Synthesis and Pharmacological Evaluation of Fluorine Containing D_3 Dopamine Receptor Ligands

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Contents of Supporting Information:

1. Supplemental Experimental Section

General Method of Preparing 2-Fluoroethoxy Substituted Benzoic Acids (9a-e)

4-(2-Fluoroethoxy)benzoic acid (9a). 4-Hydroxyl benzoic acid, **8a** (2.76 g, 20 mmol) was dissolved in 60 mL methanol, and 10 mL concentrated sulfuric acid (98%) was carefully added to the above solution while stirring. After the reaction mixture was refluxed overnight, the excess methanol was removed by using rotary evaporator under reduced pressure. The residue was neutralized with 1.0 N aqueous NaOH solution to pH = 7 and extracted with ethyl acetate (30 mL). The combined extracts were dried over Na_2SO_4 and then concentrated under reduced pressure. The residue was purified on silica gel column using ethyl acetate/hexane (30/70, v/v) as mobile phase to afford the intermediate, methyl 4-hydroxybenzoate as a white solid (2.03 g, 67%). ^{1}H NMR ($CDCl_3$): δ 3.89 (s, 3H), 6.87 (d, *J* = 9.3 Hz, 2H), 7.96 (d, *J* =9.3 Hz, 2H).

Methyl 4-hydroxybenzoate (0.304 g, 2.0 mmol) and 1-bromo-2-fluoroethane (1.63 g, 13 mmol) were dissolved in 50 mL acetone and potassium carbonate (1.78 g, 13 mmol) was added to the above solution. The reaction mixture was refluxed overnight until TLC indicated the reaction was complete. Volatiles were removed under reduced pressure. The residue was dissolved into ethyl acetate (60 mL), washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified on silica gel column using ethyl acetate/hexane (20/80, v/v) as mobile phase to afford the intermediate, methyl 4-(2-fluoroethoxy)benzoate (375 mg, 95%) as a colorless grease. ^{1}H NMR ($CDCl_3$): δ 3.89 (s, 3H), 4.22 (t, *J* = 4.2 Hz, 1H), 4.31 (t, *J* = 4.2 Hz, 1H), 4.70 (t, *J* = 4.1 Hz, 1H), 4.86 (t, *J* = 4.2 Hz, 1H), 6.94 (d, *J* = 9.0 Hz, 2H), 8.00 (d, *J* = 9.3 Hz, 2H).

Methyl 4-(2-fluoroethoxy)benzoate (1.72 g, 8.7 mmol) was dissolved in 30 mL methanol. 15 mL water was added to above solution followed by NaOH (1.6 g, 40 mmol). The reaction mixture was stirred overnight at ambient temperature and was determined to be complete by TLC. The mixture was adjusted to pH = 2 by adding aqueous 6 N HCl. After removing the solvent, the residue was extracted with ethyl acetate (3 x 30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under less pressure to afford **9a** (1.3 g, 81%). ^{1}H NMR ($CDCl_3$): δ 4.24 (t, *J* = 4.0 Hz, 1H), 4.34 (t, *J* = 4.2 Hz, 1H), 4.71 (t, *J* = 4.2 Hz, 1H), 4.87 (t, *J* = 4.1 Hz, 1H), 6.98 (d, *J* = 4.5 Hz, 2H), 8.07 (d, *J* = 9.3, 2H).

2-(2-Fluoroethoxy)-5-methylbenzoic acid (9b). The same procedure was followed to afford **9b.** Yield: 80%. ^{1}H NMR ($CDCl_3$): δ 2.34 (s, 3H), 4.41 (t, *J* = 4.1 Hz, 1H), 4.49 (t, *J* = 4.1 Hz, 1H), 4.75 (t, *J* = 4.1 Hz, 1H), 4.91 (t, *J* = 4.2 Hz, 1H), 6.94 (d, *J* = 7.2 Hz, 1H), 7.38 - 7.41 (m, 1H), 8.00 (d, *J* = 3.2 Hz, 1H).

5-Bromo-2-(2-fluoroethoxy)benzoic acid (9c). The same procedure was followed to afford **9c.** Yield: 70%. ^{1}H NMR ($CDCl_3$): δ 4.40 - 4.46 (m, 1H), 4.49 - 4.54 (m, 1H), 4.75 - 4.80 (m, 1H), 4.91 - 4.96 (m, 1H); 6.98 (d, *J* = 4.5 Hz, 1H), 7.62 - 7.72 (q, 1H), 8.28 - 8.34 (m, 1H), 10.6 (br s, 1H).

2-(2-Fluoroethoxy)-5-iodobenzoic acid (9d). The same procedure was followed to afford **9d.** Yield: 94%. ^{1}H NMR ($CDCl_3$): δ 4.42 (t, *J* = 4.1 Hz, 1H), 4.51 (t, *J* = 3.9 Hz, 1H), 4.78 (t, *J* = 3.9 Hz, 1H), 4.94 (t, *J*=4.1, 1H), 8.20 (d, *J* = 9.0, 1H), 8.44 (dd, *J* = 2.1, 8.1 Hz, 1H), 8.47 (d, *J* = 2.4 Hz, 1H).

5-Bromo-2-(2-fluoroethoxy)-3-methoxybenzoic acid (9e). The same procedure was followed to afford **9e**. Yield: 83%. ^{1}H NMR ($CDCl_3$): δ 3.92 (s, 3H), 4.45 (t, *J* = 4.1 Hz, 1H), 4.55 (t, *J* = 4.1 Hz, 1H), 4.67 (t, *J* = 3.9 Hz, 1H), 4.83 (t, *J* = 4.2 Hz, 1H), 7.25 (dd, *J* = 2.4, 2.7 Hz, 1H), 7.86 (d, *J* = 2.1 Hz, 1H).

Methyl 4-(2-(2-hydroxyethoxy)ethoxy)benzoate (10a). Methyl 4-hydroxybenzoate (1.52 g, 10 mmol), 2-(2-chloroethoxy)ethanol (3.72 g, 30 mmol) and K_2CO_3 (4.14 g, 30 mmol) in DMF (10 mL) were stirred and refluxed overnight. After cooling to ambient temperature, the reaction mixture was slowly poured into water (100 mL) and extracted with ethyl ether (3 x 40 mL). The combined organic layers were dried over Na_2SO_4. Volatiles were removed under reduced pressure and the residue was purified by silica gel column chromatography using ethyl acetate/hexane (50/50, v/v) as the mobile phase to afford **10a** (2.34 g, 98%) as the colorless syrup. ^{1}H NMR ($CDCl_3$): δ 3.62 - 3.70 (m, 2H), 3.72 - 3.81 (m, 2H), 3.86 - 3.91 (m, 5H), 4.19 (t, *J* = 5.1 Hz, 2H), 6.93 (d, *J* = 9.3 Hz, 2H), 7.98 (d, *J* = 8.7 Hz, 2H).

Methyl 4-(2-(2-(2-hydroxyethoxy)ethoxy)ethoxy)benzoate (10b). Methyl 4-hydroxybenzoate (0.8 g, 5.26 mmol) and 2-(2-(2-chloroethoxy)ethoxy)ethanol (2.66 g, 15.7 mmol) and K_2CO_3 (2.19 g, 15.9 mmol) in DMF (20 mL) were stirred and refluxed overnight. After cooling to ambient temperature, the mixture was partitioned between ethyl ether and water. The organic layer was dried over Na_2SO_4. After concentrating under reduced pressure, the residue was purified by silica gel column chromatography using methanol/ethyl ether (3/100, v/v) to afford **10b** (0.53 g, 38%) as colorless liquid. ^{1}H NMR ($CDCl_3$): δ 3.59 - 3.64 (m, 2H), 3.67 - 3.77 (m, 6H), 3.86 - 3.92 (m, 5H), 4.19 (t, *J* = 5.1 Hz, 2H), 6.93 (d, *J* = 9.3 Hz, 2H), 7.98 (d, *J* = 9.0 Hz, 2H).

Methyl 4-(2-(2-(2-(tosyloxy)ethoxy)ethoxy)ethoxy)benzoate (10c). Triethylamine (1.2 g, 11.9 mmol) was added to a solution of **10b** (0.5 g, 1.8 mmol) and *p*-toluenesulfonyl chloride (1.02 g, 5.3 mmol) in dichloromethane (30 mL) at 0^{o}C (ice-water bath). The reaction mixture was gradually allowed to warm to ambient temperature and stirred for an additional 12 h. The reaction mixture was washed with brine and dried over Na_2SO_4. After concentrating under reduced pressure, the residue was purified on silica gel column using ethyl acetate/hexane (40/60, v/v) as the mobile phase to afford **10c** as a colorless oil (0.77 g, 98%). ^{1}H NMR ($CDCl_3$): δ 2.43 (s, 3H), 3.58 - 3.72 (m, 6H), 3.84 (t, *J* = 4.5 Hz, 2H), 3.88 (s, 3H), 4.10 - 4.19 (m, 4H), 6.92 (d, *J* = 9.0 Hz, 2H), 7.34 (d, *J* = 8.7 Hz, 2H), 7.80 (d, *J* = 8.7 Hz, 2H), 7.97 (d, *J* = 9.0 Hz, 2H).

Methyl 4-(2-(2-fluoroethoxy)ethoxy)benzoate (11a). (Diethylamino)sulfur trifluoride (DAST) (2.36 g, 17.7 mmol) was added to a solution of **10a** (2.3 g, 9.6 mmol) in dichloromethane (10 mL) at 0^{o}C (ice water bath). The mixture was allowed to warm to ambient temperature and stirred for an additional 12 h. The mixture was diluted with ethyl acetate (100 mL) and washed with saturated $NaHCO_3$ aqueous solution (50 mL) and brine (50 mL). The organic solution was dried over Na_2SO_4. After concentrating under reduced pressure, the residue was purified by silica gel column chromatography using ethyl acetate/hexane (30/70, v/v) to afford **11a** (1.02 g, 44%) as colorless oil. ^{1}H NMR ($CDCl_3$): δ 3.74 - 3.96 (m, 7H), 4.20 (t, *J* = 4.5 Hz, 2H), 4.52 (t, *J* = 4.0 Hz, 1H), 4.68 (t, *J* = 4.2 Hz, 1H), 6.94 (d, *J* = 9.0 Hz, 2H), 7.99 (d, *J* = 9.0 Hz, 2H).

Methyl 4-(2-(2-(2-fluoroethoxy)ethoxy)ethoxy)benzoate (11b). The solution of tetrabutylammonium fluoride (TBAF) in THF (14 mL, 1M) was added in the solution of **10c** (0.78 g, 1.8 mmol) in anhydrous THF (15 mL). The reaction mixture was then refluxed for 4 h. Volatiles were removed under reduced pressure and the residue dissolved in ethyl acetate (80 mL). The organic solution was washed with water (30 mL), brine (30 mL) and saturated aqueous $NaHCO_3$ (30 mL). Then the organic layer was dried over Na_2SO_4. After filtration the filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography using ethyl acetate/hexane (30/70, v/v) to afford **11b** (0.29 g, 57%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 3.68 - 3.82 (m, 6H), 3.86 - 3.92 (m, 5H), 4.19 (t, *J* = 4.9 Hz, 2H), 4.49 (t, *J* = 4.1 Hz, 1H), 4.64 (t, *J* = 4.3 Hz, 1H), 6.93 (d, *J* = 4.3 Hz, 2H), 7.98 (d, *J* = 8.7 Hz, 2H).

4-(2-(2-Fluoroethoxy)ethoxy)benzoic acid (12a). NaOH (0.450 g, 11.3 mmol) was added into a solution of **11a** (0.960 g, 3.96 mmol) in methanol (14 mL) and water (6 mL). The reaction mixture was stirred overnight. The methanol was removed under reduced pressure and the aqueous solution was acidified to pH = 2 with concentrated aqueous HCl to afford **12a** (840 mg, 93%) as a pale yellow solid, which was used in the next step without further purification. ^{1}H NMR ($CDCl_3$): δ 3.75 - 3.95 (m, 4H), 4.18 - 4.28 (m, 2H), 4.52 (t, *J* = 4.2 Hz, 1H), 4.68 (t, *J* = 4.0 Hz, 1H), 6.97 (d, *J* = 8.7 Hz, 2H), 8.06 (d, *J* = 9.3 Hz, 2H).

4-(2-(2-(2-Fluoroethoxy)ethoxy)ethoxy)benzoic acid (12b). The same reaction conditions were used to prepare **12b** from **11b.** Yield: 78%. ^{1}H NMR ($CDCl_3$): δ 3.68 - 3.84 (m, 6H), 3.90 (t, *J* = 4.8 Hz, 2H), 4.20 (t, *J* = 5.1 Hz, 2H), 4.49 (t, *J* = 4.2 Hz, 1H), 4.64 (t, *J* = 4.3 Hz, 1H), 6.96 (d, *J* = 9.0 Hz, 2H), 8.04 (d, *J* = 9.3 Hz, 2H).

2-*trans*-(4-bromobut-2-enyl)isoindoline-1,3-dione (14). A solution of potassium phthalimide **13** (3.7 g, 20 mmol) in DMF (20 mL) was slowly added to a solution of *trans*-1,4-dibromo-2-butene (12.84 g, 60 mmol) in DMF (10 mL) at 0°C (ice bath). The ice bath was removed, and the reaction mixture was stirred at reflux for 2 h. After cooling to ambient temperature, the reaction mixture was diluted with water (150 mL) and extracted

with ethyl acetate (3 x 60 mL). The organic solution was washed with brine (3 x 30 mL) and dried over Na_2SO_4. After filtration the filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography using ethyl acetate/hexane (1/10, v/v) as the mobile phase to afford **14** (3.84 g, 69%). ^{1}H NMR ($CDCl_3$): δ 3.91 (d, *J* = 7.5 Hz, 2H), 4.31 (d, *J* = 5.7 Hz, 2H), 5.75 - 6.05 (m, 2H), 7.70 - 7.80 (m, 2H), 7.80 - 7.90 (m, 2H).

2-(4-(4-(2-Methoxyphenyl)piperazin-1-yl)butyl)isoindoline-1,3-dione (**16a**). 1-(2-methoxyphenyl)-piperazine hydrogen chloride (**15a**) (5.11 g, 22.6 mmol), 2-(4-bromobutyl)isoindoline-1,3-dione (6.37 g, 22.6 mmol) and triethylamine (13.73 g, 132 mmol) were dissolved in dichloromethane (100 mL) and the reaction mixture was stirred at ambient temperature for 15 h. The mixture was washed with saturated sodium carbonate aqueous solution (3 x 30 mL) and brine (2 x 30 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by silica gel column chromatography using ethyl acetate/hexane (50/50, v/v) as the mobile phase afforded **16a** (6.17 g, 70%) as a yellow grease. ^{1}H NMR ($CDCl_3$): δ 1.48 - 1.68 (m, 2H), 1.68 - 1.82 (m, 2H), 2.43 (t, *J* = 7.2 Hz, 2H), 2.50 - 2.70 (m, 4H), 2.96 - 3.18 (m, 4H), 3.75 (t, *J* = 3.9 Hz, 2H), 3.89 (s, 3H), 6.80 - 7.05 (m, 4H), 7.68 - 7.74 (m, 2H), 7.80 - 7.88 (m, 2H).

2-(4-(4-(2-Hydroxyphenyl)piperazin-1-yl)butyl)isoindoline-1,3-dione (16b). 16b was produced from **15b** (2.0 g, 11.2 mmol), 2-(4-bromobutyl)isoindoline-1,3-dione (3.73 g, 13.2 mmol) and triethylamine (6.0 g, 59.4 mmol) as described above for **16a**. Purification by silica gel column chromatography using ethyl acetate/hexane (50/50, v/v) as the mobile phase afforded **16b** (2.98 g, 70%) as a white solid. ^{1}H NMR ($CDCl_3$): δ 1.48 -1.68 (m, 2H), 1.68 - 1.82 (m, 2H), 2.45 (t, *J* = 8.4 Hz, 2H), 2.50 - 2.70 (m, 4H), 2.82 - 2.94 (m, 4H), 3.74 (t, *J* = 7.0 Hz, 2H), 6.81 - 6.89 (m, 1H), 6.90 - 6.96(m, 1H), 7.02 - 7.10 (m, 1H), 7.12 - 7.18 (m, 1H), 7.68 - 7.74 (m, 2H), 7.80 - 7.88 (m, 2H).

2-(4-(4-(2-Methoxyphenyl)piperazin-1-yl)-*trans*-but-2-enyl)isoindoline-1,3-dione (16c). The same procedure was used to prepare **16c** from **15a** and **14**. Yield: 1.35 g, (52.5%). ^{1}H NMR ($CDCl_3$): δ 2.50 - 2.72

(m, 4H), 2.96 - 3.18 (m, 6H), 3.85 (s, 3H), 4.26 - 4.36 (m, 2H), 5.66 - 5.82 (m, 2H), 6.81 - 7.04 (m, 4H), 7.68 - 7.76 (m, 2H), 7.80 - 7.88 (m, 2H).

2-(4-(4-(2-Hydroxyphenyl)piperazin-1-yl)-*trans*-but-2-enyl)isoindoline-1,3-dione (16d). The same procedure was used to prepare **16d** from **15b** and **14**. Yield: 71%. ^{1}H NMR ($CDCl_3$): δ 2.61 (s, 4H), 2.89 (t, *J* = 4.8 Hz, 4H), 3.00 - 3.10 (m, 2H), 4.28 - 4.38 (m, 2H), 5.70 -5.80 (m, 2H), 6.81 - 6.89 (m, 1H), 6.90 - 6.96 (m, 1H), 7.02 - 7.10 (m, 1H), 7.12 - 7.18 (m, 1H), 7.68 - 7.76 (m, 2H), 7.82 - 7.88 (m, 2H).

2-(4-(4-(2-(2-Fluoroethoxy)phenyl)piperazin-1-yl)butyl)isoindoline-1,3-dione (16e). A mixture of K_2CO_3 (3.82 g, 27.7 mmol), **16b** (1.61 g, 4.2 mmol) and 1-bromo-2-fluoroethane (3.5 g, 27.6 mmol) in acetone (60 mL) was stirred and refluxed overnight. Volatile components were removed under reduced pressure and the residue was dissolved in ethyl acetate (80 mL) and washed with water (2 x 20 mL) and then brine (10 mL). The organic layer was dried over Na_2SO_4, concentrated under reduced pressure, and the residue was purified by silica gel column chromatography using ethyl acetate/hexane (50/50, v/v) as the mobile phase to afford **16e** (1.70 g, 94%) as a yellow solid. The ^{1}H NMR ($CDCl_3$) was δ 1.48 - 1.66 (m, 2H), 1.66 - 1.81 (m, 2H), 2.36 - 2.42 (m, 2H), 2.50 - 2.68 (m, 4H), 2.96 - 3.18 (m, 4H), 3.60 - 3.78 (m, 2H), 4.19 (t, *J* = 4.0 Hz, 1H), 4.29 (t, *J* = 4.0 Hz, 1H), 4.70 (t, *J* = 4.1 Hz, 1H), 4.86 (t, *J* = 4.2 Hz, 1H), 6.82 - 6.89 (m, 1H), 6.92 - 7.00 (m, 3H), 7.68 - 7.76 (m, 2H), 7.80 -7.88 (m, 2H).

2-(4-(4-(2-(2-Fluoroethoxy)phenyl)piperazin-1-yl)-*trans*-but-2-enyl)isoindoline-1,3-dione (16f). The same procedure was used to prepare **16f** from **16d** and 1-bromo-2-fluorooethane. Yield: 94%. ^{1}H NMR ($CDCl_3$): δ 2.46 - 2.75 (m, 4H), 3.03 (t, *J* = 2.1 Hz, 2H), 3.10 (s, 4H), 4.19 (t, *J* = 4.0 Hz, 1H), 4.23 - 4.33 (m, 3H), 4.68 (t, *J* = 4.2 Hz, 1H), 4.84 (t, *J* = 4.0 Hz, 1H), 5.66 - 5.82 (m, 2H), 6.80 - 7.04 (m, 4H), 7.68 - 7.76 (m, 2H), 7.80 - 7.88 (m, 2H).

4-(4-(2-Methoxyphenyl)piperazin-1-yl)butan-1-amine (17a). Hydrazine (0.74 g, 23 mmol) was added to a solution of **16a** (7.55 g, 19.2 mmol) in ethanol (100 mL) and the reaction mixture was stirred at reflux for 5 h. After cooling, the mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue which was purified by silica gel column chromatography using dichloromethane/ethyl acetate/methanol/triethylamine (10/10/20/1, v/v/v/v) as the mobile phase to afford **17a** (4.18 g, 83%) as pale yellow grease. ^{1}H NMR ($CDCl_3$): δ 1.40 - 1.62 (m, 6H), 2.43 (t, *J* = 7.2 Hz, 2H), 2.66 (s, 4H), 2.71 (t, *J* = 6.9 Hz, 2H), 3.11 (s, 4H), 3.86 (s, 3H), 6.80 - 7.03 (m, 4H).

4-(4-(2-(2-Fluoroethoxy)phenyl)piperazin-1-yl)butan-1-amine (**17b**). The same procedure was used to prepare **17b** as a yellow syrup. Yield: 90%. ^{1}H NMR ($CDCl_3$): δ 1.44 - 1.66 (s, 4H), 1.78 - 2.06 (s, 4H), 2.42 (t, *J* = 7.2 Hz, 2H), 2.65 (s, 4H), 2.74 (t, *J* = 6.4 Hz, 2H), 3.14 (s, 4H), 4.21 (t, *J* = 4.0 Hz, 1H), 4.30 (t, *J* = 4.2 Hz, 1H), 4.70 (t, *J* = 4.0 Hz, 1H), 4.86 (t, *J* = 4.2 Hz, 1H), 6.82 - 6.89 (m, 1H), 6.92 - 7.00 (m, 3H).

4-(4-(2-methoxyphenyl)piperazin-1-yl)-*trans*-but-2-en-1-amine (17c). The same procedure was used to prepare **17c** as a light yellow syrup. Yield: 42%. ^{1}H NMR ($CDCl_3$): δ 1.56 (br s, 2H), 2.66 (s, 4H), 3.02 - 3.20 (m, 6H), 3.30 (dd, *J* = 1.0, 5.1 Hz, 2H), 3.86 (s, 3H), 5.58 - 5.62 (m 2H), 6.82 - 7.04 (m, 4H).

4-(4-(2-(2-Fluoroethoxy)phenyl)piperazin-1-yl)-*trans*-but-2-en-1-amine (**17d**). The same procedure was used to prepare **17d** as a yellow syrup. Yield: 97%. ^{1}H NMR ($CDCl_3$): δ 2.74 (s, 4H), 2.92 - 3.24 (m, 6H), 3.48 (d, *J* = 3.3 Hz, 2H), 4.11 (s, 4H), 4.20 (t, *J* = 4.1, 1H), 4.30 (t, *J* = 4.1 Hz, 1H), 4.70 (t, *J* = 4.2 Hz, 1H), 4.86 (t, *J* = 4.2 Hz, 1H), 5.76 - 5.96 (m, 2H), 6.80 - 6.90 (m, 1H), 6.90 - 7.04 (m, 3H).

HPLC Conditions to Confirm the Purity of Final compounds

The analytical HPLC system consisted of a Rheodyne injector valve with 100 μL of sample loop, a Thermo Separations P200HPLC binary pump, a Spectra Physics Spectra 100UV variable detector (254 nm), an Alltech Econosil reversed phase C18 column (250 × 4.6 mm). The mobile phase was 30% acetonitrile and 70% 0.1M ammonium formate buffer (described above) at 1.5 ml/minute flow rate. Under these conditions the benzamide analogs was eluted with a retention time varying from 5 -15 min. The purity of the final compounds was >95%.

Table 4. Elemental Analysis Results of the Target Compounds

	Molecular Formula	Theoretical values			Experimental values		
		C	H	N	C	H	N
18a	$C_{24}H_{32}FN_3O_3 \cdot 1.5H_2C_2O_4$	57.44	6.25	7.44	57.08	6.25	7.35
18b	$C_{26}H_{36}FN_3O_4 \cdot H_2C_2O_4$	59.67	6.80	7.46	59.83	6.98	7.43
18c	$C_{28}H_{40}FN_3O_5 \cdot H_2C_2O_4 \cdot 0.4H_2O$	58.60	7.02	6.83	58.89	6.95	6.84
19a	$C_{24}H_{30}FN_3O_2 \cdot 0.5H_2C_2O_4 \cdot H_2O$	63.27	7.01	8.85	62.97	7.10	8.44
19b	$C_{24}H_{30}FN_3O_3$	67.43	7.07	9.83	67.49	7.01	9.71
19c	$C_{26}H_{34}FN_3O_4 \cdot H_2C_2O_4$	59.88	6.46	7.48	59.97	6.35	7.46
19d	$C_{25}H_{32}FN_3O_3 \cdot H_2C_2O_4$	61.01	6.45	7.90	61.13	6.46	7.88
19e	$C_{24}H_{29}BrFN_3O_3$	56.92	5.77	8.30	56.85	5.86	8.15
19f	$C_{24}H_{29}FIN_3O_3 \cdot H_2C_2O_4 \cdot 0.5H_2O$	47.86	4.94	6.44	48.08	5.27	6.18
19g	$C_{25}H_{31}BrFN_3O_4 \cdot H_2C_2O_4$	51.76	5.31	6.71	51.99	5.41	6.73
20a	$C_{25}H_{35}FN_4O_2 \cdot H_2C_2O_4$	60.89	7.00	10.52	60.89	7.36	10.69
20b	$C_{25}H_{33}F_2N_3O_2 \cdot 0.5H_2C_2O_4$	63.66	6.99	8.57	63.69	6.87	8.58
20c	$C_{25}H_{33}F_2N_3O_3 \cdot H_2C_2O_4$	58.79	6.40	7.62	58.62	6.44	7.57
20d	$C_{27}H_{37}F_2N_3O_4 \cdot H_2C_2O_4$	58.48	6.60	7.05	58.55	6.93	7.17
20e	$C_{27}H_{32}FN_3O_2S \cdot H_2C_2O_4$	60.93	5.99	7.35	60.87	6.00	7.38
20f	$C_{29}H_{41}F_2N_3O_5 \cdot H_2C_2O_4$	58.21	6.78	6.57	58.52	6.83	6.72
21a	$C_{25}H_{33}FN_4O_2 \cdot H_2C_2O_4 \cdot H_2O$	59.11	6.80	10.21	59.30	7.10	10.18
21b	$C_{25}H_{31}F_2N_3O_2 \cdot 0.5H_2C_2O_4$	63.92	6.60	8.60	64.11	6.72	8.60
21c	$C_{25}H_{31}F_2N_3O_3 \cdot 2H_2C_2O_4$	54.46	5.52	6.57	54.41	5.56	6.48
21d	$C_{27}H_{35}F_2N_3O_4 \cdot 1.5H_2C_2O_4$	56.42	6.00	6.58	56.71	6.14	6.58
21e	$C_{27}H_{30}FN_3O_2S$	67.62	6.30	8.76	67.32	6.53	8.51
21g	$C_{22}H_{28}FN_3O_2S \cdot H_2C_2O_4$	56.79	5.96	8.28	56.57	6.01	8.21
21h	$C_{21}H_{25}BrFN_3O_2S \cdot 0.5H_2C_2O_4$	50.10	4.97	7.97	50.15	4.99	7.90