

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
19 February 2004 (19.02.2004)

PCT

(10) International Publication Number
WO 2004/014350 A2

(51) International Patent Classification⁷: **A61K 31/00**

(21) International Application Number:
PCT/GB2003/003525

(22) International Filing Date: 13 August 2003 (13.08.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0218830.8 13 August 2002 (13.08.2002) GB

(71) Applicant (*for all designated States except US*): **SIRUS PHARMACEUTICALS LTD** [GB/GB]; Babraham Hall, Babraham, Cambridge CB2 4AT (GB).

(72) Inventor; and

(75) Inventor/Applicant (*for US only*): **CLARK, Jonathan** [GB/GB]; Sirus Pharmaceuticals Ltd, Babraham Hall, Babraham, Cambridge CB2 4AT (GB).

(74) Agent: **GILL JENNINGS & EVERY**; Broadgate House, 7 Eldon Street, London EC2M 7LH (GB).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: ANAESTHETIC CONJUGATES

(57) Abstract: The present invention relates to conjugates of anaesthetic substances with polymers, processes for preparing them, and their use in therapy. In particular there is provided a conjugate of a polymer and a local anaesthetic agent Z characterized in that the agent is an amine of a formula defined in the specification.



WO 2004/014350 A2

Anaesthetic conjugates

Field of the invention

The present invention relates to conjugates of anaesthetic substances with polymers,
5 processes for preparing them, and their use in therapy.

Background to the invention

Certain conjugates of anaesthetic substances with polymers have been described before. For example:

Farmakol Toksikol (1977) 40(5) 535-8 describes derivatives of procaine in which the
10 procaine is joined to a macromolecule either through the intermediary of a diethylamino-ethanol nitrogen or through the intermediary of a paraaminobenzoic acid nitrogen. A longer lasting anaesthetic effect is claimed;

Pharmazie (1988) 43(11) 774-6 describes conjugates of benzocaine to co-polymers formed from 1-vinyl-2-pyrrolidone and maleic anhydride optionally including a spacer. The
15 conjugates without spacer were resistant to enzymatic hydrolysis by pancreatin whereas the conjugates with epsilon-aminocaproic acid spacer showed small release of drug;

US Patent 4,650,771 (Buckler et al) describes immunogenic conjugates containing lidocaine in order that presence of lidocaine may be detected in biological fluids. These conjugates are inevitably designed to be resistant to hydrolysis;

20 US Patent 4,636,387 (Allcock et al) describes long-acting conjugates of certain anaesthetic agents to polyphosphazene, where the drug is connected to the backbone through a P-N bond;

Weiner et al (1973) J Med Chem 15, 573-4 discloses polyethylene glycol (PEG) derivatives of procaine in which a PEG molecule has conjugated to it two activated procaine
25 moieties by means of a carbamate linkage (i.e. procaine-NH-CO-O-CH₂-CH₂-PEG-CH₂CH₂O-CO-NH-procaine) with a view to lengthening duration of action;

Giammona et al (1989) 37(8) 2245-2247 describes attachment of various drugs bearing -NH² groups (eg procaine) to poly- α,β -aspartic acid via an amide bond;

Robert et al (1970) J Pharmacol Exp Therapeut 174(1), 133-140 describes a polymer
30 formed by reacting lidocaine base with polysiloxane.

Zalipsky (1995) Adv Drug Deliv Reviews 16, 157-182 has reviewed certain polymer conjugates based on polyethyleneglycol.

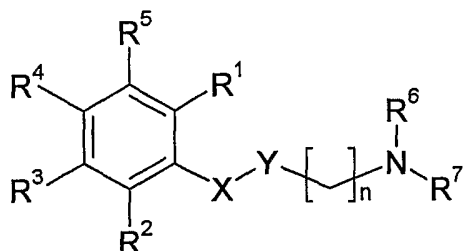
However the conjugates mentioned above suffer from the disadvantages that the drug may not be rapidly released, or may not be released without enzymatic assistance, or may not
35 be readily synthesized without complex chemistry, or employ undesirable phosphorus containing reagents, or that the conjugate may not be water-soluble.

We have now invented novel conjugates that overcome or substantially mitigate one or more of the above mentioned disadvantages.

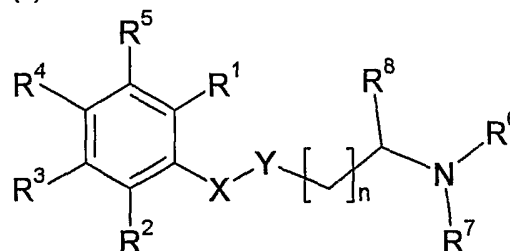
Summary of the invention

Thus according to the invention we provide a conjugate of a polymer and a local
 5 anaesthetic agent Z characterized in that the agent is an amine of any of the following chemical formulae:

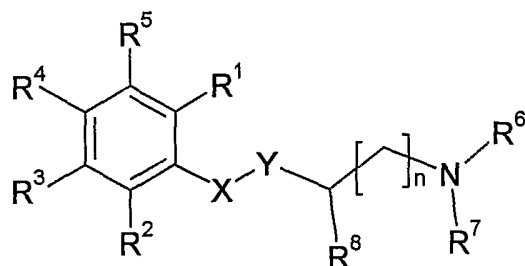
(I)



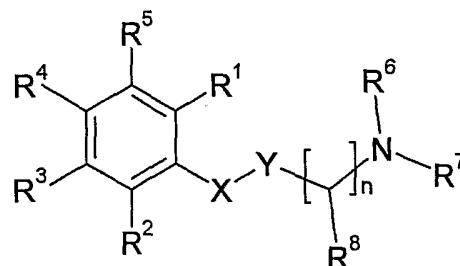
(II)



(III)



or (IV)



10 wherein:

R¹ and R² are independently selected from hydrogen, halogen, alkyl and alkyl ether groups;

X is C=O and Y is NR, or X is NR and Y is C=O, or X is C=O and Y is O, and R is selected from hydrogen, halogen, hydroxyl, alkyl, aryl and acyl;

15 R⁶ and R⁷ are independently selected from alkyl, aryl and alkylaryl groups; and

R⁸ is selected from hydrogen, halogen, hydroxyl, alkyl, aryl and alkylaryl; or

R⁷ and R⁸ may be joined, typically through a chain of carbon atoms and, optionally, heteroatoms, to form a ring 5, 6, 7 or 8 atoms in size;

n is 0, 1, 2, 3, 4 or 5; and

20 R³, R⁴ and R⁵ are each independently selected from hydrogen, hydroxyl, halogen, alkyl, aryl, hydroxyalkyl, hydroxyaryl, aminoalkyl and aminoaryl, with the proviso that at least one of R³, R⁴ and R⁵ is a hydroxyl moiety connected to the polymer (P) through a covalent bond.

The polymers according to the invention are generally water soluble, although they may not be water soluble at the very large molecular weights, depending on the nature of the
 25 further components. Sometimes they form gels. Water soluble polymers are preferred.

Description of the preferred embodiments

As used herein, the term "alkyl" means a straight or branched chain alkyl group of up to 8 carbon atoms. Examples are methyl and ethyl. "Alkyl ether" i.e. alkoxy may be interpreted accordingly. Examples are methoxy and ethoxy. "Alkyl thioether" i.e. alkylthio may also be interpreted accordingly. Examples are methylthio and ethylthio.

5 Halogen means F, Cl, Br or I.

"Aryl" means any aromatic group including heteroaromatic groups, e.g. containing up to three heteroatoms selected from N, O and S, monocyclic or bicyclic, having up to 12, e.g. 5 to 10, ring atoms. Examples are thienyl, phenyl and naphthyl. Aryl groups may optionally be substituted e.g. with one or more groups selected from hydroxy, C₁₋₄alkyl, halogen and C₁₋₄alkoxy, but are preferably unsubstituted. A preferred aryl group is phenyl. "Alkylaryl" may also be interpreted accordingly. Examples include methylphenyl. "Aryl ether" i.e. aryloxy may be interpreted accordingly.

Example of hydroxyalkyl that R³, R⁴ and R⁵ may represent include -CH₂OH.

Example of hydroxyaryl that R³, R⁴ and R⁵ may represent include hydroxyphenyl.

15 Example of aminoalkyl that R³, R⁴ and R⁵ may represent include -CH₂NH₂.

Example of aminoaryl that R³, R⁴ and R⁵ may represent include aminophenyl.

When R⁷ and R⁸ are joined they may be typically represent an alkylene chain of 3-6 methylene groups, or a variant in which one or more (eg one or two especially one) methylene groups are replaced with a heteroatom eg O, NH or S especially O. When R⁷ and R⁸ are joined preferably they represent (CH₂)₄.

Preferably R⁶ represents alkyl especially methyl or ethyl. Preferably R¹ represents alkyl especially methyl. Preferably R² represents alkyl especially methyl. Preferably those groups of R³, R⁴ and R⁵ that do not represent hydroxyl represent hydrogen. Preferably X represents NH and Y represents C=O.

25 More preferably R³ represents hydroxy and R⁴ and R⁵ represent H.

In structure (I), preferably n represents 1, 2 or 3, particularly 1 or 2 especially 1. Preferably R⁷ represents alkyl especially ethyl. Preferably R⁶ represents ethyl.

The preferred structure is that of 3- or 4-hydroxy-lidocaine, especially 3-hydroxy-lidocaine.

30 In structure (II), preferably n represents 0, 1 or 2, especially 0 or 1 particularly 0. Preferably R⁶ represents methyl or ethyl, especially ethyl. Preferably R⁷ and R⁸ are joined and represent an alkylene chain especially (CH₂)₄.

Alternatively, R⁷ and R⁸ may independently represent alkyl, especially ethyl.

The preferred structure is that of 3- or 4-hydroxy-bupivacaine, especially 3-hydroxy-bupivacaine. 3- or 4-hydroxy-mepivacaine, especially 3-hydroxy-mepivacaine is also of interest. 3- or 4-hydroxy-etidocaine, especially 3-hydroxy-etidocaine is also of interest.

In structure (III), preferably n represents 0, 1 or 2, especially 0 or 1 particularly 0.

Preferably R⁸ represents alkyl especially methyl or ethyl. Preferably R⁷ represents alkyl especially methyl or ethyl.

In structure (IV), preferably n represents 1 or 2. Preferably R⁸ represents alkyl especially methyl or ethyl, particularly methyl. Preferably R⁷ represents alkyl especially methyl
5 or ethyl.

The drug is preferably conjugated to the polymer through a hydroxy substituent, thus for example 3- or 4-hydroxy-lidocaine is conjugated through the 3- or 4-hydroxy substituent.

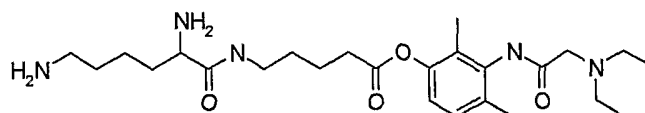
Compounds of formula (I) may be prepared by methods analogous to those described in US 5,849,737 (Chaplan et al) or by conventional methods known per se.

10 When local anaesthetic substances are incorporated into polymers according to the invention their properties may be modified in a beneficial way. For example, the therapeutic window of the substance may be widened or the duration of action may be lengthened.

One substance of particular interest is 3-hydroxylidocaine. According to US Patent 5,849,737 (Chaplan et al), 3-hydroxylidocaine is useful in the treatment of neuropathic pain.
15 However the use of this substance for this purpose is difficult because of the risk of overdose resulting in both central and cardiovascular side effects. Because of this potential risk, compounds such as local anaesthetics with similar mechanisms of action are often administered by infusion, rather than as a bolus. When incorporated into the polymers of the invention the risk of harmful effect is lessened since the body is not exposed to either high
20 local or high rapidly-achieved systemic concentrations of free drug as the release of the drug from the polymer is extended over many minutes or hours.

3-hydroxylidocaine is preferably incorporated into polymers of the invention by attaching the 3-hydroxy group to the diamine of monomer (II') preferably through a linker as just described.

25 The preferred di-amine monomer unit required for the polymerisation would have the following structure:



Examples of polymers include natural polymers such as dextran, dextrin or a synthetic
30 polymer, preferably biodegradable and non-toxic in nature. Preferably the polymer is water soluble. The drug is connected either directly to the polymer or through a linker which may be a peptide, amino acid, a short carbon chain such as succinic acid, 6-aminohexanoic acid, 5-aminopentanoic acid, 4-aminobutanoic acid, 3-aminopropanoic acid or other similar linker.

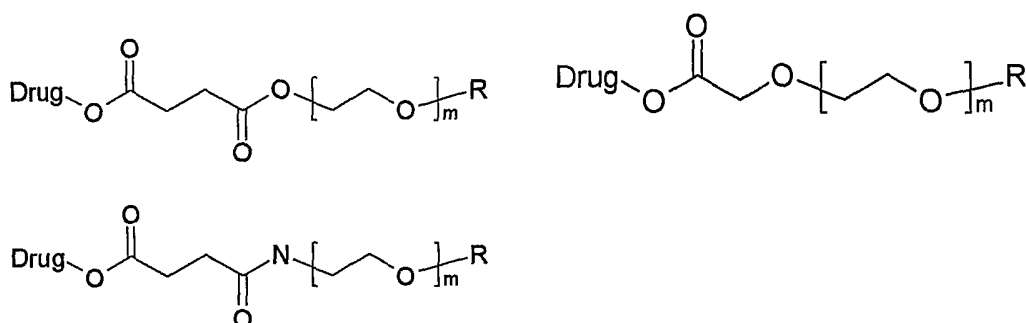
In one embodiment, the polymer is dextran. A number of dextrans are commercially
35 available e.g. where the number of units per polymer is approximately in the range of 50 to 1000. Examples of commercially available dextrans include those in which this number is 61, 185, 430 or 620. The exact value depends on the supplied batch of dextran. These are all

preferred values; by choosing different values, different levels of drug can be attached to the polymer.

In another embodiment, the polymer is dextrin. A number of dextrans are commercially available e.g. where the number of units per polymer is approximately in the range of 50 to 1000.

In another embodiment the polymer is derived from a polyethyleneglycol (PEG) e.g. a PEG acid. For example, the PEG may be condensed with a diacid (e.g. succinic acid) to yield a PEG derivative bearing an acyl group (or two acyl groups) to which the drug may be attached.

10 Examples of PEG conjugates according to this invention are:



where "Drug-O" indicates the compound of formula (I), R is hydrogen, alkyl, aryl or alkylaryl and m is an integer of 0 to 1000, preferably 5 to 1000 particularly 10 to 500. Preferably R represents COalkyl e.g. COMe. R may also represent COCH₂CH₂COO-Drug.

15 These and other acyl derivatives formed at the functional atom (the hydroxyl group on the benzene ring of the drug) are examples of conjugates of the present invention acting as pro-drugs. An acyl group may be used that endows the conjugate with desired solubility or other properties, and that can be removed, typically by hydrolysis, either by a biological process or by natural chemical decomposition, to release the free functional group and thus
 20 the active principle.

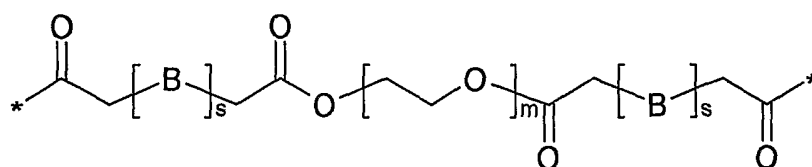
Preferably the compounds will be connected to the polymer by means of a linker. The linker may be formulated to assist in release of the anaesthetic molecule from the conjugate. For example, the anaesthetic molecule may be coupled via an ester bond which is cleaved by esterases such as lipases within the cell so that the anaesthetic molecule is rapidly
 25 released from the polymer.

Different rates of release are required depending on the anaesthetic compound being used and the therapeutic purpose.

The linker may be an amino acid. This may endow some enzyme specificity on release of the drug from the complex in addition to release based on chemistry dependent on
 30 other bonds being present. The linker can contain several amino acids in sequence (i.e. be a

peptide) to confer greater enzymatic selectivity. Examples include amino acid sequences recognised by specific peptidases eg cathepsin.

Particularly preferred conjugates according to the invention are polymers comprising units of formulae (I) and (II):



5

(I)

and



(II)

wherein B is selected from oxygen, sulphur, alkyl, alkyl ether, alkyl thioether, hydroxyl alkyl and
10 alkyl aryl;

s independently represents 0 or an integer of 1 to 100;

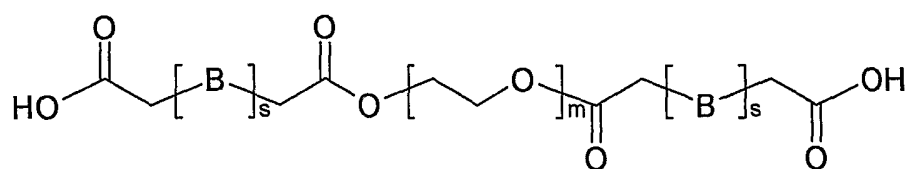
m is an integer of 1 to 1000;

n is 0 or an integer of 1 to 100; and

A is a functional group and Z is a compound of formula (I) as defined herein, in which Z is
15 connected to A by means of the ---OH group that R^3 , R^4 or R^5 may represent.

Polymers of this aspect of the present invention may comprise one or more different monomer units (I) and one or more different monomer units (II). For example the units (I) and (II) may contain different A and B groups.

Conjugates according to this aspect of the invention may be prepared by a process
20 comprises co-polymerising one or more first monomers (I'):

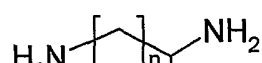


(I')

or an analogue derived from a branched PEG,

or an activated derivative thereof;

25 with one or more second monomers (II'):



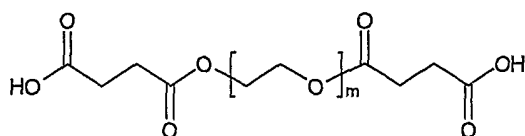
(II')

The invention also provides co-polymers obtainable by and obtained by said process.

Preferably the two carboxylic acid moieties of the diacid monomer (I') are activated.

Suitable activating groups will be well known to a skilled person. For example, they may
5 suitably be activated by treatment with N-hydroxysuccinimide.

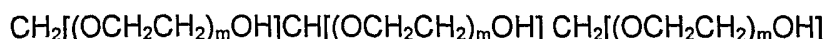
A polymer of the invention may be prepared by methods that are generally known. A typical example includes the polymerisation of a diacid and a diamine. The diacid shown below, which is illustrative of the type of diacid that may be employed according to this aspect of the invention, may be polymerised with a diamine containing substituents. A typical
10 example of a diamine is lysine. The diacid will typically have a range of values for m, the exact range mixture affecting the physical properties of the polymer produced. In one embodiment of this invention the average molecular weight of the PEG unit is 1500, which corresponds to an average value for m of 34. In other embodiments of this invention the PEG unit can have, but is not limited to, an average molecular weight of 200, 400, 600, 800, 900, 2000, 3000 and
15 4000 which corresponds to average values of m of 4.5, 9, 13.6, 18, 20.5, 45.5, 68 and 91.



20 The diacid component used in the polymerisation can be selected from a range of diacids made from different batches of PEG with different average values of m. Additionally, branched PEG can also be used, in this case the amount of diamine used in the polymerisation step is adjusted to take account of the additional acid groups introduced by the additional PEG chains.

25 Branched PEG's, which are commercially available, are generally prepared by incorporating a cross-linking monomer into the polymerisation mixture. An example of a suitable cross-linking monomer is glycerol.

For example, a simple branched PEG would be of formula



30 In one preferred embodiment of this invention the diamine is a derivative of lysine, where the two amines of the lysine become part of the polymer backbone and the acid group of the lysine has been added to a therapeutic entity (or other component), preferably through a linker such as 5-amino valeric acid. There may also be additional elements in the linker between the therapeutic and the polymer chain such as a hemiacetal group, amino acid or
35 peptide.

A typical procedure for the preparation of the polymer of the invention involves prior activation of the diacid component as an acid chloride, acid bromide, acid fluoride, or as an

active ester such as a N-hydroxysuccinimide. Alternatively the diacid can be activated in-situ using reagents commonly used for the preparation of amide bonds in peptide synthesis. Further, the polymerisation may be carried out by heating the diacid and diamine components together to dehydrate the material to effect polymerisation. The preferred method for this invention is to activate the diacid prior to use, so that the activated material can be purified and stored for use at a later stage. The preferred activation method is to form the N-hydroxysuccinimide ester from N-hydroxysuccinimide, di-isopropylcarbodiimide and the diacid in dichloromethane. The activated diacid can then be reacted with diamine in the ratio of one diacid to one diamine to provide the polymer of the invention. By controlling the exact ratio of diacid to diamine, different molecular weights can be achieved. It is possible that by limiting the diamine ratio to less than one to one of diacid, that the material will contain cyclic material. The molecular weight can also be controlled by varying the polymerisation conditions, such as temperature, time, concentration and by the addition of components which can stop the polymerisation, such as water, mono-amine, alcohols and alkoxide. As is discussed in more detail later in the specification, by the addition of branching (cross-linking) units, such as a tri-amine, the molecular weight can be increased dramatically. In these cases, the ratio of diacid to diamine must be adjusted to take into account the addition of the branching agent, which in the case of a tri-amine branching unit would reduce the amount of diamine required. The aim in this case is to keep the total amine content (triamine plus diamine) the same as with the diamine alone.

If an excess of activated diacid is used, then the termini of the polymer chains will have activated acid groups at the ends. Alternatively additional activated diacid can be added at the end of the bulk polymerisation to achieve a similar result, generally a polymer with higher molecular weight. The termini can then be reacted with further components, such as cell targeting agents, proteins, peptides, saccharides, polysaccharides or cross linking reagents such as tri-amines.

Preferably the co-polymer contains amine equivalents to acid equivalents in a ratio of 1:1 or (1:1)+1 or (1:1)-1 to take account of the fact that the termini of the polymer may be formed from the diacid monomer or the diamine monomer or one may be diacid monomer and the other may be diamine monomer. When the monomers are straight chain then this ratio will be the ratio of monomers will be (I') to (II'). However when cross linking components are used (whether acid or amine) then a correction will need to be applied accordingly.

In some cases the polymers are preferably straight-chain. In other cases they are preferably cross linked. The polymer may also be cyclic (in which case the ratio is 1:1). In order to make it more likely that one of the monomers forms the termini then an excess of that monomer can be used.

The termini of the polymer may be derivatised (capped) e.g. an acid terminus with an alcohol (to form an ester) or an amine (to form an amide) and/or an amine terminus with an acid (to form an amide).

Advantageously the polymer may be capped with a substance K capable of usefully
5 modifying the properties of the polymer. Example polymer property modifying agents include targeting agents. Such a targeting agent K will be an agent capable of directing or aiding direction of the polymer to the target for the therapeutic agent. Examples of targeting agents include cell adhesion moieties. Such substances can assist with intracellular delivery. Of particular interest in the context of the present invention are targeting agents which can direct
10 the polymer to neuronal cells, for example a neuronal cell adhesion moiety e.g. a sensory nerve adhesion moiety. Particular examples of nerve adhesion moieties include: antibodies and in particular those which have affinity for nerve cell membranes, lectins such as lectins derived from vertebrates, mammals or humans or other lectins such as plant lectins, and in particular wheat germ agglutinin, hormone receptor ligands, cytokines, growth factors, such as
15 nerve growth factor, epidermal growth factor and insulin-related growth factors, neuropeptides such as endorphins, vasoactive intestinal polypeptide, calcitonin, cholecystokinin, substance P, somatostatin, neuropeptide Y, fragments of neurotrophic viruses such as viral coat proteins of herpes simplex virus, polio virus, rabies virus or fragments thereof, bacterial toxins and in particular non-toxic fragments thereof such as cholera toxin B chain and tetanus toxin
20 fragment C, or fragments thereof.

For example if the polymer has at least one acid termini then the termini may be reacted with a substance bearing amine groups e.g. a protein with surface lysine residues. Examples include lectins such a wheat germ agglutinin. It may be necessary to activate the acid termini to facilitate reaction e.g. by reaction with N-hydroxysuccinimide.

25 Peptides as well as proteins may also conveniently be used as capping groups, and may readily be attached when the terminus is an amine or an acid.

Other capping groups of particular interest include saccharides especially mono and disaccharides.

In another embodiment of this aspect of the invention K is an agent capable of
30 enhancing the solubility of the polymer e.g. a polyethylene glycol or a derivative thereof.

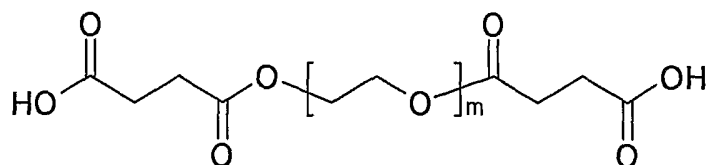
Preferably the polymer contains up to 10,000 especially up to 1000 repeats of each unit. Preferably the polymer contains at least 5, more preferably at least 10 repeats of each unit. Most preferably the number of each unit is 10-30 especially 15-20.

The molecule weight of polymer conjugates according to this aspect of the invention
35 will typically be in the range 6kDa to 2000kDa, preferably 15kDa to 250kDa excluding the contribution of the further components conjugated to A or any terminal capping groups. The total molecular weight of the polymer (including further components and capping groups) will typically be in the range 10kDa to 2500kDa, preferably 25kDa to 300kDa.

In polymers of this aspect of the invention, examples of [B]s include O and $(\text{CH}_2)_{1-3}$ e.g. CH_2 . However preferably s represents 0. Preferably n represents 1 to 10, more preferably 3-6 eg 4.

Thus monomer (I') is preferably a compound of formula:

5

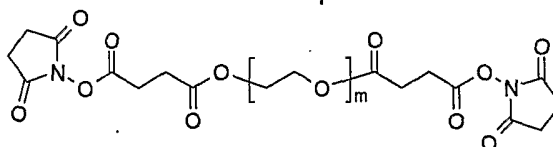


or an analogue derived from a branched PEG,

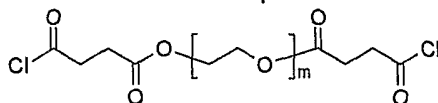
or an activated derivative thereof. Preferably m represents an integer 20-100, especially 30-40.

The preferred activated derivative is a compound of formula:

10



An alternative activated derivative is a compound of formula:



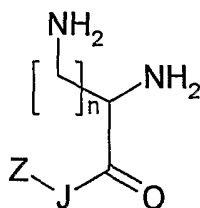
Preferably m represents an average integer of 20-100, especially 30-40.

This monomer is particularly favoured since it is capable of degradation to PEG and succinic acid products, which are physiologically benign.

The carboxylic acid groups of monomer (I') are preferably activated. Such monomers can be prepared by treating a polyethylene glycol (PEG) with succinic anhydride under standard conditions. For example the reagents may be mixed in the presence of dimethylaminopyridine (DMAP) in an inert solvent such as dichloromethane (DCM). A suitable PEG is PEG 1500 (average molecular weight 1500) which results in a value m of around 34. PEG's for use in preparing the copolymers of the invention are commercially available.

The functional group A preferably comprises a carbonyl moiety, i.e. it is derived from a carboxy group, and optional linker J such that a preferred monomer (II') is a compound of the formula:

25



wherein J is an optional linker and Z is a compound of formula (I) as defined herein wherein J-CO is connected to Z by means of the -OH group that R³, R⁴ or R⁵ may represent.

J therefore represents a linker or a bond but preferably J represents a linker.

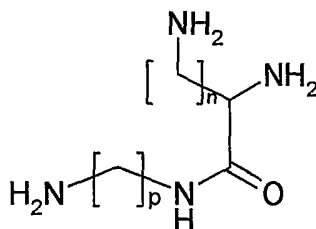
Preferably n represents an integer of 1 to 10, especially 3 to 6 particularly 4.

5 When J represents a linker it preferably represents the group J¹-J²-J³.

Suitable linkers include amino acids, peptides or a chain such as 6-aminohexanoic acid, 5-aminopentanoic acid, 4-aminobutanoic acid and 3-aminopropanoic acid. 5-Aminopentanoic acid is a particularly preferred linker.

Examples of other linkers that may usefully be used include those described in US
10 6,214,345.

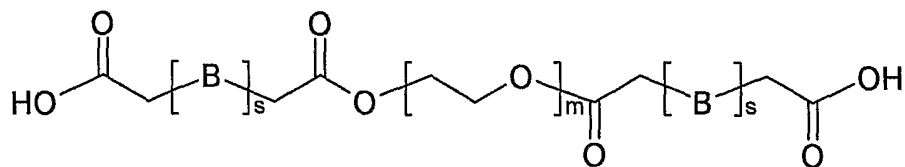
Additionally, tri-functional groups such as tri-amines can be added to the polymerisation mix to increase cross-linking, e.g. compounds of the formula:



Wherein preferably n represents 1 to 10, more preferably 3-6, especially 4 and p represents 1 to 10, more preferably 3-6 especially 4.

15 Cross linking may have a significant effect on polymer properties which would be understood by those skilled in the art of polymer chemistry. Solubility and molecular weight in particular may be altered. The degree of cross-linking also has an impact on biodegradability which would also be understood by someone skilled in the art of polymer therapeutics and delivery systems.

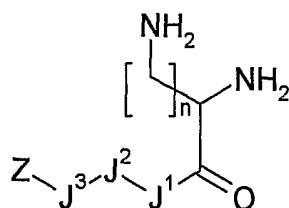
20 Thus according to a preferred aspect of the invention there is provided a process for preparing a polymer which comprises co-polymerising one or more first monomers (I'):



or an analogue derived from branched PEG,

or an activated derivative thereof;

25 with one or more second monomers (II'')



The invention also provides polymers obtainable and obtained by such a process.

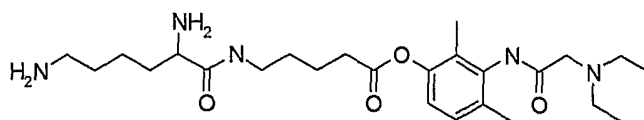
Drug moiety Z contains a free hydroxyl group which allows it to be connected to the diamine via linker J¹-J²-J³ if present. Z may then be released from the polymer by hydrolysis of the ester connection.

- 5 J¹ preferably represents a sulphur, oxygen or an amino group (e.g. NH or NMe, preferably NH), preferably oxygen or an amino group, especially an amino group. J² preferably represents a spacer group. J³ preferably represents a carbonyl group. This permits Z to be released from the polymer by hydrolysis of the ester connection between J³ and Z. Spacer group J² may represent an alkylene group e.g. a C₁₋₁₀alkylene group e.g. –
- 10 (CH₂)₃₋₆. The preferred linker J¹-J²-J³ is –NH(CH₂)₄CO–.

It will be understood that polymers according to the invention may be prepared in which more than one monomer (I') (which monomers may, for example, differ in chain length m) with more than one monomer (II') (which monomers may, for example, differ in values for n and nature of (I)).

- 15 Typically monomer (I') comprises a dispersion of chain length m based on the dispersion of the polyethylene glycol from which it is derived.

A preferred diamine monomer has the formula:



- 20 For most purposes it will be most suitable to use a single monomer (II'). However a further aspect of the invention provides the formation of multi-functional polymers in which different functional groups A are incorporated through use of two or more monomers (II').

For example, therapeutic agent Z could be different for different second monomers (i.e. the polymer would comprise more than one therapeutic agent) if combination therapy were

25 desired.

- An advantageous feature of the polymers of the present invention is that synthesis is ready and efficient. As described above, components such as therapeutically active agents, targeting agents and the like may be incorporated into the polymer by incorporating such components into monomer (II'). Alternatively it may be preferred to incorporate a precursor of
- 30 the component into the monomer, and hence into the polymer, and then convert the precursor to the component after polymerisation. In this connection, precursors include derivatives such as protected derivatives and other chemical intermediates. For example it may be desired or

necessary to incorporate the compound of formula (I) into monomer (II') in protected form and to deprotect it after polymerisation has taken place.

During the synthesis of the compounds and polymers of the invention labile functional groups in the intermediate compounds, e.g. hydroxy, carboxy and amino groups, may if
5 desired or necessary, be protected. A comprehensive discussion of the ways in which various labile functional groups may be protected and methods for cleaving the resulting protected derivatives is given in for example *Protective Groups in Organic Chemistry*, T.W. Greene and P.G.M. Wuts, (Wiley-Interscience, New York, 2nd edition, 1991).

Certain monomers are new and are claimed as an aspect of this invention.

10 As a further aspect of the invention we provide polymers which incorporate anaesthetic substances as herein described for use in therapy. We also provide pharmaceutical compositions comprising a polymer incorporating an anaesthetic substance as hereinafter described together with a pharmaceutically acceptable diluent or carrier.

Polymers incorporating anaesthetic substances according to the present invention may
15 be administered in therapy by whatever route of administration and in whatever presentation may be deemed most suitable.

For example formulations for parenteral injection may comprise a polymer according to the present invention dissolved in an aqueous carrier. The aqueous carrier may include conventional excipients such as buffers, preservatives and the like.

20 Injectable anaesthetic compositions may be administered as liquid solutions or suspensions. Solid forms suitable for solution or suspension in liquid prior to injection may also be prepared. The preparation may be emulsified.

Suitable diluents or carriers for use in compositions according to the invention will be known to those skilled in the art. For example diluents and carriers for anaesthetic
25 compositions suitably include water, saline, dextrose, glycerol, ethanol or the like and combinations thereof. An additional composition may contain minor amounts of auxiliary substances such as wetting or emulsifying agents, pH buffering agents and antibacterial agents (eg thimerosal).

Anaesthetic compositions are administered parenterally, by injection, for example
30 subcutaneously, intercostally, intramuscularly, intravenously or by epidural or spinal injection. Alternatively, the compositions may be formulated for topical administration and in particular for administration to a mucosal surface such as oral, rectal, vaginal or nasal administration. Additionally the anaesthetic compositions can be administered orally in tablet form. The compositions may also be delivered intradermally, for example using a needleless injector
35 device.

The compositions are administered in a manner compatible with the dosage required and in such amount as will be therapeutically or prophylactically effective. The quantity to be administered, which is generally in the range 5µg/kg to 10g/kg, preferably 250µg/kg to

30mg/kg per dose depends on a number of factors. These include the subject to be treated, and the degree of therapeutic or prophylactic activity desired and, if applicable, the size of the area to be treated. Precise amounts of active ingredient required to be administered may depend on the judgment of the practitioner and may be peculiar to each subject.

5 Depending on the therapeutic substance and the condition being treated, compositions of the present invention may also potentially be administered by the ocular, intraocular, intrathecal and intraarticular routes.

Further aspects of the invention include the use of polymers incorporating anaesthetic agents according to the invention in the manufacture of a medicament for the treatment of a
10 pain, eg neuropathic pain and a method of treatment of pain, eg neuropathic pain which comprises administering to a patient a polymer incorporating an anaesthetic agent according to the invention.

The conjugates of the invention have the advantage that they may have longer duration of action, may effect more complete drug release, may more rapidly release drug, may be
15 more biodegradable, may be more benign or otherwise less toxic, are susceptible to more ready or economic synthesis or have other advantages over prior art conjugates.

All documents referred to herein, including patents and patent applications, are incorporated herein in their entirety by reference.

Further details and embodiments concerning polymers conjugates containing
20 compounds according to the present invention may be obtained from a co-pending patent application in the name of the same inventors and filed on the same day entitled "Biodegradable Polymers" which is herein incorporated in its entirety by reference.

Abbreviations:

WGA	Wheat Germ Agglutinin	DCM	dichloromethane		
25 DIC	Diisopropylcarbodiimide	CBZ	benzyloxycarbonyl		
NHS	N-hydroxy-succinimide	NMM	N-methyl morpholine	Boc	t-butyloxycarbonyl
DMF	dimethylformamide	DMAP	dimethylaminopyridine	Ac	acetyl
PEG	polyethyleneglycol	Me	methyl	Et	ethyl
Su	NHS active ester	TFA	trifluoroacetic acid	Suc	succinyl
30 GPC	Gel permeation chromatography				

Description of the Figures:

Figure 1 shows analytical data for a 3-hydroxy-lidocaine polymer conjugate as per Example 1. Figure 1A shows the polymer with atom assignments, Figure 1B shows the NMR spectrum and Figure 1C shows a GPC spectrum.

35 Figure 2 shows a comparison of the effect on paw withdrawal latency of the 3-hydroxylidocaine polymer conjugate of the present invention (Example 1) with free 3-hydroxylidocaine and control.

Figure 3 shows a linear plot of the plasma concentrations of 3-hydroxylidocaine following intravenous administration of free 3-hydroxylidocaine and 3-hydroxylidocaine polymer conjugate.

Figure 4 shows a log/linear plot of the plasma concentrations of 3-hydroxylidocaine following intravenous administration of free 3-hydroxylidocaine and 3-hydroxylidocaine polymer conjugate.

Figure 5 shows a linear plots of the plasma concentrations of 3-hydroxylidocaine following intramuscular administration of free 3-hydroxylidocaine and 3-hydroxylidocaine polymer conjugate.

Figure 6 shows a log/linear plots of the plasma concentrations of 3-hydroxylidocaine following intramuscular administration of free 3-hydroxylidocaine and 3-hydroxylidocaine polymer conjugate.

Figure 7 shows a plot of percentage release of 3-hydroxylidocaine from 3-hydroxylidocaine polymer conjugate against time under two aqueous conditions.

The invention will now be illustrated by reference to the following examples:

Examples

Analytical methods

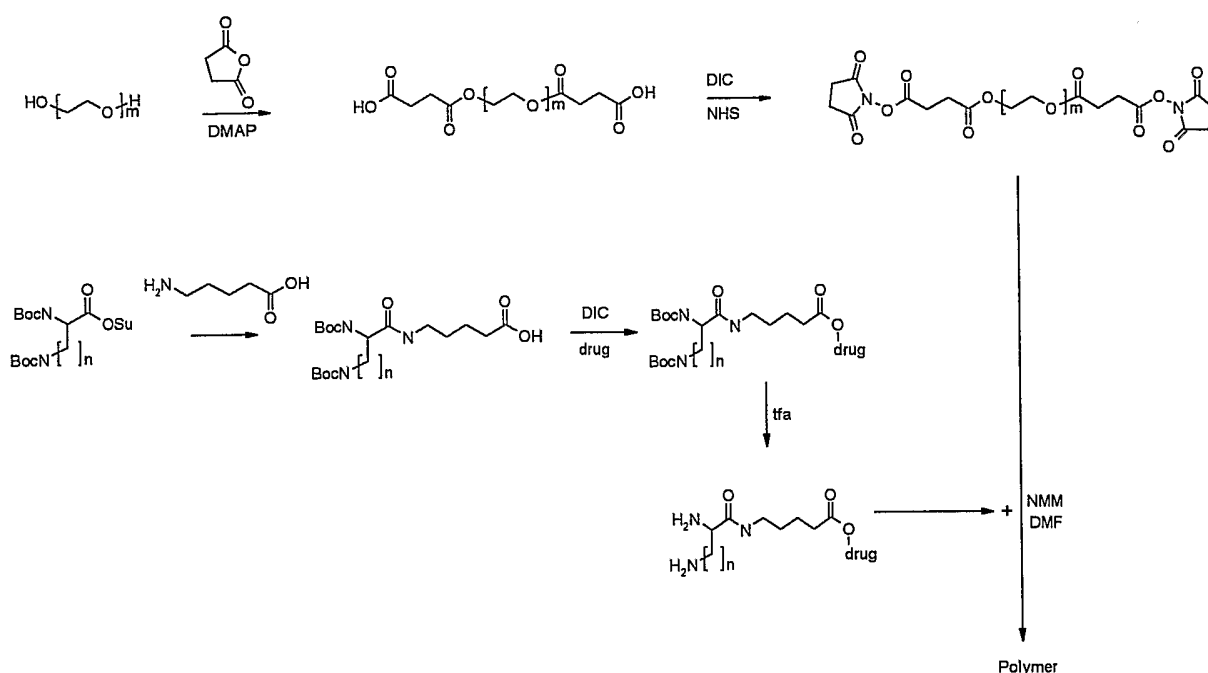
¹³C NMR spectra were obtained on a Bruker Analytik GmbH Avance 500 machine.

Spectra were run with samples dissolved in CDCl₃.

The GPC method was as follows: Viscotek GMPWXL guard and two GMPWXL columns were used. The solvent system was [(10% acetonitrile 90% water) 0.1% formic acid] used at 0.8ml/min, with a run time of 35 min. The system was then allowed to re-equilibrate for 15 min. before the next run. The samples were made to 10mg/ml in water and 100uL was injected. The detector used was a Viscotek Triple detector, model 301 TDA and PEO 25.8k and 80k were used as standards to check the machine.

Processes

Processes for preparing certain preferred conjugates according to this invention are illustrated by reference to the following flow chart:



Example 1

Conjugate of polymer with 3-hydroxylidocaine

(a) Preparation of poly(ethylene glycol)-bis succinic acid

- 5 Polyethylene glycol (Mw = 1500, 119 g), succinic anhydride (24.0 g, 237.6 mmol, 3.0 eq) and DMAP (1.0 g, 8.20 mmol, 0.1 eq) were dissolved in DCM (300 mL). The solution was then heated to reflux and left at reflux for 48h. The precipitate that formed was then filtered off and the filtrate concentrated to give a white solid, the crude diacid product. Purification via precipitation and reverse phase chromatography yielded the PEG diacid compound.

10 (b) Preparation of N-hydroxysuccinimide activated bis (succinic acid) poly(ethylene glycol) ester

- The bis (succinic acid) poly(ethylene glycol) ester (1.3 g), DIC (362 μ L, 3 eq), DMAP (1 mg, 0.01 eq) and N-hydroxysuccinimide (266 mg, 3.0 eq) were dissolved in dry DCM (10 mL) and stirred overnight. The reaction was then concentrated down and acetonitrile added. The solution was filtered, concentrated and precipitated to yield bis (succinic acid N-hydroxysuccinimide ester) poly(ethylene glycol) ester.

(c) Preparation of Boc-lysine(Boc)-5aminopentanoic acid

- 5-Aminovaleric acid monohydrochloride (693 mg, 4.5 mmol, 1.0 eq) was dissolved in water (15 mL) and MeCN (10 mL). Sodium carbonate (478 mg, 4.5 mmol, 1.0 eq) was added as a solution in water (5 mL), followed by Boc-Lys(Boc)OSu (2.0 g, 4.5 mmol, 1.0 eq) as a solution in MeCN (20 mL). The reaction was then left to stir overnight. The reaction mixture was concentrated and water added before being extracted with ethyl acetate (3 x 50 mL). The combined organic layers were then washed with 0.01N HCl (2 x 50 mL), brine, dried over

MgSO₄ and concentrated. Purification by normal phase chromatography yielded the product (1.6g, 80%).

(d) Boc-lysine(Boc)-(5-aminovaleric acid) coupling to 3-hydroxy lidocaine

Boc-lysine(Boc)-5-aminovaleric acid (1.63 g, 3.66 mmol) was dissolved in dry DCM (16 mL). To this was added DIC (573 μ L, 3.66 mmol, 1.0 eq) and DMAP (58 mg, 0.48 mmol, 0.13 eq). The now cloudy solution was left to stir for 15 min. 3-Hydroxylidocaine lidocaine (1.01 g, 4.03 mmol, 1.1 eq) was added as a solution in DCM. This was then left to stir overnight. The solvent was evaporated, the residue dissolved in ethyl acetate and washed with water. The organic layer was then washed with a weak base solution, dried and evaporated to dryness. Purification via reverse phase chromatography yielded the product (pale yellow solid, 1.85 g, 75%).

(e) Deprotection of BocLys(Boc)-(5-aminovalerate)-3-hydroxy-lidocaine ester

The BocLys(Boc)-(5-aminovalerate)-3-hydroxy-lidocaine ester (0.20 g, 0.29 mmol) was dissolved in TFA:water (95:5, 10 mL) and stirred at room temperature for 30 min. The solvents were evaporated, the residue taken up in water (15 mL) and freeze dried to give the deprotected material.

(f) Polymerisation of Lys-(5-aminovalerate)-3-hydroxy-lidocaine ester with bis (succinic acid N-hydroxysuccinimide ester) poly(ethylene glycol) ester

The Lys-(5-aminovalerate)-3-hydroxy-lidocaine ester (0.12 g, 0.15 mmol) and bis (succinic acid N-hydroxysuccinimide ester) poly(ethylene glycol) ester (0.28 g, 0.15 mmol) were dissolved in DMF (400 μ L) and treated with NMM (64 μ L, 0.58 mmol). The oil was left to stand overnight, then precipitated from ether. The resulting polymer was dried on high vac line for 30 min.

¹³C NMR and GPC analytical data on the product are shown in Figure 1. Typical GPC data are as follows: Mn = 17.5k, Mw = 27.0k, Mz = 40.2k, Mp = 21.8k, Pd = 1.54, IVw = 0.4127, dn/dc set to 0.147, calculated concentration was 10.38mg/ml. The small peak to the left of the main peak represents an impurity (N-methylmorpholine hydrochloride). This can be removed by dissolving the polymer in toluene, filtering the polymer conjugate solution to remove the impurity, and then re-precipitating the polymer conjugate with ether.

30

Example 2

Conjugate with 3-hydroxylidocaine and wheatgerm antigen (WGA)

(a) Preparation of poly(ethylene glycol)-bis succinic acid

This was prepared as for Example 1, part (a).

35 (b) Preparation of N-hydroxysuccinimide activated bis (succinic acid) poly(ethylene glycol) ester

This was prepared as for Example 1, part (b).

(c) Preparation of Boc-lysine(Boc)-5-aminovaleric acid

This was prepared as for Example 1, part (c).

(d) Boc-lysine (Boc)-5-aminovaleric acid coupling to 3-hydroxy lidocaine

Boc-lysine (Boc)-5-aminovaleric acid (1.63g, 3.66 mmol) was dissolved in dry DCM (16 mL). To this was added DIC (573 μ L, 3.66 mmol, 1.0 eq) and DMAP (58 mg, 0.48 mmol, 0.13 eq). The now cloudy solution was left to stir for 15 min. 3-Hydroxylidocaine lidocaine (1.01g, 4.03 mmol, 1.1 eq) was added as a solution in DCM. This was then left to stir overnight. The solvent was evaporated, the residue dissolved in ethyl acetate and washed with water. The organic layer was then washed with a weak base solution, dried and evaporated to dryness. Purification via reverse phase chromatography yielded the product (pale yellow solid, 1.85g, 10 75%).

(e) Deprotection of BocLys(Boc) -(5-aminovalerate)-3-hydroxy-lidocaine ester

The BocLys(Boc)-(5-aminovalerate)-3-hydroxy-lidocaine ester (0.20g, 0.29 mmol) was dissolved in TFA:water (95:5, 10 mL) and stirred at room temperature for 30 min. The solvents were evaporated, the residue taken up in water (15 mL) and freeze dried to give the 15 deprotected material.

(f) Polymerisation of Lys-(5-aminovalerate)-3-hydroxy-lidocaine ester with bis (succinic acid N-hydroxysuccinimide ester) poly(ethylene glycol) ester

The Lys-linker-3-hydroxy-lidocaine ester (0.15 mmol) and bis (succinic acid N-hydroxysuccinimide ester) poly(ethylene glycol) ester (0.165 mmol) were dissolved in DMF 20 (400 μ L) and treated with NMM (64 μ L, 0.58 mmol). The oil was left to stand overnight, then precipitated from ether. The resulting polymer was dried on high vac line for 30 min.

(g) Coupling of Wheat Germ (WGA) to PEG-3-hydroxy-lidocaine ester polymer

WGA (45mg, 0.92 eq) was dissolved in water (3mL) and the pH adjusted to 7.6 with 0.1N NaOH. This was then added to a flask containing the PEG-lidocaine polymer (product of 25 step (f)) (75mg, 1.0 eq). The solution was allowed to dissolve before being freeze-dried overnight. Water (7 mL) was then added followed by lysine hydrochloride (5mg) to quench excess NHS active ester present. After being swirled for a few min the solution was then freeze-dried again.

30 Example 3

For syntheses described herein it may be advantageous to employ a cross-linking agent.

Example of the synthesis of a crosslinking agent.

Preparation of Boc-Lys(Boc)-CONH-butyl-NHBoc

35 N-Boc-1,4-diaminobutane monohydrochloride (430 mg, 2.25 mmol, 1.0 eq) was dissolved in water (15 mL) and MeCN (10mL). Sodium carbonate (120 mg, 1.12 mmol, 0.5 eq) was added as a solution in water (5 mL), followed by Boc-Lys(Boc)OSu (1.0 g, 2.25 mmol, 1.0 eq) as a solution in MeCN (20 mL). The reaction was then left to stir overnight. The reaction

mixture was concentrated and water added before being extracted with DCM (3 x 50 mL). The combined organic layers were then washed with 0.01N HCl (2 x 50 mL), brine, dried over MgSO_4 and concentrated. Purification by normal phase chromatography yielded the product (white foam, 1.0 g, 86%).

5 Deprotection of Boc-Lys(Boc)-butyl-NHBoc

Method as for deprotection of BOC-Lys(BOC)-(5-aminovalerate)-3-hydroxy-lidocaine ester.

Biological Data

10 Example 4

Test of paw withdrawal latency for 3-hydroxylidocaine polymer conjugate

Subjects and Surgical Procedures

Male Harlan Sprague-Dawley rats were used (150-250g). Rats were housed 4-5 per cage and provided with food and water ad libitum with a 12hr/ 12hr day/night cycle.

- 15 To induce neuropathy, rats were anaesthetised with halothane/oxygen mix and the common sciatic nerve was exposed at the level of the mid thigh through the biceps femoris in a method similar to that reported (Bennett & Xie, Pain (1988) 33:87-107). The sciatic nerve was freed of connective/adhering tissue and loosely ligated three times with 4-0 G chromic cat gut suture approximately 1mm apart. The wound is then sutured. The chronic constriction injury (CCI)
- 20 model in rats is associated with hyperalgesia, allodynia and spontaneous pain and constitutes a model for peripheral neuropathic pain in humans.

Behavioural Observations

- Animals were tested pre-operatively for baseline paw withdrawal latency (PWL) responses to thermal stimulation using a Ugo Basile Hargreaves apparatus (Hargreaves, et al.,
- 25 (1988) Pain 32:77-88) which consisted of 3 separated holding boxes, each approximately 25 cm by 20 cm placed over a glass floor elevated to accommodate a mobile infrared radiant heat source underneath. Animals were given 10 minutes to acclimatise and explore their testing environment before the radiant heat source was aimed at the plantar surface of the hind paw. On appreciation of a noxious stimulation the animal withdraw the hind paw which interrupts the
- 30 reflected light to the photocell and stops the timer. Three latency measurements were recorded on each hind paw. Following chronic constriction injury, as outlined above, animals evolved hyperalgesic state on the injured side (left) over 5-7 days at which point the separation of paw withdrawal latency between ipsilateral ("ips") and contralateral ("con") sides stabilised. Test materials were administered once the PWL on the injured side stabilised.
- 35 The antihyperalgesic effect of free 3OH-lidocaine given via the intraperitoneal route was evaluated in the CCI model during chronic dosing over 4 consecutive days. The test material was made up to a stock concentration of 4.5 mg/ml in distilled water. On the first treatment day the animals were administered an equivalent of 15 mg/kg and thereafter received 7.5 mg/kg on

the subsequent 3 days treatment. Likewise, gabapentin was administered chronically over 4 days by the intraperitoneal route at a dose of 50 mg/kg per day. Testing of thermal hyperalgesia was performed approximately 45 minutes post dose. 3OH-lidocaine in a polymer according to the present invention (as per Example 1) was given as a single dose
 5 intramuscularly at 120 mg/kg. This dose of polymer delivers an equivalent of 20 mg/kg of 3-hydroxylidocaine.

Administration of gabapentin on day 1 of treatment produced an increase in PWL indicating a suppression of the thermal hyperalgesic state on the injured paw (Figure 2). No corresponding effect was seen in the non-injured PWL response. The measured antihyperalgesic effect on
 10 subsequent treatment days was less pronounced. Free 3-hydroxylidocaine produced a consistent antihyperalgesic effect through treatment which was lost on cessation of treatment. Treatment with a single dose of polymer 3-hydroxylidocaine provided an antihyperalgesic effect similar to that produced by 15 mg/kg free 3-hydroxylidocaine i.p. on day 1 of treatment and a sustained antihyperalgesic effect for the next 4 days.
 15 Data showing a comparison of the effect on paw withdrawal latency of the 3-hydroxylidocaine polymer conjugate of the present invention (Example 1) when measured on the isp and con sides with free 3-hydroxylidocaine and saline control is shown in Figure 2.

Example 5

20 Pharmacological study of 3-hydroxylidocaine polymer conjugate

Male Sprague-Dawley rats, supplied by Charles River UK Ltd, were used for pharmacodynamic studies. On the day of study the animals were in the weight range 254-283g and approximately 8 weeks old.

The test materials were dissolved in distilled water at the highest concentration
 25 required. These were 12.5 mg/ml for 3-hydroxylidocaine and 60 mg/ml for a polymer conjugate of the present invention containing 3-hydroxylidocaine polymer (as per Example 1). For the free drug, the hydrogen chloride salt of 3-hydroxylidocaine was used and allowance was made for this in preparation of doses.

These stocks were used as prepared for intramuscular administration. For intravenous
 30 administration appropriate dilutions were made using distilled water to give solutions of 1 and 10 mg/ml for 3-hydroxylidocaine and the polymer conjugate, respectively.

Four groups of three male rats were dosed as indicated below:

Group No.	Treatment	Dose (mg/kg)	Route
1	3-hydroxylidocaine	2	i.v.
2	3-hydroxylidocaine	25	i.m.
3	Polymer conjugate	20	i.v.

4	Polymer conjugate	120	i.m.
---	-------------------	-----	------

The doses were administered as a single bolus dose at a constant dose volume of 2 mL/kg into a tail vein not used for blood sampling or (for i.m.) in the rear leg muscle. Doses of 3-hydroxylidocaine are expressed as free base.

- 5 Following dosing, serial blood samples (approximately 0.3ml) were obtained from each rat via a cannula which had been previously inserted into a lateral tail vein not used for dosing. Blood samples were taken into individual heparinised containers at the time points shown.

Following collection, blood samples were centrifuged and plasma retained and stored at -20°C for bioanalysis of plasma 3-hydroxylidocaine using an LC-MS/MS methodology.

- 10 Liquid chromatography was carried out using a C8, 5micrometer, 30 x 4.6 mm analytical column. Mobile phase consisted of 10 mM ammonium acetate and methanol. The MS/MS conditions were; Ionisation mode, electrospray in +ve ion mode; m/z 251.3 → m/z 86.3 (collision energy 27 eV). No unusual clinical signs were observed in any of the intravenously or intramuscularly dosed animals.

- 15 Linear plots of the plasma concentrations of 3-hydroxylidocaine following intravenous administration and intramuscular administration of 3-hydroxylidocaine or 3-hydroxylidocaine polymer conjugate are shown in Figures 3 and 4 respectively. Log/Linear plots of the plasma concentrations of 3-hydroxylidocaine following intravenous administration and intramuscular administration of 3-hydroxylidocaine or 3-hydroxylidocaine polymer conjugate are shown in
20 Figures 5 and 6 respectively. 3-OH is the code for the free 3-hydroxylidocaine HCl salt sample and SGX355 is the code for the 3-hydroxylidocaine polymer conjugate (Example 1) sample.

- Following intravenous administration of 3-hydroxylidocaine the mean maximum plasma concentrations at 5 minutes post-dose was 892 ng/mL. The plasma concentrations then
25 declined rapidly in a mono exponential fashion with no 3-hydroxylidocaine being detected in the plasma after 60 minutes post-dose. The calculated half life for this elimination was 0.2 hours.

- In the animals dosed intramuscularly with 3-hydroxylidocaine C_{max} was seen at 30 minutes post-dose (mean value 2110 ng/mL). Plasma concentrations of 3-hydroxylidocaine again
30 declined in a monoexponential fashion with no 3-hydroxylidocaine being detected in the plasma after 4 hours post-dose. The calculated half life for this elimination was 0.6 hours.

- Following intravenous administration of polymer the maximum plasma concentrations of 3-hydroxylidocaine were seen at 5 minutes post-dose (mean value 3322 ng/mL). The plasma concentrations then declined in a mono exponential fashion with low levels of 3-
35 hydroxylidocaine being detected in the plasma at 6 hours but none at 12 hours post-dose. In the rats treated intramuscularly with polymer conjugate the maximum concentrations of 3-hydroxylidocaine were seen at 2 hours post-dose (mean value 701 ng/mL). Plasma

concentrations of 3-hydroxylidocaine again declined with low levels of 3-hydroxylidocaine being detected in the plasma at 12 hours post-dose but none at 24 hours. The calculated half life for this elimination was 2.9 hours.

These data show that administration of the polymer conjugate increases the elimination half-life of 3-hydroxylidocaine compared with that seen following administration of the free base. As a result, 3-hydroxylidocaine was present in the plasma for a much longer period than seen following administration of the free base, 6 hours as opposed to 60 minutes and 12 as opposed to 4 hours in the intravenously and intramuscularly dosed animals, respectively.

10 Example 6

Drug release from 3-hydroxylidocaine polymer conjugate

A polymer conjugate according to the present invention, wherein the polymer contained 3-hydroxylidocaine (as per Example 1), was used to examine stability in various solutions. The polymer remains stable as a lyophilised powder. A plot of percentage release of 3-hydroxylidocaine from 3-hydroxylidocaine polymer conjugate against time is shown in Figure 7. When dissolved in distilled water or phosphate buffered saline solution (PBS), pH7.5, at 40 µg/ml concentration, less than 2% 3-hydroxylidocaine was released into the solution after 48 hours, with approximately 5% drug released after 6 days.

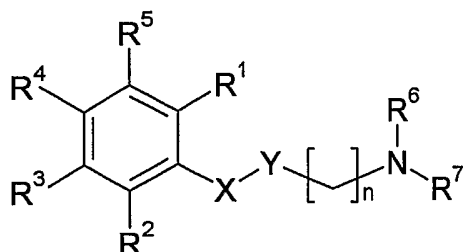
In a basic solution (Tris buffer, pH 9.5), 20% drug was released after 15 hours, 35% after 40 hours and 60% after 6 days. In plasma serum, all 3-hydroxylidocaine was released from polymer after approximately 24 h. Pre-heat treated plasma gave rise to a significantly reduced rate of release of drug from polymer. Thus, breakdown of polymer to produce free drug is catalysed by both enzymatic and chemical processes.

It was observed that in plasma obtained from animals that had been dosed intramuscularly with 3-hydroxylidocaine polymer the 3-hydroxylidocaine measured was dependent on downstream plasma handling. There appeared a discrepancy in the measured compound in those plasmas frozen immediately following in vivo sampling and analysed and those left at room temperature for, as example, >3 hours prior to bioanalysis. Moreover, the 3-hydroxylidocaine measured in samples left to incubate at room temperature was significantly greater than those maintained frozen. This observation would strongly suggest that plasma obtained from an intramuscularly dosed animal contained a mobile depot of polymer-bound 3-hydroxylidocaine as well as circulating free 3-hydroxylidocaine. Approximately 15% of the total 3-hydroxylidocaine present in the plasma is free during the first 6 hours post dose.

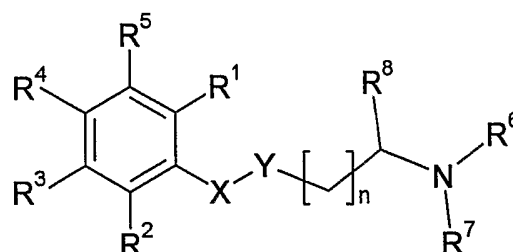
Claims

1. A conjugate of a polymer (P) and a local anaesthetic agent Z characterized in that the agent is an amine of any of the following formulae:

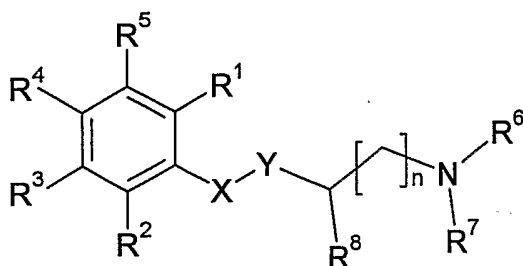
(I)



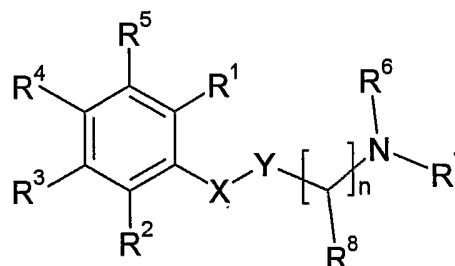
(II)



5 (III)



or (IV)



wherein:

R^1 and R^2 are independently selected from hydrogen, halogen, alkyl and alkyl ether groups;

10 X is C=O and Y is NR, or X is NR and Y is C=O, or X is C=O and Y is O, and R is selected from hydrogen, halogen, hydroxyl, alkyl, aryl and acyl;

R^6 and R^7 are independently selected from alkyl, aryl and alkylaryl groups; and

R^8 is selected from hydrogen, halogen, hydroxyl, alkyl, aryl and alkylaryl; or

R^7 and R^8 may be joined to form a ring 5, 6, 7 or 8 atoms in size;

15 n is 0, 1, 2, 3, 4 or 5; and

R^3 , R^4 and R^5 are each independently selected from hydrogen, hydroxyl, halogen, alkyl, aryl, hydroxyalkyl, hydroxyaryl, aminoalkyl and aminoaryl, with the proviso that at least one of R^3 , R^4 and R^5 is a hydroxyl moiety connected to the polymer (P) through a covalent bond.

2. A conjugate according to claim 1 wherein X-Y represents NHCO and R^1 represents alkyl.

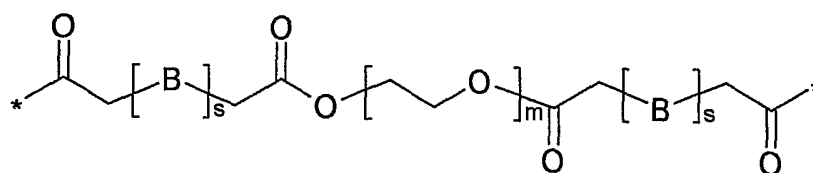
3. A conjugate according to claim 1 or claim 2 wherein R^2 represents alkyl.

4. A conjugate according to any one of claims 1 to 3 wherein one of R^3 , R^4 and R^5 represents hydroxyl and the others represent hydrogen.

5. A conjugate according to claim 4 wherein R^3 represents hydroxyl and R^4 and R^5 represent hydrogen.

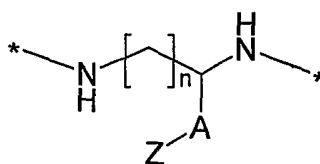
25 6. A conjugate according to any one of claims 1 to 5 wherein R^6 represents alkyl.

7. A conjugate according to any one of claims 1 to 6 wherein the amine is defined by structure (I), n represents 1 and R^7 represents alkyl.
8. A conjugate according to any one of claims 1 to 6 wherein the amine is defined by structure (II), n represents 0 and R^7 and R^8 are joined and represent $(CH_2)_4$.
- 5 9. A conjugate according to any one of claims 1 to 6 wherein the amine is defined by structure (III), n represents 0 and R^7 and R^8 independently represent alkyl.
10. A conjugate according to claim 1 wherein the amine is a derivative of lidocaine which bears a hydroxyl group on the benzene ring.
11. A conjugate according to claim 10 wherein the amine is 3-hydroxylidocaine.
- 10 12. A conjugate according to any one of claims 1 to 11 wherein the polymer (P) is a dextran.
13. A conjugate according to any one of claims 1 to 11 wherein polymer (P) is a PEG.
14. A conjugate according to any one of claims 1 to 13 wherein the amine is connected to the polymer through its hydroxyl group by means of a linker.
- 15 15. A conjugate according to any one of claims 1 to 11 wherein the polymer (P) is composed of units of formulae (I) and (II):



(I)

and



(II)

20

wherein B is selected from oxygen, sulphur, alkyl, alkyl ether, alkyl thioether, hydroxyl alkyl and alkyl aryl;

s independently represents 0 or an integer of 1 to 100;

m is 0 or an integer of 1 to 1000;

25 n is 0 or an integer of 1 to 100; and

A is a functional group and Z is a local anaesthetic agent, in which Z is connected to A by means of the hydroxyl moiety that R^3 , R^4 or R^5 may represent.

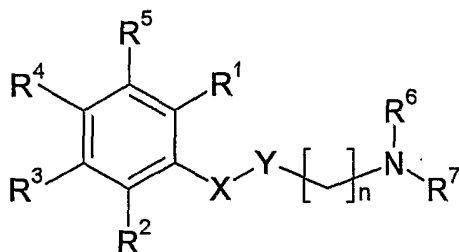
16. A conjugate according to claim 15 containing 5 or more repeats of each unit.

17. A conjugate according to claim 15 or claim 16 containing up to 10,000 repeats of each

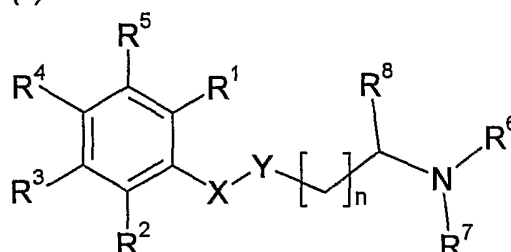
30 unit.

18. A conjugate according to any one of claims 15 to 17 wherein s represents 0.
19. A conjugate according to any one of claim 15 or 18 wherein m represents an integer 20 to 100.
20. A conjugate according to any one of claims 15 to 19 wherein n represents an integer 1 to 10.
21. A conjugate according to claim 20 wherein n represents 4.
22. A conjugate according to any one of claims 15 to 21 wherein the anaesthetic agent is connected to the polymer by means of a linker.
23. A process for preparing a conjugate according to any one of claims 1 to 14 which
- 10 comprises reacting a polymer optionally incorporating a linker or an activated and/or protected derivative thereof with a local anaesthetic agent Z of formula:

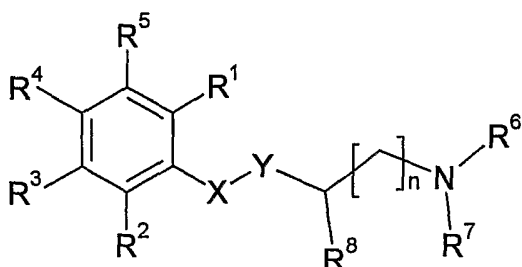
(I)



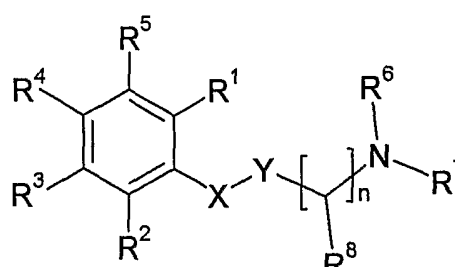
(II)



(III)



or (IV)



15

wherein:

R^1 and R^2 are independently selected from hydrogen, halogen, alkyl and alkyl ether groups;

20 X is $C=O$ and Y is NR , or X is NR and Y is $C=O$, or X is $C=O$ and Y is O , and R is selected from hydrogen, halogen, hydroxyl, alkyl, aryl and acyl;

R^6 and R^7 are independently selected from alkyl, aryl and alkylaryl groups; and

R^8 is selected from hydrogen, halogen, hydroxyl, alkyl, aryl and alkylaryl; or

R^7 and R^8 may be joined to form a ring 5, 6, 7 or 8 atoms in size;

n is 0, 1, 2, 3, 4 or 5; and

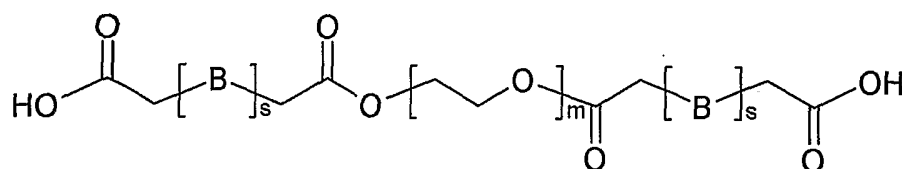
25 R^3 , R^4 and R^5 are each independently selected from hydrogen, hydroxyl, halogen, alkyl, aryl, hydroxyalkyl, hydroxyaryl, aminoalkyl and aminoaryl, with the proviso that at least one of R^3 , R^4 and R^5 is OH ;

optionally connected to a linker

or an activated and/or protected derivative thereof.

24. A process for preparing a conjugate according to any one of claims 15 to 22 which comprises co-polymerising one or more first monomers (I'):

5

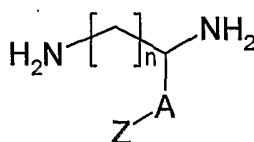


(I')

or an analogue derived from a branched PEG,

or an activated derivative thereof;

with one or more second monomers (II'):

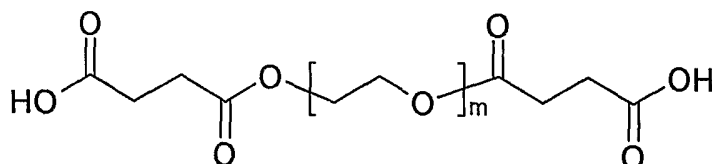


10

(II')

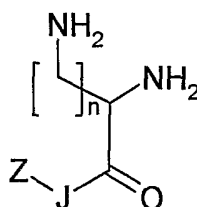
wherein Z is connected to A through the hydroxyl moiety that R³, R⁴ or R⁵ may represent.

25. A process according to claim 24 which comprises employing one or more first monomers A'



or an activated derivative thereof.

15 26. A process according to claim 24 or 25 which comprises employing one or more second monomers B'



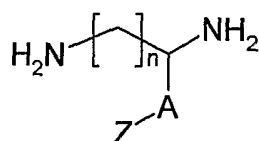
wherein J represents a bond or a linker

and wherein Z is connected to J-CO through the hydroxyl moiety that R³, R⁴ or R⁵ may

20 represent.

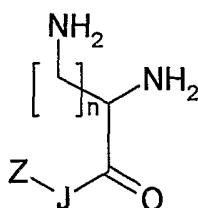
27. A process according to claim 26 wherein J represents a linker moiety J¹-J²-J³ in which J¹ is connected to CO and J³ is connected to Z.

28. A process according to claim 27 wherein J^1 represents sulphur, oxygen or an amino group.
29. A process according to claim 27 or 28 wherein J^1 represents an amino group.
30. A process according to any of claims 27 to 29 wherein J^2 represents a spacer group.
- 5 31. A process according to claim 30 wherein J^2 represents an alkylene group.
32. A process according to any one of claims 27 to 31 wherein J^3 represents a carbonyl group.
33. A conjugate obtainable by the process of any one of claims 23 to 32.
34. A conjugate obtained by the process of any one of claims 23 to 32.
- 10 35. A conjugate according to any one of claims 1 to 22, 33 or 34 wherein one or both ends of the polymer are capped with a polymer property modifying agent.
36. A conjugate according to claim 35 wherein the polymer property modifying agent is a targeting agent.
37. A conjugate according to claim 35 wherein the polymer property modifying agent is a
- 15 peptide, protein or saccharide.
38. A pharmaceutical composition comprising a conjugate according to any one of claims 1-22 or 33 to 37 together with a pharmaceutically acceptable diluent or carrier.
39. A conjugate according to any one of claims 1-22 or 33 to 37 for use in therapy.
40. Use of a conjugate according to any one of claims 1-22 or 33 to 37 in the manufacture
- 20 of a medicament for the treatment or prevention of pain.
41. Use of a conjugate according to any one of claims 1-22 or 33 to 37 in the treatment or prevention of pain.
42. A method of treating or preventing pain which comprises administering to a patient an effective amount of a conjugate according to any one of claims 1-22 or 33 to 37.
- 25 43. A compound of formula



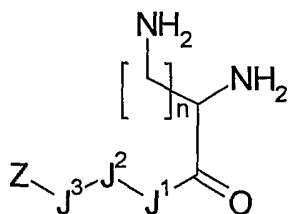
wherein Z represents a local anaesthetic agent as defined in any one of claims 1 to 14, n represents an integer 1 to 4 and A represents a functional group in which A is connected to Z by means of the hydroxyl moiety that R^3 , R^4 or R^5 may represent.

44. A compound of formula



wherein Z represents a local anaesthetic agent as defined in any one of claims 1 to 14, n represents an integer 1 to 10, J is an optional linker, and Z is connected to J-CO by means of hydroxyl moiety that R³, R⁴ or R⁵ may represent.

45. A compound of formula



5 wherein

n represents an integer 1 to 10;

J¹ represents sulphur, oxygen or amino;

J² represents a spacer group;

J³ represents carbonyl; and

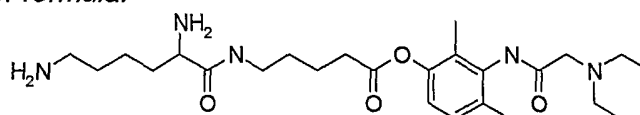
10 Z represents a local anaesthetic agent according to any one of claims 1 to 14, and Z is connected to J³ by means of hydroxyl moiety that R³, R⁴ or R⁵ may represent.

46. A compound according to any one of claims 43 to 45 wherein n represents 4.

47. A compound according to claim 45 or claim 46 wherein J¹ represents amino.

48. A compound according to any one of claims 45 to 47 wherein J² represents (CH₂)₃₋₆.

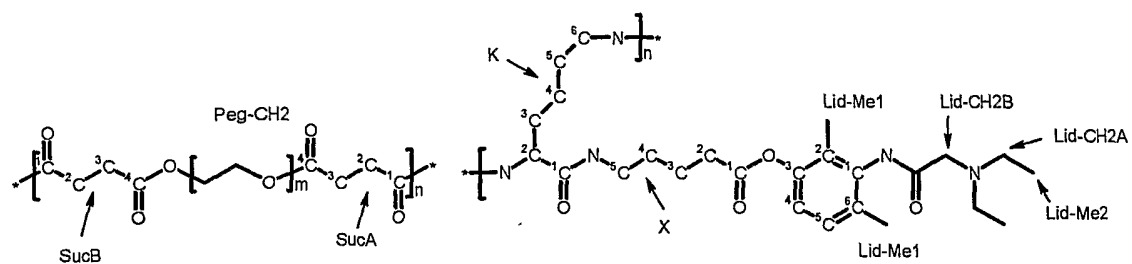
15 49. A compound of formula:



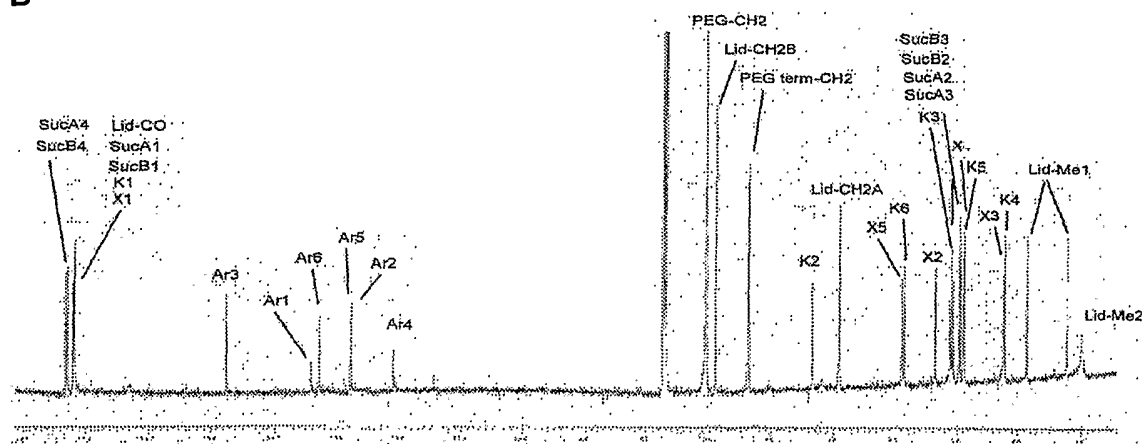
50. A conjugate of a polymer and a local anaesthetic agent substantially as described by reference to the examples.

Figure 1

A



B



C

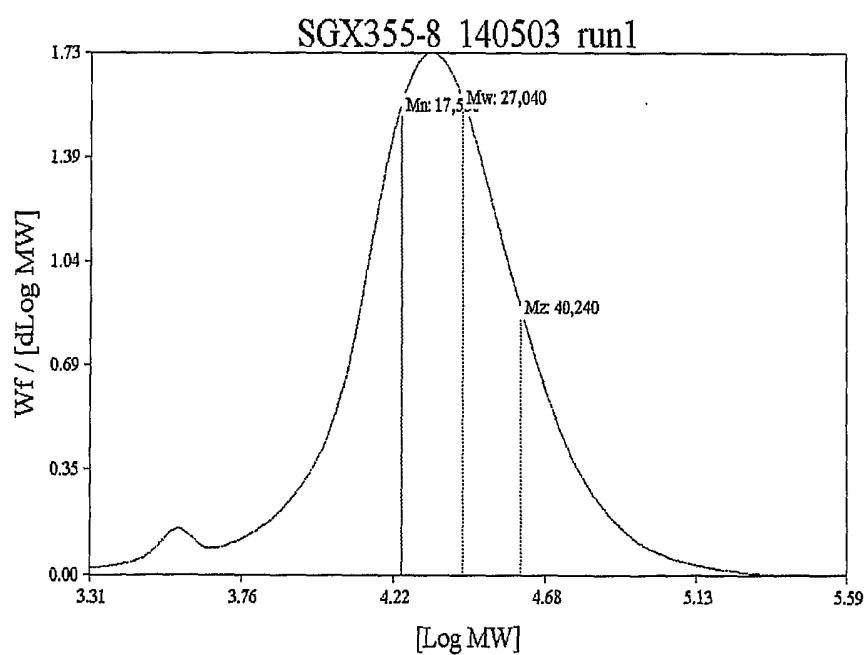


Figure 2

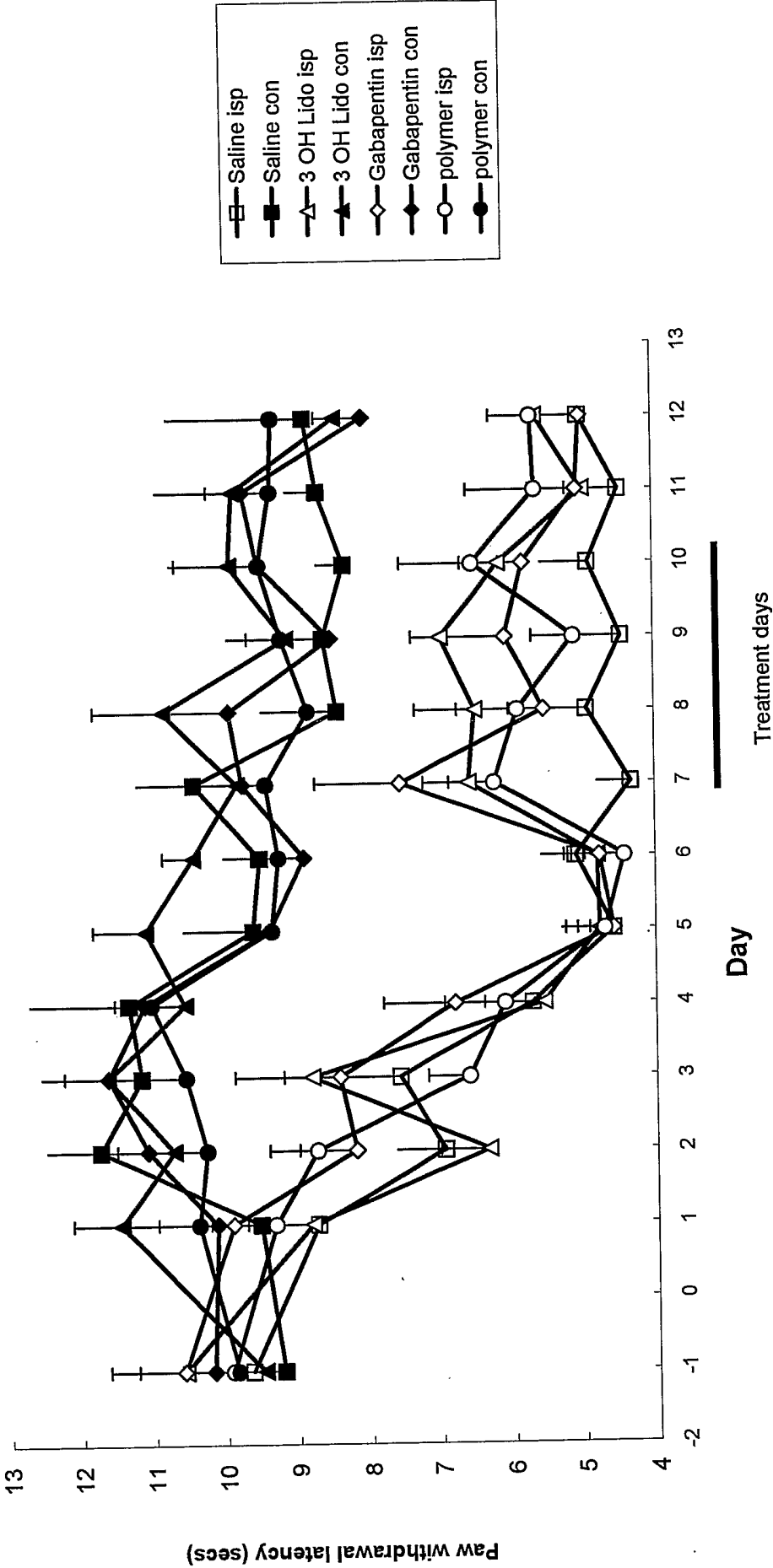
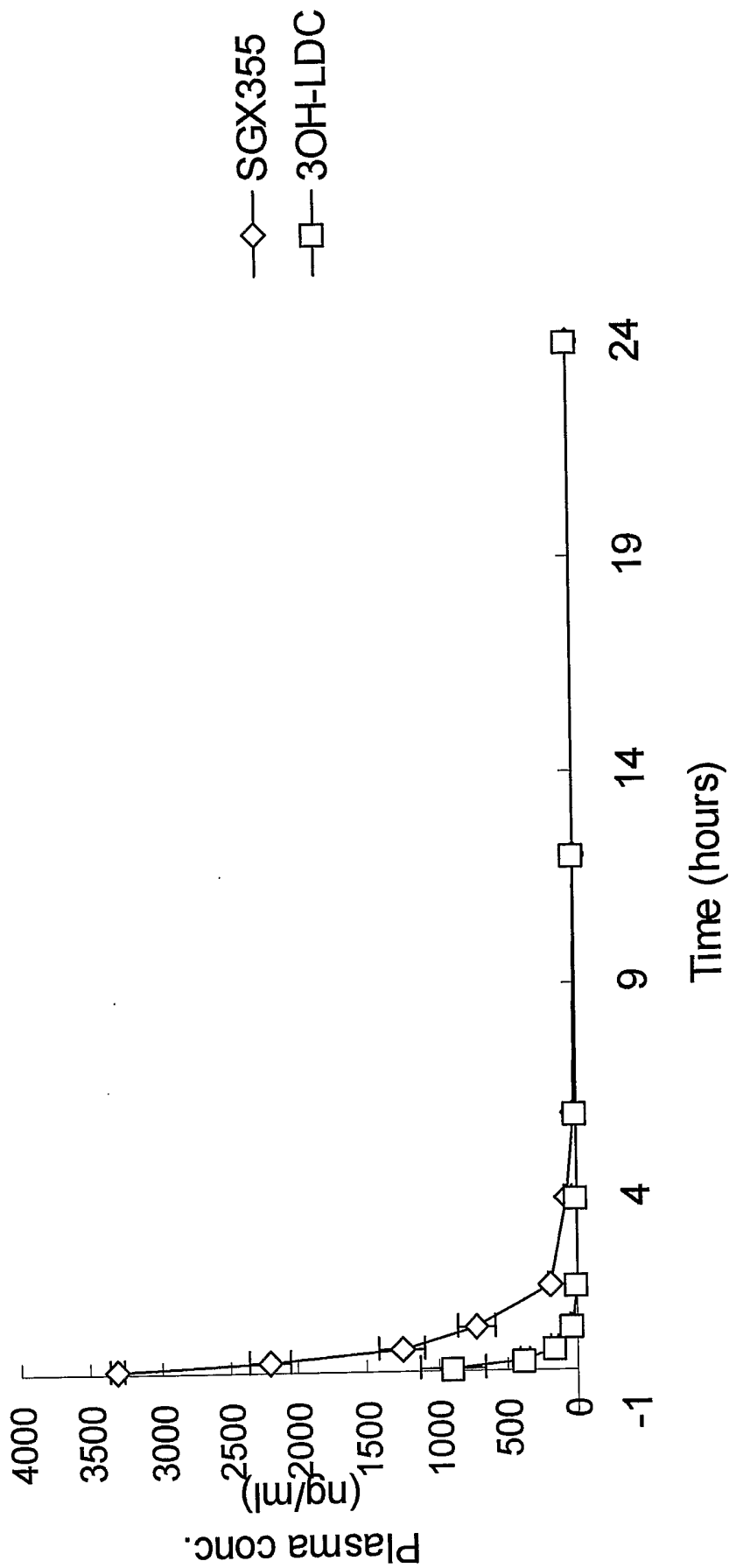


Figure 3



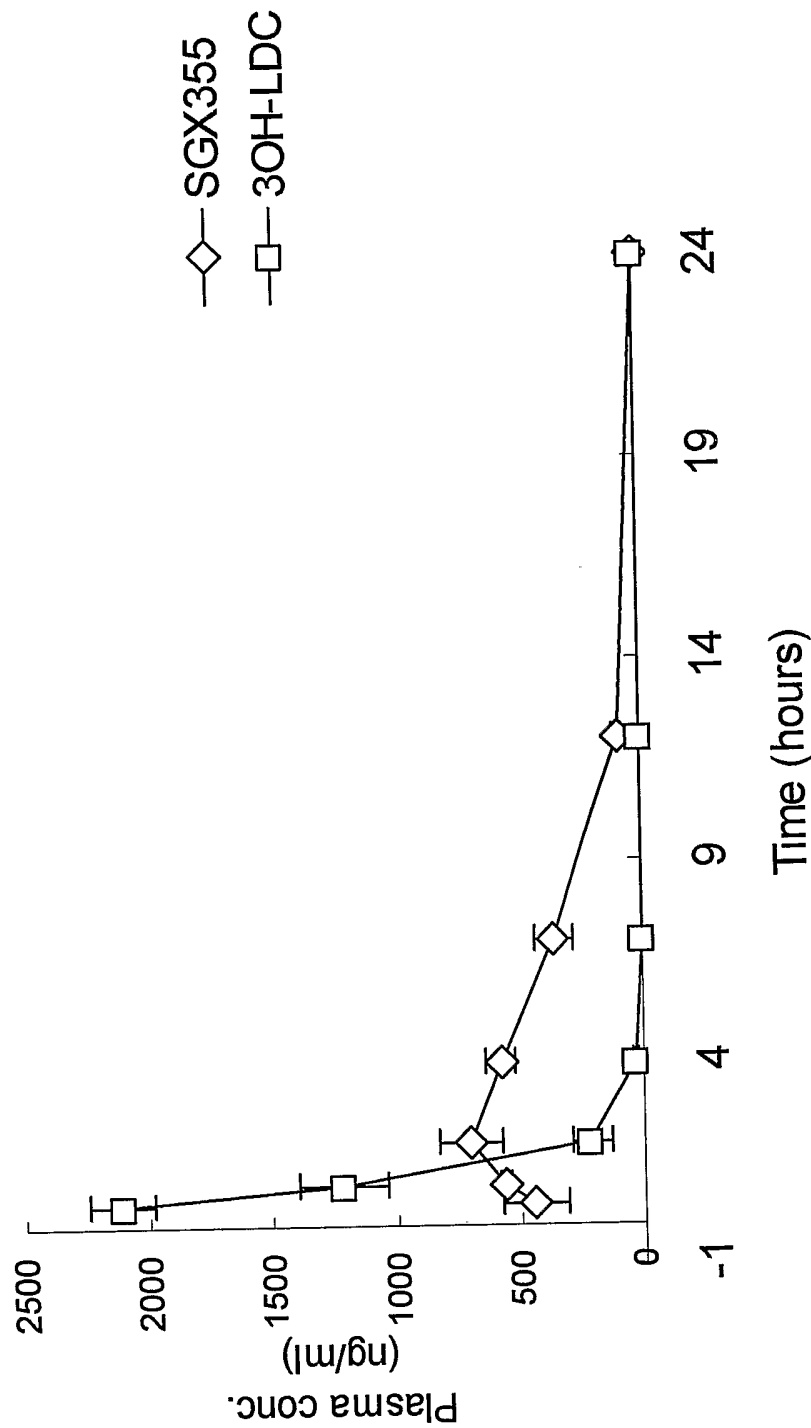
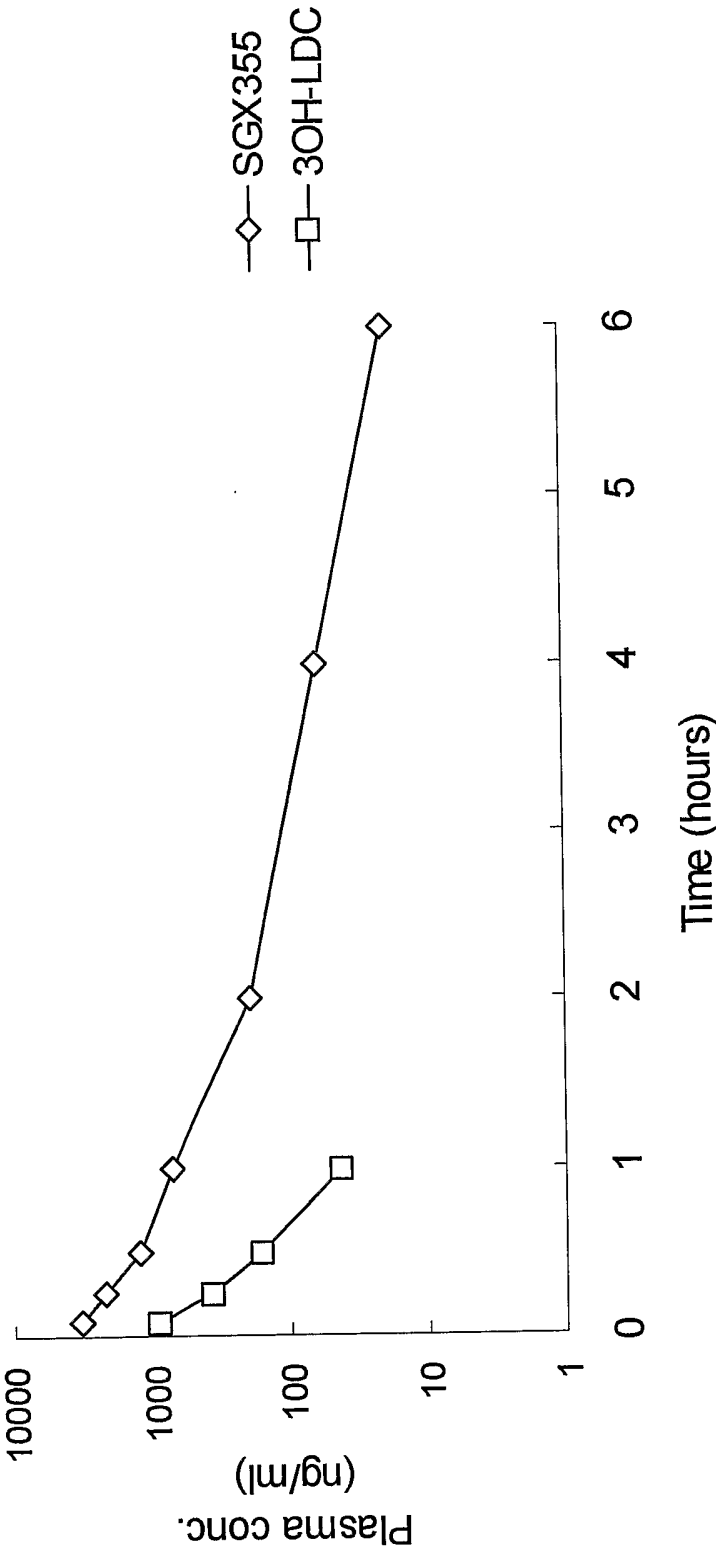


Figure 4

Figure 5



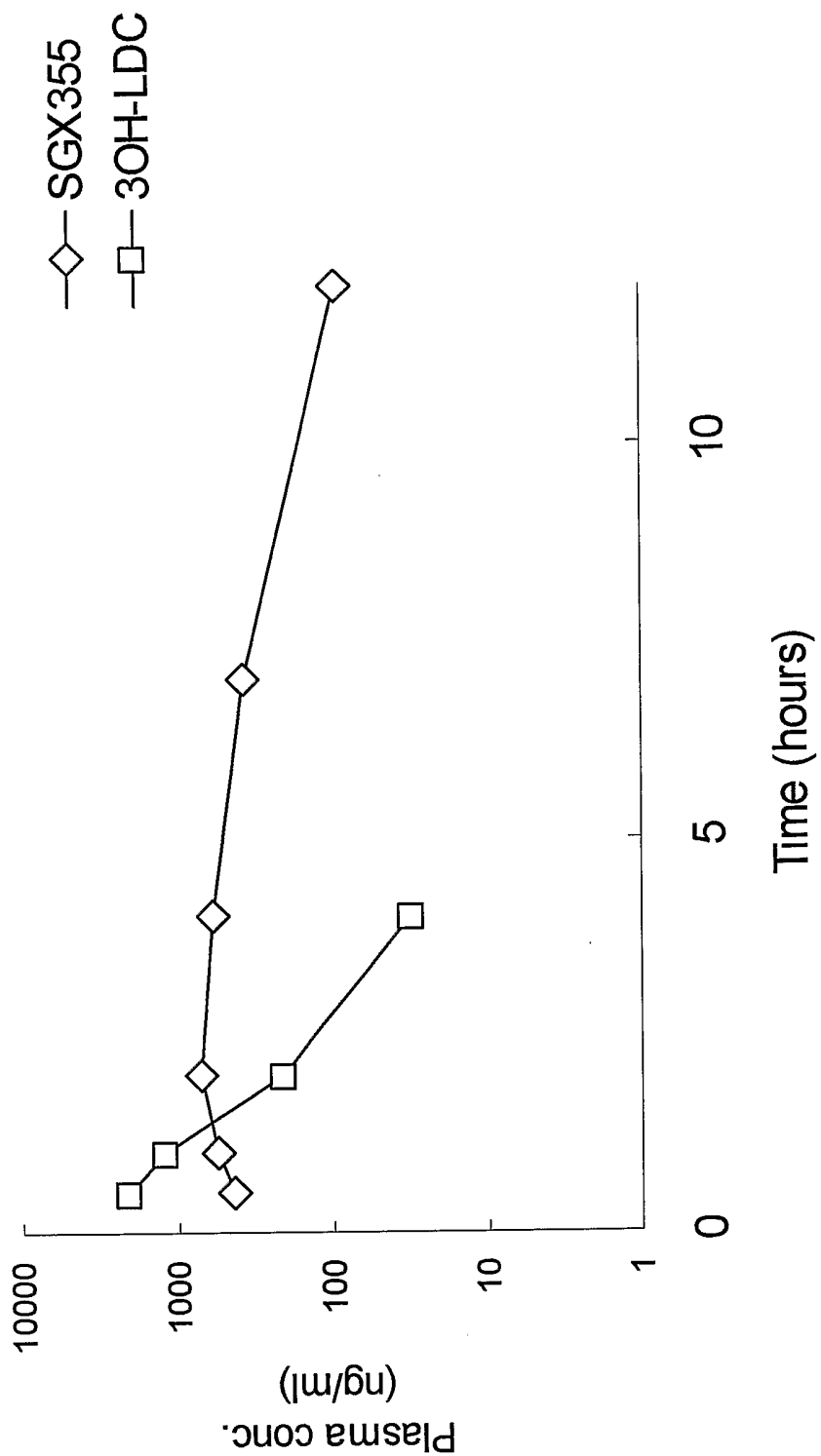


Figure 6

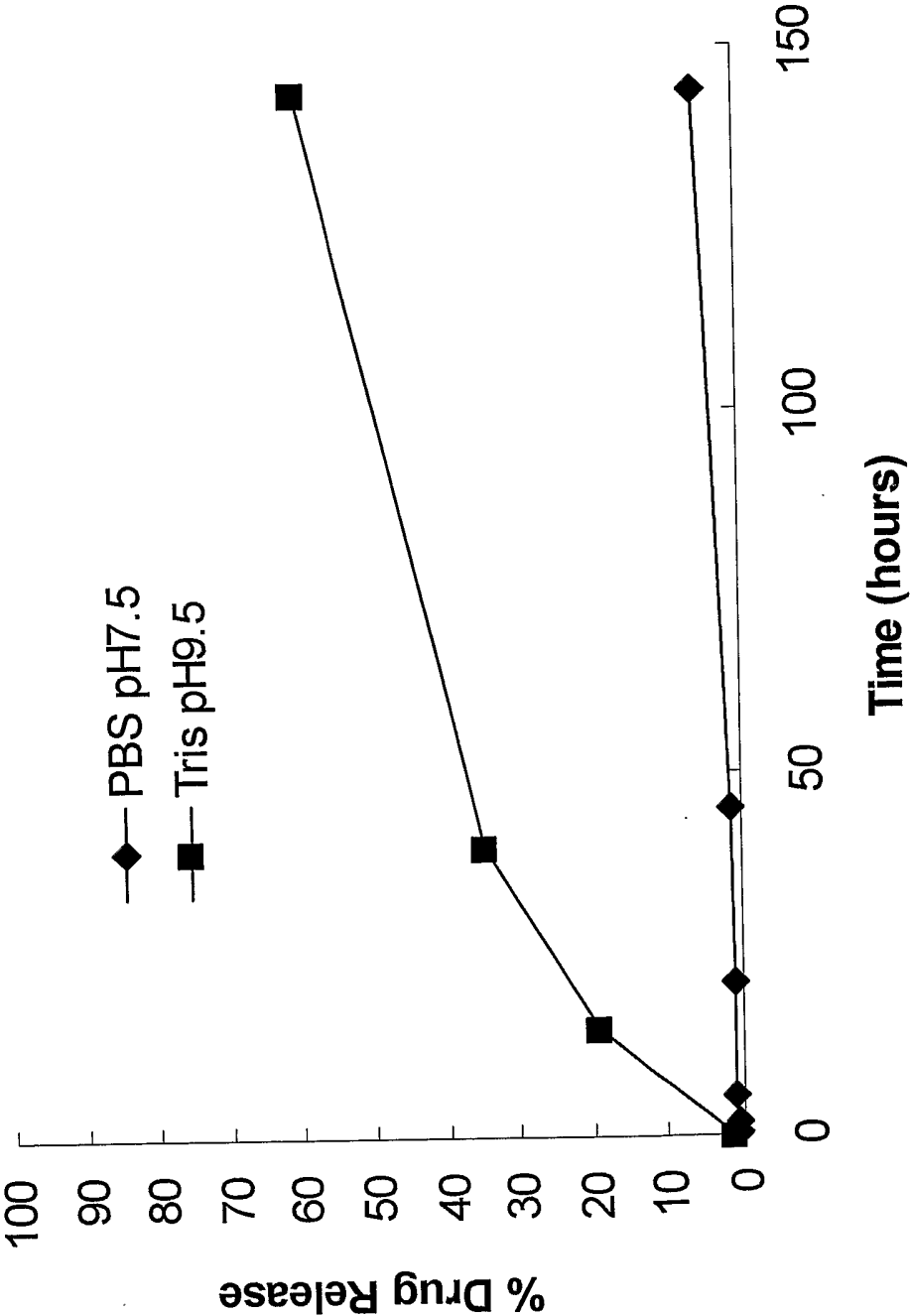


Figure 7