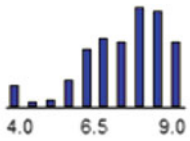
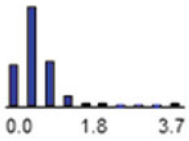
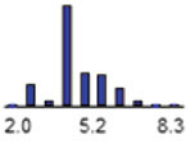
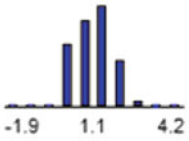
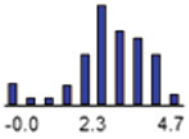
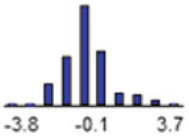
Property	pIC50 Distribution	Δ Property	Average Δ
COX-2 pIC50			0.740
COX-1 pIC50			1.067
COX-2/COX-1 selectivity			-0.327

Fig. 13 Matched molecular pair analysis for replacing methyl sulfone with a sulfonamide. Distribution plots for 188 molecules and 95 molecule pairs for COX-2 pIC50, COX-1 pIC50, and COX-2/COX-1 selectivity followed by the average change in property value are shown

indicating that the sulfonamide is always at least as potent as the methyl sulfone. A few examples of the largest effects of this structural change are shown in Fig. 14. The mean change is 0.74, indicating that – *on average* – the COX-2 IC_{50} for the sulfonamides is 5.5 times lower than for the corresponding methyl sulfone. A similar trend is observed for COX-1 activity where the average change in COX-1 pIC50 is even higher, 1.067.

This combination of effects produces an average COX-2/COX-1 selectivity (COX-2 pIC50 minus COX-1 pIC50) differential of −0.327, indicating that replacing the methyl sulfone with a sulfonamide increases COX-1 activity *more* than COX-2 activity. Thus, preferring sulfonamide analogs is in line with our goal of retaining COX-2 selectivity while increasing COX-1 potency.

11.2 QSAR Model Generation

We find that many regression models benefit from having a companion classification model to distinguish active from inactive compounds. This is because the regression model can only be trained on compounds that have quantifiable inhibitory activity, and so may not be applicable to compounds that inhibit weakly or not at all; they indicate how potent an active compound can be expected to be, but do not provide information about the much broader range of chemistries encompassed