Synthesis of the (3*R*,6*S*)-3-amino-6-(2,3-difluorophenyl)azepan-2-one of MK-0974, a calcitonin gene-related peptide receptor antagonist for the treatment of migraine headache

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Experimental Section

Unless otherwise noted, all non-aqueous reactions were carried out under a N_2 atmosphere with commercial grade reagents and solvents. The ^{1}H NMR spectra were recorded on a Varian Unity Inova 400, 500 or 600 MHz spectrometer. Chemical shifts are reported in ppm relative to tetramethylsilane. Flash column chromatography was performed using EM silica gel 60 (230-400 mesh). Reverse phase preparative HPLC were performed using a Waters Prep LC 2000 and a Waters C_{18} PrepPak 500 column. Analytical HPLC was performed using a YMC Pro C18 3.0 x 50 mm 5 mm 120 A column with a 4.2 min linear gradient from 93:7 to 0:100 0.1% H_3PO_4:CH_3CN at a flow rate of 2 mL/min with UV detection at 215 and 254 nm.

Benzyl (1R)-1-{[[2-(2,3-difluorophenyl)prop-2-enyl](2,4-dimethoxybenzyl)amino]carbonyl}but-3-enylcarbamate (**7**)

Dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium dichloromethane adduct (0.726 g, 0.889 mmol) was added to a solution of benzyl (1*R*)-1-{[(2-bromoprop-2-enyl)(2,4-dimethoxybenzyl) amino]carbonyl}but-3-enylcarbamate[1] (9.2 g, 17.8 mmol), 2,3-difluorophenylboronic acid (2.95 g, 18.7 mmol) and sodium carbonate (2M in water; 19.6 mL, 39.1 mmol) in *N,N*-dimethylformamide (60 mL) and the mixture was heated to 75 °C. After 2 h, the mixture was allowed to cool to ambient temperature and extracted with dichloromethane (3x). The combined organic extracts were washed with saturated brine, dried over magnesium sulfate, filtered and concentrated. Purification by silica gel chromatography (5% ethyl acetate/ hexanes → 55% ethyl acetate/ hexanes) gave the title compound (6.8 g, 69%). NMR is complicated due to rotamers, please see attached spectrum; $[\alpha]^{20}_D$ 41.8 (c 1.0, $CHCl_3$); HRMS calculated $C_{31}H_{33}N_2O_5F_2$ (M+1) 551.2352, found 551.2369.

Benzyl (3*R*)-6-(2,3-difluorophenyl)-1-(2,4-dimethoxybenzyl)-2-oxo-2,3,4,7-tetrahydro-1H-azepin-3-ylcarbamate (**8**)

[1,3-bis-(2,4,6-Trimethylphenyl-2-imidazolidinylidene)dichloro(phenylmethylene)-(tricyclohexylphosphine)ruthenium] (Grubbs second generation catalyst) (2.62 g, 3.09 mmol) was added to a solution of benzyl (1*R*)-1-{[[2-(2,3-difluorophenyl)prop-2-enyl](2,4-dimethoxybenzyl)amino]carbonyl}but-3-enylcarbamate (6.8 g, 12.3 mmol) in dichloromethane (1800 mL) and the solution was heated to 40 °C. After 48 h, additional catalyst (0.52 g, 0.61 mmol) was added and the reaction continued to heat at 40 °C for an additional 48 h. The mixture was allowed to cool to ambient temperature and concentrated. Purification by silica gel chromatography (5% ethyl acetate/ hexanes → 55% ethyl acetate/ hexanes) gave the title compound (3.71 g, 58%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.31 (m, 4H), 7.11 (d, *J* = 8.3 Hz, 1H), 7.02 (dd, *J* = 16.4, 8.1 Hz, 1H), 6.91 (dd, *J* = 12.8, 7.4 Hz, 1H), 6.55 (t, *J* = 7.0 Hz, 1H), 6.34 (dd, *J* = 8.3, 2.2 Hz, 1H), 6.26 (d, *J* = 2.2 Hz, 1H), 6.22 (d, *J* = 6.4 Hz, 1H), 5.76 (t, *J* = 2.3 Hz, 1H), 5.30-5.10 (m, 3H), 4.81 (d, *J* = 14.4 Hz, 1H), 4.72 (d, *J* = 17.3 Hz, 1H), 4.46 (d, *J* = 14.4 Hz, 1H), 3.80-3.74 (m, 1H), 3.75 (s, 3H), 3.58 (s, 3H), 2.95-2.90 (m, 1H), 2.38-2.32 (m, 1H). LRMS 523.1 (M+1).

Benzyl (3*R*)-6-(2,3-difluorophenyl)-2-oxo-2,3,4,7-tetrahydro-1*H*-azepin-3-ylcarbamate (**9**)

Trifluoroacetic acid (60 mL) was added to a solution of benzyl (3*R*)-6-(2,3-difluorophenyl)-1-(2,4-dimethoxybenzyl)-2-oxo-2,3,4,7-tetrahydro-1*H*-azepin-3-ylcarbamate (3.70 g, 7.08 mmol) in dichloromethane (40 mL). After 18 h, the mixture was concentrated at 25 °C. Methanol (150 mL) was added and the precipitate filtered. The filtrate was concentrated, diluted with dichloromethane (100 mL), washed with water (2x), saturated aqueous sodium bicarbonate (2x), saturated brine, dried over magnesium sulfate, filtered and concentrated. Purification by silica gel chromatography (5% ethyl acetate/ hexanes → 65% ethyl acetate/ hexanes) gave the title compound (1.75 g, 66%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.32 (m, 4H), 7.09-7.02 (m, 2H), 6.95-6.92 (m, 1H), 6.33 (br s, 1H), 6.07 (d, *J* = 6.1 Hz, 1H), 5.87 (t, *J* = 2.7 Hz, 1H), 5.14 (d, *J* = 3.2 Hz, 2H), 5.11-5.05 (m, 1H), 4.58 (d, *J* = 17.6 Hz, 1H), 3.66 (dd, *J* = 17.6, 7.6 Hz, 1H), 2.96 (dd, *J* = 18.4, 4.5 Hz, 1H), 2.46-2.40 (m, 1H). LRMS 373.1 (M+1).

tert-Butyl (3R,6S)-6-(2,3-difluorophenyl)-2-oxoazepan-3-ylcarbamate (**10**)

10% Palladium on carbon (700 mg) was added to a solution of benzyl (3*R*)-6-(2,3-difluorophenyl)-2-oxo-2,3,4,7-tetrahydro-1*H*-azepin-3-ylcarbamate (2.6 g, 6.98 mmol) and di-*tert*-butyl dicarbonate (5.03 g, 23.0 mmol) in toluene (200 mL). The reaction vessel was evacuated and back-filled with nitrogen (3x), then back-filled with hydrogen (1 atm). After 18 h, the mixture was filtered and concentrated. Purification by preparative reverse phase chromatography (DeltaPak C18, 15 μ, 47 mm x 300 mm, 70 mL/min : 80% H_2O/NH_4OAc : 20% CH_3CN to 100% CH_3CN over 60 min) afforded the pure trans title compound (1.2 g, 51%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.07-7.04 (m, 2H), 6.91-6.89 (m,1H), 6.04 (br s, 1H), 5.93 (d, *J* = 5.6 Hz, 1H), 4.46 (dd, *J* = 10.5, 4.6 Hz, 1H), 3.65-3.59 (m, 1H), 3.21 (dd, *J* = 15.1, 7.3 Hz, 1H), 3.05-3.00 (m, 1H), 2.25-2.20 (m, 1 H), 2.17-2.10 (m, 2H), 1.79-1.71 (m, 1H), 1.46 (s, 9H); $[\alpha]^{20}_D$ -37.5 (c 1.0, $CHCl_3$); HRMS calculated $C_{17}H_{23}N_2O_3F_2$ (M+1) 341.1671, found 341.1674.

<u>*tert*-Butyl (3*R*,6*S*)-6-(2,3-difluorophenyl)-2-oxo-1-(2,2,2-trifluoroethyl)azepan-3-ylcarbamate (**11**)</u>

Sodium hydride (60% dispersion in mineral oil; 0.33 g; 8.2 mmol) was added to a solution of *tert*-butyl [(3*R*,6*S*)-6-(2,3-difluorophenyl)-2-oxoazepan-3-yl]carbamate (2.54 g, 7.46 mmol) in *N*,*N*-dimethylformamide (35 mL) at 0 ºC. After 5 min, the reaction mixture was cooled to -35 ºC and 2,2,2-trifluoroethyl trichloromethanesulfonate (1.60 mL, 9.69 mmol) was added. After 18 h, additional 2,2,2-trifluoroethyltrichloromethanesulfonate (0.40 mL, 2.43 mmol) and sodium hydride (60% dispersion in mineral oil; 0.12 g; 2.93 mmol) were added. After 2 h, additional 2,2,2-trifluoroethyltrichloromethanesulfonate (0.40 mL, 2.43 mmol) was added. After 3 h, the final portions of 2,2,2-trifluoroethyl trichloromethanesulfonate (0.20 mL, 1.21 mmol) and sodium hydride (60% dispersion in mineral oil; 0.1 g; 2.48 mmol) were added. After 2 h, the mixture was quenched with water and extracted with ethyl acetate (3x). The organic extracts were washed with water (3x), saturated brine, dried over sodium sulfate, filtered and concentrated. Purification by silica gel chromatography (100% hexanes → 70% hexanes/ ethyl acetate) afforded the title compound (3.15 g, 100%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.09-7.06 (m, 2H), 6.92-6.90 (m, 1H), 5.93 (d, *J* = 5.9 Hz, 1H), 4.62 (dd, *J* = 10.7, 6.1 Hz, 1H), 4.19-4.12 (m, 1H), 4.09-4.00 (m, 2H), 3.35 (d, *J* = 15.4 Hz, 1H), 3.06-3.01 (m, 1H), 2.25-2.09 (m, 3H), 1.75-1.70 (m, 1H), 1.46 (s, 9H); $[\alpha]^{20}_D$ -25.2 (c 0.25, $CHCl_3$); HRMS calculated $C_{19}H_{24}N_2O_3F_5$ (M+1) 423.1702, found 423.1708.

<u>(3*R*,6*S*)-3-Amino-6-(2,3-difluorophenyl)-1-(2,2,2-trifluoroethyl)azepan-2-one (**2**)</u>

Trifluoroacetic acid (15 mL, 202 mmol) was added to a solution of *tert*-butyl [(3*R*,6*S*)-6-(2,3-difluorophenyl)-2-oxo-1-(2,2,2-trifluoroethyl)azepan-3-yl]carbamate (6.8 g, 16.1 mmol) in dichloromethane (60 mL). After 2 h, the mixture was concentrated. Saturated aqueous sodium bicarbonate was added and the mixture was extracted with dichloromethane (3x). The organic extracts were washed with saturated brine, dried over magnesium sulfate, filtered and concentrated to give the title compound (5.19 g, 100%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11-7.03 (m, 2H), 6.93-6.89 (m, 1H), 4.21-4.13 (m, 1H), 4.10-3.98 (m, 2H), 3.85 (d, *J* = 11.0 Hz, 1H), 3.35 (d, *J* = 15.4 Hz, 1H), 3.04-2.99 (m, 1H), 2.13-2.09 (m, 2H), 2.08-2.02 (m, 1H), 1.78-1.70 (m, 3H); $[\alpha]^{20}_D$ -19.0 (c 1.0, CH_3OH); HRMS calculated $C_{14}H_{16}N_2OF_5$ (M+1) 323.1178, found 323.1178.

<u>*N*-[(3*R*,6*S*)-6-(2,3-Difluorophenyl)-2-oxo-1-(2,2,2-trifluoroethyl)azepan-3-yl]-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidine-1-carboxamide (**1**)</u>

Triethylamine (2.45 mL, 17.6 mmol) was added to a solution of (3*R*,6*S*)-3-amino-6-(2,3-difluorophenyl)-1-(2,2,2-trifluoroethyl)azepan-2-one (5.19 g, 16.1 mmol) and 4-nitrophenyl chloroformate (3.55 g, 17.6 mmol) in tetrahydrofuran (100 mL) at 0 °C. After 1 h, 2-oxo-1-(4-piperidinyl)-2,3-dihydro-1*H*-imidazo[4,5-b]pyridine dihydrochloride[2] (7.32 g, 25.1 mmol), triethylamine (8.98 mL, 64.4 mmol), and chloroform (100 mL) were added and the mixture was allowed to warm to ambient temperature. After 18 h, the mixture was concentrated. Saturated sodium bicarbonate was added and the mixture was extracted with ethyl acetate (3x). The combined organic extracts were washed with water (2x), saturated brine, dried over $MgSO_4$, filtered, and concentrated. Purification by silica gel chromatography (100% dichloromethane → 91% dichloromethane/ methanol) afforded the title compound (7.81 g, 86%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.14 (s, 1H), 8.06 (dd, *J* = 5.3, 1.1 Hz, 1H), 7.34 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.11-7.07 (m, 2H), 7.00-6.93 (m, 2H), 6.08 (d, *J* = 5.4 Hz, 1H), 4.86 (dd, *J* = 10.7, 4.9 Hz, 1H), 4.60-4.55 (m, 1H), 4.28-4.13 (m, 3H), 4.10-4.03 (m, 2H), 3.38 (d, *J* = 15.4 Hz, 1H), 3.10-3.06 (m, 1H), 3.02-2.95 (m, 2H), 2.31-2.23 (m, 4H), 2.15-2.11 (m, 1H), 1.92 (d, *J* = 11.2 Hz, 2H), 1.75-1.72 (m, 1H); $[\alpha]^{20}_D$ -18.5 (c 1.0, $CHCl_3$); HRMS calculated $C_{26}H_{28}N_6O_3F_5$ (M+1) 567.2138, found 567.2112.

2nd route:

<u>1-Benzyl 5-methyl *N*,*N*-bis(*tert*-butoxycarbonyl)-D-glutamate (**14**)</u>

To a solution of Boc-D-Glu-OBn (**13**) (100.0 g, 296.4 mmol) in dichloromethane (800 ml) and methanol (200 ml) was added trimethylsilyldiazomethane (2.0 M solution in hexanes; 187.8 mL, 375.7 mmol) at 0 °C dropwise via an addition funnel. After 15 min, the reaction was concentrated. This residue was diluted with acetonitrile (800 mL) and $(Boc)_2O$ (97.04 g, 444.6 mmol) was added, followed by DMAP (3.62 g, 29.6 mmol). After 24 h, additional $(Boc)_2O$ (20.0 g, 91.6 mmol) and DMAP (1.0 g, 8.2 mmol) were added. After an additional 24 h, the reaction mixture was concentrated. Purification by silica gel chromatography (10% → 60% ethyl acetate/ hexanes) gave the title compound (107.9 g, 81%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.30 (m, 5H), 5.16 (d, J = 1.7 Hz, 2H), 4.98 (dd, J = 9.9, 5.0 Hz, 1H), 3.67 (s, 3H), 2.53-2.47 (m, 1H), 2.44-2.40 (m, 2H), 2.24-2.19 (m, 1H), 1.45 (s, 18H). HRMS calculated $C_{13}H_{19}NO_4$ (M+1 – 2Boc) 252.1230, found 252.1230.

Benzyl (2*R*,5*E*)-2-[bis(*tert*-butoxycarbonyl)amino]-6-nitrohex-5-enoate (**16**)

To a -78 °C solution of 1-benzyl 5-methyl *N*,*N*-bis(*tert*-butoxycarbonyl)-D-glutamate (107.9 g, 239.0 mmol) in Et_2O (800 mL) was added slowly DIBAL (1.0 M solution in toluene; 298.7 mL, 298.7 mmol), so as not to let the internal temperature exceed -65 °C. After 30 min, additional DIBAL (40.0 mL, 40.0 mmol) was added. After stirring for additional 20 min, water (600 mL) was added and the reaction mixture was allowed to warm to ambient temperature and stirred for 30 min. This mixture was further diluted with Et_2O and H_2O, the layers separated and the aqueous phase extracted with more Et_2O. The combined organics extracts were washed with a saturated solution of aqueous sodium potassium tartrate (2x), saturated brine, dried over magnesium sulfate, filtered and concentrated to give benzyl *N,N-bis*(*tert*-butoxycarbonyl)-5-oxo-D-norvalinate (**15**) (96.5 g) which was carried directly into the next step. LRMS 444.1 (M+Na).

This material was dissolved in toluene (700 mL) and nitromethane (124.0 mL, 2.29 mol) and 1,1,3,3-tetramethylguanidine (2.9 mL, 22.9 mmol) were added at 0 °C. After stirring for 30 min the nitroaldol reaction was complete, so methanesulfonyl chloride (26.6 mL, 343.4 mmol) was added followed triethylamine (47.9 mL, 343.4 mmol) at 0 °C and the reaction was allowed to warm to ambient temperature. After 1 h, additional methanesulfonyl chloride (8.0 mL, 103.4 mmol)l and triethylamine (11.0 mL, 78.9 mmol) were added. After stirring for an additional 30 min the mixture was diluted with Et_2O and $NaHCO_3$, the phases separated and the aqueous layer backwashed with another portion of Et_2O. The combined organic extracts were dried over magnesium sulfate, filtered and concentrated to give a residue that was purified by silica gel

chromatography (5% → 50% ethyl acetate/ hexanes) afforded the title compound (68 g, 61%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.30 (m, 5H), 7.01-6.98 (m, 1H), 5.16 (dd, *J* = 24.4, 12.5 Hz, 2H), 4.89 (dd, *J* = 9.4, 4.5 Hz, 1H), 2.42-2.34 (m, 3H), 2.16-2.12 (m, 1H), 1.58-1.54 (m, 1H), 1.45 (s, 18H). HRMS calculated $C_{13}H_{17}N_2O_4$ (M+1 – 2Boc) 265.1183, found 265.1178.

Benzyl (5*S*)-*N,N-bis*(*tert*-butoxycarbonyl)-5-(2,3-difluorophenyl)-6-nitro-D-norleucinate (**17**)

A solution of benzyl (2*R*,5*E*)-2-[bis(*tert*-butoxycarbonyl)amino]-6-nitrohex-5-enoate (50.0 g, 107.6 mmol), 2,3-difluorophenylboronic acid (42.5 g, 269 mmol) and water (6.79 mL, 377 mmol) in dioxane (350 mL) was degassed with argon for 15 min. To this solution was added sodium bicarbonate (4.52 g, 53.8 mmol), (*S*)-BINAP (2.01 g, 3.23 mmol) and acetylacetanotobis(ethylene)rhodium(I) (0.83 g, 3.23 mmol). The mixture was stirred at ambient temperature for 2 min then heated to 35 °C. After 6 h, the reaction mixture was diluted with DCM/$NaHCO_3$, the layers separated and the aqueous phase was extracted with DCM (4x). The combined organic extracts were dried over magnesium sulfate, filtered and concentrated to give a residue that was purified by silica gel chromatography (5% → 60% ethyl acetate/ hexanes) gave the title compound (59.6 g, 96%) contaminated with ~7% 5*R* isomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47-7.27 (m, 5H), 7.18-7.02 (m, 2H), 6.98-6.92 (m, 1H), 5.16-5.06 (m, 2H), 4.89-4.87 (m, 1H), 4.68-4.60 (m, 2H), 3.82-3.71 (m, 1H), 2.09-2.01 (m, 1H), 1.85-1.76 (m, 3H), 1.40 (s, 18 H); $[\alpha]^{20}_D$ 21.4 (c 1.0, $CHCl_3$); HRMS calculated $C_{19}H_{22}N_2O_4F_2$ (M+1 – 2Boc) 379.1464, found 379.1457.

The diastereomer ratio of the crude reaction mixture was determined by HPLC: Dupont C8 column, 4.6 mm x 150 mm; gradient = 30% H_2O → 70% MeOH with NH_4OAc (1g/L); rate = 2 mL/ min; t_r (6*R*) = 7.88 min, t_r (6*S*) = 8.86 min.

(5*S*)-N^2,N^2-Bis(*tert*-butoxycarbonyl)-5-(2,3-difluorophenyl)-D-lysine (**18**)

A solution of benzyl (5*S*)-*N,N-bis*(*tert*-butoxycarbonyl)-5-(2,3-difluorophenyl)-6-nitro-D-norleucinate (38.2 g, 66.0 mmol) and 10% Pd/C (39.1 g) in EtOH (500 mL, SureSeal from Aldrich), was hydrogenated at 55 psi. After 18 h, the reaction mixture was filtered through Celite, washed with EtOH and concentrated to afford the title compound (27.0 g, 89%). $[\alpha]^{20}_D$ 57.0 (c 1.0, $CHCl_3$); HRMS calculated $C_{22}H_{33}N_2O_6F_2$ (M+1) 459.2301, found 459.2308.

di-*tert*-Butyl [(3*R*,6*S*)-6-(2,3-difluorophenyl)-2-oxoazepan-3-yl]imidodicarbonate (**19**)

To a solution (5*S*)-N^2,N^2-bis(*tert*-butoxycarbonyl)-5-(2,3-difluorophenyl)-D-lysine (22.0 g, 48.0 mmol) in DCM (700 mL) were added EDC (11.0 g, 57.6 mmol) and HOAT (3.27 g, 24.0 mmol) followed by triethylamine (10.0 mL, 72.0 mmol). After 1 h, saturated aqueous $NaHCO_3$ was added, the layers separated and the aqueous phase backwashed with DCM (2x). The combined organics were dried over magnesium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography (1% → 10% MeOH / DCM) to give the title compound (18.0 g, 85%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08-7.02 (m, 2H), 6.93-6.90 (m, 1H), 5.92 (br s, 1H), 5.11 (d, *J* = 11.0 Hz, 1H), 3.60-3.54 (m, 1H), 3.24 (dd, *J* = 14.8, 8.2 Hz, 1H), 3.08 (t, *J* = 11.2 Hz, 1H), 2.64-2.56 (m, 1H), 2.19-2.10 (m, 2H), 2.05-1.96 (m, 1H) 1.53 (s, 18 H); LRMS 441.2 (M+1).

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tert-Butyl [(3*R*,6*S*)-6-(2,3-difluorophenyl)-2-oxoazepan-3-yl]carbamate (**10**)

To a solution of di-*tert*-butyl [(3*R*,6*S*)-6-(2,3-difluorophenyl)-2-oxoazepan-3-yl]imidodicarbonate (10.7 g, 24.3 mmol) in DCM (240 mL) was added TFA (3.74 mL, 50.3 mmol). After 1.5 h, saturated aqueous $NaHCO_3$ was added, the layers separated and the aqueous phase backwashed with DCM. The combined organic extracts were dried over magnesium sulfate, filtered and concentrated to give the title compound (8.0 g, 97%). HRMS calculated $C_{17}H_{23}N_2O_3F_2$ (M+1) 341.1671, found 341.1674.

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[1] Paone, D.V.; Shaw, A.W.; Nguyen, D.N.; Burgey, C.S.; Deng, Z.J.; Kane, S.A., Koblan, K.S., Salvatore, C.A., Hershey, J., C.; Wong, B.; Roller, S.G.; Miller-Stein, C.; Graham, S.L., Vacca, J.P.; Williams, T.M. *J. Med. Chem.* **2007**, *50*, 5564-5567.

[2] Burgey, C.S.; Stump, C.A.; Nguyen, D.N.; Deng, Z.J.; Quigley, A.G.; Norton, B.R.; Bell, I.M.; Mosser, S.D.; Salvatore, C.A., Rutledge, R.Z.; Kane, S.A., Koblan, K; Vacca, J.P.; Graham, S.L., Williams, T.M. *Bioorg. Med. Chem. Lett.* **2006**, *16,* 5052-5056