Metal complexes of maltol and close analogues in medicinal inorganic chemistry

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The family of hydroxypyrones and close congeners, the hydroxypyridinones, is a particularly versatile class of ligands. The most widely investigated for medicinal applications are the 3-hydroxy-4-pyrones and the 1,2- 3,2- and 3,4-hydroxypyridinones. Key features of these ligands are: a six-membered ring, with a ring N or O atom either *ortho* or *para* to a ketone group, and two *ortho* exocyclic oxygen atoms. Readily functionalizable, the hydroxypyrones and hydroxypyridinones allow one to achieve a range of di- and trivalent metallocomplex stabilities and can include tissue or molecular targeting features by design. Research over the past several decades has greatly expanded the array of ligands that are the subject of this *critical review*. Ligand applications as diverse as iron removal or supplementation, contrast agents in imaging applications, and mobilization of undesirable excess metal ions will be surveyed herein.

1 Introduction

Maltol, 3-hydroxy-2-methyl-4-pyrone, is one of several hydroxypyrones long known for high bioavailability and favourable toxicity profiles. Close analogues of maltol include kojic acid (5-hydroxy-2-hydroxymethyl-4-pyrone) and an increasing variety of hydroxypyridinones. These hydroxypyrones and hydroxypyridinones (Fig. 1) are characterized by synthetic versatility and a high affinity for a range of metal ions, rendering these ligands excellent choices for the formulation of therapeutic and/or diagnostic metallopharmaceuticals. The formation of exceptionally stable and, in many cases, neutrally charged complexes with a wide variety of metal ions, including the trivalent cations Fe^{3+}, Al^{3+}, Ga^{3+}, and In^{3+},[1] as well as the actinides[2] and lanthanides,[3] is a common feature of hydroxypyridinones and hydroxypyrones. The hydroxypyrones are also efficient binders of many divalent ions, including Zn^{2+}, Ru^{2+}, $[VO]^{2+}$, and $[MoO_2]^{2+}$. Recent specific reviews include those for iron overload treatment,[4,5] aluminium chelation,[6,7] vanadium-based therapeutic agents,[8] and lanthanides.[9]

Early applications of hydroxypyrones and hydroxypyridinones to medicinal inorganic chemistry generally fall into one of two main areas: 1) ligand development for potentiation of *in situ* metal-ion complex formation [and subsequent removal of excess metal ion(s)], or 2) metal ion–ligand complex formation for improving absorption and/or biodistribution characteristics of a particular metal ion. Construed roughly, either one can be seen as a means of altering metal ion homeostasis, whether to enhance uptake or to promote removal of a metal ion, depending on the therapeutic need, and governed by ligand choice.[10]

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Katherine Thompson

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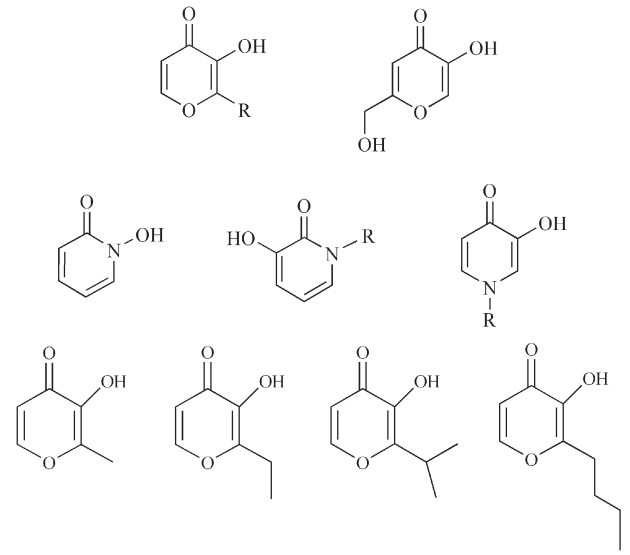


Fig. 1 The core ligands that are the subject of this review. Top row: 3-hydroxy-4-pyrones and 5-hydroxy-2-hydroxymethyl-4-pyrone (kojic acid); middle row: 1,2- 3,2- and 3,4-hydroxypyridinones; bottom row: 3-hydroxy-4-pyrones in which R = CH_3 (maltol), C_2H_5 (ethylmaltol), *i*-Pr (isopropyl maltol) or *n*-Bu (*n*-butyl maltol) (left to right), respectively.

Many of the more recent medicinal inorganic chemistry applications of hydroxypyridinones include gadolinium hydroxypyridinone complexes for magnetic resonance imaging (MRI) contrast agents, and chemotherapeutic agents of hydroxypyrones or -pyridinones complexed to trivalent metal ions of interest. In these formulations, functional substitution for optimizing metal binding, linking units and/or target tissue specificity is necessary.

Chris Orvig

Chris Orvig was born and raised in Montréal. He received his BSc in chemistry from McGill University in 1976 and subsequently pursued graduate studies (as a Natural Sciences and Engineering Research Council – NSERC – of Canada scholar) in technetium chemistry at MIT with Prof. Alan Davison, receiving the PhD in 1981. He was then an NSERC postdoctoral fellow with Prof. Kenneth N. Raymond at the University of California, Berkeley in 1981–83. After one year with the late Prof. Colin J. L. Lock at McMaster University, he joined the University of British Columbia in 1984, where he is now Professor of Chemistry and Pharmaceutical Sciences, and Director of the Medicinal Inorganic Chemistry Group. His scientific interests are firmly planted in the areas of medicinal inorganic chemistry and coordination chemistry – he has been involved over the years with radiopharmaceutical chemistry, metal ion decorporation, metal ion neurotoxicology, and chemotherapeutic metal complexes.

In a wide range of instances of metal ion imbalance, use of a hydroxypyridinone to either passivate, or speed egress, of the offending metal ions, can potentially correct the errant metal metabolism, or at least render the dysfunctional state more manageable, by depleting the body burden of that metal ion.[11,12] In a situation requiring increased metal ion uptake, one can improve absorption characteristics using hydroxypyrones, or close analogues. Thus, suitably designed ligands may increase tissue uptake of metal ions that are either deficient and requiring repletion, or pharmacologically beneficial in excess of normal physiological levels and hence requiring supplementation.[10]

Topics to be covered in this critical review include: improvement of metal ion balance in disorders of metal metabolism, *e.g.* anaemia, thalassemia, hemochromatosis, in which improved absorption or accelerated removal of metal ions is desirable; enhancement of tissue uptake and retention of metal-based insulin-enhancing agents; protection from heavy metal ion toxicity in contrast agents, chemotherapeutics, or due to harmful radioisotope exposure; and attenuation of redox metal neurotoxicity.

2 Structural characteristics of hydroxypyrones and hydroxypyridinones

The hydroxypyrones include several classes of compounds, all heterocycles with an hydroxyl group *ortho* to a ketone, providing two oxygen donor groups in close proximity.[7] One of the best known, maltol, 3-hydroxy-2-methyl-4-pyrone[13] (Fig. 1) is an approved food additive, used to impart a desirable malty taste and odor to breads, cakes, beer and other beverages. Maltol, and its ethyl analogue, ethylmaltol (2-ethyl-3-hydroxy-4-pyrone, Fig. 1),[14,15] also an approved food additive, are both commercially available; however, most other analogues require chemical synthesis. The well-studied biocompatability of maltol[16,17] and ethylmaltol[15,18] suggests a favorable toxicity profile for others in the same class of ligands. These 6-membered heterocycles have one readily ionizable proton from the hydroxyl group, giving a zwitterionic "aromatic" character.[19] Both maltol and ethylmaltol, as well as kojic acid,[20] (Fig. 1) form neutral, thermodynamically stable complexes with appropriately charged metal ions within physiological pH ranges.[21,22]

Hydroxypyridinones (hereinafter referred to as HOPOs) are structurally very similar to the hydroxypyrones—the pyrone ring oxygen is replaced with a nitrogen.[23] For HOPOs, arrangement of the binding groups can take one of three principal forms: 1,2-, 3,2 or 3,4-HOPOs (Fig. 1).[7] 3,2-Hydroxypyrone analogues of 3,2-HOPOs are known[24] and are useful starting materials for a variety of natural products;[25] however, they have not been investigated for metal-binding.

Trivalent metal ion complexes of 3,4-HOPOs have been shown by structural and solution studies to be distinctive in terms of their potential to hydrogen bond to water, forming hexagonal channels of water molecules in dodecahydrate exoclathrate arrays that utilize virtually every O atom in their unit cells.[26] The extensive H-bonding affords profound thermodynamic stability in the solid state.[27] Structural, infrared and NMR studies have shown that this feature

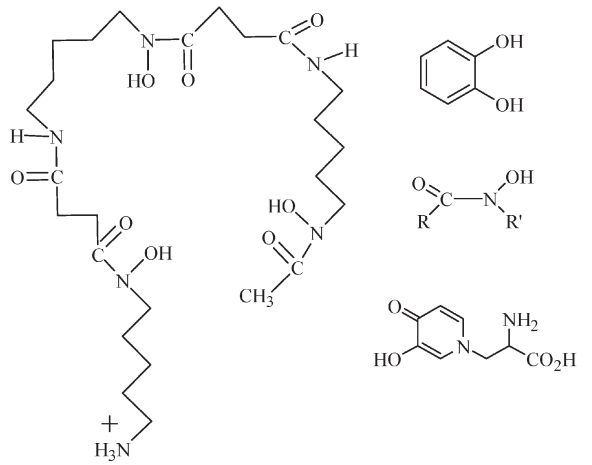


Fig. 2 Catechol (top right); generic hydroxamic acid (middle right); mimosine (bottom right); desferrioxamine-B (DFO, left). Note presence of hydroxamate motifs in DFO structure.

dominates in determining the 3,4-HOPO's, as well as, to a lesser extent, the 3,4-hydroxypyrone's physico-chemical properties, with amine, hydroxyl, and ketone functionalities all contributing to available H-bonding sites.[28]

HOPOs are, in essence, aromatic analogues of the hydroxamic acids that bind to metals by an oxyanion and an oxo group (Fig. 2).[7] Hydroxamic acids are monoprotic, whereas diprotic catechols are aromatic, thus HOPOs can be thought of as molecular hybrids of the two simpler ligands. Ease of deprotonation and a partially aromatic character are consistent features of the HOPOs. When deprotonated, HOPOs have a zwitterionic aromatic resonance form, isoelectronic with catecholate dianions. The 1,2-HOPOs, having tautomers and being negatively charged at physiological pH,[29] are generally more acidic than are the 3,4-HOPOs or the 3,2-HOPOs.[30] Like their 3,4 analogues, the 1,2 and 3,2-HOPOs bind trivalent cations tightly (for Fe^{3+}, In^{3+}, and Ga^{3+}, $\beta_3 \approx 10^{30}$ M^{-1}),[31] and commonly form tris(ligand)complexes with M^{3+}, binding in an octahedral arrangement.[7,32]

Hydroxypyrones are efficient chelators of both di- and trivalent transition metal ions.[6,33–35] Similar to HOPOs, hydroxypyrone metal chelation can be attributed to a substantial charge delocalization within the six-membered ring, as noted above. They differ from HOPOs principally in terms of aromaticity and lesser strength of bidentate binding. With respect to Fe^{3+}, this difference translates into more effective iron removal by HOPOs, and more efficient delivery by hydroxypyrones. The history of Fe^{3+}-related medicinal applications of these ligands spans several decades, and addresses the opposing needs of enhancing either uptake or removal of this redox-active metal ion (*vide infra*).[5]

3 Synthetic transformation of hydroxypyrones into hydroxypyridinones

Synthetic methods for production of HOPOs originally focused on transformation of the corresponding hydroxypyrones to their nitrogen-containing congeners. The oldest method of this type of synthesis is the ammonolysis of maltol;[36] however, this procedure is not general, is quite inconsistent and has led to synthesis *via* protected pyrones in three steps: 1) protection of the ring hydroxyl group; 2) ring ammonolysis reaction; and 3) deprotection, to give the HOPO. The deprotection step uses rigorous conditions, acid hydrolysis in HI and HBr, leading to unreliable yields.[37,38]

A desire for less costly and more efficient means of obtaining mimosine, for use in the Australian wool industry, spurred efforts to derive a chemical synthesis of the natural product. Mimosine, which is an alanine-substituted 3,4-HOPO (Fig. 2), could be obtained *via* a condensation reaction with the benzyl-protected pyrone, 3-benzoyl-4-pyrone, and a tosyl derivative of the amino acid, DL-alanine.[39,40] The benzyl protection group could be removed under less strenuous conditions (than those using HI and HBr), leading to higher yields. Mimosine, as well as other 3,4-HOPOs, turned out to be of considerable interest as binders of iron ($\beta_3 \approx 10^{37}$),[40,41] and later, various other trivalent metal ions.[42,43]

In the streamlined Harris synthesis of 3,4-HOPOs,[40] 3-benzoyloxy-4-pyrone was reacted with the non-tosylated DL-α,β-diaminopropionic acid (alanine) (pH 12.3) and then debenzylated with 45% HBr/acetic acid, skipping the step of isolating an intermediate pyridinone, and avoiding tosyl protection and then deprotection. A modest reduction in yield (from 55% overall to ~33%) was compensated for by the ease of scale-up with the modified procedure.[40] Harris' seminal work has served as the wellspring for numerous substituted HOPOs used not only as iron binding agents, but also for high affinity binding of group 13 metal ions, including Al^{3+}, Ga^{3+} and In^{3+}, as well as actinides and lanthanides (*vide infra*).

These advances in synthetic routes, permitting readily accessible alkoxypyridinones from the corresponding pyrones, have led to frequently used synthetic routes for not only 3,4-HOPOs,[30,44–47] but also 1,2-HOPOs and 3,2-HOPOs,[30,32] and analogues containing 2, 3, and 4 of these bidentate entities.[48,49] The first poly-1,2-HOPOs proved highly effective as chelators of actinides.[50] Nonetheless, concerns of ligand toxicity encouraged further development of closely related ligands, with 3,2-HOPOs being developed as possible alternatives, both for actinides[51,52] as well as other metal ions, including Fe^{3+} and Al^{3+}.[5,53,54]

4 Restoration of iron balance in anaemia by the hydroxypyrone maltol

Disorders of iron metabolism, whether due to anaemia or overload disorders, are among the most common diseases of humans.[55] Iron's redox activity makes it potentially toxic, even at concentrations as little as five times those normally found in healthy tissues; hence its homeostasis requires close regulation.[17]

Metal ion homeostasis is a well-harmonized process in normal, healthy individuals.[56] Homeostatic mechanisms can break down, however, *via* inborn error of metabolism, a particular disease state, or the degenerative processes of aging. Iron is an essential trace element in all mammals and many other living organisms. Depending on its oxidation state (Fe^{2+} *vs.* Fe^{3+}), iron is able to donate or accept electrons necessary for oxygen transport or storage, as in haemoglobin

and myoglobin, as well as in many redox enzymes.[55] Normal dietary iron has very low bioavailability, with the exception of meat-derived haem iron that has high bioavailability but is relatively harder to obtain in the non-industrialized world. A worldwide high prevalance of iron deficiency anaemia is due largely to this low bioavailability.[55]

A major difficulty with iron supplementation to counteract iron deficiency anaemia is that inorganic Fe^{3+} readily hydrolyses at physiological pH ranges, with concomitant precipitation and lack of bioavailability.[57] Fe^{2+} complexes, such as ferrous sulphate, ferrous fumarate and ferrous gluconate, are commonly prescribed for anaemia; however, due to rapid oxidation to Fe^{3+} in physiological environments, large doses are required for noticeable therapeutic effect.[58] This distinct disadvantage leads to gastrointestinal (GI) irritation and subsequent patient non-compliance.[5]

To improve the efficacy of iron supplementation, one needs a highly bioavailable, thermodynamically stable, ferrous complex.[58] Ideal properties in an iron ligand for treatment of anaemia have been defined[59] as: 1) high affinity for Fe^{3+}, to prevent catalytic formation of reactive oxidative species (ROS);[60] 2) high aqueous solubility of the Fe^{3+} complex; 3) neutrality of the complex, for passive diffusion through cell membranes; 4) non-toxicity of the ligand; and 5) an intermediate stability of the complex, such that the iron in the complex, subsequent to GI uptake, would be given over to transferrin for entry into iron's metabolic pathways in the body. All of these conditions were met by the hydroxypyrones, maltol[20] and ethylmaltol (Hema) (Fig. 1),[20] that were shown to form tris(bidentate ligand) distorted octahedral coordination complexes with Fe^{3+}, $Fe(L)_3$, where L = ma, ema.[59,61] Significantly enhanced uptake of ^{59}Fe in the presence of maltol or ethylmaltol was demonstrated in iron-deficient rats.[16,17,62] Subsequently, uptake of $Fe(ma)_3$ in normal and iron-deficient subjects was shown by Hider and co-workers to be dose-dependent.[63] In several patient trials, the iron hydroxypyrone complexes enhanced iron bioavailability by improved GI absorption, tissue uptake and transfer of the Fe^{3+} from $Fe(ma)_3$ to transferrin for systemic transport.[63] Mucosal irritation was minimized with the hydroxypyrone complex treatment, thus permitting a lower daily or weekly iron dose to achieve the clinical goal of improved iron status.[64]

5 Restoration of iron balance in iron overload disorders: hydroxypyridinones

The opposite condition to iron-deficiency anaemia is iron overload.[55] Diseases in which the metabolic problem is one of too much iron instead of too little are also remarkably common. Best known of these disorders are such inborn errors of metabolism as haemochromatosis and thalassemia major (β-thalassemia).[55,65] In both of these disorders, excess iron accumulates in the liver, heart, pancreas and other organs, with long-term consequences including fibrosis, cirrhosis, hepatocellular carcinoma, diabetes and heart disease.[66] To prevent this progressive deterioration, iron must be passivated and/or removed by appropriate ligand binding.[67] The key feature of Fe^{3+} complexation that characterizes its removal in a biological milieu is the extremely low solubility of ferric hydroxide ($K_{sp} \cong 10^{-38}$) at physiological pH,[30,32] which dictates tight binding to a sequestering agent in order to avoid hydrolysis and precipitation.

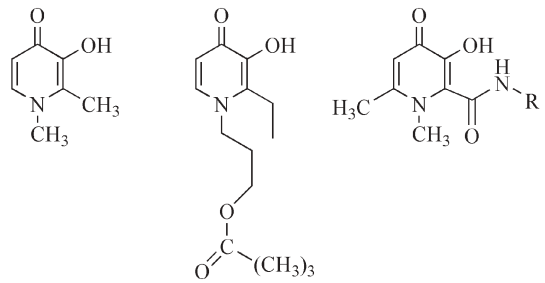


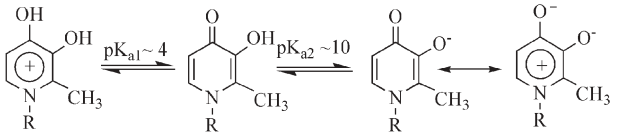
Fig. 3 Deferiprone, L1 or CP20 (left); CP117 (middle), 1-(2′-trimethylacetoxyethyl)-2-ethyl-3-hydroxypyridin-4-one; 1,6-dimethyl-3-hydroxypyridin-4-one-2-carboxy-(*N*-alkyl)-amido ligand (right, where R = CH_3), with an affinity for Fe^{3+} several orders of magnitude higher than that of deferiprone.[81]

A number of naturally occurring hydroxamates and catecholates have long been known to act as strong multidentate chelating agents for Fe^{3+}. For example, the naturally occurring microbial siderophore, desferrioxamine B (DFO) (Fig. 2), is a trihydroxamic acid that efficiently binds Fe^{3+}.[29,68] DFO is still the most commonly used chelating agent for iron-overload disorders, yet it is costly and must be administered parenterally (by injection) as an infusion over several hours.[69]

A surge of interest has been generated by the investigations of Raymond,[23,70–72] Kontoghiorghes[29,46,73] and Hider[57,74–77] and coworkers, who have all undertaken comprehensive studies of the physical properties of an array of mono- and poly-HOPOs as potential clinical chelating agents for the replacement of DFO. Solution studies have also shown that the bidentate 3,4-HOPOs (examples in Fig. 3) are promising alternatives to DFO, as they can be administered orally.[78,79] The metal–HOPO complexes are considerably more stable than are their hydroxypyrone congeners, *e.g.*, $\beta_3 \approx 10^{37}$ for $Fe(L1)_3$[5] compared to $\beta_3 \approx 10^{29}$ for $Fe(ma)_3$.[11] Hydroxypyridinones tend to be insoluble in water; however, their aqueous solubility increases several hundred-fold at physiologically relevant temperature (37 °C) compared to room temperature (25 °C).[28] In addition, the functionalizable ring nitrogen allows variation of lipophilicity without sacrifice of thermodynamic stability.[80]

The particularly high affinity of the 3,4-HOPO, L-mimosine (Fig. 2) for Fe^{3+} compared with other metal ions was first published in the early 1970s.[82] Exceptionally strong binding of HOPOs to M^{3+} in general can be traced to the extensive delocalization of the lone pair from the ring nitrogen atom that renders the carbonyl functionality more basic. Using the same principle, the stepwise formation constants for Fe^{3+}–HOPO complexes increase as the oxygen binding groups move away from the ring nitrogen (Scheme 1).[30]

The need for Fe^{3+} selectivity (*i.e.*, lack of affinity for other metal ions) and oral availability in iron overload treatment led to the choice of 1,2-dimethyl-3,4-HOPO (deferiprone, CP20 or L1),[77] and the closely related 1,2-diethyl-3,4-HOPO, which are



Scheme 1 Stepwise deprotonation of 3,4-HOPOs.

considered 'first generation DFO alternatives' (Fig. 3).[75] The Fe^{3+}–deferiprone complex is highly resistant to iron displacement by other cations, including Al^{3+}, Mg^{2+}, Ca^{2+}, Mn^{2+}, Co^{2+}, Zn^{2+} and Pb^{2+} at physiological pH.[68] Initial clinical trials of deferiprone were encouraging;[65] however, long-term use was associated with liver toxicity in some patients.[83,84] The circumstances surrounding disclosure of these adverse effects, and the ensuing industry–university conflict over trial discontinuation have inhibited further applications for FDA approval.[85] Deferiprone is nonetheless finding clinical utility in several non-North American countries.[85,86]

Combination therapy with deferiprone and DFO, allowing reduced doses of the former, and intermittent administration of the latter (still by subcutaneous injection) has been tried with notable success.[87] Another approach is to increase hydrophobicity of the 3,4-HOPO ligand[88] as a means of ensuring intact absorption from the GI tract, and bias tissue uptake towards the liver, where hepatic carboxyesterases could be expected to generate hydrophilic metabolites from designed pro-drugs.[5,75,89,90] These so-called 'second generation' DFO alternatives (Fig. 3) avoid bio-metabolic transformations that formed non-iron chelating 3-*O*-glucuronide conjugates by 1-hydroxyalkyl derivatization with 'first generation' ligands.[5,76] One example is CP117,[75] an hydrophobic ester derivative of a 3,4-HOPO, expected to undergo less biotransformation *in vivo*.

More recently, a 2-*N*-methylamido-3,4-HOPO (Fig. 3) was shown to chelate iron with an affinity more than two orders of magnitude greater than that of deferiprone (based on pFe^{3+} values[81]), and to scavenge iron effectively at lower doses than those required for deferiprone. The 1,6-dimethyl-3-hydroxypyridin-4-one-2-carboxy-(*N*-methyl)-amido ligand is a non-chiral 2-amido-3,4-HOPO derivative that showed evidence of clinical potential with $\beta_3(FeL_3) \approx 10^{34}$ coupled with high oral bioavailability.[81] Other 2-amido-3,4-HOPOs compared in this study included R′ = H, isopropyl, phenyl, benzyl, 2′-methoxyethyl, 2′-ethoxyethyl, and 3′-pyridyl substituents.

Studies are also being done to match or exceed deferiprone's stability by tethering multiple HOPOs to various backbones forming multidentate ligands.[72] The higher denticity of these ligands also has the potential to reduce toxicity by lowering the ligand dose required for efficacy. For example, Raymond and coworkers[72] have synthesized a hexadentate ligand consisting of three 3,2-HOPOs tethered together by a triserine trilactone backbone that could replace three equivalents of a bidentate ligand such as deferiprone, 1,2-dimethyl-3,4-HOPO, needed to chelate equivalent amounts of Fe^{3+}.[91] Analogous hexadentate enterobactin-like[92] and dendritic 3,4-HOPOs[93] have also recently been synthesized and shown to possess a remarkably high affinity for Fe^{3+} .

6 Hydroxypyrones and hydroxypyridinones for aluminium mobilization

Aluminium accumulation, particularly in the brain, has been a health concern for several decades.[94–96] Dialysis encephelopathy and osteomalacia in renal failure patients were associated with aluminium intoxication, and concerns were expressed that aluminium accumulation in the brain might be related pathophysiologically to the development of Alzheimer's disease.[96] There has been considerable controversy around the whole discussion of Al and Alzheimer's disease.[19,27]

Al^{3+} and Fe^{3+} share many similar attributes in terms of coordination complex formation. For example, mimosine is known as a strong binder of Fe^{3+} and its closest competitor, in a comparison of numerous metals for strength of mimosine binding, is Al^{3+}.[68] Early investigations of maltol, a known high affinity binder of Fe^{3+}, as a potential Al^{3+} sequestering agent[19,33] showed considerable promise in terms of thermodynamic and hydrolytic stability, and ease of complex formation (Fig. 4).

Anticipation of *in situ* formation of an Al^{3+} complex with maltol was expected to enhance removal of aluminium from the brain. In actual fact, the neutral charge of $Al(ma)_3$, its stability to hydrolysis, and its high aqueous solubility rendered it extremely neurotoxic.[19,97] An unanticipated side benefit of this line of investigation was production of a cheap and reliable animal model of Al neurotoxicity by enhanced uptake of aluminium, using the *ortho*-substituted hydroxypyrones as ligands for Al^{3+}.[6,19] Aluminium hydroxypyrones as aluminium mobilizing agents have been the subject of a large number of animal studies.[98,99]

Lack of an easily functionalizable site on the ring in the hydroxypyrones led to studies of the 3,4-HOPOs, that are stronger ligands for some of the same metal ions. In particular, the interaction of hydroxypyridinones with Al^{3+} has been the object of numerous studies (for review, see ref. 6).[27,42,54,78,80,100] Compared to such 3,4-HOPOs as deferiprone, neither 3,4-hydroxypyrones nor 3,2-HOPOs were as effective in Al^{3+} binding. Attempts to increase the bioavailability and efficacy of these ligands for Al^{3+} removal by increasing their lipophilicity were not successful, as increasing lipophilicity had no effect on either of these measures.[6] The bidentate 3,4-hydroxypyrones required higher molar doses, than did hexadentate tris(3,4-HOPO) scaffold compounds, to achieve the same Al^{3+} removal and were more hydrophilic which may have contributed to the greater risk of toxicity observed in Al-loaded rabbit studies.[101,102]

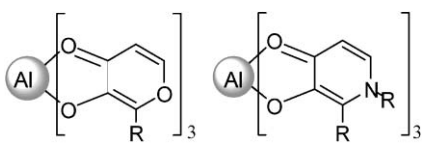
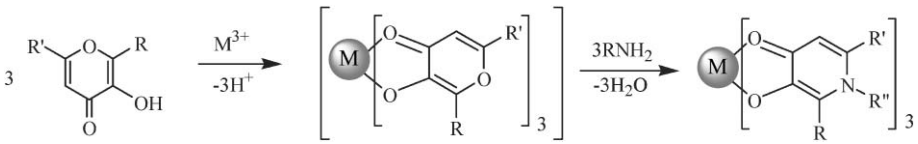


Fig. 4 Maltol and hydroxypyridinone complexes of aluminium(III). Al^{3+}coordination complexes, tris(3-hydroxy-4-pyrone)aluminium(III) (left) and tris(3,4-HOPO)Al(III) (right), where R = H, CH_3 or *n*-hexyl, used in animal models of neurotoxicity.



Scheme 2 One-pot synthesis of tris(3,4-HOPO)M(III) complexes; M = Al, Ga, In; R = CH_3, R′ = H, maltol; R = H, R′ = CH_2OH, kojic acid; R″ = CH_3 or C_2H_5.[38]

A significant advance in this field of study was the development of a one-pot method to synthesise metal–HOPO complexes (Scheme 2).[38] In this method, the metal pyrone complex is formed first *in situ*, then undergoes insertion of the primary amine into the pyrone ring to form the appropriate 3,4-HOPO, under pH control. This avoids the need for separation and purification of either the unbound HOPO or the metal–hydroxypyrone intermediates, permitting recovery of the desired metal–HOPO in high yield.

Current research directions in aluminium mobilization are focusing on the bidentate 3,4-HOPO binders that have a strong affinity for Al^{3+} coupled with a favourable hydrophilic/lipophilic balance.[6,7] *In vivo* comparisons of 1,2-, 3,2- and 3,4-HOPOs have shown that the 3,4-HOPO is more efficient than is the chief serum protein competitor, transferrin, at binding aluminium, and can therefore safely remove it from the body. *N*-Carboxyalkyl,[103] iminoacetic acid (*vide infra*),[104] and ethylenediaminetetraacetate (EDTA)[105] derivatives of 3,4-HOPOs have also all been recently investigated as decorporation agents for aluminium mobilization.

7 Hydroxypyrones and hydroxypyridinones as binders of gallium, indium

In addition to Al^{3+}, 3,4-HOPOs can bind other group 13 metal ions such as Ga^{3+} and In^{3+} for potential diagnostic and radionuclear therapeutic medicinal applications. Secure binding, coupled with rapid systemic clearance, are of particular value, both for gallium imaging agents and for indium diagnostic and therapeutic agents.

For gallium, there are two isotopes of medicinal interest: ^{67}Ga and ^{68}Ga, the former a gamma emitter ($t_{1/2}$ = 78 h, γ = 93, 185, 300 keV), predisposing its use in single photon emission computed tomography (SPECT) and the latter a positron emitter ($t_{1/2}$ = 68 min) produced from the ^{68}Ge/^{68}Ga couple, making it suitable for use in positron emission tomography (PET). Indium has one isotope, ^{111}In ($t_{1/2}$ = 68 h, γ = 245, 172 keV) and is of interest for both SPECT diagnostic imaging and radiotherapy.

Since the 1960's discovery by Edwards and Hayes that ^{67}Ga citrate localized in soft tumour tissue,[106] there has been much interest in the area of gallium chelates.[19] Gallium, in the form of ^{67}Ga citrate, has been used for several decades as a soft tumour imaging agent.[107] However, the citrate ligand is readily displaced with transferrin shortly after administration, limiting its utility; therefore, a ligand that is thermodynamically stable and resists transferrin substitution is desirable.[42]

Assessment of a series of 3,4-HOPOs as chelating agents for ^{67}Ga (compared to citrate) was carried out in mice, monitoring percent uptake per gram tissue for 24 h after injection.[108] It was found that various *N*-substitutions altered the biodistribution of the complexes without changing their stability. Mimosine, 3-hydroxy-2-methyl-4(1*H*)-pyridinone (Hmpp), 3-hydroxy-1,2-dimethyl-4-pyridinone (Hdpp), and 3-hydroxy-2-methyl-1-ethyl-4-pyridinone (Hmepp) all had similar stability constants $\beta_3 \cong 10^{38}$ for the 3 : 1 ^{67}Ga complexes; however, complexes of mimosine and Hmepp had greater tissue uptake than did those of Hmpp or Hdpp, in line with differences of lipophilicity.[109] The highest tissue levels of ^{67}Ga resulted from injection when accompanied by citrate, which gave significantly higher levels than did all other ligands tested. Mimosine and Hmepp were moderately similar, with generally greater ^{67}Ga uptake than either Hmpp or Hdpp, the latter having the highest log $\beta_{3\text{eff}}$ for formation of the gallium complex, as determined by potentiometric titration.[108]

Biodistribution studies of the 3,4-HOPOs completed in rabbits and a dog showed high heart uptake suggesting the possibility of use for heart imaging.[110] The success of these studies prompted extension of the synthetic strategies developed so far to include tris(*N*-substituted-2-methyl-3,4-HOPO)technetium(IV) cations for use as morphologic kidney imaging agents.[111] A series of these water soluble, hydrolytically stable monocations with moderate lipophilicity was tested in rabbits and mice as potential radiopharmaceuticals.[112] The 1-*p*-methoxyphenyl and 1-cyclohexyl *N*-substituents showed evidence of particularly high kidney uptake and retention of the ^{99m}Tc radionuclide.

For most *in vivo* applications of gallium and indium complexes, high stability of 1 : 1 ligand : metal complexes are critical for minimizing toxicity. By optimizing the denticity of the ligand, one can essentially cage the metal ion, *e.g.* ^{67,68}Ga or ^{111}In, obtaining complexes with highly favourable biodistribution profiles (high rate of excretion after biolocalization and no metal ion release).[1] An example of his strategy is an iminodiacetic acid derivatised 3,4-HOPO (imino-bis(acetyl(1-(3′-aminopropyl)-3-hydroxy-2-methyl-4-pyridinone)) (Fig. 5), being developed for clinical diagnosis or chemotherapy.[104]

More recently, the bifunctional chelate approach has been used for designing imaging agents utilizing ^{67}Ga and ^{111}In nuclides. This design incorporates a chelating portion of the molecule to chelate the metal ion while another substituent directs the metal complex to tissues of interest.[113] Carbohydrate-bearing 3,4-HOPO complexes (Fig. 5) with Ga and In have recently been synthesized using the bifunctional chelate concept in which the pendant sugar is intended to direct the metal complex *in vivo*.[114]

Similarly, for more effective interference with ligand substitution by transferrin, Santos *et al.* investigated functionalization of 3,4-HOPOs with *N*-carboxyethyl substitutents

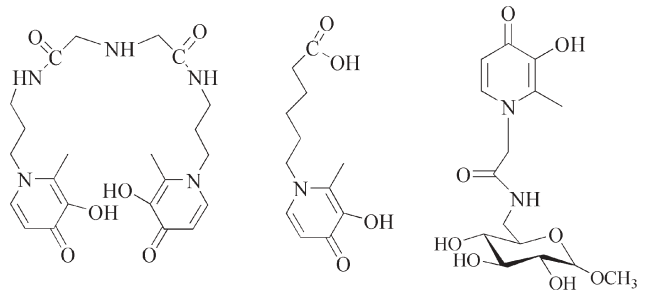


Fig. 5 Derivatives of 3,4-HOPO for improved tissue targetting; imino-bis(acetyl(1-(3′-aminopropyl)-3-hydroxy-2-methyl-4-pyridinone) (left);[104] *N*-carboxy-*n*-butyl-3-hydroxy-4-pyridinone (middle);[103] 1-[4-(β-D-glucopyranosyloxy)carbamoyl]-3-hydroxy-2-alkyl-4(1*H*)-pyridinone, HOG6GP, a carbohydrate-bearing 3,4-HOPO.[114]

specifically to compete with the serum protein (Fig. 5). Extensive stability constant determinations and *in vivo* biodistribution studies demonstrated an appreciable effect of alkyl chain length for the *N*-carboxyalkyl substituent. Shorter chain length was associated with increased gallium complex stability and an increase in bone fixation, along with a modest decrease in blood clearance. The 1-(2′-carboxyethyl)-3,4-HOPO was as efficient as deferiprone in scavenging iron, a desirable feature for clinical application of the carboxyalkyl derivative as a ^{67}Ga delivery agent.[103]

8 Multifunctional hydroxypyrones and hydroxypyridinones

For a vast array of clinical treatments, being able to follow the path of biodistribution of an administered agent is a huge benefit. Thus, adding a fluorescent probe to hydroxypyrones or HOPOs has the potential to create 'reporter molecules' that can track specific intracellular metal ion distributions.[115] Synthesis of two novel iron-reporting probes, *N*-[2-(3-hydroxy-2-methyl-4-oxopyridin-1(4*H*)-yl)ethyl]-2-(7-methoxy-2-oxo-2*H*-chromen-4-yl)acetamide and *N*-[2-(3-hydroxy-6-methyl-4*H*-pyran-2-yl)methyl]-2-(7-methoxy-2-oxo-2*H*-chromen-4-yl)acetamide, involved coupling 3,4-HOPO or 3,4-hydroxypyrone, respectively, with the fluorescent probe methoxycoumarin. The probe was designed to track Fe^{3+}, but based on pyridinone chelating functionality also had high affinity for other biologically relevant metal ions, including Cu^{2+}, that also quenched the fluorescence. The fluorescence emission at 380 nm was not changed to a significant degree when chelating Mn^{2+}, Co^{2+}, Zn^{2+}, Ca^{2+}, Mg^{2+}, Na^{+} or K^{+}.

Another example of a targeting functionality is that of a pyrone-based matrix metalloproteinase (MMP) inhibitor, in which the pyrone represents an effective zinc-binding group, and a lipophilic amine backbone serves as an enzyme hydrophobic pocket docking group.[116] The resulting compound, identified by molecular modeling of the enzymatic substrate, was substantially more potent as an MMP inhibitor compared to analogous hydroxamate inhibitors, with IC_{50}'s in the nanomolar range.

These and other bi-functional and multi-functional pyrone- and HOPO-based medicinal inorganic prodrugs are considered in more detail in a companion review.[113]

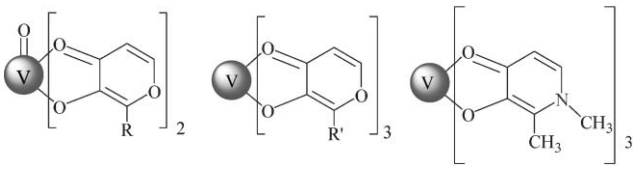


Fig. 6 Maltol and hydroxypyridinone complexes of oxovanadium(IV) and vanadium(III). Bis(3-hydroxy-4-pyronato)oxovanadium(IV) complexes (left), R = CH_3, BMOV; R = C_2H_5, BEOV; R = *i*-C_3H_7, BIOV.[127] V^{3+}coordination complexes, tris(3-hydroxy-4-pyrone)vanadium(III) (middle), R′ = CH_3 or C_2H_5; and tris(3,4-HOPO)V(III) (right), assessed for insulin mimetic potential.[128]

9 Maltol and analogues to increase efficacy and potency of insulin-enhancing agents

A well-studied example of 3,4-hydroxypyrones and analogues to enhance metal ion uptake is that of bis(maltolato) oxovanadium(IV), BMOV (Fig. 6).[117] This was the first purpose-designed, vanadium-based insulin-enhancing agent; it has spawned the field of vanadyl and vanadate chelate production for potential treatment of type 2 diabetes mellitus.

Vanadium, as sodium vanadate, was first recognized as having orally available insulin enhancing potential in the mid-1980's.[118] Although earlier anecdotal reports of anti-diabetic efficacy dated to the late 1800's (summarized in ref. 119), no formal experimental testing was carried out until after *in vitro* testing had demonstrated a potential biochemical role for vanadium.[120,121] In the first well-controlled *in vivo* trials,[118] and in many subsequent trials,[122,123] it has been shown that vanadium compounds (of both V^{5+} and V^{4+}) tend to 'mimic' insulin in their diverse biochemical actions, stimulating or inhibiting many of the same metabolic pathways *in vitro*[124,125] and in experimental animals.[126]

Not all chelated vanadium compounds are equally effective; in fact, the range of efficacies observed for a wide variety of compounds includes negative rankings (implying that uncomplexed vanadium sulfate, $VOSO_4$, is more potent).[123] The most intensively studied, and the most commonly used as 'benchmark' compounds are maltol and ethylmaltol complexes of the vanadyl ($[VO]^{2+}$) ion, the former now incorporated in several over-the-counter pharmaceutical preparations. Both bis(maltolato)oxovanadium(IV) (BMOV), and bis(ethylmaltolato)oxovanadium(IV), (BEOV) (Fig. 6), are several times more potent as insulin enhancing agents in diabetic rats than is the inorganic congener, $VOSO_4$.[117] Vanadate,[129,130] $VOSO_4$[131] and BEOV[132] have all completed phase I human clinical trials.

This same ligand-binding strategy can be used to increase the uptake of molybdate[133] and of zinc;[134] however, neither *cis*-bis(maltolato)dioxomolybdenum(VI) nor bis(maltolato)zinc(II) were found to be as effective as BMOV as potential anti-diabetic treatments.[135] Other metallocomplexes that were never tested for tissue uptake, but were screened for insulin mimetic activity included bis(maltolato)copper(II) and cobalt(II)[135] and tris(maltolato)chromium(III);[136] however, none surpassed BMOV in anti-diabetic efficacy.[135]

BMOV is two to three times more effective than is $VOSO_4$ in terms of insulin-enhancing activity[117] and has the significant added advantages of lower GI irritation and lower incidence of mortality due to hypoglycemia; however, further increases in potency and lessened likelihood of toxicity at higher pharmaceutically relevant doses would be desirable. Thus, one synthetic strategy has been to modify the maltol backbone, adding more lipophilic substituents to make isopropyl or *n*-butyl maltolato analogues (Fig. 1).[127] Promising increases in efficacy were achieved for bis(isopropylmaltolato)oxovanadium(IV) (BIOV) (Fig. 6). Preliminary pharmacokinetic profiling indicating a lower residual systemic vanadium that was nonetheless accompanied by effective blood glucose-lowering and no accompanying toxic symptoms in any of the BIOV-treated experimentally diabetic animals.[127] Longer chain substituents (as in *n*-butyl maltol, and *n*-propyl maltol, unpublished) conferred sufficiently poor aqueous solubility in the vanadyl complexes that further evaluation was not pursued.[127]

A surprising discovery was that some of the tris(3,4-hydroxypyronato)V(III) analogues (Fig. 6) of BMOV and close congeners proved comparable in terms of insulin enhancement, and were moderately resistant to oxidation.[128] A series of complexes were synthesized and characterized; R′ = CH_3, C_2H_5 for $V(ma)_3$ and $V(ema)_3$, respectively, and $V(dpp)_3$, the V^{3+}/3,4-HOPO analogue. The hydroxypyrone complex,$V(ma)_3$, was the most efficacious insulin enhancing agent in this series; $V(dpp)_3$ proved insufficiently soluble in aqueous media for extended testing. The latter compound was notable for crystallizing, as the dodecahydrate $V(dpp)_3{\cdot}12H_2O$, in an exoclathrate structure, isomorphous with the previously reported exoclathrate 3,4-HOPO dodecahydrates of other trivalent metal ions, including Al^{3+}, Ga^{3+}, In^{3+} and Fe^{3+}.[79,137]

10 Hydroxypyridinones and analogues for increased stability of gadolinium contrast agents for MRI

Today, 30–35% of all MRI studies utilize contrast agents in order to optimize the clinical imaging capabilities.[138] These agents help to distinguish between different tissues by decreasing the relaxation rate of complexed water molecules. Gd^{3+}, the metal ion commonly utilized in imaging, has a large paramagnetic moment derived from seven unpaired electrons ($4f^7$), and imparts short longitudinal relaxation times (T_1), to bound water molecules, both ideal properties for use as a relaxation agent for MRI. However, the aqua species of Gd^{3+}, $[Gd(H_2O)_8]^{3+}$, is highly toxic with a LD_{50} value of 0.1–0.2 mmol kg^{-1}, requiring this metal to be strongly bound to the ligand when administered to the patient.[139,140]

The clinically approved MRI contrast agents are all based on octadentate poly(aminocarboxylate) ligand scaffolds (DTPA, DOTA) that feature a nine-coordinate Gd^{3+} ion with a single coordinated water molecule.[138] These agents are thermodynamically stable, but exhibit relatively low proton relaxivities, attributed to the one slowly exchanging water molecule.[141,142] This low relaxivity requires higher doses of the agent in order to obtain satisfactory contrast in the images.[143,144]

A new family of MRI agents utilizing HOPOs has been synthesized by Raymond and coworkers.[145–147] The main

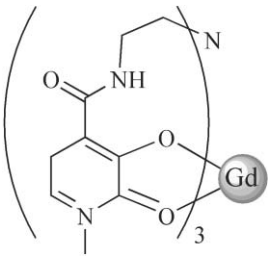


Fig. 7 Gd-TREN-Me-3,2-HOPO, a Gd^{3+} 3,2-hydroxypyridonate-based MRI contrast agent of high relaxivity.[148]

advantage of HOPOs and derivatives as binders of metal ions used in nuclear medicine (*vide supra*) and MRI applications is the very high stability that can be obtained with a variety of metal ions.[138] This new class of ligands consist of three 3,2-HOPO derivatives attached to a tris(2-aminoethyl)amine (TREN) acyclic backbone by amide bonds. The preorganization and the hexadentate binding of these ligands are expected to increase stability of the complex. Incorporating two labile water molecules is also hoped to increase potency of these contrast agents and the neutral charge should facilitate biolocalization.

The first of this family of compounds, Gd-TREN-Me-3,2-HOPO (Fig. 7), shows particular promise due to its two coordinated water molecules and the fast, near-optimal water exchange rates.[147,148] Gd-TREN-alkyl-3,2-HOPOs have relaxivities of 10.5 mM^{-1} s^{-1}; more than twice that of the commercially available contrast agents. The stability of these complexes is also comparable to currently available imaging agents showing stabilities of pGd = 19.2 compared to pGd $\cong$ 16–20 of the clinical contrast agents.[149,150]

Since then, this family of contrast agents has been extended to include a variety of chelating HOPO moieties, including mixed or heteropodal binding moieties with varying scaffold caps.[145] The effect of ligand basicity on thermodynamic stability within the overall tripodal structural motif of combined HOPO/catecholate ligands was shown to be highly pH dependent.[3] Recent modifications on this theme not only take into account the high oxophilicity of the lanthanide ions,[21] but also are designed to increase the water solubility of the complexes and to direct the complex to tissues of interest.[9,150] Terephthalamide elaboration of TREN-Me-3,2-HOPOs has led to hexadentate ligands with an increased variety of metal binding capabilities, not only for Gd^{3+} but also for Fe^{3+}.[151]

A very recent strategy for increasing the solubility of Gd-TREN-Me-3,2-HOPO was to prepare a pyrone analogue, $[Gd(TRENMAM)(H_2O)_2]$, which was inexpensively synthesized from maltol.[152] The latter derivatisation of maltol with no ring oxygen substitution and readily available hydroxyl groups (giving a desirable acidic character to the complexes) may help solve a significant problem with Gd-TREN-Me-3,2-HOPOs, which usually have poor aqueous solubility.

11 Sequestration/decorporation of actinides by multidentate HOPOs

Actinides are α-particle emitting radionuclides, with thorium being the most abundant naturally occurring radioactive

element.[153] As the potential for accidental exposure to large quantities of actinides, especially plutonium and uranium, has increased in recent years, a growing need for efficacious removal of these radioactive elements from biological systems has been taken up as a basic and applied research challenge.[50]

Taking advantage of the coordinative similarity of tetravalent actinides to trivalent iron, Raymond and coworkers[2,49,51,52,154–157] have constructed an array of actinide(IV) specific sequestering agents, many of which are synthetic variants containing 1,2-HOPOs, 3-2-HOPOs (both reviewed in ref. 2) or functionalized 3,4-HOPOs.[91,154,158] In order to extend the utility of these ligands for use in environmental contamination situtations, Xu, Raymond *et al.*[159] have devised installation of self-assembled 1,2-HOPO monolayers on nanoporous silica. This substance is compatible with vitrification processing into a glass waste that could immobilize and contain the highly hazardous actinide by-products.[159] For this application, the 1,2-HOPO ligand was chosen specifically as it has the lowest protonation constant compared to 3,2- or 3,4-HOPOs; it was therefore expected to have the highest affinity [under acidic conditions] for the lanthanides being used as model systems for the radioactive actinides, intended as the ultimate target of selective removal.[159]

12 Therapeutic removal of excess metal ions in neurodegenerative diseases

Metal ions, including Fe^{3+}, Zn^{2+}, Cu^{2+}, and Al^{3+}, have been implicated in the pathophysiology of a variety of neurodegenerative diseases, including Parkinson's disease,[160] prion disease,[161] and Alzheimer's disease (AD).[7,96,97,162] Significant elevations have been found of Al^{3+} in AD brain, of Fe^{3+}, Cu^{2+} and Zn^{2+} in amyloid plaques in AD, and of Fe^{3+} in Parkinson's disease. Iron-mediated oxidative toxicity[60] is thought to play a crucial role in Parkinson's disease, and Fe^{3+} and Cu^{2+} binding of an amyloid plaque precursor protein may also lead to increased formation of reactive oxygen species that contribute to neurodegeneration in AD.[162,163] Therapeutic interventions for neurodegenerative diseases intended to target excess metal ions are designed to both cross the blood brain barrier, and to reduce brain concentrations of metal ions without compromising overall essential metal ion balance in the body (which is not an issue for Al^{3+}, but is for iron, zinc and copper).[163–168]

Early investigative interest in Al^{3+} mobilization for alleviation of Alzheimer's disease (outlined in ref. 19), which led to preparation of a series of aluminium tris(3-hydroxy-4-pyrones) (*vide supra*), was largely superseded by an increasing focus on the role of other metal ions in neurodegeneration, as it was never proven that aluminium accumulation in the brain was a causative factor in these disorders.[169] There is nonetheless now somewhat of a renewed interest in the topic,[7,170,171] as the mere presence of excess aluminium in the brain appears to increase oxidative stress, which is clearly implicated in the pathogenesis of most neurodegenerative disorders.[164,172]

As the most prevalent oxidative-stress enhancing metal ion in the body is Fe^{3+}, there is also a keen interest in finding sequestering/mobilization agents for excess iron in the brain.[160,165,167] In a structure–function investigation[173] by Hider and co-workers, in which the yardstick of choice was radical scavenging ability, deferiprone was completely ineffective, maltol was somewhat effective, and 3,2-HOPO was the best of the representative hydroxypyrones and hydroxypyridinones examined. Desferrioxamine was by far the most effective in this regard. Thus, good antioxidant potential was not coupled with excellence of iron-binding capacity.

Comparison of a series of 3,4-HOPOs in terms of ability to cross the blood brain barrier (BBB)[174] clearly demonstrated that more lipophilic compounds penetrated the brain more effectively. The lipid solubilities of the *N*-alkyl-3,4-HOPOs in turn correlated with the length of the alkyl chain, with longer chain substituents proving to be more lipophilic, with an apparent upper limit of MW $<$ 500 for BBB crossing.

A more recent development is 'dual action' prodrugs for iron removal in neurodegenerative disease.[164,165] These compounds are composed of 3,4-HOPOs for iron chelation coupled with 3,5-disubstituted-4-hydroxyphenyl derivatives for antioxidant capacity (radical scavenging). The hybrid molecules also can be tailored to enhance lipophilicity and ensure adequate brain uptake.[165]

13 Sulfur-containing analogues of hydroxypyrones and HOPOs, the thiopyrones and hydroxypyridinethiones

Thiomaltol, 3-hydroxy-2-methyl-4-pyridinethione,[175,176] and the hydroxypyridinethiones (1,2-HOPTOs, 3,2-HOPTOs, and 3,4-HOPTOs) (Fig. 8)[177] are remarkably similar to their corresponding oxygen-coordinating hydroxypyrones and HOPOs in the surprising diversity of their medicinal inorganic applications.

Despite the *S,O*-binding moiety being softer than hydroxypyrone or HOPO *O,O*-ligands, HOPTOs are more effective binders of Ga^{3+} and In^{3+} at lower pH.[176] HOPTOs have also been proposed as Fe^{3+} sequestering agents, with sulfur ligation replacing half of the oxygen coordination present in octahedral Fe^{3+}–HOPO complexes.[178]

HOPTOs were complexed to Ga^{3+} and In^{3+} and to a range of lanthanides, including Gd^{3+} and Ho^{3+}.[176] Gallium and indium HOPTO complexes may be suitable for SPECT (^{67}Ga, ^{111}In) and PET (^{68}Ga), important radiopharmaceutical imaging modalities. HOPTO complexes with Gd^{3+} and Ho^{3+} may be suitable in future for use as MRI contrast agents, in a fashion analogous to the HOPO complexes now being

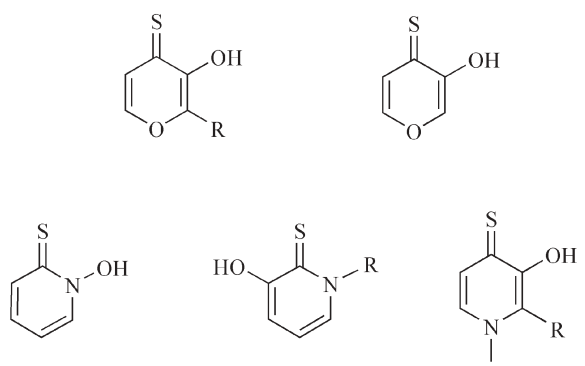


Fig. 8 Thiopyrones (upper) and hydroxypyridinethiones (lower).

evaluated.[116] 3,4-HOPTO complexes with Zn^{2+} or VO^{2+} showed some promise *in vitro* as alternative insulin-enhancing agents,[179] although the latter were not as effective *in vivo* as a range of other vanadyl complexes with hydroxypyrones and close analogues.[123,180] The potential of HOPTOs for use as antioxidant agents in Alzheimer's disease is also being investigated.[177,181]

Conclusions

The hydroxypyrones and hydroxypyridinones are monoprotic and hydrolytically stable ligands that often form neutrally charged complexes. Hydroxypyrones can usually confer aqueous solubility and hydroxypyridinones offer a range of lipophilicities and significantly higher metal ion complex stability. By shifting from hydroxypyrones to HOPOs as ligands of choice, it is possible to go from metal ion uptake enhancement to metal-ion sequestration and/or removal, in a few short synthetic steps. Along with high affinities for Fe^{3+}, actinides, group 13 metal ions, and a surprising number of other di- and tri-valent metal ions, these ligands offer a synthetic versatility that results in an impressive array of useful physicochemical properties. Their basic chemistry has been explored, and as new synthetic modifications and extensions are discovered, the increasing multiplicity of their potential medicinal applications continues to surprise and delight medicinal inorganic chemistry investigators.

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