**Table 1**. EGFRL858R/T790M inhibitors with their actual and predicted pIC50 values.

|  |
| --- |
|  **Template A (1-20) Template B (21-30) Template C (31-38)** |
| ***Noa*** | ***R1*** | ***R2*** | ***R3*** | ***Actual pIC50*** | ***Pred-pIC50*** |
| ***CoMFA*** | ***CoMSIA*** |
|  01\* |  | 2’-MeO | methyl | 8.5031 | 8.0995 | 8.1266 |
| 02 |  | 2’-MeO | methyl | 7.9393 | 8.4423 | 8.4229 |
|  03\* |  | 2’-MeO | methyl | 7.4385 | 8.1506 | 8.1021 |
|  04\* |  | 2’-MeO | methyl | 7.5399 | 8.031 |  8.1359 |
| 05 |  | 2’-MeO | methyl | 8.2865 | 8.4095 | 8.4492 |
| 06 |  | 2’-MeO | methyl | 8.284 | 8.1704 | 8.0999 |
| 07 | H | H | methyl | 7.5482 | 7.794 | 7.8832 |
| 08 |  | H | methyl | 8.9245 | 8.4697 | 8.5152 |
| 09 |  | 3’-MeO | methyl | 8.6904 | 8.439 | 8.491 |
| 10 |  | 2’-EtO | methyl | 8.1487 | 8.0226 | 8.0669 |
| 11 |  | 2’-Pr(i)O | methyl | 7.4401 | 7.9706 | 8.019 |
| 12 |  | 2’-Me | methyl | 8.3788 | 8.4792 | 8.5134 |
| 13 |  | 2’-MeO | i-propyl | 8.3546 | 8.3575 | 8.2498 |
| 14 |  | 2’-MeO | cyclo-propyl | 8.2204 | 8.5873 | 8.5618 |
|  15\* |  | 2’-MeO | phenyl (Ph) | 9.0088 | 8.1239 | 8.1099 |
| 16 |  | 2’-MeO | 2-naphthyl | 8.6126 | 8.0517 | 8.0914 |
| 17 |  | 2’-MeO | benzyl | 9.0315 | 8.1615 | 8.1105 |
|  18\* |  | 2’-MeO | 4-biphenyl | 8.3335 | 8.1855 | 8.2439 |
| 19 |  | 2’-MeO | 4-phenoxyphenyl | 8.4473 | 8.3802 | 8.51 |
|  20\* |  | 2’-MeO | 4-benzoxyphenyl | 8.2 | 8.4825 | 8.5331 |
| 21 |  | pyrrolidin-1-yl | -NHPh | 7.0706 | 7.5579 | 7.5389 |
| 22 |  | pyrrolidin-1-yl | -NHPh | 7.1831 | 7.1292 | 7.1828 |
| 23 |  | piperidin-1-yl | -NHPh | 7.3468 | 7.1093 | 7.1575 |
| 24 |  | piperidin-1-yl | -NHPh | 7.6345 | 7.1093 | 7.1575 |
|  25\* |  | morpholine-4-yl | -NHPh | 7.2741 | 7.6586 | 7.6124 |
| 26 |  | morpholine-4-yl | -NHPh | 7.2388 | 7.1207 | 7.1756 |
| 27 |  | morpholine-4-yl | -NHPh 4-F | 7.5406 | 7.1348 | 7.198 |
| 28 |  | morpholine-4-yl | -NHPh-2,4-diF | 7.5229 | 7.7083 | 7.6296 |
| 29 |  |  | -NHPh | 7.3556 | 7.1293 | 7.1165 |
| 30 |  |  | -NHPh-4-F | 7.4685 | 7.4085 | 7.3881 |
| ***Noa*** | ***Linker*** | ***Actual pIC50*** | ***Pred-pIC50*** |
| ***CoMFA*** | ***CoMSIA*** |
| 31 |  | 7.4365 | 7.7211 | 7.6179 |
| 32 |  | 7.5768 | 7.7211 | 7.6179 |
| 33 |  | 6.786 | 7.1137 | 7.0886 |
|  34\* |  | 6.4424 | 7.1137 | 7.0886 |
|  35\* |  | 6.9731 | 7.1313 | 7.0547 |
| 36 |  | 6.6232 | 7.1313 | 7.0547 |
| 37 |  | 6.8854 | 7.1462 | 7.0613 |
|  38\* |  | 7.6321 | 7.1462 | 7.0613 |

aCompound number, \*test set compounds.

**Table 2.** Statistical parameters of the comparative molecular field analysis (CoMFA) and comparative molecular similarity indices analysis (CoMSIA) models.

|  |  |
| --- | --- |
| **Model q2  r2 ONC SEE r2pred** |  **Relative contribution** |
|  **S E D H A** |
| *CoMFA*  |
|  S 0.519 0.688 1 0.378 0.551 1.000 - - - - E 0.526 0.683 1 0.376 0.429 - 1.000 - - - SE 0.541 0.698 1 0.360 0.509 0.498 0.502 - - - |
|  *CoMSIA* |
|  SEH 0.605 0.728 1 0.348 0.289 0.268 0.403 - 0.329 - SEHD 0.602 0.729 1 0.348 0.585 0.175 0.335 0.227 0.264 - SEHA 0.587 0.719 1 0.354 0.016 0.203 0.303 - 0.245 0.250 SEDA 0.603 0.815 2 0.293 0.320 0.197 0.317 0.237 - 0.240 EHDA 0.593 0.821 2 0.288 0.293 - 0.309 0.222 0.242 0.226 SEHDA 0.586 0.720 1 0.353 0.495 0.159 0.244 0.191 0.193 0.430 |

q2: cross-validated correlation coefficient; r2: non-cross-validated correlation coefficient; ONC: optimal number of components; SEE: standard error of estimate; r2pred: predictive correlation coefficient; S: steric fields; E: electrostatic fields; D: hydrogen-bond donor fields; H: hydrophobic fields; A: hydrogen-bond acceptor fields.

**Table 3.** Docking scores of the dataset compounds.

|  |  |  |
| --- | --- | --- |
| **Compound No.** | **Docking Score (ChemPLP.Fitness)** | **Docking Rescore (Chemscore.Fitness)** |
| 1 | 78.24 | 22.64 |
| 2 | 73.39 | 21.98 |
| 3 | 79.20 | 27.73 |
| 4 | 76.45 | 20.62 |
| 5 | 67.14 | 24.18 |
| 6 | 77.23 | 26.89 |
| 7 | 81.77 | 26.58 |
| 8 | 75.24 | 27.46 |
| 9 | 79.36 | 23.51 |
| 10 | 73.45 | 22.01 |
| 11 | 76.60 | 25.01 |
| 12 | 74.48 | 25.50 |
| 13 | 83.92 | 21.99 |
| 14 | 84.56 | 25.87 |
| 15 | 87.56 | 29.67 |
| 16 | 82.69 | 26.44 |
| 17 | 88.26 | 26.08 |
| 18 | 88.22 | 26.95 |
| 19 | 90.51 | 26.47 |
| 20 | 87.34 | 21.74 |
| 21 | 78.01 | 29.89 |
| 22 | 85.25 | 31.69 |
| 23 | 86.76 | 32.33 |
| 24 | 86.60 | 32.77 |
| 25 | 79.84 | 31.13 |
| 26 | 89.08 | 30.36 |
| 27 | 79.15 | 25.76 |
| 28 | 73.96 | 23.87 |
| 29 | 92.99 | 31.95 |
| 30 | 91.33 | 27.86 |
| 31 | 89.63 | 31.26 |
| 32 | 85.44 | 25.95 |
| 33 | 89.52 | 25.51 |
| 34 | 92.13 | 31.70 |
| 35 | 87.45 | 30.23 |
| 36 | 86.26 | 30.20 |
| 37 | 84.86 | 28.14 |
| 38 | 88.12 | 31.05 |
| **Gefitinib** | 79.19 | 29.02 |

**Table 4.** Chemical structures and IUPAC names of top five selected dataset compounds.

|  |  |  |
| --- | --- | --- |
| **S. No.** | **Compound** | **Chemical Structure & IUPAC Name** |
| 1 | 29 | (1-(6-(5-(4-(dimethylamino)piperazin-1-yl)pyridin-2-ylamino)-2-(phenylamino)pyrido[3,4-d]pyrimidin-4-yl)piperidin-4-yl)methanol |
| 2 | 34 | (S)-N-(1-(6-(5-(4-methylpiperazin-1-yl)pyridin-2-ylamino)-2-(phenylamino)pyrido[3,4-d]pyrimidin-4-yl)piperidin-3-yl)acrylamide |
| 3 | 26 | N6-(5-(4-(dimethylamino)piperidin-1-yl)pyridin-2-yl)-4-morpholino-N2-phenylpyrido[3,4-d]pyrimidine-2,6-diamine |
| 4 | 15 | N-(3-(7-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)-2-oxo-3-phenyl-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)acrylamide |
| 5 | 35 | (R)-1-(3-(6-(5-(4-methylpiperazin-1-yl)pyridin-2-ylamino)-2-(phenylamino)pyrido[3,4-d]pyrimidin-4-ylamino)pyrrolidin-1-yl)prop-2-en-1-one |

**Table 5.** Interaction analysis of selected five top ranked dataset compounds and co-crystalized ligand gefitinib.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **S. No** | **Compound**  | **Docking Score (ChemPLP)** | **Rescore (Chemscore)** | **Interacting residues** | **Type of interaction** | **Bond distance (Å)** |
| 1 | **Gefitinib**  | 79.19 | 29.02 | MET 793 | H-Bond | 3.4 |
| 2 | **29** | 92.99 | 31.95 | SER 720 | 2H-Bond |  2.863 & 3.062 |
| 3 | **34** | 92.13 | 31.70 | MET 793 | H-Bond | 2.679 |
| 4 | **26** | 89.08 | 30.36 | ASP 855MET 790 | H-BondShort contact | 2.9312.87 |
| 5 | **15** | 87.56 | 29.67 | ARG 841ASP 855LYS 745 | H-BondH-BondH-Bond | 2.8252.5813.047 |
| 6 | **35** | 87.45 | 30.23 | THR 854SER 720 | H-BondH-Bond | 3.0133.001 |

**Table 6.** Results of multiple sequence alignment of EGFR by PRALINE server.

|  |
| --- |
| **Alignment results for amino acids of EGFR** |
| Alignment score = 704656.00Alignment score per aligned residue pair = 15.43Sequence identities = 31475Percent sequence identity = 0.69Number of sequences = 10Alignment length = 1436Number of residues = 11347Number of gaps = 3013 |

**Table 7.** Predicted biological activities of the designed compounds.



**Template**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **No.** |  **R1** |  **R2** |  **R3** | **CoMFA Predicted pIC50** | **CoMSIA Predicted pIC50** |
| N1 |  |  |  | 7.7845 | 7.8712 |
| N2 |  |  |  | 7.7653 | 7.8706 |
| N3 |  |  |  | 7.7898 | 7.8694 |
| N4 |  |  |  | 7.8046 | 7.8725 |
| N5 |  |  |  | 7.7762 | 7.8621 |
| N6 |  |  |  | 7.7946 | 7.8865 |
| N7 |  |  |  | 7.8663 | 7.8726 |
| N8 |  |  |  | 7.8162 | 7.8837 |
| N9 |  |  |  | 7.8407 | 7.8755 |
| N10 |  |  |  | 7.8021 | 7.8729 |
| N11 |  |  |  | 7.8339 | 7.8695 |
| N12 |  |  |  | 7.8897 | 7.8652 |
| N13 |  |  |  | 7.8855 | 7.8663 |
| N14 |  |  |  | 7.8759 | 7.8698 |
| N15 |  |  |  | 7.8392 | 7.8567 |

**Table 8.** Docking scores andinteractions of newly designed compounds.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **S. No** | **Compound Name**  | **Docking Score (ChemPLP)** | **Rescore (Chemscore)** | **H-bond interactions with residues & distances (Å)** |
| 1 | **N7** | 79.5964 | 22.1072 | MET 793 (2.665 Å), ASP 800 (2.894 Å) |
| 2 | **N4** | 77.3696 | 21.4103 | MET 793 (2.704 Å), SER 720 (3.068 Å) |
| 3 | **N1** | 75.3703 | 22.7289 | MET 793 (2.729 Å), ASP 800 (2.94 Å) |

**Table 9.** In silico pharmacokinetics and drug likeness predictions of newly designed compounds.

|  |  |  |
| --- | --- | --- |
|  No. |  Pharmacokinetics  | Drug likeness |
|  | Log S (ESOL)a | GI absorption | BBB permeant | Log Po/w (MLOGP)b | Lipinski rule; Violations | Ghose rule; Violations | Bio-availabilityscore | Synthetic accessibility |
| N1 | -4.39 | High | No | 2.4 | Yes; 0 | Yes; 0 | 0.55 | 3.19 |
| N2 | -4.39 | High | No | 2.4 | Yes; 0 | Yes; 0 | 0.55 | 3.17 |
| N3 | -4.39 | High | No | 2.4 | Yes; 0 | Yes; 0 | 0.55 | 3.19 |
| N4 | -4.63 | High | No | 2.62 | Yes; 0 | Yes; 0 | 0.55 | 3.28 |
| N5 | -4.9 | High | No | 2.86 | Yes; 0 | No; 2 | 0.55 | 3.88 |
| N6 | -3.8 | High | No | 2.18 | Yes; 0 | Yes; 0 | 0.55 | 3.12 |
| N7 | -4.6 | High | No | 1.96 | Yes; 0 | No; 1 | 0.55 | 3.76 |
| N8 | -4.38 | High | No | 2.53 | Yes; 0 | No; 2 | 0.55 | 3.71 |
| N9 | -4.77 | High | No | 2.96 | Yes; 0 | Yes; 0 | 0.55 | 3.29 |
| N10 | -4.82 | High | No | 2.93 | Yes; 0 | Yes; 0 | 0.55 | 3.02 |
| N11 | -4.62 | High | No | 2.89 | Yes; 0 | Yes; 0 | 0.55 | 3.38 |
| N12 | -4.62 | High | No | 2.89 | Yes; 0 | Yes; 0 | 0.55 | 3.38 |
| N13 | -4.02 | High | No | 2.4 | Yes; 0 | Yes; 0 | 0.55 | 3.32 |
| N14 | -4.62 | High | No | 2.89 | Yes; 0 | Yes; 0 | 0.55 | 3.38 |
| N15 | -4.26 | High | No | 2.62 | Yes; 0 | Yes; 0 | 0.55 | 3.41 |

aESOL: Topological method implemented from ([Delaney, 2005](#_ENREF_9)). Solubility class: Log S scale. Insoluble < -10 < Poorly < -6 < Moderately < -4 < Soluble < -2 <Very < 0 < Highly. bMLOGP: Topological method implemented from ([Moriguchi et al., 1992](#_ENREF_23)).