Bioorganic & Medicinal Chemistry Letters 18 (2008) 4798–4801

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Highly functionalized 7-azaindoles as selective PPARγ modulators

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ARTICLE INFO

Article history:
Received 9 June 2008
Revised 22 July 2008
Accepted 24 July 2008
Available online 30 July 2008

Keywords:
PPAR
Azaindole
Indole
Selective PPAR modulator
SPPARM

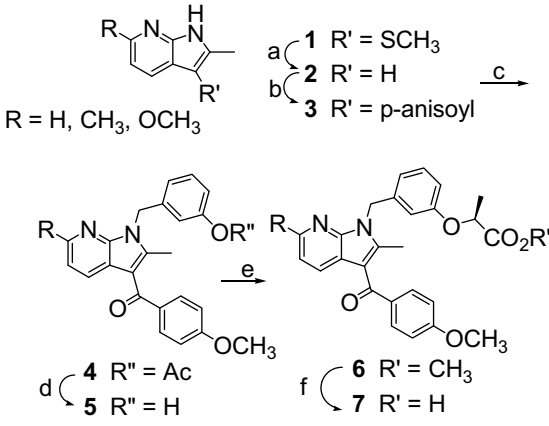
ABSTRACT

A series of highly functionalized 3-aroyl and 3-phenoxy-2-methyl-7-azaindoles have been identified, which are potent selective PPARγ modulators (SPPARγMs). Addition of substituents at the 6-position of the 7-azaindoles improves in vitro potency and pharmacokinetics. 7-Azaindoles have significantly improved off-target profiles compared to the parent indole series.

Type 2 diabetes (T2DM) has been identified as a significant health threat to the aging population of industrialized societies.[1] Peroxisome proliferator-activated receptor gamma (PPARγ) is a member of a large family of ligand-activated nuclear hormone receptors, and is known to mediate adipocyte differentiation and moderate glucose levels in individuals with T2DM.[2] Rosiglitazone and pioglitazone are full agonists of PPARγ that are currently used in the clinic to treat patients with T2DM. However, the efficacy of these compounds is tempered by a range of mechanism-based adverse effects (AEs), which include weight gain, edema, and anemia.[3] Additionally, the use of rosiglitazone and pioglitazone is contraindicated in insulin-dependent T2DM patients as well as those with congestive heart failure. A PPARγ agonist devoid of these AEs and available to a larger T2DM patient population is therefore desirable.

Recently, compounds that act as selective PPARγ modulators (SPPARγMs) have been reported.[4,5] In animal models, partial agonists such as indole **13** display potent glucose lowering activity, but unlike full agonists these do not cause cardiac hypertrophy and attenuate brown adipose tissue weight increases.[6,7] Unfortunately, many members of this indole-based class have moderate levels of cytochrome P450 liabilities (1–20 μM on 2C9, 3A4, and 2D6) as well as binding to off-target enzymes (<10 μM) as measured by a commercial screening laboratory. It was hypothesized that the relatively high log*D* values of the functionalized indoles contributed to their affinity for off-target receptors. In an effort to find SPPARγMs that have fewer potential off-target liabilities, a nitrogen was incorporated into the core structure at the 7-position of the indole.

The general route for the preparation of appropriately substituted 3-aroyl-2-methyl-7-azaindoles (**7a–j**) is shown in Scheme



Scheme 1. Synthesis of 7-azaindoles **7a–j**. Reagents and conditions: (a) Raney Nickel, EtOH, rt, 80%; (b) EtMgBr, $ZnCl_2$, *p*-anisoyl chloride, 64%; (c) 3-bromomethyl phenylacetate, Cs_2CO_3, DMF, 70%; (d) K_2CO_3, aq MeOH; (e) methyl (*R*)-lactate, DEAD, PPh_3; (f) KOH 36% (3 steps).

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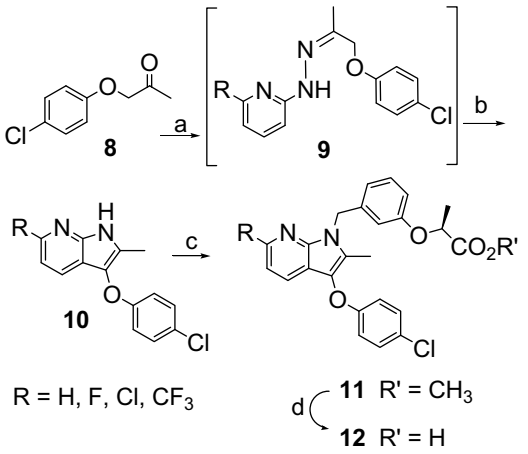
doi:10.1016/j.bmcl.2008.07.103



Scheme 2. Synthesis of 7-azaindoles **12a–h**. Reagents and conditions: (a) 2-pyridylhydrazine; (b) H_3PO_4, 35%; (c) methyl (2*S*)-2-[3-(bromomethyl)phenoxy]propanoate, Cs_2CO_3, DMF; (d) KOH, 50% (2 steps).

1. Synthesis of 2-methyl-3-thiomethyl-7-azaindole starting material (**1**) has been described previously.[8] The 3-thiomethyl group of **1** was removed upon treatment with Raney Nickel in good yield. Following the procedure of Bergman et al. acylation of the in situ transmetallated indole-Grigard occurred smoothly to give moderate yields of the 3-aroylated indole (**3**).[9] Benzylation of the *N*1 nitrogen provides the desired core structure **4**.[10] After hydrolysis of the acetate protecting group on the phenol, a Mitsunobu reaction was employed to install the *R*- or *S*-lactoyl group stereoselectively in excellent yield (**6**). Simple hydrolysis of the ester allows for isolation of the desired carboxylic acid **7** in modest overall yield (~10% 6 steps).

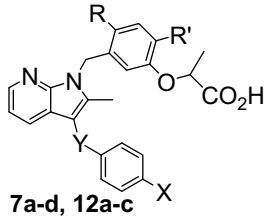
Synthesis of the 2-methyl-3-phenoxy-7-azaindoles (**12a–h**) was accomplished in four steps from 1-(4-chlorophenoxy)acetone (**8**) (Scheme 2). Standard Fischer indole synthesis provided the 7-azaindole (**10**) in modest yield (35%). Benzylation on *N*1 followed by hydrolysis of the lactoyl ester gave the desired acid **12** (~18% overall yield for three steps).

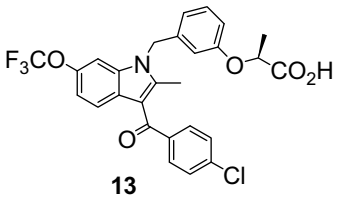
The synthesis and biological activity of functionalized 6-substituted-2-methyl-indoles as potent SPPARγMs has been previously reported.[6] Many members of the indole class are cytochrome P450 inhibitors (1–10 μM), and inhibit 15–43 enzymes (<10 μM) on a customized panel of 168 assorted radioligand binding and enzymatic assays.[11] It was postulated that nitrogen incorporated into the indole ring of the lead class may decrease the off-target activity of these molecules by decreasing the hydrophobicity of the molecules while retaining SPPARγM in vitro and in vivo potency. Gratifyingly, 7-azaindoles displayed markedly reduced CYP inhibition and off-target activity. For example, indole **13**, which is characteristic of the series, was moderately potent 2C9 inhibitor (IC_{50} = 5.6 μM) and the *R* enantiomer of **13** inhibited 26 off-target enzymes (IC_{50}, K_i < 10 μM).[11] In contrast, the azaindoles, **7b** failed to inhibit CYP 3A4 and 2C9 (IC_{50} > 100 μM) and **7c** inhibited only one off-target enzyme in the commercial screen (TxA_2 64% @ 10 μM).

As compared to **13**, 3-aroyl- or 3-phenoxy-2-methyl-7-azaindoles lost some potency in the SPA and transactivation assays (TA) (Table 1).[12] However, all of the compounds retained their partial agonism of PPARγ as defined by reaching 20–60% of the maximal activation of rosiglitazone in TA. In most cases, the *S* enantiomer was more potent than the *R* enantiomer (**7a** and **7b**, respectively). Additionally, the *R* enantiomer of many azaindoles was active on the human and/or murine PPARα isoform, while the *S* enantiomer was selective for PPARγ (data not shown).[13] Substitution of the *N*-benzyl ring with a halide either *ortho*- or *para*- to the *O*-lactoyl moiety increased the intrinsic potency approximately 10-fold, with the fluorinated **7c** being equipotent to **13**.

Having identified potent and selective SPPARγMs with improved off-target profiles, pharmacokinetic characteristics and in vivo efficacy of **7b** were examined in Sprague–Dawley rats and *db/db* mice, respectively (Table 1).[14] The PK profile of **7b** was dominated by very high clearance rates. Not surprisingly, after once daily oral dosing for 11 days at 10 mpk in *db/db* mice, **7b** failed

Table 1
In vitro human PPARγ activity of 2-methyl-7-azaindoles (**7a–d**, **12a–c**)





Compound	X	Y	R	R′	Stereochem	SPA	TA		SD rat pharmacokinetics[c]			
						IC_{50}[a]	EC_{50}	% max[b]	Clp/mL/min/kg	$t_{1/2}$ (h)	AUC[d] (μM h)	*F* (%)
13					*S*	1	1	24	21.7	1.5	0.7	45
7a	OCH_3	CO	H	H	*R*	726	2926	23				
7b	OCH_3	CO	H	H	*S*	66	27	32	115	2.0	0.1	29
7c	OCH_3	CO	F	H	*S*	5	3	43	31.7	1.8	0.6	51
7d	OCH_3	CO	H	F	*S*	10	3	47				
12a	Cl	O	Cl	H	*S*	25	36	36	21.8	1.2	1.0	61
12b	Cl	O	F	H	*S*	54	156	19	22.1	1.6	1.3	77
12c	Cl	O	H	F	*S*	106	140	19				

All values are in nM.

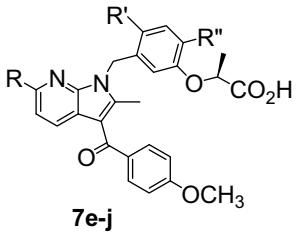
[a] IC_{50} is measured by the complete displacement of a radio-labeled full agonist indicating competitive binding to the receptor.

[b] The EC_{50} is reported; this is the compound concentration at which 50% of a given compound intrinsic maximal response has been reached. Activation levels that reach nearly equivalent maximal activation to rosiglitazone are considered full agonists, while those reaching 20–60% of rosiglitazone maximal activation are deemed partial agonists.

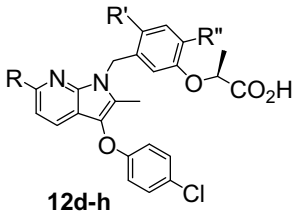
[c] All pharmacokinetic studies were preformed in Sprague–Dawley rats at dose of 0.5 mg iv, 2.0 mg po.

[d] Dose normalized AUC.

Table 2
In vitro human PPARγ activity, in vivo *db/db* mouse, and pharmacokinetic data of 6-substituted 7-azaindoles **7e–j**, **12d–h**



7e-j



12d-h

Compound	R	R′	R″	SPA[a]	TA[b]		*db/db* mouse		SD rat pharmacokinetics[c]			
				IC_{50}	EC_{50}	% max	Dose	(% glc corr)[c]	Clp/mL/min/kg	$t_{1/2}$ (h)	AUC[d] (μM h)	*F* (%)
7e	CH_3	H	H	16	9	35	10	42	28	2.4	1.0	80
7f	CH_3	F	H	4	2	27	10	63	32	1.9	1.1	105
7g	OCH_3	F	H	2	1	14	10,30,50	33,35,34	7,4	1.4	1.7	37
7h	OCH_3	H	F	1	1	29	10	23				
7i	OCH3	Cl	H	2	2	23	30	32				
7j	OCH3	H	Cl	<1	1	25	—	—				
12d	F	Cl	H	15	4	37	—	—				
12e	F	H	Cl	3	4	21	30	30	23	0.8	0.7	47
12f	F	H	F	23	94	22	—	—				
12g	Cl	H	Cl	3	4	20	10,30	32,44	27	1.2	6.8	56
12h	CF3	H	Cl	22	23	26	20,50	18,56	12.4	1.9	1.5	61

All values are in nM.
[a] IC_{50} is measured by the complete displacement of a radio-labeled full agonist indicating competitive binding to the receptor.
[b] The EC_{50} is reported; this is the compound concentration at which 50% of a given compound intrinsic maximal response has been reached. Activation levels that reach nearly equivalent maximal activation to rosiglitazone are considered full agonists, while those reaching 20–60% of rosiglitazone maximal activation are deemed partial agonists.
[c] Rosiglitazone was used as a control in the *db/db* mouse studies (10 mpk, 77–85% glucose correction). All pharmacokinetic studies were preformed in Sprague–Dawley rats at dose of 0.5 mg iv, 2.0 mg po.
[d] Dose normalized AUC.

to correct glucose levels compared to the 10 mpk rosiglitazone control (29% vs 82%, respectively). The more potent halogenated compounds (such as **7c**, **12a**, and **12b**) had improved SD rat PK. However, **7c** at a dose of 20 mpk (dose normalized AUC 21.8 μM h) resulted in a modest 44% glucose correction in *db/db* mouse study, whereas a 10-mpk rosiglitazine control reduced glucose to 90%.

In an effort to develop 7-azaindole-based agonists with more desirable in vivo activity, substitution at the 6-position was introduced on the 7-azaindole core to more closely mimic the parent indole series (Table 2). Generally, 6-substitution resulted in an overall increase in potency without loss of desired SPPARγM characteristics. Exceptions occurred with **7f** which was active on the murine PPARα receptor (500 nM, 28% max) and **7h** (489 nM human PPARα; 222 nM murine PPARα). The in vitro activity of 6-methoxy-3-anisoyl-7-azaindoles (**7g–j**) as measured in the *db/db* mouse is comparable to **13**, which exhibited 26% and 36% glucose correction at doses of 10 and 30 mpk, respectively.

Substitution at the 6-position of the 7-azaindoles resulted in moderately improved pharmacokinetics in the SD rat as compared to the unsubstituted 7-azaindoles (Tables 1 and 2). Unfortunately, low exposure in the *db/db* mouse resulted in modest glucose correction for all azaindoles tested. 7-Azaindoles were still unable to completely correct glucose in the *db/db* mouse even at high doses (**7g** and **12h** @ 50 mpk). SPPARγM **7g** corrected glucose to only 34% at doses of 10, 30, and 50 mpk. Drug levels in animal dosed at 30 mpk were low (dose normalized AUC 1.6 μM h). Both **7f** (dose normalized AUC 0.38 μM h) and **12e** (dose normalized AUC 2.6 μM h) were found to be low exposure compounds. Surprisingly, **7f** had the lowest drug exposure of the azaindoles tested, but the best in vivo efficacy as a dose of 10 mpk had 63% glucose correction (10 mpk rosiglitazone control reduced glucose 83%).

In summary, incorporation of a nitrogen at the 7-position of the indole ring results in compounds that have similar in vitro potency to the parent indole series. Additionally, the inclusion of nitrogen into the indole ring also eliminates CYP inhibition on 2C9 and 3A4, and drastically reduces off-target liabilities as compared to the parent indole series. Furthermore, substitution at the 6-position of the 7-azaindole provides compounds that have moderately improved pharmacokinetic properties as compared to the parent 7-azaindoles. Further characterization and preparation of 4-, 5-, 6-, and 7-azaindole SPPARγMs continues in an effort to explore the possibility that compounds with these features may afford beneficial glycaemic control in humans with reduced AEs. These results will be reported in due course.

Acknowledgments

We acknowledge the skills and hard work of the many scientists on the PPAR team who provided technical support in support of this project. Additional thanks to Amy F. Hasler who provided assistance with the preparation of the manuscript.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2008.07.103.

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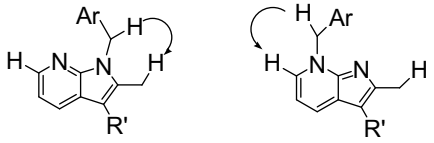
10. Benzylation on *N*1 vs *N*7 was confirmed using NOE studies:



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11. Off-target data were obtained using commercial screening laboratories. In enzyme assays, significant inhibition by the *R* enantiomer of **13** by the following enzymes was observed (IC_{50} values in parentheses): 5-LO (1.64 μM), PDE2 (29.1 μM), PDE3 (22.5 μM), EGF receptor (2.24 μM), HERG (3.23 μM), Prostanoid: DP (8.45 μM), EP_3 (1.22 μM), EP_4 (3.7 μM), FP (2.73 μM), IP (6.34 μM). In radioligand binding assays, significant displacement of radioligand from the following binding sites was observed (with estimated K_i values in parentheses): adrenergic: α_{2A} (1.65 μM), α_{2B} (0.77 μM), β_1 (4.07 μM), β_3 (4.86 μM), norepinephrine transporter (2.16 μM), dopamine: D_1 (1.53 μM), D_{25} (3.55 μM), D_3 (0.837 μM),dopamine transporter (3.41 μM), Muscarinic M_3 (1.56 μM), Muscarinic M_4 (1.34 μM), Opiate δ (1.69 μM), opiate κ (3.48 μM), opiate μ (1.86 μM), Serotonin 5-HT_{2B} (1.14 μM), serotonin transporter (0.97 μM), Tachykinin NK_2 (0.53 μM), TXA_2 (2.03 μM).
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13. With the exception of **7f** and **7h**, the *S* enantiomers of the 7-azaindoles described above do not bind to PPARα and PPARδ (IC_{50} > 50 μM).
14. *db*/*db* mice were used as described in: Berger, J.; Bailey, P.; Biswas, C.; Cullinan, C. A.; Doebber, T. W.; Hayes, N. S.; Saperstein, R.; Smith, R. G.; Liebowitz, M. D. *Endocrinology* **1996**, *137*, 4189.