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Discovery of INT131: A selective PPARγ modulator that enhances insulin sensitivity

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ABSTRACT

PPARγ is a member of the nuclear hormone receptor family and plays a key role in the regulation of glucose homeostasis. This Letter describes the discovery of a novel chemical class of diarylsulfonamide partial agonists that act as selective PPARγ modulators (SPPARγMs) and display a unique pharmacological profile compared to the thiazolidinedione (TZD) class of PPARγ full agonists. Herein we report the initial discovery of partial agonist **4** and the structure–activity relationship studies that led to the selection of clinical compound INT131 (**3**), a potent PPARγ partial agonist that displays robust glucose-lowering activity in rodent models of diabetes while exhibiting a reduced side-effects profile compared to marketed TZDs.

1. Introduction

Type 2 diabetes mellitus (T2DM) is a metabolic disorder, defined by the body's inability to regulate glucose homeostasis as a result of defective insulin signaling (insulin resistance) and eventual impairment of insulin production due to pancreatic β-cell exhaustion.[1] If left untreated, type 2 diabetes can promote a number of complications including kidney impairment, peripheral neuropathy, blindness, and heart failure. Type 2 diabetes accounts for over 90% of all cases of diabetes, and it has been estimated that 270 million people will be considered type 2 diabetics by 2025.[2,3] Despite extensive research and development of anti-diabetic therapies by the pharmaceutical industry, there remains a significant need for safe glucose-lowering agents.

Peroxisome proliferator-activated receptor γ (PPARγ) has been shown to modulate the transcription of genes responsible for adipose differentiation, glucose homeostasis and lipid metabolism[1,3,4] PPARγ is the target of the thiazolidinedione (TZD) class of antidiabetic agents that include rosiglitazone (Avandia®; GlaxoSmithKline) and pioglitazone (Actos®; Takeda) (Fig. 1).[4,5] The TZDs are orally-active small molecule PPARγ full agonists that have been clinically validated to increase insulin sensitivity and restore normal body insulin and glucose levels in hyperglycemic patients. However, treatment with TZDs has been associated with serious side effects, including weight gain, peripheral edema, hepatotoxicity, increased risk of congestive heart failure, and bone fracture. These effects have limited the utility of this class of therapeutic agents.[1,3,4,6,7] Other structurally unrelated PPARγ full agonists have

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‖ Present address: Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080, United States.
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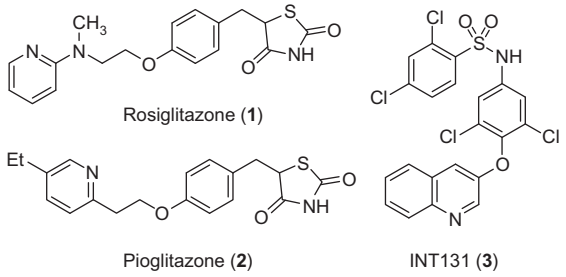


Figure 1. Marketed TZD PPARγ full agonists and selective PPARγ modulator INT131 (**3**).

displayed similar side-effect profiles, suggesting the possibility that these undesired effects could be mechanistically associated with receptor full agonism.[8,9]

Recently, we and others have disclosed next-generation ligands that selectively modulate the activity of PPARγ.[10–12] These selective PPARγ modulators (SPPARγMs) have partial agonist activity compared to the TZDs, and show increased insulin sensitivity and robust glucose-lowering activity with a reduction of the side effects observed with PPARγ full agonists, both in animal models of diabetes and in the clinical setting. The underlying mechanism for this pharmacological effect is not well understood, although recent studies by Spiegelman and co-workers have shown that insulin sensitivity is related to PPARγ phosphorylation state at Ser^{273}, suggesting that PPARγ ligands may impart their anti-diabetic effects through blocking phosphorylation of PPARγ by Cdk5 rather than by agonizing the transcriptional activity of the nuclear receptor.[13] In any case, these selective PPARγ modulators have demonstrated that insulin sensitization effects and other side effects such as edema and weight gain are not directly linked, and thus desired anti-diabetic effects can be decoupled from unwanted side effects. As a result, selective PPARγ modulators may represent improved therapies for the treatment of type 2 diabetes.

This Letter describes the discovery of a novel structural class of small-molecule selective PPARγ modulators for the treatment of type 2 diabetes, culminating in the discovery of INT131 (**3**, Fig. 1),[14] a small molecule therapeutic agent that has clinically demonstrated robust glucose-lowering ability with a decreased side effect profile compared to the marketed TZDs.

2. Results and discussion

2.1. Lead identification

A high-throughput screening (HTS) campaign was undertaken with the goal of identifying lead compounds that demonstrate high affinity for PPARγ but do not fully agonize PPARγ function compared to rosiglitazone (**1**). Two assays were established to guide this effort. Biochemical affinity was measured in a standard ligand-displacement assay using [^{3}H]-radiolabeled rosiglitazone (K_i = 10 nM).[15] Cell-based potency and efficacy were measured with a chimeric (two hybrid) PPARγ-Gal4 transactivation reporter gene assay in HEK293 cells.[16] The HTS campaign identified ethyl ester **4**, a moderately potent (IC_{50} = 80 nM) PPARγ ligand with partial agonistic activity in the Gal4 transactivation assay (EC_{50} = 200 nM; eightfold activation over basal activity levels).[17,18] A brief combinatorial hit expansion effort led to the identification of *N*-ethyl amide **5** as a promising lead (Fig. 2). *N*-ethyl amide **5** binds PPARγ with increased affinity in the ligand displacement assay (IC_{50} = 25 nM) and activates PPARγ in the cell-based Gal4 assay with an EC_{50} of 30 nM. Importantly, *N*-ethyl amide **5** displays reduced partial agonist character compared to sulfonamide **4** only

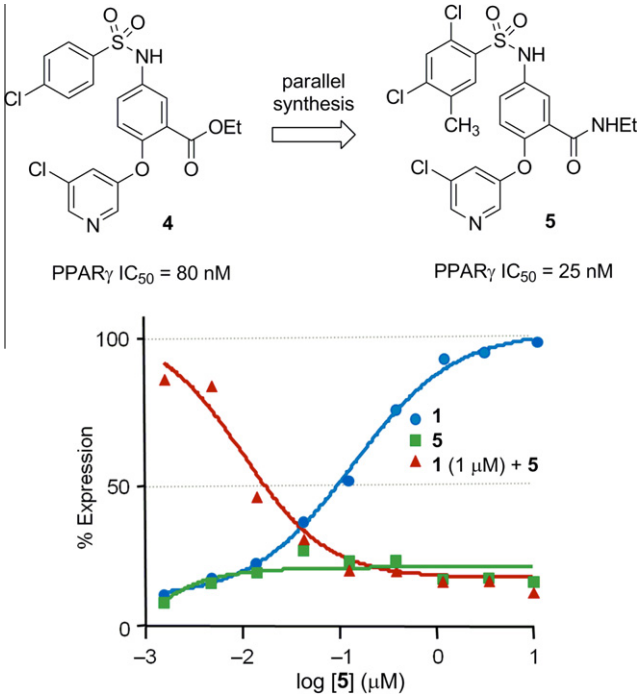


Figure 2. (a) Initial HTS hit **4** and lead **5**. (b) Gal4 dose–response curves for HEK293 cells treated with partial agonist **5** (green), full agonist rosiglitazone (**1**, blue), and partial agonist **5** after pre-treating cells with 1 μM rosiglitazone (**1**, red).

activating PPARγ by 3.5-fold over basal activity levels as compared with a 20-fold activation in the case of rosiglitazone (**1**). Diarylsulfonamide **5** also antagonizes the activity of rosiglitazone (**1**) in the same assay (Fig. 2). Finally, diarylsulfonamide **5** is highly selective for PPARγ over other nuclear receptors. No activation of human PPARα, PPARδ, FXR, LXR, PXR or RXR or of rodent PPARs was observed below a concentration of 10 μM.

Although sulfonamide **5** displayed an attractive in vitro potency and efficacy profile, it had pharmacokinetic properties that made it unsuitable for oral administration. When dosed orally in rat, sulfonamide **5** showed low oral bioavailability and low overall exposure (oral bioavailability (F_u) was 8%, $t_{1/2}$ = 40 min, and the area under the plasma concentration–time curve over 24 h ($AUC_{24\ h}$) was 1.6 μM h). In vitro, sulfonamide **5** exhibited high clearance in the presence of the S-9 fraction of rat liver microsomes. The primary metabolites identified after microsomal incubation showed oxidation at the A-ring methyl and oxidative dealkylation of the B-ring *N*-ethylamide (Fig. 3), that likely contributed to the high clearance and low in vivo exposure. Additionally, sulfonamide **5** inhibits cytochrome P450-3A4 (CYP3A4) with an IC_{50} of 0.36 μM. We initially hypothesized that the C-ring chloropyridine might

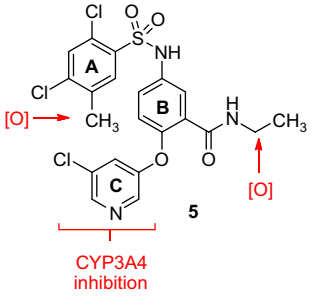
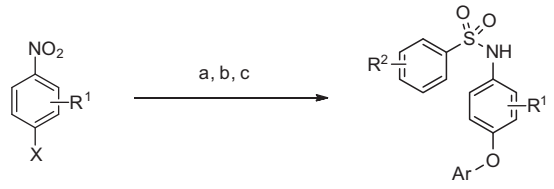


Figure 3. Metabolic liabilities associated with diarylsulfonamide **5**.

be responsible for this inhibition given the known propensity of various pyridines to cause CYP3A4 inhibition by direct heme iron coordination.[19]

2.2. Synthetic chemistry

Thus, a medicinal chemistry effort was initiated to develop SAR around this diarylsulfonamide scaffold with the goal of discovering PPARγ ligands that display reduced oxidative metabolism and cytochrome inhibition while maintaining the desirable potency and efficacy profile seen with *N*-ethyl amide **5**. A concise, robust and scalable synthetic sequence was utilized to prepare a large number of analogs (Scheme 1). S_NAr displacement of a *p*-nitrohalobenzene with an appropriately substituted alcohol or phenol (ArOH) established the B and C rings. Subsequent nitro reduction with $SnCl_2{\cdot}2H_2O$ generated aniline intermediates that could be treated with a suitably substituted benzenesulfonyl chloride in the presence of pyridine to give the target compounds in good overall yield (50–90% in most cases). This modular sequence facilitated rapid access to a large number of analogs with variations of the aryl A, B, and C-ring substituents.



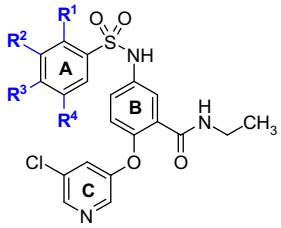
Scheme 1. General synthetic approach to selective PPARγ modulators. Reagents and conditions: (a) ArOH, Cs_2CO_3, DMF, 70 °C; (b) $SnCl_2{\cdot}2H_2O$, EtOAc, reflux; (c) R^2-benzenesulfonylchloride, pyridine, CH_2Cl_2 (50–90% yield over three steps).

2.3. In vitro SAR studies

Using the assays described above, a series of analogs with various A-ring substituents were profiled for PPARγ affinity as well as cell-based potency and efficacy (Table 1). Given the oxidative liability of the A-ring methyl group, we initially examined removal of this substituent and were pleased to see that 2,4-dichlorobenzenesulfonamide **6** had slightly improved biochemical affinity and cell-based potency compared to parent 2,4-dichloro-5-methylbenzenesulfonamide **5** with an efficacy of 25 percent of control. In fact, a variety of 2,4- and 3,4-disubstitued benzenesulfonamides exhibited similar in vitro profiles (compounds **6**–**9**). Electron-withdrawing substituents were preferred on the A-ring. Analogs with a single substituent at the A-ring 4-position (R^1, R^2, R^4 = H, $R^3 \neq$ H) were generally less potent (compounds **10**–**15**). Although these ligands maintained partial agonist efficacy, they also had larger shifts between the biochemical IC_{50} and the cell-based EC_{50} compared to the 2,4-disubstituted analogs. Electron-donating substituents ($R^3 = OCH_3$, **12**) and large 4-substituents (R^3 = *tert*-butyl, **14** or $R^3 = SO_2CH_3$, **15**) were particularly deleterious to affinity. Finally, analogs without an A-ring 4-substituent (R^3 = H), such as 2- or 3-monosubstituted phenyl analogs, and fully unsubstituted phenyl A-ring analogs, as well as heterocyclic A-ring analogs and non-aromatic A ring analogs generally lacked biochemical affinity.[20]

Next, a series of compounds with various substituents on the aniline B-ring was examined for PPARγ affinity and Gal4 potency and efficacy (Table 2). The *N*-ethylamide could be replaced with several different substituents. For example, acetophenone **16** ($R^5 = C(O)CH_3$) displayed nearly identical biochemical and cell-based potency and efficacy compared to benzamide **6**. Small halides and pseudohalides (R^5 = Cl, F, CF_3, CN; compounds **17**–**20**) were tolerated, with Cl being the best for binding affinity. Methyl, $S(O)CH_3$, and hydrogen substituents could be accommodated with

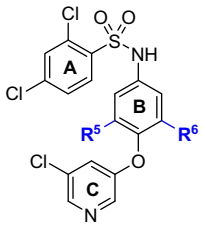
Table 1
In vitro activities of A-ring analogs **5**–**15**



Compd	R^1	R^2	R^3	R^4	PPARγ binding[a,b] IC_{50} (μM)	PPARγ transactivation[c,d] EC_{50} (μM)	Efficacy[e] (%)
Rosiglitazone (**1**)	—	—	—	—	0.20 (±0.003)	0.10	100
5	Cl	H	Cl	CH_3	0.025 (±0.003)	0.03	18
6	Cl	H	Cl	H	0.015 (±0.003)	0.015	25
7	Cl	H	CF_3	H	0.050 (±0.014)	0.03	18
8	OCF_3	H	Br	H	0.018 (±0.050)	0.015	15
9	H	Cl	Cl	H	0.035 (±0.006)	0.02	30
10	H	H	Cl	H	0.16 (±0.05)	—[f]	—[f]
11	H	H	I	H	0.025 (±0.006)	0.20	40
12	H	H	OCH_3	H	0.40 (±0.13)	2.0	33
13	H	H	NO_2	H	0.049 (±0.015)	0.40	40
14	H	H	$C(CH_3)_3$	H	>10	>30	0
15	H	H	SO_2CH_3	H	>10	>30	0

[a] Ligand displacement assay using [^{3}H]-radiolabeled rosiglitazone.
[b] Value represents the mean of at least three experiments ± standard deviation.
[c] Value from a single experiment.
[d] Two hybrid PPARγ-Gal4 transactivation assay in HEK293 cells.
[e] Efficacy is calculated as the percentage of the maximum activation obtained with rosiglitizone (**1**), that activates PPARγ 20-fold above the basal level.
[f] Not tested.

Table 2
In vitro activities of B-ring analogs **6** and **16**–**29**



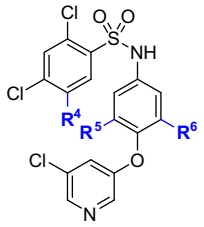
Compd	R^5	R^6	PPARγ binding[a,b]	PPARγ transactivation[c,d]	
			IC_{50} (μM)	EC_{50} (μM)	Efficacy[e] (%)
Rosiglitazone (**1**)	—	—	0.20 (±0.003)	0.10	100
6	C(O)NHEt	H	0.015 (±0.003)	0.015	25
16	$C(O)CH_3$	H	0.015 (±0.003)	0.010	18
17	Cl	H	0.021[c]	0.40	10
18	F	H	0.036 (±0.010)	1.0	18
19	CF_3	H	0.066 (±0.027)	0.3	10
20	CN	H	0.11 (±0.03)	0.30	13
21	CH_3	H	1.47 (±0.30)	0.60	10
22	$S(O)CH_3$	H	1.44 (±0.18)	0.60	15
23	OCH_3	H	0.019 (±0.004)	>30	0
24	H	H	2.00 (±0.69)	>30	0
25	CO_2H	H	>10	>30	0
26	Cl	F	0.018 (±0.001)	0.02	45
27	Cl	Cl	0.021 (±0.008)	0.006	16
28	$C(O)CH_3$	Cl	0.012 (±0.002)	0.03	80
29	CF_3	CF_3	0.031 (±0.007)	0.1	55

[a] Ligand displacement assay using [^{3}H]-radiolabeled rosiglitazone.
[b] Value represents the mean of at least three experiments ± standard deviation.
[c] Value from a single experiment.
[d] Two hybrid PPARγ-Gal4 transactivation assay in HEK293 cells.
[e] Efficacy is calculated as the percentage of the maximum activation obtained with rosiglitizone (**1**), that activates PPARγ 20-fold above the basal level.

increases in both IC_{50} and EC_{50} (compounds **21**, **22** and **24**). However, a carboxylic acid (CO_2H, **25**) was not tolerated. Interestingly, analogs with R^5 = F or OCH_3 (compounds **18** and **23**) maintained comparable biochemical affinity to benzamide **6**, but cellular potency was severely diminished. The origin of this cell shift is currently not understood. Ligands substituted with small, electron-withdrawing R^5 and R^6 substituents at both the aniline B-ring 3- and 5-position showed improved affinity and potency profiles (compounds **26**–**29**). In particular, dichloroaniline **27** binds PPARγ with an IC_{50} of 21 nM and activates PPARγ with an EC_{50} of 6 nM and an efficacy of 16% of control. Finally, substitution at the aniline B-ring C2 or C6 positions generally gave compounds with diminished PPARγ affinity. Similarly, non-aromatic B-rings were poorly tolerated.[20]

Next, we examined the in vivo PK profile of our improved PPARγ ligands that lack the metabolically labile A-ring methyl and B-ring ethylamide found in lead **5**.[21] As a class, these compounds could not be properly formulated for intravenous dosing due to solubility limitations, but nonetheless they were found to have good oral exposure. Thus we administered compound as a suspension by oral gavage and evaluated the oral exposure by comparing the area under the plasma concetration–time curve measured over 24 h ($AUC_{24\ h}$). We were pleased to see that both analogs **20** and **27** showed increased exposure in rats compared to **5** when dosed orally (Table 3). Although these ligands had improved pharmacokinetic profiles, presumably because of reduced oxidative metabolism, they still inhibited CYP3A4 with IC_{50} values around one micromolar. We hypothesized that the substituted

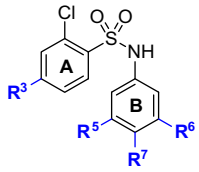
Table 3
Rat PK data and CYP3A4 inhibition data for analogs **5**, **20**, and **27**

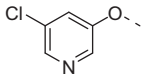
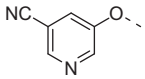
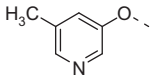
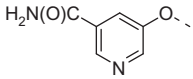
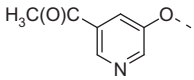
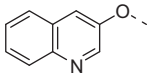
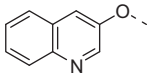
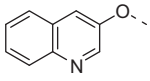
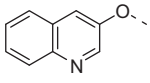
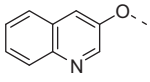
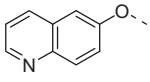
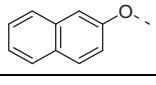


Compd	R^4	R^5	R^6	Rat PK PO $AUC_{24\ h}$[a] (μM h)	CYP3A4 inhibition IC_{50} (μM)
5	CH_3	H	C(O)NHEt	1.6	0.36
20	H	H	Cl	31	0.60
27	H	Cl	Cl	4.8	1.20

[a] Determined for a single 5 mg/kg oral dose in Sprague–Dawley rats.

Table 4
In vitro activities of C-ring analogs **3**, **27** and **30**–39



Compd	R^3	R^5	R^6	R^7	PPARγ binding[a,b] IC_{50} (μM)	PPARγ transactivation[c,d] EC_{50} (μM)	Efficacy[e] (%)	CYP3A4 inhibition IC_{50} (μM)
1[g]	—	—	—	—	0.20 (±0.003)	0.10	100	—
27	Cl	Cl	Cl		0.021 (±0.008)	0.006	16	0.60
30	Cl	Cl	Cl		0.027 (±0.005)	0.08	20	0.01
31	Cl	Cl	Cl		0.019 (±0.002)	0.09	25	0.001
32	Cl	Cl	Cl		0.032 (±0.007)	0.20	20	0.03
33	Cl	Cl	Cl		0.034 (±0.006)	0.30	25	0.36
3	Cl	Cl	Cl		0.017 (±0.001)	0.15	40	25.0
34	Cl	H	Cl		0.018 (±0.004)	0.10	30	2.6
35	Cl	H	F		0.040[c]	—	—	10.0
36	CF_3	Cl	Cl		0.025[c]	0.25	21	2.3
37	Cl	H	$C(O)CH_3$		0.030[c]	0.06	42	3.0
38	Cl	Cl	Cl		0.02 (±0.003)	0.07	10	1.0
39	Cl	H	Cl		0.48 (±0.05)	2.0	18	—

[a] Ligand displacement assay using [^{3}H]-radiolabeled rosiglitazone.
[b] Value represents the mean of at least three experiments ± standard deviation.
[c] Value from a single experiment.
[d] Two hybrid PPARγ-Gal4 transactivation assay in HEK293 cells.
[e] Efficacy is calculated as the percentage of the maximum activation obtained with rosiglitizone (**1**), that activates PPARγ 20-fold above the basal level.

pyridine C-ring might coordinate iron heme and thus be responsible for this CYP3A4 inhibition. Concerned about potential drug–drug interactions, we focused our attention on the SAR of CYP3A4 inhibition with modification of the C-ring chloropyridine.

A series of C-ring analogs was examined for PPARγ affinity, cell-based potency and efficacy, and CYP3A4 inhibition (Table 4). Various pyridines with different C3 substituents (compounds **30**–**33**) had similar biochemical affinity compared to 3-chloropyridine **27**, but showed reduced potency in the cell-based PPARγ-Gal4 transactivation assay and were potent inhibitors of CYP3A4. C-ring pyridines substituted at the C2 or C6 position generally exhibited diminished PPARγ affinity (data not shown). We undertook a survey of biaryl heterocyclic C-rings and discovered 3-alkoxyquinoline analog **3** (INT131), a ligand with an IC_{50} value of 18 nM and an EC_{50} value of 0.1 μM with 30% efficacy compared to rosiglitazone (**1**). This ring system is notable because it imparts a significant decrease in CYP3A4 inhibition (IC_{50} = 25 μM) to ligand **3**. Closely related analogs **34**–**37** display similar in vitro profiles and also show decreased inhibition of CYP3A4. The 6-alkoxyquinoline C-ring analog **38** maintained PPARγ affinity, but without a similar decrease in CYP3A4 inhibition. Other alkoxyquinoline isomers lost significant affinity (data not shown). Additionally, analogs without aromatic ring nitrogens, such as 3-alkoxynaphthalene **39**, exhibited reduced affinity.

Table 5
Rat pharmacokinetic properties for compounds **3**, and **34–37**[a]

Compd	PO $AUC_{24\ h}$ (μM h)	PO C_{max} (μM)
3	30	1.1
34	105	11
35	82	4.8
36	112	8.5
37	3.4	0.92

[a] Determined for a single 5 mg/kg oral dose in Sprague–Dawley rats.

Table 6
Dose-dependent rat pharmacokinetic properties for compound **3**[a]

Dose (mg/kg)	PO $AUC_{24\ h}$ (μM h)	PO C_{max} (μM)
0.1	1.1	0.08
0.3	2.6	0.13
1.0	5.1	0.39
2.0	8.3	0.66
30	71	4.3
100	100	6.1

[a] Determined for a single 5 mg/kg oral dose in Sprague–Dawley rats.

In addition to the attractive in vitro PPARγ binding, efficacy, and CYP3A4 inhibition profiles, quinoline INT131 (**3**) has a suitable pharmacokinetic profile for oral dosing. A 5 mg/kg oral dose in Sprague–Dawley rats resulted in an AUC of 30 μM h over 24 h with a C_{max} of 1.1 μM (Table 5). This represents a 19-fold increase in oral exposure compared to initial lead **5**. INT131 (**3**) also exhibits dose-dependent increases in oral exposure (both AUC and C_{max}) at doses ranging from 0.1–100 mg/kg (Table 6). Compounds **34**–**37** also display pharmacokinetic profiles suitable for in vivo oral administration (Table 5). Finally, INT131 (**3**) is highly selective for PPARγ over other nuclear receptors. No activation of human PPARα, PPARδ, FXR, LXR, PXR or RXR or of rodent PPARs was observed below a concentration of 10 μM.

2.4. In vivo efficacy studies

Based on suitable in vitro profiles, a lack of CYP3A4 inhibition, and improved oral PK, several compounds were profiled for efficacy in validated in vivo models. The well-established KKAy diabetic mouse model was selected because it displays hyperglycemia, insulin resistance, and severe obesity.[22] Mice were fed 30 mg/kg doses of partial agonists **3**, and **34**–**37** or 1 mg/kg dose of positive control rosiglitazone (**1**) for 3 days. On day 4, insulin, blood glucose, and body weight measurements were taken and compared to those taken in the vehicle control group (Table 7).

When dosed orally at 30 mg/kg/day, INT131 (**3**) and quinoline **36** both showed greater efficacy in lowering blood glucose and insulin levels than a 1 mg/kg/day dose of rosiglitazone (**1**).[23] Additionally, body weight gain in the animals treated with partial agonists **3** (170% of the weight gain observed in the vehicle control) was statistically lower than body weight gain in the rosiglitazone-treated group (228% of control), although food intake between the two rodent groups was statistically identical. Good glucose-lowering was also observed with quinolines **34** and **37**, while poor efficacy was observed with quinoline **35**. Weight gain and efficacy in glucose lowering did not necessarily trend together. For instance, quinoline **36**, a ligand that demonstrated the most robust glucose-lowering effect, caused less weight gain than less-efficacious analogs **1**, **3**, **34**, or **37**. Finally, these results demonstrate that in vivo glucose-lowering efficacy is not directly related to full PPARγ receptor activation, since partial agonists **3**, **34**, **36**, and **37** have as good or better efficacy in glucose lowering than the full agonist rosiglitazone (**1**). This observation is in agreement with the reported in vivo efficacy of other SPPARγMs.[12]

Table 7
Studies in KKAy diabetic mice treated with compounds **1**, **3**, and **34–37** for 3 days

Compd[a]	Insulin[d] (%)	Blood glucose[c] (%)	Body weight gain[e,f] (%)
1[b]	−18.9 (±2.5)	−18.6 (±5.5)	228 (±20)
3	−43.3 (±6.9)	−31.3 (±3.0)	170 (±28)
34	−37.0 (±5.4)	−18.3 (±5.0)	195 (±20)
35[c]	—	−5.3	102
36	−44.8 (±12.9)	−45.5 (±5.6)	143 (±14)
37	−25.6 (±4.0)	−23.8 (±4.7)	195 (±21)

[a] Dose was 30 mg/kg/day; values reported as mean ± standard deviation (n = 8).
[b] Dose of rosiglitizone (**1**) was 1.0 mg/kg/day.
[c] Insulin measurements and standard deviations not available.
[d] Change in insulin and blood glucose were calculated as the percentage change from levels measured in vehicle control.
[e] Percent increase in body weight compared to weight gain in vehicle control (weight gain control = 100%).
[f] Food intake was not statistically different between animal groups.

Quinolines **3** and **35**–**37** were further evaluated in the Zucker (fa/fa) fatty rat, an established model for type 2 diabetes that displays hyperglycemia and severe obesity (Table 8).[24] Compound was administered as a suspension by oral gavage once per day for 14 days, and then clearance of blood glucose was measured in an oral glucose tolerance test. We were pleased to see that quinolines **3**, **35**, and **36** displayed blood glucose lowering with a 3 mg/kg/day dose that was statistically indistinguishable from that provided by rosiglitazone (1) at a 1 mg/kg dose. In contrast, quinoline **37** was significantly less efficacious. Even at a daily dose of 30 mg/kg it caused less glucose-lowering than rosiglitazone at 1 mg/kg/day. The origin of the disparate efficacies induced by compounds **35** and **37** in the KKAy mouse model and the Zucker fatty rat model is currently unclear but may reflect differences in compound exposure between the two rodent species. In these single-dose studies, quinolines **3** and **36** caused body weight gain statistically indistinguishable from rosiglitazone (**1**), while quinolines **35** and **37** caused greater weight gain. Additional dose–response efficacy studies were performed to determine the dose necessary to reduce blood glucose levels by 30% compared to vehicle control ($ED_{-30\%}$). In this study, INT131 (**3**) demonstrated superior in vivo potency compared to the other quinoline analogs ($ED_{-30\%}$ = 0.5 mg/kg). Additionally, these results revealed that in the single dose study INT131 (**3**) was administered at a dose significantly higher than that required for maximal efficacy. We hypothesized that Zucker rats administered INT131 (**3**) at concentrations near the maximum efficacious dose might display decreased weight gain compared to rats administered rosiglitazone (**1**). Thus we undertook more

Table 8
Studies in Zucker (fa/fa) fatty rats treated with compounds **1**, **3**, and **35–37** for 14 days

Compd[a]	Blood glucose[d,e] (%)	Body weight gain[d,e,f] (%)	$ED_{-30\%}$[g] (mg/kg)
1[b]	−31 (±2)	33 (±7)	—
3	−30 (±7)	42 (±6)	0.5
35	−34 (±6)	55 (±8)	3.0
36	−21 (±10)	36 (±7)	5.0
37[c]	−19 (±7)	53 (±13)	>30

[a] Dose was 3.0 mg/kg/day.
[b] Dose of rosiglitazone (**1**) was 1.0 mg/kg/day.
[c] Dose was 30 mg/kg/day.
[d] Change in blood glucose and total body weight were calculated as the% change compared to vehicle control.
[e] Mean ± standard deviation (single experiment; n = 6).
[f] Food intake was not statistically different between animal groups.
[g] Dose necessary to achieve −30% glucose lowering relative to vehicle control; determined from dose–response studies conducted at 0.1, 0.3, 1.0, 3.0, and 80 mg/kg/day.

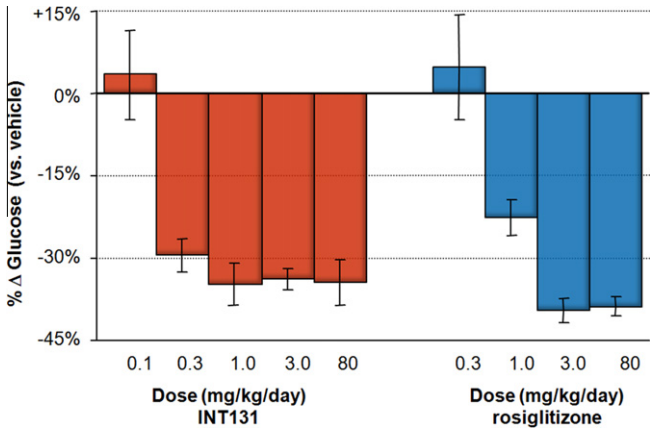


Figure 4. Dose-dependent blood glucose levels in Zucker fatty rats treated with INT131 (**3**) and rosiglitzaone (**1**).

thorough dose–response studies. Figure 4 shows the results of a full dose–response study comparing Zucker rats dosed with either INT131 (**3**) or rosiglitazone (**1**). Both compounds exhibited statistically similar maximal in vivo efficacy and lowered glucose by >30% compared to the vehicle control. However as we previously observed, INT131 (**3**) displayed nearly 10-fold superior potency, achieving nearly 30% reduction in blood glucose levels with a 0.3 mg/kg dose compared to the 3.0 mg/kg dose required to achieve similar efficacy with rosiglitazone (**1**). Additionally, INT131-treated rats were accompanied by less total body weight gain, heart weight gain, and lung weight gain than rosiglitazone-treated rats, suggesting reduced fluid retention with INT131 (**3**) treatment compared to rosiglitazone (**1**) treatment. These and other in vivo results have been previously described.[10] Given its unique pharmacological and safety profile, INT131 (**3**) was selected for further preclinical profiling.

2.5. Structural biology

To further understand the unique activity of our selective PPARγ modulators, INT131 (**3**) was co-crystallized with the ligand binding domain of PPARγ (PPARγLBD) in the presence of a peptide derived from the SRC-1 co-activator protein,[25] and the X-ray structure was solved with a resolution of 2.4 Å (Fig. 5).[26,27] The structure of the PPARγLBD co-crystallized with INT131 (**3**) was not significantly different from other previously reported PPARγLBD structures, including the orientation of the AF2 helix, which is proposed to be critical for transcriptional activity.[28–30] INT131 (**3**) occupies the ligand-binding pocket within the PPARγLBD, collapsed into a U-shaped conformation around Cys^{285} of helix 3 (H3), and partially overlaps the rosiglitazone (**1**) binding domain (Fig. 5a and b).

Like the central ring of rosiglitazone (**1**), the phenyl B-ring of INT131 (**3**) occupies a narrow hydrophobic channel between helix 3 and helix 7, sandwiched between Cys^{285} (S–Aryl distance = 3.6 Å) and Leu^{330} (CH_3–Aryl distance = 3.6 Å) at distances that have been reported for close SH···π and CH···π interactions (Fig. 5d).[31–34] One B-ring Cl substituent is oriented toward helix 3, experiencing

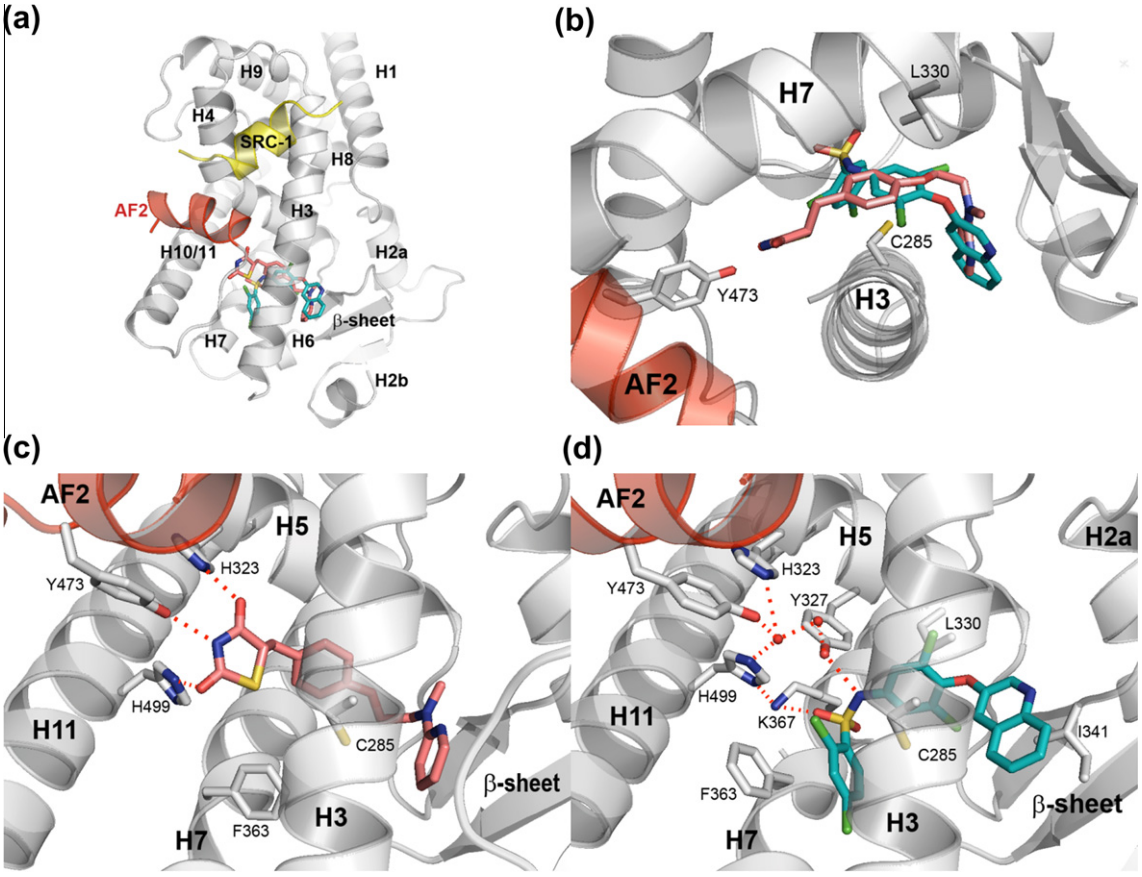


Figure 5. (a and b) X-ray structure of INT131 (**3**, blue) bound to PPARγLBD (grey, AF2 helix in red) with SRC-1 co-activator (yellow) and rosiglitazone (**1**, pink) superimposed. (c) X-ray structure of rosiglitazone bound to PPARγLBD showing direct ligand stabilization of the AF2 helix by H-bond between Tyr473 and the thiazolidinedione ring. (d) X-ray structure of INT131 bound to PPARγLBD showing indirect ligand stabilization of the AF2 helix through water-mediated H-bond network between Tyr473 and the sulfonamide linker.

hydrophobic interactions with the alkyl chain of Arg^{288} (Cl–CH_2 distance = 3.2 Å; not shown in Fig. 5d). The other Cl substituent is geared into a solvent-exposed area and does not interact with the protein.

The quinoline C-ring wraps around helix 3 and occupies the ligand entry region between helix 3 and the β-sheet, similar to the aminopyridine ring of rosiglitazone. Helix 3 Cys^{285} resides nearly in the plane formed by the C-ring, 3.6 Å from the quinoline C4, a known optimal geometry for S···H–C_{Aryl} interactions.[35] Additionally, the quinoline face experiences close packing interactions with the hydrophobic Ile^{341} side chain of the β-sheet (3.6–4.0 Å).

The sulfonamide linker and A-ring of INT131 (**3**) occupy a significantly different space in the PPARγLBD compared to the rosiglitazone (**1**) thiazolidinedione ring (Fig. 5c and d). The diarylsulfonamide binds with the nitrogen lone pair bisecting the O=S=O angle. Additionally, the sulfone is oriented with one S=O bond in plane with the aromatic A-ring, geared away from the *ortho*-Cl substituent. This is a well-known low-energy conformation for diarylsulfonamides containing an *ortho*-substituent on the sulfone aryl ring.[36] As a consequence, the side chain of Phe^{363} must rotate nearly 180° from its conformation in the rosiglitazone-bound structure[37] to induce a narrow hydrophobic pocket that accommodates the A-ring of INT131 (**3**) and establishes a parallel-displaced face-to-face aryl–aryl interaction between Phe^{363} and the ligand A-ring.[38] The A-ring 4-Cl substituent is tightly fitted into a region between helix 3 and helix 7 that contains hydrophobic side chains and does not accommodate large or polar substituents (Table 3).

The most significant consequence of the INT131 (**3**) binding mode is that INT131 (**3**) does not directly interact with the AF2 helix (Fig. 5d). This is in stark contrast to rosiglitazone (**1**), which participates in a direct hydrogen bond between the thiazolidinedione nitrogen and Tyr^{473} (Fig. 5c). Instead, stabilization of the AF2 helix in the INT131-bound structure occurs through a network of hydrogen bonds, utilizing two structurally conserved water molecules within the TZD pocket (Fig. 5d). One highly stabilized water molecule forms hydrogen bonds to Tyr^{473} of the AF2 helix (2.6 Å) as well as to His^{449} (2.9 Å), His^{323} (3.3 Å) and to a second water molecule (2.6 Å), that also forms a H-bond to Tyr^{327} (2.5 Å). The sulfonamide N–H of INT131 (**3**) participates with this network through a H-bond with Tyr^{327} (2.7 Å), and one sulfonamide oxygen atom interacts through a weak H-bond with Lys^{367} (3.4 Å) that is also H-bonded to His^{449} (3.0 Å). As previously mentioned, it has been hypothesized that the agonistic activity of rosiglitazone arises from ligand stabilization of the flexible AF2 helix into the appropriate conformation to recruit co-activator proteins and activate the transcriptional machinery.31,[39] We propose that the indirect stabilization of the AF2 helix by INT131 (**3**) and other ligands in this series only partially stabilizes the AF2 helix and results in the observed partial agonist efficacy profile.

3. Conclusions

In summary, we have discovered a novel class of selective and potent PPARγ modulators that display a unique pharmacological profile compared to the marketed TZD full agonist rosiglitazone (**1**). Starting from initial hit sulfonamide **4**, which had a poor pharmacokinetic profile, we undertook structure–activity relationship studies that culminated in the discovery of INT131 (**3**), a partial agonist in the PPARγ-Gal4 transactivation assay. In two different in vivo models for type 2 diabetes, INT131 (**3**) showed similar glucose-lowering ability and superior in vivo potency with a reduced side effect profile compared to rosiglitazone (**1**). X-ray crystallography studies revealed a unique binding mode for INT131 (**3**) that we propose is responsible for its pharmacological profile. INT131 (**3**) is currently being evaluated in advanced clinical trials and shows initial promise as a novel therapeutic for the treatment of type 2 diabetes.[40]

4. Experimental section

4.1. General chemistry methods

^{1}H NMR spectra were obtained on Bruker DRX 400 MHz or Varian Gemini 400 MHz spectrometers. Chemical shifts are reported in parts per million (ppm). The abbreviations s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and br = broad are used throughout. Melting points were determined in open-ended capillary tubes using a FP62 Mettler Toledo melting point apparatus and are uncorrected. Elemental analysis was performed by Atlantic Microlab Inc, Norcross, GA and found values are within ±0.4% of calculated values. Electrospray mass spectra were determined with a Hewlett Packard Series 1100 MSD ES mass spectrometer. Reaction progress was monitored by thin layer chromatography (TLC) using Analtech 0.25 mm precoated glass plates, visualized with UV light, I_2, or 7% phosphomolybdic acid in EtOH. Flash chromatography was performed using EM Science silica gel 60 (230–400 mesh). Solvents were of anhydrous quality purchased from Aldrich Chemical Co. and were used as received. Reagents were purchased from commercial vendors and were used as supplied, unless otherwise stated. Compound **4** was obtained for our screening library from Maybridge Chemicals as BTB07901.

4.2. General procedure for the synthesis of diarylsulfonamide PPARγ ligands 3 and 5–39

A 4-halonitrobenzene (1.0 equiv), a hydroxyarene, and Cs_2CO_3 (1.1 equiv) were combined in DMF and the resulting heterogeneous mixture was stirred vigorously at 25–70 °C until all 4-halonitrobenzene was consumed (2–24 h). The reaction mixture was diluted with H_2O and was adjusted to pH 5 with 2 N HCl (aq). The solution was extracted three times with EtOAc, and the organic layers were combined, washed once with brine solution, dried over $MgSO_4$, filtered and concentrated in vacuo to furnish the desired diaryl ether that was used directly without further purification.

The nitrodiaryl ether (1.0 equiv) and $SnCl_2{\cdot}H_2O$ (5.0 equiv) were combined in EtOAc (0.5 M), and the heterogeneous mixture was heated at reflux for 1–5 h. The reaction mixture was allowed to cool to rt, and equal volumes of 2 N NaOH (aq) solution and EtOAc were added to precipitate tin salts. The tin salts were removed by filtration through Celite® and were washed with additional EtOAc. The filtrate was transferred to a separatory funnel. The layers were separated and the organic layer was washed once with brine, dried over $MgSO_4$ and concentrated in vacuo to give the desired aniline that was used directly without further purification.

The aniline (1.0 equiv), a benzenesulfonyl chloride (1.1 equiv), and pyridine (3.0 equiv) were combined in CH_2Cl_2, and the solution was maintained at 25–60 °C until the aniline was consumed (1–24 h). The reaction was diluted with H_2O, adjusted to pH 5 with 2 N HCl (aq), and extracted three times with EtOAc. The combined organics were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give the desired sulfonamide (50–90% over the three-step sequence) that was purified by column chromatography, trituration, or recrystallization.

4.2.1. 2,4-Dichloro-*N*-(3,5-dichloro-4-(quinolin-3-yloxy) phenyl)benzenesulfonamide (INT131, 3)

3,4,5-Trichloronitrobenzene, quinolin-3-ol (prepared according to a known procedure),[41] and 2,4-dichlorobenzene sulfonyl chloride were combined according to the general procedure to give

INT131 (**3**) as a white amorphous solid, mp 192 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.40 (s, 1H); 8.85 (d, J = 3.2 Hz, 1H); 8.17 (d, J = 8.8 Hz, 1H); 8.00 (br d, J = 8.4, 1H); 7.96 (d, J = 2.4 Hz, 1H); 7.87 (br d, J = 8.4 Hz, 1H); 7.71 (dd, J = 8.4, 2.0 Hz, 1H); 7.65 (ddd, J = 8.4, 6.8, 1.6 Hz, 1H); 7.56 (ddd, J = 8.4, 7.2, 1.6 Hz, 1H); 7.44 (d, J = 2.8 Hz, 1H); 7.30 (s, 2H). ^{13}C NMR (500 MHz, DMSO-d_6), 149.8, 144.0, 142.5, 141.5, 139.3, 136.2, 135.0, 132.8, 132.1, 131.8, 129.0, 128.6, 128.3, 127.8, 127.9, 127.5, 127.4, 119.1, 115.5. IR (film) 3053, 1600, 1576, 1468, 1342, 1161, 982, 748 cm^{-1}. MS (ESI): m/z 514.8 (M+H)$^+$. Anal. Calcd for $C_{21}H_{12}Cl_4N_2O_3S$: C, 49.05; H, 2.35; N, 5.45. Found: C, 49.25; H, 2.44; N, 5.35. HPLC: 99 Area%.

4.2.2. 2-(5-Chloropyridin-3-yloxy)-5-(2,4-dichloro-5-methylphenylsulfonamido)-*N*-ethylbenzamide (5)

2-Chloro-5-nitro-*N*-ethylbenzamide, 5-chloropyridin-3-ol and 2,4-dichloro-5-methylbenzene sulfonyl chloride were combined according to the general procedure to give ligand **5** as an off-white solid, mp 186–187.5 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 (d, J = 2.4 Hz, 1H); 8.15 (d, J = 2.4 Hz, 1H); 8.04 (t, J = 5.6 Hz, 1H); 7.88 (d, J = 0.8 Hz, 1H); 7.46 (s, 1H); 7.17 (t, J = 2.4 Hz, 1H); 6.91 (d, J = 2.4 Hz, 1H); 6.85 (dd, J = 8.8, 2.8 Hz, 1H); 6.73 (d, J = 8.8 Hz, 1H); 3.04 (dq, J = 7.6, 6.0 Hz, 2H); 2.28 (s, 3H); 0.86 (t, J = 7.6 Hz, 3H). IR (film) 3412, 3134, 1636, 1162, 915 cm^{-1}. MS (ESI): m/z 514.0 (M+H)$^+$. Anal. Calcd for $C_{21}H_{18}Cl_3N_3O4S$: C, 48.99; H, 3.52; N, 8.10; Cl, 20.66. Found: C, 48.80; H, 3.51; N, 8.10; Cl, 20.81.

4.2.3. 2-(5-Chloropyridin-3-yloxy)-5-(2,4-dichlorophenylsulfonamido)-*N*-ethylbenzamide (6)

2-Chloro-5-nitro-*N*-ethylbenzamide, 5-chloropyridin-3-ol and 2,4-dichlorosulfonylbenzenesulfonyl chloride were combined according to the general procedure to give ligand **6** as an off-white solid, mp 179 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.90 (s, 1H); 8.37 (d, J = 1.9 Hz, 1H); 8.25 (t, J = 5.5 Hz, 1H); 8.23 (d, J = 2.4 Hz, 1H); 8.03 (d, J = 8.6 Hz, 1H); 7.90 (d, J = 2.0 Hz, 1H); 7.64 (dd, J = 8.8, 2.0 Hz, 1H); 7.40 (t, J = 2.1 Hz, 1H); 7.31 (d, J = 2.7 Hz, 1H); 7.19 (dd, J = 8.8, 2.7 Hz, 1H); 7.05 (d, J = 8.8 Hz, 1H); 3.11 (dq, J = 5.8, 7.1 Hz, 2H); 0.91 (t, J = 7.2 Hz, 3H). IR (film) 3407, 1634, 1538, 1350, 1223, 1162, 910, 813 cm^{-1}. MS (ESI): m/z 502.0 (M+H)$^+$. Anal. Calcd for $C_{20}H_{16}Cl_3N_3O_4S$: C, 47.93; H, 3.22; N, 8.39; Cl, 21.24. Found: C, 47.80; H, 3.22; N, 8.36; Cl, 21.51.

4.2.4. 5-(2-Chloro-4-(trifluoromethyl)phenylsulfonamido)-2-(5-chloropyridin-3-yloxy)-*N*-ethylbenzamide (7)

2-Chloro-5-nitro-*N*-ethylbenzamide, 5-chloropyridin-3-ol and 2-chloro-4-trifluoromethylsulfonylbenzenesulfonyl chloride were combined according to the general procedure to give ligand **7** as an off-white solid, mp 159 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.06 (s, 1H); 8.36 (d, J = 2 Hz, 1H); 8.25 (br t, 1H); 8.24 (br d, J = 7.6, 1H); 8.22 (d, J = 2.4 Hz, 1H); 8.15 (br s, 1H); 7.94 (d, J = 8.4 Hz, 1H); 7.40 (t, J = 2.4 Hz, 1H); 7.32 (d, J = 2.8 Hz, 1H); 7.20 (dd, J = 8.8, 2.8 Hz, 1H); 7.05 (d, J = 8.8 Hz, 1H); 3.10 (dq, J = 6.4, 7.2 Hz, 2H); 0.90 (t, J = 7.2 Hz, 3H). IR (film) 3416, 3087, 1644, 1320, 1162, 916, 836, 723 cm^{-1}. MS (ESI): m/z 534.0 (M+H)$^+$. Anal. Calcd for $C_{21}H_{16}Cl_2F_3N_3O_4S$: C, 47.20; H, 3.02; N, 7.86; Cl, 13.37; F, 10.67. Found: C, 47.37; H, 3.02; N, 7.85; Cl, 13.37; F, 10.49.

4.2.5. 5-(4-Bromo-2-(trifluoromethoxy)phenylsulfonamido)-2-(5-chloropyridin-3-yloxy)-*N*-ethylamide (8)

2-Chloro-5-nitro-*N*-ethylbenzamide, 5-chloropyridin-3-ol and 4-bromo-2-trifluoromethoxybenzenesulfonyl chloride were combined according to the general procedure to give ligand **8** as an off-white solid, mp 157 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 (d, J = 1.8 Hz, 1H), 8.30–8.23 (m, 1H), 8.25 (d, J = 2.3 Hz, 1H), 7.92 (d, J = 8.5 Hz, 1H), 7.85–7.80 (m, 2H), 7.41–7.39 (m, 1H), 7.31 (d, J = 2.5 Hz, 1H), 7.20 (dd, J = 8.5, 2.3 Hz, 1H), 7.10 (d, J = 9.1 Hz, 1H), 3.15–3.08 (m, 2H), 0.93 (t, J = 7.2 Hz, 3H). IR (film) 1636, 1576, 1540, 1472, 1248, 1162 cm^{-1}. MS (ESI): m/z 596.0 (M+H)$^+$. HPLC: 95 Area%.

4.2.6. 2-(5-Chloropyridin-3-yloxy)-5-(3,4-dichlorophenylsulfonamido)-*N*-ethylbenzamide (9)

2-Chloro-5-nitro-*N*-ethylbenzamide, 5-chloropyridin-3-ol and 3,4-dichlorophenylbenzenesulfonyl chloride were combined according to the general procedure to give ligand **9** as an off-white solid, mp 179 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.58 (s, 1H); 8.37 (d, J = 2 Hz, 1H); 8.27 (br t, 1H); 8.24 (d, J = 2.4 Hz, 1H); 7.91 (d, J = 2.4 Hz, 1H); 7.87 (d, J = 8.8 Hz, 1H); 7.70 (dd, J = 8.8, 2.4 Hz, 1H); 7.42 (t, J = 2.4 Hz, 1H); 7.31 (d, J = 2.4 Hz, 1H); 7.19 (dd, J = 8.8, 2.8 Hz, 1H); 7.07 (d, J = 8.8 Hz, 1H); 3.12 (dq, J = 6.4, 7.2 Hz, 2H); 0.92 (t, J = 7.2 Hz, 3H). IR (film) 3403, 3145, 1634, 1541, 1338, 1164, 921 cm^{-1}. MS (ESI): m/z 502.0 (M+H)$^+$. Anal. Calcd for $C_{20}H_{17}Cl_2N_3O_4S$: C, 47.97; H, 3.22; N, 8.79; Cl, 21.24. Found: C, 48.02; H, 3.17; N, 8.33; Cl, 21.23.

4.2.7. 5-(4-Chlorophenylsulfonamido)-2-(5-chloropyridin-3-yloxy)-*N*-ethylbenzamide (10)

2-Chloro-5-nitro-*N*-ethyl-benzamide, 5-chloropyridin-3-ol and 4-chloro-5-methylbenzenesulfonyl chloride were combined according to the general procedure to give ligand **10** as an off-white solid, mp 171 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.52 (s, 1H); 8.367 (d, J = 2.0 Hz, 1H); 8.25 (br t, 1H); 8.23 (d, J = 2.4 Hz, 1H); 7.76 (d, J = 8.4 Hz, 2H); 7.65 (d, J = 8.4 Hz, 2H); 7.40 (t, J = 2.4 Hz, 1H); 7.29 (d, J = 2.4 Hz, 1H); 7.19 (dd, J = 8.8, 2.8 Hz, 1H); 7.04 (d, J = 8.8 Hz, 1H); 3.14 (dq, J = 6.0, 7.2 Hz, 2H); 0.91 (t, J = 7.2 Hz, 3H). IR (film) 3495, 3407, 1641, 1161, 915, 752 cm^{-1}. MS(EI): m/z 466.0 (M+H)$^+$. Anal. Calcd for $C_{20}H_{17}Cl_2N_3O_4$: C, 51.51; H, 3.67; N, 9.01; Cl, 15.20. Found: C, 51.51; H, 3.68; N, 8.97; Cl, 15.41.

4.2.8. 2-(5-Chloropyridin-3-yloxy)-*N*-ethyl-5-(4-iodophenylsulfonamido)benzamide (11)

2-Chloro-5-nitro-*N*-ethylbenzamide, 5-chloropyridin-3-ol and 4-iodobenzenesulfonyl chloride were combined according to the general procedure to give ligand **11** as an off-white solid, mp 165 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.51 (s, 1H); 8.37 (d, J = 1.9 Hz, 1H); 8.25 (t, J = 5.6 Hz, 1H); 8.24 (d, J = 2.4 Hz, 1H); 7.97 (d, J = 8.5, 1H); 7.52 (d, J = 8.5, 1H); 7.40 (t, J = 2.2 Hz, 1H); 7.30 (d, J = 2.7 Hz, 1H); 7.19 (dd, J = 8.8, 2.7 Hz, 1H); 7.05 (d, J = 8.8 Hz, 1H); 3.12 (dq, J = 5.8, 7.1 Hz, 2H); 0.92 (t, J = 7.2 Hz, 3H). IR (film) 3412, 3169, 1640, 1266, 1159, 735 cm^{-1}. MS (ESI): m/z 558.1 (M+H)$^+$. Anal. Calcd for $C_{20}H_{17}ClIN_3O_4S$: C, 43.07; H, 3.07; N, 7.53. Found: C, 42.73; H, 3.14; N, 7.39.

4.2.9. 2-(5-Chloropyridin-3-yloxy)-*N*-ethyl-5-(4-methoxyphenylsulfonamido)benzamide (12)

2-Chloro-5-nitro-*N*-ethylbenzamide, 5-chloropyridin-3-ol and 4-methoxybenzenesulfonyl chloride were combined according to the general procedure to give ligand **12** as an off-white solid, mp 155 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.31 (s, 1H); 8.35 (d, J = 1.6 Hz, 1H); 8.25 (t, J = 5.6 Hz, 1H); 8.21 (d, J = 2.4 Hz, 1H); 7.69 (dd, J = 8.8, 2.0 Hz, 2H); 7.38 (t, J = 2.4 Hz, 1H); 7.29 (d, J = 2.4 Hz, 1H); 7.19 (dd, J = 8.8, 2.4 Hz, 1H); 7.07 (dd, J = 8.8, 2.0 Hz, 2H); 7.04 (d, J = 8.8 Hz, 1H); 3.10 (dq, J = 6.4, 7.2 Hz, 2H); 0.90 (t, J = 7.2 Hz, 3H). IR (film) 3160, 3144, 2940, 1644, 1223, 1156 cm^{-1}. MS (ESI): m/z 460.0 (M−H)$^-$. Anal. Calcd for $C_{21}H_{20}ClN_3O_5S$: C, 54.60; H, 4.36; N, 9.10. Found: C, 54.38; H, 4.36; N, 8.95.

4.2.10. 2-(5-Chloropyridin-3-yloxy)-*N*-ethyl-5-(4-nitrophenylsulfonamido)benzamide (13)

2-Chloro-5-nitro-*N*-ethylbenzamide, 5-chloropyridin-3-ol and 4-nitrobenzenesulfonyl chloride were combined according to the

general procedure to give ligand **13** as an off-white solid, mp 199–205 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.77 (s, 1H); 8.39 (d, J = 8.8 Hz, 2H); 8.37 (d, J = 2 Hz, 1H); 8.25 (br t, 1H); 8.23 (d, J = 2.4 Hz, 1H); 8.01 (d, J = 8.8 Hz, 2H); 7.43 (t, J = 2.4 Hz, 1H); 7.32 (d, J = 2.8 Hz, 1H); 7.21 (dd, J = 8.8, 2.8 Hz, 1H); 7.06 (d, J = 8.8 Hz, 1H); 3.11 (dq, J = 6.0, 7.2 Hz, 2H); 0.91 (t, J = 7.2 Hz, 3H). IR (film) 1642, 1523, 1163, 914, 895, 738 cm^{-1}. MS (ESI): m/z 477.0 (M+H)$^+$. Anal. Calcd for $C_{20}H_{17}ClN_4O_6S$: C, 50.37; H, 3.59; N, 11.75; Cl, 7.43. Found: C, 50.44; H, 3.59; N, 11.55; Cl, 7.42.

4.2.11. 5-(4-*tert*-Butylphenylsulfonamido)-2-(5-chloropyridin-3-yloxy)-*N*-ethylbenzamide (14)

2-Chloro-5-nitro-*N*-ethylbenzamide, 5-chloropyridin-3-ol and 4-*tert*-butylbenzenesulfonyl chloride were combined according to the general procedure to give ligand **14** as an off-white solid, mp 150 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.43 (s, 1H); 8.36 (d, J = 2.0 Hz, 1H); 8.26 (t, J = 5.7 Hz, 1H); 8.21 (d, J = 2.5 Hz, 1H); 7.71 (d, J = 8.6, 2H); 7.60 (d, J = 8.6 Hz, 2H); 7.38 (t, J = 2.2 Hz, 1H); 7.30 (d, J = 2.7 Hz, 1H); 7.23 (dd, J = 8.8, 2.8 Hz, 1H); 7.05 (d, J = 8.8 Hz, 1H); 3.10 (dq, J = 5.8, 7.2 Hz, 2H); 1.27 (s, 9H); 0.91 (t, J = 7.2 Hz, 3H). IR (film) 3408, 2953, 1636, 1164 cm^{-1}. MS (ESI): m/z 488.0 (M+H)$^+$.Anal. Calcd for $C_{24}H_{26}ClN_3O_4S$: C, 59.07; H, 5.37; N, 8.61; Cl, 7.26. Found: C, 58.91; H, 5.35; N, 8.62; Cl, 7.14.

4.2.12. 2-(5-Chloropyridin-3-yloxy)-*N*-ethyl-5-(4-(methylsulfonyl)phenylsulfonamido)benzamide (15)

2-Chloro-5-nitro-*N*-ethylbenzamide, 5-chloropyridin-3-ol and 4-methylsulfonylbenzenesulfonyl chloride were combined according to the general procedure to give ligand **15** as an off-white solid, mp 156 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.77 (s, 1H); 8.37 (d, J = 2.0 Hz, 1H); 8.27 (t, J = 5.5 Hz, 1H); 8.24 (d, J = 2.4 Hz, 1H); 8.14 (d, J = 8.5, 2H); 8.02 (d, J = 8.4 Hz, 2H); 7.45 (t, J = 2.2 Hz, 1H); 7.32 (d, J = 2.7 Hz, 1H); 7.23 (dd, J = 8.8, 2.8 Hz, 1H); 7.06 (d, J = 8.8 Hz, 1H); 3.29 (s, 3H); 3.11 (dq, J = 5.8, 7.2 Hz, 2H); 0.91 (t, J = 7.2 Hz, 3H). IR (film) 3414, 1639, 1169 cm^{-1}. MS (ESI): m/z 510.0 (M+H)$^+$. Anal. Calcd for $C_{21}H_{20}ClN_3O_6S_2$: C, 49.46; H, 3.95; N, 8.24; Cl, 6.95. Found: C, 48.14; H, 3.82; N, 7.93; Cl, 6.85.

4.2.13. *N*-(3-Acetyl-4-(5-chloropyridin-3-yloxy)phenyl)-2,4-dichlorobenzenesulfonamide (16)

2-Chloro-5-nitroacetophenone, 5-chloropyridin-3-ol and 2,4-dichlorobenzenesulfonyl chloride were combined according to the general procedure to give ligand **16** as an off-white solid, mp 149 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, J = 1.9 Hz, 1H); 8.23 (d, J = 2.4 Hz, 1H); 7.95 (d, J = 8.5 Hz, 1H); 7.55 (d, J = 2 Hz, 1H); 7.53 (d, J = 2.9 Hz, 1H); 7.38–7.34 (m, 2H); 7.23 (d, J = 4.4 Hz, 1H); 7.14 (s, 1H); 6.86 (d, J = 8.8 Hz, 1H); 2.54 (s, 3H). IR (film) 3225, 1666, 1481, 1258, 1167, 819 cm^{-1}. MS (ESI): m/z: 470.9 (M–H)$^-$. HPLC: 95 Area%.

4.2.14. 2,4-Dichloro-*N*-(3-chloro-4-(5-chloropyridin-3-yloxy)phenyl)benzenesulfonamide (17)

3,4-Dichloronitrobenzene, 5-chloropyridin-3-ol and 2,4-dichlorobenzenesulfonyl chloride were combined according to the general procedure to give ligand **17** as an off-white solid, mp 138 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.03 (s, 1H); 8.40 (d, J = 1.8 Hz, 1H); 8.24 (d, J = 2.4 Hz, 1H); 8.06 (d, J = 8.5 Hz, 1H); 7.90 (d, J = 2.0 Hz, 1H); 7.65 (dd, J = 8.5, 2.0 Hz, 1H); 7.48 (t, J = 2.2 Hz, 1H); 7.28 (d, J = 2.5 Hz, 1H); 7.21 (d, J = 8.8 Hz, 1H); 7.10 (dd, J = 8.8, 2.5 Hz, 1H). IR (film) 3088, 1574, 1485, 1164, 931 cm^{-1}. MS (ESI): m/z: 464.9 (M+H)$^+$. Anal. Calcd for $C_{17}H_{10}Cl_4N_2O_3S$: C, 43.99; H, 2.17; N, 6.04. Found: C, 44.06; H, 2.15; N, 6.03.

4.2.15. 2,4-Dichloro-*N*-(4-(5-chloropyridin-3-yloxy)-3-fluorophenyl)benzenesulfonamide (18)

3-Fluoro-4-chloronitrobenzene, 5-chloropyridin-3-ol and 2,4-dichlorobenzenesulfonyl chloride were combined according to the general procedure to give ligand **18** as an off-white solid, mp 155 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.05 (s, 1H); 8.39 (d, J = 1.8 Hz, 1H); 8.28 (d, J = 2.4 Hz, 1H); 8.07 (d, J = 8.6 Hz, 1H); 7.90 (d, J = 2.1Hz, 1H); 7.64 (dd, J = 8.6, 2.1 Hz, 1H); 7.52 (t, J = 2.2 Hz, 1H); 7.24 (t, J = 9.0 Hz, 1H); 7.05 (dd, J = 13.2, 2.5 Hz, 1H); 6.94 (m, 1H). IR (film) 3090, 3074, 2726, 1575, 1508, 1168, 1152, 934, 821 cm^{-1}. MS (ESI): m/z: 449.0 (M+H)$^+$. Anal. Calcd for $C_{17}H_{10}Cl_3FN_2O_3S$: C, 45.61; H, 2.25; N, 6.26. Found: C, 45.52; H, 2.22; N, 6.20.

4.2.16. 2,4-Dichloro-*N*-(4-(5-chloropyridin-3-yloxy)-3-(trifluoromethyl)phenyl)benzenesulfonamide (19)

3-Trifluoromethyl-4-chloronitrobenzene, 5-chloropyridin-3-ol and 2,4-dichlorobenzenesulfonyl chloride were combined according to the general procedure to give ligand **19** as an off-white solid, mp 136 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.12 (s, 1H); 8.45 (d, J = 1.8 Hz, 1H); 8.30 (d, J = 2.5 Hz, 1H); 8.05 (d, J = 8.5 Hz, 1H); 7.91 (d, J = 2.1 Hz, 1H); 7.65 (dd, J = 2.6, 2.4 Hz, 1H); 7.65 (dd, J = 8.6, 2.0 Hz, 1H); 7.47 (d, J = 2.6 Hz, 1H); 7.36 (dd, J = 8.4, 2.6 Hz, 1H); 7.19 (d, J = 8.9 Hz, 1H). IR (film) 3052, 2714, 1575, 1494, 1321, 1162, 1121, 931, 818 cm^{-1}. MS (ESI): m/z: 499.0 (M+H)$^+$. Anal. Calcd for $C_{18}H_{10}Cl_3F_3N_2O_3S$: C, 43.40; H, 2.03; N, 5.54. Found: C, 43.31; H, 2.03; N, 5.54.

4.2.17. 2,4-Dichloro-*N*-(4-(5-chloropyridin-3-yloxy)-3-cyanophenyl)benzenesulfonamide (20)

3-Cyano-4-chloronitrobenzene, 5-chloropyridin-3-ol and 2,4-dichlorobenzenesulfonyl chloride were combined according to the general procedure to give ligand **20** as an off-white solid, mp 162 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (br s, 1H); 8.42 (br s, 1H); 8.08 (d, J = 8.5 Hz, 1H); 7.71 (d, J = 1.8 Hz, 1H); 7.60 (d, J = 2.3 Hz, 1H); 7.53 (dd, J = 8.5, 2.0 Hz, 1H); 7.50–7.45 (m, 2H); 7.22 (br s, 1H); 6.99 (d, J = 8.8 Hz, 1H). IR (film) 3049, 2731, 2230, 1570, 1489, 1159929, 815 cm^{-1}. MS (ESI): m/z 455.9 (M+H)$^+$. Anal. Calcd for $C_{18}H_{10}Cl_3N_3O_3S$: C, 47.69; H, 2.23; N, 9.27. Found: C, 47.78; H, 2.34; N, 8.94.

4.2.18. 2,4-Dichloro-*N*-(4-(5-chloropyridin-3-yloxy)-3-methylphenyl)benzenesulfonamide (21)

3-Methyl-4-chloronitrobenzene, 5-chloropyridin-3-ol and 2,4-dichlorobenzenesulfonyl chloride were combined according to the general procedure to give ligand **21** as an off-white solid, mp 134 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (br s, 1H); 8.14 (br s, 1H); 7.95 (d, J = 8.5 Hz, 1H); 7.55 (d, J = 2.0 Hz, 1H); 7.35 (dd, J = 8.5, 2.0 Hz, 1H); 7.12 (br s, 1H); 7.09–7.05 (m, 2H); 6.96 (dd, J = 8.7, 2.6 Hz, 1H); 6.80 (d, J = 8.7 Hz, 1H); 2.15 (s, 3H). IR (film) 3259, 1570, 1167, 818 cm^{-1}. MS (ESI): m/z 445.1 (M+H)$^+$. Anal. Calcd for $C_{18}H_{13}Cl_3N_2O_3$: C, 48.72; H, 2.95; N, 6.31. Found: C, 48.81; H, 3.03; N, 6.25.

4.2.19. 2,4-Dichloro-*N*-(4-(5-chloropyridin-3-yloxy)-3-(methylsulfonyl)phenyl)benzenesulfonamide (22)

1-Chloro-2-methanesulfinyl-4-nitrobenzene, 5-chloropyridin-3-ol and 2,4-dichlorobenzenesulfonyl chloride were combined according to the general procedure to give ligand **22** as an off-white solid, mp 90 °C. ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.37 (d, J = 2.0 Hz, 1H); 8.25 (d, J = 2.4 Hz, 1H); 8.08 (d, J = 8.6 Hz, 1H); 7.82 (d, J = 2.8 Hz, 1H); 7.69 (d, J = 2.1 Hz, 1H); 7.52–7.46 (m, 3H); 7.10 (d, J = 8.8 Hz, 1H); 3.24 (s, 3H). IR (film) 1571, 1483, 1308, 1167, 1146, 819 cm^{-1}. MS (ESI): m/z: 505.0 (M–H)$^-$. HPLC: 95 Area%.

4.2.20. 2,4-Dichloro-*N*-(4-(5-chloropyridin-3-yloxy)-3-methoxyphenyl)benzenesulfonamide (23)

3-Methoxy-4-fluoronitrobenzene, 5-chloropyridin-3-ol and 2,4-dichlorobenzenesulfonyl chloride were combined according to the

general procedure to give ligand **23** as an off-white solid, mp 144 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, J = 2.0 Hz, 1H); 8.11 (d, J = 2.4 Hz, 1H); 7.95 (d, J = 8.5 Hz, 1H); 7.55 (d, J = 2.0 Hz, 1H); 7.37 (dd, J = 8.5, 2.0 Hz, 1H); 7.15 (s, 1H); 7.04 (m, 1H); 6.91–6.89 (m, 2H); 6.26 (dd, J = 8.5, 2.5 Hz, 1H); 3.74 (s, 3H). IR (film) 1716, 1574, 1505, 1445, 1341, 1165 cm^{-1}. MS (ESI): m/z 457.0 $(M-H)^-$. HPLC: 95 Area%.

4.2.21. 2-(5-Chloropyridin-3-yloxy)-5-(2,4-dichlorophenylsulfonamido)benzoic acid (24)

Ethyl 2-chloro-5-nitrobenzoate, 5-chloropyridin-3-ol and 2,4-dichlorobenzenesulfonyl chloride were combined according to the general procedure to give methyl-2-(5-chloropyridin-3-yloxy)-5-(2,4-dichlorophenylsulfonamido)benzoate. This was treated with LiOH in MeOH at rt overnight to provide ligand **24** as an off-white solid, mp 232–234 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.18 (br s, 1H); 10.98 (br s, 1H); 8.31 (d, J = 2 Hz, 1H); 8.13 (d, J = 2.8 Hz, 1H); 8.02 (d, J = 8.4 Hz, 1H); 7.88 (d, J = 2.4 Hz, 1H); 7.63 (dd, J = 8.8, 2.0 Hz, 1H); 7.63 (d, J = 2.8 Hz, 1H); 7.33 (dd, J = 8.8, 2.8 Hz, 1H); 7.30 (t, J = 2.4 Hz, 1H); 7.15 (d, J = 8.8 Hz, 1H). IR (film) 1686, 1560, 1264, 1162, 931, 746 cm^{-1}. MS (ESI): m/z 474.9 $(M+H)^+$. Anal. Calcd for $C_{18}H_{11}Cl_3N_2O_5S$: C, 45.64; H, 2.34; N, 5.91; Cl, 22.45. Found: C, 45.57; H, 2.22; N, 5.92; Cl, 22.63.

4.2.22. 2,4-Dichloro-*N*-(4-(5-chloropyridin-3-yloxy)phenyl) benzenesulfonamide (25)

4-Chloronitrobenzene, 5-chloropyridin-3-ol and 2,4-dichloro-benzenesulfonyl chloride were combined according to the general procedure to give ligand **25** as an off-white solid, mp 139 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.70 (s, 1H); 8.38 (d, J = 1.6 Hz, 1H); 8.25 (d, J = 2.0 Hz, 1H); 7.98 (d, J = 8.4 Hz, 1H); 7.87 (d, J = 2.0 Hz, 1H); 7.61 (dd, J = 8.4, 2.0 Hz, 1H); 7.48 (t, J = 2.2 Hz, 1H); 7.13 (d, J = 8.4 Hz, 2H); 7.03 (d, J = 8.4 Hz, 2H). IR (film) 3280, 1569, 1501, 1168 cm^{-1}. MS (ESI): m/z: 431.0 $(M+H)^+$. Anal. Calcd for $C_{17}H_{11}Cl_3N_2O_3S$: C, 47.52; H, 2.58; N, 6.52. Found: C, 47.68; H, 2.62; N, 6.51.

4.2.23. 2,4-Dichloro-*N*-(3-chloro-4-(5-chloropyridin-3-yloxy)-5-fluorophenyl)benzenesulfonamide (26)

3,4-Dichloro-5-fluoronitrobenzene, 5-chloropyridin-3-ol and 2,4-dichlorobenzenesulfonyl chloride were combined according to the general procedure to give ligand **26** as an off-white solid, mp 165–167 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, J = 1.9 Hz, 1H); 8.14 (d, J = 2.6 Hz, 1H); 8.03 (d, J = 8.5 Hz, 1H); 7.58 (d, J = 2 Hz, 1H); 7.43 (dd, J = 8.5, 2.0 Hz, 1H); 7.28 (br s, 1H); 7.11 (t, J = 2.2 Hz, 1H); 7.07–7.00 (m, 2H). IR (film) 3054, 1344, 1166, 1014, 930, 819, 621, 613, 562 cm^{-1}. MS (ESI): m/z: 480.9 $(M-H)^-$. Anal. Calcd for $C_{17}H_9Cl_4FN_2O_3S$: C, 42.35; H, 1.88; N, 5.81. Found: C, 42.33; H, 2.03; N, 5.41.

4.2.24. 2,4-Dichloro-*N*-(3,5-dichloro-4-(5-chloropyridin-3-yloxy)phenyl)benzenesulfonamide (27)

3,4,5-Trichloronitro benzene, 5-chloropyridin-3-ol and 2,4-dichlorobenzenesulfonyl chloride were combined according to the general procedure to give ligand **27** as an off-white solid, mp 169 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.36 (s, 1H); 8.38 (br s, 1H); 8.23 (d, J = 2.6 Hz, 1H); 8.13 (d, J = 8.5 Hz, 1H); 7.93 (br s, 1H); 7.68 (dd, J = 8.6, 2.0 Hz, 1H); 7.50 (m, 1H); 7.25 (s, 2H). IR (film) 3092, 3070, 2786, 1568, 1462, 1165, 819 cm^{-1}. MS (ESI): m/z: 499.0 $(M+H)^+$. Anal. Calcd for $C_{17}H_9Cl_5N_2O_3$: C, 40.95; H, 1.82; N, 5.62. Found: C, 41.18; H, 1.81; N, 5.55.

4.2.25. *N*-(3-Acetyl-5-chloro-4-(5-chloropyridin-3-yloxy)-phenyl)-2,4-dichlorobenzenesulfonamide (28)

2,3-Dichloro-5-nitroacetophenone, 5-chloropyridin-3-ol and 2,4-dichlorobenzenesulfonyl chloride were combined according to the general procedure to give ligand **28** as an off-white solid, mp 174–178 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, J = 2 Hz, 1H); 8.07 (d, J = 2.5 Hz, 1H); 8.03 (d, J = 8.6 Hz, 1H); 7.58 (d, J = 2 Hz, 1H); 7.52 (d, J = 2.5 Hz, 1H); 7.46–7.38 (m, 2H); 7.32 (br s, 1H); 7.00 (dd, J = 2.5, 2.0 Hz, 1H); 2.46 (s, 3H). IR (film) 3196, 1681, 1166, 930, 818, 626, 568 cm^{-1}. MS (ESI): m/z: 507.1 $(M+H)^+$. Anal. Calcd for $C_{19}H_{12}Cl_4N_2O_4S$: C, 45.08; H, 2.39; N, 5.53. Found: C, 44.71; H, 2.37; N, 5.41.

4.2.26. 2,4-Dichloro-*N*-(4-(5-chloropyridin-3-yloxy)-3,5-bis (trifluoromethyl)phenyl)benzenesulfonamide (29)

2-Bromo-5-nitro-1,3-bis(trifluoromethyl)benzene was synthesized from 2-bromo-1,3-bis(trifluoromethyl)benzene by modifying a literature procedure.[42] 1.9 mL of fuming HNO_3 was added to 2.6 mL of concentrated H_2SO_4. 2-Bromo-1,3-bis(trifluoromethyl) benzene (2.5 g, 8.5 mmol) was added in one portion to the mixture and heated with stirring to 70 °C for 30 min. The reaction mixture was cooled to room temperature and poured over 200 mL of ice. The white crystals were collected by filtration, washed with water, and dried under vacuum to give 2.69 g (93%) of product that was used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.7 (s, 2H). This material was combined with 5-chloropyridin-3-ol and 2,4-dichlorobenzenesulfonyl chloride according to the general procedure to give ligand **29** as an off-white solid, mp 160 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.8 (s, 1H), 8.39 (d, J = 1.81 Hz, 1H), 8.27 (d, J = 2.6 Hz, 1H), 8.17 (d, J = 8.6 Hz, 1H), 7.97 (d, J = 2.0 Hz, 1H), 7.77 (s, 2H), 7.73 (dd, J = 2.1, 8.6 Hz, 1H), 7.64 (t, J = 2.2 Hz, 1H). IR (film) 1474, 1209, 1171, 1126 cm^{-1}. MS (ESI): m/z 565.0 $(M-H)^-$. Anal. Calcd for $C_{19}H_9Cl_3F_6N_2O_3S$: C, 40.34; H, 1.60; N, 4.95. Found: C, 40.42; H, 1.55; N, 5.03.

4.2.27. 2,4-Dichloro-*N*-(3,5-dichloro-4-(5-cyanopyridin-3-yloxy)phenyl)benzenesulfonamide (30)

3,4,5-Trichloronitro benzene, 5-hydroxynicotinonitrile (prepared according to a known procedure),[43] and 2,4-dichloro-benzenesulfonyl chloride were combined according to the general procedure to give ligand **30** as an off-white solid, mp 87–82 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, J = 1.5 Hz, 1H); 8.45 (d, J = 2.9 Hz, 1H); 8.05 (d, J = 8.5 Hz, 1H); 7.60 (d, J = 2 Hz, 1H); 7.45 (dd, J = 8.5, 2.0 Hz, 1H); 7.24 (s, 2H); 7.23–7.18 (m, 2H). IR (film) 2237, 1457, 1166, 818, 621, 569 cm^{-1}. MS (ESI): m/z 489.9 $(M+H)^+$. Anal. Calcd for $C_{18}H_9Cl_4N_3O_3S$: C, 44.20; H, 1.85; N, 8.59. Found: C, 44.86; H, 2.22; N, 8.28.

4.2.28. 2,4-Dichloro-*N*-(3,5-dichloro-4-(5-methylpyridin-3-yloxy)phenyl)benzenesulfonamide (31)

3,4,5-Trichloronitro benzene, 5-methyl-3-hydroxypyridine, and 2,4-dichlorobenzenesulfonyl chloride were combined according to the general procedure to give ligand **31** as an off-white solid, mp 200–201 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (m, 1H); 8.03 (d, J = 8.5 Hz, 1H); 7.85 (d, J = 2.7 Hz, 1H); 7.57 (d, J = 2 Hz, 1H); 7.41 (dd, J = 8.5, 2.0 Hz, 1H); 7.20 (s, 2H); 6.99–6.94 (m, 1H); 2.33 (s, 3H). IR (film) 2635(bs), 1463, 1338, 1168, 817, 619, 567 cm^{-1}. MS (ESI): m/z 478.9 $(M+H)^+$. Anal. Calcd for $C_{18}H_{12}Cl_4N_2O_3S$: C, 45.21; H, 2.53; N, 5.86. Found: C, 45.17; H, 2.48; N, 5.89.

4.2.29. 5-(2,6-Dichloro-4-(2,4-dichlorophenylsulfonamido) phenoxy)nicotinamide (32)

A solution of nitrile **30** in *tert*-BuOH was treated with powdered KOH (5 equiv) at rt. The mixture was then maintained at reflux until all starting material was consumed according to TLC analysis. The mixture was cooled to rt, volatiles were removed in vacuo, and the resulting residue was dissolved in EtOAc and washed with 1 N HCl (aq) and brine. The organics were dried over MgSO4, filtered, and concentrated in vacuo to give ligand **32** as an off-white solid (99%), mp 186–188 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.37 (br s, 1H); 8.79 (d, J = 1.6 Hz, 1H); 8.43 (d, J = 2.9 Hz, 1H); 8.20 (br s, 1H); 8.14 (d, J = 8.5 Hz, 1H); 7.92 (d, J = 1.9 Hz, 1H); 7.72–7.64 (m,

2H); 7.49–7.46 (m, 1H); 7.28(s, 2H). IR (film) 3450, 1683, 1171, 824, 616, 573 cm^{-1}. MS (ESI): *m/z* 507.9 $(M+H)^+$. Anal. Calcd for $C_{18}H_{11}Cl_4N_3O_4S$: C, 42.63; H, 2.19; N, 8.29. Found: C, 42.78; H, 2.20; N, 8.28.

4.2.30. *N*-(4-(5-acetylpyridin-3-yloxy)-3,5-dichlorophenyl)-2,4-dichlorobenzenesulfonamide (33)

1,2,3-Trichloro-5-nitrobenzene was coupled to methyl 5-hydroxynicotinate in the presence of Cs_2CO_3 at 50 C for 18 h as described in the general procedure. The isolated product was used without further purification to give methyl 5-(2,6-dicholoro-4-nitrophenoxy)nicotinate as an off white solid (quantitative yield). ^1H NMR (400 MHz, DMSO-d_6) δ 8.98 (d, J = 1.6 Hz, 1H), 8.72 (d, J = 2.9 Hz, 1H), 8.61 (s, 2H), 7.72 (dd, J = 2.9, 1.7 Hz, 1H), 3.89 (s, 3H). MS (ESI): *m/z* 343.0 $(M+H)^+$.

Methyl 5-(2,6-dicholoro-4-nitrophenoxy)nicotinate was then converted to 1-(5-(2,6-dichloro-4-nitrophenoxy)pyridin-3-yl)ethanone by modifying a literature procedure.[44] Specific changes are as follows: (1) the acid chloride was dissolved in DMF instead of PhMe/Et_2O, (2) the diethylmalonate anion was generated using NaH in DMF at 0 °C and (3) the coupling reaction was allowed to stir 4 h as the temperature gradually rose from 0 to 25 °C. The reaction mixture was then diluted with H_2O and adjusted to pH 5 with 2 N HCl (aq) and extracted three times with EtOAc. The organic layers were combined, washed brine, dried over $MgSO_4$, and concentrated in vacuo to yield a product that was hydrolyzed and purified as described to give 1-(5-(2,6-dichloro-4-nitrophenoxy)pyridin-3-yl)ethanone (29% yield) as an amorphous solid. ^1H NMR (400 MHz, DMSO-d_6) δ 8.99 (d, J = 1.6 Hz, 1H), 8.67 (d, J = 2.9 Hz, 1H), 8.62 (s, 2H), 7.69 (dd, J = 1.7, 2.9 Hz, 1H), 2.65 (s, 3H). MS (ESI): *m/z* 327.0 $(M+H)^+$. 1-(5-(2,6-dichloro-4-nitrophenoxy)pyridin-3-yl)ethanone was reduced using $SnCl_2{\cdot}H_2O$ as described in the general procedure to give 1-(5-(4-amino-2,6-dichlorophenoxy)pyridin-3-yl)ethanone, that was used without further purification, (quantitative). ^1H NMR (400 MHz, DMSO-d_6) δ 8.92 (d, J = 1.6 Hz, 1H), 8.56 (d, J = 2.9 Hz, 1H), 7.44 (dd, J = 3.4, 1.7 Hz, 1H), 6.77 (s, 2H), 5.79 (br s, 2H), 2.64 (s, 3H). MS (ESI): *m/z* 297.0 (M+H). The aniline was coupled to 2,4-dichlorobenzenesulfonyl chloride as described in the general procedure to give ligand **33** as an off-white solid (61%), mp 86 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 11.39 (s, 1H), 8.91 (d, J = 1.4 Hz, 1H), 8.53 (d, J = 2.9 Hz, 1H), 8.15 (d, J = 8.6 Hz, 1H), 7.95 (d, J = 1.7 Hz, 1H), 7.7 (dd, J = 2.0, 8.5 Hz, 1H), 7.45 (dd, J = 1.7, 2.9 Hz, 1H), 7.30 (s, 2H), 2.62 (s, 3H). IR (film) 1694, 1572, 1460, 1277, 1165 cm^{-1}. MS (ESI): *m/z* 507.0 $(M+H)^+$. Anal. Calcd for $C_{19}H_{12}Cl_4N_2O_4S$: C, 45.08; H, 2.39; Cl, 28.02; N, 5.53. Found: C, 46.42; H, 2.92; Cl, 27.47; N, 5.36.

4.2.31. 2,4-Dichloro-*N*-(3-chloro-4-(quinolin-3-yloxy)phenyl) benzenesulfonamide (34)

3,4-Dichloronitro benzene, 3- hydroxyquinoline, and 2,4-dichlorobenzenesulfonyl chloride were combined according to the general procedure to give ligand **34** as an off-white solid, mp 122 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 11.04 (s, 1H); 8.79 (d, J = 2.9 Hz, 1H); 8.09 (d, J = 8.5 Hz, 1H); 8.15 (d, J = 8.3 Hz, 1H); 7.98 (d, J = 2.1 Hz, 1H); 7.89 (d, J = 8.2 Hz, 1H); 7.70–7.65 (m, 2H); 7.60–7.58 (m, 1H); 7.57 (d, J = 3.0 Hz, 1H); 7.33 (d, J = 2.6 Hz, 1H); 7.26 (d, J = 8.8 Hz, 1H); 7.13 (dd, J = 2.6 Hz, 1H). IR (film) 1488, 1335, 1162, 818, 616 cm^{-1}. MS (ESI): *m/z* 463.0 $(M+H)^+$. Anal. Calcd for $C_{21}H_{13}Cl_3N_2O_3S$: C, 52.41; H, 2.73; N, 5.85. Found: C, 52.41; H, 2.73; N, 5.85.

4.2.32. 2,4-Dichloro-*N*-(3-fluoro-4-(quinolin-3-yloxy) phenyl)benzenesulfonamide (35)

3,4-Difluoronitro benzene, 3-hydroxyquinoline, and 2,4-dichlorobenzenesulfonyl chloride were combined according to the general procedure to give ligand **35** as an off-white solid, mp 163 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 11.04 (s, 1H); 8.79 (d, J = 2.9 Hz, 1H); 8.09 (d, J = 8.5 Hz, 1H); 8.15 (d, J = 8.3 Hz, 1H); 7.98 (d, J = 2.1 Hz, 1H); 7.89 (d, J = 8.2 Hz, 1H); 7.70–7.65 (m, 2H); 7.60–7.58 (m, 1H); 7.57 (d, J = 3.0 Hz, 1H); 7.33 (d, J = 2.6 Hz, 1H); 7.26 (d, J = 8.8 Hz, 1H); 7.13 (dd, J = 2.6 Hz, 1H). IR (film) 1488, 1335, 1162, 818, 616 cm^{-1}. MS (ESI): *m/z* 481.0 $(M+H)^+$. Anal. Calcd for $C_{21}H_{13}Cl_2FN_2O_3S$: C, 54.72; H, 2.93; N, 6.04; F, 3.96; S, 6.93; Cl, 15.26. Found: C, 54.44; H, 2.83; N, 6.05.

4.2.33. 2-Chloro-*N*-(3,5-dichloro-4-(quinolin-3-yloxy)phenyl)-4-(trifluoromethyl)benzenesulfonamide (36)

3,4,5-Trichloronitro benzene, 3-hydroxyquinoline, and 2-chloro-4-trifluoromethylbenzenesulfonyl chloride were combined according to the general procedure to give ligand **36** as an off-white solid, mp 225 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 11.70–12.00 (br s, 1H); 8.60–8.67 (m, 1H); 8.35–8.43 (m, 1H); 7.56–8.06 (m, 6H); 7.32–7.38 (m, 2H). MS (ESI): *m/z* 560.9 $(M+H)^+$. Anal. Calcd for $C_{22}H_{12}Cl_3F_3N_2O_3S$: C, 46.86; H, 2.15; N, 4.97. Found: C, 47.01; H, 2.26; N, 4.98.

4.2.34. *N*-(3-Acetyl-4-(quinolin-3-yloxy)phenyl)-2,4-dichlorobenzenesulfonamide (37)

2-Chloro-5-nitroacetophenone, 3-hydroxyquinoline, and 2,4-dichlorobenzenesulfonyl chloride were combined according to the general procedure to give ligand **37** as an off-white solid, mp 241 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 11.58 (s, 1H); 8.86 (d, J = 2.9 Hz, 1H); 8.38 (d, J = 8.4 Hz; 1); 8.23 (s, 1H); 8.01 (d, J = 8.4 Hz, 1H); 7.86 (d, J = 8.1 Hz, 1H); 7.53–7.68 (m, 3H); 7.46 (d, J = 2.9 Hz, 1H); 7.34 (s, 2H). MS (ESI): *m/z* 487.0 $(M+H)^+$. HPLC: 95 Area%.

4.2.35. 2,4-Dichloro-*N*-(3,5-dichloro-4-(quinolin-6-yloxy) phenyl)benzenesulfonamide (38)

3,4,5-Trichloronitro benzene, 6-hydroxyquinoline, and 2,4-dichlorobenzenesulfonyl chloride were combined according to the general procedure to give ligand **38** as an off-white solid, mp 241 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 11.37 (s, 1H); 8.75 (dd, J = 4.4, 1.6 Hz, 1H); 8.23 (dd, J = 8.4, 1.2 Hz, 1H); 8.16 (d, J = 8.8 Hz, 1H); 8.02 (d, J = 9.2 Hz, 1H); 7.96 (d, J = 2.0 Hz, 1H); 7.71 (dd, J = 8.8, 2.0 Hz, 1H); 7.50 (dd, J = 9.2, 2.8 Hz, 1H); 7.47 (dd, J = 8.4, 4.0 Hz, 1H); 7.29 (s, 2H); 7.05 (d, J = 2.8 Hz, 1H). IR (film) 3274, 1573, 1455, 1323, 1147, 960, 862 cm^{-1}. MS (ESI): *m/z* 481.0 $(M+H)^+$. Anal. Calcd for $C_{21}H_{12}Cl_4N_2O_3S$: C, 49.05; H, 2.35; N, 5.45. Found: C, 49.25; H, 2.44; N, 5.35.

4.2.36. 2,4-Dichloro-*N*-(3-chloro-4-(naphthalen-2-yloxy) phenyl)benzenesulfonamide (39)

3,4,5-Trichloronitro benzene, 2-hydroxynaphthalene, and 2,4-dichlorobenzenesulfonyl chloride were combined according to the general procedure to give ligand **39** as an off-white solid, mp 152 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 10.95 (s, 1H); 8.06 (d, J = 8.6 Hz, 1H); 7.94 (d, J = 9.0 Hz, 1H); 7.92 (d, J = 2.1 Hz, 1H); 7.90 (d, J = 8.3 Hz, 1H); 7.74 (d, J = 7.9 Hz, 1H); 7.67 (dd, J = 8.6, 2.1 Hz, 1H); 7.48 (ddd, J = 8.1, 6.9, 1.3 Hz, 1H); 7.43 (ddd, J = 8.2, 6.9, 1.4 Hz, 1H); 7.30 (d, J = 2.2 Hz, 1H); 7.23 (dd, J = 8.9, 2.5 Hz, 1H); 7.16–7.12 (m, 2H); 7.10 (dd, J = 8.8, 2.3 Hz, 1H). IR (film) 3281, 1490, 1461, 1162, 819, 624 cm^{-1}. MS (ESI): *m/z* 478.0 $(M-H)^-$. Anal. Calcd for $C_{22}H_{14}Cl_3NO_3S$: C, 55.19; H, 2.95; N, 2.93; Cl, 22.21. Found: C, 54.93; H, 2.84; N, 2.96; 22.44.

4.3. General in vitro biology methods

4.3.1. Ligand displacement-filtration assay

Displacement of [^3H]-rosiglitazone by our PPARγ ligands was directly measured in a scintillation proximity assay. A 90 μL reaction slurry containing binding buffer (10 mM Tris-HCl pH 8.0, 50 mM KCl, 0.01% NP40, 10 mM dithiothreitol, 0.02% bovine serum

albumin), 350 ng GST-PPARγLBD, 20 nM [^{3}H]-rosiglitazone, and glutathione Sepharose 4B beads (Amersham Biosciences) was incubated for 15 minutes at rt. The slurry was then added to 10 μL of PPARγ ligand in Me_2SO that had been allocated into the wells of a Polyfiltronics Unifilter 350 microassay plate, and the mixture incubated for 1H with shaking at rt. The filtrate was separated from bound ligand and protein by vacuum, and the plate containing the retained material was washed twice with binding buffer before reading in a Packard TopCount.

4.3.2. Gal4-PPARγ transactivation assay

Co-transfection experiments were carried out using expression plasmids encoding chimeric *GAL4* DNA binding domain-hPPARγ ligand binding domain fusion proteins to drive transcription of UAS$_{GAL4}$-luciferase reporter genes. Transient transfection of HEK293 cells using GenePORTER2 reagent (GTS Inc., San Diego, CA) was carried out according to the manufacturer's protocol, and luciferase activity measured 24 h after the addition of compounds.[15]

4.4. General in vivo biology methods

4.4.1. KKAy mouse studies

Male KKAy obese mice (Harlan, 5–7 weeks old),[45] were prescreened for body weight and a range of clinical parameters (glucose, insulin, leptin, nonesterified free fatty acids (NEFA), triglycerides, total cholesterol, and HDL cholesterol). Blood sampling was performed from the retro-orbital plexus under ether anesthesia. The mice were singly housed and randomized into groups of n = 8/treatment group. Animal holding, room temperature, and humidity were in conformance with the *Guide for the Care and Use of Laboratory Animals*.[46] Compounds were dissolved in EtOH and added to powdered diet (irradiated PicoLab® 5053). After drying overnight to remove EtOH, food was delivered in preweighed food jars on day 1. On day 4, body weight and food intake were determined, and blood was sampled and assayed for glucose and insulin. EDTA-treated blood samples were submitted for hematology and serum samples for clinical chemistry (Quality Clinical Labs, Mountain View, CA).

4.4.2. Zucker (fa/fa) fatty rat studies

Male Zucker fatty (*fa/fa*) rats (Charles River Laboratories), aged 7–8 weeks were allowed free access to irradiated PicoLab® 5053 diet and housed on a 12 h light–dark cycle. Animal holding, room temperature, and humidity were in conformance with the *Guide for the Care and Use of Laboratory Animals*.[46] Rats were pre-bled via a tail nick while conscious and samples were analyzed for fed-state glucose, insulin, NEFA, triglycerides and total cholesterol. Area under the glucose curve ($AUC_{0-120\ min}$) was determined during an oral glucose tolerance test (OGTT; 1 g/10 mL/kg, po) performed in overnight fasted rats. Blood glucose levels were determined in whole blood expressed from a tail nick (Accu-Check Blood Glucose Monitoring System, Roche). These clinical parameters in addition to body weight were used to randomize the rats into treatment groups (n = 6). Test compounds were both prepared in 1% Tween 80/1% methylcellulose and administered by oral gavage (10 mL/kg), once daily, between 0900 and 1200 h at the doses described. At day 14 of dosing, an OGTT was performed after an overnight fast, and terminal blood samples were analyzed for the clinical endpoints described above. Body weights, food and fluid intake were recorded on a daily basis from the start of dosing, through to the day of sacrifice.

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Supplementary data

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