# Supporting Information

# Identifying the receptor subtype selectivity of retinoid X and retinoic acid receptors via quantum mechanics

Motonori Tsuji,*[,1] Koichi Shudo,[2] and Hiroyuki Kagechika[3]

[1] Institute of Molecular Function, 2-105-14 Takasu, Misato-shi, Saitama 341-0037, Japan

[2] Japan Pharmaceutical Information Center, 2-12-15 Shibuya, Shibuya-ku, Tokyo 150-0002, Japan

[3] Institute of Biomaterials and Bioengineering, Tokyo Medical and Dental University, 2-3-10 Kanda-Surugadai, Chiyoda-ku, Tokyo 101-0062, Japan

E-mail: motonori@molfunction.com

**Contents**

**Table S1.** Experimental $\Delta G^{bind}$ values [1] and calculated interaction energies of naturally occurring and synthetic retinoids.

| Receptor | Ligand | $\Delta G^{bind}$(exp)[a] (kcal/mol) | Docking IE (kcal/mol) | Flexible Docking IE (kcal/mol) |
|---|---|---|---|---|
| hRXRα | ATRA | -8.81 | -81.83 | -96.28 |
| (PDB ID: 1FM9) | 9cRA | -10.76 | -94.41 | -98.00 |
| | Am80 | nb[b] | nh[d] | nh[d] |
| | LGD1069 | -10.59 | -87.55 | -98.13 |
| hRXRβ | ATRA | -9.87 | -89.36 | -102.94 |
| (PDB ID: 1UHL) | 9cRA | -11.44 | -97.08 | -104.40 |
| | Am80 | nb[b] | nh[d] | nh[d] |
| | LGD1069 | -11.18 | -87.77 | -77.02 |
| hRXRγ | ATRA | -9.40 | -78.60 | -83.12 |
| (Model) | 9cRA | -10.81 | -83.76 | -83.96 |
| | Am80 | nb[b] | nh[d] | nh[d] |
| | LGD1069 | -10.98 | -72.02 | -78.99 |
| hRARα | ATRA | -11.52 | -95.94 | -101.01 |
| (PDB ID: 3A9E) | 9cRA | nd[c] | -94.03 | -94.41 |
| | Am80 | -11.12 | -101.63 | -103.84 |
| | LGD1069 | -9.16 | -84.03 | -97.24 |
| hRARβ | ATRA | -11.39 | -107.72 | -120.46 |
| (PDB ID: 4DM8) | 9cRA | nd[c] | -112.03 | -106.37 |
| | Am80 | -10.22 | -122.27 | -121.47 |
| | LGD1069 | -9.92 | -89.47 | -110.30 |
| hRARγ | ATRA | -14.13 | -108.99 | -117.13 |
| (PDB ID: 2LBD) | 9cRA | -12.23 | -103.19 | -113.72 |
| | Am80 | nb[b] | nh[d] | nh[d] |
| | LGD1069 | -9.35 | -60.91 | -87.14 |

[a] Ref. [1], [b] nb: does not bind, [c] nd: no data available, [d] nh: no hit

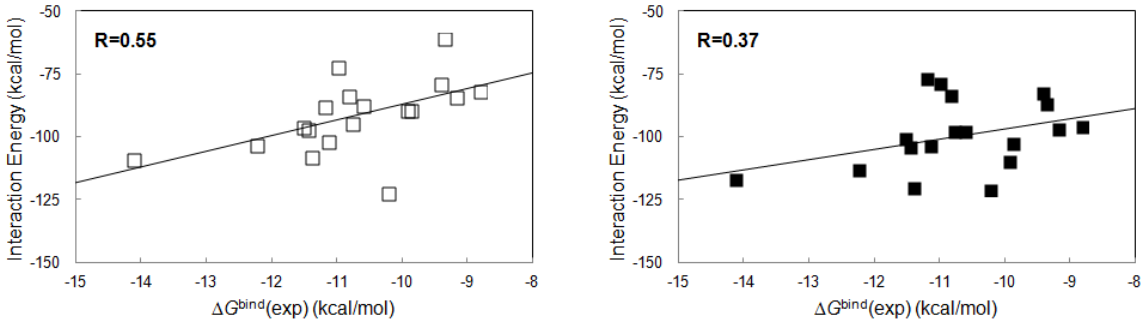


**Figure S1.** Correlations between $\Delta G^{bind}$(exp) [1] and interaction energies of the most stable complex obtained from the docking simulations [2, 3] (left: the biomacromolecule-rigid and ligand-flexible conditions; right: the biomacromolecule- and ligand-flexible conditions) for the binding of the α, β, and γ subtypes of hRXR and hRAR LBDs with ATRA, 9cRA, Am80, and LGD1069.

**Table S2.** Receptor information used in this study [2].

| Receptor | PDB ID | Ligand | Resolution [Å] | State |
|---|---|---|---|---|
| hRXRα | 1FM9 | 9cRA | 2.1 | Heterodimer with hPPARγ LBD in agonist conformation |
| hRXRβ | 1UHL | MEI[a] | 2.9 | Heterodimer with hLXRα LBD in agonist conformation |
| hRXRγ | – | 9cRA | – | Model using hRXRα LBD (1FM9)[b] |
| hRARα | 3A9E | ATRA | 2.75 | Heterodimer with mRXRα LBD in antagonist conformation |
| hRARβ | 4DM8 | 9cRA | 2.3 | Homodimer |
| hRARγ | 2LBD | ATRA | 2.0 | Monomer |

[a] MEI: methoprenic acid, [b] for preparation, see Ref. [2]

## References

1. Umemiya H, Fukasawa H, Ebisawa M, Eyrolles L, Kawachi E, Eisenmann G, Gronemeyer H, Hashimoto Y, Shudo K and Kagechika H (1997) Regulation of retinoidal actions by diazepinylbenzoic acids. Retinoid synergists which activate the RXR-RAR heterodimers. *J Med Chem* **40**, 4222−4234.

2. Tsuji M, Shudo K and Kagechika H (2015) Docking simulations suggest that all-*trans* retinoic acid could bind to retinoid X receptors. *J Comput Aided Mol Des* **29**, 975−988.

3. Tsuji M (2015) Docking Study with HyperChem, revision G1, Institute of Molecular Function, Saitama, Japan.