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Synthesis and antihyperglycemic evaluation of new 2,4-thiazolidinediones having biodynamic aryl sulfonylurea moieties

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ABSTRACT

New 2,4-thiazolidinediones with aryl sulfonylurea moieties **8a**–**h** have been synthesized by condensing various substituted sulfonamides and 5-(isocyanatomethyl) thiazolidino-2,4-dione **6**. The isocyanomethyl thiazolidinedione was obtained by using the Curtius rearrangement, starting from known 2,4-dioxo-5-thiazolidineacetic acid **4**. The newly synthesized compounds **8a**–**h** have been evaluated for the antihyperglycemic activity in normal rats model and among these compounds **8b**, **8c**, **8e** and **8f** showed significant antihyperglycemic activity in sucrose loaded rat model.

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Type 1 diabetes mellitus (Insulin dependent diabetes mellitus IDDM) and Type 2 diabetes mellitus (Non insulin dependent diabetes mellitus, NIDDM) are now recognized as serious global health problem and growing rapidly world wide.[1] Type 2 diabetes mellitus (Type 2 DM) is the most common form of diabetics and has been found 90% of all diabetics.[2] Type 2 DM is a debilitating disease characterized by hyperglycemia due to insulin resistance in the liver and peripheral tissue. Type 2 DM also occurs in older as well as in younger people due to the high caloric intake, sedentary lifestyles and lack of exercise. Patients with Type 2 DM often suffer from dyslipidemia in the form of high plasma triglycerides and low HDL cholesterol levels, both considered as risk factors for coronary heart diseases.[3] The diabetic is often associated with obesity, dyslipidemia, and hypertension, leading to cardiovascular risks.[4] When recommended dietary medication and exercise fail to control elevated blood glucose levels, then pharmacological therapy is needed.

Owing to the seriousness of NIDDM various pharmacological agents have been developed which include biguanidines, sulfonylureas, 2,4-thiazolidinediones etc. Metformin is an oral antidiabetic agent and is a biguanidine derivative, useful for the treatment of insulin-resistant overweight diabetes patients.[5] Metformin enhances insulin action at the post receptor level in peripheral tissues such as muscle.[6] Lactic acidosis is another serious fatal problem with biguanidines. The most commonly used antidiabetic agents are sulfonylureas. These agents activate pancreatic β cells to produce insulin secretion. Glibenclamide, a sulfonyl urea is a potent and selective K_{ATP} channel blocker and a potent oral hypoglycemic agent.[7] The mechanism of action of the drug consists of the interaction with a sulfonylurea receptor and the inhibition of the ATP-sensitive K^+ channel, which depolarizes the cells and leads to insulin secretion.[8] The drawbacks associated with these drugs are severe hypoglycemia, weight gain[8a] and the hyperinsulinemia, known to be a risk factor for ischemic heart disease.[9] Therefore, drugs that ameliorate the insulin resistance without stimulating insulin release from beta cells have been developed for the treatment of Type 2 DM.

2,4-Thiazolidinediones (TZDs) are a group of pharmacological agents that enhance insulin action (insulin sensitizers) and promote glucose utilization in peripheral tissue. They significantly reduce glucose, lipid in rodent models of Type 2 DM and obesity.[10] TZDs have been reported as peroxisome proliferators activated gamma receptors (PPARγ). Although their exact mechanism of the action has not been completely elucidated, it has been demonstrated that TZDs structure elicits its pharmacological actions by binding and activating nuclear receptor PPARγ. The PPARγs are a group of nuclear receptors that act as transcription factors which play a major role in the regulation of lipid metabolism storage.[11] Ciglitazone,[12] troglitazone,[12] englitazone,[13] pioglitazone,[14] rosiglitazone[15] and KRP-297[16] are the potential antidiabetic drugs and each has TZD as structural component. These drugs are associated with one or other side effects. The drug troglitazone was withdrawn because of unacceptable levels of hepatotoxicity.[17]

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Rosiglitazone has been associated with liver, cardiovascular and hematological toxicity.[18]

Literature survey reveals that there is scanty information on the molecules having both sulfonylurea and TZDs as their structural units. Considering the pharmacological importance of sulfonylureas and TZDs and also the side effects associated with existing drugs, here it was thought worthwhile to design and synthesize 2,4-thiazolidinediones having aryl sulfonylurea moieties with the hope to obtain the products with good antihyperglycemic activity.

The desired titled products have been synthesized starting from readily available materials. A convenient synthetic route has been developed and depicted in Scheme 1. 2,4-Thiazolidinedione acetic acid **4** was synthesized using the reported procedure.[19] The condensation of maleic anhydride **1** and thiourea **2** has been carried in water at reflux and obtained 2-imino-4-oxo-5-thiazolidineacetic acid **3**. The compound **3** on subsequent hydrolysis using 20% aqueous H_2SO_4 gave 2,4-thiazolidinedione acetic acid **4**. The compound **4** has been then allowed to interact with $SOCl_2$ in presence of catalytical amount of DMF in DCM for 7 h for getting 2,4-thiazolidinedione acetyl chloride. The isolated crude 2,4-thiazolidinedione acetyl chloride was dissolved in acetone and stirred. To the stirred solution of 2,4-thiazolidinedione acetyl chloride an aq solution of NaN_3 was added drop wise at 0 °C and after complete addition of the azide the reaction mass was further stirred for 3 h. The obtained 2,4-dioxo-5-thiazolidineacetic acid azide **5** was then refluxed in toluene for 6 h. It was found that the azide has completely converted to 5-(isocyanatomethyl)thiazolidine-2,4-dione **6** via Curtius rearrangement.

The freshly prepared aryl sulfonamides **7a–h**[20] were then condensed with 5-(isocyanatomethyl)thiazolidine-2,4-dione **6** in DMF at 100 °C in presence of potassium carbonate and obtained new 1-((2,4-dioxothiazolidin-5-yl)methyl)-3-benzenesulfonyl ureas **8a–h** (Scheme 1).

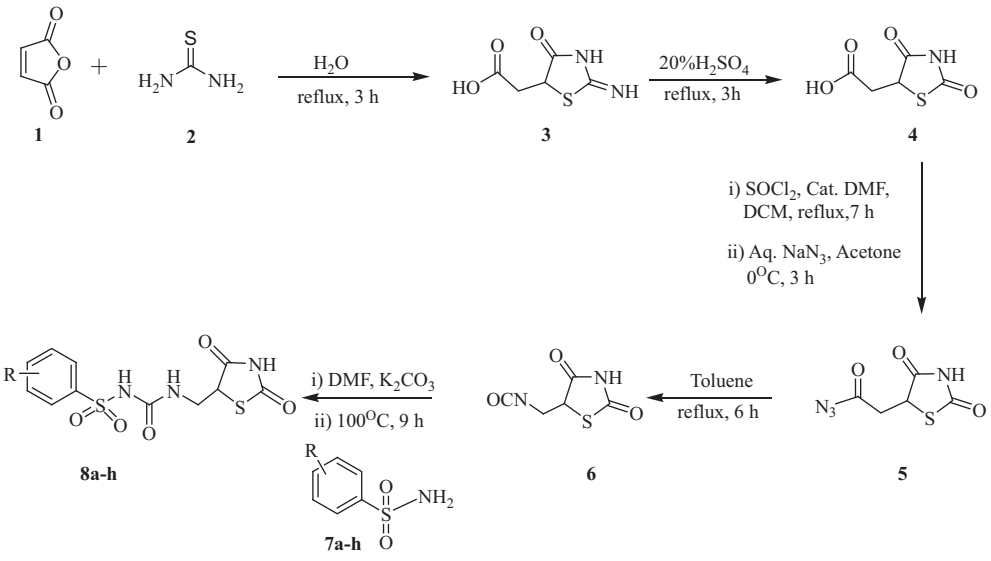
The structure of the synthesized compounds **3, 4, 5** were confirmed on the basis of ^{1}H NMR, and MS analyses. The structure to the compounds **6** and **8a–h** were elucidated on the basis of ^{1}H NMR, ^{13}C NMR and MS spectra analyses. The signal due to carbonyl carbon atom of isocynate of **6** observed at 154.05 ppm. Whereas the peaks of carbonyl carbons of sulfonylureas **8a–h** appeared in the region 162–164 ppm. These ^{13}C NMR spectral data confirmed the formation of **8a–h**. From the ^{1}H NMR spectra it has been delineated that sulphamyl protons of compounds **8a–h** displayed their signals in the region 8.67–10.73 ppm and presence of labile protons has been confirmed by D_2O exchange PMR.

Antihyperglycemic activity evaluation: The compounds (**8a–h**) were evaluated for their antihyperglycemic activity in sucrose-loaded model (SLM) Sprague–Dawley strain male albino rats.

Effect in sucrose loaded rat model: Compounds were tested for their effect on glucose tolerance curve in rats of average body weight 160 ± 20 g, an indirect effect of measuring antihyperglycemic activity. Male albino rats of Wistar strain were selected for this study. Fasting blood glucose level of each animal was checked by glucometer using glucostrips after an overnight starvation. Animals showing blood glucose level between 60 and 80 mg/dl at 0 min were finally selected and divided into groups of five animals in each. Rats of experimental group were administered the suspension of the test sample orally prepared in 1.0% gum acacia (vehicle) at desired dose levels, that is, 100 mg/kg body weight and 100 mg/kg of standard antidiabetic drug, that is, metformin. Animals of control group were given an equal amount of 1.0% gum acacia and termed as sham exposed control group. An oral sucrose load of 10 g/kg body weight was always given to each animal exactly after 30 min post administration of the test sample/vehicle. Blood glucose profile of each rat was again determined for at least 2 h, that is, 30, 60, 90 and 120 min post administration of sucrose by glucostrips. Food but not water was withheld from the cages during the course of experimentation.

Statistical analysis: Quantitative glucose tolerance of each animal was calculated by area under curve (AUC) method using Prism Software. Comparing the AUC of experimental and control groups determined the percentage antihyperglycaemic activity. Samples showing significant inhibition (p <0.05) on postprandial hyperglycemia (AUC) were considered as active samples. Statistical comparison was made by Dunnett's test.

Effect of test samples on normoglycemic rats: Table 1 presents the average blood glucose profile of sham control and the experimental groups at various time intervals. The results obtained from the variance analysis showed that most active compounds in this series are four out of the eight studied synthetic compounds significantly (p <0.05) inhibited the postprandial rise in blood glucose level of sucrose loaded rats. These compounds were of the following, that is, **8b**, **8c**, **8e** and **8f** significantly inhibited the rise in postprandial hyperglycemia to the tune of 15.8 (p <0.01), 17.2 (p <0.01), 14.3 (p <0.05) and 16.5 (p <0.01)%, respectively, Figure 1. The



Scheme 1. Synthesis of 1-((2,4-dioxothiazolidin-5-yl) methyl)-3-substitued benzene sulfonyl ureas.

Table 1
Antihyperglycemic effect of in vivo compounds and the standard drug metformin in sucrose loaded hyperglycemic rats

Compound	Dose (mg/dl)	% Activity	Significance
8a	100	11.5	p >0.05
8b	100	15.8	p <0.01
8c	100	17.2	p <0.01
8d	100	10.7	p >0.05
8e	100	14.3	p <0.05
8f	100	16.5	p <0.01
8g	100	8.66	p >0.05
8h	100	9.44	p >0.05
Metformin	100	27.0	p <0.001

standard drug Metformin caused nearly 27.0 (p <0.001)% inhibitions at 100 mg/kg dose in sucrose loaded rats whereas on the other hand the compounds **8a**, **8d**, **8g** and **8h** exhibited very mild activity in terms of 11.5, 10.7, 8.66 and 9.44%, respectively, on normoglycemic rats.

In conclusion, we have synthesized new 2,4-thiazolidinediones with aryl sulfonylurea moieties. The newly synthesized compounds **8a–h** has been evaluated for the antihyperglycemic activity in normal rat model. Among these compounds **8b, 8c, 8e** and **8f** showed significant antihyperglycemic activity in sucrose loaded rat model.

Chemicals and solvents required for the work were obtained from Merck, Spectorchem and S.D fine. ^{1}H NMR spectra were recorded at 300 MHz on Bruker DRX-300 and ^{13}C NMR spectra were scanned at 400, 300 MHz on Jeol and Bruker DRX-300, respectively. The mass spectra were recorded on JEOL–Accu TOF DART-MS-T 100Lc and on V. G. auto spectrometer. The melting points were taken in open capillary and were uncorrected.

Synthesis of 2,4-dioxo-5-thiazolidineacetic acid (**4**): A mixture of thiourea (76.12 g, 1 mol) and maleic anhydride (98.00 g, 1 mol) was refluxed in water (400 mL). After 3 h of heating the reaction mass was allowed to cool at rt and the generated solid mass was filtered and washed with water. The afforded intermediate 2-imino-4-oxo-5-thiazolidineacetic acid **3** (30 g) was then hydrolyzed using 20% aqueous H_2SO_4 (250 mL) under reflux for 3 h. The solid obtained after cooling the hot reaction mass to rt was filtered and dried. *2-imino-4-oxo-5-thiazolidineacetic acid* (**3**) Yield 92%, Lit.[19] mp 250–251 °C, Obsd mp 251–252 °C, ^{1}H NMR (300 MHz, DMSO-d_6, δ ppm):12.60 (br s, 1H, –COOH, D_2O exchangeable), 8.18–8.87 (br s, 2H, –NH, D_2O exchangeable), 4.30–4.33 (t, J = 7.60 Hz, 1H, methine proton, TZD-5-H), 3.05 (dd, J = 8.00 Hz, J = 3.60 Hz, 2H, CH_2). EI MS (m/z): 174. *2,4-dioxo-5-thiazolidineacetic acid* (**4**) Yield 80%, Lit.[19] mp 166–167 °C, Obsd mp 167–168 °C, ^{1}H NMR (300 MHz, DMSO-d_6, δ ppm): 11.99 (br s, 1H, –COOH, D_2O exchangeable), 7.10 (br s, 1H, NH, D_2O exchangeable), 4.16 (t, J = 7.10 Hz, 1H methine proton, TZD-5-H), 3.07 (dd, J = 8.10 Hz, J = 5.10 Hz, 2H, CH_2). DART MS (ESI$^+$, m/z): 176 (M^+).

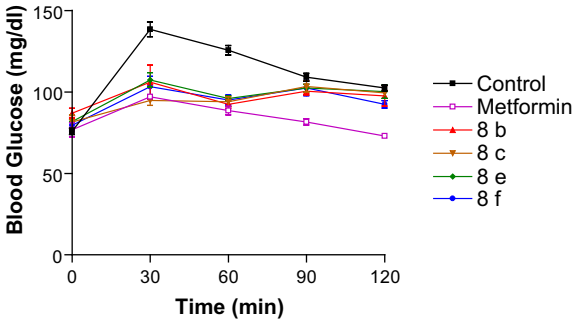


Figure 1. Effect of in vivo active compounds on blood glucose level of sucrose loaded rats at various time intervals.

Synthesis of 2,4-dioxo-5-thiazolidineacetic acid azide (**5**): A mixture of (**4**) (20 g, 114.3 mmol), thionyl chloride (60 mL) and DMF (1 mL) was refluxed in DCM (150 mL). After 7 h the reaction was allowed to cool to rt and the solvent was removed under vacuum. The crude residue, 2,4-thiazolidinedione acetyl chloride was then dissolved in acetone (30 mL) and the solution was stirred at rt. A solution of sodium azide solution (9.0 g, 137.1 mmol) in 4 mL water was added dropwise with stirring and maintaining a temperature of 0–4 °C and stirring was continued for 3 h. The obtained solid was filtered and washed with cold water. It was dried and crystallized by using ethyl acetate. *2,4-dioxo-5-thiazolidineacetic acid azide* **(5)** Yield 71%, mp 131–132 °C, ^{1}H NMR (300 MHz, DMSO-d_6, δ ppm):11.33 (br s, 1H, NH, D_2O exchangeable), 6.77 (d, J = 6.77 Hz, 2H, CH_2), 3.75 (t, 1H, J = 7.20 Hz, methine proton, TZD-5-H). DART MS (ESI$^+$, m/z): 201 (M^+).

Synthesis of 5-(isocyanomethyl) thiazolidine-2, 4-dione (**6**): A (13 g) of (**5**) was dissolved in toluene (100 mL) and the solution was refluxed. The progress of the Curtius rearrangement was monitored by thin layer chromatography. After 7 h of reflux the solvent from the the mixture was removed under vacuum and the obtained solid was crystallized using ethyl acetate and methanol.

5-(isocyanatomethyl)thiazolidine-2,4-dione (**6**): Yield 93%, mp 245–246 °C, ^{1}H NMR (300 MHz, DMSO-d_6, δ ppm):12.09 (br s, 1H, NH, D_2O exchangeable), 7.77 (d, J = 12.60 Hz, 2H, CH_2), 3.95 (t, J = 7.20 Hz, 1H, methine proton, TZD-5-H). ^{13}C NMR (75 MHz, DMSO-d_6, δ ppm): 168.17, 167.10, 154.05, 102.34, 53.26. DART-MS (ESI$^+$, m/z): 173 (M^+).

Synthesis of 1-((2, 4-dioxothiazolidin-5-yl) methyl)-3-tosylurea (**8a**): *p*-Toluene sulfonamide (1 g, 5.8 mmol) and potassium carbonate (1.70 g, 1.2 mmol) were stirred for 15 min. in DMF (20 mL) at 100 °C. To this reaction mass of (**6**) (1 g, 5.8 mmol) was added and the content was further stirred at 100 °C. The reaction was monitored by thin layer chromatography. After 9 h of heating, reaction mass was allowed to cool at rt and poured on crushed ice, and then neutralized using conc. HCl. The obtained solid crude mass was filtered and washed with water. It was dried and purified by crystallization. Similarly the other compounds **8b–h** of the series were prepared. *1-((2,4-dioxothiazolidin-5-yl)-methyl)-3-tosylurea* (**8a**) Yield 76%, mp 198–200 °C, ^{1}H NMR (300 MHz, DMSO-d_6, δ ppm):10.06 (br s, 1H, NH, D_2O exchangeable, 2,4-TZD's), 9.59 (br s, 2H, NH, D_2O exchangeable, sulfonylurea), 9.55 (br s, 2H, D_2O exchangeable, sulfonylurea), 7.75 (d, J = 7.80 Hz, 2H, ArH), 7.68 (d, J = 7.80 Hz, 2H, ArH), 3.49 (t, J = 6.60 Hz, J = 4.20 Hz, 1H, methine proton, TZD-5-H), 2.92 (d, J = 8.10 Hz, 2H, CH_2), 2.66 (s, 3H, ArH). DART MS (ESI$^+$, m/z): 344(M^+). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 169.01, 168.14, 162.51, 137.10, 131.13, 130.14 (2C), 128.34 (2C), 54.87, 39.56, 25.13.

1-((2,4-dioxothiazolidin-5-yl)methyl)-3-benzenesulfonyl urea (**8b**): Yield 74%, mp 210–210 °C, ^{1}H NMR (300 MHz, DMSO-d_6, δ) ppm: 12.45 (br s, 1H, D_2O exchangeable, 2,4-TZD's), 10.73 (br s, 1H, D_2O exchangeable, sulfonylurea), 9.95 (br s, 1H, D_2O exchangeable, sulfonylurea), 7.51–7.95 (m, 5H, ArH), 3.30–3.63 (t, 1H, J = 6.60 Hz, J = 4.20 Hz, methine proton, TZD-5-H), 2.95 (d,, J = 8.10 Hz, 2H, CH_2). DART MS (ESI$^+$, m/z): 330 (M^+). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 169.06, 168.97, 162.31, 139.06, 133.55, 129.30, 127.46, 54.92, 39.50.

1-(2,4-dioxothiazolidin-5-yl) methyl) -3- (4'-Chloro benzene sulfonyl) urea (**8c**): Yield 75%, mp 129–130 °C, ^{1}H NMR (300 MHz, DMSO-d_6, δ ppm): 12.01 (br s, 1H, D_2O exchangeable, 2,4-TZD's), 10.19 (br s, 1H, NH, D_2O exchangeable, sulfonylurea), 9.17 (br s, 1H, NH, D_2O exchangeable, sulfonylurea), 7.27–7.63 (m, 4H, ArH), 3.51 (t, J = 6.60 Hz, J = 4.20 Hz, 1H, methine proton, TZD-5-H),

3.13 (d, J = 8.10 Hz, 2H, CH_2). DART-MS (ESI^+, m/z): 364 (M^+), 366 (M^++2). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 169.10, 168.79, 162.83, 138.13, 137.43, 130.09(2C), 129.01 (2C), 54.90, 39.47.

1-((2,4-dioxothiazolidin-5-yl)methyl)-3-(4'-fluoro benzene sulfony)urea: (**8d**) Yield 76%, mp 169–170 °C, ^1H NMR (300 MHz, DMSO-d_6, δ ppm): 12.27 (br s, 1H, NH, D_2O exchangeable, 2,4-TZD's), 10.33 (br s, 1H, NH, D_2O exchangeable, sulfonylurea), 9.77 (br s, 1H, NH, D_2O exchangeable, sulfonylurea), 7.60–7.9.77 (m, 4H, ArH), 3.42 (t, J = 6.60 Hz, J = 4.20 Hz,1H, methine proton, TZD-5-H), 3.05 (d, J = 8.10 Hz, 2H, CH_2). DART-MS (ESI^+, m/z): 348 (M^+). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 169.17, 168.11, 167.61, 164.10, 135.39, 131.24, 130.75, 51.76, 39.29.

1-((2,4-dioxothiazolidin-5-yl) methyl)-3-(2',4'-dichloro benzene sulfonyl) urea (**8e**): Yield 75%, mp 158–159 °C, ^1H NMR (300 MHz, DMSO-d_6, δ ppm): 12.15 (br s, 1H, NH, D_2O exchangeable, 2,4-TZD's), 10.19 (br s, 1H, NH, D_2O exchangeable, sulfonylurea), 9.18 (br s, 1H, NH, D_2O exchangeable, sulfonylurea), 7.23–7.8.15 (m, 3H, ArH), 3.47 (t, J = 6.60 Hz, J = 4.20 Hz, 1H, methine proton, TZD-5-H), 2.95 (d, J = 8.10 Hz, 2H, CH_2). DART-MS (ESI^+, m/z): 398 (M^+), 400(M^++2), 402(M^++4). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 169.07, 168.47, 162.73, 139.61, 138.57, 133.10, 131.05, 130.81, '128.13, 51.47, 39. 30.

1-((2,4-dioxothiazolidin-5-yl) methyl)-3-(2',5'-dichloro benzene sulfonyl) urea (**8f**): Yield 73%, mp 105–106 °C, ^1H NMR (300 MHz, DMSO-d_6, δ ppm): 12.07 (br s, 1H, NH, D_2O exchangeable, 2,4-TZD's), 10.41 (br s, 1H, NH, D_2O exchangeable, sulfonylurea), 9.27 (br s, 1H, NH, D_2O exchangeable, sulfonylurea), 7.83–8.17 (m, 3H, ArH), 3.45 (t, J = 6.60 Hz, J = 4.20 Hz, 1H, methine proton, TZD-5-H), 2.98 (d, J = 8.10 Hz, 2H, CH_2). DART MS (ESI^+, m/z): 398 (M^+), 400(M^++2), 402(M^++4). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 169.15, 168.83, 163.13, 143.13, 134.15, 133.01, 129.14, 134.63, 134.15, 54.37, 39. 63.

1-((2,4-dioxothiazolidin-5-yl)methyl)-3-(2',4'-dibromo benzenesulfonyl) urea (**8g**): Yield 75%, mp 165–166 °C, ^1H NMR (300 MHz, DMSO-d_6, δ ppm): 12.18 (br s, 1H, NH, D_2O exchangeable, 2,4-TZD's), 10.23 (br s, 1H, NH, D_2O exchangeable, sulfonylurea), 8.67 (br s, 1H, NH, D_2O exchangeable, sulfonylurea), 7.95–8.17 (m, 3H, ArH), 3.54 (t, J = 6.60 Hz, J = 4.20 Hz, 1H, methine proton, TZD-5H), 3.18 (d, J = 8.10 Hz, 2H, CH_2). DART MS (ESI^+, m/z): 486 (M^+). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 169.21, 168.90, 162.58, 145.23, 138.41, 135.13, 133.61, 133.13, 55.10, 39. 73.

1-((2,4-dioxothiazolidin-5-yl)methyl)-3-(4'-Bromo benzene sulfonyl) urea (**8h**): Yield 74, mp 162–163 °C, ^1H NMR (300 MHz, DMSO-d_6, δ ppm): 11.68 (br s, 1H, NH, D_2O exchangeable, 2,4-TZD's), 10.13 (br s, 1H, NH, D_2O exchangeable, sulfonylurea), 8.56 (br s, 1H, NH, D_2O exchangeable, sulfonylurea), 7.23–7.67 (m, 4H, ArH), 3.43 (t, J = 6.60 Hz, J = 4.20 Hz, 1H, methine proton, TZD-5H), 2.81 (d, J = 8.10 Hz, 2H, CH_2). DART MS (ESI^+, m/z): 408 (M^+). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 169.00, 168.80, 163.00, 137.13, 133.13, 130.13(2C), 127.81(2C), 54.83, 39. 53.

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