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Design and synthesis of benzofused heterocyclic RXR modulators

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Abstract—Benzofused heterocyclic analogs 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 choice of heterocycle as well as the sidechain employed.

1. 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 γ (PPARγ) plays a major role in the regulation of both glucose and lipid metabolism.[3] Selective RXR modulators such as **1** (LG101506), have been described as hypoglycemic agents[4] (Fig. 1). Recently, analogs of this compound in which the 6–7 olefin of the trienoic acid moiety is locked into the *cis*-conformation showed potent RXR activity and very good selectivity.[5] As part of our ongoing SAR we replaced the trienoic acid portion of these compounds with benzofused heterocycles in an attempt to increase the stability of the trienoic acid moiety while maintaining the potent activity.

2. Chemistry

Compounds **4** and **5** were constructed using the same benzophenone intermediate **20** (Scheme 1). Compound **20** was prepared by adding the aryllithium derived from **17**[6] to aldehyde **18** followed by oxidation of **19**. Conversion to the heterocycle was accomplished by displacement of fluorine with the appropriate nucleophile and intramolecular condensation to provide **21** and **22**. A Heck coupling with methyl crotonate, followed by hydrolysis yielded the final compounds **4** and **5**.

The remainder of the compounds were synthesized by coupling of the appropriate heterocyclic triflate or halide with an aryl boronic acid. For example, in Scheme 2, the enol triflate of **25** was coupled with aryl boronic acid **26** to provide **27**. A subsequent Horner–Emmons reaction followed by hydrolysis extended ketone **27** to the fully elaborated butenoic acid.

The synthesis of compound **9**, was accomplished as depicted in Scheme 3. The known thienopyridine **29**,[7] was brominated and coupled with aryl boronic acid **31**. The ketone was converted to the butenoic acid as described above.

In Scheme 4, the butenoic acid methyl ester was attached first through a Heck coupling with **34**, followed by cyclization to the imidazopyridine **36**.[8] Suzuki coupling with the iodide **37** and subsequent hydrolysis provided compound **10**.

The indole derivatives were made in a similar fashion (Scheme 5). The protected indol-5-yl-butenoic acid methyl ester **40** was iodinated and coupled with a variety of aryl boronic acids to provide compounds **11**–**15**.

Keywords: RXR; Heterocycles; Trienoic acid.
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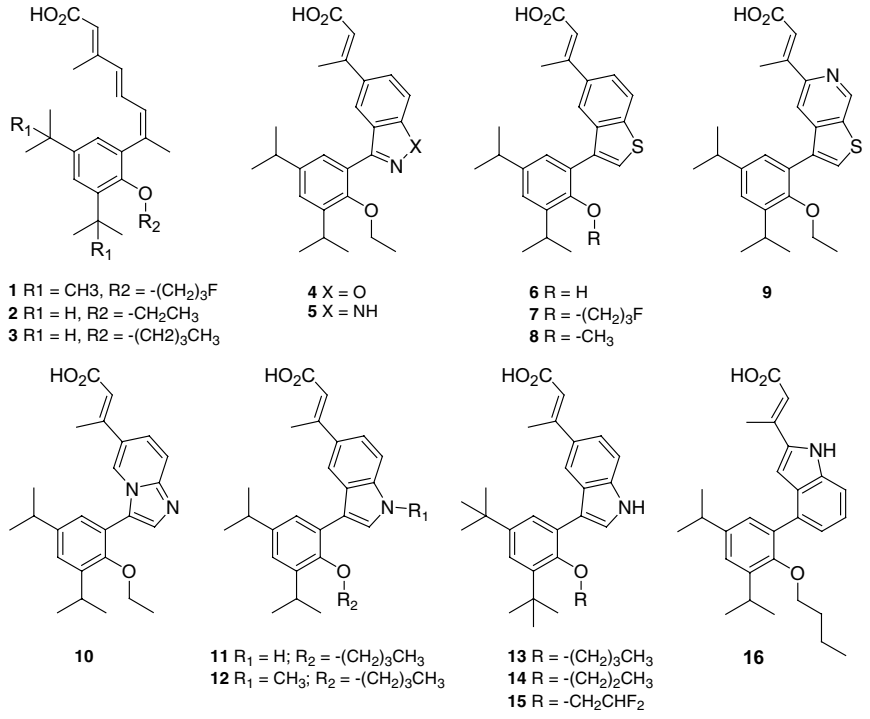
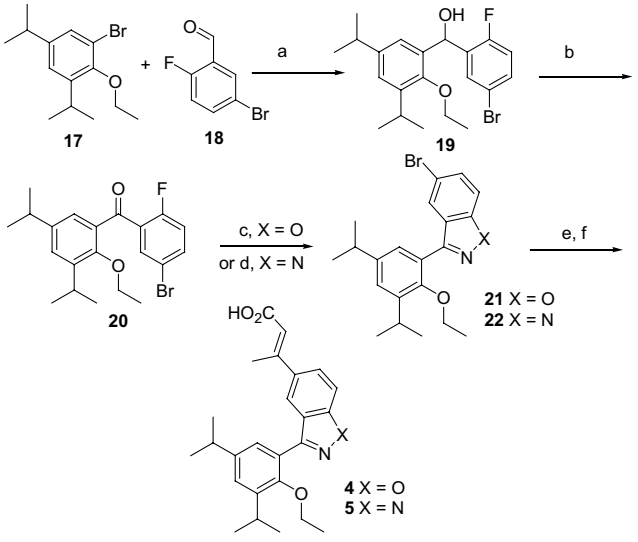
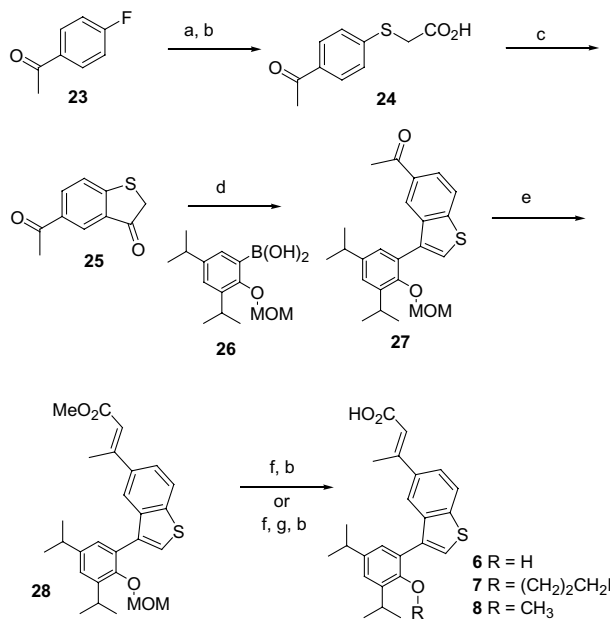


Figure 1. Benzofused heterocyclic analogs.



Scheme 1. Reagents and conditions: (a) *t*-BuLi, DME, 66%; (b) PCC, DCM, 94%; (c) acetone oxime, *t*-BuOK, THF, **21**: 40%; (d) (1) benzophenone hydrazone, *t*-BuOK, THF (2) 5 N HCl, EtOH, reflux, **22**: 16%; (e) methyl crotonate, $Pd_2(dba)_3$, P(*o*-tol)$_3$, TEA, DCM, 120 °C, X = O or N, 32%; (f) 1 N NaOH, MeOH, **4**: 80%, **5**: 80%.

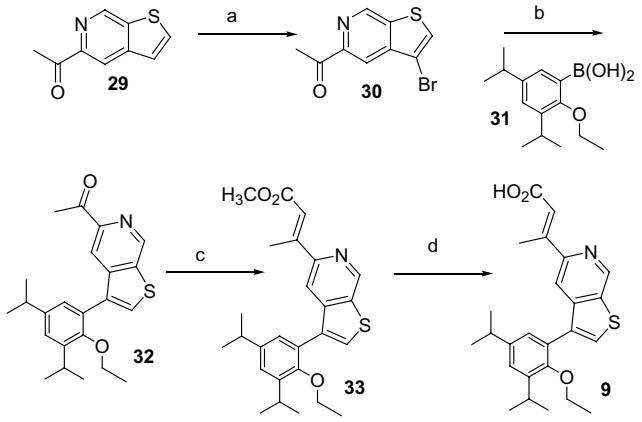


Scheme 2. Reagents and conditions: (a) $HSCH_2CO_2CH_3$, NaH, DMF, 81%; (b) LiOH, THF/H_2O, 94%; (c) $S(O)Cl_2$, $AlCl_3$, DCE, 79%; (d) (1) LDA, Tf_2NPh, THF; (2) **26**, $Pd(P(Ph_3)_4)$, 2 M Na_2CO_3, toluene, EtOH, 0 °C, 40%; (e) NaH, methyl diethylphosphonoacetate, DMF, 25%; (f) HCl, MeOH; (g) CeF, alkylhalide, DMF.

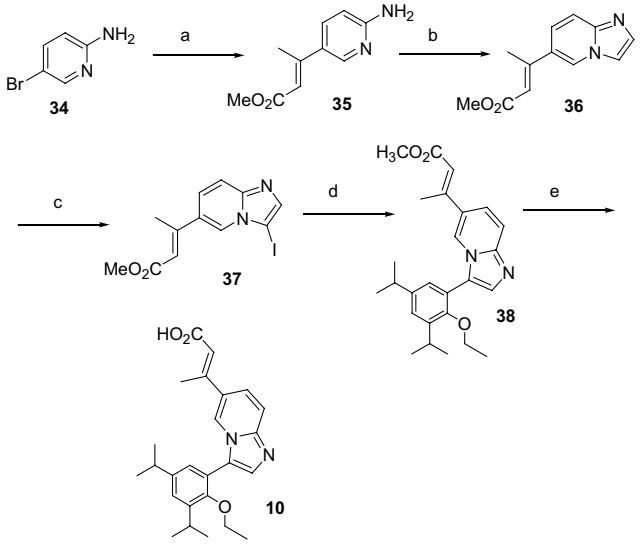
In order to further explore indole as a replacement for the trienoic acid the heterocycle orientation was reversed, as shown in Scheme 6. Gribble's methodology,[9] which takes advantage of the *ipso* directing ability of silicon, was used to access the 2-indolyl ketone **46**. A Horner–Emmons reaction resulted in **47** followed by Suzuki coupling and deprotection to give **16**.

3. 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).[10]



Scheme 3. Reagents and conditions: (a) Br_2, CCl_4/H_2O, 36%; (b) **31**, $Pd(P(Ph_3)_4)$, 2 M Na_2CO_3, toluene, EtOH, 90 °C, 91%; (c) NaH, methyl diethylphosphonoacetate, DMF, 61%; (d) 1 N NaOH, MeOH.

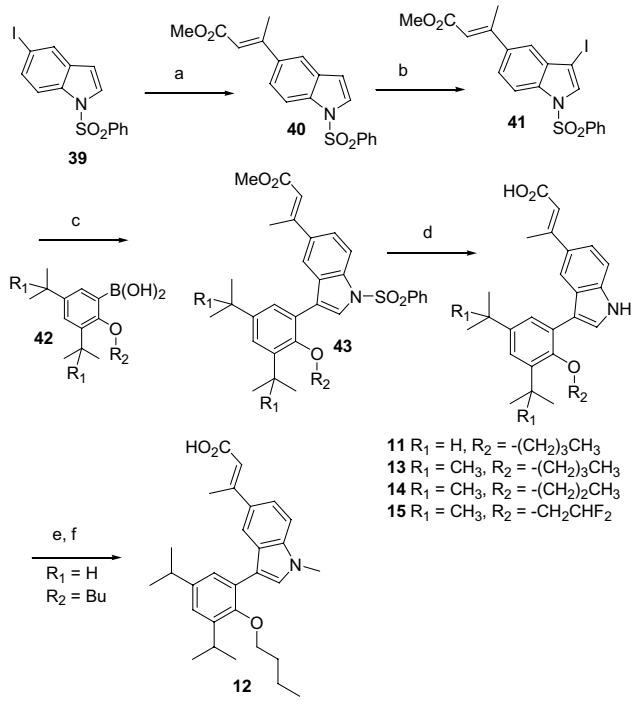


Scheme 4. Reagents and conditions: (a) methyl crotonate, $Pd_2(dba)_3$, P(*o*-tol)$_3$, TEA, DCM, 120 °C, 41%; (b) $BrCH_2CH(OCH_3)_2$, Na_2CO_3, H_2O, 31%; (c) NIS, CH_3CN, 50%; (d) **31**, $Pd(P(Ph_3)_4)$, 2 M Na_2CO_3, toluene, EtOH, 90 °C, 76%; (e) 1 N NaOH, MeOH, 78%.

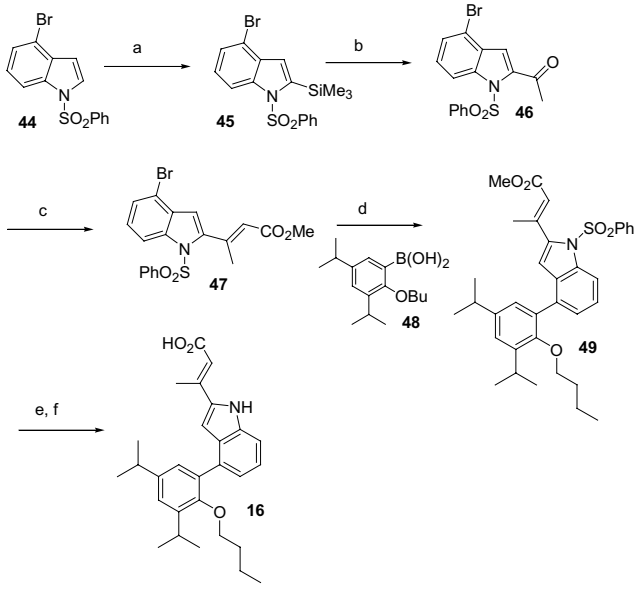
Most of the benzofused heterocycles showed significant reduction in binding to RXR. Only three scaffolds (**5**, **8**, and **11**) were below 100 nM. Of these only the indole scaffold showed binding similar to its corresponding acyclic analog (compound **3**).

The RXR homodimer transcriptional activation profile of each compound was determined in CV-1 cells and efficacy is reported relative to all-*trans*-retinoic acid.[11] All the compounds showed similar agonist and antagonist profiles to the corresponding acyclic analogs. While these compounds maintained similar efficacy to their acyclic counterparts, only the indole compound **11** had similar potency.

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.[11] Compound **1** was shown to synergize with BRL49653 to enhance activation at the RXR:PPARγ heterodimer but did not synergize with



Scheme 5. Reagents and conditions: (a) methyl crotonate, TEA, $Pd(OAc)_2$, DMF, 40%; (b) NIS, *p*-TsOH, CH_2Cl_2, Florosil pad, 44%; (c) **42**, $Pd(P(Ph_3)_4)$, 2 N Na_2CO_3, toluene, 80 °C, 31–58%; (d) 2.5 N KOH, EtOH, dioxane, 60 °C, 54%; (e) MeI, Cs_2CO_3, DMF, 40 °C, 86%; (f) 1 N NaOH, MeOH, dioxane, 60 °C, 52%.



Scheme 6. Reagents and conditions: (a) (1) LDA, THF, −73 °C; (2) TMSCl, 67%; (b) $AlCl_3$, CH_2Cl_2, Ac_2O, 51%; (c) $(EtO)_2P(O)CH_2CO_2CH_3$, KO*t*-Bu, DMF, 50 °C, 28%; (d) **48**, $Pd(P(Ph_3)_4)$, 2 N Na_2CO_3, toluene, 75 °C, 48%; (e) 1 N NaOH, MeOH, dioxane, 60 °C, 58%; (f) 2.5 N KOH, EtOH, dioxane, 60 °C, 53%.

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

Compound	RXRα binding K_i, nM[a]	RXRα agonist %efficacy (EC_{50}, nM)[b]	RXRα antagonist %efficacy (EC_{50}, nM)[b]	RXRα:PPARγ agonist %efficacy (EC_{50}, nM)[c]	RARγ binding K_i, nM[d]	RAR agonist synergy[e]
1	2.7	4	84 (6.4)	60 (3.1)	>10,000	1.4
2	2	58 (2)	7	38 (8)	>10,000	5
3	4	2	91 (4)	12 (1894)	>10,000	1
4	648.0	36 (1024)	24	65 (306.4)	>10,000	1.7
5	69.2	43 (235)	7	168 (118)	>10,000	2.4
6	131.0	37.4 (1438)	0	112 (383.54)	>10,000	3.5
7	394.7	1.78	48 (4154)	123.1 (1481)	>10,000	1.5
8	29.6	65.41 (914)	0	114.0 (224.25)	>10,000	2.7
9	NT[f]	15.1 (1442)	9	127.34 (347.3)	NT[f]	2.0
10	2078.3	7.93	9	81.82 (424.86)	>10,000	1.5
11	7.4	1.7	87 (21.1)	256.1 (15.03)	>10,000	1.3
12	740.0	2.52	86 (1533)	49 (611.9)	>10,000	2.5
13	3.2	1	93 (26.4)	105 (8.9)	>10,000	2.3
14	1.6	7	81 (30.1)	173 (7.0)	>10,000	3.4
15	1.6	15 (65)	41 (66.3)	233 (21.9)	>10,000	3.0
16	NT[e]	0.51	64 (3976.3)	24.9 (892.94)	NT[e]	1.1

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.
[f] Not tested.

TTNPB to enhance activation at the RXR:RAR heterodimer. All of the benzofused heterocyclic compounds showed better efficacy than their acyclic comparator, with many compounds showing greater than 100% (**5**, **6**, **7**, **8**, **9**, and **11**).

The indole compound (**11**) was particularly interesting. It had slightly reduced binding affinity, and was less efficacious and less potent in the homodimer profiling assay than its acyclic comparator (**3**). However, it was much more efficacious (256% for **11** compared to 12% for **3**) and much more potent in the heterodimer assay (15 nM for **11** compared to 1894 nM for **3**). Based on this data, more analogs of the indole compound **11** were synthesized.

It was quickly recognized that changes similar to those used to optimize the trienoic acid series (resulting in compound **1**) were also effective in enhancing the RXR binding of the benzofused compounds, as compounds **13**, **14**, and **15** all are more potent than the initial compound **11**. These changes did not result in improvement in the homodimer activity and in the case of compound **15** (the compound most like **1**) the antagonist efficacy and potency was significantly decreased and some agonist activity was noted. This change was also noted in the heterodimer assay as the efficacy of compounds **13**, **14**, and **15** was reduced while the change in potency was marginal. In addition, enhanced synergy with RAR was noted with compounds **13**, **14**, and **15** over **11**.

Other changes to the indole scaffold resulted in more dramatic changes in activity. For example, methylation of the indole nitrogen to give compound **12** resulted in a 100-fold reduction in binding affinity, with similar effects on the homo and heterodimer activity. Compound **16** was made to test whether the orientation of the indole made a difference in the activity of the compounds and it was less efficacious and potent than compound **11**.

In summary, we have demonstrated that benzofused heterocycles can be substituted in place of the trienoic acid moiety, and can maintain the desired in vitro profile. We have also demonstrated that the RXR homodimer activity can be altered by the type of heterocycle employed. The data suggests that the increased bulk of the heterocycle, as compared with the trienoic acid scaffold, changes the orientation of these compounds in the RXR ligand binding domain slightly so that they require less bulk on the pendant benzene ring. 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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