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<p>(54) Title: THIAZOLINE ACID DERIVATIVES</p>		
<p>(57) Abstract</p> <p>Phenyl- and pyridyl-substituted thiazoline acid derivatives useful in diagnosing and treating pathological conditions associated with an excess of trivalent metals in humans and animals.</p>		

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THIAZOLINE ACID DERIVATIVES**BACKGROUND OF THE INVENTION**

Research leading to the completion of the invention was supported in part by Grant Nos. 3203522-12, R01HL42817 and R01DK49108 awarded by the National Institutes of Health (NIH).
5 The United States Government has certain rights in and to the claimed invention.

Related Applications

This application contains subject matter related to that disclosed and claimed in copending U.S. Patent Application
10 Serial No. 08/624,289 filed March 29, 1996.

Field of the Invention

The present invention relates to novel thiazoline acids and derivatives thereof useful as chelators of trivalent metals in therapeutic applications.

Discussion of the Prior Art

15 While many organisms are auxotrophic for Fe (III), because of the insolubility of the hydroxide ($K_{sp} = 1 \times 10^{-38}$) [Acc. Chem. Res., Vol. 12, Raymond et al, "Coordination Chemistry and Microbial Iron Transport," pages 183-190 (1979)]
20 formed under physiological conditions, nature has developed

rather sophisticated iron storage and transport systems. Microorganisms utilize low molecular weight ligands, siderophores, while eukaryotes tend to utilize proteins to transport iron, e.g., transferrin, and store iron, e.g., ferritin [5 Trends in Biochem. Sci., Vol. 11, Bergeron, "Iron: A Controlling Nutrient in Proliferative Processes," pages 133-136 (1986)].

Iron metabolism in primates is characterized by a highly efficient recycling process with no specific mechanism for eliminating this transition metal [10 Clin. Physiol. Biochem., Vol. 4, Finch et al, "Iron Metabolism," pages 5-10 (1986); Ann. Rev. Nutri., Vol. 1, Hallberg, "Bioavailability of Dietary Iron in Man," pages 123-147 (1981); N. Engl. J. Med., Vol. 306, Finch et al, "Perspectives in Iron Metabolism," pages 1520-1528 (1982); and Medicine (Baltimore), Vol. 15 49, Finch et al, "Ferrokinetics in Man," pages 17-53 (1970)]. Because it cannot be effectively cleared, the introduction of "excess iron" into this closed metabolic loop leads to chronic overload and ultimately to peroxidative tissue damage [20 The Molecular Basis of Blood Diseases, Seligman et al, "Molecular Mechanisms of Iron Metabolism," page 219 (1987); Biochem. J., Vol. 229, O'Connell et al, "The Role of Iron in Ferritin- and Haemosiderin-Mediated Lipid Peroxidation in Liposomes," pages 135-139 (1985); and J. Biol. Chem., Vol. 260, Thomas et al, 25 "Ferritin and Superoxide-Dependent Lipid Peroxidation," pages

3275-3280 (1985)]. There are a number of scenarios which can account for "iron overload," e.g., high-iron diet, acute iron ingestion or malabsorption of the metal. In each of these situations, the patient can be treated by phlebotomy [Med. Clin. N. Am., Vol. 50, Weintraub et al, "The Treatment of Hemochromatosis by Phlebotomy," pages 1579-1590 (1966)]. However, there are iron-overload syndromes secondary to chronic transfusion therapy, e.g., aplastic anemia and thalassemia, in which phlebotomy is not an option [Iron in Biochemistry and Medicine, Vol. II, Hoffbrand, "Transfusion Siderosis and Chelation Therapy," page 499 (London, 1980)]. The patient cannot be bled, as the origin of the excess iron is the transfused red blood cells; thus, the only alternative is chelation therapy. However, to be therapeutically effective, a chelator must be able to remove a minimum of between 0.25 and 0.40 mg of Fe/kg per day [Semin. Hematol., Vol. 27, Brittenham, "Pyridoxal Isonicotinoyl Hydrazone: An Effective Iron-Chelator After Oral Administration," pages 112-116 (1990)].

Although considerable effort has been invested in the development of new therapeutics for managing thalassemia, the subcutaneous (sc) infusion of desferrioxamine B, a hexacoordinate hydroxamate iron chelator produced by Streptomyces pilosus [Helv. Chim. Acta, Vol. 43, Bickel et al, "Metabolic Properties of Actinomycetes. Ferrioxamine B," pages 2129-2136 (1960)], is still the protocol of choice. Although the drug's

efficacy and long-term tolerability are well-documented, it suffers from a number of shortcomings associated with low efficiency and marginal oral activity.

Although a substantial number of synthetic iron
5 chelators have been studied in recent years as potential orally active therapeutics, e.g., pyridoxyl isonicotinoyl hydrazone (PIH) [FEBS Lett., Vol. 97, Ponka et al, "Mobilization of Iron from Reticulocytes: Identification of Pyridoxal Isonicotinoyl Hydrazone as a New Iron Chelating Agent," pages
10 317-321 (1979)], hydroxypyridones [J. Med. Chem., Vol. 36, Uhlir et al, "Specific Sequestering Agents for the Actinides. 21. Synthesis and Initial Biological Testing of Octadentate Mixed Catecholate-hydroxypyridinonate Ligands," pages 504-509 (1993); and Lancet, Vol. 1, Kontoghiorghes et al, "1,2-Dimethyl-3-hydroxypyrid-4-one, an Orally Active Chelator for
15 the Treatment of Iron Overload," pages 1294-1295 (1987)] and bis(o-hydroxybenzyl)-ethylenediaminediacetic acid (HBED) analogues [Ann. N.Y. Acad. Sci., Vol. 612, Grady et al, "HBED: A Potential Oral Iron Chelator," pages 361-368 (1990)], none
20 has yet proven to be completely satisfactory. Interestingly, the siderophores have remained relatively untouched in this search. Their evaluation as iron-clearing agents has not at all paralleled the rate of their isolation and structural elucidation. In fact, until recently, beyond DFO, only two or
25 some 100 siderophores identified have been studied in animal

models: enterobactin [Gen. Pharmac., Vol. 9, Guterman et al, "Feasibility of Enterochelin as an Iron-Chelating Drug: Studies with Human Serum and a Mouse Model System," pages 123-127 (1978)] and rhodotorulic acid [J. Pharmacol. Exp. Ther., Vol. 209, Grady et al, "Rhodotorulic Acid-Investigation of its Potential as an Iron-Chelating Drug," pages 342-348 (1979)]. While the former was only marginally effective at clearing iron, the latter compound was reasonably active. Unfortunately, both of these cyclic siderophores exhibited unacceptable toxicity, and neither possessed any oral activity. They were abandoned as there were any number of synthetic chelators with equally unsatisfactory properties from which to choose.

U.S. Patent Application Serial No. 08/624,289 filed March 29, 1996, the entire contents and disclosure of which are incorporated herein by reference, discloses certain 2-pyridyl- Δ^2 -thiazoline-4-carboxylic acids and derivatives thereof useful for the treatment of human and non-human animals in need of therapy entailing the prevention of deposition of trivalent metals and compounds thereof in their tissues, as well as the elimination of such metals and compounds from biological systems overloaded therewith.

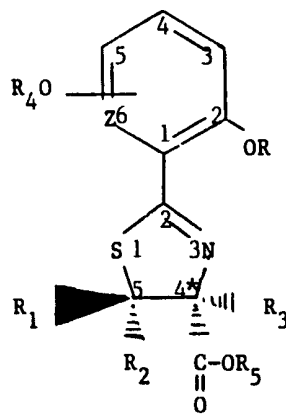
It is an object of the present invention to provide additional novel thiazoline acids and derivatives thereof which, because of different volumes of distribution is

patients and different lipophilicities than the derivatives of the prior art, provide the ability to control the pharmacokinetic properties and toxicities of the drugs.

Another object of the present invention is to provide novel pharmaceutical compositions for and methods of treatment of human and non-human animals in need of therapy entailing the prevention of deposition of trivalent metals and compounds thereof in tissues thereof, as well as the elimination of such metals and compounds from systems overloaded therewith.

SUMMARY OF THE INVENTION

The above and other objects are realized by the present invention, one embodiment of which comprises compounds of the formula:



wherein: Z is CH or N;

R is H or acyl;

R₁, R₂, R₃ and R₅ may be the same or different and represent H, alkyl or hydrocarbyl arylalkyl having up to 14
5 carbon atoms; and

R₄ is H or alkyl having 1-4 carbon atoms;

a salt thereof with a pharmaceutically acceptable acid or a pharmaceutically acceptable complex thereof.

Another embodiment of the invention relates to
10 pharmaceutical compositions in unit dosage form comprising a therapeutically effective amount of the above compound and a pharmaceutically acceptable carrier therefor.

An additional embodiment of the invention concerns
15 methods of preventing or treating a pathological condition in a human or non-human animal that is associated with an excess of a trivalent metal, ion or compound thereof comprising administering to the animal a therapeutically effective amount of the compound defined above.

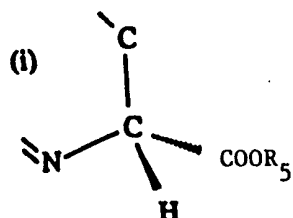
BRIEF DESCRIPTION OF THE DRAWING

Fig. 1 depicts a reaction scheme for preparing the compounds of the invention.

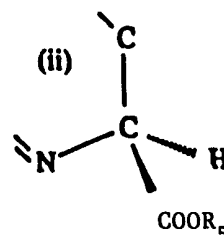
DETAILED DESCRIPTION OF THE INVENTION

5 The present invention is predicated on the discovery that compounds of the above formula are valuable bioactive chelators or sequestrants for trivalent metals such as Fe, Al and Cr. They can be administered to human and non-human mammals to prevent the deposition of, e.g., iron, in the
10 tissues thereof. They are also useful for the elimination of, e.g., iron, from such mammals afflicted with, e.g., haemochromatosis, haemosiderosis and also cirrhosis. They also find application in dialysis, encephalopathy, osteomalacia and Alzheimer's disease.

15 The compounds described above are characterized by the asymmetric carbon atom marked with an asterisk (*). The bonds surrounding these carbon atoms are arranged tetrahedrally and the substituents thus bonded to the asymmetric carbon atoms are in fixed positions. The formula represents
20 optical antipodes exhibiting either the (S) or (R) conformation as shown in (i) and (ii) below:



(S) conformation



(R) conformation

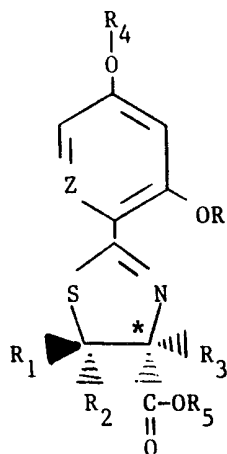
In the above formula, R is preferably H, but may also be a suitable acyl group which is cleavable under physiological conditions to the free hydroxyl compounds and a biologically acceptable acid. Such acyl groups are known in the art, e.g., the acyl radical of a carbonic acid semiester, in particular carbonic acid semi-C₁-C₄-alkyl ester or carbonic acid semi-oxaalkyl ester in which oxaalkyl has 4-13 chain members such as an acyl radical -C(=O)-(O-CH₂-CH₂)_n-O-Alk in which n is an integer from 0 to 4 and Alk represents C₁-C₄ alkyl, in particular methyl or ethyl. Such acyl groups are, for example, methoxycarbonyl, ethoxycarbonyl or 2-(methoxyethoxy)-ethoxycarbonyl. Further acyl radicals are, for example, C₁-C₃-alkanoyl such as acetyl or propionyl, or mono-substituted or di-substituted carbamoyl such as di-C₁-C₄-alkyl carbamoyl, for example, dimethylcarbamoyl or diethylcarbamoyl,

or C₁-C₄-alkoxycarbonyl-C₁-C₄-alkylcarbamoyl, for example, methoxycarbonylmethylcarbamoyl, ethoxycarbonylmethylcarbamoyl or 2-ethoxycarbonylethylcarbamoyl.

5 R₁, R₂, R₃ and R₅ may be the same or different and may be H, straight or branched chain alkyl having up to 14 carbon atoms, e.g., methyl, ethyl, propyl and butyl or arylalkyl wherein the aryl portion is hydrocarbyl and the alkyl portion is straight or branched chain, the arylalkyl group having up to 14 carbon atoms.

10 R₄ is H or straight or branched chain alkyl having 1 to 4 carbon atoms, e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl.

Preferred among compounds of the above formula are those of the formula:



wherein: Z, R, R₁, R₂, R₃, R₄ and R₅ have the meanings ascribed above, as well as salts thereof with pharmaceutically acceptable acids and pharmaceutically acceptable complexes thereof.

Particularly preferred are those compounds of the above formula wherein:

a. Z is CH and R = R₁ = R₂ = R₃ = R₄ = R₅ = H;

b. Z is N and R = R₁ = R₂ = R₃ = R₄ = R₅ = H;

and most preferably, the optically pure isomers thereof.

It will be understood that salts of the compounds of the above formula with pharmaceutically acceptable acids also comprise part of the present invention. Suitable such acids include hydrochloric, sulfuric or phosphoric acids, as well as methanesulfonic, arginine, lysine, and the like.

The invention also includes pharmaceutically acceptable salts of the carboxylic acids of the above formula. Thus, ammonium salts and metal salts such as the alkali metal and alkaline earth metals salts, e.g., sodium, potassium, magnesium or calcium salts, as well as divalent metal salts such as zinc, and salts with suitable organic amines, there coming into consideration such salt formation especially aliphatic, cycloaliphatic, cycloaliphatic-aliphatic or araliphatic primary, secondary or tertiary mono-, di- or poly-amines, and also heterocyclic bases. Such amines are, for example, lower

alkylamines, for example, triethylamine, hydroxy-lower alkyl-
amines, for example, 2-hydroxyethylamine, bis-(2-hydroxy-
ethyl)-amine or tris-(2-hydroxyethyl)-amine, basic aliphatic
esters of carboxylic acids, for example, 4-aminobenzoic acid
5 2-diethylaminoethyl ester, lower alkyleneamines, for example,
1-ethylpiperidine, cycloalkylamines, for example, dicyclo-
hexylamine, or benzylamines, for example, N,N'-dibenzyl-
ethylenediamine, also bases of the pyridine type, for example,
pyridine, collidine or quinoline. Further salts include
10 internal salts (zwitterionic forms of compounds of the inven-
tion), wherein a basic group, for example, the basic nitrogen
atom present in the pyridine ring, is protonated by a hydrogen
ion originating from an acid group in the molecule.

Owing to their high solubility and good tolerabil-
15 ity, metal ion complexes of compounds of the above formulae,
especially with suitable paramagnetic and/or radioactive
metals, can be used as contrast agents in diagnostic medicine,
for example, X-ray, radionuclide, ultrasound and/or magnetic
resonance diagnostics.

20 Compounds of the above formulae may be synthesized
according to the reaction scheme set forth in Fig. 1 wherein
D-cys is D-cysteine or a reactive functional derivative
thereof.

Free hydroxy groups present in the compounds of the above formulae are optionally protected by conventional protecting groups. Such protecting groups protect the hydroxy groups from undesired condensation reactions, substitution reactions and the like. The protecting groups can be introduced and removed easily, i.e., without undesirable secondary reactions taking place, for example, by solvolysis or reduction, in a manner known per se. Protecting groups and the methods by which they are introduced and split off are described, for example, in "Protective Groups in Organic Chemistry," Plenum Press, London, New York (1973) and also in "Methoden der organischen Chemie," Houben-Weyl, 4th edition, Vol. 15/1, Georg Thieme Verlag, Stuttgart (1974).

Suitable hydroxy-protecting groups are, for example, acyl radicals such as lower alkanoyl optionally substituted, for example, by halogen such as 2,2-dichloroacetyl, or acyl radicals of carbonic acid semiesters, especially tert.-butoxycarbonyl, optionally substituted benzyloxycarbonyl, for example, 4-nitrobenzyloxycarbonyl, or diphenylmethoxycarbonyl, alkenyloxycarbonyl, for example, allyloxycarbonyl, or 2-halo-lower alkoxycarbonyl such as 2,2,2-trichloroethoxycarbonyl also trityl or formyl, or organic silyl radicals, also etherifying groups that can readily be split off such as tert.-lower alkyl, for example, tert.-butyl, or 2-oxa- or 2-thia-cycloalkyl having 5 or 6 ring atoms, for example

tetrahydrofuryl or 2-tetrahydropyranyl or corresponding thia analogues, and also optionally substituted 1-phenyl-lower alkyl such as optionally substituted benzyl or diphenylmethyl, there coming into consideration as substituents of the phenyl radicals, for example, halogen such as chlorine, lower alkoxy such as methoxy, and/or nitro.

A reactive functional derivative of a carboxy group (Y) is, for example, an acid anhydride, an activated ester or an activated amide, cyano, a group of the formula $-C(OR_a)_3$ or $-C(=NH)-R_a$ in which R_a is lower alkyl. Corresponding derivatives are well known in the art.

Of the anhydrides, the mixed anhydrides are especially suitable. Mixed anhydrides are, for example, those with inorganic acids such as hydrohalic acids, i.e., the corresponding acid halides, for example, chlorides or bromides, also with hydrazoic acid, i.e., the corresponding acid azides. Further mixed anhydrides are, for example, those with organic carboxylic acids such as with lower alkanecarboxylic acids optionally substituted, for example, by halogen such as fluorine or chlorine, for example, pivalic acid or trichloroacetic acid, or with semiesters, especially lower alkyl semiesters of carbonic acid such as the ethyl or isobutyl semiester of carbonic acid, or with organic, especially aliphatic or aromatic, sulfonic acids, for example, p-toluenesulfonic acid. Of the activated esters, there may be mentioned, for

example, esters with vinylogous alcohols (i.e., enols such as vinylogous lower alkenols), or iminomethyl ester halides such as dimethyliminomethyl ester chloride (prepared from the carboxylic acid and, for example, dimethyl-(1-chloroethylidene)-iminium chloride of the formula $(\text{CH}_3)_2\text{N}^{\oplus}=\text{C}(\text{Cl})\text{CH}_2\text{Cl}^{\ominus}$, which can be obtained, for example, from N,N-dimethylacetamide and phosgene), or aryl esters such as preferably suitable substituted phenyl esters, for example, phenyl ester substituted by halogen such as chlorine, and/or by nitro, for example, 4-nitrophenyl ester, 2,3-dinitrophenyl ester or 2,3,4,5,6-pentachlorophenyl ester, N-hetero-aromatic esters such as N-benzotriazole esters, for example, 1-benzotriazole ester, or N-diacylimino esters such as N-succinylamino or N-phthalyl-imino ester. Suitable activated amides are, for example, imidazolides, also 1,2,4-triazolides, tetrazolides or 1,2,4-oxadiazolinonides.

A preferred form of this process according to the invention is the reaction of a compound of the nitrile with a cysteine derivative. The reaction is carried out in an inert solvent such as an aqueous solvent at ambient temperature or, preferably, at slightly elevated temperature, for example, at about 50° to 80°C, and preferably under an inert gas atmosphere.

In resulting compounds in which one or more functional (hydroxy) groups are protected, the latter can be freed, optionally in stages or simultaneously, in a manner known per se, by means of solvolysis, especially hydrolysis or acidolysis, or in some cases also by means of careful reduction. Silyl protecting groups are advantageously split off with fluorides, for example, tetraethylammonium fluoride.

Salts of compounds of the invention can be manufactured in a manner known per se. Thus, salts of compounds having acidic groups can be formed, for example, by treating with metal compounds such as alkali metal salts of suitable organic carboxylic acids, for example, the sodium salt of α -ethylcaproic acid, or with inorganic alkali metal or alkaline earth metal salts, for example, sodium bicarbonate, or with ammonia or a suitable organic amine, preferably stoichiometric quantities or only a small excess of the salt-forming agent being used. Acid addition salts of compounds of the invention are obtained in a customary manner, for example, by treating with an acid or a suitable anion-exchange reagent. Internal salts of compounds of the invention (zwitterionic forms) can be formed, for example, by neutralizing the compounds or salts such as acid addition salts, to the isoelectric point, for example, with weak bases, or by treating with liquid ion exchangers.

Salts can be converted in a customary manner into the free compounds: metal and ammonium salts can be converted into the free compounds, for example, by treating with suitable acids, and acid addition salts, for example, by treating
5 with a suitable basic agent.

The starting materials are available commercially and/or known or can be manufactured by known processes.

The racemate can be split in a manner known per se, for example, after conversion of the optical antipodes into
10 diastereoisomers, for example, by reaction with optically active acids or bases.

The pharmacologically acceptable compounds of the present invention can be used, for example, for the manufacture of pharmaceutical compositions which contain an effective
15 amount of the active substance together or in admixture with inorganic or organic, solid or liquid, pharmaceutically acceptable carriers.

The pharmaceutical compositions according to the invention are those which are suitable for enteral, such as
20 oral, administration and for parenteral, such as subcutaneous, administration to warm-blooded animals, especially humans, and which contain the pharmacologically active substance on its own or together with a pharmaceutically acceptable carrier. The dosage of the active substance depends on the species of
25 warm-blooded animal and on the age and individual condition.

the illness to be treated and also on the mode of administration.

5 The novel pharmaceutical preparations contain from approximately 10% to approximately 95%, and preferably from approximately 20% to approximately 90%, of the active substance. Pharmaceutical compositions according to the invention can, for example, be in unit dose form, such as dragées, tablets, capsules, suppositories or ampoules, and contain from approximately 0.05 g to approximately 10.0 g, and preferably
10 from approximately 0.3 g to approximately 1.0 g, of the active ingredient.

The pharmaceutical compositions of the present invention are manufactured in a manner known per se, for example, by means of conventional mixing, granulating, confectioning, dissolving or lyophilizing processes. Pharmaceu-
15 tical compositions for oral use can be obtained by combining the active substance with one or more solid carriers, if desired, granulating a resulting mixture and processing the mixture or granulate, if desired or necessary after the addi-
20 tion of suitable adjuncts, to form tablets or dragée cores. In so doing, they can also be incorporated into plastic carriers which release the active substances or allow them to diffuse in controlled amounts.

Suitable carriers are especially fillers such as
guars, for example, lactose, saccharose, mannitol or sorbitol,
cellulose preparations and/or calcium phosphates, for example,
tricalcium phosphate or calcium hydrogen phosphate, also
5 binders such as starches, for example, corn, wheat, rice or
potato starch, gelatine, tragacanth, methylcellulose, hydroxy-
propylmethylcellulose, sodium carboxymethylcellulose and/or
polyvinylpyrrolidone, and/or, if desired, disintegrators such
as the above-mentioned starches, also carboxymethyl starch,
10 cross-linked polyvinylpyrrolidone, agar, alginic acid or a
salt thereof such as sodium alginate. Adjuncts are especially
flow-regulating and lubricating agents, for example, silica,
talc, stearic acid or salts thereof such as magnesium or cal-
cium stearate, and/or polyethylene glycol. Dragée cores are
15 provided with suitable coatings that are, if desired, resis-
tant to gastric juice, there being used, inter alia, concen-
trated sugar solutions which optionally contain gum arabic,
talc, polyvinylpyrrolidone, polyethylene glycol and/or titani-
um dioxide, lacquer solutions in suitable organic solvents or
20 solvent mixtures or, for the manufacture of coatings that are
resistant to gastric juice, solutions of suitable cellulose
preparations such as acetylcellulose phthalate or hydroxypro-
pylmethylcellulose phthalate. Coloring substances or pigments
can be added to the tablets or dragée coatings, for example

for the purpose of identification or for indicating different doses of active substance.

Other orally administrable pharmaceutical compositions are dry-filled capsules made of gelatin and also soft, sealed capsules made of gelatin and a plasticizer such as glycerol or sorbitol. The dry-filled capsules may contain the active ingredient in the form of a granulate, for example, in admixture with fillers such as corn starch, binders and/or glidants such as talc or magnesium stearate and optionally stabilizers. In soft capsules, the active ingredient is preferably dissolved or suspended in suitable liquids or wax-like substances such as fatty oils, paraffin oil or polyethylene glycols, it being possible also for stabilizers to be added.

Other forms of oral administration are, for example, syrups prepared in a customary manner that contain the active ingredient in, for example, suspended form and in a concentration of approximately from 5% to 20%, and preferably approximately 10%, or in a similar concentration that provides a suitable single dose when administered, for example, in measures of 5 or 10 ml. Also suitable are, for example, powdered or liquid concentrates for preparing shakes, for example, in milk. Such concentrates can also be packed in single-dose quantities.

Particularly suitable dosage forms for parenteral administration are sterile aqueous solutions of an active ingredient in water-soluble form, for example, a water-soluble salt, or sterile aqueous injection suspensions which contain substances increasing the viscosity, for example, sodium, carboxymethyl cellulose, sorbitol and/or dextran, and optionally stabilizers. In addition, the active ingredient, with or without adjuvants, can also be in lyophilized form and brought into solution prior to parenteral administration by the addition of suitable solvents.

The invention also relates to compositions for diagnostic purposes that contain a suitable metal complex of a compound of the formula wherein Z, R, R₁, R₂, R₃, R₄ and R₅ are as previously defined.

The invention also relates to a method of treatment of pathological conditions in a mammal, especially human, which as has been described hereinabove, are associated with an excess of a trivalent metal cation such as aluminum or, especially, iron (III), in the body, which method comprises administering, preferably orally, a prophylactically or therapeutically effective amount of a compound of the formula or of a pharmaceutically acceptable salt thereof. There are used for this purpose especially the above-mentioned pharmaceutical

compositions, a daily dose of from approximately 50 mg to approximately 10,000 mg, and preferably from approximately 300 mg to approximately 1,000 mg, of a compound of the present invention being administered to a warm-blooded animal of approximately 70 kg body weight. The dosage can be administered orally in several, for example, three, individual doses. For systemic, e.g., subcutaneous, administration, the more water-soluble salt forms of the compounds of the formula, e.g., the sodium salt, are preferred, for example, orally, or alternatively, subcutaneously.

The following examples serve to illustrate the invention, but should not be construed as a limitation thereof. Temperatures are given in degrees Centigrade.

Preparation of Drugs. Drug solutions were prepared in 60% water, 40% Cremophor RH-40.

EXAMPLE 1

2,4-Dihydroxybenzonitrile was prepared according to the method of Marcus in Ber. dtsh. chem. Ges. 1981, 24, 3651, as follows:

A mixture of 2,4-dihydroxybenzaldehyde (5.0 g, 36.7 mmol), sodium acetate (5.94 g, 72.4 mmol), nitroethane (5.46 g, 72.4 mmol) and glacial acetic acid (10 ml) was refluxed for 6 hours. After cooling, the mixture was poured onto ice (100

g) and extracted with ethyl acetate (4 x 50 ml). The combined organic layers were washed with saturated NaHCO₃ until the pH of the aqueous layer remained at 8, dried (Na₂SO₄) and the solvent removed in vacuo. Flash chromatography (SiO₂, cyclohexane : ethyl acetate = 1 : 1) afforded 2,4-dihydroxybenzonitrile (2.87 g, 59%) as a pale yellow solid. ¹H NMR (300 MHz, DMSO-d₆) δ 6.33 (d, 1 H, J = 8.6 Hz), 6.43 (s, 1 H), 7.37 (d, 1 H, J = 8.6 Hz), 10.35 (s, 1 H), 10.78 (s, 1 H). IR (KBr) 2200 cm⁻¹.

10

EXAMPLE 2

4,5-Dihydro-2-(2,4-dihydroxyphenyl)-thiazole-4(S)-carboxylic acid was prepared as follows:

15

D-cysteine hydrochloride monohydrate (6.8 g, 38.7 mmol) was added to a solution of 2,4-dihydroxybenzonitrile (3.5 g, 25.9 mmol) prepared in Example 1, in a mixture of degassed methanol (105 ml) and 0.1 M phosphate buffer, pH 5.95 (70 ml). NaHCO₃ (3.25 g, 38.7 mmol) was carefully added and the mixture was stirred at 70°C under Ar for 54 hours. Volatile components were removed under reduced pressure and the solution was acidified with 1 N HCl to pH 2. The resulting brown precipitate was vacuum filtered and the solid was washed with water (40 ml) and ethanol (20 ml). The crude product was

20

dissolved in saturated NaHCO_3 (700 ml) and the aqueous solution washed with ethyl acetate (2 x 200 ml). The aqueous layer was filtered through a fine frit and acidified with 1 N HCl to pH 2. The precipitated product was vacuum filtered.

5 The aqueous layer was extracted with ethyl acetate (4 x 400 ml), the combined organic extracts were dried (Na_2SO_4) and the solvent was removed in vacuo. The remaining solid was combined with the precipitated product and dried under high vacuum at 40°C for 12 hours to give 4,5-dihydro-2-(2,4-

10 dihydroxyphenyl)-thiazole-4(S)-carboxylic acid (4.08 g, 66%), mp 266-268°C (dec) [Ind. J. Chem., Vol. 15B, Kishore et al, pages 255-257 (1977) for (L)-isomer: 261-262°C]. ^1H NMR (300 MHz, DMSO-d_6) δ 3.61 (m, 2 H), 5.38 (dd, 1 H, $J = 7.2/9.4$ Hz), 6.31 (d, 1 H, $J = 2.3$ Hz), 6.38 (dd, 1 H, $J = 2.3/8.6$ Hz),

15 7.25 (d, 1 H, $J = 8.6$ Hz), 10.25 (br s, 1 H), 12.60 (br s, 1 H), 13.15 (br s, 1 H). Anal. calc. for $\text{C}_{10}\text{H}_9\text{NO}_4\text{S}$: C 50.20, H 3.79, N 5.85. Found: C 50.13, H 3.82, N 5.85.

Compounds of the invention in the scheme of Fig. 1 wherein Z is N may be prepared as described above in Examples

20 1 and 2 substituting the corresponding pyridyl aldehyde for 2,4-dihydroxybenzaldehyde.

The biological activity and properties of the compounds of the invention were evaluated as follows employing

25 4,5-dihydro-2-(2,4-dihydroxyphenyl)-thiazole-4(S)-carboxylic acid (1).

EXAMPLE 3**In Rats**

Initial testing of 1 was performed in the non-iron-overloaded, bile duct-cannulated rat [J. Med. Chem., Vol. 34, Bergeron et al, "Synthesis and Biological Evaluation of Hydroxamate-Based Iron Chelators," pages 3182-3187 (1991)]. The drug was prepared as a solution in 40% Cremophor-H₂O and administered at a dose of 150 μmol/kg p.o. The rats were fasted for 24 hours before dosing. The efficiency of iron excretion induced by 1 was 2.4 ± 0.92%.

EXAMPLE 4**In Monkeys**

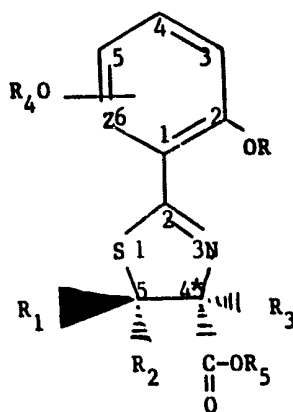
Given the results in the rat model, the ability of 1 to promote iron excretion in the iron-overloaded primate model [Blood, Vol. 79, Bergeron et al, "A Comparison of the Iron-Clearing Properties of 1,2-Dimethyl-3-Hydroxypyrid-4-One, 1,2-Diethyl-3-Hydroxypyrid-4-One and Deferoxamine," pages 1882-1890 (1992)] was evaluated. The drug was prepared as a solution in 40% Cremophor-H₂O and administered at a dose of 150 μmol/kg p.o. The monkeys were fasted for 24 hours before dosing. Immediately prior to drug administration, the monkeys were sedated with ketamine (7-10 mg/kg. i.m.) and given scopolamine (0.04-0.07 mg/kg/ i.m. to prevent ketamine-related

salivation and vomiting. At the dose of 150 $\mu\text{mol/kg}$, the efficiency of 1 was $4.2 \pm 1.4\%$ ($n = 4$).

THIAZOLINE ACID DERIVATIVES

I CLAIM:

- 1 1. A compound of the formula:



3 wherein: Z is CH or N;

4 R is H or acyl;

5 R₁, R₂, R₃ and R₅ may be the same or different and
 6 represent H, alkyl or hydrocarbyl arylalkyl having up to 14
 7 carbon atoms; and

8 R₄ is H or alkyl having 1-4 carbon atoms;

9 a salt thereof with a pharmaceutically acceptable acid or a
10 pharmaceutically acceptable complex thereof.

1 2. A compound of claim 1 wherein Z is CH and R =
2 $R_1 = R_2 = R_3 = R_4 = R_5 = H$.

1 3. A compound of claim 1 wherein Z is N and R = R_1
2 $= R_2 = R_3 = R_4 = R_5 = H$.

1 4. A compound of claim 1 wherein Z is CH, R = R_1
2 $= R_2 = R_3 = R_5 = H$, and R_4 is alkyl having 1-4 carbon atoms.

1 5. A compound of claim 4 wherein R_4 is methyl,
2 ethyl, n-propyl, isopropyl, n-butyl, isobutyl or t-butyl.

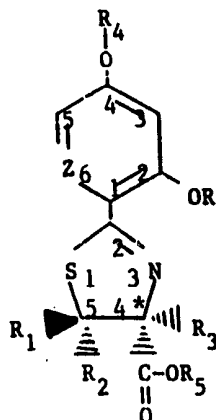
1 6. A compound of claim 1 wherein Z is N, R = $R_1 =$
2 $R_2 = R_3 = R_5 = H$, and R_4 is alkyl having 1-4 carbon atoms.

1 7. A compound of claim 6 wherein R_4 is methyl,
2 ethyl, n-propyl, isopropyl, n-butyl, isobutyl or t-butyl.

1

8. A compound of claim 1 having the formula:

2



3 wherein: Z, R, R₁, R₂, R₃, R₄ and R₅ have the meanings ascribed
 4 thereto in claim 1;
 5 a salt thereof with a pharmaceutically acceptable acid or a
 6 pharmaceutically acceptable complex thereof.

1

9. A compound of claim 8 wherein Z is CH and R =

2

R₁ = R₂ = R₃ = R₄ = R₅ = H.

1

10. A compound of claim 8 wherein Z is N and R = R₁

2

= R₂ = R₃ = R₄ = R₅ = H.

1

11. A compound of claim 8 wherein Z is CH, R = R₁

2

= R₂ = R₃ = R₅ = H, and R₄ is alkyl having 1-4 carbon atoms.

1 12. A compound of claim 11 wherein R_4 is methyl,
2 ethyl, n-propyl, isopropyl, n-butyl, isobutyl or t-butyl.

1 13. A compound of claim 8 wherein Z is N, $R = R_1 =$
2 $R_2 = R_3 = R_5 = H$, and R_4 is alkyl having 1-4 carbon atoms.

1 14. A compound of claim 13 wherein R_4 is methyl,
2 ethyl, n-propyl, isopropyl, n-butyl, isobutyl or t-butyl.

1 15. A compound of claim 8 wherein Z is CH, $R = R_4$
2 $= R_1 = R_2 = R_5 = H$, and R_3 is alkyl having 1-4 carbon atoms.

1 16. A compound of claim 8 wherein Z is CH, $R = R_4$
2 $= R_1 = R_3 = R_5 = H$, and R_2 is alkyl having 1-4 carbon atoms.

1 17. A compound of claim 8 wherein Z is CH, $R = R_4$
2 $= R_3 = R_2 = R_5 = H$, and R_1 is alkyl having 1-4 carbon atoms.

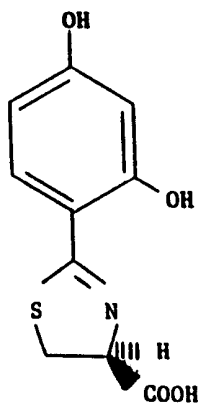
1 18. A compound of claim 8 wherein Z is N, $R = R_4 =$
2 $R_1 = R_2 = R_5 = H$, and R_3 is alkyl having 1-4 carbon atoms.

1 19. A compound of claim 8 wherein Z is N, $R = R_4 =$
2 $R_1 = R_3 = R_5 = H$, and R_2 is alkyl having 1-4 carbon atoms.

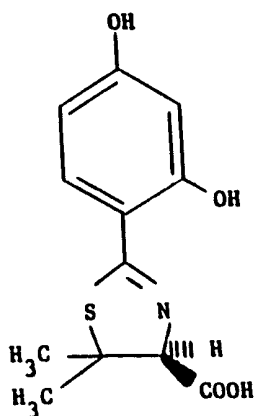
1 20. A compound of claim 8 wherein Z is N, $R = R_4 =$
2 $R_3 = R_2 = R_5 = H$, and R_1 is alkyl having 1-4 carbon atoms.

1 21. An optically pure compound of claim 1 or 8.

1 22. An (S)-enantiomer compound of claim 8 having
2 the formula:

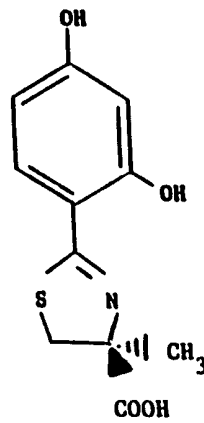


1 23. An (S)-enantiomer compound of claim 8 having
2 the formula:



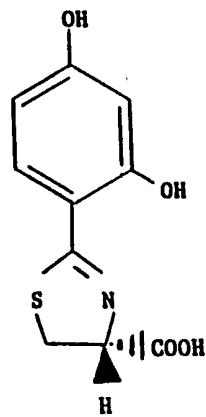
- 1 24. An (S)-enantiomer compound of claim 8 having
 2 the formula:

3

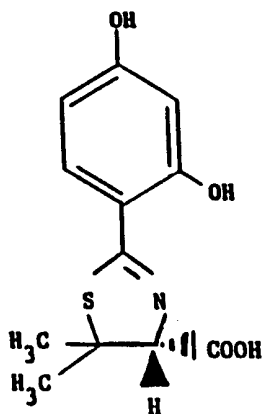


- 1 25. An (R)-enantiomer compound of claim 8 having
 2 the formula:

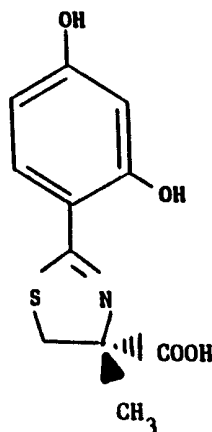
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- 1 26. An (R)-enantiomer compound of claim 8 having
2 the formula:



- 1 27. An (R)-enantiomer compound of claim 8 having
2 the formula:



- 1 28. A pharmaceutical composition in unit dosage
2 form comprising a therapeutically effective amount of a com-
3 pound according to claim 1 or 8 and a pharmaceutically accept-
4 able carrier therefor.

1 29. A method of preventing or treating a pathologi-
2 cal condition in a human or non-human animal that is associ-
3 ated with an excess of a trivalent metal, ion or compound
4 thereof comprising administering to said animal a therapeutic-
5 ally effective amount of a compound according to claim 1 or 8.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/19691

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :C07D 277/12; A61K 31/426
US CL :514/365; 548/201

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/365; 548/201

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4,457,936 A (DRAEGER et al) 03 July 1984, col 5, line 10	1, 2, 8, 9
----- Y		----- 21, 22, 25

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

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|---|--|
| * Special categories of cited documents: | *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention |
| *A* document defining the general state of the art which is not considered to be of particular relevance | *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone |
| *B* earlier document published on or after the international filing date | *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art |
| *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) | *a* document member of the same patent family |
| *O* document referring to an oral disclosure, use, exhibition or other means | |
| *P* document published prior to the international filing date but later than the priority date claimed | |

Date of the actual completion of the international search 07 DECEMBER 1999	Date of mailing of the international search report 19 JAN 2000
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