**3D-QSAR-aided design of potent c-Met inhibitors using molecular dynamics simulation and binding free energy calculation.**

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**Supplementary Material**

**Tables**

**Table.S1** Structure and Biological values of c-Met inhibitors

|  |
| --- |
|  Compounds 1-16 Compounds 17-79 |
| **Compound** | **L** | **R1** | **R2** | **R3** | **R4** | **R5** | **pIC50** |
| 1\* | - | -CH3 |  | - | - | - | 6.193 |
| 2 | - | -OH |  | - | - | - | 6.000 |
| 3\* | - | -OH |  | - | - | - | 6.000 |
| 4 | - | -OH |  | - | - | - | 6.000 |
| 5 | - | -H |  |  | - | - | 8.004 |
| 6 | - | - |  | - | - | - | 7.177 |
| 7 | - | - |  | - | - | - | 7.878 |
| 8\* | - | **-** |  | - | - | - | 7.798 |
| 9\* | - | - |  | - | - | - | 7.398 |
| 10 | - | - |  | - | - | - | 7.908 |
| 11 | - | - |  | - | - | - | 7.756 |
| 12\* | - | - |  | - | - | - | 7.755 |
| 13 | - | - |  | - | - | - | 7.554 |
| 14 | - | - |  | - | - | - | 7.090 |
| 15 | - | - |  | - | - | - | 7.609 |
| 16 | - | - |  | - | - | - | 7.478 |
| 17 | -CH(CH3)- | - |  | - | - | - | 8.604 |
| 18 | -CH(CH3)- | - |  | - | - | - | 7.415 |
| 19\* | -CH(CH3)- | - |  | - | - | - | 7.943 |
| 20\* | -CH(CH3)- | - |  | - | - | - | 7.896 |
| 21\* | -CH(CH3)- | - |  | - | - | - | 8.435 |
| 22 | -CH(CH3)- | - |  | - | - | - | 8.287 |
| 23\* | -CH(CH3)- | - |  | - | - | - | 8.193 |
| 24 | -CH(CH3)- | - |  | - | - | - | 8.403 |
| 25\* | -CH(CH3)- | - |  | - | - | - | 8.562 |
| 26\* | -CH(CH3)- | - |  | - | - | - | 8.482 |
| 27\* | -CH(CH3)- | - |  | - | - | - | 7.818 |
| 28 | -CH(CH3)- | - |  | H | H | F | 7.037 |
| 29\* | -CH(CH3)- | - |  | H | F | H | 8.796 |
| 30 | -CH(CH2CH3)- | - |  | H | F | H | 7.975 |
| 31\* | -CH(CH2CH3)- | - |  | F | H | H | 7.870 |
| 32 | -CH(CH3)- | - |  | F | F | H | 9.000 |
| 33 | -CH(CH3)- | - |  | CH3 | H | H | 8.495 |
| 34 | -CH(CH3)- | - |  | H | CH3 | H | 7.487 |
| 35 | -CH(CH3)- | - |  | H | H | F | 6.555 |
| 36\* | -CH(CH3)- | - |  | H | F | H | 8.444 |
| 37\* | -CH(CH2CH3)- | - |  | H | F | H | 8.061 |
| 38 | -CH(CH2CH3)- | - |  | F | H | H | 7.424 |
| 39 | -CH(CH3)- | - |  | CH3 | H | H | 8.569 |
| 40 | -CH(CH3)- | - |  | H | F | H | 8.347 |
| 41 | -CH(CH2CH3)- | - |  | H | F | H | 8.032 |
| 42 | -CH(CH2CH3)- | - |  | F | H | H | 7.648 |
| 43 | -CH(CH3)- | - |  | F | F | H | 9.000 |
| 44 | -CH(CH3)- | - |  | CH3 | H | H | 8.377 |
| 45 | -CH(CH3)- | - |  | H | H | F | 6.721 |
| 46 | -CH(CH3)- | - |  | H | F | H | 8.420 |
| 47 | -CH(CH2CH3)- | - |  | H | F | H | 7.851 |
| 48\* | -CH(CH2CH3)- | - |  | F | H | H | 7.000 |
| 49 | -CH(CH3)- | - |  | F | F | H | 8.796 |
| 50 | -CH(CH3)- | - |  | CH3 | H | H | 8.357 |
| 51 | -CH(CH3)- | - |  | H | CH3 | H | 7.166 |
| 52 | -CH(CH3)- | - |  | H | H | F | 6.809 |
| 53 | -CH(CH3)- | - |  | H | F | H | 8.337 |
| 54 | -CH(CH2CH3)- | - |  | H | F | H | 7.551 |
| 55 | -CH(CH2CH3)- | - |  | F | H | H | 7.092 |
| 56 | -CH(CH3)- | - |  | F | F | H | 8.745 |
| 57 | -CH(CH3)- | - |  | H | F | H | 8.538 |
| 58 | -CH(CH2CH3)- | - |  | H | F | H | 7.742 |
| 59 | -CH(CH2CH3)- | - |  | F | H | H | 7.407 |
| 60 | -CH(CH3)- | - |  | F | F | H | 8.310 |
| 61 | -CH(CH3)- | - |  | CH3 | H | H | 8.229 |
| 62\* | -CH(CH3)- | - |  | H | CH3 | H | 7.190 |
| 63 | -CH(CH3)- | - |  | H | F | H | 8.638 |
| 64 | -CH(CH2CH3)- | - |  | H | F | H | 8.027 |
| 65 | -CH(CH2CH3)- | - |  | F | H | H | 8.114 |
| 66\* | -CH(CH3)- | - |  | H | CH3 | H | 7.509 |
| 67 | -CH(CH3)- | - |  | H | F | H | 8.770 |
| 68\* | -CH(CH2CH3)- | - |  | H | F | H | 8.602 |
| 69\* | -CH(CH2CH3)- | - |  | F | H | H | 8.796 |
| 70 | -CH(CH3)- | - |  | H | CH3 | H | 7.932 |
| 71 | -CH(CH3)- | - |  | H | H | F | 6.874 |
| 72 | -CH(CH3)- | - |  | H | F | H | 8.469 |
| 73 | -CH(CH2CH3)- | - |  | H | F | H | 7.765 |
| 74 | -CH(CH2CH3)- | - |  | F | H | H | 7.785 |
| 75 | -CH(CH3)- | - |  | F | F | H | 8.886 |
| 76 | -CH(CH3)- | - |  | CH3 | H | H | 8.310 |
| 77 | -CH(CH3)- | - |  | H | CH3 | H | 7.419 |
| 78\* | -CH(CH3)- | - |  | H | H | F | 6.000 |
| 79\* | -CH(CH3)- | - |  | F | F | H | 7.623 |

**\***Test set compounds

**Table.S2** Detailed statistical values obtained for different combination of COMSIA descriptors.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **COMSIA** | **ONC** | ***q*2** | **SEP** | ***r*2** | **SEE** | **LFO** | **F value** | **Percentage contribution** |
| **S** | **E** | **H** | **A** | **D** |
| SEH | 6 | 0.720 | 0.409 | 0.899 | 0.300 | 0.691 | 67.655 | 13.3 | 43.7 | 43.0 | - | - |
| SEA | 6 | 0.620 | 0.476 | 0.822 | 0.326 | 0.522 | 55.248 | 20.7 | 49.4 | - | 29.9 | - |
| SED | 6 | 0.594 | 0.492 | 0.821 | 0.327 | 0.510 | 55.095 | 22.6 | 41.6 | - | - | 35.8 |
| EHA | 6 | 0.780 | 0.362 | 0.897 | 0.248 | 0.743 | 104.781 | - | 36.2 | 42.4 | 21.4 | - |
| EHD | 6 | 0.716 | 0.412 | 0.905 | 0.238 | 0.715 | 114.821 | - | 35.1 | 38.2 | - | 26.7 |
| SHA | 6 | 0.621 | 0.476 | 0.768 | 0.372 | 0.565 | 39.755 | 13.9 | - | 56.8 | 29.3 | - |
| SHD | 6 | 0.448 | 0.574 | 0.764 | 0.375 | 0.440 | 38.892 | 15.6 | - | 47.2 | - | 37.2 |
| EAD | 6 | 0.533 | 0.528 | 0.708 | 0.403 | 0.494 | 32.091 | - | 41.4 | - | 23.5 | 35.1 |
| HAD | 6 | 0.394 | 0.601 | 0.727 | 0.404 | 0.727 | 31.920 | - | - | 49.4 | 21.2 | 29.5 |
| **SEHD** | **6** | **0.722** | **0.407** | **0.915** | **0.226** | **0.708** | **128.603** | **10.7** | **31.1** | **30.8** | **-** | **27.4** |
| SEHA | 6 | 0.755 | 0.382 | 0.893 | 0.252 | 0.698 | 100.468 | 9.8 | 34.0 | 36.9 | 19.3 | - |
| SEAD | 6 | 0.588 | 0.496 | 0.802 | 0.344 | 0.555 | 48.500 | 15.3 | 33.1 | - | 18.7 | 32.8 |
| EHAD | 6 | 0.694 | 0.427 | 0.883 | 0.264 | 0.697 | 90.997 | - | 28.8 | 31.1 | 15.3 | 24.8 |
| SHAD | 6 | 0.394 | 0.601 | 0.719 | 0.409 | 0.348 | 30.713 | 11.7 | - | 37.6 | 18.4 | 32.3 |
| SEHAD | 6 | 0.693 | 0.423 | 0.890 | 0.256 | 0.686 | 97.207 | 8.6 | 26.5 | 26.2 | 13.2 | 25.5 |

Final chosen model for COMSIA analysis is indicated in bold font. ONC=optimum number of components. *q2*=cross-validated correlation coefficient. SEP=standard error of prediction. *r2*=non-cross-validated correlation coefficient. SEE=standard error of estimate. LFO=Leave-out-Five cross validation. Fvalue=ANOVA test value. BS*-r2*=bootstrapping *r2*. BS-SD=Bootstrapping standard deviations. S=steric, E=electrostatic, H=hydrophobic, A=acceptor, D=donor.

**Table S3.** Experimental and predicted pIC50 values with their residuals of selected CoMFA and COMSIA models.

|  |  |  |  |
| --- | --- | --- | --- |
| **Compound** | **Actual pIC50** | **CoMFA** | **COMSIA** |
| **Predicted** | **Residual** | **Predicted** | **Residual** |
| 1\* | 6.193 | 5.758 | 0.435 | 5.738 | 0.455 |
| 2 | 6.000 | 5.886 | 0.114 | 6.104 | -0.104 |
| 3\* | 6.000 | 5.420 | 0.580 | 5.564 | 0.436 |
| 4 | 6.000 | 5.618 | 0.382 | 5.781 | 0.219 |
| 5 | 8.004 | 7.999 | 0.005 | 8.118 | -0.114 |
| 6 | 7.177 | 7.310 | -0.133 | 7.466 | -0.289 |
| 7 | 7.878 | 7.825 | 0.053 | 7.684 | 0.194 |
| 8\* | 7.798 | 7.795 | 0.003 | 8.007 | -0.209 |
| 9\* | 7.398 | 7.887 | -0.489 | 7.481 | -0.083 |
| 10 | 7.908 | 7.983 | -0.075 | 8.102 | -0.194 |
| 11 | 7.756 | 7.728 | 0.028 | 7.794 | -0.038 |
| 12\* | 7.755 | 7.534 | 0.221 | 7.578 | 0.177 |
| 13 | 7.554 | 7.673 | -0.119 | 7.378 | 0.176 |
| 14 | 7.090 | 7.264 | -0.174 | 7.334 | -0.244 |
| 15 | 7.609 | 7.719 | -0.110 | 7.467 | 0.142 |
| 16 | 7.478 | 7.811 | -0.333 | 7.586 | -0.108 |
| 17 | 8.604 | 8.329 | 0.275 | 8.103 | 0.501 |
| 18 | 7.415 | 7.693 | -0.278 | 7.240 | 0.175 |
| 19\* | 7.943 | 8.155 | -0.212 | 7.670 | 0.273 |
| 20\* | 7.896 | 8.143 | -0.247 | 8.001 | -0.105 |
| 21\* | 8.435 | 8.344 | 0.091 | 8.224 | 0.211 |
| 22 | 8.287 | 8.134 | 0.153 | 8.134 | 0.153 |
| 23\* | 8.193 | 8.453 | -0.260 | 8.195 | -0.002 |
| 24 | 8.403 | 8.722 | -0.319 | 8.662 | -0.259 |
| 25\* | 8.562 | 8.750 | -0.188 | 8.718 | -0.156 |
| 26\* | 8.482 | 8.397 | 0.085 | 7.950 | 0.532 |
| 27\* | 7.818 | 8.522 | -0.704 | 8.009 | -0.191 |
| 28 | 7.037 | 7.144 | -0.107 | 7.216 | -0.179 |
| 29\* | 8.796 | 8.662 | 0.134 | 8.683 | 0.113 |
| 30 | 7.975 | 7.915 | 0.060 | 7.981 | -0.006 |
| 31\* | 7.870 | 7.646 | 0.224 | 7.710 | 0.160 |
| 32 | 9.000 | 8.812 | 0.188 | 8.990 | 0.010 |
| 33 | 8.495 | 8.462 | 0.033 | 8.623 | -0.128 |
| 34 | 7.487 | 7.457 | 0.030 | 7.825 | -0.338 |
| 35 | 6.555 | 6.969 | -0.414 | 6.783 | -0.228 |
| 36\* | 8.444 | 8.487 | -0.043 | 8.250 | 0.194 |
| 37\* | 8.061 | 7.743 | 0.317 | 7.548 | 0.512 |
| 38 | 7.424 | 7.477 | -0.053 | 7.276 | 0.148 |
| 39 | 8.569 | 8.288 | 0.281 | 8.190 | 0.379 |
| 40 | 8.347 | 8.638 | -0.291 | 8.568 | -0.221 |
| 41 | 8.032 | 7.895 | 0.137 | 7.865 | 0.166 |
| 42 | 7.648 | 7.619 | 0.029 | 7.596 | 0.052 |
| 43 | 9.000 | 8.785 | 0.215 | 8.877 | 0.123 |
| 44 | 8.377 | 8.436 | -0.059 | 8.511 | -0.134 |
| 45 | 6.721 | 6.947 | -0.226 | 6.892 | -0.171 |
| 46 | 8.420 | 8.464 | -0.044 | 8.359 | 0.061 |
| 47 | 7.851 | 7.763 | 0.088 | 7.678 | 0.173 |
| 48\* | 7.000 | 7.499 | -0.499 | 6.607 | 0.393 |
| 49 | 8.796 | 8.617 | 0.179 | 8.666 | 0.130 |
| 50 | 8.357 | 8.261 | 0.096 | 8.299 | 0.058 |
| 51 | 7.166 | 7.266 | -0.100 | 7.501 | -0.335 |
| 52 | 6.809 | 6.740 | 0.069 | 6.685 | 0.124 |
| 53 | 8.337 | 8.258 | 0.079 | 8.153 | 0.184 |
| 54 | 7.551 | 7.411 | 0.140 | 7.405 | 0.146 |
| 55 | 7.092 | 7.486 | -0.395 | 7.715 | -0.624 |
| 56 | 8.745 | 8.414 | 0.331 | 8.462 | 0.283 |
| 57 | 8.538 | 8.385 | 0.153 | 8.262 | 0.276 |
| 58 | 7.742 | 7.661 | 0.081 | 7.578 | 0.164 |
| 59 | 7.407 | 7.384 | 0.023 | 7.308 | 0.099 |
| 60 | 8.310 | 8.538 | -0.228 | 8.571 | -0.261 |
| 61 | 8.229 | 8.178 | 0.051 | 8.203 | 0.026 |
| 62\* | 7.190 | 7.186 | 0.004 | 7.403 | -0.213 |
| 63 | 8.638 | 7.924 | 0.714 | 8.731 | -0.093 |
| 64 | 8.027 | 8.183 | -0.156 | 8.047 | -0.020 |
| 65 | 8.114 | 7.914 | 0.200 | 7.776 | 0.338 |
| 66\* | 7.509 | 7.727 | -0.218 | 7.872 | -0.363 |
| 67 | 8.770 | 8.748 | 0.022 | 8.878 | -0.108 |
| 68\* | 8.602 | 8.008 | 0.594 | 8.195 | 0.407 |
| 69\* | 8.796 | 8.141 | 0.655 | 7.924 | 0.872 |
| 70 | 7.932 | 7.552 | 0.380 | 8.019 | -0.087 |
| 71 | 6.874 | 7.046 | -0.173 | 7.023 | -0.150 |
| 72 | 8.469 | 8.564 | -0.095 | 8.491 | -0.022 |
| 73 | 7.765 | 7.849 | -0.085 | 7.807 | -0.043 |
| 74 | 7.785 | 7.572 | 0.213 | 7.536 | 0.249 |
| 75 | 8.886 | 8.715 | 0.171 | 8.800 | 0.086 |
| 76 | 8.310 | 8.360 | -0.050 | 8.431 | -0.121 |
| 77 | 7.419 | 7.367 | 0.052 | 7.632 | -0.213 |
| 78\* | 6.000 | 6.012 | -0.012 | 5.690 | 0.310 |
| 79\* | 7.623 | 7.684 | -0.061 | 7.467 | 0.156 |

\*Test set compounds

**Table S4.** Comparison of binding affinity of the designed compounds with the most active compound 32.

|  |  |
| --- | --- |
| **Designed Compounds** | **Binding Energy** **(kcal/mol)** |
| Compound 32 | -10.00 |
| D01 | -16.31 |
| D02 | -14.93 |
| D03 | -14.99 |
| D04 | -14.27 |
| D05 | -14.42 |
| D06 | -14.37 |
| D07 | -15.30 |
| D08 | -14.70 |
| D09 | -14.87 |
| D10 | -14.99 |
| D11 | -14.51 |
| D12 | -14.74 |
| D13 | -14.29 |
| D14 | -14.61 |
| D15 | -15.01 |
| D16 | -15.36 |
| D17 | -15.52 |
| D18 | -15.47 |
| D19 | -14.98 |
| D20 | -14.68 |
| D21 | -15.12 |
| D22 | -15.68 |
| D23 | -14.02 |
| D24 | -15.37 |
| D25 | -14.04 |
| D26 | -13.37 |
| D27 | -14.36 |

**Figures**

**Fig.S1** Design strategy obtained from the 3D-QSAR contour maps

