Investigation of angiotensin-I-converting enzyme (ACE) inhibitory tri-peptides: a combination of 3D-QSAR and molecular docking simulations

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Table S1
Summary of QSAR results for ACE peptides based on template ligand-based alignment.

|                      | CoMF |                      | CoMSIA |
|----------------------|------|----------------------|--------|
|                      | SE   | S        | E    | H    | D    | A    | SE   | SH   | SD |
| $R^2_{cv}$           | 0.761 | 0.667   | 0.009 | 0.39 | 0.449 | -0.312 | 0.824 | 0.578 | 0.678 |
| $R^2_{n(cv)}$        | 0.953 | 0.797   | 0.466 | 0.705 | 0.775 | 0.166 | 0.952 | 0.957 | 0.67 |
| SEE                  | 0.243 | 0.479   | 0.776 | 0.577 | 0.549 | 0.970 | 0.458 | 0.248 | 0.410 |
| F                    | 86.617 | 37.193  | 8.276 | 22.717 | 11.018 | 1.884 | 120.16 | 55.634 | 27.649 |
| $R^2_{pred}$         | 0.6257 | 0.4567  | 0.2113 | 0.4994 | 0.428 | 0.582 | 0.5199 | 0.46 | 0.6783 |
| SEP                  | 0.549 | 0.613   | 1.058 | 0.829 | 0.859 | 1.261 | 0.458 | 0.776 | 0.637 |
| $N_C$                | 4     | 2       | 2     | 5     | 2     | 3     | 6     | 4     |

Field contribution

| S | 0.675 | 1.000 | - | - | - | - | 0.528 | 0.366 | 0.439 |
| E | 0.325 | -     | 1.000 | - | - | - | - | 0.472 | - |
| H | -     | -     | - | 1.000 | - | - | - | - | 0.634 |
| D | - | - | - | - | 1.000 | - | - | - | 0.561 |
| A | - | - | - | - | - | 1.000 | - | - | - |

CoMSIA

|                      | SA   | EH   | ED   | EA   | HD   | HA   | DA   | SEH  | SED |
|----------------------|------|------|------|------|------|------|------|------|-----|
| $R^2_{cv}$           | 0.726 | 0.532 | 0.658 | 0.04 | 0.426 | 0.53 | 0.445 | 0.625 | 0.746 |
| $R^2_{n(cv)}$        | 0.941 | 0.932 | 0.322 | 0.659 | 0.801 | 0.931 | 0.916 | 0.947 | 0.956 |
| SEE                  | 0.264 | 0.292 | 0.322 | 0.656 | 0.487 | 0.287 | 0.347 | 0.25 | 0.237 |
| F                    | 94.216 | 58.665 | 31.845 | 8.206 | 24.169 | 80.957 | 27.139 | 76.128 | 91.351 |
| $R^2_{pred}$         | 0.459 | 0.4876 | 0.7901 | 0.0241 | 0.4753 | 0.4113 | 0.684 | 0.5094 | 0.6199 |
| SEP                  | 0.571 | 0.768 | 0.699 | 1.100 | 0.827 | 0.819 | 0.891 | 0.687 | 0.566 |
| $N_C$                | 3     | 4     | 6     | 4     | 3     | 6     | 4     | 4     |

Field contribution

| S | 0.618 | - | - | - | - | - | - | 0.237 | 0.319 |
| E | - | 0.364 | 0.292 | 0.653 | - | - | - | 0.301 | 0.266 |
| H | - | 0.636 | - | - | 0.567 | 0.675 | - | - | 0.462 |
| D | - | - | 0.708 | - | 0.433 | - | 0.670 | - | 0.414 |
Table S2.
Summary of QSAR results for ACE peptides based on docking-based alignment.

|          | CoMF A | CoMSIA |
|----------|--------|--------|
|          | SE     | S      | E     | H     | D     | A     | SE     | SH    | SD    |
| $R^2_{cv}$ | 0.005  | 0.174  | -1.162| 0.202 | -0.197| 0.208 | -0.057 | 0.193 | 0.245 |
| $R^2_{ncv}$ | 0.858  | 0.816  | 0.812 | 0.892 | 0.635 | 0.892 | 0.900  | 0.931 | 0.983 |
| SEE      | 0.411  | 0.468  | 0.487 | 0.359 | 0.642 | 0.369 | 0.354  | 0.296 | 0.158 |
| F        | 36.386 | 26.623 | 18.334| 49.448| 16.514| 35.165| 38.392 | 56.982| 140.992|
| $R^2_{pred}$ | 6E-5   | 0.1141 | 0.1596| 0.0088| 0.019 | 0.0257| 0.0003 | 0.119 | 0.1819|
| SEP      | 1.089  | 0.992  | 1.210 | 0.975 | 1.162 | 0.999 | 1.155  | 1.009 | 1.039 |

| CoMSIA  | SEA | SHD | SHA | SDA | EHD | EHA | EDA | HDA | SEHD |
|---------|-----|-----|-----|-----|-----|-----|-----|-----|------|
| $R^2_{cv}$ | 0.778| 0.553| 0.649| 0.74 | 0.532| 0.558| 0.581| 0.585| 0.613 |
| $R^2_{ncv}$ | 0.952| 0.850| 0.971| 0.968| 0.947| 0.956| 0.917| 0.967| 0.956 |
| SEE     | 0.240| 0.423| 0.202| 0.214| 0.266| 0.236| 0.343| 0.218| 0.242 |
| F       | 117.73| 33.883| 85.198| 75.773| 57.387| 27.777| 91.664| 27.777| 72.333 |
| $R^2_{pred}$ | 0.5015| 0.6328| 0.6427| 0.6693| 0.6138| 0.7827| 0.7628| 0.6428 |
| SEP     | 0.514| 0.729| 0.708| 0.609| 0.792| 0.747| 0.774| 0.770| 0.720 |
| $N_C$   | 3    | 3    | 6    | 6    | 5    | 4    | 6    | 6    | 5    |

Field contribution

|          | S     | E     | H     | D     | A     |
|----------|-------|-------|-------|-------|-------|
| $R^2_{cv}$ | 0.005 | 0.174 | -1.162| 0.202 | -0.197|
| $R^2_{ncv}$ | 0.858 | 0.816 | 0.812 | 0.892 | 0.635 |
| SEE      | 0.411 | 0.468 | 0.487 | 0.359 | 0.642 |
| F        | 36.386| 26.623| 18.334| 49.448| 16.514|
| $R^2_{pred}$ | 6E-5 | 0.1141| 0.1596| 0.0088| 0.019 |
| SEP      | 1.089 | 0.992 | 1.210 | 0.975 | 1.162 |
| \( N_C \) | 3 | 3 | 4 | 3 | 2 | 4 | 4 | 4 | 6 |
|---|---|---|---|---|---|---|---|---|---|
| **Field contribution** | | | | | | | | | |
| S | 0.546 | 1.000 | - | - | - | - | 0.484 | 0.376 | 0.465 |
| E | 0.454 | - | 1.000 | - | - | - | 0.516 | - | - |
| H | - | - | - | 1.000 | - | - | 0.624 | - | - |
| D | - | - | - | - | 1.000 | - | - | 0.535 | - |
| A | - | - | - | - | - | 1.000 | - | - | - |
| **CoMSIA** | | | | | | | | | |
| | SA | EH | ED | EA | HD | HA | DA | SEH | SED |
| \( R_{cv}^2 \) | 0.288 | 0.126 | -0.104 | 0.056 | 0.163 | 0.268 | 0.026 | 0.127 | -0.002 |
| \( R_{ncv}^2 \) | 0.981 | 0.92 | 0.869 | 0.793 | 0.945 | 0.856 | 0.928 | 0.930 | 0.914 |
| SEE | 0.166 | 0.317 | 0.407 | 0.483 | 0.264 | 0.403 | 0.301 | 0.298 | 0.329 |
| \( F \) | 126.43 | 49.191 | 28.176 | 36.67 | 72.654 | 56.480 | 55.018 | 56.242 | 45.275 |
| \( R_{pred}^2 \) | 0.0028 | 0.0608 | 0.0765 | 0.0755 | 0.0001 | 1E-05 | 0.0108 | 0.0038 | 0.0006 |
| SEH | 1.008 | 1.050 | 1.180 | 1.032 | 1.027 | 0.909 | 0.108 | 1.049 | 1.124 |
| \( N_C \) | 6 | 4 | 4 | 2 | 4 | 2 | 4 | 4 | 4 |
| **Field contribution** | | | | | | | | | |
| S | 0.402 | - | - | - | - | - | - | 0.253 | 0.312 |
| E | - | 0.404 | 0.508 | 0.446 | - | - | - | 0.298 | 0.333 |
| H | - | 0.596 | - | - | 0.590 | 0.507 | - | 0.449 | - |
| D | - | - | 0.492 | - | 0.410 | - | 0.393 | - | 0.355 |
| A | 0.598 | - | - | 0.554 | - | 0.493 | 0.607 | - | - |
| **CoMSIA** | | | | | | | | | |
| | SEA | SHD | SHA | SDA | EHD | EHA | EDA | HDA | SEHD |
| \( R_{cv}^2 \) | 0.096 | 0.192 | 0.234 | 0.176 | 0.097 | 0.181 | 0.02 | 0.208 | 0.102 |
| \( R_{ncv}^2 \) | 0.934 | 0.986 | 0.948 | 0.936 | 0.928 | 0.836 | 0.921 | 0.944 | 0.939 |
| SEE | 0.288 | 0.141 | 0.256 | 0.284 | 0.300 | 0.430 | 0.316 | 0.265 | 0.278 |
| \( F \) | 60.507 | 177.47 | 77.748 | 62.304 | 55.089 | 48.428 | 49.493 | 72.191 | 64.890 |
| \( R_{pred}^2 \) | 0.0238 | 0.0755 | 0.0092 | 0.0025 | 0.0605 | 0.0017 | 0.0199 | 0.0011 | 0.0007 |
| SEH | 1.068 | 1.075 | 0.983 | 1.019 | 1.067 | 0.961 | 1.111 | 0.999 | 1.064 |
| \( N_C \) | 4 | 6 | 4 | 4 | 4 | 2 | 4 | 4 | 4 |
| **Field contribution** | | | | | | | | | |
| S | 0.274 | 0.255 | 0.234 | 0.292 | - | - | - | - | 0.200 |
| E | 0.292 | - | - | - | 0.283 | 0.285 | 0.302 | - | 0.221 |
| H | - | 0.416 | 0.388 | - | 0.428 | 0.364 | - | 0.388 | 0.341 |
| D | - | 0.329 | - | 0.295 | 0.288 | - | 0.290 | 0.255 | 0.239 |
| A | 0.434 | - | 0.377 | 0.413 | - | 0.351 | 0.408 | 0.357 | - |
| **CoMSIA** | | | | | | | | | |
| | SEHA | SEDA | SHDA | EHDA | SEHDA |
| \( R_{cv}^2 \) | 0.159 | 0.056 | 0.216 | 0.164 | 0.147 |
| \( R_{ncv}^2 \) | 0.941 | 0.930 | 0.952 | 0.936 | 0.944 |
| SEE | 0.273 | 0.297 | 0.245 | 0.284 | 0.265 |
| \( F \) | 67.663 | 56.660 | 85.170 | 62.241 | 72.263 |
| R²_{pred} | 0.0018 | 0.0096 | 0.004   | 0.0259 | 0.0034 |
| SEP      | 1.030  | 1.091  | 0.994   | 1.027  | 1.037  |
| N_C      | 4      | 4      | 4       | 4      | 4      |

**Field contribution**

|   | S   | E   | H   | D   | A   |
|---|-----|-----|-----|-----|-----|
| N_C| 0.179 | 0.217 | 0.11 | -   | 0.154 |
|   | 0.206 | 0.226 | -   | 0.203 | 0.166 |
|   | 0.317 | -    | 0.308 | 0.311 | 0.262 |
|   | -    | 0.236 | 0.211 | 0.203 | 0.177 |
|   | 0.298 | 0.322 | 0.289 | 0.283 | 0.241 |

**Table S3.**

Summary of QSAR results for ACE peptides based on common scaffold-based alignment.

|        | CoMFA          | CoMSIA         |
|--------|----------------|----------------|
|        | SE  | S   | E   | H   | D   | A   | SE  | SH  | SD  |
| R²_{cv} | -0.133 | 0.147 | -0.213 | 0.416 | -0.234 | -0.475 | -0.188 | 0.367 | 0.066 |
| R²_{ncv} | 0.985 | 0.862 | 0.405 | 0.908 | 0.951 | 0.324 | 0.504 | 0.931 | 0.991 |
| SEE    | 0.140 | 0.395 | 0.798 | 0.323 | 0.265 | 0.851 | 0.729 | 0.279 | 0.115 |
| F      | 215.94 | 59.186 | 13.621 | 93.384 | 48.510 | 9.598 | 20.291 | 127.84 | 269.813 |
| SEP    | 1.155 | 4      | 2     | 1    | 6    | 1    | 6    | 6    | 6    |

**Field contribution**

|   | S   | E   | H   | D   | A   |
|---|-----|-----|-----|-----|-----|
| N_C| 0.675 | 1.000 | -   | -   | -   |
|   | 0.325 | -    | 1.000 | -   | -   |
|   | -    | -    | 1.000 | -   | -   |
|   | -    | -    | -    | 1.000 | -   |
|   | 0.57 | 0.489 | -    | 0.371 | 0.398 |

|        | CoMSIA          |
|--------|----------------|
|        | SA  | EH | ED | EA | HD | HA | DA | SEH | SED |
| R²_{cv} | -0.337 | 0.222 | -0.268 | -0.313 | 0.338 | 0.181 | -0.387 | 0.173 | -0.193 |
| R²_{ncv} | 0.961 | 0.994 | 0.789 | 0.421 | 0.996 | 0.997 | 0.982 | 0.988 | 0.844 |
| SEE    | 0.229 | 0.096 | 0.501 | 0.788 | 0.077 | 0.068 | 0.162 | 0.128 | 0.431 |
| F      | 78.588 | 387.93 | 22.458 | 14.547 | 593.27 | 770.31 | 133.32 | 259.42 | 32.398 |
| SEP    | 1.192 | 1.358 | 1.229 | 1.186 | 0.972 | 1.082 | 1.408 | 1.053 | 1.238 |

**Field contribution**

|   | S   | E   | H   | D   | A   |
|---|-----|-----|-----|-----|-----|
| N_C| 0.426 | -    | -   | -   | -   |
|   | -    | 0.351 | 0.395 | 0.511 | -   |
|   | -    | 0.649 | -    | 0.525 | 0.629 |
|   | -    | 0.605 | -    | 0.475 | 0.602 |
|   | 0.57 | -    | 0.489 | -    | 0.371 |

**CoMSIA**

|        | CoMSIA          |
|--------|----------------|
|        | SE  | SH  | SD  |
| SEP    | 1.037 | 1.037 | 1.037 | 1.037 | 1.037 | 1.037 | 1.037 | 1.037 | 1.037 |

CoMSIA
|       | SEA | SHD  | SHA  | SDA  | EHD  | EHA  | EDA  | HDA  | SEHD |
|-------|-----|------|------|------|------|------|------|------|------|
| $R^2_{cv}$ | -0.301 | 0.311 | 0.13 | -0.131 | 0.238 | 0.062 | -0.32 | 0.158 | 0.209 |
| $R^2_{ncv}$ | 0.477 | 0.996 | 0.986 | 0.994 | 0.997 | 0.995 | 0.440 | 0.998 | 0.997 |
| SEE   | 0.748 | 0.072 | 0.137 | 0.093 | 0.067 | 0.086 | 0.775 | 0.058 | 0.067 |
| F     | 18.261 | 682.53 | 224.72 | 406.62 | 788.89 | 480.87 | 15.700 | 1063.9 | 784.446 |
| $R^2_{pred}$ | 0.4822 | 0.2337 | 0.4592 | 0.1004 | 0.1366 | 0.4134 | 0.463 | 0.1005 |
| SEP   | 1.181 | 0.992 | 1080 | 1.271 | 1.043 | 1.158 | 1.189 | 1.097 | 1.063 |
| $N_C$ | 1 | 6 | 5 | 6 | 6 | 6 | 6 | 6 | 6 |

**Field contribution**

| | S | E | H | D | A |
|---|---|---|---|---|---|
| S | 0.197 | 0.169 | 0.209 | 0.231 | - |
| E | 0.411 | - | - | - | 0.197 |
| H | - | 0.421 | 0.493 | - | 0.426 |
| D | - | 0.409 | - | 0.466 | 0.377 |
| A | 0.392 | - | 0.298 | 0.303 | - |

|       | SEHA | SEDA | SHDA | EHDA | SEHDA |
|-------|------|------|------|------|------|
| $R^2_{cv}$ | 0.047 | -0.234 | 0.168 | 0.093 | 0.096 |
| $R^2_{ncv}$ | 0.996 | 0.994 | 0.998 | 0.997 | 0.997 |
| SEE   | 0.078 | 0.090 | 0.057 | 0.066 | 0.064 |
| F     | 591.463 | 434.943 | 1087.702 | 808.664 | 881.448 |
| $R^2_{pred}$ | 0.2907 | 0.0478 | 0.3037 | 0.2797 | 0.1973 |
| SEP   | 1.167 | 1.328 | 1.090 | 1.138 | 1.137 |
| $N_C$ | 6 | 6 | 6 | 6 | 6 |

**Field contribution**

| | S | E | H | D | A |
|---|---|---|---|---|---|
| S | 0.156 | 0.176 | 0.140 | - | - |
| E | 0.211 | 0.199 | - | 0.171 | 0.148 |
| H | 0.389 | - | 0.342 | 0.337 | 0.293 |
| D | - | 0.362 | 0.320 | 0.296 | 0.266 |
| A | 0.244 | 0.263 | 0.198 | 0.196 | 0.178 |

Fig. S1 (A) The alignment for ACE from the docking-based alignment. (B) The alignment for ACE from the common scaffold-based alignment.