Iron salts (e.g. iron(II) sulfate, iron(II) fumarate, iron(III) chloride, iron(II) aspartate, iron(II) succinate) are another important constituent for the treatment of iron deficiency symptoms and iron deficiency anemias.

These iron salts are very problematic in that, in part, they are highly incompatible (up to 50%) in the form of nausea, vomiting, diarrhea and also obstipation and cramps. Moreover, free iron(II) ions which catalyze the formation (inter alia Fenton reaction) of reactive oxygen species (ROS) occur during the use of these iron(II) salts. These ROS cause damage to DNA, lipids, proteins and carbohydrates which has far-reaching effects in cells, tissue and organs. This complex of problems is known and, in the literature, is largely considered the cause for the high incompatibility and referred to as oxidative stress.

Therefore, iron(III)-1-hydroxy-1H-pyrimidine-2-one or pyrimidine-2-ol-1-oxide complex compounds, respectively, have not been described in the prior art neither as a medicament nor in particular for the use in the treatment and/or for prophylaxis of iron deficiency symptoms and iron deficiency anemia so far.

Summary~~Object~~:

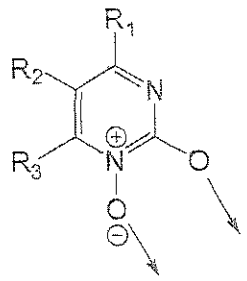
The object of the present disclosure~~invention~~ **lay in developing new** therapeutically effective compounds that can be used for an effective therapy for the preferably oral treatment of iron deficiency symptoms and iron deficiency anemias. In this case, these iron complexes were supposed to exhibit significantly fewer side effects than the classically used Fe(II) salts. Furthermore, these iron complexes, in contrast to the known polymeric iron complex compounds, were, if possible, supposed to have a defined structure (stoichiometry) and be preparable by simple synthesis processes. Finally, the iron complex compounds should have a very low toxicity

and can be therefore administered in very high dosages. This goal was achieved by the development of novel Fe(III) complex compounds.

Furthermore, the novel iron complexes were supposed to be designed such that they are taken up into the intestinal cells directly via the membrane in order thus to release their complex-bound iron directly to the ferritin or the transferrin or to reach the bloodstream directly as an intact complex. Because of their properties, these new complexes are supposed to virtually not lead to the occurrence of high concentrations of free iron ions. For it is precisely the free iron ions that lead to the occurrence of ROS which are ultimately responsible for the side effects that occur.

In order to be able to meet these requirements, the inventors developed new Fe(III) complex compounds with a molecular weight that is not too large, medium lipophila and an optimal complex stability.

In an aspect, there is provided iron(III) pyrimidine-2-ol-1-oxide complex compounds, containing at least one ligand of the formula (I):



(I)

wherein

the arrows respectively represent a coordinate bond to one or different iron atoms, and

R_1, R_2, R_3 may be the same or different and are selected from the group consisting of:

- hydrogen,
- optionally substituted alkyl,
- halogen,
- optionally substituted alkoxy,
- optionally substituted aryl,
- optionally substituted alkoxycarbonyl,
- optionally substituted amino, and
- optionally substituted aminocarbonyl or

R_1 and R_2 or R_2 and R_3 together with the carbon atoms to which they are bonded, form an optionally substituted saturated or unsaturated

5- or 6-membered ring, which may optionally contain one or more heteroatoms, or pharmaceutically acceptable salts thereof, for use as medicaments.

In another aspect, there is provided iron(III) pyrimidine-2-ol-1-oxide complex compounds as defined herein in solid form.

In another aspect, there is provided the use of iron(III) pyrimidine-2-ol-1-oxide complex compounds as defined herein in the manufacture of a medicament for treatment and prophylaxis of iron deficiency symptoms and iron deficiency anemias and the symptoms associated therewith.

In another aspect, there is provided medicament, containing iron(III) complex compounds as defined herein and at least one physiological compatible carrier or excipient.

In another aspect, there is provided composition containing iron(III) complex compounds as defined herein, in combination with at least one further medicament which acts on the iron metabolism.

Description of the invention:

The inventors surprisingly found that Fe(III) complex compounds with pyrimidine-2-ol-1-oxide ligands were particularly suitable for the above-described requirements. It was possible to demonstrate that these Fe complex compounds exhibited a high iron uptake, whereby a quick therapeutic success in the treatment of iron deficiency anemia could be achieved. Especially in comparison to iron salts, the complex compounds according to the invention exhibited a faster and higher utilization. Furthermore, these new systems have significantly reduced side effects than the classically used iron salts since there is no noteworthy occurrence of free iron irons in this case. The complex compounds according to the invention exhibit almost no oxidative stress since there is no formation of free radicals. Thus, significantly fewer side effects occur in the case of