Pergamon

Tetrahedron Vol. 50, No. 29, pp. 8617-8632, 1994

0040-4020/94 $7.00+0.00

0040-4020(94)00494-3

An Efficient Synthesis of Some 6-Substituted 4,8-Diaza-3,3,9,9-tetramethylundeca-2,10-dione Dioximes (Propylene Amine Oximes, PnAOs): Ligands for ^{99m}Tc Complexes Used in Structure Distribution Relationship (SDR) Studies

Palaniappa Nanjappan, Natarajan Raju, Kondareddiar Ramalingam, David P. Nowotnik*

Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ 08543-4000

ABSTRACT

Technetium complexes of the ligand PnAO [4,8-diaza-3,3,9,9-tetramethylundeca-2,10-dione dioximes (3)] are of interest as commercial radiopharmaceuticals. In general, PnAOs are synthesized by alkylation of a propylenediamine derivative with 3-chloro-3-methyl-2-nitrosobutane (2). This alkylation reaction proved to be low yielding. With modestly bulky substituents at the 2-position of 1,3-diaminopropane, little or none of the required PnAO was obtained. As a result, an alternative approach of the synthesis of PnAO was developed. This method involved the alkylation of the propylenediamine with 3-bromo-3-methylbutan-2-one (18) followed by oximation of the resulting diamine-diketone (19). By this method, PnAOs were prepared in good yield, even with bulky C-2 substituents. Fourteen PnAO derivatives were prepared by this method. We also describe the syntheses of several new propylenediamine derivatives.

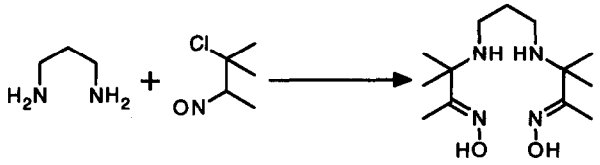
INTRODUCTION

Several technetium based agents for the diagnosis of ischemia in heart and brain are now commercially available (^{99m}Tc-d,l-HMPAO[1,2] and ^{99m}Tc-L,L,-ECD[3] as brain perfusion agents; ^{99m}Tc-MIBI[4] and ^{99m}Tc-teboroxime[5-7] as cardiac perfusion agents). There is a clinical need to augment this collection of perfusion tracers with complexes which localize specifically in hypoxic regions and demonstrated tissue viability. To this end, Tc-BATO complexes[8,9] were adapted to contain the 2-nitroimidazole moiety[10]. However, these nitroimidazole-BATO complexes proved to be inadequate for the purpose of imaging hypoxia in vivo and an alternate Tc-'core' for a hypoxia-localizing radiopharmaceutical was sought. The ligand propylene amine oxime (PnAO) appeared to be suitable for this purpose. Troutner and Volkert[11,12] had synthesized a stable Tc-complex from PnAO and ethylene amine oxime (EnAO). They also demonstrated that these ^{99m}Tc-PnAO and ^{99m}Tc-EnAO complexes were stable enough to permit parenteral administration for imaging[12]. The structure of the Tc-PnAO complex has been determined[13]; Tc-PnAO complexes have a square pyramidal geometry with the metal in the +5 oxidation state. The metal is bound to the four nitrogen atoms of the ligand and a single oxygen atom, and the oximes form a hydrogen-bonded bridge which enhances complex stability. In-house studies demonstrated that Tc-PnAO complexes (unlike the BATOs) were able to diffuse across cell membranes in an *in vitro* model involving cultured bovine brain

endothelial cells[14]. This ability to traverse lipophilic membranes is attributed to the fact that the Tc-PnAO complexes are compact, neutral and lipophilic. Therefore, appropriate derivatives of these complexes have the potential to perform as probes of intracellular biochemical events such as hypoxia[15]. However, attachment of substituents to the ligand will have an impact on the membrane permeability of their complexes. Therefore, a series of substituted propylene amine oximes (PnAOs) were synthesized to determine structure-distribution relationships (SDR) in these complexes. The SDR data will be reported in greater detail elsewhere, but, in general, it appears that lipophilicity is the major determinant in membrane permeability in this series of complexes. This paper describes the syntheses of substituted propylene amine oximes (PnAOs) **3** ligands.

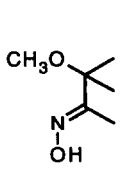
RESULTS AND DISCUSSION

Our plan for the synthesis of propylene amine oximes (PnAOs) **3** was to adapt the route developed by Troutner and coworkers[12] which involves *N*-alkylation of 1,3-diaminopropane (**1a**) with 3-chloro-3-methyl-2-nitrosobutane (**2**) in methanol as shown below.

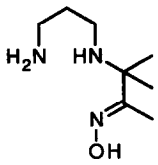


1a **2** **3a**

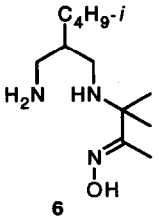
Propylene amine oximes **3a**, **3b** and **3k** were prepared by the alkylation of the corresponding 1,3-diaminopropanes **1a**, **1b** and **1k** respectively with 3-chloro-3-methyl-2-nitrosobutane (**2**) in methanol, following the literature method[12,16]. This route has a number of disadvantages. The preparation of 3-chloro-3-methyl-2-nitrosobutane (**2**) requires fast workup and the nitroso compound so obtained is unstable at room temperature and should be kept in the freezer. The yield of the 3-chloro-3-methyl-2-nitrosobutane (**2**) does not exceed more than 30%. Under the reaction conditions described in the literature[12,16] for the preparation of PnAO derivatives, 3-chloro-3-methyl-2-nitrosobutane (**2**) undergoes solvolysis in methanol providing 3-methoxy-3-methylbutan-2-one (**4**) as a major product. In addition, "diamine monooxime", 3-(3-aminopropyl)amino-3-methylbutan-2-one oxime[16] (**5**) was invariably found to be present in significant amounts, making the purification of the desired PnAO difficult. When the reaction was extended to hindered 1,3-diamines, e.g. 2-*i*-butyl-1,3-diaminopropane (**1c**), 3-(3-amino-2-*i*-butylpropyl)amino-3-methylbutan-2-one oxime (**6**) was the predominant product.



4



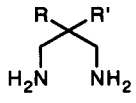
5



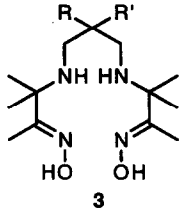
6

Furthermore, amine hydrochlorides could not be used since *in situ* liberation of free amine from the salt before the addition of 3-chloro-3-methyl-2-nitrosobutane (**2**) did not yield PnAO derivatives. This is a major drawback of the literature method[12,16] since functionalized 1,3-diaminopropanes are normally purified as hydrochlorides. So it was thought desirable to synthesize the PnAO derivatives by an alternate method. Accordingly, we have developed a two step procedure for the preparation of PnAO derivatives in good yields.

The key starting materials for the synthesis of PnAO derivatives described herein are amines **1a-1n.** 2-Methyl- (**1b**), 2,2-diethyl- (**1e**), 2-amino- (**1h**) and 2-methoxy-1,3-diaminopropane (**1l**) were prepared following the procedure reported elsewhere[17]. The 2-substituted 1,3-diaminopropanes **1c**, **1f** and **1g** were prepared from the corresponding diethylmalonate **7c**, **7f**, and **7g** as shown in the Scheme I. Diethylmalonate was alkylated with isobutylbromide in the presence of NaOEt in ethanol to furnish diethyl 2-isobutylmalonate **7c**. Treatment of **7c** with methanolic ammonia gave



1

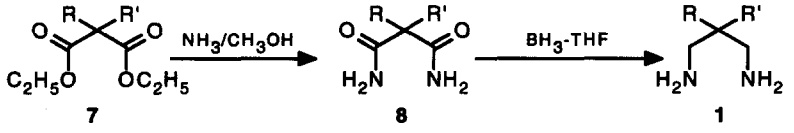


3

	R	R'
a	H	H
b	H	CH_3
c	H	i-C_4H_9
d	CH_3	CH_3
e	C_2H_5	C_2H_5
f	H	F
g	F	F
h	H	NH_2
i	H	$NHCOCH_3$
j	H	$NHCOC_2H_5$
k	H	OH
l	H	OCH_3
m	H	CN
n	H	$COOCH_3$

the diamide **8c** in 60% yield which on borane-THF complex reduction afforded the diamine **1c**. Likewise, 2-fluoro- (**8f**) and 2,2-difluoromalonamide (**8g**) were reduced with BH_3-THF. The resultant amines were isolated as bis-boc derivatives, which on treatment with methanolic HCl provided the aminehydrochlorides **1f** and **1g**, respectively.

Scheme I

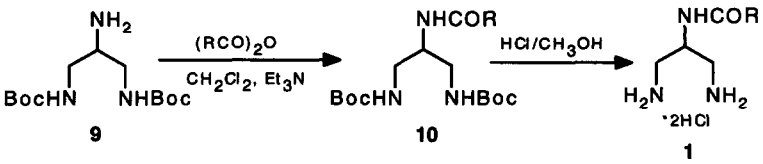


7 **8** **1**

	R	R'
c	H	*i*-C_4H_9
f	H	F
g	H	F

Treatment of 1,3-bis-*N*-*t*-butyloxycarbonyl-2-aminopropane[17] (**9**) with acetic anhydride in CH_2Cl_2 in the presence of triethylamine furnished the amide **10i**. In a similar fashion, **9** was converted to **10j** using propionic anhydride. Deprotection of **10i** and **10j** with methanolic HCl furnished **1i** and **1j**, respectively, as a hydrochloride salt. 2-Cyano-1,3-diaminopropane (**1m**) was synthesized as shown in the Scheme III. The reaction of 1,3-bis-*N*-*t*-butyloxycarbonyl-2-methanesulfonylpropane[17] (**11**) with NaCN in anhydrous DMSO at 75 °C in the presence of 18-crown-6-ether as a catalyst provided a mixture of chromatographically separable isomers **13** and **14** *via* 2-(aminomethyl)aziridine

Scheme II

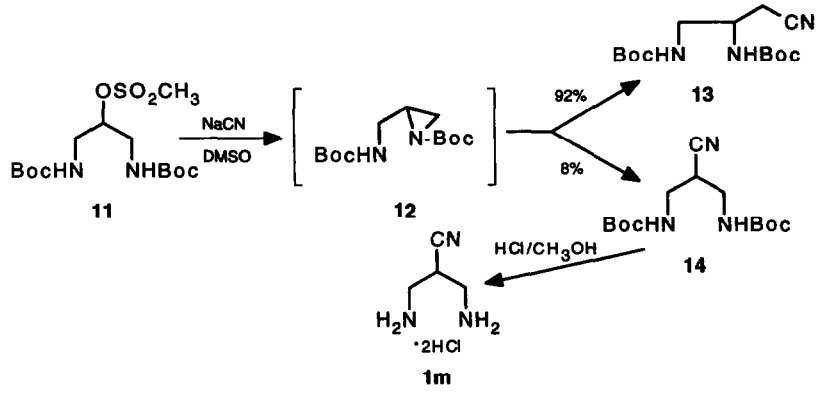


9 **10** **1**

i, R = CH_3; j, R = C_2H_5

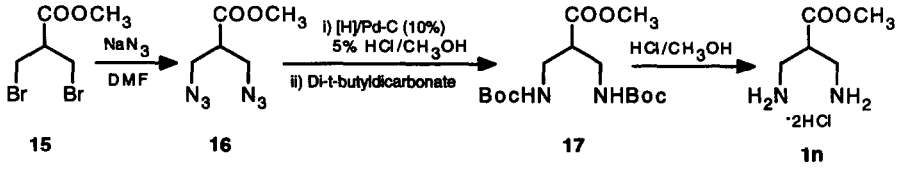
derivative[18,19] (**12**) in the ratio ~9:1 with difference in the R_f 0.10 (silica gel, hexane-ethyl acetate, 7:3). Isomers **13** and **14** were separated in pure form by silica gel chromatography and their structures were confirmed by ^1H NMR, MS and analytical data. The isomer 1,3-bis-*N*-*t*-butyloxycarbonyl-2-cyanopropane (**14**) was deprotected with methanolic HCl and the cyano compound **1m** was obtained as a hydrochloride salt.

Scheme III



Methyl 3-amino-2-(aminomethyl)propionate (**1n**) was prepared from methyl 3-bromo-2-(bromomethyl)propionate (**15**) via a three step procedure as shown in the Scheme IV. The bisbromo ester **15** was reacted with NaN_3 and catalytic reduction of the resultant diazide **16** provided the crude methyl 3-amino-2-(aminomethyl)propionate (**1n**). The diamine **1n** was isolated as its bis-boc derivative **17** in pure form. Deprotection of **17** with methanolic HCl provided **1n** as a hydrochloride.

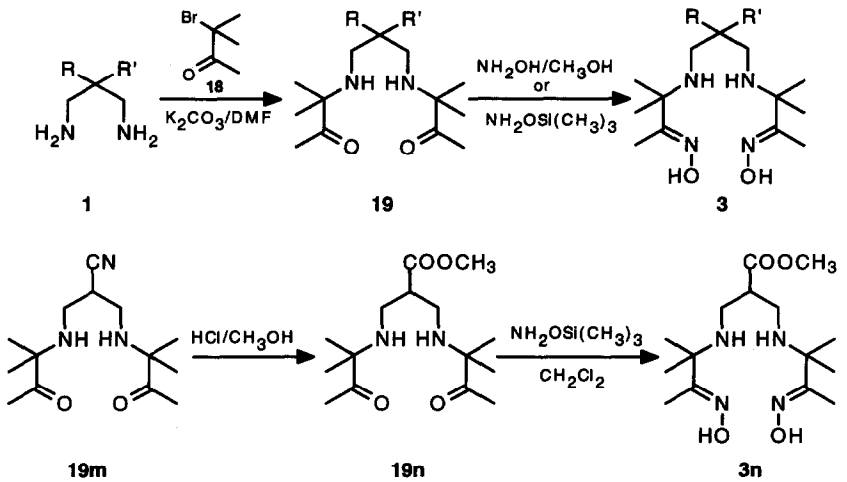
Scheme IV



The 1,3-diaminopropanes **1a-1e** and **1k** were alkylated with 3-chloro-3-methyl-2-nitrosobutane (**2**) to prepare their corresponding PnAO derivatives **3a-3e** and **3k**. This chloronitroso method was found to provide PnAO derivatives in poor yields when applied to diamines with bulky groups at 2-position and the results are summarized in the table 1. We therefore investigated an alternative approach which involved the alkylation of the 1,3-diaminopropanes **1a-1n** with 3-bromo-3-methyl-2-butanone[20] (**18**) in dry DMF in the presence of anhydrous K_2CO_3 (Scheme V). Oximation of the diketone **19** with either O-(trimethylsilyl)hydroxylamine or NH_2OH permitted the isolation of the desired PnAO as depicted in Scheme V. The use of O-(trimethylsilyl)hydroxylamine to derivatize the diketones **19** in CH_2Cl_2 was found to be much

superior to the use of freshly prepared NH_2OH from $NH_2OH{\cdot}HCl$ by neutralization. During the isolation of the final product, and especially for diketones with groups like -CN and $-COOCH_3$ sensitive to NH_2OH, better yields of PnAO derivatives were obtained in the case of $NH_2OSi(CH_3)_3$. In general, this bromo-ketone method provided PnAO derivatives in high yield (see table 1). Only in the case of amine **1n** did this strategy fail to provide the desired PnAO. The reaction of amine **1n** with 3-bromo-3-methyl-2-butanone (**18**) in dry DMF in the presence of either anhydrous K_2CO_3 or Et_3N or $(i\text{-}C_3H_7)_2NC_2H_5$ provided an intractable mixture, presumably due to the formation of various intra- and intermolecular amine-methyl ester condensation products. However, the methyl ester-diketone **19n** was prepared successfully by methanolysis of cyanodiketone **19m** with dry HCl/CH_3OH (Scheme V). The methyl ester diketone **19n** on oximation with O-(trimethylsilyl)hydroxylamine in CH_2Cl_2 afforded 4,8-diaza-3,3,9,9-tetramethyl-6-carbomethoxy-undeca-2,10-dione dioxime (**3n**).

Scheme V



1 **19** **3**

19m **19n** **3n**

Table 1. Comparison of the yields of PnAOs from chloronitroso and bromoketone methods

PnAO derivative	% Yield*	
R	Chloronitroso method	Bromoketone method
H (**3a**)	40	94
CH_3 (**3b**)	38	86
$(CH_3)_2$ (**3d**)	30	89
$CH_2CH(CH_3)_2$ (**3c**)	6	83
OCH_3 (**3l**)	-	60

* Yield is based on diamine

The method described here for the synthesis of these PnAO derivatives represents a significant improvement over the previously published method of Troutner *et. al.*[12] The key starting material, 3-bromo-3-methylbutan-2-one (**18**) was prepared[20] in 50% yield from isopropyl methylketone and may be stored at room temperature for extended periods without any decomposition. Although, the synthesis of PnAO derivatives utilizing 3-bromo-3-methylbutan-2-one (**18**) involves one extra-step, the overall yield (50-95%) of the final product was found to be far greater than that obtained from the chloronitroso method. This method provided the required product without any side products. It involved an easy workup procedure, and could be scaled-up to individual investigator's requirement without any isolation and purification problem. Some PnAO derivatives [such as PnAO-6-F (**3f**), PnAO-6,6-diF (**3g**), PnAO-6-NH_2 (**3h**), PnAO-6-$NHCOCH_3$ (**3i**), PnAO-6-$NHCOC_2H_5$ (**3j**), PnAO-6-CN (**3m**), PnAO-6-$COOCH_3$ (**3n**)] which could not be prepared *via* chloronitroso method were synthesized efficiently using bromoketone method. Thus this method offers a practical and versatile alternative method to synthesize a variety of PnAO derivatives which are otherwise difficult to prepare *via* the chloronitroso method.

CONCLUSIONS

Some 6-substituted propyleneamine oximes **3** (PnAOs) were prepared from their corresponding 2-substituted 1,3-diaminopropanes **1** by reacting them with either 3-chloro-3-methyl-2-nitrosobutane (**2**) in methanol or with 3-bromo-3-methylbutan-2-one (**18**) followed by oximation. The latter method, although it involves one extra step, proved to be much more efficient than the literature route.

EXPERIMENTAL

*Melting points were taken on Thomas Hoover Capillary melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a JEOL GSX/GX MULTIPLEXES (270 MHz) NMR Spectrometer and are reported in δ values relative to tetramethylsilane. High resolution mass spectra were taken on a VG Analytical-ZAB-2F and/or a Finnigan TSQ Spectrometer. Thin layer chromatography (TLC) was carried out on precoated Kieselgel 60 F_{254} on 0.25 mm glass plates and visualized by UV irradiation from a Mineralight shortwave UV lamp or in an iodine chamber. All solvents were reagent grade and used directly as purchased except for THF which was distilled over sodium with benzophenone ketyl as indicator. 1,3-Diaminopropane (**1a**), 1,3-diamino-2,2-dimethylpropane (**1d**), 1,3-diamino-2-hydroxypropane (**1k**) and diethyl 2-fluoromalonate (**7f**) were purchased from Aldrich. 2,2-Difluoromalonamide (**8g**) was obtained from Fluorochem, Inc. UK.*

*Diethyl i-butylmalonate (**7c**):* To a solution of sodium ethoxide [prepared from sodium (11.5 g, 0.5 mol) in absolute ethanol (500 mL)] was added diethyl malonate (80.0 g, 0.5 mole). After stirring for 1 h at room temperature a precipitate was formed. *i*-Butyl bromide was added neat to the above precipitate in ethanol at 0 °C dropwise over a period of 1 h with vigorous stirring. After the addition, the reaction mixture was stirred at room temperature for 2 h and then refluxed with stirring under nitrogen overnight. Ethanol was removed under reduced pressure and the residue was treated with 0.5N HCl carefully cooling in ice until acidic, extracted with ether and the organic layer was dried. Removal of solvent followed by distillation under reduced pressure furnished the product as a colorless liquid. Yield: 82.4 g (80%); bp 100-102 °C/10 mm; ^1H NMR ($CDCl_3$) δ 4.2(q, 4H), 3.4(dd, 1H), 1.8(t, 2H), 1.3(t, 6H) and 0.99(d, 6H). MS m/e 217 $(M+H)^+$.

*2-i-Butyl malonamide (**8c**):* Diethyl *i*-butylmalonate (**7c**) (40.0 g, 0.19 mol) was dissolved in absolute methanol (100 mL) and treated with sodium methoxide (0.02 g) and then saturated with ammonia gas at 0 °C. The reaction mixture was left overnight at room temperature and again was saturated with ammonia gas and then left in the freezer for 48 h. The precipitated solid was filtered off and the filtrate was concentrated to yield some more solid. The combined solid was recrystallized from methanol/toluene to provide the title compound **8c** as a colorless solid. Yield: 20.7 g (71%); mp191-192 °C; ^{1}H NMR (DMSO-d_6) δ 7.3(s, 2H), 7.1(s, 2H), 3.15(t, 1H), 1.6(t, 2H), 1.5(m, 1H) and 0.9(d, 6H). MS m/e 159 $(M+H)^+$.

*2-i-Butyl-1,3-diaminopropane (**1c**):* To a solution of borane in THF (1M, 480 mL), the solid diamide **8c** (10.00 g, 63.29 mmol) was added in portions with stirring under nitrogen over a period of 1 h and the mixture was refluxed for 24 h under nitrogen. The mixture was acidified carefully at 0 °C with 6N HCl and the solution was concentrated. The residue was repeatedly coevaporated with methanol (5 x 200 mL) and then neutralized with 10% NaOH. The aqueous solution was then saturated with sodium chloride and extracted with dichloromethane (5 x 100 mL). The combined organic layer was dried, concentrated and the resulting oil was distilled under reduced pressure to provide the diamine **1c** as a colorless oil. Yield: 6.46 g (78.5%); bp 123-125 °C/75 mm; ^{1}H NMR ($CDCl_3$) δ 2.8(m, 4H), 1.7(m, 1H), 1.5(m, 1H), 1.1(t, 2H) and 0.9(d, 6H). MS m/e 131 $(M+H)^+$. HRMS for $C_7H_{19}N_2$ $(M+H)^+$ calcd 131.1548, found 131.1498.

*2-Fluoromalonamide (**8f**):* A solution of diethyl fluoromalonate (**7f**) (1 g, 5.61 mmol) in dry methanol (10 mL) was saturated with ammonia at 0 °C and stirred at room temperature overnight. The colorless product which precipitated was then filtered and dried. Yield: 0.63 g (94%); mp. 199-201 °C; ^{1}H NMR (DMSO-d_6) δ 5.18 and 5.35(2s, 1H, C*H*F, J_{HFgem} = 48.83 Hz), 7.75(d, 4H, N*H*$_2$). MS m/e 121 $(M+H)^+$.

*1,3-Diamino-2-fluoropropane (**1f**) via 1,3-bis-N-t-butyloxycarbonyl-2-fluoropropane:* To a suspension of 2-fluoromalon-amide (**8f**) (1.3 g, 10.80 mmol) in dry THF (20 mL) was added diborane in THF (5.58 g, 64.93 mmol, 1M THF solution, 65.0 mL) from a syringe dropwise over a period of 30 min. The reaction mixture was then stirred at 45 °C under nitrogen atmosphere for 24 h. To the ice-cold reaction mixture, HCl (2N, 20 mL) was added and stirred for 30 min. The solvent was removed on a rotary evaporator and the semi-solid thus obtained was co-evaporated with dry methanol (5 x 20 mL) to remove the boric acid. The residue was dissolved in water (20 mL) and loaded onto a column of basic anion-exchange resin (Dowex 1-X8, 100-220 mesh). After elution with water, the fractions showing positive test with ninhydrin spray reagent were pooled and evaporated to provide a colorless solid. For further purification, the solid was dissolved in water (10 mL) and treated with di-*t*-butyl-dicarbonate (6.0 g, 27.50 mmol) in dioxane (40 mL) and sodium carbonate (3.0 g, 28.30 mmol) in water (10 mL), and stirred overnight at room temperature. The reaction mixture was then concentrated (10 mL), extracted with ethyl acetate (4 x 25 mL) and the combined extracts on evaporation under vacuum gave a colorless oil which was triturated with hexane to afford 1,3-bis-*N*-t-butyloxycarbonyl-2-fluoropropane as a colorless crystalline solid (2.5 g, 79%); mp. 88-90 °C; ^{1}H NMR ($CDCl_3$) δ 1.45(s, 18H, -C_4H_9), 3.34(m, 4H, NHC*H*$_2$), 4.49 and 4.66(2m, 1H, C*H*F, J_{HFgem} = 47.50 Hz), 5.02(bs, 2H, N*H*); Anal. calcd for $C_{13}H_{25}N_2O_4F$: C, 53.39; H, 8.62; N, 9.59; F, 6.50. Found: C, 53.49; H, 8.73; N, 9.64; F, 6.32. MS m/e 293 $(M+H)^+$. Then a solution of 1,3-bis-*N*-*t*-butyloxycarbonyl-2-fluoropropane in methanol (2 mL) was treated with methanol saturated with HCl (10 mL), stirred for 10 min and cooled to 0 °C. The colorless crystalline solid precipitated was filtered and dried to afford 1,3-diamino-2-fluoropropane (**1f**) as a hydrochloride salt; mp. 238-240 °C; ^{1}H NMR (D_2O) δ 3.21(m, 4H, NHC*H*$_2$), 4.95 and 5.14(2m, 1H, C*H*F, J_{HFgem} = 50.81 Hz); MS m/e 93 $(M+H)^+$. HRMS for $C_3H_{10}FN_2$ $(M+H)^+$ calcd 93.0828, found 93.0795.

*1,3-Diamino-2,2-difluoropropane (**1g**) via 1,3-bis-N-t-butyloxycarbonyl-2,2-difluoropropane:* The title compound **1g** was prepared from 2,2-difluoromalonamide (**8g**) (10 g, 90%, 65.22 mmol) and BH_3-THF (350 mmol, 1M, 350 mL) following the procedure employed for the synthesis of 1,3-diamino-2-fluoropropane (**1f**). Yield: 9.70 g (48%); TLC[silica gel, hexane-ethyl acetate (6:4)] R_f 0.54; mp. 125-127 °C; ^{1}H NMR ($CDCl_3$) δ 1.45[s, 18H, C(C*H*$_3$)$_3$], 3.52(m, 4H, NHC*H*$_2$) and 5.26 (bt, 2H, N*H*). Anal. calcd for $C_{13}H_{24}N_2O_4F_2$: C, 50.29; H, 7.80; N, 9.03; F, 12.25. Found: C, 50.48; H, 7.55; N, 9.21; F, 12.10. MS m/e 311 $(M+H)^+$. A solution of 1,3-bis-

N-t-butyloxycarbonyl-2,2-difluoropropane (4.5 g, 14.52 mmol) in CH_2Cl_2 (5 mL) was treated with CF_3COOH (5 mL) at 0 °C and stirred for 20 min. The removal of the volatiles under vacuum afforded a colorless crystalline solid of **1g** as a TFA salt in near quantitative yield (4.85 g); mp. 187-190 °C; ^1H NMR (D_2O) δ 3.62(t, J_{HF} = 16.20 Hz, 4H, $NHCH_2$). MS m/e 111 $(M+H)^+$. HRMS for $C_3H_9FN_2$ $(M+H)^+$ calcd 111.0733, found 111.0720.

2-Acetamido-1,3-bis-N-t-butyloxycarbonylpropane (10i): To a cooled (0 °C) solution of 2-amino-1,3-bis-*N-t*-butyloxy-carbonylpropane[17] (**9**) (6.22 g, 21.5 mmol) and triethylamine (5.56 g, 7.73 mL, 55 mmol) in methylene chloride (100 mL) was added acetic anhydride (5.1 g, 4.7 mL, 50 mmol) and the mixture was stirred at 0 °C for 0.5 h and at room temperature for 12 h. Methylene chloride was removed on a rotary evaporator and the residue was treated with water. The precipitated solid of **10i** was filtered and washed several times with water and air dried. Yield: 6.52 g (92%). It was recrystallized from water; mp. 142-143 °C. ^1H NMR ($CDCl_3$) δ 1.45(s, 18H, Boc), 1.92(s, 3H, CH_3), 3.1-3.4(m, 4H, CH_2), 3.78 (m, 1H, CH), 5.4(m, 2H, N*H*Boc) and 6.9 (m, 1H, N*H*CO). MS m/e 332 $(M+H)^+$.

2-Acetamido-1,3-diaminopropane (1i): 2-Acetamido-1,3-bis-*N-t*-butyloxycarbonylpropane (**10i**) (2.0 g) was dissolved in methanol (10 mL) saturated with hydrogen chloride gas and stirred at 0 °C for 1 h. The volatiles were removed under reduced pressure at room temperature and the resulting solid was dried under vacuum for 12 h to afford the title compound **1i** as a hydrochloride salt in near quantitative yield. ^1H NMR (D_2O) δ 2.41(s, 3H, CH_3), 3.21(m, 4H, NCH_2) and 4.02(m, 1H, CHNHCOCH$_3$). MS m/e 132 $(M+H)^+$. HRMS for $C_5H_{14}N_3O$ $(M+H)^+$ calcd 132.1137, found 132.1189.

2-Propionamido-1,3-bis-N-t-butyloxycarbonylpropane (10j): To a solution of 2-amino-1,3-bis-*N-t*-butyloxycarbonyl-propane[17] (**9**) (3.9 g, 13.49 mmol) in dry dichloromethane, triethylamine (3.04 g, 30 mmol) was added and the solution was cooled in an ice-bath. Propionic anhydride (3.5 g, 27 mmol) was added neat and stirred under nitrogen for 16 h. All the volatiles were removed under reduced pressure and the residue was taken up in dichloromethane (50 mL). The organic layer was washed with brine and then with water. Removal of dichloromethane yielded a colorless solid which was washed with ether. The solid was analytically pure and was taken up to the next step. Yield: 3.75 g (79%); mp 144-146 °C. ^1H NMR ($CDCl_3$) δ 1.2(t, 3H, CH_2CH_3), 1.45(s, 18H, CMe_3), 2.2(q, 2H, CH_2CH_3), 3.3(m, 4H, NCH_2), 3.75(m, 1H, CHNHCOEt), 5.4(m, 2H, N*H*COOtBu) and 7.0(bs, 1H, N*H*COEt). MS m/e 346 $[M+H]^+$.

2-Propionamido-1,3-diaminopropane (1j): 2-Propionamido-1,3-bis-*N-t*-butyloxycarbonyl-propane (**10j**) (3.75 g) was dissolved in methanol (10 mL) saturated with hydrogen chloride gas and stirred at 0 °C for 1 h. The volatiles were removed under reduced pressure at room temperature and the resulting solid was dried under vacuum at room temperature for 12 h. The dihydrochloride of **1h** was very hygroscopic and it tended to undergo discoloration on standing in air at room temperature. So it was taken on to the next step without any further purification. Yield: 2.3 g (100%). ^1H NMR (D_2O) δ 1.0(t, 3H, CH_2CH_3), 2.4(q, CH_2CH_3), 3.2(m, 4H, NCH_2) and 4.2(m, 1H, CHNHCOEt). MS m/e 146 $(M+H)^+$. HRMS for $C_6H_{16}N_3O$ $(M+H)^+$ calcd 146.1293, found 146.1290.

1,3-Bis-N-t-butyloxycarbonyl-2-cyanopropane (14): A solution of 1,3-bis-*N-t*-butyloxy-carbonyl-2-methanesulfonyl-propane[17] (**11**) (10.0 g, 27.17 mmol), NaCN (5.0 g, 102.04 mmol) and 18-crown-6 (0.5 g) in dry DMSO (20 mL) was heated at 75 °C with stirring for 18 h. After cooling to room temperature, the reaction mixture was poured into ice-cold water (100 mL) and the precipitated product was filtered off, washed well with water and dried. The solid was dissolved in ethyl acetate (10 mL), was added silica gel (5 g) and the solvent evaporated to give a powder. The silica gel impregnated with the compound was loaded onto a silica gel column (150 g) and eluted with ethyl acetate-hexane (15:85). The fractions were monitored by TLC (silica gel) and the first 15 fractions from the column were collected and the solvent was removed on a rotary evaporator to give a colorless crystalline solid. This compound was found to be the desired 1,3-bis-*N-t*-butyloxycarbonyl-2-cyanopropane (**14**). Yield: 0.65 g (8%); TLC [silica gel, ethyl acetate-hexane (3:7)] R_f 0.70; mp 112-113 °C; ^1H NMR ($CDCl_3$) δ 1.55(s,

18H, $COOC_4H_9$), 3.02(m, 1H, CHCN), 3.25 & 3.70(m, 4H, $NHCH_2$) and 5.38(bs, 2N, NH). Anal. calcd for $C_{14}H_{25}N_3O_4$: C, 56.15; H, 8.42; N, 14.04. Found: C, 56.38; H, 8.73; N, 14.43. MS m/e 300 $(M+H)^+$. On further elution with ethyl acetate-hexane (2:8) and evaporation of the fractions with R_f 0.60 on TLC, gave 3,4-bis-*N*-*t*-butyloxycarbonylbutyronitrile (**13**) in 92% yield (7.47 g) as a colorless crystalline solid; TLC [silica gel, ethyl acetate-hexane (3:7)] R_f 0.60; mp 125-127 °C; ^1H NMR ($CDCl_3$) δ 1.55(2s, 18H, $COOC_4H_9$), 2.75 & 3.42(2m, 4H, $NHCH_2$ & CH_2CN), 4.02(m, 1H, $CHCH_2CN$), and 4.97 & 5.58(2bs, 2N, NH). Anal. calcd for $C_{14}H_{25}N_3O_4$: C, 56.15; H, 8.42; N, 14.04. Found: C, 56.43; H, 8.89; N, 14.34. MS m/e 300 $(M+H)^+$.

*2-Cyano-1,3-diaminopropane (**1m**):* A solution of 1,3-bis-*N*-*t*-butyloxycarbonyl-2-cyano-propane (**14**) (0.20 g, 0.67 mmol) in methanol (2 mL) was treated with methanol saturated with HCl (2 mL) and stirred at 0 °C for 10 min. The solvent was removed on a rotary evaporator to provide a colorless solid of the title compound **1m** as the hydrochloride salt in near quantitative yield (0.12 g); mp 210-212 °C (decomp); ^1H NMR (D_2O) δ 3.38(m, 4H, CH_2NH_2) and 3.65(m, 1H, CHCN). MS m/e 100 $(M+H)^+$. HRMS for $C_4H_{10}N_3$ $(M+H)^+$ calcd 100.0875, found 100.0905.

*Methyl 3-azido-2-(azidomethyl)propionate (**16**):* To a solution of methyl 3-bromo-2-(bromomethyl)propionate (**15**) (5.00 g, 19.23 mmol) in dry DMF (20 mL) was added sodium azide (3.0 g, 46.25 mmol) and the reaction mixture was stirred at room temperature for 15 h under nitrogen atmosphere. After removal of the solvent under vacuum, the residue was taken up in ethyl acetate (150 mL) and washed with water (2 x 30 mL). The organic layer was dried (Na_2SO_4) and evaporated to afford the title compound **16** along with an olefinic compound, methyl 2-azidomethyl-acrylate (~20%) as a colorless paste (4.5 g). This crude material was taken to next step without purification. ^1H NMR ($CDCl_3$) δ 2.79(m, 1H, $CHCOOCH_3$), 3.68(m, 4H, CH_2N_3) and 3.78(s, 3H, CH_3). MS m/e 185 $(M+H)^+$.

*1,3-Bis-N-t-butyloxycarbonyl-2-carbomethoxypropane (**17**):* The crude azide **16** (4.5 g) was dissolved in methanol (30 mL) containing 5% HCl, purged with nitrogen, and to the solution was added 10%Pd-C, and hydrogenated on a Parr hydrogenator at 35 psi for 15 h. The solution was then filtered through a celite bed to remove the Pd-C and the solution was evaporated to furnish a colorless paste which was then dissolved in dioxane-water (20 mL, 7:3). To this ice-cooled solution was added Na_2CO_3 (2.0 g, 18.88 mmol) and di-*t*-butyl-dicarbonate (8.0 g, 36.70 mmol) in dioxane-water (15 mL, 7:3) and stirred at room temperature for 18 h. The solution was then concentrated on a rotary evaporator to ~15 mL and the pH of the solution was adjusted to 4.00 with $KHSO_4$ solution. The mixture was then extracted with ethyl acetate (3 x 50 mL), the organic layer was washed with water and dried. After removal of the solvent, the light yellow colored paste obtained was chromatographed on a silica gel column (100 g) and eluted with hexane-ethyl acetate (8:2). The fractions with the compound were pooled together and evaporated to yield the title compound **17** as a colorless paste. Yield: 2.50 g (31.3%); TLC[silica gel, hexane-ethyl acetate (7:3)] R_f 0.48; ^1H NMR ($CDCl_3$) δ 1.52(s, 18H, C_4H_9), 2.48(m, 1H, $CHCOOCH_3$), 3.30(m, 2H, $NHCH_2$), 3.67(m, 2H, $NHCH_2$), 3.80(s, 3H, CH_3) and 5.34(bs, 2H, NH). Anal. calcd for $C_{13}H_{28}N_2O_6$: C, 54.19; H, 8.49; N, 8.43. Found: C, 54.52; H, 8.21; N, 8.23. MS m/e 333 $(M+H)^+$.

*Methyl 3-amino-2-(aminomethyl)propionate (**1n**):* To a solution of 1,3-bis-*N*-*t*-butyloxy-carbonyl-2-carbomethoxypropane (**17**) (2.00 g, 6.02 mmol) in methanol (5 mL) was added methanol saturated with HCl (5 mL) and stirred at room temperature for 30 min. After removal of the solvent under vacuum, the paste obtained was crystallized from dry methanol-ether to provide the title compound **1n** as colorless crystalline solid. Yield: 1.05 g (81%); mp. 145-148 °C. ^1H NMR (D_2O) δ 3.24(m, 4H, CH_2NH_2), 3.48(m, 1H, $CHCOOCH_3$) and 3.65(s, 3H, $COOCH_3$). MS m/e 133 $(M+H)^+$. HRMS for $C_5H_{13}N_2O_2$ $(M+H)^+$ calcd 133.0977, found 133.0987.

*General procedure for the preparation of PnAOs (**3**) using 3-chloro-3-methyl-2-nitroso-butane (**2**):* For 1 mmol of the diamine 2.2 mmol of 3-chloro-3-methyl-2-nitrosobutane (**2**) was used. One gram of the diamine (**1**) was taken up in 1 mL of dry methanol and for every one gram of the chloro compound (**2**) 5 mL of dry methanol was used to dissolve the nitrosobutane. Heating

was avoided while dissolving the nitrosobutane. To an ice cooled solution of the diamine, 3-chloro-3-methyl-2-nitrosobutane (**2**) was added dropwise while the reaction temperature was kept around 0 °C. After the addition the reaction mixture was allowed to warm to room temperature over a period of 2 h and then refluxed with stirring for an additional 6 h. Methanol was removed under reduced pressure and the residue was treated with saturated sodium carbonate to neutralize the acid. The pH was then adjusted to 10 with 1N NaOH. The precipitated solid was filtered off and washed with ice cold water. The solid was then recrystallized from the appropriate solvent mixture to obtain a pure product. In the case of isobutyl-PnAO (**3c**) the oil obtained after neutralizing with NaOH was extracted with dichloromethane and chromatographed to obtain the product which was recrystallized to obtain analytically pure product.

*4,8-Diaza-3,3,9,9-tetramethyl-6-hydroxy-undeca-2,10-dione dioxime (**3k**, PnAO-6-OH):* Yield: 45%; mp. 143-144 °C (lit.[16] 143-145 °C) (hydrochloride salt); ^{1}H NMR (D_2O) δ 1.12[s, 12H, C(C*H*$_3$)$_2$], 1.78[s, 6H, C(=N)C*H*$_3$], 2.14 & 2.39(m, 4H, NHC*H*$_2$), 3.61(m, 1H, C*H*OH). ^{13}C NMR(DMSO-d_6) 9.0[C(*C*H$_3$)=N), 25.6 & 26.0[C(*C*H$_3$)$_2$], 47.7(NH*C*H$_2$), 56.6[(*C*(CH$_3$)$_2$], 70.2(*C*HOH) and 160.0(*C*=N). Anal. Calcd for $C_{13}H_{287}N_4O_3 \cdot 0.07H_2O$: C, 53.90; H, 9.79; N, 19.34. Found: C, 54.12; H, 9.93; N, 19.12. MS m/e 289 $(M+H)^+$.

*3-Methoxy-3-methylbutan-2-one oxime (**4**):* Mp 65-67 °C; ^{1}H NMR ($CDCl_3$) δ 1.35[s, 6H, C(C*H*$_3$)$_2$], 1.92[s, 3H, C(=N)C*H*$_3$], 3.12(s, 3H, OC*H*$_3$) and 9.68(s, 1H, NO*H*). MS m/e 132 $(M+H)^+$.

*3-(3-Amino-2-i-butylpropyl)-amino-3-methylbutan-2-one oxime (**6**):* Mp. 84-85 °C; ^{1}H NMR ($CDCl_3$) δ 0.84[d, 6H, CH(C*H*$_3$)$_2$], 1.05(m, 2H, CHC*H*$_2$CH), 1.13[s, 6H, C(C*H*$_3$)$_2$], 1.35[m, 1H, C*H*(CH$_3$)$_2$], 1,58(m, 1H, CH$_2$C*H*CH$_2$), 1.72[3, 3H, C(=N)C*H*$_3$], 2,17(m, 2H, NHC*H*$_2$), 2.50(d, 2H, NH$_2$C*H*$_2$) and 10.35(s, 1H, NO*H*). Anal. Calcd for $C_{12}H_{27}N_3O$: C, 62.82; H, 11.87; N, 18.83. Found: C, 63.10; H, 12.09; N, 18.63. MS m/e 230 $(M+H)^+$.

*General procedure for the preparation of 6-substituted 4,8-diaza-3,3,9,9-tetramethyl-undeca-2,10-dione (**19**):* To a suspension of anhydrous K_2CO_3 (10.0 mmol, 325 mesh, Aldrich) in dry DMF (5 mL) was added 2-substituted 1,3-diaminopropane (**1**) (4.0 mmol) and 3-bromo-3-methyl-butan-2-one (**18**) (10.0 mmol) and stirred at room temperature or at 45 °C under nitrogen atmosphere for 18 h. Then dichloromethane (20 mL) was added and stirred for 10 min and filtered. The filtrate was then evaporated under vacuum to provide a light yellow oil which was then treated with silica gel (3 g) and dichloromethane (5 mL). The solid obtained after evaporation of the solvent was loaded onto a silica gel (40 g) column and eluted with CH_2Cl_2-CH_3OH (95:5) solvent mixture. The fractions containing the product were pooled and evaporated to afford the corresponding diaza-tetramethylundeca-2,10-dione (**19**) as a colorless paste. To prepare hydrochloride salt of these diketone compounds, the paste thus obtained was dissolved in dry methanol (2 mL), treated with methanol saturated with HCl (5 mL) and the solvent was evaporated to semi-solid on a rotary evaporator. The solid was crystallized from methanol-ether mixture to afford the diaza-diketone (**19**) as hydrochloride salt.

*4,8-Diaza-3,3,9,9-tetramethyl-undeca-2,10-dione (**19a**):* Yield: 94%; TLC(silica gel, CH_2Cl_2-CH_3OH, 9:1) R_f 0.70; ^{1}H NMR ($CDCl_3$) δ 1.18[s, 12H, C(C*H*$_3$)$_2$], 1.55(m 2H, CH$_2$C*H*$_2$CH$_2$), 1.85(bs, 2H, N*H*), 2.18(s, 6H, COC*H*$_3$), 2.40(m, 4H, NHC*H*$_2$). Hydrochloride: mp. 255-256 °C; ^{1}H NMR (D_2O) δ 1.42[s, 12H, C(C*H*$_3$)$_2$], 1.95(m, 1H, CH$_2$C*H*CH$_2$), 2.19(s, 6H, COC*H*$_3$), 2.92(m, 4H, NHC*H*$_2$). ^{13}C NMR(DMSO-d_6) 22.2 [C(*C*H$_3$)$_2$], 25.5(CH$_2$*C*H$_2$CH$_2$), 25.8[C(=O)*C*H$_3$], 41.7(NH*C*H$_2$), 69.4[*C*(CH$_3$)$_2$] and 210.2(*C*O). MS m/e 243 $(M+H)^+$.

*4,8-Diaza-3,3,6,9,9-pentamethyl-undeca-2,10-dione (**19b**):* Yield: 86%; TLC(silica gel, CH_2Cl_2-CH_3OH, 9:1) R_f 0.68. Hydrochloride: mp. 182-184 °C; ^{1}H NMR (D_2O) δ 1.12(d, 3H, CHC*H*$_3$), 1.50[s, 12H, C(C*H*$_3$)$_2$], 1.58(m, 1H, C*H*CH$_3$), 2.28(s, 6H, COC*H*$_3$), 2.85 and 3.05(m,4H, NHC*H*$_2$). ^{13}C NMR(DMSO-d_6) 16.7[C(=O)*C*H3], 22.1 & 22.4[C(*C*H$_3$)$_2$], 25.9(CH*C*H$_3$), 31.5[*C*HCH$_3$], 48.2(NHCH$_2$), 69.9[C(CH$_3$)$_2$] and 210.2(CO). MS m/e 257 $(M+H)^+$.

4,8-Diaza-3,3,9,9-tetramethyl-6-i-butyl-undeca-2,10-dione (19c): Yield: 83%; TLC(silica gel, CH_2Cl_2-CH_3OH, 9:1) R_f 0.73; ^1H NMR ($CDCl_3$) δ 0.89[d, 6H, $CH(CH_3)_2$], 1.18(m, 2H, $CH_2CH(CH_3)_2$), 1.22[s, 12H, $COC(CH_3)_2$], 1.58[m, 2H, CH-*i*-Bu and $CH(CH_3)$], 1.92(m, 2H, NH), 2.18(s, 6H, $COCH_3$), 2.32(m,4H, $NHCH_2$); Hydrochloride: mp. 170-172 °C; ^1H NMR (D_2O) δ 0.85[d, 6H, $CH(CH_3)_2$], 1.32[m, 3H, $CH(CH_3)_2$ and $CH_2CH(CH_3)_2$], 1.61[s & m, 13H, CH and $COC(CH_3)_2$], 2.29(s, 6H, $COCH_3$), 3.02(m,4H, $NHCH_2$). MS m/e 299 $(M+H)^+$.

4,8-Diaza-3,3,6,6,9,9-hexamethyl-undeca-2,10-dione (19d): Yield: 88%; mp. 61-62 °C; ^1H NMR ($CDCl_3$) δ 0.89[s, 6H, $CH_2(CH_3)_2$], 1.22[s, 12H, $NHC(CH_3)_2$], 1.64(bs, 2H, NH), 2.18(s, 6H, $COCH_3$) and 2.20(s, 4H, $NHCH_2$). ^{13}C NMR(DMSO-d_6) 24.0[$C(CH_3)$=N), 25.0[$CH_2C(CH_3)_2$], 26.9[$C(CH_3)_2$], 35.0($NHCH_2$), 53.0(CH_2CCH_2), 63.1[$NC(CH_3)_2$], 210.6(C=O). MS m/e 271 $(M+H)^+$.

4,8-Diaza-3,3,9,9-tetramethyl-6,6-diethyl-undeca-2,10-dione (19e): Yield: 65%; mp. 47-48 °C; ^1H NMR ($CDCl_3$) δ 0.75(t, J = 7.0 Hz, 6H, CH_2CH_3), 1.22[s, 12H, $C(CH_3)_2$], 1.23(m, 4H, CH_2CH_3), 1.68(bs, 2H, NH), 2.17(s, 6H, $COCH_3$) and 2.18(s, 4H, $NHCH_2$). ^{13}C NMR(DMSO-d_6) 8.0(CH_2CH_3), 24.1[$C(CH_3)$=N), 24.8(CH_2CH_3), 26.9[$C(CH_3)_2$], 39.9(CH_2NH), 47.5[$C(C_2H_5)_2$], 62.7[$C(CH_3)_2$], 210.6(C=O). MS m/e 299 $(M+H)^+$.

4,8-Diaza-3,3,9,9-tetramethyl-6-fluoro-undeca-2,10-dione (19f): Yield: 55%; TLC(silica gel, CH_2Cl_2-CH_3OH, 9:1) R_f 0.65; ^1H NMR ($CDCl_3$) δ 1.20[s, 12H, $C(CH_3)_2$], 1.34(m, 2H, NH), 2.12(s, 6H, $COCH_3$), 2.62(m, 4H, $NHCH_2$), 4.45 and 4.67(2m, 1H, CHF, J_{HFgem} = 49.52 Hz). Hydrochloride salt: mp. 225-227 °C; ^1H NMR (D_2O) δ 1.55[s, 12H, $C(CH_3)_2$], 2.28(s, 6H, $COCH_3$), 3.32(m, 4H, $NHCH_2$), 5.14 and 5.35(2m, 1H, CHF, J_{HFgem} = 50.85 Hz). ^{13}C NMR(DMSO-d_6) 22.2[$C(CH_3)$=N), 22.6 & 23.0[$C(CH_3)_2$], 41.9($NHCH_2$), 45.5(d, J = 19.60 Hz, CHF), 66.3[$C(CH_3)_2$] and 211.0 (CO). MS m/e 261 $(M+H)^+$.

4,8-Diaza-3,3,9,9-teramethyl-6,6-difluoro-undeca-2,10-dione (19g): Yield: 23%; TLC[silica gel, CH_2Cl_2-methanol (95:5)] R_f 0.75; ^1H NMR ($CDCl_3$) δ 1.26[s, 12H, $C(CH_3)_3$], 1.89(bs, 2H, NH), 2.19[s, 6H, $C(=O)CH_3$] and 2.89(t, J_{HF} = 13.85 Hz, 4H, $NHCH_2$). ^{13}C NMR(DMSO-d_6) 23.6[$C(CH_3)$=N), 24.1[$C(CH_2)_2$], 42.9($NHCH_2$), 46.3(t, J = 25.40 Hz, CF_2), 67.1[$C(CH_3)_2$] and 209.9(C=O). MS m/e 279 $(M+H)^+$.

4,8-Diaza-3,3,9,9-tetramethyl-6-acetamido-undeca-2,10-dione (19l): Yield: 45%; ^1H NMR ($CDCl_3$) δ 1.25[s,12H, $C(CH_3)_2$], 1.83(bs, 2H, NH), 2.02(s, 3H, $NHCOCH_3$), 2.17(s, 6H, $COCH_3$), 2.55(m, 4H, CH_2), 3.90(m, 1H, CH), 6.43(bd, 1H, NH). MS m/e 300 $(M+H)^+$.

4,8-Diaza-3,3,9,9-tetramethyl-6-propionamido-undeca-2,10-dione (19j): Yield: 32.5 %; ^1H NMR ($CDCl_3$) δ 1.1(t, 3H, CH_2CH_3), 1.2(s, 12H, CMe_2), 2.1(s, 6H, COMe), 2.2(q, 2H, CH_2CH_3), 2.5(m, 4H, NCH_2), 3.9(m, 1H, CHNHCOEt) and 6.4(d, 1H, NHCOEt). MS m/e 314 $(M+H)^+$.

4,8-Diaza-3,3,9,9-tetramethyl-6-methoxy-undeca-2,10-dione (19l): Yield: 44%; ^1H NMR (D_2O) δ 1.24 [s, 12H, $C(CH_3)_2$], 2.22 (s, 6H, CH_3), 2.56 (m, 4H, CH_2), 3.4 (s, 3H, OCH_3 and m, 1H, CH).

4,8-Diaza-3,3,9,9-tetramethyl-6-cyano-undeca-2,10-dione (19m): Yield: 52%; TLC [silica gel, dichloromethane-methanol (9:1)] R_f 0.62; ^1H NMR ($CDCl_3$) δ 1.28[s, 12H, $C(CH_3)_2$], 1.81(bs, 2H, NH), 2.21(s, 6H, $COCH_3$) and 2.72(m & s, 5H, CH_2 & CHCN). ^{13}C NMR(DMSO-d_6) 21.4[$C(CH_3)$=O), 22.5[$C(CH_3)_2$], 28.5(CHCN), 45.5($NHCH_2$), 63.6[$C(CH_3)_2$], 120.4(CH_2CN) and 210.2(C=O). MS m/e 268 $(M+H)^+$.

*4,8-Diaza-3,3,9,9-tetramethyl-6-carboxymethoxy-undeca-2,10-dione (**19n**):* To a solution of 4,8-diaza-3,3,9,9-tetra-methyl-6-cyano-undeca-2,10-dione (**19m**) (0.2 g, 0.75 mmol) in dry methanol (0.2 mL) was added freshly prepared dry methanol (5 mL) saturated with dry HCl at 0 °C and stirred at room temperature for 24 h. After evaporation of the solvent under vacuum, the paste thus obtained was treated with methanol (2 mL) and triethylamine (0.5 g) and stirred for 10 min, and then solvent was removed. The yellowish brown paste was dissolved in dichloromethane (5 mL) and silica gel (0.5 g) was added. After evaporation of the solvent, the silica gel powder impregnated with compound was loaded onto a silica gel column (15 g) and eluted with dichloromethane:methanol (98:2). The fractions with compound were collected and evaporated on a rotary evaporator to a colorless paste of the title compound. Yield: 0.05 g (20%). TLC [silica gel, dichloromethane-methanol (9:1)] R_f 0.60; ^{1}H NMR ($CDCl_3$) δ 1.21[s, 12H, C(CH_3)$_2$], 1.79(bs, 2H, N*H*), 2.15(s, 6H, COCH_3), 2.62(m, 5H, CH_2 & C*H*COOCH_3) and 3.70(s, 3H, COOCH_3). ^{13}C NMR(DMSO-d_6) 24.8[C(*C*H$_3$)=N), 25.1[C(*C*H$_3$)$_2$], 40.5(*C*HCOOCH$_3$), 44.9(NH*C*H$_2$), 54.5(COO*C*H$_3$), 66.5[*C*(CH$_3$)$_2$], 168.3(*C*OOCH$_3$) and 211.0(*C*OCH$_3$). MS m/e 301 (M+H)$^+$.

*General procedure for the preparation of 6-substituted 4,8-diaza-3,3,9,9-tetramethyl-undeca-2,10-dione dioxime (**3**):* Solid hydroxylamine hydrochloride (15.0 mmol) was added to NaOH (14.0 mmol) in methanol (15 mL) and stirred at 0 °C for 2 h. NaCl formed was removed by filtration and to this free hydroxylamine in methanol, the diaza-diketone compound (**19**) (2.0 mmol) was added and stirred at room temperature for 18 h. The solvent was then removed under vacuum and the residue was treated with small amount of water (2 mL) and triturated. The colorless solid which formed was filtered off and recrystallized from ethyl acetate-methanol mixture or from an appropriate solvent mixture to afford the 6-substituted PnAO derivative (**3**).

*4,8-Diaza-3,3,9,9-tetramethyl-undeca-2,10-dione dioxime (**3a**, PnAO):* Yield: 94%; mp. 185-187 °C (hydrochloride salt); ^{1}H NMR (DMSO-d_6) δ 1.42[s, 12H, C(CH_3)$_2$], 1.95(s, 6H, COCH_3), 2.22(m, 1H, CH$_2$C*H*CH$_2$), 2.93(m, 4H, NHCH_2), 3.58(bs, 2H, N*H*), 9.70(s, 2H, NO*H*). ^{13}C NMR(DMSO-d6) 9.9[C(*C*H3)=N], 22.3[C(*C*H3)2], 23.3(CH2*C*H2CH2), 40.8(N*C*H2), 61.8[*C*(CH3)2] and 153.9(*C*=N). MS m/e 273 (M+H)$^+$.

*4,8-Diaza-3,3,6,9,9-pentamethyl-undeca-2,10-dione dioxime (**3b**, PnAO-6-Me):* Yield: 85%; mp. 135-137 °C. ^{1}H NMR (DMSO-d_6) δ 0.89(d, 3H, CHCH_3), 1.19[s, 12H, C(CH_3)$_2$], 1.51(m, 1H, C*H*CH$_3$), 1.78(s, 6H, COCH_3), 2.08 and 2.25(m, 4H, NHCH_2), 2.58(bs, 2H, N*H*), 10.41(s, 2H, NO*H*). ^{13}C NMR(DMSO-d_6) 9.1[C(*C*H$_3$)=N), 17.2(CH*C*H$_3$), 25.6 & 25.9[C(CH$_3$)$_2$], 34.5(*C*HCH$_3$), 48.0(NH*C*H$_2$), 56.6[*C*(CH$_3$)$_2$] and 160.8(*C*=N). MS m/e 287 (M+H)$^+$. Anal. Calcd for $C_{14}H_{30}N_4O_2$: C, 58.71; H, 10.56; N, 19.56. Found: C, 59.02; H, 10.81; N, 19.73.

*4,8-Diaza-3,3,9,9-tetramethyl-6-i-butyl-undeca-2,10-dione dioxime (**3c**, PnAO-6-i-Bu):* Yield: 82%; mp. 190-192 °C; ^{1}H NMR (DMSO-d_6) δ 0.89[d, 6H, CH(CH$_3$)$_2$], 1.15[m, 2H, CH_2CH(CH$_3$)$_2$], 1.41[2s, 12H, C(CH_3)$_2$], 1.65[m, 1H, C*H*(CH$_3$)$_2$], 1.95(s, 6H, COCH_3), 2.02(m,1H, NHCH$_2$C*H*), 2.65(m, 6H, N*HC*H$_2$), 10.91(s, 2H, NO*H*). ^{13}C NMR(DMSO-d_6) 9.8[C(*C*H$_3$)=N), 23.5[C(*C*H$_3$)$_2$], 25.5[*C*H$_2$CH(CH$_3$)$_2$], 26.6[C(*C*H$_3$)$_2$], 38.2 (CHCH$_2$*C*H(CH$_3$)$_2$], 40.1(CH$_2$*C*HCH$_2$), 46.8(NHCH$_2$), 57.2[*C*(CH$_3$)$_2$] and 160.2 (*C*=N). MS m/e 329 (M+H)$^+$. Anal. Calcd for $C_{17}H_{36}N_4O_2$·0.03H_2O: C, 62.07; H, 11.05; N, 17.03. Found: C, 62.29; H, 11.36; N, 16.81.

*4,8-Diaza-3,3,6,6,9,9-hexamethyl-undeca-2-10-dione dioxime (**3d**, PnAO-6,6-diMe):* Yield: 90%; mp. 154-155 °C; ^{1}H NMR (DMSO-d_6) δ 1.19[s, 6H, CH$_2$(CH_3)$_2$], 1.55[s, 12H, NHC(CH_3)$_2$], 2.02(bs, 2H, N*H*), 2.15[s, 6H, C(=N)CH_3], 2.42(s, 4H, NHCH_2) and 10.78(s, 2H, NO*H*). ^{13}C NMR(DMSO-d_6) 9.1[C(*C*H$_3$)=N), 24.4[*C*H$_2$C(CH$_3$)$_2$], 25.7[C(*C*H$_3$)$_2$], 33.9(NH*C*H$_2$), 51.4(CH$_2$*C*CH$_2$), 56.4[N*C*(CH$_3$)$_2$], 159.9(*C*=N). MS m/e 301 (M+H)$^+$. Anal. Calcd for $C_{15}H_{32}N_4O_2$: C, 59.97; H, 10.74; N, 18.65. Found: C, 60.81; H, 10.85; N, 18.99.

*4,8-Diaza-3,3,9,9-tetramethyl-6,6-diethylundeca-2,10-dione dioxime (**3e**, PnAO-6,6-diEt):* Yield: 90%); mp. 135-136 °C; ^{1}H NMR ($CDCl_3$) δ 0.72(t, J = 7.2 Hz, 6H, CH$_2$CH_3), 1.25[s, 12H,

$C(CH_3)_2$], 1.26(m, 4H, CH_2CH_3), 1.61(bs, 2H, NH), 1.89[s, 6H, C(=N)CH_3] and 2.08(s, 4H, $NHCH_2$) and 9.22(s, 2H, NOH). ^{13}C NMR(DMSO-d_6) 7.7(CH_2CH_3), 9.6[$C(CH_3)$=N), 25.0(CH_2CH_3), 26.2[$C(CH_3)_2$], 38.7(CH_2NH), 46.6[$C(C_2H_5)_2$], 56.8[$C(CH_3)_2$], 160.3(C=N). MS m/e 329 $(M+H)^+$. Anal. Calcd for $C_{17}H_{36}N_4O_2$: C, 62.16; H, 11.05; N, 17.06. Found: C, 62.49; H, 11.09; N, 17.20.

*4,8-Diaza-3,3,9,9-tetramethyl-6-fluoro-undeca-2,10-dione dioxime (**3f**, PnAO-6-F):* Yield: 80.70%; mp. 186-187 °C; ^1H NMR (D_2O) δ 1.48[s, 12H, $C(CH_3)_2$], 1.78(s, 6H, $COCH_3$), 3.30(m, 4H, $NHCH_2$), 5.07 and 5.20 (2m, 1H, CHF, J_{HFgem} = 51.47 Hz). ^{13}C NMR(DMSO-d_6) 9.2[$C(CH_3)$=N), 21.8 & 21.9[$C(CH_3)_2$], 40.7($NHCH_2$), 43.3(d, J = 19.60 Hz, CHF), 61.7[$C(CH_3)_2$] and 153.4(C=N). MS m/e 291 $(M+H)^+$. HRMS for $C_{13}H_{28}N_4O_2F$ $(M+H)^+$ calcd 291.2196, found 291.2195.

*4,8-Diaza-3,3,9,9-tetramethyl-6,6-difluoro-undeca-2,10-dione dioxime (PnAO-6,6-difluoro) (**3g**):* Yield: 82%; mp. 118-120 °C; ^1H NMR ($CDCl_3$) δ 1.24[s, 12H, $C(CH_3)_3$], 1.65(bs, 2H, NH), 1.87[s, 6H, C(=N)CH_3] and 2.82(t, J_{HF} = 14.51 Hz, 4H, $NHCH_2$). MS m/e 309 $(M+H)^+$. For further purification the compound was loaded onto a semi-preparative HPLC (C_{18}) column and eluted with water (0.1%TFA)-acetonitrile (0.1%TFA) (98:2). The fractions with compound of >99% purity after analyzing *via* analytical HPLC system were combined and freeze-dried to provide TFA salt of **3g** as a colorless glassy solid; mp.145-147 °C; ^1H NMR ($CDCl_3$) δ 1.35[s, 12H, $C(CH_3)_3$], 1.78[s, 6H, C(=N)CH_3] and 3.31(t, J_{HF} = 16.51 Hz, 4H, $NHCH_2$). ^{13}C NMR(DMSO-d_6) 9.5[$C(CH_3)$=N), 23.4[$C(CH_2)_2$], 40.1($NHCH_2$), 45.0(t, J = 25.40 Hz, CF_2), 60.8[$C(CH_3)_2$] and 155.6(C=N). HRMS for $C_{13}H_{27}F_2N_4O_2$ $(M+H)^+$ calcd 309.2102, found 309.2115.

*4,8-Diaza-3,3,9,9-tetramethyl-6-amino-undeca-2,10-dione dioxime (**3h**, PnAO-6-NH_2):* 4,8-Diaza-3,3,9,9-tetramethyl-6-acetamido-undeca-2,10-dione (**19l**) (600 mg, 2.0 mmol) was dissolved in 6N HCl (2.0 mL) and heated under reflux for 6 h. The solution was evaporated under vacuum and the semi-solid obtained was dissolved in water (10.0 mL). Hydroxylamine hydrochloride (700 mg) was added to this solution and pH of the solution was adjusted to 7.5 by the addition of 1N sodium hydroxide. A white solid was formed in about 30 min. The reaction mixture was stirred at room temperature overnight. The solid formed was filtered and recrystallized from water. Hydrochloride: mp. 170-172 °C. ^1H NMR (D_2O) δ 1.51[s,12H, $C(CH_3)_2$], 1.95(s, 6H, $COCH_3$), 3.25(m, 4H, CH_2), 4.45(m, 1H, CH). MS m/e 288 $(M+H)^+$. Anal. Calcd for $C_{13}H_{29}N_5O_2 \cdot 1.34\ H_2O$: C, 50.11; H, 10.25; N, 22.48. Found: C, 52.37; H, 9.97; N, 20.22.

*4,8-Diaza-3,3,9,9-tetramethyl-6-acetamido-undeca-2,10-dione dioxime (**3i**, PnAO-6-$NHCOCH_3$):* Yield: 95%; mp. 126-127 °C; ^1H NMR (D_2O) δ 1.1[s,12H, $C(CH_3)_2$], 1.70(s,6H,$COCH_3$), 1.88(s, 3H, $NHCOCH_3$), 2.42(m, 4H, CH_2), 3.75(m, 1H, CH). ^{13}C NMR(DMSO-d_6) 9.0[$C(CH_3)$=N), 22.8($COCH_3$), 25.7 & 25.8[$C(CH_3)_2$], 45.3($NHCH_2$), 50.1 (CHNHCOCH$_3$), 56.7[$C(CH_3)_2$], 160.0(C=N) and 169.9($NHCOCH_3$). MS m/e 330 $(M+H)^+$. Anal. Calcd for $C_{17}H_{36}N_4O_2 \cdot 0.07H_2O$: C, 54.47; H, 9.49; N, 21.17. Found: C, 54.76; H, 9.69; N, 20.88.

*4,8-Diaza-3,3,9,9-tetramethyl-6-propionamido-undeca-2,10-dione dioxime (**3j**, PnAO-6-$NHCOC_2H_5$):* To a solution of the 4,8-diaza-3,3,9,9-tetramethyl-6-propionamido-undeca-2,10-dione (**19j**) (1.1 g, 3.5 mmol) in dry dichloromethane (10 mL), neat O-(trimethylsilyl)hydroxylamine (1.1 g, 10.5 mmol) was added and stirred at room temperature for 16 h under nitrogen. All the volatiles were removed under vacuum and the residue was treated with 5 mL of methanol. The paste thus obtained was crystallized from dichloromethane/isopropyl ether to yield a colorless solid which was fractionally crystallized from water to yield analytically pure sample. Yield: 20%; mp. 146-148 °C. ^1H NMR (DMSO-d_6) δ 0.85 (t, 3H, CH_2CH_3), 1.1 [s, 12H, $C(CH_3)_2$], 1.6 (s, 6H, N=CCH_3), 1.8 (bs, 1H, NH), 1.9 (q, 2H, $COCH_2CH_3$), 2.2 (m, 4H, NCH_2), 3.2 (bs, 1H, NH), 3.5 (m, 1H, CHNHCOEt), 7.2 (d, 1H, NHCOEt) and 10.2 (s, 2H, N=OH). ^{13}C NMR(DMSO-d_6) 9.9[$C(CH_3)$=N), 10.1(CH_2CH_3), 26.7[$C(CH_3)_2$], 29.9($COCH_2CH_3$), 46.5($NHCH_2$), 50.1(CHNHCO), 57.6[$C(CH_3)_2$], 160.1(C=N)

and 173.2(*C*O). MS m/e 342 $[M-H]^-$. Anal. Calcd for $C_{16}H_{33}N_5O_3$: C, 55.95, H, 9.68 and N, 20.39. Found: C, 56.13, H, 9.91 and N, 20.36.

*4,8-Diaza-3,3,9,9-tetramethyl-6-methoxy-undeca-2,10-dione dioxime (**3l**, PnAO-6-OMe):* O-(Trimethylsilyl)hydroxyl-amine (1.50 mL) was added to 4,8-diaza-3,3,9,9-tetramethyl-6-methoxy-undeca-2,10-dione (**19l**) (0.62 g, 2.3 mmol) and the homogeneous solution was heated at 80 °C for 24 h. Excess O-(trimethylsilyl)hydroxylamine was removed under aspirator pressure and the residue was reacted with methanol (10.0 mL). Methanol was removed on a rotary evaporator and the oxime (**3l**) was obtained as a thick oil which solidified on standing. It was crystallized from aqueous methanol. Yield: 0.52 g (75%). mp. 79-80 °C. ^{1}H NMR (D_2O) δ 1.10(s, 12H, C(CH_3)$_2$), 1.75(s, 6H, CH_3), 2.32(m, 4H, CH_2), 3.22(s, 3H, OCH_3 and m, 1H, C*H*). ^{13}C NMR(DMSO-d_6) 10.3[C(CH_3)=N), 24.8 & 25.8[(C(CH_3)$_2$], 45.2($NHCH_2$), 57.5[*C*(CH_3)$_2$], 58.0(OCH_3), 80.7(*C*HOCH$_3$) and 164.2(*C*=N). MS m/e 303 $(M+H)^+$. Anal. calcd for $C_{14}H_{30}N_4O_3$: C, 55.60; H, 10.00; N, 18.53. Found: C, 55.98; H, 10.02; N, 18.49.

*4,8-Diaza-3,3,9,9-tetramethyl-6-cyano-undeca-2,10-dione dioxime (**3m**, PnAO-6-CN):* A solution of 4,8-diaza-3,3,9,9-tetramethyl-6-cyano-undeca-2,10-dione (**19m**) (0.2 g, 0.75 mmol) and O-(trimethylsilyl)hydroxylamine (0.16 g, 1.52 mmol) in dry dichloromethane (0.5 mL) was stirred at room temperature for 10 h under nitrogen atmosphere. After removal of the solvent on rotary evaporator and drying under vacuum, a colorless solid of 4,8-diaza-3,3,9,9-tetramethyl-6-cyano-undeca-2,10-dione dioxime (**3m**) was isolated. ^{1}H NMR ($CDCl_3$) δ 1.22[s, 12H, C(CH_3)$_2$], 1.68(bs, 2H, N*H*), 1.89(s, 6H, $COCH_3$) and 2.57 & 2.72(2m, 5H, $NHCH_2$ & C*H*CN). ^{13}C NMR(DMSO-d_6) 9.8[C(*C*H$_3$)=N), 22.4[C(*C*H$_3$)$_2$], 24.2(*C*HCN), 44.3($NHCH_2$), 57.5[*C*(CH_3)$_2$], 118.5(CH_2CN) and 160.2(*C*=N). MS m/e 298 $(M+H)^+$. Anal. calcd for $C_{18}H_{29}F_6N_5O_6 \cdot 0.19H_2O$: C, 40.88; H, 5.60; N, 13.24. Found: C, 41.06; H, 5.69; N, 13.06.

*4,8-Diaza-3,3,9,9-tetramethyl-6-carbomethoxy-undeca-2,10-dione dioxime (**3n**, PnAO-6-COOMe):* A solution of 4,8-diaza-3,3,9,9-tetramethyl-6-carbomethoxy-undeca-2,10-dione (**19n**) (0.05 g, 0.17 mmol) in dry CH_2Cl_2 (0.5 mL) was treated with O-(trimethylsilyl)hydroxylamine (0.04 g, 0.38 mmol) and stirred at room temperature for 15 h. After removal of the solvent under vacuum, 4,8-diaza-3,3,9,9-tetramethyl-6-carbomethoxy-undeca-2,10-dione dioxime (**3n**) was isolated as a semisolid and loaded on to a reversed phase C_{18} column (4.60 x 25 cm) and eluted with 4% acetonitrile/H_2O (0.1%TFA). The fractions with compound were (analyzed by analytical HPLC) collected and freeze-dried to afford a colorless solid (hygroscopic) of the title compound. HPLC: RT 14.88 min [Dynamax C_{18}, detection at 230 nm, 0-35% acetonitrile in water was used as linear gradient containing 0.1% TFA) ^{1}H NMR ($CDCl_3$) δ 1.15[s, 12H, C(CH_3)$_2$], 1.79(bs, 2H, N*H*), 1.82(s, 6H, $COCH_3$), 2.52(m, 5H, CH_2 & *C*H$COOCH_3$) and 3.60(s, 3H, $COOCH_3$). ^{13}C NMR(DMSO-d_6) 9.4[C(*C*H$_3$)=N), 24.4[C(*C*H$_3$)$_2$], 39.4(*C*HCOOCH$_3$), 42.4($NHCH_2$), 52.4($COOCH_3$), 60.4[*C*(CH_3)$_2$], 161.9(*C*=N) and 167.5(*C*OOCH$_3$). MS m/e 331 $(M+H)^+$. HRMS for $C_{15}H_{31}N_4O_4$ $(M+H)^+$ calcd 331.2345, found 331.2334. Anal. calcd for $C_{15}H_{30}N_4O_4 \cdot 2.20\ CF_3COOH\ 0.12\ H_2O$: C, 39.94; H, 5.60; N, 9.60. Found: C, 39.94; H, 6.04; N, 9.64.

REFERENCES

1. Sharp, F. F.; Smith, F. W.; Gemmell, H. G.; Lyall, D.; Evans, N. T. S.; Gvozdanovic, D.; Davidson, J.; Tyrrell, D. A.; Pickett, R. D.; Neirinckx, R. D. *J. Nucl. Med.* **1986**, *27*, 171.
2. Costa, D. C.; Ell, P. J.; Cullum, I. D.; Jarritt, P. H. *Nucl. Med. Commun.* **1986**, *7*, 645.
3. Vallabhajosula, S.; Zimmerman, R. E.; Picard, M.; Stritzke, P.; Mena, I.; Hellman, R. S.; Tikofsky, R. S.; Stablin, M. G.; Morgan, R. A.; Goldsmith, S. J. *J. Nucl. Med.* **1989**, *30*, 599.
4. Wackers, F. J. T.; Berman, D. S.; Maddahi, J.; Watson, D. D.; Beller, G. A.; Strauss, H. W.; Boucher, C. A.; Picard, M.; Holman, B. L.; Fridrich, R.; Inglese, E.; Delaloye, B.; Bischof-Delaloye, A.; Camin, L.; McKusick, K. *J. Nucl. Med.* **1989**, *30*, 301.

5. Seldin, D. W.; Johnson, L. L.; Blood, D. K.; Muschel, M. J.; Smith, K. F.; Wall, R. M.; Cannon, P. J. *J. Nucl. Med.* **1989**, *30*, 312.
6. Narra, R. K.; Eckelman, W. C.; Kuczynski, B. L.; Silva, D.; Feld, T.; Nunn, A. D. *J. Lab. Comp. Radiopharm.* **1989**, *26*, 418.
7. Narra, R. K.; Nunn, A. D.; Kuczynski, B. L.; Feld, T.; Wedeking, P.; Eckelman, W. C. J. Nucl. Med. **1989**, *30*, 1830.
8. Treher, E. N.; Francesconi, L.C.; Gougoutas, J. Z.; Malley, M. F.; Nunn. A. D. *Inorg. Chem.* **1989**, *28*, 3411.
9. Linder, K. E.; Malley, M. F.; Gougoutas, J. Z.; Unger, S. E.; Nunn, A. D. *Inorg. Chem.* **1990**, *29*, 2428.
10. Linder, K. E.; Chan, Y.-W.; Cyr, J. E.; Nowotnik, D. P.; Eckelman, W. C.; Nunn, A. D. *Bioconjugate Chem.* **1993**, *4*, 326.
11. Volkert, W. A.; Hoffman, T. J.; Seger, S. M.; Troutner, D. E.; Holmes, R. A. *Eur. J. Nucl. Med.* **1984**, *9*, 511.
12. Troutner, D. E.; Volkert, W. A. *U.S. Patent. 4,615,876*, **1986**.
13. Fair, C.K.; Troutner, D.E.; Schlemper, E.O.; Murmann, R.K.; Hoppe, M.L. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1984**, *C40*, 1544.
14. Pirro, J. P.; DiRocco, R. J.; Narra, R. K.; Nunn, A. D. *J. Nucl. Med.* accepted for publication.
15. DiRocco, R. J.; Kuczynski, B. L.; Bauer, A.; Linder, K. E.; Ramalingam, K.; Cyr, J. E.; Chan, Y.-W.; Raju, N.; Narra, R. K.; Nowotnik, D. P.; Nunn, A. D. *J. Cereb. Blood Flow Metab.* 1993, 13, 755.
16. Nowotnik, D. P.; Canning, L. R. *European Patent Application. 0179608A2*, **1984**.
17. Ramalingam, K.; Raju, N.; Nanjappan, P.; Nowotnik, D. P. Submitted to *J. Org. Chem.* for publication.
18. Dermer, H. *Ethyleneimine and Other Aziridines*; Academic Press, Inc.: New York; **1969**.
19. Jones, D. S.; Srinivasan, A.; Kasina, S.; Fritzberg, A. R.; Wilkening, D. W. *J. Org. Chem.* **1989**, *54*, 1940.
20. Pfleiderer, W.; Zondle, H. *Leibigs Ann. Chem.* **1966**, *99*, 3008.

(*Received in USA* 9 *February* 1994; *accepted* 1 *June* 1994)