**Challenges Predicting Ligand-Receptor Interactions of Promiscuous Proteins:**

**The Nuclear Receptor PXR**

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**Table S5.** To identify which outliers are bringing down the $XV\text{-}R^2$ of the CoMFA model, the following table lists the activities as predicted by the cross-validated PLS model: The standard deviation of the residuals in the following table is 0.825, and accordingly, the two possible outliers are highlighted in bold. The two outliers are the only two inactives in the training set.

| | | Exp. Activity | Pred. Activity | Residual |
|---|---|---|---|---|
| AN01 | 17β-dihydroandrosterone | 5.38 | 5.49 | 0.108 |
| AN02 | Androstanedione | 4.90 | 5.13 | 0.234 |
| AN03 | Androstanol | 5.20 | 5.43 | 0.227 |
| AN04 | Androsterone | 4.73 | 4.71 | -0.020 |
| AN05 | Dihydrotestosterone | 4.94 | 5.24 | 0.297 |
| AN06 | Etiocholanolone | 5.24 | 4.79 | -0.454 |
| AN08 | Testosterone | 4.14 | 4.42 | 0.277 |
| AN09 | DHEA | 4.49 | 3.51 | -0.978 |
| AN10 | Androstenol | 5.26 | 4.87 | -0.390 |
| AN11 | 11β-Hydroxyetiocholanolone | 4.72 | 5.42 | 0.703 |
| AN12 | DHEA sulfate (sodium salt) | 4.32 | 4.65 | 0.333 |
| AN13 | Epiandrosterone | 5.31 | 5.11 | -0.199 |
| AN15 | Epitestosterone | 4.17 | 3.75 | -0.417 |
| AN16 | Epitestosterone glucuronide | 4.86 | 4.71 | -0.150 |
| AN18 | *Etiocholanolone glucuronide* | **2.00** | ***4.19*** | ***2.190*** |
| AN20 | 5α-Androstan-3β-ol | 6.10 | 5.56 | -0.537 |
| AN21 | 16,(5α)-Androsten-3β-ol | 5.32 | 6.08 | 0.759 |
| AN22 | 16,(5α)-Androsten-3-one | 5.52 | 5.15 | -0.373 |
| AN23 | 5β-Androstan-3α-ol | 5.85 | 5.27 | -0.581 |
| AN25 | *5,16-Androstadien-3β-ol* | **2.00** | ***4.21*** | ***2.210*** |