# Design and Synthesis of 1-(3-(dimethylamino)propyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (Citalopram) Analogues as Novel Probes for the Serotonin Transporter S1 and S2 Binding Sites

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**Supplemental Information Contents**

**Table S1: Microanalysis Data:**

| Compd | C | H | N | C | H | N |
|---|---|---|---|---|---|---|
| | Calculated | | | Found | | |
| **2, BAK 02-76** | 55.82 | 5.91 | 3.10 | 55.69 | 5.80 | 3.11 |
| **3, BAK 02-84** | 58.66 | 6.04 | 6.22 | 58.65 | 5.71 | 5.99 |
| **4, BAK 02-90** | 56.35 | 5.91 | 3.29 | 56.52 | 5.92 | 3.29 |
| **5, BAK 02-91** | 54.75 | 5.93 | 5.32 | 54.69 | 6.24 | 5.05 |
| **6, BAK 03-13** | 50.90 | 6.58 | 4.75 | 51.18 | 6.28 | 4.71 |
| **7, BAK 03-12** | 54.72 | 6.40 | 4.56 | 54.59 | 6.15 | 4.25 |
| **8, BAK 03-09** | 59.99 | 6.37 | 6.17 | 60.10 | 6.46 | 5.92 |
| **9, BAK 03-10** | 57.68 | 6.50 | 5.77 | 57.67 | 6.01 | 5.76 |
| **10, BAK 03-11** | 54.81 | 5.48 | 5.64 | 54.70 | 5.59 | 5.29 |
| **11, BAK 03-74** | 51.65 | 5.23 | 4.15 | 51.72 | 5.24 | 4.22 |
| **12, BAK 03-71** | 52.14 | 5.51 | 4.19 | 52.34 | 5.29 | 4.18 |
| **13, BAK 03-70** | 56.25 | 5.86 | 4.23 | 56.29 | 5.58 | 4.23 |
| **14, BAK 03-69** | 58.34 | 5.83 | 4.00 | 58.34 | 5.64 | 4.01 |
| **15, BAK 03-73** | 50.09 | 5.73 | 4.38 | 50.25 | 5.55 | 4.37 |
| **16, BAK 02-93** | 57.24 | 6.28 | 5.13 | 57.18 | 6.55 | 4.94 |
| **19, ZP407** | 61.98 | 5.76 | 5.16 | 61.79 | 5.29 | 5.26 |
| **20, ZP408** | 64.29 | 6.28 | 5.55 | 63.87 | 5.80 | 5.18 |
| **21, ZP409** | 69.78 | 6.62 | 2.71 | 69.71 | 6.18 | 2.67 |
| **22, ZP382** | 48.95 | 4.50 | 2.72 | 48.54 | 4.79 | 2.71 |
| **24, ZP419** | 53.56 | 5.11 | 5.68 | 53.76 | 5.05 | 5.61 |
| **25, ZP434** | 55.59 | 4.88 | 5.89 | 55.84 | 4.82 | 5.93 |
| **26, ZP437** | 68.50 | 5.75 | 5.15 | 68.18 | 5.73 | 5.45 |
| **27, ZP448** | 66.41 | 5.20 | 7.74 | 66.87 | 4.98 | 7.29 |
| **28, ZP452** | 59.71 | 5.33 | 6.74 | 60.14 | 5.17 | 6.80 |
| **37, ZP269** | 49.48 | 4.51 | 2.51 | 49.83 | 4.42 | 2.47 |
| **38, GCC** | 56.38 | 5.35 | 6.92 | 56.54 | 5.19 | 6.82 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **2-17** | | | | | | |
| **39, BAK 03-58** | 59.62 | 6.09 | 6.05 | 59.41 | 5.93 | 6.04 |
| **40, BAK 03-60** | 56.57 | 5.99 | 6.03 | 56.77 | 5.83 | 5.92 |
| **41, BAK 03-68** | 59.36 | 6.50 | 6.02 | 59.15 | 6.25 | 5.94 |
| **42, GCC 2-21** | 62.07 | 5.98 | 5.36 | 61.98 | 5.63 | 5.40 |
| **43, GCC 2-45** | 63.79 | 6.37 | 5.13 | 63.82 | 6.17 | 5.14 |
| **44, BAK 02-69** | 61.52 | 5.31 | 5.12 | 61.74 | 5.12 | 4.98 |
| **45, BAK 03-62** | 59.34 | 4.85 | 4.94 | 59.20 | 4.74 | 4.77 |
| **46, BAK 03-67** | 51.71 | 5.73 | 6.46 | 51.61 | 5.44 | 6.27 |
| **47, BAK 02-77** | 57.66 | 5.09 | 6.96 | 57.84 | 4.88 | 6.70 |
| **48, BAK 03-64** | 49.68 | 4.56 | 5.99 | 49.53 | 4.76 | 5.82 |
| **49, BAK 03-61** | 63.75 | 5.31 | 4.96 | 63.77 | 5.19 | 4.61 |
| **50, BAK 03-63** | 65.70 | 5.30 | 4.64 | 65.68 | 5.26 | 4.63 |
| **51, BAK 03-75** | 57.47 | 5.75 | 5.16 | 57.48 | 5.58 | 5.16 |
| **53, BAK 03-40** | 54.10 | 4.58 | 6.76 | 54.12 | 4.37 | 6.41 |
| **55, BAK 03-43** | 61.27 | 5.50 | 7.39 | 61.17 | 5.31 | 7.28 |
| **57, BAK 03-38** | 46.90 | 5.34 | 7.81 | 46.96 | 5.56 | 7.60 |
| **60, BAK 02-72** | 63.21 | 5.39 | 6.70 | 63.06 | 5.44 | 6.63 |

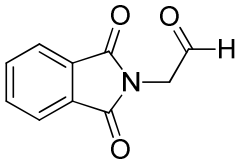
**Table S2.** Effect of previously published analogues[a] in inhibiting the dissociation of [$^3$H]**S-1** from SERT WT. The relative potency of 30μM compound in inhibiting [$^3$H]**S-1** dissociation as compared to buffer and **S-1**.

| **Compound** | **[$^3$H] S-1 dissoc. t½ (min) at 18°C** |
|---|---|
| **ZP-433** | 18.4±2.3 |
| **ZP-223** | 47±12 |
| **ZP-228** | 40.1±8.0 |
| **ZP-256** | 25.0±1.6 |
| **ZP-233** | 73.2±10.4 |
| **ZP-234** | 59.7±5.9 |
| **ZP-238** | 44.5±4.2 |
| **ZP-239** | 27.8±3.7 |
| **ZP-240** | 43.7±4.1 |
| **ZP-249** | 52.7±1.8 |
| **ZP-257** | 40.9±6.2 |
| **ZP-286** | 24.8±5.0 |
| **ZP-289** | 28.8±2.9 |
| **ZP-295** | 47±12 |
| **ZP-332** | 22.5±2.1 |
| **ZP-366** | 27.4±4.6 |

Experiments were performed on membrane preparations from COS-7 cells transiently expressing with SERT WT. [$^3$H] **S-1** was added until equilibrium were obtained and subsequently diluted in 12x buffer volumes containing 30 µM of the indicated compound. Dissociation were measured at 18°C to obtain a suitable t½ (<100 min). Values are mean±S.E. of three experiments performed in triplicate. None of these compounds was as potent as **S-1**. [a]from Zhang et al., *J. Med. Chem*. **2010**, *53 (16)* 6112-6121

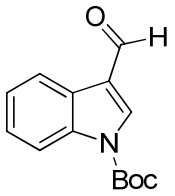
**Supplemental synthesis experimentals:**

**2-(1,3-dioxoisoindolin-2-yl)acetaldehyde**



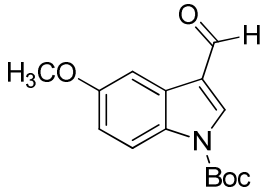

6N HCl was added to a solution of 2-(2,2-diethoxyethyl)isoindoline-1,3-dione (2.63 g, 10 mmol) in acetone (20 mL). The resulting solution was stirred at reflux for 0.5 h, allowed it to cool to room temperature, added water (20 mL), and then extracted with ethyl acetate (2X20 mL). The organic layer was dried over $MgSO_4$ and concentrated to give the product (BAK-03-95) in 98% (1.85 g) yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 9.66 (s, 1H), 7.89 (dd, *J* = 5.6, 3.2 Hz, 2H), 7.76 (dd, *J* = 5.6, 3.2 Hz, 1H), 4.57 (s, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 193.75, 167.74, 134.57, 132.15, 123.91, 47.59; GC-MS (EI) *m/z* 189.

***tert*-butyl 3-formyl-1*H*-indole-1-carboxylate**




A solution of 1H-indole-3-carbaldehyde (1.54 g, 10 mmol), di-*tert*-butyl dicarbonate (2.4 g, 11 mmol) and DMAP (0.25 g) in acetonitrile (25 mL) was stirred at rom temperature for 12 h. acetonitrile was removed under reduced pressure and the residue was dissolved in diethyl ether. The resulting solution was washed with 1M HCl (2X10 mL), water (2X10 mL). The organic layer was dried over $MgSO_4$ and concentrated to give Boc protected compound in 98% (2.4 g) yield, which was used in the next step without any further purification.. $^1$H NMR (400 MHz, $CDCl_3$) δ 10.10 (s, 1H), 8.28-8.30 (m, 1H), 8.24 (s, 1H), 8.15 (d, *J* = 7.6 Hz, 1H), 7.44-7.35 (m, 2H), 1.70 (s, 9H); GC-MS (EI) *m/z* 145 ($M^+$-Boc).

**tert-butyl 3-formyl-5-methoxy-1*H*-indole-1-carboxylate**




This compound was prepared from 5-methoxy-1*H*-indole-3-carbaldehyde (1.75 g, 10 mmol), di-*tert*-butyl dicarbonate (2.4 g, 11 mmol) and DMAP (0.25 g) by using above procedure to give Boc protected compound in 97% (2.7 g) yield, which was used in the next step without any further purification.. $^1$H NMR (400 MHz, $CDCl_3$) δ 10.07 (s, 1H), 8.19 (s, 1H), 8.01 (d, *J* = 9.2 Hz, 1H), 7.77 (d, *J* = 2.4 Hz, 1H), 7.01 (dd, *J* = 9.2, 2.4 Hz, 1H), 3.89 (s, 3H), 1.70 (s, 9H); GC-MS (EI) *m/z* 175 ($M^+$-Boc).