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Design, synthesis and structure–activity relationship of novel RXR-selective modulators

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Abstract—The synthesis and in vitro characterization of novel RXR-selective ligands possessing various substituted 1-benzofuran or 1-benzothiophene moieties are described.

Retinoids play a major role in a wide variety of biological functions, such as cell differentiation, proliferation and embryonic development in vertebrates.[1] A*ll-trans-retinoid acid* (ATRA, Fig. 1), 13-*cis*-retinoid acid (13-*cis*-RA, Fig. 1), 9-*cis*-retinoid acid (9-*cis*-RA, Panretin®, Fig. 1) and more recently the RXR selective LGD1069 (Targretin®, Fig. 1), have been administered for treatment of numerous skin diseases like psoriasis, acne, Karposi's sarcoma and CTCL.[2] Moreover, there is evidence that retinoids may be useful in the treatment and prevention of various other cancers.[3] The retinoid receptors belong to the superfamily of intracellular nuclear receptors, which function to regulate gene transcription.[4] They are divided into two families of homologous receptors, the retinoic acid receptors (RARs) and the retinoid x receptors (RXRs), each divided into three sub-types α, β and γ encoded by a single gene.[5] RXR has long been recognized to both form homodimers and to heterodimerize with various other nuclear receptors, such as RAR, TR, VDR, NGFIB, LXR, FXR and PPARs.[1,5] Because of this unique profile, RXR is a very interesting drug target and new synthetic RXR-selective ligands may have new and interesting applications.

Previously, we published the synthesis and biological evaluation of novel trienoic acids (LG101506, Fig. 1) and 6,7-locked-trienoic acid RXR-selective modulators.[6–9] Here, we describe the design and synthesis of novel RXR-selective ligands possessing a 4,5- and 6,7-'double-locked' trienoic acid moiety as shown in Figure 2.

The boronate **3** was synthesized in 74% yield from the known 2-acetyl-4-iodo-1-benzothiophene[10] using the method described by Murata and Al.[11]

2-Acetyl-7-iodo-1-benzothiophene **5** was synthesized according to the same scheme described for **2** from 2-fluoroiodobenzene. The triflate derivative **7** was easily prepared from the commercially available 2-acetyl-7-hydroxybenzofuran **6** in excellent yield (>90%) (Scheme 1).

The synthesis of the acids **32–39** possessing a 2,7-disubstituted-1-benzothiophene was realized according to Scheme 2. Suzuki coupling of **3** with the iodides **8–15** in the presence of $PdCl_2$(dppf) and 2M Na_2CO_3 in refluxing DME afforded the corresponding adducts **16–23** in good yields (>75%). The esters **24–31** were synthesized by condensation of the anion of the triethylphosphonoacetate (generated from slow addition of triethylphospho-

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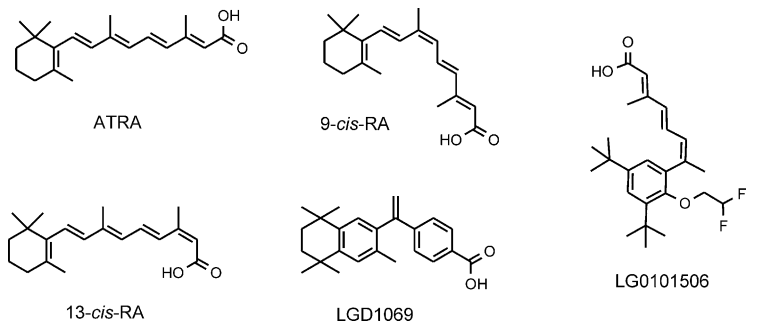


Figure 1.

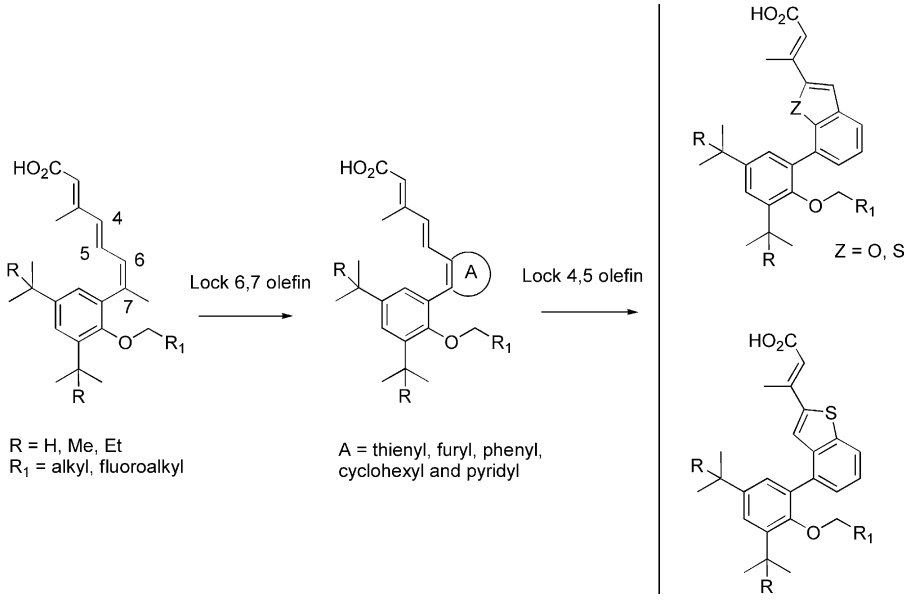
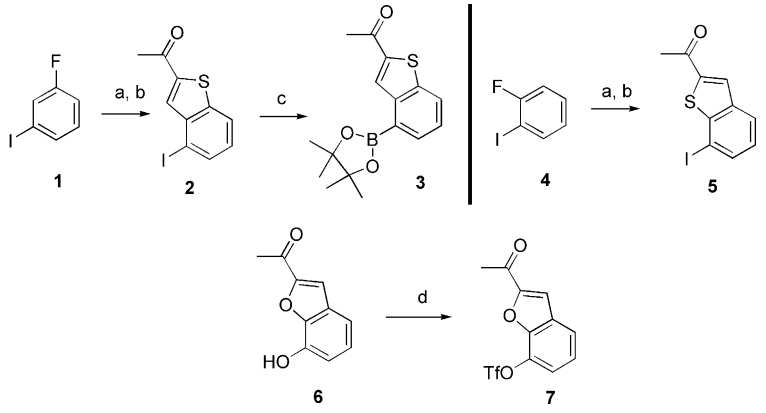
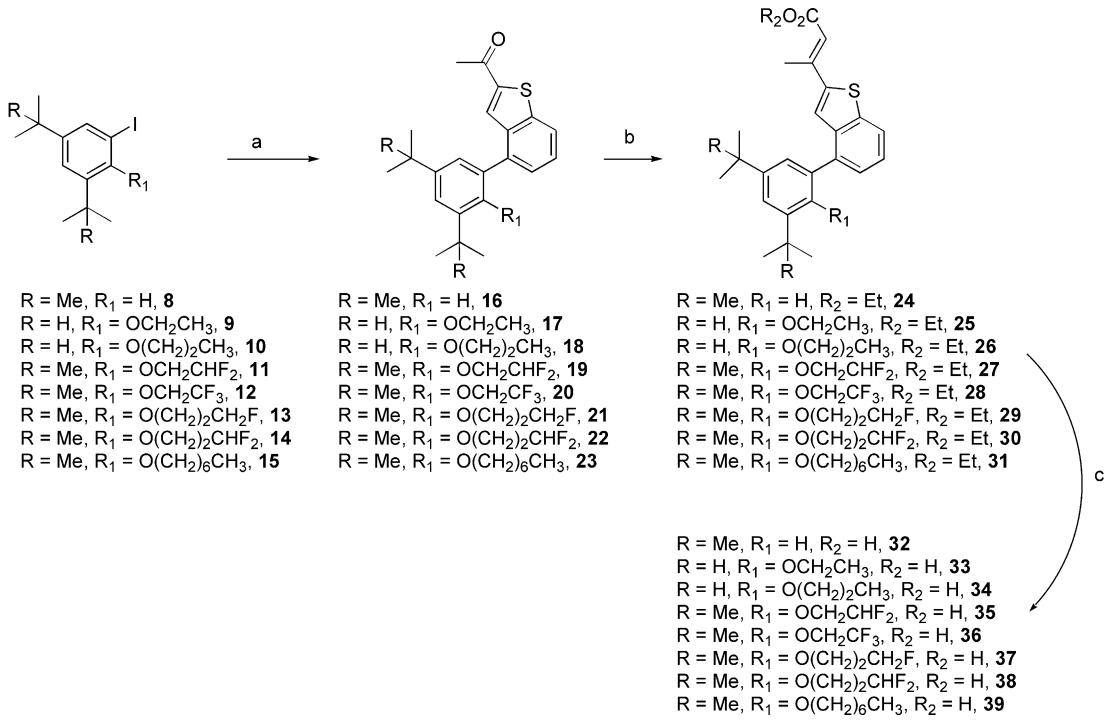


Figure 2. Design of novel RXR ligands possessing a benzo[*b*]thiophene or benzo[*b*]furan core.



Scheme 1. 2,4 and 2,7-disubstituted 1-benzothiophene and 1-benzofuran synthesis. Reagents: (a) LDA, DMF, −78 °C to rt; (b) 3-mercaptopropanone, Et_3N, DMSO, 60 °C; (c) $PdCl_2$(dppf), pinacol borane, dioxane, Et_3N, 80 °C; (d) Tf_2O, Hunig's base, CH_2Cl_2.



Scheme 2. 2,4-Disubstituted 1-benzothiophene RXR modulators synthetic scheme. Reagents: (a) $PdCl_2$(dppf), **3**, DME, 2M Na_2CO_3, reflux; (b) Triethylphosphonoacetate, NaH, DMF, 0–60 °C; (c) LiOH, THF/MeOH then HCl followed by recrystallization from CH_3CN.

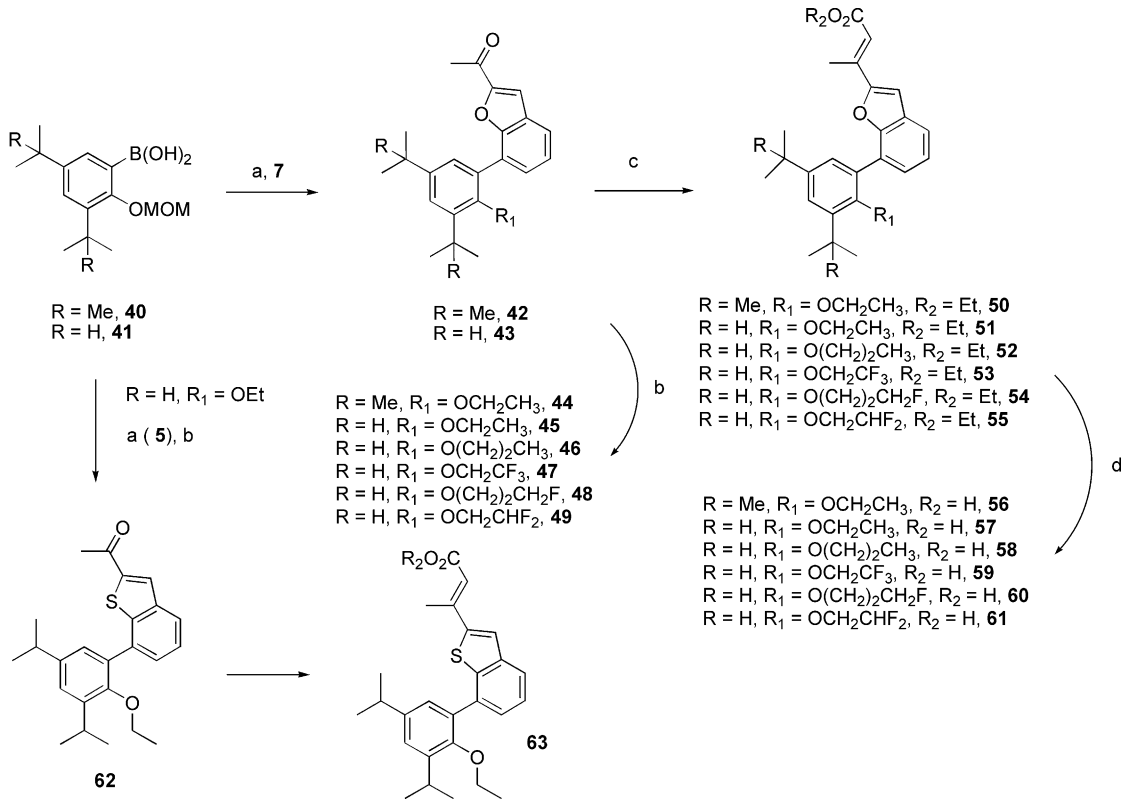
noacetate in a suspension of NaH in DMF at 0 °C) at 60 °C. Hydrolysis (LiOH/MeOH/THF, reflux) followed by recystallization from CH_3CN released the desired acids **32**–**39** in excellent yields (>80%).

The derivatives **56**–**61** and **63** possessing a 2,4-disubstituted-1-benzofuran and a 2,4-disubstituted-1-benzothiophene moieties were synthesized according to Scheme 3. The sequence follows the same general route described in Scheme 2 from the boronic acids **40** and **41** and the intermediates **5** and **7**. Alkylation of the corresponding adducts with various alkyl bromides in the presence of Cs_2CO_3 affords the derivatives **44**–**49** and **62** in excellent yields (>90%). The last steps of the sequence are identical to Scheme 2. The acids **56**–**61** and **63** were isolated after recrystalization from CH_3CN.

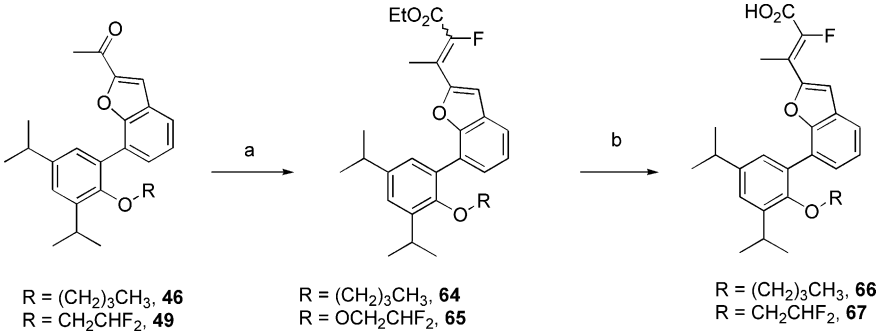
In previous communications, we demonstrated that the introduction of a fluorine on the trienoic acid moiety has a dramatic effect on the metabolic properties of such molecules.[8,9] Scheme 4 describes the introduction of a fluorine at the α-position of the acidic moiety. This was easily realized by condensation of the anion of ethyl-2-fluorophosphonoacetate (generated by addition of ethyl-2-fluorophosphonoacetate to a suspension of NaH in DMF at 0 °C) on the ketones **46** and **49**. The corresponding esters **64** and **65** were isolated in good yield (>80%) as a mixture of isomers. Hydrolysis of these esters followed by acidic work up and HPLC purification released the acids **66** and **67** in moderate yield (<50%).[12]

Tables 1 and 2 describe the binding affinity and the in vitro profiling of compounds **32**–**39**, **56**–**61**, **63**, **66**, and **67**.[13] All the compounds show a remarkable selectivity for RXRs over RARs. In fact, except **32** and **59** (Table 1, entries 3 and 14), all the compounds are more selective for RXR than our standard, LG101506 (Table 1, entry 2). LG101506 shows weak affinity for RARα and RARβ of 2745 and 3515 nM, respectively (Table 1, entry 2), **32** has a weak K_i of 1786 nM for RARα (Table 1, entry 3) and **59** has a weak K_i of 2700 nM for RARβ (Table 1, entry 14). Otherwise, no RARα,β or γ binding is generally observed (K_i > 5000 nM). All the compounds show a good affinity for RXRα, except compounds **59**, **61**, **63** or **67** (Table 1, entries 14, 16, 17 and 19) which have a K_i for RXRα > 100 nM. All the compounds possessing a 7-disubstituted-1-benzothiophene scaffold (compounds **32** to **39**) bind to RXRα with high affinity (K_i < 15 nM). This particular scaffold appears to be better for RXR activity than its 2,4-disubstituted analogues or the 2,4-disubstituted-1-benzofuran. More interestingly, the RXR binding of each compound possessing the 2,7-disubstituted-1-benzothiophene moiety remains in the same potency range independent of R_1 while both other scaffolds tested show a dramatic change in RXR binding when R_1 gets bulkier.

Table 2 describes the co-transfection activity of compounds **32**–**39**, **56**–**61**, **63**, **66** and **67**. Previous SAR studies have shown that the alkoxy side chain plays a critical role in modulating the RXR activity of such compounds.[6,14] As a general rule, a short alkoxy side chain (methoxy or ethoxy) usually produces agonist activity; while a longer one (propoxy and longer) produces antagonist activity. The same trend is observed here with compounds **32**–**39**, **56**–**61**, **63**, **66** and **67** except no compound shows a full agonist profile against LG100268 (Table 2, entry 1). Compounds **32**, **57** and **63**



Scheme 3. 2,7-Disubstituted 1-benzofuran and 1-benzothiophene RXR modulators synthetic scheme. Reagents: (a) $Pd(PPh_3)_4$, **6** or **7**, toluene/EtOH, 2 M Na_2CO_3, reflux. (b) R-Br, Cs_2CO_3, DMF, rt. Steps (c) and (d) identical of these described in Scheme 2 (b,c).



Scheme 4. Fluorinated 2,7-disubstituted-1-benzofuran RXR modulators synthetic scheme. Reagents: (a) Ethyl-2-fluorophonoacetate, NaH, DMF, 0 °C to rt; (b) 2 N aqueous LiOH, THF/MeOH, reflux then 2 N aqueous HCl and recrystallization from CH_3CN.

are RXR agonists but show only modest efficacy (Efficacy $<45\%$) in our co-transfection assay (Table 2, entries 3, 12, and 17). Moreover, compound **63** has a weak EC_{50} (390 nM) in addition to its low efficacy. Compounds **33** and **56** are partial RXR agonists and also have some RXR antagonist activity (Table 2 entries 4 and 11). All the other compounds (**34**–**39**, **58**–**61** and **66**–**67**) are RXR antagonists in our co-tranfection assay, however, compounds **39**, **58**, **59**, **60** and **61** have weak potency ($83 < IC_{50} < 347$ nM). Compounds like **36**, **37** and **66** are full RXR antagonists (Efficacy $>90\%$, $IC_{50} < 11$ nM).

As a result, we have described novel molecules acting as RXR agonists (**32**, **57**, and **63**), RXR partial agonists (**33** and **56**) and RXR antagonists (**34**–**39**, **58**–**61** and **66**–**67**). Compounds **32**–**39** and **66** possess roughly the same binding affinity for RXR (low nanomolar). Compounds **32**–**39** possess a 7-disubstituted-1-benzothiophene scaffold while **66** possess a fluorinated 2,4-disubstituted-1-benzofuran scaffold. The introduction of a fluorine in the 2-position of the crotonic acid moiety (compounds **66** and **67**) increases the binding affinity and co-transfection activity for RXR of these compound compared to their respective non-fluorinated analogues (**58** and **61**).

Table 1. Binding data for RXRα, RXRβ, RXRγ, RARα, RARβ and RARγ. All data shown in nM

Entries	Compd	RXRα K_i (nM)	RXRβ K_i (nM)	RXRγ K_i (nM)	RARα K_i (nM)	RARβ K_i (nM)	RARγ K_i (nM)
1	**LG100268**	18±1	18±12	39±21	>1000	>1000	>1000
2	**LG101506**	3±2	7.5±2.5	12±2	2745	3515	>10,000
3	**32**	7±2	33±11	54±12	1786	>10,000	>10,000
4	**33**	6±1	11±2	12±3	>10,000	5940	>10,000
5	**34**	14±2	15±4	20±3	6910	>10,000	>10,000
6	**35**	12±4	55±12	20±14	8360	>10,000	>10,000
7	**36**	3±2	10±2	20±9	>10,000	>10,000	>10,000
8	**37**	3±2	10±3	21±6	7280	>10,000	>10,000
9	**38**	7±3	12±4	37±12	>10,000	>10,000	>10,000
10	**39**	5±1	12±3	28±5	>10,000	>10,000	>10,000
11	**56**	19±11	12±3	29±5	>10,000	>10,000	>10,000
12	**57**	22±11	NT	NT	>10,000	>10,000	>10,000
13	**58**	44±1	NT	NT	8500	9200	>10,000
14	**59**	198±80	142±64	334±53	NT	2700	>10,000
15	**60**	47±10	NT	NT	>10,000	>10,000	>10,000
16	**61**	161±62	261±45	500±96	>10,000	>10,000	>10,000
17	**63**	271±95	NT	NT	6024	5736	>10,000
18	**66**	16±8	64.5±15	28±12	>10,000	>10,000	>10,000
19	**67**	101±50	4±2	49±16	>10,000	>10,000	>10,000

NT: Not tested.

Table 2. In vitro profiling of RXR modulators in CV1 cells. K_i calculated using [^{3}H]-9-*cis*-RA for RXR and [^{3}H]-ATRA for RAR. All data shown is in nM

Entries	Compd	RXRα Agonist Efficacy	RXRα Agonist EC_{50}	RXRα Antagonist Efficacy	RXRα Antagonist IC_{50}
1	**LG100268**	70±21	11±10	12	0
2	**LG101506**	4±2	NC	84±10	8±4
3	**32**	43±15	39±8	8±11	NC
4	**33**	21±13	20±10	26±6	NC
5	**34**	4	NC	81±8	16±12
6	**35**	1	NC	79±13	24±14
7	**36**	1	NC	93±1	14±5
8	**37**	0	NC	94±0	8±1
9	**38**	0	NC	94±1	16±7
10	**39**	2	NC	96±0	83±63
11	**56**	19±67	86±43	64±0	20±13
12	**57**	31±27	74±23	10±2	NC
13	**58**	4	NC	74±5	129±68
14	**59**	4	NC	76±6	347±101
15	**60**	1	NC	84±0	194±13
16	**61**	7	NC	67±6	300±74
17	**63**	35±1	390±110	5	NC
18	**66**	1	NC	93±1	11±6
19	**67**	16	NC	62±22	22±2

In conclusion, we have described a new series of RXR-selective compounds. Both a 1-benzothiophene and a 1-benzofuran moiety have been used to successfully replace the trienoic acid moiety present in our lead compound LG101506. We have demonstrated that a 2,7-disubstituted-1-benzothiophene is a better replacement of the parent trienoic acid. Using this new molecular template, we have synthesized compounds that cover a wide spectrum of activity for the RXR receptor (agonist, partial agonist and antagonist) without altering the binding affinity for RXR of such molecules. None of the compounds described bind to RAR. These new RXR-selective ligands were synthesized in only five steps from commercially available phenols or bromides.

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