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(54) Title: SULFATED PILLARARENES, METHODS OF MAKING SAME, AND USES THEREOF

(57) Abstract: Provided are sulfated pillarerenes and methods of making and using same. The pillararenes have macrocycle core having a plurality of aryl groups, attached (e.g., covalently bonded) in a para orientation to the adjacent methylene groups. The pillarerenes have a hydrophobic cavity. The hydrophobic cavity may be used to sequester various materials or to deliver materials sequestered therein.

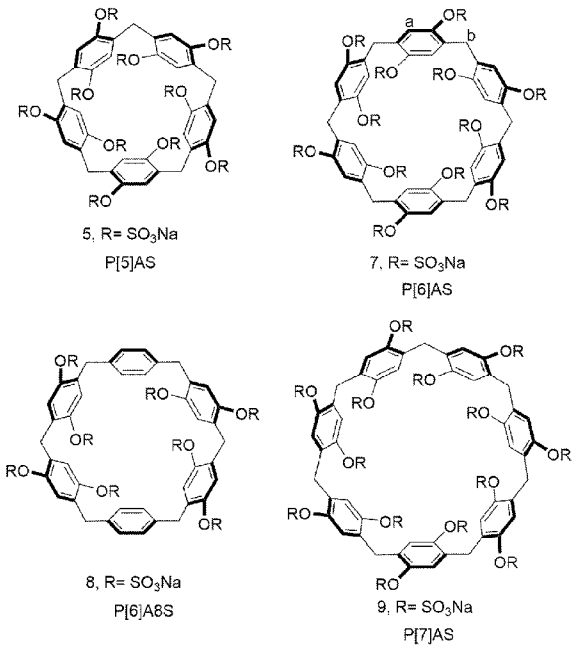


Figure 1

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SULFATED PILLARARENES, METHODS OF MAKING SAME, AND USES THEREOF

CROSS REFERENCE TO RELATED APPLICATION

[0001] This application claims priority to U.S. Provisional Application No. 62/982,460, filed on February 27, 2020, and to U.S. Provisional No. 63/013,336, filed on April 21, 2020, the disclosures of which are incorporated by reference herein.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH

[0002] This invention was made with government support under contract no. CHE-1404911 awarded by National Science Foundation. The government has certain rights in the invention.

BACKGROUND OF THE DISCLOSURE

[0003] Several classes of molecular container compounds are known, including cyclodextrins, calixarenes, cyclophanes, pillararenes, and cucurbiturils. These molecular container compounds bind to their target molecules in solution and thereby modulate the properties of the target including optical properties, solubility, odor, and even biological activity. Previous workers in the pillar[n]arene area have synthesized container molecules that feature a hydrophobic cavity and carboxylic acid solubilizing groups and showed that they bind with good affinity toward cationic targets in water. A challenge in the field is how to create new or modify existing molecular containers that maintain good solubility in water and simultaneously enhance their binding affinity toward their targets.

SUMMARY OF THE DISCLOSURE

[0004] The present disclosure provides sulfated pillararenes. The present disclosure also provides methods of making sulfated pillararenes and uses thereof.

[0005] In this disclosure, it was shown that, for example, positioning anionic solubilizing groups (e.g., sulfate groups) at the rim of the pillararene cavity significantly enhances their binding affinity toward cationic targets in water and thereby enhances their abilities as sequestering agents for a variety of applications.

[0006] In an aspect, the present disclosure provides compounds. The compounds are sulfated pillararenes. A sulfated pillararene comprises a macrocycle core comprising a plurality of aryl groups, where adjacent aryl groups are covalently connected (e.g., linked) via alkyl linking groups (e.g., $-CH_2-$ groups). The alkyl linking groups are para on the aryl groups (e.g., 1,4-phenyl linkages). The linkages may be on different phenyl rings of an aryl group

and correspond to a para linkage if the different phenyl rings were superimposed. In various examples, one or more or all of the adjacent aryl group(s) are not covalently connected by alkyl linking groups at meta positions on the aryl groups (e.g., 1,3-phenyl linkages (in the case where the linkages are on different phenyl rings or an aryl group the linkages do not correspond to a meta linkage if the different phenyl rings were superimposed)). Non-limiting examples of sulfated pillararenes are provided herein. Non-limiting examples of methods of making sulfated pillararenes are provided herein.

[0007] In an aspect, the present disclosure provides compositions comprising one or more sulfated pillararene(s). Non-limiting examples of compositions are described herein.

[0008] A composition may comprise one or more sulfated pillararene(s) and one or more pharmaceutical agent(s). In various examples, a pharmaceutical agent comprises one or more positively charged nitrogen atom(s) (e.g., ammonium ions, primary ammonium ions, secondary ammonium ions, tertiary ammonium ions, quaternary ammonium ions, or a combination thereof, where the non-hydrogen group(s) on the ammonium are chosen from aliphatic groups, alkyl groups, aryl groups, and combinations thereof).

[0009] In an aspect, the present disclosure provides uses of sulfated pillararenes. Non-limiting examples of uses of sulfated pillararenes are provided herein.

[0010] Sulfated pillararenes can be used to sequester various materials, which may be chemical compounds. In various non-limiting examples, one or more sulfated pillararene(s) is/are used to sequester one or more neuromuscular blocking agent(s) (such as, for example, rocuronium, tubocurarine, atracurium, (cis)atracurium besylate, mivacurium, gallamine, pancuronium, vecuronium, and rapacuronium, and the like); one or more anesthesia agent(s) (such as, for example, *N*-methyl *D*-aspartate (NMDA) receptor antagonists (e.g., ketamine and the like), short-acting anesthetic agents (e.g., etomidate and the like), and the like); one or more pharmaceutical agent(s) (such as, for example, a drug (e.g., anticoagulants, such as, for example, hexadimethrine and the like), drugs of abuse (e.g., methamphetamine, cocaine, fentanyl, carfentanil, and the like), and the like); one or more pesticide(s) (such as, for example, paraquat, diquat, organochlorines (e.g., DDT, aldrin, and the like), neonicotinoids (e.g., permethrin and the like), organophosphates (e.g., malathion, glyphosate, and the like), pyrethroids, triazines (e.g., atrazine and the like), and the like); one or more dyestuff(s) (such as, for example, methylene blue, nile red, crystal violet, thioflavin T, thiazole orange, proflavin, acridine orange, methylene violet, azure A, neutral red, cyanines, Direct orange 26, disperse dyes (e.g., disperse yellow 3, disperse blue 27, and the like), coumarins, congo red, and the like); one or more malodorous compound(s) (such as, for example, low molecular

weight thiols (e.g., C_1–C_4 thiols), low molecular weight amines (e.g., triethylamine, putrescein, cadaverine, and the like), and the like); or one or more chemical warfare agent(s) (such as for example, nitrogen and sulfur mustards (e.g., bis(2-chloroethyl)ethylamine, bis(2-chloroethyl)methylamine, tris(2-chloroethyl)amine, bis(2-chloroethyl) sulfide, bis(2-chloroethylthioethyl) ether, and the like), nerve agents (such as, for example, those from the G, GV, and V series of nerve agents (e.g. tabun, sarin, soman, cyclosarin, 2-(dimethylamino)ethyl *N*,*N*-dimethylphosphoramidofluoridate (GV), novichok agents, VE, VG, VM, VX, and the like), and the like); or the like, or a combination thereof.

BRIEF DESCRIPTION OF THE FIGURES

[0011] For a fuller understanding of the nature and objects of the disclosure, reference should be made to the following detailed description taken in conjunction with the accompanying figures.

[0012] Figure 1 shows examples of hosts (sulfated pillararenes).

[0013] Figure 2 shows examples of cationic guests.

[0014] Figure 3 shows examples of drugs of abuse.

[0015] Figure 4 shows examples of neuromuscular blockers.

[0016] Figure 5 shows binding constants for complexes of example hosts with cationic guests.

[0017] Figure 6 shows binding constants for complexes of example hosts with drugs of abuse.

[0018] Figure 7 shows binding constants for complexes of example hosts with neuromuscular blockers.

[0019] Figure 8 shows ^{1}H NMR spectra recorded (500 MHz, RT, 20 mM phosphate-buffered D_2O) for: a) P[6]AS, b) Methamphetamine, c) an equimolar mixture of P[6]AS and Methamphetamine (0.5 mM), and d) a 2:1 mixture of Methamphetamine (1 mM) and P[6]AS (0.5 mM).

[0020] Figure 9 shows ^{1}H NMR spectra recorded (500 MHz, RT, 20 mM phosphate-buffered D_2O) for: a) P[6]AS, b) Motor 2, c) Rocuronium, d) an equimolar mixture of P[6]AS and Rocuronium, e) an equimolar mixture of Motor 2 and Rocuronium, f) a mixture of Motor 2 and Rocuronium, then add P[6]AS, g) a mixture of P[6]AS and Rocuronium, then add Motor 2.

[0021] Figure 10 shows a crystal structure of P[6]AS.

[0022] Figure 11 shows a) structure of CB[n] and **M2**. b) Preparation of Pillar[*n*]MaxQ (P[5]AS – P[7]AS) and P[5]ACS and the structures of WP[n]. Conditions: a) Py•SO_3, pyridine, 90 °C; b) propane sultone, NaOH, acetone, 8%.

[0023] Figure 12 shows ^{1}H NMR spectra (600 MHz, D_2O, 298K) recorded for solution of: a) P[6]AS (1 mM), b) guest **25** (1 mM), c) a mixture of P[6]AS (1 mM) and guest **25** (1 mM); d) a mixture of P[6]AS (1 mM) and guest **25** (2 mM).

[0024] Figure 13 shows X-ray crystal structures of P[6]AS and P[5]ACS. a) Cross-eyed stereoview of one molecule of P[6]AS in the unit cell. Views of the packing of P[6]AS in the crystal along the b) z-axis and c) y-axis. d) Cross-eyed stereoview of one molecule of P[5]ACS in the unit cell.

[0025] Figure 14 shows a) a plot of DP versus time from the titration of a mixture of P[6]AS (100 μM) and **17** (500 μM) in the cell with **20** (1 mM) in the syringe. b) Plot of ΔH versus molar ratio of P[6]AS to **20**; the solid line represents the best fit of the data to a competitive binding model implemented in the PEAQ-ITC data analysis software with K_a = $(1.20 \pm 0.06) \times 10^{11}$ M^{-1} and ΔH = -17.1 ± 0.033 kcal mol^{-1}.

[0026] Figure 15 shows ^{1}H NMR spectra recorded (600 MHz, D_2O, RT) for: a) P[6]AS (1 mM), b) **M2** (0.5 mM), c) rocuronium (0.5 mM), d) P[6]AS•rocuronium (0.5 mM), e) **M2**•rocuronium (0.5 mM), and f) the solution from part e after treatment with 1 equiv. P[6]AS. Proton labelling for **M2**, P[6]AS, and rocuronium are given in Figure 11 and Figure 4.

[0027] Figure 16 shows ^{1}H NMR spectra (400 MHz, D_2O, RT) recorded for P[5]ACS.

[0028] Figure 17 shows ^{13}C NMR spectra (150 MHz, D_2O, EtOH as internal reference, RT) recorded for P[5]ACS.

[0029] Figure 18 shows ^{1}H NMR spectra (600 MHz, D_2O, RT) recorded for P[5]AS.

[0030] Figure 19 shows ^{13}C NMR spectra (150 MHz, D_2O, EtOH as internal reference, RT) recorded for P[5]AS.

[0031] Figure 20 shows ^{1}H NMR spectra (600 MHz, D_2O, RT) recorded for P[6]AS.

[0032] Figure 21 shows ^{13}C NMR spectra (150 MHz, D_2O and CD_3OD 10:1, RT) recorded for P[6]AS.

[0033] Figure 22 shows ^{1}H NMR spectra (600 MHz, D_2O, RT) recorded for P[7]AS.

[0034] Figure 23 shows ^{13}C NMR spectra (150 MHz, D_2O, Dioxane as external reference, RT) recorded for P[7]AS.

[0035] Figure 24 shows ^{1}H NMR spectra recorded (600 MHz, RT, 20 mM phosphate-buffered D_2O) for: a) P[5]ACS, b) **17**, c) an equimolar mixture of P[5]ACS and **17** (1 mM), and d) a 2:1 mixture of **17** (2 mM) and P[5]ACS (1 mM).

[0036] Figure 25 shows ^{1}H NMR spectra recorded (600 MHz, RT, 20 mM phosphate-buffered D_2O) for: a) P[5]ACS, b) **21**, c) an equimolar mixture of P[5]ACS and **21** (1 mM), and d) a 2:1 mixture of **21** (2 mM) and P[5]ACS (1 mM).

[0037] Figure 26 shows ^{1}H NMR spectra recorded (600 MHz, RT, 20 mM phosphate-buffered D_2O) for: a) P[5]AS, b) **23**, c) an equimolar mixture of P[5]AS and **23** (1 mM), and d) a 2:1 mixture of **23** (2 mM) and P[5]AS (1 mM).

[0038] Figure 27 shows ^{1}H NMR spectra recorded (600 MHz, RT, 20 mM phosphate-buffered D_2O) for: a) P[5]AS, b) **21**, c) an equimolar mixture of P[5]AS and **21** (1 mM), and d) a 2:1 mixture of **21** (2 mM) and P[5]AS (1 mM).

[0039] Figure 28 shows ^{1}H NMR spectra recorded (600 MHz, RT, 20 mM phosphate-buffered D_2O) for: a) P[5]AS, b) **22**, c) an equimolar mixture of P[5]AS and **22** (1 mM), and d) a 2:1 mixture of **22** (2 mM) and P[5]AS (1 mM). e) a 3:1 mixture of **22** (3 mM) and P[5]AS (1 mM), and f) a 4:1 mixture of **22** (4 mM) and P[5]AS (1 mM).

[0040] Figure 29 shows ^{1}H NMR spectra recorded (600 MHz, RT, 20 mM phosphate-buffered D_2O) for: a) P[5]AS, b) **12**, c) an equimolar mixture of P[5]AS and **12** (1 mM), and d) a 2:1 mixture of **12** (2 mM) and P[5]AS (1 mM). e) a 3:1 mixture of **12** (3 mM) and P[5]AS (1 mM), and f) a 4:1 mixture of **12** (4 mM) and P[5]AS (1 mM).

[0041] Figure 30 shows ^{1}H NMR spectra recorded (600 MHz, RT, 20 mM phosphate-buffered D_2O) for: a) P[5]AS, b) **25**, c) an equimolar mixture of P[5]AS and **25** (0.5 mM), d) a 2:1 mixture of **25** (1 mM) and P[5]AS (0.5 mM), e) a 3:1 mixture of **25** (1.5 mM) and P[5]AS (0.5 mM), and f) a 4:1 mixture of **25** (2 mM) and P[5]AS (0.5 mM).

[0042] Figure 31 shows ^{1}H NMR spectra recorded (600 MHz, RT, 20 mM phosphate-buffered D_2O) for: a) P[5]AS, b) **26**, c) an equimolar mixture of P[5]AS and **26** (0.5 mM), d) a 2:1 mixture of **26** (1 mM) and P[5]AS (0.5 mM), and e) a 3:1 mixture of **26** (1.5 mM) and P[5]AS (0.5 mM).

[0043] Figure 32 shows ^{1}H NMR spectra recorded (600 MHz, RT, 20 mM phosphate-buffered D_2O) for: a) P[6]AS, b) **23**, c) an equimolar mixture of P[6]AS and **23** (1 mM), and d) a 2:1 mixture of **23** (2 mM) and P[6]AS (1 mM).

[0044] Figure 33 shows ^{1}H NMR spectra recorded (600 MHz, RT, 20 mM phosphate-buffered D_2O) for: a) P[6]AS, b) **17**, c) an equimolar mixture of P[6]AS and **17** (1 mM), and d) a 2:1 mixture of **17** (2 mM) and P[6]AS (1 mM).

[0045] Figure 34 shows ^{1}H NMR spectra recorded (600 MHz, RT, 20 mM phosphate-buffered D_2O) for: a) P[6]AS, b) **24**, c) an equimolar mixture of P[6]AS and **24** (1 mM), and d) a 2:1 mixture of **24** (2 mM) and P[6]AS (1 mM).

[0046] Figure 35 shows ^{1}H NMR spectra recorded (600 MHz, RT, 20 mM phosphate-buffered D_2O) for: a) P[6]AS, b) **11**, c) an equimolar mixture of P[6]AS and **11** (1 mM), and d) a 2:1 mixture of **11** (2 mM) and P[6]AS (1 mM).

[0047] Figure 36 shows ^{1}H NMR spectra recorded (600 MHz, RT, 20 mM phosphate-buffered D_2O) for: a) P[6]AS, b) **12**, c) an equimolar mixture of P[6]AS and **12** (1 mM), and d) a 2:1 mixture of **12** (2 mM) and P[6]AS (1 mM).

[0048] Figure 37 shows ^{1}H NMR spectra recorded (600 MHz, RT, 20 mM phosphate-buffered D_2O) for: a) P[6]AS, b) **21**, c) an equimolar mixture of P[6]AS and **21** (1 mM), and d) a 2:1 mixture of **21** (2 mM) and P[6]AS (1 mM).

[0049] Figure 38 shows ^{1}H NMR spectra recorded (600 MHz, RT, 20 mM phosphate-buffered D_2O) for: a) P[6]AS, b) **22**, c) an equimolar mixture of P[6]AS and **22** (1 mM), and d) a 2:1 mixture of **22** (2 mM) and P[6]AS (1 mM).

[0050] Figure 39 shows ^{1}H NMR spectra recorded (600 MHz, RT, 20 mM phosphate-buffered D_2O) for: a) P[6]AS, b) **26**, c) an equimolar mixture of P[6]AS and **26** (0.5 mM), and d) a 2:1 mixture of **26** (1 mM) and P[6]AS (0.5 mM).

[0051] Figure 40 shows ^{1}H NMR spectra recorded (600 MHz, RT, 20 mM phosphate-buffered D_2O) for: a) P[7]AS, b) **11**, c) an equimolar mixture of P[7]AS and **11** (0.5 mM), and d) a 2:1 mixture of **11** (1 mM) and P[7]AS (0.5 mM).

[0052] Figure 41 shows ^{1}H NMR spectra recorded (600 MHz, RT, 20 mM phosphate-buffered D_2O) for: a) P[7]AS, b) **17**, c) an equimolar mixture of P[7]AS and **17** (0.5 mM), and d) a 2:1 mixture of **17** (1 mM) and P[7]AS (0.5 mM).

[0053] Figure 42 shows ^{1}H NMR spectra recorded (600 MHz, RT, 20 mM phosphate-buffered D_2O) for: a) P[7]AS, b) **23**, c) an equimolar mixture of P[7]AS and **23** (0.5 mM), and d) a 2:1 mixture of **23** (1 mM) and P[7]AS (0.5 mM).

[0054] Figure 43 shows ^{1}H NMR spectra recorded (600 MHz, RT, 20 mM phosphate-buffered D_2O) for: a) P[7]AS, b) **21**, c) an equimolar mixture of P[7]AS and **21** (0.5 mM), and d) a 2:1 mixture of **21** (1 mM) and P[7]AS (0.5 mM).

[0055] Figure 44 shows ^{1}H NMR spectra recorded (600 MHz, RT, 20 mM phosphate-buffered D_2O) for: a) P[7]AS, b) **22**, c) an equimolar mixture of P[7]AS and **22** (0.5 mM), and d) a 2:1 mixture of **22** (1 mM) and P[7]AS (0.5 mM).

[0056] Figure 45 shows ^{1}H NMR spectra recorded (600 MHz, RT, 20 mM phosphate-buffered D_2O) for: a) P[5]AS, b) Acetylcholine, c) an equimolar mixture of P[5]AS and Acetylcholine (0.5 mM), and d) a 2:1 mixture of Acetylcholine (1 mM) and P[5]AS (0.5 mM).

[0057] Figure 46 shows ^{1}H NMR spectra recorded (600 MHz, RT, 20 mM phosphate-buffered D_2O) for: a) P[5]AS, b) Rocuronium, c) an equimolar mixture of P[5]AS and Rocuronium (0.5 mM), d) a 2:1 mixture of Rocuronium (1 mM) and P[5]AS (0.5 mM), and e) a 3:1 mixture of Rocuronium (1.5 mM) and P[5]AS (0.5 mM).

[0058] Figure 47 shows ^{1}H NMR spectra recorded (600 MHz, RT, 20 mM phosphate-buffered D_2O) for: a) P[5]AS, b) Vecuronium, c) an equimolar mixture of P[5]AS and Vecuronium (0.5 mM), d) a 2:1 mixture of Vecuronium (1 mM) and P[5]AS (0.5 mM), and e) a 3:1 mixture of Vecuronium (1.5 mM) and P[5]AS (0.5 mM).

[0059] Figure 48 shows ^{1}H NMR spectra recorded (600 MHz, RT, 20 mM phosphate-buffered D_2O) for: a) P[5]AS, b) Pancuronium, c) an equimolar mixture of P[5]AS and Pancuronium (0.5 mM), d) a 2:1 mixture of Pancuronium (1 mM) and P[5]AS (0.5 mM), and e) a 3:1 mixture of Pancuronium (1.5 mM) and P[5]AS (0.5 mM).

[0060] Figure 49 shows ^{1}H NMR spectra recorded (600 MHz, RT, 20 mM phosphate-buffered D_2O) for: a) P[6]AS, b) Vecuronium, c) an equimolar mixture of P[6]AS and Vecuronium (0.5 mM), and d) a 2:1 mixture of Vecuronium (1 mM) and P[6]AS (0.5 mM).

[0061] Figure 50 shows ^{1}H NMR spectra recorded (600 MHz, RT, 20 mM phosphate-buffered D_2O) for: a) P[6]AS, b) Acetylcholine, c) an equimolar mixture of P[6]AS and Acetylcholine (0.5 mM), and d) a 2:1 mixture of Acetylcholine (1 mM) and P[6]AS (0.5 mM).

[0062] Figure 51 shows ^{1}H NMR spectra recorded (600 MHz, RT, 20 mM phosphate-buffered D_2O) for: a) P[6]AS, b) Rocuronium, c) an equimolar mixture of P[6]AS and Rocuronium (0.5 mM), and d) a 2:1 mixture of Rocuronium (1 mM) and P[6]AS (0.5 mM).

[0063] Figure 52 shows ^{1}H NMR spectra recorded (600 MHz, RT, 20 mM phosphate-buffered D_2O) for: a) P[6]AS, b) Pancuronium, c) an equimolar mixture of P[6]AS and Pancuronium (0.5 mM), and d) a 2:1 mixture of Pancuronium (1 mM) and P[6]AS (0.5 mM).

[0064] Figure 53 shows ^{1}H NMR spectra recorded (600 MHz, RT, 20 mM phosphate-buffered D_2O) for: a) P[7]AS, b) Vecuronium, c) an equimolar mixture of P[7]AS and Vecuronium (0.5 mM), and d) a 2:1 mixture of Vecuronium (1 mM) and P[7]AS (0.5 mM).

[0065] Figure 54 shows ^{1}H NMR spectra recorded (600 MHz, RT, 20 mM phosphate-buffered D_2O) for: a) P[7]AS, b) Rocuronium, c) an equimolar mixture of P[7]AS and Rocuronium (0.5 mM), and d) a 2:1 mixture of Rocuronium (1 mM) and P[7]AS (0.5 mM).

[0066] Figure 55 shows ^{1}H NMR spectra recorded (600 MHz, RT, 20 mM phosphate-buffered D_2O) for: a) P[7]AS, b) Pancuronium, c) an equimolar mixture of P[7]AS and Pancuronium (0.5 mM), and d) a 2:1 mixture of Pancuronium (1 mM) and P[7]AS (0.5 mM).

[0067] Figure 56 shows ^{1}H NMR spectra recorded (600 MHz, RT, 20 mM phosphate-buffered D_2O) for: a) P[7]AS, b) Cisatracurium, c) a 1:4 mixture of Cisatracurium (0.125 mM) and P[7]AS (0.5 mM), d) a 1:2 mixture of Cisatracurium (0.25 mM) and P[7]AS (0.5 mM), e) an equimolar mixture of P[7]AS and Cisatracurium (0.5 mM).

[0068] Figure 57 shows ^{1}H NMR spectra (600 MHz, D_2O, 298K) recorded for the dilution of host P[5]AS (20.0–0.1 mM). Host P[5]AS is weakly self-associated in water, which is evidenced by the upfield chemical shift changes of the aromatic region at 7.33–7.40 ppm protons.

[0069] Figure 58 shows a plot of chemical shift of P[5]AS versus [P[5]AS]. The solid line represents the best non-linear fitting of the data to a two-fold self-association model with $K_a = 19.7\ M^{-1}$.

[0070] Figure 59 ^{1}H NMR spectra (600 MHz, D_2O, 298K) recorded for the dilution of host P[6]AS (20.0–0.1 mM). Host P[6]AS is weakly self-associated in water, which is evidenced by the upfield chemical shift changes of the aromatic region at 7.34–7.38 ppm protons.

[0071] Figure 60 shows a plot of chemical shift of P[6]AS versus [P[6]AS]. The solid line represents the best non-linear fitting of the data to a two-fold self-association model with $K_a = 16.2\ M^{-1}$.

[0072] Figure 61 shows ^{1}H NMR spectra (400 MHz, D_2O) recorded for Rim-P[5]AS.

[0073] Figure 62 shows ^{13}C NMR spectra (150 MHz, D_2O, EtOH as internal reference) recorded for Rim-P[5]AS.

[0074] Figure 63 shows HepG2 toxicology assays. AK (A,C) and MTS assays (B,D) performed after the cells had been incubated with indicated containers for 24 h. UT = untreated control; Stx = staurosporine.

[0075] Figure 64 shows HEK293 toxicology assays. AK (A,C) and MTS assays (B,D) performed after the cells had been incubated with indicated containers for 24 h. UT = untreated control; Stx = staurosporine.

[0076] Figure 65 shows MTD study performed for P[6]AS. Female Swiss Webster mice (n = 5 per group) were dosed via tail vein on days 0 and 2 (denoted by *) with different concentrations of P[6]AS or phosphate buffered saline (PBS). The normalized average weight change per study group is indicated. Error bars represent SEM.

[0077] Figure 66 shows *in vivo* reversal of methamphetamine-induced hyperlocomotion by P[6]AS. Average locomotion counts for male Swiss Webster mice (n = 8; avg weight (g) ± SD: 39 ± 2.203) are plotted as a function of treatment. Treatment order was counterbalanced across days, and mice only received one treatment per day. Over six consecutive days of testing mice each received a single treatment of PBS (PBS; 0.01 M; 0.2 mL infused), P[6]AS only (P[6]AS; 4 mM; 0.178 mL infused), methamphetamine only (METH; 0.5 mg/kg; 0.022 mL infused), a premixed solution of P[6]AS and methamphetamine (Premix; ~7:1 P[6]AS:Meth; 0.178 mL P[6]AS + 0.022 mL Meth infused), P[6]AS followed by methamphetamine administered 30 s later (Blocking; 0.178 mL P[6]AS, 0.022 mL Meth infused), and methamphetamine followed by P[6]AS administered 30 s later (Reversal; 0.022 mL Meth, 0.178 mL P[6]AS infused). Bars represent average locomotion counts. Error bars represent the standard error of the mean (SEM). Dots represent counts for each mouse (n = 8). Presented p-values are only for significant ($p < 0.05$) Tukey-corrected post-hoc comparisons.

[0078] Figure 67 shows *in vivo* reversal of methamphetamine-induced hyperlocomotion effects observed after 5 minute delay between treatment with methamphetamine and P[6]AS administration. On day 7 and 8 mice (n = 8) received methamphetamine followed by an infusion of 0.01M PBS administered 5 minutes later (REV-C; 0.022 mL Meth, 0.2 mL PBS infused) or methamphetamine followed by P[6]AS administered 5 minutes later (REV-5; 0.022 mL Meth, 0.178 mL P[6]AS infused) in counterbalanced manner. Administration of P[6]AS 5 minutes after exposure to methamphetamine reduced hyperlocomotion (paired t-test, $t(7) = 2.757$, $p = 0.0282$). Bars represent average locomotion counts. Error bars represent the standard error of the mean (SEM). Dots represent counts for each mouse (n = 8).

[0079] Figure 68 shows the chemical structures for MDMA, mephedrone, heroin, and methamphetamine.

[0080] Figure 69 shows a) a plot of DP vs time from the titration of molecular container P[6]AS (100 μM) and 1,3-propanediammonium chloride (150 μM) in the cell with MDMA (1.00 mM) in the syringe in 20 mM NaH_2PO_4 buffer (pH 7.4); b) plot of the ΔH as a function of molar ratio. The solid line represents the best non-linear fit of the data to a

competition binding model (K_a = (3.92 ± 0.20) × 10^7 M^{-1}, ΔH = -13.3 ± 0.1 kcal/mol, -TΔS = 2.95 kcal/mol).

[0081] Figure 70 shows a) a plot of DP vs time from the titration of molecular container P[6]AS (10 μM) in the cell with Mephedrone (100 μM) in the syringe in 20 mM NaH_2PO_4 buffer (pH 7.4); b) plot of the ΔH as a function of molar ratio. The solid line represents the best non-linear fit of the data to a 1:1 binding model (K_a = (1.91 ± 0.19) × 10^7 M^{-1}, ΔH = -12.6 ± 0.11 kcal/mol, -TΔS = 2.68 kcal/mol).

[0082] Figure 71 shows a) a plot of DP vs time from the titration of molecular container P[6]AS (10 μM) in the cell with Heroin (100 μM) in the syringe in 20 mM NaH_2PO_4 buffer (pH 7.4); b) plot of the ΔH as a function of molar ratio. The solid line represents the best non-linear fit of the data to a 1:1 binding model (K_a = (5.78 ± 0.02) × 10^5 M^{-1}, ΔH = - 11.9 ± 0.11 kcal/mol, -TΔS = 4.01 kcal/mol).

[0083] Figure 72 shows a) a plot of DP vs time from the titration of molecular container **P[6]AS** (100 μM) and **17** (500 μM) with Rocuronium (1.00 mM) in 20 mM NaH_2PO_4 buffer (pH 7.4); b) plot of the ΔH as a function of molar ratio. The solid line represents the best non-linear fit of the data to a competition binding model (K_a = (6.33 ± 0.08) × 10^{11} M^{-1}, ΔH = - 24.9 ± 0.177 kcal/mol, -TΔS = 8.79 kcal/mol).

[0084] Figure 73 shows a) a plot of DP vs time from the titration of molecular container **P[6]AS** (100 μM) and **17** (500 μM) with Vecuronium (1.00 mM) in 20 mM NaH_2PO_4 buffer (pH 7.4); b) plot of the ΔH as a function of molar ratio. The solid line represents the best non-linear fit of the data to a competition binding model (K_a = (1.00 ± 0.34) × 10^{12} M^{-1}, ΔH = - 18.5 ± 0.095 kcal/mol, -TΔS = 2.10 kcal/mol).

[0085] Figure 74 shows a) a plot of DP vs time from the titration of molecular container **P[6]AS** (100 μM) and **17** (150 μM) with Pancuronium (1.00 mM) in 20 mM NaH_2PO_4 buffer (pH 7.4); b) plot of the ΔH as a function of molar ratio. The solid line represents the best non-linear fit of the data to a competition binding model (K_a = (7.35 ± 1.23) × 10^{10} M^{-1}, ΔH = - 16.5 ± 0.216 kcal/mol, -TΔS = 1.63 kcal/mol).

[0086] Figure 75 shows a) a plot of DP vs time from the titration of molecular container **P[7]AS** (10 μM) and with Cisatracurium (0.05 mM) in 20 mM NaH_2PO_4 buffer (pH 7.4); b) plot of the ΔH as a function of molar ratio. The solid line represents the best non-linear fit of the data to a 1:1 binding model with n = 0.5 (K_a = (1.52 ± 0.12) × 10^7 M^{-1}, ΔH = -35.0 ± 0.396 kcal/mol, -TΔS = 25.2 kcal/mol).

[0087] Figure 76 shows a) a plot of DP vs time from the titration of molecular container **P[6]AS** (100 μM) and propane-1,3-diaminium (150 μM) with Methamphetamine

(1.00 mM) in 20 mM NaH_2PO_4 buffer (pH 7.4); b) plot of the ΔH as a function of molar ratio. The solid line represents the best non-linear fit of the data to a competition binding model (K_a = (9.90 ± 0.39) × 10^6 M^{-1}, ΔH = - 10.4 ± 0.040 kcal/mol, -TΔS = 0.833 kcal/mol).

[0088] Figure 77 shows a) a plot of DP vs time from the titration of molecular container **P[6]AS** (100 μM) and propane-1,3-diaminium (1.00 mM) with Fentanyl (1.00 mM) in 20 mM NaH_2PO_4 buffer (pH 7.4); b) plot of the ΔH as a function of molar ratio. The solid line represents the best non-linear fit of the data to a competition binding model (K_a = (1.02 ± 0.03) × 10^8 M^{-1}, ΔH = - 15.0 ± 0.052 kcal/mol, -TΔS = 4.02 kcal/mol).

[0089] Figure 78 shows a) a plot of DP vs time from the titration of molecular container **P[6]AS** (100 μM) and with Cocaine (1.00 mM) in 20 mM NaH_2PO_4 buffer (pH 7.4); b) plot of the ΔH as a function of molar ratio. The solid line represents the best non-linear fit of the data to a 1:1 binding model (K_a = (1.92 ± 0.06) × 10^6 M^{-1}, ΔH = - 15.6 ± 0.047 kcal/mol, -TΔS = 7.07 kcal/mol).

[0090] Figure 79 shows a) a plot of DP vs time from the titration of molecular container **P[6]AS** (100 μM) and with Ketamine (1.00 mM) in 20 mM NaH_2PO_4 buffer (pH 7.4); b) plot of the ΔH as a function of molar ratio. The solid line represents the best non-linear fit of the data to a 1:1 binding model (K_a = (1.52 ± 0.25) × 10^5 M^{-1}, ΔH = - 22.0 ± 1.02 kcal/mol, -TΔS = 14.9 kcal/mol).

[0091] Figure 80 shows a) a plot of DP vs time from the titration of molecular container **P[6]AS** (100 μM) and propane-1,3-diaminium (150 μM) with Phencyclidine (1.00 mM) in 20 mM NaH_2PO_4 buffer (pH 7.4); b) plot of the ΔH as a function of molar ratio. The solid line represents the best non-linear fit of the data to a competition binding model (K_a = (5.85 ± 0.47) × 10^7 M^{-1}, ΔH = - 12.4 ± 0.076 kcal/mol, -TΔS = 1.84 kcal/mol).

[0092] Figure 81 shows a) a plot of DP vs time from the titration of molecular container **P[6]AS** (100 μM) and with Morphine (1.00 mM) in 20 mM NaH_2PO_4 buffer (pH 7.4); b) plot of the ΔH as a function of molar ratio. The solid line represents the best non-linear fit of the data to a 1:1 binding model (K_a = (1.36 ± 0.07) × 10^6 M^{-1}, ΔH = - 12.9 ± 0.073 kcal/mol, -TΔS = 4.49 kcal/mol).

[0093] Figure 82 shows a) a plot of DP vs time from the titration of molecular container **P[6]AS** (100 μM) and with Hydromorphone (1.00 mM) in 20 mM NaH_2PO_4 buffer (pH 7.4); b) plot of the ΔH as a function of molar ratio. The solid line represents the best non-linear fit of the data to a 1:1 binding model (K_a = (1.31 ± 0.04) × 10^6 M^{-1}, ΔH = - 11.9 ± 0.042 kcal/mol, -TΔS = 3.55 kcal/mol).

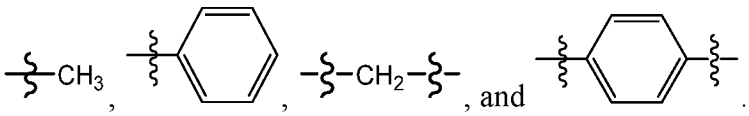
[0094] Figure 83 shows a) a plot of DP vs time from the titration of molecular container **P[6]AS** (100 μM) and with Oxycodone (1.00 mM) in 20 mM NaH_2PO_4 buffer (pH 7.4); b) plot of the ΔH as a function of molar ratio. The solid line represents the best non-linear fit of the data to a 1:1 binding model ($K_a = (9.52 \pm 0.36) \times 10^4\ M^{-1}$, ΔH = - 8.62 ± 0.097 kcal/mol, -TΔS = 1.83 kcal/mol).

DETAILED DESCRIPTION OF THE DISCLOSURE

[0095] Although claimed subject matter will be described in terms of certain examples, other examples, including examples that do not provide all of the benefits and features set forth herein, are also within the scope of this disclosure. Various structural, logical, and process step changes may be made without departing from the scope of the disclosure.

[0096] Ranges of values are disclosed herein. The ranges set out a lower limit value and an upper limit value. Unless otherwise stated, the ranges include the lower limit value, the upper limit value, and all values between the lower limit value and the upper limit value, including, but not limited to, all values to the magnitude of the smallest value (either the lower limit value or the upper limit value).

[0097] As used herein, unless otherwise stated, the term "group" refers to a chemical entity that is monovalent (i.e., has one terminus that can be covalently bonded to other chemical species), divalent, or polyvalent (i.e., has two or more termini that can be covalently bonded to other chemical species). The term "group" also includes radicals (e.g., monovalent and multivalent, such as, for example, divalent, trivalent, and the like, radicals). Illustrative examples of groups include:



[0098] As used herein, unless otherwise indicated, the term "aryl group" refers to C_5 to C_{18}, including all integer numbers of carbons and ranges of numbers of carbons therebetween, aromatic or partially aromatic carbocyclic groups (e.g., C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11}, C_{12}, C_{13}, C_{14}, C_{15}, C_{16}, C_{17}, and C_{18}). An aryl group may also be referred to as an aromatic group. The aryl groups can comprise polyaryl groups such as, for example, fused ring or biaryl groups. The aryl group can be unsubstituted or substituted with one or more substituent(s). Examples of substituents include, but are not limited to, various substituents such as, for example, halogens (-F, -Cl, -Br, and -I), azide group, aliphatic groups (e.g., alkyl groups, alkene groups, alkyne groups, and the like), aryl groups, hydroxyl

groups, alkoxide groups, carboxylate groups, carboxylic acid groups, ether groups, ester groups, amide groups, thioether groups, thioester groups, and the like, and combinations thereof. A substituent may be or further comprise a sulfonate group or a sulfate group. Examples of aryl groups include, but are not limited to, phenyl groups, biaryl groups (e.g., biphenyl groups and the like), and fused ring groups (e.g., naphthyl groups, anthracene groups, pyrenyl groups, and the like), which may be unsubstituted or substituted.

[0099] As used herein, unless otherwise indicated, the term "heteroaryl group" refers to a C_1 to C_{18} monocyclic, polycyclic, or bicyclic ring groups (e.g., aryl groups) comprising one or two aromatic rings containing at least one heteroatom (e.g., nitrogen, oxygen, sulfur, and the like) in the aromatic ring(s), including all integer numbers of carbons and ranges of numbers of carbons therebetween (e.g., C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11}, C_{12}, C_{13}, C_{14}, C_{15}, C_{16}, C_{17}, and C_{18}). The heteroaryl groups may be substituted or unsubstituted. Examples of heteroaryl groups include, but are not limited to, benzofuranyl groups, thienyl groups, furyl groups, pyridyl groups, pyrimidyl groups, oxazolyl groups, quinolyl groups, thiophenyl groups, isoquinolyl groups, indolyl groups, triazinyl groups, triazolyl groups, isothiazolyl groups, isoxazolyl groups, imidazolyl groups, benzothiazolyl groups, pyrazinyl groups, pyrimidinyl groups, thiazolyl groups, and thiadiazolyl groups, and the like. Examples of substituents include, but are not limited to, halogens (-F, -Cl, -Br, and -I), aliphatic groups (e.g., alkyl groups, alkenyl groups, alkynyl groups, and the like), aryl groups, alkoxide groups, amine groups, carboxylate groups, carboxylic acids, ether groups, alcohol groups, alkyne groups (e.g., acetylenyl groups and the like), and the like, and combinations thereof.

[0100] As used herein, unless otherwise indicated, the term "aliphatic" refers to branched or unbranched hydrocarbon groups that, optionally, contain one or more degree(s) of unsaturation. Degrees of unsaturation can arise from, but are not limited to, cyclic aliphatic groups. For example, the aliphatic groups/moieties are a C_1 to C_{40} aliphatic group, including all integer numbers of carbons and ranges of numbers of carbons therebetween (e.g., C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11}, C_{12}, C_{13}, C_{14}, C_{15}, C_{16}, C_{17}, C_{18}, C_{19}, C_{20}, C_{21}, C_{22}, C_{23}, C_{24}, C_{25}, C_{26}, C_{27}, C_{28}, C_{29}, C_{30}, C_{31}, C_{32}, C_{33}, C_{34}, C_{35}, C_{36}, C_{37}, C_{38}, C_{39}, and C_{40}). Aliphatic groups include, but are not limited to, alkyl groups, alkene groups, and alkyne groups. The aliphatic group can be unsubstituted or substituted with one or more substituent(s). Examples of substituents include, but are not limited to, various substituents such as, for example, halogens (-F, -Cl, -Br, and -I), azide group, aliphatic groups (e.g., alkyl groups, alkene groups, alkyne groups, and the like), aryl groups, hydroxyl groups, alkoxide groups,

carboxylate groups, carboxylic acid groups, ether groups, ester groups, amide groups, thioether groups, thioester groups, and the like, and combinations thereof.

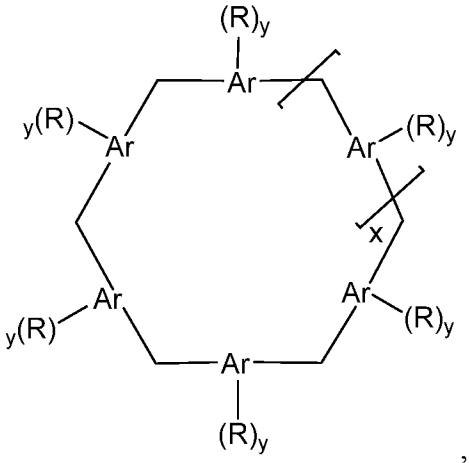
[0101] As used herein, unless otherwise indicated, the term "alkyl group" refers to branched or unbranched saturated hydrocarbon groups. Examples of alkyl groups include, but are not limited to, methyl groups, ethyl groups, n- and isopropyl groups, n-, iso-, sec-, and tert-butyl groups, and the like. For example, the alkyl group can be a C_1 to C_{12}, including all integer numbers of carbons and ranges of numbers of carbons therebetween (e.g., C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11}, and C_{12}). The alkyl group can be unsubstituted or substituted with one or more substituent(s). Examples of substituents include, but are not limited to, various substituents such as, for example, halogens (-F, -Cl, -Br, and -I), azide group, aliphatic groups (e.g., alkyl groups, alkene groups, alkyne groups, and the like), aryl groups, hydroxyl groups, alkoxide groups (-OR, where R is an alkyl group), carboxylate groups, carboxylic acid groups, ether groups, ester groups, amide groups, thioether groups, thioester groups, and the like, and combinations thereof.

[0102] The present disclosure provides sulfated pillararenes. The present disclosure also provides method making sulfated pillararenes and uses thereof.

[0103] In this disclosure, it was shown that, for example, positioning the anionic solubilizing groups at the rim of the pillararene cavity significantly enhances their binding affinity toward cationic targets in water and thereby enhances their abilities as sequestering agents for a variety of applications.

[0104] In an aspect, the present disclosure provides compounds. The compounds are sulfated pillararenes. A sulfated pillararene comprises a macrocycle core comprising a plurality of aryl groups, where adjacent aryl groups are covalently connected (e.g., linked) via alkyl linking groups (e.g., $-CH_2-$ groups). The alkyl linking groups are para on the aryl groups (e.g., 1,4-phenyl linkages). The linkages may be on different phenyl rings of an aryl group and correspond to a para linkage if the different phenyl rings were superimposed. In various examples, one or more or all of the adjacent aryl group(s) are not covalently connected by alkyl linking groups at meta positions on the aryl groups (e.g., 1,3-phenyl linkages (in the case where the linkages are on different phenyl rings or an aryl group the linkages do not correspond to a meta linkage if the different phenyl rings were superimposed)). Non-limiting examples of sulfated pillararenes are provided herein. Non-limiting examples of methods of making sulfated pillararenes are provided herein.

[0105] In various examples, a sulfated pillararene has the following structure:



,

where Ar is an aryl group attached (e.g., covalently bonded) in a para orientation to the adjacent methylene groups (e.g., 1,4-phenyl group linkage), which may be a part of a larger aryl group; each R is independently chosen from $-OS(O)_2O^-M^+$ (where M^+ is Na^+, K^+, Ca^{2+}, Mg^{2+}, Zn^{2+}, H_4N^+, Et_3NH^+, Me_4N^+, $(HOCH_2CH_2)_3NH^+$, or a cationic form of ethylenediamine, piperazine, or trishydroxymethyl aminomethane (TRIS)), $-OS(O)_2OH$, non-sulfate anionic groups (such as, for example, sulfonate (and corresponding acid) groups (e.g., $-O(CH_2)_mS(O)_2O^-M^+$ (where M^+ is Na^+, K^+, Ca^{2+}, Mg^{2+}, Zn^{2+}, H_4N^+, Et_3NH^+, Me_4N^+, $(HOCH_2CH_2)_3NH^+$, or a cationic form of ethylenediamine, piperazine, or trishydroxymethyl aminomethane (TRIS))/$-O(CH_2)_mS(O)_2OH$, where m is 1 to 8 (e.g., 1, 2, 3, 4, 5, 6, 7, 8), $-C_6H_5S(O)_2OH$, and the like and such groups where the terminal O is removed), carboxylate (and corresponding acid) groups (e.g., $-O(CH_2)_mC(O)O^-M^+$ (where M^+ is Na^+, K^+, Ca^{2+}, Mg^{2+}, Zn^{2+}, H_4N^+, Et_3NH^+, Me_4N^+, $(HOCH_2CH_2)_3NH^+$, or a cationic form of ethylenediamine, piperazine, or trishydroxymethyl aminomethane (TRIS))/$-O(CH_2)_mC(O)OH$, where n is 1 to 8 (e.g., 1, 2, 3, 4, 5, 6, 7, 8), and the like, such as for example, $-OCH_2CO_2^-M^+$/ $-OCH_2CO_2H$ groups and the like and such groups where the terminal O is removed), phosphonate (and corresponding acid) groups (e.g., $-O(CH_2)_mP(O)(OH)_2^-M^+$ (where M^+ is Na^+, K^+, Ca^{2+}, Mg^{2+}, Zn^{2+}, H_4N^+, Et_3NH^+, Me_4N^+, $(HOCH_2CH_2)_3NH^+$, or a cationic form of ethylenediamine, piperazine, or trishydroxymethyl aminomethane (TRIS))/$-O(CH_2)_mP(O)(OH)_2$, where m is 1 to 8 (e.g., 1, 2, 3, 4, 5, 6, 7, 8), and the like, such as for example, $-O(CH_2)_2P(O)(OH)_2$ and the like and such groups where the terminal O is removed), phosphate groups $-OP(O)(OH)_2$, and the like), substituted or unsubstituted aryl groups, substituted or unsubstituted heteroaryl groups, substituted or unsubstituted aliphatic groups, O-alkyl groups (comprising an alkyl group), azide groups, -H, substituted or unsubstituted alkyl groups, halogens (e.g., -Br, -F, -I, -Cl), amide groups, cyano groups, substituted or unsubstituted sulfur-containing aliphatic groups

(e.g., -S-alkyl and poly thioethers, and the like), nitro groups, amino groups, substituted or unsubstituted nitrogen-containing aliphatic groups (e.g., polyamines, aliphatic groups comprising secondary and/or tertiary amines, and the like), substituted or unsubstituted polyethylene glycol groups, polyether groups, O-aryl groups (e.g., aryloxy groups), ester groups, carbamate groups, imine groups, aldehyde groups, $-SO_3H$ groups, $-SO_3Na$ groups, $-OSO_2F$ groups, $-OSO_2CF_3$ groups, $-OSO_2OR'''$ groups (where R''' are substituted or unsubstituted aryl groups or substituted or unsubstituted alkyl groups), and the like, and combinations thereof; x is 0, 1, 2, or 3; and y is independently at each occurrence 0, 1, 2, 3, or 4, with the proviso that at least one y is 1 and at least one R group is $-OS(O)_2O^-M^+$ (where M^+ is Na^+, K^+) or $-OS(O)_2OH$, or a salt, a partial salt, a hydrate, a polymorph, a stereoisomer, conformational isomer, or a mixture thereof. The R group(s) may be at any position(s) on an aryl group. In the case of an aryl group with multiple R groups, the individual R groups may be at any combination of positions of the aryl group. In various examples, all of the aryl groups comprise an R group that is independently $-OS(O)_2O^-M^+$ (where M^+ is Na^+, K^+, Ca^{2+}, Mg^{2+}, Zn^{2+}, H_4N^+, Et_3NH^+, Me_4N^+, $(HOCH_2CH_2)_3NH^+$, or a cationic form of ethylenediamine, piperazine, and trishydroxymethyl aminomethane (TRIS)) or $-OS(O)_2OH$. In various examples, at least one aryl group does not comprise an R group that is $–OS(O)_2O^-M^+$ (where M^+ is Na^+, K^+, Ca^{2+}, Mg^{2+}, Zn^{2+}, H_4N^+, Et_3NH^+, Me_4N^+, $(HOCH_2CH_2)_3NH^+$, or a cationic form of ethylenediamine, piperazine, or trishydroxymethyl aminomethane (TRIS)) or $-OS(O)_2OH$. In various embodiments, the aryl groups may be further substituted with various substitutents, such as, for example, -H, alkyl groups, aliphatic groups, polyethylene glycol groups, or the like, or a combination thereof.

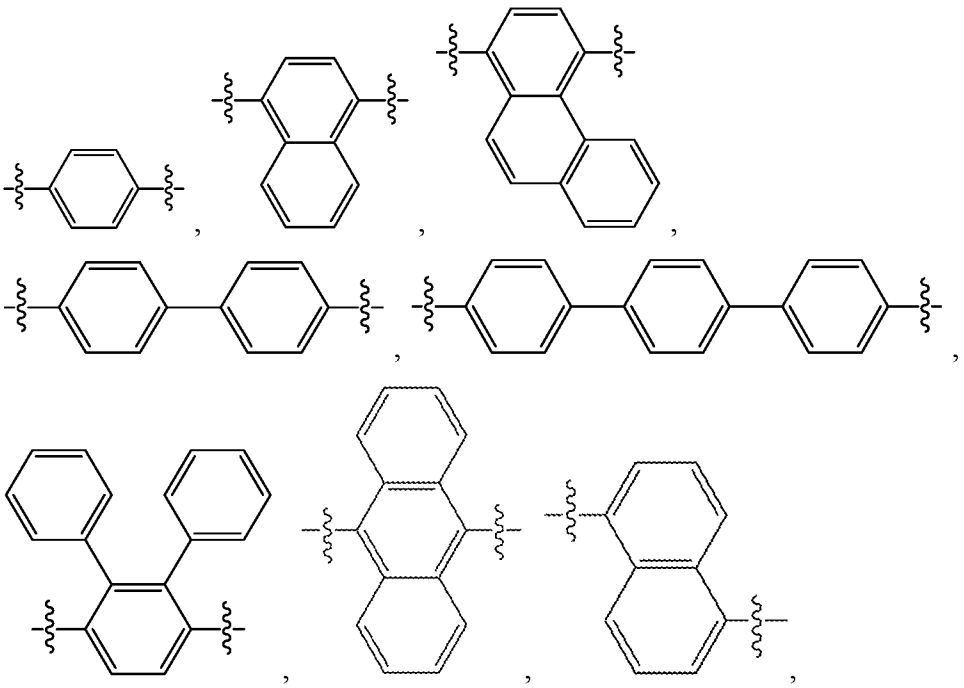
[0106] In certain embodiments, M^+ is Na^+, K^+, Ca^{2+}, Mg^{2+}, Zn^{2+}, H_4N^+, Et_3NH^+, Me_4N^+, $(HOCH_2CH_2)_3NH^+$, or a cationic form of ethylenediamine, piperazine, or trishydroxymethyl aminomethane (TRIS).

[0107] In certain embodiments, M^+ is Na^+, K^+, and H_4N^+. In certain embodiments, M^+ is Na^+.

[0108] A sulfated pillararene can comprise various aryl groups. The aryl groups may all be the same or at least two of the aryl groups are different. Non-limiting examples of aryl groups are independently at each occurrence chosen from phenyl groups, fused-ring groups (e.g., naphthyl groups, anthracenyl groups, phenanthrenyl groups, tetracenyl groups, pentacenyl groups, and the like), biaryl groups (e.g., biphenyl groups and the like), terphenyl groups, and the like, and combinations thereof. For avoidance of doubt, a phenyl group, when

it is not part of a larger aryl group, unless otherwise described, is a C_6H_4 group. A phenyl group may be referred to as a phenylene group.

[0109] Adjacent aryl groups can be linked by various linkages. The linkages are para-linked phenyl group linkages. In various examples, at least a portion or all of the linkages are 1,4-phenyl group linkage(s). Non-limiting examples of para-linked phenyl group linkages include:

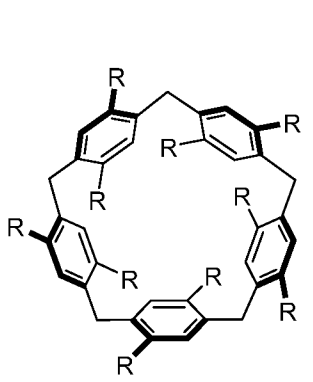
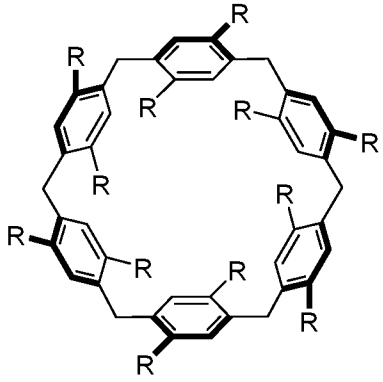


and combinations thereof. These are illustrative examples. Other para-linked phenyl group linkages are within the scope of this disclosure. In various examples, the linkage is not a meta linkage.

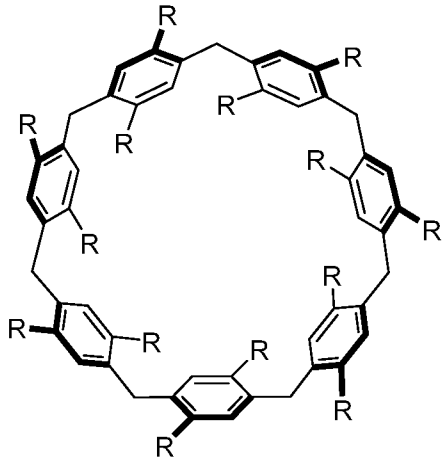
[0110] An aryl group may comprise one or more phenyl group(s). In various non-limiting examples, at least two, at least three, or at least 4, or all of the one or more phenyl group(s) of one or more of the aryl group(s) comprising the cyclic core of the compound have at least 1 or at least 2 R groups independently chosen from $-OS(O)_2O^-M^+$ (where M^+ is Na^+, K^+, Ca^{2+}, Mg^{2+}, Zn^{2+}, H_4N^+, Et_3NH^+, Me_4N^+, $(HOCH_2CH_2)_3NH^+$, or a cationic form of ethylenediamine, piperazine, or trishydroxymethyl aminomethane (TRIS)) and $-OS(O)_2OH$. All of the aryl groups, one or more or all of which may be phenyl group(s), may comprise a sulfate group $-OS(O)_2O^-M^+$ (where M^+ is Na^+, K^+, Ca^{2+}, Mg^{2+}, Zn^{2+}, H_4N^+, Et_3NH^+, Me_4N^+, $(HOCH_2CH_2)_3NH^+$, or a cationic form of ethylenediamine, piperazine, or trishydroxymethyl aminomethane (TRIS)) or $-OS(O)_2OH$. In various examples, at least one aryl group, which may be a phenyl group, does not comprise a sulfate group (e.g., $-OS(O)_2O^-M^+$ (where M^+ is

Na^+, K^+, Ca^{2+}, Mg^{2+}, Zn^{2+}, H_4N^+, Et_3NH^+, Me_4N^+, $(HOCH_2CH_2)_3NH^+$, or a cationic form of ethylenediamine, piperazine, or trishydroxymethyl aminomethane (TRIS)) or $-OS(O)_2OH$).

[0111] In various examples, a sulfated pillararene has the following structure:

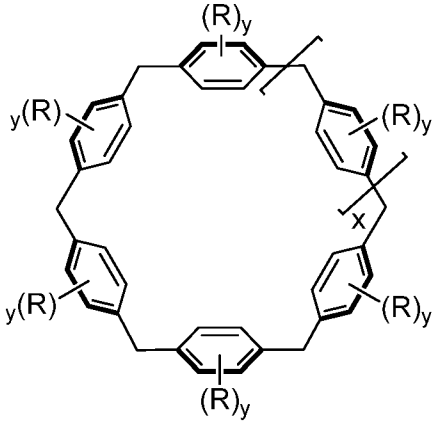



or



In various examples, each R is $-OS(O)_2O^-M^+$ (where M^+ is Na^+, K^+, Ca^{2+}, Mg^{2+}, Zn^{2+}, H_4N^+, Et_3NH^+, Me_4N^+, $(HOCH_2CH_2)_3NH^+$, or a cationic form of ethylenediamine, piperazine, or trishydroxymethyl aminomethane (TRIS)) and $-OS(O)_2OH$.

[0112] In various examples, a sulfated pillararene has the following structure:



In various examples, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22,

23, 24, 25, 26, 27, 28, 29, 30, 31, or 32 of the R groups are independently $-OS(O)_2O^-M^+$ groups (where M^+ is Na^+, K^+, Ca^{2+}, Mg^{2+}, Zn^{2+}, H_4N^+, Et_3NH^+, Me_4N^+, $(HOCH_2CH_2)_3NH^+$, or a cationic form of ethylenediamine, piperazine, or trishydroxymethyl aminomethane (TRIS)) or $-OS(O)_2OH$ groups.

[0113] In an aspect, the present disclosure provides compositions comprising one or more sulfated pillararene(s). Non-limiting examples of compositions are described herein.

[0114] A composition may comprise one or more sulfated pillararene(s) and one or more pharmaceutical agent(s). In various examples, a pharmaceutical agent comprises one or more positively charged nitrogen atom(s) (e.g., ammonium ions, primary ammonium ions, secondary ammonium ions, tertiary ammonium ions, quaternary ammonium ions, or a combination thereof, where the non-hydrogen group(s) on the ammonium are chosen from aliphatic groups, alkyl groups, aryl groups, and combinations thereof).

[0115] A composition may comprise one or more sulfated pillararene(s), one or more pharmaceutical carrier(s), and, optionally, one or more pharmaceutical agent(s). The compositions described herein can be with one or more pharmaceutically acceptable carrier(s). Suitable pharmaceutically acceptable carriers are known in the art. Some non-limiting examples of pharmaceutically acceptable carriers can be found in: *Remington: The Science and Practice of Pharmacy* (2005) 21st Edition, Philadelphia, PA. Lippincott Williams & Wilkins. In various examples, the pharmaceutical carrier is pure water or a buffer, such as PBS buffer or the like.

[0116] Compositions comprising one or more sulfated pillararene(s) combined with one or more pharmaceutical agent(s), which may form guest-host complexes, can be prepared at any point prior to use of the composition using any suitable technique. The compound-pharmaceutical agent complexes can be formed, for example, by mixing the compound and the pharmaceutical agent in a suitable solvent. It is desirable that the compound and pharmaceutical agent be soluble in the solvent such that the compound and agent form a non-covalent complex. Any suitable solvent can be used. In certain examples, the solvent is an aqueous solution, which includes, but is not necessarily limited to, water and various buffers (e.g., PBS buffer and the like). Non-aqueous solvents could also be used (e.g., MeOH, EtOH, and other organic solvents, and combinations thereof), and then removed and the compositions if desired can be re-dissolved in an aqueous solution for administration. In general, a solution of a compound(s) can be provided at a known concentration, examples of which include but are not limited to from 0.1 to 90 mM, inclusive and including all integers to the tenth decimal place there between, and a pharmaceutical agent for which enhanced

solubility is desired is added to the solution. The agent(s) can be provided, for example, in a solid form. The combination can be shaken or stirred for a period of time and the amount of pharmaceutical agent that is dissolved is monitored. If all added agent goes into solution, more agent can be added until some detectable portion of it remains undissolved (e.g., a solid). The soluble compound-agent complex can then be isolated and analyzed by any suitable technique, such by recovering a centrifuged portion and analyzing it by NMR, to determine the concentration of pharmaceutical agent in solution. In various examples, a compound is provided in a composition comprising the drug at a ratio of at least 1 to 1 as pertains to the compound-agent stoichiometry (e.g., pillararene to drug ratio). In various examples, the pillararene (e.g., pillararene sulfate) to drug ratio is 100:1 to 1:5, including all ratio values and ranges therebetween (e.g., 100:1, 5:1, 1:2, 1:3, 1:4, or 1:5).

[0117] Compositions may be prepared at a patient's bedside or by a pharmaceutical manufacture. In the latter case, the compositions can be provided in any suitable container, such as, for example, a sealed sterile vial, ampoule, or the like, and may be further packaged (the combination of which may be referred to as a kit) to include instruction documents for use by a pharmacist, physician, other health care provider, or the like. The compositions can be provided as a liquid, or as a lyophilized or powder form that can be reconstituted if necessary when ready for use. In particular, the compositions can be provided in combination with any suitable delivery form or vehicle, examples of which include but are not limited to liquids, caplets, capsules, tablets, inhalants or aerosol, etc. The delivery devices may comprise components that facilitate release of the pharmaceutical agents over certain time periods and/or intervals, and can include compositions that enhance delivery of the pharmaceuticals, such as nanoparticle, microsphere or liposome formulations, a variety of which are known in the art and are commercially available. Further, each composition described herein can comprise one or more pharmaceutical agent(s).

[0118] Compositions of the present disclsoure may comprise more than one pharmaceutical agent. Likewise, the compositions can comprise distinct host-guest complexes. For example, a first composition comprising one or more sulfated pillararene(s) and a first phamaceutical agent can be separately prepared from a composition which comprises the same compound and a second pharmaceutical agent, and such preparations can be mixed to provide a two-pronged (or more) approach to achieving the desired prophylaxis or therapy in an individual. Further, compositions can be prepared using mixed preparations of any of the sulfated pillararene compounds disclosed herein.

[0119] A solid substrate may comprise one or more sulfated pillararene(s) disposed on (e.g., chemically bonded to) at least a portion of a surface of the substrate. At least a portion or all of the sulfated pillararenes may be chemically bonded to at least a portion of a surface by covalent bonds, non-covalent bonds, or a combination thereof. Methods of conjugating sulfated pillararenes to solid surfaces are known in the art. In various examples, sulfated pillararenes are conjugated to a surface by covalent bond- and/or non-covalent bond forming reactions including, but not limited to, amide bond formation, azide alkyne cycloaddition, gold thiol interactions, silicon alcohol condensations, and the like, and combinations thereof.

[0120] A solid substrate may comprise (or be) various materials. In various non-limiting examples, a solid substrate comprises or is silica (such as, for example, silica particles), polymer beads, polymer resins (such as, for example, polystyrene, poly NIPAM, polyacrylic acid, metal nanoparticles (e.g. gold nanoparticles, silver nanoparticles, magnetic nanoparticles), a metal (such as, for example, gold and the like), or the like, or a combination thereof.

[0121] In an aspect, the present disclosure provides uses of sulfated pillararenes. Non-limiting examples of uses of sulfated pillararenes are provided herein, for example, non-limiting examples of uses of sulfated pillararenes are described in the Statements and Examples.

[0122] Sulfated pillararenes can be used to sequester various materials, which may be chemical compounds. In various non-limiting examples, one or more sulfated pillararene(s) is/are used to sequester one or more neuromuscular blocking agent(s) (such as, for example, rocuronium, tubocurarine, atracurium, (cis)atracurium besylate, mivacurium, gallamine, pancuronium, vecuronium, and rapacuronium, and the like); one or more anesthesia agent(s) (such as, for example, *N*-methyl *D*-aspartate (NMDA) receptor antagonists (e.g., ketamine and the like), short-acting anesthetic agents (e.g., etomidate and the like), and the like); one or more pharmaceutical agent(s) (such as, for example, a drug (e.g., anticoagulants, such as, for example, hexadimethrine and the like), drugs of abuse (e.g., methamphetamine, cocaine, fentanyl, carfentanil, PCP, MDMA, heroin, and the like), and the like); one or more pesticide(s) (such as, for example, paraquat, diquat, organochlorines (e.g., DDT, aldrin, and the like), neonicotinoids (e.g., permethrin and the like), organophosphates (e.g., malathion, glyphosate, and the like), pyrethroids, triazines (e.g., atrazine and the like), and the like); one or more dyestuff(s) (such as, for example, methylene blue, nile red, crystal violet, thioflavin T, thiazole orange, proflavin, acridine orange, methylene violet, azure A, neutral red,

cyanines, Direct orange 26, disperse dyes (e.g., disperse yellow 3, disperse blue 27, and the like), coumarins, congo red, and the like); one or more malodorous compound(s) (such as, for example, low molecular weight thiols (e.g., C_1–C_4 thiols), low molecular weight amines (e.g., triethylamine, putrescein, cadaverine, and the like), and the like); or one or more chemical warfare agent(s) (such as for example, nitrogen and sulfur mustards (e.g., bis(2-chloroethyl)ethylamine, bis(2-chloroethyl)methylamine, tris(2-chloroethyl)amine, bis(2-chloroethyl) sulfide, bis(2-chloroethylthioethyl) ether, and the like), nerve agents (such as, for example, those from the G, GV, and V series of nerve agents (e.g. tabun, sarin, soman, cyclosarin, 2-(dimethylamino)ethyl *N*,*N*-dimethylphosphoramidofluoridate (GV), novichok agents, VE, VG, VM, VX, and the like), and the like); one or more hallucinogen(s) (e.g., ergolines, lysergic acid diethylamide (LSD), psilocybin, tryptamines, dimethyltryptamine (DMT), phenethylamines, mescaline, ayahuasca, dextromethorphan, and the like); one or more toxin(s) (e.g., dioxins, perfluoralkylsulfonates (PFAS), perfluorooctanoic acid (PFOA), decabromobiphenyl ether (DECA), heavy metals (e.g. mercury), muscarine, tyramine, strychnine, tetrodotoxin, saxitoxin and the like, cholesterol, deoxycholic acid, N-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine, phenylalanine, tyrosine, arginine, histamine); one or more metabolite(s) (e.g., toxic metabolites, such as, for example, N-methyl-4-phenylpyridine, spermine, spermidine, N-nitroso compounds e.g. 4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanone); or the like, or a combination thereof.

[0123] A material, which may be a chemical compound, may comprise one or more cationic group. In various examples, a material, which may be a chemical compound, comprises one or more positively charged nitrogen atom(s) (e.g., ammonium ions, primary ammonium ions, secondary ammonium ions, tertiary ammonium ions, quaternary ammonium ions, or a combination thereof, where the non-hydrogen group(s) on the ammonium are chosen from aliphatic groups, alkyl groups, aryl groups, and combinations thereof).

[0124] In various examples, a method for sequestering one or more neuromuscular blocking agent(s), one or more anesthesia agent(s), one or more pharmaceutical agent(s), one or more pesticide(s), one or more dyestuff(s), one or more malodorous compound(s), one or more chemical warfare agent(s), one or more hallucinogen(s), one or more toxin(s), one or more metabolite(s)or the like, or a combination thereof comprises contacting the neuromuscular blocking agent(s), the anesthesia agent(s), the pharmaceutical agent(s), the pesticide(s), the dyestuff(s), the malodorous compound(s), the chemical warfare agent(s), the hallucinogen(s), the toxin(s), the metabolite(s), or a combination thereof with one or more sulfated pillararene(s) and/or one or more composition(s), where the neuromuscular blocking

agent(s), the anesthesia agent(s), the pharmaceutical agent(s), the pesticide(s), the dyestuff(s), the malodorous compound(s), the chemical warfare agent(s), or a combination thereof are sequestered by the one or more sulfated pillararene(s) and/or one or more composition(s).

[0125] The neuromuscular blocking agent(s), the anesthesia agent(s), the pharmaceutical agent(s), the pesticide(s), the dyestuff(s), the malodorous compound(s), the chemical warfare agent(s), the hallucinogen(s), the toxin(s), the metabolite(s), or a combination thereof may be present in an aqueous sample, in a solid sample (such as, for example, a soil sample), in a gas sample, or the like. An aqueous sample may be derived (e.g., via extraction or other methods to isolate the neuromuscular blocking agent(s), the anesthesia agent(s), the pharmaceutical agent(s), the pesticide(s), the dyestuff(s), the malodorous compound(s), the chemical warfare agent(s), the hallucinogen(s), the toxin(s), the metabolite(s), or a combination thereof from the solid sample). The aqueous sample may be a wastewater sample (e.g., a municipal wastewater sample, industrial wastewater sample, and the like), an industrial water sample (e.g., water used to make a commercial product, such as, for example, a reagent, a solvent, or the like), a municipal water sample, or the like.

[0126] A composition may comprise one or more pharmaceutically active agent(s). In various non-limiting examples, at least a portion (or all) of the one or more compound(s) have a pharmaceutically active agent(s) disposed in the cavity of the one or more compound(s). Without intending to be bound by any particular theory, it is considered that a complex (which may be referred to as a guest-host complex) is formed from (e.g., one or more interaction(s) between (e.g., one or more non-covalent interactions, such as, for example, one or more non-covalent bond(s), is formed between) the compound(s), which may be referred to as hosts, and the neuromuscular blocking agent(s), the anesthesia agent(s), the pharmaceutical agent(s), which may be pharmaceutical agent(s) with undesirable (e.g., low) water solubility, the pesticide(s), the dyestuff(s), the malodorous compound(s), the chemical warfare agent(s), the hallucinogen(s), the toxin(s), the metabolite(s), or a combination thereof, which may be referred to a guest or guests. A guest-host complex can therefore be considered to be an organized chemical entity resulting from the association of the pharmaceutical agent(s) (guest(s)) and the host held together, for example, by non-covalent intermolecular forces.

[0127] A composition can comprise various pharmaceutically active agents. Non-limiting examples of pharmaceutical agents include drugs. The pharmaceutically active agent(s) may have various aqueous solubility. A pharmaceutically active agent may have hydrophobic, hydrophilic, or amphiphilic character.

[0128] The complexes may be removed from the aqueous sample, the solid sample, the gas sample, or the like. In various examples, the neuromuscular blocking agent(s), the anesthesia agent(s), the pharmaceutical agent(s), the pesticide(s), the dyestuff(s), the malodorous compound(s), the chemical warfare agent(s), the hallucinogen(s), the toxin(s), the metabolite(s), or a combination thereof are removed from the aqueous sample, the solid sample, the gas sample, or the like using a solid surface with one or more sulfated pillararene(s) disposed thereon.

[0129] Sulfated pillararenes can be used to sequester various materials in an individual. In various non-limiting examples, the neuromuscular blocking agent(s), the anesthesia agent(s), the pharmaceutical agent(s), the pesticide(s), the dyestuff(s), the malodorous compound(s), the chemical warfare agent(s), one or more hallucinogen(s), one or more toxin(s), one or more metabolite(s), or a combination thereof is present in an individual and the contacting comprises administration of the one or more compound(s) and/or one or more composition(s) to the individual.

[0130] Sulfated pillararenes can be used to reverse drug-induced neuromuscular block and/or anesthesia and/or the effects of one or more drug(s), which may be drugs of abuse in an individual.

[0131] In various non-limiting examples, a method for reversing drug-induced neuromuscular block and/or anesthesia and/or the effects of one or more pharmaceutical agent(s) (e.g., one or more drug(s) of abuse) in or on an individual comprising administering to an individual in need of reversal of neuromuscular block and/or reversal of anesthesia and/or reversal of the effects of the one or more pharmaceutical agent(s) (e.g., one or more drug(s) of abuse), one or more sulfated pillararenes, and/or one or more composition(s). The individual may be in need of reversal of drug-induced neuromuscular block. The individual may be in need of reversal of anesthesia. The individual may be in need of reversal of drug-induced neuromuscular block and anesthesia. The individual may be in need of reversal of the effects of one or more pharmaceutical agent(s), such as, for example, one or more drug(s), which may be drug(s) of abuse. The individual may have been exposed to the drug(s) of abuse (e.g., carfentanil and the like) in a terrorist attack.

[0132] The sulfated pillararene compounds may be used as containers to solubilize chemical compounds. Improvement of solubility for compounds in, for example, aqueous solutions, is desirable for studying drug compounds and for improvement of drug bioavailability for purposes such as, for example, therapeutic and/or prophylactic purposes.

For example, the sulfated pillararenes are be used to enhance the stability (e.g., decrease degradation, increase shelf life, and the like) of drugs in water, the solid state, or both.

[0133] In certain examples, the sulfated pillararene compounds can be used to rescue promising drug candidates, which have undesirable solubility and bioavailablity, and thus alleviate the attrition in the drug development process for anti-cancer agents and agents intended to treat other diseases. The containers may be used for targeted delivery of drugs to particular cell types, such as, for example, tumor cells and the like, to increase the effectiveness of existing drugs, reduce their toxic side effect(s), or both.

[0134] In various examples, a composition comprises one or more sulfated pillararene(s) and one or more pharmaceutical agent(s). Such compositions may be provided as pharmaceutical preparations as described herein.

[0135] It is important to emphasize that the pharmaceutical agent(s) that can be included in compositions comprising one or more sulfated pillararene(s) and one or more pharmaceutical agent(s) is not particularly limited. In certain examples, the pharmaceutical agent(s) combined with one or more sulfated pillararene(s) is/are a pharmaceutical agent or agents that is/are poorly water-soluble. In certain other examples, the pharmaceutical agent(s) combined with one or more sulfated pillararene(s) is/are a pharmaceutical agent or agents that is/are water soluble.

[0136] Solubility of any particular pharmaceutical agent can be determined, if desired, using any of a variety techniques that are well known to those skilled in the art. Solubility can be ascertained if desired at any pH, such as a physiological pH, and/or at any desired temperature. Suitable temperatures include, but are not necessarily limited to, from 4 °C to 70 °C, inclusive, and including all integer °C values therebetween.

[0137] In connection with poorly soluble or low solubility pharmaceutical agents suitable for use in the present disclosure, in various examples, such agents are considered to be those which have a solubility of less than 100 μM in water or an aqueous buffer.

[0138] In various other examples, poorly soluble pharmaceutical agents are considered to include compounds, which are Biopharmaceutics Classification System (BCS) class 2 or class 4 drugs. The BCS is well known to those skilled in the art and is based on the aqueous solubility of drugs reported in readily available reference literature, and for drugs that are administered orally it includes a correlation of human intestinal membrane permeability. (See, for example, Takagi et al., (2006) Molecular Pharmaceutics, Vol. 3, No. 6, pp. 631-643.) The skilled artisan will therefore readily be able to recognize a drug as a

member of BCS class 2 or class 4 from published literature, or can test a drug with an unknown BCS or other solubility value to determine whether it has properties consistent with either of those classifications, or for otherwise being suitable for use in the present disclosure. In an example, solubility is determined according to the parameters set forth in this matrix:

Solubility	Parts of solvent required for 1 part of solute	Solubility Range (mg/mL)
very soluble	<1	≥1000
freely soluble	from 1 to 10	100-1000
soluble	from 10 to 30	33-100
sparingly soluble	from 30 to 100	10-33
slightly soluble	from 100 to 1000	1-10
very slightly soluble	form 1000 to 10000	0.1-1
practically insoluble	≥10000	< 0.1

Thus, for the purposes of the present disclosure, a poorly soluble pharmaceutical agent that can be combined with one or more sulfated pillararene(s) can be any pharmaceutical agent that falls into the categories sparingly soluble, slightly soluble, very slightly soluble, and practically insoluble as set forth in the above matrix.

[0139] Again, it should be emphasized that other than being characterized as having low solubility in aqueous solution, the pharmaceutical agent with which one or more sulfated pillararene(s), which a compound can be combined is not limited. In this regard, at least one utility of the present disclosure is combination of one or more of a wide variety of distinct pharmaceutical agents with one or more sulfated pillararene(s), and as a consequence of combining these compounds with the pharmaceutical agent(s), solubility of the agent(s) is/are increased. In various examples, types of pharmaceutical agents suitable for solubilization include, but are not limited to, mitotic inhibitors (e.g., taxol, a mitotic inhibitor used in cancer chemotherapy, and the like); nitrogen mustard alkylating agents (e.g., Melphalan, trade name Alkeran used for chemotherapy, and the like); benzimidazoles (e.g., Albendazole, marketed as Albenza, Eskazole, Zentel and Andazol, for treatment of a variety of worm infestations, and the like); antagonists of the estrogen receptor in breast tissue which is used to treat breast cancers (e.g., Tamoxifen, which is an estrogen receptor antagonist when metabolized to its active form of hydroxytamoxifen, and the like); antihistamines (e.g., Cinnarizine, marketed as Stugeron and Stunarone for control of symptoms of motion sickness, and the like); thienopyridine class antiplatelet agents (e.g., Clopidogrel, marketed as Plavix for inhibiting

blood clots in coronary artery disease and for other conditions, and the like); and antiarrhythmic agents (e.g., Amiodarone, used for treatment of tachyarrhythmias, and the like). Other pharmaceutical agents not expressly listed here are also included within the scope of the disclosure. Some examples of such agents include, but are not limited to, adjuvants for use in enhancing immunological responses, analgesic agents, detectably labeled agents used for diagnostic imaging, and the like. Combinations of any of these example pharmaceutical agents may be used. Sulfated pillararenes may be combined with and improve solubility of pharmaceutical agents that are members of vastly different classes of compounds which are characterized by disparate chemical structures and biological activities.

[0140] Compositions of the present disclosure can be administered to any human or non-human animal in need of therapy or prophylaxis for one or more condition(s) for which the pharmaceutical agent is intended to provide a prophylactic of therapeutic benefit. Thus, the individual can be diagnosed with, suspected of having, or be at risk for developing any of a variety of conditions for which a reduction in severity would be desirable. Non-limiting examples of such conditions include cancer, including solid tumors, blood cancers (e.g., leukemia, lymphoma, myeloma, and the like). Specific examples of cancers include, but are not limited to, fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, pseudomyxoma peritonei, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, head and neck cancer, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilns' tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oliodendroglioma, meningioma, melanoma, neuroblastoma, retinoblastoma, leukemia, lymphoma, multiple myeloma, thymoma, Waldenstrom's macroglobulinemia, heavy chain disease, and the like.

[0141] In addition to various malignancies, compounds of the present disclosure are also suitable for providing a benefit for cardiovascular related disorders, examples of which include, but are not limited to, angina, arrhythmia, atherosclerosis, cardiomyopaathy, congestive heart failure, coronary artery disease, carotid artery disease, endocarditis, coronary

thrombosis, myocardial infarction, hypertension, hypercholesterolemia/hyperlipidemia, mitral valve prolapse, peripheral artery disease, stroke, thrombosis, embolism, other forms of ischemic damage, and the like.

[0142] In addition, the compositions of the present disclosure can be used in connection with treating a variety of infectious diseases. It is expected that a variety of agents used to treat and/or inhibit infectious diseases caused by, for example, bacterial, protozoal, helminthic, fungal origins, viral origins, or the like can be aided by use of compositions of the present disclosure.

[0143] Various methods known to those skilled in the art can be used to introduce the compounds and/or compositions of the present disclosure to an individual. These methods include, but are not limited to, intravenous, intramuscular, intracranial, intrathecal, intradermal, subcutaneous, oral routes, and the like, and combinations thereof. The dose of the composition comprising a compound and a pharmaceutical agent will necessarily be dependent upon the needs of the individual to whom the composition is to be administered. These factors include, but are not necessarily limited to, the weight, age, sex, medical history, and nature and stage of the disease for which a therapeutic or prophylactic effect is desired. The compositions can be used in conjunction with any other conventional treatment modality designed to improve the disorder for which a desired therapeutic or prophylactic effect is intended, non-limiting examples of which include surgical interventions and radiation therapies. The compositions can be administered once, or over a series of administrations at various intervals determined using ordinary skill in the art, and given the benefit of the present disclosure.

[0144] Methods of the present disclosure may be used on various individuals. In various examples, an individual is a human or non-human mammal. Examples of non-human mammals include, but are not limited to, farm animals, such as, for example, cows, hogs, sheep, and the like, as well as pet or sport animals such as, for example, horses, dogs, cats, and the like. Additional non-limiting examples of individuals include, but are not limited to, rabbits, rats, mice, and the like.

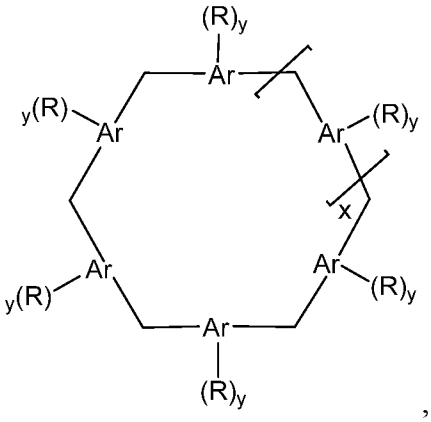
[0145] The steps of the method described in the various examples disclosed herein are sufficient to carry out the methods of the present disclosure. Thus, in an example, the method consists essentially of a combination of the steps of the methods disclosed herein. In another example, the method consists of such steps.

[0146] In an aspect, the present disclosure provides articles comprising compounds of the present disclosure.

[0147] The articles may be articles of manufacture. Non-limiting examples of articles include wipes impregnated with one or more compounds of the present disclosure. For example, such a wipe is used to decontaminate a surface from any material capable of being sequestered by a compound (e.g., pillararene of the present disclosure). For example, the wipe is used to decontaminate a surface that has or was previously exposed to a toxin, abused drug, or the like, or a combination thereof.

[0148] The following Statements illustrate various embodiments of the present disclosure.

Statement 1. A compound having the following structure:



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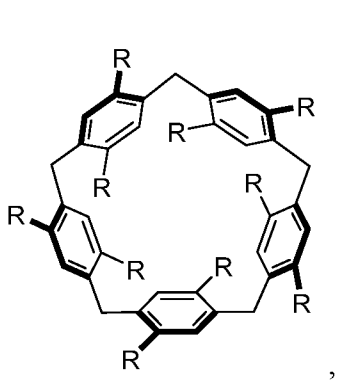
where Ar is an aryl group where adjacent aryl groups are linked by a para-linked phenyl group linkages (e.g., 1,4-phenyl group linkage(s)) (e.g., the aryl groups are attached in a para orientation to the adjacent methylene groups), which may be a part of a larger aryl group; each R is independently chosen from $-OS(O)_2O^-M^+$ (where M^+ is Na^+, K^+, Ca^{2+}, Mg^{2+}, Zn^{2+}, H_4N^+, Et_3NH^+, Me_4N^+, $(HOCH_2CH_2)_3NH^+$, or a cationic form of ethylenediamine, piperazine, or trishydroxymethyl aminomethane (TRIS)), and $-OS(O)_2OH$, non-sulfate anionic groups (such as, for example, sulfonate (and corresponding acid) groups (e.g., $-O(CH_2)_mS(O)_2O^-M^+$ (where M^+ is Na^+, K^+, Ca^{2+}, Mg^{2+}, Zn^{2+}, H_4N^+, Et_3NH^+, Me_4N^+, $(HOCH_2CH_2)_3NH^+$, or a cationic form of ethylenediamine, piperazine, or trishydroxymethyl aminomethane (TRIS))/$-O(CH_2)_mS(O)_2OH$, where n is 1 to 8 (e.g., 1, 2, 3, 4, 5, 6, 7, 8), $-C_6H_5S(O)_2OH$, and the like and such groups where the terminal O is removed), carboxylate (and corresponding acid) groups (e.g., $-O(CH_2)_mC(O)O^-M^+$ (where M^+ is Na^+, K^+, Ca^{2+}, Mg^{2+}, Zn^{2+}, H_4N^+, Et_3NH^+, Me_4N^+, $(HOCH_2CH_2)_3NH^+$, or a cationic form of ethylenediamine, piperazine, or trishydroxymethyl aminomethane (TRIS))/$-O(CH_2)_mC(O)OH$, where m is 1 to 8 (e.g., 1, 2, 3, 4, 5, 6, 7, 8), and the like, such as for example, $-OCH_2CO_2^-M^+$/$-OCH_2CO_2H$ groups and the like and such groups where the terminal O is removed), phosphonate (and corresponding acid) groups

(e.g., $-O(CH_2)_mP(O)(OH)_2^-M^+$ (where M^+ is Na^+, K^+, Ca^{2+}, Mg^{2+}, Zn^{2+}, H_4N^+, Et_3NH^+, Me_4N^+, $(HOCH_2CH_2)_3NH^+$, or a cationic form of ethylenediamine, piperazine, or trishydroxymethyl aminomethane (TRIS))/$-O(CH_2)_mP(O)(OH)_2$, where m is 1 to 8 (e.g., 1, 2 3, 4, 5, 6, 7, 8), and the like, such as for example, $-O(CH_2)_2P(O)(OH)_2$ and the like and such groups where the terminal O is removed), phosphate groups $-OP(O)(OH)_2$, and the like), substituted or unsubstituted aryl groups, substituted or unsubstituted heteroaryl groups, substituted or unsubstituted aliphatic groups, O-alkyl groups (comprising an alkyl group), polyether groups (e.g., polyethylene glycol (PEG) groups), azide groups, -H, substituted or unsubstituted alkyl groups, halogens (e.g., -Br, -F, -I, -Cl), amide groups, cyano groups, substituted or unsubstituted sulfur-containing aliphatic groups (e.g., -S-alkyl and poly thioethers, and the like), nitro groups, amino groups, substituted or unsubstituted nitrogen-containing aliphatic groups (e.g., polyamines, aliphatic groups comprising secondary and/or tertiary amines, and the like), substituted or unsubstituted polyethylene glycol groups, polyether groups, O-aryl groups (e.g., aryloxy groups), ester groups, carbamate groups, imine groups, aldehyde groups, $-SO_3H$ groups, $-SO_3Na$ groups, $-OSO_2F$ groups, $-OSO_2CF_3$ groups, $-OSO_2OR'''$ groups (where R''' are substituted or unsubstituted aryl groups or substituted or unsubstituted alkyl groups), and the like, and combinations thereof; x is 0, 1, 2, or 3; and y is independently at each occurrence 0, 1, 2, 3, or 4, with the proviso that at least one y is 1 and at least one R group is $-OS(O)_2O^-M^+$ (where M^+ is Na^+, K^+, Ca^{2+}, Mg^{2+}, Zn^{2+}, H_4N^+, Et_3NH^+, Me_4N^+, $(HOCH_2CH_2)_3NH^+$, or a cationic form of ethylenediamine, piperazine, or trishydroxymethyl aminomethane (TRIS)) or $-OS(O)_2OH$, or a salt, a partial salt, a hydrate, a polymorph, a stereoisomer, conformational isomer, or a mixture thereof. The R group(s) may be at any position(s) on an aryl group. In the case of an aryl group with multiple R groups, the individual R groups may be at any combination of positions of the aryl group. In various embodiments, the aryl groups may be further substituted with various substituents.

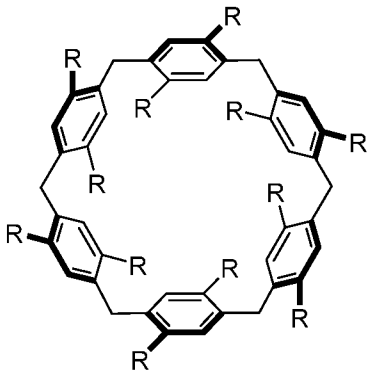
Statement 2. A compound according to Statement 1, where the aryl groups are independently at each occurrence chosen from phenyl groups, fused-ring groups (e.g., naphthyl groups, anthracenyl groups, phenanthrenyl groups, tetracenyl groups, pentacenyl groups, and the like), biaryl groups (e.g., biphenyl groups and the like), terphenyl groups, and the like.

Statement 3. A compound according to Statements 1 or 2, where at least two, at least three, or at least 4, or all of the one or more phenyl group(s) of one or more of the aryl group(s) comprising the cyclic core of the compound have at least 1 or at least 2 R groups independently chosen from $-OS(O)_2O^-M^+$ and $-OS(O)_2OH$.

Statement 4. A compound according to Statement 3, where the compound has the following structure:

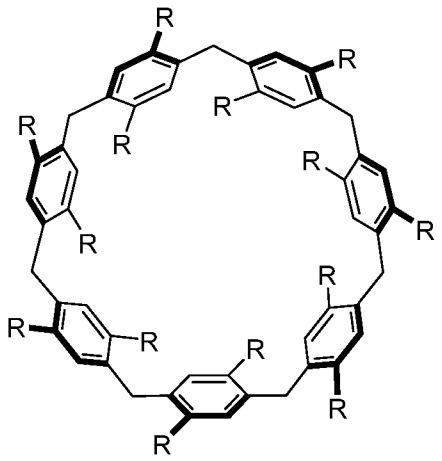


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or



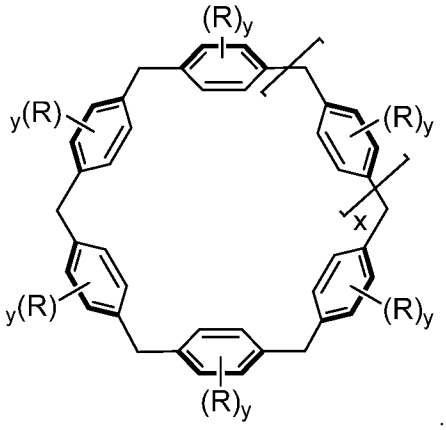
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In various examples, each R is $-OS(O)_2O^-M^+$ and $-OS(O)_2OH$.

Statement 5. A compound according to any one of the preceding Statements, where all of the aryl groups comprise an R group that is independently $-OS(O)_2O^-M^+$ or $-OS(O)_2OH$.

Statement 6. A compound according to any one of Statements 1–3, where at least one aryl group does not comprise an R group that is $-OS(O)_2O^-M^+$ or $-OS(O)_2OH$.

Statement 7. A compound according to Statement 1, where the compound has the following structure:



Statement 8. A compound according to Statement 7, where 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, or 32 of the R groups are independently $-OS(O)_2O^-M^+$ groups or $-OS(O)_2OH$ groups.

Statement 9. A compound according to Statements 7 or 8, where each phenyl group comprising the cyclic core of the compound has at least 1 or at least 2 R groups independently chosen from $-OS(O)_2O^-M^+$ and $-OS(O)_2OH$.

Statement 10. A compound according to any one of Statements 7–9, where at least one phenyl group does not comprise an R group that is $-OS(O)_2O^-M^+$ or $-OS(O)_2OH$.

Statement 11. A composition comprising one of more compound(s) according to any one of the preceding Statements.

Statement 12. A composition according to Statement 11, further comprising a pharmaceutical carrier.

Statement 13. A composition according to Statement 11, where the one or more compound(s) are disposed (e.g., chemically bonded) to at least a portion of a solid substrate.

Statement 14. A composition according to Statement 13, where the solid substrate comprises (or is) silica (such as, for example, silica particles), polymer beads, polymer resins (such as, for example, polystyrene, poly NIPAM, polyacrylic acid), metal nanoparticles (e.g. gold nanoparticles, silver nanoparticles, magnetic nanoparticles), a metal (such as, for example, gold and the like), or the like, or a combination thereof.

Statement 15. A composition according to any one Statements 11–14, where at least a portion (or all) of the one or more compound(s) have a pharmaceutically active agent(s) disposed in the cavity of the one or more compound(s) (e.g., non-covalently complexed to the compound(s)).

Statement 16. A method for sequestering: one or more neuromuscular blocking agent(s) (such as, for example, rocuronium, tubocurarine, atracurium, (cis)atracurium besylate, mivacurium, gallamine, pancuronium, vecuronium, and rapacuronium, and the like); one or more anesthesia agent(s) (such as, for example, *N*-methyl *D*-aspartate (NMDA) receptor antagonists (e.g., ketamine and the like), short-acting anesthetic agents (e.g., etomidate and the like), and the like); one or more pharmaceutical agent(s) (such as, for example, a drug (e.g., anticoagulants, such as, for example, hexadimethrine and the like), drugs of abuse (e.g., methamphetamine, cocaine, fentanyl, carfentanil, PCP, MDMA, heroin, and the like), and the like); one or more pesticide(s) (such as, for example, paraquat, diquat, organochlorines (e.g., DDT, aldrin, and the like), neonicotinoids (e.g., permethrin and the like), organophosphates (e.g., malathion, glyphosate, and the like), pyrethroids, triazines (e.g., atrazine and the like), and the like); one or more dyestuff(s) (such as, for example, methylene blue, nile red, crystal violet, thioflavin T, thiazole orange, proflavin, acridine orange, methylene violet, azure A, neutral red, cyanines, Direct orange 26, disperse dyes (e.g., disperse yellow 3, disperse blue 27, and the like), coumarins, congo red, and the like); one or more malodorous compound(s) (such as, for example, low molecular weight thiols (e.g., C_1–C_4 thiols), low molecular weight amines (e.g., triethylamine, putrescein, cadaverine, and the like), and the like); or one or more chemical warfare agent(s) (such as for example, nitrogen and sulfur mustards (e.g., bis(2-chloroethyl)ethylamine, bis(2-chloroethyl)methylamine, tris(2-chloroethyl)amine, bis(2-chloroethyl) sulfide, bis(2-chloroethylthioethyl) ether, and the like), nerve agents (such as, for example, those from the G, GV, and V series of nerve agents (e.g. tabun, sarin, soman, cyclosarin, 2-(dimethylamino)ethyl *N*,*N*-dimethylphosphoramidofluoridate (GV), novichok agents, VE, VG, VM, VX, and the like), and the like); one or more hallucinogen(s) (e.g., ergolines, lysergic acid diethylamide (LSD), psilocybin, tryptamines, dimethyltryptamine (DMT), phenethylamines, mescaline, ayahuasca, dextromethorphan, and the like); one or more toxin(s) (e.g., dioxins, perfluoralkylsulfonates (PFAS), perfluorooctanoic acid (PFOA), decabromobiphenyl ether (DECA), heavy metals (e.g. mercury), muscarine, tyramine, strychnine, tetrodotoxin, saxitoxin and the like, cholesterol, deoxycholic acid, N-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine, phenylalanine, tyrosine, arginine, histamine); one or more metabolite(s) (e.g., toxic metabolites, such as, for example, N-methyl-4-phenylpyridine, spermine, spermidine, N-nitroso compounds e.g. 4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanone); or the like, or a combination thereof are sequestered by the one or more compound(s) according to any one of Statements 1–10 and/or one or more composition(s) according to any one of Statements 11–14.

Statement 17. A method according to Statement 16, where the neuromuscular blocking agent(s), the anesthesia agent(s), the pharmaceutical agent(s), the pesticide(s), the dyestuff(s), the malodorous compound(s), the chemical warfare agent(s), the hallucinogen(s), the toxin(s), the metabolite(s), or a combination thereof is present in an aqueous sample, in a solid sample (such as, for example, a soil sample), in a gas sample, on a solid surface, or the like.

Statement 18. A method according to Statement 17, where the aqueous sample is a wastewater sample (e.g., a municipal wastewater sample, industrial wastewater sample, and the like), an industrial water sample (e.g., water used to make a commercial product, such as, for example, a reagent, a solvent, or the like), a municipal water sample, or the like.

Statement 19. A method according to any one of Statements 16–18, where a complex is formed from (e.g., one or more interaction(s) between (e.g., one or more non-covalent bond(s) is formed between) the compound(s) and the neuromuscular blocking agent(s), the anesthesia agent(s), the pharmaceutical agent(s), the pesticide(s), the dyestuff(s), the malodorous compound(s), the chemical warfare agent(s), one or more hallucinogen(s), one or more toxin(s), one or more metabolite(s), or a combination thereof.

Statement 20. A method according to any one of Statements 16–19, where the complex is removed from the aqueous sample, the solid sample, the gas sample, or the like.

Statement 21. A method according to Statement 16, where the neuromuscular blocking agent(s), the anesthesia agent(s), the pharmaceutical agent(s), the pesticide(s), the dyestuff(s), the malodorous compound(s), the chemical warfare agent(s), one or more hallucinogen(s), one or more toxin(s), one or more metabolite(s), or a combination thereof is present in and/or on an individual and the contacting comprises administration of the one or more compound(s) and/or one or more composition(s) to the individual.

Statement 22. A method according to Statement 21, where the individual is a human or a non-human mammal.

Statement 23. A method for reversing drug-induced neuromuscular block and/or anesthesia and/or the effects of one or more pharmaceutical agent(s) (e.g., one or more drug(s) of abuse) in an individual comprising administering to an individual in need of reversal of neuromuscular block and/or reversal of anesthesia and/or reversal of the effects of one or more pharmaceutical agent(s) (e.g., one or more drug(s) of abuse) one or more compound(s) according to any one of Statements 1–10 and/or one or more composition(s) according to any one of Statements 11–14.

Statement 24. A method according to Statement 23, where the individual is in need of reversal of drug-induced neuromuscular block.

Statement 25. A method according to Statement 23, where the individual is in need of reversal of anesthesia.

Statement 26. A method according to Statement 23, where the individual is in need of reversal of drug-induced neuromuscular block and anesthesia.

Statement 27. A method according to Statement 23, where the individual is in need of reversal of the effects of one or more pharmaceutical agent(s) are chosen from one or more drug(s) of abuse, one or more pesticide(s), one or more chemical warfare agent(s), one or more nerve agent(s), one or more hallucinogen(s), one or more toxin(s), and/or one or more metabolite(s). In an example, the individual was exposed to the one or more drug(s) of abuse (e.g., carfentanil and the like), one or more pesticide(s), one or more chemical warfare agent(s), one or more nerve agent(s), one or more hallucinogen(s), one or more toxin(s), one or more metabolite(s) in a terrorist attack, and combinations thereof.

Statement 28. A method according to any one of Statements 23–27, wherein the individual in need is a human.

Statement 29. A method according to any one of Statements 23–27, where the individual in need is a non-human mammal.

Statement 30. A method for prophylaxis and/or therapy of a condition in an individual comprising administering to an individual in need of the prophylaxis and/or the therapy one or more compound(s) according to any of Statements 1–10 and one or more pharmaceutical agent(s), where the compound(s) and the pharmaceutical agent(s) are present as complex (or a composition, which may be a pharmaceutical composition, comprising the complex(es)), where subsequent to the administration the therapy and/or the prophylaxis of the condition in the individual occurs.

Statement 31. A method according to Statement 30, where one or more of the pharmaceutical agent(s) has/have a solubility of less than 100 μM in an aqueous solvent.

Statement 32. A compound according to any one of Statements 1–10, a composition according to any one of Statements 11–15, or a method according to any one of Statements 16–31, where M^+ is Na^+, K^+, H_4N^+, Et_3NH^+, Me_4N^+, $(HOCH_2CH_2)_3NH^+$.

Statement 33. A compound according to any one of Statements 1–10, a composition according to any one of Statements 11–15, or a method according to any one of Statements 16–31, where M^+ is Na^+.

[0149] The following examples are presented to illustrate the present disclosure. They are not intended to be limiting in any manner.

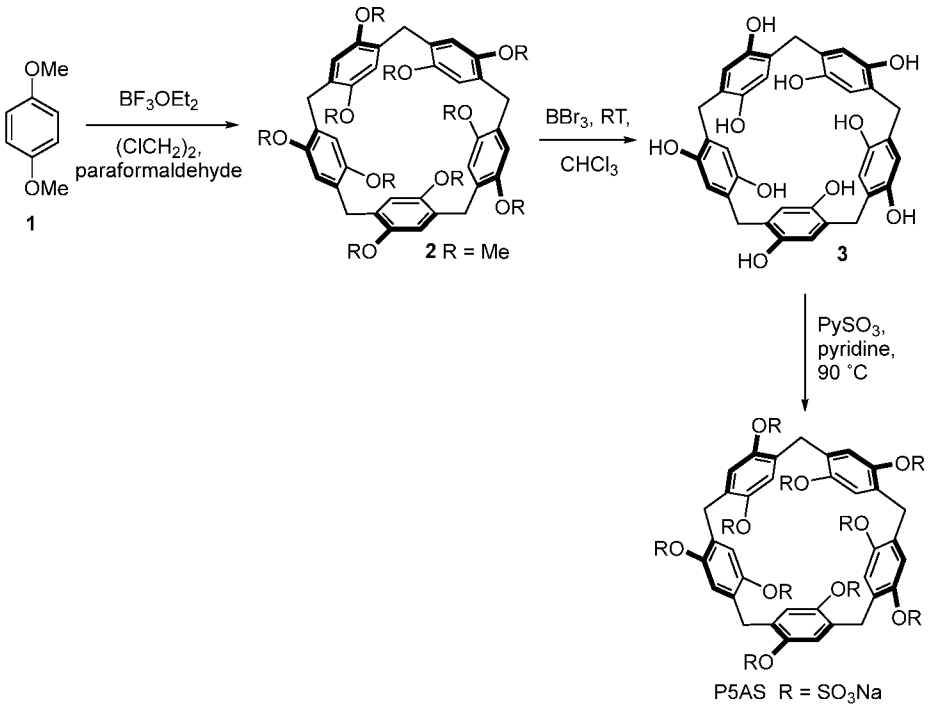
EXAMPLE 1

[0150] This example provides a description of compounds of the present disclosure, methods of making the compounds, characterization of the compounds, and uses of the compositions.

[0151] General experimental details. Starting materials were purchased from commercial suppliers and were used without further purification or were prepared by literature procedures. Melting points were measured on a Meltemp apparatus in open capillary tubes and are uncorrected. IR spectra were recorded on a JASCO FT/IR 4100 spectrometer and are reported in cm^{-1}. ^1H NMR spectra were measured on Bruker instruments operating at 400 or 600 MHz for ^1H and 100 MHz for ^{13}C. Mass spectrometry was performed using a JEOL AccuTOF electrospray instrument (ESI). ITC data was collected on a Malvern Microcal PEAQ-ITC instrument.

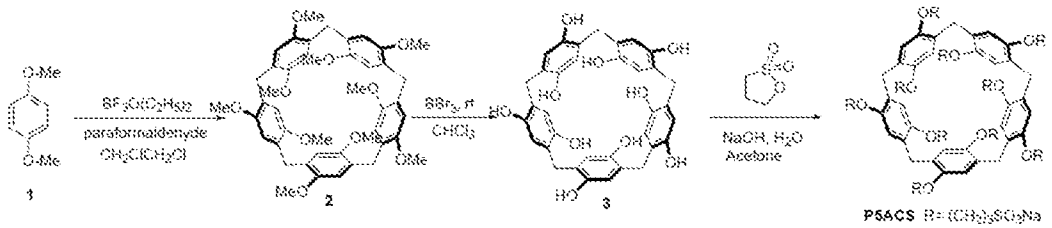
[0152] Synthetic procedures and characterization data.

[0153] Host P[5]AS.



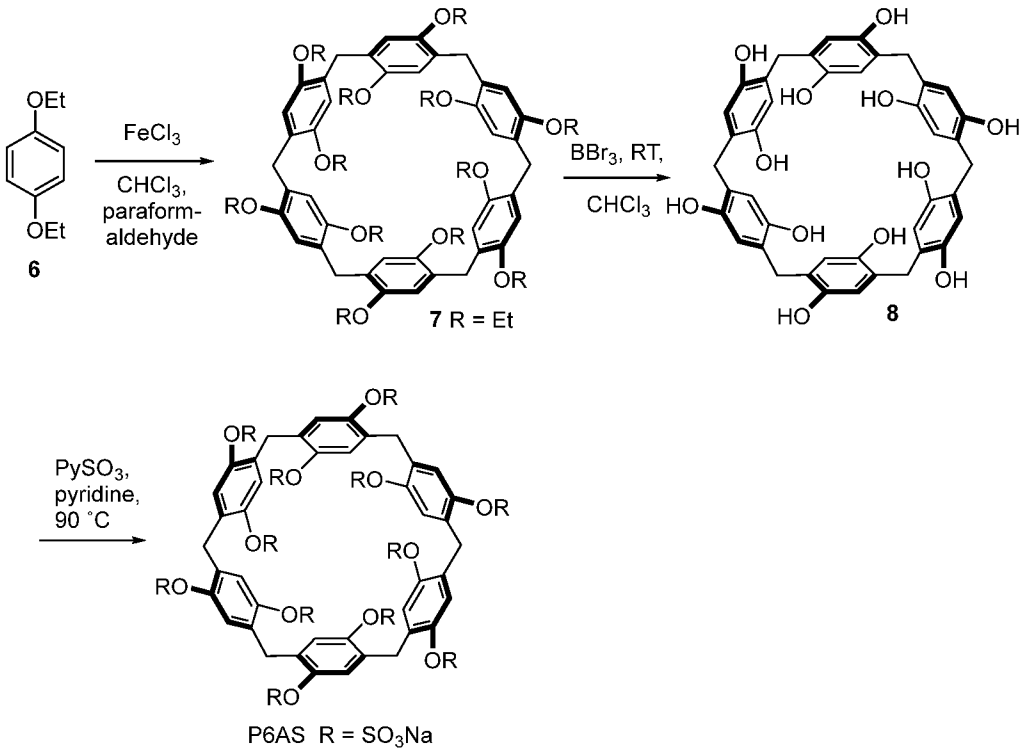
The first two compounds (**2** and **3**) were synthesized by using methods adapted from methods known in the art. The procedure for the last step was: to a mixture of compound **3** (0.200 g, 0.328 mmol) and pyridine sulfur trioxide complex (1.050 g, 6.56 mmol) was added dry pyridine (10 mL). The resulting mixture was stirred at 90 °C under N_2 for 24 hours. The reaction mixture was cooled to RT. The product precipitated out of the solution and was collected by filtration. The solid was slurried in water (5 mL), and the pH was adjusted to 8.4 by slow addition of saturated aqueous $NaHCO_3$. After addition of EtOH (35 mL), the crude product was collected by centrifugation 7000 rpm × 7 min. The precipitate was suspended in ethanol (20 mL × 2), sonicated for 30 minutes, and solid collected by centrifugation. The crude solid was redissolved in minimum amount of water (2 ml) and purified by size exclusion chromatography using Sephadex® G25 resin (30mm x 200mm) and eluted by water. Pure product was collected as the front fractions. After drying under high vacuum, the compound P[5]AS was obtained as a white solid (0.374 g, 0.229 mmol, 70 % yield). M.p. > 310 °C (decomposed). IR (ATR, cm^{-1}): 3490w, 1630m, 1497m, 1399m, 1234s, 1116s, 1042s, 995m, 941m, 858m, 806m. ^1H NMR (600 MHz, D_2O): 7.31 (s, 10H), 4.00 (s, 10H). ^{13}C NMR (150 MHz, D_2O, EtOH as internal reference): 147.4, 134.1, 125.6, 30.8. MS (ESI): m/z 791.78179 ($[M - 2Na]^{2-}$), calculated 791.79597.

[0154] Host P[5]ACS.



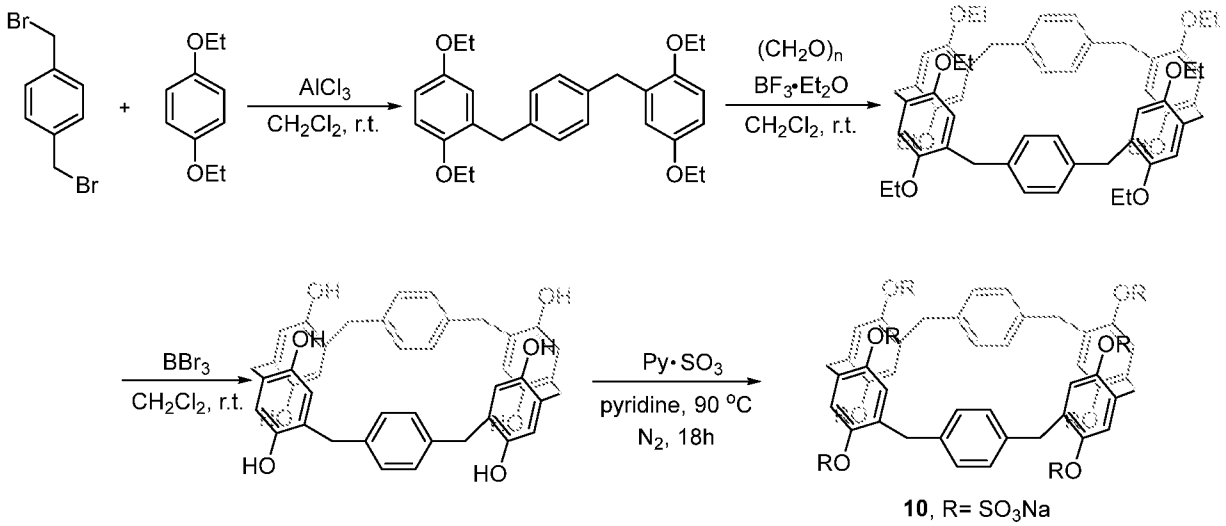
A solution of P[5]A (0.200 g, 0.28 mmol) in NaOH (10 wt%, 2 mL) was treated dropwise with a solution of propane sultone (0.687 g, 5.63 mmol) in acetone (4 mL). This solution was stirred at RT for 5 days (d) and then EtOH (25 mL) was added to the mixture to yield the crude product as a precipitate. The precipitate was obtained by filtration, the solid was dissolved in H_2O (0.5 mL), and then re-precipitated by the addition of EtOH (5 mL) to yield P[5]ACS as a light yellow solid (45 mg, 0.022 mmol, 8 %). M.p. > 300 °C (decomposed). IR (ATR, cm^{-1}): 3452w, 2936w, 1725m, 1625m, 1479m, 1471m, 1406m, 1181s, 1035s, 951w, 798m, 756m. ^1H NMR (400 MHz, D_2O): 6.76 (s, 10H), 3.90 (m, 10H), 3.86 (s, 10H), 3.68 (m, 10H), 3.05 (m, 20H), 2.08 (m, 20H). ^{13}C NMR (150 MHz, D_2O, EtOH as internal reference): δ 150.9, 129.8, 116.7, 68.5, 49.1, 31.1, 25.5. HR-MS (ESI): m/z 1002.03215 ($[M - 2Na]^{2-}$), calculated 1002.03072.

[0155] Host P[6]AS.



The first two compounds (**7** and **8**) were synthesized by using methods adapted those known in the art. The procedure for the last step was: to a mixture of compound **8** (0.200 g, 0.27 mmol) and pyridine sulfur trioxide complex (1.090 g, 6.83 mmol) was added dry pyridine (10 mL). The resulting mixture was stirred at 70 °C under N_2 for 24 hours. The reaction mixture was cooled to RT. The product precipitated out of the solution and was collected by filtration. The solid was slurried in water (5 mL), and the pH was adjusted to 8.4 by slow addition of saturated aqueous $NaHCO_3$. After addition of EtOH (35 mL), the crude product was collected by centrifugation 7000 rpm × 7 min. The precipitate was suspended in ethanol (20 mL × 2), sonicated for 30 minutes, and solid collected by centrifugation. The crude solid was redissolved in minimum amount of water (2 ml) and purified by size exclusion chromatography using Sephadex® G25 resin (30mm x 200mm) and eluted by water. Pure product was collected as the front fractions. After drying under high vacuum, the compound P[6]AS was obtained as a white solid (0.352 g, 0.18 mmol, 66 % yield). M.p. > 290 °C (decomposed). IR (ATR, cm^{-1}): 3509w, 1712m, 1630m, 1498m, 1364m, 1237m, 1113s, 1045s, 995m, 942m, 861m, 813m. ^1H NMR (600 MHz, D_2O): 7.35 (s, 12H), 4.11 (s, 12H). ^{13}C NMR (150 MHz, D_2O and CD_3OD 10:1): δ 148.1, 133.6, 125.6, 31.5. MS (ESI): m/z 954.7593 ($[M-2Na]^{2-}$), calculated 954.7537.

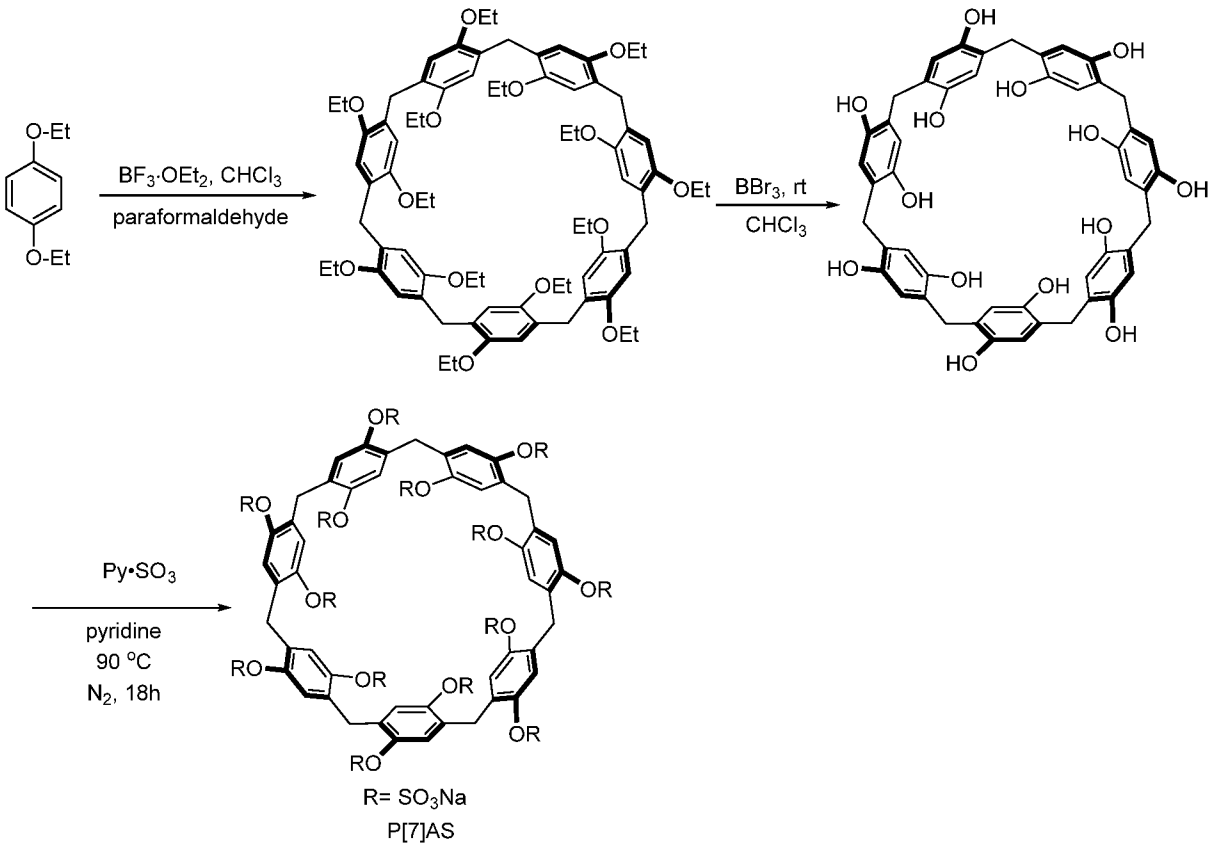
[0156] Host P[6]A8S.



10, R= SO_3Na

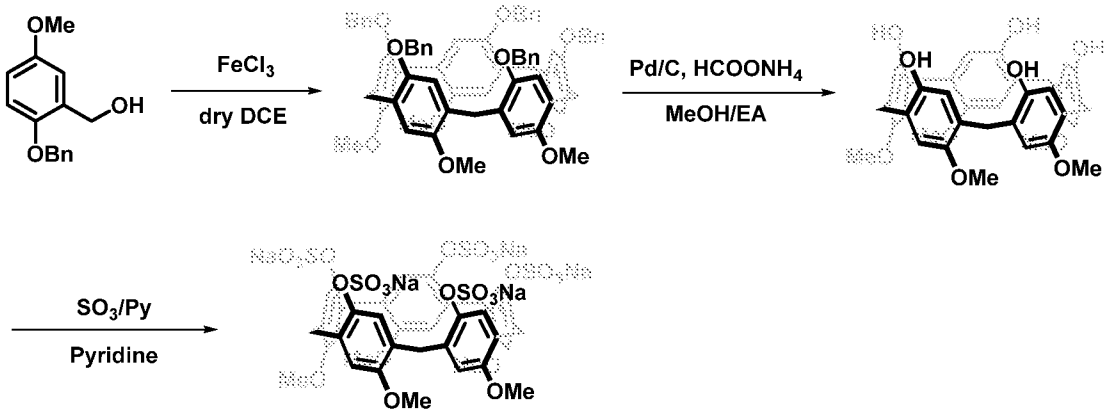
The first three compounds were synthesized by using methods adapted from those known in the art. The procedure for the last step was: to a mixture of compound octahydroxy pillar[6]arene (0.100 g, 0.15 mmol) and pyridine sulfur trioxide complex (0.479 g, 3 mmol) was added dry pyridine (5 mL). The resulting mixture was stirred at 70 °C under N_2 for 24 hours. The reaction mixture was cooled to RT. The product precipitated out of the solution and was collected by filtration. The solid was slurried in water (4 mL), and the pH was adjusted to 8.4 by slow addition of saturated aqueous Na_2CO_3. After addition of EtOH (10 mL), the crude product was collected by centrifugation 7000 rpm × 7 min. The precipitate was suspended in ethanol (10 mL × 2), sonicated for 30 minutes, and solid collected by centrifugation. The crude solid was redissolved in minimum amount of water (0.5 ml) and purified by size exclusion chromatography using Sephadex® G25 resin (30mm x 200mm) and eluted by water. Pure product was collected as the front fractions. After drying under high vacuum, the compound P[6]A8S (**10**) was obtained as a white solid (0.075 g, 0.051 mmol, 33 % yield). M.p. > 285 °C (decomposed). IR (ATR, cm^{-1}): 3491w, 1630m, 1440s, 1234s, 1078m, 1043s, 941m, 878m, 800m, 667m. ^1H NMR (600 MHz, D_2O): 7.39 (s, 4H), 7.25 (s, 4H), 7.04 (s, 8H), 4.07 (s, 4H), 3.99 (s, 8H). ^{13}C NMR (150 MHz, D_2O, EtOH as internal reference): δ 147.7, 147.6, 138.7, 134.2, 133.2, 129.2, 125.3, 125.1, 35.7, 31.1. MS (ESI): m/z 718.88334 ($[M-2Na]^{2-}$), calculated 718.88632.

[0157] Host P[7]AS.



The first two compounds were synthesized by using methods adapted from those known in the art. The procedure for the last step was: to a mixture of compound $(HO)_{14}$ pillar[7]arene (0.020 g, 0.023 mmol) and pyridine sulfur trioxide complex (0.375 g, 2.34 mmol) was added dry pyridine (3 mL). The resulting mixture was stirred at 70 °C under N_2 for 24 hours. The reaction mixture was cooled to RT. The product precipitated out of the solution and was collected by filtration. The solid was slurried in water (1 mL), and the pH was adjusted to 8.4 by slow addition of saturated aqueous Na_2CO_3. After addition of EtOH (10 mL), the crude product was collected by centrifugation 7000 rpm × 7 min. The precipitate was suspended in ethanol (10 mL × 2), sonicated for 30 minutes, and solid collected by centrifugation. The crude solid was redissolved in minimum amount of water (0.5 ml) and purified by size exclusion chromatography using Sephadex® G25 resin (30mm x 200mm) and eluted by water. Pure product was collected as the front fractions. After drying under high vacuum, the compound P[7]AS was obtained as a white solid (0.025 g, 0.011 mmol, 46 % yield). M.p. > 290 °C (decomposed). IR (ATR, cm^{-1}): 3494w, 1624m, 1444s, 1244m, 1102s, 1049s, 995m, 875m, 807m, 614s. ^1H NMR (600 MHz, D_2O): 7.29 (s, 14H), 4.14 (s, 14H). ^{13}C NMR (150 MHz, D_2O, Dioxane as external reference): δ 147.6, 132.8, 124.7, 30.8. MS (ESI): m/z 547.36023 ($[M-4Na]^{4-}$), calculated 547.36080.

[0158] Rim-P[5]AS.



Rim-P5AS

The starting material 2-(Benzyloxy)-5-methoxybenzyl alcohol was synthesized based on methods known in the art. The *penta*-hydroxy pillar[5]arene compound was synthesized by using the methods known in the art. To a mixture of penta-hydroxy pillar[5]arene (0.200 g, 0.328 mmol) and pyridine sulfur trioxide complex (1.050 g, 6.56 mmol) was added dry pyridine (10 mL). The resulting mixture was stirred at 70 °C under N_2 for 24 hours. The reaction mixture was cooled to RT. The product precipitated out of the solution and was collected by filtration. The solid was slurried in water (5 mL), and the pH was adjusted to 9 by slow addition of saturated aqueous $NaHCO_3$. Addition of EtOH (EtOH/H_2O v/v = 2:1) gave a precipitate which was removed by centrifugation (7000 rpm × 10 min). The filtrate was collected as the crude product and was redissolved in a minimum amount of water (2 mL) and purified by size exclusion chromatography using Sephadex® G25 resin (5 cm × 50 cm) with water as eluent. The front fractions eluting from the column contain pure product. After drying under high vacuum, Rim-P[5]AS was obtained as a white solid (0.374 g, 0.229 mmol, 67 % yield, content: ~92%, determined by using sodium 2-bromoethanesulfonate as ^{1}H NMR internal standard). M.p. > 300 °C (decomposed). ^{1}H NMR (400 MHz, D_2O): 7.21 (s, 5H), 6.56 (s, 5H), 3.90 (s, 10H), 3.24 (s, 15H). ^{13}C NMR (150 MHz, D_2O, EtOH as internal reference): 155.3, 143.2, 134.5, 129.6, 124.7, 114.9, 56.7, 30.6.

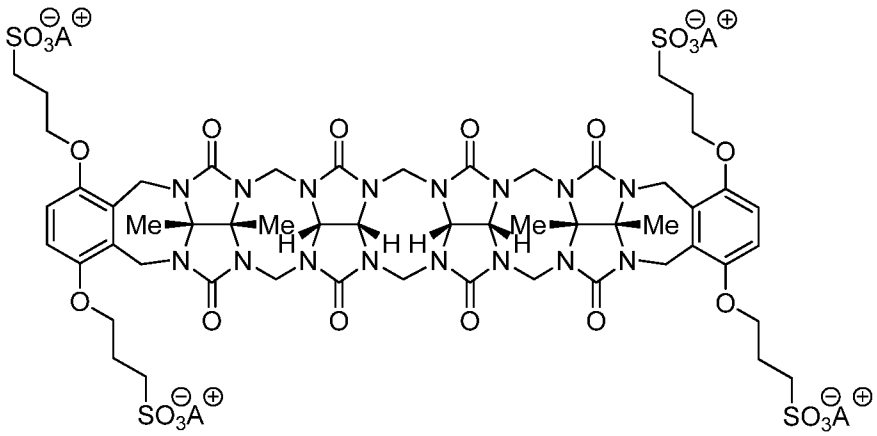
[0159] Solubility determination.

[0160] Determination of the solubility of P[5]AS in water. Compound P[5]AS was added in excess to 0.5 mL deuterium oxide. This suspension was magnetically stirred at room temperature overnight and then centrifuged (4500 rpm) twice for 10 min each time. Supernatant (50 μL) and sodium 3-(trimethylsilyl)propionate-2,2,3,3-d_4 (TMSP) (10 mM, 50 μL in D_2O) were added into 0.4 mL deuterium solvent. The concentration of P[5]AS was measured with ^{1}H NMR and calculated using sodium 3-(trimethylsilyl)propionate-2,2,3,3-d_4 (TMSP) as internal reference.

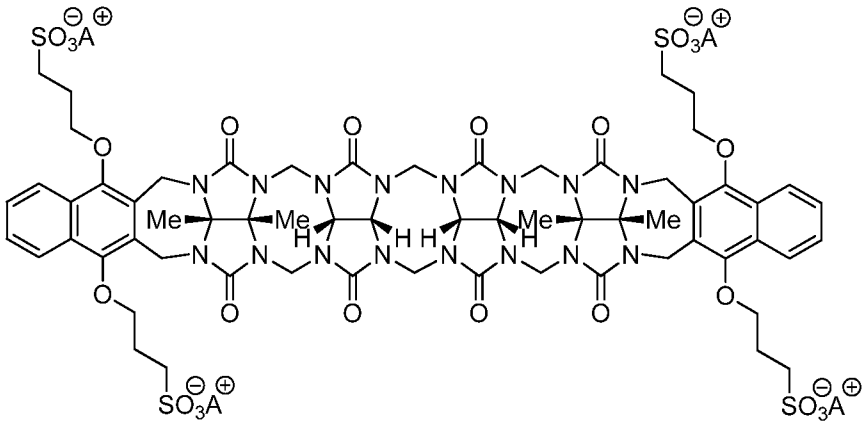
[0161] Determination of the solubility of P[6]AS in water. Compound P[6]AS was added in excess to 0.5 mL deuterium oxide. This suspension was magnetically stirred at room temperature overnight and then centrifuged (4500 rpm) twice for 10 min each time. Supernatant (50 μL) and sodium 3-(trimethylsilyl)propionate-2,2,3,3-d_4 (TMSP) (10 mM, 50 μL in D_2O) were added into 0.4 mL deuterium solvent. The concentration of P[6]AS was measured with ^1H NMR and calculated using sodium 3-(trimethylsilyl)propionate-2,2,3,3-d_4 (TMSP) as internal reference.

[0162] Determination of K_a between various hosts and cationic guests or drugs of abuse or neuromuscular blocking agents using Isothermal Titration Calorimetry (ITC). All ITC experiments were conducted in the 200 μL working volume of the sample cell of the PEAQ ITC instrument. We used an injection syringe of 40 μL capacity. In each case, the host and guest solutions were prepared in a 20 mM NaH_2PO_4 buffer (pH 7.4). The sample cell was filled to capacity (200 μL) with the host solution and the guest solution was titrated in (first injection = 0.4 μL, subsequent 18 injections = 2 μL). The binding data was fitted using the 1:1 binding model in MicroCal PEAQ-ITC analysis software. In cases where K_a was too large to determine by direct titration, competition ITC titrations were performed where a competitive guest of known K_a and ΔH was included in the ITC cell along with the host which was then titrated with the guest whose K_a was to be determined.

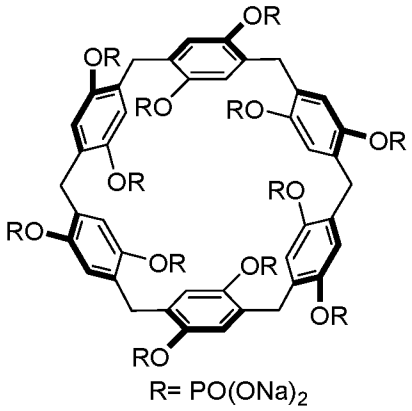
[0163] WP5, WP6, and the following were compounds used in comparative examples:



(Motor 1, also referred to as M1 or Calabadion 1)



(Motor 2, also referred to as M2 or Calabadion 2)



(P[6]AP)

[0164] ^{1}H NMR spectra of selected drugs with hosts. Figure 8 shows an example of a ^{1}H NMR spectrum of a drug (methamphetamine) with a host (P[6]AS).

[0165] ^{1}H NMR spectra of competition binding. Figure 9 shows that P[6]AS binds rocuronium stronger a previously known compound (Motor 2, which is also referred to as Calabadion 2).

[0166] The crystal structures P[6]AS was also determined. Figures 10 and 13 show a crystal structure of P[6]AS.

[0167] Table 1. Crystal data and structure refinement for P[6]AS.

Empirical formula of crystal $C_{45.44}H_{24}Na_{12}O_{65.65}S_{12}$

Formula weight	2280.86
Temperature/K	150(2)
Crystal system	trigonal
Space group	P-3c1
a/Å	15.112(2)
b/Å	15.112(2)
c/Å	20.365(3)

α/°	90
β/°	90
γ/°	120
Volume/Å3	4027.8(13)
Z	2
ρ_{calc} g/cm^3	1.881
μ/mm^{-1}	0.519
F(000)	2292.0
Crystal size/mm^3	0.28 × 0.14 × 0.08
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4 to 53.178
Index ranges	-18 ≤ h ≤ 19, -19 ≤ k ≤ 16, -25 ≤ l ≤ 25
Reflections collected	23483
Independent reflections	2810 [R_{int} = 0.0602, R_{sigma} = 0.0410]
Data/restraints/parameters	2810/387/336
Goodness-of-fit on F^2	1.000
Final R indexes [I>= 2σ (I)]	R_1 = 0.0448, wR_2 = 0.0988
Final R indexes [all data]	R_1 = 0.0646, wR_2 = 0.1097
Largest diff. peak/hole / e Å^{-3} 0.53/-0.53	

[0168] Table 2. Fractional Atomic Coordinates and Equivalent Isotropic Displacement Parameters (Å2) for P[6]AS. Ueq is defined as 1/3 of the trace of the orthogonalised UIJ tensor.

Atom	***X***	***y***	***z***	**U(eq)**
Na1	0.666667	0.333333	0.50418(10)	0.0407(5)
Na2	0.89555(10)	0.32173(10)	0.50394(7)	0.0465(3)
Na3	0.95059(17)	0.78890(17)	0.44988(12)	0.0502(5)
O1	0.77103(19)	0.4997(2)	0.45146(12)	0.0432(7)
O2	0.9062(3)	0.4595(2)	0.44087(14)	0.0568(8)
O3	0.9417(2)	0.6314(2)	0.42251(15)	0.0515(8)
S1	0.86584(19)	0.52390(18)	0.42005(7)	0.0391(2)
O4	0.83954(17)	0.49388(15)	0.34368(11)	0.0415(5)
O1A	0.9727(11)	0.6049(14)	0.4127(10)	0.046(3)
O2A	0.7988(14)	0.5652(16)	0.4356(9)	0.043(3)
O3A	0.8442(18)	0.4318(13)	0.4474(8)	0.046(3)
S1A	0.8672(13)	0.5282(13)	0.4191(5)	0.0391(2)
O4A	0.83954(17)	0.49388(15)	0.34368(11)	0.0415(5)
C1	0.8281(2)	0.5602(2)	0.30005(15)	0.0357(7)

C2	0.9039(2)	0.6110(2)	0.25344(15)	0.0326(6)
C3	1	0.6035(3)	0.25	0.0364(10)
C4	0.8884(2)	0.6688(2)	0.20704(15)	0.0329(6)
C5	0.7995(2)	0.6737(2)	0.20759(14)	0.0322(6)
C6	0.7230(2)	0.6236(2)	0.25389(15)	0.0337(7)
C7	0.6223(3)	0.6223(3)	0.25	0.0396(10)
C8	0.7392(2)	0.5664(2)	0.30113(16)	0.0369(7)
O5	0.78551(15)	0.73281(15)	0.15926(9)	0.0340(5)
S2	0.7588(5)	0.6826(6)	0.0870(2)	0.0496(5)
O6	0.6820(8)	0.5770(7)	0.0974(6)	0.074(2)
O7	0.8545(7)	0.7000(10)	0.0598(5)	0.0548(19)
O8	0.7201(10)	0.7419(12)	0.0548(4)	0.0543(18)
O5A	0.78551(15)	0.73281(15)	0.15926(9)	0.0340(5)
S2A	0.7606(7)	0.6927(7)	0.0846(3)	0.0496(5)
O6A	0.6654(8)	0.5974(9)	0.0871(6)	0.057(2)
O7A	0.8428(11)	0.6777(14)	0.0624(8)	0.058(2)
O8A	0.7537(15)	0.7752(11)	0.0543(5)	0.051(2)
O1B	0.8110(4)	0.3730(3)	0.5780(2)	0.0576(11)
C2B	0.7898(15)	0.3560(15)	0.6421(10)	0.090(7)
O3B	0.7065(9)	0.3682(11)	0.6953(5)	0.089(5)
C4B	0.838(3)	0.408(3)	0.580(2)	0.059(12)
O1C	0.9547(3)	0.8586(3)	0.3435(2)	0.0871(19)
O2C	0.9346(8)	0.7926(8)	0.3985(7)	0.086(4)
O3C	0.9615(11)	0.8970(11)	0.2808(7)	0.113(5)
O1D	0.0298(8)	0.0909(7)	0.4758(5)	0.083(4)
C2D	0	0	0.4829(5)	0.025(4)

[0169] Table 3. Anisotropic Displacement Parameters (Å2) for P[6]AS. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	**U11**	**U22**	**U33**	**U23**	**U13**	**U12**
Na1	0.0435(7)	0.0435(7)	0.0351(11)	0	0	0.0218(4)
Na2	0.0409(7)	0.0401(7)	0.0596(8)	0.0049(6)	-0.0078(6)	0.0211(6)
Na3	0.0538(13)	0.0572(13)	0.0523(13)	-0.0104(10)	-0.0086(10)	0.0374(11)
O1	0.0385(14)	0.0419(16)	0.0459(14)	0.0007(12)	0.0090(11)	0.0177(12)
O2	0.065(2)	0.0591(18)	0.0637(17)	0.0257(14)	0.0195(15)	0.0440(17)
O3	0.0451(16)	0.0385(15)	0.0556(17)	0.0123(12)	0.0006(13)	0.0094(12)
S1	0.0396(4)	0.0315(4)	0.0474(4)	0.0098(3)	0.0102(3)	0.0188(4)
O4	0.0561(13)	0.0269(10)	0.0459(11)	0.0104(9)	0.0147(10)	0.0241(10)
O1A	0.041(4)	0.042(5)	0.053(5)	0.016(5)	0.008(4)	0.021(4)
O2A	0.041(4)	0.042(5)	0.048(5)	0.003(4)	0.007(4)	0.021(4)
O3A	0.049(5)	0.037(4)	0.050(5)	0.019(4)	0.011(5)	0.019(4)
S1A	0.0396(4)	0.0315(4)	0.0474(4)	0.0098(3)	0.0102(3)	0.0188(4)
O4A	0.0561(13)	0.0269(10)	0.0459(11)	0.0104(9)	0.0147(10)	0.0241(10)
C1	0.0430(18)	0.0197(14)	0.0427(17)	0.0044(12)	0.0098(14)	0.0144(13)

C2	0.0351(16)	0.0177(13)	0.0433(17)	0.0006(11)	0.0061(13)	0.0118(12)
C3	0.044(3)	0.0253(15)	0.047(3)	0.0058(10)	0.012(2)	0.0218(13)
C4	0.0309(16)	0.0218(14)	0.0425(16)	0.0040(12)	0.0092(13)	0.0105(12)
C5	0.0335(16)	0.0188(13)	0.0410(16)	-0.0005(12)	0.0035(12)	0.0106(12)
C6	0.0275(15)	0.0183(13)	0.0480(17)	-0.0027(12)	0.0048(13)	0.0061(12)
C7	0.0267(15)	0.0267(15)	0.052(3)	-0.0043(11)	0.0043(11)	0.0033(18)
C8	0.0362(17)	0.0192(14)	0.0477(18)	0.0038(13)	0.0140(14)	0.0082(13)
O5	0.0356(11)	0.0339(11)	0.0360(11)	-0.0007(8)	0.0010(8)	0.0199(9)
S2	0.0455(5)	0.0650(12)	0.0464(6)	-0.0178(6)	-0.0104(4)	0.0336(7)
O6	0.057(4)	0.069(4)	0.093(5)	-0.031(3)	-0.040(3)	0.030(3)
O7	0.051(3)	0.076(4)	0.049(3)	-0.018(3)	-0.006(3)	0.041(3)
O8	0.042(4)	0.085(5)	0.045(2)	-0.005(3)	-0.008(2)	0.038(3)
O5A	0.0356(11)	0.0339(11)	0.0360(11)	-0.0007(8)	0.0010(8)	0.0199(9)
S2A	0.0455(5)	0.0650(12)	0.0464(6)	-0.0178(6)	-0.0104(4)	0.0336(7)
O6A	0.048(4)	0.062(4)	0.066(4)	-0.022(3)	-0.025(3)	0.032(3)
O7A	0.061(4)	0.074(5)	0.053(4)	-0.030(4)	-0.006(3)	0.045(3)
O8A	0.057(5)	0.060(4)	0.042(3)	-0.005(3)	-0.011(4)	0.033(4)
O1B	0.057(3)	0.050(3)	0.0423(19)	0.0027(19)	-0.0070(18)	0.009(2)
C2B	0.091(12)	0.094(13)	0.091(9)	0.012(9)	-0.009(9)	0.050(10)
O3B	0.087(9)	0.093(10)	0.094(6)	-0.018(6)	-0.028(5)	0.048(6)
C4B	0.056(15)	0.061(15)	0.050(14)	0.000(9)	-0.002(9)	0.022(10)
O1C	0.068(3)	0.099(3)	0.115(4)	0.028(3)	0.014(2)	0.057(2)
O2C	0.087(7)	0.072(6)	0.114(8)	0.008(5)	0.014(6)	0.052(5)
O3C	0.120(9)	0.107(8)	0.121(8)	0.015(6)	0.017(6)	0.064(7)
O1D	0.093(6)	0.057(6)	0.107(7)	-0.007(4)	-0.019(5)	0.043(5)
C2D	0.018(4)	0.018(4)	0.040(8)	0	0	0.0088(19)

[0170] Table 4. Bond Lengths for P[6]AS.

Atom	**Atom**	**Length/Å**	**Atom**	**Atom**	**Length/Å**
Na1	O11	2.449(3)	O3	S1	1.447(3)
Na1	O1	2.449(3)	S1	O4	1.613(3)
Na1	O12	2.449(3)	O4	C1	1.413(4)
Na1	O1B1	2.464(5)	C1	C2	1.387(4)
Na1	O1B	2.464(5)	C1	C8	1.393(4)
Na1	O1B2	2.464(5)	C2	C4	1.384(4)
Na2	O83	2.262(10)	C2	C3	1.514(4)
Na2	O1B	2.345(6)	C4	C5	1.381(4)
Na2	O2A1	2.347(14)	C5	C6	1.387(4)
Na2	O2	2.382(3)	C5	O5	1.414(3)
Na2	O11	2.435(3)	C6	C8	1.394(4)
Na2	O74	2.548(10)	C6	C7	1.514(4)
Na2	O35	2.655(3)	O5	S2	1.611(5)
Na3	O1D6	2.268(9)	S2	O6	1.445(6)
Na3	O3	2.383(4)	S2	O7	1.446(5)
Na3	O1C	2.395(5)	S2	O8	1.448(5)

Na3	O1D1	2.450(11)	O1B	C2B	1.34(2)
Na3	O77	2.632(10)	O1C	O3C	1.387(13)
Na3	O88	2.645(10)	O1C	O2C	1.426(13)
Na3	O78	2.685(13)	O3C	O3C7	1.61(3)
Na3	O1D9	2.689(11)	O1D	C2D	1.221(9)
Na3	O810	2.786(15)	O1D	C2D11	1.476(10)
O1	S1	1.439(3)	O1D	O1D12	1.563(14)
O2	S1	1.447(4)	O1D	O1D13	1.563(14)

[1]1+Y-X,1-X,+Z; [2]1-Y,+X-Y,+Z; [3]1-Y+X,1-Y,1/2-Z; [4]+X,+X-Y,1/2+Z; [5]2-X,1-Y,1-Z; [6]1-X,1-Y,1-Z; [7]2-X,1-X+Y,1/2-Z; [8]1+Y-X,+Y,1/2+Z; [9]1-Y,1+X-Y,+Z; [10]+Y,+X,1/2-Z; [11]-X,-Y,1-Z; [12]-Y+X,+X,1-Z; [13]+Y,-X+Y,1-Z

[0171] Table 5. Bond Angles for P[6]AS.

Atom	**Atom**	**Atom**	**Angle/°**	**Atom**	**Atom**	**Atom**	**Angle/°**
O11	Na1	O1	102.22(9)	O1	S1	O2	113.6(2)
O11	Na1	O12	102.22(9)	O3	S1	O2	112.4(3)
O1	Na1	O12	102.22(9)	O1	S1	O4	106.44(18)
O11	Na1	O1B1	88.89(12)	O3	S1	O4	107.14(19)
O1	Na1	O1B1	167.25(14)	O2	S1	O4	102.75(19)
O12	Na1	O1B1	81.19(14)	C1	O4	S1	120.5(2)
O11	Na1	O1B	81.19(13)	C2	C1	C8	122.0(3)
O1	Na1	O1B	88.88(12)	C2	C1	O4	117.6(3)
O12	Na1	O1B	167.25(14)	C8	C1	O4	120.2(3)
O1B1	Na1	O1B	86.63(18)	C4	C2	C1	117.6(3)
O11	Na1	O1B2	167.25(14)	C4	C2	C3	119.2(2)
O1	Na1	O1B2	81.19(14)	C1	C2	C3	123.2(3)
O12	Na1	O1B2	88.88(12)	C2	C3	C27	112.6(3)
O1B1	Na1	O1B2	86.63(18)	C5	C4	C2	120.3(3)
O1B	Na1	O1B2	86.63(18)	C4	C5	C6	122.9(3)
O83	Na2	O1B	171.3(3)	C4	C5	O5	119.0(3)
O83	Na2	O2	106.0(3)	C6	C5	O5	118.1(3)
O1B	Na2	O2	82.44(14)	C5	C6	C8	116.8(3)
O83	Na2	O11	99.0(3)	C5	C6	C7	122.0(3)
O1B	Na2	O11	83.93(14)	C8	C6	C7	121.0(2)
O2	Na2	O11	82.22(11)	C6	C7	C610	118.8(3)
O83	Na2	O74	74.2(3)	C1	C8	C6	120.4(3)
O1B	Na2	O74	97.9(3)	C5	O5	S2	114.8(4)
O2	Na2	O74	169.6(3)	O6	S2	O7	115.8(6)
O11	Na2	O74	87.5(3)	O6	S2	O8	113.6(5)
O3A	Na2	O74	151.8(6)	O7	S2	O8	113.0(6)
C4B	Na2	O74	105.8(11)	O6	S2	O5	105.1(5)
O83	Na2	O35	77.1(2)	O7	S2	O5	105.8(5)
O1B	Na2	O35	97.67(15)	O8	S2	O5	101.9(4)
O2	Na2	O35	114.95(12)	S2	O7	Na211	129.1(8)

O11	Na2	O35	162.82(10)	S2	O7	Na37	142.5(8)
O74	Na2	O35	75.3(3)	Na211	O7	Na37	88.1(2)
O2C	Na3	O1D6	123.2(6)	S2	O7	Na312	94.4(6)
O2C	Na3	O3	85.6(6)	Na211	O7	Na312	96.9(3)
O1D6	Na3	O3	151.2(3)	Na37	O7	Na312	83.4(3)
O1D6	Na3	O1C	106.7(3)	S2	O8	Na213	126.0(9)
O3	Na3	O1C	101.75(15)	S2	O8	Na312	96.0(4)
O2C	Na3	O1D1	101.2(6)	Na213	O8	Na312	94.1(3)
O3	Na3	O1D1	146.6(2)	S2	O8	Na310	132.7(7)
O1C	Na3	O1D1	81.4(3)	Na213	O8	Na310	101.3(3)
O2C	Na3	O77	98.8(6)	Na312	O8	Na310	81.3(4)
O1D6	Na3	O77	96.5(4)	C2B	O1B	Na2	133.0(9)
O3	Na3	O77	78.5(3)	C2B	O1B	Na1	116.8(9)
O1C	Na3	O77	90.6(2)	Na2	O1B	Na1	95.11(17)
O1D1	Na3	O77	68.1(3)	Na2	C4B	Na1	86.4(14)
O2C	Na3	O88	158.0(6)	O2C	O1C	Na3	15.0(5)
O1D6	Na3	O88	76.6(4)	Na3	O2C	O1C	145.1(10)
O3	Na3	O88	75.4(3)	O1C	O3C	O3C7	139.3(13)
O1C	Na3	O88	157.5(2)	C2D	O1D	C2D14	28.0(8)
O1D1	Na3	O88	89.2(4)	C2D	O1D	O1D15	62.6(4)
O2C	Na3	O78	137.9(6)	C2D14	O1D	O1D15	47.3(3)
O1D6	Na3	O78	69.6(4)	C2D	O1D	O1D16	62.6(4)
O3	Na3	O78	88.4(3)	C2D14	O1D	O1D16	47.3(3)
O1C	Na3	O78	148.5(2)	O1D15	O1D	O1D16	84.4(8)
O1D1	Na3	O78	106.4(3)	C2D	O1D	Na36	130.5(8)
O77	Na3	O78	120.7(2)	C2D14	O1D	Na36	102.8(6)
O2C	Na3	O1D9	89.7(6)	O1D15	O1D	Na36	77.1(7)
O3	Na3	O1D9	165.4(2)	O1D16	O1D	Na36	87.1(7)
O1C	Na3	O1D9	76.9(2)	C2D	O1D	Na32	102.7(6)
O77	Na3	O1D9	115.8(3)	C2D14	O1D	Na32	106.5(5)
O88	Na3	O1D9	111.4(4)	O1D15	O1D	Na32	148.7(7)
O78	Na3	O1D9	86.0(3)	O1D16	O1D	Na32	64.5(5)
S1	O1	Na22	143.8(2)	Na36	O1D	Na32	97.1(4)
S1	O1	Na1	120.26(18)	C2D	O1D	Na317	90.7(5)
Na22	O1	Na1	93.24(9)	C2D14	O1D	Na317	95.9(5)
S1	O2	Na2	151.5(2)	O1D15	O1D	Na317	57.4(4)
S1	O3	Na3	138.3(2)	O1D16	O1D	Na317	141.1(6)
S1	O3	Na25	115.3(2)	Na36	O1D	Na317	90.7(3)
Na3	O3	Na25	91.12(11)	Na32	O1D	Na317	153.9(4)
O1	S1	O3	113.6(2)				

[1]1+Y-X,1-X,+Z; [2]1-Y,+X-Y,+Z; [3]1-Y+X,1-Y,1/2-Z; [4]+X,+X-Y,1/2+Z; [5]2-X,1-Y,1-Z; [6]1-X,1-Y,1-Z; [7]2-X,1-X+Y,1/2-Z; [8]1+Y-X,+Y,1/2+Z; [9]1-Y,1+X-Y,+Z; [10]+Y,+X,1/2-Z; [11]+X,+X-Y,-1/2+Z; [12]1+Y-X,+Y,-1/2+Z; [13]-Y+X,1-Y,1/2-Z; [14]-X,-Y,1-Z; [15]-Y+X,+X,1-Z; [16]+Y,-X+Y,1-Z; [17]+Y-X,1-X,+Z

[0172] Table 6. Torsion Angles for P[6]AS.

A	B	C	D	Angle/°	A	B	C	D	Angle/°
Na21	O1	S1	O3	6.3(4)	O5	S2	O7	Na36	-126.4(4)
Na1	O1	S1	O3	-148.93(19)	O6	S2	O8	Na27	-18.9(8)
Na21	O1	S1	O2	136.3(3)	O7	S2	O8	Na27	115.5(7)
Na1	O1	S1	O2	-18.9(3)	O5	S2	O8	Na27	-131.4(6)
Na21	O1	S1	O4	-111.4(3)	O6	S2	O8	Na36	-118.5(6)
Na1	O1	S1	O4	93.4(2)	O7	S2	O8	Na36	16.0(6)
Na3	O3	S1	O1	-11.8(4)	O5	S2	O8	Na36	129.0(5)
Na22	O3	S1	O1	112.5(2)	O6	S2	O8	Na34	157.9(7)
Na3	O3	S1	O2	-142.4(3)	O7	S2	O8	Na34	-67.7(9)
Na22	O3	S1	O2	-18.1(3)	O5	S2	O8	Na34	45.4(7)
Na3	O3	S1	O4	105.5(3)	O1D8	Na3	O2C	O1C	37.0(19)
Na22	O3	S1	O4	-130.24(17)	O3	Na3	O2C	O1C	-144.4(15)
Na2	O2	S1	O1	1.7(5)	O1D9	Na3	O2C	O1C	2.5(16)
Na2	O2	S1	O3	132.3(4)	O73	Na3	O2C	O1C	-66.7(16)
Na2	O2	S1	O4	-112.8(4)	O810	Na3	O2C	O1C	-114.3(18)
O1	S1	O4	C1	80.0(3)	O710	Na3	O2C	O1C	132.9(13)
O3	S1	O4	C1	-41.8(3)	O1D11	Na3	O2C	O1C	49.4(15)
O2	S1	O4	C1	-160.4(3)	O84	Na3	O2C	O1C	116.6(16)
S1	O4	C1	C2	109.1(3)	C2D12	Na3	O2C	O1C	25.9(16)
S1	O4	C1	C8	-76.1(4)	O1D13	O1D	C2D	C2D14	-49.2(5)
C8	C1	C2	C4	-0.3(4)	O1D15	O1D	C2D	C2D14	49.2(5)
O4	C1	C2	C4	174.4(3)	Na38	O1D	C2D	C2D14	-9.8(8)
C8	C1	C2	C3	-178.4(3)	Na31	O1D	C2D	C2D14	101.3(3)
O4	C1	C2	C3	-3.7(4)	Na316	O1D	C2D	C2D14	-101.3(2)
C4	C2	C3	C23	52.2(2)	C2D14	O1D	C2D	O1D17	-101.6(11)
C1	C2	C3	C23	-129.7(3)	O1D13	O1D	C2D	O1D17	-150.8(10)
C1	C2	C4	C5	-0.7(4)	O1D15	O1D	C2D	O1D17	-52.4(14)
C3	C2	C4	C5	177.5(3)	Na38	O1D	C2D	O1D17	-111.4(13)
C2	C4	C5	C6	0.9(5)	Na31	O1D	C2D	O1D17	-0.3(14)
C2	C4	C5	O5	-179.5(2)	Na316	O1D	C2D	O1D17	157.1(10)
C4	C5	C6	C8	-0.1(4)	C2D14	O1D	C2D	O1D18	101.6(11)
O5	C5	C6	C8	-179.6(2)	O1D13	O1D	C2D	O1D18	52.4(14)
C4	C5	C6	C7	-174.4(3)	O1D15	O1D	C2D	O1D18	150.8(10)
O5	C5	C6	C7	6.0(4)	Na38	O1D	C2D	O1D18	91.8(14)
C5	C6	C7	C64	-54.9(2)	Na31	O1D	C2D	O1D18	-157.1(8)
C8	C6	C7	C64	131.0(3)	Na316	O1D	C2D	O1D18	0.3(13)
C2	C1	C8	C6	1.1(5)	C2D14	O1D	C2D	O1D13	49.2(5)
O4	C1	C8	C6	-173.4(3)	O1D15	O1D	C2D	O1D13	98.3(10)
C5	C6	C8	C1	-0.9(4)	Na38	O1D	C2D	O1D13	39.4(9)
C7	C6	C8	C1	173.5(3)	Na31	O1D	C2D	O1D13	150.4(8)
C4	C5	O5	S2	74.4(4)	Na316	O1D	C2D	O1D13	-52.1(3)
C6	C5	O5	S2	-106.1(4)	C2D14	O1D	C2D	O1D15	-49.2(5)

C5	O5	S2	O6	45.2(7)		O1D13	O1D	C2D	O1D15	-98.3(10)
C5	O5	S2	O7	-77.8(8)		Na38	O1D	C2D	O1D15	-58.9(10)
C5	O5	S2	O8	163.9(6)		Na31	O1D	C2D	O1D15	52.1(3)
O6	S2	O7	Na25	15.2(11)		Na316	O1D	C2D	O1D15	-150.5(7)
O8	S2	O7	Na25	-118.2(8)		C2D14	O1D	C2D	O1D14	-0.004(1)
O5	S2	O7	Na25	131.1(7)		O1D13	O1D	C2D	O1D14	-49.2(5)
O6	S2	O7	Na33	-157.3(12)		O1D15	O1D	C2D	O1D14	49.2(5)
O8	S2	O7	Na33	69.2(14)		Na38	O1D	C2D	O1D14	-9.8(8)
O5	S2	O7	Na33	-41.4(14)		Na31	O1D	C2D	O1D14	101.3(3)
O6	S2	O7	Na36	117.7(5)		Na316	O1D	C2D	O1D14	-101.3(2)
O8	S2	O7	Na36	-15.7(6)						

[1]1-Y,+X-Y,+Z; [2]2-X,1-Y,1-Z; [3]2-X,1-X+Y,1/2-Z; [4]+Y,+X,1/2-Z; [5]+X,+X-Y,-1/2+Z; [6]1+Y-X,+Y,-1/2+Z; [7]-Y+X,1-Y,1/2-Z; [8]1-X,1-Y,1-Z; [9]1+Y-X,1-X,+Z; [10]1+Y-X,+Y,1/2+Z; [11]1-Y,1+X-Y,+Z; [12]1+X,1+Y,+Z; [13]-Y+X,+X,1-Z; [14]-X,-Y,1-Z; [15]+Y,-X+Y,1-Z; [16]+Y-X,1-X,+Z; [17]+Y-X,-X,+Z; [18]-Y,+X-Y,+Z

[0173] Table 7. Hydrogen Atom Coordinates and Isotropic Displacement Parameters (Å2) for P[6]AS.

Atom	***Z***	***y***	***z***	**U(eq)**
H3	1.002(2)	0.569(2)	0.2874(14)	0.039(9)
H4	0.937(2)	0.703(2)	0.1741(14)	0.026(7)
H6	0.691(2)	0.532(2)	0.3338(14)	0.032(8)
H7	0.590(2)	0.588(2)	0.2112(14)	0.035(8)

[0174] Table 8. Atomic Occupancy for P[6]AS.

Atom	**Occupancy**	**Atom**	**Occupancy**	**Atom**	**Occupancy**
Na3	0.6667	O1	0.887(5)	O2	0.887(5)
O3	0.887(5)	S1	0.887(5)	O4	0.887(5)
O1A	0.113(5)	O2A	0.113(5)	O3A	0.113(5)
S1A	0.113(5)	O4A	0.113(5)	O5	0.58(3)
S2	0.58(3)	O6	0.58(3)	O7	0.58(3)
O8	0.58(3)	O5A	0.42(3)	S2A	0.42(3)
O6A	0.42(3)	O7A	0.42(3)	O8A	0.42(3)
O1B	0.85	C2B	0.285(13)	O3B	0.308(7)
C4B	0.15	O1C	0.808(11)	O2C	0.317(10)
O3C	0.306(10)	O1D	0.353(9)	C2D	0.412(17)

[0175] Experimental. A suitable single crystal of P[6]AS was selected and measured on a Bruker Smart Apex2 diffractometer. The crystal corresponded to $C_{45.44}H_{24}Na_{12}O_{65.65}S_{12}$. The crystal was kept at 150(2) K during data collection. The integral intensity were correct for absorption using SADABS software using multi-scan method. Resulting minimum and maximum transmission are 0.634 and 0.959 respectively. The structure was solved with the

ShelXT-2014 (Sheldrick, 2015a) program and refined with the ShelXL-2015 (Sheldrick, 2015c) program and least-square minimisation using ShelX software package. Number of restraints used = 387.

[0176] Crystal structure determination. Crystal data for $C_{45.44}H_{24}Na_{12}O_{65.65}S_{12}$ (*M* =2280.86 g/mol): trigonal, space group P-3c1 (no. 165), *a* = 15.112(2) Å, *c* = 20.365(3) Å, *V* = 4027.8(13) Å3, Z = 2, T = 150(2) K, μ(MoKα) = 0.519 mm^{-1}, D_{calc} = 1.881 g/cm^3, 23483 reflections measured ($4° \leq 2\Theta \leq 53.178°$), 2810 unique ($R_{int}$ = 0.0602, R_{sig} = 0.0410) which were used in all calculations. The final R_1 was 0.0448 ($I > 2\sigma(I)$) and wR_2 was 0.1097 (all data).

[0177] Refinement details. H atoms (except those in disorered solvent) were located from difference Fourier map and freely refined including Uiso. Water and ethanol sovent is heavily disordered and was modelled with partially occupied O and C atoms.

EXAMPLE 2

[0178] This Example provides synthesis, x-ray crystal structure, and molecular recognition properties of pillar[n]arene derivative P[6]AS which is referred to herein from time to time as Pillar[6]MaxQ, along with analogues P[5]AS and P[7]AS toward guests **11**–**28**. This Example demonstrates ultratight binding affinity of P[5]AS and P[6]AS toward quaternary (di)ammonium ions, which supports their use for *in vitro* and *in vivo* non-covalent bioconjugation for imaging and delivery applications and as in vivo sequestration agents.

[0179] In more detail, it will be recognized by those skilled in the art that progress in the construction of supramolecular systems for biological (e.g., imaging and drug delivery) and chemical applications (e.g., sensing, catalysis, separations) depends critically on the availability of a library of building blocks that can be easily integrated into more complex and functional systems. Molecular containers—whether prepared by covalent bond forming reactions or by self-assembly processes—occupy a central space within the field. Some of the most popular molecular containers include cyclodextrins, calix[n]arenes, crown ethers, cyclophanes, coordination cages, molecular clips and tweezers, cucurbit[*n*]urils (CB[*n*]), and H-bonded capsules. Within this group, the CB[n] family (Figure 11a) has proven particularly useful because they form tight CB[n]•guest complexes in a selective and stimuli responsive manner which allows them to be used to create sensing ensembles, supramolecular polymers, molecular machines, for bioconjugation, as a non-covalent latching system, and for drug solubilization and delivery. Given the high binding affinity of acyclic CB[n] toward their best guests, acyclic CB[n] was developed (e.g., **M2**, Figure 11a) as an *in vivo* sequestration agent

for neuromuscular blockers and drugs of abuse. Most recently, the synthesis and molecular recognition properties of the pillar[n]arenes (Figure 11b, e.g., WP[5] and WP[6]) in both organic and aqueous solutions have been extensively investigated and thoroughly reviewed with respect to their chemical and biological applications. Pillar[n]arenes represent a sweet spot for studies of molecular recognition in water in that they often display K_d values in the μM range and are more easily functionalized than CB[n]. This Example accordingly provides a description of preparation of pillar[n]arene sulfates (a.k.a. Pillar[*n*]MaxQ) that possess extreme binding affinity (K_d in pM range) toward quaternary diammonium ions in aqueous solution which make them particularly well suited as *in vivo* sequestration agents.

[0180] Contemplating the creation of new ultratight binding hosts based on pillar[n]arenes lead us to ponder the relevant structural features of CB[n] (Figure 11a). The ultratight binding features of CB[n] have been traced to their highly electrostatically negative ureidyl C=O portals and the number and energetics of water molecules within the host cavity that are released upon binding (e.g. non-classical hydrophobic effect). By virtue of their double CH_2-linkers, CB[n] possess no free rotors, cannot undergo self-complexation, and are therefore highly pre-organized hosts. The present disclosure relates to replicating these structural features in the pillar[n]arene family by rational molecular design. Although anionic Water soluble Pillararenes (e.g. WP[5] and WP[6]) are known they contain CH_2-linkers between the aromatic ring and the anionic functional groups (e.g., carboxylate, sulfonate, phosphonate). The disclosure includes removing the CH_2-linkers and changing to the highly acidic sulfate functional group to provide a higher negative charge density around the mouth of the cavity. Simultaneously, the addition of two sulfate groups per phenylene group were envisioned to electrostatically minimize the known possibility of the phenylene groups leaning into their own cavity.

[0181] Figure 11 shows the synthesis of P[5]AS–P[7]AS. The parent hydroxylated pillararenes (P[5]A–P[7]A) were prepared according to the literature procedures. Subsequently, P[5]A–P[7]A were individually reacted with pyridine•SO_3 in pyridine at 90 °C to deliver P[5]AS–P[7]AS in 70, 66, and 46% yield, respectively. To gain insight into the role of the CH_2-linkers, P[5]ACS was prepared as a control compound in poor yield (8%) by the reaction of P[5]A with propane sultone and NaOH in acetone. Lastly, known hosts WP[5] and WP[6] were prepared by methods known in the art as additional comparators. All new compounds were fully characterized by ^1H and ^{13}C NMR, IR, and high resolution electrospray ionization mass spectrometry. It is known that pillar[6]arenes may exist in five

different conformational forms due to rotation around the phenylene units. Figure 12a shows the ^{1}H NMR recorded for P[6]AS in D_2O at room temperature which consists of two relatively sharp singlets. This indicates that P[6]AS is either locked into the depicted C_6-symmetric structure or the phenylene units are rotating rapidly on the chemical shift timescale. Based on the host•guest experiments, it can be concluded that rotation of the OSO_3^- groups through the annulus of P[6]AS pillararene is fast.

[0182] The inherent aqueous solubility of the two most potent hosts (P[5]AS: 100 mM; P[6]AS: 20 mM; *vide infra*) were measured by integrating the ^{1}H NMR resonances for a solution of host against the methyl resonance for sodium 3-(trimethylsilyl)propionate-2,2,3,3-d_4 as internal standard of known concentration. Before proceeding to investigate the host•guest properties of the new hosts, we performed dilution experiments monitored by ^{1}H NMR spectroscopy to quantify their intermolecular self-association. The spectra were recorded for P[5]AS and P[6]AS as a function of concentration (P[5]AS: 20 – 0.1 mM; P[6]AS: 20 – 0.1 mM) used to calculate K_s values (P[5]AS: 19.7 M^{-1}; P[6]AS: 16.2 M^{-1}) by using a standard 2-fold self-association model. These K_s values ensure that the hosts remain monomeric at the mM concentrations used in the NMR and ITC experiments described below in this Example. Crystals of both P[6]AS and P[5]ACS were obtained and their structures as solved by x-ray diffraction measurements (Figure 13, CCDC 1996177 and CCDC 1996179). Figure 13d shows the stucture of one molecule of P[5]ACS in the crystal. As is commonly seen in pillararene crystal structures, the phenylene rings are oriented roughly perpendicular to the mean plane of the macrocycle and the substituents serve to deepen the cavity. The S•••S distances between sulfonates attached to a single phenylene ring ranges from 14.785–15.467 Å. Figure 13a shows the structure of a single molecule of P[6]AS in the crystal. In contrast to P[5]ACS, P[6]AS adopts an unusual conformation in which alternating phenylene units lean slightly into the cavity on opposite faces of the macrocycle in a geometry reminiscent of cyclotriveratrylenes. The leaning of phenylenes from perpendicular measures 35–38 degrees. Interestingly, the OSO_3^- groups do not lie in the mean plane of the phenylene units and instead are alternately displayed above and below the plane. This leaning and alternation results in the placement of the twelve OSO_3^- groups roughly at the corners and edges of a triangular antiprism of side length 11.130 Å and height 6.714 Å. Accordingly, P[6]AS packs a remarkably high charge density of -12 within a small volume (CPK molecular volume (MMFF) of P[6]AS = 1173 Å^3). The influence of the Na^+ counterions on the observed conformation of P[6]AS is unclear. The molecules of P[6]AS pack into a hexagonal array in the xy-plane as shown in Figure 13b; the OSO_3^- subunits are extensively

bridged by coordinating Na^+ ions. These hexagonally packed sheets of P[6]AS pack along the z-axis in register with each other such that the P[6]AS units define a tube (Figure 13c). The packing of P[5]ACS also displays stacked sheets held together by networks of bridging Na^+ ions.

[0183] Figure 12a shows two singlets for P[6]AS alone and a single set of sharp resonances for the P[6]AS•**25** complex (Figure 12c). The substantial upfield shifting observed for the resonances of guest **25** confirm its inclusion in the cavity of P[6]AS. At a 1:2 P[6]AS:**25** ratio, the resonances for guest **25** shift back toward those of free **25** which indicates that guest exchange occurs rapidly on the chemical shift timescale. Similar investigations were performed for different combinations of hosts and guests from Figures 2-4 and in many cases the situation was more complex. For example, in many cases the resonances for the aryl H-atoms (H_a) become broadened or split into many distinct sharp resonances upon mixing with one equivalent of guest. Of course, it is well known that pillar[*n*] arenes possess several different lower symmetry conformations (n = 5: 4 conformers; n = 6: 5 conformers) which would be expected to give rise to broadened or additional resonances as was observed in a guest dependent manner. For hosts P[6]AS and P[7]AS, upfield shifting of guest resonances was observed upon binding indicating cavity binding of the guest hydrophobic moiety. For P[5]AS, narrower guests (e.g., **21** and **23**) bind inside the cavity as indicated by upfield changes in chemical shift, but wider guests (e.g., **12** and **25**) show upfield shifts of NMe_3^+ groups rather than their hydrophobic moieties, which indicate $^+NMe_3$ binding near the portals. ITC measurements (*vide infra*) indicate that **12** and **25** bind to P[5]AS with 1:2 host:guest stoichiometry.

[0184] Initially, the molecular recognition properties of the new hosts toward guests **11**–**28** (Figure 2) by were investigated by ^{1}H NMR spectroscopy. Compounds **11**–**28** were selected because they feature different numbers of charged groups (one or two), length of hydrophobic residue, width of hydrophobic residue, and degree of ammonium ion substitution (1°, 2°, 3°, 4°) to assess the preferences of the new hosts. Figure 12 shows the ^{1}H NMR spectra recorded for P[6]AS, **25**, and 1:1 and 1:2 mixtures of P[6]AS and **25** which is a particularly well resolved example. Next, the strength of the binding interactions between the various hosts and guests was quantified. Given the complexity of the ^{1}H NMR spectra and the oberved tight binding (*vide infra*) we used isothermal titration calorimetry (ITC). For most complexes, we performed direct titration of host in the cell with guest in the syringe. Figures 5–7 shows the thermodynamic parameters determined by these direct ITC titrations and the representative experimental data is shown in Figures 69–83. Direct titrations were

inappropriate for the tighter host•guest complexes where K_a values exceeded 4 x 10^7 M^{-1} where the *c*-value exceeded the recommended range even when working at [host] = 10 μM. In these cases, competition ITC experiments were employed where a mixture of host and an excess of a weaker binding guest in the cell was titrated with a stronger binding guest in the syringe. In these ITC competition experiments, the ΔH and K_a values for the weaker host•guest complex are determined independently and used as inputs for the competitive ITC titrations. Figure 14a shows the titration of a mixture of P[6]AS and weaker binding guest **17** in the cell with the stronger binding guest **20** in the syringe. Fitting of the data (Figure 14b) to a competitive binding model allowed the extraction of the thermodynamic parameters for P[6]AS•**20** (K_a = (1.20 ± 0.06) × 10^{11} M^{-1}; ΔH = - 17.1 ± 0.033 kcal mol^{-1}). Figures 5–7 reports the results of competitive ITC titrations for the tighter host•guest complexes.

[0185] The extensive dataset presented in Figures 5–7 allows a thorough discussion of the binding preferences of the new hosts in comparison to the previously known WP[5] and WP[6]. All of the complexes are driven by favorable ΔH values which suggests these complexes benefit from the non-classical hydrophobic effect as planned. First, it is noted that P[5]ACS with its $(CH_2)_3$-linkers binds ≈ 10^1 – 10^2-fold more weakly toward alkanediammonium ions **16**–**20** than observed for WP[5], which may be a consequence of the linkers partially occluding the host cavity or the longer linker to the anionic SO_3^- group diminishing electrostatic interactions. Furthermore, P[5]ACS and WP[5] display little selectivity in binding based on the degree of methylation of the diammonium ion (e.g. 1°: **17**, 2°: **18**; 3°: **19**; 4°: **20**). In contrast, P[5]AS is a superior host toward diammonium ions than WP[5] (e.g. **17**: 41-fold; **18**: 390-fold ; **19**: 7300-fold ; **20**: 88000-fold). P[5]AS displays increasing binding affinity as the degree of methylation of the N-atoms of the guest are increased. Accordingly, this class of hosts was dubbed as Pillar[*n*]MaxQ to denote their generally superior binding affinity and selectivity toward quaternary ammonium ions. A comparison of the binding affinities of P[5]AS toward different length quaternary diammonium ions (e.g. **15**, **16**, **20**) shows that the C4-diammonium ion binds 317 – 458-fold more weakly than the C5- and C6-analogues presumably due to better matching of the N•••N to ^-O_3S•••SO_3^- distance and the increased hydrophobicity of the C6-hydrophobic residue. Quite interestingly, a comparison of the affinity of P[5]AS toward mono quaternary guest **13** (4.41 x 10^8 M^{-1}) and bis quaternary guest **20** (9.90 x 10^{11} M^{-1}) reveals the importance of electrostatic interactions in the recognition process. All of these narrow guests form 1:1 P[5]AS•guest complexes. In contrast, the ITC results reveal that wider guests (e.g. **12**, **25**, **27**,

cis, roc, vec, pan) cannot form inclusion complexes with P[5]AS and instead form 1:2 P[5]AS:guest complexes at the portals. The ITC titrations of P[5]AS with this subset of guests fit well to a 1:1 binding model with N = 2, and therefore the K_a values reported in Figures 5–7 have M^{-1} units and refer to each of the two independent binding events. The K_a value of P[5]AS toward Me_4N^+ (P[5]AS•**26**; $K_a = 3.11 \times 10^4$ M^{-1}) reveals that each quaternary ammonium ion head group makes a large contribution toward the observed ultrahigh affinity of P[5]AS toward (bis)quaternary ammonium ions (e.g., **20**).

[0186] Figures 5–7 show the binding constants (K_a, M^{-1}) and thermodynamic parameter (ΔH, kcal mol^{-1}) for various hosts and guests **11**–**28**, the neuromuscular blocking agents are shown in Figure 4, and drugs of abuse are show in Figure 3 and Figure 68. Conditions: H_2O, 20 mM NaH_2PO_4 buffer, pH 7.4, 298K. – not measured. n.b. = no heat change detected by ITC. [a] Measured by direct ITC titration with [host] ≥ 10 μM. [b] Measured by competitive ITC titration with **13**. [c] Measured by competitive ITC titration with **14**. [d] Measured by competitive ITC titration with **16**. [e] Measured by competitive ITC titration with **17**. [f] Measured by competitive ITC titration with **21**. [g] Measured by competitive ITC titration with **24**. [h] Measured by competitive ITC titration with **27**. [i] Measured by competitive ITC titration with **28**. [j] 1:2 host:guest complex. [k] 2:1 host:guest complex.

[0187] Related comparisons can be made between hosts WP[6] and P[6]AS which exhibit 1:1 host: guest complexation toward all the guests used in this study. For example, P[6]AS is the superior host toward 20 out of the 23 guests studied with exceptions including 1° ammonium ions **24** and **27**. Similar to P[5]AS, P[6]AS is highly selective based on guest length (e.g. **14** vs **28** vs **17**; **15** vs **16** vs **20**) and on the degree of methylation of the diammonium ion (e.g. **17** vs **20**; $K_a = 1.43 \times 10^9$ vs 1.20×10^{11} M^{-1}). Interestingly, the binding affinity of P[6]AS toward Me_4N^+ (**26**, $K_a = 2.32 \times 10^6$ M^{-1}) is 75-fold stronger than P[5]AS which suggests P[6]AS should be regarded as a powerful host for quaternary ammonium ions. In fact the K_d values of P[6]AS toward the guest panel lie in the single digit μM to 1 pM range which places P[6]AS squarely alongside CB[n] as one of the highest affinity synthetic host•guest systems in water although the balance between complexation driving forces (e.g. electrostatic versus hydrophobic effect) obviously differs. Finally, Figures 5–7 present the binding affinities of P[7]AS toward the panel of guests (**11**–**28**). In this case, comparison with the water soluble pillararene analogue (WP[7]) could not be performed since access to it failed. Regardless, a perusal of Figures 5–7 reveal that P[7]AS is a significantly less potent receptor toward the guest panel than P[6]AS with the exception of

the primary ammonium ion **24**. Although the reasons for the relatively poor performance of P[7]AS are not established, without intending to be bound by any particular theory, it was surmised the reasons may parallel those of the CB[n] host family where the size of the electrostatically negative portals and the energetics and number of bound waters in the host cavity play important roles.

[0188] Given the demonstrated preference of P[5]AS and P[6]AS toward quaternary diammonium ions the guest panel extended to include the clinically important neuromuscular blocking agents roc, vec, pan, and cis as well as acetyl choline (ACh). Macrocyclic receptors (e.g., γ-cyclodextrin derivative Sugammadex marketed by Merck as Bridion^{TM}, acyclic CB[n]-type receptor **M2**, and WP[6]) have previously been used as *in vivo* sequestration agents for NMBAs. Accordingly, the binding affinities of P[5]AS – P[7]AS, WP[5], and WP[6] were measured toward the NMBAs (Figure 7). Most strikingly, it was found that P[6]AS binds roc, vec, and pan 10^4-10^5-fold more tightly than WP[6] or Sugammadex while maintaining very good levels of discrimination against acetyl choline (10^3 – 10^4-fold), which is also present in the neuromuscular junction. In fact, P[6]AS displays >100-fold higher affinity toward roc, vec, and pan than previously reported host **M2** (K_a: **M2**•roc = 3.4 x 10^9 M^{-1}; **M2**•vec = 1.6x 10^9 M^{-1}; **M2**•pan = 5.3 x 10^8 M^{-1}), which has been demonstrated to successfully reverse the biological effects of roc, vec, and cis *in vivo* in rats. To further demonstrate the superior binding affinity of P[6]AS over **M2** toward roc a head-to-head test monitored by ^{1}H NMR spectroscopy was performed. Figure 15a–e shows the ^{1}H NMR recorded for uncomplexed P[6]AS, **M2**, and roc and the P[6]AS•roc and **M2**•roc complexes. For the **M2**•roc complex, there is splitting and downfield shifting of H_{a*} and H_{b*} into a total of 8 resonances for the enantiomerically pure complex. For both complexes, there substantial upfield shifts of the axial steroidal Me-groups (H_p and H_q) which allow monitoring of the composition of mixtures of these two competing host•guest complexes. Figure 15f shows the ^{1}H NMR spectrum recorded when a solution of **M2**•roc (0.5 mM) was treated with 1 equivalent of P[6]AS. The loss of the resonances for **M2**•roc and the appearance of resonances for P[6]AS•roc further verify the superior affinity of P[6]AS in the context of neuromuscular blockers. Previously, only reversal the *in vivo* effects of cis was achieved in rats at higher doses of **M2** (≥40 mg kg^{-1}) due to the lower binding affinity of the **M2**•cis complex (K_a = 4.8 x 10^6 M^{-1}). Experimentally, it was found that P[7]AS and cis form a $(P[7]AS)_2$•cis complex where the benzylisoquinolinium endgroups are each complexed by a P[7]AS host. The ITC data for $(P[7]AS)_2$•cis could be fitted to a 1:1 binding model with N_{sites}

= 2 and $K_a = 1.52 \times 10^7\ M^{-1}$. Accordingly, P[7]AS has potential for translation into an *in vivo* reversal agent for cis.

[0189] In summary, this Example describes the synthesis of P[5]AS – P[7]AS, the x-ray crystal structures of P[5]ACS and P[6]AS, and their molecular recognition properties toward (di)ammonium ions in aqueous solution. P[*n*]AS packs 2*n* negative charges into a small volume near the portals of the receptors which augments the electrostatic contributions to binding free energy. It was found that P[5]AS and P[6]AS display significantly higher binding affinity than WP[5] and WP[6] toward (bis)quaternary (di)ammonium ions. Accordingly, the suggested family name is Pillar[*n*]MaxQ. The picomolar affinity of P[6]AS toward roc and vec greatly exceeds that of acyclic CB[n]-type receptor **M2** and Sugammadex which is used in clinical practice under the trade name BRIDION™. The ultratight binding (e.g. picomolar K_d) displayed by P[5]AS and P[6]AS places them alongside CB[n] as some of the most potent synthetic receptors in water. The ultratight binding of P[5]AS and P[6]AS suggests that sulfated pillararenes and their functionalized derivatives may be used as non-covalent connectors for bioconjugation, in (bio)chemical separations, for theranostics, as well as for sequestration and remediation in chemical and biological systems.

[0190] Determination of K_a between various hosts and cationic guests using Isothermal Titration Calorimetry (ITC). All ITC experiments were conducted in the 200 µL working volume of the sample cell of the PEAQ ITC instrument. An injection syringe of 40 µL capacity was used. In each case, the host and guest solutions were prepared in a 20 mM NaH_2PO_4 buffer (pH 7.4). The sample cell was filled to capacity (200 µL) with the host solution and the guest solution was titrated in (first injection = 0.4 µL, subsequent 18 injections = 2 µL). The binding data was fitted using the 1:1 binding model or the competitive binding models in MicroCal PEAQ-ITC analysis software.

EXAMPLE 3

[0191] This Example provides *in vivo* effects of P[6]AS on reversal of methamphetamine induced hyperlocomotion in a pertinent mouse model. This Example also provides results from an *in vivo* toxicology study of P[5]AS and P[6]AS.

[0192] Cell Cytotoxicity Data for P[5]AS and P[6]AS. To test the Cytotoxicity and Cell Viability of the above compounds we used two different assays: an MTS (CellTiter 96 AQueous Kit®) assay that measures cellular metabolism, and the AK (Toxilight®BioAssay Kit) assay that measures cell death through release of the cytosolic enzyme adenylate kinase into the supernatant. Both assays were performed with two different cell lines. HEK293 and

Hep G2cells, are frequently used in drug toxicity studies. HEK293, a human kidney cell line, is used to evaluate the effect of the drug on the renal system and Hep G2, a human hepatocyte cell line, is used to assess the response of liver cells where drugs are metabolized. The MTS and AK assays for both cell lines were conducted after 24 h of incubation with the compounds at concentrations of 0.01 mM, 0.03 mM, 0.1 mM, 0.3 mM, and 1 mM. Eight technical replicates were designated for untreated cells and four technical replicates were designated for the cells treated with each compound and staurosporine (apoptosis inducer).

[0193] The collected absorbance and relative luminescence data were normalized to percent cell viability (MTS) and percent cell death (AK) using equations 1 and 2:

1)% cell viability = (Abs sample/ Average Abs UT) ×100

2)% cell death = (RLU samples/Average RLU Distilled water) ×100

[0194] Toxicity studies using the MTS and AK assays for the liver cell line, HepG2 suggests that **P[5]AS** demonstrates low cytotoxicity up to a concentration of 1 mM and high cell tolerance up to a concentration of 0.3 mM (Figure 63A,B). **P[6]AS** demonstrates low cytotoxicity up to a concentration of 1 mM with human HepG2 cells and high cell tolerance up to a concentration of 0.1 mM (Figure 63C,D).

[0195] Similarly toxicity studies performed on human kidney (HEK293) cells suggest that P[5]AS demonstrates low cytotoxicity up to a concentration of 1 mM and high cell tolerance up to a concentration of 0.1 mM (Figure 64A,B). P[6]AS demonstrates low cytotoxicity up to a concentration of 1 mM and high cell tolerance up to a concentration of 0.03 mM (Figure 64C-D).

[0196] *In Vivo* Maximum Tolerated Dose Study (MTD). Animals studies were performed at the University of Maryland, Microbiology Building under the supervision of Dr. Volker Briken (IACUC #R-JAN-17-25). A total of 20 female Swiss Webster were used for this study. Three different concentrations of P[6]AS (11.31 mM, 7.54 mM, 3.77 mM) were used. A PBS control group was also included. Each concentration and control group contained 5 mice. The mice received the compound in 0.150 ml of PBS via tail vein injection, with 48 hours between injections. The weight and health status of the mice were monitored for 2 weeks following the last injection. Behavior summary: 11.31 mM dose group showed dose-dependent adverse effects in the form of freeze ups and some labored breathing. The 11.31 mM dose group returned to baseline behavior (that observed with the PBS control) ≈2-3 hours after injection. The lowest dose group 3.77 mM overall exhibited no adverse effects and behavior on par with the PBS control group.

[0197] MTD study performed for P[6]AS. Female Swiss Webster mice (n = 5 per group) were dosed via tail vein on days 0 and 2 (denoted by *) with different concentrations of P[6]AS or phosphate buffered saline (PBS). The normalized average weight change per study group is indicated. Error bars represent SEM.

[0198] *In Vivo* Reversal of Methamphetamine Induced Hyperlocomotion by P[6]AS

[0199] Animals. Eight male Swiss Webster (CFW) mice were obtained from Charles River Laboratories that weighed ~30g upon arrival. Mice were individually housed in a temperature- and humidity- controlled room on a 12 h light/ dark schedule with lights on at 6:00 am EST. For the duration of both experiments mice had *ad libitum* access to food and water. All behavioral testing occurred between 6:30 am and 2:00 pm EST, and all experimental procedures were approved by the University of Maryland Animal Care and Use Committee and conformed to the guidelines set forth by the National Research Council

[0200] Surgical Procedures. Mice were anesthetized with an intraperitoneal (IP) injection of ketamine (100 mg/ kg) / xylazine (10 mg/kg) (n = 8) and were implanted with jugular catheters with head-mounted ports. All surgical procedures were conducted using aseptic technique, with body temperature monitored and maintained throughout surgery. Catheters were placed in the right jugular vein with the port passed subcutaneously out towards the top of skull. Ports (5MM Up Pedestal; P1 Technologies) were fixed to the skull with a combination of super glue (Loctite) and dental cement. Following surgery, mice received an immediate injection of Rimadyl (5 mg/kg) and 0.4 mL of warm sterile saline. Mice were treated post-operatively for two days with Rimadyl (5 mg/ kg) and given a minimum of 5 days to recover before resuming training. Catheters were flushed daily with 0.1 mL sterile saline solution containing gentamycin (0.33 mg/ mL) and 0.1 mL sterile saline solution containing heparin (20 IU/ mL) in order to reduce clotting and maintain catheter patency. Catheter patency was assessed daily from the first day following surgery until the end of testing. Any mouse whose catheter exhibited significant flowback on a majority of days was excluded from analysis.

[0201] Behavioral Testing. Mice were trained on a standard autoshaping task described previously. All behavioral procedures were conducted in a Med Associates test chamber equipped with a food cup, a retractable lever, and 4 floor IR photobeams. Time stamps were generated from head entries into the food cup, downward deflections of the lever, or disruption of floor beams and recorded by the behavioral computer.

[0202] Mice were given one day of magazine training that consisted of the delivery of thirty 20 mg sucrose pellets (Bioserv) randomly delivered on a variable interval 30 ± 15

schedule, in order to habituate mice to the box and pellet delivery. In order to minimize the impact of novelty-induced suppression of feeding, mice were given five to six 20 mg sucrose pellets each in their home cage for 2-3 days prior to the beginning of training.

[0203] Following magazine training, mice began Pavlovian training sessions, which consisted of the presentation of the lever (CS) for 8 s, which was immediately followed by the delivery of a sucrose pellet and the retraction of the lever. The CS was presented on a random interval of 90 ± 30 s schedule. Each Pavlovian session consisted of 30 trials. Pavlovian training continued for 4 days prior to surgery. Following surgery and recovery, mice underwent Pavlovian training for an additional 8 days while being exposed to various treatments.

[0204] Experimental Design. P[6]AS's efficacy was assessed using a semi-counterbalanced design where all mice received each possible experimental treatment. The purpose of the experiments was to: (1) verify that binding of methamphetamine by P[6]AS would not be compromised *in vivo*, (2) verify that P[6]AS would not alter locomotor behavior, and (3) to demonstrate that P[6]AS can sequester methamphetamine *in vivo*. On the first day, regardless of experiment, mice underwent a refresher session free of treatment. On the following six sessions mice were treated with one of six possible treatments: 0.01M PBS (0.2 mL infused), P[6]AS only (4 mM; 0.178 mL infused), methamphetamine only (0.5 mg/kg; 0.022 mL infused), a premixed solution of P[6]AS and methamphetamine (Premix; ~7:1 P[6]AS:Meth; 0.178 mL P[6]AS + 0.022 mL Meth infused), P[6]AS followed by methamphetamine administered 30 s later (0.178 mL P[6]AS, 0.022 mL Meth infused), and methamphetamine followed by P[6]AS administered 30 s later (0.022 mL Meth, 0.178 mL P[6]AS infused). Mice only received only one infusion per day. The dose of methamphetamine was chosen based on previously published values that observed reliable hyperlocomotion in mice. It was sought to choose smallest dosage that reliably induced hyperlocomotion.

[0205] Following completion of the first six sessions, mice completed another two days of behavioral testing. On day 7, half of the mice (n = 4) received P[6]AS followed by methamphetamine administered 5 minutes later (0.178 mL P[6]AS, 0.022 mL Meth infused), followed by infusion of methamphetamine followed by P[6]AS administered 5 minutes later (0.022 mL Meth, 0.178 mL P[6]AS infused) administered on the eighth day of testing. The other half of the mice (n = 4) received the same exact treatment but in reverse order across days 7 and 8.

[0206] For each experiment, total locomotion counts (i.e., the total number of beam breaks) were obtained for each mouse across the entirety of each training session. For each experiment, locomotion counts were then analyzed across treatments using one-way repeated measures ANOVAs with tukey-corrected pairwise post-hoc t-tests in Graphpad Prism (Version 9.0.0).

[0207] *In vivo* reversal of methamphetamine-induced hyperlocomotion effects observed after 5 minute delay between treatment with methamphetamine and P[6]AS administration. On day 7 and 8 mice (n = 8) received methamphetamine followed by an infusion of 0.01M PBS administered 5 minutes later (REV-C; 0.022 mL Meth, 0.2 mL PBS infused) or methamphetamine followed by P[6]AS administered 5 minutes later (REV-5; 0.022 mL Meth, 0.178 mL P[6]AS infused) in counterbalanced manner. Administration of P[6]AS 5 minutes after exposure to methamphetamine reduced hyperlocomotion (paired *t*-test, $t(7) = 2.757$, $p = 0.0282$). Bars represent average locomotion counts. Error bars represent the standard error of the mean (SEM). Dots represent counts for each mouse (n = 8).

[0208] It will be recognized from the foregoing that this Example provides an analysis of the efficacy of P[6]AS in the sequestration of methamphetamine *in vivo*. Eight male Swiss Webster (CFW) mice were trained on an Pavlovian autoshaping task described previously and locomotion values were obtained and analyzed accordingly. To establish methamphetamine induced hyperlocomotion and examine the efficacy of P[6]AS mice were first treated single infusions of PBS (0.01M), P[6]AS only, methamphetamine only, a premixed solution of P[6]AS and methamphetamine, P[6]AS followed by methamphetamine administration 30s later, or methamphetamine followed by P[6]AS administered 30s later in counterbalanced manner. Figure 66 depicts the results of this experiment by plotting locomotion counts as a function of treatment. Mixed effects analysis revealed a significant main effect of treatment ($F(5,35) = 7.116$, $p = 0.0001$) with Tukey-corrected post-hoc comparison showing a significant increase in locomotion counts for treatment with methamphetamine against all other treatments (p's < 0.05). Critically, there was no difference in locomotion for the comparison between reversal (i.e., meth first, followed by P[6]AS 30s later) suggesting that P[6]AS on its own has no negative effect on locomotor behavior, and that sequential administration of P[6]AS reduces methamphetamine-induced hyperlocomotion to control levels.

[0209] Although the results of this first analysis are suggestive of the potential efficacy of P[6]AS in the sequestration of methamphetamine and inducing behavioral change, it is possible that the 30 second (s) interval between methamphetamine administration and

P[6]AS administration in the reversal condition is too short to be ethologically relevant. To address this, a follow up experiment was conducted where on days 7 and 8 of testing, mice (n = 8) were administered either methamphetamine followed by administration of 0.01 M PBS 5 minutes later (REV-C) or methamphetamine followed by P[6]AS 5 minutes later (REV-5) in a counterbalanced manner before completing the autoshaping task. Figure 67 plots locomotion counts as a function of either REV-C or REV-5 treatment. A significant decrease was observed in locomotion in the REV-5 condition relative to REV-C (paired *t*-test, $t(7) = 2.757$, $p = 0.0282$). Although not directly comparable from an experimental design perspective, importantly locomotion levels in the REV-5 condition closely approximate those observed in control conditions on Day 1–6, while locomotion counts in the REV-C condition appear to approximate those observed with the methamphetamine only treatment. Collectively these findings suggest that P[6]AS is capable of sequestering methamphetamine *in vivo* and reversing methamphetamine-induced hyperlocomotion, with little to no effect on the locomotor behavior of the animal itself.

EXAMPLE 4

[0210] The following example shows ITC data for the binding of various drugs with hosts of the present disclosure.

[0211] Table 10. K_a of MDMA, mephedrone, and heroin.

Drug	K_a with **P[6]AS** (M^{-1}) ΔH, *C or app. C*
MDMA	$(3.92 \pm 0.20) \times 10^{7\,a}$ -13.30 ± 0.04 49.8
Mephedrone	$(1.91 \pm 0.19) \times 10^{7\,b}$ -12.60 ± 0.11 191
Heroin	$(5.78 \pm 0.02) \times 10^{5\,c}$ -11.9 ± 0.11 57.8

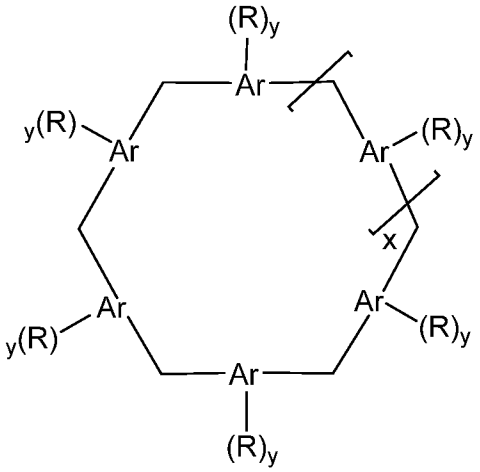
[a] Measured by the ITC competition titration of Host (0.1 mM) and 1,3-propanediammonium chloride (0.15 mM) in the cell with Guest (1 mM) in the syringe. [b] Measured directly by the ITC titration of Host (10 μM) in the cell with Guest (100 μM) in the syringe. [c] Measured directly by the ITC titration of Host (0.1 mM) in the cell with Guest (1 mM) in the syringe.

[0212] Figures 69–71 shows ITC data of P[6]AS and MDMA, mephedrone, and heroin.

[0213] Although the present disclosure has been described with respect to one or more particular example(s), it will be understood that other examples of the present disclosure may be made without departing from the scope of the present disclosure.

Claims:

1. A compound having the following structure:



,

wherein

Ar is an aryl group wherein the aryl groups are attached in a para orientation to the adjacent methylene groups;

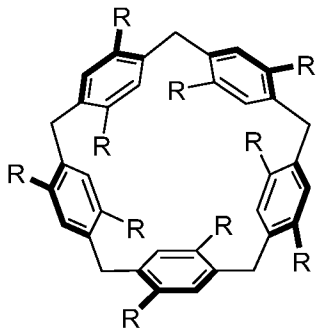
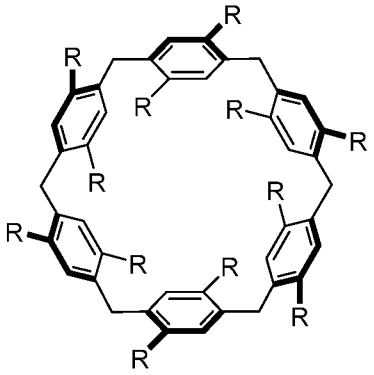
each R is independently chosen from: $-OS(O)_2O^-M^+$, $-OS(O)_2OH$, non-sulfate anionic groups, carboxylic acid/carboxylate groups, phosphonic acid/phosphonate groups, phosphate groups, substituted or unsubstituted aryl groups, substituted or unsubstituted heteroaryl groups, substituted or unsubstituted aliphatic groups, O-alkyl groups, -H, substituted or unsubstituted alkyl groups, halogens, amide groups, cyano groups, substituted or unsubstituted sulfur-containing aliphatic groups, nitro groups, amino groups, substituted or unsubstituted nitrogen-containing aliphatic groups, substituted or unsubstituted polyethylene glycol groups, polyether groups, O-aryl groups, ester groups, carbamate groups, imine groups, aldehyde groups, $-SO_3H$ groups, $-SO_3Na$ groups, $-OSO_2F$ groups, $-OSO_2CF_3$ groups, $-OSO_2OR'''$ groups, wherein R''' are substituted or unsubstituted aryl groups or substituted or unsubstituted alkyl groups, and combinations thereof, wherein M^+ is Na^+, K^+, Ca^{2+}, Mg^{2+}, Zn^{2+}, H_4N^+, Et_3NH^+, Me_4N^+, $(HOCH_2CH_2)_3NH^+$, or a cationic form of ethylenediamine, piperazine, or trishydroxymethyl aminomethane (TRIS),

x is 0, 1, 2, or 3; and y is independently at each occurrence 0, 1, 2, 3, or 4, with the proviso that at least one y is 1 and at least one R group is $-OS(O)_2O^-M^+$, wherein M^+ is Na^+, K^+, Ca^{2+}, Mg^{2+}, Zn^{2+}, H_4N^+, Et_3NH^+, Me_4N^+, $(HOCH_2CH_2)_3NH^+$, or a cationic form of ethylenediamine, piperazine, or trishydroxymethyl aminomethane (TRIS) or $-OS(O)_2OH$, or a salt, a partial salt, a hydrate, a polymorph, a stereoisomer, conformational isomer, or a mixture thereof.

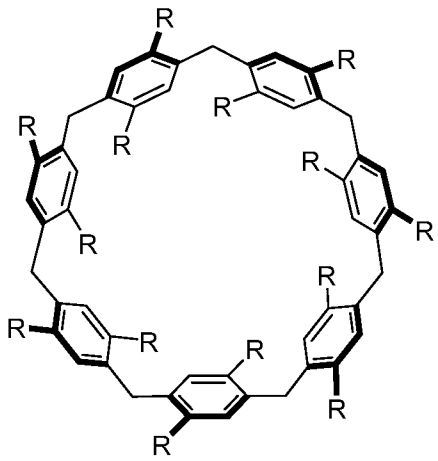
2. The compound of claim 1, wherein the aryl groups are independently at each occurrence chosen from phenyl groups, fused-ring groups, biaryl groups, and terphenyl groups.

3. The compound of claim 1, wherein at least two of the one or more phenyl group(s) of one or more of the aryl group(s) comprising the cyclic core of the compound have at least 1 R groups independently chosen from $-OS(O)_2O^-M^+$ and $-OS(O)_2OH$.

4. The compound of claim 3, wherein the compound has the following structure:


,

,

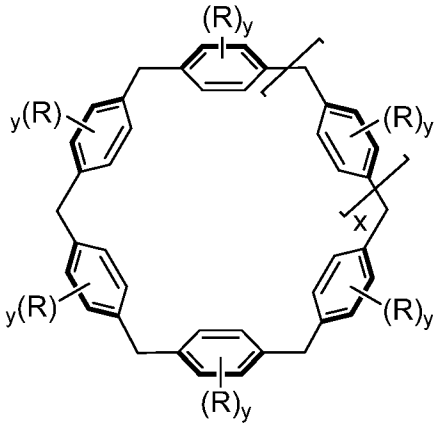
or


.

5. The compound of claim 1, wherein all of the aryl groups comprise an R group that is independently $-OS(O)_2O^-M^+$ or $-OS(O)_2OH$.

6. The compound of claim 1, wherein at least one aryl group does not comprise an R group that is $-OS(O)_2O^-M^+$ or $-OS(O)_2OH$.

7. The compound of claim 1, wherein the compound has the following structure:



8. The compound of claim 7, wherein 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, or 32 of the R groups are independently $-OS(O)_2O^-M^+$ groups or $-OS(O)_2OH$ groups.

9. The compound of claim 7, wherein each phenyl group comprising the cyclic core of the compound has at least 1 R group independently chosen from $-OS(O)_2O^-M^+$ and $-OS(O)_2OH$.

10. The compound of claim 7, wherein at least one phenyl group does not comprise an R group that is $-OS(O)_2O^-M^+$ or $-OS(O)_2OH$.

11. The compound of claim 1, wherein M^+ is Na^+, K^+, H_4N^+, Et_3NH^+, Me_4N^+, $(HOCH_2CH_2)_3NH^+$.

12. The compound of claim 11, wherein M^+ is Na^+.

13. A composition comprising one of more compound(s) of claim 1.

14. The composition of claim 13, further comprising a pharmaceutical carrier.

15. The composition of claim 13, wherein the one or more compound(s) are disposed on at least a portion of a solid substrate.

16. The composition of claim 15, wherein the solid substrate comprises silica, polymer beads, polymer resins, metal nanoparticles, a metal, or a combination thereof.

17. The composition of claim 13, wherein at least a portion or all of the one or more compound(s) have a pharmaceutically active agent(s) disposed in a cavity of the one or more compound(s).

18. A method for sequestering one or more neuromuscular blocking agent(s), one or more anesthesia agent(s), one or more pharmaceutical agent(s), one or more pesticide(s), one or more dyestuff(s), one or more malodorous compound(s), one or more chemical warfare agent(s), one or more hallucinogen(s), one or more toxin(s), one or more metabolite(s), or a combination thereof comprising:

contacting the neuromuscular blocking agent(s), the anesthesia agent(s), the pharmaceutical agent(s), the pesticide(s), the dyestuff(s), the malodorous compound(s), the chemical warfare agent(s), one or more hallucinogen(s), one or more toxin(s), one or more metabolite(s), or a combination thereof with one or more compound(s) of claim 1,

wherein the neuromuscular blocking agent(s), the anesthesia agent(s), the pharmaceutical agent(s), the pesticide(s), the dyestuff(s), the malodorous compound(s), the chemical warfare agent(s), one or more hallucinogen(s), one or more toxin(s), one or more metabolite(s), or a combination thereof are sequestered by the one or more compound(s).

19. The method of claim 18, wherein the neuromuscular blocking agent(s), the anesthesia agent(s), the pharmaceutical agent(s), the pesticide(s), the dyestuff(s), the malodorous compound(s), the chemical warfare agent(s), one or more hallucinogen(s), one or more toxin(s), one or more metabolite(s), or a combination thereof is present in an aqueous sample, in a solid sample, in a gas sample, or on a solid surface.

20. The method of claim 19, wherein the aqueous sample is a wastewater sample, an industrial water sample, or a municipal water sample.

21. The method of claim 18, wherein a complex is formed from the one or more compound(s) and the neuromuscular blocking agent(s), the anesthesia agent(s), the pharmaceutical agent(s), the pesticide(s), the dyestuff(s), the malodorous compound(s), the chemical warfare agent(s), one or more hallucinogen(s), one or more toxin(s), one or more metabolite(s), or a combination thereof.

22. The method of claim 18, wherein the complex is removed from the aqueous sample, the solid sample, or the gas sample.

23. The method of claim 18, wherein the neuromuscular blocking agent(s), the anesthesia agent(s), the pharmaceutical agent(s), the pesticide(s), the dyestuff(s), the malodorous compound(s), the chemical warfare agent(s), one or more hallucinogen(s), one or more toxin(s), one or more metabolite(s), or a combination thereof is present in and/or on an individual and the contacting comprises administration of the one or more compound(s).

24. The method of claim 23, wherein the individual is a human or a non-human mammal.

25. A method for reversing drug-induced neuromuscular block and/or anesthesia and/or the effects of one or more pharmaceutical agent(s) in an individual comprising administering to an individual in need of reversal of neuromuscular block and/or reversal of anesthesia and/or reversal of the effects of one or more pharmaceutical agent(s) one or more compound(s) of claim 1.

26. The method of claim 25, wherein the individual is in need of reversal of drug-induced neuromuscular block.

27. The method of claim 25, wherein the individual is in need of reversal of anesthesia.

28. The method of claim 25, wherein the individual is in need of reversal of drug-induced neuromuscular block and anesthesia.

29. The method of claim 25, wherein the individual is in need of reversal of the effects of one or more pharmaceutical agent(s).

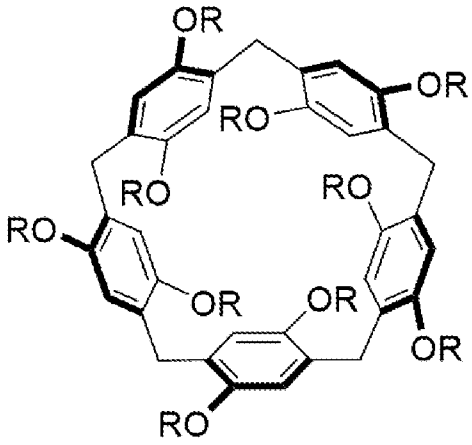
30. The method of claim 29, wherein the one or more pharmaceutical agent(s) are chosen from one or more drug(s) of abuse, one or more pesticide(s), one or more chemical warfare agent(s), one or more nerve agent(s), one or more hallucinogen(s), one or more toxin(s), one or more metabolite(s), and combinations thereof.

31. The method of claim 25, wherein the individual in need is a human.

32. The method of claim 25, wherein the individual in need is a non-human mammal.

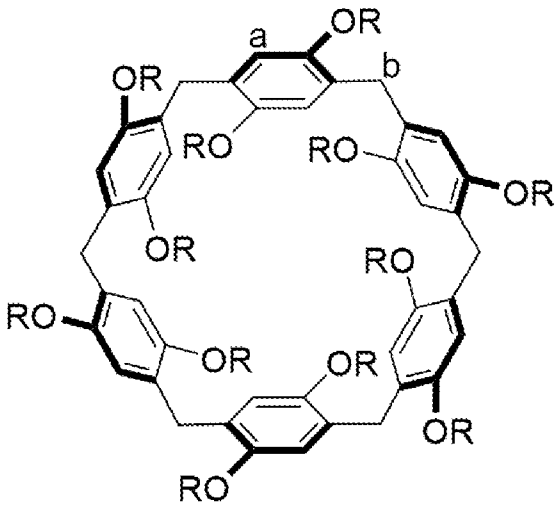
33. A method for prophylaxis and/or therapy of a condition in an individual comprising administering to an individual in need of the prophylaxis and/or the therapy one or more compound(s) of claim 1 and one or more pharmaceutical agent(s), wherein the compound(s) and the pharmaceutical agent(s) are present as complex, wherein subsequent to the administration the therapy and/or the prophylaxis of the condition in the individual occurs.

34. The method of claim 33, wherein one or more of the pharmaceutical agent(s) has/have a solubility of less than 100 μM in an aqueous solvent.



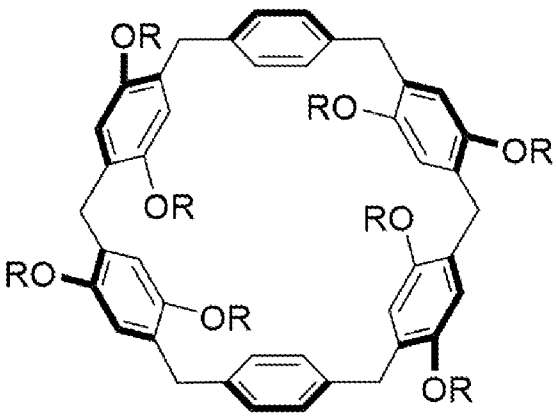
5, R= SO_3Na

P[5]AS



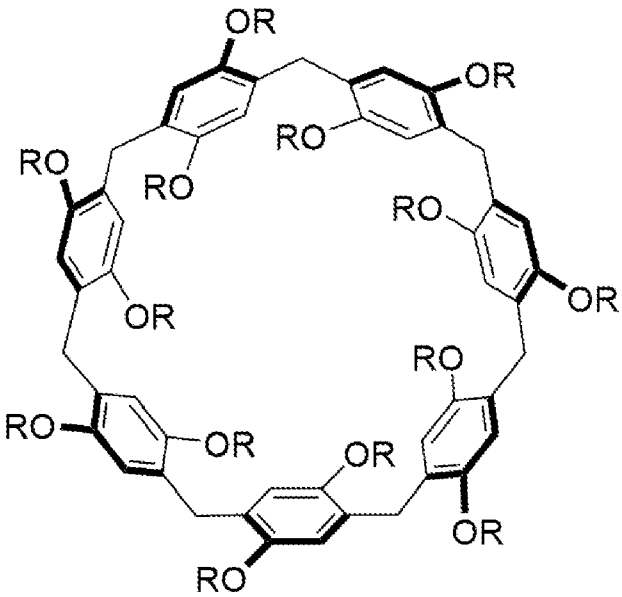
7, R= SO_3Na

P[6]AS



8, R= SO_3Na

P[6]A8S



9, R= SO_3Na

P[7]AS

Figure 1

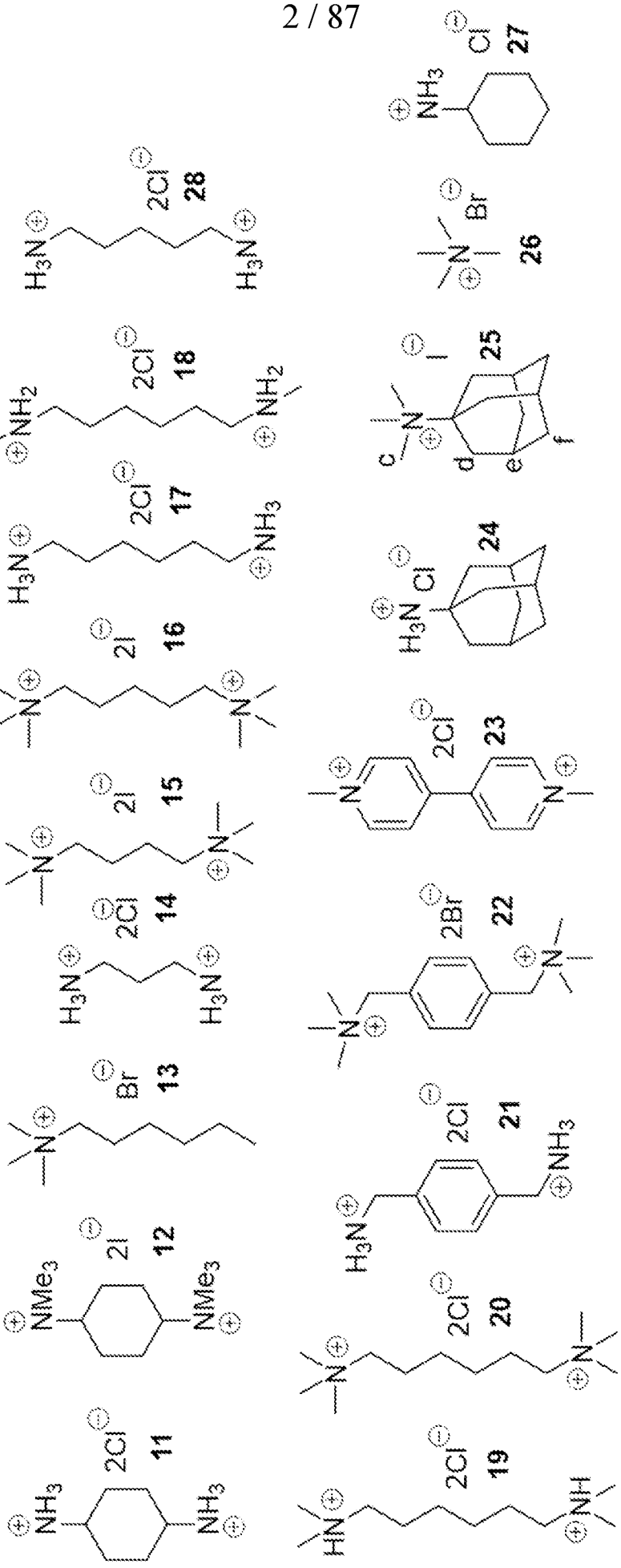

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28
2Cl
2I
Br
2Br
NMe3
NH3
NH2
NH
H3N
HN
Cl
I
a
b
c
d
e
f

Figure 2

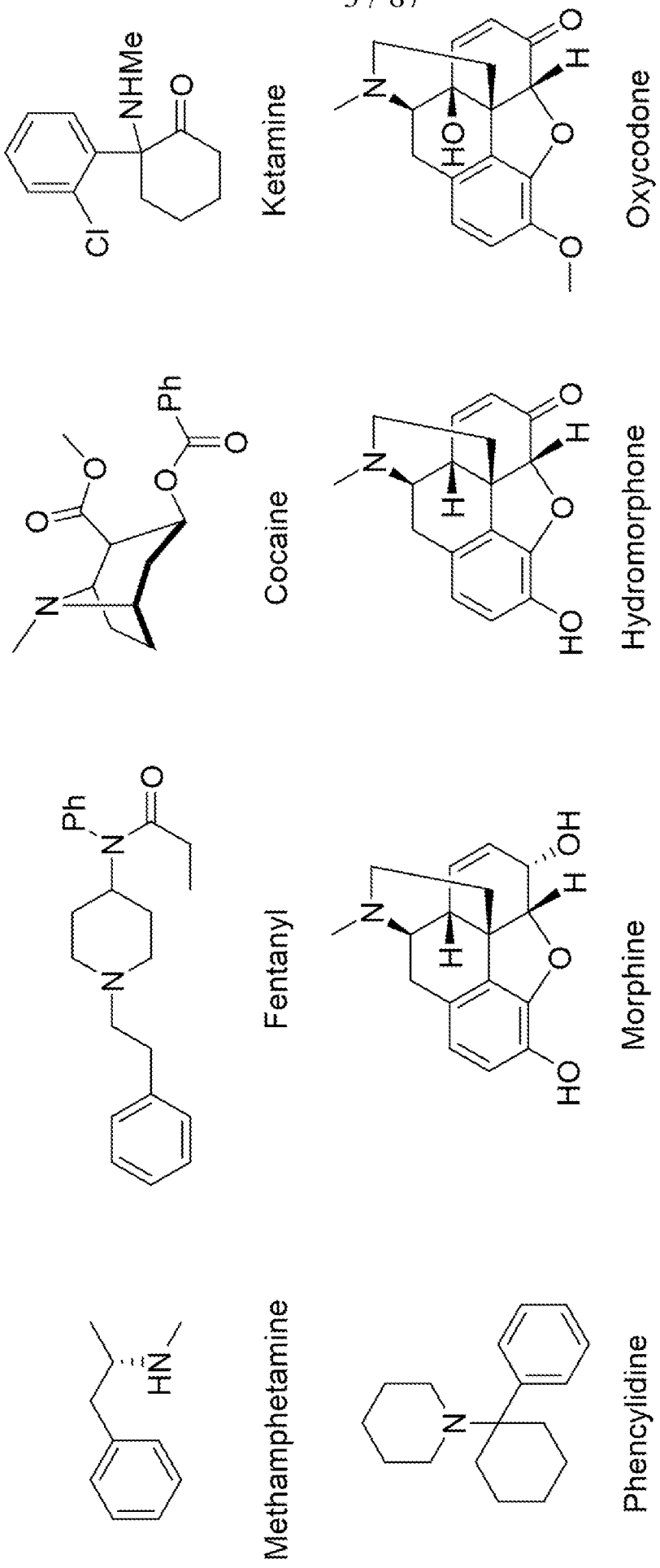

Ketamine
Oxycodone
Cocaine
Hydromorphone
Fentanyl
Morphine
Methamphetamine
Phencylidine

Figure 3

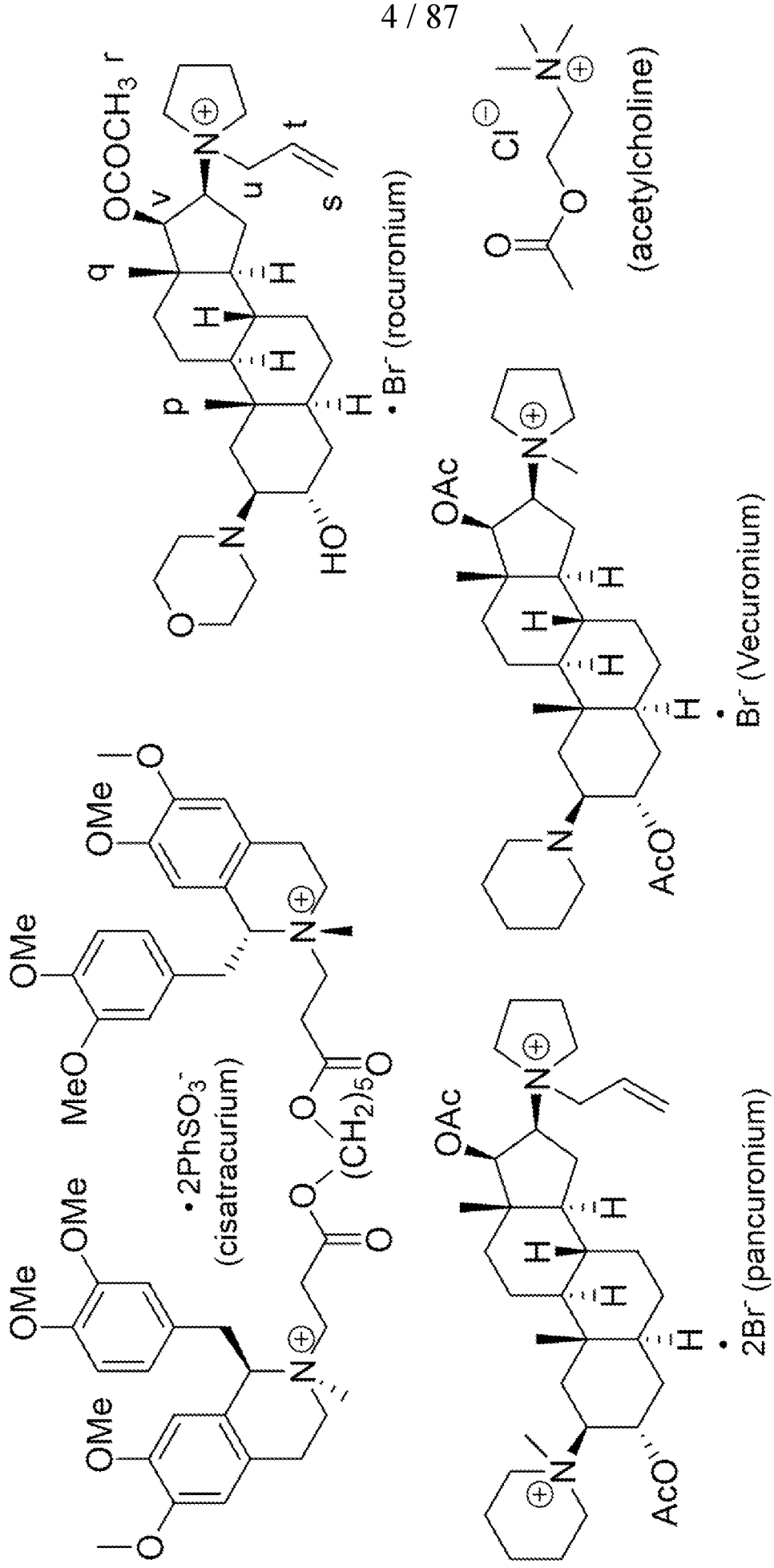

OCOCH3
r
q
v
u
t
s
p
H
HO
N
O
• Br⁻ (rocuronium)
Cl⁻
(acetylcholine)
OAc
AcO
• Br⁻ (Vecuronium)
OMe
MeO
• 2PhSO3⁻
(cisatracurium)
(CH2)5
• 2Br⁻ (pancuronium)

Figure 4

Guest	K_a with **P5ACS** (M^{-1}) ΔH and C value	K_a with **WP5**(M^{-1}) ΔH and C value	K_a with **P5AS** (M^{-1}) ΔH and C value	K_a with **WP6** (M^{-1}) ΔH and C value	K_a with **P6AS** (M^{-1}) ΔH and C value	K_a with **P6AS** (M^{-1}) ΔH and C	K_a with **P7AS** (M^{-1}) ΔH and C	K_a with **P6AP** (M^{-1}) ΔH and C
11	n.b.[a]	n.b.[a]	n.b.[a]	(1.60±0.20) x 10^{7}[f] -3.42±0.104 9.09	(2.06±0.18) x 10^{6}[b] -7.06±0.026 44.8	(1.12±0.08) x 10^{6}[b] -3.92±0.038 112	(2.84±0.33) x 10^{6}[e] -4.62±0.043 142	(1.40±0.19) x 10^{7}[e] -4.85±0.087 140
12	n.b.[a]	n.b.[a]	(8.55±1.41) x 10^{5}[e] -5.48±0.145 85.5	(5.26±0.59) x 10^{7}[g] -5.42±0.041 55	(2.32±0.24) x 10^{11}[k] -13.2±0.044 108	(1.37±0.12) x 10^{6}[e] -13.6±0.090 112	(3.64±0.46) x 10^{6}[e] -11.9±0.183 182	(8.13±0.49) x 10^{6}[e] -13.4±0.106 81.3
13	(3.89±0.71) x 10^{5}[b] -5.71±0.209 38.9	(1.38±0.04) x 10^{6}[b] -8.41±0.025 138	(4.41±0.22) x 10^{6}[e] -13.3±0.065 12.6	(1.35±0.04) x 10^{6}[b] -6.56±0.024 135	(1.08±0.01) x 10^{6}[e] -11.8±0.063 15.8	(1.11±0.09) x 10^{7}[e] -8.00±0.075 100.6	(2.67±0.40) x 10^{6}[b] -9.30±0.136 267	(7.36±0.38) x 10^{6}[b] -4.97±0.087 7.3
14	n.b.[a]	n.b.[a]	n.b.[a]	n.b.[a]	(5.18±0.15) x 10^{5}[b] -5.51±0.028 51.8	n.b.[a]	n.b.[a]	(5.65±0.10) x 10^{6}[e] -5.40±0.025 282.5
15	(2.78±0.14) x 10^{5}[b] -4.75±0.048 27.8	n.b.[a]	(2.16±0.14) x 10^{6}[e] -11.6±0.033 68	(1.53±0.24) x 10^{7}[f] -4.18±0.098 7.41	(7.87±0.63) x 10^{10}[k] -13.5±0.05 37.6	(1.11±0.16) x 10^{6}[e] -12.8±0.182 91.7	(1.64±0.20) x 10^{6}[e] -15.9±0.276 81.8	(1.20±0.10) x 10^{7}[e] -14.6±0.146 120
16	(3.33±0.22) x 10^{5}[b] -3.16±0.040 33.3	(1.10±0.09) x 10^{6}[b] -2.04±0.027 110	(6.85±0.01) x 10^{11}[k] -15.4±0.034 69.4	(2.60±0.20) x 10^{7}[g] -6.15±0.043 28.4	(1.86±0.10) x 10^{11}[k] -14.8±0.031 93.5	(1.75±0.27) x 10^{6}[e] -12.8±0.165 145	(4.27±0.27) x 10^{6}[e] -9.80±0.062 213.7	(2.62±0.33) x 10^{7}[e] -13.2±0.135 263
17	(1.12±0.05) x 10^{5}[b] -2.95±0.051 11.2	(2.11±0.19) x 10^{7}[f] -4.30±0.047 11.6	(8.77±0.37) x 10^{6}[e] -10.6±0.021 26.7	(2.62±0.36) x 10^{7}[g] -4.82±0.049 20.8	(1.43±0.01) x 10^{6}[e] -10.2±0.03 30	(3.92±0.36) x 10^{6}[e] -5.32±0.100 39.2	(5.08±0.50) x 10^{6}[e] -8.23±0.243 5.08	(2.79±0.20) x 10^{7}[e] -6.67±0.046 279
18	(3.52±0.18) x 10^{5}[b] -3.62±0.034 35.2	(3.55±0.30) x 10^{7}[f] -5.68±0.065 21.5	(1.38±0.10) x 10^{10}[k] -12.2±0.048 83.3	(2.87±0.22) x 10^{7}[g] -5.14±0.029 28	(4.98±0.04) x 10^{6}[e] -15.1±0.214 60.6	(3.28±0.38) x 10^{7}[g] -7.37±0.065 19.7	(5.92±1.14) x 10^{6}[e] -7.52±0.329 29.6	(3.53±0.43) x 10^{7}[e] -9.23±0.111 353

Figure 5

Guest	K_a with **P5ACS** (M^{-1}) ΔH and C value	K_a with **WP5**(M^{-1}) ΔH and C value	K_a with **P5AS** (M^{-1}) ΔH and C value	K_a with **WP6** (M^{-1}) ΔH and C value	K_a with **P6AS** (M^{-1}) ΔH and C value	K_a with **P6A8S** (M^{-1}) ΔH and C	K_a with **P7AS** (M^{-1}) ΔH and C	K_a with **P6AP** (M^{-1}) ΔH and C
19	(7.19±0.67) x $10^{5\,b}$ -3.98±0.056 71.9	(4.48±0.33) x $10^{7\,z}$ -6.18±0.06 27.9	(3.26±0.19) x $10^{11\,ae}$ -14.9±0.024 210	(4.35±0.31) x $10^{7\,z}$ -7.39±0.049 50.2	(1.68±0.09) x $10^{11\,k}$ -15.3±0.038 85.5	(6.29±1.12) x $10^{7\,z}$ -11.7±0.267 51.3	(6.49±0.82) x $10^{9\,x}$ -10.8±0.274 32.5	(2.16±0.23) x $10^{7\,z}$ -8.40±0.095 216
20	(3.97±0.27) x $10^{5\,b}$ -3.47±0.042 39.7	(1.13±0.08) x $10^{7\,z}$ -7.29±0.086 70.9	(9.90±0.02) x $10^{11\,ae}$ -18.6±0.092 217	(6.67±0.63) x $10^{7\,z}$ -8.68±0.069 79.4	(1.20±0.06) x $10^{11\,ae}$ -17.1±0.033 188	(2.90±0.66) x $10^{8\,x}$ -15.1±0.274 241.5	(3.60±0.33) x $10^{9\,x}$ -18.6±0.173 180	(2.71±0.23) x $10^{7\,z}$ -12.4±0.098 271
21	n.b.[a]	(6.54±0.78) x $10^{5\,z}$ -7.75±0.162 4.00	(1.39±0.03) x $10^{6\,d}$ -2.63±0.096 13.9	(6.70±0.33) x $10^{7\,z}$ -7.44±0.045 78.7	(1.80±0.10) x $10^{8\,w}$ -8.76±0.035 38.8	(9.09±0.80) x $10^{5\,b}$ -4.84±0.057 90.9	(3.30±0.16) x $10^{9\,x}$ -7.74±0.040 165	(1.64±0.17) x $10^{6\,z}$ -3.79±0.163 16.4
22	n.b.[a]	n.b.[a]	(2.22±0.20) x $10^{6\,z}$ -7.37±0.068 222	(8.47±1.09) x $10^{7\,z}$ -6.47±0.059 96	(4.52±0.36) x $10^{11\,k}$ -15.0±0.033 233	(2.01±0.38) x $10^{8\,x}$ -12.4±0.236 114	(2.58±0.25) x $10^{9\,x}$ -13.4±0.167 129	(1.25±0.08) x $10^{6\,z}$ -13.8±0.243 12.5
23	(2.04±0.13) x $10^{5\,b}$ -4.04±0.060 20.4	(8.52±0.47) x $10^{6\,z}$ -6.30±0.048 4.90	(1.46±0.05) x $10^{9\,x}$ -11.8±0.040 117	(3.14±0.46) x $10^{7\,z}$ -5.86±0.087 31.7	(6.49±0.66) x $10^{10\,k}$ -12.9±0.056 31	(1.36±0.27) x $10^{8\,x}$ -14.1±0.341 84.7	(3.52±0.28) x $10^{9\,x}$ -10.2±0.084 176	(1.26±0.11) x $10^{7\,z}$ -14.1±0.149 126
24	n.b.[a]	n.b.[a]	(8.47±0.84) x $10^{6\,b}$ -7.62±0.300 8.47	(2.11±0.10) x $10^{7\,z}$ -10.1±0.058 27	(7.04±1.19) x $10^{5\,b}$ -3.63±0.112 70.4	n.b.[a]	(1.35±0.12) x $10^{6\,b}$ -5.54±0.055 135	(9.01±0.59) x $10^{4\,b}$ -2.98±0.064 9.01
25	n.b.[a]	n.b.[a]	(1.64±0.19) x $10^{6\,z}$ -6.36±0.197 16.4	(3.69±0.16) x $10^{10\,ae}$ -16.6±0.031 216	(2.02±0.01) x $10^{9\,x}$ -11.0±0.051 59.5	(9.43±0.79) x $10^{8\,x}$ -8.61±0.096 94.3	(1.78±0.14) x $10^{7\,z}$ -9.67±0.071 178	(2.44±0.17) x $10^{9\,x}$ -9.28±0.062 244

Figure 5 (cont.)

SUBSTITUTE SHEET (RULE 26)

Guest	K_a with **P5ACS** (M^{-1}) ΔH and C value	K_a with **WP5** (M^{-1}) ΔH and C value	K_a with **P5AS** (M^{-1}) ΔH and C value	K_a with **WP6** (M^{-1}) ΔH and C value	K_a with **P6AS** (M^{-1}) ΔH and C value	K_a with **P6A8S** (M^{-1}) ΔH and C	K_a with **P7AS** (M^{-1}) ΔH and C	K_a with **P6AP** (M^{-1}) ΔH and C
26	n.b.[a]	n.b.[a]	(3.11±0.57) x 10^{8} [f] -1.63±0.121 3.11	(9.26±0.53) x 10^{6} [b] -4.07±0.070 9.26	(2.32±0.08) x 10^{6} [b] -7.57±0.024 232	(1.59±0.06) x 10^{5} [b] -5.17±0.050 15.9	(9.26±1.09) x 10^{4} [b] -3.27±0.142 9.26	(1.03±0.06) x 10^{6} [b] -8.15±0.080 103
27	n.b.[a]	n.b.[a]	(9.90±2.18) x 10^{8} [f] -3.84±0.236 9.9	(4.35±0.27) x 10^{5} [a] -3.21±0.033 43.5	(2.23±0.16) x 10^{5} [a] -9.64±0.171 22.3	n.b.[a]	n.b.[a]	(3.75±0.27) x 10^{6} [b] -2.58±0.078 3.75
28	n.b.[a]	n.b.[a]	(1.69±0.01) x 10^{7} [o] -7.87±0.030 15.1	(1.99±0.14) x 10^{6} [a] -5.62±0.039 199	(2.42±0.12) x 10^{7} [u] -7.81±0.038 100.9	(6.49±0.75) x 10^{5} [a] -4.53±0.083 64.9	n.b.[a]	(1.98±0.21) x 10^{7} [c] -4.88±0.055 198

[a] n.b. = no inclusion binding detected by ITC. [b] Measured directly by ITC during the titration of Host (0.1 mM) in the cell with Guest (1 mM) in the syringe. [c] Measured directly by ITC during the titration of Host (0.01 mM) in the cell with Guest (0.1 mM) in the syringe. [d] Measured directly by ITC during the titration of Host (1.0 mM) in the cell with Guest (10 mM) in the syringe. [e] Measured directly by ITC during the titration of Host (0.05 mM) in the cell with Guest (1 mM) in the syringe and the N sites is 2. [f] Measured by competition with **13** (0.15 mM). [g] Measured by competition with **27** (0.2 mM). [h] Measured by competition with **14** (1 mM). [i] Measured by competition with **14** (10 mM). [j] Measured by competition with **16** (0.15 mM). [k] Measured by competition with **17** (0.15 mM). [l] Measured by competition with **17** (0.2 mM). [m] Measured by competition with **17** (0.5 mM). [n] Measured by competition with **17** (1.0 mM). [o]Measured by competition with **21** (10 mM). [p] Measured by competition with **24** (0.9 mM). [q] Measured by competition with **28** (0.11 mM). [r] Measured by competition with **28** (0.2 mM). [s] Measured by competition with **28** (1.0 mM). [t] Measured directly by ITC during the titration of Host (0.1 mM) in the cell with Guest (2 mM) in the syringe and the N sites is 2. [u] Measured by competition with **14** (5 mM). [v] Measured directly by ITC during the titration of Host (0.05 mM) in the cell with Guest (0.5 mM) in the syringe.

Figure 5 (cont.)

Guest	K_a with P5ACS (M^{-1}) ΔH, C	K_a with WP5 (M^{-1}) ΔH, C	K_a with P5AS (M^{-1}) ΔH, C	K_a with WP6 (M^{-1}) ΔH, C	K_a with P6AS (M^{-1}) ΔH, C	K_a with P6ASS (M^{-1}) ΔH, C	K_a with P7AS (M^{-1}) ΔH, C	K_a with Calabadion 1 (M^{-1})	K_a with Calabadion 2 (M^{-1})
Meth	n.b.[d]	n.b.[d]	n.b.[d]	$(1.72 \pm 0.05) \times 10^{6[a]}$ -7.75±0.023 172	$(9.90 \pm 0.39) \times 10^{6[b]}$ -10.4±0.04 11	$(3.88 \pm 0.12) \times 10^{5[a]}$ -5.95±0.030 38.8	$(2.03 \pm 0.13) \times 10^{5[a]}$ -6.86±0.098 20.3	(7.5 ± 2.9) x 10^6	$(4.3 \pm 1.0$ x 10^6
Fentanyl	$(8.33 \pm 0.58) \times 10^{5[a]}$ -9.17±0.089 83.3	$(4.42 \pm 0.18) \times 10^{4[a]}$ -8.33±0.155 4.42	$(6.62 \pm 0.45) \times 10^{5[a]}$ -9.78±0.115 66.2	$(1.69 \pm 0.06) \times 10^{6[a]}$ -11.9±0.051 169	$(1.02 \pm 0.03) \times 10^{6[c]}$ -15.0±0.052 21.8	$(1.38 \pm 0.09) \times 10^{6[a]}$ -12.2±0.094 138	$(6.85 \pm 0.44) \times 10^{6[f]}$ -14.1±0.131 68.5	(1.1 ± 0.0) x 10^7	$(7.6 \pm 0.5$ x 10^5
Cocaine	n.b.[d]	n.b.[d]	n.b.[d]	n.b.[d]	$(1.92 \pm 0.06) \times 10^{6[a]}$ -15.6±0.047 192	n.b.[d]	n.b.[d]	(6.6 ± 0.4) x 10^5	$(1.0 \pm 0.1$ x 10^6
Ketamine	n.b.[d]	n.b.[d]	$(1.09 \pm 0.14) \times 10^{5[a]}$ -14.2±0.635 10.9	n.b.[d]	$(1.52 \pm 0.25) \times 10^{5[a]}$ -22.0±1.02 15.2	$(5.85 \pm 0.17) \times 10^{4[a]}$ -11.2±0.118 5.85	$(2.99 \pm 0.09) \times 10^{5[a]}$ -12.7±0.078 29.9	(1.1 ± 0.1) x 10^6	$(1.8 \pm 0.1$ x 10^5
Phencyclidine	n.b.[d]	n.b.[d]	$(2.31 \pm 0.45) \times 10^{5[a]}$ -6.74±0.302 25.1	$(9.01 \pm 0.19) \times 10^{4[a]}$ -8.64±0.053 9.01	$(5.85 \pm 0.47) \times 10^{7[c]}$ -12.4±0.076 71.9	$(7.04 \pm 0.91) \times 10^{5[a]}$ -7.23±0.147 70.4	$(1.08 \pm 0.06) \times 10^{7[f]}$ -12.4±0.082 108	(4.7 ± 0.5) x 10^6	$(2.1 \pm 0.1$ x 10^5
Morphine	n.b.[d]	n.b.[d]	n.b.[d]	$(4.15 \pm 0.11) \times 10^{5[a]}$ -11.7±0.052 41.5	$(1.36 \pm 0.07) \times 10^{6[a]}$ -12.9±0.073 136	$(8.62 \pm 0.31) \times 10^{4[a]}$ -7.53±0.084 8.62	$(8.85 \pm 0.93) \times 10^{5[a]}$ -15.3±0.257 88.5	(5.3 ± 0.3) x 10^5	$(6.3 \pm 0.4$ x 10^5

Figure 6

Guest	K_a with P5ACS (M^{-1}) ΔH, C	K_a with WP5 (M^{-1}) ΔH, C	K_a with P5AS (M^{-1}) ΔH, C	K_a with WP6 (M^{-1}) ΔH, C	K_a with P6AS (M^{-1}) ΔH, C	K_a with P6ASS (M^{-1}) ΔH, C	K_a with P7AS (M^{-1}) ΔH, C	K_a with Calabadion 1 (M^{-1})	K_a with Calabadion 2 (M^{-1})
Hydromorphone	n.b.[d]	n.b.[d]	n.b.[d]	$(8.55 \pm 0.16) \times 10^{4}$[a] -10.6±0.056 8.55	$(1.31 \pm 0.04) \times 10^{6}$[a] -11.9±0.042 131	$(6.95 \pm 0.28) \times 10^{4}$[c] -6.45±0.114 5.95	$(1.87 \pm 0.26) \times 10^{6}$[c] -18.0±0.290 187	$(1.8 \pm 0.0) \times 10^{5}$	$(6.8 \pm 10^{5}$
Oxycodone	n.b.[d]	n.b.[d]	n.b.[d]	n.b.[d]	$(9.52 \pm 0.36) \times 10^{4}$[a] -8.62±0.097 9.52	$(7.35 \pm 1.22) \times 10^{4}$[c] -2.94±0.194 7.35	$(1.58 \pm 0.13) \times 10^{6}$[c] -18.1±0.162 158		

[a] Measured directly by ITC during the titration of Host (0.1 mM) in the cell with Guest (1 mM) in the syringe. [b] Measured by competition with **14** (0.15 mM). [c] Measured by competition with **14** (1 mM). [d] n.b. = no inclusion binding detected by ITC. [e] Measured directly by ITC during the titration of Host (0.05 mM) in the cell with Guest (1 mM) in the syringe and the N sites is 2. [f] Measured directly by ITC during the titration of Host (0.01 mM) in the cell with Guest (0.1 mM) in the syringe.

Figure 6 (cont.)

Guest	K_a with WP5 (M^{-1}) ΔH and C	K_a with P5AS (M^{-1}) ΔH and C	K_a with WP6 (M^{-1}) ΔH and C	K_a with P6AS (M^{-1}) ΔH and C	K_a with P6A8S (M^{-1}) ΔH and C	K_a with P7AS (M^{-1}) ΔH and C	K_a with P6AP (M^{-1}) ΔH and C	K_a with Calabadion 1 (M^{-1})	K_a with Calabadion 2 (M^{-1})
cisatracurium	$(1.52 \pm 0.02) \times 10^{5a}$ -18.6±0.75 15.2	$(2.60 \pm 0.27) \times 10^{5a}$ -11.4±0.255 26	$(1.05 \pm 0.01) \times 10^{5a}$ -17.3±0.084 10.3	$(9.52 \pm 2.12) \times 10^{5a}$ -22.4±0.747 95.2	$(4.29 \pm 0.34) \times 10^{5a}$ -11.9±0.161 42.9	$(1.52 \pm 0.12) \times 10^{5a}$ -35.0±0.396 152	n.b.[b]	$(9.7 \pm 0.8) \times 10^{5}$	$(4.8 \pm 0.9) \times 10^{6}$
rocuronium	n.b.[b]	$(4.42 \pm 0.16) \times 10^{5d}$ -13.4±0.082 42.2	$(1.42 \pm 0.05) \times 10^{6de}$ -13.6±0.018 142	$(6.33 \pm 0.08) \times 10^{11c}$ -24.9±0.177 172	$(7.04 \pm 0.84) \times 10^{5e}$ -15.5±0.295 70.4	$(1.41 \pm 0.09) \times 10^{5f}$ -13.3±0.090 141	$(4.24 \pm 0.22) \times 10^{5e}$ -12.7±0.109 42.4	$(8.4 \pm 0.9) \times 10^{6}$	$(3.4 \pm 0.6) \times 10^{6}$
vecuronium	n.b.[b]	$(1.12 \pm 0.07) \times 10^{6d}$ -7.46±0.063 112	$(2.87 \pm 0.31) \times 10^{6de}$ -8.01±0.078 287	$(1.00 \pm 0.34) \times 10^{12c}$ -18.5±0.095 266	$(6.21 \pm 0.62) \times 10^{5e}$ -12.1±0.190 62.1	$(0.35 \pm 0.58) \times 10^{6f}$ -15.8±0.133 93.5	$(8.93 \pm 0.59) \times 10^{5e}$ -9.38±0.082 89.3	$(5.8 \pm 0.9) \times 10^{6}$	$(1.6 \pm 0.2) \times 10^{6}$
pancuronium	n.b.[b]	$(1.51 \pm 0.14) \times 10^{6d}$ -8.35±0.092 151	$(1.57 \pm 0.06) \times 10^{6de}$ -8.10±0.030 157	$(7.35 \pm 1.23) \times 10^{6def}$ -16.3±0.216 32.7	$(4.33 \pm 0.55) \times 10^{5ef}$ -12.5±0.291 43.3	$(7.58 \pm 0.61) \times 10^{6d}$ -18.1±0.198 75.8	$(2.90 \pm 0.12) \times 10^{5ef}$ -9.75±0.077 29	$(4.5 \pm 0.1) \times 10^{5}$	$(5.3 \pm 0.5) \times 10^{6}$
acetylcholine	n.b.[b]	$(3.79 \pm 0.13) \times 10^{5a}$ -9.59±0.06 37.9	$(1.87 \pm 0.21) \times 10^{5a}$ -6.28±0.170 18.7	$(5.15 \pm 0.38) \times 10^{7e}$ -14.8±0.094 67.6	n.b.[b]	n.b.[b]	n.b.[b]	$(2.4 \pm 0.1) \times 10^{4}$	$(1.8 \pm 0.2) \times 10^{5}$

Figure 7

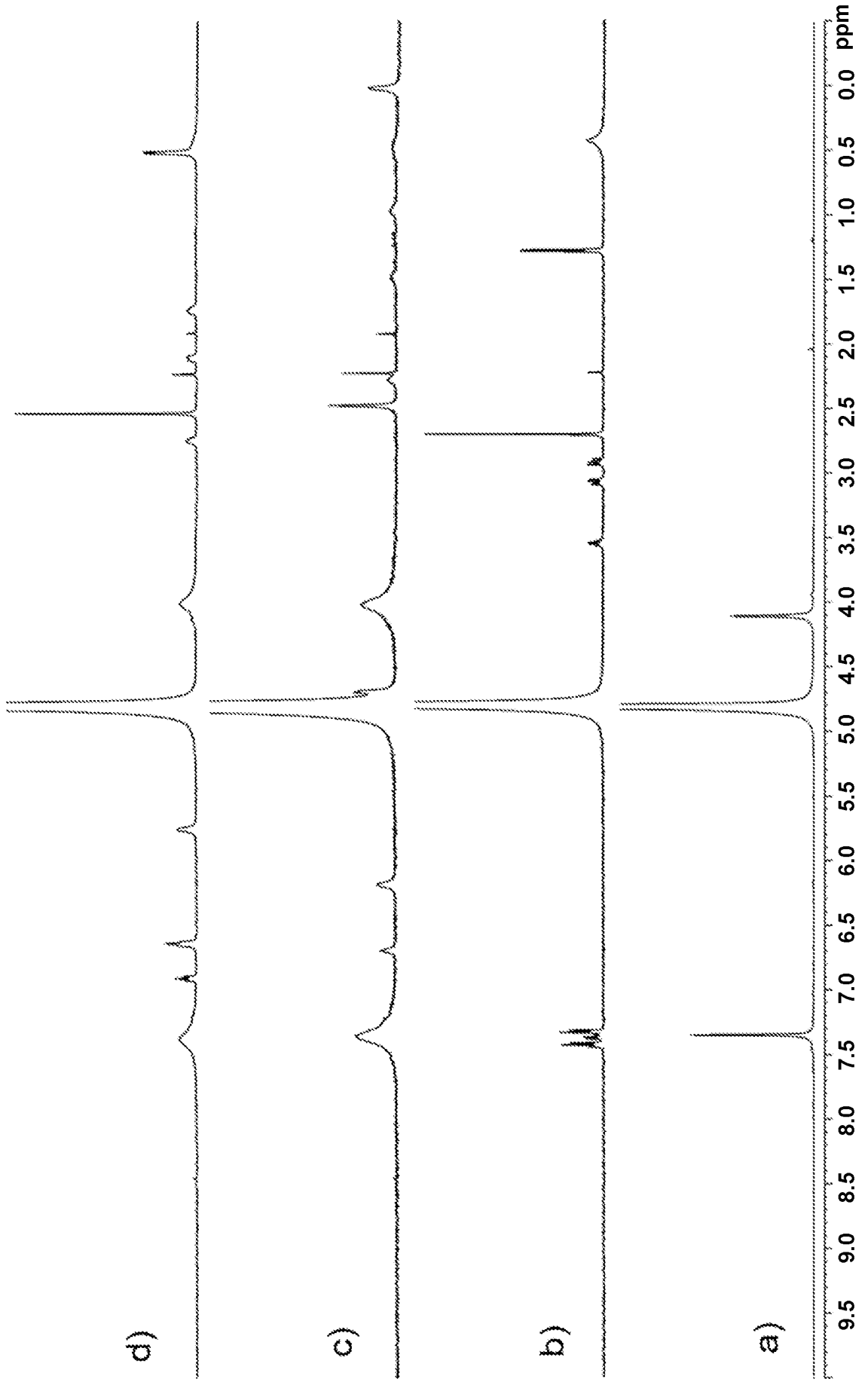


Figure 8

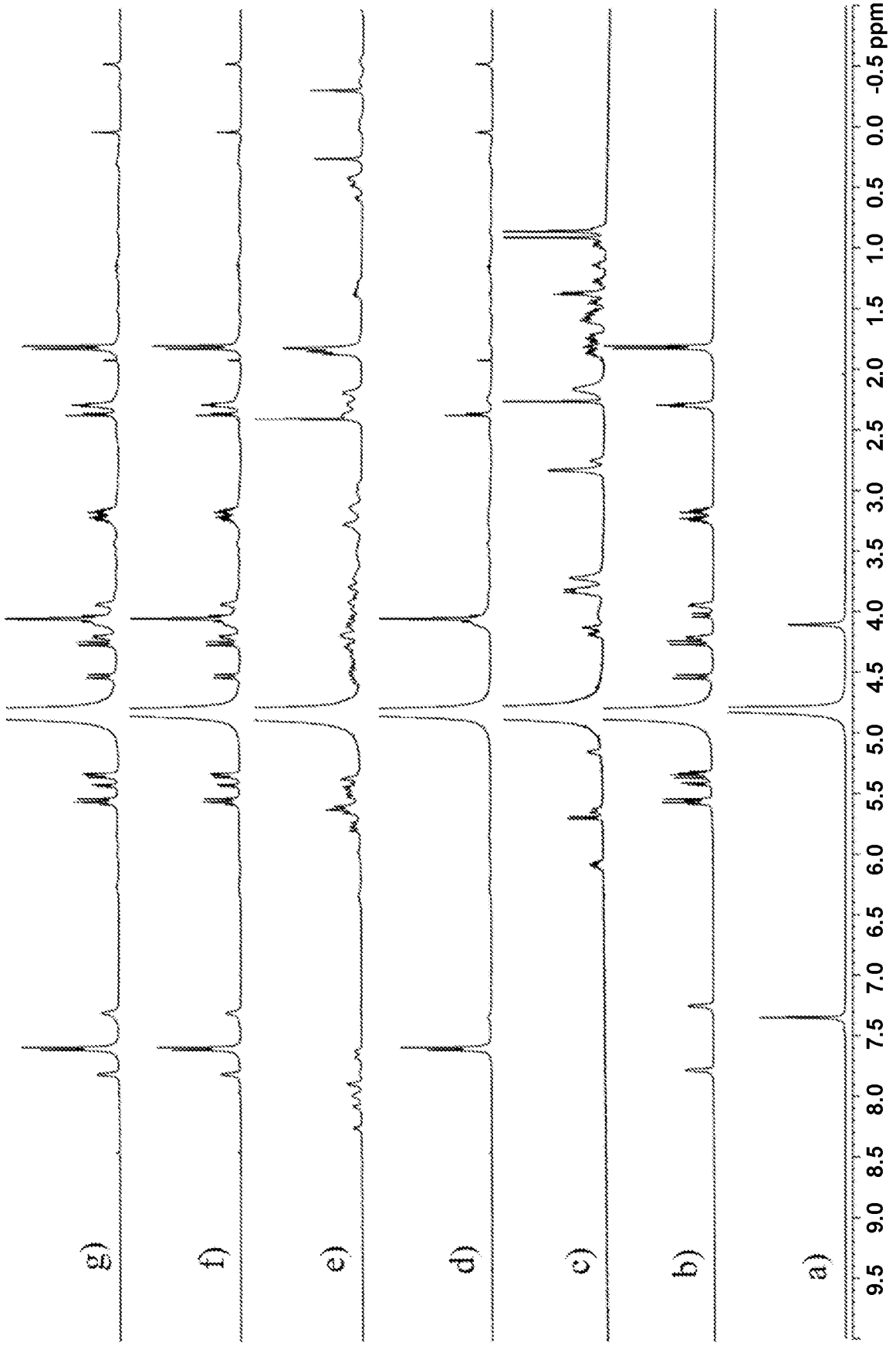

g)
f)
e)
d)
c)
b)
a)
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 ppm

Figure 9

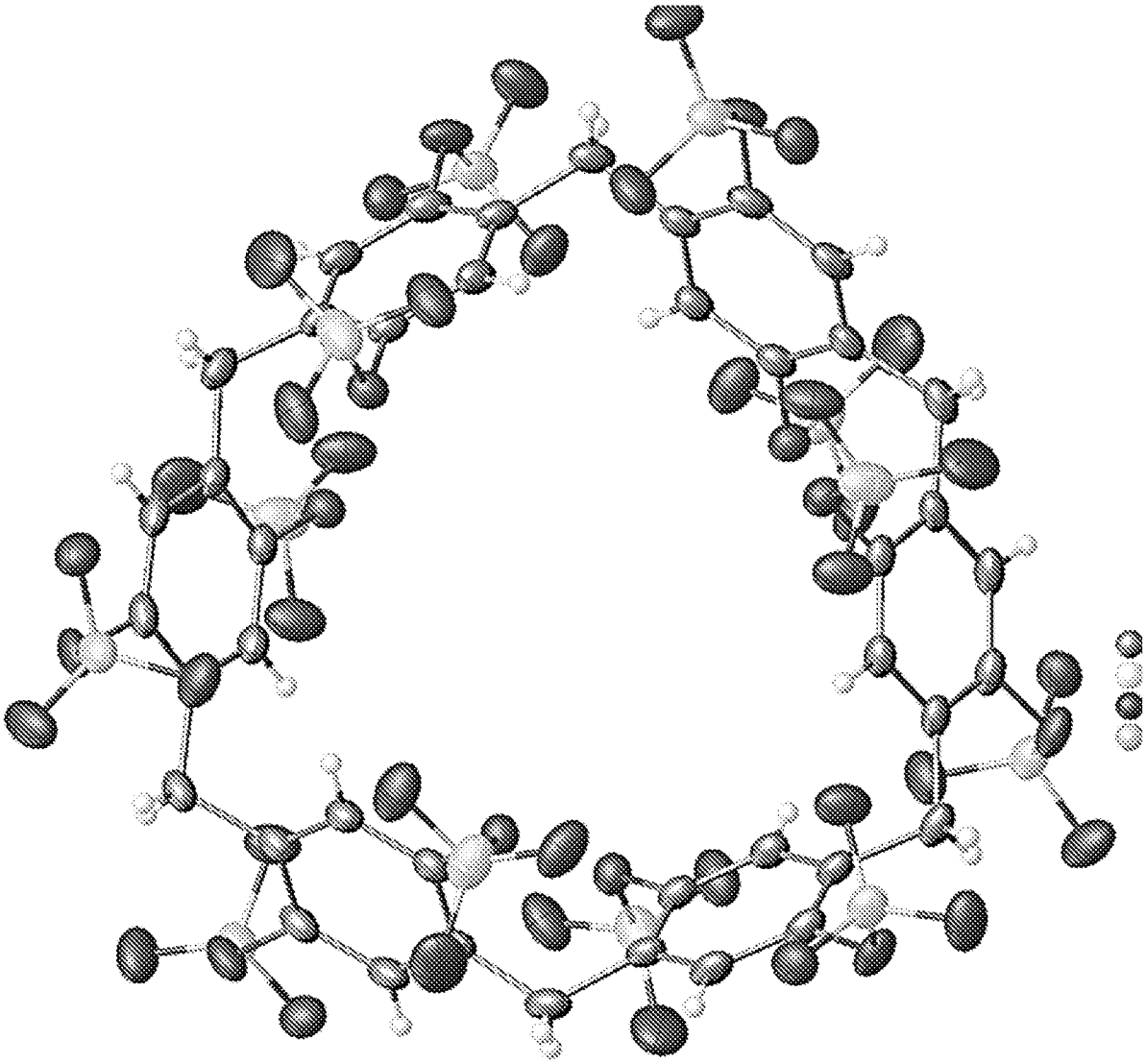


Figure 10

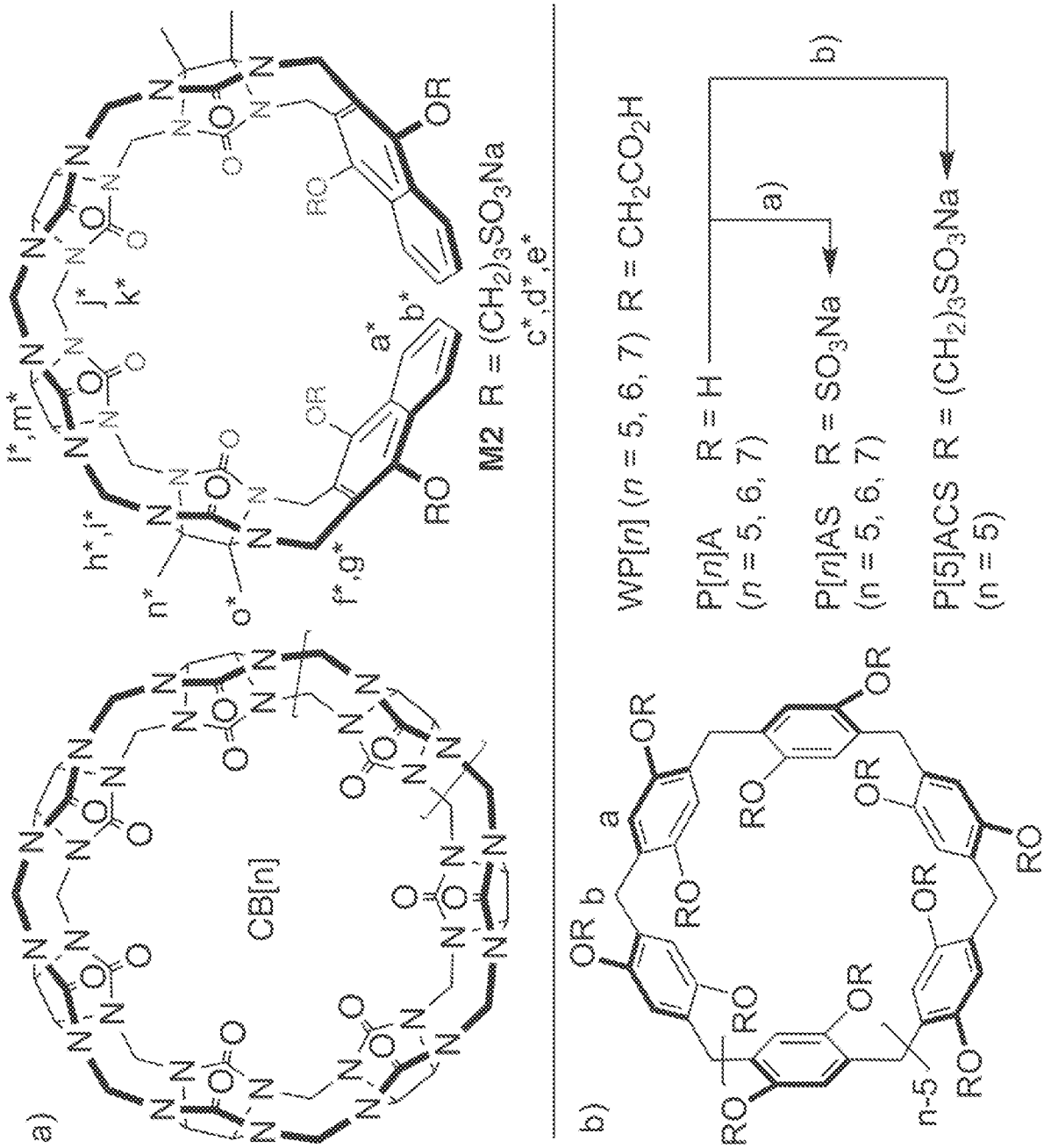

a)
OB[n]
M2 R = (CH2)3SO3Na
c*,d*,e*
f*,g*
h*,i*
l*,m*
n*
o*
a*
b*
OR
RO
b)
WP[n] (n = 5, 6, 7) R = CH2CO2H
P[n]A R = H
(n = 5, 6, 7)
P[n]AS R = SO3Na
(n = 5, 6, 7)
P[5]ACS R = (CH2)3SO3Na
(n = 5)
a)
b)
n-5

Figure 11

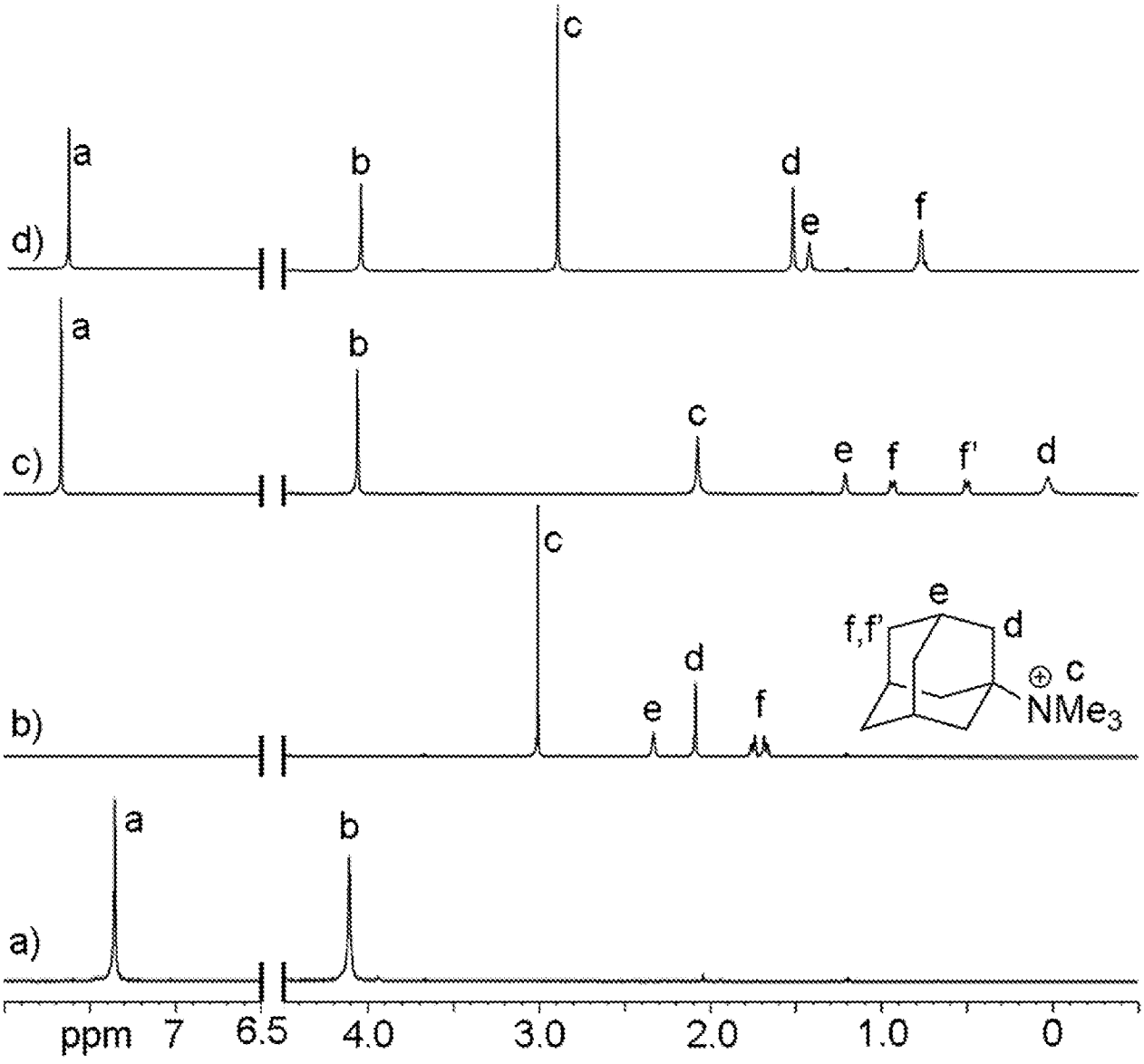


Figure 12

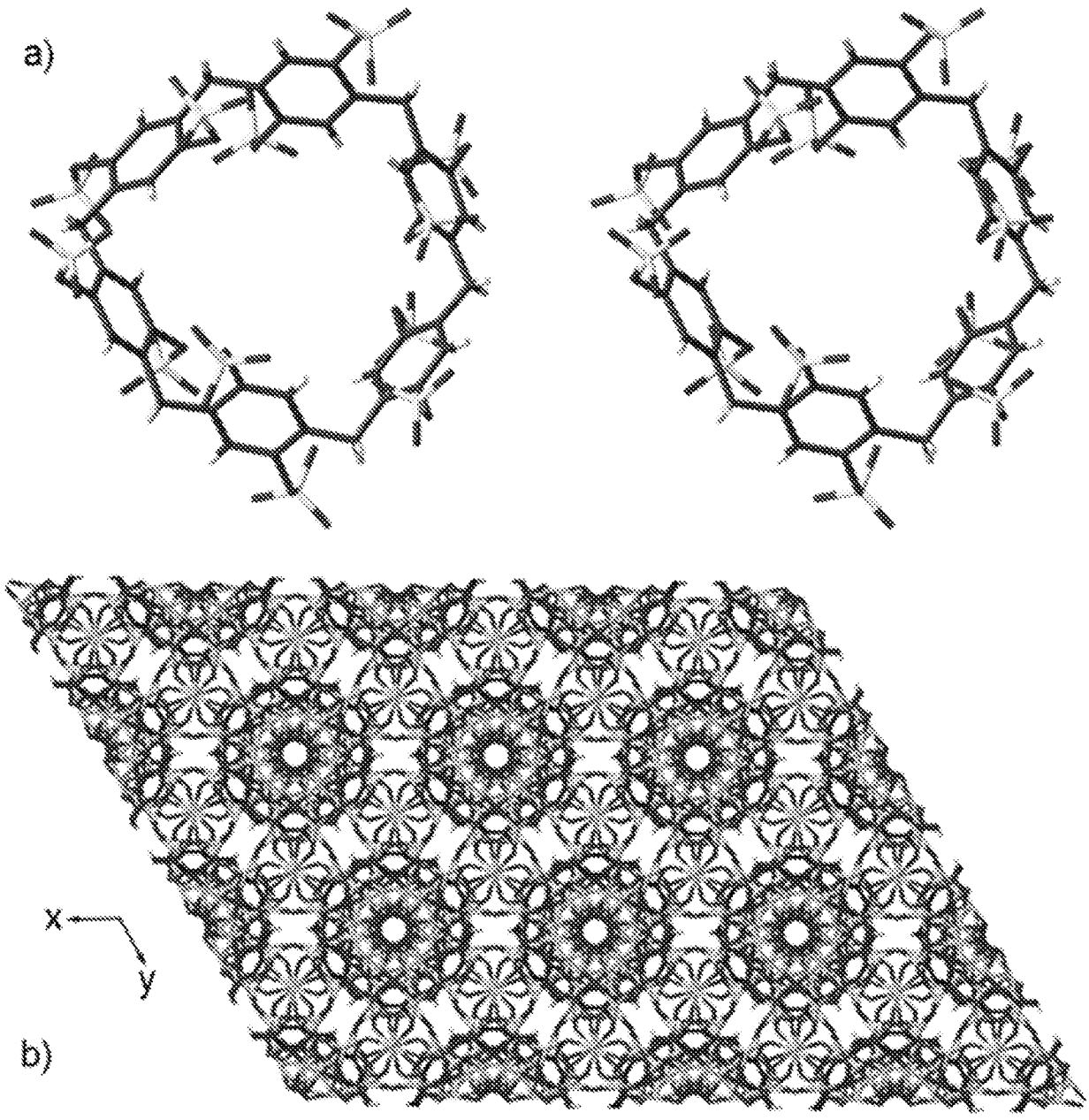


Figure 13

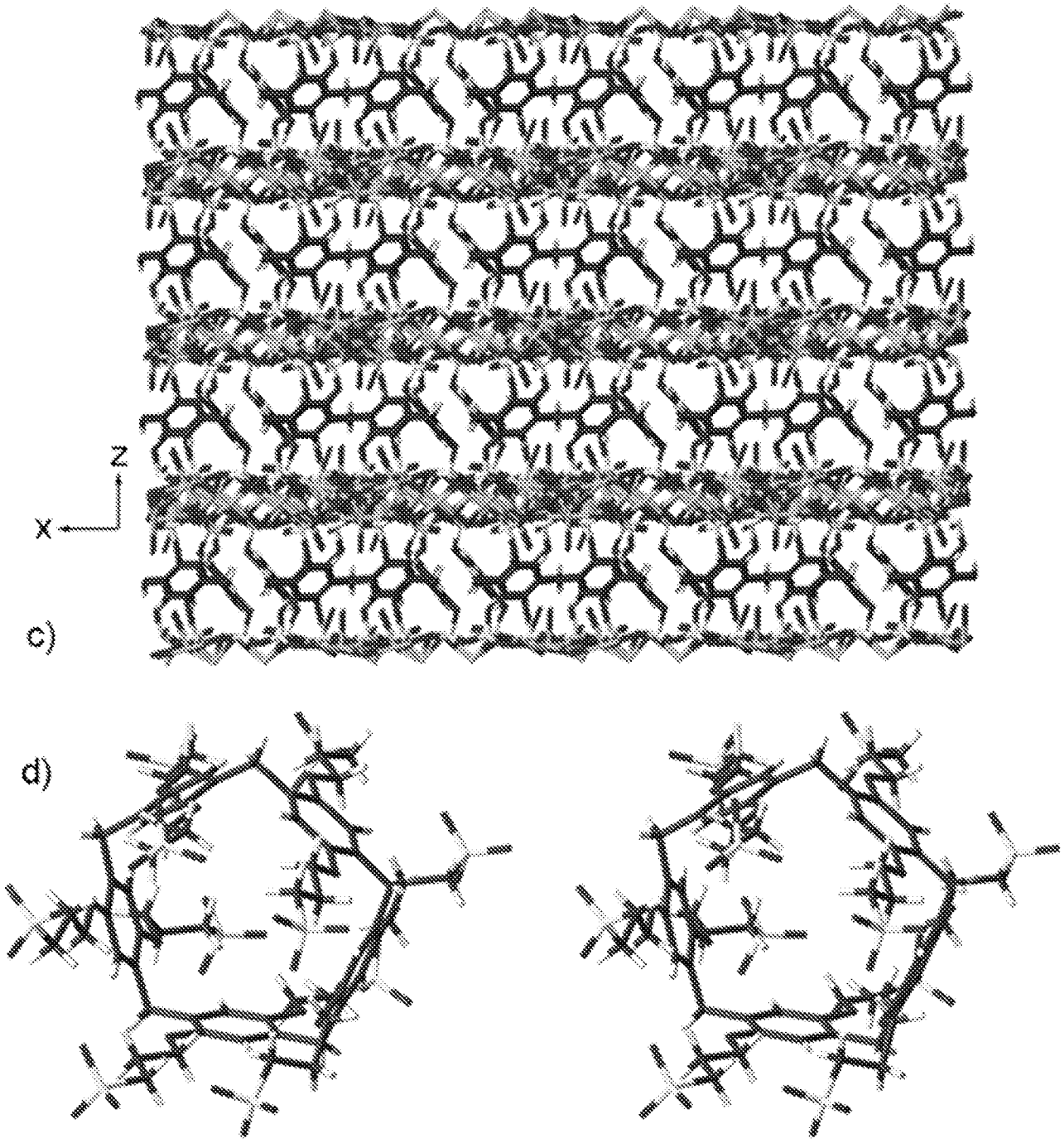


Figure 13 (cont.)

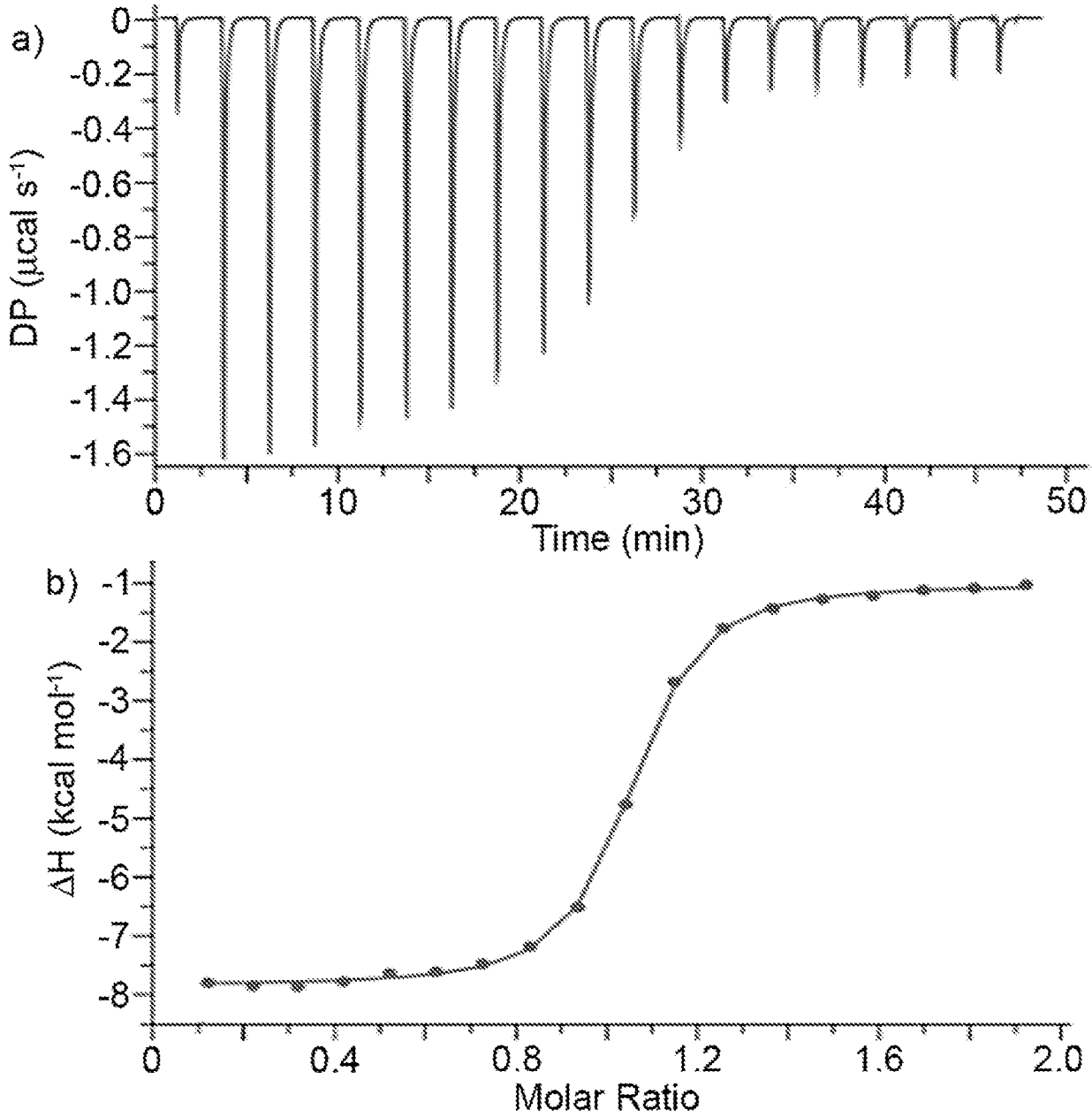

a)
DP (µcal s-1)
0
-0.2
-0.4
-0.6
-0.8
-1.0
-1.2
-1.4
-1.6
0
10
20
30
40
50
Time (min)
b)
ΔH (kcal mol-1)
-1
-2
-3
-4
-5
-6
-7
-8
0
0.4
0.8
1.2
1.6
2.0
Molar Ratio

Figure 14

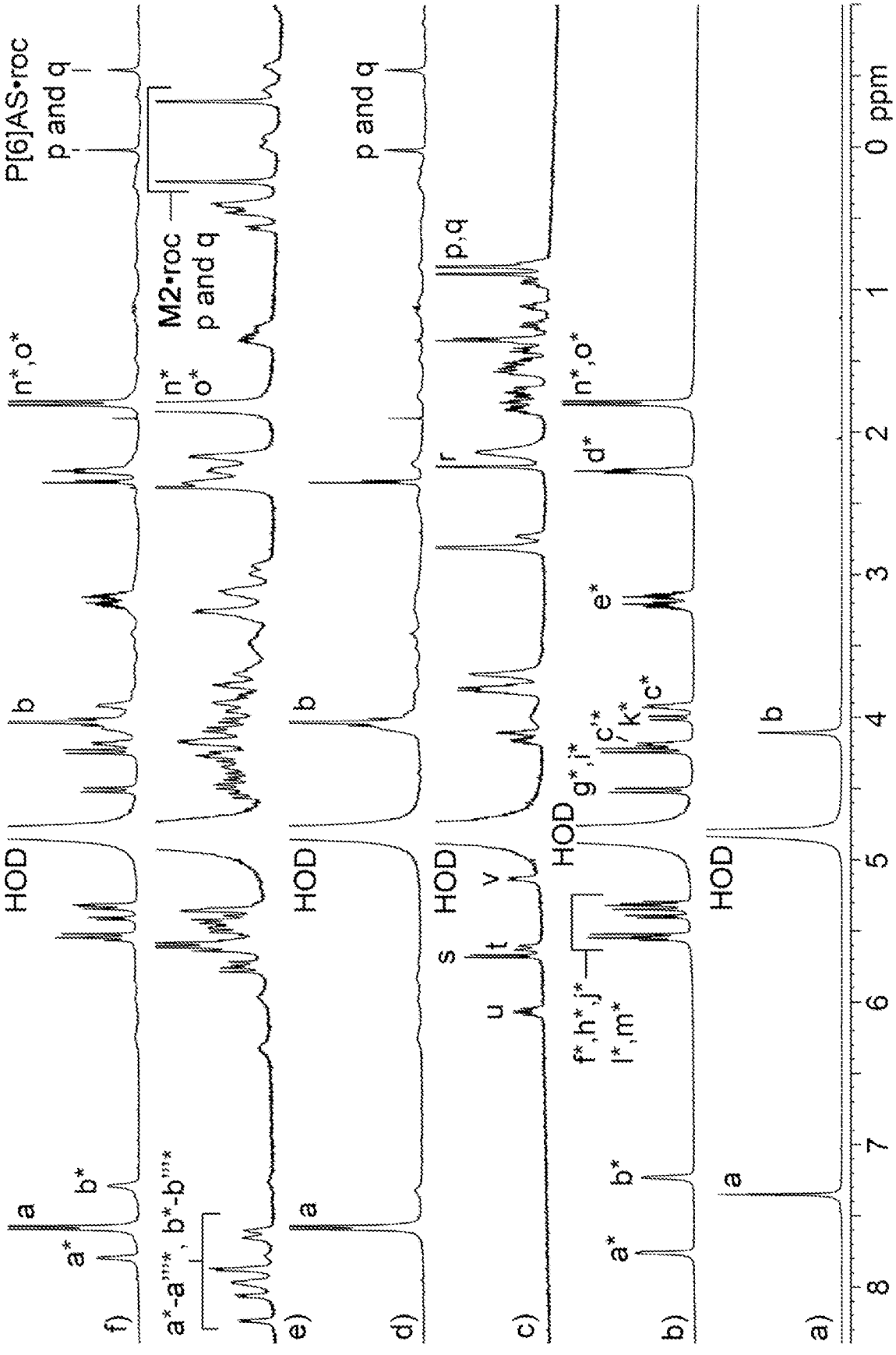

P[6]AS•roc
p and q
n*,o*
b
HOD
a
a*
b*
f)
a*-a'''*, b*-b'''*
n*
o*
M2•roc
p and q
e)
d)
p,q
r
s
t
u
v
g*,i*
c'*
k*
c*
e*
d*
f*,h*,j*
l*,m*
b)
a)
0 ppm

Figure 15

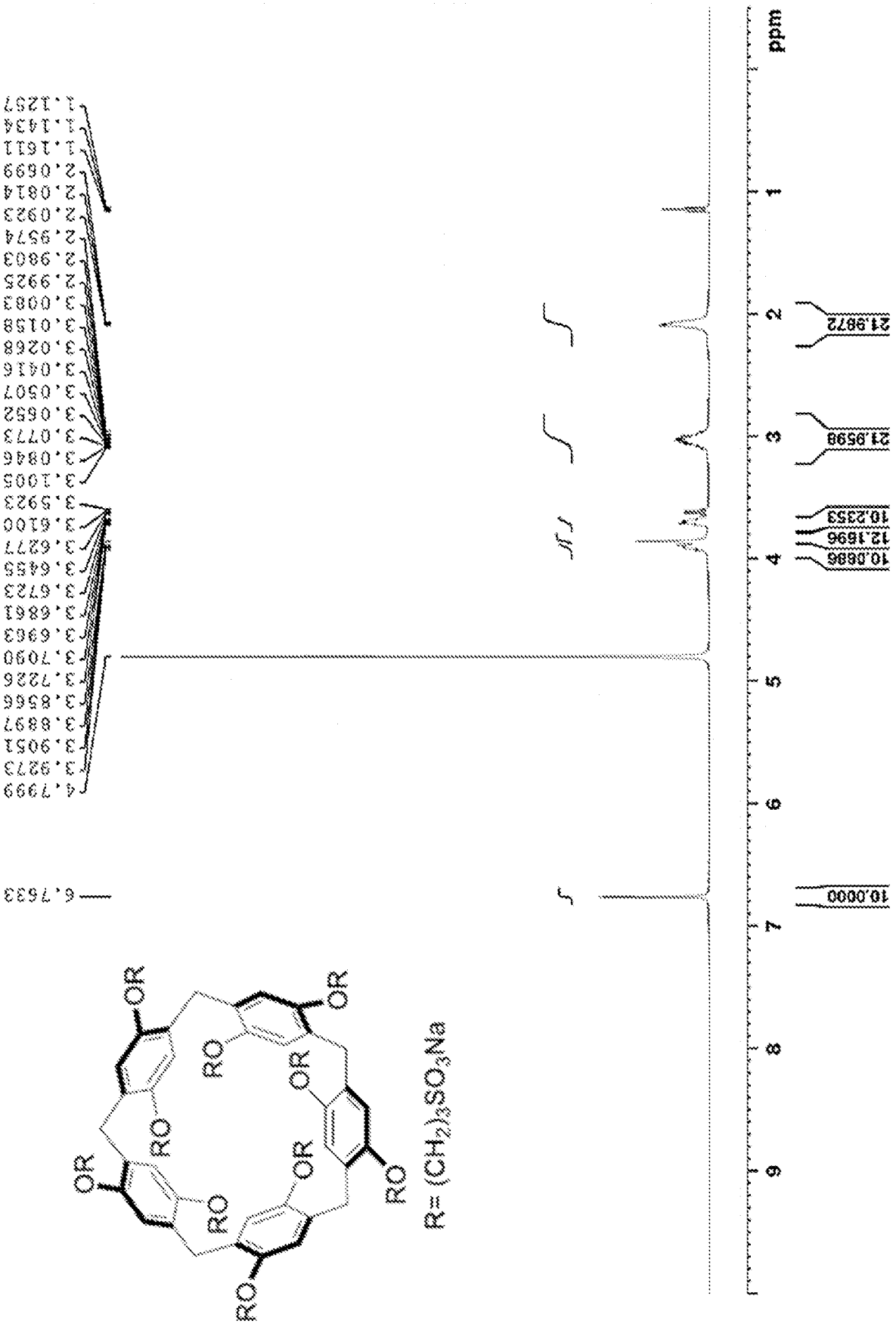

ppm
10.0000
21.9872
21.9598
10.0686
12.1696
10.2353
6.7633
4.7999
3.9273
3.9051
3.8897
3.8566
3.7226
3.7090
3.6963
3.6861
3.6723
3.6455
3.6277
3.6100
3.5923
3.1005
3.0846
3.0773
3.0652
3.0507
3.0416
3.0268
3.0158
3.0083
2.9925
2.9803
2.9574
2.0923
2.0814
2.0699
1.1611
1.1434
1.1257
OR
RO
R= (CH2)3SO3Na

Figure 16

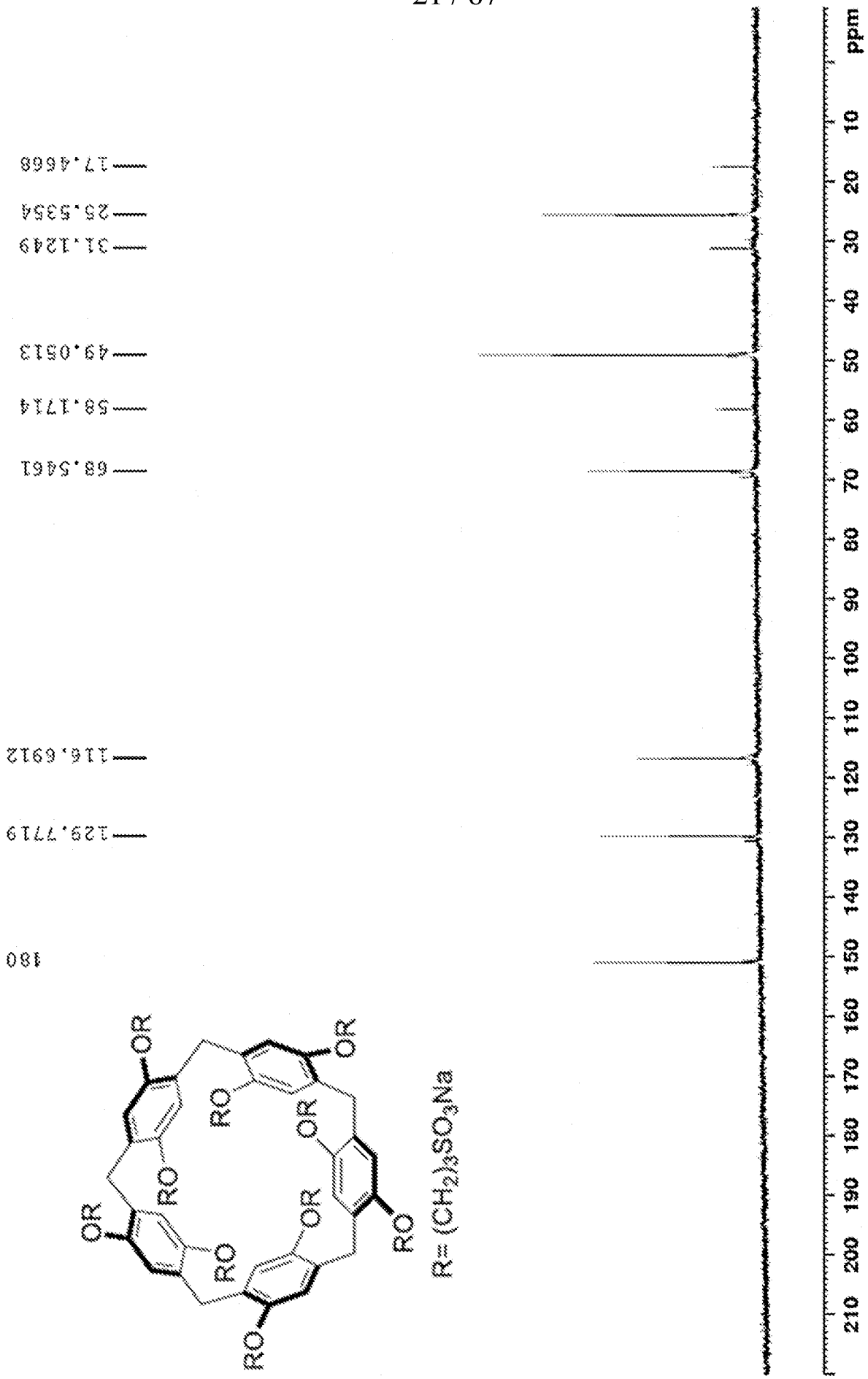

17.4668
25.5354
31.1249
49.0513
58.1714
68.5461
116.6912
129.7719
180
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
OR
RO
R= $(CH_2)_3SO_3Na$

Figure 17

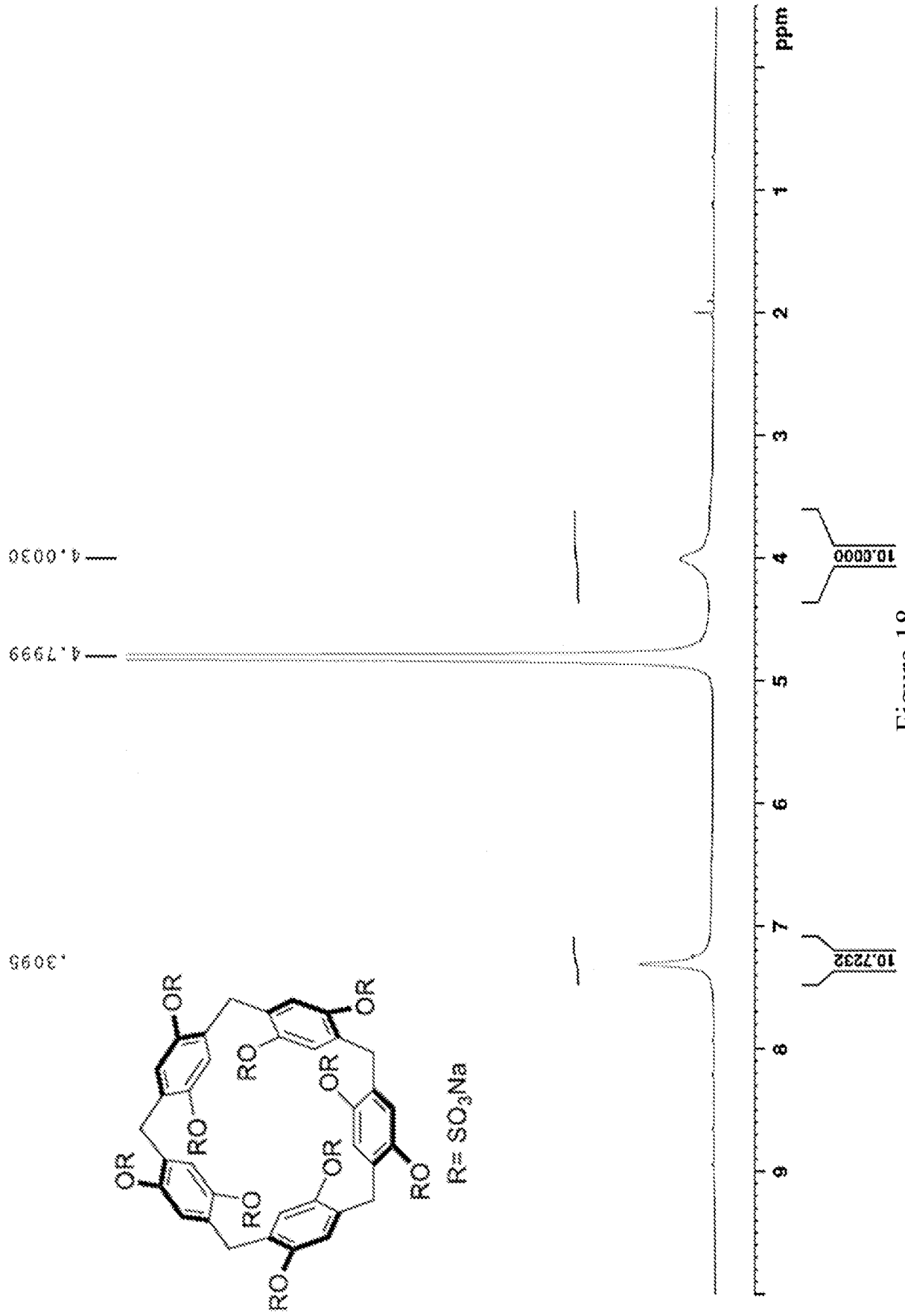


Figure 18

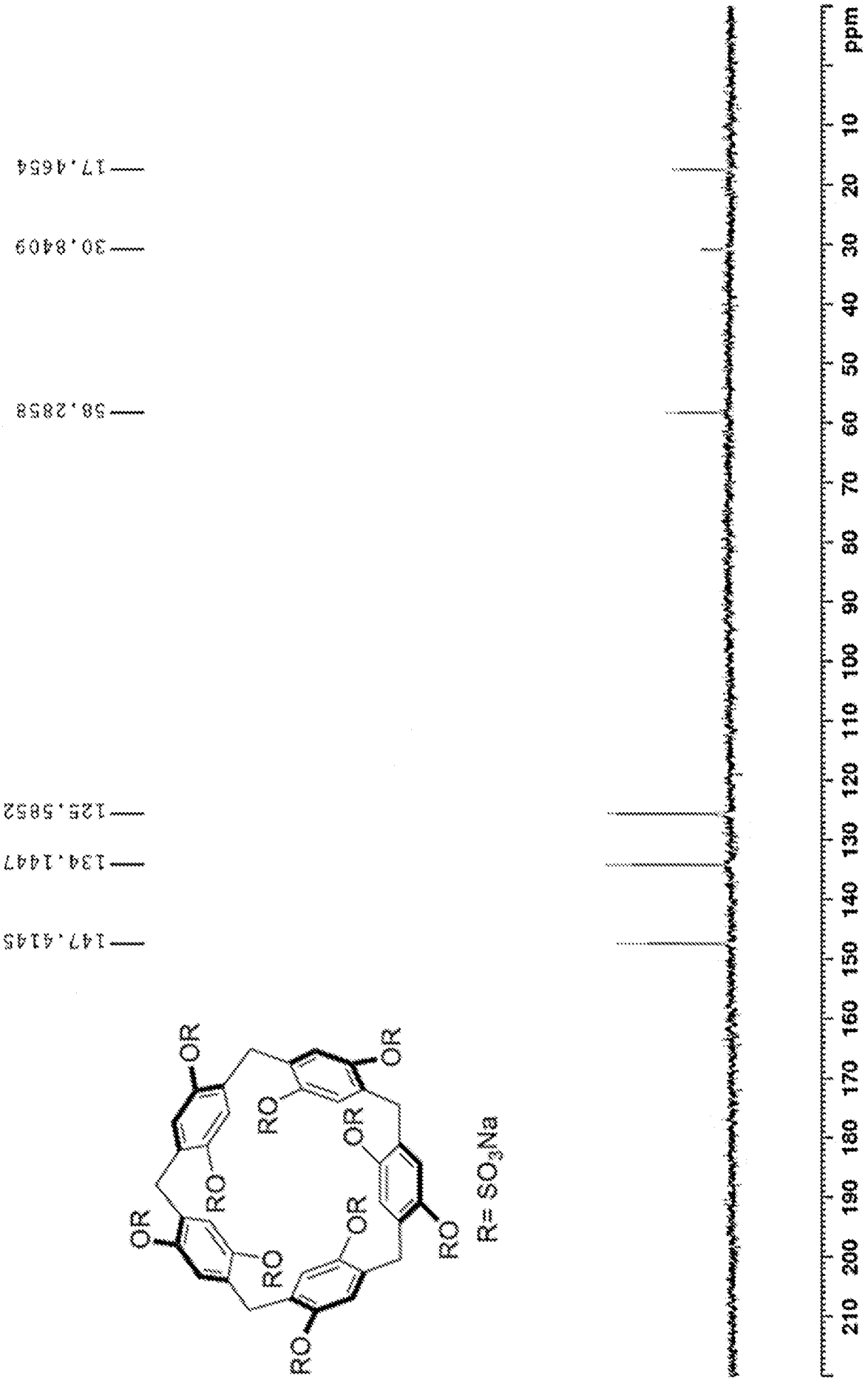

17.4654
30.8409
58.2858
125.5852
134.1447
147.4145
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
OR
RO
R= SO_3Na

Figure 19

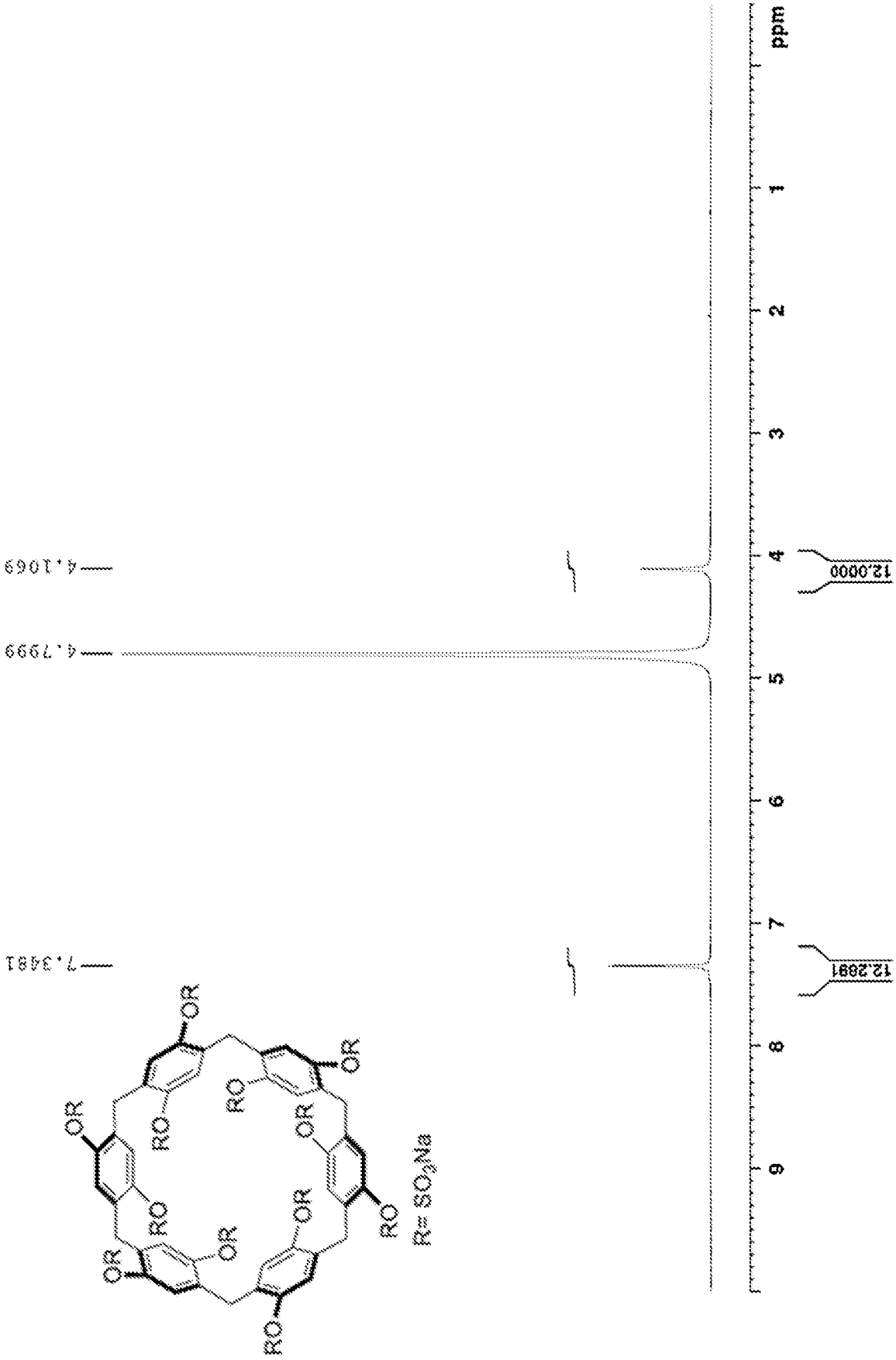


Figure 20

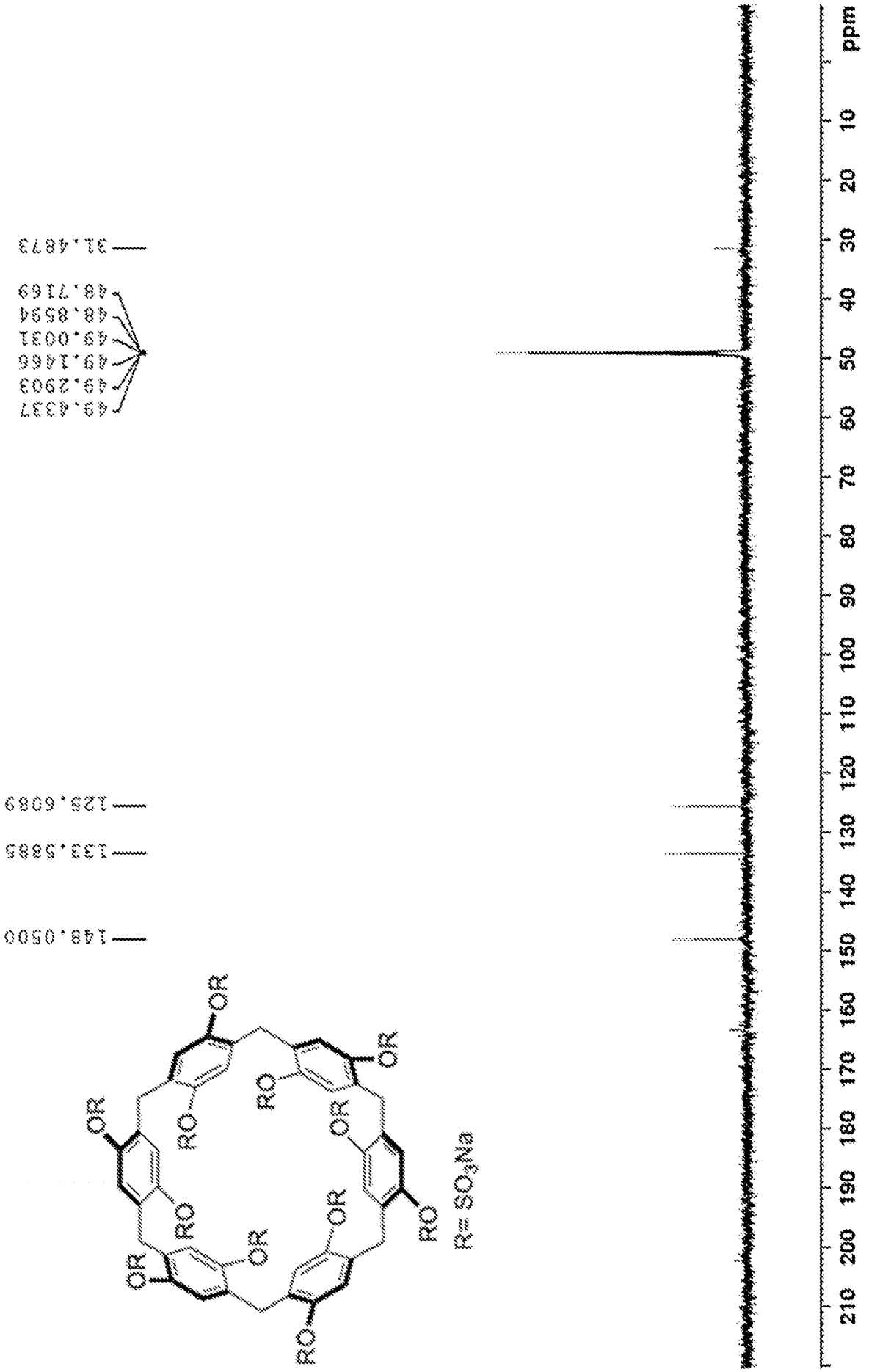

31.4873
48.7169
48.8594
49.0031
49.1466
49.2903
49.4337
125.6089
133.5885
148.0500
OR
RO
R= SO_3Na
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

Figure 21

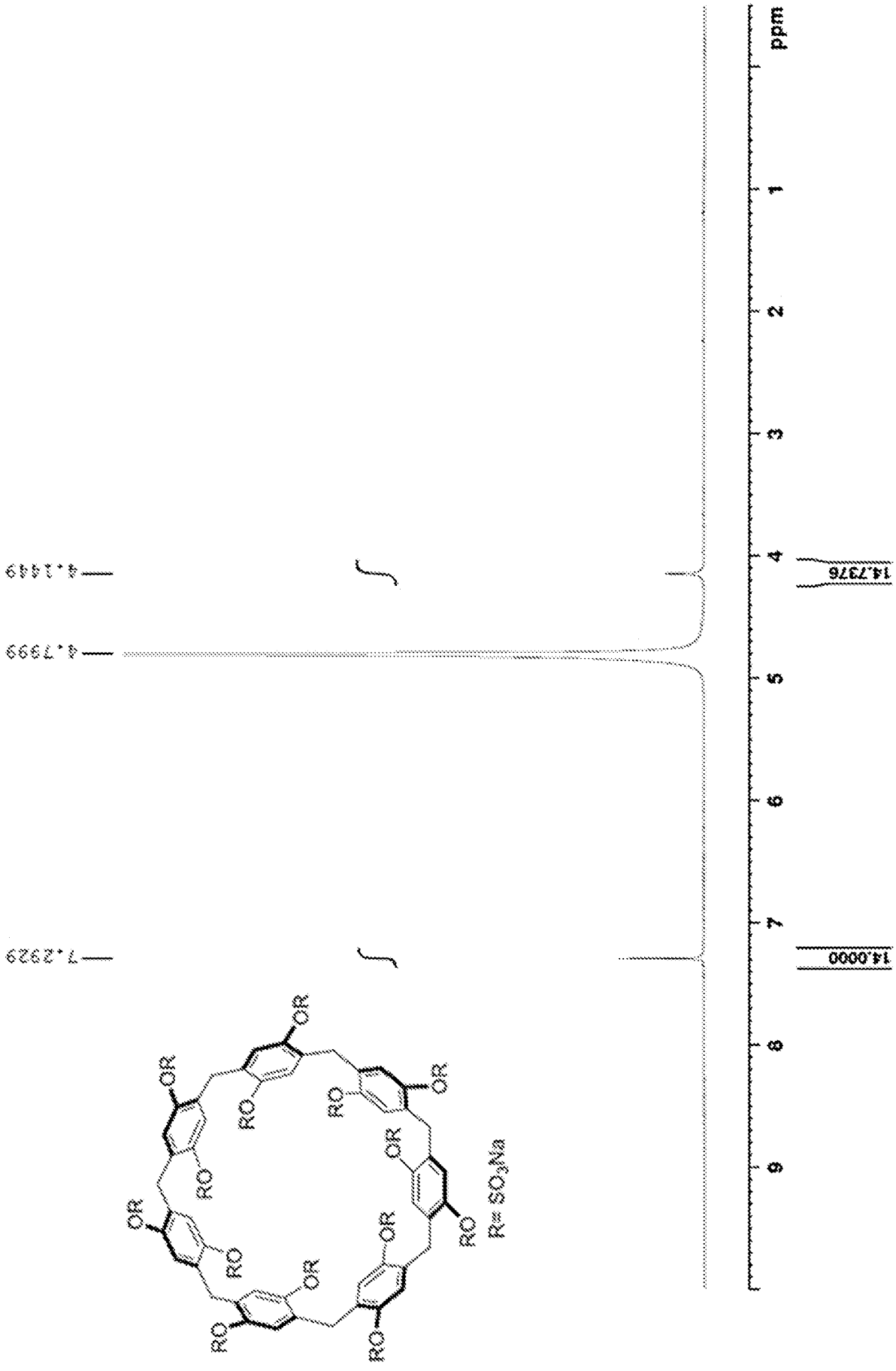


Figure 22

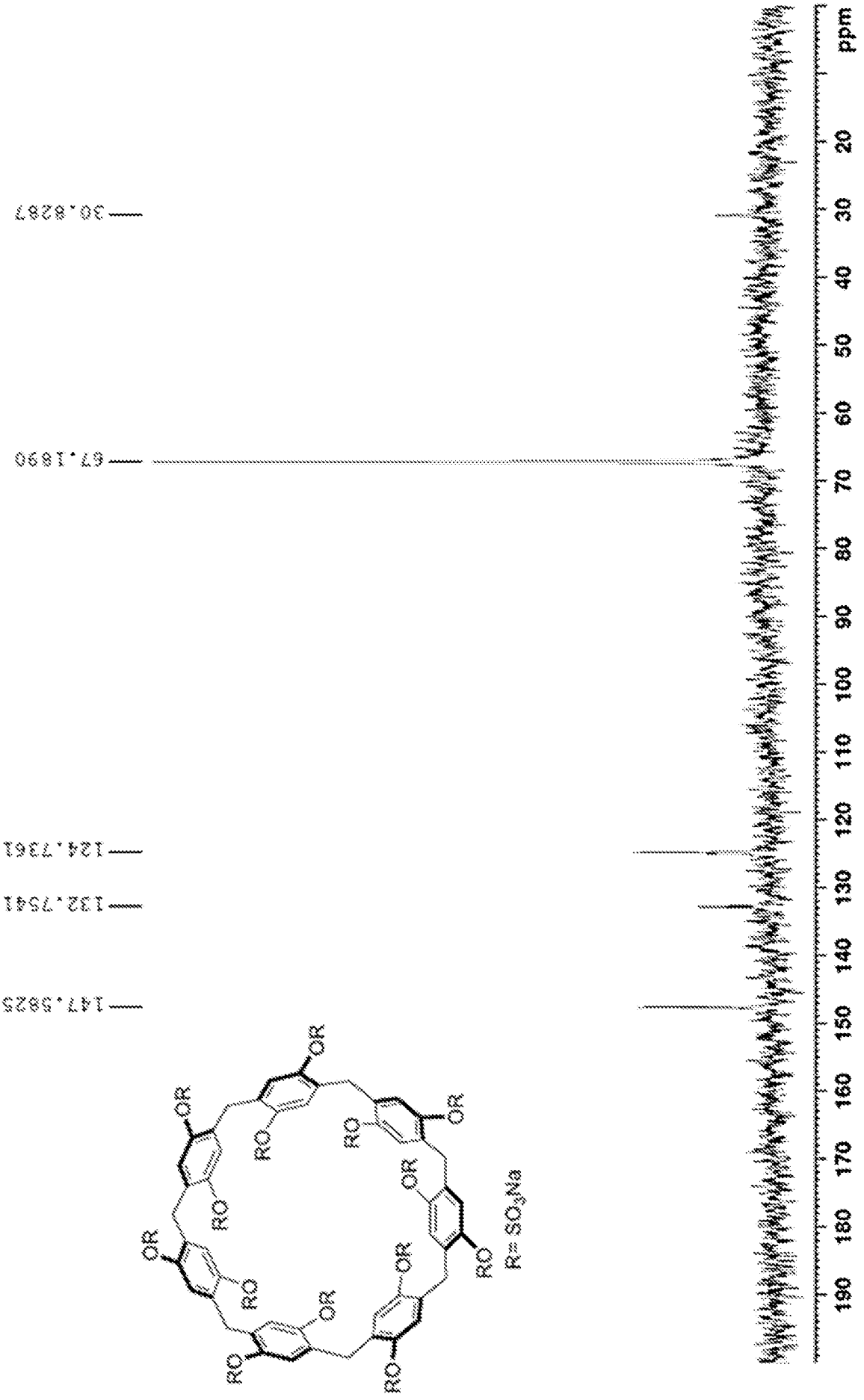

30.8287
67.1890
124.7361
132.7541
147.5825
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
OR
RO
R= SO_3Na

Figure 23

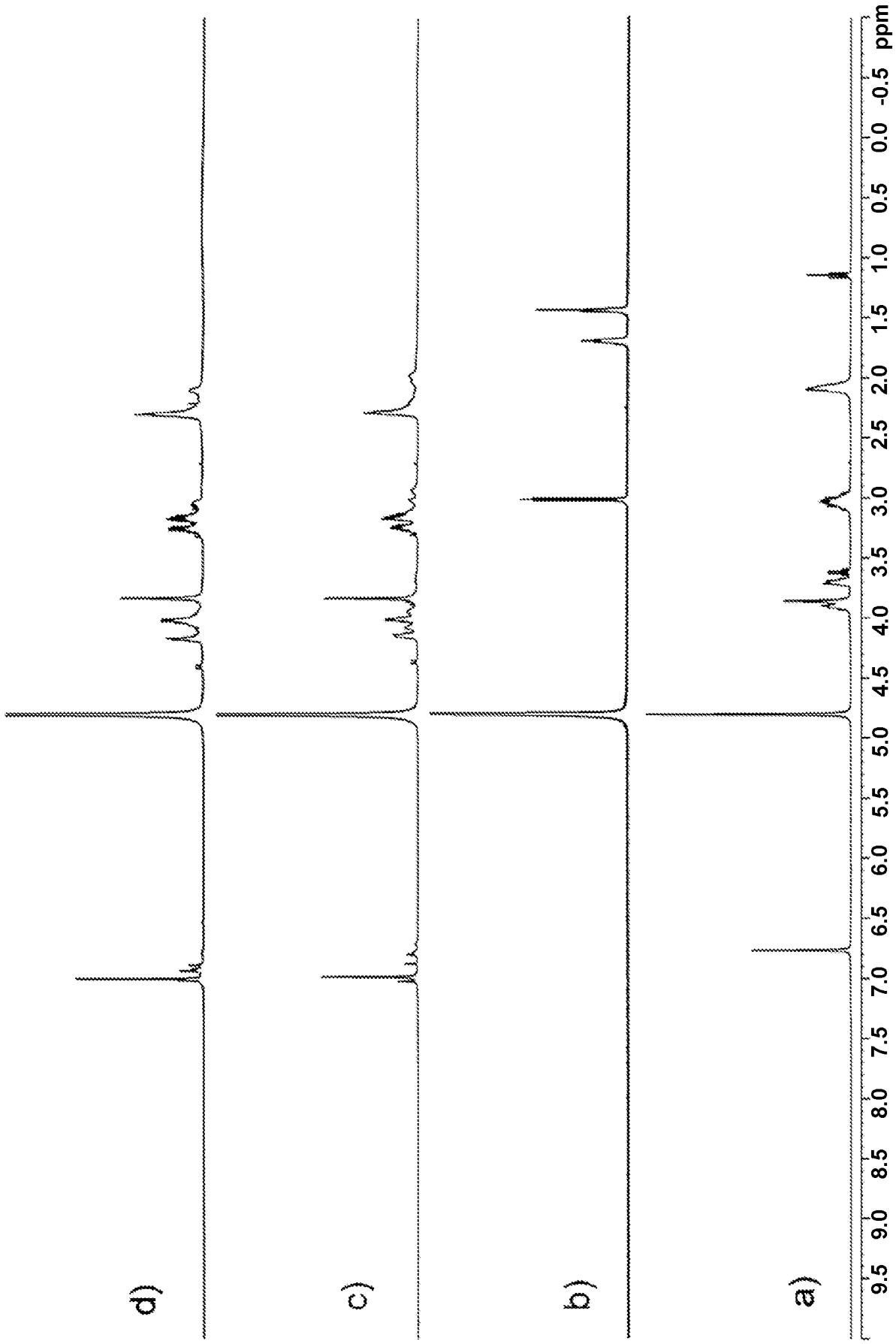


Figure 24

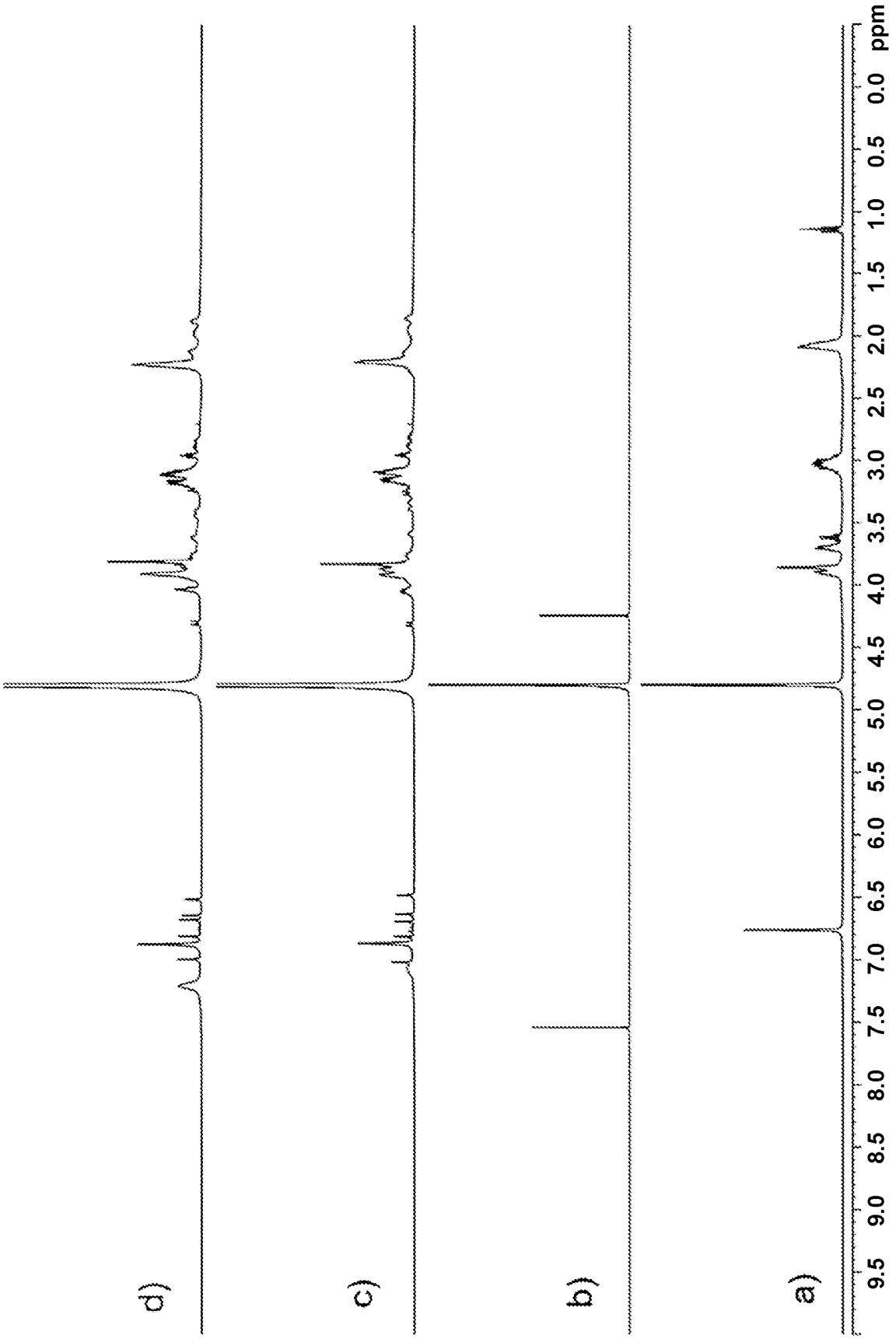


Figure 25

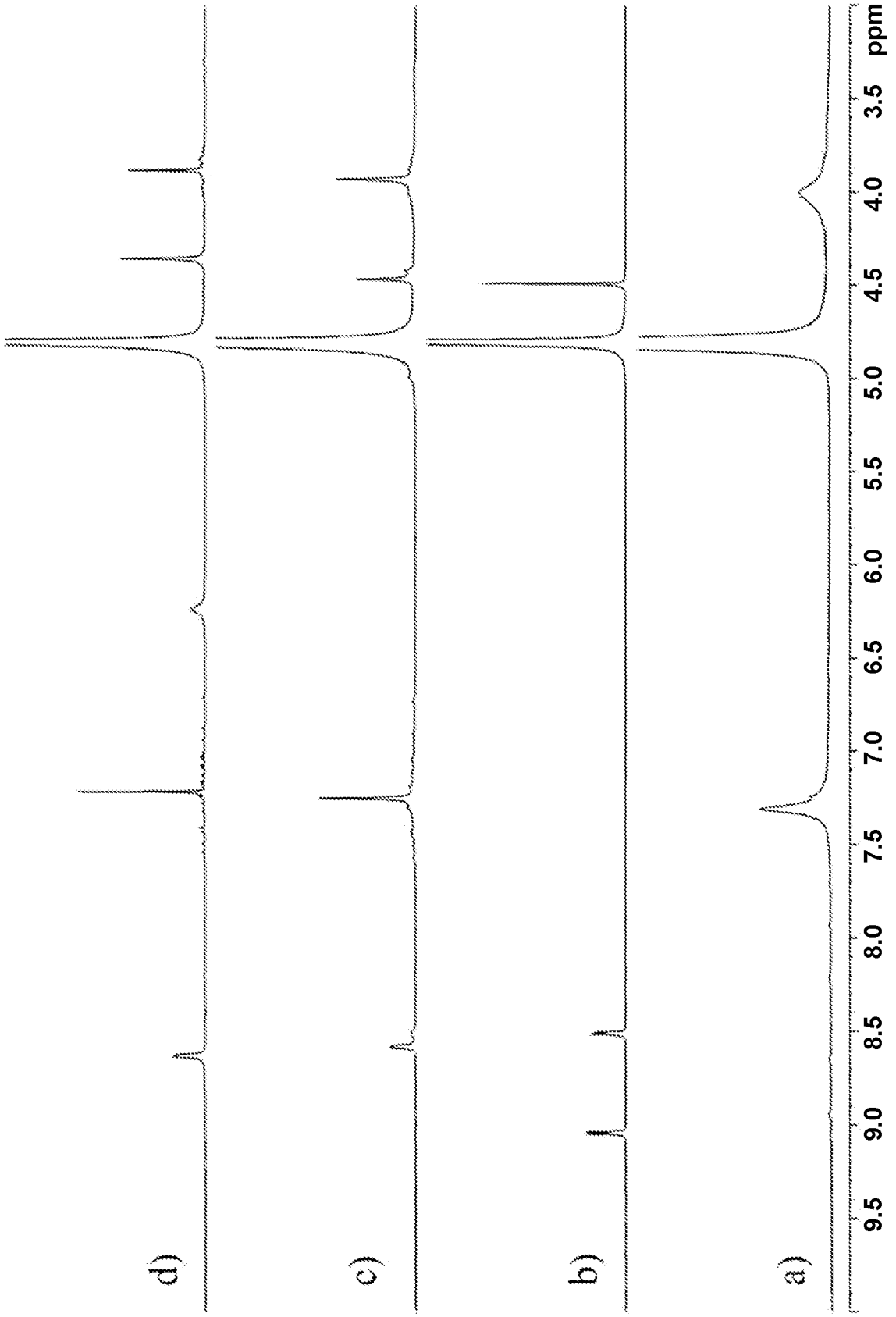


Figure 26

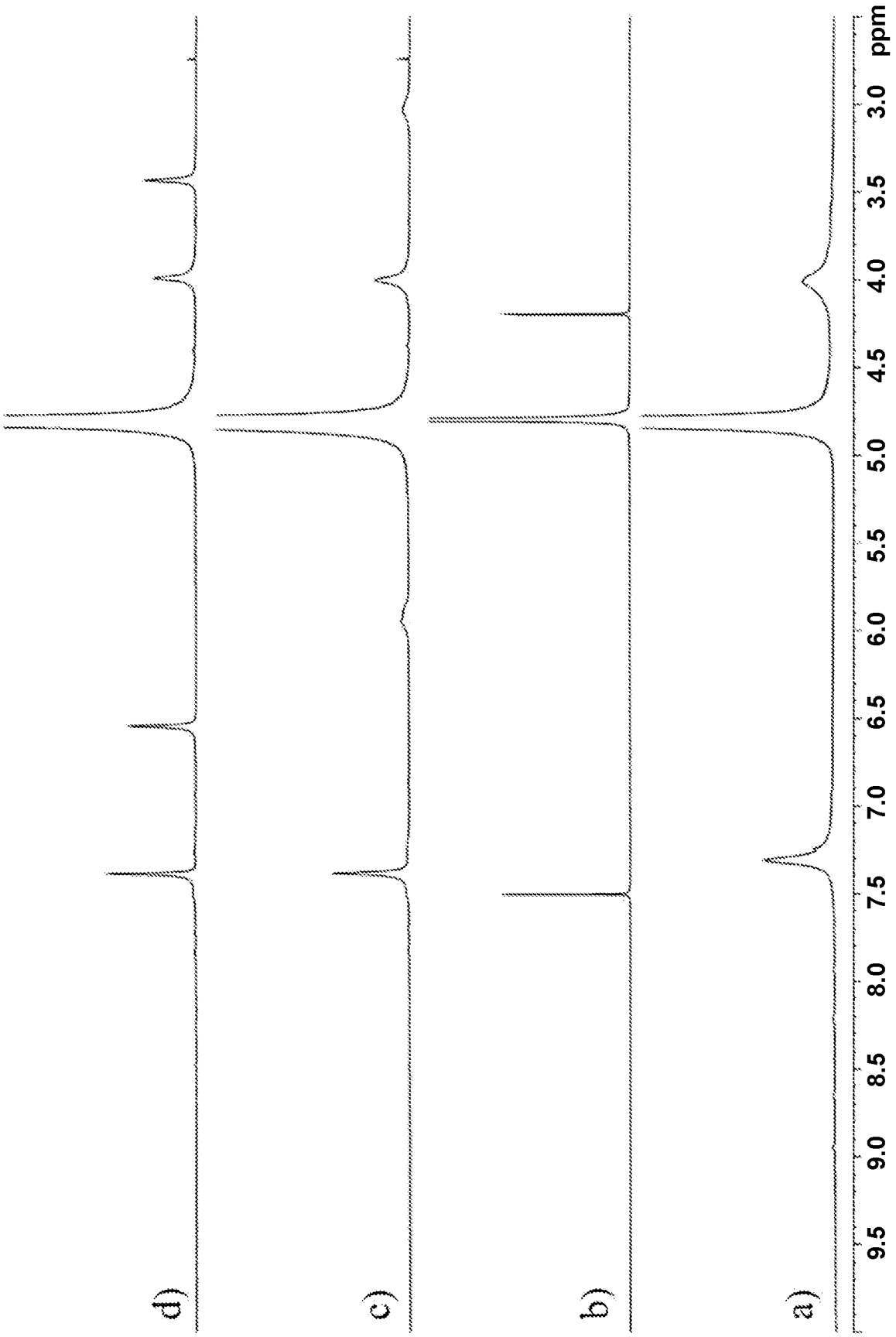


Figure 27

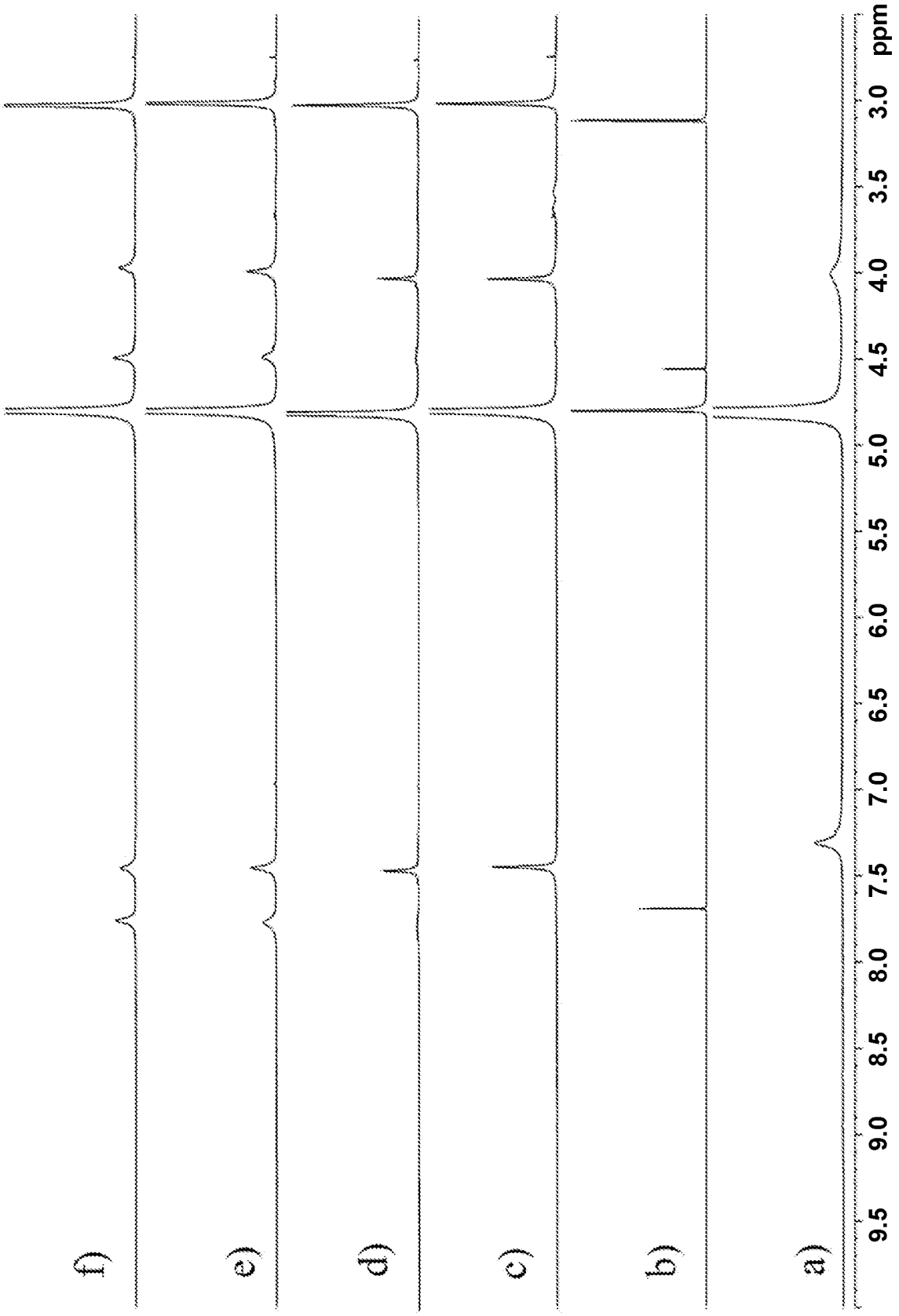


Figure 28

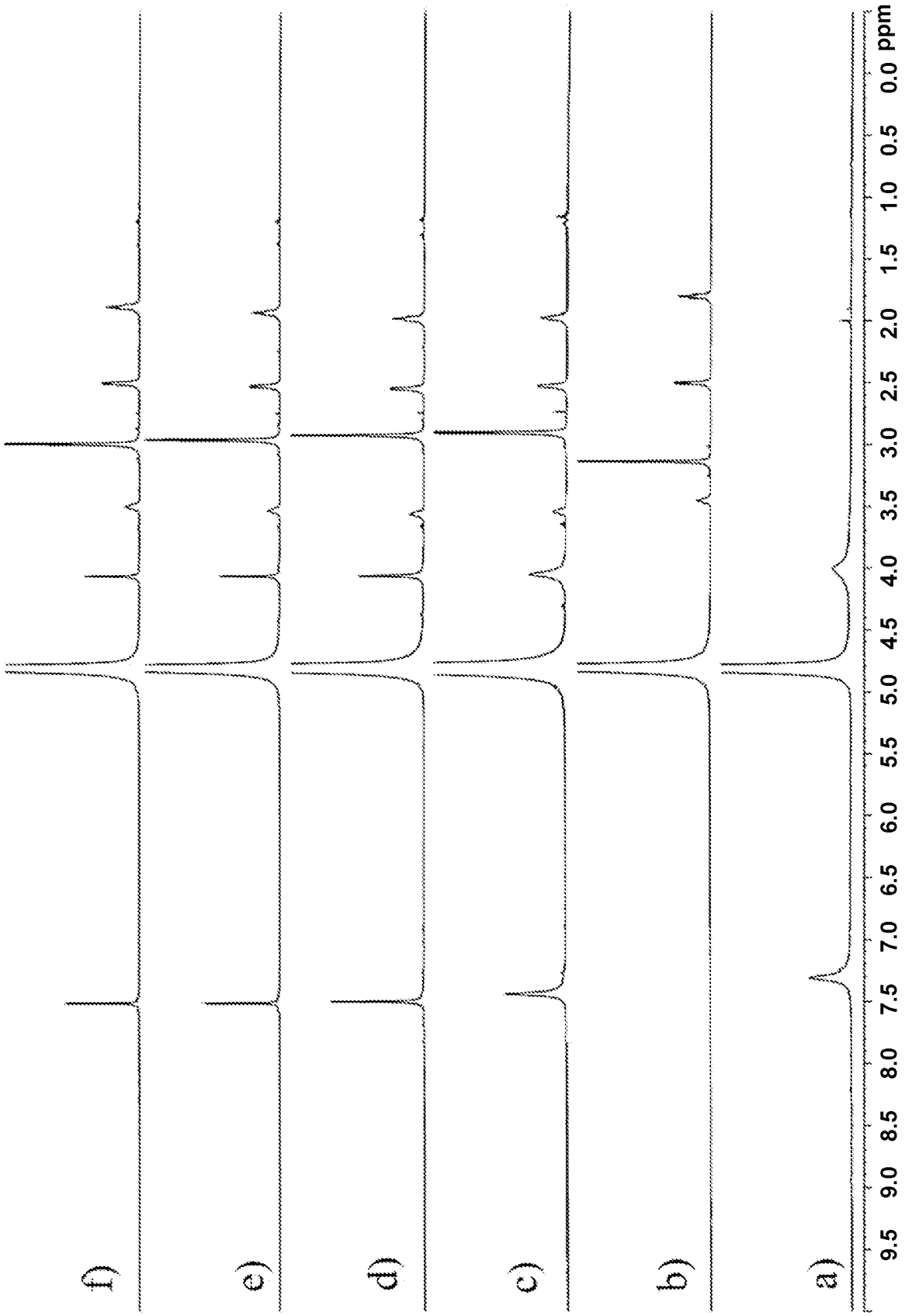


Figure 29

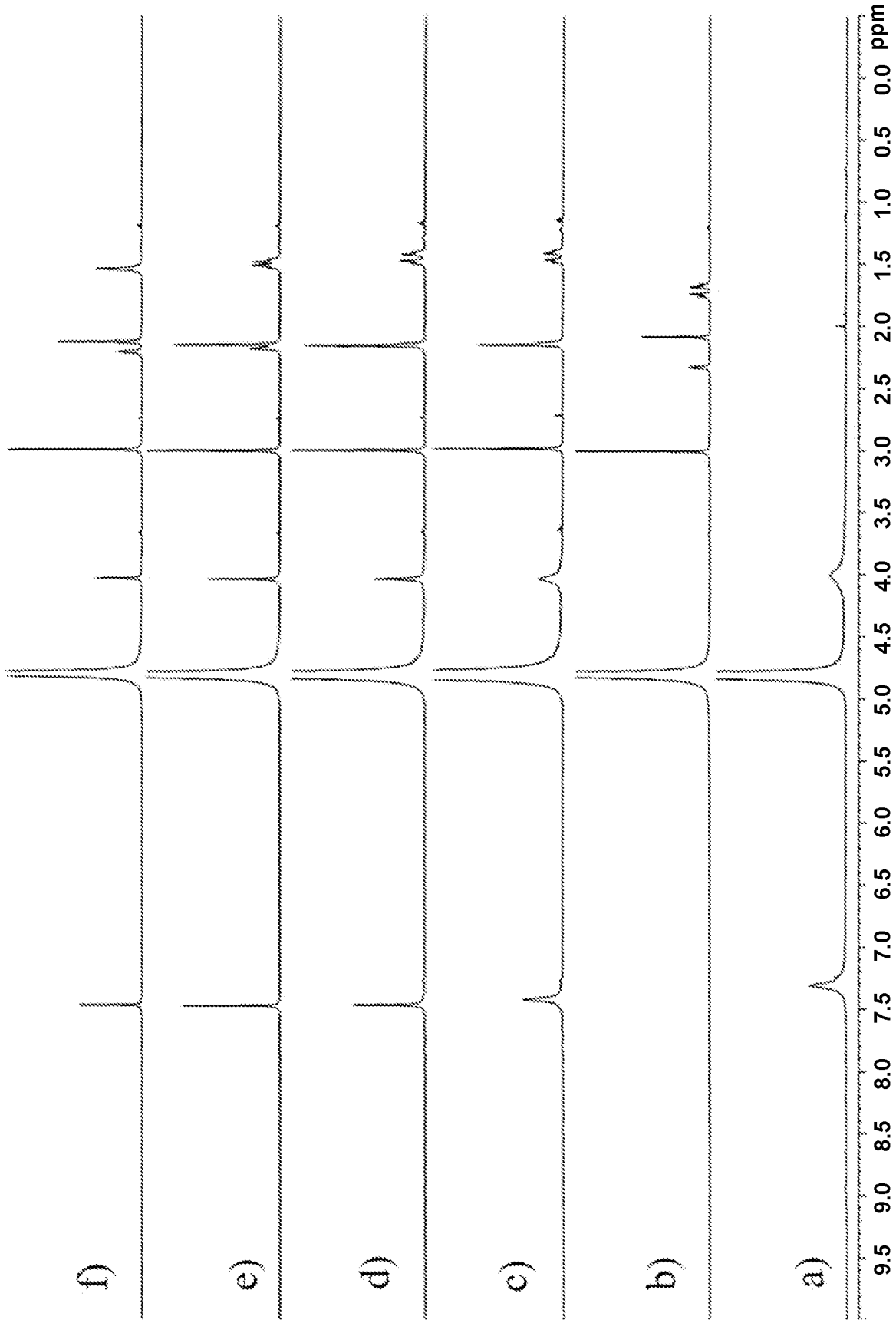


Figure 30

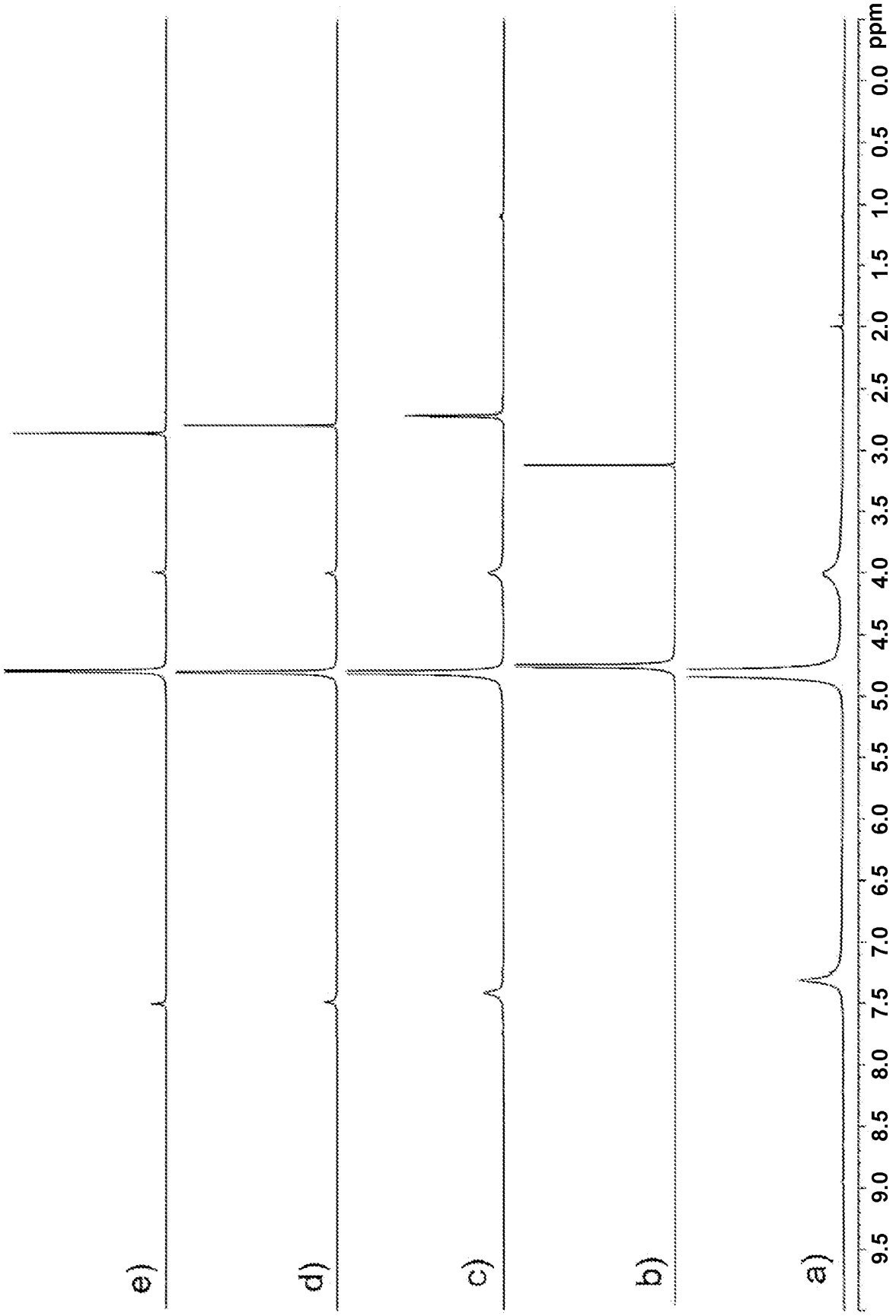


Figure 31

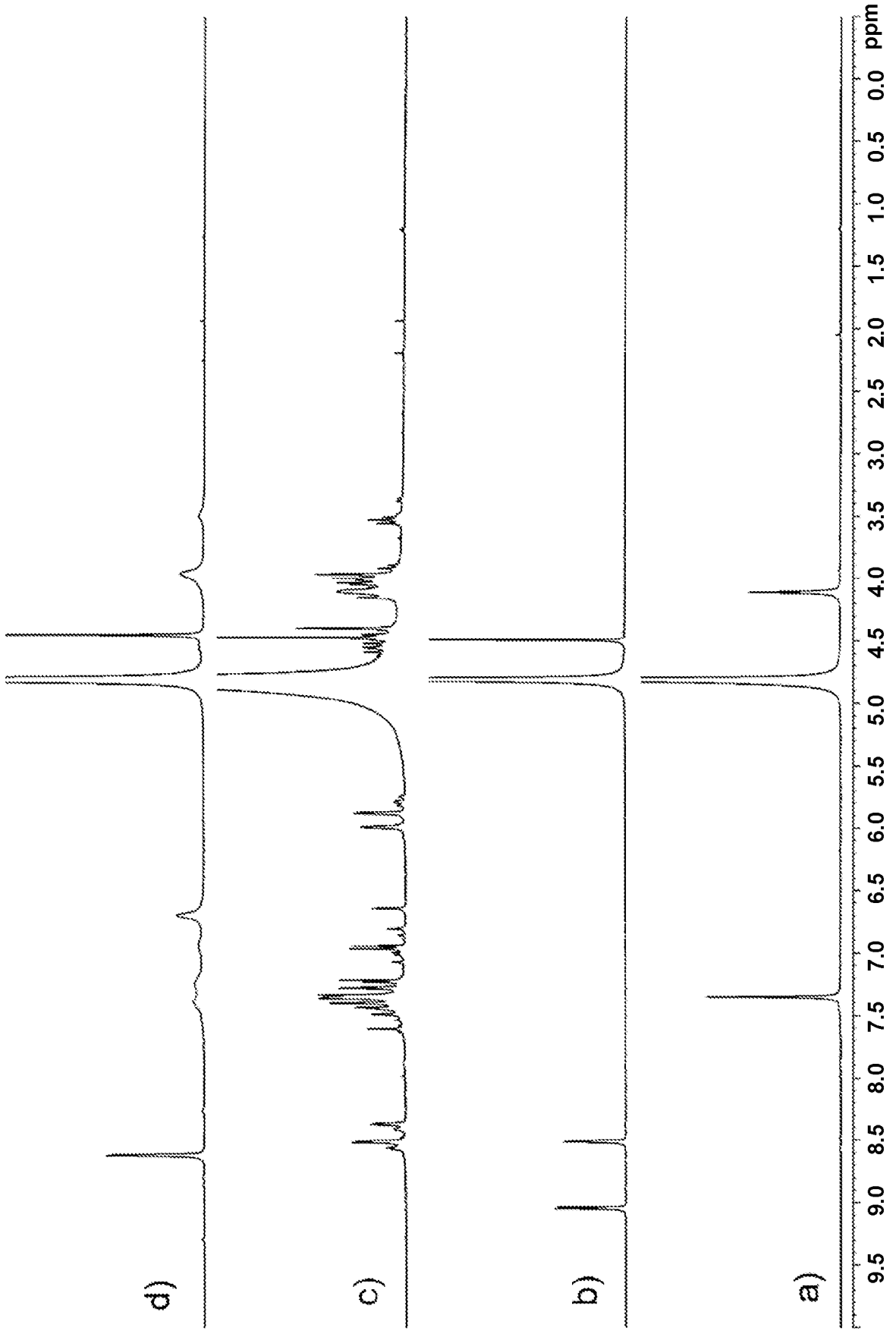


Figure 32

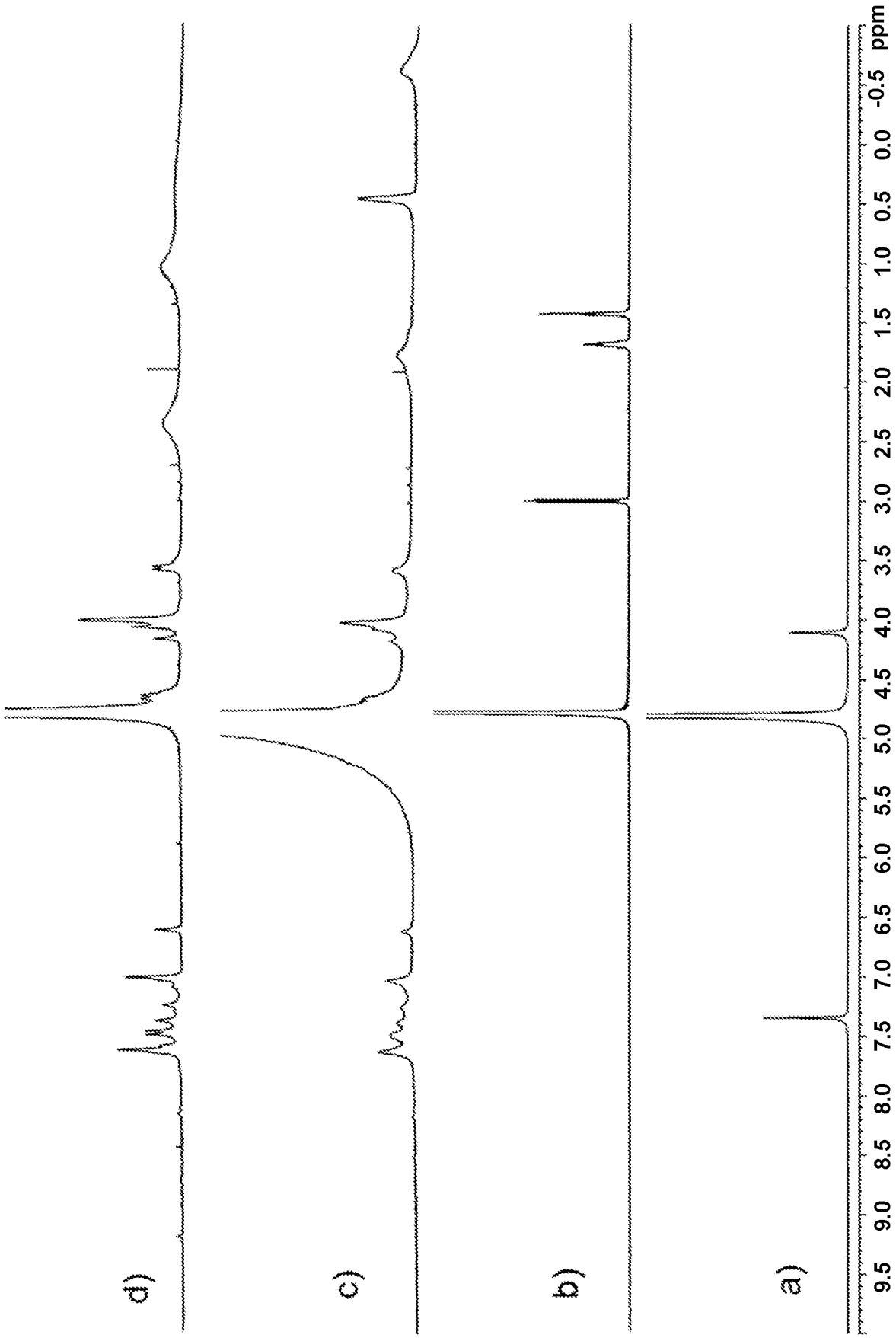


Figure 33

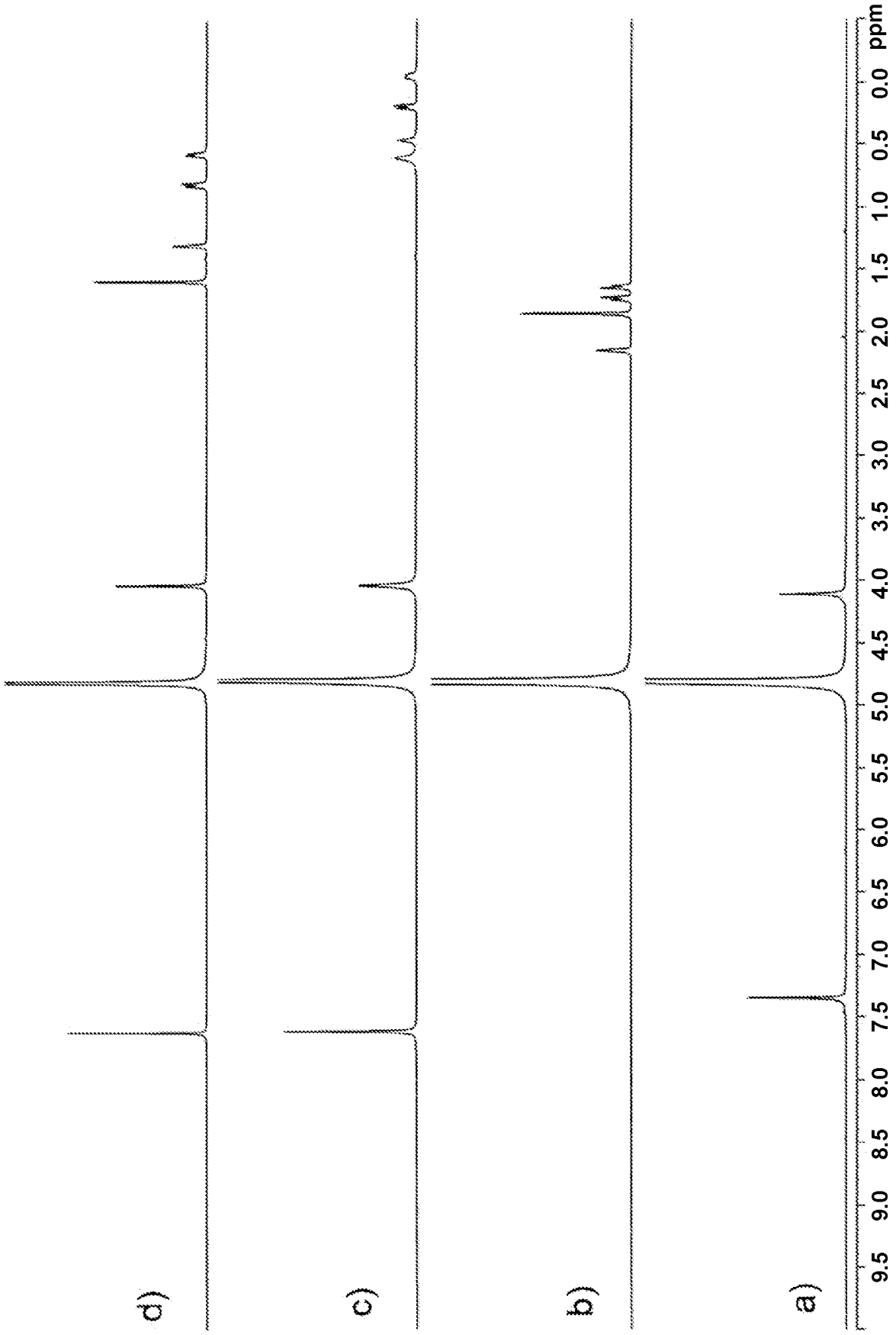


Figure 34

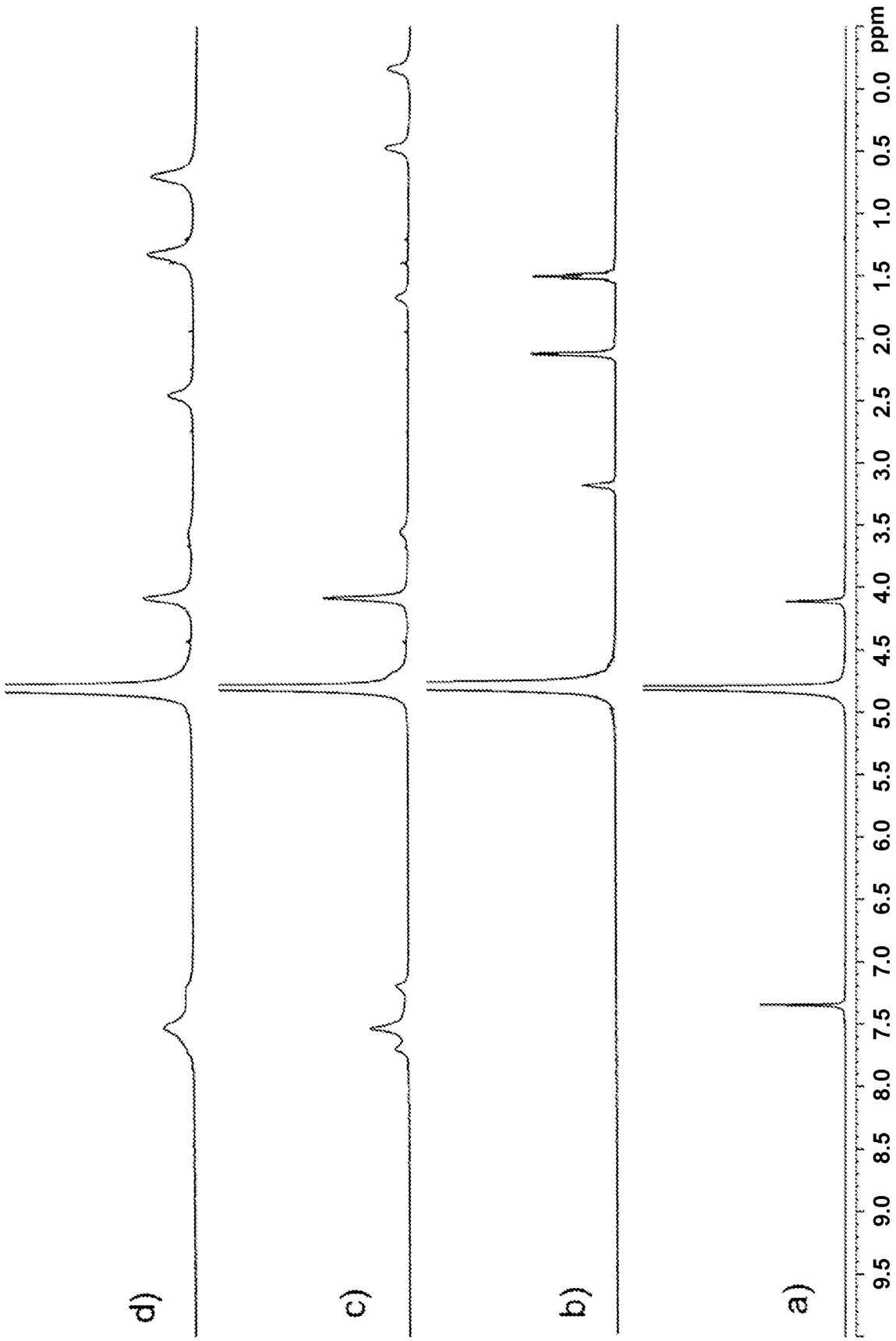


Figure 35

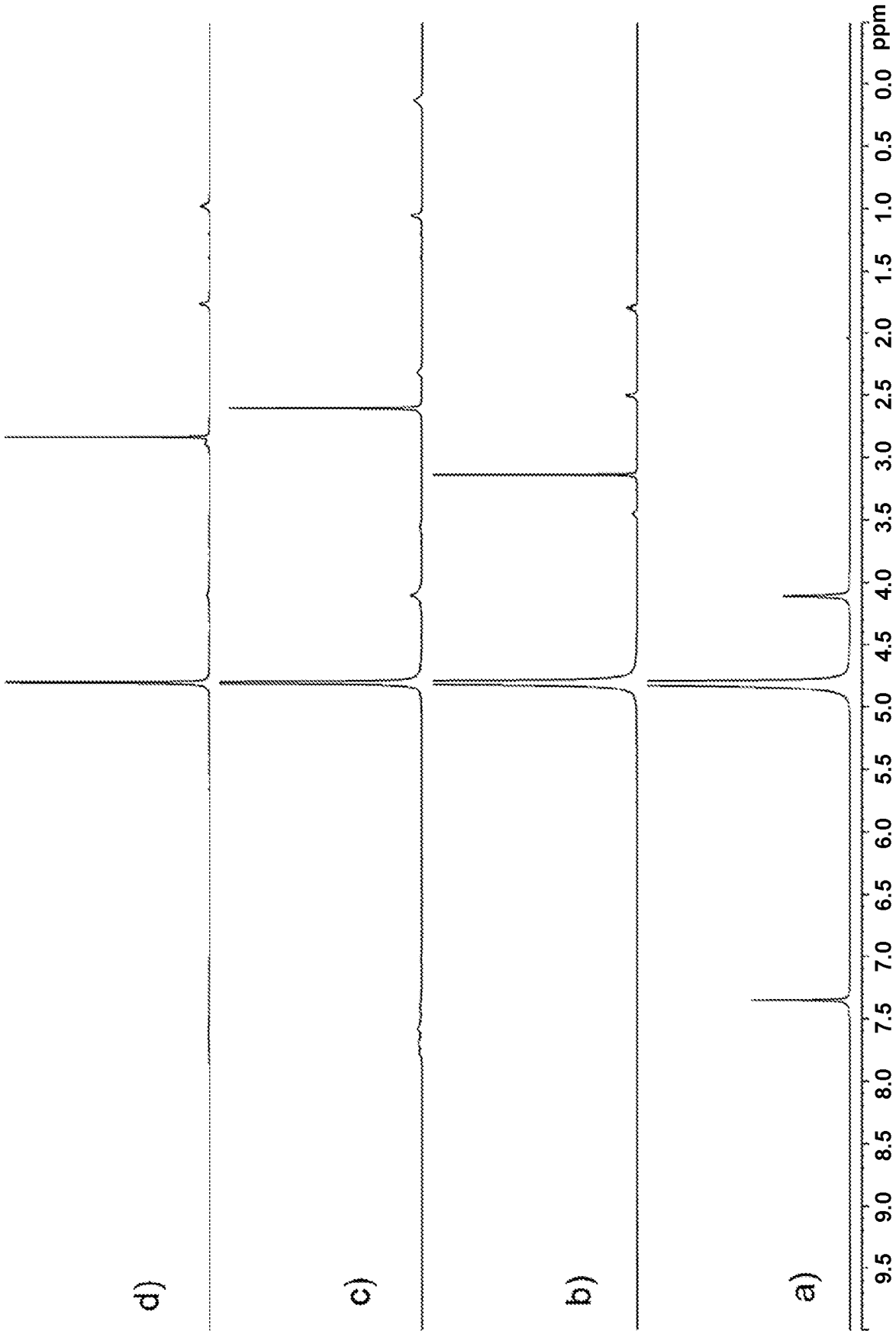


Figure 36

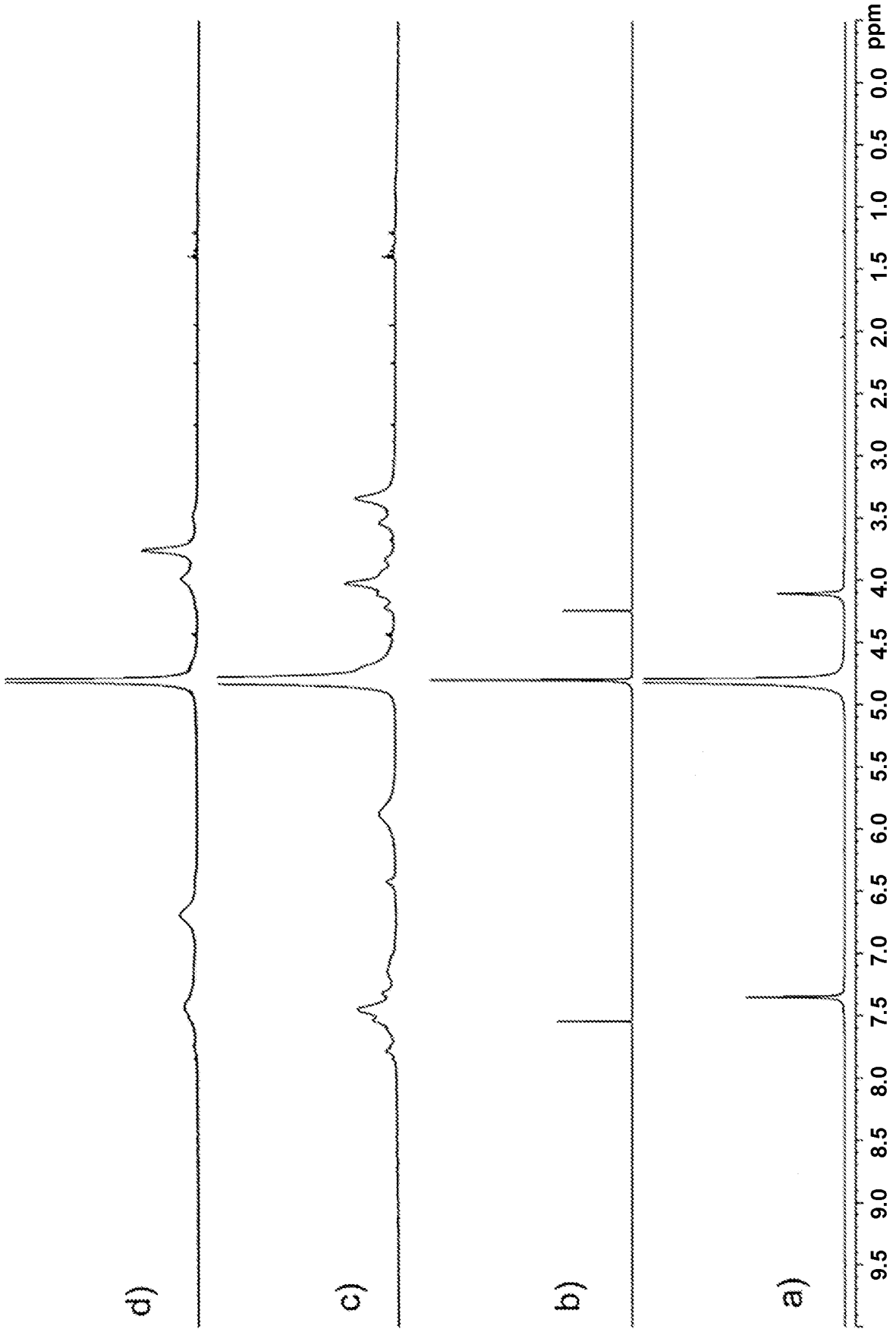


Figure 37

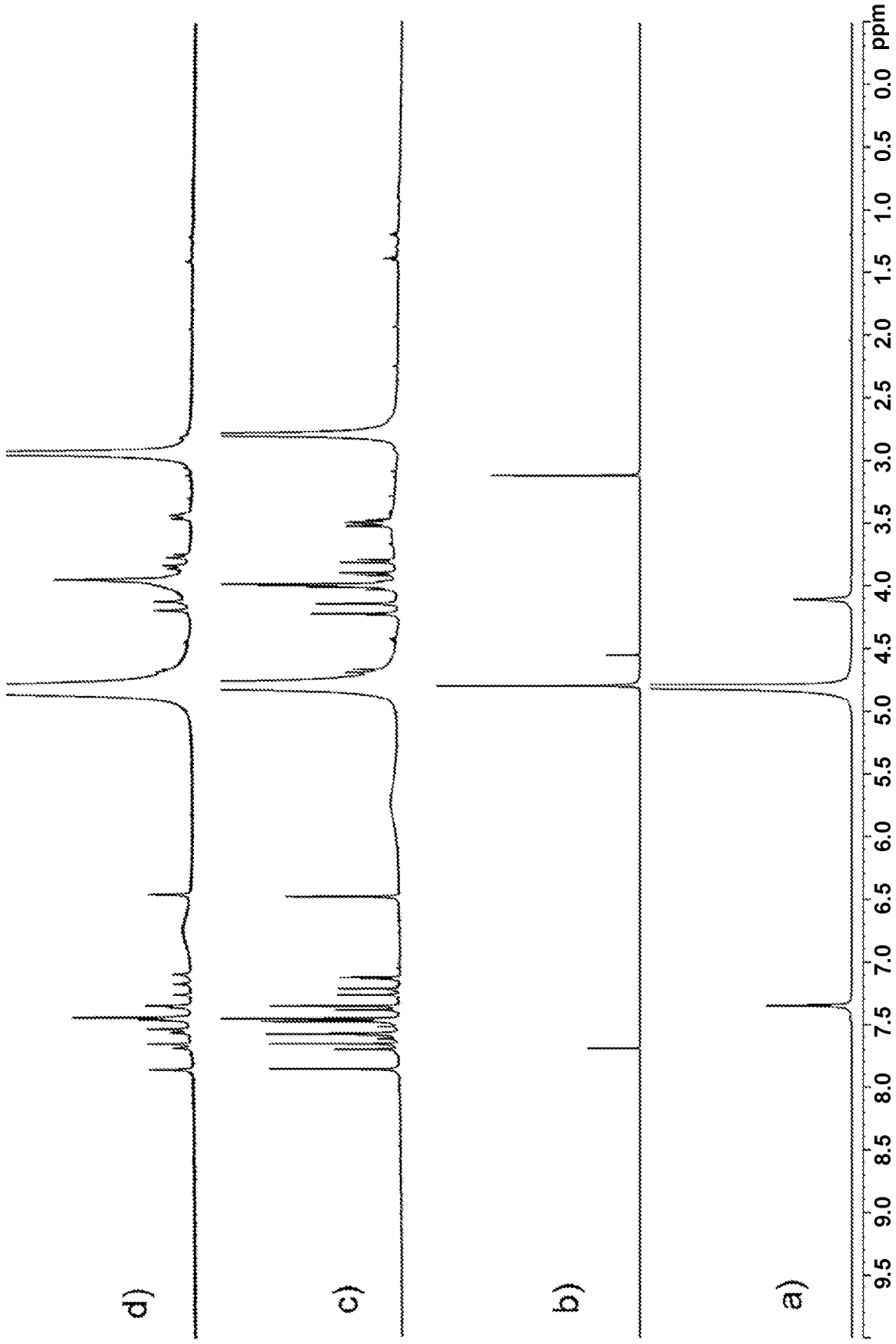


Figure 38

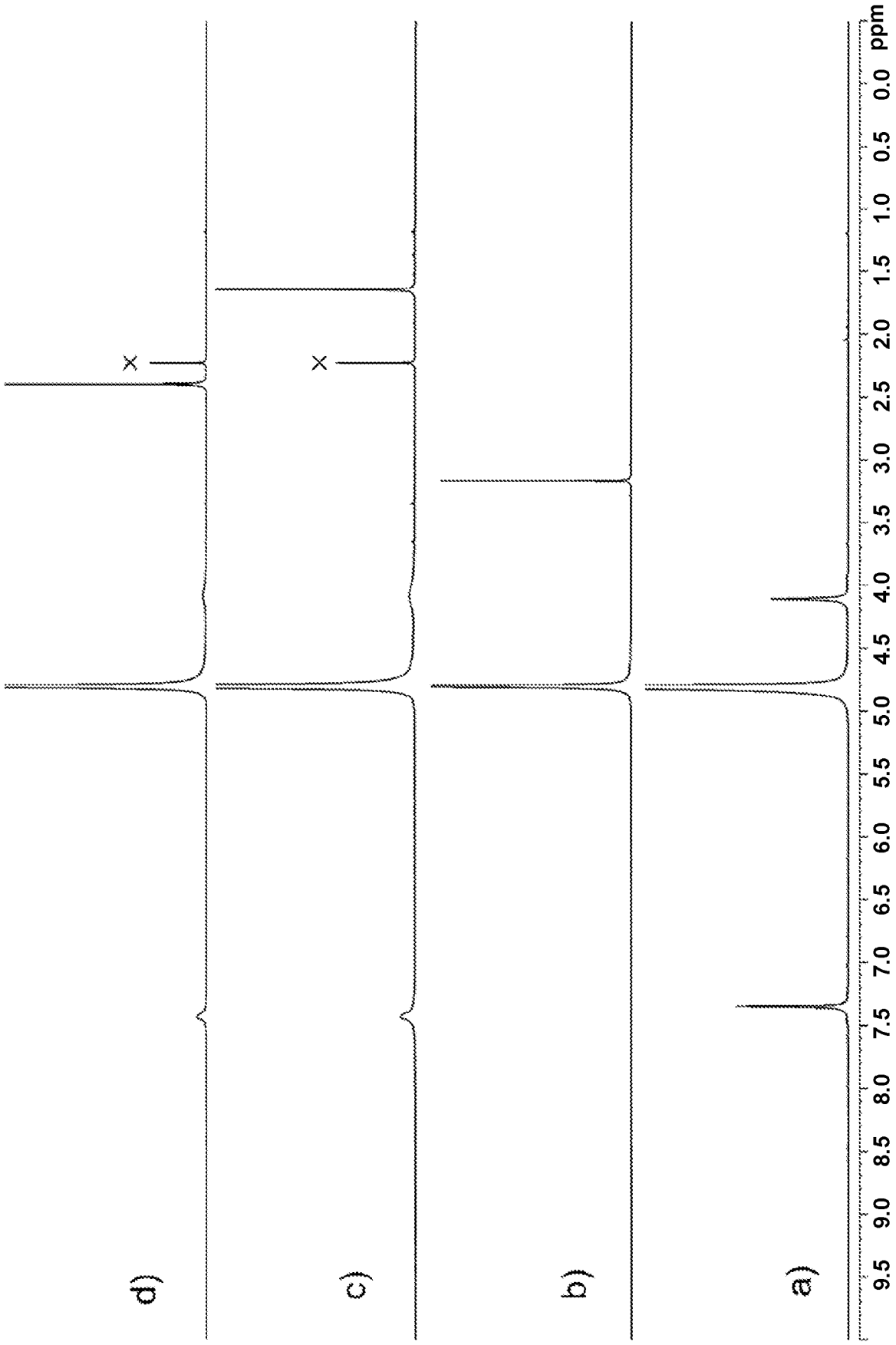


Figure 39

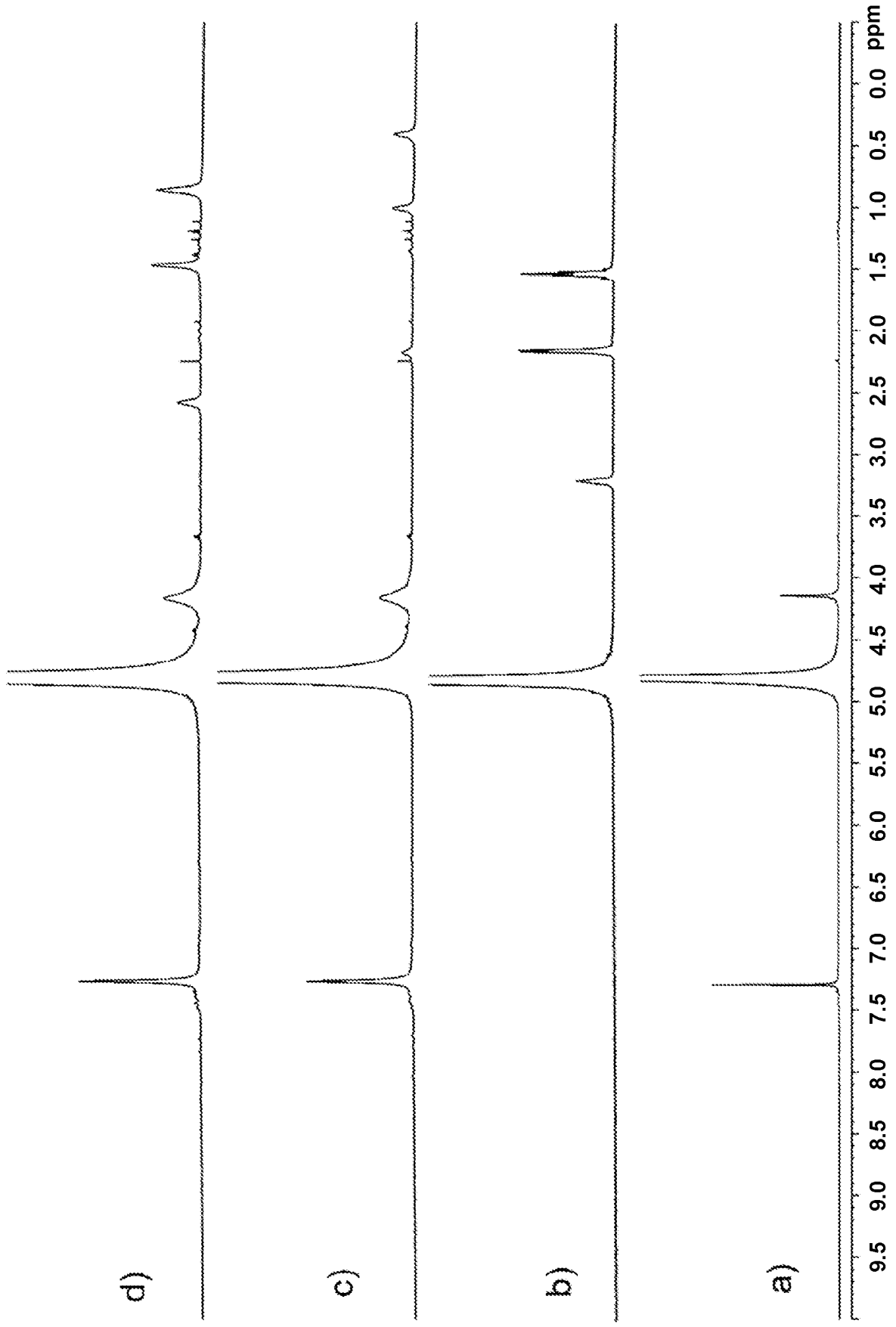


Figure 40

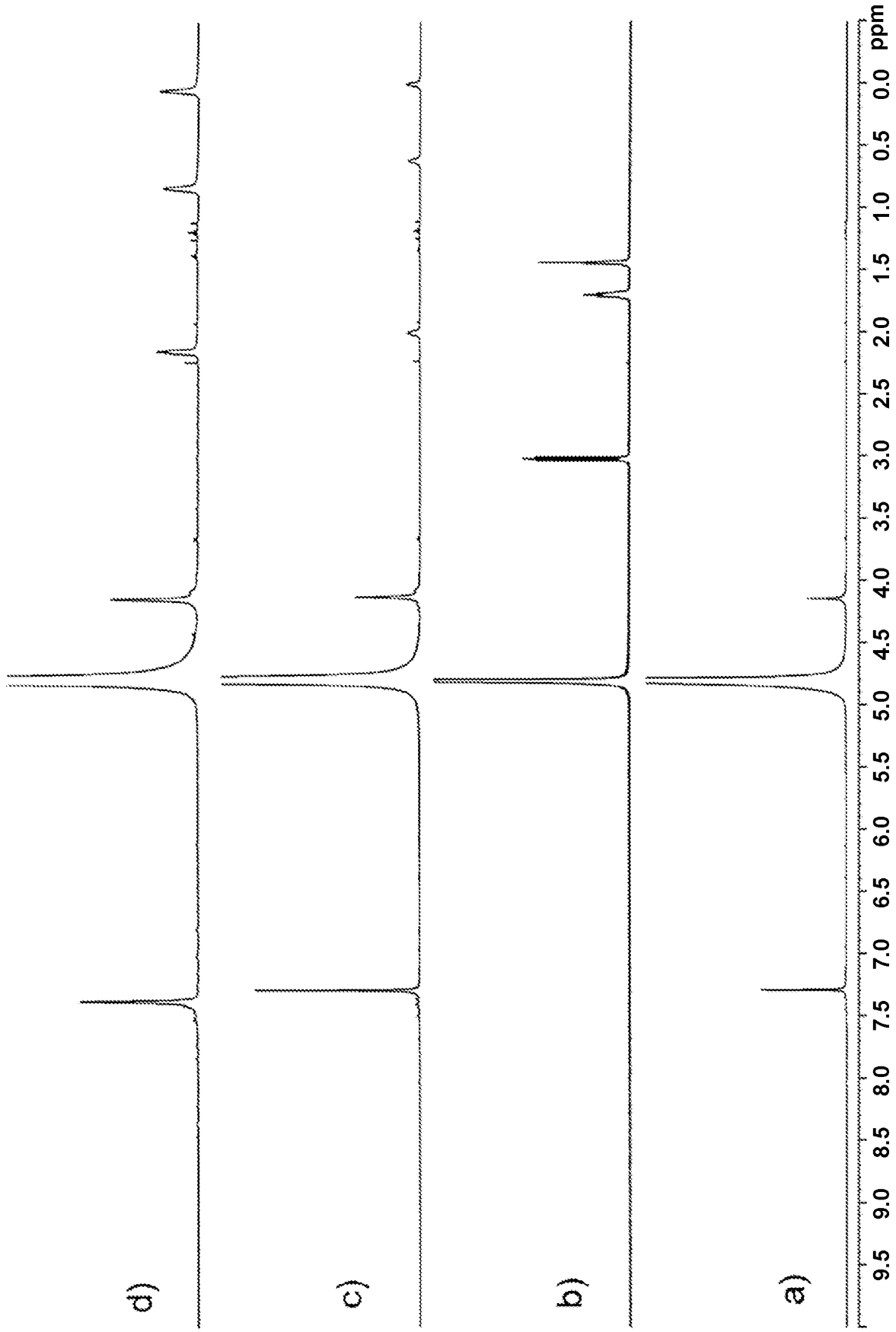


Figure 41

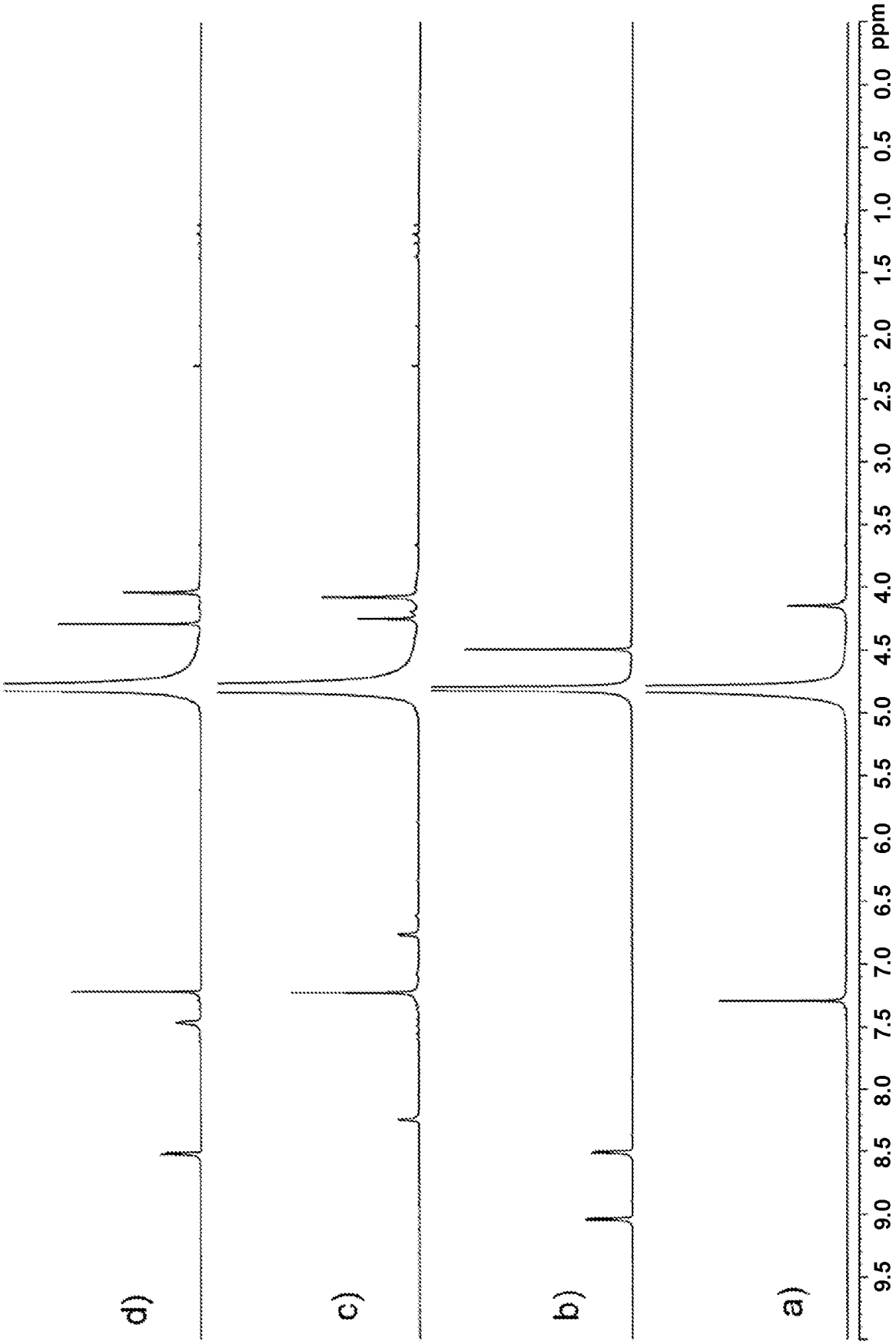


Figure 42

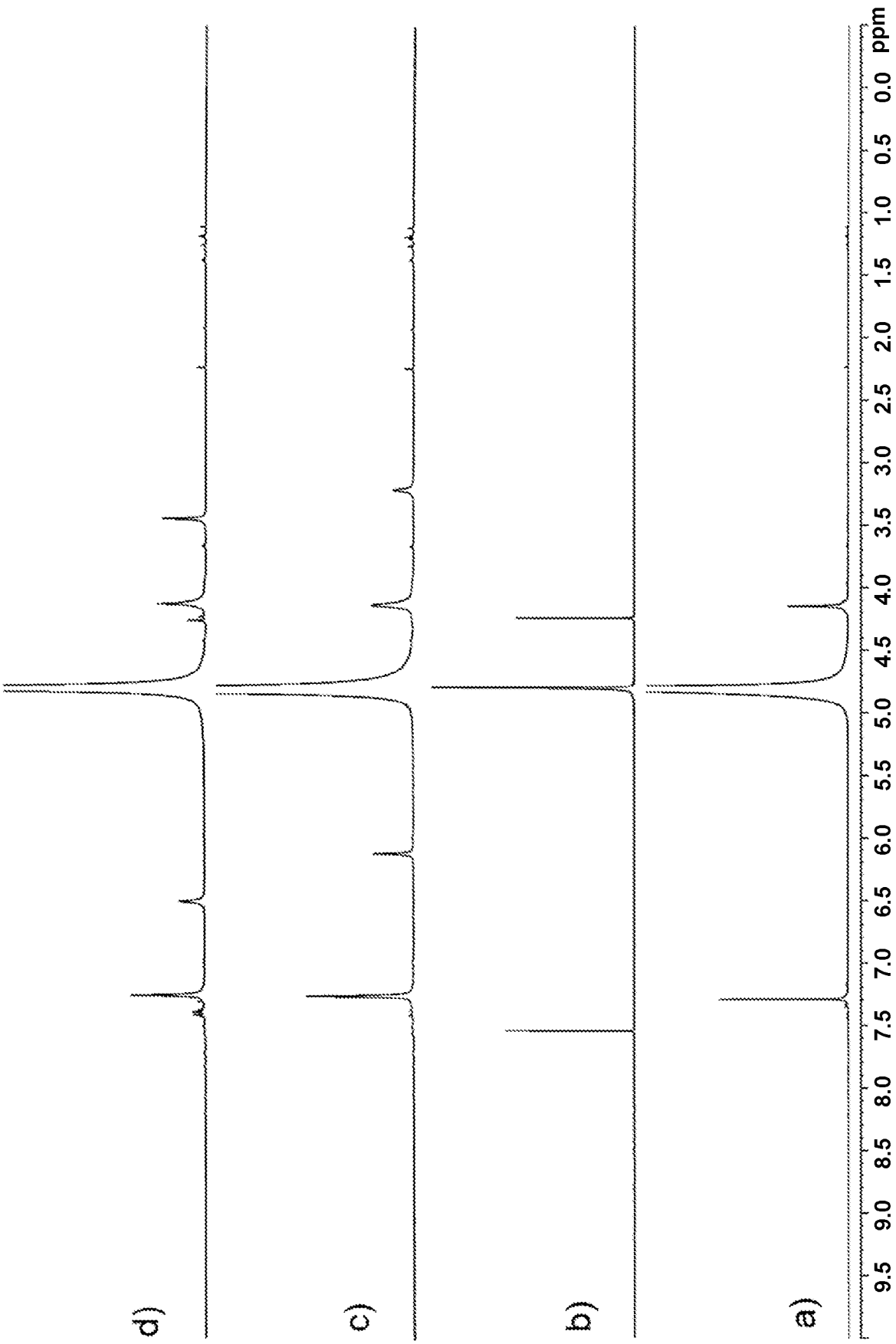


Figure 43

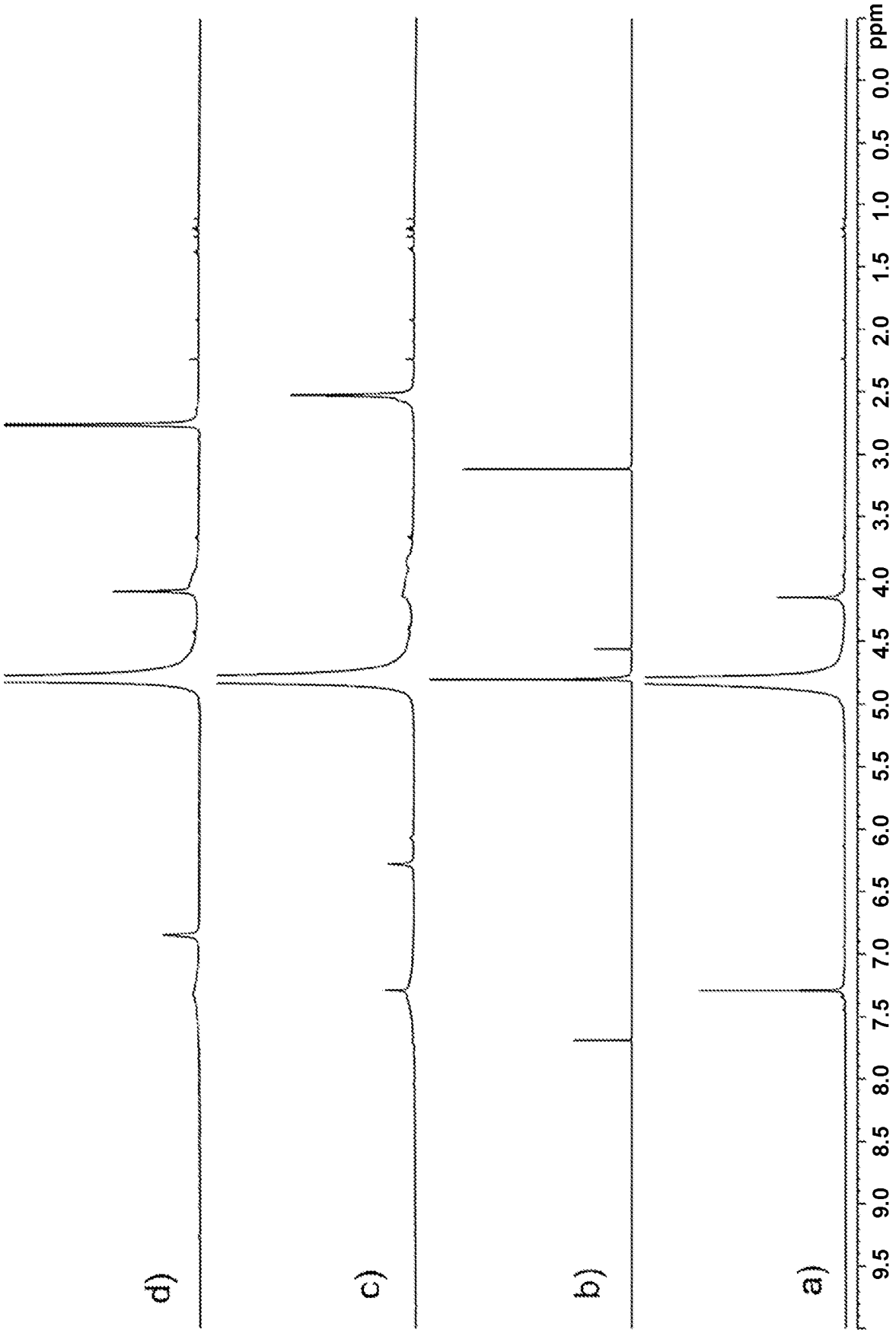


Figure 44

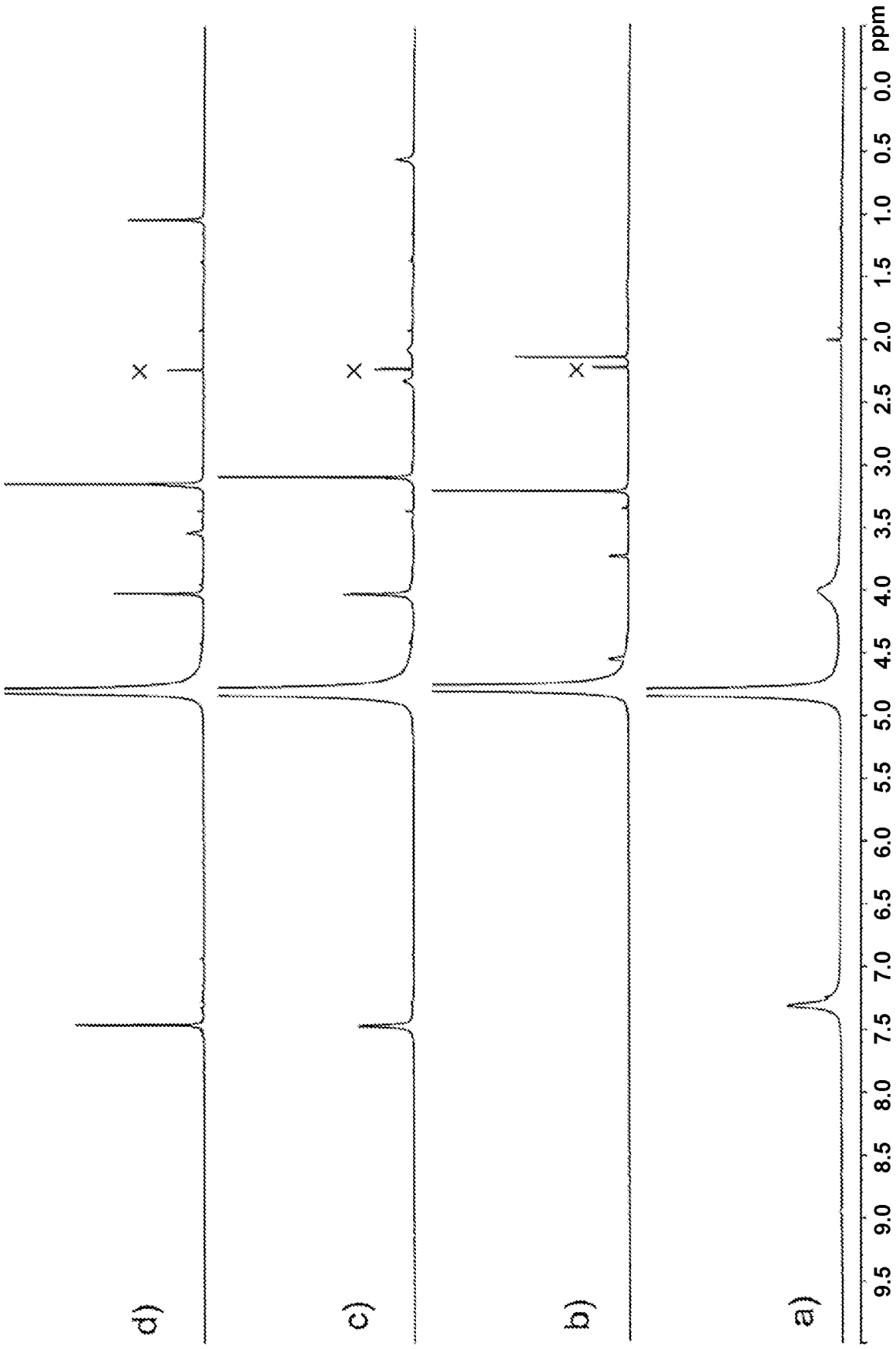

d)
c)
b)
a)
X
X
X
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm

Figure 45

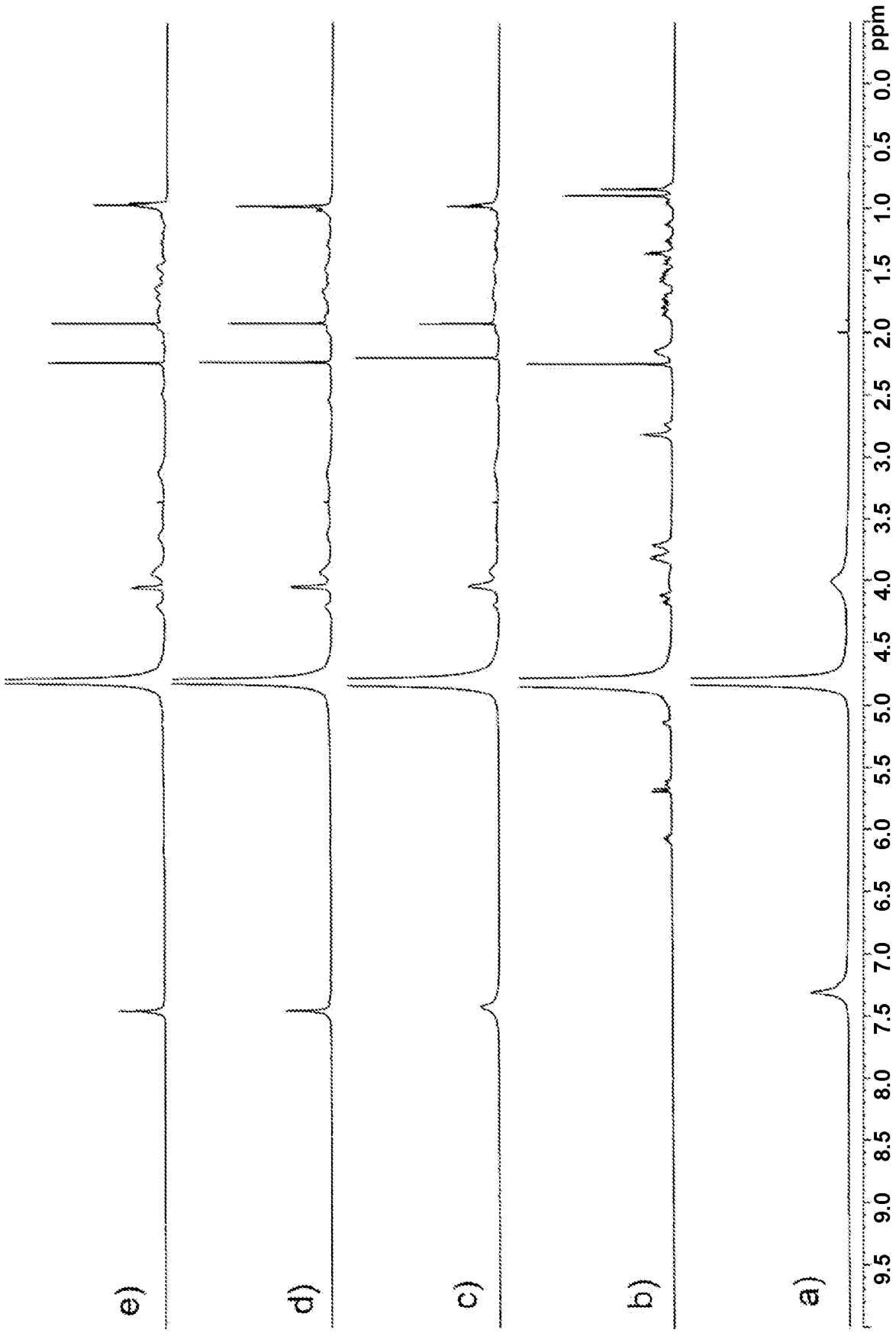


Figure 46

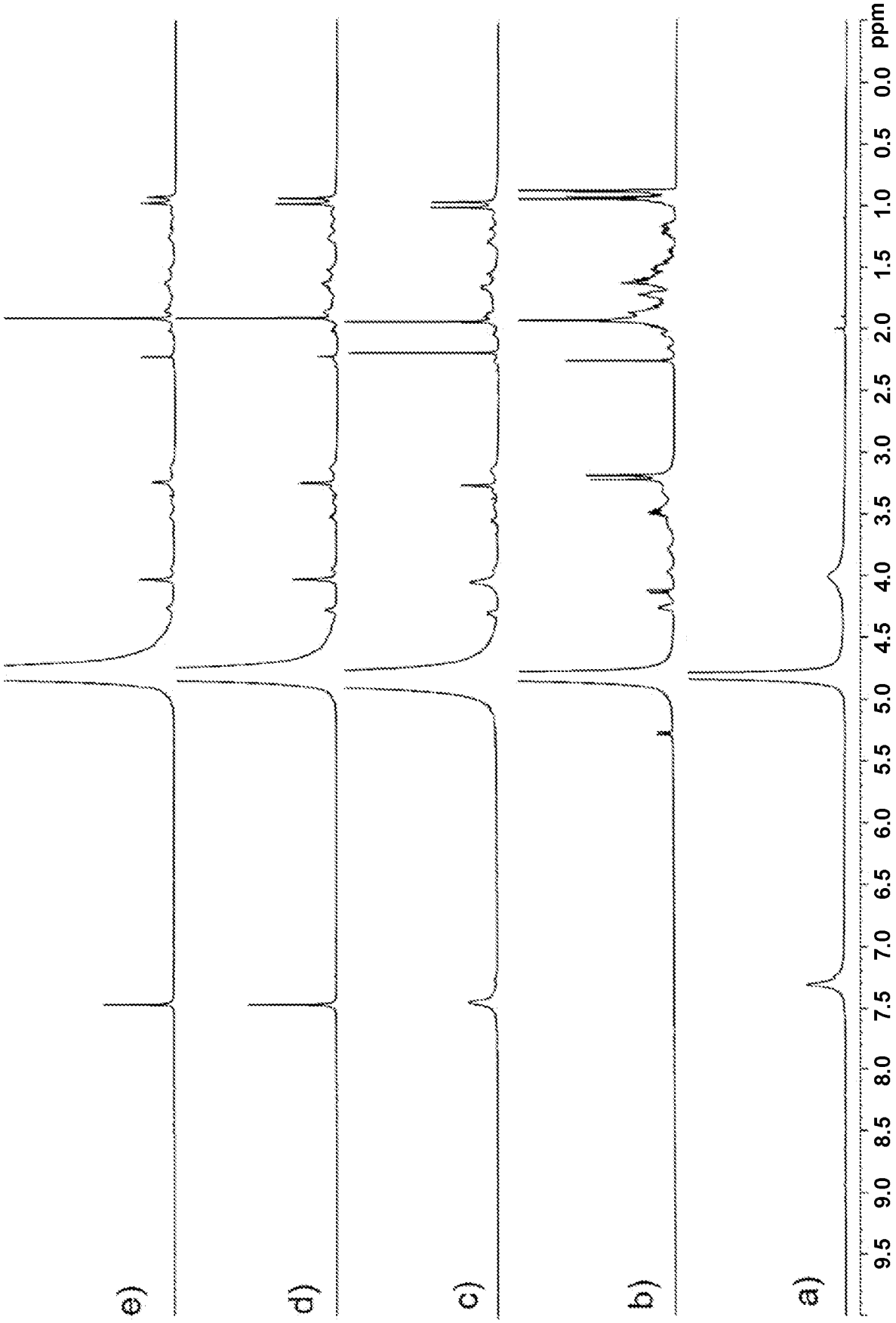


Figure 47

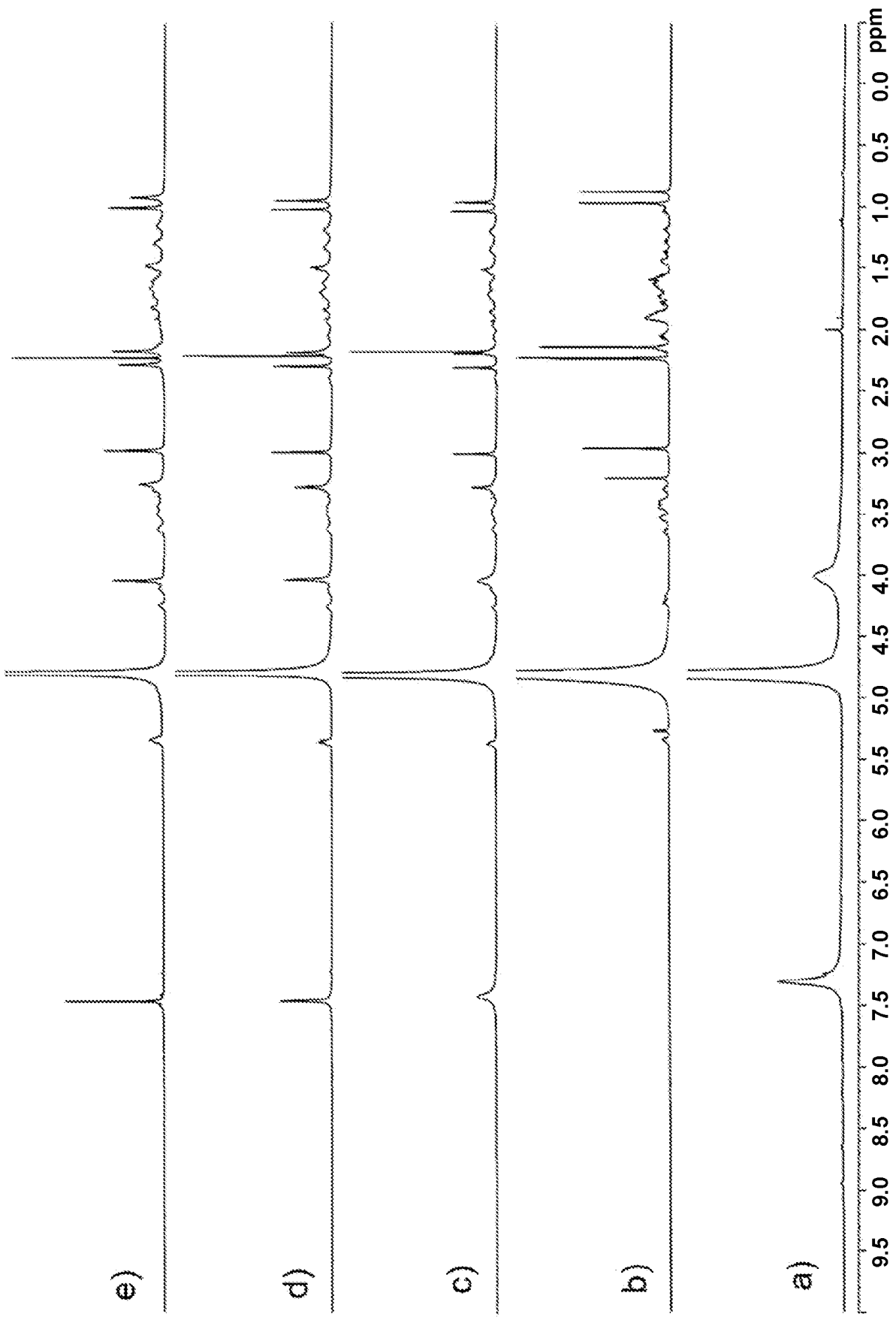


Figure 48

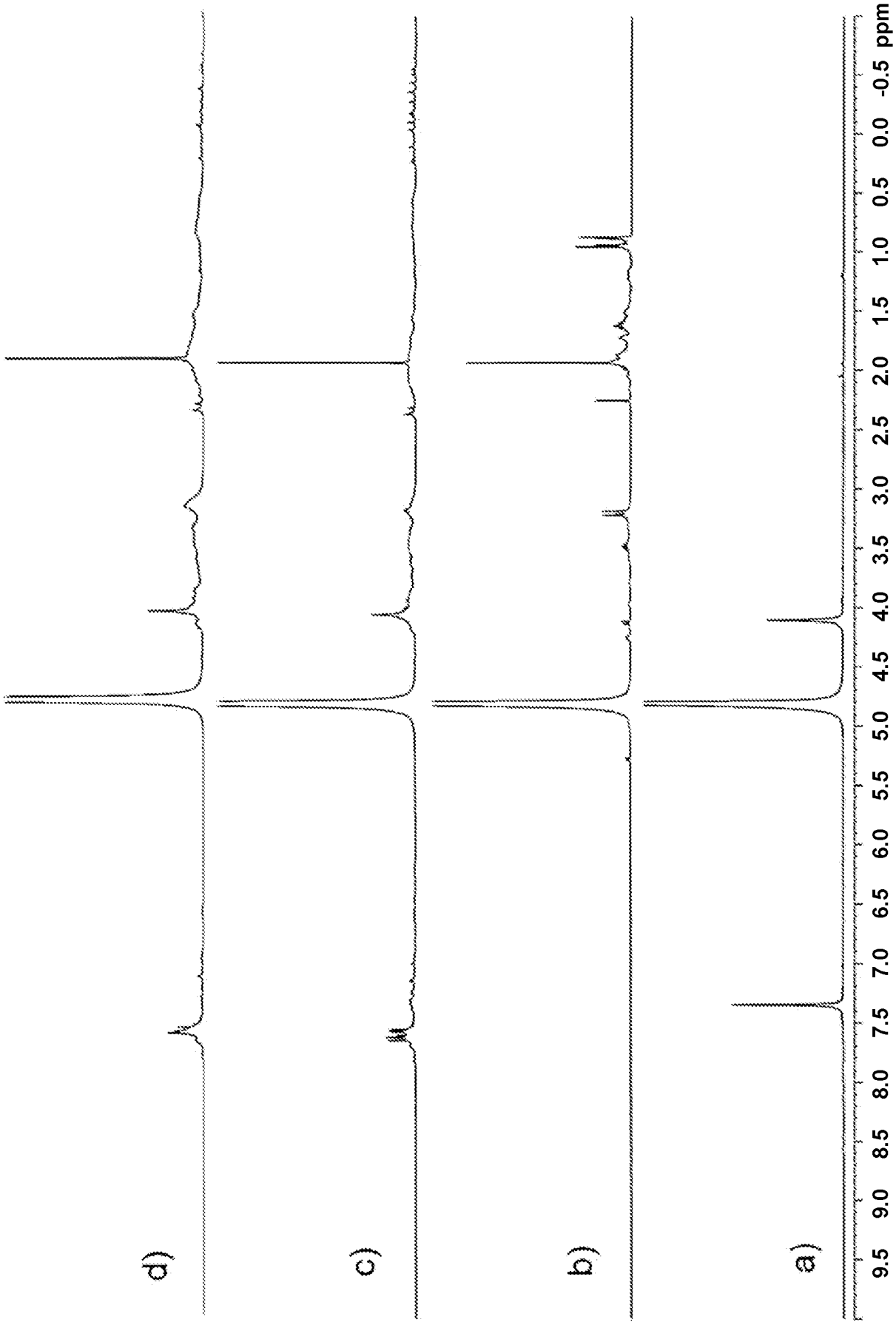


Figure 49

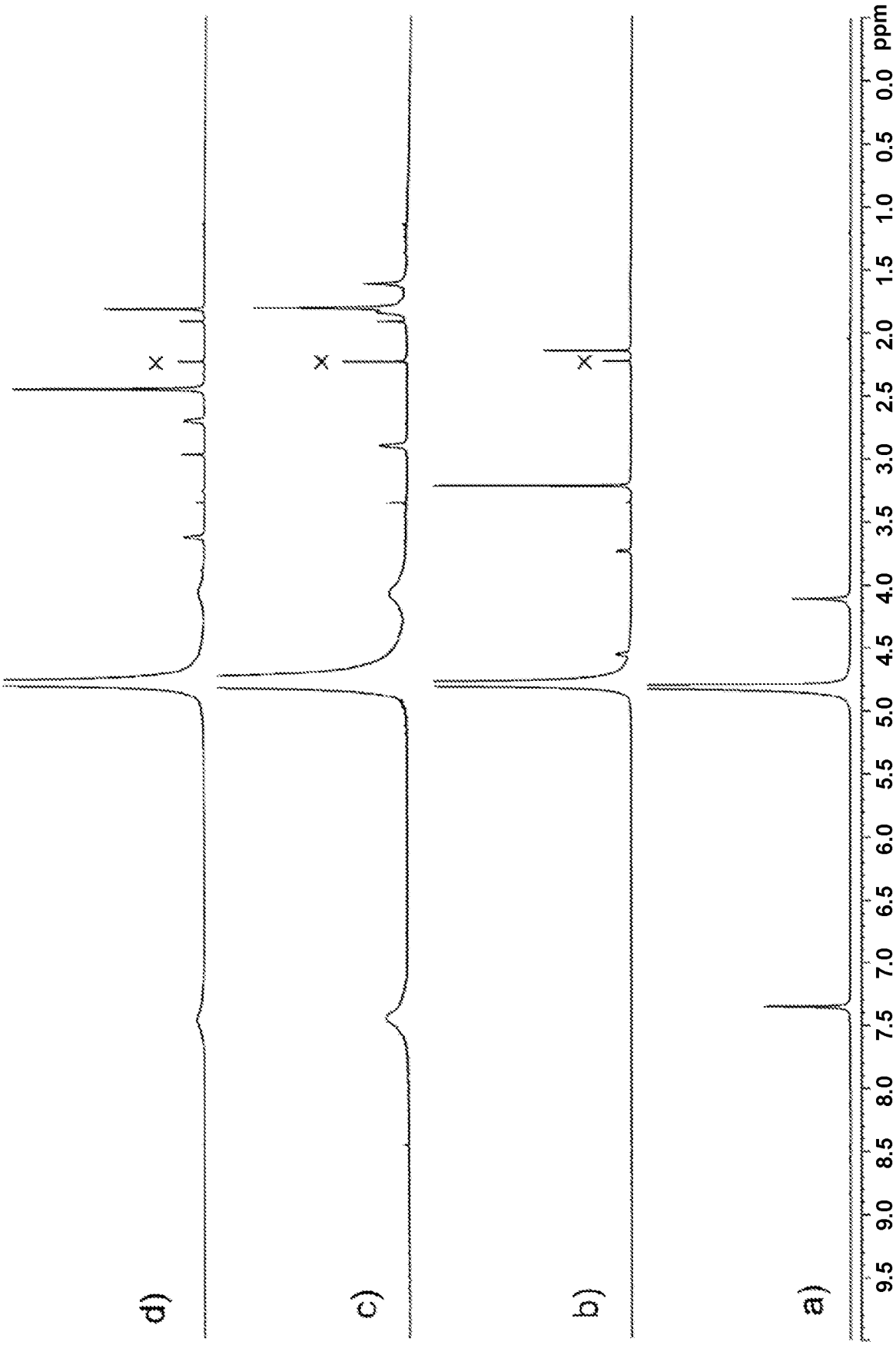

d)
c)
b)
a)
X
X
X
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm

Figure 50

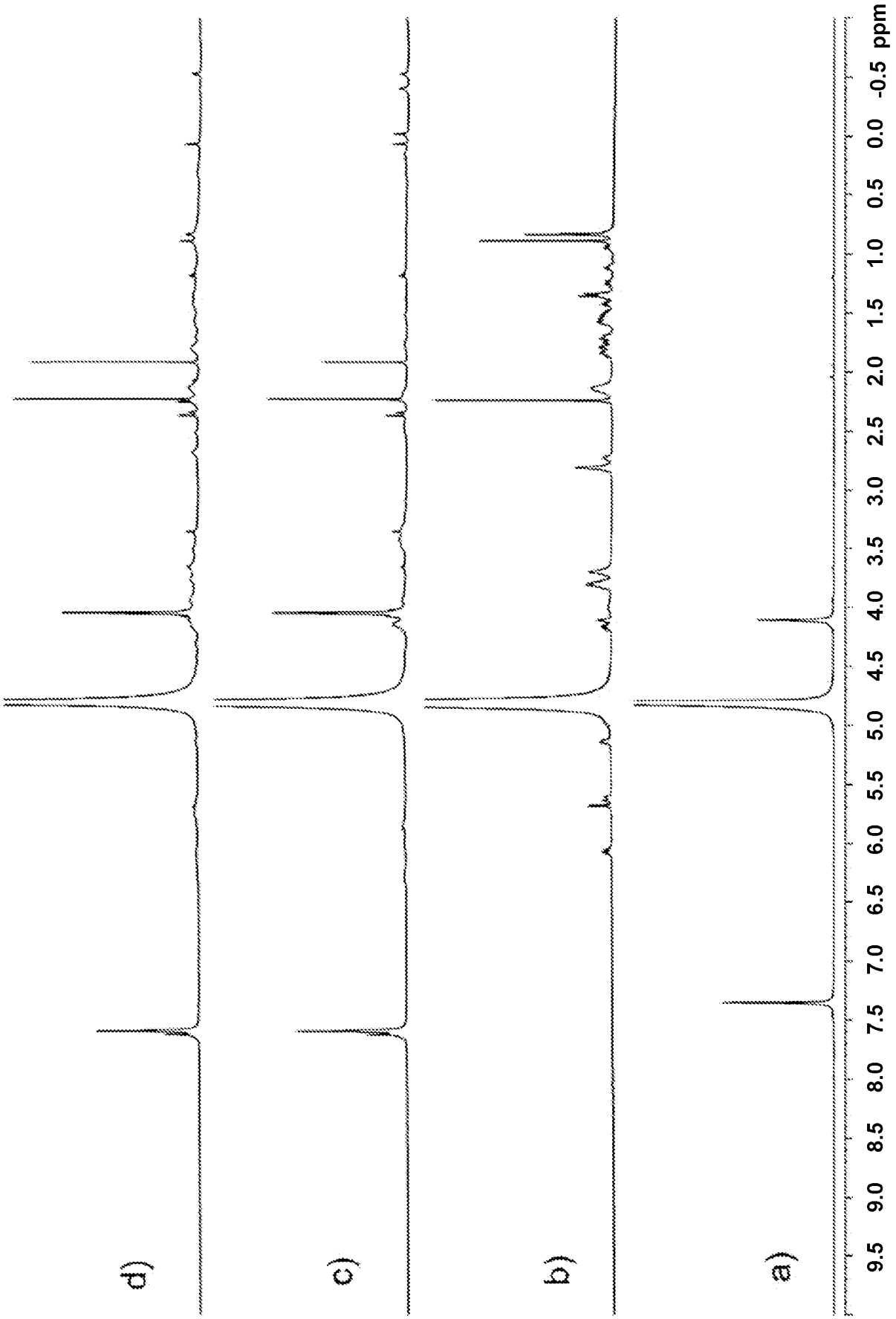


Figure 51

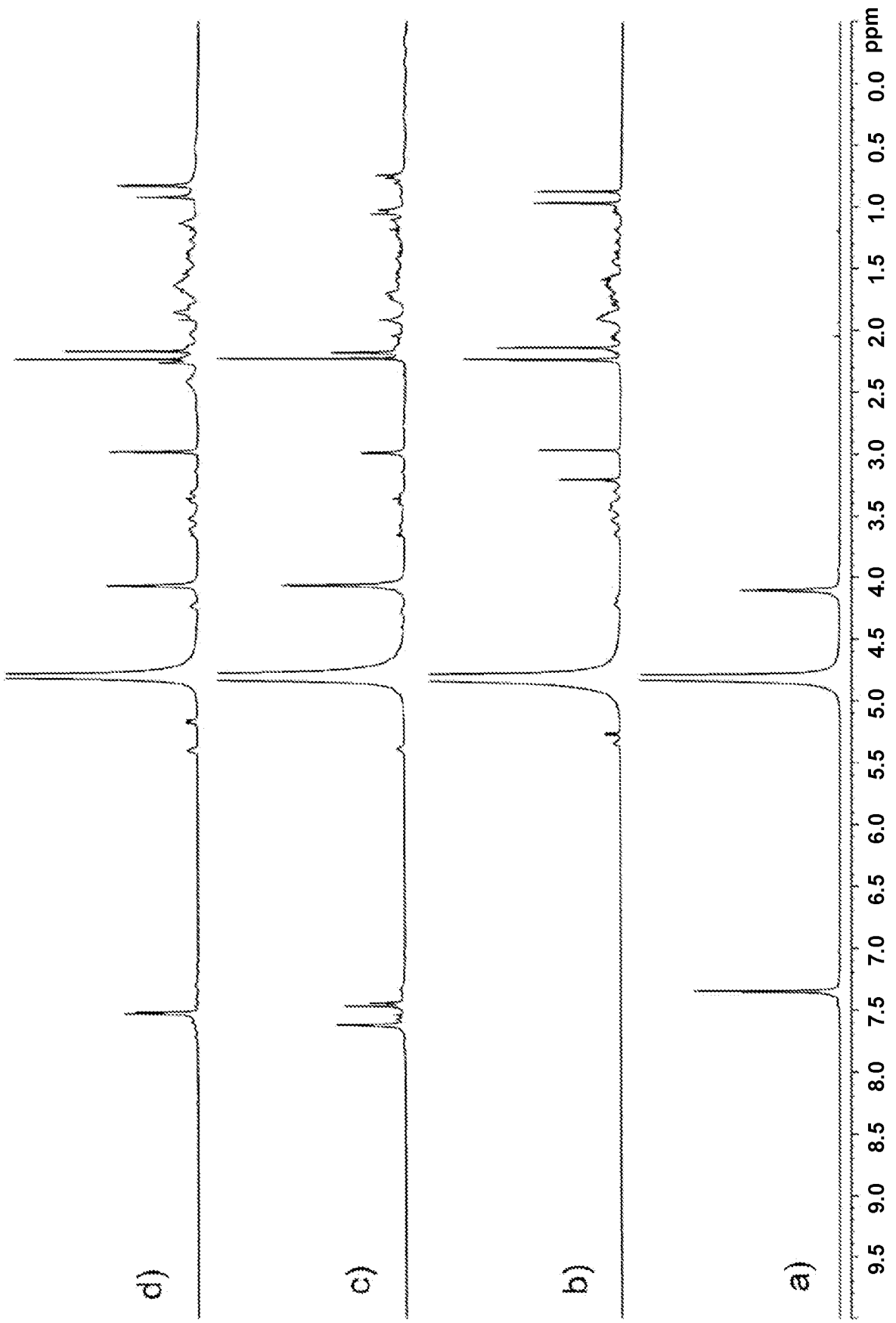


Figure 52

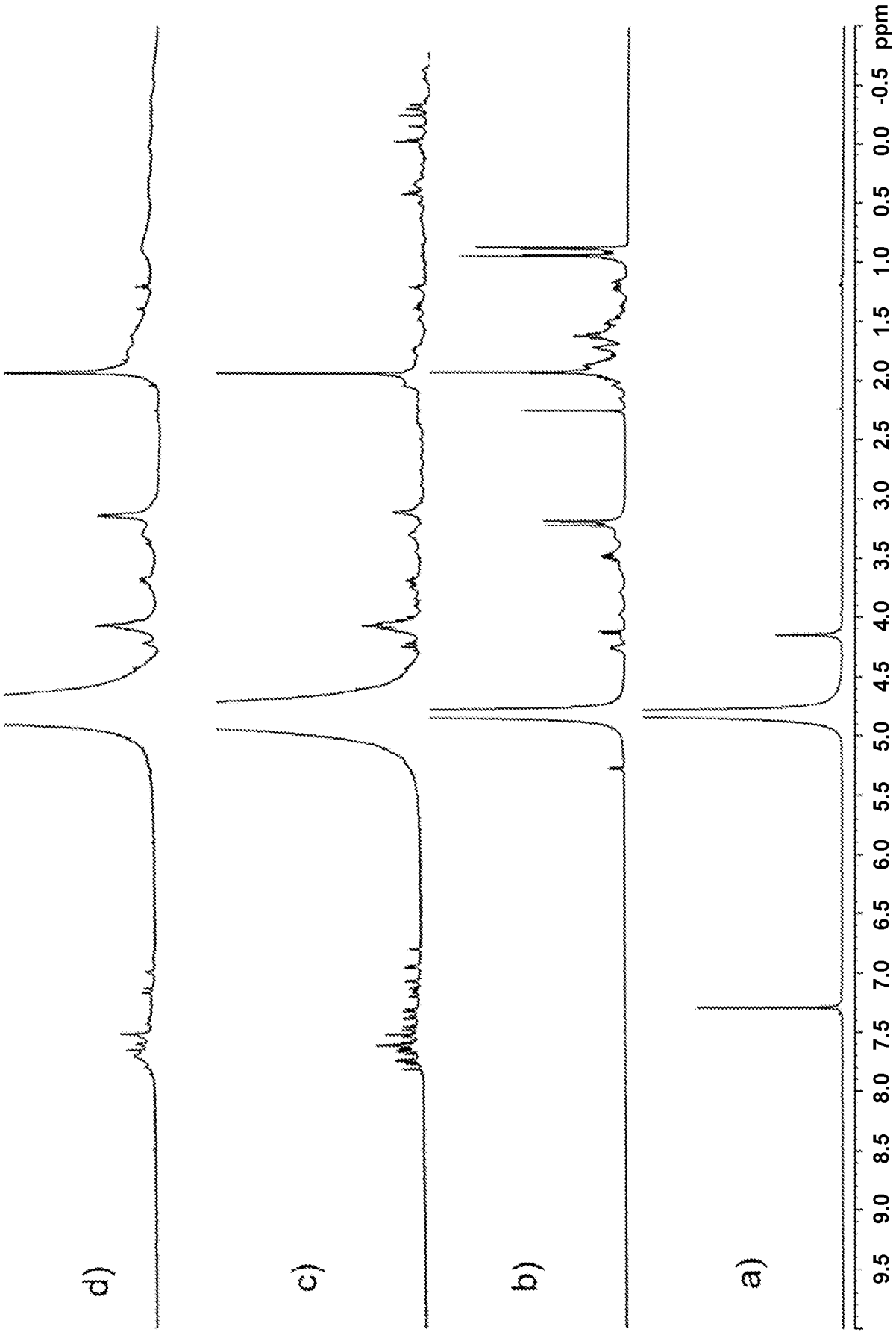


Figure 53

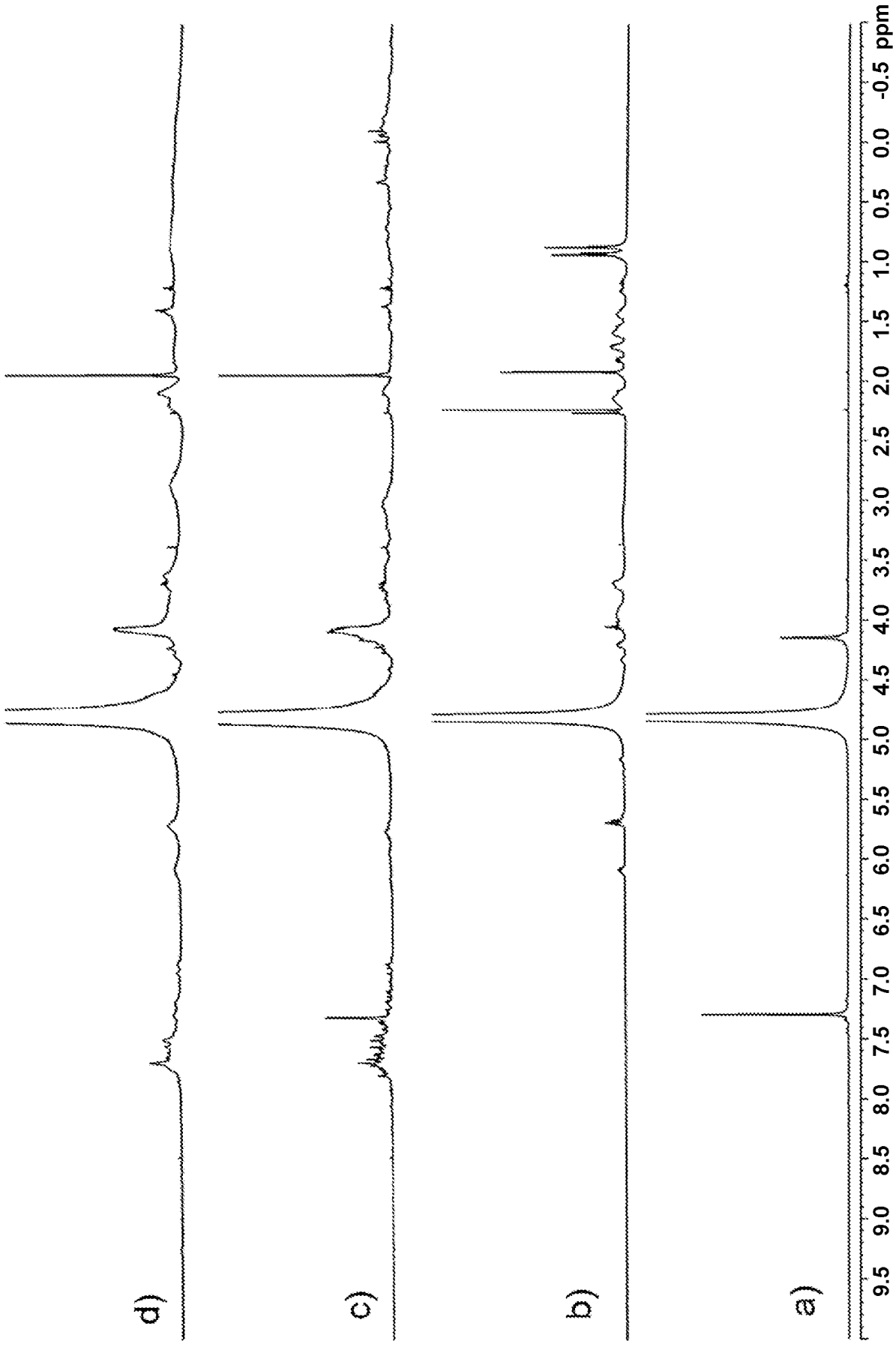


Figure 54

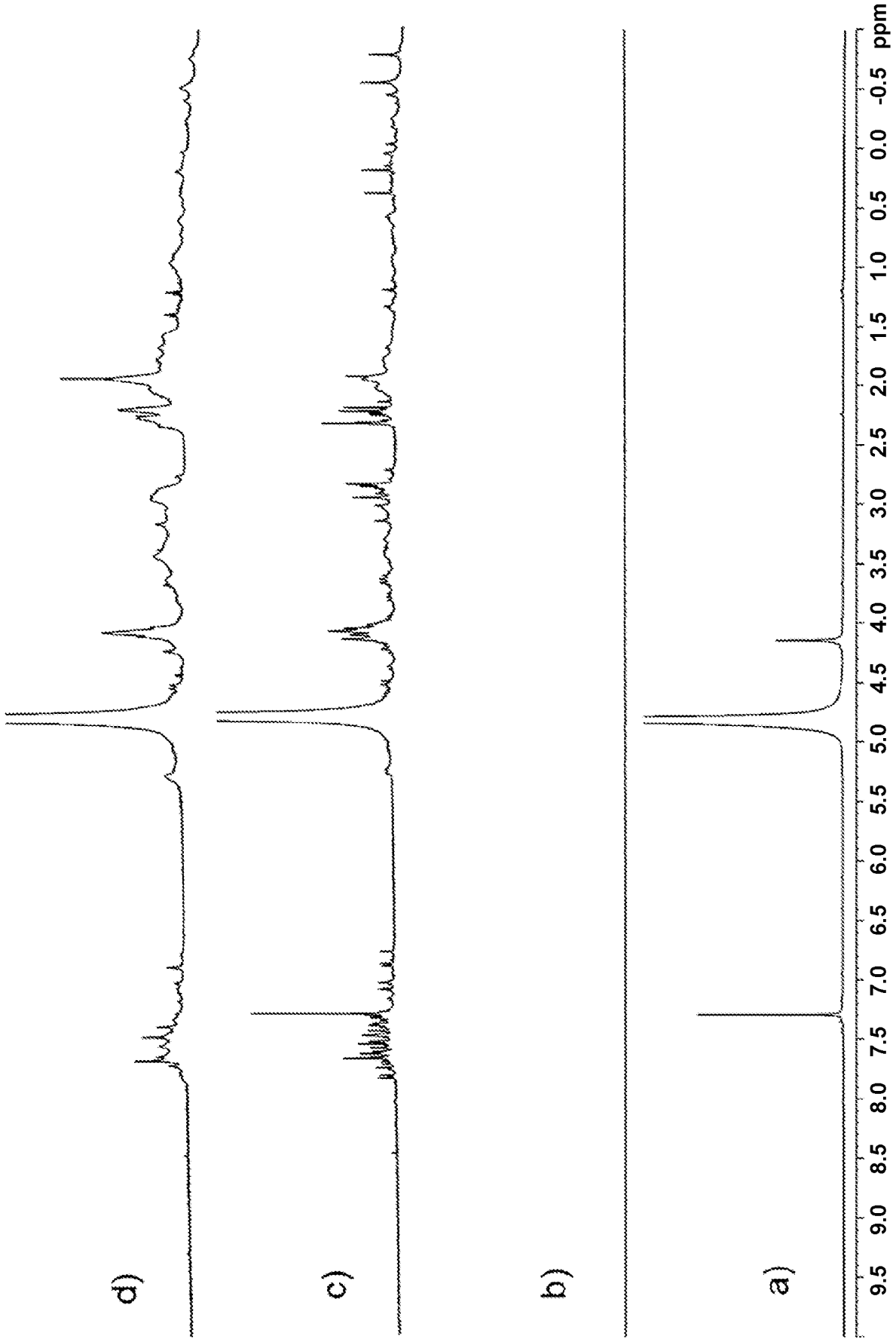


Figure 55

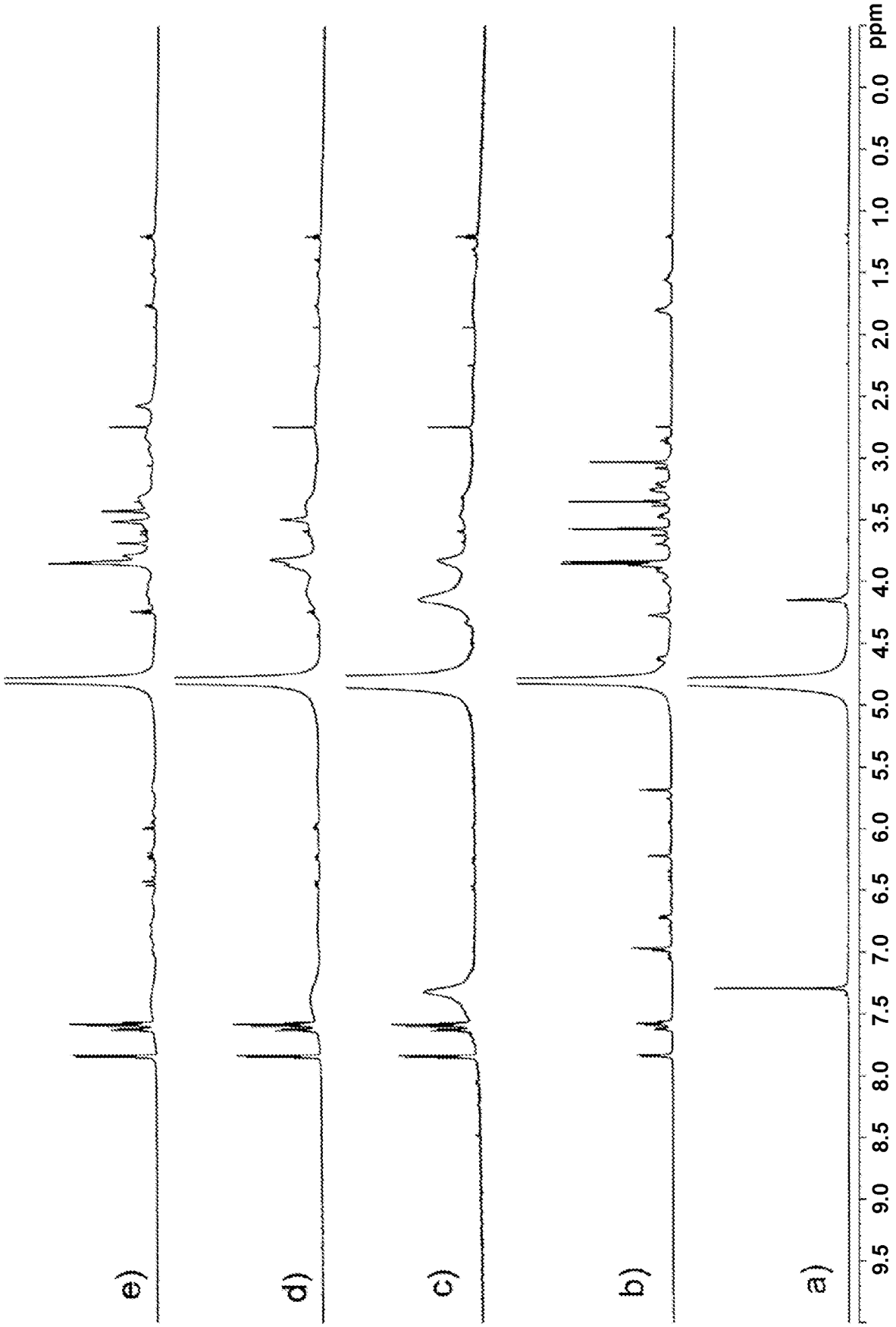


Figure 56

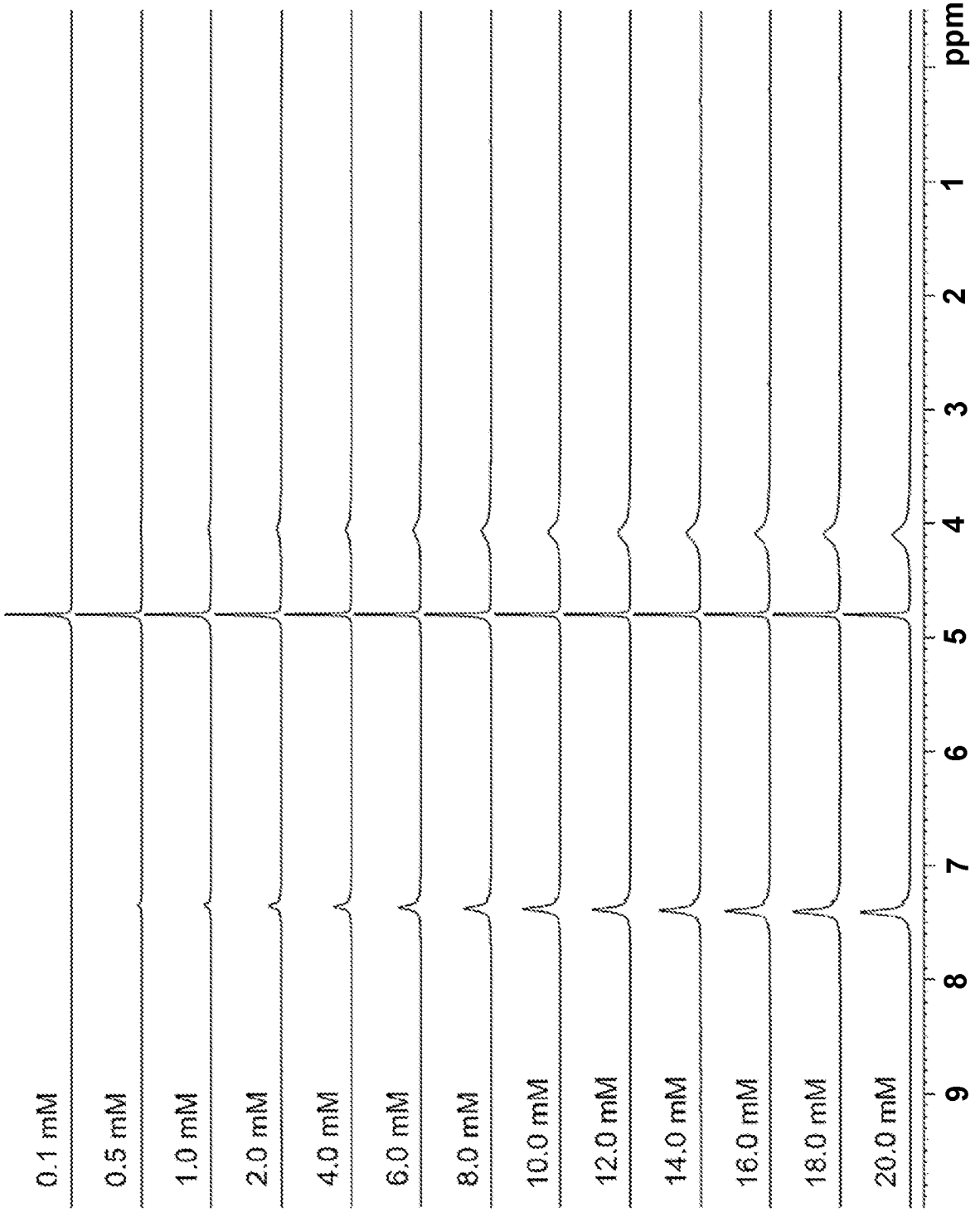

0.1 mM
0.5 mM
1.0 mM
2.0 mM
4.0 mM
6.0 mM
8.0 mM
10.0 mM
12.0 mM
14.0 mM
16.0 mM
18.0 mM
20.0 mM
9
8
7
6
5
4
3
2
1
ppm

Figure 57

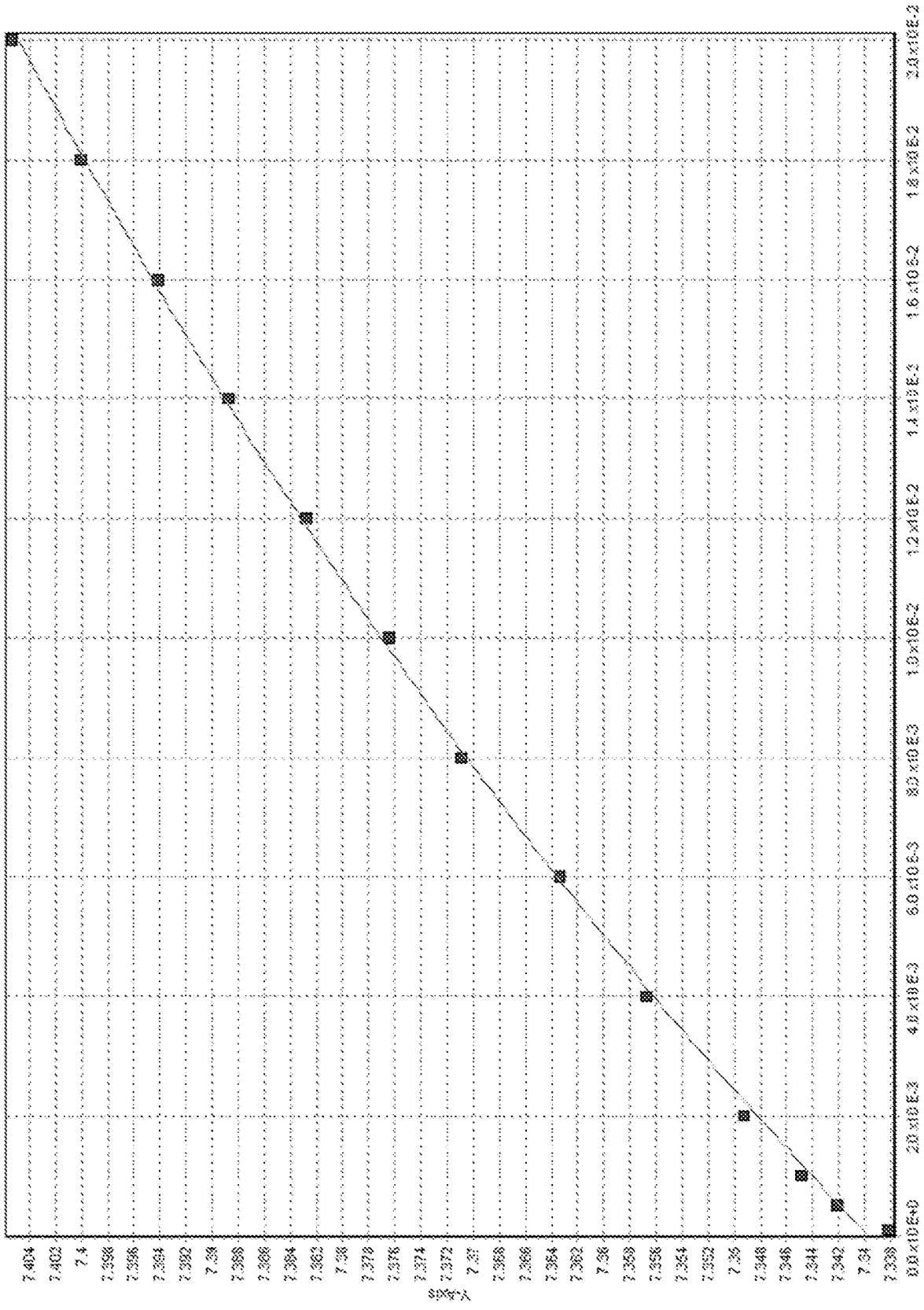

7.404
7.402
7.4
7.398
7.396
7.394
7.392
7.39
7.388
7.386
7.384
7.382
7.38
7.378
7.376
7.374
7.372
7.37
7.368
7.366
7.364
7.362
7.36
7.358
7.356
7.354
7.352
7.35
7.348
7.346
7.344
7.342
7.34
7.338
Y-Axis
0.0x10E+0
2.0x10E-3
4.0x10E-3
6.0x10E-3
8.0x10E-3
1.0x10E-2
1.2x10E-2
1.4x10E-2
1.6x10E-2
1.8x10E-2
2.0x10E-2
CONCTOT-Axis

Figure 58

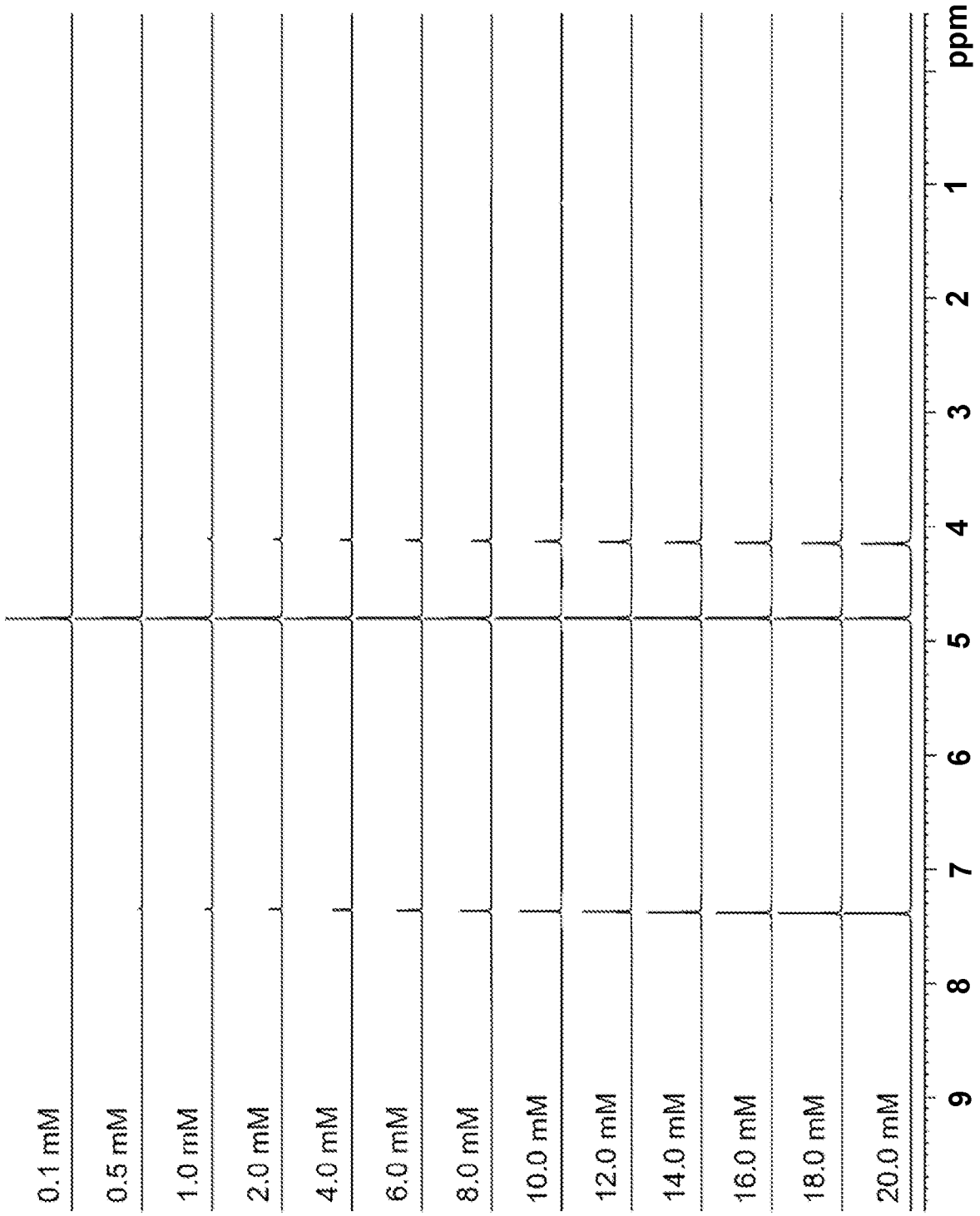

0.1 mM
0.5 mM
1.0 mM
2.0 mM
4.0 mM
6.0 mM
8.0 mM
10.0 mM
12.0 mM
14.0 mM
16.0 mM
18.0 mM
20.0 mM
9
8
7
6
5
4
3
2
1
ppm

Figure 59

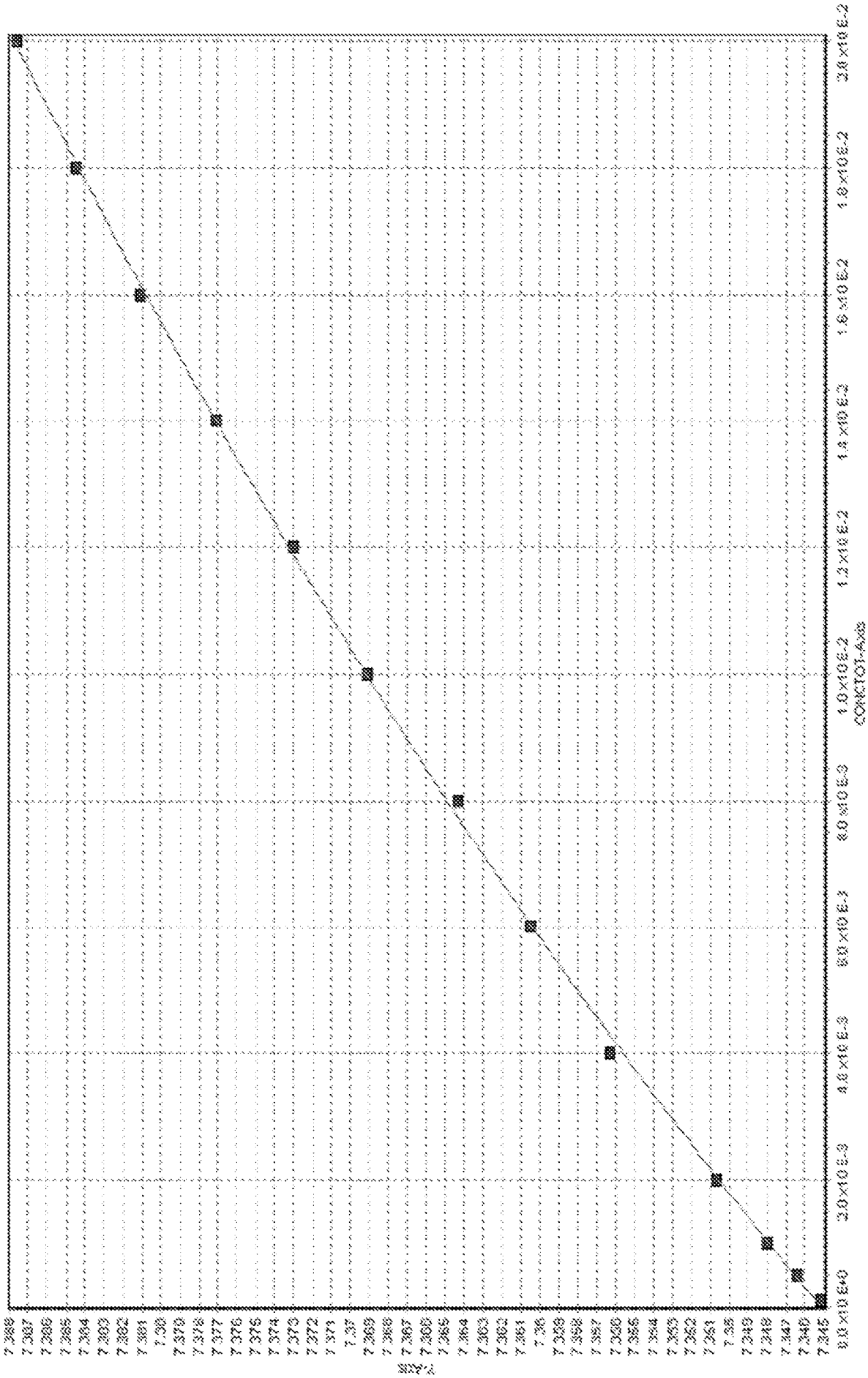

CONCTOT-Axis
0.0×10 E0
2.0×10 E-3
4.0×10 E-3
6.0×10 E-3
8.0×10 E-3
1.0×10 E-2
1.2×10 E-2
1.4×10 E-2
1.6×10 E-2
1.8×10 E-2
2.0×10 E-2

Figure 60

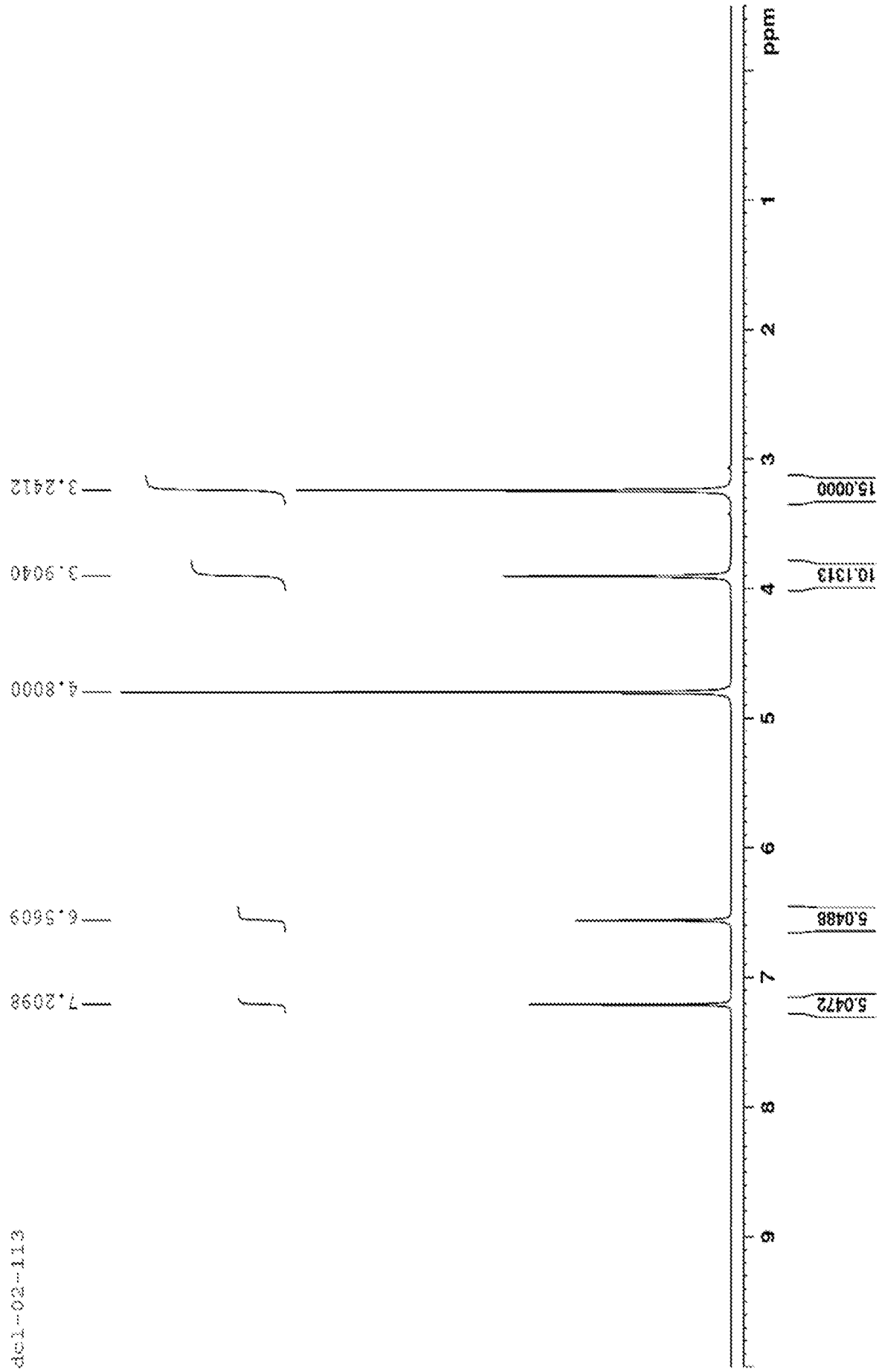

ppm
1
2
3
4
5
6
7
8
9
15.0000
10.1313
5.0488
5.0472
3.2412
3.9040
4.8000
6.9609
7.2098
dc1-02-113

Figure 61

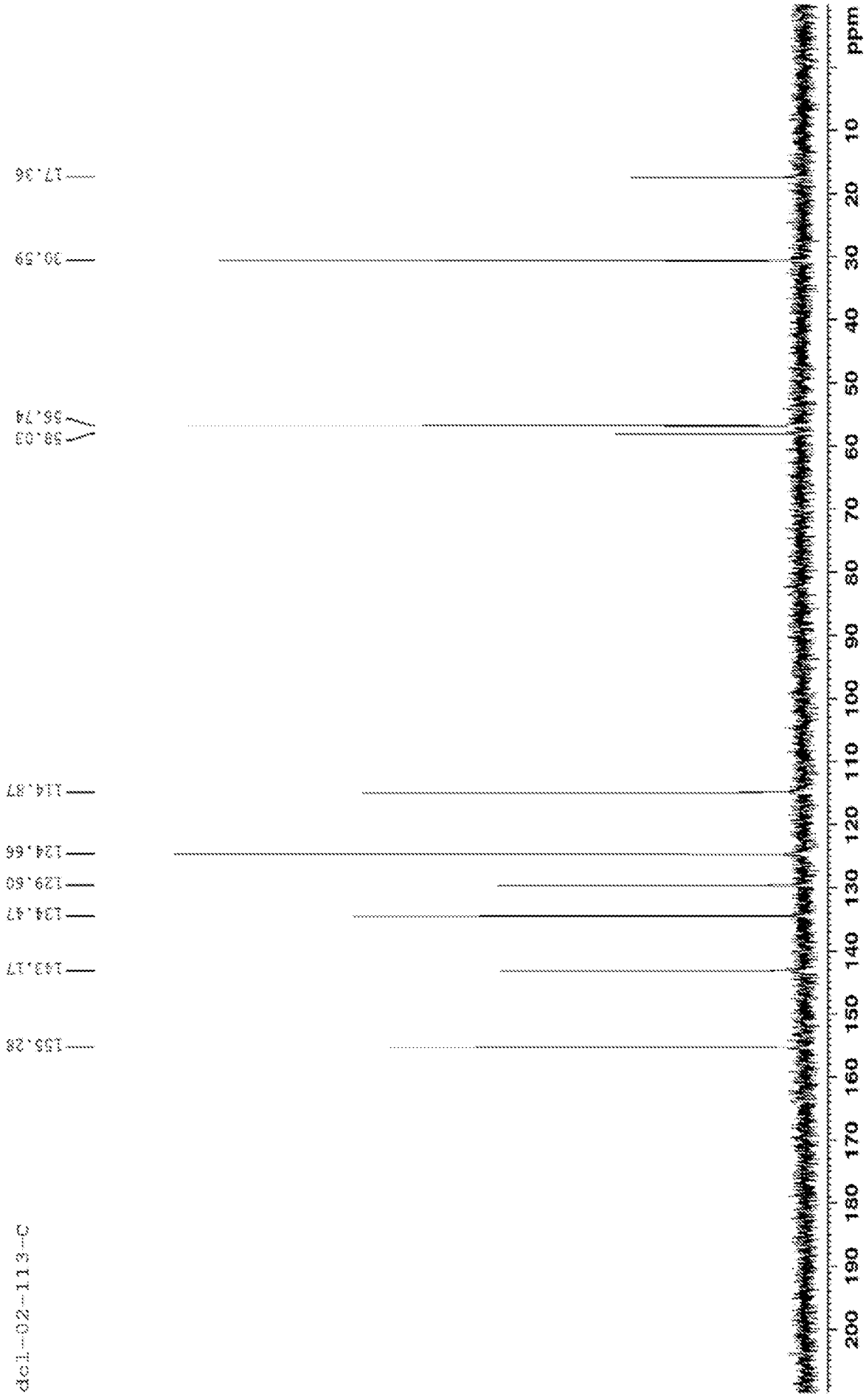

17.36
30.59
55.74
58.03
114.87
124.66
129.60
134.47
143.17
155.28
dcl-02-113-C
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200

Figure 62

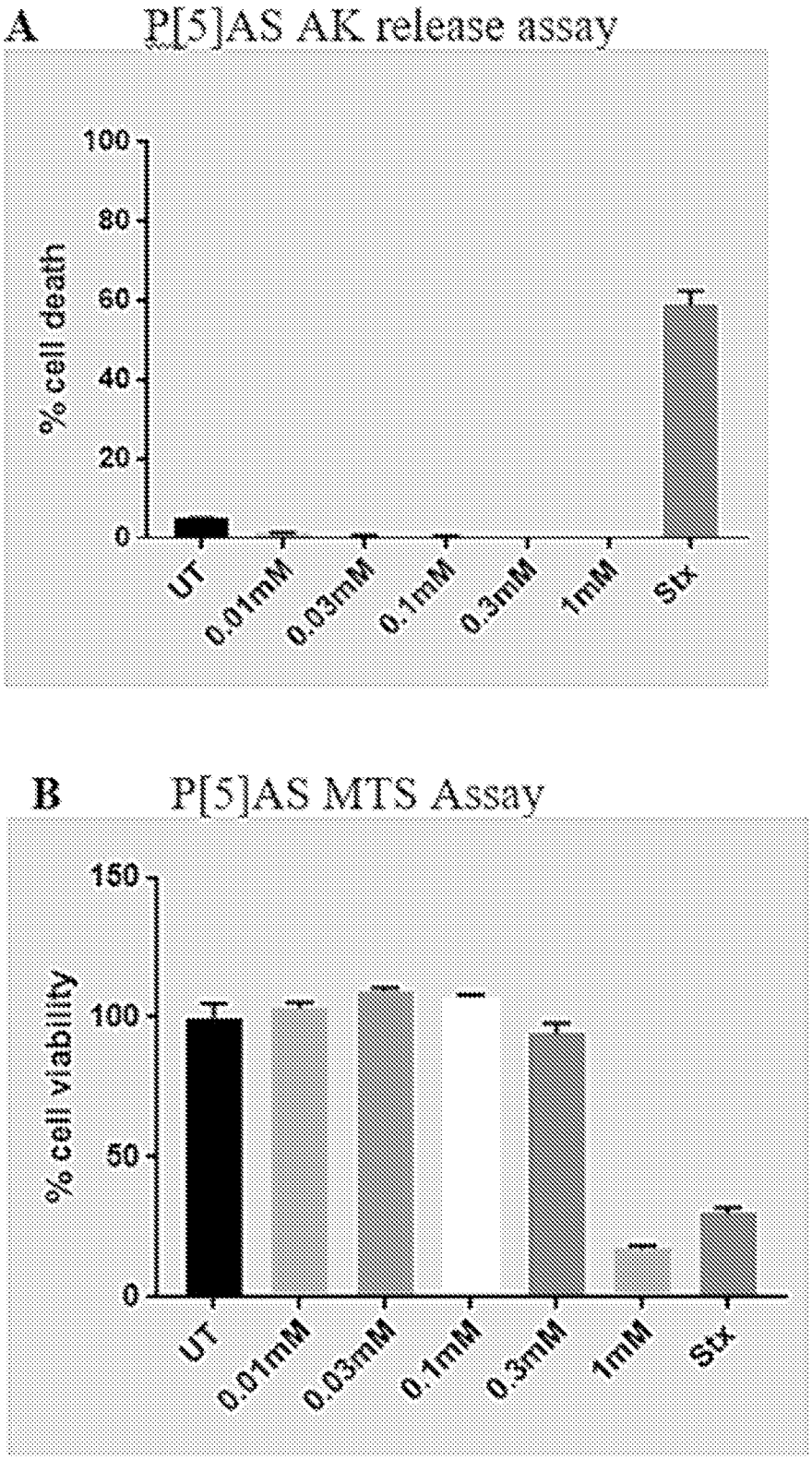
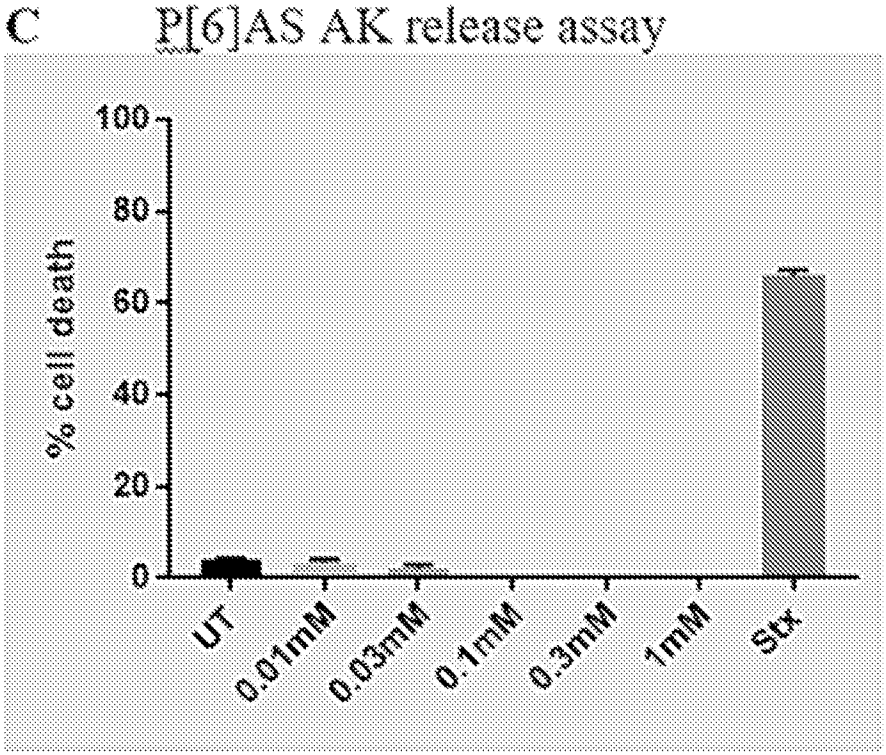

A
P[5]AS AK release assay
% cell death
100
80
60
40
20
0
UT
0.01mM
0.03mM
0.1mM
0.3mM
1mM
Stx
B
P[5]AS MTS Assay
% cell viability
150
100
50
0
UT
0.01mM
0.03mM
0.1mM
0.3mM
1mM
Stx

Figure 63



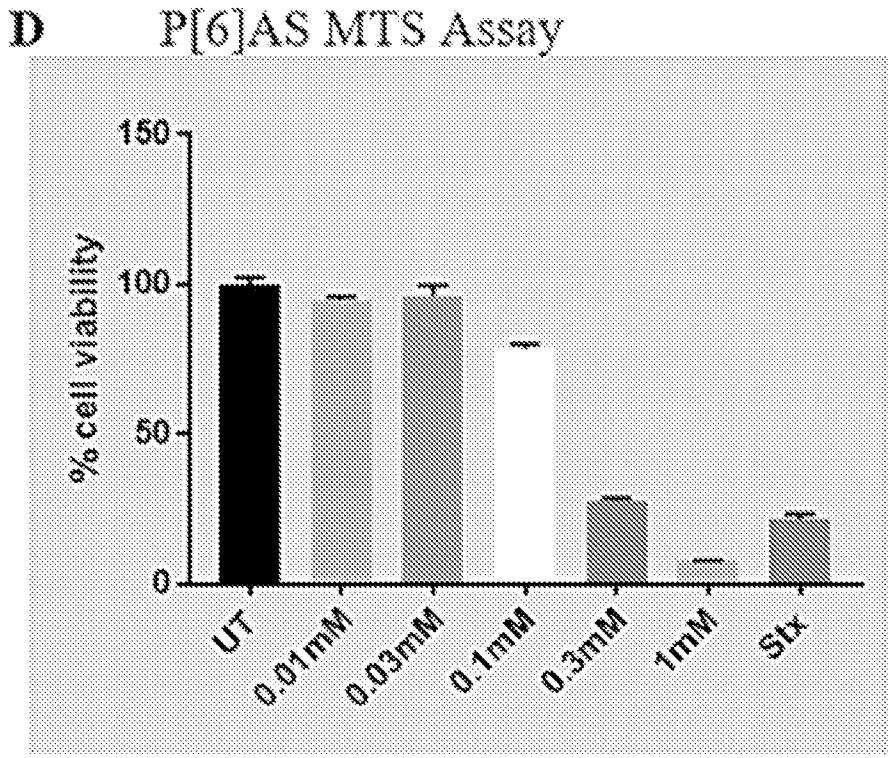


Figure 63 (cont.)

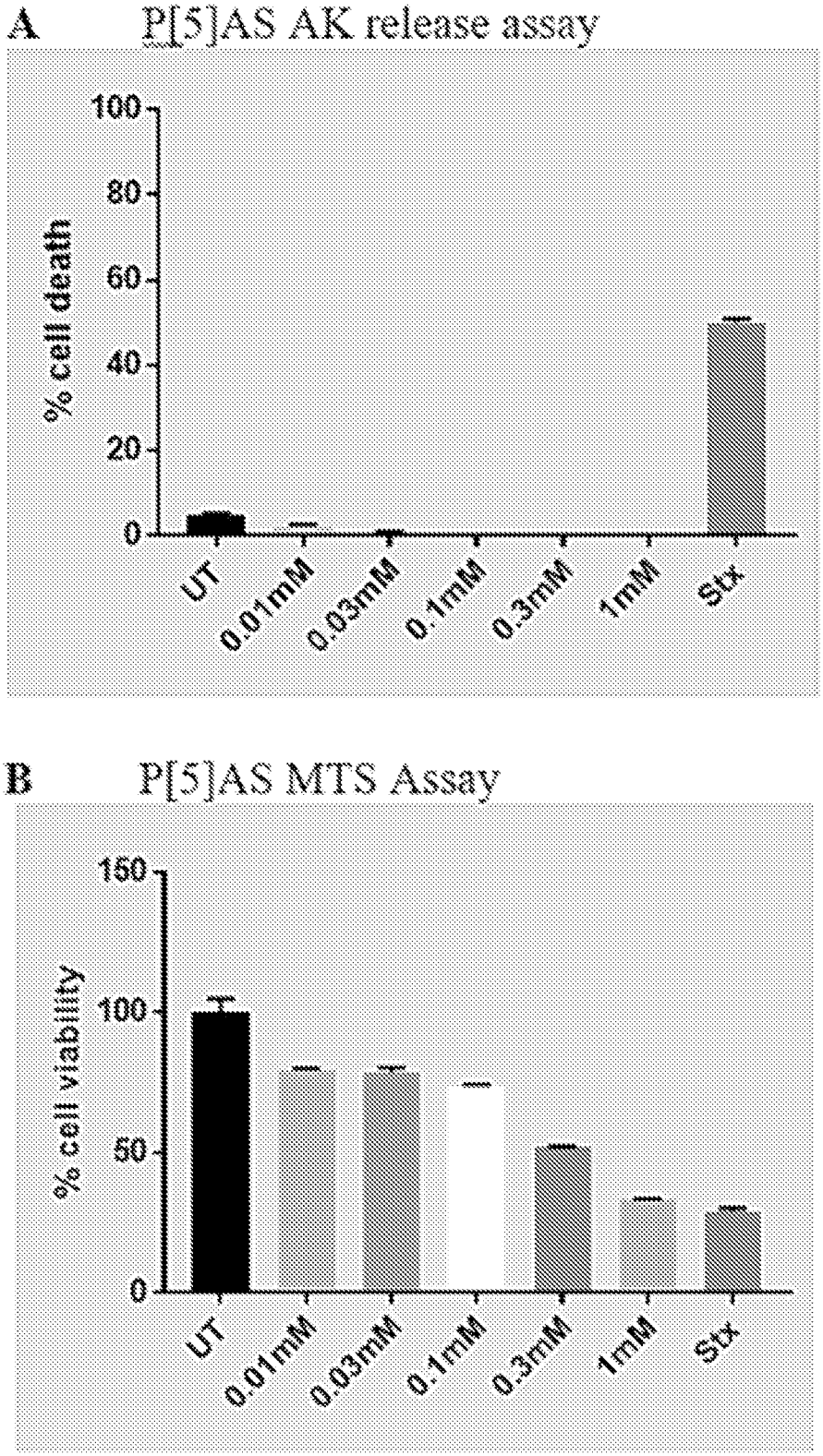
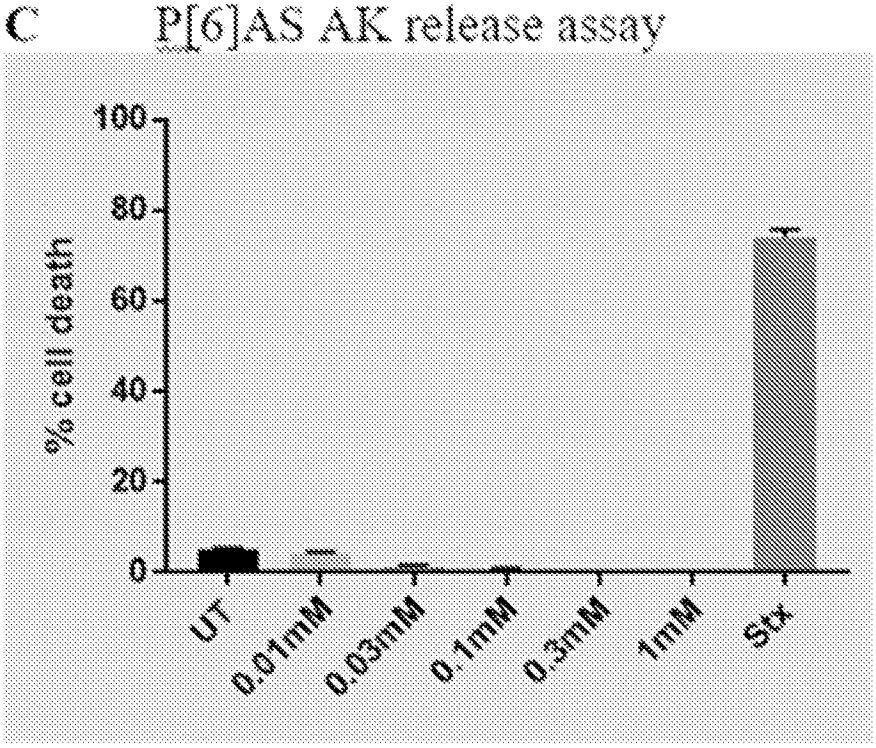

A
P[5]AS AK release assay
% cell death
100
80
60
40
20
0
UT
0.01mM
0.03mM
0.1mM
0.3mM
1mM
Stx
B
P[5]AS MTS Assay
% cell viability
150
100
50
0
UT
0.01mM
0.03mM
0.1mM
0.3mM
1mM
Stx

Figure 64



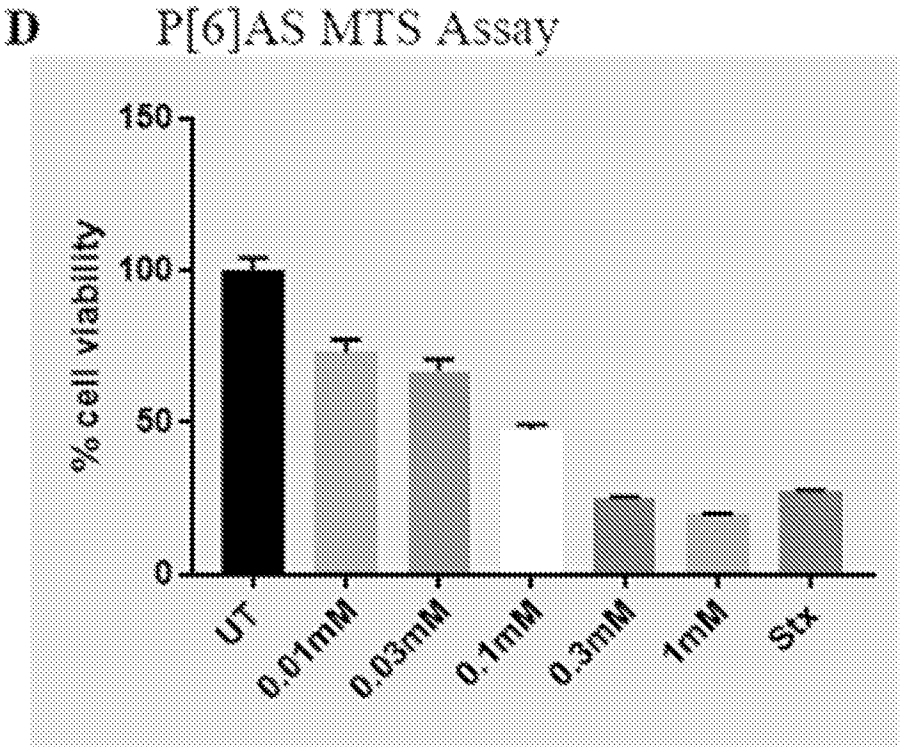


Figure 64 (cont.)

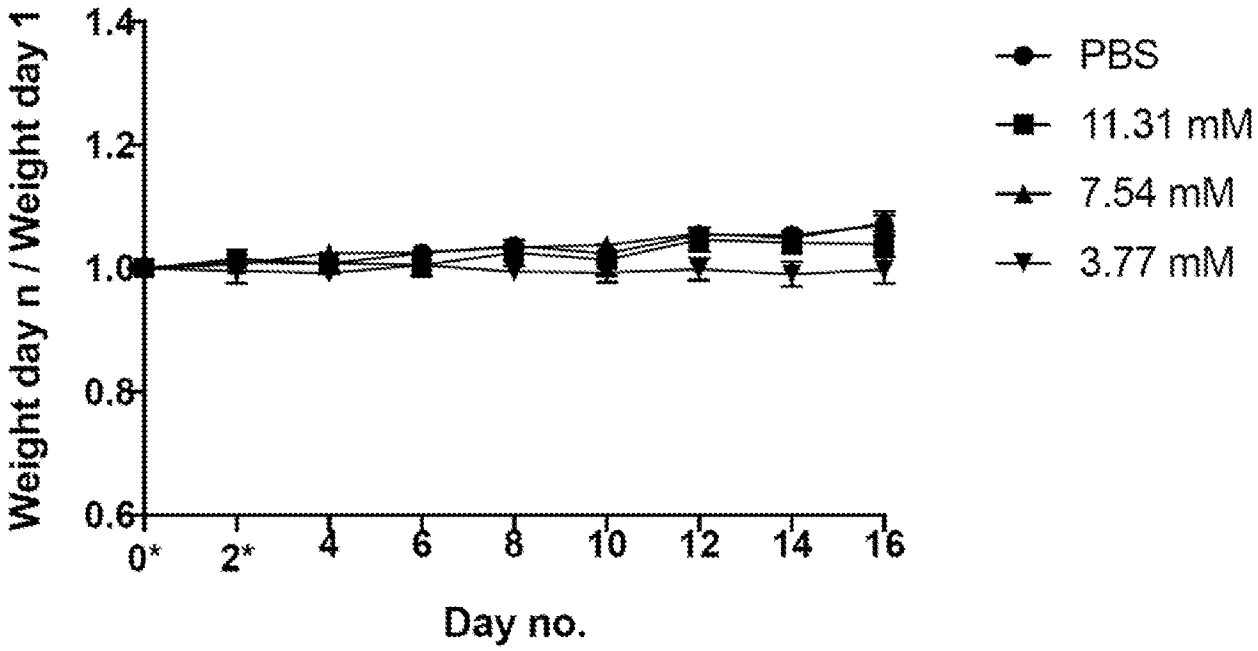


Figure 65

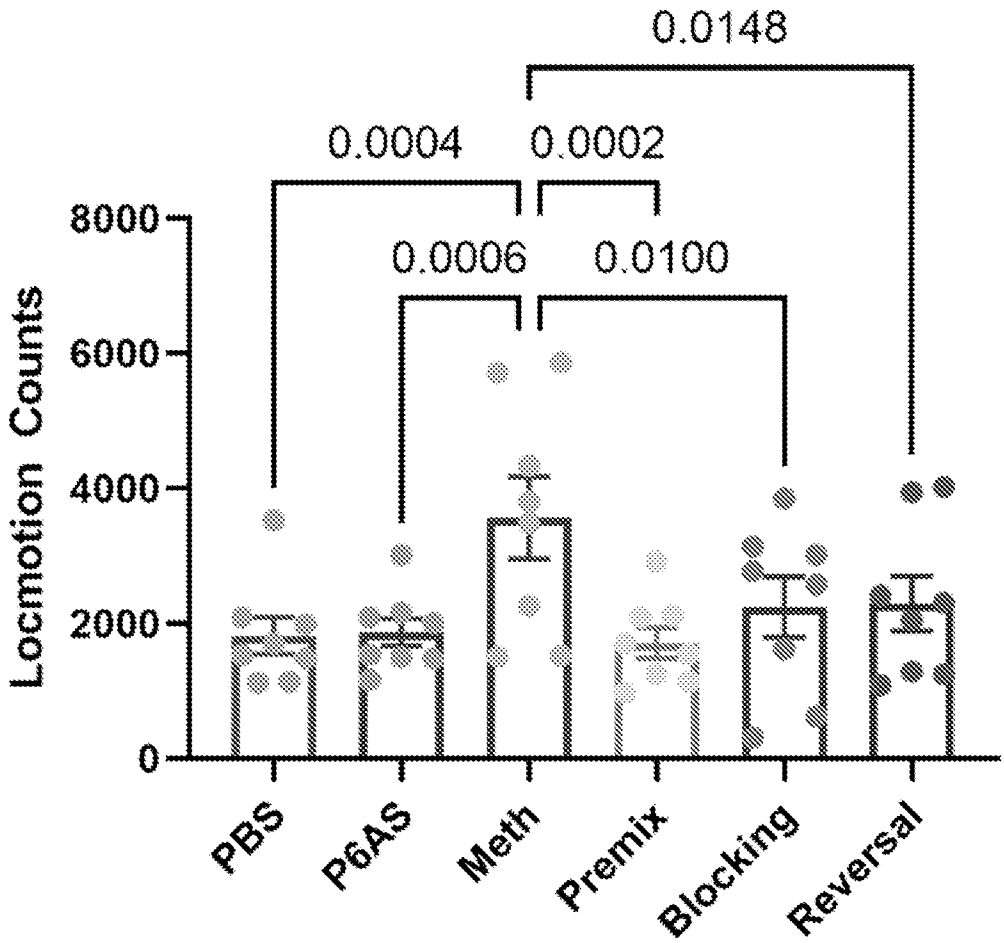


Figure 66

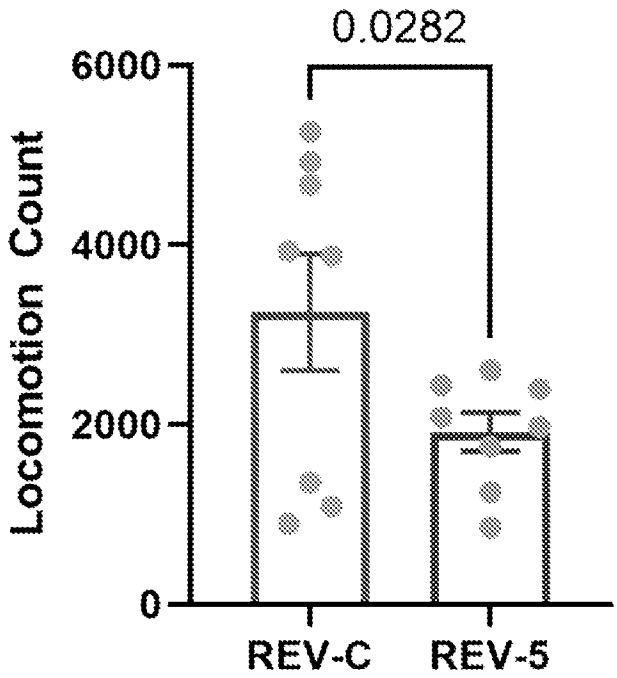


Figure 67

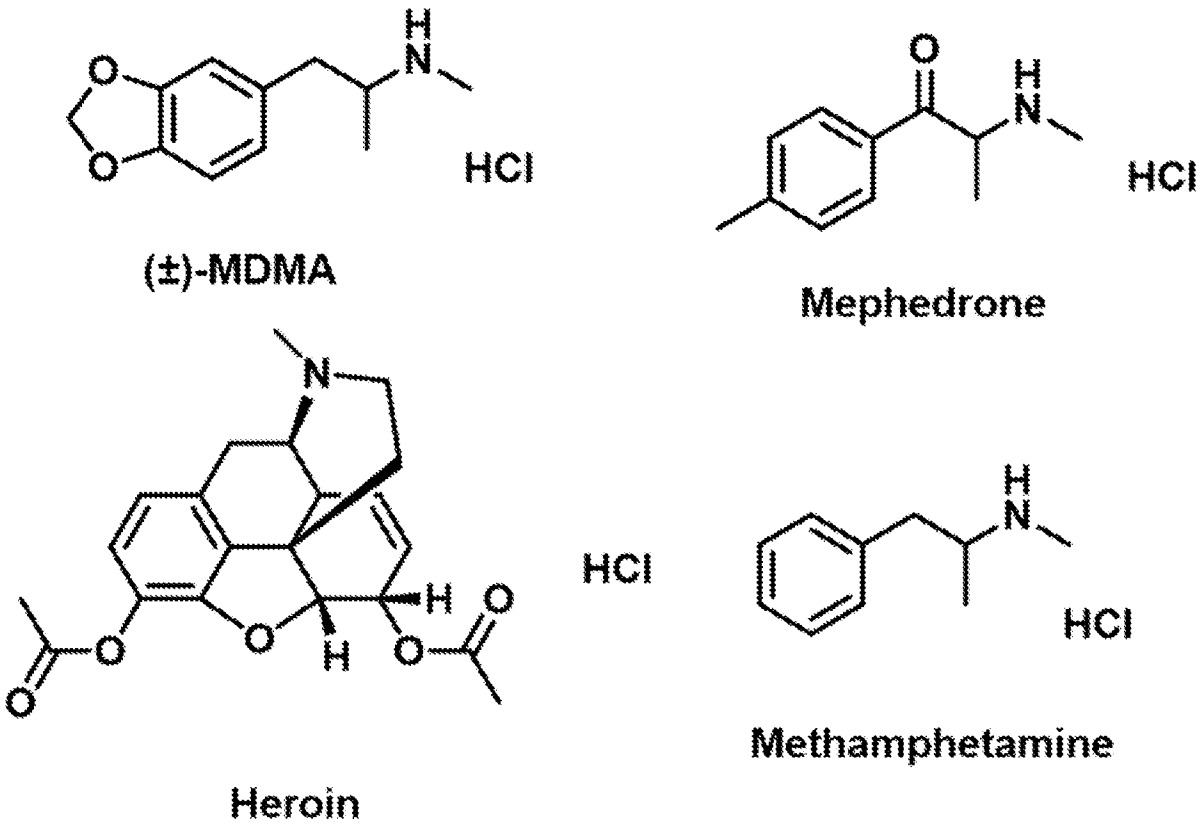


Figure 68

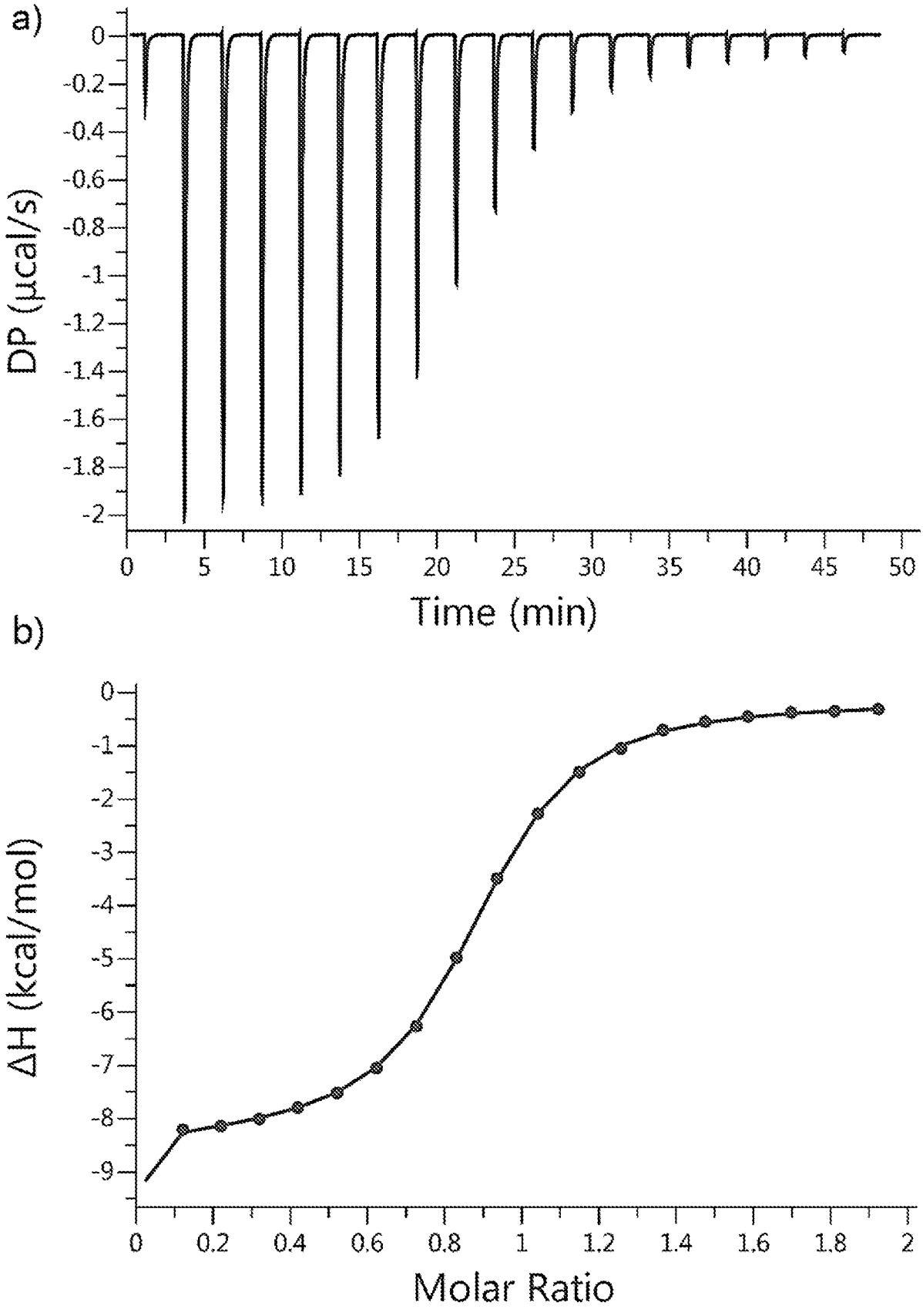

a)
DP (µcal/s)
0
-0.2
-0.4
-0.6
-0.8
-1
-1.2
-1.4
-1.6
-1.8
-2
0
5
10
15
20
25
30
35
40
45
50
Time (min)
b)
ΔH (kcal/mol)
0
-1
-2
-3
-4
-5
-6
-7
-8
-9
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6
1.8
2
Molar Ratio

Figure 69

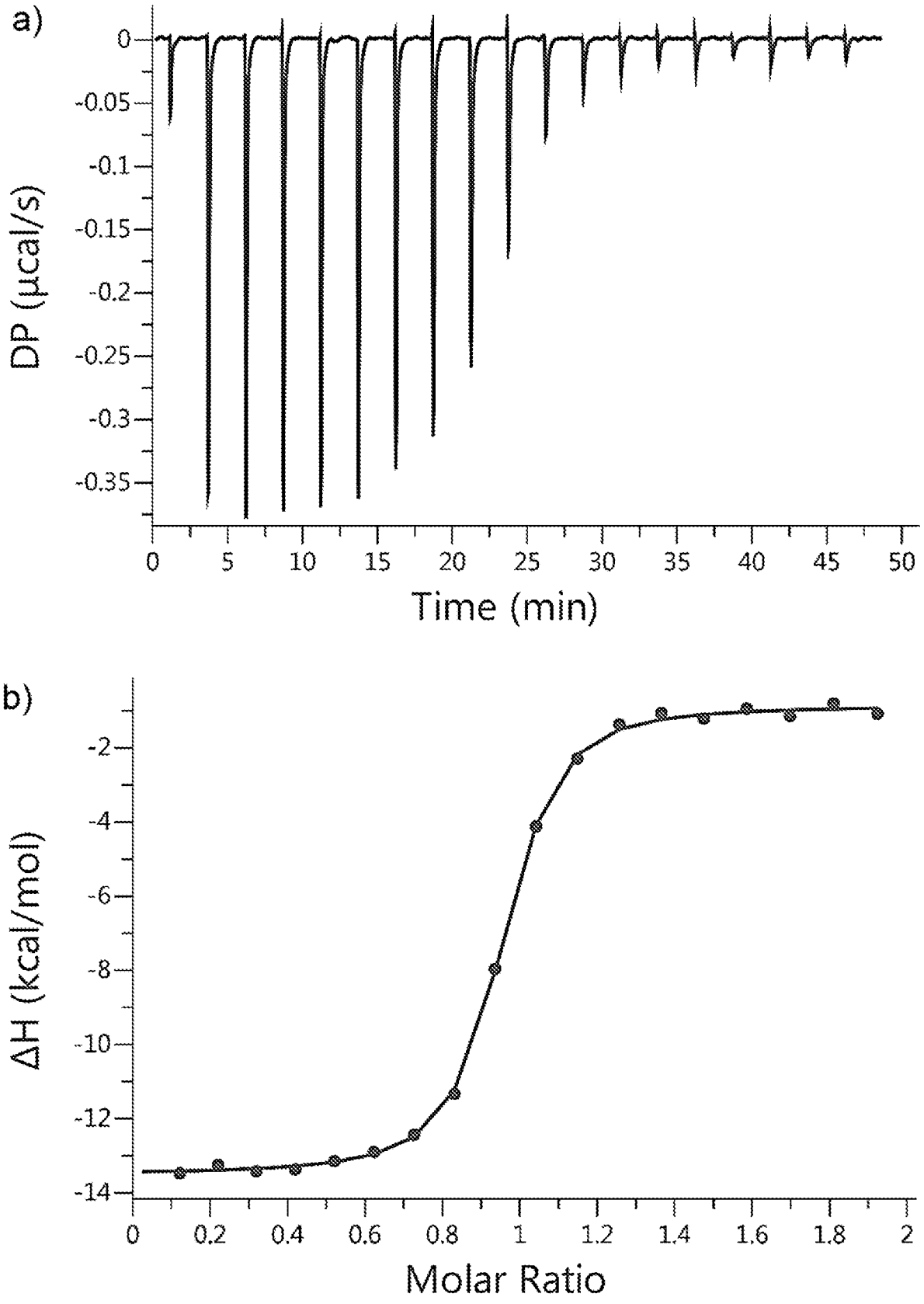

a)
DP (µcal/s)
0
-0.05
-0.1
-0.15
-0.2
-0.25
-0.3
-0.35
0
5
10
15
20
25
30
35
40
45
50
Time (min)
b)
ΔH (kcal/mol)
-2
-4
-6
-8
-10
-12
-14
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6
1.8
2
Molar Ratio

Figure 70

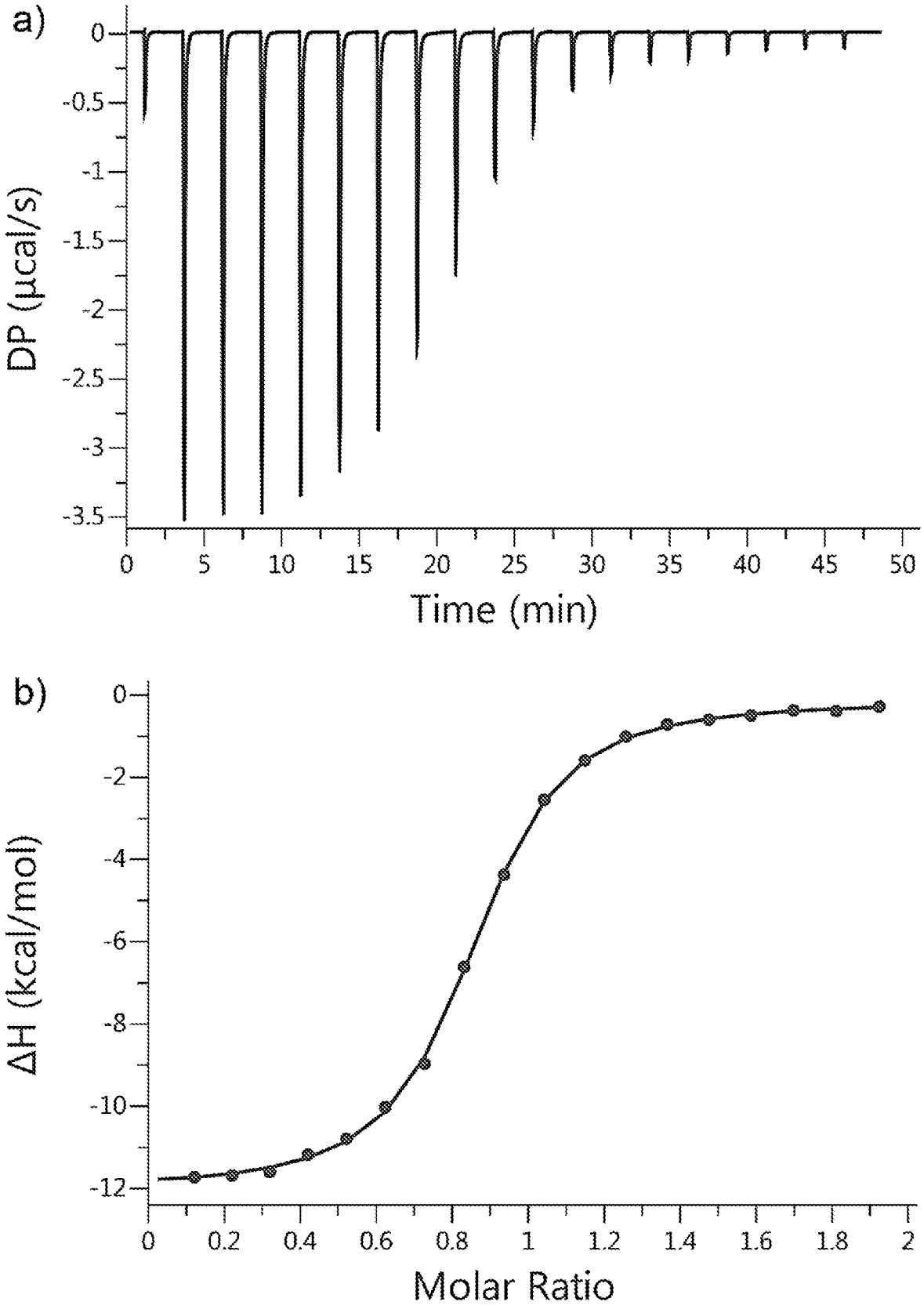

a)
DP (µcal/s)
0
-0.5
-1
-1.5
-2
-2.5
-3
-3.5
0
5
10
15
20
25
30
35
40
45
50
Time (min)
b)
ΔH (kcal/mol)
0
-2
-4
-6
-8
-10
-12
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6
1.8
2
Molar Ratio

Figure 71

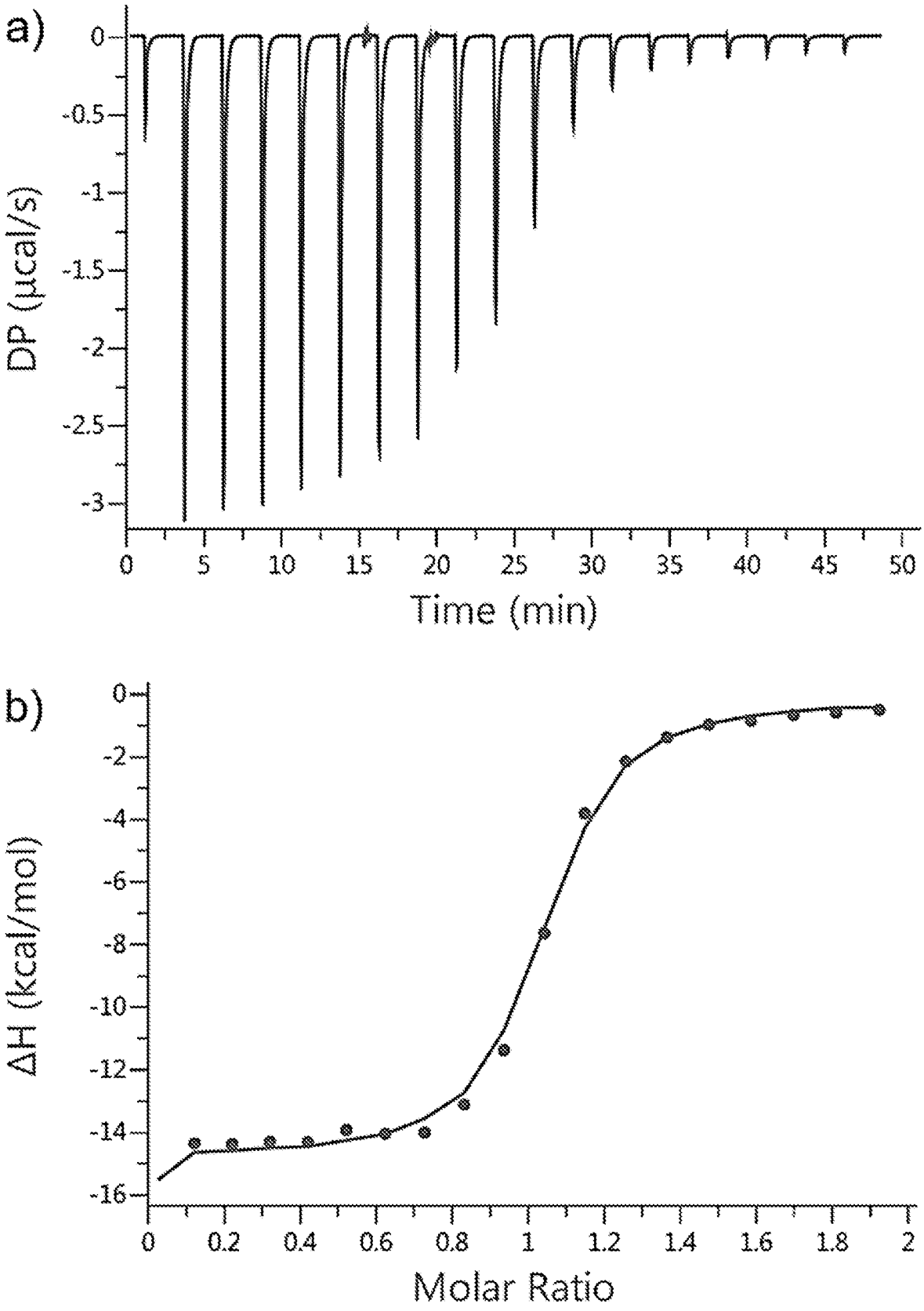

a)
DP (µcal/s)
0
-0.5
-1
-1.5
-2
-2.5
-3
0
5
10
15
20
25
30
35
40
45
50
Time (min)
b)
ΔH (kcal/mol)
0
-2
-4
-6
-8
-10
-12
-14
-16
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6
1.8
2
Molar Ratio

Figure 72

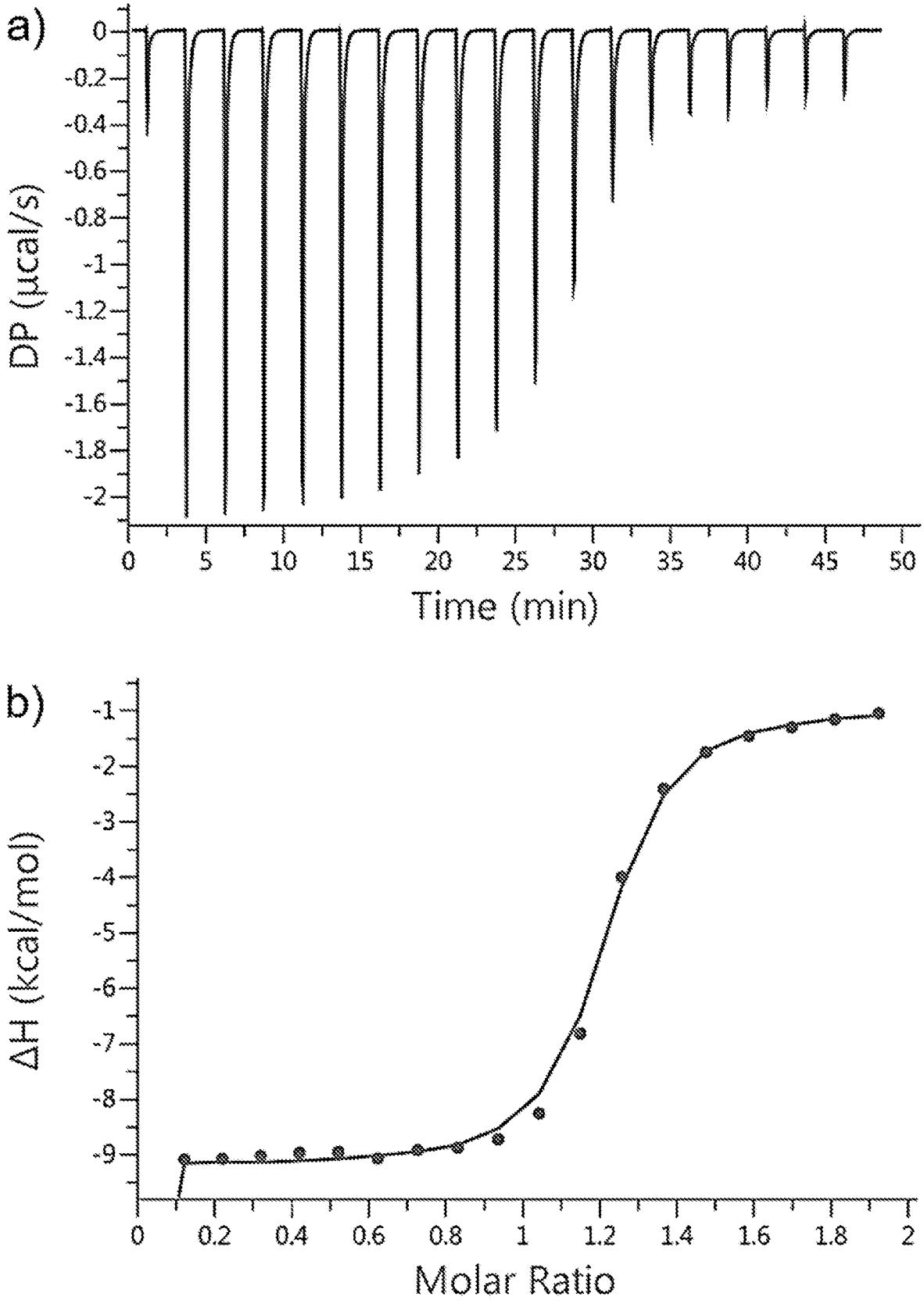

a)
DP (µcal/s)
0
-0.2
-0.4
-0.6
-0.8
-1
-1.2
-1.4
-1.6
-1.8
-2
0 5 10 15 20 25 30 35 40 45 50
Time (min)
b)
ΔH (kcal/mol)
-1
-2
-3
-4
-5
-6
-7
-8
-9
0 0.2 0.4 0.6 0.8 1 1.2 1.4 1.6 1.8 2
Molar Ratio

Figure 73

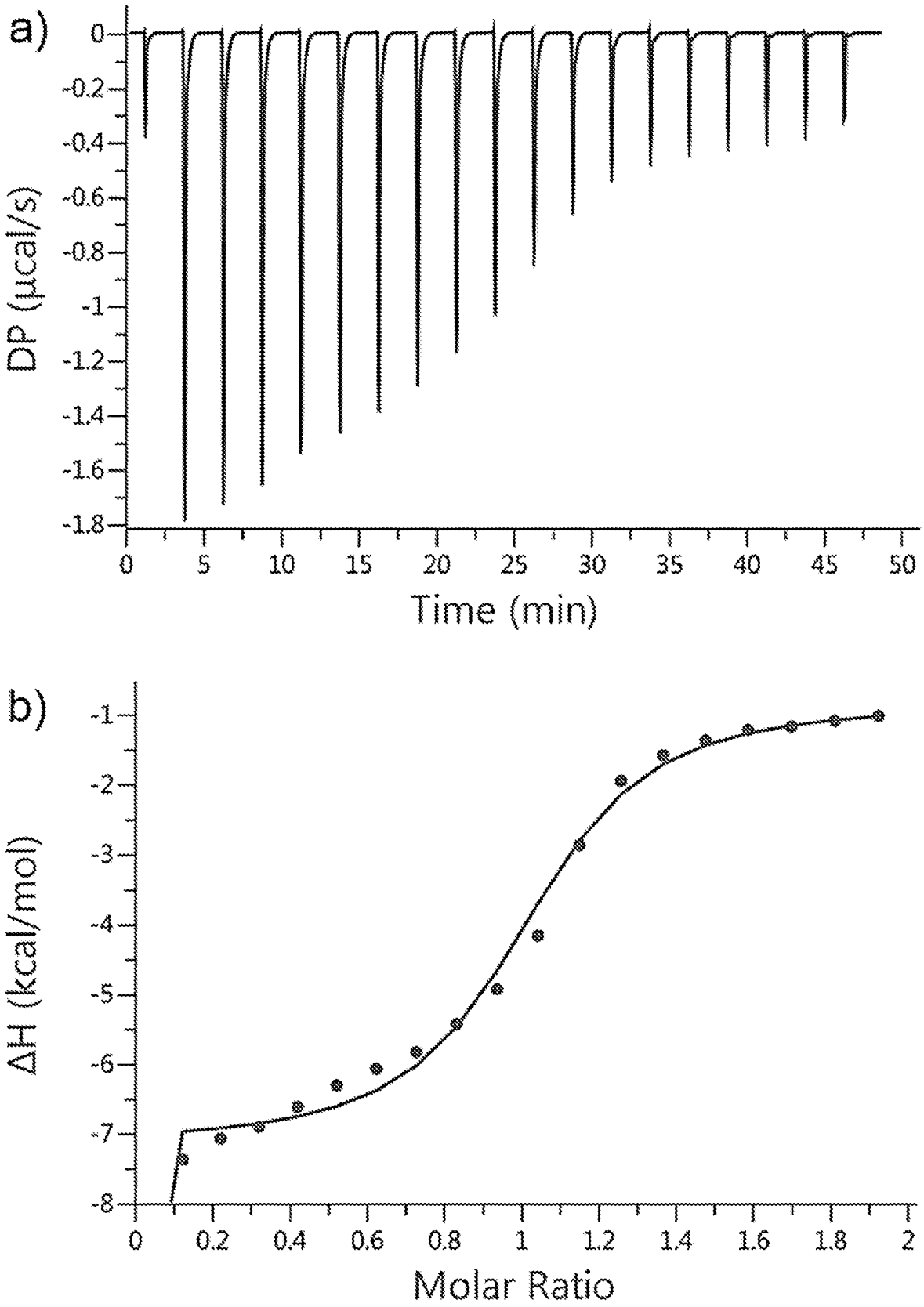

a)
DP (µcal/s)
0
-0.2
-0.4
-0.6
-0.8
-1
-1.2
-1.4
-1.6
-1.8
0
5
10
15
20
25
30
35
40
45
50
Time (min)
b)
ΔH (kcal/mol)
-1
-2
-3
-4
-5
-6
-7
-8
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6
1.8
2
Molar Ratio

Figure 74

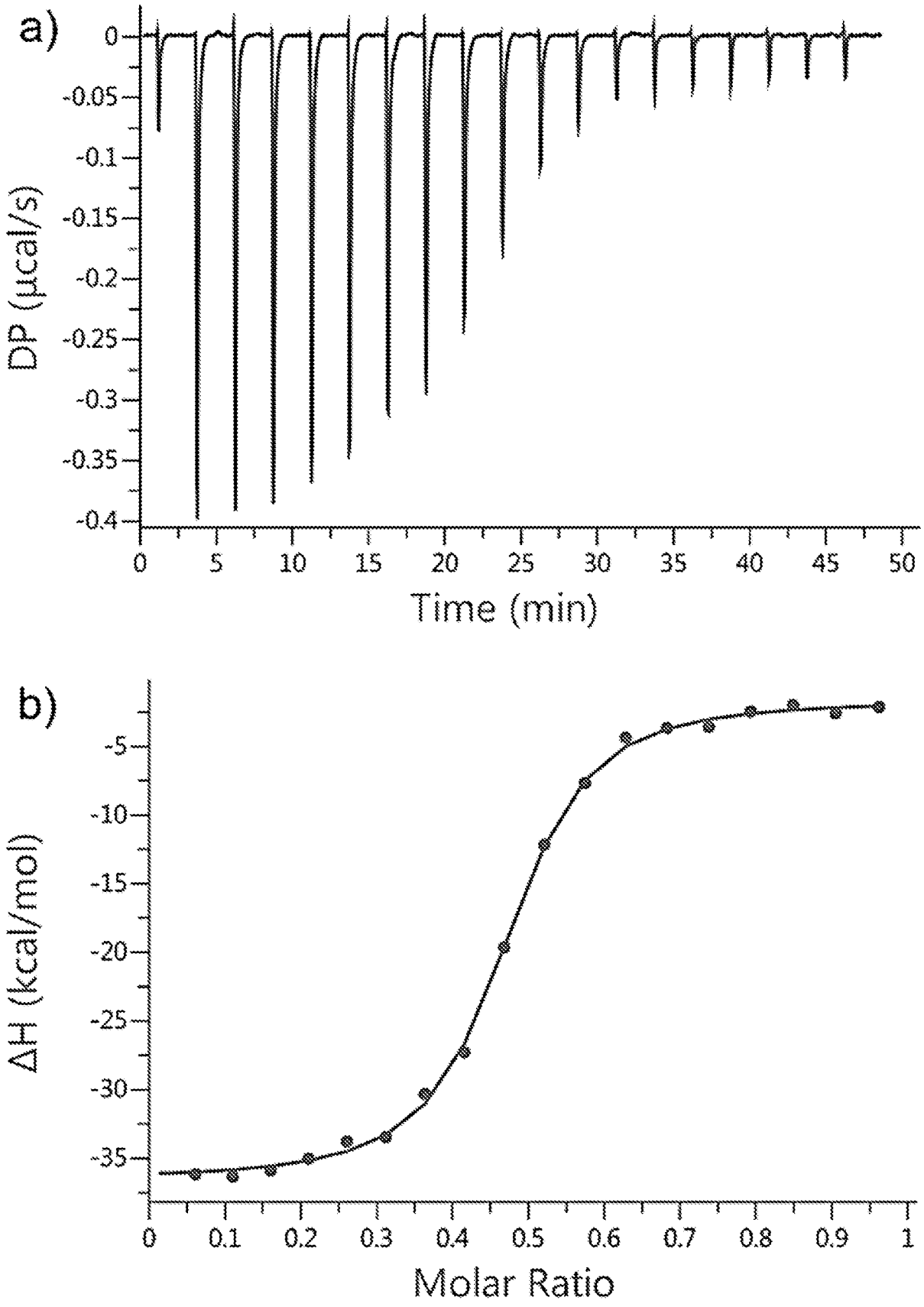

a)
DP (µcal/s)
0
-0.05
-0.1
-0.15
-0.2
-0.25
-0.3
-0.35
-0.4
0 5 10 15 20 25 30 35 40 45 50
Time (min)
b)
ΔH (kcal/mol)
-5
-10
-15
-20
-25
-30
-35
0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1
Molar Ratio

Figure 75

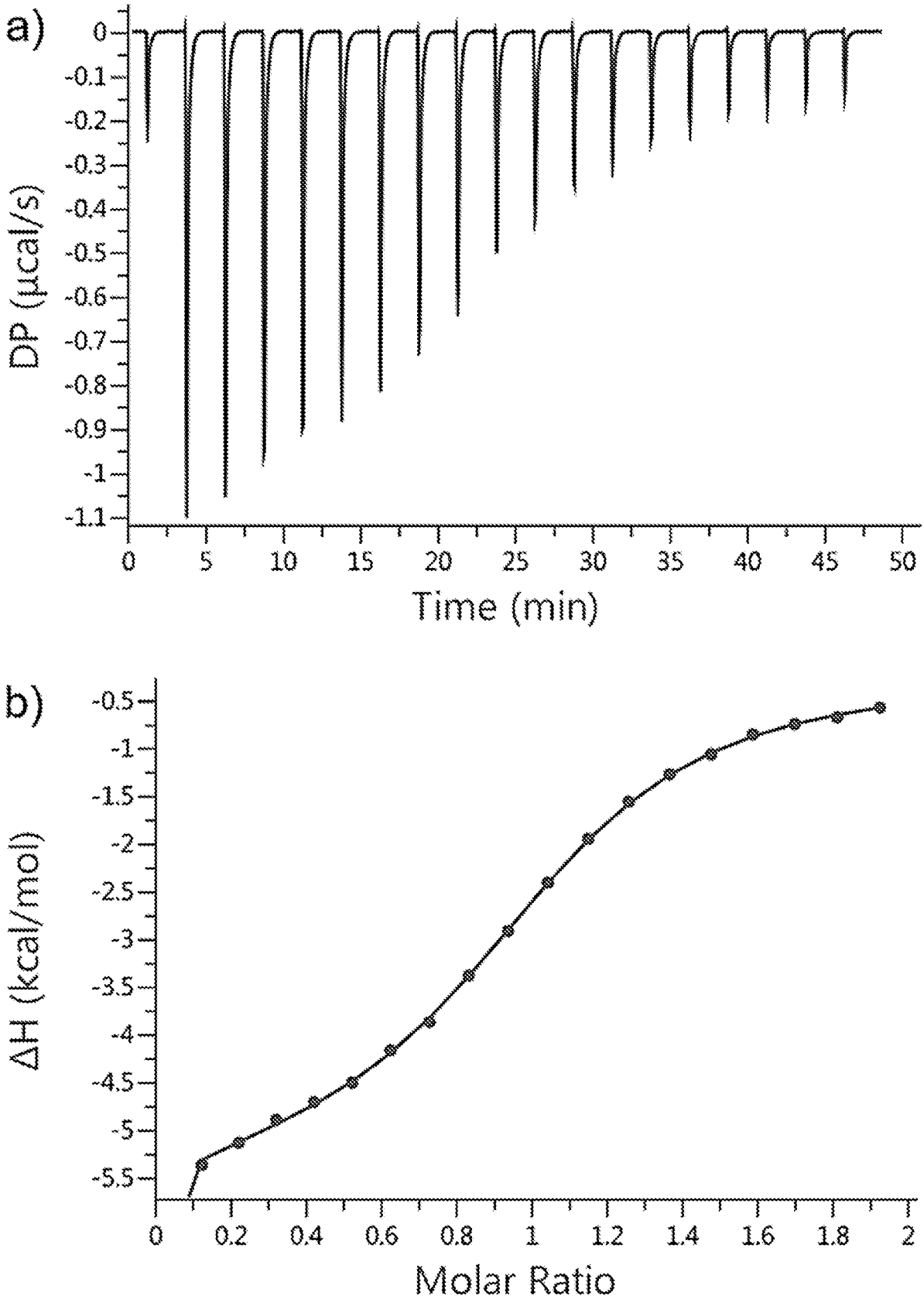

a)
DP (µcal/s)
0
-0.1
-0.2
-0.3
-0.4
-0.5
-0.6
-0.7
-0.8
-0.9
-1
-1.1
0
5
10
15
20
25
30
35
40
45
50
Time (min)
b)
ΔH (kcal/mol)
-0.5
-1
-1.5
-2
-2.5
-3
-3.5
-4
-4.5
-5
-5.5
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6
1.8
2
Molar Ratio

Figure 76

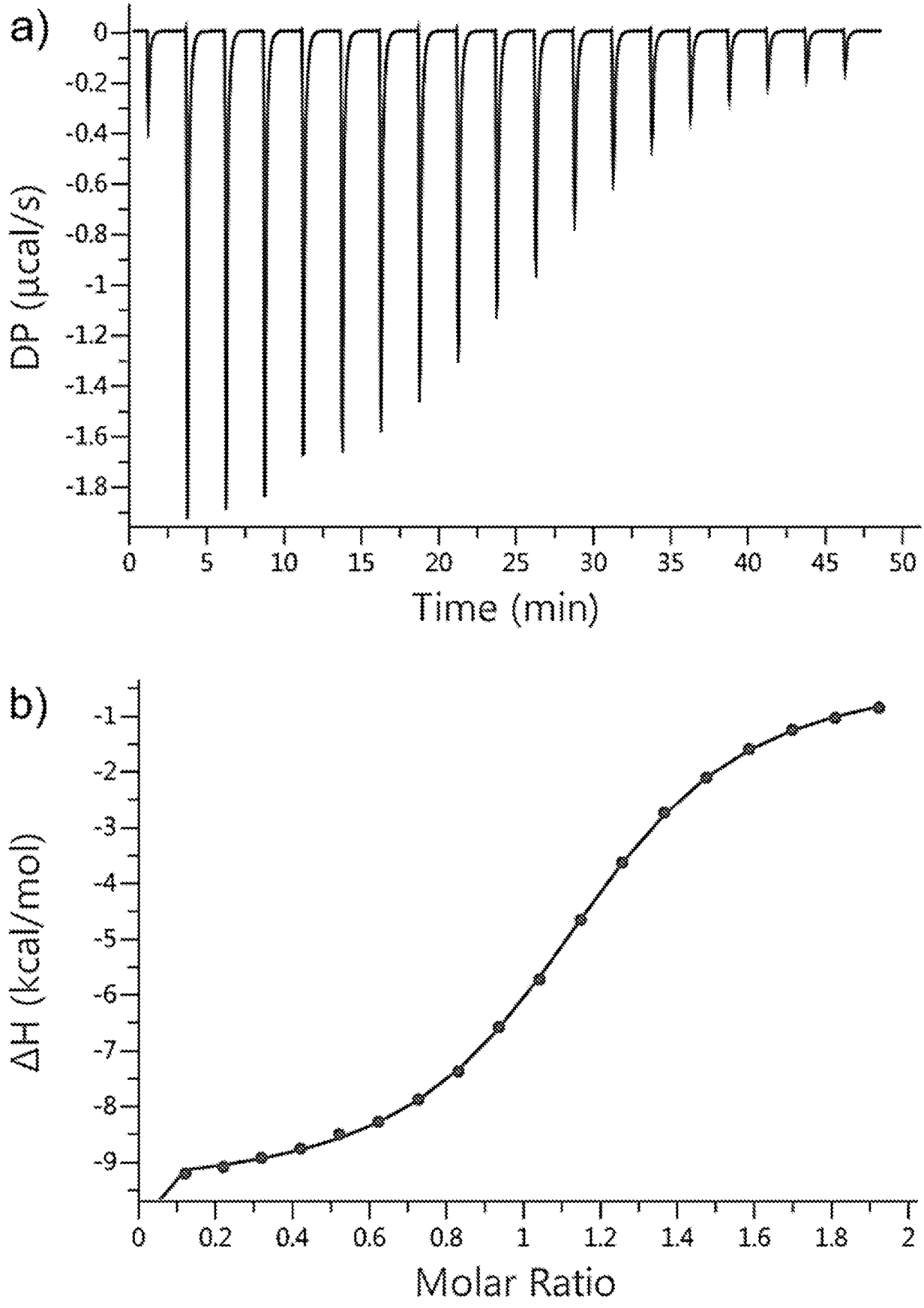

a)
DP (µcal/s)
0
-0.2
-0.4
-0.6
-0.8
-1
-1.2
-1.4
-1.6
-1.8
0
5
10
15
20
25
30
35
40
45
50
Time (min)
b)
ΔH (kcal/mol)
-1
-2
-3
-4
-5
-6
-7
-8
-9
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6
1.8
2
Molar Ratio

Figure 77

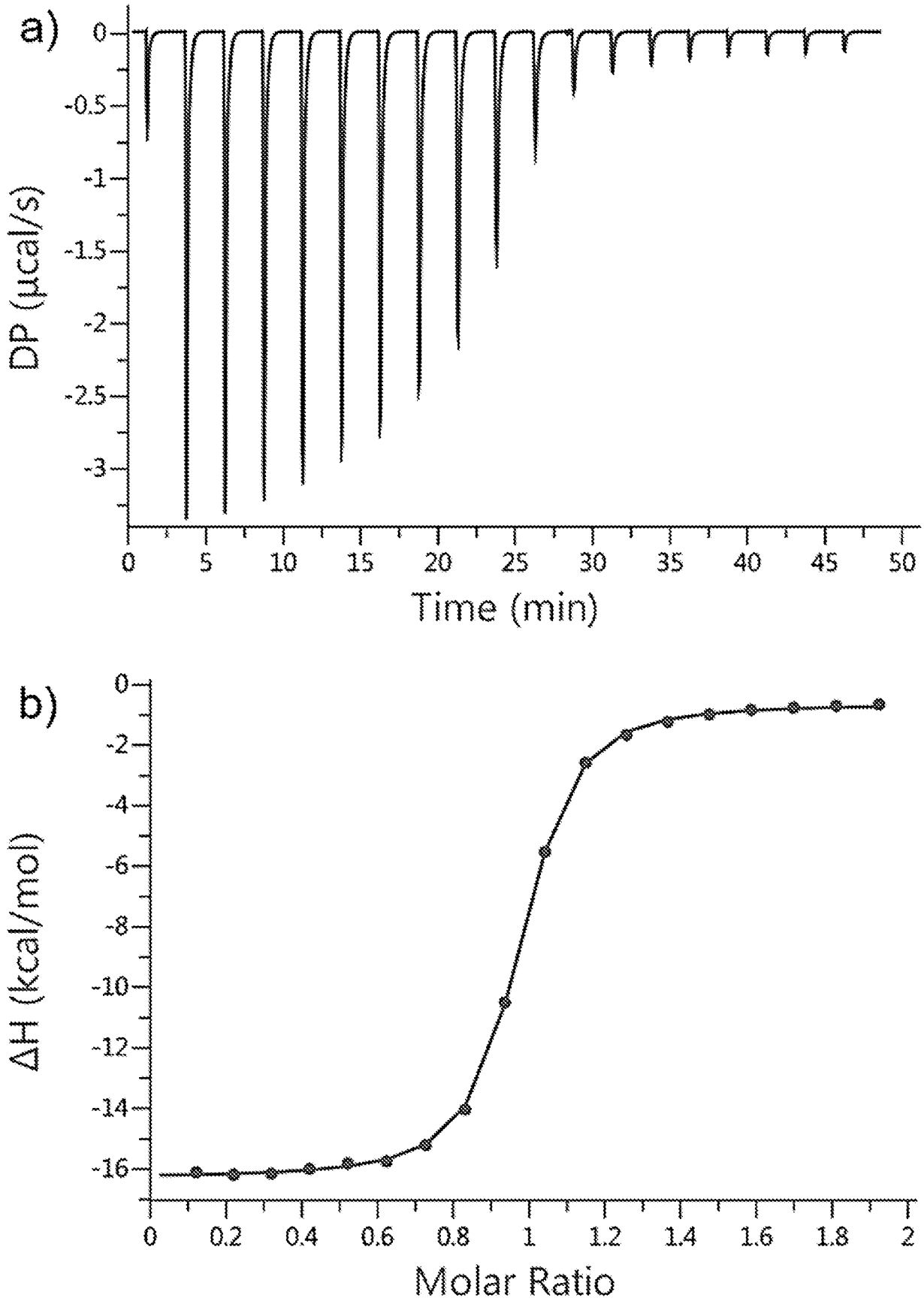

a)
DP (µcal/s)
0
-0.5
-1
-1.5
-2
-2.5
-3
0
5
10
15
20
25
30
35
40
45
50
Time (min)
b)
ΔH (kcal/mol)
0
-2
-4
-6
-8
-10
-12
-14
-16
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6
1.8
2
Molar Ratio

Figure 78

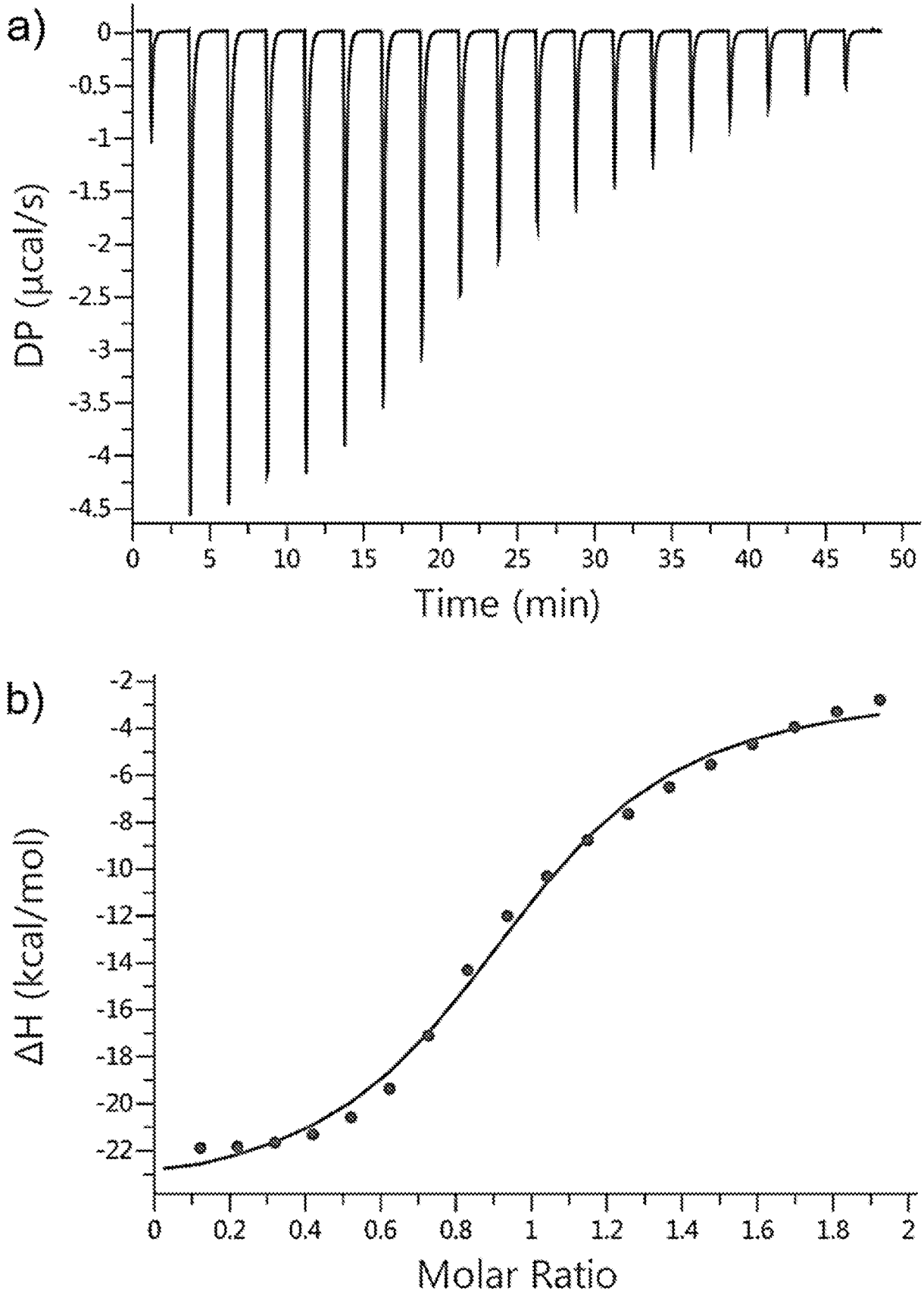

a)
DP (µcal/s)
0
-0.5
-1
-1.5
-2
-2.5
-3
-3.5
-4
-4.5
0
5
10
15
20
25
30
35
40
45
50
Time (min)
b)
ΔH (kcal/mol)
-2
-4
-6
-8
-10
-12
-14
-16
-18
-20
-22
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6
1.8
2
Molar Ratio

Figure 79

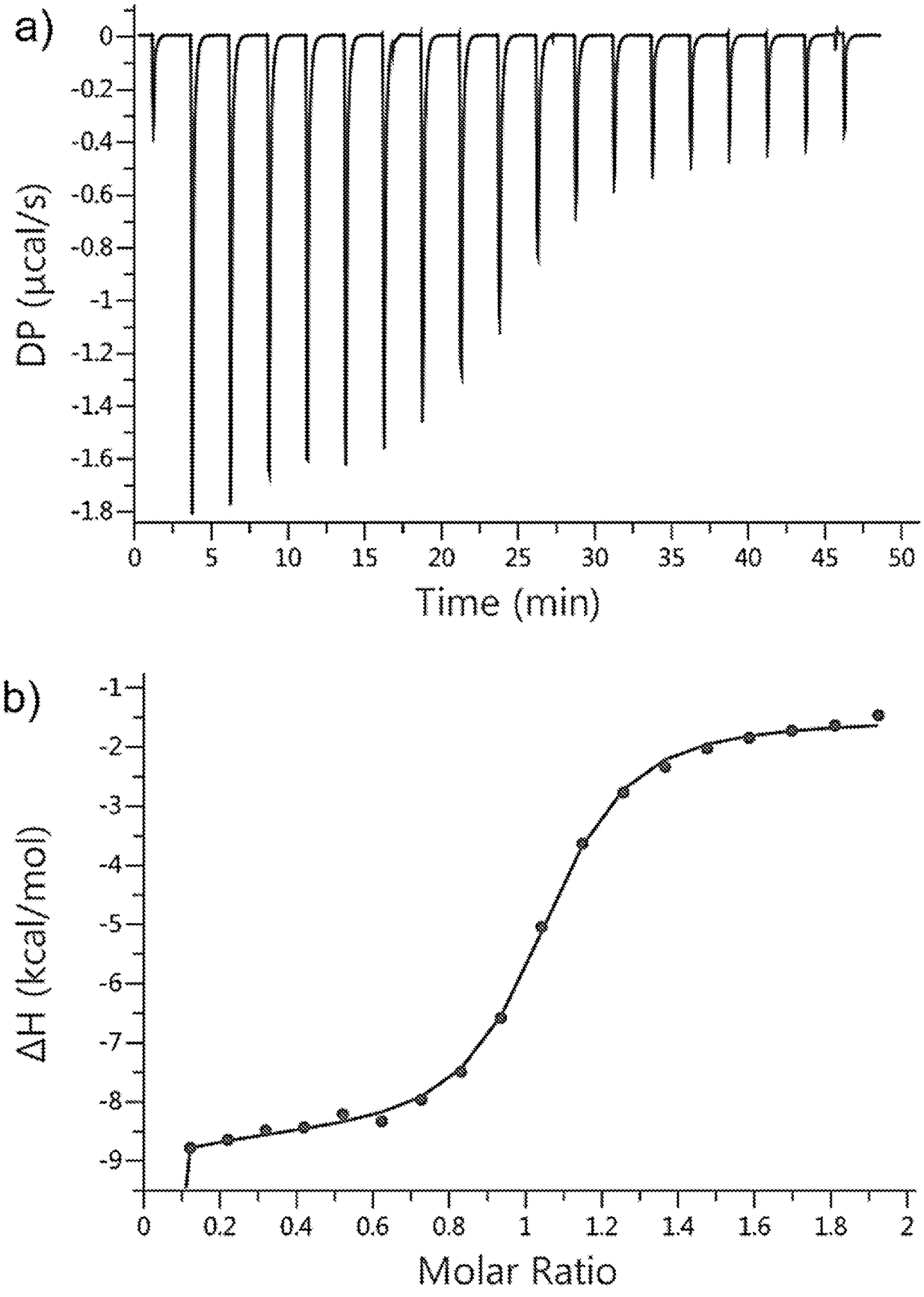

a)
DP (µcal/s)
0
-0.2
-0.4
-0.6
-0.8
-1
-1.2
-1.4
-1.6
-1.8
0
5
10
15
20
25
30
35
40
45
50
Time (min)
b)
ΔH (kcal/mol)
-1
-2
-3
-4
-5
-6
-7
-8
-9
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6
1.8
2
Molar Ratio

Figure 80

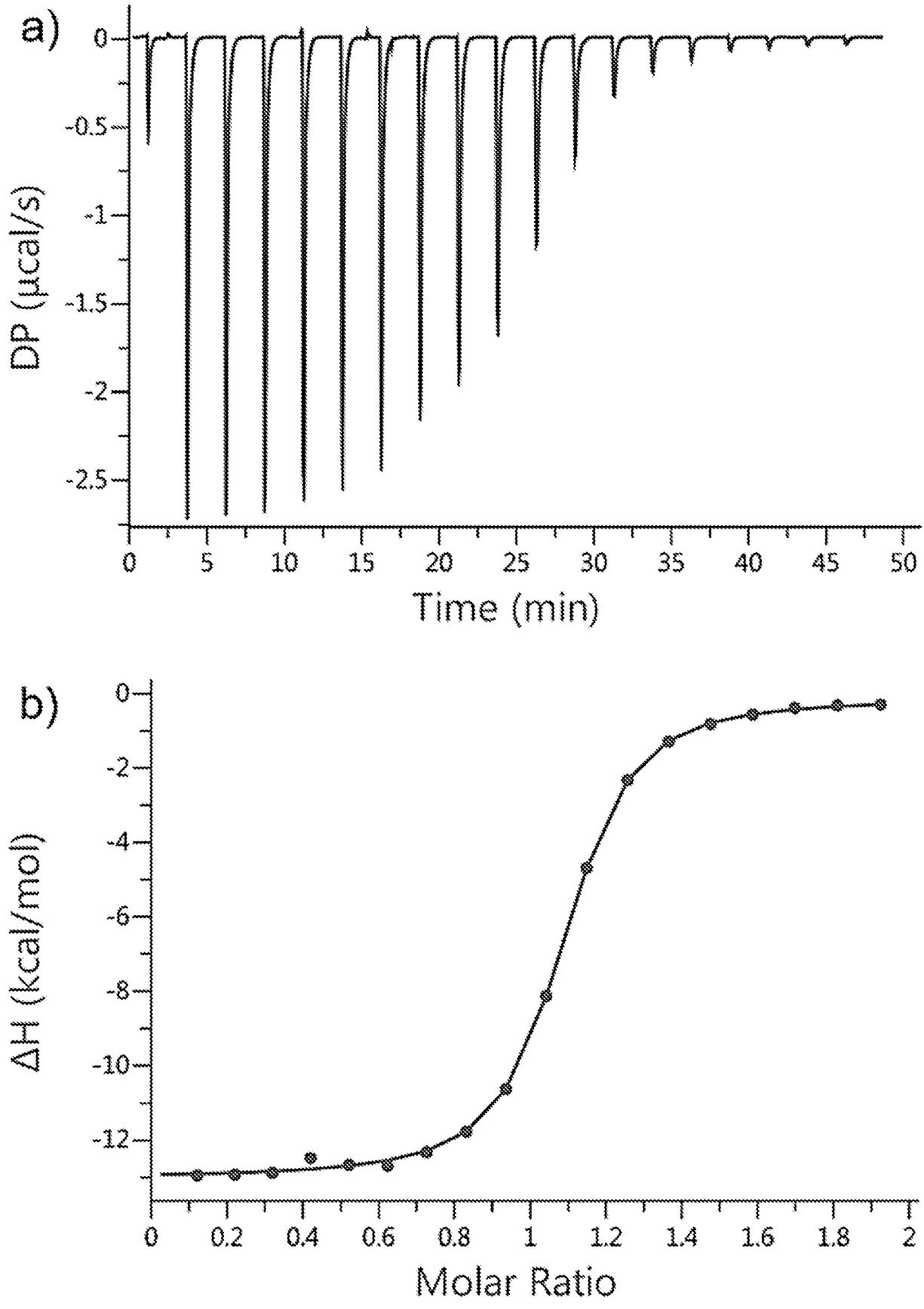

a)
DP (µcal/s)
0
-0.5
-1
-1.5
-2
-2.5
0
5
10
15
20
25
30
35
40
45
50
Time (min)
b)
ΔH (kcal/mol)
0
-2
-4
-6
-8
-10
-12
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6
1.8
2
Molar Ratio

Figure 81

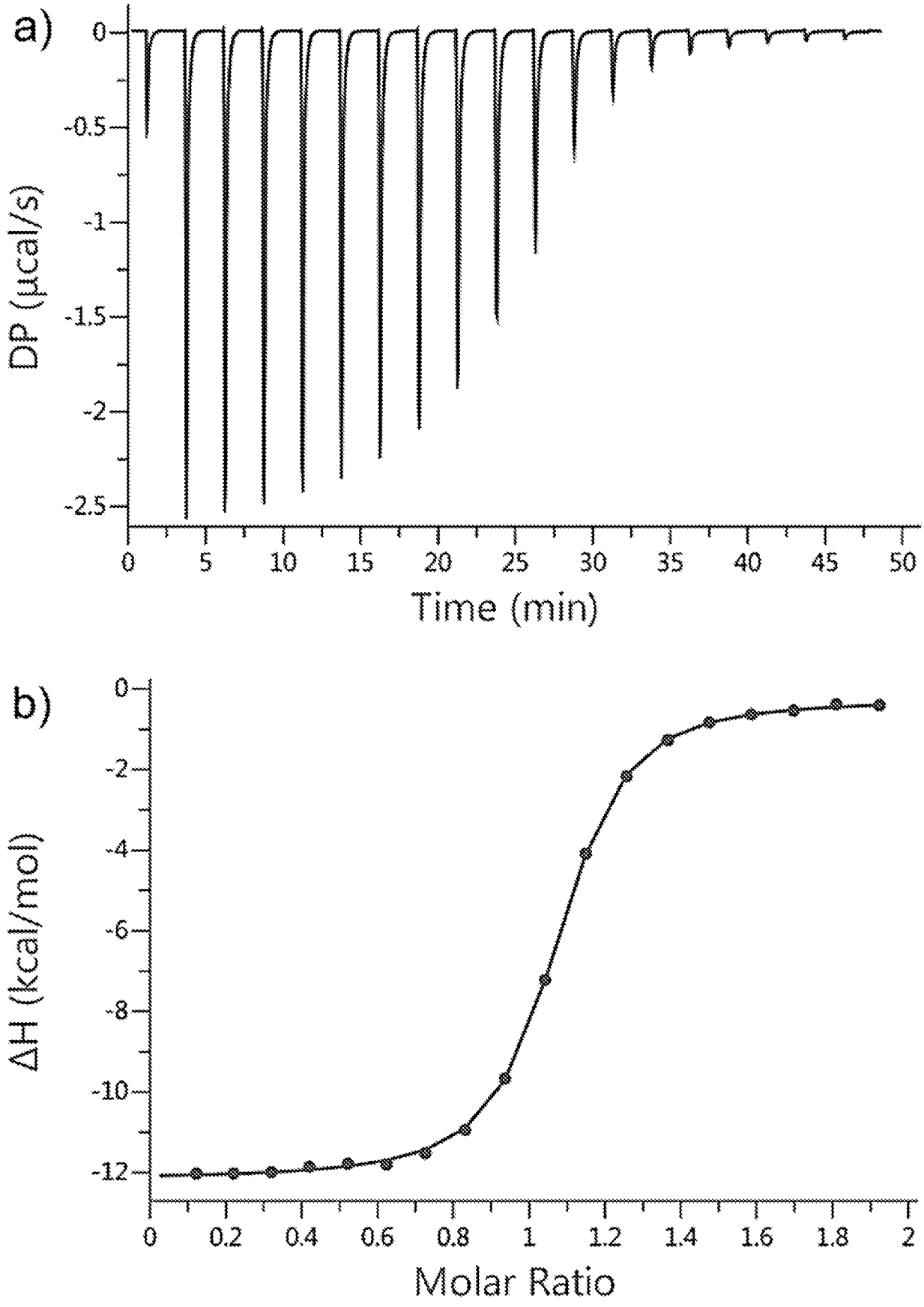

a)
DP (µcal/s)
0
-0.5
-1
-1.5
-2
-2.5
0
5
10
15
20
25
30
35
40
45
50
Time (min)
b)
ΔH (kcal/mol)
0
-2
-4
-6
-8
-10
-12
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6
1.8
2
Molar Ratio

Figure 82

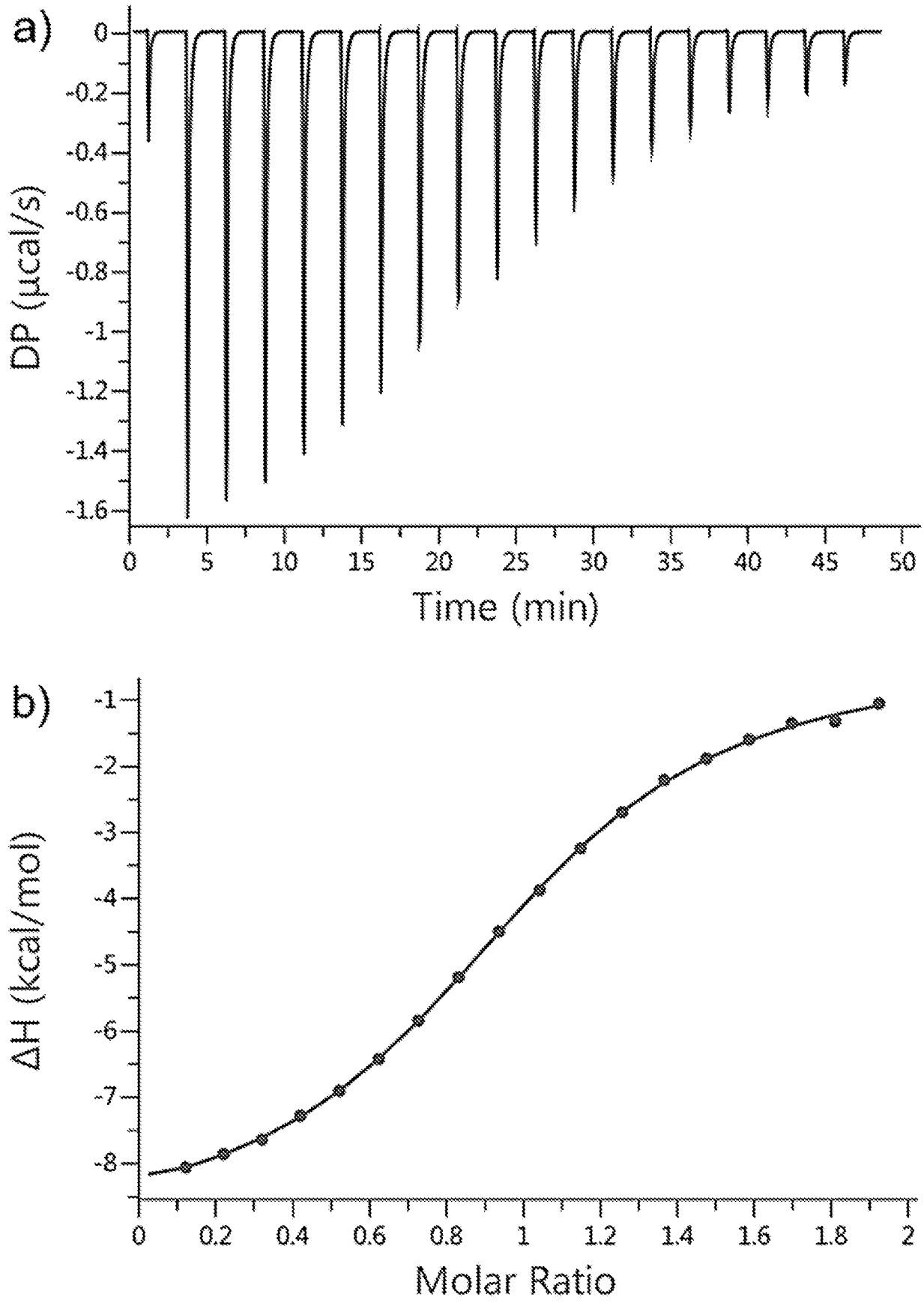

a)
DP (µcal/s)
0
-0.2
-0.4
-0.6
-0.8
-1
-1.2
-1.4
-1.6
0
5
10
15
20
25
30
35
40
45
50
Time (min)
b)
ΔH (kcal/mol)
-1
-2
-3
-4
-5
-6
-7
-8
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6
1.8
2
Molar Ratio

Figure 83

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US21/20333

A. CLASSIFICATION OF SUBJECT MATTER

IPC - C07C 305/22; C07C 305/02; C08G 61/02; A62D 3/30; A23L 5/20; A61P 31/04; A61P 43/00 (2021.01)

CPC - C07C 305/22; C07C 305/02; C08G 61/02; A62D 3/30; A23L 5/20; A61P 31/04; A61P 43/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y --- A	WO 2019/121946 A1 (FREIE UNIVERSITAT BERLIN) 27 June 2019; page 3, lines 1-15; page 5, lines 1-5; page 6, lines 8-37; page 7, lines 1-5; page 9, lines 10-20; page 11, lines 10-20; claim 8	1-25, 27, 29, 31-33 --- 26, 28, 30, 34
Y	(ESPANOL, ES et al.) Calixarenes: Generalities and Their Role in Improving the Solubility, Biocompatibility, Stability, Bioavailability, Detection, and Transport of Biomolecules. Biomolecules. 5 March 2019, Vol. 9, No. 3, Article 90; pages 1-15; page 1, first paragraph; page 4, figure 4; page 5, paragraph 5; DOI: 10.3390/biom9030090	1-25, 27, 29, 31-33
Y --- A	WO 2014/186702 A1 WO 2014/186702 A1 (MARQUETTE UNIVERSITY) 20 November 2014; paragraphs [0013], [0015], [0041]	14, 17-19, 21-24, 33 --- 34
Y	US 2017/0283560 A1 (THE SCHOOL CORPORATION KANSAI UNIVERSITY) 5 October 2017; paragraphs [0062], [0122]-[0123]	16
Y	(YANG, Y et al.) Preparation and Characterization of Cationic Water-Soluble Pillar[5]arene-Modified Zeolite for Adsorption of Methyl Orange. ACS Omega. 18 October 2019, Vol. 4, No. 18; pages 17741-17751; abstract; page 17741, first column, first paragraph; page 17744, second column, fourth paragraph; DOI: 10.1021/acsomega.9b02180	18-20
Y --- A	(CRAGG, PJ.) Pillar[n]arenes at the Chemistry-Biology Interface. Israel Journal of Chemistry. 10 July 2018, Vol. 58, No. 11; pages 1194-1208; page 1, figure 1; page 8, first column, sixth paragraph; DOI: 10.1002/ijch.201800013	25, 27, 29, 31-32 --- 26, 28, 30

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

* Special categories of cited documents:
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"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
24 May 2021 (24.05.2021)	JUN 04 2021
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US21/20333

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	(YU, G et al.) Host–Guest Chemistry in Supramolecular Theranostics. Theranostics. 15 May 2019, Vol. 9, No. 11; pages 3041-3074; page 3059, second column, second paragraph; page 3063, first column, second paragraph; page 3063, second column, second paragraph; DOI: 10.7150/thno.31653	26, 28, 30
A	(TIAN, MM et al.) Pillararene-functionalized Fe3O4 nanoparticles as magnetic solid-phase extraction adsorbent for pesticide residue analysis in beverage samples. RSC Advances. 16 September 2013, Vol. 3; pages 22111-22119; abstract; DOI: 10.1039/C3RA43752C	30
A	(MENG, LB et al.) pH-Responsive Supramolecular Vesicles Assembled by Water-Soluble Pillar[5]arene and BODIPY Photosensitizer for Chemo-Photodynamic Dual Therapy. Chemical Communications. 1 October 2015, Epub 13 August 2015, Vol. 51, No. 76; pages 14381-14384; page 3, first column, second paragraph; DOI: 10.1039/c5cc05785j	34