Supplemental Information

"Rigid *versus* flexible anilines or anilides confirm the bicyclic ring as the hydrophobic portion for optimal σ_2 receptor binding and provide novel tools for the development of future σ_2 receptor PET radiotracer"

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General procedure for the synthesis of 3-Chloro-*N*-Phenylpropanamides (3a-c).

One of the appropriate anilines (2.5 mmol) was dissolved in anhydrous CH_2Cl_2 (10 mL) and after cooling at 0 ºC, Et_3N (1 mmol, 0.13 mL) was added under a stream of N_2. 3-Chloropropionyl chloride was then added to the solution in a dropwise manner, and the resulting mixture was stirred for 2 h at 0 ºC. The solution was then quenched with H_2O and extracted with CH_2Cl_2 (3 × 10 mL). The collected organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to afford a crude solid, which was used for the next step without purification (75 % yield).

3-Chloro-*N*-phenylpropanamides (3a): GC-MS *m/z* 185 (M^+ + 2, 10), 183 (M^+, 30), 93 (100).

3-Chloro-*N*-3-methoxyphenylpropanamides (3b): GC-MS *m/z* 215 (M^+ + 2, 10), 213 (M^+, 35), 123 (100). IR cm^{-1}: 3300, 3090, 1664, 1610.

3-Chloro-*N*-4-fluorophenylpropanamides (3c): GC-MS *m/z* 203 (M^+ + 2, 10), 201 (M^+, 30), 111 (100).

General procedures for the synthesis of alkyl chloride derivatives (9a-c)

To a suspension of NaH (0.16 g, 6.80 mmol) in dry DMF (15 mL), a solution in DMF (5 mL) of the appropriate 3,4-dihydroquinolin-2(1*H*)-one (**8a-c**) (2.7 mmol), was added in a dropwise manner, at 0 °C under a stream of N_2. After 30 min, 1-bromo-3-chloropropane (3 mmol, 0.29 mL) was added in a dropwise manner and the mixture was allowed to warm to room temperature and was stirred for 4 h. After cooling to 0 °C H_2O was added and the solvent was removed under reduced pressure. The residue was taken up with water and extracted with CH_2Cl_2 (3 × 15 mL). The organic layers were collected, dried over Na_2SO_4 and evaporated under reduced pressure to afford a crude residue as a brown solid.

1-(3-Chloropropyl)-3,4-dihydroquinolin-2(1*H*)-one (9a) was purified by column chromatography with CH_2Cl_2/AcOEt (8:2) as eluent to provide a yellow oil (0.33 g, 55%); GC-MS *m/z* 225 (M^+ + 2, 15), 223 (M^+, 45), 188 (55), 132 (100).

1-(3-Chloropropyl)-5-methoxy-3,4-dihydroquinolin-2(1*H*)-one (9b) the crude residue was used for the next step with no purification (0.39 g, 58%); GC-MS *m/z* 255 (M^+ + 2, 25), 253 (M^+, 75), 218 (85), 162 (100).

1-(3-Chloropropyl)-6-fluoro-3,4-dihydroquinolin-2(1*H*)-one (9c) was purified by column chromatography with CH_2Cl_2/AcOEt (9:1) as eluent to provide a colorless oil (0.42 g, 65%); GC-MS *m/z* 243 (M^+ + 2, 15), 243 (M^+, 45), 206 (60), 150 (100).

Table of Elemental Analyses

	Calculated			Found		
Compound	**C**	**H**	**N**	**C**	**H**	**N**
4a	63.74	6.69	7.43	63.56	6.70	7.34
4b	61.99	6.69	6.88	62.10	6.73	7.00
4c	60.83	6.13	7.09	61.10	6.30	7.12
5a	70.15	7.07	7.01	70.30	7.20	7.11
5b	58.13	7.09	6.46	58.02	6.98	6.46
5c	56.94	6.57	6.64	57.08	6.51	6.91
6a	61.82	7.43	6.55	61.25	7.06	6.73
6b	59.81	6.73	5.58	59.81	6.43	5.66
6c	62.48	6.67	6.62	62.30	6.56	6.70
7a	61.82	7.55	6.55	62.03	7.43	6.60
7b	60.39	7.49	6.12	60.56	7.40	6.21
7c	59.33	7.02	6.29	59.24	7.13	6.40
10a	66.26	7.01	6.72	66.06	6.97	6.81
10b	60.58	7.25	5.89	60.32	6.97	5.95
10c	61.60	6.63	6.25	61.56	6.44	6.26
11a	62.23	7.38	6.31	62.13	7.29	6.32
11b	60.82	7.34	5.91	60.82	7.33	6.00
11c	59.80	6.87	6.06	59.56	6.85	6.08

Table of Physical Properties of Novel Compounds

Compound	Formula[a]	mp, ˚C
4a	$C_{20}H_{24}N_2O_3 \cdot HCl \cdot 0.25H_2O$[b]	232-235
4b	$C_{21}H_{26}N_2O_4 \cdot HCl \cdot 0.75H_2O$[b]	195-197
4c	$C_{20}H_{23}N_2O_3 \cdot HCl \cdot 0.25H_2O$[b]	244-246
5a	$C_{20}H_{26}N_2O_2 \cdot 2HCl \cdot 0.75H_2O$[b]	230-232
5b	$C_{21}H_{28}N_2O_3 \cdot 2HCl \cdot 0.25H_2O$[b]	235-237
5c	$C_{20}H_{25}N_2O_2F \cdot 2HCl \cdot 0.25H_2O$[b]	248-250
6a	$C_{22}H_{28}N_2O_3 \cdot HCl \cdot 1.25H_2O$[b]	129-132
6b	$C_{23}H_{30}N_2O_4 \cdot (COOH)_2 \cdot 0.75H_2O$[b]	119-121
6c	$C_{22}H_{27}N_2O_3F \cdot HCl \cdot 0.25H_2O$[b]	126-129
7a	$C_{22}H_{30}N_2O_2 \cdot 2HCl \cdot 0.75H_2O$[b]	187-190
7b	$C_{23}H_{32}N_2O_3 \cdot 2HCl \cdot 1.25H_2O$[b]	174-176
7c	$C_{22}H_{29}N_2O_2F \cdot 2HCl \cdot 0.25H_2O$[b]	210-213
10a	$C_{23}H_{28}N_2O_3 \cdot HCl$[b]	191-193
10b	$C_{24}H_{30}N_2O_4 \cdot HCl \cdot 1.6H_2O$[b]	188-190
10c	$C_{23}H_{27}N_2O_3F \cdot HCl \cdot 0.75H_2O$[b]	225-227
11a	$C_{23}H_{30}N_2O_2 \cdot 2HCl \cdot 0.25H_2O$[b]	211-213
11b	$C_{24}H_{32}N_2O_3 \cdot 2HCl \cdot 0.25H_2O$[b]	181-183
11c	$C_{23}H_{29}N_2O_2F \cdot 2HCl \cdot 0.25H_2O$[b]	230-232

[a]Elemental analyses for C, H, N were within ±0.4% of the theoretical values for the formulas given.

[b]Recrystallized from MeOH.