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STRUCTURAL MODIFICATIONS OF 6-NAPHTHALENE-2-CARBOXYLATE RETINOIDS

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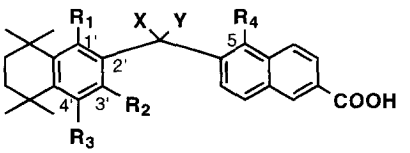
Abstract The keto linker of 2-naphthoate retinoid **1** has been found nonessential for RAR transactivation activity and can be replaced with heteroatoms such as S, O, N without significant reduction of the activity. On the other hand, substitutions on the aromatic rings of retinoids **1** and **2** resulted in analogs with reduced potentcy and RAR selectivity.

We have previously demonstrated that the naphthalene ring of **1** and **2** is important for their potency and retinoic acid receptor selectivity.[1] In this study, we investigated the effects of substituents at varied positions of the aromatic rings of retinoids **1** and **2** (Chart 1), and replacement of the keto or the alcohol linker between the aromatic rings with heteroatoms (Chart 2).

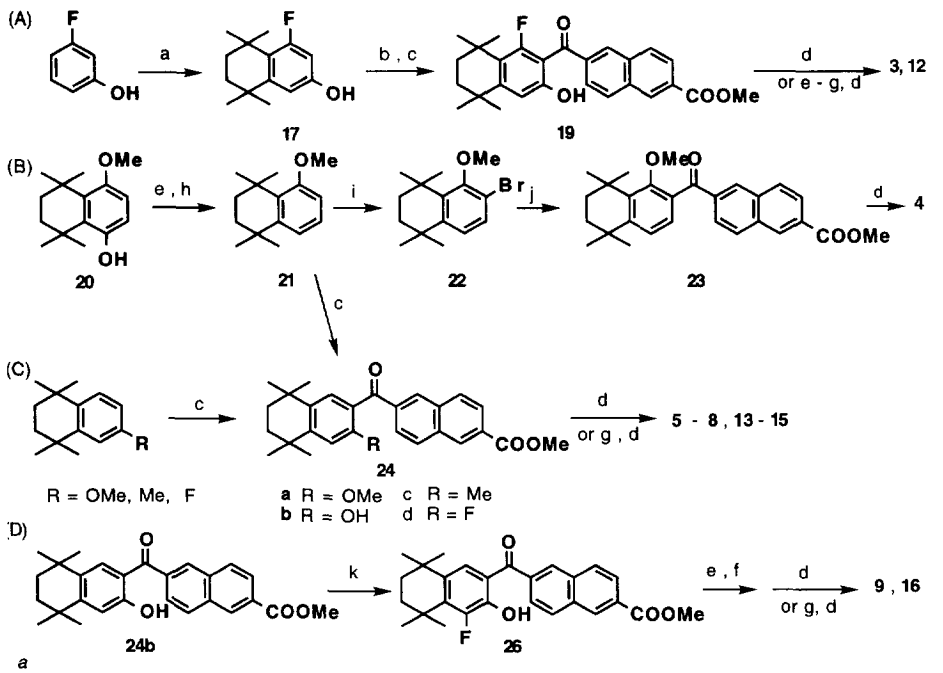
Chart 1



Compd No.	X,Y	R_1	R_2	R_3	R_4	Compd No.	X,Y	R_1	R_2	R_3	R_4
1	O	H	H	H	H	**9**	O	H	H	F	H
2	OH, H	H	H	H	H	**10**	O	H	H	H	OMe
3	O	F	OH	H	H	**11**	O	H	H	H	OH
4	O	OMe	H	H	H	**12**	OH,H	F	H	H	H
5	O	H	OH	H	H	**13**	OH,H	H	OH	H	H
6	O	H	Me	H	H	**14**	OH,H	H	Me	H	H
7	O	H	F	H	H	**15**	OH,H	H	F	H	H
8	O	H	OMe	H	H	**16**	OH,H	H	H	F	H

The synthesis of these substituted naphthoate derivatives is shown in Schemes 1 and 2. To prepare the 1'-fluoro substituted derivatives **3** and **12** (Scheme 1A), *m*-fluorophenol was treated with 2,5-dimethyl-2,5-hexanediol in the presence of aluminium chloride to afford fluorophenol **17**. The phenol was protected as a methyl ether, which was acylated with naphthalene-2,6-dicarboxylate monomethyl ester acid chloride (**18**), accompanied with the hydrolysis of the methyl ether, to give **19**. It is worth noting that without protection of the phenol, the Friedel-Crafts reaction gave only the recovered starting material. Ester **19** can be hydrolyzed to give retinoid **3** or dehydroxylated by converting the phenol to a triflate, followed by reduction with ammonium formate in the presence of palladium acetate and triphenylphosphine.[2] Reduction of the ketone with sodium borohydride and hydrolysis of the ester provided retinoid **12**. In a similar approach (Scheme 1B), phenol **20**[3] was dehydroxylated to provide **21** using the triflation-reduction procedure described above, except that the reduction was performed in a Parr apparatus using H_2-Pd/C.[4] Reduction of the triflate with the formate or triisopropyl silane gave no reaction. Early attempts to acylate **21**

Scheme 1[a]



a

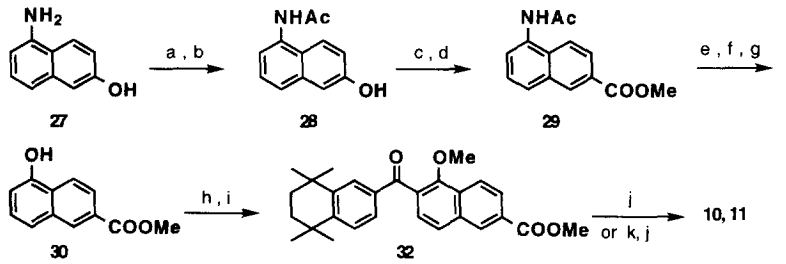
(a) $((CH_3)_2COHCH_2)_2$; $AlCl_3$; (b) NaH, MeI; (c) **18**, $AlCl_3$; (d) NaOH; (e) Tf_2O, DIEA or pyridine; (f) HCOOH, Et_3N, $Pd(OAc)_2$, PPh_3; (g) $NaBH_4$; (h) 10% Pd/C, H_2, Et_3N; (i) Br_2, AcOH ; (j) *t*-BuLi; **18**; (k) **25**.

with **18** gave a 3'-methoxy acylated compound (**24a**) rather than 1'-methoxy product due to Lewis acid catalyzed rearrangement of **20** to the more stable 2-methoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalene. Saponification of this side product yielded 3'-methoxy substituted retinoid **8**. Alternatively, **21** was treated with bromine in acetic acid[5] to provide a mixture of 2-brominated and 4-brominated products in a 2:1 ratio. The 2-brominated naphthol (**22**) was separated by silica gel chromatography, eluting with hexane and ethyl acetate (2:1), and then treated with *t*-butyl lithium, followed by addition of acid chloride **18** to provide **23**. Saponification of **23** yielded **4**. For 3'-hydroxy, 3'-methyl- or 3'-fluoro derivatives (**5-7**, and **13-15**), the synthesis was straightforward, and shown in Scheme 1C. To prepare 4'-fluoro derivative **9**, intermediate **24b** obtained from Scheme 1C was fluorinated with 3,5-dichloro-1-fluoropyridinium triflate (**25**)[6] in refluxing methylene chloride to afford **26** (Scheme 1D). The triflate-reduction procedure and saponification shown in the scheme yielded retinoid **9**. Reduction of the fluoro ketone intermediate with $NaBH_4$ followed by saponification produced retinoid **16**.

The synthesis of 5-methoxy- and 5-hydroxy-naphthoate retinoids **10** and**11** is shown in Scheme 2. 5-Amino-2-naphthol (**27**) was bisacetylated and selectively saponified to provide acetamide **28**. The resulting phenol was converted to a methyl ester (**29**) through carbonylation of the corresponding triflate in the presence of palladium catalyst.[7] The acetamide was hydrolyzed and the amino group was transformed to a phenol (**30**) by diazotization[8] followed by hydrolysis.[9] Friedel-Crafts reaction of the methyl ether of **30** with 1.3 equiv of 5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalene-2-carboxylic acid chloride (**31**) and 2 equiv of $AlCl_3$ in nitromethane at 65 °C

smoothly provided **32**. Saponification of the ester yielded **10**. When **32** was treated with boron tribromide followed by saponification, the 5-hydroxy derivative **11** was obtained.

Scheme 2[a]



a
(a) Ac_2O, Pyr.; (b) NaOH; H^+; (c) Tf_2O, DMAP; (d) CO, $Pd(OAc)_2$, dppp, Et_3N, MeOH; (e) HCl-MeOH; (f) $NaNO_2$, HBF_4; (g) aq. H_2SO_4; (h) NaH, MeI; (i) **31**, $AlCl_3$; (j) NaOH; (k) BBr_3.

All of the retinoids prepared were evaluated in the RAR transactivation assays.[10] For the substituted ketone derivatives **3**-**11**, methoxy substitution at the 1 position of the 5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalene (TTN) ring of ketone **1** resulted in an inactive retinoid **4**. Introduction of substituents such as OH, Me, and OMe at the 3-position of the TTN ring (retinoids **5**, **6**, and **8** respectively) also decreases activity. However, fluorination at the 1', 3', or 4' position of the TTN ring (**3**, **7**, and **9**) in general had only a slight effect on potency or receptor selectivity. These results seem to suggest that bulky substituents at the 1 and 3 positions of the TTN ring, which affect the dihedral angle of the TTN and the naphthoic acid ring, decrease the activity, while a smaller substituent like fluorine has a less effect on activity. In the naphthoic acid portion, compounds with methoxy or hydroxy substitution

Table 1. RAR Transactivation Assays of the Substituted 2-Naphthoic Acid Retinoids[a]

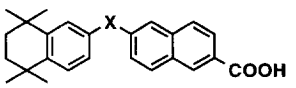
Compound Number	EC_{50}[b]			% Max[c]		
	RAR-α	RAR-β	RAR-γ	RAR-α	RAR-β	RAR-γ
1	13	3	1.4	65	82	93
2	NA	133	14	0	77	95
3	100	6.7	15	46	87	92
4	NA	NA	NA	0	0	0
5	25	7.5	20	44	76	70
6	25	25	75	26	81	58
7	25	15	3	34	81	70
8	8	14	6	23	61	53
9	10	4	6.7	63	81	100
10	NA	NA	NA	0	0	0
11	NA	NA	NA	0	0	0
12	NA	133	15	0	74	90
13	NA	NA	30	0	18	47
14	NA	100	5.6	0	96	82
15	NA	133	100	0	30	70
16	NA	NA	NA	0	0	0

(a) Compounds were evaluated at concentrations ranging from 10^{-10} to 10^{-6} M. NA: not active. (b) The EC_{50} ratio of each compound was obtained by dividing the concentration required to obtain 50% of the maximum transactivation activity of each compound with that of retinoic acid. (c) % Max is the maximum transactivtion activity of the tested compound relative to that of retinoic acid at 10^{-6} M.

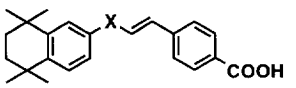
at the 5-position (**10** or **11**), surprisingly gave no activity at all in the transactivation assays. For the alcohol derivatives of **2**, **12**-**16**, the SAR is very different from that of the ketone series described above. For instance, fluorination at the 1 position of the TTN ring (**12**) maintains the activity of **2**. However, fluorination at 3 and 4 positions (**15** and **16**, respectively) dramatically decreases activity. On the other hand, a methyl substitution at the 3 position of the TTN ring has very little effect on the activity, indicating that the alcohol series might have better steric tolerance at this position. These results suggest that for ketone **1**, the size of the substituents at the 1 and 3 position of the TTN ring has a very strong impact on the activity of ketone **1**. However, such a steric effects seem to be less important in the alcohol series **2**.

Because attempts to improve potency and the RAR receptor selectivity of **1** by the substituent modification described above were unsuccesful, we turned our attention to the modification of the keto linker of **1**. The retinoids synthesized with varied heteroatom linkers (**33**-**40**) are shown in Chart 2.

Chart 2



33 X = S
34 SO
35 SO_2
36 NH
37 O



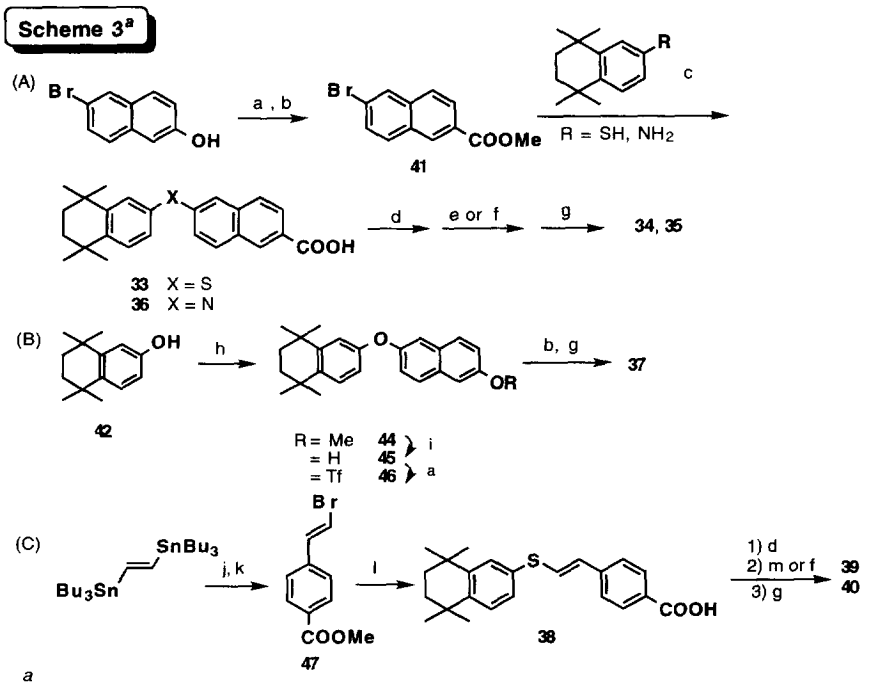
38 X = S
39 SO
40 SO_2
Ch80 CO

Scheme 3A depicts the synthesis of the retinoids **33**-**36**. The common intermediate for preparing these derivatives, methyl 6-bromo-2-naphthoate (**41**) was easily prepared from 6-bromo-2-naphthol by selective carbonylation of the corresponding triflate in the presence of palladium catalyst.[8] Bromide **41** was then displaced with either 2-thio-[11] or 2-amino-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalene in the presence of *t*-BuOK and $Pd(PPh_3)_4$,[12] accompanied by hydrolysis of the methyl esters, to afford **33** and **36**, respectively. Acid **33** was further treated with diazomethane to give the methyl ester which was oxidized with 1.05 equiv or 4 equiv of magnesium monoperoxyphthalate (MMPP),[13] followed by saponification to give the sulfoxide **34** and sulfone **35**, respectively. The same strategy was used in an attempt to prepare the ether analogue **37** by coupling phenol **42** with methyl 6-bromo-2-naphthote (**41**). However, this gave only recovered starting materials. Alternatively, Ullmann reaction[14] of **42** with 2-bromo-6-methoxynaphthalene (**43**) provided **44** (Scheme 3B). Methyl ether **44** was partially purified and subsequently treated with BBr_3 to give naphthol **45**. Naphthol **45** was converted to an ester via triflate **46**. Hydrolysis of the ester afforded ether retinoid **37**. In a similar approach to prepare **33**, 2-thio-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalene reacted with **47**[15] to give retinoid **38** (Scheme 3C). Oxidation of the sulfide ester of **38** with 4 equiv of MMPP afforded the ester of sulfone **40**. However, when the sulfide was oxidized with 1.05 equivalents of MMPP, an inseparable mixture of sulfone and sulfoxide was obatined. Using milder reaction conditions, the sulfide was oxidized with sodium perborate[16] to cleanly give the sulfoxide ester. Saponification of the ester of the vinyl sulfoxide or sulfone provided retinoids **39** and **40**, respectively.

The RAR transactivation activity of the heteroatom-linker retinoids is shown in Table 2. The results clearly indicate that the keto linker of **1** can be replaced with heteroatoms such as S, N, or O (e.g., **33**, **36**, and **37**) without significant loss of the transactivation activity. Similarly, the vinyl sulfide retinoid (**38**) is more potent than **Ch 80**[17] in the transactivation assay. Notably, when the sulfur linker was oxidized to a sulfoxide or sulfone (e.g., **34**, **35**, **39**, and

40), the activity of the retinoids is dramatically reduced. Furthermore, we have found that these naphthoate retinoids retain RAR β, γ selectivity, while the benzoate retinoid such as **38**, is RAR non-selective. The results support our previous observation that the naphthoate ring of **1** is crucial for its RAR β, γ activity.[1] In the in vivo utriculi reduction assay[18] (Figure 1), ketone **1** and sulfide **33** were shown to be as potent as retinoic acid (RA), while vinyl

Scheme 3[a]



a

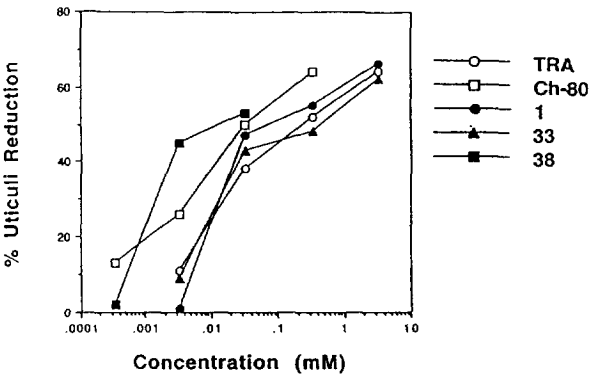
(a) Tf_2O, DIEA; (b) CO, MeOH, $Pd(OAc)_2$, dppp; (c) $Pd(PPh_3)_4$, *t*-BuOK; (d) CH_2N_2; (e) MMPP (1.05 equiv); (f) MMPP (4 equiv); (g) NaOH; (h) **43**, $K_2C\,O_3$, pyr, Cu; (i) BBr_3; (j) methyl *p*-bromobenzoate, $Pd(PPh_3)_4$; (k) Br_2; (l) 2-thio-TTN, $Pd(PPh_3)_4$, *t*-BuOK; m) $NaBO_3$.

Table 2. RAR Transactivation Assays of the Naphthoic Acid Retinoids 33-40.

Compound	EC_{50}			% Max		
Number	RAR-α	RAR-β	RAR-γ	RAR-α	RAR-β	RAR-γ
1	13	3	1.4	65	82	93
Ch 80	0.7	1.2	1.0	100	91	98
33	25	10	2	45	88	83
34	NA	167	100	0	52	64
35	NA	133	100	0	32	64
36	25	17	15	27	92	91
37	63	20	8	56	120	78
38	1.3	0.8	0.2	118	158	77
39	38	40	8	42	96	64
40	NA	200	150	0	35	64

NA: not active

Figure 1. In Vivo Utriculi Reduction of The Retinoids



sulfide **38** is more potent than **Ch80** and causes skin peeling at concentrations above 0.03 mM. The results are consistent with that of the in vitro transactivation assay. RAR β, γ selective retinoid **2**, on the other hand, showed only one tenth the activity of ketone **1** in the assay.[1]

In summary, the substitution at varied positions of the aromatic rings of **1** and **2** produces no significant improvement in terms of potency or RAR selectivity. Nevertheless, these compounds in general still retain RAR β, γ selectivity. In addition, we have found that the keto linker of **1** can be replaced with heteroatoms such as S, O,and N without significant reduction of the transactiviation activity. Among these heteroatom linker retinoids, sulfide **33** is as active as ketone **1**, and vinyl sulfide **38** is more potent than **Ch80**.

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