**Table S4.** Results of retrospective screening using the UGI database. Three different dissimilarity metrics were used a) Euclidian distance, b) Manhattan distance c) Cosine similarity. The highest ROC-AUC for each model is marked in bold.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  | no scaling | | | | block scaling | | | | scaling to one | | | |
| enzyme | PDB ID | pocket(s) 1) | cluster radius [Å] 2) | ROC-AUC | (σ) | BEDROC | (σ) | ROC-AUC | (σ) | BEDROC | (σ) | ROC-AUC | (σ) | BEDROC | (σ) |
| fXa a) | 2bok | 1. 6. 13. 17 | 1.5 | 0.60 | (0.00) | 0.17 | (0.00) | 0.53 | (0.00) | 0.16 | (0.00) | 0.60 | (0.00) | 0.17 | (0.00) |
|  | 2bok | 1. 6. 13. 18 | 1.9 | 0.59 | (0.00) | 0.16 | (0.00) | 0.53 | (0.00) | 0.13 | (0.00) | **0.61** | (0.00) | 0.15 | (0.00) |
|  | 2bok | 1. 6. 13. 19 | 4 | 0.55 | (0.00) | 0.14 | (0.00) | 0.58 | (0.00) | 0.13 | (0.00) | 0.58 | (0.00) | 0.13 | (0.00) |
| fXa b) | 2bok | 1. 6. 13. 17 | 1.5 | 0.60 | (0.00) | 0.18 | (0.00) | 0.56 | (0.00) | 0.16 | (0.00) | 0.60 | (0.00) | 0.17 | (0.00) |
|  | 2bok | 1. 6. 13. 18 | 1.9 | 0.59 | (0.00) | 0.16 | (0.00) | 0.57 | (0.00) | 0.13 | (0.00) | **0.62** | (0.00) | 0.16 | (0.00) |
|  | 2bok | 1. 6. 13. 19 | 4 | 0.54 | (0.00) | 0.14 | (0.00) | 0.59 | (0.00) | 0.11 | (0.00) | 0.58 | (0.00) | 0.12 | (0.00) |
| fXa c) | 2bok | 1. 6. 13. 17 | 1.5 | 0.59 | (0.00) | 0.17 | (0.00) | 0.53 | (0.00) | 0.12 | (0.00) | 0.59 | (0.00) | 0.17 | (0.00) |
|  | 2bok | 1. 6. 13. 18 | 1.9 | **0.62** | (0.00) | 0.16 | (0.00) | 0.54 | (0.00) | 0.13 | (0.00) | 0.61 | (0.00) | 0.16 | (0.00) |
|  | 2bok | 1. 6. 13. 19 | 4 | 0.59 | (0.00) | 0.13 | (0.00) | 0.57 | (0.00) | 0.11 | (0.00) | 0.59 | (0.00) | 0.13 | (0.00) |
| UPA a) | 2o8t | 1 | 1.5 | 0.64 | (0.00) | 0.20 | (0.00) | 0.48 | (0.00) | 0.12 | (0.00) | 0.64 | (0.00) | 0.28 | (0.00) |
|  | 2o8t | 1 | 1.9 | **0.65** | (0.00) | 0.21 | (0.00) | 0.53 | (0.00) | 0.14 | (0.00) | 0.64 | (0.00) | 0.29 | (0.00) |
|  | 2o8t | 1 | 4 | 0.64 | (0.00) | 0.20 | (0.00) | 0.55 | (0.00) | 0.11 | (0.00) | 0.63 | (0.00) | 0.29 | (0.00) |
| UPA b) | 2o8t | 1 | 1.5 | **0.60** | (0.00) | 0.09 | (0.01) | 0.58 | (0.00) | 0.13 | (0.00) | 0.56 | (0.00) | 0.09 | (0.00) |
|  | 2o8t | 1 | 1.9 | 0.57 | (0.00) | 0.04 | (0.00) | 0.49 | (0.00) | 0.06 | (0.00) | 0.53 | (0.00) | 0.07 | (0.01) |
|  | 2o8t | 1 | 4 | 0.46 | (0.01) | 0.04 | (0.00) | 0.49 | (0.00) | 0.06 | (0.00) | 0.43 | (0.00) | 0.06 | (0.00) |
| UPA c) | 2o8t | 1 | 1.5 | 0.48 | (0.00) | 0.09 | (0.00) | 0.50 | (0.00) | 0.11 | (0.00) | 0.48 | (0.00) | 0.08 | (0.00) |
|  | 2o8t | 1 | 1.9 | 0.52 | (0.00) | 0.09 | (0.00) | 0.50 | (0.00) | 0.07 | (0.00) | **0.53** | (0.00) | 0.09 | (0.00) |
|  | 2o8t | 1 | 4 | 0.50 | (0.00) | 0.09 | (0.00) | 0.51 | (0.00) | 0.06 | (0.00) | 0.50 | (0.00) | 0.09 | (0.00) |
| trypsin a) | 1dpo | 1 | 1.5 | **0.55** | (0.00) | 0.06 | (0.00) | 0.52 | (0.00) | 0.10 | (0.00) | 0.52 | (0.01) | 0.09 | (0.01) |
|  | 1dpo | 1 | 1.9 | 0.54 | (0.00) | 0.05 | (0.00) | 0.49 | (0.01) | 0.06 | (0.00) | 0.50 | (0.01) | 0.09 | (0.01) |
|  | 1dpo | 1 | 4 | 0.48 | (0.00) | 0.04 | (0.00) | 0.54 | (0.00) | 0.06 | (0.00) | 0.44 | (0.01) | 0.08 | (0.01) |
| trypsin b) | 1dpo | 1 | 1.5 | 0.67 | (0.00) | 0.58 | (0.00) | 0.62 | (0.00) | 0.44 | (0.00) | **0.69** | (0.00) | 0.65 | (0.00) |
|  | 1dpo | 1 | 1.9 | 0.67 | (0.00) | 0.60 | (0.00) | 0.60 | (0.00) | 0.42 | (0.00) | 0.67 | (0.00) | 0.67 | (0.00) |
|  | 1dpo | 1 | 4 | 0.66 | (0.00) | 0.52 | (0.01) | 0.60 | (0.00) | 0.33 | (0.00) | 0.65 | (0.00) | 0.59 | (0.00) |
| trypsin c) | 1dpo | 1 | 1.5 | 0.70 | (0.00) | 0.58 | (0.00) | 0.55 | (0.00) | 0.31 | (0.00) | 0.70 | (0.00) | 0.58 | (0.00) |
|  | 1dpo | 1 | 1.9 | **0.71** | (0.00) | 0.56 | (0.00) | 0.57 | (0.00) | 0.37 | (0.00) | 0.71 | (0.00) | 0.56 | (0.00) |
|  | 1dpo | 1 | 4 | 0.71 | (0.00) | 0.53 | (0.00) | 0.59 | (0.00) | 0.37 | (0.00) | 0.71 | (0.00) | 0.53 | (0.00) |
| tryptase a) | 2fpz | 2. 4. 17 | 1.5 | 0.67 | (0.00) | 0.59 | (0.00) | 0.54 | (0.00) | 0.34 | (0.01) | **0.70** | (0.00) | 0.65 | (0.00) |
|  | 2fpz | 2. 4. 18 | 1.9 | 0.67 | (0.00) | 0.59 | (0.00) | 0.54 | (0.00) | 0.39 | (0.00) | 0.70 | (0.00) | 0.62 | (0.00) |
|  | 2fpz | 2. 4. 19 | 4 | 0.66 | (0.00) | 0.57 | (0.00) | 0.57 | (0.00) | 0.33 | (0.00) | 0.70 | (0.00) | 0.58 | (0.00) |
| tryptase b) | 2fpz | 2. 4. 17 | 1.5 | 0.61 | (0.00) | 0.19 | (0.00) | 0.52 | (0.00) | 0.14 | (0.00) | 0.61 | (0.00) | 0.25 | (0.00) |
|  | 2fpz | 2. 4. 18 | 1.9 | 0.61 | (0.00) | 0.18 | (0.00) | 0.59 | (0.00) | 0.16 | (0.00) | **0.61** | (0.00) | 0.26 | (0.00) |
|  | 2fpz | 2. 4. 19 | 4 | 0.58 | (0.00) | 0.16 | (0.00) | 0.57 | (0.00) | 0.11 | (0.00) | 0.58 | (0.00) | 0.24 | (0.00) |
| tryptase c) | 2fpz | 2. 4. 17 | 1.5 | 0.68 | (0.00) | 0.22 | (0.00) | 0.47 | (0.00) | 0.12 | (0.00) | 0.68 | (0.00) | 0.22 | (0.00) |
|  | 2fpz | 2. 4. 18 | 1.9 | **0.70** | (0.00) | 0.23 | (0.00) | 0.56 | (0.00) | 0.13 | (0.00) | 0.70 | (0.00) | 0.23 | (0.00) |
|  | 2fpz | 2. 4. 19 | 4 | 0.68 | (0.00) | 0.23 | (0.00) | 0.56 | (0.00) | 0.10 | (0.00) | 0.68 | (0.00) | 0.23 | (0.00) |

1) The numbering corresponds to the PocketPicker output.

2) LIQUID cluster radius for lipophilic interactions.