**Supplementary data**

**Computational assessment of the reactivity and pharmaceutical potential of Novel Triazole Derivatives: An approach combining DFT calculations, molecular dynamics simulations, and molecular docking**

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**Table S1.** Chemical structures and inhibitory activities of the compounds studied

|  |  |  |
| --- | --- | --- |
| Performance  parameter | Formula | Description |
| R², R² Pred |  | plained determination, square variance; coefficient of of the multiple  correlation coefficient |
| RMSE |  | Root mean square error |
| MAE |  | Mean absolute error |
| CCC |  | oefficient of concordance, concordance correlation coefficient |
| Q²F1 |  | Definition set 1 in for Q2 of the external test TR: training set, EXT: external test set |
| Q²F2 |  | Definition set, 2 in for Q2 of the external test  EXT: external test set |
| Q²F3 |  | Definition set 3 in for Q2 of the external test  TR: training set, EXT: external test set |
| K |  | K and K′ are the slope of the plot of calculated versus experimental for the test set at zero intercept, respectively. |
| K’ |  | slope of the plot of of experimental versus calculated activity for the test set at zero intercept |
| R²0 |  | R20 are the coefficients for determining calculated values and those experimental for the test set with zero interception. |
| R’²0 |  | R’20 are the coefficients for determining of xperimental values and those calculated for the test set with zero interception. |
| R²m |  | See above |
| R’²m |  | 𝑟𝑚′2is the same as  𝑟²𝑚 with x and y axis exchanged |
| ΔR²m |  | See above |
|  |  | See above |

**Table 2.**Statistical results of CoMSIA models with different combinations of molecular fields.

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Models | leave/one/out | |  | Non/cross/validation | | |  | Field contribution (%) | | | | |
| R2 | SEE |  | F | Q2 | NOC |  | Ster | Elec | Hyd | HBD | HBA |
| CoMFA | 0.988 | 0.063 |  | 143.043 | 0.702 | **5** |  | 0.67.6 | 32.4 |  |  |  |
| S | 0.828 | 0.244 |  | 8.027 | 0.362 | 2 |  | 1 | - | - | - | - |
| E | 0.720 | 0.311 |  | 4.28 | 0.045 | 2 |  | - | - | - | - | - |
| H | 0.968 | 0.106 |  | 49.890 | 0.595 | 6 |  | - | - | - | - | - |
| A | 0.587 | 0.378 |  | 2.369 | -0.142 | 2 |  | - | - | - | - | - |
| SE | 0.979 | 0.085 |  | 77.794 | 0.804 | 5 |  | 54.2 | 0.45.8 | - | - | - |
| SH | 0.972 | 0.099 |  | 57.749 | 0.596 | **6** |  | 32.4 | **-** | 67.6 | **-** | **-** |
| SA | 0.949 | 0.132 |  | 31.233 | 0.797 | 6 |  | 58.6 | - | - |  | 41.4 |
| EH | 0.983 | 0.077 |  | 94.922 | 0.743 | 6 |  |  | 29.3 | 70.7 |  |  |
| EA | 0.680 | 0.333 |  | 3.539 | -0.014 | 2 |  |  | 44.9 |  |  | 55.1 |
| HA | 0.966 | 0.109 |  | 47.258 | 0.785 | 5 |  |  |  | 69.7 |  | 30.3 |
| SEH | 0.981 | 0.080 |  | 88.247 | 0.725 | 5 |  | 30.4 | 23.9 | 45.6 |  |  |
| **SEA** | **0.979** | **0.086** |  | **75.893** | **0.820** | **5** |  | **50.0** | **25.2** |  |  | **24.7** |
| SHA | 0.967 | 0.107 |  | 48.898 | 0.749 | 5 |  | 29.5 |  | 46.9 |  | 23.6 |
| EHA | 0.985 | 0.073 |  | 106.654 | 0.797 | 6 |  |  | 19.6 | 59.7 |  | 20.7 |
| SEHA | 0.982 | 0.079 |  | 91.870 | 0.778 | 6 |  | 28.9 | 17.5 | 36.0 |  | 176 |

Q²: cross-validated R2; SEE: standard error of estimation.

The best model isshown in bold.

**Table 3.** HQSAR analysis of several combination fragment distinctions up fragment size (4 – 7)

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Model | Fragment distinction | Q² | SEECV | R² | SEE | Best HL | | NC | |
| 1 | A | 0.814 | 0.253 | 0.947 | 0.136 | 257 | 6 | |
| 2 | C | 0.634 | 0.325 | 0.940 | 0.132 | 199 | 4 | |
| 3 | H | 0.366 | 0.396 | 0.619 | 0.307 | 151 | 2 | |
| 4 | Ch | 0.366 | 0.396 | 0.619 | 0.307 | 151 | 2 | |
| 5 | DA | 0.839 | 0.236 | 0.953 | 0.127 | 97 | 6 | |
| 6 | A/B | 0.738 | 0.287 | 0.965 | 0.105 | 97 | 5 | |
| 7 | A/C | 0.517 | 0.409 | 0.966 | 0.108 | 353 | 6 | |
| 8 | A/H | 0.108 | 0.454 | 0.321 | 0.396 | 199 | 1 | |
| 9 | A/Ch | 0.826 | 0.245 | 0.971 | 0.101 | 199 | 6 | |
| 10 | A/DA | 0.790 | 0.246 | 0.880 | 0.186 | 307 | 4 | |
| 11 | B/C | 0.600 | 0.372 | 0.973 | 0.096 | 97 | 6 | |
| 12 | B/DA | 0.90 | 0.158 | 0.958 | 0.115 | 199 | 5 | |
| 13 | C/H | 0.634 | 0.325 | 0.940 | 0.132 | 199 | 4 | |
| 14 | C/Ch | 0.634 | 0.325 | 0.940 | 0.132 | 199 | 4 | |
| 15 | C/DA | 0.817 | 0.240 | 0.939 | 0.138 | 151 | 5 | |
| 16 | H/Ch | 0.366 | 0.396 | 0.619 | 0.307 | 151 | 2 | |
| 17 | H/DA | 0.839 | 0.236 | 0.953 | 0.127 | 97 | 6 | |
| 18 | Ch/DA | 0.839 | 0.236 | 0.953 | 0.127 | 97 | 6 | |
| 19 | A/B/C | 0.559 | 0.342 | 0.873 | 0.184 | 97 | 3 | |
| 20 | A/B/H | 0.126 | 0.449 | 0.367 | 0.382 | 199 | 1 | |
| 21 | A/B/Ch | 0.773 | 0.280 | 0.985 | 0.072 | 97 | 6 | |
| 22 | A/B/DA | 0.841 | 0.223 | 0.932 | 0.147 | 97 | 5 | |
| 23 | A/C/H | 0.098 | 0.456 | 0.395 | 0.374 | 151 | 1 | |
| 24 | A/C/Ch | 0.506 | 0.414 | 0.981 | 0.081 | 257 | 6 | |
| 25 | A/C/DA | 0.805 | 0.237 | 0.901 | 0.169 | 97 | 4 | |
| 26 | A/H/CH | 0.099 | 0.456 | 0.325 | 0.395 | 199 | 1 | |
| 27 | A/H/DA | 0.581 | 0.348 | 0.939 | 0.939 | 307 | 4 | |
| 28 | A/Ch/DA | 0.771 | 0.257 | 0.893 | 0.175 | 353 | 4 | |
| 29 | B/C/H | 0.600 | 0.372 | 0.973 | 0.096 | 97 | 6 | |
| 30 | B/C/Ch | 0.600 | 0.372 | 0.973 | 0.096 | 97 | 6 | |
| 31 | B/C/DA | 0.849 | 0.228 | 0.956 | 0.123 | 97 | 6 | |
| **32** | **B/Ch/DA** | **0.910** | **0.168** | **0.958** | **0.115** | **199** | **5** | |
| 33 | C/H/Ch | 0.634 | 0.325 | 0.940 | 0.132 | 199 | 4 | |
| 34 | C/H /DA | 0.817 | 0.240 | 0.939 | 0.939 | 151 | 5 | |
| 35 | C/Ch/DA | 0.817 | 0.240 | 0.939 | 0.939 | 151 | 5 | |
| 36 | H/Ch/DA | 0.839 | 0.236 | 953 | 0.127 | 97 | 6 | |
| 37 | A/B/C/H | 0.140 | 0.445 | 0.407 | 0.370 | 257 | 1 | |
| 38 | A/ B/C/Ch | 0.659 | 0.328 | 0.978 | 0.083 | 97 | 5 | |
| 39 | A/B/C/DA | 0.819 | 0.239 | 0.913 | 0.166 | 199 | 5 | |
| 40 | A/B/H/Ch | 0.078 | 0.461 | 0.369 | 0.381 | 307 | 1 | |
| 41 | A/B/H/DA | 0.476 | 0.374 | 0.937 | 0.129 | 151 | 3 | |
| 42 | A/B/Ch/DA | 0.804 | 0.248 | 0.937 | 0.141 | 151 | 5 | |
| 43 | A/C/H/Ch | 0.062 | 0.465 | 0.359 | 0.384 | 97 | 1 | |
| 44 | A/C/H/DA | 0.297 | 0.432 | 0.928 | 0.138 | 257 | 3 | |
| 45 | A/C/Ch/DA | 0.781 | 0.276 | 0.952 | 0.128 | 151 | 6 | |
| 46 | B/C/H/Ch | 0.600 | 0.372 | 0.973 | 0.096 | 97 | 6 | |
| 47 | B/C/H/DA | 0.849 | 0.228 | 0.956 | 0.123 | 97 | 6 | |
| 48 | B/C/Ch/DA | 0.849 | 0.228 | 0.956 | 0.123 | 97 | 6 | |
| 49 | B/H/Ch/DA | 0.90 | 0.158 | 0.958 | 0.115 | 199 | 5 | |
| 50 | C/H/Ch/DA | 0.817 | 0.240 | 0.939 | 0.138 | 151 | 5 | |
| 51 | A/H/Ch/DA | 0.565 | 0.388 | 0.974 | 0.095 | 151 | 6 | |
| 52 | A/B/C/H/Ch | 0.112 | 0.453 | 0.415 | 0.367 | 257 | 1 | |
| 53 | A/B/C/H/DA | 0.437 | 0.387 | 0.957 | 0.107 | 199 | 3 | |
| 54 | A/B/C/Ch/DA | 0.805 | 0.260 | 0.976 | 0.091 | 307 | 6 | |
| 55 | A/B/H/Ch/DA | 0.360 | 0.430 | 0.959 | 0.109 | 257 | 4 | |
| 56 | A/C/H/Ch/DA | 0.255 | 0.415 | 0.555 | 0.320 | 97 | 1 | |
| 57 | B/C/H/Ch/DA | 0.849 | 0.228 | 0.956 | 0.123 | 97 | 6 | |
| 58 | A/B/C/H/CH/DA | 0.352 | 0.432 | 0.972 | 0.090 | 257 | 4 | |

Q²LOO: cross-validated R² ; SEE: standard error of estimation. The best model is shown in bold

**Table S3.** Statistical results of the best HQSAR model by changing the different fragment sizes.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Model18 | Fragment distinction | Q2 | SEE cv | R2 | SEE | Best LH | NC |
| 1-4 | B/H/DA | 0.578 | 0.349 | 0.929 | 0.143 | 151 | 4 |
| 2-5 | B/H/DA | 0.620 | 0.363 | 0.963 | 0.113 | 97 | 6 |
| 3-6 | B/H/DA | 0.903 | 0.175 | 0.957 | 0.116 | 199 | 5 |
| 4-7 | B/H/DA | 0.910 | 0.168 | 0.958 | 0.115 | 199 | 5 |
| **5-8** | **B/H/DA** | **0.919** | **0.159** | **0.962** | **0.109** | **97** | **5** |
| 6-9 | B/H/DA | 0.900 | 0.186 | 0.966 | 0.109 | 151 | 6 |
| 7-10 | B/H/DA | 0.907 | 0.179 | 0.965 | 0.965 | 307 | 6 |
| 8 -11 | B/H/DA | 0.908 | 0.178 | 0.965 | 0.110 | 199 | 6 |
| 9 -12 | B/H/DA | 0.907 | 0.179 | 0.965 | 0.965 | 257 | 6 |
| 10-13 | B/H/DA | 0.907 | 0.179 | 0.965 | 0.965 | 257 | 6 |
| 11 -14 | B/H/DA | 0.918 | 0.168 | 0.966 | 0.108 | 199 | 6 |
| 12-15 | B/H/DA | 0.916 | 0.171 | 0.966 | 0.109 | 257 | 6 |
| 13-16 | B/H/DA | 0.913 | 0.173 | 0.965 | 0.110 | 257 | 6 |
| 14-17 | B/H/DA | 0.906 | 0.181 | 0.964 | 0.111 | 257 | 6 |
| 15-18 | B/H/DA | 0.886 | 0.194 | 0.953 | 0.135 | 151 | 6 |

Q²LOO: cross-validated R² ; SEE: standard error of estimation. The best model is shown in bold



**Fig. S1.** The human DNA topoisomerase IIα (PDB 1ZXM) co-crystal structure asteroid plots, The inner shell residues were those that had direct contact with the ligand molecule, whereas the outer shell residues were those that had indirect interactions with the ligand. The number of contacts residues formed with the ligand was represented by the size of the circular nodes.