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HIGH AFFINITY RETINOIC ACID RECEPTOR ANTAGONISTS: ANALOGS OF AGN 193109

Alan T. Johnson,* Liming Wang, Samuel J. Gillett,
and Roshantha A. S. Chandraratna*

Retinoid Research, Department of Chemistry, Allergan Inc., Irvine, CA 92713, U.S.A.

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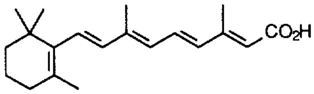
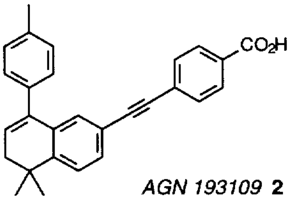
Abstract: A series of high affinity retinoic acid receptor (RAR) antagonists were prepared based upon the known antagonist AGN 193109 (**2**). Introduction of various phenyl groups revealed a preference for substitution at the *para*-position relative to the *meta*-site. Antagonists with the highest affinities for the RARs possessed hydrophobic groups, however, the presence of polar functionality was also well tolerated.

The natural hormone *all-trans*-retinoic acid (ATRA, **1**) (Chart 1) is capable of regulating gene transcription by binding to and activating retinoic acid receptors (RARα, -β, and -γ) located in the cell nucleus.[1] As a result, ATRA has been implicated in the control of fundamental cellular processes such as proliferation and differentiation.[2] Given the effects of these activities on various disease states such as psoriasis, acne, and cancer, the use of ATRA and other retinoids has been the focus of considerable interest in the treatment of these and other disorders.[3–5] Recently, we[6] and others[7–10] have identified compounds that function as antagonists at the RARs. In this paper we present our results from the preparation of various analogs of the high affinity RAR antagonist, AGN 193109 (**2**).

Chart 1



all-trans Retinoic Acid **1**



AGN 193109 **2**

The synthetic route used to prepare each of the RAR antagonists is outlined in Scheme 1. Bromination of the readily available tetralone **3**[11] afforded ketone **4**. A sequence of palladium catalyzed coupling reactions were used to introduce the acetylene group and the benzoate moiety to give **5** in 39% overall yield from **3**. The key intermediate in this route is vinyl triflate **6**, which was prepared following Comins' procedure.[12] Introduction of the remaining aryl group to afford each RAR antagonist was then carried out in the same manner. Metal–halogen exchange of the specific aryl halide[13] was followed by transmetallation with $ZnCl_2$.

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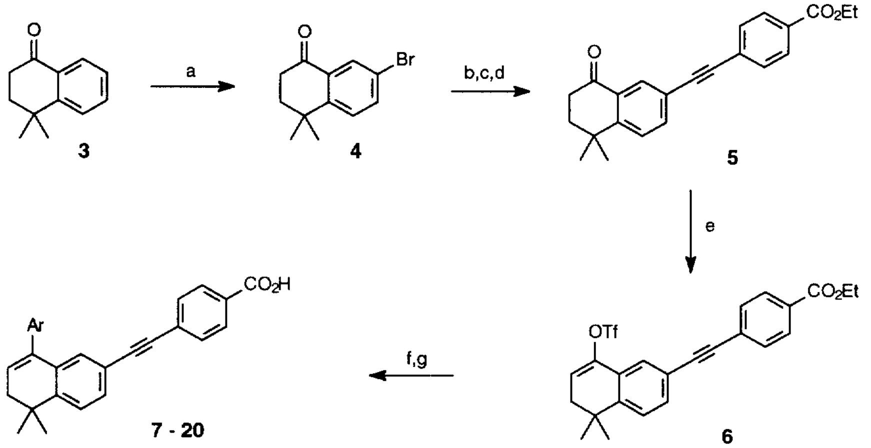
Scheme 1



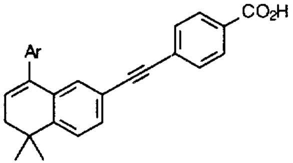
(a) $AlCl_3/Br_2/CH_2Cl_2$/70 °C (80%); (b) TMS-acetylene/$Pd(PPh_3)_2Cl_2$/CuI/Et_3N/60 °C; (c) K_2CO_3/MeOH (76% for b and c); (d) 4-$IC_6H_4CO_2Et$/$Pd(PPh_3)_2Cl_2$/CuI/Et_3N/25 °C (64%); (e) $NaN(SiMe_3)_2$/THF/-78 °C/*N*-(5-chloro-2-pyridyl)triflimide to 25 °C (77%); (f) ArZnCl/$Pd(PPh_3)_4$/THF/50 °C (53-85%); (g) NaOH/EtOH/H_2O or LiOH/THF/H_2O (76-96%).

The resulting aryl zinc reagent was then combined with vinyl triflate **6** and a catalytic amount of $Pd(PPh_3)_4$ in THF at 50 °C.[14] Isolation of the resulting benzoate esters was followed by hydrolysis under basic conditions to afford retinoids **7** to **20** (Table 1) in good overall yield.

The affinity of each compound for the RARs was determined in competition binding assays[15] and transcriptional activity was measured using RAR holoreceptors and a TRE_{pal}-luciferase reporter gene.[16] All of the compounds in Table 1, with the exception of **7**, **8**, and **14** which displayed weak agonist activity at RARβ, were completely inactive in the transactivation assays at each of the RARs. In contrast, all of the retinoids were able to bind to each of the RAR subtypes with moderate to high affinity. Further, all of the analogs **7–20**, were capable of blocking the functional activity of the natural ligand ATRA (**1**).[17]

The phenyl compound **7** binds with an approximate twofold lower affinity relative to ATRA(**1**). The introduction of a methyl group in *ortho*-postion afforded **8**, which was indistinguishable from the parent compound **7** at all three RAR subtypes. Placing the methyl group in the *meta*-position to give **9** resulted in no significant change in the observed binding affinities. However, the placement of a methyl group in the *para*-position as in **2**, provided a compound with affinities equivalent to the natural hormone ATRA at RARα and RARβ and approximately twofold higher at RARγ. The decrease in binding affinity observed with the addition of a second *meta*-substituent as in **10** suggested that exploring further modifications at the *meta*-position would lead to analogs with even lower affinity for the RARs.

Table 1: K_d Values[a] (nM) for ATRA (**1**), AGN 193109 (**2**), and Antagonists **7–20** at each of the RAR Subtypes



Compd	Ar	RAR		
		α	β	γ
ATRA(**1**)		15±2	13±3	18±1
7	C_6H_5-	147±27	33±6	42±9
8	2-Me-C_6H_5-	103±17	29±8	35±9
9	3-Me-C_6H_5-	276±175	51±22	67±30
2	4-Me-C_6H_5-	16±5	7±3	7±1
10	3,5-DiMe-C_6H_5-	1051±802	274±45	408±146
11	4-Et-C_6H_5-	40±16	10±2	19±8
12	4-*i*-Pr-C_6H_5-	90±10	11±4	171±51
13	4-*t*-Bu-C_6H_5-	178±81	21±4	94±63
14	4-F-C_6H_5-	85±45	52±30	82±35
15	4-Cl-C_6H_5-	58±9	18±2	27±8
16	4-CF_3-C_6H_5-	44±7	29±5	57±28
17	3-OH-C_6H_5-	919±250	162±85	254±118
18	4-OH-C_6H_5-	229±48	72±21	98±24
19	4-OMe-C_6H_5-	60±29	16±1	36±7
20	4-CN-C_6H_5-	38±5	14±3	51±15

[a] K_d values were determined via competition binding experiments using $[^3H]$-(*all-E*)-retinoic acid (5 nM) with unlabeled test retinoid at baculovirus expressed RARs.

Given the apparent benfit of *para*-susbtitution on the phenyl ring, and the desire to avoid molecules with axial dissymmetry by further substitutions at the *ortho*-site, we concentrated on modifications at the *para*-position. The effect of increasing the steric bulk in this region was investigated with the preparation of the alkyl substituted compounds **11** to **13**. Of the three RAR subtypes, RARβ appears the least sensitive to the size of the hydrophobic group introduced at this position. In contrast, RARα and RARγ appear less tolerant, displaying a decrease in binding affinity with an increase in the size of the alkyl group. These data suggest that a *para*-substituent of a size similar to a methyl or ethyl group is optimal for RAR binding.

We next looked at the effect of changing the electronic nature of the functional group on the aryl ring. The 4-fluoro analog **14** binds to the RARs with affinities similar to the parent compound **7**, suggesting that this region of the receptor in relatively insensitive to electrostatic field effects. The K_d values for the 4-chloro derivative **15** and the 4-trifluoromethyl analog **16** support this conclusion by displaying binding affinities for the RARs in the same range as the 4-ethyl analog **11**. The effect of introducing a hydroxyl group, which can act as a hydrogen bond donor or acceptor, was studied with preparation of **17** and **18**. In each case this modification proved detrimental to binding, with the *meta*-hydroxy substituent in **17** being particularly disfavored. In contrast, the data for the 4-methoxy analog **19** appears to correlate with the steric effect discussed above possessing binding affinities for each RAR subtype that are similar to the 4-ethyl analog **11**.

In summary, a series of RAR antagonists were prepared as analogs of the potent antagonist AGN 193109(**2**). The compounds having subtituents in the *para*-postion of the appended phenyl ring were found to have the highest binding affinities with the observed K_d values dependent upon the size rather than the polarity of the attached group. In addition, functionality introduced at the *meta*-position appeared to produce antagonists with reduced binding affinity for the RARs.

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