Supporting Information

Discovery and pharmacology of a novel somatostatin subtype 5 (SSTR5) antagonist: Synergy with DPP-IV inhibition

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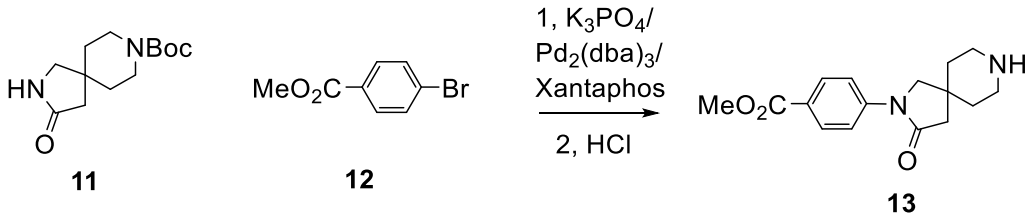
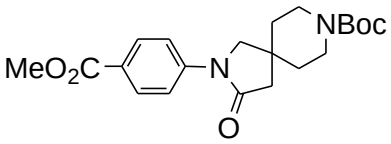
1) Syntheses of key compounds

Synthetic Materials and Methods. Reagents and solvents were obtained from commercial suppliers and were used without futher purification. Flash chromatography was performed on a Teledyne Isco CombiFlash instrument using pre-packed RediSepRf Gold silica gel columns. ^{1}HNMR spectra were recorded in the deuterated solvents specified on a Varian Unity INOVA 500 MHz instrument. C-13 NMR spectra were recorded in the deuterated solvents specified on a Bruker AS500 MHz instrument. LC-MS was measured using HP1100 and Micromass ZQ instruments. Preparative HPLC purification were performed on Gilson 500 instrument with C8 or C18 reverse phase preparative HPLC column eluting with MeCN/water with modifiers of either TFA or NH_4OH. High resolution mass spectrometry was performed on Thermo Orbitrap XL. Polarity: positive ; 0.1%FA in ACN:H2O:MeOH:DMSO 40:40:10:10 Direct infusion ; Sheath gas flow rate:5 ; Capillary temperature: 320 ^{o}C ; Spray voltage: 5kv. All compounds reported in this communication are at least 90% pure judged by HPLC UV detection (254 nM), LC-MS, and optionally NMR.

Scheme 1, intermediate **13**

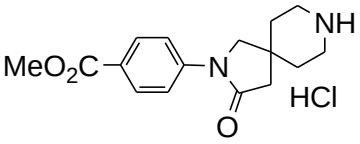


Synthesis of *tert*-Butyl-2-[4-(methoxycarbonyl)phenyl]-3-oxo-2,8-diazaspiro-[4.5]decane-8-carboxylate



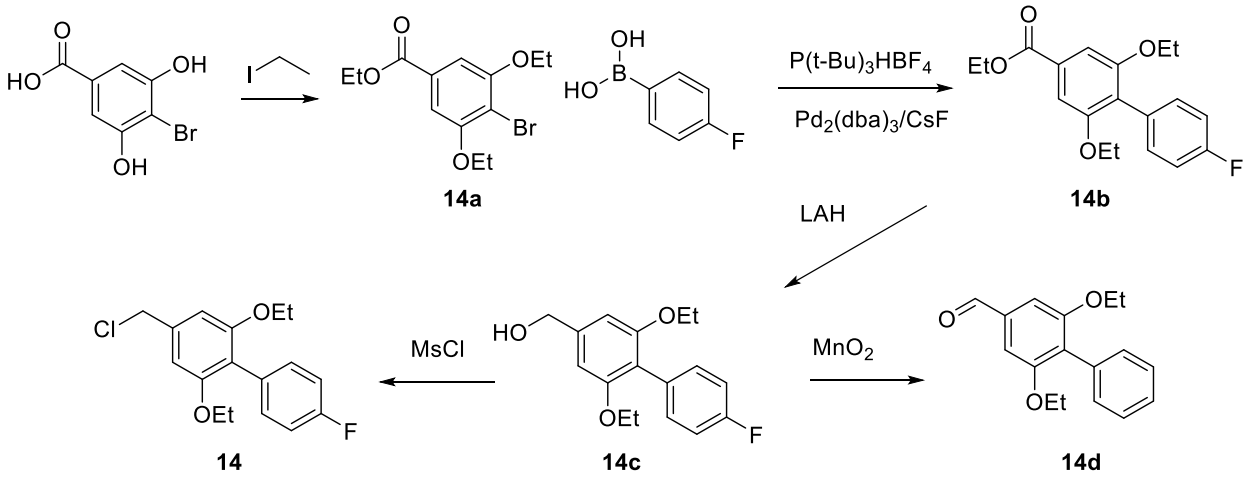
To a round bottom flask was added *tert*-butyl 3-oxo-2,8-diazaspiro[4.5]decane-8-carboxylate (**11**) (2 g, 7.86 mmol); methyl 4-bromobenzoate (**12**) (2.5 g, 11.8 mmol); K_3PO_4 (5.0 g, 23.6 mmol); $Pd_2(dba)_3$ (0.072 g, 0.079 mmol); 9,9-dimethyl-4,5-bis(diphenylphosphino)-xanthene (Xantaphos) (0.091 g, 0.157 mmol); and 15 mL dioxane. The reaction mixture was thoroughly degassed with nitrogen, and heated at 100 °C overnight. After cooling to room temperature, the reaction mixture was diluted with a mixture of 75 mL EtOAc/75 mL ether, and washed with 120 mL water. The organic layer was separated, dried over sodium sulfate, filtered and concentrated. The resulting crude material was purified via silica gel chromatography by eluting with a gradient of: 1:3 to 2:1 ethyl acetate/hexane to give the title compound as light yellow solid (2.69 g, 88%). ^{1}H-NMR ($CDCl_3$) δppm: 8.06 (d, *J* = 7 Hz, 2H), 7.73 (d, *J* = 8.9 Hz, 2H), 3.93 (s, 3H), 3.71 (s, 2H), 3.64 (b, 2H), 3.35 (m, 2H), 2.59 (s, 2H), 1.71 (m, 4H), 1.49 (s, 9H). LC-MS (ESI) *m/z*: $[M+H]^+$ 389.2.

Synthesis of Methyl 4-(3-oxo-2,8-diazaspiro[4.5]dec-2-yl)benzoate hydrochloride (**13**)

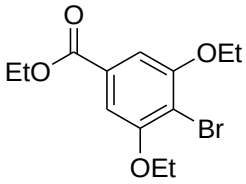


To a solution of *tert*-butyl-2-[4-(methoxycarbonyl)phenyl]-3-oxo-2,8-diazaspiro-[4.5]decane-8-carboxylate (2.4 g, 6.2 mmol) in 10 mL of EtOAc was added HCl in dioxane (9.3 mL, 4 M). The resulting reaction mixture was stirred at room temperature overnight, then diluted with 100 mL hexane, filtered and air dried to give the title compound as light yellow solid (1.7g, 95%). ^{1}H-NMR (CD_3OD) δppm: 8.04 (d, *J* = 7 Hz, 2H), 7.79 (d, *J* = 8.9 Hz, 2H), 3.90 (s, 3H), 3.89 (s, 2H), 3.3 (m, 4H), 3.35 (m, 2H), 2.69 (s, 2H), 1.9 (m, 4H). LC-MS *m/z*: $[M+H]^+$ 289.3.

Scheme 2, intermediate **14**

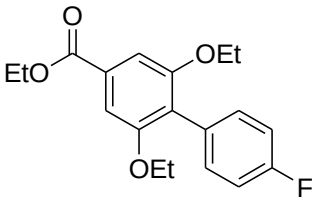


Synthesis of Ethyl 4-bromo-3,5-diethoxybenzoate (**14a**)



Iodoethane (17.3 mL, 215 mmol) was added to a stirred mixture of 4-bromo-3,5-dihydroxybenzoic acid (10 g, 42.9 mmol) and potassium carbonate (26.7 g, 193 mmol) in DMF (50 mL). The mixture was stirred at room temperature for 18 hours, and then partitioned between EtOAc (70 mL) and water (50 mL). The aqueous phase was extracted with EtOAc (3x50 mL). The combined organic phases were washed with water (2x), brine, dried ($MgSO_4$) and concentrated to give the title compound as a pale yellow solid (13.4g, 98%). ^{1}H NMR ($CDCl_3$) δppm: 7.2 (s, 2H), 4.4 (q, 2H), 4.2 (q, 4H), 1.5 (t, 6H), 1.4 (t, 3H).

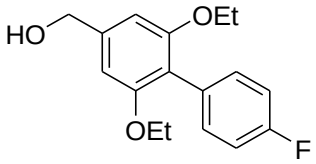
Synthesis of ethyl 2,6-diethoxy-4'-fluorobiphenyl-4-carboxylate (**14b**)



Dioxane (120 mL) was added to a degassed mixture of tri-*t*-butylphosphonium tetrafluoroborate (0.73 g, 2.5 mmol) 4-fluorophenylboronic acid (11.8 g, 84 mmol) tris(dibenzylideneacetone)dipalladium(0) (0.77 g, 0.84 mmol), CsF (23.7 g, 156 mmol) and ethyl 4-bromo-3,5-diethoxybenzoate (**14a**) (13.4 g, 42 mmol). The mixture was degassed and refilled with nitrogen and stirred at 90°C under nitrogen for 20 hours, and then partitioned between EtOAc and water. The aqueous phase was filtered and extracted with

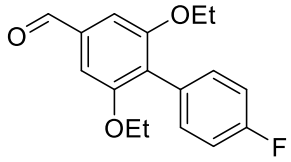
EtOAc. The combined organic phases were washed with water, brine, dried ($MgSO_4$), and concentrated. The resulting residue was chromatographed on silica gel column by eluting with EtOAc/hexane. The product fractions were combined and concentrated to give the title compound as a tan solid (11.5 g, 82%). ^{1}H-NMR ($CDCl_3$) δppm: 7.4 (m, 2H), 7.2 (s, 2H), 7.1 (m, 2H), 4.4 (q, 2H), 4.1 (q, 4H), 1.45 (t, 3H), 1.3 (t, 6H). LC-MS *m/z*: $[M+H]^+$ 333.1.

Synthesis of (2,6-Diethoxy-4'-fluorobiphenyl-4-yl)methanol (**14c**)



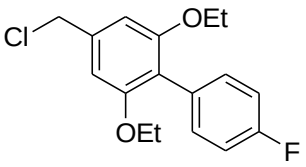
A solution of lithium aluminumhydride (34 ml, 34 mmol) in THF was added dropwise over 30 min to a stirred solution of ethyl 2,6-diethoxy-4'-fluorobiphenyl-4-carboxylate (**14b**) (14 g, 42 mmol) in THF (120 mL) at room temperature. After 2 hours at room temperature, the reaction mixture was refrigerated overnight and then quenched by the sequential addition of water (4 mL), aqueous NaOH (0.5 M, 4 mL), and water (4 mL). The mixture was filtered through CELITE®, washed thoroughly with EtOAc, and concentrated to give the title compound as white solid (10 g, 71%). ^{1}H-NMR ($CDCl_3$) δppm: 7.4 (m, 2H). 7.1 (m, 2H), 6.7 (s, 2H), 4.7 (d, 2H), 4.0 (q, 4H), 1.8 (t, 1H), 1.3 (t, 6H).

Synthesis of 3,5-diethoxy-4-(4'-fluorophenyl)benzaldehyde (**14d**)



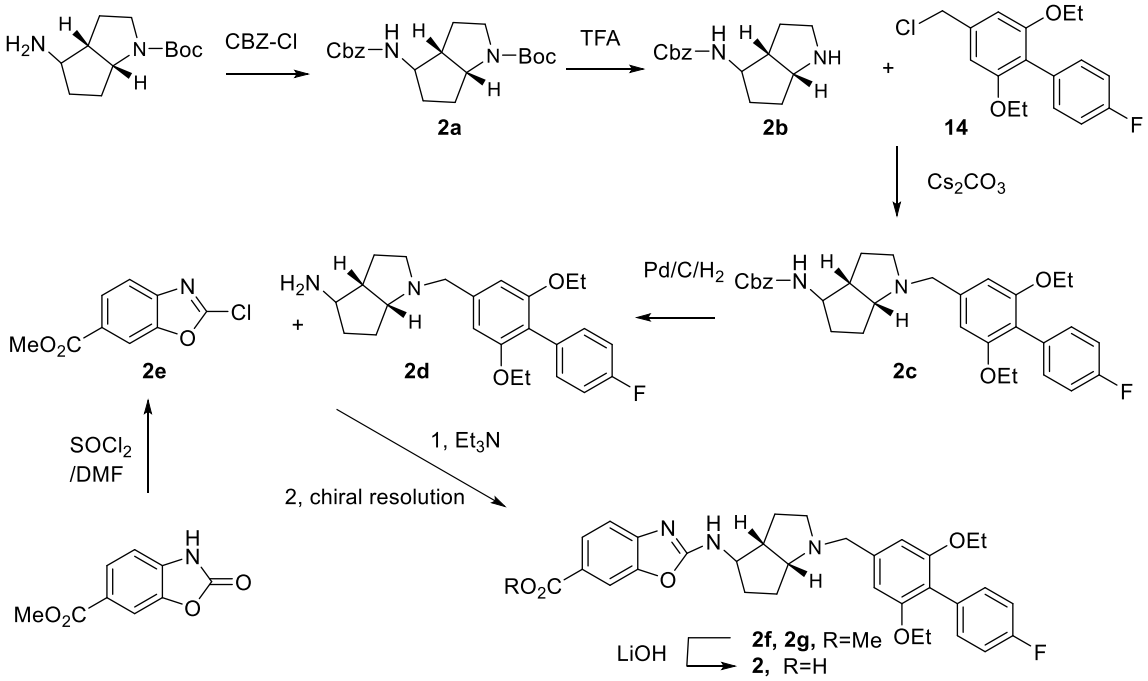
To a solution of (2,6-Diethoxy-4'-fluorobiphenyl-4-yl)methanol (**14c**) (20 g, 67 mmol) in anhydrous dichloromethane (500 mL) was added MnO_2 (30 g, 345 mmol) in one portion, then the mixture was stirred at reflux for 2 h and another MnO_2 (30 g, 345 mmol) was added. The resulting mixture was stirred at reflux for another 2 h and TLC showed the reaction was completed. The resulting mixture was filtered and concentrated, and the crude product was purified via column chromatography to afford product (18 g, yield 93 %). ^{1}H-NMR ($CDCl_3$) δppm: 9.93 (s, 1H), 7.30~7.36 (m, 2H), 7.12 (s, 2H), 7.04~7.10 (m, 2H), 4.05 (q, J = 7.0 Hz, 4H), 1.28 (t, J = 7.0 Hz, 6H). LC- *m/z*: $[M+H]^+$ 289.2

Synthesis of 4-(Chloromethyl)-2,6-diethoxy-4'-fluorobiphenyl (**14**)

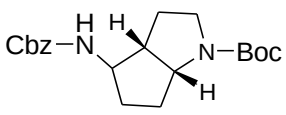


Methanesulfonyl chloride (1.6 mL, 20.7 mmol) was added dropwise to a stirred solution of (2,6-Diethoxy-4'-fluorobiphenyl-4-yl)methanol (**14c**) (5 g, 17.2 mmol) and triethylamine (3.6 mL, 25.8 mmol). The mixture was stirred at room temperature for 18 hours, and then partitioned between EtOAc and water. The aqueous phase was extracted with EtOAc. The combined organic phases were washed with water, brine, dried ($MgSO_4$) and concentrated. The resulting residue was chromatographed on a silica gel column by eluting with EtOAc/hexane. The product fractions were combined and concentrated to give the title compound (4.6g, 84%). ^{1}H-NMR ($CDCl_3$) δppm: 7.4 (m, 2H), 7.1 (m, 2H), 6.7 (s, 2H), 4.6 (s, 2H), 4.0 (q, 4H), 1.3 (t, 6H). LC-MS *m/z*: $[M+H]^+$ 309.1.

Compound **2**

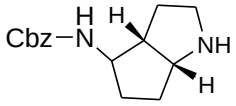


Synthesis of tert-butyl (3a,6a cis)-4-(((benzyloxy)carbonyl)amino)hexahydrocyclopenta[b]pyrrole-1(2H)-carboxylate (**2a**, diastereomers at C-4)



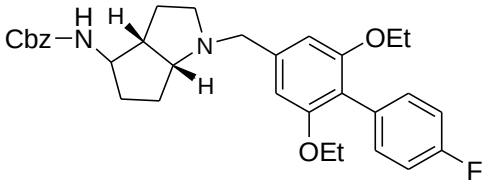
Benzyl chloroformate (1.76 mL, 12.3 mmol) was added dropwise to a stirred and cooled (0 °C) mixture of tert-butyl (3a,6a cis)-4-amino-3,3a,4,5,6,6a-hexahydro-2H-cyclopenta[b]pyrrole-1-carboxylate (diastereomers at C-4, 1.4 g, 6.2 mmol) and triethylamine (3.5 mL, 24.7 mmol) in dichloromethane, and the resulting mixture was stirred at room temperature overnight. The reaction mixture was diluted with dichloromethane and washed with saturated aqueous $NaHCO_3$, water and brine. The mixture was dried ($MgSO_4$), filtered and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with EtOAc/hexane to give compound **2a** as colorless oil. LC-MS *m/z*: $[M+H\text{-}Boc]^+$ 261.3

Synthesis of benzyl ((3a,6a cis)-octahydrocyclopenta[b]pyrrol-4-yl)carbamate (**2b**, diastereomers at C-4)



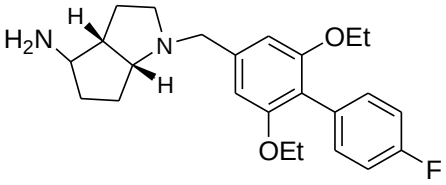
To a solution of compound **2a** (1.18 g, 3.3 mmol) in 8 mL of dioxane, HCl in dioxane (4M, 16 ml, 64 mmol) was added at room temperature. After 2 hour, LC-MS showed no starting material, and product peak presented. The solvent was removed under reduced pressure, and then the product material was dried using high vacuum to give compound **2b** (680mg, 79%). LC-MS *m/z*: $[M+H]^+$ 261.3

Synthesis of benzyl ((3a,6a cis)-1-((2,6-diethoxy-4'-fluoro-[1,1'-biphenyl]-4-yl)methyl)octahydrocyclopenta[b]pyrrol-4-yl)carbamate (**2c**, diastereomers at C-4)



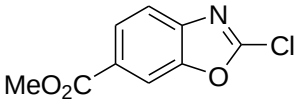
The reactants, intermediate **14** (379 mg, 1.2 mmol), compound **2b** (364 mg, 1.2 mmol), and cesium carbonate (1.2 g, 3.3 mmol) were mixed in 10 mL of DMF and stirred at room temperature overnight. The resulting mixture was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), filtered and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with EtOAc/Hexanes to give racemic compound **2c** as a colorless oil (540 mg, 88%). LC-MS *m/z*: $[M+H]^+$ 533.5.

Synthesis of (3a,6a cis)-1-((2,6-diethoxy-4'-fluoro-[1,1'-biphenyl]-4-yl)methyl)octahydrocyclopenta[b]pyrrol-4-amine (**2d**, diastereomers at C-4)



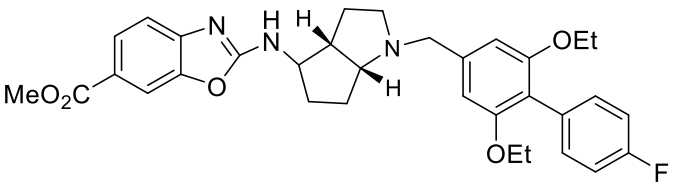
To a solution of of compound **2c** (137 mg, 0.25 mmol) in MeOH (2.5 mL) $Pd(OH)_2$ on carbon (50% wt, 29 mg, 0.1 mmol) was added at room temperature. The reaction vessel was purged with nitrogen three times. Then the reaction mixture was stirred under a hydrogen balloon for 1 h. The reaction mixture was filtered through CELITE (diatomaceous earth) and concentrated to give compound **2d** as a colorless gum (98 mg, 96%). LC-MS *m/z*: $[M+H]^+$ 399.2.

Synthesis of Methyl 2-chloro-1,3-benzoxazole-6-carboxylate (**2e**)



Methyl 2-mercapto-1,3-benzoxazole-6-carboxylate (2 g, 9.5 mmol), $SOCl_2$ (9.8 ml, 134 mmol) and DMF (0.8 mL, 10 mmol) was added at room temperature. The reaction mixture was heated to reflux for 15 min. The solvent was removed under reduced pressure. The crude oil was azeotroped with xylene twice. The residue was dissolved in a minimum amount of DCM / MeOH, and then loaded onto a silica gel column, eluting with EtOAc/hexane to give intermediate **2e** as a white solid (1.8g, 89%). ^{1}H-NMR ($CDCl_3$) δppm: 8.3 (s, 1H), 8.1 (d, 1H), 7.8 (d, 1H), 4.0 (s, 3H). LC-MS *m/z*: $[M+H]^+$ 212.1

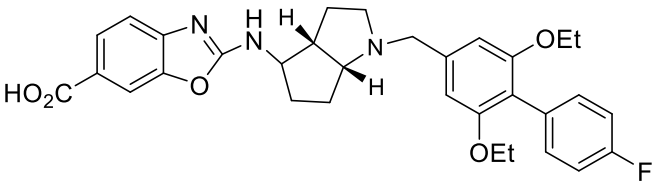
Synthesis of methyl 2-(((3a,6a cis)-1-((2,6-diethoxy-4'-fluoro-[1,1'-biphenyl]-4-yl)methyl)octahydrocyclopenta[b]pyrrol-4-yl)amino)benzo[d]oxazole-6-carboxylate (**2f**, diastereomers)



To a solution of compound **2d** (98 mg, 0.25 mmol) in acetonitrile (1.5 mL), compound **2e** (62.4 mg, 0.3 mmol) and triethylamine (0.07 ml, 0.5 mmol) were added. The reaction mixture was heated in a sealed tube at 80^{o}C for 1 h. The solvent was removed under reduced pressure, and the residue was purified by preparative thin layer chromatograph (5% MeOH/DCM) to give a white foam (83 mg, 58%). The mixture

of diastereomers were separated with a Chiral OD column (5% iPrOH/Heptane. 9 ml/min flow rate). The first peak eluted from the column was concentrated to dryness to obtain compound **2f**(38 mg, 47%), LC-MS *m/z*: $[M+H]^+$ 574.3. The second peak eluted from the column was also concentrated to dryness to obtain the second diasteromer **2g**,(40 mg, 48%), LC-MS *m/z*: $[M+H]^+$ 574.3

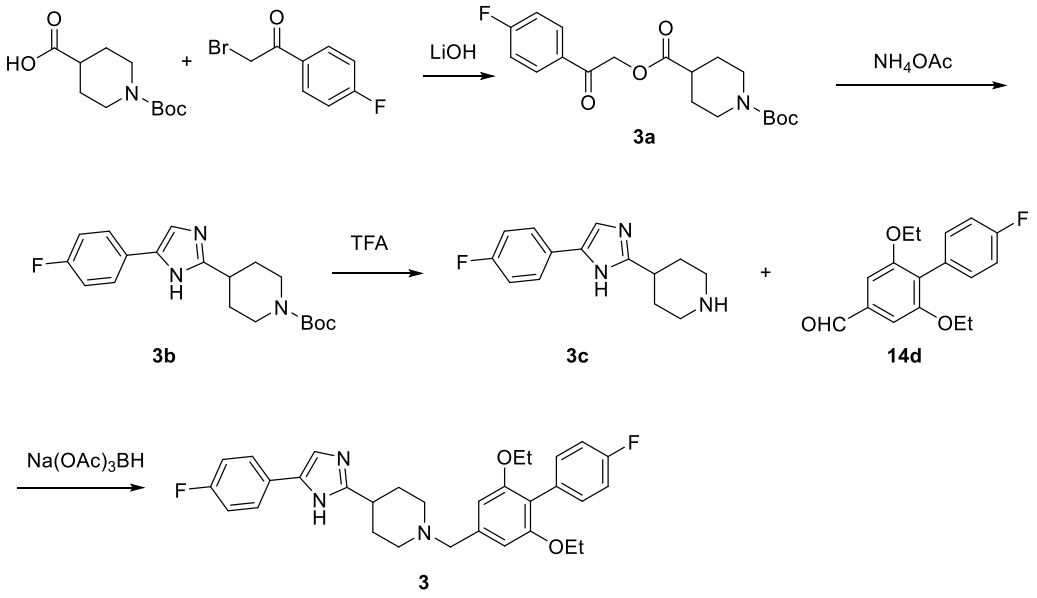
Synthesis of 2-(((3a,6a cis)-1-((2,6-diethoxy-4'-fluoro-[1,1'-biphenyl]-4-yl)methyl)octahydrocyclopenta[b]pyrrol-4-yl)amino)benzo[d]oxazole-6-carboxylic acid (**2**)



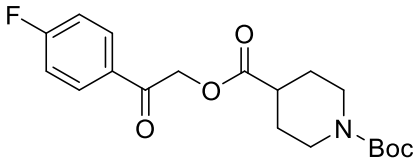
To a stirred solution of compound **2f** (38 mg, 0.07 mmol) in THF/MeOH/H_2O (1 / 0.5 / 0.5 mL) lithium hydroxide monohydrate (52 mg, 1.7 mmol) was added. The reaction mixture was warmed up to 50^{o}C for 2.5 h. The reaction mixture was acidified with 50% formic acid/CH_3CN, and then purified by reverse phase HPLC (C18) followed by lyophilization to give compound **2** as white solid (27 mg, 69%). ^{1}H-NMR ($CDCl_3$) δppm: 8.8/8.6 (s, 1H), 8.0 (d, J=7.5 Hz, 1H), 7.7 (broad, 1H), 7.4 (m, 3H), 7.1 (m, 2H), 7.0 (s, 2H), 4.8 (m, 1H), 4.5 (m, 1H), 4.0 (m, 5H), 3.8 (m, 1H), 3.6 (m, 1H), 3.2 (m, 1H), 3.0 (m, 1H), 2.2 (m, 2H), 2.0 (m, 3H), 1.6 (m, 1H), 1.2 (t, J=7.0 Hz, 6H). LC-MS (M+1): 560.4. ^{13}C-NMR (DMSO-d_6) δppm: 169.6, 167.7, 164.0, 162.4, 160.5, 156.7, 148.2, 147.9, 133.2, 133.1, 132.3, 130.1, 126.6, 123.3, 119.1, 115.2, 114.7, 114.6, 109.8, 108.9, 70.1, 64.4, 57.8, 55.4, 55.0, 44.8, 30.3, 28.8, 28.5, 26.7, 24.6, 23.7, 22.9, 14.9, 14.4, 11.3. HRMS (ESI): (*m/z*): calculated for $[C_{32}H_{34}FN_3O_5+H]^+$: 560.2561, found: 560.2558.

The same reaction was performed on the second diasteromer (**2g**):
To a stirred solution of compound **2g** (19 mg, 0.033 mmol) in THF/MeOH/H_2O (1 / 0.5 / 0.5 mL) lithium hydroxide monohydrate (2M, 0.25 ml, 0.5 mmol) was added. The reaction mixture was warmed up to 50^{o}C for 2.5 h. The reaction mixture was acidified with 50% formic acid/CH_3CN, and then purified by reverse phase HPLC (C18) followed by lyophilization to give the diasteromer B corresponding to comopund **2** as white solid (15.6 mg, 74.6%). ^{1}H-NMR (500MHz, $CDCl_3$, ppm): 8.15 (s, 2H), 7.50 (d, J=7.2 Hz, 1H), 7.32 (broad, 2H), 7.13 (m, 4H), 4.75 (m, 1H), 4.35 (m, 3H), 4.12 (m, 4H), 3.5-3.8 (m, 4H), 3.6 (m, 1H), 3.2-3,4 (m, 2H), 2.0-2.3 (m, 4H), 1.7-1.9 (m, 2H), 1.3 (t, J=7.0 Hz, 6H). LC-MS *m/z*: $[M+H]^+$ 560.2. This compound is much less potent than compound **2** in human SSTR5 binding (IC_{50} = 63 nM) assay and cell based hSSTR5 c-AMP antagonist (IC_{50} = 171.5 nM) assay.

Compound **3**

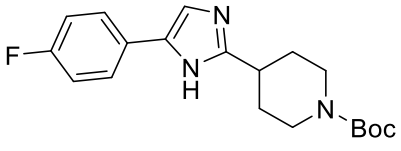


Synthesis of 1-tert-butyl 4-(2-(4-fluorophenyl)-2-oxoethyl) piperidine-1,4-dicarboxylate (**3a**)



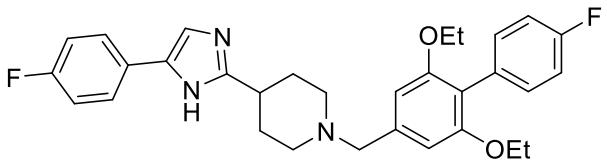
To a solution of 1-(tert-butoxycarbonyl)piperidine-4-carboxylic acid (2g, 8.5 mmol) in MeOH (20 mL) and water (10 mL) was added lithium hydroxide (205 mg, 8.5 mmol) dissolved in 5 mL of water. The mixture was stirred at room temperature for 1 hr and concentrated to dryness. The residue was re-dissolved in dry DMF (5 mL) to which was added dropwise a solution of 2-bromo-1-(4-fluorophenyl)ethanone (1.85g, 8.5 mmol) in DMF (5 mL). The mixture was stirred at room temperature for 2 hours and concentrated to dryness at 60 ^{o}C under high vacuum. The residue was purified by silica gel column, eluting with EtOAc/Hexane gradient 0-100% to give product (3g, 97%) as a gel, LC-MS *m/z*: $[M+H]^+$ 366.4.

Synthesis of tert-butyl 4-(5-(4-fluorophenyl)-1H-imidazol-2-yl)piperidine-1-carboxylate (**3b**)



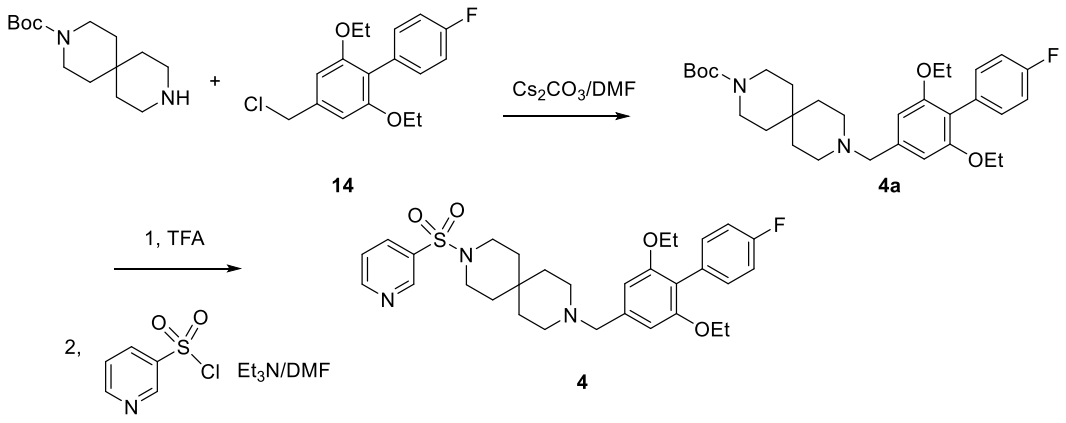
To a solution of 1-tert-butyl 4-(2-(4-fluorophenyl)-2-oxoethyl) piperidine-1,4-dicarboxylate (**3a**, 3g, 8.21 mmol) in xylene (30 ml) was added ammonium acetate (4.43g, 57.5 mmol). The mixture was heated to 130 ^{o}C for 2 hours. The mixture was cooled to RT and filtered through celite. The filtrate was concentrated to dryness and the residue was purified by silica gel column, eluting with EtOAc/Hexane gradient 0-100% to give product as a white solid (2.8g, 76%). LC-MS *m/z*: $[M+H]^+$ 446.5

Synthesis of 1-((2,6-diethoxy-4'-fluoro-[1,1'-biphenyl]-4-yl)methyl)-4-(5-(4-fluorophenyl)-1H-imidazol-2-yl)piperidine (**3**)

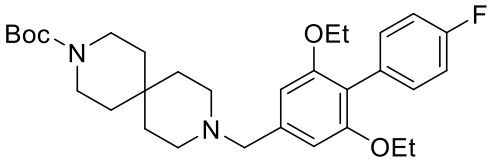


To a solution of tert-butyl 4-(5-(4-fluorophenyl)-1H-imidazol-2-yl)piperidine-1-carboxylate (**3b**) (100mg, 0.28 mmol) in DCM (5 ml) was added TFA (2 ml). The mixture was stirred at RT for 4 hours and then concentrated to dryness under nitrogen. This residue (**3c**) was re-dissolved in DMF (2 mL) followed by addition of 3,5-diethoxy-4-(4'-fluorophenyl)benzaldehyde (**14d**) (80 mg, 0.28 mmol) and trimethylamine (280 mg, 2.8 mmol). The mixture was stirred at RT for 30 min followed by addition of acetic acid (50 mg, 0.84 mmol) and sodium triacetoxyborohydride (86 mg, 0.4 mmol) portion wise. The mixture was then stirred at RT overnight, diluted with water (20 mL) and extracted with EtOAc (3x10 mL). The organic extracts were combined, dried over $MgSO_4$ and concentrated to dryness. The residue was purified by silica gel column, eluting with EtOAc/Hexane gradient 0-100% to give product as a white solid (100 mg, 0.2 mmol, 71%). ^{1}H-NMR (DMSO-d) δppm: 7.95 (d, *J* = 8 Hz, 2H), 7.35 (d, *J* = 8 Hz, 2H), 7.29 (m, 3H), 7.17 (d, *J* = 7.5 Hz , 2H), 6.84 (d, *J* = 2.5 Hz , 2H), 4.25 (m, 4H), 3.9 (s, 2H), 3.2-3.6 (b, 4H), 2.2-2.6 (m, 5H),1.9-2.2 (b, 4H),1.25 (t, *J* = 7 Hz, 6H). LC-MS for $[C_{31}H_{34}F_2N_3O_2]^+$ *m/z*: $[M+H]^+$ calc: 518.3; found: 518.7.

Compound **4**

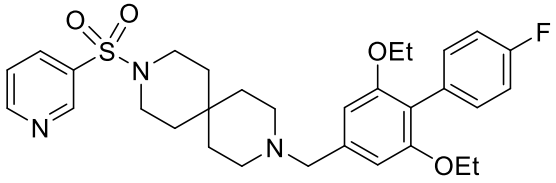


Synthesis of tert-butyl 9-((2,6-diethoxy-4'-fluoro-[1,1'-biphenyl]-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate (**4a**)



To a solution of tert-butyl 3,9-diazaspiro[5.5]undecane-3-carboxylate (100 mg, 0.39 mmol) in DMF (2 ml) was added 4-(chloromethyl)-2,6-diethoxy-4'-fluorobiphenyl (**14**) (120 mg, 0.39 mmol), and cesium carbonate (380 mg, 1.17 mmol). The mixture was stirred at room temperature overnight, diluted with water (5 mL), and extracted with EtOAc (3x10 mL). The organic extracts were combined, dried over $MgSO_4$ and concentrated to dryness. The residue was purified by silica gel column, eluting with EtOAc/Hexane gradient 0-100% to give product (178 mg, 87%) as a tan solid. LC-MS *m/z*: $[M+H]^+$ 527.4.

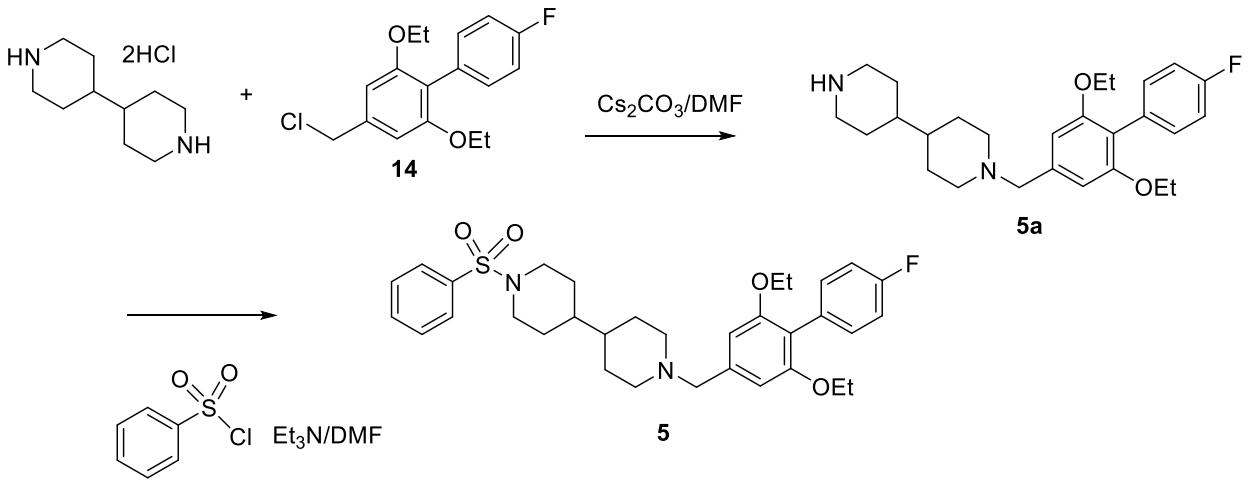
Synthesis of 3-((2,6-diethoxy-4'-fluoro-[1,1'-biphenyl]-4-yl)methyl)-9-(pyridin-3-ylsulfonyl)-3,9-diazaspiro[5.5]undecane (**4**)



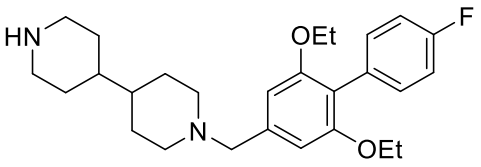
To a solution of tert-butyl 9-((2,6-diethoxy-4'-fluoro-[1,1'-biphenyl]-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate (**4a**) (150 mg, 0.28 mmol) in dichloromethane (3 mL) was added TFA (2 mL). The mixture was stirred at room temperature for 2 hours and concentrated to dryness under nitrogen. The resulting residue was re-dissolved in DMF (1.5 mL) followed by addition of triethylamine

(141 mg, 1.4 mmol) and pyridine-3-sulfonyl chloride (50 mg, 0.28 mmol). The mixture was stirred at RT overnight and injected directly to Prep HPLC for purification. Fractions containing correct molecular weight were collected and freeze-dried to obtain final product as a white powder. LC-MS for $[C_{31}H_{39}FN_3O_4S]^+$ *m/z*: $[M+H]^+$ calc: 568.3; found: 568.4.

Compound **5**

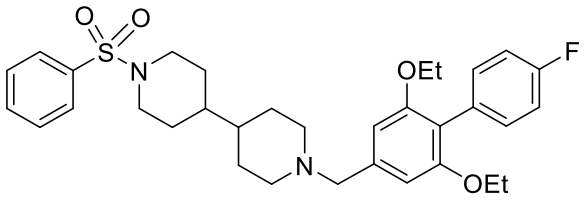


Synthesis of 1-((2,6-diethoxy-4'-fluoro-[1,1'-biphenyl]-4-yl)methyl)-4,4'-bipiperidine (**5a**)



To a solution of 4,4'-bipiperidine (200 mg, 1.2 mmol) in DMF (2 mL) was added 4-(chloromethyl)-2,6-diethoxy-4'-fluoro-1,1'-biphenyl (**14**) (100 mg, 0.3 mmol) and cesium carbonate (390 mg, 1.2 mmol). The mixture was stirred at room temperature for 4 hours, diluted with water (5 mL) and extracted with EtOAc (3x5 mL). The organic extracts were combined, dried over $MgSO_4$ and concentrated to dryness. The residue was purified by silica gel column chromatography eluting with Hexane/EtOAc gradient (0-100%) to obtain product as a white solid (120 mg, 88%). LC-MS *m/z*: $[M+H]^+$ 441.4

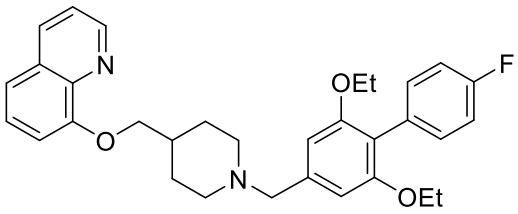
Synthesis of 1-((2,6-diethoxy-4'-fluoro-[1,1'-biphenyl]-4-yl)methyl)-1'-(phenylsulfonyl)-4,4'-bipiperidine (**5**)



To a solution of 1-((2,6-diethoxy-4'-fluoro-[1,1'-biphenyl]-4-yl)methyl)-4,4'-bipiperidine (**5a**) (120 mg, 0.28 mmol) in diethyl ether (5 mL) was added triethyl amine (84 mg, 0.83 mmol) followed by benzenesulfonyl chloride (74 mg, 0.42 mmol). The mixture was stirred at room temperature for 2 hours and concentrated to dryness. The residue was purified by silica gel column chromatography eluting with DCM/MeOH gradient (0-5%) to obtain product (110 mg, 68%). ^{1}H-NMR ($CDCl_3$) δppm: 7.79 (d, *J* = 8 Hz, 2H), 7.63 (m, 1H), 7.58 (d, *J* = 8 Hz, 2H), 7.32 (m, 2H), 7.18 (m, 2H), 6.65 (S, 2H), 4.14 (brs, 2H), 3.98 (m, 4H), 3.83 (m, 2H), 3.64 (m, 2H), 2.62 (m, 2H), 2.21 (m, 2H), 2.12 (b, 2H), 1.92 (m, 2H), 1.80 (m, 3H), 1.32 (m, 3H), 1.25 (t, *J* = 7 Hz, 6H). LC-MS *m/z*: $[M+H]^+$ 581.3. ^{13}C-NMR (DMSO-d_6) δppm: 169.6, 162.4, 160.5, 156.8, 135.9, 133.6, 133.2, 133.1, 131.0, 129.9, 129.8, 127.7, 119.3, 114.8, 114.6, 108.7, 64.4, 59.9, 52.3, 46.7, 37.8, 28.3, 26.4, 14.9. HRMS (ESI) (*m/z*): calculated for $[C_{33}H_{41}FN_2O_4S+H]^+$: 581.2849, found: 581.2843.

Compound **6**

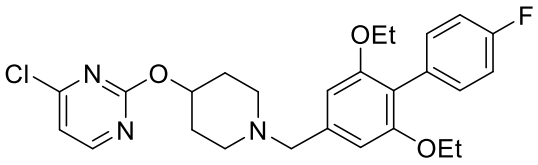
Synthesis of 8-((1-((2,6-diethoxy-4'-fluoro-[1,1'-biphenyl]-4-yl)methyl)piperidin-4-yl)methoxy)quinolone (**6**)



To a solution of 8-(piperidin-4-ylmethoxy)quinoline (39 mg, 0.16 mmol) in DMSO (1 mL) was added 4-(chloromethyl)-2,6-diethoxy-4'-fluoro-1,1'-biphenyl (**14**) (50 mg, 0.16 mmol) and cesium carbonate (100 mg, 0.32 mmol). The mixture was stirred at RT for 4 hours and filtered. The filtrate was injected directly to Prep HPLC for purification to obtain product as a while solid (20 mg, 24%). ^{1}H-NMR (CD_3OD) δppm: 9.05~9.12 (m, 2H), 8.03~8.08 (m, 1H), 7.85~7.90 (m, 2H), 7.60~7.63 (m, 1H), 7.27~7.32 (m, 2H), 7.05~7.11 (s, 2H), 6.90 (s, 2H), 4.32~4.48 (m, 4H), 4.00~4.07 (m, 2H), 2.27~2.41 (m, 3H), 1.93~2.05 (m, 2H), 1.26 (t, *J*=6.9Hz, 6H). LC-MS for $[C_{32}H_{36}FN_2O_3]$+ *m/z*: $[M+H]^+$ calc: 515.3; found: 515.5.

Compound **7**

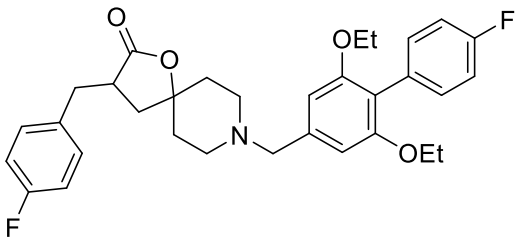
Synthesis of 2-((1-((2,6-diethoxy-4'-fluoro-[1,1'-biphenyl]-4-yl)methyl)piperidin-4-yl)oxy)-4-methylpyridine (**7**)



This compound was prepared as part of a 12 compound library as described below: All reagents: 4-chloro-2-(piperidin-4-yloxy)pyrimidine (14 mg, 0.065 mmol), 4-(chloromethyl)-2,6-diethoxy-4'-fluoro-1,1'-biphenyl (**14**) (20 mg, 0.065 mmol), and cesium carbonate (42 mg, 0.13 mmol) were dissolved in DMF and allowed to stir overnight at room temperature, added 0.5 mL water and allowed to stir for one hour, then added 0.5 mL ethyl acetate and allowed to stir for 15 minutes. Retained organic layer and removed solvent under a stream of nitrogen, then purified using a 20 minute HPLC gradient to obtain the product (7.9 mg, 25%) . LC-MS for $[C_{26}H_{30}ClFN_3O_3]^+$ *m/z*: $[M+H]^+$ calc: 486.2; found: 486.0

Compound **8**

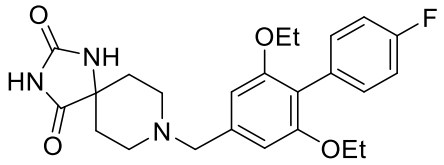
Synthesis of 8-((2,6-diethoxy-4'-fluoro-[1,1'-biphenyl]-4-yl)methyl)-3-(4-fluorobenzyl)-1-oxa-8-azaspiro[4.5]decan-2-one (racemic) (**8**)



To a solution of 3-(4-fluorobenzyl)-1-oxa-8-azaspiro[4.5]decan-2-one (30 mg, 0.114 mmol) in DMF (1 ml) was added 4-(chloromethyl)-2,6-diethoxy-4'-fluoro-1,1'-biphenyl (**14**) (35 mg, 0.114 mmol) and cesium carbonate (110 mg, 0.34 mmol). The mixture was stirred at room teperature overnight, diluted with water (2 mL) and extracted with EtOAc (2x5 mL). The organic extracts were combined, dried over $MgSO_4$ and concentrated to dryness. The residue was purified by Prep-HPLC to obtain product as a while solid (38 mg, 59%). ^{1}H-NMR ($CDCl_3$) δppm: 8.47 (s, 1H), 7.29 (m, 2H), 7.21 (m, 2H), 7.01-7.18 (m, 4H), 6.67 (s, 2H), 4.01 (m , 4H), 3.82 (s , 2H), 3.21 (m, 1H), 3.05 (m, 2H), 2.70-2.90(m, 2H), 2.05-2.20 (m, 2H),1.70-1.90 (m, 2H),1.30 (t, *J* = 7 Hz, 6H). LC-MS for $[C_{32}H_{36}F_2NO_4]^+$ *m/z*: $[M+H]^+$ calc: 536.3; found: 536.1.

Compound **9**

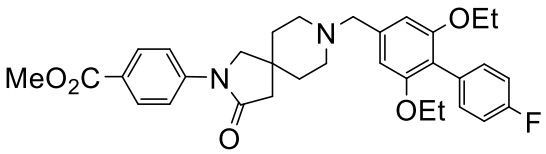
Synthesis of 8-((2,6-diethoxy-4'-fluoro-[1,1'-biphenyl]-4-yl)methyl)-1,3,8-triazaspiro[4.5]decane-2,4-dione (**9**)



To a solution of 1,3,8-triazaspiro[4.5]decane-2,4-dione (50 mg, 0.28 mmol) in DMF (2 ml) was added 3,5-diethoxy-4-(4'-fluorophenyl)benzaldehyde (**14d**) (80 mg, 0.28 mmol) and trimethylamine (280 mg, 2.8 mmol). The mixture was stirred at room teperature for 30 min followed by addition of acetic acid (50 mg, 0.84 mmol) and sodium triacetoxyborohydride (86 mg, 0.4 mmol) portion wise. The mixture was then stirred at room teperature overnight, diluted with water (20 mL) and extracted with EtOAc (3x10 mL). The organic extracts were combined, dried over $MgSO_4$ and concentrated to dryness. The residue was purified by prep-HPLC to give product as a while solid (32 mg, 26%)). ^{1}H-NMR (DMSO-d_6) δppm：7.24~7.26 (m, 2H), 7.05~7.08 (m, 2H), 6.93 (m, 2H), 4.29~4.32 (m, 2H), 4.00~4.03 (m, 4H), 3.65~3.68 (m, 1H), 3.48~3.52 (m, 2H), 3.29~3.31 (m, 1H), 1.91~2.29 (m, 4H), 1.22 (t, *J*=7.2Hz, 6H). LC-MS *m/z*: $[M+H]^+$ 442.3. ^{13}C-NMR (DMSO-d_6) δppm: 162.1, 160.5, 156.9, 133.2, 133.1, 114.8, 114.6, 109.0, 64.4, 47.9, 14.9. HRMS (ESI): (*m/z*): calculated for $[C_{24}H_{28}FN_3O_4+H]^+$: 442.2142, found: 442.2143.

Compound **10**

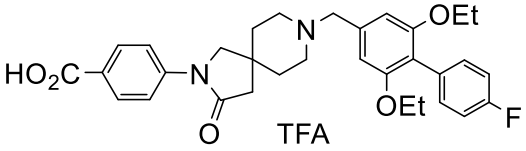
Synthesis of Methyl 4-{8-[(2,6-diethoxy-4'-fluorobiphenyl-4-yl)methyl]-3-oxo-2,8-diazaspiro [4.5]dec-2-yl}benzoate trifluoromethyl acetate



To a solution of methyl 4-(3-oxo-2,8-diazaspiro[4.5]dec-2-yl)benzoate hydrochloride (**13**) (1.4 g, 3.48 mmol) in DMF (10 mL) was added of 4-(chloromethyl)-2,6-diethoxy-4'-fluorobiphenyl (**14**) (1,29 g, 4.18 mmol) and DIEA (1.35 g, 10.44 mmol). The reaction mixture was stirred at RT overnight, diluted with water (5 mL) and extracted with EtOAc. The organic layer was separated, dried over sodium sulfate,

filtered and concentrated. The resulting crude material was purified by flash SiO_2 column chromatography eluding with dichloromethane and methanol (10:1) to give a brown solid (1.95 g, 86%) . ^{1}H-NMR (CD_3OD) δppm: 8.04 (b, 2H), 7.8 (b, 2H), 7.28 (m, 2H), 7.09 (m, 2H), 6.84 (s, 2H), 4.35 (s, 2H), 4.0 (m, 4H), 3.9 (s, 3H), 3.2-3.6 (b, 4H), 2.2-2.6 (b, 2H),1.9-2.2 (b, 4H),1.25 (t, *J* = 7 Hz, 6H). LC-MS *m/z*: $[M+H]^+$ 561.3.

Synthesis of 4-{8-[(2,6-diethoxy-4'-fluorobiphenyl-4-yl)methyl]-3-oxo-2,8-diazaspiro[4.5]dec-2-yl}benzoic acid trifluoromethyl acetate (**10**)

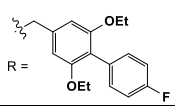
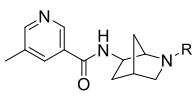


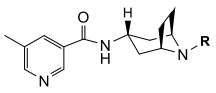
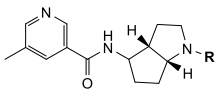
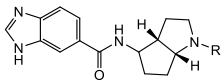
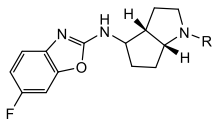
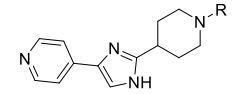
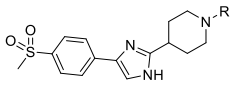
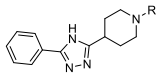
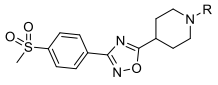
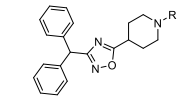
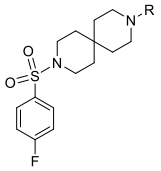
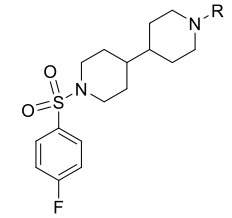
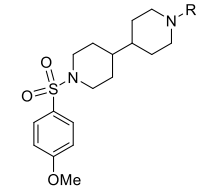
To a vial was added methyl 4-{8-[(2,6-diethoxy-4'-fluorobiphenyl-4-yl)methyl]-3-oxo-2,8-diazaspiro [4.5]dec-2-yl}benzoate trifluoromethyl acetic acid salt (673 mg, 1.2 mmol); LiOH (172 mg, 7.2 mmol); 8 mL MeOH; and 0.5 mL water. The resulting reaction mixture was heated at 50 °C overnight, then the volatiles were removed. The resulting residue was acidified with TFA and purified by HPLC with a reverse phase column by eluting with a gradient of 90/10 to 10/90 of water/acetonitrile (containing 0.1% TFA) as the eluent to give the title compound (630 mg, 79%). ^{1}H-NMR (CD_3OD) δppm: 8.05 (d, *J* = 8.8 Hz, 2H), 7.77 (d, *J* = 8.8 Hz, 2H), 7.27 (m, 2H), 7.08 (m, 2H), 6.84 (s, 2H), 4.3 (s, 2H), 4.03 (q, *J* = 7.0 Hz, 4H), 3.9 (b, 2H), 3.3 (b, 4H), 2.7 (b, 2H), 2.04 (b, 4H), 1.25 (t, *J* = 7 Hz, 6H). ^{13}C-NMR (DMSO-d_6) δppm: 167.3, 157.8, 133.2, 133.1, 130.6, 119.0, 114.8, 114.6, 64.4, 15.0. HRMS (ESI): (*m/z*): calculated for $[C_{32}H_{35}FN_2O_5+H]^+$: 547.2608, found: 547.2606.

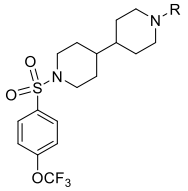
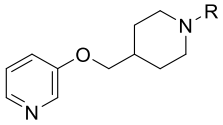
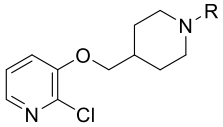
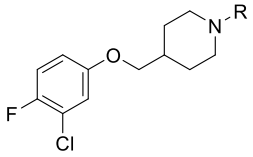
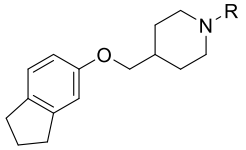
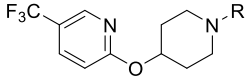
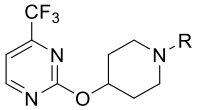
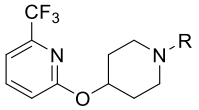
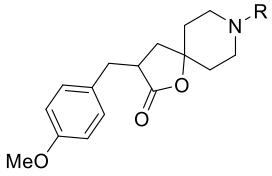
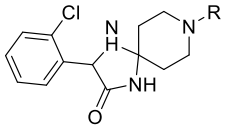
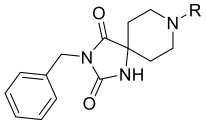
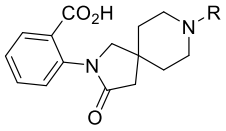
2) **SAR Table of representative analogs**

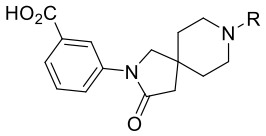
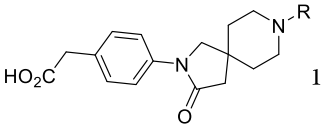
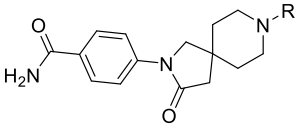
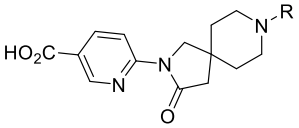
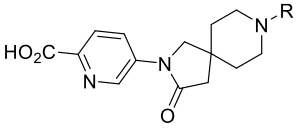
Using the methods and intermediates outlined above, the additional anlogues listed in table S1 were prepared and evaluated to further inform the SSTR5 antagonist SAR of this lead series.

Table S1. Representative analogs synthesized during lead discovery of compound 2-10

ID	Structure	hSSTR5 Binding[a] IC_{50} (nM)	hSSTR5 cAMP[b] IC_{50} (nM)	LC-MS Parent ion *m/z*, $[M+H]^+$
	R = 			
S1		619	12600	504.1

S2		12.5	451	518.1
S3		6.7	113	518.1
S4		61	196	543.2
S5		7.2	372	534.3
S6		2.5	44	501.2
S7		2.8	41	578.3
S8		8.5	78	501.2
S9		727	1390	580.2
S10		44	81	592.2
S11		4.9	85	585.2
S12		0.58	22	599.3
S13		0.50	16.5	611.2

S14		1.0	5.4	665.3
S15		3.9	63	465.1
S16		7.1	54	499.1
S17		36	567	516.1
S18		87	2447	504.3
S19		208	3000	519.3
S20		117	559	520.2
S21		173	3790	519.4
S22		1.3	43	548.2
S23		17.7	84	538.9
S24		30.7	110	518.2
S25		49.1	515	547.0

S26		6.4	49.4	547.4
S27		17.1	26.7	561.3
S28		8.7	32.5	546.3
S29		7.7	4.7	548.3
S30		5.2	6.1	548.3

[a] IC50 values were calculated as the mean of duplicate experiments.
[b] Activity against human SSTR5.

Table S2. Physical chemical properties of compound **1-10**

ID	MW	cLogD[a]	LE[b]	LLE[c]	BEI[d]	Solubility, pH 7[e] (μM)	PSA[f] (Å^2)
1	491.61	3.96	0.34	4.91	18.05	75.5	67.4
2	559.64	2.90	0.24	4.29	12.86	74.0	106.1
3	517.62	5.22	0.29	2.90	15.69		51.9
4	567.73	4.25	0.27	3.65	13.91		78.3
5	580.77	6.22	0.31	2.97	15.82		65.4
6	514.64	5.95	0.31	2.58	16.58		46.7
7	485.99	4.80	0.31	2.88	15.79		57.5
8	535.64	5.38	0.31	3.42	16.42		53.1
9	441.51	2.90	0.30	4.18	16.04	57	97.6
10	546.64	2.36	0.30	6.31	15.85	152	88.2

[a] Calculated LogD at pH 7.4, from ACD labs software
[b] LE, ligand efficiency, based on hSSTR5 binding potency
[c] LLE, lipophilic ligand efficieny, based on cLogD data from ACD labs
[d] BEI, binding efficiency index, based on hSSTR5 binding potency
[e] Solubility measured in phosphate-buffered saline at pH7
[f] PSA, calculated polar surface area, calculated from ACD labs

3) In Vitro Assays

SSTR Binding Assays:

The receptor-ligand binding assays of all 5 subtype of SSTRs were performed with membranes isolated from Chinese hamster ovary (CHO)-K1 cells stably expressing the cloned human somatostatin receptors in 96-well format as previously reported. (Yang *et al. PNAS 95*:10836-10841, (1998), Birzin *et al. Anal. Biochem.307*:159-166, (2002)).

The stable cell lines for SSTR1-SSTR5 were developed by stably transfecting with DNA for all five *SSTRs* using Lipofectamine. Neomycin-resistant clones were selected and maintained in medium containing 400 μg/mL G418 (Rohrer *et al. Science 282*:737–740, (1998)). Binding assays were performed using (3-^{125}I-Tyr11)-SRIF-14 or (3-^{125}I-Tyr11)-SRIF-28 as the radioligand (used at 0.1 nM) and The Packard Unifilter assay plate. The assay buffer consisted of 50 mM TrisHCl (pH 7.8) with 1 mM EGTA, 5 mM $MgCl_2$, leupeptin (10 μg/mL), pepstatin (10 μg/mL), bacitracin (200 μg/mL), and aprotinin (0.5 μg/mL). CHO-K1 cell membranes, radiolabeled somatostatin, and unlabeled test compounds were resuspended or diluted in this assay buffer. Unlabeled test compounds were examined over a range of

concentrations from 0.01 nM to 10,000 nM. The K_i values for compounds were determined as described by Cheng and Prusoff, *Biochem Pharmacol. 22*:3099–3108 (1973).

Functional Assay to Assess the Inhibition of SSTR5 Mediated Cyclic AMP Production:

The effects of compounds that bind to human and murine SSTR5 with various affinities on the functional activity of the receptor were assessed by measuring cAMP production in the presence of Forskolin (FSK) alone or FSK plus SS-28 in SSTR5 expressing CHO cells. FSK acts to induce cAMP production in these cells by activating adenylate cyclases, whereas SS-28 suppresses cAMP production in the SSTR5 stable cells by binding to SSTR5 and the subsequent inhibition of adenylate cyclases via an alpha subunit of GTP-binding protein (Gαi).

To measure the agonism activity of the compounds, human or mouse SSTR5 stable CHO cells were pre-incubated with the compounds for 15 min, followed by a one-hour incubation of the cells with 5 μM FSK (in the continuous presence of the compounds). The amount of cAMP produced during the incubation was quantified with the Lance cAMP assay kit (PerkinElmer, CA) according to the manufacturer's instruction, as well as, an IC_{50} value was obtained by an eight-point titration.

Enhancement of Glucose Dependent Insulin Secretion (GDIS) by SSTR5 antagonists in Isolated Mouse Islet Cells:

Pancreatic islets of Langerhans were isolated from the pancreas of normal C57BL/6J mice (Jackson Laboratory, Maine) by collagenase digestion and discontinuous Ficoll gradient separation, a modification of the original method of Lacy and Kostianovsky (Lacy *et al., Diabetes 16*:35-39, 1967). The islets were cultured overnight in RPMI 1640 medium (11 mM glucose) before GDIS assay.

To measure GDIS, islets were first preincubated for 30 minutes in the Krebs-Ringer bicarbonate (KRB) buffer with 2 mM glucose (in petri dishes). The KRB medium contains 143.5 mM Na^+, 5.8 mM K^+, 2.5 mM Ca^{2+}, 1.2 mM Mg^{2+}, 124.1 mM Cl^-, 1.2 mM PO_4^{3-}, 1.2 mM SO_4^{2+}, 25 mM CO_3^{2-}, 2 mg/mL bovine serum albumin (pH 7.4). The islets were then transferred to a 96-well plate (one islet/well) and incubated at 37 °C for 60 minutes in 200 μl of KRB buffer with 2 or 16 mM glucose, and other agents to be tested such as octreotide and a SST3 antagonist. (Zhou *et al., J. Biol. Chem. 278*:51316-51323, 2003.) Insulin was measured in aliquots of the incubation buffer by ELISA with a commercial kit (ALPCO Diagnostics, Windham, NH).

4) In Vivo Assays

Materials and Methods

All experimental protocols described in this study were approved by the Merck and Co., Inc. Institutional Animal Care and Use Committee and conducted in accordance with the Guide for Care and Use of Laboratory Animals (Institute of Laboratory Animal Resources, 1996). All efforts were made to minimize animal suffering, to reduce the number of animals used and to use alternatives to in vivo methods where possible. Specific details of species, strain, and weight are given within the methods for each section. Rats, mouse, rhesus, and beagle dogs were used in these studies in order to determine whether the effects of SSTR5 antagonists are similar across species. We believe that examining the effects of SSTR5 in multiple species increases our confidence that the compound might have effects in additional species, such as humans. Temperature and relative humidity were maintained at 21–24 °C and 50–55 %, respectively. Food and water were available ad libitum unless otherwise noted.

Glucose Tolerance Test in Mice:

Male C57BL/6N mice (7-12 weeks of age) are housed 10 per cage and given access to normal diet rodent chow and water *ad libitum*. Mice are randomly assigned to treatment groups and fasted 4 to 6 h. Baseline blood glucose concentrations are determined by glucometer from tail nick blood. Animals are then treated orally with vehicle (0.5% methylcellulose) or test compound. Blood glucose concentration is measured at a set time point after treatment (t = 0 min) and mice are then challenged with dextrose orally (3-5 g/kg). One group of vehicle-treated mice is challenged with saline as a negative control. Blood glucose levels are determined from tail bleeds taken at 20, 40, 60 minutes after dextrose challenge. The blood glucose excursion profile from t = 0 to t = 120 min is used to integrate an area under the curve (AUC) for each treatment. Percent inhibition values for each treatment are generated from the AUC data normalized to the vehicle-challenged controls.

5) Figure S1, SSTR5 antagonist study in WT and KO mice

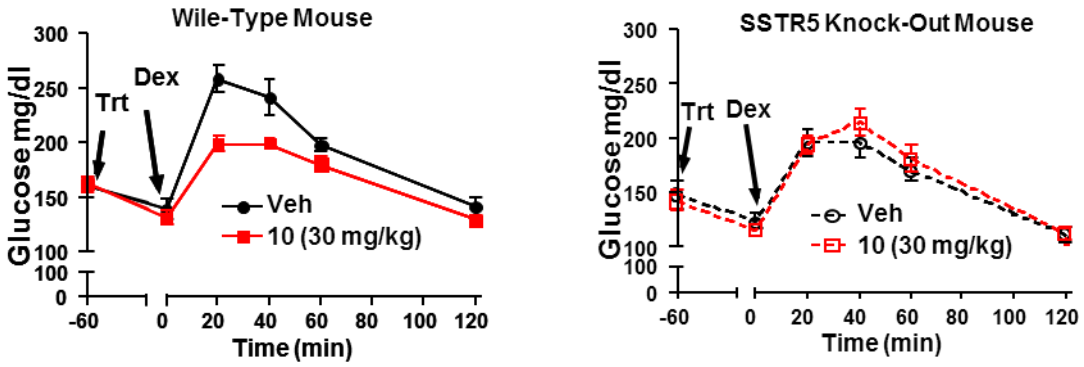
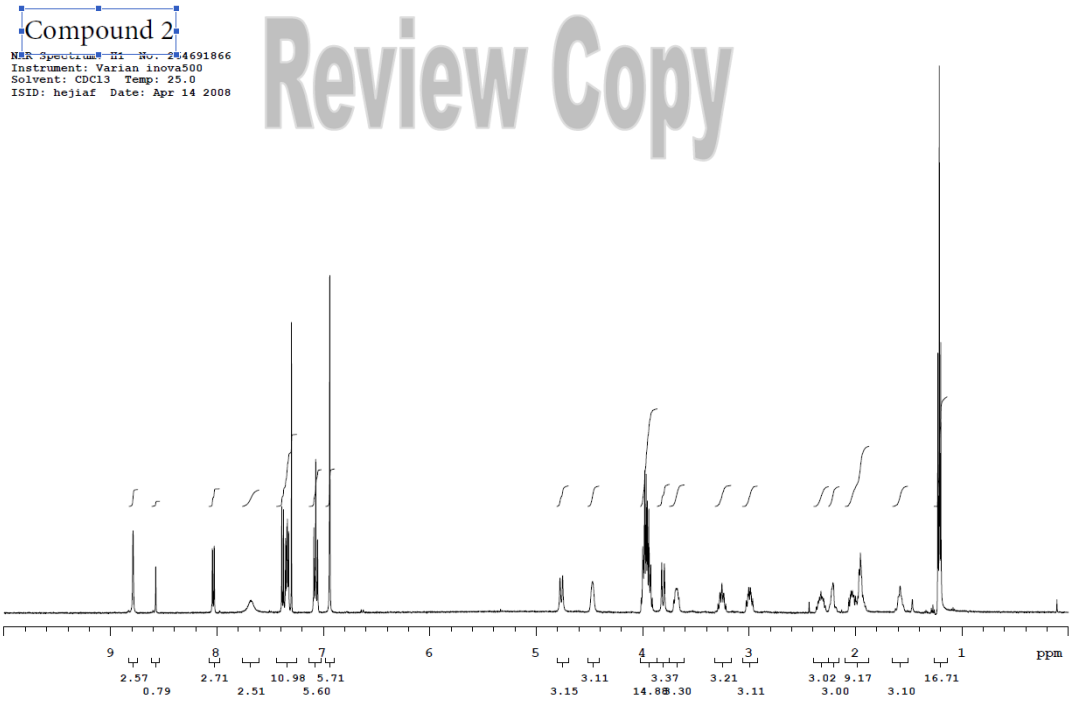
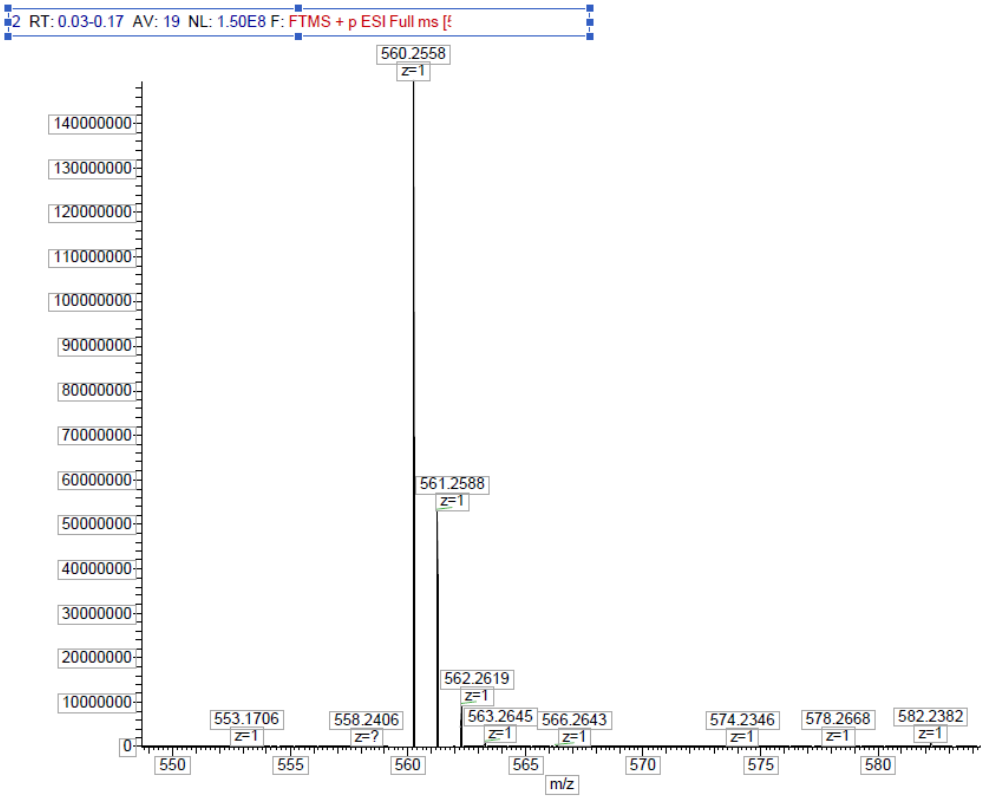


Figure S1. SSTR5 antagonist (compound **10**) reduces glucose excursion in HFD WT mouse OGTT, and the effect is fully ablated in the SSTR5 KO mouse

6) ^{1}H-MMR and HRMS of key compounds

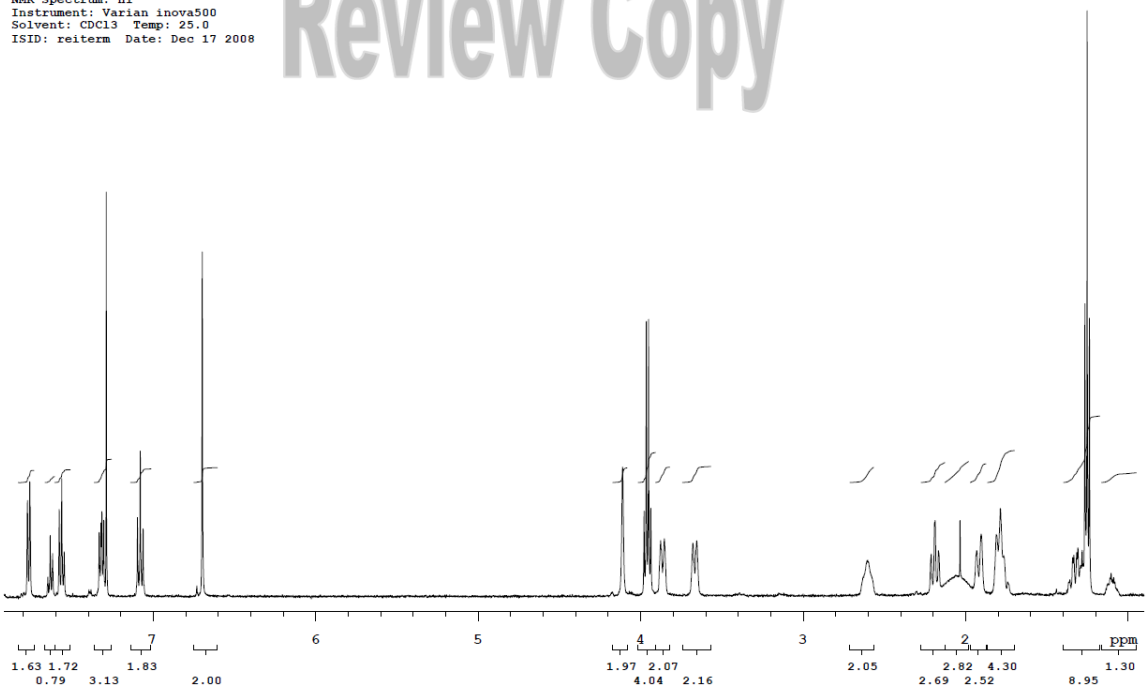


HRMass spectrum of Compound 2

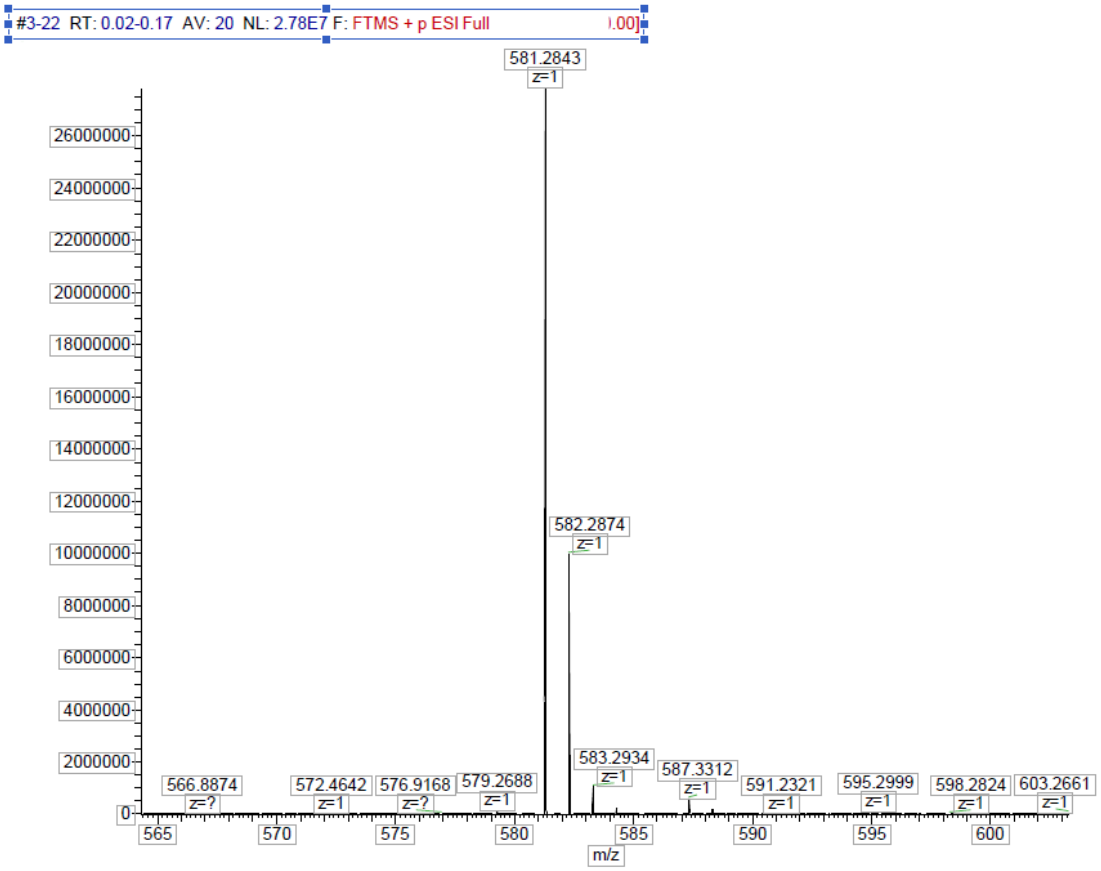


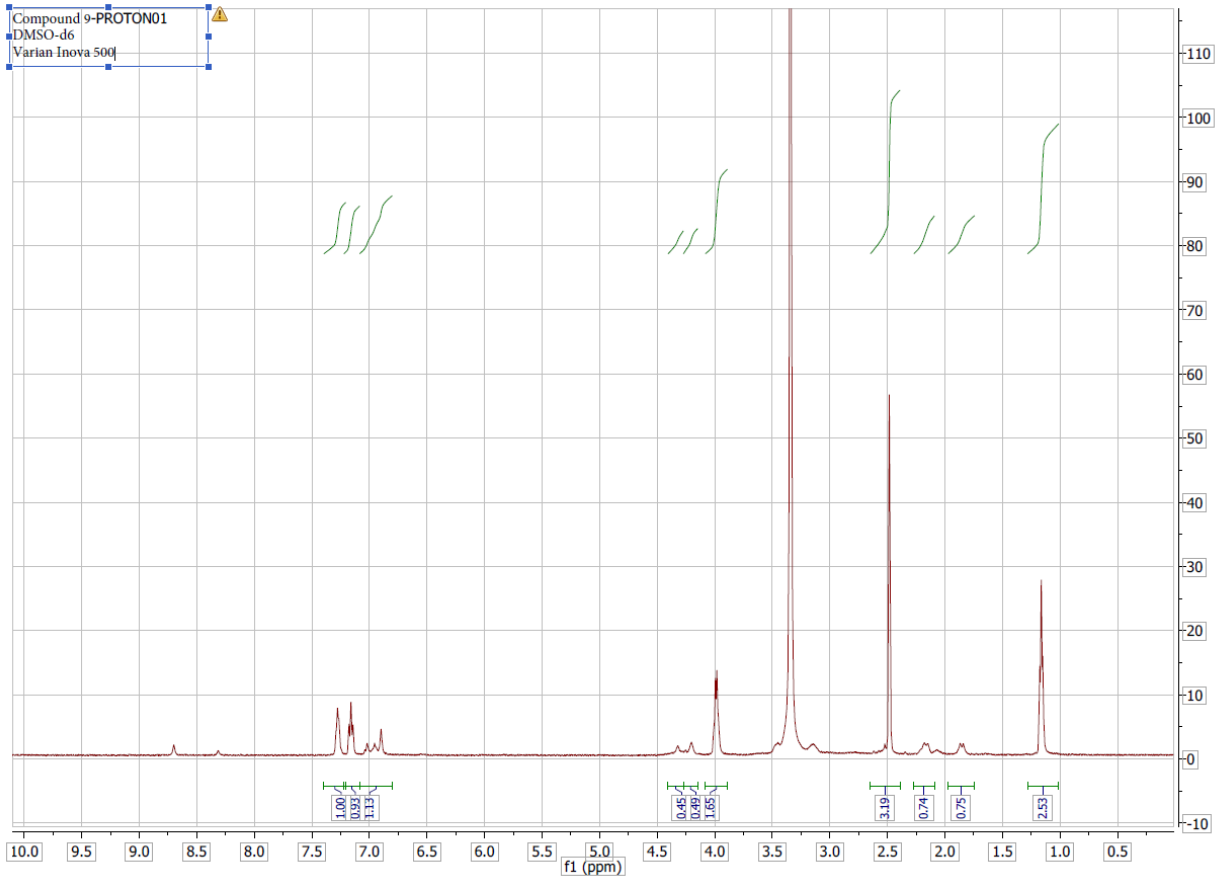
Compound 5

NMR Spectrum: H1
Instrument: Varian inova500
Solvent: CDCl3 Temp: 25.0
ISID: reiterm Date: Dec 17 2008

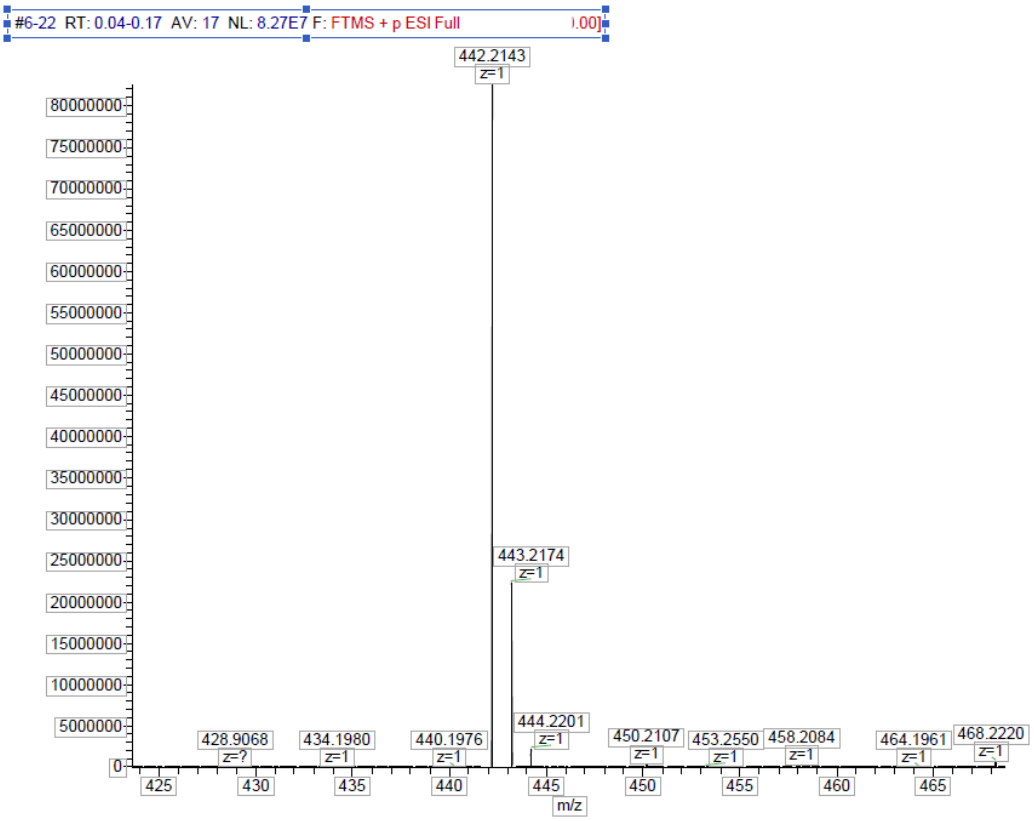


HRMass spectrum of Compound 5




Compound 9-PROTON01
DMSO-d6
Varian Inova 500
1.00
0.93
1.13
0.45
0.49
1.65
3.19
0.74
0.75
2.53
f1 (ppm)

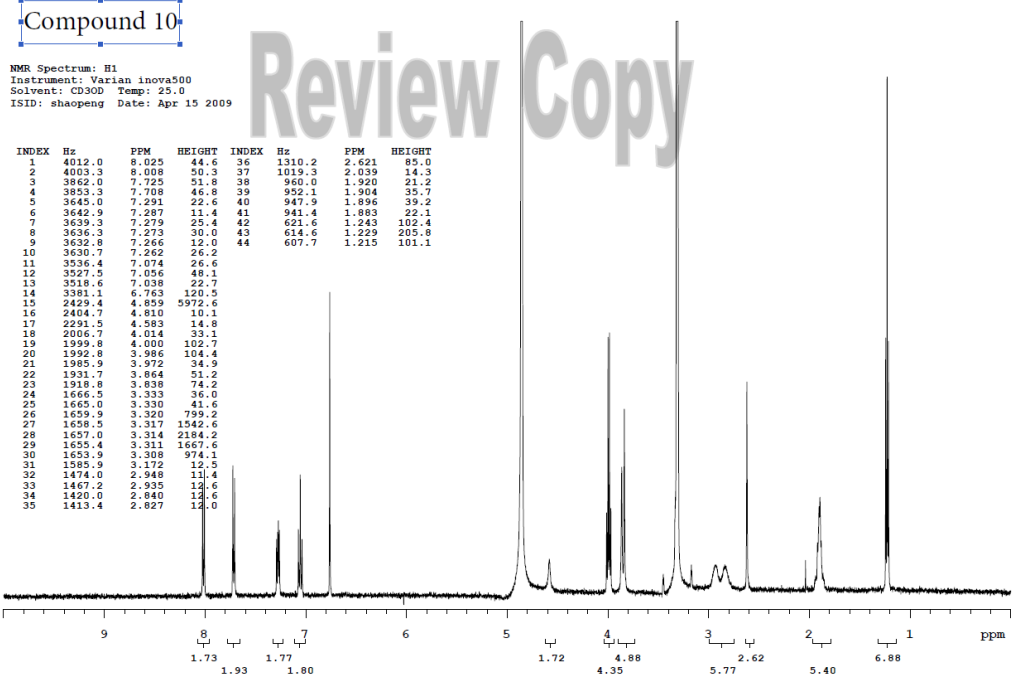
HRMass spectrum of Compound 9

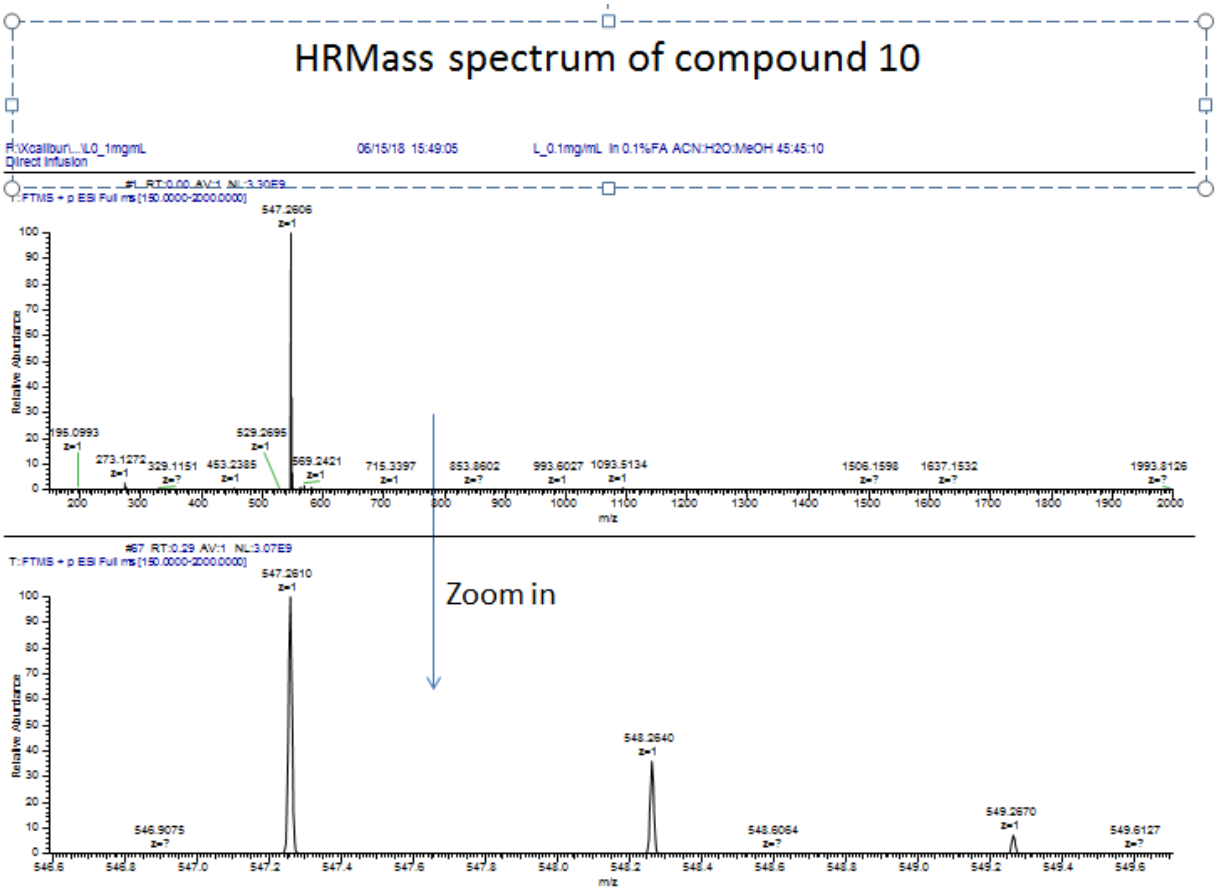


Compound 10

NMR Spectrum: H1
Instrument: Varian inova500
Solvent: CD3OD Temp: 25.0
ISID: shaopeng Date: Apr 15 2009

INDEX	Hz	PPM	HEIGHT	INDEX	Hz	PPM	HEIGHT
1	4012.0	8.025	44.6	36	1310.2	2.621	85.0
2	4003.3	8.008	50.3	37	1019.3	2.039	14.3
3	3862.0	7.725	51.8	38	960.0	1.920	21.2
4	3853.3	7.708	46.8	39	952.1	1.904	35.7
5	3645.0	7.291	22.6	40	947.9	1.896	39.2
6	3642.9	7.287	11.4	41	941.4	1.883	22.1
7	3639.3	7.279	25.4	42	621.6	1.243	102.4
8	3636.3	7.273	30.0	43	614.6	1.229	205.8
9	3632.8	7.266	12.0	44	607.7	1.215	101.1
10	3630.7	7.262	26.2				
11	3536.4	7.074	26.6				
12	3527.5	7.056	48.1				
13	3518.6	7.038	22.7				
14	3381.1	6.763	120.5				
15	2429.4	4.859	5972.6				
16	2404.7	4.810	10.1				
17	2291.5	4.583	14.8				
18	2006.7	4.014	33.1				
19	1999.8	4.000	102.7				
20	1992.8	3.986	104.4				
21	1985.9	3.972	34.9				
22	1931.7	3.864	51.2				
23	1918.8	3.838	74.2				
24	1666.5	3.333	36.0				
25	1665.0	3.330	41.6				
26	1659.9	3.320	799.2				
27	1658.5	3.317	1542.6				
28	1657.0	3.314	2184.2				
29	1655.4	3.311	1667.6				
30	1653.9	3.308	974.1				
31	1585.9	3.172	12.5				
32	1474.0	2.948	11.4				
33	1467.2	2.935	12.6				
34	1420.0	2.840	14.6				
35	1413.4	2.827	12.0				




HRMass spectrum of compound 10
R:\Xcalibur\...\L0_1mgmL
06/15/18 15:49:05
L_0.1mg/mL In 0.1%FA ACN:H2O:MeOH 45:45:10
Direct Infusion
#1 RT:0.00 AV:1 NL:3.30E9
T:FTMS + p ESI Full ms [150.0000-2000.0000]
547.2606
z=1
Relative Abundance
m/z
Zoom in
#67 RT:0.29 AV:1 NL:3.07E9
T:FTMS + p ESI Full ms [150.0000-2000.0000]
547.2610
z=1
548.2640
z=1
549.2670
z=1
546.9075
549.6127