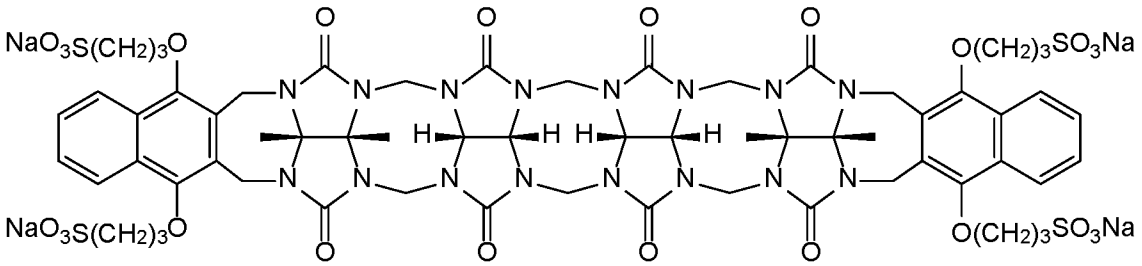
f is 0 or 1;

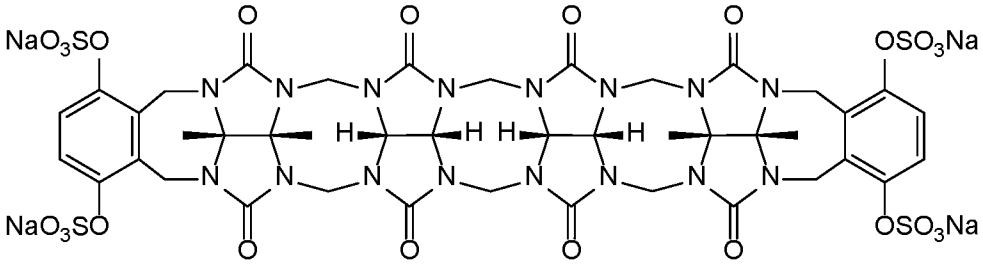
R is H or C_{1-3} alkyl; and

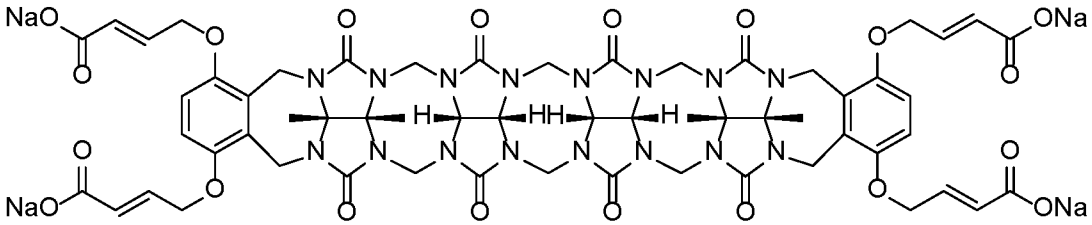
each X^1 is independently selected from selected from H, C_1-C_6 alkyl, alkali metal cation, and quaternary ammonium cation.

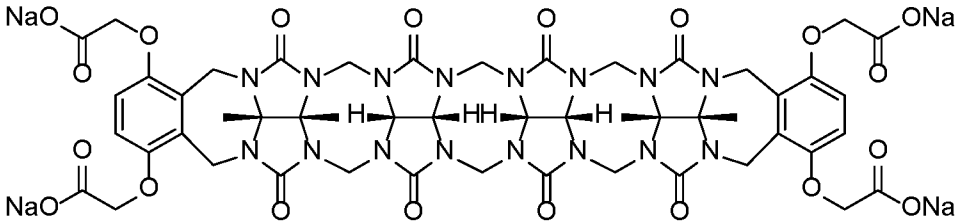
31. The method according to claim 13, wherein the cucurbituril compound has a structure according to one of the following:

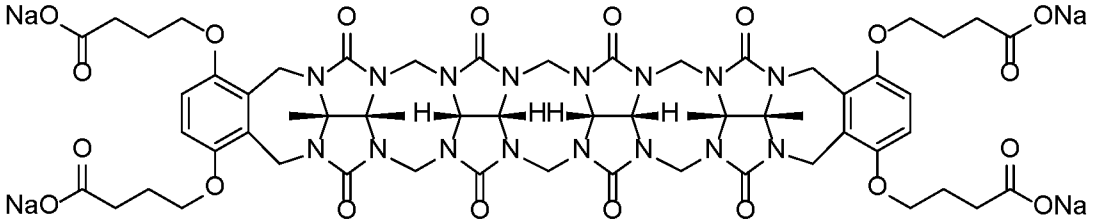






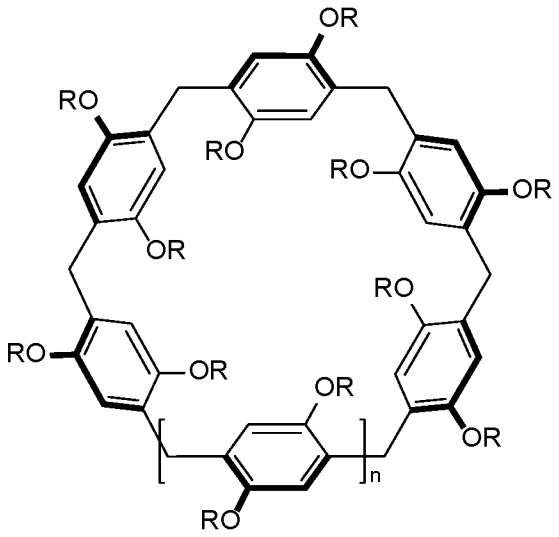






32. The method according to any one of claims 1 to 10, wherein the sequestration agent is a pillararene.

33. The method of claim 32, wherein the sequestration agent is a pillararene having the structure:



or a pharmaceutically acceptable salt thereof, wherein

n is selected from 0, 1, 2 or 3,

each R is independently selected from $-(CH_2)_aS(O)_bX^1$, $-(CH_2)_aCO_2X^1$, and $-(CH_2)_aPO_bX^1$;

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

b is 2 or 3; and

each X^1 is independently selected from selected from H, -OH, alkali metal cation, and quaternary ammonium cation.

34. The method of claim 33, wherein each R is selected from $-(CH_2)_aSO_3X^{1a}$, $-(CH_2)_aCO_2X^{1a}$, and $-(CH_2)_aPO_3X^{1a}$; a is 0, 1, 2 or 3; and X^{1a} is H, alkali metal cation, and quaternary ammonium cation.

35. The method of claim 33, wherein R is SO_3H or a salt thereof (e.g., SO_3Na), or $-CH_2COOH$ or a salt thereof (e.g., CH_2COONa).

36. The method of claim 33, wherein R is selected from SO_3H and SO_3Na; and n is 1.

37. A method to prevent or treat an overdose from one or more drugs of abuse in a patient in need thereof, the method comprising:

at a time after the administration of the one or more drugs of abuse to the patient, administering to the patient a therapeutically effective amount of a sequestration agent; wherein the one or more drugs of abuse comprises an α2 adrenergic receptor agonist.

38. The method of claim 37, wherein the α2 adrenergic receptor agonist is xylazine.

39. The method of claim 37 or claim 38, wherein the one or more drugs of abuse further comprises one or more of amphetamine stimulants, barbiturates, opioids, benzodiazepines and psychedelics.

40. The method of claim 37 or claim 38, wherein the one or more drugs of abuse further comprises one or more of methamphetamine, fentanyl and cocaine.

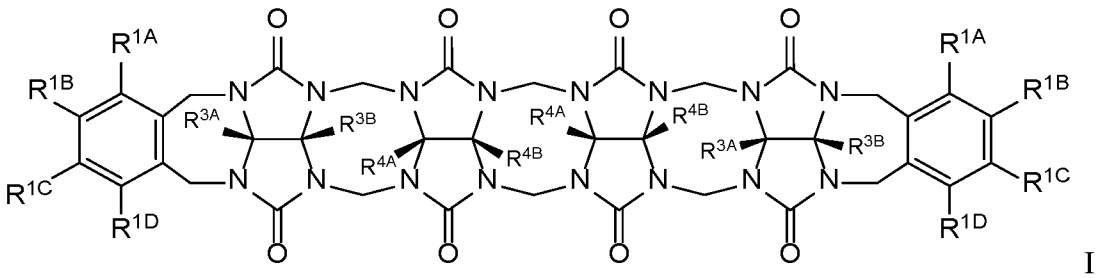
41. The method of claim 37 or claim 38, wherein the one or more drugs of abuse further comprises fentanyl or a fentanyl analog.

42. The method of claim 41, wherein the fentanyl analog is carfentanil.

43. The method according to any one of claims 37 to 42, wherein the sequestration agent comprises a cucurbituril, a pillararene, or a calixarene.

44. The method according to any one of claims 37 to 43, wherein the sequestration agent comprises a cucurbituril compound.

45. The method according to claim 44, wherein the cucurbituril compound has a structure of formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

each R^{1A} and R^{1D} is independently selected from hydrogen, halogen, -OH, C_1-C_6 alkyl, 2 to 6 membered heteroalkyl, C_3-C_6 cycloalkyl, 5 to 6 membered heterocycloalkyl, phenyl, 5 to 6 membered heteroaryl, $-O-(CH_2)_{n1}S(O)_{v1}X^1$, $-O-(CH_2)_{n1}CO_2X^1$, and $-O-(CH_2)_{n1}PO_{v1}X^1$;

each R^{1B} and R^{1C} is independently selected from hydrogen, halogen, -OH, C_1-C_6 alkyl, 2 to 6 membered heteroalkyl, C_3-C_6 cycloalkyl, 5 to 6 membered heterocycloalkyl, phenyl, 5 to 6 membered heteroaryl, $-O-(CH_2)_{n1}S(O)_{v1}X^1$, $-O-(CH_2)_{n1}CO_2X^1$, and $-O-(CH_2)_{n1}PO_{v1}X^1$; or

additionally or alternatively, two R^{1A}, R^{1B}, R^{1C} and R^{1D} attached on the same phenyl ring at adjacent positions, together with atoms to which they are attached, are joined to form a fused C_6-C_{12} aryl, 5 to 12 membered heteroaryl, or 5 to 7 membered heterocycle, which are optionally substituted with 1 to 3 substituents independently selected halogen, -OH, $-NH_2$, substituted or unsubstituted C_1-C_6 alkyl, or substituted or unsubstituted 2 to 6 membered heteroalkyl;

each R^{3A} and R^{3B} is independently selected from hydrogen, halogen, -OH, C_1-C_6 alkyl, phenyl, substituted phenyl and 2 to 6 membered heteroalkyl;

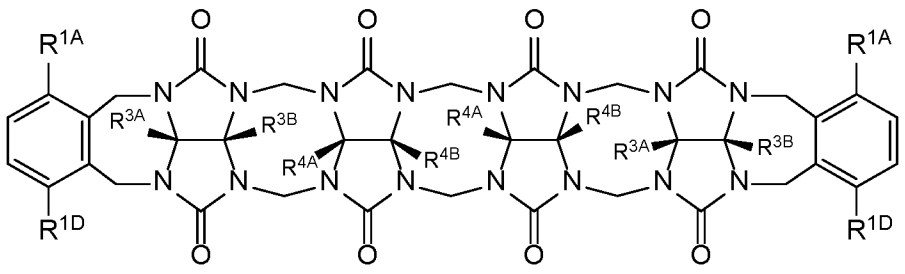
each R^{4A} and R^{4B} is independently selected from hydrogen, halogen, -OH, C_1-C_6 alkyl, phenyl, substituted phenyl and 2 to 6 membered heteroalkyl;

each n1 is independently selected from 0 to 5;

each v1 is independently selected from 2 or 3; and

each X^1 is independently selected from selected from H, -OH, C_1-C_6 alkyl, alkali metal cation, and quaternary ammonium cation.

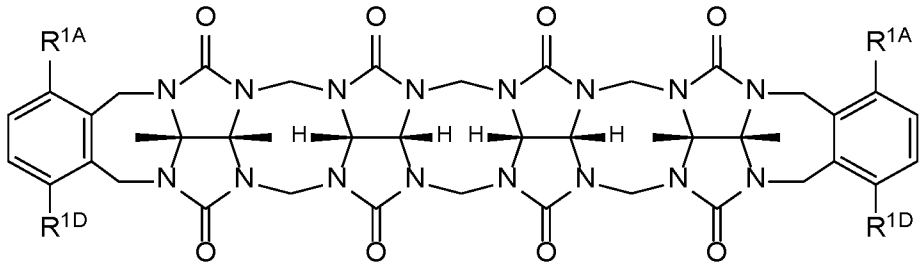
46. The method according to claim 44, wherein the cucurbituril compound has a structure of formula (I-a):



(I-a)

or a pharmaceutically acceptable salt thereof, wherein R^{1A}, R^{1D}, R^{3A}, R^{3B}, R^{4A}, and R^{4B} are defined for formula I.

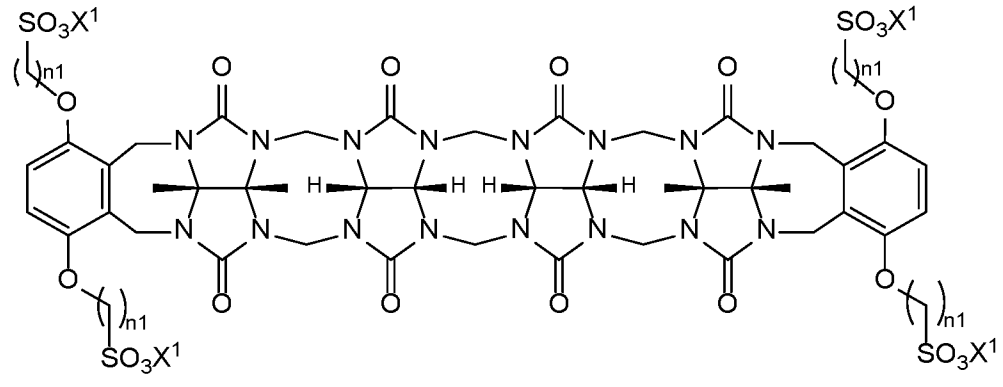
47. The method according to claim 44, wherein the cucurbituril compound has a structure of formula (I-b):



(I-b)

or a pharmaceutically acceptable salt thereof, wherein R^{1A} and R^{1D} are as described for formula I.

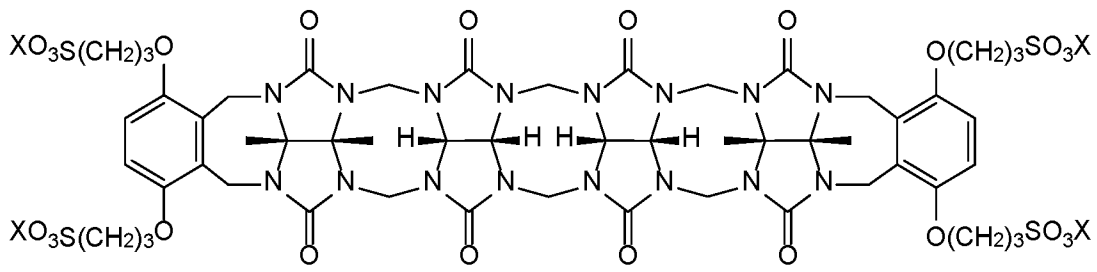
48. The method according to claim 44, wherein the cucurbituril compound has a structure of formula (I-c):



(I-c)

or a pharmaceutically acceptable salt thereof, wherein X^1 and n1 are as described for formula I.

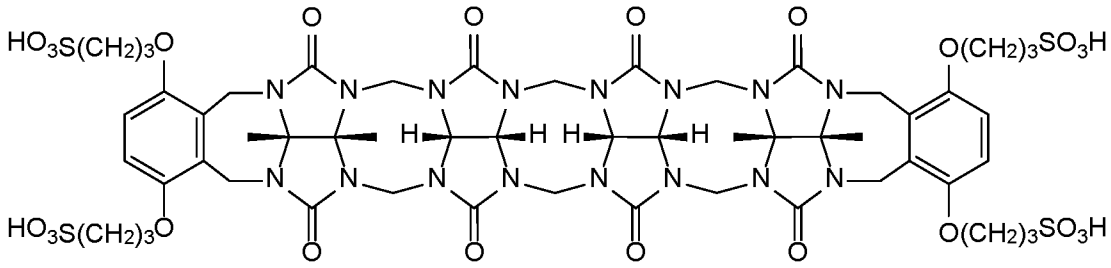
49. The method according claim 44, wherein the cucurbituril compound has a structure of formula (I-A)



(I-A),

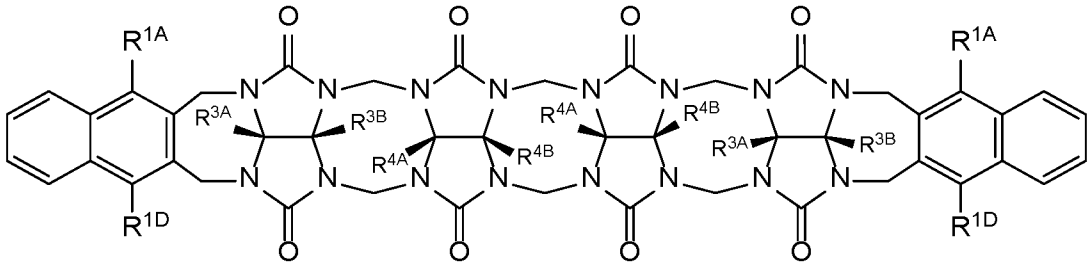
or a pharmaceutically acceptable salt thereof, wherein each X is independently H, alkali metal cation, or quaternary ammonium cation.

50. The method according to claim 44, wherein the cucurbituril compound is Compound A, having the following structure:



or a pharmaceutically acceptable salt thereof.

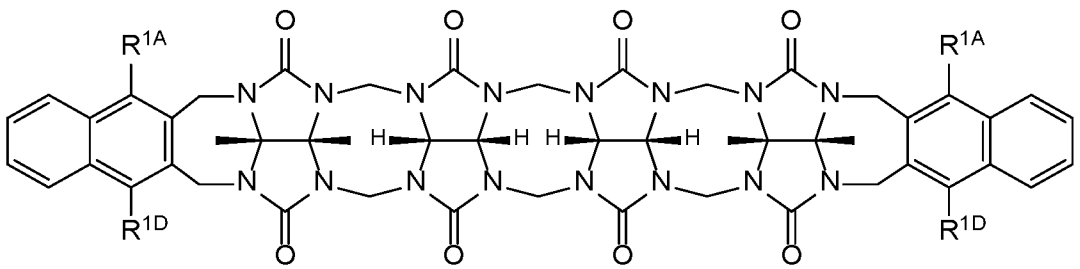
51. The method according to claim 44, wherein the cucurbituril compound has a structure of formula (I-D)



(I-D),

or a pharmaceutically acceptable salt thereof, wherein R^{1A}, R^{1D}, R^{3A}, R^{3B}, R^{4A}, and R^{4B} are as described for formula I.

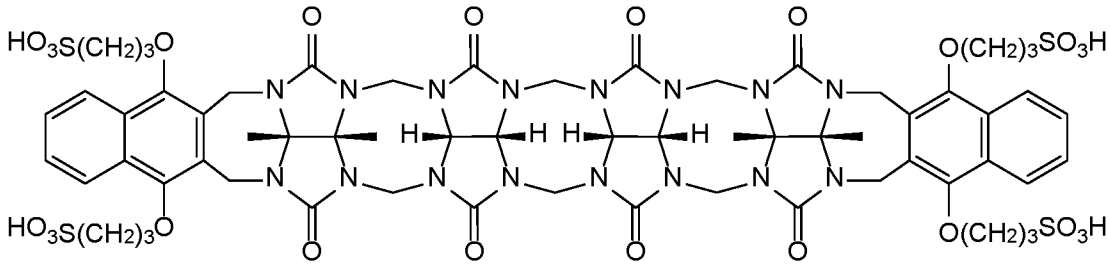
52. The method according to claim 44, wherein the cucurbituril compound has a structure of formula (X):



(X)

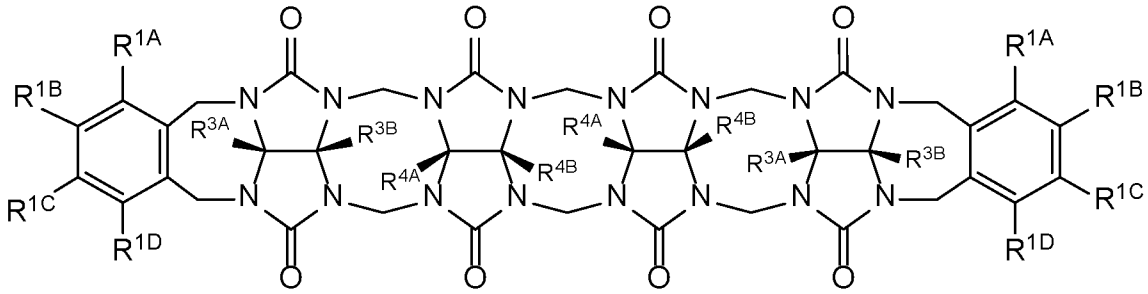
or a pharmaceutically acceptable salt thereof, wherein R^{1A} and R^{1D} are as described for formula I.

53. The method according to claim 44, wherein the cucurbituril compound is Compound B, having the following structure:



or a pharmaceutically acceptable salt thereof.

54. The method according to claim 44, wherein the cucurbituril compound has a structure of formula XI:



XI

or a pharmaceutically acceptable salt thereof, wherein:

each R^{1A} and R^{1D} is independently selected from -O-L-CO_2X^1 and -O-L-SO_3X^1;

each L is independently selected from a chemical bond (single), C_1 to C_{10} alkylene, C_2 to C_{10} alkenylene, $-(CH_2)_a-O-(CH_2)_b$, $-(CH_2)_c-N(R)-(CH_2)_d$, and $-(CH_2)_a-(OCH_2CH_2)_e-(Y)_f-$, each of which may be unsubstituted or substituted at any carbon with 1 to 4 substituents selected from halogen, OH, CO_2H, C_{1-3} alkyl, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl$)_2$, and O-C_{1-3} alkyl;

a is 2 to 8;

b is 0 to 6;

c is 2 to 8;

d is 0 to 6;

e is 1 to 6;

Y is NH, $N(C_{1-3}$ alkyl), or O;

f is 0 or 1;

R is H or C_{1-3} alkyl;

each R^{1B} and R^{1C} is independently selected from hydrogen, halogen, -OH, -CN, CO_2H, SO_3H, C_1-C_6 alkyl, 2 to 6 membered heteroalkyl, C_3-C_6 cycloalkyl, 5 to 6 membered heterocycloalkyl, phenyl, 5 to 6 membered heteroaryl; or

additionally or alternatively, R^{1B} and R^{1C} attached on the same phenyl ring, together with the atoms to which they are attached, are joined to form a fused C_6-C_{12} aryl, 5 to 12 membered heteroaryl, or 5 to 7 membered heterocycle, which are optionally substituted with 1 to 3 substituents independently selected halogen, -OH, $-NH_2$, substituted or unsubstituted C_1-C_6 alkyl, or substituted or unsubstituted 2 to 6 membered heteroalkyl;

each R^{3A} and R^{3B} is independently selected from hydrogen, halogen, -OH, CO_2H, CO_2R', $CONH_2$, CONHR', $CON(R')_2$, C_1-C_6 alkyl, phenyl, substituted phenyl and 2 to 6 membered heteroalkyl;

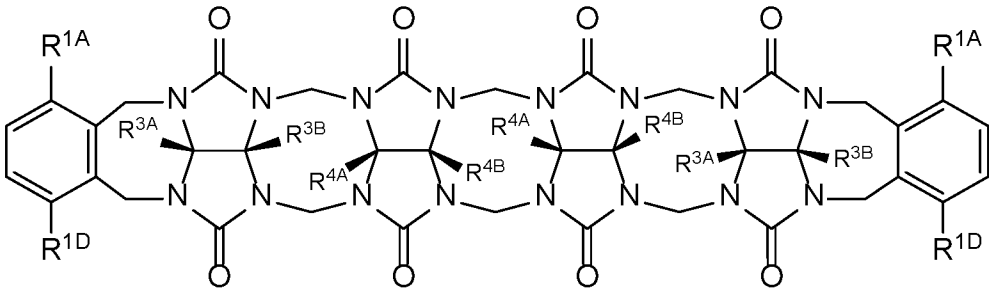
additionally or alternatively, R^{3A} and R^{3B} attached to adjacent carbon atoms, together with the carbons to which they are attached, are joined to form a 5- or 6-membered cycloalkyl or heterocycloalkyl ring;

each R^{4A} and R^{4B} is independently selected from hydrogen, halogen, -OH, CO_2H, CO_2R', $CONH_2$, CONHR', $CON(R')_2$, C_1-C_6 alkyl, phenyl, substituted phenyl and 2 to 6 membered heteroalkyl;

each R' is independently selected from $C_{1\text{-}6}$ alkyl; and

each X^1 is independently selected from selected from H, C_1-C_6 alkyl, alkali metal cation, and quaternary ammonium cation.

55. The method according to claim 54, wherein the cucurbituril compound has a structure of formula XII:



(XII)

or a pharmaceutically acceptable salt thereof, wherein:

each R^{1A} and R^{1D} is independently selected from -O-L-CO_2X^1, and -O-L-SO_3X^1;

each L is independently selected from a chemical bond, C_2 to C_{10} alkylene, C_2 to C_{10} alkenylene, $-(CH_2)_a$-O-$(CH_2)_b$, $-(CH_2)_c$-N(R)-$(CH_2)_d$, and $-(CH_2)_a$-$(OCH_2CH_2)_e$-$(Y)_f$-,

each of which may be unsubstituted or substituted at any carbon with 1 to 4 substituents selected from halogen, OH, CO_2H, C_{1-3} alkyl, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl$)_2$, and O-C_{1-3} alkyl;

a is 2 to 8;

b is 0 to 6;

c is 2 to 8;

d is 0 to 6;

e is 1 to 6;

Y is NH, $N(C_{1-3}$ alkyl), or O;

f is 0 or 1;

R is H or C_{1-3} alkyl;

each R^{3A} and R^{3B} is independently selected from hydrogen, halogen, -OH, CO_2H, CO_2R', $CONH_2$, CONHR', $CON(R')_2$, C_1-C_6 alkyl, phenyl, substituted phenyl and 2 to 6 membered heteroalkyl;

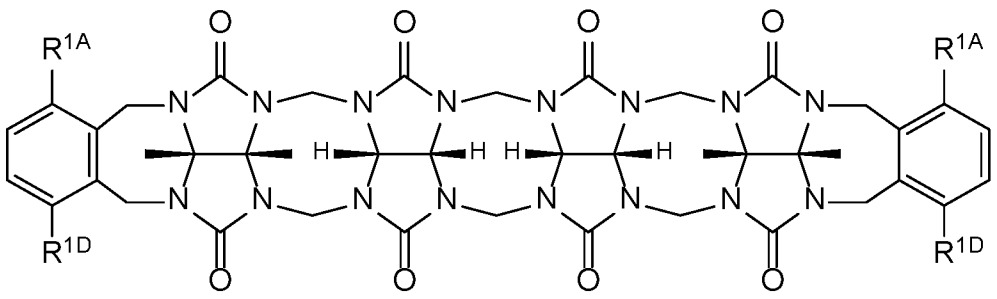
additionally or alternatively, R^{3A} and R^{3B} attached to adjacent carbon atoms, together with the carbons to which they are attached, are joined to form a 5- or 6-membered cycloalkyl or heterocycloalkyl ring;

each R^{4A} and R^{4B} is independently selected from hydrogen, halogen, -OH, CO_2H, CO_2R', $CONH_2$, CONHR', $CON(R')_2$, C_1-C_6 alkyl, phenyl, substituted phenyl and 2 to 6 membered heteroalkyl;

each R' is independently selected from C_{1-6} alkyl; and

each X^1 is independently selected from selected from H, C_1-C_6 alkyl, alkali metal cation, and quaternary ammonium cation.

56. The method according to claim 54, wherein the cucurbituril compound has a structure of formula XIIa:



(XIIa)

or a pharmaceutically acceptable salt thereof, wherein

each R^{1A} and R^{1D} is independently selected from -O-L-CO_2X^1 and -O-L-SO_3X^1;

each L is independently selected from a chemical bond, C_1 to C_{10} alkylene, C_2 to C_{10} alkenylene, $-(CH_2)_a-O-(CH_2)_b$, $-(CH_2)_c-N(R)-(CH_2)_d$, and $-(CH_2)_a-(OCH_2CH_2)_e-(Y)_f-$, each of which may be unsubstituted or substituted at any carbon with 1 to 4 substituents selected from halogen, OH, CO_2H, C_{1-3} alkyl, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl$)_2$, and O-C_{1-3} alkyl;

a is 2 to 8;

b is 0 to 6;

c is 2 to 8;

d is 0 to 6;

e is 1 to 6;

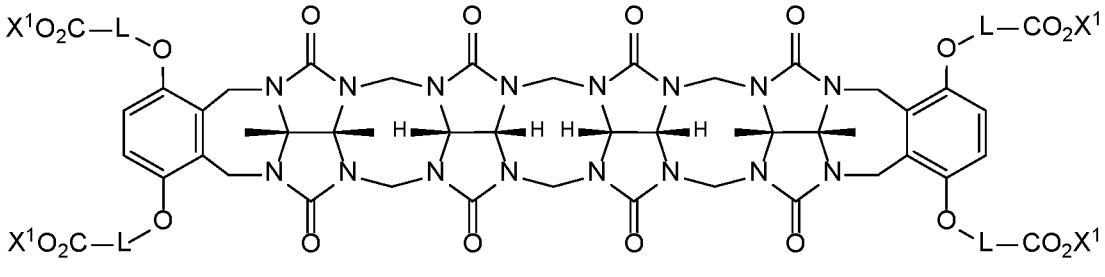
Y is NH, $N(C_{1-3}$ alkyl), or O;

f is 0 or 1;

R is H or C_{1-3} alkyl; and

each X^1 is independently selected from selected from H, C_1-C_6 alkyl, alkali metal cation, and quaternary ammonium cation.

57. The method according to claim 54, wherein the cucurbituril compound has a structure of formula XIIb:



(XIIb)

or a pharmaceutically acceptable salt thereof, wherein

each L is independently selected from C_1 to C_{10} alkylene, C_2 to C_{10} alkenylene, $-(CH_2)_a-O-(CH_2)_b$, $-(CH_2)_c-N(R)-(CH_2)_d$, and $-(CH_2)_a-(OCH_2CH_2)_e-(Y)_f-$, each of which may be unsubstituted or substituted at any carbon with 1 to 4 substituents selected from halogen, OH, CO_2H, C_{1-3} alkyl, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl$)_2$, and O-C_{1-3} alkyl;

a is 2 to 8;

b is 0 to 6;

c is 2 to 8;

d is 0 to 6;

e is 1 to 6;

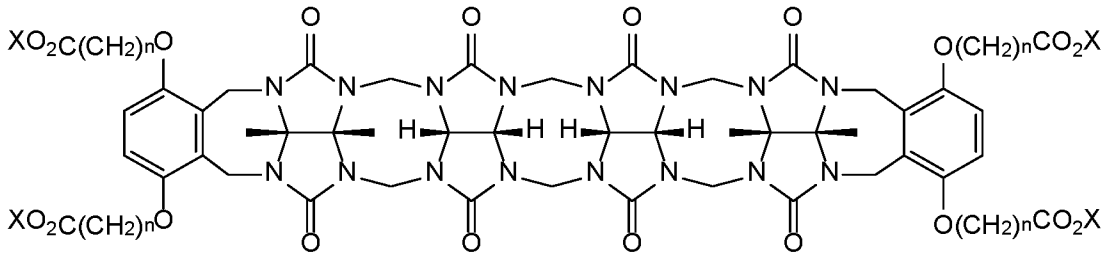
Y is NH, N(C_{1-3} alkyl), or O;

f is 0 or 1;

R is H or C_{1-3} alkyl; and

each X^1 is independently selected from selected from H, C_1-C_6 alkyl, alkali metal cation, and quaternary ammonium cation.

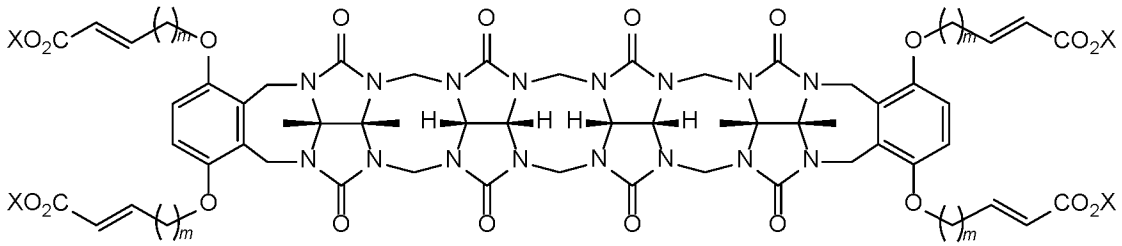
58. The method according to claim 54, wherein the cucurbituril compound has a structure of formula XIIc:



(XIIc),

or a pharmaceutically acceptable salt thereof, wherein each X is independently H, alkali metal cation, an ammonium cation, or combination thereof; and each n is independently 1, 2, 3 or 4.

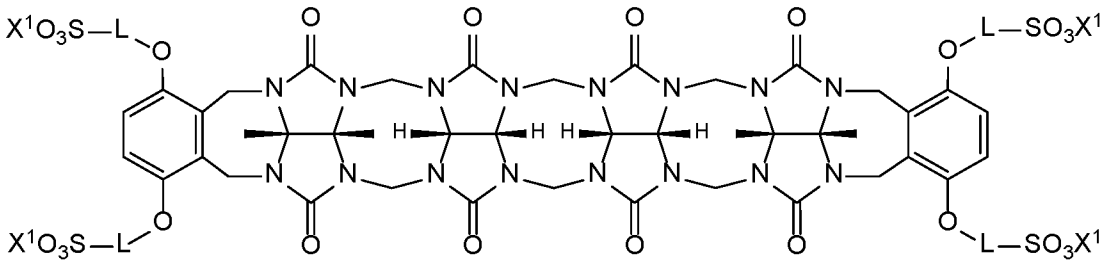
59. The method according to claim 54, wherein the cucurbituril compound has a structure of formula XIId:



(XIId)

or a pharmaceutically acceptable salt thereof, wherein each X is independently H, alkali metal cation, an ammonium cation, or combination thereof; and each m is independently 1, 2, 3 or 4.

60. The method according to claim 54, wherein the cucurbituril compound has a structure of formula XIIe:



(XIIe)

or a pharmaceutically acceptable salt thereof, wherein:

each L is independently selected from a chemical bond, C_1 to C_{10} alkylene, C_2 to C_{10} alkenylene, $-(CH_2)_a-O-(CH_2)_b$, $-(CH_2)_c-N(R)-(CH_2)_d$, and $-(CH_2)_a-(OCH_2CH_2)_e-(Y)_f-$, each of which may be unsubstituted or substituted at any carbon with 1 to 4 substituents selected from halogen, OH, CO_2H, C_{1-3} alkyl, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl$)_2$, and $O-C_{1-3}$ alkyl;

a is 2 to 8;

b is 0 to 6;

c is 2 to 8;

d is 0 to 6;

e is 1 to 6;

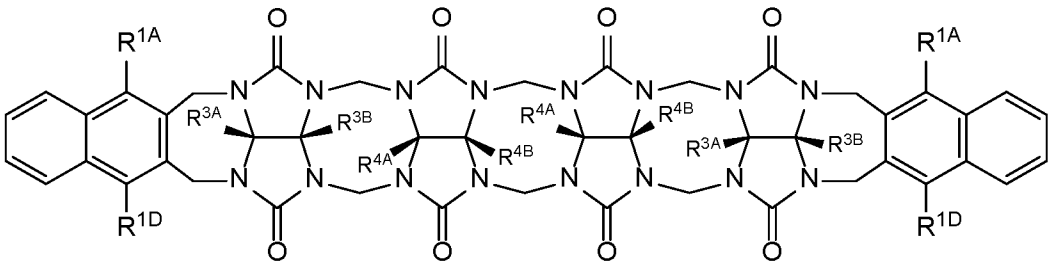
Y is NH, $N(C_{1-3}$ alkyl), or O;

f is 0 or 1;

R is H or C_{1-3} alkyl; and

each X^1 is independently selected from selected from H, C_1-C_6 alkyl, alkali metal cation, and quaternary ammonium cation.

61. The method according to claim 54, wherein the cucurbituril compound has a structure of formula XIII:



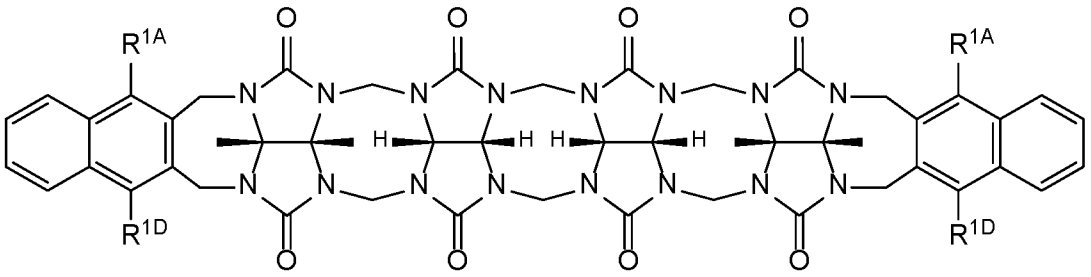
(XIII)

or a pharmaceutically acceptable salt thereof, wherein:

each R^{1A} and R^{1D} is independently selected from $-O-L-CO_2X^1$ and $-O-L-SO_3X^1$;

each L is independently selected from a chemical bond, C_1 to C_{10} alkylene, C_2 to C_{10} alkenylene, $-(CH_2)_a-O-(CH_2)_b$, $-(CH_2)_c-N(R)-(CH_2)_d$, and $-(CH_2)_a-(OCH_2CH_2)_e-(Y)_f-$, each of which may be unsubstituted or substituted at any carbon with 1 to 4 substituents selected from halogen, OH, CO_2H, C_{1-3} alkyl, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl$)_2$, and
$O-C_{1-3}$ alkyl;
a is 2 to 8;
b is 0 to 6;
c is 2 to 8;
d is 0 to 6;
e is 1 to 6;
Y is NH, $N(C_{1-3}$ alkyl), or O;
f is 0 or 1;
R is H or C_{1-3} alkyl;
each R^{3A} and R^{3B} is independently selected from hydrogen, halogen, CO_2H, CO_2R', $CONH_2$, CONHR', $CON(R')_2$, -OH, C_1-C_6 alkyl, phenyl, substituted phenyl and 2 to 6 membered heteroalkyl;
additionally or alternatively, R^{3A} and R^{3B} attached to adjacent carbon atoms, together with the carbons to which they are attached, are joined to form a 5- or 6-membered cycloalkyl or heterocycloalkyl ring;
each R^{4A} and R^{4B} is independently selected from hydrogen, halogen, -OH, CO_2H, CO_2R', $CONH_2$, CONHR', $CON(R')_2$, C_1-C_6 alkyl, phenyl, substituted phenyl and 2 to 6 membered heteroalkyl;
each R' is independently selected from C_{1-6} alkyl; and
each X^1 is independently selected from selected from H, C_1-C_6 alkyl, alkali metal cation, and quaternary ammonium cation.

62. The method according to claim 54, wherein the cucurbituril compound has a structure of formula XIIIa:



(XIIIa)

or a pharmaceutically acceptable salt thereof, wherein:

each R^{1A} and R^{1D} is independently selected from -O-L-CO_2X^1 and -O-L-SO_3X^1;

each L is independently selected from a chemical bond, C_1 to C_{10} alkylene, C_2 to C_{10} alkenylene, -$(CH_2)_a$-O-$(CH_2)_b$-, -$(CH_2)_c$-N(R)-$(CH_2)_d$-, and -$(CH_2)_a$-$(OCH_2CH_2)_e$-$(Y)_f$-, each of which may be unsubstituted or substituted at any carbon with 1 to 4 substituents selected from halogen, OH, CO_2H, C_{1-3} alkyl, NH_2, NH(C_{1-3} alkyl), N(C_{1-3} alkyl)$_2$, and

O-C_{1-3} alkyl;

a is 2 to 8;

b is 0 to 6;

c is 2 to 8;

d is 0 to 6;

e is 1 to 6;

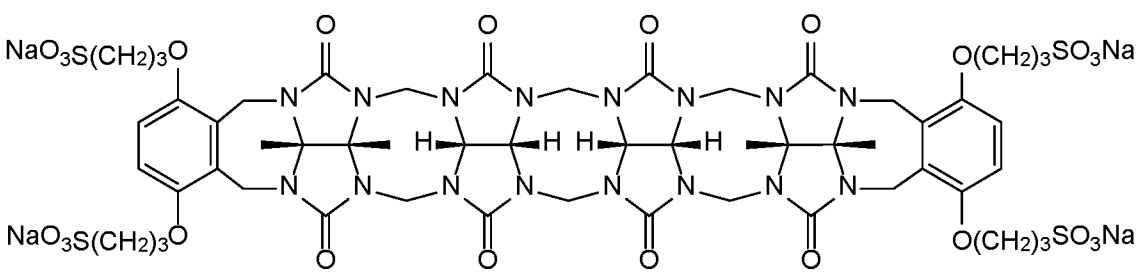
Y is NH, N(C_{1-3} alkyl), or O;

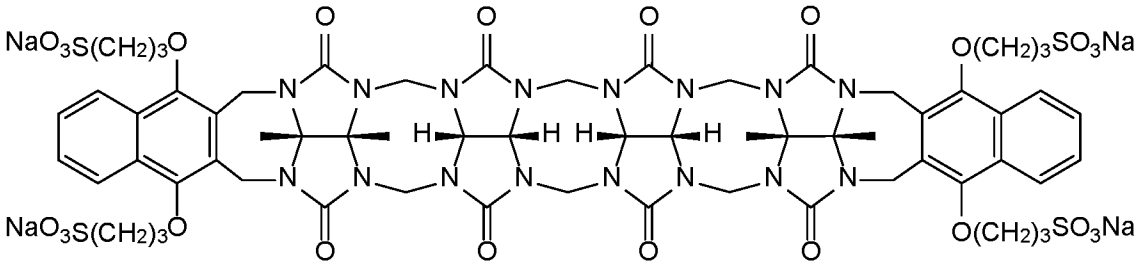
f is 0 or 1;

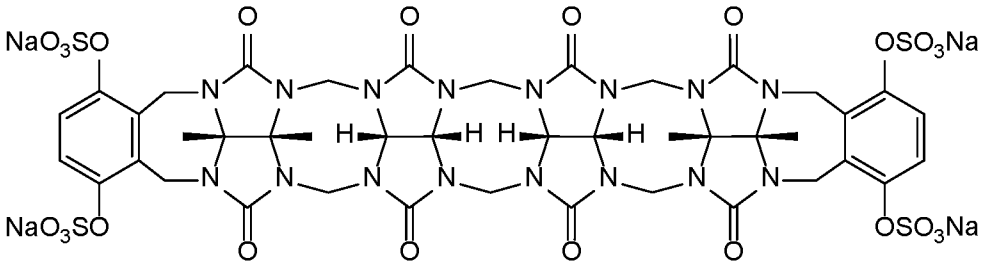
R is H or C_{1-3} alkyl; and

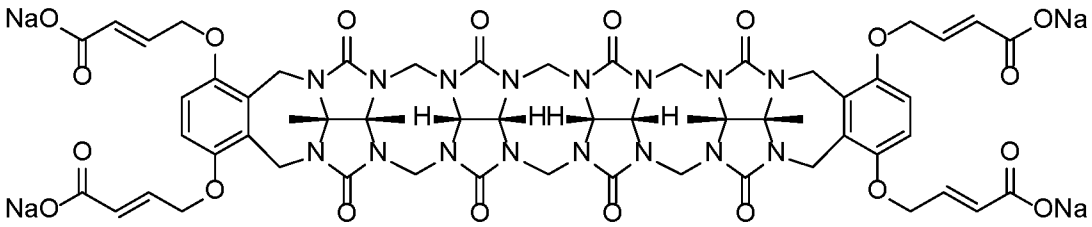
each X^1 is independently selected from selected from H, C_1-C_6 alkyl, alkali metal cation, and quaternary ammonium cation.

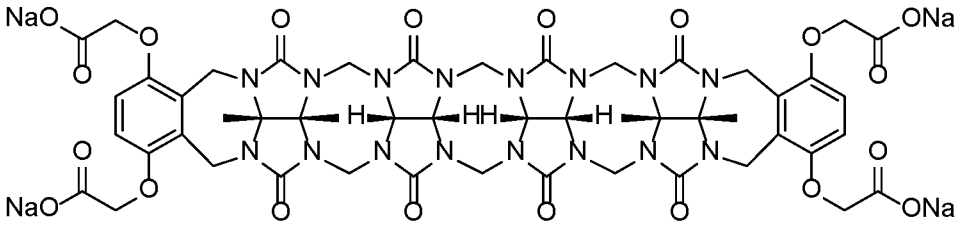
63. The method according to claim 54, wherein the cucurbituril compound has a structure according to one of the following:

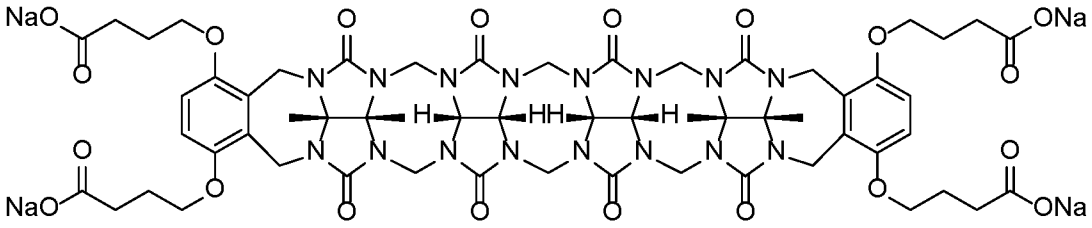






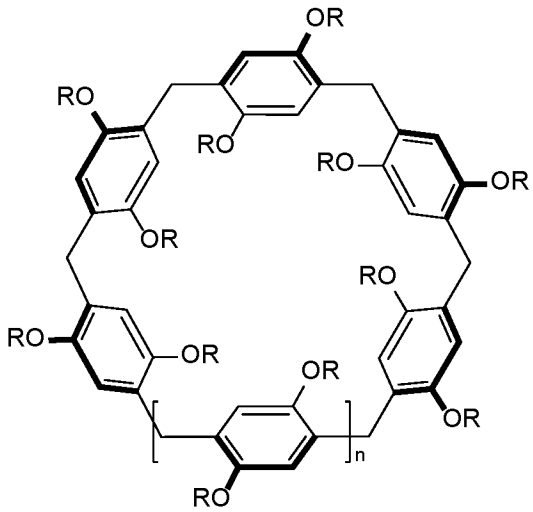






64. The method according to any one of claims 27 to 33, wherein the sequestration agent is a pillararene.

65. The method of claim 64, wherein the sequestration agent is a pillararene having the structure:



or a pharmaceutically acceptable salt thereof, wherein

n is selected from 0, 1, 2 or 3,

each R is independently selected from $-(CH_2)_aS(O)_bX^1$, $-(CH_2)_aCO_2X^1$, and $-(CH_2)_aPO_bX^1$;

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

b is 2 or 3; and

each X^1 is independently selected from selected from H, -OH, alkali metal cation, and quaternary ammonium cation.

66. The method of claim 65, wherein each R is selected from $-(CH_2)_aSO_3X^{1a}$, $-(CH_2)_aCO_2X^{1a}$, and $-(CH_2)_aPO_3X^{1a}$; a is 0, 1, 2 or 3; and X^{1a} is H, alkali metal cation, and quaternary ammonium cation.

67. The method of claim 65, wherein R is SO_3H or a salt thereof (e.g., SO_3Na), or $-CH_2COOH$ or a salt thereof (e.g., CH_2COONa).

68. The method of claim 65, wherein R is selected from SO_3H and SO_3Na; and n is 1.

FIG. 1

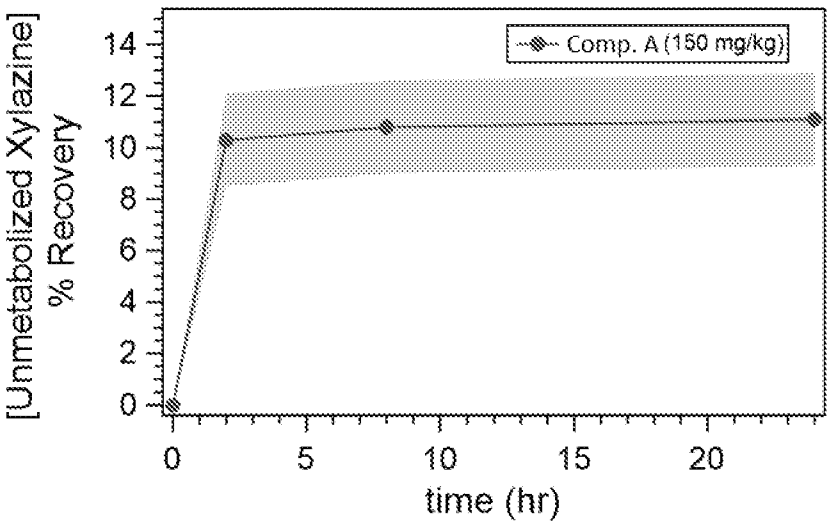

[Unmetabolized Xylazine]
% Recovery
14
12
10
8
6
4
2
0
0
5
10
15
20
time (hr)
Comp. A (150 mg/kg)

FIG. 2

Fig. 2a

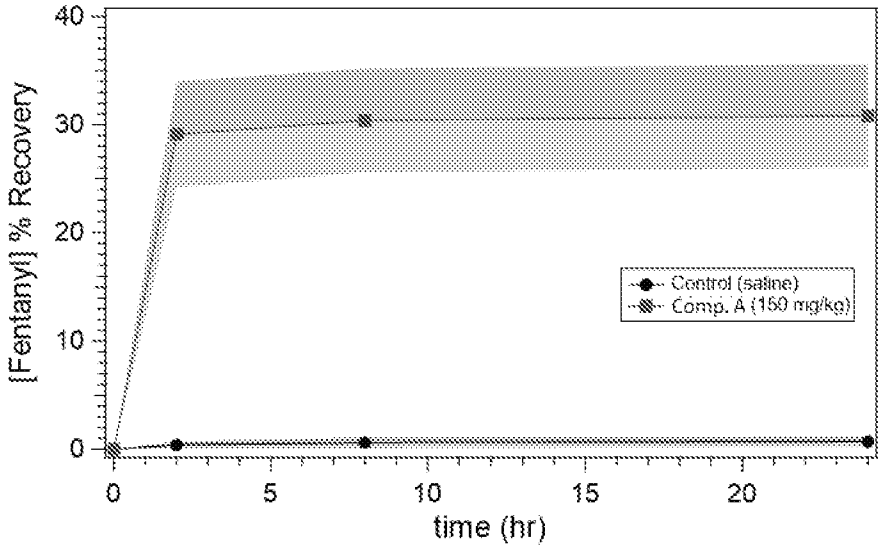


Fig. 2b

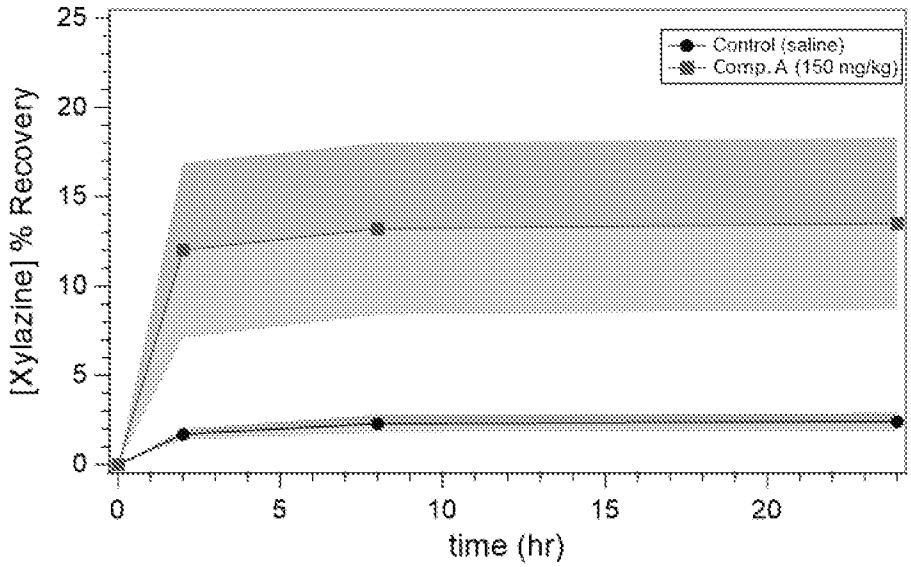
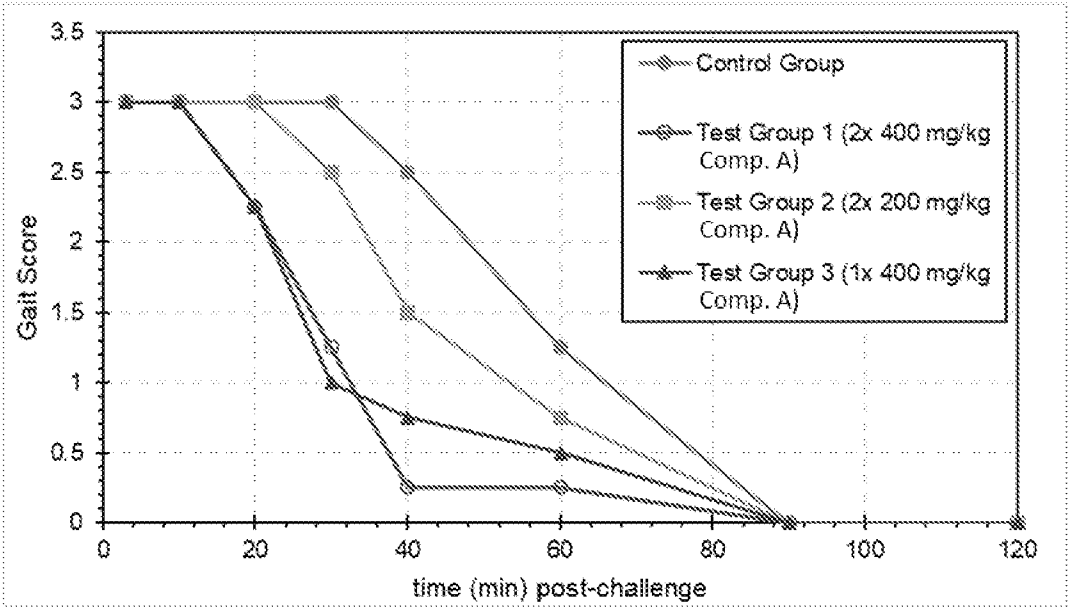


FIG. 3


Gait Score
time (min) post-challenge
Control Group
Test Group 1 (2x 400 mg/kg Comp. A)
Test Group 2 (2x 200 mg/kg Comp. A)
Test Group 3 (1x 400 mg/kg Comp. A)
0
0.5
1
1.5
2
2.5
3
3.5
0
20
40
60
80
100
120