The mono(catecholamine) derivatives as iron chelators: synthesis, solution thermodynamic stability and antioxidant properties research

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There is a growing interest in the development of new iron chelators as novel promising therapeutic strategies for neurodegenerative disorders. In this article, a series of mono(catecholamine) derivatives, 2,3-bis(hydroxy)-N-(hydroxyacyl)benzamide, containing a pendant hydroxy, have been synthesized and fully characterized by nuclear magnetic resonance, Fourier transform infrared spectroscopy and mass spectrum. The thermodynamic stability of the chelators with Fe\textsuperscript{III}, Mg\textsuperscript{II} and Zn\textsuperscript{II} ions was then investigated. The chelators enable formation of (3 : 1) Fe\textsuperscript{III} complexes with high thermodynamic stability and exhibited improved selectivity to Fe\textsuperscript{III} ion. Meanwhile, the results of 1,1-diphenyl-2-picrylhydrazyl assays of mono(catecholamine) derivatives indicated that they all possess excellent antioxidant properties. These results support the hypothesis that the mono(catecholamine) derivatives be used as high-affinity chelator for iron overload situations without depleting essential metal ions, such as Mg\textsuperscript{II} and Zn\textsuperscript{II} ions.

1. Introduction

Iron is essential to the proper functioning of most organisms, but it is toxic when present in excess. In the presence of molecular
oxygen, loosely bound iron is able to redox cycle between the two stable oxidation states Fe\textsuperscript{II} and Fe\textsuperscript{III}, then catalyse the production of oxygen-derived free radicals, such as hydroxyl radical, which lead to an increase in oxidative stress markers in the substantia nigra, an increase in dopamine turnover and loss of dopamine in the striatum, α-synuclein pathology, and Lewy-body generation and membranal degeneration in neurons [1,2], thereby inducing neurodegenerative disorders, such as Alzheimer disease and Parkinson’s disease. Therefore, we needed to develop new iron chelators as novel promising therapeutic strategies [3,4].

Over the decades, the design of hexadentate chelating agents for Fe\textsuperscript{III} was inspired by siderophores enterobactin, a natural microbial Fe\textsuperscript{III} chelating agent, which possesses favourable geometric arrangement for Fe\textsuperscript{III} coordination preference and highest pFe\textsuperscript{III} value [5,6]. Lots of hexadentate chelators were synthesized based on chelate moieties of siderophores, such as catecholamine [7–10], hydroxypyridinone [11–15], and hydroxamate [16]. Most of these hexadentate chelators have a high Fe\textsuperscript{III} binding ability, but almost all chelating agents with high molecular weight (greater than 500), high hydrogen bond donors (greater than 5) and high hydrogen bond acceptors (greater than 10), which lead to a poor absorption, have not attracted more attention as potential therapeutic chelators. While deferiprone is a very simple bidentate structure chelator which possesses low molecular weight (139), low hydrogen bond donors (1) and low hydrogen bond acceptors (3) it satisfies design guidelines [17] for good absorption. Hence, deferiprone has good oral activity, which has been a well-researched iron chelating agent for the treatment of iron overload [18–20]. After twenty years of clinical observations we know that deferiprone can induce agranulocytosis [21]. Therefore, we urgently needed to develop new high affinity, selective, orally and nontoxic iron chelators.

Catecholamine moiety possesses a high affinity for Fe\textsuperscript{III}. This extremely strong interaction with tripotitive metal cations results from the high electron density of both oxygen atoms [22]. Therefore, an iron chelating agent which satisfies design guidelines [17] should be rationally designed, synthesized and developed based on catecholamine moiety. The new mono(catecholamine) derivatives have structural features that are unusual for a siderophore. It has a very simple bidentate structure unlike most known siderophores. Meanwhile, it has a pendant hydroxide group, which makes the ligand very hydrophilic, which is proposed to play an important role like ferrioxamine B and aminochelin (see figure 1 for structure) with a pendant amine group [23,24].

In this study, we reported the synthesis of mono(catecholamine) derivatives, the solution thermodynamic stability of these chelators with Fe\textsuperscript{III}, Mg\textsuperscript{II} and Zn\textsuperscript{II} ions in aqueous solution and antioxidant activity.

2. Results and discussion

2.1. Synthesis and characterization

The synthesis of the bidentate chelator mono(catecholamine) derivatives 4a–c are shown in figure 2. First, 2,3-bis(dibenzyloxy)benzonic acid 2 (80%) was generated from commercially available 2,3-bis(hydroxyl)benzonic acid 1 [25]. Aminoalcohol 3a–c and 2 were condensed using 1-hydroxybenzotriazole/dicyclohexylcarbodiimide (HOBt/DCC) to obtain the desired benzamides 4a–c with up to 90% yield [26]. Deprotection of the hydroxyl groups under typical catalytic hydrogenation conditions with removal of the benzyl group (room temperature, 130 ml min\textsuperscript{−1} H\textsubscript{2}, atmospheric pressure and palladium on activated charcoal (Pd/C) in tetrahydrofuran) produced 5a–c (L\textsuperscript{1–3}H\textsubscript{2}) with up to 99% yield.
The mono(catecholamine) derivatives were fully characterized by nuclear magnetic resonance (MNR), Fourier transform infrared spectroscopy (FTIR) and mass spectrum (MS). The FTIR spectra of the derivatives showed distinct absorption peaks at 1639–1647 cm$^{-1}$ of benzamide carbonyl stretching vibration, 1583–1593 and 1540–1548 cm$^{-1}$ of benzene ring skeleton vibration. The 1H NMR signals of the catecholamine aromatic protons of the chelators in (CD$_3$)$_2$CO were identified as doublets at 7.22–7.28 ppm (d, $J = 7.8$ Hz, 1H, Ar–H), doublet of doublets at 6.96 ppm (dd, $J = 7.8$, 1.2 Hz, 1H, Ar–H) and triplets at 6.69–6.71 ppm (t, $J = 7.8$ Hz, 1H, Ar–H). The signals of methylene of benzyl at 5.15–5.16 ppm (s, 9H, O–CH$_2$–Ar) and 5.09–5.10 ppm (s, 9H, O–CH$_2$–Ar) disappeared. Meanwhile, the 13C NMR signals of methylene of benzyl also disappeared in the mono(catecholamine) derivatives. Results indicated that the structure of mono(catecholamine) derivatives is as we expected.

2.2. Solution thermodynamics

In its neutral form, mono(catecholamine) derivatives (hereafter also designed as L$_{1-3}$H$_2$) have two dissociable protons, corresponding to catecholamine moieties. Because catecholamine moieties require deprotonation for efficient metal chelation, their metal affinity is necessarily pH dependent. In the presence of dissolved metal ions (M$^{a+}$) and protonated chelator (LH$_i$, where L is a chelator with $i$ removable protons), the pH-dependent metal–chelator complex with a general formula M$_m$L$_l$H$_h$ forms.

The relative amount of each species in solution is determined by equation (2.1), whose rearrangement provides the standard formation constant notation of log $\beta_{mlh}$ (equation (2.2)). The log $\beta_{mlh}$ value describes a cumulative formation constant. For convenience, these are discussed as stepwise association constants, either for complex formation log $K_{1n0}$ (equation (2.3)) or ligand protonation log $K_{01h}$ (equation (2.4)). When addressing protonation constants, the stepwise formation constants are commonly reported as protonation constants (log $K_{h}^H$, $h = 1, 2, 3, \ldots$):

\[
[M_mL_lH_h] = \beta_{mlh}[M]^m[L]^l[H]^h, \tag{2.1}
\]

\[
\log \beta_{mlh} = \log \left( \frac{[M_mL_lH_h]}{[M]^m[L]^l[H]^h} \right), \tag{2.2}
\]

\[
\log K_{01h} = \log \left( \frac{[LH_h]}{[LH_{h-1}][H]} \right) = \log \left( \frac{\beta_{01h}}{\beta_{01(h-1)}} \right), \tag{2.3}
\]

\[
\log K_{1n0} = \log \left( \frac{[ML_n]}{[ML_{n-1}][L]} \right) = \log \left( \frac{\beta_{1n0}}{\beta_{1(n-1)0}} \right). \tag{2.4}
\]

The log $K_{h}^H$ were determined from a combination of potentiometric and spectrophotometric titration. The obtained data were analysed using HYPSpec 2014 and HYPQUAD 2013 [27,28]. The determined log $K_{h}^H$ of L$_{1-3}$H$_2$ and different phenolate type chelators are listed in table 1. All the chelators contain two basic sites from the phenolate oxygen atoms of the catechol moieties. Therefore, L$_{1-3}$H$_2$ were both treated as diprotic acids for data analysis. The potentiometric titration curves of L$_{1-3}$H$_2$ are shown in figure 3, the $a$ value is the mol ratio of added base per chelators. The deprotonation of phenolic hydroxy in an orthoposition relative to amide gives rise to the buffer region at low pH (pH < 9.0), and its inflection points at $a = 1$, which indicated the orthophenolic hydroxy complete dissociation. These potentiometric titrations data were used to obtain the log $K_{2}^H$ values, whereas spectrophotometric
titration data were required to accurately determine the higher log \( K_1^H \) values. The spectrophotometric titration spectrogram of L\(^1\)H\(_2\) was selected for illustration because it is similar to that of L\(^2\)–3H\(_2\), as shown in figure 4. The spectograms of L\(^2\)–3H\(_2\) are shown in the electronic supplementary material, figures S1–S2. The initial absorbance peaks at 310 nm shifted to 330 nm with the increase of pH (5.3–9.0), which was attributed to the deprotonation of the phenolic hydroxy in an orthoposition relative to amide. Subsequently, the peaks width gradually broadened, and the intensity was gradually decreasing with the increase of pH (9.0–12.5), which was attributed to the further deprotonation. At pH 9.0, about 90% of L\(^1\)–3H\(_2\) are in anionic form (L\(^1\)–3H\(^-\)) (figure 5 and electronic supplementary material, figures S3–S4), which indicated one more lost acidic proton of catechol moiety.

The values log \( K_2^H \) of L\(^1\)–3H\(_2\) are ascribed to the protonations of the oxygen atoms of the catecholamine dianions in an ortho position relative to amide. The values log \( K_2^H \) of L\(^1\)–3H\(_2\) were comparable with the corresponding values for N-methyl-2,3-dihydroxybenzamide (MDHB) [29], N,N-dimethyl-2,3-dihydroxybenzamide (DMB) [5] and catechol [30] (table 1). The results in this working were in good agreement with the value of log \( K_2^H = 7.50 \) for MDHB. At the same time, the values were about one logarithm unit lower than those of DMB, which was attributed to an intramolecular hydrogen bond of the secondary amide with ortho position phenolate oxygen [14,31,32] moiety and the negative inductive effect of tertiary amide in catecholamine moiety. Meanwhile, the values were about two logarithm units lower than those of catechol, which not only was attributed to an intramolecular hydrogen bond [14,31,32], but also the inductive effect of the secondary amide. In fact,
Figure 5. Species distribution curves calculated for the chelator L₁H₂, calculative condition: [L₁H₂] = 5.0 × 10⁻⁴ M, the charge numbers are omitted for clarity.

Figure 6. The spectrophotometric titration spectrogram of Fe³⁺–L₁H₂ complex, condition: [L₁H₂] = 3 × [Fe³⁺] = 2.0 × 10⁻⁴ M, μ = 0.10 M KCl, T = 298.2 K, pH range = 3.9–11.0.

Table 1. The log $K_{H}^{n}$ of L₁⁻⁻⁻HS and different phenolate type chelators.

| chelators   | log $K_{H}^{1}$ | log $K_{H}^{2}$ |
|-------------|-----------------|-----------------|
| L₁H₂⁴⁺      | 11.60           | 7.63            |
| L₂H₂⁴⁺      | 11.40           | 7.50            |
| L₃H₂⁴⁺      | 11.37           | 7.31            |
| MDHB⁵⁺      | 11.20           | 7.50            |
| DMB⁶⁺       | 12.10           | 8.42            |
| catechol⁷⁺  | 13.00           | 9.24            |

⁴Determined from a combination of potentiometric and spectrophotometric titrations: [L₁⁻⁻⁻HS] = 2.0 × 10⁻⁴ M, μ = 0.10 M KCl, T = 298.2 K.
⁵MDHB in [29].
⁶DMB in [5].
⁷Catechol in [30].

Theoretical calculations, analysis of crystal structures and experimental potentiometric data for series of catecholamine derivatives indicated that the presence of amide on the catechol increased the second protonation constant of the nearby oxygen atoms of catechol dianions by about two logarithm units [33].
Figure 7. Proposed complexation processes of ligands L\textsuperscript{1−3}H\textsubscript{2}, the charge numbers are omitted for clarity.

Table 2. Wavelength and extinction coefficients for FeL\textsubscript{n} species extracted from spectrophotometric titrations\textsuperscript{a}.

| chelator | FeL | FeL\textsubscript{2} | FeL\textsubscript{3} |
|----------|-----|---------------------|---------------------|
| L\textsubscript{1}H\textsubscript{2} | 660 (415) | 561 (1085) | 485 (1050) |
| L\textsubscript{2}H\textsubscript{2} | 657 (506) | 558 (1220) | 485 (1330) |
| L\textsubscript{3}H\textsubscript{2} | 655 (442) | 558 (1260) | 485 (1335) |

\textsuperscript{a}The pH range indicates the calculated pH values in which that species predominates, conditions: [L\textsubscript{1−3}H\textsubscript{2}] = 3 × [Fe\textsuperscript{3+}] = 2.0 × 10\textsuperscript{-4} M, μ = 0.10 M KCl, T = 298.2 K.  
\textsuperscript{b}λ\textsubscript{max} in nm and ε in M\textsuperscript{-1} cm\textsuperscript{-1}.

The spectrophotometric titration spectrogram of the Fe\textsuperscript{III}–L\textsubscript{1}H\textsubscript{2} complex was selected for illustration because it is similar to that of L\textsubscript{2−3}H\textsubscript{2}, as shown in figure 6. The spectrograms of L\textsubscript{2−3}H\textsubscript{2} are shown in the electronic supplementary material, figures S5–S6. In the titration spectrogram, intense ligand-to-metal charge transfer (LMCT) bands of the Fe\textsuperscript{III} complexes allow the proton-dependent equilibria to be monitored spectrophotometrically. All of the chelator L\textsubscript{1−3}H\textsubscript{2} possess at least three spectrophotometrically distinguishable species that can be assigned by comparison to the well-defined Fe\textsuperscript{III}–catechol system [34–36]. For the sake of clarity, we will use the FeL\textsubscript{n} notation to ignore the charge state of the complexes, which varies across our series of chelator. In all cases, a light green solution was observed under acidic conditions, corresponding to FeL forms. Upon addition of alkali, a blue solution was observed, which is indicative of FeL\textsubscript{2} predominates. The solution converts, under more alkaline conditions, to red that is assigned as FeL\textsubscript{3}. So, we proposed the complexation processes are that complete deprotonation bidentate gradually replaced solvent molecules with the increased pH value (figure 7).

The specific species and the LMCT band wavelengths with their corresponding extinction coefficients for each FeL\textsubscript{n} spectral are compiled in table 2.

The affinities of chelator L\textsuperscript{1−3}H\textsubscript{2} with metal ions were determined by spectrophotometric titration data, which were analysed using the program HYPSPEC 2014 [27]. The species distribution diagrams of metal-complexes were obtained using the simulation program HySS [37]. The species distribution diagrams of Fe\textsuperscript{III} complexes are shown in figure 8 and the electronic supplementary material, figures S7–S8. The log β\textsubscript{mlh} of L\textsuperscript{1−3}H\textsubscript{2} with Fe\textsuperscript{III} are listed in table 3. But, log β\textsubscript{mlh} values are species dependent, therefore, a species-independent metric is needed to compare metal affinities of various ligands. In this regard, pM is the metric employed, where pM = −log[M\textsubscript{free}]. ‘M\textsubscript{free}’ refers to solvated metal ions free of complexation by ligands or hydroxides; high pM corresponds to low concentrations of uncomplexed metal ions in the solution. In this study, pM values are calculated using standard conditions of [M] = 10\textsuperscript{-6} M, [L] = 10\textsuperscript{-5} M and pH = 7.4. The pFe\textsuperscript{III} values of chelator L\textsuperscript{1−3}H\textsubscript{2} and related compounds are listed in table 3. The pFe\textsuperscript{III} values of the chelator L\textsuperscript{1−3}H\textsubscript{2} are significantly higher than those of deferiprone [38] and aminochelin [24]. Meanwhile, changes in minor log K\textsubscript{H} values are an insignificant factor in determining Fe\textsuperscript{III} affinity in chelators L\textsuperscript{1−3}H\textsubscript{2}, the higher affinity of L\textsubscript{1}H\textsubscript{2} is presumably owing to favourable geometric arrangement between the ligand and the Fe\textsuperscript{III} coordination preference. The fact...
Figure 8. Species distribution curves of Fe$^{III}$–L$_1$H$_2$ complex, calculative condition: [L$_1$H$_2$] = 3 × [Fe$^{III}$] = 2.0 × 10$^{-4}$ M, the charge numbers are omitted for clarity.

Table 3. The log $\beta_{mlh}$ and pFe$^{III}$ of L$_1$–3H$_2$ and related compounds.

| chelator   | log $\beta_{110}$ | log $\beta_{120}$ | log $\beta_{130}$ | pFe$^{III}$a |
|------------|--------------------|--------------------|--------------------|--------------|
| L$^1$H$_2$ | 19.96(2)           | 31.94(3)           | 42.66(3)           | 19.37(4)     |
| L$^2$H$_2$ | 19.23(3)           | 31.36(4)           | 41.66(2)           | 19.23(2)     |
| L$^3$H$_2$ | 19.19(2)           | 31.04(5)           | 41.10(3)           | 19.06(4)     |

deferiprone$^b$ 15.21 26.97 36.75 20.5

aminochelin$^c$ 19.10 30.80 41.30 17.6

$^a$pFe$^{III}$ = −log[Fe$^{III}_{free}$], [Fe$^{III}$] = 10$^{-6}$ M and [L] = 10$^{-5}$ M.

$^b$Deferriprone in [39].

$^c$Aminochelin in [24].

Table 4. The log $\beta_{mlh}$, pMg$^{II}$ and pZn$^{II}$ of L$_1$–3H$_2$ and related compounds.

| chelator   | Mg$_{II}$L$_1$H$_2$ | pMg$^{II}$a | Zn$_{II}$L$_1$H$_2$ | pZn$^{II}$b |
|------------|---------------------|-------------|--------------------|-------------|
| Mg$_{III}$ | [Mg$^{III}_{free}$] | 10.05(2)    | 6.54(2)            |
| Mg$_{II}$  | [Mg$^{II}_{free}$]  | 10.08(4)    | 6.56(3)            |
| Mg$_{III}$ | [Mg$^{III}_{free}$] | 10.11(1)    | 6.58(1)            |
| Mg$_{II}$  | [Mg$^{II}_{free}$]  | 7.19        | 6.28               |
| DTPA$^d$   | —                   | 6.40        | 15.10              |

$^a$pMg$^{II}$ = −log[Mg$^{II}_{free}$], [Mg$^{II}$] = 10$^{-6}$ M and [L] = 10$^{-5}$ M.

$^b$pZn$^{II}$ = −log[Zn$^{II}_{free}$], [Zn$^{II}$] = 10$^{-6}$ M and [L] = 10$^{-5}$ M.

$^c$The pZn$^{II}$ was calculated by the log $K_{H}$ and log $\beta_{mlh}$ values of deferiprone in [39].

$^d$DTPA in [40].

that the pFe$^{III}$ value of L$^1$H$_2$ is higher than that of L$^2$–3H$_2$ indicated a shorter pendant hydroxide group with lesser steric hindrance, which favours higher Fe$^{III}$ affinity.

Metal affinity studies have focused on the Fe$^{III}$ ion; however, the presence of Mg$^{II}$ and Zn$^{II}$ ions in biological systems leads us to evaluate the affinity of the chelators with Mg$^{II}$ and Zn$^{II}$ ions. The Mg$^{II}$ and Zn$^{II}$ ions affinities of L$^1$–3H$_2$ were determined through spectrophotometric titrations under the same conditions above. The spectrophotometric titration spectrograms of Mg$^{II}$–L$_1$–3H$_2$ and Zn$^{II}$–L$^1$–3H$_2$ complexes are shown in the electronic supplementary material, figures S9–S14. The log $\beta_{mlh}$, pMg$^{II}$ and pZn$^{II}$ values of L$^1$–3H$_2$ and related compounds are listed in table 4.
The pMgII and pZnII values of L1−3H2 were significantly lower than those of the efficient chelator diethylenetriaminepentaacetic acid (DTPA) [40]. The low pMgII and pZnII values were similar to those of catechol chelators [8,10,40–44], indicating the formation of chelators L1−3H2 with weak MgII and ZnII affinity, as predicted.

2.3. Antioxidant activity

1,1-Diphenyl-2-picryl-hydrazyl (DPPH) is a stable free radical [45], which is widely used to monitor the free radical scavenging ability of various antioxidants [46–48]. The assays were carried out in methanol, and the results were expressed as EC50, which represented the antioxidant concentration required to decrease the initial DPPH concentration by 50%. Low EC50 values indicate a highly radical scavenging capacity. This parameter is widely used to measure antioxidant capacity but does not consider the reaction time. The time needed to reach the steady state to the concentration corresponding at EC50 (TEC50) was calculated, and antiradical efficiency (AE) was introduced as a parameter to characterize antioxidant compounds [46]. AE was determined by the following equation:

\[
AE = \frac{1}{EC50 \times T_{EC50}}.
\]

The EC50 value of antioxidant L1−3H2 and their FeIII complexes were obtained from the curves of the percentage of remaining DPPH at the steady state against the concentration n, where n is the molar ratio of antioxidant to DPPH (mol AH/mol DPPH). The percentage of remaining DPPH was determined from the kinetic curves of different concentrations n, figure 9 and electronic supplementary material, figures S15–S19. The EC50 and AE values of L1−3H2, complexes FeIII−L1−3H2, (BHA) butylated hydroxyanisole, catechol and ascorbic acid [46,49] are listed in table 3 (aAntioxidant. bBHA and ascorbic acid in Ref. [46]. cCatechol in Ref. [49]).

The structures of phenolic derivatives have great influence on antioxidant activity [50,51]. L1−3H2, BHA and catechol possess similar bisphenolic structures, which lead them with approximate EC50 values.

For the results of L1−3H2 and FeIII−L1−3H2, the increase in AE values can be explained by mechanism of the DPPH’s reaction with phenols (ArOH). The antioxidant capacity of antioxidant L1−3H2 was influenced by amide group and coordination reaction. DPPH reacted with ArOH through an electron-transfer process from ArOH or its phenoxide anion (ArO−) to DPPH (electron transfer mechanism) [52]. The electron-transfer process from ArO− to DPPH was fast. The presence of amide group in L1−3H2 increased the quantity of ArO− and the observed values of the reaction rate, which conferred high AE values. The AE values of the complexes FeIII−L1−3H2 reduce generally, the FeIII coordination reaction produced acids and ArO–M complex. The acids and coordination reaction all reduced the quantity of ArO− and antioxidant capacity. The results were as expected.

Figure 9. (a) The kinetic curves of antioxidant L1H2 with different concentrations n. (b) The curve of percentage of remaining DPPH against concentration n.
3. Conclusion

In this article, a series of mono(catecholamine) derivatives, 2,3-bis(hydroxy)-N-(hydroxyacyl)benzamide, containing a pendant hydroxy, were synthesized and fully characterized. The results of thermodynamic stability with a set of metal ions showed that the chelators possess high thermodynamic stability and exhibited improved selectivity to the Fe\(^{III}\) ion. Meanwhile, the results of DPPH assays of mono(catecholamine) derivatives indicated they all possess excellent antioxidant properties. These results also indicated that mono(catecholamine) derivatives have a potential application prospect as chelator for the iron overload situations without depletion of essential metal ions such as Mg\(^{II}\) and Zn\(^{II}\) ions.

4. Experimental section

4.1. General

The organic reagents used were pure commercial products from Aladdin. The solvents were purchased from Chengdu Kelong Chemical Reagents Co. The 300–400 mesh silica gels were purchased from Qingdao Hailang Chemical Reagents Co. \(^1\)H NMR and \(^13\)C NMR spectra were recorded on a Bruker Avance III 600 MHz, CDCl\(_3\) and CD\(_3\)OD were used as the solvents, tetramethylsilane as the internal standard. The FTIR spectra were obtained from a Nicolet 380 FTIR spectrophotometer (Thermo Fisher Nicolet, USA) with a resolution of 4 cm\(^{-1}\). The ultraviolet (UV)–vis spectrophotometer (Thermo Scientific Evolution 201, USA) used had a double-beam light source from 190 to 1100 nm. Mass spectral analysis was conducted using a Varian 1200 LC/MS.

4.2. Synthesis of the chelators

**Synthesis of 2,3-bis(benzyloxy)benzoic acid (2).** A solution of 2,3-dihydroxybenzoic acid (10.20 g, 65.9 mmol), benzyl bromide (22.2 g, 130.0 mmol) and K\(_2\)CO\(_3\) (18.0 g, 130.0 mmol) in acetone (220 ml) was refluxed and stirred for 24 h. After filtration, the solution was concentrated in vacuo and the residue purified by flash column chromatography (volume ratio of acetone/hexane 2 : 3) to give the product 2 as clear oil (80%). \(^1\)H NMR (600 MHz, CDCl\(_3\)):\(\delta\) (ppm) = 7.50–7.10 (m, 12H, Ar–H), 7.03 (t, \(J = 8.0\) Hz, 1H, Ar–H), 5.12 (s, 2H, O–CH\(_2\)–Ar), 5.09 (s, 2H, O–CH\(_2\)–Ar). \(^13\)C NMR (150 MHz, CDCl\(_3\)):\(\delta\) (ppm) = 165.38 (C=O), 151.54 (ArC), 147.32 (ArC), 136.07 (ArCH), 134.87 (ArCH), 129.51 (ArCH), 129.06 (ArCH), 129.03 (ArCH), 128.77 (ArCH), 128.00 (ArCH), 125.25 (ArCH), 124.67 (ArCH), 123.27 (ArCH), 119.21 (ArCH), 71.77 (CH\(_2\)). FTIR (KBr, cm\(^{-1}\)) = 3347, 1625, 1577, 1555, 1498, 1028.

**Synthesis of 2,3-bis(benzyloxy)-N-(hydroxyethyl)benzamide (4a).** A solution of 2,3-bis(benzyloxy)benzoic acid 2 (1.67 g, 5.0 mmol), HOBr (0.12 g, 0.9 mmol) and DCC (1.24 g, 6.0 mmol) in CH\(_2\)Cl\(_2\) (50 ml) was stirred for 30 min at room temperature. Ethanalamine (0.34 g, 5.5 mmol) was added dropwise over 3 min and the mixture stirred for 10 h. The solution was filtered to remove the dicyclohexyl urea. The filtrate was concentrated in vacuo and the residue purified by flash column chromatography (volume ratio of acetone/hexane 2 : 3) to give the product 4a as clear oil (80%). \(R_f = 0.4\). \(^1\)H NMR (600 MHz, CDCl\(_3\)):\(\delta\) (ppm) = 8.30 (br s, 1H, CO–NH), 7.71 (m, 1H, Ar–H), 7.50–7.10 (m, 12H, Ar–H), 5.15 (s, 2H, O–CH\(_2\)–Ar), 5.10 (s, 2H, O–CH\(_2\)–Ar), 3.62 (t, \(J = 5.4\) Hz, 2H, CH\(_2\)), 3.40 (s, 2H, CH\(_2\)), 2.87 (br s, 1H, OH). \(^13\)C NMR (150 MHz, CDCl\(_3\)):\(\delta\) (ppm) = 165.78 (C=O), 150.95 (ArC), 146.15 (ArC), 135.60 (ArC), 127.99 (ArCH), 127.94 (ArCH), 127.52 (ArCH), 126.92 (ArCH), 126.83 (ArCH), 126.49 (ArCH), 115.60 (ArCH), 75.72 (CH\(_2\)), 70.56 (CH\(_2\)), 61.88 (CH\(_2\)), 42.10 (CH\(_2\)). FTIR (KBr, cm\(^{-1}\)) = 3347, 1625, 1577, 1555, 1498, 1028. APCI-MS (m/z): 333.4 [M-H]^−.

**Synthesis of 2,3-bis(benzyloxy)-N-(3-hydroxypropyl)benzamide (4b).** A solution of 2,3-bis(benzyloxy)benzoic acid 2 (1.67 g, 5.0 mmol), HOBt (0.12 g, 0.9 mmol) and DCC (1.24 g, 6.0 mmol) in CH\(_2\)Cl\(_2\) (50 ml) was stirred for 30 min at room temperature. 3-Amino-1-propanol (0.41 g, 5.5 mmol) was added dropwise over 3 min and the mixture stirred for 10 h. The solution was filtered to remove the dicyclohexyl urea. The filtrate was concentrated in vacuo and the residue purified by flash column chromatography (volume ratio of acetone/hexane 2 : 3) to give the product 4b as clear oil (85%). \(R_f = 0.5\) (volume ratio 2 : 3 acetone/hexane). \(^1\)H NMR (600 MHz, CDCl\(_3\)):\(\delta\) (ppm) = 8.12 (br s, 1H, CO–NH), 7.72 (m, 1H, Ar–H), 7.50–7.12 (m, 12H, Ar–H), 5.16 (s, 2H, O–CH\(_2\)–Ar), 5.09 (s, 2H, O–CH\(_2\)–Ar), 3.50 (t, \(J = 5.4\) Hz, 2H, CH\(_2\)), 3.39 (m, 2H, CH\(_2\)), 1.52 (m, 2H, CH\(_2\)). \(^13\)C NMR (150 MHz, CDCl\(_3\)):\(\delta\) (ppm) = 165.69 (C=O), 150.94 (ArC), 136.07 (ArCH), 134.87 (ArCH), 129.51 (ArCH), 129.06 (ArCH), 129.03 (ArCH), 128.77 (ArCH), 128.00 (ArCH), 125.25 (ArCH), 124.67 (ArCH), 123.27 (ArCH), 119.21 (ArCH), 71.77 (CH\(_2\)).
146.11 (ArC), 135.58 (ArC), 128.08 (ArCH), 127.98 (ArCH), 127.54 (ArCH), 126.89 (ArCH), 126.71 (ArCH), 122.54 (ArCH), 116.43 (ArCH), 75.76 (CH2), 70.55 (CH2), 57.89 (CH2), 34.89 (CH2), 31.69 (CH2). FTIR (KBr, cm$^{-1}$): 3327, 1635, 1577, 1542, 1452, 1028. APCI-MS (m/z): 392.0 [M + H]$^+$.  

**Synthesis of 2,3-bis(benzyloxy)-N-(4-hydroxybutyl)benzamide (4c).** A solution of 2,3-bis(benzyloxy) benzoic acid 2 (1.67 g, 5.0 mmol), HOBT (0.12 g, 0.9 mmol) and DCC (1.24 g, 6.0 mmol) in CH$_2$Cl$_2$ (50 ml) was stirred for 30 min at room temperature. 4-Amino-1-butanol (0.49 g, 5.5 mmol) was added dropwise over 3 min and the mixture stirred for 10 h. The solution was filtered to remove the dichlorehxyl ether. The filtrate was concentrated in vacuo and the residue purified by flash column chromatography (volume ratio of acetone/hexane 2:3) to give the product 4c as clear oil (90%). $R_f$ = 0.5. $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ (ppm) = 8.01 (br s, 1H, CO–NH), 7.74 (m, 1H, Ar–H), 7.50–7.10 (m, 12H, Ar–H), 5.16 (s, 2H, O–CH$_2$–Ar), 3.58 (m, 2H, CH$_2$), 3.32 (m, 2H, CH$_2$), 1.46 (m, 4H, CH$_2$–CH$_2$). $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ (ppm) = 164.17.  

(C–O), 150.93 (ArC), 145.99 (ArC), 135.64 (ArC), 127.99 (ArCH), 127.50 (ArCH), 126.90 (ArCH), 123.68 (ArCH), 122.52 (ArCH), 116.17 (ArCH), 75.59 (CH2), 70.52 (CH2), 61.56 (CH2), 38.57 (CH2), 29.06 (CH2), 25.03 (CH2). FTIR (KBr, cm$^{-1}$): 3327, 1635, 1577, 1542, 1452, 1033. APCI-MS (m/z): 406.2 [M + H]$^+$.  

**Synthesis of 2,3-dihydroxy-N-(2-hydroxyethyl)benzamide (5a).** A mixture of 4a (0.40 g, 1.06 mmol) and Pd/C (5%) (200 mg) in ethanol (50 ml) was stirred under H$_2$ atmosphere (130 ml·min$^{-1}$) for 5 h. The resulting mixture was filtered over Celite®, evaporated to dryness and dried under vacuum to give 5a as grey powder (yield of 99%). $^1$H NMR (600 MHz, (CD$_3$)$_2$CO): $\delta$ (ppm) = 8.14 (br s, 1H, CO–NH), 7.28 (d, $J = 7.8$ Hz, 1H, Ar–H), 6.96 (dd, $J = 7.8$, 1.2 Hz, Ar–H), 6.71 (t, $J = 7.8$ Hz, 1H, Ar–H), 3.73 (t, $J = 6.0$ Hz, 2H, CH$_2$), 3.53 (m, 2H, CH$_2$). $^{13}$C NMR (150 MHz, (CD$_3$)$_2$CO): $\delta$ (ppm) = 171.36 (C–O), 150.56 (Ar–C), 147.14 (Ar–C), 119.18 (Ar–CH), 119.03 (Ar–CH), 117.70 (Ar–CH), 115.49 (Ar–CH), 61.06 (CH$_2$), 42.89 (CH$_2$). FTIR (KBr, cm$^{-1}$): 3426, 3371, 2930, 1647, 1593, 1540, 1466, 736. APCI-MS (m/z): 198.1 [M + H]$^+$.  

**Synthesis of 2,3-dihydroxy-N-(3-hydroxypropyl)benzamide (5b).** A mixture of 4b (0.40 g, 1.02 mmol) and Pd/C (5%) (200 mg) in ethanol (50 ml) was stirred under H$_2$ atmosphere (130 ml·min$^{-1}$) for 5 h. The resulting mixture was filtered over Celite®, evaporated to dryness and dried under vacuum to give 5b as grey powder (yield of 99%). $^1$H NMR (600 MHz, (CD$_3$)$_2$CO): $\delta$ (ppm) = 8.29 (br s, 1H, CO–NH), 7.22 (d, $J = 7.8$ Hz, 1H, Ar–H), 6.96 (dd, $J = 7.8$, 1.2 Hz, Ar–H), 6.70 (t, $J = 7.8$ Hz, 1H, Ar–H), 3.67 (t, $J = 6.0$ Hz, 2H, CH$_2$), 3.53 (m, 2H, CH$_2$), 1.82 (m, 2H, CH$_2$). $^{13}$C NMR (150 MHz, (CD$_3$)$_2$CO): $\delta$ (ppm) = 172.04 (C–O), 150.58 (Ar–C), 147.15 (Ar–C), 119.17 (Ar–CH), 119.00 (Ar–CH), 117.52 (Ar–CH), 115.49 (Ar–CH), 60.22 (CH$_2$), 37.67 (CH$_2$), 32.69 (CH$_2$). FTIR (KBr, cm$^{-1}$): 3366, 2933, 1639, 1589, 1548, 1460, 741. APCI-MS (m/z): 212.2 [M + H]$^+$.  

**Synthesis of 2,3-dihydroxy-N-(4-hydroxybutyl)benzamide (5c).** A mixture of 4c (0.40 g, 0.99 mmol) and Pd/C (5%) (200 mg) in ethanol (50 ml) was stirred under H$_2$ atmosphere (130 ml·min$^{-1}$) for 5 h. The resulting mixture was filtered over Celite®, evaporated to dryness and dried under vacuum to give 5c as grey powder (yield of 99%). $^1$H NMR (600 MHz, (CD$_3$)$_2$CO): $\delta$ (ppm) = 8.29 (br s, 1H, CO–NH), 7.26 (d, $J = 7.8$ Hz, 1H, Ar–H), 6.96 (dd, $J = 7.8$, 1.2 Hz, Ar–H), 6.69 (t, $J = 7.8$ Hz, 1H, Ar–H), 3.60 (t, $J = 6.0$ Hz, 2H, CH$_2$), 3.43 (m, 2H, CH$_2$), 1.70 (m, 2H, CH$_2$), 1.60 (m, 2H, CH$_2$). $^{13}$C NMR (150 MHz, (CD$_3$)$_2$CO): $\delta$ (ppm) = 171.05 (C–O), 150.57 (Ar–C), 147.08 (Ar–C), 119.10 (Ar–CH), 118.92 (Ar–CH), 117.55 (Ar–CH), 115.55 (Ar–CH), 62.02 (CH$_2$), 39.98 (CH$_2$), 30.27 (CH$_2$), 26.60 (CH$_2$). FTIR (KBr, cm$^{-1}$): 3409, 3238, 2954, 1644, 1583, 1543, 1475, 763. APCI-MS (m/z): 226.1 [M + H]$^+$.  

### 4.3. Titration solution and methods

An INESA ZDJ-4B automatic potential titrator was used to measure the pH of the experimental solutions. Meanwhile, it was used for incremental additions of base standard solution to the titration cup under N$_2$ atmosphere. Titrations were performed in 0.10 M KCl supporting electrolyte. The temperature of the experimental solution was maintained at 298.2 K by an externally thermostat water bath. UV–visible spectra for incremental titrations and batch titrations were recorded on a Thermo Scientific Evolution 201 UV–vis spectrophotometer. Solid reagents were weighed on a Sartorius BT25S analytical balance accurate to 0.01 mg. All titration solutions were prepared using distilled water from Ulupure ULUP-IV ultra water system and degassed by an ultrasonic device. Standard solution of 0.10 M KOH and HNO$_3$ were purchased from Aladdin. Chelator stock solutions were made by dissolving a weighed amount of chelator accurate to 0.01 mg in 0.10 M KCl supporting electrolyte in a volumetric flask. A stock solution of 2.5 × 10$^{-3}$ M metal ion (Fe$^{III}$, Mg$^{II}$ and Zn$^{II}$ ions) was made by dissolving a weighed amount of corresponding metal salt (FeCl$_3$, ZnCl$_2$ and MgCl$_2$·6H$_2$O 99.95% metals basis) in 1.0 vol % HNO$_3$ standard solution. Fe$^{III}$ ion titrations were conducted with a 3:1 chelator:metal ratio. Mg$^{II}$ and Zn$^{II}$
ions titrations were conducted with a 1:1 chelator:metal ratio. Metal-to-chelator ratios were controlled by careful addition of a chelator solution of known concentration and a metal ion stock solution to the titration cup. All titrations were repeated a minimum of three times.

4.4. Titration and treatment

Spectrophotometric titration data were analysed using the program HypSpec 2014 [27], using nonlinear least-squares regression to determine formation constants. Wavelengths between 400–800 nm of Fe(III) titration curves and 250–550 nm of Mg(II), Zn(II) titration curves were used for data refinement. The number of absorbing species to be refined upon was determined by factor analysis within the HypSpec 2014 [27]. Speciation diagrams were generated using HySS [37] titration simulation software. The protonation constants and metal complex formation constants were determined by potentiometric and spectrophotometric titration experiments.

4.5. Antioxidant assay methods

An aliquot of methanol (0.1 ml) and different aliquot stock methanol solutions of 1.0 × 10⁻⁴ M antioxidant were added to the 2.5 ml methanol solution of 6.0 × 10⁻⁵ M DPPH, and the volume was adjusted to a final value of 3.0 ml with methanol. Absorbances at 517 nm were measured immediately at 10 s intervals on a Thermo Scientific Evolution 201 UV–vis spectrophotometer until the reaction reached steady state. Five different concentrations were measured for each assay. Then the EC₅₀ were plotted to obtain from the graph the percentage of remaining DPPH at the steady state against the molar ratio antioxidant to DPPH. Moreover, the time needed to reach the steady state to EC₅₀ concentration (Tₜₐ₅₀) and the AE values was also calculated.

Data accessibility. This article does not contain any additional data.

Authors’ contributions. Q.C.Z. and B.J. conceived and designed the experiments and wrote the paper. Q.C.Z., X.E.W., J.Z. and Z.T.S performed the experiments. Q.C.Z., S.L., Q.Q.L. and R.F.P. analysed the data. B.J. and R.F.P. contributed reagents/materials/analysis tools.

Competing interests. The authors declare no competing interests.

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