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OPPI BRIEF

Synthesis of a Nitroxide Spin-labeled Varenicline (Chantix) Derivative

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The progress made during the past three decades on the synthesis and application of stable nitroxide free radicals has facilitated understanding of the structure and function of macromolecular systems.[1] Spin-labeled drugs and biomolecules have been constructed for target-specific applications such as the study of biological systems,[2] utilization in therapy, and studying drug formulation problems.[3] Our laboratory has a long-standing interest in the synthesis and application of carbo- and heterocycle-fused pyrroline nitroxides;[4] we recently reported the efficient synthesis of pyrroline nitroxide-fused pyrazine and quinoxaline derivatives.[5] Pyrazine derivatives exhibit numerous advantageous pharmaceutical effects including antibacterial, antifungal, antiviral, anticancer, antiproliferative, antidiabetic, diuretic, hypnotic, and analgesic properties.[6] A notable pyrazine derivative is the nicotinic receptor agonist varenicline **1** (Chantix, Scheme 1). Clinically, it is effective as a smoking cessation drug, which attenuates the effect of nicotine by selectively binding to neuronal $\alpha4\beta2$ nicotine acetylcholine receptors.[7]

Building on our previous work, we now report on an analog of varenicline, **7** (Scheme 2), which incorporates a rigid 1-oxyl-2,2,5,5-tetramethylpyrrolidine nitroxide spin-label fused to the pyrazine ring. Commercially available dinitro compound **2** was hydrogenated using a H-Cube® Mini Plus flow reactor equipped with a 20% $Pd(OH)_2$/C cartridge at a pressure of 6×10^5 Pa H_2 in a 1:1 (v/v) mixture of THF/MeOH to furnish an intermediate diamine, which was condensed immediately with 1,2-diketone[5] **3** to yield pyrazine **4**. The *N*-OMe function was deprotected with 2.0 equivalents of 3-chloroperbenzoic acid[8] (*m*-CPBA) in CH_2Cl_2 (DCM) to yield a mixture of nitroxide **5** and the pyrazine-*N*-oxide nitroxide **6** side product. Compound **6** was obtained as a non-separable mixture of diastereomers. After chromatographic separation of **5** from **6**, the trifluoroacetyl group was removed from nitroxide **5** by treatment with aqueous Na_2CO_3/MeOH[9] to furnish the spin-labeled varenicline analog **7**. In conclusion, a facile method was developed for synthesis of a spin labeled derivative of varenicline without affecting the key functional groups of the original molecule, providing an access for a possible new theranostic[10] agent.

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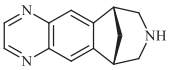
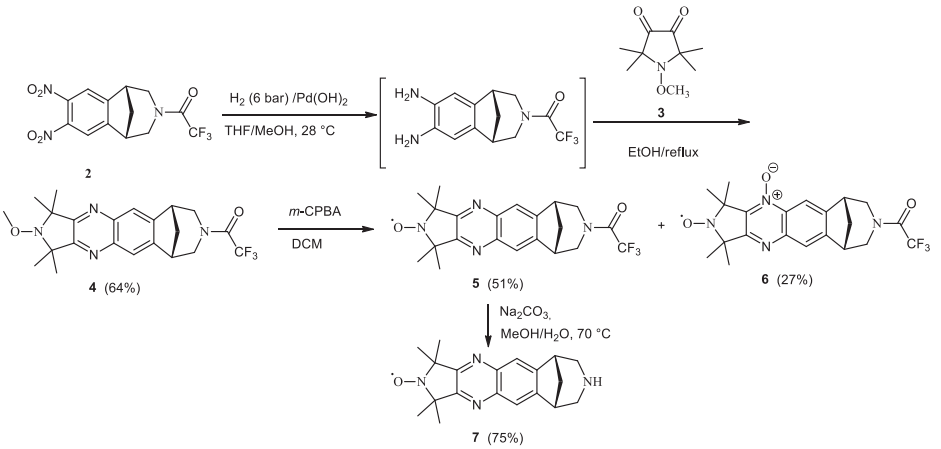


1

Scheme 1. Structure of varenicline.



Scheme 2. Synthesis of spin-labeled varenicline analog **7**.

Experimental section

Mass spectra were recorded using a GCMS-2020 (Shimadzu Corporation) gas chromatograph mass spectrometer operated in EI mode (70 eV). Elemental analyses were measured on a Fisons EA 1110 CHNS elemental analyzer and melting points were determined on a Boetius micro-melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded in DMSO-d_6 using a Bruker Avance III Ascend 500 spectrometer operating at 500 MHz and 125 MHz respectively; chemical shifts are referenced to TMS. The *in situ* reduction of nitroxide radicals was achieved by the addition of five equivalents of hydrazobenzene (DPPH)/radical. EPR spectra were recorded on a MiniScope MS 200 spectrometer. IR spectra were obtained using a Bruker Alpha FT-IR instrument with an ATR accessory on a diamond plate. Hydrogenations were performed with a ThalesNano H-Cube® Mini Plus reactor with 20% $Pd(OH)_2/C$ cartridge (Pearlman's catalyst, Thalesnano, cat. no. THS-01115). Compound **2** was purchased from Toronto Research Chemicals (cat. no. T293705). ^{1}H NMR, ^{13}C NMR, spectra of all compounds and EPR spectrum of compound 7 can be found via the "Supplementary Content" section of this article's webpage.

2,2,2-Trifluoro-1-(2-methoxy-1,1,3,3-tetramethyl-2,3,6,7,9,10-hexahydro-6,10-methanoazepino[4,5-g]pyrrolo[3,4-b]quinoxalin-8(1H)-yl)ethanone (4)

A solution of compound **2** (345 mg, 1.0 mmol) in a mixture of anhydrous THF/MeOH (1:1 v/v, 80 mL) was reduced by hydrogenation using a H-Cube® Mini Plus flow reactor equipped with a 20% $Pd(OH)_2/C$ cartridge at a pressure of 6×10^5 Pa H_2 and a flow

rate of 0.7 mL min^{-1}. After consumption of the starting material (monitored by TLC, Merck Silica gel 60 F_{254}, hexane/EtOAc, 2:1), the solvents were evaporated. The residue was dissolved in anhydrous EtOH (10 mL), and a solution of compound **3** (185 mg, 1.0 mmol) in anhydrous EtOH (10 mL) was added. The mixture was refluxed for 3 h and allowed to stand in air overnight. The solvent was evaporated, and the residue was purified by flash column chromatography (Merck Silica gel 60, 0.040-0.063 mm, hexane–Et_2O, 2:1) to give an off-white powder (278 mg, 64%); mp 200-202 °C; R_f = 0.32 (Merck Silica gel 60 F_{254}, hexane/EtOAc, 2:1); IR: (neat) 2980, 2932, 1685 cm^{-1}. ^1H NMR (DMSO-d_6, 500 MHz): δ (ppm) 1.49 (s, 12H), 2.18 (d, J = 11 Hz, 1H), 2.28 (m, 1H), 3.35 (s, 2H), 3.56 (s, 2H), 3.78 (s, 3H), 3.89 (d, J = 12 Hz, 1H), 4.37 (d, 1H, J = 12 Hz), 7.94 (s, 1H), 7.96 (s, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ (ppm) 23.2 (2C), 28.9 (2C), 41.3 (2C), 48.6 (2C), 50.7 (1C), 65.7 (1C), 65.8 (2C), 122.4 (1C), 122.6 (1C), 142.8 (2C), 147.1 (2C), 147.6 (2C), 158.9 (d, J = 9 Hz, 1C) (CF_3 signal is missing). MS (EI): m/z (%) = 434 (3, $[M]^+$). 419 (100), 373 (22), 69 (7), 57 (11), 43 (13).

Anal. Calc. for $C_{22}H_{25}F_3N_4O_2$: C, 60.82; H, 5.80; N, 12.90. Found: C, 60.78; H, 5.82; N, 12.72.

2,2,2-Trifluoro-1-(2-oxyl-1,1,3,3-tetramethyl-2,3,6,7,9,10-hexahydro-6,10-methanoazepino[4,5-g]pyrrolo[3,4-b]quinoxalin-8(1H)-yl))ethanone radical (5) and (6R(S),10R(S))-2-oxyl-1,1,3,3-tetramethyl-8-(2,2,2-trifluoroacetyl)-1,2,3,6,7,8,9,10-octahydro-6,10-methanoazepino[4,5-g]pyrrolo[3,4-b]quinoxaline 4-oxide radical (6)

To a stirred solution of compound **4** (220 mg, 0.506 mmol) in anhydrous DCM (20 mL), 3-chloroperbenzoic acid (~60%, 290 mg, 1.01 mmol, 2.0 eq) was added in 2-3 portions at 0 °C over a period of 10 min and stirring was continued at ambient temperature with continuous monitoring by TLC (Merck Silica gel 60 F_{254}, hexane/EtOAc, 2:1). Consumption of the starting material (after ~30 min) resulted in the formation of deprotected nitroxide **5** together with pyrazine-*N*-oxide nitroxide **6** as a side product. The solution was washed with 10% aq. Na_2CO_3 solution (20 mL × 2), and the organic phase was separated, dried ($MgSO_4$), filtered, and evaporated. The residue was purified by flash column chromatography (Merck Silica gel 60, 0.040-0.063 mm, hexane–EtOAc, 2:1) to give compound **5** as a yellow powder (108 mg, 51%); mp 212–215 °C; R_f = 0.44 (Merck Silica gel 60 F_{254}, $CHCl_3/Et_2O$, 2:1); IR: (neat) 2985, 2879, 1685 cm^{-1}. ^1H-NMR (DMSO-d_6 + $(PhNH)_2$, 500 MHz): δ (ppm) 1.43 (s, 6H), 1.44 (s, 6H), 2.13 (d, J = 11 Hz, 1H), 2.26 (m, 1H), 3.25 (d, J = 12 Hz, 1H), 3.72 (d, J = 12 Hz, 1H), 3.87 (d, J = 12 Hz, 1H), 4.25 (d, J = 12 Hz, 1H), 7.64(s, 1H), 8.09 (s, 1H). ^{13}C-NMR (DMSO-d_6, 125 MHz): δ (ppm) 25.1 (1C), 25.2 (1C), 25.4 (1C), 25.5 (1C), 41.4 (1C), 48.6 (2C), 50.7 (2C), 65.2 (2C), 116.5 (q, J = 287 Hz, 1C), 122.4 (1C), 122.6 (1C), 142.8 (2C), 146.7 (2C), 147.2 (2C), 159.7 (d, J = 8 Hz, 1C). MS (EI): m/z (%) = 419 (70, $[M]^+$), 389 (100), 374 (36), 262 (58), 139 (26).

Anal. Calc. for $C_{21}H_{22}F_3N_4O_2$: C, 60.14; H, 5.29; N, 13.36. Found: C, 60.02; H, 5.31; N, 13.25.

Compound **6** was obtained as a yellow powder (60 mg, 27%); mp 228–230 °C; R_f = 0.37 (Merck Silica gel 60 F_{254}, $CHCl_3/Et_2O$, 2:1); IR: (neat) 3012, 2871, 1688, 1583 cm^{-1}. ^1H NMR (DMSO-d_6 + $(PhNH)_2$, 500 MHz): δ (ppm) 1.40 (s, 3H), 1.42 (s, 3H), 1.45 (s, 3H), 1.54 (s, 3H), 2.16 (d, J = 11 Hz, 1H), 2.27 (m, 1H), 3.34 (d, J = 12 Hz,

1H), 3.53-3.58 (m, 2H), 3.75 (d, $J = 12$Hz, 1H), 3.89 (d, $J = 12$ Hz, 1H), 4.24 (d, $J = 12$ Hz, 1H), 7.98(d, $J = 13$ Hz, 1H), 8.38 (d, $J = 15$Hz, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ (ppm) 21.9-22.3 (2C), 25.0-25.2 (2C), 44.3 (1C), 48.4 (2C), 50.6 (2C), 65.1 (1C), 66.4 (1C), 112.0 (1C), 122.7 (1C), 137.0 (1C), 141.0 (1C), 145.7 (1C), 147.1 (1C), 147.6 (1C), 148.7 (1C), 149.2 (1C), 162.1 (d, $J = 8$ Hz, 1C). MS (EI): m/z (%) = 435 (4, $[M]^+$). 405 (39), 388 (100), 98 (52).

Anal. Calcd. for $C_{21}H_{22}F_3N_4O_3$: C, 57.93; H, 5.09; N, 12.87. Found C, 58.02; H, 5.13; N, 12.70.

1,1,3,3-Tetramethyl-3,6,7,8,9,10-hexahydro-6,10-methanoazepino[4,5-g]pyrrolo[3,4-b]quinoxalin-2(1H)-yloxyl radical (7)

To a solution of compound **5** (100 mg, 0.23 mmol) MeOH (2.0 mL) was added in a solution of Na_2CO_3 (48.7 mg, 0.46 mmol, 2.0 eq) in distilled water (2.0 mL). The mixture was warmed to 70 °C for 2 h, then the solvents were evaporated. The residue was treated with distilled water (20 mL) and extracted with DCM (10 mL × 3). The organic phase was separated, dried ($MgSO_4$), filtered, evaporated, and the crude reaction mixture was purified by flash column chromatography (Merck Silica gel 60, 0.040-0.063 mm, hexane–EtOAc 2:1, then $CHCl_3$/MeOH, 9:1) to give an orange powder (56 mg, 75%); mp 205–207 °C; R_f = 0.33 (Merck Silica gel 60 F_{254}, $CHCl_3$/MeOH, 5:1); IR: (neat) 3321, 3076, 2974, 1574 cm^{-1}. ^{1}H-NMR (DMSO-d_6, 500 MHz): δ (ppm) 1.46 (s, 12H), 1.89 (s, 1H), 1.95 (d, $J = 10$ Hz, 1H), 2.31 (bs, 1H), 2.74 (d, $J = 11$ Hz, 2H), 2.95 (d, $J = 12$Hz, 2H) 3.11 (s, 2H), 7.80 (s, 2H), ^{13}C-NMR (DMSO-d_6, 125 MHz): δ (ppm) 25.3 (2C), 25.4 (2C), 42.1 (1C), 43.4 (2C), 50.2 (2C), 65.2 (2C), 122.6 (2C), 143.0 (2C), 149.2 (2C), 158.9 (2C). MS (EI): m/z (%) = 323 (45, $[M]^+$), 293 (11), 280 (13), 250 (100), 98(49), 57(61). EPR triplet line, a_N = 15.3 G, radical content > 98% (in 0.15 M glycine buffer, pH = 3.1).

Anal. Calc. for $C_{19}H_{23}N_4O$: C, 70.56; H, 7.17; N, 17.32. Found: C, 70.48; H, 7.09; N, 17.18.

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