SUPPLEMENTARY INFORMATION

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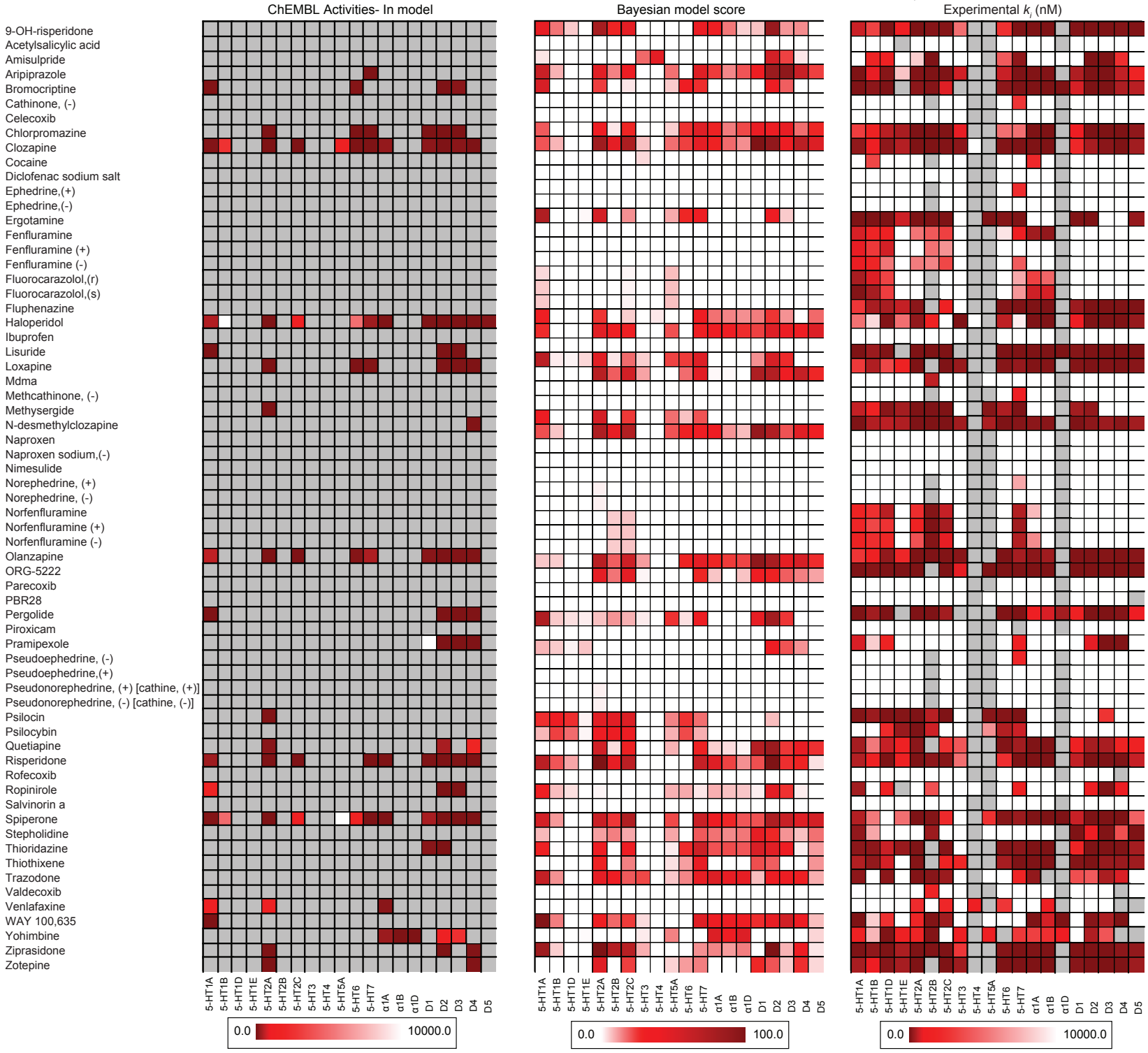
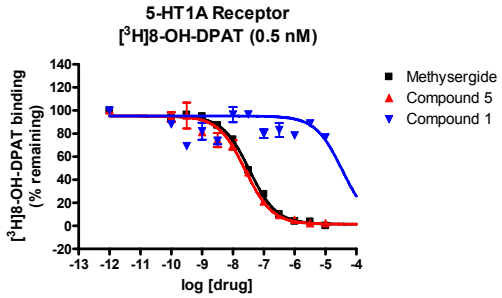
Supplementary Figure 1: PDSP compounds, activities in ChEMBL, bayesian prediction and experimental k_i from PDSP database

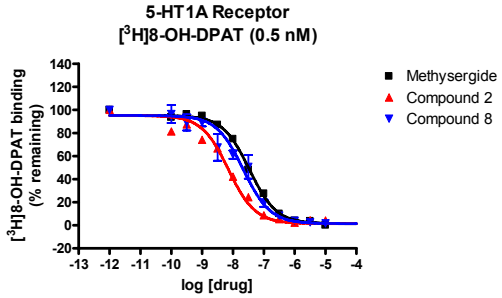


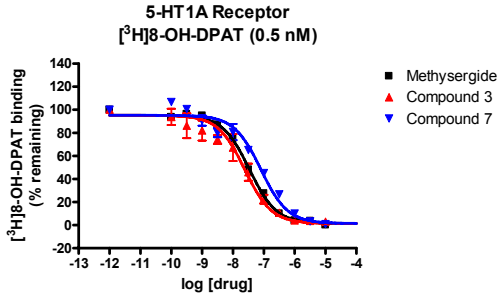
Supplementary Figure 1: Predicting polypharmacology profiles. The three matrices present are, from left to right, (i) all experimental activities of the respective compounds in ChEMBL for the 20 receptors analysed in the study (irrespective of confidence assignment); (ii) Bayesian model predictions for the compounds across models for the 20 receptors. The Bayesian model are constructed using the high confidence activity data in ChEMBL (see Methods); experimental k_i data from PDSP k_i database. Data was downloaded from the PDSP k_i database website, and the version used is kidb110121 (http://pdsp.med.unc.edu/kidb.php). Compounds were filtered to select those that had at least 15 recorded activities from the 20 GPCR receptors used in our screening study, in the PDSP k_i database. Then compounds were manually mapped to a ChEMBL identifier when it was possible and to respect the stereochemistry. Data from ChEMBL02 was retrieved from each compound to identify activities present in the GPCR models. For the prediction every compounds was scored for each GPCR receptors as described in Methods section. Of the 1300 datapoint predictions in the matrix (65 compounds x 20 receptor assays) 909 were experimentally confirmed correct ($p < 2.2e^{-16}$), with a probability of success of 0.70 (95% confidence interval: 0.67 - 0.72). (Colour scheme: grey – no data; white – measure or predicted inactive; red shade – Bayesian score or k_i value).

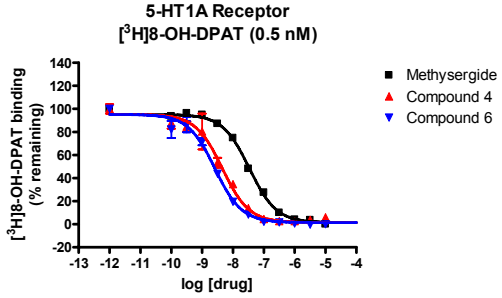
Supplementary Figure 2: Experimental testing of ligand predictions

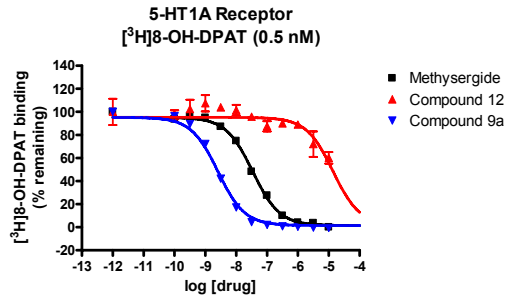
Figure is of all k_i for drugs 1 to 29r against a panel of 20 GPCR receptors. Receptors tested were 11 serotonergic receptors: 5-HT1A, 5-HT1B, 5-HT1D, 5-HT1E, 5-HT2A, 5-HT2B, 5-HT2C, 5-HT3, 5-HT5A, 5-HT6 and 5-HT7; 3 alpha adrenergic receptors: α1A, α1B and α1D; and 5 dopaminergic receptors: D1, D2, D3, D4 and D5.


5-HT1A Receptor
[3H]8-OH-DPAT (0.5 nM)
[3H]8-OH-DPAT binding (% remaining)
log [drug]
Methysergide
Compound 5
Compound 1


5-HT1A Receptor
[3H]8-OH-DPAT (0.5 nM)
[3H]8-OH-DPAT binding (% remaining)
log [drug]
Methysergide
Compound 2
Compound 8


5-HT1A Receptor
[3H]8-OH-DPAT (0.5 nM)
[3H]8-OH-DPAT binding (% remaining)
log [drug]
Methysergide
Compound 3
Compound 7


5-HT1A Receptor
[3H]8-OH-DPAT (0.5 nM)
[3H]8-OH-DPAT binding (% remaining)
log [drug]
Methysergide
Compound 4
Compound 6


5-HT1A Receptor
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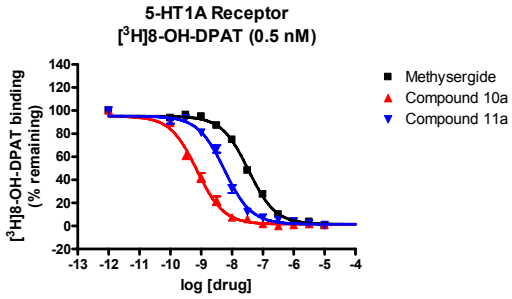
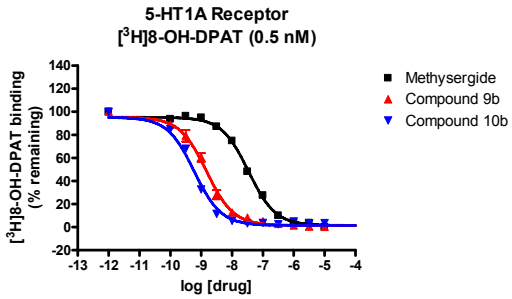
[3H]8-OH-DPAT binding
(% remaining)
log [drug]
Methysergide
Compound 12
Compound 9a


5-HT1A Receptor
[3H]8-OH-DPAT (0.5 nM)
[3H]8-OH-DPAT binding
(% remaining)
log [drug]
Methysergide
Compound 10a
Compound 11a


5-HT1A Receptor
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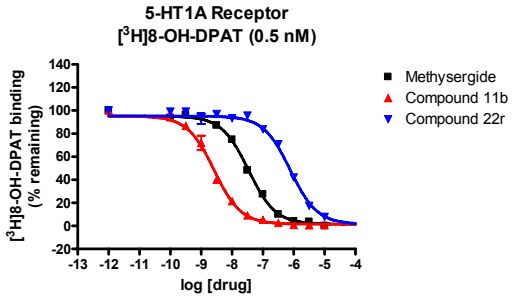
(% remaining)
log [drug]
Methysergide
Compound 9b
Compound 10b


5-HT1A Receptor
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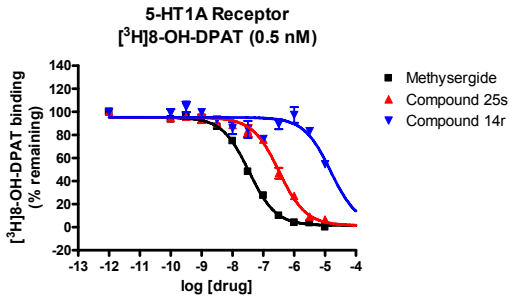
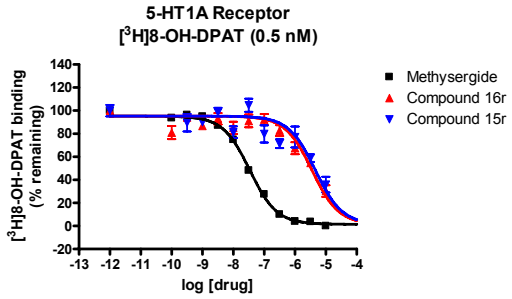
(% remaining)
log [drug]
Methysergide
Compound 11b
Compound 22r


5-HT1A Receptor
[3H]8-OH-DPAT (0.5 nM)
[3H]8-OH-DPAT binding (% remaining)
log [drug]
Methysergide
Compound 25s
Compound 14r


5-HT1A Receptor
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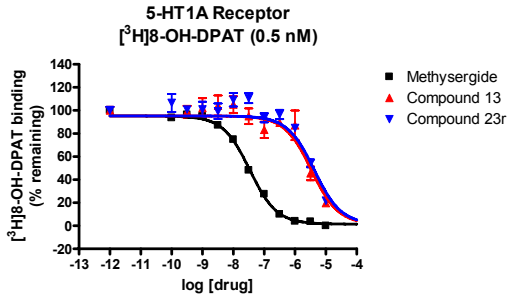
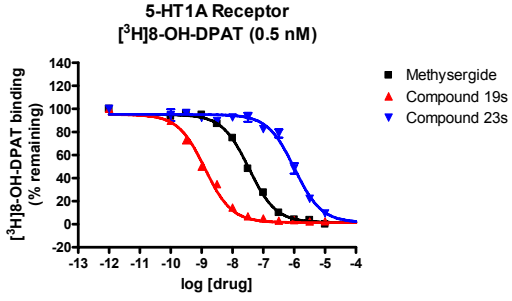
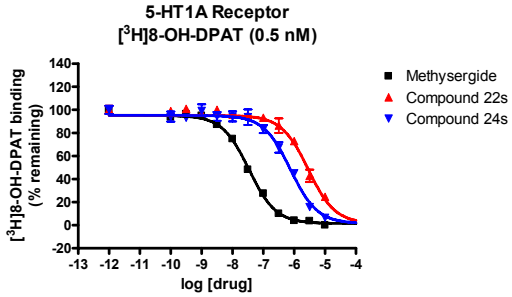
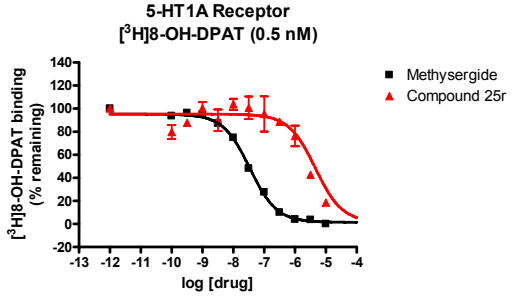
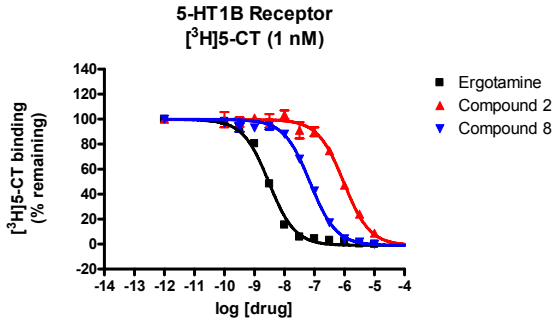
[3H]8-OH-DPAT binding (% remaining)
log [drug]
Methysergide
Compound 16r
Compound 15r

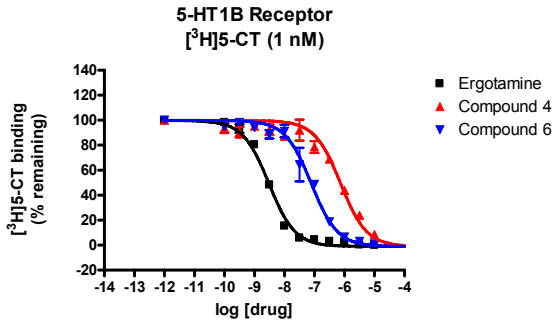

5-HT1A Receptor
[3H]8-OH-DPAT (0.5 nM)
[3H]8-OH-DPAT binding (% remaining)
log [drug]
Methysergide
Compound 13
Compound 23r

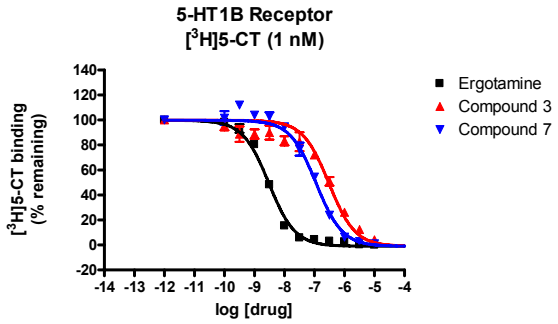

5-HT1A Receptor
[3H]8-OH-DPAT (0.5 nM)
[3H]8-OH-DPAT binding (% remaining)
log [drug]
Methysergide
Compound 19s
Compound 23s

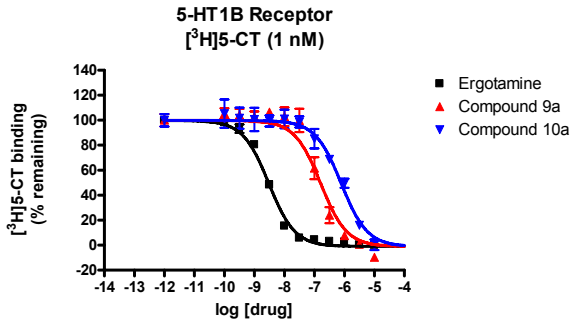

5-HT1A Receptor
[3H]8-OH-DPAT (0.5 nM)
[3H]8-OH-DPAT binding
(% remaining)
140
120
100
80
60
40
20
0
-20
-13 -12 -11 -10 -9 -8 -7 -6 -5 -4
log [drug]
Methysergide
Compound 22s
Compound 24s

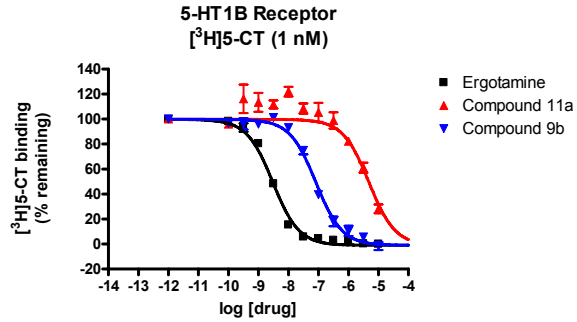

5-HT1A Receptor
[3H]8-OH-DPAT (0.5 nM)
[3H]8-OH-DPAT binding
(% remaining)
140
120
100
80
60
40
20
0
-20
-13 -12 -11 -10 -9 -8 -7 -6 -5 -4
log [drug]
Methysergide
Compound 25r

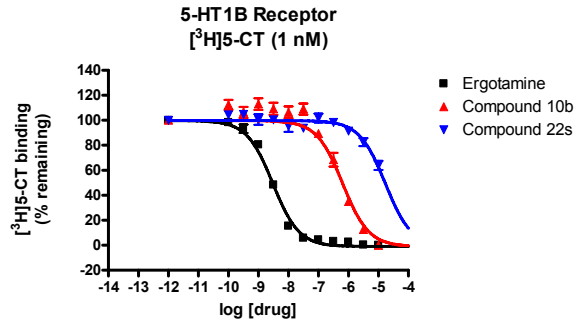

5-HT1B Receptor
[3H]5-CT (1 nM)
[3H]5-CT binding
(% remaining)
log [drug]
Ergotamine
Compound 2
Compound 8

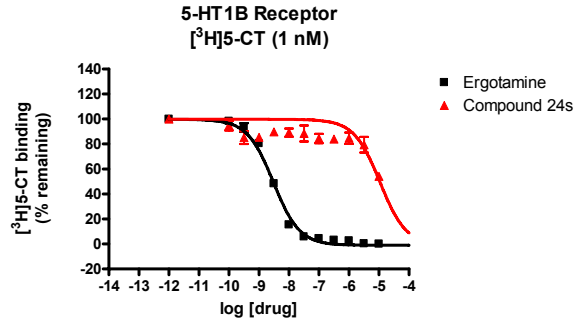

5-HT1B Receptor
[3H]5-CT (1 nM)
[3H]5-CT binding
(% remaining)
log [drug]
Ergotamine
Compound 4
Compound 6

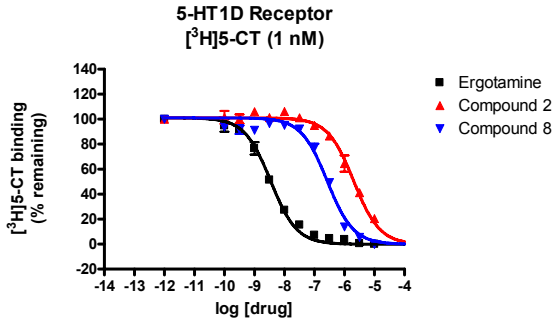

5-HT1B Receptor
[3H]5-CT (1 nM)
[3H]5-CT binding
(% remaining)
log [drug]
Ergotamine
Compound 3
Compound 7

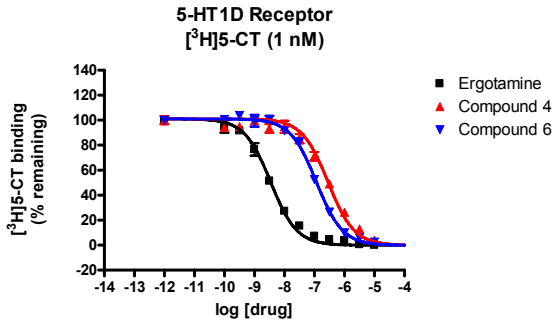

5-HT1B Receptor
[3H]5-CT (1 nM)
[3H]5-CT binding
(% remaining)
log [drug]
Ergotamine
Compound 9a
Compound 10a


5-HT1B Receptor
[3H]5-CT (1 nM)
[3H]5-CT binding
(% remaining)
log [drug]
Ergotamine
Compound 11a
Compound 9b


5-HT1B Receptor
[3H]5-CT (1 nM)
[3H]5-CT binding
(% remaining)
log [drug]
Ergotamine
Compound 10b
Compound 22s


5-HT1B Receptor
[3H]5-CT (1 nM)
[3H]5-CT binding
(% remaining)
log [drug]
Ergotamine
Compound 24s


5-HT1D Receptor
[3H]5-CT (1 nM)
[3H]5-CT binding
(% remaining)
log [drug]
Ergotamine
Compound 2
Compound 8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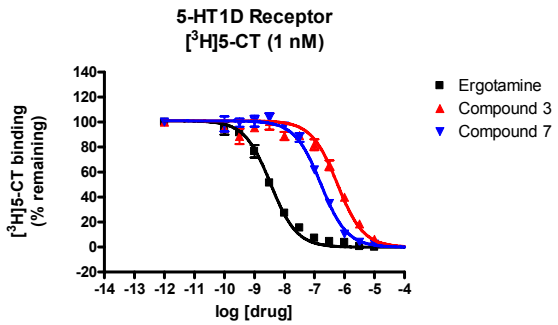
(% remaining)
log [drug]
Ergotamine
Compound 4
Compound 6


5-HT1D Receptor
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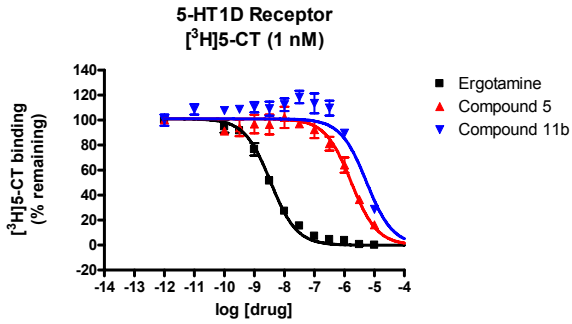
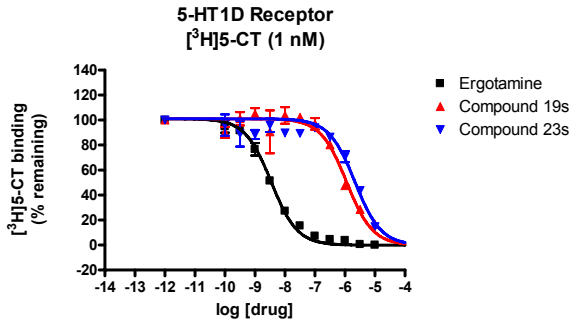
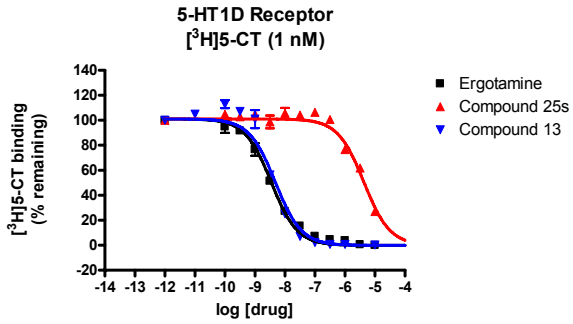
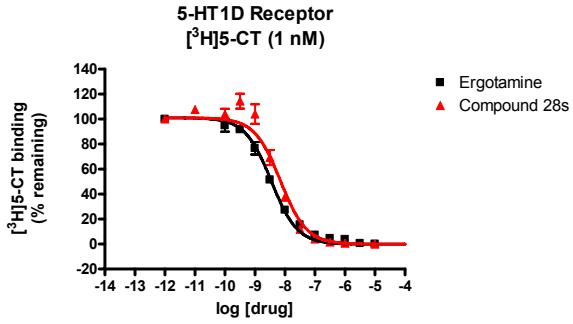
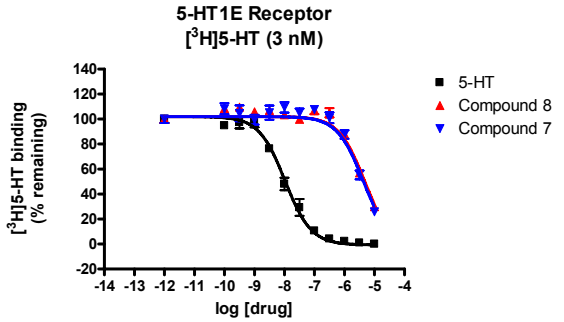
[3H]5-CT binding
(% remaining)
log [drug]
Ergotamine
Compound 3
Compound 7

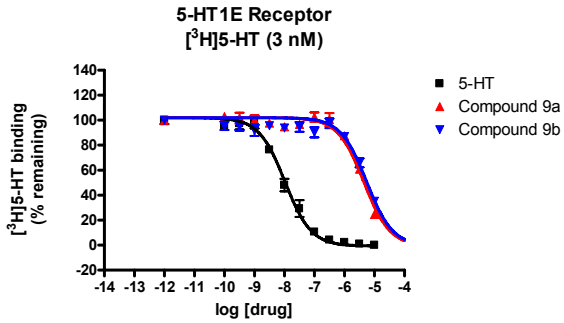

5-HT1D Receptor
[3H]5-CT (1 nM)
[3H]5-CT binding
(% remaining)
log [drug]
Ergotamine
Compound 5
Compound 11b

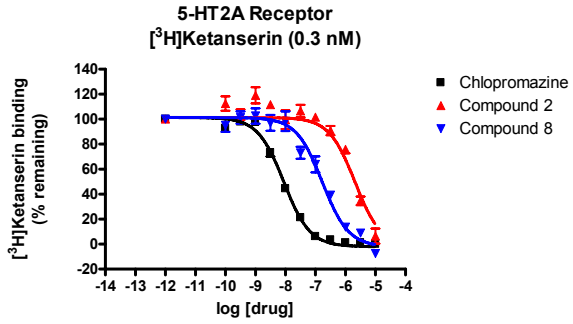

5-HT1D Receptor
[3H]5-CT (1 nM)
[3H]5-CT binding
(% remaining)
140
120
100
80
60
40
20
0
-20
-14 -13 -12 -11 -10 -9 -8 -7 -6 -5 -4
log [drug]
Ergotamine
Compound 19s
Compound 23s

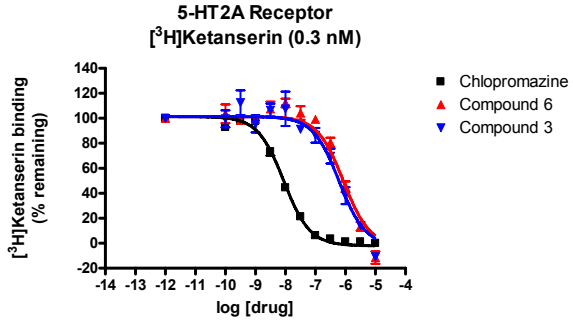

5-HT1D Receptor
[3H]5-CT (1 nM)
[3H]5-CT binding
(% remaining)
140
120
100
80
60
40
20
0
-20
-14 -13 -12 -11 -10 -9 -8 -7 -6 -5 -4
log [drug]
Ergotamine
Compound 25s
Compound 13

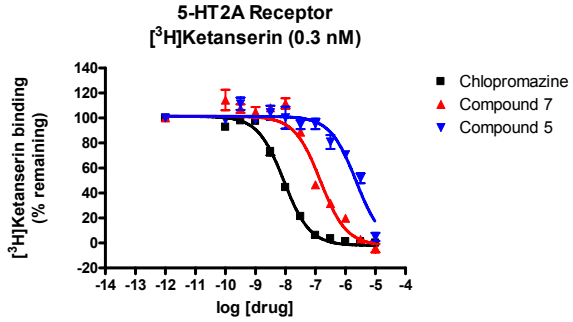

5-HT1D Receptor
[3H]5-CT (1 nM)
[3H]5-CT binding
(% remaining)
140
120
100
80
60
40
20
0
-20
-14 -13 -12 -11 -10 -9 -8 -7 -6 -5 -4
log [drug]
Ergotamine
Compound 28s

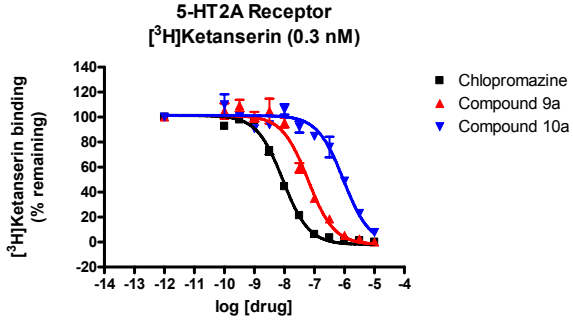

5-HT1E Receptor
[3H]5-HT (3 nM)
[3H]5-HT binding
(% remaining)
140
120
100
80
60
40
20
0
-20
-14 -13 -12 -11 -10 -9 -8 -7 -6 -5 -4
log [drug]
5-HT
Compound 8
Compound 7

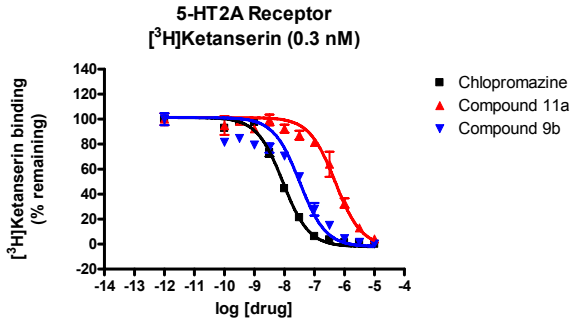

5-HT1E Receptor
[3H]5-HT (3 nM)
[3H]5-HT binding
(% remaining)
140
120
100
80
60
40
20
0
-20
-14 -13 -12 -11 -10 -9 -8 -7 -6 -5 -4
log [drug]
5-HT
Compound 9a
Compound 9b

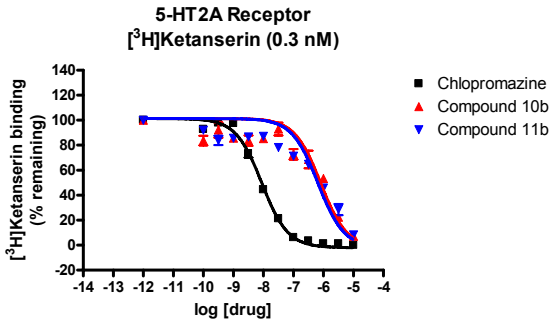

5-HT2A Receptor
[3H]Ketanserin (0.3 nM)
[3H]Ketanserin binding
(% remaining)
log [drug]
Chlopromazine
Compound 2
Compound 8

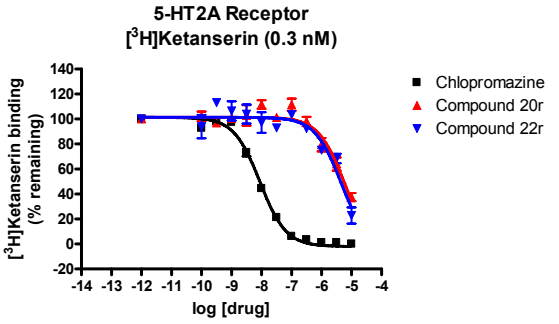

5-HT2A Receptor
[3H]Ketanserin (0.3 nM)
[3H]Ketanserin binding
(% remaining)
log [drug]
Chlopromazine
Compound 6
Compound 3

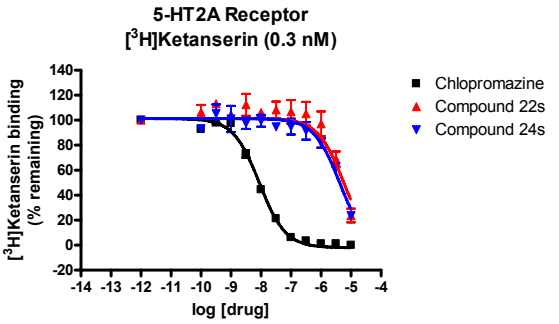

5-HT2A Receptor
[3H]Ketanserin (0.3 nM)
[3H]Ketanserin binding
(% remaining)
log [drug]
Chlopromazine
Compound 7
Compound 5

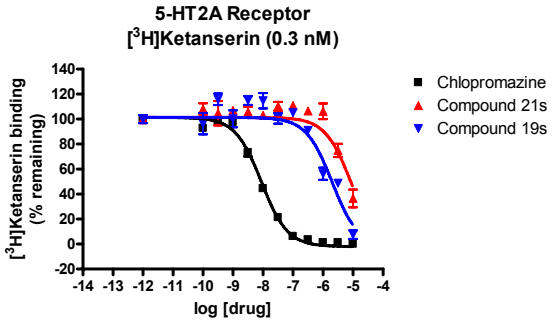

5-HT2A Receptor
[3H]Ketanserin (0.3 nM)
[3H]Ketanserin binding
(% remaining)
log [drug]
Chlopromazine
Compound 9a
Compound 10a

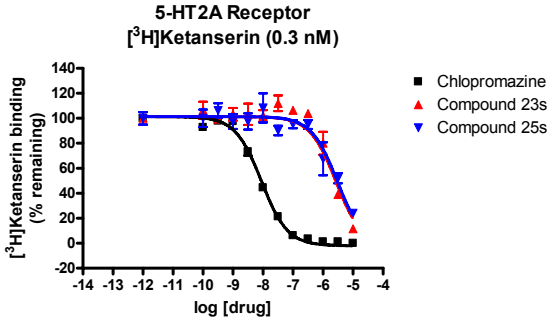

5-HT2A Receptor
[3H]Ketanserin (0.3 nM)
[3H]Ketanserin binding (% remaining)
log [drug]
Chlopromazine
Compound 11a
Compound 9b

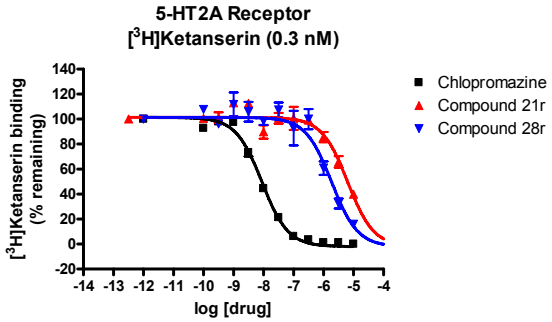

5-HT2A Receptor
[3H]Ketanserin (0.3 nM)
[3H]Ketanserin binding (% remaining)
log [drug]
Chlopromazine
Compound 10b
Compound 11b

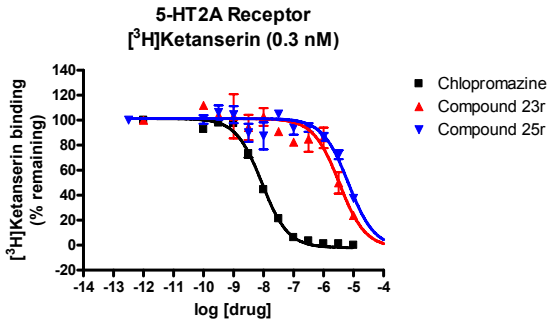

5-HT2A Receptor
[3H]Ketanserin (0.3 nM)
[3H]Ketanserin binding (% remaining)
log [drug]
Chlopromazine
Compound 20r
Compound 22r

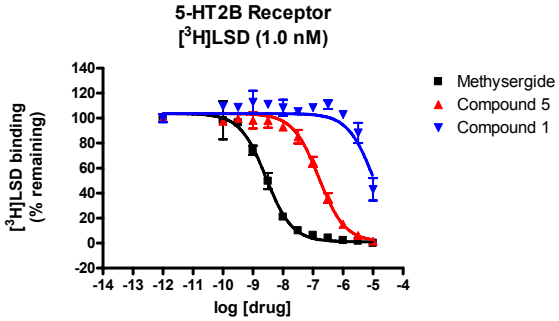

5-HT2A Receptor
[3H]Ketanserin (0.3 nM)
[3H]Ketanserin binding (% remaining)
log [drug]
Chlopromazine
Compound 22s
Compound 24s

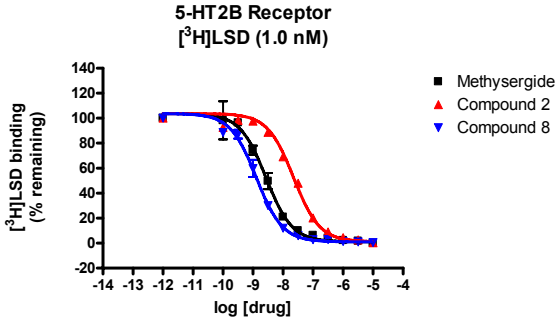

5-HT2A Receptor
[3H]Ketanserin (0.3 nM)
[3H]Ketanserin binding
(% remaining)
log [drug]
Chlopromazine
Compound 21s
Compound 19s

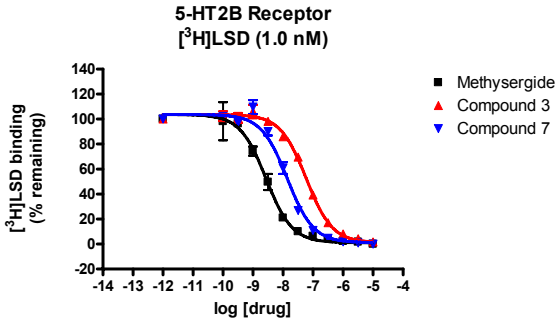

5-HT2A Receptor
[3H]Ketanserin (0.3 nM)
[3H]Ketanserin binding
(% remaining)
log [drug]
Chlopromazine
Compound 23s
Compound 25s

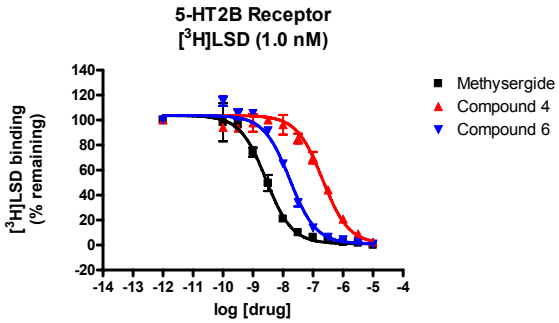

5-HT2A Receptor
[3H]Ketanserin (0.3 nM)
[3H]Ketanserin binding
(% remaining)
log [drug]
Chlopromazine
Compound 21r
Compound 28r

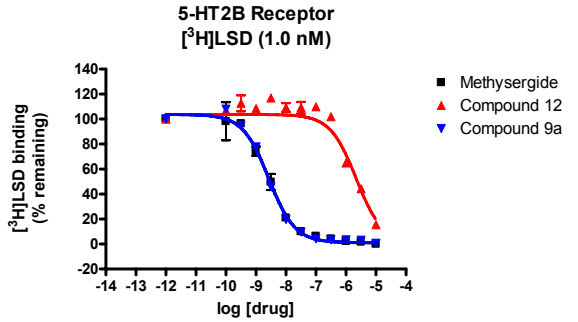

5-HT2A Receptor
[3H]Ketanserin (0.3 nM)
[3H]Ketanserin binding
(% remaining)
log [drug]
Chlopromazine
Compound 23r
Compound 25r

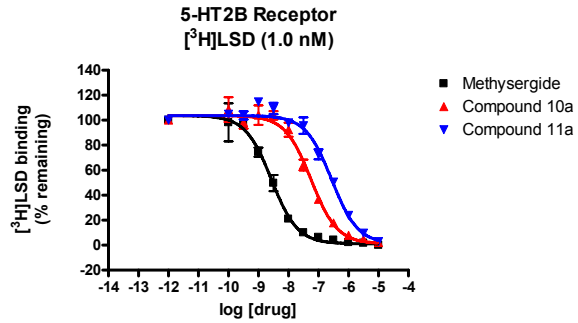

5-HT2B Receptor
[3H]LSD (1.0 nM)
[3H]LSD binding
(% remaining)
log [drug]
Methysergide
Compound 5
Compound 1

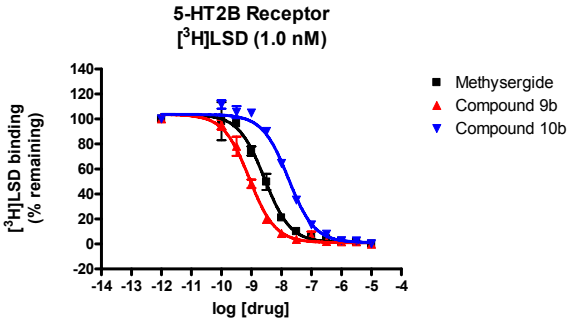

5-HT2B Receptor
[3H]LSD (1.0 nM)
[3H]LSD binding
(% remaining)
log [drug]
Methysergide
Compound 2
Compound 8

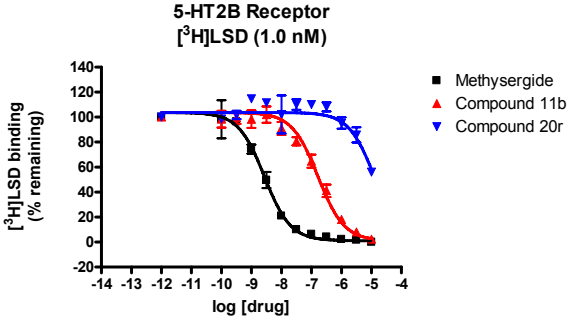

5-HT2B Receptor
[3H]LSD (1.0 nM)
[3H]LSD binding
(% remaining)
log [drug]
Methysergide
Compound 3
Compound 7

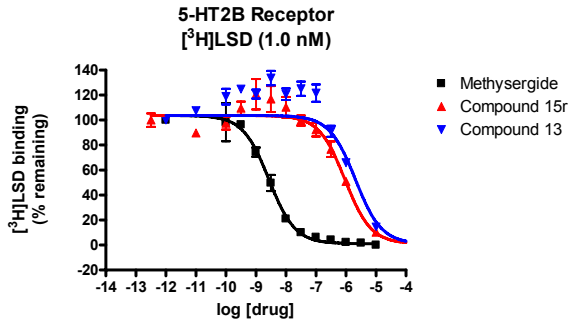

5-HT2B Receptor
[3H]LSD (1.0 nM)
[3H]LSD binding
(% remaining)
log [drug]
Methysergide
Compound 4
Compound 6

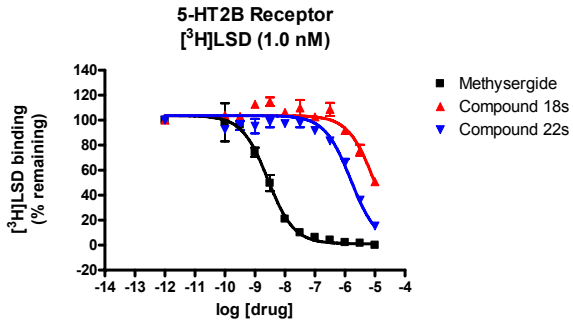

5-HT2B Receptor
[3H]LSD (1.0 nM)
[3H]LSD binding
(% remaining)
log [drug]
Methysergide
Compound 12
Compound 9a

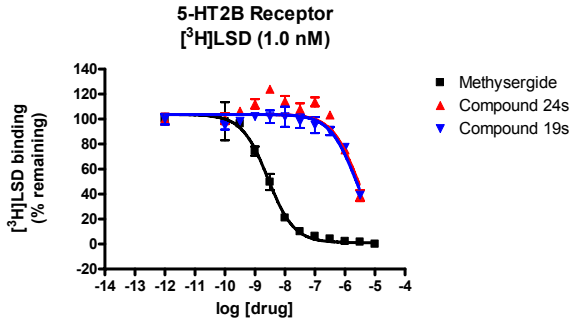

5-HT2B Receptor
[3H]LSD (1.0 nM)
[3H]LSD binding
(% remaining)
log [drug]
Methysergide
Compound 10a
Compound 11a

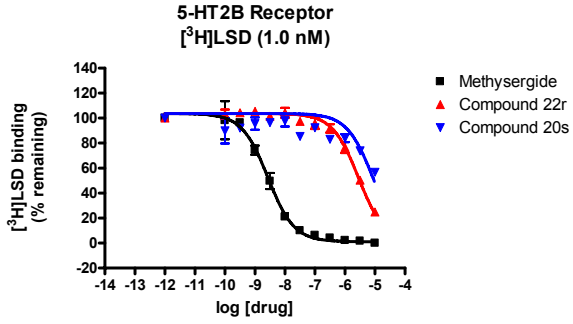

5-HT2B Receptor
[3H]LSD (1.0 nM)
[3H]LSD binding
(% remaining)
log [drug]
Methysergide
Compound 9b
Compound 10b

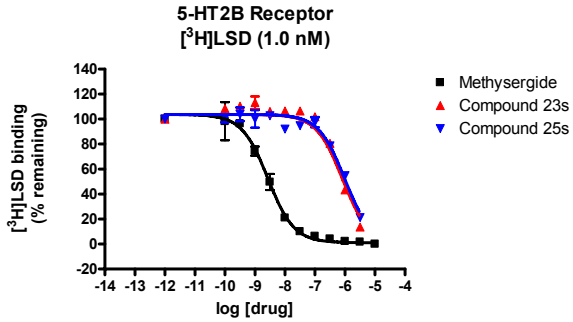

5-HT2B Receptor
[3H]LSD (1.0 nM)
[3H]LSD binding
(% remaining)
log [drug]
Methysergide
Compound 11b
Compound 20r

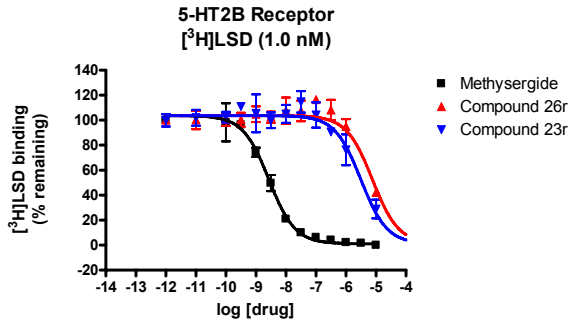

5-HT2B Receptor
[3H]LSD (1.0 nM)
[3H]LSD binding
(% remaining)
log [drug]
Methysergide
Compound 15r
Compound 13

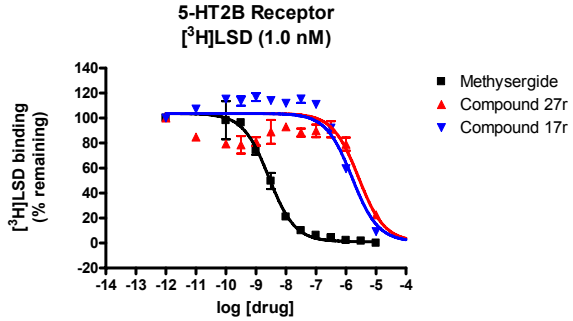

5-HT2B Receptor
[3H]LSD (1.0 nM)
[3H]LSD binding
(% remaining)
log [drug]
Methysergide
Compound 18s
Compound 22s

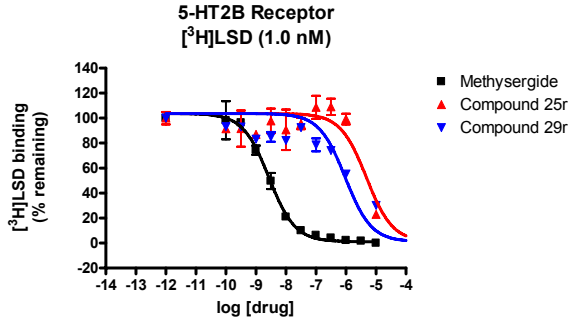

5-HT2B Receptor
[3H]LSD (1.0 nM)
[3H]LSD binding
(% remaining)
log [drug]
Methysergide
Compound 24s
Compound 19s

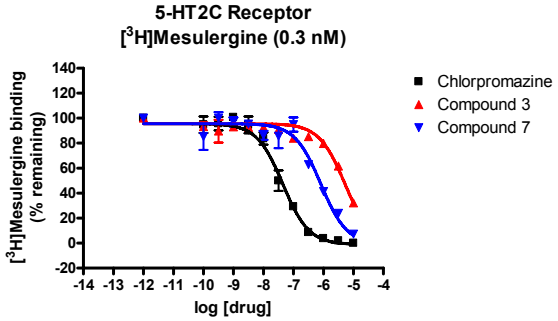

5-HT2B Receptor
[3H]LSD (1.0 nM)
[3H]LSD binding
(% remaining)
log [drug]
Methysergide
Compound 22r
Compound 20s

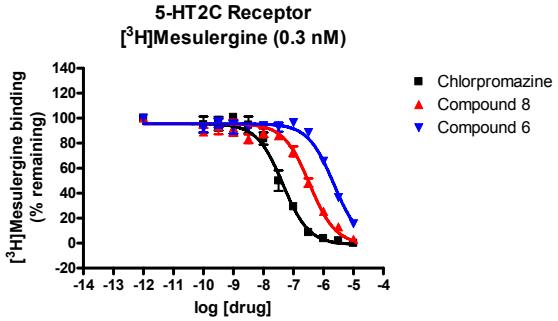

5-HT2B Receptor
[3H]LSD (1.0 nM)
[3H]LSD binding
(% remaining)
log [drug]
Methysergide
Compound 23s
Compound 25s

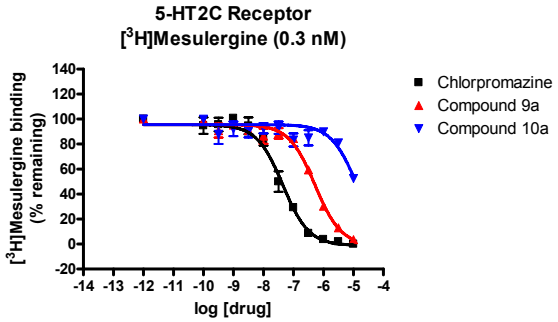

5-HT2B Receptor
[3H]LSD (1.0 nM)
[3H]LSD binding
(% remaining)
log [drug]
Methysergide
Compound 26r
Compound 23r

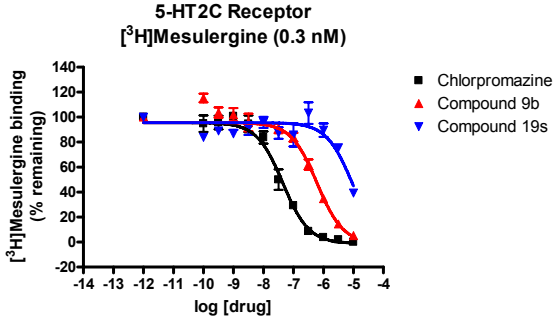

5-HT2B Receptor
[3H]LSD (1.0 nM)
[3H]LSD binding
(% remaining)
log [drug]
Methysergide
Compound 27r
Compound 17r

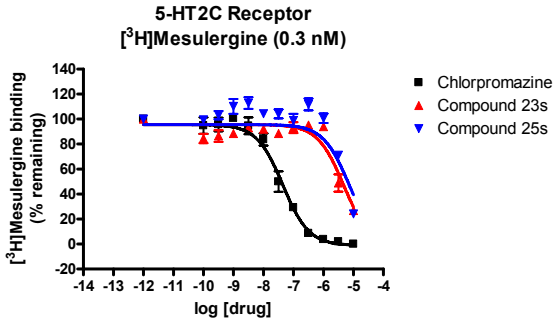

5-HT2B Receptor
[3H]LSD (1.0 nM)
[3H]LSD binding
(% remaining)
log [drug]
Methysergide
Compound 25r
Compound 29r

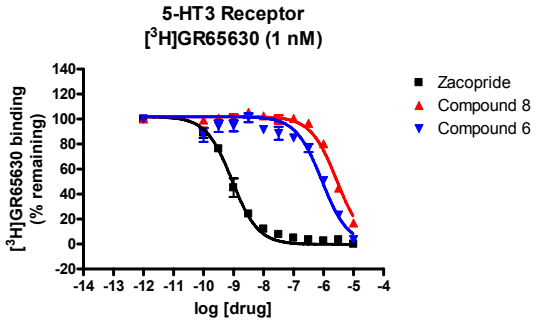

5-HT2C Receptor
[3H]Mesulergine (0.3 nM)
[3H]Mesulergine binding (% remaining)
log [drug]
Chlorpromazine
Compound 3
Compound 7

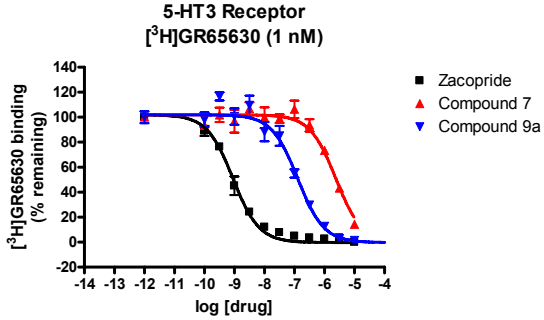

5-HT2C Receptor
[3H]Mesulergine (0.3 nM)
[3H]Mesulergine binding (% remaining)
log [drug]
Chlorpromazine
Compound 8
Compound 6

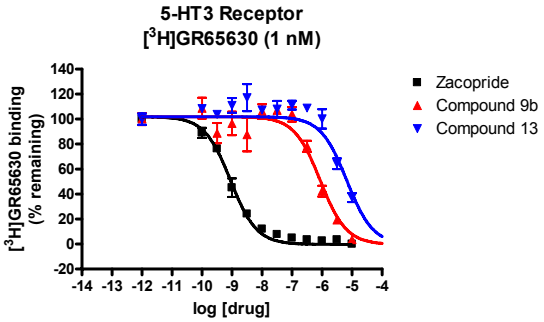

5-HT2C Receptor
[3H]Mesulergine (0.3 nM)
[3H]Mesulergine binding (% remaining)
log [drug]
Chlorpromazine
Compound 9a
Compound 10a

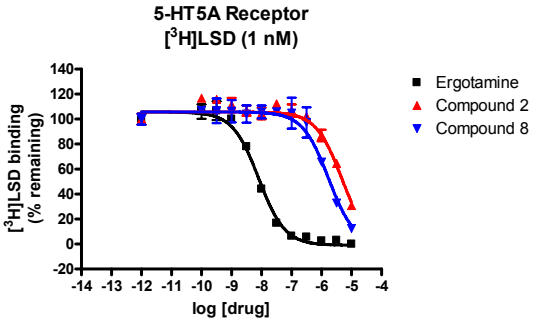

5-HT2C Receptor
[3H]Mesulergine (0.3 nM)
[3H]Mesulergine binding (% remaining)
log [drug]
Chlorpromazine
Compound 9b
Compound 19s

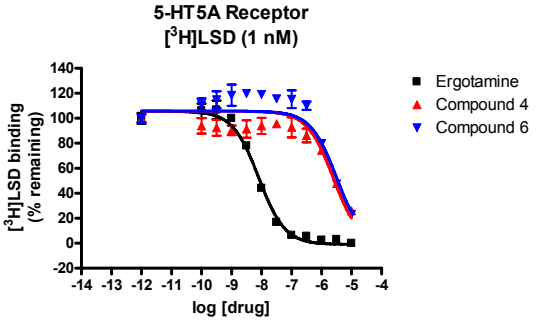

5-HT2C Receptor
[3H]Mesulergine (0.3 nM)
[3H]Mesulergine binding
(% remaining)
140
120
100
80
60
40
20
0
-20
-14 -13 -12 -11 -10 -9 -8 -7 -6 -5 -4
log [drug]
Chlorpromazine
Compound 23s
Compound 25s

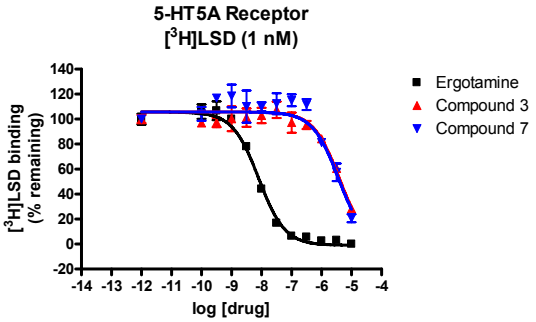

5-HT3 Receptor
[3H]GR65630 (1 nM)
[3H]GR65630 binding
(% remaining)
log [drug]
Zacopride
Compound 8
Compound 6

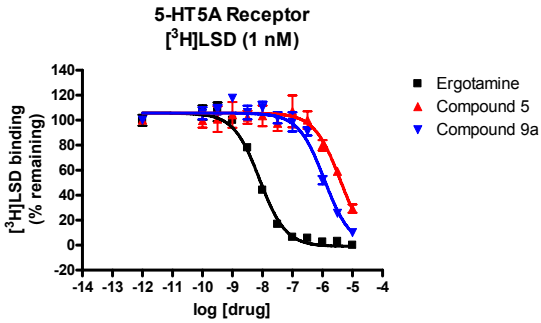

5-HT3 Receptor
[3H]GR65630 (1 nM)
[3H]GR65630 binding
(% remaining)
log [drug]
Zacopride
Compound 7
Compound 9a

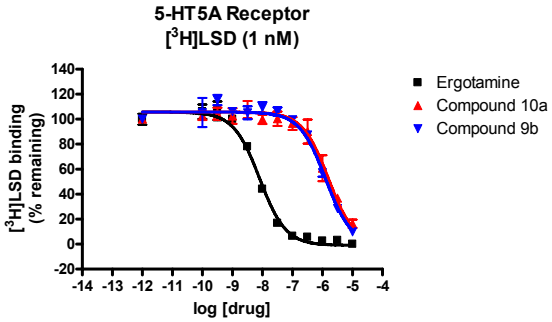

5-HT3 Receptor
[3H]GR65630 (1 nM)
[3H]GR65630 binding
(% remaining)
log [drug]
Zacopride
Compound 9b
Compound 13

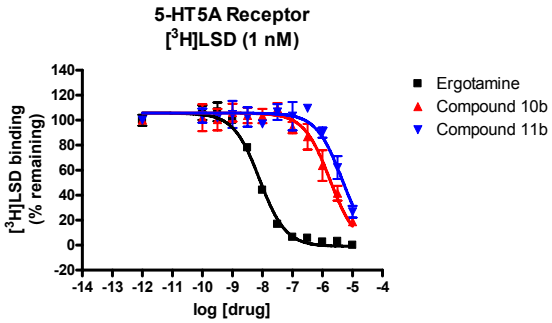

5-HT5A Receptor
[3H]LSD (1 nM)
[3H]LSD binding
(% remaining)
log [drug]
Ergotamine
Compound 2
Compound 8

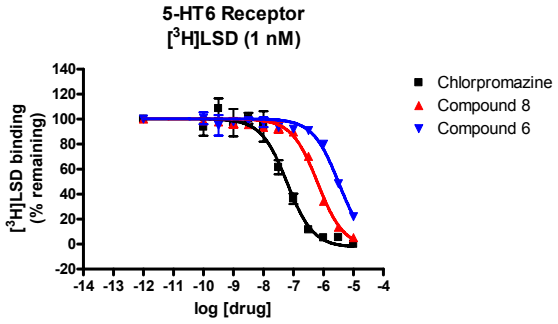

5-HT5A Receptor
[3H]LSD (1 nM)
[3H]LSD binding
(% remaining)
log [drug]
Ergotamine
Compound 4
Compound 6

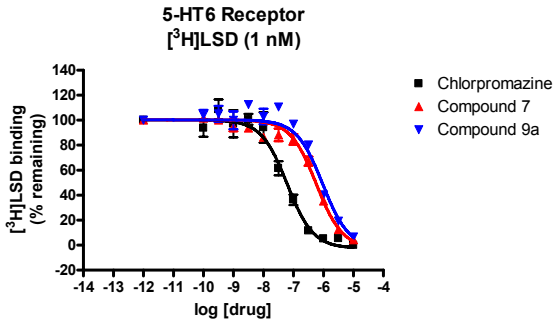

5-HT5A Receptor
[3H]LSD (1 nM)
[3H]LSD binding
(% remaining)
log [drug]
Ergotamine
Compound 3
Compound 7

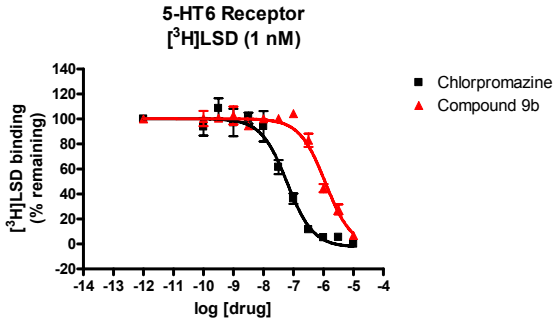

5-HT5A Receptor
[3H]LSD (1 nM)
[3H]LSD binding
(% remaining)
log [drug]
Ergotamine
Compound 5
Compound 9a

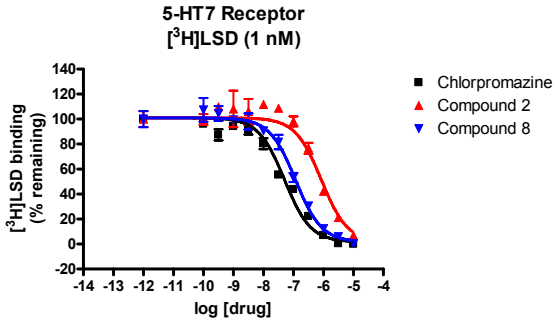

5-HT5A Receptor
[3H]LSD (1 nM)
[3H]LSD binding
(% remaining)
log [drug]
Ergotamine
Compound 10a
Compound 9b

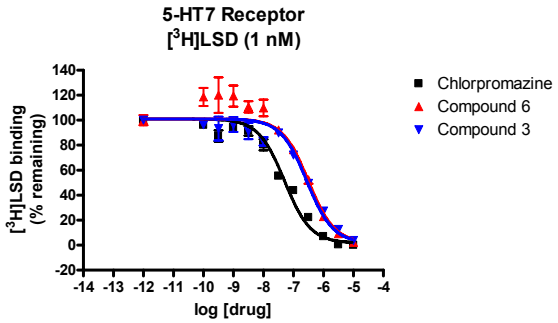

5-HT5A Receptor
[3H]LSD (1 nM)
[3H]LSD binding
(% remaining)
log [drug]
Ergotamine
Compound 10b
Compound 11b

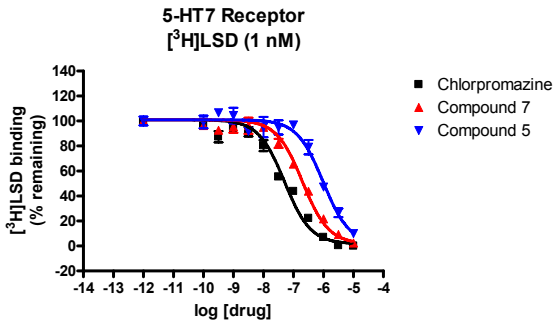

5-HT6 Receptor
[3H]LSD (1 nM)
[3H]LSD binding
(% remaining)
log [drug]
Chlorpromazine
Compound 8
Compound 6

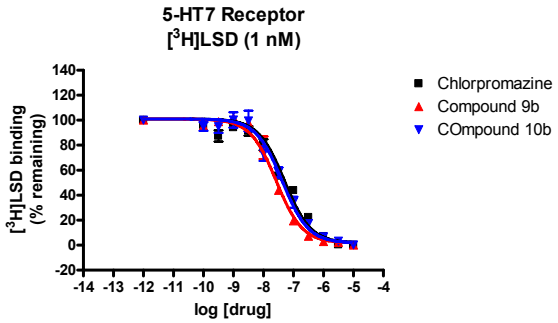

5-HT6 Receptor
[3H]LSD (1 nM)
[3H]LSD binding
(% remaining)
log [drug]
Chlorpromazine
Compound 7
Compound 9a

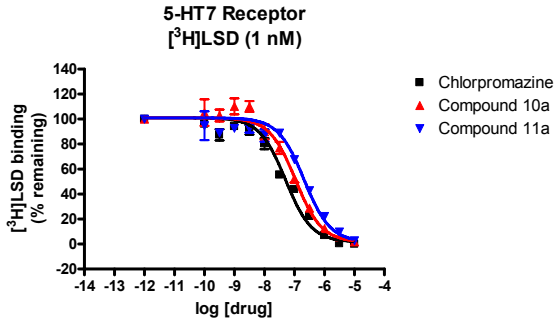

5-HT6 Receptor
[3H]LSD (1 nM)
[3H]LSD binding
(% remaining)
log [drug]
Chlorpromazine
Compound 9b

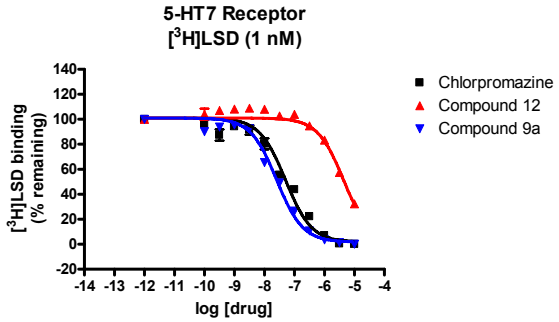

5-HT7 Receptor
[3H]LSD (1 nM)
[3H]LSD binding
(% remaining)
log [drug]
Chlorpromazine
Compound 2
Compound 8

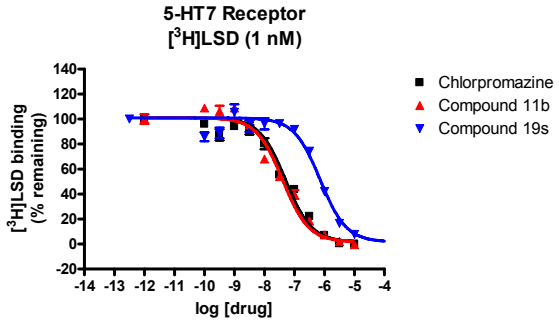

5-HT7 Receptor
[3H]LSD (1 nM)
[3H]LSD binding
(% remaining)
log [drug]
Chlorpromazine
Compound 6
Compound 3

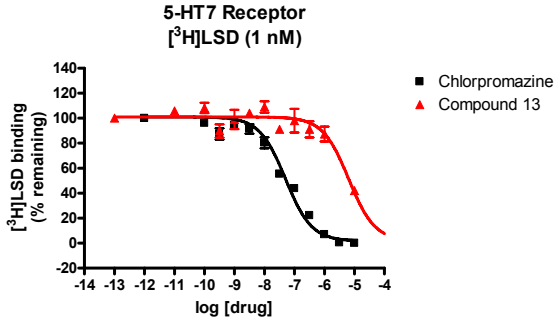

5-HT7 Receptor
[3H]LSD (1 nM)
[3H]LSD binding
(% remaining)
log [drug]
Chlorpromazine
Compound 7
Compound 5

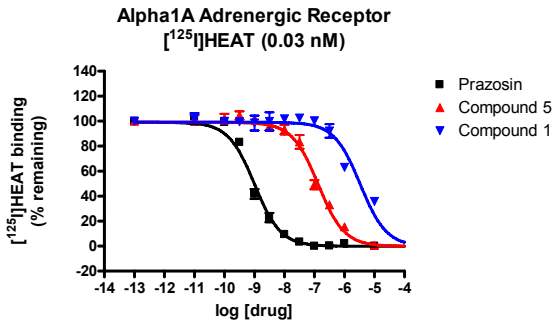

5-HT7 Receptor
[3H]LSD (1 nM)
[3H]LSD binding
(% remaining)
log [drug]
Chlorpromazine
Compound 9b
COmpound 10b

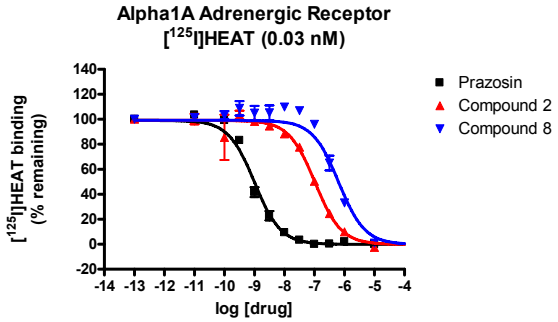

5-HT7 Receptor
[3H]LSD (1 nM)
[3H]LSD binding
(% remaining)
log [drug]
Chlorpromazine
Compound 10a
Compound 11a

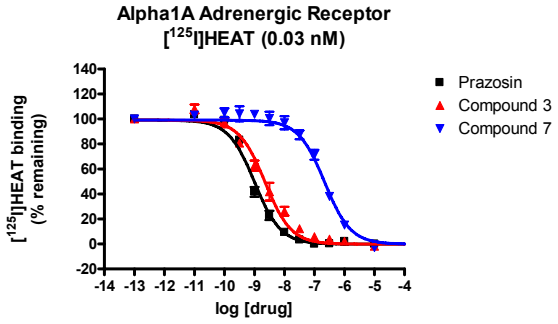

5-HT7 Receptor
[3H]LSD (1 nM)
[3H]LSD binding
(% remaining)
log [drug]
Chlorpromazine
Compound 12
Compound 9a

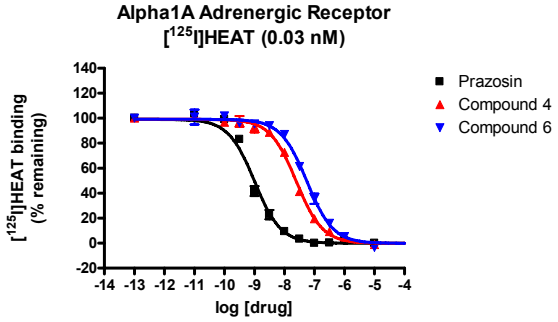

5-HT7 Receptor
[3H]LSD (1 nM)
[3H]LSD binding
(% remaining)
log [drug]
Chlorpromazine
Compound 11b
Compound 19s

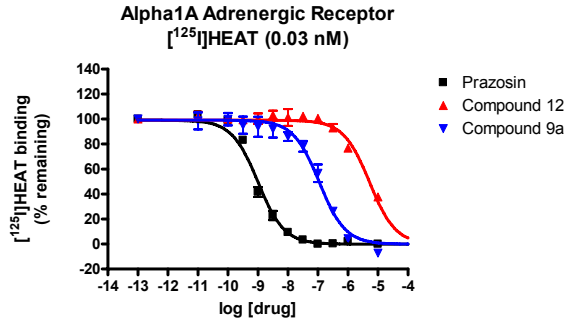

5-HT7 Receptor
[3H]LSD (1 nM)
[3H]LSD binding
(% remaining)
log [drug]
Chlorpromazine
Compound 13

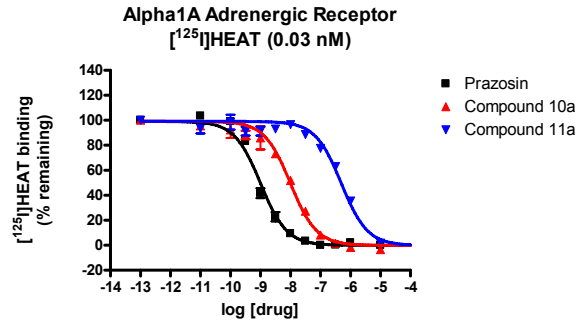

Alpha1A Adrenergic Receptor
[125I]HEAT (0.03 nM)
[125I]HEAT binding
(% remaining)
log [drug]
Prazosin
Compound 5
Compound 1

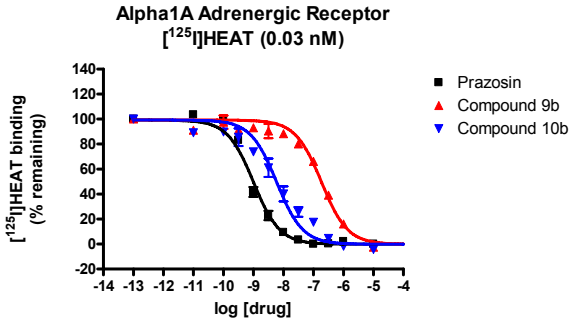

Alpha1A Adrenergic Receptor
[125I]HEAT (0.03 nM)
[125I]HEAT binding
(% remaining)
log [drug]
Prazosin
Compound 2
Compound 8

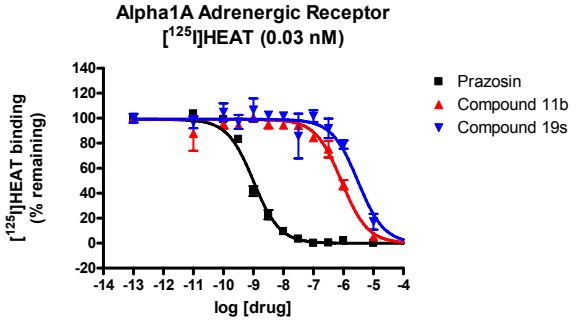

Alpha1A Adrenergic Receptor
[125I]HEAT (0.03 nM)
[125I]HEAT binding
(% remaining)
log [drug]
Prazosin
Compound 3
Compound 7

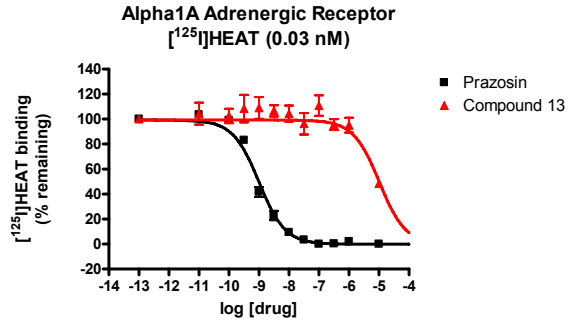

Alpha1A Adrenergic Receptor
[125I]HEAT (0.03 nM)
[125I]HEAT binding
(% remaining)
log [drug]
Prazosin
Compound 4
Compound 6

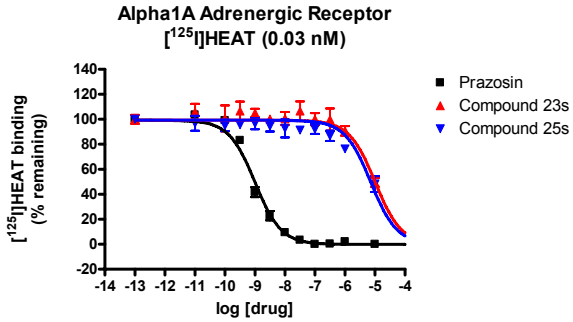

Alpha1A Adrenergic Receptor
[125I]HEAT (0.03 nM)
[125I]HEAT binding
(% remaining)
log [drug]
Prazosin
Compound 12
Compound 9a

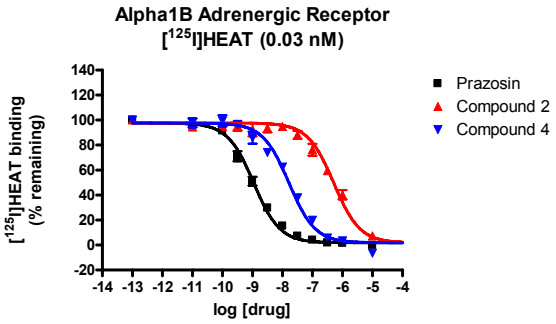

Alpha1A Adrenergic Receptor
[125I]HEAT (0.03 nM)
[125I]HEAT binding
(% remaining)
log [drug]
Prazosin
Compound 10a
Compound 11a

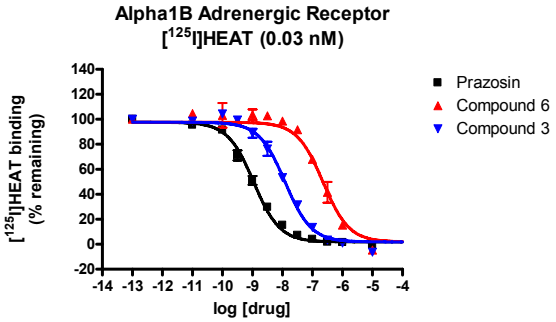

Alpha1A Adrenergic Receptor
[125I]HEAT (0.03 nM)
[125I]HEAT binding
(% remaining)
log [drug]
Prazosin
Compound 9b
Compound 10b

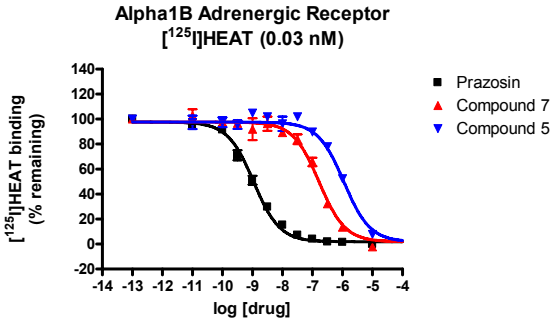

Alpha1A Adrenergic Receptor
[125I]HEAT (0.03 nM)
[125I]HEAT binding
(% remaining)
log [drug]
Prazosin
Compound 11b
Compound 19s

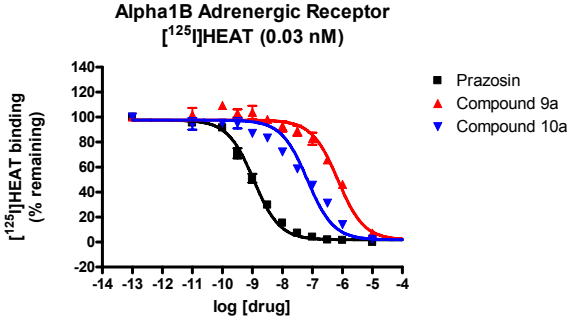

Alpha1A Adrenergic Receptor
[125I]HEAT (0.03 nM)
[125I]HEAT binding
(% remaining)
140
120
100
80
60
40
20
0
-20
-14 -13 -12 -11 -10 -9 -8 -7 -6 -5 -4
log [drug]
Prazosin
Compound 13

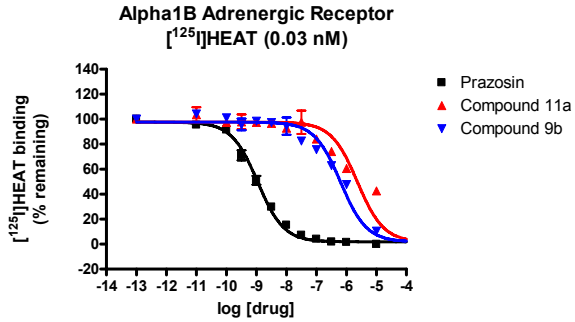

Alpha1A Adrenergic Receptor
[125I]HEAT (0.03 nM)
[125I]HEAT binding
(% remaining)
140
120
100
80
60
40
20
0
-20
-14 -13 -12 -11 -10 -9 -8 -7 -6 -5 -4
log [drug]
Prazosin
Compound 23s
Compound 25s

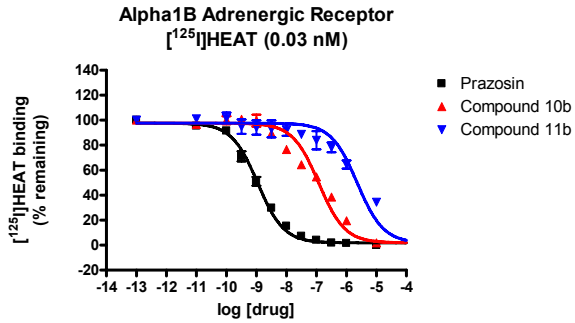

Alpha1B Adrenergic Receptor
[125I]HEAT (0.03 nM)
[125I]HEAT binding
(% remaining)
log [drug]
Prazosin
Compound 2
Compound 4

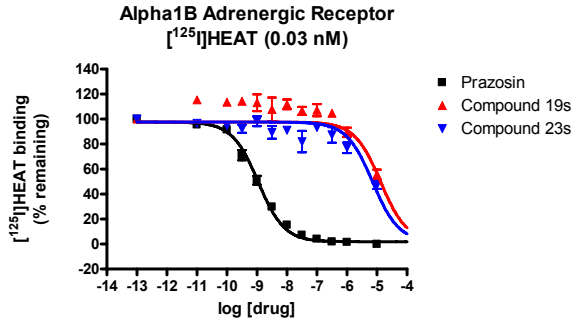

Alpha1B Adrenergic Receptor
[125I]HEAT (0.03 nM)
[125I]HEAT binding
(% remaining)
log [drug]
Prazosin
Compound 6
Compound 3

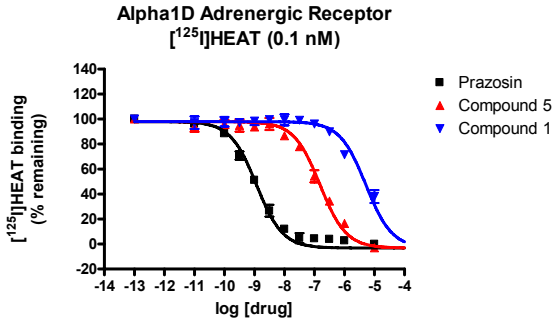

Alpha1B Adrenergic Receptor
[125I]HEAT (0.03 nM)
[125I]HEAT binding
(% remaining)
log [drug]
Prazosin
Compound 7
Compound 5

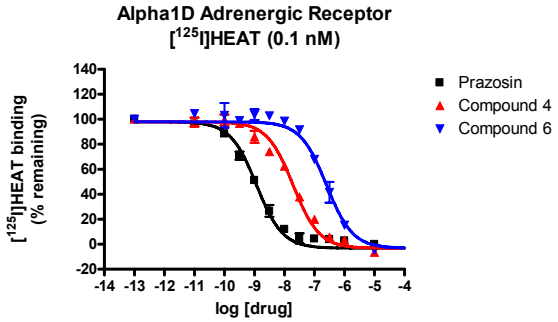

Alpha1B Adrenergic Receptor
[125I]HEAT (0.03 nM)
[125I]HEAT binding
(% remaining)
log [drug]
Prazosin
Compound 9a
Compound 10a

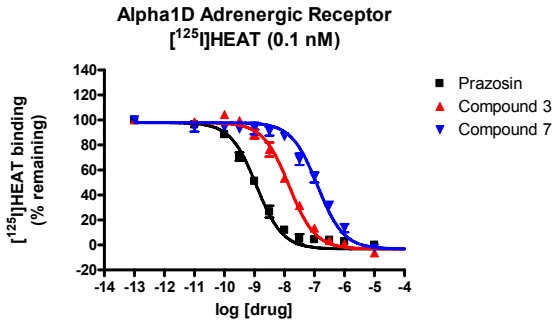

Alpha1B Adrenergic Receptor
[125I]HEAT (0.03 nM)
[125I]HEAT binding
(% remaining)
log [drug]
Prazosin
Compound 11a
Compound 9b

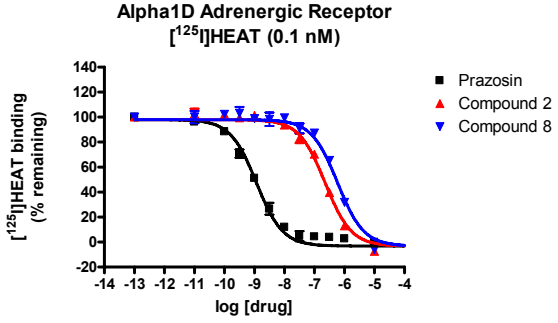

Alpha1B Adrenergic Receptor
[125I]HEAT (0.03 nM)
[125I]HEAT binding
(% remaining)
log [drug]
Prazosin
Compound 10b
Compound 11b

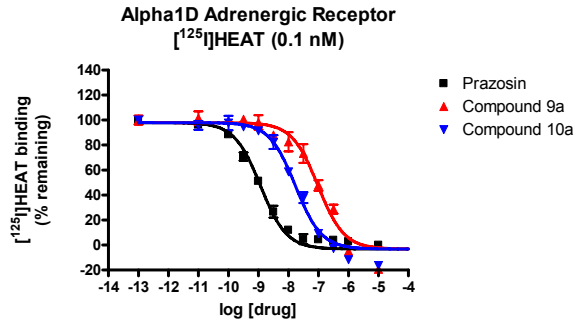

Alpha1B Adrenergic Receptor
[125I]HEAT (0.03 nM)
[125I]HEAT binding
(% remaining)
log [drug]
Prazosin
Compound 19s
Compound 23s

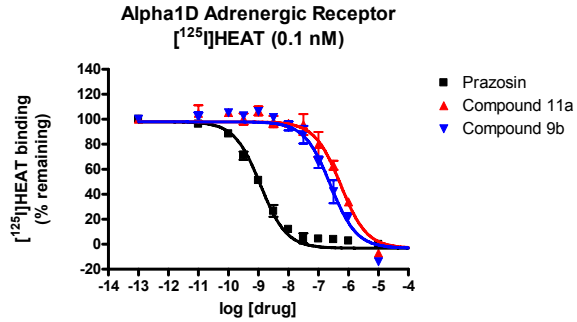

Alpha1D Adrenergic Receptor
[125I]HEAT (0.1 nM)
[125I]HEAT binding
(% remaining)
140
120
100
80
60
40
20
0
-20
-14 -13 -12 -11 -10 -9 -8 -7 -6 -5 -4
log [drug]
Prazosin
Compound 5
Compound 1

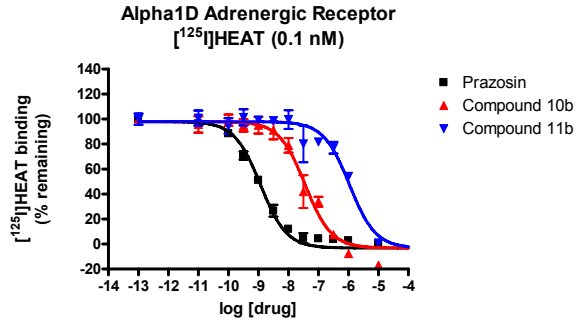

Alpha1D Adrenergic Receptor
[125I]HEAT (0.1 nM)
[125I]HEAT binding
(% remaining)
140
120
100
80
60
40
20
0
-20
-14 -13 -12 -11 -10 -9 -8 -7 -6 -5 -4
log [drug]
Prazosin
Compound 4
Compound 6

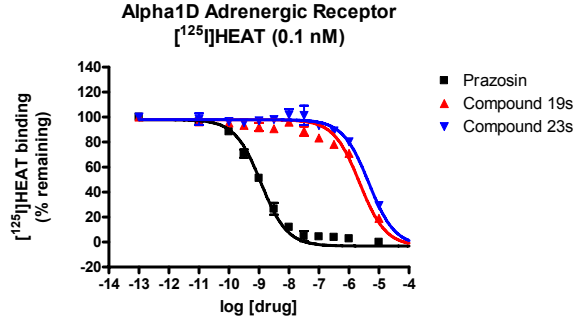

Alpha1D Adrenergic Receptor
[125I]HEAT (0.1 nM)
[125I]HEAT binding
(% remaining)
140
120
100
80
60
40
20
0
-20
-14 -13 -12 -11 -10 -9 -8 -7 -6 -5 -4
log [drug]
Prazosin
Compound 3
Compound 7

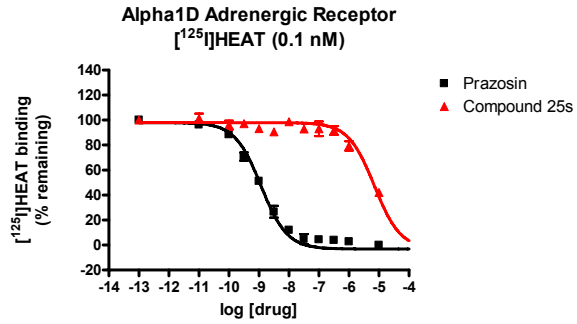

Alpha1D Adrenergic Receptor
[125I]HEAT (0.1 nM)
[125I]HEAT binding
(% remaining)
140
120
100
80
60
40
20
0
-20
-14 -13 -12 -11 -10 -9 -8 -7 -6 -5 -4
log [drug]
Prazosin
Compound 2
Compound 8

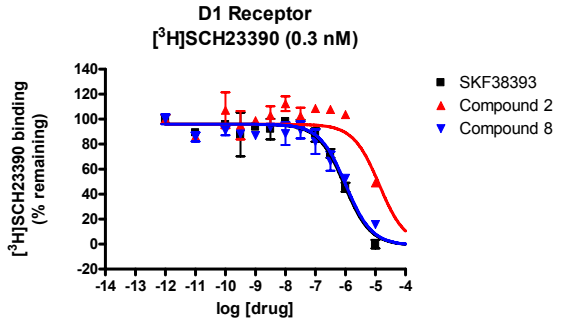

Alpha1D Adrenergic Receptor
[125I]HEAT (0.1 nM)
[125I]HEAT binding
(% remaining)
log [drug]
Prazosin
Compound 9a
Compound 10a

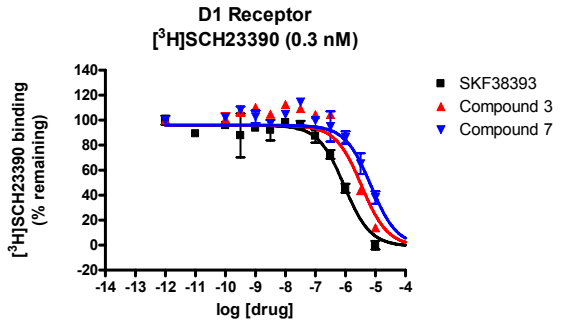

Alpha1D Adrenergic Receptor
[125I]HEAT (0.1 nM)
[125I]HEAT binding
(% remaining)
log [drug]
Prazosin
Compound 11a
Compound 9b

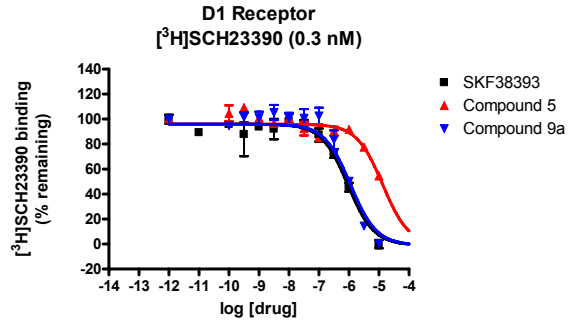

Alpha1D Adrenergic Receptor
[125I]HEAT (0.1 nM)
[125I]HEAT binding
(% remaining)
log [drug]
Prazosin
Compound 10b
Compound 11b

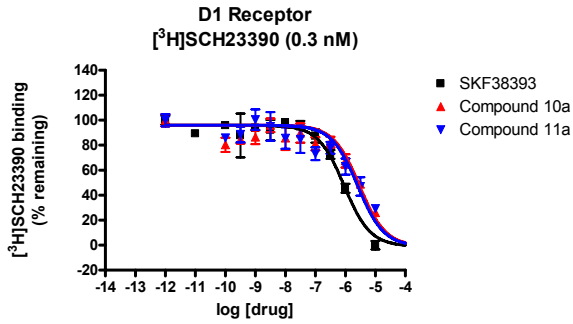

Alpha1D Adrenergic Receptor
[125I]HEAT (0.1 nM)
[125I]HEAT binding
(% remaining)
log [drug]
Prazosin
Compound 19s
Compound 23s

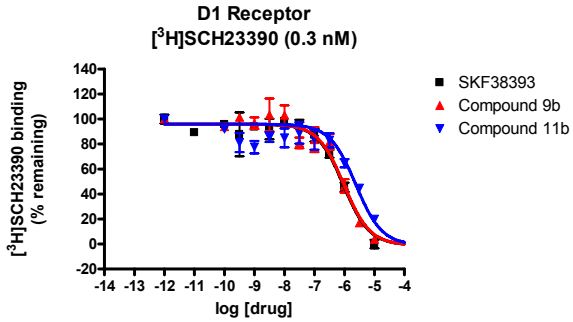

Alpha1D Adrenergic Receptor
[125I]HEAT (0.1 nM)
[125I]HEAT binding
(% remaining)
140
120
100
80
60
40
20
0
-20
-14 -13 -12 -11 -10 -9 -8 -7 -6 -5 -4
log [drug]
Prazosin
Compound 25s

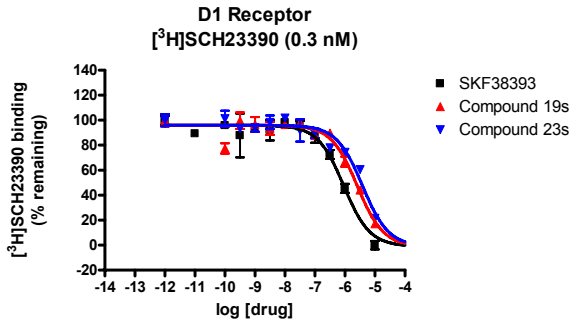

D1 Receptor
[3H]SCH23390 (0.3 nM)
[3H]SCH23390 binding
(% remaining)
log [drug]
SKF38393
Compound 2
Compound 8

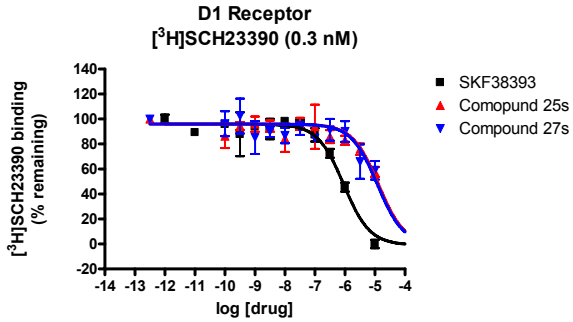

D1 Receptor
[3H]SCH23390 (0.3 nM)
[3H]SCH23390 binding
(% remaining)
log [drug]
SKF38393
Compound 3
Compound 7

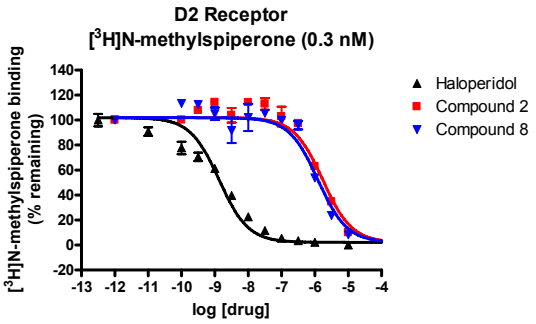

D1 Receptor
[3H]SCH23390 (0.3 nM)
[3H]SCH23390 binding
(% remaining)
log [drug]
SKF38393
Compound 5
Compound 9a

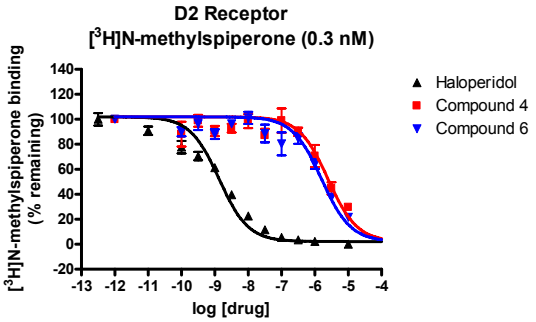

D1 Receptor
[3H]SCH23390 (0.3 nM)
[3H]SCH23390 binding
(% remaining)
log [drug]
SKF38393
Compound 10a
Compound 11a

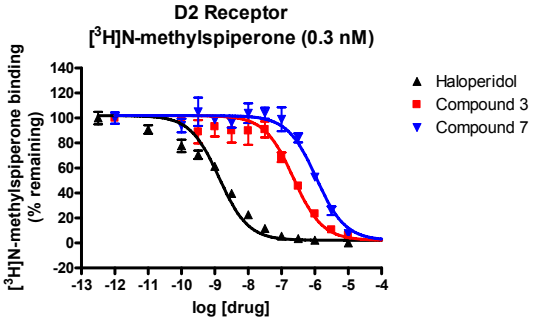

D1 Receptor
[3H]SCH23390 (0.3 nM)
[3H]SCH23390 binding
(% remaining)
log [drug]
SKF38393
Compound 9b
Compound 11b

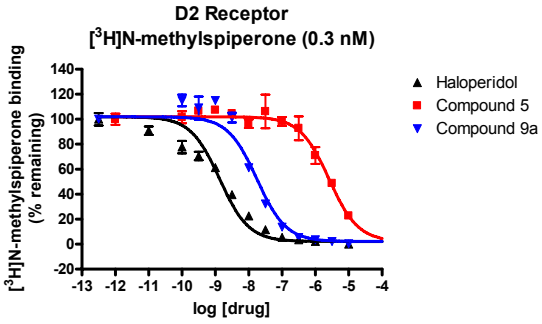

D1 Receptor
[3H]SCH23390 (0.3 nM)
[3H]SCH23390 binding
(% remaining)
log [drug]
SKF38393
Compound 19s
Compound 23s

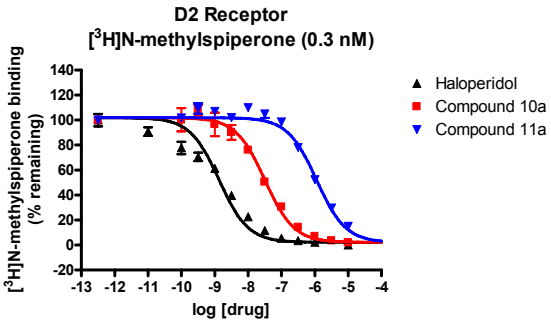

D1 Receptor
[3H]SCH23390 (0.3 nM)
[3H]SCH23390 binding
(% remaining)
log [drug]
SKF38393
Comopund 25s
Compound 27s

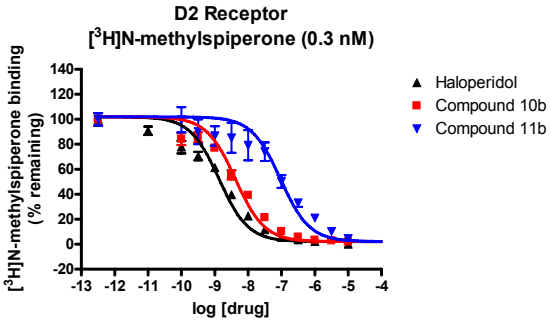

D2 Receptor
[3H]N-methylspiperone (0.3 nM)
[3H]N-methylspiperone binding (% remaining)
log [drug]
Haloperidol
Compound 2
Compound 8

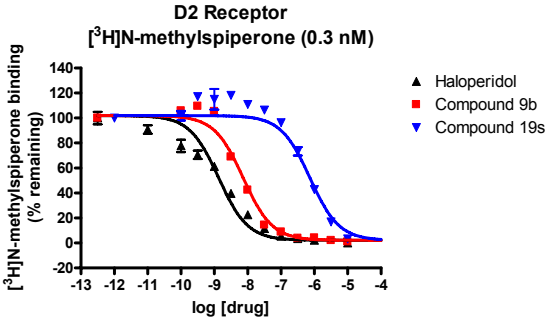

D2 Receptor
[3H]N-methylspiperone (0.3 nM)
[3H]N-methylspiperone binding (% remaining)
log [drug]
Haloperidol
Compound 4
Compound 6

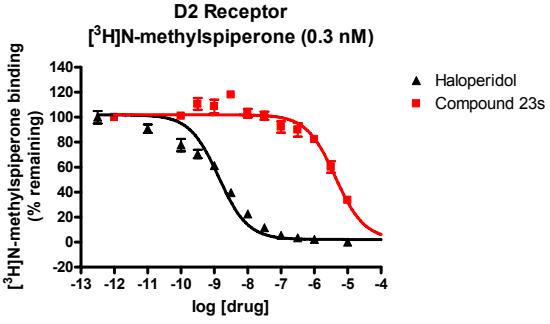

D2 Receptor
[3H]N-methylspiperone (0.3 nM)
[3H]N-methylspiperone binding (% remaining)
log [drug]
Haloperidol
Compound 3
Compound 7

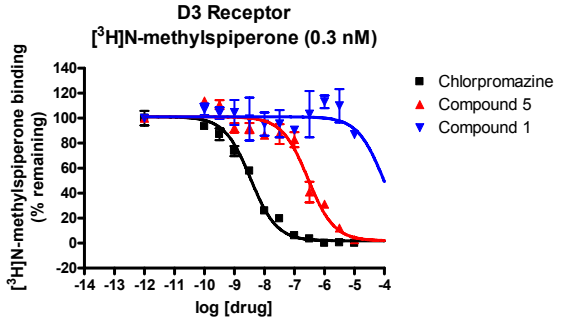

D2 Receptor
[3H]N-methylspiperone (0.3 nM)
[3H]N-methylspiperone binding (% remaining)
log [drug]
Haloperidol
Compound 5
Compound 9a

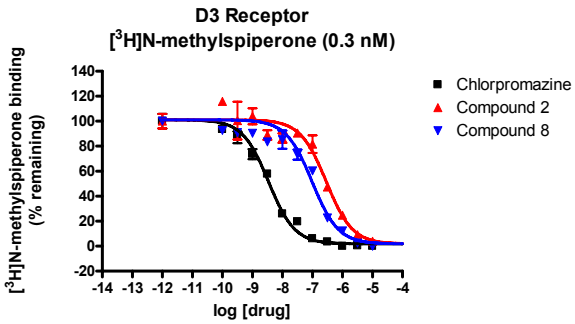

D2 Receptor
[3H]N-methylspiperone (0.3 nM)
[3H]N-methylspiperone binding (% remaining)
log [drug]
Haloperidol
Compound 10a
Compound 11a

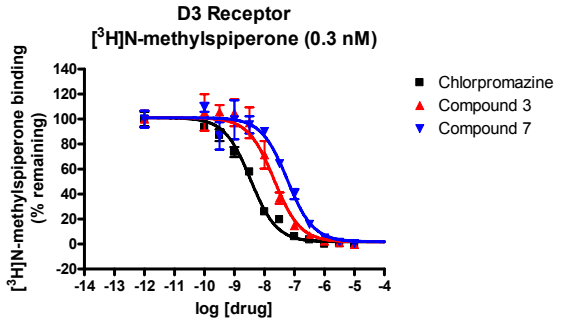

D2 Receptor
[3H]N-methylspiperone (0.3 nM)
[3H]N-methylspiperone binding (% remaining)
log [drug]
Haloperidol
Compound 10b
Compound 11b

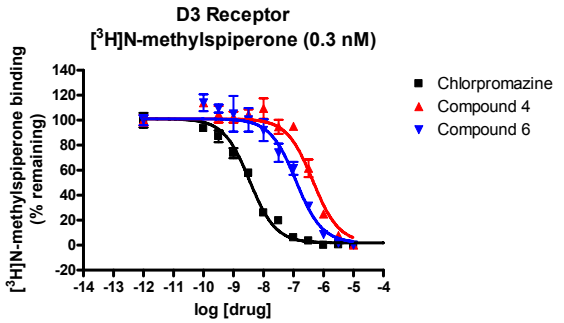

D2 Receptor
[3H]N-methylspiperone (0.3 nM)
[3H]N-methylspiperone binding (% remaining)
log [drug]
Haloperidol
Compound 9b
Compound 19s

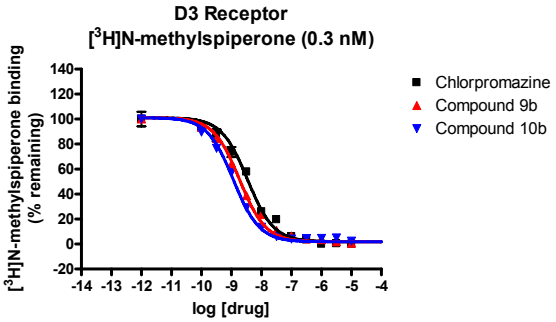

D2 Receptor
[3H]N-methylspiperone (0.3 nM)
[3H]N-methylspiperone binding (% remaining)
log [drug]
Haloperidol
Compound 23s

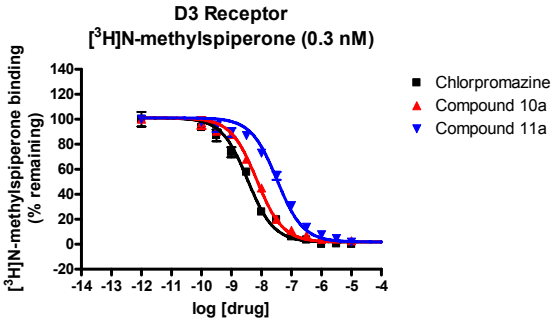

D3 Receptor
[3H]N-methylspiperone (0.3 nM)
[3H]N-methylspiperone binding (% remaining)
log [drug]
Chlorpromazine
Compound 5
Compound 1

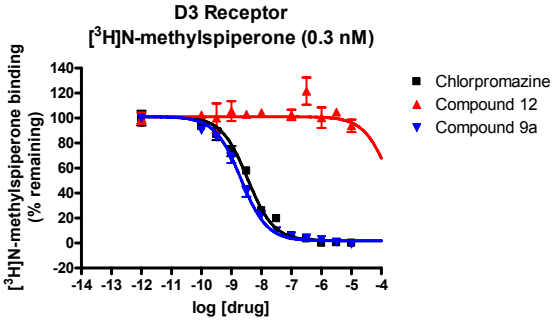

D3 Receptor
[3H]N-methylspiperone (0.3 nM)
[3H]N-methylspiperone binding (% remaining)
log [drug]
Chlorpromazine
Compound 2
Compound 8

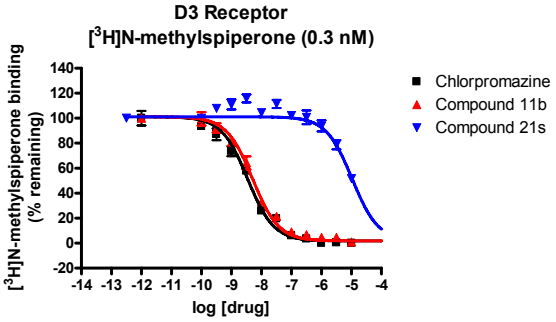

D3 Receptor
[3H]N-methylspiperone (0.3 nM)
[3H]N-methylspiperone binding (% remaining)
log [drug]
Chlorpromazine
Compound 3
Compound 7

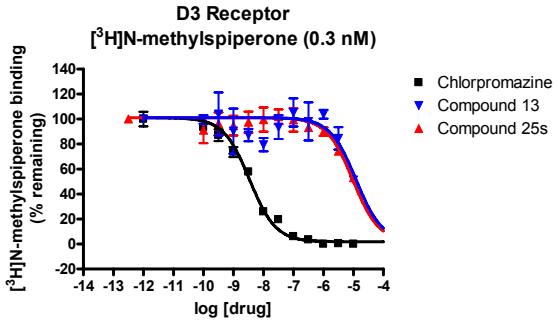

D3 Receptor
[3H]N-methylspiperone (0.3 nM)
[3H]N-methylspiperone binding (% remaining)
log [drug]
Chlorpromazine
Compound 4
Compound 6

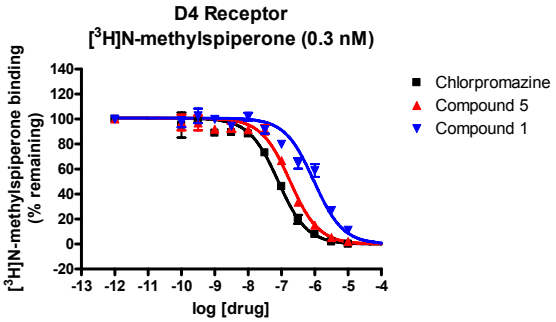

D3 Receptor
[3H]N-methylspiperone (0.3 nM)
[3H]N-methylspiperone binding (% remaining)
log [drug]
Chlorpromazine
Compound 9b
Compound 10b

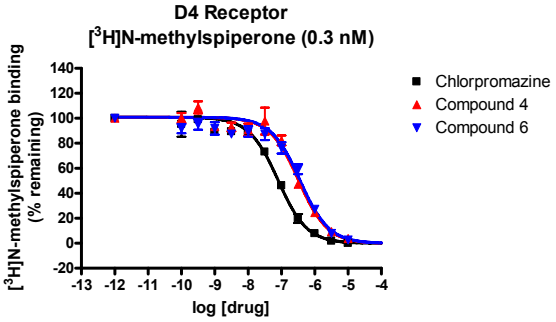

D3 Receptor
[3H]N-methylspiperone (0.3 nM)
[3H]N-methylspiperone binding (% remaining)
log [drug]
Chlorpromazine
Compound 10a
Compound 11a

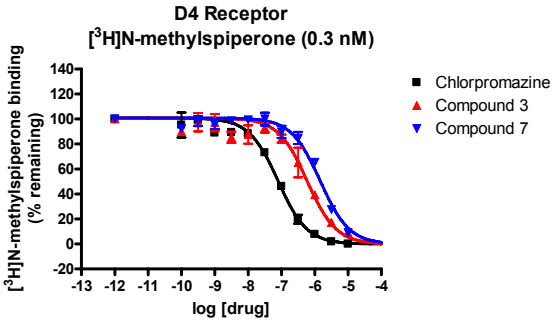

D3 Receptor
[3H]N-methylspiperone (0.3 nM)
[3H]N-methylspiperone binding (% remaining)
log [drug]
Chlorpromazine
Compound 12
Compound 9a

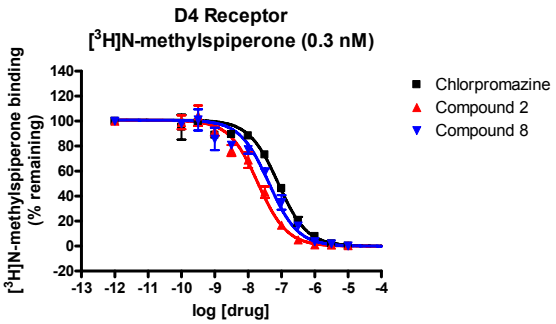

D3 Receptor
[3H]N-methylspiperone (0.3 nM)
[3H]N-methylspiperone binding (% remaining)
log [drug]
Chlorpromazine
Compound 11b
Compound 21s

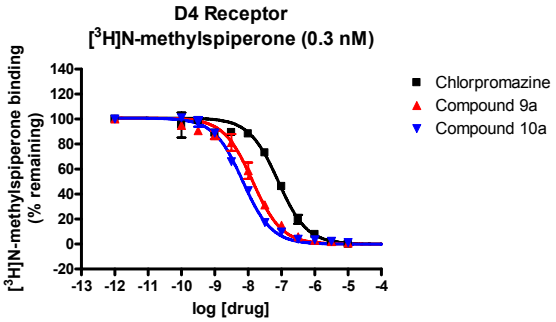

D3 Receptor
[3H]N-methylspiperone (0.3 nM)
[3H]N-methylspiperone binding
(% remaining)
140
120
100
80
60
40
20
0
-20
-14 -13 -12 -11 -10 -9 -8 -7 -6 -5 -4
log [drug]
Chlorpromazine
Compound 13
Compound 25s

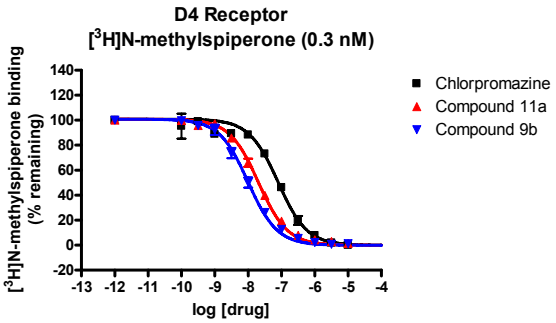

D4 Receptor
[3H]N-methylspiperone (0.3 nM)
[3H]N-methylspiperone binding (% remaining)
log [drug]
Chlorpromazine
Compound 5
Compound 1

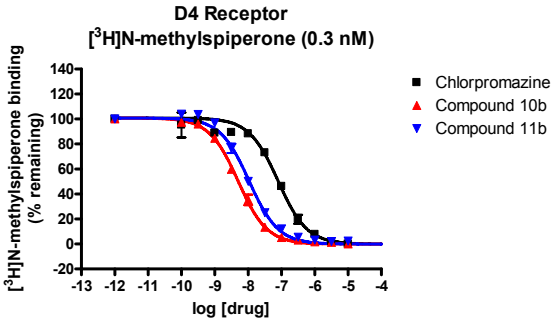

D4 Receptor
[3H]N-methylspiperone (0.3 nM)
[3H]N-methylspiperone binding (% remaining)
log [drug]
Chlorpromazine
Compound 4
Compound 6

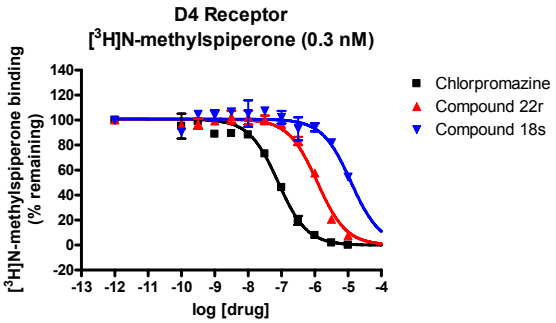

D4 Receptor
[3H]N-methylspiperone (0.3 nM)
[3H]N-methylspiperone binding (% remaining)
log [drug]
Chlorpromazine
Compound 3
Compound 7

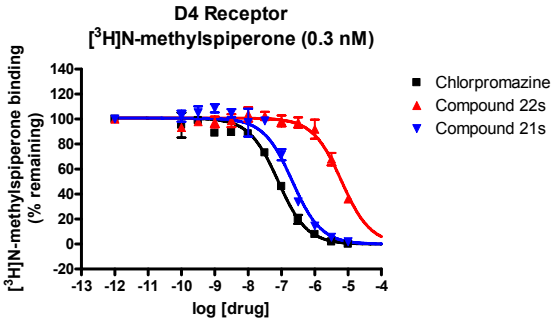

D4 Receptor
[3H]N-methylspiperone (0.3 nM)
[3H]N-methylspiperone binding (% remaining)
log [drug]
Chlorpromazine
Compound 2
Compound 8

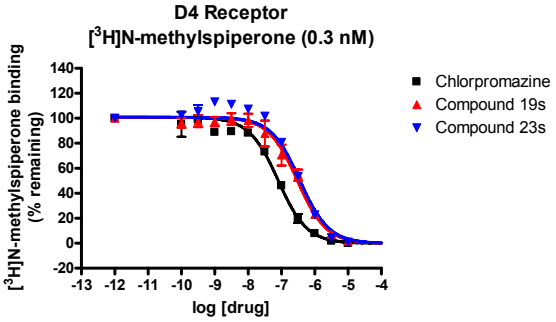

D4 Receptor
[3H]N-methylspiperone (0.3 nM)
[3H]N-methylspiperone binding (% remaining)
log [drug]
Chlorpromazine
Compound 9a
Compound 10a

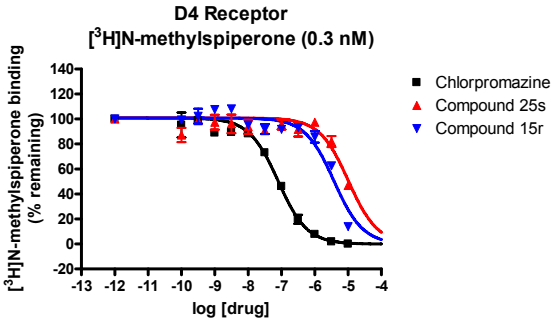

D4 Receptor
[3H]N-methylspiperone (0.3 nM)
[3H]N-methylspiperone binding (% remaining)
log [drug]
Chlorpromazine
Compound 11a
Compound 9b

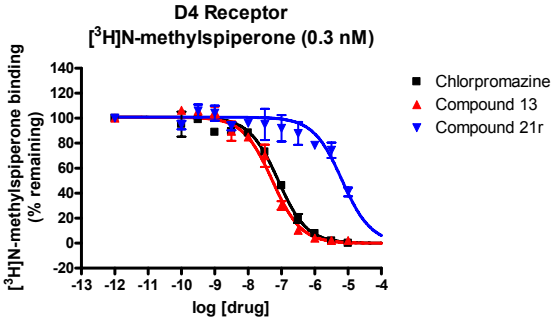

D4 Receptor
[3H]N-methylspiperone (0.3 nM)
[3H]N-methylspiperone binding (% remaining)
log [drug]
Chlorpromazine
Compound 10b
Compound 11b

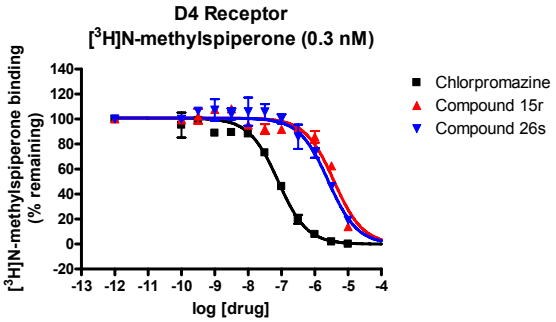

D4 Receptor
[3H]N-methylspiperone (0.3 nM)
[3H]N-methylspiperone binding (% remaining)
log [drug]
Chlorpromazine
Compound 22r
Compound 18s

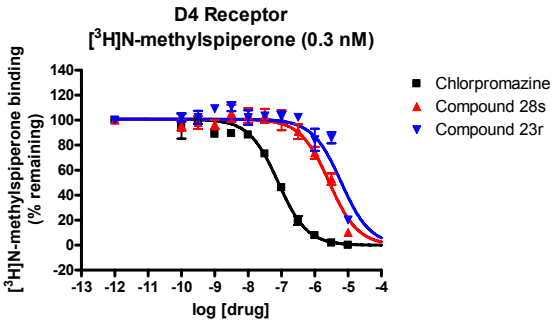

D4 Receptor
[3H]N-methylspiperone (0.3 nM)
[3H]N-methylspiperone binding (% remaining)
log [drug]
Chlorpromazine
Compound 22s
Compound 21s

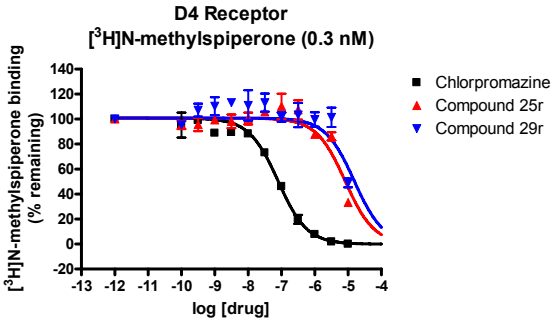

D4 Receptor
[3H]N-methylspiperone (0.3 nM)
[3H]N-methylspiperone binding (% remaining)
log [drug]
Chlorpromazine
Compound 19s
Compound 23s

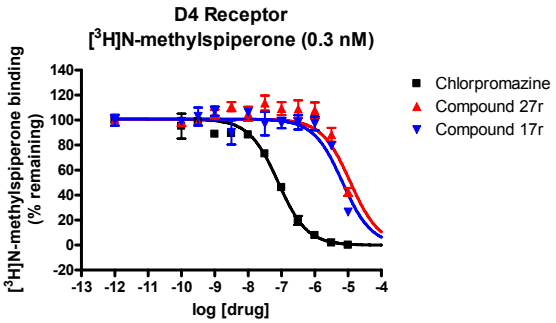

D4 Receptor
[3H]N-methylspiperone (0.3 nM)
[3H]N-methylspiperone binding (% remaining)
log [drug]
Chlorpromazine
Compound 25s
Compound 15r

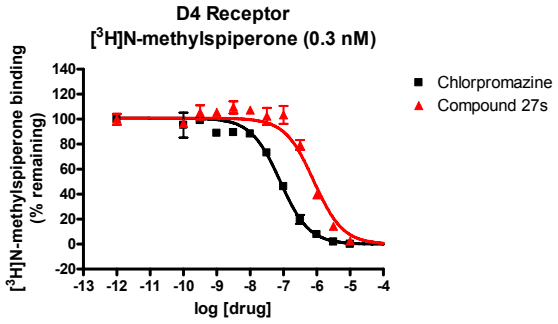

D4 Receptor
[3H]N-methylspiperone (0.3 nM)
[3H]N-methylspiperone binding (% remaining)
log [drug]
Chlorpromazine
Compound 13
Compound 21r

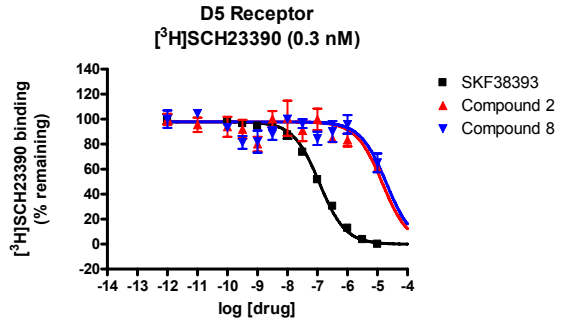

D4 Receptor
[3H]N-methylspiperone (0.3 nM)
[3H]N-methylspiperone binding (% remaining)
log [drug]
Chlorpromazine
Compound 15r
Compound 26s

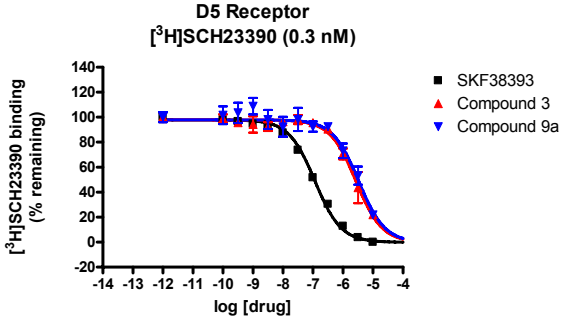

D4 Receptor
[3H]N-methylspiperone (0.3 nM)
[3H]N-methylspiperone binding (% remaining)
log [drug]
Chlorpromazine
Compound 28s
Compound 23r

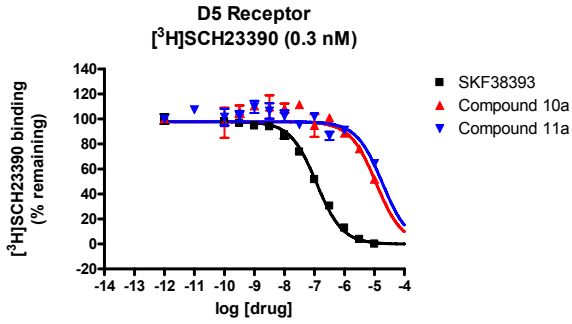

D4 Receptor
[3H]N-methylspiperone (0.3 nM)
[3H]N-methylspiperone binding (% remaining)
log [drug]
Chlorpromazine
Compound 25r
Compound 29r

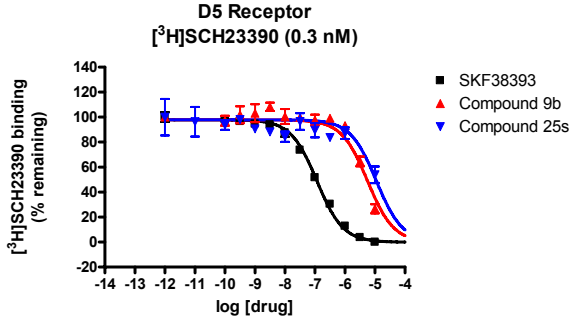

D4 Receptor
[3H]N-methylspiperone (0.3 nM)
[3H]N-methylspiperone binding (% remaining)
log [drug]
Chlorpromazine
Compound 27r
Compound 17r


D4 Receptor
[3H]N-methylspiperone (0.3 nM)
[3H]N-methylspiperone binding
(% remaining)
140
120
100
80
60
40
20
0
-20
-13
-12
-11
-10
-9
-8
-7
-6
-5
-4
log [drug]
Chlorpromazine
Compound 27s


D5 Receptor
[3H]SCH23390 (0.3 nM)
[3H]SCH23390 binding
(% remaining)
log [drug]
SKF38393
Compound 2
Compound 8


D5 Receptor
[3H]SCH23390 (0.3 nM)
[3H]SCH23390 binding
(% remaining)
log [drug]
SKF38393
Compound 3
Compound 9a


D5 Receptor
[3H]SCH23390 (0.3 nM)
[3H]SCH23390 binding
(% remaining)
log [drug]
SKF38393
Compound 10a
Compound 11a


D5 Receptor
[3H]SCH23390 (0.3 nM)
[3H]SCH23390 binding
(% remaining)
log [drug]
SKF38393
Compound 9b
Compound 25s

Supplementary Figure 3: Experimental testing of ligand function

Figure 3A: Dopamine receptor D2 and D4 agonist assays for compounds 1, 3, 13, 22r and the drug chlorpromazine (CPZ). A control assay is also performed.

Quinpirole is used as standard in the assays, for D2 agonist, pXC50 = 8.182 (SE = 0.089) and for D4 agonist, pXC50 = 8.348 (SE = 0.094).

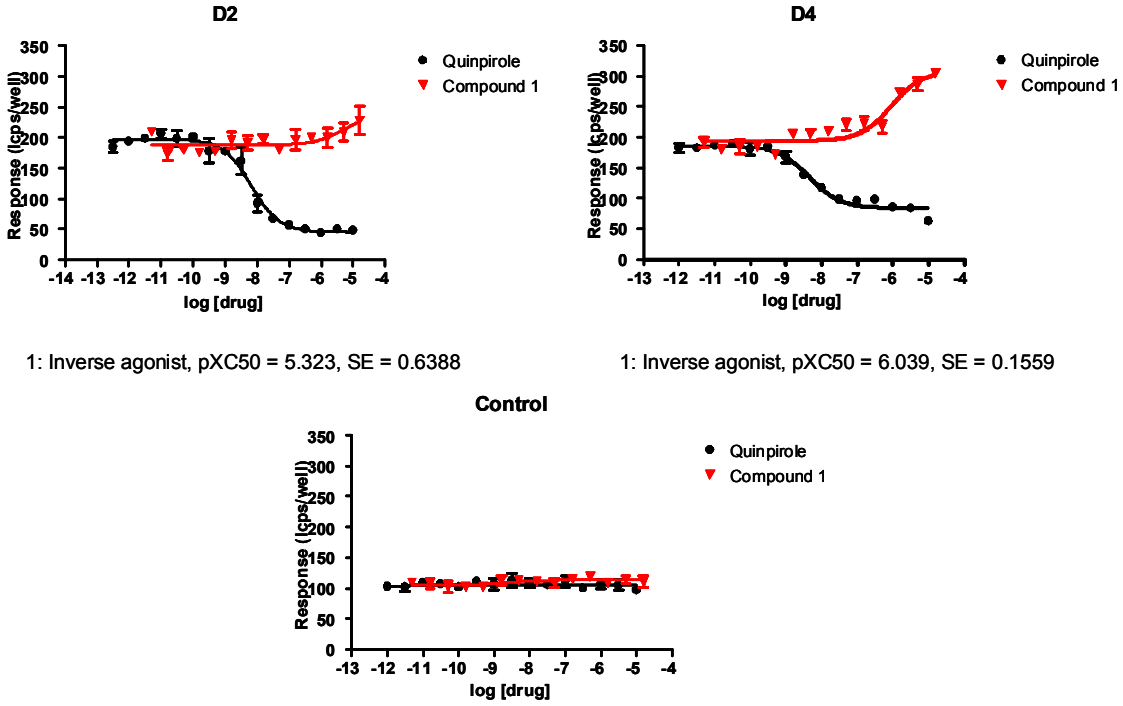
Figure 3B: Comparison for dopamine D2 and D4 on agonist and antagonist functional assays for compounds 1, 3, 13, 22r and the drug chlorpromazine (CPZ). A control agonist assay is performed in the absence of dopamine receptor in order to asses whether the agonist activity is non-specific (Glo agonist assay).

Quinpirole is used as standard in the assays, for D2 agonist, logEC50 =-8.7 (SE = 0.1), D4 agonist, logEC50 = -8.6 (SE = 0.1), and no activity on the D2 and D4 antagonist assays.

Figure 3C: 5-HT2B Ca mobilization functional assay (with FLIPR) for compounds 15r and 23s.

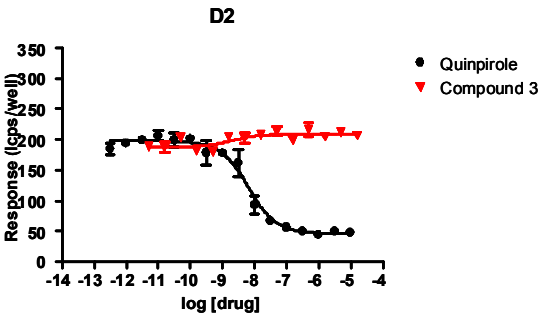
Figure 3D: hERG inhibition by PatchXpress (electrophysiology) assay for compounds 2, 11a, 11b, 15r, 19s, 21s, 22r, 12s and 27s.

Figure 3A: Dopamine receptor D2 and D4 agonist assays

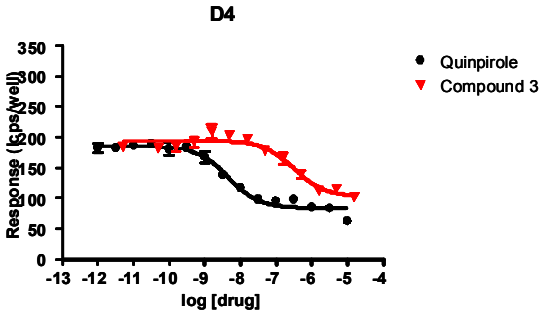


1: Inverse agonist, pXC50 = 5.323, SE = 0.6388

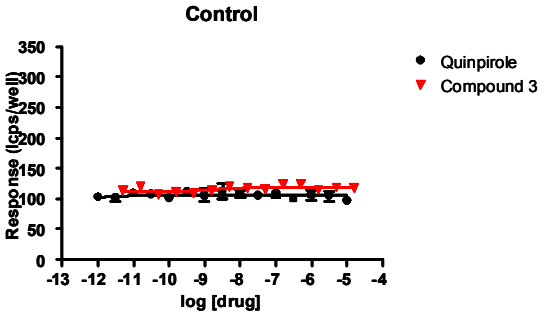
1: Inverse agonist, pXC50 = 6.039, SE = 0.1559

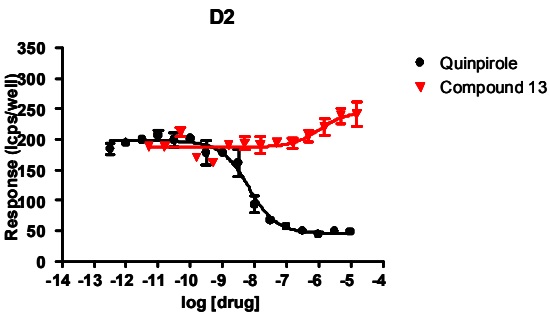


3: Inverse agonist, pXC50 = 6.702, SE = 0.388

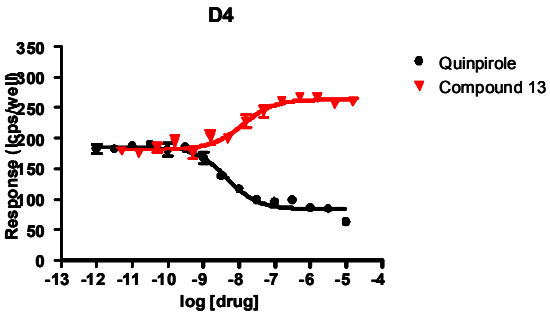


3: Agonist, pXC50 = 8.254, SE = 0.3003

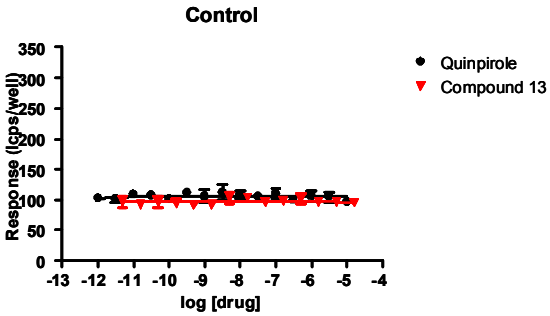


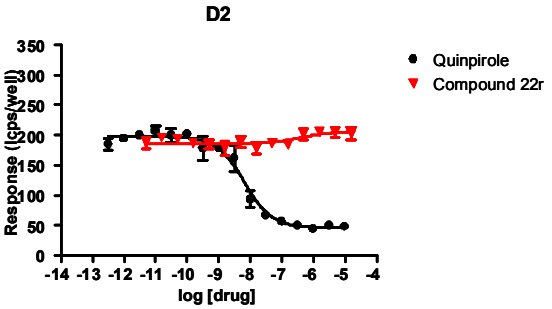


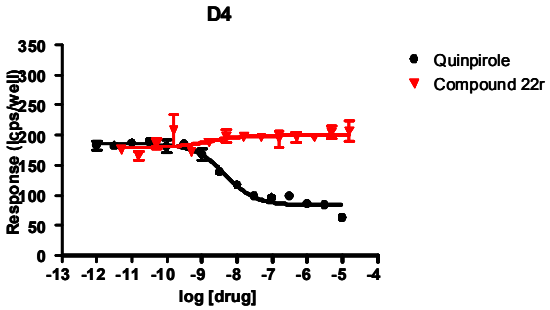
13: Inverse agonist, pXC50 = 5.952, SE = 0.3303



13: Inverse agonist, pXC50 = 7.884, SE = 0.1276

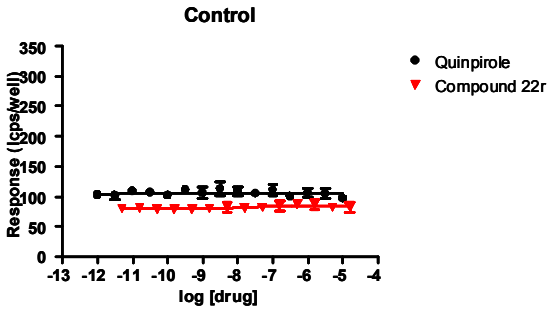


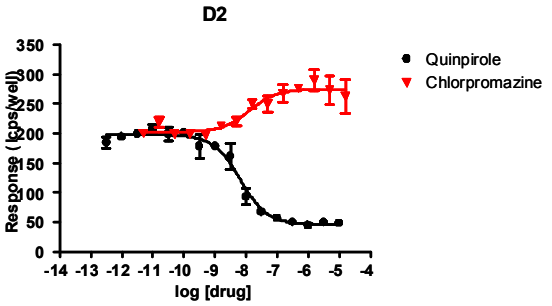


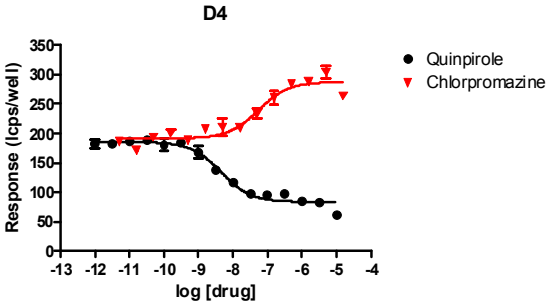


22r: Inverse agonist, pXC50 = 6.371, SE = 0.6079

22r: Inverse agonist, pXC50 = 8.767, SE = 0.8187







Cpz: Inverse agonist, pXC50 = 7.894, SE = 0.2445

Cpz: Inverse agonist, pXC50 = 7.267, SE = 0.1421

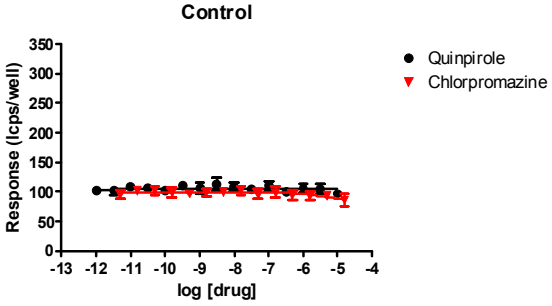
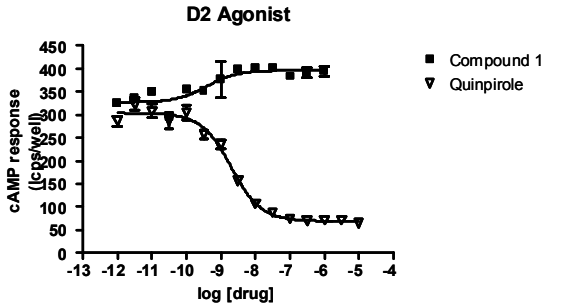
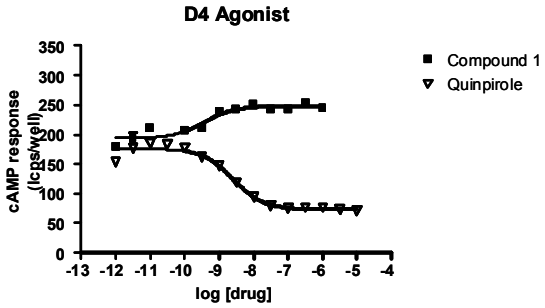


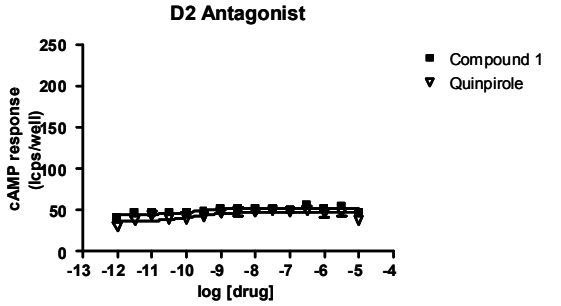
Figure 3B: Comparison agonist, antagonist for D2 and D4 receptors



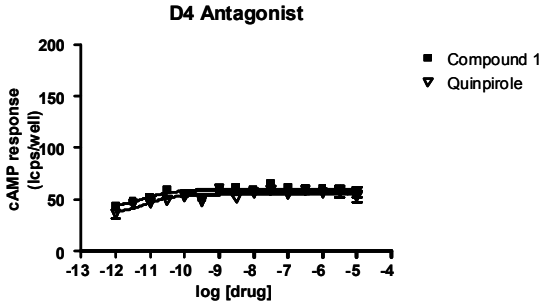
Compound 1: logEC50 = -9.4 , SE = 0.3



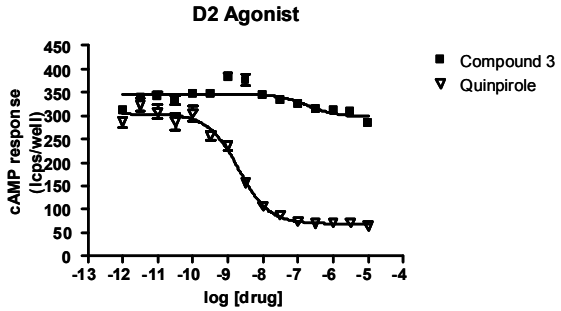
Compound 1: logEC50 = -9.4 , SE = 0.2



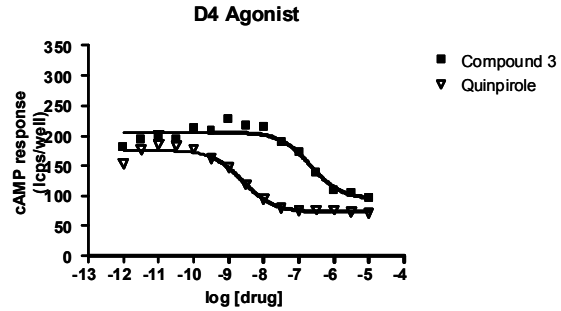
Compound 1: logIC50 = NA



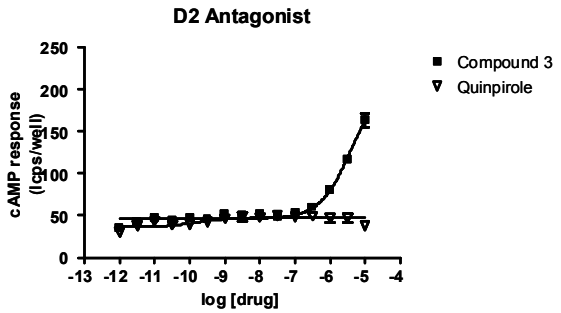
Compound 1: logIC50 = NA



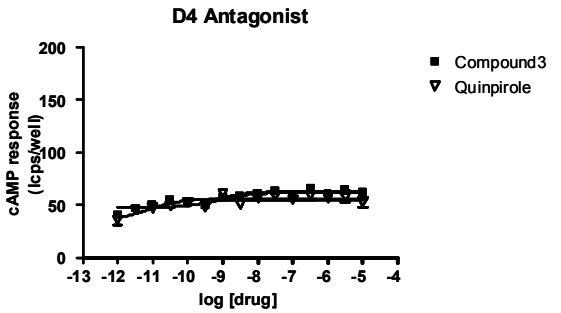
Compound 3: logEC50 = -6.7 , SE = 0.4



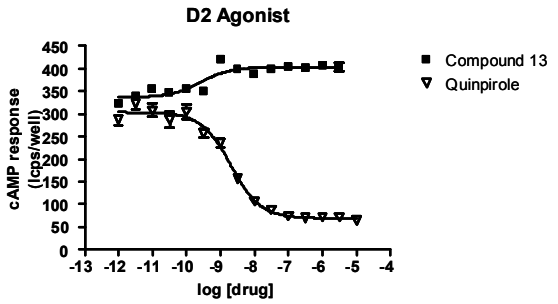
Compound 3: logEC50 = -6.7 , SE = 0.1



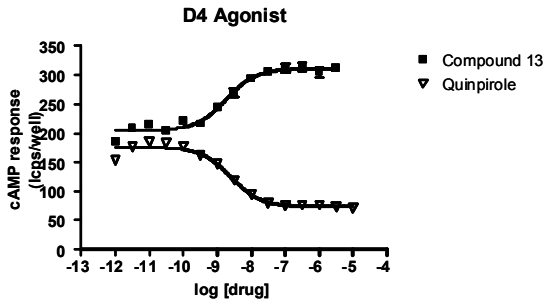
Compound 3: logIC50 = -5.4 , SE = 0.1



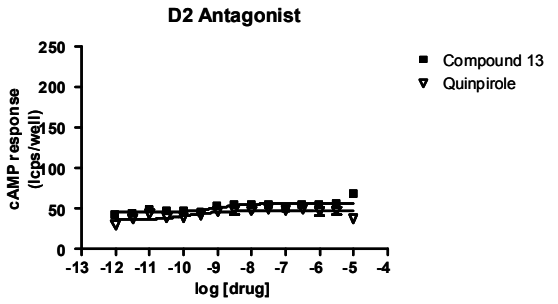
Compound 3: logIC50 = -5.4 , SE = 0.1



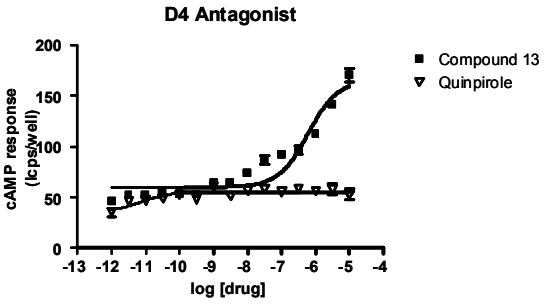
Compound 13: logEC50 = -9.6 , SE = 0.2



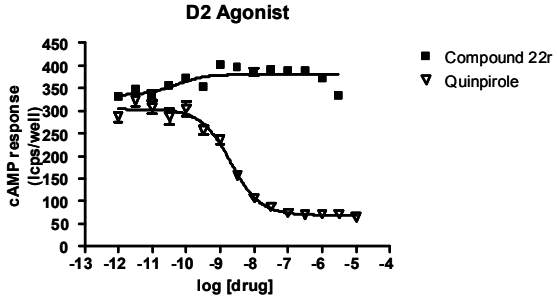
Compound 13: logEC50 = -8.7 , SE = 0.1



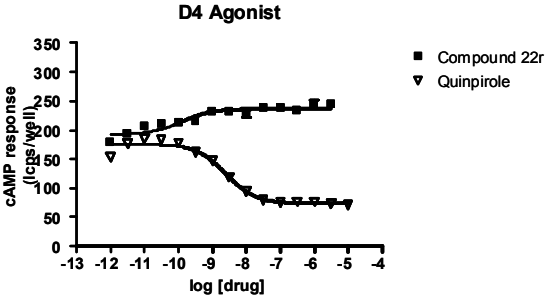
Compound 13: logIC50 = NA



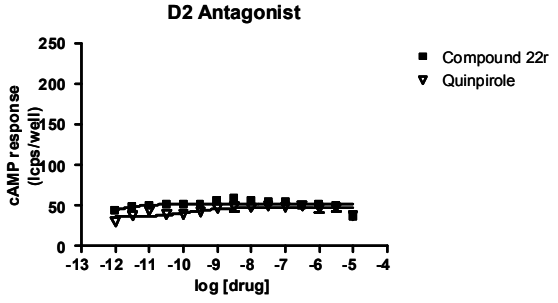
Compound 13: logIC50 = -6.2 , SE = 0.1



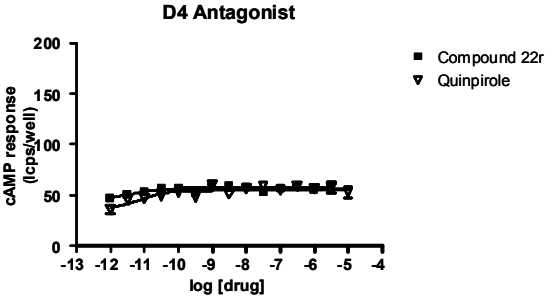
Compound 22r: logEC50 = -10.3 , SE = 0.4



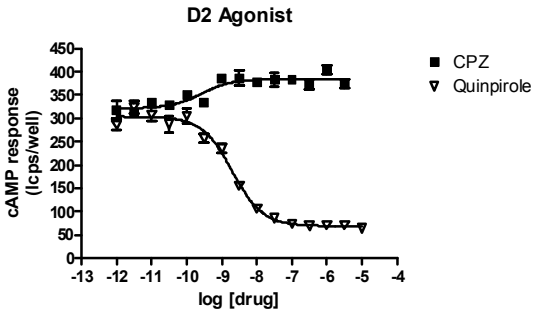
Compound 22r: logEC50 = -9.9 , SE = 0.2



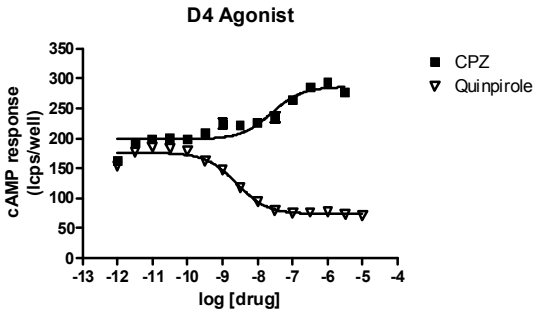
Compound 22r: logIC50 = NA



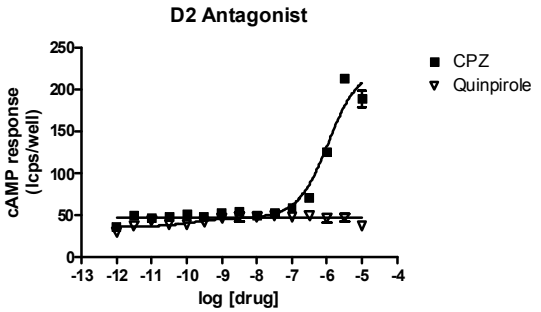
Compound 22r: logIC50 = NA



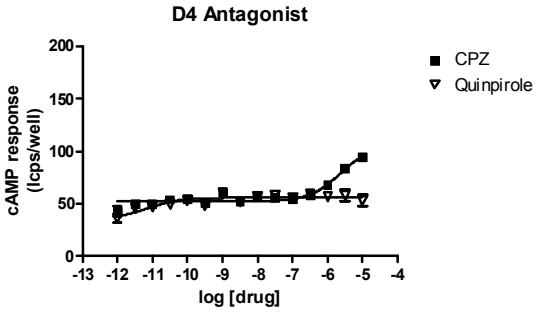
CPZ: logEC50 = -9.6 , SE = 0.3



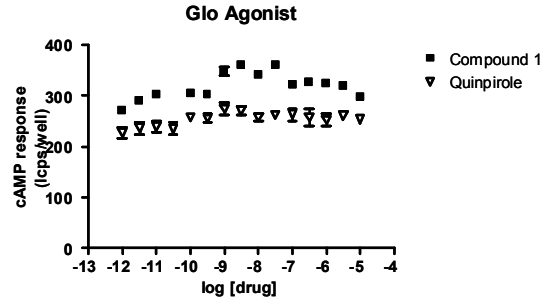
CPZ: logEC50 = -7.6 , SE = 0.2

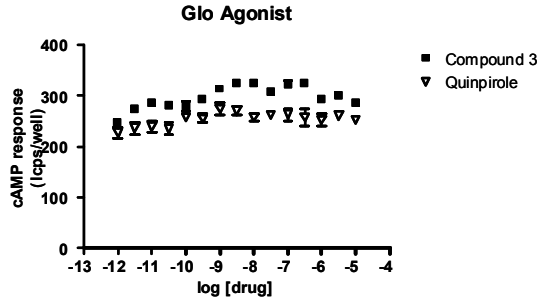


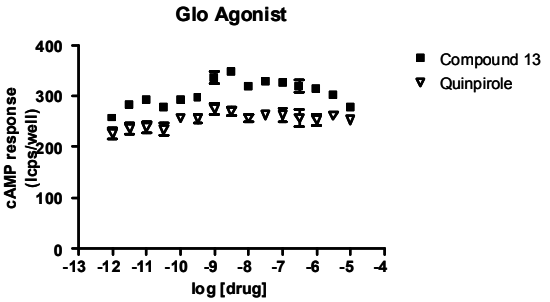
CPZ: logIC50 = -6 , SE = 0.1

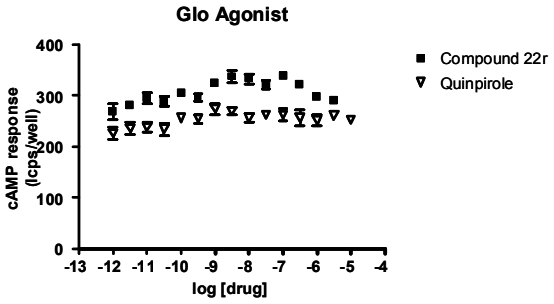


CPZ: logIC50 = -5.6 , SE = 0.1









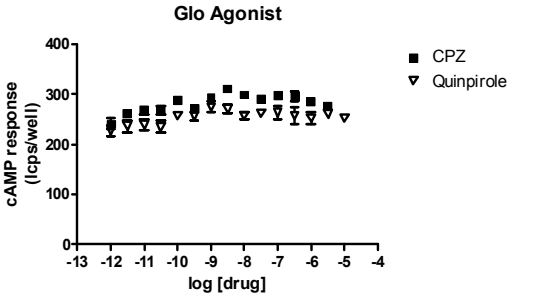
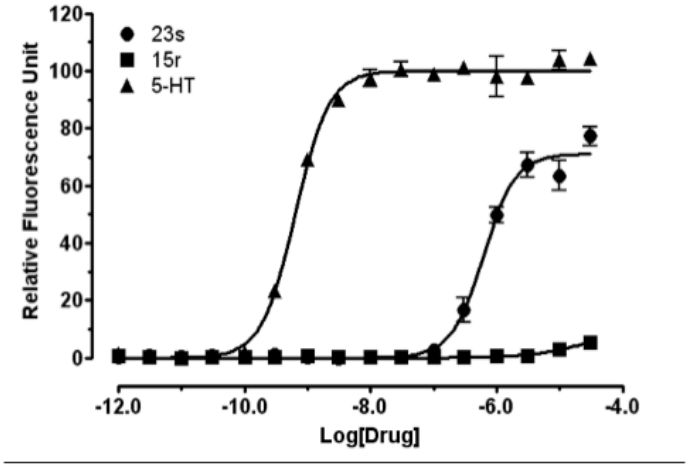


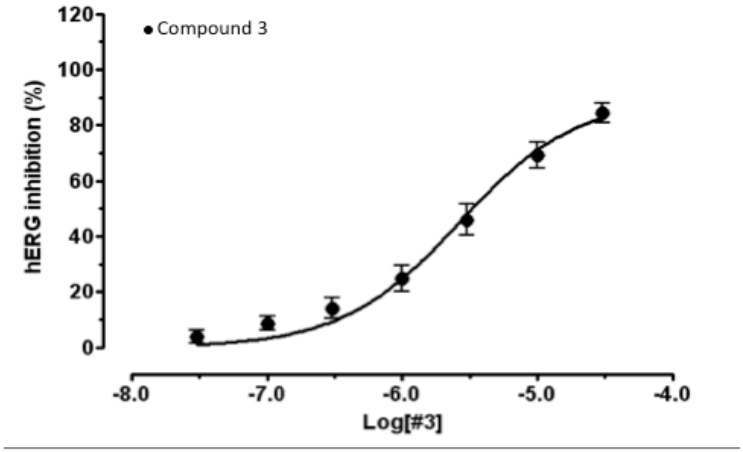
Figure 3C: 5-HT2B functional assay



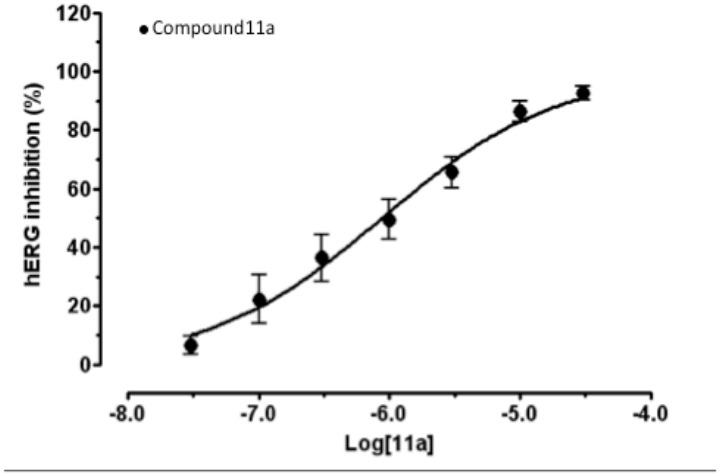
15r: Emax (%) = 6.9 ± 1.6; pEC50 = 4.92 ± 0.18 ; Hill slope = 1.50 ±0.51

23s: Emax (%) = 71.2 ± 1.7; pEC50 = 6.21 ± 0.04 ; Hill slope = 1.67 ±0.18

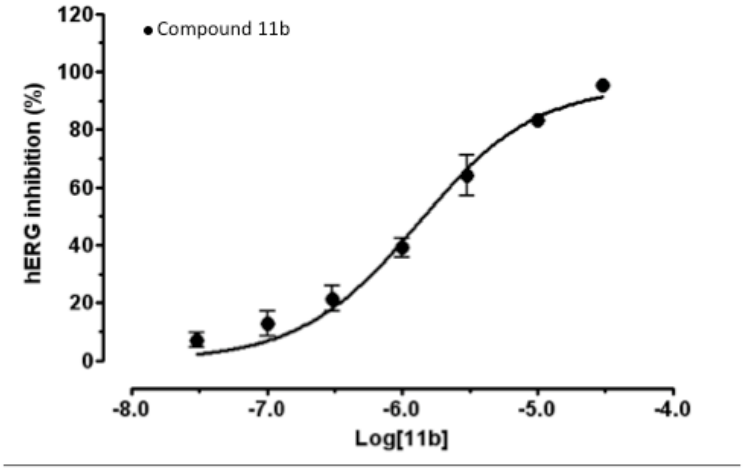
Figure 3D: hERG inhibition by PatchXpress (electrophysiology)



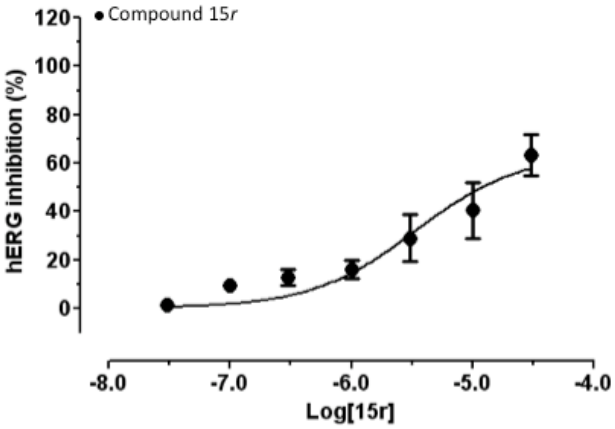
3: Emax (%) = 89.8 ± 4.6; pEC50 = 5.58 ± 0.08 ; Hill slope = 1



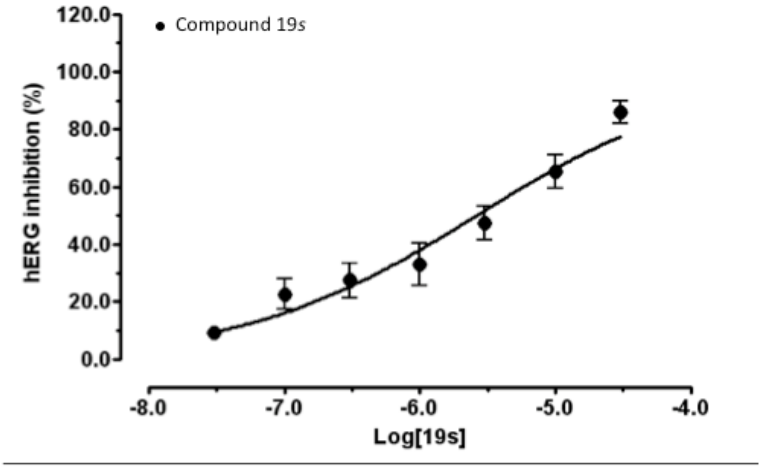
11a: Emax (%) = 100 ; pEC50 = 6.06 ± 0.22 ; Hill slope = 0.65 ± 0.14



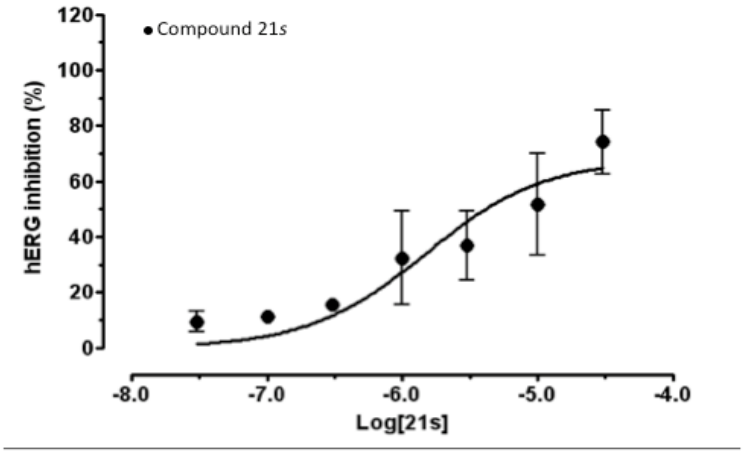
11b: Emax (%) = 95.2 ± 5.2; pEC50 =5.89 ± 0.08 ; Hill slope = 1



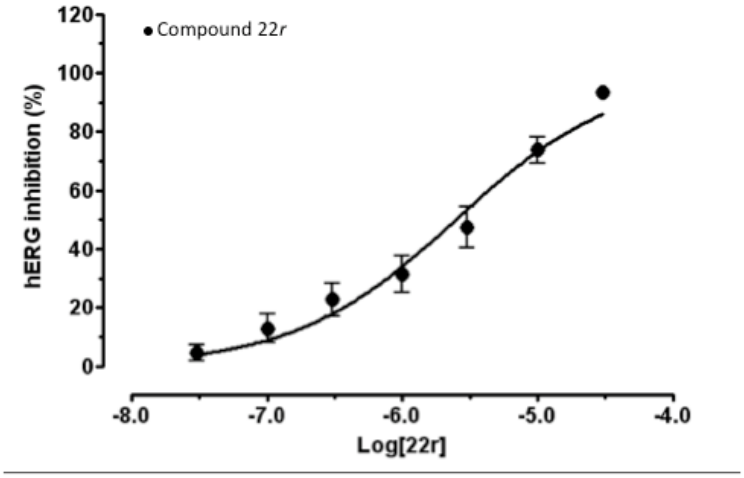
15r: Emax (%) = 64.3 ± 8.8; pEC50 = 5.47 ± 0.19 ; Hill slope = 1



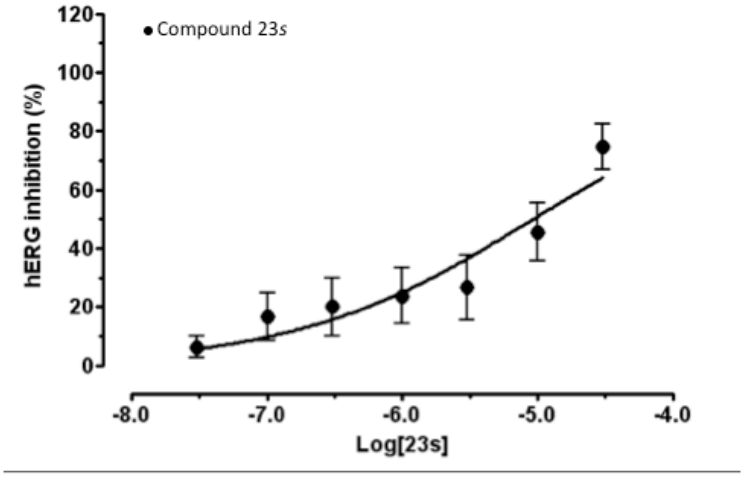
19s: Emax (%) = 100 ; pEC50 =5.58 ± 0.54 ; Hill slope = 0.51 ± 0.15



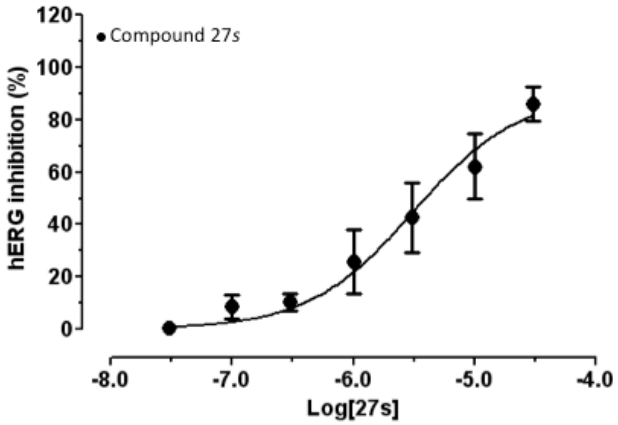
21s: Emax (%) = 68 ± 9.8; pEC50 = 5.83 ± 0.25 ; Hill slope = 1



22r: Emax (%) = 100 ; pEC50 = 5.60 ± 0.23 ; Hill slope = 0.73 ± 0.15

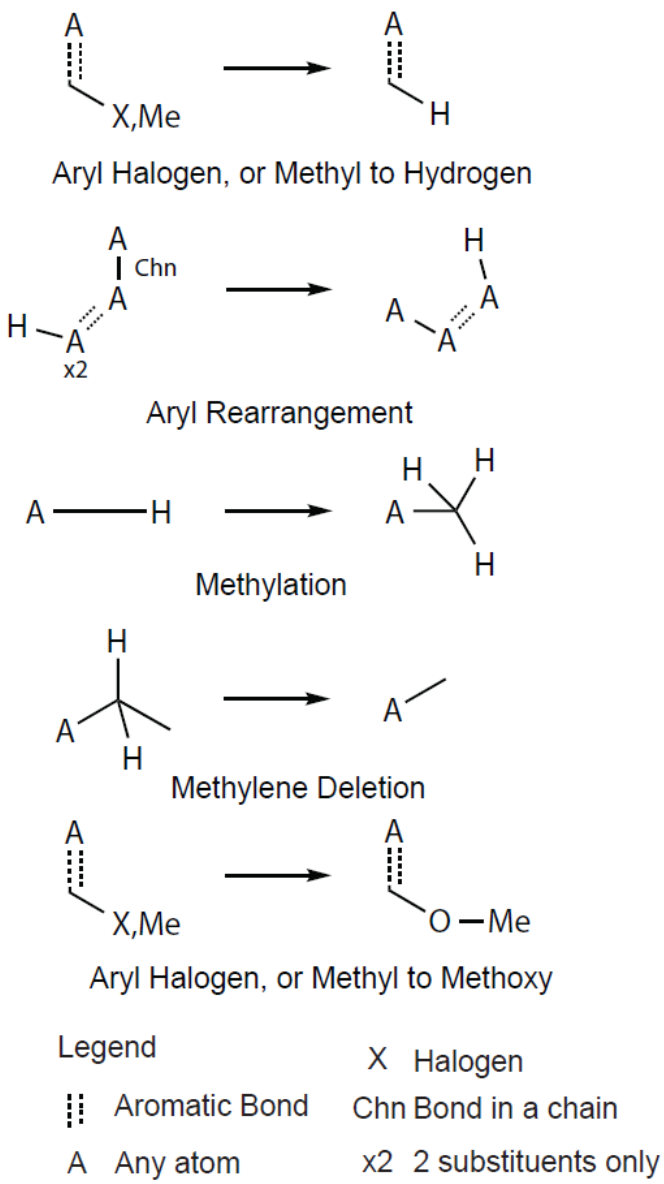


23s Emax (%) = 100 ; pEC50 = 5.03 ± 1.65 ; Hill slope = 0.49 ± 0.30



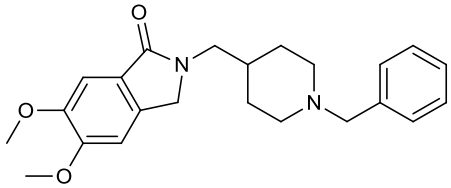
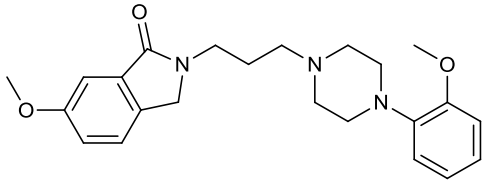
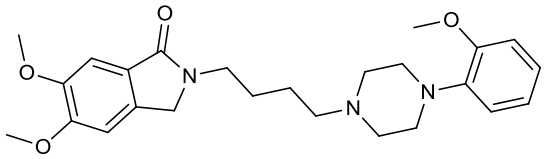
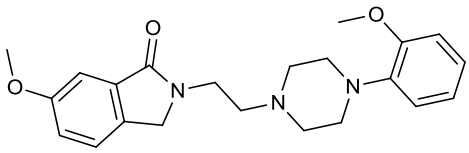
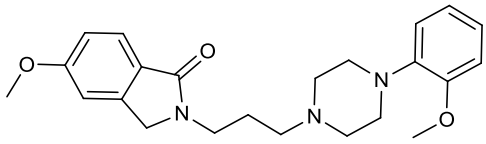
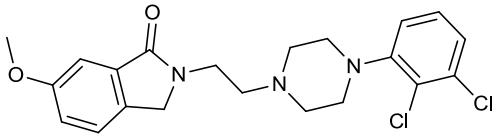
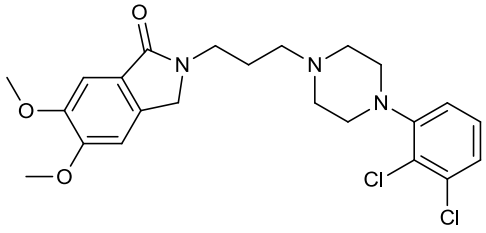
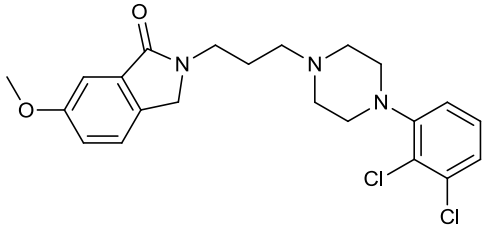
27s: Emax (%) = 89.9 ± 10.0 ; pEC50 = 5.51 ± 0.17 ; Hill slope = 1

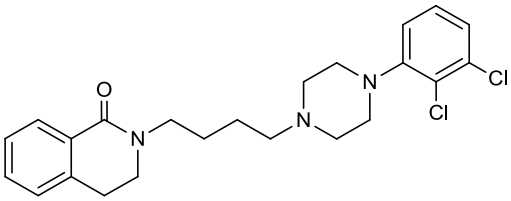
Supplementary Figure 4: Example of transformations



A database of chemical transformation rules are derived from systematically mining the background knowledge encoded in the ChEMBL database of structure-activity data extracted from the literature. Examples of the top 5 most common transformation in ChEMBL are shown.

Supplementary Figure 5: Chemical structures of profiled ligands

Structure	Name
	1
	2
	3
	4
	5
	6
	7
	8



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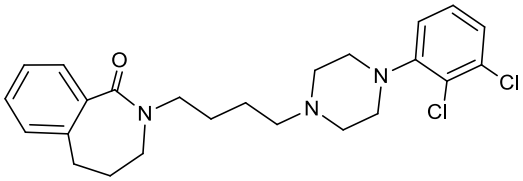

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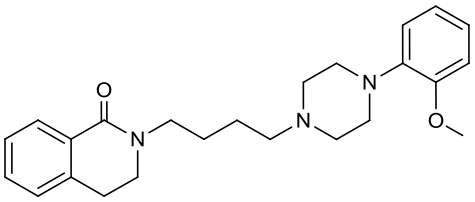

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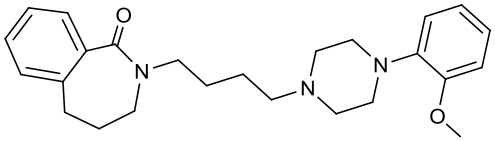

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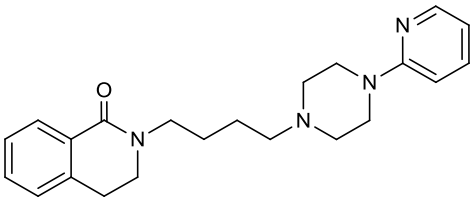
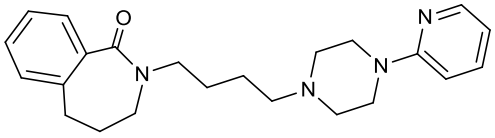


11a



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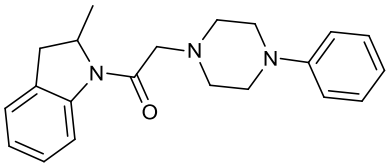

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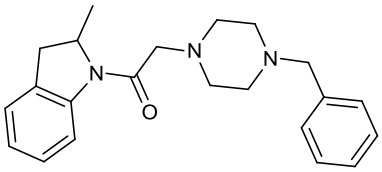

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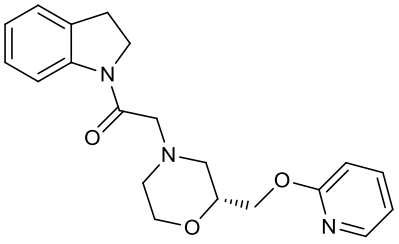

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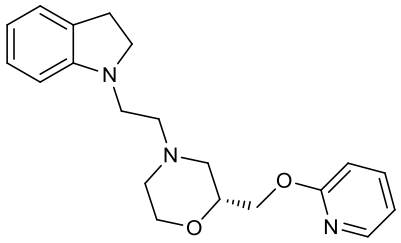

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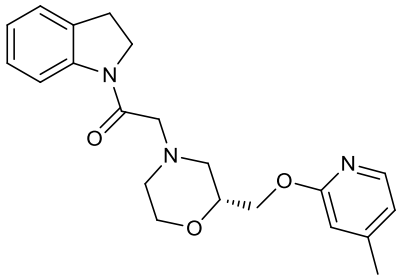

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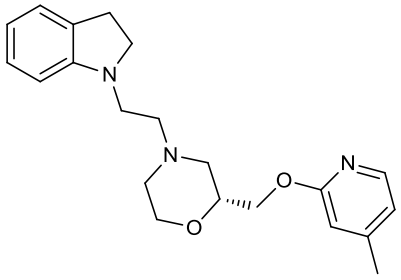

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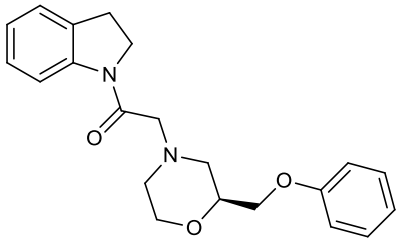

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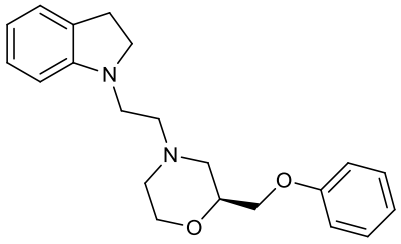

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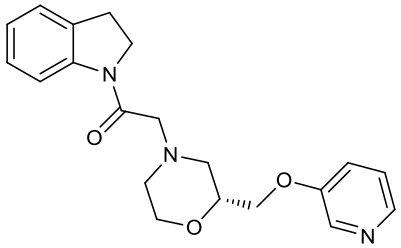

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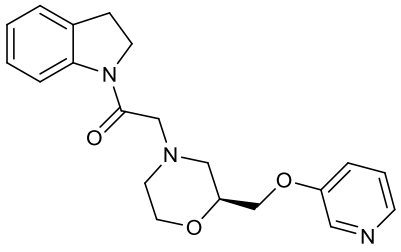

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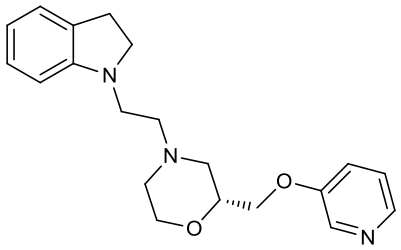

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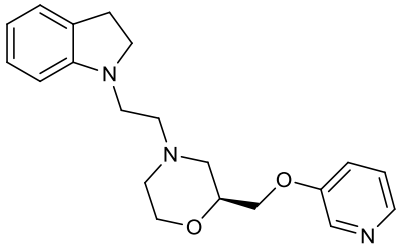

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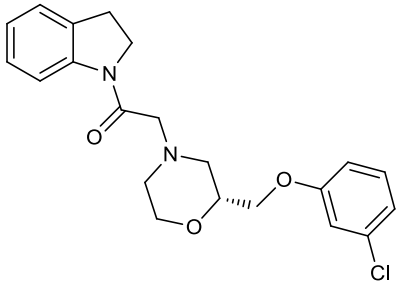

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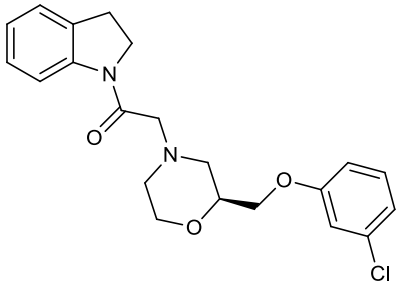

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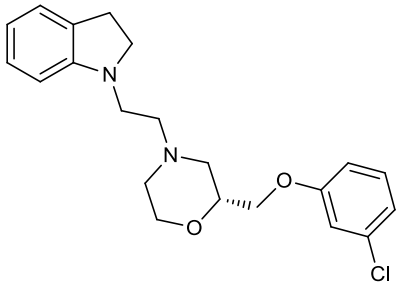

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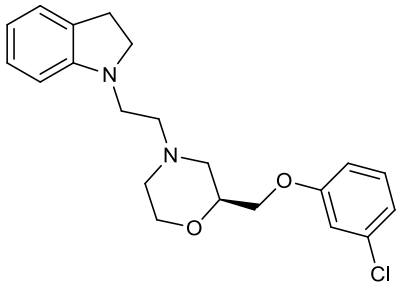

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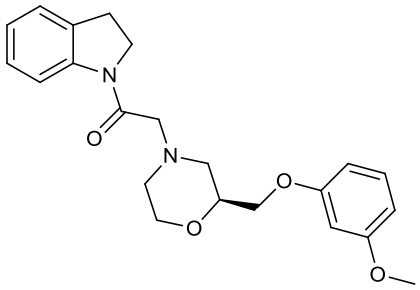

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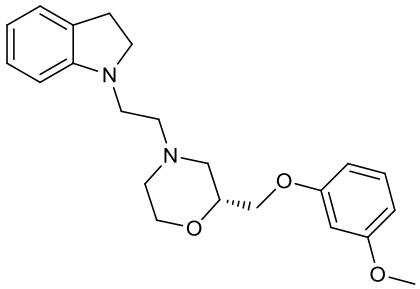

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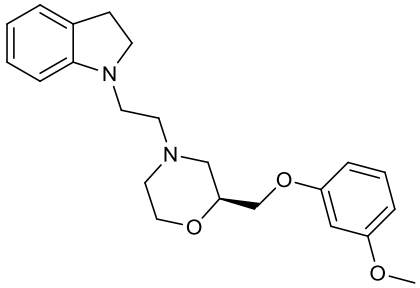

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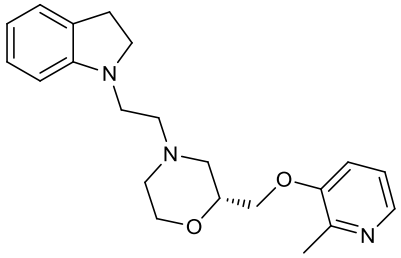

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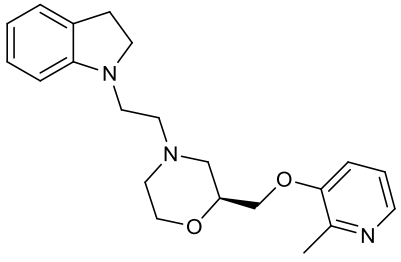

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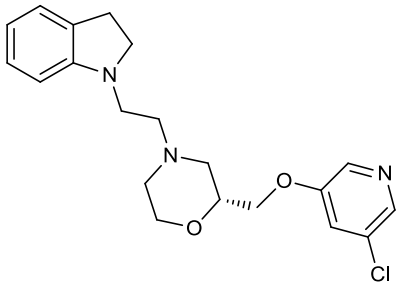

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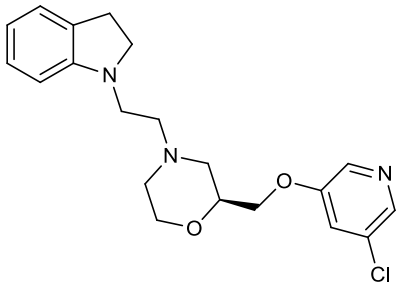

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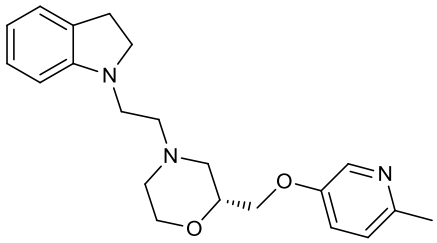

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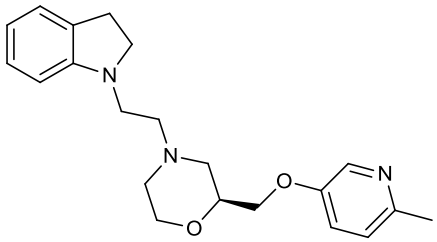

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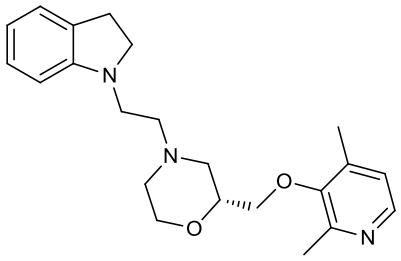
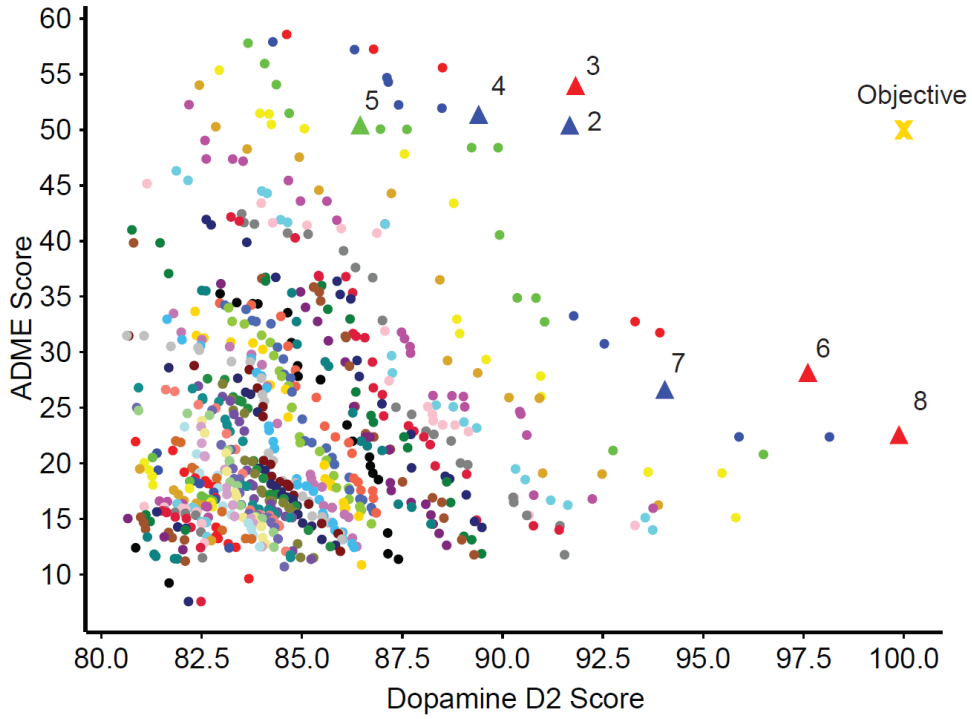


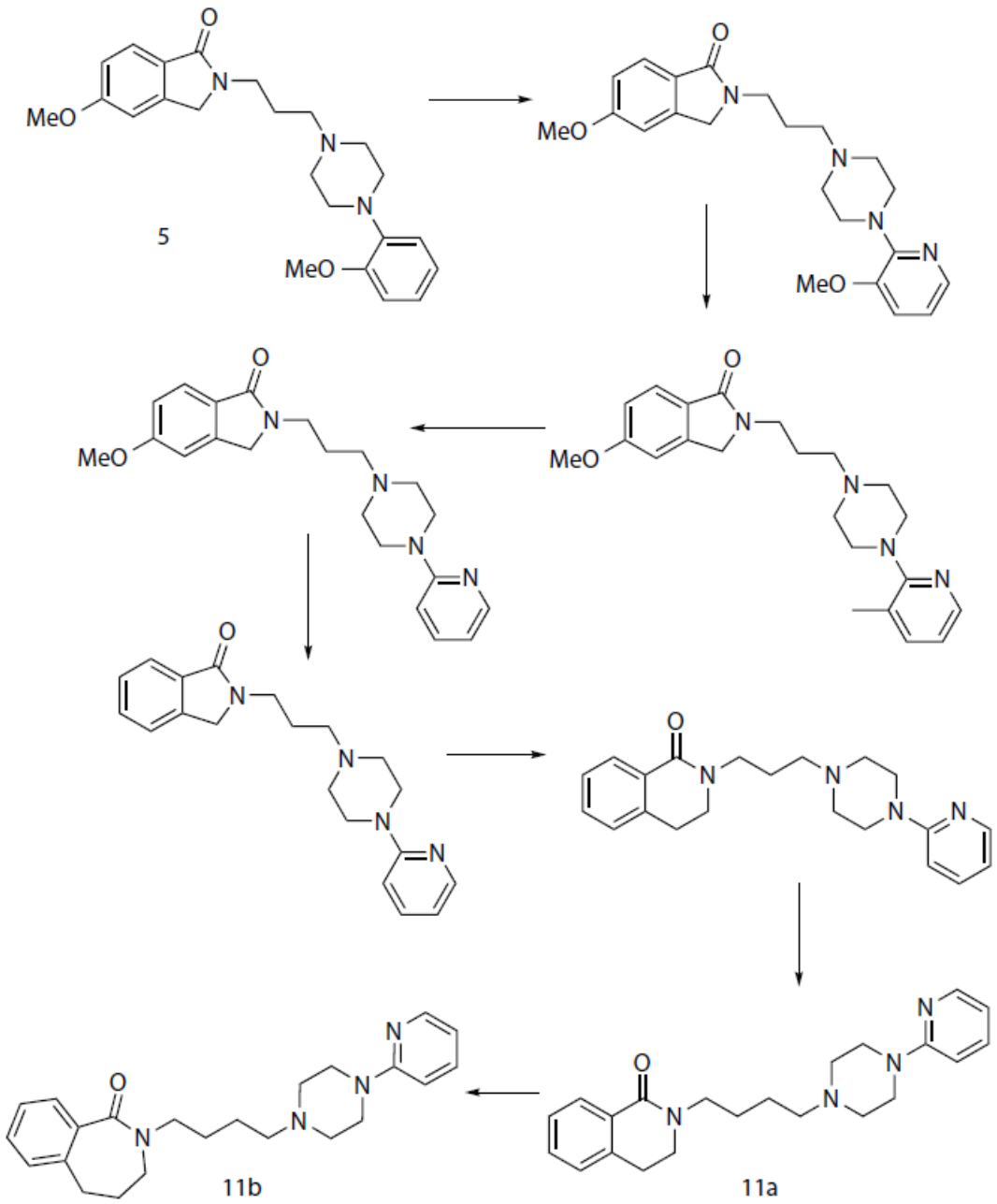
29r

Supplementary Figure 6: Evolution of novel dopamine D2 ligands from donepezil



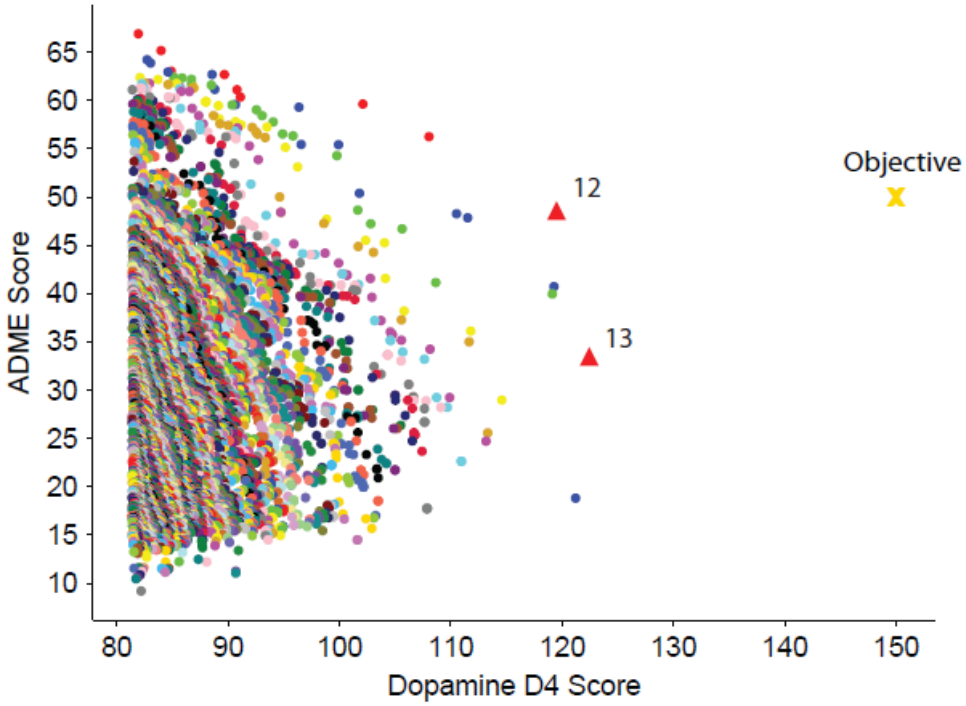
Evolved compound population from donepezil after six generations. The calculated dopamine D2 Bayesian and ADME scores for the final 10,000 compounds, generated by the algorithm, are plotted as coloured circles and triangles. The compounds are coloured by the Pareto frontier ranking (red = 1, blue = 2, green = 3, yellow = 4, brown = 5). The defined achievement objective (Dopamine D2 Bayesian score = 100, CNS ADME score = 50) is defined as a gold cross. The compounds chosen for synthesis and testing (**2**-**8**) are represented as triangles.

Supplementary Figure 7: Evolution pathway from compound 5 to 11a and 11b



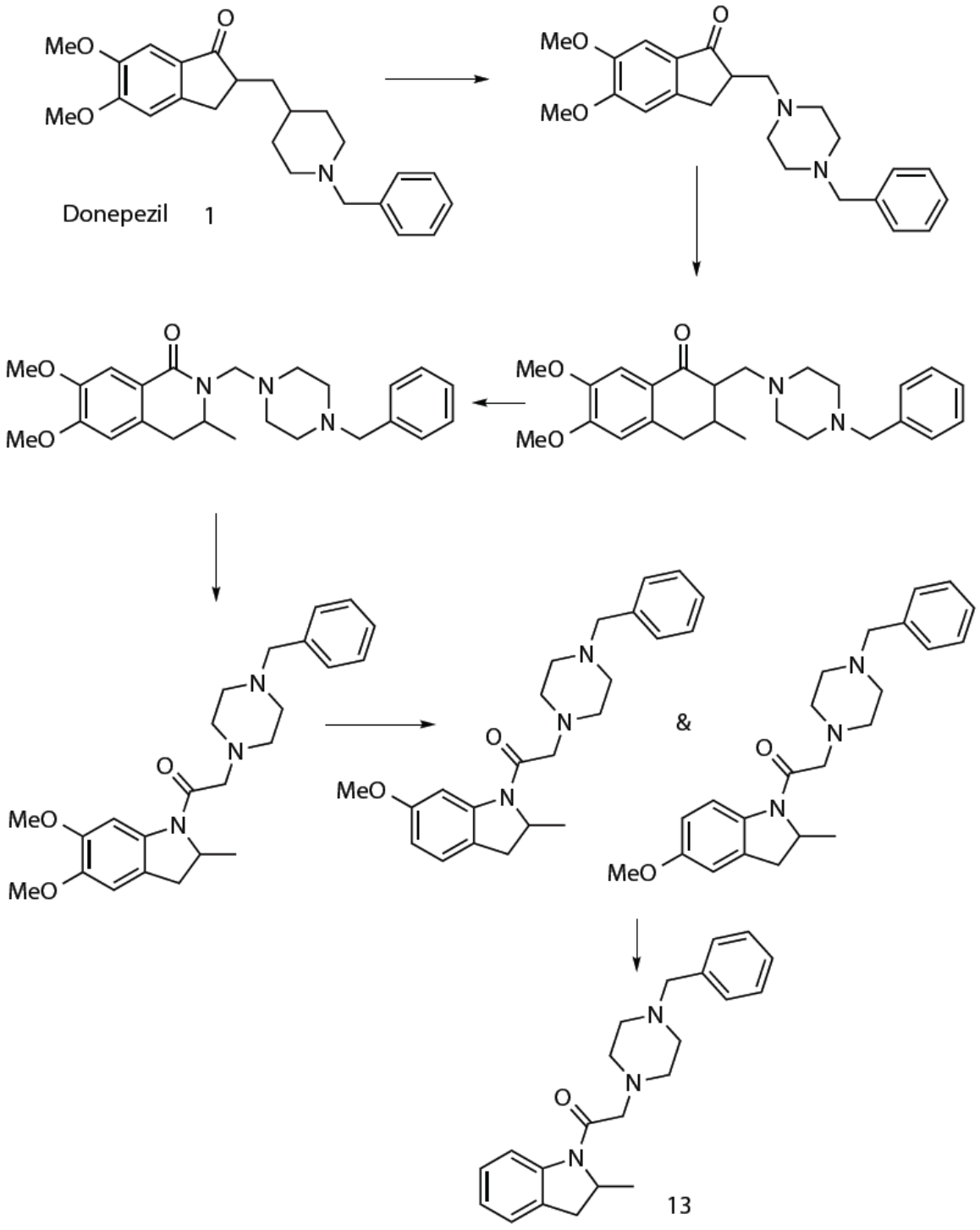
Evolution of the prioritized benzolactam analogues (compound **11a** and **11b**) from a parent isoindole analogue (**5**)

Supplementary Figure 8: Evolution of novel dopamine D4 ligands from donepezil



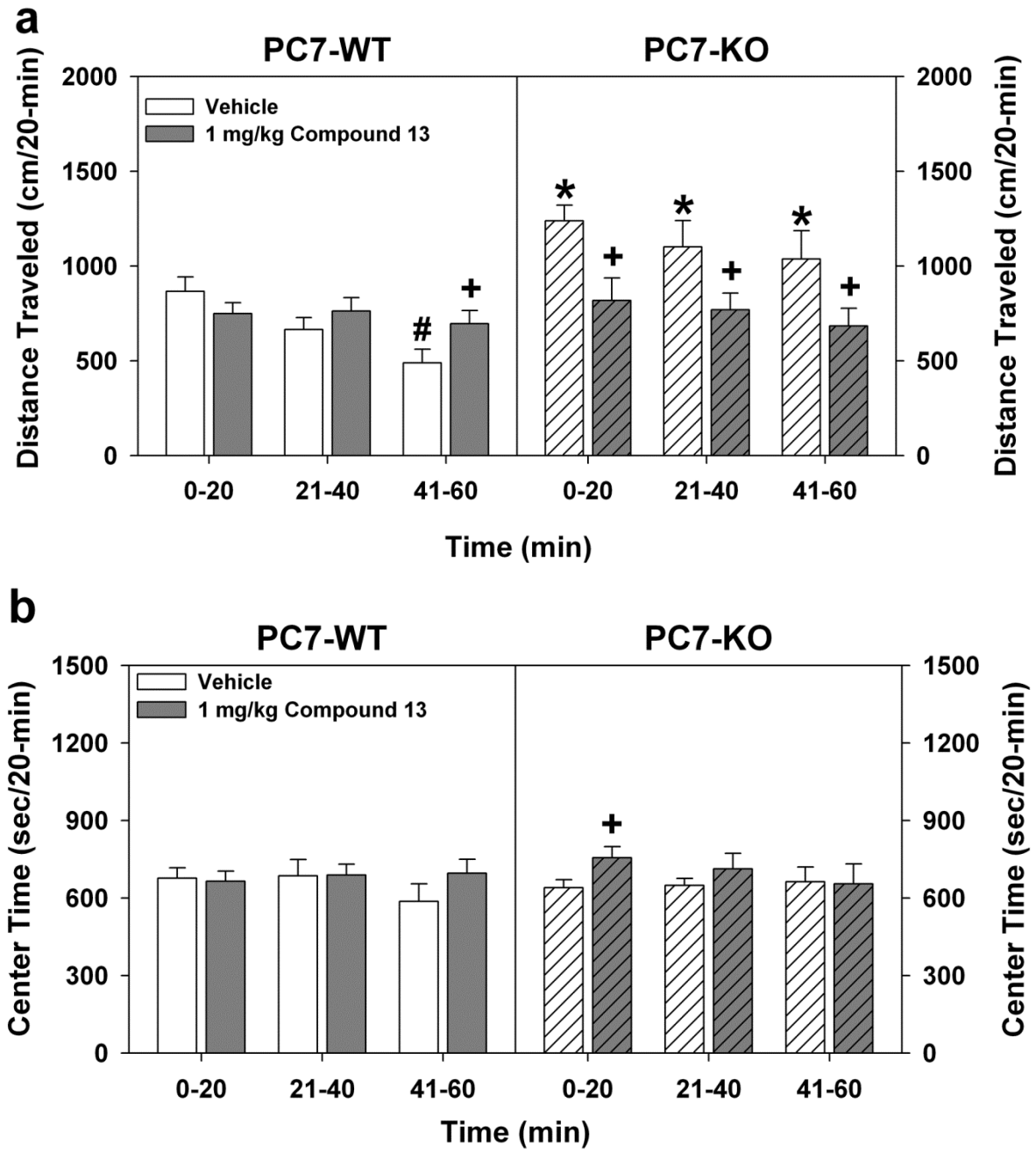
Evolved compound population from donepezil after six generations. The calculated dopamine D4 Bayesian and ADME scores for the final 10,000 compounds generated by the algorithm that are evolved from donepezil and selected for dopamine D4 and CNS ADME objectives, are plotted as coloured circles and triangles. The compounds are coloured by the Pareto frontier ranking as in Fig. 2a. The defined achievement objective (Dopamine D4 Bayesian score = 150, CNS ADME score = 50) is defined as a gold cross. The compounds chosen for testing (**12** and **13**) are represented as triangles

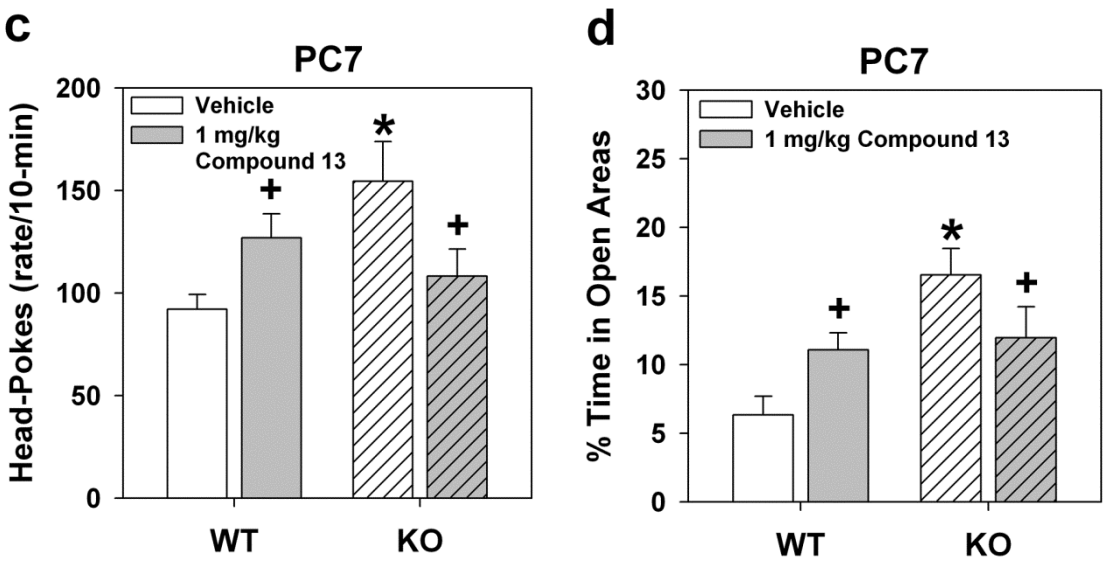
Supplementary Figure 9: Evolution pathway from donepezil to compound **13**



Evolution of donepezil (**1**) (dopamine D4 Bayesian score = 26, D4 k_i = 614nM) into dopamine D4 inverse agonist **13** (dopamine D4 Bayesian score = 112, D4 k_i = 8.9nM). The Tanimoto similarity between donepezil and compound **13** is only 0.26

Supplementary Figure 10: Behavioural responses of PC7 mice to Compound **13**

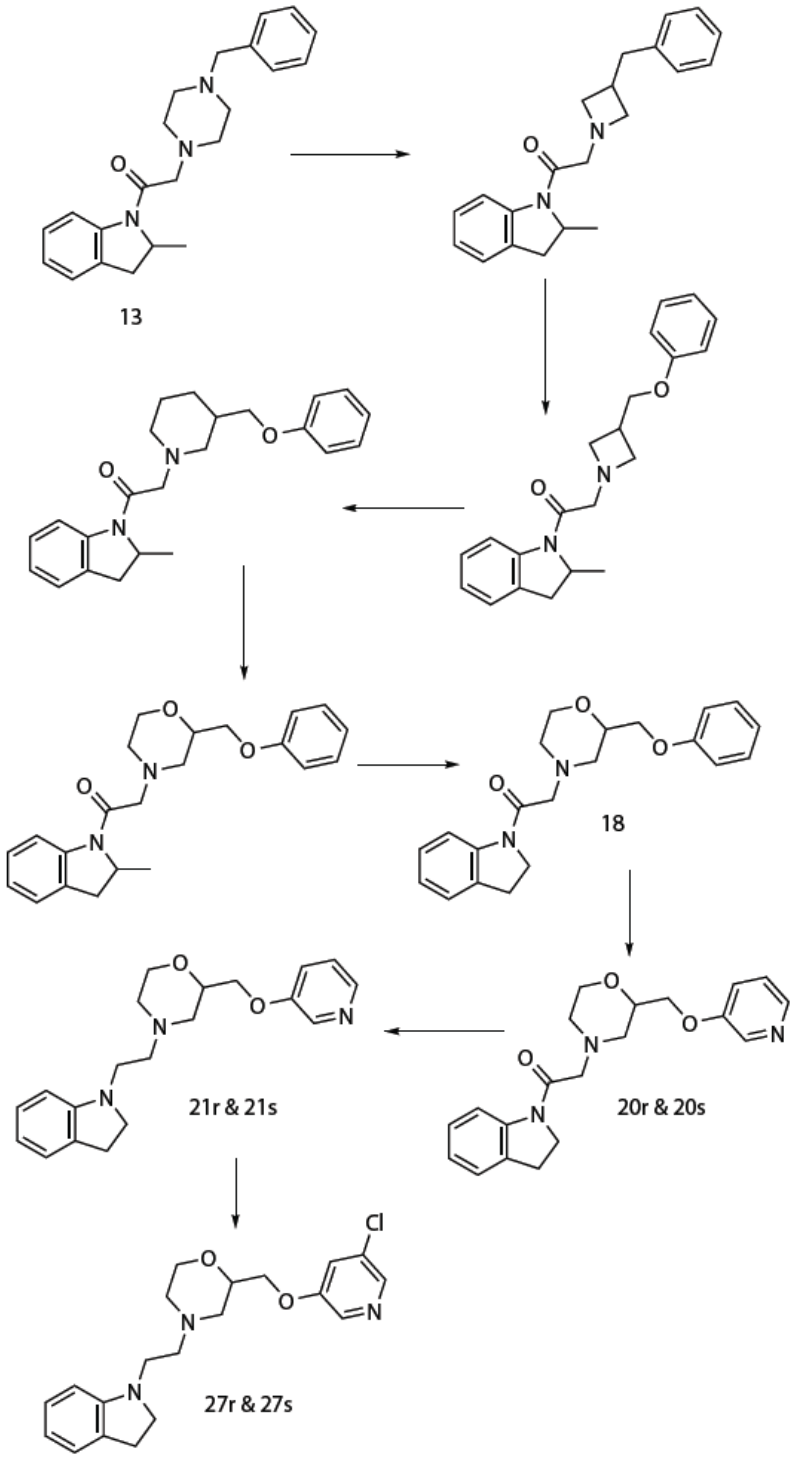




(a) Distance travelled in the open field over 60 min by PC7 animals. Mice were given (*i.p.*) vehicle or 1 mg/kg compound **13** and tested immediately over 60 min. **(b)** Time spent in the centre zone in the open field. **(c)** The numbers of head-pokes in the hole-board test in PC7 mice. Animals were injected with vehicle or 1 mg/kg compound **13** and were tested 30 min later over 10 min. **(d)** Percent time in the open areas of the zero maze in PC7 mice. Animals were administered vehicle or 1 mg/kg compound **13** and tested 30 min later for 5 min. N=9-16 PC7 mice/genotype/treatment-condition. *p<0.05, WT versus PC7-KO mice; +p<0.05, comparisons within genotype to the vehicle given in the same time-block; #p<0.05, compared to the 0-20 min time-point within genotype.

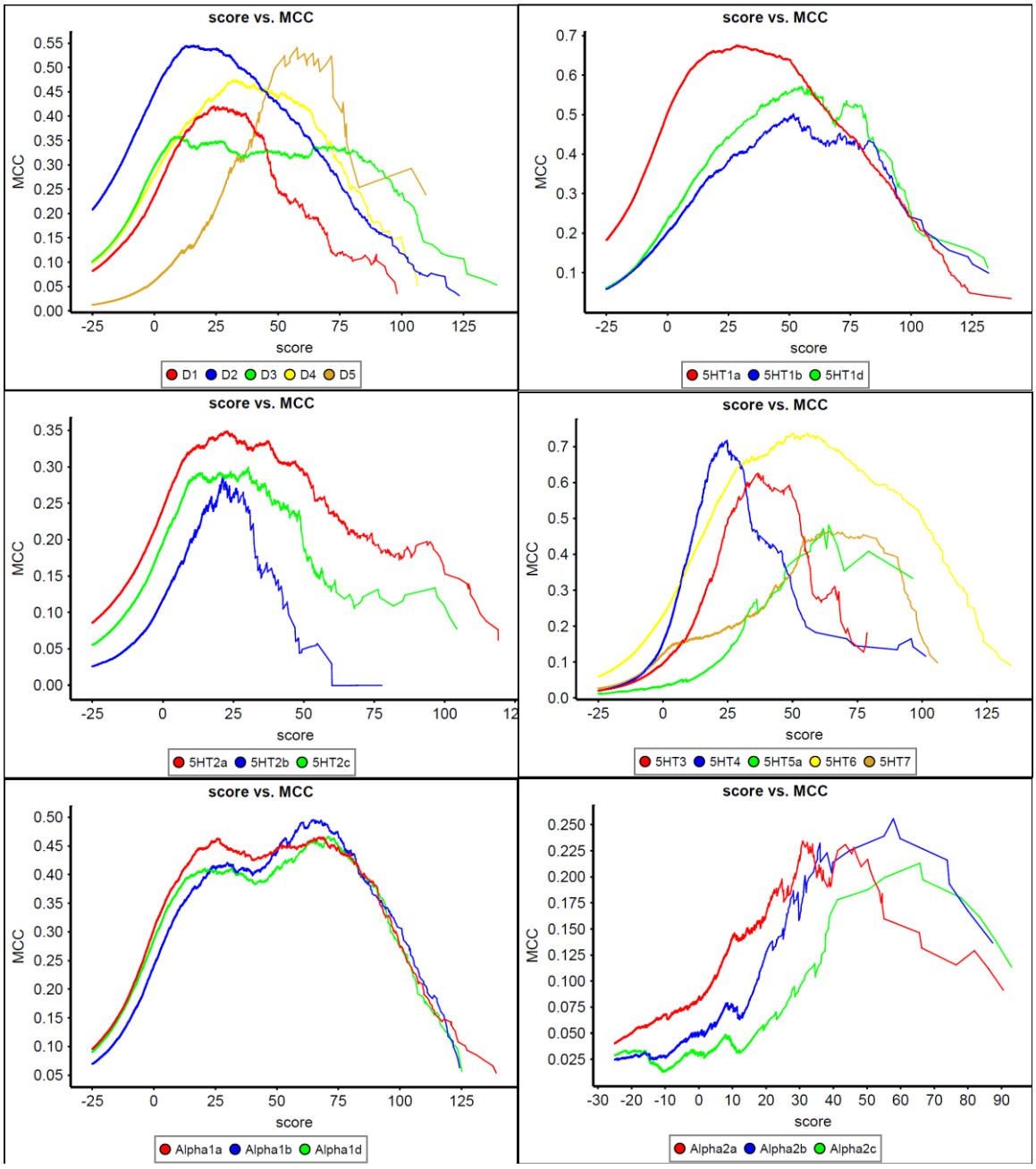
Note: p-values are rounded to the nearest 0.05 value [example, p<0.0549 would round to p<0.05 whereas p<0.0550 would round to p<0.06 and be considered not significant (N.S.) or marginally significant].

Supplementary Figure 11: Evolution pathway from compound **13** to new morpholino series

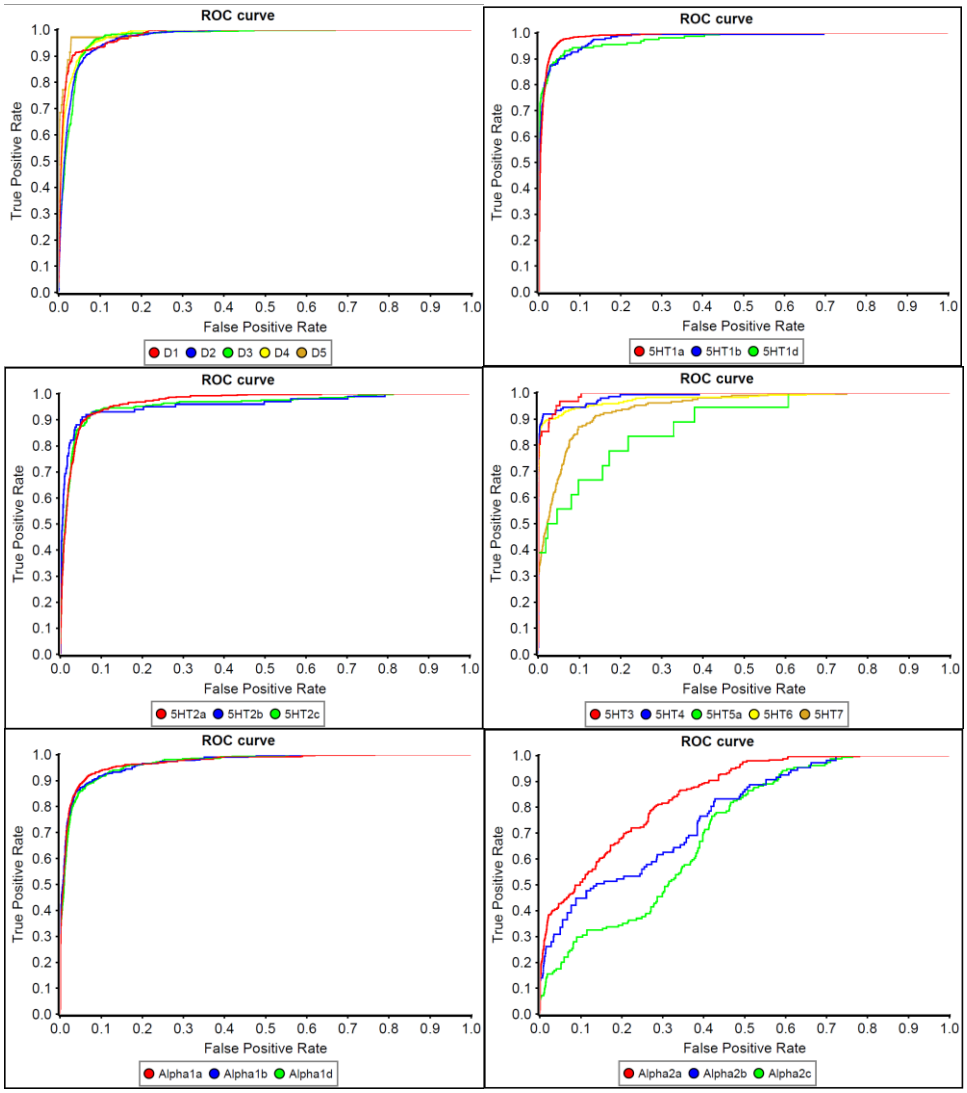


Evolution of selective novel dopamine D4 ligands. Compound **13** is further evolved by selection towards novelty and D4 selectivity into the morpholino analogues **18**, **20** (***r*** and ***s***), **21** (***r*** and ***s***) and **27** (***r*** and ***s***).

Supplementary Figure 12: Matthews correlation coefficient vs model score of test sets



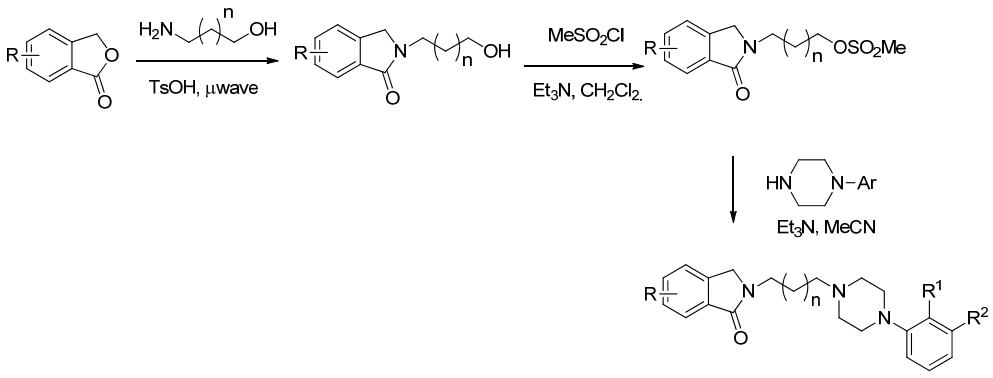
Supplementary Figure 13: Receiver operating characteristic curves of the test sets



Supplementary Methods

1. Synthesis of isoindole analogues

The isoindole series was prepared according to scheme S1



Scheme S1: Synthesis of isoindoles

1.1 General Procedures

General procedure A

Lactone (1 mmol), amino alcohol (2 mmol) and *p*-toluenesulfonic acid (0.2 mmol) were stirred together into a microwave vial and irradiated for 1 h at 200 ^{o}C. The brown mixture was then diluted with diethyl ether and washed with water. The aqueous phase was further extracted with ethylacetate. The collected organic fractions were dried over $MgSO_4$ and concentrated under reduced pressure to a residue, which was used for the next step without further purification.

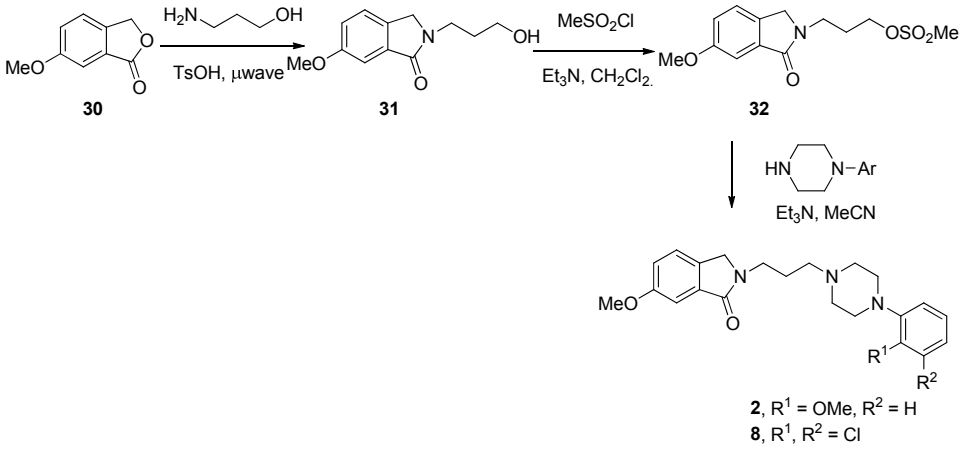
General procedure B

To a cooled solution of alcohol (1 mmol) and triethylamine (1.5 mmol) in dry dichloromethane, was slowly added mesyl chloride (1.5 mmol) with a syringe. The reaction was warmed to room temperature, stirred for 3 h and quenched with a saturated solution of $NaHCO_3$. The phases were separated and the aqueous layer was further extracted with dichloromethane. The solvents were dried over $MgSO_4$ and removed *in vacuo*. The final residue was purified by flash column chromatography or used for the next step without further purification.

General procedure C

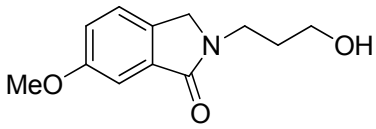
A microwave vial was charged with the appropriate mesylate or alkyl halide (1 mmol), corresponding piperidine (1.05 mmol), triethylamine (1.2 mmol) and acetonitrile (2 mL). The vial was sealed and irradiated for 30 min at 100 ^{o}C. The solvent was removed under reduced pressure and the crude residue was purified by flash column chromatography. The free amine was converted into HCl salt for the biological assay by addition of 2M HCl in ether to a solution of the free amine

1.2 Compounds 2 and 8



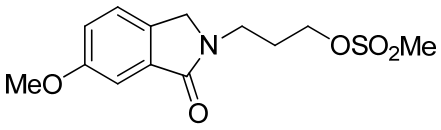
Scheme S2

2-(3-Hydroxypropyl)-6-methoxyisoindolin-1-one (31)



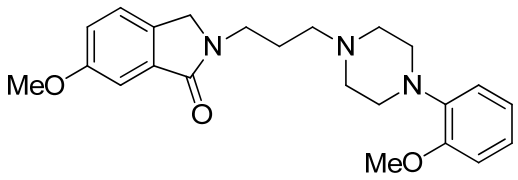
General procedure A starting from (6-methoxy)isobenzofuranone **30** (200 mg, 1.21 mmol), 3-amino-1-propanol (0.18 mL, 2.42 mmol), *p*-toluenesulfonic acid (34 mg, 0.15 mmol). Compound **31** was obtained as a colourless oil, 159 mg, (59%).
^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.85 (qt, 2H, J = 6.1 Hz, C$\underline{H}_2$), 3.57-3.59 (m, 2H, C$\underline{H}_2$N), 3.71 (bs, 1H, O$\underline{H}$), 3.79 (t, 2H, J = 6.1 Hz, C$\underline{H}_2$O), 3.88 (2, 3H, OC$\underline{H}_3$), 4.36 (s, 2H, Ar-C$\underline{H}_2$), 7.12-7.14 (m, 1H, Ar$\underline{H}$), 7.35-7.39 (m, 2H, Ar$\underline{H}$). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 30.9, 38.9, 50.0, 55.7, 58.3, 106.5, 120.0, 123.6, 133.3, 133.6, 160.1, 169.8. LCMS: m/z 222.12 ($[M+H]^+$, 100%); Rt 0.7 min, purity >99% DAD (180-450 nm).

3-(6-Methoxy-1-oxoisoindolin-2-yl)propyl methanesulfonate (32)



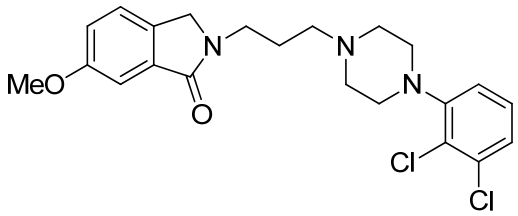
General procedure B from **31** (152 mg, 0.69 mmol), mesyl chloride (0.08 ml, 1.03 mmol), triethylamine (0.14 ml, 1.03 mmol) and dichloromethane (8 mL). Compound **32** was obtained as a slightly green solid, 205 mg (99%) and used for the next step without further purification.
LCMS: m/z 616.22 ($[2M+NH_4]^+$, 100%); Rt 4.5 min, purity >99% DAD (180-450 nm).

6-Methoxy-2-(3-(4-(2-methoxyphenyl)piperazin-1-yl)propyl)isoindolin-1-one (2)



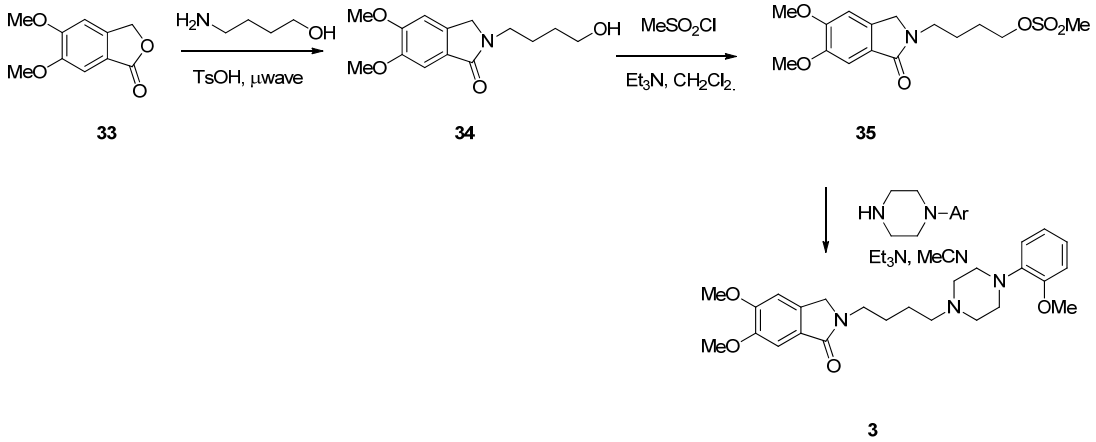
General procedure C from **32** (100 mg, 0.33 mmol), (2-methoxyphenyl)piperazine (67 mg, 0.35 mmol), triethylamine (0.05 ml, 0.40 mmol) and acetonitrile (1.5 mL). Yellowish oil, 90 mg (69%). ^{1}H-NMR (500 MHz, D_2O) δ: 2.16 (qt, 2H, *J* = 7 Hz, C*H*$_2$), 3.23-3.26 (m, 2H, C*H*$_2$N), 3.45 (bs, 8H, 2 x (C*H*$_2$)$_2$N), 3.69 (t, 2H, *J* = 6.6 Hz, CONC*H*$_2$), 3.81, 3.83 (2s, 6H, 2 x OC*H*$_3$), 4.45 (s, 2H, Ar-C*H*$_2$), 6.98 (t, 1H, *J* = 7.7 Hz, Ar*H*), 7.04 (d, 1H, *J* = 8.2 H, Ar*H*), 7.10 (d, 1H, *J* = 8.9 Hz, Ar*H*), 7.16-7.22 (m, 3H, Ar*H*), 7.46 (d, 1H, *J* = 8.4 Hz, Ar*H*). ^{13}C-NMR (125 MHz, D_2O) δ: 22.6, 39.7, 47.9, 50.5, 54.2, 55.3, 55.8, 106.6, 112.1, 119.1, 119.8, 121.3, 124.3, 126.0, 141.8, 151.9, 159.3, 170.8. LCMS: m/z 396.24 ([M+H]$^+$, 100%), Rt 0.8 min, purity >99% DAD (180-450 nm). HRMS: Found 396.2296 $C_{23}H_{30}N_3O_3$ [M + H]$^+$ requires 396.2282. Converted to HCl salt for assay.

2-(3-(4-(2,3-Dichlorophenyl)piperazin-1-yl)propyl)-6-methoxyisoindolin-1-one (8).



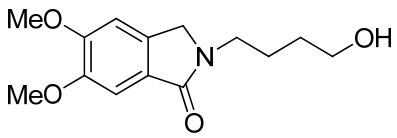
General procedure C from **32** (100 mg, 0.33 mmol), (2,2-dichlorophenyl)piperazine (118 mg, 0.44 mmol), triethylamine (0.14 ml, 0.81 mmol) and acetonitrile (2 mL). Yellowish oil, 41 mg (25%). ^{1}H-NMR (500 MHz, CD_3OD) δ: 2.23 (qt, 2H, *J* = 6.6 Hz, C*H*$_2$), 3.19 (bs, 2H, CH_2N), 3.21-3.29 (m, 2H, C*H*$_2$), 3.73 (bs, 2H, C*H*$_2$N), 3.57 (bs, 2H, C*H*$_2$N), 3.70 (bs, 2H, C*H*$_2$N), 3.81 (t, 2H, *J* = 6.6 Hz, C*H*$_2$), 3.89 (s, 3H, OC*H*$_3$), 4.55 (s, 2H, Ar-C*H*$_2$N), 7.19 (dd, 1H, *J* = 7.0, 2.5, Ar*H*), 7.23 (dd, 1H, *J* = 8.4, 2.5 Hz, Ar*H*), 7.31-7.35 (m, 3H, Ar*H*), 7.51 (dd, 1H, *J* = 8.4, 0.5, Ar*H*). LCMS: m/z 434.15 ([M+H]$^+$, 100%); Rt 0.8 min, purity >95% DAD (180-450 nm). Converted to HCl salt for assay.

1.3 Compound 3



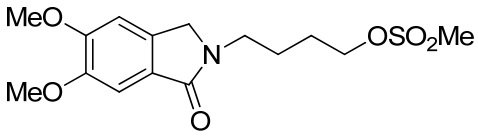
Scheme S3

2-(4-Hydroxybutyl)-5,6-dimethoxyisoindolin-1-one (34)



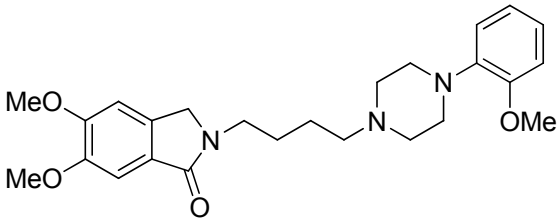
General procedure A starting from (5,6-dimethoxy)isobenzofuranone **33** (100 mg, 0.51 mmol), 4-amino-1-butanol (0.095 mL, 1.02 mmol), *p*-toluenesulfonic acid (19 mg, 0.10 mmol) and toluene (0.5 mL). The title compound was obtained as a colourless oil, 5 mg (4%).
LCMS: m/z 266.14 ($[M+H]^+$, 100%); Rt 4.5 min, purity >99% DAD (180-450 nm).

4-(5,6-Dimethoxy-1-oxoisoindolin-2-yl)butyl methanesulfonate (35)



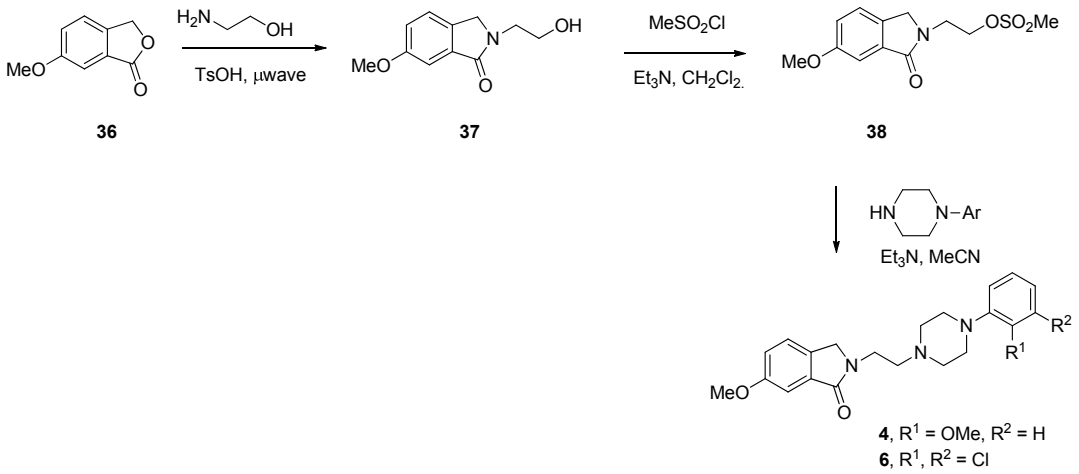
General procedure B starting from **34** (5 mg, 0.018 mmol), mesyl chloride (0.016 mL, 0.020 mmol), triethylamine (0.036 ml, 0.023 mmol) and dichloromethane (0.5 mL). Compound **34** was isolated as a white wax, 6 mg (97%) and used for the next step without further purification.
LCMS: m/z 344.12 ($[M+H]^+$, 100%).

5,6-dimethoxy-2-(4-(4-(2-methoxyphenyl)piperazin-1-yl)butyl)isoindolin-1-one (3)



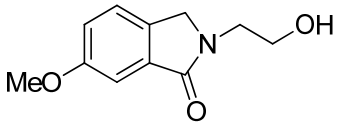
General procedure C from mesylate **35** (6 mg, 0.018 mmol), (2-methoxyphenyl)piperazine (3.8 mg, 0.019 mmol), triethylamine (0.03 mL, 0.023 mmol) and acetonitrile (0.75 mL). Colourless oil, 4 mg (50%).
^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.51-1.57 (m, 2H, C<u>*H*</u>$_2$), 1.62-1.68 (m, 2H, C<u>*H*</u>$_2$), 2.41 (t, 2H, *J* = 7.3 Hz, C<u>*H*</u>$_2$N), 2.59 (bs, 4H, (C<u>*H*</u>$_2$)$_2$N), 3.02 (bs, 4H, (C<u>*H*</u>$_2$)$_2$N), 3.56 (t, 2H, *J* = 7.2 Hz, C<u>*H*</u>$_2$N), 3.79 (s, 3H, OC<u>*H*</u>$_3$), 3.87 (s, 3H, OC<u>*H*</u>$_3$), 4.23 (s, 2H, Ar-C<u>*H*</u>$_2$), 6.78 (dd, 1H, *J* = 8.0, 1.2 Hz, Ar<u>*H*</u>), 6.82-6.87 (m, 3H, Ar<u>*H*</u>), 6.91-6.94 (m, 1H, Ar<u>*H*</u>), 7.24 (s, 1H, Ar<u>*H*</u>). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 26.5, 42.3, 49.6, 50.5, 53.4, 55.4, 56.2, 56.2, 58.2, 105.0, 105.4, 111.2, 118.2, 121.0, 122.9, 133.0, 134.6, 149.7, 152.3, 152.4, 172.8. LCMS: m/z 440.26 ($[M+H]^+$, 100%); Rt 5.8 min, purity >99% DAD (180-450 nm). HRMS: Found 440.2551 $C_{25}H_{34}N_3O_4$ $[M + H]^+$ requires 440.2544. Converted to HCl salt for assay.

1.3 Compound 4 and 6



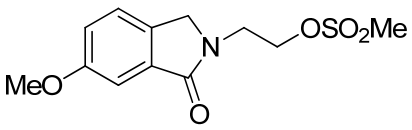
Scheme S4

2-(2-Hydroxyethyl)-6-methoxyisoindolin-1-one (37)



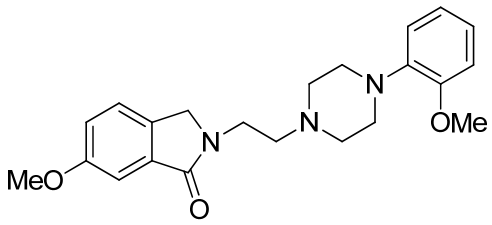
General procedure A from (6-methoxy)isobenzofuranone **36** (200 mg, 1.21 mmol), 2-amino-1-ethanol (0.15 mL, 2.42 mmol), *p*-toluenesulfonic acid (34 mg, 0.15 mmol). Compound **37** was isolated as colourless oil, 97 mg (38%).
^{1}H-NMR (500 MHz, $CDCl_3$) δ: 3.68 (t, 2H, *J* = 5 Hz, C*H*$_2$N), 3.77 (s, 3H, OC*H*$_3$), 3.82-3.85 (m, 2H, C*H*$_2$OH), 4.36 (S, 2H, Ar-C*H*$_2$), 7.01 (dd, 1H, *J* = 8.5, 2.3, Ar*H*), 7.23-7.24 (m, 2H, Ar*H*). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 42.8, 55.5, 62.1, 64.0, 113.9, 116.0, 131.5, 132.2, 136.9, 159.3, 170.3. LCMS: m/z 208.12 ($[M+H]^+$, 100%); Rt 0.8 min, purity >99% DAD (180-450 nm).

2-(6-Methoxy-1-oxoisoindolin-2-yl)ethyl methanesulfonate (38)



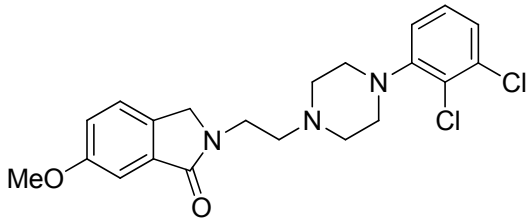
General procedure B from **37** (90 mg, 0.43 mmol), mesyl chloride (0.04 ml, 0.52 mmol), triethylamine (0.07 mL, 0.52 mmol) and dichloromethane (2 mL). Compound **38** was isolated as a brownish solid, 117 mg (quantitative) and used for the next step without further purification.
LCMS: m/z 286.08 ($[M+H]^+$, 100%); Rt 0.8 min, purity >95% DAD (180-450 nm).

6-methoxy-2-(2-(4-(2-methoxyphenyl)piperazin-1-yl)ethyl)isoindolin-1-one (4)



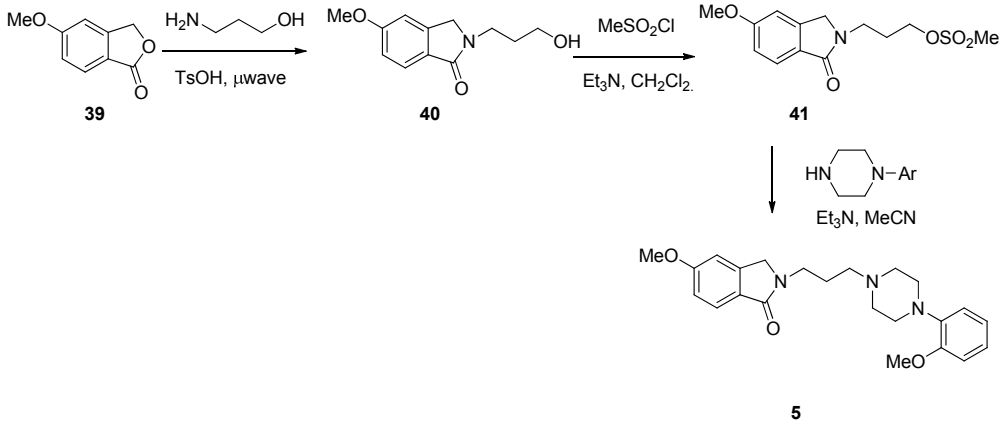
General procedure C starting from mesylate **38** (60 mg, 0.21 mmol), (2-methoxyphenyl)piperazine (43 mg, 0.22 mmol), triethylamine (0.044 mL, 0.32 mmol) in acetonitrile (1 mL). Compound **4** was obtained as a yellowish oil, 58 mg (72%).
^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.73-2.75 (m, 6H, (C*H*$_2$)$_2$N + C*H*$_2$N), 3.10 (m, 4H, (C*H*$_2$)$_2$N), 3.81 (t, 2H, *J* = 6.4 Hz, C*H*$_2$N), 3.88 (s, 3H, OC*H*$_3$), 3.89 (s, 3H, OC*H*$_3$), 4.49 (s, 2H, Ar-C*H*$_2$), 6.89 (dd, 1H, *J* = 7.8, 1.2, Ar*H*), 6.92-6.96 (m, 2H, Ar*H*), 7.00-7.03 (m, 1H, Ar*H*), 7.13 (dd, 1H, *J* = 8.3, 2.5 Hz, Ar*H*), 7.35 (dd, 1H, *J* = 8.4, 0.5 Hz, Ar*H*), 7.37 (d, 1H, *J* = 2.4 Hz, Ar*H*). ^{13}C-NMR (125 MHz, CD_3OD) δ: 38.9, 49.3, 51.5, 53.6, 56.2, 56.2, 56.5, 107.7, 113.3, 120.4, 121.2, 122.4, 125.3, 126.7, 135.9, 139.0, 154.0, 161.7, 172.3. LCMS: m/z 382.22 ($[M+H]^+$, 100%); Rt 5.0 min, purity >99% DAD (180-450 nm). HRMS: Found 382.2121 $C_{22}H_{28}N_3O_3$ $[M + H]^+$ requires 382.2125. Converted to HCl salt for assay.

2-(2-(4-(2,3-Dichlorophenyl)piperazin-1-yl)ethyl)-6-methoxyisoindolin-1-one (6)



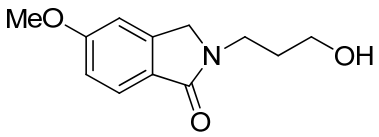
General procedure C from mesylate **38** (57 mg, 0.20 mmol), (2,3-dichlorophenyl)piperazine (59 mg, 0.22 mmol), triethylamine (0.06 mL, 0.44 mmol) in acetonitrile (1 mL). Yellowish oil, 28 mg (45%).
^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.61 (bs, 4H, (C*H*$_2$)$_2$N), 2.63 (t, 2H, *J* = 6.4 Hz, C*H*$_2$N), 2.94 (bs, 4H, (C*H*$_2$)$_2$N), 3.67 (t, 2H, *J* = 6.4 Hz, C*H*$_2$N), 3.76 (s, 3H, OC*H*$_3$), 4.34 (s, 2H, Ar-C*H*$_2$), 6.82 (dd, 1H, *J* = 7.4, 2.2 Hz, Ar*H*), 6.98-7.05 (m, 3H, Ar*H*), 7.23 (dd, 1H, *J* = 8.8, 0.5 Hz, Ar*H*), 7.46 (d, 1H, *J* = 2.4 Hz, Ar*H*). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 37.0, 50.3, 51.3, 53.3, 55.7, 56.6, 106.5, 118.6, 119.6, 123.4, 124.6, 127.4, 127.5, 133.6, 134.0, 134.2, 151.2, 160.0, 168.5. LCMS: m/z 420.12 ($[M+H]^+$, 100%); Rt 5.6 min, purity >99% DAD (180-450 nm). HRMS: Found 420.1240 $C_{21}H_{24}Cl_2N_3O_2$ $[M + H]^+$ requires 420.1240. Converted to HCl salt for assay.

1.5 Compound 5



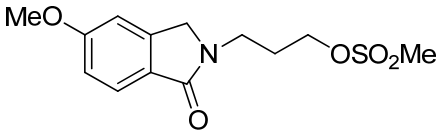
Scheme S5

2-(3-Hydroxypropyl)-5-methoxyisoindolin-1-one (40)



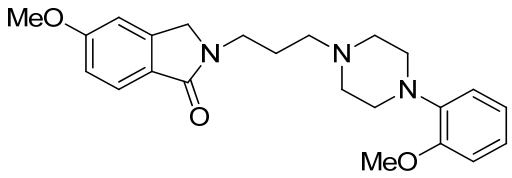
General procedure A starting from (5-methoxy)isobenzofuranone **39** (100 mg, 0.61 mmol), 3-amino-1-propanol (0.093 mL, 1.21 mmol), *p*-toluenesulfonic acid (11 mg, 0.15 mmol). Compound **40** was isolated as a colourless oil, 33 mg (24%).
^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.82 (qt, 2H, *J* = 6.0 Hz, C*H*$_2$), 3.57 (t, 2H, *J* = 5.7 Hz, C*H*$_2$), 3.73 (t, 2H, *J* = 6.3 Hz, C*H*$_2$), 3.87 (s, 3H, OC*H*$_3$), 4.35 (s, 2H, Ar-C*H*$_2$), 6.93 (d, 1H, *J* = 1.7 Hz, Ar*H*), 6.97 (dd, 1H, *J* = 8.4, 2.2 Hz, Ar*H*), 7.73 (d, 1H, *J* = 8.4 Hz, Ar*H*). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 29.6, 30.8, 38.7, 55.6, 58.3, 107.7, 114.7, 124.8, 124.9, 143.5, 162.0, 169.6. LCMS: m/z 222.10 ($[M+H]^+$, 100%); Rt 0.6 min, purity >99% DAD (180-450 nm).

3-(5-Methoxy-1-oxoisoindolin-2-yl)propyl methanesulfonate (41)



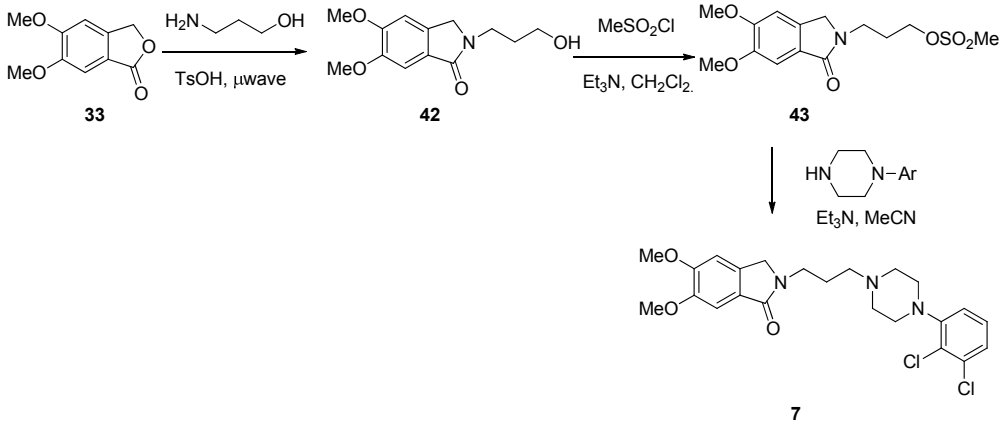
General procedure B from alcohol **40** (33 mg, 0.15 mmol), mesyl chloride (0.14 mL, 0.179 mmol), triethylamine (0.025 mL, 0.179 mmol) and dichloromethane (1 mL). Compound **41** was obtained as colourless oil, 40 mg (89%), used for the next step without purification.
LRMS: m/z 300.09 ($[M+H]^+$, 100%).

5-Methoxy-2-(3-(4-(2-methoxyphenyl)piperazin-1-yl)propyl)isoindolin-1-one (5)



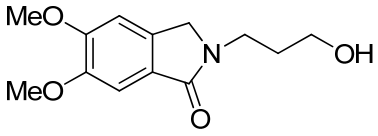
General procedure C from mesylate **41** (40 mg, 0.13 mmol), (2-methoxyphenyl)piperazine (26 mg, 0.20 mmol), triethylamine (0.038 mL, 0.27 mmol) and acetonitrile (1.5 mL). Yellowish oil, 10 mg (19%).
^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.93 (qt, 2H, *J*= 7.4 Hz, C$\underline{H}_2$), 2.52 (t, 2H, *J* = 7.4 Hz, C$\underline{H}_2$), 2.68 (bs, 4H, (C$\underline{H}_2$)$_2$N), 3.09 (bs, 4H, (C$\underline{H}_2$)$_2$N), 3.68 (t, 2H, *J* = 7.1 Hz, C$\underline{H}_2$), 3.88 (s, 3H, OC$\underline{H}_3$), 3.89 (s, 3H, OC$\underline{H}_3$), 4.38 (s, 2H, Ar-C$\underline{H}_2$), 6.91-6.96 (m, 3H, Ar$\underline{H}$), 6.99-7.03 (m, 3H, Ar$\underline{H}$), 7.29 (d, 1H, *J* = 0.6 Hz, Ar$\underline{H}$). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 25.9, 40.8, 49.9, 50.6, 53.5, 55.4, 55.6, 55.9, 107.7, 111.2, 114.5, 118.2, 121.0, 122.9, 124.9, 125.7, 141.3, 143.4, 152.3, 162.6, 168.5. LCMS: m/z 396.24 ([M+H]$^+$, 100%); Rt 0.7 min, purity >99% DAD (180-450 nm). HRMS: Found 396.2294 $C_{23}H_{30}N_3O_3$ [M + H]$^+$ requires 396.2282. Converted to HCl salt for assay.

1.6 Compound 7



Scheme S6

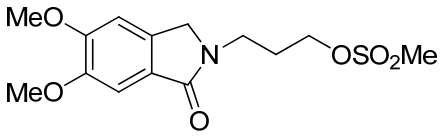
2-(3-Hydroxypropyl)-5,6-dimethoxyisoindolin-1-one (42)



General procedure A starting from (5,6-dimethoxy)isobenzofuranone **33** (100 mg, 0.51 mmol), 3-amino-1-propanol (0.078 mL, 1.02 mmol), *p*-toluenesulfonic acid (19 mg, 0.1 mmol) and toluene (0.5 mL). Compound **42** was obtained as a colourless oil, 12 mg (8%).

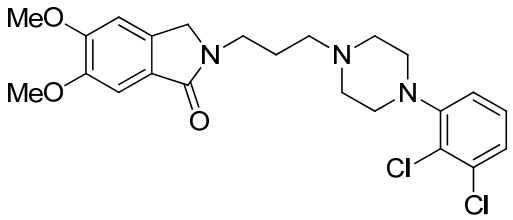
LRMS: m/z 252.13 ([M+H]$^+$, 100%).

3-(5,6-Dimethoxy-1-oxoisoindolin-2-yl)propyl methanesulfonate (43)



General procedure B from alcohol **42** (12 mg, 0.047 mmol), mesyl chloride (0.04 mL, 0.05 mmol), triethylamine (0.08 mL, 0.06 mmol) and dichloromethane (1 mL). Colourless oil, 32 mg crude used for the next step without further purification.

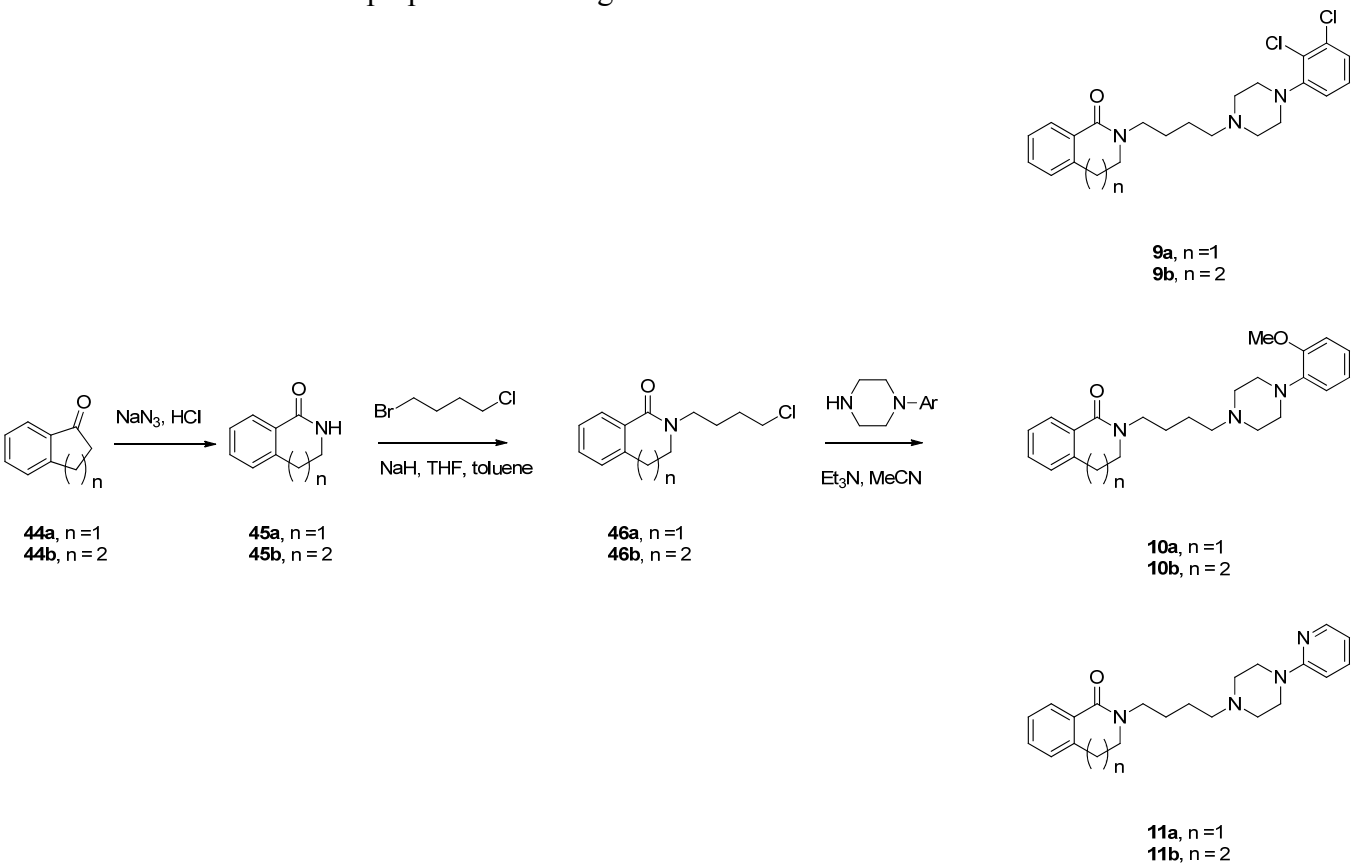
2-(3-(4-(2,3-Dichlorophenyl)piperazin-1-yl)propyl)-5,6-dimethoxyisoindolin-1-one (7)



General procedure C from the crude mesylate **43** (32 mg, 0.099 mmol), (2,3-dichlorophenyl)piperazine (29 mg, 0.10 mmol), triethylamine (0.034 mL, 0.24 mmol) and acetonitrile (0.5 mL). Yellowish solid, 28 mg (67%).
^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.83 (qt, 2H, *J* = 7.4 Hz, C$\underline{H}_2$), 2.43 (t, 2H, *J* = 7.4 Hz, C$\underline{H}_2$N), 2.57 (bs, 4H, (C$\underline{H}_2$)$_2$N), 2.98 (bs, 4H, (C$\underline{H}_2$)$_2$N), 3.61 (t, 2H, *J* = 7.4 Hz, C$\underline{H}_2$N), 3.87 (s, 3H, OC$\underline{H}_3$), 3.88 (s, 3H, OC$\underline{H}_3$), 4.26 (s, 2H, Ar-C$\underline{H}_2$), 6.85-6.87 (m, 2H, Ar$\underline{H}$), 7.04-7.09 (m, 2H, Ar$\underline{H}$), 7.25 (s, 1H, Ar$\underline{H}$).
^{13}C-NMR (125 MHz, $CDCl_3$) δ: 26.0, 28.4, 31.0, 33.5, 37.9, 38.5, 40.8, 44.5, 51.3, 53.3, 56.3, 105.4, 118.6, 124.4, 127.4, 134.9, 140.3, 145.7, 154.4, 164.5. LCMS: m/z 464.16 ([M+H]$^+$, 100%)%); Rt 6.5 min, purity >99% DAD (180-450 nm). Converted to HCl salt for assay.

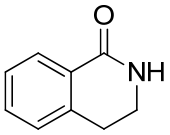
2. Synthesis of benzolactam analogues

The benzolactam series was prepared according to scheme S7.



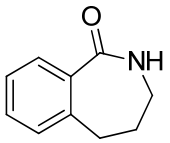
Scheme S7

3,4-Dihydroisoquinolin-1(2H)-one (45a)



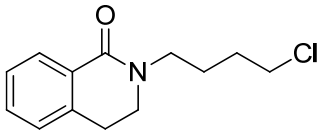
Compound **45a** was synthesised following the reported methods[1,2] using α-Indanone **44a** (1 g, 7.56 mmol), NaN_3 (983 mg, 15.13 mmol) and conc. HCl (19 mL). Purified by flash column chromatography (Silica, Pet. Ether/DCM 1:0 to 4:6). Off-white solid, 410 mg (37%).
^{1}H-NMR (500 MHz, $CDCl_3$) δ: 3.02 (t, 2H, *J* = 6.6 Hz, Ar-C$\underline{H}_2$), 3.60 (dt, *J* = 6.6, 2.90 Hz, C$\underline{H}_2$NH), 6.39 (bs, 1H, N$\underline{H}$), 7.23-7.25 (m, 1H, Ar$\underline{H}$), 7.38 (ttt, 1H, *J* = 8.2, 0.6, 0.5 Hz, Ar$\underline{H}$), 7.47 (dt, 1H, *J* = 7.5, 1.5 Hz, Ar$\underline{H}$), 8.10 (dd, 1H, *J* = 7.7, 1.1 Hz, Ar$\underline{H}$). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 28.4, 40.2, 127.0, 127.2, 128.0, 132.1, 138.8, 166.3. LCMS: m/z 148.07 ($[M+H]^+$, 100%); Rt 4.0 min, purity >99% DAD (180-450 nm).

2,3,4,5-Tetrahydro-1H-benzo[c]azepin-1-one (45b).



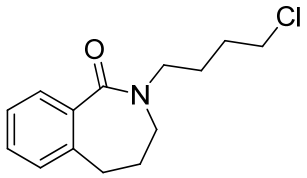
Same procedure as for compound **45a** with α-tetralone **44b** (1 g, 6.84 mmol), NaN_3 (890 mg, 13.7 mmol) and conc. HCl (17 mL). Purified by flash column chromatography (Silica, Pet. Ether/DCM 0:1 to 4:6). Off-white solid, 435 mg (39%).
^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.05 (qt, 2H, *J* = 6.9 Hz, CH_2), 2.89 (t, 2H, *J* = 7.1 Hz, CH_2), 3.14 (q, 2H, *J* = 6.5 Hz, CH_2), 6.58 (bs, 1H, N*H*), 7.21 (d, 1H, *J* = 7.4 Hz, Ar*H*), 7.37 (dt, 1H, *J* = 1.3, 7.5 Hz, Ar*H*), 7.43 (dt, 1H, *J* = 7.4, 1.5 Hz, Ar*H*), 7.73 (dd, 1H, *J* = 7.6, 1.4 Hz, Ar*H*). LCMS: m/z 162.09 ($[M+H]^+$, 100%); Rt 4.2 min, purity >99% DAD (180-450 nm).

2-(4-Chlorobutyl)-3,4-dihydroisoquinolin-1(2H)-one (46a)



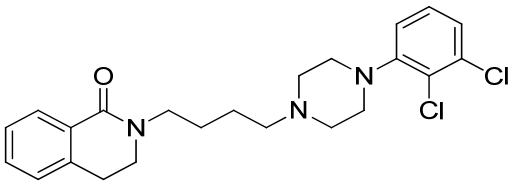
NaH (95%, 74 mg, 3.06 mmol) was added to a solution of lactam **45a** (410 mg, 2.78 mmol), 4-chloro-1-bromo butane (0.35 mL, 3.06 mmol) in 1:1 THF/toluene (8 mL). The reaction was irradiated with microwaves for 1 h at 100 °C. After quenching with water, the phases were separated and the organic layer was filtered and concentrated to dryness. The residue was purified by flash column chromatography (Silica, DCM/MeOH 99:1 to 95:5). Yellowish oil, 269 mg (41%).
^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.78-1.86 (m, 4H, 2 x C*H*$_2$), 2.99 (t, 2H, *J* = 6.9 Hz, C*H*$_2$), 3.55 (t, 2H, *J* = 6.9 Hz, C*H*$_2$), 3.58-3.62 (m, 4H, 2 x C*H*$_2$), 7.17 (d, 1H, *J* = 8.0 Hz, Ar*H*), 7.33 (t, 1H, *J* = 7.5 Hz, Ar*H*), 7.40 (dt, 1H, *J* = 7.4, 1.4 Hz, Ar*H*), 8.07 (d, 1H, *J* = 7.7 Hz, Ar*H*). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 24.9, 28.2, 29.8, 44.7, 45.9, 46.3, 126.9, 127.0, 128.2, 129.5, 131.6, 137.9, 164.4. LCMS: m/z 238.0 ($[M+H]^+$, 100%); Rt 4.8 min, purity >99% DAD (180-450 nm).

2-(4-Chlorobutyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-1-one (46b)



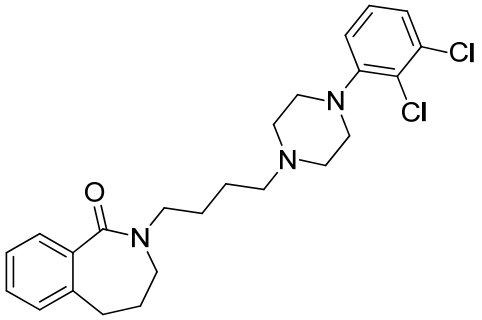
Same procedure as compound **46a** with lactam **45b** (418 mg, 2.59 mmol), 4-chloro-1-bromo butane (0.47 mL, 3.88 mmol) in 1:1 THF/Toluene (10 mL). Compound **46b** was isolated as a colourless oil, 322 mg (49%).
^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.80-1.92 (m, 4H, 2 x C*H*$_2$), 2.06 (qt, 2H, *J* = 6.7 Hz, C*H*$_2$), 2.80 (t, 2H, *J* = 7.1 Hz, C*H*$_2$), 3.23 (t, 2H, *J* = 6.5 Hz, C*H*$_2$), 3.62-3.65 (m, 4H, 2 x C*H*$_2$), 7.15 (dd, 1H, *J* = 7.3, 0.9 Hz, Ar*H*), 7.33 (dt, 1H, *J* = 7.5, 1.5, Ar*H*), 7.37 (dt, 1H, *J* = 7.4, 1.5 Hz, Ar*H*), 7.67 (dd, 1H, *J* = 7.4, 1.4, Ar*H*). LCMS: m/z 252.0 ($[M+H]^+$, 100%); Rt 4.9 min, purity >85% DAD (180-450 nm).

2-(4-(4-(2,3-Dichlorophenyl)piperazin-1-yl)butyl)-3,4-dihydroisoquinolin-1(2H)-one (9a)



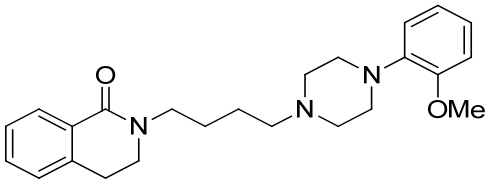
General procedure C from chloride **46a** (90 mg, 0.38 mmol), (3-chlorophenyl)piperazine hydrochloride (122 mg, 0.46 mmol), triethylamine (0.105 mL, 0.76 mmol) and acetonitrile (2 mL). Colourless oil, 101 mg (61%).
^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.64-1.66 (m, 2H, C$\underline{H}_2$), 1.69-1.75 (m, 2H, C$\underline{H}_2$), 2.49 (t, 2H, *J* = 7.1 Hz, C$\underline{H}_2$), 2.66 (bs, 4H, (C$\underline{H}_2$)$_2$N), 3.01 (t, 2H, *J* = 6.6 Hz, C$\underline{H}_2$), 3.08 (bs, 4H, (C$\underline{H}_2$)$_2$N), 3.59 (t, 2H, *J* = 7.0 Hz, C$\underline{H}_2$), 3.63 (t, 2H, *J* = 7.4 Hz, C$\underline{H}_2$), 6.97 (dd, 1H, *J* = 6.9, 2.6 Hz, Ar$\underline{H}$), 7.14-7.20 (m, 3H, Ar$\underline{H}$), 7.36 (t, 1H, *J* = 7.6 Hz, Ar$\underline{H}$), 7.43 (dt, 1H, *J* = 7.4, 1.4, Ar$\underline{H}$), 8.10 (d, 1H, *J* = 11.7 Hz, Ar$\underline{H}$). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 24.3, 25.8, 28.2, 46.1, 47.3, 51.3, 53.3, 58.3, 118.6, 124.5, 126.8, 127.0, 127.4, 127.5, 128.24, 129.7, 131.5, 134.0, 137.9, 151.35, 164.31. LCMS: m/z 432.1 ([M+H]$^+$, 100%); Rt 5.7 min, purity >99% DAD (180-450 nm). Converted to HCl salt for assay.

2-(4-(4-(2,3-Dichlorophenyl)piperazin-1-yl)butyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-1-one (9b)



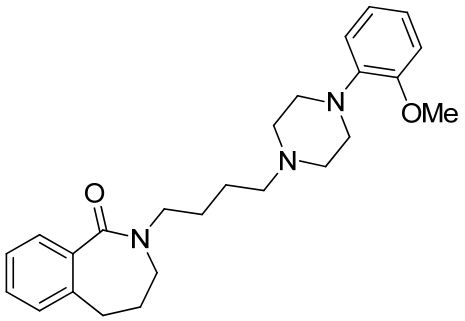
General procedure C from chloride **46b** (95 mg, 0.38 mmol), (3-chlorophenyl)piperazine hydrochloride (122 mg, 0.46 mmol), triethylamine (0.105 mL, 0.76 mmol) and acetonitrile (2 mL). Colourless oil, 117 mg (69%).
^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.62-1.76 (m, 4H, 2 x C$\underline{H}_2$), 2.06 (qt, 2H, *J* = 6.8 Hz, C$\underline{H}_2$), 2.51 (t, 2H, *J* = 7.5 Hz, C$\underline{H}_2$), 2.67 (bs, 4H, (C$\underline{H}_2$)$_2$N), 2.82 (t, 2H, *J* = 7.1 Hz, C$\underline{H}_2$), 3.10 (bs, 4H, 2 x C$\underline{H}_2$), 3.23 (t, 2H, *J* = 6.5 Hz, C$\underline{H}_2$N), 3.63 (t, 2H, *J* = 7.4 Hz, C$\underline{H}_2$N), 6.98 (dd, 1H, *J* = 6.8, 2.7 Hz, Ar$\underline{H}$), 7.14-7.17 (m, 3H, Ar$\underline{H}$), 7.32-7.40 (m, 2H, Ar$\underline{H}$), 7.69 (dd, 1H, *J* = 7.4, 1.7 Hz, Ar$\underline{H}$). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 24.4, 26.9, 30.0, 30.3, 46.2, 47.2, 51.4, 53.4, 58.3, 118.6, 124.5, 126.9, 127.4, 128.1, 128.6, 130.6, 136.5, 137.2, 170.9. LCMS: m/z 446.18 ([M+H]$^+$, 100%)); Rt 5.7 min, purity >99% DAD (180-450 nm). Converted to HCl salt for assay.

2-(4-(4-(2-Methoxyphenyl)piperazin-1-yl)butyl)-3,4-dihydroisoquinolin-1(2H)-one (10a)



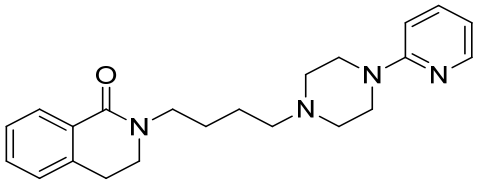
General procedure C from chloride **46a** (90 mg, 0.38 mmol), (2-methoxyphenyl)piperazine (88 mg, 0.46 mmol), triethylamine (0.105 mL, 0.76 mmol) and acetonitrile (2 mL). Colourless oil, 84 mg (56%).
^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.60-1.74 (m, 4H, 2 x C$\underline{H}_2$), 2.49 (t, 2H, *J* = 7.1 Hz, C$\underline{H}_2$), 2.68 (bs, 4H, (C$\underline{H}_2$)$_2$N), 3.01 (t, 2H, *J* = 6.6 Hz, C$\underline{H}_2$), 3.12 (bs, 4H, (C$\underline{H}_2$)$_2$N), 3.59 (t, 2H, *J* = 6.6 Hz, C$\underline{H}_2$), 3.63 (t, 2H, *J* = 7.3 Hz, C$\underline{H}_2$), 3.88 (s, 3H, OC$\underline{H}_3$), 6.88 (d, 1H, *J* = 7.9, Ar$\underline{H}$), 6.92-7.03 (m, 3H, Ar$\underline{H}$), 7.19 (d, 2H, *J* = 7.2 Hz, Ar$\underline{H}$), 7.36 (t, 1H, *J* = 7.4 Hz, Ar$\underline{H}$), 7.42 (dt, 1H, *J* = 7.4, 1.4 Hz, Ar$\underline{H}$), 8.10 (d, 1H, *J* = 7.7 Hz, Ar$\underline{H}$). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 24.3, 25.8, 28.2, 46.1, 47.3, 50.6, 51.3, 53.3, 55.3, 58.3, 118.6, 124.5, 126.8, 127.0, 127.4, 127.5, 128.24, 129.7, 131.5, 134.0, 137.9, 151.35, 164.31. LCMS: m/z 394.2 ([M+H]$^+$, 100%), Rt 5.2 min, purity >99% DAD (180-450 nm). Converted to HCl salt for assay.

2-(4-(4-(2-Methoxyphenyl)piperazin-1-yl)butyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-1-one (10b)



General procedure C from chloride **46b** (95 mg, 0.38 mmol), (2-methoxyphenyl)piperazine (88 mg, 0.46 mmol), triethylamine (0.105 mL, 0.76 mmol) and acetonitrile (2 mL). Colourless oil, 100 mg (64%).
^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.65-1.77 (m, 4H, 2 x C$\underline{H}_2$), 2.06 (qt, 2H, *J* = 6.8 Hz, C$\underline{H}_2$), 2.51 (bs, 2H, C$\underline{H}_2$), 2.70 (bs, 4H, (C$\underline{H}_2$)$_2$N), 2.82 (t, 2H, *J* = 7.1 Hz, C$\underline{H}_2$), 3.13 (bs, 4H, 2 x C$\underline{H}_2$), 3.23 (t, 2H, *J* = 6.4 Hz, C$\underline{H}_2$N), 3.63 (t, 2H, *J* = 7.4 Hz, C$\underline{H}_2$N), 3.89 (s, 3H, OC$\underline{H}_3$), 6.89 (dd, 1H, *J* = 8.0, 1.8 Hz, Ar$\underline{H}$), 6.92-7.04 (m, 3H, Ar$\underline{H}$), 7.16 (dd, 1H, *J* = 7.4, 1 Hz Ar$\underline{H}$), 7.33 (dt, 1H, *J* = 7.4, 1.5 Hz, Ar$\underline{H}$), 7.38 (dt, 1H, *J* = 7.4, 1.5 Hz, Ar$\underline{H}$), 7.68 (dd, 1H, *J* = 7.4, 4.2 Hz, Ar$\underline{H}$). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 26.0, 27.0, 30.0, 30.3, 46.2, 50.6, 52.8, 53.5, 55.4, 107.9, 111.2, 114.2, 121.0, 122.9, 126.9, 128.1, 128.5, 130.6, 136.5 146.1, 152.3, 161.5. LCMS: m/z 408.2 ([M+H]$^+$, 100%); Rt 5.2 min, purity >99% DAD (180-450 nm). Converted to HCl salt for assay.

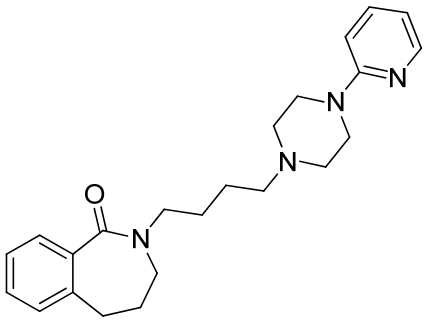
2-(4-(4-(Pyridin-2-yl)piperazin-1-yl)butyl)-3,4-dihydroisoquinolin-1(2H)-one (11a)



General procedure C from chloride **46a** (90 mg, 0.38 mmol), (2-pyridyl)piperazine (0.067 ml, 0.46 mmol), triethylamine (0.105 mL, 0.76 mmol) and acetonitrile (2 mL). Colourless oil, 84 mg (62%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.60-1.74 (m, 4H, 2 x C$\underline{H_2}$), 2.46 (t, 2H, *J* = 7.3 Hz, C$\underline{H_2}$), 2.57 (t, 4H, *J* = 5.0 Hz, (C$\underline{H_2}$)$_2$N), 3.01 (t, 2H, *J* = 6.6 Hz, C$\underline{H_2}$), 3.55-3.60 (m, 6H, (C$\underline{H_2}$)$_2$N + C$\underline{H_2}$), 3.63 (t, 2H, *J* = 7.1 Hz, C$\underline{H_2}$), 6.64-6.61 (m, 1H, Ar$\underline{H}$), 6.65 (dd, 1H, *J* = 8.6, 0.7 Hz, Ar$\underline{H}$), 7.19 (d, 2H, *J* = 8.1 Hz, Ar$\underline{H}$), 7.36 (t, 1H, *J* = 8, Ar$\underline{H}$), 7.42 (dt, 1H, *J* = 7.5, 1.4 Hz, Ar$\underline{H}$), 7.47-7.50 (m, 1H, Ar$\underline{H}$), 8.09 (d, 1H, *J* = 8.1 Hz, Ar$\underline{H}$), 8.20 (m, 1H, Ar$\underline{H}$). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 24.2, 25.8, 28.2, 45.2, 46.0, 47.2, 53.1, 58.4, 107.0, 113.2, 126.8, 127.0, 128.2, 129.7, 131.5, 137.4, 137.9, 147.9, 159.6, 164.3. LCMS: m/z 365.2 ([M+H]$^+$, 100%); Rt 4.9 min, purity >99% DAD (180-450 nm). Converted to HCl salt for assay.

2-(4-(4-(Pyridin-2-yl)piperazin-1-yl)butyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-1-one (11b)



General procedure C from chloride **46b** (95 mg, 0.38 mmol), (2-pyridyl)piperazine (0.067 ml, 0.46 mmol), triethylamine (0.105 mL, 0.76 mmol) and acetonitrile (2 mL). Colourless oil, 116 mg (80%).
^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.62-1.77 (m, 4H, 2 x C$\underline{H_2}$), 2.06 (qt, 2H, *J* = 7.0 Hz, C$\underline{H_2}$), 2.48 (t, 2H, *J* = 7.4 Hz, C$\underline{H_2}$), 2.59 (t, 4H, *J* = 5.0 Hz, 2 x(C$\underline{H_2}$)$_2$N), 3.23 (t, 2H, *J* = 6.5 Hz, C$\underline{H_2}$), 3.58 (t, 4H, *J* = 5.0 Hz, (C$\underline{H_2}$)$_2$N), 3.64 (t, 2H, *J* = 7.2 Hz, C$\underline{H_2}$), 6.25-6.65 (m, 1H, Ar$\underline{H}$), 6.67 (d, 1H, *J* = 8.6 Hz, Ar$\underline{H}$), 7.15 (dd, 1H, *J* = 8.1, 1.5 Hz, Ar$\underline{H}$), 7.34 (dt, 1H, *J* = 7.5, 1.5 Hz, Ar$\underline{H}$), 7.38 (dt, 1H, *J* = 7.4, 1.4 Hz, Ar$\underline{H}$), 7.47-7.51 (m, 1H, Ar$\underline{H}$), 7.69 (dd, 1H, *J* = 7.4, 1.6 Hz, Ar$\underline{H}$), 8.20-8.22 (m, 1H, Ar$\underline{H}$). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 24.3, 26.9, 30.0, 30.3, 45.2, 46.2, 53.1, 58.4, 96.7, 101.4, 107.0, 113.2, 118.9, 126.9, 128.1, 128.6, 130.6, 137.4, 137.4, 147.9, 159.6, 164.3. LCMS: m/z 379.2 ([M+H]$^+$, 100%); Rt 4.1 min, purity >97% DAD (180-450 nm). Converted to HCl salt for assay.

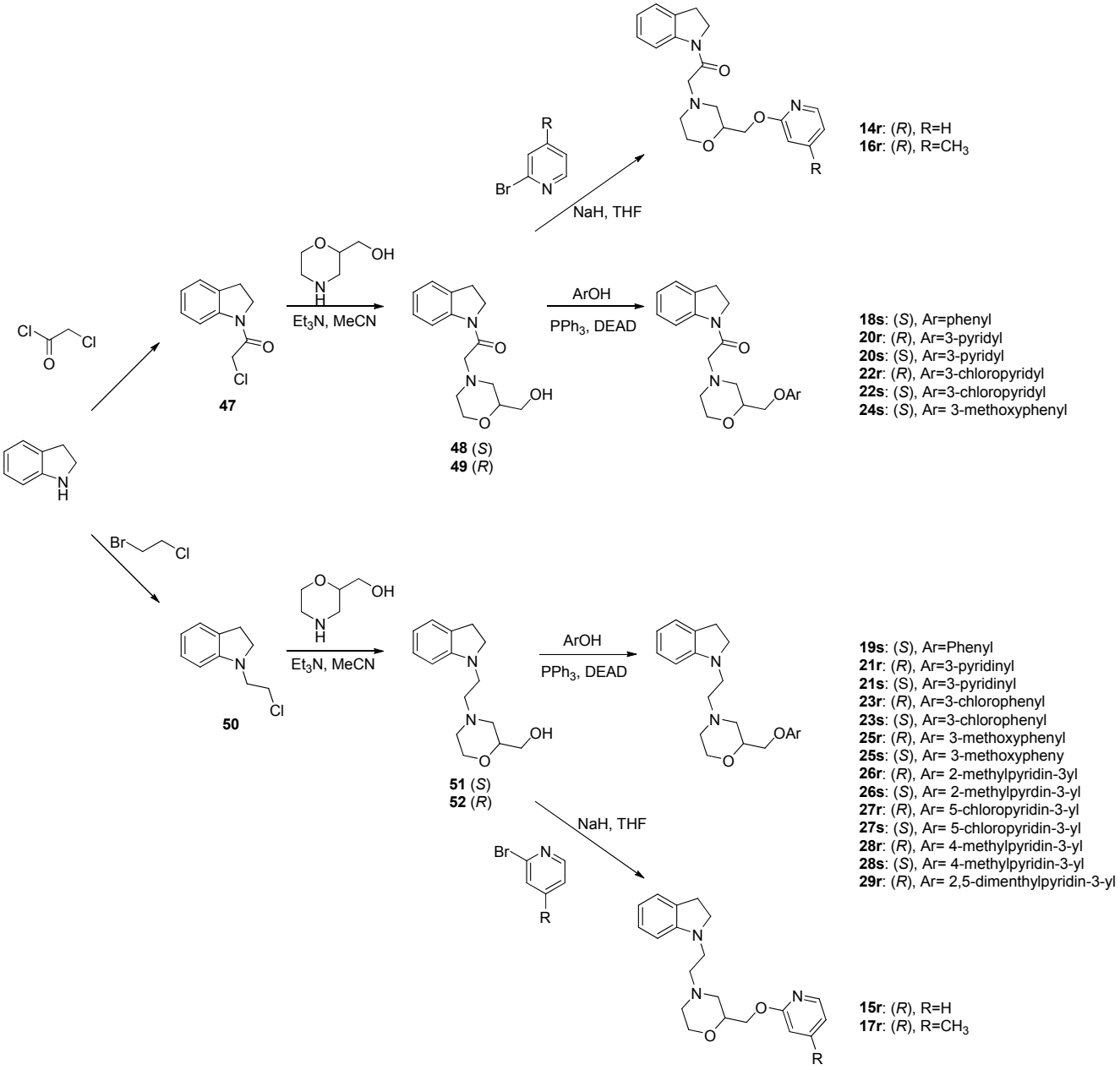
3. 2-Methyl-Indole

Compounds 12 and 13 were obtained from Innovapharm Ltd. (Kiev, Ukraine).

The compound 13 was freeze-dried and converted to the HCl salt for assay, giving satisfactory LCMS and ^{1}H NMR.

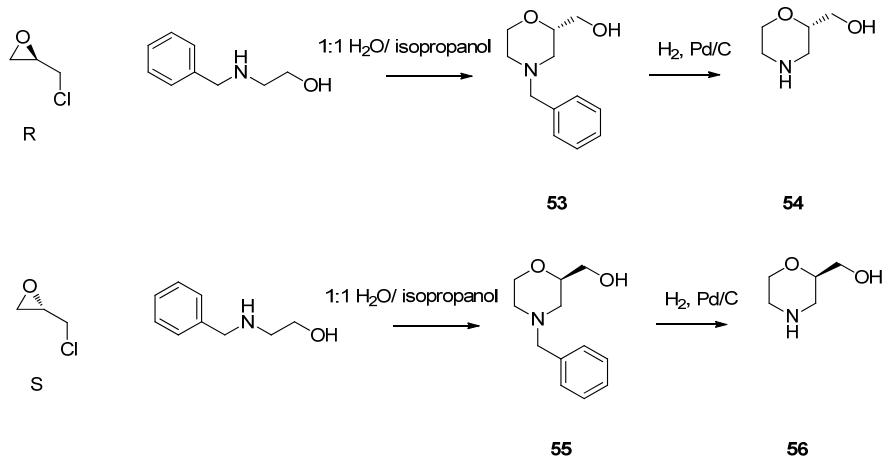
4. Synthesis of morpholino analogues

The morpholino series was made according to the general scheme S8.



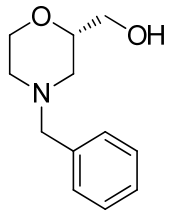
Scheme S8

The first step was to prepare the morpholino core; both enantiomers were prepared according to scheme S9[3].



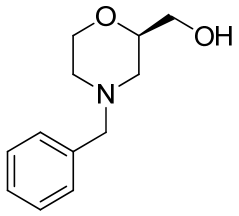
Scheme S9

(S)-(4-benzylmorpholin-2-yl)methanol (53)



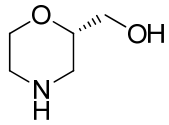
(*R*)-Epichlorohydrin (1.7 ml, 21.6 mmol) was added to a solution of *N*-benzylethanolamine (3.73 mL, 25.7 mmol) in 1:1 water/isopropanol (7 mL), keeping the temperature between 20-25 ^{o}C. After 6 h, the milky suspension was stored at -20 ^{o}C overnight. The solution was allowed to come to room temperature before 40% tetraethylammonium hydroxide in water (12.3 mL) was added. The mixture was stirred at 20 ^{o}C for 1 h and then quenched with 1M HCl (4 mL), keeping the pH around 10. The suspension was diluted with water (7 mL) and extracted with dichloromethane (3x13 mL). The combined organic layers were dried and concentrated. The residue was purified by flash column chromatography (Silica, DCM/MeOH 1:0 to 92:8). The product was isolated from the slow eluting fraction as a colourless oil, 2.3 g (52%).
^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.03 (dd + bs, 2H, *J* = 11.5, 9.9 Hz, O*H* + CH*H*N), 2.22 (dt, 1H, *J* = 11.5, 3.3 Hz, C*H*HN), 2.68-2.73 (m, 2H, CH_2N), 3.53 (AB syst., 2H, CH_2-Ph), 3.56-3.71 (m, 3H, CH_2OC*H*CH$_2$), 3.73 (dt, 1H, *J* = 11.2, 2.5 Hz, CH*H*OH), 3.91-3.94 (m, 1H, C*H*HOH), 7.27-7.30 (m, 1H, Ar*H*), 7.33-7.35 (m, 4H, Ar*H*). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 53.1, 54.6, 63.4, 64.3, 66.7, 76.0, 127.2, 128.3, 129.2, 137.6. LCMS: m/z 208.14 ($[M+H]^+$, 100%); Rt 3.6 min, purity >99% DAD (180-450 nm).

(R)-(4-benzylmorpholin-2-yl)methanol (55)



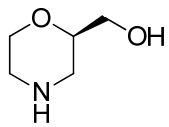
Same procedure as for compound **53** with (S)-Epichlorohydrin (2.5 g, 2.70 mmol), N-benzylethanolamine (3.73 mL, 2.60 mmol) and tetraethylammonium hydroxide (12.3 mL). Compound **55** was obtained as a colourless oil, 2.7 g (50%).
For NMR data see **53** LCMS: m/z 208.1 ($[M+H]^+$, 100%); Rt 3.8 min, purity >99% DAD (180-450 nm).

(S)-morpholin-2-ylmethanol (54)



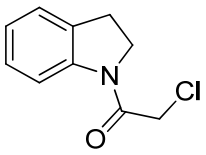
Benzyl ether **53** (960 mg, 4.61 mmol) was stirred for 4 h under the pressure of 50 psi of hydrogen in the presence of 10% Pd/C (200 mg) in methanol (10 mL) After filtration through a celite pad and evaporation of the solvents, compound **54** was isolated as a colourless oil, 478 mg (88%).
^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.57 (bs, 2H, N*H* + O*H*), 2.69-2.72 (m, 1H, CH*H*N), 2.85-2.90 (m, 3H, C*H*$_2$N + C*H*HN), 3.48-3.63 (m, 3H, C*H*$_2$OC*H*CH$_2$), 3.66 (dt, 1H, J = 11.5, 3.3 Hz, CH*H*OH), 3.90-3.93 (m, 1H, C*H*HOH). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 45.66, 47.33, 64.00, 67.66, 76.78. LCMS: m/z 117.09 ($[M+H]^+$, 100%); Rt 0.5 min, purity >99% DAD (180-450 nm).

(R)-morpholin-2-ylmethanol (56)



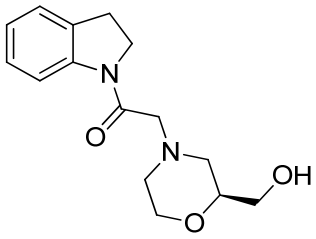
Same procedure as for compound **54** with compound **55** (1.4 g, 6.76 mmol), 10% Pd/C (350 mg), methanol (15 mL). After filtration through a celite pad and evaporation of the solvents, compound **56** was obtained as a colourless oil (712 mg, 88%).
For NMR data see **54**.

2-Chloro-1-(indolin-1-yl)ethanone (47)



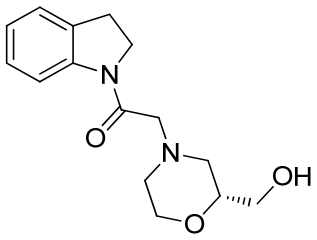
Chloroacetyl chloride (0.37 mL, 4.6 mmol) was added to a solution of indoline (0.47 mL, 4.19 mmol) and triethylamine (0.70 mL, 5.03 mmol) in dichloromethane (15 mL). The mixture was stirred for 3 h at room temperature and then quenched with water (5 mL). The phases were separated and the aqueous layer was extracted with dichloromethane (3x5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated to a dark brown residue, 1g (quantitative), which was used for the next step without further purification.
^{1}H-NMR (500 MHz, $CDCl_3$) δ: 3.27 (t, 2H, *J* = 8.3 Hz, C*H*$_2$), 4.17-4.21 (m, 4H, C*H*$_2$Cl + C*H*$_2$N), 7.09 (dt, 1H, *J* = 7.5, 1.0 Hz, Ar*H*), 7.22-7.27 (m, 2H, Ar*H*), 8.24 (d, 1H, *J* = 8.1 Hz, Ar*H*). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 28.2, 43.1, 47.9, 117.4, 124.5, 124.6, 127.7, 131.1, 142.5, 163.9. LCMS: m/z 196.06 ($[M+H]^+$, 100%); Rt 4.8 min, purity >99% DAD (180-450 nm).

(S)-2-(2-(Hydroxymethyl)morpholino)-1-(indolin-1-yl)ethanone (48)



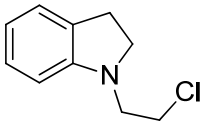
A microwave vial was charged with 1-(chloroacetyl)-indoline **47** (390 mg, 2.00 mmol), hydroxymethylmorpholine **54** (280 mg, 2.39 mmol), triethylamine (0.55 mL, 4.00 mmol) and acetonitrile (2 mL). The vial was sealed and irradiated for 30 min at 100 °C. The crude mixture was purified by flash column chromatography (Silica, DCM/MeOH 1:0 to 92:8). White solid, 435 mg (79%).
^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.97 (bs, 1H, O*H*), 2.23 (t, 1H, *J* = 10.5 Hz, 1 of 1 of (C*H*$_2$)$_2$N), 2.40 (dt, 1H, *J* = 11.0, 3.0 Hz, 1 of (C*H*$_2$)$_2$N), 2.88 (t, 2H, *J* = 13.0 Hz, 1 of (C*H*$_2$)$_2$N), 3.23 (t, 2H, *J* = 8.3 Hz, 1 of C*H*$_2$N), 3.29 (AB syst, 2H, ArC*H*$_2$), 3.56-3.69 (m,2H, C*H*$_2$OH), 3.74-3.82 (m, 2H, COC*H*$_2$N), 3.94-3.97 (m, 1H, C*H*CH$_2$), 4.18 (t, 2H, *J* = 8.5 Hz, CONC*H*$_2$), 7.06 (dt, 1H, *J* = 7.4, 1.0 Hz, Ar*H*), 7.21-7.24 (m, 2H, Ar*H*), 8.25 (d, 1H, *J* = 8.1 Hz, Ar*H*). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 28.3, 47.4, 53.3, 54.8, 62.7, 64.1, 66.5, 75.9, 117.1, 123.9, 124.5, 127.6, 167.2. LCMS: m/z 277.1 ($[M+H]^+$, 100%); Rt 4.2 min, purity >99% DAD (180-450 nm).

(R)-2-(2-(hydroxymethyl)morpholino)-1-(indolin-1-yl)ethanone (49)



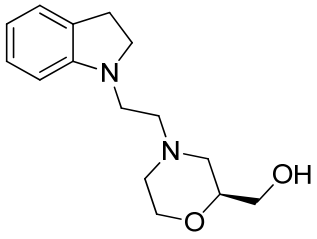
Same procedure as **48** with 1-(chloroacetyl)-indoline **47** (471 mg, 2.41 mmol), **56** (341 mg, 2.90 mmol), triethylamine (0.67 mL, 4.83 mmol) and acetonitrile (5 mL). Purified by flash column chromatography (Silica, DCM/MeOH 1:0 to 92:8). White solid, 376 mg (56%).
^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.97 (bs, 1H, O*H*), 2.23 (t, 1H, *J* = 10.5 Hz, 1 of 1 of (C*H*$_2$)$_2$N), 2.40 (dt, 1H, *J* = 11.2, 3.2 Hz, 1 of (C*H*$_2$)$_2$N), 2.88 (t, 2H, *J* = 12.8 Hz, 1 of (C*H*$_2$)$_2$N), 3.23 (t, 2H, *J* = 8.4 Hz, 1 of C*H*$_2$N), 3.26-3.33 (m, 2H, ArC*H*), 3.58-3.83 (m, 4H, C*H*$_2$OH + COC*H*$_2$N), 3.91-3.97 (m, 1H, C*H*CH$_2$), 4.18 (t, 2H, *J* = 8.2 Hz, CONC*H*$_2$), 7.05 (dt, 1H, *J* = 7.4, 1.0 Hz, Ar*H*), 7.21-7.24 (m, 2H, Ar*H*), 8.25 (d, 1H, *J* = 13.0 Hz, Ar*H*). LCMS: m/z 277.1 ([M+H]$^+$, 100%); Rt 4.3 min, purity >94% DAD (180-450 nm).

1-(2-Chloroethyl)indoline (50)



A microwave vial was charged with indoline (0.5 g, 4.19 mmol), 2-chloro-1-bromoethane (0.502 mL, 6.25 mmol), triethylamine (0.7 mL, 6.25 mmol) and acetonitrile (10 mL). The vial was irradiated with microwaves for 1 h at 80 ^{o}C. The mixture was diluted with dichloromethane and washed with water (1x10 mL). The organic layer was dried and concentrated and the residue was purified by flash column chromatography (Silica, Hex/EtOAc 95:5 to 0:1). The product was isolated as a violet solid, 400 mg (52%).
^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.93 (t, 2H, *J* = 8.4 Hz, C*H*$_2$), 3.35-3.43 (m, 4H, C*H*$_2$C*H*$_2$), 3.60 (t, 2H, *J* = 6.8 HZ, C*H*$_2$), 6.40 (d, 1H, *J* = 7.7 Hz, Ar*H*), 6.59 (dt, 1H, *J* = 7.4, 0.9 Hz, Ar*H*), 6.89-7.01 (m, 2H, Ar*H*). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 28.6, 41.5, 51.4, 53.5, 106.5, 117.9, 124.6, 127.4, 129.6, 151.6. LCMS: m/z 182.1 ([M+H]$^+$, 100%); Rt 5.3 min, purity >96% DAD (180-450 nm).

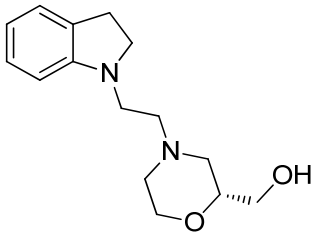
(*S*)-(4-(2-(Indolin-1-yl)ethyl)morpholin-2-yl)methanol (51)



A microwave vial was charged with 1-(chloroethyl)-indoline **50** (724 mg, 4.00 mmol), hydroxymethylmorpholine **54** (562 mg, 4.80 mmol), triethylamine (2.2 mL, 16.00 mmol) and

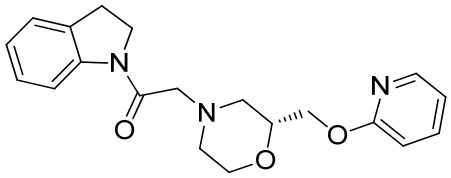
acetonitrile (4 mL). The vial was irradiated with microwaves for 2 h at 100 °C, 40 min at 120 °C and 1 h at 110 °C. Purified by flash column chromatography (Silica, DCM/MeOH 1:0 to 8:2). Off-white solid, 347 mg (33%).^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.01 (bs, 1H, O*H*), 2.12 (t, 1H, *J* = 10.8 Hz, 1 of 1 of (CH_2)$_2$N), 2.28 (dt, 1H, *J* = 11.4, 3.3 Hz, 1 of (CH_2)$_2$N), 2.64 (dt, 2H, *J* = 7.5, 2.7 Hz, CH_2N), 2.81 (t, 2H, *J* = 11.5 Hz, 2 of (CH_2)$_2$N), 2.99 (t, 2H, *J* = 8.3 Hz, CH_2N), 3.26 (t, 2H, *J* = 8.3 Hz, 1 of CH_2N), 3.43 (t, 2H, *J J* = 8.3 Hz, ArCH_2), 3.56-3.78 (m, 4H, CH_2,COCH_2N), 3.94-3.97 (m, 1H, C*H*CH_2), 6.50 (d, 1H, *J* = 7.7 Hz, Ar*H*), 6.67 (dt, 1H, *J* = 7.3, 0.8 Hz, Ar*H*), 7.07-7.10 (m, 2H, Ar*H*). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 28.7, 46.9, 53.3, 53.7, 55.2, 56.32, 64.3, 66.7, 75.8, 106.7, 117.2, 124.5, 127.3, 129.8, 152.3.

(*R*)-(4-(2-(Indolin-1-yl)ethyl)morpholin-2-yl)methanol (52)



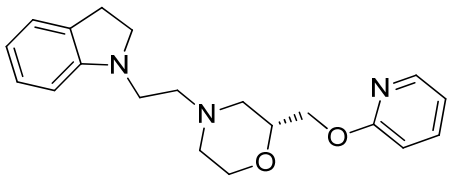
Same procedure as for compound **51** with 1-(chloroethyl)-indoline **50** (1.93 g, 10.67 mmol), hydroxymethylmorpholine **56** (1.50 g, 12.8 mmol), triethylamine (5.87 mL, 42.7 mmol) and acetonitrile (10 mL). Off-white solid, 882 mg (32%).
For NMR data see **51**.

(*R*)-1-(Indolin-1-yl)-2-(2-((pyridin-2-yloxy)methyl)morpholino)ethanone (14r)



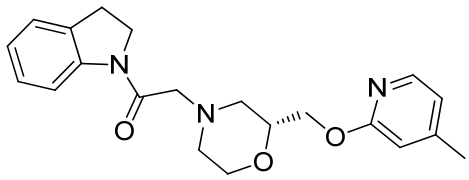
Alcohol **49** (76 mg, 0.28 mmol) and NaH (13 mg, 0.55 mmol) were placed in a microwave vial. Dry tetrahydrofuran (2 mL) was added and the mixture was stirred at room temperature for 5 min before 2-bromopyridine (52 µL, 0.55 mmol) was added. The vial was sealed and irradiated with microwaves for 1.5 h at 170 ^{o}C. After this time the solvent was removed and the crude mixture purified by flash column chromatography (Silica, Hex/EtOAc 7:3 to 0:1) to afford **14r**,22 mg (23%).
^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.28 (apparent t, 1H, *J* = 10.7 Hz, 1 of (CH_2)$_2$N), 2.42 (td, 1H, *J* = 11.3, 2.9 Hz, 1 of (CH_2)$_2$N), 2.85 (d, 1H, *J* = 11.3 Hz, 1 of (CH_2)$_2$N), 3.00 (d, 1H, *J* = 10.7 Hz, 1 of (CH_2)$_2$N), 3.19 (t, 2H, *J* = 8.4 Hz, ArCH_2CH_2N), 3.24-3.32 (2H, COCH_2), 3.80 (td, 1H, *J* = 11.3, 2.3 Hz, 1 of OCH_2CH_2), 3.92-3.98 (m, 1H, 1 of OCH_2CH_2), 3.98-4.06 (m, 1H, OCH), 4.08-4.21 (m, 2H, ArCH_2CH_2N), 4.31-4.38 (m, 2H, OCH_2CH), 6.76-6.81 (m, 1H, Ar*H*), 6.85 (ddd, 1H, *J* = 7.1, 5.1, 0.9 Hz, Ar*H*), 6.99-7.05 (m, 1H, Ar*H*), 7.16-7.22 (m, 2H, Ar*H*), 7.54 (ddd, 1H, *J* = 8.4, 7.1, 2.0 Hz, Ar*H*), 8.11 (ddd, 1H, *J* = 5.1, 2.0, 0.7 Hz, Ar*H*), 8.23 (d, 1H, *J* = 8.0 Hz, Ar*H*). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 28.2, 47.5, 53.1, 55.4, 62.8, 66.6, 66.7, 74.1, 111.3, 116.9, 117.1, 123.9, 124.5, 127.6, 131.0, 138.6, 143.0, 146.7, 163.4, 167.2. LCMS: m/z 354.1803 ($[M+H]^+$, 100%); Rt 4.8 min DAD (180-450 nm). HRMS: Found 354.1802 $C_{20}H_{23}N_3O_3$ $[M + H]^+$ requires 354.1812. Converted to HCl salt for assay.

(*R*)-4-(2-(Indolin-1-yl)ethyl)-2-((pyridin-2-yloxy)methyl)morpholine (15r)



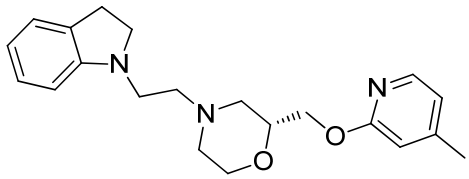
Alcohol **52** (76 mg, 0.29 mmol) and NaH (13.9 mg, 0.58 mmol) were placed in a microwave vial. Dry tetrahydrofuran (2 mL) was added and the mixture was stirred at room temperature for 5 min before 2-bromopyridine (55 µL, 0.58 mmol) was added. The vial was sealed and irradiated with microwaves for 1.5 h at 170 ^{o}C. After this time the solvent was removed and the crude mixture purified by flash column chromatography (Silica, Hex/EtOAc 1:0 to 0:1) to afford **15r** as a slightly yellow oil, 71 mg (72%).
^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.11-2.21 (m, 1H, 1 of (C$\underline{H}_2$)$_2$N), 2.30 (td, 1H, *J* = 11.3, 3.2 Hz, 1 of (C$\underline{H}_2$)$_2$N), 2.64 (t, 2H, *J* = 7.1 Hz, N(C$\underline{H}_2$)$_2$N), 2.81 (m, 1H, 1 of (C$\underline{H}_2$)$_2$N), 2.92-3.00 (m, 3H, ArC$\underline{H}_2$CH$_2$N + 1 of (C$\underline{H}_2$)$_2$N), 3.25 (t, 2H, *J* = 7.1 Hz, N(C$\underline{H}_2$)$_2$N), 3.37-3.45 (m, 2H, ArCH$_2$C$\underline{H}_2$N), 3.76 (td, 1H, *J* = 11.3, 2.1 Hz, 1 of OC$\underline{H}_2$CH$_2$), 3.93-4.02 (m, 2H, OC$\underline{H}$ + 1 of OC$\underline{H}_2$CH$_2$), 4.33-4.38 (m, 2H, OC$\underline{H}_2$CH), 6.48 (d, 1H, *J* = 7.7 Hz, Ar$\underline{H}$), 6.65 (t, 1H, *J* = 7. 3 Hz, Ar$\underline{H}$), 6.81 (dd, 1H, *J* = 8.3, 0.7 Hz, Ar$\underline{H}$), 6.84-6.89 (1H, m, Ar$\underline{H}$), 7.03-7.11 (m, 2H, Ar$\underline{H}$), 7.53-7.61 (m, 1H, Ar$\underline{H}$), 8.09-8.19 (m, 1H, Ar$\underline{H}$). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 28.7, 46.9, 53.4, 53.7, 55.7, 56.3, 66.8, 66.9, 74.1, 106.8, 111.4, 117.0, 117.6, 124.5, 127.3, 129.9, 138.6, 146.7, 152.3, 163.5. LCMS: m/z 340.2004 ($[M+H]^+$, 100%); Rt 5.3 min, purity >93% DAD (180-450 nm). HRMS: Found 340.2004 $C_{20}H_{25}N_3O_2$ $[M+H]^+$ requires 340.2020. Compound was re-purified to assay (39.4 mg, purity >99%). Converted to HCl salt for assay.

(*R*)-1-(Indolin-1-yl)-2-(2-(((4-methylpyridin-2-yl)oxy)methyl)morpholino)ethanone (16r)



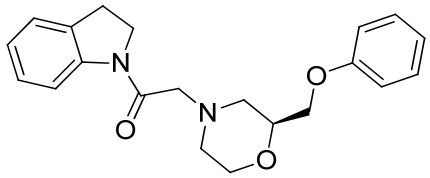
Same procedure as **14r** with 2-bromo-4-methylpyridine (92 µL, 0.83 mmol). The crude mixture was purified by flash column chromatography (Silica, Hex/EtOAc 7:3 to 0:1) to afford **16r**, 29 mg (29%).
^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.23-2.30 (m, 4H, 1 of (C$\underline{H}_2$)$_2$N + Me), 2.40 (td, 1H, *J* = 11.1, 2.8 Hz, 1 of (C$\underline{H}_2$)$_2$N), 2.85 (d, 1H, *J* = 11.1 Hz, 1 of (C$\underline{H}_2$)$_2$N), 2.99 (d, 1H, *J* = 11.0 Hz, 1 of (C$\underline{H}_2$)$_2$N), 3.18 (t, 2H, *J* = 8.4 Hz, ArC$\underline{H}_2$CH$_2$N), 3.23-3.31 (m, 2H, COC$\underline{H}_2$), 3.78 (td, 1H, *J* = 11.3, 2.2 Hz, 1 of OC$\underline{H}_2$CH$_2$), 3.91-3.97 (m, 1H, 1 of OC$\underline{H}_2$CH$_2$), 3.97-4.04 (m, 1H, OC$\underline{H}$), 4.08-4.20 (m, 2H, ArCH$_2$C$\underline{H}_2$N), 4.28-4.36 (m, 2H, OC$\underline{H}_2$CH), 6.60 (s, 1H, Ar$\underline{H}$), 6.65-6.69 (m, 1H, Ar$\underline{H}$), 6.98-7.04 (m, 1H, Ar$\underline{H}$), 7.15-7.22 (m, 2H, Ar$\underline{H}$), 7.96 (d, 1H, *J* = 5.2 Hz, Ar$\underline{H}$), 8.22 (d, 1H, *J* = 8.0 Hz, Ar$\underline{H}$). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 20.9, 28.2, 47.4, 53.1, 55.4, 62.7, 66.5, 66.7, 74.1, 111.3, 117.1, 118.5, 123.9, 124.5, 127.5, 131.0, 143.0, 146.2, 149.9, 163.8, 167.2. LCMS: m/z 368.1964 ($[M+H]^+$, 100%); Rt 4.9 min DAD (180-450 nm). HRMS: Found 368.1964 $C_{21}H_{25}N_3O_3$ $[M + H]^+$ requires 368.1969 Converted to HCl salt for assay.

(*R*)-4-(2-(Indolin-1-yl)ethyl)-2-(((4-methylpyridin-2-yl)oxy)methyl)morpholine (17r)



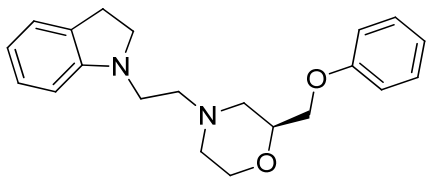
Same procedure as **15r** with 2-bromo-4-methylpyridine (96 µL, 0.86 mmol). The crude mixture was purified by flash column chromatography (Silica, Hex/EtOAc 1:0 to 0:1) to afford **17r**, 82 mg (80%).
^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.10-2.18 (m, 1H, 1 of $(C\underline{H}_2)_2N$), 2.35-2.33 (m, 4H, Me + 1 of $(C\underline{H}_2)_2N$), 2.63 (t, 2H, *J* = 7.1 Hz, $N(C\underline{H}_2)_2N$), 2.77-2.83 (m, 1H, 1 of $(C\underline{H}_2)_2N$), 2.92-2.99 (m, 3H, $ArC\underline{H}_2CH_2N$ + 1 of $(C\underline{H}_2)_2N$), 3.22-3.28 (m, 2H, $N(C\underline{H}_2)_2N$), 3.35-3.45 (m, 2H, $ArCH_2C\underline{H}_2N$), 3.75 (td, 1H, *J* = 11.4, 2.4 Hz, 1 of $OC\underline{H}_2CH_2$), 3.93-4.00 (m, 2H, $OC\underline{H}$ + 1 of $OC\underline{H}_2CH_2$), 4.29-4.37 (m, 2H, $OC\underline{H}_2CH$), 6.48 (d, 1H, *J* = 7.7 Hz, Ar$\underline{H}$), 6.62-6.67 (m, 2H, Ar$\underline{H}$), 6.68-6.71 (m, 1H, Ar$\underline{H}$), 7.03-7.09 (m, 2H, Ar$\underline{H}$), 7.99 (d, 1H, *J* = 5.2 Hz, Ar$\underline{H}$). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 20.9, 28.6, 46.9, 53.4, 53.7, 55.7, 56.3, 66.7, 68.8, 74.1, 106.8, 111.4, 117.6, 118.6, 124.4, 127.3, 129.9, 146.2, 150.0, 152.3, 163.8. LCMS: m/z 354.2173 ($[M+H]^+$, 100%); Rt 4.3 min, purity >96% DAD (180-450 nm). HRMS: Found 354.2173 $C_{21}H_{27}N_3O_2$ $[M + H]^+$ requires 354.2176. Converted to HCl salt for assay.

(*S*)-1-(Indolin-1-yl)-2-(2-(phenoxymethyl)morpholino)ethanone (18s)



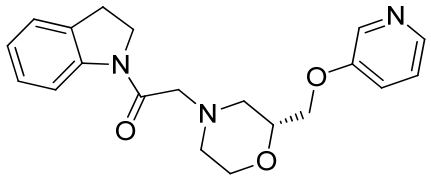
Using the same procedure as described[4], with compound **48** (55 mg, 0.2 mmol), phenol (28 mg, 0.3 mmol), triphenylphosphine (78 mg, 0.3 mmol), DEAD (0.05 ml, 0.3 mmol), tetrahydrofuran (1 mL). The crude residue was purified twice by flash column chromatography to afford the title compound as a colourless oil, 44 mg (62%). Converted to HCl salt for assay.
^{1}H-NMR (500 MHz, CD_3OD) δ: 3.29 (t, 2H, *J* = 8.2 Hz. $ArC\underline{H}_2$), 3.37-3.42 (m, 2H, $C\underline{H}_2N$), 3.70 (bs, 1H, 1 of $(C\underline{H}_2)_2N$), 3.85 (bs, 1H, 1 of $(C\underline{H}_2)_2N$), 4.05-4.24 (m, 6H, $ArCH_2C\underline{H}_2$ + $C\underline{H}_2N$ + $C\underline{H}_2O$), 4.30-4.44 (m, 3H, $C\underline{H}CH_2$ + $C\underline{H}_2O$), 6.97-6.99 (m, 3H, Ar$\underline{H}$), 7.12 (dt, 1H, *J* = 7.4, 0.7 Hz, Ar$\underline{H}$), 7.22 (d, 1H, *J* = 7.5 Hz, Ar$\underline{H}$), 7.28-7.32 (m, 3H, Ar$\underline{H}$), 8.17 (d, 1H, *J* = 8.2 Hz, Ar$\underline{H}$). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 28.7, 46.9, 53.4, 53.7, 56.0, 56.3, 66.9, 69.1, 74.1, 76.8, 106.8, 114.6, 117.6, 121.0, 124.5, 127.3, 129.5, 129.9, 152.3, 158.7.

(*S*)-4-(2-(Indolin-1-yl)ethyl)-2-(phenoxymethyl)morpholine (19s)



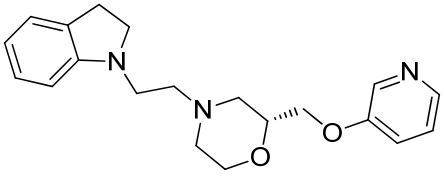
Same procedure as compound **18s** with **51** (52 mg, 0.2 mmol), phenol (28 mg, 0.3 mmol), triphenylphosphine (78 mg, 0.3 mmol), DEAD (0.05 ml, 0.3 mmol), tetrahydrofuran (1 mL). The crude residue was purified twice by flash column chromatography to afford the title compound as a colourless oil, 28 mg (41%).
^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.06-2.10 (m, 1H, 1 of (C$\underline{H}_2$)$_2$N), 2.34 (dt, 1H, *J* = 11.3, 3.3 Hz, 1 of (C$\underline{H}_2$)$_2$N), 2.68 (t, 2H, *J* = 6.9 Hz, 2 of N(C$\underline{H}_2$)$_2$N), 2.83 (dd, 1H, *J* = 13.1, 1.9 Hz, 1 of (C$\underline{H}_2$)$_2$N), 2.98-3.03 (m, 3H, ArC$\underline{H}_2$ + 1 of (C$\underline{H}_2$)$_2$N), 3.28 (t, 2H, *J* = 7.4 Hz, 2 of N(C$\underline{H}_2$)$_2$N), 3.43 (dt, 2H, *J* = 8.3, 1.8 Hz, ArCH$_2$C$\underline{H}_2$N), 3.79 (dt, 1H, *J* = 11.3, 2.5 Hz, 1 of OC$\underline{H}_2$CH$_2$), 3.95-4.01 (m, 3H, OC$\underline{H}$ + 1 of OC$\underline{H}_2$CH$_2$), 4.05-4.09 (m, 1H, 1 of OC$\underline{H}_2$CH), 6.52 (d, 1H, *J* = 7.6 Hz, Ar$\underline{H}$), 6.67 (dt, 1H, *J* = 7.4, 0.9 Hz, Ar$\underline{H}$), 6.94-7.00 (m, 3H, Ar$\underline{H}$), 7.07-7.10 (m, 2H, Ar$\underline{H}$), 7.28-7.32 (m, 2H, Ar$\underline{H}$). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 28.7, 46.9, 53.4, 53.7, 55.9, 56.0, 56.3, 66.9, 69.4, 73.9, 76.8, 106.8, 113.1, 115.1, 117.6, 121.2, 124.5, 127.4, 129.9, 130.2, 134.9, 152.3, 159.4. HRMS: Found 339.2072 $C_{21}H_{27}N_2O_2$ [M + H]$^+$ requires 339.2067. Converted to HCl salt for assay.

(*R*)-1-(Indolin-1-yl)-2-(2-((pyridin-3-yloxy)methyl)morpholino)ethanone (20r)



Same procedure as compound **18s** with alcohol **49** (90 mg, 0.326 mmol), 3-hydroxypyridine (46 mg, 0.49 mmol), triphenylphosphine (128 mg, 0.49 mmol), DIAD (0.10 mL, 0.49 mmol), tetrahydrofuran (1 mL). The crude residue was purified twice by flash column chromatography (Silica, DCM/MeOH 1:0 to 8:2) to afford the title compound as a colourless oil, 6 mg (5%).
^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.35 (t, 1H, *J* = 10.5 Hz, 1 of 1 of (C$\underline{H}_2$)$_2$N), 2.48 (dt, 1H, *J* = 12, 3.8 Hz, 1 of (C$\underline{H}_2$)$_2$N), 2.89 (d, 1H, *J* = 12 Hz, 1 of (C$\underline{H}_2$)$_2$N), 3.08 (d, 1H, *J* = 11 Hz, 1 of (C$\underline{H}_2$)$_2$N), 3.24 (t, 2H, *J* = 8.5 Hz, 1 of ArC$\underline{H}_2$), 3.31-3.33 (m, 2H, COC$\underline{H}_2$N), 3.85 (dt, 1H, *J* = 11.2, 2.4 Hz, 1 of CHC$\underline{H}_2$OAr), 3.97-4.14 (m, 4H, C$\underline{H}_2$OC$\underline{H}$CH$_2$ + 1 of C$\underline{H}_2$OAr), 4.18-4.21 (m, 2H, ArCH$_2$C$\underline{H}_2$), 7.06 (dt, 1H, *J* = 7.4, 1.0 Hz, Ar$\underline{H}$), 7.21-7.24 (m, 4H, Ar$\underline{H}$), 8.26 (d, 1H, *J* = 7.9 Hz, Ar$\underline{H}$), 8.36 (bs, 1H, Ar$\underline{H}$). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 28.3, 47.5, 53.1, 55.3, 62.6, 66.8, 69.4, 73.9, 117.1, 121.3, 123.9, 124.6, 127.6, 138.1, 142.5, 167.1. LCMS: m/z 556.2 ([M+H]$^+$, 100%); Rt 5.0 min, purity >99% DAD (180-450 nm). Converted to HCl salt for assay.

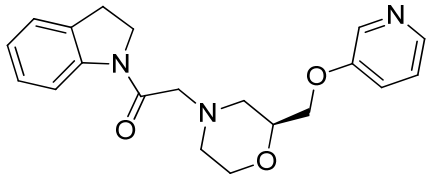
(*R*)-4-(2-(Indolin-1-yl)ethyl)-2-((pyridin-3-yloxy)methyl)morpholine (21r)



Same procedure as **18s** with alcohol **52** (80 mg, 0.30 mmol) triphenylphosphine (120 mg, 0.46 mmol), DIAD (90 µL, 0.46 mmol) and 3-hydroxypyridine (44 mg, 0.46 mmol). Purified by flash column chromatography (Silica, DCM/MeOH 1:0 to 94:6). Colourless oil, 61 mg (59%).
^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.14-2.21 (m, 1H, 1 of (C$\underline{H}_2$)$_2$N), 2.31 (td, 1H, *J* = 11.3, 3.3 Hz, 1 of (C$\underline{H}_2$)$_2$N), 2.66 (t, 2H, *J* = 7.1 Hz, N(C$\underline{H}_2$)$_2$N), 2.79-2.83 (m, 1H, 1 of (C$\underline{H}_2$)$_2$N), 2.93-3.01 (m, 3H,

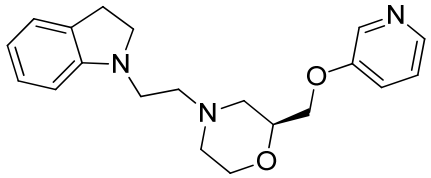
ArC$\underline{H_2}$CH$_2$N + 1 of (C$\underline{H_2}$)$_2$N), 3.26 (t, 2H, *J* = 7.1 Hz, N(C$\underline{H_2}$)$_2$N), 3.37-3.45 (m, 2H, ArCH$_2$C$\underline{H_2}$N), 3.77 (td, 1H, *J* = 11.3, 2.5 Hz, 1 of OC$\underline{H_2}$CH$_2$), 3.93-4.02 (m, 3H, OC$\underline{H}$ + 1 of OC$\underline{H_2}$CH$_2$ + 1 of OC$\underline{H_2}$CH), 4.04-4.10 (m, 1H, 1 of OC$\underline{H_2}$CH), 6.48 (d, 1H, *J* = 7.7 Hz, Ar$\underline{H}$), 6.65 (td, 1H, *J* = 7.5, 0.9 Hz, Ar$\underline{H}$), 7.01-7.12 (m, 2H, Ar$\underline{H}$), 7.20-7.23 (m, 2H, Ar$\underline{H}$), 8.21-8.24 (m, 1H, Ar$\underline{H}$), 8.32-8.35 (m, 1H, Ar$\underline{H}$). ^{13}C-NMR (125 MHz, CDCl$_3$) δ: 28.7, 47.0, 53.4, 53.7, 55.7, 56.3, 66.9, 69.4, 73.9, 106.7, 117.6, 121.3, 123.8, 124.5, 127.3, 129.9, 138.0, 142.5, 152.3, 154.9. LCMS: m/z 340.2017 ([M+H]$^+$, 100%); Rt 4.9 min, purity >99% DAD (180-450 nm). HRMS: Found 340.2017 $C_{20}H_{25}N_3O_2$ [M + H]$^+$ requires 340.2020. Converted to HCl salt for assay.

(*S*)-1-(Indolin-1-yl)-2-(2-((pyridin-3-yloxy)methyl)morpholino)ethanone (20s)



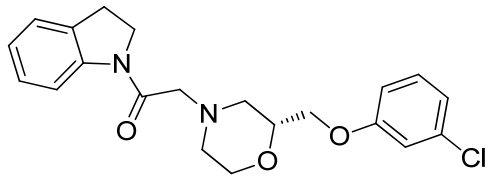
Same procedure as compound **18s** with alcohol **48** (55 mg, 0.2 mmol), 3-hydroxypyridine (28 mg, 0.3 mmol), triphenylphosphine (78 mg, 0.3 mmol), DEAD (0.05 mL, 0.3 mmol), tetrahydrofuran (1 mL). The crude residue was purified twice by flash column chromatography (Silica, DCM/MeOH 1:0 to 8:2) to afford the title compound as a colourless oil, 53 mg (74%). Converted to HCl salt for assay.
^{1}H-NMR (500 MHz, *CD3OD*) δ: 3.31 (m, 2H, 1 of ArC$\underline{H_2}$), 3.47-3.41 (m, 2H, NC$\underline{H_2}$), 3.71 (bs, 1H, 1 of C$\underline{H_2}$N), 3.90 (bs, 1H, 1 of C$\underline{H_2}$N), 4.07-4.25 (m, 4H, ArCH$_2$C$\underline{H_2}$ + C$\underline{H_2}$N), 4.40-4.50 (m, 5H, C$\underline{H_2}$OC$\underline{H}$C$\underline{H_2}$), 7.12 (t, 1H, *J* = 7.5 Hz, Ar$\underline{H}$), 7.22 (t, 1H, *J* = 8.3 Hz, Ar$\underline{H}$), 7.31 (d, 1H, 7.6 Hz, Ar$\underline{H}$), 7.99-8.01 (m, 1H, Ar$\underline{H}$), 8.17 (d, 1H, *J* = 8.3 Hz, Ar$\underline{H}$), 8.25 (d, 1H, *J* = 7.90 Hz, Ar$\underline{H}$), 8.49 (d, 1H, *J* = 5.5 Hz, Ar$\underline{H}$), 8.67 (s, 1H, Ar$\underline{H}$).

(*S*)-4-(2-(Indolin-1-yl)ethyl)-2-((pyridin-3-yloxy)methyl)morpholine (21s)



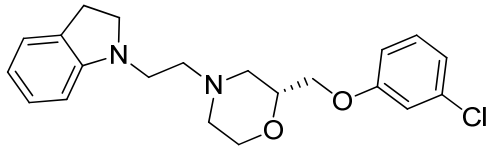
Same procedure as compound **18s** with alcohol **52** (52 mg, 0.2 mmol), 3-hydroxypyridine (28 mg, 0.3 mmol), triphenylphosphine (78 mg, 0.3 mmol), DEAD (0.05 ml, 0.3 mmol), tetrahydrofuran (1 mL). The crude residue was purified twice by flash column chromatography (Silica, DCM/MeOH 1:0 to 8:2) to afford compound **21s** as a colourless oil, 28 mg (41%).
^{1}H-NMR (500 MHz, CDCl$_3$) δ: 2.18-2.22 (m, 1H, 1 of (C$\underline{H_2}$)$_2$N), 2.34 (dt, 1H, *J* = 11.3, 3.3 Hz, 1 of (C$\underline{H_2}$)$_2$N), 2.68 (t, 2H, *J* = 6.9 Hz, N(C$\underline{H_2}$)$_2$N), 2.83 (dd, 1H, *J* = 11.4, 1.9 Hz, 1 of (C$\underline{H_2}$)$_2$N), 2.99-3.00 (m, 3H, ArC$\underline{H_2}$ + 1 of (C$\underline{H_2}$)$_2$N), 3.28 (t, 2H, *J* = 7.2 Hz, N(C$\underline{H_2}$)$_2$N), 3.43 (dt, 2H, *J* = 8.3, 1.3 Hz, ArCH$_2$C$\underline{H_2}$N), 3.78 (dt, 1H, *J* = 11.3, 2.5 Hz, 1 of OC$\underline{H_2}$CH$_2$), 3.96-4.02 (m, 3H, OC$\underline{H}$ + 1 of OCH_2CH$_2$ + 1 of OCHC$\underline{H_2}$), 4.08-4.11 (m, 1H, 1 of OC$\underline{H_2}$CH), 6.51 (d, 1H, *J* = 7.7 Hz, Ar$\underline{H}$), 6.67 (dt, 1H, *J* = 7.4, 0.9 Hz, Ar$\underline{H}$), 7.07-x7.10 (m, 2H, Ar$\underline{H}$), 7.23-7.24 (m, 2H, Ar$\underline{H}$), 8.25-8.26 (m, 1H, Ar$\underline{H}$), 8.37 (bs, 1H, Ar$\underline{H}$). ^{13}C-NMR (125 MHz, CDCl$_3$) δ: 28.7, 46.9, 53.4, 53.7, 55.7, 56.3, 66.9, 69.5, 73.9, 76.81, 106.7, 117.6, 121.3, 123.8, 124.5, 127.3, 129.8, 138.1, 142.5, 152.3, 154.9. HRMS: Found 340.2019 $C_{20}H_{26}N_3O_2$ [M + H]$^+$ requires 340.2020. Converted to HCl salt for assay.

(*R*)-2-(2-((3-chlorophenoxy)methyl)morpholino)-1-(indolin-1-yl)ethanone (22r)



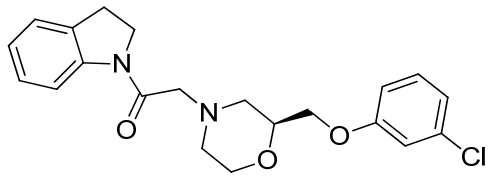
Same procedure as compound **18s** with alcohol **49** (90 mg, 0.326 mmol), 3-chlorophenol (63 mg, 0.49 mmol), triphenylphosphine (128 mg, 0.49 mmol), DIAD (0.10 mL, 0.49 mmol), tetrahydrofuran (1 mL). The crude residue was purified twice by flash column chromatography (Silica, DCM/MeOH 1:0 to 8:2) to afford compound **22r** as a colourless oil, 42 mg (33%).
^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.22 (t, 1H, *J* = 11.2 Hz, 1 of 1 of (C$\underline{H}_2$)$_2$N), 2.37 (dt, 1H, *J* = 11.2, 3.7 Hz, 1 of (C$\underline{H}_2$)$_2$N), 2.78 (d, 1H, *J* = 14 Hz, 1 of (C$\underline{H}_2$)$_2$N), 2.95 (d, 1H, *J* = 14 Hz, 1 of (C$\underline{H}_2$)$_2$N), 3.13 (t, 2H, *J* = 9.7 Hz, 1 of ArC$\underline{H}_2$), 3.23 (s, 2H, COC$\underline{H}_2$N), 3.73 (dt, 1H, *J* = 11.6, 2.0 Hz, 1 of CHC$\underline{H}_2$OAr), 3.83-3.95 (m, 4H, C$\underline{H}_2$OC$\underline{H}$CH$_2$ + 1 of C$\underline{H}_2$OAr), 4.10 (t, 2H, *J* = 8.7 Hz, ArCH$_2$C$\underline{H}_2$), 6.71-6.73 (m, 1H, Ar$\underline{H}$), 6.84-6.87 (m, 2H, Ar$\underline{H}$), 6.95 (t, *J* = 7.3 Hz, Ar$\underline{H}$), 7.09-7.15 (m, 3H, Ar$\underline{H}$), 8.16 (d, 1H, *J* = 9.8 Hz, Ar$\underline{H}$). LCMS: m/z 387.14 ([M+H]$^+$, 100%); Rt 5.5 min, purity >99% DAD (180-450 nm). Converted to HCl salt for assay.

(*R*)-2-((3-Chlorophenoxy)methyl)-4-(2-(indolin-1-yl)ethyl)morpholine (23r)



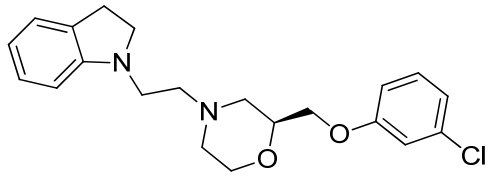
Same procedure as compound **18s** with alcohol **52** (80 mg, 0.30 mmol), 3-chlorophenol (59 mg, 0.46 mmol), triphenylphosphine (120 mg, 0.46 mmol), DIAD (90 µL, 0.46 mmol) and tetrahydrofuran (1.5 mL). The crude mixture was purified twice by flash column chromatography (Silica, DCM/MeOH 1:0 to 96:4 then Hex/EtOAc 1:0 to 0:1) to afford **23r**, 5 mg (4%).
^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.12-2.20 (m, 1H, 1 of (C$\underline{H}_2$)$_2$N), 2.31 (td, 1H, *J* = 11.3, 3.3 Hz, 1 of (C$\underline{H}_2$)$_2$N), 2.65 (t, 2H, *J* = 7.1 Hz, N(C$\underline{H}_2$)$_2$N), 2.79-2.85 (m, 1H, 1 of (C$\underline{H}_2$)$_2$N), 2.94-3.01 (m, 3H, ArC$\underline{H}_2$CH$_2$N + 1 of (C$\underline{H}_2$)$_2$N), 3.26 (t, 2H, *J* = 7.1 Hz, N(C$\underline{H}_2$)$_2$N), 3.37-3.46 (m, 2H, ArCH$_2$C$\underline{H}_2$N), 3.76 (td, 1H, *J* = 11.3, 2.4 Hz, 1 of OC$\underline{H}_2$CH$_2$), 3.88-4.05 (m, 4H, OC$\underline{H}$ + OC$\underline{H}_2$CH + 1 of OC$\underline{H}_2$CH$_2$), 6.49 (d, 1H, *J* = 7.7 Hz, Ar$\underline{H}$), 6.63-6.68 (m, 1H, Ar$\underline{H}$), 6.79-6.83 (m, 1H, Ar$\underline{H}$), 6.90-6.96 (m, 2H, Ar$\underline{H}$), 7.04-7.10 (m, 2H, Ar$\underline{H}$), 7.19 (t, 1H, *J* = 8.1 Hz, Ar$\underline{H}$). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 28.7, 46.9, 53.4, 53.7, 55.8, 56.3, 66.9, 69.4, 73.9, 106.8, 113.1, 115.0, 117.6, 121.2, 124.5, 127.3, 129.9, 130.2, 134.8, 152.3, 159.4. LCMS: m/z 373.17 ([M+H]$^+$, 100%); Rt 5.8 min, purity >95% DAD (180-450 nm). HRMS: Found 373.1665 $C_{21}C_{25}ClN_2O_2$ requires 373.1677. Converted to HCl salt for assay.

(*S*)-2-(2-((3-Chlorophenoxy)methyl)morpholino)-1-(indolin-1-yl)ethanone (22s)



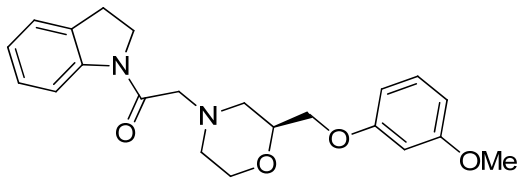
Same procedure as compound **18s** with alcohol **48** (55 mg, 0.2 mmol), 3-chlorophenol (39 mg, 0.3 mmol), triphenylphosphine (78 mg, 0.3 mmol), DEAD (0.05 ml, 0.3 mmol), tetrahydrofuran (1 mL). The crude residue was purified twice by flash column chromatography (Silica, DCM/MeOH 1:0 to 8:2) to afford compound **22s** as a colourless oil, 51 mg (65%). Converted to HCl salt for assay. ^{1}H-NMR (500 MHz, CD_3OD) δ: 3.30 (t, 2H, *J* = 8.3 Hz, ArC$\underline{H_2}$), 3.36-3.38 (m, 2H, C$\underline{H_2}$N), 3.69 (bs, 1H, 1 of C$\underline{H_2}$N), 3.82 (bs, 1H, 1 of C$\underline{H_2}$N), 4.04-4.23 (m, 6H, $ArCH_2C\underline{H_2}$ + C$\underline{H_2}$N, + C$\underline{H_2}$O), 4.30 (bs, 1H, 1 of C$\underline{H_2}$O), 4.44 (s, 2H, 1 of C$\underline{H_2}$O + OC$\underline{H}$), 6.93 (d, 1H, *J* = 8.1 Hz, Ar$\underline{H}$), 6.99-7.02 (m, 2H, Ar$\underline{H}$), 7.12 (t, 1H, *J* = 7.4 Hz, Ar$\underline{H}$), 7.22 (t, 1H, *J* = 7. Hz, Ar$\underline{H}$), 7.27-7.30 (m, 2H, Ar$\underline{H}$), 8.17 (d, 1H, *J* = 8.2 Hz, Ar$\underline{H}$).

(*S*)-2-((3-chlorophenoxy)methyl)-4-(2-(indolin-1-yl)ethyl)morpholine (23s)



Same procedure as compound **18s** with **51** (52 mg, 0.2 mmol), 3-chlorophenol (39 mg, 0.3 mmol), triphenylphosphine (78 mg, 0.3 mmol), DEAD (0.05 ml, 0.3 mmol), tetrahydrofuran (1 mL). The crude residue was purified twice by flash column chromatography (Silica, DCM/MeOH 1:0 to 8:2) to afford compound **23s** as a colourless oil, 30 mg (40%).
^{1}H NMR (500 MHz, $CDCl_3$) δ 2.19 (dd, 1H, *J* = 10.8, 10.1 Hz, 1 of (C$\underline{H_2}$)$_2$N), 2.34 (td, 1H, *J* = 11.3, 3.3 Hz, 1 of (C$\underline{H_2}$)$_2$N), 2.65 (t, 2H, *J* = 6.9 Hz, N(C$\underline{H_2}$)$_2$N), 2.83 (dt, 1H, *J* = 11.0, 5.5 Hz, 1 of (C$\underline{H_2}$)$_2$N), 2.98-3.07 (m, 3H, ArC$\underline{H_2}$ + 1 of (C$\underline{H_2}$)$_2$N), 3.28 (t, 2H, *J* = 7.4 Hz, N(C$\underline{H_2}$)$_2$N), 3.45 (dt, 2H, *J* = 8.3, 1.5 Hz, $ArCH_2C\underline{H_2}$), 3.79 (td, 1H, *J* = 11.3, 2.5 Hz, 1 of OC$\underline{H_2}CH_2$), 4.08 – 3.91 (m, 4H, OC$\underline{H}$C$\underline{H_2}$ + 1 of C$\underline{H_2}$O), 6.52 (d, 1H, *J* = 7.7 Hz, Ar$\underline{H}$), 6.68 (dt, 1H, *J* = 7.4, 9 Hz, Ar$\underline{H}$), 6.84 (ddd, 1H, *J* = 8.4, 2.4, 0.9 Hz, Ar$\underline{H}$), 6.93-7.00 (m, 2H, Ar$\underline{H}$), 7.10 (t, 2H, *J* = 7.6 Hz, Ar$\underline{H}$), 7.22 (dt, 1H, *J* = 8.2, 0.3 Hz, Ar$\underline{H}$). ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.7, 46.9, 53.4, 53.7, 55.6, 56.3, 66.9, 69.4, 73.9, 106.7, 113.3, 115.1, 117.6, 121.2, 124.5, 127.3, 129.8, 130.2, 134.9, 152.3, 159.4. HRMS: Found 373.1673 $C_{21}H_{26}ClN_2O_2$ $[M + H]^+$ requires 373.1677. Converted to HCl salt for assay.

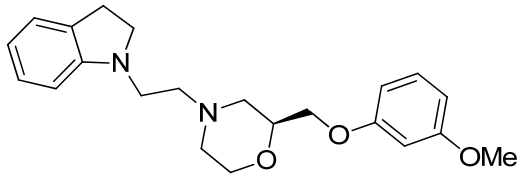
(*S*)-1-(Indolin-1-yl)-2-(2-((3-methoxyphenoxy)methyl)morpholino)ethanone (24s)



Same procedure as compound **18s** with alcohol **48** (55 mg, 0.2 mmol), 3-methoxyphenol (0.032 mL, 0.3 mmol), triphenylphosphine (78 mg, 0.3 mmol), DEAD (0.05 mL, 0.3 mmol) and tetrahydrofuran (1

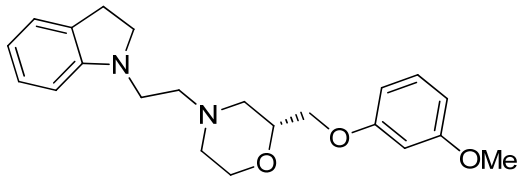
mL). The crude residue was purified twice by flash column chromatography (Silica, DCM/MeOH 1:0 to 8:2)to afford compound **24s** as a colourless oil, 60 mg (78%). Converted to HCl salt for assay.
^{1}H-NMR (500 MHz, CD_3OD) δ: 3.31 (t, 2H, *J* = 8.1 Hz, ArC$\underline{H}_2$), 3.36-3.38 (bs, 2H, C$\underline{H}_2$N), 3.73 (bs, 1H, 1 of (C$\underline{H}_2$)$_2$N), 3.78 (s, 3H, OC$\underline{H}_3$), 3.86 (bs, 1H, 1 of (C$\underline{H}_2$)$_2$N), 4.04-4.25 (m, 6H, ArCH$_2$C$\underline{H}_2$ + C$\underline{H}_2$N + C$\underline{H}_2$O), 4.29 (bs, 1H, 1 of OC$\underline{H}_2$), 4.45 (s, 2H, OC$\underline{H}$ + 1 of OC$\underline{H}_2$), 6.54-6.58 (m, 3H, Ar$\underline{H}$), 7.12 (t, 1H, *J* = 7.6 Hz, Ar$\underline{H}$), 7.18-7.24 (m, 2H, Ar$\underline{H}$), 7.30 (d, 1H, *J* = 7.9 Hz, Ar$\underline{H}$), 8.17 (d, 1H, *J* = 8.0 Hz, Ar$\underline{H}$).

(*S*)-4-(2-(Indolin-1-yl)ethyl)-2-((3-methoxyphenoxy)methyl)morpholine (25s)



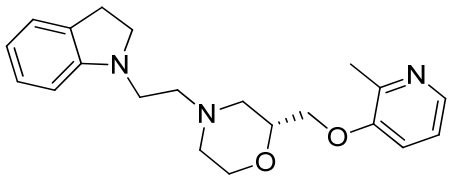
Same procedure as compound **18s** with alcohol **51** (52 mg, 0.2 mmol), 3-methoxyphenol (0.032 mL, 0.3 mmol), triphenylphosphine (78 mg, 0.3 mmol), DEAD (0.05 mL, 0.3 mmol) and tetrahydrofuran (1 mL). The crude residue was purified twice by flash column chromatography (Silica, DCM/MeOH 1:0 to 8:2) to afford compound **25s** as a colourless oil, 46 mg (62%).
^{1}H NMR (500 MHz, $CDCl_3$) δ 2.24–2.13 (m, 1H, 1 of (C$\underline{H}_2$)$_2$N), 2.34 (td, 1H, *J* = 11.3, 3.3 Hz, 1 of (C$\underline{H}_2$)$_2$N), 2.67 (t, 2H, *J* = 7.1 Hz, N(C$\underline{H}_2$)$_2$N), 2.84 (dd, 1H, *J* = 11.4, 1.6 Hz, 1 of (C$\underline{H}_2$)$_2$N), 2.98-3.02 (m, 3H, ArC$\underline{H}_2$ + 1 of (C$\underline{H}_2$)$_2$N), 3.28 (t, 2H, *J* = 7.2 Hz, N(C$\underline{H}_2$)$_2$N), 3.44 (dt, 2H, *J* = 8.2 2.0, ArCH$_2$C$\underline{H}_2$), 3.78 (dt, 1H, *J* = 11.3, 2.5 Hz, 1 of OC$\underline{H}_2$CH$_2$), 3.81 (s, 3H, OC$\underline{H}_3$), 4.08 – 3.93 (m, 4H, OC$\underline{H}$C$\underline{H}_2$ + 1 of CH$_2$O), 6.57 – 6.49 (m, 4H, Ar$\underline{H}$), 6.68 (t, 1H, *J* = 7.1 Hz, Ar$\underline{H}$), 7.07 -7.11 (m, 2H, Ar$\underline{H}$), 7.20 (dt, 1H *J* = 8.1 0.5 Hz, Ar$\underline{H}$). ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.67, 46.9, 53.4, 53.7, 55.3, 56.0, 56.3, 66.9, 69.2, 74.0, 101.1, 106.6, 106.7, 106.8, 117.6, 124.5, 127.3, 129.9, 152.3, 159.9, 160.8. HRMS: Found 369.2162 $C_{22}H_{29}N_2O_3$ $[M + H]^+$ requires 369.2173. Converted to HCl salt for assay.

(*R*)-4-(2-(Indolin-1-yl)ethyl)-2-((3-methoxyphenoxy)methyl)morpholine (25r)



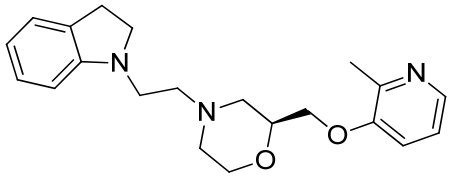
Same procedure as **18s** with alcohol **52** (80 mg, 0.30 mmol), 3-methoxyphenol (50 µL, 0.46 mmol), triphenylphosphine (120 mg, 0.46 mmol), DIAD (90 µL, 0.46 mmol) and tetrahydrofuran (1.5 mL). The crude mixture was purified twice by flash column chromatography (Silica, DCM/MeOH 1:0 to 94:6 then Hex/EtOAc 1:0 to 0:1) to afford **25r**, 18 mg (16%).
For NMR data see **25s**. LCMS: m/z 369.22 ($[M+H]^+$, 100%); Rt 5.5 min, purity >98% DAD (180-450 nm). Converted to HCl salt for assay.

(*R*)-4-(2-(Indolin-1-yl)ethyl)-2-(((2-methylpyridin-3-yl)oxy)methyl)morpholine (26r)



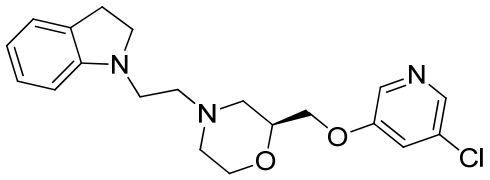
Same procedure as **18s** with alcohol **52** (80 mg, 0.30 mmol), 2-methyl-3-hydroxypyridine (50 mg, 0.46 mmol), triphenylphosphine (120 mg, 0.46 mmol), DIAD (90 µL, 0.46 mmol) and tetrahydrofuran (1.5 mL). The crude mixture was purified by flash column chromatography (Silica, DCM/MeOH 1:0 to 94:6) to afford **26r**, 49 mg (46%).
^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.15-2.22 (m, 1H, 1 of (C$\underline{H}_2$)$_2$N), 2.30 (td, 1H, *J* = 11.3, 3.3 Hz, 1 of (C$\underline{H}_2$)$_2$N), 2.47 (s, 3H, Me), 2.66 (t, 2H, *J* = 7.0 Hz, N(C$\underline{H}_2$)$_2$N), 2.80-2.85 (m, 1H, 1 of (C$\underline{H}_2$)$_2$N), 2.97 (t, 2H, *J* = 8.3 Hz, ArC$\underline{H}_2$CH$_2$N), 3.01-3.06 (m, 1H, 1 of (C$\underline{H}_2$)$_2$N), 3.21-3.31 (m, 2H, N(C$\underline{H}_2$)$_2$N), 3.36-3.46 (m, 2H, ArCH$_2$C$\underline{H}_2$N), 3.77 (td, 1H, *J* = 11.3, 2.5 Hz, 1 of OC$\underline{H}_2$CH$_2$), 3.88-4.01 (m, 3H, OCH + 1 of OC$\underline{H}_2$CH$_2$ + 1 of OC$\underline{H}_2$CH), 4.01-4.06 (m, 1H, 1 of OC$\underline{H}_2$CH), 6.49 (d, 1H, *J* = 7.7 Hz, Ar$\underline{H}$), 6.65 (td, 1H, *J* = 7. 5, 0.9 Hz, Ar$\underline{H}$), 7.03-7.10 (m, 4H, Ar$\underline{H}$), 8.07-8.10 (m, 1H, Ar$\underline{H}$). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 19.4, 28.7, 47.0, 53.4, 53.7, 55.7, 56.2, 66.9, 69.3, 73.9, 106.7, 117.6, 117.7, 121.7, 124.5, 127.3, 129.9, 140.8, 149.1, 152.3, 153.0. LCMS: m/z 354.22 ([M+H]$^+$, 100%); Rt 5.1 min, purity >97% DAD (180-450 nm). HRMS: Found 354.2185 $C_{21}H_{27}N_3O_2$ [M + H]$^+$ requires 354.2176. Converted to HCl salt for assay.

(*S*)-4-(2-(Indolin-1-yl)ethyl)-2-(((2-methylpyridin-3-yl)oxy)methyl)morpholine (26s)



Same procedure as **18s** with alcohol **51** (80 mg, 0.30 mmol), 2-methyl-3-hydroxypyridine (50 mg, 0.46 mmol), triphenylphosphine (120 mg, 0.46 mmol), DIAD (90 µL, 0.46 mmol) and tetrahydrofuran (1.5 mL). The crude mixture purified by flash column chromatography (Silica, DCM/MeOH 1:0 to 94:6) to afford **26s**, 75 mg (71%).
For NMR data see **26r**. Converted to HCl salt for assay.

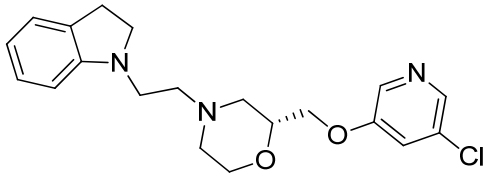
(*S*)-2-(((5-Chloropyridin-3-yl)oxy)methyl)-4-(2-(indolin-1-yl)ethyl)morpholine (27s)



Same procedure as **18s** with alcohol **51** (80 mg, 0.30 mmol), 5-chloro-3-hydroxypyridine (59 mg, 0.46 mmol), triphenylphosphine (120 mg, 0.46 mmol), DIAD (90 µL, 0.46 mmol) and tetrahydrofuran (1.5 mL). The crude mixture was purified twice by flash column chromatography (Silica, DCM/MeOH 1:0 to 94:6 then Hex/EtOAc 1:0 to 0:1) to afford **27s**, 71 mg (91%).

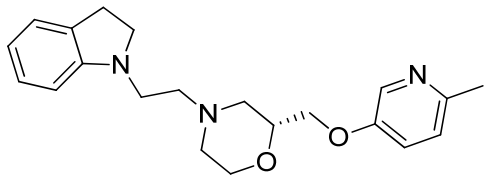
^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.13-2.20 (m, 1H, 1 of (C<u>*H*</u>$_2$)$_2$N), 2.31 (td, 1H, *J* = 11.3, 3.3 Hz, 1 of (C<u>*H*</u>$_2$)$_2$N), 2.65 (t, 2H, *J* = 7.1 Hz, N(C<u>*H*</u>$_2$)$_2$N), 2.79-2.85 (m, 1H, 1 of (C<u>*H*</u>$_2$)$_2$N), 2.92-3.00 (m, 3H, ArC<u>*H*</u>$_2$CH$_2$N + 1 of (C<u>*H*</u>$_2$)$_2$N), 3.25 (t, 2H, *J* = 7.1 Hz, N(C<u>*H*</u>$_2$)$_2$N), 3.36-3.45 (m, 2H, ArCH$_2$C<u>*H*</u>$_2$N), 3.76 (td, 1H, *J* = 11.3, 2.4 Hz, 1 of OC<u>*H*</u>$_2$CH$_2$), 3.92-4.01 (m, 3H, OCH + 1 of OC<u>*H*</u>$_2$CH$_2$ + 1 of OC<u>*H*</u>$_2$CH), 4.02-4.09 (m, 1H, 1 of OC<u>*H*</u>$_2$CH), 6.49 (d, 1H, *J* = 7.7 Hz, Ar<u>*H*</u>), 6.63-6.68 (m, 1H, Ar<u>*H*</u>), 7.04-7.10 (m, 2H, Ar<u>*H*</u>), 7.22-7.25 (m, 1H, Ar<u>*H*</u>), 8.20 (d, 1H, *J* = 2.0 Hz, Ar<u>*H*</u>), 8.22 (d, 1H, *J* = 2.6 Hz, Ar<u>*H*</u>). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 28.6, 47.0, 53.4, 53.7, 55.7, 56.3, 66.9, 69.5, 73.9, 106.7, 117.6, 121.3, 123.8, 124.5, 127.3, 129.9, 138.0, 139.7, 142.5, 152.3, 154.9. LCMS: m/z 374.16 ($[M+H]^+$, 100%); Rt 5.3 min, purity = 91% DAD (180-450 nm). HRMS: Found 374.1619 $C_{20}H_{24}N_3O_2Cl$ $[M + H]^+$ requires 374.1630. Compound was re-purified to assay (36.7 mg, purity 100%). Converted to HCl salt for assay.

(*R*)-2-(((5-Chloropyridin-3-yl)oxy)methyl)-4-(2-(indolin-1-yl)ethyl)morpholine (27r)



Same procedure as **18s** with alcohol **52** (80 mg, 0.30 mmol), 5-chloro-3-hydroxypyridine (59 mg, 0.46 mmol), triphenylphosphine (120 mg, 0.46 mmol), DIAD (90 µL, 0.46 mmol) and tetrahydrofuran (1.5 mL). The crude mixture was purified by flash column chromatography (Silica, DCM/MeOH 1:0 to 94:6) to afford **27r**, 100 mg.
For NMR data see **27s**. LCMS: m/z 374.16 ($[M+H]^+$, 100%); Rt 5.3 min, purity = 90% DAD (180-450 nm). A sample of **27r** was re-purified to assay (purity >97%). Converted to HCl salt for assay.

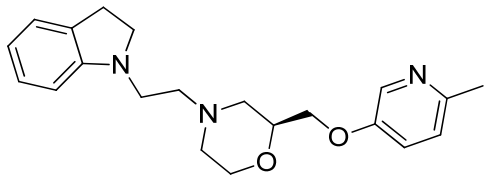
(*R*)-4-(2-(Indolin-1-yl)ethyl)-2-(((6-methylpyridin-3-yl)oxy)methyl)morpholine (28r)



Same procedure as **18s** with alcohol **52** (80 mg, 0.30 mmol), 6-methyl-3-hydroxypyridine (50 mg, 0.46 mmol), triphenylphosphine (120 mg, 0.46 mmol), DIAD (90 µL, 0.46 mmol) and tetrahydrofuran (1.5 mL). The crude mixture was purified by flash column chromatography (Silica, DCM/MeOH 1:0 to 94:6) to afford **28r**, 57 mg (54%).
^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.13-2.21 (m, 1H, 1 of (C<u>*H*</u>$_2$)$_2$N), 2.31 (td, 1H, *J* = 11.4, 3.3 Hz, 1 of (C<u>*H*</u>$_2$)$_2$N), 2.48 (s, 3H, Me), 2.65 (t, 2H, *J* = 7.1 Hz, N(C<u>*H*</u>$_2$)$_2$N), 2.79-2.85 (m, 1H, 1 of (C<u>*H*</u>$_2$)$_2$N), 2.92-2.99 (m, 3H, ArC<u>*H*</u>$_2$CH$_2$N + 1 of (C<u>*H*</u>$_2$)$_2$N), 3.22-3.27 (m, 2H, N(C<u>*H*</u>$_2$)$_2$N), 3.35-3.44 (m, 2H, ArCH$_2$C<u>*H*</u>$_2$N), 3.76 (td, 1H, *J* = 11.4, 2.4 Hz, 1 of OC<u>*H*</u>$_2$CH$_2$), 3.88-3.99 (m, 3H, OCH + 1 of OC<u>*H*</u>$_2$CH$_2$ + 1 of OC<u>*H*</u>$_2$CH), 3.99-4.06 (m, 1H, 1 of OC<u>*H*</u>$_2$CH), 6.48 (d, 1H, *J* = 7.7 Hz, Ar<u>*H*</u>), 6.64 (td, 1H, *J* = 7. 5, 0.8 Hz, Ar<u>*H*</u>), 7.02-7.09 (m, 3H, Ar<u>*H*</u>), 7.13 (dd, 1H, *J* = 8.5, 3.0 Hz, Ar<u>*H*</u>), 8.20 (d, 1H, *J* = 2.9 Hz, Ar<u>*H*</u>). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 23.4, 28.6, 46.9, 53.3, 53.7, 55.7, 56.2, 66.8, 69.7, 73.9, 106.8, 117.7, 122.6, 123.6, 124.3, 127.3, 129.9, 136.3, 150.6, 152.3, 153.0. LCMS: m/z 354.22

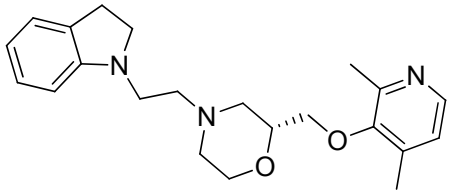
([M+H]$^+$, 100%); Rt 5.1 min, purity >96% DAD (180-450 nm). HRMS: Found 354.2190 $C_{21}H_{28}N_3O_2$ [M + H]$^+$ requires 354.2176. Converted to HCl salt for assay.

(*S*)-4-(2-(Indolin-1-yl)ethyl)-2-(((6-methylpyridin-3-yl)oxy)methyl)morpholine (28s)



Same procedure as **18s** with alcohol **51** (80 mg, 0.30 mmol), 6-methyl-3-hydroxypyridine (50 mg, 0.46 mmol), triphenylphosphine (120 mg, 0.46 mmol), DIAD (90 µL, 0.46 mmol) and tetrahydrofuran (1.5 mL). The crude mixture was purified by flash column chromatography (Silica, DCM/MeOH 1:0 to 94:6) to afford **28s**, 58 mg (55%).
For NMR data see **28r**. LCMS: m/z 354.22 ([M+H]$^+$, 100%); Rt 5.1 min, purity >94% DAD (180-450 nm). Converted to HCl salt for assay.

(*R*)-2-(((2,4-Dimethylpyridin-3-yl)oxy)methyl)-4-(2-(indolin-1-yl)ethyl)morpholine (29r)



Same procedure as **18s** with alcohol **52** (80 mg, 0.30 mmol), 2,4-dimethyl-3-hydroxypyridine (57 mg, 0.46 mmol), triphenylphosphine (120 mg, 0.46 mmol), DIAD (90 µL, 0.46 mmol) and tetrahydrofuran (1.5 mL). The crude mixture was purified by flash column chromatography (Silica, DCM/MeOH 1:0 to 94:6) to afford **29r**, 48 mg (44%).
^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.17-2.24 (m, 1H, 1 of (C$\underline{H_2}$)$_2$N), 2.29-2.38 (m, 4H, 1 of (C$\underline{H_2}$)$_2$N + Me), 2.53 (s, 3H, Me), 2.68 (t, 2H, *J* = 7.1 Hz, N(C$\underline{H_2}$)$_2$N), 2.83-2.88 (m, 1H, 1 of (C$\underline{H_2}$)$_2$N), 2.96-3.05 (m, 3H, ArC$\underline{H_2}$CH$_2$N + 1 of (C$\underline{H_2}$)$_2$N), 3.26-3.32 (m, 2H, N(C$\underline{H_2}$)$_2$N), 3.39-3.48 (m, 2H, ArCH$_2$C$\underline{H_2}$N), 3.76-3.89 (m, 3H, OCH + OC$\underline{H_2}$CH$_2$), 3.96-4.03 (m, 2H, OC$\underline{H_2}$CH), 6.51 (d, 1H, *J* = 7.7 Hz, Ar$\underline{H}$), 6.65-6.70 (m, 1H, Ar$\underline{H}$), 6.97 (d, 1H, *J* = 4.9 Hz, Ar$\underline{H}$), 7.05-7.12 (m, 2H, Ar$\underline{H}$), 8.14 (d, 1H, *J* = 4.9 Hz, Ar$\underline{H}$). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 15.7, 19.4, 28.6, 46.9, 53.3, 53.7, 55.7, 56.3, 66.8, 73.5, 74.6, 106.7, 117.6, 124.2, 124.5, 127.3, 129.9, 139.7, 144.4, 152.2, 152.3. LCMS: m/z 368.23 ([M+H]$^+$, 100%); Rt 5.1 min, purity >99% DAD (180-450 nm). HRMS: Found 368.2333 $C_{22}H_{30}N_3O_2$ [M + H]$^+$ requires 368.2333. Converted to HCl salt for assay.

5. *In vitro* metabolic stability

Each test compound (0.5µM) was incubated with pooled female mouse liver microsomes (Tebu-Bio, UK; 0.5mg/mL 50mM potassium phosphate buffer, pH7.4) and the reaction started with addition of excess NADPH (8mg/mL 50mM potassium phosphate buffer, pH7.4). Immediately, at time zero, then at 3, 6, 9, 15 and 30 minutes an aliquot (50uL) of the incubation mixture was removed and mixed with acetonitrile (100uL) to stop the reaction. Internal standard was added to all samples, the samples centrifuged to sediment precipitated protein and the plates then sealed prior to UPLCMSMS analysis using a Quattro Premier XE (Waters, USA).

XLfit (IDBS, UK) was used to calculate the exponential decay and consequently the rate constant (k) from the ratio of peak area of test compound to internal standard at each timepoint. The rate of intrinsic clearance (CLi) of each compound was then calculated using the following equation below

$$CLi(mL/min/g\ liver) = k \times V \times Microsomal\ protein\ yield$$

Where V (mL/mg protein) is the incubation volume/mg protein added and microsomal protein yield is taken as 52.5mg protein/ g liver

Verapamil was used as a positive control to confirm acceptable assay performance.

Compound	CLi
9a	31.1mL/min/g
9b	>50mL/min/g
11a	7.7mL/min/g
11b	14.6mL/min/g
13	13.8mL/min/g
27s	25 mL/min/g

6. Assessment of brain penetration and brain tissue binding

6.1. Brain penetration

Test compound was dosed intravenously at 1mg free base/kg to female NMRI mice (n=3 mice/compound). Dose formulation was 10% DMSO:90% saline and dose volume was 5mL/kg. Each mouse was placed under terminal anaesthesia with isofluorane at 5 minutes post-dose. Blood was taken by cardiac puncture into two volumes distilled water and the brain removed. After suitable sample preparation, the concentration of test compound in blood and brain was determined by UPLCMSMS using a Quattro Premier XE (Waters, USA) and the brain:blood ratio determined.

Compound **13** was dosed intraperitoneally at 10mg free base/kg to female NMRI mice (n=6). Dose formulation was 10% DMSO;40% PEG400;50% MilliQ water and dose volume was 10mL/kg. Mice (n=3) were placed under terminal anaesthesia with isofluorane at 15 minutes or 60 minutes post-dose. Blood was taken by cardiac puncture into two volumes distilled water and the brain removed. After suitable sample preparation, the concentration of test

compound in blood and brain was determined by UPLCMSMS using a Quattro Premier XE (Waters, USA) and the brain:blood ratio determined.

Mouse	Time	Blood Conc (ng/ml)	Brain conc. (ng/ml)	Brain:Blood Ratio	Mean B:B ratio
1	15	197	2025	10.29	9.8
2		216	1943	9.01	
3		142	1422	10.04	
4	60	71	590	8.29	8.5
5		86	699	8.18	
6		81	735	9.11	

6.2 Assessment of brain tissue binding

The methodology employed was a modification of that reported previously.[5] In brief, a 96 well equilibrium dialysis apparatus was used to determine the free fraction in the brain for the test compound (HT Dialysis LLC, Gales Ferry, CT). Membranes (12-14kDA cut-off) were conditioned in deionised water for 60 minutes, followed by conditioning in 80:20 deionised water:ethanol for 20 minutes, and then rinsed in artificial cerebrospinal fluid (CSF) before use. Mouse brain was removed from the freezer and allowed to thaw on the day of experiment. Thawed brain tissue was homogenised with artificial CSF to a final composition of 1:2 brain:artificial CSF using a Covaris S2 (K Biosciences, Hoddesdon, UK). Diluted brain homogenate was spiked with the test compound (10 ug/g), and 150µL aliquots (n=6 replicate determinations) loaded into the 96-well equilibrium dialysis plate. Dialysis vs artificial CSF (150µL) was carried out for 5 hours in a temperature controlled incubator at *ca.* 37ºC (Barworld scientific Ltd, UK) using an orbital microplate shaker at 125 revolutions/minute (Barworld scientific Ltd, UK). At the end of the incubation period, aliquots of brain homogenate or artificial CSF were transferred to micronic tubes (Micronic B.V., the Netherlands) and the composition in each tube balanced with control fluid, such that the volume of artificial CSF to brain is the same. Sample extraction was performed by the addition of 400µL of acetonitrile containing an appropriate internal standard. Samples were allowed to mix for 1 minute and then centrifuged at 3000rpm in 96-well blocks for 15 minutes (Allegra X12-R, Beckman Coulter, USA). All samples were analysed by means of UPLC/MS/MS on a Quattro Premier XE Mass Spectrometer (Waters Corporation, USA). The unbound fraction was determined as the ratio of the peak area in artificial CSF to that in brain, with correction for dilution factor according to equation below[6]

$$Undiluted\ f_u = \frac{1/D}{1/f_{u\ apparent} - 1 + 1/D}$$

where D = dilution factor in brain homogenate and $f_{u,apparent}$ is the measured free fraction of diluted brain homogenate.

Compound **13** Brain Fu = 0.184

7. Detailed Behavioural Results

Open field activity: Locomotor activity for DR4-WT and KO mice was aggregated into three 20-min blocks. A three-way repeated measures ANOVA (RMANOVA) for distance traveled observed significant main effects of time [$F_{(2,98)}$=55.573, p<0.001], a significant time by genotype interaction [$F_{(2,98)}$=6.679, p<0.002], and a significant time by genotype by treatment interaction [$F_{(2,98)}$=3.167, p<0.017] (Fig. 4c). Bonferroni corrected pair-wise comparisons found that vehicle-treated D4R-WT mice had decreased locomotion at 21-40 and 41-60 min compared to the 0-20 min time-point (ps<0.001). In D4R-WT animals 0.7 mg/kg compound **13** was without effect; however, the 1 mg/kg dose reduced activity during the first 20 min relative to animals given vehicle (p<0.003). Locomotor activities in vehicle- or compound **13**-treated D4R-KO mice did not differ within any of the time-points. Nevertheless, the 1 mg/kg dose attenuated activity at 21-40 and 41-60 min relative to 0-20 min (ps<0.005). When locomotion was examined between genotypes, activity was higher at 41-60 min in vehicle-treated D4R-KO mice than in any of the three D4R-WT groups (ps<0.022). Responses to compound **13** were not distinguished by genotype.

In PC7 mice a RMANOVA for locomotion found the within subject effects for time [$F_{(2,72)}$=21.651, p<0.001] and the time by treatment [$F_{(2,72)}$=6.250, p<0.001] and the time by treatment by genotype [$F_{(2,72)}$=3.387, p<0.039] interactions to be significant (Supplementary Fig. 10a). Bonferroni comparisons noted that locomotor activity in vehicle-treated PC7-WT mice was decreased at 41-60 min relative to the first 20 min (p<0.001). No changes in locomotion were observed across time in compound **13**-treated PC7-WT animals. Nevertheless, locomotion in PC7-WT mice administered 1 mg/kg compound **13** was higher than that in the animals given vehicle at 41-60 min (p<0.044). Vehicle-treated PC7-KO showed no evidence of habituation, whereas a diminution in activity was seen with compound **13** at all time-points relative to vehicle-treated mutants (ps<0.005). Robust genotype differences in locomotion were observed in vehicle-treated PC7-KO mice relative to the PC7-WT vehicle controls at all time points (ps<0.001).

When time in the center zone of the open field was analyzed for D4R mice, a three-way RMANOVA reported that only the time by genotype [$F_{(2,98)}$=5.248, p<0.007] and time by treatment by genotype interactions were significant [$F_{(2,98)}$=2.554, p<0.044] (Fig. 4d). For D4R-WT mice Bonferroni tests showed that time spent in the center zone at 0-20 min was increased with both doses of compound **13** compared to the vehicle controls (ps<0.006) and this center time was similar to that of the D4R-KO mice. Although the 0.7 mg/kg dose in D4R-WT animals marginally enhanced time spent in the center zone relative to the vehicle at 41-60 min (p=0.06), the 1.0 mg/kg dose exerted no significant effects at any time. In D4R-KO mice the 0.7 mg/kg dose was without effect. By comparison the 1 mg/kg dose in D4R-KO animals reduced time spent in the center zone during the final 20 min of testing (ps<0.053) compared to the vehicle or the 0.7 mg/kg dose. Additionally, vehicle-treated D4R-KO mice spent more time in the center than the respective D4R-WT animals at 21-40 and 41-60 min (ps<0.023).

In PC7 mice, a repeated measures ANOVA for time spent in the center zone only found the time by genotype by treatment interaction to be significant [$F_{(2,72)}$=5.926, p<0.004] (Supplementary Fig. 10b). Bonferroni tests reported that PC7-KO mice administered 1 mg/kg compound **13** spent more time in the center of the open field than the PC7-KO vehicle controls at 0-20 min (p<0.047).

Hole-board test: A two-way ANOVA for the rate of head-pokes by D4R animals demonstrated significant main effects of genotype [$F_{(1,45)}$=29.579, p<0.001] and a significant genotype by treatment interaction [$F_{(2,45)}$=6.815, p<0.003] (Fig. 4e). Bonferroni pair-wise comparisons noted that head-poke rates were higher in D4R-KO mice than in the respective D4R-WT animals given either vehicle or 0.7 mg/kg compound **13** (ps<0.001). Nonetheless, rates were similar between genotypes with the 1 mg/kg dose. While in D4R-WT mice the 0.7 mg/kg dose potentiated the rate of head-pokes, only the 1 mg/kg dose significantly increased this rate above that of animals receiving the vehicle (p<0.053). Interestingly, the rate of head pokes for D4R-WT animals given the 1 mg/kg dose was similar to that for the three groups of D4R-KO mice. In D4R-KO animals, the 0.7 mg/kg dose exerted no effects. By contrast 1 mg/kg compound **13** reduced this rate relative to the vehicle or the 0.7 mg/kg dose (ps<0.043).

In PC7 mice the two-way ANOVA detected only the genotype by treatment interaction to be significant [$F_{(1,35)}$=3.686, p<0.053] (Supplementary Fig. 10c). Bonferroni tests confirmed that the rate of head pokes was higher for vehicle-treated PC7-KO mice than PC7-WT controls (p<0.043). Notably, 1 mg/kg compound 13 enhanced head-pokes in the PC7-WT animals (p<0.032) to levels that were not different from those of the PC7-KO vehicle controls. Conversely, in PC7-KO mice this same dose depressed head-pokes (p<0.037).

Elevated zero maze: In D4R mice a two-way ANOVA for percent time in the open areas noted significant main effects of genotype [$F_{(1,54)}$=20.395, p<0.001] and treatment [$F_{(2,54)}$=3.998, p<0.024], and a significant genotype by treatment interaction [$F_{(2,54)}$=3.151, p<0.051] (Fig. 4f). Bonferroni corrected pair-wise comparisons found that vehicle- and 0.7 mg/kg-treated D4R-KO mice spent more time in the open areas than the respective D4R-WT animals (ps<0.011); no genotype differences were detected between genotypes given 1 mg/kg compound **13**. D4R-WT mice administered the 0.7 mg/kg dose showed marginal increases in open area time compared to the vehicle controls. Nevertheless, open area time was significantly augmented with the 1 mg/kg dose (p<0.048) in DR4-WT mice relative to similar conspecifics given vehicle or 0.7 mg/kg compound **13**. In contrast, the compound was without effect in D4R-KO mice.

In PC7 mice the ANOVA revealed significant main effects of genotype [$F_{(1,40)}$=10.143, p<0.001] and a significant treatment by genotype interaction [$F_{(1,40)}$=7.205, p<0.011] (Supplementary Fig. 10d). Bonferroni corrected pair-wise comparisons showed that vehicle-treated PC7-KO mice spent significantly more time in the open areas than similarly treated WT controls (p<0.001); no genotype differences were seen with the 1 mg/kg dose. In PC7-WT animals 1 mg/kg compound **13** increased open area time relative to the vehicle controls (p<0.048), whereas this same dose reduced open area time in the PC7-KO mice (p<0.052).

Statistics details and legend for figure 4 c-f and supplementary information figure 10:

Note: p-values are rounded to the nearest 0.05 value [example, p<0.0549 would round to p<0.05 whereas p<0.0550 would round to p<0.06 and be considered not significant (N.S.) or marginally significant].

Supplementary Table 1a: High confidence Bayesian model predictions against 20 GPCRs

Compound Name	5-HT1a	5-HT1b	5-HT1d	5-HT1e	5-HT2a	5-HT2b	5-HT2c	5-HT3	5-HT4	5-HT5a	5-HT6	5-HT7
Donepezil (Cpd 1)	-12.5	-11.1	-13.2	-4.1	-1.4	-0.9	-2.3	-2.2	-10.4	-10.6	-15.6	-6.9
Compound 2	93.1	28.4	-3	-4	53.3	32	41.8	7	-18.5	9.1	-6.4	67.4
Compound 3	81.7	27.4	-6.3	-3.5	48.9	37.2	41.1	12.9	-13.2	7.9	-12.4	65.2
Compound 4	87.7	36.1	-7.7	-4.7	51.4	29.9	47.1	7.4	-20	4.3	-6.2	61.8
Compound 5	88.2	24.6	-6.6	-4.1	50.6	27.2	37.8	6.2	-18	8.6	-7.7	67
Compound 6	76.4	12.5	-17.1	-4.6	52.8	19.3	55	0.6	-15.7	3.7	-9.4	35.1
Compound 7	67.8	2.5	-15.3	-3.6	50	22.8	47.9	5.7	-5.9	5.1	-13.8	34.4
Compound 8	81.8	4.8	-12.4	-3.9	54.7	21.4	49.8	0.2	-14.2	8.4	-9.6	40.7
Compound 9a	90.5	2.8	-17.2	-1.9	60.2	30.4	54.3	-3.2	-18.6	6.4	-12.4	53.2
Compound 9b	91.4	0.1	-19.6	-2.2	57.6	26.5	51.4	-3.9	-19.2	3.4	-15.5	57.1
Compound 10a	103.5	26.4	-9.3	-3.3	59.4	41.6	47.6	3.9	-17.8	7.5	-9	81.1
Compound 10b	104.4	23.6	-11.7	-3.6	56.8	37.7	44.7	3.2	-18.4	4.5	-12	85
Compound 11a	78.3	0.2	-19.5	-1.8	41.4	23.7	18.7	-8.7	-26.1	-3.6	-21.8	46.5
Compound 11b	79.2	-2.5	-21.9	-2.1	38.8	19.8	15.9	-9.3	-26.8	-6.6	-24.8	50.4
Compound 12	14.1	0.4	-1.4	-3.2	19.6	6.8	8.7	5.1	-25.4	-4.8	-15.4	27
Compound 13	-9.8	-9.5	-7	-4.1	2.4	3.4	-1.5	-3.1	-27.6	-8.5	-22.4	2.1
Compound 14r	-1.9	-14.2	-13.5	-2.4	-8.6	-4	-5.6	-5.7	-14.9	-13.7	-29.4	2.3
Compound 15r	14.7	3	-5.9	-3.5	13.4	10.9	20	-2.1	-13.7	-7.6	-17.9	11.6
Compound 16r	-13.1	-14.7	-14.8	-3	-9.8	-3.9	-7.2	-2	-16.1	-16.2	-29	5.4
Compound 17r	3.5	2.5	-7.2	-4.1	12.1	11.1	18.5	1.6	-14.9	-10	-17.5	14.7
Compound 18s	-12.9	-12.9	-14.2	-2.5	-8.7	-9.6	-6.4	-6.6	-16.8	5	-26.3	5.2
Compound 19s	3.7	4.3	-6.6	-3.5	13.3	5.4	19.3	-3	-15.6	11.1	-14.8	14.6
Compound 20r	-23.8	-18.9	-18.6	-2.8	-16.7	-8	-14.5	-7.9	-25.3	-13.8	-40.1	-5.6
Compound 20s	-23.8	-18.9	-18.6	-2.8	-16.7	-8	-14.5	-7.9	-25.3	-13.8	-40.1	-5.6
Compound 21r	-7.2	-1.7	-11	-3.8	5.3	7	11.2	-4.3	-24	-7.6	-28.7	3.7
Compound 21s	-7.2	-1.7	-11	-3.8	5.3	7	11.2	-4.3	-24	-7.6	-28.7	3.7
Compound 22r	-3.8	-13.3	-13.3	-2.3	-4	-5.7	-6.1	-2.4	-10.4	-1.9	-21.4	3.7
Compound 22s	-3.8	-13.3	-13.3	-2.3	-4	-5.7	-6.1	-2.4	-10.4	-1.9	-21.4	3.7
Compound 23r	12.7	3.9	-5.7	-3.3	17.9	9.2	19.6	1.2	-9.1	4.2	-9.9	13.1
Compound 23s	12.7	3.9	-5.7	-3.3	17.9	9.2	19.6	1.2	-9.1	4.2	-9.9	13.1
Compound 24s	-6.8	-13.4	-15.3	-2.9	-10.3	-8.9	-9.1	-6.4	-11.2	0.9	-22.2	6.3
Compound 25r	9.7	3.8	-7.7	-4	11.6	6	16.6	-2.8	-9.9	7.1	-10.8	15.6
Compound 25s	9.7	3.8	-7.7	-4	11.6	6	16.6	-2.8	-9.9	7.1	-10.8	15.6
Compound 26r	1.7	1	-11.7	-4.8	11.5	13.4	18.2	1.9	-14.7	-9.4	-16.3	13.8
Compound 26s	1.7	1	-11.7	-4.8	11.5	13.4	18.2	1.9	-14.7	-9.4	-16.3	13.8
Compound 27r	-3.8	-0.4	-10.3	-3.7	8.2	8.5	13.9	0.3	-10.9	-4.6	-19.3	8.9
Compound 27s	-3.8	-0.4	-10.3	-3.7	8.2	8.5	13.9	0.3	-10.9	-4.6	-19.3	8.9
Compound 28r	-5.2	-1.1	-9.5	-4.9	8.3	8.7	15.4	-1.2	-15.7	-5.6	-17.7	9.4
Compound 28s	-5.2	-1.1	-9.5	-4.9	8.3	8.7	15.4	-1.2	-15.7	-5.6	-17.7	9.4
Compound 29r	0	0.8	-9.7	-4.6	8.9	10.1	16.2	0.4	-16.9	-10.4	-18.9	11.8

Compound Name	Alpha-1a	Alpha-1b	Alpha-1d	D1	D2	D3	D4	D5
Donepezil (Cpd 1)	-5.7	-10.7	-8.5	6.8	9	22.7	26.3	-3.6
Compound 2	68.3	64	65.1	43.9	81.3	66.2	54	36.2
Compound 3	78.6	66.4	74.6	47.4	79.8	77.9	52.3	33.8
Compound 4	70	64.4	69.3	48	79.4	64.6	56.6	31.7
Compound 5	67.6	62.8	64	39.3	75.8	67.4	53.3	34.2
Compound 6	42	25.8	38.7	52.3	89.4	83.9	67.7	21.7
Compound 7	51.3	27.8	44.1	47.2	85.3	90.2	61.4	22.9
Compound 8	40.2	25.5	34.5	48.2	91.3	85.5	65	26.2
Compound 9a	44.6	27.4	36.8	64.6	101.6	95.8	73.3	35.9
Compound 9b	47	32.6	40.1	62.7	103.4	92.9	69.4	36.8
Compound 10a	74.4	67.3	69.1	60.4	92.6	78.1	63.1	46.3
Compound 10b	76.8	72.4	72.4	58.4	94.4	75.2	59.2	47.3
Compound 11a	35.5	28.9	29.1	17.4	77.9	55.3	70.2	19.9
Compound 11b	37.9	34	32.3	15.4	79.7	52.3	66.2	20.9
Compound 12	7.8	10.5	9.5	18.7	72.6	20.6	111.1	19.2
Compound 13	-18.8	-15.8	-19.5	6.3	67.7	10.3	112.1	3.1
Compound 14r	-11.7	-9.7	-11.1	-1.3	27.9	-1.8	84	13.3
Compound 15r	8.3	6.7	7.2	14	16.3	14.2	61.3	18.9
Compound 16r	-11.9	-11.4	-11.6	0.4	22.3	-3.2	82.6	12.2
Compound 17r	8	5	6.8	15.6	10.7	12.7	59.9	17.8
Compound 18s	-21.6	-17.8	-20.2	1.5	29.5	0.6	88.8	20.4
Compound 19s	-1.7	-1.5	-1.8	16.8	17.9	16.6	66.1	26
Compound 20r	-24.1	-20.5	-22.8	-7.7	14.6	-9.7	77.2	10
Compound 20s	-24.1	-20.5	-22.8	-7.7	14.6	-9.7	77.2	10
Compound 21r	-4.1	-4.1	-4.4	7.6	3	6.2	54.5	15.6
Compound 21s	-4.1	-4.1	-4.4	7.6	3	6.2	54.5	15.6
Compound 22r	-17.3	-16.6	-17.9	1.4	32.2	2.5	89.7	23.6
Compound 22s	-17.3	-16.6	-17.9	1.4	32.2	2.5	89.7	23.6
Compound 23r	2.7	-0.3	0.4	16.7	20.6	18.5	67	29.1
Compound 23s	2.7	-0.3	0.4	16.7	20.6	18.5	67	29.1
Compound 24s	-19.3	-16.3	-18.7	-1.7	25	-0.4	86.2	26
Compound 25r	0.6	0	-0.4	13.6	13.4	15.5	63.5	31.6
Compound 25s	0.6	0	-0.4	13.6	13.4	15.5	63.5	31.6
Compound 26r	11.8	10.6	11	16.8	11.6	15.8	74.8	18.7
Compound 26s	11.8	10.6	11	16.8	11.6	15.8	74.8	18.7
Compound 27r	-1.5	-2.8	-2.7	16	6.1	10.9	58.1	23
Compound 27s	-1.5	-2.8	-2.7	16	6.1	10.9	58.1	23
Compound 28r	-1	-0.8	-0.8	12.1	3	8.5	55.6	19.8
Compound 28s	-1	-0.8	-0.8	12.1	3	8.5	55.6	19.8
Compound 29r	5.9	3.2	4.4	16.4	9.6	13.7	57.7	18.2

Supplementary Table 1b: All compound Bayesian model predictions for compounds 1 to 8

Compound Name	5-HT1a	5-HT1b	5-HT1d	5-HT1e	5-HT2a	5-HT2b	5-HT2c	5-HT3	5-HT4	5-HT5a	5-HT6	5-HT7
Donepezil (Cpd 1)	-12.5	-11.1	-13.2	-4.1	-1.4	-0.9	-2.3	-2.2	-10.4	-10.6	-15.6	-6.9
Compound 2	93.1	28.4	-3	-4	53.3	32	41.8	7	-18.5	9.1	-6.4	67.4
Compound 3	81.7	27.4	-6.3	-3.5	48.9	37.2	41.1	12.9	-13.2	7.9	-12.4	65.2
Compound 4	87.7	36.1	-7.7	-4.7	51.4	29.9	47.1	7.4	-20	4.3	-6.2	61.8
Compound 5	88.2	24.6	-6.6	-4.1	50.6	27.2	37.8	6.2	-18	8.6	-7.7	67
Compound 6	76.4	12.5	-17.1	-4.6	52.8	19.3	55	0.6	-15.7	3.7	-9.4	35.1
Compound 7	67.8	2.5	-15.3	-3.6	50	22.8	47.9	5.7	-5.9	5.1	-13.8	34.4
Compound 8	81.8	4.8	-12.4	-3.9	54.7	21.4	49.8	0.2	-14.2	8.4	-9.6	40.7

Compound Name	Alpha-1a	Alpha-1b	Alpha-1d	D1	D2	D3	D4	D5
Donepezil (Cpd 1)	-5.7	-10.7	-8.5	11.3	24.6	29.2	35.3	-21.6
Compound 2	68.3	64	65.1	42.4	91.7	71.3	62.9	4.3
Compound 3	78.6	66.4	74.6	48.4	91.8	80.5	62.9	4.8
Compound 4	70	64.4	69.3	44	89.4	67.1	63.3	3.8
Compound 5	67.6	62.8	64	37.8	86.5	72.4	62.2	1.4
Compound 6	42	25.8	38.7	47.2	97.6	84.3	74	-6.6
Compound 7	51.3	27.8	44.1	46.2	94	93.1	70.2	-7.8
Compound 8	40.2	25.5	34.5	45.6	99.9	88.6	73.6	-6.1

Supplementary Table 1c: High confidence Bayesian predictions for Figure 3b

Compound Name	5-HT1a	5-HT1b	5-HT1d	5-HT1e	5-HT2a	5-HT2b	5-HT2c	5-HT3	5-HT4	5-HT5a	5-HT6	5-HT7
Donepezil (Cpd 1)	-12.5	-11.1	-13.2	-4.1	-1.4	-0.9	-2.3	-2.2	-10.4	-10.6	-15.6	-6.9
Compound 5	88.2	24.6	-6.6	-4.1	50.6	27.2	37.8	6.2	-18	8.6	-7.7	67
Compound 9a	90.5	2.8	-17.2	-1.9	60.2	30.4	54.3	-3.2	-18.6	6.4	-12.4	53.2
Compound 9b	91.4	0.1	-19.6	-2.2	57.6	26.5	51.4	-3.9	-19.2	3.4	-15.5	57.1
Compound 10a	103.5	26.4	-9.3	-3.3	59.4	41.6	47.6	3.9	-17.8	7.5	-9	81.1
Compound 10b	104.4	23.6	-11.7	-3.6	56.8	37.7	44.7	3.2	-18.4	4.5	-12	85
Compound 11a	78.3	0.2	-19.5	-1.8	41.4	23.7	18.7	-8.7	-26.1	-3.6	-21.8	46.5
Compound 11b	79.2	-2.5	-21.9	-2.1	38.8	19.8	15.9	-9.3	-26.8	-6.6	-24.8	50.4

Compound Name	Alpha-1a	Alpha-1b	Alpha-1d	D1	D2	D3	D4	D5
Donepezil (Cpd 1)	-5.7	-10.7	-8.5	6.8	9	22.7	26.3	-3.6
Compound 5	67.6	62.8	64	39.3	75.8	67.4	53.3	34.2
Compound 9a	44.6	27.4	36.8	64.6	101.6	95.8	73.3	35.9
Compound 9b	47	32.6	40.1	62.7	103.4	92.9	69.4	36.8
Compound 10a	74.4	67.3	69.1	60.4	92.6	78.1	63.1	46.3
Compound 10b	76.8	72.4	72.4	58.4	94.4	75.2	59.2	47.3
Compound 11a	35.5	28.9	29.1	17.4	77.9	55.3	70.2	19.9
Compound 11b	37.9	34	32.3	15.4	79.7	52.3	66.2	20.9

Supplementary Table 1d: High confidence Bayesian predictions for compounds 1 and 12 to 29r

Compound Name	5-HT1a	5-HT1b	5-HT1d	5-HT1e	5-HT2a	5-HT2b	5-HT2c	5-HT3	5-HT4	5-HT5a	5-HT6	5-HT7
Donepezil (Cpd 1)	-12.5	-11.1	-13.2	-4.1	-1.4	-0.9	-2.3	-2.2	-10.4	-10.6	-15.6	-6.9
Compound 12	14.1	0.4	-1.4	-3.2	19.6	6.8	8.7	5.1	-25.4	-4.8	-15.4	27
Compound 13	-9.8	-9.5	-7	-4.1	2.4	3.4	-1.5	-3.1	-27.6	-8.5	-22.4	2.1
Compound 14r	-1.9	-14.2	-13.5	-2.4	-8.6	-4	-5.6	-5.7	-14.9	-13.7	-29.4	2.3
Compound 15r	14.7	3	-5.9	-3.5	13.4	10.9	20	-2.1	-13.7	-7.6	-17.9	11.6
Compound 16r	-13.1	-14.7	-14.8	-3	-9.8	-3.9	-7.2	-2	-16.1	-16.2	-29	5.4
Compound 17r	3.5	2.5	-7.2	-4.1	12.1	11.1	18.5	1.6	-14.9	-10	-17.5	14.7
Compound 18s	-12.9	-12.9	-14.2	-2.5	-8.7	-9.6	-6.4	-6.6	-16.8	5	-26.3	5.2
Compound 19s	3.7	4.3	-6.6	-3.5	13.3	5.4	19.3	-3	-15.6	11.1	-14.8	14.6
Compound 20r	-23.8	-18.9	-18.6	-2.8	-16.7	-8	-14.5	-7.9	-25.3	-13.8	-40.1	-5.6
Compound 20s	-23.8	-18.9	-18.6	-2.8	-16.7	-8	-14.5	-7.9	-25.3	-13.8	-40.1	-5.6
Compound 21r	-7.2	-1.7	-11	-3.8	5.3	7	11.2	-4.3	-24	-7.6	-28.7	3.7
Compound 21s	-7.2	-1.7	-11	-3.8	5.3	7	11.2	-4.3	-24	-7.6	-28.7	3.7
Compound 22r	-3.8	-13.3	-13.3	-2.3	-4	-5.7	-6.1	-2.4	-10.4	-1.9	-21.4	3.7
Compound 22s	-3.8	-13.3	-13.3	-2.3	-4	-5.7	-6.1	-2.4	-10.4	-1.9	-21.4	3.7
Compound 23r	12.7	3.9	-5.7	-3.3	17.9	9.2	19.6	1.2	-9.1	4.2	-9.9	13.1
Compound 23s	12.7	3.9	-5.7	-3.3	17.9	9.2	19.6	1.2	-9.1	4.2	-9.9	13.1
Compound 24s	-6.8	-13.4	-15.3	-2.9	-10.3	-8.9	-9.1	-6.4	-11.2	0.9	-22.2	6.3
Compound 25r	9.7	3.8	-7.7	-4	11.6	6	16.6	-2.8	-9.9	7.1	-10.8	15.6
Compound 25s	9.7	3.8	-7.7	-4	11.6	6	16.6	-2.8	-9.9	7.1	-10.8	15.6
Compound 26r	1.7	1	-11.7	-4.8	11.5	13.4	18.2	1.9	-14.7	-9.4	-16.3	13.8
Compound 26s	1.7	1	-11.7	-4.8	11.5	13.4	18.2	1.9	-14.7	-9.4	-16.3	13.8
Compound 27r	-3.8	-0.4	-10.3	-3.7	8.2	8.5	13.9	0.3	-10.9	-4.6	-19.3	8.9
Compound 27s	-3.8	-0.4	-10.3	-3.7	8.2	8.5	13.9	0.3	-10.9	-4.6	-19.3	8.9
Compound 28r	-5.2	-1.1	-9.5	-4.9	8.3	8.7	15.4	-1.2	-15.7	-5.6	-17.7	9.4
Compound 28s	-5.2	-1.1	-9.5	-4.9	8.3	8.7	15.4	-1.2	-15.7	-5.6	-17.7	9.4
Compound 29r	0	0.8	-9.7	-4.6	8.9	10.1	16.2	0.4	-16.9	-10.4	-18.9	11.8

Compound Name	Alpha-1a	Alpha-1b	Alpha-1d	D1	D2	D3	D4	D5
Donepezil (Cpd 1)	-5.7	-10.7	-8.5	6.8	9	22.7	26.3	-3.6
Compound 12	7.8	10.5	9.5	18.7	72.6	20.6	111.1	19.2
Compound 13	-18.8	-15.8	-19.5	6.3	67.7	10.3	112.1	3.1
Compound 14r	-11.7	-9.7	-11.1	-1.3	27.9	-1.8	84	13.3
Compound 15r	8.3	6.7	7.2	14	16.3	14.2	61.3	18.9
Compound 16r	-11.9	-11.4	-11.6	0.4	22.3	-3.2	82.6	12.2
Compound 17r	8	5	6.8	15.6	10.7	12.7	59.9	17.8
Compound 18s	-21.6	-17.8	-20.2	1.5	29.5	0.6	88.8	20.4
Compound 19s	-1.7	-1.5	-1.8	16.8	17.9	16.6	66.1	26
Compound 20r	-24.1	-20.5	-22.8	-7.7	14.6	-9.7	77.2	10
Compound 20s	-24.1	-20.5	-22.8	-7.7	14.6	-9.7	77.2	10
Compound 21r	-4.1	-4.1	-4.4	7.6	3	6.2	54.5	15.6
Compound 21s	-4.1	-4.1	-4.4	7.6	3	6.2	54.5	15.6
Compound 22r	-17.3	-16.6	-17.9	1.4	32.2	2.5	89.7	23.6
Compound 22s	-17.3	-16.6	-17.9	1.4	32.2	2.5	89.7	23.6
Compound 23r	2.7	-0.3	0.4	16.7	20.6	18.5	67	29.1
Compound 23s	2.7	-0.3	0.4	16.7	20.6	18.5	67	29.1
Compound 24s	-19.3	-16.3	-18.7	-1.7	25	-0.4	86.2	26
Compound 25r	0.6	0	-0.4	13.6	13.4	15.5	63.5	31.6
Compound 25s	0.6	0	-0.4	13.6	13.4	15.5	63.5	31.6
Compound 26r	11.8	10.6	11	16.8	11.6	15.8	74.8	18.7
Compound 26s	11.8	10.6	11	16.8	11.6	15.8	74.8	18.7
Compound 27r	-1.5	-2.8	-2.7	16	6.1	10.9	58.1	23
Compound 27s	-1.5	-2.8	-2.7	16	6.1	10.9	58.1	23
Compound 28r	-1	-0.8	-0.8	12.1	3	8.5	55.6	19.8
Compound 28s	-1	-0.8	-0.8	12.1	3	8.5	55.6	19.8
Compound 29r	5.9	3.2	4.4	16.4	9.6	13.7	57.7	18.2

Supplementary Table 2: Experimental radioligand percentage inhibition

Compound Name	5-HT1A	5-HT1B	5-HT1D	5-HT1E	5-HT2A	5-HT2B	5-HT2C	5-HT3	5-HT4	5-HT5A	5-HT6	5-HT7
Donepezil (Cpd 1)	19.1	-3.2	27.3	0.4	29.7	67.6	-2.2	10.7	3.7	17.3	15.1	35.9
Compound 2	92.5	72.3	76.3	6.8	73	95.3	65.6	-3.4	6.9	64.5	-11.3	88.4
Compound 3	93.3	89.9	87.6	16.5	90.3	95.6	91.3	10.4	4.4	61.4	11.3	91.8
Compound 4	92.4	83	93.8	-1.5	38.4	93.9	74.3	-19.5	11.8	65.8	-15.8	5.3
Compound 5	98.3	42.5	79	3.5	77.9	96.6	58.5	7.9	10.7	60	6	84.8
Compound 6	99.2	98.5	98.5	17.2	92.6	95.1	91.9	77.2	12.6	72.2	66.1	90
Compound 7	97.7	98.7	98.6	66.7	97.4	95.4	86	67.8	14.6	77.6	93.8	95.9
Compound 8	98.2	99	97.3	63.6	96.7	96.6	95.9	77.2	20.6	84.9	94.5	93.3
Compound 9a	99.5	94.4	96.9	64.5	98.7	95.3	93.8	99.5	24.3	89.9	89.8	100
Compound 9b	99	96	97.5	65.1	101	85.3	95.5	95.7	11.2	87.8	87.6	101.2
Compound 10a	100.7	84.2	88	-14.7	91.5	95.6	77.2	27.1	9.7	72	14.8	98.2
Compound 10b	97.9	86.1	91.5	-11.4	93.5	85.2	77.1	18.2	-2	72.8	22.8	99.1
Compound 11a	100.9	60.1	68.9	-6.5	95.2	88.4	63	36.6	10.7	49.6	3.6	93.3
Compound 11b	99	45.8	77	-8.6	89.2	83.3	42.6	19.4	13.2	58.8	18.9	98.4
Compound 12	56.5	-2.1	8.7	-2.8	34.5	80	10.5	-0.3	0.2	12.7	6.1	58
Compound 13	55.8	6.6	63	-6.5	42.9	80	0.3	72.4	29.4	12.9	23.4	67.9
Compound 14r	76.4	-14.1	1.2	-4.6	18.8	27.5	28.7	-7	-16.8	-19.1	-19.2	-15.6
Compound 15r	51.7	9.2	20.2	-35.2	47.5	75.6	15.5	24	-2.4	24.4	27.2	28.1
Compound 16r	74.9	1.9	-0.3	-8.9	-1.1	36.1	20.3	-10.9	-0.2	-29	-17.5	-18.9
Compound 17r	27.5	-1.1	22.9	-13.1	41.9	84.6	10.5	20.9	45	-11.6	12.3	45.6
Compound 18s	47.6	36.4	10.2	-4.9	-11.3	74.4	42.6	9.9	8.3	40.5	26.7	10.4
Compound 19s	79	43.5	76.8	-13.8	73.7	70.5	70.5	8.4	10.6	11.2	24.2	74.4
Compound 20r	30.4	14	-5.2	-5	73.3	54	44.2	6.9	3.6	25.8	21.4	1
Compound 20s	21.7	10.8	-6.8	-4.4	-7	58.8	36.4	2.6	10.6	23	16.6	-1.2
Compound 21r	24.1	-5.9	46.9	-9	66	41.2	24.2	-16	5.6	-20.7	8.1	45.3
Compound 21s	55.3	33.7	22.4	-10.6	61.8	23.4	40.8	3.2	8.8	3.2	-10.6	17.7
Compound 22r	89.3	10.7	20.9	4.5	62.8	74.6	48	14.8	7.6	28.9	26.7	-4
Compound 22s	72.9	51.8	18.9	-16.3	60	88.8	47.2	8.3	15	2	17.3	21.7
Compound 23r	57.5	24.7	33.2	-15.8	60.8	88	13.6	-3.7	27.8	6.1	9.2	43.8
Compound 23s	83	32.6	74	-16.4	78	88.3	79.1	8.4	11.7	5.5	29	25.9
Compound 24s	91.3	50.9	17.2	-11.4	52.1	80.8	34	18.6	10.9	14.6	8.9	13.5
Compound 25r	65	30.2	25.9	-15.1	69.1	76.2	3.1	-6.8	10.3	-8.5	11.6	45.8
Compound 25s	80.6	31.6	55.6	-10.8	78	87.4	78.1	12.2	13.4	-9.8	19.4	22.6
Compound 26r	26.5	5.9	23.4	-20	33.6	50.9	2.1	-12.7	20.3	-14.1	10.7	64.2
Compound 26s	22.3	8	33.2	-13.2	33.9	28.1	1.7	-15.2	28.8	-13	7.6	39.2
Compound 27r	13.6	-4.5	35.4	-12.3	37.8	60.5	-14.6	-9.7	26	-16.6	8.5	42.4
Compound 27s	22.4	4.6	45.3	-8.6	39.9	36.1	4.4	3.6	24.4	16.1	10.6	7.6
Compound 28r	49	-0.6	33.8	-11.7	72.1	23.3	1.6	-15	13.1	-9.3	10.9	48.2
Compound 28s	30.3	6.2	37.1	-11.3	27.8	27.9	7.1	-0.4	2.4	-18.8	8.5	23.5
Compound 29r	36.3	-7.6	34.5	-10	53.9	61.2	1.5	-12.9	48.6	-16.4	3	42.1

Compound Name	Alpha-1A	Alpha-1B	Alpha-1D	D1	D2	D3	D4	D5
Donepezil (Cpd 1)	77.2	29.8	90.1	13.3	18.6	55.7	89.2	8.7
Compound 2	102.2	102.5	99.3	49.5	85	94.1	99.6	31.8
Compound 3	102.7	101.5	96.8	91.3	96.2	100.5	91.6	75.1
Compound 4	101.2	104.4	97.3	29.3	66.6	98.1	97.2	21.8
Compound 5	99.1	52.4	100.5	54.5	82.1	94.7	97.3	32.5
Compound 6	102.8	104.1	98.5	45.8	84.6	98.4	97.6	28.7
Compound 7	101	101.3	99	85.1	93.6	102.8	89.6	29.4
Compound 8	99.7	102.1	92.1	81.9	95.5	101.1	99.1	47.2
Compound 9a	100.6	95.9	104.4	99.8	99.3	99.7	100.4	76.6
Compound 9b	102.4	89.6	102.8	89.8	99	99.7	101.1	73.3
Compound 10a	103.6	96.4	105	74	97.5	99.2	100	57.1
Compound 10b	102.1	97.6	104.7	43.6	96.9	98.6	100.2	42.6
Compound 11a	97.1	63.8	92.4	53.9	86.6	98	100.1	31.5
Compound 11b	93.8	63.6	90.3	74.4	93	99.1	100.4	36.7
Compound 12	64.8	-19.8	31.1	-1	2	51	6.9	18
Compound 13	55.5	30.6	23.4	35.1	69	59.7	99.4	8.1
Compound 14r	8.1	24.9	24.3	47.9	-15.6	4.5	0.4	38.5
Compound 15r	16.5	16.7	10.5	29.9	32.1	85.6	72.4	42.4
Compound 16r	-1.3	31	28	63.7	-7.3	2.5	44.1	16.1
Compound 17r	14.9	8	12.1	56.4	0.3	0.2	81.1	23.7
Compound 18s	38.4	21.6	12.5	21.3	13.6	17.5	58.5	3.6
Compound 19s	92.7	63.3	78.9	83	92.8	72.7	103	48.2
Compound 20r	23	-2.2	-8.3	9.8	5.5	27.6	38.9	-6.4
Compound 20s	22.3	-3.7	-0.5	2.5	9.9	11.7	28.1	-7.2
Compound 21r	-2.1	4.2	-11.9	52.4	36.3	26.7	61.8	12.7
Compound 21s	33.1	23.2	-0.2	18.7	20.9	26.9	102.4	5.5
Compound 22r	39.1	25.7	22.1	23	23.7	27.3	96.6	7.1
Compound 22s	24.5	25.1	46.1	43.2	15.1	18.9	72.9	5.6
Compound 23r	25.4	31.7	-0.6	31	63.1	40.4	89.9	-4.8
Compound 23s	84.5	52.1	68.8	72.5	62.7	52	103.6	22.7
Compound 24s	14.1	48.9	18.2	26.3	9.5	15	41.9	-6.2
Compound 25r	18.6	19.4	-5.4	37.6	31.5	0.3	79.6	24.9
Compound 25s	68	42.4	54.4	48.7	36.5	48.2	101.5	6.1
Compound 26r	7.9	10.8	-13.5	44	26.5	50	45.4	17.1
Compound 26s	31.1	44.8	32.5	41.3	15.2	11.7	92.7	7.7
Compound 27r	13.5	5.2	2.6	44.1	37.8	1.3	66.2	10.2
Compound 27s	42.4	43.3	36.5	93.6	60	-8.3	97.3	33.7
Compound 28r	9	4.9	14.3	13.3	16.2	37.7	43	3.5
Compound 28s	25.7	39.1	16.5	44.1	18.8	34.5	94.2	-2.7
Compound 29r	-18.9	25.3	-1.3	33.9	6.1	4.7	54.6	27.1

Supplementary Table 3: Experimental competition binding affinity

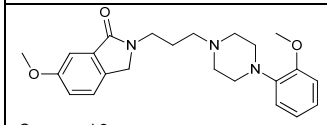
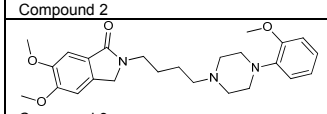
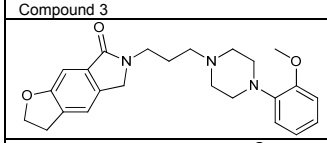
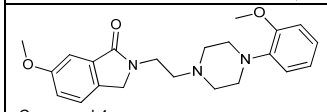
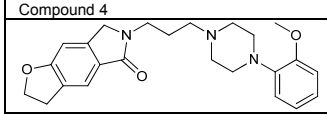
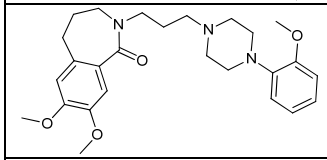
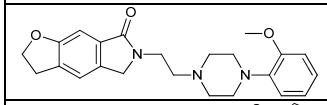
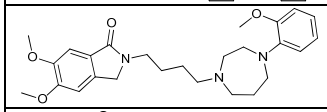
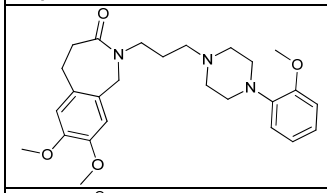
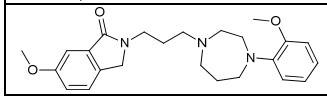
Compound Name	5-HT1A	5-HT1B	5-HT1D	5-HT1E	5-HT2A	5-HT2B	5-HT2C	5-HT3	5-HT4	5-HT5A	5-HT6	5-HT7
Donepezil (cpd 1)	>10,000					6761						
Compound 2	6.5	362	1002		956	19	>10,000			2903		545
Compound 3	23	130	298		270	41	3428			2437		228
Compound 4	3.5	306	139			160	>10,000			2154		
Compound 5	19		829		1004	117	>10,000			2471		732
Compound 6	2.3	33	59		387	12	1450	767		1982	2192	181
Compound 7	62	41	80	3339	65	10	543	1794		2367	417	164
Compound 8	20	27	130	3683	76	1	217	2406		1056	430	75
Compound 9a	1.5(AVE)	73	>10,000	3448	39	1.8	354	99		773	544	21
Compound 9b	1.3(AVE)	73	>10,000	4367	24	0.6	317	677		809	669	20
Compound 10a	0.9(AVE)	217	>10,000		583	40	9253			1053		77
Compound 10b	0.7(AVE)	232	>10,000		755	12	>10,000			1131		31
Compound 11a	4.0(AVE)	834	>10,000		384	192	>10,000					150
Compound 11b	1.2		2112		645	121				3082		26
Compound 12	8430					1454						2824
Compound 13	1488					846.7		3350				4037
Compound 14r	7324											
Compound 15r	2883					599.7						
Compound 16r	2298											
Compound 17r						788						
Compound 18s						6416						
Compound 19s	0.6		590		817	1445	6736					467.5
Compound 20r					2663	8808						
Compound 20s						7641						
Compound 21r					3584							
Compound 21s	10,000.0(AVE)				3545							
Compound 22r	384				2066	2358						
Compound 22s	1388	7765			2718	1096						
Compound 23r	1848				2671	1846						
Compound 23s	545		1121		1275	551	3386					
Compound 24s	371	4827			1945	1654						
Compound 25r	1469				3779	2692						
Compound 25s	174		1976		1399	658	3763					
Compound 26r						3169						>10,000
Compound 26s												
Compound 27r						2561						
Compound 27s												
Compound 28r					1482							
Compound 28s												
Compound 29r					>10,000	1326						

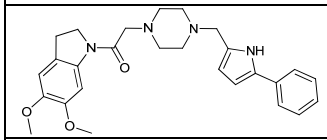
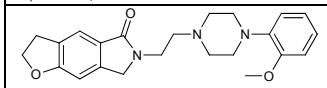
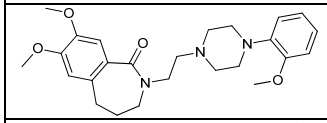
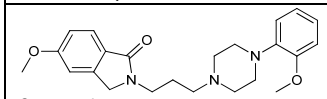
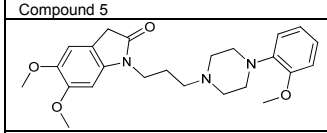
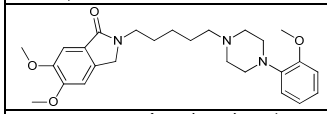
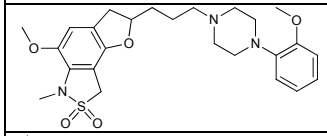
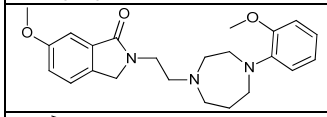
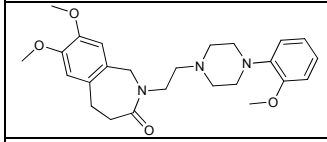
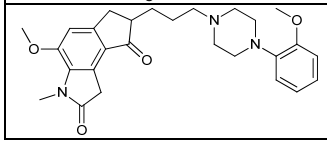
AVE = Average value from at least two experiments, and curation from experts

Compound Name	Alpha-1A	Alpha-1B	Alpha-1D	D1	D2	D3	D4	D5
Donepezil (cpd 1)	1463		1918			>10,000	614	
Compound 2	64.9	322.8	81.1	6220	1,503.0(AVE)	389.0(AVE)	8.4(AVE)	8285
Compound 3	0.9	19.3	4.4	531	156	11	436	1886
Compound 4	15.9	38.7	12.4(AVE)		1651	208	191	
Compound 5	59.9	608.1	56	2734	1367	152	115	
Compound 6	35.8	152.5	72.2(AVE)		1112	56	264	
Compound 7	75.5	91	49.6	1406	585	32	925	
Compound 8	257.5	3577	212.8	1,131.3(AVE)	871.5(AVE)	79.5(AVE)	20.5(AVE)	>10,000
Compound 9a	117.2	649	78.4	511	14	1	13	2385
Compound 9b	216.8	656.7	209.6	500	5.8	1	9	3577
Compound 10a	11.1	76.6	14.2	1618	25	4	6	6865
Compound 10b	7.2	125.3	37.6		9.3(AVE)	0.7	3.1(AVE)	
Compound 11a	555.4	1375	467.3	1,658.0(AVE)	805.5(AVE)	41.5(AVE)	14.5(AVE)	9,359.0(AVE)
Compound 11b	866.6	2542	979.6	1257	209.4(AVE)	3	6.5(AVE)	>10,000
Compound 12	2010					>10,000		
Compound 13	7695				>10,000	6895	8.9	
Compound 14r								
Compound 15r						>10,000	814.0(AVE)	
Compound 16r				>10,000				
Compound 17r				>10,000			1931	
Compound 18s							5526	
Compound 19s	2720	7211.1	2307	1353	342	2827	132	
Compound 20r								
Compound 20s								
Compound 21r				>10,000			2406	
Compound 21s				>10,000	>10,000	8,359.0(AVE)	182.0(AVE)	>10,000
Compound 22r							536	
Compound 22s							2858	
Compound 23r					>10,000		1666	
Compound 23s	9037	6637.4	4181	2041	1892	6645	146	
Compound 24s								
Compound 25r							2486	
Compound 25s	8350		6448	8,366.0(AVE)	10,000.0(AVE)	8,285.5(AVE)	3,361.7(AVE)	8,525.5(AVE)
Compound 26r						>10,000		
Compound 26s							434.7	
Compound 27r							3618	
Compound 27s				5852	>10,000		90.0(AVE)	
Compound 28r								
Compound 28s							502.9	
Compound 29r							4947	

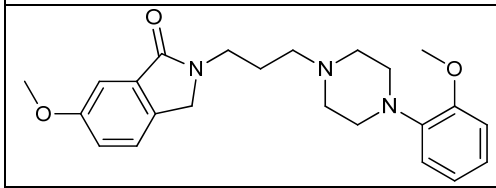
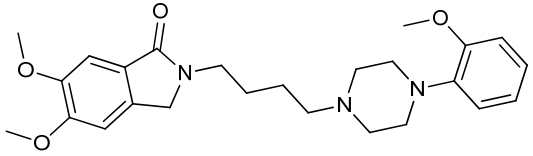
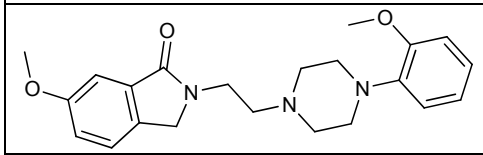
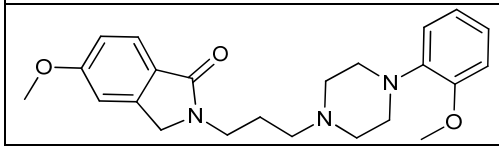
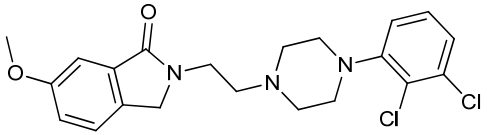
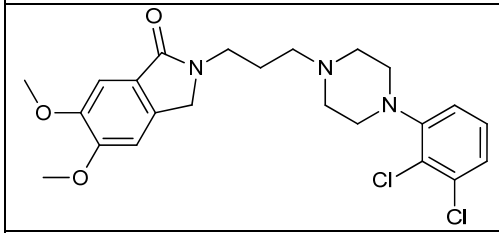
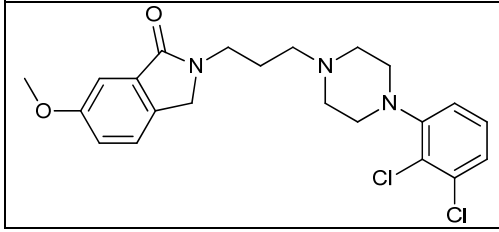
AVE = Average value from at least two experiments, and curation from experts

Supplementary Table 4: Optimisation results for D2/CNS objectives

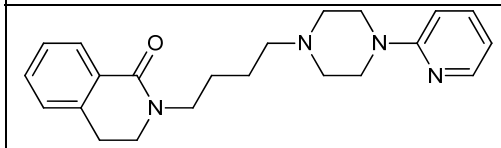
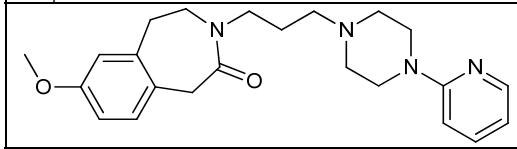
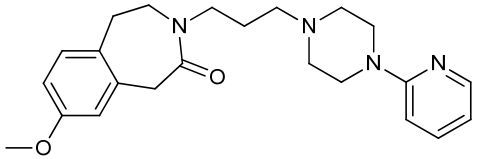
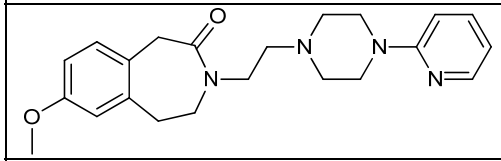
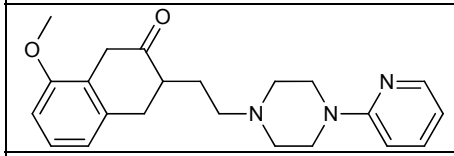
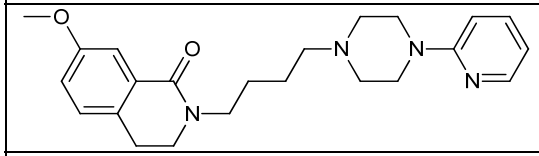
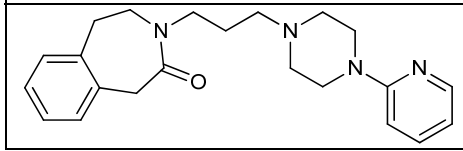
Structure	Desirability Synthesis	Complexity Score	Fragment Score	Pareto Front	ADME Score	Dopamine D2	Distance (D2 to 100, ADME to 50)	Top 5 predictions	
 Compound 2	0.794	1.24	1.94	2	50	92	8	Serotonin 1a (5-HT1a) receptor Dopamine D2 receptor Serotonin 7 (5-HT7) receptor Alpha-1a adrenergic receptor Dopamine D3 receptor	93 82 70 69 66
 Compound 3	0.792	1.26	1.90	1	54	92	9	Serotonin 1a (5-HT1a) receptor Dopamine D2 receptor Alpha-1a adrenergic receptor Dopamine D3 receptor Alpha-1d adrenergic receptor	82 80 79 78 74
	0.742	1.76	1.50	3	48	90	10	Serotonin 1a (5-HT1a) receptor Dopamine D2 receptor Alpha-1a adrenergic receptor Alpha-1b adrenergic receptor Alpha-1d adrenergic receptor	95 78 71 66 66
 Compound 4	0.793	1.24	1.91	2	51	89	11	Serotonin 1a (5-HT1a) receptor Dopamine D2 receptor Alpha-1a adrenergic receptor Alpha-1d adrenergic receptor Dopamine D3 receptor	88 80 70 69 65
	0.743	1.76	1.50	3	48	89	11	Serotonin 1a (5-HT1a) receptor Dopamine D2 receptor Alpha-1a adrenergic receptor Alpha-1b adrenergic receptor Alpha-1d adrenergic receptor	94 78 71 67 66
	0.791	1.26	1.90	2	52	88	12	Alpha-1a adrenergic receptor Alpha-1d adrenergic receptor Serotonin 1a (5-HT1a) receptor Dopamine D2 receptor Alpha-1b adrenergic receptor	84 80 79 77 70
	0.741	1.75	1.46	3	50	88	12	Serotonin 1a (5-HT1a) receptor Dopamine D2 receptor Alpha-1a adrenergic receptor Alpha-1d adrenergic receptor Alpha-1b adrenergic receptor	89 77 72 70 67
	0.786	1.26	1.80	4	48	88	13	Serotonin 1a (5-HT1a) receptor Dopamine D2 receptor Alpha-1a adrenergic receptor Dopamine D3 receptor Serotonin 7 (5-HT7) receptor	73 73 72 69 68
	0.787	1.26	1.82	1	56	89	13	Dopamine D3 receptor Alpha-1a adrenergic receptor Dopamine D2 receptor Alpha-1d adrenergic receptor Serotonin 1a (5-HT1a) receptor	80 79 79 75 73
	0.789	1.25	1.84	2	52	87	13	Serotonin 1a (5-HT1a) receptor Dopamine D2 receptor Serotonin 7 (5-HT7) receptor Alpha-1a adrenergic receptor Alpha-1d adrenergic receptor	84 74 71 62 58

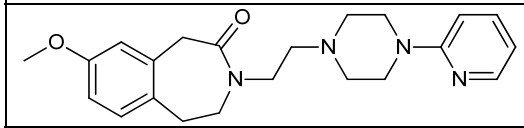
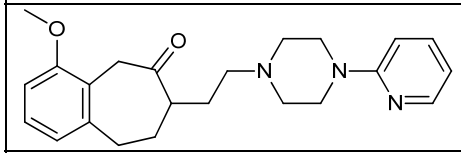
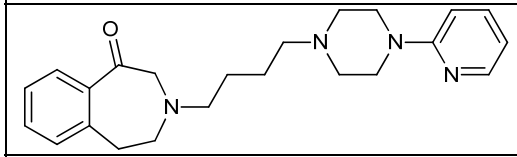
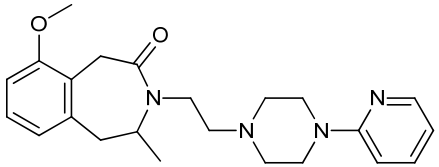
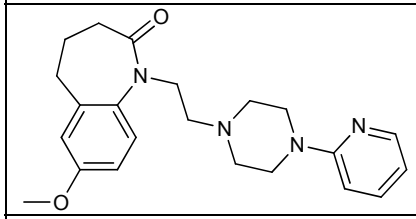
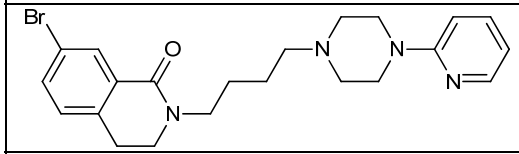
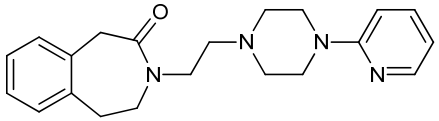
Structure	Desirability Synthesis	Complexity Score	Fragment Score	Pareto Front	ADME Score	Dopamine D2	Distance (D2 to 100, ADME to 50)	Top 5 predictions	
	0.755	1.27	1.23	4	43	89	13	Dopamine D2 receptor Dopamine D4 receptor Cytochrome P450 1A2 Dopamine D3 receptor Muscarinic acetylcholine receptor M4	80 66 26 24 19
	0.741	1.75	1.46	3	50	87	13	Serotonin 1a (5-HT1a) receptor Dopamine D2 receptor Alpha-1a adrenergic receptor Alpha-1d adrenergic receptor Alpha-1b adrenergic receptor	89 76 72 70 67
	0.790	1.26	1.88	2	54	87	14	Alpha-1a adrenergic receptor Alpha-1d adrenergic receptor Dopamine D2 receptor Serotonin 1a (5-HT1a) receptor Alpha-1b adrenergic receptor	86 84 77 74 70
 Compound 5	0.795	1.24	1.96	3	50	86	14	Serotonin 1a (5-HT1a) receptor Dopamine D2 receptor Serotonin 7 (5-HT7) receptor Alpha-1a adrenergic receptor Dopamine D3 receptor	89 76 69 68 67
	0.782	1.25	1.72	2	55	87	14	Serotonin 1a (5-HT1a) receptor Alpha-1a adrenergic receptor Dopamine D3 receptor Dopamine D2 receptor Alpha-1d adrenergic receptor	79 79 77 76 75
	0.792	1.26	1.91	4	41	90	14	Alpha-1a adrenergic receptor Serotonin 1a (5-HT1a) receptor Dopamine D2 receptor Alpha-1d adrenergic receptor Dopamine D3 receptor	80 80 79 77 75
	0.682	2.47	1.08	5	44	87	14	Dopamine D2 receptor Serotonin 1a (5-HT1a) receptor Alpha-1a adrenergic receptor Alpha-1b adrenergic receptor Alpha-1d adrenergic receptor	76 73 67 67 66
	0.788	1.24	1.81	4	50	85	15	Serotonin 1a (5-HT1a) receptor Dopamine D2 receptor Serotonin 7 (5-HT7) receptor Alpha-1a adrenergic receptor Alpha-1d adrenergic receptor	80 73 68 64 62
	0.785	1.26	1.79	1	57	87	15	Alpha-1a adrenergic receptor Alpha-1d adrenergic receptor Dopamine D3 receptor Dopamine D2 receptor Alpha-1b adrenergic receptor	80 79 78 78 72
	0.688	2.47	1.21	5	48	85	15	Serotonin 1a (5-HT1a) receptor Dopamine D2 receptor Alpha-1a adrenergic receptor Serotonin 7 (5-HT7) receptor Alpha-1b adrenergic receptor	80 73 69 68 66

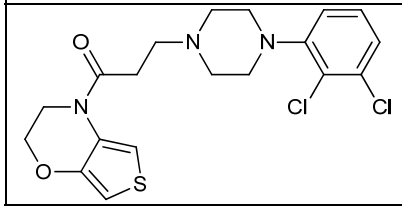
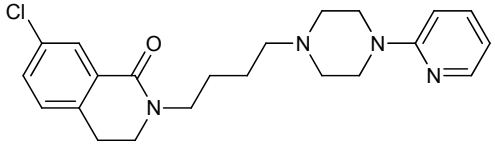
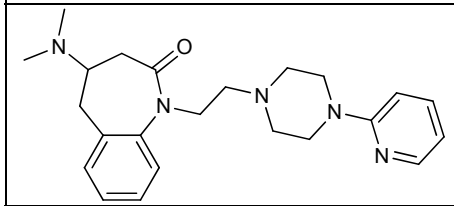
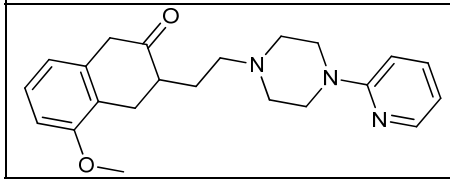
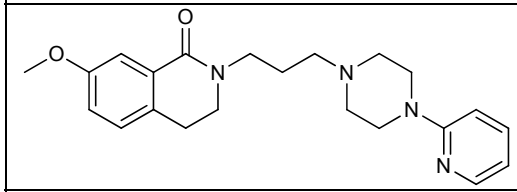
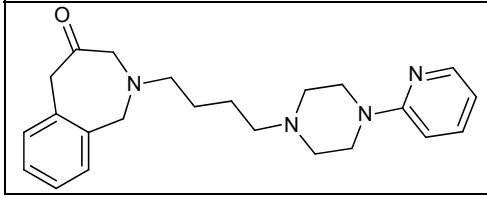
Supplementary Table 5: Predictions of synthesized isoindoles

Structure	Desirability Synthesis	Complexity Score	Fragment Score	Name	Pareto Front	ADME Score	Dopamine D2	Distance (D2 to 100, ADME to 50)	Top 5 predictions
	0.794	1.24	1.94	2	2	50	92	8	Serotonin 1a (5-HT1a) receptor 93 Dopamine D2 receptor 82 Serotonin 7 (5-HT7) receptor 70 Alpha-1a adrenergic receptor 69 Dopamine D3 receptor 66
	0.792	1.26	1.90	3	1	54	92	9	Serotonin 1a (5-HT1a) receptor 82 Dopamine D2 receptor 80 Alpha-1a adrenergic receptor 79 Dopamine D3 receptor 78 Alpha-1d adrenergic receptor 74
	0.793	1.24	1.91	4	2	51	89	11	Serotonin 1a (5-HT1a) receptor 88 Dopamine D2 receptor 80 Alpha-1a adrenergic receptor 70 Alpha-1d adrenergic receptor 69 Dopamine D3 receptor 65
	0.795	1.24	1.96	5	3	50	86	14	Serotonin 1a (5-HT1a) receptor 89 Dopamine D2 receptor 76 Serotonin 7 (5-HT7) receptor 69 Alpha-1a adrenergic receptor 68 Dopamine D3 receptor 67
	0.784	1.24	1.73	6	1	28	98	22	Dopamine D2 receptor 88 Dopamine D3 receptor 82 Serotonin 1a (5-HT1a) receptor 77 Dopamine D4 receptor 67 Serotonin 2c (5-HT2c) receptor 55
	0.782	1.25	1.72	7	2	27	94	24	Dopamine D3 receptor 88 Dopamine D2 receptor 84 Serotonin 1a (5-HT1a) receptor 68 Dopamine D4 receptor 61 Serotonin 2a (5-HT2a) receptor 52
	0.785	1.24	1.76	8	1	23	100	27	Dopamine D2 receptor 90 Dopamine D3 receptor 84 Serotonin 1a (5-HT1a) receptor 82 Dopamine D4 receptor 65 Serotonin 2a (5-HT2a) receptor 56

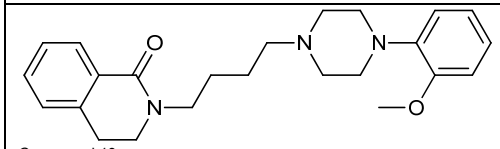
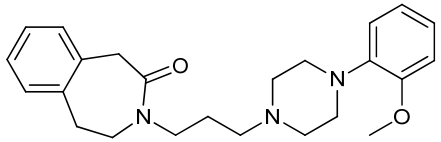
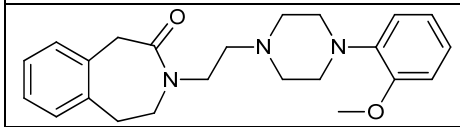
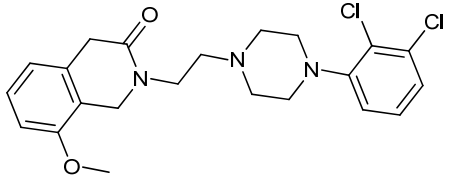
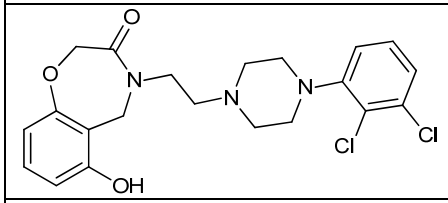
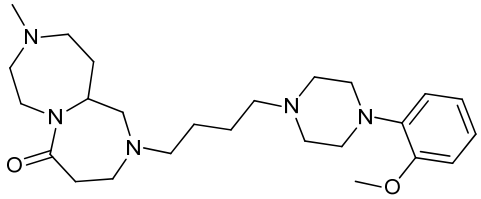
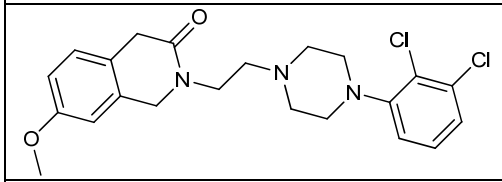
Supplementary Table 6: Optimisation results for 5-HT1A/D2/D3/D4/α1 selectivity/CNS objectives

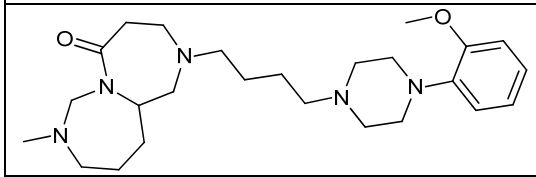
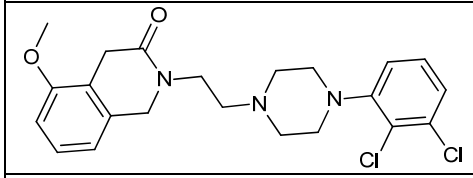
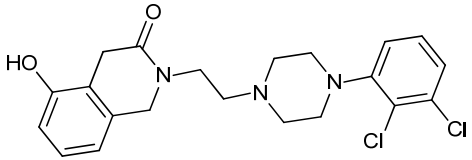
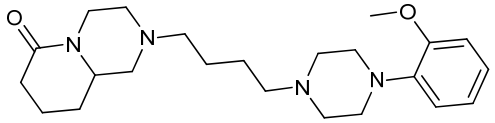
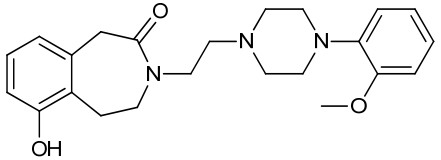
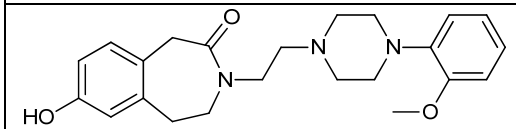
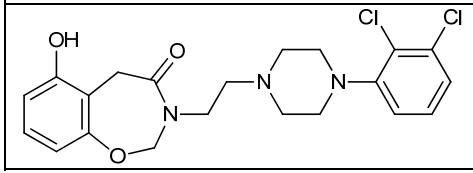
Structure	Desirability Synthesis	Complexity Score	Fragment Score	Pareto Front	ADME Score (IV CNS)	Distance (Objectives to 150, ADME to 100)	Rank	Objectives	Main Side Effect
 Compound 11a	0.784	1.23	1.73	1	48	179	1	5HT1a = 78 D2 = 78 D3 = 55 D4 = 70	Alpha-1a = 61
	0.783	1.24	1.72	1	46	180	2	5HT1a = 66 D2 = 73 D3 = 68 D4 = 76	Alpha-1a = 64
	0.783	1.24	1.73	1	46	181	3	5HT1a = 67 D2 = 72 D3 = 65 D4 = 75	Alpha-1a = 64
	0.781	1.24	1.69	1	46	182	4	5HT1a = 61 D2 = 73 D3 = 66 D4 = 78	Alpha-1a = 64
	0.735	1.93	1.52	1	49	183	5	5HT1a = 66 D2 = 68 D3 = 60 D4 = 77	Alpha-1a = 59
	0.793	1.24	1.91	1	30	183	6	5HT1a = 78 D2 = 78 D3 = 59 D4 = 76	Alpha-1a = 66
	0.770	1.23	1.47	1	49	183	7	5HT1a = 62 D2 = 72 D3 = 63 D4 = 75	Alpha-1a = 63

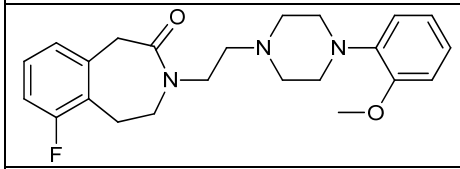
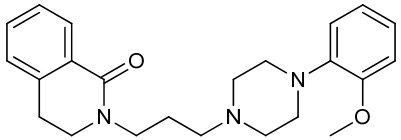
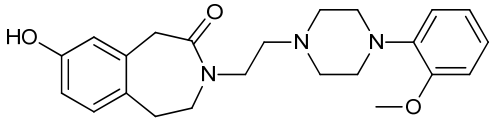
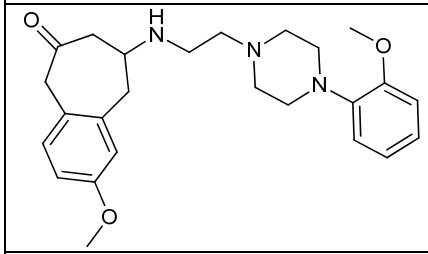
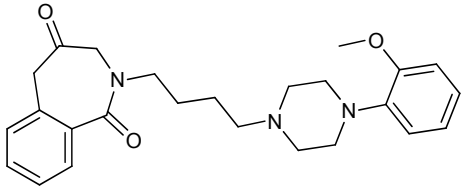
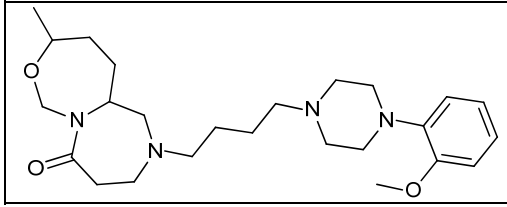
Structure	Desirability Synthesis	Complexity Score	Fragment Score	Pareto Front	ADME Score (IV CNS)	Distance (Objectives to 150, ADME to 100)	Rank	Objectives	Main Side Effect
	0.782	1.24	1.70	1	46	183	8	5HT1a = 62 D2 = 72 D3 = 63 D4 = 78	Alpha-1a = 64
	0.731	1.93	1.45	1	48	184	9	5HT1a = 70 D2 = 68 D3 = 60 D4 = 73	Alpha-1a = 61
	0.782	1.24	1.71	1	52	184	10	5HT1a = 62 D2 = 66 D3 = 63 D4 = 72	Alpha-1a = 56
	0.722	1.94	1.29	1	45	185	11	5HT1a = 74 D2 = 69 D3 = 54 D4 = 78	Alpha-1a = 65
	0.790	1.24	1.85	1	53	185	12	5HT1a = 58 D2 = 68 D3 = 64 D4 = 73	Alpha-1a = 61
	0.777	1.24	1.62	2	38	185	13	5HT1a = 62 D2 = 73 D3 = 62 D4 = 74	Alpha-1a = 58
	0.767	1.23	1.43	1	48	186	14	5HT1a = 57 D2 = 72 D3 = 62 D4 = 78	Alpha-1a = 64

Structure	Desirability Synthesis	Complexity Score	Fragment Score	Pareto Front	ADME Score (IV CNS)	Distance (Objectives to 150, ADME to 100)	Rank	Objectives	Main Side Effect
	0.750	1.23	1.10	1	35	186	15	5HT1a = 60 D2 = 71 D3 = 67 D4 = 76	Alpha-1a = 59
	0.787	1.24	1.79	1	44	186	16	5HT1a = 64 D2 = 76 D3 = 54 D4 = 77	Alpha-1a = 65
	0.727	1.94	1.38	1	56	187	17	5HT1a = 62 D2 = 68 D3 = 57 D4 = 74	Alpha-1a = 64
	0.734	1.93	1.51	1	49	187	18	5HT1a = 67 D2 = 66 D3 = 55 D4 = 74	Alpha-1a = 60
	0.791	1.24	1.87	1	51	187	19	5HT1a = 72 D2 = 71 D3 = 49 D4 = 72	Alpha-1a = 64
	0.763	1.24	1.36	1	56	187	20	5HT1a = 55 D2 = 64 D3 = 63 D4 = 71	Alpha-1a = 54

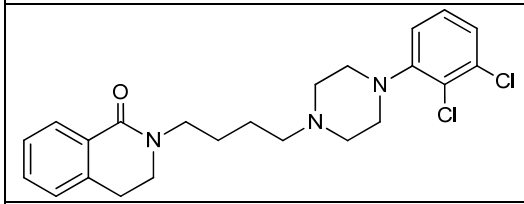
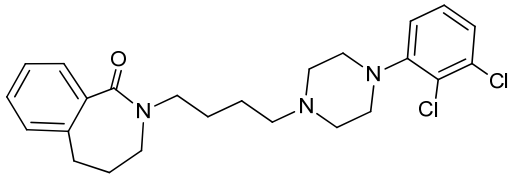
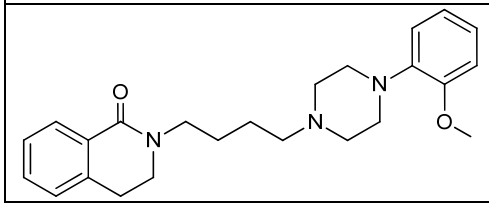
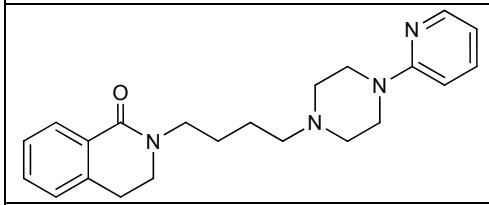
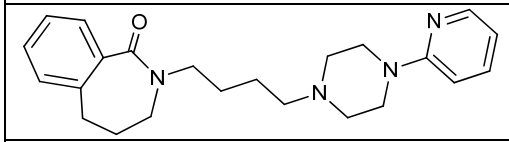
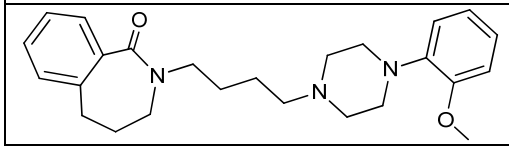
Supplementary Table 7: Optimisation results for 5-HT1A/D2/D3/D4/CNS objectives

Structure	Desirability Synthesis	Complexity Score	Fragment Score	Pareto Front	ADME Score (IV CNS)	Distance (Objectives to 150, ADME to 100)	Rank	Objectives	Main Side Effect
 Compound 10a	0.800	1.24	2.04	1	35	174	1	5HT1a = 103 D2 = 93 D3 = 78 D4 = 63	Alpha-1a = 88
	0.786	1.24	1.79	1	42	174	2	5HT1a = 87 D2 = 87 D3 = 86 D4 = 68	Alpha-1a = 91
	0.785	1.24	1.76	1	46	174	3	5HT1a = 83 D2 = 86 D3 = 85 D4 = 71	Alpha-1a = 91
	0.762	1.24	1.33	1	20	175	4	5HT1a = 80 D2 = 91 D3 = 97 D4 = 74	Alpha-1a = 85
	0.757	1.24	1.25	1	33	175	5	5HT1a = 79 D2 = 91 D3 = 84 D4 = 63	Alpha-1a = 76
	0.744	1.95	1.72	1	24	175	6	5HT1a = 82 D2 = 81 D3 = 93 D4 = 77	Alpha-1a = 83
	0.774	1.24	1.57	1	20	175	7	5HT1a = 67 D2 = 89 D3 = 102 D4 = 74	Alpha-1a = 75

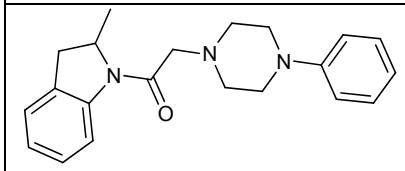
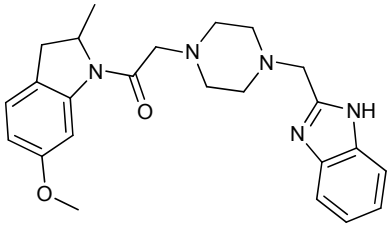
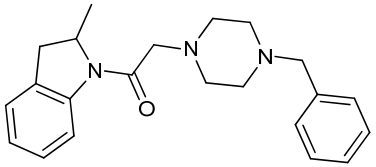
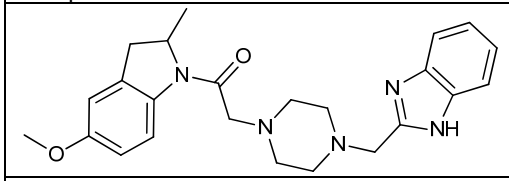
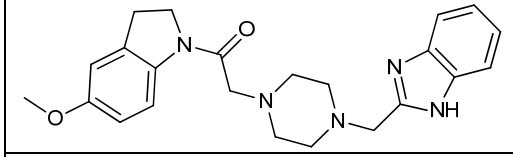
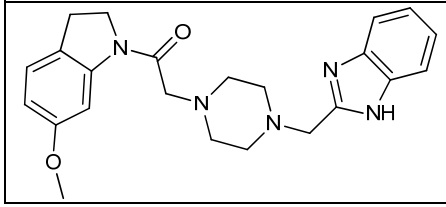
Structure	Desirability Synthesis	Complexity Score	Fragment Score	Pareto Front	ADME Score (IV CNS)	Distance (Objectives to 150, ADME to 100)	Rank	Objectives	Main Side Effect
	0.724	1.95	1.35	1	22	176	8	5HT1a = 84 D2 = 84 D3 = 93 D4 = 71	Alpha-1a = 81
	0.761	1.24	1.32	1	20	176	9	5HT1a = 80 D2 = 91 D3 = 97 D4 = 72	Alpha-1a = 86
	0.750	1.24	1.11	1	26	177	10	5HT1a = 73 D2 = 88 D3 = 91 D4 = 64	Alpha-1a = 72
	0.756	1.94	1.91	1	17	177	11	5HT1a = 79 D2 = 84 D3 = 96 D4 = 76	Alpha-1a = 82
	0.779	1.24	1.65	1	36	178	12	5HT1a = 96 D2 = 88 D3 = 78 D4 = 62	Alpha-1a = 88
	0.788	1.24	1.82	1	36	178	13	5HT1a = 80 D2 = 86 D3 = 85 D4 = 65	Alpha-1a = 84
	0.744	1.24	1.02	2	29	178	14	5HT1a = 79 D2 = 90 D3 = 83 D4 = 61	Alpha-1a = 76

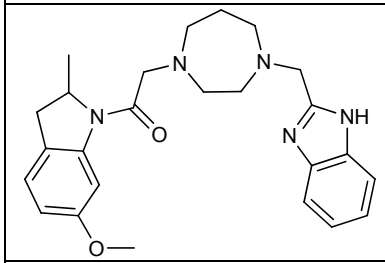
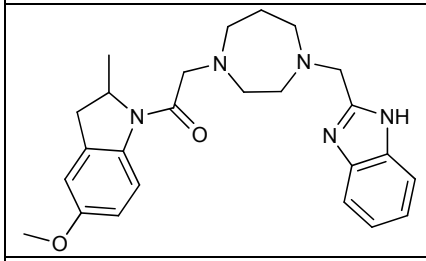
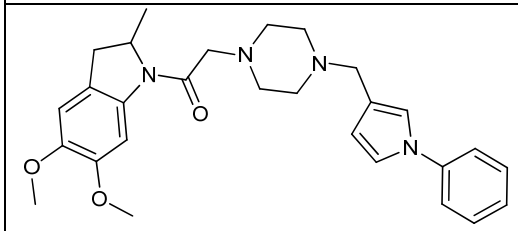
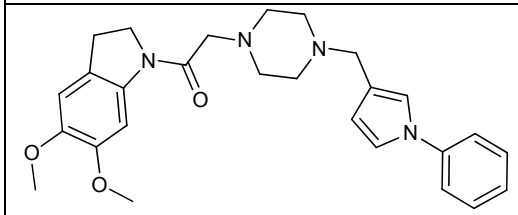
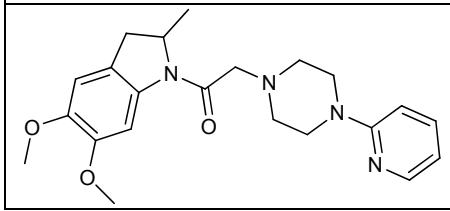
Structure	Desirability Synthesis	Complexity Score	Fragment Score	Pareto Front	ADME Score (IV CNS)	Distance (Objectives to 150, ADME to 100)	Rank	Objectives	Main Side Effect
	0.774	1.24	1.56	1	44	179	15	5HT1a = 98 D2 = 87 D3 = 82 D4 = 58	Alpha-1a = 94
	0.797	1.24	1.99	1	48	179	16	5HT1a = 97 D2 = 85 D3 = 68 D4 = 60	Alpha-1a = 87
	0.788	1.24	1.82	1	36	179	17	5HT1a = 82 D2 = 86 D3 = 83 D4 = 64	Alpha-1a = 86
	0.739	1.95	1.62	1	11	179	18	5HT1a = 81 D2 = 81 D3 = 90 D4 = 75	Alpha-1a = 73
	0.784	1.25	1.76	1	24	179	19	5HT1a = 97 D2 = 89 D3 = 79 D4 = 60	Alpha-1a = 82
	0.719	2.36	1.65	1	19	180	20	5HT1a = 81 D2 = 81 D3 = 89 D4 = 74	Alpha-1a = 82

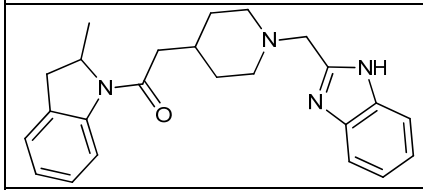
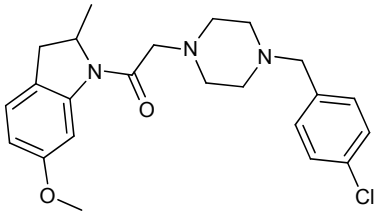
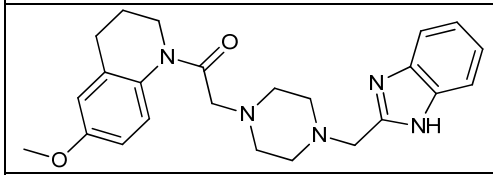
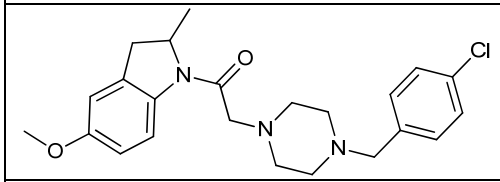
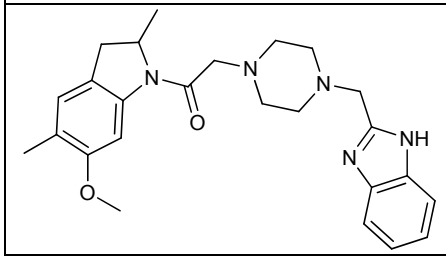
Supplementary Table 8: Predictions of synthesized benzolactams

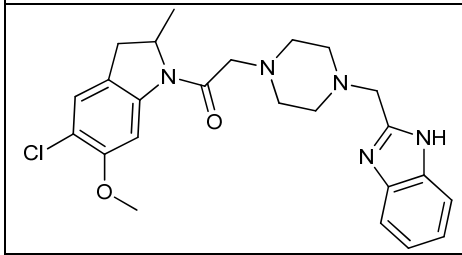
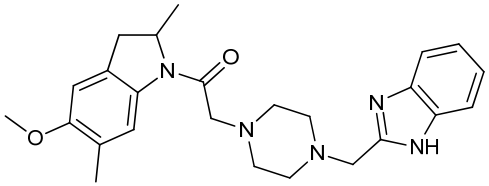
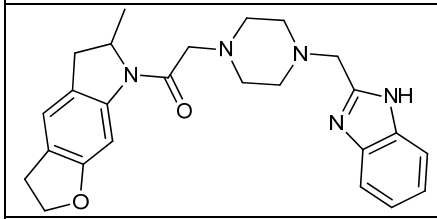
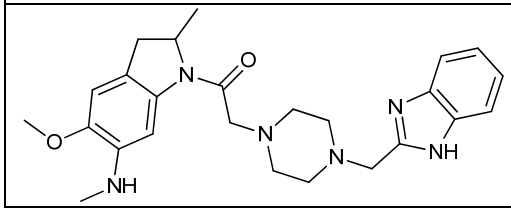
Structure	Desirability Synthesis	Complexity Score	Fragment Score	Name	Pareto Front	ADME Score (IV CNS)	Distance (Objectives to 150, ADME to 100)	Rank	Objectives	Main Side Effect
	0.782	1.24	1.72	9a	1	7	171	1	5HT1a = 91 D2 = 102 D3 = 96 D4 = 73	Alpha-1a = 77
	0.781	1.25	1.70	9b	1	7	173	2	5HT1a = 91 D2 = 103 D3 = 93 D4 = 69	Alpha-1a = 78
	0.800	1.24	2.04	10a	1	35	174	3	5HT1a = 103 D2 = 93 D3 = 78 D4 = 63	Alpha-1a = 88
	0.784	1.23	1.73	11a	1	48	179	4	5HT1a = 78 D2 = 78 D3 = 55 D4 = 70	Alpha-1a = 61
	0.782	1.24	1.71	10b	1	47	182	5	5HT1a = 79 D2 = 80 D3 = 52 D4 = 66	Alpha-1a = 61
	0.798	1.25	2.01	11b	1	17	184	6	5HT1a = 104 D2 = 94 D3 = 75 D4 = 59	Alpha-1a = 89

Supplementary Table 9: Optimisation results for D4/CNS objectives

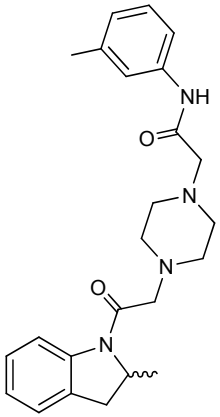
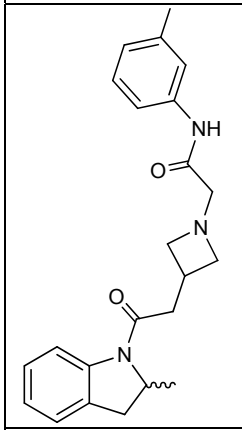
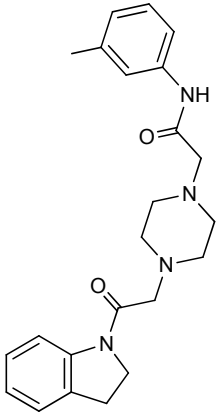
Structure	Desirability Synthesis	Complexity Score	Fragment Score	Pareto Front	ADME Score	Dopamine D4	Distance (D4 to 150, ADME to 50)	Top 5 predictions
 Compound 12	0.742	1.92	1.64	1	49	120	31	Dopamine D4 receptor 112 Dopamine D2 receptor 73 Tripeptidyl aminopeptidase 28 Serotonin 7 (5-HT7) receptor 27 Voltage-gated T-type calcium channel alpha-1G subunit 23
	0.700	2.46	1.40	2	41	119	32	Dopamine D4 receptor 112 Dopamine D2 receptor 31 Tripeptidyl aminopeptidase 23 Serotonin 3b (5-HT3b) receptor 15 Serotonin 3a (5-HT3a) receptor 15
 Compound 13	0.748	1.92	1.75	1	33	122	32	Dopamine D4 receptor 113 Dopamine D2 receptor 68 Sigma opioid receptor 29 Tripeptidyl aminopeptidase 26 Muscarinic acetylcholine receptor M3 23
	0.706	2.46	1.51	3	40	119	32	Dopamine D4 receptor 113 Tripeptidyl aminopeptidase 32 Dopamine D2 receptor 31 Serotonin 3b (5-HT3b) receptor 17 Serotonin 3a (5-HT3a) receptor 17
	0.750	1.76	1.63	2	48	112	39	Dopamine D4 receptor 106 Dopamine D2 receptor 31 Cytochrome P450 1A2 24 Serotonin 3b (5-HT3b) receptor 20 Serotonin 3a (5-HT3a) receptor 19
	0.747	1.76	1.59	2	48	111	40	Dopamine D4 receptor 105 Dopamine D2 receptor 30 Cytochrome P450 1A2 21 Serotonin 3b (5-HT3b) receptor 18 Serotonin 3a (5-HT3a) receptor 18

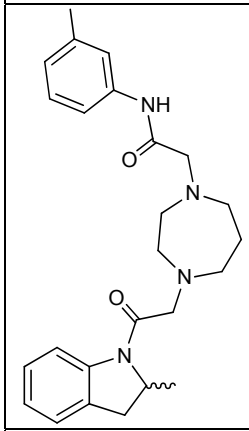
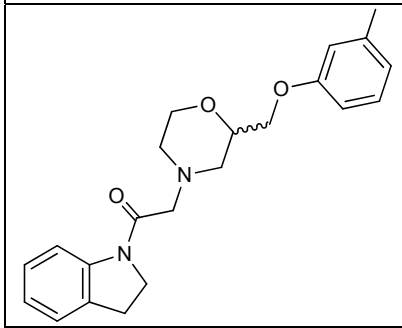
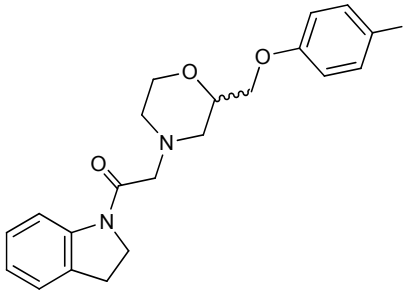
Structure	Desirability Synthesis	Complexity Score	Fragment Score	Pareto Front	ADME Score	Dopamine D4	Distance (D4 to 150, ADME to 50)	Top 5 predictions	
	0.698	2.46	1.38	4	36	112	41	Dopamine D4 receptor Dopamine D2 receptor Tripeptidyl aminopeptidase Serotonin 7 (5-HT7) receptor Alpha-2c adrenergic receptor	105 29 22 13 12
	0.704	2.46	1.49	5	35	112	41	Dopamine D4 receptor Tripeptidyl aminopeptidase Dopamine D2 receptor Serotonin 3b (5-HT3b) receptor Serotonin 3a (5-HT3a) receptor	105 31 28 13 13
	0.715	1.97	1.19	4	29	115	41	Dopamine D4 receptor Dopamine D3 receptor Dopamine D2 receptor Cytochrome P450 3A4 Serotonin 7 (5-HT7) receptor	106 46 40 15 11
	0.762	1.27	1.36	3	41	109	42	Dopamine D4 receptor Dopamine D3 receptor Dopamine D2 receptor Cytochrome P450 1A2 Cytochrome P450 3A4	101 53 40 27 22
	0.734	1.94	1.52	1	56	108	42	Dopamine D4 receptor Dopamine D2 receptor Dopamine D3 receptor Alpha-2a adrenergic receptor Serotonin 1a (5-HT1a) receptor	99 62 26 15 14

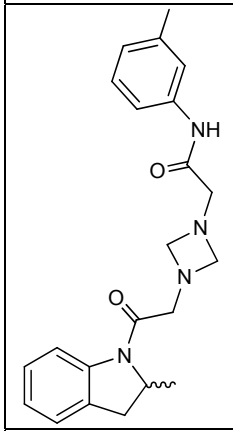
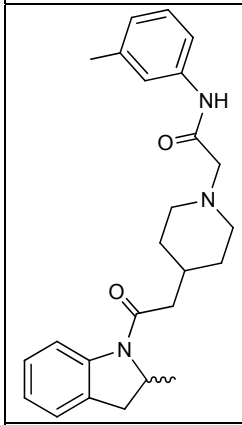
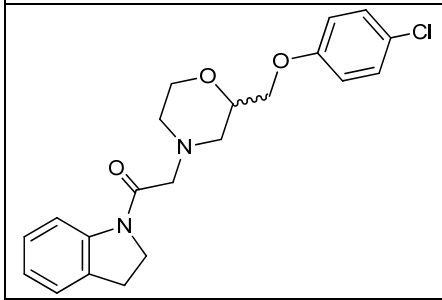
Structure	Desirability Synthesis	Complexity Score	Fragment Score	Pareto Front	ADME Score	Dopamine D4	Distance (D4 to 150, ADME to 50)	Top 5 predictions
	0.694	2.45	1.28	2	19	121	42	Dopamine D4 receptor 119 Dopamine D2 receptor 43 Tripeptidyl aminopeptidase 14 Serotonin 3b (5-HT3b) receptor 14 Serotonin 3a (5-HT3a) receptor 14
	0.745	1.94	1.72	5	26	113	44	Dopamine D4 receptor 103 Dopamine D2 receptor 58 Voltage-gated T-type calcium channel alpha-1G subunit 27 Sigma opioid receptor 18 Dopamine D3 receptor 14
	0.748	1.76	1.60	3	47	106	45	Dopamine D4 receptor 99 Dopamine D2 receptor 25 Serotonin 3b (5-HT3b) receptor 19 Serotonin 3a (5-HT3a) receptor 19 Tripeptidyl aminopeptidase 18
	0.752	1.94	1.85	6	25	113	45	Dopamine D4 receptor 103 Dopamine D2 receptor 57 Voltage-gated T-type calcium channel alpha-1G subunit 26 Sigma opioid receptor 17 3-beta-hydroxysteroid-delta(8),delta(7)-isomerase 17
	0.690	2.46	1.23	6	34	108	45	Dopamine D4 receptor 102 Dopamine D2 receptor 23 Serotonin 3b (5-HT3b) receptor 22 Serotonin 3a (5-HT3a) receptor 22 Tripeptidyl aminopeptidase 18

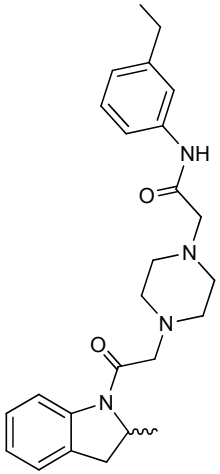
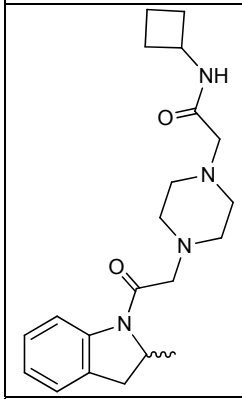
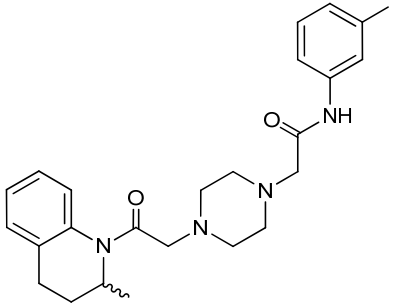
Structure	Desirability Synthesis	Complexity Score	Fragment Score	Pareto Front	ADME Score	Dopamine D4	Distance (D4 to 150, ADME to 50)	Top 5 predictions	
	0.694	2.46	1.30	6	29	110	45	Dopamine D4 receptor Dopamine D2 receptor Serotonin 3b (5-HT3b) receptor Serotonin 3a (5-HT3a) receptor Tripeptidyl aminopeptidase	102 25 24 24 17
	0.692	2.46	1.26	7	33	108	46	Dopamine D4 receptor Dopamine D2 receptor Serotonin 3b (5-HT3b) receptor Serotonin 3a (5-HT3a) receptor Tripeptidyl aminopeptidase	101 23 21 21 18
	0.657	2.80	0.946	4	38	106	46	Dopamine D4 receptor Dopamine D2 receptor Serotonin 3b (5-HT3b) receptor Serotonin 3a (5-HT3a) receptor Tripeptidyl aminopeptidase	98 28 22 22 20
	0.685	2.47	1.13	7	28	110	46	Dopamine D4 receptor Dopamine D2 receptor Serotonin 3b (5-HT3b) receptor Serotonin 3a (5-HT3a) receptor Tripeptidyl aminopeptidase	103 26 24 24 18

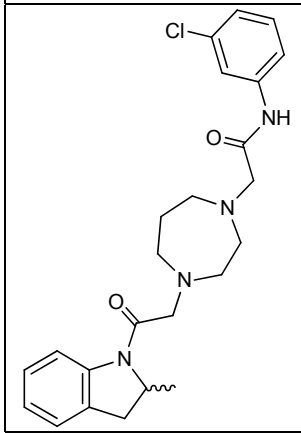
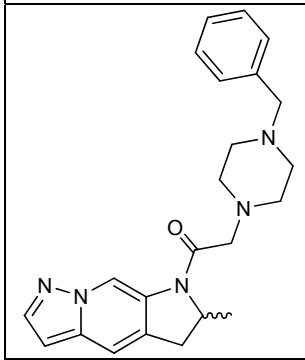
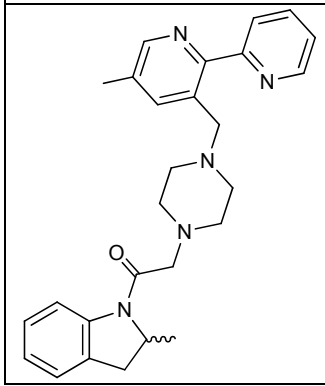
Supplementary Table 10: Optimisation results for novelty/D4 selectivity/CNS objectives

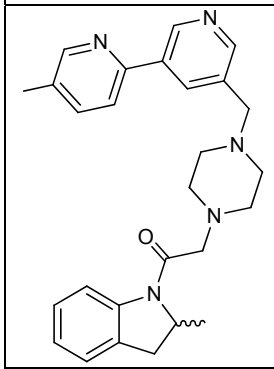
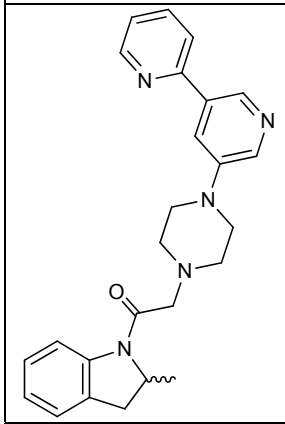
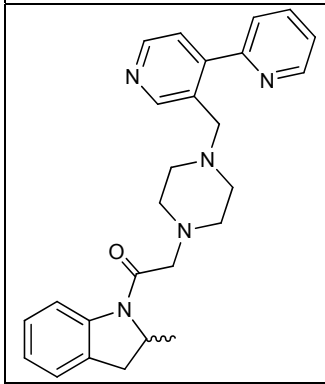
Structure	Desirability Synthesis	Complexity Score	Fragment Score	Pareto Front	ADME Score	Dopamine D4	Distance (ADME = 75; D4=150)	Top 5 predictions	
	0.740	1.94	1.64	1	40	114	74	Dopamine D4 receptor Dopamine D2 receptor Palmitoyl-CoA oxidase Tripeptidyl aminopeptidase Neuropeptide Y receptor type 5	114 29 28 23 23
	0.727	1.93	1.37	1	36	93	76	Dopamine D4 receptor Tripeptidyl aminopeptidase Dopamine D2 receptor Neuropeptide Y receptor type 5 Ecdysone receptor	93 23 22 20 13
	0.786	1.24	1.78	3	42	92	77	Dopamine D4 receptor Palmitoyl-CoA oxidase Neuropeptide Y receptor type 5 Vasopressin V2 receptor Dopamine D2 receptor	92 30 25 20 18

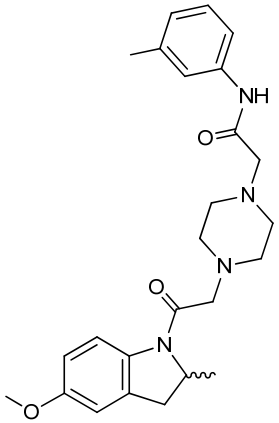
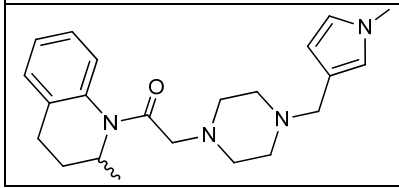
Structure	Desirability Synthesis	Complexity Score	Fragment Score	Pareto Front	ADME Score	Dopamine D4	Distance (ADME = 75; D4=150)	Top 5 predictions	
	0.738	1.95	1.60	1	37	108	78	Dopamine D4 receptor Dopamine D2 receptor Palmitoyl-CoA oxidase Neuropeptide Y receptor type 5 Tripeptidyl aminopeptidase	108 27 23 23 23
	0.729	1.93	1.41	4	37	92	79	Dopamine D4 receptor Dopamine D2 receptor Dopamine D5 receptor Vasopressin V1a receptor Neuronal acetylcholine receptor protein alpha-10 subunit	92 29 20 11 10
	0.731	1.93	1.46	5	36	93	80	Dopamine D4 receptor Dopamine D2 receptor Vasopressin V1a receptor Dopamine D5 receptor Hormone sensitive lipase	93 31 19 17 13

Structure	Desirability Synthesis	Complexity Score	Fragment Score	Pareto Front	ADME Score	Dopamine D4	Distance (ADME = 75; D4=150)	Top 5 predictions	
	0.727	1.93	1.38	1	40	92	81	Dopamine D4 receptor Tripeptidyl aminopeptidase Dopamine D2 receptor Neuropeptide Y receptor type 5 Ecdysone receptor	92 25 23 20 15
	0.734	1.94	1.52	2	22	113	82	Dopamine D4 receptor Neuropeptide Y receptor type 5 Dopamine D2 receptor Tripeptidyl aminopeptidase Palmitoyl-CoA oxidase	113 33 29 22 14
	0.732	1.93	1.48	4	31	94	82	Dopamine D4 receptor Dopamine D2 receptor Dopamine D5 receptor Vasopressin V1a receptor Hormone sensitive lipase	95 31 21 15 14

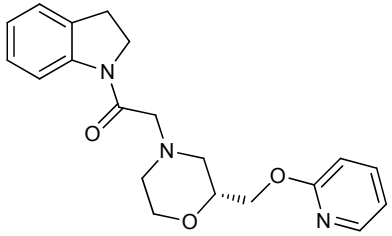
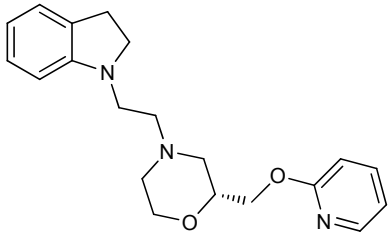
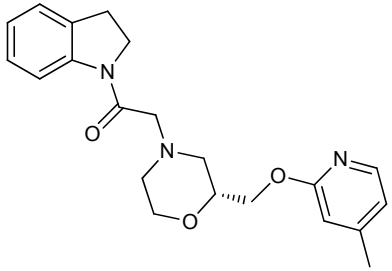
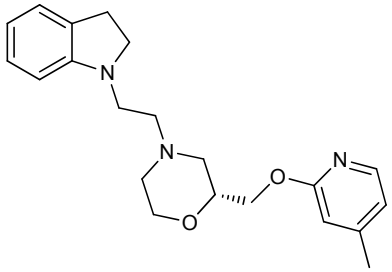
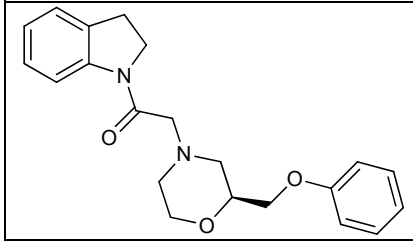
Structure	Desirability Synthesis	Complexity Score	Fragment Score	Pareto Front	ADME Score	Dopamine D4	Distance (ADME = 75; D4=150)	Top 5 predictions	
	0.740	1.95	1.63	1	36	100	82	Dopamine D4 receptor Tripeptidyl aminopeptidase Dopamine D2 receptor Palmitoyl-CoA oxidase Tryptase beta-2	101 26 24 19 18
	0.733	1.93	1.48	6	42	96	83	Dopamine D4 receptor Dopamine D2 receptor Tripeptidyl aminopeptidase Neuropeptide Y receptor type 5 Muscarinic acetylcholine receptor M3	97 47 30 17 16
	0.740	1.95	1.63	1	39	98	84	Dopamine D4 receptor Palmitoyl-CoA oxidase Neuropeptide Y receptor type 5 Dopamine D2 receptor Tripeptidyl aminopeptidase	98 28 27 20 17

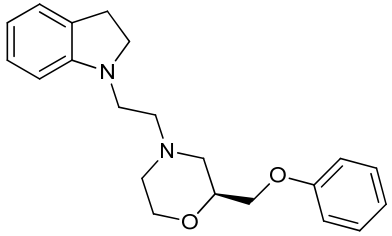
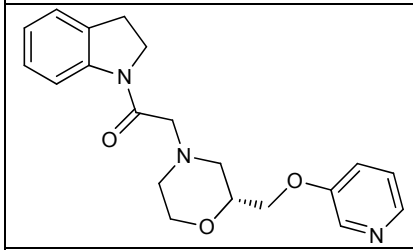
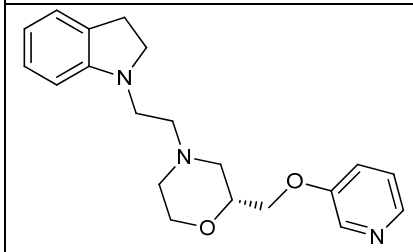
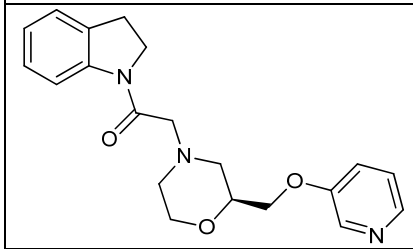
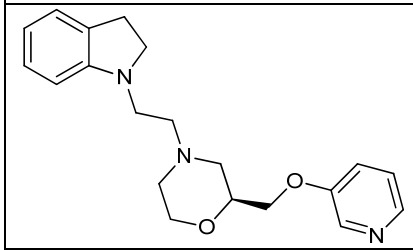
Structure	Desirability Synthesis	Complexity Score	Fragment Score	Pareto Front	ADME Score	Dopamine D4	Distance (ADME = 75; D4=150)	Top 5 predictions	
	0.742	1.95	1.68	2	33	98	85	Dopamine D4 receptor Dopamine D2 receptor Tripeptidyl aminopeptidase Palmitoyl-CoA oxidase Neuropeptide Y receptor type 5	98 29 23 22 21
	0.673	2.45	0.905	4	49	96	85	Dopamine D4 receptor Dopamine D2 receptor Dopamine D3 receptor Sigma opioid receptor Muscarinic acetylcholine receptor M3	97 56 26 21 19
	0.720	1.96	1.28	2	50	107	86	Dopamine D4 receptor Dopamine D2 receptor Tripeptidyl aminopeptidase TGF-beta receptor type I TGF-beta receptor type II	108 56 25 13 12

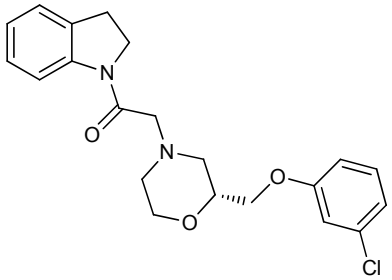
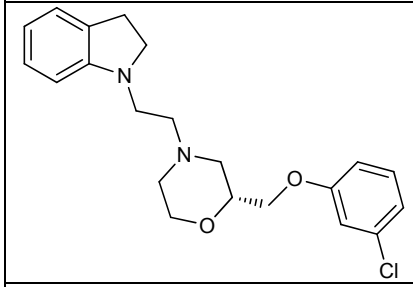
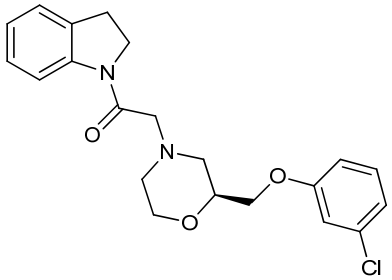
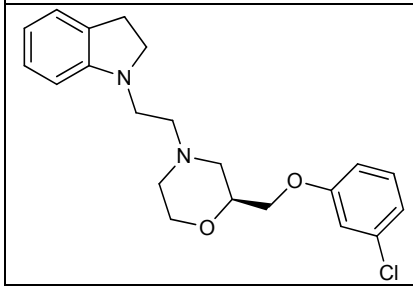
Structure	Desirability Synthesis	Complexity Score	Fragment Score	Pareto Front	ADME Score	Dopamine D4	Distance (ADME = 75; D4=150)	Top 5 predictions	
	0.716	1.96	1.20	1	50	110	86	Dopamine D4 receptor Dopamine D2 receptor Tripeptidyl aminopeptidase Dopamine D3 receptor Muscarinic acetylcholine receptor M3	111 58 24 7 7
	0.719	1.95	1.24	2	52	103	86	Dopamine D4 receptor Dopamine D2 receptor Tripeptidyl aminopeptidase Dopamine D3 receptor Serotonin 7 (5-HT7) receptor	104 58 24 11 10
	0.718	1.95	1.24	1	55	100	86	Dopamine D4 receptor Dopamine D2 receptor Tripeptidyl aminopeptidase TGF-beta receptor type II Muscarinic acetylcholine receptor M3	101 54 24 6 6

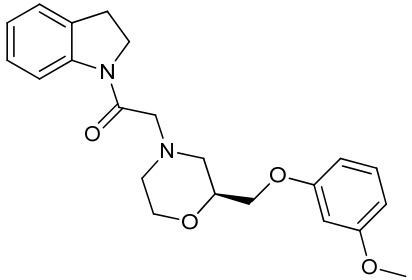
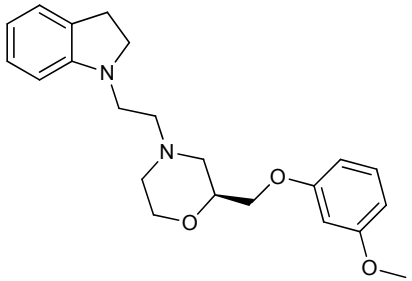
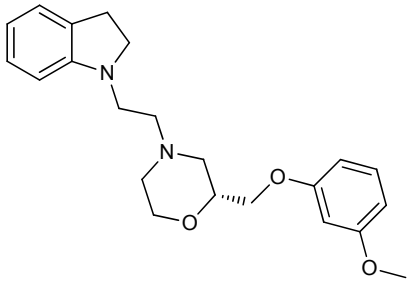
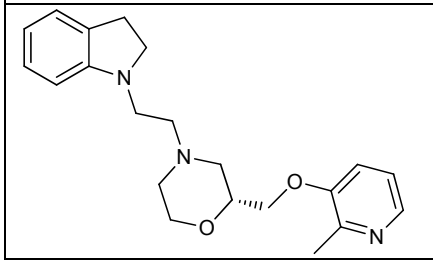
Structure	Desirability Synthesis	Complexity Score	Fragment Score	Pareto Front	ADME Score	Dopamine D4	Distance (ADME = 75; D4=150)	Top 5 predictions	
	0.743	1.95	1.70	1	41	96	86	Dopamine D4 receptor Neuropeptide Y receptor type 5 Palmitoyl-CoA oxidase Tyrosine-protein kinase receptor FLT3 Stem cell growth factor receptor	96 30 30 16 16
	0.705	1.93	0.967	5	50	91	86	Dopamine D4 receptor Dopamine D2 receptor Tripeptidyl aminopeptidase Dopamine D3 receptor Muscarinic acetylcholine receptor M1	91 52 24 19 18

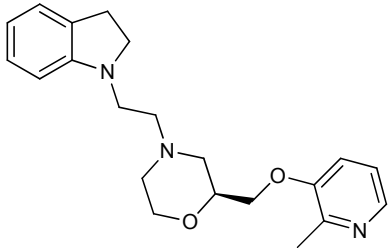
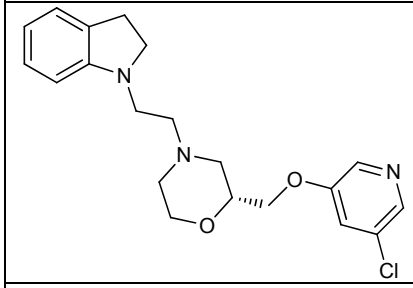
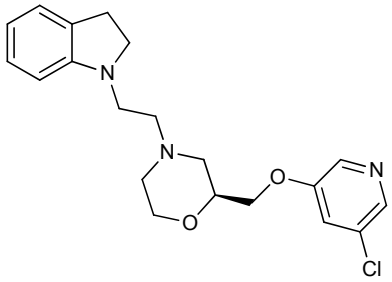
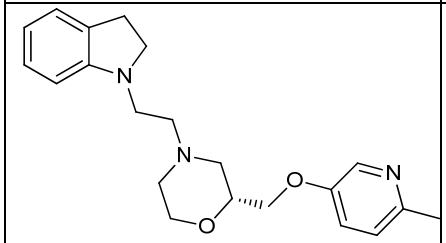
Supplementary Table 11: Predictions of synthesized morpholinos

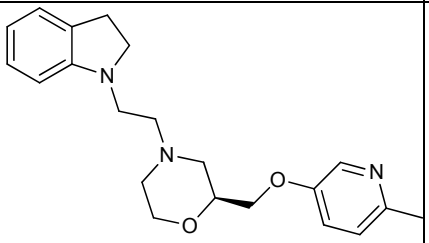
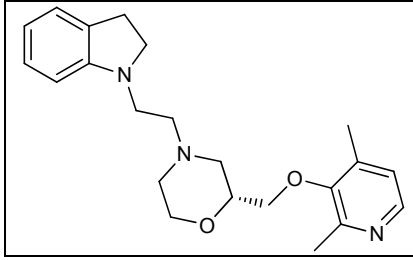
Structure	Desirability Synthesis	Complexity Score	Fragment Score	Name	Pareto Front	ADME Score	Dopamine D4	Distance (ADME = 75; D4=150)	Top 5 predictions		Rank
	0.712	1.92	1.09	14r	1	57	84	76	Dopamine D4 receptor Dopamine D2 receptor Dopamine D5 receptor Vasopressin V2 receptor Tripeptidyl aminopeptidase	84 28 14 11 10	2
	0.710	1.92	1.05	15r	2	54	61	95	Dopamine D4 receptor Dopamine D5 receptor Serotonin 2c (5-HT2c) receptor Dopamine D2 receptor Dopamine D1 receptor	61 19 18 16 15	12
	0.714	1.93	1.13	16r	1	59	83	74	Dopamine D4 receptor Dopamine D2 receptor Dopamine D5 receptor Vasopressin V2 receptor Vasopressin V1a receptor	83 22 13 11 10	1
	0.713	1.92	1.10	17r	1	56	60	95	Dopamine D4 receptor Dopamine D5 receptor Dopamine D1 receptor Serotonin 2c (5-HT2c) receptor Serotonin 7 (5-HT7) receptor	60 18 17 17 15	11
	0.727	1.92	1.38	18s	1	34	89	81	Dopamine D4 receptor Dopamine D2 receptor Dopamine D5 receptor Neuronal acetylcholine receptor protein alpha-10 subunit Vasopressin V1a receptor	89 28 21 14 13	5

Structure	Desirability Synthesis	Complexity Score	Fragment Score	Name	Pareto Front	ADME Score	Dopamine D4	Distance (ADME = 75; D4=150)	Top 5 predictions		Rank
	0.727	1.92	1.36	19s	2	26	66	100	Dopamine D4 receptor Dopamine D5 receptor Neuronal acetylcholine receptor protein alpha-10 subunit Dopamine D1 receptor Serotonin 2c (5-HT2c) receptor	66 26 18 18 18	18
	0.724	1.92	1.31	20r	2	57	77	80	Dopamine D4 receptor Cytochrome P450 1A2 Dopamine D2 receptor Cytochrome P450 3A4 Cytochrome P450 11B1	77 16 15 15 12	4
	0.723	1.92	1.29	21r	3	54	55	103	Dopamine D4 receptor Cytochrome P450 3A4 Dopamine D5 receptor Cytochrome P450 11B1 Cytochrome P450 1A2	55 23 16 15 12	21
	0.724	1.92	1.31	20s	2	57	77	80	Dopamine D4 receptor Cytochrome P450 1A2 Dopamine D2 receptor Cytochrome P450 3A4 Cytochrome P450 11B1	77 16 15 15 12	3
	0.723	1.92	1.29	21s	3	54	55	103	Dopamine D4 receptor Cytochrome P450 3A4 Dopamine D5 receptor Cytochrome P450 11B1 Cytochrome P450 1A2	55 23 16 15 12	22

Structure	Desirability Synthesis	Complexity Score	Fragment Score	Name	Pareto Front	ADME Score	Dopamine D4	Distance (ADME = 75; D4=150)	Top 5 predictions		Rank
	0.730	1.93	1.43	22r	1	29	90	83	Dopamine D4 receptor Dopamine D2 receptor Dopamine D5 receptor Neuronal acetylcholine receptor protein alpha-10 subunit Estradiol 17-beta-dehydrogenase 3	90 32 24 16 15	10
	0.730	1.92	1.42	23r	2	14	67	107	Dopamine D4 receptor Dopamine D5 receptor Neuronal acetylcholine receptor protein alpha-10 subunit Dopamine D2 receptor Dopamine D3 receptor	67 29 21 20 19	23
	0.730	1.93	1.43	22s	1	29	90	83	Dopamine D4 receptor Dopamine D2 receptor Dopamine D5 receptor Neuronal acetylcholine receptor protein alpha-10 subunit Estradiol 17-beta-dehydrogenase 3	90 32 24 16 15	9
	0.730	1.92	1.42	23s	2	14	67	107	Dopamine D4 receptor Dopamine D5 receptor Neuronal acetylcholine receptor protein alpha-10 subunit Dopamine D2 receptor Dopamine D3 receptor	67 29 21 20 19	24

Structure	Desirability Synthesis	Complexity Score	Fragment Score	Name	Pareto Front	ADME Score	Dopamine D4	Distance (ADME = 75; D4=150)	Top 5 predictions		Rank
	0.734	1.93	1.52	24s	1	33	86	81	Dopamine D4 receptor Dopamine D5 receptor Dopamine D2 receptor Neuronal acetylcholine receptor protein alpha-10 subunit Melatonin receptor 1B	86 26 25 19 17	8
	0.734	1.93	1.51	25s	2	27	64	102	Dopamine D4 receptor Dopamine D5 receptor Neuronal acetylcholine receptor protein alpha-10 subunit Serotonin 7 (5-HT7) receptor Dopamine D3 receptor	64 32 24 17 16	19
	0.734	1.93	1.51	25r	2	27	64	102	Dopamine D4 receptor Dopamine D5 receptor Neuronal acetylcholine receptor protein alpha-10 subunit Serotonin 7 (5-HT7) receptor Dopamine D3 receptor	64 32 24 17 16	20
	0.718	1.92	1.20	26r	1	56	75	81	Dopamine D4 receptor Dopamine D5 receptor Dopamine D1 receptor Dopamine D3 receptor Serotonin 2c (5-HT2c) receptor	75 19 18 17 16	6

Structure	Desirability Synthesis	Complexity Score	Fragment Score	Name	Pareto Front	ADME Score	Dopamine D4	Distance (ADME = 75; D4=150)	Top 5 predictions		Rank
	0.718	1.92	1.20	26s	1	56	75	81	Dopamine D4 receptor Dopamine D5 receptor Dopamine D1 receptor Dopamine D3 receptor Serotonin 2c (5-HT2c) receptor	75 19 18 17 16	7
	0.717	1.92	1.18	27r	3	52	58	99	Dopamine D4 receptor Dopamine D5 receptor Neuronal acetylcholine receptor protein alpha-4 subunit Dopamine D1 receptor Cytochrome P450 3A4	58 23 18 17 16	16
	0.717	1.92	1.18	27s	3	52	58	99	Dopamine D4 receptor Dopamine D5 receptor Neuronal acetylcholine receptor protein alpha-4 subunit Dopamine D1 receptor Cytochrome P450 3A4	58 23 18 17 16	15
	0.718	1.92	1.20	28r	1	56	56	98	Dopamine D4 receptor Dopamine D5 receptor Cytochrome P450 3A4 Dopamine D1 receptor Serotonin 2c (5-HT2c) receptor	56 20 15 13 13	14

Structure	Desirability Synthesis	Complexity Score	Fragment Score	Name	Pareto Front	ADME Score	Dopamine D4	Distance (ADME = 75; D4=150)	Top 5 predictions		Rank
	0.718	1.92	1.20	28s	1	56	56	98	Dopamine D4 receptor Dopamine D5 receptor Cytochrome P450 3A4 Dopamine D1 receptor Serotonin 2c (5-HT2c) receptor	56 20 15 13 13	13
	0.704	1.93	0.946	29r	1	47	58	99	Dopamine D4 receptor Dopamine D5 receptor Dopamine D1 receptor Serotonin 2c (5-HT2c) receptor Dopamine D3 receptor	58 19 18 14 14	17

Supplementary Table 12: Bayesian model statistics

Table 12a is the general statistics for the high confidence models for the GPCR receptors using ChEMBL data and high confidence score.
Table 12b represents specific validation using MCC to define a cut-off score for good/bad predictions for the GPCR receptors using ChEMBL data and high confidence score.
Table 12c is the results of the pipeline pilot internal validation on the dopamine models using all data and a pre release of ChEMBL.

Supplementary Table 12a: Chembl (release 1) high confidence model statistics

Target	Set Of compounds	Active	Inactive	AUC	Recall 5%	SLR	SLR Limit	BEDROC
Alpha-1a adrenergic receptor	TestSet	682	68507	0.971	86.95	4431	6875	0.783
	TrainingSet	410	63780	0.995	98.54	2276	4095	0.923
	WholeSet	1092	132287	0.996	98.63	6885	11740	0.940
Alpha-1b adrenergic receptor	TestSet	501	68688	0.970	86.43	3159	5045	0.779
	TrainingSet	273	63917	0.996	99.27	1422	2721	0.930
	WholeSet	774	132605	0.996	98.97	4673	8314	0.941
Alpha-1d adrenergic receptor	TestSet	623	68566	0.968	83.95	4076	6278	0.753
	TrainingSet	342	63848	0.996	99.12	1802	3413	0.943
	WholeSet	965	132414	0.997	99.48	5947	10371	0.949
Alpha-2a adrenergic receptor	TestSet	239	68950	0.851	42.68	1870	2399	0.400
	TrainingSet	135	64055	0.999	100.00	579	1340	0.979
	WholeSet	374	133005	0.998	100.00	1971	4007	0.973
Alpha-2b adrenergic receptor	TestSet	107	69082	0.773	33.64	883	1068	0.311
	TrainingSet	103	64087	0.999	99.03	420	1020	0.979
	WholeSet	210	133169	0.998	99.52	1062	2244	0.972
Alpha-2c adrenergic receptor	TestSet	154	69035	0.710	17.53	1396	1541	0.184
	TrainingSet	105	64085	0.999	99.05	422	1040	0.981
	WholeSet	259	133120	0.998	99.23	1251	2770	0.980
Dopamine D1 receptor	TestSet	383	68806	0.981	91.38	2420	3853	0.805
	TrainingSet	366	63824	0.998	99.45	1900	3653	0.962
	WholeSet	749	132630	0.998	99.60	4442	8044	0.960
Dopamine D2 receptor	TestSet	1959	67230	0.972	73.66	14331	19800	0.740
	TrainingSet	2281	61909	0.994	93.29	15751	22890	0.926
	WholeSet	4240	129139	0.994	94.10	32072	45688	0.918
Dopamine D3 receptor	TestSet	693	68496	0.973	81.82	4736	6986	0.703
	TrainingSet	628	63562	0.995	98.41	3630	6282	0.927
	WholeSet	1321	132058	0.995	98.71	8576	14208	0.935
Dopamine D4 receptor	TestSet	734	68455	0.980	86.38	4800	7401	0.785
	TrainingSet	689	63501	0.995	99.13	4094	6894	0.929
	WholeSet	1423	131956	0.996	99.23	9357	15307	0.941
Dopamine D5 receptor	TestSet	35	69154	0.989	97.14	150	345	0.881
	TrainingSet	72	64118	0.999	100.00	272	711	0.987
	WholeSet	107	133272	0.999	100.00	464	1138	0.986

Target	Set Of compounds	Active	Inactive	AUC	Recall 5%	SLR	SLR Limit	BEDROC
Serotonin 1a (5-HT1a) receptor	TestSet	1649	67683	0.988	91.81	11181	16664	0.876
	TrainingSet	1649	62398	0.995	97.63	10906	16534	0.928
	WholeSet	3298	130081	0.996	98.30	24000	35527	0.942
Serotonin 1b (5-HT1b) receptor	TestSet	203	69129	0.981	89.66	1118	2036	0.837
	TrainingSet	479	63568	0.998	99.58	2565	4786	0.970
	WholeSet	682	132697	0.998	99.56	3966	7323	0.963
Serotonin 1d (5-HT1d) receptor	TestSet	159	69173	0.978	89.94	818	1592	0.856
	TrainingSet	405	63642	1.000	100.00	2048	4044	0.994
	WholeSet	564	132815	0.999	99.82	3075	6052	0.988
Serotonin 2a (5-HT2a) receptor	TestSet	514	68818	0.970	85.02	3478	5178	0.717
	TrainingSet	871	63176	0.993	98.74	5422	8720	0.899
	WholeSet	1385	131994	0.993	98.92	9399	14898	0.899
Serotonin 2b (5-HT2b) receptor	TestSet	101	69231	0.958	88.12	610	1008	0.788
	TrainingSet	187	63860	0.998	100.00	877	1860	0.971
	WholeSet	288	133091	0.999	100.00	1487	3082	0.974
Serotonin 2c (5-HT2c) receptor	TestSet	334	68998	0.959	86.53	2223	3358	0.721
	TrainingSet	516	63531	0.995	99.61	2982	5157	0.920
	WholeSet	850	132529	0.996	99.76	5311	9132	0.939
Serotonin 3a (5-HT3a) receptor	TestSet	61	69271	0.992	95.08	264	606	0.904
	TrainingSet	113	63934	1.000	100.00	452	1120	0.991
	WholeSet	174	133205	1.000	100.00	774	1857	0.992
Serotonin 4 (5-HT4) receptor	TestSet	147	69185	0.988	93.20	691	1471	0.917
	TrainingSet	38	64009	0.999	100.00	118	372	0.984
	WholeSet	185	133194	0.999	99.46	814	1975	0.986
Serotonin 5a (5-HT5a) receptor	TestSet	18	69314	0.882	55.56	110	175	0.510
	TrainingSet	53	63994	0.999	100.00	172	521	0.990
	WholeSet	71	133308	0.999	100.00	273	752	0.980
Serotonin 6 (5-HT6) receptor	TestSet	242	69090	0.979	90.50	1227	2429	0.900
	TrainingSet	243	63804	0.999	100.00	1130	2420	0.985
	WholeSet	485	132894	0.999	99.79	2598	5202	0.981
Serotonin 7 (5-HT7) receptor	TestSet	208	69124	0.945	67.31	1359	2086	0.614
	TrainingSet	121	63926	0.995	99.17	561	1200	0.924
	WholeSet	329	133050	0.996	99.39	1804	3523	0.931

AUC = Area under ROC curve

Recall 5% = Percent of active retrieve in the top 5% of the data

$$RIE = \frac{\frac{1}{n}\sum_{i=1}^{n} e^{-\alpha x_i}}{\frac{1}{N}\left(\frac{1-e^{-\alpha}}{e^{\alpha/N}-1}\right)}$$

$$BEDROC = RIE \times \frac{\frac{1}{N}\sinh(\alpha/2)}{\cosh(\alpha/2) - \cosh(\alpha/2 - \alpha\frac{n}{N})} + \frac{1}{1 - e^{\alpha\left(\frac{N-n}{N}\right)}}$$

$$SLR = -\sum_{i=1}^{n} \log(r_i)$$

$$SLR_{limit} = \text{nlog(N)-}Gamma\text{(n,1)}$$

where N is the number of compounds, n the number of active compounds, r_i is the rank of the ith active in the ordered list, x_i is the relative rank when scaled ($x_i=r_i/N$) and α a tuning parameter (α was set to 20, which means that 80% of the contribution to the BEDROC score comes from the top 8% of the data)[5].

A method is significantly better than random ($p<0.05$) if SLR is less than SLR_{limit}[6].

Supplementary Table 12b: Chembl (release 1) high confidence model statistics: values for the cut-off score where MCC is maximal.

Target	Set of Compounds	Score	TP	FP	TN	FN	Specificity	Sensitivity	FPR	FNR	Precision	F_Measure	MCC
Alpha-1a adrenergic receptor	TestSet	67	234	131	68376	448	0.998	0.343	0.002	0.657	0.641	0.447	0.465
	TrainingSet	83	242	112	63668	168	0.998	0.590	0.002	0.410	0.684	0.634	0.633
	WholeSet	85	715	159	132128	377	0.999	0.655	0.001	0.345	0.818	0.727	0.730
Alpha-1b adrenergic receptor	TestSet	65	187	94	68594	314	0.999	0.373	0.001	0.627	0.665	0.478	0.496
	TrainingSet	70	179	138	63779	94	0.998	0.656	0.002	0.344	0.565	0.607	0.607
	WholeSet	81	522	179	132426	252	0.999	0.674	0.001	0.326	0.745	0.708	0.707
Alpha-1d adrenergic receptor	TestSet	71	187	68	68498	436	0.999	0.300	0.001	0.700	0.733	0.426	0.466
	TrainingSet	72	257	130	63718	85	0.998	0.751	0.002	0.249	0.664	0.705	0.705
	WholeSet	86	660	126	132288	305	0.999	0.684	0.001	0.316	0.840	0.754	0.756
Alpha-2a adrenergic receptor	TestSet	31	33	49	68901	206	0.999	0.138	0.001	0.862	0.402	0.206	0.234
	TrainingSet	40	110	56	63999	25	0.999	0.815	0.001	0.185	0.663	0.731	0.734
	WholeSet	72	213	30	132975	161	1.000	0.570	0.000	0.430	0.877	0.690	0.706
Alpha-2b adrenergic receptor	TestSet	58	7	0	69082	100	1.000	0.065	0.000	0.935	1.000	0.123	0.256
	TrainingSet	36	90	65	64022	13	0.999	0.874	0.001	0.126	0.581	0.698	0.712
	WholeSet	39	165	159	133010	45	0.999	0.786	0.001	0.214	0.509	0.618	0.632
Alpha-2c adrenergic receptor	TestSet	66	7	0	69035	147	1.000	0.045	0.000	0.955	1.000	0.087	0.213
	TrainingSet	36	91	62	64023	14	0.999	0.867	0.001	0.133	0.595	0.705	0.717
	WholeSet	49	184	46	133074	75	1.000	0.710	0.000	0.290	0.800	0.753	0.753
Dopamine D1 receptor	TestSet	24	273	805	68001	110	0.988	0.713	0.012	0.287	0.253	0.374	0.420
	TrainingSet	64	272	80	63744	94	0.999	0.743	0.001	0.257	0.773	0.758	0.756
	WholeSet	64	568	237	132393	181	0.998	0.758	0.002	0.242	0.706	0.731	0.730
Dopamine D2 receptor	TestSet	16	1542	2304	64926	417	0.966	0.787	0.034	0.213	0.401	0.531	0.545
	TrainingSet	45	1951	686	61223	330	0.989	0.855	0.011	0.145	0.740	0.793	0.787
	WholeSet	44	3681	1616	127523	559	0.987	0.868	0.013	0.132	0.695	0.772	0.769
Dopamine D3 receptor	TestSet	9	586	3040	65456	107	0.956	0.846	0.044	0.154	0.162	0.271	0.358
	TrainingSet	67	377	75	63487	251	0.999	0.600	0.001	0.400	0.834	0.698	0.705
	WholeSet	68	799	188	131870	522	0.999	0.605	0.001	0.395	0.810	0.692	0.697
Dopamine D4 receptor	TestSet	33	475	851	67604	259	0.988	0.647	0.012	0.353	0.358	0.461	0.474
	TrainingSet	51	550	333	63168	139	0.995	0.798	0.005	0.202	0.623	0.700	0.702
	WholeSet	59	1081	491	131465	342	0.996	0.760	0.004	0.240	0.688	0.722	0.720
Dopamine D5 receptor	TestSet	58	16	9	69145	19	1.000	0.457	0.000	0.543	0.640	0.533	0.541
	TrainingSet	58	57	19	64099	15	1.000	0.792	0.000	0.208	0.750	0.770	0.770
	WholeSet	88	50	16	133256	57	1.000	0.467	0.000	0.533	0.758	0.578	0.595
Serotonin 1a (5-HT1a) receptor	TestSet	28	1247	769	66914	402	0.989	0.756	0.011	0.244	0.619	0.680	0.675
	TrainingSet	46	1418	694	61704	231	0.989	0.860	0.011	0.140	0.671	0.754	0.753
	WholeSet	52	2792	950	129131	506	0.993	0.847	0.007	0.153	0.746	0.793	0.789
Serotonin 1b (5-HT1b) receptor	TestSet	52	107	116	69013	96	0.998	0.527	0.002	0.473	0.480	0.502	0.501
	TrainingSet	60	413	167	63401	66	0.997	0.862	0.003	0.138	0.712	0.780	0.782
	WholeSet	69	520	256	132441	162	0.998	0.762	0.002	0.238	0.670	0.713	0.713
Serotonin 1d (5-HT1d) receptor	TestSet	55	96	81	69092	63	0.999	0.604	0.001	0.396	0.542	0.571	0.571
	TrainingSet	73	366	37	63605	39	0.999	0.904	0.001	0.096	0.908	0.906	0.905
	WholeSet	81	451	44	132771	113	1.000	0.800	0.000	0.200	0.911	0.852	0.853

Target	Set of Compounds	Score	TP	FP	TN	FN	Specificity	Sensitivity	FPR	FNR	Precision	F_Measure	MCC
Serotonin 2a (5-HT2a) receptor	TestSet	23	329	1325	67493	185	0.981	0.640	0.019	0.360	0.199	0.304	0.349
	TrainingSet	49	625	480	62696	246	0.992	0.718	0.008	0.282	0.566	0.633	0.631
	WholeSet	44	1131	1403	130591	254	0.989	0.817	0.011	0.183	0.446	0.577	0.598
Serotonin 2b (5-HT2b) receptor	TestSet	21	48	230	69001	53	0.997	0.475	0.003	0.525	0.173	0.253	0.285
	TrainingSet	46	149	175	63685	38	0.997	0.797	0.003	0.203	0.460	0.583	0.604
	WholeSet	48	230	255	132836	58	0.998	0.799	0.002	0.201	0.474	0.595	0.614
Serotonin 2c (5-HT2c) receptor	TestSet	30	140	496	68502	194	0.993	0.419	0.007	0.581	0.220	0.289	0.299
	TrainingSet	38	439	592	62939	77	0.991	0.851	0.009	0.149	0.426	0.568	0.598
	WholeSet	44	673	689	131840	177	0.995	0.792	0.005	0.208	0.494	0.608	0.623
Serotonin 3a (5-HT3a) receptor	TestSet	37	44	37	69234	17	0.999	0.721	0.001	0.279	0.543	0.620	0.626
	TrainingSet	60	97	36	63898	16	0.999	0.858	0.001	0.142	0.729	0.789	0.791
	WholeSet	69	139	45	133160	35	1.000	0.799	0.000	0.201	0.755	0.777	0.777
Serotonin 4 (5-HT4) receptor	TestSet	25	103	37	69148	44	0.999	0.701	0.001	0.299	0.736	0.718	0.717
	TrainingSet	86	25	2	64007	13	1.000	0.658	0.000	0.342	0.926	0.769	0.780
	WholeSet	89	147	14	133180	38	1.000	0.795	0.000	0.205	0.913	0.850	0.852
Serotonin 5a (5-HT5a) receptor	TestSet	64	5	1	69313	13	1.000	0.278	0.000	0.722	0.833	0.417	0.481
	TrainingSet	52	42	10	63984	11	1.000	0.792	0.000	0.208	0.808	0.800	0.800
	WholeSet	93	36	0	133308	35	1.000	0.507	0.000	0.493	1.000	0.673	0.712
Serotonin 6 (5-HT6) receptor	TestSet	56	148	18	69072	94	1.000	0.612	0.000	0.388	0.892	0.725	0.738
	TrainingSet	58	188	17	63787	55	1.000	0.774	0.000	0.226	0.917	0.839	0.842
	WholeSet	58	382	55	132839	103	1.000	0.788	0.000	0.212	0.874	0.829	0.829
Serotonin 7 (5-HT7) receptor	TestSet	62	54	10	69114	154	1.000	0.260	0.000	0.740	0.844	0.397	0.467
	TrainingSet	64	62	24	63902	59	1.000	0.512	0.000	0.488	0.721	0.599	0.607
	WholeSet	69	193	101	132949	136	0.999	0.587	0.001	0.413	0.656	0.620	0.620

TP = true positive
FP = false positive
TN = true negative
FN = false negative

Specificity = TN / (FP + TN)
Sensitivity = TP / (TP + FN)
False positive rate (FPR) = FP / (FP + TN)
False negative rate (FNR) = FN / (TP + FN)
Precision = TP / (TP + FP)

$$Fmeasure = \frac{2TP}{2TP + FN + FP}$$

$$MCC = \frac{TP \times TN - FP \times FN}{\sqrt{(TP + FP)(TP + FN)(TN + FP)(TN + FN)}}$$

Supplementary Table 12c: Dopamine models using Chembl (pre-release) data: all compound model statistics.

Pipeline Pilot internal validation[7]: a leave-one-out cross-validation is performed: one compound is removed from the set, a model is built with the remaining data and the compound is scored; the process is repeated until every compound is scored.
Once the validation is done, some information can be calculated:

- AUC: The area under ROC curve
- Cut-off: the best split score that minimizes the sum of the percent misclassified for category members and for category nonmembers
- TP/FN & FP/TN: Contingency table generated using the split value cut-off

Output	**AUC**	**Cut-off**	**TP/FN FP/TN**	**Active in Category**
Dopamine D1 receptor	0.804	12.132	839/601 4528/209139	1440
Dopamine D2 receptor	0.836	14.873	4435/1324 6320/203028	5759
Dopamine D3 receptor	0.803	12.032	1468/673 7862/205104	2141
Dopamine D4 receptor	0.812	13.898	1498/519 8025/205065	2017
Dopamine D5 receptor	0.665	-4.737	532/8 97050/117517	540
Other (non dopamine receptor)	0.820	-3.861	203587/4934 1550/5036	208521

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