Supporting Information

Discovery, Synthesis and Molecular Pharmacology of Selective Positive Allosteric Modulators of the δ-Opioid Receptor

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Table S1. Physicochemical properties displaying non-zero variance across the 15 ligands of Table 1

Physicochemical Property	**Description (taken from the QikProp 4.2 user manual)**
X.stars	Number of property or descriptor values that fall outside the 95% range of similar values for known drugs.
X.rotor	Number of non-trivial (not CX3), non-hindered (not alkene,amide, small ring) rotatable bonds.
CNS	Predicted central nervous system activity on a –2 (inactive) to +2 (active) scale.
mol.MW	Molecular weight of the molecule.
dipole	Computed dipole moment of the molecule.
SASA	Total solvent accessible surface area (SASA) in square angstroms using a probe with a 1.4 Å radius.
FOSA	Hydrophobic component of the SASA (saturated carbon and attached hydrogen).
FISA	Hydrophilic component of the SASA (SASA on N, O, H on heteroatoms, carbonyl C).
PISA	π (carbon and attached hydrogen) component of the SASA.
WPSA	Weakly polar component of the SASA (halogens, P, and S).
volume	Total solvent-accessible volume in cubic angstroms using a probe with a 1.4 Å radius.
donorHB	Estimated number of hydrogen bonds that would be donated by the solute to water molecules in an aqueous solution. Values are averages taken over a number of configurations, so they can be non-integer.
accptHB	Estimated number of hydrogen bonds that would be accepted by the solute from water molecules in an aqueous solution. Values are averages taken over a number of configurations, so they can be non-integer.
dip.2.V	Square of the dipole moment divided by the molecular volume. This is the key term in the Kirkwood-Onsager equation for the free energy of solvation of a dipole with volume V.
ACxDN..5.SA	Index of cohesive interaction in solids. This term represents the relationship $((accptHB(\sqrt{donorHB}))/(SA)$.
glob	Globularity descriptor, $(4\pi r^2)/(SASA)$, where r is the radius of a sphere with a volume equal to the molecular volume. Globularity is 1.0 for a spherical molecule.
QPpolrz	Predicted polarizability in cubic angstroms.
QPlogPC16	Predicted hexadecane/gas partition coefficient.
QPlogPoct	Predicted octanol/gas partition coefficient.
QPlogPw	Predicted water/gas partition coefficient.
QPlogPo.w	Predicted octanol/water partition coefficient.
QPlogS	Predicted aqueous solubility, log S. S in mol dm^{-3} is the concentration of the solute in a saturated solution that is in equilibrium with the crystalline solid.
CIQPlogS	Conformation-independent predicted aqueous solubility,

	log S. S in mol dm^{-3} is the concentration of the solute in a saturated solution that is in equilibrium with the crystalline solid.
QPlogHERG	Predicted IC50 value for blockage of HERG K^+ channels.
QPPCaco	Predicted apparent Caco-2 cell permeability in nm/sec. Caco-2 cells are a model for the gut-blood barrier. QikProp predictions are for non-active transport.
QPlogBB	Predicted brain/blood partition coefficient. Note: QikProp predictions are for orally delivered drugs so, for example, dopamine and serotonin are CNS negative because they are too polar to cross the blood-brain barrier.
QPPMDCK	Predicted apparent MDCK cell permeability in nm/sec. MDCK cells are considered to be a good mimic for the bloodbrain barrier. QikProp predictions are for non-active transport.
QPlogKp	Predicted skin permeability, log Kp.
IP.eV.	PM3 calculated ionization potential (negative of HOMO energy).
EA.eV.	PM3 calculated electron affinity (negative of LUMO energy).
X.metab	Number of likely metabolic reactions.
QPlogKhsa	Prediction of binding to human serum albumin.
PercHOA	Predicted human oral absorption on 0 to 100% scale. The prediction is based on a quantitative multiple linear regression model. This property usually correlates well with HumanOral-Absorption, as both measure the same property.
SAfluorine	Solvent-accessible surface area of fluorine atoms.
PSA	Van der Waals surface area of polar nitrogen and oxygen atoms and carbonyl carbon atoms.
X.NandO	Number of nitrogen and oxygen atoms.
RuleOfFive	Number of violations of Lipinski's rule of five. The rules are: mol_MW < 500, QPlogPo/w < 5, donorHB ≤ 5, accptHB ≤ 10. Compounds that satisfy these rules are considered drug-like. (The "five" refers to the limits, which are multiples of 5.)
X.nonHatm	Number of heavy atoms (nonhydrogen atoms).

Table S2: Calculated values of the physicochemical properties displaying non-zero variance across the 15 ligands of Table 1

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
X.stars	1.00	3.00	3.00	3.00	2.00	2.00	2.00	3.00	3.00	3.00	3.00	3.00	1.00	1.00	3.00
X.rotor	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	4.00	4.00	4.00	5.00	3.00
CNS	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00	0.00	0.00	0.00	-1.00	-1.00	0.00
mol.MW	456.58	470.61	470.61	470.61	474.57	474.57	474.57	491.02	525.47	535.48	522.59	540.58	534.67	486.61	524.58
dipole	8.80	8.81	8.49	8.50	8.59	10.80	10.62	8.76	10.21	8.70	6.79	9.51	8.50	8.74	6.42
SASA	810.51	824.70	842.70	842.71	818.32	819.51	819.55	826.43	846.08	829.35	848.01	845.30	854.55	840.34	847.94
FOSA	442.04	498.59	530.17	530.23	436.94	442.06	442.05	435.90	435.45	435.58	461.45	439.67	493.28	465.77	428.27
FISA	58.34	58.33	58.34	58.34	58.35	58.33	58.33	58.35	58.34	58.35	58.33	58.34	120.62	107.11	58.33
PISA	310.13	267.78	254.19	254.15	286.60	272.14	272.14	276.48	239.37	275.06	251.82	249.14	240.66	267.45	259.62
WPSA	0.00	0.00	0.00	0.00	36.43	46.98	47.02	55.70	112.92	60.36	76.41	98.14	0.00	0.00	101.72
volume	1491.94	1536.28	1551.85	1551.91	1504.71	1508.06	1508.08	1527.19	1566.62	1534.36	1586.43	1589.81	1619.44	1558.62	1574.55
donorHB	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00	0.00
acceptHB	5.25	5.25	5.25	5.25	5.25	5.25	5.25	5.25	5.25	5.25	5.25	5.25	9.25	6.95	5.25
dip.2.V	0.05	0.05	0.05	0.05	0.05	0.08	0.07	0.05	0.07	0.05	0.03	0.06	0.04	0.05	0.03
ACxDN..5.SA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.00
glob	0.78	0.78	0.77	0.77	0.78	0.78	0.78	0.78	0.77	0.78	0.78	0.78	0.78	0.77	0.77
QPpolrz	54.59	55.96	56.45	56.45	54.88	54.87	54.87	55.68	56.90	55.95	57.17	57.28	58.39	55.57	57.41
QPlogPC16	14.81	14.91	15.04	15.04	14.55	14.41	14.41	15.31	15.85	15.40	14.79	14.64	15.91	15.73	14.61
QPlogPoct	21.53	21.95	21.99	21.99	21.73	22.14	22.11	22.11	22.98	22.22	22.39	22.94	25.14	24.31	22.59
QPlogPw	8.69	8.43	8.38	8.38	8.56	8.46	8.46	8.52	8.33	8.51	8.19	8.17	12.46	11.50	8.47
QPlogPo.w	6.43	6.67	6.76	6.76	6.63	6.67	6.67	6.83	7.27	6.90	7.27	7.37	4.80	5.72	7.30
QPlogS	-8.34	-8.61	-8.95	-8.95	-8.65	-8.71	-8.71	-8.88	-9.51	-8.96	-9.22	-9.26	-6.92	-8.11	-9.49
CIQPlogS	-7.44	-7.74	-7.74	-7.74	-7.82	-7.82	-7.82	-8.17	-8.90	-9.11	-8.84	-9.22	-7.24	-7.43	-8.88
QPlogHERG	-6.59	-6.36	-6.48	-6.48	-6.52	-6.45	-6.45	-6.47	-6.38	-6.47	-6.36	-6.29	-6.23	-6.47	-6.46
QPPCaco	2771.38	2771.86	2771.29	2771.40	2770.64	2771.75	2771.50	2770.69	2770.91	2770.62	2771.72	2771.08	711.37	955.29	2771.80
QPlogBB	-0.26	-0.26	-0.28	-0.28	-0.17	-0.15	-0.15	-0.13	0.01	-0.12	-0.14	-0.08	-1.00	-0.93	-0.02
QPPMDCK	1488.85	1489.13	1488.80	1488.87	2356.68	2693.19	2694.29	3005.10	6185.16	3187.05	3903.73	5133.81	342.36	470.85	5371.79
QPlogKp	-1.21	-1.36	-1.41	-1.41	-1.30	-1.35	-1.35	-1.33	-1.46	-1.34	-1.32	-1.33	-2.51	-2.07	-1.39
IP.eV.	8.74	8.73	8.73	8.73	8.72	8.82	8.83	8.72	8.77	8.70	8.70	8.74	8.74	8.72	8.83
EA.eV.	0.51	0.51	0.51	0.51	0.49	0.54	0.56	0.50	0.52	0.49	0.48	0.49	0.60	0.51	0.53
X.metab	7.00	8.00	8.00	8.00	7.00	7.00	7.00	7.00	7.00	7.00	8.00	8.00	7.00	8.00	8.00
QPlogKhsa	1.42	1.55	1.59	1.59	1.45	1.46	1.46	1.52	1.63	1.54	1.65	1.66	0.68	1.25	1.66
PercHOA	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	93.15	100.00	100.00
SAfluorine	0.00	0.00	0.00	0.00	36.43	46.98	47.02	0.00	0.00	0.00	76.41	98.14	0.00	0.00	101.72
PSA	64.00	63.69	63.99	64.00	64.81	63.99	64.00	64.37	64.33	64.30	71.24	70.08	96.66	86.01	63.48
X.NandO	4.00	4.00	4.00	4.00	4.00	4.00	4.00	4.00	4.00	4.00	5.00	5.00	6.00	5.00	4.00
RuleOfFive	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	2.00	2.00	2.00	2.00	1.00	1.00	2.00
X.nonHatm	34.00	35.00	35.00	35.00	35.00	35.00	35.00	35.00	36.00	35.00	38.00	39.00	38.00	36.00	38.00

Table S3. Statistics of the best predictive model for δ EC_{50}.

	Estimate	Std. Error	t value	Pr(>|t|)
(Intercept)	225.1429	30.9535	7.27	0.0000
SASA	-0.1003	0.0168	-5.97	0.0001
PISA	-0.0606	0.0125	-4.86	0.0005
IP.eV.	-14.2752	2.4131	-5.92	0.0001

Table S4. Statistics of the best predictive model for μ EC_{50}.

	Estimate	Std. Error	t value	Pr(>|t|)
(Intercept)	6.7258	1.7255	3.90	0.0025
mol.MW	-0.0220	0.0040	-5.56	0.0002
PSA	-0.0989	0.0265	-3.74	0.0033
X.NandO	2.3097	0.4570	5.05	0.0004

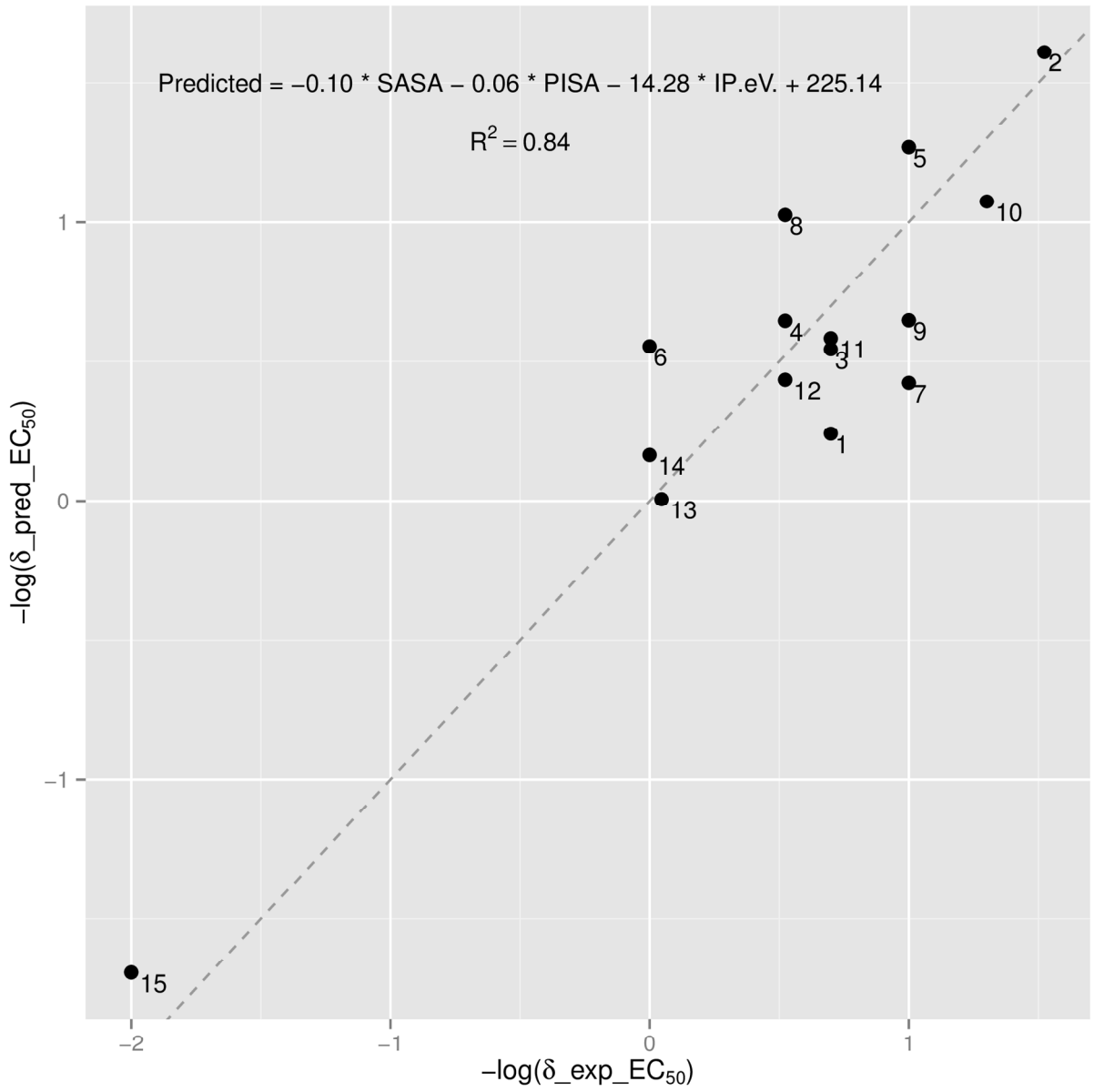

Figure S1. Predictive model for δ EC_{50}. Numbered black dots represent each individual compound in Table 1. δ_exp_EC_{50} and δ_pred_EC_{50} stand for experimental δ EC_{50} and predicted δ EC_{50}, respectively. The ideal correlation is indicated by a dotted line.

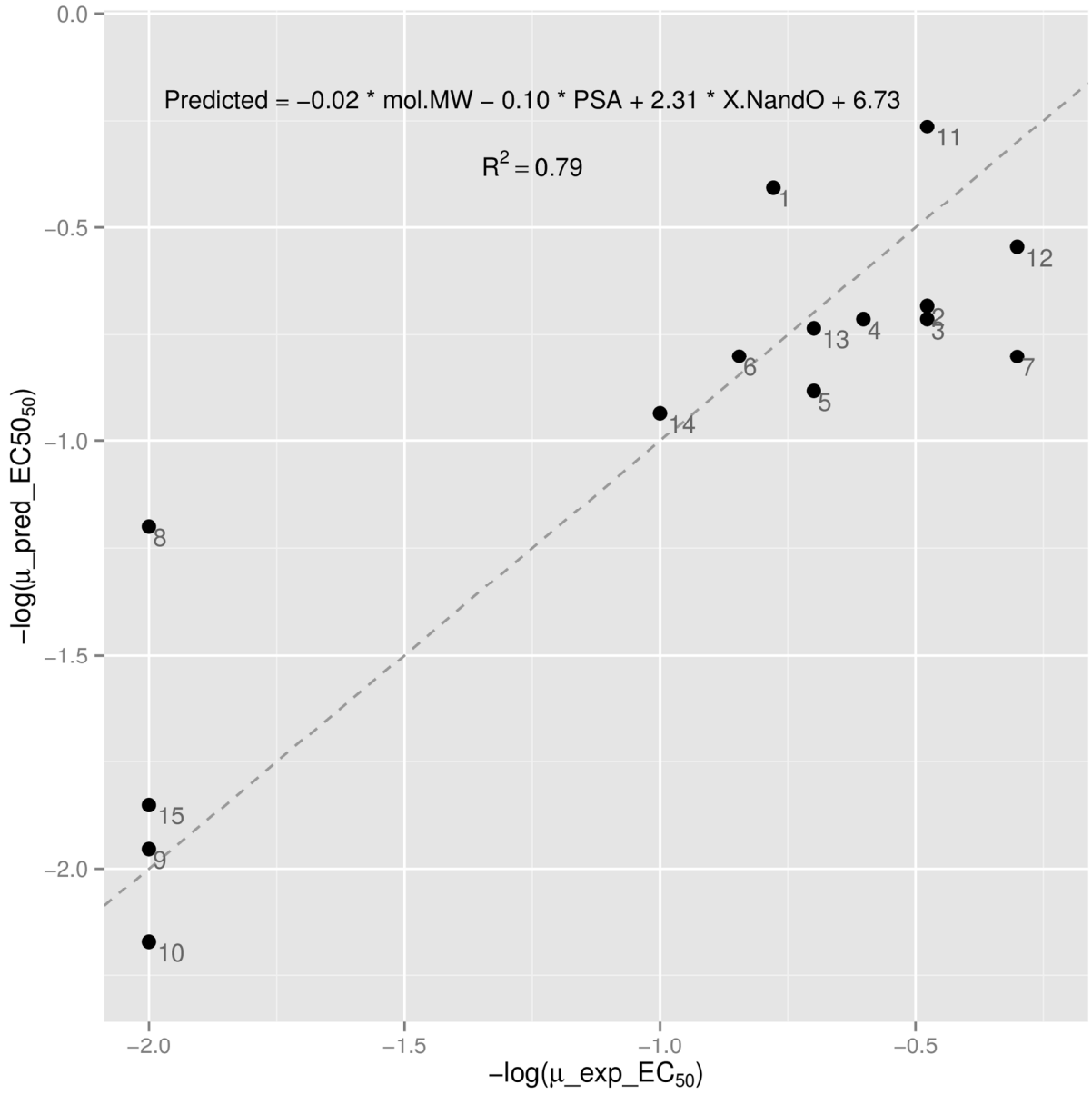

Figure S2. Predictive model for μ EC_{50}. Numbered black dots represent each individual compound in Table 1. μ_exp_EC_{50} and μ_pred_EC_{50} stand for experimental μ EC_{50} and predicted μ EC_{50}, respectively. The ideal correlation is indicated by a dotted line.

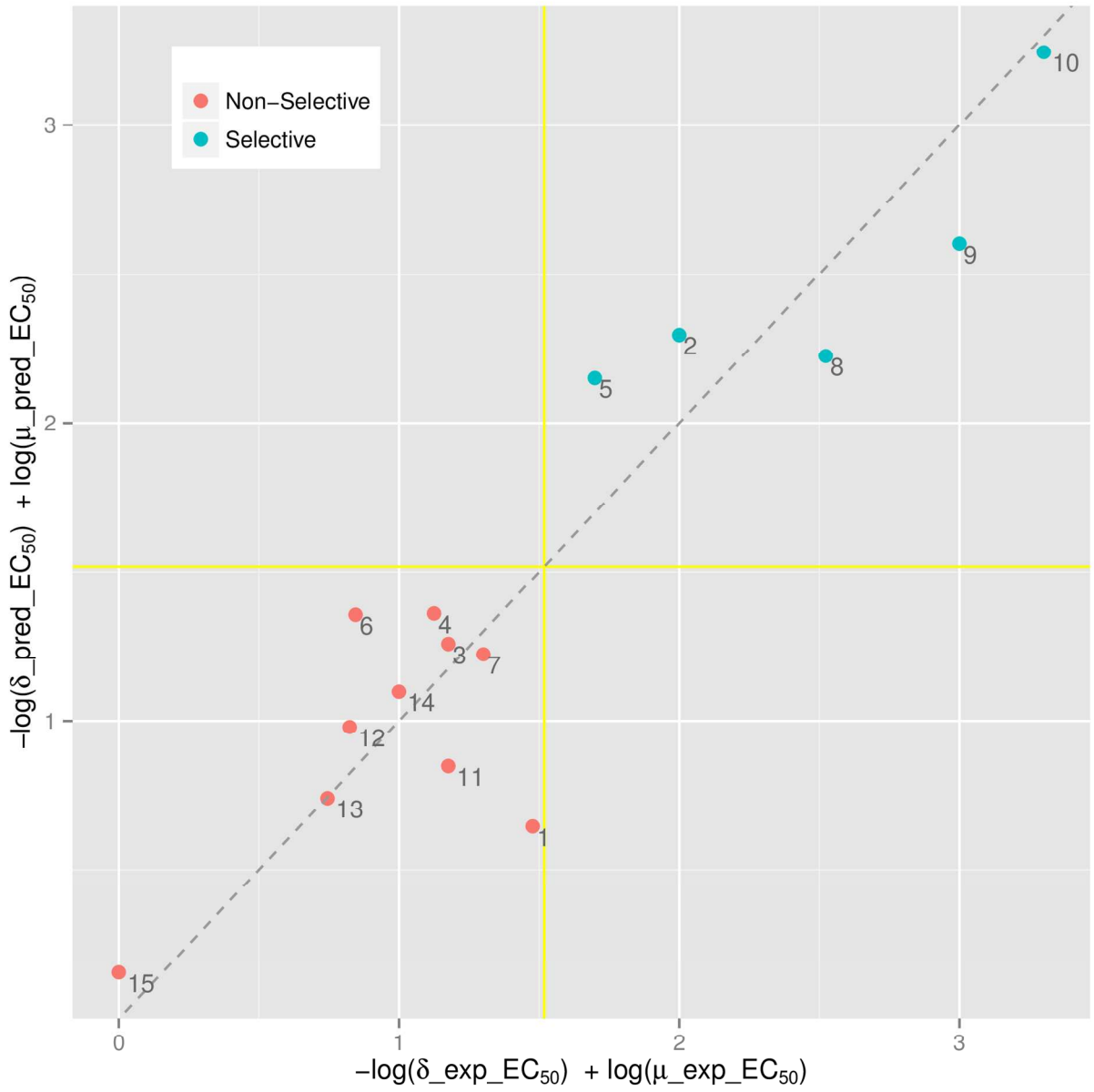

Figure S3. Predictive model for δ/μ selectivity (arbitrarily set to more than 33-fold). Selective and non-selective compounds are represented as red and blue dots, respectively. The ideal correlation is indicated by a dotted line. The yellow lines indicate the 33-fold selectivity cut-off.