**Table S1** Inhibitory activities for CCR5 inhibitors

| No | *K*i (nM) | No | *K*i (nM) | No | *K*i (nM) | No | *K*i (nM) |
|---|---|---|---|---|---|---|---|
| 1 | 58 | 2 | 68 | 3 | 33 | 4 | 25 |
| 5 | 55 | 6 | 110 | 7 | 155 | 8 | 86 |
| 9 | 33 | 10 | 596 | 11 | 360 | 12 | 54 |
| 13 | 190 | 14 | 62 | 15 | 8 | 16 | 29 |
| 17 | 25 | 18 | 2 | 19 | 48 | 20 | 2 |
| 21 | 78 | 22 | 9 | 23 | 4 | 24 | 33 |
| 25 | 33 | 26 | >30 | 27 | 3.4 | 28 | 18 |
| 29 | 4.5 | 30 | 3 | 31 | 1.1 | 32 | 1.1 |
| 33 | 26 | 34 | >30 | 35 | 7 | 36 | 43 |
| 37 | >30 | 38 | 2.1 | 39 | >30 | 40 | >30 |
| 41 | 16 | 42 | 19 | 43 | 5.3 | 44 | 7.6 |
| 45 | 30 | 46 | 24 | 47 | 3.8 | 48 | 4.4 |
| 49 | 20 | 50 | 5.6 | 51 | 30 | 52 | 1300 |
| 53 | 440 | 54 | 62 | 55 | 30 | 56 | 20 |
| 57 | 8 | 58 | 5 | 59 | 12 | 60 | 7 |
| 61 | 1 | 62 | 5 | 63 | 5 | 64 | 3 |
| 65 | 5 | 66 | 15 | 67 | 0.7 | 68 | 2.7 |
| 69 | 5.23 | 70 | 18 | 71 | 3 | 72 | 10 |
| 73 | 10 | 74 | 12 | 75 | 11 | 76 | 38 |
| 77 | 0.1 | 78 | 590 | 79 | 0.3 | 80 | 2.3 |
| 81 | 8.8 | 82 | 0.4 | 83 | 1.2 | 84 | 0.7 |
| 85 | 4.7 | 86 | 2.2 | 87 | 2 | 88 | 14 |
| 89 | 8.1 | 90 | 11 | 91 | 3.3 | 92 | 2.1 |
| 93 | 3.2 | 94 | 5.7 | 95 | 60 | 96 | 315 |
| 97 | 43 | 98 | 25 | 99 | 5.3 | 100 | 1.3 |
| 101 | 7 | 102 | 2.3 | 103 | 7 | | |

**Table S2** ADMET properties prediction for screened compounds[a]

| Compound | Absorption[1] | Solubility[2] | BBB[3] | CYD2D6[4] | Hepatotoxicity[5] | PPB[6] | AlogP98 | PSA_2D | vROF[7] |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 0 | 2 | 2 | 1 | 1 | 2 | 4.443 | 77.623 | 0 |
| 15 | 0 | 4 | 3 | 0 | 0 | 1 | 0.976 | 100.145 | 0 |
| 18 | 0 | 2 | 3 | 0 | 1 | 2 | 3.188 | 89.448 | 0 |
| 20 | 0 | 2 | 3 | 0 | 1 | 2 | 2.985 | 89.448 | 0 |
| 25 | 0 | 3 | 3 | 0 | 1 | 1 | 3.206 | 100.145 | 0 |
| 29 | 0 | 2 | 3 | 0 | 1 | 1 | 3.305 | 92.035 | 0 |
| 32 | 0 | 3 | 3 | 0 | 0 | 2 | 2.232 | 84.787 | 0 |
| 33 | 0 | 3 | 3 | 0 | 0 | 2 | 2.301 | 84.787 | 0 |
| 34 | 0 | 3 | 3 | 0 | 0 | 2 | 2.232 | 84.787 | 0 |
| 38 | 0 | 2 | 3 | 0 | 1 | 1 | 3.285 | 97.037 | 0 |
| 42 | 0 | 3 | 3 | 0 | 0 | 2 | 2.301 | 84.787 | 0 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 43 | 0 | 3 | 3 | 0 | 0 | 2 | 2.232 | 84.787 | 0 |
| 45 | 0 | 2 | 2 | 0 | 0 | 1 | 3.729 | 84.787 | 0 |

[a] The data was determined with Accelrys Discovery Studio.

[1] Absorption level (0 = good, 1 = moderate, 2 = low, 3 = very low).

[2] Solubility level (0 = extremely low, 1 = very low but soluble, 2 = low, 3 = good, 4 = optimal).

[3] BBB, Blood brain barrier (0=very high, 1=high, 2=medium and 3=low).

[4] CYP2D inhibition (0 = non inhibitor, 1 = likely to inhibit).

[5] Hepatotoxicity (0=Non toxic and 1=toxic).

[6] PPB, Plasma protein binding(0=PPB<90% and 2=PPB>95%).

[7] Violation of Lipinski's rule of five.

**Table S3** Binding free energies and its components for screened compounds[a]

| Compound | $\Delta G_{vdW}$ | $\Delta G_{ele}$ | $\Delta G_{ele,sol}$ | $\Delta G_{nonpol,sol}$ | $\Delta TS$ | $\Delta G$ |
|---|---|---|---|---|---|---|
| 1 | -65.72 | -23.25 | 39.15 | -13.57 | -15.44 | -47.95 |
| 15 | -53.38 | -53.80 | 59.24 | -18.67 | -23.79 | -42.82 |
| 18 | -62.15 | -23.22 | 33.88 | -17.68 | -24.87 | -44.30 |
| 20 | -68.04 | -13.72 | 40.44 | -18.45 | -15.41 | -44.36 |
| 25 | -68.39 | -42.24 | 55.88 | -18.64 | -22.47 | -50.92 |
| 29 | -69.65 | -29.72 | 40.21 | -17.98 | -19.00 | -58.14 |
| 32 | -59.72 | -23.43 | 28.65 | -10.01 | -21.70 | -42.81 |
| 33 | -54.52 | -26.50 | 30.01 | -19.38 | -23.32 | -47.07 |
| 34 | -53.51 | -18.93 | 31.31 | -18.14 | -22.27 | -37.00 |
| 38 | -62.86 | -32.42 | 40.89 | -18.36 | -25.87 | -46.88 |
| 42 | -66.47 | -26.19 | 44.26 | -19.78 | -21.61 | -46.57 |
| 43 | -60.81 | -9.00 | 30.10 | -13.62 | -17.67 | -35.66 |
| 45 | -68.17 | -18.23 | 31.54 | -20.24 | -20.11 | -54.99 |

[a] All energies were in kcal/mol. TΔS: the entropy changes. ΔG: the calculated binding free energy by MM-GBSA method.

**Table S4.** Energy contributions of key residues for CCR5 bound systems in the active site[a]

| Residue | CCR5-25 | CCR5-29 | CCR5-45 | CCR5-MAR | CCR5-NIF |
|---|---|---|---|---|---|
| 37 | -0.052 | -0.279 | -0.001 | 0.008 | -0.031 |
| 86 | -1.258 | -3.140 | -2.651 | -2.461 | -3.326 |
| 89 | -0.163 | -1.775 | -0.842 | -0.925 | -1.366 |
| 108 | -0.504 | -1.289 | -0.957 | -0.769 | -1.467 |
| 109 | -0.548 | -1.076 | -0.725 | -0.691 | -1.244 |
| 112 | 0.027 | -0.486 | -0.067 | -0.402 | -0.564 |

| | | | | | |
|---|---|---|---|---|---|
| 194 | -0.480 | -1.198 | -0.849 | -0.338 | -0.766 |
| 195 | 0.123 | -1.301 | -0.304 | -0.691 | -0.236 |
| 198 | -0.599 | -0.852 | -0.651 | -1.898 | -1.031 |
| 248 | 0.050 | -1.080 | 0.106 | -0.005 | -0.116 |
| 251 | 0.734 | -0.561 | 0.031 | -0.646 | -0.354 |
| 255 | -1.142 | -0.169 | -1.448 | -0.832 | -0.322 |
| 259 | 0.089 | 0.026 | -0.057 | -0.001 | -0.003 |
| 279 | -1.100 | -0.059 | -0.612 | -0.200 | -0.117 |
| 283 | 2.449 | -0.461 | 1.240 | 1.623 | 0.800 |
| 287 | -0.485 | -1.639 | -1.022 | -0.358 | -1.571 |

[a] All energies were in kcal/mol.

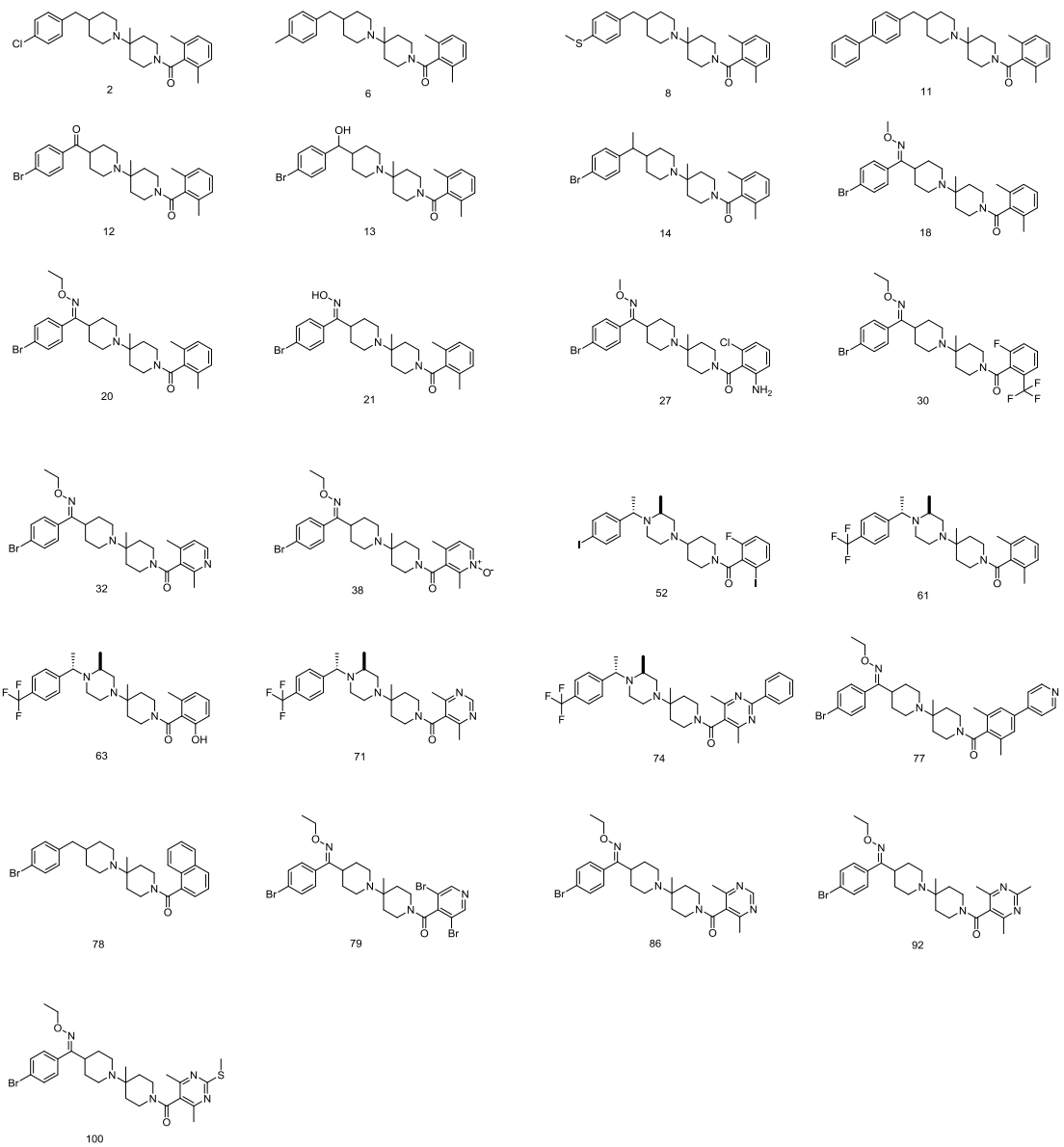
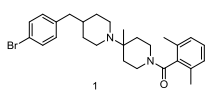



**Fig. S1.** Chemical structures of training set compounds.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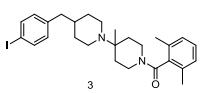
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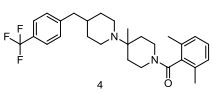
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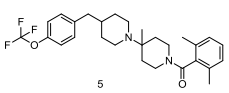
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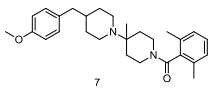
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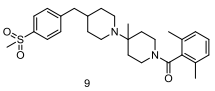
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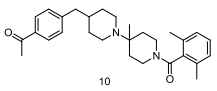
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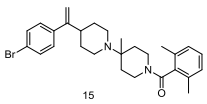
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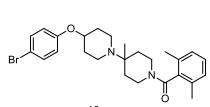
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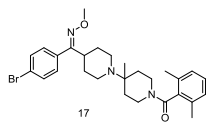
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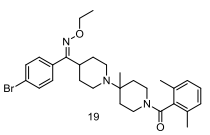
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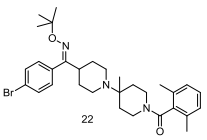
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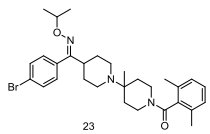
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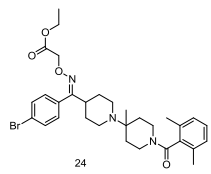
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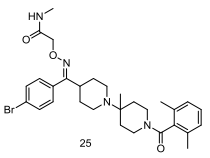
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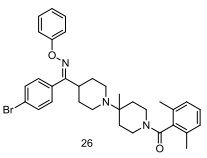
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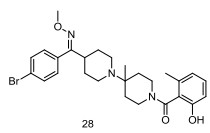
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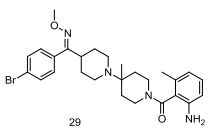
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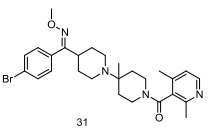
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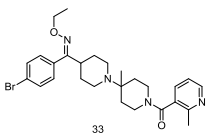
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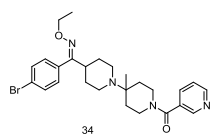
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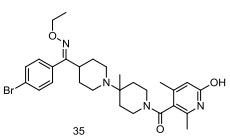
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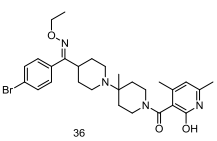
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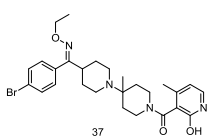
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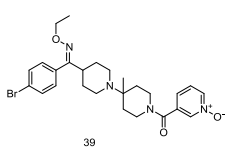
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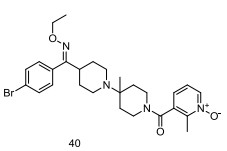
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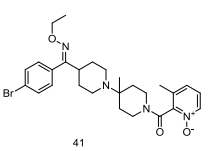
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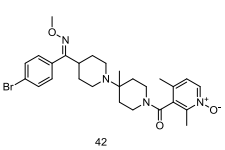
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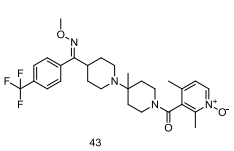
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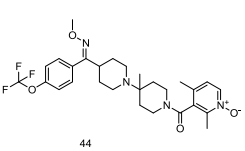
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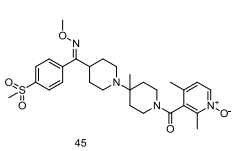
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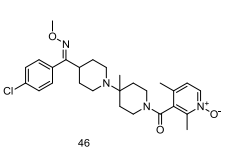
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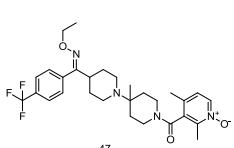
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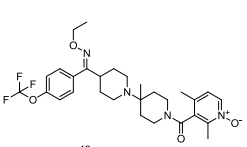
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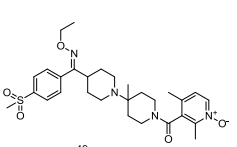
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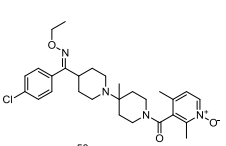
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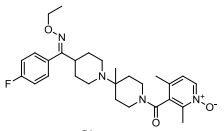

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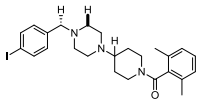

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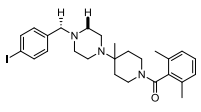

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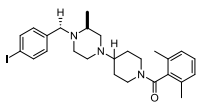

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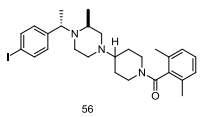

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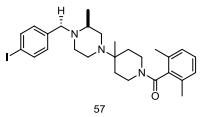

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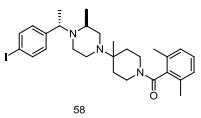

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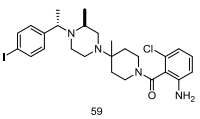

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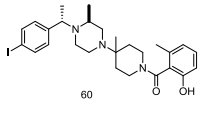

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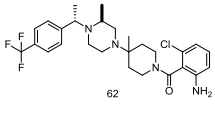

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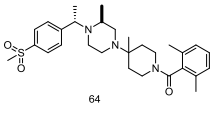

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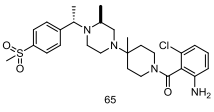

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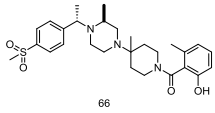

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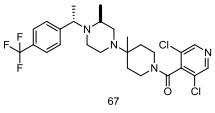

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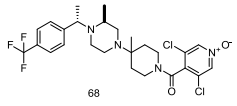

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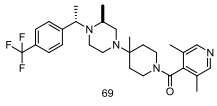

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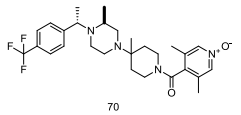

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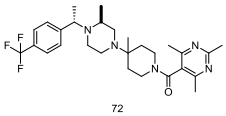

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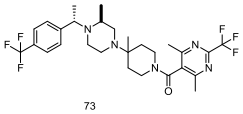

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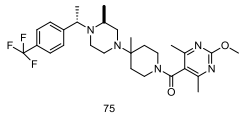

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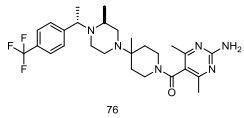

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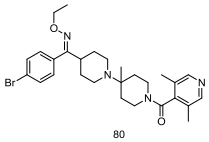

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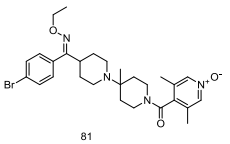

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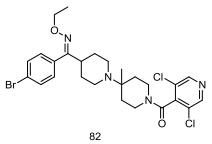

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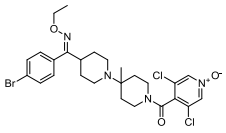

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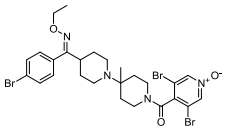

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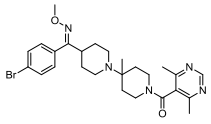

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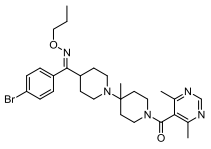

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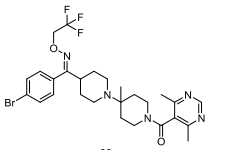

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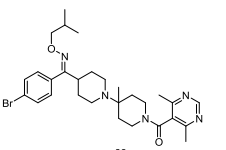

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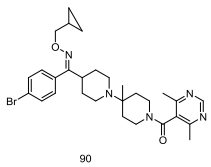

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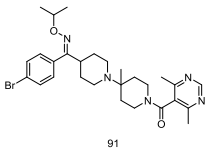

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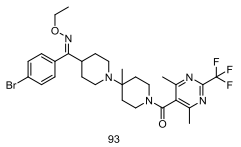

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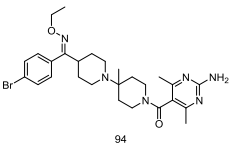

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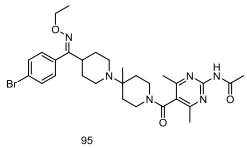

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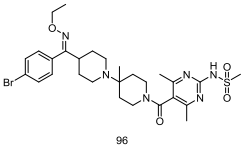

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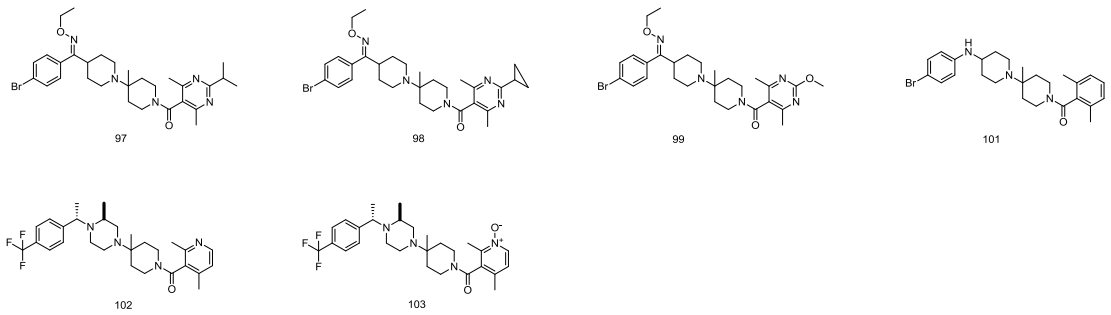



**Fig. S2.** Chemical structures of test set compounds.

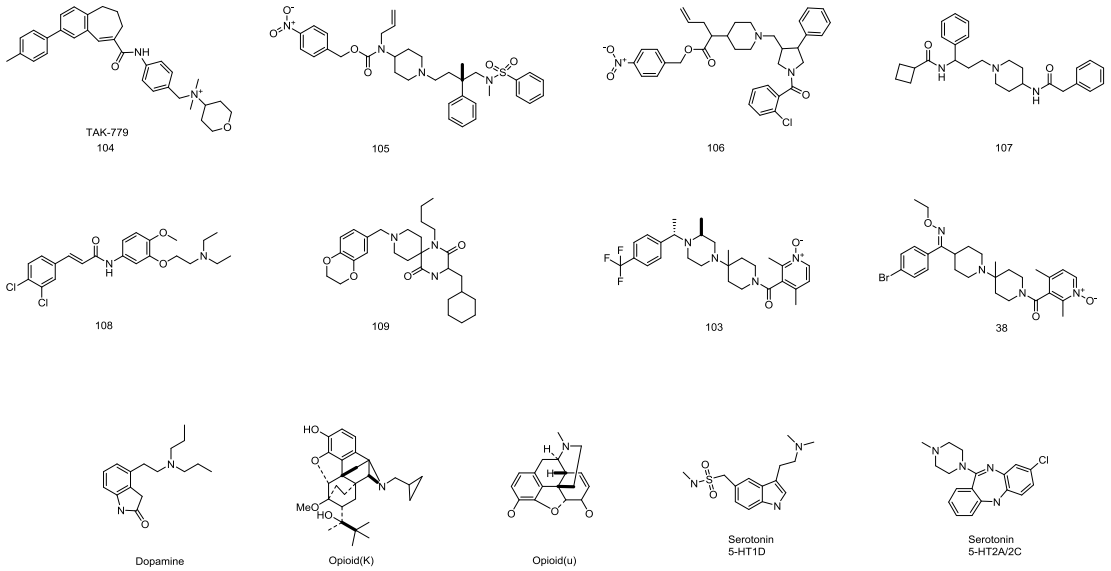



**Fig. S3.** Chemical structures of potent CCR5 inhibitors and CNS drugs.

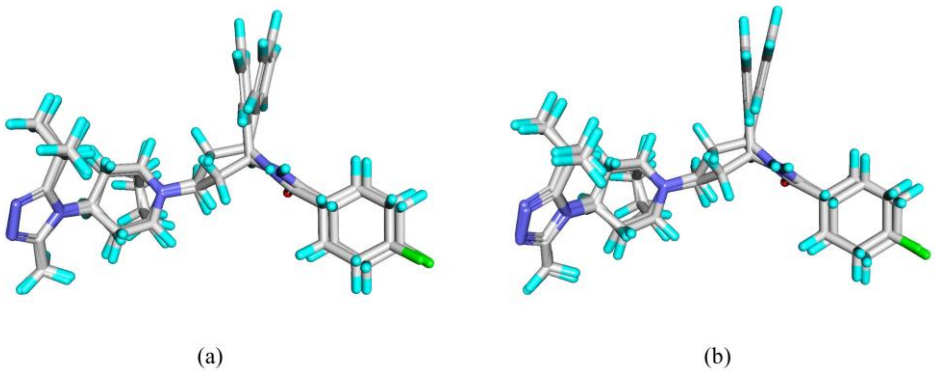
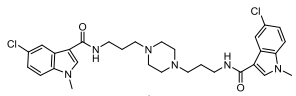



**Fig. S4.** Comparison of conformational alignments. (a) The binding conformations of cocrystal ligand derived by LibDock method. (b) The binding conformations of cocrystal ligand derived by Surflex-Dock method.



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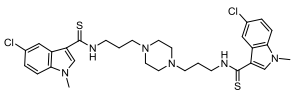

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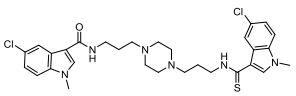

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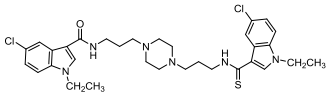

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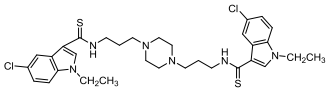

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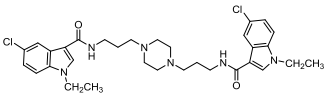

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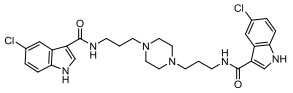

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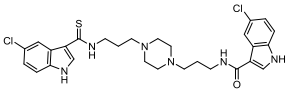

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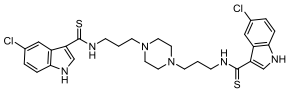

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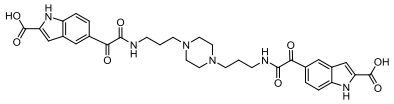

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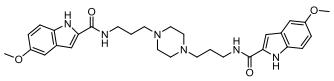

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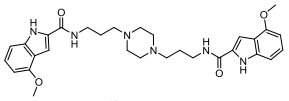

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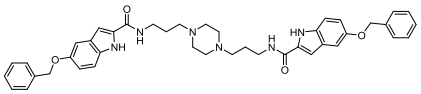

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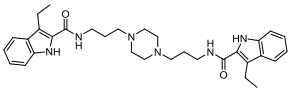

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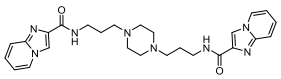

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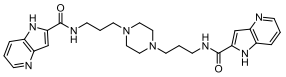

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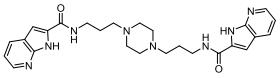

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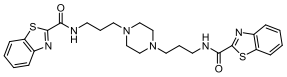

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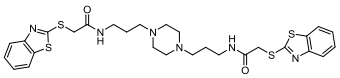

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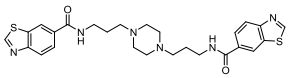

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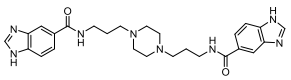

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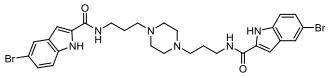

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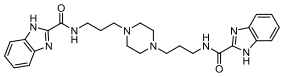

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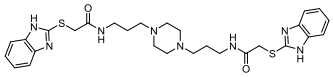

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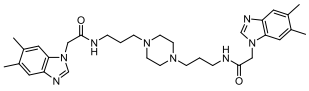

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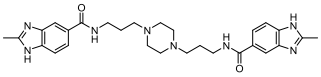

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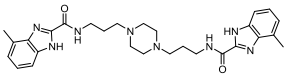

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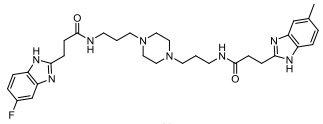

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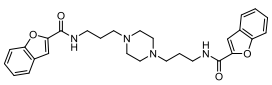

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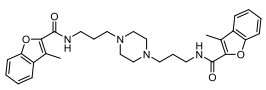

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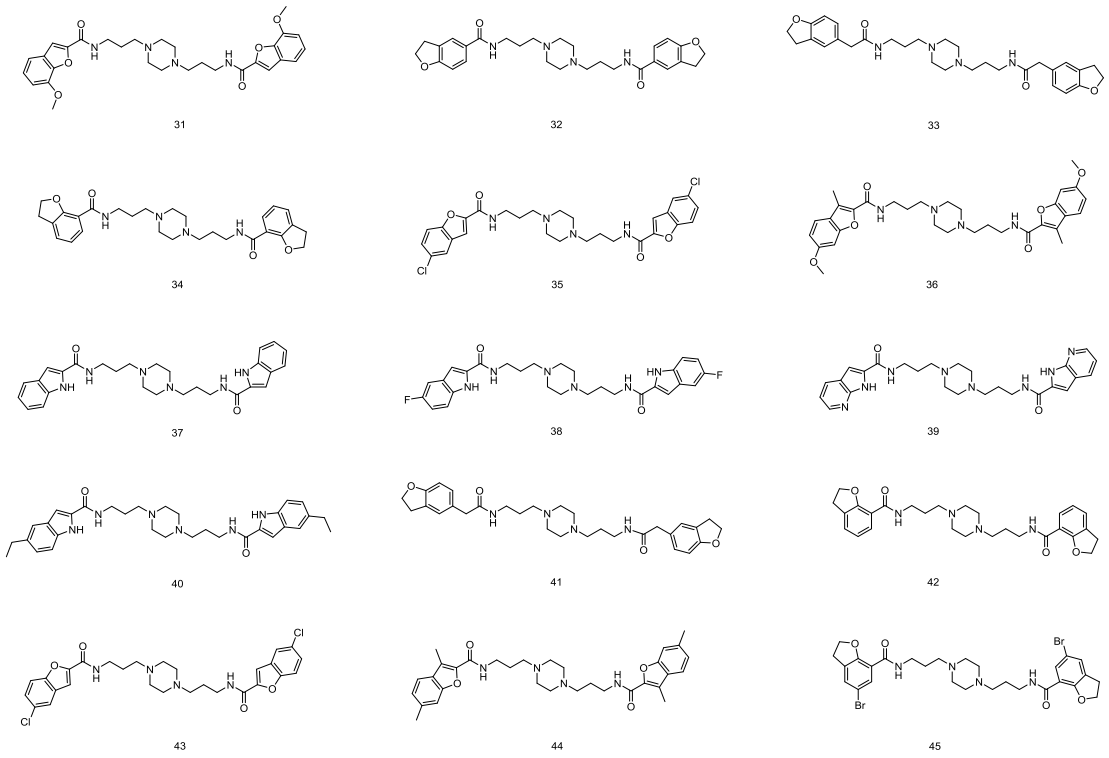


**Fig. S5.** Chemical structures of candidates.

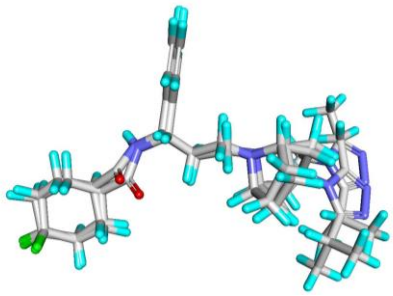

**Fig. S6.** Comparison of conformational alignments. (a) The binding conformations of cocrystal ligand derived by MD simulation.

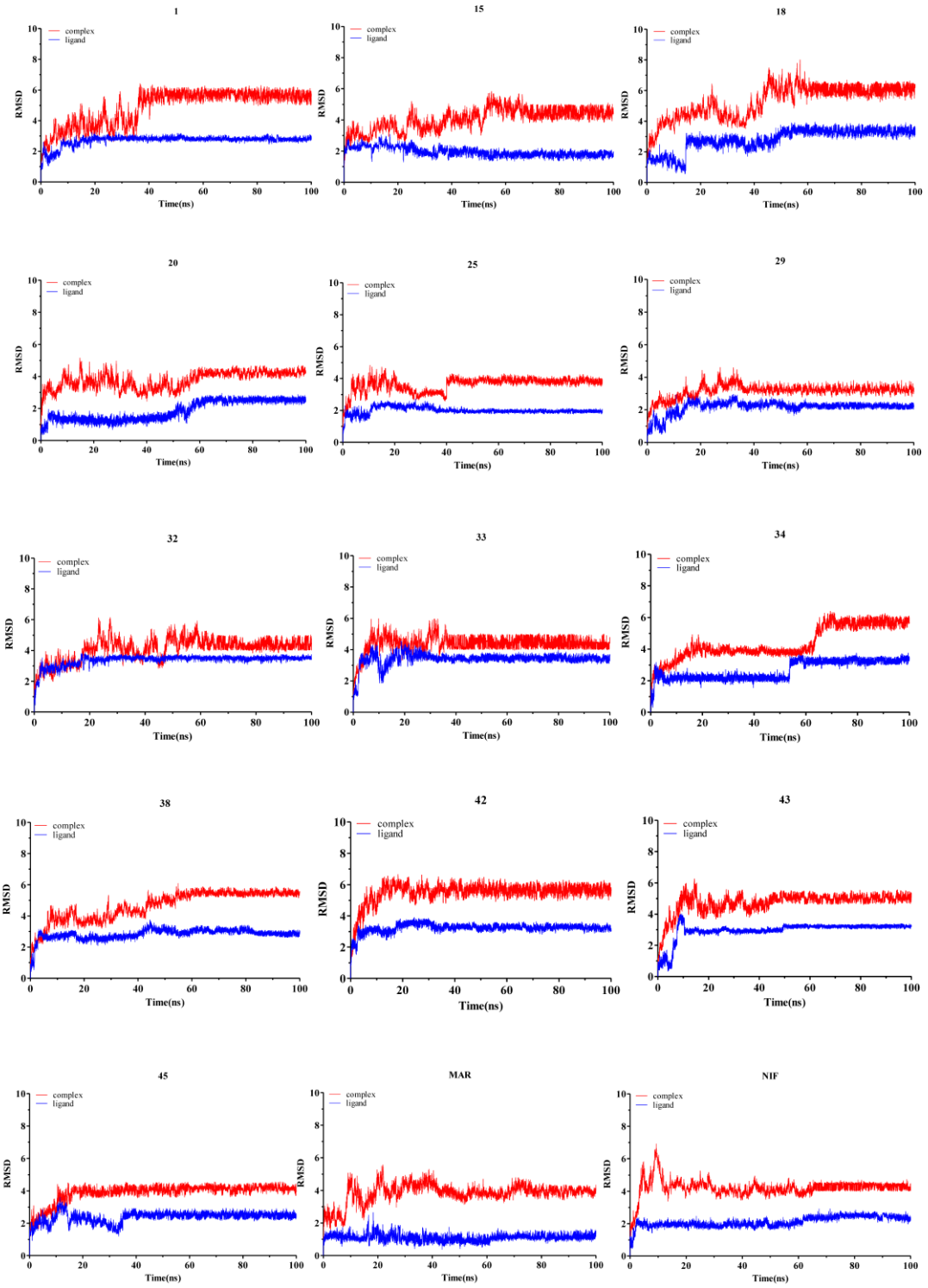


**Fig. S7.** RMSDs of backbone atoms (C, Cα, and N) for CCR5-analogs complex systems and RMSDs of heavy atoms for ligands.

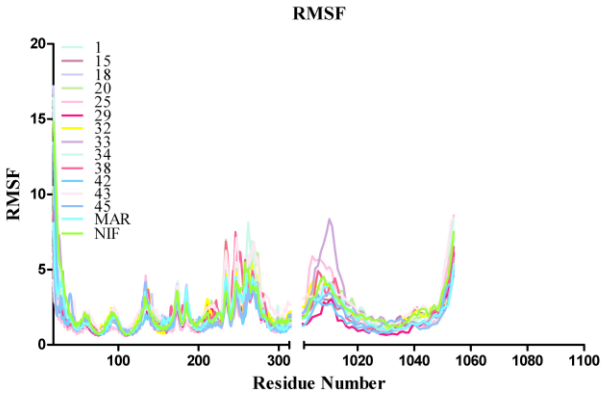


**Fig. S8.** RMSF of each residue for CCR5-analogs complex systems.

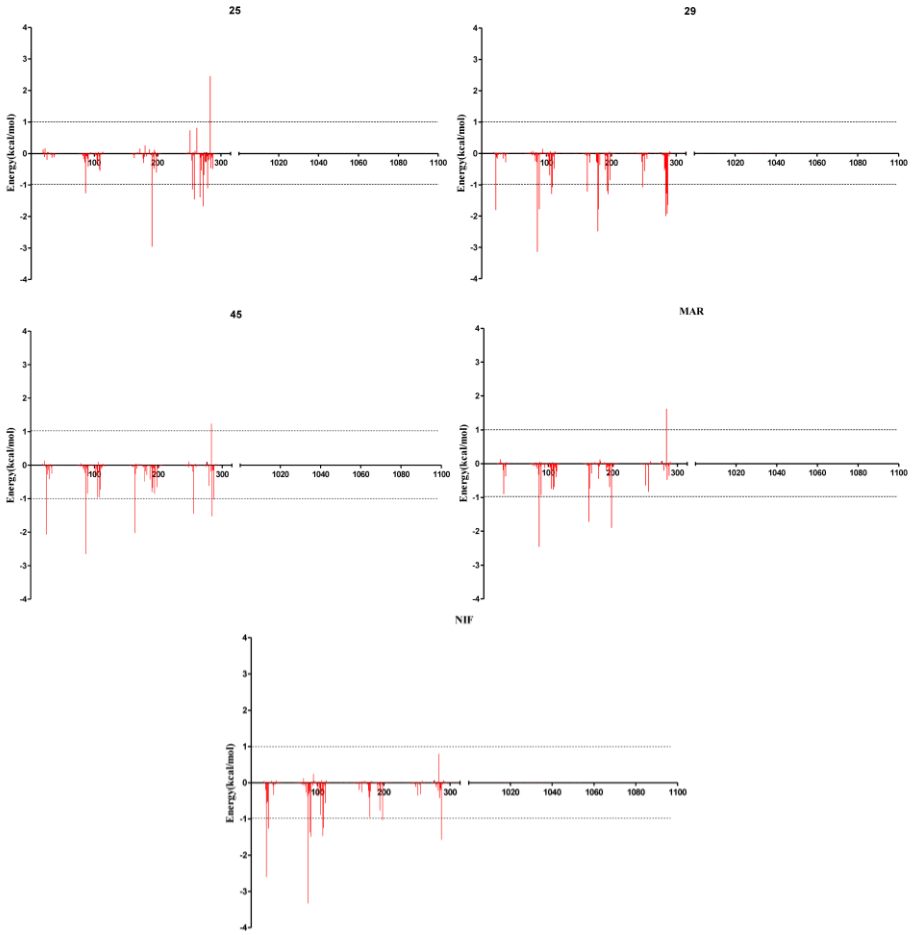


**Fig. S9.** The residue interaction spectrum for potent CCR5 inhibitors.