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Tetrahedron
Tetrahedron 60 (2004) 1167–1174

Design and synthesis of new ethylenediamine or propylenediamine diacetic acid derivatives for Re(I) organometallic chemistry

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Received 4 August 2003; revised 3 November 2003; accepted 20 November 2003

Abstract—A general synthetic approach for a novel range of bifunctional chelating agent (BCA) for the '*fac*-$[M(CO)_3]^+$' core (M=^{99m}Tc, ^{99}Tc or Re) has been developed. The strategy includes the facile preparation of these tridentate ligands possessing a tertiary amine bearing two carboxylic acid functions as coordinating site and an aromatic amino group for coupling to a biovector. First complexation study has shown that these compounds act exclusively as tridentate ligands (via the two acids and the tertiary amine functions). The convenient synthesis of these new ligands coupled with their high affinity for Re(I) make them quite promising for biomedical applications.

1. Introduction

The technetium-99m is the most important radionuclide in diagnostic nuclear medicine. This preferential use of ^{99m}Tc-radiopharmaceuticals reflects the ideal nuclear properties of the isotope ($T_{1/2}$=6 h, 140 keV gamma emitter), as well as its low cost and its convenient availability from commercial generators. Consequently, it is of high priority to develop efficient molecules with a chelating group specific for this radionuclide.[1] Efforts to design new chelate systems for this nuclide and rhenium for subsequent use, respectively, in diagnostic and therapy have led to the development of new Tc or Re-specific ligands.

Whereas in the past, the Tc or Re compounds bore preferentially N,S tetradentate ligands[2] which form stable technetium(V) or rhenium(V) complexes,[3] over the last 20 years, organometallic technetium and rhenium complexes in low oxidation states have gained considerable attention in the development of novel target-specific radiopharmaceuticals.[4–9] Because of the high kinetic inertness and their ease of preparation, Tc(I)/Re(I)-tricarbonyl complexes are attractive for use in labelling site-specific biomolecules.[10]

Previous in vitro studies on the macroscopic and n.c.a (non carrier added) level suggested that ideal chelating systems for the '*fac*-$[M(CO)_3]^+$' core, in respect of a potential radiopharmaceutical application, should contain one or more amine functionalities (preferentially aromatic *N*-heterocycles) in combination with a carboxylic acid function.[11] Recently, Schibli and co-workers[12] have compared the in vivo and in vitro behaviours of different ^{99m}Tc(I)-tricarbonyl complexes with various bi- and tridentate ligand systems. They have concluded that for the radiolabelling with *fac*-$[^{99m}Tc(CO)_3]^+$or *fac*-$[^{186/188}Re(CO)_3]^+$, tridentate chelating systems were preferable since they formed organometallic compounds with more favourable pharmacokinetics.

We here provide a facile and convenient synthetic approach for the tridentate bifunctional chelating agent (BCA) which incorporates the design features illustrated in Figure 1; these include: (i) a tridentate coordinating site for low oxidation state metal carbonyls, (ii) a linking site to a biomolecule via the amino functionality (iii) a tethering moiety (an ethylene or propylene bridge) between the linking and coordinating sites. The enhancement of bridge size should limit the possible interaction between the secondary aromatic amine

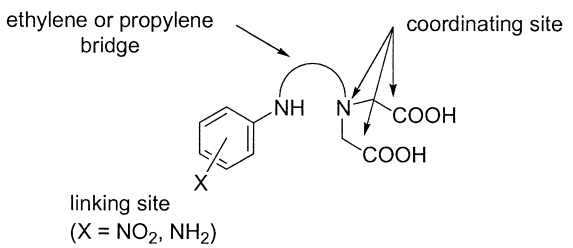

Figure 1. Design features of novel Re(I) ligands.

Keywords: Bifunctional chelating agent; Imino diacetic acid; Rhenium(I).
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doi:10.1016/j.tet.2003.11.058

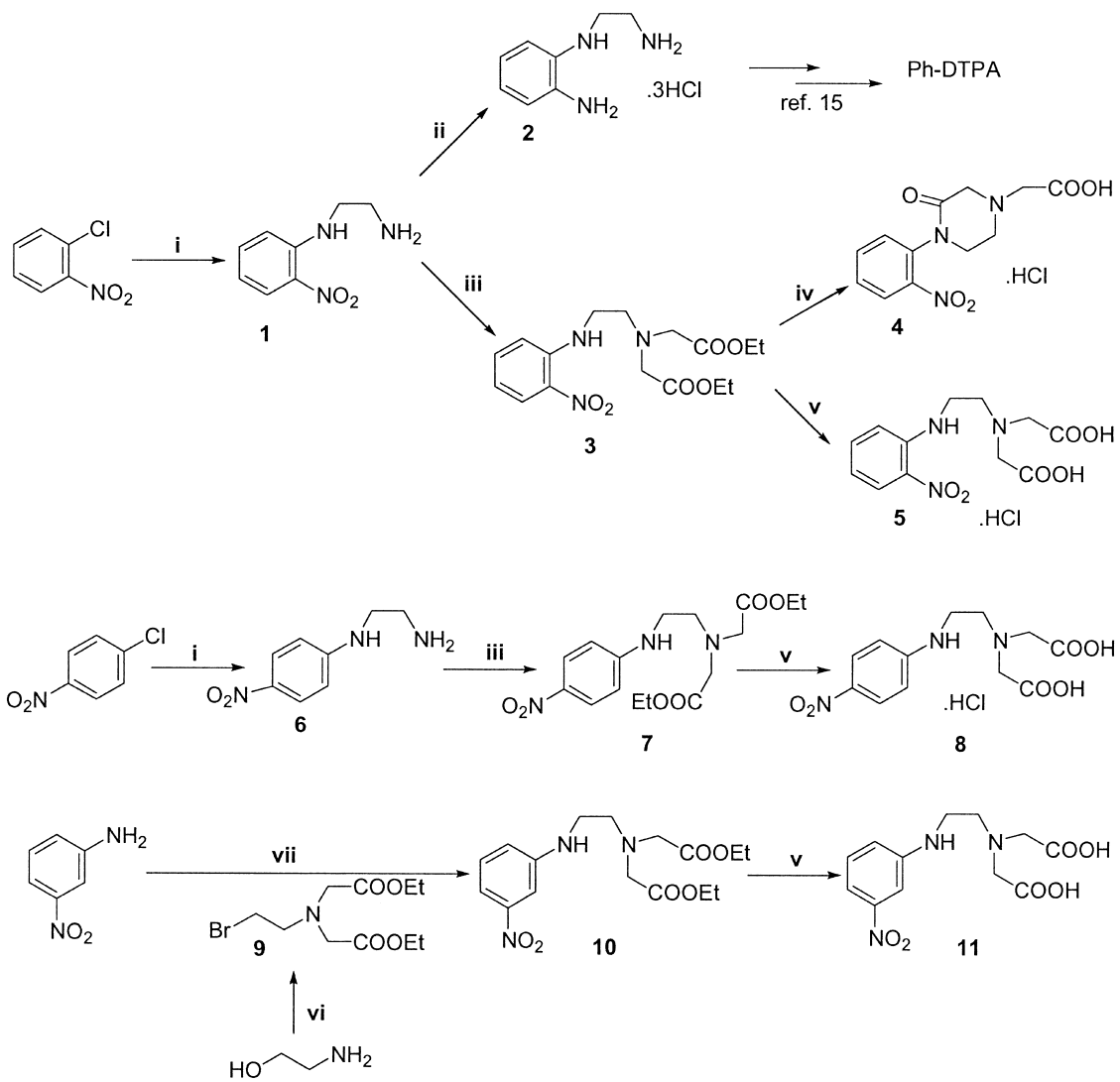
and the iminodiacetic acid group during the complexation reaction. In this paper, we describe the synthesis of a range of new ethylenediamine diacetic acid derivatives (EDDA) and propylenediamine diacetic acid derivatives (PDDA) which, on preliminary examination, exhibits significant Re(I)-specificity.

2. Results and discussion

Amino polycarboxylic acid based ligand systems like iminodiacetic acid react readily with the *fac*-$[M(CO)_3]^+$ core to form complexes which have a stable octahedral coordination sphere, where substitution reaction via a dissociative or an associative mechanism is unlikely.[12,13] Our synthetic strategy offers a simple method for generating aminodiacetic acid derivatives bearing an aromatic amino group for coupling to biomolecules.

The syntheses of nitrophenylethylenediaminediacetic acid derivatives (NO_2Ph-EDDA) were performed in three steps as described in Scheme 1. The key step was the introduction of the nitro group (future linking site) during the synthesis of the chelating moiety.

For *ortho* and *para*-NO_2Ph-EDDA ligands, we used an elegant and rapid route to synthesise nitrophenyldiamine intermediates.[14] By refluxing *o*- or *p*-chloronitrobenzene with an excess of ethylenediamine, we obtained **1** and **6** respectively in 93 and 85% yield. This one-step substitution reaction gave better yields than the Gabriel two-steps synthesis using 2-bromoethylphtalimide as starting material. Another advantage of this first step was the rapid access to the triamine **2** by reduction of the nitro group using $SnCl_2$ as reducing agent in acidic conditions. This compound **2** obtained in two steps with an overall yield of 86% was a versatile intermediate in the synthesis of Ph-DTPA, (phenyleneetylenetriamine pentaacetic acid) a potent ligand for radioimmunotherapy. This method proved more suitable than that described by Gouin et al.[15]



Scheme 1. *o,m,p*-NO_2Ph-EDDA ligand synthesis *Reagents and conditions:* (i) ethylenediamine, 100 °C, 1 h–1 h 30 min 85–93% (ii) (a) $SnCl_2$, HCl, 100 °C, 1 h (b) H_2S 92% (iii) $BrCH_2COOEt$, K_2CO_3, KI, ACN, 60 °C, 12 h, 83–90% (iv) 6 N HCl, 110 °C, 1 day, 70% (v) 2 N NaOH/EtOH, 70 °C, 3 h then 2 N HCl 78–90% (vi) Ref. 19, 62% (vii) **9**, K_2CO_3, KI, ACN, 60 °C, 3 h, 60%.

which uses a classical three-step sequence (peptidic coupling–amine deprotection–amide reduction) providing an overall yield of no more than 73%.

The second step was the dialkylation of the primary amine function of **1** and **6**. According to the classical alkylation method,[16] diethyl esters **3** and **7** were obtained with good yields through the action of two equivalents of ethylbromoacetate in the presence of a catalytic amount of KI and a slight excess of K_2CO_3 in acetonitrile. Even with a large excess of ethylbromoacetate, the desactivating nitro group did not allowed the alkylation of the aromatic amine function. Recently, a report has been published on *N*,*N*-dialkylation of *p*-nitroaniline using CsF-Celite/alkyl halides/acetonitrile combination[17] but in our case, these conditions afforded mainly the dialkylated ester and the trialkylated ester only in minor proportion (>5%).

Attempts to prepare and obtain pure *ortho*-NO_2Ph-EDDA by the direct acid hydrolysis of **3** failed and resulted in the formation of the six-membered azalactam **4** in 70% yield. Genik–Sas–Berezowsky et al.[18] have already noticed that cyclization of the non-fully substituted EDDA derivatives took place quite readily under acid conditions. To circumvent this lactamisation, compounds **3** and **7** were hydrolysed in smooth basic conditions followed by acidification step providing easily the corresponding pure hydrochloride salts of diacids **5** and **8** in 80% yield.

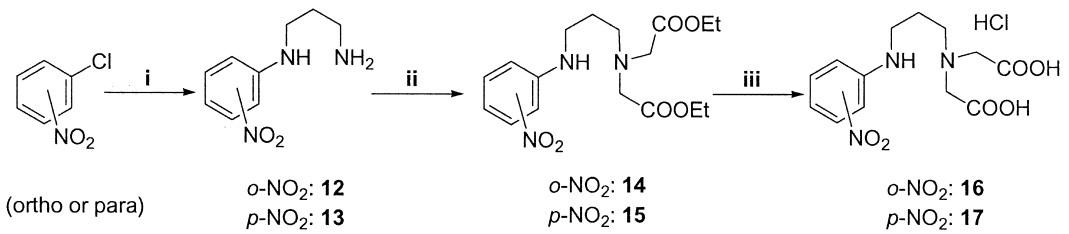
An alternative pathway was investigated to obtain the *meta*-NO_2Ph-EDDA **11**. *m*-nitroaniline was converted to the dialkylated ester **10** after alkylation reaction with compound **9**. This intermediate was first prepared by a well-known two-steps synthesis using ethanolamine as starting material.[19] Basic hydrolysis of the ester followed by acidification step afforded the ligand **11** in 90% yield.

The three *o*-, *p*-, *m*-NO_2Ph-EDDA derivatives were achieved respectively in 67, 55 and 33% yield and the yields of each step, especially the amine alkylation step, were not affected by the position of the nitro group on the aromatic ring.

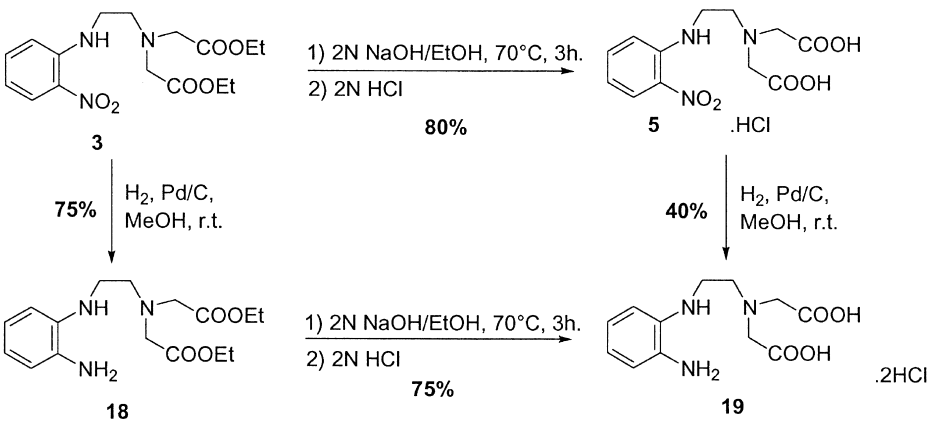
Using the same versatile route than for the ligands **5** and **8**, we also synthesized the *o*- and *p*-NO_2Ph-PDDA substituting ethylenediamine by 1,3-diaminopropane as starting material in the first step (Scheme 2). These two ligands **16** and **17**, having one carbon more between the linking and chelating moieties, have been obtained respectively in 67 and 60% yield.

For rapid functionalization of a biomolecule, the introduction of the nitro group is a decisive advantage of the presented synthetic strategy. For example, as shown in Scheme 3, bifunctional chelating agent **19** was achieved in 40% yield by catalytic hydrogenation of the nitro group of **5**. Nevertheless, **19** was obtained with a better overall yield in two steps, starting from **3** (56%). We found that it was easier to purify intermediates using reduction then basic hydrolysis sequence than the opposite. The aromatic amine function allows e.g. in the case of **19**, the coupling to a carboxylic acid of a biomolecule. The same synthetic procedure of functionalization could be applied to all our ligands.

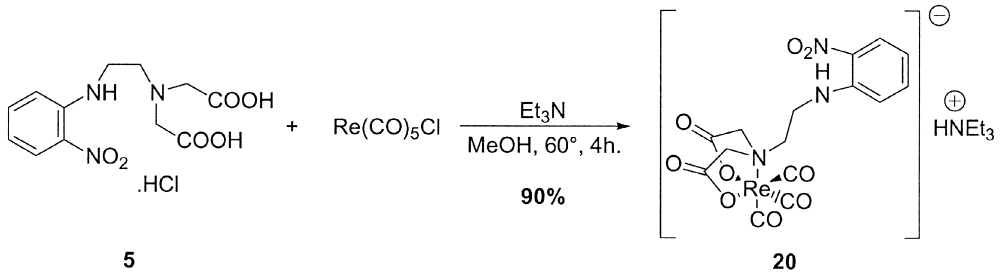
The coordination chemistry behaviour of one of our ligands has also been investigated. When reacted with the $Re(CO)_5Cl$ precursor in methanol and in the presence of



Scheme 2. *o*,*p*-NO_2Ph-PDDA derivatives *Reagents and conditions*: (i) (a) 1,3-diaminopropane, 100 °C, 1 h 92% (ii) $BrCH_2COOEt$, K_2CO_3, KI, ACN, 60 °C, 12 h, 83–90% (iii) 2 N NaOH/EtOH, 70 °C, 3 h then 2 N HCl, 80%.



Scheme 3. BCA synthesis.



5 20

Scheme 4. Re(I) complex formation.

triethylamine, the ligand **5** formed almost quantitatively a well-defined species with a metal-to-ligand ratio of 1:1 as evident by proton NMR spectroscopy and mass spectra (Scheme 4).

In the free ligand, the two methylene groups appear as an unique singlet (3.59 ppm). After complexation with $Re(CO)_5Cl$, the singlet splits into two doublets forming the pattern of two AB-spin systems at 3.48 and 3.65 ppm (J=16 Hz). This feature is in accordance with the proposed tridentate coordination via the tertiary amine and the two carboxylic acids. The complex was a $NHEt_3^+$ salt as evident by elemental analysis. This is confirmed by the negative Electrospray spectrum that presents two prominent ion peaks with an isotope distribution pattern consistent with the monomeric anion $[Re(CO)_3(NO_2Ph\text{-}EDDA)]^-$. The IR spectrum revealed firstly the presence of N–H stretching band of secondary aromatic amine and secondly three bands in the carbonyl stretching region (2029–1887 cm^{-1}) which is characteristic of a *fac*-octahedral tricarbonyl metal moiety.[20] This proved the tridentate coordination of the metal-tricarbonyl core via the EDDA ligand. The complex is soluble in all polar organic solvents and is stable to aerial oxidation.

3. Conclusion

A versatile way to produce tridentate chelating systems for low oxidation state metal carbonyls like $M(CO)_3$ fragment (M=Tc or Re) was presented. While still maintaining a simplicity of synthesis and high overall yield, we have developed a new range of amino diacetic acid derivatives. A decisive advantage of the presented synthetic strategy is that this kind of molecules already possesses a linking site for future coupling to biomolecule. First complexation study has shown that these compounds act exclusively as tridentate ligands (via the two acids functions and the tertiary amine). The convenient synthesis of this new range of molecules coupled with their high affinity for Re(I) make them promising candidates for radiopharmaceuticals. Rhenium(I) and technetium(I) chemistry of all our ligands are currently in progress.

4. Experimental

All chemicals were of the highest purity commercially available. Solvents were purified by standard methods before use and stored over 0.3 nm molecular sieves. Silica gel (0.060–0.200 nm) was purchased from Acros. TLC was performed using precoated Kieselgel 60 plates F_{254} (TLC plates, Merck) and was visualized by UV or iodine.

NMR spectra were recorded on a Bruker AC 200 (50.323 MHz for ^{13}C and 200.133 MHz for ^1H), 250 (62.896 MHz for ^{13}C and 250.133 MHz for ^1H) or 300 apparatus (75.467 MHz for ^{13}C and 300.13 MHz for ^1H). Chemical shifts are indicated in δ values (ppm) downfield from internal TMS, and coupling constants (J) are given in Hertz (Hz). Multiplicities were recorded as s (singlet), d (doublet), t (triplet) q (quadruplet), qt (quintuplet) and m (multiplet). For aromatic ring NMR assignments, the protons (or carbons) were numbered from 1 to 6 starting from carbon bearing the secondary aromatic amine and turning clockwise. Infrared spectrum was recorded as KBr pellets on a BRUKER Vector 22 spectrophotometer in the range 4000–400 cm^{-1}. Electrospray or DCI-Mass spectra were obtained on a NERMAG R 10–10 mass spectrometer. Microanalysis was performed by the microanalytical department of the Ecole Nationale Supérieure de Chimie de Toulouse. Melting points were determinated on a stuart melting point SMP3 apparatus and are uncorrected.

4.1. Synthesis of EDDA derivatives

4.1.1. *N*-(2-Nitrophenyl)ethylenediamine (1). 2-Nitrochlorobenzene (10 g, 0.063 mol) and ethylenediamine (40 g, 0.67 mol) were stirred 1 h under reflux. After distillation of the excess of ethylenediamine, the crude was acidified at pH 6 with 2 N HCl, then heated and filtrated. After cooling, 13.02 g of *N*-(2-nitrophenyl)ethylenediamine hydrochloride were collected as yellow needles.

The product was dissolved in water (10 mL). The solution was basified at pH 12 and extracted twice with chloroform (15 mL). The organic layer was dried with sodium sulfate, filtered and concentrated to dryness under reduce pressure to give **1** as an orange oil (10.60 g, 93%)

^1H NMR (200 MHz, $CDCl_3$) δ_H (ppm): 1.32 (bs, 2H, NH_2); 3.04 (m, 2H, CH_2); 3.35 (m, 2H, CH_2); 6.62 (m, 1H, H-5); 6.85 (m, 1H, H-3); 7.41 (m, 1H, H-4); 8.13 (m, 1H, H-6); 8.24 (s, 1H, NH); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ_C (ppm): 40.8 (CH_2); 45.7 (CH_2); 113.6 (C-3); 115.3 (C-5); 127.0 (C-6); 133.0 (C-2); 136.3 (C-4); 145.6 (C-1); MS (DCI/NH_3): 182 ($M+H^+$); 199 ($M+NH_4^+$); mp=261 °C; Anal.: found (as hydrochloride salt): C, 44.2; H, 5.6; N, 19.7%; $C_8H_{12}N_3O_2Cl$ requires: C, 44.2; H, 5.6; N, 19.3%.

4.1.2. *N*-(2-Aminophenyl)ethylenediamine trihydrochloride (2). 3.00 g (16.6 mmol) of **1** and 13.5 g

(59.8 mmol) of $SnCl_2.2H_2O$ were heated at 100 °C in concentrated chlorhydric acid (30 mL). After 1 h, the mixture was cooled and filtrated. The residue was dissolved in water and H_2S gas was bubbled into the solution to precipitate tin salt. After filtration, the filtrate was concentrated to dryness under reduce pressure to give **2** as pale yellow crystals (3.97 g, 92%).

^{1}H NMR (200 MHz, D_2O) δ_H (ppm): 3.13 (m, 2H, CH_2); 3.44 (m, 2H, CH_2); 6.77–6.87 (m, 2H, ArH); 7.17–7.33 (m, 2H, ArH); ^{13}C NMR (50.3 MHz, D_2O) δ_C (ppm): 40.7 (CH_2); 42.4 (CH_2); 116.8 (C-5); 120.4 (C-3); 122.0 (C-6); 126.7 (C-4); 134.0 (C-1); 143.0 (C-2); MS (DCI/NH_3): 152 [(M−3HCl)+H$^+$]; mp=214 °C; Anal.: found (as trihydrochloride salt): C, 37.0; H, 6.3; N, 15.8%; $C_8H_{16}N_3Cl_3$ requires: C, 36.9; H, 6.1; N, 16.1%.

4.1.3. *N*-(2-Nitrophenyl)ethylenediamine-*N′*,*N′*-diethyldiacetate (3). A mixture of **1** (785 mg, 4.34 mmol), potassium iodide (1.44 g, 0.87 mmol), potassium carbonate (9.00 g, 6.51 mmol) and ethyl bromoacetate (1.00 mL, 9.02 mmol) in acetonitrile (100 mL), over an atmosphere of nitrogen, was boiled one night at 60 °C. The insoluble materials were filtered off and the solvent was removed under reduced pressure. The crude material was purified by column chromatography on silica gel (eluent: CH_2Cl_2 then CH_2Cl_2/AcOEt: 4/6) to give **3** as an orange oil (1.38 g, 90%).

^{1}H NMR (200 MHz, $CDCl_3$) δ_H (ppm): 1.24 (t, 6H, *J*=7.1 Hz, $2CH_3$); 3.13 (m, 2H, NCH_2); 3.37 (m, 2H, NCH_2); 3.60 (s, 4H, $2NCH_2$); 4.15 (q, 4H, *J*=7.1 Hz, $2OCH_2$); 6.63 (m, 1H, H-5); 6.82 (m, 1H, H-3); 7.40 (m, 1H, H-4); 8.15 (m, H, H-6); 8.35 (bs, 1H, NH); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ_C (ppm): 14.2 (CH_3); 41.0 (NCH_2); 52.1 (NCH_2); 55.5 ($2NCH_2$); 60.8 (2 OCH_2); 113.9 (C-3); 115.1 (C-5); 126.8 (C-6); 136.1 (C-2); 139.0 (C-4); 145.2 (C-1); 171.0 (2CO); MS (DCI/NH_3): 354 (M+H$^+$).

4.1.4. 4-(2-Nitrophenyl)-3-oxopiperazin-1-yl acetic acid (4). 1.12 g (3.17 mmol) of compound **3** into 10 mL of 6 N HCl were refluxed during 24 h. After cooling, the solvent was removed under reduced pressure. The crude product was taken in 10 mL of ethyl acetate and the organic layer was washed twice with water (30 mL), dried with sodium sulfate and concentrated under vacuum to give **4** as a yellow solid (620 mg, 70%).

^{1}H NMR (200 MHz, D_2O) δ_H (ppm): 3.70 (m, 2H, NCH_2); 4.16 (m, 4H, $2NCH_2$); 4.26 (m, 2H, NCH_2); 7.50 (m, 1H, H-6); 7.70 (m, 1H, H-4); 7.84 (m, 1H, H-5); 8.16 (m, 1H, H-3); ^{13}C NMR (50.3 MHz, D_2O) δ_C (ppm): 46.3 (NCH_2); 51.4 (NCH_2); 55.5 (NCH_2); 58.5 (NCH_2); 126.5 (C-3); 131.6 (C-5); 133.7 (C-6); 134.7 (C-2); 136.5 (C-4); 147.3 (C-1); 165.7 (CO); 169.8 (COOH); MS (DCI/NH_3): 280 (M+H$^+$); 297 (M+NH_4^+). Anal.: found (as hydrochloride salt): C, 41.0; H, 4.7; N, 11.4%; mp=204 °C; $C_{12}H_{15}N_3O_5Cl_2$ requires: C, 40.9; H, 4.3; N, 11.9%.

4.1.5. *N*-(2-Nitrophenyl)ethylenediamine-*N′*,*N′*-diacetic acid hydrochloride salt (5). 353 mg (1 mmol) of diester **3** in 10 mL of a 2 N NaOH/ethanol (1/1) solution were heated at 70 °C for 3 h. After cooling, the solution was acidified with 2 N HCl until pH was 1 and left a few hours at 4 °C. The obtained precipitate was filtered and dried under vacuum to give **5** as yellow powdery product (267 mg, 80%).

^{1}H NMR (250 MHz, DMSO-d_6) δ_H (ppm): 3.02 (m, 2H, NCH_2); 3.43 (m, 2H, NCH_2); 3.59 (s, 4H, $2NCH_2$); 6.67 (m, 1H, H-5); 7.06 (m, 1H, H-3); 7.52 (m, 1H, H-4); 8.03 (m, 1H, H-6); 8.33 (bs, 1H, NH); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ_C (ppm): 40.6 (NCH_2); 51.8 (NCH_2); 54.3 (NCH_2); 114.5 (C-3); 115.0 (C-5); 126.0 (C-6); 130.9 (C-2); 136.4 (C-4); 144.9 (C-1); 171.8 (2CO); MS (DCI/NH_3): 298 (M+H$^+$). Anal.: found (as hydrochloride salt): C, 43.4; H, 4.8; N, 12.2%; mp=219 °C; $C_{12}H_{16}N_3O_6Cl$ requires: C, 43.2; H, 4.8; N, 12.6%.

4.1.6. *N*-(4-Nitrophenyl)ethylenediamine (6). 4-nitrochlorobenzene (10 g, 0.063 mol) and ethylenediamine (40 g, 0.67 mol) were stirred 1 h and half under reflux. After distillation of the excess of ethylenediamine, the crude was taken in hot distillated water (150 mL) and filtrated. After cooling, **6** was collected as an orange solide (9.70 g, 85%).

^{1}H NMR (200 MHz, $CDCl_3$) δ_H (ppm): 1.36 (s, 2H, NH_2); 3.01 (m, 2H, CH_2); 3.25 (m, 2H, CH_2); 5.29 (s, 1H, NH); 6.66 (d, 2H, *J*=9.4 Hz, H-2, H-6); 8.05 (d, 2H, *J*=9.4 Hz, H-3, H-5); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ_C (ppm): 40.5 (CH_2); 45.2 (CH_2); 111.1 (C-2, C-6); 126.5 (C-3, C-5); 137.8 (C-4); 154.4 (C-1); MS (DCI/NH_3): 182 (M+H$^+$), 199 (M+NH_4^+); mp=142 °C, Anal.: found: C, 52.8; H, 6.0; N, 22.7%; $C_8H_{11}N_3O_2$ requires: C, 52.7; H, 6.0; N, 23.1%.

4.1.7. *N*-(4-Nitrophenyl)ethylenediamine-*N′*,*N′*-diethyldiacetate (7). Using the same procedure than **3**, 786 mg of **6** gave **7** as an orange oil (1.27 g, 83%).

^{1}H NMR (250 MHz, $CDCl_3$) δ_H (ppm): 1.28 (t, 6H, *J*=7.1 Hz, $2CH_3$); 3.00 (m, 2H, NCH_2); 3.13 (m, 2H, NCH_2); 3.52 (s, 4H, $2NCH_2$); 4.12 (q, 4H, *J*=7.1 Hz, $2OCH_2$); 6.41 (bs, 1H, NH); 6.82 (d, 2H, *J*=9.2 Hz, H-2, H-6); 8.01 (d, 2H, *J*=9.2 Hz, H-3, H-5); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ_C (ppm): 13.9 (CH_3); 40.5 (NCH_2); 51.9 (NCH_2); 54.9 ($2NCH_2$); 60.9 (2 OCH_2); 110.7 (C-2, C-6); 126.5 (C-3, C-5); 137.2 (C-4); 153.8 (C-1); 171.7 (2CO); MS (DCI/NH_3): 354 (M+H$^+$).

4.1.8. *N*-(4-Nitrophenyl)ethylenediamine-*N′*,*N′*-diacetic acid hydrochloride salt (8). Using the same procedure than **5**, 353 mg of compound **7** gave **8** as orange powdery product (260 mg, 78%).

^{1}H NMR (250 MHz, DMSO-d_6) δ_H (ppm): 2.93 (~t, 2H, *J*=6.2 Hz, NCH_2); 3.23 (~t, 2H, *J*=6.2 Hz, NCH_2); 3.50 (s, 4H, $2NCH_2$); 6.65 (d, 2H, *J*=9.3 Hz, H-2, H-6); 7.30 (bs, 1H, NH); 8.03 (d, 2H, *J*=9.3 Hz, H-3, H-5); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ_C (ppm): 40.4 (NCH_2); 52.1 (NCH_2); 54.6 (NCH_2); 110.7 (C-2, C-6); 126.1 (C-3, C-5); 135.5 (C-4); 154.2 (C-1); 172.3 (2CO); MS (DCI/NH_3): 298 (M+H$^+$). Anal.: found (as hydrochloride salt): C, 43.3; H, 4.6; N, 12.7%; mp=186 °C; $C_{12}H_{16}N_3O_6Cl$ requires: C, 43.2; H, 4.8; N, 12.6%.

4.1.9. *N*-(3-Nitrophenyl)ethylenediamine-*N′*,*N′*-diethyldiacetate (10). In an atmosphere of nitrogen, a mixture of

3-nitroaniline (310 mg, 2.24 mmol), potassium iodide (310 mg, 1.87 mmol), potassium carbonate (514 mg, 3.73 mmol) and compound **9** (663 mg, 2.24 mmol) in acetonitrile (100 mL) was boiled under reflux for 3 h. The insoluble materials were filtered off and the solvent was removed under reduced pressure. The crude material was purified by column chromatography on silica gel, eluting with CH_2Cl_2 to give **10** as a brown oil (474 mg, 60%).

^{1}H NMR (250 MHz, $CDCl_3$) δ_H (ppm): 1.27 (m, 6H, $2CH_3$); 3.15 (m, 4H, $2NCH_2$); 3.57 (s, 4H, NCH_2); 4.19 (s, 4H, $2OCH_2$); 5.60 (bs, 1H, NH); 6.90 (m, 1H, H-6); 7.35 (m, 3H, H-2, H-4, H-5); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ_C (ppm): 13.9 (CH_3); 42.2 (NCH_2); 52.7 (NCH_2); 55.2 ($2NCH_2$); 60.8 (2 OCH_2); 105.4 (C-2); 110.6 (C-6); 118.4 (C-4); 129.5 (C-5); 148.2 (C-3); 149.2 (C-1); 171.7 (2CO); MS (DCI/NH_3): 354 ($M+H^+$).

4.1.10. *N*-(3-Nitrophenyl)ethylenediamine-*N′*,*N′*-diacetic acid (11). Using the same procedure than **5**, 353 mg of compound **10** gave **11** as brown crystals (267 mg, 90%).

^{1}H NMR (250 MHz, DMSO-d_6) δ_H (ppm): 2.88 (~t, 2H, J=6.3 Hz, NCH_2); 3.15 (~t, 2H, J=6.3 Hz, NCH_2); 3.51 (s, 4H, $2NCH_2$); 6.35 (bs, 1H, NH); 6.98 (m, 1H, H-6); 7.33 (m, 3H, H-2, H-4, H-5); ^{13}C NMR (50.3 MHz, DMSO-d_6) δ_C (ppm): 41.0 (NCH_2); 52.3 (NCH_2); 54.7 (NCH_2); 105.1 (C-2); 109.6 (C-6); 118.2 (C-4); 129.9 (C-5); 148.7 (C-3); 149.7 (C-1); 172.7 (2CO); MS (DCI/NH_3): 298 ($M+H^+$); mp=150 °C; Anal.: found: C, 48.0; H, 5.2; N, 13.9%; $C_{12}H_{15}N_3O_6$ requires: C, 48.5; H, 5.0; N, 14.1%.

4.2. Synthesis of PDDA derivatives

4.2.1. *N*-(2-Nitrophenyl)propylenediamine (12). Using the same procedure than **1** and substituting ethylenediamine by 1,3-diaminopropane (46.62 g, 0.63 mol), we obtained after purification **12** as an orange-red oil (11.42 g, 93%).

^{1}H NMR (250 MHz, $CDCl_3$) δ_H (ppm): 1.20 (bs, 2H, NH_2); 1.82 (q, 2H, J=7.0 Hz, CH_2); 2.82 (t, J=7.0 Hz, 2H, NCH_2); 3.33 (m, 2H, NCH_2); 6.56 (m, 1H, H-5); 6.80 (m, 1H, H-3); 7.35 (m, 1H, H-4); 8.04 (m, 1H, H-6); 8.11 (bs, 1H, NH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ_C (ppm): 32.3 (CH_2); 39.8 (NCH_2); 41.0 (NCH_2); 113.9 (C-3); 115.7 (C-5); 126.9 (C-6); 131.8 (C-2); 136.4 (C-4); 145.7 (C-1); MS (DCI/NH_3): 196 ($M+H^+$); 213 ($M+NH_4^+$); mp=174 °C; Anal.: found (as hydrochloride salt): C, 46.8; H, 6.2; N, 18.2%; $C_9H_{14}N_3O_2Cl$ requires: C, 46.7; H, 6.1; N, 18.2%.

4.2.2. *N*-(4-Nitrophenyl)propylenediamine (13). Using the same procedure than **6** and substituting ethylenediamine by 1,3-diaminopropane (46.62 g, 0.63 mol), we obtained after purification **13** as an orange solide (11.30 g, 92%).

^{1}H NMR (200 MHz, $CDCl_3$) δ_H (ppm): 1.40 (s, 2H, NH_2); 1.75 (m, 2H, CH_2); 2.89 (m, 2H, CH_2); 3.30 (m, 2H, CH_2); 5.76 (bs, 1H, NH); 6.92 (d, 2H, J=9.4 Hz, H-2, H-6); 7.21 (d, 2H, J=9.4 Hz, H-3, H-5); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ_C (ppm): 31.3 (CH_2); 40.5 (CH_2); 42.5 (CH_2); 110.8 (C-2, C-6); 126.5 (C-3, C-5); 140.8 (C-6); 153.7 (C-1); MS (DCI/NH_3): 196 ($M+H^+$); 213 ($M+NH_4^+$); Anal.: found: C, 55.1; H, 6.7; N, 21.3%; mp=94 °C; $C_9H_{13}N_3O_2$ requires: C, 55.1; H, 6.6; N, 21.4%.

4.2.3. *N*-(2-Nitrophenyl)propylenediamine-*N′*,*N′*-diethyl-diacetate (14). Using the same procedure than **3**, 846 mg of compound **12** gave **14** as an orange oil (1.44 g, 90%).

^{1}H NMR (250 MHz, $CDCl_3$) δ_H (ppm): 1.19 (t, 6H, J=7.0 Hz, $2CH_3$); 1.81 (qt, J=6.7 Hz, 2H, CH_2); 2.81 (m, 2H, NCH_2); 3.45 (m, 2H, NCH_2); 3.55 (s, 4H, $2NCH_2$); 4.15 (q, 4H, J=7.0 Hz, $2OCH_2$); 6.55 (m, 1H, H-5); 6.86 (m, 1H, H-3); 7.35 (m, 1H, H-4); 8.09 (m, 1H, H-6); 8.19 (bs, 1H, NH); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ_C (ppm): 13.9 (CH_3); 27.0 (CH_2); 40.8 (NCH_2); 51.5 (NCH_2); 55.1 ($2NCH_2$); 60.5 (2 OCH_2); 113.7 (C-3); 115.1 (C-5); 126.7 (C-6); 131.7 (C-2); 136.2 (C-4); 145.6 (C-1); 171.1 (2CO); MS (DCI/NH_3): 368 ($M+H^+$).

4.2.4. *N*-(4-Nitrophenyl)propylenediamine-*N′*,*N′*-diethyl-diacetate (15). Using the same procedure than **3**, 846 mg of compound **13** gave **15** as an orange oil (1.33 g, 83%).

^{1}H NMR (250 MHz, $CDCl_3$) δ_H (ppm): 1.23 (t, 6H, J=7.0 Hz, $2CH_3$); 1.69 (m, 2H, CH_2); 2.78 (m, 2H, NCH_2); 3.35 (m, 2H, NCH_2); 3.49 (s, 4H, $2NCH_2$); 4.17 (q, 4H, J=7.0 Hz, $2OCH_2$); 6.51 (d, 2H, J=9.4 Hz, H-2, H-6); 7.72 (bs, 1H, NH); 8.00 (d, 2H, J=9.4 Hz, H-3, H-5); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ_C (ppm): 14.4 (CH_3); 25.3 (CH_2); 41.9 (NCH_2); 52.4 (NCH_2); 54.9 ($2NCH_2$); 60.8 (2 OCH_2); 110.6 (C-2, C-6); 126.5 (C-3, C-5); 136.4 (C-4); 154.2 (C-1); 171.3 (2CO); MS (DCI/NH_3): 368 ($M+H^+$).

4.2.5. *N*-(2-Nitrophenyl)propylenediamine-*N′*,*N′*-diacetic acid hydrochloride salt (16). Using the same procedure than **5**, 367 mg of compound **14** gave **16** as a yellow powder (278 mg, 80%).

^{1}H NMR (250 MHz, DMSO-d_6) δ_H (ppm): 1.47 (m, 2H, CH_2); 2.77 (m, 2H, NCH_2); 3.48 (m, 6H, $3NCH_2$); 6.70 (m, 1H, H-5); 7.09 (m, 1H, H-3); 7.56 (m, 1H, H-4); 8.02 (m, H, H-6); 8.30 (bs, 1H, NH); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ_C (ppm): 26.2 (CH_2); 40.6 (NCH_2); 51.0 (NCH_2); 54.5 (NCH_2); 114.3 (C-3); 114.8 (C-5); 126.1 (C-6); 130.7 (C-2); 136.4 (C-4); 145.1 (C-1); 172.2 (2CO); MS (DCI/NH_3): 312 ($M+H^+$). Anal.: found (as hydrochloride salt): C, 44.6; H, 5.1; N, 12.4%; mp=158 °C; $C_{13}H_{18}N_3O_6Cl$ requires: C, 44.9; H, 5.2; N, 12.1%.

4.2.6. *N*-(4-Nitrophenyl)propylenediamine-*N′*,*N′*-diacetic acid hydrochloride salt (17). Using the same procedure than **5**, 367 mg of compound **15** gave **17** as an hydroscopic orange powder (274 mg, 79%).

^{1}H NMR (250 MHz, DMSO-d_6) δ_H (ppm): 1.67 (q, J=6.6 Hz, 2H, CH_2); 2.77 (t, 2H, J=6.6 Hz, NCH_2); 3.20 (m, 2H, NCH_2); 3.44 (s, 4H, $2NCH_2$); 6.64 (d, 2H, J=9.5 Hz, H-2, H-6); 7.50 (bs, 1H, NH); 7.56 (d, 2H, J=9.5 Hz, H-3, H-5); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ_C (ppm): 26.2 (CH_2); 40.6 (NCH_2); 51.4 (NCH_2); 54.6 (NCH_2); 110.6 (C-2, C-6); 126.2 (C-3, C-5); 135.2 (C-4); 154.5 (C-1); 172.4 (2CO); MS (DCI/NH_3): 312 ($M+H^+$); mp=130 °C; Anal.: found (as hydrochloride salt): C, 40.7;

H, 4.9; N, 11.2% $C_{13}H_{18}N_3O_6Cl.2H_2O$ requires: C, 40.7; H, 5.7; N, 11.0%.

4.3. Synthesis of bifunctional chelating agent

4.3.1. *N*-(2-Aminophenyl)ethylenediamine-*N*′,*N*′-diethyldiacetate (18). Catalytic hydrogenation of **3** (0.54 g, 1.53 mmol) in methanol (25 mL) over 10% Pd/C (20% w/w) was carried out at atmospheric pressure. After 30 min, the catalyst was filtered off (Celite), and the solvent was removed under reduced pressure. The crude material was purified by column chromatography on silica gel, eluting with methanol to give **18** as a brown oil (0.37 g, 75%).

^{1}H NMR (250 MHz, $CDCl_3$) δ_H (ppm): 1.24 (t, 6H, J=7.1 Hz, $2CH_3$); 3.07 (m, 4H, $2NCH_2$); 3.55 (s, 4H, $2NCH_2$); 4.13 (q, 4H, J=7.1 Hz, $2OCH_2$); 6.57–6.67 (m, 4H, ArH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ_C (ppm): 14.2 (CH_3); 41.6 (NCH_2); 53.0 (NCH_2); 55.1 ($2NCH_2$); 60.7 (2 OCH_2); 111.2 (C-3); 115.6 (C-5); 118.0 (C-6); 119.8 (C-2); 134.6 (C-4); 137.3 (C-1); 171.7 (2CO); MS (DCI/NH_3): 324 ($M+H^+$).

4.3.2. *N*-(2-Aminophenyl)ethylenediamine-*N*′,*N*′-diacetic acid dihydrochloride salt (19). *Method A*: 200 mg (0.62 mmol) of diester **18** in 10 mL of a 2 N NaOH/ethanol (1/1) solution was heated at reflux for 3 h. After cooling, the solution was acidified until pH was 1 with 2 N HCl. The solution was concentrated and the residue was taken twice with acetone (20 mL). After filtration, the filtrate was evaporated, dried under vacuum to afford a brown solid (168 mg, 75%).

Method B: Catalytic hydrogenation of **5** (510 mg, 1.53 mmol) in methanol (25 mL) over 10% Pd/C (20% w/w) was carried out at atmospheric pressure. After 30 min, the catalyst was filtered off (Celite), and the solvent was removed under reduced pressure. The residue was taken in water and the solution was acidified until pH was 1. After filtration, the filtrate was concentrated and dried under vacuum. The crude material was purified by a short column chromatography on silica gel, eluting with methanol to give **19** as a brown solid (221 mg, 40%).

^{1}H NMR (200 MHz, D_2O) δ_H (ppm): 2.74 (m, 2H, NCH_2); 3.04 (m, 2H, NCH_2); 3.14 (s, 4H, NCH_2); 6.72 (m, 4H, ArH); ^{13}C NMR (62.9 MHz, D_2O) δ_C (ppm): 44.8 (NCH_2); 55.9 (NCH_2); 61.5 ($2NCH_2$); 116.2 (C-6); 118.9 (C-4); 122.4 (C-3); 123.3 (C-2); 137.2 (C-5); 139.3 (C-1); 182.4 (2CO); MS (DCI/NH_3): 268 ($M+H^+$); mp=221 °C; Anal.: found (as dihydrochloride salt): C, 43.0; H, 5.6; N, 12.7% $C_{12}H_{19}N_3O_4Cl_2$ requires: C, 43.4; H, 6.1; N, 12.4%.

4.4. Synthesis of Re(I) tricarbonyl complex

4.4.1. Re(I) tricarbonyl *o*-NO_2Ph-PDDA complex (20). 100 mg (0.3 mmol) of the ligand **5**, 250 mg (0.3 mmol) of commercial $Re(CO)_5Cl$ and 1.26 ml (0.9 mmol) of Et_3N were solved in MeOH (20 mL) and stirred at 60 °C for 4 h. The solution was evaporated to dryness and the residue was washed with ether (3×30 mL) then was dissolved in a minimum of MeOH (5 mL). Addition of ether (30 mL) afforded a yellow precipitate which was filtered and concentrated to dryness under reduce pressure. The crystallisation step was repeated twice. In these conditions, produced Et_3NHCl staid in the filtrate and **20** was obtained as a yellow powder (triethylamine hydrochloride salt, 180 mg, 90%).

NMR ^{1}H (300 MHz, DMSO-d_6) δ_H (ppm): 1.07 (t, 9H, J=7.1 Hz, CH_3); 3.01 (q, 6H, J=7.1 Hz, NCH_2); 3.39 (m, 2H, NCH_2); 3.48 (AB system, 2H, J=16.0 Hz, CH_2CO); 3.59 (m, 2H, NCH_2); 3.65 (AB system, 2H, J=16.0 Hz, CH_2CO); 6.63 (m, 1H, H-6); 7.17 (d, 1H, J=8.5 Hz, H-4); 7.50 (m, 1H, H-5); 8.00 (dd, 1H, J=8.5 and 1.5 Hz, H-3); 8.13 (t, J=6,0 Hz, 1H, NH).^{13}C NMR (75.5 MHz, DMSO-d_6) δ_C (ppm): 9.17 (CH_3); 38.5 (NCH_2); 46.2 (NCH_2); 63.2 (CH_2CO); 67.2 (NCH_2); 114.9 (C-6); 116.0 (C-4); 126.8 (C-3); 131.8 (C-2); 137.2 (C-5); 145.0 (C-1); 178.8 (2CO); 199.1, 199.4 (3CO), IR (KBr): 3369 br, 2029 s, 1917 s, 1887 s, 1666 s cm^{-1}; MS (ES^-): 564 (60), 566 (100) [M^-]; mp=217 °C; Anal.: found: C, 38.1; H, 4.3; N, 8.4%; $C_{21}H_{29}N_4O_9Re$ requires: C, 37.8; H, 4.3; N, 8.4%.

Acknowledgements

The authors thank the C.M.I.F.M. (Comité Mixte Inter Universitaire Franco-Marocain) for financial support (project MA/02/35).

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