

PhenanthrolinePhosphonic Acid Derivative And Preparation Method Therefor And Application Thereof

Field of Invention

The present invention relates to a novel phenanthroline phosphonic acid compound and a pharmaceutical salt thereof, preparation of the compound, as well as an application of the compound and the pharmaceutical salt thereof as collagen prolyl-4-hydroxylase inhibitors in the preparation of drugs for preventing or treating collagen prolyl-4-hydroxylase related disease.

Background

The following description of the background of the invention is provided to aid in understanding the invention, but is not admitted to be, or to describe, prior art to the invention. All cited publications are incorporated by reference in their entirety.

Hepatic fibrosis is an extracellular matrix deposition process of the liver that excess collagen (especially collagen I) is synthesized (*Clin. Sci.* **1997**, 92, 103). The biosynthesis of collagen includes series of post-translational modification of procollagen. Five enzymes, 3 collagen hydroxylases and 2 collagen glycosyltransferases, are involved in this process. Among these hydroxylases, prolyl-4-hydroxylase is the rate limiting enzyme in the synthesis of 21 different collagen (*Critical Reviews in Biochemistry and Molecular Biology* **2010**, 45, 106). It is a tetramer of 2 α subunits (P4H α 1, P4H α 2) and 2 β subunits. β Subunit is responsible for the enzyme's localization to and retention in the endoplasmic reticulum, and the α subunit is responsible for both peptide binding and catalytic activity. P4H catalyzes the formation of 4-hydroxyproline, from the proline residue on X-Pro-Gly sequence, in the presence of Fe²⁺, O₂, 2-oxoglutarate and ascorbate. P4H catalyzes the process from proline to 4-hydroxyproline (4-HYP) in certain positions of the procollagen, thus enhances the stability of collagen by forming triple helixes under physiological circumstances. With less 4-HYP content, the collagen is unable to form stable triple helixes structure and degrades (*Matrix Biol.* **2003**, 22,

15) . Therefore, inhibition of P4H activity is widely accepted as a valid method for controlling excess collagen synthesis (fibrosis). (*Hepatology*.**1998**, 28, 404). Several small molecule P4H inhibitors were verified to be effective in preventing collagen synthesis *in vitro* and *in vivo*(*J.Hepatology*.**1997**, 27, 185; *Hepatology*.**1996**, 23, 755; *Hepatology*.**1998**, 28, 404; *Biochem. J.***1994**, 300, 525; *J. Hepatology*.**1991**, 13, S35). For example, P4H inhibitor HOE077 (N, N'-di(2-methoxyethyl) pyridinyl-2,4-dicarboxamide) inhibits expression of procollagen mRNA and hepatic stellate cells proliferation (*Hepatology. Res.***2002**, 23, 1; *J. Hepatology*.**1997**, 27, 185), also inhibits activation of hepatic stellate cells (*Hepatology*.**1996**, 23, 755). The inhibitory effect of HOE077 on procollagen gene and protein was dose-dependent, but no effect on the synthesis of total protein was observed. The inhibitory effect of HOE077 is possibly due to the inhibition of tissue metalloproteinase-1 (TIMP-1, inhibitor of matrix-degrading metalloproteinase) to expedite fibril degradation process(*J. Gastroenterol.***1999**, 34, 376). Several P4H inhibitors showed anti-fibrotic effects in various animal liver fibrosis models (CCl₄, TAA etc.). (*Hepatology*.**1998**, 28, 404; *Hepatology*.**1996**, 23, 755; *J. Hepatology*.**1997**, 27, 185) Another P4H inhibitor FG-041 (1,4-dihydrophenanthrol-4-one-3-carboxylic acid) was reported to prevent myocardial infarction (*Circulation* **2001**, 104, 2216). P4H inhibitors were also reported in treatment of bladder block (*Urology* **2012**, 80, 1390).

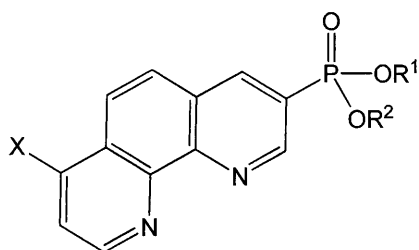
P4H exists everywhere in body. Thus, organ-targeted delivery of P4H inhibitors is the key to successful development. In 1990s, Hoechst developed HOE077 to treat liver cirrhosis (*Hepatology*.**1996**, 23, 755; *J. Hepatology*.**1997**, 27, 185). Preclinical experiments showed promising results though severe side effects (cataract) were observed in clinical trials. Inhibition of collagen synthesis in ECM could cause effusion of macromolecules, thus affect organ functions, for example, eyes and kidneys (*J. Biol. Chem.***2010**, 285, 42023). The key to developing anti liver fibrosis drug is specific delivery to liver. Prodrugs have been widely used in targeted therapeutic areas (*J. Pharmacol. Exp. Ther.***2005**, 312, 554). 1,3-Propane diols could form cyclic phosphonate esters with phosphonic acids, which were reported liver targeting (*J. Med. Chem.***2008**, 51, 666). The present invention

relatestomodification of parent drug to form inactive prodrug.The prodrug may only be metabolized under the catalysis of liver-specific enzymes, for example, cytochrome P450, to release the active parent drug in liver.

Detailed Description of the Invention

The present invention is directed towards novel phosphorus-containing phenanthrolinone compounds that are inhibitors of collagen prolyl-4-hydroxylase (P4H). In one aspect, the invention is directed toward phosphonic acids and prodrugs thereof. In another aspect, the present invention is directed to the preparation and the clinical use of these P4H inhibitors as a method of treatment or prevention of diseases responsive to inhibition of excess or impaired collagen synthesis.

In one aspect, the present invention relates to compounds of Formula I or Formula II, and pharmaceutically acceptable salts and prodrugs thereof as represented by Formula I or Formula II:



Formula I

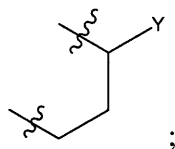
wherein:

X is -Cl, -OR³;

R¹, R² is independently selected from H, C₁-C₆ alkyl, -CH₂OCO-(C₁-C₆ alkyl), -CH₂OCOO-(C₁-C₆ alkyl);

R³ is -H, -C(O)-(C₁-C₆ alkyl) or,

or R¹ and R² join to form a group having the formula:



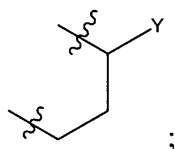
Y is aryl, heteroaryl;

In one aspect, X is independently selected from the group consisting of -Cl, and -OR³;

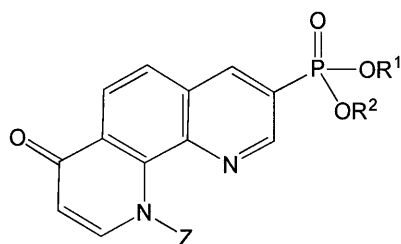
In another aspect, R¹ and R² are independently selected from H, C₁-C₆ alkyl, -CH₂OCO-(C₁-C₆ alkyl), -CH₂OCOO-(C₁-C₆ alkyl);

R³ is -H, -C(O)-(C₁-C₆ alkyl) or,

or R¹ and R² join to form a group having the formula:



Y is aryl, heteroaryl



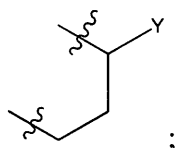
Formula II

wherein:

Z is -H, -CH₂OPO(OH)₂;

R¹, R² is independently selected from H, C₁-C₆ alkyl, -CH₂OCO-(C₁-C₆ alkyl), -CH₂OCOO-(C₁-C₆ alkyl);

or R¹ and R² join to form a group having the formula:

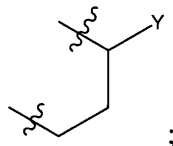


Y is aryl, heteroaryl;

In one aspect, Z is independently selected from the group consisting of -H, and -CH₂OPO(OH)₂;

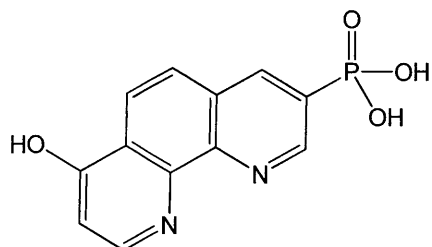
In another aspect, R^1 and R^2 are independently selected from H, C₁-C₆ alkyl, -CH₂OCO-(C₁-C₆ alkyl), -CH₂OCOO-(C₁-C₆ alkyl);

Or R^1 and R^2 join to form a group having the formula:

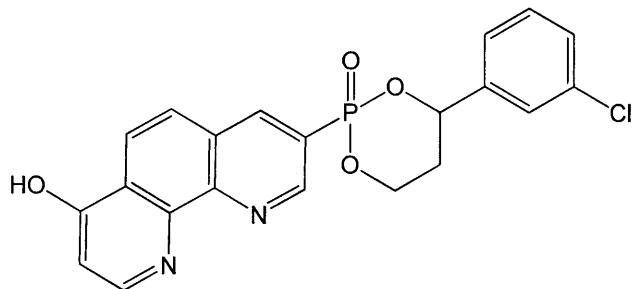


Y is aryl, heteroaryl;

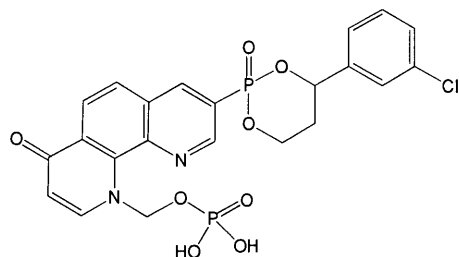
In one aspect, the invention comprises a compound of the following formula:



In another aspect, the invention comprises a compound of the following formula:



In another aspect, the invention comprises a compound of the following formula:



Also provided are preparation of a compound of Formula I and Formula II, or pharmaceutically acceptable salts thereof.

Also provided are applications of the compound of Formula I and Formula II and the pharmaceutical salt thereof as collagen prolyl-4-hydroxylase inhibitors in the preparation of drugs for preventing or treating collagen prolyl-4-hydroxylase related disease.

Also provided are applications of the compound of Formula I and Formula II and the pharmaceutical salt thereof in the preparation of drugs for preventing or treating collagen prolyl-4-hydroxylase related disease.

Also provided are applications of the compound of Formula I and Formula II and the metabolite thereof as collagen prolyl-4-hydroxylase inhibitors.

Also provided are methods to protect liver function, the methods comprise the step of administering to a patient with chronic liver injuries a therapeutically effective amount of a compound of Formula I and Formula II, or pharmaceutically acceptable salts thereof.

Also provided are methods for treating liver fibrosis, the methods comprise the step of administering to a patient with chronic liver injuries a therapeutically effective amount of a compound of Formula I and Formula II, or pharmaceutically acceptable salts thereof.

Also provided are methods for preventing liver fibrosis, the methods comprise the step of administering to a patient at risk for developing fibrosis a therapeutically effective amount of a compound of Formula I and Formula II, or pharmaceutically acceptable salts thereof.

Description of Figures

Figure 1. The IC₅₀ of Compound 9c against P4H enzyme

Figure 2. Concentration-time curve of compound 16c in plasma after iv dosing 16c and PO dosing 27

Figure 3. H&E staining of rat liver (SHAM group)

Figure 4. H&E staining of rat liver (BDL 2 weeks)

Figure 5. H&E staining of rat liver (BDL, PO administration of 27, 30 mpk, 2 weeks)

Definitions

In accordance with the present invention and as used herein, the following terms are defined with the following meanings, unless explicitly stated otherwise.

The term “alkyl” refers to saturated aliphatic groups including straight-chain, branched chain and cyclic groups, up to and including 20 carbon atoms. Suitable alkyl groups include methyl, ethyl, n-propyl, isopropyl, and cyclopropyl. The alkyl may be optionally substituted with 1-3 substituents.

The term “aryl” refers to aromatic groups which have 5-14 ring atoms and at least one ring having a conjugated pi electron system and includes carbocyclic aryl, heterocyclic aryl and biaryl groups, all of which may be optionally substituted. The aryl may be optionally substituted with 1-6 substituents.

Heterocyclic aryl or heteroaryl groups are groups which have 5-14 ring atoms wherein 1 to 4 heteroatoms are ring atoms in the aromatic ring and the remainder of the ring atoms being carbon atoms. Suitable heteroatoms include oxygen, sulfur, nitrogen, and selenium. Suitable heteroaryl groups include furanyl, thienyl, pyridyl, pyrrolyl, N-lower alkyl pyrrolyl, pyridyl-N-oxide, pyrimidyl, pyrazinyl, imidazolyl, and the like, all optionally substituted.

The term “optionally substituted” or “substituted” includes groups substituted by one to four substituents, independently selected from lower alkyl, lower aryl, lower aralkyl, lower cyclic alkyl, lower heterocycloalkyl, hydroxy, lower alkoxy, lower aryloxy, perhaloalkoxy, aralkoxy, lower heteroaryl, lower heteroaryloxy, lower heteroarylalkyl, lower heteroaralkoxy, azido, amino, halo, lower alkylthio, oxo, lower acylalkyl, lower carboxy esters, carboxyl, -carboxamido, nitro, lower acyloxy, lower aminoalkyl, lower alkylaminoaryl, lower alkylaryl, lower alkylaminoalkyl, lower alkoxyaryl, lower arylamino, lower aralkylamino, sulfonyl, lower -carboxamidoalkylaryl, lower -carboxamidoaryl, lower hydroxyalkyl, lower haloalkyl, lower alkylaminoalkylcarboxy-, lower aminocarboxamidoalkyl-, cyano, lower alkoxyalkyl, lower perhaloalkyl, and lower arylalkyloxyalkyl. “Substituted aryl” and “substituted heteroaryl” refers to aryl and heteroaryl groups substituted with 1-6 substituents.

These substituents are selected from the group consisting of lower alkyl, lower alkoxy, lower perhaloalkyl, halo, hydroxy, and amino.

The term “halogen” or “halo” refers to -F, -Cl, -Br and -I.

The phrase “therapeutically effective amount” means an amount of a compound or a combination of compounds that ameliorates, attenuates or eliminates one or more of the symptoms of a particular disease or condition or prevents, modifies, or delays the onset of one or more of the symptoms of a particular disease or condition.

The term “pharmaceutically acceptable salt” includes salts of compounds of Formula I and Formula II and an organic or inorganic acid or base. Suitable acids include acetic acid, adipic acid, benzenesulfonic acid, (+)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptane-1-methanesulfonic acid, citric acid, 1,2-ethanedisulfonic acid, dodecyl sulfonic acid, fumaric acid, glucoheptonic acid, gluconic acid, glucuronic acid, hippuric acid, hydrochloride hemiethanolic acid, HBr, HCl, HI, 2-hydroxyethanesulfonic acid, lactic acid, lactobionic acid, maleic acid, methanesulfonic acid, methylbromide acid, methyl sulfuric acid, 2-naphthalenesulfonic acid, nitric acid, oleic acid, 4,4'-methylenebis [3-hydroxy-2-naphthalenecarboxylic acid], phosphoric acid, polygalacturonic acid, stearic acid, succinic acid, sulfuric acid, sulfosalicylic acid, tannic acid, tartaric acid, terphthalic acid, and *p*-toluenesulfonic acid.

The term “patient” refers to an animal being treated including a mammal, such as a dog, a cat, a cow, a horse, a sheep, and a human. Another aspect includes a mammal, both male and female.

The term “prodrug” as used herein refers to any compound that when administered to a biological system generates a biologically active compound as a result of spontaneous chemical reaction(s), enzyme catalyzed chemical reaction(s), and/or metabolic chemical reaction(s), or a combination of each. Standard prodrugs are formed using groups attached to functionality, *e.g.* HO-, HS-, HOOC-, R₂N-, associated with the drug, that cleave *in vivo*. Standard prodrugs include but are not limited to carboxylate esters where the group is alkyl, aryl, aralkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl as well as esters of hydroxyl, thiol and amines where the group attached is an acyl group, an alkoxycarbonyl, aminocarbonyl, phosphate or sulfate. The groups illustrated are

exemplary, not exhaustive, and one skilled in the art could prepare other known varieties of prodrugs. Such prodrugs of the compounds of Formula I fall within this scope. Prodrugs must undergo some form of a chemical transformation to produce the compound that is biologically active or is a precursor of the biologically active compound. In some cases, the prodrug is biologically active, usually less than the drug itself, and serves to improve drug efficacy or safety through improved oral bioavailability, pharmacodynamic half-life, etc. Prodrug forms of compounds may be utilized, for example, to improve bioavailability, improve subject acceptability such as by masking or reducing unpleasant characteristics such as bitter taste or gastrointestinal irritability, alter solubility such as for intravenous use, provide for prolonged or sustained release or delivery, improve ease of formulation, or provide site-specific delivery of the compound. Prodrugs are described in *The Organic Chemistry of Drug Design and Drug Action*, by Richard B. Silverman, Academic Press, San Diego, 1992. Chapter 8: "Prodrugs and Drug delivery Systems" pp.352-401; *Design of Prodrugs*, edited by H. Bundgaard, Elsevier Science, Amsterdam, 1985; *Design of Biopharmaceutical Properties through Prodrugs and Analogs*, Ed. by E. B. Roche, American Pharmaceutical Association, Washington, 1977; and *Drug Delivery Systems*, ed. by R. L. Juliano, Oxford Univ. Press, Oxford, 1980.

The term "percent enantiomeric excess (% ee)" refers to optical purity. It is obtained by using the following formula:

$$\frac{[R] - [S]}{[R] + [S]} \times 100 = \%R - \%S$$

where [R] is the amount of the R isomer and [S] is the amount of the S isomer.

This formula provides the % ee when R is the dominant isomer.

The terms "treating" or "treatment" of a disease includes preventing the disease from occurring in an animal that may be predisposed to the disease but does not yet experience or exhibit symptoms of the disease (prophylactic treatment), inhibiting the disease (slowing or arresting its development), providing relief from the symptoms or

side-effects of the disease (including palliative treatment), and relieving the disease (causing regression of the disease).

Formulations

Compounds of the invention are administered in a total daily dose of 0.01 to 2500 mg. In one aspect the range is about 5 mg to about 500 mg. The dose may be administered in as many divided doses as is convenient.

Compounds of this invention when used in combination with other agents may be administered as a daily dose or an appropriate fraction of the daily dose (*e.g.*, *bid*). The compounds of this invention may be used in a multidrug regimen, also known as combination or 'cocktail' therapy, wherein, multiple agents may be administered together, may be administered separately at the same time or at different intervals, or administered sequentially. The compounds of this invention may be administered after a course of treatment by another agent, during a course of therapy with another agent, administered as part of a therapeutic regimen, or may be administered prior to therapy by another agent in a treatment program.

For the purposes of this invention, the compounds may be administered by a variety of means including orally, parenterally, by inhalation spray, topically, or rectally in formulations containing pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used here includes subcutaneous, intravenous, intramuscular, and intraarterial injections with a variety of infusion techniques. Intraarterial and intravenous injection as used herein includes administration through catheters. Intravenous administration is generally preferred.

Pharmaceutically acceptable salts include acetate, adipate, besylate, bromide, camsylate, chloride, citrate, edisylate, estolate, fumarate, gluceptate, gluconate, glucoranate, hippurate, hyclate, hydrobromide, hydrochloride, iodide, isethionate, lactate, lactobionate, maleate, mesylate, methylbromide, methylsulfate, napsylate,

nitrate, oleate, palmoate, phosphate, polygalacturonate, stearate, succinate, sulfate, sulfosalicylate, tannate, tartrate, terphthalate, tosylate, and triethiodide.

Pharmaceutical compositions containing the active ingredient may be in any form suitable for the intended method of administration. When used for oral use for example, tablets, troches, lozenges, aqueous or oil suspensions, dispersible powders or granules, emulsions, hard or soft capsules, syrups or elixirs may be prepared. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents including sweetening agents, flavoring agents, coloring agents and preserving agents, in order to provide a palatable preparation. Tablets containing the active ingredient in admixture with non-toxic pharmaceutically acceptable excipient which are suitable for manufacture of tablets are acceptable. These excipients may be, for example, inert diluents, such as calcium or sodium carbonate, lactose, calcium or sodium phosphate; granulating and disintegrating agents, such as maize starch, or alginic acid; binding agents, such as starch, gelatin or acacia; and lubricating agents, such as magnesium stearate, stearic acid or talc. Tablets may be uncoated or may be coated by known techniques including microencapsulation to delay disintegration and adsorption 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 alone or with a wax may be employed.

Formulations for oral use may be also presented as hard gelatin capsules where the active ingredient is mixed with an inert solid diluent, for example calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, such as peanut oil, liquid paraffin or olive oil.

Aqueous suspensions of the invention contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients include a suspending agent, such as sodium carboxymethylcellulose, methylcellulose, ethylcellulose, hydroxypropylcellulose, hydroxypropyl methylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia, and dispersing or wetting agents such as a naturally occurring phosphatide (*e.g.*, lecithin), a condensation

product of an alkylene oxide with a fatty acid (*e.g.*, polyoxyethylene stearate), a condensation product of ethylene oxide with a long chain aliphatic alcohol (*e.g.*, heptadecaethyleneoxycetanol), a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride (*e.g.*, polyoxyethylenesorbitanmonooleate). The aqueous suspension may also contain one or more preservatives such as ethyl or n-propyl p-hydroxy-benzoate, one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose or saccharin.

Oil suspensions may be formulated by suspending the active ingredient in a vegetable oil, such as arachid oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oral suspensions may contain a thickening agent, such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid. Dispersible powders and granules of the invention suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent, and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those disclosed above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachid oil, a mineral oil, such as liquid paraffin, or a mixture of these. Suitable emulsifying agents include naturally-occurring gums, such as gum acacia and gum tragacanth, naturally occurring phosphatides, such as soybean lecithin, esters or partial esters derived from fatty acids and hexitol anhydrides, such as sorbitanmonooleate, and condensation products of these partial esters with ethylene oxide, such as polyoxyethylenesorbitanmonooleate. The emulsion may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, such as glycerol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, a flavoring or a coloring agent.

The pharmaceutical compositions of the invention may be in the form of a sterile injectable preparation, such as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, such as a solution in 1,3-butane-diol or prepared as a lyophilized powder. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile fixed oils may conventionally be employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid may likewise be used in the preparation of injectables.

The amount of active ingredient that may be combined with the carrier material to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a time-release formulation intended for oral administration to humans may contain 20 to 2000 μmol (approximately 10 to 1000 mg) of active material compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95% of the total compositions. It is preferred that the pharmaceutical composition be prepared which provides easily measurable amounts for administration. For example, an aqueous solution intended for intravenous infusion should contain from about 0.05 to about 50 μmol (approximately 0.025 to 25 mg) of the active ingredient per milliliter of solution in order that infusion of a suitable volume at a rate of about 30 mL/hr can occur.

As noted above, formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid

emulsion or a water-in-oil liquid emulsion. The active ingredient may also be administered as a bolus, electuary or paste.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free flowing form such as a powder or granules, optionally mixed with a binder (*e.g.*, povidone, gelatin, hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (*e.g.*, sodium starch glycolate, cross-linked povidone, cross-linked sodium carboxymethyl cellulose) surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropyl methylcellulose in varying proportions to provide the desired release profile. Tablets may optionally be provided with an enteric coating, to provide release in parts of the gut other than the stomach. This is particularly advantageous with the compounds of Formula I when such compounds are susceptible to acid hydrolysis.

Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavored base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Formulations suitable for parenteral administration include aqueous and non-aqueous isotonic sterile injection solutions which may contain antioxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may

include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose sealed containers, for example, ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Formulations suitable for parenteral administration may be administered in a continuous infusion manner via an indwelling pump or via a hospital bag. Continuous infusion includes the infusion by an external pump. The infusions may be done through a Hickman or PICC or any other suitable means of administering a formulation either parenterally or i.v.

Preferred unit dosage formulations are those containing a daily dose or unit, daily sub-dose, or an appropriate fraction thereof, of a drug.

It will be understood, however, that the specific dose level for any particular patient will depend on a variety of factors including the activity of the specific compound employed; the age, body weight, general health, sex and diet of the individual being treated; the time and route of administration; the rate of excretion; other drugs which have previously been administered; and the severity of the particular disease undergoing therapy, as is well understood by those skilled in the art.

Synthesis of the Compounds of the Invention

The compounds in this invention may be prepared by the processes described in the following discussions, as well as relevant published literature procedures that are used by those skilled in the art. It should be understood that the following discussions are provided solely for the purpose of illustration and do not limit the invention which is defined by the claims. Typically the synthesis of a compound of Formula I includes the following general steps (listed in reversed order): (1) Preparation of a prodrug; (2) Deprotection of a phosphonate ester; (3) Modifications of an existing thiazole; (4) Construction of a thiazole; and (5) Preparation of key precursors. Protection and

deprotection in the Schemes may be carried out according to the procedures generally known in the art (*e.g.*, "Protecting Groups in Organic Synthesis," 3rd Edition, Wiley, 1999).

All stereoisomers of the compounds of the instant invention are contemplated, either in admixture or in pure or substantially pure form. The compounds of the present invention can have stereogenic centers at the phosphorus atom and at any of the carbons including any of the R substituents. Consequently, compounds of Formula I can exist in enantiomeric or diastereomeric forms or in mixtures thereof. The processes for preparation can utilize racemates, enantiomers or diastereomers as starting materials. When enantiomeric or diastereomeric products are prepared, they can be separated by conventional methods. For example, chromatography or fractional crystallization can be used to separate diastereomeric mixtures, while derivatives of enantiomeric isomers can be separated via chromatography.

1) Preparation of a prodrug

Prodrugs can be introduced at different stages of the synthesis. Most often these prodrugs are introduced at the later stage of a synthesis due to the lability of various prodrugs, while prodrugs could also be introduced at an early stage of the synthesis due to other considerations.

Phosphonic acids of Formula I wherein both R¹ and R² are H, which may be in a suitably protected form, can be alkylated with electrophiles such as alkyl halides and alkyl sulfonates under nucleophilic substitution conditions to give phosphonate esters. For example, compounds of Formula I wherein R¹ and R² are acyloxyalkyl groups can be prepared by direct alkylation of compounds of Formula I wherein both R¹ and R² are H with an appropriate acyloxyalkyl halide (*e.g.* Cl, Br, I; *Phosphorus Sulfur***1990**, 54, 143; *Synthesis***1988**, 62) in the presence of a suitable base (*e.g.* pyridine, TEA, diisopropylethylamine) in suitable solvents such as DMF (*J. Med. Chem.***1994**, 37, 1875). The carboxylate component of these acyloxyalkyl halides includes but is not limited to acetate, propionate, isobutyrate, pivalate, benzoate, carbonate and other carboxylates.

Reactive dichlorophosphonates can be generated from the corresponding phosphonic acids with a chlorinating agent (e.g. thionyl chloride, *J. Med. Chem.* **1994**, 1857; oxalyl chloride, *Tetrahedron Lett.* **1990**, 31, 3261; phosphorous pentachloride, *Synthesis* **1974**, 490). Alternatively, a dichlorophosphonate can be generated from its corresponding disilyl phosphonate esters (*Synth. Commu.* **1987**, 17, 1071) or dialkyl phosphonate esters (*Tetrahedron Lett.* **1983**, 24, 4405; *Bull. Soc. Chim.* **1993**, 130, 485).

Cyclic phosphonate esters of substituted 1,3-propane diols can be synthesized by either reactions of the corresponding dichlorophosphonate with a substituted 1,3-propanediol or coupling reactions using suitable coupling reagents (e.g. DCC, EDCI, PyBOP; *Synthesis* **1988**, 62). The reactive dichlorophosphonate intermediates can be prepared from the corresponding acids and chlorinating agents such as thionyl chloride (*J. Med. Chem.*, **1994**, 1857), oxalyl chloride (*Tetrahedron Lett.*, **1990**, 31: 3261) and phosphorus pentachloride (*Synthesis*, **1974**, 490). Alternatively, these dichlorophosphonates can also be generated from disilyl esters (*Synth. Commun.*, **1987**, 17: 1071) and dialkyl esters (*Tetrahedron Lett.*, **1983**, 24: 4405; *Bull. Soc. Chim. Fr.*, **1993**, 130: 485).

Alternatively, these cyclic phosphonate esters of substituted 1,3-propane diols are prepared from phosphonic acids by coupling with diols under Mitsunobu reaction conditions (*Synthesis* 1 (1981); *J. Org. Chem.* 52:6331 (1992)), and other acid coupling reagents including, but not limited to, carbodiimides (*Collect. Czech. Chem. Commun.* 59:1853 (1994); *Bioorg. Med. Chem. Lett.* 2:145 (1992); *Tetrahedron Lett.* 29:1189 (1988)), and benzotriazolyloxytris-(dimethylamino) phosphonium salts (*Tetrahedron Lett.* 34, 6743 (1993)).

One aspect of the present invention provides methods to synthesize and isolate single isomers of prodrugs of phosphonic acids of Formula I. Because phosphorus is a stereogenic atom, formation of a prodrug with a racemic substituted-1,3-propane-diol will produce a mixture of isomers. For example, formation of a prodrug with a racemic 1-(Y)-substituted-1,3-propane diol gives a racemic mixture of cis-prodrugs and a racemic mixture of trans-prodrugs. In another aspect, the use of the enantioenriched substituted-1,3-propane diol with the R-configuration gives enantioenriched R-cis-and

R-trans-prodrugs. These compounds can be separated by a combination of column chromatography and/or fractional crystallization.

Another prodrug can be introduced for expected properties. Compounds of Formula I (X = OH) can be connected with different protecting groups on the O atom of N atom of the hydroxypyridine ring. For example, compounds of formula I (R³ is carboxyl group) could be prepared from compound of formula I (R³ is H) with appropriate carboxyl halide under suitable reaction conditions (J. Org. Chem. 1989, 54, 166); compounds of formula I (X is Cl) could be generated from compound of formula I (X is OH) with different chlorinating reagent (for example: POCl₃, J. Org. Chem. 1950, 15, 1224; CCl₃CN, Tetrahedron Lett. 2012, 53, 674) under appropriate conditions.

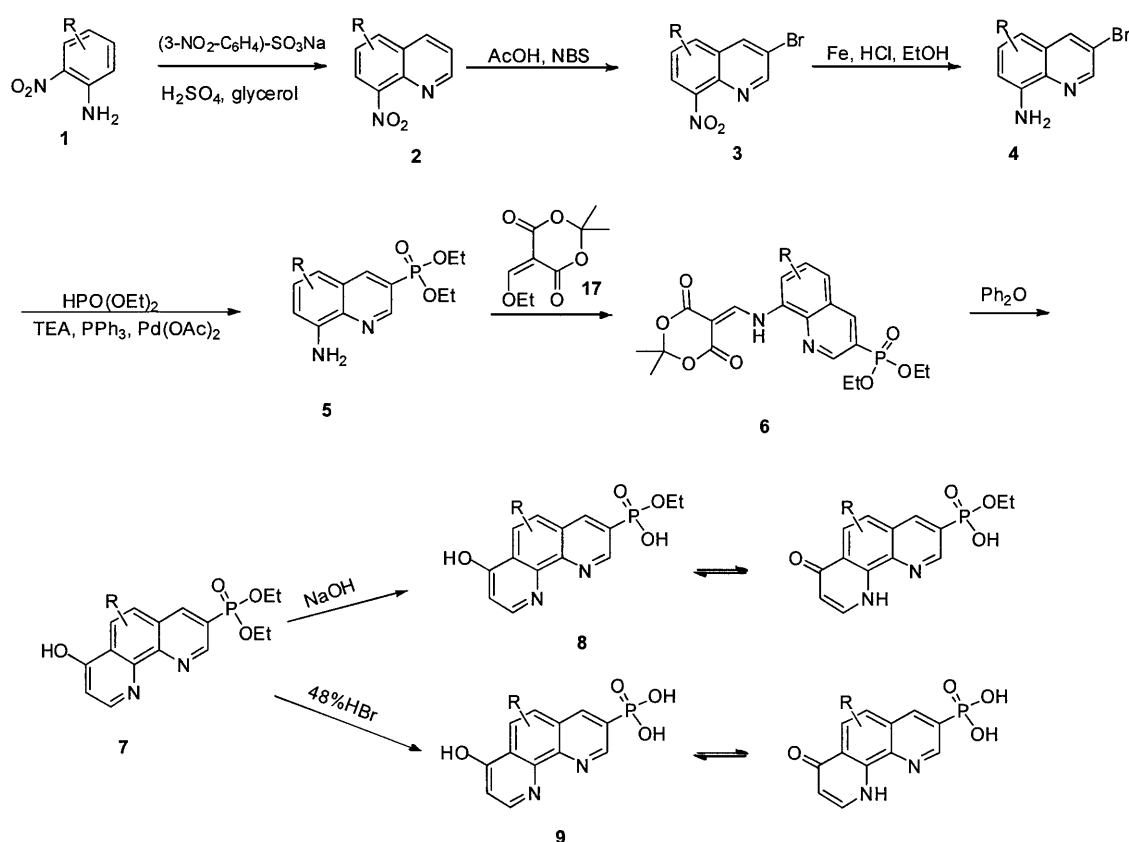
2) Deprotection of a phosphonate ester

Compounds of Formula I wherein R¹ is H may be prepared from phosphonate esters using known phosphate and phosphonate ester cleavage conditions. Silyl halides are generally used to cleave various phosphonate esters, and subsequent mild hydrolysis of the resulting silyl phosphonate esters give the desired phosphonic acids. When required, acid scavengers (e.g. 1,1,1,3,3,3-hexamethyldisilazane, 2,6-lutidine, etc.) can be used for the synthesis of acid labile compounds. Such silyl halides include chlorotrimethylsilane (Rabinowitz, *J. Org. Chem.*, **1963**, 28: 2975), and bromotrimethylsilane (McKenna, et al, *Tetrahedron Lett.*, 1977, 155), and iodotrimethylsilane (Blackburn, et al., *J. Chem. Soc., Chem. Commun.*, **1978**, 870). Alternately, phosphonate esters can be cleaved under strong acidic conditions (e.g. HBr or HCl : Moffatt, et al, *U.S. Patent 3,524,846*, **1970**). These esters can also be cleaved via dichlorophosphonates, prepared by treating the esters with halogenating agents (e.g. phosphorus pentachloride, thionyl chloride, BBr₃ : Pelchowicz et al., *J. Chem. Soc.*, **1961**, 238) followed by aqueous hydrolysis to give phosphonic acids. Aryl and benzyl phosphonate esters can be cleaved under hydrogenolysis conditions (Lejczak, et al., *Synthesis*, **1982**, 412; Elliott, et al., *J. Med. Chem.*, **1985**, 28: 1208; Baddiley, et al., *Nature*, **1953**, 171: 76) or metal reduction conditions (Shafer, et al., *J. Am. Chem. Soc.*, 1977, 99: 5118). Electrochemical (Shono, et al., *J. Org. Chem.*, **1979**, 44: 4508) and

pyrolysis (Gupta, *et al.*, *Synth. Commun.*, **1980**, *10*: 299) conditions have also been used to cleave various phosphonate esters.

(3) Synthesis of phosphorus-containing phenantholinones

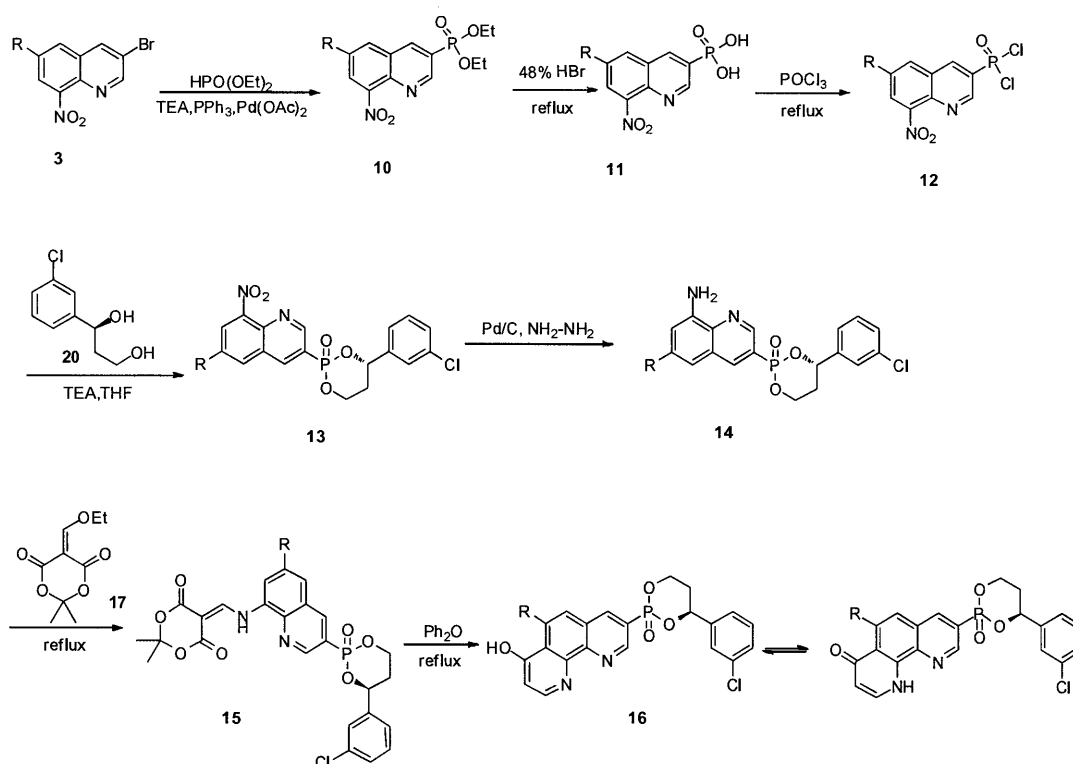
Construction of the phenantholinone core could be carried out using well-established literature methods. For example, a thermal cyclization strategy is illustrated in the following scheme.



Treatment of aniline **1** with sodium 3-nitrobenzenesulfonate, sulfuric acid and glycerol provided quinolone **2**. Bromination of quinolone **2** using NBS in acetic acid provided compound **3** which was reduced using iron to give compound **4**. Phosphonylation of compound **4** gave phosphonate **5** which was treated with compound **16** and followed by a thermal cyclization reaction to provide phenantholinone **7** wherein R is H (compounds of formula I wherein X is OH, $\text{R}^1 = \text{R}^2 = \text{Et}$). Treatment of compound **7** with sodium hydroxide provided compound **8** wherein R is H (compounds of formula

I wherein X is OH, $R^1 = H$, $R^2 = Et$); on the other hand, treatment of compound **7** with 48% HBr provided compound **9** wherein R is H (compounds of formula I wherein X is OH, $R^1 = R^2 = H$). In some cases, the desired substituents are not compatible with subsequent reactions, and therefore modifications of an existing phenanthrolinone are envisioned using conventional chemistry (Larock, *Comprehensive organic transformations*, VCH, New York, **1989**; Trost, *Comprehensive organic synthesis*; Pergamon press, New York, **1991**).

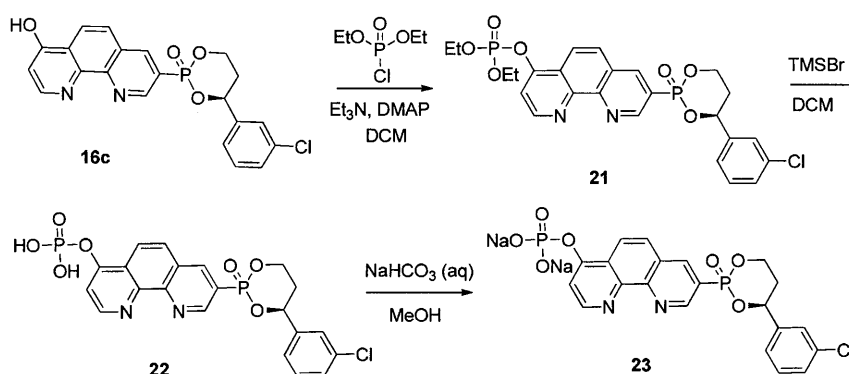
Prodrugs often are introduced at the later stage of a synthesis, while some prodrugs could also be introduced at an early stage of the synthesis due to other considerations. For example, the cyclic phosphonate diester prodrugs could be prepared as illustrated in the following scheme.



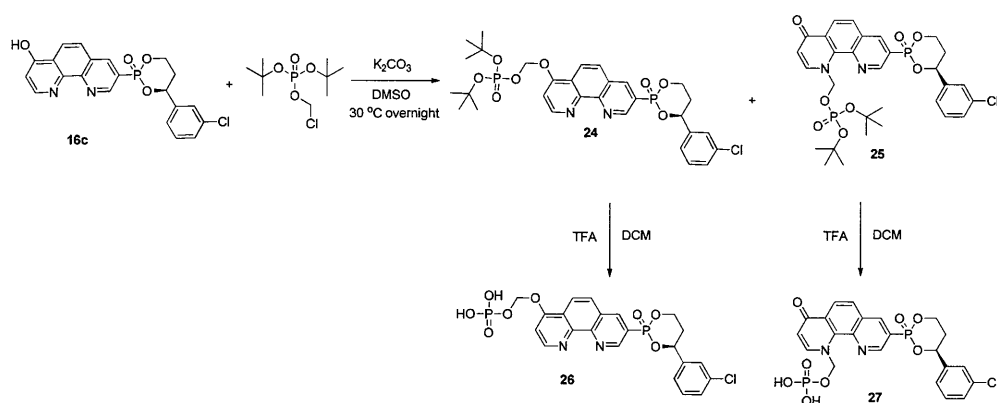
Phosphonylation of compound **3** gave phosphonate **10** which was deprotected using 48% HBr to give phosphonic acid **11**. Treatment of compound **11** with $POCl_3$ gave the reactive dichloridate **12** which was immediately coupled with diol **20** (*J. Am. Chem. Soc.* **2004**, 5154) to give compound **13**. Reduction of the nitro group in

compound **13** followed by reaction with compound **17** and then thermal ring closure to give phenanthrolinone **16** wherein R is H (compounds of formula I wherein X is OH, R¹ and R² together form a cyclic group).

Another prodrug can be introduced for expected properties. For example, a phosphate prodrug could be prepared as illustrated in the following scheme. Phenanthroline **16c** reacted with chlorophosphate under suitable base (for example: Et₃N) and catalyst (for example: 4-dimethylaminopyridine) in suitable solvent (for example: CH₂Cl₂) to yield phosphate **21**. The deprotection of diethyl phosphate can be achieved by using phosphate deprotecting reagent. For example, deprotection of phosphate **21** by trimethylsilyl bromide gave phosphoric acid **22**, which can be converted to sodium salt. For example, compound **22** mixed with sodium bicarbonate in water and methanol could give disodium salt **23**.



In another example, other types of prodrugs could be formed for different expected properties. For example, di-*t*-butylchloromethyl phosphate reacted with phenanthroline **16c** under suitable base (for example: K₂CO₃) in suitable solvent (for example: DMSO) to afford phosphate ester **24** and **25**. Common *t*-butyl deprotecting groups could be used to remove di-*t*-butyl groups. For example, deprotection of **24** and **25** with trifluoroacetic acid in dichloromethane gave phosphoric acid **26** and **27**, respectively. Compound **26** and **27** could be further converted to desired salts.

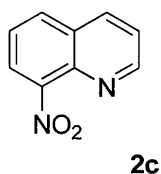


Examples

The compounds used in this invention and their preparation can be understood further by the Examples, which illustrate some of the processes by which these compounds are prepared. These Examples should not however be construed as specifically limiting the invention, and variations of the compounds, now known or later developed, are considered to fall within the scope of the present invention as hereinafter claimed.

Example 1. Syntheses of compounds

8-nitroquinoline(2c)

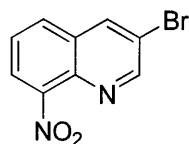


A mixture was prepared to which 47 g of H_2SO_4 , 20ml of H_2O , 23.4 g (0.104mol) of sodium 3-nitrobenzene sulfonate, and 22ml of glycerol were added in that order. It was warmed gently with stirring to form a solution, and 11 g 2-nitroaniline **1c** (0.08mol) was added in portions. The mixture was heated to 135 °C slowly with vigorous stirring and continued for 5 h. After cooling, the mixture was diluted with 600ml H_2O and adjusted to pH 6–7 with NH_4OH . The product was recovered by filtration, washed with H_2O , and dried. The crude product was purified by silica flash chromatography (elution with EA :

PE = 1: 5) to give 8-nitroquinoline **2c** 6.177g in 44% as Yellow solid.

¹H NMR (300 MHz, CDCl₃) 9.09 (dd, J = 1.8 Hz, 4.5 Hz, 1H), 8.28 (dd, J = 1.8 Hz, 8.4 Hz, 1H), 8.05 (d, J = 9 Hz, 2H), 7.66-7.55 (m, 2H).

3-bromo-8-nitroquinoline (3c)

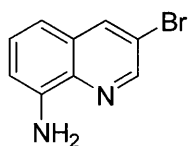


3c

To 110ml of acetic acid were added 8-nitroquinoline **2c** 6.177g (35.5mmol) and 6.651g NBS (35.5mmol). The mixture was heated to 50 °C with stirring for 2h. The solution was poured into 600ml H₂O with stirring, and the product was removed by filtration. The cake was purified by silica flash chromatography (elution with EA : PE = 1: 15) to give 3-bromo-8-nitroquinoline **3c** 2.625g in 29% as Yellow solid.

¹H NMR (300 MHz, CDCl₃) 9.06 (d, J = 2.1 Hz, 1H), 8.44 (d, J = 2.4 Hz, 1H), 8.06 (d, J = 7.5 Hz, 1H), 7.98 (d, J = 8.1 Hz, 1H), 7.67 (t, J = 7.8 Hz, 1H).

3-bromoquinolin-8-amine (4c)

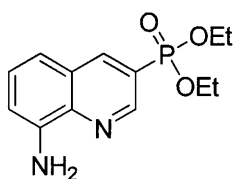


4c

To a stirred solution of 3-bromo-8-nitroquinoline **3c** (13.0 g, 51.6 mmol) in EtOH (150 mL) was added iron powder (11.6 g, 206.4 mmol), NH₄Cl (11.0 g, 206.4 mmol) and H₂O (150 mL). The resulting solution was stirred for overnight at reflux. The reaction solution was cooled to rt, filtered through Celite, washed with EA, the filtrate was concentrated in vacuo, the crude material was purified by flash chromatography (silica gel, 10% - 20% EA / PE) to yield 3-bromoquinolin-8-amine **4c** 8.23 g as a yellow solid in 72%.

¹H NMR (300 MHz, CDCl₃) 8.72 (d, J = 2.1 Hz, 1H), 8.21 (d, J = 2.1 Hz, 1H), 7.35 (t, J = 7.8 Hz, 1H), 7.05 (dd, J = 1.2 Hz, 8.1 Hz, 1H), 7.61 (dd, J = 1.2 Hz, 7.5 Hz, 1H), 4.98 (s, 2H).

Diethyl 8-aminoquinolin-3-ylphosphonate (5c)

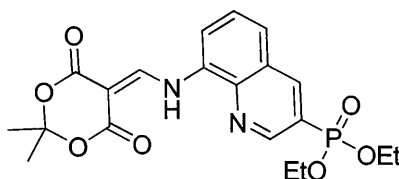


5c

To a stirred solution of 3-bromoquinolin-8-amine **4c** (4.0 g, 17.9 mmol) in EtOH (53 mL) was added HPO(OEt)₂ (3.0 mL, 23.3 mmol), TEA (3.7 mL, 26.9 mmol), Ph₃P (1.27 g, 4.8 mmol) and Pd(OAc)₂ (0.8 g, 3.58 mmol) under N₂. The resulting solution was stirred for overnight at reflux. The reaction solution was cooled to rt, quenched with H₂O (100 mL), extracted with EA (80 mL * 3). The organic layer was washed with brine, dried over anhydrous Na₂SO₄, concentrated in vacuo. The crude material was purified by flash chromatography (silica gel, 50% EA / PE) to yield diethyl 8-aminoquinolin-3-ylphosphonate **5c** 1.4 g in 25% as a yellow oil.

¹H NMR (300 MHz, CDCl₃) 8.98 (dd, J = 1.8 Hz, 4.2 Hz, 1H), 8.59 (dd, J = 2.1 Hz, 15.3 Hz, 1H), 7.38 (d, J = 7.8 Hz, 1H), 7.21 (d, J = 7.5 Hz, 1H), 7.01 (t, J = 7.5 Hz, 1H), 4.20 – 4.07 (m, 4H), 1.35 (t, J = 6.9 Hz, 6H)

Diethyl 8-((2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)methylamino)quinolin-3-ylphosphonate (6c)

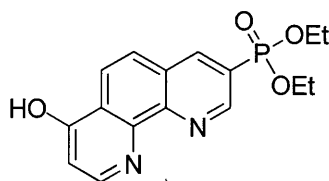


6c

To a stirred solution of Diethyl 8-aminoquinolin-3-ylphosphonate **5c** (1.4 g, 5 mmol) in EtOH (40 mL) under N₂, was added 5-(ethoxymethylene)-2,2-dimethyl-1,3-dioxane-4,6-dione **13** (1.3 g, 6.5 mmol). The resulting solution was stirred for overnight at reflux. The solution was concentrated in vacuo, the residue was purified by flash chromatography (silica gel, elution with PE : EA = 1 : 1) to give the product **6c** (1.125 g) as a yellow solid, the yield was 52%.

¹H NMR (300 MHz, CDCl₃) 12.8 (d, J = 15 Hz, 1H), 9.20 (dd, J = 1.8 Hz, 4.2 Hz, 1H), 8.91 (d, J = 14.7 Hz, 1H), 8.74 (dd, J = 1.8 Hz, 15.3 Hz, 1H), 7.80-7.76 (m, 2H), 7.67 (t, J = 7.8 Hz, 1H), 4.30 – 4.09 (m, 4H), 1.81 (s, 6H), 1.35 (t, J = 6.9 Hz, 6H).

Diethyl 7-hydroxy-1,10-phenanthrolin-3-ylphosphonate (7c)

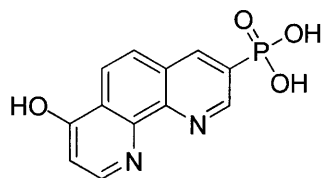


7c

Diphenyl ether (110ml) was heated to boiling ($T = 251\text{ }^{\circ}\text{C}$), diethyl 8-((2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)methylamino)quinolin-3-ylphosphonate **6c** (1.1 g, 2.5 mmol) was added to rapidly. The resulting solution was stirred for 2 min at reflux. The mixture was cooled to $100\text{ }^{\circ}\text{C}$, poured into PE (640 mL), the precipitate was filtered, washed with PE. The filter was purified with silica flash chromatography (elution with 5% MeOH in DCM) to give diethyl 7-hydroxy-1,10-phenanthrolin-3-ylphosphonate **7c** 650 mg in 77% as yellow solid.

^1H NMR (300 MHz, CDCl_3) δ 10.8 (s, 1H), 9.31 (dd, $J = 1.8\text{ Hz}, 5.1\text{ Hz}$, 1H), 8.72 (dd, $J = 1.8\text{ Hz}, 14.7\text{ Hz}$, 1H), 8.49 (d, $J = 8.7\text{ Hz}$, 1H), 7.94 (d, $J = 7.5\text{ Hz}$, 1H), 7.71 (d, $J = 9\text{ Hz}$, 1H), 6.62 (d, $J = 7.5\text{ Hz}$, 1H), 4.35 – 4.14 (m, 4H), 1.39 (t, $J = 6.9\text{ Hz}$, 6H).

7-hydroxy-1,10-phenanthrolin-3-ylphosphonic acid (9c)

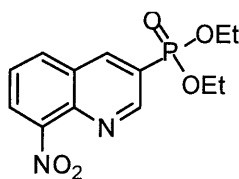


9c

Diethyl 7-hydroxy-1,10-phenanthrolin-3-ylphosphonate **7c** (650 mg) was dissolved in 48% HBr aq. The resulting solution was stirred for overnight at reflux. The mixture was concentrated in vacuo, the residue was stirred in H_2O , filtered. The filter was washed with EtOH, dried to yield 7-hydroxy-1,10-phenanthrolin-3-ylphosphonic acid **9c** 513 mg in 95% as gray solid.

^1H NMR (300 MHz, D_2O) δ 8.99 (dd, $J = 4.5\text{ Hz}, 1.8\text{ Hz}$, 1H), 8.30 (dd, $J = 12.6\text{ Hz}, 1.8\text{ Hz}$, 1H), 7.62 (d, $J = 6.9\text{ Hz}$, 1H), 7.40 (d, $J = 8.7\text{ Hz}$, 1H), 7.26 (d, $J = 8.7\text{ Hz}$, 1H), 6.19 (d, $J = 7.2\text{ Hz}$, 1H).

Diethyl 8-nitroquinolin-3-ylphosphonate (10c)

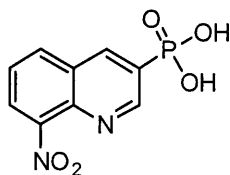


10c

To a solution of 3-bromo-8-nitroquinoline **3c** (30 g) in Toluene (300 mL) was added $\text{HPO}(\text{OEt})_2$ (18.4 mL), KOAc (23.4 g), $\text{Pd}(\text{dppf})_2\text{Cl}_2 \cdot \text{CH}_2\text{Cl}_2$ (1 g) under N_2 . The resulting solution was stirred for 3 hrs at reflux. The reaction solution was cooled to rt, diluted with EtOAc, filtered through Silica gel, concentrated to afford Diethyl 8-nitroquinolin-3-ylphosphonate **10c** 46 g.

^1H NMR (300 MHz, CDCl_3) 9.28 (dd, $J = 1.8$ Hz, 4.2 Hz, 1H), 8.82 (dd, $J = 1.8$ Hz, 15 Hz, 1H), 8.16 (t, $J = 6$ Hz, 2H), 7.21 (d, $J = 7.5$ Hz, 1H), 7.74 (t, $J = 8.1$ Hz, 1H), 4.33 – 4.11 (m, 4H), 1.37 (t, $J = 6.9$ Hz, 6H).

8-nitroquinolin-3-ylphosphonic acid (11c)

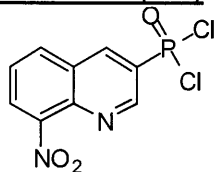


11c

Diethyl 8-nitroquinolin-3-ylphosphonate **10c** (44.5 g) was dissolved in 48% HBr aq (230 mL). The resulting solution was stirred for 4 hrs at reflux. The mixture was concentrated in vacuo, washed with EtOH/EtOAc, filtered to give **11c** 31.5 g as yellow solid.

^1H NMR (300 MHz, D_2O) 9.18 (dd, $J = 1.8$ Hz, 6 Hz, 1H), 8.98 (dd, $J = 1.8$ Hz, 13.2 Hz, 1H), 8.54 (d, $J = 7.8$ Hz, 1H), 8.36 (d, $J = 8.4$ Hz, 1H), 7.81 (t, $J = 7.8$ Hz, 1H).

8-nitroquinolin-3-ylphosphonic dichloride (12c)

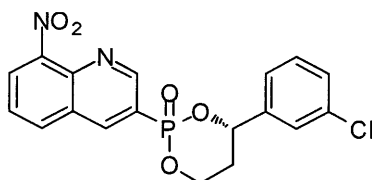


12c

8-nitroquinolin-3-ylphosphonic acid **10c** (50.3 g) was dissolved in CH_2Cl_2 (650

mL), DMF (3.6 mL) and (COCl)₂ (42 mL) was added dropwise. The resulting solution was stirred for overnight at reflux. Solvents were removed in vacuo to give the crude product 8-nitroquinolin-3-ylphosphonic dichloride **12c** as dark solid that was used without further purification in the subsequent reaction.

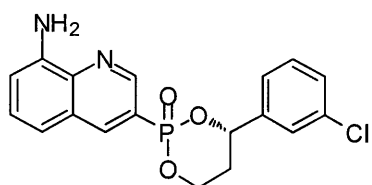
(4S)-4-(3-chlorophenyl)-2-(8-nitroquinolin-3-yl)-1,3,2-dioxaphosphin-2-one (13c)



13c

A solution of (S)-1-(3-chlorophenyl)propane-1,3-diol (36.95 g) in CH₂Cl₂ (540 mL) was added TiCl₄ (22 mL) dropwise under -78 °C. After 5 minutes' stirring in ice bath, TEA (110 mL) was added to the mixture. The resulting mixture was added dropwise to the solution of phosphonic dichloride **12c** in dichloromethane. After stirring at room temperature overnight, the reaction was diluted with CH₂Cl₂ (700 mL), quenched with 10% tartaric acid (210 mL). The mixture was filtered through celite, extracted with CH₂Cl₂. The organic layer was dried over Na₂SO₄, and the solvent removed in vacuo. The residue was recrystallized from CH₃CN to give **13c** 35.5 g in 44% as pale yellow solid. m/z: 405.1 [M+1];

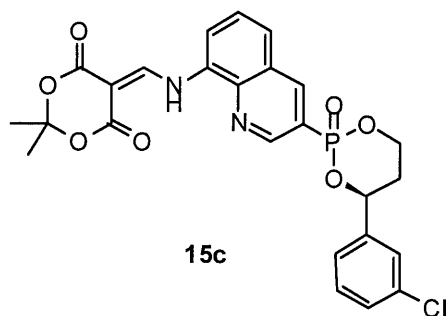
(4S)-4-(3-chlorophenyl)-2-(8-aminoquinolin-3-yl)-1,3,2-dioxaphosphin-2-one (14c)



14c

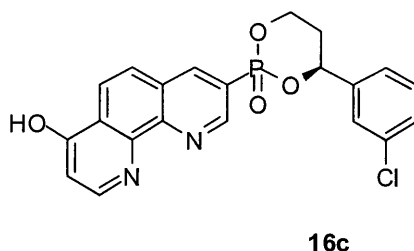
To a solution of nitroquinoline **13c** (62.9 g) in EtOH (160 mL) and AcOH (160 mL), was added Fe (43.6 g) and heated to 40 °C for 10 min. The resulting mixture was adjusted to pH 6 with sat. NaHCO₃ solution, extracted with CH₂Cl₂. The organic layer was dried over Na₂SO₄, and evaporated to give **14c** 50 g in 86% as yellow solid. m/z: 375.0 [M+1];

(4S)-4-(3-chlorophenyl)-2-(8-((2,2-dimethyl-1,3-dioxane-4,6-dione)-5-methylene)aminoquinolin-3-yl)-1,3,2-dioxaphosphin-2-one (15c)



To a solution of aminoquinoline **14c** (49 g) in EtOH (320 mL) was added 5-(ethoxymethylene)-2,2-dimethyl-1,3-dioxane-4,6-dione **17** (31.4 g) under N₂. The resulting solution was stirred for 2 hrs at reflux. The solution was cooled to rt, filtered, evaporated to give the product **15c** 60 g in 87% as yellow solid. m/z: 529.0 [M+1], 471.0 was found.

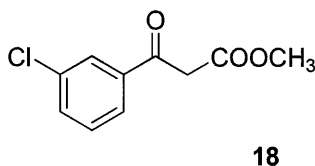
(4S)-4-(3-chlorophenyl)-2-(7-hydroxy-1,10-phenanthrolin-3-yl)-1,3,2-dioxaphosphin-2-one (16c)



Diphenyl ether was heated to boiling, compound **15c** (3 g) was added to rapidly. The resulting solution was stirred for 50 s at reflux. The mixture was cooled to 100 °C, poured into petroleum ether, the precipitate was filtered, washed with PE. The solid was purified with silica flash chromatography (elution with DCM : MeOH = 30 : 1) to give **16c** 1.676 g in 70% as yellow solid.

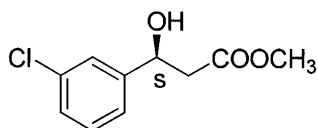
¹H NMR (300 MHz, DMSO) 12.53 (s, 1H), 9.34 (dd, J = 2.1 Hz, 5.1 Hz, 1H), 9.15 (dd, J = 1.8 Hz, 15.3 Hz, 1H), 8.27 (d, J = 8.7 Hz, 1H), 8.12-7.98 (m, 2H), 7.56 (s, 1H), 7.47-7.43 (m, 3H), 6.36 (d, J = 7.2 Hz, 1H), 5.96 (d, J = 11.1 Hz, 1H), 4.88 - 4.76 (m, 1H), 4.65 - 4.55 (m, 1H), 2.68-2.54 (m, 1H), 2.34 - 2.22 (m, 1H).

methyl 3-(3-chlorophenyl)-3-oxopropanoate (18)



The flask was flushed with nitrogen and charged sequentially with THF (50mL), potassium t-butoxide (15 g). The resulting mixture was stirred at ambient temperature for 15 min. 1-(3-chlorophenyl)ethanone (10g) and diethylcarbonate (11mL) was added slowly to the stirred potassium t-butoxide solution at 0 °C. After the addition was complete, the cooling bath was removed and the solution was stirred for 1.5 h. The reaction solution was charged with ice water (40mL) and concentrated hydrochloric acid (1.3 ml of 12 M solution). The solution was quenched into the aqueous acid and the mixture was stirred for 15 min. The layers were separated and the aqueous phase was extracted again with toluene. The combined organic extracts were washed with saturated brine, dried with NaSO₄, filtered and concentrated under reduced pressure to provide 13.22g in 96% as a brown oil. The oil was used without further purification for the next step.

(S)-methyl 3-(3-chlorophenyl)-3-hydroxypropanoate(19)

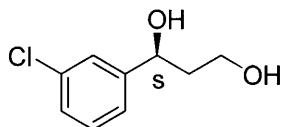


19

The flask was flushed with nitrogen and charged with formic acid (9.8g). Triethylamine (5.38g) was added slowly with stirring at 0 °C. After the addition was complete, the solution was stirred with the ice bath applied for 20 min., then at ambient temperature for an additional 1 h. The flask was charged sequentially with methyl 3-(3-chlorophenyl)-3-oxopropanoate (11.3 g), DMF (45mL) and (S,S)-Ts-DPEN-Ru-C1-(p-cymene) (68mg). The resulting solution was stirred overnight at 60 °C. The reaction solution was cooled to ambient temperature, quenched with H₂O, extracted with EA. The organic layer was washed with brine, dried over anhydrous Na₂SO₄, concentrated in vacuo. The crude material was purified by flash chromatography (elution with EtOAc : Petroleum Ether = 1:10) to yield 10.434g in 91% as a orange-red oil.

¹H NMR (300 MHz, CDCl₃) 7.45 (s, 1H), 7.37-7.27 (m, 3H), 5.16 (t, J = 6.9 Hz, 1H), 3.78 (s, 3H), 2.78 (d, J = 1.8 Hz, 1H), 2.76 (s, 1H).

(S)-1-(3-chlorophenyl)propane-1,3-diol(20)

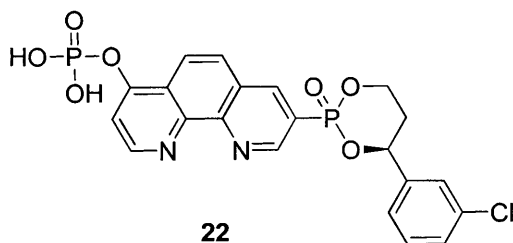


20

The flask was flushed with nitrogen and charged sequentially with sodium borohydride (1.84 g), 1-butanol (37.5 mL), and water (0.62 mL). The crude hydroxyester **19** (10.4 g) was dissolved in 1-butanol (3.8 mL) and was added slowly at 0 °C. After addition was complete, the mixture was stirred for 0.5 h. The resulting solution was stirred for 4 h at 90 °C. The reaction solution was cooled to ambient temperature and was quenched with aqueous potassium carbonate solution (10 wt/vol %, 23 mL) and the mixture was stirred for 10 min. The layers were separated and the butanol phase was washed with aqueous potassium carbonate solution (10 wt/vol %, 8 mL) and brine (8 mL), dried over anhydrous Na₂SO₄, concentrated in vacuo. The crude material was purified by flash chromatography (elution with DCM : CH₃OH = 30:1) to yield 7.75 g in 85.5% as a yellow oil.

¹H NMR (300 MHz, CDCl₃) δ 7.36 (s, 1H), 7.30-7.20 (m, 3H), 4.92 (q, J = 4.5 Hz, 1H), 3.90-3.79 (m, 2H), 2.82 (s, 2H), 2.03-1.85 (m, 2H).

3-(4S-4-(3-chlorophenyl)-1,3,2-dioxaphospin-2-on-2-yl)-1,10-phenanthroline-7-yl phosphoric acid (22)



22

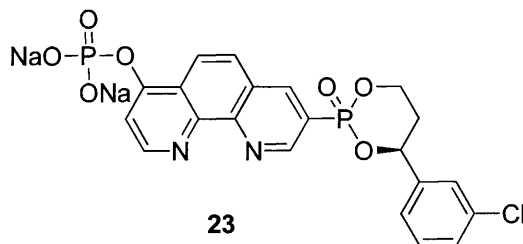
To a solution of phenanthroline **16c** (2 g) in dichloromethane (100 mL), triethylamine (2 mL) and 4-dimethylamino pyridine (54 mg) were added. The reaction mixture was stirred in ice bath, diethyl chlorophosphate (2 mL) in dichloromethane (20 mL) was added. The mixture was allowed to react for one hour in ice bath and 2 hours at room temperature. The reaction was quenched with brine. The aqueous layer was extracted with dichloromethane. The organic layers were combined, dried over anhydrous sodium sulfate, concentrated in vacuo. The crude material was purified by flash

chromatography to yield **21** 1.7 g. Trimethylsilyl bromide (4 mL) was added to the solution of Diethyl phosphate **21** (1.7 g) in dichloromethane (2 mL) in ice bath. After 1 hr in ice bath, diethyl ether (50 mL) was added to the reaction mixture. The resulting mixture was filtered, cake was collected and stirred in methanol for 10 minutes. The solvent was evaporated and residue was purified by flash chromatography to give **22** 600 mg in 25% yield as a white solid.

m/z:507.0[M+1];

¹H NMR (300 MHz, dmso) 13.84 (m, 1H), 9.27 (dd, J = 4.8, 1.8 Hz, 1H), 8.99 (dd, J = 14.3, 1.8 Hz, 1H), 8.39 (d, J = 7.1 Hz, 1H), 8.30 (d, J = 8.9 Hz, 1H), 8.13 (d, J = 9.0 Hz, 1H), 7.50 (s, 1H), 7.45 – 7.38 (m, 1H), 7.35 – 7.25 (m, 2H), 6.85 (d, J = 7.1 Hz, 1H), 5.35 (dd, J = 9.0, 5.9 Hz, 1H), 4.11 – 3.98 (m, 2H), 2.68 – 2.55 (m, 1H), 2.50 – 2.34 (m, 1H).

Disodium 3-(4S-4-(3-chlorophenyl)-1,3,2-dioxaphospin-2-on-2-yl)-1,10-phenanthrolin-7-yl phosphate (23)



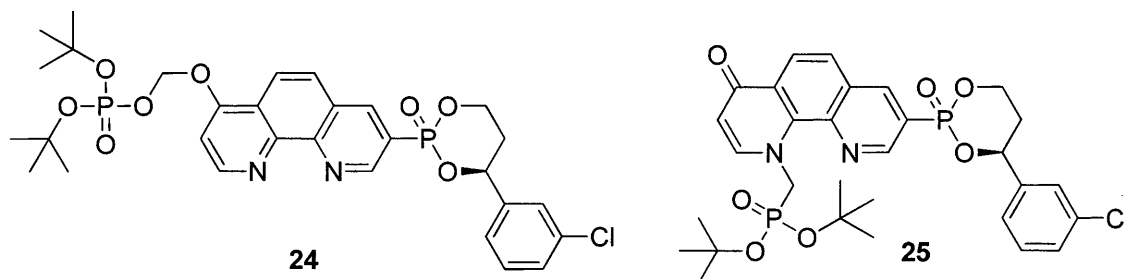
Phosphoric acid **22** (500 mg) was mixed with methanol (10 mL), 1N NaHCO₃ solution (2 mL) was added to the mixture slowly. The reaction mixture was allowed to stir for 20 minutes, the solvent was evaporated to collect disodium salt **23** 540 mg in 100% yield as a white solid.

m/z:550.0[M+1], found 507;

¹H NMR (300 MHz, dmso) 9.27 (dd, J = 4.8, 1.8 Hz, 1H), 8.99 (dd, J = 14.3, 1.8 Hz, 1H), 8.39 (d, J = 7.1 Hz, 1H), 8.30 (d, J = 8.9 Hz, 1H), 8.13 (d, J = 9.0 Hz, 1H), 7.50 (s, 1H), 7.45 – 7.38 (m, 1H), 7.35 – 7.25 (m, 2H), 6.85 (d, J = 7.1 Hz, 1H), 5.35 (dd, J = 9.0, 5.9 Hz, 1H), 4.11 – 3.98 (m, 2H), 2.68 – 2.55 (m, 1H), 2.50 – 2.34 (m, 1H).

(3-(4S-4-(3-chlorophenyl)-1,3,2-dioxaphospin-2-on-2-yl)-1,10-phenanthrolin-7-one)-7-methyl di-*t*-butyl phosphate (24) and (3-(4S-4-(3-chlorophenyl)-1,3,2-

dioxaphospin-2-on-2-yl)-1,10-phenanthroline-7-one)-10(7H)-methyl di-*t*-butyl phosphate (25)



To a solution of phenanthroline **16c** (200 mg) in DMSO (2 mL), potassium carbonate (195 mg) was added. The resulting mixture was stirred for 15 minutes under 30 °C. Di-*t*-butyl chloromethyl phosphate (146 mg) was added to the reaction mixture and stirred overnight. The reaction was quenched with brine, the aqueous layer extracted with dichloromethane. The organic layers were combined, dried over sodium sulfate, concentrated and purified by flash chromatography to yield intermediate **24** and **25**.

m/z : 649.2[M+1];

O-alkylated phenanthroline **24**:

^1H NMR (300 MHz, dmso) 9.48 (dd, J = 4.9, 1.9 Hz, 1H), 9.14 (dd, J = 15.4, 1.9 Hz, 1H), 9.10 (d, J = 5.3 Hz, 1H), 8.31 (d, J = 9.1 Hz, 1H), 7.63–7.58 (m, 2H), 7.55–7.41 (m, 3H), 6.11–5.91 (m, 3H), 4.92–4.75 (m, 1H), 4.71–4.53 (m, 1H), 2.73–2.55 (m, 1H), 2.36–2.19 (m, 1H), 1.37 (s, 18H)

^{13}C NMR (75 MHz, dmso) 158.59, 151.37, 150.71, 150.54, 147.15, 146.18, 142.12, 142.01, 141.71, 133.29, 130.57, 128.41, 126.26, 125.79, 124.59, 121.53, 120.83, 106.97, 87.59, 82.98, 77.56, 66.24, 33.30, 29.38

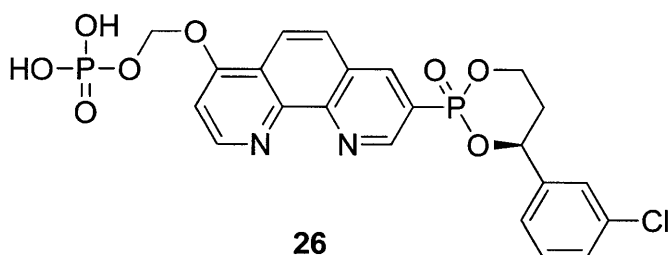
N-alkylated phenanthroline **25**:

^1H NMR (300 MHz, dmso) 9.39 (dd, J = 4.6, 2.1 Hz, 1H), 9.19 (dd, J = 15.6, 2.0 Hz, 1H), 8.43 (d, J = 8.7 Hz, 1H), 8.22 (d, J = 8.1 Hz, 1H), 8.18 (d, J = 8.4 Hz, 1H), 7.58 (s, 1H), 7.50–7.44 (m, 3H), 7.18–6.99 (m, 2H), 6.49 (d, J = 7.9 Hz, 1H), 5.98 (d, J = 11.2 Hz, 1H), 4.93–4.72 (m, 1H), 4.69–4.49 (m, 1H), 2.72–2.52 (m, 1H), 2.34–2.19 (m, 1H), 1.21 (s, 9H), 1.19 (s, 9H).

^{13}C NMR (75 MHz, dmso) 176.22, 148.52, 147.50, 142.91, 141.99, 141.88,

136.23, 133.28, 130.54, 129.08, 128.91, 128.46, 125.72, 125.00, 124.60, 124.08, 121.52, 112.53, 82.30, 80.38, 77.54, 66.52, 33.21, 29.16.

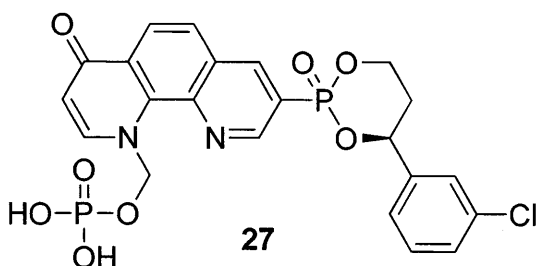
(3-(4S-4-(3-chlorophenyl)-1,3,2-dioxaphospin-2-on-2-yl)-1,10-phenanthrolin-7-one)-7-methyl phosphoric acid (26)



O-alkylated phenanthroline 24 (50 mg) was dissolved in dichloromethane, TFA (1 mL) was added to the solution at room temperature. The reaction was stirred for 30 minutes at room temperature. The solvent was evaporated, methanol (1 mL) was added to the residue, and the mixture was filtered to afford phosphoric acid **26** as solid.

¹H NMR (300 MHz, dmsO) 9.46 (dd, J = 5.0, 1.8 Hz, 1H), 9.23 – 9.05 (m, 2H), 8.37 – 8.21 (m, 2H), 7.68 (d, J = 5.6 Hz, 1H), 7.56 (s, 1H), 7.51 – 7.36 (m, 3H), 6.12 – 5.90 (m, 3H), 4.90 – 4.74 (m, 1H), 4.71 – 4.50 (m, 1H), 2.71 – 2.54 (m, 1H), 2.33 – 2.21 (m, 1H)

(3-(4S-4-(3-chlorophenyl)-1,3,2-dioxaphospin-2-on-2-yl)-1,10-phenanthrolin-7-one)-10(7H)-methyl phosphoric acid (27)



N-alkylated phenanthroline 25 (50 mg) was dissolved in dichloromethane, TFA (1 mL)

was added to the solution at room temperature. The reaction was stirred for 30 minutes at room temperature. The solvent was evaporated, methanol (1 mL) was added to the residue, and the mixture was filtered to afford phosphoric acid **27** as solid.

¹H NMR (300 MHz, dmsO) δ 9.38 (dd, J = 4.5, 2.0 Hz, 1H), 9.13 (dd, J = 15.6, 2.0 Hz, 1H), 8.40 (d, J = 8.7 Hz, 1H), 8.19 (d, J = 8.3 Hz, 1H), 8.13 (d, J = 8.7 Hz, 1H), 7.58 (s, 1H), 7.54 – 7.35 (m, 3H), 7.04 (t, J = 9.9 Hz, 1H), 6.91 (t, J = 9.8 Hz, 1H), 6.43 (d, J = 7.8 Hz, 1H), 5.95 (d, J = 10.8 Hz, 1H), 4.88 – 4.76 (m, 1H), 4.69 – 4.45 (m, 1H), 2.74 – 2.56 (m, 1H), 2.31 – 2.22 (m, 1H).

Example 2. Clone, expression and purification of human recombinant P4H

Human recombinant P4H was expressed in *E. coli*. Briefly, DNA encoding the signal sequence of P4H was cloned into pET28_N-His_TEV, the resulting plasmid pET28_N-His_TEV_P4HA1/PDI was transferred to *E. coli* Origami2(DE3) and co-expressed. The enzyme obtained was purified by MonoQ ion-exchange column, TEV digested and confirmed by MS, passed through Histrap HP column, finally purified by Hiload16/60 superdex200 column.

Example 3. Assays of enzymatic activity

Assays were performed at 25°C in 100mM Tris (pH7.0), 0.1mM (NH₄)₂Fe(SO₄)₂, 0.1 mM ascorbic acid, 0.2 mM CoA, 0.2mM ATP, 0.5uM succinyl CoA synthase, 100uM 2-oxoglutarate, 100uM (Pro-Pro-Gly)₁₀peptide, 50nM P4H enzyme, 50ul total. After 45min reaction, 10ul MLG R1 was added and reacted for 10min, 10ul MLG R2 was added and reacted for 20min. 2-Oxoglutarate will react with polypeptide under catalysis of P4H, the product succinic acid will react with succinyl CoA synthase to give phosphate. The phosphate level could be determined by MLG, green product (MG⁺) (H₂PMo12O₄₀) was detected at OD 630 nm, from which P4H enzyme activity could be determined.

The compound inhibition assays were performed in duplicates. Phenanthrolinephosphonic acid **9c** was added before the addition of P4H enzyme in

following concentrations: 0.01, 0.03, 0.1, 0.3, 1, 3, 30, 100, 300 nM. The data was analyzed by Prism. IC₅₀ of compound 9c is 8.1 μ M (Figure 1) .

Example 4. Pharmacokinetic studies of 16c and 27 in rats:

Wistar rats (200 $\pm$ 20 g) were divided into 2 groups, 6 each, half female and half male in each group. The first group was given compound 16c 3 mg $\cdot$ kg⁻¹ intravenously. The second group was orally administered disodium salt of compound 27 (39 mg $\cdot$ kg⁻¹). Blood (0.3 mL) was collected from retroorbital vein at time point 0 h, 0.08 h, 0.17 h, 0.33 h, 0.5 h, 0.75 h, 1 h, 1.5 h, 2 h, 3 h, 5 h, 7 h, placed into cold heparinized Eppendorf tubes. The samples were centrifuged at 4°C (15000 rpm) for 5 min. Transfer 100 μ L plasma sample to -80°C freezer for test.

Quantitative LC-MS/MS analysis methods of compound 9c and compound 16c in plasma were set up, using diazepam and mildronate as internal standard, respectively. (Prodrug 27 was not detected under experimental condition) Drug levels in plasma were tested. (Table 1 and Figure 2) .

Table 1: Levels of 16c in plasma after compound 16c iv dosing and compound 27 PO dosing

Compound	Route of administration	C _{max} * (ng $\cdot$ mL ⁻¹)	t _{1/2} ** (h)	AUC _{0-t} *** (μ g $\cdot$ h $\cdot$ L ⁻¹)	AUC _{0-∞} **** (μ g $\cdot$ h $\cdot$ L ⁻¹)
16c	IV	1617.80	1.50	2064.58	2136.40
27	PO	1440	2.79	5235.70	6805.74

* C_{max} Peak concentration in plasma

** t_{1/2} half life of drug in plasma

*** AUC_{0-t} Area under concentration-time curve until final test time

**** AUC_{0- ∞} Area under concentration-time curve until total clearance of drug

Oral Bioavailability:

Oral Bioavailability was calculated according to the drug level of compound 16c in plasma. Area under concentration-time curve (AUC) of PO dosing was divided by AUC of iv dosing of same amount of drugs, expressed as absorption percentage:

Bioavailability (F) = $\text{AUC}_{\text{po}} \cdot \text{M}_{\text{iv}} / \text{AUC}_{\text{iv}} \cdot \text{M}_{\text{po}} \times 100\%$. Wherein, M_{iv} means the molar concentration of drugs by iv dosing, and M_{po} means the molar concentration of drugs by PO dosing.

Based on the concentration of 16c in plasma, the oral bioavailability of compound 27 (F) is 25.4%.

Drug levels of 16c and 9c in liver:

16 Wistar rats (200 ± 20 g), were divided into 4 groups randomly, female and male each half in each group. After PO dosing of compound 27 ($39 \text{ mg} \cdot \text{kg}^{-1}$), one group was sacrificed at each time point 15 min, 45 min, 8 h, 24 h. Liver samples were collected, washed off blood with saline, cut into small pieces. 1 g was weighed, added into 1 mL Methanol/water, homogenated, additional 1 mL methanol/water was added, followed by sonication for 15 seconds, centrifuged (4500 rpm) for 10 minutes. The upper clear solution was tested using LC-MS/MS method for compound 16c and 9c concentrations at different time points (table 2). Prodrug 27 converted to 16c in rat after PO dosing, and 16c converted to parent drug 9c in liver.

Table 2: Drug levels of 16c and 9c ($\text{ng} \cdot \text{g}^{-1}$) in liver at different time points after oral administration of compound 27

	0.25h	0.75h	8h	24h
16c	521.50	662.5	584.50	50.88
9c	16.13	64.25	44.68	3.55

Example 5. Bile Duct Ligation Model study:

This experiment used Bile Duct Ligation to induce liver fibrosis model in rats. Treatment of BDL rats with PO dosing prodrug 27 was studied.

Briefly, Wistar rats (200 ± 20 g) were divided into 3 groups, half female and half male in each group:

SHAM group: 6 rats were anaesthetized, the common bile duct was exposed by an upper abdominal midline incision of 1 cm. Muscle and skins were sutured separately.

MODEL group: 12 rats were anaesthetized, the common bile duct was exposed by an upper abdominal midline incision of 1 cm and was ligated twice and resected between the ligature. Muscle and skins were sutured separately.

Dosing group: 12 rats were anaesthetized, the common bile duct was exposed by an upper abdominal midline incision of 1 cm and was ligated twice and resected between the ligature. Muscle and skins were sutured separately. Disodium salt of compound 27 (30mg/kg) was dissolved in water and dosed orally to the rats once per day.

Endpoint outcome measures:

After 2 weeks, liver enzymes (ALT and AST)

After 2 weeks, Histology of liver slices

The influence of compound 27 on liver enzymes (ALT and AST) of fibrotic rats:

BDL significantly increase liver enzymes (ALT and AST). After 2 weeks oral administration of compound 27, BDL induced ALT and AST were significantly decreased (**P<0.01, Table 3 and Table 4) .

Table3: Compound 27 decreased BDL induced ALT (IU/L)

groups	ALT in serum	ALT in liver
SHAM	67.1±5.45	68.2±8.33
MODEL	144.4±15.94	136.8±16.48
Compound 27 (30mg/kg)	74.4±17.82**	76.4±11.35**

**P<0.01, compared to MODEL group

Table 4: Compound 27 decreased BDL induced AST (IU/L)

groups	AST in serum	AST in liver
SHAM	67.7±4.67	67.40±5.28
MODEL	207.2±30.96	198.75±27.70
Compound 27 (30mg/kg)	87.2±12.51**	91.42±8.79**

**P<0.01, compared to MODEL group

Compound 27 decreased fibrotic conditions in BDL rats:

H&E staining results as follow:

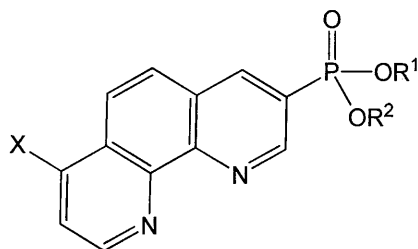
Sham group: depicted in Figure 3, normal structure

Model group: depicted in Figure 4, normal structure of hepatocytes destroyed, lots of inflammatory cells infiltration, liver bile duct proliferation, fibrils proliferation.

Dosing group: depicted in Figure 5, pathological changes of fibrosis prevented.

WHAT IS CLAIMED IS:

1. A compound of formula (I) or formula (II):



(I)

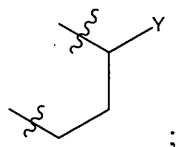
or a pharmaceutically acceptable salt thereof,

wherein:

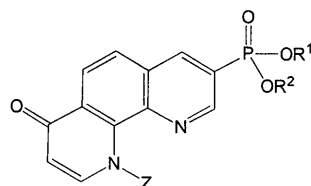
X is $-Cl$, $-OR^3$;

R^1 , R^2 is independently selected from H, C_1 - C_6 alkyl, $-CH_2OCO-(C_1-C_6$ alkyl), $-CH_2OCOO-(C_1-C_6$ alkyl);

or R^1 and R^2 join to form a group having the formula:



Y is aryl, heteroaryl;



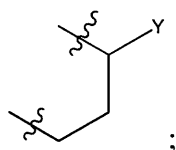
(II)

wherein:

Z is $-H$, $-CH_2OPO(OH)_2$;

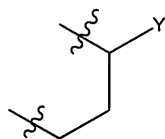
R^1 , R^2 is independently selected from H, C_1 - C_6 alkyl, $-CH_2OCO-(C_1-C_6$ alkyl), $-CH_2OCOO-(C_1-C_6$ alkyl);

or R^1 and R^2 join to form a group having the formula:



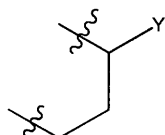
Y is aryl, heteroaryl.

2. The compound of formula I in claim 1, wherein X is -OH .
3. The compound of formula I in claim 1, wherein X is -OPO(OH)_2 .
4. The compound of formula I in claim 1, wherein X is $\text{-OCH}_2\text{OPO(OH)}_2$.
5. The compound of formula I in claim 1, wherein $\text{R}^1 = \text{R}^2 = \text{H}$.
6. The compound of formula I in claim 1, wherein R^1 and R^2 together form a group having the formula:



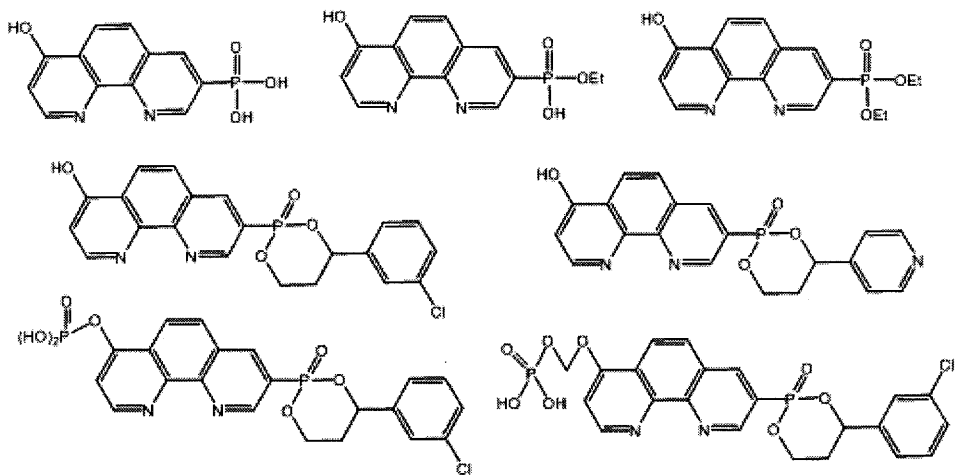
Y is aryl.

7. The compound of formula I in claim 1, wherein R^1 and R^2 together form a group having the formula:

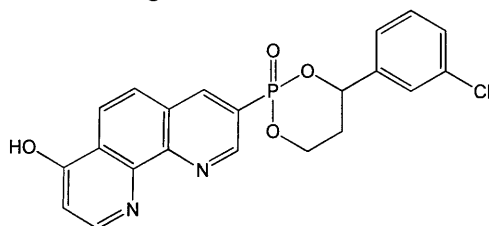


Y is heteroaryl.

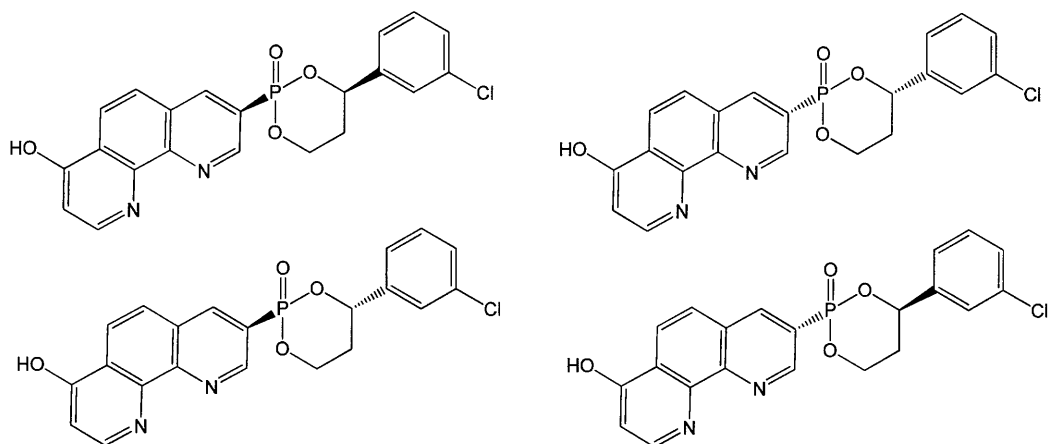
8. The compound of formula I in claim 1 having the structure:



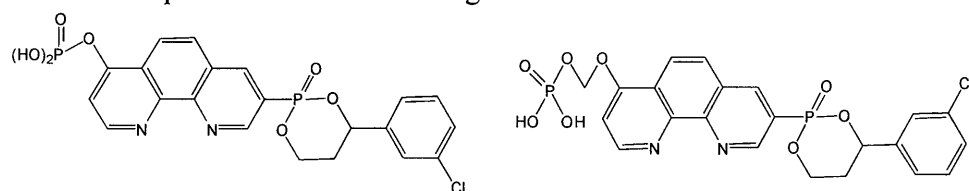
9. The compound of claim 8 having the structure:



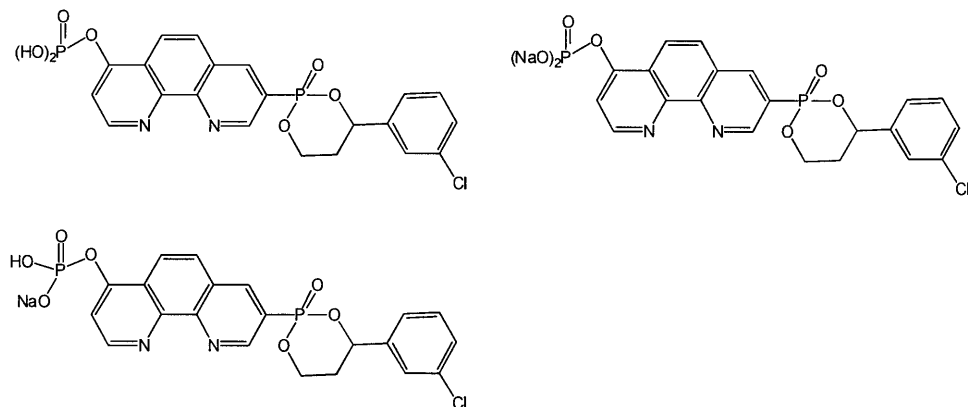
10. The compound of claim 9 having the structure:



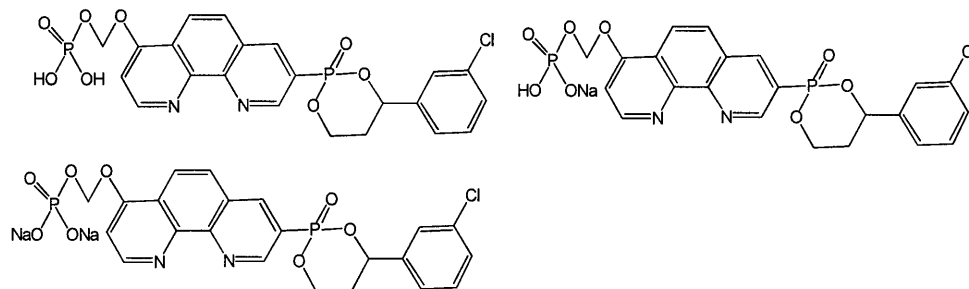
11. The compound of claim 10 having the structure:



12. The compound of claim 11 having the structure:



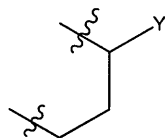
13. The compound of claim 11 having the structure:



14. The compound of Formula II in claim 1, wherein Z is $-\text{CH}_2\text{OPO}(\text{OH})_2$.

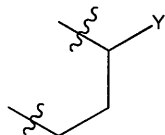
15. The compound of formula II in claim 1, wherein $\text{R}^1 = \text{R}^2 = \text{H}$.

16. The compound of formula II in claim 1, wherein R^1 and R^2 together form a group having the formula:



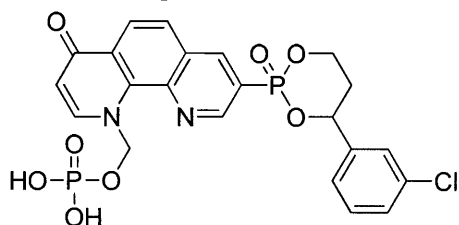
Y is aryl.

17. The compound of formula II in claim 1, wherein R¹ and R² together form a group having the formula:

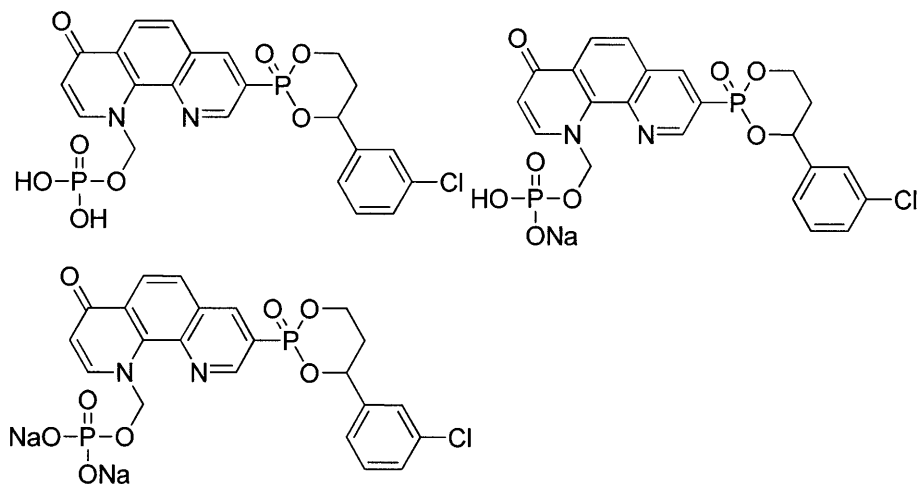


Y is heteroaryl.

18. The compound of formula II in claim 1 having the structure:



19. The compound of claim 18 having the structure:



20. The application of a compound of claim 1-19 and pharmaceutically acceptable salts thereof as collagen prolyl-4-hydroxylase inhibitors.

21. The application of a compound of claim 1-19 and pharmaceutically acceptable salts thereof in the preparation of drugs for preventing or treating collagen prolyl-4-hydroxylase related disease.

22. The application of a compound of claim 1-19 and pharmaceutically acceptable salts thereof in the preparation of drugs for preventing or treating fibro proliferative disease.

23. The application of a compound of claim 1-19 and pharmaceutically acceptable salts thereof in the preparation of drugs for preventing or treating liver fibrosis.

24. The application of a compound of claim 1-19 and pharmaceutically acceptable salts thereof in the preparation of drugs for protecting liver functions.