ORIENTAL JOURNAL OF CHEMISTRY
An International Open Access, Peer Reviewed Research Journal
www.orientjchem.org
ISSN: 0970-020 X
CODEN: OJCHEG
2025, Vol. 41, No.(6):
Pg. 2071-2077

In silico, Synthesis and Biologicale Valuation of Sulfonylhydrazones-Based Molecules Targeting Type 2 Diabetes

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http://dx.doi.org/10.13005/ojc/410619

(Received: July 12, 2025; Accepted: November 07, 2025)

ABSTRACT

Diabetes is a global metabolic disorder, and PPAR-γ, a nuclear receptor in adipose tissue, is vital for regulating glucose and lipid metabolism, improving insulin sensitivity, and reducing inflammation. In this study, twelve novel 4-trifluoromethylbenzene sulfonylhydrazone analogues (SF1–SF12) were synthesized via nucleophilic addition–elimination, amide, and imine formation, and characterized by IR, ^{1}H NMR, and TLC. Among them, SF5, SF9, and SF10 showed strong PPAR-γ activation, comparable to pioglitazone. Molecular docking indicated high binding affinities (–9.6 to –10.5 kcal/mol), particularly for SF4 and SF5, supported by stable hydrogen bonding and hydrophobic interactions. ADME analysis confirmed favorable drug-like properties. Overall, these sulfonylhydrazones emerge as promising PPAR-γ agonists for type 2 diabetes therapy.

Keywords: Sulfonylchloride, Docking, 4-trifluoromethylsulfonylhydrazones, PPAR-Gamma, Insulin, type-2 diabetes.

INTRODUCTION

Diabetes is a metabolic condition that influences the metabolism of proteins, fats, and carbohydrates.[1] A primary characteristic of diabetes mellitus is the inadequate or ineffective secretion of insulin, which complicates the body's ability to use carbohydrates (glucose) and leads to elevated blood glucose levels.[2] Commonly termed "sugar," (DM) it stands as the most widespread endocrine disorder, typically arising from either insufficient insulin production or a failure in insulin's action.[2,3] The rise in diabetes cases significantly strains the nation's healthcare system and economic resources. Projections indicate that by 2030, the number of individuals diagnosed with diabetes could reached out 657 million. It is anticipated that the total will grow to 657 million in 2030 and further to 793 million by 2050.[4]

Diabetes stands as the primary contributor to end-stage renal disease, adult-onset blindness, and non- traumatic amputations of the low limbs. Alarmingly, approximately 56 million adults in the U.S are classified as having "pre-diabetes," A condition identified by heightened blood sugar levels that are inadequate of the thresholds required for a formal

diabetes diagnosis.[4,5] At present, diabetes treatment encompasses one or more diverse therapeutic strategies that are used but, Despite advances in treatment, managing diabetes effectively requires the discovery of new molecular targets to improve glycemic control and reduce complications.[5,6]

Becuase T2DM can result in severe chronic complications such as vision loss, vascular disorders, impaired wound healing, and limb amputation. Additionally, it induces various dysfunctions across multiple organs and tissues. Despite the availability of numerous therapeutic options, only a limited proportion of individuals with T2DM manage to achieve sustained glycemic control. Moreover, glycemic control in diabetes could also be achieved by inhibiting the PPAR Gamma enzyme with effective inhibitors they are mainly used for type 2 diabetes.[7,8] Sulfonylhydrazones are acknowledged as important scaffolds in the process of drug development, thanks to their diverse biological and pharmacological properties, such as anti-cancer, anti-diabetic, anti-fungal, anti-depressant and anti-tumor activities, Moreover, it can serve as an inhibitor for ROCK and CAII enzymes, in addition to acting as a PPAR-gamma agonist. In this paper we mainly focus on sulfonylhydrazones it's the main pharmacophore for this paper and The sulfone functional group found in sulfonyl hydrazone contributes to increased solubility and is often used.[9] Furthermore, in the course of this research, sulfonyl hydrazones were created by choosing fluorinated sulfonyl chlorides, which are noted for their binding selectivity, metabolic stability, and the lipophilic characteristics of fluorinated compounds. Sulfonyl hydrazones hold significant relevance in pharmaceutical chemistry due to their unique structures.[10,11]

The presence of nitrogen atoms in hydrazones contributes to their pharmacophore properties. Fluorine plays a crucial role in influencing the structure, reactivity, and functionality of fluorinated compounds that are commonly synthesized in the field of medicinal chemistry. In recent years, compounds featuring fluorine atoms alongside a heterocyclic moiety have emerged as a significant motif in medicinal chemistry.[12,13]

The properties of derivatives of sulfonylhydrazones include a wide array of activities like anti- diabetic, anti depressant, anti-oxidant, anti-analgesic, antifungal, anti-Alzheimer's, antibacterial, anticancer, and among others. Specifically, they have shown efficacy against PPAR Gamma inhibitors in *in vitro* studies.[4,14]

MATERIALS AND METHODS

All reagents and chemicals used in this investigation were sourced from reputable commercial suppliers, including BLD Pharma, Hyderabad, (India) and AVRA Laboratories (India),the synthesized compound's reaction progress and purity were monitored frequently using ALUGRAM Xtra SIL G/UV254 pre-coated thin layer chromatography (TLC) plates.

Infrared (IR) spectra were analyzed using the "IR Prestige-21 (Shimadzu)", at the Anushandhan and Biochemical Research Laboratory, Mhow (Indore). ^{1}H and ^{13}C NMR spectra were recorded on an "ADVANCE NEO Ascend 400 Bruker BioSpin International AG spectrometer", using ($CDCL_3$)as solvents at the Indian Institute of Technology, Indore. Melting points were assessed using an ANALAB (μThermoCal50) melting point apparatus at SGSITS, Indore and the Biological activity were analyzed using the "BMG Fluostar software" at the Deshpande laboratories Pvt. Ltd. Bhopal.

EXPERIMENTAL

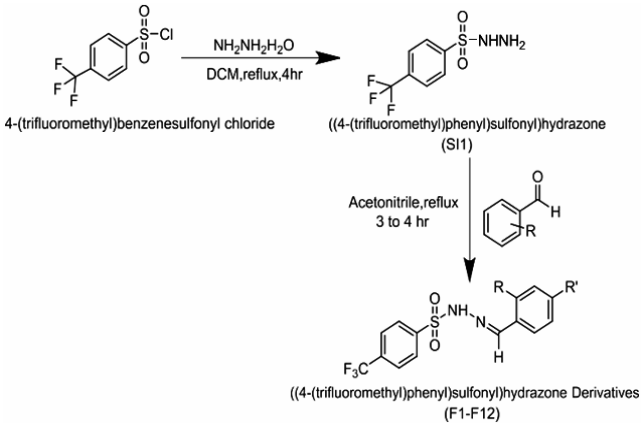
Synthesis of 4-Trifluoromethyl benzene sullfonyl chloride (I_1)

Trifluoromethyl benzene sulfonyl chloride (200mg, 0.0008mol,)with hydrazine hydrate (0.08ml,0.0008mol) were combined in 10 mL of DCM within a 50 mL RBF was refluxed and was conducted for a duration of 4 hours. The analysis was performed using (TLC), which involved monitoring the emergence of a new product spot alongside the reduction of the initial reactants. Upon confirming the completion of the reaction, it was quenched with cold water, and the resultant solid was collected through filtration and subsequently allowed to dry overnight at room temperature.

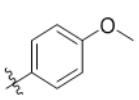
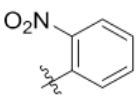
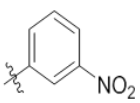
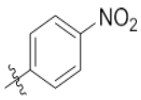
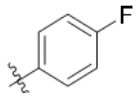
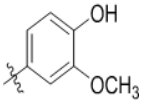
General procedure for synthesis of 4-(trifluoromethyl)phenyl)sulfonyl)hydrazone Derivatives (SF1-SF12)

An appropriate substituted benzaldehyde (0.05 mL) was reacted with intermediate-1

(150 mg, 0.0004 mol) in acetonitrile (1 mL, 0.0004 mol). A few drops of glacial acetic acid were added to the reaction mixture, which was then refluxed for 4 hours. After completion of the reaction, the mixture was basified using sodium bicarbonate. The resulting solid was collected by filtration, washed thoroughly with water, and dried. Final purification was achieved through recrystallization using ethanol.



Scheme 1. Synthetic route of 4-(trifluoromethyl)phenyl)sulfonyl)hydrazone Derivatives (SF1-SF12)

Code	SF1	SF2	SF3	SF4	SF5	SF6
R						
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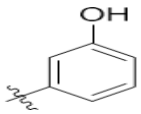
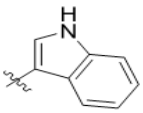
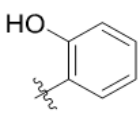
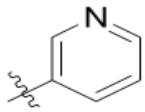
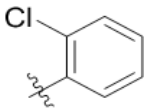
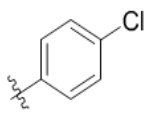
R						

RESULT AND DISCUSSION

4-Trifluoromethyl benzene sulfonyl chloride (I1)

Appearance: Whi te solid; m.p.: 120-150°C; Yield: 175 mg (85%), Molecular formula: $C_7H_7F_3N_2O_2S$. IR (KBr, in cm^{-1}): 1163.08(C-F) (Str.), 1404.18 (Ar. C=C), 1317.38(O=S=O), 1060.85(N-N), 1296.16(N-H). ^1H NMR (400 MHz, $CDCL_3$): δ 7.50 (d, *J* = 8.1 Hz, 2H), 7.28 (s, 1H), 5.28 (s, 1H), 3.08 (s, 2H), 1.03 (s, 1H).

N'-(4-methoxybenzylidene)-4(trifluoromethyl) benzenesulfonohydrazide)(SF1) Appearance:

Pale white; m.p.: 150-160°C; Yield: 100 mg (75%), Molecular formula: $C_{15}H_{13}F_3N_2O_3S$. IR (KBr, in cm^{-1}): 1163.08(C-F) (Str.), 1404.18 (Ar. C=C), 1321.24(O=S=O), 1041.56(N-N), 1512.19(C=N).

N'-(2-nitrobenzylidene)-4-(trifluoromethyl) benzenesulfonohydrazide (SF2)

Appearance: Yellow; m.p.: 180-190°C; Yield: 69mg (70%), Molecular formula: $C_{14}H_{10}F_3N_3O_4S$ IR (KBr, in cm^{-1}):1163.08(C-F) (Str.), 1404.18 (Ar. C=C), 1319.31(O=S=O), 1058.92 (N-N), 1517.84(C=N).

N'-(3-nitrobenzylidene)-4-(trifluoromethyl) benzenesulfonohydrazide(SF3)

Appearance: Pale Yellow; m.p.: 150-160°C; Yield: 80mg (70%), Molecular formula: $C_{14}H_{10}F_3N_3O_4S$. IR (KBr, in cm^{-1}):1161.15(C-F) (Str.), 1402.25 (Ar. C=C), 1317.38(O=S=O), 1058.92 (N-N), 1517.27(C=N).

N'-(4-nitrobenzylidene)-4-(trifluoromethyl) benzenesulfonohydrazide(SF4)

Appearance: Pale Yellow; m.p.: 180-190°C; Yield: 85mg (75%), Molecular formula: $C_{14}H_{10}F_3N_3O_4S$. IR (KBr, in cm^{-1}):1165(C-F) (Str.), 1404.18 (Ar. C=C), 1321.24(O=S=O), 1058.92 (N-N), 1517.98(C=N).

N'-(4-fluorobenzylidene)-4-(trifluoromethyl) benzenesulfonohydrazide(SF5)

Appearance White;m.p.: 135-140°C; Yield: 200mg (95%), Molecular formula: $C_{15}H_{13}F_3N_2O_2S$. IR (KBr, in cm^{-1}):1163.08(C-F) (Str.), 1404.18 (Ar. C=C), 1323.17(O=S=O), 1062.78 (N-N), 1517.98(C=N). ^1H NMR (400 MHz, $CDCL_3$): δ 8.13 (d, *J* = 8.1 Hz, 2H), 8.01 (d, *J* = 4.5 Hz, 1H), 7.81 (d, *J* = 8.2 Hz, 2H), 7.76 (s,1H), 7.62 – 7.54 (m, 2H), 7.07 (t, *J* = 8.5 Hz, 2H). 13C NMR (101 MHz, $CDCl_3$) δ 164.06 (d, *J* = 251.9 Hz), 147.29, 141.50, 134.89 (d, *J* = 33.1 Hz), 130.76 – 122.78 (m), 115.86 (d, *J* = 22.1 Hz), 77.04.

N'-(4-hydroxy-3-methoxybenzylidene)-4-(trifluoromethyl)benzenesulfonohydrazide(SF6)

Appearance Brown; m.p.: 200-220°C; Yield: 69mg (65%), Molecular formula: $C_{15}H_{13}F_3N_2O_4S$. IR (KBr, in cm^{-1}):1163.08(C-F) (Str.), 1402.25 (Ar. C=C), 1321.24(O=S=O), 1062.78 (N-N), 1517.98(C=N). 1H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.1 Hz, 2H), 7.79 (d, *J* = 8.1 Hz, 2H), 7.71 (s, 1H), 7.67 (s,1H), 7.26 (s, 2H), 6.89 (d, *J* = 8.1 Hz, 1H), 5.88 (s, 1H), 3.93 (s, 3H).

N'-(3-hydroxybenzylidene)-4-(trifluoromethyl) benzenesulfonohydrazide(SF7)

Appearance Brown; m.p.: 190-200°C; Yield: 65mg (60%), Molecular formula: $C_{14}H_{11}F_3N_2O_3S$. IR (KBr, in cm^{-1}):1166.93(C-F) (Str.), 1404.18 (Ar. C=C), 1321.24(O=S=O), 1060.85 (N-N), 1517.98(C=N).

N'-((1H-indol-3-yl)methylene)4-(trifluoromethyl) benzenesulfonohydrazide(SF8)

Appearance White; m.p.:200-220°C; Yield: 80mg (70%), Molecular formula: $C_{16}H_{11}F_3N_3O_2S$. IR (KBr, in cm^{-1}): 1166.93(C-F) (Str.), 1404.18 (Ar. C=C), 1321.24(O=S=O), 1060.85 (N-N), 1517.98(C=N).

N'-(2-hydroxybenzylidene)-4-(trifluoromethyl) benzenesulfonohydrazide(SF9)

Appearance Pale Yellow; m.p.: 150-160°C; Yield: 190mg (85%), Molecular formula: $C_{14}H_{11}F_3N_2O_3S$ IR (KBr, in cm^{-1}):1161.15(C-F) (Str.), 1406.11 (Ar. C=C), 1325.1(O=S=O), 1060.85 (N-N), 1517.98(C=N). ^1H NMR (400 MHz, $CDCl_3$) δ 9.29 (s, 1H), 7.47 (s, 1H), 7.36 (d, *J* = 8.2 Hz, 2H), 7.26 (s, 1H), 7.09 (d, *J* = 8.2 Hz, 2H), 6.64–6.50 (m, 1H), 6.41 (dd, *J* = 7.7, 1.6 Hz, 1H), 6.26–6.12 (m, 2H).

N'-(pyridin-3-ylmethylene)-4-(trifluoromethyl) benzenesulfonohydrazide (SF10)

Appearance White; m.p.: 180-190°C; Yield: 200mg (90%), Molecular formula: $C_{13}H_{10}F_3N_3O_2S$. IR (KBr, in cm^{-1}):1159.22(C-F) (Str.), 1404.18 (Ar. C=C), 1319.31(O=S=O), 1058.92 (N-N), 1517.98(C=N). ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.2 Hz, 1H), 7.98 (d, *J* = 8.1 Hz, 1H), 7.85–7.76 (m, 1H), 2.17 (s, 1H), 1.25 (s, 2H), 0.83 (s, 4H).

N'-(2-chlorobenzylidene)-4-(trifluoromethyl) benzenesulfonohydrazide (SF11)

Appearance White; m.p.: 130-140°C; Yield: 180mg (80%), Molecular formula: $C_{14}H_{10}ClF_3N_2O_2S$ IR (KBr, in cm^{-1}):1165(C-F) (Str.), 1404.18 (Ar. C=C), 1319.31(O=S=O), 1060.85 (N-N), 1518.98(C=N). ^1H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1H), 8.14 (d, *J* = 8.1 Hz, 2H), 7.95 – 7.87 (m, 1H), 7.81 (d, *J* = 8.2 Hz, 2H), 7.39 (s, 1H), 7.38 – 7.24 (m, 3H).

N'-(4-chlorobenzylidene)-4-(trifluoromethyl) benzenesulfonohydrazide(SF12)

Appearance White; m.p.: 150-160°C; Yield: 400mg (82%), Molecular formula: $C_{14}H_{10}ClF_3N_2O_2S$ IR (KBr, in cm^{-1}): 1165(C-F) (Str.), 1402.25 (Ar. C=C), 1321.24(O=S=O), 1062.78 (N-N), 1529.55(C=N).

Anti-diabetic activity

The PPAR Gamma Activation results revealed distinct performance levels among the tested compounds (SF5, SF9 and SF10). They were evaluated for in vitro activity on PPAR- Gamma target at 10μM. The percentage activation for each compound was calculated and illustrated in the accompanying bar graph Fig. 1. Among the tested compounds SF5 appeared as the most promising contender, demonstrating notable activation activity with value of 61.3 μM. which approaches the potency of the reference drug pioglitazone 49.24 μM. The compound SF5 is more potent because it has the fluorine on its para-position it boost binding affinity, metabolic stability, and selectivity with the receptor. At the tested concentration, further confirming its potential as an effective anti-diabetic agent. SF9 showed moderate activity, exhibiting weaker but still significant activation compared to SF5, suggesting it may serve as a secondary lead compound for further optimization. In contrast, SF10 displayed substantially weaker activation, performing poorly relative to both SF5 and SF9 , which indicates that its structural configuration may be less favourable for PPAR-Gamma activation. These results provide valuable insights for structure-activity relationship analysis and highlight SF5 as the most promising derivative warranting further investigation.

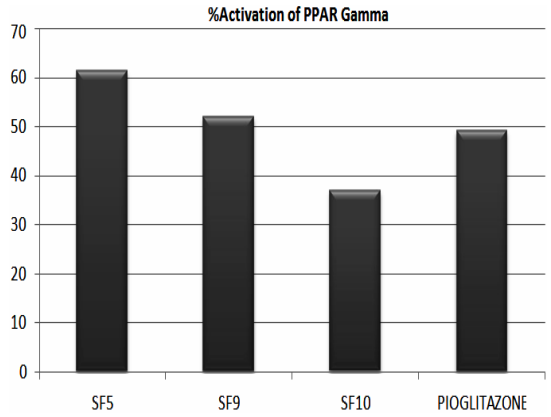


Fig. 1: PPAR-ϒ activation of SF5, SF9 and SF10 compared to pioglitazone

10µM	% Activation
S1CF42	61.3
S1CF26	51.9
S1CF43	36.9
Pioglitazone	49.24

In silico Study

Molecular docking studies were conducted using freely available AutoDock Vina 1.1.2 integrated within the PyRx Virtual Screening Tool (version 0.8). Initially, ChemDraw Ultra 16.0 was employed to create sketches of the chemical structures of the synthesized derivatives, followed by exporting them in mol file format. Subsequently, Chem Draw 3D was utilized to further minimize the energy of these structures to achieve optimal geometries. The protein structure (PDB ID: 1FM9), along with the minimized ligand structures, was then imported into PyRx and converted into the required pdbqt format for docking simulations. Docking parameters were established using AutoDock Tools version 1.5.6. A three-dimensional grid box was defined with the following dimensions: 7.7293(x), -1.7559(y), and 42.6563(z). An exhaustiveness value of 8 was set during the docking process to ensure thorough sampling. The BIOVIA Discovery Studio Visualizer was utilized to identify potential active site residues within the target protein. Table 1 presents the binding affinities of the synthetic compounds alongside their physiochemical properties. The physiochemical properties were calculated using Swiss ADME, and Fig. 1 and Fig. 2 illustrate the molecule exhibiting the strongest binding interaction. Binding affinity of the synthesized compounds and their physiochemical properties are listed in Table 1. The physiochemical properties were calculated using Swiss ADME and the bind interaction of the compound having highest binding interaction is shown in Figure 2 and Figure 3.

Table 1: Binding affinity and physiochemical properties of synthesized compounds

Compound No	Binding Affinity	Molecular mass	HBD	HBA	Log P	Molar Refractivity
SF1	-9.9	358.34	1	7	3.02	82.00
SF2	-10.1	373.31	1	6	2.92	84.33
SF3	-10.2	373.31	1	8	2.92	84.33
SF4	-10.4	373.31	1	8	2.92	84.33
SF5	-10.5	342.34	1	7	3.15	75.47
SF6	-9.8	374.33	2	8	2.73	84.03
SF7	-9.6	344.04	2	7	2.72	77.53
SF8	-10.3	367.35	2	6	3.49	87.37
SF9	-10.0	344.31	2	7	2.72	77.53
SF10	-10.2	329.04	1	7	2.41	73.31
SF11	-10.2	362.75	1	6	3.67	80.52
SF12	-9.7	362.75	1	6	3.67	80.52

Compound SF4 showed interaction with amino acids of receptor proteins such as C-H bond, Pi- sigma, Pi-sulphur alkyl, and pi-alkyl interactions. C-H Bond stacked on ALA327, Pi-sigma stacked with ALA272, ILE268 indicating strong aromatic interactions. Halogen bonds (Fluorine) stacked with PHE439 and ILE345 (via electron-rich sites on fluorine). Alkyl and Pi-Alkyl interactions with Involving CYS432, LEU436, LEU309, VAL265, VAL342 stabilizing the hydrophobic core Figure 2.

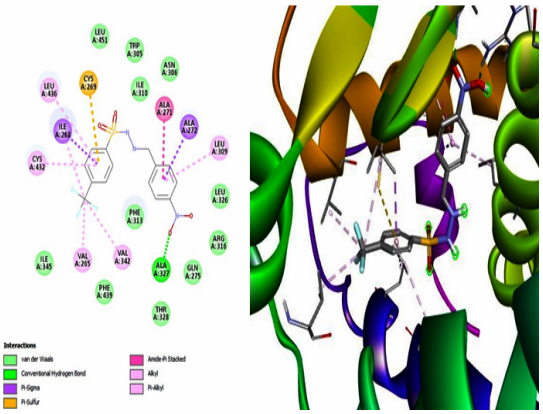


Fig. 2. 2D and 3D interaction of SF4 by Discovery studio biovia

Compound SF5 showed interaction with amino acids of receptor proteins such as C-H bond, alkyl, and pi-alkyl interactions, Pi-donor hydrogen bond, Amide-Pi. Halogen Bond (Fluorine) between PHE346, ILE345. Pi-Alkyl/Alkyl between LEU309, ALA272, ILE268. VanderWaals between GLN275, ILE310, PHE313, LEU436. A Amide-Pi stacked on ALA271 gives strong attraction with aromatic ligand in place Figure 3.

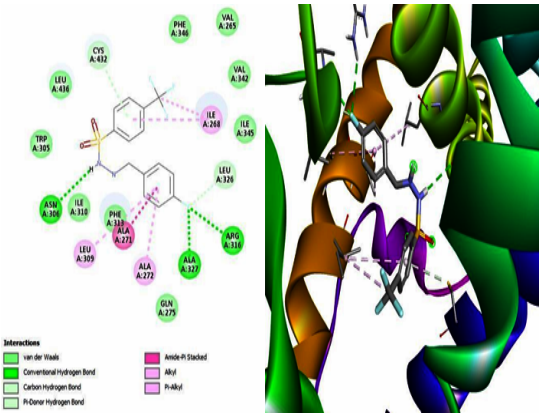


Fig. 3. 2D and 3D interaction of SF5 by Discovery studio biovia

CONCLUSION

This study reports the design and synthesis of twelve novel 4-(trifluoromethyl) phenylsulfonylhydrazone analogues (SF1–SF12) as potential PPAR-γ agonists for diabetes management. The derivatives were prepared via nucleophilic addition–elimination, amide, and imine formation, and their structures confirmed by IR, ^{1}H NMR, and TLC. Molecular docking revealed strong binding affinities to the PPAR-γ receptor, with SF4 and SF5 showing the highest scores (–10.5 kcal/mol), supported by stable hydrogen bonding and hydrophobic interactions. ADMET predictions indicated favorable pharmacokinetic profiles, including appropriate logP values (2.41–3.67) and metabolic stability. Substituents such as nitro and fluoro groups enhanced receptor affinity and improved drug-like properties. *In vitro* PPAR-γ activation assays demonstrated that SF5, SF9, and SF10 were potent activators, with SF5 exhibiting the highest activity, comparable to pioglitazone. These findings highlight the 4-(trifluoromethyl)phenylsulfonylhydrazone scaffold as a promising framework for next-generation PPAR-γ agonists. Future research should include comprehensive in vivo studies to validate efficacy and safety, thereby advancing these compounds toward development as effective antidiabetic therapeutics.

AKNOWLEDGEMENT

The authors express their deep gratitude to the Department of Pharmacy, SGSITS, Indore, for its unwavering support, including access to advanced research facilities, which were instrumental in the execution of this study.

Conflict of interest

The authors do not have any conflict of interest regarding the publication and content of this article.

REFERENCE

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