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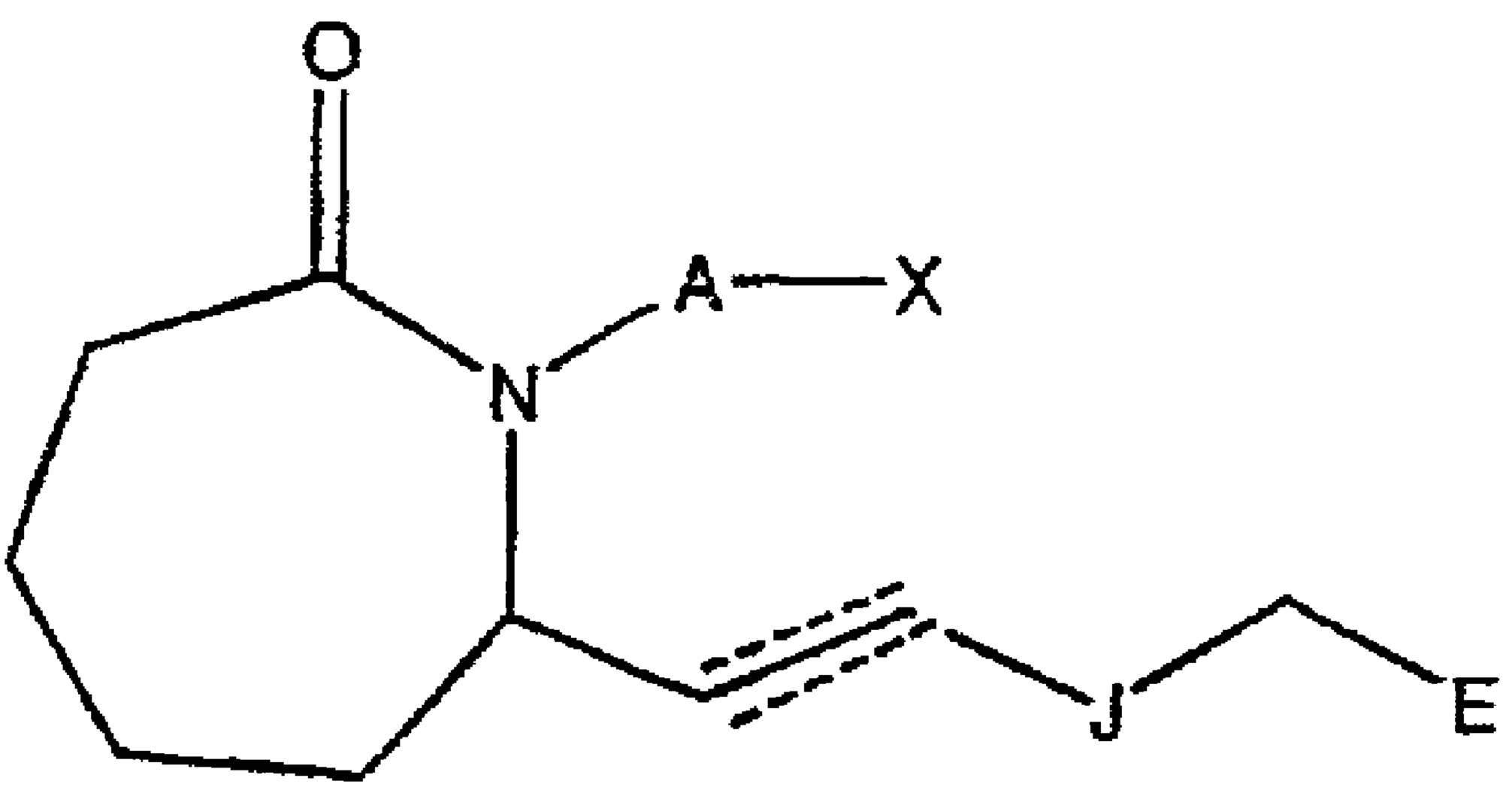
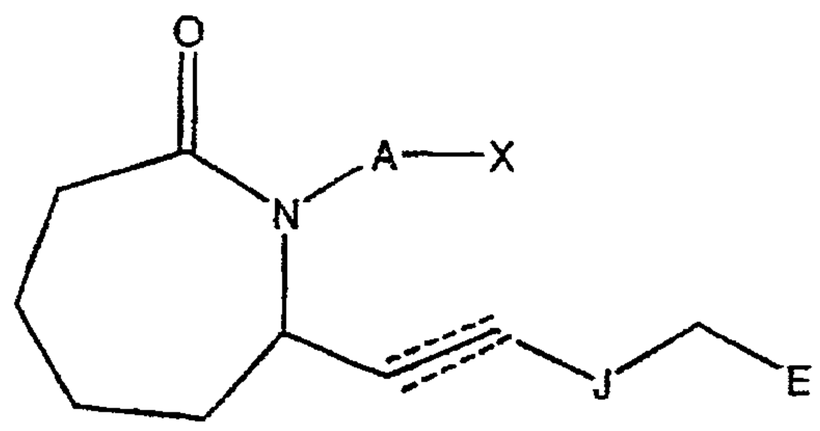
(54) Title: PROSTAGLANDIN ANALOGS



(57) Abrégé/Abstract:
Compounds of the general formula: (see above formula) or a pharmaceutically acceptable salt or prodrug thereof are provided. These compounds are useful for treating diseases including glaucoma and/or ocular hypertension.

Abstract

Compounds of the general formula:



or a pharmaceutically acceptable salt or prodrug thereof are provided. These compounds are useful for treating diseases including glaucoma and/or ocular hypertension.

PROSTAGLANDIN ANALOGS

By Inventors

David W. Old, Danny T. Dinh, and Robert M. Burk

FIELD OF THE INVENTION

This invention relates to compounds which are useful as therapeutic agents. Among other potential uses, these compounds are believed to have properties which are characteristic of prostaglandins.

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

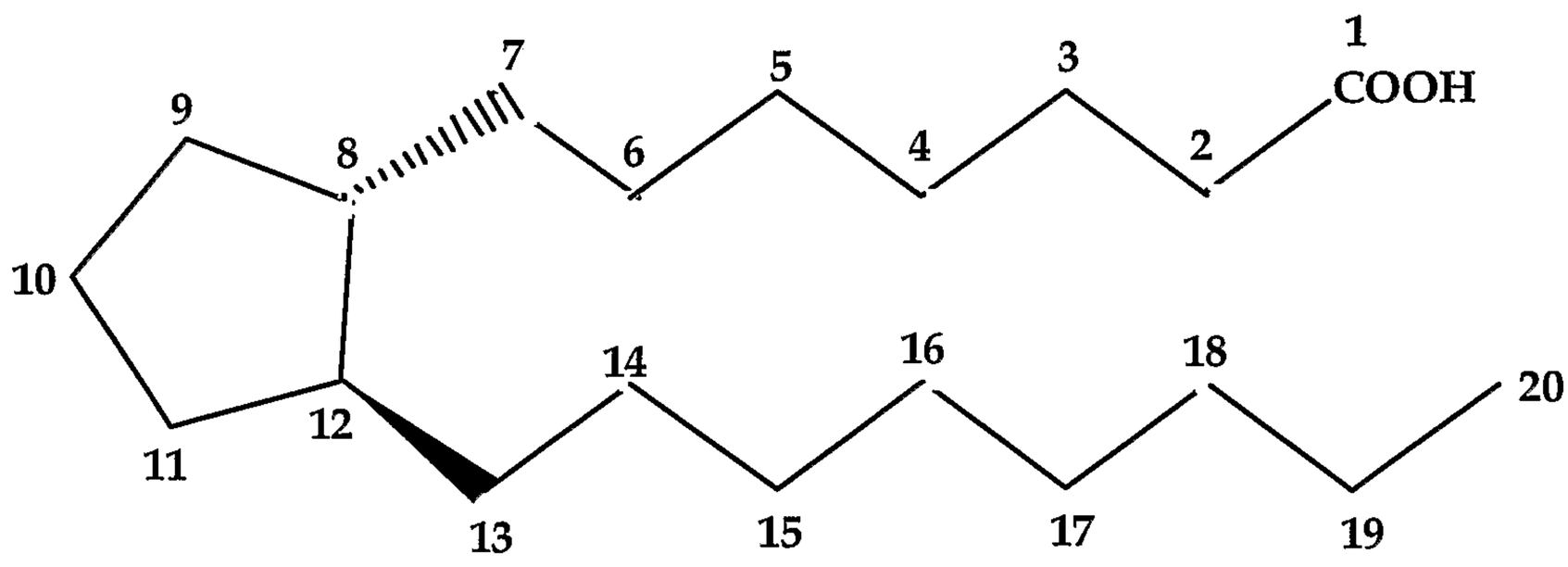
precipitate an acute attack. Eyes with narrow anterior chamber angles are predisposed to acute angle-closure glaucoma attacks of various degrees of severity.

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 β-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 two decades 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)].

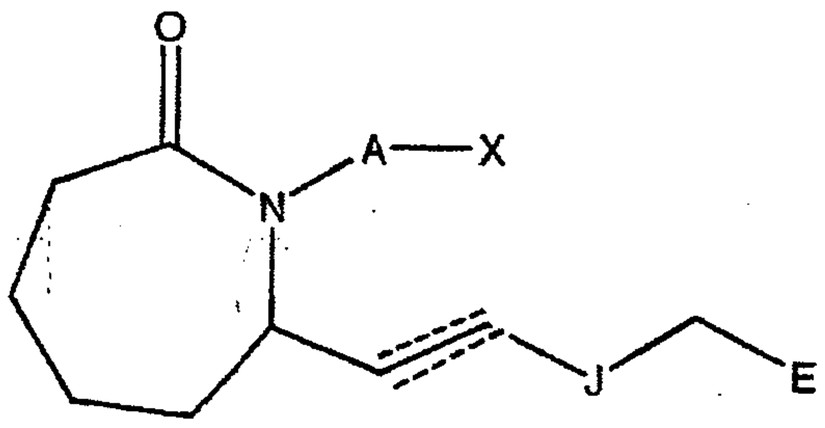
The isopropyl ester of $PGF_{2\alpha}$ has been shown to have significantly greater hypotensive potency than the parent compound, presumably as a result of its more effective penetration through the cornea. In 1987, this compound was described as "the most potent ocular hypotensive agent ever reported" [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 United States patents assigned to Allergan, Inc. prostaglandin esters with increased ocular hypotensive activity accompanied with no or substantially reduced side-effects are disclosed. Some representative examples are U.S. Patent 5,446,041, U.S. Patent 4,994,274, U.S. Patent 5,028,624 and U.S. Patent 5,034,413.

BRIEF DESCRIPTION OF THE INVENTION

A compound comprising

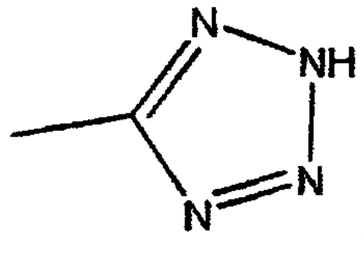


or a pharmaceutically acceptable salt or a prodrug thereof, is disclosed herein;

wherein a dashed line represents the presence or absence of a double bond or a triple bond;

A is $-(CH_2)_6-$, *cis* $-CH_2CH=CH-(CH_2)_3-$, or $-CH_2C\equiv C-(CH_2)_3-$, wherein 1 or 2 carbon atoms may be substituted with S or O;

X is selected from the group consisting of CO_2H, $CONHR_2$, $CONR_2$, $CON(OR)R$, $CON(CH_2CH_2OH)_2$, $CONH(CH_2CH_2OH)$, CH_2OH, $P(O)(OH)_2$, $CONHSO_2R$, SO_2NR_2, SO_2NHR, and



;

J is C=O, CHOH, or CH_2CHOH;

R is independently H, C_1-C_6 alkyl, phenyl, or biphenyl; and

E is C_3-C_6 alkyl, C_4-C_{10} cycloalkyl, phenyl or napthyl having from 0 to 2 substituents, or a heteroaromatic moiety having from 0 to 2 substituents, wherein said substituents comprise up to 4 non-hydrogen atoms.

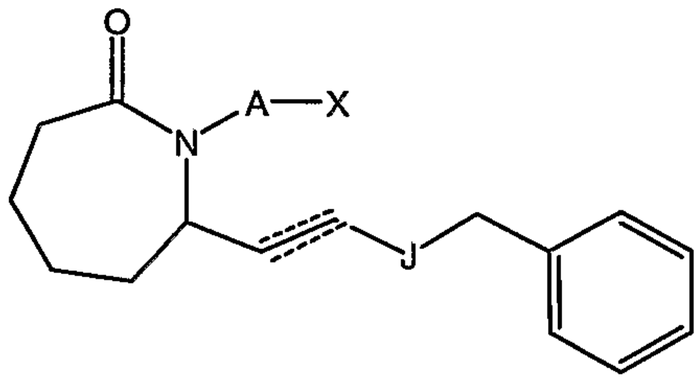
Methods of treating certain conditions or diseases, and compositions and medicaments related thereto are also contemplated.

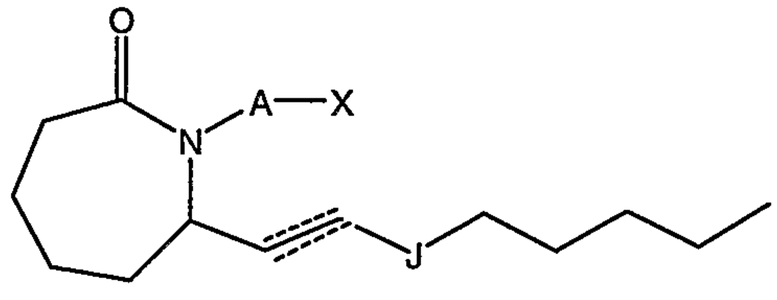
BRIEF DESCRIPTION OF THE DRAWING FIGURES

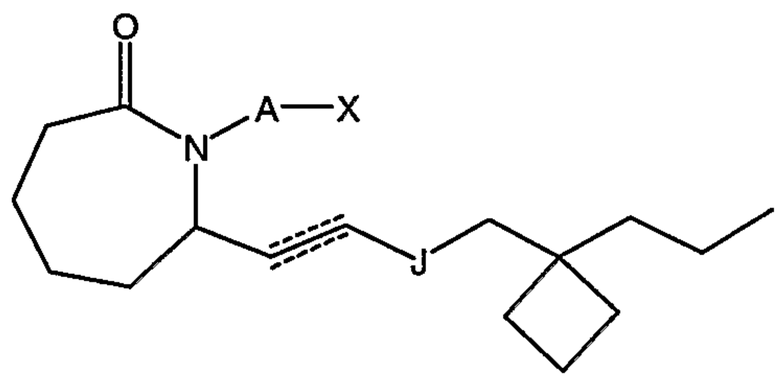
Schemes 1 - 3 illustrate three methods of preparing the compounds disclosed herein.

DETAILED DESCRIPTION OF THE INVENTION

While not intending to limit the scope of the invention in any way, compounds comprising

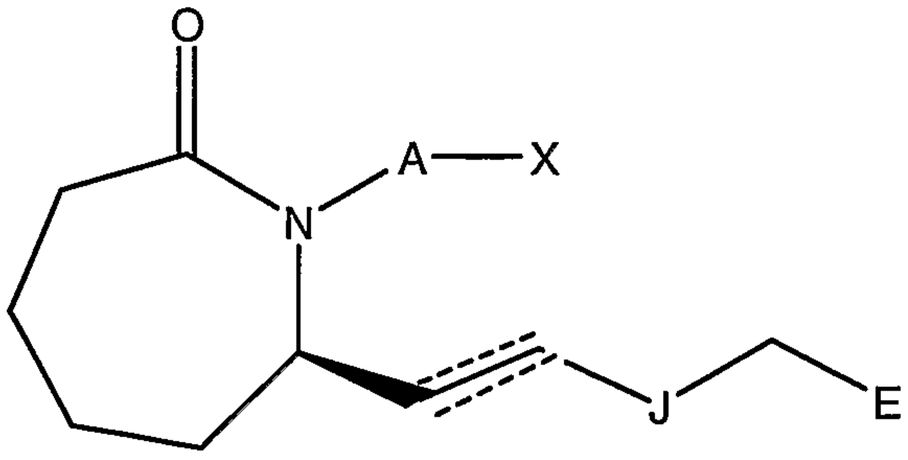






or pharmaceutically acceptable salts, or prodrugs thereof, are useful for the purposes disclosed herein.

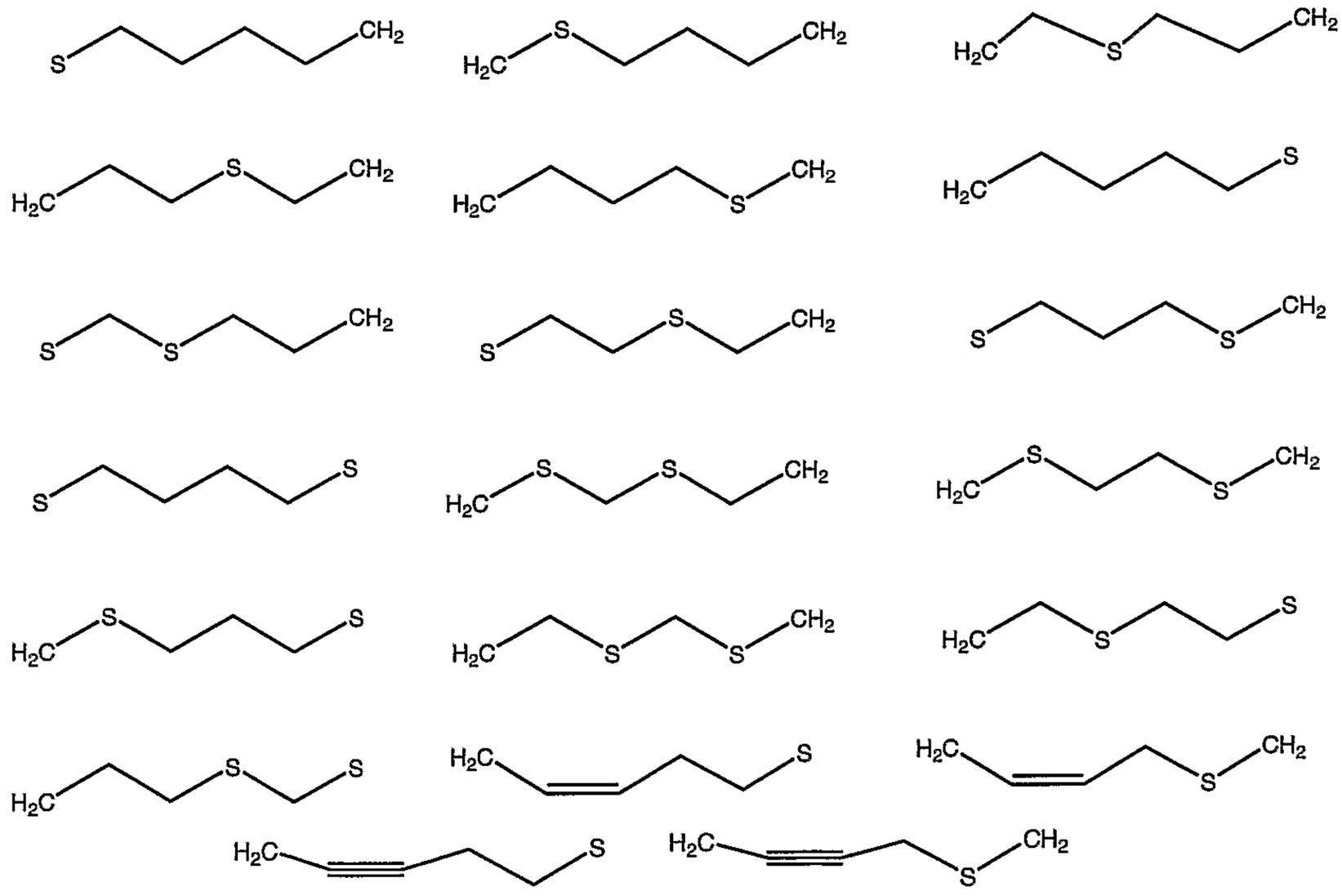
While not intending to limit the scope of the invention in any way, compounds having the stereochemistry indicated in the structure below may be particularly useful.



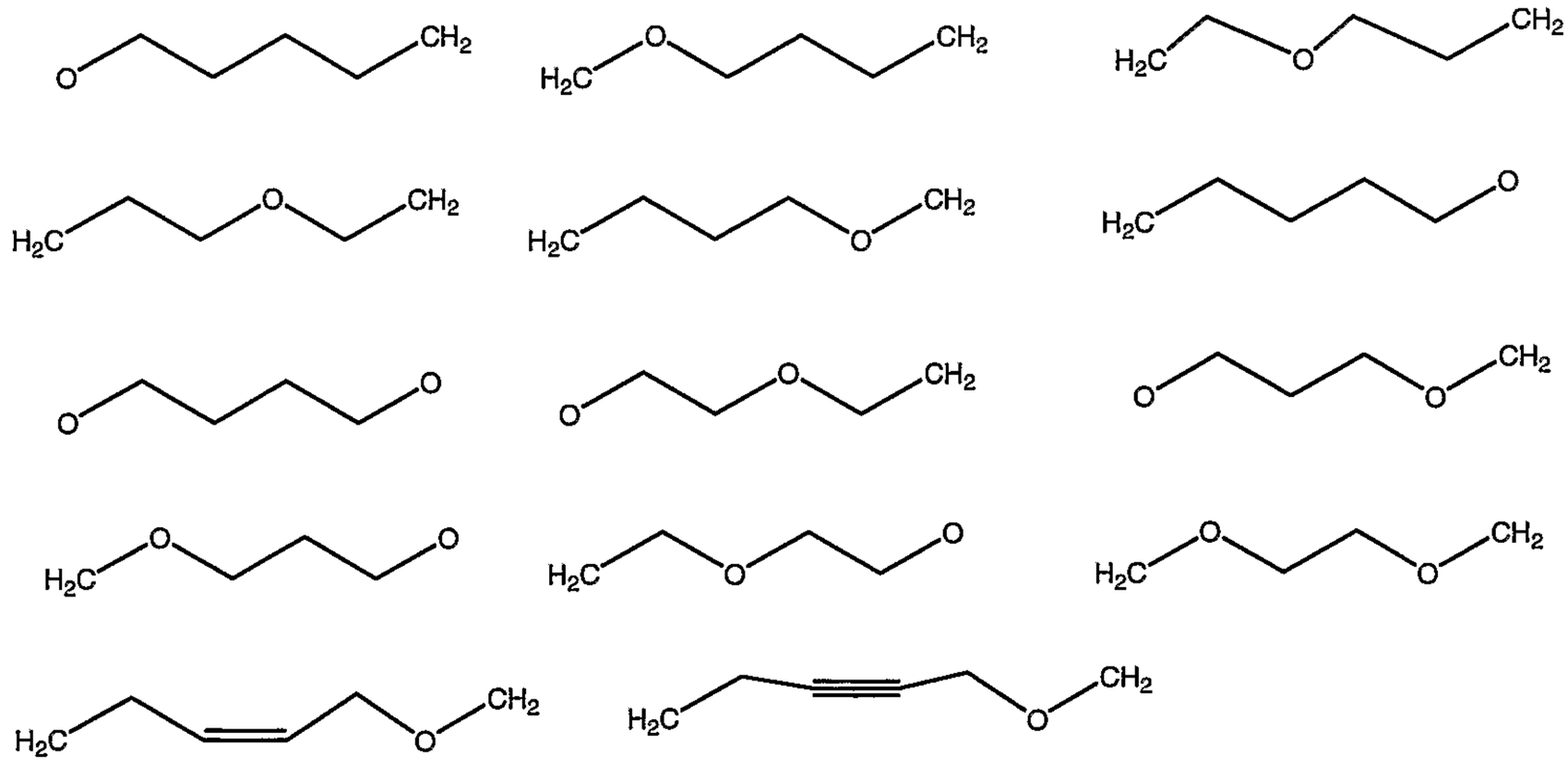
Pharmaceutically acceptable salts or prodrugs of compounds of the structure above are also considered to be particularly useful

A person of ordinary skill in the art understands the meaning of the stereochemistry associated with the hatched wedge/solid wedge structural features. For example, an introductory organic chemistry textbook (Francis A. Carey, Organic Chemistry, New York: McGraw-Hill Book Company 1987, p. 63) states "a wedge indicates a bond coming from the plane of the paper toward the viewer" and the hatched wedge, indicated as a "dashed line", "represents a bond receding from the viewer."

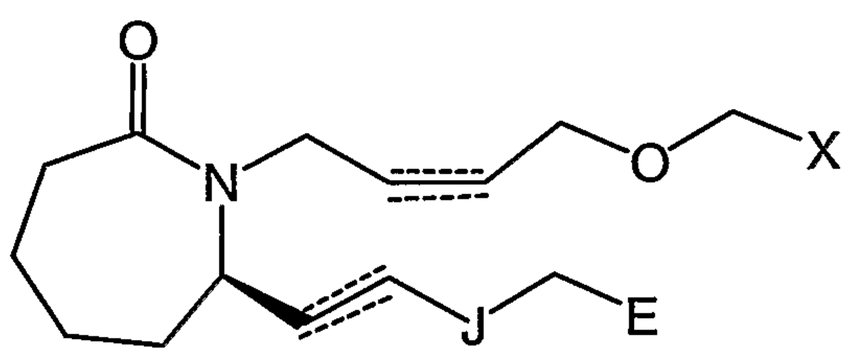
In relation to the identity of A disclosed in the chemical structures presented herein, in the broadest sense, A is $-(CH_2)_6-$, *cis* $-CH_2CH=CH-(CH_2)_3-$, or $-CH_2C\equiv C-(CH_2)_3-$, wherein 1 or 2 carbon atoms may be substituted with S or O. In other words, A may be $-(CH_2)_6-$, *cis* $-CH_2CH=CH-(CH_2)_3-$, $-CH_2C\equiv C-(CH_2)_3-$, or A may be a group which is related to one of these three moieties in that any carbon is substituted with S or O. For example, while not intending to limit the scope of the invention in any way, A may be an S substituted moiety such as one of the following or the like.



Alternatively, while not intending to limit the scope of the invention in any way, A may be an O substituted moiety such as one of the following or the like.

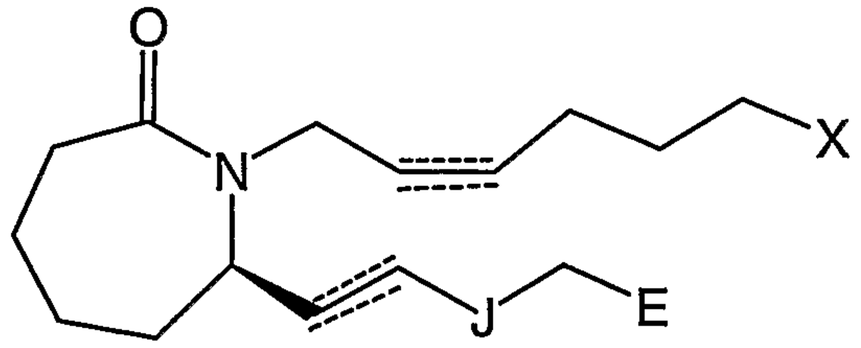


In certain compounds A is $-(CH_2)_4OCH_2$-, $-CH_2CH=CHCH_2OCH_2$-, or $-CH_2C\equiv CCH_2OCH_2$-, that is they can be generically described by the structure shown below.



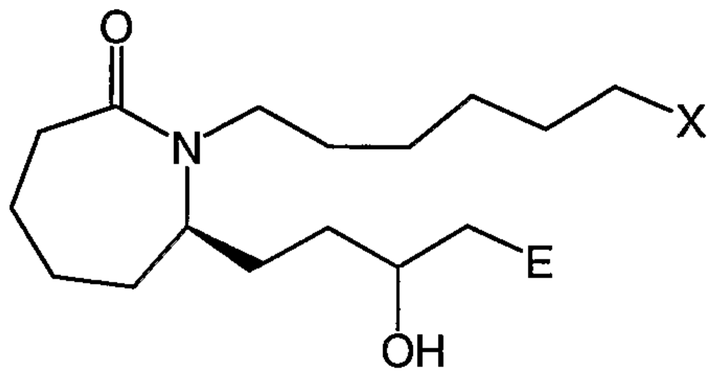
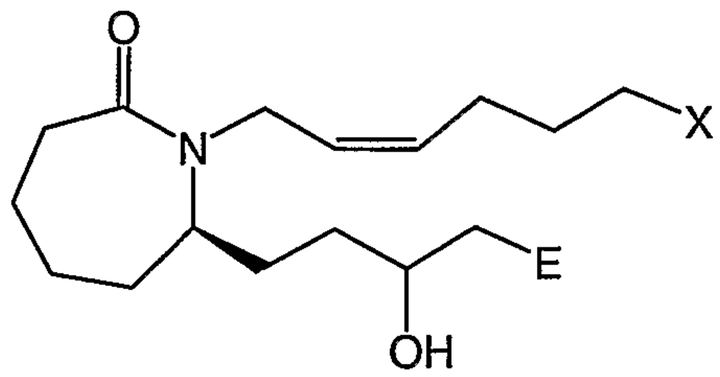
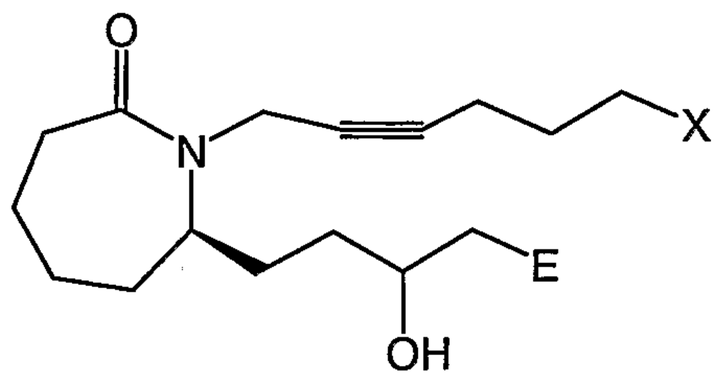
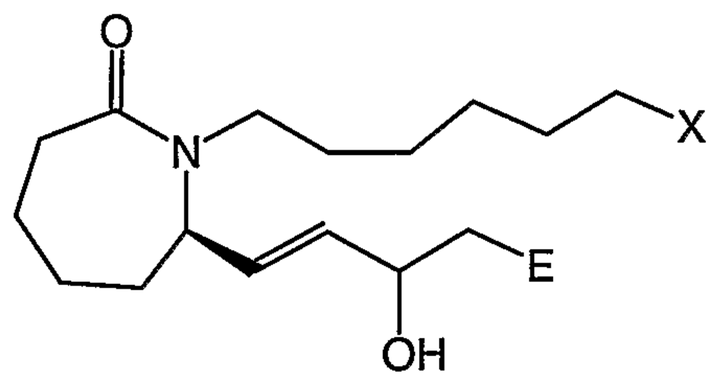
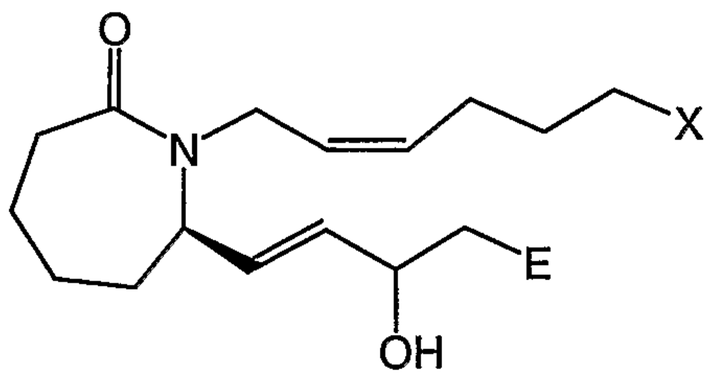
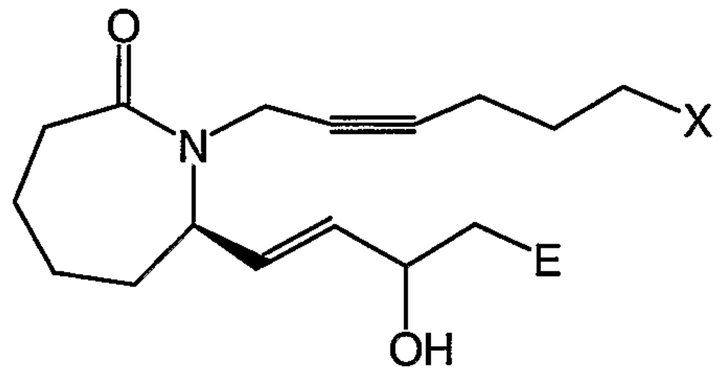
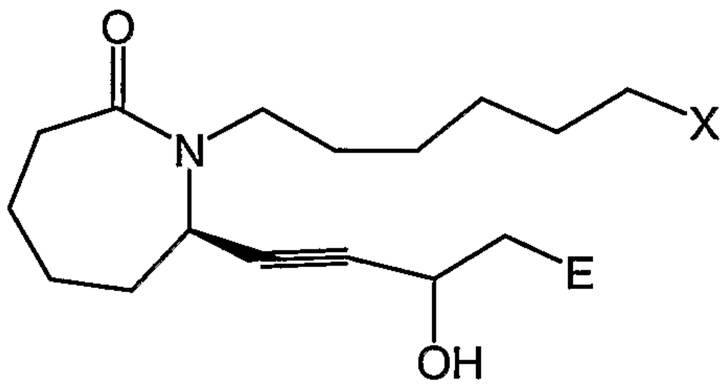
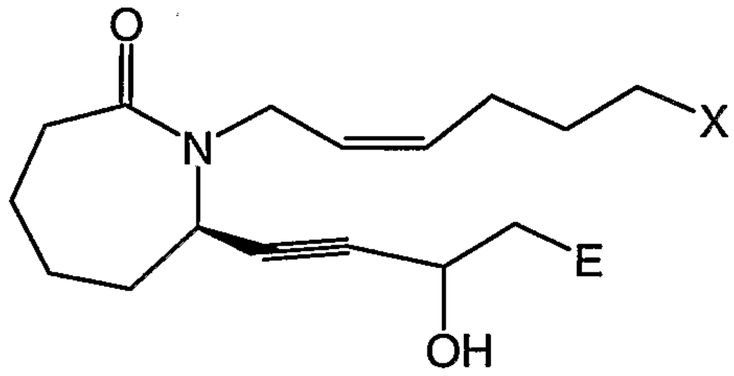
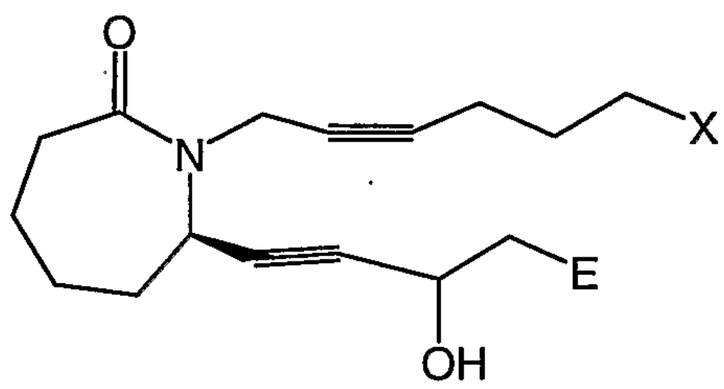
Pharmaceutically acceptable salts and prodrugs thereof are also contemplated.

In other embodiments, A is $-(CH_2)_6$-, *cis* $-CH_2CH=CH-(CH_2)_3$-, or $-CH_2C\equiv C-(CH_2)_3$- having no heteroatom substitution, that is they can be generically described by the structure shown below.



Pharmaceutically acceptable salts and prodrugs thereof are also contemplated.

While not intending to limit the scope of the invention in any way, compounds according to the structures below are specifically contemplated.

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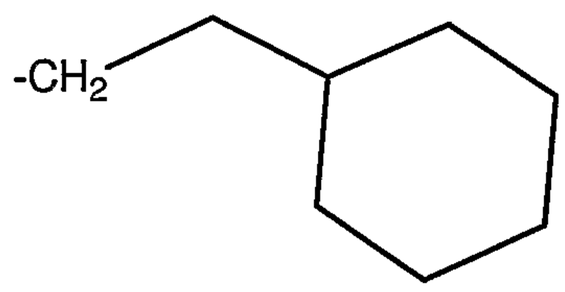
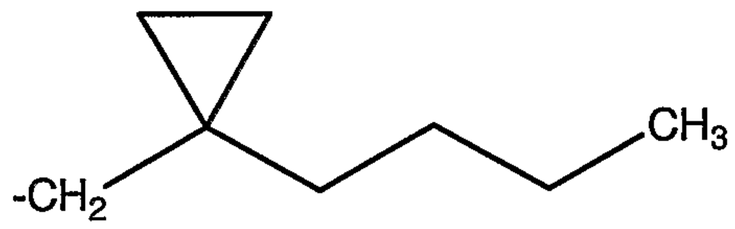
Pharmaceutically acceptable salts or prodrugs of compounds of these structures are also contemplated.

10 E can vary broadly, as E may be C_3-C_6 alkyl, C_4-C_{10} cycloalkyl, phenyl or napthyl having from 0 to 2 substituents, or a heteroaromatic moiety having from 0 to 2 substituents, wherein said substituents comprise up to 4 non-hydrogen atoms.

Thus, E may be C_3-C_6 alkyl, including linear alkyl such as *n*-propyl, *n*-butyl, *n*-penyl, or *n*-hexyl; branched alkyl such as *iso*-propyl, *iso*-butyl and other branched butyl isomers, *iso*-pentyl and other branched pentyl isomers, and the branched hexyl isomers. E may also be C_4-C_{10} cycloalkyl, including cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, and cyclodecyl; cycloalkyl with linear or branched substituents are also considered cycloalkyl such as methylcyclohexyl, methylcyclobutyl, ethylcyclohexyl and the like. A cycloalkyl ring may also be attached the remainder of the molecule via a linear or branched alkyl fragment, such as for example, the following moieties





and the attaching fragment as well as the cyclic part is considered to be the entire cycloalkyl moiety. Additionally, any other hydrocarbon moiety which can be conceived by a person of ordinary skill in the art which consists of a cycloalkyl ring in any form with any other combination of linear or branched alkyl groups is a cycloalkyl moiety.

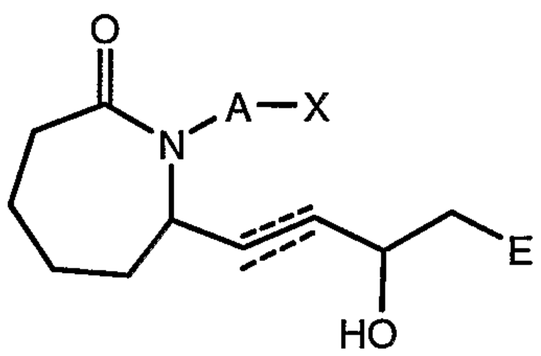
E may also be phenyl or naphthyl having from 0 to 2 substituents.

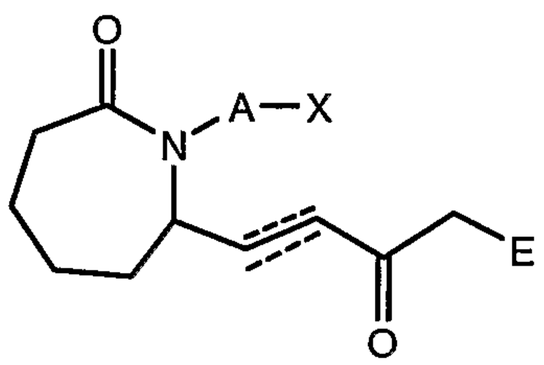
E may also be a heteroaromatic moiety having from 0 to 2 substituents.

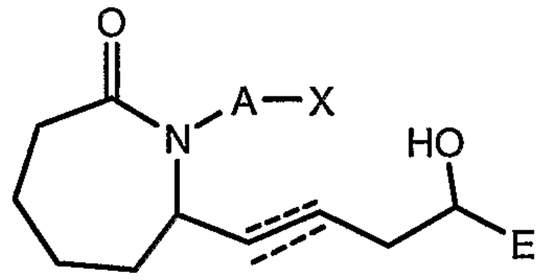
The substituents comprise up to 4 non-hydrogen atoms, in other words, there are from 1 to 4 atoms which are not hydrogen, and any number of hydrogen atoms required to form the complete substituent. For example, a methyl substituent has 1 carbon atom and 3 hydrogen atoms. Other example substituents include hydrocarbon moieties comprising from 1 to 4 carbon atoms including alkyl such as ethyl, propyl, isopropyl, and butyl and isomers thereof; cyclic and unsaturated hydrocarbons having from 2 to 4 carbon atoms such as ethylenyl, propenyl, propynyl, cyclopropyl, cyclobutyl, etc ; CO_2H and salts thereof; alkoxy up to C_3 such as methoxy, ethoxy, propoxy, isopropoxy, and the like; carboxylic acid esters; CN; NO_2; CF_3; F; Cl; Br; I; sulfonyl esters; SO_3H and salts thereof; and the like. Thus, for example, E may be phenyl, a naphthyl, or a heteroaromatic moiety such as thienyl, furyl, pyridinyl, benzothienyl,

benzofuryl, and the like, having no substituents. Alternatively the aromatic or heteroaromatic moiety may be monoalkylsubstituted moiety such as methylphenyl, ethylbenzofuryl, propylthienyl, etc.; a monohalosubstituted moiety such as fluorophenyl, chlorofuryl, bromopyridinyl, etc.; or a monosubstituted aromatic moiety with another substituent having less than 4 non-hydrogen atoms. The aromatic or heteroaromatic moiety may also be a disubstituted moeity having the same or different substituents. These substituents may be in any reasonable position on the aromatic or heteroaromatic ring.

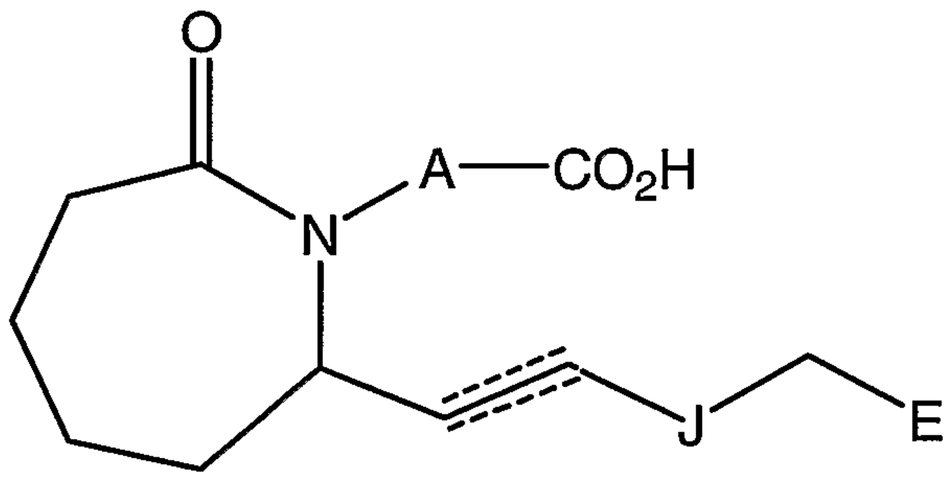
J is C=O, CHOH, or CH_2CHOH, meaning that the following types of compounds, or pharmaceutically acceptable salts or prodrugs thereof, are contemplated.





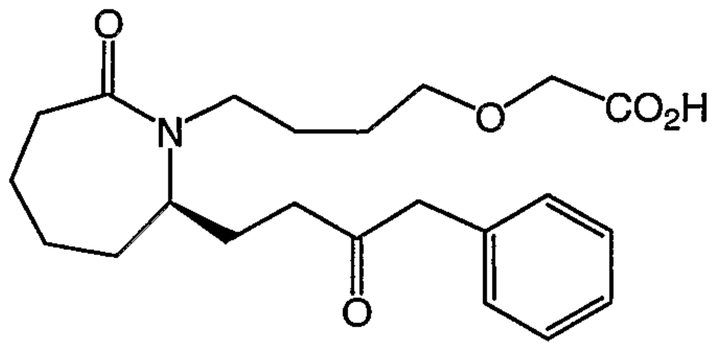


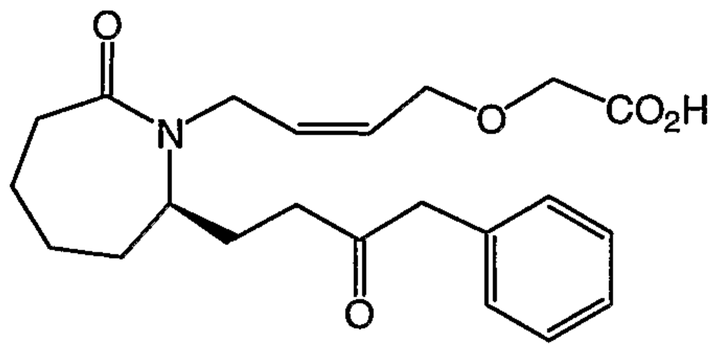
In other compounds, X is CO_2H, as depicted in the structure below.

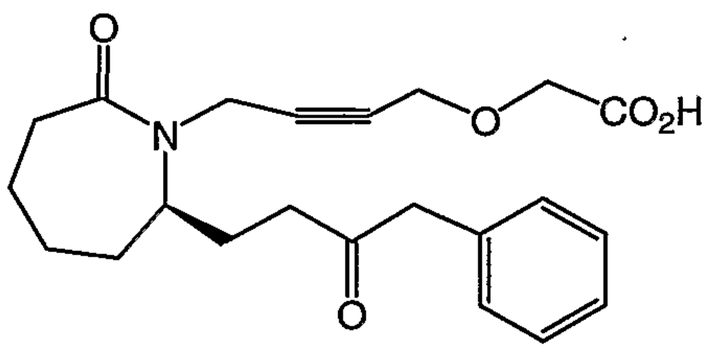


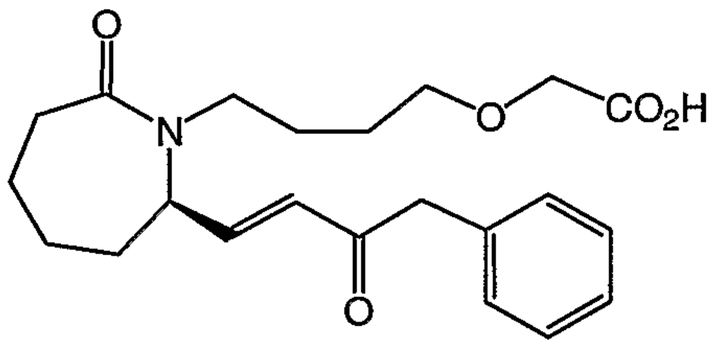
Pharmaceutically acceptable salts and prodrugs of compounds represented by the structure above are also contemplated.

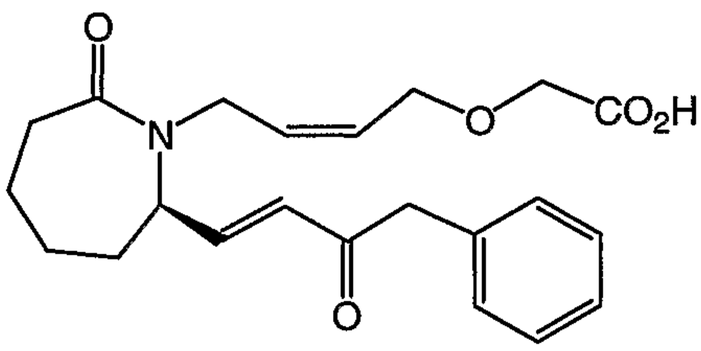
Thus, while not intending to limit the scope of the invention in any way, the compounds shown below, and pharmaceutically acceptable salts and prodrugs thereof, are of interest.

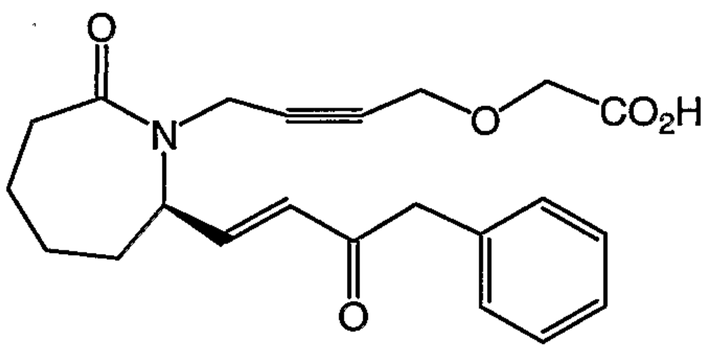


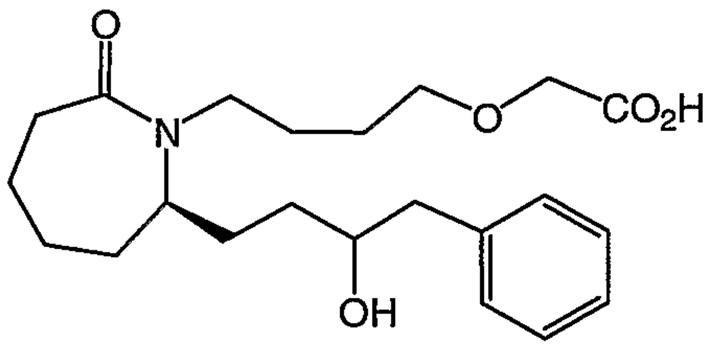


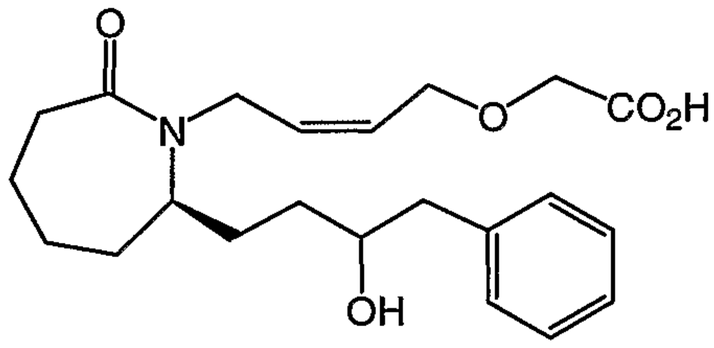


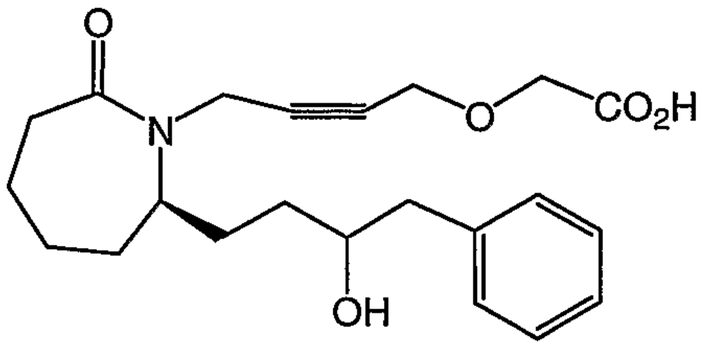


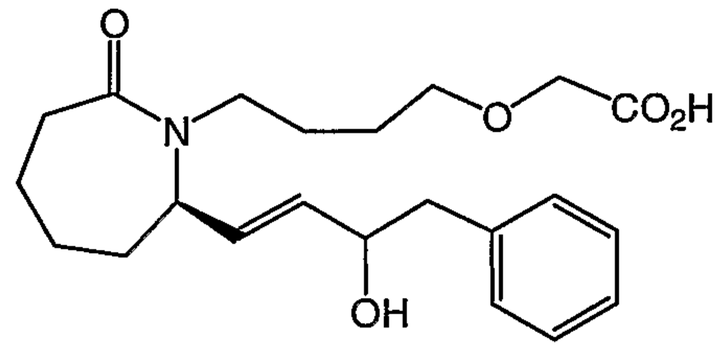


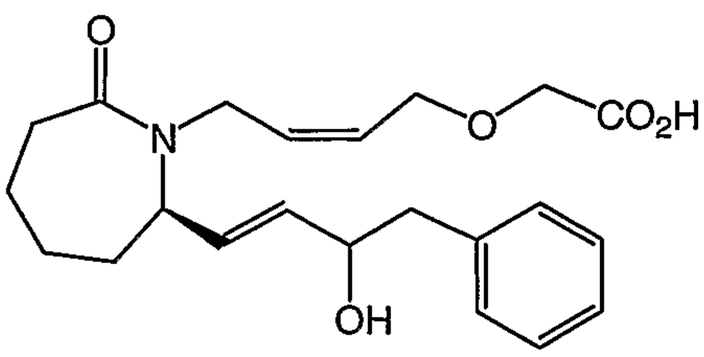


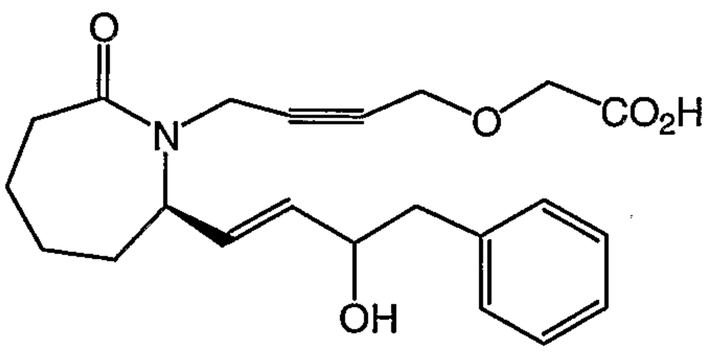












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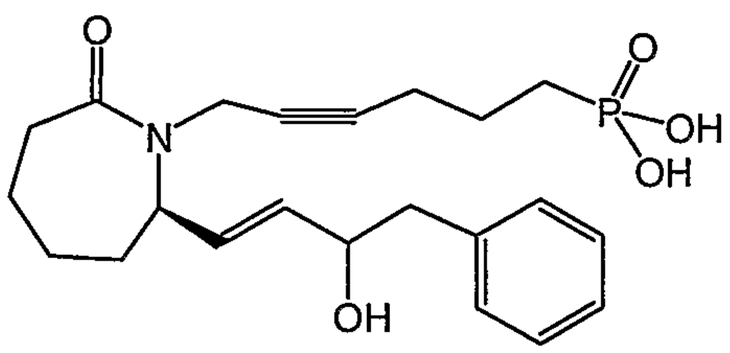
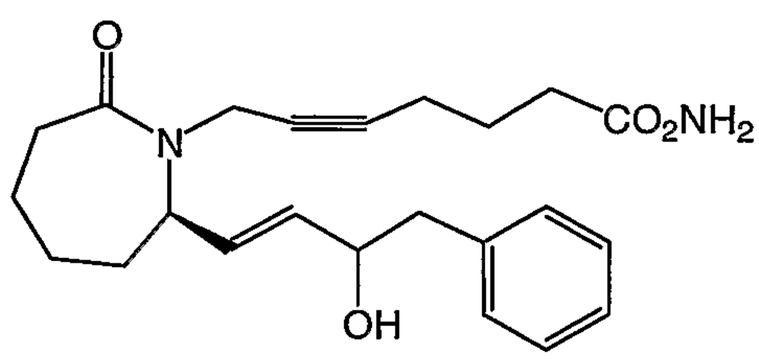
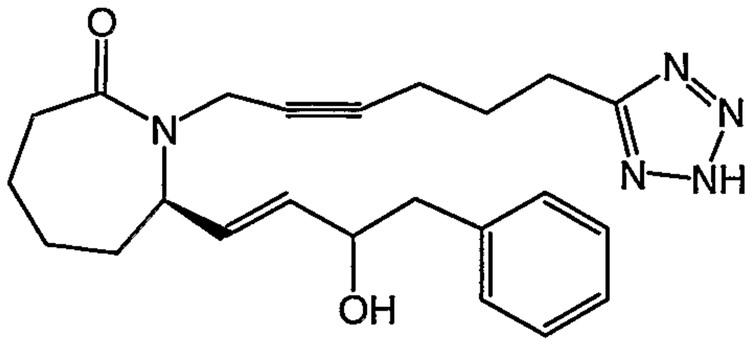
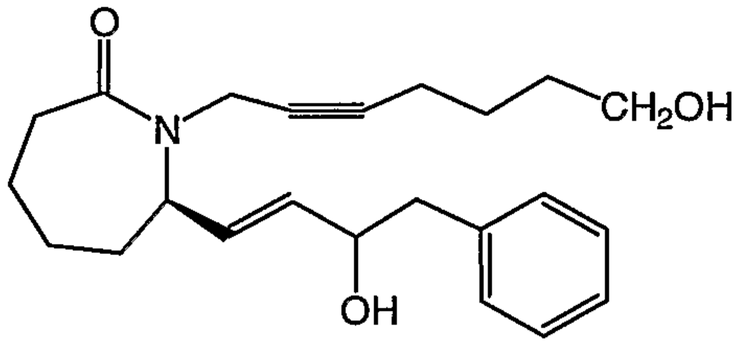
For compounds characterized by the phrases "X is CO_2H" or the like, where the group could be converted to a pharmaceutically acceptable salt, or where a derivative of the group would make the compound a prodrug, a term for a group such as "CO_2H" or "NH" is intended to mean the actual group, the pharmaceutically salts, or the derivatives of the group which make the compound a prodrug.

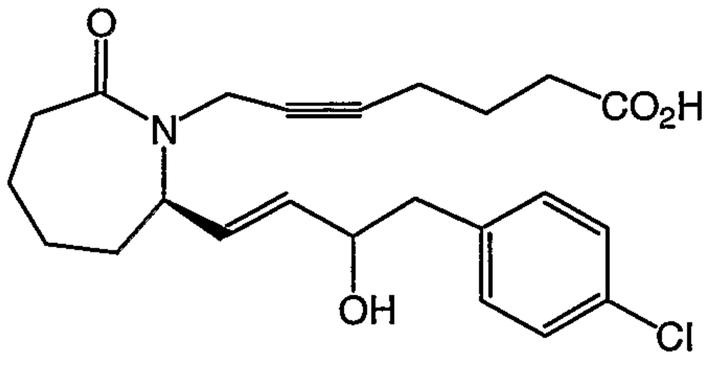
While not intending to limit the scope of the invention in any way, other compounds of particular interest herein are those of the structures shown below, and pharmaceutically acceptable salts and prodrugs thereof.

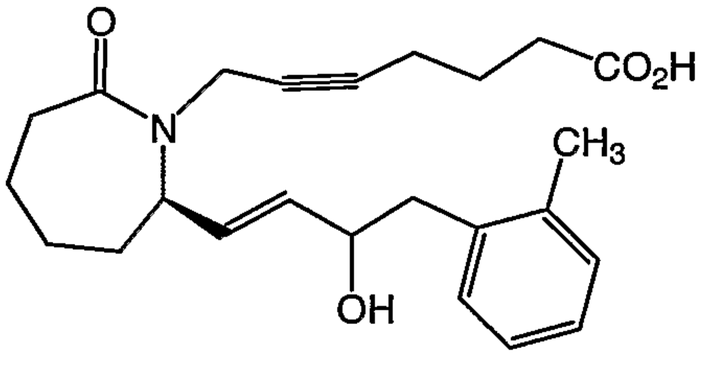


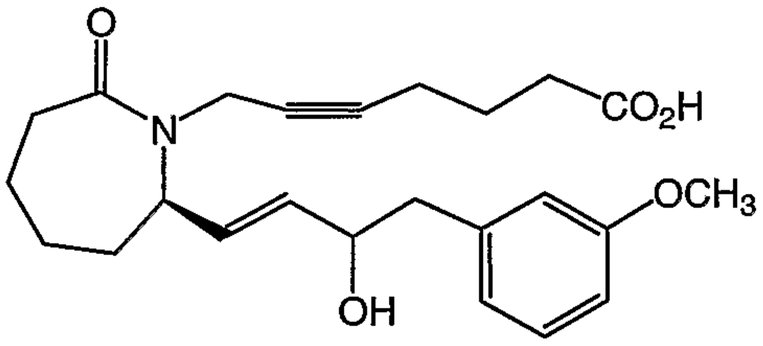


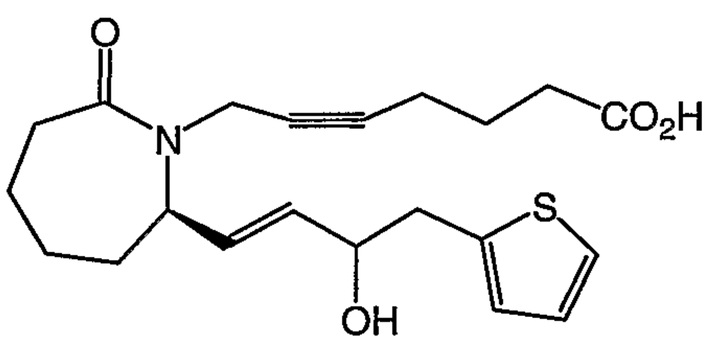


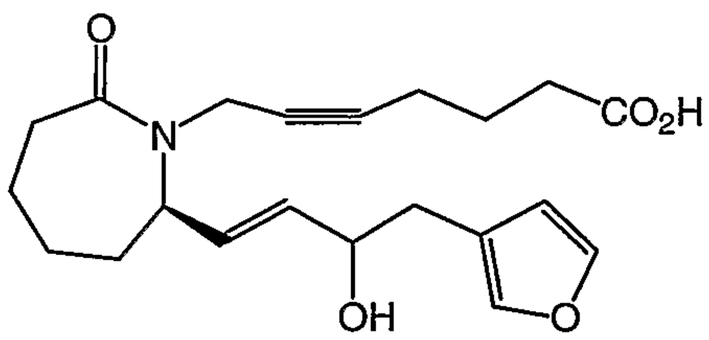


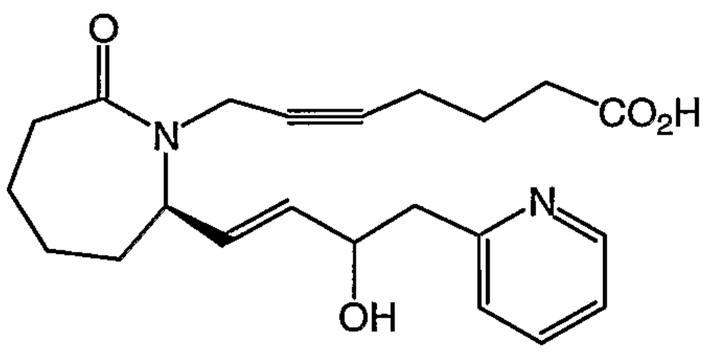












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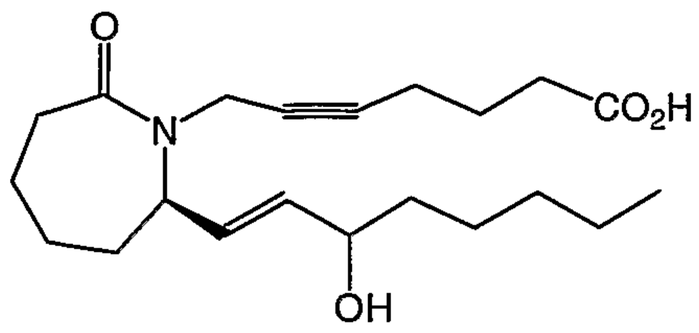
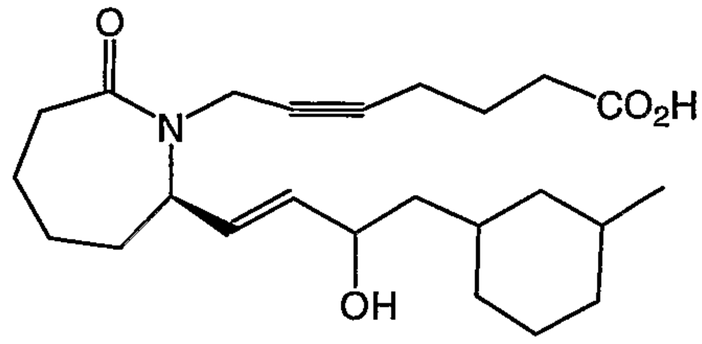
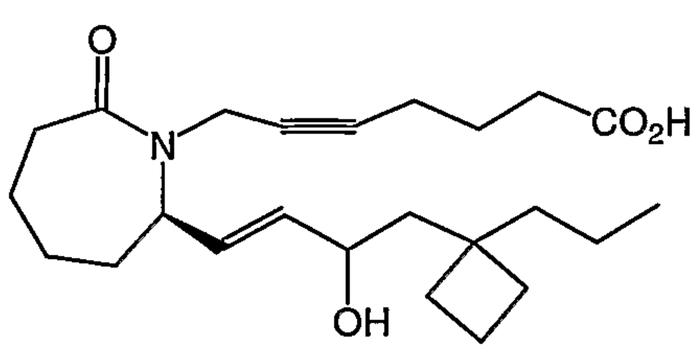
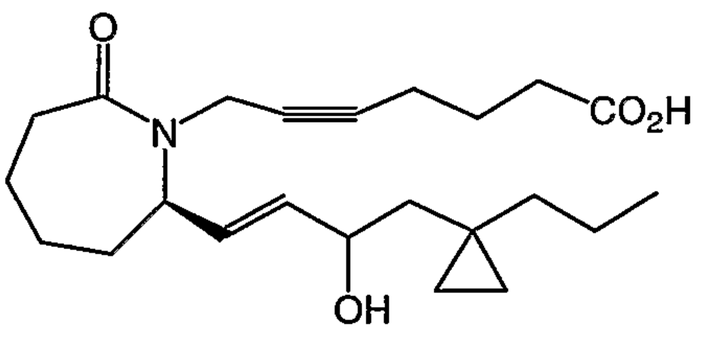








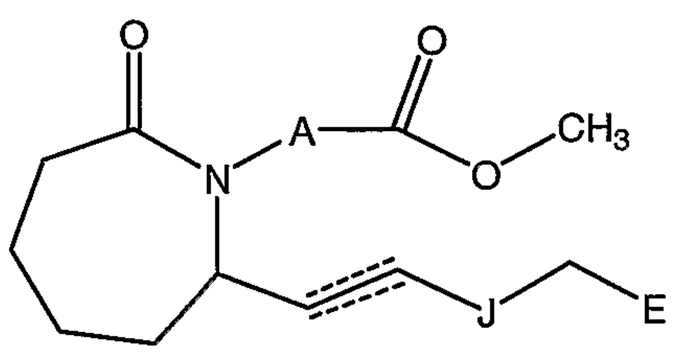
A "pharmaceutically acceptable salt" is any salt that retains the activity of the parent compound and does not impart any additional deleterious or untoward effects on the subject to which it is administered and in the context in which it is administered compared to the parent compound. A pharmaceutically acceptable salt also refers to any salt which may form in vivo as a result of administration of an acid, another salt, or a prodrug which is converted into an acid or salt.

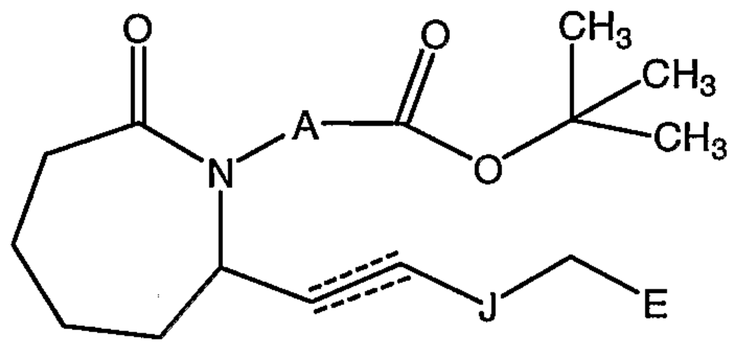
Pharmaceutically acceptable salts of acidic functional groups may be derived from organic or inorganic bases. The salt may comprise a mono or polyvalent ion. Of particular interest are the inorganic ions, lithium, sodium, potassium, calcium, and magnesium. Organic salts may be made with amines, particularly ammonium salts such as mono-, di- and trialkyl amines or ethanol amines. Salts may also be formed with caffeine, tromethamine and similar molecules. Hydrochloric acid or some other pharmaceutically acceptable acid may form a salt with a compound that includes a basic group, such as an amine or a pyridine ring.

A "prodrug" is a compound which is converted to a therapeutically active compound after administration, and the term should be interpreted as broadly herein as is generally understood in the art. While not intending to limit the scope of the invention, conversion may occur by hydrolysis of an ester group or some other biologically labile group. Generally, but not necessarily, a prodrug is inactive or less active than the therapeutically active compound to which it is converted. Ester prodrugs of the compounds disclosed herein are

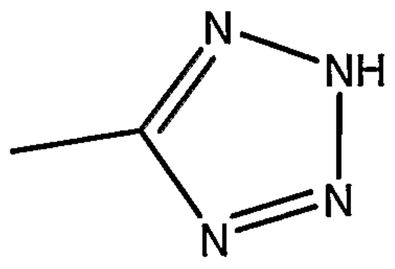
specifically contemplated. An ester may be derived from a carboxylic acid of C1 (i.e. the terminal carboxylic acid of a natural prostaglandin), or an ester may be derived from a carboxylic acid functional group on another part of the molecule, such as on a phenyl ring. While not intending to be limiting, an ester may be an alkyl ester, an aryl ester, or a heteroaryl ester. The term alkyl has the meaning generally understood by those skilled in the art and refers to linear, branched, or cyclic alkyl moieties. C_{1-6} alkyl esters are particularly useful, where alkyl part of the ester has from 1 to 6 carbon atoms and includes, but is not limited to, methyl, ethyl, propyl, isopropyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *t*-butyl, pentyl isomers, hexyl isomers, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and combinations thereof having from 1-6 carbon atoms, etc.

While not intending to limit the scope of the invention in any way, examples of prodrugs of the useful compounds disclosed herein include those shown below.

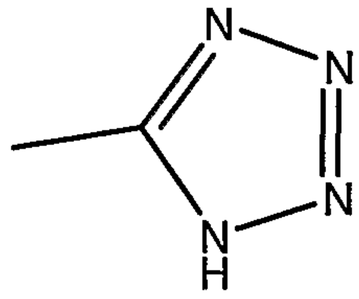




The tetrazole group,



has two tautomeric forms, which can rapidly interconvert in aqueous or biological media, and are thus equivalent to one another. The tautomer of the tetrazole shown above is shown below.



For the purposes disclosed herein, all tautomeric forms should be considered equivalent in every way.

The compounds disclosed herein are useful for the prevention or treatment of glaucoma or ocular hypertension in mammals, or for the manufacture of a medicament for the treatment of glaucoma or ocular hypertension.

Those skilled in the art will readily understand that for administration or the manufacture of medicaments the compounds disclosed herein can be admixed with pharmaceutically acceptable excipients which per se are well known in the art. Specifically, a drug to be administered systemically, it may be confected as a powder, pill, tablet or the like, or as a solution, emulsion, suspension, aerosol, syrup or elixir suitable for oral or parenteral administration or inhalation.

For solid dosage forms or medicaments, non-toxic solid carriers include, but are not limited to, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, the polyalkylene glycols, talcum, cellulose, glucose, sucrose and magnesium carbonate. The solid dosage forms may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the technique described in the U.S. Pat. Nos. 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release. Liquid pharmaceutically administrable dosage forms can, for example, comprise a solution or suspension of one or more of the presently useful compounds and optional pharmaceutical adjutants in a carrier, such as for example, water, saline, aqueous dextrose, glycerol, ethanol and the like, to thereby form a solution or suspension. If desired, the pharmaceutical composition to be administered may also contain minor amounts of nontoxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents and the like. Typical examples of such auxiliary agents are sodium acetate, sorbitan monolaurate, triethanolamine, sodium acetate, triethanolamine oleate, etc. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, Mack

Publishing Company, Easton, Pa., 16th Edition, 1980. The composition of the formulation to be administered, in any event, contains a quantity of one or more of the presently useful compounds in an amount effective to provide the desired therapeutic effect.

Parenteral administration is generally characterized by injection, either subcutaneously, intramuscularly or intravenously. Injectables can be prepared in conventional forms, either as liquid solutions or suspensions, solid forms suitable for solution or suspension in liquid prior to injection, or as emulsions. Suitable excipients are, for example, water, saline, dextrose, glycerol, ethanol and the like. In addition, if desired, the injectable pharmaceutical compositions to be administered may also contain minor amounts of non-toxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents and the like.

The amount of the presently useful compound or compounds administered is, of course, dependent on the therapeutic effect or effects desired, on the specific mammal being treated, on the severity and nature of the mammal's condition, on the manner of administration, on the potency and pharmacodynamics of the particular compound or compounds employed, and on the judgment of the prescribing physician. The therapeutically effective dosage of the presently useful compound or compounds is preferably in the range of about 0.5 or about 1 to about 100 mg/kg/day.

A liquid composition which is formulated for topical ophthalmic use is formulated such that it can be administered topically to the eye. The comfort should be maximized as much as possible, although sometimes formulation considerations (e.g. drug stability) may necessitate less than optimal comfort. In the case that comfort cannot be maximized, the liquid should be formulated such that the liquid is tolerable to the patient for topical ophthalmic use. Additionally, an ophthalmically acceptable liquid should either be packaged for single use, or contain a preservative to prevent contamination over multiple uses.

For ophthalmic application, solutions or medicaments are often prepared using a physiological saline solution as a major vehicle. Ophthalmic solutions

should preferably be maintained at a comfortable pH with an appropriate buffer system. The formulations may also contain conventional, pharmaceutically acceptable preservatives, stabilizers and surfactants.

Preservatives that may be used in the pharmaceutical compositions disclosed herein include, but are not limited to, benzalkonium chloride, chlorobutanol, thimerosal, phenylmercuric, acetate and phenylmercuric nitrate. A useful surfactant is, for example, Tween* 80. Likewise, various useful vehicles may be used in the ophthalmic preparations disclosed herein. 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 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. A useful chelating agent is edetate 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

Trademark*

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%

For topical use, creams, ointments, gels, solutions or suspensions, etc., containing the compound disclosed herein are employed. Topical formulations may generally be comprised of a pharmaceutical carrier, cosolvent, emulsifier, penetration enhancer, preservative system, and emollient.

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 compounds disclosed herein are also useful in combination with other drugs useful for the treatment of glaucoma or other conditions.

For the treatment of glaucoma, combination treatment with the following classes of drugs are contemplated:

β-Blockers (or β-adrenergic antagonists) including carteolol, levobunolol, metiparanolol, timolol hemihydrate, timolol maleate, β1-selective antagonists such as betaxolol, and the like, or pharmaceutically acceptable salts or prodrugs thereof;

Adrenergic Agonists including

non-selective adrenergic agonists such as epinephrine borate, epinephrine hydrochloride, and dipivefrin, and the like, or pharmaceutically acceptable salts or prodrugs thereof; and

α_2-selective adrenergic agonists such as apraclonidine, brimonidine, and the like, or pharmaceutically acceptable salts or prodrugs thereof;

Carbonic Anhydrase Inhibitors including acetazolamide, dichlorphenamide, methazolamide, brinzolamide, dorzolamide, and the like, or pharmaceutically acceptable salts or prodrugs thereof;

Cholinergic Agonists including

direct acting cholinergic agonists such as carbachol, pilocarpine hydrochloride, pilocarbine nitrate, pilocarpine, and the like, or pharmaceutically acceptable salts or prodrugs thereof;

chlolinesterase inhibitors such as demecarium, echothiophate, physostigmine, and the like, or pharmaceutically acceptable salts or prodrugs thereof;

Glutamate Antagonists and other neuroprotective agents such as Ca^{2+} channel blockers such as memantine, amantadine, rimantadine, nitroglycerin, dextrophan, detromethorphan, CGS-19755, dihydropyridines, verapamil, emopamil, benzothiazepines, bepridil, diphenylbutylpiperidines, diphenylpiperazines, HOE 166 and related drugs, fluspirilene, eliprodil, ifenprodil, CP-101,606, tibalosine, 2309BT, and 840S, flunarizine, nicardipine, nifedimpine, nimodipine, barnidipine, verapamil, lidoflazine, prenylamine lactate, amiloride, and the like, or pharmaceutically acceptable salts or prodrugs thereof;

Prostamides such as bimatoprost, or pharmaceutically acceptable salts or prodrugs thereof; and

Prostaglandins including travoprost, UFO-21, chloprostenol, fluprostenol, 13,14-dihydro-chloprostenol, isopropyl unoprostone, latanoprost and the like.

Cannabinoids including CB1 agonists such as WIN-55212-2 and CP-55940 and the like, or pharmaceutically acceptable salts or prodrugs thereof.

For treatment of diseases affecting the eye including glaucoma, these compounds can be administered topically, periocularly, intraocularly, or by any other effective means known in the art.

Treatment of inflammatory bowel disease may be accomplished by the administration of the compounds described herein to the suffering mammal. Inflammatory bowel disease describes a variety of diseases characterized by inflammation of the bowels including, but not limited to, ulcerative colitis and Crohn's disease. Treatment may be accomplished by oral administration, by suppository, or parenteral administration, or some other suitable method.

For the treatment of inflammatory bowel disease and similar disorders, the compounds disclosed herein may be used in combination with other therapeutically active agents.

For the treatment of inflammatory bowel disease, combination treatment with the following classes of drugs are contemplated:

aminosalicylates including sulfasalazaline, mesalazine, sulfasalazine, mesalamine, Olsalazine, balsalazide

corticosteroids including methotrexate, cortisone, hydrocortisone, prednisone, prednisolone, methylprednisone, triamcinolone, fluoromethalone, dexamethasone, medrysone, betamethasone, loteprednol, fluocinolone, flumethasone, or mometasone

immunomodulators including azathioprine, 6-mercaptopurine, cyclosporine, and the like.

While not intending to limit the scope of the invention in any way, delivery of the compounds disclosed herein to the colon via oral dosage forms may be accomplished by any of a number of methods known in the art. For example, reviews by Chourasia and Jain in J Pharm Pharmaceut Sci 6 (1): 33-66, 2003 and Shareef et. al (AAPS PharmSci 2003; 5 (2) Article 17) describe a number of useful methods. While not intending to limit the scope of the invention in any way these methods include 1) administration of a prodrug, including an azo or a carbohydrate based prodrug; 2) coating the drug with, or encapsulating or impregnating the drug into a polymer designed for delivery to the colon, 3) time released delivery of the drug, 4) use of a bioadhesive system; and the like.

While not intending to be bound in any way by theory, it is believed that intestinal microflora are capable of reductive cleavage of an azo bond leaving the two nitrogen atoms as amine functional groups. While not intending to limit the scope of the invention in any way, the azo prodrug approach has been used to deliver to 5-aminosalicylic acid to the colons of humans in clinical trials for the treatment of inflammatory bowel disease. It is also believed that bacteria of the lower GI also have enzymes which can digest glycosides, glucuronides, cyclodextrins, dextrans, and other carbohydrates, and ester prodrugs formed from these carbohydrates have been shown to deliver the parent active drugs selectively to the colon. For example, in vivo and in vitro studies on rats and guinea pigs with prodrugs of dexamethasone, prednisolone, hydrocortisone, and

fludrocortisone, suggest that glycoside conjugates may be useful for the delivery of steroids to the human colon. Other in vivo studies have suggested that glucouronide, cyclodextrin, and dextran prodrugs of steroids or non-steroidal anti-inflammatory drugs are useful for delivery of these drugs to the lower GI tract. An amide of salicylic acid and glutamic acid has been shown to be useful for the delivery of salicylic acid to the colon of rabbit and dog.

While not intending to limit the scope of the invention in any way, carbohydrate polymers such as amylase, arabinogalactan, chitosan, chondroiton sulfate, dextran, guar gum, pectin, xylin, and the like, or azo-group containing polymers can be used to coat a drug compound, or a drug may be impregnated or encapsulated in the polymer. It is believed that after oral administration, the polymers remain stable in the upper GI tract, but are digested by the microflora of the lower GI thus releasing the drug for treatment.

Polymers which are sensitive to pH may also be used since the colon has a higher pH than the upper GI tract. Such polymers are commercially available. For example, Rohm Pharmaceuticals, Darmstadt, Germany, markets pH dependent methacrylate based polymers and copolymers which have varying solubilities over different pH ranges based upon the number of free carboxylate groups in the polymer under the tradename Eudragit®. Several Eudragit® dosage forms are currently used to deliver salsalazine for the treatment of ulcerative colitis and Crohn's disease. Time release systems, bioadhesive systems, and other delivery systems have also been studied.

Example 1

Preparation of the seven-membered lactam structure such as that shown in Scheme 1 may be accomplished according to a number of published procedures.

The United States Patent No. US 6,747,037 and United States Patent 7,179,820 entitled "Piperidinyl Prostaglandin E Analogs", Filed June 3, 2004, in the name of inventors David W. Old and Danny T. Dinh (hereafter referred to as the Old Application)

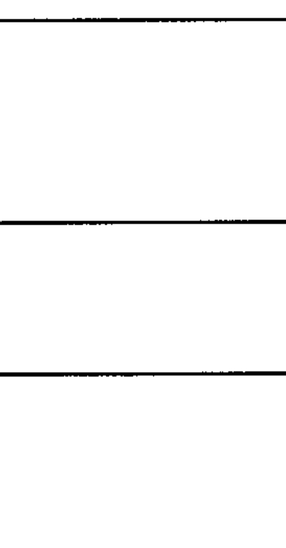
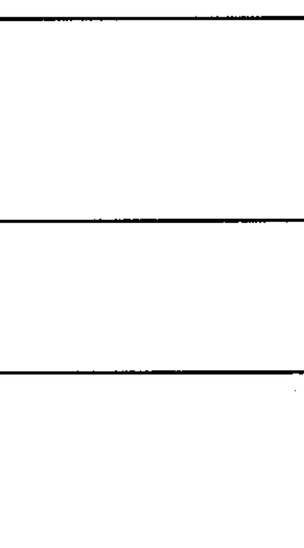
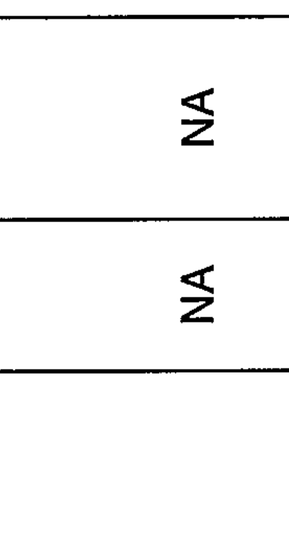
disclose a method for cyclizing amino acid esters such as 2-aminoadipic acid diethyl ester by heating the compound. By a similar procedure, 2-aminopimelic acid diethyl ester in Scheme 1 is heated and purified according to routine procedures to produce the cyclic 7-oxo-azepane-2-carboxylic acid ethyl ester in Scheme 1.

Alternatively, Almstead et. al. (*J. Med. Chem.*, **42** (22), 4547 -4562) discloses a procedure for preparing 7-Carbomethoxy-tetrahydro-2(3H)-azepinone as follows:

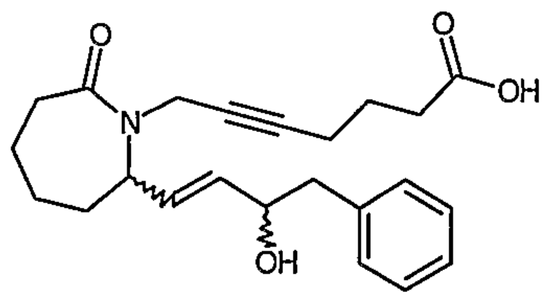
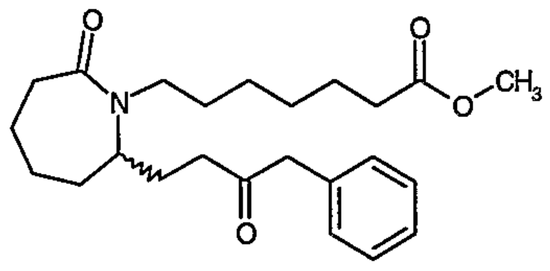
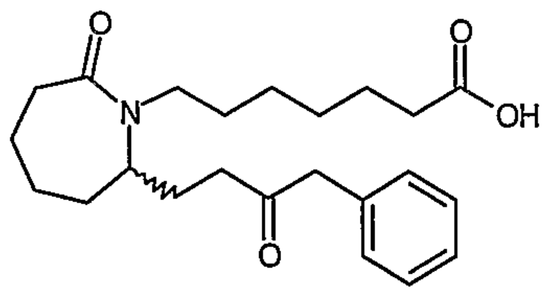
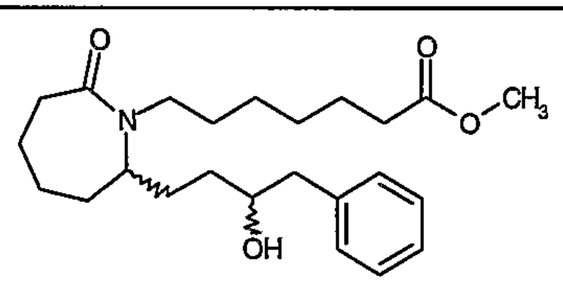
> "Ethyl 2-cyclohexanonecarboxylate (15.0 g, 88.12 mmol) was dissolved in chloroform (200 mL) and cooled to 0 ° C. Methanesulfonic acid (84.7 g, 881.2 mmol) was added followed by the addition of sodium azide. The reaction mixture was stirred at room temperature for 30 min and then heated to reflux for 5 h. Ice was added to the reaction mixture and the resulting solution was stirred for several minutes. Ammonium hydroxide was added until the reaction was made basic. The mixture was extracted with methylene chloride, and the organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to an oil."

7-Carbomethoxy-tetrahydro-2(3H)-azepinone may be used to prepare compounds disclosed herein using the synthesis described in the Old Application or similar methods known in the art. Aspects of this synthesis are also summarized in Scheme 2.

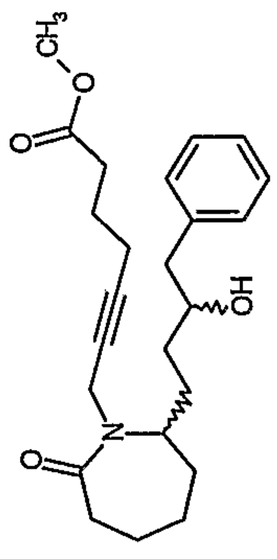
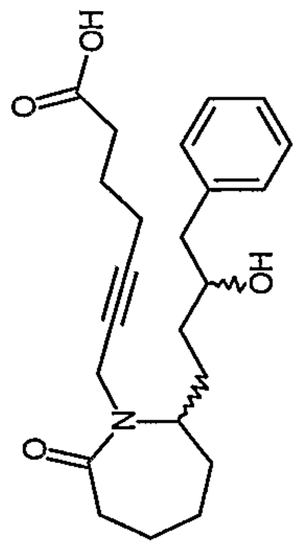
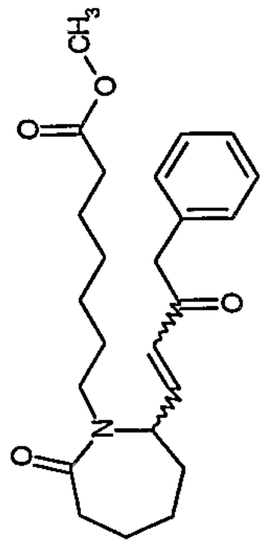
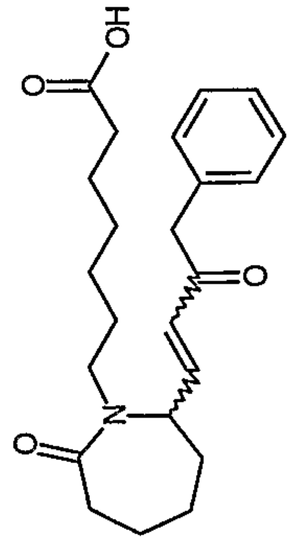
Alternatively, a method such as the one depicted in Scheme 3 could be used. In this method, a hydroxyl group-containing cyclic ketone is oximated, and the oximated product is then subjected to Beckmann rearrangement to obtain the ring-enlarged lactam according to a procedure described in detail in JP 05086034. The compounds disclosed herein are then prepared from this compound using the methods of the Old application or similar methods known in the art.

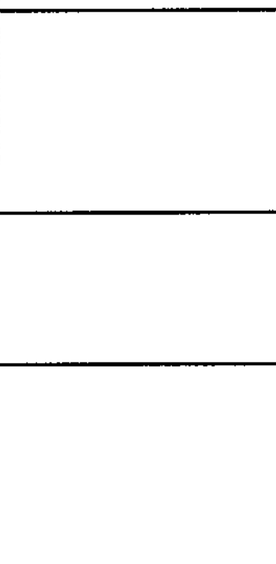
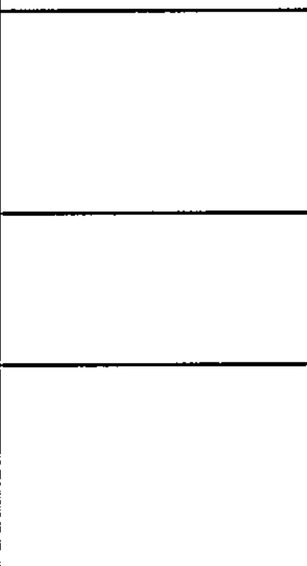
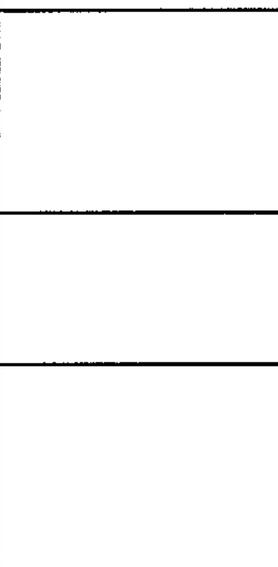
Structure				
Binding Data	hEP2			NA
	hEP4			
	hFP			NA
	hEP1			NA
	hEP2	NA	NA	NA
	hEP3A		NA	
	hEP4	>10000	>10000	3082
Functional Data (EC50 in nM)	hTP			NA
	hIP			NA
	hDP			NA

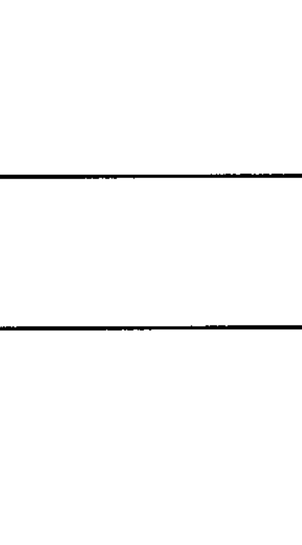
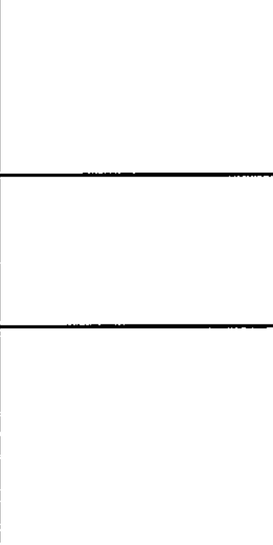
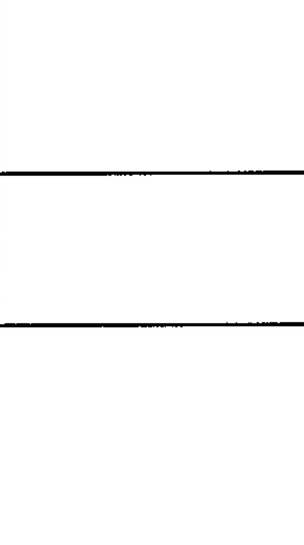
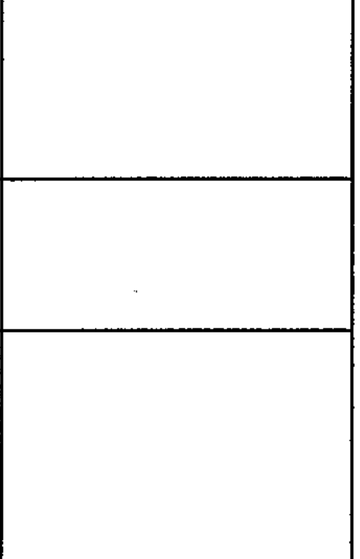
5

Structure	Binding Data		Functional Data (EC50 in nM)							
	hEP2	hEP4	hFP	hEP1	hEP2	hEP3A	hEP4	hTP	hIP	hDP
	NA		NA	NA	NA	NA	1225	278	NA	NA
					NA		>10000			
					NA		>10000			
			NA	NA	NA	>10000	3282	NA	NA	NA

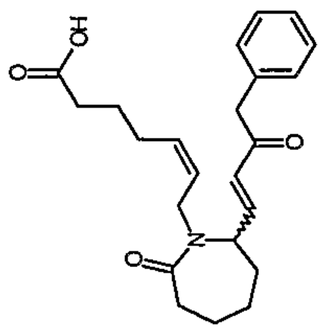
	Binding Data					Functional Data (EC50 in nM)						
	hEP2	hEP4	hFP	hEP1	hEP3A	hEP2	hEP4	hIP	hTP	hDP		
Structure												
			NA	NA	NA	NA	451	1636	549	NA		
						NA	>10000					
			NA	NA	NA	NA	2386	NA	41	NA		

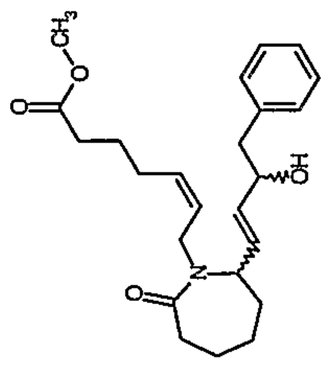
Functional Data (EC50 in nM)	hEP2	NA	NA	NA	NA
	hEP3A		NA		
	hEP4	>10000	2001	NA	>10000
	hTP		112		
	hIP		NA		
	hDP		NA		
Binding Data	hEP2				
	hEP4				
	hFP		NA		
	hEP1		NA		
	hEP2				
	hEP3A				
	hEP4				
	hTP				
	hIP				
	hDP				
Structure					

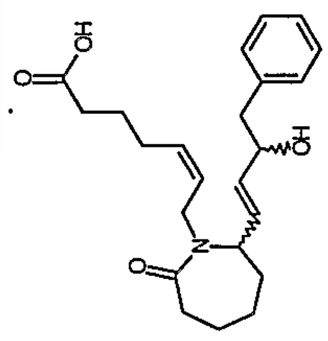
Structure					
Binding Data	hEP2				
	hEP4				
	hFP				
	hEP1				
	hEP2	NA	NA	NA	
	hEP3A				
	hEP4	>10000	NA	>10000	
	hTP				
	hIP				
	hDP				
Functional Data (EC50 in nM)					

Structure					
Binding Data	hEP2				
	hEP4				
	hFP				
	hEP1				
Functional Data (EC50 in nM)	hEP2	NA	NA	NA	NA
	hEP3A				
	hEP4	NA	>10000	>10000	NA
	hTP				
	hIP				
	hDP				

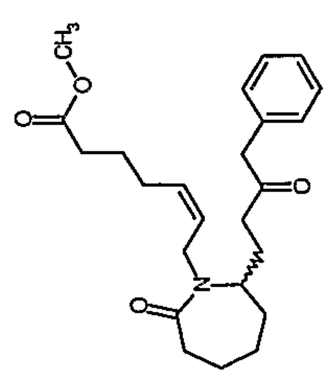
Structure					
Binding Data	hEP2				
	hEP4				
	hFP				
	hEP1				
	hEP2				
	hEP3A				
Functional Data (EC50 in nM)	hEP4				
	hTP				
	hIP				
	hDP				

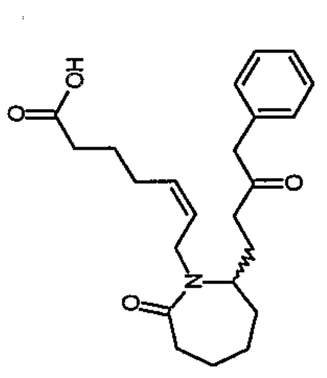


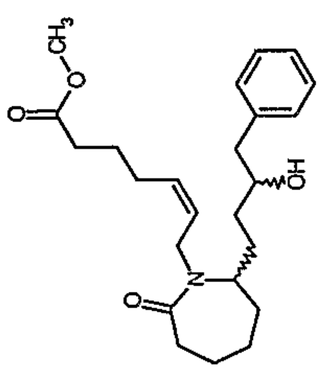


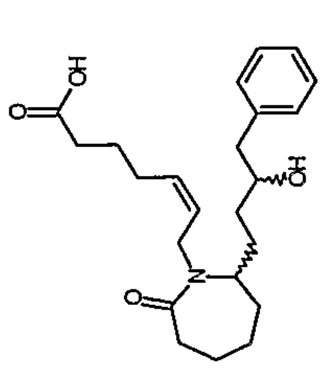


	Binding Data						Functional Data (EC50 in nM)						
	hEP2	hEP4	hFP	hEP1	hEP2	hEP3A	hEP4	hTP	hIP	hDP			
Structure	NA	>10000	NA	NA	NA	NA	13262	NA	NA	NA			
			NA	NA	NA	NA	>10000		NA	NA			
			NA	NA	NA	NA	2143	NA	NA	NA			
	NA	>10000	NA	NA	NA	NA	116		NA	NA			









Structure	Binding Data			Functional Data (EC50 in nM)					
	hEP2	hEP4	hFP	hEP1	hEP2	hEP3A	hEP4	hTP	hIP	hDP

The biological activity of the compounds of Table 1 were be tested using the following procedures.

Radioligand Binding

Cells Stably Expressing EP_1, EP_2, EP_4 and FP Receptors

HEK-293 cells stably expressing the human or feline FP receptor, or EP_1, EP_2, or EP_4 receptors are 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 is 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 is centrifuged at 19000 r.p.m. for 20 min at 4° C using a Beckman Ti-60 rotor. The resultant pellet is resuspended in TME buffer to give a final 1 mg/ml protein concentration, as determined by Biorad assay. Radioligand binding competition assays vs. [^{3}H-]17 –phenyl $PGF_{2\alpha}$ (5 nM) are performed in a 100μl volume for 60 min. Binding reactions are started by adding plasma membrane fraction. The reaction is terminated by the addition of 4 ml ice-cold TRIS-HCl buffer and rapid filtration through glass fiber GF/B filters using a Brandel cell harvester. The filters are washed 3 times with ice-cold buffer and oven dried for one hour.

[^{3}H-] PGE_2 (specific activity 180 Ci mmol) is used as the radioligand for EP receptors. [^{3}H] 17-phenyl $PGF_{2\alpha}$ is employed for FP receptor binding studies. Binding studies employing EP_1, EP_2, EP_4 and FP receptors are performed in duplicate in at least three separate experiments. A 200μl assay volume is used. Incubations are for 60 min at 25°C and are terminated by the addition of 4 ml of ice-cold 50 mM TRIS-HCl, followed by rapid filtration through Whatman GF/B filters and three additional 4 ml washes in a cell harvester (Brandel). Competition studies are performed using a final concentration of 5 nM [^{3}H]-PGE_2, or 5 nM [^{3}H] 17-phenyl $PGF_{2\alpha}$ and non-specific binding determined with 10^{-5}M of unlabeled PGE_2, or 17-phenyl $PGF_{2\alpha}$, according to receptor subtype studied.

METHODS FOR FLIPR™ STUDIES

(a) CELL CULTURE

HEK-293(EBNA) cells, stably expressing one type or subtype of recombinant human prostaglandin receptors (prostaglandin receptors expressed: hDP/Gqs5; hEP_1; hEP_2/Gqs5; hEP_{3A}/Gqi5; hEP_4/Gqs5; hFP; hIP; hTP), are cultured in 100 mm culture dishes in high-glucose DMEM medium containing 10% fetal bovine serum, 2 mM l-glutamine, 250 μg/ml geneticin (G418) and 200 μg/ml hygromycin B as selection markers, and 100 units/ml penicillin G, 100 μg/ml streptomycin and 0.25 μg/ml amphotericin B.

(b) CALCIUM SIGNAL STUDIES ON THE FLIPR™

Cells are seeded at a density of $5x10^4$ cells per well in Biocoat® Poly-D-lysine-coated black-wall, clear-bottom 96-well plates (Becton-Dickinson) and allowed to attach overnight in an incubator at 37 °C. Cells are then washed two times with HBSS-HEPES buffer (Hanks Balanced Salt Solution without bicarbonate and phenol red, 20 mM HEPES, pH 7.4) using a Denley Cellwash plate washer (Labsystems). After 45 minutes of dye-loading in the dark, using the calcium-sensitive dye Fluo-4 AM at a final concentration of 2 μM, plates are washed four times with HBSS-HEPES buffer to remove excess dye leaving 100 μl in each well. Plates are re-equilibrated to 37 °C for a few minutes.

Cells are excited with an Argon laser at 488 nm, and emission is measured through a 510-570 nm bandwidth emission filter (FLIPR™, Molecular Devices, Sunnyvale, CA). Drug solution is added in a 50 μl volume to each well to give the desired final concentration. The peak increase in fluorescence intensity is recorded for each well. On each plate, four wells each serve as negative (HBSS-HEPES buffer) and positive controls (standard agonists: BW245C (hDP); PGE_2 (hEP_1; hEP_2/Gqs5; hEP_{3A}/Gqi5; hEP_4/Gqs5); $PGF_{2\alpha}$ (hFP); carbacyclin (hIP); U-46619 (hTP), depending on receptor). The peak fluorescence change in each drug-containing well is then expressed relative to the controls.

Compounds are tested in a high-throughput (HTS) or concentration-response (CoRe) format. In the HTS format, forty-four compounds per plate are examined in duplicates at a concentration of 10^{-5} M. To generate concentration-

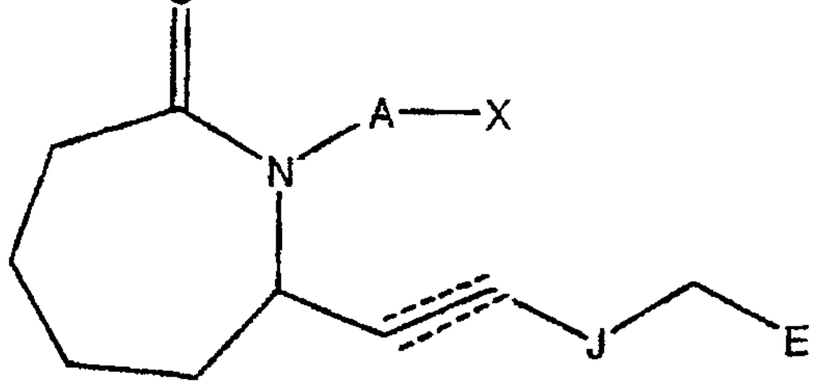
response curves, four compounds per plate are tested in duplicates in a concentration range between 10^{-5} and 10^{-11} M. The duplicate values are averaged. In either, HTS or CoRe format each compound is tested on at least 3 separate plates using cells from different passages to give an $n \geq 3$.

The results of these assays will demonstrate that the compounds disclosed herein have activity characteristic of prostaglandins, and will thus be useful in treating diseases such as glaucoma which are amenable to treatment by prostaglandins.

CLAIMS

What is claimed is:

1. A compound defined by the general formula:

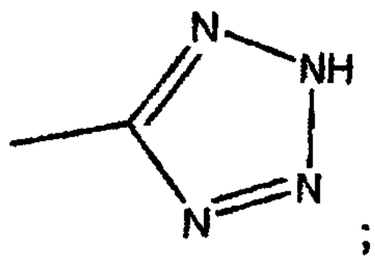


or a pharmaceutically acceptable salt or a prodrug thereof;

wherein a dashed line represents the presence or absence of a double bond or a triple bond;

A is $-(CH_2)_6-$, *cis* $-CH_2CH=CH-(CH_2)_3-$, or $-CH_2C\equiv C-(CH_2)_3-$, wherein 1 or 2 carbon atoms may be substituted with S or O;

X is selected from the group consisting of CO_2H, $CONHR_2$, $CONR_2$, $CON(OR)R$, $CON(CH_2CH_2OH)_2$, $CONH(CH_2CH_2OH)$, CH_2OH, $P(O)(OH)_2$, $CONHSO_2R$, SO_2NR_2, SO_2NHR, and



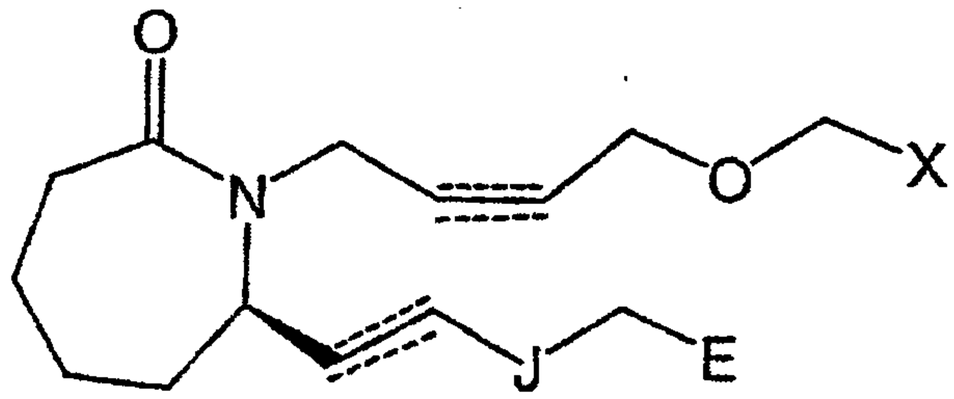
;

J is C=O, CHOH, or CH_2CHOH;

R is independently H, C_1-C_6 alkyl, phenyl, or biphenyl; and

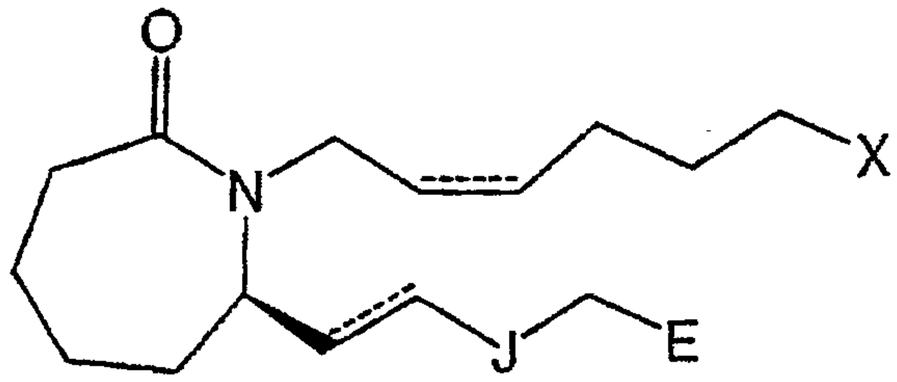
E is C_3-C_6 alkyl, C_4-C_{10} cycloalkyl, phenyl or napthyl having from 0 to 2 substituents, or a heteroaromatic moiety having from 0 to 2 substituents, wherein said substituents comprise up to 4 non-hydrogen atoms.

2. The compound of claim 1 defined by the general formula:



or a pharmaceutically acceptable salt or a prodrug thereof.

3. The compound of claim 1 defined by the general formula:



or a pharmaceutically acceptable salt or a prodrug thereof.

4. The compound of claim 3 wherein J is C=O.

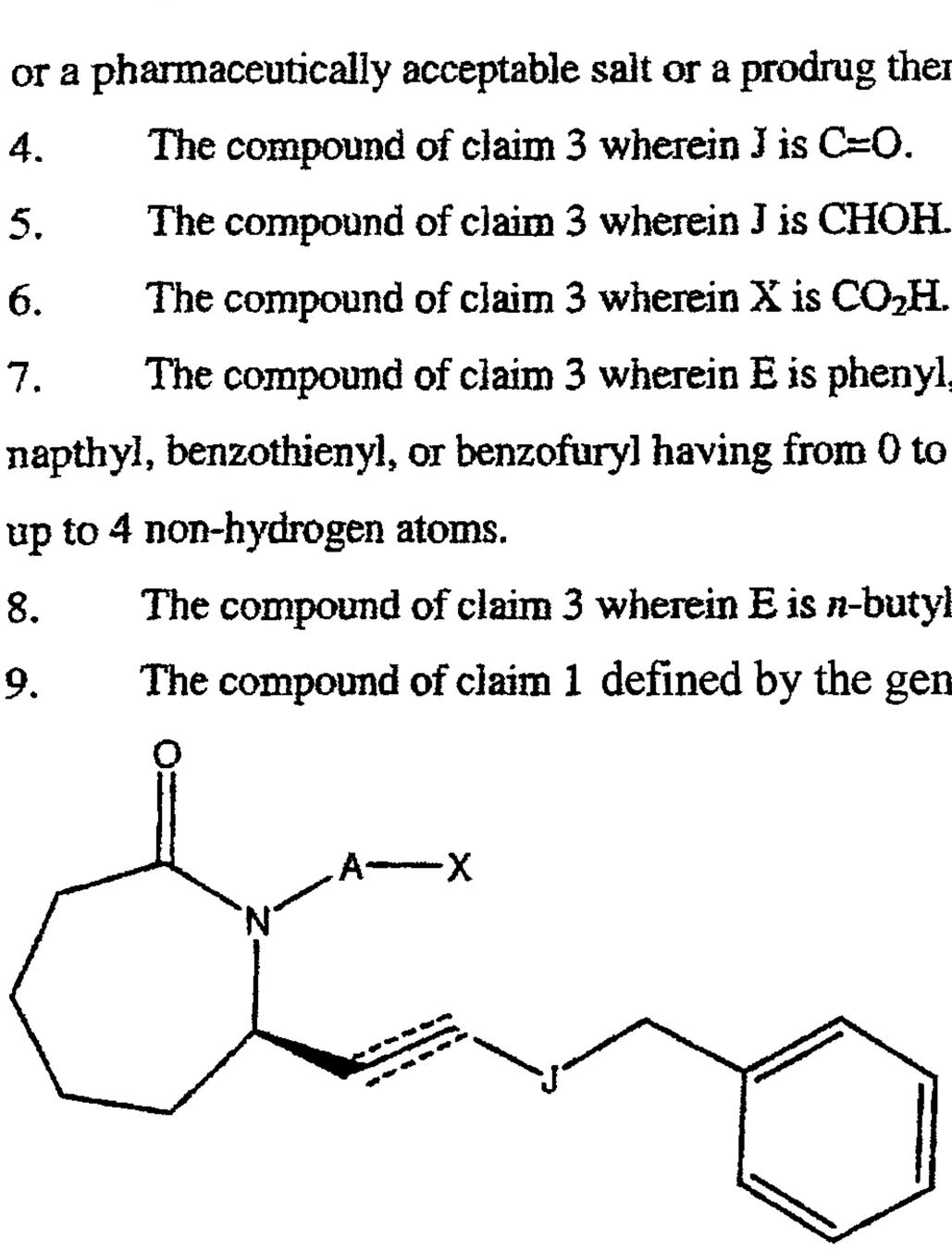
5. The compound of claim 3 wherein J is CHOH.

6. The compound of claim 3 wherein X is CO_2H.

7. The compound of claim 3 wherein E is phenyl, thienyl, furyl, pyridinyl, napthyl, benzothienyl, or benzofuryl having from 0 to 2 substituents comprising up to 4 non-hydrogen atoms.

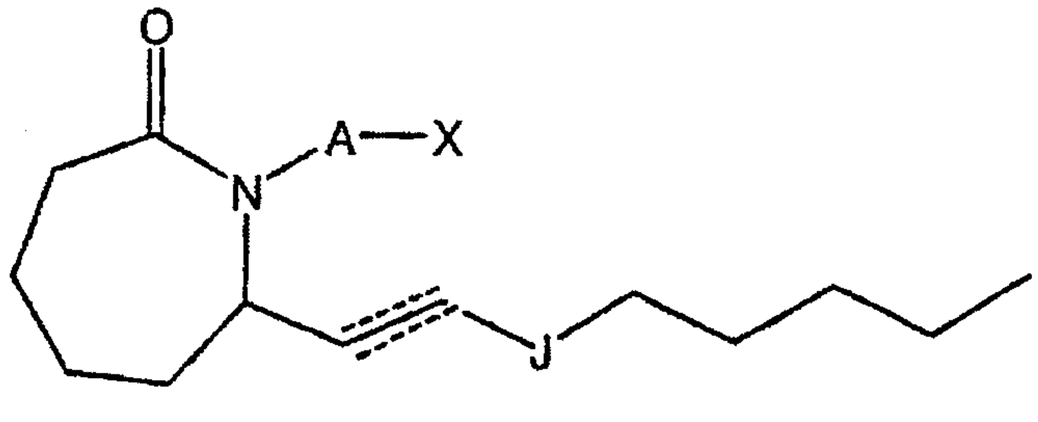
8. The compound of claim 3 wherein E is *n*-butyl.

9. The compound of claim 1 defined by the general formula:



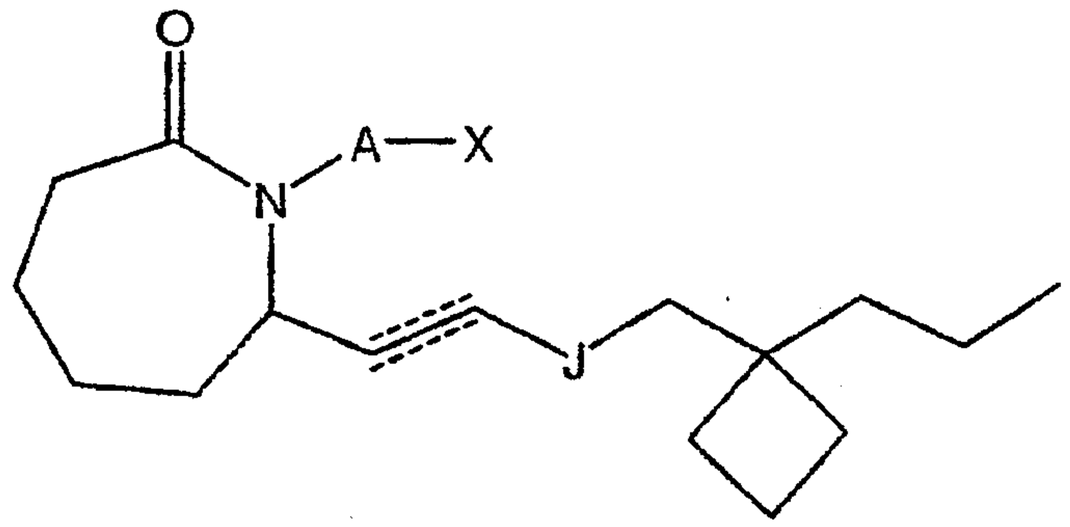
or a pharmaceutically acceptable salt or a prodrug thereof.

10. The compound of claim 1 defined by the general formula:



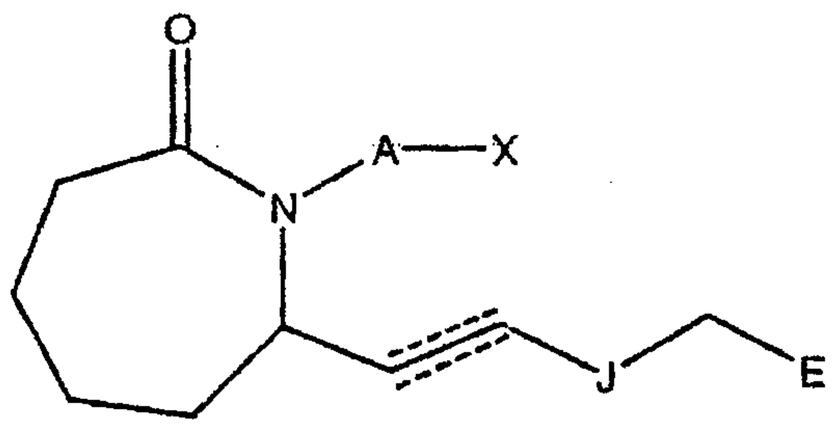
or a pharmaceutically acceptable salt or a prodrug thereof.

11. The compound of claim 1 defined by the general formula:



or a pharmaceutically acceptable salt or a prodrug thereof.

12. A liquid composition comprising a compound defined by the general formula:

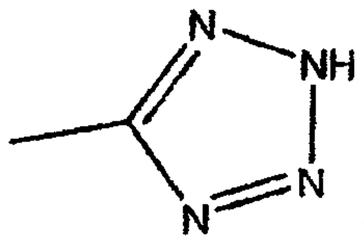


or a pharmaceutically acceptable salt or a prodrug thereof;

wherein a dashed line represents the presence or absence of a double bond or a triple bond;

A is $-(CH_2)_6-$, *cis* $-CH_2CH=CH-(CH_2)_3-$, or $-CH_2C\equiv C-(CH_2)_3-$, wherein 1 or 2 carbon atoms may be substituted with S or O;

X is selected from the group consisting of CO_2H, $CONHR_2$, $CONR_2$, $CON(OR)R$, $CON(CH_2CH_2OH)_2$, $CONH(CH_2CH_2OH)$, CH_2OH, $P(O)(OH)_2$, $CONHSO_2R$, SO_2NR_2, SO_2NHR, and



;

J is C=O, CHOH, or CH_2CHOH;

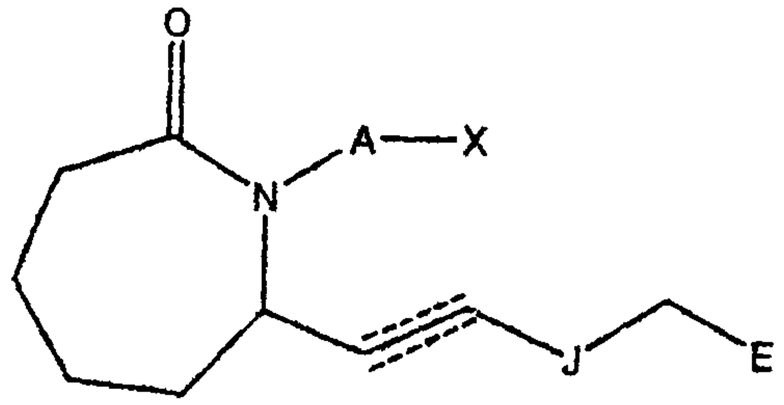
R is independently H, C_1-C_6 alkyl, phenyl, or biphenyl; and

E is C_3-C_6 alkyl, C_4-C_{10} cycloalkyl, phenyl or napthyl having from 0 to 2 substituents, or a heteroaromatic moiety having from 0 to 2 substituents, wherein said substituents comprise up to 4 non-hydrogen atoms;

and a pharmaceutically acceptable carrier; and

wherein said liquid is formulated for ophthalmic use.

13. Use for treating glaucoma or ocular hypertension in a mammal of a compound having the formula

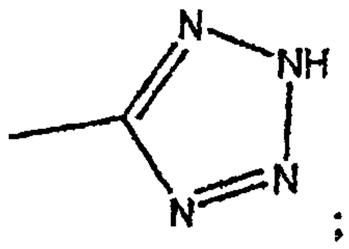


or a pharmaceutically acceptable salt or a prodrug thereof;

wherein a dashed line represents the presence or absence of a double bond or a triple bond;

A is $-(CH_2)_6-$, *cis* $-CH_2CH=CH-(CH_2)_3-$, or $-CH_2C\equiv C-(CH_2)_3-$, wherein 1 or 2 carbon atoms may be substituted with S or O;

X is selected from the group consisting of CO_2H, $CONHR_2$, $CONR_2$, $CON(OR)R$, $CON(CH_2CH_2OH)_2$, $CONH(CH_2CH_2OH)$, CH_2OH, $P(O)(OH)_2$, $CONHSO_2R$, SO_2NR_2, SO_2NHR, and



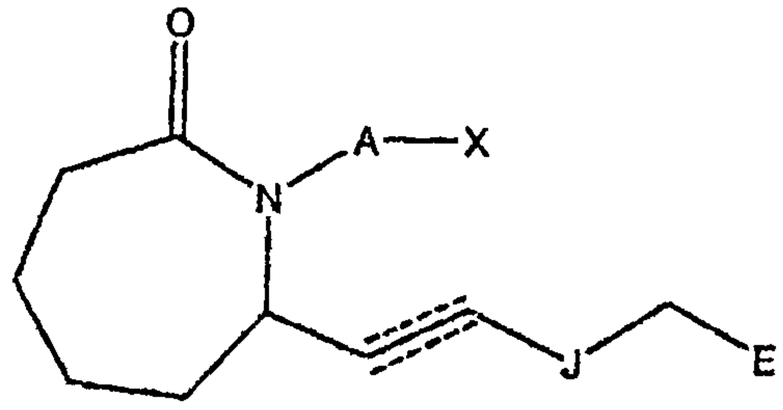
;

J is C=O, CHOH, or CH_2CHOH;

R is independently H, C_1-C_6 alkyl, phenyl, or biphenyl; and

E is C_3-C_6 alkyl, C_4-C_{10} cycloalkyl, phenyl or napthyl having from 0 to 2 substituents, or a heteroaromatic moiety having from 0 to 2 substituents, wherein said substituents comprise up to 4 non-hydrogen atoms.

14. Use in the manufacture of a medicament for treating glaucoma or ocular hypertension in a mammal of a compound having the formula

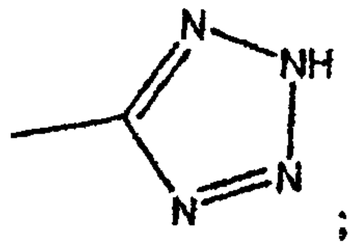


or a pharmaceutically acceptable salt or a prodrug thereof;

wherein a dashed line represents the presence or absence of a double bond or a triple bond;

A is $-(CH_2)_6-$, *cis* $-CH_2CH=CH-(CH_2)_3-$, or $-CH_2C\equiv C-(CH_2)_3-$, wherein 1 or 2 carbon atoms may be substituted with S or O;

X is selected from the group consisting of CO_2H, $CONHR_2$, $CONR_2$, $CON(OR)R$, $CON(CH_2CH_2OH)_2$, $CONH(CH_2CH_2OH)$, CH_2OH, $P(O)(OH)_2$, $CONHSO_2R$, SO_2NR_2, SO_2NHR, and



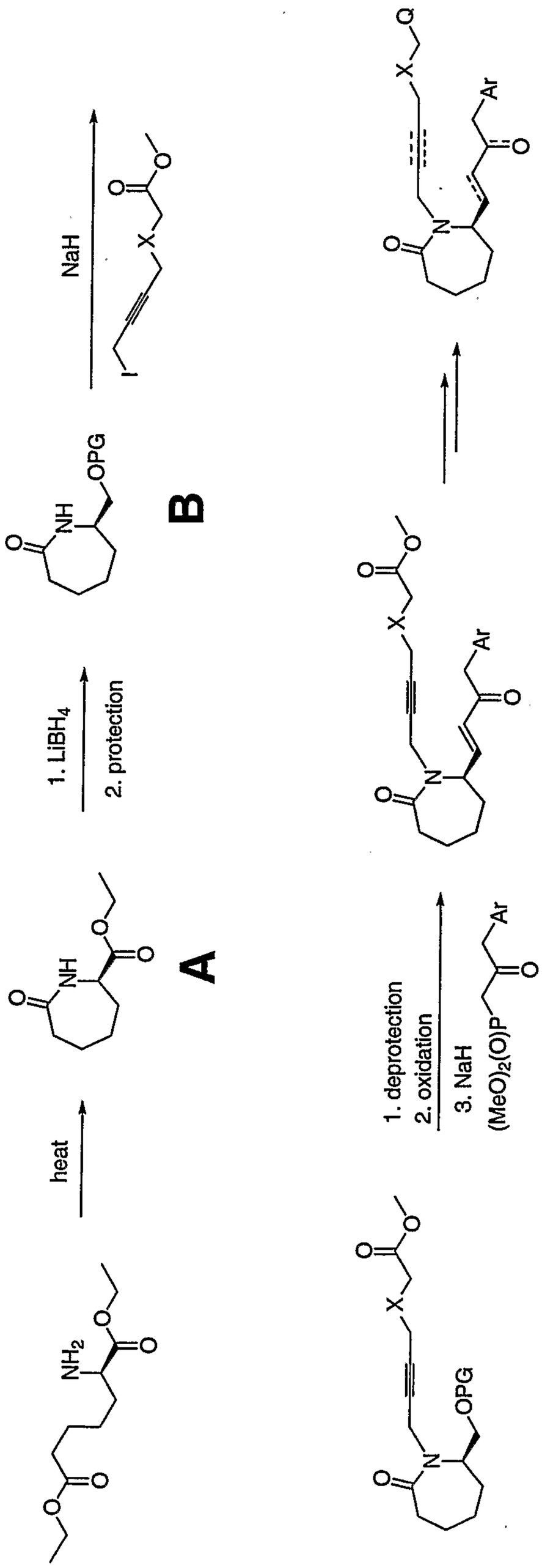
;

J is C=O, CHOH, or CH_2CHOH;

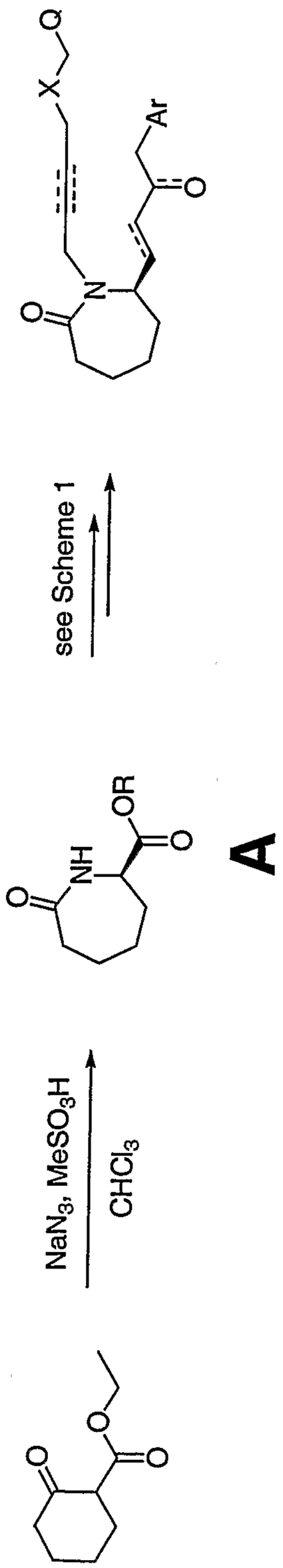
R is independently H, C_1-C_6 alkyl, phenyl, or biphenyl; and

E is C_3-C_6 alkyl, C_4-C_{10} cycloalkyl, phenyl or napthyl having from 0 to 2 substituents, or a heteroaromatic moiety having from 0 to 2 substituents, wherein said substituents comprise up to 4 non-hydrogen atoms.

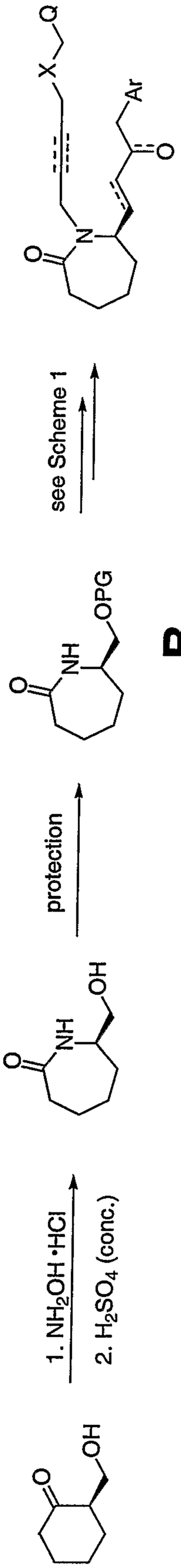
Scheme 1


heat
1. LiBH4
2. protection
A
B
NaH
OPG
NH
O
X
Ar
1. deprotection
2. oxidation
3. NaH
(MeO)2(O)P
NH2
OPG
PG: Protecting Group

Scheme 2

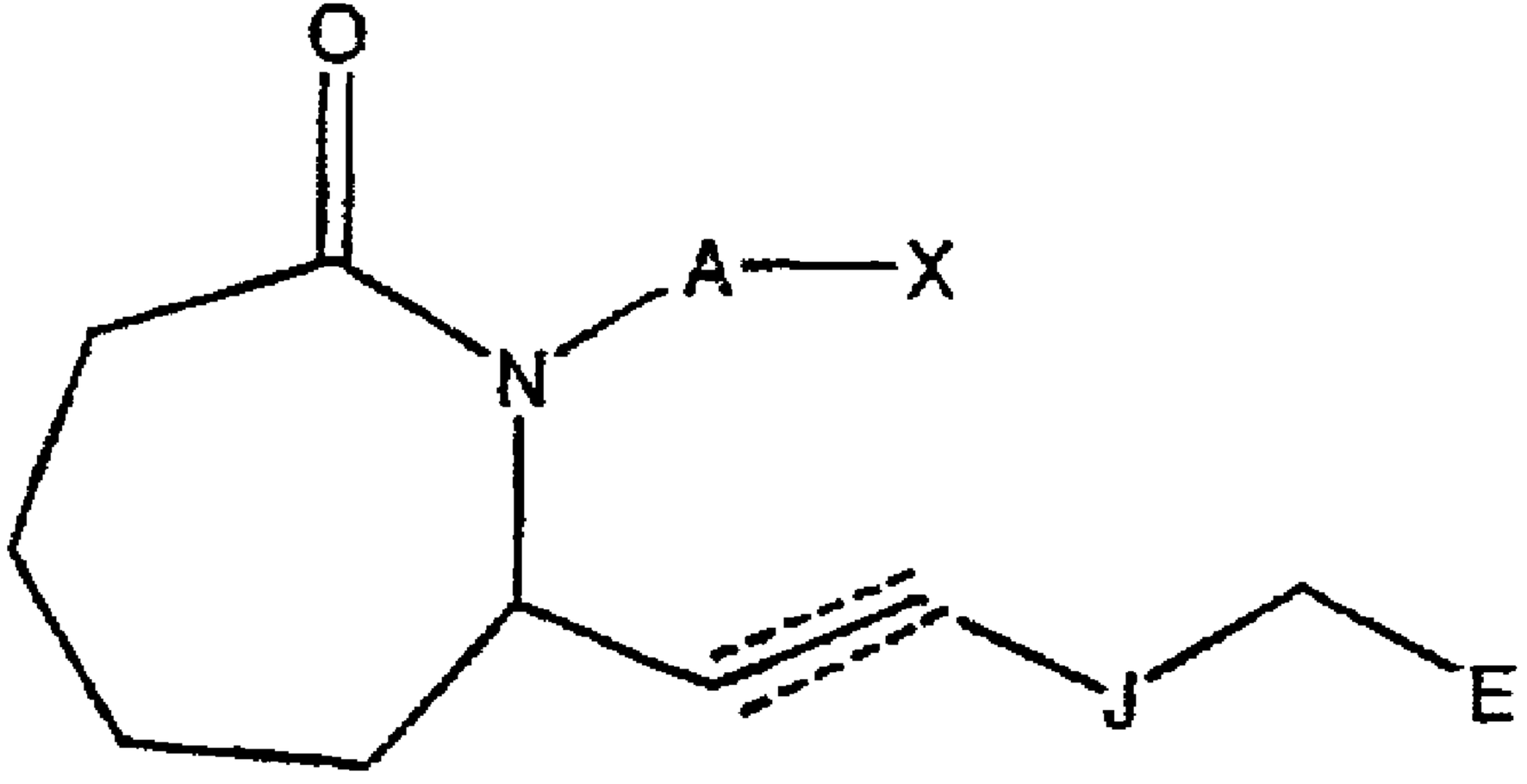

see Scheme 1
A
NaN3, MeSO3H
CHCl3
see: J. Med. Chem. 1999, 42, 4547-4562.

Scheme 3



see: Jpn. Kokai Tokkyo Koho (1993) JP 05086034

PG: Protecting group


O
A
X
N
J
E