Supplementary Information

Impact of domain knowledge on predictions of binding energies by alchemical free energy calculations

A. S.J.S. Mey, J. Juárez-Jiménez, J. Michel

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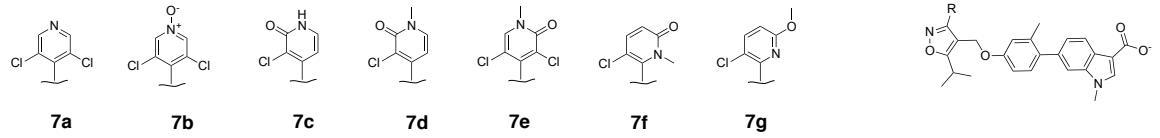
Contents

1 Datasets

The chemical structure of compounds used for relative free energy calculations can be found in figure 1 and figure 2. The four different data sets, LitSet 1, LitSet 2, and D3R grand challenge set 1 and 2 are shown.

LitSet 1



LitSet 2

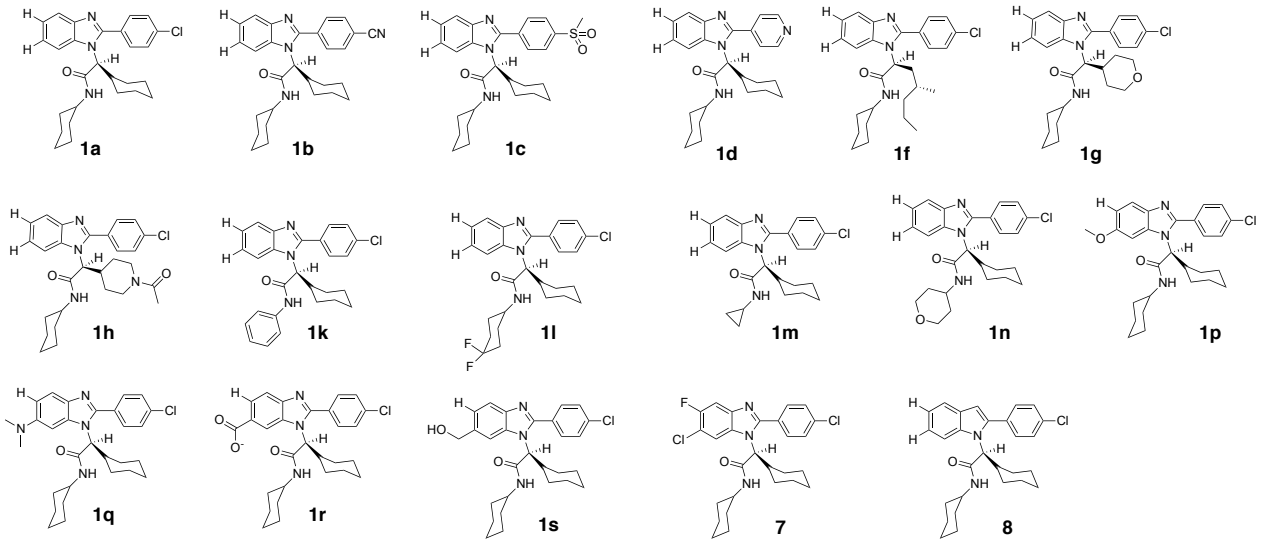
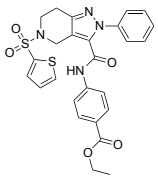
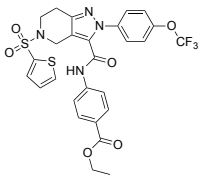


Figure 1: Compounds of the literature data sets used for the computations

Set 1



FXR_17



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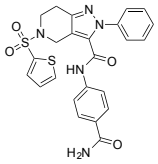

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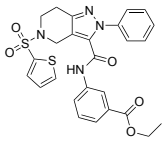

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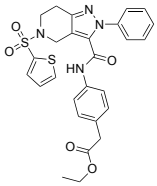

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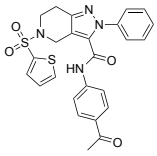

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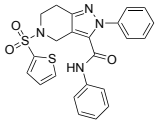

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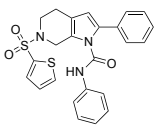

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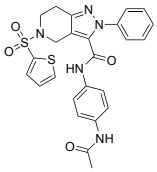

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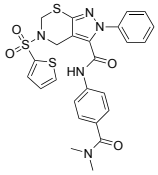

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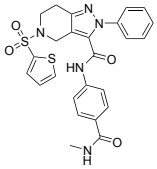

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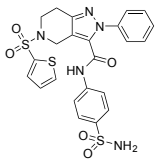

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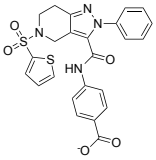

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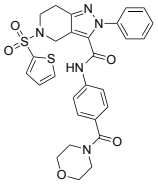
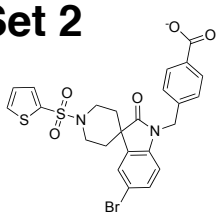


FXR_102

Set 2



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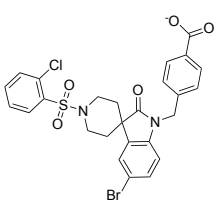

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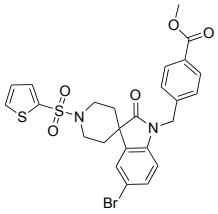

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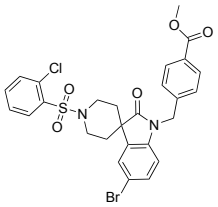

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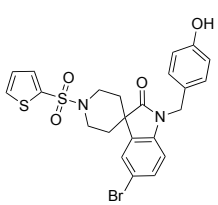

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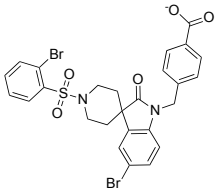

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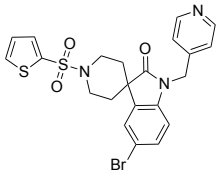

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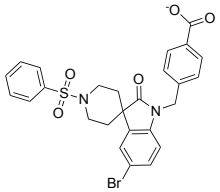

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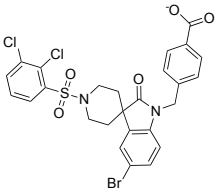

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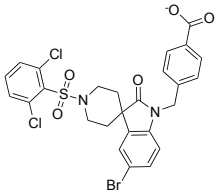

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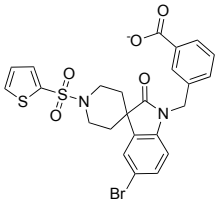

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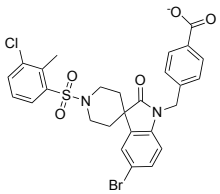

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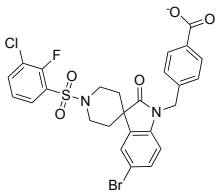

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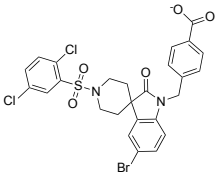

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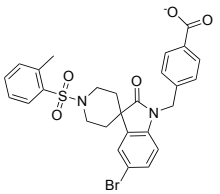

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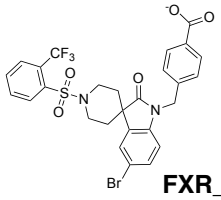

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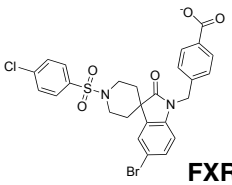


FXR_89

Figure 2: D3R grand challenge datasets set1 and set2

Table 1: Summary of perturbation λ windows for run1 and run2 of Set1 stage2, if perturbation not listed, then 17 windows were used.

Number of λ windows	
9	26
FXR99∼FXR91	FXR95∼FXR48
FXR49∼FXR46	FXR101∼FXR91
FXR46∼FXR49	FXR91∼INT02_BM2
FXR98∼FXR46	FXR96∼FXR91
FXR49∼INT01	INT01∼FXR102
INT01∼FXR49	FXR102∼INT01
	FXR91∼FXR96
	INT02_BM2∼FXR91

2 Details of Alchemical free energy protocols for Set1 and Set2

For set1 all perturbations were run twice. The following perturbations were additionally run, using the same number of windows as before and using a forwards and backwards perturbation: **49-91**, **102-INT01**, **INT02_BM2, 91**, **96-98** and **100-98**. For set2 data 68 of the perturbations were run using 9 windows, 22 using 17 windows and 18 using 26 windows and a summary can be found in file: jobtype_set2_stage2.dat, all perturbations were run twice and perturbation with irregularities were run 3 times. These additional runs were, both in forwards and backwards direction: **10_BM1-Int01_BM1**, **76-77_BM2**, **83_BM2,82_BM2** and **79_BM1B-Int01_BM1**. All relevant input files for repeating calculations and analysis can be found on github: `https://github.com/michellab/D3R_GC2_Data`.

3 Perturbation networks

The perturbation network of LitSet1 and LitSet2 can be found in figure 3 and figure 4.

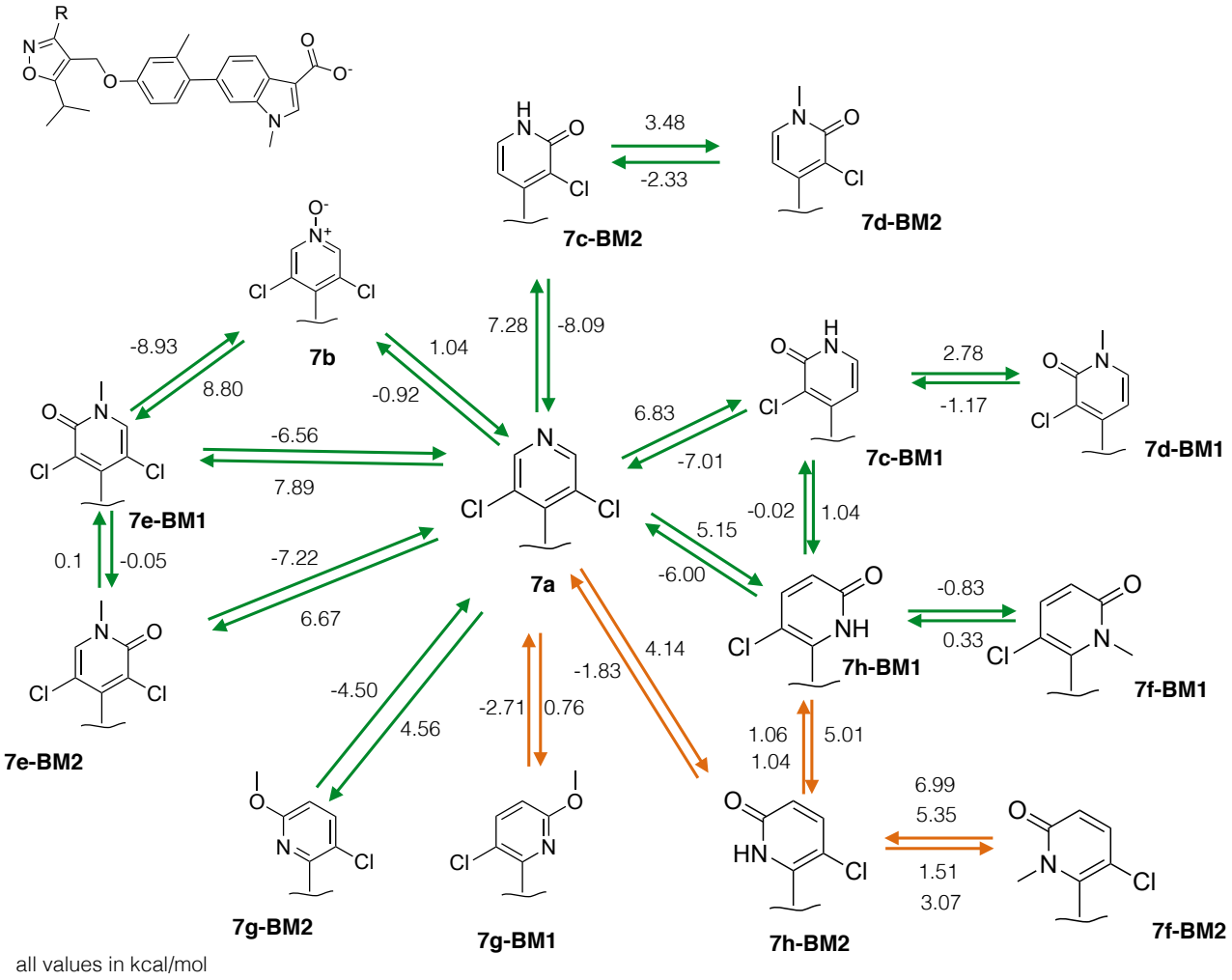


Figure 3: Perturbation map for LitSet1

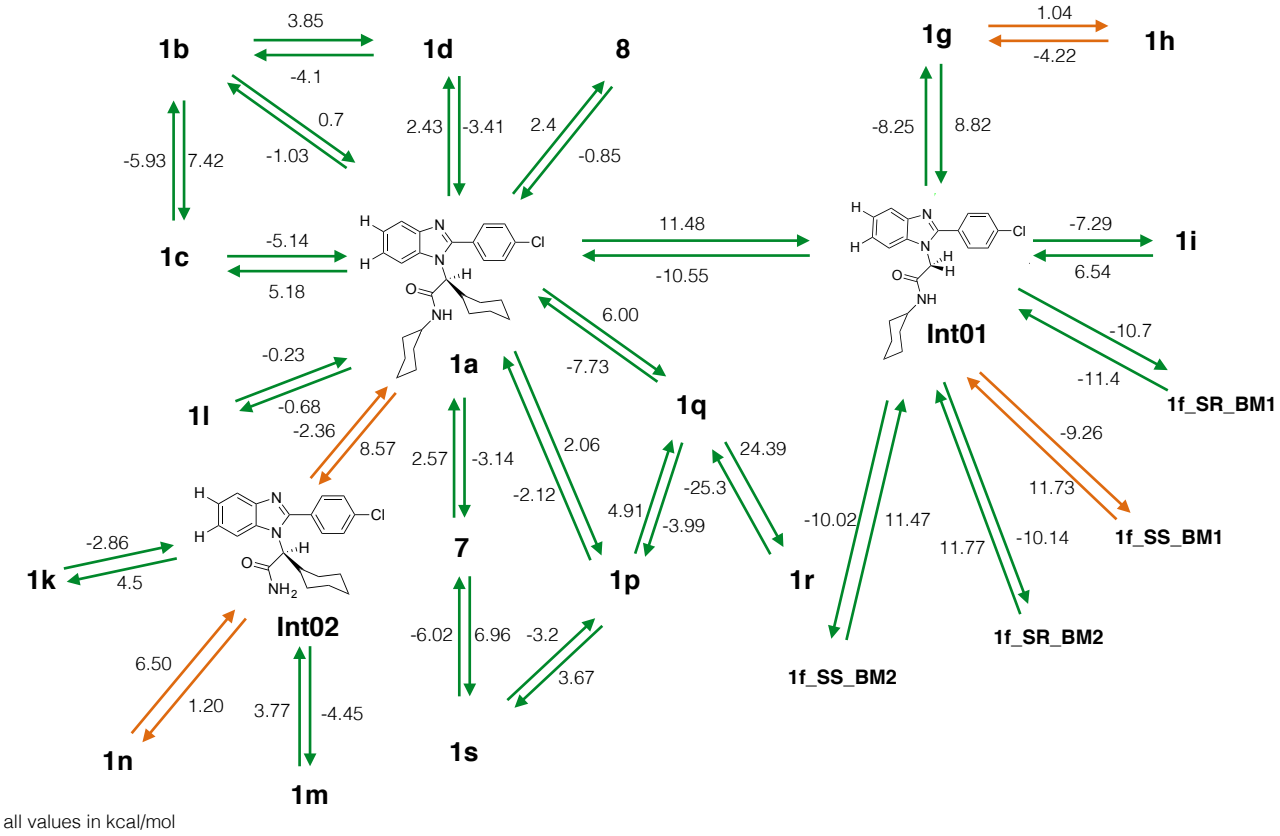


Figure 4: Perturbation map for LitSet2

The perturbation network of set1 and set2 of the D3R grand challenge 2 can be found in figure 5, figure 6, and figure 6.

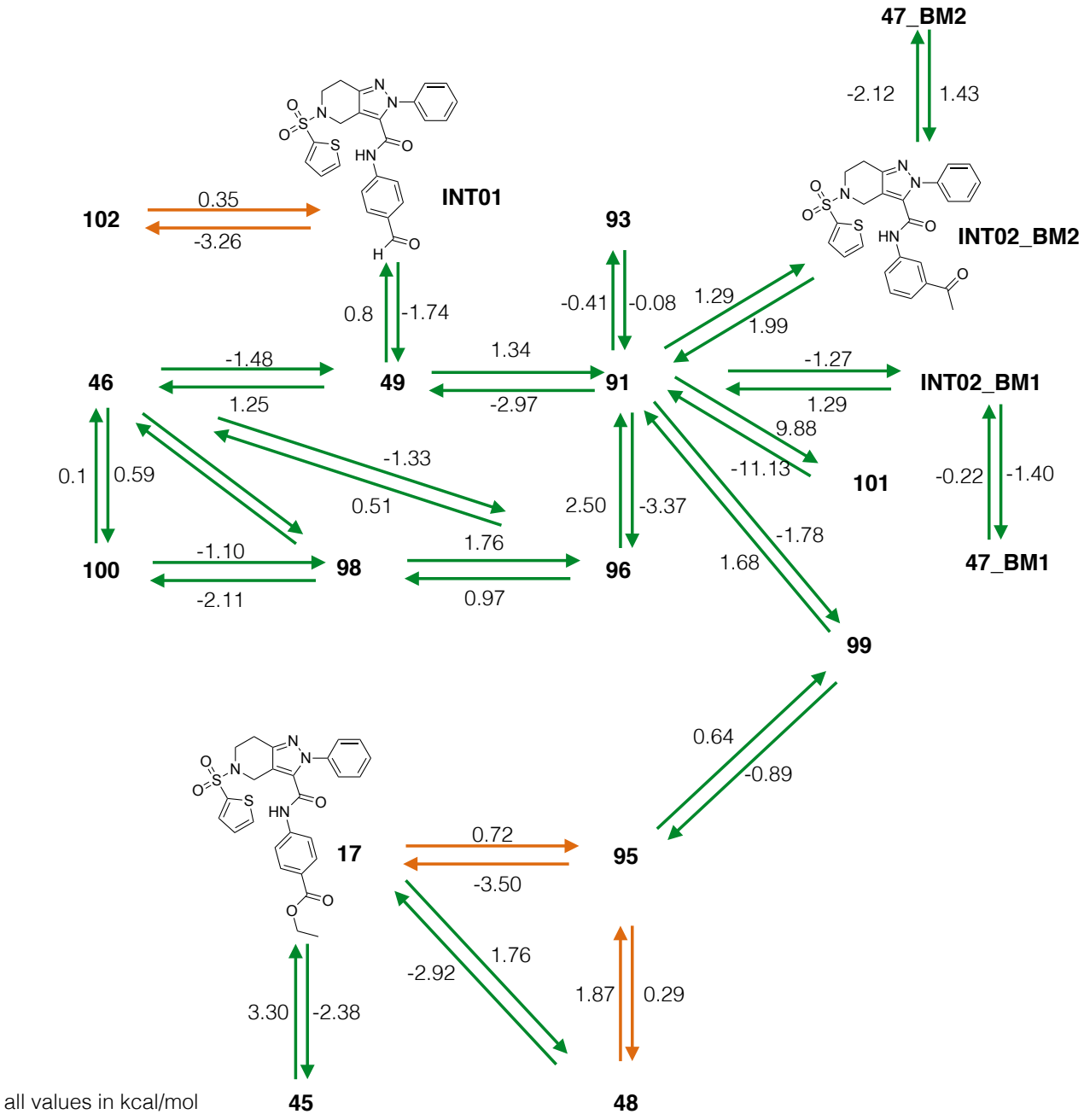


Figure 5: Perturbation map for set1 of the D3R grand challenge

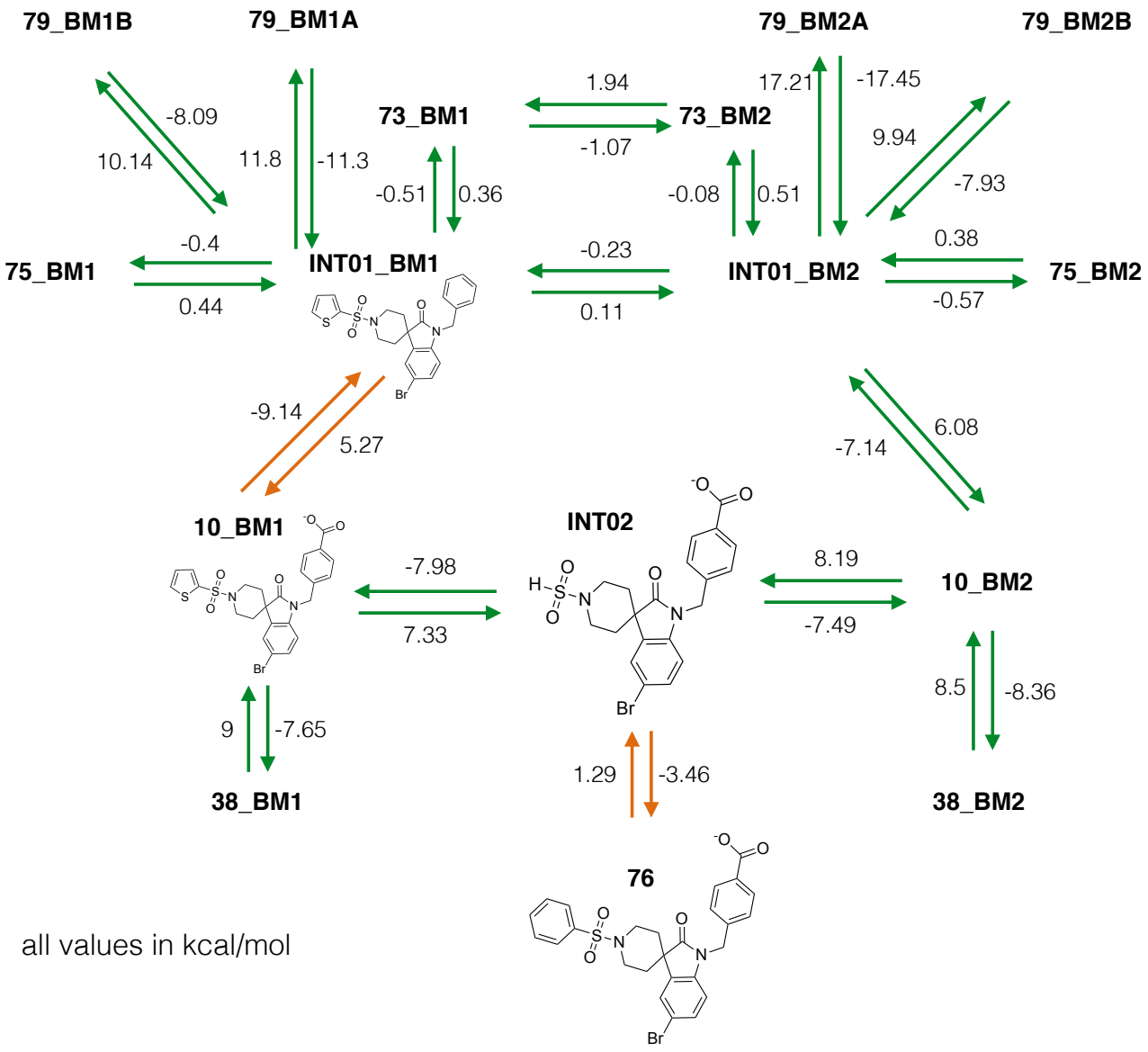


Figure 6: First part of the perturbation network for set2 of the D3R grand challenge

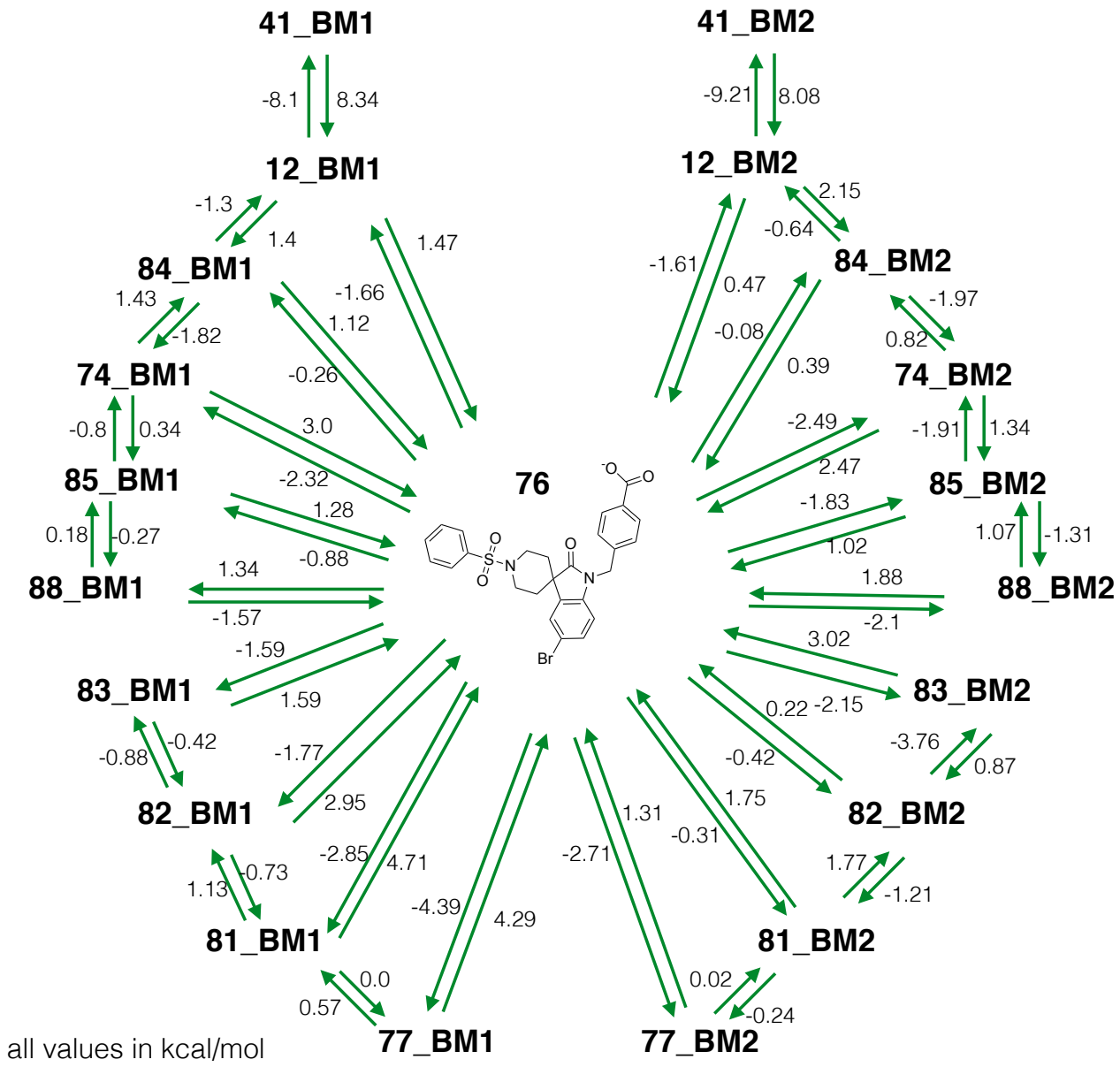


Figure 7: Second part of the perturbation network for set2 of the D3R grand challenge

4 Scaling for LitSet1 and LitSet2

Figure 3 and figure 4, show the scaling (1 - 0.5 and experimental values) of the estimated free energies (A) and the resulting Pearson correlation coefficient (B) for LitSet1 and LitSet2 respectively.

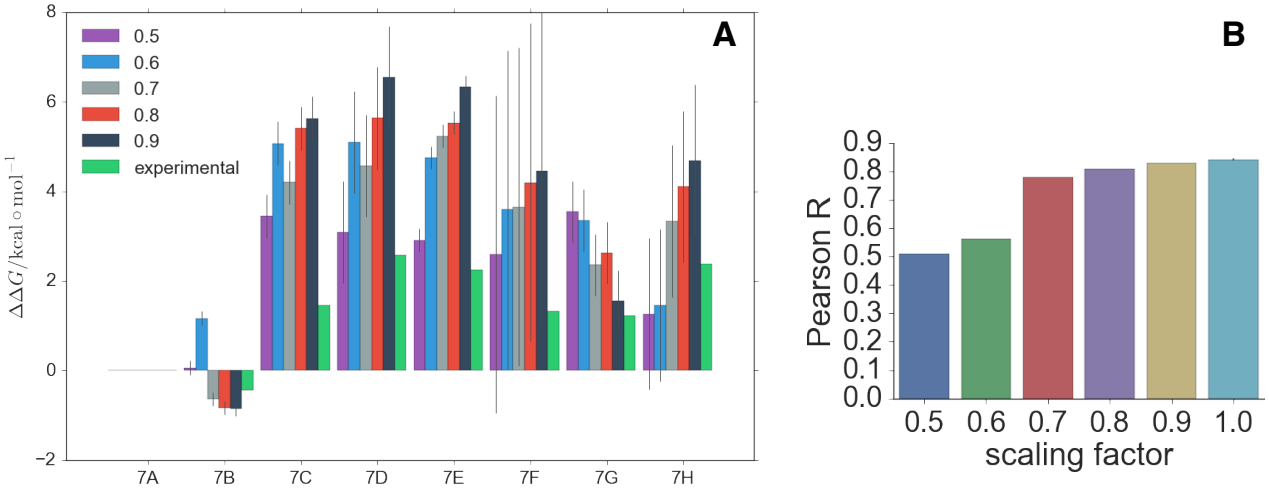


Figure 8: A: Scaling of estimated free energies for LitSet1 compounds, B: resulting correlation for scaling

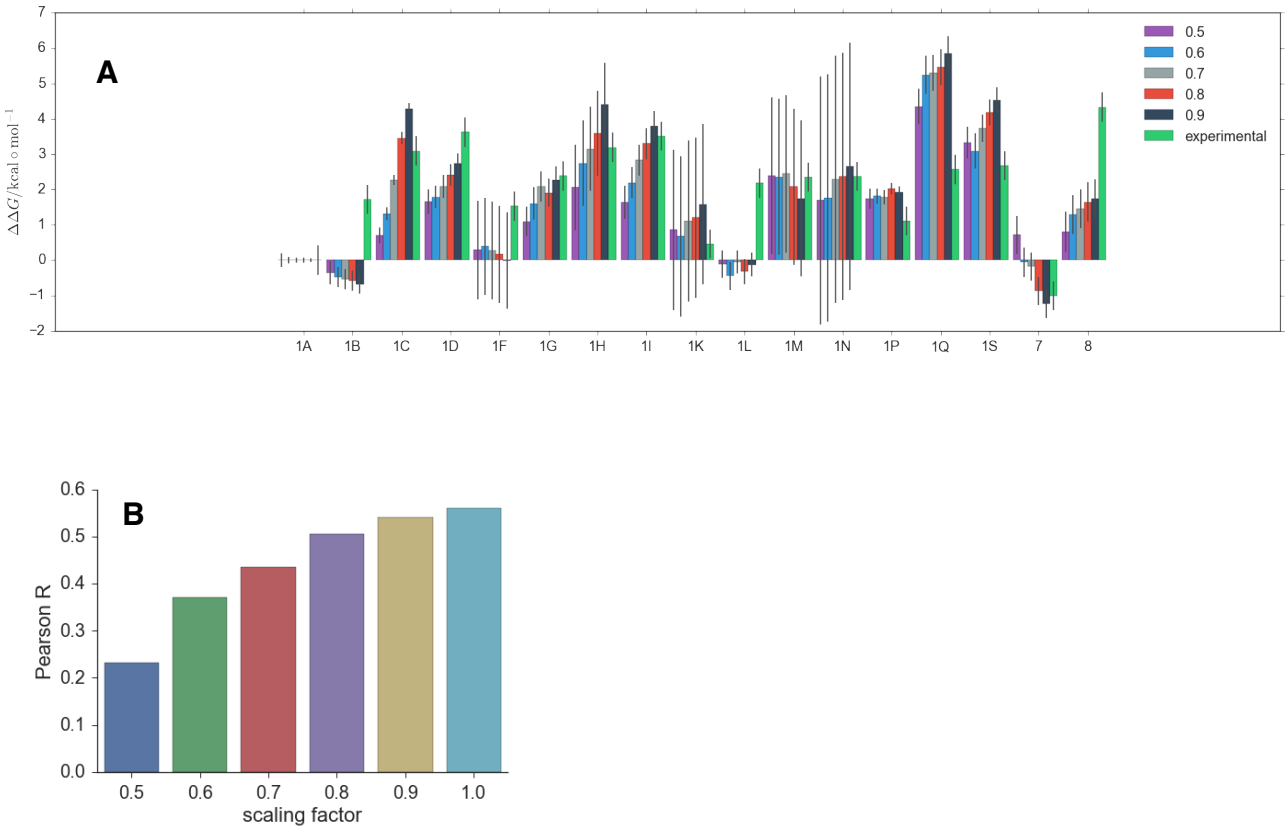


Figure 9: A: Scaling of estimated free energies for LitSet2 compounds, B: resulting correlation for scaling

5 Comparison to other Protocols

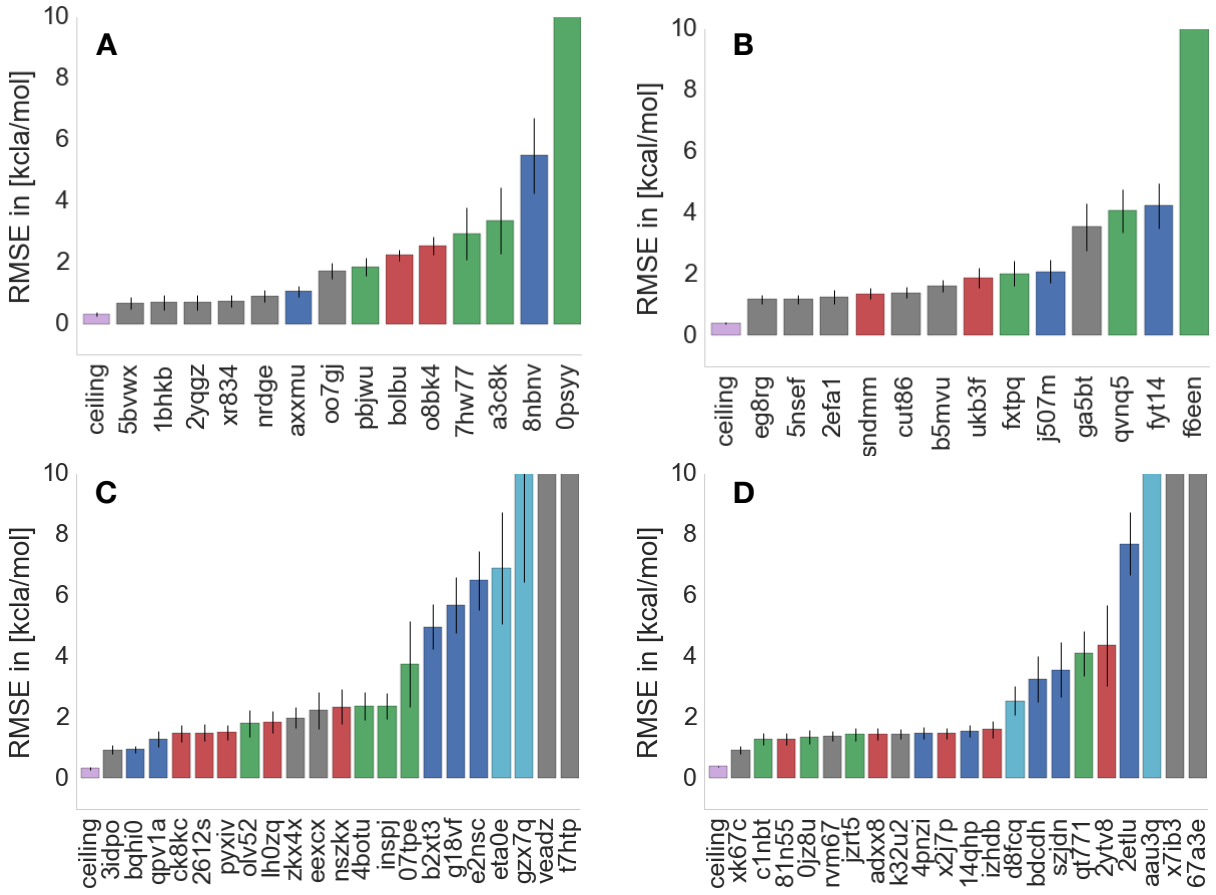
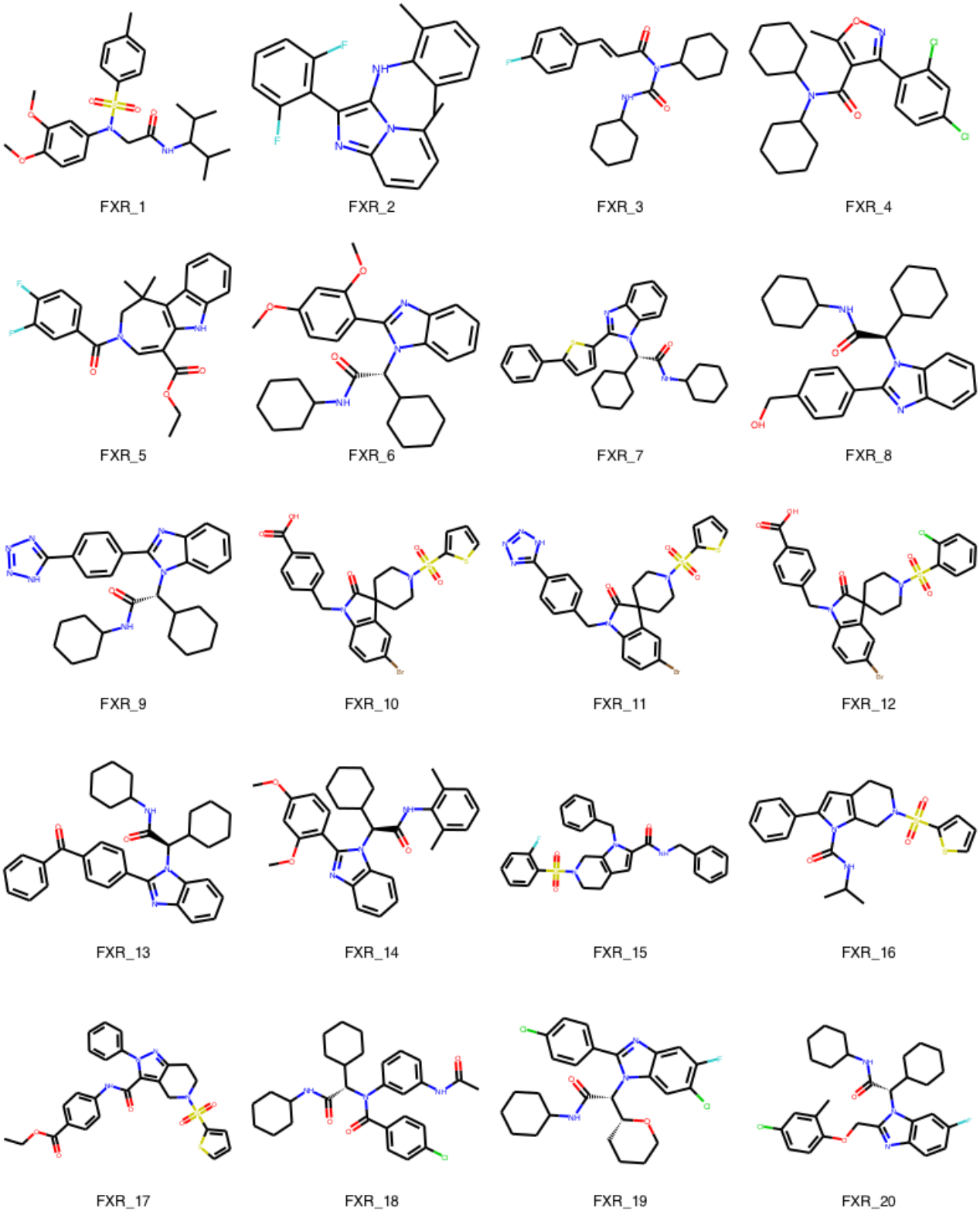
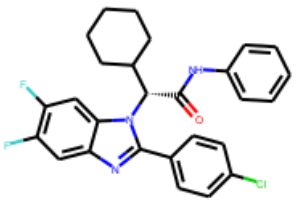


Figure 10: A: set1 stage 1, B: set2 stage 1, C: set1 stage 2, D: set2 stage 2. RMSD deviation of all submission protocols.

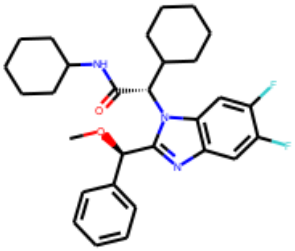
6 Complete ligand library

Figure 6 shows all 2D structures of the 102 inhibitors in the dataset provided.

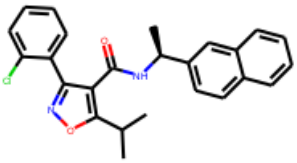




FXR_21



FXR_22



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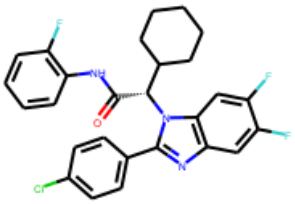

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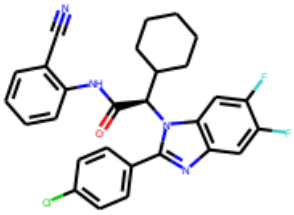

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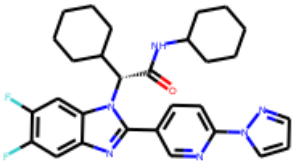

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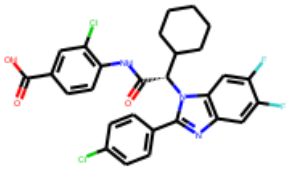
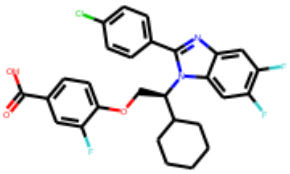
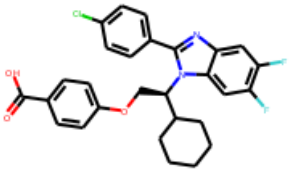


FXR_27



FXR_28



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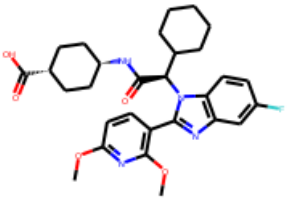

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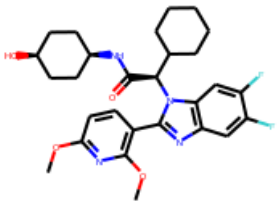
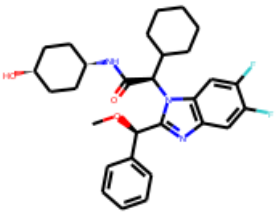


FXR_31



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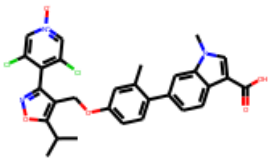

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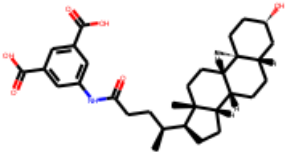

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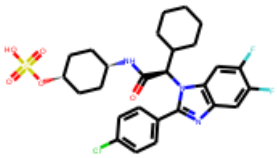

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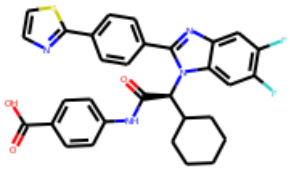

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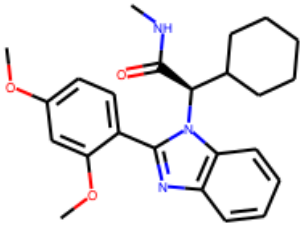

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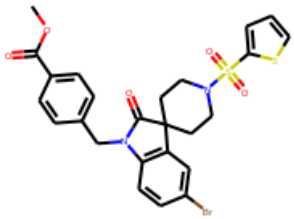

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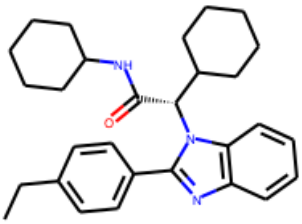

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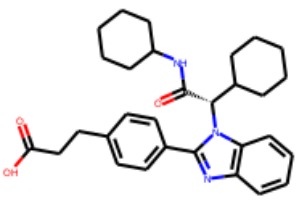

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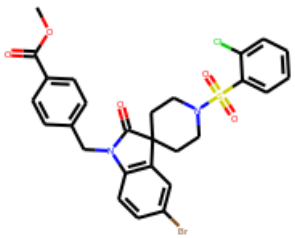

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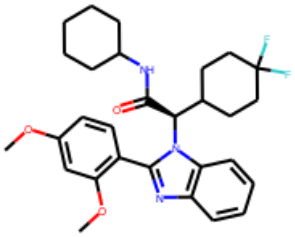

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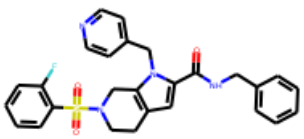

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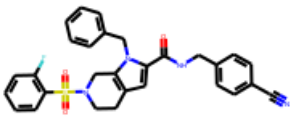

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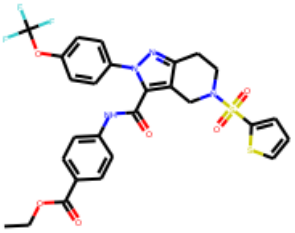

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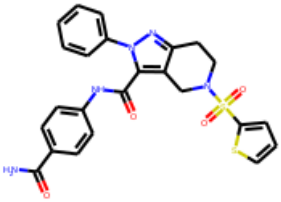

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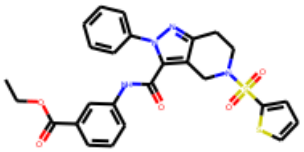

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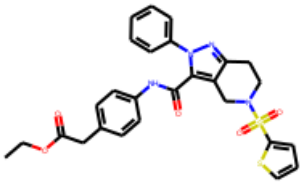

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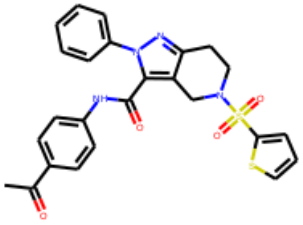

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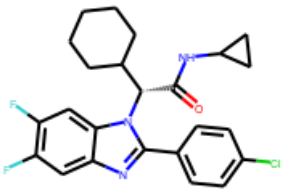

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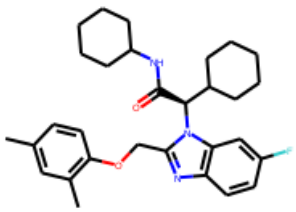

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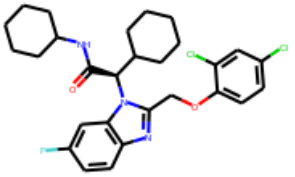

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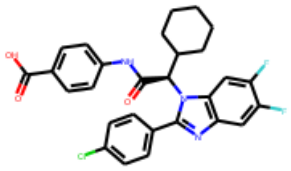

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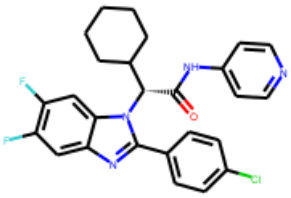

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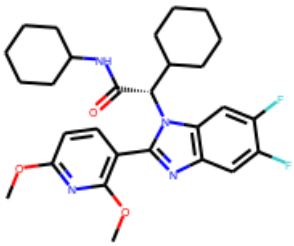

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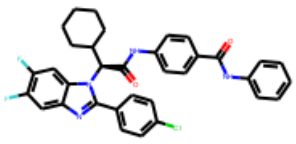

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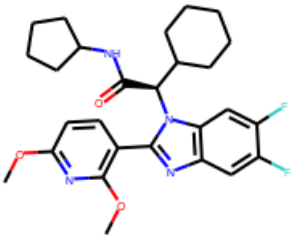

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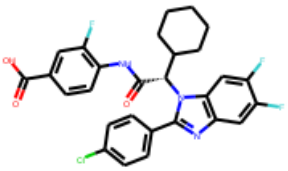

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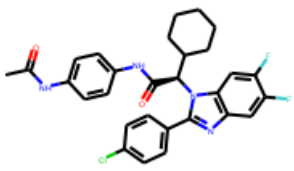

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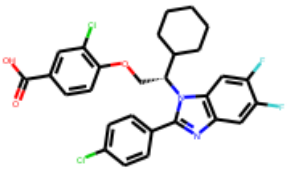

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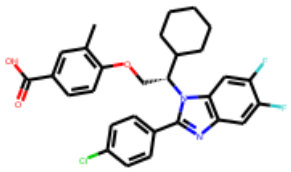

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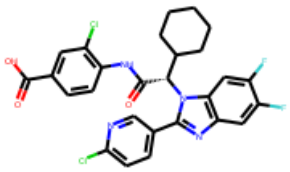

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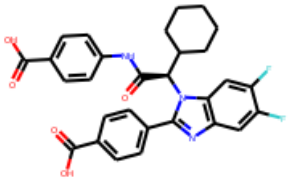

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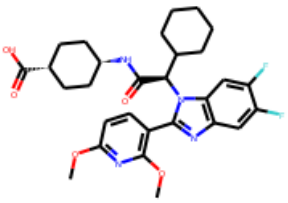

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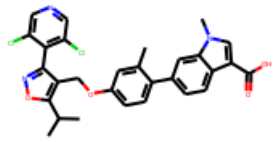

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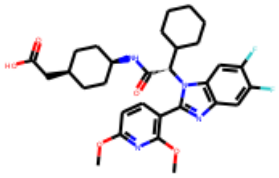

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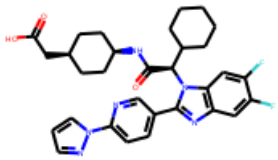

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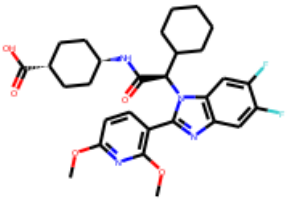

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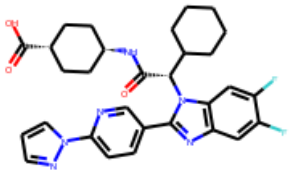

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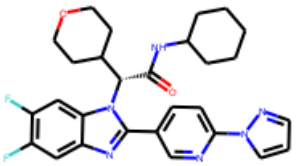

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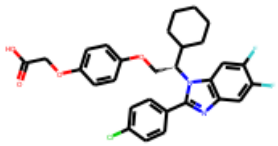

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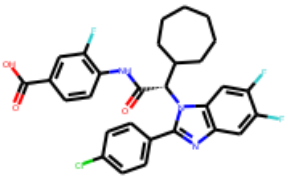

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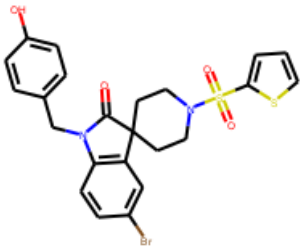

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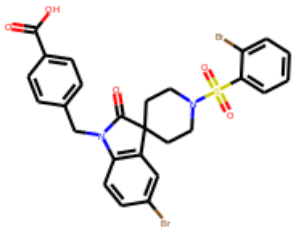

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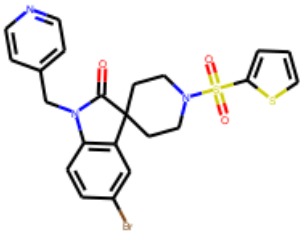

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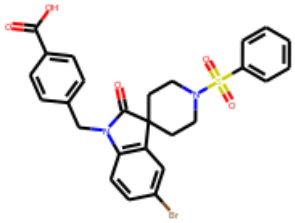

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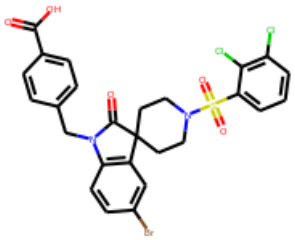

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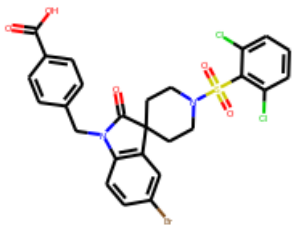

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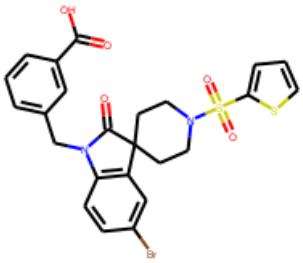

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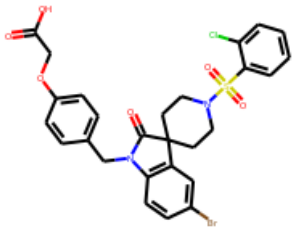

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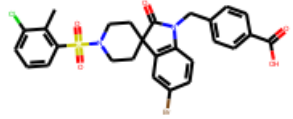
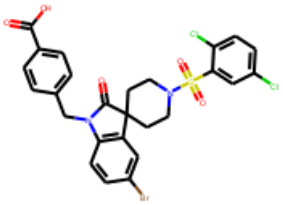


FXR_81

FXR_82



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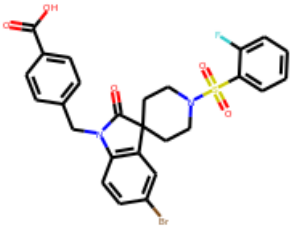

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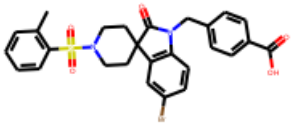

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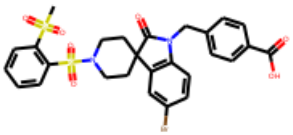
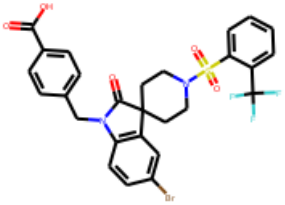


FXR_86

FXR_87



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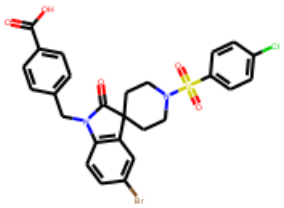

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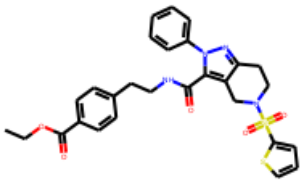

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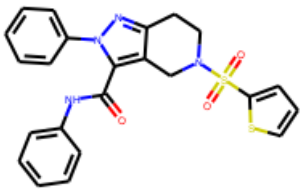
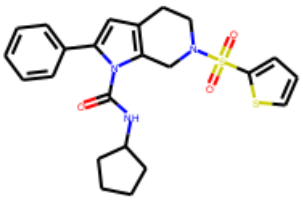


FXR_91



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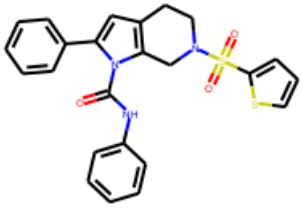

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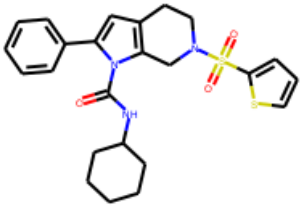

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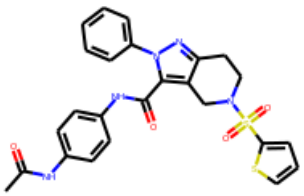

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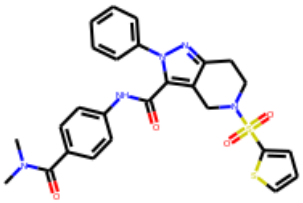

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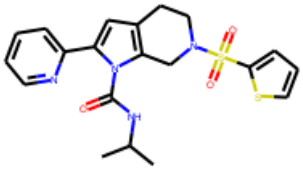

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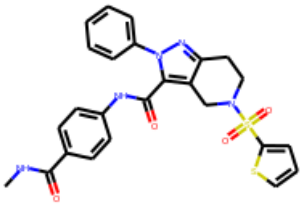

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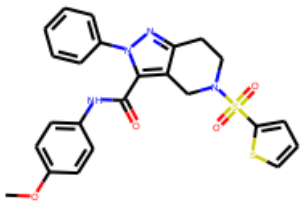

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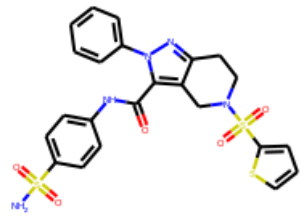

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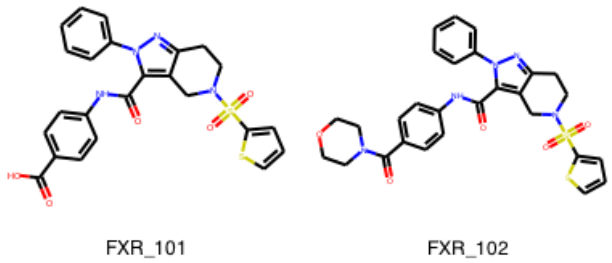

Figure 11: Inhibitor data set consisting of 102 ligands and their 2D structural representations and dataset ID.