Design and Synthesis of Systemically Active Metabotropic Glutamate Subtype-2 and -3 ($mGlu_{2/3}$) Receptor Positive Allosteric Modulators (PAMs): Pharmacological Characterization and Assessment in a Rat Model of Cocaine Dependence.

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Supporting Information

Plasma-Protein Binding

Pipeline Pilot was used to determine an estimate of plasma-protein binding for selected analogues. The details of the QSAR model used for prediction are as follows:

The model was trained on a data set of 260 compounds as described in Dixon and Merz, *J. Med. Chem.*, **44**, 2001, pp. 3795-3809, and an additional 594 compounds from Votano et. al, *J. Med. Chem.*, **49**, 2006, pp. 7169-7181. However, the modeling methodology described in the Dixon et. al. paper was not used; instead, modified Bayesian learning (described in Xia, Maliski, Gallant, and Rogers, *J. Med. Chem.*, **47**, 2004, pp. 4463-4470) was performed.

This component contains a model useful for predicting Plasma-Protein binding, that is, whether

or not a compound is likely to be highly bound (≥ 90% bound) to carrier proteins in the blood. The model outputs the value *ADMET_EXT_PPB#Prediction*. If true, the compound is predicted to be a binder (≥ 90%). Otherwise, it is predicted to be a weak or non-binder (< 90%).

The outputs in Table S1 defined as follows:

§ NormalizedProbability (PPB): The standard Laplacian-modified Bayesian score.

§ Enrichment (PPB#Enrichment): An estimate of enrichment, that is, the increased likelihood (versus random) of this sample being in the "good" category.

§ EstPGood (PPB#EstPGood): The estimated probability that the sample is in the "good" category, based on an assumed normal distribution of scores within the good and non-good categories.

§ Prediction: A True/False prediction using the best cutoff value estimated from leave-one-out cross-validation. The cutoff is chosen to minimize the average of the false positive rate and false negative rate.

Table S1: Predicted plasma protein binding for selected compounds.

Compound	PPB	PPB#Enrichment	PPB#EstPGood	PPB#Prediction
20	3.830	1.540	0.593	True (≥ 90%)
36	6.190	1.611	0.621	True (≥ 90%)
44	4.720	1.568	0.604	True (≥ 90%)
50	4.374	1.557	0.600	True (≥ 90%)
60	5.996	1.605	0.618	True (≥ 90%)
65	5.531	1.592	0.613	True (≥ 90%)
68	4.294	1.554	0.599	True (≥ 90%)
72	4.219	1.552	0.598	True (≥ 90%)
73	4.565	1.563	0.602	True (≥ 90%)
74	4.183	1.551	0.598	True (≥ 90%)
75	6.292	1.613	0.622	True (≥ 90%)

Table S2. Off-target profiling data for compound **72.**[a]

Receptor/Target	Species	Cpd 72 % inhibition[b]
Adrenergic α_{1A}	Human	-10.5
Adrenergic α_{1B}	Human	-17.1
Adrenergic α_{1D}	Human	-3.6
Adrenergic α_{2A}	Human	-7.7
Adrenergic α_{2B}	Human	11.5
Adrenergic α_{2C}	Human	0.6
Adrenergic β_1	Human	-7.3
Adrenergic β_2	Human	0.7
Adrenergic β_3	Human	24.8
Benzodiazepine (brain, [^{3}H]Flunitrazepam)	Rat	-11.2
Dopamine D_1	Human	1.9
Dopamine D_2	Human	1.0
Dopamine D_3	Human	-28.2
Dopamine D_4	Human	-2.9
Dopamine D_5	Human	-0.9
$GABA_A$ (brain, [^{3}H]Muscimol)	Rat	11.0
Histamine H_1	Human	0.2
Histamine H_2	Human	(> 10 μM)
Histamine H_3	Guinea pig	-5.2
Histamine H_4	Human	(> 10 μM)
Muscarinic M_1	Human	-6.6
Muscarinic M_2	Human	-1.0
Muscarinic M_3	Human	8.3
Muscarinic M_4	Human	-0.9
Muscarinic M_5	Human	-3.8
Opiate δ (OP1, DOP)	Human	13.7
Opiate κ (OP2, KOP)	Human	31.2
Opiate μ (OP3, MOP)	Human	11.1
Peripheral benzodiazepine receptor ([^{3}H]PK11195)	Rat	1.0
Serotonin (5-Hydroxytryptamine) 5-HT_{1A}	Human	-10.2
Serotonin (5-Hydroxytryptamine) 5-HT_{1B}	Human	16.2
Serotonin (5-Hydroxytryptamine) 5-HT_{1D}	Human	60.7 (> 10 μM)
Serotonin (5-Hydroxytryptamine) 5-HT_{1E}	Human	-5.2
Serotonin (5-Hydroxytryptamine) 5-HT_{2A}	Human	-0.6
Serotonin (5-Hydroxytryptamine) 5-HT_{2B}	Human	7.9
Serotonin (5-Hydroxytryptamine) 5-HT_{2C}	Human	20.2
Serotonin (5-Hydroxytryptamine) 5-HT_3	Human	-15.3
Serotonin (5-Hydroxytryptamine) 5-HT_{5A}	Human	4.5
Serotonin (5-Hydroxytryptamine) 5-HT_6	Human	-1.1
Serotonin (5-Hydroxytryptamine) 5-HT_7	Human	1.8
Sigma σ_1	Rat	-11.3
Sigma σ_2	Rat	6.6
Transporter, Dopamine (DAT)	Human	-7.7
Transporter, Norepinephrine (NET)	Human	-4.8
Transporter, Serotonin (5-Hydroxytryptamine) (SERT)	Human	0.3

[a]Compound **72** was tested for displacement of radioligand binding activity at 10 μM. Assays were performed by the NIMH Psychoactive Drug Screening Program (UNC Chapel Hill) unless otherwise noted. [b]Inhibition at 10 μM as a percentage of displacement of the respective radioligand at each target. IC_{50} values where applicable are shown in parentheses.