*Supplementery material For*

**Probing the Binding Mechanism of Substituted Pyridine Derivatives as Effective and Selective Lysine Specific Demethylase 1 Inhibitors using 3D-QSAR, Molecular Docking and Molecular Dynamics Simulations**

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Figure S1. Williams plot of standardized residuals versus leverage values for CoMFA model. The horizontal lines represent ±3 standardized residual, and the vertical line represents warning leverage (h\* = 0.27)



Figure S2. Williams plot of standardized residuals versus leverage values for CoMSIA model. The horizontal lines represent ±3 standardized residual, and the vertical line represents warning leverage (h\* = 0.74)

Table S1.Statistical results of CoMFA and different combination of CoMSIA models with structure based alignment by PLS analysis.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| NO. | q2 | N | r2 | SEE | F | fields contribution |
| S | E | H | D | A |
| CoMFA | 0.595 | 6 | 0.977 | 0.287 | 130.924 | 0.437 | 0.563 | - | - | - |
| CoMSIA-SED | 0.601 | 7 | 0.956 | 0.273 | 128.797 | 0.216 | 0.535 | - | 0.250 | - |
| CoMSIA-SEH | 0.706 | 6 | 0.971 | 0.233 | 142.974 | 0.142 | 0.542 | 0.316 | - | - |
| CoMSIA-SEA | 0.600 | 3 | 0.881 | 0.358 | 61.109 | 0.123 | 0.445 | - | - | 0.431 |
| CoMSIA-SHD | 0.388 | 6 | 0.844 | 0.440 | 34.092 | 0.183 | - | 0.387 | 0.430 | - |
| CoMSIA-EHD | 0.658 | 6 | 0.959 | 0.259 | 136.657 | - | 0.443 | 0.333 | 0.224 | - |
| CoMSIA-HDA | 0.568 | 5 | 0.975 | 0.218 | 156.683 | - | - | 0.259 | 0.365 | 0.377 |
| CoMSIA-SHA | 0.587 | 4 | 0.956 | 0.250 | 157.583 | 0.173 | - | 0.364  | - | 0.463 |
| CoMSIA-EHA | 0.672 | 4 | 0.956 | 0.249 | 157.945 | - | 0.356 | 0.256 | - | 0.388 |
| CoMSIA-SDA | 0.475 | 4 | 0.901 | 0.341 | 73.946 | 0.124 | - | - | 0.386 | 0.490 |
| CoMSIA-EDA | 0.521 | 2 | 0.835 | 0.407 | 47.349 | - | 0.308 | - | 0.293 | 0.399 |
| CoMSIA-SEHD | 0.670 | 7 | 0.973 | 0.237 | 136.069 | 0.109 | 0.429 | 0.249 | 0.213 | - |
| CoMSIA-SEDA | 0.546 | 4 | 0.906 | 0.332 | 135.730 | 0.090 | 0.277 | - | 0.222 | 0.411 |
| CoMSIA-EHDA | 0.615 | 5 | 0.954 | 0.299 | 164.986 | - | 0.251 | 0.213 | 0.218 | 0.317 |
| CoMSIA-SEHA | 0.683 | 4 | 0.959 | 0.244 | 159.857 | 0.090 | 0.321 | 0.228 | - | 0.362 |
| CoMSIA-SHDA | 0.579 | 5 | 0.952 | 0.253 | 162.994 | 0.090 | - | 0.233 | 0.323 | 0.355 |
| CoMSIA-SEHDA | 0.733 | 5 | 0.983 | 0.193 | 170.916 | 0.072 | 0.233 | 0.193 | 0.203 | 0.298 |

Table S2. Hydrogen bond analysis from the results of MD simulations

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Complex | Donor | Acceptor | Occupancy (%) | Distance (Å) | Angle (°) |
| LSD1-**8** | Lys661@N-H | ligand@C≡N | 5.62 | 2.1 | 142.8 |
|  | WAT@O-H | ligand@C≡N | 91.91 | 1.9 | 155.1 |
|  | WAT@O-H | FAD@N | 97.79 | 2.0 | 159.2 |
|  | Lys661@N-H | WAT@O | 90.22 | 2.7 | 156.4 |
|  | ligand@N+-H | Asp555@O | 98.15 | 1.6 | 158.8 |
| LSD1-**14** | Lys661@N-H | ligand@C≡N | 7.39 | 2.2 | 140.2 |
|  | WAT@O-H | ligand@C≡N | 90.24 | 1.9 | 154.5 |
|  | WAT@O-H | FAD@N | 96.53 | 1.9 | 156.4 |
|  | Lys661@N-H | WAT@O | 91.36 | 2.6 | 157.7 |
|  | ligand@N+-H | Asp555@O | 94.73 | 1.7 | 163.3 |
| LSD1-**24** | ligand@N+-H | Asp555@O | 95.27 | 1.8 | 166.4 |
|  | ligand@N+-H | Gln358@O | 70.86 | 1.9 | 151.3 |
|  | WAT@O-H | FAD@N | 96.60 | 1.9 | 165.3 |
|  | Lys661@N-H | WAT@O | 90.71 | 2.9 | 153.4 |
| LSD1-**27** | Lys661@N-H | ligand@C≡N | 6.34 | 2.2 | 148.3 |
|  | WAT@O-H | ligand@C≡N | 92.54 | 2.1 | 161.3 |
|  | WAT@O-H | FAD@N | 94.16 | 2.1 | 167.1 |
|  | Lys661@N-H | WAT@O | 93.90 | 2.6 | 159.4 |
|  | ligand@N+-H | Asp555@O | 97.83 | 1.8 | 169.2 |