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DESIGN AND SYNTHESIS OF NOVEL RETINOID SYNERGISTS HAVING A DIBENZODIAZEPINE SKELETON

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Abstract – Based on the structures of potent RXR agonists **2** and **3**, novel dibenzodiazepine derivatives **4** – **6**, containing two diphenylamine substructures, were designed as RXR modulator candidates and synthesized by utilizing Pd-catalyzed and Cu-promoted diphenylamine-generating reactions as key reactions. These compounds showed retinoid-synergistic activity, enhancing the HL-60 cell differentiation-inducing ability of the RAR agonist Am80.

Retinoids have a broad spectrum of biological activities related to cellular differentiation and proliferation, and are essential for normal embryonic development in vertebrates.[1] Their biological responses are mediated by binding to and activation of retinoic acid receptors (RARs),[2] which act in the form of heterodimers with another class of retinoid nuclear receptors, retinoid X receptors (RXRs).[3] All-*trans* retinoic acid (ATRA) binds to RARs, and its 9-*cis* isomer (9-cisRA) binds to both RARs and RXRs (Figure 1).[4] Various synthetic retinoids, such as Am80 (**1**), bind only to RARs with an affinity that correlates well with most retinoidal activities.[5] RXRs are transcriptionally silent partners of RARs, and RAR-RXR heterodimers activated by RAR ligands regulate the expression of specific genes.[3] We have developed several RXR-specific agonists and reported their retinoid synergistic activities.[6] For example, RXR agonists, such as HX600 (**2**)[7] and DA023 (**3**),[8] themselves exhibited no retinoidal activity, but strongly enhanced the potency of ATRA or Am80 (**1**). Since RXRs form heterodimers with various nuclear receptors, such as vitamin D_3 receptor, thyroid hormone receptors and peroxisome proliferator-activated receptors, RXR ligands may modulate the behaviors of the partner receptors, as well

as retinoidal activities.[3] Therefore, we have focused on the development of RXR agonists and designed novel dibenzodiazepine-based RXR modulator candidates **4** – **6** by combining the structures of **2** and **3** (Figure 1). In this paper, we describe the synthesis and biological activities of the novel dibenzodiazepine derivatives **4** – **6**.

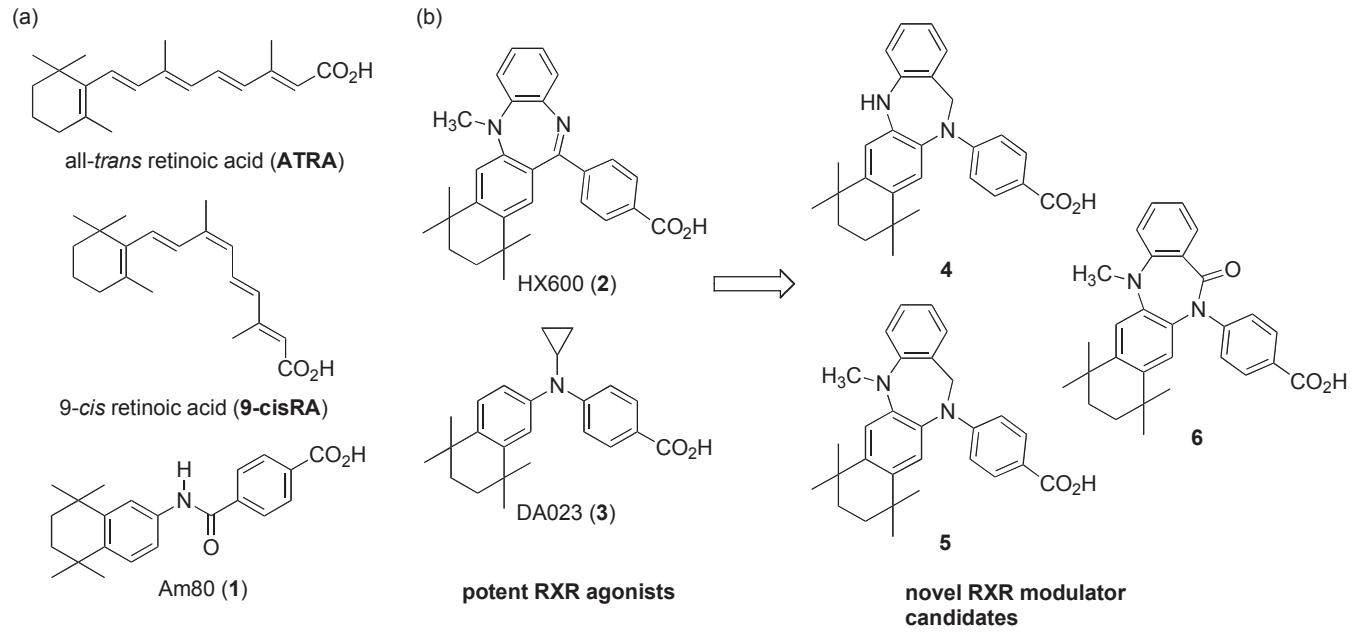
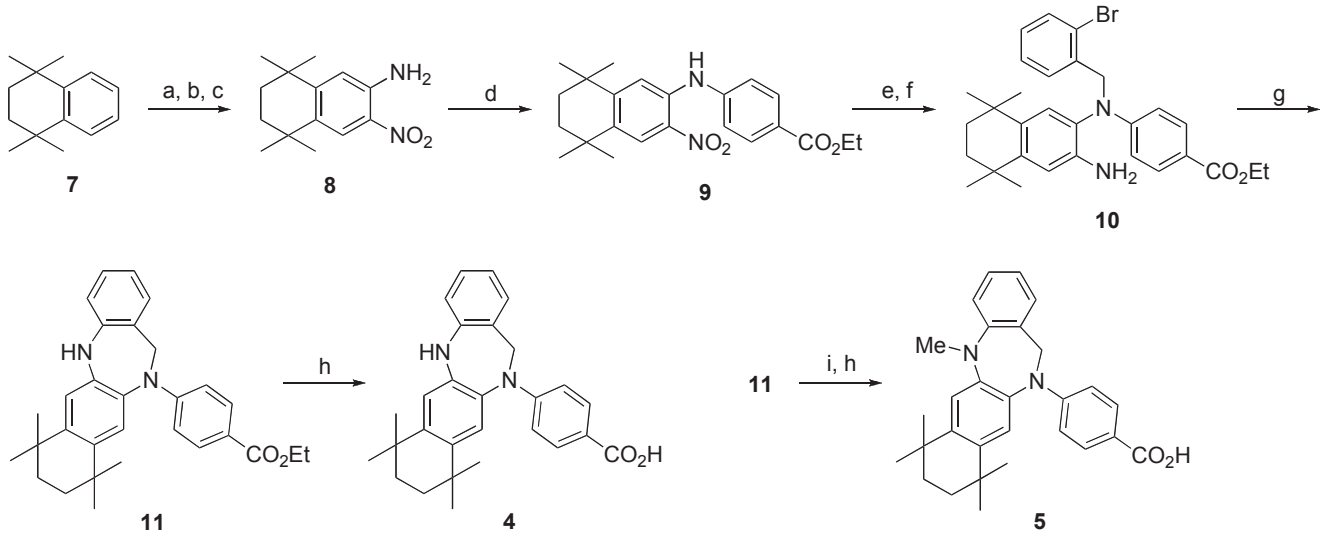


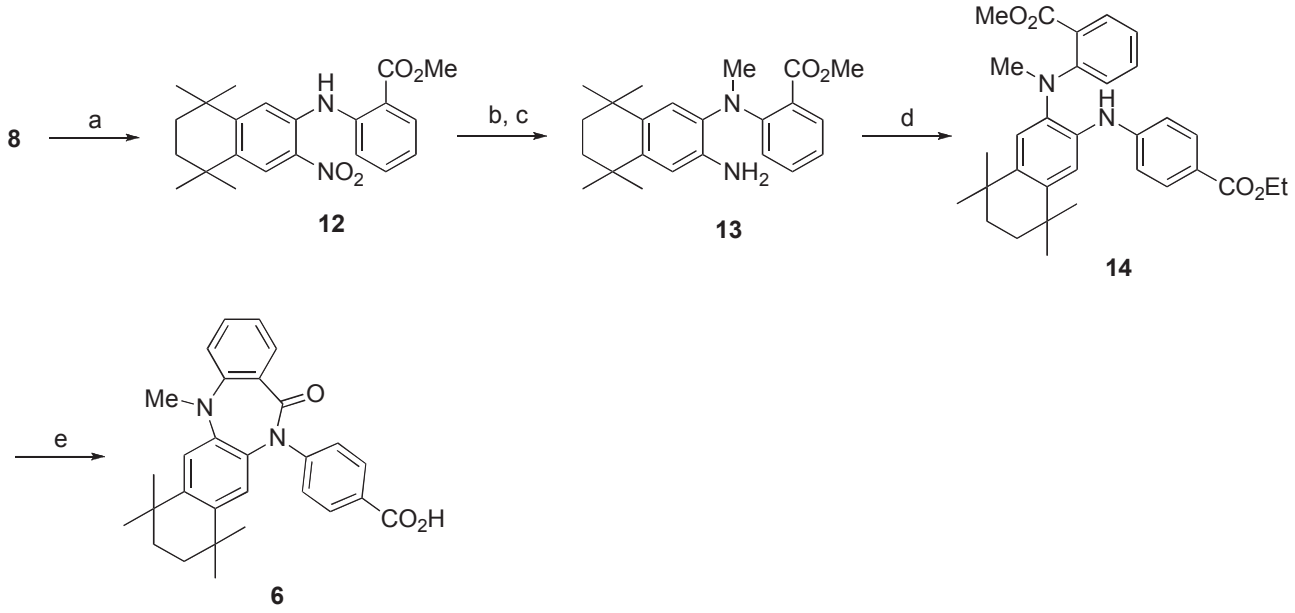
Figure 1. (a) Structures of endogenous and synthetic agonists for RARs and RXRs; (b) Design of novel dibenzodiazepine-based RXR agonists

The synthesis of compounds **4** and **5** is summarized in Scheme 1. Compound **8**, which was prepared from 1,2,3,4-tetrahydro-1,1,4,4-tetramethylnaphthalene (**7**) according to the literature procedure,[9] was reacted with ethyl 4-iodobenzoate in the presence of Pd catalyst to afford diphenylamine **9**.[10] An *o*-bromobenzyl group was introduced at the nitrogen atom of the diphenylamine skeleton of **9** with the corresponding benzyl bromide, followed by reduction of the nitro group with Zn in AcOH to afford compound **10**. Construction of a dibenzodiazepine skeleton was accomplished by means of an intramolecular Pd-catalyzed amination between the aniline and bromobenzene moieties of **10** to afford compound **11** in quantitative yield.[10] Hydrolysis of the ethyl ester group with aqueous 20% KOH solution afforded compound **4**. *N*-Methylation by using NaH as a base and MeI, followed by hydrolysis of the ester group, afforded *N*-methyl dibenzodiazepine derivative **5** in quantitative yield. Dibenzodiazepinone **6** was synthesized as shown in Scheme 2. Compound **8** was reacted with methyl 2-chlorobenzoate in the presence of excess amount of CuI (Ullmann coupling) to afford diphenylamine derivative **12** in 65% yield.[11] *N*-Methylation by using NaH as a base and MeI, followed by catalytic hydrogenation of the nitro group with Pd/C afforded aniline derivative **13**. Compound **14** containing two diphenylamine substructures was prepared from **13** by means of Buchwald-Hartwig amination with ethyl 4-iodobenzoate

using Pd-catalyst.[10] Lactamization reaction between the diphenylamine and methyl ester moieties of **14** was performed in the presence of excess NaH, followed by hydrolysis of the ethyl ester group with NaOH, which was prepared in situ from excess NaH and H_2O added to the reaction mixture, afforded compound **6**.



Scheme 1. Synthesis of dibenzodiazepine derivatives **4** and **5**; Reagents and conditions: (a) c.H_2SO_4, HNO_3, AcOH, rt, 44%; (b) Pd/C, H_2, EtOH, rt, 94%; (c) c.H_2SO_4, HNO_3, TFA, rt, 38%; (d) $Pd_2(dba)_3$, *rac*-BINAP, NaO^{t}Bu, ethyl 4-iodobenzoate, toluene, reflux, 34%; (e) NaH, *o*-bromobenzyl bromide, DMF, rt, 98%; (f) Zn, AcOH, rt, 43%; (g) $Pd_2(dba)_3$, *rac*-BINAP, NaO^{t}Bu, toluene, reflux, 100%; (h) 20% KOH aq., EtOH, rt, quant; (i) NaH, MeI, DMF, rt, quant.



Scheme 2. Synthesis of compound **6**; Reagents and conditions: (a) K_2CO_3, CuI, methyl 2-chlorobenzoate, xylene, reflux, 65%; (b) NaH, CH_3I, DMF, rt; (c) Pd/C, H_2, rt, 2 steps: 75%; (d) $Pd_2(dba)_3$, *rac*-BINAP, NaO^{t}Bu, ethyl 4-iodobenzoate, toluene, reflux, 21%; (e) NaH (excess), xylene, reflux, then H_2O, rt, 2steps: 56%.

The biological activities of the synthesized compounds were evaluated in terms of the activity to induce differentiation of HL-60 cells into mature granulocytes in the presence or absence of a synthetic retinoid, Am80 (**1**).[12] The differentiated cells were identified by nitro blue tetrazolium (NBT) reduction assay.[12] None of the test compounds induced cell differentiation of HL-60 alone (data not shown), while all of them showed moderate synergistic retinoid activity with Am80 (Figure 2). Their potency is weaker than that of **2**. Compound **5**, bearing a *N*-methyl group on the diazepine ring, showed more potent synergistic activity than compound **4** without the *N*-methyl group. Introduction of a carbonyl group into the diazepine skeleton led to a decrease of the activity; i.e. the synergistic activity of compound **6** was weaker than that of **5**. These results suggest that polar functional groups on the diazepine skeleton are unfavorable for the expression of retinoid synergistic activity. Further syntheses and structure-activity relationship studies, particularly for compounds with an oxygen and a sulfur atom instead of the *N*-methyl group of compound **5**, are in progress.

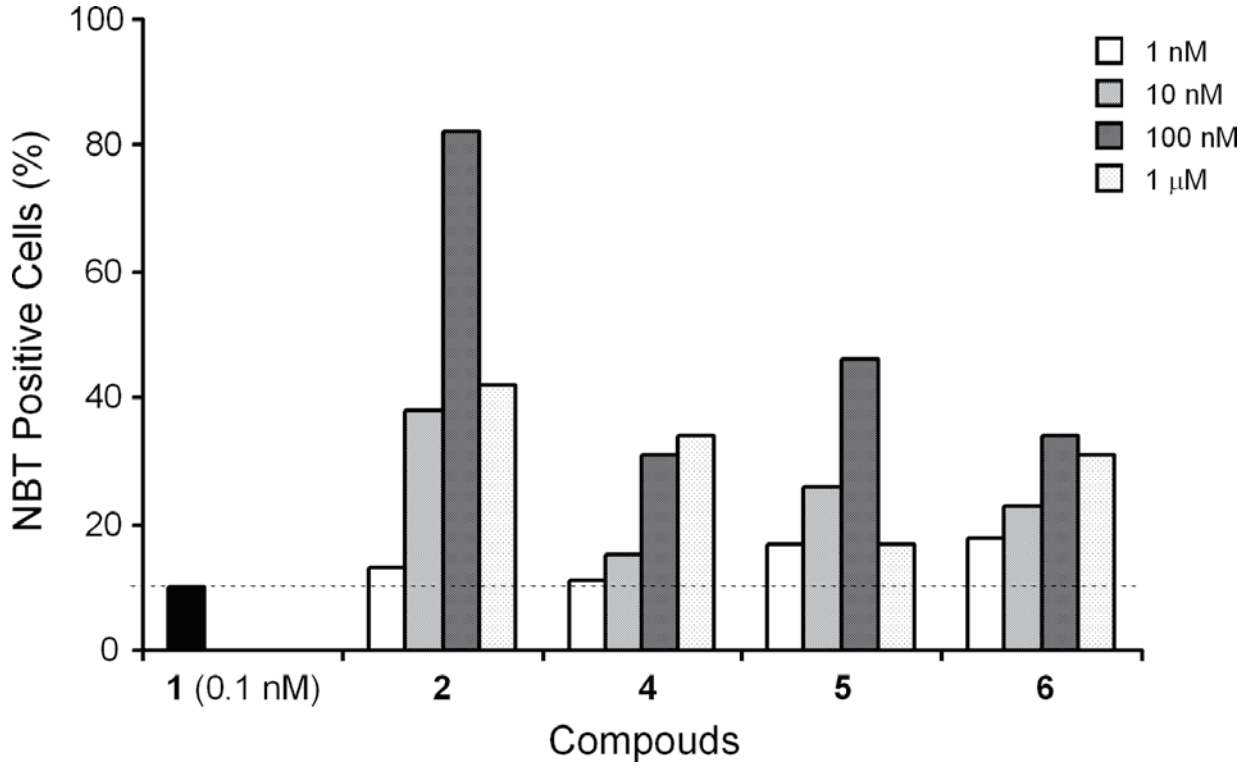


Figure 2. Synergistic effects of dibenzodiazepine derivatives **4** – **6** on HL-60 cell differentiation induced by 0.1 nM Am80 (**1**)

In conclusion, newly designed benzodiazepine derivatives **4** – **6** were efficiently synthesized by utilizing Pd-catalyzed and Cu-promoted diphenylamine-generating reactions as key reactions. Compounds **4** – **6** acted as retinoid synergists, and enhanced the cell differentiation induced by 0.1 nM Am80 (**1**). Although the potency of these compounds is not great, this efficient synthetic method for novel dibenzodiazepine

structure bearing two diphenylamine substructures should be applicable elsewhere in the medicinal-chemical study of retinoids and other nuclear receptor ligands.

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