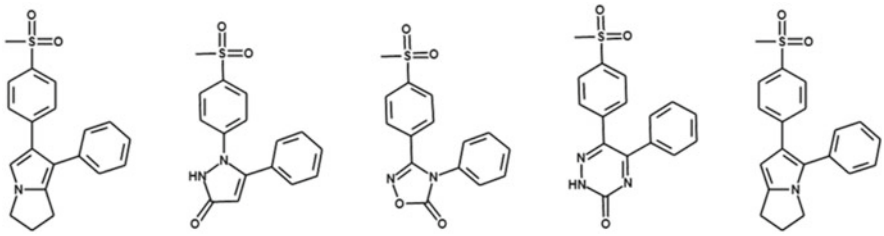

Fig. 18 Scaffold ideas generated by fragment assembly

13 Combinatorial Library Generation

Each of the nine scaffolds was decorated with 60 "A" rings and 2 "B" rings. The scaffolds are unsymmetrical so *two* 2×60 sub-libraries were created for each scaffold in order to cover more chemistry space. This is illustrated for **Scaffold 7** in Fig. 19. Thus, the nine virtual libraries each contained 240 compounds.

14 Candidate Selection

We used our cyclooxygenase classification and regression models to predict COX-1 and COX-2 activity of the virtual compounds, and we predicted their ADMET Risk scores. Distribution plots of each of these predicted properties for the various virtual libraries are shown in Fig. 20. The COX-2 classification model predicts that most of the thiolactone molecules will inhibit COX-2. Most of the scaffolds obtained from fragment assembly lead to compounds predicted to inhibit COX-2, except for compounds bearing **Scaffold 8**.

The predicted COX-2 pIC50 values are above 7 ($IC_{50} < 100$ nM) for **Scaffolds 1–6** and **9. Scaffold 7** has fewer compounds predicted to have a COX-2 pIC50 above 7 compared to these libraries. The COX-2 pIC50 values for **Scaffold 8** are typically 7 or less, consistent with the classification model. The predicted COX-1 pIC50 values are considerably lower than the COX-2 pIC50 values. **Scaffold 5** has the highest predicted COX-1 activity, although **Scaffolds 1–3** also contain fairly potent COX-1 inhibitors.

ADMET Risk is greater than 6 for about 10% of the focused WDI subset. Thus, a value of 7 or more indicates significant barriers to drug development. Only 7 of the 2,160 virtual compounds had an ADMET Risk of 7 or more. Thus, overall, the molecules have good predicted ADMET properties. **Scaffold 4** had the least favorable ADMET Risk distribution, whereas **Scaffold 6** had the most favorable distribution.

The next step in the process involved filtering the virtual libraries for "out-of-scope" predictions and adequate COX-1 and COX-2 potency. In ADMET