








| Molecule | Observed COX-2 Inhibitor? | Predicted COX-2 Inhibitor? | Molecule | Observed COX-2 Inhibitor? | Predicted COX-2 Inhibitor? |
|---|---------------------------|----------------------------|--|---------------------------|---|
|  Celecoxib | Yes | Yes(97%) |  20-2 | No | No(59%) |
|  Valdecoxib | Yes | Yes(89%) |  20-3a | Yes | No(60%) False negative |
|  Etoricoxib | Yes | Yes(97%) |  Rofecoxib | Yes | Yes(68%) |
|  DuP-697 | Yes | Yes(92%) | | | |

Fig. 15 COX-2 classification results for marketed COX-2-selective inhibitors and other compounds. The numbers in parentheses are the confidence estimates

We planned on only synthesizing a small number of compounds, so we were willing to accept a false negative. False-positive predictions are much more costly because the compound could be selected for synthesis and result in an inactive compound.

Plots of observed versus predicted values for COX-2 pIC₅₀, COX-1 pIC₅₀, and COX-1/COX-2 selectivity are shown in Fig. 16. Table 3 shows statistics for each regression model.

12 Scaffold Hopping

Rofecoxib was used as the starting structure for combinatorial transformations using the default settings in MedChem Studio. Forty-six new analogs were generated. Of these, 11 were missing the phenylsulfonyl group and were discarded as unlikely to be of interest. Thirteen of the remaining 35 compounds were modified in the phenyl ring or had a methylene group inserted between the scaffold and one of the side chain rings. These compounds and three additional products where the scaffold was opened were also eliminated from further consideration.

The thiolactones shown in Fig. 17 were chosen as interesting scaffolds to pursue. Our metabolic models indicated that **Scaffold 1** is at risk of getting hydroxylated at carbon number 5. Adding a methyl group in this position to block oxidation yields **Scaffold 2**. **Scaffold 3** features a spirocyclopropyl group at C 5, which should completely block metabolism.