Original Article

Synthesis and Anti-hyperglycaemic Study of Aryl Sulfonate Ester Conjugated 5-arylidene-thiazolidine-2,4-diones

Mukul Mehta[1], Manoj Kumar Mahapatra[1,2,*]

[1]University Institute of Pharmaceutical Sciences, Panjab University, Chandigarh, INDIA
[2]Kanak Manjari Institute of Pharmaceutical Sciences, Chhend, Rourkela, Odisha, INDIA.

ABSTRACT

Background: Diabetes mellitus, a lifestyle related global health crisis has rapidly engulfed the entire world. In the past, various thiazolidinedione derivatives have been successfully developed for management of diabetes. **Materials and Methods:** Herein, we report synthesis, characterization (^{1}H-NMR, ^{13}C-NMR and mass spectroscopy methods) of novel aryl sulfonyloxy-5-arylidene thiazolidine-2,4-dione analogues. Anti-hyperglycaemic action (Alloxan-induced method) was performed for evaluating the antidiabetic potential of the synthesized compounds. Docking analysis of the final compounds were carried out to reveal interactions with the active site pocket of enzymes like protein tyrosine phosphatase 1B, aldose reductase and peroxisome proliferator activated-γ. The synthesized compounds were further subjected to ADME (Absorption, Distribution, Metabolism, Elimination) prediction studies to prove their drug-like potential. **Results:** Compound 10 and 12 showed comparable reduction in blood sugar as that with pioglitazone. Docking studies helped in understanding the probable binding mode inside the binding cavity of the concerned receptors. **Conclusion:** Aryl sulfonate esters with phenyl and chloro phenyl substituents were found to have superior anti-hyperglycaemic activity.

Key words: ADME, Anti-hyperglycaemic, Aryl sulfonyloxy-5-arylidenethiazolidine-2,4-dione, Docking, Spectral characterization.

INTRODUCTION

Diabetes mellitus (DM) has become a very familiar disease in our society and also emerged as a global health care problem. DM, a lifestyle related disease, is a metabolic disorder caused by insulin deficiency, acquired insulin resistance and improper glucose homeostasis. Rapidly growing urbanization, cultural and social changes, aging, obesity, genetic factors, and sedentary lifestyle patterns are the principal reasons behind this disease. The classical symptoms of DM include polyuria, polydipsia, polyphagia, weight loss, slow healing, blurred vision etc. Chronic hyperglycaemia often leads to complications like retinopathy with potential vision loss, nephropathy, renal failure, neuropathy, ischemic cardiac disease, peripheral vascular diseases, cerebrovascular diseases.[1] Various pathogenic processes like β-cell dysfunction and insulin resistance are primary reasons known to precede the onset of diabetes. Usually, β-cell dysfunction starts around 10-12 years before the onset of diabetes.[2] Insulin resistance is a condition where muscle, fat, and liver cells of the body can't use insulin effectively, leads to type 2 DM. Insulin resistance is often induced by obesity, high fat diets which leads to hyperinsulinemia and weight gain. Therefore, diabetes can be correctly described as "obesity dependent diabetes mellitus" or "diabesity".[3] Its psychological and economic impact on society along with the associated costs (annual global health expenditure 760 billion USD) are overwhelming which will continuously rise in future.[4,5] WHO fact sheet

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Correspondence:
Dr. Manoj Kumar Mahapatra
Kanak Manjari Institute of Pharmaceutical Sciences
Chhend, Rourkela-769015
Odisha, INDIA.
Phone no: +91 9356684535
Email id: manojbit07@gmail.com

www.ijper.org

reports that currently 422 million people are living with DM across the globe which attributes to 1.6 million death every year. As per Diabetes Atlas 9th edition, published by International Diabetes Federation (IDF), the number of diabetes cases is projected to be 700 million by 2045, where India is expected to be on second position.[5,6] By 2045, the first three countries with maximum number of diabetic cases are predicted to be China (147.2 million), India (134.2 million) and Pakistan (37.1 million).[5] One in every six diabetic patient in the world belongs to India; as per 2019 reports, India has 77 million adults suffering from diabetes and currently on second position in top 10 countries list.[5]

2,4-thiazolidinediones (TZD) constitute a class of drugs called glitazones which was approved for anti-hyperglycaemic use clinically.[7] TZD analogues have been explored as insulin sensitizer, aldose reductase inhibitor, PTP 1B inhibitor and peroxisome proliferator activated receptor-γ (PPAR- γ) agonist. TZD containing anti-hyperglycaemic agents act by various mechanisms like promoting peripheral glucose utilization and improving insulin resistance.[8] Many of the TZD derivatives have been discontinued clinically due to adverse effects, but pioglitazone is still in clinical use.[9] The amidic proton of TZD moiety resembling carboxylate ion is responsible for its binding to PPAR-γ receptor.[10,11] Reports of anti-hyperglycaemic potential of various 5-arylidene TZD derivatives have been published from various laboratories.[10,12-18] Various TZD containing PTP 1B inhibitors incorporated with weakly polar sulfonyl moiety (hydrogen bond acceptor) have revealed interactions with many binding site residues (Ala 217, Ile 221, Gln 262, Arg 254, Tyr 20, Arg 24, Arg 47, Asp 48 and Phe 182) of both catalytic as well as non-catalytic sites of PTP 1B enzyme.[19-22] Many substituted TZD derivatives have also been reported as aldose reductase inhibitors which have potential to treat type 2 diabetes and the related secondary complications.[23] A representative pharmacophoric skeleton of the proposed compounds has been depicted in Figure 1. In this study, we reported a series of 5-arylidene TZD derivatives condensed with aryl sulfonate moiety at *m*- position and evaluated their anti-hyperglycaemic potential along with *in silico* studies. Molecular docking was also carried out to provide additional report to the *in vivo* findings.

MATERIALS AND METHODS

Melting point was determined with the help of Veego-540 melting point apparatus by capillary method. The reaction progress was carefully monitored using silica gel coated aluminium sheets in TLC (Thin Layer Chromatography).

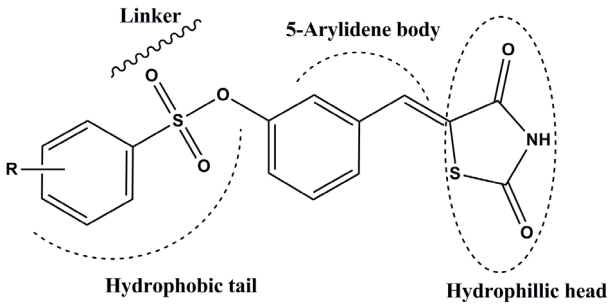
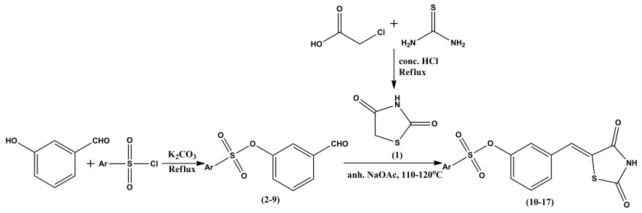


Figure 1: Pharmacophoric scaffold of the proposed compounds.



Scheme 1: Synthetic outline of compounds 10-17.

Bruker AC-400F, 400 MHz spectrometer recorded the and ^{13}C- and ^{1}H-NMR spectra of the synthesized compounds dissolved in either CDCl3 (deuterated chloroform) or DMSO-*d*6 (deuterated dimethylsulfoxide) solvent and taking internal standard TMS (tetramethyl silane). Micromass LCT instrument (electrospray ionisation mode) was utilized for recording mass spectra of the compounds.

Scheme 1 represented the synthetic methodology followed for synthesizing the compounds.

Preparation of thiazolidine-2,4-dione (1)

TZD was prepared via dissolving 56.7 g of chloroacetic acid (0.6 M) and 45.6 g of thiourea (0.6 Mmol) in 125 mL of water, followed by drop wise addition of 60 mL conc. hydrochloric acid. This mixture was kept for 12-hr reflux, after which it was cooled using an ice-bath. White needle shaped crude TZD crystals were separated and filtered. They were repeatedly washed, dried and finally recrystallized using methanol to afford pure thiazolidine-2,4-dione.[24]

White crystals (m. p.: 123-125°C; Yield: 88.2 %, 62.58 g,))

Rf: 0.49 (Methanol: Chloroform :: 1:10)

IR (KBr): 615, 1662, 1739, 3132 cm^{-1}

^{1}H-NMR (DMSO-*d6*): δ 11.98 (s, 1H, N*H*), 4.09 (s, 2H, CH_2) ppm

^{13}C-NMR (DMSO-*d6*): δ 173.54 (*C*O), 172.79 (*C*O), 35.65 (Ar-*C*) ppm.

Synthesis of intermediate compounds 2-9

A combination of 1.71 g/14.05 mM 3-hydroxybenzaldehyde in 20 mL ethyl acetate was prepared, to which

anhydrous potassium carbonate (3.87g, 28.10 mM) was added under continuous stirring. To this mixture, various substituted sulphonyl chlorides (14.05 mM) were added and kept for 24-hr reflux. Repeated washing with water and brine solution (3x20 mL) followed by removal of solvent provided crude product, which on purification yielded the intermediates as solid product (2-9).

3-Formylphenyl benzenesulfonate (2)

(Yield: 2.80 g, 76.29 %; m.p.: 52-54°C; Brown solid) *Rf*: 0.76 (Methanol : Chloroform :: 0.2:9.8); IR (KBr): 3066, 1688, 1585, 1372, 1178 cm^{-1}; ^{13}C-NMR (DMSO-*d6*): δ 121.86, 127.97, 128.21, 128.90, 129.87, 131.10, 133.89, 135.23, 137.74 and 149.34 (Ar-*C*), 191.92 (-*C*HO) ppm; ^{1}H-NMR (DMSO-*d6*): δ 7.36-7.39 (m, 1H, Ar-*H*), 7.57 (t, 1H, Ar-*H*, *Jm* = 2.32 Hz), 7.63-7.73 (m, 3H, Ar-*H*), 7.86 (t, 1H, Ar-*H*, *Jo* = 7.68 Hz), 7.90-7.92 (m, 3H, Ar-*H*), 9.98 (s, 1H, -C*H*O) ppm.

3-Formylphenyl-4-methylbenzenesulfonate (3)

Light brown solid (Yield: 2.95 g, 76.42 %; m.p.: 69-71°C) *Rf*: 0.65 (Methanol : Chloroform :: 0.2:9.8); IR (KBr): 3073, 2816, 1698, 1588, 1371, 1176 cm^{-1}; ^{13}C-NMR (DMSO-*d6*): δ 21.23 (-CH_3), 122.05, 127.67, 127.97, 128.29, 129.77, 130.37, 131.18, 137.51, 145.60 and 149.49 (Ar-*C*), 190.64 (-*C*HO) ppm; ^{1}H-NMR (DMSO-*d6*): δ2.46 (s, 3H, -CH_3), 7.22-7.25 (m, 1H, Ar-*H*), 7.40 (d, 2H, Ar-H, *Jo* = 8.16 Hz), 7.53 (t, 2H, Ar-*H*, *Jo* = 9.56 Hz), 7.69 (d, 2H, Ar-*H*, *Jo* = 6.8 Hz), 7.83 (d, 1H, Ar-*H*, *Jo* = 5.10 Hz), 9.95 (s, 1*H*, -CHO) ppm.

3-Formylphenyl-4-chlorobenzenesulfonate (4)

Brown solid (Yield: 2.76 g, 66.66 %; m.p.: 71-73°C) *Rf*: 0.62 (Methanol : Chloroform :: 0.2:9.8); IR (KBr): 3089, 2839, 1695, 1579, 1375, 1187 cm^{-1}; ^{13}C-NMR (DMSO-*d6*): δ 121.63, 127.69, 128.62, 129.82, 130.72, 132.74, 137.70, 140.50, 149.28 and 157.91 (Ar-*C*), 191.00 (-*C*HO) ppm; ^{1}H-NMR (DMSO-*d6*): δ7.25-7.36 (m, 1H, Ar-*H*), 7.57-7.61 (m, 2H, Ar-*H*), 7.65-7.68 (m, 2H, Ar-*H*), 7.84-7.89 (m, 3H, Ar-*H*), 9.98 (s, 1H, -C*H*O) ppm.

3-Formylphenyl 2,4,6-trimethylbenzenesulfonate (5)

(Yield: 1.85 g, 65.37 %; m.p.: 81-83°C; Brown solid) *Rf*: 0.68 (Methanol : Chloroform :: 0.2:9.8); IR (KBr): 3081, 2938, 1699, 1591, 1360, 1178 cm^{-1}; ^{13}C-NMR ($CDCl_3$): δ 21.17, 22.79 and 22.96 (-CH_3), 128.20, 128.39, 130.44, 131.96, 137.78, 140.47, 144.39 and 150.01, (Ar-*C*), 190.77 (-*C*HO) ppm; ^{1}H-NMR ($CDCl_3$): δ 2.34 (s, 3H, -CH_3), 2.56 (s ,6H, -CH_3), 7.01 (d, 2H, Ar-*H*, *Jm* = 1.62 Hz), 7.28 (d, 1H, Ar-*H*, *Jo*= 8.24 Hz), 7.47 (t, 2H, Ar-*H*, *Jo* = 8.38 Hz), 7.77 (d, 1H, Ar-*H*, *Jo* = 7.64 Hz), 9.91 (s, 1H, -C*H*O) ppm.

3-Formylphenyl-4-bromobenzenesulfonate (6)

(Yield: 2.0 g, 84.0 %; m.p.: 79-81°C; Light brown solid) *Rf*: 0.65 (Methanol : Chloroform :: 0.2:9.8); IR (KBr): 3084, 2871, 1688, 1573, 1378, 1181 cm^{-1}; ^{13}C-NMR (DMSO-*d6*): δ 122.03, 127.74, 128.69, 129.44, 129.95, 130.86, 132.78, 133.24, 137.76 and 149.27 (Ar-*C*), 191.27 (-*C*HO) ppm; ^{1}H-NMR (DMSO-*d6*): δ 7.32-7.35 (m, 1H, Ar-*H*), 7.59-7.63 (m, 2H, *Ar-H*), 7.79 (d, 2H, Ar-*H*, *Jo*= 8.72 Hz), 7.85 (d, 2H, Ar-*H*, *Jo*= 8.72 Hz), 7.89 (d, 1H, Ar-*H*, *Jo*= 7.72 Hz), 9.99 (s, 1H, -*CH*O) ppm.

3-Formylphenyl-2-nitrobenzenesulfonate (7)

(Yield: 0.96 g, 33.56 %; m.p.: 103-105°C; Cream solid) *Rf*: 0.69 (Methanol : Chloroform :: 0.2:9.8); IR (KBr): 3106, 3074, 1700, 1583, 1374, 1184 cm^{-1}; ^{13}C-NMR (DMSO-*d6*): δ 121.81, 125.36, 125.94, 127.69, 129.16, 131.21, 131.73, 132.89, 137.00, 137.91, 147.97, 149.03 (Ar-*C*) and 191.45 (-*C*HO) ppm; ^{1}H-NMR (DMSO-*d6*): δ 7.47 (d, 1H, Ar-*H*, *Jo*= 8.08 Hz), 7.63 (t, 1H, Ar-*H*, *Jo*= 7.88 Hz), 7.68 (s, 1H, Ar-*H*), 7.84 (t, 1H, Ar-*H*, *Jo*= 7.52 Hz), 7.91 (d, 1H, Ar-*H*, *Jo*= 7.60 Hz) ,7.96-8.04 (m, 1H, Ar-*H*), 8.09 (d, 1H, Ar-*H*, *Jo*= 7.80 Hz) ppm, 9.99 (s, 1H, -C*H*O) ppm.

3-Formylphenyl naphthalene-2-sulfonate (8)

Light yellow solid (Yield: 3.93g, 89.93 %; m.p.: 74-76°C) *Rf*: 0.59 (Methanol : Chloroform :: 0.2:9.8); IR (KBr): 3065, 2859, 1690, 1582, 1373, 1175 cm^{-1}; ^{13}C-NMR (DMSO-*d6*): δ 122.04, 122.26, 127.76, 127.87, 127.92, 128.61, 129.48, 129.83, 129.89, 130.31, 130.78, 131.04, 131.39, 135.09, 137.70 and 149.47 (Ar-*C*), 191.34 (-*C*HO) ppm ^{1}H-NMR (DMSO-*d6*): δ 7.28 (d, 1H, Ar-*H*, *Jo* = 8.12 Hz), 7.45 (t, 1H, Ar-*H*, *Jo* = 7.88 Hz), 7.54 (t, 1H, Ar-*H*, *Jm* = 1.94 Hz), 7.65 (t, 1H, Ar-*HJo* = 6.9 Hz), 7.70 (t, 1H, Ar-*H*, *Jo*= 7.52 Hz), 7.76 (d, 1H, Ar-*H*, *Jo* = 6.6 Hz), 7.84 (dd, 1H, Ar-*H*, *Jo* = 6.84 Hz, *Jm* = 1.88 Hz), 7.91 (t, 2H, Ar-*H*, *Jo* = 8.06 Hz), 8.01 (d, 1H, Ar-*H*, *Jo* = 8.72 Hz), 8.38 (s, 1H, Ar-*H*), 9.88 (s, 1H,-*CH*O) ppm.

3-Formylphenyl-4-methoxybenzenesulfonate (9)

Light brown solid (Yield: 2.91g, 71.10 %; m.p.: 56-58°C) *Rf*: 0.59 (Methanol: Chloroform :: 0.2:9.8); IR (KBr): 3084, 2938, 2837, 1695, 1587, 1367, 1165 cm^{-1}; ^{13}C-NMR (DMSO-*d6*): δ 55.90 (-OCH_3), 115.00, 122.03, 125.03, 128.03, 128.68, 130.68, 131.03, 137.72 and 149.47 (Ar-*C*), 164.16 (*C*-attached to-OCH_3), 191.98 (-*C*HO) ppm; ^{1}H-NMR (DMSO-*d6*): δ 3.86 (s, 3H, -CH_3), 7.15-7.18 (m, 2H, Ar-*H*), 7.32-7.35 (m, 1H, Ar-*H*), 7.56 (t, 1H, Ar-*H*, *Jm* = 2.30 Hz), 7.62 (t, 1H, Ar-*H*, *Jo* = 7.88 Hz),

7.79-7.81 (m, 2H, Ar-*H*), 7.88 (d, 1H, Ar-*H*, *Jo* = 6.95 Hz) 9.96 (s, 1H, -*CH*O) ppm.

Synthesis of compounds 10-17

A mixture of 0.7 g of thiazolidine-2,4-dione (6 mM) and 6 mM/0.49 g of anhydrous sodium acetate in glacial acetic acid was allowed to reflux process for 20 min at 110-120°C. Intermediate compound (6 mM, sulphonate ester) was added to mixture, attached to Dean-Stark apparatus and allowed to reflux for 36 hr. The resultant reaction mixture was added into crushed ice under continuous mixing using the stirrer to obtain the crude product, which was sieved, repeatedly washed and dried. Final products (10-17) were obtained by recrystallization from ethanol.

(Z)-3-((2,4-Dioxothiazolidin-5-ylidene)methyl) phenyl benzenesulfonate (10)

Light brown solid (Yield: 1.54 g, 65.25 %; m.p.: 152-154°C)

Rf: 0.64 (Methanol : Chloroform :: 1 : 9); IR (KBr): 3351, 3037, 2762, 1745, 1689, 1602, 1375, 1180 cm^{-1}; ^{13}C-NMR (DMSO-*d6*): 122.70 (>*C*=, TZD), 123.75, 125.50, 128.20, 129.01, 129.78, 129.92, 130.95, 134.02, 134.93, 135.14 (Ar-*C*), 149.27 (=*C*H attached to Ar-*C*), 167.01, 167.41 (>*CO,* TZD) ppm; ^{1}H-NMR (DMSO-*d6*):δ 7.13-7.16 (m, 1H, Ar-*H*), 7.20 (s, 1H, Ar-*H*), 7.51-7.53 (m, 2H, Ar-*H*), 7.66-7.69 (m, 3H, 1 =C*H* and 2 Ar-*H*), 7.80-7.85 (m, 1H, Ar-*H*), 7.87-7.90 (m, 2H, Ar-*H*), 12.69 (br s, 1H, -N*H*) ppm; Mass (EI): 361.1363 $[M]^+$, 360.9604 $[M-1]^+$.

(Z)-3-((2,4-Dioxothiazolidin-5-ylidene)methyl) phenyl-4-methylbenzenesulfonate (11)

(Yield: 1.10 g, 41.19 %; m.p.: 186-188°C, Yellow color solid)

Rf: 0.62 (Methanol : Chloroform :: 1 : 9); IR (KBr): 3367, 3037, 2762, 1745, 1689, 1602, 1375, 1180 cm^{-1}; ^{13}C-NMR (DMSO-*d6*) : δ 21.23 (-CH_3), 122.34 (>*C*=, TZD), 123.66, 125.28, 128.03, 128.91, 129.77, 129.93, 130.35, 131.17 134.70 (Ar-*C*), 145.66 (=*C*H attached to Ar-*C*), 149.33 (Ar-*C*), 166.84, 167.08 (*CO,* TZD) ppm; ^{1}H-NMR (DMSO-*d6*) : δ 2.44 (s, 3H, -CH_3), 7.09 (s, 1H, Ar-*H*), 7.12-7.15 (m, 1H, Ar-*H*), 7.46 (d, 2H, Ar-*H*, *Jo* = 8.16 Hz), 7.51-7.53 (m, 2H, Ar-*H*) 7.70-7.75 (m, 3H, 1 =C*H* and 2 Ar-*H*), 12.69 (br s, 1H, N*H*) ppm; Mass (EI): 375.8449 $[M]^+$, 374.7404 $[M-1]^+$.

(Z)-3-((2,4-Dioxothiazolidin-5-ylidene)methyl) phenyl-4-chlorobenzenesulfonate (12)

(Yield: 1.20 g, 41.30 %; m.p.: 175-177°C; Light brown solid)

Rf: 0.61 (Methanol : Chloroform :: 1 : 9); IR (KBr): 3378, 3078, 1746, 1689, 1618, 1376, 1168 cm^{-1}; ^{13}C-NMR (DMSO-*d6*): δ 122.62 (>*C*=, TZD), 123.50, 125.41, 128.88, 129.70, 129.73, 129.84, 130.57, 132.73, 134.90 (Ar-*C*), 140.53 (=*C*H attached to Ar-*C*), 149.14 (Ar-*C*), 166.86, 167.00 (*CO,* TZD) ppm; ^{1}H-NMR (DMSO-*d6*):δ 7.09-7.13 (m ,1H, Ar-*H*), 7.15 (s, 1H, Ar-*H*), 7.47-7.52 (m, 2H, Ar-*H*), 7.65-7.68 (m, 3H, 1 =C*H* and 2 Ar-*H*), 7.85 (d, 2H, Ar-*H*, *Jo* = 6.88 Hz, *Jm* = 1.80 Hz), 12.55 (br s, 1H, -N*H*) ppm; Mass (EI): 396.0284 $[M]^+$, 394.9622 $[M-2]^+$.

(Z)-3-((2,4-Dioxothiazolidin-5-ylidene)methyl) phenyl-2,4,6-trimethylbenzenesulfonate (13)

(Yield: 1.23 g, 59.70 %; m.p.: 200-202°C; Cream solid)

Rf: 0.49 (Methanol : Chloroform :: 1 : 9); IR (KBr): 3379, 3145, 3032, 1743, 1687, 1602, 1369, 1183 cm^{-1}; ^{1}H-NMR (DMSO-*d6*):δ 2.33 (s, 3H, -CH_3), 2.49 (s, 6H, -CH_3), 7.01(s, 1H, Ar-*H*), 7.12-7.15 (m, 3H, Ar-*H*), 7.49-7.52 (m, 2H, Ar-*H*), 7.69(s, 1H, =C*H),* 12.65 (br s, 1H, N*H*) ppm; ^{13}C-NMR (DMSO-*d6*): δ 20.61, 22.19 (-CH_3), 121.88 (>*C*=, TZD), 123.76, 125.30, 129.29, 129.40, 129.77, 130.51, 131.86, 134.74, 139.71, (Ar-*C*), 144.23 (=*C*H attached to Ar-*C*), 149.15 (Ar-*C*), 166.91, 167.16 (*CO,* TZD) ppm; Mass (EI): 402.8141 $[M-1]^+$, 403.9103 $[M]^+$.

(Z)-3-((2,4-Dioxothiazolidin-5-ylidene)methyl) phenyl-4-bromobenzenesulfonate (14)

(Yield: 1.90 g, 59.93 %; m.p.: 188-190°C; Brown solid)

Rf: 0.60 (Methanol : Chloroform :: 1 : 9); IR (KBr): 3421, 3158, 3060, 1740, 1690, 1612, 1377, 1162 cm^{-1}; ^{1}H NMR (DMSO-*d6*): δ 7.09-7.12 (m, 1H, Ar-*H*), 7.15 (s, 1H, Ar-*H*), 7.50 (t, 2H, Ar-*H*, *Jm* = 2.62 Hz), 7.69 (s, 1H, =C*H*), 7.75 (dd, 2H, Ar-*H*, *Jo* = 6.78 Hz, *Jm* = 1.98 Hz) 7.82 (dd, 2H, Ar-*H*, *Jo* = 4.88, *Jm* = 1.92 Hz), 12.58 (br s, 1H, -N*H*) ppm; ^{13}C NMR (DMSO-*d6*): δ 122.64 (>*C*=, TZD), 123.56, 125.44, 128.97, 129.48, 129.75, 129.93, 130.69, 132.78, 133.24 and134.96 (Ar-*C*), 149.16 (=*C*H attached to Ar-*C*), 166.87, 167.02 (*CO,* TZD) ppm; Mass (EI): 438.7659 $[M-2]^+$, 440.7690 $[M]^+$.

(Z)-3-((2,4-Dioxothiazolidin-5-ylidene)methyl) phenyl-2-nitrobenzenesulfonate (15)

(Yield: 1.53 g, 73.55 %; m.p.: 171-173°C, Yellow brown solid)

Rf: 0.67 (Chloroform : Methanol :: 9 : 1); IR (KBr): 3370, 3137, 3035, 1744, 1691, 1600, 1372, 1190 cm^{-1}; ^{13}C NMR (DMSO-*d6*): δ 122.45 (>*C*=, TZD), 123.41, 125.32, 125.63, 126.05, 129.40, 129.66, 130.94, 131.77, 132.80, 135.18, 136.82, (Ar-*C*), 147.99 (=*C*H attached to Ar-*C*) 148.93 (Ar-*C*), 167.86, 167.08 (*CO,* TZD) ppm

^{1}H NMR (DMSO-*d6*): δ 7.26-7.28 (m, 1H, Ar-*H*), 7.32 (s, 1H, Ar-*H*), 7.54 (d, 2H, Ar-*H*, *Jo* = 6.62 Hz), 7.71 (s, 1H, =C*H*), 7.85 (t, 1H, Ar-*H*, *Jo* = 7.72 Hz), 7.96 (d, 1H, Ar-*H*, *Jo* = 7.92 Hz), 8.01-8.05 (m, 1H, Ar-*H*), 8.14 (d, 1H, Ar-*H*, J = 7.92 Hz), 12.61 (br s, 1H, -N*H*) ppm; Mass (EI): 406.8639 $[M]^+$, 405.7734 $[M-1]^+$.

(Z)-3-((2,4-Dioxothiazolidin-5-ylidene)methyl) phenyl-naphthalene-2-sulfonate (16)

(Yield: 1.80 g, 85.0%; m.p.: 185-187°C; Light brown solid)

Rf: 0.71 (Chloroform : Methanol :: 9 : 1); IR (KBr): 3370, 3159, 3045, 1745, 1689, 1602, 1380, 1175 cm^{-1}; ^{1}H NMR (DMSO-*d6*):δ 7.06-7.09 (m, 1H, Ar-*H*), 7.11 (s, 1H, Ar-*H*), 7.42 (t, 2H, Ar-*H*, *Jm* = 2.62 Hz), 7.61 (s, 1H, =C*H*), 7.66 (t, 1H, Ar-*H*, *J0* = 7.97 Hz), 7.73 (t, 1H, Ar-*H*, *Jo* = 8.58 Hz), 7.84 (m, 1H, Ar-*H*), 8.01 (d, 1H, Ar-*H*, *Jo* = 8.64 Hz), 8.06 (d, 1H, Ar-*H*, *Jo* = 8.12 Hz), 8.12 (d, 1H, Ar-*H*, *Jo* = 8.72 Hz), 8.45 (d, 1H, Ar-*H*, *Jm* = 1.36 Hz), 12.42 (s, 1H, -N*H*) ppm; ^{13}C NMR (DMSO-*d6*): δ 122.29 (>*C*=, TZD), 122.60, 123.67, 125.35, 127.87, 127.97, 128.98, 129.47, 129.76, 129.87, 130.00, 130.30, 130.72, 131.03, 131.46, 134.88, 135.13 (Ar-*C*), 149.36 (=*C*H attached to Ar-*C*), 166.87, 167.02 (*CO,* TZD) ppm; Mass (EI): $[M]^+$ 411.9126, $[M-1]^+$ 410.8253.

(Z)-3-((2,4-Dioxothiazolidin-5-ylidene)methyl) phenyl-4-methoxybenzenesulfonate (17)

(Yield: 0.93 g, 46.50 %; m.p.: 218-220°C; Brown solid)

Rf: 0.59 (Methanol : Chloroform :: 1 : 9); IR (KBr): 3367, 3143, 3032, 1745, 1689, 1591, 1380, 1156 cm^{-1}; ^{13}C NMR (DMSO-*d6*): δ 55.78 (CH_3), 114.90 (>*C*=, TZD), 122.51, 123.86, 125.16, 125.29, 129.04, 129.88, 130.54, 130.67, 134.79, (Ar-*C*), 149.39 (=*C*H attached toAr-*C*), 164.14 (Ar-*C* attached to -OCH_3), 166.94, 167.22 (*CO,* TZD) ppm; ^{1}H NMR (DMSO-*d6*): δ 3,85 (s, 3H ,-OCH_3), 7.09-7.14 (m, 4H, Ar-*H*), 7.48-7.50 (m, 2H, Ar-*H*), 7.68 (s, 1H, =C*H*), 7.75 (dd, 2H, Ar-*H*, *Jo*=6.96 Hz, *Jm*=2.74 Hz), 12.59 (br s, 1H, -N*H*) ppm;Mass (EI): 391.9239 $[M]^+$, 390.8344 $[M-1]^+$.

Anti-hyperglycaemic study

Alloxan-induced diabetic albino mice of Laca strain (both male and females) model were used for the *in vivo* study. The mice were kept under standard laboratory conditions (6 mice/cage; 25 ± 2°C temperature; 60-70% humidity; 12 hr natural day-night cycle). With prior approval from Institutional Animal Ethics Committee, Panjab University, Chandigarh under letter no. PU/IAEC/S/14/105. The experiments were performed following Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) guidelines. Mice (fasted overnight) were administered alloxan (single *i.p.* injection; 150 mg/kg body weight); which was prepared by dissolving physiological saline to induce hyperglycaemia. A 5% glucose solution was given to the mice for the first 12 hr to prevent development of hypoglycaemic shock. Blood sugar level was measured with a glucometer after 72 hr and mice with blood sugar level ≥ 250 mg/dL were considered hyperglycaemic.[25,26]

Acute antihyperglycaemic study

The animals were divided into three groups (6 animals in each group): negative control (treated with only vehicle but no drug), positive control (treated with standard drug pioglitazone) and test group (treated with the synthesized compounds). Fasting blood sugar level of the animals (with overnight fasting) were established at 0 hr. A fixed dose (30 mg/kg body weight) was administered orally in the form of homogenised suspension (0.5% CMC + Tween 80) to both the pioglitazone and final compounds treatment groups. The vehicle treated mice were administered with the same volume and quantity of 0.5% CMC with Tween 80 whereas the control group mice were not given any drug or vehicle. Blood obtained through tail prick technique was utilized for monitoring the blood sugar level (2^{nd}, 4^{th}, 6^{th} and 24^{th} hr) after administering the test compounds. Percentage decrease in blood sugar was determined with reference to that of control group animals. At least 10% decrease in blood sugar indicated a positive screening outcome.

Sub-acute anti-hyperglycaemic study

The animals were divided into three groups: negative control group (treated with only vehicle but no drug), positive control group (treated with standard drug pioglitazone) and test group (treated with the synthesized compounds). The standard drug pioglitazone along with the synthesized or test compounds prepared in the form a homogenised suspension (with 0.5% CMC + Tween 80) were administered once daily (body weight dose = 30 mg/kg) for a week and preferably at the same time of the day. After seven days of test compound administration, percentage reduction observed in blood sugar concentration was measured. The readings were represented as mean with their standard error for each treatment group; one-way ANOVA along with Dunnett's test were performed to prove the statistical significance ($P < 0.05$) and reliability of the data.

Molecular docking

The 2D structures of the molecules were built and energy minimized in Chemdraw 12.0. The ligands were imported into Autodock, polar hydrogens added. PTP1B, AR, PPAR-γ receptors are commonly involved with the pathogenesis and complications of diabetes. The crystal structures of PTP1B (2NT7), AR (3G5E) and PPAR-γ (2XKW) were downloaded from protein data bank (PDB). These proteins were imported into Auto Dock Tools (ADT) where they were pre-processed (deletion of water molecules, addition of polar hydro-

gens) and finally a grid box was created to define the active binding location. Molecular docking studies were performed with Autodock Vina.[27] Co-crystallized ligand present in the enzyme was extracted and re-docked with their corresponding enzyme structures to validate the docking protocol. The synthesized compounds were converted to pdbqt format and then docked within the grid box defined for PTP1B (2NT7), PPAR-gamma (2XKW) and AR (3G5E). Binding conformation of the final compounds (having good activity), nature of interactions with various residues was studied using the graphics package provided with Autodock Tools 1.5.6.[28]

ADME prediction

A better understanding and correlation of synthesized compounds with their experimental biological activity could be drawn by tracing various physico-chemically significant properties of the final compounds using online server of ADMET predictor 7.2.[29] Various ADME parameters precited: logP (Octanol-water partition coefficient); MlogP (Moriguchi model of logP); S+logP (Artificial neural network ensemble model of logP); S+logD (logP at a specific pH, e.g. pH=7.4); Rule of 5 (Lipinski's rule of five- indicating drug likeness of a molecule where molecular weight < 500, log*P* < 5, donorHB ≤ 5, HAB ≤ 10); M_NO (Number of nitrogen and oxygen atom in molecule); TPSA (Topological surface area); MWt (Molecular weight); HBDH (Number of hydrogen bond donor hydrogens).

RESULTS AND DISCUSSION

Synthesis

Sulfonylation at carbonyl "O" of 3-hydroxybenzaldehyde provided intermediate aryl sulfonate esters (2-9), which undergone condensation with TZD to provide the *Z*-isomers of final compounds 10-17. ^{1}H-NMR, ^{13}C-NMR along with mass spectroscopy results established the structure of intermediate as well as final compounds. A *Z*-configuration was established for the final compounds 10-17, confirmed from the previous studies as well as the vinylic proton range (7.61 to 7.75 ppm) in the ^{1}H-NMR spectra.[30,31]

In vivo method for determining anti-hyperglycaemic activity

In acute study, decrease in blood sugar level was observed up to 4 hr which was followed by a gradual rise up to 24 hr. After the treatment for a week (sub-acute study), a fall in plasma sugar level was observed; 14.17 to 39.19 % for test groups against 37.47 % decrease in pioglitazone treated group. Among the final compounds (10-17), only 10 and 12 exhibited maximum anti-hyperglycaemic activity of 39.19 % and 36.55 % respectively which were comparable to that of pioglitazone (Table 1). The % reduction in blood sugar level as observed in various treatment groups has been depicted in Figure 2. There was statistically significant difference observed between different treatment groups, as signified by the probability value $P < 0.05$.

In negative control group (treated with only vehicle), the blood sugar level was found to be increased throughout the study period. But in positive control group (treated with pioglitazone) and with test group, the blood sugar level was found to be decreased over time. However in both the groups, the maximal reduction in % blood sugar was achieved at 4th hr. The % change in blood sugar has been presented as Mean ± Standard error of mean (SEM) at significance level $P < 0.05$ in Table 1. In test group, a single dose of the test compounds achieved maximum reduction in blood sugar level up to 4 hr, after which the effect gradually reduced at 6th

Table 1: Anti-hyperglycaemic activity.

Groups		2 hr	4 hr	6 hr	24 hr	7th day
Negative Control (Vehicle)		1.16±0.70	1.35±0.47	2.31±0.42	6.76±1.52	8.02±0.70
Positive Control (pioglitazone)		-36.02±0.87	-44.78±1.66	-40.67±1.49	-34.93±0.79	-37.47±2.15
Test Group (10-17)	10	-29.62±0.64	-42.90±0.15	-33.83±0.01	-26.59±0.41	-39.19±2.30
	11	-21.99±0.10	-29.75±0.32	-25.91±0.72	-16.18±0.14	-30.71±1.59
	12	-27.91±2.37	-39.94±0.54	-31.40±0.43	-20.18±2.05	-36.55±1.29
	13	-18.97±0.80	-23.72±0.76	-21.53±1.38	-14.34±1.62	-22.45±0.28
	14	-25.15±1.50	-36.15±2.39	-29.61±0.37	-17.19±0.16	-34.04±2.12
	15	-22.18±0.24	-31.47±0.58	-28.54±0.84	-16.82±0.09	-29.78±1.12
	16	-17.61±1.99	-20.79±1.22	-18.56±2.16	-11.34±0.42	-14.17±1.17
	17	-23.45±1.35	-28.43±1.29	-25.00±0.94	-17.77±0.80	-27.36±1.34

Values expressed as mean ± SEM; In negative control group the +ve value indicates % increase in blood sugar level; In positive control and test groups, -ve sign indicates decrease in % blood sugar; $P < 0.05$ (significant);

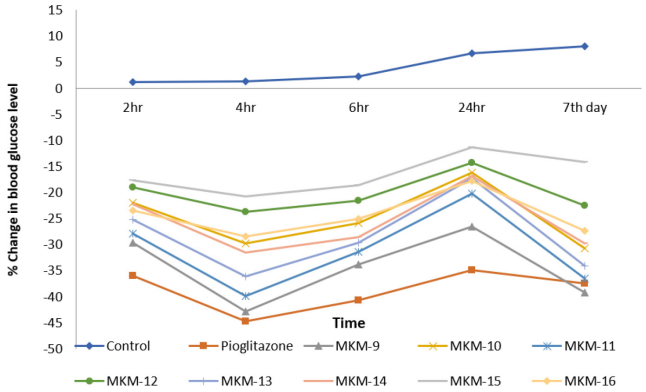


Figure 2: % reduction in blood sugar level in various treatment groups.

and 24th hr. All the test compounds showed similar pattern of anti-hyperglycaemic activity. Among the test compounds, 10 and 12 had shown 42.90 % and 39.94 % reduction in blood sugar level at 4th hr against 44.78 % decrease observed with pioglitazone group. After 7 days of once-daily treatment, phenyl sulfonate ester was found to possess maximum anti-hyperglycaemic activity (39.19 %) whereas it's p-chloro analogue was having comparable anti-hyperglycaemic activity (36.55) with that of the pioglitazone (37.47). Phenyl ester and various analogues with electron withdrawing groups have shown significant reduction in blood sugar level as compared to the esters with electron donating substituents. Amongst the electron withdrawing group substituents, chloro analogue demonstrated improved activity than bromo derivative. Introduction of naphthyl group increased the lipophilicity which caused a decrease in anti-hyperglycaemic activity. The % decrease in blood sugar level values were found to be significant at $P < 0.05$ as compared to the negative and positive control group.

Molecular docking

Validation of the molecular docking protocol was performed in which root mean square deviation values were found to be less than 2 Å; obtained values were 0.89, 0.61 and 0.74 Å respectively for PTP1B, AR and PPAR-γ respectively. Docking studies on binding conformation of the active compounds (10 and 12) within the active site pocket of AR, PTP1B, PPAR-γ enzymes were studied.

PTP1B (2NT7): Compound 10 and 12 have shown H-bonding interactions with amino acid residues Arg 24, Gln 262, Ala 264. Amidic nitrogen of TZD exhibited H-bonding with carbonyl oxygen of Gln 262. In compound 10 the C-2 carbonyl oxygen stabilized amino acid residue Ala 264 through formation of H-bond with its amino proton, whereas the same residue was stabilized by the C-4 carbonyl oxygen of TZD moiety in compound 12 (Figure 3).

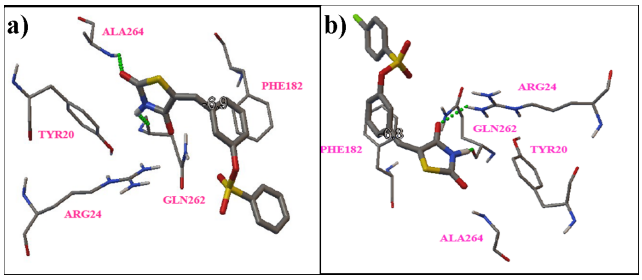


Figure 3: Binding pose of the ligands inside PTP1B binding pocket: a) Compound 10 b) Compound 12.

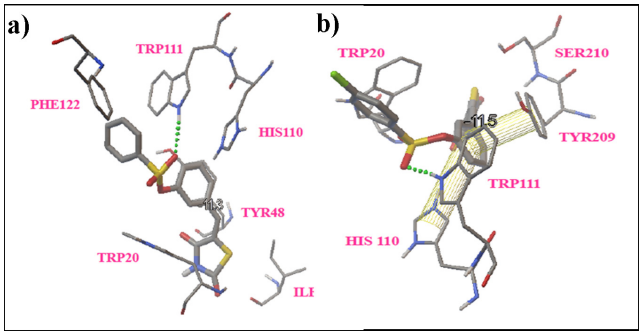


Figure 4: Binding pose of the ligands inside the binding pocket of AR: a) Compound 10 b) Compound 12.

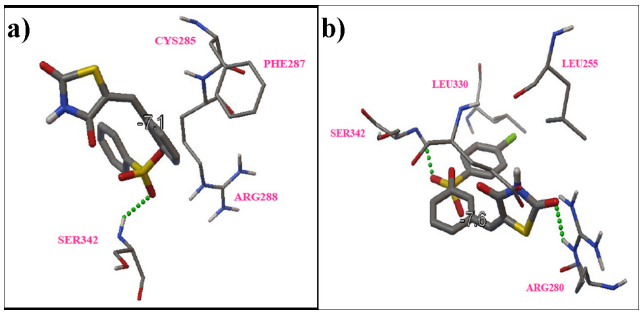


Figure 5: Binding pose of the ligands inside the binding pocket of PPAR-γ : a) Compound 10 b) Compound 12.

AR (3G5E): The oxygen of sulphonyl group in both of the active compounds stabilized amino acid residue TRP 111 through formation of a H-bond with its secondary amino proton of indole ring. The arylidene moiety of the compound 12 was involved in pi-pi interactions with imidazole ring of His 110 and phenyl ring of Tyr 209 (Figure 4).

PPAR-γ (2XKW): In both the compounds, oxygen of sulphonyl moiety stabilized the amino acid residue Ser 342 through formation of H-bond with its amino proton. Compound 12 showed an additional H-bonding with amino acid residue Arg 280 (Figure 5).

Table 2: Predicted ADME parameters.								
Title	Mol Wt (Da)	M logP	S + logP	S + logD	Rule of 5	M_NO	TPSA	HBDH
10	361.397	1.204	2.335	1.59	0	6	89.54	1
11	375.424	1.448	2.835	2.142	0	6	89.54	1
12	395.842	1.716	3.076	2.316	0	6	89.54	1
13	403.478	1.918	3.525	2.931	0	6	89.54	1
14	440.298	1.835	3.131	2.488	0	6	89.54	1
15	406.394	1.324	1.889	1.108	0	9	135.36	1
16	411.457	2.004	3.382	2.716	0	6	89.54	1
17	391.423	0.957	2.599	1.918	0	7	98.77	1

ADME prediction

Prediction of pharmacokinetic profile of all the final compounds was carried out by putting the structures on online server of ADMET predictor 7.2. Various properties of the synthesized compounds were evaluated like Mol wt, S + logP, M logP, S + logD, Rule of 5, T_PSA, M_NO and HBDH. Various pharmacokinetically significant parameters were assessed to be tolerable for most of the compounds, signifying their drug-likeness. Table 2 depicts various ADMET parameters suitable for human usage which were found acceptable.

CONCLUSION

Aryl sulfonate esters conjugated 5-arylidene-thiazolidine-2,4-diones were synthesized and their anti-hyperglycaemic activity was studied by alloxan-induced diabetic mice model. Incorporation of benzene sulfonate and it's chloro analogue of 5-arylidene TZD produced the most potent compounds among the series; compound-10 *(Z)*-3-((thiazolidin-2,4-dioxo-5-ylidene)methyl) phenylbenzenesulfonate and 12 *(Z)*-3-((thiazolidin-2,4-dioxo-5-ylidene)methyl)phenyl-4-chlorobenzenesulfonate respectively. Incorporation of electron withdrawing groups like NO_2, Cl and Br on sulfonate ester part caused significant rise in anti-hyperglycaemic activity whereas electron donors ($-CH_3$, $-OCH_3$) showed decrease in activity. Amongst the electron withdrawing group attached derivatives, chloro analogue demonstrated improved activity than bromo derivative. Introduction of naphthyl group increased the lipophilicity which resulted into decrease in anti-hyperglycaemic activity. The findings would be beneficial in further designing more active TZD derivatives as anti-hyperglycaemic agents. Molecular docking study provided additional support for good binding of the compounds with the receptors like PTP1B, AR and PPAR-γ responsible for causing diabetes. Predicted ADME parameters assured about the pharmacokinetic profile of the active compounds. Various substituted derivatives of the active compound 10 are under study and would be reported in due course of time.

ACKNOWLEDGEMENT

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

TZD: 2,4-Thiazolidinediones; **PTP1B:** Protein Tyrosine Phosphatase 1B; **AR:** Aldose Reductase; **PPAR-γ:** Peroxisome Proliferator Activated Receptor-γ; **ADME:** Absorption Distribution Metabolism Elimination; **M logP:** Octanol water partition co-efficient predicted by Moriguchi model; **S+logP:** Octanol water partition co-efficient predicted by artificial neural network ensemble; **S+logD:** Predicted octanol-water distribution coefficient at physiological pH; **TPSA:** Total Polar Surface Area; **M_NO:** Number of nitrogen and oxygen atoms in the molecule; **HBDH:** Hydrogen Bond Donors.

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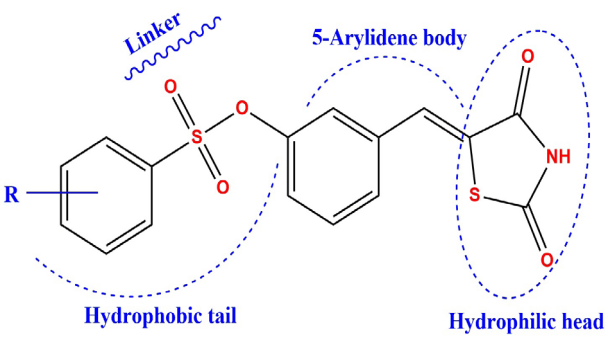
PICTORIAL ABSTRACT



SUMMARY

- Aryl sulfonyloxy-5-arylidene thiazolidine-2,4-dione analogues (compounds 10-17) were synthesized and characterized using ^{1}H-NMR, ^{13}C-NMR and mass spectroscopy methods.
- The binding interactions with various enzymes responsible for diabetes (PTP1B, AR, PPAR-γ) were studied through molecular docking.
- The compounds were screened for drug-like potential by ADME prediction.
- Alloxan induced diabetes model was utilized to evaluate the anti-hyperglycaemic activity, in which compound 10 and 12 showed comparable anti-hyperglycaemic potential with that of pioglitazone.

About Authors

Dr. Manoj Kumar Mahapatra, Kanak Manjari Institute of Pharmaceutical Sciences, Chhend, Rourkela-769015, Odisha, INDIA.

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