

Binding Assay: Membranes from NIH 3T3 cells expressing CCR5 were incubated with  $^{125}\text{I}$ -RANTES in the presence or absence of compound for one hour at room temperature. The reaction cocktails (Buffer: 50 mM HEPES pH = 7.4, 5 mM  $\text{MgCl}_2$ , 1 mM  $\text{CaCl}_2$ , 0.2% BSA) were harvested through glass fiber filters, washed with 10 mM HEPES pH = 7.4, 150 mM NaCl at 4°C and counted to determine the amount of bound RANTES. The binding affinity constant,  $K_i$ , was determined from the experimental  $\text{IC}_{50}$  values using the Graph pad prism software analysis.

Entry assay: Adapted from Connor, R. I.; Chen, B. K.; Choe, S.; Landau, N. R. Vpr is required for efficient replication of human immunodeficiency virus type-1 in mononuclear phagocytes. *Virology*, **1995**, *206*, 935-944. Replication-defective HIV-1 virus containing the reporter gene for luciferase was used to infect U-87 cells expressing CD4 and CCR5. Infections were carried out in the presence or absence of compound and luciferase activity measured after 3 days. The data are reported as the concentration of compound required to reduce luciferase production by 50% compared with control cultures. Compounds were tested in triplicate at 8 concentrations ranging from 0.1-100 nM. The triplicates were averaged and dose-response curves generated using GraphPad PRISM software. Typically, the 95% confidence limit for experimental  $\text{IC}_{50}$  was within 1 log and the  $R^2$  variance values between 0.9-1.0 Intra-experimental  $\text{IC}_{50}$  values typically varied less than 0.5 log.

(b) Replication assay: Adapted from Trkola, A.; Ketas, T. J.; Nagashima, K. A.; Zhao, L.; Cilliers, T.; Morris, L.; Moore, J. P.; Maddon, P. J.; Olson, W. C Potent, broad spectrum inhibition of human immunodeficiency virus type 1 by the CCR5 monoclonal antibody PRO 140. *J. Virol.* **2001**, *75*, 579-588. Peripheral Blood Mononuclear cells (PBMC)

were pretreated with compound for an hour at 37 °C and subsequently infected in triplicate with a panel of CCR5-tropic HIV-1 isolates for 3 hours. Following infection, the cells were washed to remove residual viral inoculum and cultured in the presence of compound for 4-6 days. Culture supernatants were harvested and viral replication measured by determination of viral p24 antigen concentration by ELISA. Compounds were tested in triplicate at 11 concentrations ranging from 1000-0.001 nM. The triplicates were averaged and dose-response curves generated using GraphPad PRISM software. Typically, the 95% confidence limit for experimental IC<sub>50</sub> was within 1 log or less and the R<sup>2</sup> (variance) of the dose response curve between 0.85-1.0. Since primary PBMCs from different donors can vary widely in both CCR5 expression and viral infectivity, the IC<sub>50</sub> values for a single viral isolate could vary as much as 1.5 logs between experiments using different donor cells. Therefore compounds were typically compared head to head in the same experiment using the same donor and viral inoculum.

Elemental analysis were performed by the Physical-Analytical Chemistry Department, Schering-Plough Research Institute on either a Leeman CE 440 or a FISIONS EA 1108 elemental analyzer. Mass Spectra were recorded using either EXTREL 401 (CI), JEOL or MAT-90 (FAB), VG ZAB-SE (SIMS), or Finnigan MAT-CH-5 (EI) spectrometer. In general, NMR structure determinations of the compounds were made using chemical shifts, coupling constants, coupling information from COSY spectra, and 1D NOE experiments. The <sup>1</sup>H and <sup>13</sup>C NMR spectra were obtained on either a Varian VXR-200 (200 MHz, <sup>1</sup>H), Varian Gemini-300 (300 MHz, <sup>1</sup>H; 75.5 MHz, <sup>13</sup>C) or XL-400 (400 MHz, <sup>1</sup>H; 100 MHz, <sup>13</sup>C) and are reported as ppm down field from Me<sub>4</sub>Si with number of protons, multiplicities, and coupling constants in Hertz

indicated parenthetically. For  $^{13}\text{C}$  NMR, a Nalorac Quad nuclei probe was used.

Compound purity was checked by TLC and LC/MS analysis using an Applied Biosystems API-100 mass spectrometer and Shimadzu SCL-10A LC column: Altech platinum C18, 3 micron, 33mm x 7mm ID.

**Preparation of *N*-trifluoroacetylisonipecotylchloride (4).** Trifluoroacetic anhydride (TFAA) (300 mL, 2.1 mol) was added to isonipecotic acid (96 g, 0.74 mol) at 0°C. Afterwards, the reaction mixture was heated at reflux for 4h. Excess TFAA was removed and the reaction mixture was taken up in EtOAc, washed with water, and concentrated to give 160 g of the amide. This crude amide (50 g) was treated with 300 mL of thionyl chloride and the reaction mixture was heated at reflux overnight. At the end of this time, excess thionyl chloride was removed in vacuo to give 54 g (32%) of the acid chloride 4 which was used without further purification.

**Preparation of 4-[2-(4-bromophenyl)-1,3-dioxolan-2-yl]-1-trifluoroacetylpiperidine (6).** Aluminium chloride (11g, 0.082 mol) was added slowly to a solution of acid chloride 4 (10 g, 0.041 mol) in bromobenzene (40 mL, 0.38 mol) at ambient temperature after which the reaction mixture was heated at reflux for 4 h. It was then cooled and poured into a mixture of conc. HCl and ice and the product was extracted with EtOAc. The organic layer was separated and washed with water, half saturated sodium bicarbonate solution, and concentrated to give 16.2 g of the crude ketone 5.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.75 (d,  $J = 7.8$  Hz, 2 H), 7.60 (d,  $J = 7.7$  Hz, 2 H), 4.41(m, 1 H), 4.00 (m, 1 H), 3.50 (m, 1 H), 3.30 (m, 1 H), 3.07 (m, 1 H), 1.70-2.05 (m, 4 H).

The crude ketone 5 (16.21 g, 0.045 mol) from the above step was dissolved in toluene (200 mL) containing ethylene glycol (25 mL) and *p*-toluenesulfonic acid (0.5 g). The reaction mixture was heated at reflux with azeotropic removal of water until no further water was collected. The reaction mixture was concentrated to give 17.4 g of the crude ketal 6.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.75 (d,  $J = 7.8$  Hz, 2 H), 7.60 (d,  $J = 7.7$  Hz, 2 H),

4.51 (m, 1 H), 3.90-4.00 (m, 3 H), 3.70 (m, 2 H), 2.90 (m, 1 H), 2.55 (m, 1 H), 2.01 (m, 1 H), 1.30-1.80 (m, 4 H).

**Preparation of 4-[2-(4-bromophenyl)-1,3-dioxolan-2-yl]-piperidine (7).** The crude ketal **6** (17.4 g, 0.042 mol) was dissolved in methanol (100 mL) and to this is added 25 mL of water and 12 g of potassium carbonate. The reaction mixture was stirred at ambient temperature overnight. The reaction mixture was diluted with water and extracted with EtOAc. The organic layer was separated and washed with water and brine and concentrated to give 12.55 g (95%) of amine **7**.  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  7.45 (d,  $J = 7.8$  Hz, 2 H), 7.25 (d,  $J = 7.7$  Hz, 2 H), 3.98 (m, 2 H), 3.70 (m, 2 H), 3.09 (m, 2 H), 2.40-2.55 (m, 3 H), 1.85 (m, 1 H), 1.70 (m, 1 H), 1.20-1.35 (m, 2 H).

**Preparation of 4-[2-(4-bromophenyl)-1,3-dioxolan-2-yl]-1'-(*t*-butoxycarbonyl)-4'-cyano-1,4'-bipiperidine (8).** To a stirred solution of amine **7** (7.2 g, 23 mmol) and *N*-*t*-butoxycarbonyl piperidinone (4.8 g, 24 mmol) in 1,2-dichloroethane (20 mL) was added titanium isopropoxide (6.7 mL, 32.3 mmol) and stirred for 12 h at rt. The reaction mixture was concentrated and a 1.0 M solution of diethylaluminium cyanide (35 mL) was added at rt. The reaction mixture was stirred for 3 h and then diluted with EtOAc, and quenched with water (5 mL) and stirred a further 2 h. The mixture was then filtered through Celite and the resulting filtrate was then concentrated and chromatographed with 30% EtOAc/hexanes to afford 7.3 g (63%) of compound **8**.  $R_f$  0.25 (20% EtOAc / hexanes);  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  7.45 (d,  $J = 7.8$  Hz, 2 H), 7.25 (d,  $J = 7.7$  Hz, 2 H), 3.90-4.00 (m, 4 H), 3.70 (m, 2 H), 3.00-3.25 (m, 4 H), 2.00-2.15 (m, 3 H), 1.60-1.85 (m, 4 H), 1.45 (s, 9 H), 1.30-1.45 (m, 4 H).

**Preparation of 4-[2-(4-bromophenyl)-1,3-dioxolan-2-yl]-1'-(*t*-butoxycarbonyl)-4'-methyl-1,4'-bipiperidine (9).** To a stirred solution of cyanide **8** (7.3 g, 14.03 mmol) in THF (100 mL) was added 3.0M solution MeMgBr in ether (14.0 mL, 42 mmol) at rt and the reaction mixture was stirred for 2 h. The reaction mixture was then quenched with saturated aqueous ammonium chloride and extracted twice with methylene chloride. The

extracts were concentrated to afford 7.0 g (98%) of desired methylated compound **9**.  $R_f$  0.36 (35% EtOAc / hexanes);  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  7.45 (d,  $J = 7.8$  Hz, 2 H), 7.25 (d,  $J = 7.7$  Hz, 2 H), 3.95 (m, 2 H), 3.73 (m, 2 H), 3.25 (m, 2 H), 2.85 (m, 2 H), 1.75-2.00 (m, 3 H), 1.45 (s, 9 H), 1.20-1.75 (m, 10 H), 0.95 (m, 3 H).

**Preparation of 4-(4-bromobenzoyl)-1'-(t-butoxycarbonyl)-4'-methyl-1,4'-**

**bipiperidine (10)**. The crude ketal **9** from the above reaction was dissolved in EtOAc (100 mL) and added 6 N HCl (40 mL) and stirred at rt for 24 h. The reaction mixture was then neutralized with 20% NaOH and extracted with EtOAc. The organic layer was dried and concentrated to yield 5.0 g (98%) of crude amine.

To a stirred solution of the above amine (5.0 g, 13.6 mmol) in ether (200 mL) was added 10% NaOH (50 mL) and  $\text{BOC}_2\text{O}$  and the mixture was stirred at rt overnight. The layers were separated and the organic layer was washed with brine, dried, concentrated and chromatographed with 20% EtOAc/hexanes to yield 5.1 g (79%) of BOC protected amine **10**.  $R_f$  0.50 (35% EtOAc / hexanes);  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  7.80 (d,  $J = 7.8$  Hz, 2 H), 7.60 (d,  $J = 7.7$  Hz, 2 H), 3.50 (m, 2 H), 3.10-3.25 (m, 3 H), 2.95 (m, 2 H), 2.20 (m, 2 H), 1.75-1.90 (m, 6 H), 1.45 (s, 9 H), 1.20-1.40 (m, 2 H), 0.90 (m, 3 H).

**Preparation 2,6-dimethylnicotinicacid-N-oxide:** To a stirred solution of 2,6-

dimethylnicotinic acid (2.00g, 13.24 mmol) in DMF-MeOH (100-40 mL) was added a 48% solution of HF (0.99 mL, 23.84 mmol) followed by *m*-CPBA (6.07 g, 26.49 mmol). The reaction mixture was stirred at rt for 24 h before being poured into cold water (300 mL) with stirring. The reaction mixture was then filtered and the filtrate was then concentrated in vacuo. The resulting precipitate was then washed with chloroform and dried to afford 1.36 g (61%) of the title *N*-oxide as a white solid.  $^1\text{H NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$  8.2 (d,  $J = 6.9$  Hz, 2 H), 7.15 (d,  $J = 2$  H), 2.30 (s, 3 H), 2.00 (s, 3 H).

**General procedure for preparation of oximes 17, 18a-1 and 19a:** To a stirred solution of ketone **10** (1.5 g, 3.22 mmol) in MeOH (50 mL) was added sodium acetate (5.0 g, 47 mmol) and O-methyl hydroxylamine hydrochloride or O-ethyl hydroxylamine hydrochloride and the reaction was stirred at rt for 24 h. The resulting mixture was then poured into aqueous NaOH (10%) and extracted twice with methylene chloride. The combined extracts were then dried, concentrated and chromatographed to yield 1.5 g (94%) of oxime as a mixture of E and Z isomers.

To a stirred solution of oxime (1.5 g, 3.0 mmol) in methylene chloride (10 mL) was added trifluoroacetic acid (3 mL) and stirred at rt for 2 h. The reaction mixture was concentrated and poured into 10% NaOH and extracted with twice methylene chloride. The combined extracts were dried and concentrated to afford 1.2 g (100%) of amine.

To stirred solution of amine (1.3 g, 3.2 mmol) in methylene chloride (50 mL) was added 2,6-dimethyl benzoic acid (0.74 g, 4.96 mmol), EDCI (0.94 g, 4.94 mmol), DIPEA (0.84 g, 6.58 mmol) and HOBT (0.66 g, 4.94 mmol) and the mixture was stirred for 12 h at rt. The reaction mixture was quenched with saturated NaHCO<sub>3</sub> and extracted with twice methylene chloride. The combined extracts were dried and concentrated to yield 1.6 g of oxime as a mixture of E and Z isomers. The isomers were separated by chromatography eluting with methylene chloride:ether (4:1) to afford 0.77 g of E isomer **17** and 0.49 g of Z isomer **18a** as a colorless solid. Purity was checked by LC/MS analysis.

**4-[(E)-(4-Bromophenyl)(methoxyimino)methyl]-1'-(2,6-dimethylbenzoyl)-4'-methyl-1,4'-bipiperidine (17):** <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.50 (d, *J* = 7.70 Hz, 2 H), 7.23 (m, 2 H), 7.10 (m, 1 H), 6.90 (d, *J* = 7.65 Hz, 2 H), 4.03 (m, 1 H), 3.90 (s, 3 H), 3.55 (m, 1 H), 3.20 (m, 3 H), 3.00 (m, 3 H), 2.82 (m, 1 H), 2.24 (s, 3 H), 2.23 (s, 3 H), 2.15 (m, 3 H), 1.80 - 1.20 (m, 5 H), 0.92 (s, 3 H); mass spectrum FAB+ observed = 526.2070; estimated = 526.2069

**4-[(Z)-(4-Bromophenyl)(methoxyimino)methyl]-1'-(2,6-dimethylbenzoyl)-4'-methyl-1,4'-bipiperidine (18a):**  $^1\text{H NMR}$   $\text{CDCl}_3$   $\delta$  7.50 (d,  $J = 7.70$  Hz, 2 H), 7.15 -6.95 (m, 5 H), 4.15 (m, 1 H), 3.80 (s, 3 H), 3.45 (m, 1 H), 3.25 (m, 1 H), 3.00 (m, 2 H), 2.24 (s, 3 H), 2.25 (s, 3 H), 2.10 (m, 2 H), 1.80- 1.50 (m, 7 H), 0.92 (s, 3 H);  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  169.3, 159.9, 136.7, 133.7, 133.5, 132.9, 131.4, 129.2, 128.0, 127.4, 122.5, 61.7, 53.9, 44.8, 42.6, 41.7, 36.5, 36.4, 35.6, 32.5, 30.6, 30.5, 19.1, 17.8; mass spectrum FAB+ observed = 526.2072; estimated = 526.2069. Anal. Calc. For  $\text{C}_{28}\text{H}_{36}\text{BrN}_3\text{O}_2$ : C, 63.87; H, 6.89; N, 7.98. Found: C, 63.62; H, 6.91; N, 8.03.

**4-[(Z)-(4-Bromophenyl)(ethoxyimino)methyl]-1'-(2,6-dimethylbenzoyl)-4'-methyl-1,4'-bipiperidine (19a):** The title compound was prepared from *N*-ethyl hydroxylamine hydrochloride by following the general procedure described above to afford the ethoxime, which was then converted to compound **19a** in subsequent steps by removal of BOC and treatment of the resulting amine with 2,6-dimethyl benzoic acid.  $^1\text{H NMR}$   $\text{CDCl}_3$   $\delta$  7.50 (d,  $J = 7.70$  Hz, 2 H), 7.15 -6.95 (m, 5 H), 4.15 (m, 1 H), 4.05 (q,  $J = 7.1$  Hz, 2 H), 3.20-3.55 (m, 2 H), 2.90-3.05 (m, 2 H), 2.80 (m, 1 H), 2.35 (m, 1 H), 2.24 (m, 3 H), 2.25 (s, 3 H), 2.10 (m, 2 H), 1.40- 2.00 (m, 7 H), 1.25 (m, 1 H), 1.28 (t,  $J = 7.1$  Hz, 3 H), 0.92 (s, 3 H); mass spectrum FAB+ observed = 540.5210; estimated = 540.5269.

**1'-(2-Amino-6-chlorobenzoyl)-4-[(Z)-(4-bromophenyl) (methoxyimino) methyl]-4'-methyl-1,4'-bipiperidine (18b):** The title compound was prepared from *N*-methyl hydroxylamine hydrochloride by following the general procedure described above to afford methoxime, which was then converted to compound **18b** as a colorless solid in subsequent steps by removal of the BOC and treatment of the resulting amine with 2-amino-6-chlorobenzoic acid. Compound **18b** exists as a mixture of non-separable rotational isomers.  $^1\text{H NMR}$   $\text{CDCl}_3$   $\delta$  7.55 (m, 2 H), 7.30 (m, 2 H), 7.15 (t,  $J = 7.70$  Hz, 1 H), 6.75 (d,  $J = 7.8$  Hz, 1 H), 6.60 (d,  $J = 7.8$  Hz, 1 H), 4.25 (m, 2 H), 3.80 (s, 3 H), 3.40 (m, 2 H), 2.80-3.20 (m, 3 H), 2.40 (m, 1 H), 1.40-2.20 (m, 13 H), 0.90 (s, 3 H); mass spectrum FAB+ observed = 549.2133; estimated = 526.2130.

**1'-(2-Amino-6-methylbenzoyl)-4-[(z)-(4-bromophenyl) (methoxyimino) methyl]-4'-methyl-1,4'-bipiperidine (18c):** The title compound was prepared from *N*-methyl hydroxylamine hydrochloride by following the general procedure described above to afford methoxime, which was then converted to compound **18c** in subsequent steps by removal of BOC and treatment of the resulting amine with 2-amino-6-methyl benzoic acid. **18c** exists as a mixture of non-separable rotational isomers. <sup>1</sup>H NMR CDCl<sub>3</sub> δ 7.55 (d, *J* = 7.75 Hz, 2 H), 7.25 (m, 1 H), 7.15 (m, 1 H), 6.50-6.60 (m, 2 H), 4.25 (m, 2 H), 3.80 (s, 3 H), 3.40 (m, 2 H), 2.80-3.20 (m, 3 H), 2.40 (m, 1 H), 2.20 (m, 3 H), 1.40-2.20 (m, 13 H), 0.90 (s, 3 H); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) δ 168.6, 168.4, 159.8, 143.0, 142.7, 134.7, 134.6, 132.9, 132.8, 131.3, 129.1, 129.0, 123.1, 122.9, 122.4, 120.0, 113.4, 113.4, 61.7, 53.9, 44.7, 42.6, 42.1, 42.0, 36.9, 36.8, 35.7, 36.5, 35.7, 35.6, 30.5, 35.7, 35.6, 30.6, 30.5, 19.2, 19.1, 17.9, 16.6; mass spectrum FAB+ observed = 529.1017; estimated = 529.1015.

**1'-(2-Hydroxy-6-methylbenzoyl)-4-[(z)-(4-bromophenyl) (methoxyimino) methyl]-4'-methyl-1,4'-bipiperidine (18d):** The title compound was prepared from *N*-methyl hydroxylamine hydrochloride by following the general procedure described above to afford methoxime, which was then converted to compound **18d** in subsequent steps by removal of the BOC and treatment of the resulting amine with 2-hydroxy -6-methyl benzoic acid. **18d** exists as a mixture of non-separable rotational isomers. <sup>1</sup>H NMR CDCl<sub>3</sub> δ 7.55 (m, 2 H), 7.15 (m, 1 H), 6.90 (m, 2 H), 6.35 (m, 1 H), 6.20 (m, 1 H), 4.40 (m, 2 H), 4.00-4.20 (m, 1 H), 3.80 (s, 3 H), 3.40 (m, 2 H), 2.80-3.20 (m, 3 H), 2.40 (m, 1 H), 2.10 (s, 3 H), 1.20-1.90 (m, 13 H), 0.90 (s, 3 H); Anal. Calc. for C<sub>27</sub>H<sub>35</sub>BrClN<sub>3</sub>O<sub>3</sub>•H<sub>2</sub>O (hydrochloride salt): C, 55.72; H, 6.01; N, 7.22. Found: C, 55.91; H, 6.36; N, 6.86.

**4-[(Z)-(4-Bromophenyl)(methoxyimino)methyl]-1'-[(2,6-dimethyl-3-pyridinyl)carbonyl]-4'-methyl-1,4'-bipiperidine (18e):** The title compound was prepared from *N*-methyl hydroxylamine hydrochloride by following the general



procedure described above to afford methoxime, which was then converted to compound **18e** in subsequent steps by removal of the BOC and treatment of the resulting amine with 2,6-dimethyl nicotinic acid.  $^1\text{H NMR CDCl}_3$   $\delta$  8.35 (d,  $J = 7.8$  Hz, 1H), 7.25 (AB system, 4H), 6.98 (d,  $J = 7.8$  Hz, 1 H), 4.22 (m, 1 H), 3.82 (s, 3 H), 3.45 (m, 1 H), 3.25 (m, 1 H), 2.80-3.00 (m, 2 H), 2.45 (d, 3 H), 2.24 (d, 3 H), 2.10 (m, 2 H), 1.80- 1.20 (m, 7 H), 0.92 (s, 3 H); mass spectrum FAB+ observed = 527.2787; estimated = 527.2022.

**4-[(Z)-(4-Bromophenyl)(methoxyimino)methyl]-1'-[(2,6-dimethyl-3-pyridinyl)carbonyl]-4'-methyl-1,4'-bipiperidine N-oxide (18f):** The title compound was prepared from *N*-methyl hydroxylamine hydrochloride by following the general procedure described above to afford methoxime, which was then converted to compound **18f** in subsequent steps by removal of the BOC and treatment of the resulting amine with 2,6-dimethyl nicotinic acid-N-oxide.  $^1\text{H NMR CDCl}_3$   $\delta$  8.15 (d,  $J = 7.8$  Hz, 1H), 7.25 (AB system, 4H), 6.98 (d,  $J = 7.8$  Hz, 1 H), 4.22 (m, 1 H), 3.80 (s, 3 H), 3.45 (m, 1 H), 3.25 (m, 1 H), 2.80-3.00 (m, 2 H), 2.50 (m, 3 H), 2.24 (s, 3 H), 2.10 (m, 2 H), 1.80- 1.20 (m, 7 H), 0.92 (s, 3 H); mass spectrum FAB+ observed = 545.1949; estimated = 545.1920.

**4-[(Z)-(4-Bromophenyl)(ethoxyimino)methyl]-1'-[(2,6-dimethyl-3-pyridinyl)carbonyl]-4'-methyl-1,4'-bipiperidine (19b):** The title compound was prepared from *N*-ethyl hydroxylamine hydrochloride by following the general procedure described above to afford methoxime, which was then converted to compound **19b** in the subsequent steps by removal of the BOC and treatment of the resulting amine with 2,6-dimethyl nicotinic acid.  $^1\text{H NMR CDCl}_3$   $\delta$  8.35 (d,  $J = 7.8$  Hz, 1H), 7.25 (AB system, 4H), 6.98 (d,  $J = 7.8$  Hz, 1 H), 4.22 (m, 1 H), 4.05 (q,  $J = 7.1$  Hz, 2 H), 3.45 (m, 1 H), 3.30 (m, 1 H), 2.80-3.00 (m, 2 H), 2.45 (d, 3 H), 2.24 (d, 3 H), 2.10 (m, 2 H), 1.20- 1.80 (m, 7 H), 1.20 (t,  $J = 7.1$  Hz, 3 H), 0.92 (s, 3 H); mass spectrum FAB+ observed = 541.2188; estimated = 541.2178.

**4-[(Z)-(4-Bromophenyl)(ethoxyimino)methyl]-1'-[(2,6-dimethyl-3-pyridinyl)carbonyl]-4'-methyl-1,4'-bipiperidine N-oxide (1):** The title compound was prepared from *N*-ethyl hydroxylamine hydrochloride by following the general procedure described above to afford methoxime, which was then converted to compound **1** in the subsequent steps by removal of the BOC and treatment of the resulting amine with 2,6-dimethyl nicotinic acid-*N*-oxide. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.15 (d, *J* = 7.8 Hz, 1H), 7.25 (AB system, 4H), 7.00 (d, *J* = 7.8 Hz, 1 H), 4.20 (m, 1 H), 4.02 (q, *J* = 7.1 Hz, 2 H), 3.25-3.45 (m, 2 H), 2.80-3.00 (m, 2 H), 2.50 (d, 3 H), 2.24 (s, 3 H), 2.10 (m, 2 H), 1.20-1.85 (m, 7 H), 1.20 (t, *J* = 7.1 Hz, 3 H), 0.92 (s, 3 H); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) δ 165.1, 164.7, 159.1, 145.0, 138.3, 133.0, 131.3, 129.3, 124.8, 122.3, 69.4, 53.8, 44.8, 44.7, 42.4, 42.0, 37.0, 36.9, 36.4, 36.3, 35.5, 32.5, 30.6, 18.4, 18.0, 17.8, 15.2, 15.2, 14.6; mass spectrum FAB+ observed = 557.2130; estimated = 557.2127. Anal. Calc. for C<sub>32</sub>H<sub>43</sub>BrN<sub>4</sub>O<sub>9</sub> (tartarate salt): C, 54.32; H, 6.13; N, 7.92. Found: C, 54.37; H, 6.43; N, 7.58.