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(54) Title
NOVEL QUATERNARY AMMONIUM SALTS AND USE THEREOF AS MEDICINE

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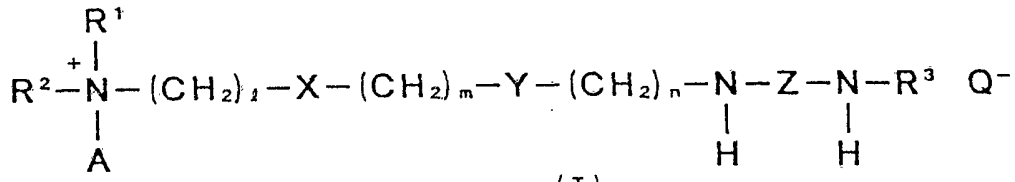
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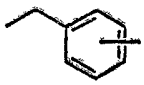
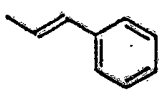
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(57) Claim

1. A quaternary ammonium salt represented by the following formula (I):

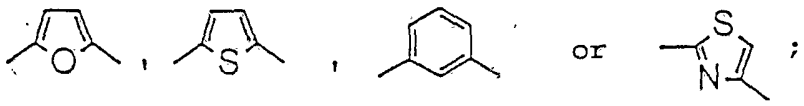


(I)

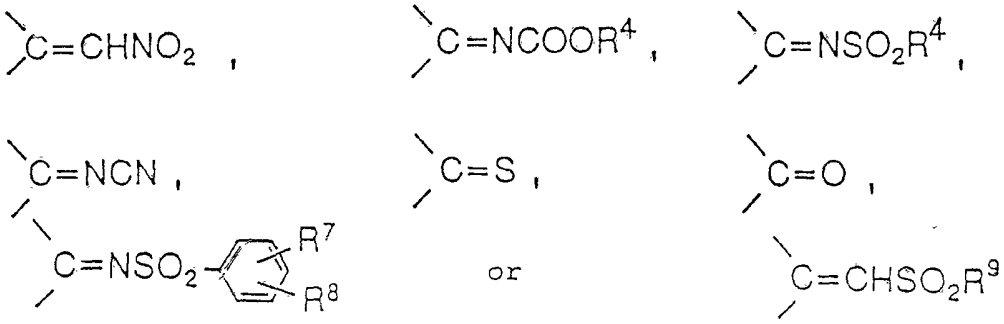
[wherein $R^1$ and $R^2$ represent lower alkyl groups which may be the same or different from each other; $R^3$ represents hydrogen, lower alkyl, phenyl, benzyl, or $-COOR^4$ (wherein $R^4$ represents lower alkyl); A represents lower alkyl, lower alkenyl, lower alkynyl, $-(CH_2)_p-COOR^5$ (wherein $R^5$ represents hydrogen or lower alkyl, and p represents an integer of from 1 to 5),  or  (wherein $R^6$ represents hydrogen, hydroxyl, nitro, lower alkyl, $-COOR^5$, or $-SO_3R^5$); $Q^-$ represents a counter anion of

.../2

quaternary ammonium salt; X represents

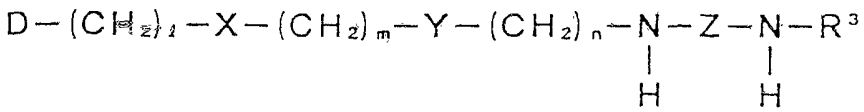


Y represents methylene, oxygen or sulfur; Z represents



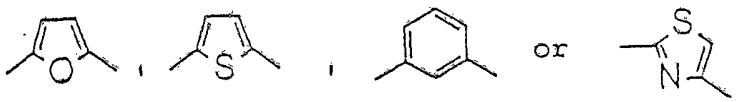
(wherein $R^7$ and $R^8$ are the same or different from each other and independently represent hydrogen, halogen, nitro, lower alkyl or lower alkoxyl, and $R^9$ represents lower alkyl or phenyl); 1 and m represent each an integer of 1 or 2; and n represents an integer of from 1 to 3].

3. A compound represented by the following formula (IX):

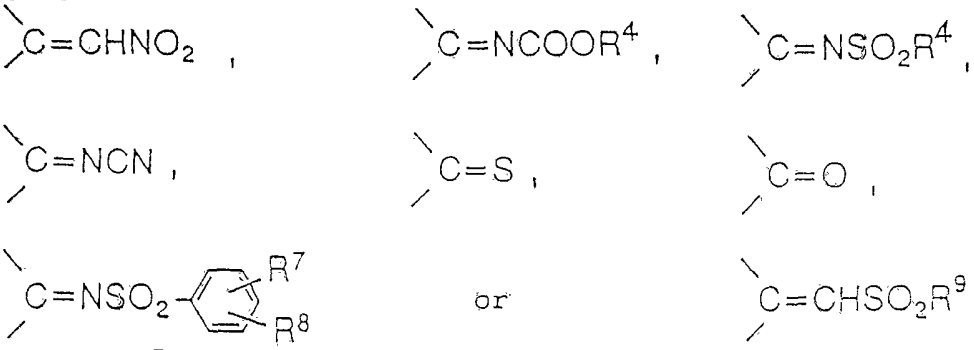


(IX)

[wherein $R^3$ represents hydrogen, lower alkyl, phenyl, benzyl, or -COOR6 (wherein $R^6$ represents lower alkyl); D represents halogen or an active ester residue; X represents



Y represents methylene, oxygen or sulfur; Z represents



(wherein $R^7$ and $R^8$ are the same different from each other and independently represent hydrogen, halogen, nitro, lower alkyl or lower alkoxyl, and $R^9$ represents lower alkyl or phenyl); 1 and m represent each an integer of 1 or 2; and n represents an integer of 1 to 3].

7. A composition for the treatment of gastrointestinal disorders including a compound according to claim 1 and a biologically acceptable carrier.

8. A composition for the treatment of gastrointestinal disorders including a compound according to claim 3 and a biologically acceptable carrier.

SEARCH QUALITY ASSURANCE

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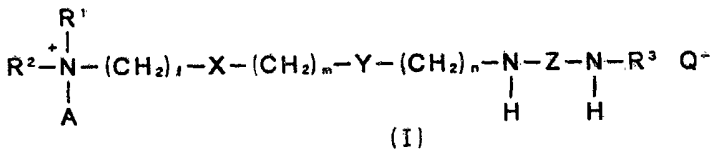
(81) 指定国
AT(欧州特許), AU, BE(欧州特許), CA, CH(欧州特許),
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添付公開書類 国際調査報告書

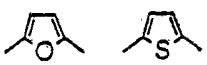
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(54) Title : NOVEL QUATERNARY AMMONIUM SALTS AND USE THEREOF AS MEDICINE

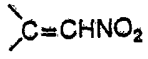
(54) 発明の名称 新規第4級アンモニウム塩類およびそれらの医薬としての使用



(I)



(a) (b)



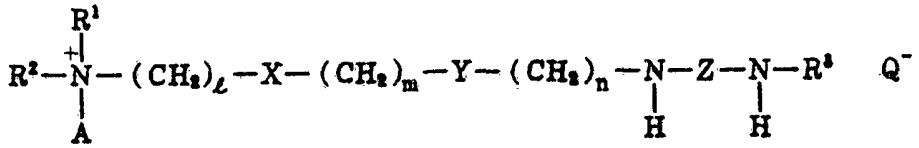
(c)

(57) Abstract

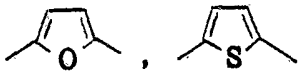
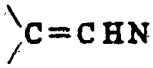
Quaternary ammonium salts represented by general formula (I) and use thereof as medicines, wherein $R^1$ and $R^2$ represent lower alkyl groups which may be the same or different from each other; $R^3$ represents hydrogen, lower alkyl, etc.; A represents lower alkyl, etc.; $Q^-$ represents an anion; X represents (a), (b), etc.; Y represents methylene, oxygen or sulfur; Z represents (c), etc.; l and m represent each an integer of 1 or 2; and n represents an integer of 1 to 3.

(57) 要約

一般式（Ⅰ）で表される第4級アンモニウム塩類およびそれらの医薬としての使用。



（Ⅰ）

〔式中、$R^1$ および $R^2$ は同一のまたは異なる低級アルキル基を示し、$R^3$ は水素原子、低級アルキル基などを示し、Aは低級アルキル基などを示し、$Q^-$ は陰イオンを示し、Xは  などを示し、Yはメチレン基、酸素原子またはイオウ原子を示し、Zは  などを示し、$\ell$ および m は1または2の整数を示し、nは1から3の整数を示す。〕

情報としての用途のみ
PCTに基づいて公開される国際出願のパンフレット第1頁にPCT加盟国を同定するために使用されるコード

AT オーストリア
AU オーストラリア
BB バルバドス
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BF ブルキナ・ファソ
BG ブルガリア
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CS チェコスロヴァキア
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TD チャード
TG トーゴ
UA ウクライナ
US 米国
VN ヴェトナム

DESCRIPTION

# NOVEL QUATERNARY AMMONIUM SALTS AND USE THEREOF AS MEDICINE

## Technical Field

The present invention relates to novel quaternary ammonium salts and use of the salts as medicines.

## Background Art

Conventionally, trimebutine maleate has been primarily used as a gastroprokinetic agent.

Trimebutine maleate has wide utility due to its dual activities of promoting and suppressing the gastric contractions. However, it is not necessarily satisfactory in that relatively high dose, i.e., 300 mg per day is required, and that adverse side effects are involved.

Therefore, studies have been conducted in search for gastroprokinetic agents which can replace trimebutine maleate (Japanese Patent Application Laid-open (kokai) No. 163074/1991).

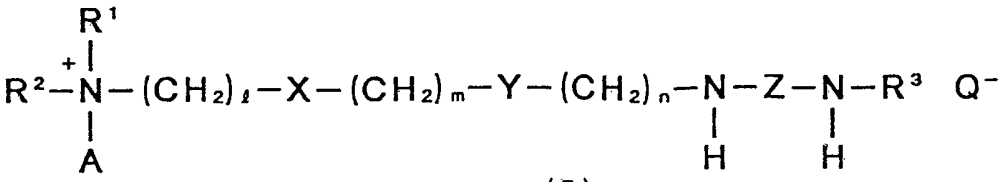
However, the results have not necessarily been successful in providing gastroprokinetics. Accordingly, development of drugs which possess much stronger activity in enhancement of gastrointestinal motility has still been desired.

## Disclosure of the Invention

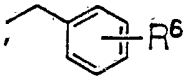
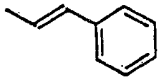
Accordingly, the present invention provides novel quaternary ammonium salts represented by the following

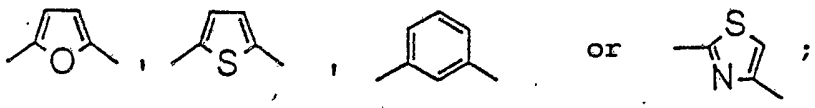
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formula (I):

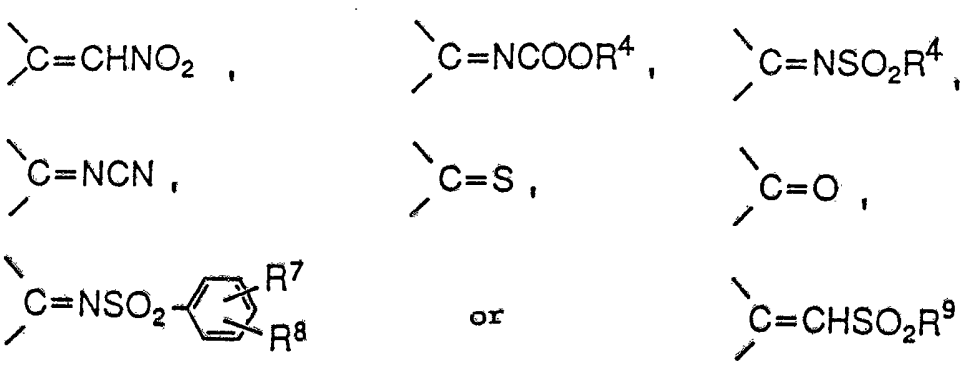


(I)

[wherein $R^1$ and $R^2$ represent lower alkyl groups which may be the same or different from each other; $R^3$ represents hydrogen, lower alkyl, phenyl, benzyl, or $-COOR^4$ (wherein $R^4$ represents lower alkyl); A represents lower alkyl, lower alkenyl, lower alkynyl, $-(CH_2)_p-COOR^5$ (wherein $R^5$ represents hydrogen or lower alkyl, and p represents an integer of from 1 to 5),  or  (wherein $R^6$ represents hydrogen, hydroxyl, nitro, lower alkyl, $-COOR^5$, or $-SO_3R^5$); $Q^-$ represents a counter anion of quaternary ammonium salt; X represents



Y represents methylene, oxygen or sulfur; Z represents



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(wherein $R^7$ and $R^8$ are the same or different from each other and independently represent hydrogen, halogen, nitro, lower alkyl or lower alkoxyl, and $R^9$ represents lower alkyl or phenyl); l and m represent each an integer of 1 or 2; and n represents an integer of from 1 to 3], and use of the salts as medicines.

Since the compounds according to the present invention have an activity of accelerating the gastrointestinal contractions, i.e., they improve the gastrointestinal motility remarkably, as well as high safety, they have utility in the medical field of treating the gastrointestinal disorders and the like.

Best Mode for Carrying Out the Invention

In the present invention, the term "lower alkyl" encompasses alkyl groups having 1 to 5 carbon atoms, examples of which include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, tert-pentyl and the like.

The term "lower alkenyl" encompasses alkenyl groups having 2 to 5 carbon atoms, which include vinyl, allyl, butenyl, 3-methyl-2-butenyl and the like.

The term "lower alkynyl" encompasses alkynyl groups having 2 to 5 carbon atoms, which include ethynyl, propargyl and the like.

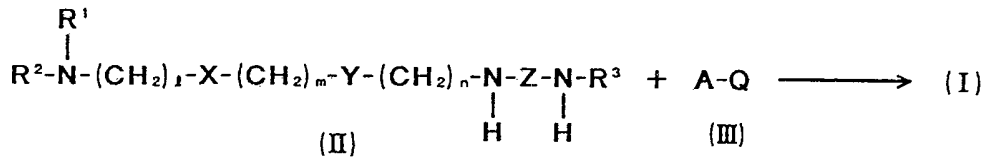
Examples of the counter anion of quaternary ammonium salt include fluorine ion, chlorine ion, bromine ion, iodine ion, $HSO_4^-$, $ClO_3^-$, $NO_3^-$, cyanide

AUSTRALIA PATENT OFFICE MAS

ion, $HSO_3^-$ ion, $IO_3^-$ ion, $HCO_2^-$, $CH_3CO_2^-$, $OH^-$, phenolate ion, methanesulfonate ion, toluenesulfonate ion and the like.

The compound (I) of the present invention is prepared, for example, by the following reaction scheme:

Method A



(wherein $R^1$, $R^2$ , $R^3$, A, Q, X, Y, Z, l, m and n have the same meaning as defined hereinbefore).

That is, compound (I) is obtained by reacting compound (II) which is obtainable by applying a known method (Japanese Patent Application Laid-open (kokai) No. 40956/1983; Japanese Patent Application Laid-open (kokai) No. 91980/1982; R. Soc. Chem., 42, Regul. Biol. Mech., 45-47, 1982) with compound (III).

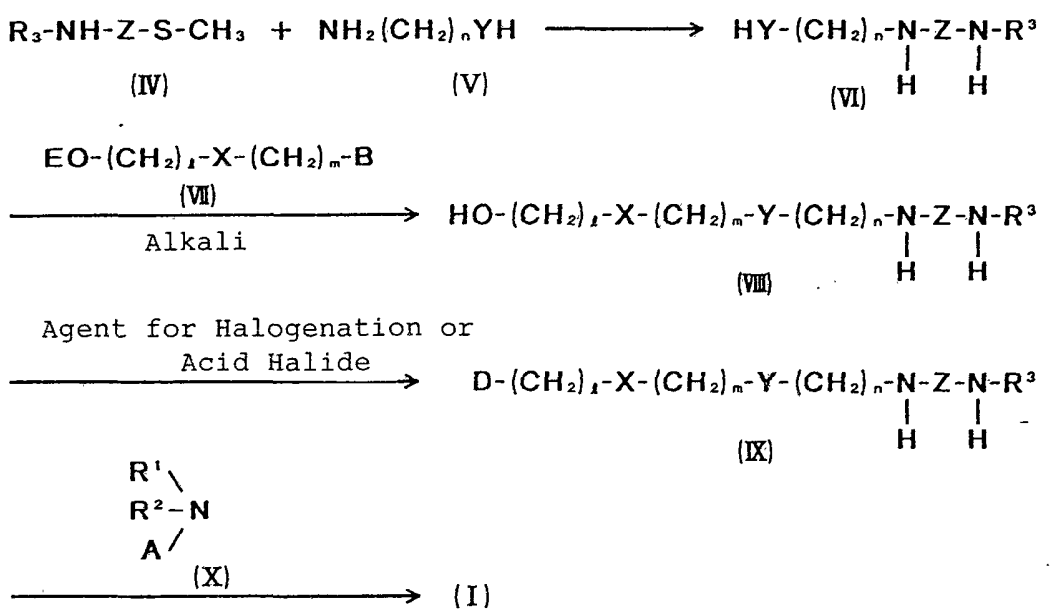
The above reaction is preferably carried out in an inert solvent such as methanol, ethanol, dichloromethane, chloroform, ethyl acetate, dimethylformamide, dimethylsulfoxide and water, in a temperature range of 0°C to a reflux temperature. It is preferred that the compounds (II) and (III) be used in an equimolar amount, or one be used in a slightly larger amount than the other. The reaction time is desirably varied according to the progress and condition of the reaction.

Alternatively, the compound (I) of the present

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invention may be prepared according to the following reaction scheme:

Method B




(wherein $R^1$, $R^2$ , $R^3$, A, X, Y, Z, l, m and n have the same meaning as defined hereinbefore, E represents a protective group for an alcohol such as benzoyl and acetyl, B represents a halogen atom, and D represents a halogen atom or an acid residue).

That is, compound (I) of the present invention is obtained by reacting a halogen compound or an ester compound (IX) with an amine compound (X).

The reaction for synthesizing the compound (VI) is preferably carried out in an anhydrous organic solvent, especially under stream of an inert gas such as argon. The reaction temperature is preferably within the range of 0°C

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to a boiling point, and more preferably, at room temperature. The reaction for synthesizing the compound (VIII) is carried out in the presence of an alkali such as KOH, NaOH and the like, during which the protective group is removed. In the reaction for synthesizing the compound (IX), an organic base may be added if desired. Preferable examples of the agent for halogenation include phosphorus oxychloride. Preferable examples of the acid halide include methanesulfonic acid chloride and toluenesulfonic acid chloride.

The compound (I) of the present invention has excellent activity in stimulation of gastrointestinal motility as will be described later in this specification.

The compound (I) of the present invention can be formulated into a drug preparation for oral or parenteral administration after blended with pharmaceutically acceptable adjuvants. In the manufacture of oral-route preparations, the compound of the invention is blended with suitable additives, for example, vehicles such as lactose, mannitol, corn starch and crystalline cellulose; binders such as cellulose derivatives, gum arabic and gelatin; disintegrators such as carboxymethylcellulose calcium; and lubricants such as talc and magnesium stearate, and formed into tablets, powders, granules, capsules and the like. The obtained solid preparations may further be coated using coating bases such as hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose acetate succinate,

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cellulose acetate phthalate and methacrylate copolymers and formed into enteric preparations. In the manufacture of parenteral preparations, the compounds of the invention may be combined, for example, with water, ethanol, glycerol or surfactants which are commonly used in this technical field and prepared into injection preparations; or combined with suppository bases to prepare suppositories.

The amounts of administration of the compound (1) of the present invention vary depending on age, body weight, symptom of the disease, goal of the treatment, manner of administration, period of administration, etc. Generally, in the case of oral administration, the compound is administered in amounts of 1-2000 mg/day, preferably 10-300 mg/day, as divided in 1 to 3 times a day.

Action

Acceleration of Gastrointestinal Motility:

The test was performed according to the method of Itoh et al. (Am. J. Dig. Dis. 22, 117-124, 1977).

In detail, laparotomy was made to male dogs (body weight: 9-10 kg) under anesthesia with Nembutal (30 mg/kg, i.v.). Force transducers (F-121S, manufactured by Star Medical Co.) were implanted so that the contraction of circular muscle could be monitored on serosa of the gastric body, gastric antrum (about 3 cm proximal to the pylorus), duodenum and jejunum. In addition, a silicone tube was inserted from the right external carotid artery, and the tube was indwelled in the superior vena cava. The

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transducers and the silicone tube were subcutaneously exteriorized out of the body.

The dog was submitted to the test with consciousness and without restraint after about 3 weeks from the operation.

The contractile signals from each transducer were amplified with an amplifier (RTA-1200; manufactured by Nihon Kohden Co.), and recorded with a recording apparatus and a computer. The test compounds were dissolved in saline and intravenously administered (0.5 ml/kg) to the dogs through a silicone tube about 10 minutes after the termination of phase III contractions of interdigestive migrating contractions (IMC) in the antrum.

Evaluation Method:

Contractile signals from the antrum amplified in analog voltage were converted to digital signals, which were integrated to calculate the motor activity. The quantity of work which allows to sustain the maximum contraction in phase III contractions of IMC for 6 seconds was considered as 1 unit, and the motor index (units/30 min) in the period of 30 minutes after the administration of the test compound was obtained. The thus calculated motor index was compared with the motor index obtained after saline was administered.

The results are shown in Table 1.

AUSTRALIA PATENT OFFICE

Table 1

| Test Compounds | Dose (mg/Kg) | Motor Index (units/30min) |
|---|---|---|
| Example 1 | 5 | 7.5 |
| Example 6 | 5 | 6.1 |
| Example 9 | 5 | 7.1 |
| Example 11 | 5 | 10.9 |
| Example 12 | 5 | 9.4 |
| Example 14 | 5 | 6.6 |
| Example 16 | 5 | 4.3 |
| Saline | - | 0.1 |

Toxicity Test:

Groups of 4 - 5 week old ICR mice, each group consisting of 6 mice, were provided for the test. The compounds obtained in the Examples were respectively suspended in 5% gum arabic and each suspension was orally administered to the mice at a dose of 1000 mg/kg. The mice were observed for 1 week. None of the mice died in any dosage groups.

Examples

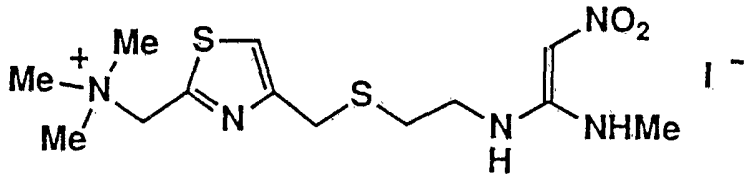
The present invention will hereinafter be described in more detail by way of examples, which however should not be construed as limiting the invention thereto.

Example 1:

Trimethyl=[4-[[[2-[(1-methylamino-2-nitroethenyl)-

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amino]ethyl]thio]methyl]-2-thiazolyl]methylammonium=iodide



N-[2-[[[2-[dimethylamino)methyl-4-thiazolyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine (5 g) was dissolved in chloroform (50 ml). To this mixture, methyl iodide (2.19 g) was added dropwise while cooling on ice. After stirring for 24 hours at 0°C, the solvent was distilled off. The residue was purified by alumina column chromatography (chloroform - water) to obtain 6.8 g of the title compound.

IR (KBr) $cm^{-1}$ : 1380

MS (m/z) : 346 $(M-I)^+$

NMR (DMSO-$d_6$) $\delta$ : 2.55-2.90 (5H, m), 3.15 (9H, s), 3.33-3.47 (2H, m), 3.97 (2H, s), 4.94 (2H, s), 6.50 (1H, brd), 7.25 (1H, brs), 7.80 (1H, s), 9.99 (1H, brd)

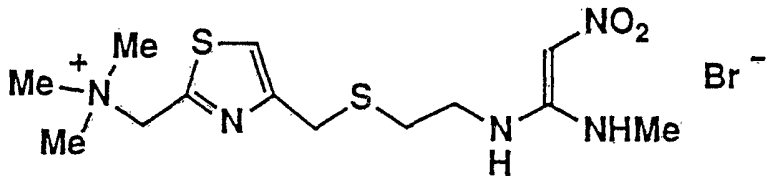
Examples 2 to 18:

The procedure of Example 1 was repeated, using starting materials which were suitably selected to obtain the compounds of Examples 2 to 18.

Example 2:

Trimethyl=[4-[[[2-[(1-methylamino-2-nitroethenyl)-amino]ethyl]thio]methyl]-2-thiazolyl]methylammonium=bromide

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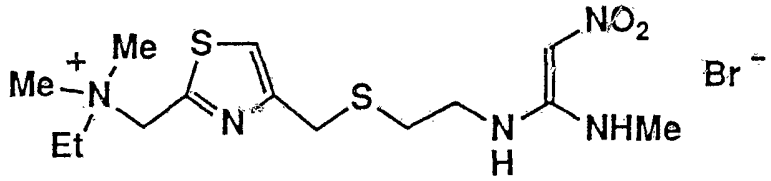
IR (nujol) $cm^{-1}$ : 1380

MS (m/z) : 346 $(M-Br)^+$

NMR (DMSO-$d_6$) $\delta$ : 2.60-2.95 (5H, m), 3.19 (9H, s), 3.30-3.50 (2H, m), 3.98 (2H, s), 5.01 (2H, s), 6.50 (1H, brd), 7.36 (1H, brs), 7.83 (1H, s), 9.99 (1H, brd)

Example 3:

Ethyl=dimethyl=[4-[[[2-[(1-methylamino-2-nitroethenyl)-amino]ethyl]thio]methyl]-2-thiazolyl]methylammonium=bromide



IR (KBr) $cm^{-1}$ : 1385

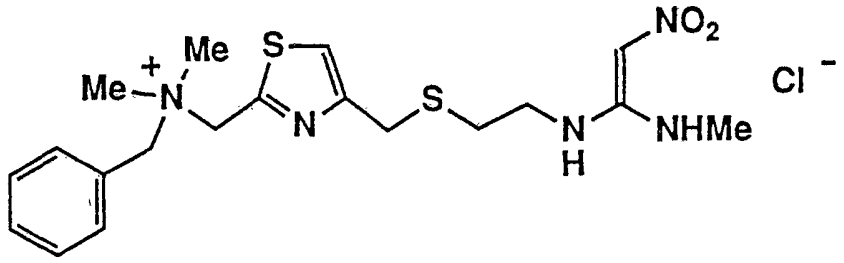
MS (m/z) : 360 $(M-Br)^+$

NMR (DMSO-$d_6$) $\delta$ : 1.34 (3H, t), 2.60-3.00 (5H, m), 3.08 (6H, s), 3.30-3.50 (2H, m), 3.44 (2H, q), 3.97 (2H, s), 4.94 (2H, s), 6.50 (1H, brd), 7.31 (1H, brs), 7.81 (1H, s), 9.95 (1H, brd)

Example 4:

Benzyl=dimethyl=[4-[[[2-[(1-methylamino-2-nitroethenyl)amino]ethyl]thio]methyl]-2-thiazolyl]-methylammonium=chloride

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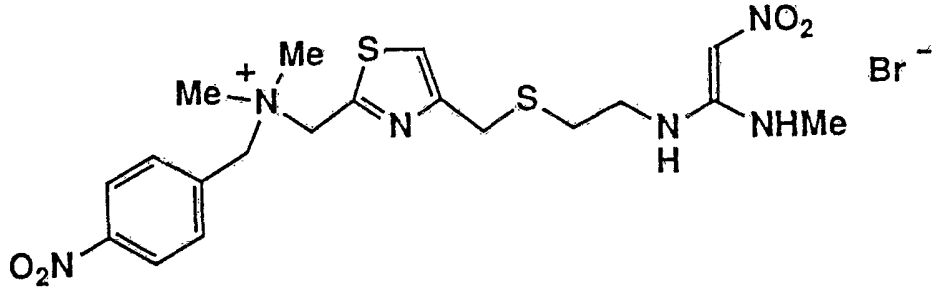
IR (KBr) $cm^{-1}$ : 1385

MS (m/z) : 422 $(M-C\ell)^+$

NMR (DMSO-$d_6$) $\delta$ : 2.60-2.95 (5H, m), 3.04 (6H, s), 3.30-3.60 (2H, m), 4.01 (2H, s), 4.75 (2H, s), 4.99 (2H, s), 6.50 (1H, brd), 7.40-7.70 (6H, m), 7.86 (1H, s), 9.95 (1H, brd)

Example 5:

Dimethyl=4-nitrobenzyl=[4-[[[2-[(1-methylamino-2-nitroethenyl)amino]ethyl]thio]methyl]-2-thiazolyl]-methylammonium=bromide



IR (KBr) $cm^{-1}$ : 1385

MS (m/z) : 467 $(M-Br)^+$

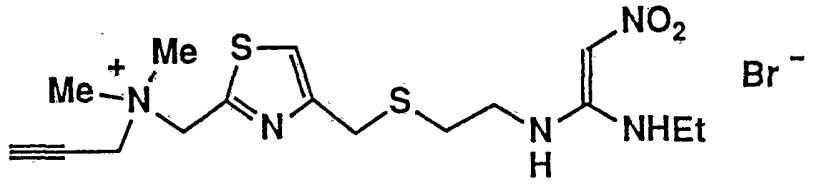
NMR (MeOH-$d_4$) $\delta$ : 2.75-2.95 (5H, m), 3.18 (6H, s), 3.48 (2H, t), 4.02 (2H, s), 4.89 (2H, s), 4.98 (2H, s), 6.70 (1H, brs), 7.73 (1H, s), 8.01 (2H, d), 8.38 (2H, d)

Example 6:

Dimethyl=propargyl=[4-[[[2-[(1-ethylamino-2-nitroethenyl)amino]ethyl]thio]methyl]-2-thiazolyl]-

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methylammonium=bromide



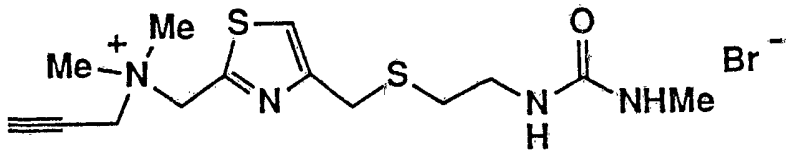
IR (KBr) $cm^{-1}$ : 2120, 1390

MS (m/z) : 384 $(M-Br)^+$

NMR (DMSO-$d_6$) $\delta$ : 1.09 (3H, brs), 2.69 (2H, brs), 3.19 (6H, s),
3.05-3.55 (4H, m), 3.94 (2H, s), 4.08 (1H, s), 4.51 (2H, s),
5.03 (2H, s), 6.48 (1H, s), 7.31 (1H, brs), 7.81 (1H, s),
10.00 (1H, brd)

Example 7:

Dimethyl=propargyl=[4-[[[2-[(3-methylureido)ethyl]-thio]methyl]-2-thiazolyl]methylammonium=bromide



IR (KBr) $cm^{-1}$ : 2125, 1690

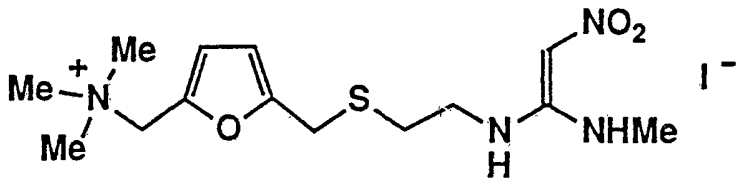
MS (m/z) : 327 $(M-Br)^+$

NMR (DMSO-$d_6$) $\delta$ : 2.50-2.56 (5H, m), 3.12-3.40 (2H, m), 3.21 (6H, s),
3.92 (2H, s), 4.12 (1H, brs), 4.50 (2H, d), 5.02 (2H, s),
5.86 (1H, brs), 6.06 (1H, brs), 7.81 (1H, s)

Example 8:

Trimethyl=[2-[[[2-[(1-methylamino-2-nitroethenyl)-amino]ethyl]thio]methyl]-5-furanyl]methylammonium=iodide

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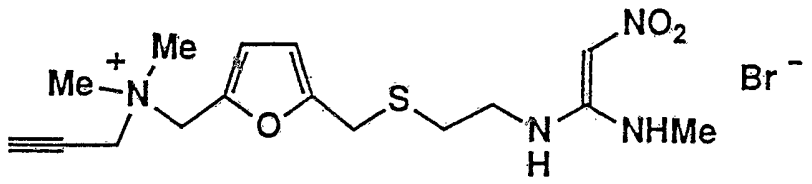
IR (KBr) $cm^{-1}$ : 1385

MS (m/z) : 329 $(M-I)^+$

NMR (DMSO-$d_6$) $\delta$ : 2.60-2.90 (5H, m), 3.04 (9H, s), 3.30-3.48 (2H, m), 3.89 (2H, s), 4.61 (2H, s), 6.46 (1H, d), 6.48 (1H, brs), 6.76 (1H, d), 7.22 (1H, brs), 9.98 (1H, brd)

Example 9:

Dimethyl=propargyl=[2-[[[2-[(1-methylamino)-2-nitroethenyl)amino]ethyl]thio]methyl]-5-furanyl]-methylammonium=bromide



IR (KBr) $cm^{-1}$ : 2125, 1385

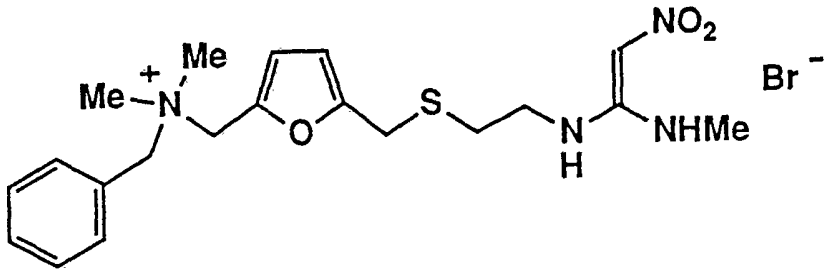
MS (m/z) : 353 $(M-Br)^+$

NMR (DMSO-$d_6$) $\delta$ : 2.62-2.93 (5H, m), 3.07 (6H, s), 3.30-3.50 (2H, m), 3.89 (2H, s), 4.09 (1H, t), 4.35 (2H, d), 4.68 (2H, s), 6.47 (1H, d), 6.50 (1H, brs), 6.79 (1H, d), 7.32 (1H, brd), 9.99 (1H, brd)

Example 10:

Benzyl=dimethyl=[2-[[[2-[(1-methylamino-2-nitroethenyl)amino]ethyl]thio]methyl]-5-furanyl]-methylammonium=bromide

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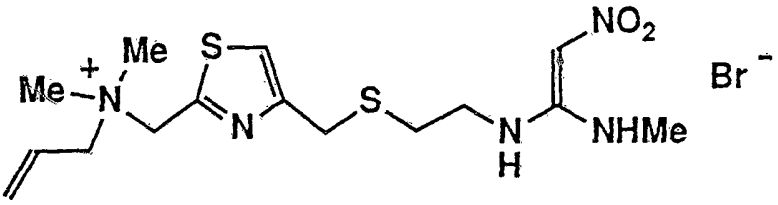
IR (KBr) $cm^{-1}$ : 1385

MS (m/z) : 405 $(M-Br)^+$

NMR (DMSO-$d_6$) $\delta$ : 2.61-2.95 (5H, m), 2.97 (6H, s), 3.31-3.61 (2H, m),
3.94 (2H, s), 4.73 (2H, s), 4.78 (2H, s), 6.46 (1H, brs),
6.48 (1H, d), 6.86 (1H, d), 7.42 (1H, brs),
7.50-7.58 (3H, m), 7.64-7.71 (2H, m), 10.01 (1H, brd)

Example 11:

Allyl=dimethyl=[4-[[[2-[(1-methylamino-2-nitroethenyl)amino]ethyl]thio]methyl]-2-thiazolyl]-methylammonium=bromide



IR (KBr) $cm^{-1}$ : 1380

MS (m/z) : 372 $(M-Br)^+$

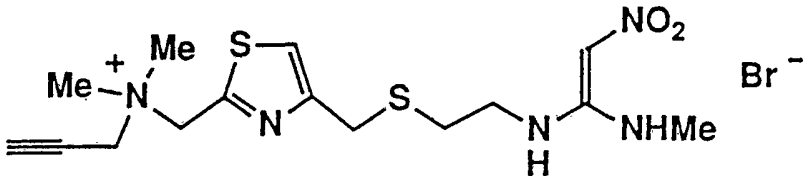
NMR (DMSO-$d_6$) $\delta$ : 2.55-3.00 (5H, m), 3.09 (6H, s), 3.33-3.55 (2H, m),
3.98 (2H, s), 4.10 (2H, d), 4.95 (2H, s), 5.62-5.73 (2H, m),
6.02-6.23 (1H, m), 6.46 (1H, brd), 7.30 (1H, brs),
7.81 (1H, s), 9.99 (1H, brd)

Example 12:

Dimethyl=propargyl=[4-[[[2-[(1-methylamino-2-

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nitroethenyl)amino]ethyl]thio]methyl]-2-thiazolyl]-methylammonium=bromide



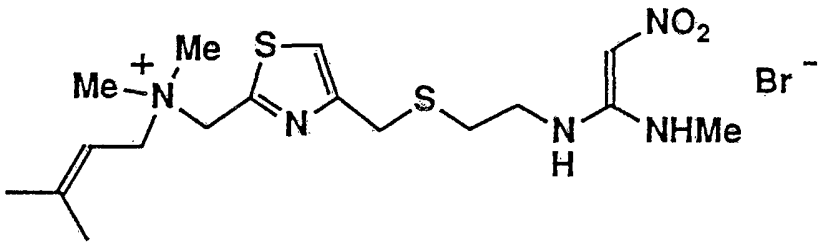
IR (KBr) $cm^{-1}$ : 2120, 1380

MS (m/z) : 370 $(M-Br)^+$

NMR (DMSO-$d_6$) $\delta$ : 2.53-2.92 (5H, m), 3.19 (6H, s), 3.39-3.60 (2H, m), 3.97 (2H, s), 4.12 (1H, t), 4.47 (2H, d), 5.00 (2H, s), 6.49 (1H, brd), 7.30 (1H, brs), 7.82 (1H, s), 9.99 (1H, brd)

Example 13:

Dimethyl=3-methyl-2-butenyl=[4-[[[2-[(1-methylamino-2-nitroethenyl)amino]ethyl]thio]methyl]-2-thiazolyl]-methylammonium=bromide



IR (KBr) $cm^{-1}$ : 1380

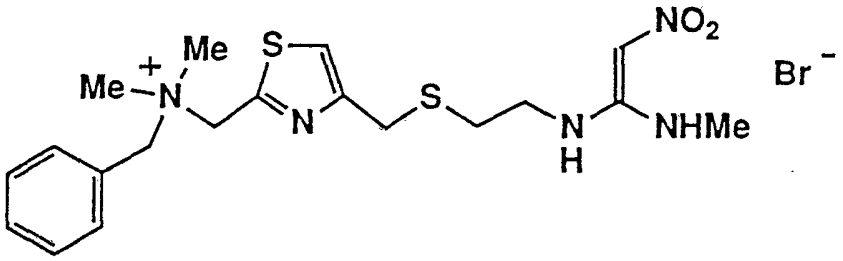
MS (m/z) : 400 $(M-Br)^+$

NMR (DMSO-$d_6$) $\delta$ : 1.78 (3H, s), 1.85 (3H, s), 2.60-2.90 (5H, m), 3.03 (6H, s), 3.30-3.50 (2H, m), 3.98 (2H, s), 4.06 (2H, d), 4.92 (2H, s), 5.50 (1H, t), 6.44 (1H, brs), 7.28 (1H, s), 7.37 (1H, brs), 9.98 (1H, brd)

Example 14:

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Benzyl=dimethyl=[4-[[[2-[(1-methylamino-2-nitroethenyl)amino]ethyl]thio]methyl]-2-thiazolyl]-methylammonium=bromide



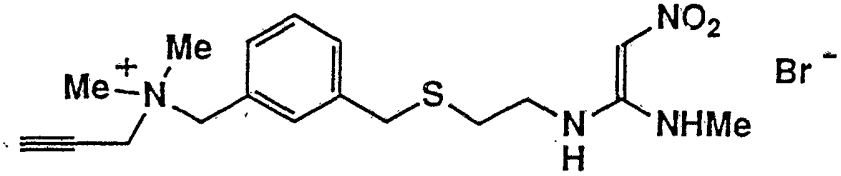

IR (KBr) $cm^{-1}$ : 1380

MS (m/z) : 422 $(M-Br)^+$

NMR (DMSO-$d_6$) $\delta$ : 2.60-2.90 (5H, m), 3.06 (6H, s), 3.37-3.55 (2H, m), 4.01 (2H, s), 4.78 (2H, s), 5.01 (2H, s), 6.48 (1H, brd), 7.37 (1H, brs), 7.49-7.57 (3H, m), 7.67-7.70 (2H, m), 7.86 (1H, s), 9.95 (1H, brd)

Example 15:

Dimethyl=propargyl=[3-[[[2-[(1-methylamino-2-nitroethenyl)amino]ethyl]thio]methyl]benzylammonium=bromide




IR (KBr) $cm^{-1}$ : 2120, 1385

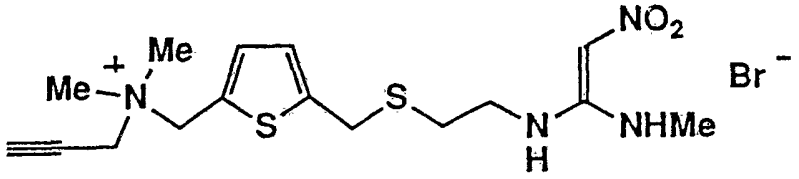
MS (m/z) : 363 $(M-Br)^+$

NMR (DMSO-$d_6$) $\delta$ : 2.50-2.90 (5H, m), 3.05 (6H, s), 3.25-3.45 (2H, m), 3.86 (2H, s), 4.15 (1H, t), 4.30 (2H, d), 4.59 (2H, s), 6.46 (1H, brs), 7.27 (1H, brs), 7.44-7.54 (4H, m), 9.97 (1H, brd)

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Example 16:

Dimethyl=propargyl=[2-[[[2-[(1-methylamino-2-nitroethenyl)amino]ethyl]thio]methyl]-5-thienyl]-methylammonium=bromide



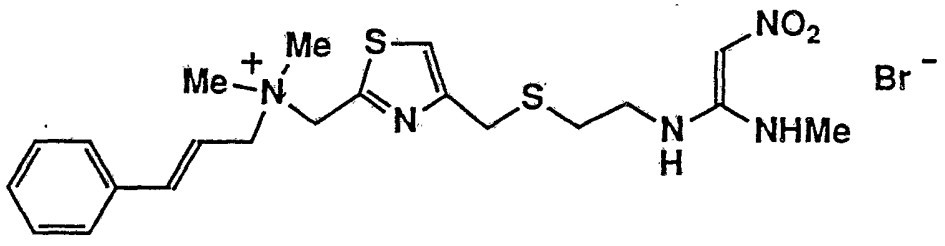
IR (KBr) $cm^{-1}$ : 2110, 1380

MS (m/z) : 369 $(M-Br)^+$

NMR (DMSO-$d_6$) $\delta$ : 2.60-2.95 (5H, m), 3.11 (6H, s), 3.30-3.50 (2H, m), 4.12 (2H, s), 4.15 (1H, s), 4.36 (2H, s), 4.85 (2H, s), 6.46 (1H, s), 7.12 (1H, d), 7.28 (1H, d), 7.35 (1H, brs), 10.00 (1H, brd)

Example 17:

Cinnamyl=dimethyl=[4-[[[2-[(1-methylamino-2-nitroethenyl)amino]ethyl]thio]methyl]-2-thiazolyl]-methylammonium=bromide



IR (KBr) $cm^{-1}$ : 1380

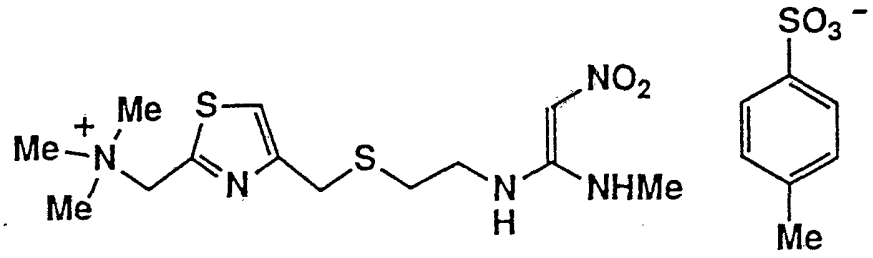
MS (m/z) : 448 $(M-Br)^+$

NMR (DMSO-$d_6$) $\delta$ : 2.57-2.85 (5H, m), 3.13 (6H, s), 3.20-3.50 (2H, m), 4.00 (2H, s), 4.24 (2H, d), 4.98 (2H, s), 6.44 (1H, brs), 6.56 (1H, dt), 6.95 (1H, d), 7.25 (1H, brs), 7.36-7.63 (5H, m), 7.82 (1H, s), 9.97 (1H, brd)

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Example 18:

Trimethyl=[4-[[[2-[(1-methylamino-2-nitroethenyl)-amino]ethyl]thio]methyl]-2-thiazolyl]methylammonium=p-toluenesulfonato



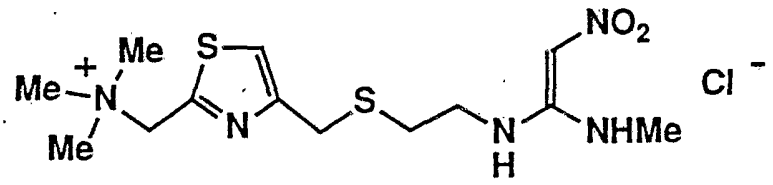
IR (KBr) $cm^{-1}$ : 1390

MS (m/z) : 346 $(M-C_7H_7SO_3)^+$

NMR (DMSO-$d_6$) $\delta$ : 2.29 (3H, s), 2.60-2.90 (5H, m), 3.16 (9H, s), 3.42 (2H, m), 3.96 (2H, s), 4.95 (2H, s), 6.50 (1H, brd), 7.13 (2H, d), 7.32 (1H, brs), 7.51 (2H, d), 7.80 (1H, s), 10.00 (1H, brd)

Example 19:

Trimethyl=[4-[[[2-[(1-methylamino-2-nitroethenyl)-amino]ethyl]thio]methyl]-2-thiazolyl]methylammonium=chloride



Method A:

The compound (20g) obtained in Example 1 was allowed to pass through an anion exchange resin column (IRA-900, Cl-type), and eluted with purified water. The solvent in the eluted fraction was distilled off under reduced pressure to

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obtain 14.6 g of the target compound.

IR (nujol) $cm^{-1}$ : 1380

MS (m/z) : 346 $(M-C\ell)^+$

NMR (DMSO-$d_6$) $\delta$ : 2.51-2.91 (5H, m), 3.21 (9H, s), 3.30-3.50 (2H, m), 3.99 (2H, s), 5.07 (2H, s), 6.50 (1H, brd), 7.80 (1H, brs), 7.86 (1H, s), 9.99 (1H, brd)

Method B:

(1) N-[2-[[(2-hydroxymethyl-4-thiazolyl)methyl]-thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine

Under stream of argon, 1-methylamino-1-methylthio-2-nitroethene (16.6 g) was dissolved in absolute methanol (300 ml), to which 2-aminoethanethiol (8.64 g) was added. The obtained mixture was stirred for 30 minutes at room temperature, and the solvent was distilled off under reduced pressure. The residue was dissolved in an aqueous KOH solution (1.1 N, 200 ml). This aqueous solution was added dropwise to a mixture of 2-benzoyloxymethyl-4-chloromethylthiazol (25.0 g) and methanol (250 g) while cooling on ice. The resulting mixture was stirred for 1 hour in an ice bath, and further for 4 hours at room temperature. Subsequently, the solvent was distilled off under reduced pressure. The residue was purified by alumina column chromatography (chloroform - methanol), recrystallized from methanol-ethyl acetate to obtain 12.4 g of the title compound.

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m.p. 131.3-132.3℃

IR (KBr) $cm^{-1}$ : 3165, 1625, 1560, 1375

MS (m/z) : 305 ($MH^+$)

NMR (DMSO-$d_6$) $\delta$ : 2.70 (3H, brd), 2.83 (2H, brd), 3.36 (2H, brd), 3.84 (2H, s), 4.69 (2H, d), 6.01 (1H, t), 6.44 (1H, brd), 7.22 (1H, brd), 7.39 (1H, s), 10.04 (1H, brd)

(2) N-[2-[(2-chloromethyl-4-thiazolyl)methyl]-thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine

N-[2-[[(2-hydroxymethyl-4-thiazolyl)methyl]thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine (1 g) obtained in (1) above was added to phosphorus oxychloride (15 ml), and the mixture was stirred for 21 hours at room temperature. The reaction mixture was concentrated under reduced pressure. The residue was combined with ice-water, and then extracted with ethyl acetate. The extract was washed with saturated NaCl solution, followed by drying over magnesium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography (chloroform - methanol) to obtain 420 mg of the title compound.

IR ($CHCl_3$) $cm^{-1}$ : 1610, 1570, 1385

MS (m/z) : 323 ($MH^+$)

NMR (DMSO-$d_6$) $\delta$ : 2.75 (2H, t), 2.78 (3H, d), 3.38 (2H, q), 3.88 (2H, s), 5.00 (2H, s), 6.43 (1H, s), 7.24 (1H, brd), 7.51 (1H, s), 10.05 (1H, brd)

(3) Trimethyl=[4-[[[2-[(1-methylamino-2-nitroethenyl)-amino]ethyl]thio]methyl]-2-thiazolyl]methylammonium=

AUSTRALIA PATENT OFFICE MB

chloride

N-[2-[[(2-chloromethyl-4-thiazolyl)methyl]-thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine (394 mg) obtained in (2) above was dissolved in methanol (10 ml), into which trimethylamine was blown while cooling the mixture on ice. The resulting mixture was stirred overnight at room temperature, and the solvent was distilled off under reduced pressure. The residue was purified by alumina column chromatography (chloroform - methanol) to obtain 250 mg of the title compound.

IR (nujol) $cm^{-1}$ : 1380

MS (m/z) : 346 $(M-C\ell)^+$

NMR (DMSO-$d_6$) $\delta$ : 2.51-2.91 (5H, m), 3.21 (9H, s), 3.30-3.50 (2H, m), 3.99 (2H, s), 5.07 (2H, s), 6.50 (1H, brd), 7.80 (1H, brs), 7.86 (1H, s), 9.99 (1H, brd)

Formulation Example 1:

| | |
|---|---|
| Compound of Example 1 | 20 g |
| Lactose | 315 g |
| Corn starch | 125 g |
| Crystalline cellulose | 25 g |

The above ingredients were blended into a uniform mixture, to which 200 ml of 7.5% aqueous hydroxypropyl-cellulose solution was added, and then passed an extruder equipped with a screen of 0.5 mm in diameter to prepare granules. Immediately thereafter, the granules were rounded with a marumerizer and dried to obtain a granule preparation.

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Formulation Example 2:

| | |
|---|---|
| Compound of Example 11 | 20 g |
| Lactose | 100 g |
| Corn starch | 36 g |
| Crystalline cellulose | 30 g |
| Carboxymethylcellulose calcium | 10 g |
| Magnesium stearate | 4 g |

The above ingredients were blended into a uniform mixture, and prepared into tablets each weighing 200 mg with a single-shot tableting machine equipped with a pestle having a diameter of 7.5 mm.

Formulation Example 3:

| | |
|---|---|
| Compound of Example 12 | 100 mg |
| Sodium acetate | 2 mg |
| Acetic acid (for adjusting pH to 5.8) | suitable amount |
| Purified water | suitable amount |
| | Total: 10 ml/vial |

The above formulation was prepared into an injection preparation by a method known *per se*.

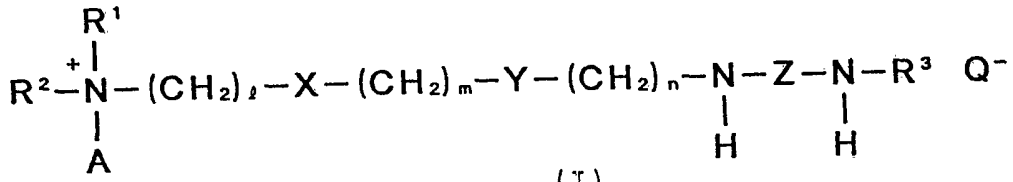
Industrial Applicability

Since the compounds according to the present invention have activity of accelerating the gastrointestinal contraction or of improving the gastrointestinal motility remarkably as well as high safety, they have utility in the medical field of treating gastrointestinal disorders, etc.

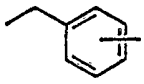
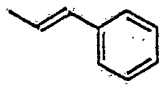
AUSTRALIA PATENT OFFICE MTB

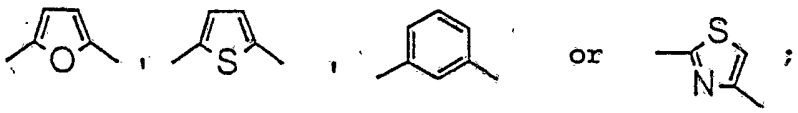
## CLAIMS

1. A quaternary ammonium salt represented by the following formula (I):

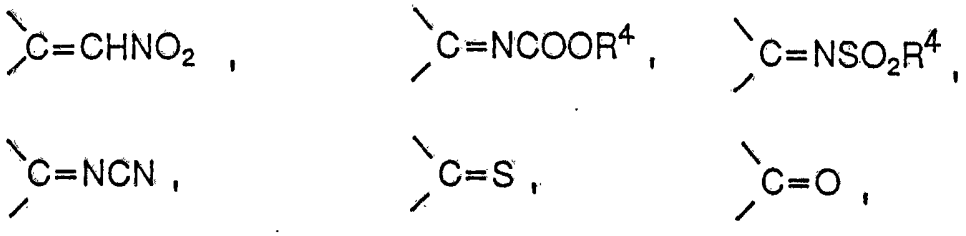


(I)

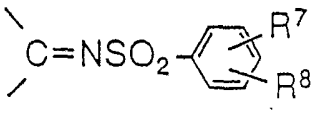
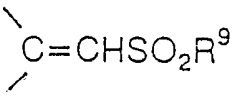
[wherein $R^1$ and $R^2$ represent lower alkyl groups which may be the same or different from each other; $R^3$ represents hydrogen, lower alkyl, phenyl, benzyl, or $-COOR^4$ (wherein $R^4$ represents lower alkyl); A represents lower alkyl, lower alkenyl, lower alkynyl, $-(CH_2)_p-COOR^5$ (wherein $R^5$ represents hydrogen or lower alkyl, and p represents an integer of from 1 to 5),  or  (wherein $R^6$ represents hydrogen, hydroxyl, nitro, lower alkyl, $-COOR^5$, or $-SO_3R^5$); $Q^-$ represents a counter anion of quaternary ammonium salt; X represents



Y represents methylene, oxygen or sulfur; Z represents



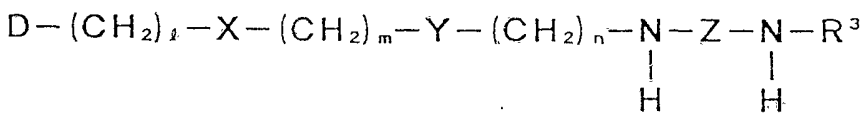
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or


(wherein $R^7$ and $R^8$ are the same or different from each other and independently represent hydrogen, halogen, nitro, lower alkyl or lower alkoxyl, and $R^9$ represents lower alkyl or phenyl); 1 and m represent each an integer of 1 or 2; and n represents an integer of from 1 to 3].

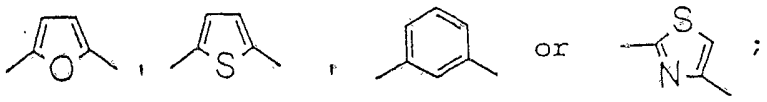
2. Use of the quaternary ammonium salt of claim 1 as medicines.

3. A compound represented by the following formula (IX):

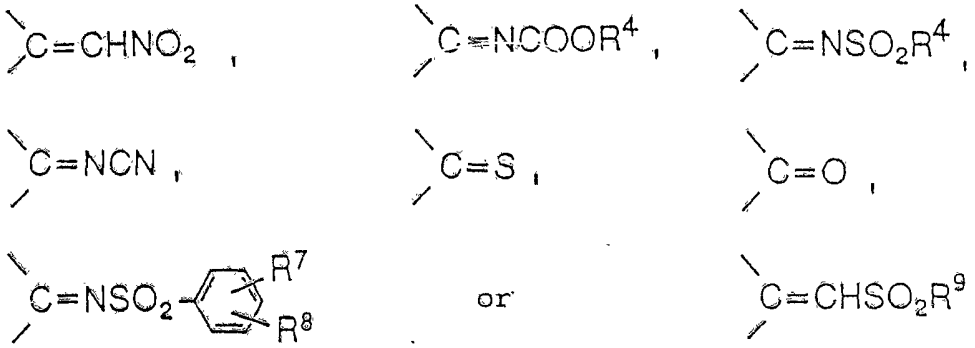


(IX)

[wherein $R^3$ represents hydrogen, lower alkyl, phenyl, benzyl, or -COOR6 (wherein $R^6$ represents lower alkyl); D represents halogen or an active ester residue; X represents



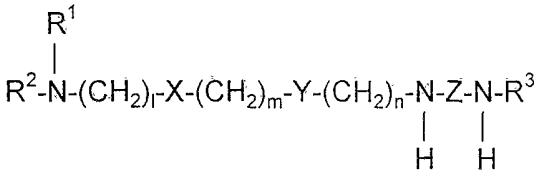
Y represents methylene, oxygen or sulfur; Z represents



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(wherein $R^7$ and $R^8$ are the same different from each other and independently represent hydrogen, halogen, nitro, lower alkyl or lower alkoxyl, and $R^9$ represents lower alkyl or phenyl); 1 and m represent each an integer of 1 or 2; and n represents an integer of 1 to 3].

4. A process for preparing a compound according to claim 1 including reacting a compound of formula (II)



(II)

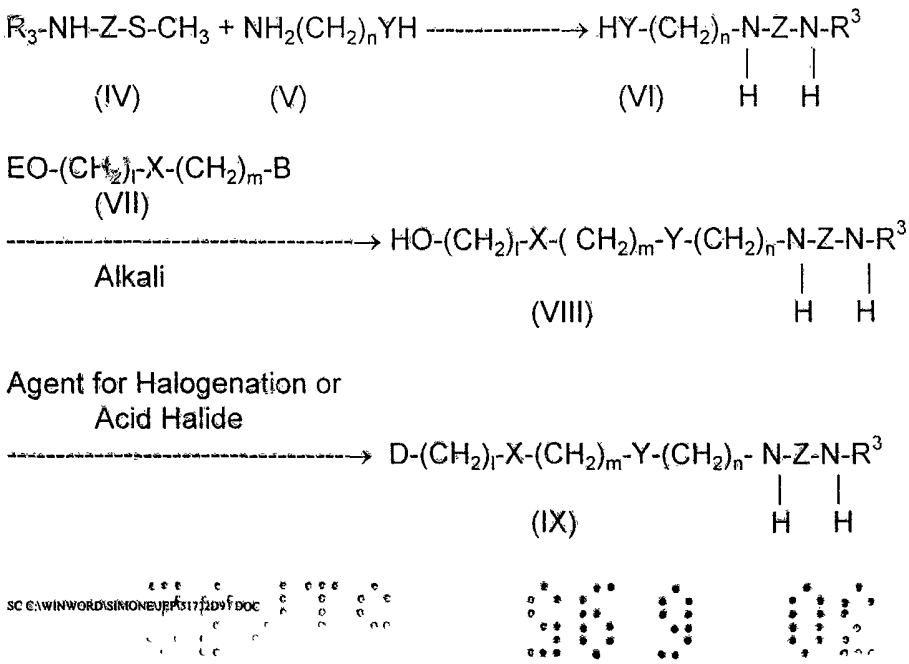
with a compound of formula (III)

A - Q (III)

wherein $R^1$, $R^2$, $R^3$, A, Q, X, Y, Z, l, m and n have the same meaning as hereinbefore described.

5. A process according to claim 4 including reacting the compound of formula (II) with a compound of formula (III) in the presence of an inert solvent including methanol, ethanol, dichloromethane, chloroform, ethyl acetate, dimethyl-formamide, dimethylsulfoxide or water.

6. A process for preparing a compound according to claim 1 including reacting a halogen compound or an ester compound with an amine compound according to the reaction scheme

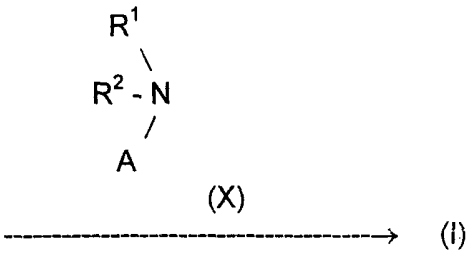


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(wherein $R^1$, $R^2$, $R^3$, A, X, Y, Z, l, m and n have the same meaning as defined hereinbefore, E represents a protective group for an alcohol such as benzoyl and acetyl, B represents a halogen atom, and D represents a halogen atom or an acid residue.

7. A composition for the treatment of gastrointestinal disorders including a compound according to claim 1 and a biologically acceptable carrier.

8. A composition for the treatment of gastrointestinal disorders including a compound according to claim 3 and a biologically acceptable carrier.

9. A method of treating a gastrointestinal disorder including administering an effective amount of a compound according to claim 1.

10. A compound according to claim 1 or claim 3 substantially as hereinbefore described with reference to the examples.

DATED : 29 June, 1995

PHILLIPS ORMONDE & FITZPATRICK

Attorneys For:

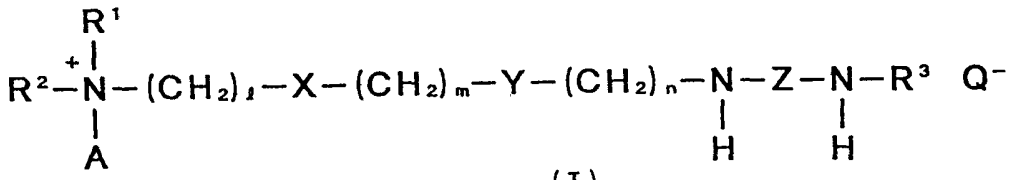
ZERIA PHARMACEUTICAL CO LTD

David B Fitzpatrick

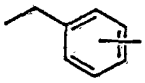
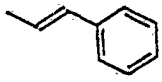
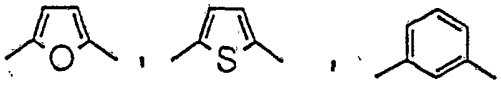
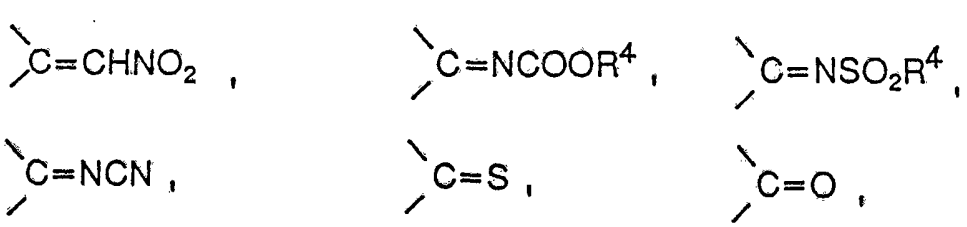
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## ABSTRACT

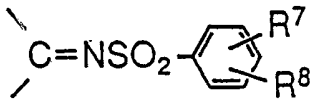
Quaternary ammonium salts represented by the following formula (I):



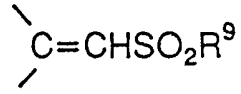
(I)

[wherein $R^1$ and $R^2$ represent lower alkyl groups which may be the same or different from each other; $R^3$ represents hydrogen, lower alkyl, phenyl, benzyl, or $-COOR^4$ (wherein $R^4$ represents lower alkyl); A represents lower alkyl, lower alkenyl, lower alkynyl, $-(CH_2)_p-COOR^5$ (wherein $R^5$ represents hydrogen or lower alkyl, and p represents an integer of from 1 to 5),  or  (wherein $R^6$ represents hydrogen, hydroxyl, nitro, lower alkyl, $-COOR^5$, or $-SO_3R^5$); $Q^-$ represents a counter anion of quaternary ammonium salt; X represents  ; Y represents methylene, oxygen or sulfur; Z represents 


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or



(wherein $R^7$ and $R^8$ are the same or different from each other and independently represent hydrogen, halogen, nitro, lower alkyl or lower alkoxyl, and $R^9$ represents lower alkyl or phenyl); l and m represent each an integer of 1 or 2; and n represents an integer of 1 to 3].

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# INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP93/00607

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl$^5$ C07C211/63, 217/48, 229/06, 275/10, 275/24, 279/24, 279/28, 311/05, 311/18, C07C317/28, 323/29, 335/12,

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Int. Cl$^5$ C07C211/63, 217/48, 229/06, 275/10, 275/24, 279/24, 279/28, 311/05, 311/18, C07C317/28, 323/29, 335/12,

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

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

CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | JP, A, 53-149936 (Allen and Hanbaries Ltd.), December 27, 1978 (27. 12. 78), & GB, A, 1604674 & US, A, 5021429 | 1-4 |
| A | JP, A, 54-109963 (Glakuso Group Ltd.), August 29, 1979 (29. 08. 79), & US, A, 4233302 | 1-4 |
| A | JP, A, 57-165348 (Teikoku Hormone Mfg. Co., Ltd.), October 12, 1982 (12. 10. 82), (Family: none) | 1-4 |

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:

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

"E" earlier 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)

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

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

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

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

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

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| July 22, 1993 (22. 07. 93) | August 10, 1993 (10. 08. 93) |
| Name and mailing address of the ISA/ Japanese Patent Office<br>Facsimile No. | Authorized officer<br>Telephone No. |

Form PCT/ISA/210 (second sheet) (July 1992)

**INTERNATIONAL SEARCH REPORT**

International application No.
PCT/JP93/00607

A(Continuation). CLASSIFICATION OF SUBJECT MATTER

Int. Cl$^5$ 335/16, 335/28, 211/29, 217/08, 219/22, C07D277/28, 307/52, 333/20, A61K31/14, 31/18, 31/185, 31/19, 31/215, 31/27, 31/275, 31/34, 31/38, 31/425

B(Continuation). FIELDS SEARCHED

Int. Cl$^5$ 335/16, 335/28, 211/29, 217/08, 219/22, C07D277/28, 307/52, 333/20, A61K31/14, 31/18, 31/185, 31/19, 31/215, 31/27, 31/275, 31/34, 31/38, 31/425

国際調査報告

国際出願番号 PCT/JP 93/00607

A. 発明の属する分野の分類（国際特許分類（IPC））

Int. Cl[5] C07C211/63, 217/48, 229/06, 275/10, 275/24, 279/24, 279/28, 311/05,

B. 調査を行った分野

調査を行った最小限資料（国際特許分類（IPC））

Int. Cl[5] C07C211/63, 217/48, 229/06, 275/10, 275/24, 279/24, 279/28, 311/05,

最小限資料以外の資料で調査を行った分野に含まれるもの

国際調査で使用した電子データベース（データベースの名称、調査に使用した用語）

CAS ONLINE

C. 関連すると認められる文献

| 引用文献のカテゴリー* | 引用文献名 及び一部の箇所が関連するときは、その関連する箇所の表示 | 関連する請求の範囲の番号 |
|---|---|---|
| A | JP, A, 53-149936（アレン・アンド・ハンバリーズ・リミテッド）<br>27. 12月. 1978（27. 12. 78）<br>&GB, A, 1604674&US, A, 5021429 | 1-4 |
| A | JP, A, 54-109963（グラクソ・グループ・リミテッド）<br>29. 8月. 1979（29. 08. 79）<br>&US, A, 4233302 | 1-4 |

☑ C欄の続きにも文献が列挙されている。

☐ パテントファミリーに関する別紙を参照。

* 引用文献のカテゴリー
「A」特に関連のある文献ではなく、一般的技術水準を示すもの
「E」先行文献ではあるが、国際出願日以後に公表されたもの
「L」優先権主張に疑義を提起する文献又は他の文献の発行日若しくは他の特別な理由を確立するために引用する文献（理由を付す）
「O」口頭による開示、使用、展示等に言及する文献
「P」国際出願日前で、かつ優先権の主張の基礎となる出願の日の後に公表された文献
「T」国際出願日又は優先日後に公表された文献であって出願と矛盾するものではなく、発明の原理又は理論の理解のために引用するもの
「X」特に関連のある文献であって、当該文献のみで発明の新規性又は進歩性がないと考えられるもの
「Y」特に関連のある文献であって、当該文献と他の1以上の文献との、当業者にとって自明である組合せによって進歩性がないと考えられるもの
「&」同一パテントファミリー文献

| 国際調査を完了した日 | 国際調査報告の発送日 |
|---|---|
| 22. 07. 05 | 10.08.93 |

| 名称及びあて先 | 特許庁審査官（権限のある職員） |
|---|---|
| 日本国特許庁（ISA/JP）<br>郵便番号100<br>東京都千代田区霞が関三丁目4番3号 | 佐藤 修 印 4H 9280<br>電話番号 03-3581-1101 内線 3444 |

様式PCT/ISA/210（第2ページ）（1992年7月）

| 国際調査報告 | 国際出願番号 PCT/JP 93/00607 |
|---|---|

C（続き）. 関連すると認められる文献

| 引用文献のカテゴリー* | 引用文献名 及び一部の箇所が関連するときは、その関連する箇所の表示 | 関連する請求の範囲の番号 |
|---|---|---|
| A | JP, A, 57-165348（帝国臓器製薬株式会社）<br>12. 10月. 1982（12. 10. 82）（ファミリーなし） | 1－4 |

A. 分類の続き（国際特許分類（ＩＰＣ））

Int. Cl[5] 311/18, C07C317/28, 323/29,
335/12, 335/16, 335/28, 211/29,
217/08, 219/22, C07D277/28,
307/52, 333/20, A61K31/14, 31/18,
31/185, 31/19, 31/215, 31/27,
31/275, 31/34, 31/38, 31/425

B. 調査を行った最小限資料の続き（国際特許分類（ＩＰＣ））

Int. Cl[5] 311/18, C07C317/28, 323/29,
335/12, 335/16, 335/28, 211/29,
217/08, 219/22, C07D277/28,
307/52, 333/20, A61K31/14, 31/18,
31/185, 31/19, 31/215, 31/27,
31/275, 31/34, 31/38, 31/425