A compound for use in the treatment of prophylaxis of or diagnosis on disorders caused by the toxine Shigella dysenteriae having formula (I), wherein R1 and R2 independently are hydrogen, lower alkyl or acyl, with the proviso that R2 is not hydrogen when R3 is acetyl, or R1 and R2 together with the nitrogen atom to which they are connected form a cyclic imide, for example phthalimide, and wherein R3 is hydrogen, an organic residue, such as a carbohydrate residue, or the residue of a natural or synthetic glycoconjugate; composition including such compound in combination with a pharmaceutically acceptable carrier or diluent; method for treatment determining the presence of the toxine; method for identification or quantification of such compound; and method for isolating the toxine.
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A compound and a composition for therapeutic or diagnostic
use and the use of such compound and composition for the-
terapeutic treatment and isolation of Shigatoxine.

5 The present invention relates to compounds and com-
positions which are useful for therapeutic treatment of dis-
orders caused by the toxine of *Shigella dysenteriae* as well
as prophylaxis and diagnosis in connection herewith. The in-
vention also relates to a method of therapeutic treatment of
mammals including man and a process for isolating the toxine
in question.

Necrosis of the epithelium of the colon is part of the
pathogenesis of bacillary dysentery after infection with
*Shigella dysenteriae* (see Davis, B.D., Dulbecco, R., Eisen,
H.N., and Ginsberg, N.S. (eds) *Microbiology* Harper and Row,
is due to an invasion of the bacterium into the epithelium to
produce therein a toxine which appears to inhibit protein
synthesis (see Brown, J.E., Rothman, S.W. and Doctor, B.P.
molecular weight of about 70 000 (see Brown, J.E., Griffin,
996-1005) and is composed of one heavy and four to five light
subunits similar to the case for cholera toxine (see Olsnes,
xine has recently been purified on a milligram scale (see
Brown, J.E., Griffin, D.E., Rothman, S.W. and Doctor, B.P.
(1982) *Infect. Immun.* 36, 996-1005), which has enabled more
detailed studies of its mechanism of action.

The present invention has for its main object to pro-
vide a compound or a composition which can be used therape-
utically for the treatment of disorders due to infection
with *Shigella dysenteriae* and which can also be used for
diagnosing the toxine generated by the just mentioned bac-
terium.

Another object of the invention is to provide a method
for therapeutic treatment of mammals including man.
Still another object of the invention is to provide a process for isolating the toxine of *Shigella dysenteriae*. In connection with extensive research and experimentation it has now been found that the active receptor substance vis-à-vis the toxine of *Shigella dysenteriae* has the formula (I):

\[
\begin{align*}
\text{CH}_2\text{OH} & & \text{CH}_2\text{OH} & & \text{CH}_2\text{OH} \\
\text{HO} & & \text{OH} & & \text{OH} \\
\text{O} & & \text{O} & & \text{O} \\
N & & \text{OR}_3 & & \text{R}_1 \\
\text{R}_1 & & \text{R}_2 & & \text{R}_3
\end{align*}
\]

(II)

wherein \( R_1 \) and \( R_2 \) independently are hydrogen, lower alkyl or acyl, with the proviso that \( R_1 \) is not hydrogen at the same time as \( R_2 \) is acetyl, or \( R_1 \) and \( R_2 \) together with the nitrogen atom to which they are connected form a cyclic imide, for example phthalimide, and wherein \( R_3 \) is hydrogen, an organic residue, such as a carbohydrate residue, or the residue of a natural or synthetic glycoconjugate.

A preferred compound according to the invention falling within formula (I) above has the formula (II):

\[
\begin{align*}
\text{CH}_2\text{OH} & & \text{CH}_2\text{OH} & & \text{CH}_2\text{OH} & & \text{CH}_2\text{OH} \\
\text{HO} & & \text{OH} & & \text{OH} & & \text{OH} \\
\text{O} & & \text{O} & & \text{O} & & \text{O} \\
N & & \text{OR}_4 & & \text{R}_1 \\
\text{R}_1 & & \text{R}_2 & & \text{R}_3 & & \text{R}_4
\end{align*}
\]

(II)

wherein \( R_1 \) and \( R_2 \) have the above meaning and wherein \( R_4 \) is hydrogen, an organic residue, such as a carbohydrate residue, or the residue of a natural or synthetic glycoconjugate.
In the compounds given above it is preferred that \( R_1 \) is hydrogen or lower alkyl and \( R_2 \) is hydrogen, lower alkyl or acyl. A preferred proviso is that \( R_1 \) and \( R_2 \) are not simultaneously hydrogen.

In a particularly preferred embodiment of the invention, in the above formula, \( R_1 \) is hydrogen, whereas \( R_2 \) has the formula (III):

\[
\begin{align*}
\text{O} & \quad \text{R}_5 \\
\text{C - C} & \quad \text{R}_6 \\
\text{R}_7 &
\end{align*}
\]

wherein \( R_5 \), \( R_6 \) and \( R_7 \) independently are hydrogen, lower alkyl or halogen. It is particularly preferred that \( R_5 \), \( R_6 \) and \( R_7 \) all are fluoro or chloro, particularly fluoro. With regard to compound (II) it is preferred that \(-\text{OR}_3\) is in \( \beta \)-configuration.

The expression "lower" used in the present disclosure refers to a group containing 1-6 carbon atoms, particularly 1-4 carbon atoms and especially 1 or 2 carbon atoms.

The active substance constituted by the compound of formular (I) can be used as such or in combination with a pharmaceutically acceptable carrier.

The active substances according to the present invention can be formulated for use in human or veterinary medicine for therapeutic, prophylactic or diagnostic uses. In clinical practice the active constituents are normally administered orally or rectally or by injection in the form of a pharmaceutical preparation containing the active constituents in combination with a pharmaceutically acceptable carrier, which may be solid, semisolid or liquid, or as a capsule, and in such compositions constitute a further aspect of the invention. The compounds may also be used as such without carrier and in a form of an aqueous solution for injection. As examples of pharmaceutical preparations there may be mentioned tablets, drops, solutions and suppositories. The ac-
tive substance usually constitutes from 0.05 to 99% by weight of the preparation, for example from 0.1 to 50% for preparations intended for oral administration.

To manufacture pharmaceutical preparations in the form of dose units for oral application containing a compound according to the invention the active constituents can be admixed with a solid pulverulent or other carrier, for example lactose, saccharose, sorbitol, mannitol, starch, such as potatoe starch, corn starch, amylopectin, a cellulose derivative or gelatin and may also include lubricants, such as magnesium or calcium stearate, or polyethylene glycol waxes compressed to form tablets or cause for dragées.

By using several layers of the active drug separated by slowly dissolving layers tablets of delayed release are obtained.

Liquid preparations for oral application can be in the form of elixires, syrups or suspensions, for example solutions containing from 0.1 to 20% by weight of active substance, sugar and a mixture of ethanol, water, glycerol, propylene, glycol and optionally other additives of a conventional character.

The dose by which the active constituents are administered may vary within wide limits and depend on different factors, such as the severity of the disorder, the age and the weight of the patient and can be individually adjusted. As a conceivable range for the quantity of active constituents that may be administered per day there may be mentioned from 0.1 to 2000 mg or from 1 mg to 2000 mg.

The present invention has also for an object to provide a method for therapeutic treatment of mammals including man, and in this treatment a therapeutically active amount of a substance or a composition in accordance with the invention is administered.

The present invention has furhtermore for an object to provide use of the composition or the substance according to the invention for therapeutic treatment or diagnosis.
The composition or compound according to the present invention is thus useful in treatment of prophylaxis or diagnosis of disorders caused by the toxine of *Shigella dysenteriae*.

As is clear from the definition of compound (I) given above R₃ of formula (I) can designate the residue of a natural or synthetic glycoconjugate. Substituent R₃ may also be constituted by a macromolecular carrier to which the active part of the compound according to the invention is coupled.

The coupling can suitably be provided by a covalent coupling obtained via a coupling arm. As a macromolecular carrier there may be used a synthetically or naturally occurring polypeptide, polysaccharide, other polymer or particle.

In actual practice the coupling arm between the structural element and macromolecular carrier suitably consists of:

```plaintext
- O 0 NHCSNH-
- O 0 N=N-
- NH-(CH₂)ₙ CH₂ O NGCSNH-
- NH-(CH₂)ₙ CH₂ O N=N-
- NH-(CH₂)ₙ CONH-
- NH-
```

According to another aspect of the invention the compound or composition according to the invention can be used to determine the presence of the toxine of *Shigella dysenteriae* in a sample taken from a mammal including man. In this context one determines the degree of interaction between the toxine in question and the compound or composition in question. This interaction can be determined by inhibition or induction of adhesion of the toxine to cells or to other surfaces.

According to yet another aspect of the invention the compound which constitutes active receptor vis-a-vis the Shigatoxine can be identified or quantified in native biological
material, the procedure using antibodies, the generation of which has been induced by the use of a compound or a composition according to the invention.

Moreover, the invention can be used for isolation of the toxine of *Shigella dysenteriae* from a culture containing such toxine, a compound according to the invention being associated with a macromolecular or particular carrier and the culture being brought into contact with the carrier to bind the toxine thereto, the toxine being then released from the carrier and recovered. The toxine can suitably be released by providing in a column containing such carrier a change in pH. The toxine may also be released by displacement while utilizing a compound according to the invention in free form. Alternatively, the toxine may be released by treatment with a borate buffer or by treatment with so called chaotropic ions.

Regarding the meaning of substituent R₃ and R₄ in the compound of formula (I) or formula (II) as given above it can be of any type as long as it does not negatively effect the conditions in connection with the practical application of the invention. Thus, the said substituent may be hydrogen, lower alkyl or lower acyl, but R₄ can also be constituted by the residue of a natural or synthetic glycoconjugate, whereby the compound according to the invention thus is a glycoconjugate, for example a glycolipid.

The invention will in the following be further described in relation to non-limiting examples.

**EXAMPLES**

1. Synthesis of β-D-GalNAc-(1-3)-α-D-Galp-(1-4)-β-D-
   -Galp-(1-4)-D-Glc

![Chemical structure diagram](image-url)
Globotetraosylceramide (from human red cell membranes) was treated with trifluoroacetic acid/trifluoroacetic acid anhydride (TFA/TFAA) (1:100; v/v; 20 ml) at 100°C for 48 hours. After cooling the reaction mixture was evaporated to dryness. The residue was dissolved in 10 ml glacial acetic acid, 10 ml distilled water being then added. The mixture was heated at 100°C for 4 hours and then evaporated into dryness. 10 ml water and 10 ml chloroform/methanol (2:1; v/v) were added and the mixture was shaken. The organic phase was separated and another 10 ml chloroform/methanol were added. After shaking the organic phase was separated and the aqueous phase was evaporated into dryness.

The crude product was gel chromatographed on Sephadex G15 (2 x 100 cm) using water as an eluent. The fractions containing tetrasaccharide were combined and freeze-dried, 43 mg of product being obtained.

The product was analyzed using FAB-techniques (VG ZAB) in a mass spectrometer, and (M+1)+m/e 762 was obtained. When adding NaCl there was obtained (M+Na)+m/e 784.

$^1$H NMR, 500 MHz (D$_2$O), TSP, 70°C:

Spectroscopic data for NTF $^1$HNMR, 500 MHz (D$_2$O, TSP, 70°C):

$^1$H NMR

| δ  | 5.23 | (d, 0.38H, γ=3.7Hz, H-1x) |
|δ  | 4.95 | (d, 1H, γ=3.7Hz, H-1') |
|δ  | 4.80 | (d, 1H, γ=8.2Hz, H-1''') |
|δ  | 4.66 | (d, 0.64H, γ=7.9Hz, H-1β) |
|δ  | 4.52 | (d, <1H, γ=7.8Hz, H-1') |
|δ  | 4.52 | (d, <1H, γ=7.8Hz, H-1'β) |
|δ  | 4.31 | (I, broad), 1H, γ₁ ≈ γ₂ ≈ 6.5Hz, H-5') |
|δ  | 4.24 | (m, 1H, H-4'') |
|δ  | 3.28 | (t, 0.62H, γ₁ ≈ γ₂ = 7.9Hz, H-2β) |

$^{13}$C; δ 0.3 MHz (D$_2$O, TSP, 21°C):
The identity of 1H- and 13C-resonances was confirmed by homo- and heteronuclear 2D-correlation spectra.

Analysis of the product using gas chromatography after reduction with NaBD₄ (1 mg/ml, 1 hour, 20°C) and permethylation showed a pique on SE 30 glass capillary column (25 mm) at 330°C. Mass spectrum (E.I.) of reduced and permethylated product showed the expected result according to what is shown below:
2. Binding of Shigella dysenteriae type 1 toxine to HeLa- and Vero-cells.

Two HeLa-cells lines originally coming from Walter Reed Army Institute of Research, Washington D.C. were used. They are called "sensitive" and "resistent" based on the 10 000 fold difference for the cytotoxic effects of the toxine. TheVero-cell line came from the Governmental Bacteriological Laboratory, Stockholm.

The cells were cultivated in Eagle's minimal essential medium having added thereto a fetal calf serum (Gibco), final concentration 5%; 10mM NaHCO₃; 1mM glutamin; and 100 IU/ml streptomycin and penicillin (Gibco). The cell cultures were incubated in 3% CO₂ at 37°C for 3 days (HeLa-cells) or for 7 days (Vero-cells). Trypsinized cells for experimental use were suspended in medium, centrifuged and resuspended either in phosphate-buffered physiological saline (PBS) (0.05 M, pH 7.2) for the binding studies or in a medium for toxicity studies. The cells were counted under microscope and immediately used.

Toxine (18 μg protein in 10 μl PBS) were labelled with 250 μCi ¹²⁵I using Bolton Hunter reagent (2200 Ci mmol; New England Nuclear). Separation of the toxine from unbound isotope was obtained using gel chromatography with Sephadex G25 column (10x0.6 cm) (Pharmacia Fine Chemicals) and PBS as an eluting liquid. Labelled toxine was stored at +4°C until used.

Isotope-labelled toxine was dialutated to a concentration of 1.25 μg protein/ml with PBS having added thereto bovine serum albumin (BSA, Sigma Chemical) 1 mg/ml. Dialutated toxine was preincubated with antigen, compound (I) according to Example 1 above dialutated in PBS or only with PBS for 1 hour at +25°C. Then cells were added suspended in PBS and the mixture was stirred for 1 hour at +25°C. Controls containing toxine but no cells were incubated in parallel. The total volume of each experiment was 0.3 ml. Each reaction mixture was then stored on top of a discontinuous Percoll gradient (Pharmacia Fine Chemicals). The gradient was prepared by adding 1 ml of 100% Percoll (9 ml concentrate + 1
ml 15% NaCl) to a polycarbonate tube, 4 ml of 20% Percoll in PBS and at last 1 ml PBS being added on top. The gradient was centrifuged for 15 minutes at 800xg +4°C. The cells form bands between 20% and 100% Percoll. The top layers containing toxine not bound to the cells were transferred with a Pasteur pipette to another polycarbonate tube. Both fractions are counted in a gammacounter (Packard Instruments).

On the appended drawings 1-3 the results of the experiments as carried out are presented in the form of diagrams.

In Fig. 1 the binding of the toxine to cells as a function of the quantity of labelled toxine is shown. The binding is shown in relation to Vero-cells (●), to HeLa-cells (+), to resistant HeLa-cells (○) and no cells (▲).

In Fig. 2 there is a corresponding diagram concerning 125I-labelled toxine binding to Vero-cells after competition of labelled toxine (100 ng) with unlabelled toxine.

In Fig. 3 there is shown a diagram over the inhibition of the binding of 125I-labelled Shigatoxine to Vero-cells. Toxine (100 ng) was in the experiments preincubated with galabiose (+), globotetraose (▲), 1,1',1''-triacetylcitotriose (○) and the compound according to Example 1 above (○), respectively, before the addition of 2 x 10⁵ Vero-cells. Each testpoint in the diagram represents the average of two experiments.

As is clear from Fig. 3 there is obtained 50% inhibition at a concentration of the active compound of about 1.2 mg/ml.
1. A compound having the formula (I):

\[
\begin{align*}
\text{CH}_2\text{OH} & \quad \text{CH}_2\text{OH} & \quad \text{CH}_2\text{OH} \\
\text{OH} & \quad \text{O} & \quad \text{O} \\
\text{OH} & \quad \text{OH} & \quad \text{OR}_3 \\
\text{N} & \quad \text{R}_1 & \quad \text{R}_2
\end{align*}
\]

wherein \( R_1 \) and \( R_2 \) independently are hydrogen, lower alkyl or acyl, with the proviso that \( R_1 \) is not hydrogen when \( R_2 \) is acetyl, or \( R_1 \) and \( R_2 \) together with the nitrogen atom to which they are connected form a cyclic imide, for example phthalamidc, and

wherein \( R_3 \) is hydrogen, an organic residue, such as a carbohydrate residue, or the residue of a natural or synthetic glycoconjugate.

2. A compound according to claim 1 having the formula (II):

\[
\begin{align*}
\text{CH}_2\text{OH} & \quad \text{CH}_2\text{OH} & \quad \text{CH}_2\text{OH} \\
\text{OH} & \quad \text{O} & \quad \text{O} \\
\text{OH} & \quad \text{OH} & \quad \text{OR}_4 \\
\text{N} & \quad \text{R}_1 & \quad \text{R}_2
\end{align*}
\]

wherein \( R_1 \) and \( R_2 \) have the meaning given in claim 1 and

wherein \( R_4 \) is hydrogen, an organic residue, such as a carbohydrate residue, or the residue of a natural or synthetic glycoconjugate.

3. A compound according to claim 1 or 2, characterized thereby that \( R_1 \) is hydrogen or lower alkyl and \( R_2 \) is hydrogen, lower alkyl or acyl.
4. A compound according to claim 1 or 2, characterized thereby that R₁ and R₂ are not simultaneously hydrogen.

5. A compound according to claim 1 or 2, characterized thereby that R₁ is hydrogen and R₂ has the formula (III):

\[
\begin{array}{c}
\text{O} \\
\hline
\text{C} \quad \text{C} \quad \text{O} \\
\text{R₅} \\
\text{R₆} \\
\text{R₇}
\end{array}
\]

(III)

wherein R₅, R₆ and R₇ independently are hydrogen, lower alkyl or halogen.

6. A compound according to claim 5, wherein R₅, R₆ and R₇ all are fluoro or chloro.

7. A compound according to claim 6, wherein R₅, R₆ and R₇ all are fluoro.

8. A compound according to claim 2, wherein -OR₃ is in β-configuration.

9. A composition for use in treatment of prophylaxis or diagnosis of disorders caused by the toxine of *Shigella dysenteriae*, comprising a compound according to any of the preceding claims in combination with a pharmaceutically acceptable carrier or diluent.

10. A composition according to claim 9, characterized thereby that it contains a residue of the compound coupled to a macromolecular carrier.

11. A composition according to claim 10, characterized thereby that it contains said residue covalently coupled to a macromolecular carrier via a coupling arm.

12. A composition according to claims 10 or 11, characterized by using as a macromolecular carrier a synthetically or naturally occurring polypeptide, polysaccharide, other polymer or particle.

13. A composition according to any of claims 10-12, characterized thereby that the coupling arm between the structural element and macromolecular carrier consists of:
- O----------\-NHCSNH-
- O----------\-N=N-
- NH-(CH₂)ₙ-CH₂-----\-NH-
- NH-(CH₂)ₙ-CH₂-----\-NGCSNH-
- NH-(CH₂)ₙ-CONH-
- NH-

wherein R is an alkyl- or an aryl residue and wherein n may vary from 1 to 20.

14. A compound according to any of claims 1-8 or a composition according to any of claims 9-13 for use as a receptor to the toxine Shigella dysenteriae.

15. A method for therapeutic treatment of mammals including man, characterized by administering a therapeutically active amount of a compound according to any of claims 1-8 or a composition according to any of claims 9-14.

16. A method for determining the presence of the toxine of Shigella dysenteriae in a sample taken from a mammal including man, characterized by determining the degree of interaction between the toxine in the sample and the compound according to any of claims 1-8 or the composition according to claims 9-15.

17. A method according to claim 16, characterized by determining the interaction by inhibition or induction of the adhesion of the toxine to cells or to other surfaces.

18. A method for identification or quantification of the compound according to any of claims 1-8 in native biological material from mammal including man, characterized in using antibodies the generation of which has been induced by the use of the compound according to any of claims 1-8 or the composition according to any of claims 9-15.

19. A method of isolating the toxine of Shigella dysenteriae from a culture containing said toxine, characterized by associating a compound according to any of claims 1-8 with a macromolecular or particular carrier, bringing the culture into contact with the carrier, binding the toxine to said carrier, the toxine being then released
from the carrier and recovered.

20. A method according to claim 19, characterized by releasing the toxine by providing in a column a change in pH.

21. A method according to claim 20, characterized by releasing the toxine by displacement while utilizing a compound according to any of claims 1-8 in free form.

22. A method according to claim 19, characterized by releasing the toxine by treatment with a borate buffer.

23. A method according to claim 19, characterized by releasing the toxine by treatment with chaotropic ions.
INTERNATIONAL SEARCH REPORT

According to International Patent Classification (IPC) or to both National Classification and IPC:
C 07 H 3/06, 15/04, 15/12, A 61 K 31/70, A 61 K 39/112,
G 01 N 33/569

II. FIELDS SEARCHED

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Documentation Searched other than Minimum Documentation to the extent that such Documents are Included in the Fields Searched:

SE, NO, DK, FI classes as above

III. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>Acta Chemica Scandinavica, B 36, 1982, No. 8, K-E. Falk et al., &quot;Proton NMR studies of a tetrasaccharide which is a receptor for uropathogenic E. coli bacteria&quot;, pages 558-560</td>
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* Special categories of cited documents: 10
**A** document defining the general state of the art which is not considered to be of particular relevance
**E** earlier document but published on or after the international filing date
**L** document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
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**P** document published prior to the international filing date but later than the priority date claimed

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

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IV. CERTIFICATION

Date of the Actual Completion of the International Search: 1986-03-17
Date of Mailing of this International Search Report: 1986-03-19

International Searching Authority

Swedish Patent Office

Signature of Authorized Officer: Gunilla Claesson

Form PCT/ISA/210 (second sheet) (January 1985)
II Fields searched (cont).

US Cl 53, 54, 55, 115, 116, 118, 120, 122;
       514 § 23, 25, 42, 61

V. Observations where certain claims were found unsearchable

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. Claim numbers 15, because they relate to subject matter not required to be searched by this Authority, namely:

A method for treatment of the human or animal body by therapy.

2. Claim numbers, because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. Claim numbers, because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 8.4(a).

VI. Observations where unity of invention is lacking

This international Searching Authority found multiple inventions in this international application as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest
- The additional search fees were accompanied by applicant's protest.
- No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (supplemental sheet (2)) (January 1985)
<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of Document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to Claim No</th>
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<tbody>
<tr>
<td>Y</td>
<td>EP, A1, 0 089 939 (SVENSKA SOCKERFABRIKS AB) 28 September 1983 &amp; AU, 12625/83 JP, 58174327</td>
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<tr>
<td>Y</td>
<td>EP, A2, 0 098 252 (SVENSKA SOCKERFABRIKS AB) 11 January 1984 &amp; JP, 59025399</td>
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<tr>
<td>P</td>
<td>EP, A2, 0 133 170 (K-A. KALARSSON, A.A. LINDBERG) 13 February 1985</td>
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<tr>
<td>Y</td>
<td>EP, A2, 0 035 484 (KÄLLENIUS, GUNILLA PETTERSSON ET AL) 9 September 1981 &amp; WO, 81/02520 AU, 67795/81 SE, 8001748 AT, 9062 AU, 546148</td>
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