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# Synthesis of bifunctional biscatecholamine chelators for uranium decorporation

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ABSTRACT

New 1,3-dicarbonyl biscatecholamide ligands were synthesized to decorporate uranium for nuclear contamination. The derivatives were characterized via $^{1}$H NMR spectroscopy, $^{13}$C NMR spectroscopy, FTIR spectroscopy and mass spectrometry. The complexation abilities of ligands **8a**–**8d** with $UO_2^{2+}$, $Cu^{2+}$ and $Zn^{2+}$ were determined through spectrophotometric and potentiometric titrations technology. The antioxidant capacities of the ligands were assessed through DPPH antioxidant assay. Results indicated that ligands **8a**–**8d** are potential decorporating agents for uranyl ion ($pUO_2$ up to 22.41) and copper(II) ion (pCu up to 17.71) without depletion of the essential element zinc (pZn lower than 7.48).



## 1. Introduction

Uranium, commonly used as a nuclear fuel and constituent of nuclear weapons for civilian and military purposes, can be introduced into the living system by ingestion, inhalation or through wounds [1]. Hexavalent uranyl ion ($UO_2^{2+}$, U(VI)) is the most stable form in aqueous solutions and serum in vivo [2–4]. Uranyl ion is mainly complexed by blood transferrin and natural low-molecular-weight complexing agents, such as citrates, bicarbonates and phosphates [5], forming stable complexes at the physiological pH. However, the uranyl ion complexes retained in target organs, especially in kidneys, liver and marrow after chelation within blood, are a source of cancer and chemical intoxication [6,7]. Furthermore, the alpha particles emitted by uranium can produce free radicals that can kill cells [8–10]. Thus, the present study aims to find nontoxic bifunctional chelating agents that can efficiently promote the excretion of uranyl ion and scavenge free radicals.

Among the common chelating agents that have been reported [11–16], sulfocatecholamides can chelate lanthanides efficiently. In 1950, Lusky et al. [17] first found Tiron (disodium salt of 1,2-dihydroxybenzene-3,5-disulfonic acid), which forms a stable U(VI) complex within a pH range of 6–8. Given its reasonably small size and high chelating capacity, Tiron has been used as an important complexing and masking agent for metal ions [18]. Subsequently, O'Brien et al. [19] found a catechol derivative (Enterobactin, Scheme 1) claimed to be the most effective natural Fe(III) ligand in vivo. The similar coordination features of iron(III) and uranium suggest that multidentate sulfocatecholamide (CAMS) ligands are effective for U(VI) chelation. This inference has been confirmed by some experimental studies. Leydier et al. [20,21] synthesized a series of sulfocatecholamides to chelate uranyl ion, in which the association constant (log*K*) of CYCAMS (*N*,*N*-bis(2,3-dihydroxy-5-sulfonylbenzoyl)cyclohexane-(1,3)-bis-methyamine) reaches 17.5 under neutral pH.

Catecholamide exerts an antioxidative effect, which may be related to its hydroxy and amine groups [22,23]. As a result, catecholamide can be used to scavenge free radicals generated in the human body.

1,3-Dicarbonyl compounds are important in synthetic organic chemistry because the obtained skeletons are intermediates for the synthesis of various biologically active compounds [24–26]. Catecholamide ligands have attracted considerable attention because of their high affinity and potential clinical applications as decorporation agents for heavy metal ions [27–29]. Our previous study showed that ethylenediamine derivatives demonstrate higher complexation capability but lower antioxidant capacity than aminoalcohol [30]. Therefore, we investigated ligands with a high complexation capability and antioxidant capacity, and synthesized a new family of 1,3-dicarbonyl biscatecholamide ligands through efficient synthetic routes from different backbones (Scheme 2). Moreover, the chelating abilities of $UO_2^{2+}$, $Cu^{2+}$ (free

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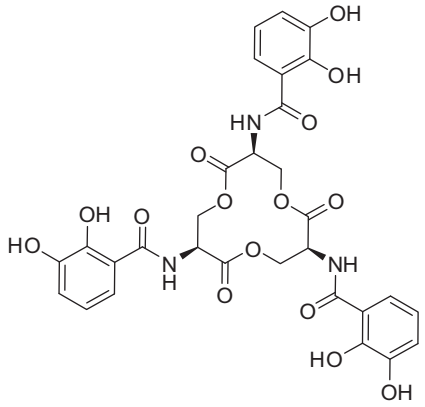
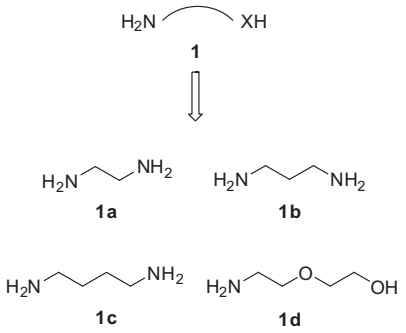


**Scheme 1.** Chemical structure of Enterobactin.




**Scheme 2.** Diamine and aminoalcohol backbones.

copper ions in body induce the damages of various biomolecules) [31] and $Zn^{2+}$ (essential trace element) were studied through spectrophotometric titrations. The structures of all products were characterized, and their antioxidant capacities were investigated using DPPH (2,2-diphenyl-1-picrylhydrazyl) antioxidant assay.

## 2. Experimental

### 2.1. General

All the organic reagents used were pure commercial products from Aladdin expect $UO_2(NO_3)_2{\cdot}6H_2O$ (from HuBei ChuShengWei Chemistry Co., Ltd.). Anhydrous solvents were purchased from Chengdu Kelong Chemical Reagents Co., Ltd. and dry $CH_2Cl_2$ was distilled after processed with anhydrous calcium chloride overnight and refluxed in the presence of calcium hydride for three hours. Flash chromatography was carried out on the 300–400 mesh silica gel from Qingdao Hailang. $^1H$ NMR, $^{13}C$ NMR spectra were recorded on Bruker Avance 300, Avance 400 or Avance 600 spectrometer. FTIR spectra were collected from Nicolet 380 FTIR spectrophotometer (Thermo Fisher Nicolet, USA) with a resolution of 4 $cm^{-1}$ from 400 $cm^{-1}$ to 4000 $cm^{-1}$. UV–Vis spectrophotometer (Thermo Scientific Evolution 201, USA) with a double-beam light source from 190 nm to 1100 nm was used. Mass spectrometry (MS) was conducted using Varian 1200 LC/MS.

### 2.2. Titration Methods

Potentiometric titrations were carried out on ZDJ-4B automatic potential titrator (Shanghai INESA Scientific Instrument Co., Ltd.). Spectrophotometric titrations were performed using a Thermo Scientific Evolution 201 UV–Vis spectrophotometer. All titrations were determined at 25.0 ± 0.1 °C under $N_2$ atmosphere with stirring. Solids reagents were weighed on a Sartorius BT25S analytical balance accurate to 0.01 mg. Titration solutions were prepared using distilled water from Ulupure ULUP-IV ultra water system and degassed by ultrasonic device. The 0.1 M nitrate standard solution and 0.1 M KOH standard solution were commercial products from Aladdin. Certain amount of KCl were weighed accurately and dissolved with water to 1 L in volumetric flasks. The ligands stock solutions were $2 \times 10^{-4}$ M while the metal ions (made from $UO_2(NO_3)_2{\cdot}6H_2O$, $Cu(NO_3)_2{\cdot}3H_2O$ and $Zn(NO_3)_2{\cdot}6H_2O$, respectively) stock solutions were 0.01 M. Certain amounts of the ligands **8a–8d** were weighed accurately with 1 vol% ethanol dissolved, and then diluted with 0.1 M KCl aqueous solution to 250 mL in volumetric flasks. And the metal ions stock solutions were obtained by certain amounts of metal salts directly diluted with 0.1 M KCl aqueous solution to 25 mL in volumetric flasks.

The protonation constants of ligands **8a–8d** were performed with 25 mL ligands, and spectrophotometric titrations [32–35] were used with the UV–Vis spectrophotometer until no significant changes on spectrophotometric curves. The spectrophotometric titrations were calculated by the HypSpec 2014 program [36] to obtain the first two protonation constants because of the limitation of the potential titrator at a high pH. Potentiometric titrations [37–40] were used to obtain the last two protonation constants by the Hyperquad 2013 program [41] holding the values previously determined by spectrophotometric titrations. For the titrations, the ligand concentration was $2 \times 10^{-4}$ M, and the concentrations of base (KOH) were 0.1 and 0.01 M in spectrophotometric and potentiometric titrations, respectively. The stability constants of ligands **8a–8d** with metal ions ($UO_2^{2+}$, $Cu^{2+}$ and $Zn^{2+}$) were all determined by spectrophotometric titrations. To a mixture of 0.5 mL metal ions stock solutions and 1.5 mL nitrate standard solution (0.5 mL just for ligands with $Zn^{2+}$), 25 mL ligands stock solutions were added. The UV–Vis spectra were measured from 250 to 550 nm with the KOH solution gradually adding into the titration cup. HypSpec 2014 program were used to calculate global formation constants ($\log \beta_{pqr}$) in the presence of global protonation constants. All the concentration distribution curves were generated with the HySS program [42]. The UV–Vis spectra of ligands **8a–8d** in the presence of metal ions and concentration distribution curves for the complexes of ligands **8a–8d** with $Cu^{2+}$ and $Zn^{2+}$ are included in Supporting Information.

### 2.3. Antioxidant method

The antioxidant activities of **8a–8d** were determined using DPPH antioxidant assay, i.e., 0.2 mL of **8a–8d** aqueous solution ($2 \times 10^{-4}$ mol/L) or 0.2 mL of water was added to 2.8 mL of DPPH ethanol solution ($1.15 \times 10^{-4}$ mol/L). The absorbance was rapidly determined for 4000 s at 1 s intervals at 517 nm because of the intense absorption at the wavelength.

### 2.4. Compounds synthesis

#### 2.4.1. Synthesis of (2-aminobutyl)carbamic acid tert-butyl ester (**2a**)

Di-*tert*-butyl dicarbonate (3.63 g, 0.017 mol, dissolved in 10 mL methanol) was added into a solution of diamine **1a** (3.0 g, 0.05 mol) in triethylamine and methanol (10% TEA in MeOH, 110 mL), and the obtained solution was stirred at room temperature overnight. The methanol and TEA were removed in vacuo to yield an oily residue that was dissolved in dichloromethane (100 mL) and washed with a solution of 10% aq sodium carbonate ($2 \times 100$ mL). The organic layer was dried over anhydrous $Na_2SO_4$, filtered, and evaporated to dryness to give translucent oil. The crude product was chromatographed on silica gel ($NH_4OH$: MeOH:$CHCl_3$, 1:10:89) to give **2a** as yellow oils (1.91 g, 70%).

$R_f$ = 0.4. $^1$H NMR (600 MHz, $CDCl_3$, 298.0 K) $\delta$ (ppm): 5.01 (br s, 1H, NH–CO), 3.17 (t, *J* 5.4 Hz, 2H, $CH_2$), 2.79 (t, *J* 6.0 Hz, 2H, $CH_2$), 1.71 (br s, 2H, $NH_2$), 1.44 (s, 9H, $CH_3$); FTIR (KBr) $\nu$ ($cm^{-1}$): 3355, 2975, 2932, 1694, 1522, 1392, 1366, 1276, 1252, 1046; APCI-MS: *m*/*z* $(M+1)^+$ = 161.

*2.4.2. Synthesis of (3-aminobutyl)carbamic acid tert-butyl ester (**2b**)*

Using the same procedure as **2a**. Purification on silica gel ($NH_4OH$:MeOH:$CHCl_3$, 1:10:89) afforded **2b** as yellow oil (72%). $R_f$ = 0.4. $^1$H NMR (600 MHz, $CDCl_3$, 298.0 K) $\delta$ (ppm): 4.94 (br s, 1H, NH–CO), 3.14 (t, *J* 6.3 Hz, 2H, $CH_2$), 2.70 (t, *J* 6.9 Hz, 2H, $CH_2$), 1.55 (m, 2H, $CH_2$), 1.37 (s, 9H, $CH_3$); FTIR (KBr) $\nu$ ($cm^{-1}$): 3368, 2931, 2875, 1652, 1538, 1453, 1375, 1265; APCI-MS: *m*/*z* $(M+1)^+$ = 175.

*2.4.3. Synthesis of (4-aminobutyl)carbamic acid tert-butyl ester (**2c**)*

Using the same procedure as **2a**. Purification on silica gel ($NH_4OH$:MeOH:$CHCl_3$, 1:10:89) afforded **2c** as yellow oil (75%). $R_f$ = 0.4. $^1$H NMR (600 MHz, $CDCl_3$, 298.0 K) $\delta$ (ppm): 4.82 (br s, 1H, NH–CO), 3.08 (t, *J* 4.2 Hz, 2H, $CH_2$), 2.70 (t, *J* 6.3 Hz, 2H, $CH_2$), 1.48 (m, 2H, $CH_2$), 1.40 (m, 11H, $CH_3$ and $CH_2$); FTIR (KBr) $\nu$ ($cm^{-1}$): 3388, 2944, 2870, 1701, 1648, 1518, 1452, 1366, 1270, 1058; APCI-MS: *m*/*z* $(M+1)^+$ = 189.

*2.4.4. Synthesis of 2,3-bis(benzyloxy)benzoic acid (**3**)*

Benzyl bromide (22.2 g, 130 mmol) was added into a solution of 2,3-dihydroxybenzoic acid (10.15 g, 65.86 mmol) and $K_2CO_3$ (18.0 g, 130 mmol) in acetone (200 mL), and the mixture was refluxed for 24 h. After filtration of the reaction mixture, the solvent was evaporated under reduced pressure to obtain the crude product as clear oil. The crude product was dissolved in 200 mL methanol, and 15.07 g $LiOH{\cdot}H_2O$ (359.1 mmol) was slowly added with refluxing for 3 h. Then, the solution was acidified with 3 M HCl until *ca.* pH = 2 and filtered to give **3** as a white solid (17.62 g, 80%). $^1$H NMR (400 MHz, $CDCl_3$, 298.0 K) $\delta$ (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, $CDCl_3$, 298.0 K) $\delta$ (ppm): 165.38 (C=O), 151.54 (Ar–C), 147.32 (Ar–C), 136.07 (Ar–CH), 134.87 (Ar–CH), 129.25 (Ar–CH), 129.07 (Ar–CH), 129.03 (Ar–CH), 128.78 (Ar–CH), 128.01 (Ar–CH), 125.25 (Ar–CH), 124.67 (Ar–CH), 123.27 (Ar–CH), 119.21 (Ar–CH), 77.35 ($CH_2$), 71.77 ($CH_2$); FTIR (KBr) $\nu$ ($cm^{-1}$): 3063, 3032, 2944, 2876, 1692, 1598, 1577, 1498, 1472, 1260, 1035, 766; APCI-MS: *m*/*z* $(M-1)^-$ = 333.

*2.4.5. Synthesis of N-(N′-tert-butyloxycarbonylethane diamino)-2,3-bis(benzyloxy)benzamide (**4a**)*

A mixture of 2,3-bis(benzyloxy)benzoic acid **2** (2.18 g, 6.5 mmol), *N*–hydroxybenzotriazole (HOBt, 0.14 g, 1.0 mmol) and dicyclohexylcarbodiimide (DCC, 1.62 g, 7.8 mmol) was dissolved in 80 mL $CH_2Cl_2$ and stirred for 30 min. Then 1.04 g (2-aminobutyl) carbamic acid *tert*-butyl ester **2a** (6.5 mmol) was added dropwise and the reaction proceeded at room temperature overnight. The obtained white solution was filtered to remove the dicyclohexylurea, and the filtrate was concentrated in vacuo. The residue was chromatographed on a silica gel column (ethanol:$CH_2Cl_2$, 1:10) to give **4a** as yellow solid (2.72 g, 88%). $R_f$ = 0.4. $^1$H NMR (600 MHz, $CDCl_3$, 298.0 K) $\delta$ (ppm): 7.99 (br s, 1H, CO–NH), 7.64 (m, 1H, Ar–H), 7.46–7.00 (m, 12H, Ar–H), 5.09 (s, 2H, O–$CH_2$–Ar), 5.02 (s, 2H, O–$CH_2$–Ar), 3.29 (m, 2H, $CH_2$), 3.09 (m, 2H, $CH_2$), 1.33 (s, 9H, $CH_3$); $^{13}$C NMR (150 MHz, $CDCl_3$, 298.0 K) $\delta$ (ppm): 166.17 (C=O), 156.22 (C=O), 153.15 (Ar–C), 151.91 (Ar–CH), 147.00 (Ar–C), 136.57 (Ar–CH), 129.06 (Ar–CH), 129.02 (Ar–CH), 128.98 (Ar–CH), 128.90 (Ar–CH), 128.49 (Ar–CH), 127.88 (Ar–CH), 124.62 (Ar–CH), 123.43 (Ar–CH), 117.36 (Ar–CH), 79.43 ($CH_2$), 76.68 ($CH_2$), 71.17 ($CH_2$), 41.10 ($CH_2$), 39.80 ($CH_2$), 28.57 ($CH_3$); FTIR (KBr) $\nu$ ($cm^{-1}$): 3353, 3062, 3030, 2980, 2931, 1686, 1638, 1577, 1498, 1448, 1368, 1270, 741; APCI-MS: *m*/*z* $(M+1)^+$ = 477.

*2.4.6. Synthesis of N-(N′-tert-butyloxycarbonylpropane diamino)-2,3-bis(benzyloxy)benzamide (**4b**)*

Using the same procedure as **4a**. Purification on silica gel (acetone:hexane, 1:3) afforded **4b** as yellow solid (86%). $R_f$ = 0.4. $^1$H NMR (300 MHz, $CDCl_3$, 298.0 K) $\delta$ (ppm): 7.97 (br s, 1H, CO–NH), 7.69 (m, 1H, Ar–H), 7.50–7.00 (m, 12H, Ar–H), 5.16 (s, 2H, O–$CH_2$–Ar), 5.10 (s, 2H, O–$CH_2$–Ar), 3.29 (q, *J* 6.4 Hz, 2H, $CH_2$), 3.01 (q, *J* 6.1 Hz, 2H, $CH_2$), 1.51–1.43 (m, 11H, $CH_3$ and $CH_2$); $^{13}$C NMR (150 MHz, $CDCl_3$, 298.0 K) $\delta$ (ppm): 165.80 (C=O), 156.20 (C=O), 151.84 (Ar–C), 146.96 (Ar–CH), 136.57 (Ar–CH), 136.57 (Ar–CH), 136.55 (Ar–CH), 128.88 (Ar–CH), 128.83 (Ar–CH), 128.81 (Ar–CH), 128.39 (Ar–CH), 127.78 (Ar–CH), 117.23 (Ar–CH), 76.57 ($CH_2$), 71.47 ($CH_2$), 37.54 ($CH_2$), 36.66 ($CH_2$), 34.08 ($CH_2$), 30.08 ($CH_2$), 28.57 ($CH_3$); FTIR (KBr) $\nu$ ($cm^{-1}$): 3433, 3346, 3068, 2938, 1673, 1620, 1573, 1536, 1452, 1275, 757; APCI-MS: *m*/*z* $(M+1)^+$ = 491.

*2.4.7. Synthesis of N-(N′-tert-butyloxycarbonylbutane diamino)-2,3-bis(benzyloxy)benzamide (**4c**)*

Using the same procedure as **4a**. Purification on silica gel (ethanol:$CH_2Cl_2$, 1:50) afforded **4c** as yellow solid (90%). $R_f$ = 0.5. $^1$H NMR (600 MHz, $CDCl_3$, 298.0 K) $\delta$ (ppm): 7.87 (br s, 1H, CO–NH), 7.64 (m, 1H, Ar–H), 7.46–7.00 (m, 12H, Ar–H), 5.07 (s, 2H, O–$CH_2$–Ar), 5.00 (s, 2H, O–$CH_2$–Ar), 3.18 (q, *J* 6.4 Hz, 2H, $CH_2$), 2.94 (m, 2H, $CH_2$), 1.36 (s, 9H, $CH_3$), 1.26 (m, 4H, $CH_2$); $^{13}$C NMR (150 MHz, $CDCl_3$, 298.0 K) $\delta$ (ppm): 165.22 (C=O), 156.05 (C=O), 151.88 (Ar–C), 147.04 (Ar–CH), 136.67 (Ar–C), 136.63 (Ar–CH), 128.83 (Ar–CH), 128.81 (Ar–CH), 128.80 (Ar–CH), 128.37 (Ar–CH), 127.78 (Ar–CH), 117.27 (Ar–CH), 76.52 ($CH_2$), 71.57 ($CH_2$), 39.43 ($CH_2$), 28.58 ($CH_3$), 27.61 ($CH_2$), 26.78 ($CH_2$); FTIR (KBr) $\nu$ ($cm^{-1}$): 3364, 2978, 2934, 1691, 1526, 1278, 781; APCI-MS: *m*/*z* $(M+1)^+$ = 505.

*2.4.8. Synthesis of N-(aminoethyl)-2,3-bis(benzyloxy)benzamide, TFA salt (**5a**)*

A mixture of TFA (trifluoroacetic acid)/$CH_2Cl_2$ (20 vol%, 15 mL) was dropped into a solution of *N-(N-tert*-butyloxycarbonylethane diamino)-2,3-bis(benzyloxy)benzamide **4a** (0.95 g, 2.0 mmol) in $CH_2Cl_2$ (15 mL) at 0 °C, and the obtained solution was stirred at room temperature for 3 h. Then, the solution was concentrated in vacuo, and the residue was dissolved in 0.5 mL of hot ethanol with 30 mL ether added and the white crystal was precipitated. Then the solution was filtered to give **5a** as white solid (0.75 g, 77%). $^1$H NMR (300 MHz, $CDCl_3$, 298.0 K) $\delta$ (ppm): 8.42 (br s, 1H, CO–NH), 7.56 (m, 1H, Ar–H), 7.50–7.00 (m, 12H, Ar–H), 5.14 (s, 2H, O–$CH_2$–Ar), 5.11 (s, 2H, O–$CH_2$–Ar), 3.33 (q, *J* 4.8 Hz, 2H, $CH_2$), 2.93 (t, *J* 4.8 Hz, 2H, $CH_2$); $^{13}$C NMR (150 MHz, $CD_3OD$, 298.0 K) $\delta$ (ppm): 168.26 (C=O), 152.03 (Ar–C), 146.20 (Ar–C), 136.72 (Ar–CH), 128.66 (Ar–CH), 128.26 (Ar–CH), 128.22 (Ar–CH), 128.18 (Ar–CH), 127.95 (Ar–CH), 127.88 (Ar–CH), 127.62 (Ar–CH), 124.17 (Ar–CH), 121.46 (Ar–CH), 117.20 (Ar–CH), 75.94 ($CH_2$), 70.86 ($CH_2$), 39.37 ($CH_2$), 37.19 ($CH_2$); FTIR (KBr) $\nu$ ($cm^{-1}$): 3379, 3064, 1688, 1576, 1453, 1273, 1200, 1056, 755, 741; APCI-MS: *m*/*z* $(M+1)^+$ = 491.

*2.4.9. Synthesis of N-(3-aminopropyl)-2,3-bis(benzyloxy)benzamide, TFA salt (**5b**)*

Using the same procedure as **5a**, **5b** was obtained as white solid (76%). $^1$H NMR (600 MHz, $CD_3OD$, 298.0 K) $\delta$ (ppm): 7.90 (br s, 1H, CO–NH), 7.49 (m, 1H, Ar–H), 7.45–7.10 (m, 12H, Ar–H), 5.19 (s, 2H, O–$CH_2$–Ar), 5.12 (s, 2H, O–$CH_2$–Ar), 3.33 (m, 2H, $CH_2$), 2.84 (t, *J* 7.2 Hz, 2H, $CH_2$), 1.78 (m, 2H, $CH_2$); $^{13}$C NMR (150 MHz, $CD_3OD$, 298.0 K) $\delta$ (ppm): 168.11 (C=O), 151.99 (Ar–C), 146.13 (Ar–C),

136.83 (Ar–CH), 128.53 (Ar–CH), 128.36 (Ar–CH), 128.26 (Ar–CH), 128.18 (Ar–CH), 128.15 (Ar–CH), 127.87 (Ar–CH), 127.62 (Ar–CH), 124.13 (Ar–CH), 121.19 (Ar–CH), 116.91 (Ar–CH), 75.77 ($CH_2$), 70.83 ($CH_2$), 36.74 ($CH_2$), 35.74 ($CH_2$), 27.32 ($CH_2$); FTIR (KBr) $\upsilon$ ($cm^{-1}$): 3345, 3064, 3032, 2971, 2929, 2852, 1712, 1679, 1665, 1576, 1528, 1454, 1261, 755; APCI-MS: $m/z$ $(M+1)^+$ = 505.

### 2.4.10. Synthesis of N-(4-aminobutyl)-2,3-bis(benzyloxy)benzamide, TFA salt (**5c**)

Using the same procedure as **5a**, **5b** was obtained as white solid (78%). $^1$H NMR (600 MHz, $CD_3OD$, 298.0 K) $\delta$ (ppm): 8.36 (br s, 1H, CO–NH), 7.48 (m, 1H, Ar–H), 7.45–7.10 (m, 12H, Ar–H), 5.16 (s, 2H, O–$CH_2$–Ar), 5.09 (s, 2H, O–$CH_2$–Ar), 3.30 (m, 2H, $CH_2$), 2.84 (t, $J$ 7.5 Hz, 2H, $CH_2$), 1.59 (m, 2H, $CH_2$), 1.47 (m, 2H, $CH_2$); $^{13}$C NMR (150 MHz, $CD_3OD$, 298.0 K) $\delta$ (ppm): 168.78 (C═O), 153.52 (Ar–C), 147.82 (Ar–C), 138.43 (Ar–CH), 138.26 (Ar–CH), 130.15 (Ar–CH), 129.89 (Ar–CH), 129.74 (Ar–CH), 129.68 (Ar–CH), 129.61 (Ar–CH), 129.34 (Ar–CH), 129.08 (Ar–CH), 125.63 (Ar–CH), 122.88 (Ar–CH), 118.52 (Ar–CH), 77.36 ($CH_2$), 72.53 ($CH_2$), 40.46 ($CH_2$), 39.93 ($CH_2$), 27.41 ($CH_2$), 26.01 ($CH_2$), 25.62 ($CH_2$); FTIR (KBr) $\upsilon$ ($cm^{-1}$): 3367, 3033, 2951, 2882, 1728, 1649, 1577, 1454, 1203, 757; APCI-MS: $m/z$ $(M+1)^+$ = 519.

### 2.4.11. Synthesis of N-(2-(2-aminoethoxy)ethanol)-2,3-bis(benzyloxy) benzamide (**6d**)

Using the same procedure as **4a**. Purification on silica gel (acetone:hexane, 2:3) afforded **6d** as yellow solid (90%). $R_f$ = 0.4. $^1$H NMR (600 MHz, $CDCl_3$, 298.0 K) $\delta$ (ppm): 8.01 (br s, 1H, CO–NH), 7.74 (m, 1H, Ar–H), 7.50–7.10 (m, 12H, Ar–H), 5.15 (s, 2H, O–$CH_2$–Ar), 5.08 (s, 2H, O–$CH_2$–Ar), 3.60–3.40 (m, 8H, $CH_2$); $^{13}$C NMR (150 MHz, $CDCl_3$, 298.0 K) $\delta$ (ppm): 165.50 (C═O), 151.93 (Ar–C), 146.85 (Ar–C), 136.55 (Ar–C), 128.98 (Ar–CH), 128.81 (Ar–CH), 128.72 (Ar–CH), 128.41 (Ar–CH), 127.85 (Ar–CH), 117.12 (Ar–CH), 76.39 ($CH_2$), 72.25 ($CH_2$), 71.41 ($CH_2$), 69.75 ($CH_2$), 61.78 ($CH_2$), 39.57 ($CH_2$); FTIR (KBr) $\upsilon$ ($cm^{-1}$): 3369, 3062, 3036, 2936, 2878, 2852, 1658, 1627, 1576, 1454, 1271, 757, 741; APCI-MS: $m/z$ $(M+1)^+$ = 422.

### 2.4.12. Synthesis of N,N′-bis(N″-(aminoethyl)-2,3-bis(benzyloxy) benzamido)malonamide (**7a**)

*N*-(aminoethyl)-2,3-bis(benzyloxy)-benzamide, TFA salt **5a** (1.96 g, 4 mmol) in 20 mL 1.25 M NaOH aqueous solution was stirred 20 min. $CH_2Cl_2$ extraction (20 mL × 3), the organic layer was dried over anhydrous $Na_2SO_4$, filtered, and evaporated to dryness to give *N*-(aminoethyl)-2,3-bis(benzyloxy)benzamide **6a** as clear oil (1.3 g, 87%). A mixture of malonyl dichloride (0.28 g, 2 mmol) and $Et_3N$ (0.2 g, 2 mmol) was dissolved in 20 mL $CH_2Cl_2$ and then dropped to a solution of **6a** in 20 mL $CH_2Cl_2$ under ice bath and vigorous stirring conditions. The stirring was maintained at room temperature for 5 h. Purification on silica gel (ethanol:$CH_2Cl_2$, 1:20) afforded **7a** as clear oil (1.34 g, 82%). $R_f$ = 0.5. $^1$H NMR (600 MHz, $CDCl_3$, 298.0 K) $\delta$ (ppm): 8.12 (t, $J$ 8.7 Hz, 2H, CO–NH), 7.65 (m, 2H, Ar–H), 7.50–7.23 (m, 22H, Ar–H), 7.13 (m, 2H, Ar–H), 5.14 (s, 4H, O–$CH_2$–Ar), 5.08 (s, 4H, O–$CH_2$–Ar), 3.34 (m, 4H, $CH_2$), 3.22 (m, 4H, $CH_2$), 2.97 (s, 2H, CO–$CH_2$–CO); $^{13}$C NMR (150 MHz, $CDCl_3$, 298.0 K) $\delta$ (ppm): 167.87 (C═O), 166.54 (C═O), 151.90 (Ar–C), 146.93 (Ar–C), 136.53 (Ar–CH), 129.89 (Ar–CH), 129.02 (Ar–CH), 128.98 (Ar–CH), 128.94 (Ar–CH), 128.88 (Ar–CH), 128.78 (Ar–CH), 128.47 (Ar–CH), 127.85 (Ar–CH), 127.24 (Ar–CH), 126.61 (Ar–CH), 124.64 (Ar–CH), 123.22 (Ar–CH), 117.37 (Ar–C), 76.63 ($CH_2$), 71.46 ($CH_2$), 42.99 ($CH_2$), 40.18 ($CH_2$), 39.19 ($CH_2$); FTIR (KBr) $\upsilon$ ($cm^{-1}$): 3296, 3065, 3032, 2934, 1666, 1637, 1576, 1533, 1497, 1450, 753, 731; APCI-MS: $m/z$ $(M+1)^+$ = 821.

### 2.4.13. Synthesis of N,N′-bis(N″-(aminopropyl)-2,3-bis(benzyloxy) benzamide)malonamide (**7b**)

Using the same procedure as **7a**. Purification on silica gel (ethanol:$CH_2Cl_2$, 1:20) afforded **7b** as clear oil (83%). $R_f$ = 0.5. $^1$H NMR (600 MHz, $CDCl_3$, 298.0 K) $\delta$ (ppm): 8.02 (t, $J$ 6.0 Hz, 2H, CO–NH), 7.67 (m, 2H, Ar–H), 7.70–7.20 (m, 22H, Ar–H), 7.13 (m, 2H, Ar–H), 5.15 (s, 4H, O–$CH_2$–Ar), 5.09 (s, 4H, O–$CH_2$–Ar), 3.28 (m, 4H, $CH_2$), 3.26–3.10 (m, 6H, $CH_2$ and CO–$CH_2$–CO), 1.49 (t, $J$ 6.3 Hz, 2H, $CH_2$); $^{13}$C NMR (150 MHz, $CDCl_3$, 298.0 K) $\delta$ (ppm): 167.58 (C═O), 166.06 (C═O), 151.91 (Ar–C), 147.06 (Ar–C), 136.63 (Ar–CH), 128.98 (Ar–CH), 128.95 (Ar–CH), 128.93 (Ar–CH), 128.89 (Ar–CH), 128.46 (Ar–CH), 127.85 (Ar–CH), 128.47 (Ar–CH), 127.85 (Ar–CH), 127.24 (Ar–CH), 126.61 (Ar–CH), 124.64 (Ar–CH), 123.22 (Ar–CH), 117.38 (Ar–C), 76.71 ($CH_2$), 71.58 ($CH_2$), 43.25 ($CH_2$), 36.83 ($CH_2$), 36.64 ($CH_2$), 29.56 ($CH_2$); FTIR (KBr) $\upsilon$ ($cm^{-1}$): 3368, 2980, 2936, 1686, 1530, 1479, 779; APCI-MS: $m/z$ $(M+1)^+$ = 849.

### 2.4.14. Synthesis of N,N′-bis(N″-(aminobutyl)-2,3-bis(benzyloxy) benzamide)malonamide (**7c**)

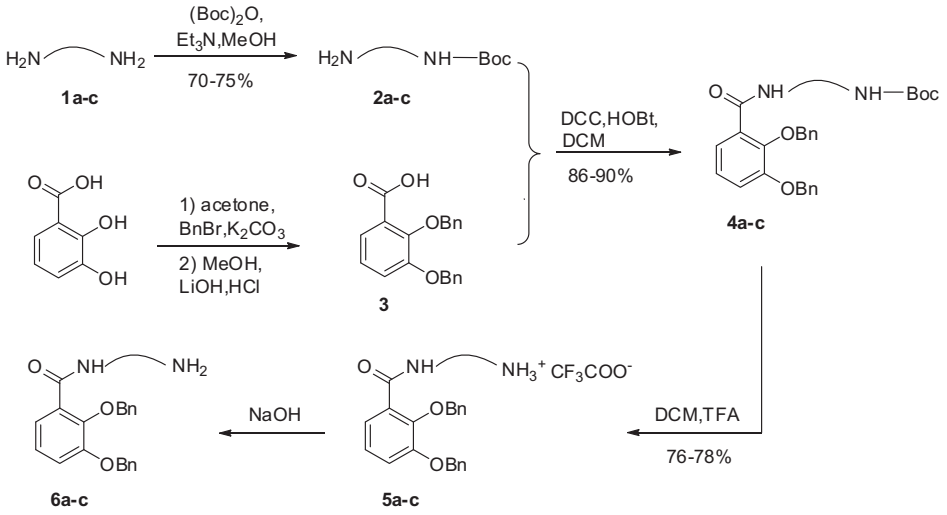
Using the same procedure as **7a**. Purification on silica gel (ethanol:$CH_2Cl_2$, 1:20) afforded **7c** as clear oil (81%). $R_f$ = 0.5. $^1$H NMR (600 MHz, $CDCl_3$, 298.0 K) $\delta$ (ppm): 7.89 (t, $J$ 5.4 Hz, 2H, CO–NH), 7.61 (m, 2H, Ar–H), 7.40–7.10 (m, 22H, Ar–H), 7.04 (m, 2H, Ar–H), 5.05 (s, 4H, O–$CH_2$–Ar), 4.99 (s, 4H, O–$CH_2$–Ar), 3.16 (m, 4H, $CH_2$), 3.10–3.00 (m, 6H, $CH_2$ and CO–$CH_2$–CO), 1.40–1.20 (m, 8H, $CH_2$); $^{13}$C NMR (150 MHz, $CDCl_3$, 298.0 K) $\delta$ (ppm): 167.57 (C═O), 165.44 (C═O), 151.89 (Ar–C), 147.00 (Ar–C), 136.63 (Ar–CH), 136.61 (Ar–CH), 128.92 (Ar–CH), 128.90 (Ar–CH), 128.87 (Ar–CH), 128.45 (Ar–CH), 127.85 (Ar–CH), 127.24 (Ar–CH), 126.61 (Ar–CH), 124.64 (Ar–CH), 123.22 (Ar–CH), 117.24 (Ar–C), 76.70 ($CH_2$), 71.52 ($CH_2$), 42.82 ($CH_2$), 39.40 ($CH_2$), 39.28 ($CH_2$), 27.17 ($CH_2$), 26.61 ($CH_2$); FTIR (KBr) $\upsilon$ ($cm^{-1}$): 3378, 3065, 3032, 2930, 2870, 1650, 1575, 1535, 1498, 1454, 755, 698; APCI-MS: $m/z$ $(M+1)^+$ = 877.

### 2.4.15. Synthesis of bis(2,3-bis(benzyloxy)-N-(2-(2-aminoethoxy) ethanol)benzamide)malonate (**7d**)

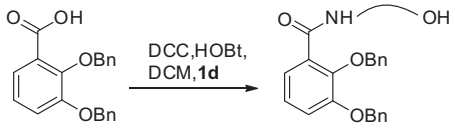
A mixture of malonyl dichloride (0.28 g, 2 mmol) and $Et_3N$ (0.2 g, 2 mmol) was dissolved in 20 mL $CH_2Cl_2$ and then dropped to a solution of **6d** (1.68 g, 4 mmol) in 20 mL $CH_2Cl_2$ under ice bath and vigorous stirring conditions. The stirring was maintained at room temperature for 5 h. Purification on silica gel (toluene:ethyl acetate, 1:1) afforded **7d** as clear oil (82%). $R_f$ = 0.6. $^1$H NMR (400 MHz, $CDCl_3$, 298.0 K) $\delta$ (ppm): 8.21 (br s, 2H, CO–NH), 7.69 (m, 2H, Ar–H), 7.50–7.10 (m, 24H, Ar–H), 5.13 (s, 4H, O–$CH_2$–Ar), 5.05 (s, 4H, O–$CH_2$–Ar), 4.07 (t, $J$ 4.8 Hz, 4H, $CH_2$), 3.55–3.40 (m, 12H, $CH_2$), 3.29 (s, 2H, $CH_2$); $^{13}$C NMR (150 MHz, $CDCl_3$, 298.0 K) $\delta$ (ppm): 166.54 (C═O), 165.50 (C═O), 151.94 (Ar–C), 146.78 (Ar–C), 136.52 (Ar–CH), 129.01 (Ar–CH), 128.82 (Ar–CH), 128.73 (Ar–CH), 128.67 (Ar–CH), 127.85 (Ar–CH), 117.02 (Ar–C), 76.32 ($CH_2$), 71.34 ($CH_2$), 69.61 ($CH_2$), 68.54 ($CH_2$), 64.48 ($CH_2$), 41.18 ($CH_2$), 39.60 ($CH_2$); FTIR (KBr) $\upsilon$ ($cm^{-1}$): 3399, 3366, 3063, 3032, 2933, 2872, 1758, 1732, 1657, 1576, 1533, 1454, 757, 698; APCI-MS: $m/z$ $(M+1)^+$ = 911.

### 2.4.16. Synthesis of N,N′-bis(N″-(aminoethyl)-2,3-bis(hydroxy) benzamide)malonamide (**8a**)

A mixture of **7a** (0.82 g, 1 mmol) and 10% Pd/C (200 mg) was dissolved in 50 mL THF (tetrahydrofuran) and stirred under $H_2$ (130 mL/min) atmosphere for 5 h. The resulting mixture was filtered over Celite, and the filtrate was concentrated in vacuo to give **8a** as clear oil (0.45 g, 99%). $^1$H NMR (600 MHz, $(CD_3)_2CO$, 298.0 K) $\delta$ (ppm): 13.01 (br s, 2H, Ar–OH), 8.40 (s, 2H, CO–NH), 7.96 (s, 2H, CO–NH), 7.72 (br s, 2H, Ar–OH), 7.24 (dd, $J$ 7.8 and 1.2 Hz, 2H, Ar–H), 6.96 (dd, $J$ 7.8 and 1.2 Hz, 2H, Ar–H), 6.71 (t, $J$ 7.8 Hz, 2H, Ar–H), 3.53 (m, 4H, $CH_2$), 3.47 (m, 4H, $CH_2$), 3.21 (s, 2H, CO–$CH_2$–CO); $^{13}$C NMR (150 MHz, $(CD_3)_2CO$, 298.0 K) $\delta$ (ppm):




**Scheme 3.** Synthetic routes for benzamides **6a**–**6c**.




**Scheme 4.** Synthesis of benzamide **6d**.

171.60 (C=O), 150.93 (Ar–C), 147.29 (Ar–C), 119.26 (Ar–CH), 119.02 (Ar–CH), 117.74 (Ar–CH), 115.36 (Ar–C), 40.50 ($CH_2$), 39.63 ($CH_2$), 30.71 ($CH_2$); FTIR (KBr) $\upsilon$ ($cm^{-1}$): 3323, 2945, 1644, 1589, 1545, 1489, 1459, 741; APCI-MS: $m/z$ $(M+1)^+$ = 461.

*2.4.17. Synthesis of N,N′-bis(N″-(3-aminopropyl)-2,3-bis(hydroxy) benzamide)malonamide (**8b**)*

Using the same procedure as **8a**, **8b** was obtained as clear oil (99%). $^1$H NMR (600 MHz, $(CD_3)_2CO$, 298.0 K) $\delta$ (ppm): 8.39 (s, 2H, CO–NH), 7.82 (s, 2H, CO–NH), 7.26 (dd, $J$ 7.8 and 1.2 Hz, 2H, Ar–H), 6.96 (dd, $J$ 7.8 and 1.2 Hz, 2H, Ar–H), 6.71 (t, $J$ 8.4 Hz, 2H, Ar–H), 3.47(m, 4H, $CH_2$), 3.37 (m, 4H, $CH_2$), 3.26 (s, 2H, CO–$CH_2$–CO), 1.78 (m, 4H, $CH_2$); $^{13}$C NMR (150 MHz, $(CD_3)_2CO$, 298.0 K) $\delta$ (ppm): 171.04 (C=O), 168.90 (C=O), 150.62 (Ar–C), 147.18 (Ar–C), 119.14 (Ar–CH), 119.09 (Ar–CH), 117.52 (Ar–CH), 115.49 (Ar–C), 36.99 ($CH_2$), 36.73 ($CH_2$), 34.99 ($CH_2$), 30.71 ($CH_2$); FTIR (KBr) $\upsilon$ ($cm^{-1}$): 3328, 2934, 1642, 1589, 1546, 1488, 1459, 787, 741; APCI-MS: $m/z$ $(M+1)^+$ = 489.

*2.4.18. Synthesis of N,N′-bis(N″-(4-aminobutyl)-2,3-bis(hydroxy) benzamide)malonamide (**8c**)*

Using the same procedure as **8a**, **8c** was obtained as clear oil (99%). $^1$H NMR (600 MHz, $(CD_3)_2CO$, 298.0 K) $\delta$ (ppm): 8.23 (s, 2H, CO–NH), 7.68 (s, 2H, CO–NH), 7.28 (dd, $J$ 8.4 and 1.2 Hz, 2H, Ar–H), 6.96 (dd, $J$ 7.8 and 1.2 Hz, 2H, Ar–H), 6.70 (t, $J$ 8.4 Hz, 2H, Ar–H), 3.44 (m, 4H, $CH_2$), 3.26 (m, 4H, $CH_2$), 3.12 (s, 2H, CO–$CH_2$–CO), 1.65 (m, 4H, $CH_2$), 1.57 (m, 4H, $CH_2$); $^{13}$C NMR (150 MHz, $(CD_3)_2CO$, 298.0 K) $\delta$ (ppm): 171.14 (C = O), 168.09 (C = O), 150.61 (Ar–C), 147.16 (Ar–C), 119.11 (Ar–CH), 118.99 (Ar–CH), 117.61 (Ar–CH), 115.49 (Ar–C), 39.64 ($CH_2$), 39.36 ($CH_2$), 30.70 ($CH_2$), 27.66 ($CH_2$), 27.25 ($CH_2$); FTIR (KBr) $\upsilon$ ($cm^{-1}$): 3366, 2933, 2870, 1641, 1589, 1546, 1486, 1459, 742; APCI-MS: $m/z$ $(M+1)^+$ = 517.

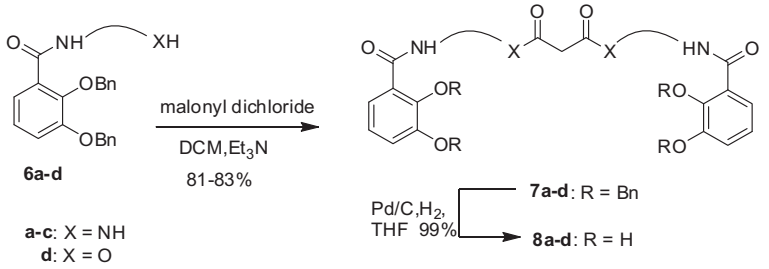
*2.4.19. Synthesis of bis(2,3-bis(hydroxy)-N-(2-(2-aminoethoxy) ethanol)benzamide)malonate (**8d**)*

Using the same procedure as **8a**, **8d** was obtained as clear oil (99%). $^1$H NMR (600 MHz, $(CD_3)_2CO$, 298.0 K) $\delta$ (ppm): 8.02 (s, 2H, CO–NH), 7.13 (dd, $J$ 7.8 and 1.8 Hz, 2H, Ar–H), 6.83 (dd, $J$ 7.8 and 1.8 Hz, 2H, Ar–H), 6.58 (t, $J$ 7.8 Hz, 2H, Ar–H), 4.10 (m, 4H, $CH_2$), 3.60–3.40 (m, 12H, $CH_2$), 3.28 (s, 2H, $CH_2$); $^{13}$C NMR (150 MHz, $(CD_3)_2CO$, 298.0 K) $\delta$ (ppm): 170.46 (C=O), 166.45 (C=O), 149.81 (Ar–C), 146.34 (Ar–C), 118.46 (Ar–CH), 118.24 (Ar–CH), 116.83 (Ar–CH), 114.57 (Ar–C), 68.93 ($CH_2$), 68.34 ($CH_2$), 64.21 ($CH_2$), 39.19 ($CH_2$), 39.07 ($CH_2$); FTIR (KBr) $\upsilon$ ($cm^{-1}$): 3390, 2956, 1747, 1641, 1487, 1459; APCI-MS: $m/z$ $(M+1)^+$ = 551.

## 3. Results and discussion

### 3.1. Synthesis and characterization of ligands *8a*–*8d*

In this work, the first step in ligand synthesis was protecting 2,3-dihydroxybenzoic acid. Diamines **1a**–**1c** reacted directly with 2,3-bis(benzyloxy)benzoic acid **3** to yield the main products *N,N′*-bis(2,3-bis(benzyloxy)benzamide) diamides rather than our




**Scheme 5.** General synthetic routes of biscatecholamide ligands **8a**–**8d**.

**Table 1**
Protonation constants ($\log K_i^H$) of the tetradentate ligands **8a**–**8d** and catechol for comparison.

| $\log K_i^H$ | **8a** | **8b** | **8c** | **8d** | Catechol[b] |
|---|---|---|---|---|---|
| $\log K_1^H$[a] | 11.80(2) | 11.70(1) | 11.47(2) | 12.37(3) | 13.0 |
| $\log K_2^H$ | 10.66(3) | 10.73(1) | 10.65(1) | 10.11(3) | 9.24 |
| $\log K_3^H$ | 8.49(1) | 8.08(3) | 8.36(2) | 7.36(1) | – |
| $\log K_4^H$ | 7.41(2) | 7.11(2) | 7.18(2) | 7.14(2) | – |

[a] $I$ = 0.1 M KCl, 25.0 ± 0.1 °C. $K_i^H = [H_iL]/([H_{i-1}L]\,[H])$.
[b] Ref. [34].

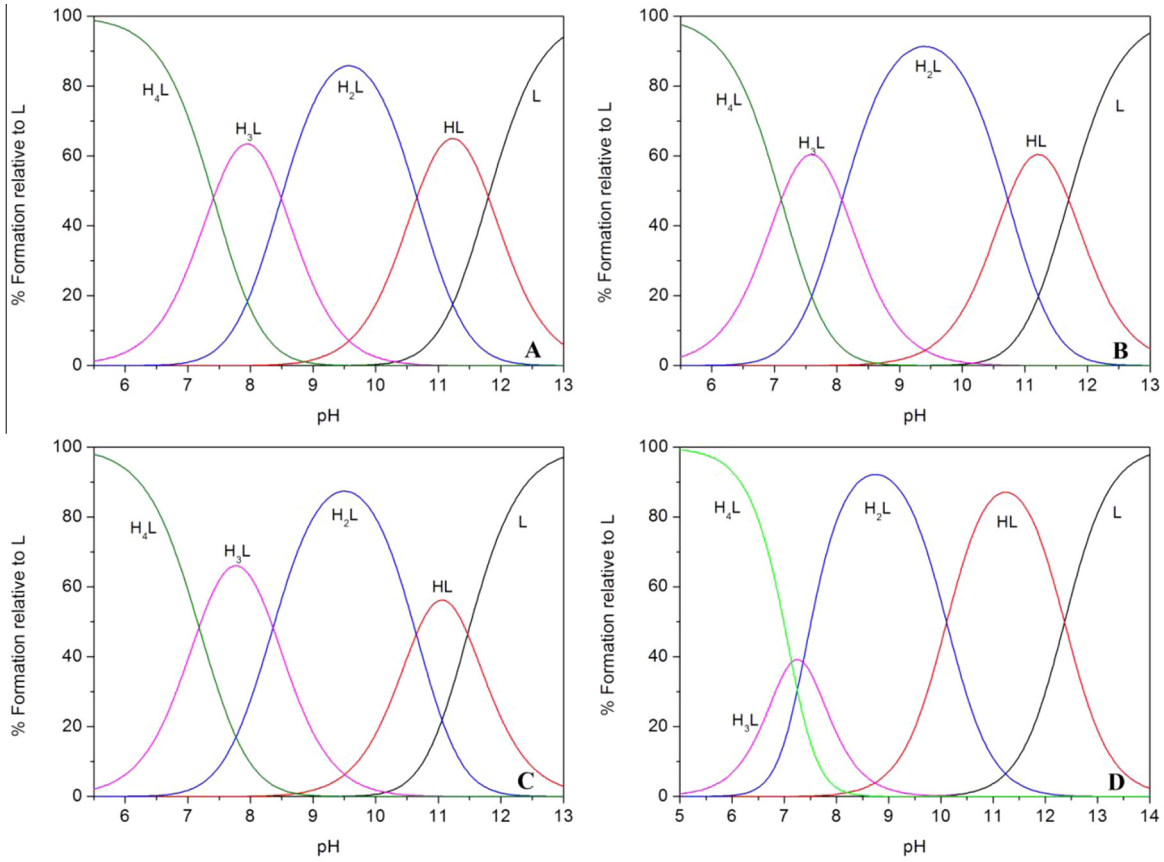


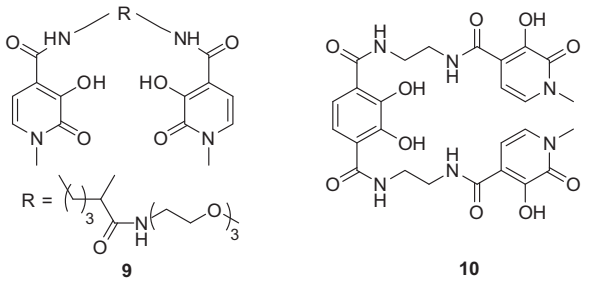

**Fig. 1.** Concentration distribution curves calculated for the free ligands in aqueous solution: ligands **8a** (A), **8b** (B), **8c** (C) and **8d** (D). $C_L = 2.0 \times 10^{-4}$ M.

**Table 2**
Global formation constants ($\log \beta_{pqr}$) for complexes of ligands **8a**–**8d** with $UO_2^{2+}$; pM values for these compounds and some relevant synthetic ligands at pH = 7.4.[a]

| (*p*, *q*, *r*) | $\log \beta_{pqr}$ | | | | | |
|---|---|---|---|---|---|---|
| | **8a** | **8b** | **8c** | **8d** | **9**[b] | **10**[c] |
| (1, −1, 1) | 21.54(3) | 20.11(1) | 20.83(2) | 22.02(3) | 6.97 | – |
| (1, 0, 1) | 27.76(2) | 29.07(2) | 26.74(2) | 28.83(2) | 13.9 | 21.95 |
| (1, 1, 1) | 32.66(2) | 35.06(2) | 31.90(3) | 34.04(2) | – | 26.86 |
| (1, 2, 1) | 35.68(3) | 37.87(3) | 34.55(3) | 37.02(4) | – | 30.79 |
| **$pUO_2$** | **20.85** | **21.51** | **20.68** | **22.41** | **15.39** | **19.2** |

[a] $I$ = 0.1 M KCl, 25.0 ± 0.1 °C. pM = −log[M] with $C_L/C_M$ = 10 and $C_M = 10^{-6}$ M. $\beta_{pqr} = [M_pH_qL_r]/([M]^p[H]^q[L]^r)$.
[b] Ref. [44].
[c] Ref. [45].

target molecules because of the same activity of the two terminal amines [7]. Thus, mono-protecting diamines **1a**–**1c** are necessary. The synthesis of **6a**–**6c** is shown in Scheme 3. First, mono-Boc protections of diamines **2a**–**2c** from commercially available diamines **1a**–**1c** were obtained. Then, *N*-Boc-diamines **2a**–**2c** were added into the mixture of 2,3-bis(benzyloxy)benzoic acid **3** and DCC/HOBt to yield the desired benzamides **4a**–**4c** in 86–90% yields. Benzamides **5a**–**5c** were generated using 20% trifluoroacetic acid/$CH_2Cl_2$ in an ice bath, and then 1.25 M NaOH aqueous solution was used to obtain the desired amides **6a**–**6c**.




**Scheme 6.** Molecular structure of ligands **9** and **10**.

Another route was used to obtain **6d** (Scheme 4) because amino has a greater nucleophilicity than hydroxyl. The addition of 2-(2-aminoethoxy)ethanol **1d** on 2,3-bis (benzyloxy) benzoic acid **3** in the presence of HOBt/DCC produced *N*-(2-(2-aminoethoxy) ethanol)-2,3-bis (benzyloxy)benzamide **6d** in good yield.

The synthesis of **8a**–**8d** is reported in Scheme 5. The addition of malonyl dichloride to benzamides **6a**–**6d** assisted by $Et_3N$ as the deacid reagent produced the biscatecholamide analogs **7a**–**7d** in 81–83% yield. Deprotection of the hydroxyl groups under typical benzyl group-removal catalytic hydrogenation conditions (room temperature, 130 mL/min $H_2$, atmospheric pressure, and Pd/C in THF produced **8a**–**8d** in 99% yield.

The structures of biscatecholamide ligands **8a**–**8d** were fully confirmed by their $^1$H NMR, $^{13}$C NMR, FTIR spectroscopy, UV–Vis spectrophotometry and mass spectrometry. Resonance signals of the catechol protons of symmetric biscatecholamides **8a**–**8d** were recorded in $(CD_3)_2CO$ solution using TMS as internal standard. The NMR, FTIR and mass spectra data of ligands **8a**–**8d** are listed in Experimental section. The UV–Vis spectra of ligands **8a**–**8d** were recorded in aqueous solution. All absorption bands of ligands $n \rightarrow \pi^*$ transitions range within 319–322 nm, and those of $\pi \rightarrow \pi^*$ transitions range within 208–214 nm and 246–249 nm, respectively.

### 3.2. Complexation studies

The complexation behavior of biscatecholamide ligands **8a**–**8d** was studied as follows. The measurements were carried out beyond the pH 3–11 range of the experiments, and the fitting analyses of the corresponding spectrophotometric titration curve by the HypSpec 2014 program and potentiometric titration curve by the Hyperquad 2013 program yielded the global protonation constants ($\log\beta$). These constants were used to calculate the stepwise protonation constants ($\log K_i^H$) presented in Table 1. The protonation constant for the previously reported catechol is also listed in this table for comparison. In neutral form, ligands **8a**–**8d** have four dissociable protons. The first two protonation constants are easily assigned to the *meta* hydroxyl groups, whereas the last two protonation constants are assigned to the *ortho* hydroxyl groups. Both the average $\log K_i^H$ values of the first two protonation constants and the last two protonation constants are lower than the two values of catechol. This result indicates that the obtained ligands **8a**–**8d** have slightly more acidic protonation constants than catechol. This acidifying effect can be explained by the electron-withdrawing effect of the amide carbonyl groups [43].

The concentration distribution of ligands **8a**–**8c** can be accomplished on the basis of the calculated protonation constants with

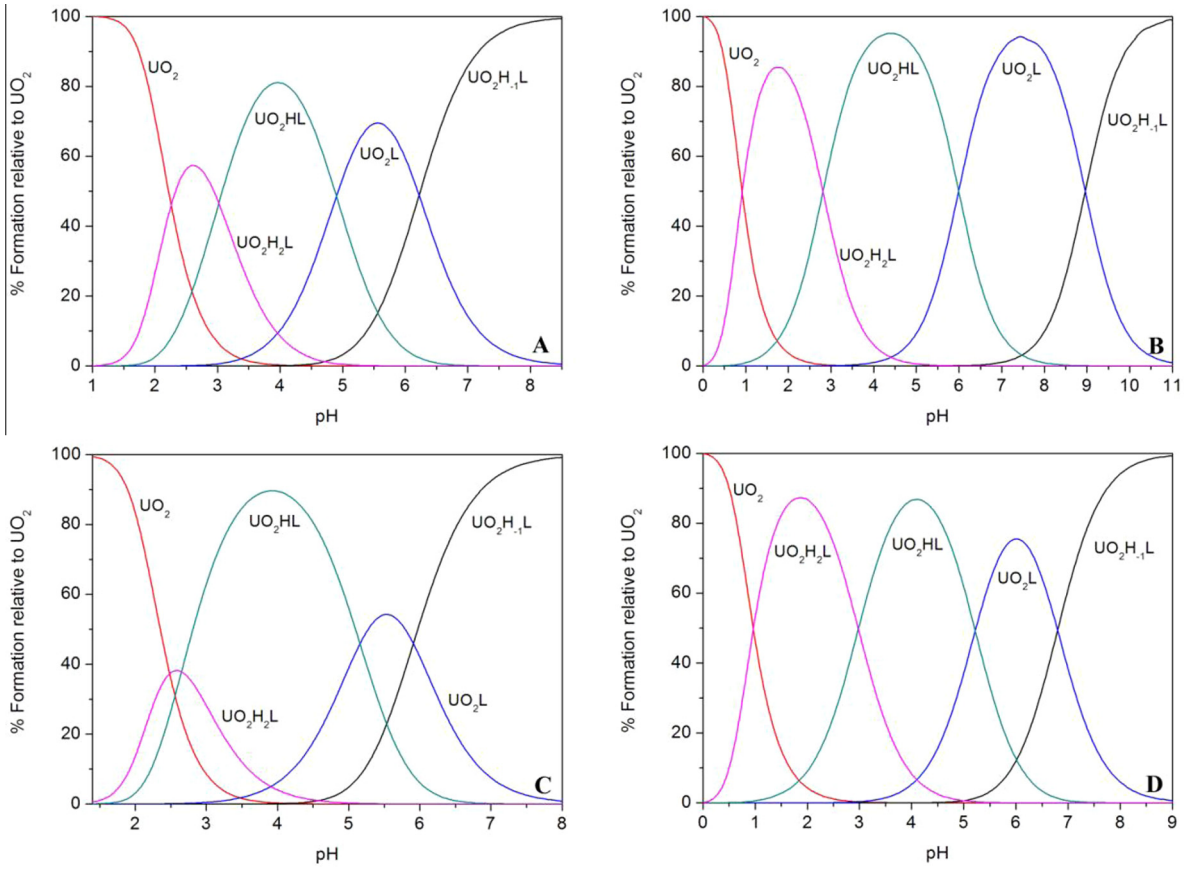
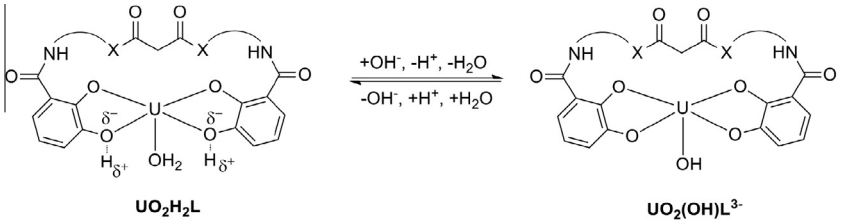



**Fig. 2.** Concentration distribution curves of the complexes formed in the system $UO_2^{2+}$-ligands **8a**–**8d** at a 1:1 metal-to-ligand ratio: $UO_2^{2+}$-ligands **8a** (A), **8b** (B), **8c** (C) and **8d** (D). $C_L = C_M = 1.852 \times 10^{-4}$ M.




**Scheme 7.** Proposed speciation in uranyl titrations with chelating agents **8a–8d** (Uranyl oxo atoms are omitted).

**Table 3**
Global formation constants ($\log\beta_{pqr}$) for complexes of ligands **8a–8d** with $Cu^{2+}$ and $Zn^{2+}$; pM values for these compounds at pH = 7.4.[a]

| | ($p$, $q$, $r$) | $\log\beta_{pqr}$ | | | |
|---|---|---|---|---|---|
| | | **8a** | **8b** | **8c** | **8d** |
| $[Cu_pH_qL_r]$ | (1, 0, 1) | 23.94(1) | 24.02(3) | 23.30(1) | 24.82(5) |
| | (1, 1, 1) | 29.40(2) | 29.45(2) | 28.65(3) | 30.04(3) |
| | (1, 3, 1) | 39.69(2) | 39.86(1) | 39.28(2) | 40.23(2) |
| | (1, 4, 1) | 44.20(2) | 43.65(1) | 43.28(1) | 44.07(3) |
| | **pCu** | **15.82** | **16.43** | **15.74** | **17.71** |
| $[Zn_pH_qL_r]$ | (1, 0, 1) | 15.48(2) | 14.37(1) | 14.35(2) | 13.97(3) |
| | (1, 1, 1) | 22.29(3) | 21.16(1) | 21.21(2) | 20.83(3) |
| | (1, 3, 1) | 35.57(1) | 34.65(2) | 34.65(3) | 34.14(2) |
| | **pZn** | **7.48** | **6.94** | **6.96** | **7.02** |

[a] $I$ = 0.1 M KCl, 25.0 ± 0.1 °C. pM = −log[M] with $C_L/C_M$ = 10 and $C_M = 10^{-6}$ M. $\beta_{pqr} = [M_pH_qL_r]/([M]^p[H]^q[L]^r)$.

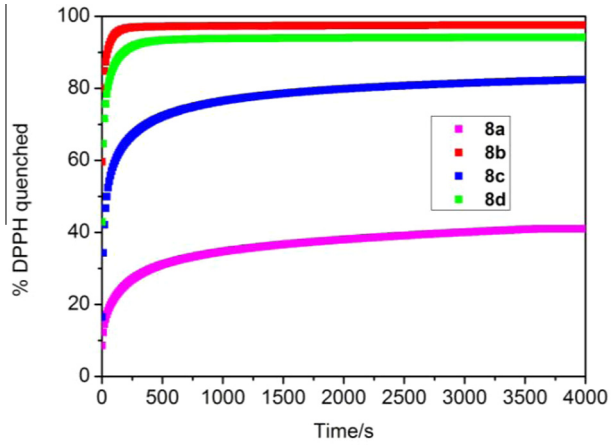



**Fig. 3.** Antioxidant results of **8a–8d** aqueous solutions determined by scavenging DPPH radical at 517 nm.

the Hyss program. As shown in Fig. 1, the major species of ligands **8a–8c** is $H_3L$ about 60% at the physiological pH. However, $H_3L$ of ligand **8d** at this pH is just 40%, which can be attributed to the different backbone.

The uranyl affinities of ligands **8a–8d** were determined by performing spectrophotometric titrations under experimental conditions. $UO_2^{2+}$ has two axial oxygen atoms and equatorial 4–6 sites, and commonly forms 1:1 species with tetradentate ligands [44,45]. Uranyl titrations were monitored using a 1:1 metal-to-ligand ratio and titration data were calculated using the HypSpec 2014 program with hydrolysis constants of $UO_2^{2+}$ [46], and the coordination stability constants of ligands **8a–8d** with $UO_2^{2+}$ at the physiological pH are listed in Table 2. Global formation constants ($\log\beta_{pqr}$) for complexes are species dependent, so it is difficult to compare the uranyl affinities. Thus, a species independent pM value is used. Studies of tetradentate catechol ligands with $UO_2^{2+}$ by using spectrophotometric titrations are rare in the literature. Table 2 listed the global formation constants and $pUO_2$ values of ligands **8a–8d** and reported tetradentate ligands **9** [42] and **10** [43] (Table 2 and Scheme 6). In general, a higher pM represents a lower concentration of uncomplexed metal ion in solution, which indicates that the corresponding metal ion and ligand exhibit a strong complexation ability. The pM values are calculated at standard conditions of [M] = $10^{-6}$ M and [L] = $10^{-5}$ M, and the minimum pM value is 6.0 while no metal complexing. As shown in Table 2, the $pUO_2$ values of ligands **8a–8d** are significantly higher than those of **9** and **10** at the physiological pH, which may be attributed to their low protonation constants. And it also reveals that the uranyl affinity is closely related to the structure of chelators.

The corresponding concentration distribution curves of the complexes formed in the system $UO_2^{2+}$-ligands **8a–8d** were plotted using the Hyss program with the global protonation constants ($\log\beta$) and global formation constants ($\log\beta_{pqr}$), as shown in Fig. 2. Upon deprotonation and uranyl coordination to form a $[UO_2H_2L]$ complexes at a low pH, amide carbonyl groups of ligands **8a–8d** gain a intramolecular hydrogen-bonding interaction with the *ortho* oxygen protons and the $UO_2^{2+}$ ion bonding two *ortho* oxygen donors while two *meta* hydroxyl groups remained. At pH 3–4, the $[UO_2HL]^-$ complexes display a rapid increase in the total metal concentration, indicating the formation of complexes with the simultaneous deprotonation of these ligands. Following generating $[UO_2L(H_2O)]^{2-}$ complexes, stepwise deprotonation was unreasonable. A partial hydrolysis of the uranyl center occurs upon increasing pH, resulting in a $[UO_2L(OH)]^{3-}$ species, which can be attributed to the switching of hydroxy and solvent in solution at the fifth equatorial coordination position on uranyl [44,45], and the proposed speciation is shown in Scheme 7.

The stability constants of ligands **8a–8d** with $Cu^{2+}$ and $Zn^{2+}$ were also investigated under the same experimental conditions, and the distribution curves are shown in Supporting Information (Figs. S13 and S14). The hydrolysis constants of $Cu^{2+}$ and $Zn^{2+}$ have also been taken into account according to the literature [47,48]. The global formation constants $\log\beta_{pqr}$ and the pM (M = $Cu^{2+}$ and $Zn^{2+}$) values for the complex of ligands **8a–8d** are listed in Table 3. The complexes for ligands **8a–8d** are four species with $Cu^{2+}$,

$[CuL]^{2-}$, $[CuHL]^{-}$, $[CuH_3L]^{+}$ and $[CuH_4L]^{2+}$, as well as three species with $Zn^{2+}$, $[ZnL]^{2-}$, $[ZnHL]^{-}$ and $[ZnH_3L]^{+}$ [31]. Concentration distribution curves show the formation of $[CuL]^{2-}$ complexes (≈100% at pH 7), $[CuHL]^{-}$ complexes (≈40% at pH 5.5), $[CuH_3L]^{+}$ complexes (≈60–80% at pH 4.5) and form $[CuH_4L]^{2+}$ complexes at a lower pH. The complexing affinities of ligands **8a–8d** for $Zn^{2+}$ are lower than $Cu^{2+}$, the complexes start to form at pH 3 and many $Zn^{2+}$ remained in the solution. The pCu values of ligands **8a–8d** are of the same order as $pUO_2$ values and the structures of **8a–8d** favor the effective coordination of $Cu^{2+}$. The pCu and pZn of ligands **8a–8d** are approximately 17 and 7 respectively, indicating that these ligands are also potential decorporations for copper(II) without the depletion of the essential element zinc in biological systems.

### 3.3. Antioxidant studies

The antioxidant results of **8a–8d** are shown in Fig. 3. Antioxidants (AOs) **8b** and **8d**, which are superior to the aminoalcohol backbone ligands we have studied previously,[30] achieved high percentages of DPPH quenched $\left(\frac{A_{DPPH}-A_{AOs}}{A_{DPPH}}\times 100\%\right)$ at 97.5% and 94.2%, respectively. Thus, the results confirm that 1,3-dicarbonyl biscatecholamide antioxidants can be used to scavenge free radicals generated by uranium.

## 4. Conclusions

New ligands **8a–8d** containing two catechol chelating units attached to a 1,3-dicarbonyl skeleton were prepared and characterized via $^{1}H$ NMR spectroscopy, $^{13}C$ NMR spectroscopy, FTIR spectroscopy and mass spectrometry. The complexation behaviors of the ligands toward uranyl ion, copper(II) and zinc were determined through spectrophotometric titrations, and the DPPH scavenging abilities of the ligands were assessed using UV–Vis spectrophotometry under the neutral pH. Results showed that ligands **8a–8d** presented a higher efficacy for uranyl ion than the tetradentate ligand **10** and aminoalcohol backbone ligands we previously reported. In addition, ligands **8b** and **8d** showed a high ratio of DPPH radical scavenged. These results indicate that 1,3-dicarbonyl biscatecholamide ligands **8b** and **8d** are potential bifunctional decorporating agents for uranyl ion and show strong free radical scavenging activities.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.poly.2016.09.006.

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