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Description

This invention relates to compounds for use in medicine, particularly in the treatment of iron overload.

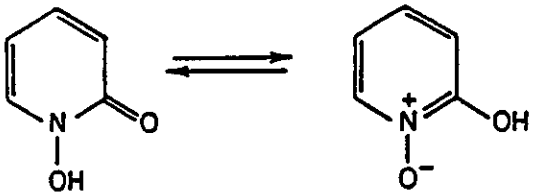
Certain pathological conditions such as thalassaemia, sickle cell anaemia, idiopathic haemochromatosis and aplastic anaemia are treated by regular blood transfusions. It is commonly found that such transfusions lead to a widespread iron overload, which condition can also arise through increased iron absorption by the body in certain other circumstances. Iron overload is most undesirable since, following saturation of the ferritin and transferrin in the body, deposition of iron can occur and many tissues can be adversely affected, particular toxic effects being degenerative changes in the myocardium, liver and endocrine organs. Such iron overload is most often treated by the use of desferrioxamine. However, this compound is an expensive natural product obtained by the culture of *Streptomyces* and, as it is susceptible to acid hydrolysis, it cannot be given orally to the patient and has to be given by a parenteral route. Since relatively large amounts of desferrioxamine may be required daily over an extended period, these disadvantages are particularly relevant and an extensive amount of research has been directed towards the development of alternative drugs. However, work has been concentrated on three major classes of iron chelating agents or siderophores, namely hydroxamates, ethylenediamine tetra-acetic acid (EDTA) analogues and catechols. The hydroxamates generally suffer from the same defects as desferrioxamine, being expensive and acid labile, whilst the other two classes are ineffective at removing iron from intracellular sites. Moreover, some cathechol derivatives are retained by the liver and spleen and EDTA analogues possess a high affinity for calcium and so are also likely to have associated toxicity problems.

We have accordingly studied the iron chelating ability of a wide range of compounds and have identified a group of compounds as being of particular use for the treatment of conditions involving iron overload. These compounds consist of a 1-hydroxypyrid-2-one in which one or more of the hydrogen atoms attached to ring carbon atoms are replaced by one of a carefully selected group of substituents. Although certain of the substituted compounds described herein have previously been suggested for therapeutic use, particularly as anti-microbial agents, the evidence of such activity is somewhat mixed. Thus, the initial reports of one group of workers were contradicted by subsequent tests reported from the same source (Nishimura *et al*, Ann. Rept. Shionogi Res. Lab., 1966, *16*, 37) which showed the compounds to have negligible activity. *In vitro* tests illustrated the lack of anti-bacterial and anti-fungal activity and, although some compounds showed some anti-protozoal activity *in vitro*, when tested in mice against the fungus *Trichomonas vaginalis* all of the compounds tested proved to be inactive. In particular, however, although it has been reported that 1-hydroxypyrid-2-one will form metal complexes, including an iron complex, it has never before been appreicated that certain substituted derivatives of this compound might be used with great advantage in a pharmaceutical context for the treatment of conditions producing toxic concentrations of metals, for example iron, in the body.

Accordingly the present invention comprises the use of a compound being a 1-hydroxypyrid-2-one in which one or more of the hydrogen atoms attached to ring carbon atoms are replaced by a substituent selected from carbamoyl, mono- and di-C_{1-3} aliphatic hydrocarbyl N-substituted carbamoyl, formylamino, (C_{1-3} aliphatic hydrocarbyl)-carbonylamino, mono-C_{1-3} aliphatic hydrocarbyl N-substituted formylamino and N-substituted (C_{1-3} aliphatic hydrocarbyl)-carbonylamino, hydroxy, C_{1-4} alkoxy and C_{3-4} cycloalkoxy groups; C_{2-4} alkoxy and C_{3-4} cycloalkoxy groups substituted by a C_{1-4} alkoxy, C_{3-4} cycloalkoxy, carbamoyl, mono- or di-C_{1-3} aliphatic hydrocarbyl N-substituted carbamoyl, formylamino, (C_{1-3} aliphatic hydrocarbyl)-carbonylamino, mono-C_{1-3} aliphatic hydrocarbyl N-substituted formylamino or N-substituted (C_{1-3} aliphatic hydrocarbyl)-carbonylamino, or hydroxy group; C_{1-3} aliphatic hydrocarbon groups; and C_{1-3} aliphatic hydrocarbon groups substituted by a C_{1-4} alkoxy, C_{3-4} cycloalkoxy or hydroxy group; but excluding compounds in which said replacement of hydrogen atoms is effected only by substituents selected from C_{1-3} aliphatic hydrocarbon groups, or a physiologically acceptable salt thereof, for the manufacture of a medicament for use in effecting a reduction in toxic levels of a metal in a patient's body.

Such compounds may be used in both human and veterinary treatment but are of particular interest for the treatment of the human body by therapy, especially in the context of the treatment of iron overload. particular interest for the treatment of the human body by therapy, especially in the context of the treatment of iron overload.

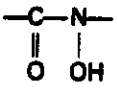
The 1-hydroxypyrid-2-ones are tautomeric compounds, being alternatively named as 2-hydroxypyridine 1-oxides, the two tautomeric structures being shown below for the unsubstituted parent compound.



The ability of both the free compound and its iron complex to permeate membranes is important in the context of the treatment of iron overload, and it is also desirable for both to possess some degree of water

solubility. A good indication of the physical properties of a compound and its iron 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 compounds show a value of K_{part} for the free compound of above 0.02 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 3:1 hydroxypyridone:iron(III) complex of above 0.02 but less than 6.0, especially of above 0.2 but less than 1.0. The following comments upon preferences among the groups used for replacement of hydrogen atoms attached to carbon atoms of the pyridone ring are directed towards the use of compounds having partition coefficients in the free and complexed state which lie in these preferred ranges. For examples of measured partition coefficients of specific compounds reference should be made to Example 4.

More than one of the ring carbon atoms may be substituted, for example two of such atoms, either by the same substituent group or by different substituent groups, for example by halogen or especially by an aliphatic hydrocarbon group together with another type of substituent, although compounds in which only one of the ring carbon atoms is substituted are preferred. Substitution may occur at any of the 3-, 4-, 5- and 6-positions or at a combination of two or more of these positions. Particularly when the ring carbon atoms are substituted by the larger groups, however, there may be an advantage in avoiding substitution on a carbon alpha to the



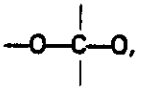
system.

The system is involved in the complexing with iron and the close proximity of one of the larger aliphatic hydrocarbon groups may lead to steric effects which inhibit complex formation. Substitution at the 5- and particularly the 4-position is thus of some especial interest.

Where reference is made to a ring carbon atom being substituted by an aliphatic hydrocarbon group it will be appreciated that 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 or especially a straight chain. Among the C_{1-3} aliphatic hydrocarbon groups it is the saturated groups which are preferred, these being either cyclic groups such as the cycloalkyl group cyclopropyl or, more particularly, acyclic groups such as the alkyl groups isopropyl, n-propyl, ethyl and especially methyl. However, although substitution by an aliphatic hydrocarbon group, for example methyl, in addition to another substituent as specified above is quite acceptable, it will not generally contribute with any particular advantage to the properties of the compound and is thus not of especial interest.

In the case of substituted aliphatic hydrocarbon groups, the preferences as to the nature of these groups are broadly as expressed above with regard to the hydrocarbon group and hereinafter with regard to the substituent, for example these groups conveniently being substituted alkyl groups of 1 to 3 carbon atoms and particularly substituted methyl groups such as ethoxymethyl and especially hydroxymethyl. In general, however, substituents as defined hereinbefore other than aliphatic hydrocarbon groups and substituted aliphatic hydrocarbon groups are of the most interest. Various preferences may be expressed among such other substituent groups, the following comments applying equally to these groups when substituted on the ring directly and, where appropriate, also to the groups when substituted on an aliphatic hydrocarbon or alkoxy group which is itself substituted on the ring.

The alkoxy and cycloalkoxy groups may conveniently contain similar alkyl and cycloalkyl groups to those described above as being preferred as an aliphatic hydrocarbon group substituent on the ring, examples of such substituents being ethoxy and particularly methoxy. Alkoxy and cycloalkoxy groups which are substituted, however, may often conveniently contain 2 or more carbon atoms in view of the relative instability of groups such as



etc., so that a particular substituted alkoxy group of interest is $—OCH_2CH_2OCH_3$. Moreover, the presence of a hydrophilic substituent on an alkoxy or cycloalkoxy group will tend to offset the hydrophobic effect of the aliphatic hydrocarbon group which that alkoxy or cycloalkoxy group contains, thereby sometimes favouring the use of slightly larger alkoxy and cycloalkoxy groups when these are substituted. Substituted alkoxy and cycloalkoxy groups are of particular interest in the context of the present invention and are discussed in more detail hereinafter.

The various forms of amide substituent each contain a carbonyl group. The substituent may be of the unsubstituted form $—CONH_2$, i.e. being a carbamoyl group, or may contain a nitrogen atom which is mono- or di-substituted by an aliphatic hydrocarbon group, for example an alkyl or cycloalkyl group such as is described above as a substituent at a ring carbon atom, for example being a group $—CONHCH_3$, etc. Alternatively, the

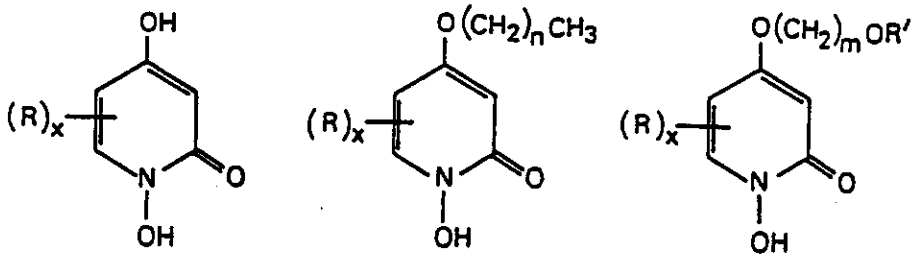
grouping of the amide substituent may be arranged in the opposite sense so that the nitrogen atom of the amide grouping is attached to the ring, the carbonyl group being attached to an aliphatic hydrocarbon group, for example an alkyl or cycloalkyl group such as is described hereinbefore as a substituent, or to hydrogen. In the case of this latter form of amide group, the amide nitrogen atom may carry a hydrogen atom or be mono-substituted as discussed for amide substituents of the first mentioned carbamoyl form, that form of amide substituent being the one of particular interest.

Among preferred substituents are the hydroxy group, and also alkoxy and cycloalkoxy groups, especially ethoxy and particularly methoxy, and, more particularly, substituted alkoxy and cycloalkoxy groups, especially those substituted by a hydroxy group or another alkoxy or cycloalkoxy group, for example the substituted ethoxy groups such as $-OCH_2CH_2NHCOCH_3$ and especially $-OCH_2CH_2OH$ and $-OCH_2CH_2OCH_3$. Hydroxy substituted aliphatic hydrocarbon groups, for example hydroxymethyl, are also of generally greater interest than other substituted aliphatic hydrocarbon groups.

Although simple alkoxy and cycloalkoxy substituents, the alkoxy and cycloalkoxy groups of hydroxyalkoxy and hydroxycycloalkoxy substituents and both components of alkoxy- and cycloalkoxy-substituted alkoxy and cycloalkoxy substituents may, as indicated previously, be of a range of sizes, certain factors result in a preference for groups of a particular size. Thus, the hydrophilic/hydrophobic balance in a compound, which is indicated by its K_{part} value, may be adjusted to a value in the preferred range quoted hereinbefore by the use of additional ring substituents, so that the hydrophobic effect of a larger unsubstituted alkoxy or cycloalkoxy group can be offset by the presence of a further hydrophilic substituent, such as a hydroxy group, on another carbon atom of the ring. However, it is generally preferable to use a single substituent which itself confers the appropriate degree of balance. Accordingly, of particular interest are unsubstituted alkoxy (and cycloalkoxy) group substituents in the range of 1 to 3 carbon atoms, preferably being alkoxy groups of 1 or 2 carbon atoms, and hydroxy substituted alkoxy (and cycloalkoxy) group substituents in the range of 2 to 4, preferably 2 or 3 carbon atoms (substituted methoxy groups being of less interest in view of the instability of the —O—C—O-linkage referred to previously). For similar reasons there is particular interest in alkoxy (and cycloalkoxy) substituted alkoxy (and cycloalkoxy) group substituents or in the range of 2 to 4 carbon atoms, preferably 2 or 3 carbon atoms, in the first alkoxy (or cycloalkoxy) group substituted onto the ring and in the range of 1 to 4 carbon atoms, preferably 1 to 3 carbon atoms in the second alkoxy (or cycloalkoxy) group which is substituted onto the first alkoxy (or cycloalkoxy) group, with the proviso that the overall number of carbon atoms is preferably no greater than 6, and especially no greater than 3 or 4 carbon atoms.

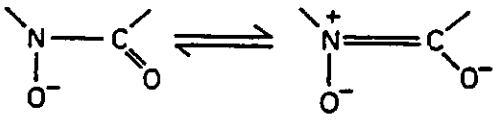
Although the hydroxy, methoxy, hydroxymethoxy and methoxyethoxy groups already referred to are of particular interest as substituents, other specific examples of alkoxy and substituted alkoxy groups, in addition to those specifically mentioned previously, are 3-hydroxypropoxy, 2-hydroxy-1-methylethoxy and 3-methoxypropoxy.

Hydroxy, alkoxy, cycloalkoxy, substituted alkoxy and cycloalkoxy and other groups may conveniently be substituted at the 4-position of a 1-hydroxypyrid-2-one, for example at the 4-position of 1-hydroxy-6-methylpyrid-2-one or other C-methyl substituted 1-hydroxypyrid-2-one or, more especially, at the 4-position of otherwise unsubstituted 1-hydroxypyrid-2-one. Specific examples of compounds according to the present invention are thus as follows:



wherein R is a substituent group as defined hereinbefore, for example methyl and especially 6-methyl, hydroxy, etc., x is 0, 1, 2 or 3 (the ring not containing any further substituent R when x is 0), n is 0, 1, 2 or 3, m is 1, 2, 3 or 4 and R′ is hydrogen or $-(CH_2)_nCH_3$, preferences among the groups at the 4-position being as described hereinbefore. In particular, the following compounds may be mentioned, 1-hydroxy-4-methoxy-pyrid-2-one, 4-ethoxy-1-hydroxypyrid-2-one, 1,4-dihydroxypyrid-2-one, 1-hydroxy-4-(2′-hydroxyethoxy)-pyrid-2-one, 1-hydroxy-4-(3′-hydroxypropoxy)-pyrid-2-one and 1-hydroxy-4-(2′-methoxyethoxy)-pyrid-2-one.

The compounds may, if desired, be used in the form of physiologically acceptable salts, for example a salt may be formed with the



system produced by the loss of a proton from the hydroxy group N-substituted at the 1-position of the ring (or C-substituted at the 2-position of the ring in the tautomeric form). Such salts contain a physiologically acceptable cation, for example the cation of an alkali metal such as sodium, quaternary ammonium ions or protonated amines such as the cation derived from tris (tris represents 2-amino-2-hydroxymethyl propane 1,3-diol). Salt formation may be advantageous in increasing the water solubility of a compound but, in general, the use of the compounds themselves rather than their salts, is preferred.

Certain of the substituted 1-hydroxypyrid-2-ones described herein are known compounds, for example the compounds having a single substituent at the 4-position which is an acetamido, butoxy, carbamyl, ethoxy, methoxy or propoxy group, but other compounds described above are believed to be novel. The present invention thus includes, *per se*, a compound being a 1-hydroxypyrid-2-one in which one or more of the hydrogen atoms attached to ring carbon atoms are replaced by a substituent which is a C_{2-4} alkoxy or C_{3-4} cycloalkoxy group substituted by a C_{1-4} alkoxy, C_{3-4} cycloalkoxy, carbamoyl, mono- or di-C_{1-3} aliphatic hydrocarbyl N-substituted carbamoyl, formylamino, (C_{1-3} aliphatic hydrocarbyl)-carbonylamino, mono-C_{1-3} aliphatic hydrocarbyl N-substituted formylamino or N-substituted (C_{1-3} aliphatic hydrocarbyl)-carbonylamino, or hydroxy group, and wherein a further one or more of the hydrogen atoms attached to ring carbon atoms are optionally replaced by a substituent selected from carbamoyl, mono- and di-C_{1-3} aliphatic hydrocarbyl N-substituted carbamoyl, formylamino, (C_{1-3} aliphatic hydrocarbyl)-carbonylamino, mono-C_{1-3} aliphatic hydrocarbyl N-substituted formylamino and N-substituted (C_{1-3} aliphatic hydrocarbyl)-carbonylamino, hydroxy, C_{1-4} alkoxy and C_{3-4} cycloalkoxy groups; C_{1-3} aliphatic hydrocarbon groups; and C_{1-3} aliphatic hydrocarbon groups substituted by a C_{1-4} alkoxy, C_{3-4} cycloalkoxy or hydroxy group; or a physiologically acceptable salt thereof.

The substituted 1-hydroxypyrid-2-ones (or 2-hydroxypyridine N-oxides) for use in the present invention may be synthesised by various routes applying standard reactions for the introduction of the substituent groups within the art of pyridine chemistry. In particular, substituents may be introduced either by replacement of a hydrogen atom or of an existing substituent at the appropriate position or positions in a pyridine or pyridine 1-oxide ring system. Pyridine compounds may conveniently be converted to the corresponding pyridine 1-oxide by the use of an oxidizing agent such as peracetic or perbenzoic acid. The oxygen atom at the 2-position of compounds according to the present invention may conveniently be introduced by the basic hydrolysis of a halogen group or the acidic hydrolysis of an alkoxy or cycloalkoxy group, for example a methoxy group, at that position, preferably in a pyridine 1-oxide rather than a pyridine and conveniently following introduction of the other substituent groups or groups. Such a procedure will introduce a hydroxy group at the 2-position as in the 2-hydroxypyridine N-oxide tautomeric form shown hereinbefore.

Such procedures and the preparation of various suitable intermediates are described in the art, for example by Shaw *et al*, J. Amer. Chem. Soc., 1949, *71*, 70 and ibid, 1950, *72*, 4362, and particularly by Mizukami *et al*, Ann. Rept. Shionogi Res. Lab., 1966, *16*, 29. A particularly useful type of intermediate for the preparation of the compounds described herein is a nitro substituted 2-chloro-pyridine N-oxide, 4-nitro, 5-nitro and 3,5-dinitro substituted compounds all being reported in the literature. Thus, 2-chloro-4-nitro-pyridine-1-oxide, for example, may be subjected to nucleophilic substitution to replace the nitro group by an alkoxy or cycloalkoxy group or alkoxy- or cycloalkoxy-substituted alkoxy or cycloalkoxy group, for example —OCH_3 or —$OCH_2CH_2OCH_3$, the chloro group then being converted to a hydroxy group by basic hydrolysis. Alternatively, a nitro group substituent may be reduced to give an amino group which is then acylated.

The compounds may be converted to salts, for example those formed with the anion produced by the loss of the hydroxy group proton, by reaction with the appropriate base or acid according to standard procedures.

In general, it is preferred that the compounds are isolated in substantially pure form, i.e. substantially free from by-products of manufacture.

It will be appreciated that these are not the only routes available to these compounds and that various alternatives may be used as will be apparent to those skilled in the art, as will be the routes to the various intermediates required.

Moreover, it will be appreciated that certain of the compounds may be converted *in vivo* to other compounds which will be involved in the metal binding activity observed *in vivo*.

The compounds may be formulated for use as pharmaceuticals for veterinary, for example in an avian or particularly a mammalian context, or particularly 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 most usually will be employed for parenteral administration and therefore will be sterile and pyrogen free. However, it will be appreciated from the foregoing discussion in relation to desferrioxamine that oral administration is to be preferred and the compounds 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 preferred to use compositions incorporating a solid carrier, for example a conventional solid carrier material such as starch, lactose, dextrin or magnesium stearate, the oral composition then conveniently being of a formed type, for example as tablets, capsules (including spansules — Registered Trade Mark), etc.

Other forms of administration than by injection or through the oral route may also be considered in

both human and veterinary contexts, for example other forms known in the art such as the use of suppositories or pessaries, particularly for human administration.

The present invention accordingly further comprises a pharmaceutical composition containing a compound being a 1-hydroxypyrid-2-one in which one or more of the hydrogen atoms attached to ring carbon atoms are replaced by a substituent which is a C_{2-4} alkoxy or C_{3-4} cycloalkoxy group substituted by a C_{1-4} alkoxy, C_{3-4} cycloalkoxy, carbamoyl, mono- or di-C_{1-3} aliphatic hydrocarbyl N-substituted carbamoyl, formylamino, (C_{1-3} aliphatic hydrocarbyl)-carbonylamino, mono-C_{1-3} aliphatic hydrocarbyl N-substituted formylamino or N-substituted (C_{1-3} aliphatic hydrocarbyl)-carbonylamino, or hydroxy group, and wherein a further one or more of the hydrogen atoms attached to ring carbon atoms are optionally replaced by a substituent selected from carbamoyl, mono- and di-C_{1-3} aliphatic hydrocarbyl N-substituted carbamoyl, formylamino, (C_{1-3} aliphatic hydrocarbyl)-carbonylamino, mono-C_{1-3} aliphatic hydrocarbyl N-substituted formylamino and N-substituted (C_{1-3} aliphatic hydrocarbyl)-carbonylamino, hydroxy, C_{1-4} alkoxy and C_{3-4} cycloalkoxy groups, C_{1-3} aliphatic hydrocarbon groups; and C_{1-3} aliphatic hydrocarbon groups substituted by a C_{1-4} alkoxy, C_{3-4} cycloalkoxy or hydroxy group; or a physiologically acceptable salt thereof.

Compositions may be formulated in unit dosage form, i.e. in the form of discrete portions each comprising a unit dose, or a multiple or sub-multiple of a unit dose. Whilst the dosage of active compound given will depend on various factors, including the particular compound which is employed in the composition, it may be stated by way of guidance that satisfactory control of the amount of iron present in the human body will often be achieved using a daily dosage of about 0.1 g to 5 g, particularly of about 0.5 g to 2 g, veterinary doses being on a similar g/Kg body weight ratio. However, it will be appreciated that it may be appropriate under certain circumstances to give daily dosages either below or above these levels. Where desired, more than one compound according to the present invention may be administered in the pharmaceutical composition or, indeed, other active compounds may be included in the composition.

We have found that the 1-hydroxypyrid-2-ones described herein are particularly suited to the removal of iron from patients having an iron overload. The compounds form neutral 3:1 iron complexes at most physiological pH values, and have the advantage that they do not co-ordinate calcium or magnesium. Both the compounds and their complexes will partition into n-octanol indicating that they will permeate biological membranes, this property being confirmed in practice by tests of the ability of the ^{59}Fe labelled iron complexes to permeate erythrocytes.

The 1-hydroxypyrid-2-ones possess a high affinity for iron(III), as evidenced by log K_{sol} values (log K_{sol} is defined as being equal to $\log \beta_{Fe(L)n} + 21 - [pK_{sp} + n \log a_L(H^+) + m \log a_L(Ca^{++})]$ where $\log \beta_{Fe(L)n}$ is the cumulative affinity constant of the ligand in question for iron(III), pK_{sp} is the negative logarithm of the solubility product for $Fe(OH)_3$ and has a value of 39, n and m are the number of hydrogen and calcium ions, respectively, which are bound to the ligand, and $a_L(H^+)$ and $a_L(Ca^{++})$ are the affinities of the ligand for hydrogen ions and calcium ions, respectively). In order to solubilise iron(III) hydroxide, log K_{sol} must be greater than 0 and in order to remove iron from transferrin, log K_{sol} should be in excess of 6.0. The log K_{sol} values for 1,4-dihydroxypyrid-2-one and 1-hydroxy-4-methoxypyrid-2-one by way of example, are 9.9 and 11.3, respectively, thus comparing favourably with those of the bidentate hydroxamates at about 4.0, of catechols at about 8.0, of desferrioxamine at 6.0, and of diethylenetriamine penta-acetic acid (DTPA) at 2.0. Moreover, the ability of the compounds to remove iron efficiently has been confirmed both by *in vitro* tests and also by *in vivo* tests in mice. It is particularly significant that these latter tests are successful whether the compound is given intraperitoneally or orally by stomach tube, the compounds generally either being stable under acidic conditions or being converted thereby to acid stable active compounds. Oral activity is not generally present among the other types of compound previously suggested for use as iron co-ordinating drugs and although certain EDTA analogues do show such activity, they possess drawbacks for pharmaceutical use.

In addition to the use described hereinbefore for the treatment of general iron overload, the hydroxypyridones described herein are also of interest for use in certain pathological conditions where there may be an excess of iron deposited at certain sites even though the patient does not exhibit a general iron overload, this being the case, for example, in certain arthritic and cancerous conditions. Indeed in some patients having such conditions, the patient may exhibit an overall anaemia and the metal-free 1-hydroxypyrid-2-ones may then be used in conjunction with an iron complex, for example an iron complex of the same or another of these 1-hydroxypyrid-2-ones, the iron complex acting to correct the overall anaemia whilst the metal-free compound acts to remove iron from pathological to physiological sites. Such iron complexes of the 1-hydroxypyrid-2-ones and their use in this context are discussed in detail hereinafter.

Although the major use of the metal-free compounds of the present invention is in the removal of iron, they are also of potential interest for the removal of some other metals present in the body in deleterious amounts, for example copper, plutonium and other related transuranic metals, and especially aluminium.

Uses of the compounds of the present invention for combination with metals other than iron may extend to the treatment of body fluids outside the body or even to quite other contexts than the treatment of patients. One particular area of some interest involves the treatment of patients on haemodialysis who may show a dangerous build up of aluminium in the body. For the treatment of such patients the compounds of the present invention may be insolubilised through attachment to a support material and

then contacted with the patient's blood to remove aluminium therefrom. The support material may conveniently be one of various types of polymer described in the art for use in similar contexts, for example a carbohydrate material which may be of an agarose, dextran or other type, or a polystyrene or other material such as is used in ion-exchange resins.

Various approaches known in the art may be used for effecting attachment of the compounds to such support materials but one convenient approach is to use an acidic or basic group on the support material to provide an amide type linkage through reaction with the hydroxypyridone. Hydroxypyridones of particular interest in this context are those containing acidic or basic substituents on a ring carbon atom, i.e. those containing an aliphatic amine or a sulpho or especially a carboxy group substituent. (Substituted hydroxypyridones containing such a substituent are not utilised in the pharmaceutical compositions of the present invention in view of their less effective membrane permeating properties.)

The present invention further comprises a compound being a 1-hydroxypyrid-2-one in which one or more of the hydrogen atoms attached to ring carbon atoms are replaced by a substituent selected from carbamoyl, mono- and di-C_{1-3} aliphatic hydrocarbyl N-substituted carbamoyl, formylamino, (C_{1-3} aliphatic hydrocarbyl)-carbonylamino, mono-C_{1-3} aliphatic hydrocarbyl N-substituted formylamino and N-substituted (C_{1-3} aliphatic hydrocarbyl)-carbonylamino, hydroxy, C_{1-4} alkoxy and C_{3-4} cycloalkoxy groups; C_{2-4} alkoxy and C_{3-4} cycloalkoxy groups substituted by a C_{1-4} alkoxy, C_{3-4} cycloalkoxy, carbamoyl, mono- or di-C_{1-3} aliphatic hydrocarbyl N-substituted carbamoyl, formylamino, (C_{1-3} aliphatic hydrocarbyl)-carbonylamino, mono-C_{1-3} aliphatic hydrocarbyl N-substituted formylamino or N-substituted (C_{1-3} aliphatic hydrocarbyl)-carbonylamino, or hydroxy group; C_{1-3} aliphatic hydrocarbon groups; and C_{1-3} aliphatic hydrocarbon groups substituted by a C_{1-4} alkoxy, C_{3-4} cycloalkoxy or hydroxy group; at least one of the hydrogen atoms being replaced by an amide group or an alkoxy or cycloalkoxy group substituted by an amide group, or a physiologically acceptable salt thereof, the 1-hydroxypyrid-2-one or salt thereof being linked to a support material through said amide group.

Such 1-hydroxypyrid-2-ones linked to a support material through an amide group may conveniently be prepared by utilising a precursor corresponding to the linked 1-hydroxypyrid-2-one but having an acidic substituent containing a carboxy or sulpho group or a basic substituent containing an amine group in place of the substituent present in the final product which contains the linked amide group.

Carboxy and sulpho substituents in the precursors may consist of a group —CO_2H or —SO_3H, or the anion derived therefrom in combination with a physiologically acceptable cation, for example the cation of an alkali metal such as sodium, quaternary ammonium ions or protonated amines such as the cation derived from tris. Amine substituents may consist of a group —NH_2 or its charged equivalent, a group —NH_3 which will be associated with a physiologically acceptable anion, for example a chloride or other halide ion, a solubilising ion such as that from methane sulphonic or isethionic acid, or an anion derived from the hydroxy group of the ring (OH → O^-), or such a —NH_2 or —NH_3 group in which one of the hydrogen atoms is replaced by an aliphatic hydrocarbon group, for example an alkyl group such as is described hereinbefore as a substituent at a ring carbon atom.

The 1-hydroxypyrid-2-ones containing amine, carboxy and sulpho groups may be prepared by modifications of the procedures already discussed. Thus, as already mentioned, in one procedure a 1-hydroxypyrid-2-one containing a nitro group substituent may be prepared and this substituent reduced to give an amino group.

Where it is desired to utilise the acidic or basic 3-hydroxypyridone in the form of a salt of the amine, carboxy or sulpho group, the compound may be reacted with the appropriate base of acid according to standard procedures (amino substituted compounds of a zwitterion type containing a cation from the amino group and an anion from the 3-hydroxy group may be prepared by crystallation from aqueous media at pH of about 9.

Just as iron overload can pose problems in some patients, iron deficiency anaemia can pose problems in others. As well as being of value as the metal-free compounds for the treatment of conditions involving iron overload, the substituted 1-hydroxypyrid-2-ones described hereinbefore are of interest in the iron complex form for the treatment of iron deficiency anaemia.

An adequate supply of iron to the body is an essential requirement for tissue growth in both man and animals. Although there is normally an ample amount of iron in the diet, the level of absorption of iron from food is generally low so that the supply of iron to the body can easily become critical under a variety of conditions. Iron deficiency anaemia is commonly encountered in pregnancy and may also present a problem in the newly born, particularly in certain animal species such as the pig. Moreover, in certain pathological conditions there is a mal distribution of body iron leading to a state of chronic anaemia. This is seen in chronic diseases such as rheumatoid arthritis, certain haemolytic diseases and cancer.

Although a wide range of iron compounds is already marketed for the treatment of iron deficiency anaemia, the level of iron uptake by the body from these compounds is often quite low, necessitating the administration of relatively high dosage levels of the compound. The administration of high dose, poorly absorbed, iron complexes may cause siderosis of the gut wall and a variety of side effects such as nausea, vomiting, constipation and heavy malodorous stools. We have now found that the iron complexes of the substituted 1-hydroxypyrid-2-ones described hereinbefore, which have never previously been thought to be of value in a pharmaceutical context, are of particular value in the treatment of such conditions.

Accordingly the present invention further comprises an iron complex of a 1-hydroxypyrid-2-one in

which one or more of the hydrogen atoms attached to ring carbon atoms are replaced by a substituent selected from carbamoyl, mono- and di-C_{1-3} aliphatic hydrocarbyl N-substituted carbamoyl, formylamino, (C_{1-3} aliphatic hydrocarbyl)-carbonylamino, mono-C_{1-3} aliphatic hydrocarbyl N-substituted formylamino and N-substituted (C_{1-3} aliphatic hydrocarbyl)-carbonylamino, hydroxy, C_{1-4} alkoxy and C_{3-4} cycloalkoxy groups; C_{2-4} alkoxy and C_{3-4} cycloalkoxy groups substituted by a C_{1-4} alkoxy, C_{3-4} cycloalkoxy, carbamoyl, mono- or di-C_{1-3} aliphatic hydrocarbyl N-substituted carbamoyl, formylamino, (C_{1-3} aliphatic hydrocarbyl)-carbonylamino, mono-C_{1-3} aliphatic hydrocarbyl N-substituted formylamino or N-substituted (C_{1-3} aliphatic hydrocarbyl)-carbonylamino, or hydroxy group; C_{1-3} aliphatic hydrocarbon groups; and C_{1-3} aliphatic hydrocarbon groups substituted by a C_{1-4} alkoxy, C_{3-4} cycloalkoxy or hydroxy group; but excluding compounds in which said replacement of hydrogen atoms is effected only by substituents selected from C_{1-3} aliphatic hydrocarbon groups and also the specific compound 1-hydroxy-5-methoxy-6-methylpyrid-2-one, for use in therapy and particularly in the treatment of iron deficiency anaemia (in the broad sense of this term).

The comments made hereinbefore in relation to K_{part} values for the metal-free compounds and their corresponding iron complexes in the case of preferred compounds apply equally to the selection of preferred metal-free compounds and of preferred iron complexes. The comments made hereinbefore with regard to preferences as to the nature and position of substituents thus apply equally in relation to the iron complexes. Thus, for example of particular interest are the iron complexes of 1-hydroxy-4-methoxypyrid-2-one, 4-ethoxy-1-hydroxypyrid-2-one, 1,4-dihydroxypyrid-2-one, 1-hydroxy-4-(2'-hydroxyethoxy)-pyrid-2-one, 1-hydroxy-4-(3'-hydroxypropoxy)-pyrid-2-one and 1-hydroxy-4-(2'-methoxyethoxy)-pyrid-2-one.

The iron complexes present in the pharmaceutical compositions according to the present invention preferably contain iron in the ferric state. Although the use of complexes containing iron in the ferrous state may be considered, such complexes tend to be less stable and are thus of less interest. The iron complexes are preferably neutral, i.e. there being an internal balance of charges between the metal cation and the ligand(s) bound covalently thereto without the necessity for the presence of a non-covalently bound ion or ions, for example a chloride ion, to achieve balance. It is preferred, therefore, that the balance of charges is achieved by complexing with the iron cation the appropriate number of anions derived from a hydroxypyridone by the loss of a hydroxy proton which are necessary to produce neutrality, and the iron complexes of choice for use in the present invention are thus neutral 3:1 complexes containing three hydroxypyridone anions complexed with a ferric cation. It will be appreciated, however, that the invention does not exclude the use of complexes of the 1:1 or particularly the 2:1 form, usually in association with a physiologically acceptable anion or anions to achieve an overall balance of charges, for example the chloride ion. It will be appreciated, therefore, that the invention particularly includes as compounds, *per se*, a neutral 3:1 1-hydroxypyrid-2-one:iron(III) complex of a 1-hydroxypyrid-2-one as defined hereinbefore.

The iron complexes are conveniently prepared by the reaction of the hydroxypyridone and iron ions, the latter conveniently being derived from an iron salt, particularly a ferric halide and especially ferric chloride. The reaction is conveniently effected in a suitable mutual solvent and water may often be used for this purpose. If desired, however, an aqueous/organic solvent mixture may be used or an organic solvent, for example ethanol, methanol, chloroform and mixtures of these solvents together and/or with water where appropriate. In particular, methanol or especially ethanol may be used as the solvent 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 iron complex is retained in solution. Alternative procedures may, however, be used and will be apparent to those skilled in the art.

It will be appreciated that the nature of the iron complex obtained by the reaction of a hydroxypyridone and iron ions will depend both on the proportion of these two reactants and upon the pH of the reaction medium. Thus, for the preparation of the 3:1 ferric complex, for example, the hydroxypyridone and the ferric salt are conveniently mixed in solution in a 3:1 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 hydroxypyridone:iron is employed, but no adjustment is made of the acidic pH which results on the admixture of the hydroxypyridone and an iron salt such as ferric chloride, then a mixture of the 2:1 and 1:1 complex will instead 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 or particular interest when preparing the iron complexes in batches of 20 g or more. When using a hydroxide base, the reaction may conveniently be carried out in a medium containing water as the solvent, for example in water or an ethanol:water mixture, 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 iron complex on evaporation of the solvent (a chloride where the iron salt is ferric chloride). However, this can be removed, if desired, by procedures such as crystallisation from a suitable solvent system or sublimation in the particular case of ammonium chloride.

Reaction to form the iron 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 solid iron complex. This 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.

Whilst for some uses it may be appropriate to prepare the iron 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 3:1 [hydroxypyridone:iron(III)] complex is of particular interest in a form free from by-products which are complexes containing different proportions of hydroxypyridone and iron, in particular the 2:1 and 1:1 complexes. Accordingly the present invention includes an iron complex, for example the 3:1 hydroxypyridone:iron(III) complex, of a 1-hydroxypyrid-2-one as defined hereinbefore, when in a form substantially free from iron complexes of the hydroxypyridone containing other proportions of iron. As indicated hereinafter, it may be advantageous under some circumstances for the iron complex to be used in admixture with the free hydroxypyridone and, if desired, such a mixture may be obtained directly by reacting a molar proportion of the hydroxypyridone and iron ions of greater than 3:1.

The iron complexes may be formulated as pharmaceuticals for veterinary, for example in an avian or particularly a mammalian context, or human use by a variety of methods and the invention includes a pharmaceutical composition comprising an iron complex as hereinbefore defined together with a physiologically acceptable diluent or carrier. The comments made hereinbefore with regard to the formulation of the metal-free compounds apply equally to the iron complexes, although in this instance compositions for parenteral administration are of greater interest particularly in the context of animal treatment. The problems of iron deficiency anaemia in newly born pigs arise primarily during the first three weeks or so of their life when a very rapid weight gain takes place. The iron complexes of the present invention may be used to treat piglets directly by a parenteral route, such as intramuscular or oral, for example as a liquid preparation "injected into the mouth".

However, an alternative approach is to enhance the iron content of the milk on which the piglets are feeding by treating the mother pig using oral or parenteral administration, for example an injectable slow release preparation (such an approach may also be of interest in a human context). When it is applicable to feed piglets on foodstuffs other than the milk of the mother pig, it may also be possible to effect the pharmaceutical administration of the iron complex in this other foodstuff.

As with the metal-free compounds, the dosage of the hydroxypyridone iron complex which is given will depend on various factors, including the particular compound which is employed in the composition. It may be stated by way of guidance, however, that maintenance of the amount of iron present in the human body at a satisfactory level will often be achieved using a daily dosage, in terms of the iron content of the compound which lies in a range from about 0.1 to 100 mg and often in a range from 0.5 to 10 mg, for example 1 or 2 mg, veterinary doses being on a similar g/kg body weight ratio. 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 iron 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.

Where desired, an iron complex of more than one hydroxypyridone as described above may be present in the pharmaceutical composition or indeed other active compounds may be included in the composition, for example compounds having the ability to facilitate the treatment of anaemia, such as folic acid. Another additional component which may be included in the composition, if desired, is a source of zinc. Iron compounds used in the treatment of iron deficiency anaemia can inhibit the mechanism of zinc uptake in the body and this can cause serious side effects in the foetus when treating anaemia in a pregnant female. It is believed, however, that the iron complexes of the present invention have a further advantage in that they either do not have this effect or exhibit the effect at a lower level than the compounds at present used in the treatment of anaemia. Accordingly, it may often be the case that the level of zinc-providing compound added to the composition may not require to be high or, with preferred formulations of the iron complexes, may be dispensed with altogether.

We have found that the iron complexes described herein are of value in the treatment of iron deficiency anaemia both in humans and also in a veterinary context, particularly for the treatment of various mammalian species and especially pigs. The complexes will partition into n-octanol indicating that they are able to permeate biological membranes, this property being confirmed in practice by tests of the ability of the ^{59}Fe labelled iron complexes to permeate erythrocytes. The ability of the compounds in this respect will depend on the nature of the substituent(s) present therein and the reflection of this ability in the K_{part} values of various compounds has been referred to hereinbefore.

The ability of the iron complexes of the present invention to promote iron uptake with a high level of efficiency, as compared with a range of other iron complexes currently marketed for the treatment of iron deficiency anaemia, has been confirmed by measurements in the rat small intestine. Once present in the bloodstream, the complexes will donate iron to transferrin, a position of equilibrium being set up between the complexes and transferrin. It is because of the existence of this equilibrium that the corresponding free hydroxypyridones may equally be used in the treatment of iron overload, although certain of these compounds may be of particular value for use in the free state for iron removal and others may be of particular value for use as iron complexes for iron supply.

Certain aspects of their formulation may enhance the activity of the complexes in particular contexts. Thus, although the neutral 3:1 ferric complexes are of particular value as being stable over a wide pH range

from about 4 or 5 up to 10, they will dissociate at the pH values of less than 4 prevailing in the stomach to form a mixture of the 2:1 and 1:1 complex together with the free hydroxypyridone. If these complexes and the free hydroxypyridone are cleared simultaneously from the stomach, when they reach the small intestine a large proportion of the 3:1 complex should reform under the alkaline conditions present therein. However, in the event that this dissociation under acid conditions leads to a significant reduction in the uptake of iron by the body, due for instance to absorption of the free hydroxypyridone through the stomach wall, the uptake may be improved by using one or more of the following procedures in the formulation of the iron complex.

Firstly, one of several variations may be employed which avoid or reduce exposure of the iron 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 stabilized 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 iron complexes at such a time.

A particularly convenient approach to a controlled release composition involves encapsulating the iron 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 3:1 iron(III) complexes can therefore survive the acid environment of the stomach without dissociating to the 2:1 and 1:1 complexes, and the free hydroxypyridone. On entry into the small intestine, the pancreatic enzymes rapidly destroy the phospholipid-dependent structure of the liposomes thereby releasing the 3:1 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, 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 Marcel Decker). One particular method of encapsulation involves the use of gelatine capsules coated with a cellulose acetate phthalate/diethylphthalate 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 3:1 iron(III) 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 hydrogel formulations which do not actually encapsulate the iron complex but which are resistant to dissociation under acidic conditions.

A second approach to countering the effect of the acidic conditions prevailing in the stomach is to formulate the iron complex in the pharmaceutical composition together with the metal-free hydroxypyridone from which it is derived. The dissociation of the neutral 3:1 ferric complex, for example, involves various equilibria between this complex, and 2:1 and 1:1 complexes, and the metal-free compound, so that the presence of the latter will inhibit this dissociation. Any proportion of the free compound can be advantageous in this context but little further advantage accrues from increasing the proportion beyond a certain level. A preferred range for the molar proportion of the free compound present in compositions according to the present invention is thus from 0 to 100 moles free hydroxypyridone:1 mole of iron complex, particularly the neutral 3:1 iron(III) complex. Conveniently, a proportion of up to no more than 20, 30 or 50 moles:1 mole is used with a lower level of 0.5, 1 or 2 moles:1 mole. Although to obtain a marked effect upon dissociation of the iron complex a proportion of at least 5 or 10 moles:1 mole is usually employed it should be emphasised that even a molar ratio such as 1:1 will achieve a noticeable degree of acid stabilisation of the iron complex. Thus, although a range of, for example, from 10 moles:1 to 20 moles:1 mole of metal-free hydroxypyridone:iron complex will often be suitable to produce a marked effect, a range of, for example, 3 or even 1 mole:1 mole to 10 moles:1 mole will still produce a worthwhile effect without requiring administration of the larger amounts of the hydroxypyridone. The use of such a mixture is an important feature of the present invention since it can enable one to obtain almost quantitative uptake of iron from the complex. It should be appreciated, however, that the equilibrium between the complexes of various types and the metal-free compound will be affected by any take up of the latter in the body and the degree of such uptake from the stomach, for example, will depend on the particular metal-free compound.

A further advantage than prevention of dissociation of the iron complex under acidic conditions may accrue from the use of a free hydroxypyridone in admixture with its iron complex. Thus, as referred to hereinbefore, in certain pathological conditions there may be an excess of iron deposited at certain sites even though the patient exhibits an overall anaemia. In patients having such conditions the use of such a mixture has the advantage that the iron complex will remedy the overall anaemia whilst the free hydroxypyridone will act to remove iron from pathological to physiological sites. Moreover, there may be an advantage in formulating the iron complex of one hydroxypyridone as described herein with another one of such hydroxypyridones in free form or with a mixture of the corresponding free hydroxypyridone, present primarily to prevent dissociation of the iron complex, and of another such hydroxypyridone in free form, present primarily to effect iron transfer. Thus, it is preferable for the hydroxypyridone present in an iron donor to be rapidly metabolized so as to effect its removal from the system once it has given up its iron at an appropriate site in the system, whilst it is preferable for a hydroxypyridone being used as an iron remover not to be rapidly metabolized so that it remains in the system, taking up iron, for an extended period. For this reason the use of different hydroxypyridones in the free form and as the iron complex has certain advantages. Moreover, different hydroxypyridones may, for other reasons, function more efficiently either in the free form as an iron remover or in complex form as an iron donor. If desired, the free hydroxypyridone may alternatively be used in the form of a salt such as that formed with the anion produced by the loss of a hydroxy proton and containing a physiologically acceptable cation, for example the cation of an alkali metal such as sodium, quaternary ammonium ions or protonated amines such as the cation derived from tris.

It will be appreciated that, as an alternative to combination with a different free hydroxypyridone of the same type, the iron complex may be used in combination with another iron chelating agent, for example an alternative form of hydroxypyridone such as is described in UK patent application 8308056 (European patent application 0093498) and 8407181 (European patent application 0120669).

When a free 1-hydroxypyrid-2-one is present in admixture with an iron complex of the same or a different 1-hydroxypyrid-2-one for the purpose of acting as an iron remover, then the amount of the metal-free compound may be different than when the free hydroxypyridone necessarily corresponds to that present in the iron complex and is present primarily to prevent dissociation. Thus the daily dosage of the iron complex may be as above and the daily dosage of the free hydroxypyridone may be that described in relation to the use of such compounds in iron overload conditions. Thus, it will be seen that the proportion of iron complex and free hydroxypyridone used in such a context may extend across a wide range but preferred amounts of the free compound tend to be higher than in the other instance involving the prevention of dissociation of the complex.

It will be appreciated that the present invention also includes the use of an iron complex of a 1-hydroxypyrid-2-one in which one or more of the hydrogen atoms attached to ring carbon atoms are replaced by a substituent selected from carbamoyl, mono- and di-C_{1-3} aliphatic hydrocarbyl N-substituted carbamoyl, formylamino, (C_{1-3} aliphatic hydrocarbyl)-carbonylamino, mono-C_{1-3} aliphatic hydrocarbyl N-substituted formylamino and N-substituted (C_{1-3} aliphatic hydrocarbyl)-carbonylamino, hydroxy, C_{1-4} alkoxy and C_{3-4} cycloalkoxy groups; C_{2-4} alkoxy and C_{3-4} cycloalkoxy groups substituted by a C_{1-4} alkoxy, C_{3-4} cycloalkoxy, carbamoyl, mono- or di-C_{1-3} aliphatic hydrocarbyl N-substituted carbamoyl, formylamino, (C_{1-3} aliphatic hydrocarbyl)-carbonylamino, mono-C_{1-3} aliphatic hydrocarbyl N-substituted formylamino or N-substituted (C_{1-3} aliphatic hydrocarbyl)-carbonylamino, or hydroxy group; C_{1-3} aliphatic hydrocarbon groups; and C_{1-3} aliphatic hydrocarbon groups substituted by a C_{1-4} alkoxy, C_{3-4} cycloalkoxy or hydroxy group; but excluding compounds in which said replacement of hydrogen atoms is effected only by substituents selected from C_{1-3} aliphatic hydrocarbon groups, for the manufacture of a medicament of use in effecting an increase in the level of iron in a patient's bloodstream.

In addition to the pharmaceutical uses of the iron complexes discussed above they are also of potential interest as a source of iron in various other contexts including in cell and bacterial growth, in plant growth, as a colouring agent and in the control of iron transport across membranes.

This invention is illustrated by the following Examples.

EXAMPLES

Example 1

The preparation of 1,4-dihydroxypyrid-2-one

(1) 2-Chloro-4-nitropyridine-1-oxide

2-Chloro-pyridine-1-oxide (10 g) is cooled in an ice bath and treated with concentrated H_2SO_4 (15 ml), followed by the dropwise addition of a mixture of concentrated H_2SO_4 (15 ml) and fuming HNO_3 (27 ml, s.g. 1.5) over a 70 minute period. The acidic solution is heated in a steam bath for 2.5 hours, then allowed to reach room temperature and poured onto ice water (600 ml), stirring being continued until all the ice has melted. The resultant solid is filtered off and dissolved in hot chloroform, the solution being dried and the solvent evaporated *in vacuo* to give a yellow solid. The aqueous filtrate obtained after the removal of the original solid is neutralised with saturated aqueous Na_2CO_3 and extracted continuously with chloroform, the extract being dried and evaporated *in vacuo* to yield a yellow solid. The two yellow solids are combined and recrystallised from ethanol to give 2-chloro-4-nitro-pyridine-1-oxide as yellow crystals (7.46 g, 56%).

(2) 2,4-Dimethoxypyridine-1-oxide

Sodium methoxide is prepared by dissolving sodium metal (0.66 g) in methanol (33 ml). This solution is mixed with 2-chloro-4-nitropyridine-1-oxide (2.3 g) in methanol (20 ml) and the mixture is refluxed for 6 hours, then filtered and the solvent evaporated *in vacuo*. The resultant solid is extracted with chloroform, the chloroform solution then being reduced in volume and left to crystallise, yielding 2,4-dimethoxypyridine-1-oxide in 54% yield.

(3) 1,4-Dihydroxypyrid-2-one

2,4-Dimethoxypyrid-1-oxide is refluxed together with 20% w/v HCl for 13 hours. On cooling the solution 2,4-dihydroxy-pyridine-1-oxide or 1,4-dihydroxypyrid-2-one is obtained as an orange-white solid (0.42 g, 30%), δ (d_6DMSO + trace of D_2O), 6.08 (s, 1H), 6.12 (q, 1H), 7.88 (d, 1H).

Example 2

The preparation of 1-hydroxy-4-methoxypyrid-2-one

(1) 2-Chloro-4-methoxypyridine-1-oxide

Sodium (0.46 g) is dissolved in absolute methanol (50 ml) and the resultant solution of sodium methoxide is added to a solution of 2-chloro-4-nitropyridine-1-oxide (3.5 g, prepared as described in Example 1) in methanol (10 ml). The reaction mixture is allowed to stand at room temperature for 50 hours and is then subjected to rotary evaporation to give 2-chloro-4-methoxypyridine-1-oxide.

(2) 1-Hydroxy-4-methoxypyrid-2-one

2-Chloro-4-methoxypyridine-1-oxide (3.3 g) is dissolved in 10% w/v aqueous NaOH (33 ml) and the mixture is heated on a steam bath for 3.5 hours when it is cooled and acidified with concentrated HCl to a pH of 2.5 to yield white crystals. Recrystallisation of these from water gives 1-hydroxy-4-methoxypyrid-2-one (0.75 g, 20%), m.p. 174—175°C, δ (D_2O) 5.9 (s, 1H), 6.00 (q, 1H), 7.5 (d, 1H).

Example 3

Preparation of 1-hydroxy-4-(2'-methoxyethoxy)-pyrid-2-one

(1) 2-Chloro-4-(2'-methoxyethoxy)-pyridine-1-oxide

Sodium metal (0.23 g) is dissolved in redistilled methoxyethanol (30 ml). The resulting solution is added to 2-chloro-4-nitro-pyridine-1-oxide (1.75 g, prepared as described in Example 1) and stirred for 28 hours at 20°C. The methoxyethanol is removed by distillation under reduced pressure leaving an oily brown solid which is washed with diethyl ether (25 ml) and then dissolved in water (25 ml). The aqueous solution is extracted into chloroform (3 × 25 ml) and the extracts are then evaporated *in vacuo* to give 2-chloro-4-(2'-methoxyethoxy)pyridine-2-oxide as a yellow solid.

(2) 1-Hydroxy-4-(2'-methoxyethoxy)-pyrid-2-one

2-Chloro-4-(2'-methoxyethoxy)-pyridine-1-oxide is treated with 10% w/v aqueous NaOH and the mixture is heated on a steam bath for 3 hours. The resulting solution is acidified to pH 2 with concentrated HCl, then reduced in volume by evaporating *in vacuo* and left to crystallise. The resultant white solid is recrystallised from ethanol to give 1-hydroxy-4-(2'-methoxyethoxy)-pyrid-2-one (0.58 g, 29%), m.p. 134°C, δ ($CDCl_3$) 3.42 (s, 3H), 3.7 (t, 1H), 4.08 (t, 1H), 6.05 (d, 1H), 6.05 (q, 1H), 7.62 (t, 1H).

Example 4

Partition data on 1-hydroxypyrid-2-ones and their iron complexes

The partition coefficient K_{part}, being the ratio (concentration of compound in n-octanol)/(concentration of compound in aqueous phase) on partition between n-octanol and aqueous tris hydrochloride (20 mM, pH 7.4), is measured at 20°C for the compounds of Examples 1 to 3 and 1-hydroxypyrid-2-one by way of comparison, and for their iron complexes (at 10^{-4} M) by spectrophotometry. Acid washed glassware is used throughout and, following mixing of 5 ml of the 10^{-4} M aqueous solution with 5 ml 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 by spectrophotometry on each. For the free hydroxypyridones, the range 220—340 nm is used for concentration determinations whilst for the iron complexes, the range 340—640 nm is used.

Values typical of those obtained are shown in Table 1.

Table 1

Partition coefficients

Compound	Partition coefficient K_{part}	
	Free compound	Iron complex $[Fe^{III}-)compound)_3]$
1-hydroxypyrid-2-one	0.3	0.95
1,4-dihydroxypyrid-2-one	0.04	0.04
1-hydroxy-4-methoxypyrid-2-one	0.15	4.85
1-hydroxy-4-(2'-methoxyethoxy)-pyrid-2-one	0.14	0.6

Example 5

In vitro tests of iron binding capacity

The 1-hydroxypyrid-2-ones used in this Example were prepared as described in Examples 1, 2 and 3, and 1-hydroxypyrid-2-one was also used for comparative purposes.

(1) Mobilisation of iron from ferritin

Horse spleen ferritin (Sigma) was used without further purification and its iron content was estimated spectrophotometrically at 420 nm. The ferritin solution in phosphate buffered saline (Dulbecco-OXOID — Registered Trade Mark, 10^{-6} M, pH 7.4) was enclosed in a Visking (Registered Trade Mark) dialysis tube and dialysed against a 3×10^{-3} M buffered solution of one of various pyridones as indicated in Table 2. The absorption spectrum of the resulting iron(III) complex in the dialysis solution was recorded after 6 and 24 hours. For comparative purposes, the procedure was repeated using a blank control.

The results are shown in Table 2 where the percentage of ferritin-bound iron removed by the compound under test is shown. For comparative purposes, results reported in the literature for similar tests with 1×10^{-3} M desferrioxamine (Crichton *et al*, J. Inorganic Biochem., 1980, *13*, 305) and with 6×10^{-3} M LICAMS (Tufano *et al*, Biochem. Biophys. Acta, 1981, *668*, 420) are also given in the Table. It will be seen that the pyridone compounds are able to remove iron effectively from ferritin in contrast with desferrioxamine and LICAMS (although the latter will remove iron in the presence of ascorbic acid such a mixture is very difficult to manage clinically). These results shown in Table 2 may be confirmed by separating apoferritin (in admixture with ferritin) and the particular hydroxypyridone iron(III) complex from the reaction product in each case by chromatography on Sephadex G10 (Registered Trade Mark).

Table 2

Removal of iron from ferritin

Compound	Percentage of iron removed	
	6 hours	24 hours
Control	0	0
1-hydroxypyrid-2-one	34(1)	-
1,4-dihydroxypyrid-2-one	22	54
1-hydroxy-4-methoxypyrid-2-one	13	46
1-hydroxy-4-(2'-methoxyethoxy)-pyrid-2-one	2	8
Desferrioxamine (1mM)	1.5	-
LICAMS (6mM+12mM ascorbic acid)	7	-

(1)1-hydroxypyrid-2-one iron complex precipitated from incubation medium.

(2) Mobilisation of iron from transferrin

Human transferrin (Sigma) was loaded with iron (III) by the method of Bates and Schlaback, J. Biol. Chem. (1973) *248*, 3228. ^{59}Iron(III) transferrin (10^{-5} M) was incubated with a 4×10^{-3} M solution in tris HCl (0.1 M, pH 7.4) of one of various pyridones as indicated in Table 3 for periods of 6 hours and 24 hours. The solution was then dialysed against phosphate buffered saline for 24 hours. The ^{59}Fe remaining in the dialysis tube was then recorded. For comparative purposes, this procedure was repeated with desferrioxamine and EDTA.

The results are shown in Table 3 in terms of the percentage of transferrin bound iron removed by the compound under test and illustrate the efficiency of the compounds at iron removal. The results shown in Table 3 may be confirmed by separating apotransferrin (in admixture with transferrin) and the particular hydroxypyridone iron complex from the reaction product in each case by chromatography on Sephadex G10.

Table 3

Removal of iron from transferrin

Compound	Percentage of iron removed	
	6 hours	24 hours
1-hydroxypyrid-2-one	60	73
1,4-dihydroxypyrid-2-one	80	91
1-hydroxy-4-methoxypyrid-2-one	70	71
1-hydroxy-4-(2'-methoxyethoxy)-pyrid-2-one	72	75
Desferrioxamine	17	22
EDTA	27	67

Example 6

In vivo tests of iron binding capacity

The 1-hydroxypyrid-2-one used in this Example was prepared as described in Example 1.

Mice were injected intraperitoneally with iron dextran (2 mg) at weekly intervals over a four week period. Two weeks after the final injection, the mice were injected via the tail vein with ^{59}Fe lactoferrin (human lactoferrin, 1 mg per injection 2 µCi). The mice were then caged individually. After a ten day period, 1,4-hydroxypyrid-2-one was administered to groups of 8 mice at 10 mg per mouse either intraperitoneally or intragastrically (in each case 3 of the mice received only one dose whilst 5 received 2 doses at a 24 hour interval. The excretion of iron was recorded at either 12 or 24 hourly intervals over a three day period before and a two day period after administration of the compound. For comparative purposes, the procedure was repeated with a blank control and with desferrioxamine, also at 10 mg per mouse (the intraperitoneally treated mice receiving one dose of desferrioxamine and the intragastrically treated mice two doses at a 24 hour interval.

The results are shown in Table 4, being given on the basis of the control representing 100% excretion, and illustrate the particular advantage of the pyridones as compared with desferrioxamine for oral administration. It should be mentioned that the large standard deviation (SD) values are somewhat misleading as uniformly positive results can yield high SDs which might be taken to suggest that the results are not significantly different from zero. However, this is not the case here, the large SD values being a consequence of the large range among the positive responses.

Table 4

Excretion of iron in vivo

Compound	Intraperitoneal Administration		Intragastric Administration	
	Number of Mice	Excretion of $^{59}Fe \pm SD$ percent	Number of Mice	Excretion of $^{59}Fe \pm SD$ percent
Control	12	100 ± 10	-	-
1,4-dihydroxypyrid-2-one	11	195 ± 57	6	166 ± 40

Example 7

Preparation of iron complexes

The iron complex of 1-hydroxy-4-methoxypyrid-2-one is prepared by either procedure (a) or procedure (b).

(a) An aqueous solution of ferric chloride is reacted for 5 minutes at room temperature with an aqueous solution containing 3 molar equivalents[1] of 1-hydroxy-4-methoxypyrid-2-one. The resultant solution is adjusted to pH 7.0 using 2 molar aqueous sodium hydroxide and is then freeze dried. The resulting powder is extracted with chloroform, filtered and the filtrate subjected to rotary evaporation to give an essentially quantitative yield of the neutral complex containing the 1-hydroxy-4-methoxypyrid-2-one anion and the ferric cation in 3:1 proportion. Recrystallisation of the 3:1 complex from ethanol gives orange crystals, m.p. 103—106°C.

(b) An ethanolic solution of ferric chloride is reacted for 5 minutes at room temperature with a chloroform solution containing 3 molar equivalents of 1-hydroxy-4-methoxypyrid-2-one. The resultant solution is neutralised by the addition of solid sodium carbonate, the precipitated sodium chloride removed by filtration and the filtrate evaporated to give an essentially quantitative yield of the 3:1 complex, m.p. 103—106°C.

The 3:1 iron(III) complexes of 1,4-dihydroxypyrid-2-one and 1-hydroxy-4-(2'-methoxyethoxy)-pyrid-2-one may be prepared in an exactly similar manner.

When an excess (5 to 50 molar equivalents) of any pyridone is used, both procedure (a) and procedure (b) lead to an essentially quantitative yield of the excess pyridone in free form in admixture with the 3:1 complex.

Example 8

The ability of iron complexs to donate iron to apotransferrin

Apotransferrin (10^{-4} M) and the iron complex of 1-hydroxy-4-methoxypyrid-4-one (10^{-4} M; prepared as described in Example 7) 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 ^{59}Fe associated with both the apotransferrin and the ligand was estimated and it was found that over 90% of the iron was removed from the iron complex.

Example 9

In vitro tests on permeation of rat rejunal sac by iron complexes

The iron uptake into the serosal space of the inverted rat jejunal sac was compared for various iron compounds. Rats (male Sprague Dawley, 60 g) were killed and the jejunum removed, everted and cut into

[1]The concentration of the hydroxypyridone is 0.1M although this figure may be varied, 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 reactions solvent.

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 ^{59}Fe complexes at 37°C for periods up to 1 hour. The contents of the sac were counted for ^{59}Fe and measure spectrophotometrically.

The results obtained for the three iron complexes described in Example 7 and for seven other iron compounds which are each contained in preparations marketed for the treatment of iron deficiency anaemia are shown in Table 5, the iron uptake for each compound being shown relative to that for ferric chloride as 1. It will be seen that the complexes of Example 7 each provide a level of iron uptake which is significantly higher than the levels observed for any of the 7 compounds in current use for the treatment of iron deficiency anaemia.

Table 5

Compound	Relative Iron Uptake	Compound	Relative Iron Uptake
$FeCl_3$	1	$FeCl_3$	1
Fe^{III} complex of:		Fe^{II} sulphate	2.4
1,4-dihydroxypyrid-2-one	9.4	Fe^{II} fumarate	4.0
1-hydroxy-4-methoxypyrid-2-one	12.3	Fe^{II} gluconate	1.6
1-hydroxy-4-(2'-methoxyethoxy)-pyrid-2-one	11.4	Fe^{II} succinate	2.0
		Fe^{III} EDTA	3.6
		Fe^{III} ascorbate	0.4
		Fe^{III} citrate	2.0

Claims

1. The use of a compound being a 1-hydroxyprid-2-one in which one or more of the hydrogen atoms attached to ring carbon atoms are replaed by a substituent selected from carbamoyl, mono- and di-C_{1-3} aliphatic hydrocarbyl N-substituted carbamoyl, formylamino, (C_{1-3} aliphatic hydrocarbyl)-carbonylamino, mono-C_{1-3} aliphatic hydrocarbyl N-substituted formylamino and N-substituted (C_{1-3} aliphatic hydrocarbyl)-carbonylamino, hydroxy, C_{1-4} alkoxy and C_{3-4} cycloalkoxy groups; C_{2-4} alkoxy and C_{3-4} cycloalkoxy groups substituted by a C_{1-4} alkoxy, C_{3-4} cycloalkoxy, carbamoyl, mono- or di-C_{1-3} aliphatic hydrocarbyl N-substituted carbamoyl, formylamino, (C_{1-3} aliphatic hydrocarbyl)-carbonylamino, mono-C_{1-3} aliphatic hydrocarbyl N-substituted formylamino or N-substituted (C_{1-3} aliphatic hydrocarbyl)-carbonylamino, or hydroxy group; C_{1-3} aliphatic hydrocarbon groups; and C_{1-3} aliphatic hydrocarbon groups substituted by a C_{1-4} alkoxy, C_{3-4} cycloalkoxy or hydroxy group; but excluding compounds in which said replacement of hydrogen atoms is effected only by substituents selected from C_{1-3} aliphatic hydrocarbon groups, or a physiologically acceptable salt thereof, for the manufacture of a medicament for use in effecting a reduction in toxic levels of a metal in a patient's body.

2. The use according to Claim 1, in which the metal is iron.

3. The use according to Claim 1 or 2, in which at least one of the ring carbon atom substituents is a hydroxy, alkoxy, substituted alkoxy or substituted aliphatic hydrocarbon group.

4. The use according to Claim 3, in which at least one of the ring carbon atom substituents is a hydroxy group or a C_{1-3} alkoxy group.

5. The use according to Claim 3, in which at least one of the ring carbon atom substituents is a C_{2-3} alkoxy group substituted by a hydroxy group or by a C_{1-3} alkoxy group.

6. The use according to Claim 5, in which the total number of carbon atoms in the alkoxyalkoxy group is 3 or 4.

7. The use according to any of Claims 3 to 6, in which the ring carbon atoms of the 1-hydroxypyrid-2-one are substituted by a single one of said substituents and optionally in addition by one or more C_{1-3} aliphatic hydrocarbon atoms.

8. The use according to any of Claims 1 to 7, in which any aliphatic hydrocarbon group is methyl.

9. The use according to any of Claims 1 to 6, in which the ring carbon atoms of the 1-hydroxypyrid-2-one are substituted only by a single one of said substituents.

10. The use according to Claim 7 or 9, in which the single one of said substituents is located at the 4-position of the 1-hydroxypyrid-2-one.

11. The use according to Claim 1 or 2, in which the 1-hydroxypyrid-2-one is 1-hydroxy-4-methoxypyrid-2-one, 4-ethoxy-1-hydroxypyrid-2-one, 1,4-dihydroxypyrid-2-one, 1-hydroxy-4-(2'-hydroxyethoxy)-pyrid-2-one, 1-hydroxy-4-(3'-hydroxypropoxy)-pyrid-2-one or 1-hydroxy-4-(2'-methoxyethoxy)-pyrid-2-one, or a physiologically acceptable salt thereof.

12. A compound being a 1-hydroxypyrid-2-one in which one or more of the hydrogen atoms attached to ring carbon atoms are replaced by a substituent which is a C_{2-4} alkoxy or C_{3-4} cycloalkoxy group substituted by a C_{1-4} alkoxy, C_{3-4} cycloalkoxy, carbamoyl, mono- or di-C_{1-3} aliphatic hydrocarbyl N-substituted carbamoyl, formylamino, (C_{1-3} aliphatic hydrocarbyl)-carbonylamino, mono-C_{1-3} aliphatic hydrocarbyl N-substituted formylamino or N-substituted (C_{1-3} aliphatic hydrocarbyl)-carbonylamino, or hydroxy group, and wherein a further one or more of the hydrogen atoms attached to ring carbon atoms are optionally replaced by a substituent selected from carbamoyl, mono- and di-C_{1-3} aliphatic hydrocarbyl N-substituted carbamoyl, formylamino, (C_{1-3} aliphatic hydrocarbyl)-carbonylamino, mono-C_{1-3} aliphatic hydrocarbyl N-substituted formylamino and N-substituted (C_{1-3} aliphatic hydrocarbyl)-carbonylamino, hydroxy, C_{1-4} alkoxy and C_{3-4} cycloalkoxy groups; and C_{1-3} aliphatic hydrocarbon groups; and C_{1-3} aliphatic hydrocarbon groups substituted by a C_{1-4} alkoxy, C_{3-4} cycloalkoxy or hydroxy group; or a physiologically acceptable salt thereof.

13. A compound according to Claim 12, in which one or more of the hydrogen atoms attached to the ring carbon atoms are replaced by a substituent selected from C_{2-4} alkoxy groups substituted by a C_{1-4} akoxy group, by an amide group which is unsubstituted or mono- or di-substituted by C_{1-3} alkyl groups or by a hydroxy group and wherein a further one or more of the hydrogen atoms are optionally replaced by a hydroxy group or a C_{1-3} alkyl group.

14. A compound according to Claim 13, in which one of the hydrogen atoms attached to ring carbon atoms of the 1-hydroxypyrid-2-one is replaced by a C_{2-3} alkoxy group substituted by a hydroxy group, or by a C_{2-3} alkoxy group substituted by a C_{1-3} alkoxy group, the total number of carbon atoms in the alkoxyalkoxy group being 3 or 4, and wherein a further one or more of the hydrogen atoms are optionally replaced by a C_{1-3} alkyl group.

15. A compound according to any of Claims 12, 13 and 14, in which any aliphatic hydrocarbon or alkyl group is methyl.

16. A compound according to any of Claims 12 to 15, in which a substituted alkoxy group substituent is present at the 4-position of the 1-hydroxypyrid-2-one.

17. A compound according to any of Claims 12 to 16, in which only one of the hydrogen atoms attached to a ring carbon atom is replaced by a substituent.

18. A compound according to Claim 12, being 1-hydroxy-4-(2'hydroxyethoxy)-pyrid-2-one, 1-hydroxy-4-(3'-hydroxypropoxy)-pyrid-2-one or 1-hydroxy-4-(3'-hydroxypropoxy)-pyrid-2-one or 1-hydroxy-4-(2'-methoxyethoxy)-pyrid-2-one, or a physiologically acceptable salt thereof.

19. A compound according to any of Claims 12 to 18, for use in therapy.

20. A pharmaceutical composition comprising a compound as defined in any of Claims 12 to 18, together with a physiologically acceptable diluent or carrier.

21. A pharmaceutical composition according to Claim 20 in a form adapted for oral administration.

22. A compound being a 1-hydroxypyrid-2-one in which one or more of the hydrogen atoms attached to ring carbon atoms are replaced by a substituent selected from carbamoyl, mono- and di-C_{1-3} aliphatic hydrocarbyl N-substituted carbamoyl, formylamino, (C_{1-3} aliphatic hydrocarbyl)-carbonylamino, mono-C_{1-3} aliphatic hydrocarbyl N-substituted formylamino and N-substituted (C_{1-3} aliphatic hydrocarbyl)-carbonylamino, hydroxy, C_{1-4} alkoxy and C_{3-4} cycloalkoxy groups; C_{2-4} alkoxy and C_{3-4} cycloalkoxy groups substituted by a C_{1-4} alkoxy, C_{3-4} cycloalkoxy, carbamoyl, mono- or di-C_{1-3} aliphatic hydrocarbonyl N-substituted carbamoyl, formylamino, (C_{1-3} aliphatic hydrocarbonyl)-carbonylamino, mono-C_{1-3} aliphatic hydrocarbyl N-substituted formylamino or N-substituted (C_{1-3} aliphatic hydrocarbyl)-carbonylamino, or hydroxy group; C_{1-3} aliphatic hydrocarbon groups; and C_{1-3} aliphatic hydrocarbon groups substituted by a C_{1-4} alkoxy, C_{3-4} cycloalkoxy or hydroxy group; at least one of the hydrogen atoms being replaced by an amide group or an alkoxy or cycloalkoxy group substituted by an amide group, or a physiologically acceptable salt thereof, the 1-hydroxypyrid-2-one or salt thereof being linked to a support material through said amide group.

23. An iron complex of a 1-hydroxypyrid-2-one in which one or more of the hydrogen atoms attached to ring carbon atoms are replaced by a substituent selected from carbamoyl, mono- and di-C_{1-3} aliphatic hydrocarbyl N-substituted carbamoyl, formylamino, (C_{1-3} aliphatic hydrocarbyl)-carbonylamino, mono-C_{1-3} aliphatic hydrocarbyl N-substituted formylamino and N-substituted (C_{1-3} aliphatic hydrocarbyl)-carbonylamino, hydroxy, C_{1-4} alkoxy and C_{3-4} cycloalkoxy groups; C_{2-4} alkoxy and C_{3-4} cycloalkoxy

groups substituted by a C_{1-4} alkoxy, C_{3-4} cycloalkoxy, carbamoyl, mono- or di-C_{1-3} aliphatic hydrocarbyl N-substituted carbamoyl, formylamino, (C_{1-3} aliphatic hydrocarbonyl)-carbonylamino, mono-C_{1-3} aliphatic hydrocarbyl N-substituted formylamino or N-substituted (C_{1-3} aliphatic hydrocarbyl)-carbylamino, or hydroxy group; C_{1-3} aliphatic hydrocarbon groups; and C_{1-3} aliphatic hydrocarbon groups substituted by a C_{1-4} alkoxy, C_{3-4} cycloalkoxy or hydroxy group; but excluding compounds in which said replacement of hydrogen atoms is effected only by substituents selected from C_{1-3} aliphatic hydrocarbon groups and also the specific compound 1-hydroxy-5-methoxy-6-methylpyrid-2-one, for use in therapy.

24. A complex according to Claim 23, in which the iron complex is the neutral 3:1 1-hydroxypyrid-2-one:iron(III) complex.

25. A neutral 3:1 1-hydroxypyrid-2-one:iron(III) complex of a 1-hydroxypyrid-2-one in which one or more of the hydrogen atoms attached to ring carbon atoms are replaced by a substituent selected from carbamoyl, mono- and di-C_{1-3} aliphatic hydrocarbyl N-substituted carbamoyl, formylamino, (C_{1-3} aliphatic hydrocarbyl)-carbonylamino, mono-C_{1-3} aliphatic hydrocarbyl N-substituted formylamino and N-substituted (C_{1-3} aliphatic hydrocarbyl)-carbonylamino, hydroxy, C_{1-4} alkoxy and C_{3-4} cycloalkoxy groups; C_{2-4} alkoxy and C_{3-4} cycloalkoxy groups substituted by a C_{1-4} alkoxy, C_{3-4} cycloalkoxy, carbamoyl, mono- or di-C_{1-3} aliphatic hydrocarbonyl N-substituted carbamoyl, formylamino, (C_{1-3} aliphatic hydrocarbonyl)-carbonylamino, mono-C_{1-3} aliphatic hydrocarbyl N-substituted formylamino or N-substituted (C_{1-3} aliphatic hydrocarbyl)-carbonylamino, or hydroxy group; C_{1-3} aliphatic hydrocarbon groups; and C_{1-3} aliphatic hydrocarbon groups substituted by a C_{1-4} alkoxy, C_{3-4} cycloalkoxy or hydroxy group; but excluding compounds in which said replacement of hydrogen atoms is effected only by substituents selected from C_{1-3} aliphatic hydrocarbon groups and also the specific compound 1-hydroxy-5-methoxy-6-methylpyrid-2-one.

26. A complex according to Claim 23, 24 or 25, in which the 1-hydroxypyrid-2-one is as defined in any of Claims 3 to 18.

27. A pharmaceutical composition comprising a neutral 3:1 1-hydroxypyrid-2-one:iron(III) complex as defined in any of Claims 23 to 26, together with a physiologically acceptable diluent or carrier.

28. A pharmaceutical composition according to Claim 27, which comprises a sterile, pyrogen-free diluent.

29. A pharmaceutical composition according to Claim 27, which comprises a solid carrier.

30. A pharmaceutical composition according to Claim 27 or 29, which is adapted to release of the iron complex in the intestine rather than in the stomach.

31. A pharmaceutical composition according to any of Claims 27 to 30 in unit dosage form.

32. The use of an iron complex of a 1-hydroxypyrid-2-one in which one or more of the hydrogen atoms attached to ring carbon atoms are replaced by a substituent selected from carbamoyl, mono- and di-C_{1-3} aliphatic hydrocarbyl N-substituted carbamoyl, formylamino, (C_{1-3} aliphatic hydrocarbyl)-carbonylamino, mono-C_{1-3} aliphatic hydrocarbyl N-substituted formylamino and N-substituted (C_{1-3} aliphatic hydrocarbyl)-carbonylamino, hydroxy, C_{1-4} alkoxy and C_{3-4} cycloalkoxy groups; C_{2-4} alkoxy and C_{3-4} cycloalkoxy groups substituted by a C_{1-4} alkoxy, C_{3-4} cycloalkoxy, carbamoyl, mono- or di-C_{1-3} aliphatic hydrocarbyl N-substituted carbamoyl, formylamino, (C_{1-3} aliphatic hydrocarbyl)-carbonylamino, mono-C_{1-3} aliphatic hydrocarbyl N-substituted formylamino or N-substituted (C_{1-3} aliphatic hydrocarbyl)-carbonylamino, or hydroxy group; C_{1-3} aliphatic hydrocarbon groups; and C_{1-3} aliphatic hydrocarbon groups substituted by a C_{1-4} alkoxy, C_{3-4} cycloalkoxy or hydroxy group; but excluding compounds in which said replacement of hydrogen atoms is effected only by substituents selected from C_{1-3} aliphatic hydrocarbon groups, for the manufacture of a medicament of use in effecting an increase in the level of iron in a patient's bloodstream.

33. The use according to Claim 32, in which the iron complex is the neutral 3:1 1-hydroxypyrid-2-one:iron(III) complex.

34. The use according to Claim 32 or 33, in which the 1-hydroxypyrid-2-one is as defined in any of Claims 3 to 18.

Patentansprüche

1. Verwendung einer Verbindung, die ein 1-Hydroxypyrid-2-on ist, bei dem ein oder mehrere der am Ringkohlenstoffatome gebundenen Wasserstoffatome ersetzt ist/sind durch einen Substituenten, ausgewählt aus Carbamoyl-, mono- und di-C_{1-3}-aliphatisches Hydrocarbyl N-substituierte Carbamoyl-, Formylamino-, (C_{1-3}-aliphatisches Hydrocarbyl)-carbonylamino-, mono-C_{1-3}-aliphatisches Hydrocarbyl N-substituierte Formylamino- und N-substituierte (C_{1-3}-aliphatisches Hydrocarbyl)-carbonylamino-, Hydroxy-, C_{1-4}-Alkoxy- und C_{3-4}-Cycloalkoxygruppen; C_{2-4}-Alkoxy- und C_{3-4}-Cycloalkoxygruppen substituiert mit einer C_{1-4}-Alkoxy-, C_{3-4}-Cycloalkoxy-, Carbamoyl-, mono- oder di-C_{1-3}-aliphatisches Hydrocarbyl N-substituierte Carbamoyl-, Formylamino-, (C_{1-3}-aliphatisches Hydrocarbyl)-carbonylamino-, mono-C_{1-3}-aliphatisches Hydrocarbyl N-substituierte Formylamino- oder N-substituierte (C_{1-3}-aliphatisches Hydrocarbyl)-carbonylamino- oder Hydroxygruppe; C_{1-3}-aliphatische Kohlenwasserstoffgruppen; und C_{1-3}-aliphatische Kohlenwasserstoffgruppen substituiert mit einer C_{1-4}-Alkoxy-, C_{3-4}-Cycloalkoxy- oder Hydroxygruppe; jedoch unter Ausschluß von Verbindungen, bei denen Wasserstoffatome nur mit Substituenten ausgewählt aus C_{1-3}-aliphatischen Kohlenwasserstoffgruppen ersetzt worden

sind, oder eines physiologisch annehmbaren Salzes davon, für die Herstellung eines Medikamentes zur Verwendung, um eine Verringerung von toxischen Spiegeln eines Metalls im Körper eines Patienten zu bewirken.

2. Verwendung nach Anspruch 1, dadurch gekennzeichnet, daß das Metall Eisen ist.

3. Verwendung nach Anspruch 1 oder 2, dadurch gekennzeichnet, daß die Substituenten an den Ringkohlenstoffatomen Hydroxy-, Alkoxy-, substituierte Alkoxy- oder substituierte aliphatische Kohlenwasserstoffgruppen sind.

4. Verwendung nach Anspruch 3, dadurch gekennzeichnet, daß mindestens einer der Substituenten an den Ringkohlenstoffatomen eine Hydroxygruppe oder eine C_{1-3}-Alkoxygruppe ist.

5. Verwendung nach Anspruch 3, dadurch gekennzeichnet, daß mindestens einer der Substituenten an den Ringkohlenstoffatomen eine C_{2-3}-Alkoxygruppe ist, die mit einer Hydroxygruppe oder mit einer C_{1-3}-Alkoxygruppe substituiert ist.

6. Verwendung nach Anspruch 5, dadurch gekennzeichnet, daß die Gesamtzahl der Kohlenstoffatome in der Alkoxygruppe 3 oder 4 beträgt.

7. Verwendung nach einem der Ansprüche 3 bis 6, dadurch gekennzeichnet, daß die Ringkohlenstoffatome des 1-Hydroxypyrid-2-ons nur mit einem einzigen der genannten Substituenten substituiert sind, und gegebenenfalls zusätzlich durch ein oder mehrere C_{1-3}-aliphatische Kohlenwasserstoffgruppen.

8. Verwendung nach einem der Ansprüche 1 bis 7, dadurch gekennzeichnet, daß jede aliphatische Kohlenwasserstoffgruppe Methyl ist.

9. Verwendung nach einem der Ansprüche 1 bis 6, dadurch gekennzeichnet, daß das Ringkohlenstoffatom des 1-Hydroxypyrid-2-ons nur mit einem einzigen der genannten Substituenten substituiert ist.

10. Verwendung nach Anspruch 7 oder 9, dadurch gekennzeichnet, daß der einzige Substituent sich in der 4-Stellung des 1-Hydroxypyrid-2-ons befindet.

11. Verwendung nach Anspruch 1 oder 2, dadurch gekennzeichnet, daß das 1-Hydroxypyrid-2-on ein 1-Hydroxy-4-methoxypyrid-2-on, 4-Ethoxy-1-hydroxypyrid-2-on, 1,4-Dihydroxypyrid-2-on, 1-Hydroxy-4-(2'-hydroxy-ethoxy)-pyrid-2-on 1-Hydroxy-4-(3'-hydroxypropoxy)-pyrid-2-on oder 1-Hydroxy-4-(2'-methoxy-ethoxy)-pyrid-2-on, oder ein physiologisch annehmbares Salz davon ist.

12. Eine Verbindung, die ein 1-Hydroxypyrid-2-on ist, bei dem ein oder mehrere der an Ringkohlenstoffatomen gebundenen Wasserstoffatome durch einen Substituenten ersetzt ist/sind, der eine C_{2-4}-Alkoxy- oder C_{3-4}-Cycloalkoxygruppe ist, substituiert mit einer C_{1-4}-Alkoxy-, C_{3-4}-Cycloalkoxy-, Carbamoyl-, mono- oder di-C_{1-3}-aliphatisches Hydrocarbyl N-substituierte Carbamoyl-, Formylamino-, (C_{1-3}-aliphatisches Hydrocarbyl)-carbonylamino-, mono-C_{1-3}-aliphatisches Hydrocarbyl N-substituierte Formylamino- oder N-substituierte (C_{1-3}-aliphatisches Hydrocarbyl)-carbonylamino- oder Hydroxygruppe und bei dem ein weiteres oder mehrere der an Ringkohlenstoffatome gebundenen Wasserstoffatome gegebenenfalls ersetzt ist/sind durch einen Substituenten, ausgewählt aus Carbamoyl-, mono- und di-C_{1-3}-aliphatisches Hydrocarbyl N-substituierte Carbamoyl-, Formylamino-, (C_{1-3}-aliphatisches Hydrocarbyl)-carbonylamino-, mono-C_{1-3}-aliphatisches Hydrocarbyl N-substituierte Formylamino- und N-substituierte (C_{1-3}-aliphatisches Hydrocarbyl)-carbonylamino, Hydroxy-, C_{1-4}-Alkoxy- und C_{3-4}-Cycloalkoxygruppen; C_{1-3}-aliphatische Kohlenwasserstoffgruppen; und C_{1-3}-aliphatische Kohlenwasserstoffgruppen substituiert mit einer C_{1-4}-Alkoxy-, C_{3-4}-Cycloalkoxy-, oder Hydroxygruppe, oder ein physiologisch annehmbares Salz davon.

13. Verbindung nach Anspruch 12, dadurch gekennzeichnet, daß eines oder mehrere der an die Ringkohlenstoffatome gebundenen Wasserstoffatome ersetzt ist/sind durch einen Substituenten ausgewählt aus C_{2-4}-Alkoxy-gruppen, substituiert mit einer C_{1-4}-Alkoxygruppe, mit einer Amidgruppe, die unsubstituiert ist oder mono- oder disubstituiert mit C_{1-3}-Alkylgruppen oder mit einer Hydroxygruppe, und bei der weiterhin eines oder mehrere der Wasserstoffatome gegebenenfalls ersetzt ist/sind durch eine Hydroxygruppe oder eine C_{1-3}-Alkylgruppe.

14. Verbindung nach Anspruch 13, dadurch gekennzeichnet, daß eines der an Ringkohlenstoffatome gebundenen Wasserstoffatome des 1-Hydroxypyrid-2-ons ersetzt ist durch eine C_{2-3}-Alkoxygruppe, substituiert mit einer Hydroxygruppe, oder durch eine C_{2-3}-Alkoxygruppe, Substituiert mit einer C_{1-3} Alkoxygruppe wobei die Gesmatzahl der Kohlenstoffatome in den Alkoxyalkoxygruppen 3 oder 4 beträgt, und wobei weiter eines oder mehrere der Wasserstoffatome gegebenenfalls ersetzt ist/sind durch eine C_{1-3}-Alkylgruppe.

15. Verbindung nach einem der Ansprüche 12, 13 und 14, dadurch gekennzeichnet, daß jede aliphatische Kohlenwasserstoff- oder Alkylgruppe Methyl ist.

16. Verbindung nach einem der Ansprüche 12 bis 15, dadurch gekennzeichnet, daß eine substituierte Alkoxygruppe als Substituent in der 4-Stellung des 1-Hydroxypyrid-2-ons vorhanden ist.

17. Verbindung nach einem der Ansprüche 12 bis 16, dadurch gekennzeichnet, daß nur eines der an Ringkohlenstoffatome gebundenen Wasserstoffatome durch einen Substituenten ersetzt ist.

18. Verbindung nach Anspruch 12, die 1-Hydroxy-4-(2'-hydroxyethyl)-pyrid-2-on, 1-Hydroxy-4-(3'-hydroxypropoxy)-pyrid-2-on oder 1-Hydroxy-4-(3'-hydroxypropoxy)-pyrid-2-on oder 1-Hydroxy-4-(2'-methoxyethoxy)-pyrid-2-on oder ein physiologisch annehmbares Salz davon ist.

19. Verbindung nach einem der Ansprüche 12 bis 18 zur Verwendung in der Therapie.

20. Pharmazeutisches Mittel, enthaltend eine Verbindung, wie in einem der Ansprüche 12 bis 18 definiert, zusammen mit einem physiologisch annehmbaren Verdünungsmittel oder Träger.

21. Pharmazeutisches Mittel nach Anspruch 20 in einer für orale Verabreichung geeigneten Form.

22. Verbindung, die ein 1-Hydroxypyrid-2-on ist, bei dem eines oder mehrere der an Ringkohlenstoffatome gebundenen Wasserstoffatome ersetzt ist/sind durch einen Substituenten, ausgewählt aus Carbamoyl-, mono- und di-C_{1-3}-aliphatisches Hydrocarbyl N-substituierte Carbamoyl-, Formylamino-, (C_{1-3}-aliphatisches Hydrocarbyl)-carbonylamino-, mono-C_{1-3}-aliphatisches Hydrocarbyl N-substituierte Formylamino- und N-substituierte (C_{1-3}-aliphatisches Hydrocarbyl)-carbonylamino-, Hydroxy-, C_{1-4}-Alkoxy- und C_{3-4}Cycloalkoxygruppen; C_{2-4}-Alkoxy- und C_{3-4}-Cycloalkoxygruppen substituiert mit einer C_{1-4}-Alkoxy-, C_{3-4}-Cycloalkoxy-, Carbamoyl-, mono- oder di-C_{1-3}-aliphatisches Hydrocarbyl N-substituierte Carbamoyl-, Formylamino-, (C_{1-3}-aliphatisches Hydrocarbyl)-carbonylamino-, mono-C_{1-3}-aliphatisches Hydrocarbyl N-substituierte Formylamino- oder N-substituierte (C_{1-3}-aliphatisches Hydrocarbyl)-carbonylamino- oder Hydroxygruppe; C_{1-3}-aliphatische Kohlenwasserstoffgruppen; und C_{1-3}-aliphatische Kohlenwasserstoffgruppen substituiert mit einer C_{1-4}-Alkoxy-, C_{3-4}-Cycloalkoxy-, oder Hydroxygruppe; wobei mindestens eines der Wasserstoffatome ersetzt ist durch eine Amidgruppe oder eine Alkoxy- oder Cycloalkoxygruppe, substituiert mit einer Amidgruppe, oder ein physiologisch annehmbares Salz davon, wobei das 1-Hydroxypyrid-2-on oder Salz davon über die Amid-gruppe an ein Trägermaterial gebunden ist.

23. Ein Eisenkomplex eines 1-Hydroxypyrid-2-ons, bei dem eines oder mehrere der an Ringkohlenstoffatome gebundenen Wasserstoffatome ersetzt ist/sind durch einen Substituenten, ausgewählt aus Carbamoyl-, mono- und di-C_{1-3}-aliphatisches Hydrocarbyl N-substituierte Carbamoyl-, Formylamino-, (C_{1-3}-aliphatisches Hydrocarbyl)-carbonylamino-, mono-C_{1-3}-aliphatisches Hydrocarbyl N-substituierte Formylamino- und N-substituierte (C_{1-3}-aliphatisches Hydrocarbyl)-carbonylamino-, Hydroxy-, C_{1-4}-Alkoxy- und C_{3-4}Cycloalkoxygruppen substiutiert mit einer C_{1-4}-Alkoxy-, C_{3-4}-Cycloalkoxy-, Carbamoyl-, mono- oder di-C_{1-3}-aliphatisches Hydrocarbyl N-substituierte Carbamoyl-, Formylamino-, (C_{1-3}-aliphatisches Hydrocarbyl)-carbonylamino-, mono-C_{1-3}-aliphatisches Hydrocarbyl N-substituierte Formylamino- oder N-substituierte (C_{1-3}-aliphatisches Hydrocarbyl)-carbonylamino- oder Hydroxygruppe; C_{1-3}-aliphatische Kohlenwasserstoffgruppen; und C_{1-3}-aliphatische Kohlenwasserstoffgruppen substituiert mit einer C_{1-4}-Alkoxy-, C_{3-4}-Cycloalkoxy-, oder Hydroxygruppe; jedoch unter Ausschluß von Verbindungen, bei denen Wasserstoffatome nur durch Substituenten, ausgewählt aus C_{1-3}-aliphatischen Kohlenwasserstoffgruppen, ersetzt sind und auch der spezifischen Verbindung 1-Hydroxy-5-methoxy-6-methylpyrid-2-on, zur Verwendung in Therapie.

24. Komplex nach Anspruch 23, dadurch gekennzeichnet, daß der Eisenkomplex der neutrale 3:1 1-Hydroxypyrid-2-on: Eisen(III)-Komplex ist.

25. Neutraler 3:1 1-Hydroxypyrid-2-on: Eisen(III)-Komplex eines 1-Hydroxypyrid-2-ons, bei dem eines oder mehrere der an Ringkohlenstoffatome gebundenen Wasserstoffatome ersetzt ist/sind durch einen Substituenten, ausgewählt aus Carbamoyl-, mono- und di-C_{1-3}-aliphatisches Hydrocarbyl N-substituierte Carbamoyl-, Formylamino-, (C_{1-3}-aliphatisches Hydrocarbyl)-carbonylamino-, mono-C_{1-3}-aliphatisches Hydrocarbyl N-substituierte Formylamino- und N-substituierte (C_{1-3}-aliphatisches Hydrocarbyl)-carbonylamino-, Hydroxy-, C_{1-4}-Alkoxy- und C_{3-4}Cycloalkoxygruppen; C_{2-4}-Alkoxy- und C_{3-4}-Cycloalkoxygruppen substiutiert mit einer C_{1-4}-Alkoxy-, C_{3-4}-Cycloalkoxy-, Carbamoyl-, mono- oder di-C_{1-3}-aliphatisches Hydrocarbyl N-substituierte Carbamoyl-, Formylamino-, (C_{1-3}-aliphatisches Hydrocarbyl)-carbonylamino-, mono-C_{1-3}-aliphatisches Hydrocarbyl N-substituierte Formylamino- oder N-substituierte (C_{1-3}-aliphatisches Hydrocarbyl)-carbonylamino- oder Hydroxygruppe; C_{1-3}-aliphatische Kohlenwasserstoffgruppen; und C_{1-3}-aliphatische Kohlenwasserstoffgruppen substituiert mit einer C_{1-4}-Alkoxy-, C_{3-4}-Cycloalkoxy-, oder Hydroxygruppe; jedoch unter Ausschluß von Verbindungen, bei denen Wasserstoffatome nur mit Substituenten, ausgewählt aus C_{1-3}-aliphatischen Kohlenwasserstoffgruppen, ersetzt worden sind, und auch der spezifischen Verbindung 1-Hydroxy-5-methoxy-6-methylpyrid-2-on.

26. Komplex nach Anspruch 23, 24 oder 25, dadurch gekennzeichnet, daß das 1-Hydroxypyrid-2-on wie in einem der Ansprüche 3 bis 18 definiert ist.

27. Pharmazeutisches Mittel, enthaltend einen neutralen 3:1 1-Hydroxypyrid-2-on:Eisen(III)-Komplex, wie in einem der Ansprüche 23 bis 26 definiert, zusammen mit einem physiologisch annehmbaren Verdünnungsmittel oder Träger.

28. Pharmazeutisches Mittel nach Anspruch 27, dadurch gekennzeichnet, daß es ein steriles pyrogenfreies Verdünnungsmittel enthält.

29. Pharmazeutisches Mittel nach Anspruch 27, dadurch gekennzeichnet, daß es einen festen Träger enthält.

30. Pharmazeutisches Mittel nach Anspruch 27 oder 29, das so ausgebildet ist, daß es den Eisenkomplex im Darm anstelle im Magen freisetzt.

31. Pharmazeutisches Mittel nach einem der Ansprüche 27 bis 30 in Einheitsdosis-Form.

32. Verwendung eines Eisenomplexes eines 1-Hydroxypyrid-2-ons, bei dem eines oder mehrere der an Ringkohlenstoffatome gebundenen Wasserstoffatome ersetzt sind durch einen Substituenten, ausgewählt aus Carbamoyl-, mono- und di-C_{1-3}-aliphatisches Hydrocarbyl N-substituierte Carbamoyl-, Formylamino-, (C_{1-3}-aliphatisches Hydrocarbyl)-carbonylamino-, mono-C_{1-3}-aliphatisches Hydrocarbyl N-substituierte Formylamino- und N-substituierte (C_{1-3}-aliphatisches Hydrocarbyl)-carbonylamino-, Hydroxy-, C_{1-4}-Alkoxy- und C_{3-4}Cycloalkoxygruppen; C_{2-4}-Alkoxy- und C_{3-4}-Cycloalkoxygruppen substiutiert mit einer C_{1-4}-Alkoxy-, C_{3-4}-Cycloalkoxy-, Carbamoyl-, mono- oder di-C_{1-3}-aliphatisches Hydrocarbyl N-substituierte Carbamoyl-, Formylamino-, (C_{1-3}-aliphatisches Hydrocarbyl)-carbonylamino-, mono-C_{1-3}-aliphatisches

Hydrocarbyl N-substituierte Formylamino- oder N-substituierte (C_{1-3}-aliphatisches Hydrocarbyl-carbonylamino- oder Hydroxygruppe; C_{1-3}-aliphatische Kohlenwasserstoffgruppen; und C_{1-3}-aliphatische Kohlenwasserstoffgruppen substituiert mit einer C_{1-4}-Alkoxy-, C_{3-4}-Cycloalkoxy-, oder Hydroxygruppe; jedoch unter Ausschluß von Verbindungen, bei denen Wasserstoffatome nur mit Substituenten ausgewählt aus C_{1-3}-aliphatischen Kohlenwasserstoffgruppen ersetzt worden sind, zur Herstellung eines Arzneimittels zur Verwendung, um eine Zunahme des Eisenspiegels im Blutstrom eines Patienten zu bewirken.

33. Verwendung nach Anspruch 32, dadurch gekennzeichnet, daß der Eisenkomplex der neutrale 3:1 1-Hydroxypyrid-2-on:Eisen(III)-Komplex ist.

34. Verwendung nach Anspruch 32 oder 33, dadurch gekennzeichnet, daß das 1-Hydroxypyrid-2-on wie in einem der Ansprüche 3 bis 18 definiert ist.

Revendications

1. Utilisation d'un composé qui est une 1-hydroxypyrid-2-one dans laquelle un ou plusieurs des atomes d'hydrogène fixés aux atomes de carbone du cycle sont remplacés par un substituant choisi parmi un groupe carbamoyle, un groupe carbamoyle mono- et disubstitué sur l'atome de N par un radical hydrocarbyle aliphatique en C_{1-3}, un groupe formylamino, un groupe (hydrocarbyl aliphatique en C_{1-3}) carbonylamino, un groupe formylamino monosubstitué sur l'atome de N par un radical hydrocarbyle aliphatique en C_{1-3} et un groupe carbonylamino substitué sur l'atome de N par un radical hydrocarbyle aliphatique en C_{1-3}, un groupe hydroxy, des groupes alkoxy en C_{1-4} et cycloalkoxy en C_{3-4}; des groupes alkoxy en C_{2-4} et cycloalkoxy en C_{3-4} substitués par un groupe alkoxy en C_{1-4}, cycloalkoxy en C_{3-4}, un groupe carbamoyle, un groupe carbamoyle mono- ou disubstitué sur l'atome de N par un radical hydrocarbyle aliphatique en C_{1-3}, un groupe formylamino, un groupe (hydrocarbyl) aliphatique en C_{1-3}) carbonylamino, un groupe formylamino monosubstitué sur l'atome de N par un radical hydrocarbyle aliphatique en C_{1-3} ou un groupe carbonylamino substitué sur l'atome de N par un radical hydrocarbyle aliphatique en C_{1-3} ou un groupe hydroxy; des groupes hydrocarbonés aliphatiques en C_{1-3}; et des groupes hydrocarbonés aliphatiques en C_{1-3} substitués par un groupe alkoxy en C_{1-4}, cycloalkoxy en C_{3-4} ou hydroxy; mais à l'exclusion des composés dans lesquels ce remplacement des atomes d'hydrogène est réalisé uniquement par des substituants choisis parmi des groupes hydrocarbonés aliphatiques en C_{1-3}, ou d'un sel physiologiquement acceptable de celle-ci, pour la fabrication d'un médicament utilisable pour abaisser les niveaux toxiques d'un métal dans l'organisme d'un patient.

2. Utilisation selon la revendication 1 dans laquelle le métal est le fer.

3. Utilisation selon la revendication 1 ou 2, dans laquelle au moins un des substituants d'un atome de carbone du cycle est un groupe hydroxy, alkoxy, alkoxy substitué ou un groupe hydrocarboné aliphatique substitué.

4. Utilisation selon la revendication 3 dans laquelle un au moins des substituants d'un atome de carbone du cycle est un groupe hydroxy ou un groupe alkoxy en C_{1-3}.

5. Utilisation selon la revendication 3, dans laquelle un au moins des substituants des atomes de carbone du cycle est un groupe alkoxy en C_{2-3} substitué par un groupe hydroxy ou par un groupe alkoxy en C_{1-3}.

6. Utilisation selon la revendication 5 dans laquelle le nombre total d'atomes de carbone dans le groupe alkoxyalkoxy est de 3 ou 4.

7. Utilisation selon l'une des revendications 3 à 6 dans laquelle les atomes de carbone du cycle de la 1-hydroxypyrid-2-one sont substitués par un seul de ces substituants et éventuellement, en outre, par un ou plusieurs groupes hydrocarbonés aliphatiques en C_{1-3}.

8. Utilisation selon l'une des revendications 1 à 7 dans laquelle l'un des groupes hydrocarbonés aliphatiques est le groupe méthyle.

9. Utilisation selon l'une des revendications 1 à 6 dans laquelle les atomes de carbone du cycle de la 1-hydroxypyrid-2-one sont substitués uniquement par un seul de ces substituants.

10. Utilisation selon la revendication 7 ou 9, dans laquelle le seul de ces substituants est situé en position 4 de la 1-hydroxypyrid-2-one.

11. Utilisation selon la revendication 1 ou 2, dans laquelle la 1-hydroxypyrid-2-one est la 1-hydroxy-4-méthoxypyrid-2-one, la 4-éthoxy-1-hydroxypyrid-2-one, la 1,4-dihydroxypyrid-2-one, la 1-hydroxy-4-(2'-hydroxyéthoxy)-pyrid-2-one, la 1-hydroxy-4-(3'-hydroxypropoxy)-pyrid-2-one ou la 1-hydroxy-4-(2'-méthoxyéthoxy)-pyrid-2-one, ou un sel physiologiquement acceptable de celle-ci.

12. Composé qui est une 1-hydroxypyrid-2-one dans laquelle un ou plusieurs des atomes d'hydrogène fixés aux atomes de carbone du cycle sont remplacés par un substituant qui est un groupe alkoxy en C_{2-4} ou cycloalkoxy en C_{3-4} substitué par un groupe alkoxy en C_{1-4}, cycloalkoxy en C_{3-4}, un groupe carbamoyle, un groupe carbamoyle mono- ou disubstitué sur l'atome de N par un radical hydrocarbyle aliphatique en C_{1-3}, un groupe formylamino, un groupe (hydrocarbyl aliphatique en C_{1-3}) carbonylamino, un groupe formylamino mono-substitué sur l'atome de N par un radical hydrocarbyle aliphatique en C_{1-3}, ou un groupe carbonylamino substitué sur l'atome de N par un radical hydrocarbyle aliphatique en C_{1-3}, ou un groupe hydroxy, et dans laquelle un autre ou plusieurs autres des atomes d'hydrogène fixés aux atomes de carbone du cycle sont éventuellement replacés par un substituant choisi parmi un groupe carbamoyle, un

groupe carbamoyle mono- ou disubstitué sur l'atome de N par un radical hydrocarbyl aliphatique en C_{1-3}, un groupe formylamino, un groupe (hydrocarbyl) aliphatique en C_{1-3}) carbonylamino, un groupe formylamino substitué sur l'atome de N par un groupe hydrocarbyle aliphatique en C_{1-3}, ou un groupe carbonylamino substitué sur l'atome de N par un radical hydrocarbyle aliphatique en C_{1-3}, un groupe hydroxy, des groupes alkoxy en C_{1-4} et cycloalkoxy en C_{3-4}; des groupes hydrocarbonés aliphatiques en C_{1-3}; et des groupes hydrocarbonés aliphatiques en C_{1-3} substitués par un groupe alkoxy en C_{1-4}, cycloalkoxy en C_{3-4} ou hydroxy; ou un sel physiologiquement acceptable de celle-ci.

13. Composé selon la revendication 12 dans lequel un ou plusieurs des atomes d'hydrogène fixés aux atomes de carbone du cycle sont remplacés par un substituant choisi parmi des groupes alkoxy en C_{2-4} substitués par un groupe alkoxy en C_{1-4}, par un groupe amide qui est non substitué ou mono- or disubstitué par des groupes alkyle en C_{1-3} ou par un groupe hydroxy et dans lequel en outre un ou plusieurs des atomes d'hydrogène sont éventuellement remplacés par un groupe hydroxy ou un groupe alkyle en C_{1-3}.

14. Composé selon la revendication 13 dans lequel un des atomes d'hydrogène fixés aux atomes de carbone du cycle de la 1-hydroxypyrid-2-one est remplacé par un groupe alkoxy en C_{2-3} substitué par un groupe hydroxy, ou par un groupe alkoxy en C_{2-3} substitué par un groupe alkoxy en C_{1-3}, le nombre total d'atomes de carbone dans le groupe alkoxyalkoxy étant de 3 ou 4, et dans lequel un autre ou plusieurs autres des atomes d'hydrogène sont éventuellement remplacés par un groupe alkyle en C_{1-3}.

15. Composé selon l'une des revendications 12, 13 et 14 dans lequel un groupe hydrocarboné aliphatique ou alkyle est le groupe méthyle.

16. Composé selon l'une des revendications 12 à 15 dans lequel un substituant qui est un groupe alkoxy substitué est présent en position 4 de la 1-hydroxypyrid-2-one.

17. Composé selon l'une des revendications 12 à 16 dans lequel un seul des atomes d'hydrogène fixés à un atome de carbone du cycle est remplacé par un substituant.

18. Composé selon la revendication 12 qui est la 1-hydroxy-4-(2'-hydroxyéthoxy)-pyrid-2-one, la 1-hydroxy-4-(3'-hydroxypropoxy)-pyrid-2-one ou la 1-hydroxy-4-(2'-méthoxyéthoxy)-pyrid-2-one ou un sel physiologiquement acceptable de celle-ci.

19. Composé selon l'une des revendications 12 à 18 destiné à l'utilisation en thérapie.

20. Composition pharmaceutique comprenant un composé tel que défini dans une des revendications 12 à 18 ainsi qu'un diluant ou un excipient physiologiquement acceptable.

21. Composition pharmaceutique selon la revendication 20 sous une forme adaptée à l'administration orale.

22. Composé qui est une 1-hydroxypyrid-2-one dans laquelle un ou plusieurs des atome d'hydrogène fixés aux atomes de carbone du cycle sont remplacés par un substituant choisi parmi un groupe carbamoyle, un groupe carbamoyle mono- et disubstitué sur l'atome de N par un radical hydrocarbyle aliphatique en C_{1-3}, un groupe formylamino, un groupe (hydrocarbyl aliphatique en C_{1-3}) carbonylamino, un groupe formylamino monosubstitué sur l'atome de N par un radical hydrocarbyle aliphatique en C_{1-3} et un groupe carbonylamino substitué sur l'atome de N par un radical hydrocarbyle aliphatique en C_{1-3}, un groupe hydroxy, des groupes alkoxy en C_{1-4} et cycloalkoxy en C_{3-4}; des groupes alkoxy en C_{2-4} et cycloalkoxy en C_{3-4} substitués par un groupe alkoxy en C_{1-4}, cycloalkoxy en C_{3-4}, un groupe carbamoyle, un groupe carbamoyle mono- ou disubstitué sur l'atome de N par un radical hydrocarbyle aliphatique en C_{1-3}, un groupe formylamino, un groupe (hydrocarbyl aliphatique en C_{1-3}) carbonylamino, un groupe formylamino monosubstitué sur l'atome de N par un radical hydrocarbyle aliphatique en C_{1-3} ou un groupe carbonylamino substitué sur l'atome de N par un radical hydrocarbyle aliphatique en C_{1-3} ou un groupe hydroxy; des groupes hydrocarbonés aliphatiques en C_{1-3}; et des groupes hydrocarbonés aliphatiques en C_{1-3} substitués par un groupe alkoxy en C_{1-4}, cycloalkoxy en C_{3-4} ou hydroxy; l'un au moins des atomes d'hydrogène étant remplacé par un groupe amide ou par un groupe alkoxy ou cycloalkoxy substitué par un groupe amide, ou un sel physiologiquement acceptable de celle-ci, la 1-hydroxypyrid-2-one ou le sel de celle-ci étant lié à un matériau support par ledit groupe amide.

23. Complexe de fer d'une 1-hydroxypyrid-2-one dans laquelle un ou plusieurs des atomes d'hydrogène fixés aux atomes de carbone du cycle sont remplacés par un substituant choisi parmi un groupe carbamoyle, un groupe carbamoyle mono- et disubstitué sur l'atome de N par un radical hydrocarbyle aliphatique en C_{1-3}, un groupe formylamino, un groupe hydrocarbyl aliphatique en C_{1-3}, carbonylamino, un groupe formylamino monosubstitué sur l'atome de N par un radical hydrocarbyle aliphatique en C_{1-3} et un groupe carbonylamino substitué sur l'atome de N par un radical hydrocarbyle aliphatique en C_{1-3}, un groupe hydroxy, des groupes alkoxy en C_{1-4} et cycloalkoxy en C_{3-4}; des groupes alkoxy en C_{2-4} et cycloalkoxy en C_{3-4} substitués par un groupe alkoxy en C_{1-4}, cycloalkoxy en C_{3-4}, un groupe carbamoyle, un groupe carbamoyle mono- ou disubstitué sur l'atome de N par un radical hydrocarbyle aliphatique en C_{1-3}, un groupe formylamino, un groupe (hydrocarbyl aliphatique en C_{1-3}) carbonylamino, un groupe formylamino substitué sur l'atome de N par un radical hydrocarbyle aliphatique en C_{1-3} ou un groupe carbonylamino substitué sur l'atome de N par un radical hydrocarbyle aliphatique en C_{1-3}, un groupe hydroxy; des groupes hydrocarbonés aliphatiques en C_{1-3}; et des groupes hydrocarbonés aliphatiques en C_{1-3} substitués par un groupe alkoxy en C_{1-4}, cycloalkoxy en C_{3-4} ou hydroxy; mais à l'exclusion des composés dans lesquels ce remplacement des atomes d'hydrogène est

réalisé uniquement par des substituants choisis parmi les groupes hydrocarbonés aliphatiques en C_{1-3} et aussi du composé spécifique 1-hydroxy-5-méthoxy-6-méthylpyrid-2-one, destiné à l'utilisation en thérapie.

24. Complexe selon la revendication 23, dans laquelle le complexe de fer est le complexe 1-hydroxypyrid-2-one: fer(III) 3:1 neutre.

25. Complexe 1-hydroxypyrid-2-one:fer(III) 3:1 neutre d'une 1-hydroxypyrid-2-one dans laquelle un ou plusieurs des atomes d'hydrogène fixés aux atomes de carbone du cycle sont remplacés par un substituant choisi parmi un groupe carbamoyle, un groupe carbamoyle mono- et disubstitué sur l'atome de N par un radical hydrocarbyle aliphatique en C_{1-3}, un groupe formylamino, un groupe (hydrocarbyl aliphatique en C_{1-3}) carbonylamino, un groupe formylamino substitué sur l'atome de N par un radical hydrocarbyle aliphatique en C_{1-3} et un groupe carbonylamino substitué sur l'atome de N par un radical hydrocarbyle aliphatique en C_{1-3}, un groupe hydroxy, des groupes alkoxy en C_{1-4} et cycloalkoxy en C_{3-4}; des groupes alkoxy en C_{2-4} et cycloalkoxy en C_{3-4} substitués par un groupe alkoxy en C_{1-4}, cycloalkoxy en C_{3-4}, un groupe carbamoyle, un groupe carbamoyle mono- ou disubstitué sur l'atome de N par un radical hydrocarbyle aliphatique en C_{1-3}, un groupe formylamino, un groupe (hydrocarbyl aliphatique en C_{1-3}) carbonylamino, un groupe formylamino monosubstitué sur l'atomes de N par un radical hydrocarbyle aliphatique en C_{1-3} ou un groupe carbonylamino substitué sur l'atome de N par un radical hydrocarbyle aliphatique en C_{1-3} ou un groupe hydroxy; des groupes hydrocarbonés aliphatiques en C_{1-3} substitués par un groupe alkoxy en C_{1-4}, cycloalkoxy en C_{3-4} ou hydroxy; mais à l'exclusion des composés dans lesquels ce remplacement des atomes d'hydrogène est réalisé uniquement par des substituants choisis parmi les groupes hydrocarbonés aliphatiques en C_{1-3} et aussi du composé spécifique 1-hydroxy-5-méthoxy-6-méthylpyrid-2-one.

26. Complexe selon la revendication 23, 24 ou 25 dans lequel la 1-hydroxypyrid-2-one est telle qu'elle a été définie dans l'une des revendications 3 à 18.

27. Composition pharmaceutique comprenant un complexe 1-hydroxypyrid-2-one:fer(III) 3:1 neutre tel qu'il a été défini dans l'une des revendications 23 à 26, ainsi qu'un diluant ou excipient physiologiquement accetable.

28. Composition pharmaceutique selon la revendication 27 qui comprend un diluant stérile exempt de pyrogènes.

29. Composition pharmaceutique selon la revendication 27, qui comprend un véhicule solide.

30. Composition pharmaceutique selon la revendication 27 ou 29 qui est adaptée à la libération du complexe de fer dans l'intestin plutôt que dans l'estomac.

31. Composition pharmaceutique selon l'une des revendications 27 à 30 sous forme de doses unitaires.

32. Utilisation d'un complexe de fer d'une 1-hydroxypyrid-2-one dans laquelle un ou plusieurs des atomes d'hydrogène fixés aux atomes de carbone du cycle sont remplacés par un substituant choisi parmi un groupe carbamoyle, un groupe carbamoyle mono- et disubstitué sur l'atome de N par un radical hydrocarbyle aliphatique en C_{1-3}, un groupe formylamino, un groupe (hydrocarbyl aliphatique en C_{1-3}) carbonylamino, un groupe formylamino monosubstitué sur l'atome de N par un radical hydrocarbyl aliphatique en C_{1-3} et un groupe carbonylamino substitué sur l'atome de N par un radical hydrocarbyle aliphatique en C_{1-3}, un groupe hydroxy, des groupes alkoxy en C_{1-4} et cycloalkoxy en C_{3-4}; des groupes alkoxy en C_{2-4} et cycloalkoxy en C_{3-4} substitués par un groupe alkoxy en C_{1-4}, cycloalkoxy en C_{3-4}, un groupe carbamoyle, un groupe carbamoyle mono- ou disubstitué sur l'atome de N par un radical hydrocarbyle aliphatique en C_{1-3}, un groupe formylamino, un groupe (hydrocarbyl aliphatique en C_{1-3}) carbonylamino, un groupe formylamino monosubstitué sur l'atome de N par un radical hydrocarbyle aliphatique en C_{1-3} ou un groupe carbonylamino substitué sur l'atome de N par un radical hydrocarbyle aliphatique en C_{1-3}, ou un groupe hydroxy; des groupes hydrocarbonés aliphatiques en C_{1-3} substitués par un groupe alkoxy en C_{1-4}, cycloalkoxy en C_{3-4} ou hydroxy mais à l'exclusion des composés dans lesquels ce remplacement des atomes d'hydrogène est réalisé uniquement par des substituants choisis parmi les groupes hydrocarbonés aliphatiques en C_{1-3}, pour la fabrication d'un médicament utilisable pour élever le niveau de fer dans la circulation sanguine d'un patient.

33. Utilisation selon la revendication 32 dans lequelle le complexe de fer est le complexe 1-hydroxypyrid-2-one:fer(III) 3:1 neutre.

34. Utilisation selon la revendication 32 ou 33 dans laquelle la 1-hydroxypyrid-2-one est telle qu'elle a été définie dans l'une des revendications 3 à 18.

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