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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
3 March 2016 (03.03.2016)

WIPO | PCT

(10) International Publication Number
WO 2016/033115 A1

(51) International Patent Classification:
C07C 209/08 (2006.01) *C07C 211/27* (2006.01)
C07C 211/14 (2006.01) *C07C 211/17* (2006.01)

(21) International Application Number:
PCT/US2015/046810

(22) International Filing Date:
25 August 2015 (25.08.2015)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/041,588 25 August 2014 (25.08.2014) US

(71) Applicants: **CURZA GLOBAL, LLC** [US/US]; 5152 Edgewood Drive, Suite 375, Provo, Utah 84604 (US). **UNIVERSITY OF UTAH RESEARCH FOUNDATION** [US/US]; 201 South President's Circle, Salt Lake City, Utah 84112 (US).

(72) Inventors: **LOOPER, Ryan**; 5152 Edgewood Drive, Suite 375, Provo, Utah 84604 (US). **SEBAHAR, Paul R.**; 5152 Edgewood Drive, Suite 375, Provo, Utah 84604 (US). **HAUSSENER, Travis**; 5152 Edgewood Drive, Suite 375, Provo, Utah 84604 (US).

(74) Agents: **ZYLSTRA, Eric J.** et al.; Kilpatrick Townsend & Stockton LLP, Two Embarcadero Center, 8th Floor, San Francisco, California 94111 (US).

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

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

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

(54) Title: METHOD OF PRODUCING N-ALKYL POLYAMINES

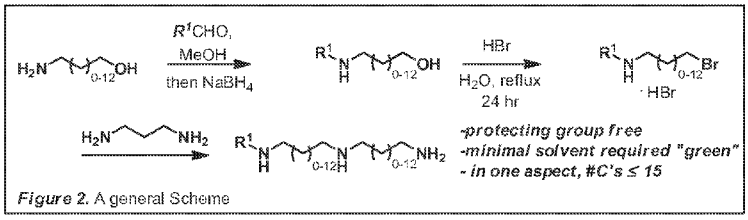


Figure 2. A general Scheme

FIG. 2

(57) Abstract: In one embodiment, the invention presents a process for the preparation of N-alkyl polyamines that includes (i) the conversion of an amino alcohol to an aminoalkyl alkylating agent with a halo or aldehyde reactive group and (ii) the addition of amines to an aminecontaining alkylating agent to make an N-alkyl polyamine.

WO 2016/033115 A1

METHOD OF PRODUCING N-ALKYL POLYAMINES

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 62/041,588 (filed August 25, 2014). This application is incorporated by reference in its entirety for all purposes.

FIELD OF THE INVENTION

[0002] The present invention is directed to methods of synthesizing *N*-alkyl polyamine compounds in high purity. Various aspects and embodiments relate generally to intermediate compounds and to methods of preparing, purifying, and using such compounds.

BACKGROUND OF THE INVENTION

[0003] Methods for preparing amines include, for example, U.S. Pat. Nos. 4,967,008 and 3,223,695; Int'l. Pat. Publ. No. WO 2014/016407 (i.e., U.S. Pat. Appl. Publ. No. 2015/0212132); German Pat. Publ. No. DE 3732508; Renault, J. *et al.* "Solid-phase combinatorial synthesis of polyamine derivatives using aminoalcohol building blocks," *Tetrahedron Lett.* **2001**, *42(38)*, 6655-58; Carboni, B. *et al.* "A new polyamine synthesis," *Tetrahedron Lett.* **1988**, *29(11)*, 1279-82; Cowan, J. C.; Marvel, C. S. "Ammonium salts from bromopropylamines. VI. Salts of polymeric tertiary amines," *J. Am. Chem. Soc.* **1936**, *58*, 2277-9. See also *J. Am. Chem. Soc.* **1936**, *52*, 287; Carboni, B. *et al.* "Aliphatic amino azides as key building blocks for efficient polyamine syntheses," *J. Org. Chem.* **1993**, *58*, 3736-41; and Farzaliev, V. M. *et al.* "Derivatives of N-alkyl(aryl)-1,2(1,3)-diazacycloalkanes. Antimicrobial properties," *Chem. Technol. Fuels Oils* **2009**, *45(2)*, 98-102.

[0004] The physiochemical properties of polyamine intermediates and products make synthesis of high-purity compounds challenging, as the products and reactants are often highly polar, difficult-to-separate compounds. The monitoring and purifications of reactions are complicated by the inability to distinguish products and side-products by NMR or LCMS. Methods to produce these polyamines are limited and typically protecting-group-intense as well as impractical for large-scale synthesis. *See, e.g.* Bergeron, R. J. *et al.* "Reagents for the Stepwise Functionalization of Spermidine, Homospermidine and Bis(3-aminopropyl)amine." *J. Org. Chem.* **1984**, *49*, 2997-3001; Saab, N. H. *et al.* "Synthesis and evaluation of

unsymmetrically substituted polyamine analogues as modulators of human spermidine/spermine-N1-acetyltransferase (SSAT) and as potential antitumor agents." *J. Med. Chem.* **1993**, *36*, 2998–3004; Bergeron, R. J. *et al.* "Synthetic Polyamine Analogues as Antineoplastics." *J. Med. Chem.* **1988**, *31*, 1183-90; Renault, S. C. *et al.* "Solid-phase Organic Synthesis of Unnatural Polyamine Analogues Bearing a Dansyl or Acridine Moiety." *Pharm. Pharmacol. Commun.* **1999**, *5*, 151-57.

[0005] For a scalable process, a protecting-group-free synthesis of polyamines would be advantageous. A protecting group-free synthesis with few synthetic steps would likely be more efficient for making various polyamine analogs because of the lack of protection and deprotection steps. Avoiding chromatographic purification would also be helpful for successful scale-up because of its high cost at large scale. The inventive process provides an improved method for addressing at least these problems. In preferred aspects, the inventive process solves one or more of the problems of simplifying the separation or purification of the product, avoiding protection/deprotection steps, and improving yield.

BRIEF SUMMARY OF THE INVENTION

[0006] In one embodiment, the invention presents a process for the preparation of *N*-alkyl polyamines that includes (i) the conversion of an amino alcohol to an aminoalkyl alkylating agent with a halo or aldehyde reactive group and (ii) the addition of amines to an amine-containing alkylating agent to make an *N*-alkyl polyamine.

BRIEF DESCRIPTION OF THE DRAWINGS

[0007] **Figure 1. (A)** An aspect of the claimed method, in which a *N*-isobutyl norspermidine is prepared. **(B)** The use of the *N*-isobutyl norspermidine to prepare a di-(*N*-alkyl polyamino) compound.

[0008] **Figure 2.** A general method for preparation and use of a alkylamino alkylating agent comprising a halo group.

[0009] **Figure 3.** Exemplary substrates for preparation according to the disclosed methods.

[0010] The accompanying drawings are discussed in reference to the numerals provided therein so as to enable one skilled in the art to practice embodiments of the present invention. The skilled artisan will understand, however, that the inventions described below can be practiced without employing these specific details, or that they can be used for purposes other

than those described herein. Indeed, they can be modified and can be used in conjunction with products and techniques known to those of skill in the art in light of the present disclosure. The drawings and descriptions are intended to be exemplary of various aspects of the invention and are not intended to narrow the scope of the appended claims. Furthermore, it will be appreciated that the drawings may show aspects of the invention in isolation and the elements in one figure may be used in conjunction with elements shown in other figures.

DETAILED DESCRIPTION OF THE INVENTION

[0011] It will be appreciated that reference throughout this specification to aspects, features, advantages, or similar language does not imply that all of the aspects and advantages that may be realized with the present invention should be or are in any single embodiment of the invention. Rather, language referring to the aspects and advantages is understood to mean that a specific aspect, feature, advantage, or characteristic described in connection with an embodiment is included in at least one embodiment of the present invention. Thus, discussion of the aspects and advantages, and similar language, throughout this specification may, but does not necessarily, refer to the same embodiment.

[0012] The described aspects, features, advantages, and characteristics of the invention may be combined in any suitable manner in one or more further embodiments. Furthermore, one skilled in the relevant art will recognize that the invention may be practiced without one or more of the specific aspects or advantages of a particular embodiment. In other instances, additional aspects, features, and advantages may be recognized and claimed in certain embodiments, but may not be present in all embodiments of the invention.

Definitions

[0013] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety, including U.S. Pat. Appl. No. 62/001,604 (docket no. 96175-909657-000451US). In case of conflict, the present specification, including these definitions, will control.

[0014] The terms "a," "an," or "the" as used herein not only includes aspects with one member, but also includes aspects with more than one member. For example, an embodiment including "a polyamine compound and an excipient" should be understood to present certain aspects with at least a second polyamine compound, at least a second excipient, or both.

[0015] The term "about" as used herein to modify a numerical value indicates a defined range around that value. If "X" were the value, "about X" would generally indicate a value from 0.95X to 1.05X. Any reference to "about X" specifically indicates at least the values X, 0.95X, 0.96X, 0.97X, 0.98X, 0.99X, 1.01X, 1.02X, 1.03X, 1.04X, and 1.05X. Thus, "about X" is intended to teach and provide written description support for a claim limitation of, *e.g.*, "0.98X." When the quantity "X" only includes whole-integer values (*e.g.*, "X carbons"), "about X" indicates from (X-1) to (X+1). In this case, "about X" as used herein specifically indicates at least the values X, X-1, and X+1.

[0016] When the term "about" is applied to the beginning of a numerical range, it applies to both ends of the range. Thus, "from about 5 to 20%" is equivalent to "from about 5% to about 20%." When "about" is applied to the first value of a set of values, it applies to all values in that set. Thus, "about 7, 9, or 11%" is equivalent to "about 7%, about 9%, or about 11%." However, when the modifier "about" is applied to describe only the end of a range or only a later value in a set of values, it applies only to that value or that end of the range. Thus, the range "about 2 to 10" is the same as "about 2 to about 10," but the range "2 to about 10" is not.

[0017] The term "acyl" as used herein includes an alkanoyl, aroyl, heterocycloyl, or heteroaroyl group as defined herein. Examples of acyl groups include, but are not limited to, acetyl, benzoyl, and nicotinoyl.

[0018] The term "alkanoyl" as used herein includes an alkyl-C(O)- group wherein the alkyl group is as defined herein. Examples of alkanoyl groups include, but are not limited to, acetyl and propanoyl.

[0019] The term "agent" as used herein includes a compound or mixture of compounds that, when added to a composition, tend to produce a particular effect on the composition's properties. For example, a composition comprising a thickening agent is likely to be more viscous than an otherwise identical comparative composition that lacks the thickening agent.

[0020] The term "alkenyl" as used herein includes a straight or branched chain hydrocarbon containing at least one carbon-carbon double bond. The chain may contain an indicated number of carbon atoms. For example, "C_1-C_{12} alkenyl" indicates that the group may have from 1 to 12 (inclusive) carbon atoms and at least one carbon-carbon double bond. When the indicated number of carbon atoms is 1, then the C_1 alkenyl is double bonded to a carbon (*i.e.*, a carbon analog to an oxo group). In certain aspects, the chain includes 1 to 12, about 2 to 15, about 2 to 12, about 2 to 8, or about 2 to 6 carbon atoms. Examples of an alkenyl group may include, but are not limited to, ethenyl (*i.e.*, vinyl), allyl, propenyl, butenyl, crotyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl, decenyl, dodecenyl, cyclopentenyl, cyclohexenyl, 2-isopentenyl, allenyl, butadienyl, pentadienyl, 3-(1,4-pentadienyl), and hexadienyl.

[0021] In some aspects, an alkenyl group is unsubstituted. In some aspects, an alkenyl group is optionally substituted. When optionally substituted, one or more hydrogen atoms of the alkenyl group (*e.g.*, from 1 to 4, from 1 to 2, or 1) may be replaced with a moiety independently selected from the group consisting of fluoro, hydroxy, alkoxy, amino, alkylamino, acylamino, thio, and alkylthio, with the proviso that no hydrogen atom substituent on the carbon-carbon double bond is replaced by a hydroxy, amino, or thio group.

[0022] The term "alkyl" as used herein includes an aliphatic hydrocarbon chain that may be straight chain or branched. The chain may contain an indicated number of carbon atoms: For example, C_1-C_{12} indicates that the group may have from 1 to 12 (inclusive) carbon atoms in it. If not otherwise indicated, an alkyl group about 1 to about 20 carbon atoms. In some aspects, alkyl groups have 1 to about 12, 1 to about 10, 1 to about 8, 1 to about 6, or 1 to about 4 carbon atoms in the chain. In another aspect, alkyl groups ("lower alkyl") have 1 to about 6, 1 to 5, 1 to 4, or 1 to 3 carbon atoms in the chain. Examples may include, but are not limited to, methyl, ethyl, propyl, isopropyl (iPr), 1-butyl, 2-butyl, isobutyl (iBu), tert-butyl, pentyl, 2-methylbutyl, 1,1-dimethylpropyl, hexyl, heptyl, octyl, nonyl, decyl, dodecyl, cyclopentyl, or cyclohexyl. In some aspects, an alkyl group can exclude methyl (*e.g.*, 2 to 6 carbon atoms in the chain).

[0023] An alkyl group can be unsubstituted or optionally substituted. When optionally substituted, one or more hydrogen atoms of the alkyl group (*e.g.*, from 1 to 4, from 1 to 2, or 1) may be replaced with a moiety independently selected from the group consisting of fluoro,

hydroxy, alkoxy, amino, alkylamino, acylamino, thio, and alkylthio. In some aspects, the alkyl group is unsubstituted or not optionally substituted.

[0024] The term "alkoxy" as used herein includes a straight or branched chain saturated or unsaturated hydrocarbon containing at least one oxygen atom in an ether group (e.g., EtO-). The chain may contain an indicated number of carbon atoms. For example, "C_1-C_{12} alkoxy" indicates that the group may have from 1 to 12 (inclusive) carbon atoms and at least one oxygen atom. Examples of a C_1-C_{12} alkoxy include, but are not limited to, methoxy, ethoxy, isopropoxy, butoxy, n-pentoxy, isopentoxy, neopentoxy, and hexoxy.

[0025] An alkoxy group can be unsubstituted or optionally substituted. When optionally substituted, one or more hydrogen atoms of the alkoxy group (*e.g.*, from 1 to 4, from 1 to 2, or 1) may be replaced with a moiety independently selected from the group consisting of fluoro, hydroxy, alkoxy, amino, alkylamino, acylamino, thio, and alkylthio, with the proviso that no hydrogen atom alpha to the ether oxygen is replaced by a hydroxy, amino, or thio group. In some aspects, the alkoxy group is unsubstituted or not optionally substituted.

[0026] The term "alkynyl" as used herein includes a straight, branched, or cyclic hydrocarbon containing at least one carbon–carbon triple bond. Examples may include, but are not limited to, ethynyl, propargyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl, decynyl, or decynyl.

[0027] An alkynyl group can be unsubstituted or optionally substituted. When optionally substituted, one or more hydrogen atoms of the alkynyl group (*e.g.*, from 1 to 4, from 1 to 2, or 1) may be replaced with a moiety independently selected from the group consisting of fluoro, hydroxy, alkoxy, amino, alkylamino, acylamino, thio, and alkylthio, with the proviso that no sp hydrogen atom substituent is replaced by a hydroxy, amino, or thio group. In some aspects, the alkynyl group is unsubstituted or not optionally substituted.

[0028] The term "aroyl" as used herein includes an aryl-CO- group wherein aryl is as defined herein. Examples include, but are not limited to, benzoyl, naphth-1-oyl and naphth-2-oyl.

[0029] The term "aryl" as used herein includes cyclic aromatic carbon ring systems containing from 6 to 18 carbons. Examples of an aryl group include, but are not limited to, phenyl, naphthyl, anthracenyl, tetracenyl, biphenyl and phenanthrenyl.

[0030] An aryl group can be unsubstituted or optionally substituted. When optionally substituted, one or more hydrogen atoms of the aryl group (*e.g.*, from 1 to 5, from 1 to 2, or 1) may be replaced with a moiety independently selected from the group consisting of alkyl, cyano, acyl, halo, hydroxy, alkoxy, amino, alkylamino, acylamino, thio, and alkylthio. In some aspects, the aryl group is unsubstituted or not optionally substituted.

[0031] The term "arylalkyl" or "aralkyl" as used herein includes an alkyl group as defined herein where at least one hydrogen substituent has been replaced with an aryl group as defined herein. Examples include, but are not limited to, benzyl, 1-phenylethyl, 4-methylbenzyl, and 1,1,-dimethyl-1-phenylmethyl.

[0032] A group can be unsubstituted or optionally substituted as per its component parts. For example, but without limitation, the aryl group of an arylalkyl group can be substituted, such as in the arylalkyl group 4-methylbenzyl. In some aspects, and preferably, the group is unsubstituted or not optionally substituted, especially if it includes a defined substituent, such as a hydroxyalkyl or alkylaminoalkoxy group.

[0033] The linking term "comprising" or "comprise" as used herein is not closed. For example, "a composition comprising A" must include the component A, but it may incorporate one or more other components (*e.g.*, B; B and C; and the like).

[0034] The term "cycloalkyl" as used herein includes a cyclic hydrocarbon group that may contain an indicated number of carbon atoms: For example, C_3-C_{12} indicates that the group may have from 3 to 12 (inclusive) carbon atoms in it. If not otherwise indicated, a cycloalkyl group includes about 3 to about 20 carbon atoms. In some aspects, cycloalkyl groups have 3 to about 12 carbon atoms in the group. In another aspect, cycloalkyl groups have 3 to about 7 carbon atoms in the group. Examples may include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 4,4-dimethylcyclohexyl, and cycloheptyl.

[0035] A cycloalkyl group can be unsubstituted or optionally substituted. When optionally substituted, one or more hydrogen atoms of the cycloalkyl group (*e.g.*, from 1 to 4, from 1 to 2, or 1) may be replaced with a moiety independently selected from the group consisting of fluoro, hydroxy, alkoxy, amino, alkylamino, acylamino, thio, and alkylthio. In some aspects, a substituted cycloalkyl group can incorporate an exo- or endocyclic alkene (*e.g.*, cyclohex-2-en-1-yl). In some aspects, a cycloalkyl group is unsubstituted or not optionally substituted.

[0036] The term "effective amount" or "effective dose" as used herein includes an amount sufficient to achieve the desired result and accordingly will depend on the ingredient and its desired result. Nonetheless, once the desired effect is identified, determining the effective amount is within the skill of a person skilled in the art.

[0037] As used herein, "fluoroalkyl" includes an alkyl group wherein the alkyl group includes one or more fluoro- substituents. Examples include, but are not limited to, trifluoromethyl.

[0038] As used herein, "geminal" substitution includes two or more substituents that are directly attached to the same atom. An example is 3,3-dimethyl substitution on a cyclohexyl or spirocyclohexyl ring.

[0039] As used herein, "halo" or "halogen" includes fluoro, chloro, bromo, or iodo. Preferably, for a *N*-(haloalkyl) alkylamine, "halo" includes bromo or chloro.

[0040] An alkylene "halide" as described herein is a haloalkyl group. For example, *N*-alkyl propylene halide is equivalent to *N*-alkyl halopropane (*i.e.*, comprising a C-X bond, where X is halogen). In contrast, a salt with a halide counterion is, *e.g.*, an alkylammonium bromide (*i.e.*, a A^+ cation and an X^- anion).

[0041] The term "heteroaryl" includes mono and bicyclic aromatic groups of about 4 to about 14 ring atoms (*e.g.*, 4 to 10 or 5 to 10 atoms) containing at least one heteroatom. Heteroatom as used in the term heteroaryl refers to oxygen, sulfur and nitrogen. A nitrogen atom of a heteroaryl is optionally oxidized to the corresponding N-oxide. Examples include, but are not limited to, pyrazinyl, furanyl, thienyl, pyridyl, pyrimidinyl, isoxazolyl, isothiazolyl, oxazolyl, thiazolyl, pyrazolyl, furazanyl, pyrrolyl, pyrazolyl, triazolyl, 1,2,4-thiadiazolyl, pyrazinyl, pyridazinyl, quinoxalinyl, phthalazinyl, imidazo[1,2-a]pyridine, imidazo[2,1-b]thiazolyl, benzofurazanyl, indolyl, azaindolyl, benzimidazolyl, benzothienyl, quinolinyl, imidazolyl, thienopyridyl, quinazolinyl, thienopyrimidyl, pyrrolopyridyl, imidazopyridyl, isoquinolinyl, benzoazaindolyl, and 1,2,4-triazinyl, benzothiazolyl.

[0042] A heteroaryl group can be unsubstituted or optionally substituted. When optionally substituted, one or more hydrogen atoms of the heteroaryl group (*e.g.*, from 1 to 5, from 1 to 2, or 1) may be replaced with a moiety independently selected from the group consisting of alkyl, cyano, acyl, halo, hydroxy, alkoxy, amino, alkylamino, acylamino, thio, and alkylthio. In some aspects, the heteroaryl group is unsubstituted or not optionally substituted.

[0043] The term "heteroaroyl" as used herein includes a heteroaryl-C(O)- group wherein heteroaryl is as defined herein. Heteroaroyl groups include, but are not limited to, thiophenoyl, nicotinoyl, pyrrol-2-ylcarbonyl, and pyridinoyl.

[0044] The term "heterocycloyl" as used herein includes a heterocyclyl-C(O)- group wherein heterocyclyl is as defined herein. Examples include, but are not limited to, N-methyl prolinoyl and tetrahydrofuranoyl.

[0045] As used herein, "heterocyclyl" includes a non-aromatic saturated monocyclic or multicyclic ring system of about 4 to about 10 ring atoms (*e.g.*, 5 to about 8 ring atoms, or 5 to about 6 ring atoms), in which one or more of the atoms in the ring system is an element or elements other than carbon, *e.g.*, nitrogen, oxygen or sulfur. A heterocyclyl group optionally comprises at least one sp^2-hybridized atom (*e.g.*, a ring incorporating an carbonyl, endocyclic olefin, or exocyclic olefin). In some embodiments, a nitrogen or sulfur atom of the heterocyclyl is optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Examples of monocyclic heterocyclyl rings include, but are not limited to, piperidinyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,3-dioxolanyl, 1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothiophenyl, and tetrahydrothiopyranyl.

[0046] A heterocycyl group can be unsubstituted or optionally substituted. When optionally substituted, one or more hydrogen atoms of the group (*e.g.*, from 1 to 4, from 1 to 2, or 1) may be replaced with a moiety independently selected from the group consisting of fluoro, hydroxy, alkoxy, amino, alkylamino, acylamino, thio, and alkylthio. In some aspects, a substituted heterocycyl group can incorporate an exo- or endocyclic alkene. In some aspects, the heterocycyl group is unsubstituted or not optionally substituted.

[0047] As used herein, the term "hydroxyalkyl" includes an alkyl group where at least one hydrogen subtituent has been replaced with an alcohol (-OH) group. In certain aspects, the hydroxyalkyl group has one alcohol group. In certain aspects, the hydroxyalkyl group has one or two alcohol groups, each on a different carbon atom. In certain aspects, the hydroxyalkyl group has 1, 2, 3, 4, 5, or 6 alcohol groups. Examples may include, but are not limited to, hydroxymethyl, 2-hydroxyethyl, and 1-hydroxyethyl.

[0048] When any two substituent groups or any two instances of the same substituent group are "independently selected" from a list of alternatives, the groups may be the same or different. For example, if R^a and R^b are independently selected from the group consisting of alkyl, fluoro, amino, and hydroxyalkyl, then a molecule with two R^a groups and two R^b

groups could have all groups be alkyl group (e.g., four different alkyl groups). Alternatively, the first R^a could be alkyl, the second R^a could be fluoro, the first R^b could be hydroxyalkyl, and the second R^b could be amino (or any other substituents taken from the group). Alternatively, both R^a and the first R^b could be fluoro, while the second R^b could be alkyl (*i.e.*, some pairs of substituent groups may be the same, while other pairs may be different).

[0049] As used herein, "polyamine" includes a compound that has at least two amine groups, which may be the same or different. The amine group may be a primary amine, a secondary amine, a tertiary amine, or quaternary ammonium salt. Examples may include, but are not limited to, 1,3-diaminopropane, 1,4-diaminobutane, hexamethylenediamine, dodecan-1,12-diamine, spermine, spermidine, norspermine, and norspermidine.

[0050] As used herein, "or" should in general be construed non-exclusively. For example, an embodiment of "a composition comprising A or B" would typically present an aspect with a composition comprising both A and B. "Or" should, however, be construed to exclude those aspects presented that cannot be combined without contradiction (*e.g.*, a composition pH that is between 9 and 10 or between 7 and 8).

[0051] As used herein, "spirocycloalkyl" as used herein includes a cycloalkyl in which geminal substituents on a carbon atom are replaced to join in forming a 1,1-substituted ring. For example, but without limitation, for a $-C(R^1)(R^2)-$ group that was part of a longer carbon chain, if R^1 and R^2 joined to form a cyclopropyl ring incorporating the carbon to which R^1 and R^2 were bonded, this would be a spirocycloalkyl group (i.e., spirocyclopropyl).

[0052] As used herein, "spiroheterocyclyl" as used herein includes a heterocycloalkyl in which geminal substituents on a carbon atom are replaced to join in forming a 1,1-substituted ring. For example, but without limitation, for a $-C(R^1)(R^2)-$ group that was part of a longer carbon chain, if R^1 and R^2 joined to form a pyrrolidine ring incorporating the carbon to which R^1 and R^2 were bonded, this would be a spiroheterocyclyl group.

Method

[0053] In one embodiment, the invention sets forth a method of preparing an N-alkyl polyamine, wherein the method comprises the steps:

reacting an aminoalkyl alkylating agent in a reaction mixture comprising an excess amount of a polyaminoalkane to produce a N-alkyl polyamine, wherein the aminoalkyl alkylating agent

comprises (i) a secondary or tertiary amino group and (ii) a halo or aldehyde group; and wherein the N-alkyl polyamine has from 5 to 30 carbon atoms; and

distilling a crude product comprising the N-alkyl polyamine to provide a purified N-alkyl polyamine.

[0054] In one aspect, amino alcohols present several advantages as a starting material for the inventive process, including: 1) options for synthetic manipulation of the amine without affecting the alcohol functionality on the chain (e.g., selective monoalkylation of the amine by controlled reductive amination); and 2) a leaving group synthon (*i.e.*, the hydroxyl) that can be activated for displacement later. Direct alkylation of a diamine typically produced bis-alkylated impurities that decreased the efficiency of the reaction and purification. A further advantage is the low cost and ready availability in large quantities (>20 kg) of some amine alcohols (e.g., 3-amino-1-propanol).

[0055] In one aspect, the N-alkyl polyamine has from 20 to 30 carbon atoms. In a more specific aspect, the N-alkyl polyamine has from 20 to 26 carbon atoms.

[0056] In an alternative aspect, the N-alkyl polyamine has from 5 to 20 carbon atoms. In a more specific aspect, the N-alkyl polyamine has from 10 to 20 carbon atoms. In an alternative more specific aspect, the N-alkyl polyamine has from 5 to 15 carbon atoms. In an alternative more specific aspect, the N-alkyl polyamine has from 10 to 15 carbon atoms.

[0057] In one aspect, the step of reacting the aminoalkyl alkylating agent is performed at a temperature from -78 °C to 150 °C (*e.g.*, about -78 °C, about -40 °C, about -35 °C, about -30 °C, about -25 °C, about -20 °C, about -15 °C, about -10 °C, about -5 °C, about 0 °C, about 5 °C, about 10 °C, about 15 °C, about 20 °C, about 25 °C, about 30 °C, or about 35 °C). In a more specific aspect, the step of reacting the aminoalkyl alkylating agent is performed at a temperature from -78 °C to 120 °C. In a more specific aspect, the step of reacting the aminoalkyl alkylating agent is performed at a temperature from -78 °C to 100 °C. In a more specific aspect, the step of reacting the aminoalkyl alkylating agent is performed at a temperature from -25 °C to 100 °C. In a more specific aspect, the step of reacting the aminoalkyl alkylating agent is performed at a temperature from -10 °C to 100 °C. In a more specific aspect, the step of reacting the aminoalkyl alkylating agent is performed at a temperature from 0 °C to 100 °C. In a more specific aspect, the step of reacting the aminoalkyl alkylating agent is performed at a temperature from 0 °C to 80 °C. In a more specific aspect, the step of reacting the aminoalkyl alkylating agent is performed at a

temperature from 0 °C to 60 °C. In a more specific aspect, the step of reacting the aminoalkyl alkylating agent is performed at a temperature from 0 °C to 40 °C (e.g., at room temperature, ca. 20 °C) . In a more specific aspect, the step of reacting the aminoalkyl alkylating agent is performed at a temperature from 10 °C to 25 °C. In a more specific aspect, the step of reacting the aminoalkyl alkylating agent is performed at a temperature from about 0 °C to 20 °C.

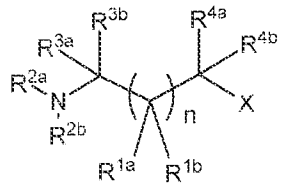
[0058] In one aspect, the step of distilling the crude product is performed at below atmospheric pressure. In a more specific aspect, the step of distilling the crude product is performed at a pressure from 10 mm Hg to 25 mm Hg. In an alternative more specific aspect, the step of distilling the crude product is performed at a pressure from 1 mm Hg to 10 mm Hg. In an alternative more specific aspect, the step of distilling the crude product is performed at a pressure from 0.01 mm Hg to 1 mm Hg.

[0059] In one preferred aspect, the present invention ensures that the excess amine reacted with the aminoalkyl alkylating agent has a boiling point that is low enough to allow easy separation of it from the desired *N*-alkyl polyamine product under the distillation conditions. In one aspect, the distilled product has a boiling point at least 20 °C higher than the excess amine (*e.g.*, diaminoalkane). In one aspect, the desired product has a boiling point at least 25 °C, at least 30 °C, at least 35 °C, at least 40 °C, at least 45 °C, at least 50 °C, at least 60 °C, or at least 75 °C higher than the excess amine (*e.g.*, the excess diaminoalkane, such as norspermine or norspermidine).

[0060] In one preferred aspect, the present invention ensures that any significant byproducts and impurities of the reaction (*e.g.*, overalkylation products of high molecular weight compared to the desired product) have a boiling point that is high enough to allow easy separation of them from the desired *N*-alkyl polyamine product under the distillation conditions. In one aspect, the significant byproducts and impurities are not volatile under the distillation conditions. In one aspect, the desired product has a boiling point at least 20 °C lower than such high-boiling byproducts and impurities. In one aspect, the desired product has a boiling point at least 25 °C, at least 30 °C, at least 35 °C, at least 40 °C, at least 45 °C, at least 50 °C, at least 60 °C, or at least 75 °C than such high-boiling byproducts and impurities.

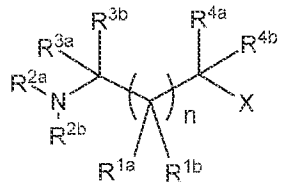
[0061] In one aspect, the step of reacting the aminoalkyl alkylating agent includes no added solvent. In an alternative aspect, the step of reacting the aminoalkyl alkylating agent includes added solvent.

[0062] In one aspect, the aminoalkyl alkylating agent is of the formula



wherein each R substituent is an independently selected hydrogen, alkyl, alkoxy alkenyl, or alkynyl group, with the proviso that the R^2 substituents are not hydrogen; and wherein X is -CHO.

[0063] In one aspect, the aminoalkyl alkylating agent is of the formula



wherein each R substituent is an independently selected hydrogen, alkyl, alkoxy alkenyl, or alkynyl group; wherein at least one R^2 substituent is not hydrogen; and wherein X is a halo group.

[0064] In a more specific aspect, at least one R^{1a} and R^{1b} are alkyl. In a more specific aspect, at least one R^{1a} and R^{1b} are methyl. In an alternative more specific aspect, R^{1a} and R^{1b} are hydrogen. In an alternative more specific aspect, R^{1a} and R^{1b} are joined to form a spirocyclopropyl ring.

[0065] In a more specific aspect, R^{2a} is an alkyl and R^{2b} is hydrogen. In an alternative more specific aspect, R^{2a} is an alkyl and R^{2b} is an alkyl.

[0066] In a more specific aspect, R^{3a} and R^{3b} are hydrogen.

[0067] In a more specific aspect, R^{4a} and R^{4b} are hydrogen.

[0068] In a more specific aspect, X is chloro, bromo, or iodo. In an alternative more specific aspect, X is a chloro.

[0069] In one aspect, the aminoalkyl alkylating agent is an N-alkyl propylene halide or aldehyde. In an alternative aspect, the aminoalkyl alkylating agent is an N-alkyl butylene halide or aldehyde. In an alternative aspect, the aminoalkyl alkylating agent is an N-alkyl ethylene halide or aldehyde. In an alternative aspect, the aminoalkyl alkylating agent is an N-alkyl pentylene halide or aldehyde. In an alternative aspect, the aminoalkyl alkylating agent is an N-alkyl hexylene halide or aldehyde.

[0070] In one aspect, the N-alkyl group is butyl. In an alternative aspect, the N-alkyl group is isobutyl. In an alternative aspect, the N-alkyl group is hexyl. In an alternative aspect, the N-alkyl group is (cyclohexyl)methyl. In an alternative aspect, the N-alkyl group is octyl. In an alternative aspect, the N-alkyl group is isopropyl. In an alternative aspect, the N-alkyl group is methyl. In an alternative aspect, the N-alkyl group is ethyl. In an alternative aspect, N-alkyl group is cyclohexyl. In an alternative aspect, the N-alkyl group is prenyl. In an alternative aspect, the N-alkyl group is propargyl. In an alternative aspect, the N-alkyl group is cyclopropyl.

[0071] In one aspect, the halide or halo is chloride. In an alternative aspect, the halide or halo is bromide.

[0072] In one aspect, the aminoalkyl alkylating agent is a crystalline salt with a halide counterion.

[0073] In one aspect, the polyaminoalkane is spermidine. In an alternative aspect, the polyaminoalkane is norspermidine.

[0074] In one aspect, the excess amount of diamine is about 2 or at least 2 equivalents (*e.g.*, about 2, 2.5, 3, 3.5, 4, 4.5, or 5 equivalents). In an alternative aspect, the excess amount is about 5 or at least 5 equivalents (*e.g.*, about 5, 6, 7, or 8 equivalents). In an alternative aspect, the excess amount is about 8 or at least 8 equivalents (*e.g.*, about 8, 9, 10, 11, or 12 equivalents). In an alternative aspect, the excess amount is about 12 or at least 12 equivalents (*e.g.*, about 12, 13, 14, 15, or 16 equivalents). In an alternative aspect, the excess amount is about 16 or at least 16 equivalents (*e.g.*, about 16, 17, 18, 19, or 20 equivalents). In an alternative aspect, the excess amount is about 10 to 20 equivalents (*e.g.*, about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 equivalents). In an alternative aspect, the excess amount is about 20 or at least 20 equivalents (*e.g.*, about 20, 21, 22, 23, or 24 equivalents). In an alternative aspect, the excess amount is about 24 or at least 24 equivalents (*e.g.*, about 24, 25, 26, 27, or 28 equivalents). In an alternative aspect, the excess amount is about 28 or at least 28

equivalents (*e.g.*, about 28, 29, 30, 31, or 32 equivalents). In an alternative aspect, the excess amount is about 32 or at least 32 equivalents (*e.g.*, about 32, 33, 34, 35, or 36 equivalents). In an alternative aspect, the excess amount is about 36 or at least 36 equivalents (*e.g.*, about 36, 37, 38, 39, or 40 equivalents). In an alternative aspect, the excess amount is about 40 or at least 40 equivalents (*e.g.*, about 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 equivalents). In an alternative aspect, the excess amount is about 50 or at least 50 equivalents (*e.g.*, about 50, 51, 52, 53, 54, 55, 60, 65, 70, or 75 equivalents).

[0075] In one aspect, the method further comprises a step of distilling the crude product to produce a purified diaminoalkane. In one aspect, the distilling step is under reduced pressure. In one aspect, the excess diaminoalkane is at least partially removed by aqueous extraction.

[0076] In one aspect, the method further comprises reusing the purified diaminoalkane as a substrate for alkylation.

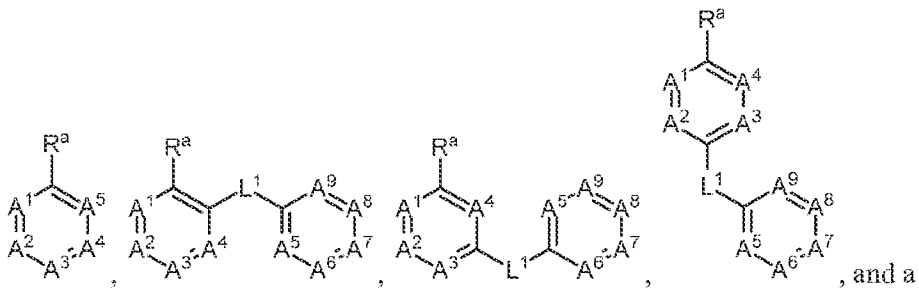
[0077] In one aspect, the method further comprises a step of reacting an aminoalkyl alcohol precursor to produce the aminoalkyl alkylating agent, e.g., as a crystalline salt. In one aspect, the step is the conversion of an alcohol to a halide (*e.g.*, to a bromide). In one aspect, the step comprises treatment with an acidic solution of a nucleophile (*e.g.*, an hydrobromic acid solution, such as concentrated aqueous HBr at reflux). In one aspect, the crude salt product is prepared by distillation of the volatile reagents. In one aspect, the crude crystalline product is purified by recrystallization (*e.g.*, with MeOH/Et_2O or isopropanol).

[0078] In one aspect, the method further comprises a step of reacting a primary aminoalkyl alcohol with an alkyl aldehyde or a cycloalkylmethyl aldehyde to produce the aminoalkyl alcohol precursor (*e.g.*, by condensation to produce an imine and reduction of the imine to an amine, *e.g.*, with sodium borohydride in water). In an alternative more specific aspect, the method further comprises a step of reacting a secondary aminoalkyl alcohol with an alkyl aldehyde or a cycloalkylmethyl aldehyde to produce the aminoalkyl alcohol precursor. In some aspects, the step is a selective reduction that produces a secondary amine.

[0079] In one aspect, the method further comprises a step of reacting the purified N-alkyl polyamine with an aldehyde or halide (preferably, an aryl, heteroaryl, or phenyl group with a haloalkyl or aldehyde substituent) to produce an oligomeric polyamine. In a more specific aspect, the step is a reductive amination (*e.g.*, with sodium borohydride in methanol).

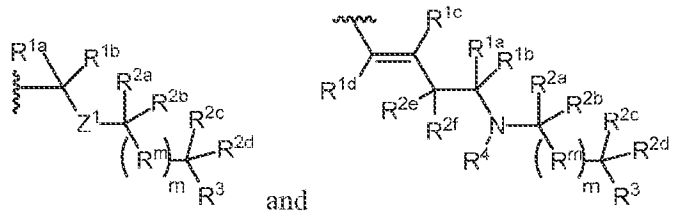
[0080] In one further aspect, the method further comprises a step of reacting the purified N-alkyl polyamine with a polyaldehyde or polyhalide (preferably, a phenyl group with haloalkyl or aldehyde substituents) to produce an oligomeric polyamine. In a more specific aspect, the oligomeric polyamine is a compound set forth in U.S. Appl. Nos. 62/001,604 (docket no. 96175-909657-000451US) or 14/076,143 (i.e., U.S. Patent No. 8,853,278). In an alternative more specific aspect, the oligomeric polyamine is a compound set forth in U.S. Appl. No. 14/507,701 (*i.e.*, U.S. Pat. Appl. Publ. No. 2015/0038512).

[0081] In a more specific aspect, the oligomeric polyamine is a polyamine compound selected from the group including


, and a

salt thereof; wherein:

[0082] each R^a is a member independently selected from the including


and ;

[0083] A^1, A^2, A^3, A^4, A^5, A^6, A^7, A^8, and A^9 are each an A^n member independently selected from the group including N, CR^a, and CR^5; or, alternatively, a pair of adjacent A^n members join to form an independently selected aryl, cycloalkyl, heterocyclyl, or heterocycloaryl ring that is fused with an A^n ring at the pair's A^n ring positions; wherein at least one A^n member and at most five A^n members are an independently selected CR^a;

[0084] each R^{1a}, R^{1b}, R^{1c}, and R^{1d} is a member independently selected from the group including hydrogen, fluoro, alkyl, and fluoroalkyl; or, alternatively, an R^{1a} and an R^{1b} join to form an oxo group;

[0085] each R^{2a}, R^{2b}, R^{2c}, R^{2d}, R^{2e}, and R^{2f} is a member independently selected from the group including hydrogen, alkyl, fluoroalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, and

heteroarylalkyl; alternatively, a pair of R^2 members from the same R^a group independently selected from R^{2a} and R^{2b}, R^{2c} and R^{2d}, or R^{2e} and R^{2f} join to form a member independently selected from the group including spirocycloalkyl, spiroheterocycyl, and oxo; or, alternatively, an R^{2a} and an R^{2c} from the same R^a group join to form a ring independently selected from the group including cycloalkyl and heterocycyl;

[0086] each R^m is a member independently selected from the group including $-CR^{2a}R^{2b}-$, $-CR^{2c}R^{2d}-$, $-C(R^{2a})=(R^{2b})-$, -CC-, and $-C(R^{2a})(R^{2b})-L^2-C(R^{2c})(R^{2d})-$;

[0087] each m is an integer independently selected from 1 to 20;

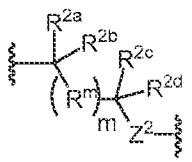
[0088] each L^1 and L^2 is a member independently selected from the group including a bond, -O-, -C(O)O-, $-NR^4-$, $-NR^4C(O)-$, and $-C(O)NR^4-$;

[0089] each R^3 is a member independently selected from the group including $-Z^1-R^4$, $-Z^1-Y^1-R^4$, $-Z^1-Y^1-Y^2-R^4$, and $-Z^1-Y^1-Y^2-Y^3-R^4$;

[0090] each R^4 is a member independently selected from the group including hydrogen, alkyl, fluoroalkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, arylalkyl, cycloalkylalkyl, and heteroarylalkyl; or, alternatively, for an $-N(R^4)_2$ group, one of the two R^4 in the group is a member selected from the group consisting of $-(CO)OR^{6a}$, $-(CO)N(R^{6a})(R^{6b})$, and $-C(NR^{6a})N(R^{6b})(R^{6c})$; or, alternatively, for an $-N(R^4)_2$ group, the two R^4 groups join to form a heterocyclic ring;

[0091] each R^5 is a member independently selected from the group including hydrogen, alkyl, hydroxyl, alkoxy, aminoalkoxy, alkylamino, alkylaminoalkoxy, alkenyl, alkynyl, aryl, aryloxy, arylamino, cycloalkyl, cycloalkoxy, cycloalkylalkoxy, cycloalkylamino, cycloalkylalkylamino, heterocyclyl, heterocycyloxy, heterocycylamino, halo, haloalkyl, fluoroalkyloxy, heteroaryl, heteroaryloxy, heteroarylamino, arylalkyl, arylalkyloxy, arylalkylamino, heteroarylalkyl, heteroarylalkyloxy, heteroarylalkylamino, hydroxyalkyl, aminoalkyl, and alkylaminoalkyl;

[0092] each Y^1, Y^2, and Y^3 is an independently selected group of Formula IA:

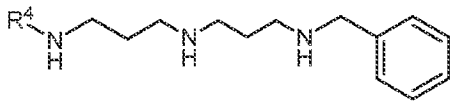


IA

[0093] each Z^1 and Z^2 is a member independently selected from the group including $N(R^4)$- and -O-; and

[0094] each R^{6a}, R^{6b}, and R^{6c} is a member independently selected from the group including hydrogen, alkyl, fluoroalkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, arylalkyl, heteroarylalkyl, and cycloalkylalkyl; or, alternatively, two R^6 members R^{6a} and R^{6b} or R^{6a} and R^{6c} join to form a heterocycyl ring; and wherein the polyamine compound comprises at least two primary or secondary amino groups.

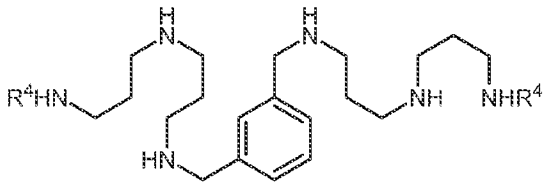
[0095] In a more specific aspect, the oligomeric polyamine is



or a salt thereof; and

wherein R^4 is hydrogen or alkyl

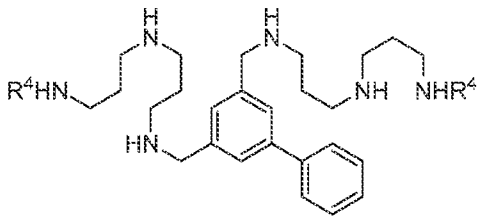
[0096] In a more specific aspect, the oligomeric polyamine is



or a salt thereof; and

wherein R^4 is hydrogen or alkyl

[0097] In a more specific aspect, the oligomeric polyamine is



or a salt thereof; and

wherein R^4 is hydrogen or alkyl.

[0098] In one aspect, the invention sets forth a composition for use in a method that is set forth herein.

Examples

General Experimental Conditions

[0099] Unless otherwise noted, materials were obtained from commercial sources and used without purification; otherwise, materials were purified according to Purification of Laboratory Chemicals. All reactions requiring anhydrous conditions were performed under a positive pressure of nitrogen using flame-dried glassware. Methanol (MeOH) was distilled over magnesium prior to its usage. Diaminopropane is highly toxic and should be handled with great care. Any volatile polyamine synthesized should also be regarded as toxic and should be handled with care and always stored under N_2 due to reactivity with O_2 and CO_2. Distillations were carried out under reduced pressure with a sodium bicarbonate ($NaHCO_3$) scrubber for distillations involving HBr and a citric acid scrubber for any distillations involving amines. Yields were calculated for material judged homogeneous by thin-layer chromatography and ^{1}H NMR. Thin-layer chromatography was performed on silica plates eluting with the solvents indicated and visualized by a 254 nm UV lamp or permanganate stain.

[0100] ^{1}H NMR spectra were recorded at 500 or 300 MHz as indicated. The chemical shifts (δ) of proton resonances are reported relative to the deuterated solvent peak: 7.26 for $CDCl_3$ and 4.79 for H_2O using the following format: chemical shift [multiplicity (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, pent = pentet, hex = hextet, sept = septet, oct = octet, non = nonet m = multiplet),coupling constant(s) (J in Hz), integral]. ^{13}C NMR spectra were recorded at 125 MHz. The chemical shifts of carbon resonances are reported relative to the deuterated solvent peak: 77.00 (first line) for $CDCl_3$. Certain carbon experiments conducted with the VXR500 MHz NMR contained an artifact peak between 170.0-174.0 ppm. Mass spectra were obtained by ESI+/APCI for LRMS or ESI+/APCI-TOF for HRMS.

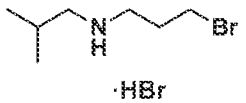
Polyamine Naming

[0101] These examples include a simplified naming system for the polyamine side chains that were synthesized. Hence, derivatives may be named as "[side chain group] [polyamine group]." For example, the compound N^1-(3-aminopropyl)-N^3-butylpropane-1,3-diamine would alternatively be referred to as "*n*-butyl norspermidine." The compound N^1-(3-(isobutylamino)-propyl)butane-1,4-diamine would alternatively be referred to as "*i*-butyl spermidine" (or, equivalently, "*iso*-butyl spermidine" or "isobutyl spermidine").

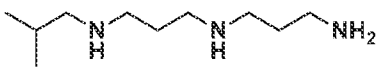
Example 1: Synthesis of Isobutyl Norspermidine



[0102] 3-(Isobutylamino)propan-1-ol: 3-Amino-1-propanol (35.4 g, 0.58 mol, 1.0 equiv.) and 3 Å mol. sieves were placed in a round bottomed flask. The solution was cooled to 0 °C (ice/water), and isobutyraldehyde (41.8 g, 0.58 mol, 1.0 equiv.) was added over the span of 20 min. The reaction was left to warm and stirred for 8 h. Sodium borohydride (11.0 g, 0.29 mol, 0.5 equiv.) in water (100 mL) was added slowly to the reaction mixture. After bubbling had ceased, the solution was extracted with EtOAc (2 x 200 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the 3-(isobutylamino)propan-1-ol as a yellow oil (65.8 g, 97%). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 3.79 (t, J = 5.1 Hz, 2H), 2.84 (t, J = 5.7 Hz, 2H), 2.40 (d, J = 6.6 Hz, 2H), 1.70-1.62 (m, 3H), 0.88 (d, J = 6.9 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 65.0, 58.2, 50.7, 30.8, 28.6, 21.0.



[0103] 3-Bromo-*N*-(isobutyl)propan-1-amine hydrobromide: 3-(Isobutylamino)propan-1-ol (46.0 g, 0.39 mol, 1 equiv.) was placed in a round bottomed flask and cooled to 0 °C (ice/water). To this mixture was carefully added HBr (294 mL in H_2O). The reaction mixture was heated to reflux for 16 h. The remaining HBr in H_2O was distilled off at 110 °C to provide the crude material as a brown solid, which was recrystallized from MeOH/Et_2O to afford the 3-bromo-*N*-(isobutyl)propan-1-amine hydrobromide as white crystals (47.9 g, 45%). ^{1}H NMR (500 MHz, D_2O) δ ppm 3.54 (t, *J* = 6.5 Hz, 2H), 3.21 (t, *J* = 8 Hz, 2H), 2.92 (d, *J* = 7 Hz, 2H), 2.30-2.23 (m, 2H), 2.02 (sept, *J* = 7 Hz, 1H), 0.99 (d, *J* = 6.5 Hz, 6H). ^{13}C NMR (125 MHz, D_2O) 55.0, 46.9, 30.0, 28.5, 25.8, 19.4. HRMS (ESI+) Calculated for $C_7H_{16}BrN$ m/z 194.0544 (M+H), Obsd. 194.0546.



[0104] Isobutyl norspermidine [N^1-(3-Aminopropyl)-N^3-(isobutyl)propane-1,3-diamine]: A round bottomed flask was charged with 1,3-diaminopropane (61.8 g, 0.83 mol, 10 equiv.), cooled to 0 °C (ice/water) and to this solution was added 3-bromo-*N*-isobutylpropan-1-amine hydrobromide salt (15.5 g, 0.08 mol, 1 equiv.) portionwise over the span of 1.5 h. The reaction mixture was left to warm and stirred for 12-16 h. Excess 1,3-diaminopropane was removed under reduced pressure, and the remaining semi-solid was

taken up in 5% aqueous NaOH (100 mL) and extracted with 85:15 $CHCl_3$/*i*-PrOH (5 x 100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification was accomplished by fractional distillation (oil bath set at 210 °C, distillate collected at 110 °C) to afford isobutyl norspermidine as a clear oil (7.4 g, 50%, best 71%). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.76 (t, *J* = 6.9 Hz, 2H), 2.70-2.63 (m, 6H), 2.39 (d, *J* = 6.9 Hz, 2H), 1.80-1.59 (m, 5H), 1.49 (bs, 4H), 0.89 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 58.4, 49.0, 48.9, 48.2, 40.8, 34.2, 30.7, 28.5, 20.9. HRMS (ESI+) Calculated for $C_{10}H_{25}N_3$ m/z 188.2127 (M+H), Obsd. 188.2123.

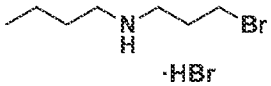
[0105] As exemplified in the synthesis of isobutyl norspermidine, this process is efficient and inexpensive, producing an *N*-alkyl polyamine in three steps for less than $0.30/g (Fig. 1A). The product can be further processed into oligomeric polyamines. A bis-reductive amination (cf. Baxter, E. W. & Reitz, A. B. Reductive Aminations of Carbonyl Compounds with Borohydride and Borane Reducing Agents. *Org Reac* 1, 59 (2004)) with a hydrophobic core and crystallization of the hexahydrochloride salt provides a di(*N*-alkyl polyamino) compound in four linear steps with no chromatography (judged to be >95% pure by 1H NMR and >97% pure by LCMS (UV)) as shown in Fig. 1B. This approach is cost-effective and amenable to commercial scale manufacturing required for environmental applications.

[0106] Thus, in a preferred aspect, the invention sets forth a process to produce N-alkyl polyamines as set forth in Fig. 2 in which the total number of carbons in the polyamine chain should be less than or equal to 15.

[0107] The exemplary norspermidine and spermidine derivatives as shown in Figure 3 have been prepared according to the process discussed in this and the following examples.

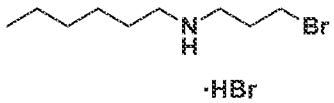
Example 2: Synthesis of *N*-(Bromoalkyl) Alkylamines

[0108] Selected *N*-(bromoalkyl)alkylamines were prepared according to the procedure of Example 1. In general, the substituted amino alcohol intermediates were used without further purification. If desired, vacuum distillation could be performed on the substituted amino alcohol intermediates to ensure purity.

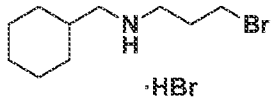


[0109] ***N*-(3-Bromopropyl)butan-1-amine hydrobromide:** ^{1}H NMR (500 MHz, D_2O) δ ppm 3.55 (t, *J* = 6.5 Hz, 2H), 3.22 (t, *J* = 8.0 Hz, 2H), 3.07 (t, *J* = 7.5 Hz, 2H), 2.29-2.23 (m, 2H), 1.70-1.64 (m, 2H), 1.39 (sext, *J* = 7.5 Hz, 2H), 0.93 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125

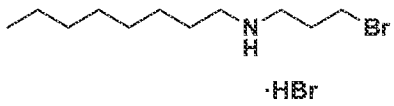
MHz, $CDCl_3$) δ ppm 48.2, 46.8, 29.8, 28.6, 27.8, 20.1, 13.6. HRMS (ESI+) Calculated for $C_7H_{16}BrN$ m/z 194.0544 (M+H), Obsd. 194.0546. Yield (22% from 3-amino-1-propanol).



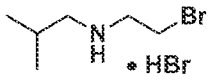
[0110] ***N*-(3-Bromopropyl)hexan-1-amine hydrobromide:** ^{1}H NMR (500 MHz, D_2O) δ ppm 3.51 (t, *J* = 6.0 Hz, 2H), 3.18 (t, *J* = 7.0 Hz, 2H), 3.03 (t, *J* = 7.5 Hz, 2H), 2.23 (quint, *J* = 6.5 Hz, 2H), 1.65 (quint, *J* = 8 Hz, 2H), 1.36-1.27 (m, 6H), 0.84 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, D_2O) δ ppm 48.0, 46.2, 30.6, 29.7, 28.5, 25.6, 25.5, 21.9, 13.4. HRMS (ESI+) Calculated for $C_9H_{20}BrN$ m/z 222.0857 (M+H), Obsd. 222.0862. Yield (53% from 3-amino-1-propanol).



[0111] **3-Bromo-*N*-(cyclohexylmethyl)propan-1-amine hydrobromide:** ^{1}H NMR (500 MHz, D_2O) δ ppm 3.54 (t, *J* = 6.0 Hz, 2H), 3.20 (t, *J* = 7.5 Hz, 2H), 2.92 (d, *J* = 7.0 Hz, 2H), 2.28-2.23 (m, 2H), 1.74-1.64 (m, 6H), 1.30-1.13 (m, 3H), 1.04-0.97 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 54.2, 47.3, 34.5, 30.9, 29.9, 28.4, 25.8, 25.3. HRMS (ESI+) Calculated for $C_{10}H_{20}BrN$ m/z 234.0857 (M+H), Obsd. 234.0862. Yield (41% from 3-amino-1-propanol).

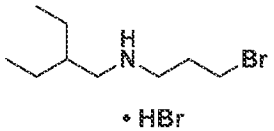


[0112] ***N*-(3-Bromopropyl)octan-1-amine hydrobromide:** ^{1}H NMR (500 MHz, D_2O) δ ppm 3.53 (t, J = 6.0 Hz, 2H), 3.20 (t, J = 7.5 Hz, 2H), 3.05 (t, J = 8.0 Hz, 2H), 2.27-2.22 (m, 2H), 1.67 (quint, J = 7.0 Hz, 2H), 1.38-1.27 (m, 10H), 0.85 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 48.3, 46.6, 31.7, 29.8, 29.1, 29.0, 28.6, 26.8, 25.8, 22.6, 14.1. HRMS (ESI+) Calculated for $C_{11}H_{24}BrN$ m/z 250.1170 (M+H), Obsd. 250.1176. Yield (21% from 3-amino-1-propanol).

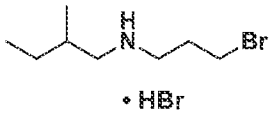


[0113] ***N*-(2-Bromoethyl)-2-methylpropan-1-amine, hydrobromide salt:** ^{1}H NMR (500 MHz, D_2O) δ ppm 3.73 (t, *J* = 6.0 Hz, 2H), 3.55 (t, *J* = 6.0 Hz, 2H), 2.98 (d, *J* = 7.5 Hz, 2H), 2.06 (non, *J* = 7.0 Hz, 1H), 1.01 (d, *J* = 6.5 Hz, 6H). ^{13}C NMR (125 MHz, D_2O) 54.6, 48.9,

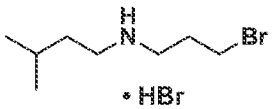
25.9, 25.5, 19.3. HRMS (ESI+) Calculated for $C_6H_{14}BrN$ m/z 180.0388 (M+H), Obsd. 180.0394. Yield (12%, two steps from ethanolamine).



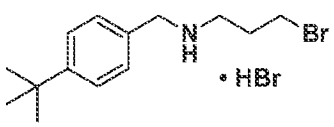
[0114] ***N*-(3-Bromopropyl)-2-ethylbutan-1-amine, hydrobromide salt:** ^{1}H NMR (500 MHz, D_2O) δ ppm 3.53 (t, *J* = 6.0 Hz, 2H), 3.21 (t, *J* = 7.5 Hz, 2H), 3.00 (d, *J* = 7.0 Hz, 2H), 2.29-2.23 (m, 2H), 1.66 (sept, *J* = 7.0 Hz, 1H), 1.39 (p, *J* = 7.0 Hz, 4H), 0.87 (t, *J* = 7.0 Hz, 6H). ^{13}C NMR (125 MHz, D_2O) δ ppm 50.8, 46.8, 37.6, 29.6, 28.1, 22.4, 9.4. HRMS (ESI+) Calculated for $C_9H_{20}BrN$ m/z 222.0857 (M+H), Obsd. 222.0856. Yield (45% from 3-amino-1-propanol).



[0115] ***N*-(3-Bromopropyl)-2-methylbutan-1-amine, hydrobromide salt:** ^{1}H NMR (500 MHz, D_2O) δ ppm 3.51 (t, *J* = 6.0 Hz, 2H), 3.18 (t, *J* = 7.0 Hz, 2H), 3.00(dd, *J* = 6.5, 12 Hz, 1H), 2.86 (dd, *J* = 8.0, 12.5 Hz, 1H), 2.26-2.21 (m, 2H), 1.78 (oct, *J* = 7.0 Hz, 1H), 1.43-1.35 (m, 1H), 1.25-1.17 (m, 1H), 0.94 (d, *J* = 6.5 Hz, 3H), 0.86 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, D_2O) δ ppm 53.3, 46.7, 31.7, 29.7, 28.2, 26.2, 16.1, 10.1. HRMS (ESI+) Calculated for $C_8H_{18}BrN$ m/z 208.0701 (M+H), Obsd. 208.0703. Yield (36% from 3-amino-1-propanol).



[0116] ***N*-(3-Bromopropyl)-3-methylbutan-1-amine, hydrobromide salt:** ^{1}H NMR (500 MHz, D_2O) δ ppm 3.54 (t, *J* = 6.5 Hz, 2H), 3.20 (t, *J* = 8.0 Hz, 2H), 3.08 (t, *J* = 8.0 Hz, 2H), 2.27-2.22 (m, 2H), 1.66 (non, *J* = 6.5 Hz, 1H), 1.58-1.54 (m, 2H), 0.91 (d, *J* = 7.0 Hz, 6H). ^{13}C NMR (125 MHz, D_2O) δ ppm 46.5, 46.3, 34.4, 29.9, 28.6, 25.4, 21.6. HRMS (ESI+) Calculated for $C_8H_{18}BrN$ m/z 208.0701 (M+H), Obsd. 208.0705. Yield (42% from 3-Amino-1-propanol).



[0117] **3-Bromo-*N*-(4-(*tert*-butyl)benzyl)propan-1-amine, hydrobromide salt:** ^{1}H NMR (500 MHz, D_2O) δ ppm 7.54 (d, J = 8.5 Hz, 2H), 7.41 (d, J = 7.5 Hz, 2H), 4.20 (s, 2H), 3.66 (t, J = 5.5 Hz, 2H), 3.12 (t, J = 7.5 Hz, 2H), 1.91 (pent, J = 6.5 Hz, 2H), 1.27 (s, 9H). ^{13}C NMR (125 MHz, D_2O) δ ppm 153.3, 129.7, 127.7, 126.2, 58.9, 50.5, 44.6, 34.1, 30.4, 27.8. HRMS (ESI+) Calculated for $C_{14}H_{22}BrN$ m/z 284.1014 (M+H), Obsd. 284.1017. Yield (33% from 3-amino-1-propanol).

Example 3: Synthesis of *N*-Alkyl Norspermidines

[0118] Selected *N*-alkyl norspermidines were prepared according to the general procedure of Example 1 or a minor variant, which is disclosed below:



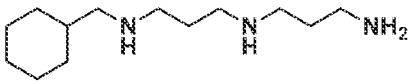
[0119] **N^1-(3-Aminopropyl)-N^3-isobutylpropane-1,3-diamine:** A round bottomed flask was charged with 1,3 diaminopropane (61.8 g, 0.83 mol, 10 equiv.), and cooled to 0 °C (ice/water). To this solution was added 3-bromo-*N*-isobutylpropan-1-amine hydrobromide (15.5 g, 0.08 mol, 1.0 equiv.) portionwise over the span of 1 h. The reaction mixture was left to warm and stirred for 12-16 h. Excess 1,3-diaminopropane was removed under reduced pressure, and the remaining semi-solid was taken up in 5% NaOH (100 mL) and extracted with $CHCl_3$ (2 x 100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification was accomplished by fractional distillation (oil bath set at 210 °C, distillate collected at 110 °C) to afford pure N^1-(3-aminopropyl)-N^3-isobutylpropane-1,3-diamine as a clear oil (7.4 g, 50%). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.76 (t, J = 6.9 Hz, 2H), 2.70-2.63 (m, 6H), 2.39 (d, J = 6.9 Hz, 2H), 1.80-1.59 (m, 5H), 1.49 (bs, 4H), 0.89 (d, J = 6.6 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 58.4, 49.0, 48.9, 48.2, 40.8, 34.2, 30.7, 28.5, 20.9.



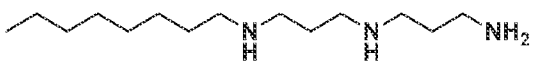
[0120] **N^1-(3-Aminopropyl)-N^3-butylpropane-1,3-diamine:** ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 2.64-2.46 (m, 10H), 1.56-1.49 (m, 4H), 1.37-1.30 (m, 2H), 1.27-1.18 (m, 6H), 0.81-0.77 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 50.1, 48.9, 48.8, 48.1, 40.8, 34.2, 32.5, 30.7, 20.7, 14. HRMS (ESI+) Calculated for $C_{10}H_{25}N_3$ m/z 188.2127 (M+H), Obsd. 188.2126. Yield (45%, 7.01 g).



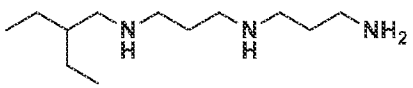
[0121] **N^1-(3-Aminopropyl)-N^3-hexylpropane-1,3-diamine (hexyl norspermidine):** ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 2.75 (t, J = 7 Hz, 2H), 2.65 (td, J = 2.5 Hz, 7.0 Hz, 6H), 2.57 (t, J = 7.5 Hz, 2H), 1.69-1.59 (m, 4H), 1.47-1.43 (m, 2H), 1.32-1.22 (m, 6H), 1.13 (bs, 4H), 0.87 (t, J = 6.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 50.3, 48.9, 48.8, 48.1, 40.8, 33.7, 32.0, 30.2, 27.3, 22.8, 14.3. HRMS (ESI+) Calculated for $C_{12}H_{29}N_3$ m/z 216.2440 (M+H), Obsd. 216.2443. Yield (55%, 12.74 g).



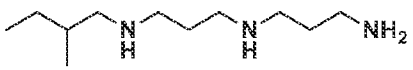
[0122] **N^1-(3-Aminopropyl)-N^3-(cyclohexylmethyl)propane-1,3-diamine (cyclohexylmethyl norspermidine):** ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 2.75 (t, J = 7.0 Hz, 2H), 2.66-2.61 (m, 6H), 2.40 (d, J = 7.0 Hz, 2H), 1.72-1.59 (m, 9H), 1.47-1.38 (m, 1H), 1.27-1.03 (m, 7H), 0.91-0.84 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 57.2, 49.0, 48.2, 40.8, 38.2, 34.2, 31.7, 30.7, 26.9, 26.3. HRMS (ESI+) Calculated for $C_{13}H_{29}N_3$ m/z 228.2440 (M+H), Obsd. 228.2439. Yield (38%, 3.43 g).



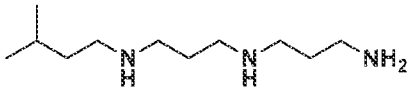
[0123] **N^1-(3-Aminopropyl)-N^3-octylpropane-1,3-diamine (octyl norspermidine):** ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 2.75 (t, *J* = 7.0 Hz, 2H), 2.66 (t, *J* = 7.0 Hz, 6H), 2.57 (t, *J* = 7.5 Hz, 2H), 1.69-1.60 (m, 4H), 1.49-1.42 (m, 2H), 1.27 (s, 10H), 1.04 (bs, 4H), 0.87 (t, *J* = 6.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) 50.1, 48.7, 48.6, 47.9, 40.5, 33.6, 31.8, 30.1, 30.0, 29.5, 29.2, 27.4, 22.6, 14.1. HRMS (ESI+) Calculated for $C_{14}H_{33}N_3$ m/z 244.2753 (M+H), Obsd. 244.2756. Yield (43%, 6.70 g).



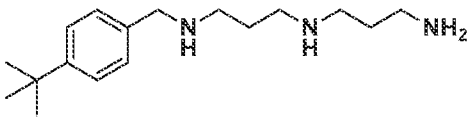
[0124] **N^1-(3-Aminopropyl)-N^3-(2-ethylbutyl)propane-1,3-diamine (gem-diethyl norspermidine):** ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.64 (t, *J* = 6.9 Hz, 2H), 2.58-2.51 (m, 6H), 2.36 (d, *J* = 5.4 Hz, 2H), 1.53 (sept, *J* = 6.6 Hz, 4H), 1.25-1.15 (m, 5H), 0.97 (bs, 4H), 0.74 (t, *J* = 6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 53.1, 49.1, 49.0, 48.1, 41.0, 40.7, 34.2, 30.5, 24.2, 11.1. HRMS (ESI+) Calculated for $C_{12}H_{29}N_3$ m/z 216.2440 (M+H), Obsd. 216.2439. Yield (56%, 11.92 g).



[0125] **N^1-(3-Aminopropyl)-N^3-(2-methylbutyl)propane-1,3-diamine:** ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 2.71 (t, *J* = 7.0 Hz, 2H), 2.63-2.58 (m, 6H), 2.46 (dd, *J* = 6.0, 11.5 Hz, 1H), 2.31 (dd, *J* = 7.5, 12.0 Hz, 1H), 1.65-1.55 (m, 4H), 1.51-1.42 (m, 1H), 1.39-1.30 (m, 1H), 1.12-1.05 (m, 5H), 0.85-0.82 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 56.5, 49.0, 48.1, 40.7, 34.9, 34.2, 30.6, 27.7, 17.8, 11.5. HRMS (ESI+) Calculated for $C_{11}H_{27}N_3$ m/z 202.2283 (M+H), Obsd. 202.2287. Yield (51%, 10.06 g).



[0126] **N^1-(3-Aminopropyl)-N^3-isopentylpropane-1,3-diamine (isoamyl norspermidine):** ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 2.75 (t, *J* = 6.5 Hz, 2H), 2.66 (t, *J* = 12.0 Hz, 6H), 2.58 (t, *J* = 13.0 Hz, 2H), 1.72-1.55 (m, 5H), 1.39-1.32 (m, 6H), 0.88 (d, *J* = 11.0 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 48.7, 48.2, 47.9, 40.5, 39.2, 33.9, 30.4, 26.1, 22.6. HRMS (ESI+) Calculated for $C_{11}H_{27}N_3$ m/z 202.2283 (M+H), Obsd. 202.2283. Yield (61%, 16.89 g).



[0127] **N^1-(3-Aminopropyl)-N^3-(4-(*tert*-butyl)benzyl)propane-1,3-diamine (*tert*-butyl-benzyl norspermidine):** ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.34 (d, *J* = 8.0 Hz, 2H), 7.23 (d, *J* = 8.0 Hz, 2H), 3.74 (s, 2H), 2.75 (t, *J* = 7.0 Hz, 2H), 2.71-2.64 (m, 6H), 1.70 (pent, *J* = 7.0 Hz, 2H), 1.62 (pent, *J* = 7.0 Hz, 2H), 1.43 (bs, 4H), 1.31 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 149.8, 137.2, 127.9, 125.3, 53.6, 48.4, 47.8, 47.7, 40.2, 34.5, 32.8, 31.4, 29.9. LRMS Calculated for $C_{17}H_{31}N_3$ m/z 278.2596 $[M+H]^+$, Obsd. 278.2594. Yield (38%, 5.16 g).

Example 4: Synthesis of *N*-Alkyl Spermidines

[0128] Selected *N*-alkyl spermidines were prepared according to the general procedures of Example 1 or 3:

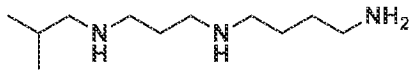


[0129] **N^1-(3-Butylamino)propyl)butane-1,4-diamine (butyl spermidine):** ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.67-2.51 (m, 10H), 1.62 (pent, *J* = 7.2 Hz, 2H), 1.52-1.34 (m, 6H),

1.30 (pent, J = 7.2 Hz, 2H), 0.98 (bs, 4H), 0.86 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 50.2, 50.1, 48.8, 48.8, 42.4, 32.5, 31.9, 30.8, 27.7, 20.7, 14.2. HRMS (ESI+) Calculated for $C_{11}H_{27}N_3$ m/z 202.2283 (M+H), Obsd. 201.2284. Yield (48%, 5.28 g).



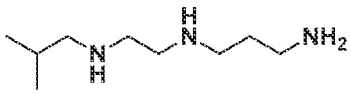
[0130] **N^1-(3-(Hexylamino)propyl)butane-1,4-diamine (hexyl spermidine):** ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.80 (bs, 4H), 2.65-2.50 (m, 10H), 1.65-1.59 (m, 2H), 1.46-1.38 (m, 6H), 1.25-1.17 (m, 6H), 0.81 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 50.2, 49.9, 48.6, 42.0, 31.9, 31.3, 30.2, 30.1, 27.4, 27.2, 22.7, 14.2. HRMS (ESI+) Calculated for $C_{13}H_{31}N_3$ m/z 230.2596 (M+H), Obsd. 230.2601. Yield (51%, 4.54 g).



[0131] **N^1-(3-(Isobutylamino)propyl)butane-1,4-diamine (isobutyl spermidine):** ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 2.66-2.54 (m, 8H), 2.35-2.33 (m, 2H), 1.70-1.59 (m, 3H), 1.49-1.40 (m, 4H), 0.98 (bs, 4H), 0.85-0.83 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 58.4, 50.1, 48.9, 48.9, 42.4, 31.9, 30.6, 28.4, 27.7, 20.8. HRMS (ESI+) Calculated for $C_{11}H_{27}N_3$ m/z 202.2283 (M+H), Obsd. 202.2284. Yield (53%, 7.95 g).

Example 5: Synthesis of *N*-Alkyl Polyamines

[0132] Some other exemplary *N*-alkyl polyamines were prepared according to the general procedures of Examples 1 or 3:

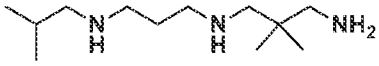


[0133] **N^1-(2-(Isobutylamino)ethyl)propane-1,3-diamine:** ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 2.71 (t, J = 7.0 Hz, 2H), 2.64 (s, 4H), 2.62 (t, J = 7.0 Hz, 2H), 2.33 (d, J = 7.0 Hz, 2H), 1.97 (bs, 4H), 1.66 (sept, J = 6.5 Hz, 1H), 1.58 (pent, J = 7.0 Hz, 2H), 0.82 (d, J = 6.5 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 58.1, 49.5, 49.4, 47.9, 40.6, 33.4, 28.4, 20.8. HRMS (ESI+) Calculated for $C_9H_{23}N_3$ m/z 174.1970 (M+H), Obsd. 174.1977. Yield (42%, 4.04 g).



[0134] **N^1-(2-Aminoethyl)-N^3-hexylpropane-1,3-diamine:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.68 (t, J = 6.0 Hz, 2H), 2.58-2.54 (m, 6H), 2.47 (t, J = 7.0 Hz, 2H), 1.57 (pent, J = 7.0 Hz, 2H), 1.39-1.31 (m, 2H), 1.22-1.07 (m, 10H), 0.77 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz,

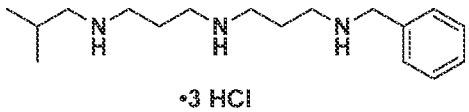
$CDCl_3$) δ ppm 52.7, 50.2, 48.6, 48.4, 41.8, 31.8, 30.5, 30.2, 27.1, 22.6, 14.1. HRMS (ESI+) Calculated for $C_{11}H_{27}N_3$ m/z 202.2283 (M+H), Obsd. 202.2291. Yield (47%, 3.23 g).



[0135] ***N*^{1}-(3-(Isobutylamino)propyl)-2,2-dimethylpropane-1,3-diamine:** ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 2.63 (t, *J* = 7.0 Hz, 4H), 2.50 (s, 2H), 2.39-2.37 (m, 4H), 1.77-1.62 (m, 3H), 1.02 (bs, 4H), 0.88 (d, *J* = 7.0 Hz, 6H), 0.84 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 59.1, 58.5, 51.7, 49.9, 49.0, 35.6, 30.5, 28.5, 23.9, 20.9. HRMS (ESI+) Calculated for $C_{12}H_{29}N_3$ m/z 216.2440 (M+H), Obsd. 216.2444. Yield (55%, 8.60 g).

Example 6: Synthesis of *N,N*-Dialkyl Polyamines

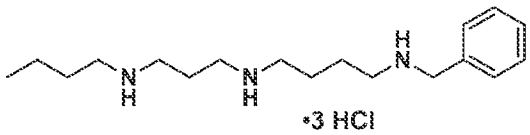
[0136] Selected *N,N*-dialkyl polyamines were prepared according to the general procedure set forth below:



•3 HCl

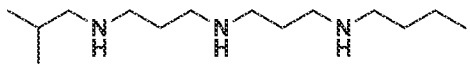
[0137] ***N*^{1}-Benzyl-*N*^{3}-(3-(isobutylamino)propyl)propane-1,3-diamine, hydrochloride salt:** Benzaldehyde (0.16 g, 1.56 mmol, 1 equiv.) was added dropwise to a cooled solution (0 °C) of isobutyl norspermidine (0.29 g, 1.56 mmol, 1 equiv.) in methanol (5 mL), and the reaction was left to stir for 16 h. Sodium borohydride (.24 g, 6.24 mmol, 4 equiv.) was then added portionwise, and the reaction mixture was stirred for 1 h. The excess methanol was evaporated and the crude solid was partitioned between ethyl acetate (50 mL) and 10% aq. NaOH (1 x 50 mL). The aqueous layer was then back extracted with ethyl acetate (1 x 50 mL) dried over Na_2SO_4, and evaporated to afford the crude free base, which was carried forward without further purification. The crude free base was acidified with HCl in MeOH (50 mL) and then placed at 0 °C for 1 h. The resulting precipitate was filtered and dried to afford the pure HCl salt as a white solid (52%). ^{1}H NMR (500 MHz, D_2O) δ ppm 7.51 (s, 5 H), 4.28 (s, 2H), 3.23-3.14 (m, 8H), 2.93 (d, *J* = 6.5 Hz, 2H), 2.19-2.12 (m, 4H), 2.02 (sept, *J* = 6.5 Hz, 1H), 1.00 (d, *J* = 7.0 Hz, 6H). ^{13}C NMR (125 MHz, D_2O) δ ppm 130.6, 130.1, 130.0, 129.5, 55.1, 51.4, 45.0, 44.9, 44.8, 44.0, 25.8, 22.8, 22.7, 19.3. Yield (52%, 0.31 g).

[0138] The following compounds were prepared similarly to *N*^{1}-benzyl-*N*^{3}-(3-(isobutylamino)propyl)propane-1,3-diamine, hydrochloride salt:



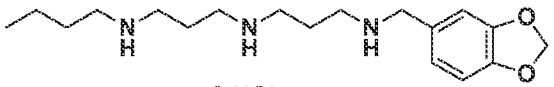
•3 HCl

[0139] **N^1-Benzyl-N^3-(3-(butylamino)propyl)propane-1,3-diamine, hydrochloride salt:** ^{1}H NMR (500 MHz, D_2O) δ ppm 7.52-7.49 (m, 5H), 4.28 (s, 2H), 3.22-3.13 (m, 8H), 3.07 (t, J = 7.5 Hz, 4H), 2.18-2.09 (m, 4H), 1.66 (pent, J = 7.5 Hz, 2H), 1.39 (hex, J = 7.5 Hz, 2H), 0.93 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, D_2O) δ ppm 130.5, 130.0, 130.0, 129.5, 51.4, 47.8, 44.8, 44.8, 44.4, 44.0, 27.7, 22.8, 19.3, 12.9. HRMS (ESI+) Calculated for $C_{18}H_{33}N_3$ m/z 292.2753 (M+H), Obsd. 292.2753. Yield (45%, 0.82 g).



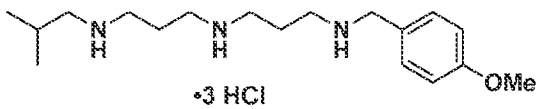
•3 HCl

[0140] **N^1-Butyl-N^3-(3-(Isobutylamino)propyl)propane-1,3-diamine, hydrochloride salt:** ^{1}H NMR (500 MHz, D_2O) δ ppm 3.19-3.13 (m, 8H), 3.06 (t, J = 7.5 Hz, 2H), 2.92 (d, J = 7.5 Hz, 2H), 2.16-2.08 (m, 4H), 2.01 (sept, J = 7.0 Hz, 1H), 1.65 (pent, J = 7.5 Hz, 2H), 1.38 (hex, J = 7.0 Hz, 2H), 0.98 (d, J = 6.5 Hz, 6H), 0.91 (t, J = 8.0 Hz, 3H). ^{13}C NMR (125 MHz, D_2O) δ ppm 55.1, 47.8, 44.9, 44.8, 44.4, 27.7, 25.8, 22.8, 22.7, 19.3, 19.2, 12.9. HRMS (ESI+) Calculated for $C_{14}H_{33}N_3$ m/z 244.2753 (M+H), Obsd. 244.2750. Yield (45%, 0.24 g).



•3 HCl

[0141] **N^1-(Benzo[d][1,3]dioxol-5-ylmethyl)-N^3-(3-(butylamino)propyl)propane-1,3-diamine, hydrochloride salt:** ^{1}H NMR (500 MHz, D_2O) δ ppm 6.98-6.92 (m, 3H), 6.00 (s, 2H), 4.16 (s, 2H), 3.17-3.11 (m, 8H), 3.05 (t, J = 7.0 Hz, 2H), 2.15-2.08 (m, 4H), 1.64 (pent, J = 7.5 Hz, 2H), 1.37 (hex, J = 7.0 Hz, 2H), 0.90 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, D_2O) δ ppm 148.4, 147.9, 124.4, 124.2, 110.1, 109.1, 108.1, 51.2, 47.8, 44.8, 44.8, 43.8, 27.7m, 22.9, 19.3, 12.9. HRMS (ESI+) Calculated for $C_{18}H_{31}N_3O_2$ m/z 322.2511 (M+H), Obsd. 322.2494. Yield (55%, 0.17 g).



•3 HCl

[0142] **N^1-Isobutyl-N^3-(3-((4-methoxybenzyl)amino)propyl)propane-1,3-diamine, hydrochloride salt:** ^{1}H NMR (500 MHz, D_2O) δ ppm 7.44 (d, J = 8.0 Hz, 2H), 7.05 (d, J =

9.0 Hz, 2H), 4.22 (s, 2H), 3.84 (s, 3H), 3.19-3.14 (m, 8H), 2.93 (d, J = 7.0 Hz, 2H), 2.18-2.11 (m, 4H), 2.02 (sept, J = 7.0 Hz, 1H), 1.00 (d, J = 7.0 Hz, 6H). ^{13}C NMR (125 MHz, D_2O) δ ppm 160.0, 131.8, 123.0, 114.8, 55.6, 55.1, 50.9, 45.0, 44.8, 43.8, 25.8, 22.8, 22.7, 19.3. HRMS (ESI+) Calculated for $C_{18}H_{33}N_3O$ m/z 308.2702 (M+H), Obsd. 308.2702. Yield (60%, 0.58 g).

WHAT IS CLAIMED IS:

1. A method of preparing an *N*-alkyl polyamine, wherein the method comprises the steps:

reacting an aminoalkyl alkylating agent in a reaction mixture comprising an excess amount of a polyaminoalkane to produce a *N*-alkyl polyamine, wherein the aminoalkyl alkylating agent comprises (i) a secondary or tertiary amino group and (ii) a halo or aldehyde group; and wherein the *N*-alkyl polyamine has from 5 to 30 carbon atoms; and

distilling a crude product comprising the *N*-alkyl polyamine to provide a purified *N*-alkyl polyamine.

2. The method of claim 1, wherein the *N*-alkyl polyamine has from 20 to 30 carbon atoms.

3. The method of claim 1, wherein the *N*-alkyl polyamine has from 20 to 26 carbon atoms.

4. The method of claim 1, wherein the *N*-alkyl polyamine has from 5 to 20 carbon atoms.

5. The method of claim 4, wherein the *N*-alkyl polyamine has from 10 to 20 carbon atoms.

6. The method of claim 4, wherein the *N*-alkyl polyamine has from 5 to 15 carbon atoms.

7. The method of claim 6, wherein the *N*-alkyl polyamine has from 10 to 15 carbon atoms.

8. The method of any one of the preceding claims, wherein the step of reacting the aminoalkyl alkylating agent is performed at a temperature from -78 °C to 150 °C.

9. The method of any one of the preceding claims, wherein the step of reacting the aminoalkyl alkylating agent is performed at a temperature from -78 °C to 120 °C.

10. The method of any one of the preceding claims, wherein the step of reacting the aminoalkyl alkylating agent is performed at a temperature from -78 °C to 100 °C.

11. The method of any one of the preceding claims, wherein the step of reacting the aminoalkyl alkylating agent is performed at a temperature from -25 °C to 100 °C.

12. The method of any one of the preceding claims, wherein the step of reacting the aminoalkyl alkylating agent is performed at a temperature from -10 °C to 100 °C.

13. The method of any one of the preceding claims, wherein the step of reacting the aminoalkyl alkylating agent is performed at a temperature from 0 °C to 100 °C.

14. The method of any one of the preceding claims, wherein the step of reacting the aminoalkyl alkylating agent is performed at a temperature from 0 °C to 80 °C.

15. The method of any one of the preceding claims, wherein the step of reacting the aminoalkyl alkylating agent is performed at a temperature from 0 °C to 60 °C.

16. The method of any one of the preceding claims, wherein the step of reacting the aminoalkyl alkylating agent is performed at a temperature from 0 °C to 40 °C.

17. The method of any one of the preceding claims, wherein the step of reacting the aminoalkyl alkylating agent is performed at a temperature from 10 °C to 25 °C.

18. The method of any one of the preceding claims, wherein the step of distilling the crude product is performed at below atmospheric pressure.

19. The method of any one of the preceding claims, wherein the step of distilling the crude product is performed at a pressure from 10 mm Hg to 25 mm Hg.

20. The method of any one of the preceding claims, wherein the step of distilling the crude product is performed at a pressure from 10 mm Hg to 25 mm Hg.

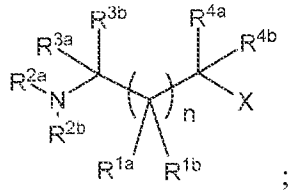
21. The method of any one of claims 1–19, wherein the step of distilling the crude product is performed at a pressure from 1 mm Hg to 10 mm Hg.

22. The method of any one of claims 1–19, wherein the step of distilling the crude product is performed at a pressure from 0.01 mm Hg to 1 mm Hg.

23. The method of any one of claims 1–22, wherein the step of reacting the aminoalkyl alkylating agent includes no added solvent.

24. The method of any one of claims 1–22, wherein the step of reacting the aminoalkyl alkylating agent includes added solvent.

25. The method of any one of the preceding claims, wherein the aminoalkyl alkylating agent is of the formula



;

wherein each R substituent is an independently selected hydrogen, alkyl, alkoxy alkenyl, or alkynyl group; wherein at least one R^2 substituent is not hydrogen; and wherein X is
-CHO or a halo group.

26. The method of claim 25, wherein at least one R^{1a} and R^{1b} are alkyl.

27. The method of claim 26, wherein at least one R^{1a} and R^{1b} are methyl.

28. The method of claim 25, wherein R^{1a} and R^{1b} are hydrogen.

29. The method of claim 25, wherein R^{1a} and R^{1b} are joined to form a spirocyclopropyl ring.

30. The method of any one of claims 25–28, wherein R^{2a} is an alkyl and R^{2b} is hydrogen.

31. The method of any one of claims 25–28, wherein R^{2a} is an alkyl and R^{2b} is an alkyl.

32. The method of any one of claims 25–31, wherein R^{3a} and R^{3b} are hydrogen.

33. The method of any one of claims 25–32, wherein R^{4a} and R^{4b} are hydrogen.

34. The method of any one of claims 25–33, wherein X is –CHO.

35. The method of any one of claims 25–33, wherein X is a halo group.

36. The method of any one of claims 25, 34, and 35, wherein the aminoalkyl alkylating agent is an *N*-alkyl propylene halide or aldehyde.

37. The method of any one of claims 1–25, 34, and 35, wherein the aminoalkyl alkylating agent is an *N*-alkyl butylene halide or aldehyde.

38. The method of any one of claims 1–25, 34, and 35, wherein the aminoalkyl alkylating agent e is an *N*-alkyl ethylene halide or aldehyde.

39. The method of any one of claims 1–25, 34, and 35, wherein the aminoalkyl alkylating agent is an *N*-alkyl pentylene halide or aldehyde.

40. The method of any one of claims 1–25, 34, and 35, wherein the aminoalkyl alkylating agent is an *N*-alkyl hexylene halide or aldehyde.

41. The method of any one of the preceding claims, wherein the N-alkyl group is butyl.

42. The method of any one of claims 1–40, wherein the N-alkyl group is isobutyl.

43. The method of any one of claims 1–40, wherein the N-alkyl group is hexyl.

44. The method of any one of claims 1–40, wherein the N-alkyl group is (cyclohexyl)methyl.

45. The method of any one of claims 1–40, wherein the N-alkyl group is octyl.

46. The method of any one of claims 1–40, wherein the N-alkyl group is isopropyl.

47. The method of any one of claims 1–40, wherein the N-alkyl group is methyl.

48. The method of any one of claims 1–40, wherein the N-alkyl group is ethyl.

49. The method of any one of claims 1–40, wherein the N-alkyl group is cyclohexyl.

50. The method of any one of claims 1–40, wherein the N-alkyl group is prenyl.

51. The method of any one of claims 1–40, wherein the N-alkyl group is propargyl.

52. The method of any one of claims 1–40, wherein the N-alkyl group is cyclopropyl.

53. The method of any one of the preceding claims, wherein the halide or halo is Cl.

54. The method of any one of the preceding claims, wherein the halide or halo is Br.

55. The method of any one of the preceding claims, wherein the aminoalkyl alkylating agent is a crystalline salt with a halide counterion.

56. The method of any one of the preceding claims, wherein the polyaminoalkane is spermidine.

57. The method of any one of claims 1–54, wherein the polyaminoalkane is norspermidine.

58. The method of any one of the preceding claims, wherein the excess amount is at least 2 equivalents.

59. The method of any one of the preceding claims, wherein the excess amount is at least 5 equivalents.

60. The method of any one of the preceding claims, wherein the excess amount is at least 8 equivalents.

61. The method of any one of the preceding claims, wherein the excess amount is at least 12 equivalents.

62. The method of any one of the preceding claims, wherein the excess amount is at least 16 equivalents.

63. The method of any one of the preceding claims, wherein the excess amount is at least 20 equivalents.

64. The method of any one of the preceding claims, wherein the excess amount is at least 24 equivalents.

65. The method of any one of the preceding claims, wherein the excess amount is at least 28 equivalents.

66. The method of any one of the preceding claims, wherein the excess amount is at least 32 equivalents.

67. The method of any one of the preceding claims, wherein the excess amount is at least 36 equivalents.

68. The method of any one of the preceding claims, wherein the excess amount is at least 40 equivalents.

69. The method of any one of the preceding claims, wherein the excess amount is at least 50 equivalents.

70. The method of any one of the preceding claims, wherein the distilling step is under reduced pressure.

71. The method of any one of the preceding claims, wherein the method further comprises a step of distilling the crude product to produce a purified diaminoalkane.

72. The method of claim 71, wherein the method further comprises reusing the purified diaminoalkane as a substrate for alkylation.

73. The method of any one of the preceding claims, wherein the method further comprises a step of reacting an aminoalkyl alcohol precursor to produce the aminoalkyl alkylating agent as a crystalline salt.

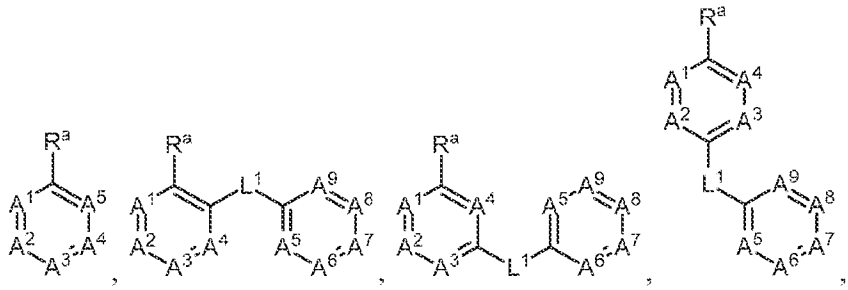
74. The method of claim 73, wherein the method further comprises a step of reacting a primary aminoalkyl alcohol with an alkyl aldehyde or a cycloalkylmethyl aldehyde to produce the aminoalkyl alcohol precursor.

75. The method of claim 73, wherein the method further comprises a step of reacting a secondary aminoalkyl alcohol with an alkyl aldehyde or a cycloalkylmethyl aldehyde to produce the aminoalkyl alcohol precursor.

76. The method of any one of the preceding claims, wherein the method further comprises a step of reacting the purified *N*-alkyl polyamine with an aldehyde or halide to produce an oligomeric polyamine.

77. The method of any one of the preceding claims, wherein the method further comprises a step of reacting the purified *N*-alkyl polyamine with a polyaldehyde or polyhalide to produce an oligomeric polyamine.

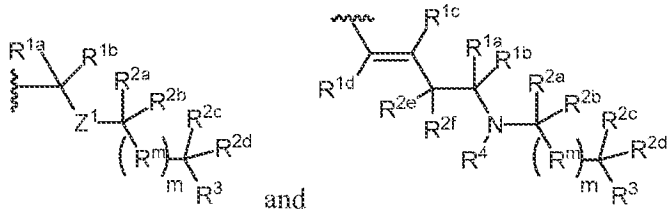
78. The method of claim 77, wherein the oligomeric polyamine is a polyamine compound selected from the group consisting of



, and a salt thereof;

wherein:

each R^a is a member independently selected from the group consisting of



and ;

A^1, A^2, A^3, A^4, A^5, A^6, A^7, A^8, and A^9 are each an A^n member independently selected from the group consisting of N, CR^a, and CR^5; or, alternatively, a pair of adjacent A^n members join to form an independently selected aryl, cycloalkyl, heterocyclyl, or heterocycloaryl ring that is fused with an A^n ring at the pair's A^n ring positions; wherein at least one A^n member and at most five A^n members are an independently selected CR^a;

each R^{1a}, R^{1b}, R^{1c}, and R^{1d} is a member independently selected from the group consisting of hydrogen, fluoro, alkyl, and fluoroalkyl; or, alternatively, an R^{1a} and an R^{1b} join to form an oxo group;

each R^{2a}, R^{2b}, R^{2c}, R^{2d}, R^{2e}, and R^{2f} is a member independently selected from the group consisting of hydrogen, alkyl, fluoroalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, and heteroarylalkyl; alternatively, a pair of R^2 members from the same R^a group independently selected from R^{2a} and R^{2b}, R^{2c} and R^{2d}, or R^{2e} and R^{2f} join to form a member independently selected from the group consisting of spirocycloalkyl, spiroheterocycyl, and oxo; or, alternatively, an R^{2a} and an R^{2c} from the same R^a group join to form a ring independently selected from the group consisting of cycloalkyl and heterocycyl;

each R^m is a member independently selected from the group consisting of -$CR^{2a}R^{2b}$-, -$CR^{2c}R^{2d}$-, -$C(R^{2a})$=(R^{2b})-, -CC-, and -$C(R^{2a})(R^{2b})$-L^2-$C(R^{2c})(R^{2d})$-;

each m is an integer independently selected from 1 to 20;

each L^1 and L^2 is a member independently selected from the group consisting of a bond, -O-, -C(O)O-, -NR^4-, -NR^4C(O)-, and -C(O)NR^4-;

each R^3 is a member independently selected from the group consisting of -Z^1-R^4,

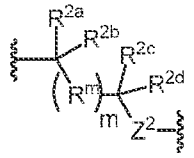
-Z^1-Y^1-R^4, -Z^1-Y^1-Y^2-R^4, and -Z^1-Y^1-Y^2-Y^3-R^4;

each R^4 is a member independently selected from the group consisting of hydrogen, alkyl, fluoroalkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, arylalkyl, cycloalkylalkyl, and heteroarylalkyl; or, alternatively, for an -$N(R^4)_2$ group, one of the two R^4 in the group is a member selected from the group consisting of -(CO)OR^{6a}-, -(CO)$N(R^{6a})(R^{6b})$, and -$C(NR^{6a})N(R^{6b})(R^{6c})$; or, alternatively, for an -$N(R^4)_2$ group, the two R^4 groups join to form a heterocyclic ring;

each R^5 is a member independently selected from the group consisting of hydrogen, alkyl, hydroxyl, alkoxy, aminoalkoxy, alkylamino, alkylaminoalkoxy, alkenyl, alkynyl, aryl, aryloxy, arylamino, cycloalkyl, cycloalkoxy, cycloalkylalkoxy, cycloalkylamino, cycloalkylalkylamino, heterocyclyl, heterocycyloxy, heterocycylamino,

halo, haloalkyl, fluoroalkyloxy, heteroaryl, heteroaryloxy, heteroarylamino, arylalkyl, arylalkyloxy, arylalkylamino, heteroarylalkyl, heteroarylalkyloxy, heteroarylalkylamino, hydroxyalkyl, aminoalkyl, and alkylaminoalkyl;

each Y^1, Y^2, and Y^3 is an independently selected group of Formula IA:



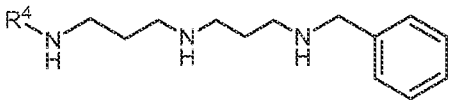
IA

each Z^1 and Z^2 is a member independently selected from the group consisting of -N(R^4)-and -O-; and

each R^{6a}, R^{6b}, and R^{6c} is a member independently selected from the group consisting of hydrogen, alkyl, fluoroalkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, arylalkyl, heteroarylalkyl, and cycloalkylalkyl; or, alternatively, two R^{6n} members R^{6a} and R^{6b} or R^{6a} and R^{6c} join to form a heterocycyl ring; and

wherein the polyamine compound comprises at least two primary or secondary amino groups.

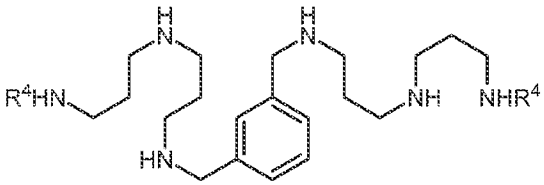
79. The method of claim **78**, wherein the oligomeric polyamine is



or a salt thereof; and

wherein R^4 is hydrogen or alkyl.

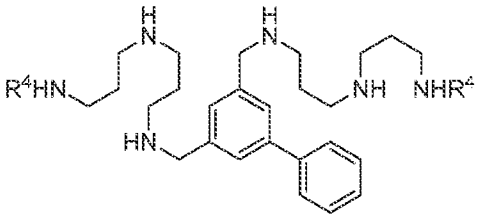
80. The method of claim **78**, wherein the oligomeric polyamine is



or a salt thereof; and

wherein R^4 is hydrogen or alkyl.

81. The method of claim **78**, wherein the oligomeric polyamine is



or a salt thereof; and

wherein R^4 is hydrogen or alkyl.

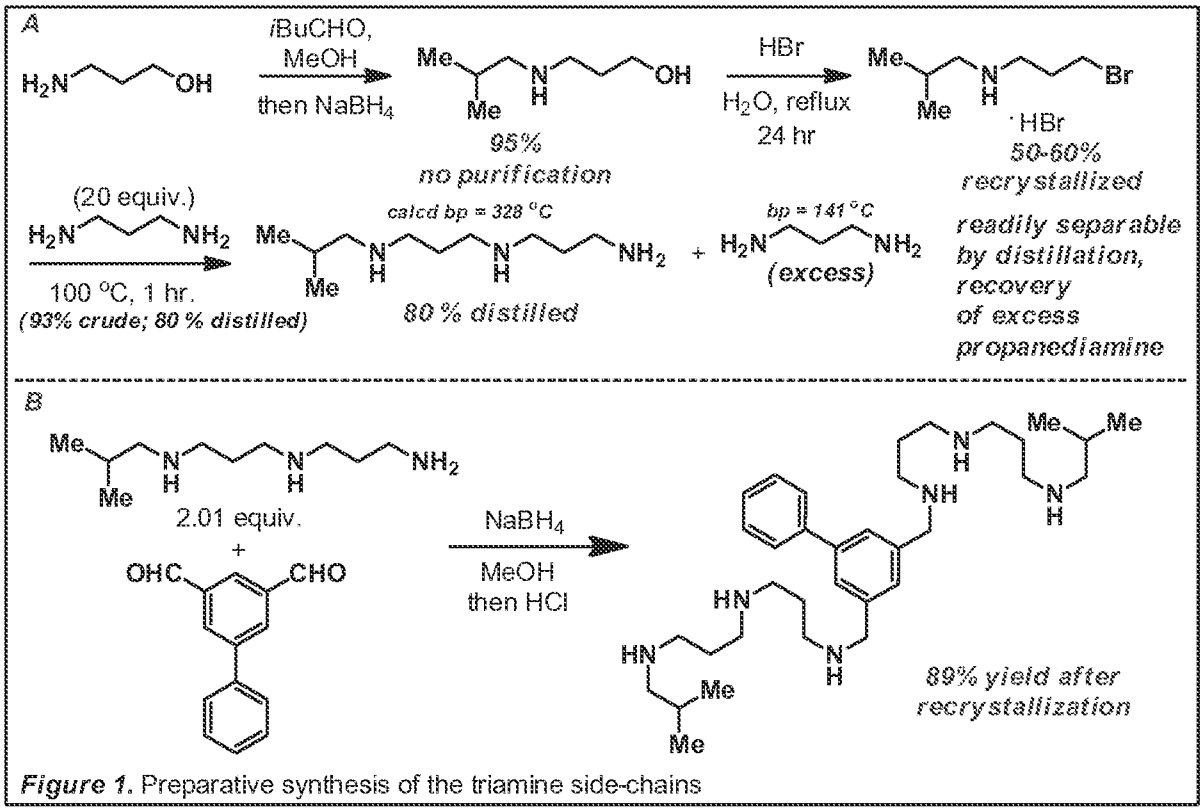


Figure 1. Preparative synthesis of the triamine side-chains

FIG. 1

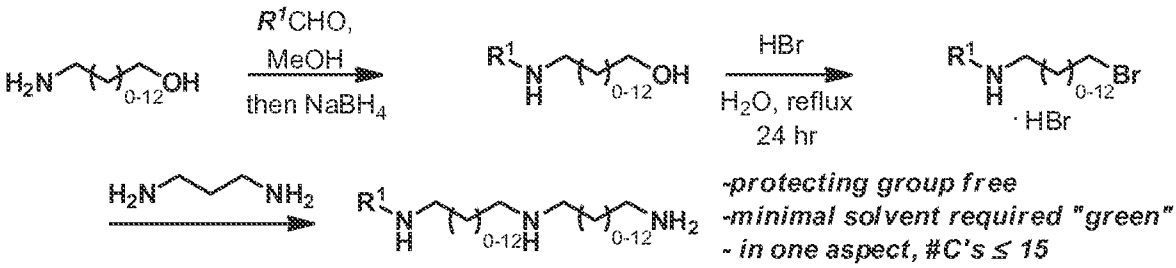


Figure 2. A general Scheme

FIG. 2

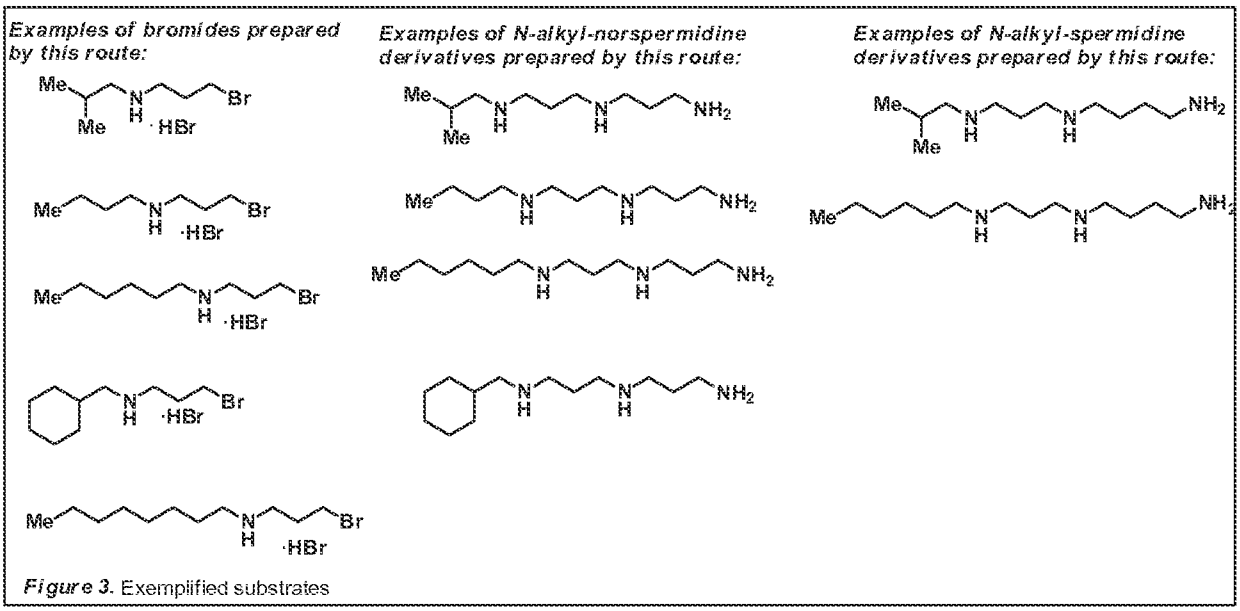


Figure 3. Exemplified substrates

FIG. 3

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2015/046810

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C209/08 C07C211/14 C07C211/27 C07C211/17
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07C

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	LOUIS J. SACCO ET AL: "The Synthesis of N,N-Bis-([beta]-diethylaminoethyl)-amine and Some N-Substituted Alkanesulfonamides", JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 76, no. 1, 1 January 1954 (1954-01-01), pages 303-305, XP055222235, US ISSN: 0002-7863, DOI: 10.1021/ja01630a100 page 304, column 2, lines 9-44 -----	1-81
Y	DE 37 32 508 A1 (HOECHST AG [DE]) 6 April 1989 (1989-04-06) column 2, lines 64-68 claims 1-7 examples 1-4 -----	1-81
	-/--	

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 October 2015	28/10/2015

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Fitz, Wolfgang

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2015/046810

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	ANGIOLINI L ET AL: "The conformational analysis of saturated heterocycles. LXXIV. 3-Alkyltetrahydro-1,3-Thiazines", GAZZETTA CHIMICA ITALIANA, SOCIET GBP A CHIMICA ITALIANA, IT, vol. 106, 1 January 1976 (1976-01-01), pages 111-118, XP008099774, ISSN: 0016-5603 page 112, reaction scheme, compounds 7,8 page 112, third paragraph of experimental section	1-81
A	WO 2010/101560 A1 (ALBEMARLE CORP [US]; BROWN WILLIAM R [US]; LEE JOHN Y [US]; WIGGINS PA) 10 September 2010 (2010-09-10) last sentence of paragraph [0082]	1-81

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2015/046810

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 3732508 A1	06-04-1989	NONE	
WO 2010101560 A1	10-09-2010	NONE	