

Description

This invention relates to zinc compounds and to various mixtures containing these compounds for use in pharmaceutical compositions, especially for the treatment of zinc depletion, and in foodstuffs.

5 An adequate supply of zinc to the body is an essential requirement for tissue growth in both man and animals. Moreover, a deficiency of zinc can produce various clinical effects, for example leading to skin lesions, alopecia and mental disturbance. Although there is normally an ample amount of zinc in the diet, the level of absorption of zinc from food is generally low so that the supply of zinc to the body can become critical under a variety of conditions. Zinc depletion is commonly encountered in the mother during
10 pregnancy with consequent depletion of zinc in the foetal tissues together with idiopathic retardation of intrauterine growth. Certain diets may inhibit zinc absorption due to their phytic acid content, and many orally administered iron preparations can seriously inhibit zinc absorption.

Various preparations for the systemic treatment of zinc depletion are marketed but these contain zinc in the salt form, particularly as zinc sulphate, and the level of zinc uptake by the body from these
15 preparations is quite low thereby necessitating the administration of relatively high dosage levels. The administration of high dose, poorly absorbed, zinc salts can create various problems. Thus, zinc salts are generally astringent, causing irritation and toxicity to membrane tissue, and systemic treatment may be associated with a variety of side effects including nausea, vomiting, headache, myalgia, chills and fever. It should be noted that zinc sulphate and zinc acetate are recognized emetics.

20 The present invention involves the treatment of zinc depletion through the administration of zinc in complex, rather than salt form, utilising a group of zinc complexes which we have identified as being of particular value for use at relatively low dosage levels, the value of these complexes in this context hitherto having been quite unrecognised.

The use in the treatment of iron deficiency anaemia of iron complexes containing ligands present in
25 certain of the zinc complexes of the present invention has been described in UK Patent Applications 8308053, 8327615 and 8407180, published respectively as GB 2,117,766A, GB 2,128,998A and GB 2,136,806A. However, there has never been any suggestion that the hydroxypyridones and hydroxypyrones contained in the iron complexes described in those applications might serve any role in the treatment of zinc depletion. In particular, it will be appreciated that the successful administration of iron
30 and zinc are two quite separate problems as is confirmed by the fact that very many different complexes of iron are marketed for the treatment of iron deficiency anaemia, whilst the products marketed for the treatment of zinc depletion are zinc salts.

In addition to the hydroxypyridone and hydroxypyryone ligands, the presence of at least one of which is mandatory in the complexes used in the present invention, complexes may optionally also contain ligands
35 derived from an alternative compound providing a physiologically acceptable, monobasic, bidentate ligand which is capable of bonding covalently to zinc. US Patent 4,225,614 describes zinc complexes containing some such alternative ligands but those complexes do not additionally contain a hydroxypyridone or hydroxypyryone ligand and, moreover, they are used in the systemic treatment of mucocutaneous herpes simplex infections. A small number of zinc hydroxypyridone and hydroxypyryone complexes are described
40 in the literature but not in any therapeutic context. Thus, hydroxypyryone complexes of zinc are prepared and their physical properties reported by Morita *et al*, Bulletin of the Chemical Society of Japan, 1976, 49, 2461 (Chemical Abstracts, 1978, 89, 765; abstract 35629b) and by Choux and Benoit, Bulletin de la Societe Chimique de France, 1967, 8, 2920 (Chemical Abstracts 1968, 68, 841; abstract 8872k). The preparation as a solid of the 2:1 zinc(II) complex of 3-hydroxy-2-methyl-4-pyrone, in particular, in both dihydrated and
45 unhydrated forms is described by Gerard, Bulletin de la Societe Chimique de France, 1979, No. 11-12, 1-451, in the context of studies on its spectral properties. Certain zinc(II) hydroxypyridone complexes, and in particular the complex with 3-hydroxy-1-methylpyrid-4-one, are described by Stunzi *et al*, Australian Journal of Chemistry, 1979, 32, 21, in the context of studies on stability constants.

The zinc complexes of the present invention are of particular interest in that some of the compounds
50 from which the zinc complexes are derived have previously been used either as the meal-free compound or as its iron complex in foodstuffs, thereby indicating their non-toxic nature and the consequent suitability for pharmaceutical use of the zinc complexes of these compounds.

Accordingly the present invention comprises a zinc(II) complex in which at least one ligand is provided by a compound being:

55 (1) 3-hydroxy-4-pyrone or a 3-hydroxy-4-pyrone in which one or more of the hydrogen atoms attached to ring carbon atoms are replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms;

(2) a 3-hydroxypyrid-2-one or 3-hydroxypyrid-4-one in which the hydrogen atom attached to the nitrogen atom is replaced by an aliphatic acyl group, by an aliphatic hydrocarbon group of 1 to 6 carbon atoms, or by an aliphatic hydrocarbon group substituted by one or more substituents selected from
60 aliphatic acyl, alkoxy, aliphatic amide, aliphatic ester, halogen and hydroxy groups and, optionally, in which one or more of the hydrogen atoms attached to ring carbon atoms are replaced by one of said substituents, by an aliphatic hydrocarbon group of 1 to 6 carbon atoms, or by an aliphatic hydrocarbon group substituted by an alkoxy, aliphatic ester, halogen or hydroxy group; or

(3) an alternative compound providing a physiologically acceptable, monobasic, bidentate ligand

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which is capable of bonding covalently to zinc; but with the proviso that at least one of the ligands is of type (1) or (2);
for use in therapy.

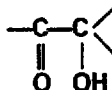
The zinc complexes of use in the present invention contain zinc in the divalent state. The complexes are preferably neutral, i.e. there being an internal balance of charges between the zinc cation and the ligand(s) bound covalently thereto without the necessity for the presence of a non-covalently bound ion or ions to achieve such balance. An internal balance of charges is achieved by complexing with the zinc cation two monobasic, bidentate ligands, such ligands being provided by the hydroxypyrones and hydroxypyridones described above through the loss of a proton from the hydroxy group ($\text{OH} \rightarrow \text{O}^-$). Zinc(II) complexes containing a 2:1 proportion of monobasic, bidentate ligand:zinc(II) are therefore preferred since complexes containing a 1:1 or 3:1 proportion of monobasic, bidentate ligand:zinc(II) require an additional physiologically acceptable ion, for example a chloride anion or a sodium cation, respectively, to establish neutrality. It will be appreciated, however, that although of less interest, the use of such 3:1 and especially 1:1 complexes is not excluded from the invention, particularly when in admixture with the 2:1 complex.

It will be appreciated that the zinc complexes of use in the present invention may exist in either a tetrahedral or an octahedral form and, although complexes containing a 2:1 proportion of monobasic, bidentate ligand:zinc(II) will usually have the tetrahedral form, it is possible for them to adopt the octahedral form by combination with two additional neutral ligands, in particular water molecules. The preferred 2:1 neutral complexes may conveniently therefore be used in either the anhydrous or the dihydrate form, the anhydrous form possibly being converted to the dihydrate form in an *in vivo* aqueous environment.

The preferred complexes according to the present invention having a 2:1 proportion of monobasic, bidentate ligand:zinc(II) may contain various different combinations of the ligands of the types (1)–(3) described above, subject to the requirement that at least one is a hydroxypyridone or hydroxypyrene ligand. Thus, all of the ligands may be of type (1) or of type (2), although optionally differing within these types, or the ligands may be of two different types, (1) and (3), (2) and (3) or particularly (1) and (2). Complexes of particular interest are those containing two ligands of type (2) or particularly of type (1), these ligands conveniently being identical.

Although complexes containing identical ligands are of particular interest, by virtue of their greater simplicity of preparation and use, complexes containing different ligands do have certain properties which may be of value in particular circumstances. Thus, firstly, the inclusion in a complex of a mixture of different ligands provides an added dimension to the design of complexes having optimised properties for uptake *in vivo* to provide a controlled supply of zinc applicable in a particular human or veterinary context. Secondly, apart from the behaviour of the complexes *in vivo*, the use of mixed ligand complexes may confer certain advantages in relation to formulation.

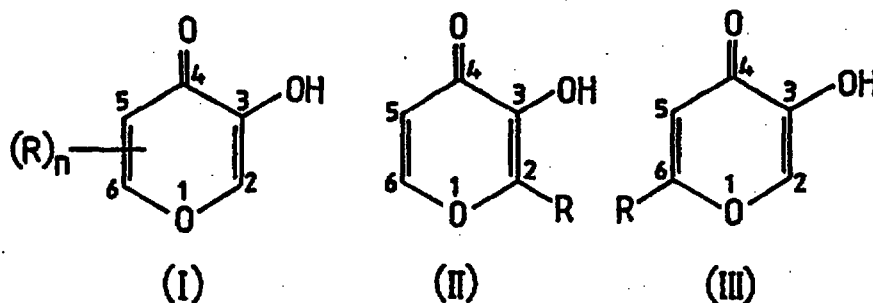
As indicated, the hydroxypyrene ligands of type (1) are of particular interest and the complexes according to the present invention may conveniently contain at least one such ligand. The substituted 3-hydroxy-4-pyrones may carry more than one type of aliphatic hydrocarbon group but this is not usual and, indeed, substitution by one rather than two or three aliphatic hydrocarbon groups is preferred. The term aliphatic hydrocarbon group is used herein to include both acyclic and cyclic groups which may be unsaturated or saturated, the acyclic groups having a branched chain or especially a straight chain. Groups of 1 to 4 carbon atoms and particularly of 1 to 3 carbon atoms are of most interest. Saturated aliphatic hydrocarbon groups are preferred, these being either cyclic groups such as the cycloalkyl groups cyclopropyl and especially cyclohexyl or, more particularly, acyclic groups such as the alkyl groups n-propyl and isopropyl, and especially ethyl and methyl. Substitution at the 2- or 6-position is of especial interest although, when the ring is substituted by the larger aliphatic hydrocarbon groups, there may be an advantage in avoiding substitution on a carbon atom from alpha to the



system.

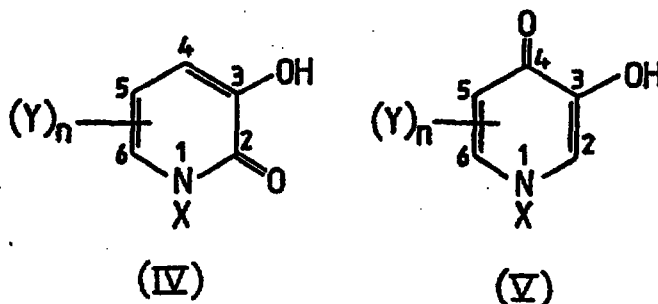
This system is involved in the complexing with zinc and the close proximity of one of the larger aliphatic hydrocarbon groups may lead to steric effects which inhibit complex formation.

Examples of hydroxypyrones providing ligands which may be used in complexes according to the present invention have the formula (I), specific hydroxypyrones of particular interest having the formulae (II) and (III):—



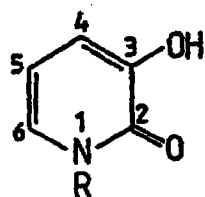
in which R is an alkyl or cycloalkyl group, for example methyl, ethyl, n-propyl isopropyl or butyl, and n is 0, 1, 2 or 3 (the ring being unsubstituted by any alkyl group when n is 0). Among these compounds 3-hydroxy-2-methyl-4-pyrone (maltol; II, R = CH₃) is of most interest, whilst 3-hydroxy-4-pyrone (pyromeconic acid; I, n = 0) 3-hydroxy-6-methyl-4-pyrone (isomaltol; III, R = CH₃) and particularly 2-ethyl-3-hydroxy-4-pyrone (ethylpyromeconic acid; II, R = C₂H₅) are also of especial interest. The names maltol and ethylpyromeconic acid are used hereinafter in the description for simplicity.

As regards the hydroxypyridone ligands of type (2), these may be derived from hydroxypyridones of the type described in UK Patent Application No. 8308056, published as GB 2,118,176A, or of the type described in UK Patent Application No. 8407181, published as GB 2,136,807A. The former consist of a 3-hydroxypyrid-2-one or 3-hydroxypyrid-4-one in which the hydrogen atom attached to the nitrogen atom is replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms and, optionally, in which one or more of the hydrogen atoms attached to ring carbon atoms are also replaced by the same or a different aliphatic hydrocarbon group of 1 to 6 carbon atoms, whilst the latter include 3-hydroxypyrid-2-ones and 3-hydroxypyrid-4-ones substituted as defined under (2) hereinbefore but excluding those compounds in which the replacement of hydrogen atoms is effected only by aliphatic hydrocarbon groups, these compounds being the substituted hydroxypyridones of the former application. Hydroxypyridones providing ligands which may be used in complexes according to the present invention have the formulae (IV) and (V)

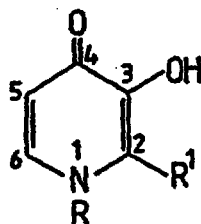


in which X and Y are substituents as defined hereinbefore for hydroxypyridone substitution and n is 0, 1, 2 or 3, the 3-hydroxypyrid-2-ones generally being of somewhat greater interest than the 3-hydroxypyrid-4-ones.

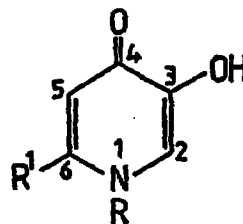
Preferences as to the nature and position of the substituent groups present in the hydroxypyridones are broadly as expressed in the two earlier applications. Thus substituted aliphatic hydrocarbon groups present in the hydroxypyridones may conveniently contain 1 to 8 and particularly 1 to 6 carbon atoms and, as indicated, may carry more than one substituent group, although it is preferred that only one substituent group is present. However, the simpler hydroxypyridones of UK Patent Application GB 2,118,176A containing only unsubstituted aliphatic hydrocarbon group substituents are of the greatest interest. The preferences among the aliphatic hydrocarbon groups present in these hydroxypyridones, with methyl groups conveniently being used for substitution on ring carbon atoms but larger alkyl and cycloalkyl groups also being of particular interest for substitution on the ring nitrogen atoms. Substitution of the ring carbon atoms, which is again preferably by one rather than two or three aliphatic hydrocarbon groups, is of particular interest in the case of the 3-hydroxypyrid-4-ones, for example at the 6- or particularly the 2-position, whilst the 3-hydroxypyrid-2-ones may more often be used without any additional aliphatic hydrocarbon group substituent on the ring carbon atoms. Specific hydroxypyridones of particular interest have formulae (VI), (VII), and (VIII)



(VI)



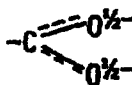
(VII)



(VIII)

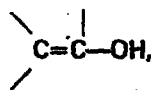
in which R is an alkyl or cycloalkyl group, for example methyl, ethyl, n-propyl, isopropyl or butyl, and R¹ is hydrogen or particularly an alkyl or cycloalkyl group, for example methyl. Among such compounds 3-hydroxy-1-methylpyrid-2-one, 1-ethyl-3-hydroxypyrid-2-one, 3-hydroxy-1-propylpyrid-2-one, 3-hydroxy-1-(1-methylethyl)-pyrid-2-one, 1-butyl-3-hydroxypyrid-2-one, 3-hydroxy-1,2-dimethylpyrid-4-one, 1-ethyl-2-methyl-3-hydroxypyrid-4-one, 2-methyl-1-propyl-3-hydroxypyrid-4-one, 3-hydroxy-2-methyl-1-(1-methylethyl)-pyrid-4-one and 1-butyl-3-hydroxy-2-methylpyrid-4-one are of particular interest with the 3-hydroxypyrid-2-ones such as 1-ethyl-3-hydroxypyrid-2-one being especially preferred.

The ligands of type (3) may be derived from various forms of compound, many of which are naturally occurring, and include various physiologically acceptable, monobasic, bidentate ligands known in the art. The compounds which provide such ligands will generally comprise (a) a first grouping containing an acidic proton which is lost to provide both the single negative charge on the ligand and also one of its chelating sites and (b) a second grouping which provides the second chelating site. The grouping (a) is preferably either an enolic hydroxy group or a carboxy group whilst the grouping (b) is preferably an amine group, conveniently a primary amino group, or a hydroxy group. In a particular case, one grouping can fulfil both function (a) and function (b). Thus, some monocarboxylic acids can provide an anion capable of a bidentate mode and containing a grouping



which will fulfil both functions.

Apart from such monocarboxylic acids, for example formic acid, propionic acid and particularly acetic acid, many other forms of acid are of interest for providing type (3) ligands. These include various hydroxy acids, for example lactic acid, gluconic acid, etc., and various amino acids, for example glycine, isoleucine, leucine, methionine, phenylalanine, tyrosine and valine. Also of interest are peptides, particularly the smaller compounds such as tri- and especially di-peptides, for example those containing the same or different amino acids selected from those listed above such as glycyl-leucine, leucyl-glycine and especially glycyl-glycine and leucyl-leucine. Apart from such carboxylic acids, the other group of compounds of particular interest is those containing a grouping



a particular example of this class being ascorbic acid (vitamin C). It should be noted that ascorbic acid is capable of providing a dibasic rather than a monobasic anion but compounds such as this are quite suitable for use in providing ligands of type (3) where they have a single pK_a, only, which is less than 10, since in use under physiological conditions, the ascorbate or other such anion will be monobasic. It will be appreciated from the foregoing discussion that the carbohydrate compounds gluconic acid and ascorbic acid are of interest in providing type (3) ligands and this interest extends to other carbohydrates, including particularly the monosaccharide sugars and related compounds. In selecting carbohydrate or other compounds for providing type (3) ligands, and more hydrophobic compounds are generally of greater interest so that among the amino acids, for example, the more complex amino acids than glycine may be of greater value.

Examples of specific zinc(II) complexes according to the present invention are the 2:1 zinc complexes containing two identical ligands drawn from the lists of hydroxypyrones and hydroxypyridones of particular interest given hereinbefore, particularly the hydroxypyrones, for example (maltol)₂ zinc(II) and (ethylpyromeconic acid)₂ zinc(II). Among complexes containing two different ligands, specific examples are (1-ethyl-3-hydroxypyrid-2-one)(1-butyl-3-hydroxypyrid-4-one) zinc(II), (maltol)(1-ethyl-3-hydroxypyrid-2-one) zinc(II), (maltol)(leucine) zinc(II), (maltol)(glycine) zinc(II), (maltol)(ascorbic acid) zinc(II), (maltol)(gluconic acid) zinc(II) and especially (maltol)(ethylpyromeconic acid) zinc(II). It will be appreciated that

"maltol" is used in the names of these complexes to represent the ligand derived from maltol, and similarly for the other ligands, this usage being employed throughout the specification.

In the case of maltol, as mentioned hereinbefore, the preparation of the solid 2:1 zinc maltol complex has been reported in the literature by Gérard, whilst the previously mentioned papers by Choux and Benoit and by Stünzi *et al* report the preparation in the case of 3-hydroxy-4-pyrone, 3-hydroxy-6-methyl-4-pyrone and 3-hydroxy-1-methyl-pyrid-4-one of the 2:1 zinc complexes containing two identical ligands, but only in solution. In the case of the zinc complexes containing identical ligands derived from all other compounds than these four and of all zinc complexes in which at least two ligands are different, however, the zinc complexes are believed to be entirely novel and are included, *per se*, by the present invention.

The zinc complexes are conveniently prepared by the reaction in a suitable mutual solvent of the ligand-providing compound(s) and zinc ions, the latter conveniently being derived from a zinc salt, particularly a zinc halide and especially zinc chloride. For the best results, it is preferred to avoid the use of water alone as a reaction solvent, the use of an aqueous/organic solvent mixture or particularly an organic solvent being preferred. The solvent may, for example, be ethanol, methanol or chloroform and mixtures of these solvents together and/or with water where appropriate. In particular, methanol or especially ethanol, or a mixture thereof with chloroform, may be used where it is desired to effect the separation of at least a major part of a by-product such as sodium chloride by precipitation whilst the zinc complex is retained in solution.

The nature of the product obtained will depend in part upon the molar proportion of the various reactants but also upon the pH of the reaction medium. Thus, for the preparation of 2:1 zinc complexes, for example, the ligand-providing compound(s) and the zinc salt are conveniently mixed in solution in a 2:1 molar proportion and the pH adjusted to a value in the range of 6 to 9, for example 7 or 8. If a similar excess of the compound(s):zinc is employed but no adjustment is made of the acidic pH which results on the admixture of the compound(s) and a zinc salt such as zinc chloride then a mixture of the 2:1 complex or complexes and the 1:1 complex or complexes will be obtained. Adjustment of the pH may conveniently be effected by the addition either of sodium carbonate or of a hydroxide base such as sodium or ammonium hydroxide, the use of a hydroxide base being of particular interest when preparing the zinc complexes in batches of 20 g or more. When using a hydroxide base, the reaction may conveniently be carried out in a medium containing a proportion of water as the solvent, for example in an ethanol: water mixture such as 4:1 v/v ethanol: water, and the pH adjusted by the addition of a 2 molar aqueous solution of the base. It will be appreciated that the presence of water in the reaction mixture will lead to the retention of a by-product in the zinc complex on evaporation of the solvent (a chloride where the salt is zinc chloride). However, this can be removed, if desired, by procedures such as crystallisation from a suitable solvent system where possible or sublimation in the particular case of ammonium chloride. In general, however, the use of a non-aqueous reaction medium in conjunction with sodium carbonate is preferred.

When preparing a 2:1 zinc(II) complex containing different ligands, the individual ligand-providing compounds may conveniently each be used in a 1 molar proportion, together with a 1 molar proportion of the zinc salt. It will be appreciated, however, that the use of such a proportion will not lead exclusively to the mixed 2:1 ligand:zinc(II) complex since, although this form of complex will predominate providing the ligand-providing compounds are of similar reactivity, it will be obtained in admixture with the two 2:1 complexes containing identical ligands.

Reaction to form the zinc complex is generally rapid and will usually have proceeded substantially to completion after 5 minutes at about 20°C, although a longer reaction time may be used if necessary. Following separation of any precipitated by-product, such as sodium chloride in the case of certain solvent systems, the reaction mixture may conveniently be evaporated on a rotary evaporator or freeze dried to yield the zinc complex which is usually in solid form. A solid complex may, if desired, be crystallised from a suitable solvent, for example water, an alcohol such as ethanol, or a solvent mixture, including mixtures containing an ether. Whether the zinc complex is obtained in anhydrous or dihydrate form will depend both on the solvent system used for the reaction and on the subsequent working up procedure. Thus rigorous drying may remove the water molecules from a hydrated complex formed in a reaction mixture containing water and recrystallisation from an aqueous medium may add them. If a dihydrate is specifically required, freeze drying of the mixture resulting from the reaction of the ligand-providing compound(s) and a zinc salt such as the chloride or acetate in an aqueous/organic solvent medium may be employed.

Whilst for some uses it may be appropriate to prepare the zinc complex in substantially pure form, i.e. substantially free from by-products of manufacture, in other cases, for example with a solid oral formulation as described hereinafter, the presence of by-products such as sodium chloride may be quite acceptable. In general, however, the neutral 2:1 ligand:zinc(II) complexes in which the ligands are identical are of particular interest in a form which is substantially free at least from those by-products which are complexes containing different overall proportions of the ligand and zinc, in particular the 1:1 complex. When, as discussed hereinafter, it is desired to use the 2:1 zinc complex together with an excess of the metal-free ligand-providing compound(s), this may be achieved by using a greater molar proportion of the compound(s):zinc than 2:1 in the reaction mixture to thereby provide a product containing such an excess.

Certain of the ligand-providing compounds, such as maltol, are available commercially. With others, routes for their preparation are described in UK Patent Applications GB 2,118,176A, GB 2,128,998A and GB 2,136,807A referred to hereinbefore. Thus, for example, with the hydroxypyrones a convenient starting

material in many instances consists of pyromeconic acid which is readily obtainable by the decarboxylation of meconic acid and may be reacted with an aldehyde to insert a 1-hydroxyalkyl group at the 2-position, which group may then be reduced to produce a 2-alkyl-3-hydroxy-4-pyrone. The preparation of ethylpyromeconic acid, 2-ethyl-3-hydroxy-4-pyrone, etc., by this route is described in published US Application Serial No. 310,141 (series of 1960), which is referred to in U.S. Patent 3,376,317.

It will be appreciated that these are not the only routes available to these compounds and their zinc complexes and that various alternatives may be used as will be apparent to those skilled in the art. Moreover, it will be appreciated that certain of the compounds may be converted *in vivo* to other compounds which are responsible for the activity observed *in vivo*. This will be true, for example, of compounds containing ester groups which are likely to be converted to carboxy groups when the compounds are administered orally.

The zinc complexes according to the present invention may be formulated for use as pharmaceuticals for both veterinary, for example in an avian or particularly a mammalian context, and especially human use by a variety of methods. For instance, they may be applied as an aqueous, oily or emulsified composition incorporating a liquid diluent which may often be employed for parenteral administration and therefore may conveniently be sterile and pyrogen free. Oral administration is often preferred for the treatment of zinc depletion in humans and the complexes of the present invention may be given by such a route. Although compositions incorporating a liquid diluent may be used for oral administration, it is more usual, at least in humans, to use compositions incorporating a solid carrier, for example a conventional solid carrier material such as starch, lactose, dextrin or magnesium stearate. It may even be possible in human and particularly veterinary contexts to use the corresponding metal-free ligand-providing compound or compounds as the solid carrier material or in an extreme instance to use the zinc complex or complexes in solid form as their own carrier. Such solid compositions may conveniently be of a formed type, for example as tablets, capsules (including spansules), etc.

Although solid compositions may be preferred in important contexts such as the oral treatment of zinc depletion in humans, liquid compositions are however of interest in other contexts, for example in veterinary oral administration. In principle liquid formulations of zinc complexes would also be desirable for intramuscular administration in both a veterinary and a human context. In such contexts the complexes containing mixed ligands may have a particular advantage, by virtue of greater solubility, in enabling more concentrated liquid compositions to be prepared.

Other forms of administration that by injection or through the oral route may also be considered in both human and veterinary contexts, for example the use of suppositories or pessaries for human administration.

Compositions may be formulated in unit dosage forms, i.e. in the form of discrete portions containing a unit dose, or a multiple or sub-unit dose. Whilst the dosage of the zinc complex given will depend on various factors, including the particular nature of the complex which is employed in the composition, it may be stated by way of guidance that maintenance at a satisfactory level of the amount of zinc present in the human body will often be achieved using a daily dosage, in terms of the zinc content of the compound, which lies in a range from about 1 to 100 mg and often in a range from 5 to 30 mg, for example 15 mg. (Veterinary doses may be on a similar mg of zinc per kg of body weight basis.) However, it will be appreciated that it may be appropriate under certain circumstances to give daily dosages either below or above these levels. In general, the aim should be to provide the amount of zinc required by the patient without administering any undue excess and the properties of the pharmaceutical compositions according to the present invention are particularly suited to the achievement of this aim. Similarly, the concentration of zinc complex in the pharmaceutical composition may vary quite widely, for example over a range from about 0.01 to about 100% w/w. However, it is more usual for the concentration to exceed 0.1% w/w and it may often exceed 0.5 or 1% w/w, whilst a more usual limit for the upper end of the range is about 50% w/w.

Where desired, more than one zinc complex as described above may be present in the pharmaceutical composition, for example a mixture of the 2:1 maltol:zinc(II) and ethylpyromeconic acid:zinc(II) complexes being used. Other active compounds may also be included in the composition, for example compounds having the ability to facilitate the treatment of zinc depletion. Other components of interest are compounds having the ability to facilitate the treatment of iron deficiency anaemia (in its broadest sense), such as folic acid and, more particularly, a compound providing a source of iron, for example one of those presently marketed for the treatment of iron deficiency anaemia, such as ferrous sulphate, ferrous fumarate, ferrous gluconate, ferrous succinate, ferric EDTA, ferric ascorbate and ferric citrate.

Of particular interest in the context of pharmaceutical compositions containing an iron compound in addition to the zinc complex are those in which this iron compound is an iron complex, particularly a neutral 3:1 iron(III) complex in which the ligands are selected from the same compounds as are discussed hereinbefore for providing the ligands of the zinc complexes. Iron complexes such as this are the subject of the UK Patent Applications GB 2,117,766A, GB 2,128,998A and GB 2,136,806A referred to hereinbefore and of UK Patent Application GB 2,157,686A (8410289). Of especial interest among these iron complexes are those in which at least one and conveniently all of the ligands derived from a hydroxypyrrone. Iron complexes in which each ligand is derived from the same compound are also of especial interest so that the iron complexes in which each ligand is derived from the same hydroxypyrrone are preferred. Although the ligands present in the iron complex need not be the same as those present in the zinc complex, there is a

particular interest in pharmaceutical compositions in which at least one and conveniently all of the ligands of each iron and zinc complex are derived from hydroxypyrones, particularly the identical hydroxypyrene for each ligand of the zinc complex and the same or another hydroxypyrene for each ligand of the iron complex. A particularly preferred combination is that of a zinc complex, especially the neutral 2:1 complex, of maltol or of ethylpyromeconic acid and an iron complex, especially the neutral 3:1 complex, of maltol or of ethylpyromeconic acid. The combinations may consist of two maltol complexes, two ethylpyromeconic acid complexes or one maltol and one ethylpyromeconic acid complex. Combinations containing both zinc complexes and/or both iron complexes may also be used as may combinations which involve complexes containing mixed maltol and ethylpyromeconic acid ligands.

The daily requirement of iron for the adult human is generally regarded to be 2 to 4 mg whilst that of zinc is 10 to 15 mg. A suitable human daily dosage for the preferred forms of iron complex referred to above is thus somewhat less than the dosage quoted hereinbefore for the zinc complexes being, in terms of the iron content of the complex, in a range from about 0.1 to 10 mg and often in a range from 0.5 to 10 mg, for example 1 to 2 mg, veterinary doses being on a similar g/kg of body weight ratio. However, the relative requirement for zinc and iron can vary quite widely from one patient to another depending on the actual degree of zinc depletion and iron deficiency anaemia exhibited by that patient. As with existing combined mixed iron and zinc preparations, therefore, a range of zinc/iron ratios may be present, for example spanning any combination within the range of 1 part by weight of zinc to 0.25 or 0.4 parts by weight of iron up to 1 part by weight of zinc to 30 or 50 parts by weight of iron. A preferred range is 1 part by weight of zinc to from 1 to 20 parts by weight of iron, for example a 1:7.5 ratio. In general, mixtures containing the higher proportions of zinc are of value when the patient is already exhibiting both zinc depletion and iron deficiency anaemia whilst the lower proportions of zinc are of value when the patient is exhibiting only iron deficiency anaemia but it is desired to avoid any possible zinc depletion.

There are many reports in the literature of the non-specific binding of zinc to cell surfaces and also of a mutual inhibition of bioavailability between zinc and iron. For example Solomons, *Nutritional Bioavailability of Zinc*, A.C.S. Symposium Series, edited by Inglett, A. C. S., Washington 1983, 210, 247. In experiments with radiolabelled zinc in the everted rat jejunum we have found that, in the absence of binding to hydroxypyridone and particularly hydroxypyrene ligands such as maltol and ethylpyromeconic acid, zinc is rapidly removed from the incubation medium by binding to the mucosal surface but that, despite this extensive binding, little permeation occurs. In contrast, when the zinc is bound to such ligands, such non-specific binding is avoided. As discussed hereinafter in more detail, it is desirable, in order to ensure that the zinc is bound, for an excess of the ligand-providing compound to be present, for example to provide a 1:5 or larger molar ratio of zinc:ligand-providing compound or compounds (both bound and unbound), since in the absence of an excess of the compound(s) above the 1:2 molar ratio required to form the 2:1 neutral complex much of the zinc may not in fact be bound. Such non-specific binding may well be associated with the powerful emetic properties of zinc compounds, so that the use of the zinc complexes according to the present invention may well abolish this undesirable side effect. Moreover, studies with radiolabelled iron and zinc in the everted rat jejunum have shown that there is no inhibition on the uptake of zinc from the 2:1 maltol:zinc(II) complex when it is used in admixture with either the 3:1 maltol:iron(III) complex or with ferrous sulphate, nor is there any inhibition on the uptake of iron from the 3:1 maltol:iron(III) complex when it is in admixture with the 2:1 maltol:zinc(II). In each case the avoidance of inhibition is assisted by the presence of excess maltol.

In view of the complicated relationship between iron and zinc the use of the zinc complexes according to the present invention in conjunction with iron complexes containing ligands selected from a similar group of compounds is of particular value in the treatment of iron deficiency anaemia, particularly the rather more complicated forms of anaemia in which both zinc and iron levels are depressed.

When orally administered, zinc is absorbed by the intestine and is transferred via the portal blood stream where it is predominantly bound to apotransferrin. Although the affinity of apotransferrin for zinc is considerably less than that for iron, apotransferrin is rarely saturated with iron and normally carries only about 35% of the possible saturation level. The apotransferrin in the body thus usually has the potential for further metal complexing and the affinity of zinc for apotransferrin, despite being lower than that of iron is nevertheless quite considerable, the value of β_2 being 14.6. In order for a zinc complex to donate zinc efficiently with apotransferrin, the β_2 value for the compound(s) from which the complex is derived should be similar to or less than that of apotransferrin. The affinity of maltol for zinc ($\beta_2 = 9.8$) is therefore such that a complex formed with this compound is very suitable for the oral administration of zinc, since the affinity is relatively high but at the same time is less than that of apotransferrin, thereby allowing the efficient exchange of zinc bound to maltol with apotransferrin. It should be noted that maltol is also suitable for the oral administration of zinc in that it has a lower affinity for calcium ($\beta_2 = 7.2$) than for zinc. Interference with phytic acid, phosphate and tetracycline is predicted to be minimal. Moreover, although the neutral 2:1 maltol:zinc complex is thermodynamically stable; it is also extremely labile and is therefore able to donate zinc to high affinity sites, such as those found in apotransferrin.

It will be appreciated, however, that in addition to possessing properties such as those described above for zinc maltol, a compound which is to act as a source of zinc through oral administration is required to show a high level of membrane permeability. A good indication of the physical properties of a ligand-providing compound and of a zinc complex in this respect is provided by the value of the partition

coefficient (K_{part}) obtained on partition between n-octanol and Tris hydrochloride (20 mM, pH 7.4; Tris representing 2-amino-2 hydroxymethylpropane 1,3-diol) at 20°C and expressed as the ratio (concentration in organic phase)/(concentration in aqueous phase). Preferred complexes show a value of K_{part} for each ligand-providing compound of above 0.02 or 0.05 but less than 3.0, especially of above 0.2 but less than 1.0, together with a value of K_{part} for the neutral 2:1 ligand:zinc(II) complex of above 0.02 but less than 6.0, especially of 0.05 or 0.1 to 1.0. The value of K_{part} for maltol is 0.66 and for the neutral 2:1 maltol:zinc(II) complex is 0.11 which values lie in the especially preferred ranges. It will be appreciated, however, that the wide range of ligands which may be present in zinc complexes according to the present invention allows the preparation of complexes having partition coefficients lying throughout the entire ranges given. Thus, for example, a 2:1 complex having a higher partition coefficient than 0.1 may be obtained by using maltol as one ligand and another compound as the second ligand. Alternatively, higher partition coefficients may be obtained, if desired, by the use of hydroxypyrrone compounds containing additional and/or larger aliphatic hydrocarbon group substituents on the ring. Thus, for example the values of K_{part} for ethylpyrromeconic acid and its 2:1 zinc complex are higher than those for maltol, the higher partition coefficient for the ethyl compound being reflected in the greater uptake of the 2:1 complex in tests on the permeation of erythrocytes (further specific data on partition coefficients is to be found in the Examples and, as regards the free compounds, in the earlier applications previously referred to). It should be emphasised, however, that despite the fact that its K_{part} value is not particularly high, the 2:1 complex containing two ligands derived from maltol has proved to be very suitable as an *in vivo* source of zinc in the tests we have carried out.

Certain aspects of their formulation will enhance the activity of the zinc complexes of the present application in particular contexts. Thus, the preparation of the 2:1 neutral zinc(II) complexes can be effected at neutral pH in essentially quantitative yield using a 2:1 molar proportion of the ligand and a zinc salt, such preparations involving the use of relatively concentrated solutions which preferably contain an organic solvent. However, when a 2:1 ratio of the ligand-providing compound:zinc is present at low concentration, for example 10^{-4}M , in water at pH 7.4 it has been found that only a small proportion of the zinc will be present as the 2:1 zinc(II) complex, a significant proportion being present as the free metal and the 1:1 complex. Thus, in the case of a 2:1 ratio of maltol:zinc ions the proportions of zinc present as the 2:1 zinc(II) complex under these conditions is only about 15%, about 30% being present as the 1:1 complex and about 50% as the free metal, whilst very little of the 3:1 complex is present. In the presence of a higher ratio of free ligand-providing compound:zinc ions, however, the proportion of zinc present as the 2:1 maltol:zinc(II) complex is much increased, being about 68% for a 10:1 ratio of maltol:zinc and about 82% for a 20:1 ratio. The position is similar with the hydroxypyridone ligands but with a slightly higher proportion of the 2:1 zinc(II) complex at any particular ratio.

The uptake of zinc from complexes according to the present invention will occur primarily from the intestine and it is desirable, for optimum uptake, that the zinc is present in the intestine in the form of the neutral 2:1 zinc(II) complex. This is best achieved by the administration of such a neutral 2:1 complex but it is also necessary for optimum uptake to ensure that this complex does not dissociate to a substantial degree in the intestine. However, at the pH of 7 to 9 prevailing in the small intestine and at low concentrations, the neutral 2:1 complex will be dissociated to form a similar mixture as is described above for a 2:1 ratio of maltol:zinc at a pH of 7.4 (although with a slight increase in the indicated proportion of the 2:1 complex relative to the free metal if the pH is nearer to 9 than 7). The problems posed by this dissociation, which are particularly relevant in the case of the preferred hydroxypyrrone ligands, may however be overcome by formulating the 2:1 complex in the presence of the free compound(s) which provide the ligand(s) present in the complex, the dissociation then being opposed through a mass action effect. The extent of this effect is illustrated by the figures quoted above of 15, 68 and 82% for the proportion of zinc present as the 2:1 zinc(II) complex with maltol:zinc ratios of 2:1, 10:1 and 20:1, respectively.

When using a mixture of one 2:1 neutral zinc complex containing two identical ligands derived from one compound and a second 2:1 neutral zinc complex containing two identical ligands derived from another compound, it will be usual to combine this mixture together with both ligand-providing compounds in the free form. It will also be usual to use the mixture of both ligand-providing compounds in the free form when the 2:1 neutral zinc complex contains two ligands derived from different compounds. A specific example of such a mixture of complexes and free compounds is the mixture consisting of zinc maltol, zinc ethylpyrromeconic acid, maltol and ethylpyrromeconic acid. A mixture of these compounds in the solid form may either be produced by admixture of the four individual components or directly by reaction of a mixture of an excess maltol and ethylpyrromeconic acid with a zinc salt in solution, followed by the isolation of a solid product which will also contain a proportion of the mixed (maltol)(ethylpyrromeconic acid) 2:1 neutral zinc complex. Mixtures containing more than one metal-free compound may also be used with advantage when a 2:1 neutral zinc complex containing two ligands derived from one compound is used together with a 3:1 neutral iron complex containing three ligands derived from another compound.

It can be advantageous therefore to include any proportion of the metal-free compound or compounds in admixture with the zinc complexes according to the present invention, particularly the 2:1 neutral complexes, but little further advantage accrues from increasing the proportion beyond a certain level and the administration of large amounts of the free compound or compounds may be physiologically

undesirable in certain instances. A preferred range for the molar proportion of the free compound present in compositions according to the present invention which contain a zinc complex in which each ligand is identical is thus from 0 to 100 moles of free compound:1 mole of zinc complex, particularly of the neutral 2:1 zinc complex. Conveniently, a proportion of up to no more than 50, 30 or especially 20 moles: 1 mole is used with a lower level of 0.5, 1 or 2 moles: 1 mole. A particularly preferred range is from 2 or 3 up to 18 or 20 moles of free compound:1 mole of zinc complex, particularly 2 or 3 up to 8 or 10 moles:1 mole. When there is more than one zinc bound ligand present in the composition, either in the form of a mixed ligand zinc complex and/or a mixture of zinc complexes, then the proportion of each free ligand-providing compound to the zinc complex containing that ligand may conveniently also fall in the ranges indicated above. It will be appreciated, however, when more than one ligand-providing compound is present it is less likely that the proportion of each will be towards the upper end of the widest range of 0 to 100 moles of free compound: 1 mole of zinc complex, the proportion being more likely to lie in a range of 0.5 to 50 moles:1 mole or such lower ranges as are quoted above. When a iron complex is present containing a different ligand from any present in a zinc complex, it may be advantageous to include in the composition a similar proportion of free compounds to iron complex as discussed above for the zinc complexes.

By way of further exemplification it may be stated that a typical composition in unit dosage form may often comprise an amount of zinc complex or complexes containing from 1 to 15 mg of zinc together with a total amount of 20 to 25 mg of the ligand-providing compound or compounds in both free and complexed form, for example 5 mg of zinc with 100 mg of a hydroxypyrrone or hydroxypyrrone mixture. In the case of mixed zinc complex/iron complex compositions, these may typically contain from 1 to 10 mg of zinc together with 10 to 20 mg of iron and a total amount of 90 to 360 mg of the ligand-providing compound or compounds in both free and complexed form, for example 2 mg of zinc together with 15 mg of iron and 135 mg of a hydroxypyrrone or hydroxypyrrone mixture.

It will be appreciated that such metal-free compound/zinc complex mixtures in the proportions described above are novel and that such novel mixtures are included by the present invention.

Zinc complexes according to the present invention, such as the 2:1 neutral maltol:zinc(II) complex, are superior when used alone to zinc sulphate which is currently in use for the treatment of zinc depletion, both in relation to absorption and to emetic effect. However, it should be stressed that the use of these complexes in admixture with the free ligand-providing compound or compounds leads to an even further improvement with a significantly higher uptake of zinc, and that such mixtures are therefore a very important feature of the present invention.

Before a zinc complex administered orally reaches the intestine it must of course pass through the stomach and, unless steps are taken to prevent it, dissociation of the complex will occur. At the acidic pH of 1 to 3 such as prevails in the stomach a 2:1 complex will be almost completely dissociated to the free metal together with the free ligand-providing compound. The use of the complex in admixture with the metal-free compound(s) in the same way as described above will have some effect on the dissociation of the zinc complex in the stomach. In contrast with the corresponding Iron complexes, however, where a relatively small amount of the free compound(s) can be significantly inhibit dissociation under acidic condition, (the presence of the free compound in the proportions previously indicated therefore serving a further function in mixed zinc complex/iron complex formulations), the bias towards the formation of the free metal at a low pH is so marked for the zinc complexes that a significant degree of dissociation will still occur unless a very large proportion of the free compound is used, and this may be undesirable from a physiological point of view in certain instances.

Once it passes from the stomach the dissociated complex should reform in the small intestine if the free metal and the metal-free compound in a suitable proportion are cleared simultaneously from the stomach, particularly if some amount of the free compound is present in the initial formulation. However, it is preferred to formulate the zinc complex in such a way as to prevent or reduce such dissociation (such methods of formulation also having a similar advantageous effect with respect to preventing dissociation of the iron complexes of mixed zinc/iron formulations). In particular, one of several variations may be employed which avoid or reduce exposure of the zinc complex to the acidic conditions of the stomach. Such approaches may involve various types of controlled release system, ranging from one, which may for example be based on a polymer, which simply provides a delayed release of the complex with time, through a system which is resistant to dissociation under acidic conditions, for example by the use of buffering, to a system which is biased towards release under conditions such as prevail in the small intestine, for example a pH sensitive system which is stabilised towards a pH of 1 to 3 such as prevails in the stomach but not one of 7 to 9 such as prevails in the small intestine. Since the pH of the stomach is higher after a meal, it may be advantageous, whatever method of formulation is used, to administer the zinc complexes at such a time.

A particularly convenient approach to a controlled release composition involves encapsulating the zinc complex by a material which is resistant to dissociation in the stomach but which is adapted towards dissociation in the small intestine (or possibly, if the dissociation is slow, in the large intestine). Such encapsulation may be achieved with liposomes, phospholipids generally being resistant to dissociation under acidic conditions. The liposomally entrapped 2:1 zinc(II) complexes can therefore survive the acid environment of the stomach without dissociating. On entry into the small intestine the pancreatic enzymes rapidly destroy the phospholipid-dependent structure of the liposomes thereby releasing the 2:1 complex.

Liposome disruption is further facilitated by the presence of bile salts. However, it is usually more convenient to effect the encapsulation, including microencapsulation, by the use of a solid composition of a pH sensitive nature.

The preparation of solid compositions adapted to resist dissociation under acidic conditions but adapted towards dissociation under non-acidic conditions is well known in the art and most often involves the use of enteric coating, whereby tablets, capsules (including spansules), etc., or the individual particles or granules contained therein, are coated with a suitable material. Such procedures are described, for example, in the article entitled "Production of enteric coated capsules" by Jones in *Manufacturing Chemist and Aerosol News*, May 1970, and in such standard reference books as "Pharmaceutical Dosage Forms", Volume III by Liebermann and Lackmann (published by Marcell Decker). One particular method of encapsulation involves the use of gelatine capsules coated with a cellulose acetate phthalate/diethyl-phthalate layer. This coating protects the gelatin capsule from the action of water under the acid conditions of the stomach where the coating is protonated and therefore stable. The coating is however destabilised under the neutral/alkaline conditions of the intestine where it is not protonated, thereby allowing water to act on the gelatin. Once released in the intestine the rate of permeation of the intestine wall by the water soluble 2:1 zinc(II) complex is relatively constant irrespective of the position within the intestine, i.e. whether in the jejunum, ileum or large intestine. Other examples of methods of formulation which may be used include the use of polymeric hydrogen formulations which do not actually encapsulate the zinc complex but which are resistant to dissociation under acidic conditions.

In addition to their pharmaceutical use in the treatment of zinc depletion, the zinc complexes of the present invention also have potential for use in other pharmaceutical applications. Various zinc compounds have been shown to have bactericidal and fungicidal properties, being used particularly in dermatological preparations and in preparations for the treatment of infections of the eye. There is also evidence that zinc deficiency is associated with impaired wound healing, zinc compounds therefore also having a useful role in this context. However, many of the existing zinc compounds used pharmaceutically have an irritant/astringent action which is undesirable and the zinc complexes of the present invention are of potential value for use in such other pharmaceutical contexts by virtue of their lack of irritancy, astringency and toxicity as compared with the previously used compounds. The zinc complexes of the present invention, including the 3:1 and especially the 1:1 complexes as well as the 2:1 complexes, are thus of marked interest in the treatment of topical reactions involving either bacteria or fungi where there is an overlying inflammatory component and/or delayed wound healing.

For such different pharmaceutical uses various forms of composition as described hereinbefore may be used although compositions suited to localised treatment such as creams, lotions or drops, and including shampoos, are of particular interest. It should be appreciated that the presence of the metal-free ligand-providing compound(s) in such compositions in the proportions discussed hereinbefore may again be of value for the same or other reasons to those previously discussed.

In addition to use in the form of a purely pharmaceutical composition, the zinc complexes described herein are of interest for use as an active ingredient of foodstuffs, particularly for incorporation into the so-called infant formulae for baby feeding. The lack of irritancy/astringency referred to above and the consequent quite acceptable taste of the zinc complexes, for example the neutral 2:1 complexes of zinc maltol and zinc ethylpyromeconic acid, renders them particularly suited to this role.

Such infant formulae are well known, being described for example by Lönnerdal *et al* in the *American Journal of Diseases of the Child*, 1983, 137, 433, being based on a human milk substitute such as cow's milk or soy protein and often containing supplies of other metals such as iron, copper and manganese. Of particular interest are foodstuffs which comprise a zinc complex/iron complex mixture as discussed hereinbefore in view of the lack of mutual inhibitory effect on bioavailability of the metals as previously discussed. It will be appreciated, however, that where the complex(es) contained in the foodstuff are not protected from the acid conditions of the stomach the additional incorporation into the foodstuff of the metal-free compound will be of particular convenience in controlling dissociation, and/or aiding reformation of the complex on clearance from the stomach, a quite large excess of the free compound sometimes being appropriate in these circumstances.

The present invention thus further includes a foodstuff which comprises a nutritional material and a zinc complex as defined hereinbefore.

The invention is illustrated by the following Examples:—

EXAMPLES

Example 1

(A) The preparation of zinc maltol

A chloroform solution of maltol⁽¹⁾ is mixed with a 1M solution of zinc chloride in ethanol to provide a 2:1 molar ratio of maltol:zinc in the mixture. After 5 minutes at 20°C, a 10 molar excess of solid sodium carbonate is added and the mixture is stirred for 10 minutes. The mixture is then filtered and the solvent evaporated to give the neutral complex containing maltol and Zn⁺⁺ in a 2:1 proportion. Recrystallisation of the 2:1 complex from ethanol gives a white crystalline solid in essentially quantitative yield, m.p. 203—204°C (with decomposition); $\nu_{\max}$ (nujol) 1632, 1603 cm⁻¹; δ (d₆DMSO) 7.96 (d, 1H), 6.40 (d, 1H), 2.20 (s, 3H).

(B) The preparation of zinc ethylpyromeconic acid

The procedure described under (A) is followed with ethylpyromeconic acid in place of maltol to give the neutral 2:1 complex from ethanol as a white crystalline solid in essentially quantitative yield, m.p. 271—272°C; $\nu_{\max}$ (nujol) 1620, 1560, 1530 cm⁻¹; δ (d₆DMSO) 8.0 (d, 2H), 6.4 (d, 2H), 2.6 (q, 4H), 1.0 (t, 6H).

Example 2

The preparation of (maltol)(ethylpyromeconic) acid zinc complex

A chloroform solution containing 1 molar equivalent of each of maltol and ethylpyromeconic acid⁽²⁾ is mixed with a 1M solution of zinc chloride in ethanol to provide a 2:1 molar ratio of ligand providing compound:zinc in the mixture. After 5 minutes at 20°C, a 10 molar excess of solid sodium carbonate is added and the mixture is stirred for 10 minutes. The mixture is then filtered and the solvent evaporated to give a white crystalline solid containing the neutral 2:1 (maltol)(ethylpyromeconic acid) zinc(II) complex as the predominant product, m.p. 136—138°C; $\nu_{\max}$ (nujol) 1610, 1570 cm⁻¹; δ (d₆DMSO) 8.0 (d, 2H), 6.4 (d, 2H), 2.6 (q, 2H), 2.2 (s, 3H), 1.0 (t, 3H). (The solid is not recrystallised as this could lead to a redistribution of the ligands.)

Example 3

(A) The preparation of zinc 1-ethyl-3-hydroxypyrid-2-one

A chloroform solution of 1-ethyl-3-hydroxypyrid-2-one⁽³⁾ is mixed with a 1M solution of zinc chloride in ethanol to provide a 2:1 molar ratio of hydroxypyridone:zinc in the mixture. After 5 minutes at 20°C, a 10 molar excess of solid sodium carbonate is added and the mixture is stirred for 10 minutes. The mixture is then filtered and the solvent evaporated to give the neutral complex containing the hydroxypyridone and Zn⁺⁺ in a 2:1 proportion. Recrystallisation of the 2:1 complex from ethanol gives a white crystalline solid in essentially quantitative yield, m.p. 200°C (with decomposition); $\nu_{\max}$ 1620 cm⁻¹; δ (d₆DMSO), 6.80 (q, 1H), 6.30 (m, 2H), 4.01 (q, 2H), 3.3 (s, 3H), 1.23 (t, 3H).

(B) The preparation of zinc 3-hydroxy-1,2-dimethylpyrid-4-one

The procedure described under (A) is followed with 3-hydroxy-1,2-dimethylpyrid-4-one in place of 1-ethyl-3-hydroxypyrid-2-one to give the neutral 2:1 complex from ethanol as a white crystalline solid in essentially quantitative yield, m.p. 190°C (with decomposition); $\nu_{\max}$ 1655, 1612 cm⁻¹; δ (d₆DMSO); 7.53 (d, 1H), 6.20 (d, 1H), 3.70 (s, 3H), 2.33 (s, 3H).

Example 4

Partition data on zinc complexes and on ligand-providing compounds

The partition coefficient K_{part} being the ratio (concentration in n-octanol)/(concentration in aqueous phase) on partition between n-octanol and aqueous tris hydrochloride (20 mM, pH 7.4; Tris represents 2-amino-2-hydroxymethylpropane 1,3-diol), is measured at 20°C for zinc complexes containing various ligands and for their corresponding ligand-providing compounds as listed in Table 1. In the case of certain of the complexes the partition coefficient for the 2:1 ligand:zinc(II) complex is also measured in the presence of various amounts of the metal-free ligand-providing compound in excess of a 1:2 zinc(II):compound ratio.

⁽¹⁾ The concentration of the maltol is 0.02M although this figure may be varied for this and other hydroxypyrones, for example in a range of 0.01 to 0.5M, being constrained at the upper end of the range by the solubility of the compound in the reaction solvent.

⁽²⁾ The concentration of both maltol and ethyl pyromeconic acid is 0.02M in each case although this figure may be varied as discussed in the footnote to Example 1.

⁽³⁾ The concentration of the 1-ethyl-3-hydroxypyrid-2-one is 0.02M although this figure may be varied for this and other hydroxypyridones, for example in a range of 0.01 to 0.5M, being constrained at the upper end of the range by the solubility of the compound in the reaction solvent.

In each case, the material is dissolved initially in the aqueous Tris hydrochloride at a concentration of 10^{-4} M in relation to zinc. The zinc complexes radiolabelled with ^{65}Zn are prepared *in situ* in the buffer by the addition of ^{65}Zn labelled ZnCl_2 to an appropriate amount of the metal-free ligand-providing compound and subsequent adjustment of the pH to 7.4 by the addition of Tris free base. Acid washed glassware is used throughout and, following mixing of 5 ml of the 10^{-4} M aqueous solution with 5 ml of n-octanol for 1 minute, the aqueous n-octanol mixture is centrifuged at 1,000 g for 30 seconds. The two resulting phases are separated for a concentration determination. In the case of the ligand-providing compounds the determination is effected by spectrophotometry in the range 220—340 nm whilst in the case of the complexes the determination is effected by counting the ^{65}Zn .

Results typical of those obtained are shown in Table 1, the partition coefficients being quoted for the first two zinc complexes for different overall ratios of zinc:compound, the first two molar proportions of the compound:zinc being available for binding to the zinc in a 2:1 ligand:zinc(II) complex and the others representing free compound (i.e. a 1:4 zinc(II):compound ratio indicating 1 molar proportion of the 2:1 complex and 2 molar proportions of the free compound if a complete conversion of zinc to the 2:1 complex occurs, although it will be appreciated that not all of the zinc will in fact be present as the 2:1 complex, the proportion in this form being increased by a mass action effect as the proportion of ligand-free compound increases).

By the use of simultaneous equations and the known populations of complexes containing different proportions of zinc:ligand present under the conditions used in this experiment, it is possible to calculate theoretical K_{part} values for neutral 2:1 ligand:zinc(II) complexes of maltol and ethylpyromeconic acid, those being 0.11 and 1.33 respectively as quoted hereinbefore. It will be seen that the value quoted in the Table for a 1:2 zinc(II):compound ratio is in each case considerably less but it will be appreciated that these are measured values which reflect the fact that only a proportion of the maltol or ethylpyromeconic acid is bound to zinc as the 2:1 ligand:zinc(II) complex under these conditions. As the ratio is increased with a consequent increase in the amount of the 2:1 complex which is present, it will be seen that the measured values approach the calculated values.

TABLE 1
Partition coefficients

Ligand-providing compound	Free compound K_{part}	Zinc complex	
		Zinc:compound molar ratio	K_{part}
maltol	0.66	1:2	0.038
		1:6	0.078
		1:20	0.109
ethylpyromeconic acid	0.75	1:2	0.172
		1:6	0.653
		1:20	1.241
3-hydroxy-1-methylpyrid-2-one	0.44	1:2	0.13
1-ethyl-3-hydroxypyrid-2-one	0.52	1:2	0.76
3-hydroxy-1-propylpyrid-2-one	0.78	1:2	2.74

Example 5

The ability of zinc complexes to donate zinc to apotransferrin

Apotransferrin (10^{-4} M) and the ^{65}Zn radiolabelled zinc complex of maltol (the complex being prepared *in situ* in the buffer using ^{65}Zn radiolabelled ZnSO_4 at a concentration of 10^{-4} M and a 10 molar proportion of maltol) were incubated together in Tris hydrochloride (50 mM, buffered to pH 7.4) at 37°C for 10 minutes when a 1 ml aliquot was removed from the medium and added to a PD10 column. 0.5 ml fractions were collected directly into scintillation vials for counting. The ^{65}Zn associated with both the apotransferrin and the maltol was estimated and it was found that over 95% of the zinc had been removed from the zinc complex.

Example 6

In vitro tests on permeation of zinc complexes into human erythrocytes

The accumulation of zinc by human erythrocytes which are associated with the neutral 2:1 ligand:zinc(II) complexes of maltol and ethylpyromeconic acid was studied by incubating for 1 hour at 37°C a 5% suspension of erythrocytes in a medium consisting of the ^{65}Zn radiolabelled zinc complex in aqueous sodium chloride (130 mM) buffered to pH 7.4 by 20 mM Tris hydrochloride (2 ml). The zinc complex was formed *in situ* in the buffered solution using ^{65}Zn labelled ZnSO_4 at a concentration of 0.25 mM together with maltol or ethylpyromeconic acid in a molar ratio of zinc:compound of 1:0, 1:2, 1:5, 1:10 or 1:20, i.e. the concentration of the ligand-providing compound being 0, 0.5, 1.25, 2.5 or 5 mM, respectively. The proportions of 1:2, 1:5, 1:10 and 1:20 provide an increasing amount of the neutral 2:1 zinc(II) complex together with varying amounts of the free compound as explained in Example 4, a small amount of Tris free base (to about 2 mM) being added to avoid an acid pH on reaction to form the complex.

Following the period of incubation, an aliquot of the erythrocyte/medium mixture was placed above a layer of silicone oil and the erythrocytes separated by centrifugation through the oil. The ^{65}Zn levels associated with the erythrocytes and the incubation medium were then counted. The results obtained are shown in Table 2 where the amount of ^{65}Zn entering erythrocytes (n.mole per 20 μl of packed erythrocytes) is given, the quoted values being in each case the mean of three determinations. It will be seen that the uptake increases with an increase in the amount of free compound present as the proportion of zinc present as the 2:1 complex is increased through the mass action effect.

TABLE 2

Uptake of zinc complexes by erythrocytes

Ligand-providing compound	Zinc:compound molar ratio	Uptake of zinc (n.mole)
none	1:0	2.0
	1:2	6.7
	1:5	7.9
	1:10	8.5
	1:20	14.4
ethylpyromeconic acid	1:2	8.5
	1:5	20.0
	1:10	28.0
	1:20	35.0

Example 7

(A) In vitro tests on permeation of rat jejunal sac by zinc complexes

The zinc uptake into the serosal space of the inverted rat jejunal sac was compared for the 2:1 neutral ligand:zinc(II) complexes of maltol, ethylpyromeconic acid, 1-ethyl-3-hydroxypyrid-2-one and 3-hydroxy-1-propylpyrid-2-one. Rats (male Sprague Dawley, 60 g) were killed and the jejunum removed, everted and cut into three segments (4 cm length). The segments were tied at both ends and filled with Krebs Ringer buffer

(0.2 ml) and incubated in Krebs Ringer buffer containing ^{65}Zn complexes at 37°C for periods up to 1 hour (the zinc complexes were prepared *in situ* at similar concentrations by an analogous procedure to that described in Example 6 but not using any Tris free base). The contents of the sac were counted for ^{65}Zn , the results obtained being shown in Table 3 where the amount of ^{65}Zn entering the serosal compartment of the sac is given in n.mole, the quoted values being in each case the mean of three determinations. In the case of the hydroxypyrrone ligands it will be seen that the uptake again increases with the increase in the amount of free compound which is present as a result of an increase in the amount of the 2:1 complex which is present.

TABLE 3

Permeation of rat jejunal sac by zinc complexes

Ligand-providing compound	Zinc:compound molar ratio	Uptake of zinc (n.mole)
none	1:0	10.0
maltol	1:2	12.2
	1:5	32.4
	1:10	41.8
	1:20	76.5
ethylpyrromeconic acid	1:10	33.4
	1:20	41.9
1-ethyl-3-hydroxypyrid-2-one	1:2	36.4
	1:10	24.2
3-hydroxy-1-propylpyrid-2-one	1:2	22.0

(B) In vitro tests on permeation of rat jejunal sac by mixtures of zinc and iron

The procedure described under (A) is used to study the uptake of zinc from buffer containing a 10^{-3}M concentration of zinc in the form of ^{65}Zn radiolabelled zinc sulphate in admixture in a 1:10 molar proportion with maltol, the uptake being measured in the absence of any iron compound, and in the presence of a 10^{-3}M concentration of iron either as ferrous sulphate or as the 3:1 maltol:iron(III) complex in the presence of free maltol (1:10 overall molar proportion of ferric chloride:maltol).

In an exactly similar manner the uptake of iron from buffer containing a 10^{-3}M concentration of iron in the form of ^{59}Fe labelled ferric chloride in admixture in a 1:10 molar proportion with maltol is studied. The uptake is measured in the absence of any zinc compound and in the presence of 10^{-3}M zinc either as zinc sulphate or as the 2:1 maltol:zinc(II) complex in the presence of free maltol (1:10 overall molar proportion of zinc sulphate:maltol).

The contents of the sac are counted for ^{65}Zn or ^{59}Fe , the results obtained being shown in Tables 4 and 5 where the amount of zinc or iron entering the serosal compartment of the sac is given in n.mole, the quoted values being in each case the mean of three determinations. It will be seen that in the presence of an excess of the hydroxypyrrone ligand-providing compound there is no significant mutual inhibition of the uptake of either iron or zinc from a neutral complex formed with that hydroxypyrrone ligand. Although a slight inhibition of iron uptake from iron maltol in admixture with free maltol was observed in the presence of zinc sulphate, this inhibition was not observed in the presence of zinc maltol. (In these various experiments the 1:10 proportion of zinc:maltol is required in order to ensure that a substantial proportion of the metal is bound to the ligand in the form of the neutral 2:1 maltol:zinc(II) complex, and a similar proportion of iron:maltol is employed for conformity).

TABLE 4

Influence of zinc on iron uptake

Component containing zinc	Component containing iron	Uptake of zinc (n.mole)
1:10 zinc(II):maltol	none	42
1:10 zinc(II):maltol	iron(II) sulphate	39
1:10 zinc(II):maltol	1:10 iron(III):maltol	46

TABLE 5

Influence of zinc on iron uptake

Component containing iron	Component containing zinc	Uptake of zinc (n.mole)
1:10 iron(III):maltol	none	44
1:10 iron(III):maltol	zinc sulphate	33
1:10 iron(III):maltol	1:10 zinc(II):maltol	45

Example 8

In vivo test of action of zinc complexes in the rat

Two rats (300—350 g) were anaesthetised with Nembutal (0.25 ml) and then with ether. A mid-line incision was made and the ^{65}Zn radiolabelled sample (20 μm Zn, 1 μCi) containing a 1:10 overall molar proportion of zinc sulphate:maltol (prepared as described in Example 5) was passed into the lumen of the duodenum via a small incision. The abdominal wall was then closed with a suture. The animals were sacrificed at 2 and 4 hours, respectively, after the administration of the sample and the various organs were monitored for their ^{65}Zn content. Table 6 shows the levels of ^{65}Zn present after 2 hours and 4 hours in the various organs as a percentage of the amount of zinc administered. It will be seen that the totals do not amount to 100% since not all organs have been investigated but the assumption may be made that all the zinc not present in the gut washings has been absorbed, even if it has not all been located.

In the experiment, the blood levels of ^{65}Zn were found to be highest between 60 and 90 minutes after the intra-duodenal administration of the zinc complex. In the separated blood sample most of the radioactivity was found to be located in the higher molecular weight fraction of the plasma with none in the low molecular weight range indicating that the zinc was binding to plasma proteins (the separation into fraction was effected on a PD10 column.)

TABLE 6

Distribution of zinc in various rat tissues

Tissue	Amount of zinc as a percentage of the original dose	
	Rat sacrificed at 2 hours	Rat sacrificed at 4 hours
Gut washings	57.8	44.8
Gut wall	15.1	12.1
Bone marrow	1.3	2.0
Liver	6.4	10.4
Kidnies and urine	1.0	2.0
Blood	2.3	2.5
Spleen	0.2	0.4
Heart	0.1	0.2
Skeletal muscle	N.D. ⁽¹⁾	2.7
Lungs	N.D.	0.3
Testes	N.D.	0.1
Brain	N.D.	<0.01

(1) N.D. indicates that these values were not determined in the rat sacrificed at 2 hours.

Example 9

Capsule formulation of zinc maltol

(A) A preparation of the 2:1 maltol:zinc(II) complex in admixture with maltol (containing 1 part by weight of zinc to 20 parts by weight of maltol) is obtained by mixing the complex prepared as described in Example 1 with maltol in a 1:3.2 proportion by weight. The resulting preparation is divided into 50 mg quantities and added to standard gelatine capsules (16 x 5 mm), each capsule containing about 2.5 mg of zinc. The capsules are then coated with a cellulose acetate phthalate/diethylphthalate layer (6 mg coat per cm² of capsule surface) in a small scale procedure analogous to the procedure described by Jones, *ibid.* Such capsules are resistant to dissociation in the stomach but will undergo dissociation in the intestine.

(B) In an alternative preparation, the mixture of the 2:1 maltol:zinc(II) complex and maltol used in (A) is replaced by a mixture of the 2:1 maltol:zinc(II) complex, the 3:1 maltol:iron(III) complex and maltol in a 2:23:5 proportion by weight to provide a 2:15:135 proportion by weight of zinc:iron:maltol (bound and unbound). Each capsule contains about 0.65 mg of zinc and 5 mg of iron.

Claims

1. A zinc(II) complex in which the liquid or each ligand separately is provided by a compound being:
 - (1) 3-hydroxy-4-pyrone or a 3-hydroxy-4-pyrone in which one or more of the hydrogen atoms attached to ring carbon atoms are replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms;
 - (2) a 3-hydroxypyrid-2-one or 3-hydroxypyrid-4-one in which the hydrogen atom attached to the

TABLE 6

Distribution of zinc in various rat tissues

Tissue	Amount of zinc as a percentage of the original dose	
	Rat sacrificed at 2 hours	Rat sacrificed at 4 hours
Gut washings	57.8	44.8
Gut wall	15.1	12.1
Bone marrow	1.3	2.0
Liver	6.4	10.4
Kidnies and urine	1.0	2.0
Blood	2.3	2.5
Spleen	0.2	0.4
Heart	0.1	0.2
Skeletal muscle	N.D. ⁽¹⁾	2.7
Lungs	N.D.	0.3
Testes	N.D.	0.1
Brain	N.D.	<0.01

(1) N.D. indicates that these values were not determined in the rat sacrificed at 2 hours.

Example 9

Capsule formulation of zinc maltol

(A) A preparation of the 2:1 maltol:zinc(II) complex in admixture with maltol (containing 1 part by weight of zinc to 20 parts by weight of maltol) is obtained by mixing the complex prepared as described in Example 1 with maltol in a 1:3.2 proportion by weight. The resulting preparation is divided into 50 mg quantities and added to standard gelatine capsules (16 x 5 mm), each capsule containing about 2.5 mg of zinc. The capsules are then coated with a cellulose acetate phthalate/diethylphthalate layer (6 mg coat per cm² of capsule surface) in a small scale procedure analogous to the procedure described by Jones, *ibid*. Such capsules are resistant to dissociation in the stomach but will undergo dissociation in the intestine.

(B) In an alternative preparation, the mixture of the 2:1 maltol:zinc(II) complex and maltol used in (A) is replaced by a mixture of the 2:1 maltol:zinc(II) complex, the 3:1 maltol:iron(III) complex and maltol in a 2:23:5 proportion by weight to provide a 2:15:135 proportion by weight of zinc:iron:maltol (bound and unbound). Each capsule contains about 0.65 mg of zinc and 5 mg of iron.

Claims

1. A zinc(II) complex in which the ligand or each ligand separately is provided by a compound being:
 - (1) 3-hydroxy-4-pyrone or a 3-hydroxy-4-pyrone in which one or more of the hydrogen atoms attached to ring carbon atoms are replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms;
 - (2) a 3-hydroxypyrid-2-one or 3-hydroxypyrid-4-one in which the hydrogen atom attached to the



nitrogen atom is replaced by an aliphatic acyl group, by an aliphatic hydrocarbon group of 1 to 6 carbon atoms, or by an aliphatic hydrocarbon group substituted by one or more substituents selected from aliphatic acyl, alkoxy, aliphatic amide, aliphatic ester, halogen and hydroxy groups and, optionally, in which one or more of the hydrogen atoms attached to ring carbon atoms are replaced by one of said substituents, by an aliphatic hydrocarbon group of 1 to 6 carbon atoms, or by an aliphatic hydrocarbon group substituted by an alkoxy, aliphatic ester, halogen or hydroxy group; or

(3) an alternative compound providing a physiologically acceptable, monobasic, bidentate ligand which is capable of bonding covalently to zinc; but with the proviso that at least one of the ligands is of type (1) or (2); for use in therapy.

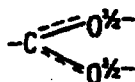
2. A zinc(II) complex in which the ligand or each ligand separately is provided by a compound being:

(1) 3-hydroxy-4-pyrone or a 3-hydroxy-4-pyrone in which one or more of the hydrogen atoms attached to ring carbon atoms are replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms;

(2) a 3-hydroxypyrid-2-one or 3-hydroxypyrid-4-one in which the hydrogen atom attached to the nitrogen atom is replaced by an aliphatic acyl group, by an aliphatic hydrocarbon group of 1 to 6 carbon atoms, or by an aliphatic hydrogen group substituted by one or more substituents selected from aliphatic acyl, alkoxy, aliphatic amide, aliphatic ester, halogen and hydroxy groups and, optionally, in which one or more of the hydrogen atoms attached to ring carbon atoms are replaced by one of said substituents, or by an aliphatic hydrocarbon group of 1 to 6 carbon atoms, or by an aliphatic hydrocarbon group substituted by an alkoxy, aliphatic ester, halogen or hydroxy group; or

(3) an alternative compound providing a physiologically acceptable, monobasic, bidentate ligand which is capable of bonding covalently to zinc; but with the proviso that at least one of the ligands is of type (1) or (2) and excluding complexes in which the ligand is provided by a compound, or each ligand is provided by the same compound, which is 3-hydroxy-4-pyrone, 3-hydroxy-2-methyl-4-pyrone, 3-hydroxy-6-methyl-4-pyrone or 3-hydroxy-1-methylpyrid-4-one.

3. A complex according to Claim 1 or 2, in which the compound of type (3) either contains a first grouping which is an enolic hydroxy group or a carboxy group and a second grouping which is an amine group of a hydroxy group, or is a monocarboxylic acid providing an anion containing a grouping



4. A complex according to Claim 3, in which the compound of type (3) is formic acid, acetic acid, propionic acid, lactic acid, gluconic acid, ascorbic acid, glycine, leucine, isoleucine, methionine, phenylalanine, tyrosine, valine or a di- and tri-peptide containing the same or different amino acid residues selected from this last mentioned group of seven amino acids.

5. A complex according to Claim 4, in which the compound of type (3) is gluconic acid, ascorbic acid, glycine or leucine.

6. A complex according to any one of Claims 1 to 5, in which the ligand or each ligand separately is provided by a compound selected from those of types (1) and (2).

7. A complex according to any of Claims 1 to 5, in which at least two ligands are provided by compounds of different types among (1), (2) and (3).

8. A complex according to Claim 1 or 2, in which at least two ligands are provided by compounds of different types among (1) and (2).

9. A complex according to any of Claim 1 to 7, in which at least one ligand is provided by a compound of type (1).

10. A complex according to Claim 1, in which each ligand separately is provided by a compound selected from those of type (1).

11. A complex according to Claim 2, in which each ligand separately is provided by a compound selected from those of type (1).

12. A complex according to Claim 10 or 11, in which each ligand is provided by the same compound of type (1).

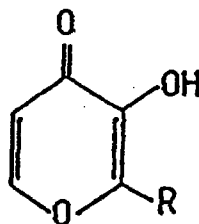
13. A complex according to any one of the preceding claims, in which the compound of type (1) is 3-hydroxy-4-pyrone or a 3-hydroxy-4-pyrone in which one or more of the hydrogen atoms attached to ring carbon atoms are replaced by an acyclic group of 1 to 4 carbon atoms.

14. A complex according to Claim 13, in which the compound is 3-hydroxy-4-pyrone or a 3-hydroxy-4-pyrone in which one or more of the hydrogen atoms attached to ring carbon atoms are replaced by the same or different substituents selected from methyl, ethyl, n-propyl and isopropyl groups.

15. A complex according to Claim 14, in which the substituted 3-hydroxy-4-pyrone has a single substituent at the 2- or 6-position.

16. A complex according to Claim 13, in which the compound is of formula





wherein R is methyl, ethyl, n-propyl, isopropyl or butyl.

17. A complex according to Claim 14, in which the compound is 3-hydroxy-4-pyrone, 3-hydroxy-2-methyl-4-pyrone, 3-hydroxy-6-methyl-4-pyrone or 2-ethyl-3-hydroxy-4-pyrone.

18. A complex according to any of Claims 1 to 7, in which at least one ligand is provided by a compound of type (2).

19. A complex according to Claim 18, in which each ligand separately is provided by a compound selected from those of type (2).

20. A complex according to Claim 19, in which each ligand is provided by the same compound of type (2).

21. A complex according to Claim 18, 19 or 20, in which the compound of type (2) is a 3-hydroxypyrid-2-one or 3-hydroxypyrid-4-one in which the hydrogen atom attached to the nitrogen atom is replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms and, optionally, in which one or more of the hydrogen atoms attached to ring carbon atoms are replaced by the same or different aliphatic hydrocarbon group of 1 to 6 carbon atoms.

22. A complex according to Claim 21, in which the or each aliphatic hydrocarbon group is an acyclic group of 1 to 4 carbon atoms.

23. A complex according to any one of Claims 18 to 22, in which the compound of type (2) is a 3-hydroxypyrid-2-one.

24. A complex according to Claim 23, in which the compound is 3-hydroxy-1-methylpyrid-2-one, 1-ethyl-3-hydroxypyrid-2-one, 3-hydroxy-1-propylpyrid-2-one or 3-hydroxy-1-(1'-methylethyl)-pyrid-2-one.

25. A complex according to any one of the preceding claims, which is a neutral 2:1 ligand:zinc(II) complex.

26. A neutral 2:1 hydroxypyrene:zinc(II) complex in which each of the two ligands is provided by the same hydroxypyrene being 3-hydroxy-4-pyrone or a 3-hydroxy-4-pyrone in which one or more of the hydrogen atoms attached to ring carbon atoms are replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms, for use in therapy.

27. A complex according to Claim 26, in which the hydroxypyrene is as defined in any of Claims 13 to 17.

28. A neutral 2:1 hydroxypyrene:zinc(II) complex in which each ligand separately is provided by 3-hydroxy-2-methyl-4-pyrone or 2-ethyl-3-hydroxy-4-pyrone, for use in therapy.

29. A neutral 2:1 hydroxypyrene:zinc(II) complex in which each of the two ligands is provided by the same hydroxypyrene being a 3-hydroxy-4-pyrone in which one or more of the hydrogen atoms attached to ring carbon atoms are replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms, but excluding 3-hydroxy-2-methyl-4-pyrone and 3-hydroxy-6-methyl-4-pyrone.

30. A complex according to Claim 29, in which the hydroxypyrene is as defined in any of Claims 13 to 17.

31. The neutral 2:1 hydroxypyrene:zinc(II) complex of 2-ethyl-3-hydroxy-4-pyrone.

32. A mixture of (a) one or more neutral 2:1 ligand:zinc(II) complexes in which each ligand is separately provided by a compound being:

(1) 3-hydroxy-4-pyrone or a 3-hydroxy-4-pyrone in which one or more of the hydrogen atoms attached to ring carbon atoms are replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms;

(2) a 3-hydroxypyrid-2-one or 3-hydroxypyrid-4-one in which the hydrogen atom attached to the nitrogen atom is replaced by an aliphatic acyl group, by an aliphatic hydrocarbon group of 1 to 6 carbon atoms, or by an aliphatic hydrocarbon group substituted by one or more substituents selected from aliphatic acyl, alkoxy, aliphatic amide, aliphatic ester, halogen and hydroxy groups and, optionally, in which one or more of the hydrogen atoms attached to ring carbon atoms are replaced by one of said substituents, by an aliphatic hydrocarbon group of 1 to 6 carbon atoms, or by an aliphatic hydrocarbon group substituted by an alkoxy, aliphatic ester, halogen or hydroxy group; or

(3) an alternative compound providing a physiologically acceptable, monobasic, bidentate ligand which is capable of bonding covalently to zinc; but with the proviso that at least one of the ligands is of type (1) or (2); and

(b) an uncomplexed compound or compounds corresponding to one or more of the ligands in the complex or complexes; the molar proportion of each uncomplexed compound:zinc complex containing that compound being from 0.5:1 to 100:1.



33. A mixture according to Claim 32, in which each ligand separately is provided by a compound selected from those of type (1).

34. A mixture according to Claim 32 or 33, in which either (a) a single zinc complex containing two identical ligands is present together with the uncomplexed compound corresponding to those ligands or (b) a single zinc complex containing two non-identical ligands or more than one zinc complex is present together with uncomplexed compounds corresponding to each of the ligands present in the complex or complexes.

35. A mixture of (a) one or more neutral 2:1 hydroxypyrrone:zinc(II) complexes in which each ligand separately is provided by 3-hydroxy-2-methyl-4-pyrone or 2-ethyl-3-hydroxy-4-pyrone and (b) each ligand-providing compound in uncomplexed form, the molar proportion of each uncomplexed compound:zinc complex containing that compound being from 0.5:1 to 100:1.

36. A mixture of (a) a zinc(II) complex in which the ligand or each ligand separately is provided by a compound being:

(1) 3-hydroxy-4-pyrone or a 3-hydroxy-4-pyrone in which one or more of the hydrogen atoms attached to ring carbon atoms are replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms;

(2) a 3-hydroxypyrid-2-one or 3-hydroxypyrid-4-one in which the hydrogen atom attached to the nitrogen atom is replaced by an aliphatic acyl group, by an aliphatic hydrocarbon group of 1 to 6 carbon atoms, or by an aliphatic hydrocarbon group substituted by one or more substituents selected from aliphatic acyl, alkoxy, aliphatic amide, aliphatic ester, halogen and hydroxy groups and, optionally, in which one or more of the hydrogen atoms attached to ring carbon atoms are replaced by one of said substituents, by an aliphatic hydrocarbon group of 1 to 6 carbon atoms, or by an aliphatic hydrocarbon group substituted by an alkoxy, aliphatic ester, halogen or hydroxy group; or

(3) an alternative compound providing a physiologically acceptable, monobasic, bidentate ligand which is capable of bonding covalently to zinc; but with the proviso that at least one of the ligands is of type (1) or (2); and

(b) a physiologically acceptable iron complex or iron salt.

37. A mixture of (a) a neutral 2:1 ligand:zinc(II) complex in which each ligand is separately provided by a compound being:

(1) 3-hydroxy-4-pyrone or a 3-hydroxy-4-pyrone in which one or more of the hydrogen atoms attached to ring carbon atoms are replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms;

(2) a 3-hydroxypyrid-2-one or 3-hydroxypyrid-4-one in which the hydrogen atom attached to the nitrogen atom is replaced by an aliphatic acyl group, by an aliphatic hydrocarbon group of 1 to 6 carbon atoms, or by an aliphatic hydrocarbon group substituted by one or more substituents selected from aliphatic acyl, alkoxy, aliphatic amide, aliphatic ester, halogen and hydroxy groups and, optionally, in which one or more of the hydrogen atoms attached to ring carbon atoms are replaced by one of said substituents, by an aliphatic hydrocarbon group of 1 to 6 carbon atoms, or by an aliphatic hydrocarbon group substituted by an alkoxy, aliphatic ester, halogen or hydroxy group; or

and (b) a neutral 3:1 ligand:iron(III) complex in which each ligand separately is provided by a compound as defined under (1) and (2).

38. A mixture according to Claim 39, in which each ligand separately in the zinc and iron complexes is provided by a compound selected from those of type (1).

39. A mixture according to Claim 37 or 38, in which the ligands of the iron complex are provided by the same compound or one or more of the same compounds which provide the ligand or ligands present in the zinc complex.

40. A mixture of (a) one or more neutral 2:1 hydroxypyrrone:zinc(II) complexes in which each ligand separately is provided by 3-hydroxy-2-methyl-4-pyrone or 2-ethyl-3-hydroxy-4-pyrone and (b) one or more neutral 3:1 hydroxypyrrone:iron(III) complexes in which each ligand separately is provided 3-hydroxy-2-methyl-4-pyrone or 2-ethyl-3-hydroxy-4-pyrone.

41. A mixture according to any of Claims 37 to 40 which additionally contains an uncomplexed compound or compounds corresponding to one or more of the ligands complexed to zinc or iron.

42. A mixture according to Claim 41, in which an uncomplexed compound or compounds are present corresponding to each of the ligands complexed to zinc and iron.

43. A pharmaceutical composition comprising a zinc(II) complex in which the ligand or each ligand separately is provided by a compound being:

(1) 3-hydroxy-4-pyrone or a 3-hydroxy-4-pyrone in which one or more of the hydrogen atoms attached to ring carbon atoms are replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms;

(2) a 3-hydroxypyrid-2-one or 3-hydroxypyrid-4-one in which the hydrogen atom attached to the nitrogen atom is replaced by an aliphatic acyl group, by an aliphatic hydrocarbon group of 1 to 6 carbon atoms, or by an aliphatic hydrocarbon group substituted by one or more substituents selected from aliphatic acyl, alkoxy, aliphatic amide, aliphatic ester, halogen and hydroxy groups and, optionally, in which one or more of the hydrogen atoms attached to ring carbon atoms are replaced by one of said substituents, by an aliphatic hydrocarbon group of 1 to 6 carbon atoms, or by an aliphatic hydrocarbon group substituted by an alkoxy, aliphatic ester, halogen or hydroxy group; or

(3) an alternative compound providing a physiologically acceptable, monobasic, bidentate ligand which is capable of bonding covalently to zinc; but with the proviso that at least one of the ligands is of type



(1) or (2) and excluding complexes in which the ligand is provided by a compound, or each ligand is provided by the same compound, which is 3-hydroxy-4-pyrone, 3-hydroxy-2-methyl-4-pyrone, 3-hydroxy-6-methyl-4-pyrone or 1-methyl-3-hydroxypyrid-4-one; together with a physiologically acceptable diluent or carrier.

44. A pharmaceutical composition comprising a zinc(II) complex in which the ligand or each ligand separately is provided by a compound being:

(1) 3-hydroxy-4-pyrone or a 3-hydroxy-4-pyrone in which one or more of the hydrogen atoms attached to ring carbon atoms are replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms;

(2) a 3-hydroxypyrid-2-one or 3-hydroxypyrid-4-one in which the hydrogen atom attached to the nitrogen atom is replaced by an aliphatic acyl group, by an aliphatic hydrocarbon group of 1 to 6 carbon atoms, or by an aliphatic hydrocarbon group substituted by one or more substituents selected from aliphatic acyl, alkoxy, aliphatic amide, aliphatic ester, halogen and hydroxy groups and, optionally, in which one or more of the hydrogen atoms attached to ring carbon atoms are replaced by one of said substituents, by an aliphatic hydrocarbon group of 1 to 6 carbon atoms, or by an aliphatic hydrocarbon group substituted by an alkoxy, aliphatic ester, halogen or hydroxy group; or

(3) an alternative compound providing a physiologically acceptable, monobasic, bidentate ligand which is capable of bonding covalently to zinc; but with the proviso that at least one of the ligands is of type (1) or (2);

together with a physiologically acceptable diluent or carrier but excluding any liquid which is not sterile and pyrogen-free.

45. A pharmaceutical composition comprising a zinc(II) complex in which the ligand or each ligand separately is provided by a compound being:

(1) 3-hydroxy-4-pyrone or a 3-hydroxy-4-pyrone in which one or more of the hydrogen atoms attached to ring carbon atoms are replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms;

(2) a 3-hydroxypyrid-2-one or 3-hydroxypyrid-4-one in which the hydrogen atom attached to the nitrogen atom is replaced by an aliphatic acyl group, by an aliphatic hydrocarbon group of 1 to 6 carbon atoms, or by an aliphatic hydrocarbon group substituted by one or more substituents selected from aliphatic acyl, alkoxy, aliphatic amide, aliphatic ester, halogen and hydroxy groups and, optionally, in which one or more of the hydrogen atoms attached to ring carbon atoms are replaced by one of said substituents, by an aliphatic hydrocarbon group of 1 to 6 carbon atoms, or by an aliphatic hydrocarbon group substituted by an alkoxy, aliphatic ester, halogen or hydroxy group; or

(3) an alternative compound providing a physiologically acceptable, monobasic, bidentate ligand which is capable of bonding covalently to zinc; but with the proviso that at least one of the ligands is of type (1) or (2);

together with a physiologically acceptable diluent or carrier, said composition being adapted for topical administration and having the form of a cream or shampoo.

46. A pharmaceutical composition according to any of Claims 43, 44 and 45, in which the complex contains ligands as defined in any of Claims 3 to 24.

47. A pharmaceutical composition according to any of Claims 43 to 46, in which the complex is a neutral 2:1 ligand:zinc(II) complex.

48. A pharmaceutical composition according to any of Claims 43 to 47 which additionally contains an uncomplexed compound or compounds corresponding to one or more of the ligands in the complex.

49. A pharmaceutical composition comprising a mixture of the neutral 2:1 3-hydroxy-2-methyl-4-pyrone:zinc(II) complex, the neutral 2:1 2-ethyl-3-hydroxy-4-pyrone:zinc(II) complex, 3-hydroxy-2-methyl-4-pyrone and 2-ethyl-3-hydroxy-4-pyrone, together with a physiologically acceptable diluent or carrier.

50. A pharmaceutical composition according to Claim 49 which additionally comprises the neutral 3:1 3-hydroxy-2-methyl-4-pyrone:iron(III) complex and/or the neutral 3:1 2-ethyl-3-hydroxy-4-pyrone:iron(III) complex.

51. The use of a zinc complex in which the ligand or each ligand separately is provided by a compound being:

(1) 3-hydroxy-4-pyrone or a 3-hydroxy-4-pyrone in which one or more of the hydrogen atoms attached to ring carbon atoms are replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms;

(2) a 3-hydroxypyrid-2-one or 3-hydroxypyrid-4-one in which the hydrogen atom attached to the nitrogen atom is replaced by an aliphatic acyl group, by an aliphatic hydrocarbon group of 1 to 6 carbon atoms, or by an aliphatic hydrocarbon group substituted by one or more substituents selected from aliphatic acyl, alkoxy, aliphatic amide, aliphatic ester, halogen and hydroxy groups and, optionally, in which one or more of the hydrogen atoms attached to ring carbon atoms are replaced by one of said substituents, by an aliphatic hydrocarbon group of 1 to 6 carbon atoms, or by an aliphatic hydrocarbon group substituted by an alkoxy, aliphatic ester, halogen or hydroxy group; or

(3) an alternative compound providing a physiologically acceptable, monobasic, bidentate ligand which is capable of bonding covalently to zinc; but with the proviso that at least one of the ligands is of type (1) or (2);

for the manufacture of a medicament for use in effecting an increase in the level of zinc in a patient's bloodstream or for use in the topical treatment of bacterial or fungal infections.



52. The use according to Claim 51, in which the complex contains ligands as defined in any of Claims 3 to 24.

53. The use according to Claim 51 or 52, in which the complex is a neutral 2:1 ligand:zinc(II) complex.

54. A foodstuff comprising a zinc complex in which the ligand or each ligand separately is provided by a compound being:

(1) 3-hydroxy-4-pyrone or a 3-hydroxy-4-pyrone in which one or more of the hydrogen atoms attached to ring carbon atoms are replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms;

(2) a 3-hydroxypyrid-2-one or 3-hydroxypyrid-4-one in which the hydrogen atom attached to the nitrogen atom is replaced by an aliphatic acyl group, by an aliphatic hydrocarbon group of 1 to 6 carbon atoms, or by an aliphatic hydrocarbon group substituted by one or more substituents selected from aliphatic acyl, alkoxy, aliphatic amide, aliphatic ester, halogen and hydroxy groups and, optionally, in which one or more of the hydrogen atoms attached to ring carbon atoms are replaced by one of said substituents, by an aliphatic hydrocarbon group of 1 to 6 carbon atoms, or by an aliphatic hydrocarbon group substituted by an alkoxy, aliphatic ester, halogen or hydroxy group; or

(3) an alternative compound providing a physiologically acceptable, monobasic, bidentate ligand which is capable of bonding covalently to zinc; but with the proviso that at least one of the ligands is of type (1) or (2);

together with a nutritional material.

55. A foodstuff according to Claim 54, in which the complex contains ligands as defined in any of Claims 3 to 24.

56. A foodstuff according to Claim 54 or 55, in which the complex is a neutral 2:1 ligand:zinc(II) complex.

Patentansprüche

1. Zink(II)-Komplex, worin der Ligand oder jeder Ligand separat durch eine Verbindung wie folgt zur Verfügung gestellt wird:

(1) 3-Hydroxy-4-pyrone oder ein 3-Hydroxy-4-pyrone, worin eines oder mehrere der Wasserstoffatome, die an Ringkohlenstoffatome gebunden sind, durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen ersetzt ist bzw. sind;

(2) ein 3-Hydroxypyrid-2-on oder 3-Hydroxypyrid-4-on, worin das Wasserstoffatom, das an das Stickstoffatom gebunden ist, durch eine aliphatische Acylgruppe, eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen oder durch eine aliphatische Kohlenwasserstoffgruppe, die durch einen oder mehrere Substituenten, ausgewählt aus aliphatischen Acyl-, Alkoxy-, aliphatischen Amid-, aliphatischen Ester-, Halogen- und Hydroxylgruppen substituiert ist, ersetzt ist, und worin gegebenenfalls eines oder mehrere der Wasserstoffatome, die an Ringkohlenstoffatome gebunden sind, durch einen der genannten Substituenten durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen oder durch eine aliphatische Kohlenwasserstoffgruppe, die durch eine Alkoxy-, aliphatische Ester-, Halogen- oder Hydroxylgruppe substituiert ist, ersetzt ist, bzw. sind; oder

(3) eine alternative Verbindung, die einen physiologisch annehmbaren einbasischen, zweizähnigen Liganden zur Verfügung stellt, der covalent an Zink binden kann; aber mit der Maßgabe, daß mindestens einer der Liganden vom Typ (1) oder (2) ist; zur therapeutischen Verwendung.

2. Zink(II)-Komplex, worin der Ligand oder jeder Ligand separat durch eine Verbindung wie folgt zur Verfügung gestellt wird:

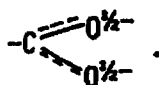
(1) 3-Hydroxy-4-pyrone oder ein 3-Hydroxy-4-pyrone, worin eines oder mehrere der Wasserstoffatome, die an Ringkohlenstoffatome gebunden sind, durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen ersetzt ist bzw. sind;

(2) ein 3-Hydroxypyrid-2-on oder 3-Hydroxypyrid-4-on, worin das Wasserstoffatom, das an das Stickstoffatom gebunden ist, durch eine aliphatische Acylgruppe, eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen oder durch eine aliphatische Kohlenwasserstoffgruppe, die durch einen oder mehrere Substituenten, ausgewählt aus aliphatischen Acyl-, Alkoxy-, aliphatischen Amid-, aliphatischen Ester-, Halogen- und Hydroxylgruppen substituiert ist, ersetzt ist, und worin gegebenenfalls eines oder mehrere der Wasserstoffatome, die an Ringkohlenstoffatome gebunden sind, durch einen der genannten Substituenten durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen oder durch eine aliphatische Kohlenwasserstoffgruppe, die durch eine Alkoxy-, aliphatische Ester-, Halogen- oder Hydroxylgruppe substituiert ist, ersetzt ist, bzw. sind; oder

(3) eine alternative Verbindung, die einen physiologisch annehmbaren einbasischen, zweizähnigen Liganden zur Verfügung stellt, der covalent an Zink binden kann; aber mit der Maßgabe, daß mindestens einer der Liganden vom Typ (1) oder (2) ist und ausgenommen die Komplexe, in denen der Ligand durch eine Verbindung zur Verfügung gestellt wird, oder jeder Ligand durch die gleiche Verbindung zur Verfügung gestellt wird, die 3-Hydroxy-4-pyrone, 3-Hydroxy-2-methyl-4-pyrone, 3-Hydroxy-6-methyl-4-pyrone oder 3-Hydroxy-1-methyl-pyrid-4-on ist.



3. Komplex nach Anspruch 1 oder 2, dadurch gekennzeichnet, daß die Verbindung vom Typ (3) entweder eine erste Gruppierung, die eine Enolhydroxylgruppe oder eine Carboxylgruppe ist und eine zweite Gruppierung, die eine Aminogruppe oder eine Hydroxylgruppe ist, enthält, oder eine Monocarbonsäure ist, deren Anion, das eine Gruppierung



enthält, zur Verfügung stellt.

4. Komplex nach Anspruch 3, dadurch gekennzeichnet, daß die Verbindung vom Typ (3) Ameisensäure, Essigsäure, Propionsäure, Milchsäure, Gluconsäure, Ascorbinsäure, Glycin, Leucin, Isoleucin, Methionin, Phenylalanin, Tyrosin, Valin oder ein Di- und Tri-peptid, das die gleichen oder verschiedene Aminosäurereste, ausgewählt aus dieser zuletzt erwähnten Gruppe von sieben Aminosäuren, enthält, ist.

5. Komplex nach Anspruch 4, dadurch gekennzeichnet, daß die Verbindung von Typ (3) Gluconsäure, Ascorbinsäure, Glycin oder Leucin ist.

6. Komplex nach einem der Ansprüche 1 bis 5, dadurch gekennzeichnet, daß der Ligand oder jeder Ligand separat durch eine Verbindung, ausgewählt aus solchen der Typen (1) und (2), zur Verfügung gestellt wird.

7. Komplex nach einem der Ansprüche 1 bis 5, dadurch gekennzeichnet, daß mindestens zwei Liganden durch Verbindungen von verschiedenen Typen unter (1), (2) und (3) zur Verfügung gestellt werden.

8. Komplex nach Anspruch 1 oder 2, dadurch gekennzeichnet, daß mindestens zwei Liganden durch Verbindungen von verschiedenen Typen unter (1) und (2) zur Verfügung gestellt werden.

9. Komplex nach Ansprüche 1 bis 7, dadurch gekennzeichnet, daß mindestens ein Ligand durch eine Verbindung vom Typ (1) zur Verfügung gestellt wird.

10. Komplex nach Anspruch 1, dadurch gekennzeichnet, daß jeder Ligand separat durch eine Verbindung, ausgewählt aus solchen vom Typ (1), zur Verfügung gestellt wird.

11. Komplex nach Anspruch 2, dadurch gekennzeichnet, daß jeder Ligand separat durch eine Verbindung, ausgewählt aus solchen vom Typ (1), zur Verfügung gestellt wird.

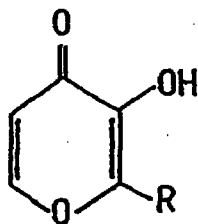
12. Komplex nach Anspruch 10 oder 11, dadurch gekennzeichnet, daß jeder Ligand durch dieselbe Verbindung vom Typ (1) zur Verfügung gestellt wird.

13. Komplex nach einem der vorausgehenden Ansprüche, dadurch gekennzeichnet, daß die Verbindung vom Typ (1) 3-Hydroxy-4-pyron oder ein 3-Hydroxy-4-pyron, worin eines oder mehrere der Wasserstoffatome, die an Ringkohlenstoffatome gebunden sind, durch eine acyclische Gruppe mit 1 bis 4 Kohlenstoffatomen ersetzt ist bzw. sind.

14. Komplex nach Anspruch 13, dadurch gekennzeichnet, daß die Verbindung 3-Hydroxy-4-pyron oder ein 3-Hydroxy-4-pyron, worin eines oder mehrere der Wasserstoffatome, die an Ringkohlenstoffatome gebunden sind, durch gleiche oder verschiedene Substituenten, ausgewählt aus Methyl-, Ethyl-, n-Propyl- und Isopropylgruppen, ersetzt ist bzw. sind.

15. Komplex nach Anspruch 14, dadurch gekennzeichnet, daß das substituierte 3-Hydroxy-4-pyron einen einzigen Substituenten an der 2- oder 6-Position besitzt.

16. Komplex nach Anspruch 13, dadurch gekennzeichnet, daß die Verbindung durch die Formel



dargestellt wird, worin R für Methyl, Ethyl, n-Propyl, Isopropyl oder Butyl steht.

17. Komplex nach Anspruch 14, dadurch gekennzeichnet, daß die Verbindung 3-Hydroxy-4-pyron, 3-Hydroxy-2-methyl-4-pyron, 3-Hydroxy-6-methyl-4-pyron oder 2-Ethyl-3-hydroxy-4-pyron ist.

18. Komplex nach einem der Ansprüche 1 bis 7, dadurch gekennzeichnet, daß mindestens ein Ligand durch eine Verbindung vom Typ (2) zur Verfügung gestellt wird.

19. Komplex nach Anspruch 18, dadurch gekennzeichnet, daß jeder Ligand separat durch eine Verbindung, ausgewählt aus solchen vom Typ (2), zur Verfügung gestellt wird.

20. Komplex nach Anspruch 19, dadurch gekennzeichnet, daß jeder Ligand durch die gleiche Verbindung vom Typ (2) zur Verfügung gestellt wird.



21. Komplex nach Anspruch 18, 19 oder 20, dadurch gekennzeichnet, daß die Verbindung vom Typ (2) ein 3-Hydroxypyrid-2-on oder 3-Hydroxypyrid-4-on ist, worin das Wasserstoffatom, das an das Stickstoffatom gebunden ist, durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen ersetzt ist, und worin gegebenenfalls eines oder mehrere der Wasserstoffatome, die an Ringkohlenstoffatome gebunden sind, durch die gleiche oder eine andere aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen ersetzt ist bzw. sind.
22. Komplex nach Anspruch 21, dadurch gekennzeichnet, daß die oder jede aliphatische Kohlenwasserstoffgruppe eine Acylgruppe mit 1 bis 4 Kohlenstoffatomen ist.
23. Komplex nach einem der Ansprüche 18 bis 22, dadurch gekennzeichnet, daß die Verbindung vom Typ (2) ein 3-Hydroxypyrid-2-on ist.
24. Komplex nach Anspruch 23, dadurch gekennzeichnet, daß die Verbindung 3-Hydroxy-1-methylpyrid-2-on, 1-Ethyl-3-hydroxypyrid-2-on, 3-Hydroxy-1-propyl-pyrid-2-on oder 3-Hydroxy-1-(1'-methylethyl)-pyrid-2-on ist.
25. Komplex nach einem der vorausgehenden Ansprüche, dadurch gekennzeichnet, daß er ein neutraler 2:1 Ligand:Zink(II)-Komplex ist.
26. Neutraler 2:1 Hydroxypyron:Zink(II)-Komplex, worin jeder der zwei Liganden durch das gleiche Hydroxypyron, nämlich 3-Hydroxy-4-pyron oder ein 3-Hydroxy-4-pyron, worin eines oder mehrere der Wasserstoffatome, die an Ringkohlenstoffatome gebunden sind, durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen ersetzt ist bzw. sind, zur Verfügung gestellt wird, zur therapeutischen Verwendung.
27. Komplex nach Anspruch 26, dadurch gekennzeichnet, daß das Hydroxypyron wie in einem der Ansprüche 13 bis 17 definiert ist.
28. Neutraler 2:1 Hydroxypyron:Zink(II)-Komplex, worin jeder Ligand separat durch 3-Hydroxy-2-methyl-4-pyron oder 2-Ethyl-3-hydroxy-4-pyron zur Verfügung gestellt wird, zur therapeutischen Verwendung.
29. Neutraler 2:1 Hydroxypyron:Zink(II)-Komplex, worin jeder der zwei Liganden durch das gleiche Hydroxypyron, nämlich 3-Hydroxy-4-pyron, worin eines oder mehrere der Wasserstoffatome, die an Ringkohlenstoffatome gebunden sind, durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen ersetzt ist bzw. sind, aber mit Ausschluß von 3-Hydroxy-2-methyl-4-pyron und 3-Hydroxy-6-methyl-4-pyron, zur Verfügung gestellt wird.
30. Komplex nach Anspruch 29, dadurch gekennzeichnet, daß das Hydroxypyron wie in einem der Ansprüche 13 bis 17 definiert ist.
31. Neutraler 2:1 Hydroxypyron:Zink(II)-Komplex von 2-Ethyl-3-hydroxy-4-pyron.
32. Gemisch aus (a) einem oder mehreren neutralen 2:1 Ligand:Zink(II)-Komplexen, worin jeder Ligand separat durch eine Verbindung wie folgt zur Verfügung gestellt wird:
- (1) 3-Hydroxy-4-pyron oder ein 3-Hydroxy-4-pyron, worin eines oder mehrere der Wasserstoffatome, die an Ringkohlenstoffatome gebunden sind, durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen ersetzt ist bzw. sind;
- (2) ein 3-Hydroxypyrid-2-on oder 3-Hydroxypyrid-4-on, worin das Wasserstoffatom, das an das Stickstoffatom gebunden ist, durch eine aliphatische Acylgruppe, eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen oder durch eine aliphatische Kohlenwasserstoffgruppe, die durch einen oder mehrere Substituenten, ausgewählt aus aliphatischen Acyl-, Alkoxy-, aliphatischen Amid-, aliphatischen Ester-, Halogen- und Hydroxylgruppen substituiert ist, ersetzt ist, und worin gegebenenfalls eines oder mehrere der Wasserstoffatome, die an Ringkohlenstoffatome gebunden sind, durch einen der genannten Substituenten durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen oder durch eine aliphatische Kohlenwasserstoffgruppe, die durch eine Alkoxy-, aliphatische Ester-, Halogen- oder Hydroxylgruppe substituiert ist, ersetzt ist, bzw. sind; oder
- (3) eine alternative Verbindung, die einen physiologisch annehmbaren einbasischen, zweizähligen Liganden zur Verfügung stellt, der covalent an Zink binden kann; aber mit der Maßgabe, daß mindestens einer der Liganden vom Typ (1) oder (2) ist; und (b) einer nicht koordinativ gebundenen Verbindung oder Verbindungen, entsprechend einem oder mehreren der Liganden in dem Komplex oder Komplexen; wobei das molare Verhältnis von jeder nicht koordinativ gebundenen Verbindung zu dem Zinkkomplex, der diese Verbindung enthält, von 0,5:1 bis 100:1 beträgt.
33. Gemisch nach Anspruch 32, dadurch gekennzeichnet, daß jeder Ligand separat durch eine Verbindung, ausgewählt aus denen vom Typ (1), zur Verfügung gestellt wird.
34. Gemisch nach Anspruch 32 oder 33, dadurch gekennzeichnet, daß entweder (a) ein einzelner Zinkkomplex, der zwei identische Liganden enthält, zusammen mit der nicht koordinativ gebundenen Verbindung entsprechend diesen Liganden, vorliegt oder (b) ein einzelner Zinkkomplex, der zwei nicht identische Liganden enthält, oder mehr als ein Zinkkomplex, zusammen mit nicht koordinativ gebundenen Verbindungen, entsprechend jedem der Liganden, der in dem Komplex oder den Komplexen vorliegt, vorliegt.
35. Gemisch nach (a) einem oder mehreren neutralen 2:1 Hydroxypyron:Zink(II)-Komplexen, worin jeder Ligand separat durch 3-Hydroxy-2-methyl-4-pyron oder 2-Ethyl-3-hydroxy-4-pyron zur Verfügung



gestellt wird und (b) jeder Verbindung, die einen Liganden zur Verfügung stellt, in nicht koordinativ gebundener Form, wobei das mol-Verhältnis von jeweils nicht koordinativ gebundener Verbindung:Zinkkomplex, der diese Verbindung enthält, von 0,5:1 bis 100:1, beträgt.

36. Gemisch aus (a) einem Zink(II)-Komplex, worin der Ligand oder jeder Ligand separat durch eine Verbindung wie folgt zur Verfügung gestellt wird:

(1) 3-Hydroxy-4-pyron oder ein 3-Hydroxy-4-pyron, worin eines oder mehrere der Wasserstoffatome, die an Ringkohlenstoffatome gebunden sind, durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen ersetzt ist bzw. sind;

(2) ein 3-Hydroxypyrid-2-on oder 3-Hydroxypyrid-4-on, worin das Wasserstoffatom, das an das Stickstoffatom gebunden ist, durch eine aliphatische Acylgruppe, eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen oder durch eine aliphatische Kohlenwasserstoffgruppe, die durch einen oder mehrere Substituenten, ausgewählt aus aliphatischen Acyl-, Alkoxy-, aliphatischen Amid-, aliphatischen Ester-, Halogen- und Hydroxylgruppen substituiert ist, ersetzt ist, und worin gegebenenfalls eines oder mehrere der Wasserstoffatome, die an Ringkohlenstoffatome gebunden sind, durch einen der genannten Substituenten durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen oder durch eine aliphatische Kohlenwasserstoffgruppe, die durch eine Alkoxy-, aliphatische Ester-, Halogen- oder Hydroxylgruppe substituiert ist, ersetzt ist, bzw. sind; oder

(3) eine alternative Verbindung, die einen physiologisch annehmbaren einbasischen, zweizähligen Liganden zur Verfügung stellt, der covalent an Zink binden kann; aber mit der Maßgabe, daß mindestens einer der Liganden vom Typ (1) oder (2) ist;

und (b) einem physiologisch annehmbaren Eisenkomplex oder Eisensalz.

37. Gemisch aus (a) einem neutralen 2:1 Ligand:Zink(II)-Komplex worin jeder Ligand separat durch eine Verbindung wie folgt zur Verfügung gestellt wird:

(1) 3-Hydroxy-4-pyron oder ein 3-Hydroxy-4-pyron, worin eines oder mehrere der Wasserstoffatome, die an Ringkohlenstoffatome gebunden sind, durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen ersetzt ist bzw. sind;

(2) ein 3-Hydroxypyrid-2-on oder 3-Hydroxypyrid-4-on, worin das Wasserstoffatom, das an das Stickstoffatom gebunden ist, durch eine aliphatische Acylgruppe, eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen oder durch eine aliphatische Kohlenwasserstoffgruppe, die durch einen oder mehrere Substituenten, ausgewählt aus aliphatischen Acyl-, Alkoxy-, aliphatischen Amid-, aliphatischen Ester-, Halogen- und Hydroxylgruppen substituiert ist, ersetzt ist, und worin gegebenenfalls eines oder mehrere der Wasserstoffatome, die an Ringkohlenstoffatome gebunden sind, durch einen der genannten Substituenten durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen oder durch eine aliphatische Kohlenwasserstoffgruppe, die durch eine Alkoxy-, aliphatische Ester-, Halogen- oder Hydroxylgruppe substituiert ist, ersetzt ist, bzw. sind; oder

oder/und (b) einem neutralen 3:1 Ligand:Eisen(III)-Komplex, worin jeder Ligand separat durch eine Verbindung, wie unter (1) und (2) definiert, zur Verfügung gestellt wird.

38. Gemisch nach Anspruch 37, dadurch gekennzeichnet, daß jeder Ligand separat in den Zink- und Eisenkomplexen durch eine Verbindung, ausgewählt aus denen vom Typ (1), zur Verfügung gestellt wird.

39. Gemisch nach Anspruch 37 oder 38, dadurch gekennzeichnet, daß die Ligand des Eisenkomplexes durch die gleiche Verbindung oder eine oder mehrere der gleichen Verbindungen, die den Liganden oder die Liganden, die in dem Zinkkomplex vorliegen, zur Verfügung stellen, zur Verfügung gestellt werden.

40. Gemisch aus (a) einem oder mehreren neutralen 2:1 Hydroxypyron:Zink(II)-Komplexen, worin jeder Ligand separat durch 3-Hydroxy-2-methyl-4-pyron oder 2-Ethyl-3-hydroxy-4-pyron zur Verfügung gestellt wird, und (b) einem oder mehreren neutralen 3:1 Hydroxypyron:Eisen(III)-Komplexen, worin jeder Ligand separat durch 3-Hydroxy-2-methyl-4-pyron oder 2-Ethyl-3-hydroxy-4-pyron zur Verfügung gestellt wird.

41. Gemisch nach einem der Ansprüche 37 bis 40, dadurch gekennzeichnet, daß es zusätzlich eine nicht koordinativ gebundene Verbindung oder Verbindungen, entsprechend einem oder mehreren der Liganden, die mit Zink oder Eisen komplexiert sind, enthält.

42. Gemisch nach Anspruch 41, dadurch gekennzeichnet, daß eine nicht komplexierte Verbindung oder Verbindungen, entsprechend jedem der Liganden, die mit Zink und Eisen komplexiert sind, vorliegt bzw. vorliegen.

43. Pharmazeutisches Präparat, dadurch gekennzeichnet, daß es einen Zink(II)-Komplex, in dem der Ligand oder jeder Ligand separat durch eine Verbindung wie folgt zur Verfügung gestellt wird.

(1) 3-Hydroxy-4-pyron oder ein 3-Hydroxy-4-pyron, worin eines oder mehrere der Wasserstoffatome, die an Ringkohlenstoffatome gebunden sind, durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen ersetzt ist bzw. sind;

(2) ein 3-Hydroxypyrid-2-on oder 3-Hydroxypyrid-4-on, worin das Wasserstoffatom, das an das Stickstoffatom gebunden ist, durch eine aliphatische Acylgruppe, eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen oder durch eine aliphatische Kohlenwasserstoffgruppe, die durch einen oder mehrere Substituenten, ausgewählt aus aliphatischen Acyl-, Alkoxy-, aliphatischen Amid-, aliphatischen Ester-, Halogen- und Hydroxylgruppen substituiert ist,



ersetzt ist, und worin gegebenenfalls eines oder mehrere der Wasserstoffatome, die an Ringkohlenstoffatome gebunden sind, durch einen der genannten Substituenten durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen oder durch eine aliphatische Kohlenwasserstoffgruppe, die durch eine Alkoxy-, aliphatische Ester-, Halogen- oder Hydroxylgruppe

5 substituiert ist, ersetzt ist, bzw. sind; oder

(3) eine alternative Verbindung, die einen physiologisch annehmbaren einbasischen, zweizähligen Liganden zur Verfügung stellt, der covalent an Zink binden kann; aber mit der Maßgabe, daß mindestens einer der Liganden vom Typ (1) oder (2) ist und ausgenommen Komplexe, in denen der Ligand durch eine Verbindung zur Verfügung gestellt wird oder jeder Ligand durch die gleiche Verbindung zur Verfügung

10 gestellt wird, die 3-Hydroxy-4-pyron, 3-Hydroxy-2-methyl-4-pyron, 3-Hydroxy-6-methyl-4-pyron oder 1-Methyl-3-hydroxy-pyrid-4-on ist;

zusammen mit einem physiologisch annehmbaren Diluenten oder Träger umfaßt.

44. Pharmazeutisches Präparat, dadurch gekennzeichnet, daß es einen Zink(II)-Komplex, in dem der Ligand oder jeder Ligand separat durch eine Verbindung wie folgt zur Verfügung gestellt wird.

15 (1) 3-Hydroxy-4-pyron oder ein 3-Hydroxy-4-pyron, worin eines oder mehrere der Wasserstoffatome, die an Ringkohlenstoffatome gebunden sind, durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen ersetzt ist bzw. sind;

(2) ein 3-Hydroxypyrid-2-on oder 3-Hydroxypyrid-4-on, worin das Wasserstoffatom, das an das Stickstoffatom gebunden ist, durch eine aliphatische Acylgruppe, eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen oder durch eine aliphatische Kohlenwasserstoffgruppe, die durch einen oder mehrere Substituenten, ausgewählt aus aliphatischen Acyl-, Alkoxy-, aliphatischen Amid-, aliphatischen Ester-, Halogen- und Hydroxylgruppen substituiert ist, ersetzt ist, und worin gegebenenfalls eines oder mehrere der Wasserstoffatome, die an Ringkohlenstoffatome gebunden sind, durch einen der genannten Substituenten durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen oder durch eine aliphatische Kohlenwasserstoffgruppe, die durch eine Alkoxy-, aliphatische Ester-, Halogen- oder Hydroxylgruppe substituiert ist, ersetzt ist, bzw. sind; oder

(3) eine alternative Verbindung, die einen physiologisch annehmbaren einbasischen, zweizähligen Liganden zur Verfügung stellt, der covalent an Zink binden kann; aber mit der Maßgabe, daß mindestens einer der Liganden vom Typ (1) oder (2) ist;

30 zusammen mit einem physiologisch annehmbaren Diluenten oder Träger aber unter Ausschluß jeder Flüssigkeit, die nicht steril und pyrogenfrei ist, umfaßt.

45. Pharmazeutisches Präparat, dadurch gekennzeichnet, daß es einen Zink(II)-Komplex, in dem der Ligand oder jeder Ligand separat durch eine Verbindung wie folgt zur Verfügung gestellt wird.

35 (1) 3-Hydroxy-4-pyron oder ein 3-Hydroxy-4-pyron, worin eines oder mehrere der Wasserstoffatome, die an Ringkohlenstoffatome gebunden sind, durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen ersetzt ist bzw. sind;

(2) ein 3-Hydroxypyrid-2-on oder 3-Hydroxypyrid-4-on, worin das Wasserstoffatom, das an das Stickstoffatom gebunden ist, durch eine aliphatische Acylgruppe, eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen oder durch eine aliphatische Kohlenwasserstoffgruppe, die durch einen oder mehrere Substituenten, ausgewählt aus aliphatischen Acyl-, Alkoxy-, aliphatischen Amid-, aliphatischen Ester-, Halogen- und Hydroxylgruppen substituiert ist, ersetzt ist, und worin gegebenenfalls eines oder mehrere der Wasserstoffatome, die an Ringkohlenstoffatome gebunden sind, durch einen der genannten Substituenten durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen oder durch eine aliphatische Kohlenwasserstoffgruppe, die durch eine Alkoxy-, aliphatische Ester-, Halogen- oder Hydroxylgruppe substituiert ist, ersetzt ist, bzw. sind; oder

(3) eine alternative Verbindung, die einen physiologisch annehmbaren einbasischen, zweizähligen Liganden zur Verfügung stellt, der covalent an Zink binden kann; aber mit der Maßgabe, daß mindestens einer der Liganden vom Typ (1) oder (2) ist;

50 zusammen mit einem physiologisch annehmbaren Diluenten oder Träger, umfaßt, wobei das Präparat der topischen Verabreichung angepaßt ist und in der Form einer Creme oder eines Shampoos vorliegt.

46. Pharmazeutisches Präparat nach einem der Ansprüche 43, 44 und 45, dadurch gekennzeichnet, daß der Komplex Liganden, wie in einem der Ansprüche 3 bis 24 definiert, enthält.

55 47. Pharmazeutisches Präparat nach einem der Ansprüche 43 bis 46, dadurch gekennzeichnet, daß der Komplex ein neutraler 2:1 Ligand:Zink(II)-Komplex ist.

48. Pharmazeutisches Präparat nach einem der Ansprüche 43 bis 47, dadurch gekennzeichnet, daß es zusätzlich eine nicht koordinativ gebundene Verbindung oder Verbindungen, entsprechend einem oder mehreren der Liganden des Komplexes, enthält.

60 49. Pharmazeutisches Präparat, dadurch gekennzeichnet, daß es ein Gemisch aus dem neutralen 2:1 3-Hydroxy-2-methyl-4-pyron:Zink(II)-Komplex, dem neutralen 2:1 2-Ethyl-3-hydroxy-4-pyron:Zink(II)-Komplex, 3-Hydroxy-2-methyl-4-pyron und 2-Ethyl-3-hydroxy-4-pyron, zusammen mit einem physiologisch annehmbaren Diluenten oder Träger, umfaßt.

50. Pharmazeutisches Präparat nach Anspruch 49, dadurch gekennzeichnet, daß es zusätzlich den neutralen 3:1 3-Hydroxy-2-methyl-4-pyron:Eisen(III)-Komplex und/oder den neutralen 3:1 2-Ethyl-3-



hydroxy-4-pyron:Eisen(III)-Komplex umfaßt.

51. Verwendung eines Zinkkomplexes, worin der Ligand oder jeder Ligand separat durch eine Verbindung wie folgt zur Verfügung gestellt wird:

(1) 3-Hydroxy-4-pyron oder ein 3-Hydroxy-4-pyron, worin eines oder mehrere der Wasserstoffatome, die an Ringkohlenstoffatome gebunden sind, durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen ersetzt ist bzw. sind;

(2) ein 3-Hydroxypyrid-2-on oder 3-Hydroxypyrid-4-on, worin das Wasserstoffatom, das an das Stickstoffatom gebunden ist, durch eine aliphatische Acylgruppe, eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen oder durch eine aliphatische Kohlenwasserstoffgruppe, die durch einen oder mehrere Substituenten, ausgewählt aus aliphatischen Acyl-, Alkoxy-, aliphatischen Amid-, aliphatischen Ester-, Halogen- und Hydroxylgruppen substituiert ist, ersetzt ist, und worin gegebenenfalls eines oder mehrere der Wasserstoffatome, die an Ringkohlenstoffatome gebunden sind, durch einen der genannten Substituenten durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen oder durch eine aliphatische Kohlenwasserstoffgruppe, die durch eine Alkoxy-, aliphatische Ester-, Halogen- oder Hydroxylgruppe substituiert ist, ersetzt ist, bzw. sind; oder

(3) eine alternative Verbindung, die einen physiologisch annehmbaren einbasischen, zweizähligen Liganden zur Verfügung stellt, der covalent an Zink binden kann; aber mit der Maßgabe, daß mindestens einer der Liganden vom Typ (1) oder (2) ist;

zur Herstellung eines Medikaments zur Verwendung zur Erhöhung des Zinkspiegels im Blutstrom eines Patienten oder zur Verwendung zur topischen Behandlung von bakteriellen Infektionen oder Pilzinfektionen.

52. Verwendung nach Anspruch 51, dadurch gekennzeichnet, daß der Komplex Liganden, wie in einem der Ansprüche 3 bis 24 definiert, enthält.

53. Verwendung nach Anspruch 51 oder 52, dadurch gekennzeichnet, daß der Komplex ein neutraler 2:1 Ligand:Zink(II)-Komplex ist.

54. Lebensmittel, dadurch gekennzeichnet, daß es einen Zinkkomplex, in dem der Ligand oder jeder Ligand separat durch eine Verbindung wie folgt zur Verfügung gestellt wird:

(1) 3-Hydroxy-4-pyron oder ein 3-Hydroxy-4-pyron, worin eines oder mehrere der Wasserstoffatome, die an Ringkohlenstoffatome gebunden sind, durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen ersetzt ist bzw. sind;

(2) ein 3-Hydroxypyrid-2-on oder 3-Hydroxypyrid-4-on, worin das Wasserstoffatom, das an das Stickstoffatom gebunden ist, durch eine aliphatische Acylgruppe, eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen oder durch eine aliphatische Kohlenwasserstoffgruppe, die durch einen oder mehrere Substituenten, ausgewählt aus aliphatischen Acyl-, Alkoxy-, aliphatischen Amid-, aliphatischen Ester-, Halogen- und Hydroxylgruppen substituiert ist, ersetzt ist, und worin gegebenenfalls eines oder mehrere der Wasserstoffatome, die an Ringkohlenstoffatome gebunden sind, durch einen der genannten Substituenten durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen oder durch eine aliphatische Kohlenwasserstoffgruppe, die durch eine Alkoxy-, aliphatische Ester-, Halogen- oder Hydroxylgruppe substituiert ist, ersetzt ist, bzw. sind; oder

(3) eine alternative Verbindung, die einen physiologisch annehmbaren einbasischen, zweizähligen Liganden zur Verfügung stellt, der covalent an Zink binden kann; aber mit der Maßgabe, daß mindestens einer der Liganden vom Typ (1) oder (2) ist;

zusammen mit einem nahrhaften Material, umfaßt.

55. Lebensmittel nach Anspruch 54, dadurch gekennzeichnet, daß der Komplex Liganden, wie in einem der Ansprüche 3 bis 24 definiert, enthält.

56. Lebensmittel nach Anspruch 54 oder 55, dadurch gekennzeichnet, daß der Komplex ein neutraler 2:1 Ligand:Zink(II)-Komplex ist.

Revendications

1. Complexe de zinc(II) dans lequel le ligand ou chaque ligand séparément est fourni par un composé qui est:

(1) la 3-hydroxy-4-pyrone ou une 3-hydroxy-4-pyrone dont un ou plusieurs des atomes d'hydrogène fixés aux atomes de carbone cycliques sont remplacés par un groupe hydrocarboné aliphatique de 1 à 6 atomes de carbone;

(2) une 3-hydroxypyrid-2-one ou 3-hydroxypyrid-4-one dont l'atome d'hydrogène fixé à l'atome d'azote est remplacé par un groupe acyle aliphatique, par un groupe hydrocarboné aliphatique de 1 à 6 atomes de carbone, ou par un groupe hydrocarboné aliphatique substitué par un ou plusieurs substituants choisis parmi les groupes acyle aliphatique, alcoxy, amide aliphatique, ester aliphatique, halogéno et hydroxyle, et, facultativement, dont un ou plusieurs des atomes d'hydrogène fixés aux atomes de carbone cycliques sont remplacés par l'un desdits substituants, par un groupe hydrocarboné aliphatique de 1 à 6 atomes de carbone ou par un groupe hydrocarboné aliphatique substitué par un groupe alcoxy, ester



aliphatique, halogéno ou hydroxyle; ou

(3) un autre composé fournissant un ligand bidentate monoacide physiologiquement acceptable qui est capable de se lier par covalence au zinc; mais à condition qu'au moins l'un des ligands soit du type (1) ou (2); pour son utilisation en thérapie.

5 2. Complexe de zinc(II) dans lequel le ligand ou chaque ligand séparément est fourni par un composé qui est:

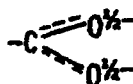
(1) la 3-hydroxy-4-pyrone ou une 3-hydroxy-4-pyrone dont un ou plusieurs des atomes d'hydrogène fixés aux atomes de carbone cycliques sont remplacés par un groupe hydrocarboné aliphatique de 1 à 6 atomes de carbone;

10 (2) une 3-hydroxypyrid-2-one ou 3-hydroxypyrid-4-one dont l'atome d'hydrogène fixé à l'atome d'azote est remplacé par un groupe acyle aliphatique, par un groupe hydrocarboné aliphatique de 1 à 6 atomes de carbone, ou par un groupe hydrocarboné aliphatique substitué par un ou plusieurs substituants choisis parmi les groupes acyle aliphatique, alcoxy, amide aliphatique, ester aliphatique, halogéno et hydroxyle, et, facultativement, dont un ou plusieurs des atomes d'hydrogène fixés aux atomes de carbone cycliques sont remplacés par l'un desdits substituants, par un groupe hydrocarboné aliphatique de 1 à 6 atomes de carbone ou par un groupe hydrocarboné aliphatique substitué par un groupe alcoxy, ester aliphatique, halogéno ou hydroxyle; ou

(3) un autre composé fournissant un ligand bidentate monoacide physiologiquement acceptable qui est capable de se lier par covalence au zinc; mais à condition qu'au moins l'un des ligands soit du type (1) ou (2) et à l'excursion des complexes dans lesquels le ligand est fourni par un composé, ou bien chaque ligand est fourni par ce même composé, qui est la 3-hydroxy-4-pyrone, la 3-hydroxy-2-méthyl-4-pyrone, la 3-hydroxy-6-méthyl-4-pyrone ou la 3-hydroxy-1-méthylpyrid-4-one.

3. Complexe selon la revendication 1 ou 2, dans lequel le composé du type (3) contient un premier groupement qui est un groupe hydroxyle énolique ou un groupe carboxyle et un second groupement qui est un groupe amino ou un groupe hydroxyle, ou bien est un acide monocarboxylique fournissant un anion contenant un groupement

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4. Complexe selon la revendication 3, dans lequel le composé du type (3) est l'acide formique, l'acide acétique, l'acide propionique, l'acide lactique, l'acide gluconique, l'acide ascorbique, la glycine, la leucine, l'isoleucine, la méthionine, la phénylalanine, la tyrosine, la valine ou un di- ou tripeptide contenant des résidus d'acides aminés identiques ou différents choisis dans le groupe de sept acides aminés mentionnés en dernier lieu.

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5. Complexe selon la revendication 4, dans lequel le composé du type (3) est l'acide gluconique, l'acide ascorbique, la glycine ou la leucine.

6. Complexe selon l'une quelconque des revendications 1 à 5, dans lequel le ligand ou chaque ligand séparément est fourni par un composé choisi parmi ceux des types (1) et (2).

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7. Complexe selon l'une quelconque des revendications 1 à 5, dans lequel au moins deux ligands sont fournis par des composés de types différents parmi (1), (2) et (3).

8. Complexe selon la revendication 1 ou 2, dans lequel au moins deux ligands sont fournis par des composés de types différents parmi (1) et (2).

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9. Complexe selon l'une quelconque des revendications 1 à 7, dans lequel au moins un ligand est fourni par un composé du type (1).

10. Complexe selon la revendication 1, dans lequel chaque ligand séparément est fourni par un composé choisi parmi ceux du type (1).

11. Complexe selon la revendication 2, dans lequel chaque ligand séparément est fourni par un composé choisi parmi ceux du type (1).

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12. Complexe selon la revendication 10 ou 11, dans lequel chaque ligand est fourni par un même composé du type (1).

13. Complexe selon l'une quelconque des revendications précédentes, dans lequel le composé du type (1) est la 3-hydroxy-4-pyrone ou une 3-hydroxy-4-pyrone dont l'un ou plusieurs des atomes d'hydrogène fixés aux atomes de carbone cycliques sont remplacés par un groupe acyclique de 1 à 4 atomes de carbone.

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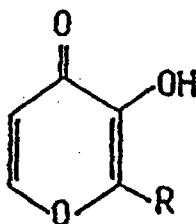
14. Complexe selon la revendication 13, dans lequel le composé est la 3-hydroxy-4-pyrone ou une 3-hydroxy-4-pyrone dont l'une ou plusieurs des atomes d'hydrogène fixés aux atomes de carbone cycliques sont remplacés par des substituants identiques ou différents choisis parmi les groupes méthyle, éthyle, *n*-propyle et isopropyle.

15. Complexe selon la revendication 14, dans lequel la 3-hydroxy-4-pyrone substituée comporte un unique substituant à la position 2 ou 6.

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16. Complexe selon la revendication 13, dans lequel le composé répond à la formule



où R est le groupe méthyle, éthyle, *n*-propyle, isopropyle ou butyle.

17. Complexe selon la revendication 14, dans lequel le composé est la 3-hydroxy-4-pyrone, la 3-hydroxy-2-méthyl-4-pyrone, la 3-hydroxy-6-méthyl-4-pyrone ou la 2-éthyl-3-hydroxy-4-pyrone.

18. Complexe selon l'une quelconque des revendications 1 à 7, dans lequel au moins un ligand est fourni par un composé du type (2).

19. Complexe selon la revendication 18, dans lequel chaque ligand séparément est fourni par un composé choisi parmi ceux du type (2).

20. Complexe selon la revendication 19, dans lequel chaque ligand est fourni par un même composé du type (2).

21. Complexe selon la revendication 18, 19 ou 20, dans lequel le composé du type (2) est une 3-hydroxy-pyrid-2-one ou 3-hydroxypyrid-4-one dont l'atome d'hydrogène fixé à l'atome d'azote est remplacé par un groupe hydrocarboné aliphatique de 1 à 6 atomes de carbone et, facultativement, dont l'un ou plusieurs des atomes d'hydrogène fixés aux atomes de carbone cycliques sont remplacés par un

22. Complexe selon la revendication 21, dans lequel le ou chaque groupe hydrocarboné aliphatique est un groupe acyclique de 1 à 4 atomes de carbone.

23. Complexe selon l'une quelconque des revendications 18 à 22, dans lequel le composé du type (2) est une 3-hydroxypyrid-2-one.

24. Complexe selon la revendication 23, dans lequel le composé est la 3-hydroxy-1-méthylpyrid-2-one, la 1-éthyl-3-hydroxypyrid-2-one, la 3-hydroxy-1-propylpyrid-2-one ou la 3-hydroxy-1-(1'-méthyléthyl)pyrid-2-one.

25. Complexe selon l'une quelconque des revendications précédentes, qui est un complexe neutre ligand:zinc(II) à 2:1.

26. Complexe neutre hydroxypyrrone:zinc(II) 2:1, dans lequel chacun des deux ligands est fourni par la même hydroxypyrrone qui est la 3-hydroxy-4-pyrone ou une 3-hydroxy-4-pyrone dont l'un ou plusieurs des atomes d'hydrogène fixés aux atomes de carbone cycliques sont remplacés par un groupe hydrocarboné aliphatique de 1 à 6 atomes de carbone, pour son utilisation en thérapie.

27. Complexe selon la revendication 26, dans lequel l'hydroxypyrrone est telle que définie dans l'une quelconque des revendications 13 à 17.

28. Complexe neutre hydroxypyrrone:zinc(II) 2:1, dans lequel chaque ligand séparément est fourni par la 3-hydroxy-2-méthyl-4-pyrone ou la 2-éthyl-3-hydroxy-4-pyrone, pour son utilisation en thérapie.

29. Complexe neutre hydroxypyrrone:zinc(II) 2:1, dans lequel chacun des deux ligands est fourni par la même hydroxypyrrone qui est une 3-hydroxy-4-pyrone dont l'un ou plusieurs des atomes d'hydrogène fixés aux atomes de carbone cycliques sont remplacés par un groupe hydrocarboné aliphatique de 1 à 6 atomes de carbone, mais à l'exclusion de la 3-hydroxy-2-méthyl-4-pyrone et de la 3-hydroxy-6-méthyl-4-pyrone.

30. Complexe selon la revendication 29, dans lequel l'hydroxypyrrone est telle que définie dans l'une quelconque des revendications 13 à 17.

31. Complexe neutre hydroxypyrrone:zinc(II) 2:1, de la 2-éthyl-3-hydroxy-4-pyrone.

32. Mélange de (a) un ou plusieurs complexes neutres ligand:zinc(II) 2:1 dans lesquels chaque ligand est séparément fourni par un composé qui est:

(1) la 3-hydroxy-4-pyrone ou une 3-hydroxy-4-pyrone dont l'un ou plusieurs des atomes d'hydrogène fixés aux atomes de carbone cycliques sont remplacés par un groupe hydrocarboné aliphatique de 1 à 6 atomes de carbone;

(2) une 3-hydroxypyrid-2-one ou 3-hydroxypyrid-4-one dont l'atome d'hydrogène fixé à l'atome d'azote est remplacé par un groupe acyle aliphatique, par un groupe hydrocarboné aliphatique de 1 à 6 atomes de carbone, ou par un groupe hydrocarboné aliphatique substitué par un ou plusieurs substituants choisis parmi les groupes acyle aliphatique, alcoxy, amide aliphatique, ester aliphatique, halogéno et hydroxyle, et, facultativement, dont un ou plusieurs des atomes d'hydrogène fixés aux atomes de carbone cycliques sont remplacés par l'un desdits substituants, par un groupe hydrocarboné aliphatique de 1 à 6 atomes de carbone ou par un groupe hydrocarboné aliphatique substitué par un groupe alcoxy, ester aliphatique, halogéno ou hydroxyle; ou

(3) un autre composé fournissant un ligand bidentate monoacide physiologiquement acceptable qui est capable de se lier par covalence au zinc; mais à condition qu'au moins l'un des ligands soit du type (1) ou (2); et



(b) un ou des composés non complexés correspondants à l'un ou plusieurs des ligands contenus dans le ou les complexes; le rapport molaire de chaque composés non complexé au complexe de zinc contenant ce composé étant de 0,5:1 à 100:1.

33. Mélange selon la revendication 32, dans lequel chaque ligand séparément est fourni par un composé choisi parmi ceux du type (1).

34. Mélange selon la revendication 32 ou 33, dans lequel soit (a) un unique complexe de zinc contenant deux ligands identiques est présent en association avec le composé non complexé correspondant à ces ligands, soit (b) un unique complexe de zinc contenant deux ligands non identiques ou plus d'un complexe de zinc est présent en association avec les composés non complexés correspondant à chacun des ligands présents dans le ou les complexes.

35. Mélange de (a) un ou plusieurs complexes neutres hydroxypyrrone:zinc(II) 2:1 dans lesquels chaque ligand est séparément fourni par la 3-hydroxy-2-méthyl-4-pyrone ou la 2-éthyl-3-hydroxy-4-pyrone et (b) chaque composé fournissant un ligand sous forme non complexée, le rapport molaire de chaque composé non complexé au complexe de zinc contenant ce composé étant de 0,5:1 à 100:1.

36. Mélange de (a) un complexe de zinc(II) dans lequel le ligand ou chaque ligand séparément est fourni par un composé qui est:

(1) la 3-hydroxy-4-pyrone ou une 3-hydroxy-4-pyrone dont un ou plusieurs des atomes d'hydrogène fixés aux atomes de carbone cycliques sont remplacés par un groupe hydrocarboné aliphatique de 1 à 6 atomes de carbone;

(2) une 3-hydroxypyrid-2-one ou 3-hydroxypyrid-4-one dont l'atome d'hydrogène fixé à l'atome d'azote est remplacé par un groupe acyle aliphatique, par un groupe hydrocarboné aliphatique de 1 à 6 atomes de carbone, ou par un groupe hydrocarboné aliphatique substitué par un ou plusieurs substituants choisis parmi les groupes acyle aliphatique, alcoxy, amide aliphatique, ester aliphatique, halogéno et hydroxyle, et, facultativement, dont un ou plusieurs des atomes d'hydrogène fixés aux atomes de carbone cycliques sont remplacés par l'un desdits substituants, par un groupe hydrocarboné aliphatique de 1 à 6 atomes de carbone ou par un groupe hydrocarboné aliphatique substitué par un groupe alcoxy, ester aliphatique, halogéno ou hydroxyle; ou

(3) un autre composé fournissant un ligand bidentate monoacide physiologiquement acceptable qui est capable de se lier par covalence au zinc; mais à condition qu'au moins l'un des ligands soit du type (1) ou (2); et

(b) un complexe de fer ou sel de fer physiologiquement acceptable.

37. Mélange de (a) un complexe neutre ligand:zinc(II) 2:1 dans lequel chaque ligand séparément est fourni par un composé qui est:

(1) la 3-hydroxy-4-pyrone ou une 3-hydroxy-4-pyrone dont un ou plusieurs des atomes d'hydrogène fixés aux atomes de carbone cycliques sont remplacés par un groupe hydrocarboné aliphatique de 1 à 6 atomes de carbone;

(2) une 3-hydroxypyrid-2-one ou 3-hydroxypyrid-4-one dont l'atome d'hydrogène fixé à l'atome d'azote est remplacé par un groupe acyle aliphatique, par un groupe hydrocarboné aliphatique de 1 à 6 atomes de carbone, ou par un groupe hydrocarboné aliphatique substitué par un ou plusieurs substituants choisis parmi les groupes acyle aliphatique, alcoxy, amide aliphatique, ester aliphatique, halogéno et hydroxyle, et, facultativement, dont un ou plusieurs des atomes d'hydrogène fixés aux atomes de carbone cycliques sont remplacés par l'un desdits substituants, par un groupe hydrocarboné aliphatique de 1 à 6 atomes de carbone ou par un groupe hydrocarboné aliphatique substitué par un groupe alcoxy, ester aliphatique, halogéno ou hydroxyle; et

(b) un complexe neutre ligand:fer(III) 3:1 dans lequel chaque ligand séparément est fourni par un composé tel que défini en (1) et (2).

38. Mélange selon la revendication 39, dans lequel chaque ligand séparément contenu dans les complexes de zinc et de fer est fourni par un composé choisi parmi ceux du type (1).

39. Mélange selon la revendication 37 ou 38, dans lequel les ligands du complexe de fer sont fournis par la même composé ou un ou plusieurs des mêmes composés qui ceux qui fournissent le ou les ligands présents dans le complexe de zinc.

40. Mélange de (a) un ou plusieurs complexes neutres hydroxypyrrone:zinc(II) 2:1 dans lesquels chaque ligand séparément est fourni par la 3-hydroxy-2-méthyl-4-pyrone ou la 2-éthyl-3-hydroxy-4-pyrone, et (b) un ou plusieurs complexes neutres hydroxypyrrone:fer(III) 3:1 dans lesquels chaque ligand séparément est fourni par la 3-hydroxy-2-méthyl-4-pyrone ou la 2-éthyl-3-hydroxy-4-pyrone.

41. Mélange selon l'une quelconque des revendications 37 à 40, qui contient, de plus, un ou plusieurs composés non complexés correspondant à l'un ou plusieurs des ligands complexés au zinc ou au fer.

42. Mélange selon la revendication 41, dans lequel sont présents un ou plusieurs composés non complexés correspondant à chacun des ligands complexés au zinc et fer.

43. Composition pharmaceutique comprenant un complexe de zinc(II) dans lequel le ligand ou chaque ligand séparément est fourni par un composé qui est:

(1) la 3-hydroxy-4-pyrone ou une 3-hydroxy-4-pyrone dont un ou plusieurs des atomes d'hydrogène fixés aux atomes de carbone cycliques sont remplacés par un groupe hydrocarboné aliphatique de 1 à 6 atomes de carbone;

(2) une 3-hydroxypyrid-2-one ou 3-hydroxypyrid-4-one dont l'atome d'hydrogène fixé à l'atome



d'azote est remplacé par un groupe acyle aliphatique, par un groupe hydrocarboné aliphatique de 1 à 6 atomes de carbone, ou par un groupe hydrocarboné aliphatique substitué par un ou plusieurs substituants choisis parmi les groupes acyle aliphatique, alcoxy, amide aliphatique, ester aliphatique, halogéno et hydroxyle, et, facultativement, dont un ou plusieurs des atomes d'hydrogène fixés aux atomes de carbone cycliques sont remplacés par l'un desdits substituants, par un groupe hydrocarboné aliphatique de 1 à 6 atomes de carbone ou par un groupe hydrocarboné aliphatique substitué par un groupe alcoxy, ester aliphatique, halogéno ou hydroxyle; ou

(3) un autre composé fournissant un ligand bidentate monoacide physiologiquement acceptable qui est capable de se lier par covalence au zinc; mais à condition qu'au moins l'un des ligands soit du type (1) ou (2) et à l'exclusion des complexes dans lesquels le ligand est fourni par un composé, ou bien chaque ligand est fourni par ce même composé, qui est la 3-hydroxy-4-pyrone, la 3-hydroxy-2-méthyl-4-pyrone, la 3-hydroxy-6-méthyl-4-pyrone ou la 1-méthyl-3-hydroxypyrid-4-one; ainsi qu'un diluant ou véhicule physiologiquement acceptable.

44. Composition pharmaceutique comprenant un complexe de zinc(II) dans lequel le ligand ou chaque ligand séparément est fourni par un composé qui est:

(1) la 3-hydroxy-4-pyrone ou une 3-hydroxy-4-pyrone dont un ou plusieurs des atomes d'hydrogène fixés aux atomes de carbone cycliques sont remplacés par un groupe hydrocarboné aliphatique de 1 à 6 atomes de carbone;

(2) une 3-hydroxypyrid-2-one ou 3-hydroxypyrid-4-one dont l'atome d'hydrogène fixé à l'atome d'azote est remplacé par un groupe acyle aliphatique, par un groupe hydrocarboné aliphatique de 1 à 6 atomes de carbone, ou par un groupe hydrocarboné aliphatique substitué par un ou plusieurs substituants choisis parmi les groupes acyle aliphatique, alcoxy, amide aliphatique, ester aliphatique, halogéno et hydroxyle, et, facultativement, dont un ou plusieurs des atomes d'hydrogène fixés aux atomes de carbone cycliques sont remplacés par l'un desdits substituants, par un groupe hydrocarboné aliphatique de 1 à 6 atomes de carbone ou par un groupe hydrocarboné aliphatique substitué par un groupe alcoxy, ester aliphatique, halogéno ou hydroxyle; ou

(3) un autre composé fournissant un ligand bidentate monoacide physiologiquement acceptable qui est capable de se lier par covalence au zinc; mais à condition qu'au moins l'un des ligands soit du type (1) ou (2); ainsi qu'un diluant ou support physiologiquement acceptable, mais à l'exclusion de tout liquide qui n'est pas stérile et apyrogènes.

45. Composition pharmaceutique comprenant un complexe de zinc(II) dans lequel le ligand ou chaque ligand séparément est fourni par un composé qui est:

(1) la 3-hydroxy-4-pyrone ou une 3-hydroxy-4-pyrone dont un ou plusieurs des atomes d'hydrogène fixés aux atomes de carbone cycliques sont remplacés par un groupe hydrocarboné aliphatique de 1 à 6 atomes de carbone;

(2) une 3-hydroxypyrid-2-one ou 3-hydroxypyrid-4-one dont l'atome d'hydrogène fixé à l'atome d'azote est remplacé par un groupe acyle aliphatique, par un groupe hydrocarboné aliphatique de 1 à 6 atomes de carbone, ou par un groupe hydrocarboné aliphatique substitué par un ou plusieurs substituants choisis parmi les groupes acyle aliphatique, alcoxy, amide aliphatique, ester aliphatique, halogéno et hydroxyle, et, facultativement, dont un ou plusieurs des atomes d'hydrogène fixés aux atomes de carbone cycliques sont remplacés par l'un desdits substituants, par un groupe hydrocarboné aliphatique de 1 à 6 atomes de carbone ou par un groupe hydrocarboné aliphatique substitué par un groupe alcoxy, ester aliphatique, halogéno ou hydroxyle; ou

(3) un autre composé fournissant un ligand bidentate monoacide physiologiquement acceptable qui est capable de se lier par covalence au zinc; mais à condition qu'au moins l'un des ligands soit du type (1) ou (2); ainsi qu'un diluant ou véhicule physiologiquement acceptable, ladite composition étant adaptée à une administration locale et ayant la forme d'une crème ou d'un shampoing.

46. Composition pharmaceutique selon l'une quelconque des revendications 43, 44 et 45, dans laquelle le complexe contient des ligands tels que définis dans l'une quelconque des revendications 3 à 24.

47. Composition pharmaceutique selon l'une quelconque des revendications 43 à 46, dans laquelle le complexe est un complexe neutre ligand:zinc(II) à 2:1.

48. Composition pharmaceutique selon l'une quelconque des revendications 43 à 47, qui contient, de plus, un ou des composés non complexés correspondant à l'un ou plusieurs des ligands présents dans le complexe.

49. Composition pharmaceutique comprenant un mélange du complexe neutre 3-hydroxy-2-méthyl-4-pyrone:zinc(II) 2:1, du complexe neutre 2-éthyl-3-hydroxy-4-pyrone:zinc(II) 2:1, de 3-hydroxy-2-méthyl-4-pyrone et de 2-éthyl-3-hydroxy-4-pyrone, ainsi qu'un diluant ou véhicule physiologiquement acceptable.

50. Composition pharmaceutique selon la revendication 49, qui comprend, de plus, le complexe neutre 3-hydroxy-2-méthyl-4-pyrone:fer(III) 3:1 et/ou le complexe neutre 2-éthyl-3-hydroxy-4-pyrone:fer(III) 3:1.

51. Utilisation d'un complexe de zinc dans lequel le ligand ou chaque ligand séparément est fourni par un composé qui est:

(1) la 3-hydroxy-4-pyrone ou une 3-hydroxy-4-pyrone dont un ou plusieurs des atomes d'hydrogène fixés aux atomes de carbone cycliques sont remplacés par un groupe hydrocarboné aliphatique de 1 à 6 atomes de carbone;

(2) une 3-hydroxypyrid-2-one ou 3-hydroxypyrid-4-one dont l'atome d'hydrogène fixé à l'atome



d'azote est remplacé par un groupe acyle aliphatique, par un groupe hydrocarboné aliphatique de 1 à 6 atomes de carbone, ou par un groupe hydrocarboné aliphatique substitué par un ou plusieurs substituants choisis parmi les groupes acyle aliphatique, alcoxy, amide aliphatique, ester aliphatique, halogéno et hydroxyle, et, facultativement, dont un ou plusieurs des atomes d'hydrogène fixés aux atomes de carbone cycliques sont remplacés par l'un desdits substituants, par un groupe hydrocarboné aliphatique de 1 à 6 atomes de carbone ou par un groupe hydrocarboné aliphatique substitué par un groupe alcoxy, ester aliphatique, halogéno ou hydroxyle; ou

(3) un autre composé fournissant un ligand bidentate monoacide physiologiquement acceptable qui est capable de se lier par covalence au zinc; mais à condition qu'au moins l'un des ligands soit du type (1) ou (2); pour la fabrication d'un médicament destiné à produire une augmentation du taux de zinc dans la circulation sanguine d'un malade, ou destinée au traitement local d'infections bactériennes ou fongiques.

52. Utilisation selon la revendication 51, dans laquelle le complexe contient des ligands tels que définis dans l'une quelconque des revendications 3 à 24.

53. Utilisation selon la revendication 51 ou 52, dans laquelle le complexe est un complexe neutre ligand:zinc(II) 2:1.

54. Produit alimentaire comprenant un complexe de zinc dans lequel le ligand ou chaque ligand séparément est fourni par un composé qui est:

(1) la 3-hydroxy-4-pyrone ou une 3-hydroxy-4-pyrone dont un ou plusieurs des atomes d'hydrogène fixés aux atomes de carbone cycliques sont remplacés par un groupe hydrocarboné aliphatique de 1 à 6 atomes de carbone;

(2) une 3-hydroxypyrid-2-one ou 3-hydroxypyrid-4-one dont l'atome d'hydrogène fixé à l'atome d'azote est remplacé par un groupe acyle aliphatique, par un groupe hydrocarboné aliphatique de 1 à 6 atomes de carbone, ou par un groupe hydrocarboné aliphatique substitué par un ou plusieurs substituants choisis parmi les groupes acyle aliphatique, alcoxy, amide aliphatique, ester aliphatique, halogéno et hydroxyle, et, facultativement, dont un ou plusieurs des atomes d'hydrogène fixés aux atomes de carbone cycliques sont remplacés par l'un desdits substituants, par un groupe hydrocarboné aliphatique de 1 à 6 atomes de carbone ou par un groupe hydrocarboné aliphatique substitué par un groupe alcoxy, ester aliphatique, halogéno ou hydroxyle; ou

(3) un autre composé fournissant un ligand bidentate monoacide physiologiquement acceptable qui est capable de se lier par covalence au zinc; mais à condition qu'au moins l'un des ligands soit du type (1) ou (2); ainsi qu'une substance nutritive.

55. Produit alimentaire selon la revendication 54, dans lequel le complexe contient des ligands tels que définis dans l'une quelconque des revendications 3 à 24.

56. Produit alimentaire selon la revendication 54 ou 55, dans lequel le complexe est un complexe neutre ligand:zinc(II) 2:1.

