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Synthesis of Nitroimidazole Substituted 3,3,9,9-Tetramethyl-4,8-diazaundecane-2,10-dione Dioximes (Propylene Amine Oximes, PnAOs): Ligands for Technetium-99m Complexes with Potential for Imaging Hypoxic Tissue

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Abstract: *A series of 2-substituted-1,3-diaminopropanes (**1b-1f, 1h**) have been synthesized as precursors to nitroimidazole-substituted 3,3,9,9-tetramethyl-4,8-diazaundecane-2,10-dione dioxime (**21b, 21d, 21e** and **26a-26c**) (Propylene Amine Oxime, PnAO) ligands. 3-Chloro-3-methyl-1-(2- or 4-nitro-1H-imidazol-1-yl)-2-nitroso-butanes (**18a-e**) required for the syntheses of nitroimidazole substituted propylene amine oxime (PnAO) ligands were prepared from the corresponding dimethylallyl-nitroimidazoles (**17a-17e**) by the addition of nitrosyl chloride. A number of nitroimidazole derivatized PnAO ligands possessing potential for either electrostatic, hydrophobic, or hydrophilic interactions were synthesized as precursors to technetium-99m complexes under investigation as potential imaging agents of hypoxia. Derivatives of PnAO, substituted at carbon one, were prepared using the 3-chloro-3-methyl-1-(2- or 4-nitro-1H-imidazol-1-yl)-2-nitrosobutanes. Three PnAOs **26a-26c** derivatized at the central carbon atom, were prepared using 3-bromo-3-methylbutane-2-one (24).*

INTRODUCTION

Oxygen-deficient (hypoxic) regions of the myocardium represent living tissue which is at risk from permanent damage or tissue death. As a result, delineation of viable tissue from normal or infarct in the border zone of poorly perfused (ischemic) regions of myocardium provides useful information to the physician in the management of patients with ischemic heart disease. Radiopharmaceuticals such as ^{18}F-deoxyglucose,[1] ^{201}Tl[2], and ^{82}Rb[3] have proven useful as indicators of relative metabolic utilization or perfusion of the heart, but these compounds often provide poor discrimination between infarct and regions of ischemia. An alternative approach is to use radiopharmaceuticals based on nitroimidazoles, which are believed[4] to be selectively trapped in hypoxic tissue via enzymatic reduction of the nitro group to form reactive species which are further reduced in the absence of oxygen. With nitroimidazole-based radiopharmaceuticals, hypoxic regions appear as areas of increased uptake of radioactivity, while normal and infarcted tissue have relatively low levels of radioactivity. There has been some progress in this area with ^{18}F-misonidazole (a derivative of 2-nitroimidazole).[5] For reasons of cost, availability, half life, and physical decay characteristics, technetium-99m is the radionuclide of choice in nuclear medicine. With a view to developing a new technetium based imaging agent that will localize in hypoxic tissue we have incorporated the bioreducible nitroimidazole group onto 3,3,9,9-tetramethyl-4,8-diazaundecane-2,10-dione dioxime (Propylene Amine Oxime, PnAO), a well known ligand for Tc.[6] We have synthesized a number of 2-nitroimidazole derivatized PnAO ligands for evaluation as potential hypoxia imaging agents. The size and

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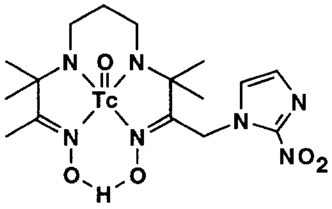
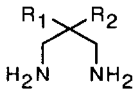
lipophilicity (factors which will influence biodistribution) of these complexes could be modified by varying the substituents (polar/non polar) on the PnAO skeleton. As the reduction potential appears to be an important variable in the hypoxia localizing ability of nitroimidazoles,[7] we have prepared 2- and 4-nitroimidazole (2-nitroimidazoles are reduced faster than 4-nitro analogs[8]) derivatives of PnAO ligands. We have also varied the position of the nitroimidazole on the PnAO skeleton and the nature of the linker group in order to study the effects of structure on biodistribution. One compound **21j** in the series provided a Tc(V)O complex (BMS-181321) with particularly promising characteristics,[9] and this is now under development. This paper details the syntheses of a number of nitroimidazole substituted PnAO ligands.



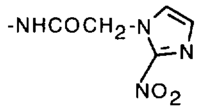
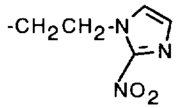
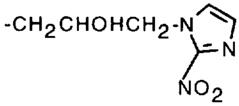
BMS-181321

RESULTS AND DISCUSSION

The syntheses of all the nitroimidazole substituted PnAOs are based upon stepwise monoalkylation of appropriately substituted 1,3-diaminopropane derivatives, as depicted in Schemes 6 and 7. Thus the key

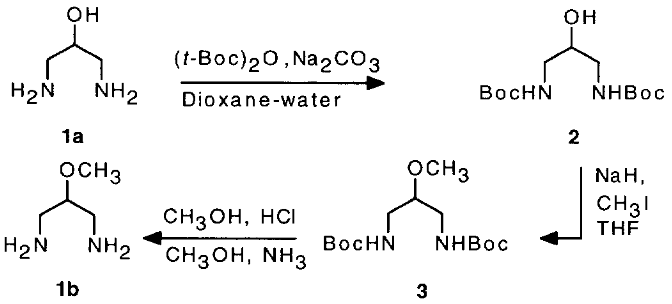


1

	R_1	R_2
a	H	OH
b	H	OCH_3
c	H	
d	H	
e	H	
f	C_2H_5	C_2H_5
g	CH_3	CH_3
h	H	CH_3
i	H	H

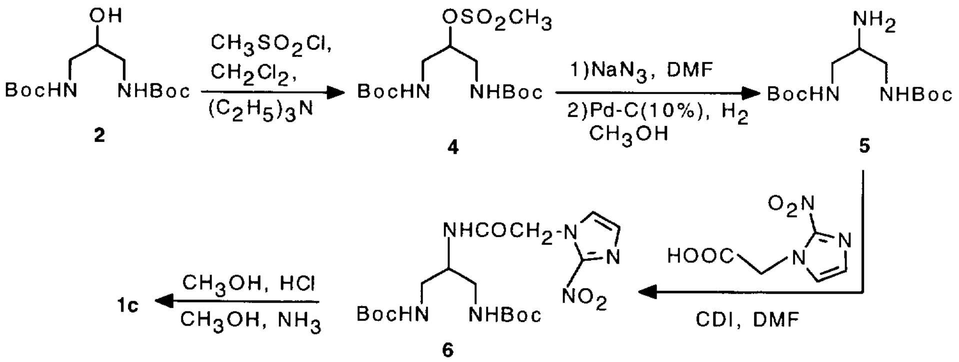
starting materials for the synthesis of nitroimidazole substituted PnAO ligands described herein are amines **1a**-**1i**. 2-Hydroxy-1,3-diaminopropane (**1a**), 2,2-dimethyl-1,3-diaminopropane (**1g**) and 1,3-diaminopropane (**1i**), were obtained from Aldrich. 2,2-Diethyl-1,3-diaminopropane (**1f**) was prepared by a modification of the literature[10] method. 2-Methyl-1,3-diaminopropane (**1h**) was prepared following the literature procedure.[11] The amine precursor **1b** was prepared in three steps from **1a** as depicted in Scheme 1. 2-Hydroxy-1,3-diaminopropane (**1a**) was reacted with di-*t*-butyl dicarbonate and sodium carbonate in dioxane-water to afford **2** (68%). O-Alkylation of the boc derivative **2** with iodomethane in THF using sodium hydride gave N,N-di-*t*-boc-2-methoxy-1,3-diaminopropane (**3**) (54%). The boc derivative **3** was reacted with methanolic HCl, and the resulting hydrochloride was neutralized with methanolic ammonia to give **1b.**

Scheme 1



N^1,N^3-Di-*t*-boc-1,2,3-triaminopropane (**5**), a key intermediate for **1c**, was prepared (Scheme 2) by converting N,N'-di-*t*-boc-2-hydroxy-1,3-diaminopropane (**2**) into mesylate **4**, then into azide and finally into amine by catalytic reduction (Pd-C, H_2). The nucleophilic displacement of the mesylate of 1,3-bis-Cbz-aminopropane-2-ol was reported to give 1,2-diamino derivatives via an aziridine intermediate.[12]

Scheme 2

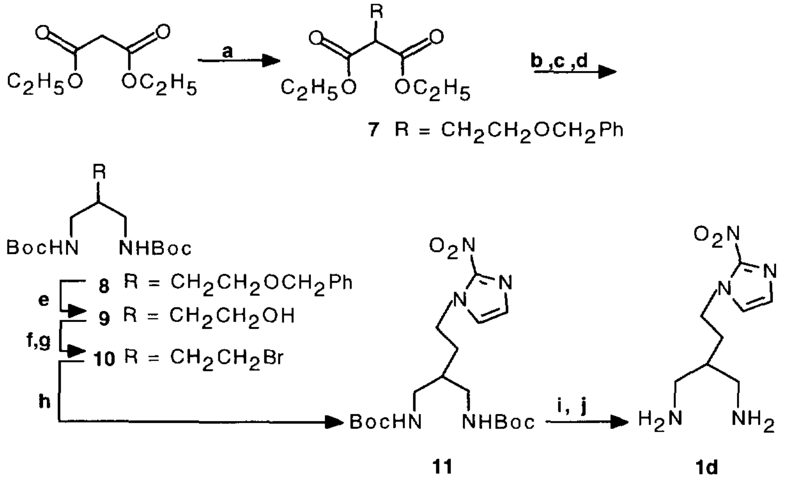


Our previous report[13] on the reaction of N,N'-di-*t*-boc-2-methanesulfonyl-1,3-diaminopropane (**4**) with sodium cyanide was consistent with those observed by Jones and coworkers[12] providing both the 1,2-

ethylenediamine and 1,3-diaminopropane derivatives in a ratio ~9:1. However, the reaction of the sodium azide with **4** afforded exclusively the corresponding 2-azido-1,3-diaminopropane derivative, presumably due to the higher nucleophilicity of the azide ion. The proton NMR spectrum of the azido-bisboc derivative confirmed the symmetrical structure of 1,3-diaminopropane derivative. The ^{1}H NMR spectra of **4**, 2-azido-1,3-bisboc derivative and **5** exhibited only one signal for the N*H*-boc indicating that the product was a symmetrical 1,3-diaminopropane derivative whereas we have clearly demonstrated from our earlier work[13] that the proton signals of the N*H*-boc in substituted ethylenediamines were separated by as much as 0.6 ppm. ^{13}C NMR of the product 2-azido-1,3-diaminopropane obtained after deprotection of 2-azido-1,3-bisboc derivative exhibited only two signals [41.3 ppm (CH_2NH_2) and 57.3 ppm (CHN_3)] confirming the structure of the product. N^1,N^3-Di-*t*-boc-1,2,3-triaminopropane (**5**) was coupled with 2-(2-nitro-1H-imidazol-1-yl)acetic acid[14] using 1,1'-carbonyldiimidazole to afford the nitroimidazole derivative **6** (61%) which was deprotected to give the diamine **1c**.

The synthesis of the nitroimidazole substituted diamine **1d** is shown in Scheme 3. Benzyl-2-bromoethyl ether[15] was used to alkylate the anion of diethyl malonate to yield diethyl 2-(benzyloxyethyl)malonate (**7**). Conversion of diester **7** to 2-(2-benzyloxyethyl)malonamide proceeded smoothly and the amide was reduced with BH_3.THF to provide the diamine which was isolated as the boc derivative **8** for purification. Reductive removal of benzyl group in **8** generated alcohol **9** which was then transformed to the corresponding bromide **10** through standard reactions (Scheme 3). For the synthesis of **1d**, 2-nitroimidazole was alkylated with **10** in DMF to yield the alkylated product **11** (42%). The boc group was removed using methanolic HCl, and the resulting hydrochloride was neutralized with methanolic ammonia to give **1d**. The preparation of the diamine **1e** from 2-allylmalonamide (**12**) has been reported.[16] Attempted repetition of the procedure failed

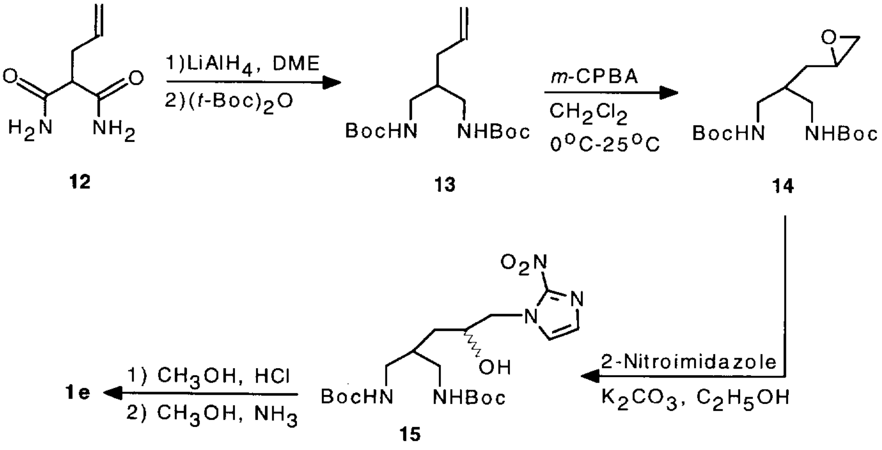
Scheme 3



a) $PhCH_2OCH_2CH_2Br$, C_2H_5ONa, C_2H_5OH; b) NH_3, CH_3OH; c) BH_3.THF; d) $(t\text{-Boc})_2O$, Na_2CO_3, dioxane-water; e) Pd-C(10%), H_2, CH_3OH; f) CH_3SO_2Cl, $(C_2H_5)_3N$, CH_2Cl_2; g) LiBr, acetone; h) 2-Nitroimidazole, K_2CO_3, DMF; i) Methanolic HCl; j) Methanolic NH_3.

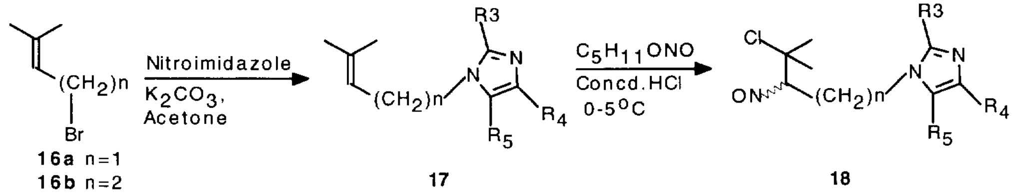
since the reduction of the diamide **12** to the diamine using lithium aluminum hydride was unsuccessful. Various temperatures and reaction times were unfruitful as **12** remained unreacted or was destroyed. However, we were able to reduce diamide **12** using lithium aluminum hydride in boiling dimethoxyethane and isolate 2-allyl-1,3-diaminopropane as the boc derivative **13** (Scheme 4). Epoxidation of **13** with *m*-chloroperoxybenzoic acid in CH_2Cl_2 at 0-25 °C gave **14** which underwent ring opening with 2-nitroimidazole in the presence of K_2CO_3 as a catalyst to provide **15**. Deprotection of the amino group in **15** with methanolic HCl, followed by neutralization with ammonia, afforded **1e**.

Scheme 4



The syntheses of several chloronitroso derivatives **18a-18e** was achieved (Scheme 5) using commercially available bromo olefins **16a** and **16b** as starting materials. Alkylation of 2-nitroimidazole with bromides **16a** and **16b** in the presence of K_2CO_3 proceeded smoothly in acetone to give **17a** and **17b** respectively. In a similar manner, **17c** was prepared by the alkylation of 4-nitroimidazole with bromide **16a**. Chromatographic separation of the reaction mixture obtained from the alkylation of 4-methyl-2-nitroimidazole (prepared by following literature procedure[17] with crucial modification as given in experimental section) with dimethylallyl bromide (**16a**) gave the isomer ($R_f = 0.51$) **17d** (60%) and isomer ($R_f = 0.41$) **17e** (15%). The structures of **17d** and **17e** were confirmed by ^{13}C NMR spectral data. ^{13}C NMR spectra of 4- and 5-methyl-2-nitroimidazole have been recorded[18] and analyzed to differentiate 4- and 5-methyl-2-nitroimidazole. For example, the imidazole ring *C*-H in 4-methyl-2-nitroimidazole resonates in the range of 120.0-123.5 ppm whereas the C-4 bearing hydrogen in 5-methyl-2-nitroimidazole resonates in the range of 127.0 and 133.1 ppm. Isomers **17d** and **17e** exhibited signals at 122.77 and 127.07 ppm, respectively, demonstrating that **17d** is the 4-methyl-2-nitroimidazole derivative and **17e** is the 5-methyl-2-nitroimidazole derivative. The key intermediate, 3-chloro-3-methyl-1-(2-nitro-1H-imidazol-1-yl)-2-nitrosobutane (**18a**), was obtained (48%) by the addition of nitrosyl chloride to the olefin **17a** at 0-5 °C. We found it possible to recover 30% of the unreacted 3-methyl-1-(2-nitro-1H-imidazol-1-yl)-2-butene **17a** which could be re-used. Formation of the chloronitroso derivatives **18b-18e** was achieved by the reaction at 0-5 °C of allyl derivatives **17b-17e** with isoamyl nitrite and concentrated hydrochloric acid.

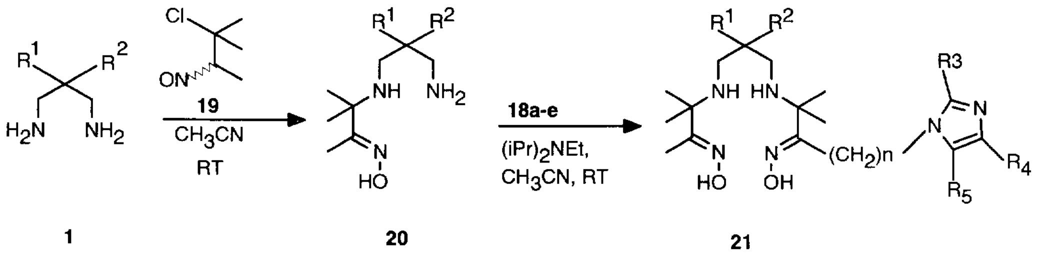
Scheme 5



17, 18	R_3	R_4	R_5	n
a	NO_2	H	H	1
b	NO_2	H	H	2
c	H	NO_2	H	1
d	NO_2	CH_3	H	1
e	NO_2	H	CH_3	1

The preparation of ligands **21a-j**, **23**, **26a-c** were realized via two different routes. The reaction sequences for the preparation of 3,3,9,9-tetramethyl-4,8-diazaundecane-2,10-dione dioximes with nitroimidazoles in the 1-position are shown in Scheme 6. This method involves the preparation of diamine

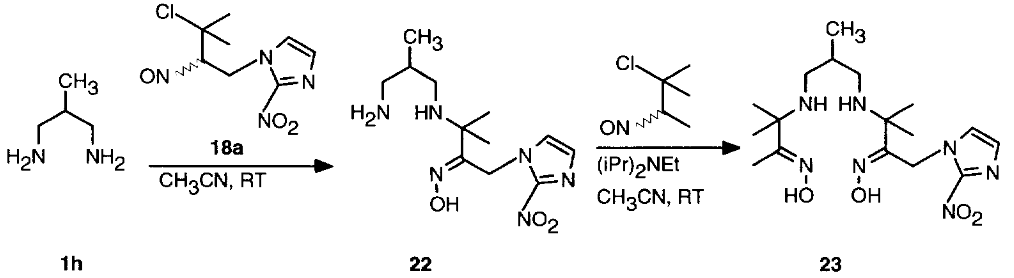
Scheme 6



1	20, 21	R_1	R_2	R_3	R_4	R_5	n
a	a	H	OH	NO_2	H	H	1
b	b	H	OCH_3	NO_2	H	H	1
g	c	CH_3	CH_3	NO_2	H	H	1
f	d	C_2H_5	C_2H_5	NO_2	H	H	1
f	e	C_2H_5	C_2H_5	H	NO_2	H	1
i	f	H	H	NO_2	CH_3	H	1
i	g	H	H	NO_2	H	CH_3	1
i	h	H	H	H	NO_2	H	1
i	i	H	H	NO_2	H	H	2
i	j	H	H	NO_2	H	H	1

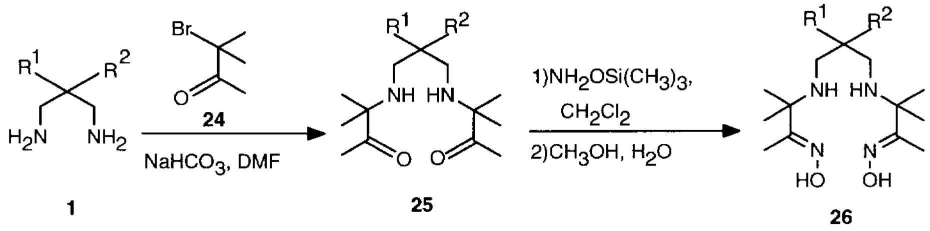
mono oximes **20a-j** by the alkylation[19] of appropriately substituted 1,3-diaminopropane (three molar excess) with 3-chloro-3-methyl-2-nitrosobutane **19**. Conversion of **20a**, **20b**, and **20d** to their corresponding boc derivatives was required for their purification. 3-[(3-Aminopropyl)amino]-3-methyl-2-butanone oxime **20j** was prepared by the method of Nowotnik and Canning[19] but with crucial modifications. The published procedure involves the addition of a methanolic solution of 3-chloro-3-methyl-2-nitrosobutane **16** to excess 1,3-diaminopropane (**1i**) in methanol. Workup followed by crystallization of the crude diamine mono oxime from ether/petroleum ether afforded **20j** with a reported mp 69-72 °C.[19] We prepared **20j** by adding the solid 3-chloro-3-methyl-2-nitrosobutane **16** to a solution of 1,3-diaminopropane (**1i**) in acetonitrile and recrystallized the product from acetonitrile. The melting point of our product was 75-76 °C. Our modification appears to give **20j** with greater purity and higher yield (63%). Ligands **21a-j** were then prepared from the diamine mono oxime **20a-j** *via* reaction with chloronitroso derivatives **18a-18e** as shown in Scheme 6, using diisopropylethylamine in acetonitrile. 2-Methyl-1,3-diaminopropane (**1h**)[11] was alkylated with **18a** to yield the intermediate **22** (Scheme 7) which was then subjected to a second alkylation with 3-chloro-3-methyl-2-nitrosobutane (**19**) to yield the required dioxime **23**.

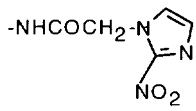
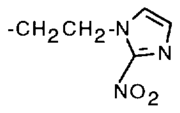
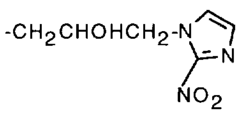
Scheme 7



Attempts to synthesize ligands **26a-c** (Scheme 8) from amines **1c-e** using the standard method[20] with 3-chloro-3-methyl-2-nitrosobutane for 3,3,9,9-tetramethyl-4,8-diazaundecane-2,10-dione dioximes failed, presumably due to the bulky nitroimidazole side chain. Therefore, an alternate route was developed to obtain ligands **26a-c** as shown in Scheme 8. 3-Bromo-3-methylbutan-2-one (**24**)[21] was reacted with amine **1c** in the presence of $NaHCO_3$ to give the diketone **25a** (60%). Application of this procedure to the amines **1d** and **1e** provided the diketones **25b** and **25c** also described in Scheme 8. Diketones **25a-c** were smoothly converted to their oxime derivatives **26a-c** with O-trimethylsilylhydroxylamine in CH_2Cl_2 at room temperature, followed by removal of the silyl protecting group.

Scheme 8



1	25, 26	R_1	R_2
c	a	H	
d	b	H	
e	c	H	

CONCLUSION

A series of nitroimidazole substituted PnAO ligands have been synthesized with a view to developing a new technetium based imaging agent that will localize in hypoxic tissue. A number of 3-chloro-3-methyl-1-(2-or 4-nitro-1H-imidazol-1-yl)-2-nitrosobutanes (**18a-e**) required for the synthesis of PnAO ligands **21a-j** were prepared from the corresponding dimethylallyl nitroimidazoles **17a-e** by the addition of nitrosyl chloride. Three PnAO ligands (**26a-c**) substituted at the central carbon were prepared by the alkylation of the corresponding diamines (**1c-e**) with 3-bromo-2-methylbutane-2-one (**24**) followed by oximation. One compound in this series (3,3,9,9-tetramethyl-1-(2-nitro-1H-imidazol-1-yl)-4,8-diaza-undecane-2,10-dione dioxime, **21j**) provided a Tc(v) complex which has the potential for routine evaluation of tissue viability in hypoxia.[9]

EXPERIMENTAL

Melting points were recorded using a Thomas-Hoover Capillary melting point apparatus and are uncorrected. Proton NMR spectra were recorded on a Jeol GSX/GX Multiplexes (270 MHz) NMR spectrometer and are reported in δ values with reference to tetramethylsilane. High resolution mass spectra were obtained from a VG Analytical-ZAB-2F and/or a Finnigan TSQ Spectrometer. Thin layer *chromatography was performed using precoated Kieselgel 60 F_{254} (E. Merck) TLC plates (0.25 mm thickness) and was visualized by UV irradiation from a Mineralight shortwave UV lamp or in an iodine chamber. All solvents and reagents were used as purchased except for THF which was distilled over sodium with benzophenone ketyl as indicator. HPLC analyses were conducted using twin Rainin pumps controlled by Gilson 712 software. A Dynamax C_{18} reversed phase silica gel column was utilized (25 x 0.46 cm, 8 micron). Water and acetonitrile (both containing 0.1% TFA) were used as the mobile phase. In all the cases a linear gradient (0-100% acetonitrile) was used for elution, and the compounds were detected at 230 nm using a Knauer variable wavelength monitor. Preparative chromatography was carried out using flash silica gel (230-400 mesh; E. Merck).*

N,N'-Di-t-boc-2-hydroxy-1,3-diaminopropane (2). To a solution of 2-hydroxy-1,3-diaminopropane (**1a**) (25 g, 277 mmol) in water (100 mL) was added di-*t*-butyl dicarbonate (133 g, 610 mmol) in dioxane (200 mL) followed by Na_2CO_3 (62 g, 700 mmol) at 0 °C and stirring for 2 h. The reaction mixture was allowed to warm to RT and was then stirred for an additional 16 h. Dioxane and water were removed under aspirator vacuum, and the paste was diluted (water, 250 mL). The solution was then thoroughly extracted with ethyl acetate (5 x 100 mL) and the combined organic layer was washed with water, brine and dried (Na_2SO_4). The dried ethyl acetate layer was concentrated to a gummy residue which was triturated with hexanes to yield a colorless solid. The solid was then recrystallized (hexanes-ether). Yield: 55.0 g (68%); mp 99-101 °C; ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 9 H, NHBoc), 3.20 (m, 4 H, $HNCH_2CHOHCH_2NH$), 3.72 (m, 1 H, $HNCH_2CHOHCH_2NH$), 5.05 (bs, 1 H, N*H*CO); Anal. Calcd for $C_{13}H_{26}N_2O_5$: C, 53.78; H, 9.03; N, 9.65. Found: C, 53.90; H, 9.15; N, 9.59.

N,N'-Di-t-boc-2-methoxy-1,3-diaminopropane (3). Sodium hydride (2.4 g, 100 mmol) was added in small portions to a solution of N,N'-di-*t*-boc-2-hydroxy-1,3-diaminopropane (**2**) (30.0 g, 103 mmol) in dry THF (600 mL) over a period of 30 min. Methyl iodide (21.3 g, 150 mmol) was added dropwise, and the mixture stirred at RT (6 h). Additional methyl iodide (21.3 g, 150 mmol) was added, and the stirring was continued (6 h). THF and excess methyl iodide were evaporated and the viscous oil thus obtained was chromatographed over silica gel (hexane:ethyl acetate 9:1). Fractions (50.0 mL, R_f 0.2) containing the N,N'-di-*t*-boc-2-methoxy-1,3-diaminopropane (**3**) were collected and evaporated to give the methoxy derivative as an oil which solidified on standing and was recrystallized (hexane). Yield: 17.2 g (54.2%); mp 74-75 °C; ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 9 H, NHBoc), 3.05-3.35 (m, 5 H, $HNCH_2CHOCH_3CH_2NH$), 3.41 (s, 3 H, OCH_3), 5.05 (bs, 1 H, N*H*CO); Anal. Calcd for $C_{14}H_{28}N_2O_5$: C, 55.24; H, 9.27; N, 9.20. Found: C, 55.31; H, 9.21; N, 9.25.

2-Methoxy-1,3-diaminopropane (1b). N,N'-Di-*t*-boc-2-methoxy-1,3-diaminopropane (**3**) (31.7 g 100 mmol) was added to methanolic HCl (100 mL) and the solution was stirred at RT for 30 min. The hydrochloride was precipitated by the addition of dry ether and crystallized from ethanol-ether. The dihydrochloride obtained was treated with methanolic ammonia to afford the amine **1b** as a thick viscous oil which was used for the next step without further purification. Yield: 9.2 g (91%). Hydrochloride: mp 183-84 °C (dec); ^{1}H NMR (D_2O) δ 3.08-3.32 (m, 4 H, $H_2NCH_2CHOCH_3CH_2NH_2$), 3.31 (s, 3 H, OCH_3), 3.52 (m, 1 H, C*H*); CIMS: 105 $(M+H)^+$; Anal. Calcd for $C_4H_{14}Cl_2N_2O$: C, 27.13; H, 7.97; N, 15.82; Cl, 40.04. Found: C, 27.29; H, 8.15; N, 15.59; Cl, 40.09.

N,N'-Di-t-boc-2-methanesulfonyl-1,3-diaminopropane (4). To a solution of **2** (55.0 g, 190 mmol) and triethylamine (30.35 g, 300 mmol) in dry dichloromethane (250 mL) was added methanesulfonyl chloride (26.0 g, 230 mmol) dropwise over a period of 1 h at 0 °C with stirring under nitrogen. After the addition, the reaction mixture was allowed to warm to RT and was then stirred (16 h). Water was slowly added to quench the reaction, and the organic layer was separated and then washed with water (5 x 100 mL). The organic layer was dried (Na_2SO_4) and then concentrated to a colorless solid which was recrystallized (hexane). Yield: 69.9 g (98%); mp 136-138 °C (dec); ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 18 H, NHBoc), 3.1 (s, 3 H, -

OSO_2CH_3), 3.4 (m, 4 H, N-CH_2), 4.7 (m, 1 H,-$CHOSO_2CH_3$) and 5.2 (m, 2 H, *NH*Boc); CIMS: 369 $(M+H)^+$. Anal. Calcd for $C_{14}H_{28}N_2O_7S$: C, 45.64; H, 7.66; N, 7.60. Found: C, 45.94; H, 7.81; N, 7.57.

N^1,N^3-Di-t-boc-1,2,3-triaminopropane (5). To a solution of the mesylate **4**, (9.2 g, 25 mmol) in dry DMF (50 mL) was added sodium azide (6.5 g, 100 mmol), and the mixture was stirred at 70 °C for 12 h. The reaction mixture was cooled and poured into water. The solid which formed was filtered, washed with water and recrystallized (hexane). Yield: 6.45 g (82%); mp 90-91 °C; ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 18 H, NHBoc), 3.15-3.35 (m, 4 H, N-CH_2), 3.64 (m, 1 H, CHN_3) and 5.04 (bt, 2 H, *NH*Boc). ^{13}C NMR ($CDCl_3$) δ 28.2[$C(CH_3)_3$], 40.7($NHCH_2$), 60.8(CHN_3), 79.6[$C(CH_3)_3$], 156.1(CO). Anal. Calcd for $C_{13}H_{25}N_5O_4$: C, 49.51; H, 7.99; N, 22.21. Found: C, 49.79; H, 7.97; N, 21.84. A methanolic solution (1 mL) of bisboc-azide derivative (50 mg) was treated with conc.HCl (0.25 mL), stirred for 5 min and evaporated under vacuum to afford 2-azido-1,3-diaminopropane as a colorless crystalline solid; mp 167-169 °C (dec). ^{1}H NMR (D_2O) δ 2.85(m, 4H, CH_2NH_2) and 3.84(m, 1H, CHN_3); ^{13}C NMR (D_2O) δ 41.3(CH_2NH_2) and 57.3(CHN_3). To a solution of the above 1,3-bisboc-azide (6.5 g, 20.5 mmol) in methanol (25 mL) was added Pd-C (10%, 1 g), and the mixture was hydrogenated at 50 psi (12 h). The catalyst was filtered and the methanol was evaporated. The resultant oil solidified on standing. Yield: 4.8 g (81%); mp 140-41 °C; ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 18 H, NHBoc), 2.88 [m, 1 H, $CH(CH_2)_2NH)$], 3.08 (m, 4 H, [CH $(CH_2)_2$], 5.24 (bs, 2 H, *NH*); FAB-HRMS: $(M+H)^+$: Calcd: 290.2080. Found: 290.2093.

2-[(2-Nitro-1H-imidazol-1-yl)acetylamino]-1,2,3-triaminopropane (1c). To a solution of 2-(2-nitro-1H-imidazol-1-yl)acetic acid[14] (3.1g, 18 mmol) in DMF (25 mL) was added N,N'-carbonyldiimidazole (3.08 g, 19 mmol), and the mixture was stirred at RT for 45 min. Boc amine **5** (5.3 g, 18 mmol) was added, and the mixture was stirred at 50 °C for 12 h. DMF was removed under vacuum and the residue was treated with water. The solid formed was filtered, air dried, and recrystallized (ethyl acetate). Yield: 6.5 g (61%); mp 174-75 °C. ^{1}H NMR ($CDCl_3$) δ 1.44 (s, 18 H, NHBoc), 2.90 (m, 1 H, *CH*), 3.08 (m, 4 H, CH_2NH) and 5.24 (bs, 2 H, *NH*Boc). Anal. Calcd for $C_{18}H_{30}N_6O_7$: C, 48.86; H, 6.83; N, 18.99. Found: C, 49.15; H, 6.84; N, 18.65. N^1,N^3-Di-*t*-boc-N^2-[(2-nitro-1H-imidazol-1yl)acetyl]-1,2,3-triaminopropane (**6**) (6.5 g) was deprotected using methanolic HCl, and the dihydrochloride was precipitated by the addition of dry ether. Yield: 4.25 g (74.9%); mp 238-40 °C; Hydrochloride: ^{1}H NMR (D_2O) δ 3.08-3.35 (m, 4 H, CH_2NH_2), 4.51 (m, 1H, *CH*), 5.31 (s, 2 H, CH_2), 7.19 (s, 1 H, imi-*H*) and 7.43 (s, 1 H, , imi-*H*). Free-amine: ^{1}H NMR (D_2O) δ 3.01-3.28 (m, 4H, CH_2NH_2), 4.45 (m, 1H, *CH*), 5.21 (s, 2H, CH_2), 7.15 (s, 1H, imi-*H*) and 7.39 (s, 1H, imi-*H*).

Diethyl 2-(benzyloxyethyl)malonate (7). Diethyl malonate (8.0 g, 50 mmol) was added to a solution of sodium ethoxide prepared from Na (1.2 g, 0.052 g atom) and ethanol (100 mL). A solution of benzyl-2-bromoethylether (10.75 g, 50 mmol) in ethanol (25 mL) was added dropwise over a period of 30 min, and the reaction mixture heated under reflux (12 h). Ethanol was evaporated, and the residue was poured into water and extracted with ether and dried (Na_2SO_4). Evaporation of ether gave an oil which was distilled under vacuum; bp 185 °C/2 mm; yield: 9.5 g (61.3%); ^{1}H NMR ($CDCl_3$) δ 1.21 (t, 6 H, CH_3), 2.24 (q, 2 H, CH_2CH_3), 3.52 (m, 3 H, $CHCH_2CH_2O$), 4.15 (m, 2 H, CH_2CH_2O), 4.45 (s, 2 H, OCH2Ar), 7.31 (m, 5 H, Ar*H*).

N,N'-Di-t-boc-2-(2-benzyloxyethyl)-1,3-diaminopropane (8). Diethyl 2-(benzyloxyethyl)malonate (**7**) (9.0 g, 31 mmol) was treated with ethanolic aqueous ammonia (100 mL), and the mixture was stirred at RT (12 h). Evaporation of the solvent gave 2-(2-benzyloxyethyl)malonamide as a white solid which was recrystallized from water. Yield: 4.5 g (62%); mp 177-78 °C; ^{1}H NMR (DMSO-d_6) δ 1.92 (m, 2 H,), 3.14 (t, 1 H, $CHCH_2$), 3.35 (m, 2 H, CH_2CH_2O), 4.12 (s, 2 H, CH_2CH_2O), 4.45 (s, 2 H, OCH2Ar), 7.05 (s, 2 H, $CONH_2$), 7.22 (s, 2 H, $CONH_2$), 7.34 (m, 5 H, Ar*H*). Anal. Calcd for $C_{12}H_{16}N_2O_3$: C, 61.00; H, 6.83; N, 11.86. Found: C, 61.01; H, 6.72; N, 11.80. To a slurry of 2-(2-benzyloxyethyl)malonamide (29 g, 123 mmol) in dry THF (500 mL) was added BH_3-THF complex (65 g, 750 mmol) over a period of 1 h, and the reaction mixture was stirred at RT (48 h). Excess borane was decomposed by the dropwise addition of water. Dilute

HCl was added until the solution became acidic, and THF was evaporated. The residue was suspended in dioxane-water (2:1, 500 mL), and sodium carbonate, (31.8 g, 300 mmol) was added to this mixture which was cooled to 0 °C. Di-*t*-butyl dicarbonate (58.9 g, 270 mmol) was added, and the mixture was stirred at 0 °C for 2 h and at RT (12 h). Dioxane-water was removed, and the residue was treated with water, and the mixture was extracted with ethyl acetate and dried (Na_2SO_4). Ethyl acetate was removed, and the resultant thick oil was chromatographed over silica gel (R_f 0.4, hexane:ethyl acetate, 7:3, silica gel 800 g). Yield: 27 g (54%); ^{1}H NMR ($CDCl_3$) δ 1.41 (s, 18 H, NHBoc), 1.52 (m, 2 H, C*H*$_2$CH), 1.72 (m, 1 H, C*H*), 2.9-3.2 [m, 4 H, CH(C*H*$_2$NHBoc)$_2$], 3.6 (m, 2 H, OC*H*$_2$), 4.5 (s, 2 H, ArC*H*$_2$), 5.2 (m, 2 H, N*H*), 7.31 (m, 5 H, Ar*H*).

*N,N'-Di-t-boc-2-(2-hydroxyethyl)-1,3-diaminopropane (**9**).* Pd-C (10%, 1 g) was added to a solution of N,N'-di-*t*-boc-2-(2-benzyloxyethyl)-1,3-diaminopropane (**8**) (6 g, 14.8 mmol) in methanol (50 mL) and hydrogenated at 50 psi (24 h). Methanol was removed, and N,N'-di-*t*-boc-2-(2-hydroxyethyl)-1,3-diamino propane (**9**) was obtained as a white solid which was recrystallized (hexane). Yield 5.0 g (87%); mp 101-102 °C; ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 18 H, NHBoc), 1.65 (m, 1 H, C*H*), 2.9-3.2 [m, 6 H, CH(C*H*$_2$NHBoc)$_2$] and C*H*$_2$CH), 3.78 (m, 2 H, OC*H*$_2$), 5.2 (m, 2 H, N*H*). Anal. Calcd for $C_{15}H_{30}N_2O_5$: C, 56.58; H, 9.50; N, 8.80. Found: C, 56.82; H, 9.44; N, 8.81.

*N,N'-Di-t-boc-2-(2-bromoethyl)-1,3-diaminopropane (**10**).* To a solution of N,N'-di-*t*-boc-2-(2-hydroxyethyl)-1,3-diaminopropane (3.5 g, 11.2 mmol) in methylene chloride (15 mL) was added triethylamine (1.36 g, 1.89 mL, 13.4 mmol), and the mixture was cooled to 0 °C. Methanesulfonyl chloride (1.43 g, 12.5 mmol) was added slowly over a period of 0.5 h, and the reaction mixture was stirred at 0 °C for 1 h and then at RT (12 h). Methylene chloride was removed, and the mesylate obtained was crystallized (hexane). Yield: 3.9 g (88.6%); mp 109-10 °C; ^{1}H NMR ($CDCl_3$) δ 1.41 (s, 18 H, NHBoc), 1.52 (m, 2 H, C*H*$_2$CH),1.72 (m, 1 H, C*H*), 3.0 (s, 3 H, C*H*$_3$),3.1 [m, 4 H, CH(C*H*$_2$NHBoc)$_2$], 4.45 (m, 2H, OC*H*$_2$), 5.15 (m, 2 H, N*H*). Anal. Calcd for $C_{16}H_{32}N_2O_7S$: C, 48.47; H, 8.13; N, 7.07. Found: C, 48.68; H, 8.38; N, 6.96. A solution of the mesylate (1.98 g, 5.0 mmol) and LiBr (4.34 g, 50.0 mmol) in acetone (50 mL) was stirred at RT (24 h). Acetone was removed and the bromide **10** was obtained as an oil which solidified and was crystallized (hexane). Yield: 1.5 g; mp 81-82 °C; ^{1}H NMR ($CDCl_3$) δ 1.44 (s, 18 H, N*H*Boc), 1.77 (m, 3 H, C*H*$_2$C*H*), 3.0 (s, 3 H, C*H*$_3$), 3.1 [m, 4 H, CH(C*H*$_2$NHBoc)$_2$], 3.55 (t, 2H, C*H*$_2$Br), 5.11 (m, 2 H, N*H*). Anal. Calcd for $C_{15}H_{29}N_2O_4Br$: C, 47.25; H, 7.67; N, 7.35. Found: C, 47.65; H, 7.96; N, 7.30.

*N,N'-Di-t-boc-2-[2-(2-nitro-1H-imidazol-1-yl)ethyl]-1,3-diaminopropane (**11**).* To a suspension of 2-nitroimidazole (0.56 g, 5 mmol) in dry acetonitrile (5 mL) was added sodium hydride (0.12 g, 5 mmol), and the mixture was stirred at RT (15 min). Acetonitrile was removed under vacuum, and the residue was dissolved in dry DMF (5.0 mL). Bromide **10** (1.14 g, 3 mmol) was added and the DMF solution was heated in an oil bath at 110 °C for 2 h. Sodium bromide was formed in ~15 min. DMF was removed under vacuum and the residue was treated with water and extracted with methylene chloride. Methylene chloride was removed and the crude product was chromatographed over silica gel (hexane:ethyl acetate, 50:50). The fractions (5 mL, R_f 0.3) containing the product were collected and evaporated to afford **11** as a thick yellow oil which solidified and was crystallized (hexane-ethyl acetate). Yield: 0.52 g (42%); mp 119-20 °C; ^{1}H NMR ($CDCl_3$) δ 1.35 (s, 18 H, NHBoc), 1.6 [m, 2 H, CH(C*H*$_2$CH$_2$N)], 3.12 [m, 5 H, CH(C*H*$_2$NH) and C*H*], 4.50 [t, 2 H, CH(CH$_2$C*H*$_2$N)], 5.12 (m, 2 H, N*H*), 7.0 and 7.25 (s, 2 H, imi-*H*); CIMS: 414 $(M+H)^+$; Anal. Calcd for $C_{18}H_{31}N_5O_6$: C, 52.29; H, 7.56; N, 16.94. Found: C, 52.37; H, 7.62; N, 16.74.

*2-[2-(2-Nitro-1H-imidazol-1-yl)ethyl]-1,3-diaminopropane (**1d**).* The boc derivative **11** (0.52 g, 1.26 mmol) was treated with methanolic HCl (2 mL) for 30 min, and the dihydrochloride was precipitated by the addition of dry ether (10 mL). The dihydrochloride was neutralized with methanolic ammonia, and the free base thus obtained was used without further purification. Yield: 0.2 g; Dihydrochloride: ^{1}H NMR (D_2O) δ 2.0 [m, 2 H, CH(C*H*$_2$CH$_2$N)], 2.20 (m, 1 H, C*H*), 3.12 [d, 4 H, CH(C*H*$_2$NH)], 4.50 [t, 2 H, CH(CH$_2$C*H*$_2$N)], 7.10 and 7.42 (s, 2 H, imi-*H*); CIMS: 214 $(M+H)^+$.

N,N'-Di-t-boc-2-allyl-1,3-diaminopropane (13). To a slurry of lithium aluminum hydride in dimethoxyethane (300 mL) was added a warm solution of 2-allylmalonamide (**12**)[16] (14.2 g, 100 mmol) in dimethoxyethane (800 mL) over a period of 1 h. The reaction mixture was stirred at 50 °C for 48 h. Excess lithium aluminum hydride was destroyed by the addition of 10% NaOH and water, and the mixture was allowed to stir for 2 h. Di-*t*-butyl dicarbonate (50.0 g, 23 mmol) was added, and the reaction mixture was stirred for 24 h. The reaction mixture was filtered, and the filter cake was washed with CH_2Cl_2 (250 mL). The filtrate and the washings were collected and evaporated to afford a thick viscous oil which was purified by column chromatography (silica gel 750 g, hexane:ethyl acetate, 9:1). Fractions (50 mL, R_f 0.35) containing **13** were collected and evaporated to give a thick oil which solidified and was recrystallized (hexane). Yield: 9.5 g (30%); mp 84-85 °C; ^1H NMR ($CDCl_3$) δ 1.4 (s, 18 H, NHBoc), 1.7 (m, 1 H, C*H*), 2.85 and 3.22 (m, 4 H, CH(CH_2NH)],), 5.0 (m, 2 H, CH_2=C), 5.75 (m, 1 H, C*H*=CH_2); CIMS: 315 $(M+H)^+$; Anal. Calcd for $C_{16}H_{30}N_2O_4$: C, 61.12; H, 9.62; N, 8.91. Found: C, 60.95; H, 9.17; N, 8.90.

N,N'-Di-t-boc-2-(2,3-epoxypropyl)-1,3-diaminopropane (14). To a 0 °C solution of N,N'-di-*t*-boc-2-allyl-1,3-diaminopropane (**13**) (5.0 g, 16 mmol) in CH_2Cl_2 (30 mL) was added *m*-chloroperoxybenzoic acid (5.0 g, 22 mmol) in portions, and the resulting solution was stirred (24 h). The precipitated *m*-chlorobenzoic acid was filtered, and the filtrate was taken up in ether (200 mL). Excess *m*-chloroperoxybenzoic acid was decomposed by the addition of sodium sulfite solution (20%, 10 mL), and the ether layer was washed with a saturated solution of sodium bicarbonate, water and dried (Na_2SO_4). Evaporation of ether gave a viscous oil which was used in the next step without further purification. Yield: 5.2 g (98%); ^1H NMR ($CDCl_3$) δ 1.5 (m, 3 H, C*H* and CH_2C*H*-), 2.45 and 2.80 (m, 2 H, epoxide), 3.0-3.4 (m, 5 H, epoxide and (CH_2NHBoc)$_2$), 5.0 and 5.5 (m, 2 H, N*H*Boc); CIMS 330 $(M+H)^+$.

N,N'-Di-t-boc-2-[2-hydroxy-3-(2-nitro-1H-imidazol-1-yl)propyl]-1,3-diaminopropane (15). To a mixture of 2-nitroimidazole (500 mg, 4.45 mmol) and potassium carbonate (70 mg, 0.5 mmol) in ethanol (50 mL) was added epoxide **14** (1 g, 3 mmol), and the mixture was boiled under nitrogen for 12 h. The reaction mixture was cooled and filtered. The precipitate was washed with water, and the off white solid obtained was chromatographed over silica gel (CH_2Cl_2:CH_3OH, 95:5). The UV visible fractions (3.0 mL) were collected and evaporated to give a white solid. Yield: 0.42 g (28%); mp 185-86 °C; ^1H NMR (DMSO-d_6) δ 1.2 (m, 2 H C*H*CH_2CHOH), 1.75 (m, 1 H, C*H*CH_2CHOH), 2.9 (m, 4 H, CH(CH_2NHboc)), 3.9 (m, 1 H, C*H*OH), 4.1-4.4 (m, 2 H, CHOHCH_2N), 5.0 (m, 1 H, O*H*), 6.65 (m, 2 H, N*H*), 7.1 and 7.52 (s, 2 H, imi.*H*). FAB-HRMS: $(M+H)^+$: Calcd: 444.2458, Found: 444.2461.

2-[2-Hydroxy-3-(2-nitro-1H-imidazol-1-yl)propyl]-1,3-diaminopropane (1e). Boc derivative **15** (0.9 g, 2 mmol) was treated with methanolic HCl (5 mL) and allowed to stir for 30 min. Methanol was removed, and the residue was neutralized with methanolic ammonia. The methanolic solution was concentrated, and the residue was dried under vacuum to yield a light yellow solid which was used in the next step without further purification. Yield: 0.38 g (80.0%); ^1H NMR (D_2O) δ 1.6 (m, 2 H, CH_2CHOHCH_2N<), 2.2 (m, 3 H, C*H*(CH_2NH), 2.98 (m, 3 H, CH_2CHOHCH_2N<), 4.05 (m, 1 H, C*H*OH), 4.3-4.55 (m, 2 H, CHOHCH_2N<); 7.1 and 7.32 (s, 2 H, imi-*H*); FAB-HRMS: $(M+H)^+$: Calcd: 244.1410. Found: 244.1413.

2,2-Diethyl-1,3-diaminopropane (1f). A solution of 2,2-diethyl-1,3-bisazidopropane[10] (CAUTION! alkyl azides are presumed to be potentially explosive) (11.0 g, 60.44 mmol) in methanol (100 mL) was purged with nitrogen for 5 min and then treated with Pd-C (10%, 1.50 g). The reaction mixture was then hydrogenated at 40 psi for 96 h. The catalyst was removed by filtration through a celite bed, and the filtrate was evaporated under vacuum to a colorless thick oil which on trituration with petroleum ether (35-60 °C) afforded 2,2-diethyl-1,3-diaminopropane (**1f**) as a colorless crystalline solid. Yield: 7.0 g (90%); mp 83-84 °C; (lit[10] mp 83-84 °C); ^1H NMR ($CDCl_3$) δ 0.85 (t, J = 7.5 Hz, 6 H, CH_2CH_3), 1.39 (q, J = 8.0 Hz, 4 H, C$H_2$$CH_3$), 2.94 (s, 4 H, C$H_2$$NH_2$) and 5.52 (bs, 4 H, N$H_2$); CIMS: m/z 131 $(M+H)^+$.

4-Methyl-2-nitroimidazole. To a stirred suspension of 4-methyl-1-tritylimidazole[17] (24.0 g, 74.1 mmol) in dry THF (750 mL) at 0 °C was added *n*-BuLi in cyclohexane (40.0 mL, 2M, 80.0 mmol) by syringe. After the addition the reaction mixture was allowed to warmup slowly to room temperature, and stirring was continued for 4 h. To the resulting dark-red solution was added isopropyl nitrate (16 mL, 160 mmol) by syringe and the stirring was continued for an additional 3 h. The brown solution was cooled to 0 °C, water (10 mL) was added and the solvent was removed on a rotary evaporator. The semi-solid thus obtained was dissolved in methanol (100 mL), and treated with 2N HCl (200 mL) and stirred at room temperature for 2 h. The reaction mixture was then concentrated to 200 mL and a saturated solution of Na_2CO_3 was added to adjust the pH of the solution to 8.50. The solution was then extracted with ethyl acetate (3 x 100 mL) and the organic layer was discarded. The pH of the aqueous phase was adjusted to 4.00 by the addition of $KHSO_4$ solution and extracted with CH_2Cl_2 (4 x 75 mL). The combined organic extracts was dried, evaporated under vacuum to afford the title compound as a crystalline yellow solid which was recrystallized from ethyl acetate-ether to afford pure 4-methyl-2-nitroimidazole; yield: 7.46 g (75%); mp. 205-207 °C (lit.[17] 205-207 °C); ^{1}H NMR (CD_3OD) δ 2.28(s, 3H, CH_3) and 7.19(s, 1H, *H*-5). CIMS m/z 128 $(M+H)^+$.

*3-Methyl-1-(2-nitro-1H-imidazol-1-yl)-2-butene (**17a**)*[22]. 4-Bromo-2-methyl-2-butene (14.9 g, 11.64 mL, 100 mmol) was added to a slurry of potassium carbonate (13.8 g, 100 mmol) and 2-nitroimidazole (11.3 g, 100 mmol) in acetone (200 mL). The reaction mixture was stirred under reflux for 12 h. Inorganic salts were removed by filtration and the acetone was removed on a rotary evaporator. The yellow oil obtained was distilled under vacuum. bp. 126-28 °C/1.5mm. The oil obtained solidified on standing. It was recrystallized from hexane. mp. 48-49 °C. Yield 13.2 g (73%). ^{1}HNMR ($CDCl_3$) δ 1.90 and 1.91 (s, 6H, CH_3), 5.12 (d, 2H, CH_2), 5.46 (m, 1H, C=*H*), 7.22 and 7.4 (s, 2H, imi-*H*); CIMS: $(M+H)^+$ =182; Anal. Calcd for $C_8H_{11}N_3O_2$: C, 53.03; H, 6.12; N, 23. 14 Found: C, 53.30; H, 6.17; N, 22.74.

*4-Methyl-1-(2-nitro-1H-imidazol-1-yl)-3-pentene (**17b**).* 5-Bromo-2-methyl-2-pentene (25 g, 154 mmol) was added to a mixture of K_2CO_3 (21.3 g, 154 mmol) and 2-nitroimidazole (17.4 g, 154 mmol) in dry DMF (200 mL). The mixture was stirred under N_2 atmosphere at 75 °C for 48 h. DMF was evaporated on a rotary evaporator and the yellow gummy residue was poured into water (150 mL) and extracted with ether (150 mL). The ether layer was washed with water and dried (Na_2SO_4). Evaporation of ether afforded a solid which was recrystallized from hexane. Yield 27.8 g (92%). mp: 49-51 °C CIMS: $(M+H)^+$= 196; ^{1}H NMR ($CDCl_3$) δ 1.45 and 1.68 (s, 6H, CH_3), 2.52 (q, 2H, CH_2CH=), 4.43 (t, 2H, CH_2), 5.08 (t, 1H, $CH_2C\underline{H}$=), 7.05 and 7.14 (s, 2H, imi-*H*); Anal. Calcd for $C_9H_{13}N_3O_2$: C, 55.37; H, 6.71; N, 21.52. Found: C, 55.70; H, 6.79; N, 21.45.

*3-Methyl-1-(4-nitro-1H-imidazol-1-yl)-2-butene (**17c**).* A solution of 4(5)-nitroimidazole (11.3 g, 100 mmol) in acetone (200 mL) was treated with potassium carbonate (13.8 g, 100 mmol) and stirred for 15 min. 4-Bromo-2-methyl-2-butene (14.9 g, 100 mmol) was added to the reaction mixture and stirred under nitrogen at 50-60 °C for 16 h. Acetone was evaporated under reduced pressure and the residue was taken up in ether (200 mL). The ether layer was washed with water and dried (Na_2SO_4). Evaporation of ether gave an oil which was chromatographed over silica gel (heane-ethyl acetate 7:3). UV visible fractions (R_f 0.6) were collected and evaporated to an yellow oil which was dissolved in hot hexane (3 X 75 mL) and kept at 0 °C for 2 h. The pale yellow solid that formed was filtered and dried under vacuum. Yield : 7.95 g (44%). ^{1}H NMR ($CDCl_3$): 1.7 (s, 3H, CH_3), 1.75 (s, 3H, CH_3), 4.6 (d, 2H, N-CH_2), 5.4 (t, 1H, C=C*H*), 7.5 (s, 1H, imi-*H*) and 7.8 (s, 1H, imi-*H*); CIMS. $(M+H)^+$ = 182; Anal. Calcd for $C_8H_{11}N_3O_2$: C, 53.03; H, 6.12; N, 23.19. Found: C, 53.09; H, 6.03; N, 22.68.

*1-(4-Methyl-2-nitro-1H-imidazol-1-yl)-3-methyl-2-butene (**17d**) and 1-(5-methyl-2-nitro-1H-imidazol-1-yl)-3-methyl-2-butene (**17e**).* To a suspension of anhydrous K_2CO_3 (13.0 g, 94.20 mmol) and 4-methyl-2-nitroimidazole (10.0 g, 78.74 mmol) in dry acetone (100 mL) was added 3,3-dimethylallyl bromide (**16**) (14.08 g, 94.49 mmol). The reaction mixture was stirred at RT under nitrogen atmosphere for 15 h. The inorganic salts were removed by filtration, and the filtrate was evaporated to afford a brown paste which was loaded onto a silica gel (500 g) column and eluted with hexane:ethyl acetate (85:15). The fractions containing the compound with R_f 0.51 (silica gel, hexane:ethyl acetate, 7:3) were collected and evaporated to afford a solid which was recrystallized (ethyl acetate-hexane) to provide **17d** as a light yellow crystalline solid. Yield: 9.21 g (60%); mp 53-54 °C; ^{1}H NMR ($CDCl_3$) δ 1.80[s, 6H, C(CH_3)$_2$], 2.26(s, 3H, imi-CH_3), 4.97(d, J = 7.26 Hz, 2H, NCH_2), 5.36(t, J = 7.26 Hz, 1H, CH_2CH) and 6.90(s, 1H, imi-C*H*); ^{13}C NMR ($CDCl_3$) δ 13.80(imi-CH_3), 18.16 & 25.70 [C(CH_3)$_2$], 47.76(NCH_2), 117.35(CH_2CH), 122.77(imi-CH), 138.09[C(CH_3)$_2$], 139.97(imi-CCH_3), and 143.53(CNO_2); CIMS m/z 196 (M+H)$^+$. The fractions containing the compound with R_f 0.41 (silica gel, hexane:ethyl acetate 7:3) were pooled and evaporated to provide a solid which was recrystallized (ethyl acetate:hexane) to afford 1-(5-methyl-2-nitro-1H-imidazol-1-yl)-3-methyl-2-butene (**17e**) as a light yellow fluffy solid. Yield: 1.02 g (15.2%); mp 78-79 °C; ^{1}H NMR ($CDCl_3$) δ 1.75 & 1.82 [2s, 6H, C(CH_3)$_2$], 2.32(s, 3H, imi-CH_3), 4.97(d, 2H, J = 6.60 Hz, NCH_2), 5.13(t, 1H, J = 6.55 Hz, CH_2C*H*) and 6.97(s, 1H, imi-C*H*). ^{13}C NMR ($CDCl_3$) δ 10.35(imi-CH_3), 18.28 & 25.62[C(CH_3)$_2$], 45.20(NCH_2), 117.69(CH_2CH), 127.07(imi-CH), 134.49 [C(CH_3)$_2$], 137.57(imi-CCH_3) and 145.52 (CNO_2); CIMS m/z 196 (M+H)$^+$.

General procedure for the preparation of chloronitroso derivatives of nitroimidazoles. The following procedure illustrates the general method used for the preparation of these compounds. Almost all of the chloronitroso derivative decomposed on attempted crystallization. Hence these derivatives were dried under high vacuum at RT (< 0.1 mm) for several hours and used in the next step without further purification.

3-Chloro-3-methyl-1-(2-nitro-1H-imidazol-1-yl)-2-nitrosobutane (18a). Concd. HCl (28.2 mL, 280 mmol) was added slowly to a mixture of 3-methyl-1-(2-nitro-1H-imidazol-1-yl)-2-butene (**17a**) (28.5 g, 160 mmol) and isoamyl nitrite (36.0 g, 41.2 mL, 300 mmol) at 0-5 °C with stirring. The reaction temperature was maintained below 5 °C during the addition of HCl and stirred for an additional 2 h. The solid which formed was filtered and washed with cold ether:ethanol (3:1, 150 mL) and dried. Yield: 12.2 g (31%); mp 104-105 °C (dec); ^{1}H NMR (DMSO-d_6) δ 1.8 (s, 6 H, CH_3), 5.45 (s, 2 H,NCH_2), 7.05 (s, 1 H, imi-*H*) and 7.25 (s, 1 H, imi-*H*); FAB-MS: m/z 247 (M+H)$^+$.

4-Chloro-4-methyl-1-(2-nitro-1H-imidazol-1-yl)-3-nitrosopentane (18b). Yield: 54%; mp 105-107 °C (dec); ^{1}H NMR (DMSO-d_6) δ 1.7 (s, 6 H, CH_3), 2.9 (t, 2 H, N=CCH_2), 4.7 (t, 2 H, NCH_2), 7.1 (s, 1 H, imi-*H*), 7.5 (s, 1 H, imi-*H*); FAB-MS: m/z 261 (M+H)$^+$.

3-Chloro-3-methyl-1-(4-nitro-1H-imidazol-1-yl)-2-nitrosobutane (18c). Yield: (16%); mp 120-122 °C (dec); ^{1}H NMR (DMSO-d_6) δ 1.9 (s, 6 H , CH_3), 5.18 (s, 2 H , NCH_2), 7.94 (s, 1 H, imi-*H*), 8.32 (s, 1 H, imi-*H*), 12.24 (s, 1 H, NO*H*); FAB-MS: m/z 247 (M+H)$^+$.

3-Chloro-3-methyl-1-(4-methyl-2-nitro-1H-imidazol-1yl)-2-nitrosobutane (18d). Yield: 62%; mp 110-113 °C (dec); ^{1}H NMR (DMSO-d_6) δ 1.81 [s, 6H, C(CH_3)$_2$], 2.16 (s, 3H, imi-CH_3), 5.36 (s, 2H, NCH_2), 7.12(s, 1H, imi-C*H*) and 11.98 (s, 1H, NO*H*); FAB-MS m/z 261 (M+H)$^+$.

3-Chloro-3-methyl-1-(5-methyl-2-nitro-1H-imidazol-1-yl)-2-nitrosobutane (18e). Yield: 54%; mp 105-107 °C (dec); ^{1}H NMR (DMSO-d_6) δ 1.73 [s, 6H, C(CH_3)$_2$], 2.32 (s, 3H, imi-CH_3), 5.53 (s, 2H, NCH_2), 6.97 (s, 1H, imi-C*H*) and 11.58 (s, 1H, NO*H*); FAB-MS m/z 261 (M+H)$^+$.

General procedure for the preparation of diamine mono oximes: 3-[(3-Amino-2-hydroxypropyl)amino]-3-methyl-2-butanone oxime (20a). To a cooled (0 °C) solution of 2-hydroxy-1,3-diaminopropane (**1a**) (14.0 g, 155 mmol) in methanol (75 mL) was added 3-chloro-3-methyl-2-nitrosobutane (**19**) (6.75 g, 50 mmol) in portions. After the addition the reaction mixture was allowed to warm to RT, and then it was heated under reflux for 12 h. Methanol was removed, and the residue was neutralized with methanolic ammonia. Excess methanol was removed, and the residue was dissolved in dioxane-water (2:1, 300 mL), and this solution was cooled to 0 °C. Sodium carbonate (31.8 g, 300 mmol) was added to this mixture followed by di-*t*-butyl dicarbonate (65.47 g, 300 mmol), and the reaction mixture was stirred at 0 °C for 2 h and at RT for 6 h. Dioxane and water were removed, and the residue was poured into water and extracted with ethyl acetate. The ethyl acetate solution was washed with water and dried (Na_2SO_4). Ethyl acetate was removed, and the oil obtained was chromatographed over silica gel (hexane:ethyl acetate 50:50). N,N'-di-*t*-boc-2-hydroxy-1,3-diaminopropane eluted in the early fractions. Fractions (50.0 mL, R_f 0.45) containing 3-[[3-(t-boc-amino)-2-hydroxypropyl]-amino]-3-methyl-2-butanone oxime were collected and evaporated to a thick oil. Yield: 4.9 g (33.9%). The oil (4.9 g) thus obtained was reacted with methanolic HCl (25 mL) for 2 h and poured into dry ether (200 mL). The precipitated hydrochloride was filtered and recrystallized (ethanol-water). CIMS 190 $(M+H)^+$; Hydrochloride mp 205-06 °C; ^1H NMR (D_2O) δ 1.5 (s, 6 H, $C(C\mathit{H}_3)_2$), 1.80 (s, 3 H,$C\mathit{H}_3$), 2.92-3.32 (m, 4 H, $C\mathit{H}_2$), 4.18 (m, 1 H, $C\mathit{H}OH$); Anal. Calcd for $C_8H_{21}N_3O_2Cl_2$: C, 36.65; H, 8.07; N, 16.03; Cl, 27.04. Found: C, 36.74; H, 8.20; N, 15.46; Cl, 26.55. The hydrochloride obtained was neutralized with methanolic ammonia to yield a white solid which was used for next step without further purification. Yield: 3.98 g (90%).

3-[(3-Amino-2-methoxypropyl)amino]-3-methyl-2-butanone oxime (20b). 2-Methoxy-1,3-diaminopropane (**1b**) (9.2 g, 91 mmol) was dissolved in absolute methanol (50 mL) and cooled to 0 °C. 3-Chloro-3-methyl-2-nitrosobutane (**19**) (6.25 g, 40 mmol) was added to the reaction mixture over a period of 1 h. The reaction mixture was stirred at 0 °C for 1 h and at RT for 12 h. Workup as described above afforded 3-[[(3-(t-Boc-amino)-2-methoxy-propyl]amino]-3-methyl-2-butanone oxime as a thick oil which solidified and was crystallized (hexane). mp. 76-77 °C. Yield: 7.5 g (25%). ^1H NMR ($CDCl_3$) δ 1.22 (s, 6H, $C\mathit{H}_3$), 1.42 (s, 9H, NHBoc), 1.6 (bs, 1H, N*H*), 1.85 (s, 3H, $C\mathit{H}_3C{=}NOH$), 2.52-3.28 (m, 4H, $HNC\mathit{H}_2CHOCH_3C\mathit{H}_2NH_2$), 3.41 (s, 3H, $OC\mathit{H}_3$), 4.12 (q, 1H, C*H*), 5.35 (bs, 1H, N*H*CO); Anal. Calcd for $C_{14}H_{29}N_3O_4$: C, 55.42; H, 9.63; N, 13.85. Found: C, 55.63; H, 9.33; N, 13.66. 3-[[(3-(t-Boc-amino)-2-methoxy-propyl]amino]-3-methyl-2-butanone oxime (7.5 g, 3.5 mmol) was converted to **20b** as described above for **20a**. No attempt was made to purify the amine prior to use in the next step. ^1H NMR (D_2O) δ 1.22 (s, 6H, $C\mathit{H}_3$), 1.81(s, $C\mathit{H}_3C{=}NOH$), 2.52-3.18 (m, 4H, $HNC\mathit{H}_2CH\text{-}CHOCH_3C\mathit{H}_2NH_2$), 3.31 (s, 3H, $OC\mathit{H}_3$), 3.52 (m, 1H, C*H*).

3-[(3-Amino-2,2-dimethylpropyl)amino]-3-methyl-2-butanone oxime (20c). To a solution of 2,2-dimethyl-1,3-diaminopropane (**1g**) (69 g, 750 mmol) in dry methanol (100 mL) was added 3-chloro-3-methyl-2-nitrosobutane (**19**) (20.55 g, 150 mmol) in portions at 0 °C over a period of 2 h. The reaction mixture was then stirred at room temperature for 20 h. The solvent was removed under reduced pressure to give a paste. Water (50 mL) was added, and the solution was cooled in an ice bath. The solution was then filtered, and the filtrate was adjusted to pH 10-11 by the addition of sodium hydroxide, after cooling and filtering, the filtrate was concentrated under reduced pressure to a paste and extracted with ether (10 x 50 mL). The ether solution was concentrated to give an oil which was crystallized (petroleum ether) to give the title compound as a colorless crystalline solid. Yield: 20 g (52%); mp 58-60 °C. ^1H NMR ($CDCl_3$) δ 0.85 (s, 6 H, $C\mathit{H}_3$), 1.23 (s, 6 H, $C\mathit{H}_3$), 1.85 (s, 3 H, N=C $C\mathit{H}_3$), 2.22 (s, 2 H, $NC\mathit{H}_2$) and 2.53 (s, 2 H, $NC\mathit{H}_2$); CIMS: 202 $(M+H)^+$.

N-(2-Ethyl-2-aminobutyl)-1-amino-1,1-dimethyl-2-butanone oxime (20e). 3-Chloro-3-methyl-2-nitrosobutane (**19**) (4.59 g, 34 mmol) was added portionwise to a cooled (0 °C) solution of 2,2-diethyl-1,3-diaminopropane (**1f**) (8.86 g, 68 mmol) in methanol (40 mL). After the addition, the reaction mixture was allowed to warm to RT and stirred (48 h). The remaining workup was as described for **20a**. The boc derivative of **20e** was crystallized (hexane) Yield: 4.2 g (43%); mp 117-18 °C; .^1H NMR ($CDCl_3$) δ 0.76 (m, 6 H, $C\mathit{H}_3$), 1.24 (m and s, 10 H, $C\mathit{H}_2CH_3$ and $C(C\mathit{H}_3)_2$), 1.46 (s, 9 H, NHBoc) 1.83 (s, 3H, $C\mathit{H}_3$), 2.22 (s, 2 H, $C\mathit{H}_2NHBoc$), 3.02 (s, 2 H, $C\mathit{H}_2NH$), 6.44 (m, 1 H, N*H*), 7.96 (s, 1 H, NO*H*); Anal. Calcd for $C_{17}H_{35}N_3O_3$: C, 61.97; H, 10.71; N, 12.75. Found: C, 62.41; H, 11.0; N, 12.61. Oxime **20e** was prepared in the same manner as **20a** from the protected diamine mono oxime. ^1H NMR (D_2O) δ 0.8 (t, 6H, $C\mathit{H}_3$), 1.43 (q, 4H, $C\mathit{H}_2$), 1.52 (s, 6H, $C(C\mathit{H}_3)_2$), 1.84 (s, 3H, $C\mathit{H}_3$), 2.99 (d, 4H, $C\mathit{H}_2$); CIMS: 230 $(M+H)^+$; Hydrochloride mp; 185-86 °C dec. (ethanol-ether); Anal. Calcd for $C_{12}H_{29}N_3OCl_2$: C, 47.68; H, 9.67; N, 13.90; Cl, 23.46. Found: C, 47.28; H, 10.04; N, 13.46; Cl, 23.03.

*3-[(3-Aminopropyl)amino]-3-methyl-2-butanone oxime (**20j**).* 3-Chloro-3-methyl-2-nitrosobutane (**19**) (13.5 g, 100 mmol) was added in small portions to a cooled (0 ^{o}C) solution of 1,3-diaminopropane (**1i**) (25 mL, 300 mmol) in acetonitrile over a period of 0.5 h. The reaction mixture was allowed to stir at 5 ^{o}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 an ice bath for 0.5 h, filtered, and 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, filtered, and washed with water (2 x 10 mL). Water was evaporated and the paste obtained was dried under vacuum to afford a solid which was recrystallized (isopropyl ether). Yield: 10.9 g (63%); mp 76.5-77.5 ^{o}C. ^{1}H NMR ($CDCl_3$) δ 1.19[s, 6H, $C(CH_3)_2$], 1.49 (t, 2H, $CH_2CH_2CH_2$), 1.78 [s, 3H, $C(=N)CH_3)_2$], 2.31 (t, 2H, CH_2NH_2) and 2.63 (t, 2H, $NHCH_2$).

*3-(3-Amino-2-methylpropylamino)-3-methyl-1-(2-nitro-1H-imidazol-1-yl)-2-butanone oxime (**22**).* To a solution of 2-methyl-1,3-diaminopropane[11] (**1h**) (3.00 g, 34.10 mmol) in dry acetonitrile (30 mL) was added 3-chloro-3-methyl-1-(2-nitro-1H-imidazol-1-yl)-2-nitrosobutane (**18a**) (1.50 g, 6.09 mmol) in portions over a period of 30 min at 50 ^{o}C with stirring. After the addition, the reaction mixture was left at 50 ^{o}C for an additional 30 min. The reaction mixture was cooled and evaporated on a rotary evaporator to a paste which was then crystallized from dichloromethane-ether to afford the title compound **22** as a light yellow solid; yield: 1.36 g (75%); mp 102-104 ^{o}C (dec); ^{1}H NMR ($CDCl_3$) δ 0.89 (d, 3H, CH_3), 1.22 [s, 6H, $C(CH_3)_2$], 1.51 (m, 1H, CH_3CH), 2.25 (d, 2H, CH_2NH_2), 2.65 (m, 2H, $NHCH_2$), 5.31 (s, 2H, imi-CH_2) and 7.03 & 7.21 (2s, 2H, imi-CH); CIMS m/z 299 $(M+H)^+$.

*General procedure for the preparation of nitroimidazole substituted PnAOs: 6-Hydroxy-3,3,9,9-tetramethyl-1-(2-nitro-1H-imidazol-1-yl)-4,8-diazaundecane-2,10-dione dioxime (**21a**).* 3-Chloro-3-methyl-1-(2-nitro-1H-imidazo-1-yl)-2-nitrosobutane (**18a**) (1.60 g, 6.50 mmol) was added to a slurry of 3-[(3-amino-2-hydroxypropyl)amino]-3-methyl-2-butanone oxime (**20a**) (1.4 g, 7.5 mmol) and N,N-diisopropylethylamine (1.0 g, 7.8 mmol) in acetonitrile (10 mL), and the mixture was stirred at RT (24 h). Acetonitrile was removed, and the thick yellow oil obtained was chromatographed over silica gel [(CH_2Cl_2:CH_3OH, (9:1)] and [CH_2Cl_2:CH_3OH, (8:2)]. Fractions containing the product (R_f 0.4) were combined and evaporated to a thick oil. Proton NMR analysis of the oil indicated the presence of the product and N,N-diisopropylethylamine. The oil was dried under vacuum for 12 h. The thick oil was then triturated several times with methylene chloride to remove the N,N-diisopropylethylamine. The residue was then dissolved in water and freeze dried. Yield: 0.65 g; mp 114-15 ^{o}C; ^{1}H NMR (D_2O) δ 1.33, 1.44 and 1.88 (s,15 H, CH_3), 2.42-2.92 (m, 4 H, CH_2),3.90 (m, 1 H,CHOH),5.34 (s, 2 H, CH_2N), 7.14 and 7.31 (s, 2 H, imi-H); FAB-HRMS: $(M+H)^+$: Calcd: 400.2308. Found: 400.2298

*3,3,9,9-Tetramethyl-6-methoxy-1-(2-nitro-1H-imidazol-1-yl)-4,8-diazaundecane-2,10-dione dioxime (**21b**).* Yield: 12%; mp 169-70 ^{o}C (acetonitrile); FAB-HRMS: $(M+H)^+$ Calcd: 414.2465. Found: 414.2472. ^{1}H NMR (DMSO-d_6): δ 1.08 and 1.18 (S, 12 H, $C(CH_3)_2$), 1.65 (s, 3 H, CH_3) 2.22 (m, 4 H, CH_2NH), 3.0 (m, 1H, $CHCH_2NH$), 3.20 (s, 3H, OCH_3), 5.21 (s, 2 H, NCH_2), 7.1 and 7.32 (s, 2H, imi-H), 10.41 and 11.42 (s, 2 H, NOH). ^{13}C NMR (DMSO-d_6) δ 9.1[$CH_3C(=N)$], 25.3, 25.4, 25.7 & 25.8[$C(CH_3)_2$], 41.1(CH_2-imidazole), 44.0 & 44.4($NHCH_2$), 56.5, 56.6 & 56.7[$CHOCH_3$ & $C(CH_3)_2$], 80.8(OCH_3), 126.6 & 127.4(imi-CH), 146.9(imi-C-NO_2) and 156.2 & 159.9(C=NOH). Anal. Calcd for $C_{17}H_{31}N_7O_5$: C, 49.38; H, 7.56; N, 23.71. Found: C, 49.70; H, 7.59; N, 23.73.

*3,3,6,6,9,9-Hexamethyl-1-(2-nitro-1H-imidazol-1-yl)-4,8-diazaundecane-2,10-dione dioxime (**21c**).* Yield: 10%; mp 118-120 ^{o}C (dec) (THF-hexanes); ^{1}H NMR ($CDCl_3$) δ 0.8 (s, 6 H, 6-$(CH_3)_2$), 1.2 (s, 12 H, C-3,9-CH_3), 1.9 (s, 3 H, $N=CCH_3$), 2.2 (2s, 4H, NCH_2), 5.4 (s, 2 H, imi-CH_2), 7.1 (s, 1 H, imi-H) and 7.15 (s, 1 H, imi-H); ^{13}C NMR (DMSO-d_6) δ 9.0 [$CH_3C(=N)$], 24.0 [$CH_2(CH_3)_2$], 25.2 & 25.5 [$NHC(CH_3)_2$], 33.7 [$CH_2C(CH_3)_2$], 40.9 (CH_2-imidazole), 51.1 & 51.5 ($NHCH_2$), 56.5 [$NHC(CH_3)_2$], 125.8 & 127.0 (imi-CH), 145.5 (imi-C-NO_2) and 156.1 & 159.6 (C=NOH). FAB-MS: 412 $(M+H)^+$. Anal. Calcd $C_{18}H_{33}N_7O_4$.0.6 THF, 0.1H_2O: C, 53.73; H, 8.39; N, 21.50. Found: C, 53.73; H, 8.55; N, 21.28. HPLC: t_R- 19.54 min.

6,6-Diethyl-3,3,9,9-tetramethyl-1-(2-nitro-1$\underline{H}$*-imidazol-1-yl)-4,8-diazaundecane-2,10-dione dioxime* ***(21d)***. Yield: 28% ($CHCl_3$); mp. 124-25 °C; ^1H NMR (DMSO-d_6): δ 0.76 (m, 6 H, $C\mathit{H}_3$), 1.24 (m and s, 16 H, $C\mathit{H}_2CH_3$ and $C(C\mathit{H}_3)_2$), 1.48 (s, 3 H, $C\mathit{H}_3$), 1.73 and 1.85 (s, 4 H, $C\mathit{H}_2NH$), 5.02 (s, 2 H, $NC\mathit{H}_2$), 7.8 and 8.24 (s, 2 H, imi-*H*), 11.1 and 11.8 (s, 2 H, NO*H*); ^{13}C NMR (DMSO-d_6) δ 7.3 ($CH_2\mathit{C}H_3$), 9.3 [$\mathit{C}H_3C(=N)$], 25.4 ($\mathit{C}H_2CH_3$), 25.7 & 25.8 [$C(\mathit{C}H_3)_2$], 38.4 [$\mathit{C}(C_2H_5)_2$], 41.4 (imi-$\mathit{C}H_2$), 45.8 & 46.1 ($NH\mathit{C}H_2$), 56.5 [$\mathit{C}(CH_3)_2$], 126.3 & 127.4 (imi-*C*H), 145.1 (imi-*C*-NO_2) and 156.1 & 159.8(*C*=NOH). Anal. Calcd for $C_{20}H_{37}N_7O_4$: C, 54.64; H, 8.48; N, 22.29. Found: C, 54.45; H, 8.50; N, 22.16.

6,6-Diethyl-3,3,9,9-tetramethyl-1-(4-nitro-1$\underline{H}$*-imidazol-1-yl)-4,8-diazaundecane-2,10-dione dioxime* ***(21e)***. Yield: 59% (acetonitrile); ^1H NMR (DMSO-d_6): δ 0.67 (m, 6 H, $C\mathit{H}_3$), 1.16 (m and s, 16 H, $C\mathit{H}_2CH_3$ and C ($C\mathit{H}_3)_2$), 1.71 (s, 3 H, $C\mathit{H}_3$) 1.99 and 2.06 (s, 4 H, $C\mathit{H}_2NH$), 5.19 (s, 2 H, $NC\mathit{H}_2$), 7.13 and 7.22 (s, 2 H, imi-*H*), 10.39 and 11.42 (s, 2 H, NO*H*); Anal. Calcd for $C_{20}H_{37}N_7O_4$ .2.71 H_2O: C, 49.19; H, 8.25; N, 20.08. Found: C, 49.17; H, 8.13; N, 19.72.

3,3,9,9-Tetramethyl-1-(4-methyl-2-nitro-1$\underline{H}$*-imidazol-1-yl)-4,8-diazaundecane-2,10-dione dioxime* ***(21f)***. Yield: 59% (acetonitrile); mp. 140-141 °C; ^1H NMR (DMSO-d_6) δ 1.12 & 1.19 [2s, 6H, $C(C\mathit{H}_3)_2$], 1.33 (m, 2H, $CH_2C\mathit{H}_2CH_2$), 1.70 (s, 3H, $C(=N)C\mathit{H}_3$], 1.79 (bs, 2H, N*H*), 2.15 (s, 3H, imi-$C\mathit{H}_3$), 2.19 (m, 4H, $NHC\mathit{H}_2$), 5.19 [s, 2H, $NC\mathit{H}_2(=N)$], 7.05 (s, 1H, imi-C*H*), 10.33 & 11.36 (2s, 2H, NO*H*). ^{13}C NMR (DMSO-d_6) δ 9.0 [$\mathit{C}H_3C(=N)$], 13.4(imi-$\mathit{C}H_3$), 25.4 & 25.7 [$C(\mathit{C}H_3)_2$], 31.3 ($CH_2\mathit{C}H_2CH_2$), 40.7 ($\mathit{C}H_2$-imi), 41.1 & 41.2($NH\mathit{C}H_2$), 56.8 [$\mathit{C}(CH_3)_2$], 123.5 (imi-*C*H), 136.4(imi-*C*-CH_3), 144.5 (imi-*C*-NO_2) and 156.5 & 160.2 (*C*=NOH). FAB-MS: 398 $(M+H)^+$. Anal. Calcd for $C_{17}H_{31}N_7O_4$ 0.10 H_2O: C, 51.14; H, 7.88; N, 24.55. Found: C, 51.39; H, 7.91; N, 24.30. HPLC: t_R- 21.28 min.

3,3,9,9-Tetramethyl-1-(5-methyl-2-nitro-1$\underline{H}$*-imidazol-1-yl)-4,8-diazaundecane-2,10-dione dioxime* ***(21g)***. Yield: 58% (acetonitrile); mp. 150-152 °C; ^1H NMR (DMSO-d_6) δ 1.01 & 1.13 [2s, 6H, $C(C\mathit{H}_3)_2$], 1.40(m, 2H, $CH_2C\mathit{H}_2CH_2$), 1.68 (s, 3H, $C(=N)C\mathit{H}_3$], 1.71 (bs, 2H, N*H*), 2.20 (s, 3H, imi-$C\mathit{H}_3$), 2.25 (m, 4H, $NHC\mathit{H}_2$), 5.36 [s, 2H, $NC\mathit{H}_2(=N)$], 6.91 (s, 1H, imi-C*H*), 10.36 & 11.06 (2s, 2H, NO*H*). ^{13}C NMR (DMSO-d_6) δ 9.0[$\mathit{C}H_3C(=N)$], 9.8 (imi-$\mathit{C}H_3$), 25.7 & 26.4 [$C(\mathit{C}H_3)_2$], 30.9 ($CH_2\mathit{C}H_2CH_2$), 40.7(imi-$\mathit{C}H_2$), 41.2 & 41.3($NH\mathit{C}H_2$), 56.8 & 57.2[$\mathit{C}(CH_3)_2$], 125.6 (imi-*C*H), 136.0 (imi-*C*-CH_3), 146.2 (imi-*C*-NO_2) and 154.5 & 160.2 (*C*=NOH). FAB-MS 398 $(M+H)^+$. Anal. Calcd for $C_{17}H_{31}N_7O_4$ 0.56 H_2O: C, 50.09; H, 7.94; N, 24.05. Found: C, 50.06; H, 7.86; N, 23.88. HPLC:t_R-20.82 min.

3,3,9,9-Tetramethyl-1-(4-nitro-1$\underline{H}$*-imidazol-1-yl)-4,8-diazaundecane-2,10-dione dioxime* ***(21h)***. Yield: 42% (acetonitrile); mp 152-154 °C; ^1H NMR (DMSO-d_6) δ 1.17 (s, 6 H, $C(C\mathit{H}_3)_2$), 1.26 (s, 6 H, $C(C\mathit{H}_3)_2$), 1.41 (m, 2 H, -$NCH_2C\mathit{H}_2CH_2N$-), 1.76 (s, 3 H, $N{=}CC\mathit{H}_3$), 2.26 (m, 4 H, -$NHC\mathit{H}_2$), 4.98 (s, 2 H, imi-$NC\mathit{H}_2$), 7.9 (s, 1 H, imi-H), 8.29 (s, 1 H, imi-H), 11.63 (s, 1 H, NO*H*); FAB-MS: 384 $(M+H)^+$. Anal. Calcd for $C_{16}H_{29}N_7O_4$.0.5 H_2O: C, 48.91, H, 7.71; N, 24.96. Found: C, 49.11, H, 7.49; N, 24.76. HPLC: t_R- 18.37 min.

5,9-Diaza-4,4,10,10-tetramethyl-1-(2-nitro-1$\underline{H}$*-imidazol-1-yl)-3,11-dodecanedione dioxime* ***(21i)***. Yield: 6% (dichloromethane:methanol, 9:1); mp 65-67 °C (dec); ^1H NMR (DMSO-d_6) δ 1.2 (s, 12 H, $C\mathit{H}_3$), 1.45 (m, 2 H, C-$C\mathit{H}_2$-C), 1.8 (s, 3 H, $N{=}CC\mathit{H}_3$), 2.3 (m, 4 H, $NHC\mathit{H}_2$), 2.85 (t, 2 H, $N{=}CC\mathit{H}_2$), 4.8 (t, 2 H, $NC\mathit{H}_2$), 7.2 (s, 1 H, imi-*H*), 7.6 (s, 1 H, imi-*H*), 10.4 (s, 1 H, NO*H*) and 10.85 (s, 1 H, NO*H*); ^{13}C NMR (DMSO-d_6) δ 9.0 [$\mathit{C}H_3C(=N)$], 25.3 & 25.6 [$C(\mathit{C}H_3)_2$], 30.9 ($CH_2\mathit{C}H_2CH_2$), 40.9 (imi-$\mathit{C}H_2$), 41.1 & 41.2 ($NH\mathit{C}H_2$), 46.0 (imi-$\mathit{C}H_2CH_2$), 56.8 [$\mathit{C}(CH_3)_2$], 127.6 & 127.9 (imi-*C*H), 145.5 (imi-*C*-NO_2) and 158.8 & 160.1(*C*=NOH). FAB-MS: 398 $(M+H)^+$. Anal. Calcd for $C_{17}H_{31}N_7O_4$: C, 51.37; H, 7.86; N, 24.67. Found C, 51.89; H, 7.89; N, 24.27. HPLC: t_R- 20.46 min.

3,3,9,9-Tetramethyl-1-(2-nitro-1$\underline{H}$*-imidazol-1-yl)-4,8-diazaundecane-2,10-dione dioxime* ***(21j)***. Yield: 57% (acetonitrile); mp 146-147 °C (dec); ^1H NMR (DMSO-d_6) δ 1.08 (s, 6 H, $C\mathit{H}_3$), 1.18 (s, 6 H, $C\mathit{H}_3$), 1.32 (m, 2 H, C-$C\mathit{H}_2$-C), 1.62 (s, 3 H, $N{=}CC\mathit{H}_3$), 2.18 (m, 4 H, $NHC\mathit{H}_2$), 5.2 (s, 2 H, $NC\mathit{H}_2$), 7.1 (s, 1 H, imi-H), 7.25 (s, 1 H, imi-*H*), 10.3 (s, 1 H, NO*H*),11.35 (s, 1 H, NO*H*); ^{13}C NMR (DMSO-d_6) δ 9.3 [$\mathit{C}H_3C(=N)$], 25.7 & 26.0 [$C(\mathit{C}H_3)_2$], 31.6 ($CH_2CH_2CH_2$), 41.2 (imi-$\mathit{C}H_2$), 41.3 & 41.5 ($NH\mathit{C}H_2$), 57.1 [$\mathit{C}(CH_3)_2$], 126.8 & 127.6 (imi-*C*H), 145.6 (imi-*C*-NO_2) and 156.7 & 160.5 (*C*=NOH). FAB-MS: 384 $(M+H)^+$. Anal. Calcd for $C_{16}H_{29}N_7O_4$: C, 50.12; H, 7.62; N, 25.57. Found: C, 50.44, H, 7.77; N, 25.27.

3,3,6,9,9-Pentamethyl-1-(2-nitro-1H-imidazol-1-yl)-4,8-diazaundecane-2,10-dione dioxime (23). Yield: 83% (acetonitrile); mp 167-168 °C. ^{1}H NMR (DMSO-d_6) δ 0.89 (d, 3H, $CHC\mathit{H}_3$), 1.31 [s, 6H, $C(C\mathit{H}_3)_2$], 1.58 [2s, 6H, $C(C\mathit{H}_3)_2$], 1.89 [s, 3H, $C(N=OH)C\mathit{H}_3$], 2.28 (m, 1H, $CH_3C\mathit{H}$), 2.62 & 2.92 (2m, 4H, $NHC\mathit{H}_2$), 5.31 (s, 2H, imi-$C\mathit{H}_2$), 7.06 & 7.22 (2s, 2H, imi-C*H*) and 10.82 & 11.69(2s, 2H, NO*H*). ^{13}C NMR (DMSO-d_6) δ 9.8 [$\mathit{C}H_3C(=N)$], 16.7 ($CHCH_3$), 22.8 & 24.8 [$C(CH_3)_2$], 31.5 ($\mathit{C}HCH_3$), 41.8 (imi-CH_2), 47.2($NH\mathit{C}H_2$), 57.6 & 61.1[$\mathit{C}(CH_3)_2$], 126.5 & 127.5(imi-*C*H), 145.2(imi-*C*-NO_2) and 154.9 (*C*=NOH). FAB-MS: 398 $(M+H)^+$. Anal. Calcd for $C_{17}H_{31}N_7O_4\cdot 0.89\ H_2O$: C, 47.37; H, 8.12; N, 22.75. Found: C, 47.37; H, 7.85; N, 22.41. HPLC: t_R-18.20 min.

3,3,9,9-Tetramethyl-6-[(2-nitro-1H-imidazol-1-yl)acetamido]-4,8-diazaundecane-2,10-dione dioxime (26a). To a slurry of the dihydrochloride of amine **1c** (4.25 g, 13.5 mmol) in dry DMF (40 mL) was added $NaHCO_3$ (5.88 g, 70 mmol) and 3-bromo-3-methylbutan-2-one (**24**) (6.1 g, 70 mmol). The reaction mixture was stirred at 45 °C (12 h). Methylene chloride (200 mL) was added to this reaction mixture and filtered. Methylene chloride was removed, and the DMF was removed under vacuum. The residue was chromatographed over silica gel and eluted with ethyl acetate-methanol (9:1). Fractions (R_f 0.5) containing the diketone **25a** were collected and the solvent was removed to yield the desired diketone. Yield 2.56 g (46.3%). It was crystallized from hexane; mp 96-97 °C. ^{1}H NMR (D_2O) δ 1.22 [d,12 H,$C(C\mathit{H}_3)_2$], 2.12 (s, 6 H, $C\mathit{H}_3$), 2.32-2.58 (m, 4 H, $CH(C\mathit{H}_2)_2NH_2$), 3.9 (m,1 H,C*H*), 5.21 (s, 2 H, $NHCOC\mathit{H}_2$), 7.15 (s, 1 H, imi-*H*) and 7.39 (s, 1 H, imi-*H*); FAB-MS: 411 $(M+H)^+$. To a solution of **25a** (550 mg, 1.33 mmol) in methylene chloride (2 mL) was added O-trimethylsilylhydroxylamine (1.0 g, 1.22 mL, 10 mmol), and the reaction mixture was allowed to stand at RT (24 h). Methanol (2.0 mL) was added to the reaction mixture, and the solvent was removed. The solid obtained was crystallized from water. Yield: 0.33 g (60%); mp 72-73 °C. ^{1}H NMR (D_2O) δ 1.12 [s, 12 H,$C(C\mathit{H}_3)_2$],1.72 (s, 6 H, $C\mathit{H}_3$), 2.22-2.45 (m, 4 H, $CH(C\mathit{H}_2)_2NH_2$), 3.8 (m, 1 H, C*H*), 5.1 (s, 2 H, $NHCOC\mathit{H}_2$), 7.15 (s ,1 H, imi-*H*) and 7.39 (s, 1 H, imi-*H*); FAB-MS: 441 $(M+H)^+$. Anal. Calcd for $C_{18}H_{32}N_8O_5$: C, 49.08; H, 7.32; N, 25.44. Found: C, 49.42; H, 7.54; N, 25.65.

3,3,9,9-Tetramethyl-6-[(2-nitro-1H-imidazol-1-yl)ethyl]-4,8-diazaundecane-2,10-dione dioxime (26b). To a mixture of amine **1d** (0.2 g, 1.0 mmol) and sodium bicarbonate (0.25 g, 3.0 mmol) was added 3-bromo-3-methylbutan-2-one (**24**) (0.5 g, 3.0 mmol), and the mixture stirred at 50 °C (24 h). DMF was removed under vacuum, and the crude product was chromatographed over silica gel (CH_2Cl_2:CH_3OH, 9:1, 8:2). Fractions containing the product (R_f 0.4) were collected and evaporated to give **25b** as a thick oil. Yield 0.11 g. ^{1}H NMR (D_2O) δ 1.33 [d and m, 13 H, $C(C\mathit{H}_3]$ and C*H*), 1.80 [m, 2 H, $CH(C\mathit{H}_2CH_2N]$, 2.19 (s, 6 H, $C\mathit{H}_3$), 2.65 [m, 4 H, $CH(C\mathit{H}_2NH]$, 4.40 [t, 2 H, $CH(CH_2C\mathit{H}_2N]$, 7.10 and 7.39 (s, 2 H, imi-*H*). Diketone **25b** (65 mg, 17 mmol) was dissolved in dry methylene chloride (0.5 mL) and treated with O-trimethylsilylhydroxylamine (0.3 mL), and the mixture refluxed for 24 h. Methylene chloride was removed, and the residue was treated with methanol. Evaporation of methanol afforded **26b** as a thick paste which was dissolved in water and freeze dried. Yield: 62 mg (88%); mp 174-76 °C; ^{1}HNMR (D_2O) δ 1.2 (d and m, 13H, $C(C\mathit{H}_3)$ and C*H*), 1.75 (s and m, 8H, $CH(C\mathit{H}_2CH_2N)$ and $C\mathit{H}_3$), 2.55 (m, 4H, $CH(C\mathit{H}_2NH)$, 4.36 (t, 2H, $CH(CH_2C\mathit{H}_2N)$, 7.06 and 7.34 (s, 2H, imi-*H*); FAB-MS: 412 m/z $(M+H)^+$. Anal. Calcd for $C_{18}H_{35}N_7O_4Cl_2$: C, 44.70; H, 7.30; N, 20.29. Found: C, 45.08; H, 7.14; N, 20.18.

3,3,9,9-Tetramethyl-6-[2-hydroxy-3-(2-nitro-1H-imidazol-1-yl)-propyl]-4,8-diazaundecane-2,10-dione dioxime (26c). To a mixture of the diamine **1e** (240 mg, 1.0 mmol) in DMF (2 mL) sodium bicarbonate (200 mg, 2.45 mmol) was added and 3-bromo-3-methylbutan-2-one (**24**) (400 mg, 2.4 mmol), and the mixture was stirred at 45 °C for 6 h. DMF was removed, and the residue was triturated with methylene chloride (3 x 5 mL). Methylene chloride was removed and the oil obtained was chromatographed over silica gel

(CH_2Cl_2:CH_3OH, 8:2). UV visible fractions (R_f 0.5) were collected and evaporated to give the diketone **25c** as an oil. Yield. 100 mg (25%); ^{1}HNMR ($CDCl_3$) δ 1.52 [d, 12 H, C(C*H*$_3$)$_2$], 2.12 (s, 6 H, C*H*$_3$>=O), 2.35-3.12 (m, 5 H, C*H*(C*H*$_2$NH), 4.1 (m, 1 H, C*H*OH), 4.3-4.6 (m, 2 H, CHOHC*H*$_2$N<), 7.1 and 7.42 (s, 2 H, imi-*H*). O-Trimethylsilylhydroxylamine (0.5 mL) was added to a solution of diketone **25c** (100 mg, 0.25 mmol) in methylene chloride (1.0 mL) and stirred at RT for 24 h. Methanol was added to the reaction mixture, and the oil obtained was chromatographed over silica gel (CH_2Cl_2:CH_3OH, 9:1). UV visible fractions (R_f 0.4) were collected and evaporated to give the dioxime **26c**. The product was dissolved in minimum amount of water and freeze dried. The freeze dried solid was recrystallized from acetonitrile. Yield: 45 mg (25%); mp 185-87 °C dec; ^{1}HNMR (D_2O) δ 1.22 [d, 12 H, C(C*H*$_3$)$_2$], 1.80 (s, 6 H, C*H*$_3$>=N), 2.8 (m, 5 H, C*H*(C*H*$_2$NH), 3.82 (m, 1 H, C*H*OH), 4.2-4.58 (m, 2 H, CHOHC*H*$_2$N<), 7.1 and 7.32 (s, 2 H, imi-*H*); FAB-MS: Calcd for $C_{19}H_{36}NO_5$ 442.2778 $(M+H)^+$. Found. 442.2781. Anal. Calcd for $C_{19}H_{37}N_7O_5Cl_2$: C, 44.36; H, 7.25; N, 19.86, Found: C, 44.04; H, 7.00; N 18.65. HPLC: t_R = 21.89 min.

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