Electronic Supplementary Material (ESI) for MedChemComm.


# Supplementary material

## Molecular modelling studies of quinazolinone derivatives as MMP-13 Inhibitors by QSAR, molecular docking and molecular dynamics simulations techniques

Shanshan Huang, Kairui Feng, and Yujie Ren*

College of Chemical and Environmental Engineering, Shanghai Institute of Technology, Shanghai, China

Correspondence

Yujie Ren, College of Chemical and Environmental Engineering, Shanghai Institute of Technology, Shanghai, China.

Email: clab@sit.edu.cn

# Outline of the Supplementary material

**1. Figures**

**Fig. S1** Region1 and Region2 used for Topomer CoMFA are shown in blue and red, respectively.

**Fig. S2** Topomer CoMFA contour maps based on compound 26. (A, B) Steric and electrostatic contour maps in Region1. (C, D) Steric and electrostatic contours in Region2.

**Fig. S3** Docking results of all designed compounds D1-8 in the MMP-13 protein.

**Fig. S4** (A) Structural comparison between initial (red) and representative snapshots from MD simulation (blue) of compound 5. (B) The binding mode of 5-MMP-13 after MD simulation.

**Fig. S5** The root-mean-square fluctuation (RMSF) of the compound 26 (black) and 5 (orange) in the MMP-13 complexes obtained from 50 ns MD simulation.

**2. Tables**

**Table S1.** Molecular structures of all compounds with their actual and predicted $pIC_{50}$ values of CoMFA and CoMSIA

**Table S2** Energy contribution of the key residues of 26-MMP-13 computed by GB method (Kcal $Mol^{-1}$)

**Table S3** Energy contribution of the key residues of D3-MMP-13 computed by GB method (Kcal $Mol^{-1}$)

**Table S4** Energy contribution of the key residues of D8-MMP-13 computed by GB method (Kcal $Mol^{-1}$)

**Table S5** Energy contribution of the key residues of 5-MMP-13 computed by GB method (Kcal $Mol^{-1}$)

**Table S6.** ADMET prediction of designed compounds

# 1. Figure captions

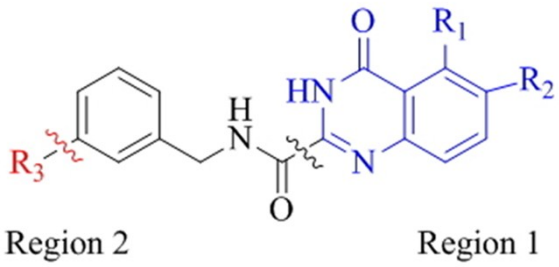



**Fig. S1** Region1 and Region2 used for Topomer CoMFA are shown in blue and red, respectively.

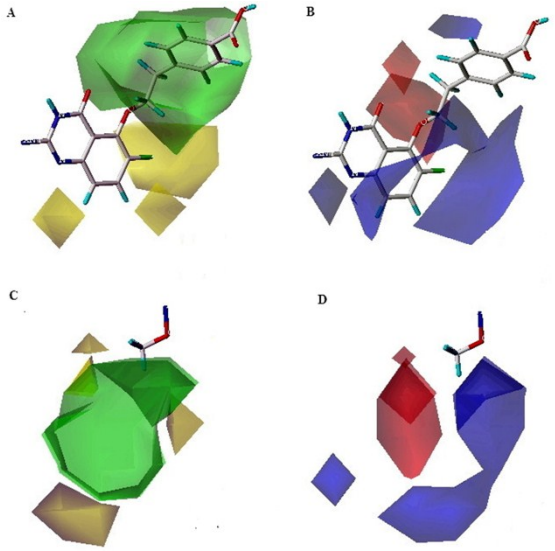



**Fig. S2** Topomer CoMFA contour maps based on compound 26. (A, B) Steric and electrostatic contour maps in Region1. (C, D) Steric and electrostatic contours in Region2.

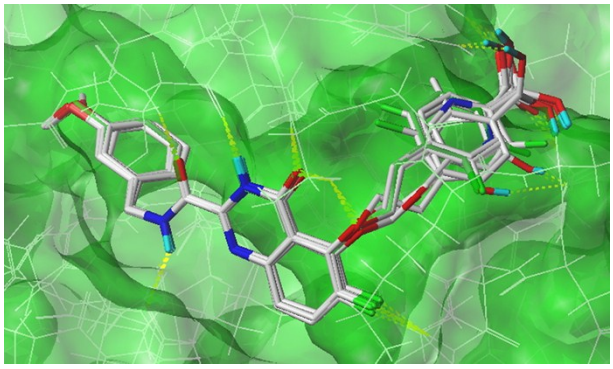


**Fig. S3** Docking results of all designed compounds D1-D8 in the MMP-13 protein

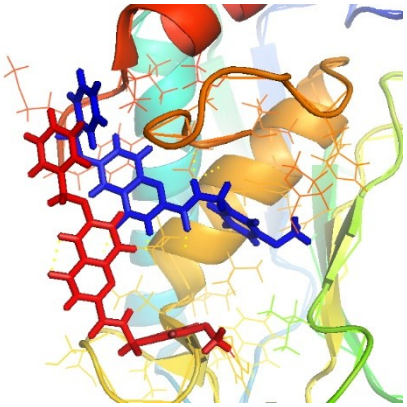


**Fig. S4** Structural comparison between initial (red) and representative snapshots from MD simulation (blue) of compound 5.

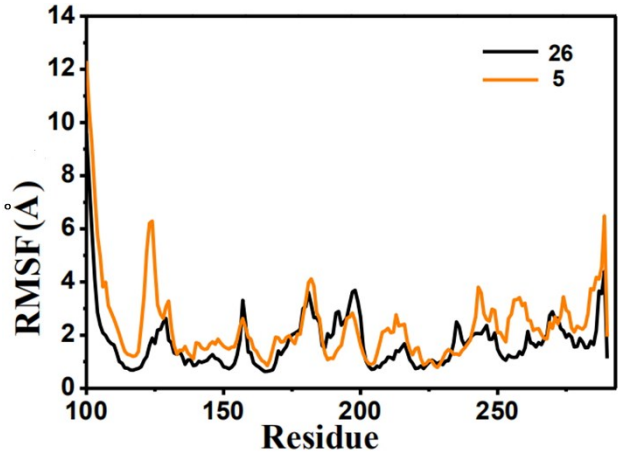
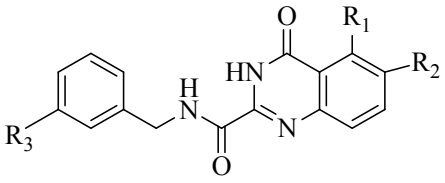



**Fig. S5** The root-mean-square fluctuation (RMSF) of the compound 26 (black) and 5 (orange) in the MMP-13 complexes obtained from 50 ns MD simulation.

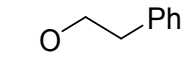
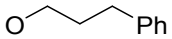
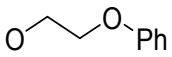
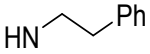
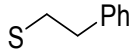
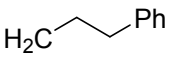
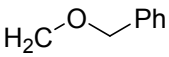
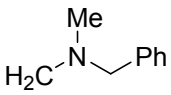
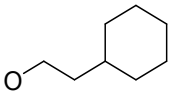
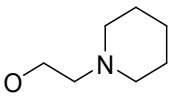
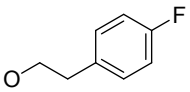
## 2. Table captions

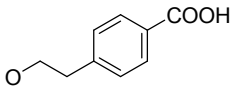
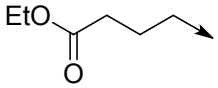
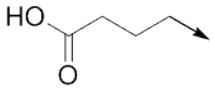
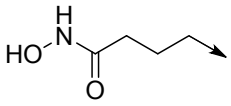
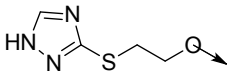
**Table S1.** Molecular structures of all compounds with their actual and predicted $pIC_{50}$ values of CoMFA and CoMSIA

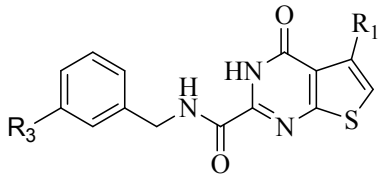


Compound 1-30

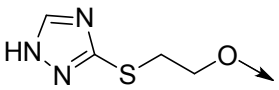
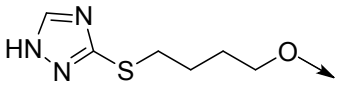
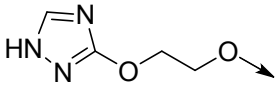
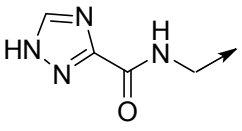
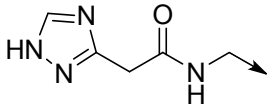
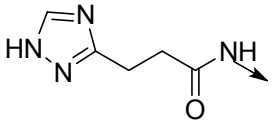
| | | | | | CoMFA | | CoMSIA | |
|---|---|---|---|---|---|---|---|---|
| **NO.** | **$R_1$** | **$R_2$** | **$R_3$** | **Exp.[a]** | **Pred.[b]** | **Res.[c]** | **Pred.[d]** | **Res.[c]** |
| **1** | -H | -H | $-OCH_3$ | 7.921 | 7.791 | 0.130 | 7.586 | 0.335 |
| **2** | -H | -F | $-OCH_3$ | 7.959 | 8.070 | -0.111 | 8.123 | -0.164 |
| **3** | -H | $-CH_3$ | $-OCH_3$ | 7.585 | 7.532 | 0.053 | 7.568 | 0.017 |

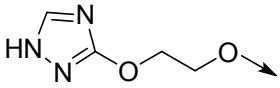
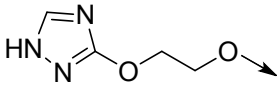
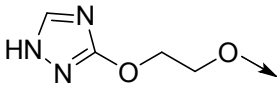
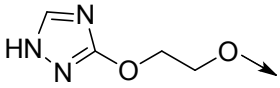
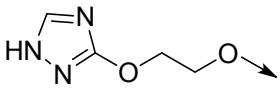
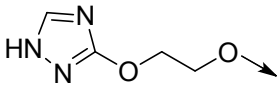
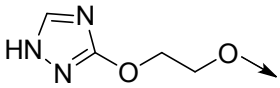
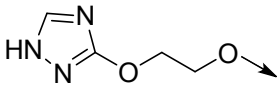
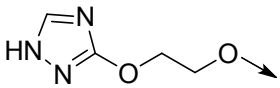
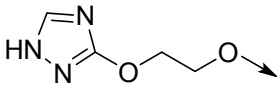
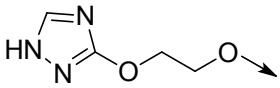
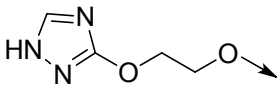
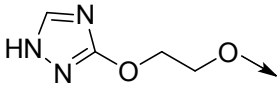
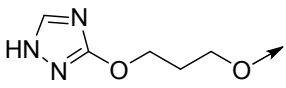
| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **4*** | -H | $-OCF_3$ | $-OCH_3$ | 7.569 | 7.396 | 0.173 | 7.877 | -0.308 |
| **5** | -H | $-OCH_2Ph$ | $-OCH_3$ | 6.959 | 6.862 | 0.097 | 6.970 | -0.011 |
| **6** | -H | $-SO_2CH_3$ | $-OCH_3$ | 7.638 | 7.642 | -0.004 | 7.667 | -0.029 |
| **7** | -H | -Ph | $-OCH_3$ | 8.009 | 8.004 | 0.005 | 8.081 | -0.072 |
| **8** | -H | -CN | $-OCH_3$ | 8.201 | 8.223 | -0.022 | 8.270 | -0.069 |
| **9** | -F | -H | $-OCH_3$ | 8.301 | 8.111 | 0.190 | 8.086 | 0.215 |
| **10** | $-CH_3$ | -H | $-OCH_3$ | 7.538 | 7.835 | -0.297 | 7.819 | -0.281 |
| **11** | $-OCH_3$ | -H | $-OCH_3$ | 7.602 | 7.734 | -0.132 | 7.640 | -0.038 |
| **12** | -CN | -H | $-OCH_3$ | 8.066 | 8.175 | -0.109 | 8.082 | -0.016 |
| **13** | -Ph | -H | $-OCH_3$ | 8.658 | 8.524 | 0.134 | 8.550 | 0.108 |
| **14** | -OPh | -H | $-OCH_3$ | 9.276 | 9.296 | -0.020 | 9.311 | -0.035 |
| **15*** |  | -H | $-OCH_3$ | 9.161 | 8.692 | 0.469 | 8.905 | 0.256 |
| **16** |  | -H | $-OCH_3$ | 9.284 | 9.251 | 0.033 | 9.276 | 0.008 |
| **17** |  | -H | $-OCH_3$ | 8.796 | 8.786 | 0.010 | 8.741 | 0.055 |
| **18*** |  | -H | $-OCH_3$ | 8.367 | 8.284 | 0.083 | 8.134 | 0.233 |
| **19** |  | -H | $-OCH_3$ | 8.013 | 8.155 | -0.142 | 8.061 | -0.048 |
| **20** |  | -H | $-OCH_3$ | 8.538 | 8.555 | -0.017 | 8.502 | 0.036 |
| **21** |  | -H | $-OCH_3$ | 8.770 | 8.690 | 0.080 | 8.705 | 0.065 |
| **22*** |  | -H | $-OCH_3$ | 7.796 | 8.656 | -0.860 | 8.051 | -0.255 |
| **23** |  | -H | $-OCH_3$ | 9.004 | 8.955 | 0.049 | 9.010 | -0.006 |
| **24** |  | -H | $-OCH_3$ | 7.469 | 7.502 | -0.033 | 7.470 | -0.001 |
| **25** |  | -F | $-OCH_3$ | 9.824 | 9.757 | 0.067 | 9.872 | -0.048 |

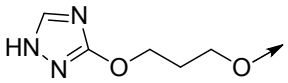
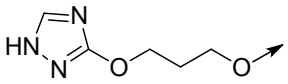
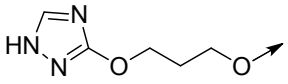
| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **26** |  | -F | $-OCH_3$ | 11.409 | 11.377 | 0.032 | 11.408 | 0.001 |
| **27** | -H | -H |  | 7.538 | 7.381 | 0.157 | 7.551 | -0.013 |
| **28** | -H | -H |  | 8.027 | 8.019 | 0.008 | 8.062 | -0.036 |
| **29** | -H | -H |  | 8.796 | 8.872 | -0.076 | 8.799 | -0.003 |
| **30*** | -H | -H |  | 9.699 | 9.871 | -0.172 | 9.596 | 0.103 |



Compound 31-53

| | | | | CoMFA | | CoMSIA | |
|---|---|---|---|---|---|---|---|
| **NO.** | **$R_1$** | **$R_3$** | **Exp.[a]** | **Pred.[b]** | **Res.[c]** | **Pred.[d]** | **Res.[c]** |
| **31** | $-CH_3$ |  | 10.131 | 10.204 | -0.073 | 10.142 | -0.011 |
| **32** | $-CH_3$ |  | 8.585 | 8.470 | 0.115 | 8.578 | 0.007 |
| **33** | $-CH_3$ |  | 10.194 | 10.087 | 0.107 | 10.160 | 0.034 |
| **34*** | $-CH_3$ |  | 8.824 | 8.879 | -0.055 | 8.266 | 0.558 |
| **35** | $-CH_3$ |  | 8.310 | 8.337 | -0.027 | 8.334 | -0.024 |
| **36** | $-CH_3$ |  | 9.538 | 9.575 | -0.037 | 9.470 | 0.068 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **37** | -*i*Pr |  | 10.041 | 10.103 | -0.062 | 10.018 | 0.023 |
| **38** | -Ph |  | 10.469 | 10.434 | 0.035 | 10.530 | -0.061 |
| **39** | 2-SH-Ph |  | 10.569 | 10.569 | 0.000 | 10.591 | -0.022 |
| **40** | 3-SH-Ph |  | 10.367 | 10.247 | 0.120 | 10.218 | 0.149 |
| **41** | 2-F-Ph |  | 10.620 | 10.486 | 0.134 | 10.403 | 0.217 |
| **42** | 3-F-Ph |  | 10.444 | 10.450 | -0.006 | 10.459 | -0.015 |
| **43** | 4-F-Ph |  | 10.032 | 9.842 | 0.190 | 9.967 | 0.065 |
| **44*** | 2-Cl-Ph |  | 10.268 | 10.691 | -0.423 | 11.008 | -0.740 |
| **45** | 3-Cl-Ph |  | 10.244 | 10.240 | 0.004 | 10.374 | -0.130 |
| **46** | 4-Cl-Ph |  | 9.357 | 9.580 | -0.223 | 9.425 | -0.068 |
| **47** | 2-$OCH_3$-Ph |  | 9.538 | 9.644 | -0.106 | 9.648 | -0.110 |
| **48** | 3-$OCH_3$-Ph |  | 10.585 | 10.687 | -0.102 | 10.698 | -0.113 |
| **49*** | 4-$OCH_3$-Ph |  | 10.000 | 9.887 | 0.113 | 9.957 | 0.043 |
| **50** | 2-F-Ph |  | 10.208 | 10.255 | -0.047 | 10.087 | 0.121 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **51** | 3-F-Ph |  | 9.854 | 9.961 | -0.107 | 9.895 | -0.041 |
| **52** | 2-Cl-Ph |  | 10.229 | 10.214 | 0.015 | 10.333 | -0.104 |
| **53** | 3-Cl-Ph |  | 10.108 | 10.119 | -0.011 | 10.065 | 0.043 |

[a] Experimental $pIC_{50}$.

[b] Predicted $pIC_{50}$ by CoMFA model.

[c] Relative error of (Predicted $pIC_{50}$ - Experimental $pIC_{50}$).

[d] Predicted $pIC_{50}$ by CoMSIA model.

[*] The samples of the test set

**Table S2** Energy contribution of the key residues of 26-MMP-13 computed by GB method (Kcal $Mol^{-1}$)

| No. | $S_{VDW}$ | $B_{VDW}$ | $S_{ELE}$ | $B_{ELE}$ | $S_{GB}$ | $B_{GB}$ | $T_{GBSUR}$ | $T_{GBTOT}$ |
|---|---|---|---|---|---|---|---|---|
| Lys140 | -0.0427 | -0.0044 | -0.0432 | -0.0015 | -0.0061 | -0.0002 | -1.0029 | -0.0801 |
| Asn215 | -0.3137 | -0.1222 | -0.6304 | -0.028 | -0.0892 | -0.004 | -1.3567 | -0.0915 |
| Ala238 | -0.2542 | -0.6753 | -0.0621 | -0.3314 | -0.0088 | -0.0469 | -0.011 | -0.6413 |
| Phe241 | -0.6656 | -0.5842 | -0.1227 | -0.3151 | -0.0174 | -0.0446 | -0.0598 | -0.2913 |
| Tyr244 | -3.1259 | -0.6191 | -0.3808 | -0.1511 | -0.0539 | -0.0214 | -0.3397 | -0.2298 |
| Thr245 | -0.4257 | 0.1220 | -0.107 | -0.759 | -0.0151 | -0.1065 | -0.0795 | -0.9358 |
| Tyr246 | -1.6733 | -0.5072 | -0.2648 | -0.0722 | -0.0375 | -0.0102 | -0.1676 | -0.2116 |
| Thr247 | -1.5744 | -0.2513 | -0.216 | -0.3584 | -0.0305 | -0.0507 | -0.7179 | -0.574 |
| Met253 | -0.0758 | -0.0143 | -0.018 | -0.0027 | -0.0025 | -0.0004 | -0.0697 | -0.0228 |

**Table S3** Energy contribution of the key residues of D3-MMP-13 computed by GB method (Kcal $Mol^{-1}$)

| No. | $S_{VDW}$ | $B_{VDW}$ | $S_{ELE}$ | $B_{ELE}$ | $S_{GB}$ | $B_{GB}$ | $T_{GBSUR}$ | $T_{GBTOT}$ |
|---|---|---|---|---|---|---|---|---|
| Lys140 | -0.0077 | -0.0013 | -0.003 | -0.0005 | -0.0004 | -0.0001 | -0.2331 | -0.0376 |
| Asn215 | -0.4545 | -0.2159 | -0.284 | -0.1031 | -0.0402 | -0.0146 | -0.6535 | -0.3231 |
| Ala238 | -0.1491 | -0.5193 | -0.0623 | -0.1961 | -0.0088 | -0.0277 | -0.01 | -0.3838 |
| Phe241 | -0.6999 | -0.5899 | -0.1617 | -0.1823 | -0.0229 | -0.0258 | -0.0485 | -0.3372 |
| Tyr244 | -2.5098 | -0.7016 | -0.5434 | -0.1929 | -0.0769 | -0.0273 | -0.859 | -0.4211 |
| Thr245 | -0.6513 | -0.2601 | -0.2447 | -0.5939 | -0.0346 | -0.084 | -0.1497 | -1.1897 |
| Tyr246 | -1.6547 | -0.5387 | -0.3214 | -0.0876 | -0.0455 | -0.0124 | -0.2558 | -0.3034 |
| Thr247 | -1.5921 | -0.3081 | -0.3037 | -0.3602 | -0.0429 | -0.0509 | -0.7909 | -0.5645 |
| Met253 | -0.0093 | -0.0172 | -0.0019 | -0.0041 | -0.0003 | -0.0006 | -0.0076 | -0.0335 |

**Table S4** Energy contribution of the key residues of D8-MMP-13 computed by GB method (Kcal $Mol^{-1}$)

| No. | $S_{VDW}$ | $B_{VDW}$ | $S_{ELE}$ | $B_{ELE}$ | $S_{GB}$ | $B_{GB}$ | $T_{GBSUR}$ | $T_{GBTOT}$ |
|---|---|---|---|---|---|---|---|---|
| Lys140 | -0.0527 | -0.0039 | -0.0288 | -0.0011 | -0.0041 | -0.0002 | -0.5245 | -0.1031 |
| Asn215 | -0.7365 | -0.2011 | 0.3604 | 0.0676 | -0.051 | -0.0096 | -0.782 | -0.1782 |
| Ala238 | -0.2250 | -0.5940 | -0.0574 | -0.3673 | -0.0081 | -0.0519 | -0.0157 | -0.675 |
| Phe241 | -0.6365 | -0.7080 | -0.0927 | -0.1632 | -0.0131 | -0.0231 | -0.0391 | -0.3509 |
| Tyr244 | -3.0677 | -0.6441 | -0.676 | -0.1802 | -0.0956 | -0.0255 | -0.8052 | -0.2374 |
| Thr245 | -0.5217 | 0.1805 | -0.1042 | -0.6227 | -0.0147 | -0.0881 | -0.0966 | -0.6479 |
| Tyr246 | -1.8250 | -0.4339 | -0.465 | -0.1176 | -0.0658 | -0.0166 | -0.3026 | -0.2354 |
| Thr247 | -1.3174 | -0.3354 | -0.5978 | -0.3488 | -0.0845 | -0.0493 | -1.5355 | -0.595 |
| Met253 | -0.0177 | -0.0094 | -0.0066 | -0.0039 | -0.0009 | -0.0006 | -0.0355 | -0.019 |

**Table S5** Energy contribution of the key residues of 5-MMP-13 computed by GB method (Kcal $Mol^{-1}$)

| No. | $S_{VDW}$ | $B_{VDW}$ | $S_{ELE}$ | $B_{ELE}$ | $S_{GB}$ | $B_{GB}$ | $T_{GBSUR}$ | $T_{GBTOT}$ |
|---|---|---|---|---|---|---|---|---|
| Lys140 | -0.0017 | -0.0009 | -0.0007 | -0.0003 | -0.0001 | -0.0001 | -0.1123 | -0.0368 |
| Asn215 | -0.1639 | -0.0954 | -0.0631 | -0.0631 | -0.0089 | -0.0089 | -0.0877 | -0.1778 |
| Ala238 | -0.0117 | -0.0351 | -0.0026 | -0.0098 | -0.0004 | -0.0014 | -0.0073 | -0.0587 |
| Phe241 | -0.1327 | -0.4949 | -0.0255 | -0.1107 | -0.0036 | -0.0157 | -0.0149 | -0.2788 |
| Tyr244 | -0.7895 | -0.4072 | -0.3623 | -0.148 | -0.0512 | -0.0209 | -0.2851 | -0.1917 |
| Thr245 | -0.2506 | -0.6661 | -0.1071 | -0.3508 | -0.0151 | -0.0496 | -0.1006 | -1.3028 |
| Tyr246 | -0.4204 | -0.3712 | -0.2027 | -0.1697 | -0.0287 | -0.024 | -0.0709 | -0.2864 |
| Thr247 | -0.2425 | -0.2108 | -0.4007 | -0.1049 | -0.0567 | -0.0148 | -1.3574 | -0.4271 |
| Met253 | -0.2636 | -0.3046 | -0.2218 | -0.1287 | -0.0314 | -0.0182 | -0.1039 | -0.2953 |

S represents the contribution of the side chain;

B represents the contribution of the main chain;

T represents the total contribution;

ELE is the vacuum electrostatic interaction;

VDW is the vacuum van der Waals interaction;

GB is the polar solvation energy calculated by GB method;

GBSUR is a non polar solvation energy;

$S_{VDW}$ is a residue side chain vacuum van der Waals interaction

**Table S6** ADMET prediction of designed compounds

| No. | ADMET Solubility | ADMET Solubility Level | ADMET BBB Level | ADMET CYP2D6 | ADMET CYP2D6 Probability | ADMET Hepatotoxicity | ADMET Hepatotoxicity Probability | ADMET Absorption Level | ADMET PPB Level | ADMET AlogP98 | ADMET PSA-2D |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 21k-Na | -4.44 | 2 | 4 | 0 | 0.346 | 1 | 0.92 | 1 | 0 | 3.41 | 115.636 |
| D1-Na | -4.755 | 2 | 4 | 0 | 0.306 | 1 | 0.913 | 1 | 0 | 3.616 | 115.636 |
| D2-Na | -4.347 | 2 | 4 | 0 | 0.306 | 1 | 0.913 | 2 | 0 | 3.168 | 136.451 |
| D3-Na | -5.079 | 2 | 4 | 0 | 0.297 | 1 | 0.913 | 1 | 0 | 3.821 | 115.636 |
| D4-Na | -5.089 | 2 | 4 | 0 | 0.306 | 1 | 0.966 | 1 | 0 | 3.821 | 115.636 |
| D5-Na | -3.979 | 3 | 4 | 0 | 0.326 | 1 | 0.907 | 1 | 0 | 2.688 | 126.897 |
| D6-Na | -4.451 | 2 | 4 | 0 | 0.306 | 1 | 0.913 | 2 | 0 | 2.985 | 147.712 |
| D7-Na | -4.637 | 2 | 4 | 0 | 0.306 | 1 | 0.913 | 1 | 0 | 3.275 | 126.897 |
| D8-Na | -5.471 | 2 | 4 | 0 | 0.386 | 1 | 0.887 | 2 | 1 | 4.271 | 124.566 |