Molecular modelling studies on pyrazole derivatives for the design of potent Rearranged during Transfection kinase inhibitors

Swapnil P. Bhujbal¹ · Seketoulie Keretsu¹ · Seung Joo Cho¹,²,*

¹Department of Biomedical Sciences, College of Medicine, Chosun University, Gwangju 501-759, Republic of Korea

²Department of Cellular·Molecular Medicine, College of Medicine, Chosun University, Gwangju 501-759, Republic of Korea

Supplementary Materials
## Tables

**Table S1.** CoMSIA models developed using different combinations of fields.

| CoMSIA | $q^2$ | ONC | SEP | $r^2$ | SEE | F value  | Percentage contribution |
|--------|-------|-----|-----|-------|-----|---------|-------------------------|
| S      | 0.332 | 6   | 0.823 | 0.767 | 0.437 | 15.320 | 100 - - - - |
| E      | 0.394 | 6   | 0.784 | 0.595 | 0.641 | 6.850  | - 100 - - - |
| H      | 0.297 | 2   | 0.790 | 0.813 | 0.435 | 20.310 | - - 100 - - |
| A      | 0.340 | 3   | 0.778 | 0.564 | 0.665 | 6.034  | - - - 100 - |
| D      | 0.204 | 2   | 0.840 | 0.446 | 0.750 | 3.752  | - - - - 100 |
| SE     | 0.415 | 6   | 0.770 | 0.850 | 0.390 | 26.38  | 59.5 40.5 - - |
| EH     | 0.467 | 5   | 0.722 | 0.780 | 0.464 | 20.556 | - 33.6 66.4 - |
| EA     | 0.444 | 6   | 0.751 | 0.633 | 0.610 | 8.047  | - 55.1 - 44.9 |
| ED     | 0.368 | 6   | 0.801 | 0.625 | 0.617 | 7.763  | - 76.9 - - 23.1 |
| SH     | 0.313 | 2   | 0.781 | 0.572 | 0.617 | 21.365 | 29.1 70.9 - - |
| SA     | 0.406 | 2   | 0.726 | 0.623 | 0.579 | 26.442 | 39.3 - - 60.7 |
| SD     | 0.300 | 2   | 0.788 | 0.761 | 0.493 | 14.829 | 76.3 - - - 23.7 |
| HA     | 0.434 | 3   | 0.720 | 0.845 | 0.397 | 25.366 | - - 69.9 30.1 |
| HD     | 0.341 | 2   | 0.765 | 0.806 | 0.443 | 19.408 | - - 84.6 - 15.4 |
| SEH    | 0.436 | 5   | 0.744 | 0.805 | 0.437 | 23.907 | 22.2 36.8 41.0 - - |
| SEA    | 0.469 | 4   | 0.709 | 0.738 | 0.498 | 21.137 | 32.5 35.9 - 31.7 |

**Notes:**
- ONC: Orthogonal Normalization Coefficient
- SEP: Self-Energy
- $r^2$: Square of the correlation coefficient
- SEE: Standard Error of Estimate
- F value: F-statistic
- Percentage contribution: Contribution of each term to the overall model.
| Compound | CoMFA | CoMSIA (EHA) |
|----------|-------|-------------|
|          | Actual pIC<sub>50</sub> | Predicted pIC<sub>50</sub> | Residual | Actual pIC<sub>50</sub> | Predicted pIC<sub>50</sub> | Residual |
| SED      | 0.420 | 4 | 0.741 | 0.715 | 0.520 | 18.772 | 36.7 | 36.6 | - | - | 26.7 |
| EHA      | 0.509 | 4 | 0.682 | 0.745 | 0.491 | 21.918 | - | 28.1 | 44.2 | 27.7 | - |
| EHD      | 0.465 | 5 | 0.724 | 0.798 | 0.445 | 22.880 | - | 32.3 | 48.9 | - | 18.8 |
| SHA      | 0.403 | 2 | 0.728 | 0.623 | 0.579 | 26.427 | 20.7 | - | 46.5 | 34.8 | - |
| SHD      | 0.360 | 2 | 0.754 | 0.540 | 0.639 | 18.809 | 18.4 | - | 37.2 | - | 44.4 |
| EAD      | 0.386 | 5 | 0.725 | 0.622 | 0.609 | 9.539 | - | 43.5 | - | 33.1 | 23.4 |
| HAD      | 0.397 | 3 | 7.444 | 0.669 | 0.551 | 20.915 | - | - | 52 | 26.5 | 21.5 |
| SEHD     | 0.469 | 6 | 0.734 | 0.855 | 0.383 | 27.566 | 23.7 | 23.2 | 36.5 | - | 16.6 |
| SEHA     | 0.471 | 4 | 0.708 | 0.767 | 0.470 | 24.688 | 19.0 | 25.4 | 32.4 | 23.2 | - |
| SEAD     | 0.458 | 4 | 0.717 | 0.818 | 0.435 | 20.408 | 43.2 | 25.1 | - | 16.1 | 15.5 |
| EHAD     | 0.478 | 4 | 0.703 | 0.739 | 0.499 | 21.022 | - | 23.9 | 40 | 19.8 | 16.3 |
| SHAD     | 0.387 | 3 | 0.749 | 0.677 | 0.544 | 21.666 | 21.5 | - | 36.6 | 21.4 | 20.5 |
| SEHAD    | 0.481 | 3 | 0.689 | 0.727 | 0.500 | 27.531 | 17 | 18.1 | 29.1 | 17.5 | 18.4 |

Table S2. Residual values of the selected CoMFA and CoMSIA models.
|    |     |     |     |     |     |     |
|----|-----|-----|-----|-----|-----|-----|
| 10 | 6.200 | 6.499 | -0.299 | 6.2 | 6.51 | -0.31 |
| 11 | 5.900 | 6.306 | -0.406 | 5.9 | 6.402 | -0.502 |
| 12 | 5.653 | 5.591 | 0.062 | 5.653 | 5.675 | -0.022 |
| 13 | 7.357 | 7.244 | 0.113 | 7.357 | 7.185 | 0.172 |
| 14 | 5.569 | 5.252 | 0.317 | 5.569 | 5.392 | 0.177 |
| 15 | 5.310 | 5.334 | -0.024 | 5.31 | 5.453 | -0.143 |
| 16 | 5.079 | 5.014 | 0.065 | 5.079 | 4.889 | 0.19 |
| 17 | 6.234 | 6.354 | -0.120 | 6.234 | 6.265 | -0.031 |
| 18 | 6.721 | 6.607 | 0.114 | 6.721 | 6.879 | -0.158 |
| 19 | 6.618 | 6.659 | -0.041 | 6.618 | 6.552 | 0.066 |
| 20 | 6.824 | 6.943 | -0.119 | 6.824 | 6.98 | -0.156 |
| 21 | 6.041 | 6.417 | -0.376 | 6.041 | 6.005 | 0.036 |
| 22 | 7.387 | 7.156 | 0.231 | 7.387 | 7.371 | 0.016 |
| 23 | 7.387 | 7.506 | -0.119 | 7.387 | 7.359 | 0.028 |
| 24 | 6.678 | 6.716 | -0.038 | 6.678 | 6.638 | 0.04 |
| 25 | 8.854 | 8.231 | 0.623 | 8.854 | 8.506 | 0.348 |
| 26 | 6.618 | 6.507 | 0.111 | 6.618 | 7.113 | -0.495 |
| 27 | 6.041 | 6.357 | -0.316 | 6.041 | 6.352 | -0.311 |
| 28 | 6.672 | 6.429 | 0.243 | 6.672 | 7.304 | -0.632 |
| 29 | 7.284 | 7.595 | -0.311 | 7.284 | 7.583 | -0.299 |
| 30 | 7.569 | 7.858 | -0.289 | 7.569 | 7.544 | 0.025 |
| 31 | 7.131 | 7.257 | -0.126 | 7.131 | 7.237 | -0.106 |
| 32 | 7.018 | 6.993 | 0.025 | 7.018 | 7.476 | -0.458 |
| 33 | 7.167 | 7.073 | 0.094 | 7.167 | 7.305 | -0.138 |
| 34 | 8.699 | 8.608 | 0.091 | 8.699 | 8.243 | 0.456 |
| 35 | 8.301 | 8.457 | -0.156 | 8.301 | 8.145 | 0.156 |

**Figures**

**Figure S1.** The graph of the number of hydrogen bonds during 100 ns MD simulation.
Figure S2. Superimposition of the initial (docked complex) and the final (100 ns) of MD structure of the compound 25 inside in the binding site of RET kinase. (Purple color shows the docked complex and salmon color denotes the 100 MD complex)