Supporting Information

Construction of a Virtual Opioid Bioprofile: a Data-driven QSAR Modeling Study to Identify New Analgesic Opioids

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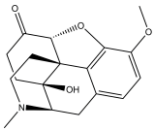
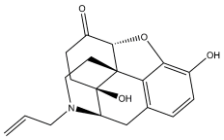
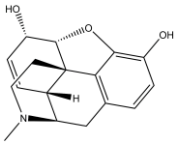
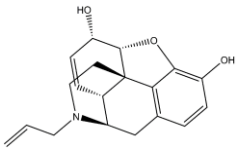
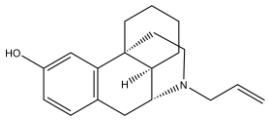
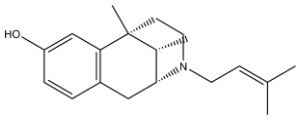
Table S1. Possible activity cliffs in QSAR model of KOR binding (PubChem AID 410720).

External Compound & its NN*	Structure	Experimental log K_i	Predicted log Ki	Chemical similarity [a]
Oxycodone (5284603)		2.83[1]	1.22	0.57
Naloxone (5284596)		0.08	-	
Morphine (5288826)		1.53[2]	0.29	0.81
Nalorphine (5284595)		-0.42	-	
Levallorphan (5359371)		1.54[3]	0.20	0.58
Fortral (9669)		0.48	-	

***NN**: chemical nearest neighbor compound in the training set, represented by name and PubChem CID.

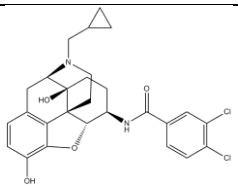
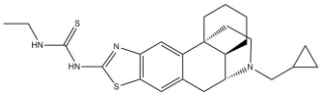
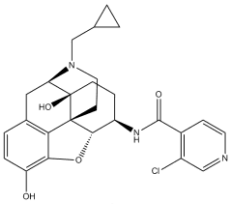
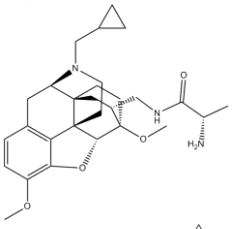
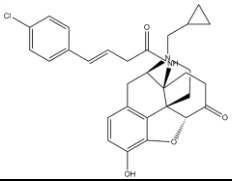
[a] Jaccard similarity calculated using FCFP6 descriptors.

Table S2. Comparisons between predictions of probe opioids and DrugBank compounds for nine PubChem assays.

PubChem AID	Mean DrugBank	Mean Probe opioid	t- statistic	p-value
147859	0.166	0.262	16.81	5.92e-62
152239	0.207	0.677	56.12	0.0
273132	0.384	0.510	19.87	5.03e-85
306450	0.390	0.512	26.09	8.81e-142
410720	0.290	0.413	30.43	1.68e-188
445095	0.290	0.325	9.17	6.15e-20
625163	0.297	0.376	19.90	3.04e-85
625217	0.272	0.477	46.99	0.0
625253	0.404	0.519	27.97	2.11e-161

Range normalized ([0,1]) pActivity (-logActivity) prediction values of 2,042 DrugBank compounds and 3,656 probe opioid compounds were used to perform two-tailed t-test.

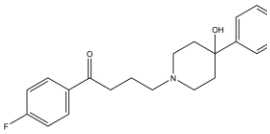
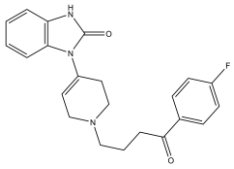
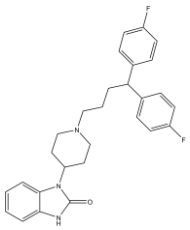
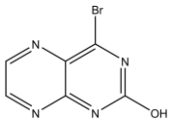
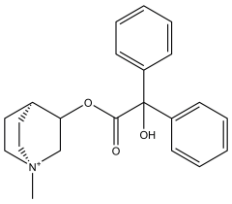
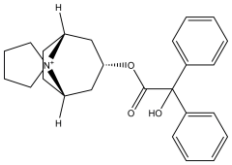
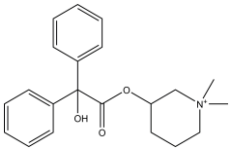
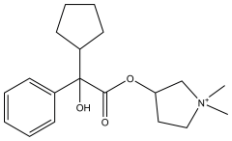
Table S3. Possible G protein signaling biased MOR ligands prioritized from probe compounds.

PubChem CID	P_{bias}*	Structure	Source
24822630	3.46		Literature (Ghirmai et al.[4])
51356591	3.40		Literature (Zhang et al.[5])
56658452	3.36		Literature (Yuan et al.[6])
89978736	3.34		Patents (Goehring et al.[7])
16087271	3.34		Literature (Rennison et al.[8])

*P_{bias} = predicted pEC_{50} of bioassay AID 779596 – predicted pEC_{50} of bioassay AID 779594

pEC_{50}: $-\log EC_{50}$

Table S4. Eight general drugs with potential opioid receptor binding activity.

DrugBank ID	Name	Structure	Target*
DB00502	Haloperidol		Dopamine receptor D2
DB00450	Droperidol		Dopamine receptor D2
DB01100	Pimozide		Dopamine receptor D2, D3
DB12401	Bromperidol		Dopamine receptor D2
DB00771	Clidinium		mAChR: M1
DB00209	Trospium		mAChR: M1, M3
DB04843	Mepenzolate		mAChR: M1, M3
DB00986	Glycopyrronium		mAChR: M1-3

*mAChR: Muscarinic acetylcholine receptor.

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