

**6-Mercapto-Cyclodextrin Derivatives:
Reversal Agents for Drug-Induced Neuromuscular Block.**

The invention relates to 6-mercapto-cyclodextrin derivatives, to their use for
5 the preparation of a medicament for the reversal of drug-induced
neuromuscular block, and to a kit for providing neuromuscular block and its
reversal.

A neuromuscular blocking agent (NMBA, also called a *muscle relaxant*) is
10 routinely used during the administration of anaesthesia to facilitate
endotracheal intubation and to allow surgical access to body cavities, in
particular the abdomen and thorax, without hindrance from voluntary or reflex
muscle movement. NMBAs are also used in the care of critically-ill patients
undergoing intensive therapy, to facilitate compliance with mechanical
15 ventilation when sedation and analgesia alone have proved inadequate, and
to prevent the violent muscle movements that are associated with
electroconvulsive therapy treatment.

Based on their mechanisms of action, NMBAs are divided into two categories:
20 depolarizing and non-depolarizing. Depolarizing neuromuscular blocking
agents bind to nicotinic acetylcholine receptors (nAChRs) at the
neuromuscular junction in a way similar to that of the endogenous
neurotransmitter acetylcholine. They stimulate an initial opening of the ion
channel, producing contractions known as fasciculations. However, since
25 these drugs are broken down only relatively slowly by cholinesterase
enzymes, compared to the very rapid hydrolysis of acetylcholine by
acetylcholinesterases, they bind for a much longer period than acetylcholine,
causing persistent depolarization of the end-plate and hence a neuromuscular
block. Succinylcholine (suxamethonium) is the best known example of a
30 depolarizing NMBA.

Non-depolarizing neuromuscular blocking agents compete with acetylcholine
for binding to muscle nAChRs, but unlike depolarizing NMBAs, they do not

activate the channel. They block the activation of the channel by acetylcholine and hence prevent cell membrane depolarization, and as a result, the muscle will become flaccid. Most of the clinically-used NMBAs belong to the non-depolarizing category. These include tubocurarine, atracurium, (cis)atracurium, mivacurium, pancuronium, vecuronium, rocuronium and rapacuronium (Org 9487).

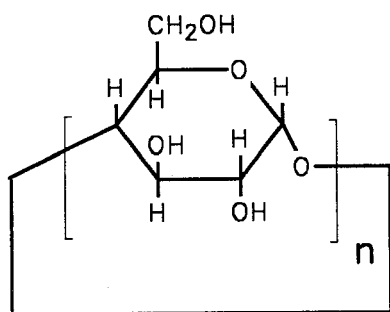
At the end of surgery or a period of intensive care, a reversal agent of NMBAs is often given to the patient to assist the recovery of muscle function. Most commonly used reversal agents are inhibitors of acetylcholinesterase (AChE), such as neostigmine, edrophonium and pyridostigmine. Because the mechanism of action of these drugs is to increase the level of acetylcholine at the neuromuscular junction by inhibiting the breakdown of acetylcholine, they are not suitable for reversal of depolarizing NMBAs such as succinylcholine. The use of AChE inhibitors as reversal agents leads to problems with selectivity, since neurotransmission to all synapses (both somatic and autonomic) involving the neurotransmitter acetylcholine is potentiated by these agents. This non-selectivity may lead to many side-effects due to the non-selective activation of muscarinic and nicotinic acetylcholine receptors, including bradycardia, hypotension, increased salivation, nausea, vomiting, abdominal cramps, diarrhoea and bronchoconstriction. Therefore in practice, these agents can be used only after or together with the administration of atropine (or glycopyrrolate) to antagonize the muscarinic effects of acetylcholine at the muscarinic receptors in the autonomic parasympathetic neuro-effector junctions (e.g. the heart). The use of a muscarinic acetylcholine receptor (mAChR) antagonist such as atropine causes a number of side-effects, e.g., tachycardia, dry mouth, blurred vision, difficulties in emptying the bladder and furthermore may affect cardiac conduction.

A further problem with anticholinesterase agents is that residual neuromuscular activity must be present (>10 % twitch activity) to allow the rapid recovery of neuromuscular function. Occasionally, either due to hypersensitivity of the patient or accidental overdose, administration of NMBAs can

cause complete and prolonged block of neuromuscular function ("profound block"). At present, there is no reliable treatment to reverse such a 'profound block'. Attempts to overcome a 'profound block' with high doses of AChE inhibitors has the risk of inducing a "cholinergic crisis", resulting in a broad
5 range of symptoms related to enhanced stimulation of nicotinic and muscarinic receptors.

In European Patent Application 99,306,411 (AKZO NOBEL N.V.) the use of chemical chelators (or sequestrants) as reversal agents has been disclosed.
10 Chemical chelators capable of forming a guest-host complex for the manufacture of a medicament for the reversal of drug-induced neuromuscular block were described. The use of chemical chelators as reversal agents for NMBAs has the advantage that they are effective in reversing the action of both depolarizing and non-depolarizing NMBAs. Their use does not increase
15 the level of acetylcholine and therefore they produce fewer side effects and none associated with the stimulation of muscarinic and nicotinic receptors seen with the AChE reversal agents. In addition, there is no need for the combined use of an AChE inhibitor and a mAChR antagonist (e.g., atropine), while the chemical chelators may further be safely employed for the reversal
20 of 'profound block'. Examples of such chemical chelators, as disclosed in EP 99,306,411, were selected from various classes of, mostly cyclic, organic compounds which are known for their ability to form inclusion complexes with various organic compounds in aqueous solution, e.g. cyclic oligosaccharides, cyclophanes, cyclic peptides, calixarenes, crown ethers and aza crown
25 ethers.

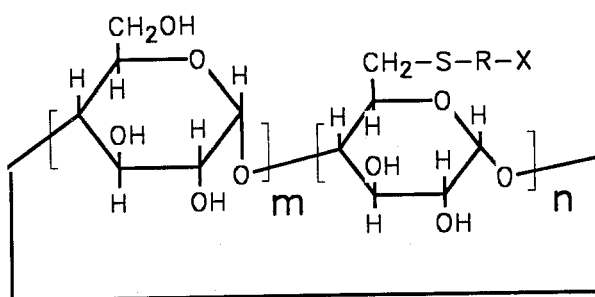
The cyclodextrins,



n = 6 - 9

a class of cyclic molecules containing six or more α -D-glucopyranose units linked at the 1,4 positions by α -linkages as in amylose, and derivatives thereof, were identified in EP 99306411 as particularly useful in the reversal of many of the commonly used neuromuscular blocking agents, or muscle relaxants, such as rocuronium, pancuronium, vecuronium, rapacuronium, mivacurium, atracurium, (cis)atracurium, succinylcholine and tubocurarine.

It has now been found that 6-mercapto-cyclodextrin derivatives having the general formula I



Formula I

wherein m is 0-7 and n is 1-8 and $m+n = 7$ or 8;

R is (C_{1-6}) alkylene, optionally substituted with 1-3 OH groups, or $(CH_2)_o$ -phenylene- $(CH_2)_p$ -;

o and p are independently 0-4;

X is $COOH$, $CONHR_1$, $NHCOR_2$, SO_2OH , $PO(OH)_2$, $O(CH_2-CH_2-O)_q-H$, OH or tetrazol-5-yl;

R_1 is H or (C_{1-3}) alkyl;

R_2 is carboxyphenyl;

q is 1-3;

or pharmaceutically acceptable salts thereof;

are highly active *in vivo* in the reversal of the action of neuromuscular blocking agents.

No protection *per se* is sought for the following 6-mercapto-cyclodextrin derivatives:

6-*per*-deoxy-6-*per*-(2-hydroxyethylthio)- β -cyclodextrin and

6-*per*-deoxy-6-*per*-(2-hydroxyethylthio)- γ -cyclodextrin, which are described by Ling, C. and Darcy, R. (J. Chem. Soc. Chem Comm. 1993, (2), 203-205);

6-mono-deoxy-6-mono-(2-hydroxyethylthio)- β -cyclodextrin, which is disclosed by Fujita, K. et al. (Tetr. Letters 21, 1541-1544, 1980);

5 6-*per*-deoxy-6-*per*-(carboxymethylthio)- β -cyclodextrin, which is described by Guillo, F. et al. (Bull. Chem. Soc. Chim. Fr. 132 (8), 857-866, 1995);

6-mono-deoxy-6-mono-(carboxymethylthio)- β -cyclodextrin, which is described by Akiie, T. et al. (Chem. Lett. 1994 (6), 1089-1092);

6A,6B-dideoxy-6A,6B-bis[(*o*-carboxyphenyl)thio]- β -cyclodextrin and

10 6A,6B-dideoxy-6A,6B-bis(carboxymethylthiol)- β -cyclodextrin, which are described by Tubashi, I. et al. (J. Am. Chem. Soc. 108, 4514-4518, 1986; and

6-*per*-deoxy-6-*per*-(2,3-dihydroxypropylthio)- β -cyclodextrin, which is described by Baer, H. H. and Santoyo-González, F. (Carb. Res. 280, 315-321, 1996). These prior art 6-mercapto-cyclodextrin derivatives have been

15 described in relation with different utilities in each instance.

However, the above mentioned prior art 6-mercapto-cyclodextrin derivatives do belong to the main aspect of the present invention which relates to the use of a 6-mercapto-cyclodextrin derivative according to the general formula I for
20 the manufacture of a medicament for the reversal of drug-induced neuromuscular block.

In one embodiment the invention relates to 6-mercapto-cyclodextrin derivatives having the general formula I,

25 wherein m is 0-7 and n is 1-8 and m+n = 7 or 8;

X is COOH, OH or CONHCH₃;

R is (C₁₋₆)alkylene or (CH₂)_o-phenylene-(CH₂)_p;

o and p are independently 0-4; or a pharmaceutically acceptable salt thereof, with the exclusion of

30 6-*per*-deoxy-6-*per*-(2-hydroxyethylthio)- β -cyclodextrin;

6-mono-deoxy-6-mono-(2-hydroxyethylthio)- β -cyclodextrin;

6-*per*-deoxy-6-*per*-(2-hydroxyethylthio)- γ -cyclodextrin;

6-*per*-deoxy-6-*per*-(carboxymethylthio)- β -cyclodextrin;
6-mono-deoxy-6-mono-(carboxymethylthio)- β -cyclodextrin;
6A,6B-dideoxy-6A,6B-bis[(*o*-carboxyphenyl)thio]- β -cyclodextrin; and
6A,6B-dideoxy-6A,6B-bis(carboxymethylthiol)- β -cyclodextrin.

5

The term (C₁₋₆)alkylene as used in the definition of formula I means a branched or straight chain bivalent carbon radical containing 1-6 carbon atoms, such as methylene, ethylene (1,2-ethandiyl), propylene (1-methyl-1,2-ethandiyl), 2-methyl-1,2-ethandiyl, 2,2-dimethyl-1,2-ethandiyl, 1,3-prop-

10

anediyl, 1,4-butanediyl, 1,5-pentanediyl and 1,6-hexanediyl.
The term phenylene means a bivalent moiety the free valencies of which can be positioned either ortho, meta or para to one another.

The term (C₁₋₃)alkyl means a branched or straight chain alkyl group containing 1-3 carbon atoms, i.e. methyl, ethyl, propyl and isopropyl.

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The term carboxyphenyl means a phenyl group which is substituted at either the ortho-, the meta- or the para-position with a carboxy-group. The ortho-carboxyphenyl group is preferred.

Compounds according to formula I wherein n+m is 7 are derivatives of β -cyclodextrin, those wherein n+m is 8 are derived from γ -cyclodextrin.

20

Preferred are the 6-mercapto-cyclodextrin derivatives of formula I wherein X is COOH, or a pharmaceutically acceptable salt thereof.

More preferred are the 6-mercapto- γ -cyclodextrin derivatives of formula I wherein n is 8, R is (C₁₋₆)alkylene and X is COOH.

25

Particularly preferred 6-mercapto-cyclodextrin derivatives of the invention are

6-*per*-deoxy-6-*per*-(2-carboxyethyl)thio- γ -cyclodextrin;

6-*per*-deoxy-6-*per*-(3-carboxypropyl)thio- γ -cyclodextrin;

6-*per*-deoxy-6-*per*-(4-carboxyphenyl)thio- γ -cyclodextrin;

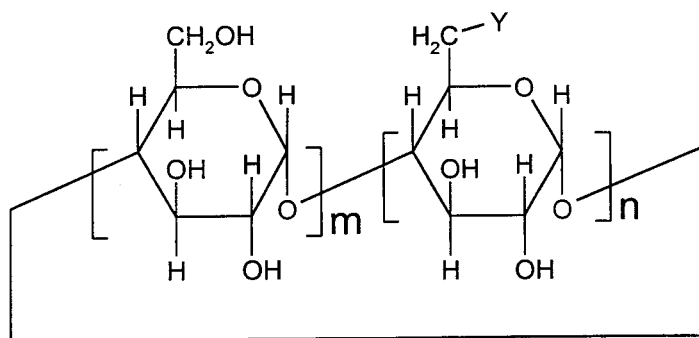
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6-*per*-deoxy-6-*per*-(4-carboxyphenylmethyl)thio- γ -cyclodextrin;

6-*per*-deoxy-6-*per*-(2-carboxypropyl)thio- γ -cyclodextrin; and

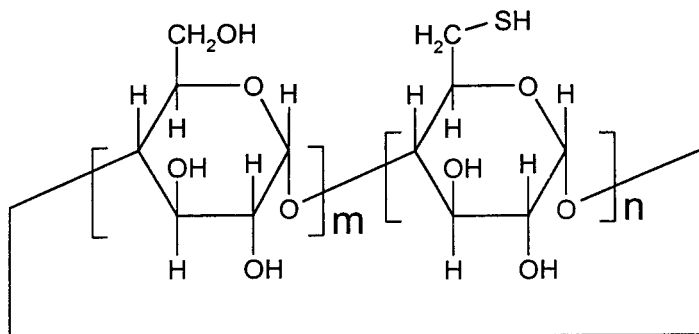
6-*per*-deoxy-6-*per*-(2-sulfoethyl)thio- γ -cyclodextrin.

The 6-mercapto-cyclodextrin derivatives of formula I can be prepared by reacting a C6-activated cyclodextrin derivative of formula II with an alkylthiol, arylalkylthiol or arylthiol derivative corresponding to H-S-R-X, wherein R and X have the meaning as previously defined, in the presence of an inorganic or organic base.



Formula II wherein m is 0-7, n is 1-8, $m+n = 7$ or 8 and Y is a leaving group which can be a halide (Cl, Br or I), sulfuric ester or a sulfonic ester function, such as a tosylate, a naphthalenesulfonate or a triflate.

Conversely the 6-mercapto-cyclodextrin derivatives of formula I can also be prepared by reacting a 6-thiol γ - or β -cyclodextrin derivative of formula III with an alkylating agent, e.g., alkyl halide, arylalkyl halide, alkyl sulfonate, arylalkyl sulfonate, corresponding to Y-X-R, wherein Y, X and R have the meanings as previously defined, or with a double bond containing reagent, e.g., vinyl alkane, acrylate, etc., or an epoxide in the presence of an inorganic or organic base.



Formula III wherein m is 0-7, n is 1-8, $m+n = 7$ or 8 .

Alternative synthesis routes for the preparation of the 6-mercapto-cyclodextrin derivatives of the invention are known to the skilled person. The chemistry of the derivatisation of cyclodextrins is well documented (see for example: *Comprehensive Supramolecular Chemistry*, Volumes 1-11, Atwood J.L., Davies J.E.D., MacNicol D.D., Vogtle F., eds; Elsevier Science Ltd., Oxford, UK, 1996).

Pharmaceutically acceptable salts of 6-mercapto-cyclodextrin derivatives of formula I wherein X represents the carboxylic acid group COOH, the sulphonic acid group SO₂OH, the phosphonic acid group PO(OH)₂ or the tetrazol-5-yl group, may be obtained by treating the acid with an organic base or a mineral base, like sodium-, potassium- or lithium hydroxide.

The 6-mercapto-cyclodextrin derivatives, or pharmaceutically acceptable salts or solvates thereof, for use in the invention are administered parenterally. The injection route can be intravenous, subcutaneous, intradermal, intramuscular, or intra-arterial. The intravenous route is the preferred one. The exact dose to be used will necessarily be dependent upon the needs of the individual subject to whom the medicament is being administered, the degree of muscular activity to be restored and the judgement of the anaesthetist/critical-care specialist. Extracorporeal application of the chemical chelators of the invention, for instance by mixing of the chemical chelator with the blood during dialysis or during plasmapheresis, is also contemplated.

In a further aspect the invention relates to a kit for providing neuromuscular block and its reversal comprising (a) a neuromuscular blocking agent, and (b) a 6-mercapto-cyclodextrin derivative according to general formula I capable of forming a guest-host complex with the neuromuscular blocking agent. With a kit according to the invention is meant a formulation, which contains separate pharmaceutical preparations, i.e. the neuromuscular blocking agent and a 6-mercapto-cyclodextrin derivative of formula I, i.e. the reversal agent. The components of such a kit of parts are to be used sequentially, i.e. the

neuromuscular blocking agent is administered to a subject in need thereof, which is followed, at a point in time when restoration of muscle function is required, by the administration of the reversal agent, i.e. a 6-mercapto-cyclodextrin derivative of the present invention.

5

A preferred kit, according to the invention, contains a 6-mercapto-cyclodextrin derivative of formula I and a neuromuscular blocking agent which is selected from the group consisting of rocuronium, vecuronium, pancuronium, rapacuronium, mivacurium, atracurium, (cis)atracurium, tubocurarine and
10 suxamethonium. A particularly preferred kit of the invention comprises rocuronium as the neuromuscular blocking agent.

Mixed with pharmaceutically suitable auxiliaries and pharmaceutically suitable liquids, e.g. as described in the standard reference, Gennaro et al.,
15 Remington's Pharmaceutical Sciences, (18th ed., Mack Publishing Company, 1990, Part 8: Pharmaceutical Preparations and Their Manufacture; see especially Chapter 84 on "Parenteral preparations, pp. 1545-1569; and Chapter 85 on "Intravenous admixtures", pp. 1570-1580) the 6-mercapto-cyclodextrin derivatives can be applied in the form of a solution, e.g. for use
20 as an injection preparation.

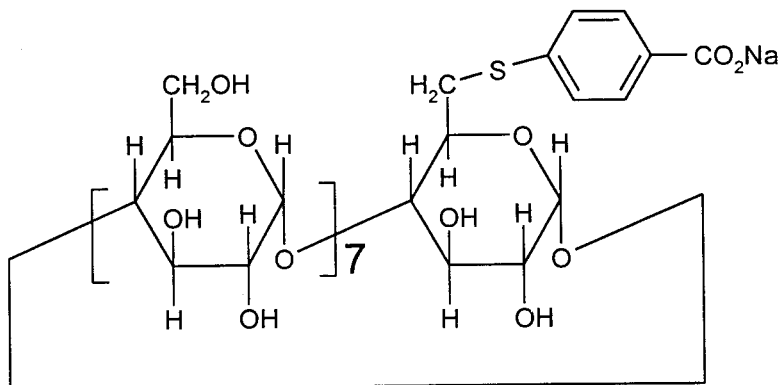
Alternatively, the pharmaceutical composition may be presented in unit-dose or multi-dose containers, for example sealed vials and ampoules, and may be stored in a freeze dried (lyophilised) condition requiring only the addition of
25 the sterile liquid carrier, for example, water prior to use.

The invention further includes a pharmaceutical formulation, as hereinbefore described, in combination with packaging material suitable for said composition, said packaging material including instructions for the use of the
30 composition for the use as hereinbefore described.

The invention is illustrated in the following examples.

Example 1.

6-Mono-deoxy-6-mono-(4-carboxyphenyl)thio- γ -cyclodextrin, sodium salt



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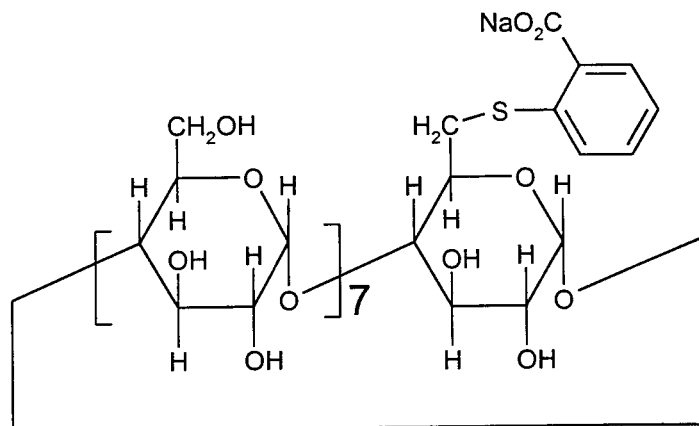
To a round bottom flask containing pyridine (120 ml) was added dry γ -cyclodextrin (2.0 g, 1.54 mmol) under nitrogen at room temperature. After dissolution, 2-naphthalenesulfonyl chloride (1.05 g, 4.64 mmol) in pyridine (20 ml) was added and the mixture stirred for 24 h. Quenched with water (50 ml) and evaporated to dryness to leave crude 6-mono-O-(2'-naphthalenesulfonyl)- γ -cyclodextrin.

10

Sodium hydride (0.38g, 15.83mmol) was suspended in dry dimethylformamide (20ml). 4-Mercaptobenzoic acid (0.7g, 4.55mmol) was then added to the suspension and the resulting mixture was stirred for 20 minutes. γ -Cyclodextrin nosylate (3.2g, 2.12mmol) was added to the mixture and the reaction was heated to 100°C for 90 minutes. After cooling, acetone was added to precipitate a solid, which was reprecipitated from water/acetone. This was then dissolved in water (20ml), pH adjusted to 7.0 by adding 2N hydrochloric acid, then chromatographed on a Sephadex DEAE A-25 column. Appropriate fractions were combined, dialysed, then precipitated, twice from water/acetone to give 400mg of the titled compound. ¹H NMR in DMSO δ 7.4 to 7.8 (ArH), 5.0 to 5.2 (8 H), 4.13 (1 H), 3.7 to 4.0 (29 H), 3.7 to 3.4 (17 H), 3.25 (1 H) ppm. ¹³C NMR in DMSO δ 129.9 and 127.5 (ArC), 103.3 and 102.9 (C1 and C1'), 85.0 (C 4'), 81.6 (C 4), 73.8 (C 3), 73.5 (C 2), 72.2 (C 5), 70.8 (C 5'), 60.6 (C 6), 34.3 (C 6') ppm. Electrospray MS [M+H]⁺ = 1455.7 and [M+Na]⁺ = 1477.7.

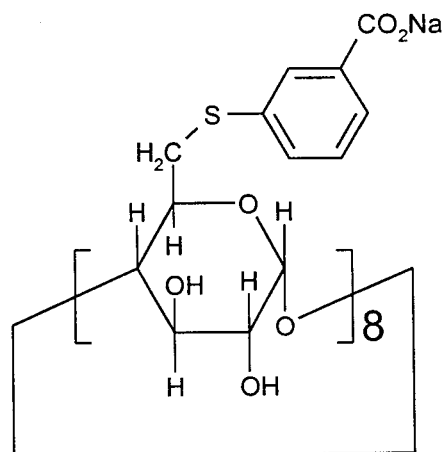
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Example 2.6-Mono-deoxy-6-mono-(2-carboxyphenyl)thio- γ -cyclodextrin, sodium salt

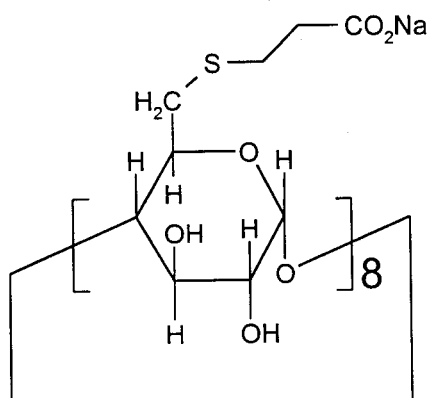
Sodium hydride (60 % dispersed in oil, 0.18 g, 4.5 mmol) was added to
 5 thiosalicylic acid (0.34 g, 2.2 mmol) in DMF (25 ml) in one portion and stirred at room
 temperature for 30 min. To this was then added the crude solution of 6-mono-O-(2'-
 naphthalenesulfonyl)- γ -cyclodextrin (2.5 g, 1.45 mmol) in DMF (15 ml) and heated to
 70 °C for 24 h. The mixture was cooled and quenched with water (20 ml) before
 evaporating to dryness. Water was then added to the residue and the resulting
 10 solution was poured into acetone (250 ml) to effect precipitation. The resulting solid
 was collected by filtration and dissolved in water (10 ml) before passing through a
 Sephadex DEAE A-25 column eluting with water then 0.2 N NaOH. Fractions
 containing the product were combined and evaporated to a low volume and dialysed
 (MWCO 1000) by changing the external water four times. Internal solution was
 15 evaporated to low volume and poured into acetone (100 ml). Solid was collected by
 filtration and dried under vacuum at 70 °C to leave the title compound (235 mg) as a
 white solid. ^1H NMR (D_2O) δ 7.50-7.10 (4 H, m, Ar-H), 5.14 (8 H, m, CyD 1-H), 4.16
 (1 H, m, CyD 5-H), 3.98-3.85 (26 H, m, CyD 3,5,2,4,-H), 3.70-3.61 (20 H, m, CyD
 2,3,4,6-H), 3.15 (1 H, m, CyD 6-H) ppm; Electrospray MS m/z 1477.6 for $[\text{M}+\text{Na}]^+$,
 20 calcd for $\text{C}_{55}\text{H}_{83}\text{NaO}_{41}\text{S}$ M 1455.304.

Example 3.6-per-deoxy-6-per-(3-carboxyphenyl)thio- γ -cyclodextrin, sodium salt

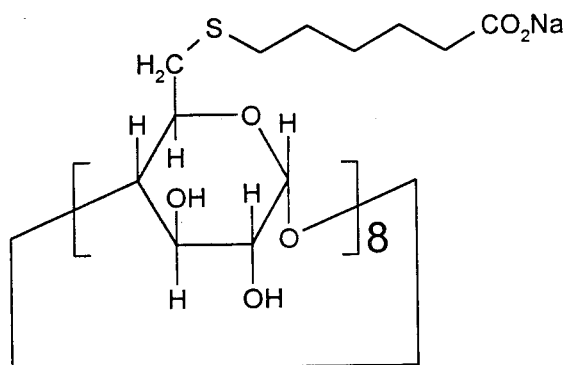


Triphenylphosphine (30.1 g, 15 eq) was dissolved with stirring in dry DMF (160 ml). To this was added iodine (30.5 g, 15.6 eq) over 10 min. with heat evolved. Dry γ -cyclodextrin (10 g, 7.7 mmol) was then added and the mixture was heated to 70 °C for 24 h. The mixture was allowed to cool, to which sodium methoxide (3.1 g sodium in 50 ml methanol) was added and the mixture was stirred for 30 min, before pouring onto methanol (800 ml) and evaporating to dryness. To the residue was added water (500 ml) and the solid was collected by filtration and washed with water (3x100 ml), then acetone (3x100 ml), and dried under vacuum at 70 °C to give 6-*per*-deoxy-6-*per*-iodo- γ -cyclodextrin as a yellow solid (16.2 g) which was used without further purification.

To a solution of 3-mercaptobenzoic acid (1.0 g, 10 eq) in DMF (30 ml) was added 60% sodium hydride dispersed in oil (476 mg, 22 eq) portionwise over 30 min. The mixture was cooled and 6-*per*-deoxy-6-*per*-iodo- γ -cyclodextrin (1.4 g) in DMF (30 ml) was added. The mixture was then stirred at 70 °C for 24 h. The mixture was allowed to cool to room temperature and quenched with the addition of water (20 ml) before evaporating to a low volume. The solution was poured into acetone (500 ml) and the precipitate was collected by filtration, dissolved in water (20 ml) and dialysed (MWCO 1000) by changing the external water four times. Internal solution was evaporated to low volume and poured into acetone (250 ml). The solid precipitate was collected by filtration and dried under vacuum at 70 °C to afford the title compound (1.45 g) as a white solid: ^1H NMR (D_2O) δ 7.77 (8 H, br s, Ar-H), 7.55 (8 H, d, $J = 6.0$ Hz, Ar-H), 7.71 (16 H, m, Ar-H), 5.16 (8 H, s, CyD 1-H), 4.00-3.94 (16 H, m, CyD 3,5-H), 3.58-3.53 (16 H, m, CyD 4,2-H), 3.43-3.40 (8 H, m, CyD 6-H), 3.24-3.20 (8 H, m, CyD 6-H); Electrospray m/z 1190.6 for $[\text{M}-8\text{Na}+6\text{H}]^2$, calcd for $\text{C}_{104}\text{H}_{104}\text{Na}_8\text{O}_{48}\text{S}_8$ M 2562.39.

Example 4.6-Per-deoxy-6-per-(2-carboxyethyl)thio- γ -cyclodextrin, sodium salt

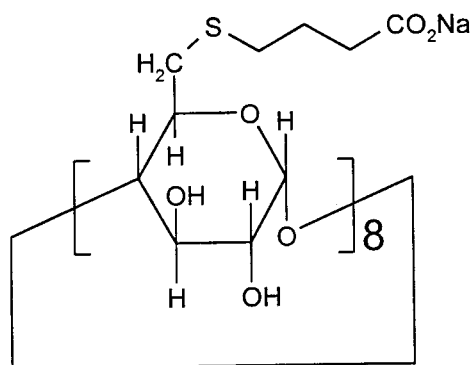
3-Mercaptopropionic acid (1.22 ml, 14.0 mmol) was dissolved in dry DMF (45
 5 ml) under N_2 at room temperature. To this solution was added in three portions
 sodium hydride (1.23 g, 30.8 mmol, 60%) and the mixture was stirred for a further 30
 min. To this mixture was then added dropwise a solution of 6-*per*-deoxy-6-*per*-iodo- γ -
 cyclodextrin (3.12 g, 1.40 mmol) in 45 ml dry DMF. After addition, the reaction
 mixture was heated at 70 °C for 12 h. After cooling, water (10 ml) was added to the
 10 mixture and the volume was reduced to 40 ml *in vacuo*, to which ethanol (250 ml)
 was added resulting in precipitation. The solid precipitate was collected by filtration
 and dialysed for 36 h. The volume was then reduced to 20 ml *in vacuo*. To this was
 added ethanol, and the precipitate was collected by filtration and dried to give the
 title compound as a white solid (1.3 g, 43%). 1H -NMR D_2O δ 2.47-2.51 (m, 16H);
 15 2.84-2.88 (m, 16H); 3.00-3.02 (t, 8H); 3.11-3.14 (t, 8H); 3.62-3.68 (m, 16H); 3.92-
 3.97 (m, 8H); 4.04-4.06 (m, 8H); 5.19 (m, 8H) ppm. MS FIA +ion at 2024.9 m/z.

Example 5.20 6-Per-deoxy-6-per-(5-carboxypentyl)thio- γ -cyclodextrin, sodium salt

The title compound was prepared in a similar way as described for Example 4 by reacting 6-mercaptohexanoic acid (1.34 g, 0.90 mmol) with 6-*per*-deoxy-6-*per*-iodo- γ -cyclodextrin. $^1\text{H-NMR}$ D_2O δ 1.40 (s, 16H); 1.57-1.64 (m, 32H); 2.17-2.21 (m, 16H); 2.67-3.00 (m, 16H); 2.85-2.90 (m, 8H); 3.15-3.20 (m, 8H); 3.52-3.59 (m, 8H); 3.60-3.63 (m, 8H); 3.87-3.93 (m, 16H); 5.16 (s, 8H) ppm. MS FIA +ions at 2362.2, 2213, 2065 and 1919 m/z

Example 6.

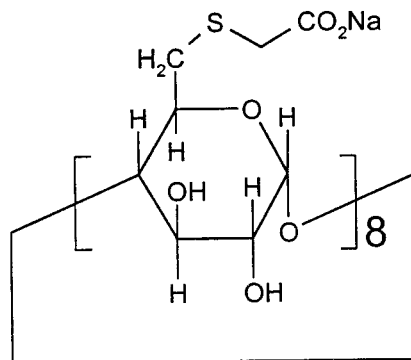
6-*Per*-deoxy-6-*per*-(3-carboxypropyl)thio- γ -cyclodextrin, sodium salt



The title compound was prepared in a similar way as described for Example 4 by reacting 4-mercaptoputyric acid (1.10 g, 0.009 mol) with 6-*per*-deoxy-6-*per*-iodo- γ -cyclodextrin. $^1\text{H-NMR}$ D_2O δ 1.87-1.88 (m, 16H); 2.27-2.30 (m, 16H); 2.67-2.71 (m, 16H); 2.98 -3.00 (m, 8H); 3.13 -3.16 (m, 8H); 3.61-3.63 (m, 16H); 3.94-4.03 (m, 16H); 5.21 (s, 8H) ppm. MS FIA +ion at 2138.8 m/z.

Example 7.

6-*Per*-deoxy-6-*per*-carboxymethylthio- γ -cyclodextrin, sodium salt



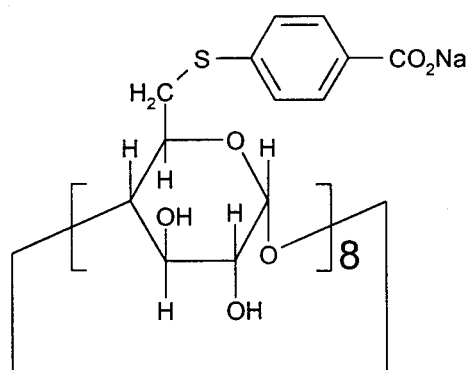
Sodium hydride (60% dispersion, 0.34g, 8.60mmol) was added to a stirred solution of ethyl 2-mercaptoacetate (0.92ml, 8.40mmol) in DMF (20 ml) under

nitrogen at room temperature. After effervescence had ceased (15 min), *per*-6-deoxy-*per*-6-iodo- γ -cyclodextrin (2.17g, 1.00mmol) was added to the system. After a further 5 min, the temperature was raised to 70°C and the reaction was left with stirring for 17h. After cooling, DMF was removed *in vacuo*. Methanol (50ml) was added and a creamy white solid slowly crystallised out of solution. This was filtered off under suction, washed with methanol and dried to give 6-*per*-deoxy-6-*per*-carbethoxymethylthio- γ -cyclodextrin as a solid (1.74g, 82%). δ_{H} (d6-dmsO) 4.95-4.85 (8H, m, 8 x anomeric CH), 4.05 (16H, q, 8 x CH₂CH₃), 3.85-3.75 (8H, m), 3.60-3.50 (8H, m), 3.40-3.20 (32H, bs, 8 x CH₂SCH₂), 3.20-3.10 (8H, m), 2.95-2.85 (8H, m), 1.20 (24H, t, 8 x CH₂CH₃).

To 1 M solution of sodium hydroxide (7 ml) was added 6-*per*-deoxy-6-*per*-carbethoxymethylthio- γ -cyclodextrin (1.00g, 0.47mmol) and the reaction was allowed to stir at room temperature. After 18h, the clear solution was dialysed for 8h, with water (2L) being replaced every 2h. After this time, the contents of the dialysis tubing was emptied into a flask and water evaporated *in vacuo*, giving the title compound as a white solid (0.62g, 64%). δ_{H} (D₂O) 5.21 (8H, d, 8 x anomeric CH), 4.18-4.05 (8H, m), 4.00 (8H, dd), 3.78 (8H, dd), 3.70 (8H, dd), 3.40 (16H, dd), 3.20 (8H, d), 3.02 (8H, dd). δ_{C} (D₂O) 178.1, 101.6, 82.8, 73.0, 72.7, 71.8, 39.0, 34.1 LC/MS TOF 1889 m/z

Example 8.

6-*Per*-deoxy-6-*per*-(4-carboxyphenyl)thio- γ -cyclodextrin, sodium salt

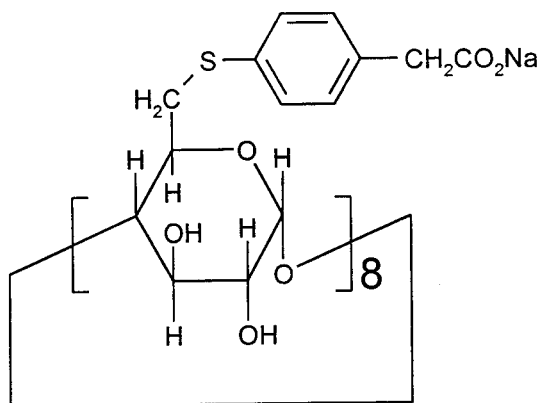


To a solution of 4-mercaptobenzoic acid (856 mg) in DMF (30 ml) was added 60% sodium hydride dispersed in oil (372 mg) portionwise over 30 min. The mixture was cooled and *per*-6-deoxy-*per*-6-bromo- γ -cyclodextrin (1.0 g) was added in one portion and the mixture was stirred at 70 °C for 24 h. The mixture was allowed to cool to room temperature and quenched with the addition of water (20 ml) before

evaporating to a low volume. The solution was poured into ethanol (250 ml) and the precipitate was collected by filtration, dissolved in water (20 ml) and dialysed (MWCO 1000) by changing the external water four times. Internal solution was evaporated to low volume and poured into acetone (250 ml). The solid precipitate was collected by filtration and dried under vacuum at 70 °C to afford the title compound (1.2 g) as a white solid. ¹H NMR (D₂O, 343K) δ 7.70 (16 H, d, *J* = 8.1 Hz, Ar-H), 7.23 (16 H, d, *J* = 7.3 Hz, Ar-H), 5.15 (8 H, s, CyD 1-H), 4.00-3.96 (16 H, m, CyD 3,5-H), 3.55-3.53 (24 H, m, CyD 6',4,2-H), 3.15 (8 H, m, CyD 6-H); MALDI-TOF *m/z* 2383.7 for [M-Na₈+H₆], calcd for C₁₀₄H₁₀₄Na₈O₄₈S₈ M 2562.39.

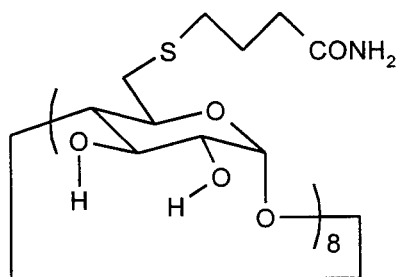
Example 9.

6-Per-deoxy-6-per-(4-carboxymethylphenyl)thio-γ-cyclodextrin, sodium salt



To a solution of 4-mercaptophenylacetic acid (10 eq) in DMF (50 ml) was added 60% sodium hydride in oil (22 eq) portionwise over 30 min. The mixture was cooled and *per*-6-deoxy-*per*-6-bromo-γ-cyclodextrin (1.0 g) was added in one portion and the mixture was stirred at 70 °C for 24 h. The mixture was allowed to cool to room temperature and quenched with the addition of water (20 ml) before evaporating to a low volume. The solution was then poured into acetone (250 ml) and the precipitate was collected by filtration, suspended in water (20 ml) and dialysed (MWCO 1000) by changing the external water four times. Internal solution was evaporated to low volume and poured into acetone (250 ml). The solid precipitate was collected by filtration and dried under vacuum at 70 °C to afford the title compound (1.44 g) as a white solid. ¹H NMR (D₂O, 343K) δ 7.15 (16 H, d, *J* = 8.0 Hz, Ar-H), 6.99 (16 H, d, *J* = 8.0 Hz, Ar-H), 4.98 (8 H, s, CyD 1-H), 3.90-3.72 (16 H, m, CyD 3,5-H), 3.51-3.43 (16 H, m, CyD 4,2-H), 3.28 (24 H, m, CH₂-Ar, CyD 6'-H), 3.15-3.10 (1 H, m, CyD 6-H); MALDI-TOF *m/z* 2495.8 for [M-Na₈+H₆], calcd for C₁₁₂H₁₂₀Na₈O₄₈S₈ M 2674.6.

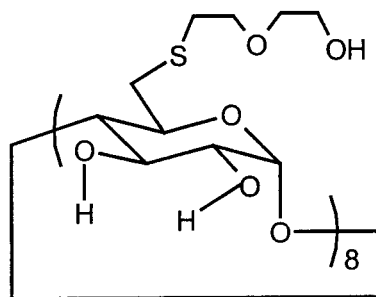
Example 10

6-Per-deoxy-6-per(3-amidopropyl)thio- γ -cyclodextrin

- 5 To a mixture of 6-*per*-deoxy-6-*per*-thio- γ -cyclodextrin (500 mg; prepared as described in Example 17) and potassium iodide (5 mg) in DMF (10 ml) was added 4-chlorobutamide (673 mg; Fries *et. al.* Biochemistry 1975, 14, 5233). Caesium carbonate (1.8 g) was added and the reaction mixture was heated to 60°C overnight. The resulting mixture was poured into acetone, filtered, washed with ethanol and
- 10 water and then dried *in-vacuo* (118 mg; 16.2%). ¹H NMR (DMSO/D₂O) δ 4.9 (1H, s), 3.8 (1H, m), 3.6 (1H, m) 3.4 (2H, m), 3.05 (1H, m), 2.85 (1H, m), 2.2 (2H, m), 1.75 (2H, m). Electrospray Mass Spectrum M-H (*m/z*) 2105.

Example 11.

- 15 6-*per*-deoxy-6-*per*(5-hydroxy-3-oxa-pentyl)thio- γ -cyclodextrin.

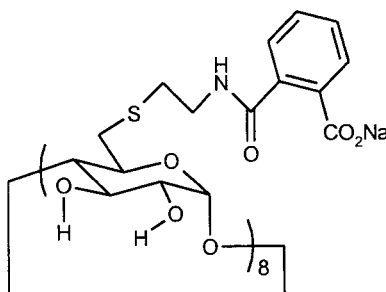


- 2-((2-Mercaptoethoxy)ethanol (1.4 g, 11.6 mmol) was dissolved in DMF (20 ml) and stirring commenced at room temperature under a nitrogen atmosphere. *Per*-6-bromo- γ -cyclodextrin (2g, 1.12 mmol) and caesium carbonate (3.2 g, 9.86 mmol)
- 20 were then added and the resultant suspension stirred at 60 °C overnight under a nitrogen atmosphere. After cooling to room temperature the suspension was poured into acetone (200 ml) and the insoluble material isolated by filtration, washed with acetone (x3) and dried *in vacuo*. The crude product was dissolved in de-ionised water (20 ml) and dialysed (10 h). The contents of the dialysis membrane were then
- 25 concentrated *in vacuo* to yield 1g of the desired product as a cream solid.

^1H NMR (D_2O , 400MHz): δ 2.81-3.00 (m, 24H), 3.21-3.31 (d, 8H), 3.49 (t, 8H), 3.55-3.75 (m, 56H), 3.82 (t, 8H), 3.89 (t, 8H), 5.11 (d, 8H). ESI-MS: 2175 (M-H) $^-$

Example 12.

5 6-per-deoxy-6-per[(2(2-carboxybenzoyl)amino)ethyl]thio- γ -cyclodextrin, sodium salt.



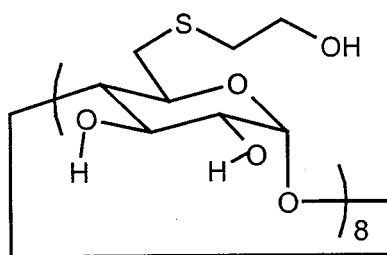
Per-6-mercapto- γ -cyclodextrin (1 g, 0.7 mmol; see example 17) was dissolved in DMF (10 ml) and stirring commenced at room temperature under a nitrogen atmosphere. N-(2-Bromoethyl)phthalimide (1.57 g, 6.17 mmol) and caesium carbonate (2 g, 6.17 mmol) were added and the resultant suspension was stirred at 10 60 °C overnight under a nitrogen atmosphere. After cooling to room temperature the DMF was removed *in vacuo* and water (100 ml) was added with vigorous stirring. The precipitate was isolated by filtration, washed with water (x3) and dried *in vacuo* to yield 1.67 g of a cream solid. Aqueous sodium hydroxide (1M, 20 ml) was then

15 added to the crude product (600 mg) and the resultant solution stirred at room temperature overnight under a nitrogen atmosphere. The solution was then dialysed with de-ionised water until constant pH and the contents of the dialysis membrane dried *in vacuo* to yield 500mg of the desired product as a glassy solid.

^1H NMR (D_2O , 400MHz): δ 2.76-2.96 (m, 24H), 3.10-3.30 (m, 8H), 3.35-3.62 (m, 20 32H), 3.78-3.95 (m, 16H), 5.02 (d, 8H), 7.30-7.62 (m, 32H);
ESI-MS: 1477 (M-2H) $^{2-}$

Example 13.

6-per-deoxy-6-per(2-hydroxyethyl)thio- γ -cyclodextrin.



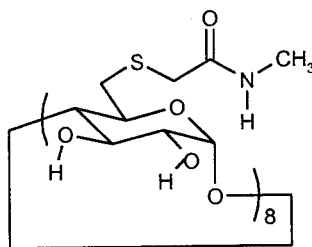
To a stirred solution of 2-mercaptoethanol (10.85 g, 10 eq) in DMF (500 ml) under nitrogen was added 60% sodium hydride dispersed in oil (11.7 g, 21 eq) portion-wise over 30 min. The mixture was stirred at room temperature for 90 minutes. *Per*-6-deoxy-6-*per*-bromo- γ -cyclodextrin (25.0 g) was added and the mixture heated to 70 °C for 24 h. The mixture was allowed to cool to room temperature and quenched by addition of water (50 ml) before evaporating to a low volume. The residue was taken up in water (100 ml) and poured onto 1:1 methanol / acetone (500 ml). The solid formed was collected by filtration, dissolved in water (500 ml) and dialysed (MWCO 1000) changing the external water four times. The internal solution was evaporated to low volume and then re-crystallised from hot water to afford the title compound (8.5 g) as white cross-shaped crystals.

¹H NMR (400MHz; DMSO) δ 5.91 (16 H, br s, 2,3-OH), 4.92 (8 H, s, 1-H), 4.71 (8H, t, *J* 4.4 Hz, SCH₂CH₂OH), 3.75 [8H, t, *J* 8.0 Hz, 3-H (or 5-H)], 3.60-3.50 [24H, m, 5-H (or 3-H), SCH₂CH₂OH], 3.40-3.30 (16H, m, 4-H, 2-H), 3.08 (8H, d, *J* 13.6 Hz, 6-H), 2.82 (8H, dd, *J* 13.6, 6.8 Hz, 6-H), 2.66 (16H, t, *J* 6.8 Hz, SCH₂CH₂OH); *m/z* (electrospray) 1775.4 for [M-H]⁻, calcd for C₆₄H₁₁₂S₈O₄₀ M 1776.45.

The preparation of this compound by a similar method has been published previously: *J. Chem. Soc., Chem. Commun.*, 203 (1993).

Example 14.

6-*per*-deoxy-6-*per*-(N-methylamidomethyl)thio- γ -cyclodextrin



To a stirred solution of *N*-methylmercaptoacetamide (0.58 g, 10 eq) in DMF (30 ml) under nitrogen was added 60% sodium hydride dispersed in oil (0.22 g, 10 eq) portion-wise over 30 min. The mixture was stirred at room temperature for 30 minutes. *Per*-6-deoxy-6-*per*-bromo- γ -cyclodextrin (1.0 g) was added and the mixture heated to 60-70 °C for 48 h. The mixture was allowed to cool to room temperature and quenched by addition of water (20 ml) before evaporating to a low volume. The residual solution was poured onto ethanol (100 ml). The solid formed was collected

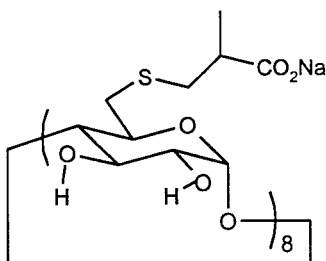
by filtration, dissolved in water (200 ml) and dialysed (MWCO 1000), changing the external water four times. The internal solution was evaporated to low volume and poured onto ethanol (100 ml). The precipitate was collected by filtration and dried under vacuum to afford the title compound (0.55 g) as a white solid.

- 5 ^1H NMR (400MHz; D_2O) δ 5.29 (8H, d, J 4.0 Hz, 1-H), 4.10 (8H, br t, J 9.6 Hz, 5-H), 4.05 (8H, t, J 9.8 Hz, 3-H), 3.83 (8H, dd, J 10.0, 3.6 Hz, 2-H), 3.74 (8H, t, J 9.2 Hz, 4-H), 3.58-3.49 [16H, AB system, $\text{SCH}_2\text{C}(\text{O})\text{NHCH}_3$], 3.36 (8H, br d, J 12.8 Hz, 6-H), 3.07 (8H, dd, J 14.0, 8.4 Hz, 6-H), 2.94 (24H, s, $\text{SCH}_2\text{C}(\text{O})\text{NHCH}_3$); m/z (electrospray) 1991.7 for $[\text{M}-\text{H}]^-$, calculated for $\text{C}_{72}\text{H}_{120}\text{N}_8\text{S}_8\text{O}_{40}$ M 1992.54.

10

Example 15.

6-per-deoxy-6-per(2-carboxypropyl)thio- γ -cyclodextrin, sodium salt.

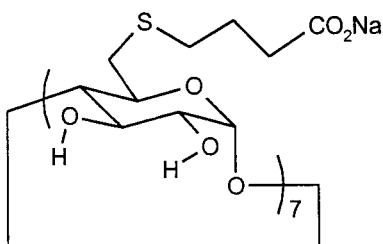


- Sodium hydride (60% in oil) (0.44 g) was added to methyl 3-mercapto-2-methylpropionate (1.474 g; *J. Med. Chem.*, 1994, 1159) in dimethylformamide (25 ml). After 15 30 minutes *per*-6-deoxy-*per*-6-bromo- γ -cyclodextrin (2.25 g), dissolved in dimethylformamide (25 ml), was added. A crystal of sodium iodide was added and the mixture heated at 75°C overnight. The solvent was distilled off and the residue crystallised from methanol to give the methyl ester (1.3 g). Mass spec. (M-H) 2224;
- 20 ^1H NMR ($\text{dmso } \text{D}_6$): δ 1.41 (d, 24H), 2.68 (m, 16H), 2.80 (m, 16H), 3.00 (m, 8H), 3.61 (3, 24H), 3.79 (m, 8H), 4.95 (s, 8H).

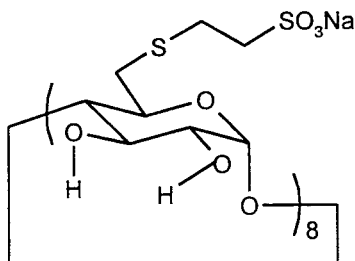
This product was then stirred overnight with sodium hydroxide solution (M, 13 ml). The resulting mixture was filtered, dialysed to neutrality, and evaporated to dryness to give the title compound (1.13 g). Mass spec. (M-H) 2112;

- 25 ^1H NMR (D_2O): δ 1.15 (d, 24H), 2.5 (m, 8H), 2.65 (m, 8H), 2.8-3.1 (m, 24H), 3.65 (m, 16H), 4.0 (m, 16H), 5.2 (s, 8H).

30

Example 16.6-per-deoxy-6-per(3-carboxypropyl)thio- β -cyclodextrin, sodium salt.

5 *Per*-6-deoxy-*per*-6-bromo- β -cyclodextrin (2.25 g), methyl-4-mercaptobutyrate (1.7 g;
Tetrahedron 1998, 2652), cesium carbonate (4.24 g) and dimethylformamide (25 ml)
 were stirred and heated together for three days. The mixture was cooled, poured into
 water and filtered. The solid was washed with methanol and dried (2.1 g). This was
 stirred overnight with sodium hydroxide solution (M, 21 ml), filtered and the filtrate
 10 dialysed to neutrality. This was evaporated to dryness giving the title compound (1.7
 g). Mass Spec.(M-H) 1848.8. ^1H NMR (D_2O): δ 1.75 (m, 16H), 2.15 (m, 16H), 2.6 (m,
 16H), 2.85 (m, 8H), 3.05 (m, 8H), 3.55 (m, 16H) 3.87 (m, 16H), 5.07 (s, 8H)

Example 17.6-Per-deoxy-6-per(2-sulfoethyl)thio- γ -cyclodextrin, sodium salt

15

A: *Per*-6-deoxy-*per*-6-thio- γ -cyclodextrin

Per-6-deoxy-*per*-6-bromo- γ -cyclodextrin (20 g), thiourea (13.5 g) and
 dimethylformamide (100 ml) were heated together for three days at 65 °C and then
 ethanolamine (20 ml) was added and heating continued for two hours. The mixture
 20 was cooled, diluted with ice water and the product separated by centrifuge. The solid
 was washed twice with water and dried in vacuum at 65 °C giving the thiol (7.34 g).
 Mass spec. (M-H) 1424.

^1H NMR (dmso D_6): δ 2.82 (m, 8H), 3.20 (d, 8H), 3.35 (m, 16H), 6.65 (t, 8H), 7.75 (t,
 8H), 5.0 (s, 8H).

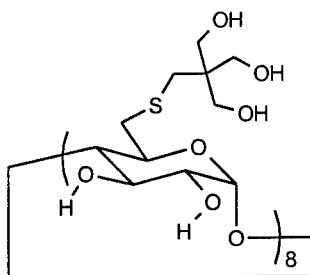
25 B: 6-Per-deoxy-6-per(2-sulfoethyl)thio- γ -cyclodextrin, sodium salt

The above *per*-thiol (1 g), 2-bromoethane sulphonic acid sodium salt (1.42 g),

cesium carbonate (2.2 g) and dimethylformamide (10 ml) were stirred and heated overnight at 64°C. Most of the solvent was evaporated under vacuum and the residue dissolved in water. Sodium bicarbonate solution (5% w/w, 5 ml) was added and the solution dialysed three times with water. This solution was evaporated to dryness and the residue dissolved in sodium bicarbonate solution (10 ml), dialysed and evaporated as before. This process was repeated, the resulting solid was dissolved in a small volume of water and the product precipitated with methanol. This was dissolved in water and evaporated to dryness giving the title compound (1.18 g).
¹H NMR (D₂O): δ 3.9 (m, 24H), 3.2 (m, 24H), 3.55-3.65 (m, 16H), 3.9 (m, 8H), 4.05 (m, 8H), 5.15 (s, 8H)

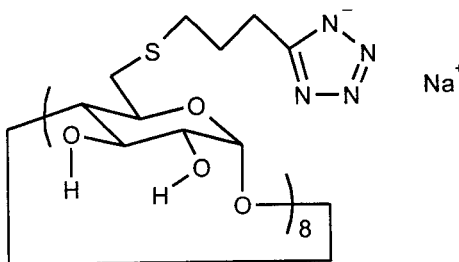
Example 18.

6-per-deoxy-6-per(2,2-di(hydroxymethyl)-3-hydroxy-propyl)thio-γ-cyclodextrin.



Per-6-deoxy-*per*-6-thio-γ-cyclodextrin (500 mg; Example 17), 3-bromo-2,2-dihydroxy-methylpropanol (670 mg), cesium carbonate (550 mg) and dimethylformamide (10 ml) were heated and stirred for 35 days at 65°C until analysis by LCMS showed conversion to the required product. The mixture was evaporated to dryness, dissolved in water, dialysed against water, evaporated to low volume and precipitated with acetone. Drying under vacuum gave the title compound (550 mg).
Mass spec. FIA (M-H) 2369.

¹H NMR (D₂O): δ 2.84 (m, 16H), 3.15 (m, 8H), 3.24 (m, 8H), 3.69 (s, 64H), 3.85-4.19 (m, 16H), 5.25 (s, 8H).

Example 19.6-per-deoxy-6-per(3-(tetrazol-5-yl)propyl)thio- γ -cyclodextrin, sodium salt.

- 5 *Per*-6-deoxy-*per*-6-thio- γ -cyclodextrin (1 g), 4-bromobutyronitrile (1 g), cesium carbonate (1 g) and dimethylformamide (10 ml) were stirred together at 60°C over the weekend. The mixture was cooled, water added and the precipitate separated by centrifuge. After washing and drying the *per*-butyronitrile (1.4 g) was obtained. This product (1 g), sodium azide (1.3 g), triethylamine hydrochloride (2.8 g) and dimethylformamide (13 ml) were stirred and heated together for 7 days at 100°C.
- 10 The mixture was cooled, diluted with water, acidified and the precipitated filtered off. This was washed with water, sonicated with methanol, separated by centrifuge, dried and dissolved in sodium hydroxide solution (M, 10 ml), filtered and dialysed to neutrality. This solution was evaporated to dryness to give the title compound (600 mg). Mass spec. (M-2H) 1152.8.
- 15 ¹H NMR (D₂O); δ 1.95 (m, 16H), 2.55 (m, 16H), 2.85 (m, 24H), 3.05 (d, 8H), 3.5 (m, 8H), 3.6 (m, 8H), 3.9 (m, 16H), 5.06 (s, 8H).

Example 20.Reversal of neuromuscular blockade in anaesthetized guinea pigs *in vivo*.

- 20 Male Dunkin-Hartley guinea pigs (bodyweight: 600-900 g) were anaesthetized by i.p. administration of 10 mg/kg pentobarbitone and 1000 mg/kg urethane. After tracheotomy, the animals were artificially ventilated using a Harvard small animal ventilator. A catheter was placed into the carotid artery for continuous monitoring of arterial blood pressure and the taking of blood samples for blood gas
- 25 analysis. Heart rate was derived from the blood pressure signal. The sciatic nerve was stimulated (rectangular pulses of 0.5 ms duration at 10 s (0.1 Hz) intervals at a supramaximal voltage, using a Grass S88 Stimulator) and the force of M. gastrocnemius contractions was measured using a Grass FT03 force-displacement transducer. Contractions, blood pressure and heart rate were recorded on a
- 30 multichannel Grass 7D recorder. Catheters were placed in both jugular veins. One

catheter was used for the continuous infusion of a neuromuscular blocking agent. The infusion rate of the neuromuscular blocking agent was increased until a steady-state block of 85-90% was obtained. The other catheter was used for administration of increasing doses of the reversal agent. During continuous infusion of the neuromuscular blocking agent, single doses of increasing concentration of reversal agent were given. At the end of the experiment, the measured force of muscle contractions was plotted against the concentration of reversal agent, and using regression analysis techniques, the 50% reversal concentration was calculated.

Results for the reversal of the neuromuscular block, induced by the muscle relaxant rocuronium bromide (Roc), by the 6-mercapto-cyclodextrin derivatives of Examples 1-19 are presented in **Table I**. For comparison, the reversal activity of the parent compounds β -cyclodextrin and γ -cyclodextrin are included as well.

TABLE I

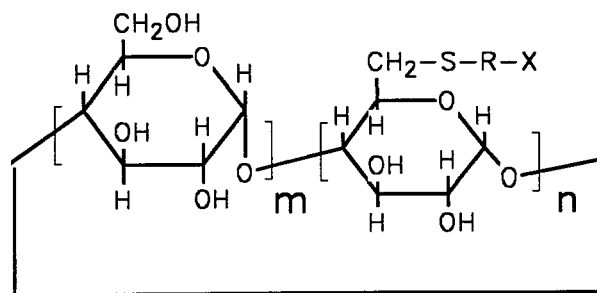
Dose (ED₅₀, $\mu\text{mol.kg}^{-1}$) producing 50% reversal of steady-state neuromuscular block in anaesthetized guinea pigs and concentration at maximum reversal.

Compound	ED ₅₀ $\mu\text{mol.kg}^{-1}$	% max reversal at conc. ($\mu\text{mol.kg}^{-1}$)
γ -cyclodextrin (γ -CD)	4	104 (47)
β -cyclodextrin (β -CD)	20	93 (113)
6-mono-deoxy-6-mono-(4-carboxyphenyl)thio- γ -cyclodextrin, Na salt (example 1)	0.94	102 (8.0)
6-mono-deoxy-6-mono-(2-carboxyphenyl)thio- γ -cyclodextrin (example 2)	1.30	93 (11)
6- <i>per</i> -deoxy-6- <i>per</i> -(3-carboxyphenyl)thio- γ -cyclodextrin (example 3)	0.28	102 (1.28)
6- <i>per</i> -deoxy-6- <i>per</i> -(2-carboxyethyl)thio- γ -cyclodextrin, Na salt (example 4)	0.09	97 (0.53)
6- <i>per</i> -deoxy-6- <i>per</i> -(5-carboxypentyl)thio- γ -cyclodextrin, Na salt (example 5)	0.74	78 (2.5)
6- <i>per</i> -deoxy-6- <i>per</i> -(3-carboxypropyl)thio- γ -cyclodextrin, Na salt (example 6)	0.09	108 (0.48)
6- <i>per</i> -deoxy-6- <i>per</i> -carboxymethylthio- γ -cyclodextrin, Na salt (example 7)	0.21	88 (1.92)
6- <i>per</i> -deoxy-6- <i>per</i> -(4-carboxyphenyl)thio- γ -cyclodextrin, Na salt (example 8)	0.10	95 (0.48)
6- <i>per</i> -deoxy-6- <i>per</i> -(4-carboxyphenylmethyl)thio- γ -cyclodextrin, Na salt (example 9)	0.13	100 (0.50)
6- <i>per</i> -deoxy-6- <i>per</i> -(3-amidopropyl)thio- γ -cyclodextrin (example 10)	0.57	94 (33)
6- <i>per</i> -deoxy-6- <i>per</i> -(5-hydroxy-3-oxa-pentyl)thio- γ -cyclodextrin (example 11)	0.47	92 (2.1)
6- <i>per</i> -deoxy-6- <i>per</i> -[(2(2-carboxybenzoyl)amino)ethyl]-thio- γ -cyclodextrin, sodium salt (example 12)	0.085	95 (0.48)
6- <i>per</i> -deoxy-6- <i>per</i> -(2-hydroxyethyl)thio- γ -cyclodextrin (example 13)	0.20	96 (2.0)

Compound	ED ₅₀ μmol.kg ⁻¹	max. reversal at conc. (μmol.kg ⁻¹)
6- <i>per</i> -deoxy-6- <i>per</i> -(N-methylamidomethyl)thio-γ-cyclodextrin (example 14)	1.54	102 (7.3)
6- <i>per</i> -deoxy-6- <i>per</i> -(2-carboxypropyl)thio-γ-cyclodextrin, sodium salt. (example 15)	0.10	103 (0.48)
6- <i>per</i> -deoxy-6- <i>per</i> -(3-carboxypropyl)thio-β-cyclodextrin, sodium salt (example 16)	0.5	100 (3.2)
6- <i>per</i> -deoxy-6- <i>per</i> -(2-sulfoethyl)thio-γ-cyclodextrin, sodium salt (example 17)	0.055	106 (1.7)
6- <i>per</i> -deoxy-6- <i>per</i> -(2,2-di(hydroxymethyl)-3-hydroxypropyl)thio-γ-cyclodextrin (example 18)	2.9	63 (4.9)
6- <i>per</i> -deoxy-6- <i>per</i> -(3-(tetrazol-5-yl)propyl)thio-γ-cyclodextrin, sodium salt (example 19)	0.22	109 (1.2)

Claims.

1. A 6-mercapto-cyclodextrin derivative having the general formula I



Formula I

wherein m is 0-7 and n is 1-8 and $m+n = 7$ or 8 ;

R is (C_{1-6}) alkylene, optionally substituted with 1-3 OH groups,

or $(CH_2)_o$ -phenylene- $(CH_2)_p$;

o and p are independently 0-4;

X is $COOH$, $CONHR_1$, $NHCOR_2$, SO_2OH , $PO(OH)_2$, $O(CH_2-CH_2-O)_q-H$,

OH or tetrazol-5-yl;

R_1 is H or (C_{1-3}) alkyl;

R_2 is carboxyphenyl;

q is 1-3;

or pharmaceutically acceptable salts thereof;

with the exclusion of

6-*per*-deoxy-6-*per*-(2-hydroxyethylthio)- β -cyclodextrin;

6-mono-deoxy-6-mono-(2-hydroxyethylthio)- β -cyclodextrin;

6-*per*-deoxy-6-*per*-(2-hydroxyethylthio)- γ -cyclodextrin;

6-*per*-deoxy-6-*per*-(carboxymethylthio)- β -cyclodextrin;

6-mono-deoxy-6-mono-(carboxymethylthio)- β -cyclodextrin;

6A,6B-dideoxy-6A,6B-bis[(o-carboxyphenyl)thio]- β -cyclodextrin;

6A,6B-dideoxy-6A,6B-bis(carboxymethylthiol)- β -cyclodextrin and

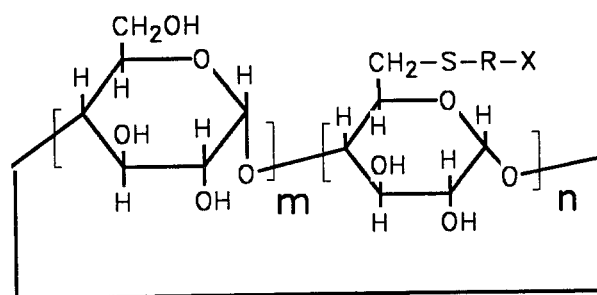
6-*per*-deoxy-6-*per*-(2,3-dihydroxypropylthio)- β -cyclodextrin.

2. The 6-mercapto-cyclodextrin derivative according to claim 1, wherein R, m and n are defined as in claim 1 and X is COOH or SO₂OH; or a pharmaceutically acceptable salt thereof.
3. The 6-mercapto-cyclodextrin derivative according to claim 1, wherein m is 0; n is 8; R is (C₁₋₆)alkylene or (CH₂)_o-phenylene-(CH₂)_p; o and p are independently 0-4; and X is COOH or SO₂OH; or a pharmaceutically acceptable salt thereof.
4. A 6-mercapto-cyclodextrin derivative according to any of claims 1-3 selected from:
6-*per*-deoxy-6-*per*-(2-carboxyethyl)thio- γ -cyclodextrin;
6-*per*-deoxy-6-*per*-(3-carboxypropyl)thio- γ -cyclodextrin;
6-*per*-deoxy-6-*per*-(4-carboxyphenyl)thio- γ -cyclodextrin;
6-*per*-deoxy-6-*per*-(4-carboxyphenylmethyl)thio- γ -cyclodextrin;
6-*per*-deoxy-6-*per*-(2-carboxypropyl)thio- γ -cyclodextrin; and
6-*per*-deoxy-6-*per*-(2-sulfoethyl)thio- γ -cyclodextrin;
or a pharmaceutically acceptable salt thereof.
5. A 6-mercapto-cyclodextrin derivative according to the general formula I of claim 1 for use in therapy.
6. The use of a 6-mercapto-cyclodextrin derivative according to the general formula I of claim 1 for the manufacture of a medicament for the reversal of drug-induced neuromuscular block.
7. A kit for providing neuromuscular block and its reversal comprising (a) a neuromuscular blocking agent, and (b) a 6-mercapto-cyclodextrin derivative according to the general formula I of claim 1.
8. The kit according to claim 6, wherein the neuromuscular blocking agent is selected from the group consisting of rocuronium, vecuronium,

pancuronium, rapacuronium, mivacurium, (cis)atracurium, tubocurarine and suxamethonium.

9. The kit according to claim 7, wherein the neuromuscular blocking agent is rocuronium.

10. A pharmaceutical composition comprising a 6-mercapto-cyclodextrin derivative having the general formula I



Formula I

wherein m is 0-7 and n is 1-8 and $m+n = 7$ or 8 ;

R is (C_{1-6}) alkylene, optionally substituted with 1-3 OH groups,

or $(CH_2)_o$ -phenylene- $(CH_2)_p$;

o and p are independently 0-4;

X is $COOH$, $CONHR_1$, $NHCOR_2$, SO_2OH , $PO(OH)_2$, $O(CH_2-CH_2-O)_q-H$,

OH or tetrazol-5-yl;

R_1 is H or (C_{1-3}) alkyl;

R_2 is carboxyphenyl;

q is 1-3;

or a pharmaceutically acceptable salt thereof, in admixture with pharmaceutically acceptable auxiliaries.

11. A method for reversal of drug-induced neuromuscular block in a patient, which comprises parenterally administering to said patient an effective amount of a 6-mercapto-cyclodextrin derivative according to the general formula I of claim 1.