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Syntheses and Evaluation of Quinoline Derivatives as Novel Retinoic Acid Receptor α Antagonists

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Abstract—In the course of studies on novel retinoids, we have designed and synthesized a series of quinoline derivatives. One of them, 4-[5-[8-(1-methylethyl)-4-phenyl-2-quinolinyl]-1*H*-2-pyrrolyl]benzoic acid (**12f**) shows potent RARα-selective antagonistic activity. © 2001 Published by Elsevier Science Ltd.

Introduction

Retinoic acid receptors (RARs) are a group of nuclear receptors belonging to the steroid receptor superfamily. There are three distinct receptor subtypes (RARα, β, and γ), which possess considerable homology in their ligand binding domains.[1] All-*trans* retinoic acid (ATRA) and synthetic analogues of ATRA (retinoids) have diverse biological activities, including induction of cellular proliferation, differentiation and death, as well as developmental changes, through activation of gene transcription mediated by RARs.[2]

Although retinoids are thought to have great therapeutic potential, their clinical application is so far limited[3] because of the wide range of toxic effects of retinoids.[4] The diverse actions of retinoids, both desirable and undesirable, reflect the existence of multiple retinoid receptor subtypes. Therefore, subtype-selective retinoids might have potential therapeutical value. In particular, RARα-selective antagonists might be effective in the treatment of airway diseases,[5] and they would also be useful tools to elucidate the mechanisms of retinoidal action. Some RARα antagonists have been reported,[6] but more potent compounds would be desirable.

In our previous reports concerning a series of novel retinoids,[7] we described that **1** (ER-27191), which has a 3-pyridylmethyl group as a bulky substituent, possesses potent RAR pan-antagonistic activity.[7a] Recently, we reported that **2** (ER-41666), which has a benzopyran skeleton as a flat structural moiety in the hydrophobic part and a 2,5-disubstituted pyrrole moiety in the linking part, exhibits moderate RARα-selective agonistic activity[7d] (Fig. 1). In the course of our attempts to introduce a polar heteroaromatic ring into the hydrophobic part in order to reduce toxicity,[8] we found that 8-isopropylquinoline derivatives show RARα selectivity, and the introduction of a bulky group at the 4-position, thereby combining the structural features of an RAR antagonist (**1**) and an RARα-selective agonist (**2**), generated potent RARα-selective antagonistic activity. In this paper, we discuss the syntheses and structure–activity relationship (SAR) of novel quinolyl-pyrrolyl-benzoic acid derivatives.

Chemistry

Aldehydes **5a**–**f** were prepared according to Scheme 1. 2-Isopropylaniline (**3**) was cyclized with crotonaldehyde under acidic conditions, followed by oxidation with SeO_2 to afford **5a**. Treatment of **3** with dimethyl acetylenedicarboxylate, followed by cyclization gave the quinolone (**6**). 4-Substituted aldehydes **5b**–**f** were synthesized from **6**.

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Chlorination of **6** with $POCl_3$ and PCl_5 afforded the ester (**8b**). The ester was reduced with DIBAL-H and oxidized under Swern conditions to afford the aldehyde (**5b**). Methylation of **6** with MeI in the presence of K_2CO_3, followed by reduction and oxidation gave the aldehyde (**5c**). The quinolone (**6**) was treated with Tf_2O in the presence of 2,6-lutidine and DMAP to afford the triflate (**7**). This was converted to alkyl- or aryl-substituted esters (**8d–f**) by palladium-catalyzed cross-coupling with organozinc reagents or arylboronic acid.[9] Transformation of the esters (**8d–f**) into the aldehydes (**5d–f**) was accomplished by reduction followed by oxidation.

Compounds **12a–f** were synthesized from the aldehydes (**5a–f**) as shown in Schemes 2 and 3. Aldehyde **5a** was treated with vinyl Grignard reagent followed by MnO_2 oxidation to gave the enone derivative (**9**), which was condensed with methyl 4-formylbenzoate in the presence of 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride and triethylamine to afford the 1,4-diketone (**10a**).[10] Aldehydes **5b–f** were condensed with methyl 4-acryloylbenzoate[7c] to afford the 1,4-diketones (**10b–f**). Treatment of the diketones (**10a–f**) with ammonium acetate gave the 2,5-disubstituted pyrrole derivatives (**11a–f**), which were hydrolyzed with NaOH to give the acids (**12a–f**).

Results and Discussion

The quinoline derivatives (**12a–f**) synthesized above were evaluated in vitro for binding affinity towards the

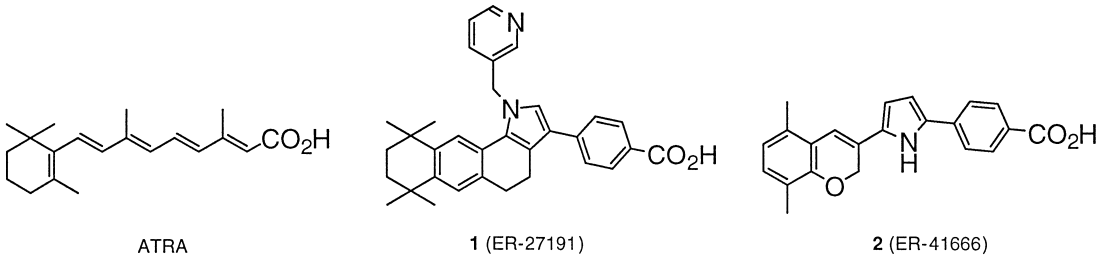
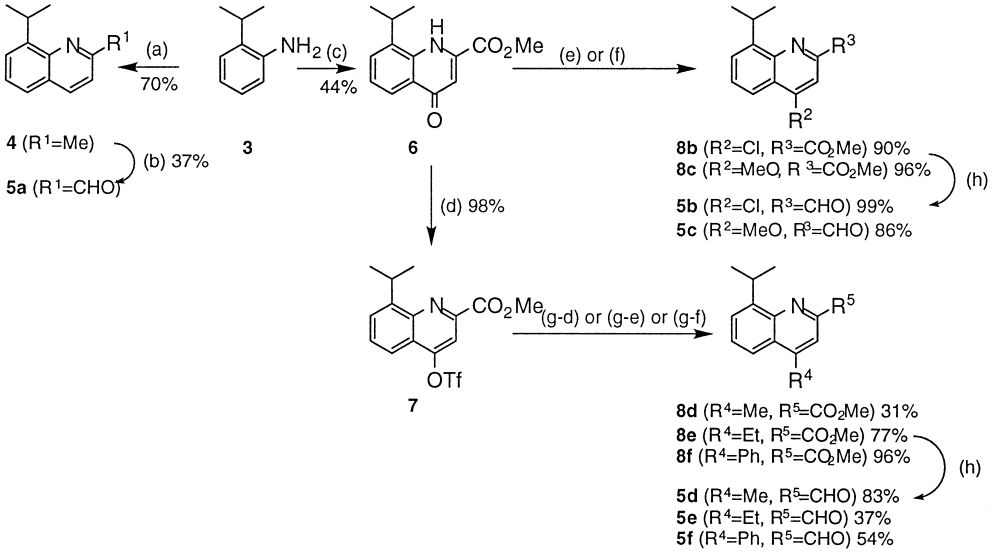
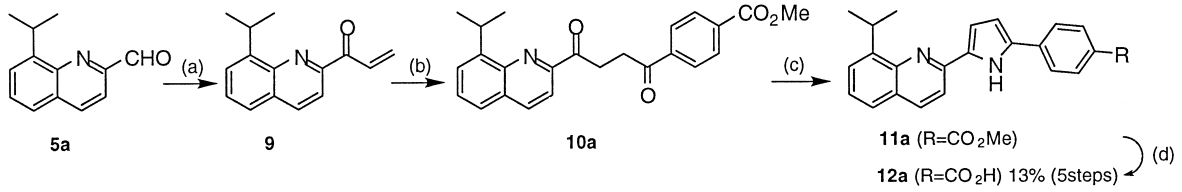


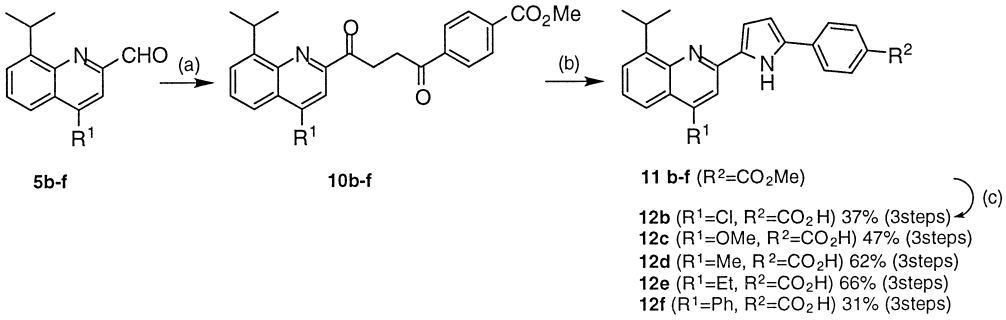
Figure 1.



Scheme 1. (a) Crotonaldehyde, 6 N HCl aq; (b) SeO_2, EtOH; (c) (i) dimethyl acetylenedicarboxylate, Triton B, MeOH; (ii) Ph_2O, 250 °C; (d) Tf_2O, 2,6-lutidine, DMAP, CH_2Cl_2; (e) PCl_5, $POCl_3$; (f) MeI, K_2CO_3, DMF; (g-d) MeLi, $ZnCl_2$, $Pd(PPh_3)_4$, THF; (g-e) EtMgBr, $ZnCl_2$, $Pd(PPh_3)_4$, THF; (g-f) phenylboric acid, Et_3N, $Pd(PPh_3)_4$, DMF; (h) (i) DIBAL-H, THF; (ii) $(COCl)_2$, DMSO, CH_2Cl_2 (**5b**, **5c**, **5d**); or MnO_2, acetone (**5e**, **5f**).



Scheme 2. (a) (i) Vinyl magnesiumbromide, Et_2O; (ii) MnO_2, CH_2Cl_2; (b) methyl 4-formylbenzoate, 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride, Et_3N, DMF; (c) $AcONH_4$, MeOH; (d) NaOH aq, EtOH.



Scheme 3. (a) Methyl 4-acryloylbenzoate, 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride, Et_3N, DMF; (b) $AcONH_4$, MeOH; (c) NaOH aq, EtOH.

Table 1. Competitive binding, transactivation, agonistic activity and antagonistic activity of the quinoline derivatives **12**

Compound		Binding affinity[a] relative IC_{50}[b]			Subtype-specific transactivation[e] relative EC_{30}[f]			HL-60	
								Agonistic activity[i]	Antagonistic activity[k]
No.	R	RARα	RARβ	RARγ	RARα	RARβ	RARγ	ED_{30} (nM)	IC_{50} (nM)
12a	H	5.7	579	—[c]	3.0	97	5767	2500	—[l]
12b	Cl	1.3	79	251	1.9	17	1160	100	—[l]
12c	MeO	0.8	475	834	—[g]	38	4460	—[j]	1.6
12d	Me	1.7	71	141	2.8	16	903	100	—[l]
12e	Et	0.7	32	22	2.5	22	180	—[j]	17
12f	Ph	1.8	535	432	—[g]	—[g]	—[g]	—[j]	6.4
ATRA		1.0 0.66 (nM)[d]	1.0 0.52 (nM)[d]	1.0 0.42 (nM)[d]	1.0 1.06 (nM)[h]	1.0 1.02 (nM)[h]	1.0 0.26 (nM)[h]	1.5 (nM)	

[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. 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]Mean of IC_{50}/ATRA IC_{50}.
[c]Not detectable (relative $IC_{50} > 1000$).
[d]Mean of ATRA IC_{50} (nM).
[e]EC_{30} values were determined from full dose–response curves ranging from 0.1 nM to 3 mM. 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]Mean of EC_{30}/ATRA EC_{30}.
[g]Not detectable ($EC_{30} > 3000$ nM).
[h]Mean of ATRA EC_{30} (nM).
[i]Agonistic activity was evaluated by HL-60 cell differentiation activity.
[j]Not detectable ($ED_{30} > 10{,}000$ nM).
[k]Antagonistic activity was evaluated in terms of inhibition of the HL-60 cell differentiation by ATRA (10 nM).

individual RARs and activity to induce gene transcription in a co-transaction assay, according to previous reports.[7c] HL-60 differentiation activity was measured using CD11b as a marker of differentiation, and antagonism was evaluated in terms of the ability to inhibit the differentiation of HL-60 cells induced by ATRA (10 nM).[7a] The results are summarized in Tables 1 and 2.

Compound **12a** showed weak affinity for RARα receptor, compared with ATRA. Introduction of a substituent at the 4-position in quinoline increased the binding affinity to RARα receptor. Compound **12b**, which has chlorine at the 4-position in quinoline, possessed moderate affinity to RARα, but showed only weak cell differentiation-inducing activity on HL-60 cells. Compound **12d**, which has a methyl group, showed similar subtype selectivity and cell differentiation activity to **12b**. Introduction of an ethyl group (compound **12e**) caused lower RARα selectivity and loss of cell differentiation-inducing activity. Moreover, compound **12e** showed partial antagonistic activity. These findings suggested that the size of the substituent at the 4-position was a critical factor for RARα agonistic or antagonistic activity in HL-60 cell assay. Compound **12c** possessed potent antagonistic activity against cell differentiation but had weak activity for RARβ transactivation. Compound **12f**, which has a phenyl group as a bulkier substituent, showed potent antagonistic activity

Table 2. Antagonistic activity on subtype-specific transactivation assay[7g] (compound **12f**)

Compound	Antagonistic activity[a] IC_{50} (nM)		
	RARα	RARβ	RARγ
12f	31.2	—[b]	—[b]

[a]Antagonistic activity was evaluated in terms of inhibition of transactivation by ATRA (50 nM).
[b]Not detectable ($IC_{50} > 3000$ nM).

on cell differentiation, and possessed selective affinity for RARα receptor. Furthermore, **12f** did not have transactivation activity for any receptor subtype, and it showed RARα-selective antagonistic activity.

In conclusion, novel benzoic acid derivatives which have an 8-isopropylquinoline moiety in the hydrophobic part and 2,5-disubstituted pyrrole moiety in the linking part possessed RARα selectivity. One of them, 4-[5-[8-(1-methylethyl)-4-phenyl-2-quinolinyl]-1*H*-2-pyrrolyl]benzoic acid (**12f**: ER-50891) showed potent RARα-selective antagonistic activity. This antagonist could be useful in studies of the role of the RARα receptor in the action of retinoids, and might be a useful lead compound for drugs to treat diseases caused by RARα-mediated gene transactivation.

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