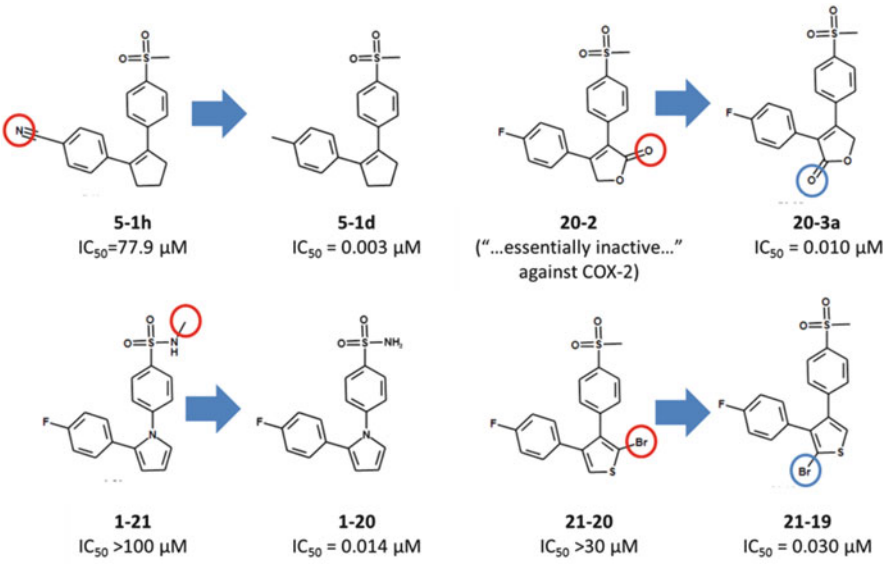

Fig. 12 Four interesting activity cliffs. COX-2 IC50 values (Chavatte, et al. 2001) are displayed below each compound's name. For compound **20-2**, the journal article reported "essentially inactive" (Prasit et al. 1999), so its IC50 was set to >100 μM. The less-active molecule is shown on the left for each pair. Structural differences between the molecules are highlighted as *red* or *blue circles*

not tolerated for the 2-furanone and thiophene scaffolds. It is important to keep these activity cliffs in mind when designing new inhibitors; however, they are dependent upon the scaffold. For example, Valdecoxib is substituted on the same side as the phenyl sulfone yet has high COX-2 potency.

The selective COX-2 inhibitors shown in Fig. 1 all bear either a methyl sulfone or a sulfonamide group at the *para* position. What are the differences in COX-1 and COX-2 activities for these functional groups across the different scaffolds in our knowledge database? Here, one can use matched molecular pair settings that correspond to small changes at single sites to gain insight into the question. Thus, the maximum number of atoms/bonds that are not a match was set to 2 and the number of sites was set to 1. This generates 586 pairs, but not all involve the methyl sulfone/sulfonamide transformation. To find pairs containing this single transformation, we used the SMIRKS string (specified in the "Reaction Query" dialog box under the "Pairs" pull-down menu) below:

$$[S:1](=[O:2])(=[O:3])[CH3:4] \gg [S:1](=[O:2])(=[O:3])[NH2:4]$$

The SMIRKS string contains an atom identifier after the colon. This creates a mapping of each atom on the left side of the "≫" to an atom on the right side. Ninety-five pairs were found. The results are displayed as distribution plots in Fig. 13. The distribution of the COX-2 pIC50 differences is either zero or positive,