

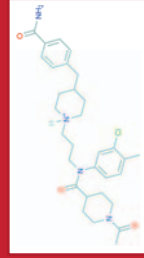


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# Rationalising and predicting the activity of CCR5 antagonists using molecular interaction fields and 3D QSAR

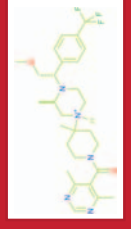
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James Melville,  
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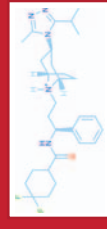


4 CCR5 ACTIVES IN 2D

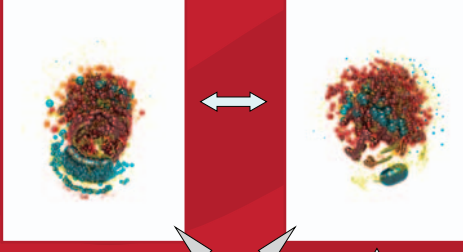
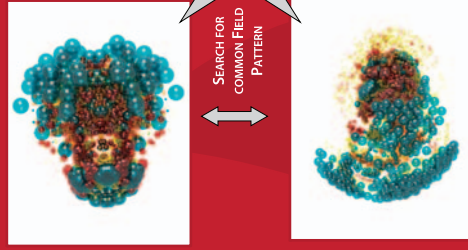
SCH-417690, Yicriviroc, Ki 1.6nM



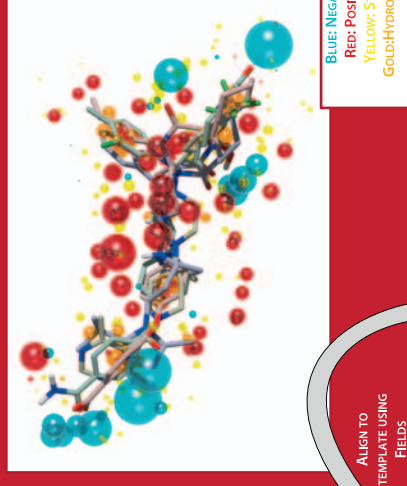
UK-427857, MARAVIROC, IC50 1nM



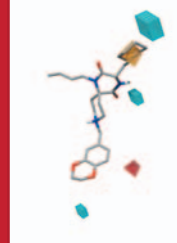
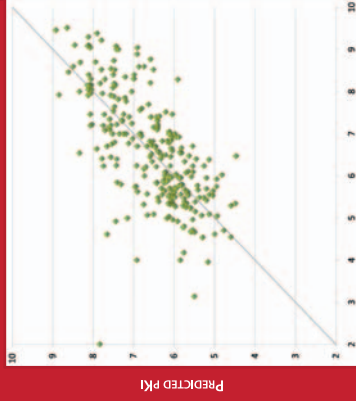
POPULATE CONFORMATION SPACE  
ADD MOLECULAR INTERACTION FIELDS TO EACH CONFORMATION



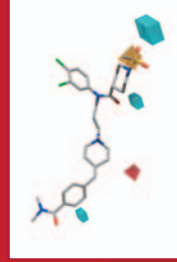
fieldtemplater™



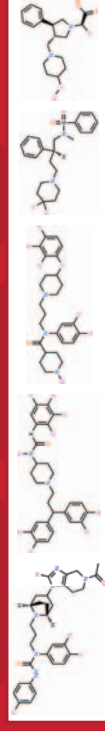
PREDICTED VS OBSERVED PKi FOR 267 CCR5 ACTIVES USING PLS



ACTIVE SHOWING SIGNIFICANT FIELD POINTS.  
TETRAHEDRA = FAVOURABLE  
RHOMBOID = UNFAVOURABLE



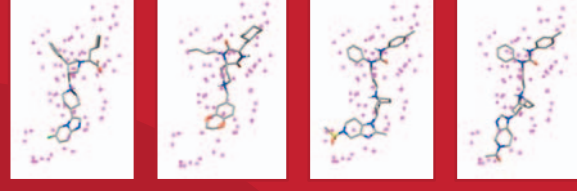
INACTIVE SHOWING SIGNIFICANT FIELD POINTS.  
TETRAHEDRA = FAVOURABLE  
RHOMBOID = UNFAVOURABLE



267 CCR5 ACTIVES IN 2D

Compound	Activity	Field Point 1	Field Point 2	Field Point 3	Field Point 4	Field Point 5	Field Point 6	Field Point 7	Field Point 8
BMCL_13_6198_L3	0	1.3977	1.4922	1.3508	-1.6992	1.4648	0	0	0
BMCL_15_2129_05	0	-0.8266	-1.0861	-0.6851	-0.7839	-0.776	0	0	0
BMCL_14_4487_10	5.5	0.2096	-1.2729	0.9397	-0.7796	1.4111	0	0	3.8
BMCL_17_1683_106	6.5	1.102	1.2225	1.1446	0	1.4077	0	0	3.4
BMCL_16_1498_34	8.1	-1.2843	-1.3355	-1.4344	-4.2827	-2.9704	0	0	0.5
BMCL_18_2000_10	8.7	1.4225	2.081	0.7242	0	-0.9088	-1.4922	0	4.8
BMCL_49_2748_16	5.7	0	0	-2.8037	0	-2.3944	2.9827	3.01	-2.2
BMCL_49_4140_14	8.3	0.7853	0.9703	0.8867	-0.9562	1.0451	-1.059	0	-3.2

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1. T. Cheeswright, M. Mackey, S. Rose, A. Vinter, Molecular Field Extrema as Descriptors of Biological Activity: Definition and Validation, *J. Chem. Inf. Model.* 2006; 46, 665-676
2. J. Ernst, R. Dahl, C. Lum, J. Sebo, J. Urban, S.G. Miller and J. Lundstrom; Bioorganic & Medicinal Chemistry Letters 18 (2008) 1498
3. G. Thomas, C. Beerli, M. Bigaud, C. Bruns, N.G. Cooke, M.B. Strel and H.-G. Zerwas; Bioorganic & Medicinal Chemistry Letters 18 (2008) 2000
4. S.-F. Lu, B. Chen, D. Davey, L. Dunning, S. Jaroch, K. May, J. Onu, G. Phillips, B. Subramanyam, J.-J. Tseng, K. G. Wei, M. Wei and Bin Ye; Bioorganic & Medicinal Chemistry Letters 17 (2007) 1883
5. J.T. Leonard and K. Roy; Bioorganic & Medicinal Chemistry Letters 16 (2006) 4467
6. H. Habashita, M. Kokubo, S. Hamano, N. Hamanaka, M. Toda, S. Shibayama, H. Tada, K. Sogaawa, D. Fukushima, K. Maeda and H. Mitsuya; *J. Med. Chem.* (2006), 49, 4140-4152
7. D. Kim, L. Wong, J.J. Hale, C.L. Lynch, R.J. Budhu, M. MacCos, S.G. Mills, J. Malkowitz, S.L. Gould, J.A. DeMartino, M.S. Springer, D. Hazuda, M. Miller, J. Kessler, R.C. Hino, G. Carver, A. Garcia, K. Henry, J. Lineberger, W.A. Schief, M. Bigaud, C. Bruns, N.G. Cooke, M.B. Strel and H.-G. Zerwas; Bioorganic & Medicinal Chemistry Letters 15 (2005) 2129
8. G. Thomas, C. Beerli, M. Bigaud, C. Bruns, N.G. Cooke, M.B. Strel and H.-G. Zerwas; Bioorganic & Medicinal Chemistry Letters 18 (2008) 2000
9. Y. Xu, H. Liu, C. Niu, X. Luo, J. Shen, K. Chen and H. Jiang; Bioorganic & Medicinal Chemistry 12 (2004) 6193