Structure-Based Approach for the Study of Thyroid Hormone Receptor Binding Affinity and Subtype Selectivity

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Table S1. Molecular structures of Indane Derivatives and their TR\(\beta\) binding affinity values (pK\(\text{d}\)).
|    |    |    |    |    |    |    |
|----|----|----|----|----|----|----|
| 9  | Br | Br | H  | ![Chemical Structure](image1) | ![Chemical Structure](image2) | 6.6234 |
| 10 | Me | -CH₂CH₂CH₂ | 4-F-C₆H₄CH₂ | ![Chemical Structure](image3) | ![Chemical Structure](image4) | 8.4318 |
| 11 | Me | -CH₂CH₂CH₂ | ![Chemical Structure](image5) | ![Chemical Structure](image6) | 7.8508 |
| 12 | Me | -CH₂CH₂CH₂ | PhCH₂CH₂ | ![Chemical Structure](image7) | ![Chemical Structure](image8) | 7.3958 |
| 13 | Me | -CH₂CH₂CH₂ | 4-F-C₆H₄CH₂CH₂ | ![Chemical Structure](image9) | ![Chemical Structure](image10) | 8.0862 |
| 14 | Me | -CH₂CH₂CH₂ | PhCH₂CH(OH) | ![Chemical Structure](image11) | ![Chemical Structure](image12) | 6.9066 |
| 15 | Me | -CH₂CH₂CH₂ | PhCH₂CO | ![Chemical Structure](image13) | ![Chemical Structure](image14) | 6.3556 |
| 16 | Me | -CH₂CH₂CH₂ | PhCH₂CH₂CH₂ | ![Chemical Structure](image15) | ![Chemical Structure](image16) | 6.6517 |
| 25 | Br | Br | H  | ![Chemical Structure](image17) | ![Chemical Structure](image18) | 9.3665 |
| 26 | Me | Me | H  | ![Chemical Structure](image19) | ![Chemical Structure](image20) | 8.0000 |
| 27 | Cl | Cl | Cl  | ![Chemical Structure](image21) | ![Chemical Structure](image22) | 8.8125 |
| 28 | Me | Me | Me | ![Chemical Structure](image23) | ![Chemical Structure](image24) | 7.6925 |
| 29 | Br | -CH₂CH₂CH₂ | ![Chemical Structure](image25) | ![Chemical Structure](image26) | 8.9245 |
| 30 | Br | -CH₂(CH₂)₂CH₂ | ![Chemical Structure](image27) | ![Chemical Structure](image28) | 6.5214 |
| 31 | Me | -CH₂CH₂CH₂ | ![Chemical Structure](image29) | ![Chemical Structure](image30) | 8.5867 |
| 32 | Me | -CH₂CH₂CH₂ | ![Chemical Structure](image31) | ![Chemical Structure](image32) | 7.821 |
| 33 | Me | -CH₂CH₂CH₂ | ![Chemical Structure](image33) | ![Chemical Structure](image34) | 6.6716 |
| Compound | 2 | 3 | 4 | pK_i(nM) |
|----------|---|---|---|---------|
| 17       | F | H | F | 7.9208  |
| 18       | H | F | F | 8.2218  |
| 19a      | CL| H | H | 7.5229  |
| 20       | H | CL| H | 7.3872  |
| 21       | H | H | CL| 7.3979  |
| 22       | OH| H | H | 7.2716  |
| 23       | H | OH| H | 7.0899  |
| 24       | H | H | OH| 7.2396  |

*represents the test set.

**Table S2.** Summary of QSAR results based on superimposition I.

| CoMFA | CoMSIA |
|-------|--------|
|       | SE     | S    | E    | H    | D    | A    | SE   | SH   | SD   |
| R^2_cv | 0.732 | 0.706 | 0.572 | 0.734 | 0.803 | 0.811 | 0.698 | 0.779 | 0.804 |
| R^2_ncv| 0.973 | 0.942 | 0.957 | 0.966 | 0.941 | 0.981 | 0.966 | 0.969 | 0.983 |
| SEE   | 0.161 | 0.243 | 0.204 | 0.193 | 0.226 | 0.1433| 0.182 | 0.179 | 0.128 |
| F     | 102.781 | 37.408 | 62.613 | 53.144 | 75.203 | 98.93 | 79.564 | 71.033 | 164.513 |
| R^2_pred | 0.7054 | 0.5247 | 0.5758 | 0.086 | 0.7051 | 0.6163 | 0.581 | 0.133 | 0.6792 |
| SEP   | 0.508 | 0.549 | 0.642 | 0.539 | 0.412 | 0.455 | 0.540 | 0.475 | 0.435 |
| N_C   | 6    | 7    | 6    | 8    | 4    | 8    | 6    | 7    | 6    |

| Field contribution |
|---------------------|
| S                   | 0.302 | 0.652 | -    | -    | -    | -    | 0.165 | 0.236 | 0.104 |
| E                   | 0.374 | -    | 0.661 | -    | -    | -    | -    | -    | -    |
| H                   | -    | -    | -    | 0.730 | -    | -    | -    | 0.476 | -    |
| D                   | -    | -    | -    | -    | 0.524 | -    | -    | -    | 0.472 |
| A                   | -    | -    | -    | -    | -    | 0.684 | -    | -    | -    |
| L2r                 | 0.190 | 0.239 | 0.165 | 0.140 | 0.283 | 0.128 | 0.187 | 0.168 | 0.252 |
| MATS4p              | 0.134 | 0.109 | 0.174 | 0.130 | 0.194 | 0.188 | 0.162 | 0.120 | 0.171 |

| CoMSIA              |
|---------------------|
| SA                  | 0.739 | 0.708 | 0.877 | 0.644 | 0.794 | 0.820 | 0.863 | 0.769 | 0.870 |
| EH                  | 0.986 | 0.970 | 0.996 | 0.931 | 0.983 | 0.992 | 0.969 | 0.984 | 0.998 |
| ED                  | 0.126 | 0.176 | 0.068 | 0.250 | 0.129 | 0.096 | 0.167 | 0.132 | 0.053 |
| EA                  | 127.602 | 73.28 | 397.284 | 48.738 | 160.718 | 197.776 | 113.463 | 116.125 | 641.592 |
| HD                  | 0.7798 | 0.4684 | 0.6065 | 0.6258 | 0.6578 | 0.5772 | 0.7179 | 0.4147 | 0.5868 |
| SEP | 0.534 | 0.547 | 0.379 | 0.569 | 0.445 | 0.459 | 0.353 | 0.502 | 0.390 |
|-----|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| Nc  | 8      | 7      | 9      | 5      | 6      | 9      | 5      | 8      | 9      |

### Field contribution

|   | S      | E      | H      | D      | A      | L2p    | MATS4p |   |   |
|---|--------|--------|--------|--------|--------|--------|--------|---|---|
|  | 0.208  | -      | -      | -      | -      | 0.191  | 0.173  |   |   |
|  | 0.129  | 0.070  | 0.346  | 0.236  | 0.195  | 0.191  | 0.195  |   |   |

### CoMSIA

|   | SEA    | SHD    | SHA    | SDA    | EHD    | EHA    | EDA    | HDA    | SEHD  |
|---|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| R²<sub>cv</sub> | 0.718  | 0.810  | 0.802  | 0.848  | 0.858  | 0.753  | 0.890  | 0.846  | 0.867  |
| R²<sub>ncv</sub> | 0.989  | 0.972  | 0.991  | 0.971  | 0.995  | 0.986  | 0.996  | 0.982  | 0.999  |

### Field contribution

|   | S      | E      | H      | D      | A      | L2p    | MATS4p |   |   |
|---|--------|--------|--------|--------|--------|--------|--------|---|---|
|  | 0.134  | 0.078  | 0.145  | 0.074  | -      | -      | -      |   |   |
|  | 0.065  | 0.200  | 0.113  | 0.256  | 0.213  | 0.213  | 0.153  |   |   |

### CoMSIA

|   | SEHA   | SEDA   | SHDA   | EHD    | EHA    | EDA    | HDA    | SEHD   |
|---|--------|--------|--------|--------|--------|--------|--------|--------|
| R²<sub>cv</sub> | 0.783  | 0.881  | 0.853  | 0.873  | 0.873  | 0.875  | 0.875  | 0.875  |
| R²<sub>ncv</sub> | 0.993  | 0.997  | 0.982  | 0.995  | 0.995  | 0.995  | 0.995  | 0.995  |

### Field contribution

|   | S      | E      | H      | D      | A      | L2p    | MATS4p |   |   |
|---|--------|--------|--------|--------|--------|--------|--------|---|---|
|  | 0.106  | 0.059  | 0.062  | -      | -      | 0.177  | 0.223  | 0.214 | 0.210 |
|  | 0.051  | 0.158  | 0.093  | 0.225  | 0.100  | 0.209  | 0.209  | 0.209  | 0.209  |
|                  | CoMFA       | CoMSIA       |
|------------------|-------------|--------------|
|                  | SE  | S  | E  | H  | D  | A  | SE  | SH  | SD  |
| R²_cv            | 0.467| 0.473| 0.445| 0.455| 0.457| 0.433| 0.447| 0.461| 0.457|
| R²_{pred}        | 0.663| 0.710| 0.622| 0.610| 0.630| 0.605| 0.633| 0.620| 0.641|
| SEE              | 0.513| 0.487| 0.543| 0.552| 0.537| 0.555| 0.535| 0.544| 0.529|
| F                | 20.658| 16.349| 78.362| 16.424| 17.874| 16.077| 18.106| 17.150| 18.749|
| SEP              | 0.645| 0.657| 0.658| 0.652| 0.651| 0.665| 0.657| 0.649| 0.651|
| Nc               | 2   | 3   | 2   | 2   | 2   | 2   | 2   | 2    | 2    |

**Field contribution**

|                  | CoMSIA       |
|------------------|--------------|
|                  | SA  | EH  | ED  | EA  | HD  | HA  | DA  | SEH  | SED  |
| R²_cv            | 0.438| 0.439| 0.433| 0.425| 0.445| 0.431| 0.429| 0.440| 0.433|
| R²_{pred}        | 0.615| 0.638| 0.612| 0.601| 0.646| 0.620| 0.607| 0.648| 0.615|
| SEE              | 0.548| 0.532| 0.538| 0.545| 0.526| 0.545| 0.541| 0.524| 0.536|
| F                | 16.785| 18.484| 34.723| 33.153| 19.132| 17.131| 33.934| 19.371| 35.075|
| SEP              | 0.662| 0.662| 0.650| 0.655| 0.658| 0.666| 0.652| 0.661| 0.650|
| Nc               | 2   | 2   | 2   | 1   | 1   | 1   | 2   | 1    | 1    |

**Field contribution**

|                  | CoMSIA       |
|------------------|--------------|
|                  | SEA | SHD | SHA | SDA | EHD | EHA | EDA | HDA | SEHD |
| R²_cv            | 0.425| 0.444| 0.432| 0.429| 0.430| 0.422| 0.427| 0.426| 0.430|
| R²_{pred}        | 0.604| 0.657| 0.631| 0.609| 0.613| 0.603| 0.614| 0.608| 0.615|
| SEE              | 0.543| 0.518| 0.537| 0.540| 0.537| 0.544| 0.536| 0.540| 0.535|
| F                | 33.519| 20.087| 17.964| 34.299| 34.836| 33.357| 34.998| 34.100| 35.167|
| \( R^2_{\text{pred}} \) | 0.6360 | 0.7478 | 0.7320 | 0.6687 | 0.6601 | 0.6421 | 0.6466 | 0.6744 | 0.6610 |
| SEP | 0.655 | 0.659 | 0.666 | 0.652 | 0.652 | 0.656 | 0.653 | 0.654 | 0.652 |
| \( N_C \) | 1 | 2 | 2 | 1 | 1 | 1 | 1 | 1 | 1 |

**Field contribution**

| \( S \) | 0.017 | 0.045 | 0.045 | 0.017 | - | - | - | - | 0.016 |
| \( E \) | 0.080 | - | - | - | 0.074 | 0.078 | 0.075 | - | 0.073 |
| \( H \) | - | 0.082 | 0.086 | - | 0.046 | 0.048 | - | 0.048 | 0.045 |
| \( D \) | - | 0.168 | - | 0.087 | 0.081 | - | 0.082 | 0.084 | 0.080 |
| \( A \) | 0.039 | - | 0.073 | 0.039 | - | 0.038 | 0.037 | 0.038 | - |
| GATS8e | 0.556 | 0.580 | 0.632 | 0.552 | 0.515 | 0.539 | 0.520 | 0.535 | 0.507 |
| Mor29m | 0.307 | 0.126 | 0.163 | 0.304 | 0.284 | 0.297 | 0.287 | 0.295 | 0.279 |

**CoMSIA**

| \( R^2_{\text{cv}} \) | 0.422 | 0.427 | 0.426 | 0.424 | 0.424 |
| \( R^2_{\text{dev}} \) | 0.605 | 0.616 | 0.610 | 0.615 | 0.617 |
| SEE | 0.542 | 0.535 | 0.539 | 0.536 | 0.534 |
| F | 33.700 | 35.336 | 34.442 | 35.093 | 35.411 |
| \( R^2_{\text{pred}} \) | 0.6431 | 0.6485 | 0.6755 | 0.6539 | 0.6553 |
| SEP | 0.656 | 0.653 | 0.654 | 0.655 | 0.655 |
| \( N_C \) | 1 | 1 | 1 | 1 | 1 |

**Field contribution**

| \( S \) | 0.017 | 0.016 | 0.017 | - | - | 0.015 |
| \( E \) | 0.076 | 0.074 | - | 0.072 | 0.071 |
| \( H \) | 0.047 | - | 0.047 | 0.044 | 0.044 |
| \( D \) | - | 0.081 | 0.083 | 0.078 | 0.077 |
| \( A \) | 0.038 | 0.036 | 0.037 | 0.035 | 0.035 |
| GATS8e | 0.530 | 0.511 | 0.526 | 0.497 | 0.489 |
| Mor29m | 0.292 | 0.282 | 0.290 | 0.274 | 0.270 |

**Table S4.** Summary of QSAR results based on superimposition III.
|     | D     | A     | GATS8e | Mor29m | 0.221 | 0.128 | 0.653 | 0.609 | 0.626 | 0.611 |
|-----|-------|-------|--------|--------|-------|-------|-------|-------|-------|-------|
| CoMSIA |       |       |        |        |       |       |       |       |       |       |
|      | SA    | EH    | ED     | EA     | HD    | HA    | DA    | SEH   | SED   |       |
| $R^2_{cv}$ | 0.474 | 0.471 | 0.449 | 0.449 | 0.489 | 0.477 | 0.467 | 0.474 | 0.454 |       |
| $R^2_{acc}$ | 0.633 | 0.671 | 0.693 | 0.666 | 0.681 | 0.651 | 0.678 | 0.678 | 0.700 |       |
| SEE  | 0.535 | 0.506 | 0.490 | 0.510 | 0.499 | 0.522 | 0.501 | 0.501 | 0.484 |       |
| F    | 18.137 | 21.447 | 23.672 | 20.970 | 22.390 | 19.599 | 22.157 | 22.106 | 24.516 |       |
| $R^2_{pred}$ | 0.7541 | 0.7443 | 0.7392 | 0.7264 | 0.7688 | 0.7700 | 0.7681 | 0.7439 | 0.7401 |       |
| SEP  | 0.641 | 0.643 | 0.656 | 0.656 | 0.632 | 0.639 | 0.645 | 0.641 | 0.653 |       |
| $N_C$ | 2     | 2     | 2      | 2      | 2     | 2     | 2     | 2     | 2     |       |

**Field contribution**

|     | S     | E     | H     | D     | A     | GATS8e | Mor29m |
|-----|-------|-------|-------|-------|-------|--------|--------|
| $R^2_{cv}$ | 0.453 | 0.491 | 0.479 | 0.470 | 0.455 | 0.445 | 0.451 | 0.455 |       |
| $R^2_{acc}$ | 0.674 | 0.687 | 0.658 | 0.686 | 0.640 | 0.631 | 0.641 | 0.638 | 0.641 |
| SEE  | 0.504 | 0.494 | 0.517 | 0.495 | 0.518 | 0.524 | 0.517 | 0.519 | 0.517 |
| F    | 21.717 | 23.042 | 20.177 | 22.919 | 39.037 | 37.649 | 39.236 | 38.831 | 39.330 |
| $R^2_{pred}$ | 0.7253 | 0.7697 | 0.7707 | 0.7686 | 0.6777 | 0.6704 | 0.6761 | 0.6910 | 0.6788 |
| SEP  | 0.653 | 0.630 | 0.638 | 0.643 | 0.637 | 0.643 | 0.640 | 0.637 | 0.637 |
| $N_C$ | 2     | 2     | 2      | 2      | 1     | 1      | 1      | 1      | 1      |

**Field contribution**

|     | S     | E     | H     | D     | A     | GATS8e | Mor29m |
|-----|-------|-------|-------|-------|-------|--------|--------|
| $R^2_{cv}$ | 0.445 | 0.451 | 0.455 | 0.455 | 0.455 |       |       |
| $R^2_{acc}$ | 0.633 | 0.643 | 0.640 | 0.649 | 0.649 | 0.650 |       |
| SEE  | 0.523 | 0.516 | 0.518 | 0.511 | 0.511 | 0.510 |       |
| Compound | Observed | Predicted | Residual |
|----------|----------|-----------|----------|
| 1        | 8.6402   | 8.615     | -0.0252  |
| 2        | 5.7794   | 5.781     | 0.0016   |
| 3        | 7.2708   | 7.15      | -0.1208  |
| 4        | 8.1068   | 8.007     | -0.0998  |
| 5        | 7.3990   | 7.406     | 0.007    |
| 6        | 7.4989   | 7.417     | -0.0819  |
| 7        | 7.7696   | 7.476     | -0.2936  |
| 8        | 8.6635   | 8.768     | 0.1045   |
| 9        | 6.6234   | 7.307     | 0.6836   |
| 10       | 8.4318   | 7.83      | -0.6018  |
| 11       | 7.8508   | 7.727     | -0.1238  |
| 12       | 7.3958   | 7.35      | -0.0458  |
| 13       | 8.0862   | 7.752     | -0.3342  |
| 14       | 6.9066   | 7.583     | 0.6764   |
| 15       | 6.3556   | 6.767     | 0.4114   |
| 16       | 6.6517   | 6.67      | 0.0183   |
| 17       | 7.9208   | 7.781     | -0.1398  |
| 18       | 8.2218   | 8.179     | -0.0428  |
| 19       | 7.5229   | 7.278     | -0.2449  |
| 20       | 7.3872   | 7.367     | -0.0202  |
| 21       | 7.3979   | 7.39      | -0.0079  |
| 22       | 7.2716   | 7.285     | 0.0134   |

| Field contribution |
|--------------------|
| S                  | 0.013   | 0.013   | 0.013   | -       | 0.012  |
| E                  | 0.078   | 0.076   | -       | 0.072   | 0.072  |
| H                  | 0.063   | -       | 0.063   | 0.059   | 0.058  |
| D                  | -       | 0.085   | 0.086   | 0.081   | 0.080  |
| A                  | 0.051   | 0.050   | 0.051   | 0.048   | 0.047  |
| GATS8e             | 0.512   | 0.501   | 0.508   | 0.477   | 0.471  |
| Mor29m             | 0.282   | 0.276   | 0.280   | 0.263   | 0.260  |

$R^2_{cv}$ = cross-validated correlation coefficient using the leave-one-out methods; 
$R^2_{ncv}$=Non-cross-validated correlation coefficient; SEE = Standard error of estimate; $F$= Ratio of $R^2_{ncv}$ explained to unexplained = $R^2_{ncv}/(1−R^2_{ncv})$; 
$R^2_{pred}$ = Predicted correlation coefficient for the test set of compounds; SEP= Standard error of prediction; $N_{C}$= Optimal number of principal components; S=steric, E=electrostatic, H=hydrophobic, D=hydrogen bond donor, A= hydrogen bond acceptor.

**Table S5.** Actual and Optimal CoMFA predicted $pK_i$ of training and test sets.
### Table S6. Actual and Optimal CoMSIA predicted pKᵢ of training and test sets.

| Compound | Observed  | Predicted  | Residual |
|----------|-----------|------------|----------|
| 1        | 8.6402    | 8.747      | 0.1068   |
| 2        | 5.7794    | 5.747      | -0.0324  |
| 3        | 7.2708    | 7.116      | -0.1548  |
| 4        | 8.1068    | 7.876      | -0.2308  |
| 5        | 7.3990    | 7.43       | 0.031    |
| 6        | 7.4989    | 7.493      | -0.0059  |
| 7        | 7.7696    | 7.638      | -0.1316  |
| 8        | 8.6635    | 8.98       | 0.3165   |
| 9        | 6.6234    | 7.226      | 0.6026   |
| 10       | 8.4318    | 7.778      | -0.6538  |
| 11       | 7.8508    | 7.574      | -0.2768  |
| 12       | 7.3958    | 7.507      | 0.1112   |
| 13       | 8.0862    | 7.816      | -0.2702  |
| 14       | 6.9066    | 7.48       | 0.5734   |
| 15       | 6.3556    | 6.903      | 0.5474   |
| 16       | 6.6517    | 6.7        | 0.0483   |
| 17       | 7.9208    | 7.822      | -0.0988  |
| 18       | 8.2218    | 8.069      | -0.1528  |
| 19       | 7.5229    | 7.531      | 0.0081   |
| 20       | 7.3872    | 7.561      | 0.1738   |
| 21       | 7.3979    | 7.551      | 0.1531   |
| 22       | 7.2716    | 7.361      | 0.0894   |
| 23       | 7.0899    | 7.142      | 0.0521   |
| 24       | 7.2396    | 7.332      | 0.0924   |
| 25       | 9.3665    | 9.422      | 0.0555   |
| 26       | 8.0000    | 7.929      | -0.071   |
| 27       | 8.8125    | 8.784      | -0.0285  |
| 28       | 7.6925    | 7.64       | -0.0525  |
| 29       | 8.9245    | 8.931      | 0.0065   |
Table S7. Descriptors used in model construction.

| Symbol | Class | Meaning |
|--------|-------|---------|
| L2p    | WHIM  | 2nd component size directional WHIM index/weighted by atomic polarizabilities |
| MATS4p | 2D autocorrelations | Moran autocorrelation-lag 4/weighted by atomic polarizabilities |
| GATS8e | 2D autocorrelations | Geary autocorrelation-lag 8/weighted by atomic masses |
| Mor29m | 3D-MoRSE | 3D-MoRSE-signal 29/weighted by atomic masses |

Figure S1. Graphs of the predicted versus the experimental pKᵢ values of the optimal models. (A) CoMFA model. (B) CoMSIA model.

Figure S2. The structure of the most active molecule used in the contour analyses.
**Figure S3.** The enlargement for compound 2 in the binding site after molecular docking, which is displayed in stick, H-bonds are shown as dotted black lines, and the nonpolar hydrogens were removed for clarity.

**Figure S4.** The enlargement for compound 1 in the binding site after molecular docking, which is displayed in stick, H-bonds are shown as dotted black lines, and the nonpolar hydrogens were removed for clarity.