**Table S5.** Results of retrospective screening using the MUV 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) |
| CathepsinG a) | 1cgh | 1 | 1.5 | 0.69 | (0.03) | 0.19 | (0.03) | 0.61 | (0.02) | 0.07 | (0.01) | 0.46 | (0.03) | 0.10 | (0.02) |
|  | 1cgh | 1 | 1.9 | 0.60 | (0.02) | 0.13 | (0.02) | 0.39 | (0.03) | 0.01 | (0.01) | 0.46 | (0.03) | 0.06 | (0.02) |
|  | 1cgh | 1 | 4 | **0.70** | (0.04) | 0.15 | (0.02) | 0.49 | (0.02) | 0.02 | (0.01) | 0.51 | (0.03) | 0.08 | (0.02) |
| CathepsinG b) | 1cgh | 1 | 1.5 | 0.62 | (0.03) | 0.16 | (0.03) | **0.69** | (0.02) | 0.10 | (0.03) | 0.49 | (0.04) | 0.14 | (0.03) |
|  | 1cgh | 1 | 1.9 | 0.52 | (0.04) | 0.16 | (0.03) | 0.62 | (0.03) | 0.08 | (0.01) | 0.46 | (0.03) | 0.10 | (0.03) |
|  | 1cgh | 1 | 4 | 0.67 | (0.02) | 0.11 | (0.02) | 0.41 | (0.02) | 0.01 | (0.01) | 0.47 | (0.04) | 0.06 | (0.02) |
| CathepsinG c) | 1cgh | 1 | 1.5 | **0.61** | (0.02) | 0.03 | (0.00) | 0.58 | (0.03) | 0.06 | (0.02) | 0.60 | (0.04) | 0.03 | (0.01) |
|  | 1cgh | 1 | 1.9 | 0.52 | (0.03) | 0.02 | (0.01) | 0.48 | (0.02) | 0.02 | (0.01) | 0.51 | (0.02) | 0.02 | (0.01) |
|  | 1cgh | 1 | 4 | 0.48 | (0.03) | 0.02 | (0.01) | 0.48 | (0.02) | 0.03 | (0.01) | 0.50 | (0.02) | 0.02 | (0.00) |
| Eph a) | 3ckh | 2 | 1.5 | 0.57 | (0.02) | 0.05 | (0.02) | 0.57 | (0.03) | 0.03 | (0.01) | 0.52 | (0.02) | 0.04 | (0.01) |
|  | 3ckh | 2 | 1.9 | 0.54 | (0.03) | 0.07 | (0.02) | **0.59** | (0.02) | 0.03 | (0.01) | 0.53 | (0.03) | 0.05 | (0.01) |
|  | 3ckh | 2 | 4 | 0.56 | (0.02) | 0.05 | (0.01) | 0.55 | (0.03) | 0.06 | (0.01) | 0.54 | (0.02) | 0.07 | (0.01) |
| Ephb) | 3ckh | 2 | 1.5 | 0.53 | (0.03) | 0.06 | (0.02) | 0.49 | (0.01) | 0.02 | (0.01) | 0.50 | (0.01) | 0.05 | (0.01) |
|  | 3ckh | 2 | 1.9 | 0.52 | (0.03) | 0.08 | (0.02) | **0.57** | (0.02) | 0.07 | (0.01) | 0.52 | (0.03) | 0.02 | (0.01) |
|  | 3ckh | 2 | 4 | 0.52 | (0.05) | 0.08 | (0.02) | 0.54 | (0.02) | 0.06 | (0.01) | 0.53 | (0.02) | 0.05 | (0.02) |
| Eph c) | 3ckh | 2 | 1.5 | 0.48 | (0.03) | 0.03 | (0.02) | 0.49 | (0.04) | 0.03 | (0.02) | 0.49 | (0.03) | 0.04 | (0.02) |
|  | 3ckh | 2 | 1.9 | 0.49 | (0.04) | 0.03 | (0.02) | 0.49 | (0.05) | 0.04 | (0.01) | 0.50 | (0.03) | 0.03 | (0.02) |
|  | 3ckh | 2 | 4 | 0.50 | (0.04) | 0.03 | (0.02) | **0.51** | (0.04) | 0.07 | (0.03) | 0.48 | (0.04) | 0.04 | (0.02) |
| ER-a a) | 1xpc | 1 | 1.5 | 0.72 | (0.02) | 0.28 | (0.03) | 0.54 | (0.01) | 0.03 | (0.01) | 0.46 | (0.03) | 0.07 | (0.02) |
|  | 1xpc | 1 | 1.9 | 0.70 | (0.02) | 0.33 | (0.02) | 0.68 | (0.01) | 0.23 | (0.03) | 0.60 | (0.04) | 0.18 | (0.03) |
|  | 1xpc | 1 | 4 | **0.75** | (0.02) | 0.35 | (0.04) | 0.66 | (0.02) | 0.06 | (0.01) | 0.63 | (0.01) | 0.18 | (0.01) |
| ER-a b) | 1xpc | 1 | 1.5 | 0.70 | (0.02) | 0.12 | (0.01) | 0.55 | (0.02) | 0.05 | (0.01) | 0.45 | (0.02) | 0.04 | (0.01) |
|  | 1xpc | 1 | 1.9 | 0.65 | (0.03) | 0.31 | (0.05) | 0.62 | (0.01) | 0.10 | (0.01) | 0.54 | (0.03) | 0.08 | (0.01) |
|  | 1xpc | 1 | 4 | *0.76* | (0.02) | 0.35 | (0.03) | 0.61 | (0.02) | 0.05 | (0.01) | 0.61 | (0.02) | 0.13 | (0.01) |
| ER-a c) | 1xpc | 1 | 1.5 | 0.57 | (0.02) | 0.08 | (0.01) | 0.51 | (0.02) | 0.03 | (0.00) | 0.56 | (0.01) | 0.08 | (0.00) |
|  | 1xpc | 1 | 1.9 | 0.55 | (0.03) | 0.07 | (0.01) | 0.59 | (0.03) | 0.10 | (0.02) | 0.54 | (0.02) | 0.07 | (0.01) |
|  | 1xpc | 1 | 4 | 0.59 | (0.02) | 0.09 | (0.01) | 0.60 | (0.03) | 0.08 | (0.01) | **0.60** | (0.03) | 0.09 | (0.01) |
| ER-b a) | 1qkm | 1 | 1.5 | 0.58 | (0.02) | 0.10 | (0.02) | 0.53 | (0.04) | 0.07 | (0.02) | 0.61 | (0.01) | 0.10 | (0.03) |
|  | 1qkm | 1 | 1.9 | 0.56 | (0.02) | 0.07 | (0.02) | 0.55 | (0.03) | 0.09 | (0.02) | 0.63 | (0.03) | 0.10 | (0.02) |
|  | 1qkm | 1 | 4 | 0.58 | (0.03) | 0.08 | (0.01) | 0.50 | (0.03) | 0.06 | (0.02) | **0.63** | (0.02) | 0.10 | (0.02) |
| ER-b b) | 1qkm | 1 | 1.5 | 0.58 | (0.02) | 0.07 | (0.02) | 0.49 | (0.03) | 0.04 | (0.02) | 0.59 | (0.03) | 0.07 | (0.01) |
|  | 1qkm | 1 | 1.9 | 0.59 | (0.03) | 0.04 | (0.02) | 0.53 | (0.02) | 0.04 | (0.01) | 0.58 | (0.02) | 0.08 | (0.02) |
|  | 1qkm | 1 | 4 | **0.63** | (0.02) | 0.08 | (0.01) | 0.50 | (0.02) | 0.06 | (0.02) | 0.62 | (0.01) | 0.08 | (0.03) |
| ER-b c) | 1qkm | 1 | 1.5 | 0.50 | (0.03) | 0.11 | (0.01) | 0.51 | (0.03) | 0.06 | (0.01) | 0.50 | (0.03) | 0.11 | (0.02) |
|  | 1qkm | 1 | 1.9 | 0.51 | (0.05) | 0.07 | (0.02) | **0.52** | (0.03) | 0.07 | (0.02) | 0.51 | (0.03) | 0.07 | (0.01) |
|  | 1qkm | 1 | 4 | 0.50 | (0.03) | 0.06 | (0.01) | 0.48 | (0.02) | 0.05 | (0.01) | 0.49 | (0.03) | 0.06 | (0.02) |
| FAK a) | 1mp8 | 1 | 1.5 | 0.65 | (0.03) | 0.11 | (0.02) | 0.59 | (0.04) | 0.08 | (0.01) | 0.62 | (0.04) | 0.13 | (0.02) |
|  | 1mp8 | 1 | 1.9 | 0.61 | (0.04) | 0.15 | (0.02) | 0.58 | (0.04) | 0.15 | (0.03) | 0.60 | (0.02) | 0.08 | (0.01) |
|  | 1mp8 | 1 | 4 | 0.57 | (0.04) | 0.11 | (0.02) | **0.70** | (0.02) | 0.08 | (0.01) | 0.60 | (0.04) | 0.07 | (0.02) |
| FAK b) | 1mp8 | 1 | 1.5 | 0.67 | (0.04) | 0.09 | (0.02) | 0.58 | (0.03) | 0.08 | (0.02) | 0.63 | (0.03) | 0.11 | (0.02) |
|  | 1mp8 | 1 | 1.9 | 0.63 | (0.01) | 0.08 | (0.02) | 0.56 | (0.03) | 0.05 | (0.02) | 0.56 | (0.04) | 0.08 | (0.02) |
|  | 1mp8 | 1 | 4 | 0.62 | (0.02) | 0.08 | (0.02) | **0.68** | (0.03) | 0.08 | (0.02) | 0.57 | (0.04) | 0.06 | (0.01) |
| FAK c) | 1mp8 | 1 | 1.5 | 0.60 | (0.02) | 0.08 | (0.02) | 0.60 | (0.04) | 0.06 | (0.01) | 0.59 | (0.02) | 0.07 | (0.02) |
|  | 1mp8 | 1 | 1.9 | 0.60 | (0.02) | 0.09 | (0.02) | 0.60 | (0.03) | 0.08 | (0.01) | **0.61** | (0.03) | 0.10 | (0.01) |
|  | 1mp8 | 1 | 4 | 0.61 | (0.04) | 0.09 | (0.02) | 0.64 | (0.05) | 0.06 | (0.02) | 0.61 | (0.03) | 0.10 | (0.02) |
| FXIa a) | 1zsj | 1 | 1.5 | **0.52** | (0.04) | 0.03 | (0.01) | 0.30 | (0.03) | 0.00 | (0.00) | 0.48 | (0.02) | 0.00 | (0.00) |
|  | 1zsj | 1 | 1.9 | 0.47 | (0.02) | 0.01 | (0.01) | 0.32 | (0.01) | 0.00 | (0.00) | 0.33 | (0.02) | 0.00 | (0.00) |
|  | 1zsj | 1 | 4 | 0.45 | (0.02) | 0.00 | (0.00) | 0.34 | (0.02) | 0.00 | (0.00) | 0.31 | (0.02) | 0.00 | (0.00) |
| FXIa b) | 1zsj | 1 | 1.5 | **0.60** | (0.03) | 0.06 | (0.01) | 0.33 | (0.03) | 0.02 | (0.01) | 0.60 | (0.03) | 0.04 | (0.02) |
|  | 1zsj | 1 | 1.9 | 0.48 | (0.02) | 0.01 | (0.01) | 0.26 | (0.02) | 0.01 | (0.01) | 0.41 | (0.01) | 0.00 | (0.00) |
|  | 1zsj | 1 | 4 | 0.36 | (0.03) | 0.00 | (0.00) | 0.26 | (0.02) | 0.00 | (0.00) | 0.32 | (0.02) | 0.00 | (0.00) |
| FXIa c) | 1zsj | 1 | 1.5 | 0.38 | (0.02) | 0.00 | (0.00) | 0.38 | (0.02) | 0.00 | (0.00) | 0.37 | (0.02) | 0.00 | (0.00) |
|  | 1zsj | 1 | 1.9 | 0.37 | (0.02) | 0.00 | (0.00) | 0.37 | (0.02) | 0.00 | (0.00) | 0.37 | (0.01) | 0.00 | (0.00) |
|  | 1zsj | 1 | 4 | 0.36 | (0.02) | 0.00 | (0.00) | **0.39** | (0.02) | 0.00 | (0.00) | 0.37 | (0.03) | 0.00 | (0.00) |
| HIV-RT a) | 2zd1 | 1 | 1.5 | 0.59 | (0.01) | 0.11 | (0.02) | 0.51 | (0.02) | 0.02 | (0.00) | 0.36 | (0.02) | 0.05 | (0.01) |
|  | 2zd1 | 1 | 1.9 | 0.54 | (0.02) | 0.08 | (0.01) | **0.63** | (0.01) | 0.09 | (0.01) | 0.32 | (0.02) | 0.05 | (0.01) |
|  | 2zd1 | 1 | 4 | 0.63 | (0.02) | 0.09 | (0.01) | 0.58 | (0.02) | 0.12 | (0.02) | 0.36 | (0.02) | 0.05 | (0.02) |
| HIV-RT b) | 2zd1 | 1 | 1.5 | 0.54 | (0.02) | 0.08 | (0.01) | 0.46 | (0.01) | 0.02 | (0.01) | 0.36 | (0.02) | 0.04 | (0.02) |
|  | 2zd1 | 1 | 1.9 | 0.44 | (0.02) | 0.08 | (0.02) | 0.63 | (0.01) | 0.09 | (0.02) | 0.32 | (0.03) | 0.05 | (0.01) |
|  | 2zd1 | 1 | 4 | **0.63** | (0.02) | 0.10 | (0.01) | 0.61 | (0.02) | 0.13 | (0.02) | 0.41 | (0.02) | 0.06 | (0.02) |
| HIV-RT c) | 2zd1 | 1 | 1.5 | 0.55 | (0.04) | 0.07 | (0.02) | 0.47 | (0.02) | 0.03 | (0.01) | 0.56 | (0.02) | 0.07 | (0.01) |
|  | 2zd1 | 1 | 1.9 | 0.63 | (0.02) | 0.10 | (0.02) | 0.57 | (0.03) | 0.10 | (0.01) | **0.64** | (0.02) | 0.09 | (0.02) |
|  | 2zd1 | 1 | 4 | 0.60 | (0.03) | 0.11 | (0.01) | 0.51 | (0.03) | 0.11 | (0.02) | 0.60 | (0.02) | 0.10 | (0.02) |
| Hsp90 a) | 1uyl | 1 | 1.5 | **0.74** | (0.03) | 0.12 | (0.02) | 0.53 | (0.02) | 0.01 | (0.00) | 0.65 | (0.03) | 0.21 | (0.03) |
|  | 1uyl | 1 | 1.9 | 0.66 | (0.03) | 0.13 | (0.02) | 0.61 | (0.01) | 0.03 | (0.01) | 0.65 | (0.04) | 0.16 | (0.03) |
|  | 1uyl | 1 | 4 | 0.68 | (0.02) | 0.13 | (0.01) | 0.64 | (0.03) | 0.24 | (0.03) | 0.68 | (0.03) | 0.18 | (0.02) |
| Hsp90 b) | 1uyl | 1 | 1.5 | 0.69 | (0.03) | 0.07 | (0.01) | 0.56 | (0.02) | 0.01 | (0.00) | 0.62 | (0.03) | 0.13 | (0.02) |
|  | 1uyl | 1 | 1.9 | 0.60 | (0.04) | 0.14 | (0.02) | 0.63 | (0.03) | 0.11 | (0.01) | 0.59 | (0.03) | 0.11 | (0.02) |
|  | 1uyl | 1 | 4 | 0.66 | (0.03) | 0.13 | (0.02) | **0.69** | (0.02) | 0.23 | (0.02) | 0.65 | (0.03) | 0.19 | (0.03) |
| Hsp90 c) | 1uyl | 1 | 1.5 | 0.66 | (0.03) | 0.14 | (0.03) | 0.56 | (0.02) | 0.01 | (0.00) | 0.63 | (0.02) | 0.12 | (0.01) |
|  | 1uyl | 1 | 1.9 | 0.65 | (0.04) | 0.12 | (0.02) | 0.62 | (0.03) | 0.08 | (0.02) | 0.66 | (0.03) | 0.13 | (0.02) |
|  | 1uyl | 1 | 4 | **0.67** | (0.04) | 0.17 | (0.03) | 0.62 | (0.05) | 0.19 | (0.03) | 0.67 | (0.03) | 0.15 | (0.03) |
| PKA a) | 2uzt | 1 | 1.5 | 0.57 | (0.03) | 0.08 | (0.02) | 0.34 | (0.03) | 0.03 | (0.01) | **0.62** | (0.02) | 0.03 | (0.01) |
|  | 2uzt | 1 | 1.9 | 0.51 | (0.03) | 0.08 | (0.01) | 0.39 | (0.04) | 0.02 | (0.01) | 0.54 | (0.03) | 0.03 | (0.01) |
|  | 2uzt | 1 | 4 | 0.49 | (0.03) | 0.06 | (0.02) | 0.52 | (0.03) | 0.07 | (0.01) | 0.50 | (0.02) | 0.03 | (0.01) |
| PKA b) | 2uzt | 1 | 1.5 | **0.68** | (0.02) | 0.08 | (0.02) | 0.40 | (0.02) | 0.08 | (0.02) | 0.65 | (0.03) | 0.05 | (0.01) |
|  | 2uzt | 1 | 1.9 | 0.58 | (0.03) | 0.07 | (0.02) | 0.39 | (0.03) | 0.05 | (0.01) | 0.58 | (0.02) | 0.05 | (0.01) |
|  | 2uzt | 1 | 4 | 0.54 | (0.02) | 0.04 | (0.01) | 0.56 | (0.05) | 0.12 | (0.03) | 0.50 | (0.02) | 0.02 | (0.01) |
| PKAc) | 2uzt | 1 | 1.5 | 0.49 | (0.04) | 0.05 | (0.03) | 0.42 | (0.04) | 0.04 | (0.02) | 0.51 | (0.02) | 0.05 | (0.01) |
|  | 2uzt | 1 | 1.9 | 0.48 | (0.02) | 0.06 | (0.02) | 0.39 | (0.03) | 0.02 | (0.01) | 0.49 | (0.02) | 0.06 | (0.02) |
|  | 2uzt | 1 | 4 | **0.56** | (0.04) | 0.05 | (0.03) | 0.51 | (0.02) | 0.07 | (0.01) | 0.55 | (0.02) | 0.06 | (0.03) |
| Rho-kinase2a) | 2f2u | 1 | 1.5 | 0.49 | (0.02) | 0.09 | (0.02) | 0.35 | (0.03) | 0.03 | (0.01) | 0.51 | (0.02) | 0.03 | (0.01) |
|  | 2f2u | 1 | 1.9 | 0.42 | (0.04) | 0.04 | (0.02) | 0.39 | (0.02) | 0.02 | (0.01) | 0.52 | (0.02) | 0.01 | (0.01) |
|  | 2f2u | 1 | 4 | 0.48 | (0.03) | 0.06 | (0.02) | 0.54 | (0.02) | 0.01 | (0.01) | **0.59** | (0.01) | 0.04 | (0.01) |
| Rho-kinase2 b) | 2f2u | 1 | 1.5 | 0.53 | (0.02) | 0.06 | (0.02) | 0.39 | (0.03) | 0.04 | (0.01) | 0.57 | (0.02) | 0.03 | (0.00) |
|  | 2f2u | 1 | 1.9 | 0.42 | (0.03) | 0.02 | (0.01) | 0.44 | (0.01) | 0.04 | (0.01) | 0.50 | (0.01) | 0.02 | (0.01) |
|  | 2f2u | 1 | 4 | 0.57 | (0.03) | 0.03 | (0.01) | **0.63** | (0.02) | 0.04 | (0.01) | 0.61 | (0.03) | 0.04 | (0.01) |
| Rho-kinase2 c) | 2f2u | 1 | 1.5 | 0.49 | (0.02) | 0.05 | (0.02) | 0.52 | (0.03) | 0.07 | (0.02) | 0.49 | (0.04) | 0.06 | (0.02) |
|  | 2f2u | 1 | 1.9 | 0.53 | (0.04) | 0.03 | (0.01) | 0.48 | (0.03) | 0.02 | (0.01) | 0.52 | (0.04) | 0.03 | (0.02) |
|  | 2f2u | 1 | 4 | **0.55** | (0.03) | 0.06 | (0.01) | 0.48 | (0.04) | 0.01 | (0.01) | 0.55 | (0.03) | 0.05 | (0.02) |

1) The numbering corresponds to the PocketPicker output.

2) LIQUID cluster radius for lipophilic interactions.