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Design, synthesis and evaluation of trifluoromethane sulfonamide derivatives as new potent and selective peroxisome proliferator-activated receptor α agonists

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Abstract—Starting from the structure of **5**, a two-step strategy was applied to identify a new generation of trifluoromethane sulfonamides as potent PPARα agonists. Synthesis, in vitro and in vivo evaluation of the most potent compound are reported.

Peroxisome proliferator-activated receptors (PPARs) are members of the superfamily of nuclear transcription factors regulating lipid metabolism. Upon ligand binding, PPARs heterodimerize with the retinoid X receptor (RXR) and the resulting heterodimers regulate gene expression by binding to specific peroxisome proliferator response elements (PPRE) located in the regulatory regions of the target genes.[1]

Three PPAR subtypes have been isolated to date (PPARα, PPARδ, and PPARγ) and each subtype displays distinct tissue-selective expression patterns, ligand selectivity, and biological actions.[2,3] PPARα is mostly expressed in organs with a high rate of fatty acid catabolism such as the liver where it regulates the expression of genes encoding for proteins involved in lipid and lipoprotein metabolism.[4] The fibrates (Fig. 1, Fenofibrate **1**, Bezafibrate **2**, Ciprofibrate **3**, and Clofibrate **4**) have been widely used for the clinical treatment of dyslipidemia since these drugs can effectively decrease triglyceride (TG), low-density lipoprotein cholesterol (LDLc), and very-low-density lipoprotein cholesterol (VLDLc) levels, and increase high-density lipoprotein cholesterol (HDLc) level.[5] These beneficial pharmacological effects of fibrates are thought to be mediated in part by PPARα activation,[6] but the fibrates are neither particularly potent nor very selective for PPARα. Consequently, in humans, fibrates must be used at very high doses (about 300–1200 mg/day) to achieve a sufficient lipid-lowering effect.[7] Therefore, the search for more potent and selective activators of PPARα could lead to the discovery of activators potentially superior to fibrates for the treatment of altered lipid homeostasis. Here, we describe the design and synthesis of novel trifluoromethane sulfonamide derivatives as potent human PPARα selective activators.

We have recently reported the design and evaluation of a novel substituted thiazole **5** (GW590735) as a potent and selective PPARα agonist.[8] In the present studies, modification or replacement of the oxyisobutyric acid found in classical fibrates was carried out starting from **5** (Fig. 2). This modification was followed by a subsequent replacement of the phenylthiazole moiety thus leading to a new class of PPARα agonists.

The oxyisobutyric acid head group was replaced by fragments containing a range of bioisosteres from the more generally used tetrazole **7** to the less common 3-hydroxy-3-cyclobutene-1,2-dione **8** (Table 1, compounds **6**–**10**).[9,10] All compounds were prepared following standard O-alkylation, N-acylation or N-sulfonylation procedures except for compound **7** which was prepared by

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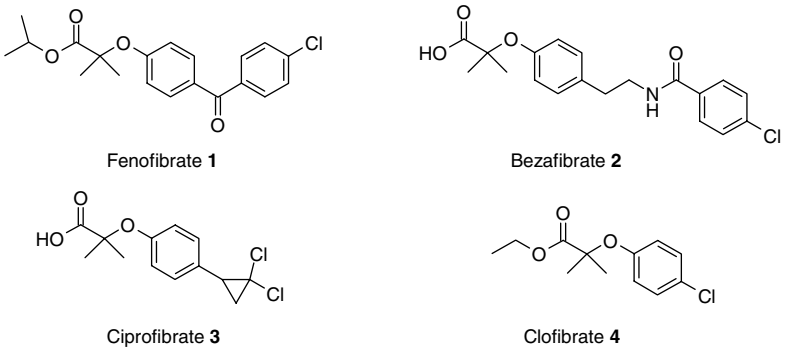


Figure 1. Chemical structures of the marketed Fibrates.

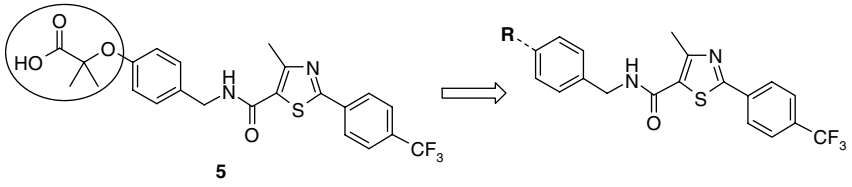
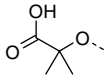
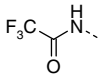
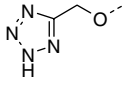
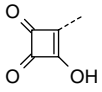
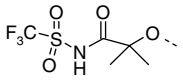
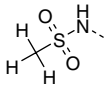


Figure 2. Design of new PPARα agonists.

Table 1. In vitro evaluation of PPARα agonists on both murine (m) and human (h) receptors[b]

Compound	R[a]	EC_{50} (μM) h PPARα (%activation)[c]	EC_{50} (μM) m PPARα (%activation)[c]	EC_{50} (μM) h PPARδ (%activation)[c]	EC_{50} (μM) m PPARδ (%activation)[c]	EC_{50} (μM) h PPARγ (%activation)[c]	EC_{50} (μM) m PPARγ (%activation)[c]
5		0.004 (95)	0.02 (103)	2.8 (82)	1.7 (101)	9.7 (29)	9.7 (19)
6		0.45 (79)	>10	>10	>10	>10	>10
7		>10	>10	>10	>10	>10	>10
8		>10	>10	>10	>10	>10	>10
9		>10	>10	>10	>10	>10	>10
10		0.06 (100)	0.8 (78)	>10	>10	>10	>10

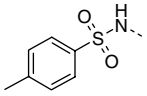
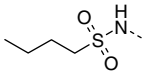
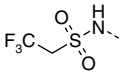
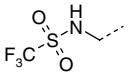
[a] The R substituent refers to Figure 2.
[b] Data generated using cell based transient transfection assays.[13]
[c] % of maximal activation of all compounds was compared to reference compounds normalized to 100%. For the PPARα activity, the reference compound was **5**. For the PPARδ and PPARγ activities, the reference compounds were GW516 and rosiglitazone, respectively.

alkylation of the phenol with chloroacetonitrile followed by the tetrazole formation using the DBTO method developed by Wittenberger and Donner,[11] and for compound **8** which was prepared via the Liebeskind stannane.[10]

Compounds **7** and **9**, employing two of the most common carboxylic acid bioisosteres, tetrazole and acyl sulfonamide,[12] showed no in vitro activity when tested for their agonist activity on PPAR-GAL4 chimeric receptors in transiently transfected CV-1 cells.[13]

However, encouraging results were observed with the methane sulfonamide analogue **10**, which showed an EC_{50} of 60 nM on human PPARα. Consequently, a set of different sulfonamide derivatives was synthesized and tested in vitro (Table 2). All compounds from Table 2 were prepared using standard N-sulfonylation proce-

Table 2. Sulfonamides as PPARα agonists[b]

Compound	R[a]	EC_{50} (μM) h PPARα (%activation)[c]	EC_{50} (μM) m PPARα (%activation)[c]	EC_{50} (μM) h PPARδ (%activation)[c]	EC_{50} (μM) m PPARδ (%activation)[c]	EC_{50} (μM) h PPARγ (%activation)[c]	EC_{50} (μM) m PPARγ (%activation)[c]
11		1 (79)	>10	>10	>10	>10	>10
12		0.05 (87)	>10	>10	>10	>10	>10
13[d]		0.32 (125)	>10	>10	>10	5.5 (69)	6.7 (52)
14		0.0003 (115)	0.002 (98)	0.4 (61)	0.3 (91)	0.5 (78)	0.6 (64)
15		0.003 (72)	0.06 (74)	>10	>10	0.3 (66)	0.3 (42)
16		0.08 (114)	>10	>10	>10	>10	>10

[a] The R substituent refers to Figure 2.
[b] Data generated using cell based transient transfection assays.[13]
[c] % of maximal activation of all compounds was compared to reference compounds normalized to 100%. For the PPARα activity, the reference compound was **5**. For the PPARδ and PPARγ activities, the reference compounds were GW516 and rosiglitazone, respectively.
[d] Sulfonylation was carried out on the 4-(*tert*-butoxycarbonylamino)aniline followed by TFA deprotection and HATU mediated coupling with 4-methyl-2-[4-(trifluoromethyl)phenyl]-1,3-thiazole-5-carboxylic acid to afford **13**.

dures using the corresponding sulfonyl chloride except for compound **14** which was prepared from triflic anhydride.

Although the aromatic sulfonamide **11** showed only weak potency, small alkyl sulfonamides were more effective (compounds **12–13**). It is noteworthy that the potency of the sulfonamides appeared to correlate with the acidity of the NH group as exemplified by compounds **10, 14**, and **15** with EC_{50}s of 60–0.3 nM. It could be hypothesized from docking experiments (not shown) that the sulfonyl group is overlapping the carboxylate of the fibrate head group making four hydrogen bonds with Ser-280, Tyr-314, Tyr-464, and His-440 as observed with GW590735.[8] The gem-dimethyl substituents of the fibrate head group which are directed into a lipophilic pocket bounded by Phe-273, Gln-277, Val-444, and Leu-456 could be replaced by the alkyl group of the sulfonamide. The selectivity versus PPARδ could arise from the relative hindrance of the protein side chains in PPARδ in this region compared to PPARα.

Having established that the trifluoromethane sulfonamide was more than ten times more potent in vitro than the original fibrate (0.3 nM for **14** vs. 5 nM for **5**), this acidic group was retained and SAR studies were performed on the remainder of the structure. Previous investigations on the SAR of **5** had demonstrated that the optimal structure for PPARα agonism comprised a benzylamine tethered to a biaryl unit via an amide bond.[8] Therefore, a further range of compounds of this general structure were prepared and tested (Fig. 3).

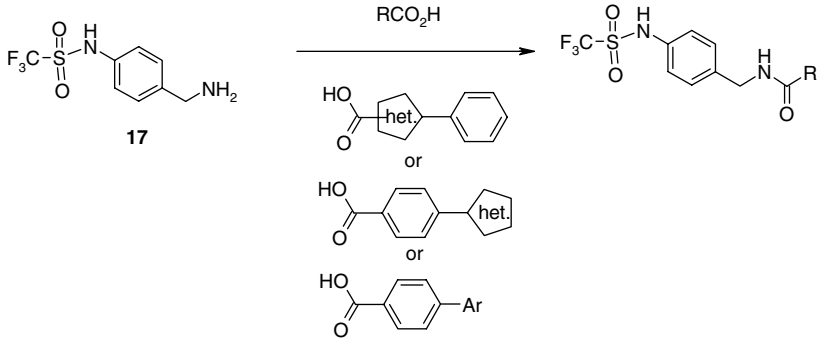
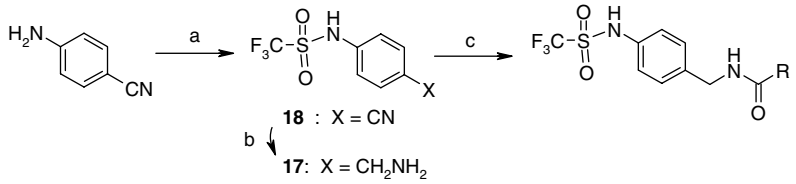


Figure 3. Focused array of trifluoromethane sulfonamides.

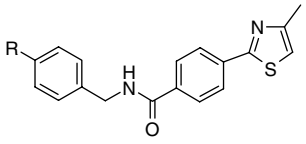
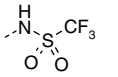
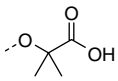
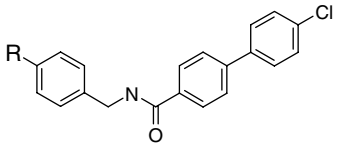
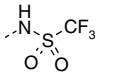
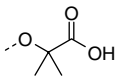
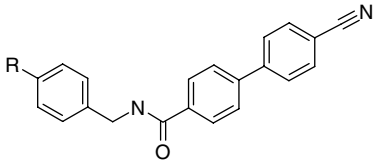
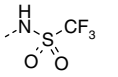
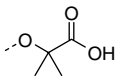
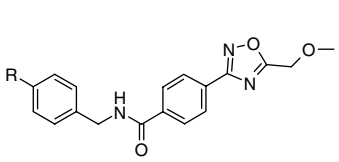
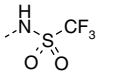
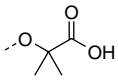
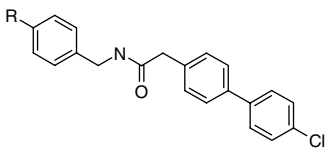
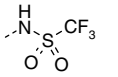
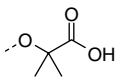
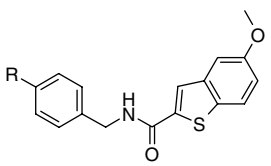
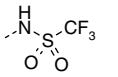
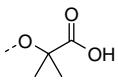
Sulfonylation of 4-cyanoaniline followed by catalytic hydrogenation of resulting nitrile **18** gave the benzylamine **17**. Further EDCI mediated coupling of **17** with the carboxylic acids furnished the targeted set of amides (Scheme 1).

A selection of the most potent and selective trifluoromethane sulfonamide agonists (EC_{50} for PPARα < 500 nM and at least 10-fold selective vs. PPARγ and PPARδ) was compared with the corresponding fibrates and in accordance with the previous observation



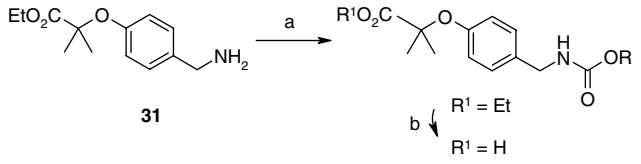
Scheme 1. Reagents and conditions: (a) $(F_3CSO_2)_2O$, Et_3N, CH_2Cl_2, 0 °C; (b) Pd/C, H_2, EtOH/AcOH, rt; (c) EDCI, DMAP, RCOOH, CH_2Cl_2, reflux then rt.

Table 3. In vitro activities of selected sulfonamides[a]

Structure	R	Compound	EC_{50} (μM) h PPARα (%activation)[b]	EC_{50} (μM) m PPARα (%activation)[b]
		**19**	0.06 (121)	0.08 (96)
		**25**	5 (107)	>25
		**20**	0.005 (138)	0.03 (123)
		**26**	0.07 (134)	1 (130)
		**21**	0.02 (133)	0.2 (152)
		**27**	1 (133)	>25
		**22**	0.36 (102)	0.7 (116)
		**28**	3 (135)	>25
		**23**	0.08 (120)	0.34 (97)
		**29**	2.8 (97)	>25
		**24**	0.08 (94)	0.13 (132)
		**30**	6 (133)	>25

[a] Data generated using cell based transient transfection assays.[13]

[b] % of maximal activation of all compounds was compared to compound **5** normalized to 100%.



Scheme 2. Reagents and conditions: (a) EDCI, DMAP, RCOOH, CH_2Cl_2, reflux then rt; (b) 1 N NaOH, EtOH, reflux.

with **14**, the trifluoromethane sulfonamide compounds were at least 8-fold more potent than their fibrate analogues (Table 3).

Interestingly, the sulfonamide derivatives were found to be more active on the murine isoform than their fibrate analogues.

Benzylamine **31** was prepared from 4-cyanophenol via alkylation with 2-bromo-2-methylpropionate and hydrogenation.[8] Fibrate derivatives were prepared from **31** by EDCI and DMAP mediated coupling followed by hydrolysis under standard conditions (Scheme 2).

The most potent trifluoromethane sulfonamide **20** was selected for in vivo evaluation to determine its efficacy in increasing HDL-cholesterol levels. The human Apo-A-I-transgenic mouse model was used because of its relevance to human disease since in this model fibrates upregulate Apo-A-I, the major lipoprotein of HDL particles.[14] The pharmacokinetic parameters of compound **20** were evaluated in mice and found to be suitable for chronic administration (Table 4). Total plasma clearance was low (0.78 mL/min/kg) with a half-life of 4.9 h. Following a single oral dose of compound **20** at 5 mg/kg, the maximum concentration of compound in the plasma was 4515 ng/mL and the bioavailability was 16%.

As shown in Table 5, oral administration of compound **20** at a dose of 20 mg/kg twice a day for 5 days induced a significant elevation of HDL-cholesterol (+102%) in addition to a lowering of serum TG and VLDL-cholesterol by 69% and 85%, respectively.

It is noteworthy that the pharmacological effects observed with compound **20** were almost exclusively PPARα related since only a weak and partial activity on PPARγ and no PPARδ activity were observed in vitro as shown in Table 6.

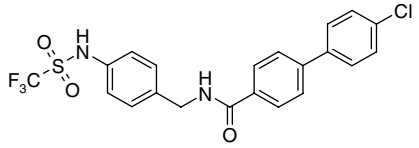
A two-step strategy was applied to the generation of new potent and selective PPARα agonists. The classical fibrate head group has been replaced by a trifluoromethane sulfonamide giving a new series of potent PPARα agonists. The finding that **20** is able to lower VLDLc and TG and increase HDL cholesterol in the Apo-A-I-transgenic mouse model suggests that it could deliver significant therapeutic benefit in the treatment of dyslipidemia and hypertriglyceridemia.

Table 4. Pharmacokinetic data for compound **20** in mice[a]

F %	Cl (mL/min/kg)	C_{max} (ng/mL)	Vd_{ss} (L/kg)	$T_{1/2}$ (h)	AUC_{po} (ng h/mL)
16	0.78	4145	0.22	4.9	18824

[a] IV dose: 0.2 mg/kg (DMSO/cyclodextrin 20% (5/95 v/v)); PO dose: 5 mg/kg (0.5% HPMC K100/0.1%Tween 80).

Table 5. In vivo activities of sulfonamide **20**[a]

Structure	Dose (mg/kg)	TG (g/l) (p)[b]	VLDLc (g/l) (p)[b]	LDLc (g/l) (p)[b]	HDLc (g/l) (p)[b]
	20	−69% ***	−85% ***	−55% ***	+102% ***

[a] Five days chronic bid C57B6 mice transgenic human Apo-A-I.
[b] *** indicates values of $p < 0.0005$, as determined by a One-Way-ANOVA.

Table 6. In vitro activities of compound 20[a]

Compound	EC_{50} (μM) h PPARα (%activation)[b]	EC_{50} (μM) m PPARα (%activation)[b]	EC_{50} (μM) h PPARδ (%activation)[b]	EC_{50} (μM) m PPARδ (%activation)[b]	EC_{50} (μM) h PPARγ (%activation)[b]	EC_{50} (μM) m PPARγ (%activation)[b]
20	0.005 (138)	0.02 (123)	>10	>10	1.1 (86)	0.6 (59)

[a] Data generated using cell based transient transfection assays.[13]
[b] % of maximal activation of all compounds was compared to reference compounds normalized to 100%. For the PPARα activity, the reference compound was **5**. For the PPARδ and PPARγ activities, the reference compounds were GW516 and rosiglitazone, respectively.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2007.11.053.

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