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Synthesis of N-(5-chloro-6-(quinolin-3-yloxy)pyridin-3-yl) benzenesulfonamide derivatives as Non-TZD Peroxisome Proliferator-Activated Receptor γ (PPARγ) agonist

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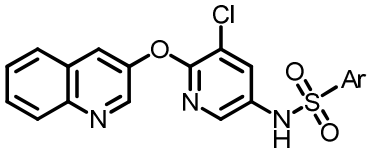
Graphical Abstract:



N-(5-chloro-6-(quinolin-3-yloxy) pyridin-3-yl)arylsulfonamides

7, Ar = 3,4-dimethoxybenzene
8, Ar = 3-chloro-4-fluorobenzene
9, Ar = 2,4-dimethylbenzene
10, Ar = 3-methylbenzene
11, Ar = 2-methylbenzene
12, Ar = 2-chloro-4-fluorobenzene
13, Ar = 2,4-difluorobenzene
14, Ar = 2-chloro-4-(trifluoromethyl)benzene
15, Ar = 2-methyl-4-fluorobenzene
16, Ar = 3,4-difluorobenzene
17, Ar = 2,5-dimethoxybenzene
18, Ar = 3-fluorobenzene
19, Ar = 3-(trifluoromethyl)benzene
20, Ar = 3,4-dichlorobenzene

Research Highlight

- N-(5-chloro-6-(quinolin-3-yloxy)pyridin-3-yl)benzenesulfonamides were synthesized
- Synthesized compounds exhibited adipogenesis activity
- PPARγ agonism of the series translated into in vivo efficacy in db/db mice.

Synthesis of N-(5-chloro-6-(quinolin-3-yloxy)pyridin-3-yl) benzenesulfonamide derivatives as Non-TZD Peroxisome Proliferator-Activated Receptor γ (PPARγ) agonist

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Abstract

The thiazolidinediones (TZDs) are a class of oral antidiabetic drugs that improve insulin sensitivity in patients with type 2 diabetes. Although the mechanism by which the TZDs lower insulin resistance is unclear, they are known to target the peroxisome proliferator–activated receptor-γ (PPARγ)-a nuclear hormone receptor. Ligands for PPARγ regulate adipocyte production and secretion of fatty acids as well as glucose metabolism, resulting in increased insulin sensitivity in adipose tissue, liver, and skeletal muscle. However, TZDs have several adverse effects, including weight gain and liver toxicity. Herein we report identification of non-TZD PPARγ agonists which exhibits beneficial effects similar to that of TZDs in animal models, but without the associated adverse effects.

Key Words: Thiazolidinediones; adipocyte; PPARγ; type 2 diabetes mellitus; adipogenesis

Introduction

The Thiazolidinediones (TZDs) class of drugs improves insulin sensitivity [1], glucose tolerance, and lipid homeostasis in vivo. TZDs decrease circulating levels of insulin [2], free fatty acids, and triglycerides and increase insulin-stimulated glucose uptake and utilization by activating the nuclear receptor PPARγ [3, 4]. A potential mechanism for these beneficial metabolic effects is the net partitioning of fatty acids from elsewhere in the body to adipose tissue for storage [5]. They bind to PPARγ with high affinity and specificity, promote interaction of PPARγ with transcriptional coactivators or corepressors, increase PPARγ mediated transcription regulation, and promote PPARγ mediated cellular effects such as adipogenesis. PPARγ and TZDs regulate the expression of several dozens of genes involved in a variety of cellular functions [6], including the metabolism of carbohydrates, fatty acids, triglycerides, and cholesterol. It is not clear which, if any, of these genes may be critical for insulin sensitization. It is also unknown which of the insulin-responsive tissues is the key target of TZDs, though adipose tissue is the leading candidate [7]. PPARγ is expressed at high levels in the adipose tissue but at much lower levels in muscle and liver tissues. PPARγ agonists regulate adipocyte differentiation and metabolism [8].

During the development of PPARγ agonists, many of these agents have been plagued with safety issues. There are few TZDs that have come to clinical use - troglitazone, rosiglitazone, and

pioglitazone (**Figure-1**) as well as several others that have been limited to pre-clinical study. The first TZD PPARγ agonist for type 2 diabetes, troglitazone was launched in the US in 1997 and withdrawn in 2000 due to serious hepatotoxicity [9] seen in a small number of patients during the postmarketing period. The currently approved PPARγ agonists, pioglitazone and rosiglitazone, do not display this hepatotoxicity. However, since weight gain and edema have been reported as side effects of these drugs, improvement of PPARγ agonists as antidiabetic agents is still required. INT-131 (**Figure-1**), a novel, non-thiazolidinedione (TZD), selective peroxisome proliferator-activated receptor gamma (PPARγ) modulator, is in development by InteKrin Therapeutics Inc for the treatment of type 2 diabetes mellitus (non-insulin dependent diabetes) [10]. In our current research program towards development of non-TZD PPARγ agonist to overcome the well-known shortcomings of thiazolidinediones, we have made efforts to synthesize ligand for PPARγ that is structurally and pharmacologically distinct from glitazone agonists. The concept of selective modulation involves targeting and activating specific genes to minimize side effects while maintaining therapeutic benefits. Modification of the structural name leads and their effects on in vitro measures of adipogenesis, hPPARγ agonism and in vivo efficacy in db/db mice are disclosed in this communication.

In this connection with the attempt of developing non-TZD selective PPARγ ligands, we have designed and synthesized N-(5-chloro-6-(quinolin-3-yloxy)pyridin-3-yl)benzenesulfonamide derivatives based on the chemical structure of INT-131 and screen them for adipogenesis in 3T3-1 adipocytes and PPARγ transactivation activity. The nuclear receptor, PPARγ, is the master regulator of adipogenesis and PPARγ active compounds exhibits adipogenic activity. Since the adipogenesis assay is an intricate phenotype-based assay, a direct structure activity relationship may not be imperative.

In vitro assays showed that N-(5-chloro-6-(quinolin-3-yloxy)pyridin-3-yl)benzenesulfonamide derivatives activate PPARγ. In adipocytes, they showed stimulation of adipocyte differentiation indicating that these compounds may activate PPARγ target genes involved in adipogenesis. The synthesis of novel non TZD ligands, N-(5-chloro-6-(quinolin-3-yloxy)pyridin-3-yl)benzenesulfonamide derivatives (**7-20**) is depicted in **scheme-1**.

Synthesis of the target componds involved straightforward chemical transformations and commenced with the preparation of 2-hydroxy-3-chloro-5-nitropyridine (**2**). Commercially available 2-hydroxy-5-nitropyridine (**1**) was treated with concentrated HCl at 50 ºC followed by aqueous solution of sodium chlorate to afforded 2-hydroxy-3-chloro-5-nitropyridine (**2**) in

quantitative yield [11]. Compound **2** was converted to required intermediate 2,3-dichloro-5-nitropyridine (**3**) by using $POCl_3$ at 120 ºC. Coupling reaction of 2,3-dichloro-5-nitropyridine (**3**) and Quinolin-3-ol (**4**) was carried out in presence of Cs_2CO_3 in DMF. Other reagents like K_2CO_3/THF also used to afford 3-((3-chloro-5-nitropyridin-2-yl)oxy)quinoline (5) in quantitative yield. Subsequent reduction of the compound **5** was carried out by using $SnCl_2.H_2O$ in ethyl acetate. Target compounds (5-chloro-6-(quinolin-3-yloxy)pyridin-3-yl)benzenesulfonamide derivatives (**7-20**) were synthesized by treating the amine **6** with different sulfonyl chlorides in DCM / pyridine at r.t. Purifications were carried out by either coloumn chromatography or by recrystallization.

The synthesized compounds exhibited stimulation of adipocyte differentiation and activate PPARγ which indicated that these compounds may activate PPARγ target genes involved in adipogenesis. A representative compound **7** was docked and compared with INT131 and exhibited comparable similarities and interactions in the active site of PPARγ pocket.

Compound **7** superposes very well on INT131 and Both the compounds hug the H3 helix with hydrophobic interactions and form water-mediated H-bonds with AF2 helix (**Figure-2**).
Figure-3 shows that N-atom of pyridine ring in compound **7** is differently placed in a hydrophobic region of the active site. This may have additional effects on the activity of the molecule. INT131 wraps around the H3 helix without getting close to the AF2 helix. While direct interaction with AF2 helix plays a major role in the binding affinity of PPARγ agonists, INT131 has water-mediated interactions with AF2 helix [12], which may reduce the strength of binding. 2,4 dichloro benzene of INT131 has dense hydrophobic interactions with hydrophobic cavity of Phe360, Phe363, Ile281, Phe282, Cys285,Leu356. In compound **7** dichlorobenzene is replaced by dimethoxybenzene. While hydrophobic interactions of aromatic ring are maintained as in INT131, interactions of Cl are lost and oxygen atoms have no hydrophobic interactions.
Gold Score for compound **7** is 90.65 which is equivalent to that of INT131 while Hydrogen Bonding Score is 6.8 for compound **7** and 7.6 for INT131. These docking data indicated that compound **7** and INT131 exhibited comparable affinity for PPARγ and similar ligand protein interactions.

All new compounds were evaluated as ligands for the human PPARγ, in HEK -293 cell-based PPARγ transactivation assay for agonist activity . Active compounds were also evaluated for their *in vitro* adipogenic potential in 3T3-L1 adipocytes. *In vitro* profiling of the compounds have been summarized in detail in **Table 1** .

Following the identification of compounds with good intrinsic potency *in vitro*, it was necessary to determine whether these compounds would retain useful in vivo efficacy in diabetes models while exhibiting an enhanced safety profile with respect to known PPARγ mechanism-based liabilities. Easily monitored liabilities include weight gain. *In vivo* testing in rodent models was used to ascertain whether this objective could be attained. Db/db mice, a genetic model of obese, insulin resistant T2DM, was used to evaluate the *in vivo* efficacy of analogs with adequate pharmacokinetic profiles. Compound **7** showed a C_{max} of 33.9 µg/mL at 0.25 h. The area under the plasma concentration-time curve ($AUC_{0\text{-}8h}$) was 146.44 µg*h/mL and the plasma half-life was 2.99 h. Based on the *in vitro* activity and pharmacokinetic profile (Table 2), we selected compound **7** and **16** for further evaluation. A number of compounds were tested in the db/db mouse model and efficacy data of the representative compound **7** is described in detail.

Compound **7** effectively reduces hyperglycemia in the db/db model after a treatment of 50 mg/kg/b.i.d for 10 days (40 % plasma glucose reduction) . In the same model the known anti diabetic agent ,rosiglitazone was effective as well in its glucose reduction activity (5 mg/kg/b.i.d, 52% glucose reduction).

Body weight gain measured in the db/db mouse amounted to only 9% at even at a high dose of 50 mg/kg/b.i.d of compound **7**, while a 14 % body weight gain was noted with rosiglitazone at a dose of 5 mg/kg/b.i.d. Therefore the efficacy study with compound **7** displayed significant glucose lowering activity (**Figure-4**) and a reduced effect on body weight gain as compared to rosiglitazone (**Figure-5**) indicating that compound **7**, a non-TZD PPARγ agonist possesses important pharmacological advantages relative to the TZD PPARγ agonist rosiglitazone in this animal model.

Conclusion

Here in this study we report design and synthesis of N-(5-chloro-6-(quinolin-3-yloxy)pyridin-3-yl) benzene-sulfonamide derivatives as novel non TZD PPARγ agonist for the develpement of safer antidiabetic agent. The synthesized molecules exhibited adipogenesis activity and PPARγ agonism leading to anti-diabetic effect in db/db mice. In comparison with the PPARγ full agonist Rosiglitazone, adverse effects such as body weight gain was attenuated. Further investigations to enhance these desirable profiles are ongoing.

Acknowledgements

We thank the Department of Analytical Chemistry for providing us with NMR, mass, HRMS and HPLC data.

Experimentals

All reagents and solvents were obtained from commercial sources and used as received.

^{1}H-NMR and ^{13}C-NMR spectra were obtained on a **'**Bruker 300 MHz' instrument equipped with a 5 mm ^{1}H/^{13}C/X (BBO) probe and the solvent indicated with tetramethylsilane as an internal standard. The data obtained so, were processed and analyzed by using Bruker software, XWIN NMR version 3.5.

Analytical HPLC was run using a Zorbax Eclipse XDB-C8 3.5 µm 4.6x75 mm column eluting with a mixture of acetonitrile and water containing 0.1% trifluoroacetic acid with a 5 minute gradient of 10-100%.

MS results were obtained on **'ESI-QTOF'** instruments of Bruker Daltonics (model MicrotofQ). 10 µl of each sample (fraction) was injected. The sample was ionized using Electron Spray Ionisation technique and analyzed using Quadruple Time of Flight. The mobile phase used was Acetonitrile and of 0.1 % formic acid (50:50) with a flow rate of 0.2 ml/min. The samples were analyzed both in the positive mode and negative mode by Direct Injection Mode.

Liquid chromatography/ mass spectroscopy studies have been carried out using '**Agilent 1100 Series/ esquire 4000'** instrument of Bruker Daltonics. Same analytical HPLC method was used with 'Phenomenex Luna C18' column. 0.1% Formic Acid and Acetonitrile (80:20) were used as mobile phase. 10µl of sample was injected on ESI source. Ion source parameters were employed as required. Nebulizer pressure = 45 psi, Dry Gas = 12 Lit/min, Dry Temp = 350^{0}C, scan = 50 to 2200, Capillary Voltage = 4500, Polarity was checked for both positive and negative mode. The data obtained so, were processed and analyzed by using Hystar software.

Automated column chromatography was performed on a CombiFlash Rf 200 (Teledyne Isco Inc.). Melting points were taken on a Mel-Temp apparatus and are uncorrected.

The protein structure of PPARg (PDB ID-3FUR), which was used for docking, was downloaded from ProteinData Bank (www.rcsb.org/pdb). This is a co-crystal structure of PPARg with INT131. Compounds

were docked to the binding site by means of CCDC's GOLD (Genetic Optimization for Ligand Docking) software, version 5.1. The binding region for the docking study was defined as all atoms within 6Å radius sphere centered on the centroid of the INT131. Thirty genetic algorithm (GA) runs were performed with automatic settings for each compound. The scoring function, GoldScore, implemented in GOLD was used to rank the docking positions of compound.

The compounds were tested for adipogenic activity in the presence of insulin in 3T3-L1 cells at a concentration of 20µg/ml. The adipogenic activity in the presence of potent PPARγ full agonist (1 µM) was defined as 100%, the maximum adipogenic activity in the presence of the test compound was defined as Emax (%). The compounds were tested for agonist activity on PPAR in transiently transfected HEK 293 cells at a concentration of 10µM. The transcriptional activity in the presence of potent PPARγ full agonist (1µM) was defined as 100%, the maximum transcriptional activity in the presence of the test compound was defined as Emax (%).

Pharmacokinetic parameters were assessed following oral dosing (100 mg/kg) using a suspension formulation (using 0.5% CMC and Tween 80; dosing volume: 10 mL/kg). Female *db/db* mice were weighed and the compounds were administered orally (n = 4 per time point). Blood samples were withdrawn at 0.08, 0.25, 0.5, 0.75, 1.0, 2.0, 6.0 and 8.0 h after dosing. Plasma samples were maintained on ice before being centrifuged (4 ºC for 5 min at 1411*g*), and aliquots were stored at -80 ºC pending the assay. Concentrations of the compounds were determined using an HPLC method developed at Piramal Healthcare Limited. Pharmacokinetic parameters were determined by non-compartmental analysis using WinNonlin Professional (Version 4.1). C_{max} and T_{max} were taken directly from the plasma concentration-time profile. The area under the curve from time 0 to the last blood sampling time (AUC_{0-t}) was calculated using the linear trapezoidal rule. The area under the curve extrapolated to infinity (AUC_{inf}) was calculated by using the plasma concentration at time t divided by slope λz, where λz is estimated by linear regression of the terminal log-linear phase of the plasma concentration-time curve. Terminal plasma elimination half life ($T_{1/2}$) was calculated as 0.693/ λz.

All animal experiments were performed according to procedures approved by the CPCSEA and as per the IAEC guidelines. In brief, 5 to 7 week-old male db/db mice, bred at Piramal Healthcare Ltd were fed a chow diet. The mice were treated with the respective compounds, body weight and biochemical parameters were evaluated at the end of the study.

Analytical Data:

2-Hydroxy-3-chloro-5-nitro pyridine (2).

2-Hydroxy-5-nitro pyridine (200 g, 1.42 mol) was added portion wise to 800 ml of concentrated HCl under constant stirring and then heated to 50o C. To this was slowly added a solution of sodium chlorate (80.0 g, 0.75 mol) in water. The reaction was maintained at the same temperature for an additional hour, and then cooled to 0o C. The precipitate obtained was filtered, washed thoroughly with water and dried to give 2-Hydroxy-3-chloro-5-nitro pyridine. Yield: 240 g, 1.37 mmol (96.0%)

M.P.: 195° - 197°C

^{1}H NMR (300 MHz, DMSO-d_6): δ 8.65 (d, 1H, *J* = 2.5 Hz), 8.36 (d, 1H, *J* = 2.5 Hz).

^{13}C NMR (300 MHz, DMSO-d_6): δ 153.40, 144.29, 143.59, 135.08, 130.44

MS (ES): 175 $(M+H)^+$

2, 3-Dichloro-5-nitro pyridine (3).

Quinoline (48.5 ml, 0.41 mol) was added to $POCl_3$ (164.0 ml 1.75 mol) at 0^o C under nitrogen. To this stirred mixture, 2-hydroxy-3-chloro-5-nitro pyridine (204 mg, 1.17 mol) was added. The reaction mixture was heated at 120^o C for 2 hours, cooled to 0^o C followed by addition of ice-cold water. The precipitate obtained was filtered, washed thoroughly with water and dried to give 2,3-Dichloro-5-nitro pyridine.

Yield: 220 g, (97%)

M.P.: 53° C.

^{1}H NMR (300 MHz, DMSO-d_6): δ 9.16 (d, 1H, *J* = 2.4 Hz), 8.94 (d, 1H, *J* = 2.4 Hz).

^{13}C NMR (300 MHz, DMSO-d_6): δ 158.69, 137.36, 132.51, 130.13, 124.39

MS (ES): 193 (M+1)

3-((3-chloro-5-nitropyridin-2-yl)oxy)quinoline (5)

In a 250 ml of round bottom flask, 14.5 g (0.1 mol) of quinolin-3-ol was placed and 100 ml of dry dimethyl formamide was added. To the stirred solution, 39.0 g (0.12 mol) of Cs_2CO_3 was added at 0 ^{0}C. Stirring was continued and after 30 minutes 1.9 g (0.1 mol) of 2,3-dichloro-5-nitro pyridine (**3**) was added. Stirring was continued further for 3-4 hours and the reaction was monitored by TLC. After completion, the reaction mixture was poured into ice-water and extracted with ethyl acetate. Organic layer was separated and dried over sodium sulfate (Na_2SO_4) solvent was removed under vacuum and to the resulting mass was added water (50 ml), extracted with ethyl acetate, dried over sodium sulfate and concentrated under vacuum to obtain crude 3-((3-chloro-5-nitropyridin-2-yl)oxy)quinoline that was purified using flash chromatography.

^{1}H NMR (300 MHz, DMSO-d_6): δ 9.03 (d, J=2.4Hz, 2H), 8.95 (d, J=2.4Hz, 1H), 8.35 (d, J=2.7Hz, 1H), 8.09 (d, J=8.1Hz, 1H), 7.98 (d, J=8.1Hz, 1H), 7.82 (t, J=6.9Hz, 1H), 7.69 (t, J=8.1Hz, 1H).

HRMS (*m*/*z*): $[M]^+$ calcd for $C_{14}H_8ClN_3O_3$, 301.0323; found, 301.1109

5-chloro-6-(quinolin-3-yloxy)pyridin-3-amine (6):

In a 250 ml of round bottom flask, 7.5 g (0.025 mol) of 3-((3-chloro-5-nitropyridin-2-yl)oxy)quinoline was placed and 100 ml of ethyl acetate was added. To the stirred solution 220 g (0.10 mol) of $SnCl_2.2H_2O$ was added at room temperature and stirring was continued for 8 hours. After completion (monitored by TLC), evaporated the solvent and added 25 ml of water followed by 1 N NaOH solution (pH was maintained between 9 and 10). Ethyl acetate (50 ml x 3) was used for extraction. The combined ethyl acetate layers was dried over sodium sulfate and concentrated under reduced pressure. The crude compound obtained was purified by column chromatography using 30% ethyl acetate in petroleum ether solvent system which gave 4.75 g (0.175 mol) of 5-chloro-6-(quinolin-3-yloxy)pyridin-3-amine. Yield: 70%

^{1}H NMR (300 MHz, DMSO-d_6): δ 8.75 (d, J=2.7Hz, 1H), 8.01 (d, J=2.7Hz, 1H), 7.92 (dd, J=7.5, 1.2Hz, 1H), 7.85 (d, J=2.7Hz, 1H), 7.70 (td, J=6.9, 1.5Hz, 1H), 7.60 (td, J=8.0, 1.2Hz, 1H), 7.49 (d, J=2.4Hz, 1H), 7.26 (d, J=2.4Hz, 1H), 5.49 (s, 2H)

HRMS (*m*/*z*): $[M]^+$ calcd for $C_{14}H_{10}ClN_3O$, 271.0511; found, 271.6109

General Procedure for the synthesis of N-(5-chloro-6-(quinolin-3-yloxy)pyridin-3-yl)benzenesulfonamide (7-19) derivatives.

868 mg (3.2 mmol) of the amine, 5-chloro-6-(quinolin-3-yloxy)pyridin-3-amine was dissolve in dry DCM and 2 ml of pyridine was added. To the stirred solution, 3.2 mmol of desired sulfonyl chloride was added. The reaction mixture was stirred at room temperature 5-6 hours. After completion, evaporated the solvent and the resulting crude product was purified using ethyl acetate and pet-ether solvent system. All purified compounds (**7-15**) were characterized by spectral analysis

N-(5-chloro-6-(quinolin-3-yloxy)pyridin-3-yl)-3,4-dimethoxybenzenesulfonamide (7).

^{1}H NMR (300 MHz, DMSO-d_6): δ 10.40 (s, 1H), 8.77 (d, J=2.4Hz, 1H), 8.14 (d, J=2.1Hz, 1H), 8.04 (d, J=7.8Hz, 1H), 7.94 (d, J=7.8Hz, 1H), 7.75 (s, 1H), 7.73 (d, J=8.1Hz, 1H), 7.71 (d, J=2.4Hz, 1H), 7.62 (t, J=7.5Hz, 1H), 7.31 (dd, J=1.8, 7.8Hz, 1H), 7.23 (d, J=1.8Hz, 1H), 7.08 (d, J=8.4Hz, 1H), 3.79 (s, 3H), 3.76 (s, 3H).

^{13}C NMR (300 MHz, DMSO-d_6): δ 154.11, 153.43, 151.31, 149.17, 144.81, 143.01, 141.53, 134.10, 133.63, 130.42, 129.61, 128.54 (2C), 127.88, 122.95, 119.43, 118.31, 116.76, 115.21, 115.10, 57.21 (2C)

HRMS (*m*/*z*): $[M]^+$ calcd for $C_{22}H_{18}ClN_3O_5S$, 471.0721; found, 471.5124

3-chloro-N-(5-chloro-6-(quinolin-3-yloxy)pyridin-3-yl)-4-fluorobenzenesulfonamide (8).

^{1}H NMR (300 MHz, DMSO-d_6): δ 10.67 (s, 1H), 8.79 (d, J=2.4Hz, 1H), 8.17 (d, J=2.4Hz, 1H), 8.05 (d, J=8.1Hz, 1H), 7.97 (d, J=2.1Hz, 1H), 7.95 (s, 1H), 7.94 (d, J=7.5Hz, 1H), 7.79 (d, J=2.4Hz, 1H), 7.77-7.73 (m, 2H), 7.72 (d, J=2.1Hz, 1H), 7.60 (d, J=9.0Hz, 1H).

^{13}C NMR (300 MHz, DMSO-d_6): δ 163.71, 153.64, 149.97, 144,83, 143.03, 141.57, 137.65, 133.67, 130.73, 129.41, 129.30, 129.08, 128.57 (2C), 127.91, 122.32, 122.11, 118.56, 118.27, 115.12

HRMS (*m*/*z*): $[M]^+$ calcd for $C_{20}H_{12}Cl_2FN_3O_3S$, 463.0532; found, 463.6125

N-(5-chloro-6-(quinolin-3-yloxy)pyridin-3-yl)-2,4-dimethylbenzenesulfonamide (9)

^{1}H NMR (300 MHz, DMSO-d_6): δ 10.67 (s, 1H), 8.76 (d, J=2.7Hz, 1H), 8.13 (d, J=2.7Hz, 1H), 8.04 (d, J=8.1Hz, 1H), 7.94 (d, J=8.1Hz, 1H), 7.75-7.59 (m, 5H), 7.23 (d, J=7.5Hz, 1H), 7.18 (d, J=8.1Hz, 1H), 2.25 (s, 3H), 2.29 (s, 3H).

^{13}C NMR (300 MHz, DMSO-d_6): δ 153.61, 149.11, 144.87, 143.03, 142.57, 141.62, 137.45, 136.91, 134.46, 133.64, 130.52, 129.11, 128.53 (2C), 128.29, 127.89, 127.77, 123.04, 118.52, 115.13, 23.42, 22.61

HRMS (*m*/*z*): $[M]^+$ calcd for $C_{22}H_{18}ClN_3O_3S$, 439.0821; found, 439.2824

N-(5-chloro-6-(quinolin-3-yloxy)pyridin-3-yl)-3-methylbenzenesulfonamide (10).

^{1}H NMR (300 MHz, DMSO-d_6): δ 10.53 (s, 1H), 8.77 (d, J=2.4Hz, 1H), 8.14 (d, J=2.4Hz, 1H), 8.04 (d, J=8.1Hz, 1H), 7.94 (d, J=8.1Hz, 1H), 7.76-7.66 (m, 3H), 7.64 (d, J=7.5Hz, 1H), 7.55 (m, 1H), 7.52 (d, J=5.4Hz, 1H), 7.44 (m, 1H), 2.25 (s, 3H).

^{13}C NMR (300 MHz, DMSO-d_6): δ 153.62, 149.13, 144.87, 142.65, 141.63, 140.53, 138.97, 133.65, 133.21, 130.54, 129.91, 129.80, 128.56 (2C), 128.41, 127.91, 127.79, 125.31, 123.03, 118.51, 115.11, 22.31

HRMS (*m*/*z*): $[M]^+$ calcd for $C_{21}H_{16}ClN_3O_3S$, 425.0611; found, 425.3214

N-(5-chloro-6-(quinolin-3-yloxy)pyridin-3-yl)-2-methylbenzenesulfonamide (11).

^{1}H NMR (300 MHz, DMSO-d_6): δ 10.74 (s, 1H), 8.76 (d, J=2.7Hz, 1H), 8.14 (d, J=2.7Hz, 1H), 8.04 (d, J=8.4Hz, 1H), 7.94 (d, J=7.8Hz, 1H), 7.75 (m, 1H), 7.73 (d, J=2.4Hz, 1H), 7.70 (d, J=2.4Hz, 1H), 7.61 (t, J=7.8Hz, 1H), 7.53 (t, J=7.8Hz, 1H), 7.39 (t, J=7.5Hz, 1H), 7.36 (d, J=5.4Hz, 1H), 2.55 (s, 3H).

^{13}C NMR (300 MHz, DMSO-d_6): δ 153.61, 149.12, 144.87, 142.59, 141.81, 141.01, 137.43, 133.61, 12.80, 132.63, 130.71, 130.71, 130.54, 129.11, 128.52, 128.39, 127.88, 123.03, 121.79, 118.52, 115.12, 23.11

HRMS (*m*/*z*): $[M]^+$ calcd for $C_{21}H_{16}ClN_3O_3S$, 425.0611; found, 425.3214

2-chloro-N-(5-chloro-6-(quinolin-3-yloxy)pyridin-3-yl)-4-fluorobenzenesulfonamide. (12)

^{1}H NMR (300 MHz, DMSO-d_6): δ 11.01 (s, 1H), 8.77 (d, J=2.7Hz, 1H), 8.15 (d, J=2.4Hz, 1H), 8.12 (dd, J=6.0, 9.0Hz, 1H), 8.04 (d, J=8.1Hz, 1H), 7.94 (d, J=8.1Hz, 1H), 7.76-7.71 (m, 4H), 7.62 (t, J=7.8Hz, 1H), 7.34 (td, J=8.7, 2.4Hz, 1H).

^{13}C NMR (300 MHz, DMSO-d_6): δ 169.53, 153.62, 149.12, 144.85, 143.01, 141.63, 136.32, 134.11, 133.61, 131.43, 130.52, 129.61, 128.52 (2C), 127.63, 123.02, 119.12, 118.53, 115.91, 115.21

HRMS (*m*/*z*): $[M]^+$ calcd for $C_{20}H_{12}Cl_2FN_3O_3S$, 463.0031; found, 463.0834

N-(5-chloro-6-(quinolin-3-yloxy)pyridin-3-yl)-2,4-difluorobenzenesulfonamide (13)

^{1}H NMR (300 MHz, DMSO-d_6): δ 10.99 (s, 1H), 8.78 (d, J=2.4Hz, 1H), 8.17 (d, J=2.4Hz, 1H), 8.04 (d, J=8.1Hz, 1H), 7.94 (d, J=8.1Hz, 1H), 7.89-7.86 (m, 2H), 7.78-7.70 (m, 2H), 7.62 (t, J=7.2Hz, 1H), 7.52 (m, 2H), 7.29 (td, J=8.4, 2.1Hz, 1H).

^{13}C NMR (300 MHz, DMSO-d_6): δ 165.34, 160.86, 153.61, 149.19, 144.86, 143.03, 141.65, 133.27, 131.53, 130.61, 129.62, 128.54 (2C), 127.68, 123.08 (2C), 118.59, 115.96, 112.56, 106.14

HRMS (*m*/*z*): $[M]^+$ calcd for $C_{20}H_{12}ClF_2N_3O_3S$, 447.0612; found, 447.1304

2-chloro-N-(5-chloro-6-(quinolin-3-yloxy)pyridin-3-yl)-4-(trifluoromethyl)benzene-sulfonamide (14)

^{1}H NMR (300 MHz, DMSO-d_6): δ 10.66 (s, 1H), 8.79 (d, J=2.7Hz, 1H), 8.15 (d, J=2.7Hz, 1H), 8.05 (d, J=8.1Hz, 1H), 7.97 (d, J=8.1Hz, 1H), 7.78-7.57 (m, 5H), 7.25 (d, J=7.5Hz, 1H), 7.19 (d, J=8.1Hz, 1H).

^{13}C NMR (300 MHz, DMSO-d_6): δ 153.62, 149.13, 144.87, 144.65, 143.03, 141.67, 141.35, 133.29, 132.83, 130.54, 130.11, 129.62, 128.55 (2C), 127.64, 126.20 (2C), 124.61, 123.10, 118.58, 115.93

HRMS (*m*/*z*): $[M]^+$ calcd for $C_{21}H_{12}Cl_2F_3N_3O_3S$, 512.9912; found, 513.1206

N-(5-chloro-6-(quinolin-3-yloxy)pyridin-3-yl)-4-fluoro-2-methylbenzenesulfonamide (15).

^{1}H NMR (300 MHz, DMSO-d_6): δ 10.76 (s, 1H), 8.76 (d, J=2.7Hz, 1H), 8.14 (d, J=2.4Hz, 1H), 8.04 (d, J=8.1Hz, 1H), 7.94-7.87 (m, 2H), 7.79-7.70 (m, 3H), 7.61 (td, J=7.8, 1.5Hz, 1H), 7.33 (dd, J=2.4, 9.6Hz, 1H), 7.22 (td, J=2.7, 8.4Hz, 1H), 2.58 (s, 3H).

^{13}C NMR (300 MHz, DMSO-d_6): δ 167.15, 153.61, 149.20, 144.82, 143.02, 141.66, 139.27, 135.54, 133.28, 130.53, 129.80, 129.60, 128.54 (2C), 127.63, 123.01, 118.57, 117.38, 115.92, 115.18, 23.03

HRMS (*m*/*z*): $[M]^+$ calcd for $C_{21}H_{15}ClFN_3O_3S$, 443.0531; found, 443.0732

N-(5-chloro-6-(quinolin-3-yloxy)pyridin-3-yl)-3,4-difluorobenzenesulfonamide (16).

^{1}H NMR (300 MHz, DMSO-d_6): δ 10.71 (s, 1H), 8.81 (d, J=2.4Hz, 1H), 8.19 (d, J=2.4Hz, 1H), 8.06 (d, J=8.4Hz, 1H), 7.97 (d, J=8.1Hz, 1H), 7.87 (t, J=7.8Hz, 1H), 7.81-7.74 (m, 3H), 7.69-7.61 (m, 3H).

^{13}C NMR (300 MHz, DMSO-d_6): δ 155.78, 147.11, 146.81, 145.42, 138.74, 136.31, 134.87, 131.02, 129.46, 129.10, 128.22 (2C), 127.81, 125.82, 125.28, 119.58, 119.33, 118.23, 117.33, 117.07

HRMS (*m*/*z*): $[M]^+$ calcd for $C_{20}H_{12}ClF_2N_3O_3S$, 447.0331; found, 447.0735

N-(5-chloro-6-(quinolin-3-yloxy)pyridin-3-yl)-2,5-dimethoxybenzenesulfonamide (17).

^{1}H NMR (300 MHz, DMSO-d_6): δ 10.35 (s, 1H), 8.76 (d, J=2.7Hz, 1H), 8.14 (d, J=2.4Hz, 1H), 8.03 (d, J=8.4Hz, 1H), 7.94 (d, J=7.5Hz, 1H), 7.76-7.70 (m, 3H), 7.64 (td, J=7.5, 1.2Hz, 1H), 7.24 (m, 1H), 7.19-7.15 (m, 2H), 3.78 (s, 3H), 3.70 (s, 3H).

^{13}C NMR (300 MHz, DMSO-d_6): δ 152.51, 146.91, 146.79, 145.56, 136.13, 134.17, 131.09, 129.65, 129.31, 128.24 (2C), 127.72, 125.62, 125.44, 121.95, 119.58, 119.33, 118.34, 117.23, 117.11, 57.21, 57.08

HRMS (*m*/*z*): $[M]^+$ calcd for $C_{22}H_{18}ClN_3O_5S$, 471.0712; found, 471.1316

N-(5-chloro-6-(quinolin-3-yloxy)pyridin-3-yl)-3-fluorobenzenesulfonamide (18).

^{1}H NMR (300 MHz, DMSO-d_6): δ 10.69 (s, 1H), 8.78 (d, J=2.7Hz, 1H), 8.17 (d, J=2.4Hz, 1H), 8.04 (d, J=8.4Hz, 1H), 7.95 (d, J=8.1Hz, 1H), 7.76-7.71 (m, 3H), 7.68-7.50 (m, 5H).

^{13}C NMR (300 MHz, DMSO-d_6): δ 162.17, 153.66, 149.19, 145.81, 142.34, 142.21, 133.63, 132.57, 130.64, 129.87, 128.23 (2C), 127.41, 127.03, 123.81, 123.04, 118.76, 118.28, 115.43, 115.18

HRMS (*m*/*z*): $[M]^+$ calcd for $C_{20}H_{13}ClFN_3O_3S$, 429.0421; found, 429.3152

N-(5-chloro-6-(quinolin-3-yloxy)pyridin-3-yl)-3-(trifluoromethyl)benzenesulfonamide (19)

^{1}H NMR (300 MHz, DMSO-d_6): δ 10.71 (s, 1H), 8.77 (d, J=2.4Hz, 1H), 8.16 (d, J=2.4Hz, 1H), 8.07 (d, J=8.4Hz, 1H), 8.01 (m, 3H), 7.95 (d, J=8.1Hz, 1H), 7.83 (t, J=8.4Hz, 1H), 7.77-7.67 (m, 3H) 7.62 (t, J=7.5Hz, 1H).

^{13}C NMR (300 MHz, DMSO-d_6): δ 152.63, 149.11, 143.86, 141.28, 141.03, 133.34, 132.27, 131.12, 130.53, 130.21, 129.62, 129.40, 128.24 (2C), 127.39, 125.15, 123.67, 122.86, 118.97, 115.54

HRMS (*m*/*z*): $[M]^+$ calcd for $C_{21}H_{13}ClF_3N_3O_3S$, 479.0311; found, 479.7215

3,4-dichloro-N-(5-chloro-6-(quinolin-3-yloxy)pyridin-3-yl)benzenesulfonamide (20).

^{1}H NMR (300 MHz, DMSO-d_6): δ 10.81 (s, 1H), 8.75 (d, J=2.4Hz, 1H), 8.17 (d, J=2.4Hz, 1H), 8.04 (d, J=7.5Hz, 1H), 7.95-7.93 (m, 2H), 7.86 (d, J=7.5Hz, 1H), 7.80 (d, J=2.1Hz, 1H), 7.74 (d, J=7.5Hz, 1H), 7.72 (d, J=2.1Hz, 1H), 7.68-7.66 (dd, J=8.4, 2.1Hz, 1H), 7.62 (t, J=7.5Hz, 1H).

^{13}C NMR (300 MHz, DMSO-d_6): δ 153.61, 149.19, 144.84, 142.97, 141.63, 140.22, 137.76, 134.73, 133.46, 131.51, 130.71, 129.33, 129.10, 128.56 (2C), 127.89, 127.78, 122.10, 117.42, 115.21

HRMS (*m*/*z*): $[M]^+$ calcd for $C_{22}H_{20}Cl_3N_3O_3S$, 480.9632; found, 480.9113

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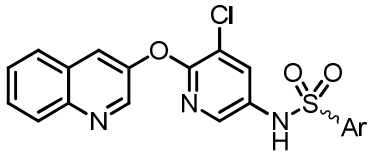
Table 1:



7	3,4-dimethoxybenzene	60	93
8	3-chloro-4-fluorobenzene	56	28
9	2,4-dimethylbenzene	67	31
10	3-methylbenzene	90	36
11	2-methylbenzene	95	43
12	2-chloro-4-fluorobenzene	51	39
13	2,4-difluorolbenzene	56	32
14	2-chloro-4-(trifluoromethyl)benzene	57	86
15	2-methyl-4-fluorobenzene	73	83
16	3,4-difluorobenzene	95	86
17	2,5-dimethoxybenzene	54	71
18	3-fluorobenzene	80	62
19	3-(trifluoromethyl)benzene	75	50
20	3,4-dichlorobenzene	35	56

[a] The compounds were tested for adipogenic activity in the presence of insulin in 3T3-L1 cells at a concentration of 20µg/ml.

[b] The compounds were tested for agonist activity on PPAR-γ in transiently transfected HEK 293 cells at a concentration of 10µM.

Table 2

Parameters	**Compound 7**	**Compound 16**
T_{max} (h)	0.25	0.50
C_{max} (µg/mL)	33.90	8.33
AUC_{0-8} (h*µg/mL)	146.44	25.44
Elimination rate constant(1/h)	0.23	0.39
Half life (h)	2.99	1.76
Volume of distribution (l/kg)	1.23	4.78
Clearance (L/h/kg)	0.28	1.87

Caption page

Fig-1: Structure of known PPARγ agonist

Scheme-1 Synthesis of N-(5-chloro-6-(quinolin-3-yloxy)pyridin-3-yl)benzenesulfonamide derivatives**:**

7, Ar = 3,4-dimethoxybenzene
8, Ar = 3-chloro-4-fluorobenzene
9, Ar = 2,4-dimethylbenzene
10, Ar = 3-methylbenzene
11, Ar = 2-methylbenzene
12, Ar = 2-chloro-4-fluorobenzene
13, Ar = 2,4-difluorobenzene
14, Ar = 2-chloro-4-(trifluoromethyl)benzene
15, Ar = 2-methyl-4-fluorobenzene
16, Ar = 3,4-difluorobenzene
17, Ar = 2,5-dimethoxybenzene
18, Ar = 3-fluorobenzene
19, Ar = 3-(trifluoromethyl)benzene
20, Ar = 3,4-dichlorobenzene

Reagents:

a. HCl / NaClO3 (aqueous), 50 oC **b**. POCl3 / Quinoline, 120 oC, 2 hrs
c. Cs2CO3, DMF, heating at 70-80 oC, 2-4 hrs **d**. SnCl2.H2O, Ethylacetate, r.t, 15 hrs
e. Pyridine, DCM, r.t, 10-15 hrs

Figure-2: Superimposition of INT131 (Brown) and compound **7** (Blue) inside the PPARγ active pocket.

Figure-3: View from the back-side of H3 helix

Table 1: Compounds with their biological activities

Table 2: Pharmacokinetic profile of compound **7** and **16**

Fig-4: Effect of compound **7** on plasma glucose in db/db mice

Fig-5: Effect of compound **7** on body weight in db/db mice

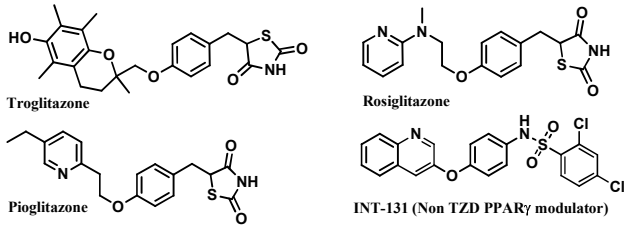


Fig-1

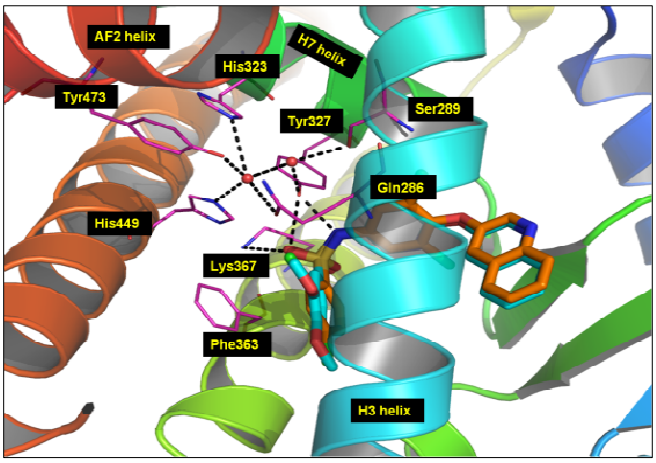


Figure-2

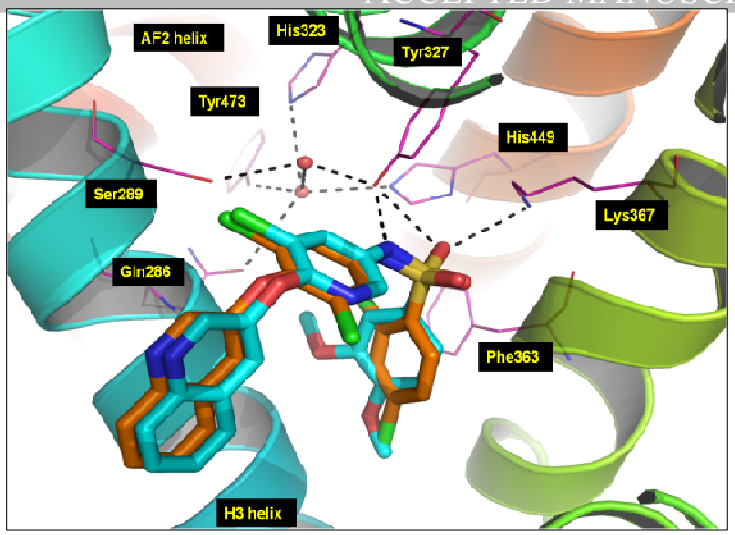


Figure-3

Fig 4

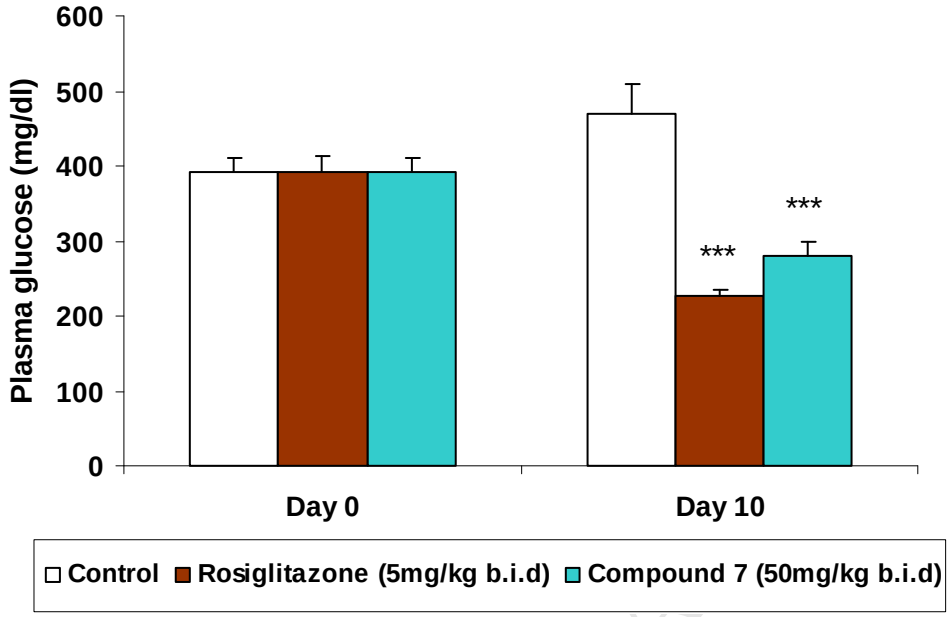
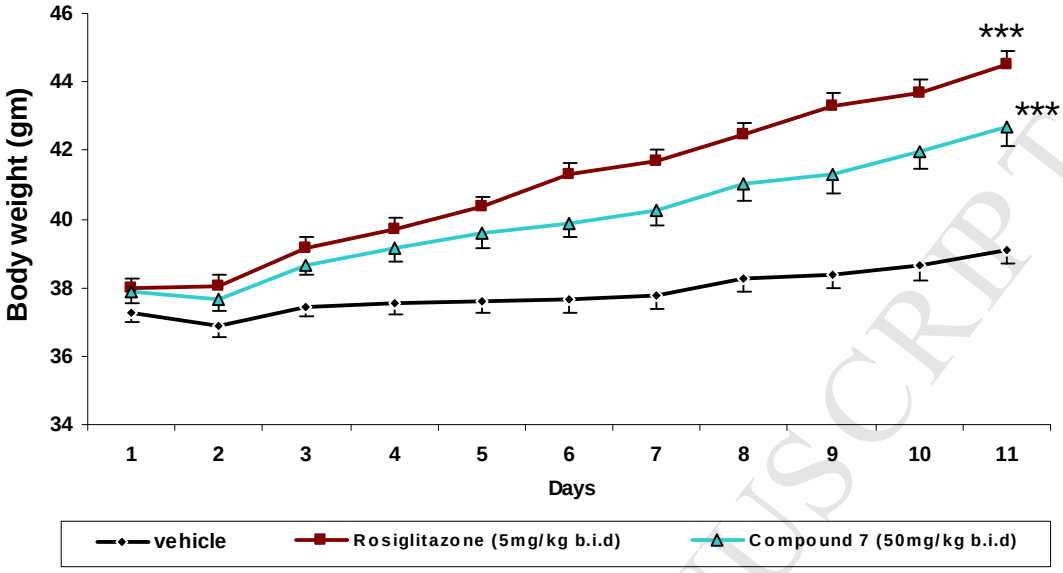
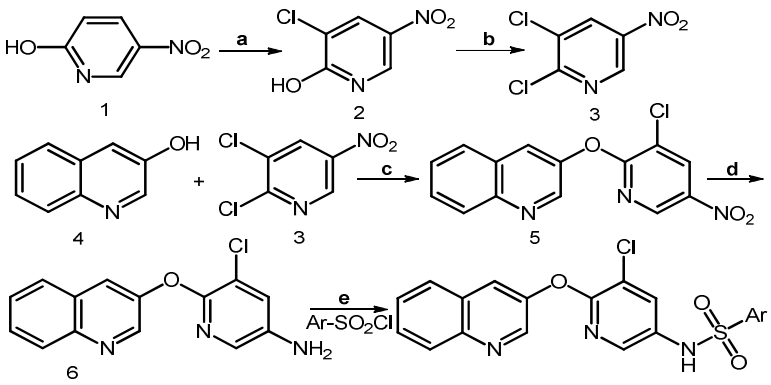


Fig 5





Scheme-1