Bioorganic & Medicinal Chemistry Letters 19 (2009) 1101–1104

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Discovery and SAR of *para*-alkylthiophenoxyacetic acids as potent and selective PPARδ agonists

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ARTICLE INFO

Article history:
Received 24 December 2008
Accepted 31 December 2008
Available online 8 January 2009

Keywords:
Selective PPARδ agonists
Dyslipidemic
Achiral analogs

ABSTRACT

Synthesis and SAR of *para*-alkylthiophenoxyacetic acids is described. Achiral compounds **30**, **31** and **32** were identified as potent and selective PPARδ agonists.

The peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors acting as metabolic sensors regulating the expression of genes involved in glucose and lipid homeostasis. Agonists of the PPARα subtype,[1,2] such as LOPID® (gemfibrozil) and TRICOR® (fenofibrate), and agonists of the PPARγ subtype,[3,4] such as AVANDIA® (rosiglitazone maleate) and ACTOS® (pioglitazone HCl), are used for the treatment of dyslipidemia and diabetes, respectively. PPARδ, involved in lipid metabolism is unlike the other two PPAR receptors, ubiquitously expressed, but the highest expression levels are found in tissues with high lipid metabolism including adipose, skeletal muscle, developing brain, intestine and heart.[5] PPARδ has both distinct and overlapping functions, particularly with PPARα, as there are many common target genes.[6] PPARδ may also act in a regulatory or complimentary manner to PPARα or PPARγ activities based on in vitro and knock-out mice studies.[7,8]

The synthesis and development of a potent and selective PPARδ agonist, GW501516, has provided a greater understanding of the role of PPARδ and the potential clinical utility of selective agonists.[9] In obese, dyslipidemic, and hyperinsulinemic rhesus monkeys treatment with GW501516 resulted in an increase in high density lipoprotein cholesterol (HDL-C), a decrease in triglycerides, an improvement in the atherogenic profile (decreases in small dense LDL particles) with little effect on glucose (although insulin levels were decreased in monkeys).[9] The increase in HDL-C was attributed to gene induction by PPARδ activation of the ABC-A1 transporter, a key gene involved in reverse cholesterol transport and HDL-C metabolism. There was also an increase in cholesterol efflux in lipid-loaded macrophages, further implicating a role for PPARδ in modulating HDL-C levels and reverse cholesterol transport. In early clinical studies with normal male volunteers, GW501516 increased circulating HDL-C and decreased triglycerides, although the decrease in triglycerides was not statistically significant.[10] On the other hand, in overweight, dyslipidemic males with the metabolic syndrome, treatment with GW501516 had no marked effect on HDL-C but rather significantly decreased plasma total cholesterol, apolipoprotein B levels and improved remnant particle clearance.[11] These data indicate that PPARδ agonists may have clinical utility in the treatment of dyslipidemia, obesity and diabetes and may complement the actions of existing therapies such as the widely used statins.

While the structure of GW501516 is shown in Figure 1,[12] there are only a few PPARδ selective agonists reported recently in literature.[13] We previously identified the Y-shaped molecules **1** as potent and selective PPARδ agonists, and the chirality at the Y intersection is pivotal to PPARδ agonist activity.[14] To reduce the 'cost of goods', we now report that certain achiral analogs of **1** may also maintain the high PPARδ agonist potency and selectivity.

PPAR agonists generally consist of three parts: a lipophilic tail moiety, a linker and a head moiety bearing a carboxylate functionality. We started with the SAR study of the substitutions on the lipophilic tail moiety, and the results were summarized in Table 1. Following the Topliss tree principle,[15] olefin compounds **2**–**10** were made, and their straight forward synthesis was shown in Scheme 1. The key intermediate **14**, a differentially activated olefin, was obtained by treatment of 2-methylene-1,3-propanediol with methylsulfonyl chloride and triethylamine in 58% yield. Phenoxide

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doi:10.1016/j.bmcl.2008.12.113

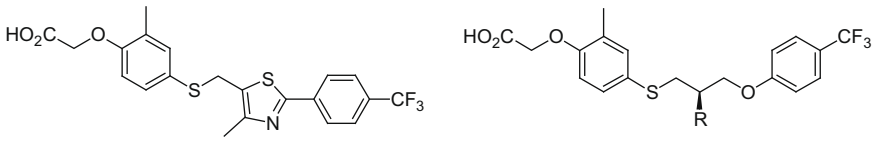
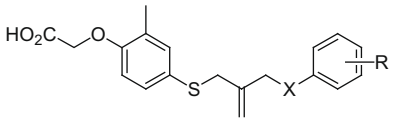


Figure 1. Structures of selective PPARδ agonists.

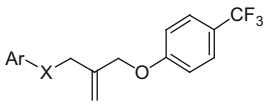
Table 1
In vitro human PPARδ potency of compounds **2–13**[a]

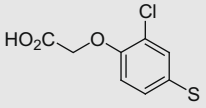
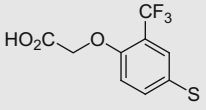
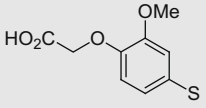
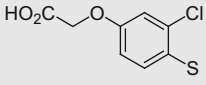
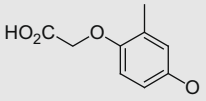


Compound	X	R	PPARδ EC_{50}[b] (nM)	Compound	X	R	PPARδ EC_{50}[b] (nM)
2	O	H	711	**8**	O	4-NMe_2	238
3	O	4-Cl	65.5	**9**	O	2,4-Cl_2	138
4	O	3,4-Cl_2	49.8	**10**	O	4-OCF_3	28.4
5	O	4-CF_3	17.1	**11**	NH	4-CF_3	>500
6	O	3-CF_3,4-Cl	>500	**12**	S	4-CF_3	54.3
7	O	4-OMe	216	**13**	CH_2	4-CF_3	26.8

[a] EC_{50} of all the compounds are >1 μM in PPARα and PPARγ assays.
[b] Values are means of at least two experiments.

Table 2
In vitro human PPARδ potency of compounds **18–22**[a]

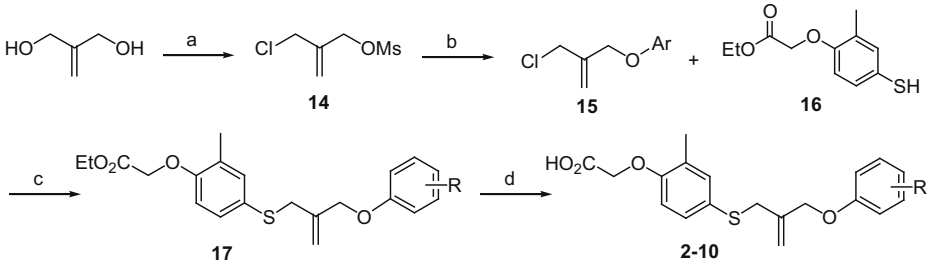


Compound	Ar–X	Human PPARδ EC_{50}[b] (nM)
18		46.7
19		>1000
20		>1000
21		>500
22		249

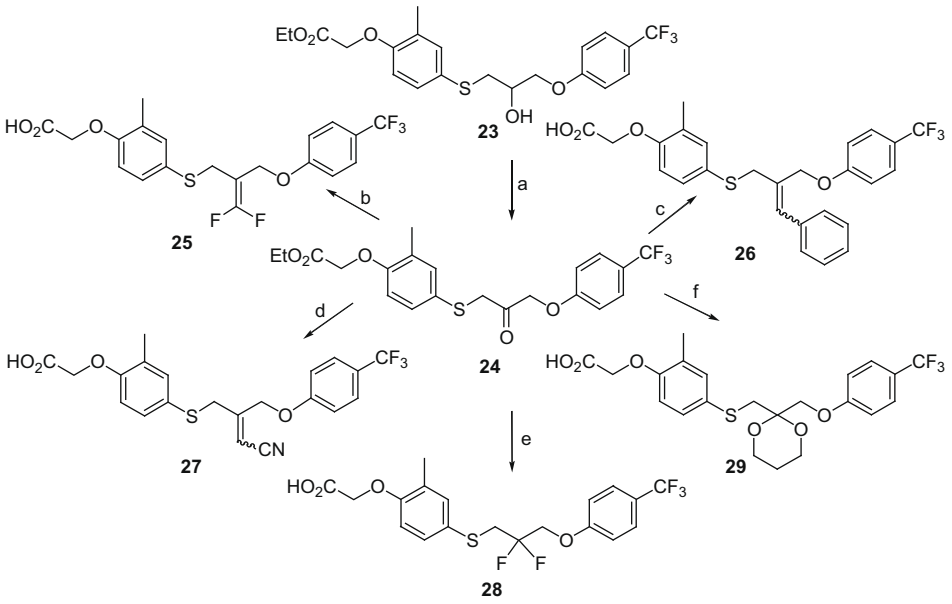
[a] EC_{50} of all the compounds are >1 μM in PPARα and PPARγ assays.
[b] Values are means of at least two experiments.

selectively replaced the more reactive methyl sulfonyl group of olefin **14**, giving the allylic chloride **15** in very good yields. Subsequent replacement of the allylic chloro group with thiol afforded esters **17**, which gave acids after hydrolysis. With the successful Topliss tree approach, we were able to efficiently identify the potent 4-CF_3-analog **5** (EC_{50} = 17.1 nM, Table 1) within nine molecules. We then explored three bioisosteres of **5** at X position. The NH isostere **11**[16] (EC_{50} > 500 nM) reduced the potency dramatically whereas the hydrophobic sulfur isostere **12** (EC_{50} = 54.3 nM) and CH_2 isostere **13**[16] (EC_{50} = 26.8 nM) displayed slightly lower potencies.

We then turned our attention to optimize the head moiety, and compounds **18–22** were synthesized and evaluated (Table 2). The synthetic route is similar to Scheme 1. The various thiophenols were obtained in a similar manner described for the synthesis of thiophenol **16**.[14] Among the new analogs prepared, **18** (EC_{50} = 46.7 nM) showed good potency although it was about 2.7-fold lower than that of **5**. To our surprise, replacement of Cl with CF_3 (**19**, EC_{50} > 1000 nM) or OMe (**20**, EC_{50} > 1000 nM) totally abolished the PPARδ activity. Moving the Cl from *meta*- to *ortho*-position (relative to sulfur) also decreased the potency dramatically (**21**, EC_{50} > 500 nM). When the sulfur atom of **5** was replaced by the more hydrophilic oxygen atom as in **22** (EC_{50} = 249 nM), the potency was reduced ~15-fold.



Scheme 1. Reagents and conditions: (a) MsCl, Et_3N, 58%; (b) NaH, corresponding phenols, 80-90%; (c) Cs_2CO_3, CH_3CN, 75–86%; (d) LiOH, 90–95%.

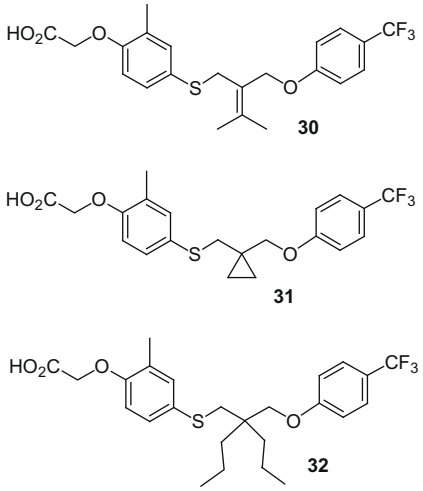


Scheme 2. Reagents and conditions: (a) DMSO, Ac_2O, 83%; (b) i—Br_2CF_2, HMPT, THF, 78%; ii—LiOH, 91%; (c) i—$Ph_3P^+CH_2Ph\ Cl^-$, NaHMDS, 44%; ii—LiOH, 90%; (d) i—$Ph_3P{=}CHCN$, 90%; ii—LiOH, 85%; (e) i—$(MeOCH_2)_2NSF_3$, 92%; ii—LiOH, 91%; (f) i—$HO(CH_2)_3OH$, PPTS, 83%; ii—LiOH, 90%.

Table 3
In vitro human PPARδ activity of compounds **25**–**32**

Compound	Human PPARδ EC_{50} (nM)	Compound	Human PPARδ EC_{50} (nM)
25	69.6	**29**	45.6
26	45.5	**30**	22.4
27	35.4	**31**	23.3
28	147	**32**	8.6

Finally, we explored the SAR on the central portion of the molecules. Scheme 2 shows the synthesis of compounds **25**–**29**. The common intermediate **24** was produced by oxidation of alcohol **23**[14] with DMSO and acetic anhydride. The ketone **24** was smoothly converted to olefinic compounds **25**,[17] **26**, and **27** by Wittig-type reactions. Treatment of the ketone with Deoxo-Fluor reagent[18] afforded *gem*-difluorinated compound **28**. The preparations of compounds **30**–**32** were achieved by a similar route as outlined in Scheme 1.



Compared with compound **5**, incorporation of difluoro (**25**, 69.6 nM), phenyl (**26**, 45.4 nM), or cyano group (**27**, 35.4 nM) on the double bond did not improve the potency (Table 3). However, *gem*-dimethyl substitution on the double bond (**30**, 22.4 nM) is better than *gem*-difluoro substitution (**25**, 69.6 nM). When the double bond of **5** was replaced with its cyclopropyl bioisostere (**31**, 23.3 nM), the potency is comparable. On the other hand, if the double bond was replaced with less bulkier difluoro group (**28**, 147 nM), the potency decreased ~9-fold. The best potency was achieved with the di-*n*-propyl substitution (**32**, 8.6 nM).

In summary, to reduce the 'cost of goods', beginning with achiral **2** (711 nM) possessing moderate PPARδ agonist potency, we identified several potent agonists (**5**, **10**, and **13**) based on the Topliss Tree study on the aromatic system. The further SAR study at the X position, left head moiety, and the central portion of the Y-shaped molecules led to the identification of achiral potent and selective PPARδ agonists (**30**, **31**, and **32**), which show favorable pharmacokinetic profiles.

References and notes

1. Isseman, I.; Green, S. *Nature* **1990**, *347*, 645.
2. Barish, G. D.; Evans, R. M. *Trends Endocrinol. Metabol.* **2004**, *15*, 158.
3. Knouff, C.; Auwerx, J. *Endocrine Rev.* **2004**, *25*, 899.
4. Willson, T. M.; Cobb, J. E.; Cowan, D. J.; Wiethe, R. W.; Correa, I. D.; Prakash, S. R.; Beck, K. D.; Moore, L. B.; Kliewer, S. A.; Lehmann, J. M. *J. Med. Chem.* **1996**, *39*, 665.
5. Braissant, O.; Foufelle, F.; Scotto, C.; Dauça, M.; Wahli, W. *Endocrinology* **1996**, *137*, 354.
6. Wang, Y.-X.; Lee, C.-H.; Tiep, S.; Yu, R. T.; Ham, J.; Kang, H.; Evans, R. M. *Cell* **2003**, *113*, 159.
7. Muoio, Deborah M.; MacLean, Paul S.; Lang, David B.; Li, Shi; Houmard, Joseph A.; Way, James M.; Winegar, Deborah A.; Christopher Corton, J.; Lynis Dohm, G.; Kraus, William E. *J. Biol. Chem.* **2002**, *27729*, 26089.
8. Shi, Y.; Hon, M.; Evans, R. M. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 2613.
9. Oliver, W. R.; Shenk, J. L.; Snaith, M. R.; Russell, C. S.; Plunket, K. D.; Bodkin, N. L.; Lewis, M. C.; Winegar, D. A.; Sznaidman, M. L.; Lambert, M. H.; Xu, H. E.; Strernbach, D. D.; Kliewer, S. A.; Hansen, B. C.; Willson, T. M. *Proc. Natl. Acad. Sci. U.S.A.* **2001**, *98*, 5306.
10. Sprecher, D.; Massien, C.; Patterson, S.; Zalewski, A.; Johnson, A. *Circulation* **2004**, *110*, 244 (Abstract).
11. Sprecher, D.; Johnson, A.; Pierce, G.; Watts, G.; Barrett, H. *Circulation* **2005**, *112*, 1211 (Abstract).
12. Sznaidman, M. L.; Haffner, C. D.; Maloney, P. R.; Fivush, A.; Chao, E.; Goreham, D.; Sierra, M. L.; LeGrumelec, C.; Xu, H. E.; Montana, V. G.; Lambert, M. H.; Willson, T. M.; Oliver, W. R.; Sternbach, D. D. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1517.

13. (a) Fujieda, H.; Usui, S.; Suzuki, T.; Nakagawa, H.; Ogura, M.; Makishima, M.; Miyata, N. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4351; (b) Epple, R.; Russo, R.; Azimioara, M.; Cow, C.; Xie, Y.; Wang, X.; Wityak, J.; Karanewsky, D.; Gerken, A.; Iskandar, M.; Saez, E.; Seidel, H. M.; Tian, S.-S. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4376; (c) Weigand, S.; Bischoff, H.; Dittrich-Wengenroth, E.; Heckroth, H.; Lang, D.; Vaupel, A.; Woltering, M. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4619.
14. Zhang, R.; DeAngelis, A.; Wang, A.; Sieber-McMaster, E.; Li, X.; Russell, R.; Pelton, P.; Xu, J.; Zhu, P.; Zhou, L.; Demarest, K.; Murray, W. V.; Kuo, G.-H. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3855.
15. Topliss, J. G. *J. Med. Chem.* **1972**, *15*, 1006.
16. Synthesis of isosters **11** and **12** is similar to that of compounds **2**–**10** shown in Scheme 1. The ethyl ester of compound **13** was prepared by olefination of the corresponding ketone with Tebbe reagent.
17. Vinson, W. A.; Prickett, K. S.; Spahic, B.; de Montellano, P. R. O. *J. Org. Chem.* **1983**, *48*, 4661.
18. Lal, G. S.; Pez, G. P.; Pesaresi, R. J.; Prozonic, F. M.; Cheng, H. *J. Org. Chem.* **1999**, *64*, 7048.