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Design and Synthesis of Fluorinated RXR Modulators

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Abstract—Fluorinated trienoic acid analogues of the RXR selective modulator **1** (LG101506) were synthesized, and tested for their ability to bind RXRα and activate RXR homo and heterodimers. Potency and efficacy were observed to be dependent upon the position of fluorination, and improvement in pharmacological profile was demonstrated in some cases.

Introduction

The retinoid X receptor (RXR) is known to regulate gene transcription through the formation of heterodimers with other nuclear receptors.[1,2] In particular the heterodimer formed with peroxisome proliferative-activated receptor gamma (PPARγ) plays a major role in the regulation of both glucose and lipid metabolism.[3] Recently, selective RXR modulators such as **1** (LG101506), **6** (LG101392), and **8** have been described as hypoglycemic agents[4] (Fig. 1). As part of ongoing SAR efforts, we endeavored to evaluate the pharmacological effects of placing a fluorine atom at different positions of the triene system.

Chemistry

Synthesis of the 6-fluoro analogue **3** has been recently described.[5] Syntheses of the 5-, 4-, and 2-fluoro positional isomers (**2**, **4**, and **5**) required the development of alternative methods as described below.

The 5-fluorotrienoic acid derivative (**2**) was synthesized as shown in Scheme 1. commercially available 2,4-di-*t*-butylphenol was alkylated with 1-bromo-2,2-difluoroethane and cesium carbonate in DMF and then treated with NIS in refluxing DCM to afford the iodo compound **10** in good yields. This compound then underwent standard Sonagashira coupling with trimethylsilyl acetylene. Treatment of **11** with dimethyl zinc and Ni(acac)2 provided the corresponding vinyl silane **12** in low yield. Treatment of **12** with iodine monochloride provided the vinyl iodide **13** as a separable mixture of isomers in a 2:1 ratio (*Z*/*E*). After separation, the *Z* isomer, was coupled with the tin reagent (**14**),[5,7] and hydrolyzed to provide 5-fluorotrienoic acid, **2**.

The 4-fluorotrienoic acid derivative (**4**) was prepared from the aldehyde **15**,[8] as shown in Scheme 2. Condensation with fluoromethyl phenyl sulfone provided the dienylsulfone **16** which underwent hydrostannylation to provide dienylstannane **17** in 38% overall yield, after separation from isomeric material.[7] Compound **17** then underwent smooth coupling with the 3-iodo-but-2-enoic acid, to provide the desired 4-fluoro analogue **4** in 81% yield.[6,9]

The 2-fluorotrienoic acid derivative (**5**) was prepared from the ester **18**,[10] as shown in Scheme 3, by four-step

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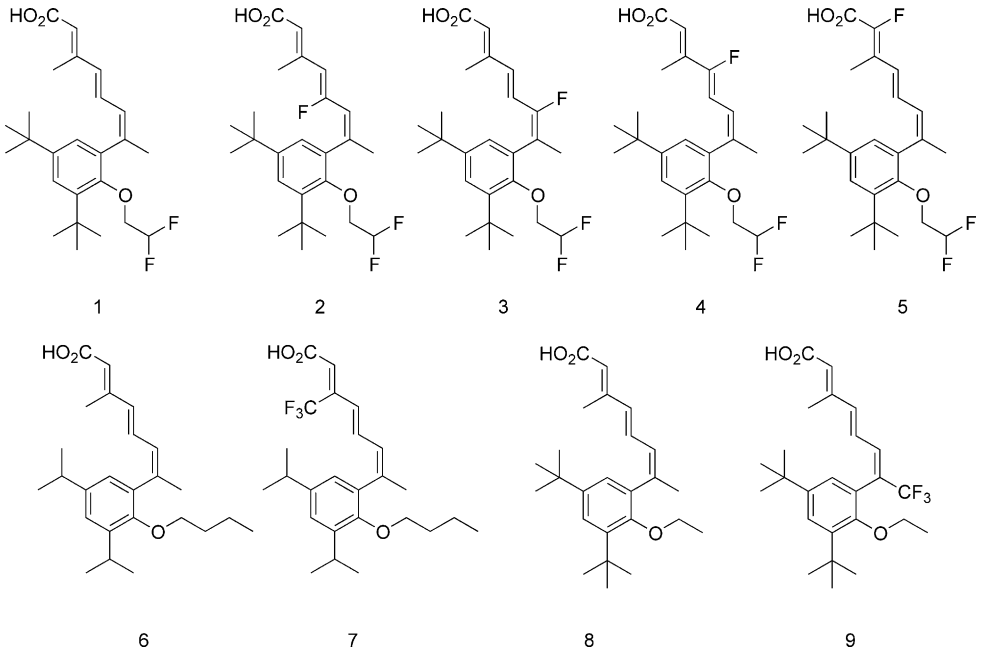
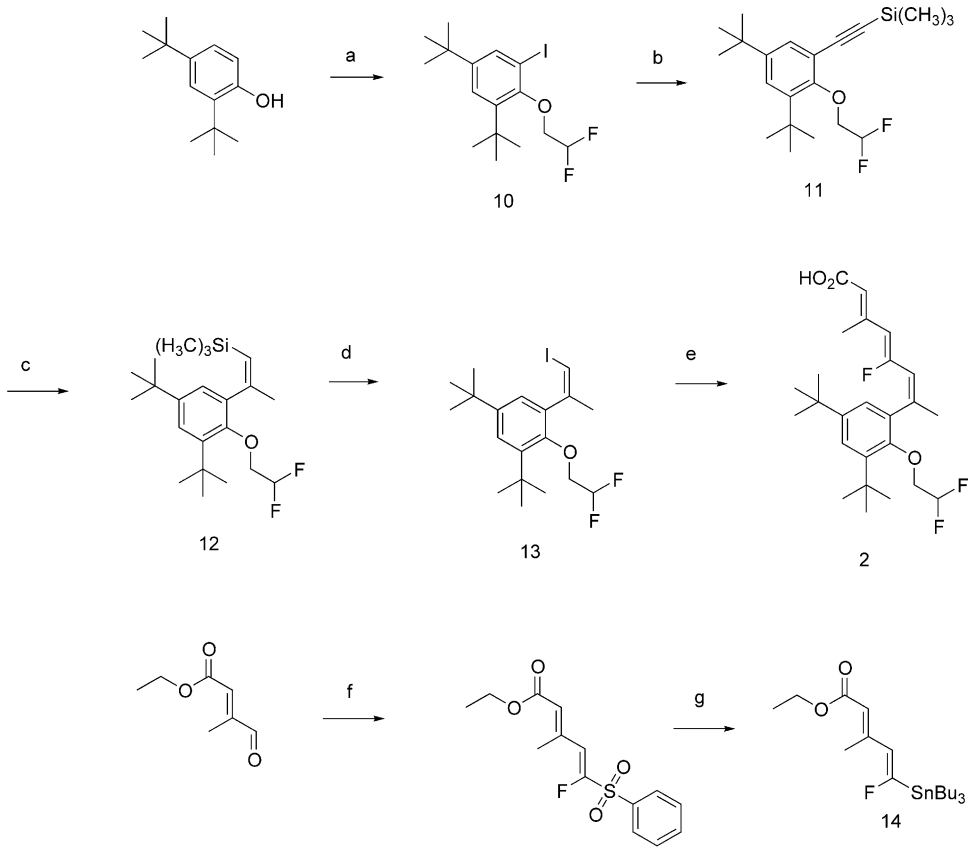
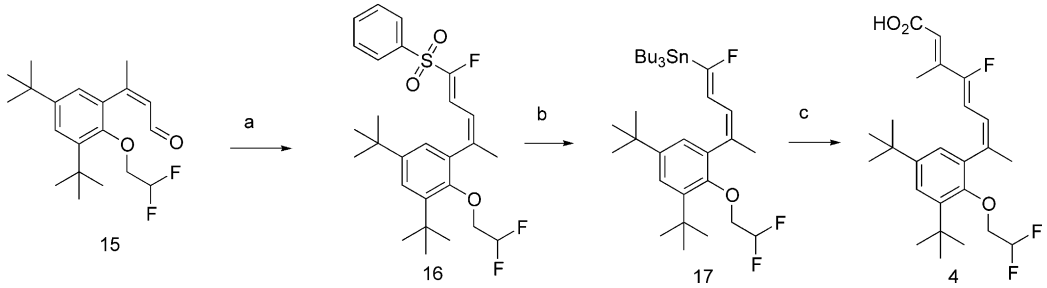


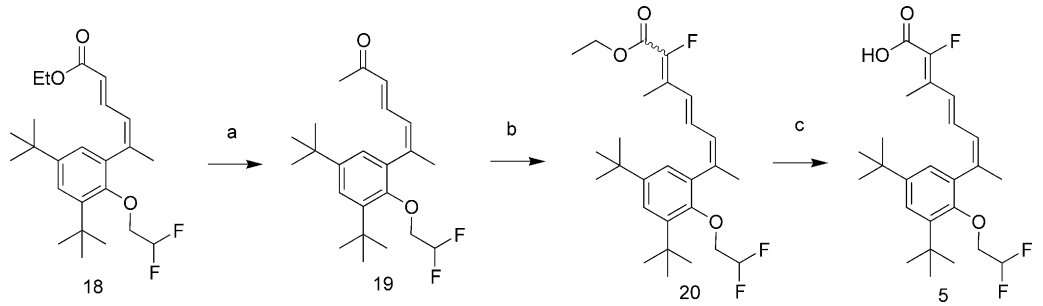
Figure 1. Fluorinated trienoic acids.



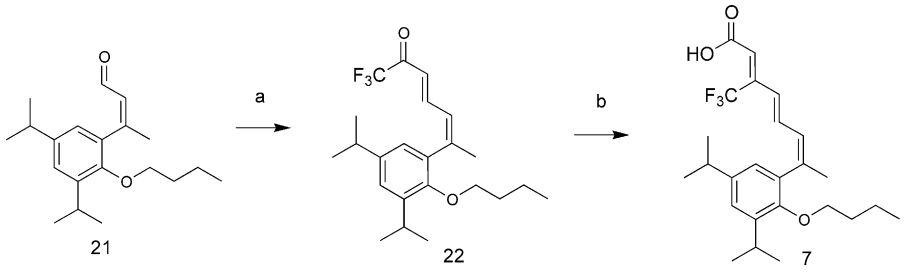
Scheme 1. 5-Fluorinated trienoic acid synthesis. Reagents and conditions: (a) (i) Cs_2CO_3, CF_2CH_2Br, DMF, 50 °C (sealed tube); (ii) NIS, *p*-TSA, DCM, reflux; 90%; (b) $Pd(PPh_3)_4$, CuI, TEA, TMS-acetylene, dioxane, 80 °C, 57%; (c) $Ni(acac)_2$, Me_2Zn, THF/NMP (3:1); 0 °C to rt, 7%; (d) ICl, CCl_4, 0 °C, 39%; (e) (i) A, $Pd(PPh_3)_2Cl_2$, DMF, 80 °C; (ii) 1 N NaOH (aq), MeOH; 60 °C, 35%; (f) ethyl 3-methyl-4-oxocrotonate, fluoromethyl phenyl sulfone, diethyl chlorophosphate, LiHMDS, THF, −78 °C; (g) $SnBu_3H$, AIBN, benzene; reflux, 58% (desired isomer).



Scheme 2. 4-Fluorinated trienoic acid synthesis. Reagents and conditions: (a) fluoromethyl phenyl sulfone, diethyl chlorophosphate, LiHMDS, THF, −78 °C; (b) $SnBu_3H$, AIBN, benzene, reflux, 38% (desired isomer); (c) 3-iodo-but-2-enoic acid, $Pd(PPh_3)_2Cl_2$, DMF, 80 °C, 81%.



Scheme 3. 2-Fluorinated trienoic acid synthesis. Reagents and conditions: (a) (i) LAH, ether, 0 °C; (ii) TPAP/NMO, DCM; (iii) MeMgBr, ether; (iv) TPAP/NMO, DCM, 56%; (b) $EtO_2CCHFP(O)(OEt)_2$, NaH, DMF, 0 °C to rt, 50%; (c) (i) LiOH, THF, MeOH; (ii) HPLC separation, 45% (desired isomer).



Scheme 4. Trifluoromethyl (**7**) synthesis. Reagents and conditions: (a) 1,1,1-trifluoroacetone, piperidine, acetic acid, THF, 31%; (b) (i) $CH_3C(O)CH_2P(O)(OMe)_2$, NaH, ether, 84%; (ii) separation of isomers, 20% (desired isomer); (iii) LiOH, MeOH, 77%.

conversion to methyl ketone **19**, followed by Horner–Emmons condensation to provide the fluorinated ester, **20**. Hydrolysis and HPLC separation of the 1:1 mixture of isomers, provided the desired final product in 45% yield.

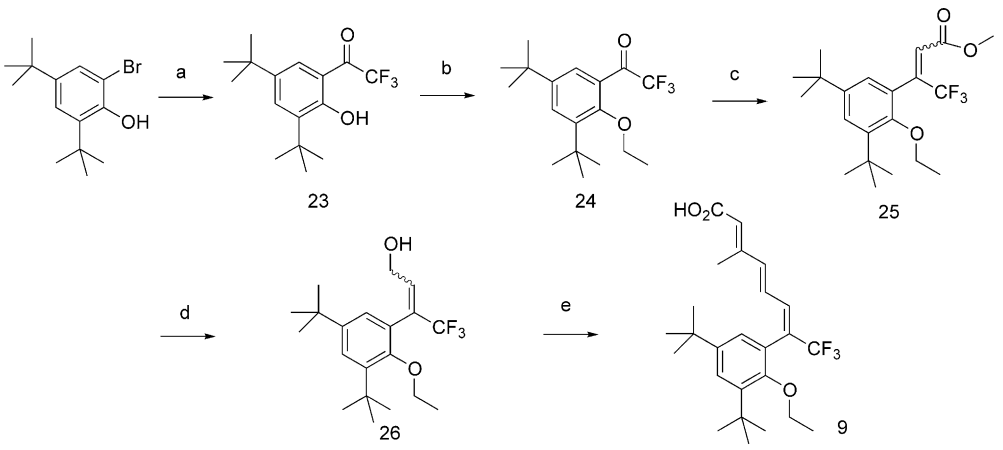
In addition to our explorations of the fluorinated triene analogues of **1**, we examined the effects of replacing the triene methyl substituents with trifluoromethyls. The 3-trifluoromethyl analogue, **7**, was synthesized from the aldehyde **21**[6] as shown in Scheme 4. Condensation with 1,1,1-trifluoro-propan-2-one followed by Horner–Emmons condensation provided a 4:1 mixture of *E*/*Z* isomers. After separation and hydrolysis the desired *Z*,*E*,*E* isomer was isolated.

The 7-trifluoromethyl analogue, **9**, was synthesized as outlined in Scheme 5. The dianion of *o*-bromophenol was quenched with ethyl trifluoroacetate, followed by alkylation to provide **23**. Sequential reduction, oxidation, Horner–Emmons condensation, and hydrolysis provided the desired 7-trifluoromethyl product in low yield after HPLC purification.

Biological Evaluation

The binding of each compound to RXRα and the retinoic acid receptor (RARγ), was characterized using ^{3}[H]-9-*cis*-retinoic acid and ^{3}[H]-all *trans*-retinoic acid respectively and the data expressed as a K_i (Table 1).[11] All of the fluorine replacements on the trienoic acid portion showed good binding and were comparable to the parent compound **1**. Compounds **7** and **9** possessing a 3- or 7-trifluoromethyl group, however, showed a decrease in binding affinity relative to comparators **6** and **8**. All of the compounds showed good binding selectivity over RAR.

The RXR homodimer transcriptional activation profile of each compound was determined in CV-1 cells efficacy is reported relative to all-*trans*-retinoic acid.[11] The



Scheme 5. Trifluoromethyl (**9**) synthesis. Reagents and conditions: (a) *n*-BuLi, ethyl trifluoroacetate, ether, −78 °C, 78%, (b) NaH, iodoethane, DMF, >99%; (c) trimethylphosphonoacetate, NaH, DMF 0 °C to rt; (d) DIBAL, ether; (e) (i) TPAP/NMO, DCM; (ii) triethyl-3-methyl-4-phosphonocrotonate, NaH, DMF, 0°C to rt; (iii) LiOH, EtOH, reflux; (iv) HPLC separation, 0.62% (desired isomer).

Table 1. In vitro evaluation of RXR modulators in CV-1 cells

Compd	RXRα binding	RXRα	RXRα	RXRα/PPARγ	RARγ binding	RAR agonist synergy[e]
	K_i, nM[a]	Agonist % efficacy (EC_{50}, nM)[b]	Antagonist % efficacy (EC_{50}, nM)[b]	Agonist % efficacy (EC_{50}, nM)[c]	K_i, nM[d]	
1	2.7	4	0	60 (3.1)	>10,000	1.4
2	8.2	270 (259)	100 (8712.8)	630 (249.1)	>10,000	8.9
3	7.8	2	87 (6.8)	63 (6.4)	>10,000	1.8
4	4.8	107	100 (4842.1)	180 (143.4)	>10,000	2.5
5	10.6	2	92 (3.4)	83 (2.7)	>10,000	1.5
6	3.8	2	91 (3.3)	39 (9.2)	>10,000	1.2
7	5208	1	65 (805.8)	40 (359.4)	>10,000	1.3
8	11.4	12	61 (6.4)	70 (2.0)	8566	2
9	50.3	22	30 (38.0)	47 (167.4)	>10,000	7

Each data point represents the mean of two measurements.
[a]Calculated using [^{3}H]-9-cis-RA.
[b]LGD1069 was used as reference.
[c]Calculated using 100 nM of BRL49653, efficacy relative to BRL49653.
[d]Calculated using [^{3}H]-ATRA.
[e]Calculated using 3 nM of TTNPB.

replacement of fluorine at the 2- and 6- positions (compounds **5** and **2**, respectively) showed the same RXR homodimer antagonist profile as **1**. Surprisingly, the compounds possessing a fluorine on the 4- and 5- positions of the trienoic acid (compounds **4** and **2**, respectively) are RXR homodimer agonists. However, while their binding affinity for RXR is still low nanomolar (K_i = 8.2 and 4.8 nM, respectively), they have weak potency for RXR homodimer activation in our co-transfection assay (Table 1, EC_{50} >4800 nM). Both the 3- and 7-trifluoromethyl compounds **7** and **9** demonstrated reduced efficacy and potency as expected in light of their lower binding affinity.

We have previously demonstrated that RXR homodimer antagonists can exhibit selective profiles of RXR heterodimer activation in combination with sub-efficacious concentrations of PPARγ (e.g., BRL49653) or RAR (e.g., TTNPB) ligands.[12] Compound **1** was shown to synergize with BRL49653 to enhance activation at the RXR/PPARγ heterodimer but did not synergize with TTNPB to enhance activation at the RXR/RAR heterodimer (Table 1). The RXR heterodimer activation profiles of the fluorinated analogues demonstrated similar trends to those observed for the homodimers above. The 2- and 6-F compounds (**5** and **3**) showed strong activation of the RXR/PPARγ heterodimer in combination with BRL49653. The 4- and 5-F compounds (**4** and **2**) also showed much lower activation, and the trifluoromethyl compounds showed poor activation. The 4- and 5-fluoro analogues also showed increased synergistic activation of the RXR/RAR heterodimer relative to **1**, while the 2- and 6-fluoro analogues maintained their selectivity for the RXR/PPARγ heterodimer.

In order to determine whether fluorination of the triene would affect pharmacokinetic parameters of these RXR modulators, we conducted an in vivo study of oral exposure (Table 2). The 6-F analogue **3**, was tested as a

Table 2. In vivo evaluation of oral exposure of selected RXR modulators

Compd	Dose (mg/kg)	Oral $AUC_{(0-6\ h)}$ (μg×h/mL)	T_{max} (h)	C_{max} (μg×h/mL)
1	30	2.09±0.45	1	1.2±0.28
3	30	17.76±4.95	3	3.69±1.89

Data collected in male ICR mouse using a dose formulation of the free acid in CMC/SLS/Povidone (30 mg/kg). Timepoints: 1, 3, 8 h (serial sacrifice, $n=3$/time point).

representative fluoro replacement compound and showed a marked improvement in AUC relative to the parent compound **1**.

In summary, we have demonstrated that fluorine substitution at specific positions in the trienoic acid moiety can maintain the desired in vitro profile exhibited by compound **1**. We have also demonstrated that the RXR homodimer activity can be dramatically altered by the position of the fluorine on the trienoic acid moiety. While the 2- and 6-fluoro analogues (compounds **5** and **3**) show the same RXR homodimer antagonist profile of our reference compound **1**, the 4- and 5-fluoro analogues (compounds **4** and **2**) are RXR homodimer agonists. In some instances, fluorine introduction may also result in improved pharmacokinetic properties for these modulators. Further studies to examine the potential of heterodimer selective RXR modulators for the treatment of NIDDM and other metabolic disorders are ongoing.

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