Chapter 2

Literature Review
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In last few decades, biomimetic analogs have been widely investigated for the chelation of iron and other bio-relevant metal ions [1]; many such compounds along with some natural siderophores have been reviewed in chapter 1. Enormous iron(III) complexing ability and effective selectivity has led to the synthesis of new biomimetic siderophore analogs. In one of the excellent recent reviews of K. N. Raymond et al., have presented the list of 125 synthetic chelators [2]. In fact, computer assisted search through Scifinder with “siderophores” entered as keywords resulted in finding more than 15,000 references over the last four decades [3] and with “tripodal siderophores” resulted in more than 2000 in last two decades, 2/3 of them being published only during the last 10 years. When restricted to “symmetric cyclic tripodal ligands” keywords, the total number of references dropped to less than 100 over the last 20 years [4]. The number gets more plunged when we specified our search to aliphatic cyclic quinolinate tripodal ligands [5]; this led us to focus on work on the titled thesis. Since the present thesis concerns with design and complexation of tripodal biomimetic chelators, some tripodal chelators containing hydroxamates, catecholates, hydroxypyridonates and mixed chelators, found in natural siderophores, will be reviewed in this chapter. Later part of this review includes on synthetic polydentate chelators containing one or more than one 8-hydroxyquinoline units, a less common function found in siderophore, with different topology.
2.1 Hydroxamates

Among the hydroxamates, several natural analogues of rohodotorulic acid have also been found. In an excellent classical review of Marvin J. Miller, it is stated that, end reactions of α-amino-ω-hydroxyamino derivatives with a variety of multiacyl containing substrates and minor elaboration provided number of trishydroxamate siderophore analogs [6]. Several decades before few retrohydroxamate and various totally synthetic hydroxamate ligands were known that could be used either as iron transport probes or as iron removal agents. Later Rodgers and Raymond reported the synthesis and iron binding properties of tris-hydroxamates Trendrox (10) and Medrox (11) analogues of the desferrichrome, where desferrichrome’s essential components (three hydroxamates appended to one central platform) have been retained [7]. Trendrox was found very effective chelating agent for ferric ion at physiological pH with log β (32.9) (2) and pM (27.8) compared to DFO (log β 30.6, pM= 26.6). A. Shanzer and J. Libman (1992) have introduced C3-symmetric tris hydroxamates from two families of tris-carboxylates (12) and (13) [8] with superior properties in terms of binding efficiency and selectivity that reproduce the essential structural features of naturally occurring ferrichrome fully reproduced its biological functions. The same group later describes a new family of linear ferrioxamine B analogs, bind Fe(III) in 1:1 stoichiometry [9]. Another trishydroxamate siderophore analog 1,5,9-tri-azacyclododecane-N,N',N"-tris(N-methylacetohydroxamic acid) (DOTRMAHA, (14)) has been developed. Structurally, DOTRMAHA shares with desferrichrome the fact of being a macrocyclic ligand with three donor hydroxamate groups which are exocyclic to the macrocyclic ring. Furthermore, the ligand formed stable 1:1 coordination complex with iron(III) with a stability constant of about $10^{24}$ [10]. Recently another class of lipophilic ferrichrome analog (15) carrying acetoxymethyl
(AM) ester moieties was published, which turn highly hydrophilic upon cell entrance by way of esterase mediated hydrolysis [11]. All these trishydroxamate analogues are presented in Table 2.1 together with their pM and their respective binding constants.

**Table 2.1:** Representative structures of synthetic chelators of trishydroxamate category with (if available) pM and their respective binding constants

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Structures</th>
<th>pM</th>
<th>Log β</th>
<th>Compounds</th>
<th>Structures</th>
<th>pM</th>
<th>Log β</th>
</tr>
</thead>
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<tr>
<td>Trendrox (10)</td>
<td><img src="image" alt="image of Trendrox (10)" /></td>
<td>27.8</td>
<td>32.9</td>
<td>Type-4 (13)</td>
<td><img src="image" alt="image of Type-4 (13)" /></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Medrox (11)</td>
<td><img src="image" alt="image of Medrox (11)" /></td>
<td>26.3</td>
<td>30.8</td>
<td>DORTRMAHA (14)</td>
<td><img src="image" alt="image of DORTRMAHA (14)" /></td>
<td>21.7</td>
<td>24.2</td>
</tr>
<tr>
<td>Type-3 (12)</td>
<td><img src="image" alt="image of Type-3 (12)" /></td>
<td>-</td>
<td>-</td>
<td>Ferrichrome analog with acetoxymethyl ester moieties (15)</td>
<td><img src="image" alt="image of Ferrichrome analog with acetoxymethyl ester moieties (15)" /></td>
<td>-</td>
<td>27.5</td>
</tr>
</tbody>
</table>

### 2.2 Catechols

Hexadentate tricatehols are iron(III) chelators per excellence enterobactin (5) typifying the group. A number of synthetic analogues have been prepared which retain the high affinity for iron(III) and with other metal ion, typical of enterobactin and yet are more stable under biological conditions, for instance, the tripodal molecular Mecam (18) (Table 2.2) [12]. Mecam is the structural analog of enterobactin, has three catechol binding units: the catecholamide groups are appended to 1, 3, 5-triaminomethyl benzene rather than to the tri-L-serine ligand backbone of enterobactin as shown in Table 2.2. During 1979, K. N. Raymond and co-workers reported the synthesis and studies related to Mecam, MecamMe (22) and its sulphonated derivative (23) exceptionally good sequestering agent for ferric ion in neutral and basic aqueous solution [12]. Mecam was
recognized at the structurally similar metal chelate region of the molecule but the
binding constant \( \log K_f = 43 \) is somewhat lower than ferric enterobactin \( \log K_f = 49 \). In
the next year they reported different polycatecholate, dimeric (LICAM, LICAMS),
trimeric (CYCAM (24), CYCAMS (25)) and tetrameric (3, 4, 3-LICAMS) ligands [13]
for actinides whose description is beyond the scope of this work. In continuation to tris-
catecholates of CAM family, they further reported N-substituted catecholamide
analogues \( i.e., \) (NMeMecam (26) and NAcMecam (28), 1981) and their sulphonated
derivatives \( i.e., \) (NMeMecam(s) (27) and NAcMecam(s) (29) (Table 2.2) [14] which
remove iron from transferrin at a significant rate and unlike other catecholamides, these
contain only tertiary amide nitrogen. The out flow of such type of catecholates which
are known to as second generation analogues of enterobactin reported in literature
includes MeMecam (20), ((Et)₃Mecam, 21), MecamMe (22), TiPMecam (30) and
TriMecam (32), along with their sulphonated derivatives like Mecam(s) (19),

**Table 2.2:** Molecular structures of synthetic Catecholate based chelators designed and
synthesised by various groups with pM and their respective binding constants.
MecamMe(s) (23), TiPMecam(s) (31) and TriMecam(s) (33) [15], presented in Table 2.2. TriMecam (32) is an isomer of Mecam in which the methylene and carbonyl groups have been interchanged. This makes a major difference in their coordination chemistry.

Apart from benzene and other cyclic based tri-catecholates, they have also reported the preparation and evaluation of variety of ferric ion sequestering agents based on β,β′,β′′ tri-amino triethylamine (Tren) and its derivative (Tpren) back bone. The most representatives of such type catecholates are Tren-cam (16), Trpncam (34) and their sulphonate derivative Tren-cam(s) (17) and Trpncam(s) (35) as shown in Table 2.2 [16]. The thermodynamics, kinetics and electrochemical studies along with biological evaluation of these ligands are reported in numerous articles and reviews [17-18].

The pioneering work of K. N. Raymond has in mimics of catecholate siderophores, have flooded the fields of inorganic and bio-inorganic chemistry. But some great contributions of few other groups can’t be neglected. M. Hayashi, K. Hirtani and coworkers have made attempts to synthesize lipophilic tripodal hexadentate ligand (36), were three bidentate moieties are attached to core by stable arms such as carbon chain and ether linkers [19] whereas M. E. Barik reported the smallest tris catecholamide siderophore analog (37) and its methylthioether derivative (38) [20], both containing C-pivot, Tris(aminomethyl)ethane (Tame) as center unit.

It must be noted that most of the work on synthetic catecholate analogs were reported by replacing cyclic L-serine unit with benzene based triamines but very few attempts were made to see the effect due to change in amide linkage [21]. Another important aspects is the ring strain due to the rigidity of the benzene ring, as it could be expected that if the sp² hybridized–atoms of benzene ring is replaced with a sp³ hybridized systems like cyclohexane ring. The resulting tripod system would be more
flexible and ring strain will be less compared to MECAM and complexes would be thermodynamically more stable. Design of such tripodal systems by replacing benzene ring with a cyclohexane ring has been reported by our research group and also by Lee and co-workers [22]. The synthesis and complexation of behaviour tripodal polycatecholate TDBAC, TMACHCAT, CYCOEACAT and tripodal hexadentate imine/amine phenols (N$_3$O$_3$-donor), TMACHSAL, Me$_3$-TMACHSAL and THAC ligands have been documented [23]. The representative structures of poly catecholate chelators are presented in Table 2.3.

**Table 2.3:** Some other reported synthetic catecholate based chelators along with their pM and formation constants values

<table>
<thead>
<tr>
<th>Chelator</th>
<th>Molecular Structures</th>
<th>pM</th>
<th>Log $\beta$</th>
<th>Chelator</th>
<th>Molecular Structures</th>
<th>pM</th>
<th>Log $\beta$</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDBAC (39)</td>
<td>-</td>
<td>16.74</td>
<td>24.47</td>
<td>TDBAC (39)</td>
<td>-</td>
<td>16.74</td>
<td>24.47</td>
</tr>
<tr>
<td>TMACHCAT (40)</td>
<td>-</td>
<td>18.62</td>
<td>27.14</td>
<td>TMACHCAT (40)</td>
<td>-</td>
<td>18.62</td>
<td>27.14</td>
</tr>
<tr>
<td>CYCOEATAC (41)</td>
<td>-</td>
<td>19.59</td>
<td>31.05</td>
<td>CYCOEATAC (41)</td>
<td>-</td>
<td>19.59</td>
<td>31.05</td>
</tr>
</tbody>
</table>

2.3 Hydroxypyridinones (HOPO)

Pursuant to the efforts to develop more effective sequestering agents for use in the treatment of human iron toxicity, other bidentate functional groups have been developed for use in these siderophore-based ligands. Among these are several Hydroxypyridinones in which the hydroxyl group is ortho to the ketone functionality.
The Hydroxypyridinones (HOPO) combine the characteristics of both hydroxamate and catechol groups, which are monoprotic acids at pH 7.0 and thus form neutral tris-iron(III) complexes. There are three classes of metal chelating HOPO ligands, namely 1-hydroxypyridin-2-one, 3-hydroxypyridin-2-one and 3-hydroxypyridin-4-one (cf. Figure 1.6 in chapter 1).

Hexadentate siderophore analogues can be constructed by derivatising prototype bidentate hydroxypyridinones and attaching them to suitable molecular frameworks. By mimicking the natural siderophores Enterobactin (5) and DFO (1), several hexadentate chelators have been proposed in the last decade with HOPO ligands [24-25]. Although 3,4-HOPO are recognized as the strongest HOPO iron chelators, the first hexadentate HOPO explored used 1-hydroxypyridin-2-one reported by Raymond group which are TREN(1,2-HOPO) (42), and Me(1,2-HOPO) (43) and then by 3-2-HOPO moieties reported Table 2.4: Representative 1,2-HOPO and 3,2-HOPO based tris-chelators with the corresponding pM values and formation constants:

<table>
<thead>
<tr>
<th>Chelator</th>
<th>Molecular Structures</th>
<th>pM</th>
<th>Log β</th>
<th>Chelator</th>
<th>Molecular Structures</th>
<th>pM</th>
<th>Log β</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tren(1,2-HOPO)</td>
<td></td>
<td>-</td>
<td>26.7</td>
<td>CP130 (45)</td>
<td></td>
<td>26.7</td>
<td>27.7</td>
</tr>
<tr>
<td>Me(1,2-HOPO)</td>
<td></td>
<td>28.7</td>
<td>25.1</td>
<td>HOPObactin</td>
<td></td>
<td>27.4</td>
<td>26.4</td>
</tr>
<tr>
<td>Tren(3,2-HOPO)</td>
<td></td>
<td>26.7</td>
<td>27.6</td>
<td>N\textsubscript{3}(etLH)</td>
<td></td>
<td>26.5</td>
<td>-</td>
</tr>
<tr>
<td>Me(3,2-HOPO)</td>
<td></td>
<td>26.7</td>
<td>27.6</td>
<td>HOPObactin</td>
<td></td>
<td>26.5</td>
<td>27.6</td>
</tr>
</tbody>
</table>
by Hider, Raymond, and Crumbliss which includes TREN(3,2-HOPO) (44), CP130 (45), HOPObactin (46), and N₃(etLH)₃ (47) [26-28] (Table 2.4). These tripodal tris-chelators have showed higher chelating efficacy than the analogues with linear supports. Despite the different design strategies to improve the chelating efficacy, it seems to be quite dependent of the steric hindrance assisting the metal complex formation (for example, CP130 (20.7), TRENHOPO (27.6)). It has been reported by R. C. Hider, that the cyclic platform did not bring any improvement to the complex stabilization, although the amine groups of triaza backbone enhanced water stability [29].

Table 2.5: Representative 3,4-HOPO tris-chelators with the corresponding pM values and formation constants

<table>
<thead>
<tr>
<th>Chelator</th>
<th>Molecular Structures</th>
<th>pM</th>
<th>Log β</th>
<th>Chelator</th>
<th>Molecular Structures</th>
<th>pM</th>
<th>Log β</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kemp(PrHP)₃(n=1)</td>
<td><img src="image1" alt="Image" /></td>
<td>26.8</td>
<td>21.8</td>
<td>NTA(PrHP)₃</td>
<td><img src="image2" alt="Image" /></td>
<td>29.4</td>
<td>22.4</td>
</tr>
<tr>
<td>Kemp(BuHP)₃(n=2)</td>
<td><img src="image3" alt="Image" /></td>
<td>28.0</td>
<td>21.2</td>
<td></td>
<td><img src="image4" alt="Image" /></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CP262 (49)</td>
<td><img src="image5" alt="Image" /></td>
<td>28.5</td>
<td>26.4</td>
<td>CP254 (52)</td>
<td><img src="image6" alt="Image" /></td>
<td>27.2</td>
<td>25.1</td>
</tr>
<tr>
<td>NTA(BuHP)₃(50)</td>
<td><img src="image7" alt="Image" /></td>
<td>27.9</td>
<td>22.0</td>
<td>Me(3,4-HOPO) (53)</td>
<td><img src="image8" alt="Image" /></td>
<td>30.5</td>
<td>32.3</td>
</tr>
</tbody>
</table>

M. A. Santos and co-workers have developed a series of hexadentate tris-(3,4-HOPOs) bearing three 3,4-HOPO-alkyamino arms attached to tris-carboxylic acid backbones, namely a cyclic skeleton (Kemp acid) and the amino-tricarboxylic acids (nitrilotriacetic acid-NTA-and nitrilotripropionic acid-NTP) namely NTA(BuHP)₃ (50) NTP(PrHP)₃ (51) [30]. Two further tripodal tris-(3,4-HP) compounds with a anchoring
scaffold, namely a tri-carboxylic acid (CP254) (52) and a tris(2-aminoethyle)amine (CP262) (49) [30], have also been recently reported. Apart from tris-pyridinones based on aliphatic backbones, they have also developed hexadentate tris-(3,4-HOPO) with benzene anchor such as (Me(3,4-HOPO) (53)) [11]. The authors claim that (53) resulted in appropriate geometry which is extremely potent for iron chelation, particularly over the pH range of 2-9, with an associated pM value of 30.5 at pH 7.4. These hexadentate 3-4, HOPO presented stronger iron chelating capacities than the hexadentate 3-2 HOPOs, as illustrated by reported pFe value, at physiological pH and the diluted conditions that prevail in biological conditions. The structures for this set of hexadentate 3-4, HOPO are also presented in Table 2.5.

Table 2.6: Molecular structures of synthetic chelators containing mixed binding units with pM and their respective binding constants

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Structures</th>
<th>pM</th>
<th>Log β</th>
<th>Compounds</th>
<th>Structures</th>
<th>pM</th>
<th>Log β</th>
</tr>
</thead>
<tbody>
<tr>
<td>(54)</td>
<td><img src="image1.png" alt="Image" /></td>
<td>-</td>
<td>-</td>
<td>(57)</td>
<td><img src="image2.png" alt="Image" /></td>
<td>32.2</td>
<td>29.5</td>
</tr>
<tr>
<td>(55)</td>
<td><img src="image3.png" alt="Image" /></td>
<td>-</td>
<td>-</td>
<td>(58)</td>
<td><img src="image4.png" alt="Image" /></td>
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<td>-</td>
</tr>
<tr>
<td>(56)</td>
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<td>-</td>
<td>-</td>
<td>(59)</td>
<td><img src="image6.png" alt="Image" /></td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
2.4 Mixed Ligands

Ligands involving different complexing units are categorized as mixed ligand. Only few mixed tripodal tris-bidentate ligands have been reported so far. The first one (54) reports the ligand with two catechols and one hydroxamate [31] and the second paper described the synthesis and iron complexing abilities of ligand (55) based on two hydroxypyridinonates and one catecholate or one 2-hydroxyisophthalamide units [32].

Other mixed ligands involving either two 8-hydroxyquinolinates or one catecholate (TRENSOX₂CAMS) (56) or one hydroxyquinolate and two catecholates moieties (TRENSOX₃CAMS₂) (57) have also been reported [33]. These chelators derived from the homoleptic O-TRENSOX and TRENÇAMS ligands, and allowed detailed solution studies like pH dependence, cooperative effects and exchange processes in iron chelation. TRENSOX₃CAMS₂ has the highest affinity towards Fe³⁺ ever reported (to the best of our knowledge) for an abiotic synthetic siderophore with a pFe value of 32.2. The molecular structures of these mixed type chelators with some other more examples are presented above in Table 2.6 along with their corresponding pM and Log β values.

2.5 8-Hydroxyquinoline Based Potential Chelators

In the earlier sections, ligand containing three major functional groups viz., catecholate, hydroxamate and hydroxypyridonate found siderophore analogues as well as some mixed ligand chelators have been described. Chelators with less common functional group found in siderophores, i.e., hydroxyquinoline, will be described in this section as the entire work of the dissertation concerns poly-hydroxyquinolines. In nature, the hydroxyquinoline ligand structure is not well-known except, (1), quinolobactin (“a” of Figure 2.1) [34]; a siderophore produced by a pyoverdine deficient mutant of Pseudomonas fluorescens. The chemistry of 8-hydroxyquinoline, a monoprotic bidentate ligand, has attracted special interest due to the fact that it is an ideal building
block in metallosupramolecular chemistry. It has been appreciated over years that the
gometry and chelating size of 8-hydroxyquinoline are the same as found for bipyridine
and catecholate [35]. 8-hydroxyquinoline (4) possesses one pyridine donor of bipyridal
(2) and one phenolate unit of catecholate (3), and can be considered as a hybrid in
between the two coordinating sites (“b” of Figure 2.1). In its deprotonated form, it is
monoanionic and bridges the gap between the neutral bipyridine and the dianionic
catecholate. Also, it possesses remarkable abilities to bind with a greater number of metal
ions especially main group, transition and rare-earth ions and has became an
interesting agent for the formation of luminescent coordination compounds either for
light emitting devices [36] or in sensors and diagnostics (e.g., in bioconjugates) [37].
Moreover, it is a privileged structural moiety observed in many biologically active
natural products, and is used as the source for many drugs diversely prescribed among a
wide range of pathologies including neurodegenerative diseases [38], parasitic amoebic
dysentery disease [39], and herpes viral diseases [40]. In addition, the chelate
compounds of 8HQ and its derivatives have found extensive applications as analytical
reagents in spectrophotometric analysis, for separation and identification of metal ions
as well as in metal ion sensing [41]. An important property that makes 8-HQ even more
attractive as a chelator is the appreciable change in its fluorescence upon metal binding
[42]. Therefore, 8-HQ has been used extensively for the development of chemosensors
for the selective and efficient detection of metal ions of important biological and/or

![Figure 2.1: (a) Chemical structure of naturally occurring siderophore. (b) Comparison of the chelating units of bipyridine, catecholate and 8-hydroxyquinolinate.](image)
environmental significance [43], in particular those with Al$^{3+}$, are major components for organic light-emitting diodes (OLEDs) [44]. Due to their high thermal stability, excellent electron-transport properties, and unique luminescent properties, [45] many derivatives of 8-hydroxyquinoline linked at 2, 3, 5, or 7 position of the oxine unit or coordinated with different metal ions have also attracted considerable interest [46].

A multidentate ligand of high denticity has favourable attributes for the applications described above. The chelate effect should impart an added stability to a multidentate chelate complex relative to a complex composed of similar ligands of lower denticity. The rate of ligand dissociation should be slower for a multidentate ligand since more metal-ligand bonds must be broken compared to the dissociation of a ligand of lower denticity [25]. Furthermore, if the metal: ligand stoichiometry is 1:1, then the complex will be stable with respect to dilution.

Depending on the number of binding 8-HQ units: one, two, three or four, attached, the section has been sub categorized for clarity.

2.5.1 Monopodal Chelators

On the basis of selectivity and affinity, particularly considering the pM value, 8-hydroxyquinoline is the optimal bidentate ligand for the chelation of trivalent metal ions over the pH range of 3.0-10.0. The hydroxyquinolines, like pyridinones are monobasic and consequently form neutral 3:1 complexes. The stability constant $\beta_3$ value for iron (III) complex of 8-hydroxyquinoline has been demonstrated to be lower than the corresponding value for catechols ($10^{37}$ vs. $10^{40}$). Although the 8-hydroxyquinoline appears to be weaker ligand for iron (III) than catechol and catechol has a much greater affinity for protons. Also catechols are neutral over a wide range of physiological pH values and are therefore predicted to permeate biological membranes with relative ease. As with catechol, the 8-hydroxyquinoline possesses two pK$_a$ values in the region of 3.6
and 10.9, and in the similar fashion, from neutral 1:3 iron (III) complex that dominates over wide pH range and hence can be easily transported across cell membrane. Realizing that 8-hydroxyquinolines could be used as orally active iron (III) chelators and also these could be synthesized with relative ease, a systematic investigation into the chelation chemistry of this family of heterocyclic molecules have been carried out [47].

More than seventy bidentate 8-hydroxyquinoline derivatives have been synthesized and many of these have been studied for their complexation and sensitization properties for lanthanides and group 13 elements. 8-hydroxyquinoline has long been known to be an efficient sensitizer of europium in the 3:1 complex, Eu(8hq)$_3$ [48], and its covalent incorporation into a highly stable, water-soluble complex has been investigated. Furthermore, the importance of the aluminium complex of 8hq (known as ‘Alq$_3$’), as both an emissive and electron-transporting material in electroluminescent polymers [49], coupled with the intense recent interest in lanthanide complexes as triplet-harvesting agents in such devices (for promoting the emission from the normally non-emissive triplet excitations) [50]. The proton-ligand dissociation constants of 5-(phenyl-azo)-8-hydroxyquinoline (5) (“a” of Figure 2.2) derivatives, and metal-ligand stability constants of their complexes with metal ions (La$^{3+}$, Ce$^{3+}$, Pr$^{3+}$, Zr$^{4+}$, Hf$^{4+}$ and Th$^{4+}$) have been determined [51]. The $p$-OCH$_3$ and $p$-CH$_3$ derivatives of 5-(phenyl-azo)-8-hydroxyquinoline (i.e. an electron-donating effect) have a lower acidic character (higher pK$_{1}^{H}$ values) than the $p$-SO$_2$H, $o$-COOH, and $p$-NO$_2$ derivatives (i.e. an electron-withdrawing effect). The authors have also reported [51] that para-substituents in the 8-hydroxyquinoline moiety have a direct influence on the pK$_{1}^{H}$ values of these compounds. 8-HQ has been also employed to build fluorescent chemosensors for metal ions via ESIPT suppression, with increased fluorescence signal upon metal binding. To
enhance metal binding selectivity of 8-HQ, introduction of additional binding sites at the C-2 and/or C-7 positions, adjacent to the original binding sites in 8-HQ (“b” of Figure 2.2), has been extensively examined [52]. The 8-HQ benzoates have been developed as fluorescent chemosensors for transition metal ions such as Hg$^{2+}$ and Cu$^{2+}$ [53]. Apart from substitution at the C-2 and C-7 positions, different derivatives with substitution at the C-5 position were also reported [54]. 5-Aminomethyl-8-hydroxyquinoline (8) has been used as a scaffold to generate dimers, trimers, and tetramer (8a–c) metalloquinolates (Figure 2.3). Recently new class of fluorescent chemosensor based on the N$_2$S$_2$-donating 12-membered macrocyclic 2,8-dithia-5-aza-2,6-pyridinophane appended with 5-chloro-8-hydroxyquinolinylmethyl pendant arm (10) (Figure 2.4) has been developed for probing Cd$^{2+}$ in living cells [55]. It has been demonstrated as a selective (CHEF)-type OFF-ON response to the presence of Cd$^{2+}$. The development of these probes is of great importance to understand in detail the intracellular equilibria and mechanisms of distribution, to localize the cellular sub-compartments of accumulation in the case of poisoning and metabolic disorder, and thus to diagnose pathological conditions in real time [56]. More recently highly selective and sensitive fluorescent chemosensor, 4-(8′-hydroxyquinolin-5′-yl) methyleneimino-1-phenyl-2,3-dimethyl-5-pyrazole prepared by Schiff-base condensation of 8-hydroxyquinoline-5-carbaldehyde (HQ5A) and 4-aminoantipyrine have been investigated (11) for Al$^{3+}$ [57].
(Figure 2.4). The pH based photoluminescence studies reported have suggested that this ligand could serve as an excellent chelator for highly toxical aluminium ion in weak acid aqueous medium. We have found from literature that monopodal bidentate 8HQ and its derivatives bind with variety of metal ions. Although binding of bidentate 8HQ to Ru(II) has received moderate attention [58]; however, the synthesis, electronic absorption and redox properties of ruthenium complexes of different tri-, tetra-, and pentadentate analogues of 8-HQ have been reported few years before [59].

![Chemical structures](image)

*Figure 2.3: The structures of the 8-hydroxyquinoline derivatives with substitution at C-5 position, and their metal chelate complexes.*
2.5.2 Tridentate Chelators (containing one or two 8HQ units)

Unlike bidentate molecules, it is not possible to synthesize simple tridentate ligands which possess oxygen anion and nitrogen coordination sites [60]. This has the adverse effect of rendering the iron(III) complex more easily reduced and therefore more susceptible towards redox cycling. Furthermore, the presence of two nitrogens in the coordination sphere reduces the selectivity of iron(III) over zinc(II) [61]. An additional problem with tridentate ligands is that without exception, they form charged iron(III) complexes, an undesirable feature for efficient iron extraction from intracellular sites. Recently, a series of tridentate ligand based on 8-HQ has been reported [59], developed by incorporation of the 8-HQ subunit into polypyridine ligand systems by Friedlander condensation. The parent member of this new ligand series is 2-(pyridin-2-yl)-8-hydroxyquinoline 12 (Figure 2.5), and, several reports of its synthesis have been appeared [62]. These tridentate ligands have shown to afford interesting complexes with Ru(II) (12a) and other metal ions.

**Figure 2.5:** Structure of 2-pyridine-8-hydroxyquinoline and its ruthenium complex.
2.5.3 Dipodal Chelators

Many tetradeutate ligands have been investigated to date as possible iron(III) chelators for oral use as well as for other biological and photochemical applications. They are most often made up of dihydroxamic acids [63-64], but diphosphonates and a bis(3-hydroxy-4-pyridinone)-IDA derivatives [65]. In order to completely saturate the six coordination positions on ferric ion or other trivalent metal ions, the denticity of these ligands requires formation of polynuclear species, which are invariably found in these systems. In particular, the most common polynuclear complex is the dimer Fe$_2$L$_3$, with a charge depending on ligand structure. A common feature of these ligands is that a small amount of mono-nuclear complexes containing an unsaturated ferric ion is always present under the experimental conditions considered for the calculation of the pFe value. The calculated pFe value is 25.8, of the same order of magnitude as that of DFO. Although we are not here dealing with the above mentioned type of tetradeutate ligands, we will discuss in this section only about the reported dipodal or tetradeutate 8-hydroxyquinolinate type of chelators. The coordination chemistry of bis(oxine) ligands with two units joined by different central frameworks and/or linkages has been extensively investigated for their chelating properties [66]. In this context two bis(8HQ) ligands linked by a bridge of 5,5'-methylene (-CH$_2$-), 5,5'-sulfonyl (-SO$_2$-), 5,5'-dimethylene sulfide (-CH$_2$-S-CH$_2$-) and (-CH$_2$-O-CH$_2$-) are reported in literature [67-68]. The same group later reported the synthesis and characterization of coordination polymers based on the bis-oxine ligand connected with a viaduct, -H$_2$C-O-Ph-O-CH$_2$ (Ph = 1,3 phenylene) and -H$_2$CO-Ph-C(CH$_3$)$_2$-Ph -OCH$_2$ [69]. This work has also been further extended recently with the view of investigation of the chelating ability of a bis-8-quinolinol ligand by introducing the bridge of N,N'-diethyl-1,3-proapne
diammine between two 8-hydroxyquinoline moieties and its coordination polymers with Zn(II), Cu(II), Ni(II), Co(II) and Mn(II) metal ions [70].

Figure 2.6: The double stranded helicates (a) schematic representation, (b) crystal structure of cu complex and (c) 2,2’-(1E,1’E)-(4,4’-methylenebis(4,1-phenylene)bis(azan-1-yl-1-ylidene))bis(methan-1-yl-1-ylidene)diquinolinol-8-ol (13).

There are numerous reports on coordination polymers that exhibit double helical motifs [71]. A special class of well-defined molecular double-stranded helical metal complexes was introduced in 1987 and was termed double-stranded helicates (Figure 2.6) [72]. Of the factors integral to helicates formation, the geometric preferences of the metal and the group that separates and links the donor atoms of the ligand are particularly influential. Ligands with an odd number of methylene units in the spacer possess a “horizontal” mirror plane as the most influential symmetry element of the idealized C_{2v} symmetry, which mirrors the two attached chiral metal-complex moieties onto each other. In this perspective, the chemosensor 13 based on two 8-hydroxyquinoline chromophores connected with 4,4’-methylene-dianiline through imine
linkage has been reported (“c” of Figure 2.6) [73]. The complexation and photophysical of the ligand with group 13 metal ions (Al\(^{3+}\), Ga\(^{3+}\) and In\(^{3+}\)) have been studied by UV-vis and fluorescent emission spectroscopy. The authors have claimed that the results support their hypothesis for the formation of helicate-type structure. Similarly, two chelators derived from 8-OH quinoline and 1,5-bis(2-aminophenoxy)-3-oxopentane have been investigated for divalent (Cu\(^{2+}\) and Zn\(^{2+}\)) and trivalent (Eu\(^{2+}\) and Sm\(^{2+}\)) metal ions [74]. The behaviour of these ligands upon deprotonation was explored spectroscopically and studies on the excited state are also reported with formation of several mononuclear metal complexes.

As far ago as the 1970s quinolinate-substituted podand-type ligands were applied for the selective complexation of various metal ions. The use of ether linked quinolines, like the derivatives 14 (Figure 2.7), for the recognition of e.g. alkaline metal cations and the thereby formed structures were thoroughly reviewed early on by Vogtle and Weber [75]. Then later this kind of ligand has experienced a renaissance. For example, compounds 15 and 16 (Figure 2.7) were reacted with silver(I) ions, both of the ligands form coordination compounds, in which they bridge two strongly distorted tetra-coordinated metal centers that in addition bind another one of the ligands. This lead a trinuclear circular compound with three ligands wrapping helically around a triangle of silver cations. Structures of this kind are termed \textit{circular helicates} [76]. Ligand 16 yields a linear polymeric structure with alternating configuration at the metal complex units [77].

\begin{figure}[h]
\centering
\includegraphics[width=0.8\textwidth]{figure2_7.png}
\caption{Quinolinate-ether dipodal ligands 14-16 which are used as for the recognition of alkali metals.}
\end{figure}
The coordination ability of the 8-hydroxyquinoline unit has been combined with the feature of crown ethers to improve the metal ion complexing abilities and selectivities by means of introducing macrocycles in the backbone. The advantage of such a conjugate is the property of the quinolinate moiety which provides concomitant changes in the photophysical properties of the system upon metal ion binding [78]. A whole series of ligands has been designed and investigated as new sensing materials [79]. The most intensively studied compounds 17 and 18 possess two chloroquinolinate units. They are depicted in Figure 2.8. Upon addition of metal ion, coordination compounds with different coordination modes occur, which have an influence on the selectivity of the binding and on the photophysical properties of the formed complexes. After inclusion of a metal ion in the crown ether, both quinolinate units can bind to the metal either from the same or from opposite sides of the ring. As an alternative, only one quinolinate coordinates to the metal, while the second quinolinate is dangling around without coordination. Respective X-ray structures have been observed for free ligands as well as for barium complexes [80]. With zinc(II) or mercury(II) related compounds are formed in which the metals are not bound by the crown ether but only by the quinolinates [81]. The same group later developed several analogues of these reported ligands, which contain various substituents on the 8-hydroxyquinoline side arms. These substituents include hydrogen rather than chlorine, nitro, and methyl groups in the 5-position, as well as extra chlorine or a hydroxy group in the 2-position [82]. They also reported the preparation and preliminary complexation studies of series of macrocyclic ligands containing bis(8-hydroxyquinoline)-substituted to tetraaza-15-crown-5, diaazatrithia-15-crown-5 and diaazatrithia-16-crown-5 (19) to selectively bind transition and post-transition metal ions with a concomitant modulation in the absorption and fluorescent spectra of the compounds [83]. The ligand 18 can be used as a sensor for
magnesium ions. The macrocycle fluoresces in the presence of Mg$^{2+}$ but not with other alkaline earth ions. The high sensitivity of 18a for magnesium and the strong response by fluorescence enable the use of this compound for the detection of the divalent ion under strongly competing conditions. It even is possible to sense magnesium within living cells. This has been used to map intracellular ion distribution and movement [84]. The corresponding nitro derivative 18b proved to be a highly selective sensor for mercury(II) ions. It displays a good affinity and selectivity for this ion over a range of $>2$ pH units [85]. Besides thermodynamic and photophysical studies as mentioned earlier, hydroxyquinoline is a privileged structural moiety used as a source for many drugs diversely prescribed among a wide range of pathologies. Recently the antitumor activity of a family of bis 8-hydroxyquinoline substituted benzyl amines with structure-activity relationships and mechanism of action by which they exert their antitumor activity have been reported [86].

![Figure 2.8: 8-hydroxyquinoline-containing, crown ether conjugates (17-18), and tetraazacrown ethers (19).](image)

### 2.5.4 Tripodal Chelators:

Hexadentate ligands can be constructed by derivatising prototype bidentate hydroxyquinolines and attaching them to suitable molecular frameworks. Although enterobactin has an extremely high stability constant for iron(III), the effectiveness of this molecule and its analogues under acid conditions is limited by their weak acidic nature and the required loss of six protons on binding iron(III). In contrast, hydroxyquinolines are stronger acids than catechols and since they are monoprotic,
hexadentate ligands formed from three such units only lose three protons on formation of a six-coordinated complex. Thus hexadentate 8-HQs competes well with hexadentate catechols at neutral pH values. Another potential advantage of these molecules is that they may not be recognized by receptors and are therefore less likely to donate iron to pathogenic organisms.

For about 20 years, several hexadentate tripodal 8-hydroxyquinoline chelators have been investigated as potential alternatives-in-development for enterobactin analogs. Hiratani et al., describe tripodal “enterobactin analogues” 20 (“a” of Figure 2.9) that bear three 8-hydroxyquinoline units as chelating sites. The ligands are prepared by a tandem-Claisen rearrangement reaction. Jobs plot analysis shows the formation of 1:1 complexes of 20b with iron(III) or gallium(III). At low pH (<4) selectivity for the gallium(III) ion is found, which is high against Al^{3+}, In^{3+} and La^{3+} and moderate against Fe^{3+} [87]. In addition, Stefan Bernhard et al., designed hemicage coordination ligand 21 (QH₃) (“b” of Figure 2.9) by connecting three individual 8-hydroxyquinoline ligands at the C₃ position through a benzene unit [88]. In the central cavity of the ligand metal ions (Al^{3+}, Ga^{3+}, or In^{3+}) can be encapsulated without changing the basic metal-ligand coordination

Figure 2.9: Tripodal ligands containing benzene as a central unit and 8-hydroxyquinoline as metal binding sites.
sphere with the formation of hemicage complexes. The hemicage structure leads to superior thermal, chemical stability and quantum efficiency enhancement of Alq₃-based devices. Many tripodal tris-8-hydroxyquinoline derivatives have been also constructed based on the tren (tri(amoioethy)amine) backbone and on amide linkages. As representative examples the compounds include O-Trenoxx 22a and its derivative (N-Trenox) 23a, are shown in Figure 2.10. In order to introduce high water solubility, sulfonate groups are attached to the chelating units in compounds (O-TRENSOX, 22b) and (N-TRENSOX, 23b). Both ligands prove to be potent iron chelators (iron(II) as well as iron(III)). The iron(III) complex of O-TRENSOX has been shown to prevent and reverse iron chlorosis in several plant species. In experiments with rat hepatocyte cultures it has been found out, that O-TRENSOX is effective in the decrease of iron uptake as well as in the increase of iron release by the cells, so it functions as a hepatoprotector against the toxicity of iron overload. Equilibrium constants for the binding of iron(III) to O and N-TRENSOX have been determined. They show a stronger binding of the metal ion by O-TRENSOX in comparison to N-TRENSOX. The affinity of different metal ions to O-TRENSOX results in a series Fe³⁺ (pM = 29.5), Cu²⁺ (22.9), Zn²⁺ (21.7), Al³⁺ (20.0), Fe²⁺ (17.4), and Ca²⁺ (13.6) [89]. Recently one more tren based tripodal ligand tris[(5-methylene-8-hyddroxyquinoine) amino-ethyl] has been developed, however with CH₂-NH-CH₂ bridges and attachment of linkage at C-5 position of 8-hydroxyquinoline units [90]. In order to be used for the treatment of iron overload or deficiency, the siderophore has to be soluble in physiological conditions. It is indeed generally claimed that access to the cell through biological membranes depends on the subtle balance between hydrophilicity and lipophilicity of the chelator or its iron complex. Another strategy has been reported by Imbert et al; 2007, based on the same chromophore and framework, but binding unit was connected by its 2-position and
methylated at amide nitrogens resulting the formation of another different chelator “T2oxMe”, and its sulfonyl derivative “T2soxMe” 24a-b [91]. All these tren based 8-hydroxyquinolinate tripodal ligands 22-24 are presented in Figure 2.10. In addition to the thermodynamic and photophysical studies of the resulting podates (Ln = Pr, Nd, Gd, Er, Yb) in water, the cytotoxicity of the Yb III chelate was also tested, as well as its ability to couple with human serum albumin (HSA). This strategy could be extended easily to the design of similar podates featuring a carbon anchor offering various derivatization possibilities. Moreover, a series of three tris-hydroxyquinolinate derivatives of O-TRENSOX containing a C-pivotal atom as spacer and/or grafted with various polyoxyethylene chains (POE) has been prepared by Serratrice group (“b” of Figure 2.10), with same pFe III values leading to the observation that the hydrophilic-lipophilic balance (quantified by the partition coefficients) of the overall neutral ferric complexes is tuned by the length of the polyoxyethylene chain. This aspect was particularly well illustrated by Hider and gave conflicting results with the ligands of the 8-hydroxyquinoline family. Contrary to the results of Hider, which are beyond doubt, the biological results obtained with the hydroxyquinoline chelators do not depend on partition coefficient: O-TRENSOX and its iron complex are water soluble and insoluble in lipophilic medium, but exhibit the same biological activity as the amphiphillic COX 750 25 (“b” of Figure 2.10). The ligands 25 provide an iron(III) binding ability, which is similar to the one of O-TRENSOX. However, the complexes of 25 possess a well-balanced hydrophilicity/hydrophobicity that makes them interesting phase transfer reagents and membrane transporters [92]. The pFe values of these hexadentate ligands reported in literature are significantly higher [29.9 (for Csox,), 29.1 (for Cox2000), and 29.5 (for Cox750 and O-Trensox)] than those of the DFO (26.9) [93].
Figure 2.10: Tripodal ligands containing (a) (tri(amoioethyl)amine) “tren” as back bone, (b) C-pivotal atom as spacer and grafted with various polyoxyethylene (POE) chains, with 8-hydroxyquinoline sub-sites.

Apart from these multidentate tripodal ligands mentioned above which have been developed on aliphatic central back bones; there are some other potential chelators possessing the most efficient organizing framework, the trilactone derived from cyclic L-serine of enterobactin that also confers the “chiral recognition area”, but coupled to 8-hydroxyquinoline chelating subunits (Figure 2.11). To date, there are only two ligands built on the enterobactin scaffold connected to 8-hydroxyquinoline binding units reported in the literature: the one lipophilic having 8-hydroxyquinoline groups (oxinobactin) and the other hydrophilic having 8-hydroxyquinoline-5-sulfonate groups (sulfoxinobactin) [94]. The efficiency of the iron complexation, measured by the pFe, is enhanced by 4 pFe units between COX2000 (having a longer polyoxyethylene chain than COX200 and COX750 allowing solubility in water) and oxinobactin over the pH range 2–9. This suggests that the predisposition of the chelating units by cyclic frame
work is responsible for the gain in stability of ferric oxinobactin over ferric COX2000 series.

*Figure 2.11: Tripodal ligands containing cyclic (a) trilactone (b) 1,4,7-triazacyclononane, as anchors with 8-hydroxyquinoline sub-sites.*

Furthermore, lanthanide complexes of quinolinate-based ligands are attracting an increasing number of studies because of their interesting NIR luminescence emission properties [95]. The 8-hydroxyquinolinate-based lanthanide podates are good candidates for the design of NIR-emitting luminescent tags for biomedical application because of their good stability, low cytotoxicity, sizable luminescence quantum yields in water, and ability to interact with proteins [96]. In this approach Mazzaniti et al; 2009 [97], have shown that the direct assembly of bidentate 8-hydroxyquinolinate units into nonadentate tripodal ligand such as H₃thqtcn (1,4,7-tris-[2-(8-hydroxyquinolinyl)methyl]-1,4,7-triazacyclononane) using a triazacyclononane anchor, earlier reported by Cross and Sammes. The nonadentate chelator provides a very good lanthanide-ligand complementarily and leads to well-defined, highly rigid, water-stable mononuclear complexes in which the metal is efficiently shielded from water molecules. Mazzanti group later described [97] the synthesis, the solid-state structural investigation, and the photophysical properties of mononuclear lanthanide complexes of the ligand H₃thqtcn and the photophysical solution properties of the water-soluble and highly water stable lanthanides complexes of the another ligand H₃thqtcnSO₃ (1,4,7-tris[2-(5-sulfo-8-
Besides using flexible tripodal and preorganized frameworks the same group report the tripodal ligand, thqN-SO$_3^-$, in which 8-hydroxyquinoline binding units were connected to the shortest tris(methylamine) anchor. The lanthanide complexes of thqN-SO$_3^-$ contain two water molecules coordinated to the lanthanide center, rendering multidentate hydroxyquinolinate ligands particularly attractive for the development of bimodal optical/MRI reporters [98]. The efficient NIR luminescence, very high stability at physiological pH and their sizable quantum yields anticipating the potential applications of these ligands in biomedical analysis [99] endowed with high relaxivities and fluorescent properties [97]. This opens real perspectives for the development of bioprobes based on these systems.

### 2.5.5 Tetrapodal Chelators

In the authors knowledge, only three potential tetrapodal ligands based on four 8-hydroxyquinoline binding units connected to N,N,N',N'-tetraaminopropyl-1,2-ethylenediamine framework ions are reported in literature [100]: Tox, Tsox and TsoxMe (28). These tetrapodal ligands have been developed based on the results obtained with the TRENSOX ligands (Figure 12). The coordination sites are designed in such a way that they are appropriate to bind large rare earth ions and to satisfy their coordination requirements. Starting with Tox 28a, sulfonation affords the water soluble derivative Tsox 28b. Methyl groups at the amide are introduced in TsoxMe 28c to avoid quenching of lanthanide emission by vibrational resonance of the NH units. The design leads to 1:1 complexes with large thermodynamic stability in aqueous solution and no water molecule bound in the inner coordination sphere [100]. Photophysical investigations show, that the ligands Tox and Tsox are good sensitizers for NIR emission of neodymium(III), erbium(III), and ytterbium(III) even in water solution
Substitution of the amide NH by N-CH$_3$ in O-TRENSOX itself also affords good sensitizers for the NIR emission of neodymium(III), erbium(III), or ytterbium(III) in water. The latter complex couples to human serum albumin leading to an increase of the NIR luminescence by 50% [101].

> **Figure 2.12:** Tetrapodal hydroxyquinoline ligands for the coordination of rare earth ions.

Even if we have deliberated details in about many hexadentate tripodal ligands based on 8-hydroxyquinoline sub-units reported in literature so far, some of these will be addressed again in later chapters for completeness and comparison as the present thesis attempts an understanding of such multidentate ligands and their complexes with Fe(III), Al(III), Cr(III), and Ln(III) in aqueous solution. How does the choice of donor atoms in a given ligand affect the stability and selectivity (the difference in stability between ions) in complexes of these ions? What effect does keeping the donor set constant, but varying the ligand framework have on metal complex stability and selectivity? These questions are addressed in this thesis.
References:


