Discovery of an Orally-Active Nonsteroidal Androgen Receptor Pure Antagonist and the Structure–Activity Relationships of Its Derivatives

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The 3-(4-cyano-3-trifluoromethylphenyl)-5,5-dimethylthiohydantoin derivatives which have carboxy-terminal side chains were synthesized and their agonistic/antagonistic activities against androgen receptor (AR) measured. Among them, compound 13b showed antagonistic activity (IC_{50}=130 nM) with no agonistic activity even at 10000 nM. This compound exhibited significant metabolic stability and oral antiandrogenic activity (ED_{50}=7 mg/kg).

Key words androgen receptor; pure antagonist; prostate cancer

Prostate cancer is the most common cancer amongst men and the second most common malignant cause of male death after lung cancer in the U.S. Since the growth of prostate cancer is dependent on androgen, androgen receptor (AR) antagonists such as flutamide (1), a precursor of its active form hydroxyflutamide (2), and bicalutamide (3) are currently used as hormone therapy (Chart 1). These antiandrogens exhibit good efficacy in many cases and comprise an important part of effective therapeutics. However, a considerable problem with these antiandrogens is that recurrence occurs after a short period of response. They have partial agonistic activities at high concentration in vitro, which may attribute to recurrence. Therefore, the search for new antiandrogenic agents that exhibit no agonistic activities, so-called “AR pure antagonists,” has been conducted.

We previously reported that some steroidal compounds that have a side chain at the position 7α such as compound 4, exhibited AR pure antagonistic activities in reporter gene assay (RGA) (Chart 1). Since the steroidal core structures have intrinsic agonistic activities, the side chains are critical for pure antagonistic activities. Drawing on the analogy between the estrogen receptor (ER), for which the molecular mechanisms of the expression of antagonistic activities have been investigated, and AR, the side chain should inhibit the folding of helix 12 of the ligand binding domain (LBD), which is necessary for agonistic activity. Thus, we considered the introduction of a side chain to an AR affinity ligand to be a useful strategy for the discovery of AR pure antagonists. However, our compounds didn’t show antiandrogenic activity in vivo, probably due to the lack of metabolic stability of the steroidal core structures.

Among a number of nonsteroidal compounds that have been reported to have binding affinities for AR, thiohydantoin derivative RU56187 (5) has a high affinity for AR and oral antiandrogenic activity in vivo (Chart 1). But this compound also showed agonistic activities in RGA. Coupled with our previous results, we speculated that these agonistic activities are caused by the lack of a side chain to inhibit the folding of helix 12. The nitrogen atom on position 1 in thiohydantoin seemed appropriate for the introduction of a side chain and we therefore hypothesized that our strategy could be applied to thiohydantoin to discover an orally active nonsteroidal AR pure antagonist.

In our previous report, terminal-carboxylic acid side chains were introduced to the steroidal core structures because the carboxylic acid was expected to increase the watersolubility and oral absorption of the compounds. Unfortunately, as mentioned above, the compounds did not show in vivo antiandrogenic activity, probably due to the lack of metabolic stability of the steroidal core structure. However, some compounds exhibited AR pure antagonistic activities in RGA, suggesting that the terminal-carboxylic acid side chains are valuable for the discovery of AR pure antagonists. Furthermore, it was found that the length or the structure of the linker part of the side chain significantly affects the pure antagonistic activities. Therefore, we decided to introduce terminal-carboxylic acid side chains with various types of linkers to the thiohydantoin core structure in order to clarify the structure–activity relationships and discover orally active AR pure antagonists.

We here report the synthesis of novel thiohydantoin derivatives and their structure–activity relationships for AR pure antagonistic activities. Moreover, we report that one of the derivatives showed a high metabolic stability in vitro and antiandrogenic activity from oral administration in vivo.

Results and Discussion

The target compounds 13a–h and 18a–d were prepared according to the synthetic sequences outlined in Charts 2—4.
In the preparation of aminonitriles 8a—l by the coupling of corresponding amines 7 with acetone cyanohydrin 6, NEt$_3$ was used when the amine was HCl salt (Chart 2). Isothiocyanate 10, which was derived from 9 and thiophosgene, was coupled with compounds 8a—l in THF in the presence of NEt$_3$ under reflux to give 5-imino-2-thioxoimidazolidines 11a—h and 14a—d. The imino groups and terminal esters of compounds 11a—h were hydrolyzed successively to give methylene linker compounds 13a—h (Chart 3). Compound 14a, in which the protecting group of phenolic OH was the methoxymethyl group, was converted to phenol-terminal thiohydantoin 16a directly by heating in 6 N-HCl and dioxane. Compounds 14b—d, in which the hydroxyl groups were protected by the methyl group, were converted to compounds 15a—c under the same conditions followed by deprotection of the methyl group by BBr$_3$. Alkylation of the hydroxyl groups of 16a—d followed by hydrolysis of the terminal esters gave phenyl-inserted derivatives 18a—d (Chart 4).

The synthesized compounds were evaluated for their in vitro binding affinities and agonist/antagonist activities for AR using the same procedures as reported previously. In the preparation of aminonitriles 8a—l by the coupling of corresponding amines 7 with acetone cyanohydrin 6, NEt$_3$ was used when the amine was HCl salt (Chart 2). Isothiocyanate 10, which was derived from 9 and thiophosgene, was coupled with compounds 8a—l in THF in the presence of NEt$_3$ under reflux to give 5-imino-2-thioxoimidazolidines 11a—h and 14a—d. The imino groups and terminal esters of compounds 11a—h were hydrolyzed successively to give methylene linker compounds 13a—h (Chart 3). Compound 14a, in which the protecting group of phenolic OH was the methoxymethyl group, was converted to phenol-terminal thiohydantoin 16a directly by heating in 6 N-HCl and dioxane. Compounds 14b—d, in which the hydroxyl groups were protected by the methyl group, were converted to compounds 15a—c under the same conditions followed by deprotection of the methyl group by BBr$_3$. Alkylation of the hydroxyl groups of 16a—d followed by hydrolysis of the terminal esters gave phenyl-inserted derivatives 18a—d (Chart 4).

The synthesized compounds were evaluated for their in vitro binding affinities and agonist/antagonist activities for AR using the same procedures as reported previously. The binding affinity for AR was determined by displacement of [${}^3$H]-mibolerone with the test compound utilizing CHO-K1/hAR cells. The agonistic and antagonistic activities of the compounds for AR were determined by RGA using hAR-transfected Hela cells. Agonistic activity was determined by the IC$_{50}$ value, the concentration of a compound that inhibits the transcriptional activity of 0.1 nM of DHT by 50%. To determine agonistic activity, we calculated the value of EC$_5$, the concentration of a compound-treated group in which the transcriptional activity is 5% of the transcriptional activity of 0.1 nM of DHT. The maximum transcriptional activity of each compound indicated as its efficacy (% of 0.1 nM of DHT). A “pure antagonist” was defined as having an EC$_5$ value greater than 10000 nM.

First, we evaluated RU56187 (5) for its binding and transcriptional activities for AR in our assay systems to estimate the validity of the compound as a template (Table 1, Fig. 1). As shown in Fig. 1, it exhibited remarkable agonistic activity at concentration as low as 1 nM. Although it tended to show antagonistic activities at lower concentrations, its own agonistic activities diminished the effect at higher concentrations, thus strongly suggesting that this compound is an appropriate template for the introduction of a side chain to verify our hypothesis.

The agonistic/antagonistic activities of the compounds with a terminal-carboxylic acid side chain are shown in Table 1. The activities of the compounds with a simple alkyl side chain (13a—h) were found to be influenced by the length of the alkyl chain. Compound 13a, with two methylene groups, did not show any agonistic or antagonistic activities, possibly because of an electric repulsion of a carboxyl group in close proximity to the hydrophobic ligand binding pocket in the LBD of AR. Compounds with more than 5 methylene groups in the side chain tended to show partial agonistic activities (13e—h). The difference
in pure antagonistic activities between $13b$ and $13e$ was investigated using the docking model illustrated in Fig. 2. In this model, the side-chain carboxyl group of $13b$ locates at a region in which the hydrophobic helix 12 would be located in the agonistic form, leading to the inhibition of the folding of helix 12. In the case of $13e$, the interaction of the terminal carboxyl group with His874 would lead the side chain in a direction allowing the folding of helix 12.

We also investigated the effects of a side chain with a phenyl ring in the center. Previously, we reported that the side chain with a 4-(3-carboxypropoxy)phenylpropyl group and a 3-(3-carboxypropoxy)phenylbutyl group exhibited pure antagonistic activities when introduced at position 7a of $17\alpha$-methyltestosterone.\(^1\(\) However, compounds $18a$ and $18d$, which have these groups as a side chain, showed relatively high agonistic activities with EC$_{50}$s of 370 nM and 54 nM, respectively. We also investigated the activities of compounds $18b$ and $18c$, in which the substituted position of the terminal carboxypropoxy groups were changed. However, these compounds also exhibited only partial agonistic activities.

The metabolic stability of the two thiohydantoin derived-

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**Table 1. Binding and Agonistic/Antagonistic Activities\(^a\) of Thiohydantoin Derivatives**

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>Binding IC$_{50}$ (nM)</th>
<th>RGA</th>
<th>EC$_{50}$ (nM)</th>
<th>IC$_{50}$ (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RU56187 (5)</td>
<td>Me</td>
<td>15</td>
<td>&lt;1 (135)</td>
<td>ND(^b)</td>
<td></td>
</tr>
<tr>
<td>$13a$</td>
<td>-(CH$_2$)$_n$CO$_2$H</td>
<td>&gt;10000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$13b$</td>
<td>-(CH$_2$)$_3$CO$_2$H</td>
<td>3900</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$13c$</td>
<td>-(CH$_2$)$_4$CO$_2$H</td>
<td>3800</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$13d$</td>
<td>-(CH$_2$)$_5$CO$_2$H</td>
<td>&gt;10000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$13e$</td>
<td>-(CH$_2$)$_6$CO$_2$H</td>
<td>6000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$13f$</td>
<td>-(CH$_2$)$_7$CO$_2$H</td>
<td>460</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$13g$</td>
<td>-(CH$_2$)$_8$CO$_2$H</td>
<td>180</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$13h$</td>
<td>-(CH$_2$)$_9$CO$_2$H</td>
<td>150</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$18a$</td>
<td>-O-(CH$_2$)$_2$COOH</td>
<td>180</td>
<td>370 (28)</td>
<td>160</td>
<td></td>
</tr>
<tr>
<td>$18b$</td>
<td>-O-(CH$_2$)$_3$COOH</td>
<td>59</td>
<td>110 (26)</td>
<td>240</td>
<td></td>
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<tr>
<td>$18c$</td>
<td>-O-(CH$_2$)$_4$COOH</td>
<td>100</td>
<td>11 (33)</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>$18d$</td>
<td>-O-(CH$_2$)$_5$COOH</td>
<td>35</td>
<td>54 (16)</td>
<td>45</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) All data are mean values of duplicate experiments. \(^b\) ND: Not determined.

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Fig. 1. Agonistic and Antagonistic Activities of RU56187 (5) and Compound $13b$ in Reporter Gene Assay with hAR-Transfected Hela Cells

(A) Dose-dependent agonistic activities of compounds without DHT. (B) Dose-dependent antagonistic activities of compounds in the presence of 0.1 nM of DHT. All data are mean values of duplicate experiments.
to affect pure antagonistic activity. Compound 13b, one of the pure antagonists found in this investigation, exhibited substantially high in vitro metabolic stabilities compared to a steroidal compound. In addition, 13b showed obvious antiandrogenic activities with an ED\textsubscript{50} of 7 mg/kg and a level of efficacy similar to castration.

**Experimental**

Column chromatography was carried out on Merck Silica gel 60 (230—400 mesh) if not otherwise specified. Rf was determined using Merck Silica gel 60 F\textsubscript{254} plates. \textsuperscript{1}H-NMR spectra were recorded on JEOL EX-270 or JEOL ECP-400. Mass spectra (MS) were measured by Thermo Electron LCQ (ESI) or Shimadzu GCMS-QP5050A (EI). High resolution mass spectra (HR-MS) were recorded by a Micromass Q-ToF Ultima API mass spectrometer or Applied Biosystems QSTAR XL MS/MS system.

**Typical Procedures for Synthesis of Carbamoylthiohydantoins (13a—h)**

4-[(Cyano dimethylmethyl)amino]butyric Acid Ethyl Ester (8b) The mixture of acetone cyanohydrin (6) (1.0 g, 11.8 mmol) and 4-aminobutyric acid ethyl ester HCl salt (7b) (1.97 g, 11.8 mmol) in NEt\textsubscript{3} (6 ml, 43.0 mmol) was stirred at room temperature for 1 h. Water was added and the mixture was extracted with ether. The organic layer was washed with brine, dried over MgSO\textsubscript{4}, filtered, and concentrated under vacuum. The purification by silica gel column chromatography (MeOH/H\textsubscript{2}O: 1—10) gave compound 8b (765 mg, 81%) as an oil. This compound was used in the next step without purification. Rf was determined using Merck Silica gel 60 F\textsubscript{254} plates. \textsuperscript{1}H-NMR (270 MHz, CDCl\textsubscript{3}) \(\delta\): 1.28 (3H, t, \(J=6.7\) Hz), 3.69—3.75 (2H, m), 4.17 (2H, q, \(J=6.8\) Hz), 7.39 (2H, m), 4.17 (2H, q, \(J=6.7\) Hz), 2.76 (2H, \(J=6.5\) Hz), 4.14 (2H, q, \(J=7.1\) Hz). 4-[(4-Cyano-3-trifluoromethylphenyl)-4-imino-5,5-dimethyl-2-thioximidazolidin-1-yl]butyric Acid Ethyl Ester (11b) To a solution of 4-isothiocyanato-2-trifluoromethylbenzonitrile (1.1 g, 5.36 mmol) and compound 8b (1.1 g, 5.37 mmol) in THF (20 ml) was added NEt\textsubscript{3} (0.2 ml, 4.43 mmol) and the mixture was stirred at reflux for 50 min. After cooling to room temperature, the mixture was concentrated under vacuum and purified by silica gel column chromatography (AcOEt/H\textsubscript{2}O = 1 : 1) to give compound 11b (938 mg, 42%) as an oil. Rf was determined using Merck Silica gel 60 F\textsubscript{254} plates. \textsuperscript{1}H-NMR (270 MHz, CDCl\textsubscript{3}) \(\delta\): 1.29 (3H, t, \(J=7.2\) Hz), 1.59 (6H, s), 2.05—2.21 (2H, m), 2.44 (2H, \(J=6.8\) Hz), 3.69—3.75 (2H, m), 4.17 (2H, q, \(J=7.2\) Hz), 7.44 (1H, s), 7.64—8.03 (3H, m).

4-[(4-Cyano-3-trifluoromethylphenyl)-5,5-dimethyl-4-oxo-2-thioximidazolidin-1-yl]butyric Acid Ethyl Ester (12b) To a solution of compound 12b
(765 mg, 1.8 mmol) in EtOH (8 ml) was added 2×NaOH (8 ml) and the mixture was stirred at room temperature for 1.5 h. After addition of 2×HCl the mixture was extracted with AcOEt. The organic layer was washed with brine, dried over Na2SO4, filtered, and concentrated under vacuum. The purification by silica gel column chromatography (MeOH/CHCl3=1:100) gave compound 13b (445 mg, 64%) as a white solid. mp 161—162°C (AcOEt-hexane); RI 0.13 (AcOEt/Hexane=1:1); 1H NMR (270 MHz, CDCl3) δ: 1.61 (6H, s), 2.14—2.20 (2H, m), 2.54 (2H, t, J=7.4 Hz), 3.75—3.81 (2H, m), 7.77 (1H, dd, J=1.7, 8.1 Hz), 7.89 (1H, d, J=8.1 Hz), 7.95 (1H, d, J=8.1 Hz); MS (ESI) m/z 400 [M+H]+. Anal. Calc'd for C10H12F3N3O3S: 326.1005. Found 326.1001.

Compounds 13a and 13c—h were prepared by a procedure similar to that described for 13b.

3-[4-(Cyano-3-trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl-pentanoic Acid (13a) White solid. mp 180—181°C (AcOEt-hexane); RI 0.10 (AcOEt/Hexane=1:1); 1H NMR (270 MHz, CDCl3) δ: 1.59 (6H, s), 1.71—1.98 (4H, m), 2.42 (2H, t, J=7.1 Hz), 3.71 (2H, t, J=8.1 Hz), 7.76 (1H, dd, J=1.6, 8.3 Hz), 7.89 (1H, d, J=1.7 Hz), 7.95 (1H, d, J=8.1 Hz); MS (ESI) m/z 414 [M+H]+. Anal. Calc'd for C16H17F3N3O3S: 391.1132. Found 391.1129.

3-[4-(Cyano-3-trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl-l-pentanoic Acid (13d) Colorless oil. 1H NMR (270 MHz, CDCl3) δ: 1.40—1.55 (2H, m), 1.58 (6H, s), 1.65—1.94 (4H, m), 2.41 (2H, t, J=7.1 Hz), 3.66—3.72 (2H, m), 7.77 (1H, dd, J=1.7, 8.3 Hz), 7.89 (1H, d, J=1.7 Hz), 7.95 (1H, d, J=8.3 Hz); MS (ESI) m/z 428 [M+H]+. HR-MS Calc'd for C16H17F3N3O3S: 391.1141. Found 391.1139.

10.29.

3-[4-(Cyano-3-trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl-heptanoic Acid (13e) White solid. mp 117—118°C (AcOEt-hexane); RI 0.10 (AcOEt/Hexane=1:1); 1H NMR (270 MHz, CDCl3) δ: 1.59 (6H, s), 1.71 (1H, dd, J=1.6, 8.1 Hz), 7.78 (1H, dd, J=1.6, 8.1 Hz), 7.95 (1H, d, J=8.1 Hz); MS (ESI) m/z 414 [M+H]+. Anal. Calc'd for C18H23F3N3O3S: 442.1406. Found 442.1428.

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added NaH (60% in oil, 6.2 mg, 0.155 mmol) and ethyl 4-bromobutyrate (22.4 μl, 0.155 mmol) at 0 °C under N₂. After stirring at room temperature for 30 min, sat.NH₄Claq. was added and the mixture was extracted with AcOEt. Organic layer was washed with brine, dried over MgSO₄, and concentrated under vacuum. The purification by silica gel column chromatography (AcOEt/hexane=1:4) gave compound 17a (15.6 mg, 21%) as colorless oil. Rf 0.63 (CHCl₃); ¹H-NMR (270 MHz, CDCl₃) δ: 1.26 (3H, t, J = 7.3 Hz), 1.52 (6H, s), 2.08—2.16 (4H, m), 2.51 (2H, t, J = 7.3 Hz), 2.67 (2H, t, J = 7.4 Hz), 3.64—3.70 (2H, m), 3.99 (2H, t, J = 6.1 Hz), 4.15 (2H, q, J = 7.2 Hz), 6.83 (2H, d, J = 8.6 Hz), 7.12 (2H, d, J = 8.6 Hz), 7.76 (1H, dd, J = 1.7, 8.3 Hz), 7.83 (1H, d, J = 1.7 Hz), 7.94 (1H, d, J = 8.3 Hz); MS (EI) m/z: 561 [M⁺].

4-(4-(3-[3-(4-Chloro-3-trifluoromethylphenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl]propyl)phenoxy)butyric Acid (18a) To a solution of compound 17a (10.6 mg, 0.0189 mmol) in MeOH (1 ml) was added 2-NaOH (0.5 ml) and the mixture was stirred at room temperature 15h. The reaction mixture was acidified by 2 N-HCl and extracted with AcOEt. Organic layer was washed with brine, dried over MgSO₄, filtered, and concentrated under vacuum. The purification by preparative TLC (AcOEt/hexane=1:1) gave compound 18a (8.4 mg, 83%) as colorless oil. Rf 0.13 (AcOEt/hexane=1:1); ¹H-NMR (270 MHz, CDCl₃) δ: 1.52 (6H, s), 2.02—2.20 (4H, m), 2.56—2.70 (4H, m), 3.64—3.70 (2H, m), 4.01 (2H, t, J = 6.0 Hz), 6.83 (2H, d, J = 8.4 Hz), 7.12 (2H, d, J = 8.4 Hz), 7.76 (1H, dd, J = 1.7, 8.3 Hz); MS (EI) m/z: 516 [M⁺].

In Vivo Metabolic Stability in Mouse Liver Microsome To a 0.1 mM potassium phosphate buffer (pH 7.4) containing 1 mM NADPH and 0.5 mg/ml mouse liver microsome, a test compound (final conc. 1 μM) was added to start the reaction. After incubation for 0.5, 5, 15, or 30 min at 37 °C, CH₃CN was added to stop the reaction. The concentration of the test compound at each time point was measured by LC/MS/MS (QTRAP, Applied Biosystems). Hepatic intrinsic clearance (CLint) was determined by the pop-toral changes in the concentration of the test compound.

In Vivo Antiandrogenic Activities on Seminal Vesicle (SV) Wet Weights in Mice Immature male ICR mice (7—8 weeks old) were cas-trated on day 0. After 1 d, animals were divided into groups and dosed on day 1 with the following: (1) control vehicle (5% gum arabic, orally); (2) TP (10 μg/body/d, subcutaneously) plus control vehicle; (3) TP plus compound 13b (2, 10, or 50 mg/kg/d in 5% gum arabic, orally). Animals were sacrificed on day 11 and SVs were collected and weighed after formalin fixation. To compare data from different experiments, organ weights were first standardized as mg/100 g of body weight. Reduction ratios were calculated by the following equation:

\[ \text{reduction ratio} = \frac{100 \times (B - A) \times \text{B/C}}{A} \]

where A: SV weights of groups under condition (3) B: SV weights of a group under condition (2) C: SV weights of a group under condition (1)

Molecular Modeling. Docking Model of Compounds 13b and 13e to AR This model was built based on the X-ray crystal structure of human AR in complex with the ligand R1881 (PDB ID: 1ecg).156 3D structures of compounds 13b and 13e were modeled independently using software SYBYL with a Tripos force field.200 Compounds 13b and 13e were manually docked into AR such that (i) the binding mode of the cyanophenyl moiety of compounds 13b and 13e is similar to that of Casodex (PDB ID: 1er5) and (ii) the thiohydantoin ring is modeled so that the side chain attached to the thiohydantoin ring of 13b and 13e is directed to helix 12 of AR. After checking the bumps between the compound and AR, energy minimization of the compound/AR complex was performed using a molecular mechanics method with the Tripos force field on condition that the coordinates of AR are fixed. Conformations obtained for 13b and 13e are local minimum energy conformations.

Docking Model of Compounds 4 and 18a to AR 3D structures of compounds 4 and 18a were modeled independently using software SYBYL with a Tripos force field. Compound 4 was manually docked into AR in a way that (i) the oxygen atom of the carbonyl group attached at position 3 of the steroid interacts with the side chain of Arg738 of AR and (ii) the hydroxy group attached to the thiohydantoin ring of 13b and 13e is directed to the helix 12 of AR. After checking the bumps between the compound and AR, energy minimization of the compound/AR complex was performed using a
molecular mechanics method with the Tripos force field on condition that the coordinates of AR are fixed.

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References
19) “SYBYL 7.3,” Tripos International, St. Louis.