**Supplementary Material**

**Comprehensive In Silico Discovery of c-Src Tyrosine Kinase Inhibitors in cancer Treatment: A Unified Approach Combining Pharmacophore Modeling, 3D QSAR, DFT, and Molecular Dynamics Simulation**

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**Table S1.**Chemical structures for the data set of 34 compounds with corresponding pIC50 values**.**

|  |  |  |  |
| --- | --- | --- | --- |
| Compounds 1-2 | Compounds 3-11 | Compounds 12-23 | Compounds 24-34 |

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **S. No.** | **R1** | **R2** | **R3** | **Experimental activity** | **Predicted activity** | **Residual** |
| 1T |  |  | H | 5.614 | 5.646 | 0.032 |
| 2 |  |  | H | 5.616 | 5.631 | 0.015 |
| 3 | 3-Methoxy | H | H | 5.917 | 5.973 | 0.056 |
| 4 | 4-Chloro | H | H | 5.928 | 5.892 | -0.036 |
| 5T | 4-Bromo | H | H | 5.754 | 5.840 | 0.086 |
| 6 | 4-Nitro | H | H | 5.853 | 5.802 | -0.050 |
| 7T | 3-Nitro | H | H | 6.022 | 5.834 | -0.187 |
| 8 | 4-Aminosulfonyl | H | H | 5.739 | 5.825 | 0.086 |
| 9 | 3-Aminosulfonyl | H | H | 7.000 | 6.927 | -0.072 |
| 10 | 4-Carbamoyl | H | H | 5.657 | 5.562 | -0.094 |
| 11T | 4-Acetamido | H | H | 5.978 | 6.100 | 0.122 |
| 12 | H | H | H | 6.124 | 6.348 | 0.224 |
| 13 | 4-Methoxy | H | H | 6.886 | 6.677 | -0.208 |
| 14 | 3-Methoxy | H | H | 6.031 | 6.018 | -0.012 |
| 15T | 3-Methyl | H | H | 6.080 | 6.030 | -0.049 |
| 16 | 4-Chloro | H | H | 6.468 | 6.251 | -0.216 |
| 17 | 4-Bromo | H | H | 6.346 | 6.158 | -0.187 |
| 18 | 4-Nitro | H | H | 6.408 | 6.459 | 0.051 |
| 19 | 3-Nitro | H | H | 6,886 | 6.876 | -0.009 |
| 20 | 4-Aminosulfonyl | H | H | 7.698 | 7.766 | 0.068 |
| 21T | 3-Aminosulfonyl | H | H | 6.920 | 6.896 | -0.023 |
| 22 | 4-Carbamoyl | H | H | 5.696 | 5.845 | 0.149 |
| 23 | 4-Acetamido | H | H | 6.187 | 6.328 | 0.141 |
| 24 | H | H | H | 5.503 | 5.843 | 0.340 |
| 25 | 4-Methoxy | H | H | 5,876 | 5.934 | 0.058 |
| 26 | 3-Methoxy | H | H | 5.920 | 5.619 | -0.300 |
| 27 | 3-Methyl | H | H | 5.602 | 5.722 | 0.120 |
| 28T | 4-Chloro | H | H | 6.161 | 5.940 | -0.220 |
| 29T | 4-Nitro | H | H | 6.107 | 6.155 | 0.048 |
| 30 | 3-Nitro | H | H | 6.468 | 6.453 | -0.014 |
| 31 | 4-Aminosulfonyl | H | H | 6.585 | 6.553 | -0.031 |
| 32T | 3-Aminosulfonyl | H | H | 6.468 | 6.362 | -0.105 |
| 33 | 4-Carbamoyl | H | H | 5.913 | 5.776 | -0.136 |
| 34 | 4-Acetamido | H | H | 5.798 | 5.854 | 0.056 |

**T:** Test set molecules

**Table S2.** Intersite distances and angles between the pharmacophoric points of DDRRR\_1.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Site 1** | **Site 2** | **Distance** | **Site 1** | **Site2** | **Site 3** | **Angle** |
| D6 | R10 | 3.94 | R9 | D6 | R10 | 92.6 |
| D6 | R8 | 3.80 | R9 | D6 | R8 | 36.0 |
| D6 | D5 | 6.64 | R9 | D6 | D9 | 37.4 |
| R9 | R10 | 5.69 | D6 | R10 | R9 | 43.7 |
| R9 | R8 | 2.39 | D6 | R10 | R8 | 25.2 |
| R9 | D5 | 4.25 | R10 | R9 | R8 | 112.5 |
| R8 | R10 | 6.67 | R8 | R9 | D6 | 39.6 |
| R8 | D5 | 2.85 | D6 | R9 | D5 | 18.6 |
|  |  |  | R9 | D5 | R8 | 32.4 |

**Table S3.** q2 and r2 values after several Y-randomization test.

|  |  |  |
| --- | --- | --- |
| **Iteration** | **R2** | **q2** |
| Random\_1 | 0.921 | 0.120 |
| Random\_2 | 0.962 | -0.116 |
| Random\_3 | 0.938 | -0.022 |
| Random\_4 | 0.927 | 0.397 |
| Random\_5 | 0.885 | 0.419 |
| Random\_6 | 0.945 | 0.230 |
| Random\_7 | 0.950 | -0.104 |
| Random\_8 | 0.939 | 0.329 |
| Random\_9 | 0.909 | 0.224 |
| Random\_10 | 0.929 | 0.103 |

**Table S4.** Frontier molecular orbitals (FMO) of studied compounds and their energy gaps.

|  |  |  |  |
| --- | --- | --- | --- |
| **PubChem ID** | **EHOMO(eV)** | **ELUMO(eV)** | **ΔE (eV)** |
| CID\_70144047 | -6.122 | -1.469 | 4.653 |
| CID\_11291395 | -4.136 | -2.258 | 1.877 |
| CID\_22844919 | -6.095 | -1.251 | 4.843 |
| CID\_134165918 | -7.319 | -2.530 | 4.789 |
| CID\_60151031 | -6.204 | -1.224 | 4.979 |

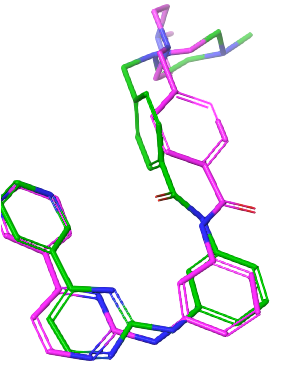
**Table S5.** ADME prediction of top five hits and reference compound.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Pubchem ID** | **QPlog**  **Po/w** | **QPlogS** | **MW** | **QPlog**  **BB** | **QPlog**  **HERG** | **QPP**  **caco** | **QPP**  **MDCK** | **QPlog**  **KP** | **% HOA** | **QPlog**  **khsa** |
| CID\_70144047 | 1.135 | -3.688 | 385.422 | -1.727 | -5.971 | 218.275 | 95.476 | -3.051 | 75.457 | -0.502 |
| CID\_11291395 | 1.474 | -3.802 | 361.787 | -0.997 | -5.557 | 410.245 | 465.650 | -2.867 | 82.345 | -0.424 |
| CID\_22844919 | 1.085 | -3.580 | 381.449 | -1.670 | -5.083 | 202.217 | 155.445 | -3564 | 74.562 | -0.541 |
| CID\_134165918 | 1.650 | -4.439 | 394.405 | -1.620 | -5.063 | 179.402 | 114484 | -4.074 | 76.944 | -0.238 |
| CID\_60151031 | 2.039 | -4.378 | 461.535 | -1.890 | -5.898 | 202.905 | 147.887 | -3..003 | 80.179 | -0.332 |
| Co-Crystal ligand | 1.703 | -4.851 | 479.583 | -0.131 | -0.131 | 2683.504 | 1437.892 | -2.622 | 85.327 | -0.348 |

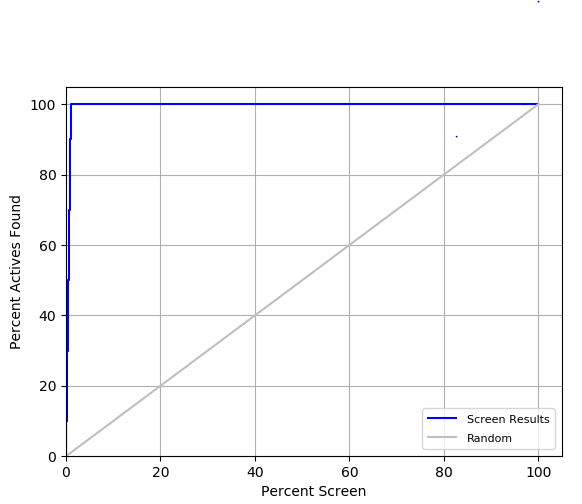
QPlogPo/w, predicted octanol/water partition coefficient (-2.0 to 6.5); QPlogS, predicted aqueous solubility in mol dm-3 (-6.5 to 0.5); QPlogHERG, HERG K+ channels (acceptable range below -6.0); QPPCaco, predicted apparent Caco-2 cell (gut-blood barrier model) permeability in nm/sec (,25 poor; .500 excellent); QPlogBB, predicted brain/blood partition coefficient (-3 to 1.2); QPlogKhsa, prediction of binding to human serum albumin (-1.5 to 0.5); percent human oral absorption (<25 poor; >80 high)

**Table S6.** Toxicity prediction of top five hits and reference compound.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Pubchem ID** | **Mutagenicity** | **Carcinogenicity** | **Hepatotoxicity** | **Cytotoxicity** | **Immunotoxicity** |
| CID\_70144047 | No | No | No | No | No |
| CID\_11291395 | No | No | Yes | No | No |
| CID\_22844919 | No | No | No | No | No |
| CID\_134165918 | No | No | Yes | No | No |
| CID\_60151031 | Yes | Yes | No | No | No |
| Co-Crystal ligand | No | No | Yes | No | Yes |



**Figure S1.** Re-docking pose and RMSD value of 1.735 A˚ (purple = Original, Green = Docked).



**Figure S2.** ROC curve obtained by DDRRR\_1 model against randomly curve.

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**Figure S3.** Plots of experimental activities against predicted activities of the (A) training set, and (B) test set.