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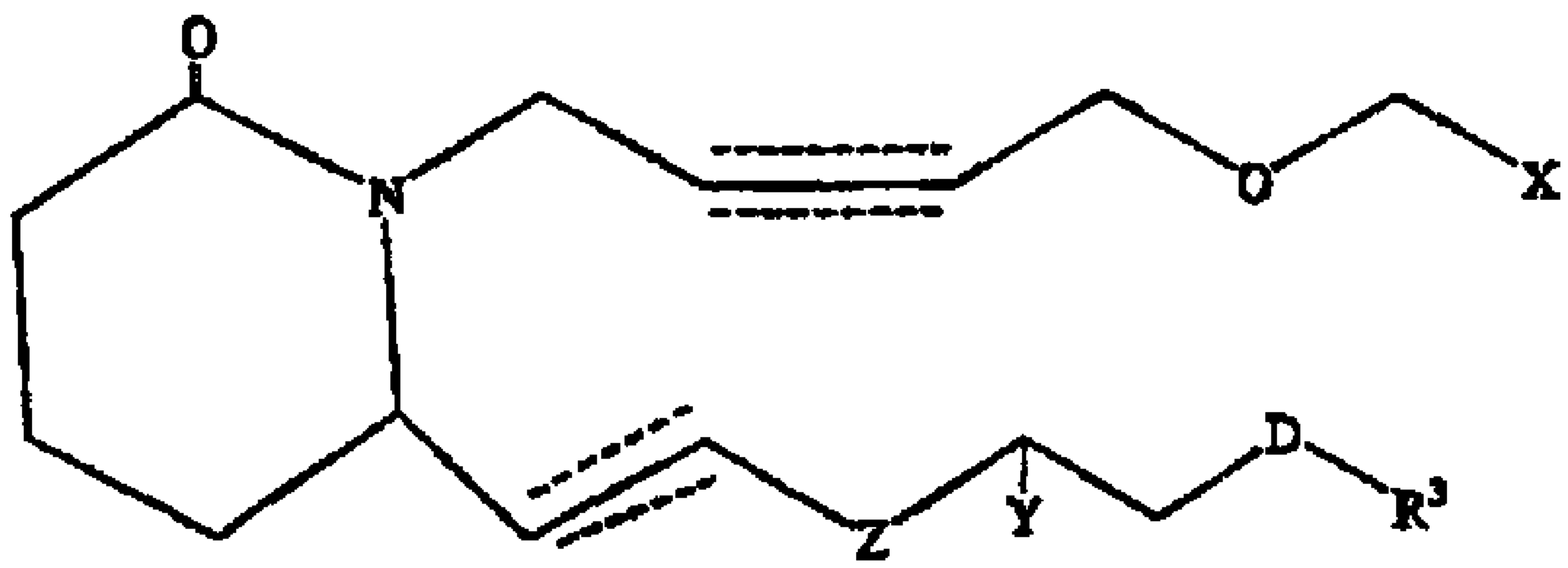
(54) Title: PIPERIDINYL PROSTAGLANDIN E ANALOGS



(57) Abrégé/Abstract:
The present invention provides a method of treating ocular hypertension or glaucoma which comprises administering to an animal having ocular hypertension or glaucoma therapeutically effective amount of a compound represented by the general formula (I); wherein X, Y, Z, D and R^3 are as defined in the specification.

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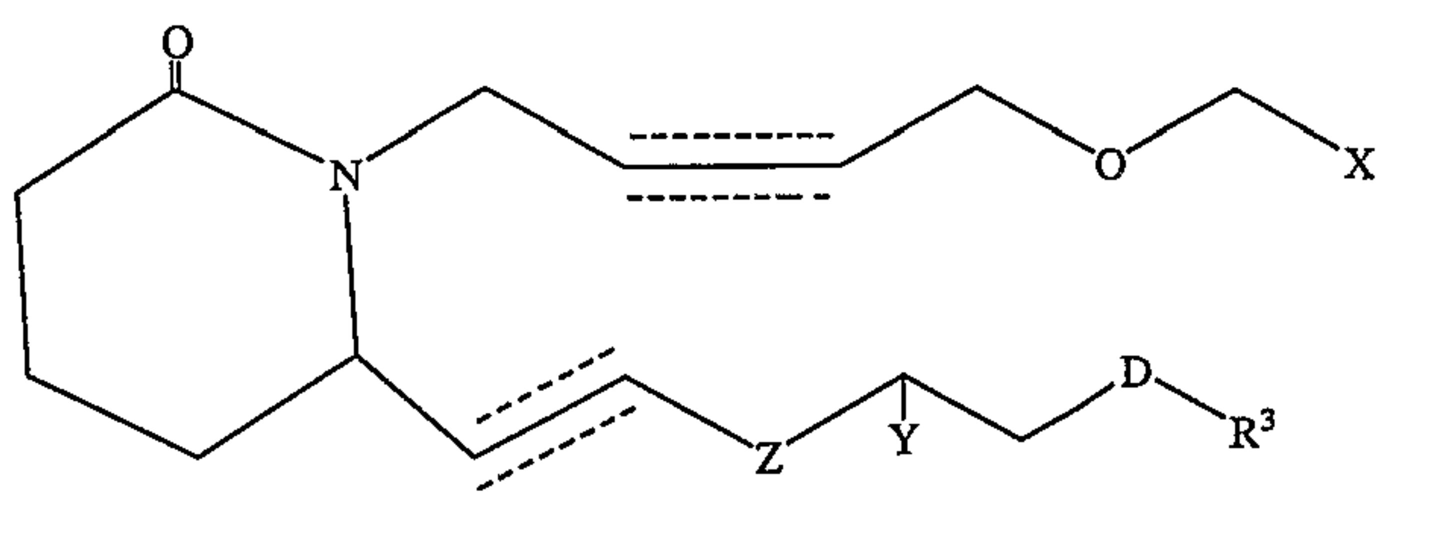
(54) **Title:** PIPERIDINYL PROSTAGLANDIN E ANALOGS



(I)

(57) **Abstract:** The present invention provides a method of treating ocular hypertension or glaucoma which comprises administering to an animal having ocular hypertension or glaucoma therapeutically effective amount of a compound represented by the general formula (I); wherein X, Y, Z, D and R^3 are as defined in the specification.

PIPERIDINYL PROSTAGLANDIN E ANALOGS

Field of the Invention

The present invention relates to piperidinyl prostaglandin E analogs useful as therapeutic agents, e.g. ocular hypotensives that are particularly suited for the management of glaucoma.

Background of the Invention

Description of Related Art

Ocular hypotensive agents are useful in the treatment of a number of various ocular hypertensive conditions, such as post-surgical and post-laser trabeculectomy ocular hypertensive episodes, glaucoma, and as presurgical adjuncts.

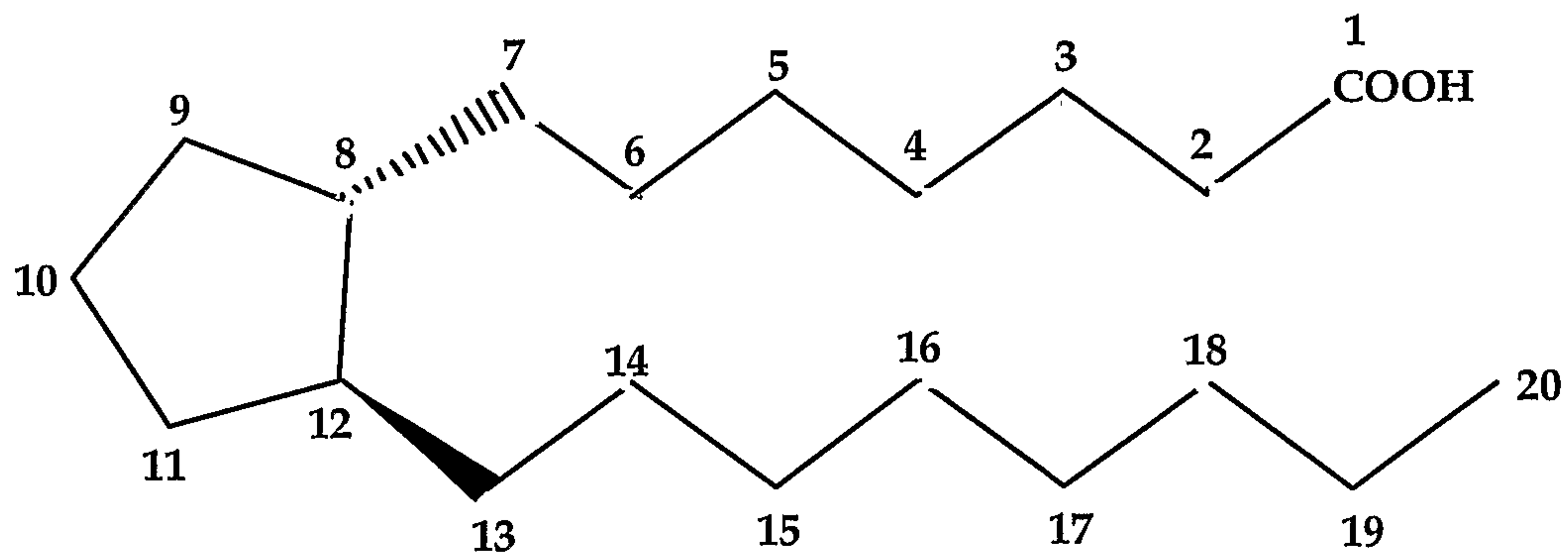
Glaucoma is a disease of the eye characterized by increased intraocular pressure. On the basis of its etiology, glaucoma has been classified as primary or secondary. For example, primary glaucoma in adults (congenital glaucoma) may be either open-angle or acute or chronic angle-closure. Secondary glaucoma results from pre-existing ocular diseases such as uveitis, intraocular tumor or an enlarged cataract.

The underlying causes of primary glaucoma are not yet known. The increased intraocular tension is due to the obstruction of aqueous humor outflow. In chronic open-angle glaucoma, the anterior chamber and its anatomic structures appear normal, but drainage of the aqueous humor is impeded. In acute or chronic angle-closure glaucoma, the anterior chamber is shallow, the filtration angle is narrowed, and the iris may obstruct the trabecular meshwork at the entrance of the canal of Schlemm. Dilation of the pupil may push the root of the iris forward against the angle, and may produce pupilary block and thus precipitate an acute attack. Eyes with narrow anterior chamber angles are predisposed to acute angle-closure glaucoma attacks of various degrees of severity.

Secondary glaucoma is caused by any interference with the flow of aqueous humor from the posterior chamber into the anterior chamber and subsequently, into the canal of Schlemm. Inflammatory disease of the anterior segment may prevent aqueous escape by causing complete posterior synechia in iris bombe, and may plug the drainage channel with exudates. Other common causes are intraocular tumors, enlarged cataracts, central retinal vein occlusion, trauma to the eye, operative procedures and intraocular hemorrhage.

Considering all types together, glaucoma occurs in about 2% of all persons over the age of 40 and may be asymptotic for years before progressing to rapid loss of vision. In cases where surgery is not indicated, topical b-adrenoreceptor antagonists have traditionally been the drugs of choice for treating glaucoma.

Certain eicosanoids and their derivatives have been reported to possess ocular hypotensive activity, and have been recommended for use in glaucoma management. Eicosanoids and derivatives include numerous biologically important compounds such as prostaglandins and their derivatives. Prostaglandins can be described as derivatives of prostanoic acid which have the following structural formula:



Various types of prostaglandins are known, depending on the structure and substituents carried on the alicyclic ring of the prostanoic acid skeleton. Further classification is based on the number of unsaturated bonds in the side chain indicated by numerical subscripts after the generic type of prostaglandin [e.g. prostaglandin E_1 (PGE_1), prostaglandin E_2 (PGE_2)], and on the configuration of the substituents on the alicyclic ring indicated by α or β [e.g. prostaglandin $F_{2\alpha}$ ($PGF_{2\beta}$)].

Prostaglandins were earlier regarded as potent ocular hypertensives, however, evidence accumulated in the last decade shows that some prostaglandins are highly effective ocular hypotensive agents, and are ideally suited for the long-term medical management of glaucoma (see, for example, Bito, L.Z. Biological Protection with Prostaglandins, Cohen, M.M., ed., Boca Raton, Fla, CRC Press Inc., 1985, pp. 231-252; and Bito, L.Z., Applied Pharmacology in the Medical Treatment of Glaucomas Drance, S.M. and Neufeld, A.H. eds., New York, Grune & Stratton, 1984, pp. 477-505. Such prostaglandins include $PGF_{2\alpha}$, $PGF_{1\alpha}$, PGE_2, and certain lipid-soluble esters, such as C_1 to C_2 alkyl esters, e.g. 1-isopropyl ester, of such compounds.

Although the precise mechanism is not yet known experimental results indicate that the prostaglandin-induced reduction in intraocular pressure results from increased uveoscleral outflow [Nilsson et.al., Invest. Ophthalmol. Vis. Sci. (suppl), 284 (1987)].

The isopropyl ester of $PGF_{2\alpha}$ has been shown to have significantly greater hypotensive potency than the parent compound, presumably as a result of its more effective penetration through the cornea. In 1987, this compound was described as "the most potent ocular hypotensive agent ever reported" [see, for example, Bito, L.Z., Arch. Ophthalmol. 105, 1036 (1987), and Siebold et.al., Prodrug 5 3 (1989)].

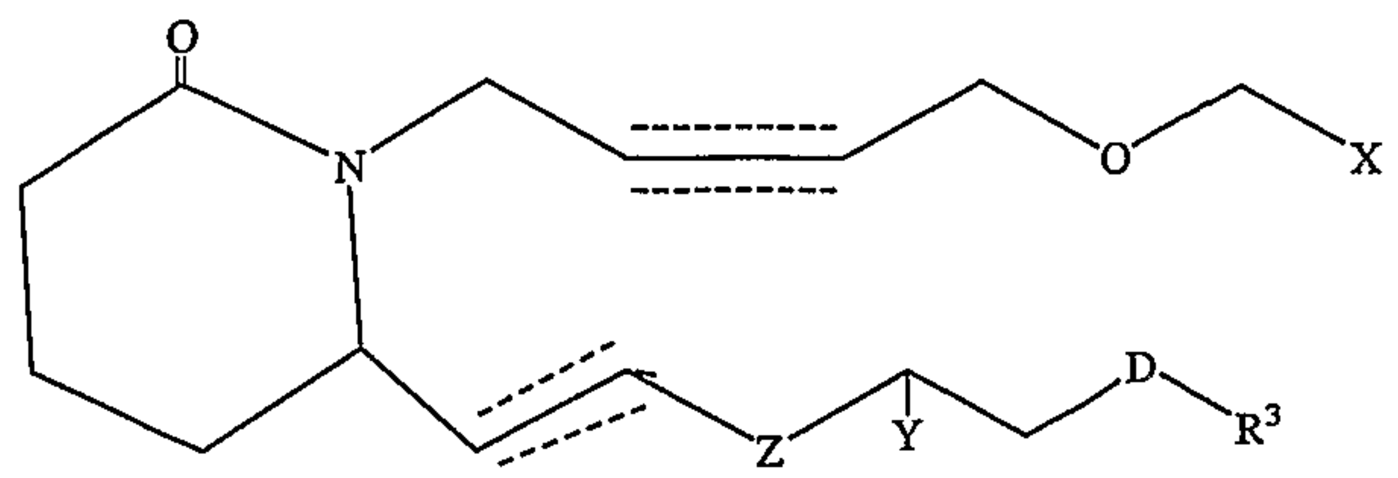
Whereas prostaglandins appear to be devoid of significant intraocular side effects, ocular surface (conjunctival) hyperemia and foreign-body sensation have been consistently associated with the topical ocular use of such compounds, in particular $PGF_{2\alpha}$ and its prodrugs, e.g., its 1-isopropyl ester, in humans. The clinical potentials of prostaglandins in the management of conditions associated with increased ocular pressure, e.g. glaucoma are greatly limited by these side effects.

In a series of co-pending United States patent applications assigned to Allergan, Inc. prostaglandin esters with increased ocular hypotensive activity accompanied with no or substantially reduced side-effects are disclosed. The co-pending USSN 596,430 (filed 10 October 1990, now U.S. Patent 5,446,041), relates to certain 11-acyl-prostaglandins, such as 11-pivaloyl, 11-acetyl, 11-isobutyryl, 11-valeryl, and 11-isovaleryl $PGF_{2\alpha}$. Intraocular pressure reducing 15-acyl prostaglandins are disclosed in the co-pending application USSN 175,476 (filed 29 December 1993). Similarly, 11,15- 9,15 and 9,11-diesters of prostaglandins, for example 11,15-dipivaloyl $PGF_{2\alpha}$ are known to have ocular hypotensive activity. See the co-pending patent applications USSN Nos. 385,645 (filed 07 July 1989, now U.S. Patent 4,994,274), 584,370 (filed 18 September 1990, now U.S. Patent 5,028,624) and 585,284 (filed 18 September 1990, now U.S. Patent 5,034,413).

Certain piperidinyl prostaglandin E analogues have been disclosed for treating glaucoma. See U.S. Patent 6,747,037, filed on June 6, 2003.

Summary of the Invention

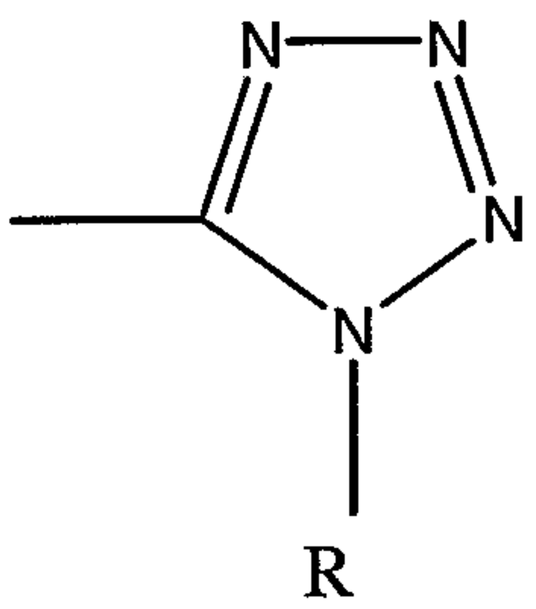
The present invention concerns piperidinyl prostaglandin E analogues which are useful in a method of treating ocular hypertension which comprises administering to a mammal having ocular hypertension a therapeutically effective amount of a compound of formula I



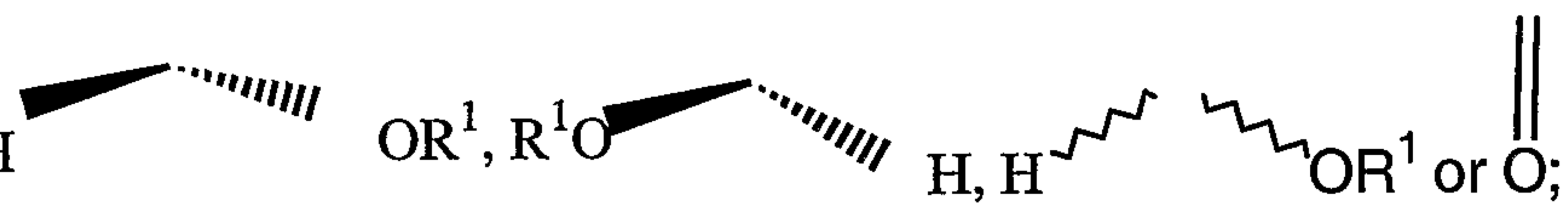
wherein hatched lines represent the α configuration, a triangle represents the β configuration, a wavy line represents either the α configuration or the β configuration and a dotted line represents the presence or absence of a double or a triple bond;

D represents a covalent bond or CH_2 , O, S or NH;

X is CO_2R, $CONR_2$, CH_2OR, $P(O)(OR)_2$, $CONRSO_2R$, $SONR_2$ or



Y is



Z is CH_2 or a covalent bond;

R is H or R^2;

R^1 is H, R^2 , phenyl, or COR^2;

R^2 is C_1-C_5 lower alkyl or alkenyl and R^3 is selected from the group consisting of R^2, phenyl, thienyl, furanyl, pyridyl, benzothienyl, benzofuranyl, naphthyl, or substituted derivatives thereof, wherein the substituents maybe selected from the group consisting of C_1-C_5 alkyl, halogen, CF_3, CN, NO_2, NR_2, CO_2R and OR .

In a still further aspect, the present invention relates to a pharmaceutical product, comprising

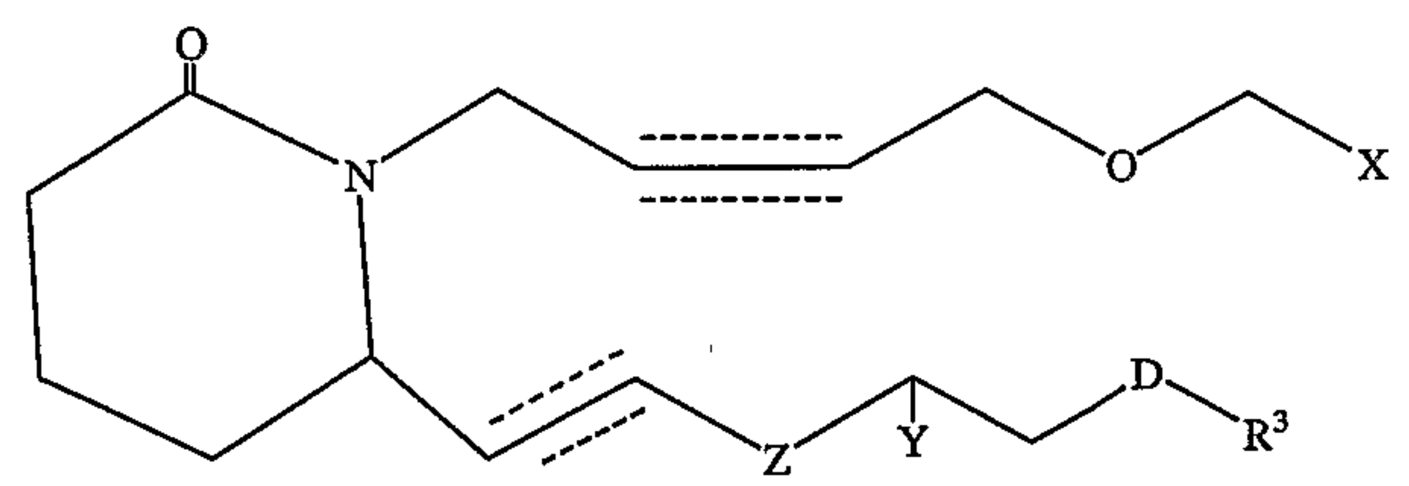
a container adapted to dispense its contents in a metered form; and

an ophthalmic solution therein, as hereinabove defined.

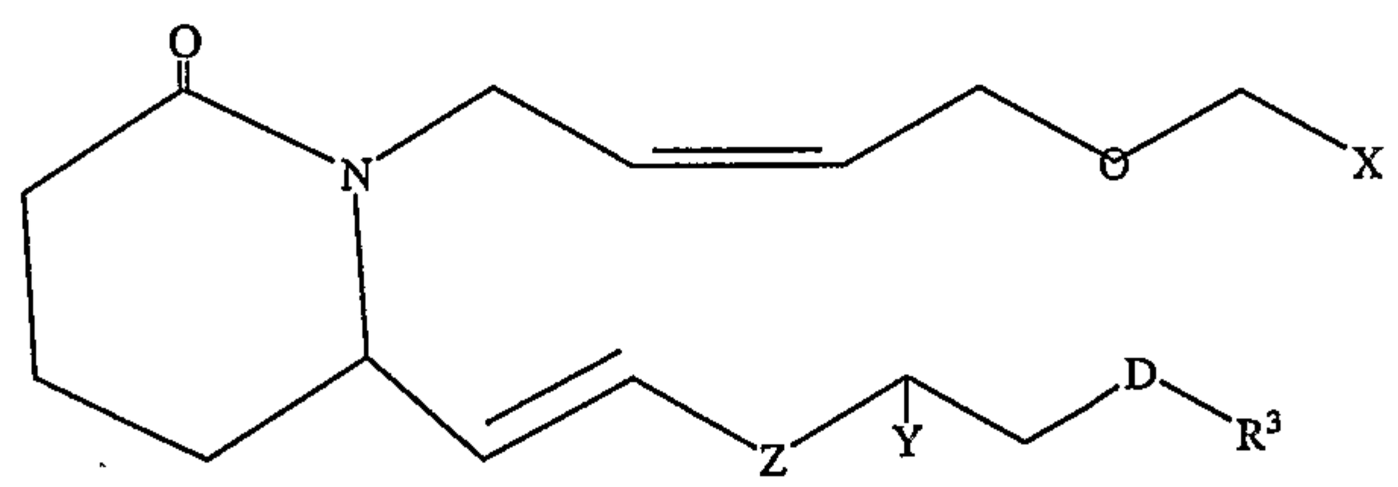
Finally, certain of the compounds represented by the above formula, disclosed below and utilized in the method of the present invention are novel and unobvious.

Detailed Description of the Invention

The present invention relates to the use of piperidinyl prostaglandin E therapeutic agents, e.g. as analogs as ocular hypotensives. The compounds used in accordance with the present invention are encompassed by the following structural formula I:



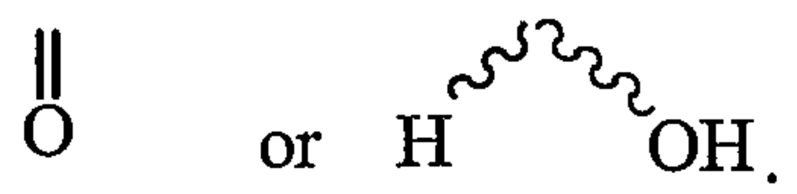
The preferred group of the compounds of the present invention includes compounds that have the following structural formula II.



In the above formulae, the substituents and symbols are as hereinabove defined.

In the above formulae:

Preferably Y is



Preferably D represents a covalent bond or is CH_2; more preferably D is CH_2 and R^3 is n-propyl or D is a covalent bond and R^3 is phenyl.

Preferably Z represents a covalent bond.

Preferably R is H or C_1-C_5 lower alkyl.

Preferably R^1 is H.

Preferably R^3 is selected from the group consisting of phenyl and n-propyl.

Preferably X is CO_2R and more preferably R is selected from the group consisting of H and methyl.

The above compounds of the present invention may be prepared by methods that are known in the art or according to the working examples below. The compounds, below, are especially preferred representative, of the compounds of the present invention.

{4-[(R)-2-Oxo-6-((E)-3-oxo-4-phenyl-but-1-enyl)-piperidin-1-yl]-butoxy}-acetic acid methyl ester

{4-[(R)-2-Oxo-6-((E)-3-oxo-4-phenyl-but-1-enyl)-piperidin-1-yl]-butoxy}-acetic acid

{4-[(R)-2-((E)-3-Hydroxy-4-phenyl-but-1-enyl)-6-oxo-piperidin-1-yl]-butoxy}-acetic acid methyl ester

{4-[(R)-2-((E)-3-Hydroxy-4-phenyl-but-1-enyl)-6-oxo-piperidin-1-yl]-butoxy}-acetic acid

{4-[(R)-2-(3-Hydroxy-4-phenyl-butyl)-6-oxo-piperidin-1-yl]-butoxy}-acetic acid methyl ester

{4-[(R)-2-(3-Hydroxy-4-phenyl-butyl)-6-oxo-piperidin-1-yl]-butoxy}-acetic acid

{(Z)-4-[(R)-2-Oxo-6-((E)-3-oxo-4-phenyl-but-1-enyl)-piperidin-1-yl]-but-2-enyloxy}-acetic acid methyl ester

{(Z)-4-[(R)-2-Oxo-6-((E)-3-oxo-4-phenyl-but-1-enyl)-piperidin-1-yl]-but-2-enyloxy}-acetic acid

{4-[(R)-2-Oxo-6-(3-oxo-4-phenyl-butyl)-piperidin-1-yl]-butoxy}-acetic acid methyl ester

{4-[(R)-2-Oxo-6-(3-oxo-4-phenyl-butyl)-piperidin-1-yl]-butoxy}-acetic acid

{(Z)-4-[(R)-2-((E)-3-Hydroxy-4-phenyl-but-1-enyl)-6-oxo-piperidin-1-yl]-but-2-enyloxy}-acetic acid methyl ester

{(Z)-4-[(R)-2-((E)-3-Hydroxy-4-phenyl-but-1-enyl)-6-oxo-piperidin-1-yl]-but-2-enyloxy}-acetic acid.

{(Z)-4-[(R)-2-Oxo-6-(3-oxo-4-phenyl-butyl)-piperidin-1-yl]-but-2-enyloxy}-acetic acid methyl ester

{(Z)-4-[(R)-2-Oxo-6-(3-oxo-4-phenyl-butyl)-piperidin-1-yl]-but-2-enyloxy}-acetic acid

{(Z)-4-[(R)-2-(3-Hydroxy-4-phenyl-butyl)-6-oxo-piperidin-1-yl]-but-2-enyloxy}-acetic acid methyl ester

{(Z)-4-[(R)-2-(3-Hydroxy-4-phenyl-butyl)-6-oxo-piperidin-1-yl]-but-2-enyloxy}-acetic acid

(4-{(R)-2-[(E)-4-(3-Chlorophenyl)-3-hydroxy-but-1-enyl]-6-oxo-piperidin-1-yl}-butoxy)-acetic acid

2-(4-{(R)-2-[(E)-4-(3-Chlor-phenyl)-3-hydroxy-but-1-enyl]-6-oxo-piperidin-1-yl}-butoxy)-acetamide

(4-{(R)-2-[(E)-4-(3-Chlorophenyl)-3-hydroxy-but-1-enyl]-6-oxo-piperidin-1-yl}-butoxy)-acetic acid isopropyl ester

(4-{(R)-2-[(E)-4-(3-Chlorophenyl)-3-oxo-but-1-enyl]-6-oxo-piperidin-1-yl}-but-2-ynyloxy)-acetic acid methyl ester

(4-{(R)-2-[(E)-4-(3-Chlorophenyl)-3-oxo-but-1-enyl]-6-oxo-piperidin-1-yl}-but-2-ynyloxy)-acetic acid

(4-{(R)-2-[(E)-4-(3-Chlorophenyl)-3-hydroxy-but-1-enyl]-6-oxo-piperidin-1-yl}-but-2-ynyloxy)-acetic acid methyl ester

(R)-6-[(E)-4-(3-Chlorophenyl)-3-hydroxy-but-1-enyl]-1-[4-(2-hydroxyethoxy)-but-2-ynyl]-piperidin-2-one

(4-{(R)-2-[(E)-4-(3-Chlorophenyl)-3-hydroxy-but-1-enyl]-6-oxo-piperidin-1-yl}-but-2-ynyloxy)-acetic acid

(4-{(R)-2-[(E)-4-(3-Chlorophenyl)-3-hydroxy-but-1-enyl]-6-oxo-piperidin-1-yl}-but-2-ynyloxy)-acetic acid isopropyl ester

Pharmaceutical compositions may be prepared by combining a therapeutically effective amount of at least one compound according to the present invention, or a pharmaceutically acceptable acid addition salt thereof, as an active ingredient, with conventional ophthalmically acceptable pharmaceutical excipients, and by preparation of unit dosage forms suitable for topical ocular use. The therapeutically efficient amount typically is between about 0.0001 and about 5% (w/v), preferably about 0.001 to about 1.0% (w/v) in liquid formulations.

For ophthalmic application, preferably solutions are prepared using a physiological saline solution as a major vehicle. The pH of such ophthalmic solutions should preferably be maintained between 6.5 and 7.2 with an appropriate buffer system. The formulations may also contain conventional, pharmaceutically acceptable preservatives, stabilizers and surfactants.

Preferred preservatives that may be used in the pharmaceutical compositions of the present invention include, but are not limited to, benzalkonium chloride, chlorobutanol, thimerosal, phenylmercuric acetate and phenylmercuric nitrate. A preferred surfactant is, for example, Tween 80. Likewise, various preferred vehicles may be used in the ophthalmic preparations of the present invention. These vehicles include, but are not limited to, polyvinyl alcohol, povidone, hydroxypropyl methyl cellulose, poloxamers, carboxymethyl cellulose, hydroxyethyl cellulose and purified water.

Tonicity adjustors may be added as needed or convenient. They include, but are not limited to, salts, particularly sodium chloride, potassium chloride, mannitol and glycerin, or any other suitable ophthalmically acceptable tonicity adjustor.

Various buffers and means for adjusting pH may be used so long as the resulting preparation is ophthalmically acceptable. Accordingly, buffers include acetate buffers, citrate buffers, phosphate buffers and borate buffers. Acids or bases may be used to adjust the pH of these formulations as needed.

In a similar vein, an ophthalmically acceptable antioxidant for use in the present invention includes, but is not limited to, sodium metabisulfite, sodium thiosulfate, acetylcysteine, butylated hydroxyanisole and butylated hydroxytoluene.

Other excipient components which may be included in the ophthalmic preparations are chelating agents. The preferred chelating agent is edentate disodium, although other chelating agents may also be used in place or in conjunction with it.

The ingredients are usually used in the following amounts:

Ingredient	Amount (% w/v)
active ingredient	about 0.001-5
preservative	0-0.10
vehicle	0-40
tonicity adjustor	1-10
buffer	0.01-10
pH adjustor	q.s. pH 4.5-7.5
antioxidant	as needed
surfactant	as needed
purified water	as needed to make 100%

The actual dose of the active compounds of the present invention depends on the specific compound, and on the condition to be treated; the selection of the appropriate dose is well within the knowledge of the skilled artisan.

The ophthalmic formulations of the present invention are conveniently packaged in forms suitable for metered application, such as in containers equipped with a dropper, to facilitate the application to the eye. Containers suitable for dropwise application are usually made of suitable inert, non-toxic plastic material, and generally contain between about 0.5 and about 15 ml solution.

This invention is further illustrated by the following non-limiting Examples.

Example 1

{4-[(R)-2-Oxo-6-((E)-3-oxo-4-phenyl-but-1-enyl)-piperidin-1-yl]-butoxy}-acetic acid methyl ester

Step 1. (R)-6-(1-Ethoxyethoxymethyl)-piperidin-2-one

Ethyl vinyl ether (1.68 mL, 17.5 mmol) and trifluoroacetic acid (0.1 mL) were added sequentially to a solution of (R)-6-hydroxymethylpiperidin-2-one (prepared from D-α-aminoadipic acid according to Huang, et al., *Synth. Commun.* **1989**, *19*, 3485-3496, 1.62 g, 12.5 mmol) in $CHCl_3$ (10 mL) at rt. The reaction mixture was stirred at rt for 18 h, then saturated aqueous $NaHCO_3$ (100 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 75 mL). The combined organic phase was dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (CH_2Cl_2 → 4% $MeOH/CH_2Cl_2$,gradient) afforded 2.03 g (80%) of (R)-6-(1-ethoxyethoxymethyl)-piperidin-2-one.

Step 2. {(Z)-4-[(R)-2-(1-Ethoxyethoxymethyl)-6-oxo-piperidin-1-yl]-but-2-enyloxy}-acetic acid ethyl ester

Sodium hydride (60% dispersion in oil, 402 mg, 10.0 mmol) was added to a solution of (R)-6-(1-ethoxyethoxymethyl)-piperidin-2-one (2.02 g, 10.0 mmol) in DMF (15 mL) at 0 °C. After 1 h, a solution of potassium iodide (1.66 g, 10.0 mmol) and ((Z)-4-chloro-but-2-enyloxy)-acetic acid ethyl ester (prepared according to PCT 2003/007941, 3.09 g, 16.0 mmol) in DMF (10 mL) was added via cannula. The reaction was allowed to warm to rt. After 18 h at rt, the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (100 mL) and the mixture was extracted with EtOAc (3 x 100 mL). The combined organic phase was washed with brine (3 x 100 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (10% EtOAc/CH_2Cl_2 $\rightarrow$ 60% EtOAc/CH_2Cl_2, gradient) afforded 1.10 g (31%) of {(Z)-4-[(R)-2-(1-ethoxyethoxymethyl)-6-oxo-piperidin-1-yl]-but-2-enyloxy}-acetic acid ethyl ester.

Step 3. [(Z)-4-((R)-2-Hydroxymethyl-6-oxo-piperidin-1-yl)-but-2-enyloxy]-acetic acid methyl ester

p-Toluenesulfonic acid hydrate (620 mg, 3.26 mmol) was added to a solution of {(Z)-4-[(R)-2-(1-ethoxyethoxymethyl)-6-oxo-piperidin-1-yl]-but-2-enyloxy}-acetic acid ethyl ester (1.10 g, 3.08 mmol) in MeOH (10 mL). After 17 h at rt, the reaction was quenched with saturated aqueous $NaHCO_3$ (20 mL) and the mixture was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic phase was dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (40% EtOAc/CH_2Cl_2 $\rightarrow$ 60% EtOAc/CH_2Cl_2, gradient, then 7% MeOH/CH_2Cl_2) afforded 538 mg (64%) of [(Z)-4-((R)-2-hydroxymethyl-6-oxo-piperidin-1-yl)-but-2-enyloxy]-acetic acid methyl ester.

Step 4. [4-((R)-2-Hydroxymethyl-6-oxo-piperidin-1-yl)-butoxy]-acetic acid methyl ester

Palladium on carbon (10 wt. %, 25 mg) was added to a solution of [(Z)-4-((R)-2-hydroxymethyl-6-oxo-piperidin-1-yl)-but-2-enyloxy]-acetic acid methyl ester (318 mg, 1.17 mmol) in MeOH (5.0 mL). A hydrogen atmosphere was established by evacuating and refilling with hydrogen (3x) and the reaction mixture was stirred under a balloon of hydrogen for 2.25 h. The reaction mixture was filtered through celite, washing with MeOH, and the filtrate was concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (30% EtOAc/CH_2Cl_2 $\rightarrow$ 50% EtOAc/CH_2Cl_2, gradient, then 2% MeOH/CH_2Cl_2 $\rightarrow$ 5% MeOH/CH_2Cl_2) afforded 285 mg (89%) of [4-((R)-2-hydroxymethyl-6-oxo-piperidin-1-yl)-butoxy]-acetic acid methyl ester.

Step 5. [4-((R)-2-Formyl-6-oxo-piperidin-1-yl)-butoxy]-acetic acid methyl ester
A solution of oxalyl chloride (0.15 mL, 1.76 mmol) in CH_2Cl_2 (1.0 mL) was added to a solution of DMSO (0.16 mL, 2.25 mmol) in CH_2Cl_2 (1.0 mL) at -78 °C. After 15 min at -78 °C, a solution of [4-((R)-2-hydroxymethyl-6-oxo-piperidin-1-yl)-butoxy]-acetic acid methyl ester (240 mg, 0.88 mmol) in CH_2Cl_2 (1.5 mL) was added via cannula. After 20 min at -78 °C, triethylamine (0.37 mL, 2.65 mmol) was added. After 20 min at -78 °C, the mixture was allowed to warm to 0 °C. After 30 min at 0 °C, the reaction was allowed to warm to rt. After 45 min at rt, saturated aqueous $NaHCO_3$ (15 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic phase was dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (40% → 70% EtOAc/CH_2Cl_2, gradient) afforded 96 mg (40%) of [4-((R)-2-formyl-6-oxo-piperidin-1-yl)-butoxy]-acetic acid methyl ester.

Step 6. {4-[(R)-2-Oxo-6-((E)-3-oxo-4-phenyl-but-1-enyl)-piperidin-1-yl]-butoxy}-acetic acid methyl ester
Sodium hydride (60% dispersion in oil, 14 mg, 0.35 mmol) was added to a solution of dimethyl 2-oxo-3-phenylpropylphosphonate (83 mg, 0.34 mmol) in THF (1.0 mL) at 0 °C. After 1 h at 0 °C, [4-((R)-2-formyl-6-oxo-piperidin-1-yl)-butoxy]-acetic acid methyl ester (94 mg, 0.35 mmol) in THF (1 mL) was added via cannula. The reaction was allowed to warm to rt. After 22 h at rt, the reaction was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic phase was washed with brine (20 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (30% → 50% EtOAc/CH_2Cl_2, gradient) afforded 42 mg (31%) of the title compound.

Example 2

{4-[(R)-2-Oxo-6-((E)-3-oxo-4-phenyl-but-1-enyl)-piperidin-1-yl]-butoxy}-acetic acid

Rabbit liver esterase (134 units/mg, 1 mg) was added to a solution of {4-[(R)-2-oxo-6-((E)-3-oxo-4-phenyl-but-1-enyl)-piperidin-1-yl]-butoxy}-acetic acid methyl ester (10 mg, 0.026 mmol) in acetonitrile (0.2 mL) and pH 7.2 phosphate buffer (3.0 mL). After 24 h, acetonitrile (5 mL) was added and the reaction mixture was concentrated to dryness in vacuo. Purification of the residue by flash column chromatography on silica gel ($CH_2Cl_2 \rightarrow$ 3% MeOH/CH_2Cl_2, gradient) afforded 7.7 mg (80%) of the title compound.

Example 3

{4-[(R)-2-((E)-3-Hydroxy-4-phenyl-but-1-enyl)-6-oxo-piperidin-1-yl]-butoxy}-acetic acid methyl ester

Sodium borohydride (4 mg, 0.11 mmol), followed by MeOH (0.25 mL), was added to a solution of {4-[(R)-2-oxo-6-((E)-3-oxo-4-phenyl-but-1-enyl)-piperidin-1-yl]-butoxy}-acetic acid methyl ester (28 mg, 0.072 mmol) in CH_2Cl_2 (0.75 mL) at 0 °C. The mixture was allowed to warm to rt. After 40 min at rt, the reaction was quenched with aqueous HCl (0.5 M) and extracted with EtOAc (3 x 7 mL). The combined organic phase was dried (Na_2SO_4), filtered and concentrated in vacuo to afford 22 mg (78%) of the title compound.

Example 4

{4-[(R)-2-((E)-3-Hydroxy-4-phenyl-but-1-enyl)-6-oxo-piperidin-1-yl]-butoxy}-acetic acid

In accordance with the procedure of example 2, {4-[(R)-2-((E)-3-hydroxy-4-phenyl-but-1-enyl)-6-oxo-piperidin-1-yl]-butoxy}-acetic acid methyl ester (12.6 mg, 0.032 mmol) was converted into 10.5 mg (86%) of the title compound.

Example 5

{4-[(R)-2-(3-Hydroxy-4-phenyl-butyl)-6-oxo-piperidin-1-yl]-butoxy}-acetic acid methyl ester

Palladium on carbon (10 wt. %, 3 mg) was added to a solution of {4-[(R)-2-((E)-3-hydroxy-4-phenyl-but-1-enyl)-6-oxo-piperidin-1-yl]-butoxy}-acetic acid methyl ester (9.5 mg, 0.024 mmol) in MeOH (2.0 mL). A hydrogen atmosphere was established by evacuating and refilling with hydrogen (3x) and the reaction mixture was stirred under a balloon of hydrogen for 4 h. The reaction mixture was filtered through celite, washing with MeOH, and the filtrate was concentrated in vacuo to afford 8.2 mg (86%) of the title compound.

Example 6

{4-[(R)-2-(3-Hydroxy-4-phenyl-butyl)-6-oxo-piperidin-1-yl]-butoxy}-acetic acid

In accordance with the procedure of example 2, {4-[(R)-2-(3-hydroxy-4-phenyl-butyl)-6-oxo-piperidin-1-yl]-butoxy}-acetic acid methyl ester (7.2 mg, 0.018 mmol) was converted into 6.9 mg (99%) of the title compound.

Example 7

{(Z)-4-[(R)-2-Oxo-6-((E)-3-oxo-4-phenyl-but-1-enyl)-piperidin-1-yl]-but-2-enyloxy}-acetic acid methyl ester

Step 1. [(Z)-4-((R)-2-Formyl-6-oxo-piperidin-1-yl)-but-2-enyloxy]-acetic acid methyl ester

Trifluoroacetic anhydride (0.24 mL, 1.70 mmol) was added to a solution of DMSO (0.14 mL, 1.97 mmol) in CH_2Cl_2 (2 mL) at -78 °C. After 15 min at -78 °C, a solution of [(Z)-4-((R)-2-hydroxymethyl-6-oxo-piperidin-1-yl)-but-2-enyloxy]-acetic acid methyl ester (from example 1, step 3, 220 mg, 0.81 mmol) in CH_2Cl_2 (1.5 mL) was added via cannula. After 20 min at -78 °C, triethylamine (0.33 mL, 2.37 mmol) was added and the reaction mixture was allowed to warm to rt. After 1 h at rt, the reaction was quenched with saturated aqueous NH_4Cl (15 mL) and the mixture was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic phase was dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (10% → 50% EtOAc/CH_2Cl_2, gradient) afforded 150 mg (69%) of [(Z)-4-((R)-2-formyl-6-oxo-piperidin-1-yl)-but-2-enyloxy]-acetic acid methyl ester.

Step 2. {(Z)-4-[(R)-2-Oxo-6-((E)-3-oxo-4-phenyl-but-1-enyl)-piperidin-1-yl]-but-2-enyloxy}-acetic acid methyl ester

Sodium hydride (60% dispersion in oil, 22 mg, 0.55 mmol) was added to a solution of dimethyl 2-oxo-3-phenylpropylphosphonate (135 mg, 0.56 mmol) in THF (1.0 mL) at 0 °C. After 1 h at 0 °C, [(Z)-4-((R)-2-formyl-6-oxo-piperidin-1-yl)-but-2-enyloxy]-acetic acid methyl ester (150 mg, 0.56 mmol) in THF (1 mL) was added via cannula. The reaction was allowed to warm to rt. After 16.5 h at rt, the reaction was quenched with saturated aqueous NH_4Cl (15 mL) and extracted with EtOAc (3 x 15 mL). The combined organic phase was washed with brine (20 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (30% → 60% EtOAc/CH_2Cl_2, gradient) afforded 91 mg (42%) of the title compound.

Example 8

{(Z)-4-[(R)-2-Oxo-6-((E)-3-oxo-4-phenyl-but-1-enyl)-piperidin-1-yl]-but-2-enyloxy}-acetic acid

In accordance with the procedure of example 2, {(Z)-4-[(R)-2-oxo-6-((E)-3-oxo-4-phenyl-but-1-enyl)-piperidin-1-yl]-but-2-enyloxy}-acetic acid methyl ester (6.3 mg, 0.016 mmol) was converted into 1.9 mg (31%) of the title compound.

Example 9

{4-[(R)-2-Oxo-6-(3-oxo-4-phenyl-butyl)-piperidin-1-yl]-butoxy}-acetic acid methyl ester

Palladium on carbon (10 wt. %, 2 mg) was added to a solution of {(Z)-4-[(R)-2-oxo-6-((E)-3-oxo-4-phenyl-but-1-enyl)-piperidin-1-yl]-but-2-enyloxy}-acetic acid methyl ester (9.7 mg, 0.025 mmol) in MeOH (1.5 mL). A hydrogen atmosphere was established by evacuating and refilling with hydrogen (3x) and the reaction mixture was stirred under a balloon of hydrogen for 19 h. The reaction mixture was filtered through celite, washing with MeOH, and the filtrate was concentrated in vacuo to afford 8.3 mg (85%) of the title compound.

Example 10

{4-[(R)-2-Oxo-6-(3-oxo-4-phenyl-butyl)-piperidin-1-yl]-butoxy}-acetic acid

In accordance with the procedure of example 2, 4-[(R)-2-oxo-6-(3-oxo-4-phenyl-butyl)-piperidin-1-yl]-butoxy}-acetic acid methyl ester (6.9 mg, 0.018 mmol) was converted into 6.2 mg (93%) of the title compound.

Example 11

{(Z)-4-[(R)-2-((E)-3-Hydroxy-4-phenyl-but-1-enyl)-6-oxo-piperidin-1-yl]-but-2-enyloxy}-acetic acid methyl ester

Sodium borohydride (4 mg, 0.11 mmol), followed by MeOH (0.25 mL), was added to a solution of {(Z)-4-[(R)-2-oxo-6-((E)-3-oxo-4-phenyl-but-1-enyl)-piperidin-1-yl]-but-2-enyloxy}-acetic acid methyl ester (28 mg, 0.073 mmol) in CH_2Cl_2 (0.75 mL) at 0 °C. The mixture was allowed to warm to rt. After 1 h at rt, the reaction was quenched with aqueous HCl (0.5 M) and extracted with EtOAc (3 x 10 mL). The combined organic phase was dried (Na_2SO_4), filtered and concentrated in vacuo to afford 22 mg (78%) of the title compound.

Example 12

{(Z)-4-[(R)-2-((E)-3-Hydroxy-4-phenyl-but-1-enyl)-6-oxo-piperidin-1-yl]-but-2-enyloxy}-acetic acid

In accordance with the procedure of example 2, {(Z)-4-[(R)-2-((E)-3-hydroxy-4-phenyl-but-1-enyl)-6-oxo-piperidin-1-yl]-but-2-enyloxy}-acetic acid methyl ester (17.7 mg, 0.046 mmol) was converted into 17 mg (99%) of the title compound.

Example 13

{(Z)-4-[(R)-2-Oxo-6-(3-oxo-4-phenyl-butyl)-piperidin-1-yl]-but-2-enyloxy}-acetic acid methyl ester

A solution of {(Z)-4-[(R)-2-oxo-6-((E)-3-oxo-4-phenyl-but-1-enyl)-piperidin-1-yl]-but-2-enyloxy}-acetic acid methyl ester (24.6 mg, 0.064 mmol) in CH_3CN (1.5 mL) was added via cannula to hydrido(triphenylphosphine)copper(I) hexamer (125 mg, 0.064 mmol) at -40 °C. After 1 h at -40 °C, the reaction was allowed to warm to rt. After 3 h at rt, the reaction was quenched by addition of a solution of NH_4OH and saturated aqueous NH_4Cl (1:1, 6 mL). The mixture was extracted with EtOAc (3 x 10 mL). The combined organic phase was washed with brine (20 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (20% → 70% EtOAc/CH_2Cl_2, gradient) afforded 19.6 mg (79%) of the title compound.

Example 14

{(Z)-4-[(R)-2-Oxo-6-(3-oxo-4-phenyl-butyl)-piperidin-1-yl]-but-2-enyloxy}-acetic acid

In accordance with the procedure of example 2, {(Z)-4-[(R)-2-oxo-6-(3-oxo-4-phenyl-butyl)-piperidin-1-yl]-but-2-enyloxy}-acetic acid methyl ester (6.1 mg, 0.016 mmol) was converted into 1.7 mg (29%) of the title compound.

Example 15

{(Z)-4-[(R)-2-(3-Hydroxy-4-phenyl-butyl)-6-oxo-piperidin-1-yl]-but-2-enyloxy}-acetic acid methyl ester

Sodium borohydride (2 mg, 0.053 mmol), followed by MeOH (0.15 mL), was added to a solution of {(Z)-4-[(R)-2-oxo-6-(3-oxo-4-phenyl-butyl)-piperidin-1-yl]-but-2-enyloxy}-acetic acid methyl ester (11.5 mg, 0.030 mmol) in CH_2Cl_2 (0.5 mL) at 0 °C. The mixture was allowed to warm to rt. After 30 min at rt, the reaction was quenched with aqueous HCl (0.5 M) and extracted with EtOAc (3 x 7 mL). The combined organic phase was dried (Na_2SO_4), filtered and concentrated in vacuo to afford 10.1 mg (87%) of the title compound.

Example 16

<u>{(Z)-4-[(R)-2-(3-Hydroxy-4-phenyl-butyl)-6-oxo-piperidin-1-yl]-but-2-enyloxy}-acetic acid</u>

In accordance with the procedure of example 2, {(Z)-4-[(R)-2-(3-hydroxy-4-phenyl-butyl)-6-oxo-piperidin-1-yl]-but-2-enyloxy}-acetic acid methyl ester (6.2 mg, 0.016 mmol) was converted into 1.6 mg (27%) of the title compound.

Example 17

<u>(4-{(R)-2-[(E)-4-(3-Chlorophenyl)-3-hydroxy-but-1-enyl]-6-oxo-piperidin-1-yl}-butoxy)-acetic acid</u>

Step 1. [(Z)-4-((R)-2-Hydroxymethyl-6-oxo-piperidin-1-yl)-but-2-enyloxy]-acetic acid ethyl ester

p-Toluenesulfonic acid hydrate (267 mg, 1.40 mmol) was added to a solution of {(Z)-4-[(R)-2-(1-ethoxyethoxymethyl)-6-oxo-piperidin-1-yl]-but-2-enyloxy}-acetic acid ethyl ester (from example 1, step 2, 477 mg, 1.33 mmol) in EtOH (6 mL). After 18 h at rt, the reaction was concentrated in vacuo and quenched with saturated aqueous $NaHCO_3$ (20 mL). The mixture was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic phase was dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel ($CH_2Cl_2 \rightarrow$ 3% MeOH/CH_2Cl_2, gradient) afforded 290 mg (76%) of [(Z)-4-((R)-2-hydroxymethyl-6-oxo-piperidin-1-yl)-but-2-enyloxy]-acetic acid ethyl ester.

Step 2. [4-((R)-2-Hydroxymethyl-6-oxo-piperidin-1-yl)-butoxy]-acetic acid ethyl ester

Palladium on carbon (10 wt. %, 15 mg) was added to a solution of [(Z)-4-((R)-2-hydroxymethyl-6-oxo-piperidin-1-yl)-but-2-enyloxy]-acetic acid ethyl ester (290 mg, 1.02 mmol) in EtOH (3.0 mL). A hydrogen atmosphere was established by evacuating and refilling with hydrogen (3x) and the reaction mixture was stirred under a balloon of hydrogen for 3 h. The reaction mixture was filtered through celite, washing with EtOH, and the filtrate was concentrated in vacuo to afford 295 mg (quant. crude) of [4-((R)-2-hydroxymethyl-6-oxo-piperidin-1-yl)-butoxy]-acetic acid ethyl ester.

Step 3. [4-((R)-2-Formyl-6-oxo-piperidin-1-yl)-butoxy]-acetic acid ethyl ester

1-(3-(Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI, 505 mg, 2.63 mmol) and DMSO (0.25 mL, 3.52 mmol) were added sequentially to a solution of [4-((R)-2-hydroxymethyl-6-oxo-piperidin-1-yl)-butoxy]-acetic acid ethyl ester (252 mg, 0.88 mmol) in benzene (5 mL). The mixture was cooled to 0 °C and pyridinium trifluoroacetate (187 mg, 0.97 mmol) was added. The reaction was allowed to warm to rt and then was stirred at rt for 4.25 h. The solution was decanted from the oily residue and the residue was washed with benzene (3 x 5 mL). The combined benzene phases were concentrated in vacuo to afford crude 4-((R)-2-formyl-6-oxo-piperidin-1-yl)-butoxy]-acetic acid ethyl ester that was used without further purification.

Step 4. (4-{(R)-2-[(E)-4-(3-Chlorophenyl)-3-oxo-but-1-enyl]-6-oxo-piperidin-1-yl}-butoxy)-acetic acid ethyl ester

Sodium hydride (60% dispersion in oil, 35 mg, 0.88 mmol) was added to a solution of [3-(3-chlorophenyl)-2-oxopropyl]-phosphonic acid dimethyl ester (221 mg, 0.80 mmol) in THF (2.0 mL) at 0 °C. After 1 h at 0 °C, [4-((R)-2-formyl-6-oxo-piperidin-1-yl)-butoxy]-acetic acid ethyl ester (0.88 mmol, crude) in THF (2 mL) was added via cannula. The reaction was allowed to warm to rt. After 18 h at rt, the reaction was quenched with aqueous acetic acid (50%, 10 mL) and extracted with EtOAc (3 x 20 mL). The combined organic phase was washed with brine (25 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (20% $\rightarrow$ 40% EtOAc/CH_2Cl_2, gradient) afforded 117 mg (34%) of (4-{(R)-2-[(E)-4-(3-chlorophenyl)-3-oxo-but-1-enyl]-6-oxo-piperidin-1-yl}-butoxy)-acetic acid ethyl ester.

Step 5. (4-{(R)-2-[(E)-4-(3-Chlorophenyl)-3-hydroxy-but-1-enyl]-6-oxo-piperidin-1-yl}-butoxy)-acetic acid ethyl ester

Sodium borohydride (10 mg, 0.26 mmol) followed by EtOH (0.25 mL) was added to a solution of (4-{(R)-2-[(E)-4-(3-chlorophenyl)-3-oxo-but-1-enyl]-6-oxo-piperidin-1-yl}-butoxy)-acetic acid ethyl ester (110 mg, 0.25 mmol) in CH_2Cl_2 (1.0 mL) at 0 °C. After 1 h at 0 °C the reaction was quenched with 1 N aqueous HCl. The reaction mixture was extracted with CH_2Cl_2 (3 x 10 mL), then the combined extracts were dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel ($CH_2Cl_2 \rightarrow$ 2% MeOH/CH_2Cl_2) afforded 88 mg (80%) of (4-{(R)-2-[(E)-4-(3-chlorophenyl)-3-hydroxy-but-1-enyl]-6-oxo-piperidin-1-yl}-butoxy)-acetic acid ethyl ester.

Step 6. (4-{(R)-2-[(E)-4-(3-Chlorophenyl)-3-hydroxy-but-1-enyl]-6-oxo-piperidin-1-yl}-butoxy)-acetic acid

In accordance with the procedure of example 2, (4-{(R)-2-[(E)-4-(3-chlorophenyl)-3-hydroxy-but-1-enyl]-6-oxo-piperidin-1-yl}-butoxy)-acetic acid ethyl ester (88 mg, 0.20 mmol) was converted into 44 mg (54%) of the title compound.

Example 18

2-(4-{(R)-2-[(E)-4-(3-Chlorophenyl)-3-hydroxy-but-1-enyl]-6-oxo-piperidin-1-yl}-butoxy)-acetamide

Triethylamine (8.8 µL, 0.063 mmol) was added to a solution of (4-{(R)-2-[(E)-4-(3-chlorophenyl)-3-hydroxy-but-1-enyl]-6-oxo-piperidin-1-yl}-butoxy)-acetic acid (12.4 mg, 0.030 mmol) in CH_2Cl_2 (0.2 mL). After cooling to 0 °C, the reaction mixture was treated with ethyl chloroformate (3.2 µL, 0.033 mmol). After 1 h at 0 °C, ammonia (0.5 M in 1,4-dioxane, 0.32 mL, 0.16 mmol) was added and the reaction mixture was allowed to warm to rt. After 18 h at rt, the reaction mixture was treated with saturated aqueous $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined extracts were dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (5% → 20% MeOH/CH_2Cl_2, gradient) afforded 1.3 mg (11%) of the title compound.

Example 19

(4-{(R)-2-[(E)-4-(3-Chlorophenyl)-3-hydroxy-but-1-enyl]-6-oxo-piperidin-1-yl}-butoxy)-acetic acid isopropyl ester

1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU, 16 µL, 0.11 mmol) was added to a solution of (4-{(R)-2-[(E)-4-(3-chlorophenyl)-3-hydroxy-but-1-enyl]-6-oxo-piperidin-1-yl}-butoxy)-acetic acid (29 mg, 0.071 mmol) in acetone (0.5 mL). After 5 min, 2-iodopropane (35 µL, 0.35 mmol) was added. After 17 h, the reaction mixture was concentrated in vacuo, EtOAc (15 mL) was added and the resultant mixture was washed with 0.5 M aqueous HCl (5 mL), saturated aqueous $NaHCO_3$ (5 mL) and brine (5 mL). The organic phase was then dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (CH_2Cl_2 → 5% MeOH/CH_2Cl_2, gradient) afforded 16 mg (50%) of the title compound.

Example 20

(4-{(R)-2-[(E)-4-(3-Chlorophenyl)-3-oxo-but-1-enyl]-6-oxo-piperidin-1-yl}-but-2-ynyloxy)-acetic acid methyl ester

Step 1. (4-Hydroxy-but-2-ynyloxy)-acetic acid methyl ester

Sodium hydride (60% dispersion in oil, 2.32 g, 58 mmol) was added to a solution of 2-butyne-1,4-diol (5.0 g, 58 mmol) in THF (60 mL) at 0 °C under nitrogen. After 1 h at 0 °C, methyl bromomethylacetate (5.5 mL, 58 mmol) was added and the reaction was allowed to warm to rt. After 18 h at rt, the reaction was quenched with 1 N HCl (60 mL) and extracted with EtOAc (3 x 100 mL). The combined extracts were washed with brine (1 x 100 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel ($CH_2Cl_2 \rightarrow$ 5% $MeOH/CH_2Cl_2$, gradient) afforded 3.2 g (35%) of (4-hydroxy-but-2-ynyloxy)-acetic acid methyl ester.

Step 2. (4-Iodo-but-2-ynyloxy)-acetic acid methyl ester

Triphenylphosphine (6.23 g, 23.8 mmol), iodine (6.03 g, 23.8 mmol) and imidazole (1.57 g, 23.8 mmol) were added sequentially to a solution of (4-hydroxy-but-2-ynyloxy)-acetic acid methyl ester (3.13 g, 19.8 mmol) in CH_2Cl_2 (30 mL). After 1 h at rt, the reaction was filtered through activity I basic alumina, washing with 20% EtOAc/Hexane. The filtrate was concentrated in vacuo then purified by flash column chromatography on silica gel (Hexane $\rightarrow$ 20% EtOAc/Hexane, gradient) to afford 2.05 g (39%) of (4-iodo-but-2-ynyloxy)-acetic acid methyl ester.

Step 3. {4-[(R)-2-(1-Ethoxy-ethoxymethyl)-6-oxo-piperidin-1-yl]-but-2-ynyloxy}-acetic acid methyl ester

Sodium hydride (60% dispersion in oil, 278 mg, 6.95 mmol) was added to a solution of (R)-6-(1-ethoxyethoxymethyl)-piperidin-2-one (from example 1, step 1, 1.40 g, 6.96 mmol) in DMF (10 mL) at 0 °C. After 1 h at 0 °C, (4-iodo-but-2-ynyloxy)-acetic acid methyl ester (2.05 g, 7.65 mmol) in DMF (10 mL) was added via cannula and the reaction was allowed to warm to rt. After 15 min at rt, the reaction mixture solidified, so more DMF (3 mL) was added. After 18 h at rt, the reaction was treated with saturated aqueous $NaHCO_3$ (50 mL) and extracted with EtOAc (3 x 70 mL). The combined extracts were washed with water (2 x 50 mL) and brine (2 x 50 mL) then dried ($MgSO_4$), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (20% → 50% EtOAc/CH_2Cl_2, gradient) afforded 500 mg (21%) of {4-[(R)-2-(1-ethoxy-ethoxymethyl)-6-oxo-piperidin-1-yl]-but-2-ynyloxy}-acetic acid methyl ester.

Step 4. [4-((R)-2-Hydroxymethyl-6-oxo-piperidin-1-yl)-but-2-ynyloxy]-acetic acid methyl ester

p-Toluenesulfonic acid hydrate (289 mg, 1.52 mmol) was added to a solution of {4-[(R)-2-(1-ethoxy-ethoxymethyl)-6-oxo-piperidin-1-yl]-but-2-ynyloxy}-acetic acid methyl ester (494 mg, 1.45 mmol) in MeOH (5.0 mL) at rt. After 20 h at rt, the mixture was concentrated in vacuo, treated with saturated aqueous $NaHCO_3$ (20 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phase was dried ($MgSO_4$), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (CH_2Cl_2 → 3% MeOH/CH_2Cl_2, gradient) afforded 100 mg (26%) of [4-((R)-2-hydroxymethyl-6-oxo-piperidin-1-yl)-but-2-ynyloxy]-acetic acid methyl ester.

Step 5. [4-((R)-2-Formyl-6-oxo-piperidin-1-yl)-but-2-ynyloxy]-acetic acid methyl ester

EDCI (214 mg, 1.12 mmol) was added to a solution of [4-((R)-2-hydroxymethyl-6-oxo-piperidin-1-yl)-but-2-ynyloxy]-acetic acid methyl ester (100 mg, 0.37 mmol) in benzene (3.5 mL). The reaction mixture was cooled to 0 °C and DMSO (0.11 mL, 1.55 mmol) was added. After 5 min at 0 °C, pyridinium trifluoroacetate (79 mg, 0.41 mmol) was added. The reaction was allowed to warm to rt and then was stirred at rt for 3 h. The solution was decanted from the oily residue and the residue was washed with benzene (3 x 3 mL). The combined benzene phases were concentrated in vacuo to afford crude [4-((R)-2-formyl-6-oxo-piperidin-1-yl)-but-2-ynyloxy]-acetic acid methyl ester, which was used without further purification.

Step 6. (4-{(R)-2-[(E)-4-(3-Chlorophenyl)-3-oxo-but-1-enyl]-6-oxo-piperidin-1-yl}-but-2-ynyloxy)-acetic acid methyl ester

Sodium hydride (60% dispersion in oil, 15 mg, 0.39 mmol) was added to a solution of [3-(3-chlorophenyl)-2-oxopropyl]-phosphonic acid dimethyl ester (97 mg, 0.35 mmol) in THF (1.5 mL) at 0 °C. After 1 h at 0 °C, a solution of [4-((R)-2-formyl-6-oxo-piperidin-1-yl)-but-2-ynyloxy]-acetic acid methyl ester (0.37 mmol, crude) in THF (1.5 mL) was added via cannula. The reaction was allowed to warm to rt. After 18 h at rt, the reaction was quenched with aqueous acetic acid (50%, 15 mL) and extracted with EtOAc (3 x 15 mL). The combined organic phase was washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (20% → 30% EtOAc/CH_2Cl_2, gradient) afforded 100 mg (68%) of the title compound.

Example 21

<u>(4-{(R)-2-[(E)-4-(3-Chlorophenyl)-3-oxo-but-1-enyl]-6-oxo-piperidin-1-yl}-but-2-ynyloxy)-acetic acid</u>

In accordance with the procedure of example 2, (4-{(R)-2-[(E)-4-(3-chlorophenyl)-3-oxo-but-1-enyl]-6-oxo-piperidin-1-yl}-but-2-ynyloxy)-acetic acid methyl ester (8.0 mg, 0.019 mmol) was converted into 7.0 mg (91%) of the title compound.

Examples 22 and 23

(4-{(R)-2-[(E)-4-(3-Chlorophenyl)-3-hydroxy-but-1-enyl]-6-oxo-piperidin-1-yl}-but-2-ynyloxy)-acetic acid methyl ester and (R)-6-[(E)-4-(3-Chlorophenyl)-3-hydroxy-but-1-enyl]-1-[4-(2-hydroxyethoxy)-but-2-ynyl]-piperidin-2-one

Sodium borohydride (5 mg, 0.13 mmol) followed by MeOH (0.5 mL) was added to a solution of (4-{(R)-2-[(E)-4-(3-chlorophenyl)-3-oxo-but-1-enyl]-6-oxo-piperidin-1-yl}-but-2-ynyloxy)-acetic acid methyl ester (48 mg, 0.11 mmol) in CH_2Cl_2 (1.0 mL) at 0 °C. After 20 min at 0 °C the reaction was quenched with 0.5 N aqueous HCl. The reaction mixture was extracted with CH_2Cl_2 (3 x 10 mL), then the combined extracts were dried ($MgSO_4$), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (CH_2Cl_2 $\rightarrow$ 2% MeOH/CH_2Cl_2) followed by preparative thin layer chromatography (5% MeOH/CH_2Cl_2) afforded 22 mg (46%) of (4-{(R)-2-[(E)-4-(3-chlorophenyl)-3-hydroxy-but-1-enyl]-6-oxo-piperidin-1-yl}-but-2-ynyloxy)-acetic acid methyl ester and 1.7 mg (4%) of (R)-6-[(E)-4-(3-chlorophenyl)-3-hydroxy-but-1-enyl]-1-[4-(2-hydroxyethoxy)-but-2-ynyl]-piperidin-2-one.

Example 24

(4-{(R)-2-[(E)-4-(3-Chlorophenyl)-3-hydroxy-but-1-enyl]-6-oxo-piperidin-1-yl}-but-2-ynyloxy)-acetic acid

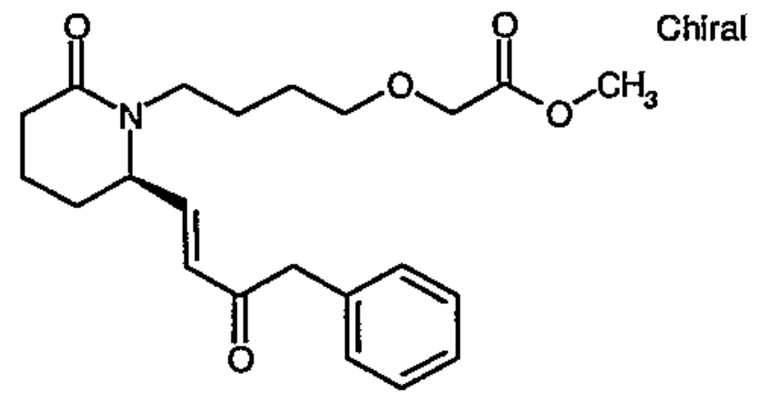
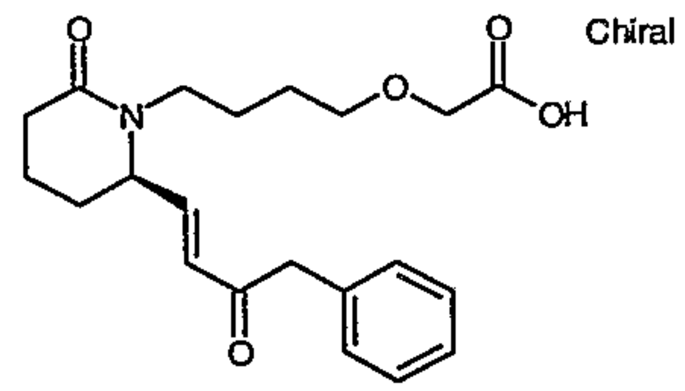
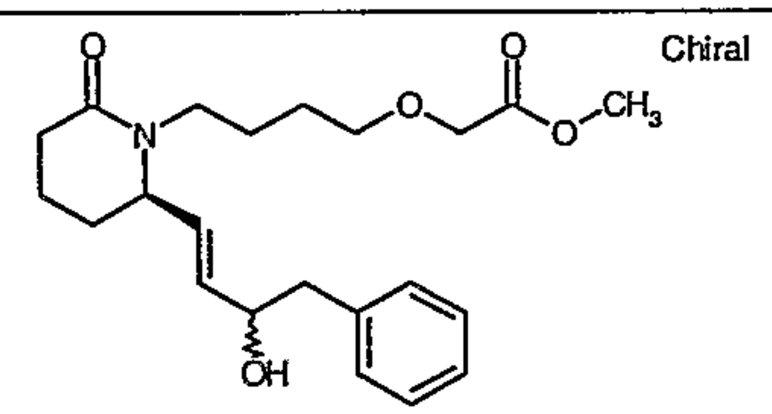
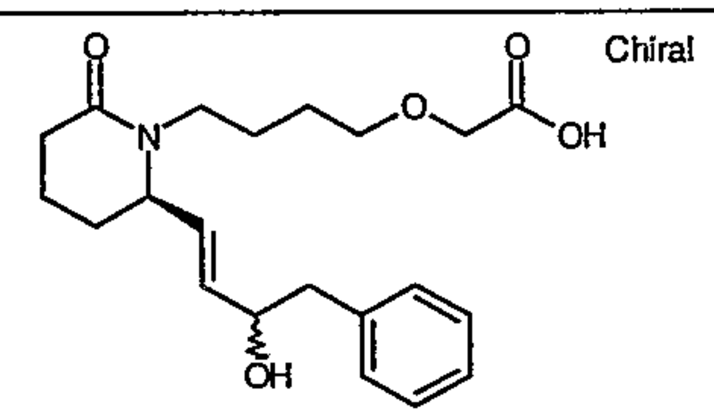
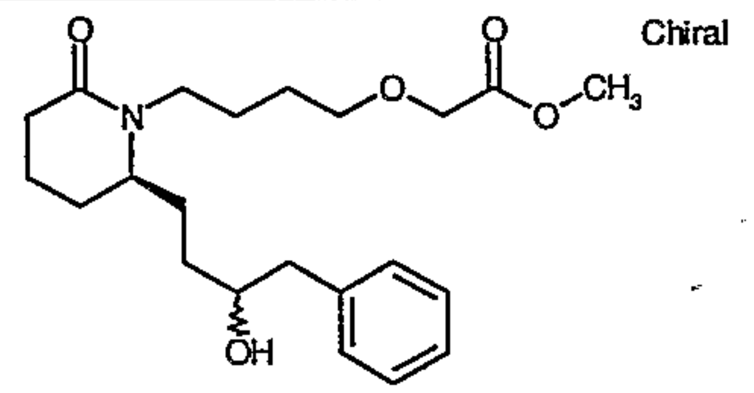
In accordance with the procedure of example 2, (4-{(R)-2-[(E)-4-(3-chlorophenyl)-3-hydroxy-but-1-enyl]-6-oxo-piperidin-1-yl}-but-2-ynyloxy)-acetic acid methyl ester (18 mg, 0.043 mmol) was converted into 15.6 mg (90%) of the title compound.

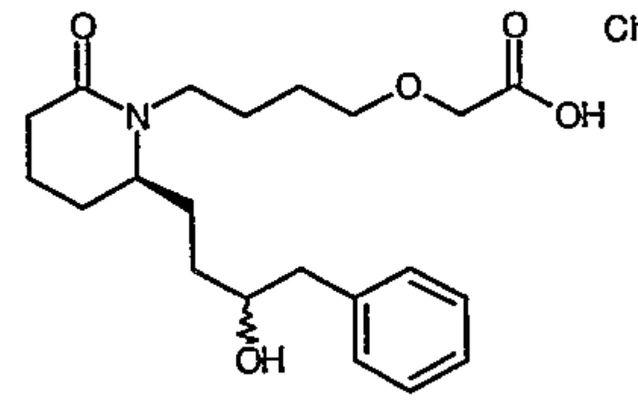
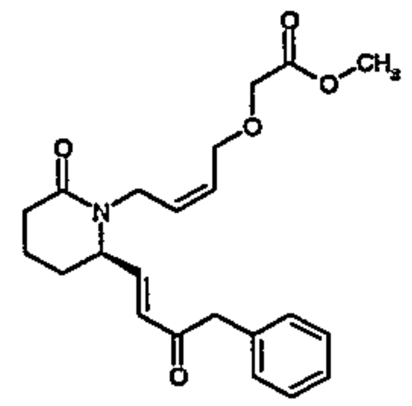
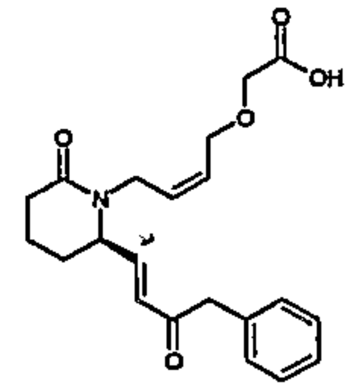
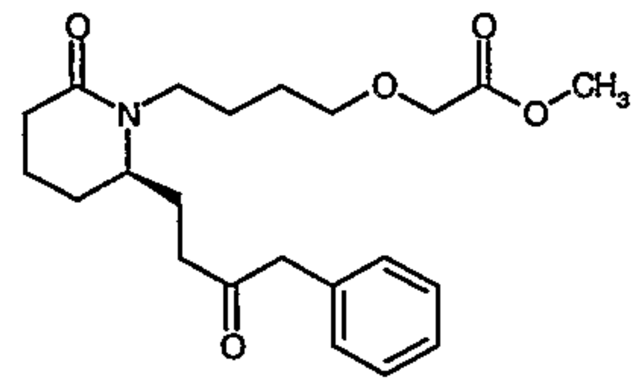
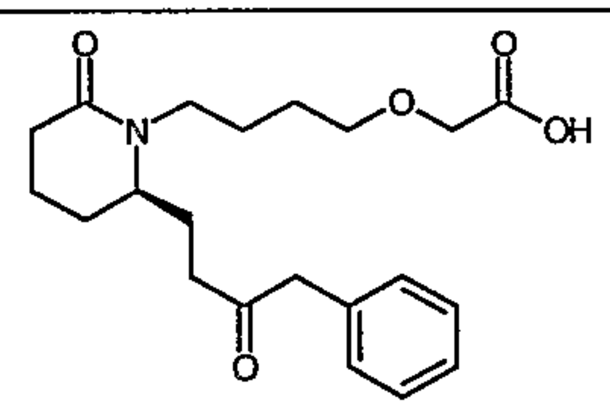
Example 25

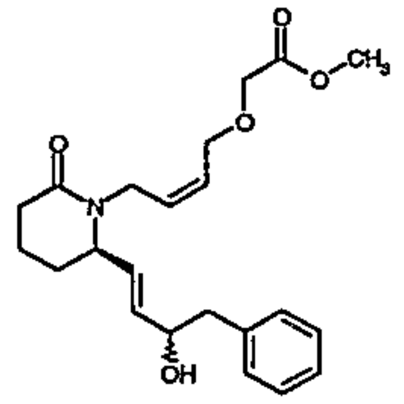
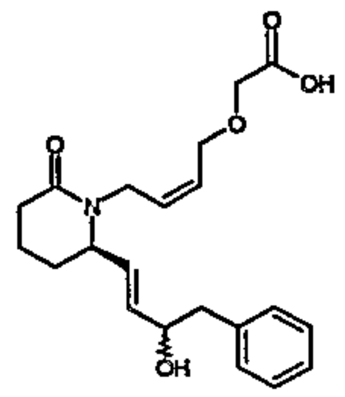
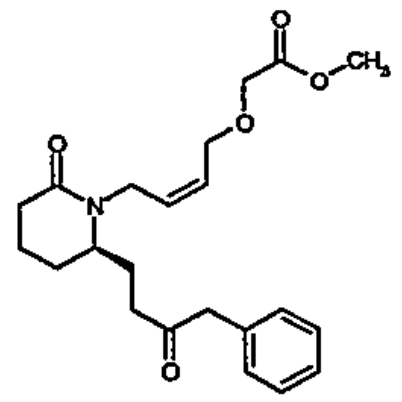
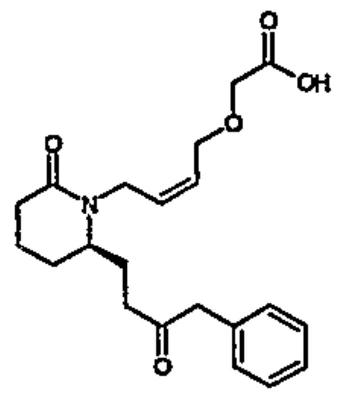
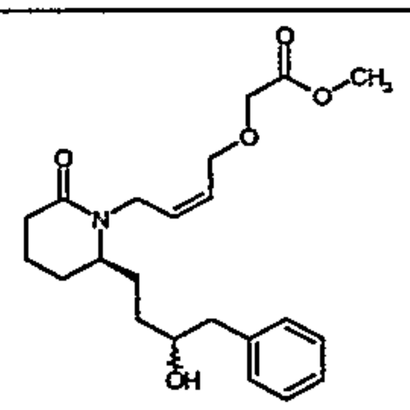
(4-{(R)-2-[(E)-4-(3-Chlorophenyl)-3-hydroxy-but-1-enyl]-6-oxo-piperidin-1-yl}-but-2-ynyloxy)-acetic acid isopropyl ester

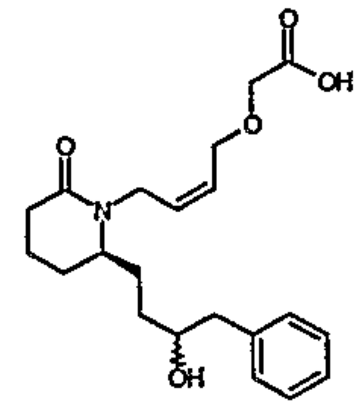
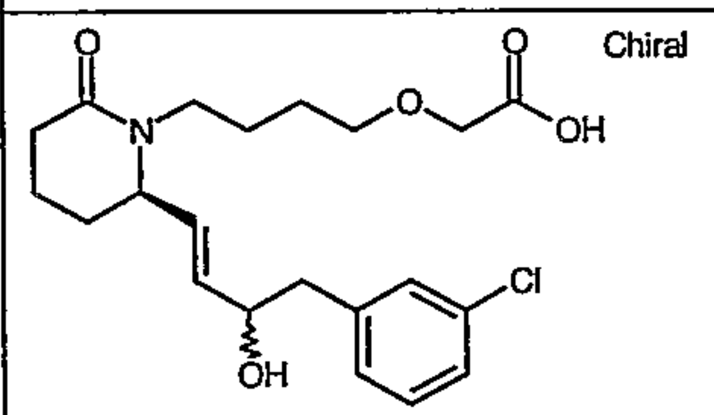
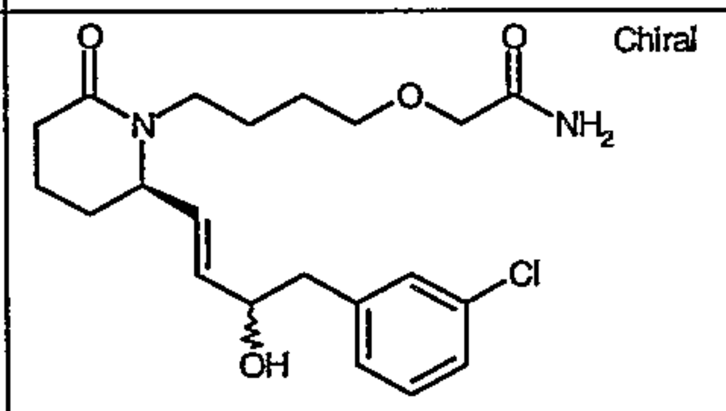
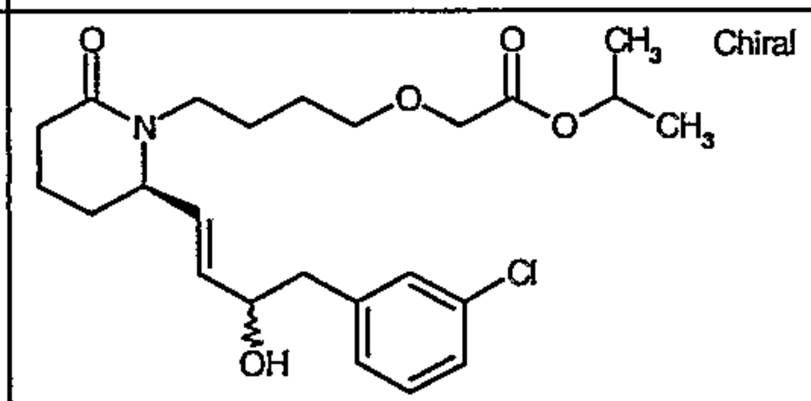
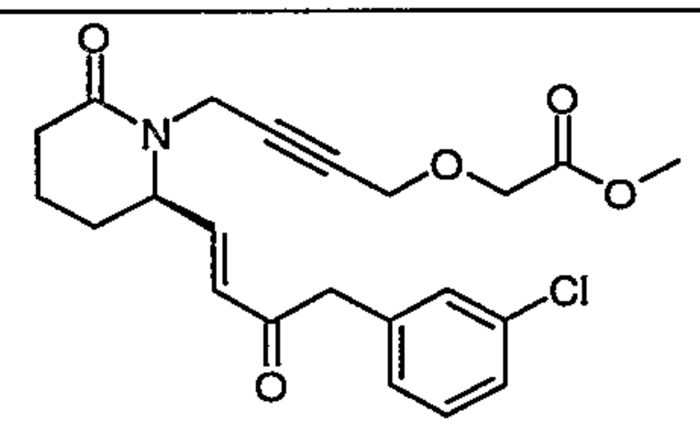
DBU (6.6 μL, 0.044 mmol) was added to a solution of (4-{(R)-2-[(E)-4-(3-chlorophenyl)-3-hydroxy-but-1-enyl]-6-oxo-piperidin-1-yl}-but-2-ynyloxy)-acetic acid (12 mg, 0.030 mmol) in acetone (0.3 mL). After 5 min, 2-iodopropane (15 μL, 0.15 mmol) was added. After 19 h, the reaction mixture was concentrated in vacuo, 0.5 M aqueous HCl (5 mL) was added and the mixture was extracted with EtOAc (3 x 5 mL). The combine organic phase was washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL) then dried ($MgSO_4$), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel ($CH_2Cl_2 \rightarrow$ 3% MeOH/CH_2Cl_2, gradient) afforded 7.9 mg (60%) of the title compound.

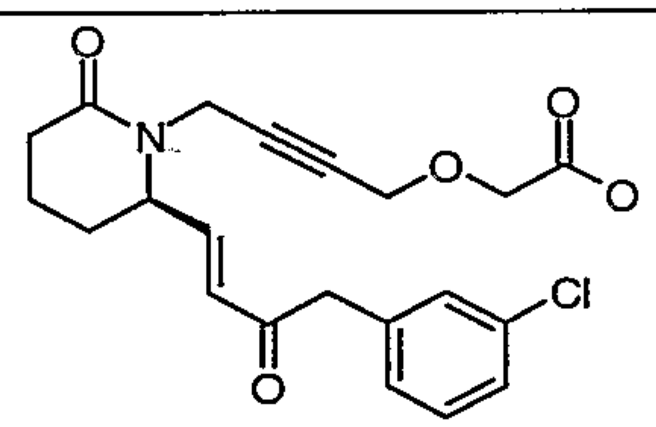
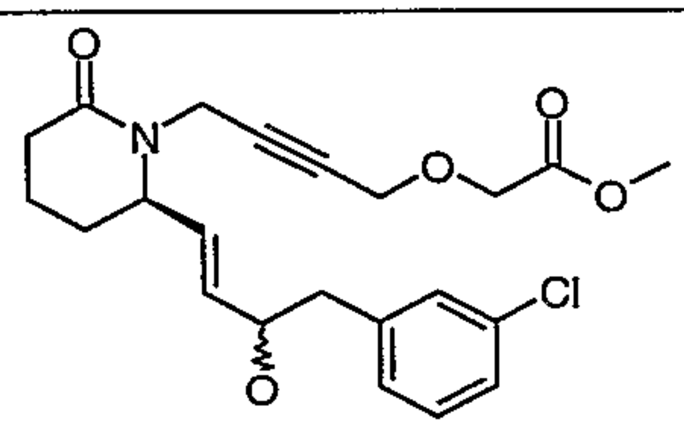
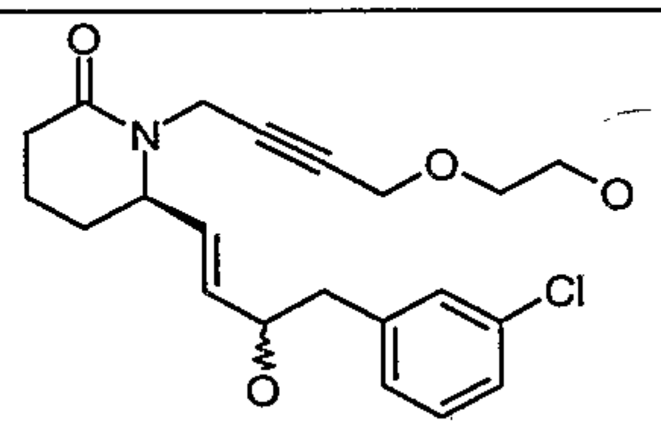
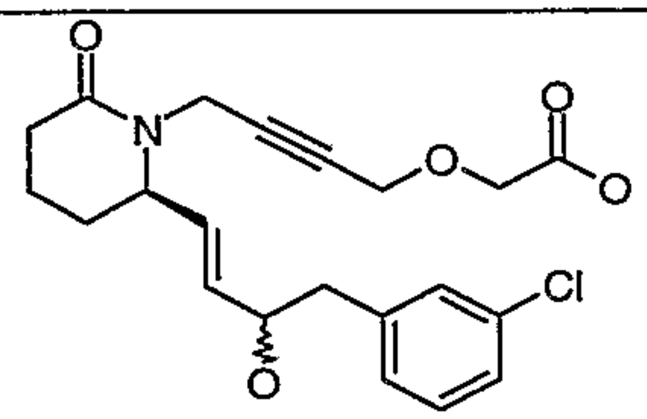
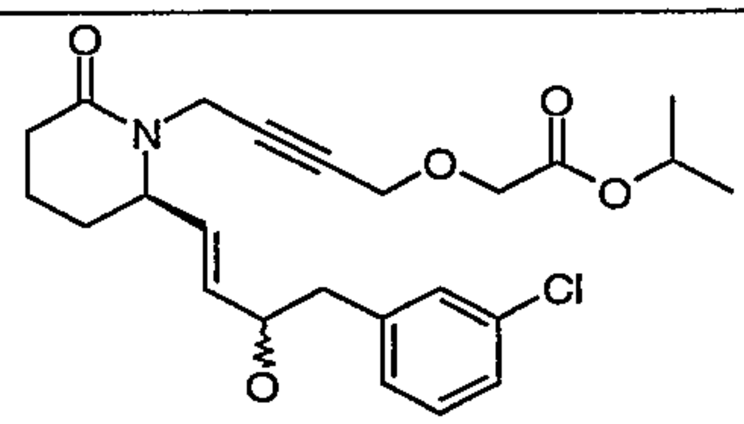
These compounds are tested for in vitro activity as described below and the results given in the Table.

Example	Structure	Binding Data (IC50 in nM)			Functional Data (EC50 in nM)							
		hEP2	hEP3D	hEP4	hFP	hEP1	hEP2	hEP3A	hEP4	hTP	hIP	hDP
1					NA	NA	NA	NA	NA	>10000	NA	NA
2					NA	NA	NA	>10000	300	2260	NA	NA
3					NA	NA	NA	NA	1104	NA	NA	NA
4					NA	NA	NA	NA	145	NA	NA	NA
5					NA	NA	NA	>10000	>10000	NA	NA	NA

Example	Structure	Binding Data (IC50 in nM)			Functional Data (EC50 in nM)							
		hEP2	hEP3D	hEP4	hFP	hEP1	hEP2	hEP3A	hEP4	hTP	hIP	hDP
6	 Chiral				NA	NA	NA	NA	>10000	NA	NA	NA
7					NA	NA	NA	NA	NA	NA	NA	NA
8					NA	NA	NA	NA	2556	>10000	NA	NA
9					NA	NA	NA	NA	7542	NA	NA	NA
10					NA	NA	NA	NA	1975	>10000	NA	NA

Example	Structure	Binding Data (IC50 in nM)			Functional Data (EC50 in nM)							
		hEP2	hEP3D	hEP4	hFP	hEP1	hEP2	hEP3A	hEP4	hTP	hIP	hDP
11					NA	NA	NA	NA	NA	NA	NA	NA
12					NA	NA	NA	NA	>10000	NA	NA	NA
13					NA	NA	NA	NA	NA	NA	NA	NA
14					NA	NA	NA	NA	>10000	>10000	NA	NA
15					NA	NA	NA	NA	NA	NA	NA	NA

Example	Structure	Binding Data (IC50 in nM)			Functional Data (EC50 in nM)							
		hEP2	hEP3D	hEP4	hFP	hEP1	hEP2	hEP3A	hEP4	hTP	hIP	hDP
16					NA	NA	NA	NA	>10000	NA	NA	NA
17					NA	>10000	>10000	NA			NA	NA
18					NA	NA	NA	NA		>10000	NA	NA
19					NA	NA	NA	NA		NA	NA	NA
20												

Example	Structure	Binding Data (IC50 in nM)			Functional Data (EC50 in nM)							
		hEP2	hEP3D	hEP4	hFP	hEP1	hEP2	hEP3A	hEP4	hTP	hIP	hDP
21												
22												
23												
24												
25												

HUMAN RECOMBINANT EP_1, EP_2, EP_3, EP_4, FP, TP, IP and DP RECEPTORS: STABLE TRANSFECTANTS.

Plasmids encoding the human EP_1, EP_2, EP_3, EP_4, FP, TP, IP and DP receptors were prepared by cloning the respective coding sequences into the eukaryotic expression vector pCEP4 (Invitrogen). The pCEP4 vector contains an Epstein Barr virus (EBV) origin of replication, which permits episomal replication in primate cell lines expressing EBV nuclear antigen (EBNA-1). It also contains a hygromycin resistance gene that is used for eukaryotic selection. The cells employed for stable transfection were human embryonic kidney cells (HEK-293) that were transfected with and express the EBNA-1 protein. These HEK-293-EBNA cells (Invitrogen) were grown in medium containing Geneticin (G418) to maintain expression of the EBNA-1 protein. HEK-293 cells were grown in DMEM with 10% fetal bovine serum (FBS), 250 $\mu g\ ml^{-1}$ G418 (Life Technologies) and 200 $\mu g\ ml^{-1}$ gentamicin or penicillin/streptomycin. Selection of stable transfectants was achieved with 200$\mu g\ ml^{-1}$ hygromycin, the optimal concentration being determined by previous hygromycin kill curve studies.

For transfection, the cells were grown to 50-60% confluency on 10 cm plates. The plasmid pCEP4 incorporating cDNA inserts for the respective human prostanoid receptor (20 μg) was added to 500 μl of 250 mM $CaCl_2$. HEPES buffered saline x 2 (2 x HBS, 280 mM NaCl, 20 mM HEPES acid, 1.5 mM $Na_2\ HPO_4$, pH 7.05 – 7.12) was then added dropwise to a total of 500 μl, with continuous vortexing at room temperature. After 30 min, 9 ml DMEM were added to the mixture. The DNA/DMEM/calcium phosphate mixture was then added to the cells, which had been previously rinsed with 10 ml PBS. The cells were then incubated for 5 hr at 37° C in humidified 95% air/5% CO_2. The calcium phosphate solution was then removed and the cells were treated with 10% glycerol in DMEM for 2 min. The glycerol solution was then replaced by DMEM with 10% FBS. The cells were incubated overnight and the medium was replaced by DMEM/10% FBS containing 250 μg ml^{-1} G418 and penicillin/streptomycin. The following day hygromycin B was added to a final concentration of 200 μg ml^{-1}.

Ten days after transfection, hygromycin B resistant clones were individually selected and transferred to a separate well on a 24 well plate. At confluence each clone was transferred to one well of a 6 well plate, and then expanded in a 10 cm dish. Cells were maintained under continuous hygromycin selection until use.

RADIOLIGAND BINDING

Radioligand binding studies on plasma membrane fractions prepared for cells stably transfected with the cat or human receptor were performed as follows. Cells washed with TME buffer were scraped from the bottom of the flasks and homogenized for 30 sec using a Brinkman PT 10/35 polytron. TME buffer was added as necessary to achieve a 40 ml volume in the centrifuge tubes. TME is comprised of 50 mM TRIS base, 10 mM $MgCl_2$, 1 mM EDTA; pH 7.4 is achieved by adding 1 N HCl. The cell homogenate was centrifuged at 19,000 rpm for 20-25 min at 4°C using a Beckman Ti-60 or Ti-70 rotor. The pellet was then resuspended in TME buffer to provide a final protein concentration of 1 mg/ml, as determined by Bio-Rad assay. Radioligand binding assays were performed in a 100 μl or 200 μl volume.

The binding of $[^3H]$(N) PGE_2 (specific activity 165 Ci/mmol) was determined in duplicate and in at least 3 separate experiments. Incubations were for 60 min at 25° C and were terminated by the addition of 4 ml of ice-cold 50 mM TRIS-HC1 followed by rapid filtration through Whatman GF/B filters and three additional 4 ml washes in a cell harvester (Brandel). Competition studies were performed using a final concentration of 2.5 or 5 nM $[^3H]$(N) PGE_2 and non-specific binding was determined with 10^{-5} M unlabelled PGE_2.

For radioligand binding on the transient transfectants, plasma membrane fraction preparation was as follows. COS-7 cells were washed with TME buffer, scraped from the bottom of the flasks, and homogenized for 30 sec using a

Brinkman PT 10/35 polytron. TME buffer was added to achieve a final 40 ml volume in the centrifuge tubes. The composition of TME is 100 mM TRIS base, 20 mM $MgCl_2$, 2M EDTA; 10N HCl is added to achieve a pH of 7.4.

The cell homogenate was centrifuged at 19000 rpm for 20 min at 4°C using a Beckman Ti-60 rotor. The resultant pellet was resuspended in TME buffer to give a final 1 mg/ml protein concentration, as determined by Biorad assay. Radioligand binding assays were performed in a 200 μl volume.

The binding of [^{3}H] PGE_2 (specific activity 165 Ci or mmol $^{-1}$) at EP_{3D}, receptors and [^{3}H]-SQ29548 (specific activity 41.5 Ci mmol^{-1}) at TP receptors were determined in duplicate in at least three separate experiments. Radiolabeled PGE_2 was purchased from Amersham, radiolabeled SQ29548 was purchased from New England Nuclear. Incubations were for 60 min at 25°C and were terminated by the addition of 4 ml of ice-cold 50 mM TRIS-HC1, followed by rapid filtration through Whatman GF/B filters and three additional 4 ml washes in a cell harvester (Brandel). Competition studies were performed using a final concentration of 2.5 or 5 nM [^{3}H]-PGE_2, or 10 nM [^{3}H]-SQ 29548 and non-specific binding determined with 10 μM of the respective unlabeled prostanoid. For all radioligand binding studies, the criteria for inclusion were >50% specific binding and between 500 and 1000 displaceable counts or better.

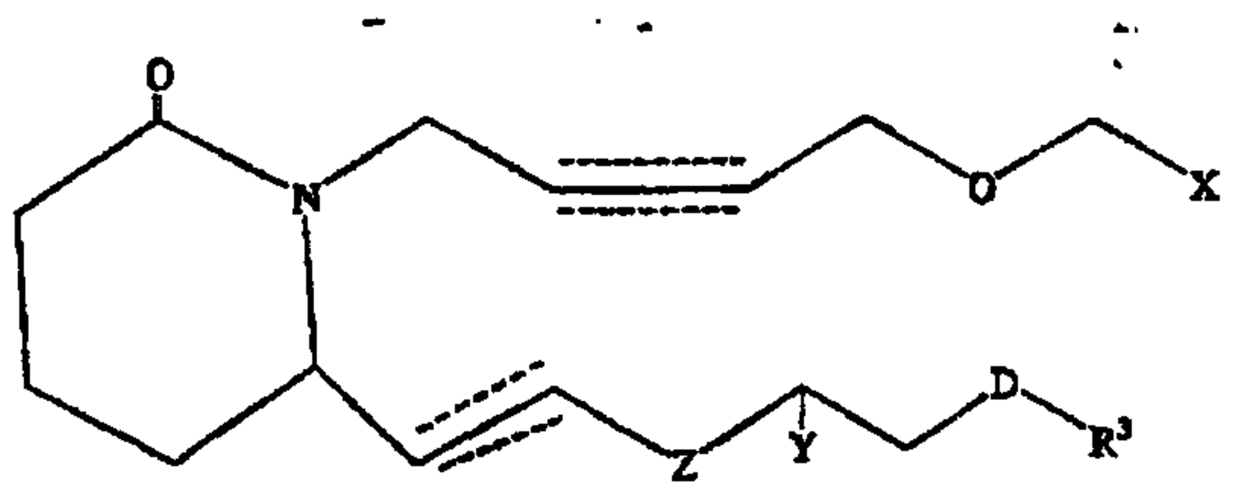
The effects of the compounds of this invention on intraocular pressure may be measured as follows. The compounds are prepared at the desired concentrations in a vehicle comprising 0.1% polysorbate 80 and 10 mM TRIS base. Dogs are treated by administering 25 μl to the ocular surface, the contralateral eye receives vehicle as a control. Intraocular pressure is measured by applanation pneumatonometry. Dog intraocular pressure is measured immediately before drug administration and at 6 hours thereafter.

The compounds of this invention are useful in lowering elevated intraocular pressure in mammals, e.g. humans.

The foregoing description details specific methods and compositions that can be employed to practice the present invention, and represents the best mode contemplated. However, it is apparent for one of ordinary skill in the art that further compounds with the desired pharmacological properties can be prepared in an analogous manner, and that the disclosed compounds can also be obtained from different starting compounds via different chemical reactions. Similarly, different pharmaceutical compositions may be prepared and used with substantially the same result. Thus, however detailed the foregoing may appear in text, it should not be construed as limiting the overall scope hereof; rather, the ambit of the present invention is to be governed only by the lawful construction of the appended claims.

CLAIMS

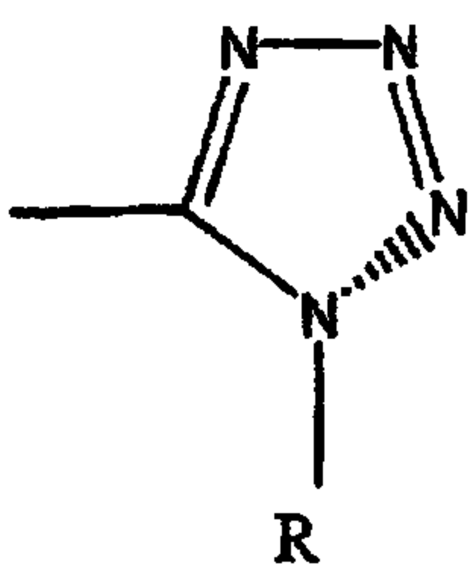
1. A compound represented by the general formula I;



wherein hatched lines represent the α configuration, a triangle represents the β configuration, a wavy line represents either the α configuration or the β configuration and a dotted line represents the presence or absence of a double or a triple bond;

D represents a covalent bond or CH_2 , O, S or NH;

X is CO_2R, $CONR_2$, CH_2OR, $P(O)(OR)_2$, $CONRSO_2R$, $SONR_2$ or



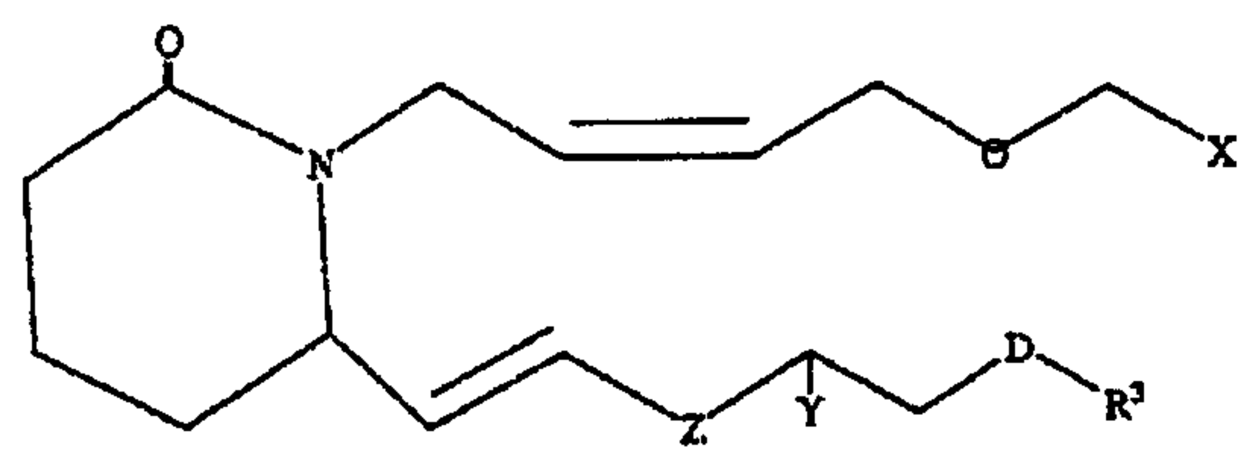
Z is CH_2 or a covalent bond;

R is H or R^2;

R^1 is H, R^2 , phenyl, or COR^2;

R^2 is C_1-C_5 lower alkyl or alkenyl and R_3 is selected from the group consisting of R^2, phenyl, thienyl, furanyl, pyridyl, benzothienyl, benzofuranyl, naphthyl, or substituted derivatives thereof, wherein the substituents maybe selected from the group consisting of C_1-C_5 alkyl, halogen, CF_3, CN, NO_2, NR_2, CO_2R and OR .

2. The compound according to claim 1 wherein said compound is represented by the general formula II;



3. The compound of claim 1 wherein Z represents a covalent bond.

4. The compound of claim 1 wherein D is CH_2.

5. The compound of claim 1 wherein X is CO_2 R.

6. The compound of claim 5 wherein R is selected from the group consisting of H and methyl.

7. The compound claim 5 wherein R is H, or C_1-C_5 alkyl.

8. The compound of claim 1 wherein R_1 is H.

9. The compound of claim 1 wherein R^3 is selected from the group consisting of phenyl and n-propyl.

10. The compound of claim 1 wherein said compound is selected from the group consisting of

{4-[(R)-2-Oxo-6-((E)-3-oxo-4-phenyl-but-1-enyl)-piperidin-1-yl]-butoxy}-acetic acid methyl ester, {4-[(R)-2-Oxo-6-((E)-3-oxo-4-phenyl-but-1-enyl)-piperidin-1-yl]-butoxy}-acetic acid,

{4-[(R)-2-((E)-3-Hydroxy-4-phenyl-but-1-enyl)-6-oxo-piperidin-1-yl]-butoxy}-acetic acid methyl ester,

{4-[(R)-2-((E)-3-Hydroxy-4-phenyl-but-1-enyl)-6-oxo-piperidin-1-yl]-butoxy}-acetic acid,

{4-[(R)-2-(3-Hydroxy-4-phenyl-butyl)-6-oxo-piperidin-1-yl]-butoxy}-acetic acid methyl ester,

{4-[(R)-2-(3-Hydroxy-4-phenyl-butyl)-6-oxo-piperidin-1-yl]-butoxy}-acetic acid,

{(Z)-4-[(R)-2-Oxo-6-((E)-3-oxo-4-phenyl-but-1-enyl)-piperidin-1-yl]-but-2-enyloxy}-acetic acid methyl ester,

{(Z)-4-[(R)-2-Oxo-6-((E)-3-oxo-4-phenyl-but-1-enyl)-piperidin-1-yl]-but-2-enyloxy}-acetic acid,

{4-[(R)-2-Oxo-6-(3-oxo-4-phenyl-butyl)-piperidin-1-yl]-butoxy}-acetic acid methyl ester,

{4-[(R)-2-Oxo-6-(3-oxo-4-phenyl-butyl)-piperidin-1-yl]-butoxy}-acetic acid,

{(Z)-4-[(R)-2-((E)-3-Hydroxy-4-phenyl-but-1-enyl)-6-oxo-piperidin-1-yl]-but-2-enyloxy}-acetic acid methyl ester,

{(Z)-4-[(R)-2-((E)-3-Hydroxy-4-phenyl-but-1-enyl)-6-oxo-piperidin-1-yl]-but-2-enyloxy}-acetic acid,

{(Z)-4-[(R)-2-Oxo-6-(3-oxo-4-phenyl-butyl)-piperidin-1-yl]-but-2-enyloxy}-acetic acid methyl ester,

{(Z)-4-[(R)-2-Oxo-6-(3-oxo-4-phenyl-butyl)-piperidin-1-yl]-but-2-enyloxy}-acetic acid,

{(Z)-4-[(R)-2-(3-Hydroxy-4-phenyl-butyl)-6-oxo-piperidin-1-yl]-but-2-enyloxy}-acetic acid methyl ester,

{(Z)-4-[(R)-2-(3-Hydroxy-4-phenyl-butyl)-6-oxo-piperidin-1-yl]-but-2-enyloxy}-acetic acid, (4-{(R)-2-[(E)-4-(3-Chlorophenyl)-3-hydroxy-but-1-enyl]-6-oxo-piperidin-1-yl}-butoxy)-acetic acid,

2-(4-{(R)-2-[(E)-4-(3-Chlorophenyl)-3-hydroxy-but-1-enyl]-6-oxo-piperidin-1-yl}-butoxy)-acetamide,

(4-{(R)-2-[(E)-4-(3-Chlorophenyl)-3-hydroxy-but-1-enyl]-6-oxo-piperidin-1-yl}-butoxy)-acetic acid isopropyl ester,

(4-{(R)-2-[(E)-4-(3-Chlorophenyl)-3-oxo-but-1-enyl]-6-oxo-piperidin-1-yl}-but-2-ynyloxy)-acetic acid methyl ester,

(4-{(R)-2-[(E)-4-(3-Chlorophenyl)-3-oxo-but-1-enyl]-6-oxo-piperidin-1-yl}-but-2-ynyloxy)-acetic acid,

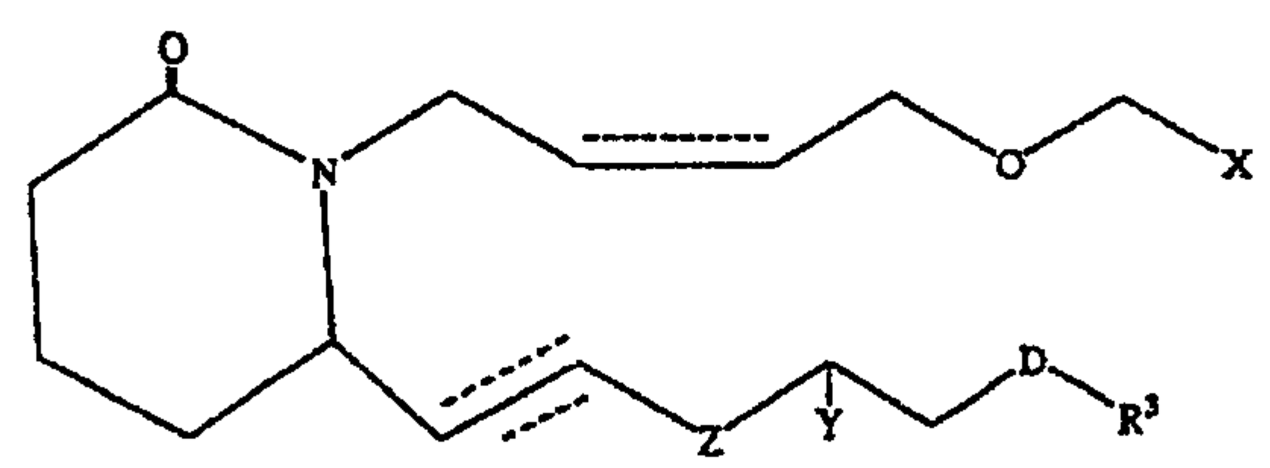
(4-{(R)-2-[(E)-4-(3-Chlorophenyl)-3-hydroxy-but-1-enyl]-6-oxo-piperidin-1-yl}-but-2-ynyloxy)-acetic acid methyl ester,

(R)-6-[(E)-4-(3-Chlorophenyl)-3-hydroxy-but-1-enyl]-1-[4-(2-hydroxyethoxy)-but-2-ynyl]-piperidin-2-one,

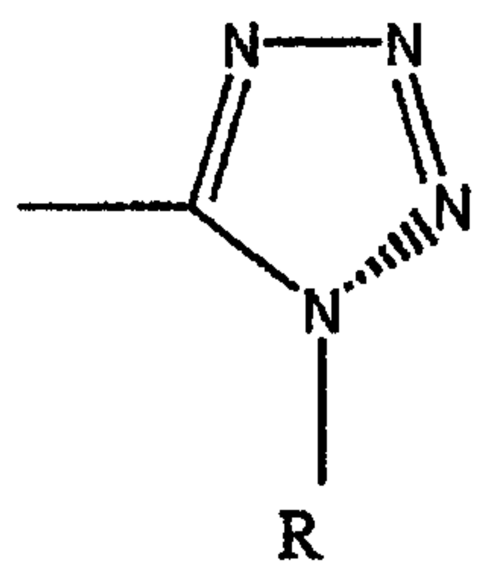
(4-{(R)-2-[(E)-4-(3-Chlorophenyl)-3-hydroxy-but-1-enyl]-6-oxo-piperidin-1-yl}-but-2-ynyloxy)-acetic acid and

(4-{(R)-2-[(E)-4-(3-Chlorophenyl)-3-hydroxy-but-1-enyl]-6-oxo-piperidin-1-yl}-but-2-ynyloxy)-acetic acid isopropyl ester.

11. An ophthalmic solution comprising a therapeutically effective amount of a compound represented by the general Formula 1;



wherein hatched lines represent the α configuration, a triangle represents the β configuration, a wavy line represents the α configuration or the β configuration and a dotted line represents the presence or absence of a double or a triple bond;
D represents a covalent bond or CH_2 , O, S or NH;

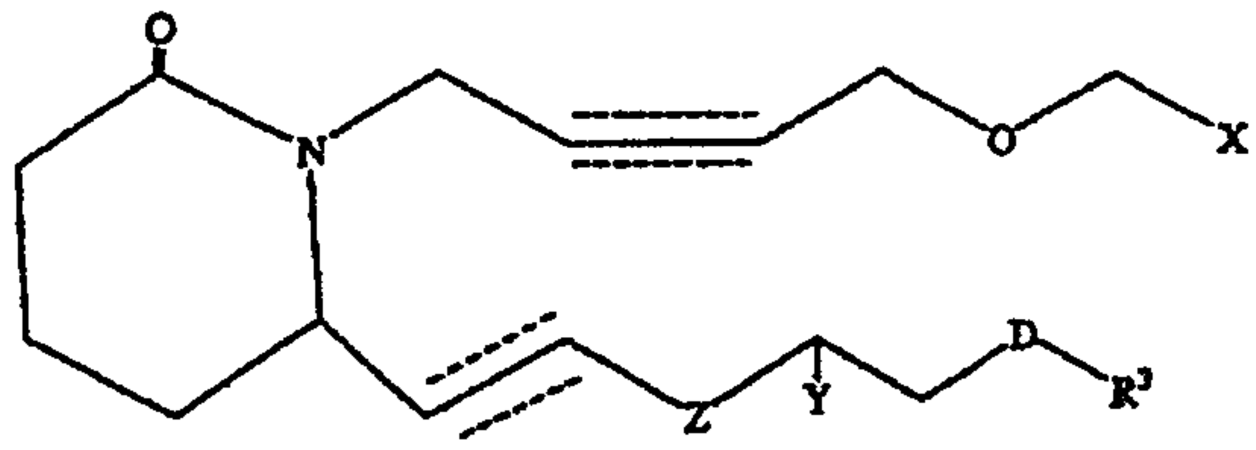


X is C
O_2R, $CONR_2$, CH_2OR, $P(O)(OR)_2$, $CONRSO_2R$ $SONR_2$ or

Z is CH_2 or a covalent bond;
R is H or R^2;
R^1 is H, R^2 , phenyl, or COR^2;
R^2 is C_1-C_5 lower alkyl or alkenyl and R_3 is selected from the group consisting of R^2, phenyl, thienyl, furanyl, pyridyl, benzothienyl, benzofuranyl, naphthyl or substituted derivatives thereof, wherein the substituents maybe selected from the group consisting of C_1-C_5 alkyl, halogen, CF_3, CN, NO_2, NR_2, CO_2R and OR in admixture with a non-toxic, ophthalmically acceptable liquid vehicle, packaged in a container suitable for metered application.

12. A pharmaceutical product, comprising a container adapted to dispense the contents of said container in metered form; and an ophthalmic solution according to claim 11 in said container.

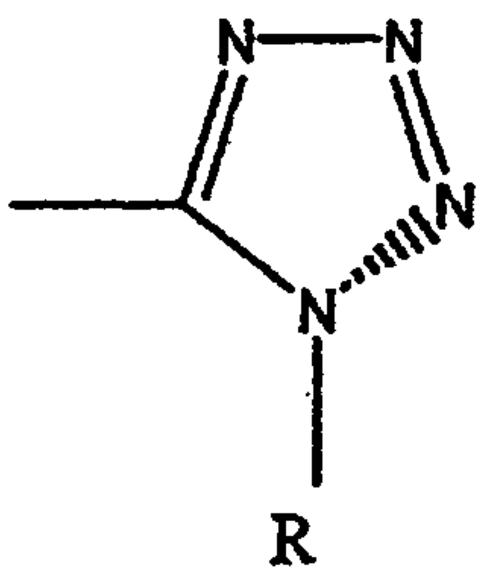
13. Use for treating ocular hypertension or glaucoma in an animal of a compound represented by the general formula I;



wherein hatched lines represent the α configuration, a triangle represents the β configuration, a wavy line represents either the α configuration or the β configuration and a dotted line represents the presence or absence of a double or a triple bond;

D represents a covalent bond or CH_2, O, S or NH;

X is CO_2R, $CONR_2$, CH_2OR, $P(O)(OR)_2$, $CONRSO_2R$, $SONR_2$ or



Y is

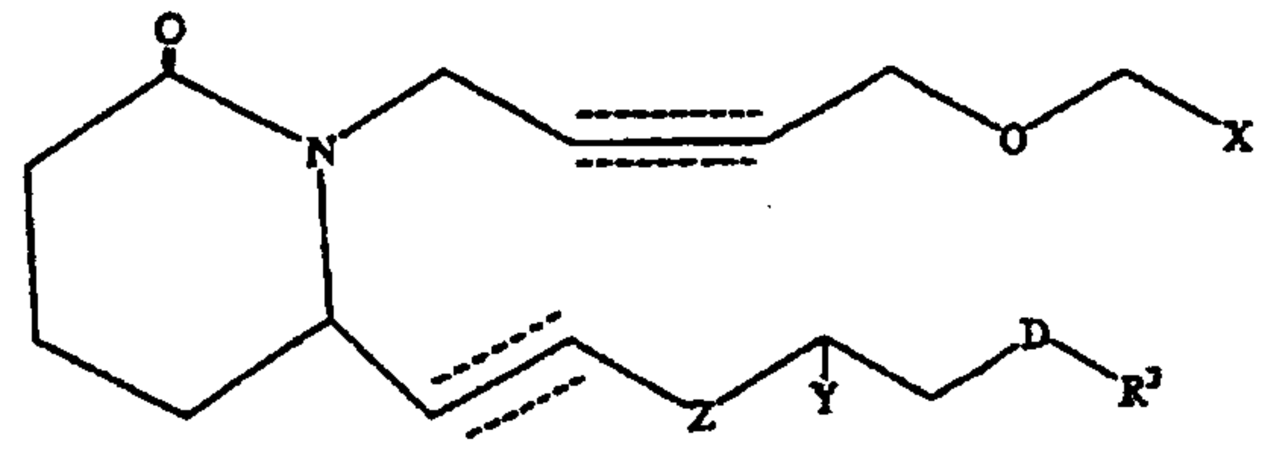
Z is CH_2 or a covalent bond;

R is H or R^2;

R^1 is H, R^2, phenyl, or COR^2;

R^2 is C_1-C_5 lower alkyl or alkenyl and R_3 is selected from the group consisting of R^2, phenyl, thienyl, furanyl, pyridyl, benzothienyl, benzofuranyl, naphthyl, or substituted derivatives thereof, wherein the substituents maybe selected from the group consisting of C_1-C_5 alkyl, halogen, CF_3, CN, NO_2, NR_2, CO_2R and OR.

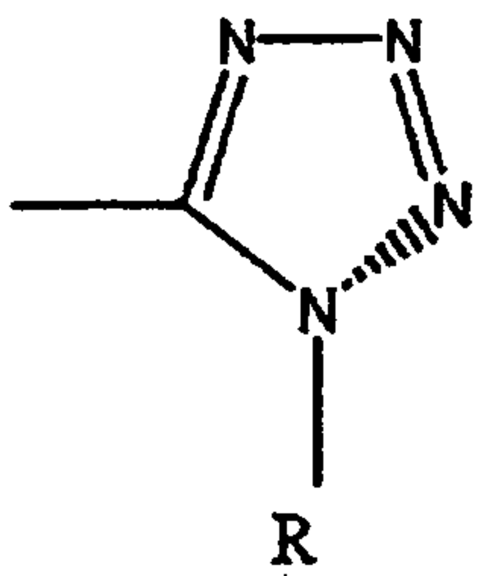
14. Use in the manufacture of a medicament for treating ocular hypertension or glaucoma in an animal of a compound represented by the general formula I;



wherein hatched lines represent the α configuration, a triangle represents the β configuration, a wavy line represents either the α configuration or the β configuration and a dotted line represents the presence or absence of a double or a triple bond;

D represents a covalent bond or CH_2, O, S or NH;

X is CO_2R, $CONR_2$, CH_2OR, $P(O)(OR)_2$, $CONRSO_2R$, $SONR_2$ or



Y is 

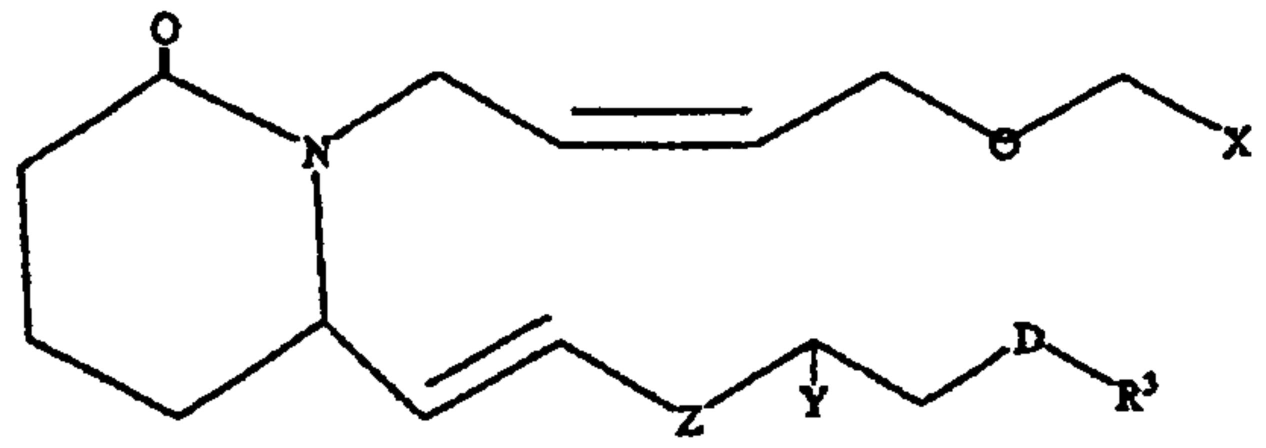
Z is CH_2 or a covalent bond;

R is H or R^2;

R^1 is H, R^2, phenyl, or COR^2;

R^2 is C_1-C_5 lower alkyl or alkenyl and R_3 is selected from the group consisting of R^2, phenyl, thienyl, furanyl, pyridyl, benzothienyl, benzofuranyl, naphthyl, or substituted derivatives thereof, wherein the substituents maybe selected from the group consisting of C_1-C_5 alkyl, halogen, CF_3, CN, NO_2, NR_2, CO_2R and OR.

15. The use according to claim 13 or 14, wherein said compound is represented by the general formula II;



16. The use of claim 13 or 14, wherein Z represents a covalent bond.

17. The use of claim 13 or 14, wherein D is CH_2.

18. The use of claim 13 or 14, wherein X is CO_2 R.

19. The use of claim 18, wherein R is selected form the group consisting of H and methyl.

20. The use of claim 18, wherein R is H, or C_1-C_5 alkyl.

21. The use of claim 13 or 14, wherein R_1 is H.

22. The use of claim 13 or 14, wherein R^3 is selected from the group consisting of phenyl and n-propyl.

23. The use of claim 13 or 14, wherein said compound is selected from the group consisting of

{4-[(R)-2-Oxo-6-((E)-3-oxo-4-phenyl-but-1-enyl)-piperidin-1-yl]-butoxy}-acetic acid methyl ester,

{4-[(R)-2-Oxo-6-((E)-3-oxo-4-phenyl-but-1-enyl)-piperidin-1-yl]-butoxy}-acetic acid,

{4-[(R)-2-((E)-3-Hydroxy-4-phenyl-but-1-enyl)-6-oxo-piperidin-1-yl]-butoxy}-acetic acid methyl ester,

{4-[(R)-2-((E)-3-Hydroxy-4-phenyl-but-1-enyl)-6-oxo-piperidin-1-yl]-butoxy}-acetic acid,

{4-[(R)-2-(3-Hydroxy-4-phenyl-butyl)-6-oxo-piperidin-1-yl]-butoxy}-acetic acid methyl ester,

{4-[(R)-2-(3-Hydroxy-4-phenyl-butyl)-6-oxo-piperidin-1-yl]-butoxy}-acetic acid,

{(Z)-4-[(R)-2-Oxo-6-((E)-3-oxo-4-phenyl-but-1-enyl)-piperidin-1-yl]-but-2-enyloxy}-acetic acid methyl ester,

{(Z)-4-[(R)-2-Oxo-6-((E)-3-oxo-4-phenyl-but-1-enyl)-piperidin-1-yl]-but-2-enyloxy}-acetic acid,

{4-[(R)-2-Oxo-6-(3-oxo-4-phenyl-butyl)-piperidin-1-yl]-butoxy}-acetic acid methyl ester,

{4-[(R)-2-Oxo-6-(3-oxo-4-phenyl-butyl)-piperidin-1-yl]-butoxy}-acetic acid,

{(Z)-4-[(R)-2-((E)-3-Hydroxy-4-phenyl-but-1-enyl)-6-oxo-piperidin-1-yl]-but-2-enyloxy}-acetic acid methyl ester,

{(Z)-4-[(R)-2-((E)-3-Hydroxy-4-phenyl-but-1-enyl)-6-oxo-piperidin-1-yl]-but-2-enyloxy}-acetic acid,

{(Z)-4-[(R)-2-Oxo-6-(3-oxo-4-phenyl-butyl)-piperidin-1-yl]-but-2-enyloxy}-acetic acid methyl ester,

{(Z)-4-[(R)-2-Oxo-6-(3-oxo-4-phenyl-butyl)-piperidin-1-yl]-but-2-enyloxy}-acetic acid,

{(Z)-4-[(R)-2-(3-Hydroxy-4-phenyl-butyl)-6-oxo-piperidin-1-yl]-but-2-enyloxy}-acetic acid methyl ester,

{(Z)-4-[(R)-2-(3-Hydroxy-4-phenyl-butyl)-6-oxo-piperidin-1-yl]-but-2-enyloxy}-acetic acid,

(4-{(R)-2-[(E)-4-(3-Chlorophenyl)-3-hydroxy-but-1-enyl]-6-oxo-piperidin-1-yl}-butoxy)-acetic acid

2-(4-{(R)-2-[(E)-4-(3-Chlorophenyl)-3-hydroxy-but-1-enyl]-6-oxo-piperidin-1-yl}-butoxy)-acetamide,

(4-{(R)-2-[(E)-4-(3-Chlorophenyl)-3-hydroxy-but-1-enyl]-6-oxo-piperidin-1-yl}-butoxy)-acetic acid isopropyl ester,

(4-{(R)-2-[(E)-4-(3-Chlorophenyl)-3-oxo-but-1-enyl]-6-oxo-piperidin-1-yl}-but-2-ynyloxy)-acetic acid methyl ester,

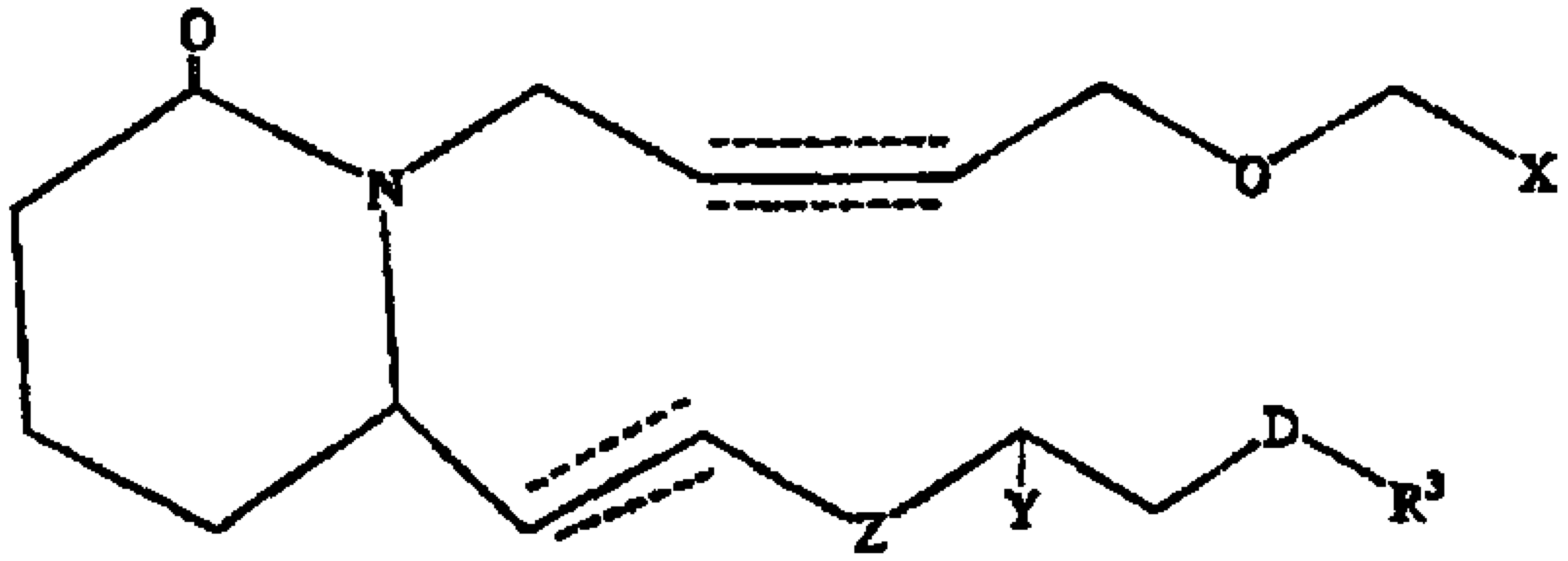
(4-{(R)-2-[(E)-4-(3-Chlorophenyl)-3-oxo-but-1-enyl]-6-oxo-piperidin-1-yl}-but-2-ynyloxy)-acetic acid,

(4-{(R)-2-[(E)-4-(3-Chlorophenyl)-3-hydroxy-but-1-enyl]-6-oxo-piperidin-1-yl}-but-2-ynyloxy)-acetic acid methyl ester,

(R)-6-[(E)-4-(3-Chlorophenyl)-3-hydroxy-but-1-enyl]-1-[4-(2-hydroxyethoxy)-but-2-ynyl]-piperidin-2-one,

(4-{(R)-2-[(E)-4-(3-Chlorophenyl)-3-hydroxy-but-1-enyl]-6-oxo-piperidin-1-yl}-but-2-ynyloxy)-acetic acid and

(4-{(R)-2-[(E)-4-(3-Chlorophenyl)-3-hydroxy-but-1-enyl]-6-oxo-piperidin-1-yl}-but-2-ynyloxy)-acetic acid isopropyl ester.



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