**Table 4** Compound filtering criteria and number of compounds remaining after each stage

| Criteria | Removed | Remaining |
|---|---|---|
| Remove OOS COX-2 classification model | 52 | 2,108 |
| Remove COX-2 classification = No | 700 | 1,408 |
| Remove OOS COX-1 regression model | 187 | 1,221 |
| Remove OOS COX-2 regression model | 40 | 979 |
| Remove COX-1 predicted $\leq$1 μM | 248 | 933 |
| Remove COX-1/COX-2 > 100 | 691 | 242 |

OOS stands for "outside of scope" of the model

Predictor, a model's applicability domain is defined as the minimum and maximum (plus a 10% tolerance) descriptor values for the training pool compounds. Prediction on compounds where one of the descriptor's values is outside of this domain is termed "out-of-scope." Table 4 shows the various filtering criteria and the number of compounds remaining after applying each filter in the sequence.

We first removed 58 compounds that were outside the scope of the COX-2 classification model. Removal of compounds predicted to be non-inhibitors of COX-2 was followed by removal of the 267 compounds that fell outside the scope of the COX-1 or COX-2 regression models. Next, compounds with COX-1 $IC_{50}$ predicted to be less than 1 μM were removed, followed by removal of compounds predicted to have a COX-1/COX-2 $IC_{50}$ ratio greater than 100. Overall, 242 compounds were excluded under our filtering criteria.

At this point, we needed to reduce the number of candidates to around 12 compounds to present to our internal review committee. We rejected compounds containing bicyclic side chains because they might be too bulky. We also rejected side chains that might cause toxicity (e.g., thiophene) or were deemed less stable.

In the end, we settled on eight candidate structures for which we solicited synthesis quotes from various contract chemistry organizations (Fig. 21). Four candidates contained a thiolactone and four shared a dihydropyrrolizine scaffold. All of the proposed compounds also contain a sulfonamide as opposed to a methyl sulfone since the MMPA indicted that sulfonamides are typically more potent for both COX-1 and COX-2. In each case, a "flipped" version in which the A and B rings were interchanged was included along with the candidate generated by the approach described above. This decision was made based on the activity cliff analysis discussed above.

No ADMET Risks were predicted for the dihydropyrrolizines. The thiolactone-containing molecules each exhibit ADMET Risks for low solubility and for low fraction unbound in plasma. The default threshold for solubility risk was 5 μg/mL, and the thiolactone-containing molecules had predicted solubilities ranging from 1 to 2 μg/mL. The predicted fraction unbound in plasma for these compounds was slightly below the ADMET Risk threshold of 0.035. These ADMET properties are shared by the marketed COX-2-selective inhibitors.