Rationalising and predicting the activity of CCR5 antagonists using molecular interaction fields and 3D QSAR

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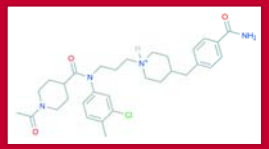
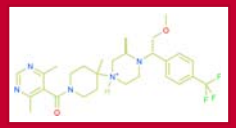
smarter chemistry | smarter decisions

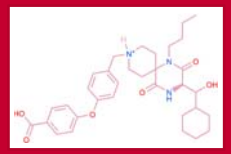


TAK-220, IC50 3.5 nM

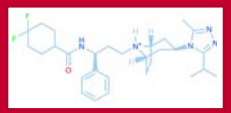


SCH-417690, Vicriviroc, KI 1.6nM

4 CCR5 Actives in 2D



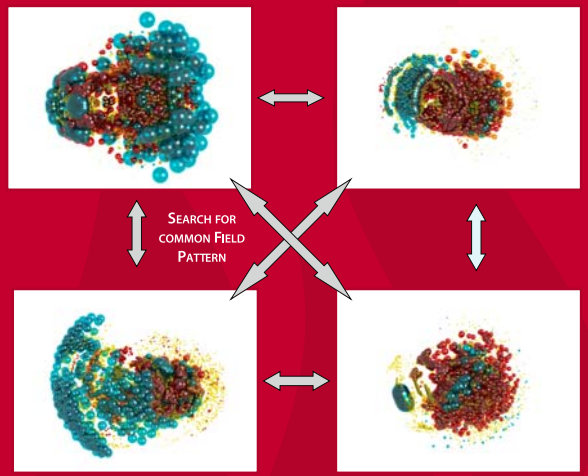
ONO-4128, Aplaviroc, IC50 0.5nM



UK-427857, Maraviroc, IC50 1nM

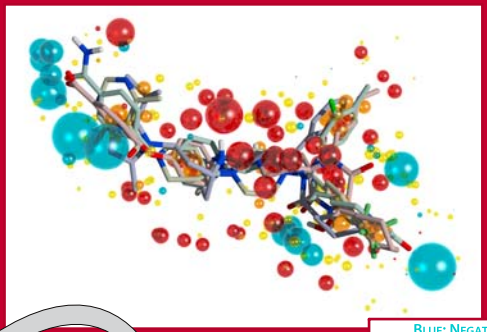
Populate conformation space

Add Molecular Interaction Fields to each conformation



Search for common Field Pattern

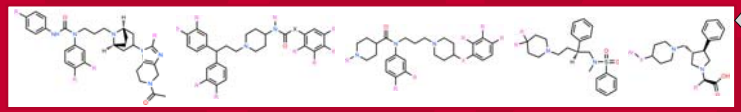
fieldtemplater™



Blue: Negative
Red: Positive
Yellow: Steric
Gold:Hydrophobic

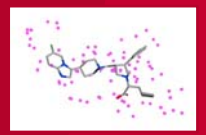
Populate conformations

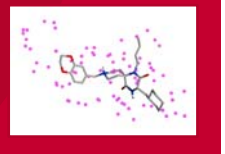
Align to template using Fields

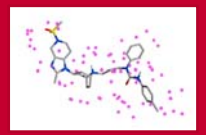


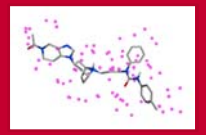
267 CCR5 Actives in 2D

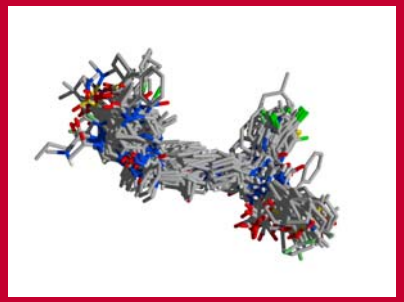
fieldalign™









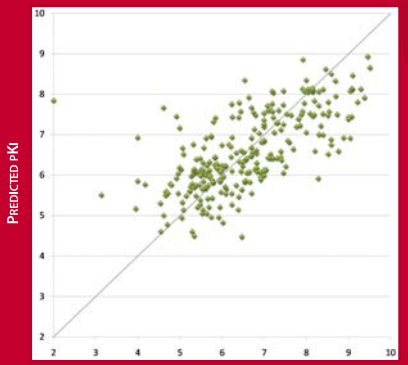


Use the Field Points of the template to sample the Field of each aligned molecule. Each sample point is a column in the QSAR table

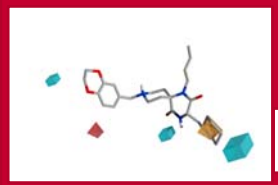
Compound	Activity	Field Point 1	Field Point 2	Field Point 3	Field Point 4	Field Point 5	Field Point 6	Field Point 7	Fi Poi
BMCL_12_6193_1	6	1.3877	1.4922	1.3588	-1.6892	1.4648	0	0	5.4
BMCL_15_2129_65	9	-0.8266	-1.2084	-0.6853	-0.7839	-0.776	0	0	
BMCL_16_4467_10	5.5	0.2096	-1.2729	0.9397	-0.7796	1.4131	0	0	3.9
BMCL_17_1883_10b	6.5	1.102	1.2225	1.1446	0	1.4677	0	0	3.4
BMCL_18_1498_34	8.1	-1.2843	-1.3355	-1.6344	-4.2827	-2.9704	0	0	0.5
BMCL_18_2000_10	8.7	1.4225	2.081	0.7142	0	-0.9898	-1.4922	0	4.0
JMC_49_2784_1b	5.7	0	0	-2.8037	0	-2.3944	2.9677	3.01	-2.8
JMC_49_4140_14	8.3	0.7853	0.9703	0.8067	-0.9562	1.0451	-1.059	0	-3.2

qsar

Predicted vs Observed pKi for 267 CCR5 actives using PLS

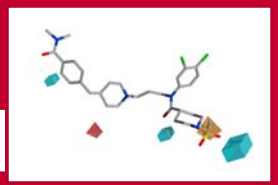


$q^2 = 0.49$;
rmse(cv) = 0.92;
$r^2 = 0.72$



Active showing significant Field Points.
Tetrahedra = Favourable
Rhomboid = Unfavourable

Blue: Negative
Red: Positive
Gold:Hydrophobic



Inactive showing significant Field Points.
Tetrahedra = Favourable
Rhomboid = Unfavourable

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