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Design and synthesis of cyclic urea compounds: a pharmacological study for retinoidal activity

Masaaki Kurihara,[a,*] Abu Shara Shamsur Rouf,[a] Hisao Kansui,[a] Hiroyuki Kagechika,[b] Haruhiro Okuda[a] and Naoki Miyata[c]

[a]*Division of Organic Chemistry, National Institute of Health Sciences, Kamiyoga, Setagaya-ku, Tokyo 158-8501, Japan*
[b]*Graduate School of Pharmaceutical Sciences, University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan*
[c]*Faculty of Graduate School of Pharmaceutical Sciences, Nagoya City University, Tanabedori, Mizuho-ku, Nagoya 467-8603, Japan*

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Abstract—Retinoids are natural and synthetic analogues of all-*trans* retinoic acid (ATRA). Cancer and other serious hyperproliferative diseases are attractive therapeutic targets for retinoids. We report here the design and synthesis of novel cyclic urea compounds with retinoidal activity. YR105 exhibited potent differentiation-inducing ability toward human promyelocytic leukemia HL-60 cells at the concentration of 10^{-9} M: its potency was almost equal to that of the native ligand, all-*trans* retinoic acid.

Retinoids, natural and synthetic analogues of all-*trans* retinoic acid (ATRA), have a variety of potent biological activities, such as induction of cell differentiation, proliferation, and apoptosis, as well as developmental changes.[1]

Retinoids also have potential chemotherapeutic and chemopreventive applications in the fields of dermatology and oncology.[2] Retinoic acid has a remarkable remedial effect on acute promyelocytic leukemia (APL).[3] Further, the inhibitory effect of retinoids on IL-6 production suggests their possible usefulness in various IL-6 associated diseases, including psoriasis and rheumatoid arthritis.[4]

It has been shown that the biological effects of retinoids are mediated by the activation of retinoic acid receptors (RARs), which are ligand-dependent gene transcription factors. There are three distinct receptor subtypes (RARα, β, γ), which possess considerable homology in their ligand binding domains.[5]

We report here the design and synthesis of novel cyclic urea compounds, which have retinoidal activity.

In earlier studies, a number of synthetic retinoid analogues were prepared, and a few of them showed potential biological effects several times higher than all natural retinoids (Fig. 1).[6] Some were selected as promising lead compounds for retinoidal activity. All the compounds consisted of two parts: a lipophilic portion fused with a hydrophilic benzoic acid moiety via amide or alkene or keto linkage. The biological activity depended on the linker type as well as the presence or absence of lipophilic moieties. Considering these aspects we selected the lipophilic moieties and the amido or alkene was changed to a urea linker, which may act as a suitable ligand for retinoid receptors. however Ur80,[7]

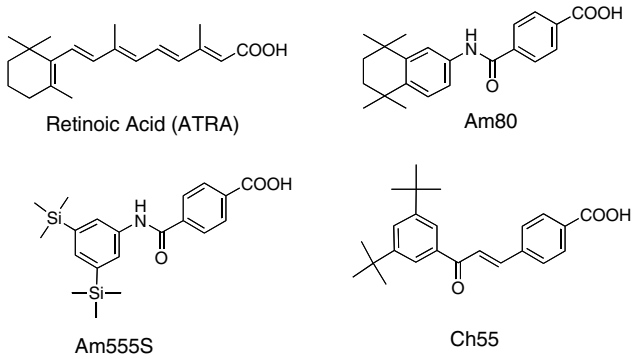

Figure 1. Structures of typical retinoid agonists.

Keywords: Cyclic urea; Retinoid; Cell differentiation; Drug design.
* Corresponding author. Tel.: +81-3-3700-1141; fax: +81-3-3707-6950; e-mail: masaaki@nihs.go.jp

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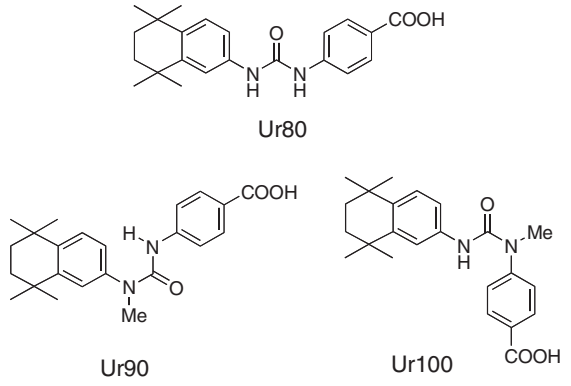
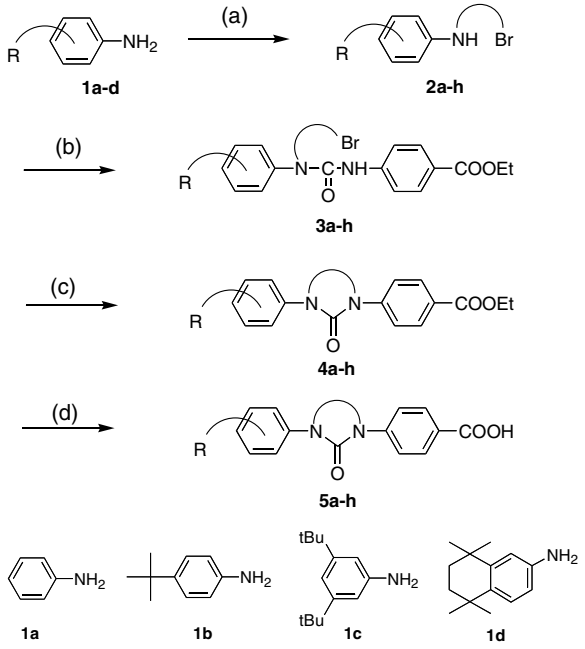


Figure 2. Conformations of methylated Ur80.

which has a urea linker, exhibited low bioactivity. Introduction of substitutes to urea nitrogen would cause flipping of stereochemistry to form Ur90 and Ur100 like Am80[8] (Fig. 2). Because of fix of conformation and lipophilicity, we chose a cyclic urea structure as the linker (Fig. 3).

A very simple method was developed to synthesize all desired cyclic urea derivatives. The synthesis of urea derivatives (**5a**–**h**) was accomplished via the following reaction sequences (Scheme 1). A number of different aromatic amines (**1a**–**d**) were utilized as the starting materials for the preparation of the desired cyclic urea compounds.

Various primary aromatic amines (**1a**–**d**) alkylated with 1,2-dibromoethane or 1,3-dibromopropane in acetonitrile resulted in formation of the respective secondary amines (**2a**–**h**). The synthesized secondary aromatic amines were allowed to react with ethyl 4-isocyanobenzoate in anhydrous benzene to form urea derivatives (**3a**–**h**). The intramolecular cyclization of the urea derivatives was performed utilizing sodium hydride as the base to obtain cyclic urea derivatives (**4a**–**h**). Finally, the ethyl ester of cyclic urea derivatives was converted to free acid form (**5a**–**h**) under basic conditions.



Scheme 1. Reagents and conditions: (a) 1,2-dibromoethane or 1,3-dibromopropane, CH_3CN, 50–70 °C, 72 h, 25–60%; (b) ethyl 4-isocyanatobenzoate, benzene, 60–70 °C, 48 h, 60–80%; (c) NaH, THF, rt, 3 h, 75–97%; (d) 5% NaOH, MeOH–H_2O (7:3), 60 °C, 1 h, 90–96%.

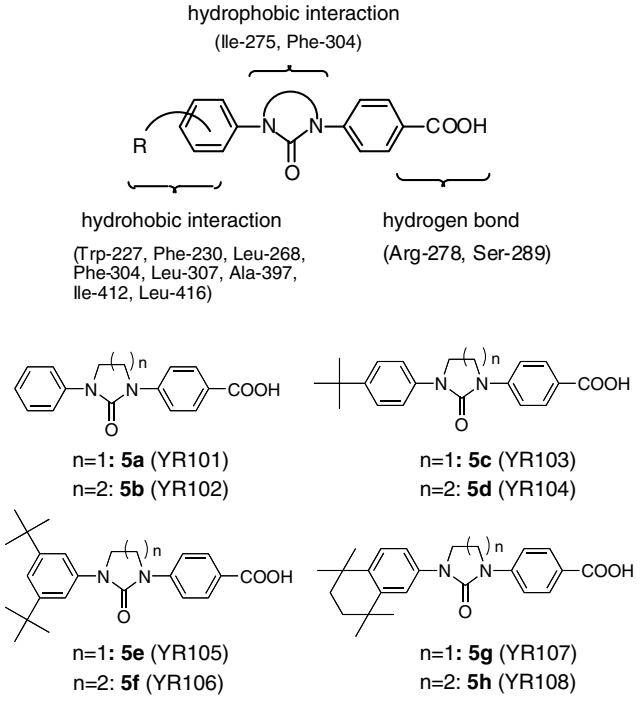


Figure 3. Design of cyclic urea compounds.

The biological activities of compounds **5a**–**h** were evaluated in terms of induction of differentiation of HL-60 cells into mature granulocytes. The results are summarized in Table 1. YR105 (**5e**) exhibited potent differentiation-inducing activity toward HL-60 cells, with an EC_{50} value of 8.3×10^{-9} M. The activity of YR105 was one order weaker than that of retinobenzoic acid Am80, and comparable to that of all-*trans* retinoic acid. YR106

Table 1. HL-60 differentiation-inducing activity of cyclic urea compounds (**5a**–**h**)

Compound	Activity (ED_{50}) (M)
5a (YR101)	Inactive
5b (YR102)	Inactive
5c (YR103)	Inactive
5d (YR104)	Inactive
5e (YR105)	8.3×10^{-9}
5f (YR106)	4.9×10^{-7}
5g (YR107)	1.2×10^{-7}
5h (YR108)	Inactive
Retinoic acid	2.4×10^{-9}
Am80	7.9×10^{-10}
Ur80	$>10^{-6}$

Inactive means there was no activity at 10^{-6} M, and $>10^{-6}$ M means there was slight activity at 10^{-6} M.

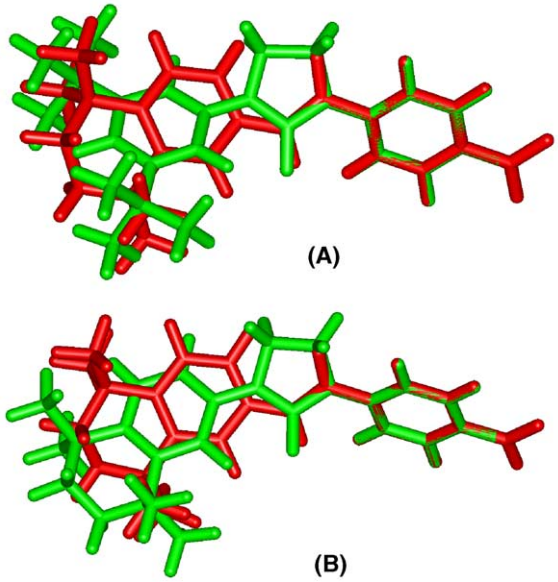


Figure 4. (A) Superimposition of energy-minimized conformations of YR105 (green) and Am80 (red). (B) Superimposition of energy-minimized conformations of YR107 (green) and Am80 (red).

(**5f**), YR107 (**5g**) decreased the activity by two orders of magnitude, compared with YR105.

Figure 4 shows superimposition of the energy-minimized structures of YR105 (**5e**) and YR107 (**5g**) on the energy-minimized structure Am80. YR105 is better overlapped with Am80 than YR107.

A docking model of YR105 (**5e**) bound to RARγ (1EXA) was constructed by molecular dynamics (MD) simulation at high temperature (1000 K) and molecular mechanics (MM) energy minimization. AMBER* was used as force field. Calculations were performed by *MacroModel* (ver. 6.5 and 8.0).[9] YR105 was well fitted to the cavity of the ligand binding domain (LBD) of RARγ, as shown in Figure 5. The bulky alkylated phenyl moiety fits well to the hydrophobic region of the LBD (Trp-227, Phe-230, Leu-268, Phe-304, Leu-307, Ala-397, Ile-412, Leu-416). The carboxylate group of the ligand interacted with Arg-278, Ser-289 by hydrogen bonds.

In conclusion, we have discovered a new class of cyclic urea compounds that exhibit retinoidal activity.

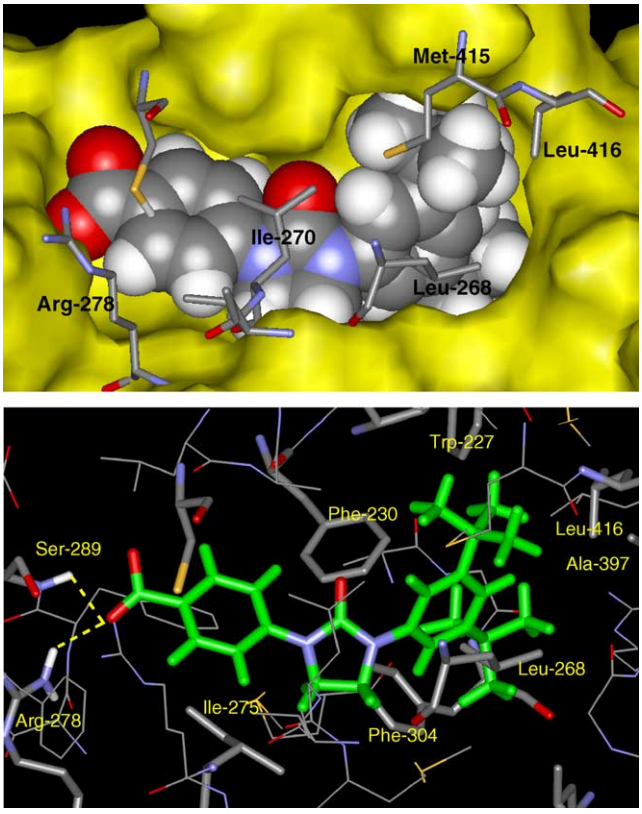


Figure 5. Stable docking model of **5e** (YR105) in the RARγ simulated from the crystal structure of RAR-BMS270394 complex (1EXA).

Acknowledgements

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