Pergamon

Bioorganic & Medicinal Chemistry Letters 10 (2000) 623–625

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Syntheses and Evaluation of Naphthalenyl- and Chromenyl-pyrrolyl-benzoic Acids as Potent and Selective Retinoic Acid Receptor α Agonists

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Received 16 December 1999; accepted 20 January 2000

Abstract—Synthesis and structure–activity relationships (SAR) of RARα-selective agonists are discussed. 4-[5-(5,8-Dimethyl-*2H*-3-chromenyl)-*1H*-2-pyrrolyl]benzoic acid (**12a**), which possesses a flat structural moiety and an oxygen atom at the hydrophobic part, showed highly selective transactivation activity at the RARα receptor. © 2000 Elsevier Science Ltd. All rights reserved.

Retinoids, natural and synthetic analogues of all-*trans* retinoic acid (ATRA), have a variety of potent biological activities, including induction of cellular proliferation, differentiation and death, as well as developmental changes.[1] There are three distinct receptor subtypes (RARα, β and γ), which possess considerable homology in their ligand-binding domains. RARs elicit their gene transcriptional activity in the form of heterodimers with retinoid X receptors (RXRs).[2] We have focused our attention on RARα agonists, because selective RARα agonists seem to be promising compounds for the treatment of dermatological diseases and immunological disorders, as described in the preceding paper.[3]

In the course of our research directed towards RAR agonists and antagonists,[4] we have introduced various novel moieties into the hydrophobic part of retinoids. We found that a naphthalenyl-triene derivative (**1**; ER-32906[5]) showed more selective binding affinity and transactivation activity for RARα than a 1,2,3,4-tetrahydro-1,1,4,4-tetramethylnaphthalenyl-triene derivative (**2**; Ro 13-6307[6]), which has a bulky moiety at the hydrophobic part (Chart 1, Table 1). Based on these results, we planned to introduce a flat moiety, such as naphthalene or benzopyran, into the hydrophobic part of ligands, with a 2,5-disubstituted pyrrole as the linker part. Such novel retinoids might be more selective for RARα than compound **3** (ER-34617[4d]), which has been reported as an RARα-selective agonist (Chart 1). Here, we discuss the syntheses and SAR of retinoids which possesses a flat moiety, such as naphthalene and benzopyran, at the hydrophobic part.

Chemistry

Naphthalenyl and benzopyranyl-pyrrolyl derivatives (**11** and **12**) were synthesized by the method of Scheme 1. The carbaldehydes (**4** and **5**), which were prepared by the reported method,[4b] were treated with vinyl Grignard reagent and oxidized with manganese(IV) oxide (activated) to afford enone derivatives (**6** and **7**). The enone derivatives (**6** and **7**) were coupled with methyl 4-formylbenzoate (**8**) to give the diketones (**9** and **10**). These derivatives (**9** and **10**) were treated with ammonium acetate to afford the corresponding pyrrole derivatives, which were hydrolyzed to the flat moiety-pyrrole-benzoic acid derivatives (**11** and **12**).

Results and Discussion

The subtype-selective competitive binding and transactivation data are summarized in Table 1. The 5,8-dimethylnaphthalene derivative **11a** did not show affinity for RARβ or RARγ, whereas it has moderate binding affinity for RARα. This compound (**11a**) is 3-fold less potent at RARα than ATRA, but was 250 and 2000-fold less potent at RARβ and RARγ, respectively. The mono 8-methyl derivative (**11b**) is less potent than the

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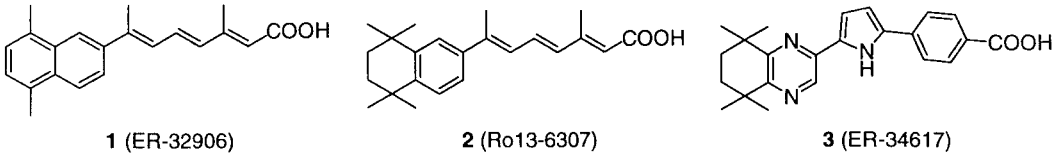
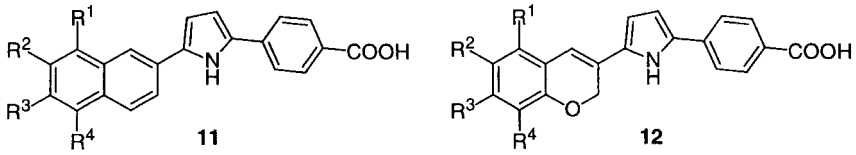
PII: S0960-894X(00)00067-6



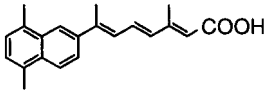
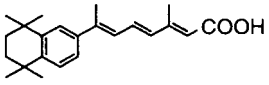
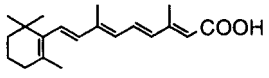
1 (ER-32906) **2** (Ro13-6307) **3** (ER-34617)

Chart 1.

Table 1. Competitive binding and transactivation data for retinoids



11 **12**

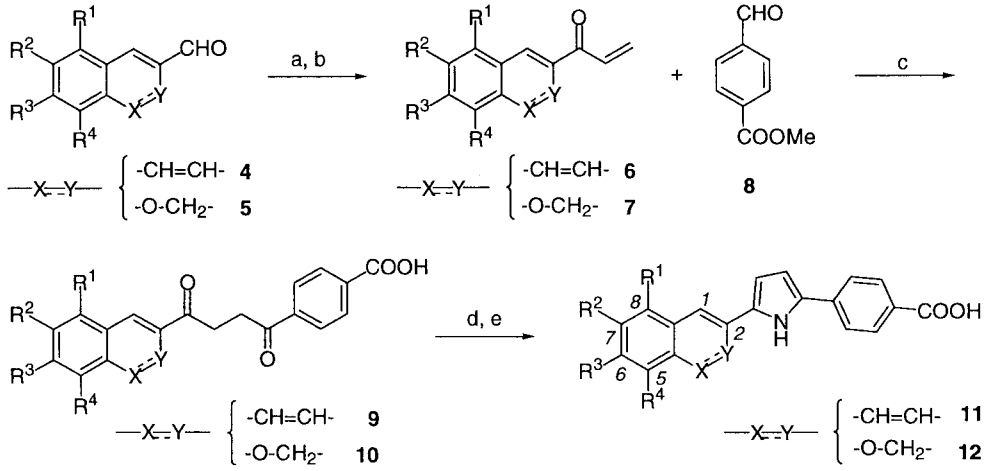
					Binding affinity[a]			Subtype-specific transactivation[e]		
					Relative IC_{50}[b]			Relative EC_{30}[f]		
Compound	R^1	R^2	R^3	R^4	RARα	RARβ	RARγ	RARα	RARβ	RARγ
11a	Me	H	H	Me	24	—[c]	—[c]	2.8	250	2200
11b	Me	H	H	H	15	—[c]	—[c]	49	—[g]	—[g]
11c	H	Me	H	Me	—[c]	—[c]	—[c]	90	—[g]	—[g]
11d	Me	Me	Me	Me	—[c]	—[c]	—[c]	—[g]	—[g]	—[g]
11e	Ph	H	H	H	1.4	—[c]	—[c]	—[g]	880	—[g]
11f	*i*-Pr	H	H	H	<1.0	—[c]	910	1.1	78	88
12a	Me	H	H	Me	9.7	—[c]	—[c]	1.8	240	3600
12b	Me	H	H	H	50	—[c]	—[c]	4.5	1030	5250
1					2.7	49	227	20	11	660
2					0.49	0.34	0.67	0.27	0.20	0.24
ATRA[h]					1.0 0.89 nM[d]	1.0 0.94 nM[d]	1.0 0.62 nM[d]	1.0 1.10 nM[h]	1.0 0.69 nM[h]	1.0 0.18 nM[h]

[a]Specific binding affinity was defined as the total binding minus the nonspecific binding, and the 50% inhibitory dose (IC_{50}) values were obtained from logarithmic plots. In some cases, Scatchard plot analysis was performed. The selectivity of test compounds for each receptor is indicated as relative IC_{50}, where the IC_{50} value for each receptor was divided by that of the natural ligand (ATRA).
[b]IC_{50}/ATRA IC_{50}.
[c]—: not detectable (relative IC_{50} >1000).
[d]ATRA IC_{50}.
[e]EC_{30} values were determined from full dose–response curves ranging from 0.1 nM to 3.0 μM. Retinoid activity is expressed in terms of relative EC_{30}, which is the concentration of retinoid required to produce 30% of the maximal observed response, normalized relative to that of ATRA.
[f]EC_{30}/ATRA EC_{30}.
[g]—: not detectable (relative EC_{30} >10,000).
[h]ATRA EC_{30}.

5,8-dimethylnaphthalene derivative (**11a**) in transactivation activity for RARα. The 5,7-dimethyl naphthalene derivative (**11c**) did not bind to any of the RARs, and showed 90-fold less RARα-agonistic activity than ATRA. The 5,6,7,8-tetramethylnaphthalene derivative (**11d**) had no affinity or transactivation potency for RARs.

These results suggest that methyl group at positions 5 and 8 specifically enhance RARα transactivation, while those at positions 6 and 7 are unfavorable. Although the 8-phenylnaphthalene derivative (**11e**) showed RARα binding affinity comparable to that of ATRA, it did not bind to any other receptor, or activate RARs. The 8-isopropylnaphthalene derivative (**11f**) possessed stronger binding affinity than ATRA at RARα, and did not show selectivity for RARα transactivation.

We introduced an oxygen atom into the hydrophobic part of the retinoid structure to obtain more polar retinoids which might show improved pharmacokinetic characteristics. The benzopyran derivatives (**12**), which



Scheme 1. Reagents and conditions: (a) vinylmagnesium bromide, THF, rt, 1–2 h; (b) MnO_2, CH_2Cl_2, rt, 12 h; 13–53% (for a and b); (c) 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride, CH_3CO_2Na, EtOH, reflux, 1–2 h; 15–82%; (d) $CH_3CO_2NH_4$, MeOH, reflux, 3–5 h; 52–95%; (e–i) NaOH aq. EtOH, reflux, 1 h; (e-ii) dil. HCl; 68–95%.

have an oxygen-containing flat structural moiety, both showed significant selectivity in transactivation activity for RARα, through **12b** is less potent than the dimethyl benzopyranyl derivative (**12a**).

HL-60 differentiation activity was measured for **11a–f** and **12a,b**, using CD11b as a marker of differentiation. Only the 8-isopropyl-naphthalenyl-pyrrole derivative (**11f**) showed moderate potency (100 nM; ED_{30}); the other compounds had no detectable activity. We also studied transactivation activity for RXRα, but these compounds (**11a–f** and **12a,b**) did not show transactivation activity (data not shown).

In conclusion, a flat structural moiety, such as naphthalene and benzopyran, in the hydrophobic part of retinoids seems to be essential for selective RARα transactivation activity. Methyl substituents at positions 5 and 8 are important for RARα selectivity in the naphthalenyl-pyrrole derivatives (**11**) and the benzopyranyl-pyrrole derivatives (**12**). Furthermore, one of the naphthalenyl-pyrrole derivatives (**11a**; ER-35368) and the benzopyranyl-pyrrole derivatives (**12a**; ER-41666) possess significant selectivity for the RARα receptor. These selective RARα agonists are potential therapeutic agents for diseases where RARα is pathogenically deactivated. 4-[5-(5,8-Dimethyl-*2H*-3-chromenyl)-*1H*-2-pyrrolyl]benzoic acid (**12a**) is a particularly potent and effective RARα agonist, and could be a lead compound for development of clinically useful RARα agonists.

References and Notes

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5. Compound **1** (ER-32906) was synthesized by employing usual retinoid chemistry as reported for the synthesis of RXR agonists[6] from **4a** (overall yield 33%).
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