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Sequestering agent for uranyl chelation: a new family of CAMS ligands

Antoine Leydier [a], Delphine Lecercle [b], Stéphane Pellet-Rostaing [a,*], Alain Favre-Reguillon [a], Frédéric Taran [b], Marc Lemaire [a]

[a] Laboratoire de Catalyse et Synthèse Organique, ICBMS, Institut de Chimie et Biochimie Moléculaires et Supramoléculaires, CNRS, UMR 5246, Université Claude Bernard LYON-1, 69622 Villeurbanne, France
[b] Service de Chimie Bio-organique et de Marquage, iBiTec-S, CEA-Saclay 91191 Gif sur Yvette, France

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ABSTRACT

The synthesis of new dipodal bis-sulfocatecholamide uranophiles is presented. Their binding abilities for uranyl cation were determined by UV spectrophotometry in aqueous media under various pH conditions and further studied by ^{1}H NMR analysis of the resonance signal of both aromatic protons of the sulfocatecholamide groups. The results showed that the efficiency of these hydrosoluble chelating agents depends on the nature of the spacers. Each ligand shows a more or less pronounced affinity for uranium. The best receptor is the ligand CYCAMS **5d** obtained as a mixture of cis/trans isomers, which achieves the best compromise between rigidity and steric hindrance.

1. Introduction

Uranium is the second most common naturally occurring actinide (after thorium), and is more widely used than thorium. Uranium is most commonly used as nuclear fuel in fission reactors for civilian purpose. The hexavalent uranyl ion (UO_2^{2+}, U(VI)) was proved to be the most stable form in aqueous solutions and in vivo[1] at physiological pH.

When actinides such as uranium are introduced in the body in the case of internal contamination or in the event of a nuclear accident by ingestion, inhalation or through wounds, they are chelated in the blood by complexing agents such as proteins or carbonates. After chelation, toxic species are distributed and retained in target organs such as kidneys, liver or bones.[2] This can induce cancer and chemical intoxication in the case of heavy contamination.[3]

To avoid these effects, heavy metals must be eliminated from the body by administering non-toxic chelating agents. Non-toxic chelating agents can form highly stable complex so that the body can rapidly excrete the poison from blood and target organs. Furthermore, the uranyl-ligand complexes must be soluble and stable in physiological fluids in a pH range of 2–9 to be subsequently eliminated from the body after crossing the renal or hepatic barriers. Thus uranyl concentrations and radiation doses, and subsequently tumour risks may be reduced.

Although sought for many years, there are only a few ligands that are able to strongly bind U(VI) in vivo, promote its excretion and efficiently prevent or reduce deposition in kidneys and bones, the two main target organs of U(VI).

During the past 30 years, several effective uranyl ligands were synthesised, based on different complexing functions. Phosphorus containing molecules, especially bisphosphonates, were found to be very effective uranyl ligands,[4–7] but few significant decorporation works have been reported so far concerning the decorporation efficacy of EHBP.[8–11]

Decorporation with bidentate methylterphthalimide (MeTAM)-based chelating ligands was also studied, which did not suit for biological decorporation due to their high toxicity.[12]

Sulfocatechol Tiron, which forms a stable U(VI) complex within the physiological pH range,[13] was injected promptly, reducing significantly tissue uranium concentration in mice.[14] However, a molar ratio greater than 200 was required to reduce U(VI) deposition in kidneys, offering only modest encouragement with regard to its possible therapeutic potential.[15,16] Nevertheless, the modest successful reduction of acute U(VI) toxicity and reduction of body U(VI) with Tiron and the favourable stability constant of U(VI)–catechol ($\log K_{ML}$=15.9) suggested that multidentate ligands containing sulfocatecholamide (CAMS) or structurally analogous hydroxylpyridone (HOPO) units would be effective for in vivo chelation of U(VI).[17,18]

A rational design of uranyl-sequestering agents based on 3-hydroxy-2(1*H*)-pyridinone (3,2-HOPO) and sulfocatecholamide (CAMS) ligands resulted in the first effective agent for mammalian

* Corresponding author. Tel.: +33 (0) 4 72 44 85 07; fax: +33 (0) 4 72 43 14 08.
E-mail address: pellet@univ-lyon1.fr (S. Pellet-Rostaing).

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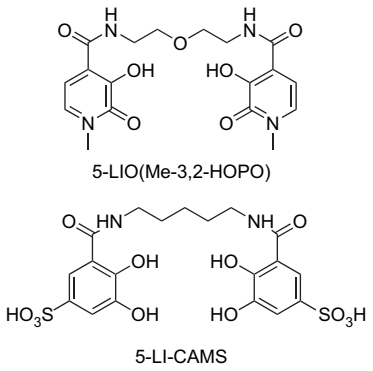


Figure 1. Low-toxicity uranyl complexants.

uranyl decorporation. Raymond found that both non-toxic ligands 5-LICAM(S) and 5-LIO(Me-3,2-HOPO) (Fig. 1) efficiently chelate circulating U(VI) in the body.[18] 5-LICAM(S) is able to divert to excretion a significant fraction of the U(VI) already deposited in bone when injected promptly (5–30 min) after contamination. Sufficient 5-LICAM(S) was orally bioavailable to reduce kidney U(VI),[12] but 5-LIO(Me-3,2-HOPO) was the most effective for the reduction of U(VI) in that organ.[18]

Structure–activity relationship[19] underscores that the linear tetradentate ligands were generally more effective for reducing whole body and kidney uranium than the higher denticity ligands with branched chains. The in vivo results also indicated that both the chain length and the number of the substituents on the linear aliphatic diamine linker of these tetradentate ligands play important roles in toxicity and in vivo U(VI) chelation efficiency. The best results were obtained with a five-unit backbone for low toxicity and high efficacy of U(VI) in vivo chelation.

So, our goal was to optimise these structures in order to increase the affinity of the ligand for the uranyl ion in physiological medium. Thus we present here the synthesis and the chelating properties of a family of CAMS derivatives containing different branched (**1b** and **c**), rigidified (**1d–g**) or chelating (**1h**) five-unit backbones.

The first part in this project involved the synthesis of a series of bis-catechol ligands linked by various substituted linear five-unit backbone diamines as platforms (Fig. 2).

Commercially available diamines **1a** and **1c**, racemic mixtures of branched diamines **1b** and **1h**, cis/trans isomers mixtures of cyclic diamine **1d** or **1g** and aromatic derivatives **1e–f** were selected as linker.

The second part concerned the comparative evaluation of the complexation constants with uranyl ions in water with 5-LICAM(S) as reference, using SCP method.[4]

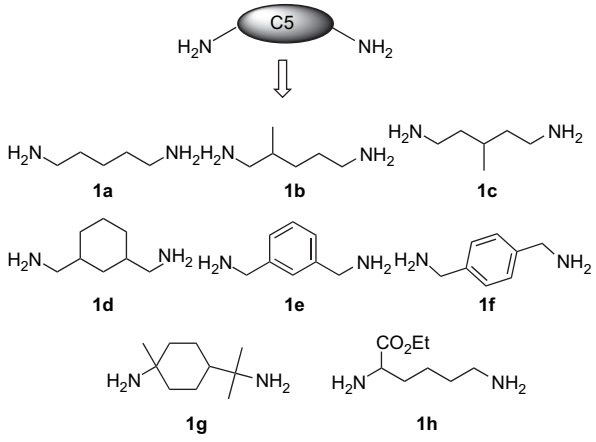
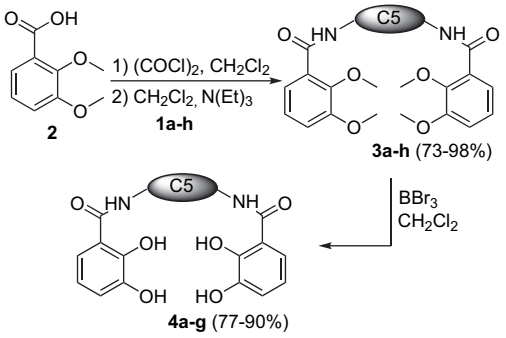


Figure 2. Diamine backbones.

2. Results and discussion

2.1. Synthesis

Based on Raymond's procedure,[18,19] the first step of the synthesis involved the reaction of an excess of oxalyl chloride with the protected catechol **2** in dichloromethane assisted by a catalytic amount of DMF to afford the corresponding acid chloride intermediate in a quantitative yield. Addition of the acid chloride on diamines **1a–h** in the presence of Et_3N gave the bis-catecholamides analogues **3a–h** in good yields (Scheme 1).

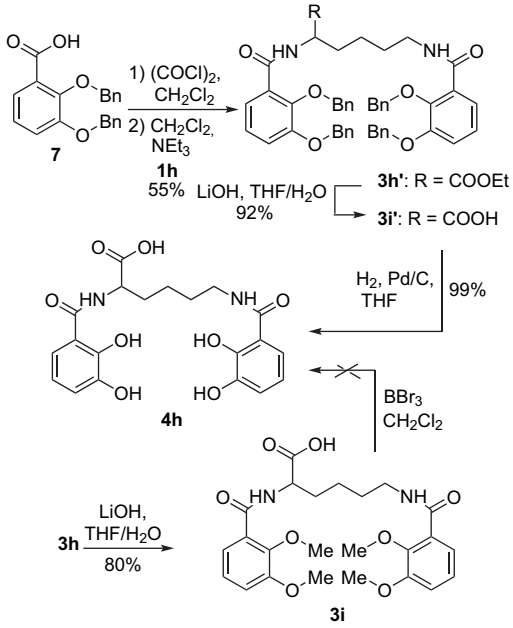


Scheme 1. General synthesis of CAMS derivatives.

Depending on the nature of the starting diamines, **3b** and **3h** were obtained as racemic mixtures of enantiomers and **3d** and **3g** as mixtures of cis/trans stereoisomers.

Deprotection of the hydroxyl groups was achieved using BBr_3 in dichloromethane rather than TMSI that often leads to partial conversions.[20]

However, total deprotection of catechol methoxy and ethyl ester could not be achieved when **1h** was used as backbone, even when the ester was first saponified (**3i**), decomposition products being recovered. In order to obtain the desired product **4h**, it was necessary to use benzylated catechol **7**, which can be deprotected under mild conditions (Scheme 2). Condensation of **7** with oxalyl



Scheme 2. Synthesis of LysCAM **4h**.

chloride and coupling with diamine **1h** afforded **3h**′ in 55% yield. Saponification followed by hydrogenolysis of **3h**′ led to **4h** as a racemic mixture of enantiomers in 91% overall yield.

Sulfonation of **4a–d** in 20% oleum followed by precipitation in diethylether gave the desired pure disulfonated compounds **5a–d** in good yields. Trisulfonated CAMS **5e** and **5f** were also obtained in good yields under these conditions. Unfortunately, these conditions caused the degradation of **4g** and **4h**. Compound **5h** was finally obtained by sulfonation in H_2SO_4 at 60 °C in 88% yield (Fig. 3).

Water-soluble CAMS ligands **5a–f**,**h** were fully characterised by ^{1}H NMR, ^{13}C NMR, mass spectroscopy and elemental analyses. Resonance signals of the catechol protons of symmetrical 5-LICAMS **5a** and 3-MeCAMS **5c** in D_2O were, respectively, identified as two doublets at 7.32 ppm and 7.62 ppm (J=2.08 Hz) and two singlets at 7.27 ppm and 7.57 ppm.

Aromatic protons of **5b** were characterised by a broad doublet at 7.28 ppm and two overlapped doublets at 7.58 ppm and 7.59 ppm demonstrating the expected dissymmetry of the structure of the ligand. Dissymmetric **5h** ligand was also characterised by a well defined spectrum with two pairs of doublets at 7.64/7.54 ppm and 7.27/7.24 ppm corresponding to the aromatic protons. A cis/trans isomer mixture of CYCAMS **5d** in an 80:20 ratio was confirmed by the presence of two pairs of doublets located at 7.36 ppm and 7.64 ppm (J=1.9 Hz) and at 7.31 ppm and 7.62 ppm (J=2.07 Hz). Dissymetric structures of *m*-BENZCAMS **5e** and *p*-BENZCAMS **5f** were established on the basis of 2D COSY experiments. Thus aromatic protons of the catechol moiety of **5f** were observed as two overlapped doublets at 7.23 ppm (J=2.08 Hz) and two doublets at 7.59 ppm and 7.55 ppm (J=2.08 Hz). Resonance signals of the aromatic protons of the central ring were observed as a singlet at 7.74 ppm and a large multiplet at 7.31 ppm. Finally, aromatic protons of catechol moiety of **5e** were observed as two overlapped doublets at 7.27 ppm (J=2.07 Hz) and two doublets at 7.58 ppm and 7.64 ppm (J=2.07 Hz). A doublet at 7.83 ppm (J=8.3 Hz), a broad singlet at 7.63 ppm and a multiplet at 7.30 ppm were allocated to the resonance signals of protons of the central aromatic ring.

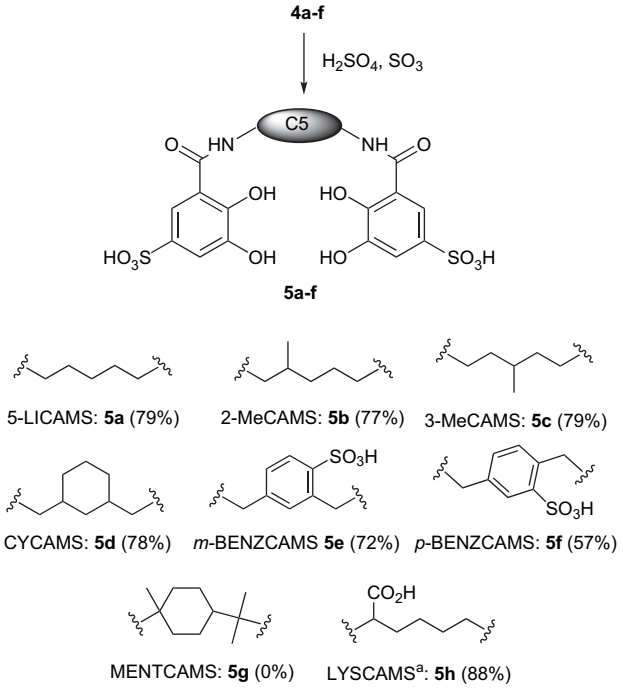


Figure 3. Sulfonation of CAM analogues ([a]H_2SO_4, 60 °C).

2.2. Complexation studies

The complexation behaviour of the water-soluble CAMS– derivatives **5a–f**,**h** towards uranyl cation was studied by the spectrophotometric method developed by Taran et al.,[4] based on competitive uranium binding by using sulfochlorophenol SCP as chromogenic chelate, which was found highly suitable for a rapid screening of putative uranium ligand library.

Comparison of the results obtained with dipodal bis-catecholamides **5a–f** showed the influence of the nature of the spacer separating the two chelating moieties. Globally, the CAMS ligands exhibit high K_{cond} enhancement in basic conditions in accordance with the previous findings.[21] The best uranyl-binding performance independent of pH was observed with CYCAMS **5d** (Table 1). At pH 5.5, all CAMS derivatives showed better constant than the reference 5-LICAMS **5a**[18] except LysCAMS **5h**, which was not able to displace more than 10% of the SCP/UO_2 complex.[4] Whatever the pH, aromatic CAMS **5e** and **5f** exhibited lower complexation efficiency towards UO_2^{2+} suggesting that these ligands are too rigid.

The ability of ligands **5a–d** to complex UO_2^{2+} was also studied by ^{1}H NMR spectroscopy. Figure 4 shows the NMR spectra of variable amount of uranyl nitrate hexahydrate in the presence of LICAMS **5a** and CYCAMS **5d** in a binary mixture of D_2O/NaOD at room temperature with sodium nitrate (0.05 mol L^{-1}). After each addition of $UO_2(NO_3)_2\cdot 6H_2O$, the pH of the deuterated solution was adjusted to 12 by addition of NaOD. In the absence of uranyl nitrate, the doublets assigned to the H_1 and H_2 protons of the catechol moieties of **5a** shifted from 7.32 ppm and 7.62 ppm in D_2O to 6.85 ppm and 7.49 ppm in D_2O/NaOD (Fig. 4a and a_1). Both pairs of doublets at 7.36/7.64 ppm and 7.31/7.62 ppm in D_2O corresponding to the resonance signals of the catechol protons of the cis/trans mixture of **5d** shift as two overlapped doublets at 6.88 ppm and 7.51 ppm in D_2O/NaOD (Fig. 4b and b_1). Addition of increasing amount of $UO_2(NO_3)_2\cdot 6H_2O$ (Fig. 4a_2–a_5 and 4b_2–b_5) led to appreciable changes and downfield shifts of the aromatic proton resonances of the phenol rings (Table 2). Upon addition of $UO_2(NO_3)_2\cdot 6H_2O$ in a deuterated solution containing **5a**, two new doublets appear, respectively, at 7.09 ppm and 7.68 ppm (Fig. 4a_2–a_4), whose signal intensities ($\Delta\delta$=0.24 ppm and 0.19 ppm) depend on the concentration of the ligand. Similarly, the changes in the level of the signals of the protons of the alkyl chains were also indicative due to the proximity of the uranyl cation nearby the altered protons. Thus, the triplet at 3.45 ppm assigned to the $CH_2NC(O)$ protons of the free ligand was located at 3.62 ppm and both multiplets corresponding to the resonance signals of $CH_2CH_2CH_2$ chain shift from 1.57 ppm and 1.72 ppm to 1.89 ppm as a broad singlet.

When uranyl nitrate hexahydrate was added to a deuterated solution of **5d**, we assumed that UO_2^{2+} was simultaneously chelated by cis and trans stereoisomers, based on the appearance of two doublets at 7.64 ppm ($\Delta\delta$=0.13 ppm) and 7.70 ppm ($\Delta\delta$=0.19 ppm) of similar integration corresponding to the resonance signals of the H_1 protons of the uranyl complexes (Fig. 4b_2). Resonance signals of H_2 shifts from 6.88 ppm to 7.10 ppm ($\Delta\delta$=0.22 ppm) as two overlapped doublets.

Table 1
K_{cond} of ligand–UO_2^{2+} at several pH values (±0.1)

pH	log K_{cond} (U–L)/(pH)		
	5.5	7.4	9.0
SCP[4]	13.4	19.7	25.5
5-LICAMS (**5a**)	11.1	17.0	19.4
2-MeCAMS (**5b**)	11.3	16.6	18.7
3-MeCAMS (**5c**)	11.5	16.8	18.6
CYCAMS (**5d**)	*11.7*	*17.5*	*19.6*
m-BENZCAMS (**5e**)	11.4	16.5	18.5
p-BENZCAMS (**5f**)	11.2	16.3	17.8
LysCAMS (**5h**)	<9	16.6	18.9

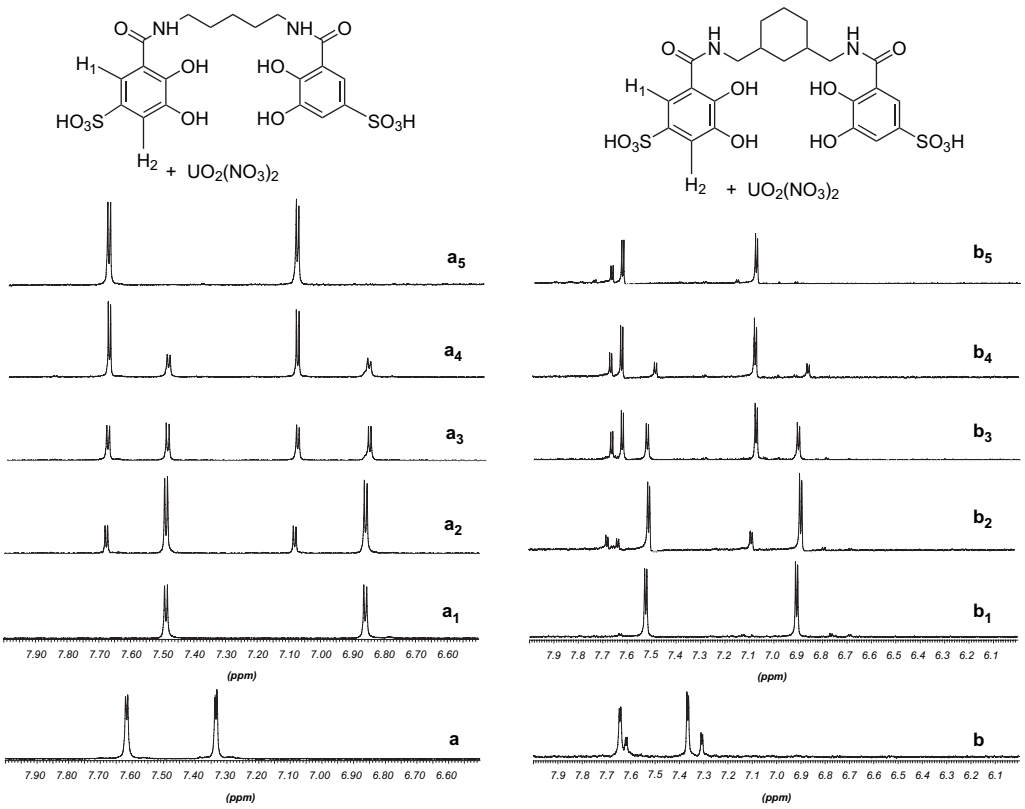


Figure 4. ^{1}H NMR spectra of **5a** (a: in D_2O, a_1: in D_2O/NaOD/$NaNO_3$ (0.05 mol L^{-1})) and **5d** (b: in D_2O, b_1: in D_2O/NaOD/$NaNO_3$ (0.05 mol L^{-1})) in the presence of various amounts of $UO_2(NO_3)_2{\cdot}6H_2O$ at pH 12 (a_2, b_2: 0.25 equiv; a_3, b_3: 0.5 equiv; a_4, b_4: 0.75 equiv; a_5, b_5: 1 equiv) at 238 K.

Table 2
Changes in the ^{1}H NMR aromatic shifts of **5a–d** and **5h** upon addition of $UO_2(NO_3)_2{\cdot}6H_2O$ (1 equiv) in D_2O/NaOD

L	H_2	H_1	L–UO_2	H_2	H_1
5a	6.85	7.49	**5a**–U	7.09	7.68
5b[a]	6.83 (6.83)	7.46 (7.46)	**5b**–U	7.06 (7.07)	7.67 (7.68)
5c	6.90	7.53	**5c**–U	7.10	7.72
5d[b]	6.88 (6.88)	7.51 (7.51)	**5d**–U	7.10 (7.10)	7.64 (7.70)
5h[a]	6.86 (6.87)	7.48 (7.49)	**5h**–U	7.10 (7.12)	7.69 (7.70)

[a] Chemical shift of H_1 and H_2 in dissymmetric structures.
[b] Chemical shift of the minor stereoisomer.

Finally, whatever the ligands **5a–d** and **5h** be, the 1:1 stoichiometry of the uranyl complexes was confirmed by the total disappearance of the two resonance signals of H_1 and H_2 protons of the free ligands without appearance of new resonance signals (Fig. 4a_5 and b_5).

3. Conclusion

The newly synthesised dipodal bis-catecholamide uranophiles **5a–f**,**h** were obtained by an efficient synthetic route from different diamines. Their binding abilities for uranyl cation were determined by UV spectrophotometry in aqueous media under acidic, neutral as well as basic pH conditions. These experiments showed that the efficiency of these hydrosoluble chelating agents depends on the nature of the spacers. The best uranophile ligand was found to be CYCAMS **5d** obtained as a mixture of cis/trans isomers, which displays association constants log *K* up to 17 under physiological conditions. These binding properties were found significantly superior than those observed with 5-LICAMS, a well known ligand that displays in vivo uranyl removal capabilities. Separation of CYCAMS isomers and evaluation of their in vivo efficiency are planned in the near future.

4. Experimental section

4.1. General

All the organic reagents used were pure commercial products from Aldrich, Acros, Fluka, Avocado and Lancaster & Maybridge except **1c**. This diamine was obtained by a Mitsunobu-like azidation of the commercial corresponding diol[22] followed by reduction. (2,3)-Dibenzyloxybenzoic acid,[23,24] *N*,*N*′-bis(2,3-dihydroxy-5-sulfonylbenzoyl)-1,5-diamino pentane (**5a**),[18,25] *N*,*N*′-[1,3-phenylenebis(methylene)]-bis-(2,3-dihydroxy benzamide) (**4e**)[26] and *N*,*N*′-(1,4-[3-(sulfophenylene)bis(methylene)]-bis-(2,3-dihydroxy-5-sulfonylbenzoyl)) (**5f**)[27] were synthesised as previously described. The solvents were purchased from Carlo Erba, Acros, Pro-Labo, Fluka and Aldrich. Anhydrous solvents were obtained from Acros; anhydrous THF and dry CH_2Cl_2 were distilled in the laboratory. Flash chromatography was carried out on Merck Silica Si60 (40–63 μm). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-200 (200.13 MHz for ^{1}H, 50.32 MHz for ^{13}C) or AC-300 FT (300.13 MHz for ^{1}H, 75.46769 MHz for ^{13}C) spectrometer; δ values are given in parts per million and *J* in hertz. Elemental analysis (C, H, N, S, O, F) was carried out by the Service Central d'Analyse of the CNRS (Solaize). High resolution mass spectra: HR LSIMS (Liquid Secondary Ionisation Mass Spectrometry: thioglycerol), HR CIMS (isobutan) and HR EIMS were carried out on a Finnegan MAT 95xL by the UCBL Centre de Spectroscopie de Masse.

4.2. 3-Methyl-(1,5)-diazopentane

DBU (6 mL, 42.5 mmol) was added dropwise to 2.03 g of 3-methyl-1,5-pentanediol (17.1 mmol) and 8.5 mL of diphenylphosphoryl azide (39.4 mmol) in 40 mL of dry DMF under argon at 0 °C. The mixture was allowed to rise to room temperature and heated at 65 °C for 16 h. The mixture was evaporated, the residue was

dissolved in 100 mL of dichloromethane and extracted subsequently with 2×50 mL of 1 M HCl, 2×50 mL of water, 100 mL of brine, dried over $MgSO_4$, filtered, evaporated and purified by silica gel column chromatography (cyclohexane/EtOAc 95:5) to give pure 3-methyl-(1,5)-diazopentane (2.21 g, 76%) as clear oil. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ=3.31 (m, 4H), 1.62 (m, 4H), 1.46 (m, 1H), 0.94 (d, J=6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ=49.6, 35.9, 28.3, 19.3.

4.3. 3-Methyl-(1,5)-diaminopentane (1c)

$LiAlH_4$ (0.6 g, 15.8 mmol) was carefully added to a solution of 0.94 g of 3-methyl-1,5-diazopentane (5.6 mmol) in 40 mL of freshly distilled THF under argon at 0 °C. The mixture was allowed to raise to room temperature and stirred for 16 h. The reaction mixture was cooled to 0 °C, 2 mL of water and then 4 mL NaOH were added slowly. The resulting precipitate was filtrated over Celite, washed with THF (100 mL) and solvents were removed under vacuum to give **1c** (0.6 g, 92%) as translucent oil. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ=2.66 (m, 4H), 1.26–1.38 (m, 5H), 0.88 (d, J=6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ=41.6, 40.4, 28.6, 20.0.

4.4. General procedure for the synthesis of compounds 3a–h

Oxalyl chloride (1.5 equiv) was added dropwise to a solution of 2,3-dimethoxybenzoic acid (1 equiv) or 2,3-dibenzyloxybenzoic acid (1 equiv) in the required volume of dry CH_2Cl_2. After adding a drop of dry DMF, the mixture was stirred until the end of HCl release. After evaporation of solvents and residual oxalyl chloride, the residue was dissolved in dry CH_2Cl_2 and added dropwise to a solution of **1a**–**h** (0.5 equiv) and triethylamine (1.1 equiv) in the required volume of dry CH_2Cl_2. After 18 h under stirring, the mixture was washed with water (2×50 mL), brine (50 mL), then dried over $MgSO_4$ and evaporated to dryness. The residue was purified by flash chromatography (SiO_2) to give **3a**–**h** (73–98%).

4.4.1. N,N′-(1,5-Pentane)bis(2,3-dimethoxybenzamide) (*3a*)

Compound **3a** was obtained from oxalyl chloride (4.8 mL, 55.8 mmol), 2,3-dimethoxybenzoic acid (5.79 g, 31.78 mmol) in CH_2Cl_2 (20 mL), 1,5-diaminopentane **1a** (1.62 g, 15.88 mmol) and 4.9 mL of triethylamine (35.2 mmol) in 20 mL of dry CH_2Cl_2. Purification on silica gel (EtOAc/cyclohexane 1:2) afforded **3a** (6.7 g, 98%) as yellow oil.[25,18] R_f 0.16. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ=8.02 (br s, 2H), 7.66 (dd, J=6.2, 2.2 Hz, 2H), 7.13 (m, 2H), 7.03 (dd, J=5.9, 2.2 Hz, 2H), 3.81 (s, 12H), 3.42–3.51 (m, 4H), 1.64–1.69 (m, 4H, 1.77), 1.50–1.53 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ=165.5, 152.9, 147.7, 127.3, 124.8, 123.1, 115.6, 61.6, 56.4, 39.9, 29.7, 24.9. HR ESIMS calculated for $C_{23}H_{30}N_2O_6 \cdot H^+$=453.2002; found=453.20006. Anal. Calcd (%) for $C_{23}H_{30}N_2O_6$: C, 64.17; H, 7.02; N, 6.51; O, 22.30. Found: C, 64.21; H, 7.09; N, 6.40.

4.4.2. N,N′-[1,5-(2-Methylpentane)]-bis-(2,3-dimethoxy benzamide) (*3b*)

Compound **3b** was obtained from oxalyl chloride (1.1 mL, 12.8 mmol), 2,3-dimethoxybenzoic acid (1.55 g, 8.5 mmol) in CH_2Cl_2 (15 mL), DITEK A **1b** (0.468 g, 4 mmol) and 1.2 mL of triethylamine (8.5 mmol) in 30 mL of dry CH_2Cl_2. Purification on silica gel (EtOAc) afforded **3b** (1.7 g, 95%) as yellow oil. R_f 0.63. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ=8.03 (br s, 2H), 7.62 (dd, J=6, 1.9 Hz, 2H), 6.88–7.09 (m, 4H), 3.85 (s, 12H), 3.26–3.43 (m, 4H), 2.11 (m, 1H), 1.27–1.79 (m, J=1.77 Hz, 4H), 0.97 (d, J=6.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ=165.6, 152.8, 147.6, 127.2, 124.7, 122.9, 115.5, 61.6, 56.4, 45.7, 40.1, 33.5, 32.1, 27.4, 18.1. HR ESIMS calculated for $C_{24}H_{32}N_2O_6 \cdot Na^+$=467.2158; found=453.2159. Anal. Calcd (%) for $C_{24}H_{32}N_2O_6$: C, 64.85; H, 7.26; N, 6.30; O, 21.60. Found: C, 64.93; H, 7.30; N, 6.17.

4.4.3. N,N′-Bis(2,3-dimethoxybenzoyl)-3-methyl-(1,5) diaminopentane (*3c*)

Compound **3c** was obtained from oxalyl chloride (1.6 mL, 18.6 mmol), 2,3-dimethoxybenzoic acid (2.19 g, 12 mmol) in CH_2Cl_2 (20 mL), 3-methylpent-(1,5)-diamine **1c** (0.64 g, 5.5 mmol) and 3.4 mL of triethylamine (24.2 mmol) in 30 mL of dry CH_2Cl_2. Purification on silica gel (EtOAc) afforded **3c** (1.79 g, 73%) as yellow oil. R_f 0.50. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ=7.90 (br s, 2H), 7.53 (dd, J=7.9, 1.7 Hz, 2H), 6.89–7.02 (m, 4H), 3.76 (s, 12H), 3.38–3.44 (m, 4H), 1.39–1.61 (m, 4H), 1.13 (m, 1H, 1.77), 0.93 (d, J=5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ=165.5, 152.8, 147.6, 127.2, 124.6, 122.8, 115.5, 61.5, 56.3, 37.9, 36.8, 29.0, 19.6. HR ESIMS calculated for $C_{24}H_{32}N_2O_6 \cdot Na^+$=467.2158; found=453.2158. Anal. Calcd (%) for $C_{24}H_{32}N_2O_6$: C, 64.85; H, 7.26; N, 6.30; O, 21.60. Found: C, 64.95; H, 7.41; N, 6.05.

4.4.4. N,N′-Bis(2,3-dimethoxybenzamido)-cyclohexane-(1,3)-bismethylamine (*3d*)

Compound **3d** was obtained from oxalyl chloride (1.1 mL, 12.6 mmol), 2,3-dimethoxybenzoic acid (1.57 g, 8.6 mmol) in CH_2Cl_2 (15 mL), (1,3)-cyclohexane-bis-(methylamine) **1d** (0.6 g, 4.2 mmol) and 1.4 mL of triethylamine (10 mmol) in 30 mL of dry CH_2Cl_2. Purification on silica gel (EtOAc) afforded **3d** (1.91 g, 97%) as an 80:20 mixture of cis (**3d$_1$**) and trans (**3d$_2$**) diastereoisomers. R_f 0.63. HR ESIMS calculated for $C_{26}H_{35}N_2O_6^+$=471.2495; found=471.2494. Anal. Calcd (%) for $C_{26}H_{34}N_2O_6$: C, 66.36; H, 7.28; N, 5.95; O, 20.40. Found: C, 66.26; H, 7.67; N, 5.67. *NMR data for the major stereoisomer* ***3d$_1$***. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ=7.99 (br t, 2H), 7.55 (dd, J=7.9, 1.7 Hz, 2H), 7.01 (t, J=7.9 Hz, 4H), 6.91 (dd, J=7.9, 1.7 Hz, 2H), 3.74 (s, 12H), 3.21 (br t, 4H), 1.68–1.73 (m, 3H), 1.53–1.55 (m, 3H), 1.11–1.29 (m, 2H), 0.82–0.89 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ=165.5, 152.8, 147.6, 127.2, 124.7, 122.9, 115.6, 61.6, 56.4, 46.2, 38.1, 35.5, 31.1, 25.7. *NMR data for the minor stereoisomer* ***3d$_2$***. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ=7.91 (br t, 2H), 7.52 (dd, J=7.9, 1.7 Hz, 2H), 6.99 (t, J=7.9 Hz, 4H), 6.91 (dd, J=7.9, 1.7 Hz, 2H), 3.72 (s, 12H), 3.30 (br t, 4H), 1.68–1.73 (m, 3H), 1.42–1.44 (m, 3H), 1.11–1.29 (m, 2H), 0.64–0.70 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ=165.5, 152.8, 147.6, 127.1, 124.7, 122.9, 115.6, 61.64, 56.4, 44.0, 33.3, 33.1, 29.7, 20.6.

4.4.5. N,N′-[1,3-Phenylenebis(methylene)]bis-(2,3-dimethoxy benzamide) (*3e*)

Compound **3e** was obtained from oxalyl chloride (1 mL, 11.6 mmol), 2,3-dimethoxybenzoic acid (1.5 g, 8.2 mmol) in CH_2Cl_2 (15 mL), *m*-xylenediamine **1e** (0.537 g, 3.9 mmol) and 1.2 mL of triethylamine (8.5 mmol) in 30 mL of dry CH_2Cl_2. Purification on silica gel (EtOAc) afforded **3e** (1.77 g, 97%) as yellow oil.[27] R_f 0.71. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ=8.37 (br s, 2H), 7.73 (dd, J=7.9, 1.7 Hz, 2H), 7.32 (m, 4H), 7.16 (t, J=8.1 Hz, 2H), 6.98 (dd, J=8.3, 1.7 Hz, 2H), 4.68 (d, J=5.6 Hz, 4H), 3.89 (s, 6H), 3.84 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ=165.6, 152.9, 147.9, 139.5, 129.4, 127.2, 127.0, 126.9, 124.8, 123.1, 115.8, 61.6, 56.4, 44.0. HR ESIMS calculated for $C_{26}H_{29}N_2O_6^+$=465.2026; found=465.2026. Anal. Calcd (%) for $C_{24}H_{32}N_2O_6$: C, 67.23; H, 6.08; N, 6.03; O, 20.67. Found: C, 67.21; H, 6.19; N, 5.93.

4.4.6. N,N′-[1,4-Phenylenebis(methylene)]bis(2,3-dimethoxy benzamide) (*3f*)

Compound **3f** was obtained from oxalyl chloride (1.8 mL, 13 mmol), 2,3-dimethoxybenzoic acid (3.24 g, 17.8 mmol) in CH_2Cl_2 (30 mL), *p*-xylenediamine **1f** (1.21 g, 8.9 mmol) and 5.2 mL of triethylamine (37.4 mmol) in 30 mL of dry CH_2Cl_2. Purification on silica gel (EtOAc/cyclohexane 1:2) afforded **3f** (1.77 g, 97%) as white solid.[28] R_f 0.35. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ=8.37 (t, J=5.4 Hz, 2H), 7.53 (dd, J=7.9, 1.7 Hz, 2H), 7.21 (s, 4H), 6.97 (t, J=8.1 Hz, 2H), 6.87 (dd, J=8.3, 1.7 Hz, 2H), 4.51 (d, J=5.6 Hz), 3.70 (s, 6H), 3.68 (s,

6H). ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ=165.5, 152.9, 147.7, 138.1, 128.2, 127.1, 124.7, 122.9, 115.7, 61.6, 56.3, 43.7. HR ESIMS calculated for $C_{26}H_{29}N_2O_6^+$=465.2026; found=465.2028. Anal. Calcd (%) for $C_{24}H_{32}N_2O_6$: C, 67.23; H, 6.08; N, 6.03; O, 20.67. Found: C, 67.35; H, 6.11; N, 5.88.

4.4.7. *N,N′-Bis(2,3-dimethoxybenzoyl)-(1,8)-diamido-p-menthane (**3g**)*

Compound **3g** was obtained from oxalyl chloride (1.7 mL, 19.8 mmol), 2,3-dimethoxybenzoic acid (3.22 g, 17.7 mmol) in CH_2Cl_2 (30 mL), 1,8-diamino-*p*-menthane **1g** (70% pure, 2.1 g, 8.8 mmol) and 2.7 mL of triethylamine (19.4 mmol) in 30 mL of dry CH_2Cl_2. Purification on silica gel (EtOAc/cyclohexane 1:2) afforded **3g** (4.08 g, 93%) as a mixture of cis/trans diastereoisomers. R_f 0.83. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ=7.80 (br s, 1H), 7.74 (br s, 1H), 7.52 (m, 2H), 7.00–7.05 (m, 2H), 6.89–6.94 (m, 2H), 3.75–3.83 (m, 12H), 2.05–2.30 (m, 3H), 1.59–1.63 (m, 2H), 1.20–1.37 (m, 13H). ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ=165.5, 164.1, 152.9, 152.8, 147.5, 147.4, 128.2, 128.1, 124.8, 124.7, 122.8, 122.7, 115.4, 115.3, 61.7, 61.6, 56.5, 56.5, 56.4, 53.3, 44.7, 37.4, 27.8, 24.7, 23.2. HR ESIMS calculated for $C_{28}H_{38}N_2O_6Na^+$=521.2628; found=521.2629. Anal. Calcd (%) for $C_{28}H_{38}N_2O_6$: C, 67.45; H, 7.68; N, 5.62; O, 19.25. Found: C, 67.55; H, 7.78; N, 5.42.

4.4.8. *Ethyl-(N,N′)-2,6-bis(2,3-dimethoxybenzamido) hexanoate (**3h**)*

Compound **3h** was obtained from oxalyl chloride (2.3 mL, 26.7 mmol), 2,3-dimethoxybenzoic acid (3.3 g, 18.1 mmol) in CH_2Cl_2 (25 mL), ethyl-2,6-diaminohexanoate dihydrochloride **1h** (2.12 g, 9 mmol) and 6.3 mL of triethylamine (45.3 mmol) in 50 mL of dry CH_2Cl_2. Purification on silica gel (EtOAc/cyclohexane 1:2) afforded **3h** (3.46 g, 76%) as yellow oil. R_f 0.43. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ=8.62 (d, J=7.7 Hz, 1H), 7.92 (m, 1H), 7.52–7.57 (m, 2H), 6.90–7.02 (m, 4H), 4.74 (m, 1H), 4.08–4.15 (q, J=7.1 Hz), 3.73–3.85 (m, 12H), 3.31–3.38 (q, J=6.2 Hz, 4H), 1.74–1.88 (m, 2H), 1.56–1.61 (m, 2H), 1.32–1.41 (m, 2H), 1.12–1.29 (m, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ=172.6, 165.5, 165.0, 153.0, 152.9, 148.1, 147.7, 127.1, 126.3, 124.6, 123.7, 122.9, 122.8, 117.3, 116.0, 115.6, 61.8, 61.7, 61.5, 56.5, 56.4, 52.7, 39.7, 32.6, 29.5, 23.1, 14.5. HR ESIMS calculated for $C_{26}H_{35}N_2O_8^+$=525.2213; found=525.2212. Anal. Calcd (%) for $C_{26}H_{34}N_2O_8$: C, 62.14; H, 6.82; N, 5.57; O, 25.47. Found: C, 62.38; H, 6.75; N, 5.40.

4.4.9. *Ethyl-(N,N′)-2,6-bis(2,3-bis(benzyloxy)benzamido) hexanoate (**3h′**)*

Compound **3h′** was obtained from oxalyl chloride (4 mL, 46 mmol), 2,3-dibenzyloxybenzoic acid **7** (8.3 g, 24.8 mmol) in CH_2Cl_2 (50 mL), ethyl-2,6-diaminohexanoate dihydrochloride **1h** (3 g, 12.1 mmol) and 8 mL of triethylamine (57.1 mmol) in 50 mL of dry CH_2Cl_2 and 50 mL of dry MeCN. Purification on silica gel (EtOAc/cyclohexane 1:2) afforded **3h′** (5.37 g, 55%) as yellow oil. R_f 0.38. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ=8.38 (d, J=7.5 Hz, 1H), 7.78 (m, 1H), 7.60–7.64 (m, 2H), 7.16–7.35 (m, 20H), 7.01–7.07 (m, 4H), 4.95–5.17 (m, 8H), 4.48 (m, 1H), 4.04–4.10 (q, J=6.6 Hz, 2H), 3.00–3.06 (m, 2H), 1.30–1.56 (m, 2H), 1.10–1.28 (m, 7H). ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ=172.6, 165.7, 165.4, 152.2, 152.1, 147.4, 147.2, 136.9, 136.8, 136.7, 136.4, 129.7, 129.6, 129.4, 129.3, 129.2, 129.1, 128.9, 128.8, 128.7, 128.6, 128.3, 128.2, 127.1, 126.5, 125.4, 124.8, 124.7, 123.7, 119.3, 117.6, 117.3, 76.8, 76.5, 71.9, 71.7, 61.6, 53.1, 39.8, 32.1, 29.2, 23.5, 14.7. HR ESIMS calculated for $C_{50}H_{51}N_2O_8^+$=807.3645; found=807.3647. Anal. Calcd (%) for $C_{50}H_{50}N_2O_8$: C, 74.42; H, 6.25; N, 3.47; O, 15.86. Found: C, 74.56; H, 6.27; N, 3.31.

4.4.10. *(N,N′)-2,6-Bis(2,3-bis(benzyloxy)benzamido) hexanoic acid (**3i′**)*

A mixture of **3h′** (5.01 g, 6.2 mmol) and lithium hydroxide (1 g, 23.8 mmol) in THF/water (3:1) (120 mL) was stirred for 18 h and evaporated to dryness. Distilled water (50 mL) was added and the pH was adjusted to 1 with 3 N HCl. The mixture was extracted with 3×50 mL of CH_2Cl_2. The combined organic phases were combined, extracted with 2×100 mL of distilled water, 100 mL brine, dried over $MgSO_4$, filtered and evaporated to dryness to give **3i′** as a white powder (4.46 g, 92%).[28] ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ=10.7 (br s, 1H), 8.47 (d, J=7.4 Hz, 1H), 7.85 (m, 1H), 7.54–7.64 (m, 2H), 6.99–7.30 (m, 24H), 4.89–5.10 (m, 8H), 4.50–4.54 (m, 1H), 2.99–3.04 (m, 2H), 1.32–1.61 (m, 2H), 1.10–1.28 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ=175.6, 166.0, 165.8, 152.2, 152.1, 147.9, 147.5, 136.8, 136.7, 136.6, 136.4, 129.7, 129.5, 129.4, 129.3, 129.2, 129.0, 128.9, 128.8, 128.7, 128.6, 128.2, 128.1, 127.5, 126.9, 125.3, 124.9, 124.6, 123.7, 119.4, 117.5, 117.2, 76.9, 76.7, 71.8, 71.7, 53.1, 40.0, 31.7, 29.2, 23.4. HR ESIMS calculated for $C_{48}H_{46}N_2O_8Na^+$=801.3152; found=801.3153. Anal. Calcd (%) for $C_{48}H_{46}N_2O_8$: C, 74.02; H, 5.95; N, 3.60; O, 16.43. Found: C, 74.13; H, 6.11; N, 3.33.

4.4.11. *(N,N′)-2,6-Bis(2,3-dimethoxybenzamido)hexanoic acid (**3i**)*

A mixture of **3h** (2.28 g, 4.54 mmol) and lithium hydroxide (0.95 mg, 22.6 mmol) in THF/water (3:1) (40 mL) was stirred for 18 h and evaporated to dryness. Distilled water (50 mL) was added and the pH was adjusted to 1 with 3 N HCl. The mixture was extracted with 3×50 mL of CH_2Cl_2. The combined organic phases were combined, extracted with 2×50 mL of distilled water, 50 mL brine, dried over $MgSO_4$, filtered and evaporated to dryness to give **3i** as a white powder (1.73 g, 80%). ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ=9.79 (br s, 1H), 8.81 (d, J=7.5 Hz, 1H), 8.07 (m, 1H), 7.59–7.67 (m, 2H), 6.97–7.08 (m, 4H), 4.80–4.86 (m, 1H), 3.80–3.89 (m, 12H), 3.40–3.42 (q, J=6.2 Hz, 4H), 1.86–2.04 (m, 2H), 1.59–1.63 (m, 2H), 1.47–1.52 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ=175.0, 166.0, 165.5, 153.0, 152.9, 148.3, 147.8, 126.9, 126.2, 124.8, 124.7, 123.1, 123.0, 116.1, 115.8, 62.0, 61.7, 56.5, 56.4, 52.9, 40.0, 32.5, 29.6, 23.1. HR ESIMS calculated for $C_{24}H_{30}N_2O_8Na^+$=497.1900; found=497.1904. Anal. Calcd (%) for $C_{24}H_{30}N_2O_8\cdot CH_2Cl_2$: C, 53.67; H, 5.40; N, 5.01; O, 22.88. Found: C, 53.71; H, 5.70; N, 4.68.

4.5. General procedure for the synthesis of compounds 4a–g

To a solution of **3a**–**g** (1 equiv) in dry CH_2Cl_2 was added dropwise a solution of BBr_3 (6–7 equiv) in dry CH_2Cl_2 under deep stirring at 0 °C. The resulting white solution was stirred overnight and the mixture was then carefully poured into crushed ice under heavy stirring until complete hydrolysis. The resulting precipitate was collected by filtration, washed with cold water (3×50 mL) and CH_2Cl_2 and dissolved in methanol. Precipitation with water and filtration afforded pure **4a**–**g**, which were dried under vacuum.

4.5.1. *N,N′-Bis(2,3-dihydroxybenzoyl)-1,5-diaminopentane (**4a**)*

Compound **4a** was obtained from **3a** (6.67 g, 15.56 mmol) in CH_2Cl_2 (200 mL) and BBr_3 (25 mL, 99 mmol) in CH_2Cl_2 (100 mL). Compound **4a** was obtained as a white powder (4.49 g, 77%).[18] ^{1}H NMR (DMSO-d_6, 300 MHz, 25 °C): δ=12.9 (s, 2H), 9.13 (s, 2H), 8.78 (br s, 2H), 7.29 (dd, J=8.1, 1 Hz, 2H), 6.90 (dd, J=8.1, 1 Hz, 2H), 6.70 (t, J=8.1 Hz, 2H), 3.29–3.27 (br q, 4H), 1.60–1.56 (m, 4H), 1.37–1.33 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ=170.1, 150.1, 146.6, 119.1, 118.2, 117.4, 115.2, 39.2, 28.9, 24.2. HR ESIMS calculated for $C_{19}H_{22}N_2O_6\cdot Na^+$=397.1376; found=397.13762. Anal. Calcd (%) for $C_{19}H_{22}N_2O_6$: C, 60.95; H, 5.92; N, 7.48; O, 25.64. Found: C, 60.92; H, 6.28; N, 7.16.

4.5.2. *N,N′-Bis(2,3-dihydroxybenzoyl)-2-methyl-1,5-diamino pentane (**4b**)*

Compound **4b** was obtained from **3b** (3.8 g, 8.56 mmol) in CH_2Cl_2 (120 mL) and BBr_3 (5.5 mL, 58 mmol) in CH_2Cl_2 (60 mL). Compound **4b** was obtained as a white powder (2.82 g, 85%). ^{1}H NMR (CD_3OD, 300 MHz, 25 °C): δ=8.43 (br s, 2H), 7.23 (d, J=7.5 Hz,

1H), 7.21 (d, J=7.5 Hz, 1H), 6.94 (d, J=7.5 Hz, 2H), 6.69 (t, J=7.5 Hz, 2H), 3.19–3.41 (m, 4H), 1.12–1.85 (m, 5H), 0.98 (d, J=8.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ=171.9, 151.0, 147.6, 119.7, 119.5, 117.4, 115.9, 46.9, 41.2, 34.7, 33.1, 28.2, 18.5. HR ESIMS calculated for $C_{20}H_{24}N_2O_6\cdot Na^+$=411.1533; found=411.1533. Anal. Calcd (%) for $C_{20}H_{24}N_2O_6$: C, 61.85; H, 6.23; N, 7.21; O, 24.71. Found: C, 61.95; H, 6.31; N, 7.03.

4.5.3. *N,N′-Bis-(2,3-dihydroxybenzoyl)-3-methyl-1,5-diamino pentane (**4c**)*

Compound **4a** was obtained from **3c** (1.75 g, 3.94 mmol) in CH_2Cl_2 (100 mL) and BBr_3 (2.4 mL, 25.4 mmol) in CH_2Cl_2 (80 mL). Compound **4c** was obtained as a white powder (1.19 g, 78%). ^{1}H NMR (CD_3OD, 300 MHz, 25 °C): δ=7.20 (d, J=7.9 Hz, 2H), 6.92 (m, J=7.9 Hz, 2H), 6.70 (t, J=7.9 Hz, 2H), 3.30–3.46 (m, 5H), 1.49–1.74 (m, 4H), 1.04 (d, J=5.7 Hz, 3H, CH–CH_3). ^{13}C NMR (CD_3OD, 75 MHz, 25 °C): δ=171.9, 150.6, 147.7, 120.0, 119.9, 119.1, 117.2, 38.9, 37.7, 30.1, 20.2. HR ESIMS calculated for $C_{20}H_{24}N_2O_6\cdot Na^+$=411.1533; found=411.1532. Anal. Calcd (%) for $C_{20}H_{24}N_2O_6$: C, 61.85; H, 6.23; N, 7.21; O, 24.71. Found: C, 62.14; H, 6.18; N, 6.97.

4.5.4. *N,N′-Bis(2,3-dihydroxybenzamido)-cyclohexane-(1,3)-bismethylamine (**4d**)*

Compound **4a** was obtained from **3d** (1.65 g, 3.94 mmol) in CH_2Cl_2 (40 mL) and BBr_3 (2.2 mL, 23.2 mmol) in CH_2Cl_2 (40 mL). Compound **4d** was obtained as an 80:20 mixture of cis (**4d$_1$**) and trans (**4d$_2$**) diastereoisomers (1.36 g, 90%). HR ESIMS calculated for $C_{22}H_{26}N_2O_6Na^+$=437.1689; found=437.1691. Anal. Calcd (%) for $C_{22}H_{26}N_2O_6$: C, 63.76; H, 6.32; N, 6.76; O, 23.16. Found: C, 63.87; H, 6.39; N, 6.58. *NMR data for the major stereoisomer **4d$_1$**.* ^{1}H NMR (CD_3OD, 300 MHz, 25 °C): δ=7.22 (dd, J=7.9, 1.1 Hz, 2H), 6.94 (dd, J=7.9, 1.1 Hz, 2H), 6.71 (t, J=7.9 Hz, 2H), 3.22 (d, J=8.4 Hz, 4H), 1.41–1.78 (m, 6H), 1.10–1.29 (m, 2H), 0.86–0.92 (m, 2H). ^{13}C NMR (CD_3OD, 75 MHz, 25 °C): δ=171.9, 164.1, 150.3, 147.7, 120.2, 120.1, 119.3, 117.3, 47.3, 39.3, 36.7, 32.2, 26.9. *NMR data for the minor stereoisomer **4d$_2$**.* ^{1}H NMR (CD_3OD, 300 MHz, 25 °C): δ=7.19 (dd, J=7.9, 1.1 Hz, 2H), 6.93 (dd, J=7.9, 1.1 Hz, 2H), 6.9 (t, J=7.9 Hz, 2H), 3.32 (d, J=8.4 Hz, 4H), 1.41–1.78 (m, 6H), 1.10–1.29 (m, 2H), 0.64–0.72 (m, 2H). ^{13}C NMR (CD_3OD, 75 MHz, 25 °C): δ=171.9, 164.1, 150.3, 147.7, 120.2, 120.1, 119.3, 117.3, 45.0, 34.5, 33.6, 30.9, 22.4.

4.5.5. *N,N′-[1,3-Phenylenebis(methylene)]-bis-(2,3-dihydroxy benzamide) (**4e**)*

Compound **4a** was obtained from **3e** (1.7 g, 3.66 mmol) in CH_2Cl_2 (40 mL) and BBr_3 (2.1 mL, 22.2 mmol) in CH_2Cl_2 (40 mL). Compound **4e** was obtained as a brown powder (1.36 g, 90%).[27] ^{1}H NMR (CD_3OD, 300 MHz, 25 °C): δ=7.22–7.37 (m, 6H), 6.92–6.96 (dd, J=7.9, 1.5 Hz, 2H), 6.69–6.74 (t, J=8 Hz, 2H), 4.59 (m, 4H). ^{13}C NMR (CD_3OD, 75 MHz, 25 °C): δ=171.9, 150.7, 147.6, 140.5, 130.4, 127.9, 120.4, 120.3, 119.4, 117.1, 44.5. HR ESIMS calculated for $C_{22}H_{20}N_2O_6\cdot Na^+$=431.1219; found=431.1222. Anal. Calcd (%) for $C_{22}H_{20}N_2O_6$: C, 64.70; H, 4.94; N, 6.86; O, 23.51. Found: C, 64.77; H, 5.04; N, 6.68.

4.5.6. *N,N′-[1,4-Phenylenebis(methylene)]-bis-(2,3-dihydroxy benzamide) (**4f**)*

Compound **4a** was obtained from **3f** (2.3 g, 4.95 mmol) in CH_2Cl_2 (150 mL) and BBr_3 (2.8 mL, 29.6 mmol) in CH_2Cl_2 (100 mL). Compound **4f** was obtained as a brown powder, which was dried under vacuum (1.7 g, 84%).[27] ^{1}H NMR (DMSO-d_6, 300 MHz, 25 °C): δ=9.28 (t, J=5.6 Hz, 2H), 7.30 (dd, J=8, 1.4 Hz, 2H), 7.25 (s, 4H), 6.87 (m, 2H), 6.65 (t, J=7.9 Hz, 2H), 4.44 (d, J=5.8 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ=170.0, 150.0, 146.6, 138.0, 127.7, 119.3, 118.4, 117.6, 115.3, 42.5. HR ESIMS calculated for $C_{22}H_{20}N_2O_6\cdot Na^+$=431.1219; found=431.1220. Anal. Calcd (%) for $C_{22}H_{20}N_2O_6$: C, 64.70; H, 4.94; N, 6.86; O, 23.51. Found: C, 64.81; H, 5.07; N, 6.62.

4.5.7. *N,N′-Bis(2,3-dihydroxybenzoyl)-(1,8)-diamido-p-menthane (**4g**)*

Compound **4a** was obtained from **3g** (1.7 g, 3.66 mmol) in CH_2Cl_2 (40 mL) and BBr_3 (2.1 mL, 22.2 mmol) in CH_2Cl_2 (40 mL). Compound **4g** was obtained as a brown powder, which was dried under vacuum (1.36 g, 90%). ^{1}H NMR (CD_3OD, 300 MHz, 25 °C): δ=7.17–7.26 (m, 2H), 6.85–6.90 (m, 2H), 6.63–6.70 (m, 2H), 2.09–2.42 (m, 3H), 1.55–1.70 (m, 2H), 1.24–1.45 (m, 13H). ^{13}C NMR (CD_3OD, 75 MHz, 25 °C): δ=170.4, 170.1, 164.2, 164.1, 149.2, 148.7, 147.5, 147.4, 120.6, 120.4, 120.2, 119.8, 119.6, 119.3, 58.7, 55.1, 45.6, 38.0, 28.2, 25.1, 24.2. HR ESIMS calculated for $C_{24}H_{30}N_2O_6Na^+$=465.2002; found=465.2006. Anal. Calcd (%) for $C_{24}H_{30}N_2O_6$: C, 65.14; H, 6.83; N, 6.33; O, 21.69. Found: C, 65.33; H, 7.00; N, 5.97.

4.5.8. *(N,N′)-2,6-Bis(2,3-dihydroxybenzamido)hexanoic acid (**4h**)*

A mixture of **3i′** (4.3 g, 5.5 mmol) and Pd/C (10%) (430 mg) in THF (150 mL) was stirred under H_2 atmosphere for 96 h. The resulting mixture was filtered over Celite, evaporated to dryness and dried under vacuum to give **4h** as a white powder (2.09 g, 99%).[28] ^{1}H NMR (DMSO-d_6, 300 MHz, 25 °C): δ=12.09 (br s, 1H), 9.13 (br s), 8.88 (d, J=7.4 Hz, 1H), 8.77 (m, 1H), 7.45 (d, J=7.8 Hz, 2H), 7.29 (d, J=7.9 Hz, 2H), 6.92–6.99 (m, 2H), 6.67–6.72 (m, 2H), 4.44–4.48 (m, 1H), 3.30–3.34 (m, 2H), 1.67–1.72 (m, 2H), 1.35–1.58 (m, 4H). ^{13}C NMR (DMSO-d_6, 75 MHz, 25 °C): δ=173.7, 170.1, 169.9, 150.0, 149.5, 146.5, 129.2, 128.5, 119.1, 118.5, 118.2, 117.4, 115.5, 115.3, 52.7, 39.1, 30.6, 28.7, 23.6. HR ESIMS calculated for $C_{20}H_{23}N_2O_8^+$=419.1454; found=419.1460. Anal. Calcd (%) for $C_{20}H_{22}N_2O_8\cdot$THF: C, 58.89; H, 5.97; N, 5.72; O, 29.42. Found: C, 59.05; H, 6.22; N, 5.38.

4.6. General procedure for the synthesis of compounds 5a–f and 5h

Compounds **4a–f** or **4h** were added portionwise to a solution of oleum (H_2SO_4/SO_3 20%) at 0 °C or H_2SO_4 96% at 50 °C under stirring. The resulting white solution was allowed to warm to room temperature and stirred overnight. The mixture was then poured into Et_2O (200 mL). The resulting precipitate was filtered off under argon and dried under vacuum to give **5a–f**.

4.6.1. *N,N′-Bis(2,3-dihydroxy-5-sulfonylbenzoyl)-1,5-diamino pentane (**5a**)*[12]

Compound **5a** was obtained from **4a** (1.99 g, 5.3 mmol) in oleum (20 mL) to give **5a** as a hygroscopic grey powder (2.4 g, 79%). ^{1}H NMR (D_2O, 300 MHz, 25 °C): δ=7.62 (s, 2H), 7.32 (s, 2H), 3.37–3.33 (t, J=6.6 Hz, 4H), 1.66–1.62 (m, 4H), 1.46–1.42 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ=169.1, 149.8, 145.1, 133.6, 116.7, 115.6, 115.2, 39.5, 28.0, 23.4. HR ESIMS calculated for $C_{19}H_{21}N_2O_{12}S_2^-$=533.0536; found=533.05365. Anal. Calcd (%) for $C_{19}H_{21}N_2O_{12}S_2\cdot 3H_2O$: C, 38.84; H, 4.63; N, 4.76; O, 40.84; S, 10.91. Found: C, 39.21; H, 4.87; N, 4.35.

4.6.2. *N,N′-Bis(2,3-dihydroxy-5-sulfonylbenzoyl)-2-methyl-1,5-diaminopentane (**5b**)*

Compound **5b** was obtained from **4b** (691 mg, 1.77 mmol) in oleum (20 mL) to give **5b** as a hygroscopic grey powder (752 mg, 77%). ^{1}H NMR (D_2O, 200 MHz, 25 °C): δ=7.59 (br d, 1H), 7.58 (br d, 1H), 7.28 (s, 2H), 3.13–3.28 (m, 4H), 1.22–1.69 (m, 5H), 0.93 (d, J=6.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz, 25 °C): δ=169.2, 149.9, 145.2, 133.4, 116.9, 116.5, 115.7, 39.5, 28.0, 23.4. HR ESIMS calculated for $C_{20}H_{24}N_2O_{12}S_2^-$=547.0692; found=547.0688. Anal. Calcd (%) for $C_{20}H_{24}N_2O_{12}S_2\cdot 6H_2O$: C, 36.58; H, 5.53; N, 4.27; O, 43.86, S, 9.77. Found: C, 36.76; H, 5.74; N, 3.87.

4.6.3. N,N′-Bis(2,3-dihydroxy-5-sulfonylbenzoyl)-3-methyl-1,5-diaminopentane (**5c**)

Compound **5c** was obtained from **4c** (595 mg, 1.5 mmol) in oleum (12 mL) to give **5c** as a hygroscopic white powder (650 mg, 79%). ^{1}H NMR (D_2O, 200 MHz, 25 °C): δ=7.57 (s, 2H), 7.27 (s, 2H), 3.25–3.73 (m, 4H), 1.09–1.50 (m, 5H). ^{13}C NMR ($CDCl_3$, 50 MHz, 25 °C): δ=169.0, 150.0, 145.2, 133.8, 116.9, 116.3, 115.9, 37.9, 35.3, 27.8, 19.0. HR ESIMS calculated for $C_{20}H_{24}N_2O_{12}S_2^{-2}$=547.0692; found=547.0691. Anal. Calcd (%) for $C_{20}H_{24}N_2O_{12}S_2\cdot 2H_2O$: C, 41.09; H, 4.83; N, 4.79; O, 38.32, S, 10.90. Found: C, 41.07; H, 5.08; N, 4.56.

4.6.4. N,N′-Bis(2,3-dihydroxy-5-sulfonylbenzoyl) cyclohexane-(1,3)-bismethylamine (**5d**)

Compound **5d** was obtained from **4d** (585 mg, 1.4 mmol) in oleum (12 mL) to give **5d** as a hygroscopic grey powder corresponding to a mixture of cis/trans diastereoisomers of 80:20 ratio (632 mg, 78%). HR ESIMS calculated for $C_{22}H_{25}N_2O_{12}S_2^{-2}$=573.0849; found=573.0846. Anal. Calcd (%) for $C_{22}H_{26}N_2O_{12}S_2\cdot 2H_2O$: C, 43.27; H, 4.95; N, 4.59; O, 36.68; S, 10.50. Found: C, 43.36; H, 5.08; N, 4.37. *NMR data for the major stereoisomer* **5d$_1$**. ^{1}H NMR (D_2O, 300 MHz, 25 °C): δ=7.64 (d, J=2 Hz, 2H), 7.36 (d, J=2 Hz, 2H), 3.23 (d, J=6.8 Hz, 4H), 1.26–1.62 (m, 6H), 0.98–1.09 (m, 2H), 0.86–0.92 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ=169.3, 149.9, 145.3, 133.9, 116.9, 115.8, 46.1, 37.4, 34.61, 30.3, 25.2. *NMR data for the minor stereoisomer* **5d$_2$**. ^{1}H NMR (D_2O, 300 MHz, 25 °C): δ=7.62 (d, J=2 Hz, 2H), 7.32 (d, J=2 Hz, 2H), 3.23 (d, J=6.8 Hz, 4H), 1.26–1.62 (m, 6H), 0.98–1.09 (m, 2H), 0.66–0.74 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ=168.9, 149.7, 145.2, 133.7, 116.5, 115.7, 43.6, 32.6, 31.8, 29.1, 20.6.

4.6.5. 2,4-Bis[(2,3-dihydroxy-5-sulfobenzoyl)aminomethyl]-benzenesulfonic acid (**5e**)

Compound **5e** was obtained from **4e**[26] (1.13 g, 2.7 mmol) in oleum (12 mL) to give **5e** as a hygroscopic grey powder (1.3 g, 72%). ^{1}H NMR (D_2O, 200 MHz, 25 °C): δ=7.83 (d, J=8.5 Hz, 1H), 7.64 (d, J=2.06 Hz, 1H), 7.63 (br s, 1H), 7.58 (d, J=2.06 Hz, 1H), 7.29–7.31 (m, 1H), 7.27 (d, J=2.06 Hz, 1H), 4.91 (s, 2H), 4.57 (s, 2H). ^{13}C NMR (D_2O, 50 MHz, 25 °C): δ=169.5, 169.3, 150.0, 150.0, 145.2, 143.4, 142.0, 139.8, 139.0, 135.6, 133.8, 127.9, 126.0, 125.4, 123.2, 117.0, 116.0, 115.6, 42.7, 41.0. HR ESIMS calculated for $C_{22}H_{19}N_2O_{12}S_2^{-2}$=646.9948; found=646.9950. Anal. Calcd (%) for $C_{22}H_{20}N_2O_{12}S_2\cdot 5H_2O$: C, 35.77; H, 4.09; N, 3.79; O, 43.32; S, 13.02. Found: C, 36.03; H, 4.30; N, 3.62.

4.6.6. 2,5-Bis[(2,3-dihydroxy-5-sulfonylbenzoyl)-aminomethyl]-benzenesulfonic acid (**5f**)

Compound **5f** was obtained from **4f** (470 mg, 1.15 mmol) in oleum (12 mL) to give **5f** as a hygroscopic grey powder (430 mg, 57%).[27] ^{1}H NMR (D_2O, 200 MHz, 25 °C): δ=7.74 (s, 1H), 7.59 (d, J=1.7 Hz, 1H), 7.55 (d, J=1.7 Hz, 1H), 7.31–7.33 (m, 2H), 7.23 (d, J=1.7 Hz, 2H), 4.82 (s, 2H), 4.42 (s, 2H). ^{13}C NMR (D_2O, 50 MHz, 25 °C): δ=169.7, 169.2, 150.2, 145.4, 141.0, 138.0, 134.4, 134.1, 130.7, 129.7, 126.4, 117.2, 116.8, 116.1, 43.0, 41.0. HR ESIMS calculated for $C_{22}H_{19}N_2O_{12}S_2^{-2}$=646.9948; found=646.9946. Anal. Calcd (%) for $C_{22}H_{20}N_2O_{12}S_2\cdot 4H_2O$: C, 36.67; H, 3.92; N, 3.89; O, 42.18; S, 13.35. Found: C, 36.58; H, 4.05; N, 3.84.

4.6.7. N,N′-[2,6-Bis(2,3-dihydroxy-5-sulfonyl-benzamido)] hexanoic acid (**5h**)

Compound **5h** was obtained from **4h** (448 mg, 1.07 mmol) in H_2SO_4 (2 mL) to give **5h** as a hygroscopic grey powder (0.55 g, 90%). ^{1}H NMR (D_2O, 300 MHz, 25 °C): δ=7.64 (d, J=2.1 Hz, 1H), 7.54 (d, J=2.1 Hz, 1H), 7.27 (d, J=2.1 Hz, 1H), 7.24 (d, J=2.1 Hz, 1H), 4.51–4.56 (m, 1H), 3.27–3.33 (m, 2H), 1.80–1.95 (m, 2H), 1.56–1.59 (m, 2H), 1.44–1.50 (m, 4H). ^{13}C NMR (DMSO-d_6, 75 MHz, 25 °C): δ=176.0, 169.11, 168.8, 149.9, 149.4, 145.1, 145.0, 133.8, 133.6, 117.4, 116.7, 116.3, 116.1, 115.9, 115.6, 52.9, 39.3, 30.7, 27.7, 23.3. HR ESIMS calculated for $C_{20}H_{21}N_2O_{14}S_2^{-2}$=577.0440; found=577.0439. Anal. Calcd (%) for $C_{20}H_{22}N_2O_8\cdot 2H_2O$: C, 39.09; H, 4.26; N, 4.56; O, 41.65; S, 10.44. Found: C, 39.15; H, 4.12; N, 4.28.

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References and notes

1. Hamilton, J. G. *Rev. Mod. Phys.* **1948**, *20*, 718–728.
2. Bulman, R. A. *Coord. Chem. Rev.* **1980**, *31*, 221–250.
3. Galle, P. *Toxiques Nucléaires*; Masson: Paris, 1997, pp 185–205.
4. Sawicki, M.; Siaugue, J.-M.; Jacopin, C.; Moulin, C.; Bailly, T.; Burgada, R.; Meunier, S.; Baret, P.; Pierre, J.-L.; Taran, F. *Chem.—Eur. J.* **2005**, *11*, 3689–3697.
5. Bailly, T.; Burgada, R.; Prange, T.; Lecouvey, M. *Tetrahedron Lett.* **2002**, *44*, 189–192.
6. Burgada, R.; Bailly, T.; Prange, T.; Lecouvey, M. *Tetrahedron Lett.* **2007**, *48*, 2315–2319.
7. Xu, G.; Yang, C.; Liu, B.; Wu, X.; Xie, Y. *Heteroat. Chem.* **2004**, *15*, 251–257.
8. Martinez, A. B.; Cabrini, R. L.; Ubios, A. M. *Health Phys.* **2000**, *78*, 668–671.
9. Ubios, A. M.; Braun, E. M.; Cabrini, R. L. *Health Phys.* **1998**, *75*, 610–613.
10. Ubios, A. M.; Braun, E. M.; Cabrini, R. L. *Health Phys.* **1994**, *66*, 540–544.
11. Fukuda, S.; Iida, H.; Ikeda, M.; Yan, X.; Xie, Y. *Health Phys.* **2005**, *89*, 81–88.
12. Durbin, P.; Kullgren, B.; Ebbe, S. N.; Xu, J.; Raymond, K. N. *Health Phys.* **2000**, *78*, 511–521.
13. Sylwester, E. R.; Allen, P. G.; Dharmawardana, U. R.; Sutton, M. *Inorg. Chem.* **2001**, *40*, 2835–2841.
14. Domingo, J. L.; Llobet, J. M.; Corbella, J. J. *Fundam. Appl. Toxicol.* **1990**, *14*, 88–95.
15. Domingo, J. L.; De la Torre, A.; Belles, M.; Mayayo, E.; Llobet, J. M.; Corbella, J. *Toxicology* **1997**, *118*, 49–59.
16. Bosque, M. A.; Domingo, J. L.; Llobet, J. M.; Corbella, J. *Toxicology* **1993**, *79*, 149–156.
17. Ramounet-Le Gall, B.; Grillon, G.; Rateau, G.; Burgada, R.; Bailly, T.; fritsch, P. *Radiat. Prot. Dosim.* **2003**, *105*, 535–538.
18. Gorden, A. E. V.; Xu, J.; Raymond, K. N.; Durbin, P. *Chem. Rev.* **2003**, *103*, 4207–4282.
19. Xu, J.; Raymond, K. N. *Inorg. Chem.* **1999**, *38*, 308–315.
20. Vickery, E. H.; Pahler, L. F.; Eisenbraun, E. J. *J. Org. Chem.* **1979**, *44*, 4444–4446.
21. Thomas, F.; Beguin, C.; Pierre, J.-L.; Serratrice, G. *Inorg. Chim. Acta* **1999**, *291*, 148–157.
22. Thompson, A. S.; Humphrey, G. R.; DeMarco, A. M.; Mathre, D. J.; Grabowski, E. J. J. *J. Org. Chem.* **1993**, *58*, 5886–5888.
23. Gardner, R. A.; Kinkade, R.; Wang, C.; Phanstiel, O. I. V. *J. Org. Chem.* **2004**, *69*, 3530–3537.
24. Laursen, B.; Denieul, M.-P.; Skrydstrup, T. *Tetrahedron* **2002**, *58*, 2231–2238.
25. Duhme, A.-K.; Dauter, Z.; Hider, R. C.; Pohl, S. *Inorg. Chem.* **1996**, *35*, 3059–3061.
26. Duhme, A.-K. *J. Chem. Soc., Dalton Trans.* **1997**, 773–778.
27. Weitl, F. L.; Harris, W. R.; Raymond, K. N. *J. Med. Chem.* **1979**, *22*, 1281–1283.
28. Schnabelrauch, M.; Wittmann, S.; Rahn, K.; Mollmann, U.; Reissbrodt, R.; Heinisch, L. *BioMetals* **2000**, *13*, 333–348.