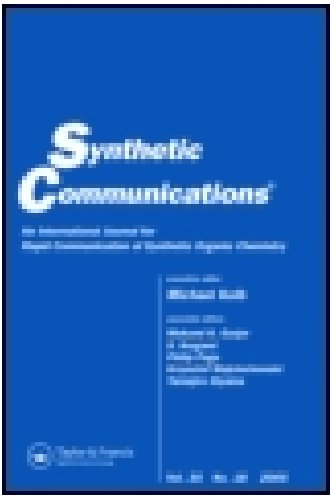

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Synthesis of Functionalized 3,3,9,9-Tetramethyl-4,8-Diazaundecane-2,10-Dione Dioximes (Propylene Amine Oximes, PnAOs)

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SYNTHESIS OF FUNCTIONALIZED 3,3,9,9-TETRAMETHYL-4,8-DIAZAUNDECANE-2,10-DIONE DIOXIMES (PROPYLENE AMINE OXIMES, PnAOs)

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ABSTRACT

The syntheses of several new derivatives of PnAO and their chloronitroso precursors are described. The PnAOs were prepared by an improvement of the reported general procedure. An unexpected product, an isooxalone, was formed while attempting to prepare 1-carbomethoxyl-PnAO.

INTRODUCTION

Technetium-99m is the most widely used radionuclide for diagnostic imaging.[1] It has been shown[2] that 3,3,9,9-tetramethyl-4,8-diazaundecane-2,10-dione dioxime (commonly known as the Propylene Amine Oxime, PnAO), can be labelled in good yield with technetium-99m. In addition to technetium, PnAO complexes have been reported[3, 4] with a number of other transition metals; the notable exception is rhenium. The neutral lipophilic Tc-99m complex of PnAO prepared by Troutner and coworkers[5] is capable of crossing cell membranes such as the blood-brain barrier,[6] thereby having the potential to provide a range of diagnostic imaging agents. We now report the preparation of a number of functionalized 3,3,9,9-tetramethyl-4,8-diazaundecane-2,10-dione dioxime ligands with the view to studying the effects of a range of substituents on cell permeability

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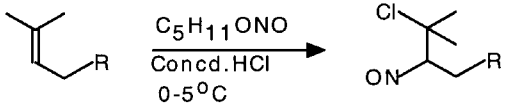
and bio-distribution of their Tc-99m complexes. With these data, we hope to be able to modify promising new technetium complexes to improve their in vivo characteristics.

RESULTS AND DISCUSSION

The synthetic scheme for the preparation of functionalized 3,3,9,9-tetramethyl-4,8-diazaundecane-2,10-dione dioximes (PnAOs) **4a-4f** is shown in schemes 1 and 2. The starting point for all compounds is the synthesis of dimethylallyl derivatives **1a-1h**. For the preparation of ethers **1a** and **1b**, commercially available 3-methyl-2-buten-1-ol (**1e**) was O-alkylated with excess of the appropriate alkyl iodide as the solvent and in the presence of silver oxide as the base. The alkyl ethers **1a** and **1b** were obtained in 87% and 51% yield respectively. Benzyl ether **1c** was obtained by the alkylation of 3-methyl-2-buten-1-ol

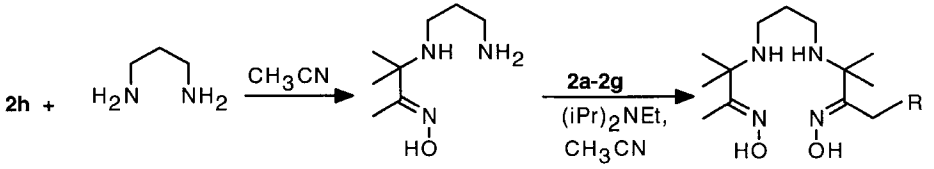
Scheme 1



1 **2**

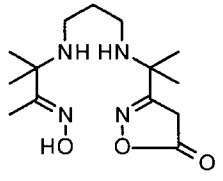
a) R = OCH_3; b) R = OC_2H_5; c) R = $OCH_2C_6H_5$; d) R = $NHCOCH_3$; e) R = OH; f) R = $CH_2CO_2CH_3$; g) R = CO_2CH_3; h) R = H.

Scheme 2



3 **4**

a) R = OCH_3; b) R = OC_2H_5; c) R = $OCH_2C_6H_5$; d) R = $NHCOCH_3$; e) R = OH; f) R = $CH_2CO_2CH_3$.



5

(**1e**) with benzyl bromide using sodium hydride. The amide **1d**, required as the starting material for the chloronitroso derivative **2d**, was prepared in 51% yield by treating dimethylallylamine[7] with acetic anhydride in methylene chloride in the presence of triethylamine. Esters **1f**[8] and **1g**[9] were prepared by the literature procedure. The key intermediates for the preparation of oximes **4a-4f** described herein are 1-substituted 3-chloro-3-methyl-2-nitrosobutanes **2a-2h**. These intermediates were prepared from the corresponding precursors **1a-1h** as shown in scheme 1. The synthesis of **2h** by this method was described previously.[10] Dimethylallyl derivatives **1a-1h** were reacted with isoamyl nitrite and concentrated HCl at 0-5 °C to afford 1-substituted 3-chloro-3-methyl-2-nitrosobutanes **2a-2h** in 50-75% yield.

3-[(3-Aminopropyl)amino]-3-methyl-2-butanone oxime (**3**), required for the preparation of functionalized PnAO derivatives, was prepared by the method of Nowotnik and Canning[10] but with crucial modifications. The published procedure[10] involves the addition of a methanolic solution 3-chloro-3-methyl-2-nitrosobutane[10] to excess of 1,3-propanediamine in methanol. HPLC analysis of the crude reaction mixture indicated the presence of the desired mono oxime and bis adduct. Workup followed by crystallization of the crude diamine mono oxime from ether/petroleum ether afforded **3** with a reported mp 69-72 °C. Under the reported reaction conditions, 3-chloro-3-methyl-2-nitrosobutane undergoes solvolysis in methanol and the major product was found to be 2-hydroxyimino-3-methoxy-3-methylbutane. We prepared **3** by adding solid 3-chloro-3-methyl-2-nitrosobutane to a solution of 1,3-propanediamine in acetonitrile and recrystallized the product from acetonitrile. The melting point of our product was 75-76 °C. Our modification appears to give **3** with greater purity (higher and sharper mp), and our yield was 63% compared to 30% for the apparently impure product reported previously.

Propylene amine oximes **4a-4c** were then prepared by the alkylation[11] of **3** with the corresponding 3-chloro-3-methyl-2-nitrosobutanes in acetonitrile in the presence of *N,N*-diisopropylethylamine. Debenzylation of oxime **4c** in methanol using Pd-C (10%) gave the oxime (**4e**) in 80% yield. Reaction of chloronitroso derivative **2d** with **3** under similar conditions for 6 h afforded a 40% yield of **4d**. The ester **2g** reacted readily with amine **3** in acetonitrile over a period of 3 h to afford an unexpected product whose structure was assigned as **5** on the basis of ^{1}H NMR, ^{13}C NMR, MS and analytical data. The alkylation of the diamine mono oxime **3** with methyl 4-chloro-4-methyl-3-nitrosopentanoate **2g** was examined in several solvent systems (including CH_3OH, CH_3CN, CH_2Cl_2) in the presence of one equivalent of base (Et_3N or $(i\text{-}C_3H_7)_2NC_2H_5$). In all cases the

isooxalone **5** was isolated, and/or observed on HPLC analysis, as the sole product. Presumably the ester-oxime was formed but cyclized to give the isooxazolone derivative **5**. On the other hand, under the same reaction conditions the homologue **2f** gave the expected product; the oxime **4f**. The details of preparation of functionalized PnAO ligands from **2a-2g** are given in the experimental section.

EXPERIMENTAL SECTION

All melting points and boiling points are uncorrected. Melting points were recorded using Thomas Hoover Capillary Melting Point Apparatus. NMR spectra were recorded on a Jeol 270 MHz spectrophotometer. Chemical shift values are reported in δ values with reference to tetramethylsilane as an internal standard. Mass spectra were recorded on a Finnigan TSQ Spectrophotometer. HPLC analyses were performed using a Rainin HPX system. A Dynamax C_{18} reversed-phase column was employed [column: Microsorb-C_{18}; 0.46 x 25.0 cm, 5 m; solvent: 0.1%TFA/water (A) and 0.1%TFA/acetonitrile (B); flow rate: 1.0 mL/min; run condition: linear gradient, 1% increase in B per min; ran at 230 and 254 nm for 50 min]. HPLC grade acetonitrile and water were obtained from J. T. Baker Inc. and were filtered and degassed prior to their use.

1-Methoxy-3-methyl-2-butene (1a). Freshly prepared silver oxide (101 g, 370 mmol) was added to a mixture of 3-methyl-2-buten-1-ol (21.0 g, 25 mL, 240 mmol) and methyl iodide (213 g, 93 mL,) and heated in an oil bath at 45 °C for 6 h with stirring. Silver salts were removed by filtration and the filter cake was washed with ether (200 mL). The filtrate and the washings were combined and evaporated to remove ether and excess methyl iodide. The oil obtained was distilled under atmospheric pressure to yield 21 g (87%) of 1-methoxy-3-methyl-2-butene[12] as a colorless liquid; bp 102-104 °C. ^{1}H NMR ($CDCl_3$) δ 1.7 (d, 6H, $C\underline{H}_3$), 3.31 (s, 3H, $OC\underline{H}_3$), 3.92 (d, 2H, $C\underline{H}_2$), 5.38 (t, 1H, $(CH_3)_2C{=}C\underline{H}$-).

1-Ethoxy-3-methyl-2-butene (1b). To a mixture of 3-methyl-2-buten-1-ol (21.0 g, 25 mL, 240 mmol) and ethyl iodide (300 mL) freshly prepared silver oxide (101 g, 370 mmol) was added and stirred at 45 °C for 12 h. Silver salts were removed by filtration and the filter cake was washed with ether (2 x 150 mL). The filtrate and the washings were combined and the ether and excess ethyl iodide was removed by distillation. The oil obtained was distilled under atmospheric pressure to yield 14.8 g (51%) of 1-ethoxy-3-methyl-2-butene[13] as a colorless liquid; bp 119-120 °C. ^{1}H NMR ($CDCl_3$) δ 1.2(t, 3H, $CH_2C\underline{H}_3$), 1.72 (d, 6H, $C\underline{H}_3$), 3.45(m, 2H,$C\underline{H}_2CH_3$), 3.95 (d, 2H, $C\underline{H}_2$), 5.38 (t, 1H, $(CH_3)_2C{=}C\underline{H}$-).

Benzyldimethylallyl ether (1c). To a solution of 3-methyl-2-buten-1-ol (25.8 g, 300 mmol) in dry THF (300 mL) was added NaH (60% mineral oil, 12 g , 300 mmol) in portions

over a period of 1 h. After the addition, the reaction mixture was stirred for 1 h at RT. Benzyl bromide (47.6 g, 280 mmol) was added dropwise to this mixture and stirred at RT for 12 h. THF was removed on a rotary evaporator and the residue was poured into water and extracted with ether. The ether layer was separated, washed with water and dried (Na_2SO_4). Ether was removed and the oil obtained was distilled under reduced pressure; bp 65 °C/0.5 mm. Yield: 25.2 g (48%). ^{1}H NMR ($CDCl_3$) δ 1.72 and 1.82 (s, 6H, $C\underline{H}_3$), 4.01, [d, 2H, $(CH_3)_2C{=}CHOC\underline{H}_2$], 4.5 (s, 2H, $OC\underline{H}_2Ph$), 5.42 [m, 1H, $(CH_3)_2C{=}C\underline{H}$-], 7.35 (m, 5H, ArH).

1-Acetylamino-3-methyl-2-butene (1d)[14]**.** Triethylamine (4.0 g, 40 mmol) was added to suspension of 3,3-dimethylallylamine hydrochloride (2.4 g, 20 mmol) in CH_2Cl_2 (50 mL) and stirred in ice bath for 15 min. Acetic anhydride (3.0 g, 200 mmol) was added dropwise to the stirred reaction mixture at 0 °C and the reaction mixture was stirred at 0 °C for 30 min and room temperature for 30 min. The resulting solution was poured into ice-water (100 mL), the organic layer was separated and washed with a saturated solution of $NaHCO_3$ (2 x 50 mL), water (2 x 50 mL), and dried over Na_2SO_4. Evaporation of solvent afforded an oil (1.5 g, 51%). ^{1}H NMR ($CDCl_3$) δ 1.70 [d, 6H, $=C(C\underline{H}_3)_2$], 1.94 (s, 3H, $C\underline{H}_3CO$), 3.82 (t, 2H, $C\underline{H}_2CH{=}$), 5.18 (t, 1H, $CH_2C\underline{H}{=}$), 6.14 (b, 1H, $N\underline{H}COCH_3$).

1-Methoxy-3-chloro-3-methyl-2-nitrosobutane (2a). Concentrated HCl (10 mL) was added to a cooled (0-5 °C) mixture of isoamyl nitrite (14.0 g, 120 mmol) and 1-methoxy-3-methyl-2-butene (6.0 g, 60 mmol). The temperature was maintained below 5 °C during the addition and the reaction mixture was stirred at 5 °C for an additional 30 min. The product was filtered and washed with cold (-20 °C) 1:1 mixture of ethanol and ether. The solid was further washed with petroleum ether to afford a white solid. Yield 5.7 g (71%); mp 126-127 °C. ^{1}H NMR ($CDCl_3$) δ 1.62 (s, 6H, $C\underline{H}_3$), 3.31 (s, 3H, $OC\underline{H}_3$), 3.9 and 4.12 (m, 2H, $C\underline{H}_2$), 6.12 [dd, 1H, $(CH_3)_2C{=}C\underline{H}$-]. MS: m/z 331 $(2M+H)^+$.

The following chloronitroso derivatives were prepared by the method described above for **2a:**

1-Ethoxy-3-chloro-3-methyl-2-nitrosobutane (2b). Yield: 6.9 g (64%); mp 84-85 °C. ^{1}H NMR ($CDCl_3$) δ 1.12 (t, 3H, $CH_2C\underline{H}_3$), 1.65 (d, 6H, $C\underline{H}_3$), 3.49 and 3.95 (m, 2H, $C\underline{H}_2OCH_2C\underline{H}_3$), 4.15 (m, 2H,$C\underline{H}_2C\underline{H}_3$), 6.12 (dd, 1H, $[CH_3)_2C{=}C\underline{H}$-]. MS: 180 $(M+H)^+$.

1-Benzyloxy-3-chloro-3-methyl-2-nitrosobutane (2c). Yield: 7.8 g (54%); mp 127-128 °C. ^{1}H NMR (DMSO-d_6) δ 1.52 and 1.58 (s, 6H, $C\underline{H}_3$), 4.01, [m, 2H, $(CH_3)_2C{=}CHOC\underline{H}_2$]

4.5 (m, 2H, OCH_2Ph), 6.12 [m, 1H, $(CH_3)_2C=CH$-], 7.35 (m, 5H, ArH). MS: m/z 241 $(2M+H)^+$.

1-Acetylamino-3-chloro-3-methyl-2-nitrosobutane (2d). Yield: 0.66 g (39%); mp 107-110 °C. MS: m/z 193 $(M+H)^+$. ^1H NMR (DMSO-d_6) δ 1.68 [d, 6H, $C(CH_3)_2$], 1.84 (s, 3H, CH_3CO), 4.10 (t, 2H, CH_2CHNO), 7.82 (b, 1H, $NHCOCH_3$), 12.02 (t, 1H, $CH_2C=NOH$).

Methyl 5-chloro-5-methyl-4-nitrosohexanoate (2f). Yield: 3.0 g (41%) mp 90-91 °C. ^1H NMR ($CDCl_3$) δ 1.68 and 1.71[2s, 6H, $C(CH_3)_2$], 2.35[m, 4H, $(CH_2)_2$], 3.73(s, 3H, $COOCH_3$) and 5.11(t, 1H, CH). MS: m/z 208 $(M+H)^+$.

Methyl 4-chloro-4-methyl-3-nitrosopentanoate (2g). Yield: 3.0 g (40%); mp 85-87 °C. ^1H NMR ($CDCl_3$) δ 1.62 and 1.63[2s, 6H, $C(CH_3)_2$], 3.05-3.45(m, 2H, CH_2), 3.66(s, 3H, $COOCH_3$) and 6.22(m, 1H, CH). MS: m/z 194 $(M+H)^+$.

3[(3-Aminopropyl)amino]-3-methyl-2-butanone oxime (3). 3-Chloro-3-methyl-2-nitrosobutane (13.5 g, 100 mmol) was added in small portions to a cooled (0 °C) stirred solution of 1,3-propanediamine (25 mL, 300 mmol) in acetonitrile over a period of 0.5 h. The reaction mixture was stirred at 5 °C for 1 h and at RT for 2 h. The acetonitrile solution was filtered and evaporated to give a white paste. This was treated with water (26 mL) and the aqueous suspension was cooled in ice bath for 0.5 h and filtered, washed with water (2 x 25 mL). The filtrate and the combined washings were made basic (pH 11) by the addition of 6N NaOH. The suspension was again cooled, and the precipitated bis adduct was filtered and washed with water (2 x 10 mL). Water was evaporated under reduced pressure and the paste obtained dried under vacuum overnight to afford a solid. It was recrystallized from acetonitrile. Yield: 10.9 g (63%); mp 76.5-77.5 °C. ^1H NMR (D_2O) δ 1.12 (s, 6H, CH_3), 1.5 9 (m, 2H, $CH_2CH_2CH_2NH_2$), 1.72 (s, 3H, $CH_3C=N$), 2.2 (t, 2H, $NHCH_2CH_2CH_2NH_2$), 2.52 (t, 2H, $NHCH_2CH_2CH_2NH_2$).

1-Methoxy-3,3,9,9-tetramethyl-4,8-diazaundecane-2,10-dione dioxime Hydrochloride (4a). Chloronitroso derivative **2a** (1.1 g, 6.6 mmol) was added to a solution of diamine mono oxime **3** (1.0 g, 5.8 mmol) and *N,N*-diisopropylethylamine (0.97 g, 7.5 mmol) in acetonitrile (5.0 mL) and stirred at room temperature for 12 h. A white solid was formed in 30 min. After the reaction, the precipitated solid was filtered and filtrate was evaporated on a rotary evaporator. The thick oil which formed was washed several times with ethyl acetate and the solid obtained was recrystallized from acetonitrile. Yield: 0.52 g (28%); mp 162-63 °C. ^1H NMR (D_2O) δ 1.28[s, 12H, $C(CH_3)_2$], 1.69(m, 2H,

NHCH$_2$C$\underline{H}_2$CH$_2$NH), 1.79(s, 3H, CH$_3$), 2.65(m, 4H, NHC$\underline{H}_2$CH$_2$C$\underline{H}_2$NH), 3.31(s, 3H, OC$\underline{H}_3$), 4.20(s, 2H, C$\underline{H}_2$OCH$_3$). ^{13}C NMR (DMSO-d$_6$) δ 9.5[*C*H$_3$(C=N)], 24.0 & 24.4[C(*C*H$_3$)$_2$], 27.1(CH$_2$*C*H$_2$CH$_2$), 40.6 & 40.8(NH*C*H$_2$), 58.7(O*C*H$_3$), 59.2[*C*(CH$_3$)$_2$], 63.0(*C*H$_2$OCH$_3$) and 155.9 & 157.0(*C*=N). MS: m/z 303 (M+H)$^+$. Anal. Calcd. for C$_{14}$H$_{31}$N$_4$O$_3$Cl 0.5H$_2$0: C, 48.33; H, 9.27; N, 16.11, Cl 10.19. Found: C, 48.28; H, 9.13; N, 16.23; Cl, 10.04.

1-Ethoxy-3,3,9,9-tetramethyl-4,8-diazaundecane-2,10-dione dioxime (4b). Chloronitroso derivative **2b** (0.90 g, 5 mmol) was added to a solution of diamine mono oxime **3** (0.85 g, 5 mmol) and *N,N*-diisopropylethylamine (0.78 g, 5 mmol) in acetonitrile (5.0 mL) and stirred at RT for 12 h. A white solid was formed in 30 min. After the reaction, the solid was filtered and acetonitrile was evaporated on a rotary evaporator. The resultant thick oil was washed several times with methylene chloride followed by hexane. The solid thus obtained was recrystallized from acetonitrile; mp 152-153 °C. ^{1}H NMR (D$_2$O) δ 1.12(t, 3H, CH$_2$C$\underline{H}_3$), 1.28[s, 12H, C(CH$_3$)$_2$], 1.69(m, 2H, NHCH$_2$C$\underline{H}_2$CH$_2$NH), 1.79(s, 3H, CH$_3$), 2.65(m, 4H, NHC$\underline{H}_2$CH$_2$C$\underline{H}_2$NH), 3.35(s, 3H, OC$\underline{H}_2$CH$_3$), 4.20(s, 2H, C$\underline{H}_2$OCH$_2$CH$_3$). ^{13}C NMR (DMSO-d$_6$) δ 9.4[*C*H$_3$(C=N)], 14.9(OCH$_2$*C*H$_3$), 23.9 & 24.3[C(*C*H$_3$)$_2$], 26.9(CH$_2$*C*H$_2$CH$_2$), 40.5 & 40.7(NH*C*H$_2$), 59.1[*C*(CH$_3$)$_2$], 60.8(*C*H$_2$OEt), 66.0(O*C*H$_2$CH$_3$) and 156.0 & 156.9(*C*=N). MS: m/z 317 (M+H)$^+$. Anal. Calcd. for C$_{15}$H$_{33}$N$_4$O$_3$Cl: C, 51.05; H, 9.43; N, 15.88; Cl, 10.05. Found: C, 50.85; H, 9.39; N, 15.68; Cl, 9.95.

1-Benzyloxy-3,3,9,9-tetramethyl-4,8-diazaundecane-2,10-dione dioxime (4c). A solution of chloronitroso derivative **2c** (2.4 g, 100 mmol) in acetonitrile (25 mL) was added to a solution of diamine mono oxime **3** (1.73 g, 100 mmol) and *N,N*-diisopropylethylamine (1.3 g, 100 mmol) in acetonitrile (25 mL) and stirred at RT for 24 h. After the reaction, the solid was filtered and dissolved in methanol and basified with methanolic ammonia. Methanol was removed and the solid thus obtained was recrystallized from acetonitrile. Yield: 0.52 g (28%); mp 162-63 °C. ^{1}H NMR (DMSO-d$_6$) δ 1.02 and 1.18[s, 12H, C(C$\underline{H}_3$)$_2$], 1.32(m, 2H, NHCH$_2$C$\underline{H}_2$CH$_2$NH), 1.72(s, 3H, CH$_3$), 2.18 and 2.28(m, 4H, NHC$\underline{H}_2$CH$_2$C$\underline{H}_2$NH), 4.21(s, 2H, C=NOC$\underline{H}_2$], 4.5(s, 2H, OC$\underline{H}_2$Ph), 7.45(m, 5H, Ar$\underline{H}$), 10.31 and 10. 81(s, 2H, OH). ^{13}C NMR (DMSO-d$_6$) δ 9.9[*C*H$_3$(C=N)], 26.4 & 27.0[C(*C*H$_3$)$_2$], 32.9(CH$_2$*C*H$_2$CH$_2$), 42.1 & 42.3(NH*C*H$_2$), 57.6 & 57.8[*C*(CH$_3$)$_2$], 62.5(*C*H$_2$OBz), 73.5(O*C*H$_2$C$_6$H$_5$), 128.3, 128.9, 129.1 & 139.1(*C*$_6$H$_5$) and 159.7 & 161.0(*C*=N). Anal. Calcd. for C$_{20}$H$_{34}$N$_4$O$_3$: C, 63.46; H, 9.05; N, 14.80. Found: C, 63.27; H, 9.14; N, 14.37.

1-Acetylamino-3,3,9,9-tetramethyl-4,8-diazaundecane-2,10-dione dioxime (4d). 3-[(3-Aminopropyl)amino]-3-methyl-2-butanone oxime **3** (0.38 g, 2.2 mmol) was mixed with *N,N*-diisopropylethylamine (0.28 g, 2.2 mmol) in acetonitrile (5 mL). To the solution was added 1-acetylamino-3-chloro-3-methyl-2-nitrosobutane (0.4 g, 2.1 mmol). The suspension was stirred under N_2 at 45 °C for 48 h, and filtered. The filtrate was evaporated to dryness and the gummy residue was treated with a saturated solution of K_2CO_3 (3 mL), and extracted with ethyl acetate (3 x 10 mL). Evaporation of the ethyl acetate gave an oil which was purified by column chromatography (silica gel, 50% MeOH-CH_2Cl_2) to give a solid. This was recrystallized from ethyl acetate-acetonitrile to afford a white powder. Yield: 0.2 g (29%); mp 113-115 °C. MS: m/z 364 $(M+Cl)^+$, 330 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 1.25 and 1.26[s, 12H, $C(C\underline{H}_3)_2$], 1.62(m, 2H, $CH_2C\underline{H}_2CH_2$), 1.86(s, 3H, $C\underline{H}_3CO$), 1.99(s, 3H, $C\underline{H}_3CNO$), 2.45 and 2.47(m, 4H, $NHC\underline{H}_2CH_2$) 4.16(d, 2H, $C\underline{H}_2CNO$), 7.01(b, 1H, $N\underline{H}COCH_3$). ^{13}C NMR (DMSO-d_6) δ 9.0[CH_3(C=N)], 22.4($COCH_3$), 25.6 & 25.8[$C(CH_3)_2$], 31.4($CH_2CH_2CH_2$), 31.9(CH_2NHCO), 41.3 & 41.4($NHCH_2$), 56.5 & 56.8[$C(CH_3)_2$], 159.3 & 160.2(C=N) and 168.8(C=O). Anal. Calcd. for $C_{15}H_{31}N_5O_3$: C, 54.69; H, 9.48; N, 21.26; O, 14.57. Found: C, 54.43; H, 9.47; N, 20.79.

1-Hydroxy-3,3,9,9-tetramethyl-4,8-diazaundecane-2,10-dione dioxime (4e). To a solution of PnAO-1-OCH_2Ph (1.9 g, 5 mmol) in methanol (50 mL), Pd-C 10% (2 g) was added and hydrogenated (50 lbs/sq.inch) for 72 h. Catalyst was removed by filtration and the methanol was removed on a rotary evaporator to afford a thick viscous oil. Recrystallization of the oil from acetonitrile gave **4e** as crystalline solid. Yield: 0.5 g (35%); mp 127-28 °C. ^1H NMR (D_2O) δ 1.12 and 1.18[s, 12H, $C(C\underline{H}_3)_2$], 1.47(m, 2H, $NHCH_2C\underline{H}_2CH_2NH$), 1.76(s, 3H, CH_3), 2.26(m, 4H, $NHC\underline{H}_2CH_2C\underline{H}_2NH$), 4.32(s, 3H, $OC\underline{H}_2OH$). ^{13}C NMR (DMSO-d_6) δ 9.0[CH_3(C=N)], 25.7 & 26.0[$C(CH_3)_2$], 31.2($CH_2CH_2CH_2$), 41.1 & 41.2($NHCH_2$), 56.8(CH_2OH), 56.9 & 57.8[$C(CH_3)_2$] and 160.2 & 161.3(C=N). MS: m/z 289 $(M+H)^+$. Anal. Calcd. for $C_{13}H_{28}N_4O_3$: C, 54.14; H, 9.79; N, 19.43. Found: C, 54.50; H, 9.91; N, 19.54.

Reaction of methyl 4-chloro-3-nitroso-4-methylpentanoate (2g) with diamine mono oxime 3. To a solution of diamine mono oxime **3** (0.50 g, 2.89 mmol) in dichloromethane (5 mL) was added methyl 4-chloro-4-methyl-3-nitrosopentanoate **2g** (0.62 g, 3.20 mmol) in portions with stirring at room temperature. After the addition, the reaction mixture was monitored for the disappearance of the diamine mono oxime **3** by analytical HPLC and the reaction was found to be over within 30 min. The solvent was then removed on a rotary

evaporator to afford a colorless solid which was then crystallized from methanol-ether. The ^{1}H NMR spectrum of the isolated compound contained no peak attributable to the methyl ester indicating the formation of a cyclized compound **5**. Yield: 0.91 g (94%); mp 137-138 °C. ^{1}H NMR (D_2O) δ 1.25 & 1.38[2s, 12H, C(CH_3)$_2$], 1.78(m, 2H, $CH_2CH_2CH_2$), 1.80[s, 3H, C(NOH)CH_3] and 2.80(m, 6H, NCH_2 & CH_2CO). ^{13}C NMR (DMSO-d_6) δ 9.9[CH_3(C=N)], 26.1 & 26.9[C(CH_3)$_2$], 33.0($CH_2CH_2CH_2$), 42.1 & 42.3($NHCH_2$), 58.2 & 58.6[C(CH_3)$_2$], 65.3(CH_2CO), 159.9 & 160.8(C=N) and 166.9(C=O). MS: m/z 299 $(M+H)^+$. HRMS for $C_{14}H_{26}N_4O_3$ $(M+H)^+$ calcd 299.2083; found 299.2082. Anal. Calcd. for $C_{14}H_{26}N_4O_3$ 0.85H_2O: C, 51.25; H, 8.46; N, 16.90. Found: C, 51.24; H, 8.12; N, 17.04. HPLC: Retention time: 15.23 min. A single peak was observed at 230 nm (99.71%) and 254 nm (99.29%).

1-Carbomethoxy-3,3,9,9-tetramethyl-4,8-diazaundecane-2,10-dione dioxime (4f). To a solution of diamine mono oxime **3** (0.42 g, 2.43 mmol) in dry dichloromethane (5 mL) was added methyl 5-chloro-5-methyl-4-nitrosohexanoate **2f** (0.50 g, 2.41 mmol) in portions with stirring under nitrogen atmosphere. After the addition the reaction mixture was stirred for 3 h at room temperature and the white precipitate which formed was removed by filtration. The filtrate was then concentrated to a paste which, after trituration with dry ether, provided a solid which was crystallized from ether to afford **4f** as a colorless solid. Yield: 0.33 g (40%); mp 114-115 °C. ^{1}H NMR ($CDCl_3$) δ 1.23[2s, 12H, C(CH_3)$_2$], 1.58(m, 2H, $CH_2CH_2CH_2$), 1.86[s, 3H, C(NOH)CH_3], 2.45(t, 4H, NCH_2) 2.68[s, 4H, (CH_2)$_2$$COOCH_3$] and 3.70(s, 3H, $COOCH_3$). ^{13}C NMR (DMSO-d_6) δ 10.1[CH_3(C=N)], 26.6 & 27.3[C(CH_3)$_2$], 33.1($CH_2CH_2CH_2$), 42.3 & 42.5($NHCH_2$), 52.8($COOCH_3$), 58.1 & 58.5[C(CH_3)$_2$], 64.5(CH_2OCH_2COO), 73.5(OCH_2COOCH_3), 160.5 & 161.9(C=N) and 167.3($COOCH_3$). MS: m/z 345 $(M+H)^+$. Anal. Calcd. for $C_{16}H_{32}N_4O_4$·0.02H_2O: C, 55.79; H, 9.36; N, 16.27. Found: C, 55.86; H, 9.38; N, 16.14. HPLC: Retention time: 20.75 min. A single peak was observed at 230 nm (100%) and 254 nm (99.50%).

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