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Synthesis and structural confirmation on selective N-alkylation of (*Z*)-5-((5-chloro-1*H*-indol-3-yl)methylene)thiazolidine-2,4-dione analogues with their molecular docking studies

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In the present investigation, a series of novel (*Z*)-5-((5-chloro-1*H*-indol-3-yl)methylene)thiazolidine-2,4-dione analogues have been designed and synthesized in good yields with the objective of selective N-alkylation at thiazolidine 2,4-dione ring in competence with indole ring under basic conditions in the presence of aprotic solvent dimethylformamide (DMF). The newly synthesized compounds have been characterized by spectral data (IR, ^{1}H and ^{13}C NMR, NOE, NOESY, ^{1}H-^{1}H-COSY and LC-MS). Further, molecular docking and ADME studies have revealed that the newly synthesized compounds have very good docking score against antidiabetic and anti-inflammation activities (PPARγ and COX-2) as compared with standard rosiglitazone.

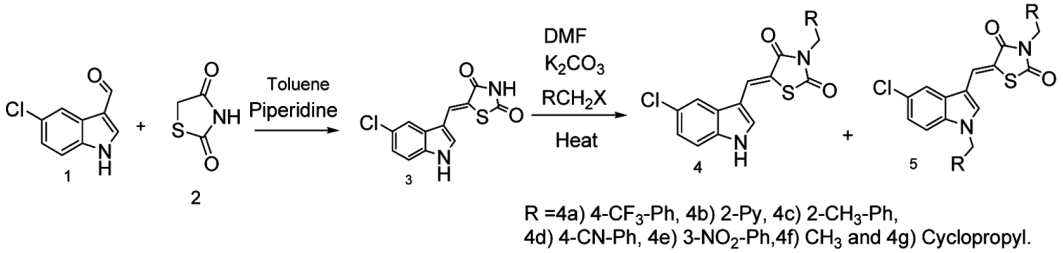
Keywords: Selective N-alkylation, 2D NMR, Molecular docking studies, ADME studies, T2DM

Diabetics and inflammation together plays an important role in the pathogenesis of obesity-related insulin resistance, impaired insulin secretion, and diabetes-related vascular complications[1].Type 2 diabetes mellitus (T2DM) is a metabolic disorder characterized by insulin resistance and hyperglycemia. T2DM is associated with chronic low-grade inflammation. During the hyperglycemia condition elevated free fatty acids synthesis may promote inflammation, with aid of glucose consumption along with alterations in oxidative phosphorylation. Patient suffering from T2DM, the islets display features of an inflammatory process by enhancing the pro-inflammatory cytokinesand various chemokines and macrophage activation[2]. The mRNA of COX-2 levels along with IL-1β have upregulated by maintenance of human islets during hyperglycemic condition[3]. However, there is currently a lack of effective drugs for preventing the development of hyperglycaemic condition in diabetic patients. Thiazolidinediones (also called glitazones) are a class of medicines that have been used for the treatment of type 2 diabetes. Substituted 3-alkyl indole moieties are of much importance as they are widely distributed in nature and reveal a broadrange of biological activity[4].Indoles with a substituent at the 3-position are considered as a venerable pharmacophore in drug discovery as well as found in various range of natural products[5]. 5-Indolyl-thiazolidine-2,4-dione derivatives have been emphasized in the field of synthetic organic chemistry[6–8]. The literature data indicated that 2,4-thiazolidinone moiety attached to the indole ring, which may prone to be potential antihyperglycemic[9,10] and anti-cancer[11,12] agents. Despite, number of methodologies reported for the synthesis N-alkylated indolyl thiazolidine 2,4-dione derivatives, the results obtained were either a disubstituted N-alkylated compounds[13]or some of the examples have shown that initially NH proton of the either thiazolidine 2,4-dione ring[14] or indole moiety were protected separately and then taken for Knoevenagel condensation reaction[6,11,13,15]. Therefore, it is essential to pay more attention for the development of new method towards synthesis of selectivemono substituted N-alkylation at thiazolidine 2,4-dione ring (N_3). Based on that, we reported a newsyntheticmethod for selective N-alkylation of (*Z*)-5-((5-chloro-1*H*-indol-3-yl)methylene) thiazol-idine-2,4-dione, analogues starting from 5-chloro-1*H*-indole-3-carboxaldehyde (1). The newly synthesizedcompounds were further investigated for molecular docking and ADME studies.

Results and Discussion

Chemistry

The synthetic route is disclosed in the Scheme I, 5-chloro-indole-3-carboxaldehyde (1) and thiazolidine-2,4-dione(2) in toluene using piperidine as base via Knoevenagel condensation led to the desired (*Z*)-5-((5-



Scheme I — Selective N-alkylation of (*Z*)-5-((5-chloro-1*H*-indol-3-yl)methylene) thiazolidine-2,4-dione (3).

Table I — Base and temperature optimization for the synthesis of **4a** [a]

Entry	Solvent	Alkylating reagent (mol%)	K_2CO_3 (mol%)	Temp (°C)	Time (h)	Yield (%)
1	Toluene	1	1	110	24	–
2	Acetone	1	1	55	16	–
3	DMF	1	–	125	–	–
4	DMF	1	1	125	5	–
5	DMF	1	3	125	3	–
6	DMF	1	3	100	3	42 [b]

[a] Reaction conditions: 3 (1.0mmol), RCH_2X (4-CF_3-$PhCH_2Br$) (1.0 mmol), K_2CO_3 (3.0mmol) and DMF (10mL).
[b] Isolated yield of the product.

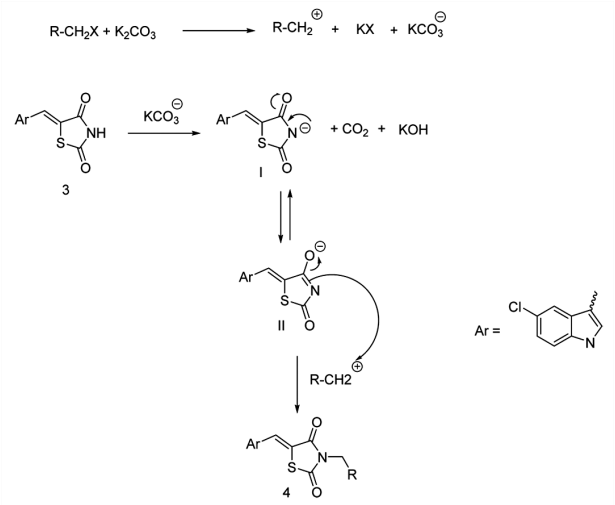
chloro-1*H*-indol-3-yl)methylene)thiazolidine-2,4-dione(3). Compound 3 was subjected for selective N-alkylation at thiazolidine 2,4-dione ring (N_3) and obtained the compound 4(a-g). To obtain the optimized reaction conditions for the synthesis of compound 4a, the study was initiated with the reactions on compound 3 by varying the base molar equivalents of potassium carbonate in presence of different solvents. Conducted experiment in aprotic solvent DMF, the high selective N-alkylation was observed at N_3 position of thiazolidine 2,4-dione ring. Further, the temperature optimum reaction was performed for the preparation of compound 4a. The reaction proceeded smoothly, and most complete conversion of reactants was observed at 100°C, with minimum formation of dialkylated compound(5). The results obtained are summarized in Table I. The higher temperature caused a decrease in yield and formation dialkylated compounds were noticed. With the optimized reaction conditions in hand, we further investigated the scope and functional group potential of our present protocol with various substituted alkylating reagents, aliphatic/ substituted benzyl and heteroaryl compounds. The reactions involving aliphatic / aryl halides, observed formation of major mono substituted compound 4a. In case of heterocyclic halides compound 4b, isolated both mono and dialkylated compounds as (4b) and (5b). The challenge was to separate both mono and di N-alkylated compounds as TLC showed very close RF values. The crude compounds were subjected for purification on instrument Biotage−Isolera one flash purification system and separate both mono and disubstituted compounds. The compounds eluted with a mixture of solvents from 5% to 20% ethyl acetate in petroleum ether. The Compounds 4b and 4g were further subjected for purification by preparative HPLC (Reverse phase method, using mobile phase 0.1% trifluoroacetic acid in acetonitrile: water and column used was C18 column) to get pure mono substituted compounds. The yields of all newly synthesized compounds (4a-g) are in the ratio from 20 to 45%.

Mechanistic rationalization for the formation of compound 4 (Scheme II)

Selective alkylated product (4) from the indole derivative (3) : Initially the alkylating reagent reacted with base K_2CO_3, to generate the reactive species, $R\text{-}CH_2^{\oplus}$ and $KCO_3^{\ominus}$where $KCO_3^{\ominus}$ abstracts NH proton of thiazolidine-2,4-dione derivative (3) results the formation of imine ion intermediate (I).Then the imine ion stabilises through its more stabilised enolic form II (because of extended conjugates). Finally the stabilised ion II react with the carbocation species $R\text{-}CH_2^{\oplus}$generated in situ, to form the selective N-alkylated product 4.

2D-NMR Studies on compounds 4a and 4b

The present work was focussed on to ascertain whether the N-alkylation reaction step is at indole nucleus (N_1) or at thiazolidine 2,4-dione nucleus (N_3). The structures were confirmed by 2D NMR data



Scheme II — Mechanistic rationalization for the formation of compound **4**

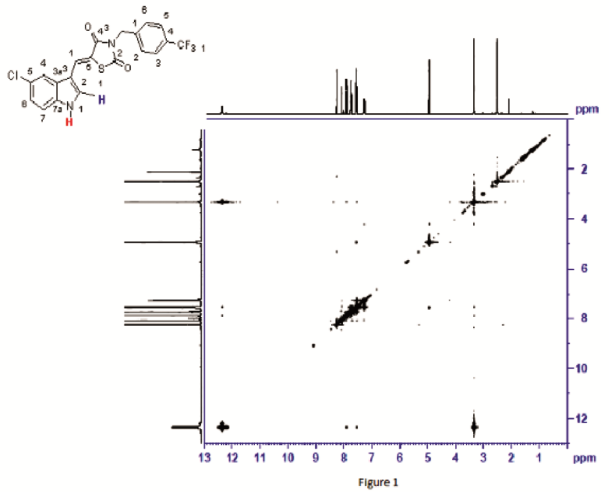


Figure 1 — Compound **4a**: NOESY data

(NOESY/NOE and 1*H*-1*H* COSY data). Two examples were considered for this study compound 4a and compound 4b.

The ^{1}H NMR analysis depicted that, characteristic singlet (N_1-H) present in the indole ring showed a chemical shift variation between δ12.06 and δ12.35ppm. The N-substitution at thiazolidine 2,4-dione nucleus (N_3-H), it was observed in spectra, the characteristic signals of aromatic protons with chemical shift around δ7.25, δ7.90, δ8.26 and aliphatic N_3-CH_2 proton at δ4.94 ppm. To confirm whether the N-alkylation took place at the indole nucleus (N_1-H) or at thiazolidine 2,4-dione –(N_3-H), a detailed study by 2D NMR data was performed on compound 4a.The NOESY spectrum has shown in Figure 1 for the compound 4a, it revealed that

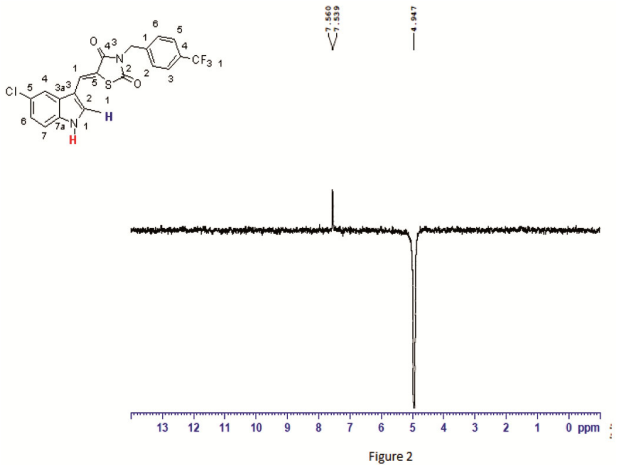


Figure2 — Compound **4a:** NOE data

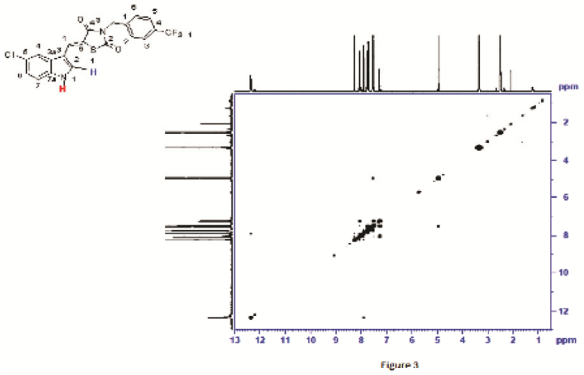


Figure 3 — Compound **4a**: ^{1}H-^{1}H COSY (Correlation spectroscopy)

correlation between NH group at δ12.35 ppm of the indole ring and neighbour hydrogen -CH- group (C_2'-H), δ7.78 ppm, the interaction of N-CH_2 at δ4.94 ppm with para pattern of aromatic doublet at δ7.52 ppm (Figure 1) has shown N-alkylation happened at ring N_3-H of thiazolidine 2,4-dione ring.

The above compound was also characterized by 1D-NOE study and irradiated the N-CH_2 proton at δ4.94 ppm; it was observed that there is an enhancement at doublet aromatic phenyl ring at δ7.56 ppm, which demonstrates N-alkylation has taken place at thiazolidine 2,4-dione ring (N_3-H), as we have not observed any interaction at the indole nucleus (Figure 2).

Spectrum of the compound 4a was observed correlation between hydrogen NH group (δ12.35ppm) of the indole ring and the neighbour hydrogen -CH group at δ7.78ppm (C_2'-H). With this result, it was clear that there is no selective substitution at NH proton of indole ring (N_1-H) (Figure 3).

In compound4b, the correlation between NH group at δ12.34ppm of the indole ring and neighbour

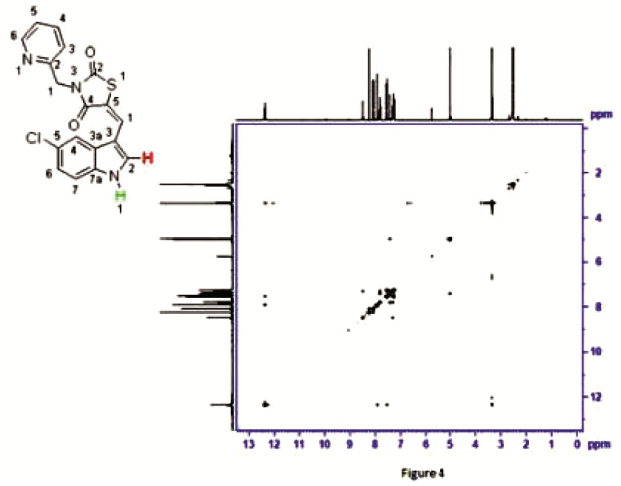


Figure 4 — Compound **4b**: NOESY data

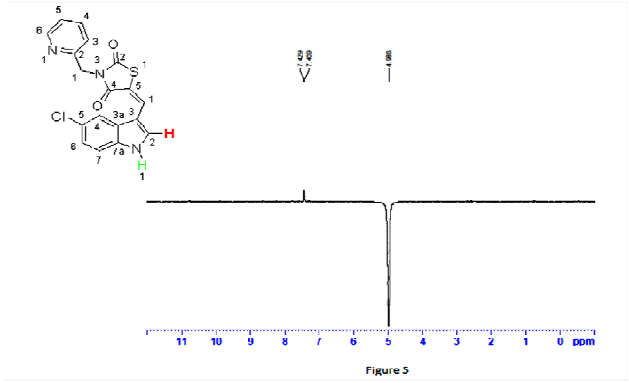


Figure5 – Compound **4b:** NOE data.

hydrogen -CHgroup ($C_{2''}$-H), δ7.91 ppm, the interaction of N-CH_2 at δ 4.94 ppm with para pattern of an aromatic doublet at δ7.54ppm (Figure 4) has shown N-alkylation has taken place at thiazolidine 2,4-dione ring (N_3-H).

Further above compound was subjected for 1D-NOE study and irradiated the N-CH_2 proton at δ 4.94 ppm; it was observed that there is an enhancement at doublet aromatic pyridinyl ring at δ7.42 ppm, which demonstrates N-alkylation has taken place at thiazolidine 2,4-dione ring (N_3-H), as we have not observed any interaction at the indole nucleus (Figure 5).

Molecular docking studies

Molecular docking is a vital role to find an unfailing and more specific depiction of the biologically active molecules at the atomic level and to afford a new insight that can use to endeavour novel therapeutic agents and also to get deeper insight into the inhibitory potency of the newly synthesized compounds. Inflammation complications in diabetes is well established[16]. The co-ordinates of COX-1, COX-2 and human peroxisome proliferator activated receptor gamma were obtained from the Brookhaven Protein Data Bank, whose PDB id are 3KK6[10], 4COX[17], and 2PRG[18] respectively. Ligand crystal structures were drawn using Maestro 2D sketcher and energy minimize was computed by OPLS 2005. Proteins were prepared by retrieving into Maestro 9.3 platform. Protein structure was corrected, by using Prime software module to correct the missing loops and in the protein. Water molecules from proteins were removed beyond 5 Å from the hetero atom respectively. Water molecules which are to be important in aiding the interaction between the receptor were optimized during protein pepwizard. Automated, necessary bonds, bond orders, hybridization, explicit hydrogens and charges were assigned. OPLS 2005 force field was applied to the protein to restrained minimization and RMSD of 0.30 Å was set to converge heavy atoms during the pre-processing of protein before starting docking. Using Extra-precision (XP) docking and scoring each compound were docking into the receptor grid of radii 20 Å and the docking calculation were judge based on the docking score, ADME results and Glide energy. QikProp, the prediction program was used to calculate ADME properties of all the ligand and molecular visualization was done under Maestro 9.3[19].

During hyperglycemia condition and the elevated free fatty acids synthesis may promote inflammation, with aid of glucose consumption along with alterations in oxidative phosphorylation. Patient suffering from T2DM, the islets display features of an inflammatory process, by elevating the proinflammatory cytokines and various chemokines and macrophage activation[2]. The mRNA of COX-2 levels along with IL-1β will get upregulated by maintenance of human islets during hyperglycemic condition[3]. The compounds synthesized were tested for their antidiabetic and inflammation pathways by cross talking with PPARγ and COX-2 respectively. The results of molecular docking studies have revealed that the compound **4a** would be molecule of choice because, it has low interaction with COX-1, which is very essential enzyme for normal physiological process, whereby the COX-2 is play an importance role in acute as well as in chronic inflammation[19]. The standard inhibitor rosiglitazone interacts with COX-1 *via* hydrogen bond with Arg120 and π-π stacking with aromatic amino acids such as Tyr385 and Tyr387. Ligand **4b** interacted very strongly with COX-1 *via* hydrogen

bond with Ser530, Arg120, and π-π stacking with Trp387 with a docking score of -10.35 kcal/mol (Table II).

In case of COX-2, ligand 4a interacted very well *via* π-cation interaction with Arg120 and hydrogen bond with Tyr355 with a docking score of -9.40 kcal/mol. The standard rosiglitazone interacted with COX-2 *via* hydrogen bonding with Ser530, Tyr355 and form salt bridge with Glu524. The insulin sensitivity towards its target is achieved by two ways by systemic insulin sensitization or by direct interaction with peroxisome proliferator-activated receptor (PPAR-γ) on the transcription of genes like GLUT2 and β-glucokinase which help in reducing the blood glucose level[18]. The A-chain and B-chain of PPAR-γ efficiently interacted with ligand 4c, *via* π-π stacking with Tyr327 of both the chains; apart from this, the ligand also interacted with His449 with the same interaction and hydrogen bond with catalytical water molecule at B-chain. These results suggest that ligands 4a and 4c would be better inhibitors for COX-2 and PPAR-γ, respectively. Based on the molecular docking studies, the docking score for PPAR-γ regarding 4a is slightly lower comparatively (Table II).

Further *in vitro* or *in vivo* assay will warranty the pharmacological activity against diabetic with an inflammatory condition.

ADME studies reveal that the newly synthesized ligands have good ADME properties as compared with the data from 95% of drug which are already available at market (Table III).

Experimental Section

Chemistry

The starting materials were purchased commercially and used without purification. Melting points were recorded on instrument BUCHI-Melting point M-65, Thin layer chromatography was performed on Silica gel G, IR spectra were recorded on FT-IR-Perkin Elmer: Spectrum.NMR recorded on Bruker instrument (400MHz), LCMS performed on Agilent Infinity Lab LC/MSD. Microanalyses were performed using Vario EL III model CHNS analyser (Vario Germany). Purification was performed on instrument BiotageIsolera one Flash purification.

Preparation of 3 from 1 and 2: (*Z*)-5-((5-chloro-1*H*-indol-3-yl)methylene) thiazolidine-2,4-dione

A mixture of 1 (1g 5.5 mmol), 2 (0.65g 5.5 mmol) and piperidine (1.5 mL) was refluxed in toluene (50 mL) for 3h. Yellow colour solid precipitated from the reaction mixture. Completion of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature,

Table II — Docking scores of the synthesized compounds **3, 4(a-g)** and **5b** against COX-1, COX-2 and Human peroxisome proliferator activated receptor gamma -A chain and B-chain. Docking scores and Glide energies (kcal/mol) as obtained through Glide docking

Activity	Anti-inflammatory								Anti-diabetic							
Protein	COX1 (PDB ID 3KK6)				COX2 (PDB ID 4COX)				Human peroxisome proliferator activated receptor gamma -A chain (PDB ID 2PRG)				Human peroxisome proliferator activated receptor gamma -B chain (PDB ID 2PRG)			
Ligand	Docking Score	Glide Emodel	Glide Energy	XP Hbond	Docking Score	Glide Emodel	Glide Energy	XP Hbond	Docking Score	Glide Emodel	Glide Energy	XP Hbond	Docking Score	Glide Emodel	Glide Energy	XP Hbond
3	-8.25	-49.66	-36.10	-0.48	-6.82	-58.33	-39.03	-0.70	-6.65	-46.55	-37.00	-1.15	-6.59	-48.76	-32.25	-0.70
4a	-4.02	8.05	-20.83	0.00	-9.40	-32.90	-40.27	-0.96	-8.56	-58.53	-46.13	0.00	-7.58	-68.49	-48.13	0.00
4b	-10.35	-28.21	-42.49	-0.71	-7.18	-31.32	-36.86	-0.93	-8.24	-57.82	-45.89	0.00	-8.84	-63.36	-44.32	-0.70
4c	-9.99	3.30	-31.66	-0.63	-7.50	-29.10	-37.17	-0.97	-8.84	-59.41	-47.78	0.00	-9.51	-63.09	-45.96	-0.70
4d	-9.31	8.86	-27.37	-0.49	-7.57	-38.20	-37.43	-0.98	-9.55	-70.15	-50.67	-0.70	-7.41	-67.31	-47.94	0.00
4e	-9.83	-25.47	-39.20	-0.30	-7.35	-41.05	-38.84	-0.93	-8.17	-64.21	-50.13	0.00	-8.89	-68.19	-45.82	-0.70
4f	-8.45	-53.15	-38.19	0.00	-7.80	-39.16	-37.90	0.00	-6.73	-54.79	-41.20	-0.17	-8.04	-50.27	-38.17	-0.62
4g	-9.29	-35.70	-39.85	-0.09	-8.53	-37.39	-31.53	-0.34	-7.42	-50.65	-40.35	0.00	-8.66	-54.85	-40.77	-0.32
5b	-8.25	-49.66	-36.10	-0.48	-7.32	-12.00	-18.91	-0.93	-8.31	-66.95	-50.69	-0.69	-3.07	-61.10	-42.96	0.00
Rosiglitazone	-8.92	-29.86	-33.26	-0.89	-6.94	-65.70	-49.35	-0.82	-7.91	-71.14	-53.48	-0.41	-8.01	-79.91	-54.26	-0.70

Table III — Computer aided ADME screening of the synthesized compound **3, 4(a-g)** and **5b**

Ligand	a*	b* (Å^3)	c* (Å^3)	d* (Å^3)	e* (Å^3)	f* (Å^3)	g* (Å^3)	h* (Å^3)	i* (nm/sec)	j* (Å^3)	k* (nm/sec)	l* (Kp in cm/hr)	m* (Å^3)	n* (%)	o*
3	24.57	8.87	13.87	8.46	2.26	-3.52	-4.40	-4.12	436.16	-0.47	895.43	-3.35	-0.03	87.44	0.00
3	24.66	8.89	13.94	8.47	2.27	-3.54	-4.40	-4.16	432.17	-0.48	877.65	-3.35	-0.03	87.41	0.00
4a	40.77	12.04	17.88	7.51	5.94	-7.65	-8.12	-6.00	1293.24	-0.05	10000.00	-1.85	1.05	100.00	1.00
4b	37.00	12.23	16.90	8.76	4.37	-5.82	-6.33	-5.98	962.31	-0.44	2097.17	-1.92	0.56	100.00	0.00
4c	39.36	12.64	17.09	7.66	5.22	-6.73	-7.00	-6.02	1139.54	-0.38	2502.92	-1.85	0.93	100.00	1.00
4d	39.14	13.22	17.97	9.40	4.20	-7.18	-7.62	-6.12	268.75	-1.13	528.69	-2.97	0.62	95.02	0.00
4e	38.32	12.97	17.47	9.28	4.06	-5.93	-6.71	-5.90	252.68	-1.12	494.60	-3.08	0.57	93.73	0.00
4f	29.63	9.54	13.71	6.69	3.60	-4.92	-5.07	-4.82	1029.58	-0.29	2257.29	-2.53	0.36	100.00	0.00
4g	32.47	10.32	14.52	6.53	4.19	-5.52	-5.41	-5.04	1167.97	-0.33	2586.56	-2.33	0.56	100.00	0.00
5b	49.00	15.57	19.74	8.78	6.24	-7.48	-8.10	-7.16	1975.21	-0.30	4570.45	-0.70	0.99	100.00	1.00
95% drug possess these criteria ranges	13to70	4to18	8to35	4to45	-2to6.5	-6.5 to 0.5		< -5	<25 poor to >500 good	-3to1.2	<25 poor to >500 good	--	-1.5to1.5	<25% is poor	Max is 4

the precipitated solid was filtered, washed with petroleum ether, and dried to obtain compound 3.

3: Yellow solid, Yield: 0.7g (48%), melting range: 250 to 264 °C, FT- IR [KBr in cm^{-1}] υ_{max}: 3424(-NH), 2930(C-H), 1783, 1670 (both -C=O), 1322 (C-N), 1588 (C=C), 651.73 (C-S),^1H -NMR (400 MHz, DMSO-d_6) (ppm) δ_H:12.33 (br, s, 1H, N_3-H), 12.24 (br, s, 1H, N_1-H), 8.05 (S, 1H, $C_{1''}$-H), 8.02(d, 1H, C_4'-H, J=1.6Hz), 7.79-7.79 (d, 1H, $C_{2''}$-H, J= 1,2Hz), 7.52-7.50(d,1H,$C_{7'}$-1H, J=8.4Hz),7.26-7.23(dd, 1H, $C_{6'}$-H, J=2Hz), LC-MS ($C_{12}H_7ClN_2O_2S$): calculated m/z: 278.71: Found: m/z : 279 (M+1).

General procedure for the synthesis of compounds 4a-g

An equimolar mixture of (*Z*)-5-((5-chloro-1*H*-indol-3-yl)methylene)thiazolidine-2,4-dione (3, 0.54mmol), alkylating reagent (0.54mmol), potassium carbonate (3 mmol), and anhydrous DMF (10 mL) was combined and heated at100°C for 3 h. The completion of the reaction was monitored by TLC. After completion of reaction, cooled to room temperature, filtered on celite bed, collected filtrate and concentrated the solvent under rota vacuum at 50°C. Residue obtained was diluted with ethyl acetate and the organic layer was washed with water, brine solution, and dried over anhydrous sodium sulphate, filtered and concentrated. Residue obtained was purified by column chromatography over silica gel (Silica gel 230-400 mesh) using petroleum ether: ethyl acetate (80:20) mixture as eluant to afford the product, (*Z*)-5-((5-chloro-1*H*-indol-3-yl)methylene)-3(aliphatic/aromatic/heterocyclic)thiazolidine-2,4-dione4(a-g). In case of compounds 4b and 5b obtained was separated and characterized.

(*Z*)-5-((5-Chloro-1*H*-indol-3-yl) methylene)-3-(4-(trifluoromethyl) benzyl) thiazolidine-2,4-dione, 4a

Yellow solid, Yield: 42.7%, melting range (257-264°C), FT- IR [KBr in cm^{-1}] V_{max}: 3424(-NH), 2930(C-H vinylic), 1676, 1604.2(-C=O), 1323.66(C-N), 1456.76(C=C), 598.10(C-S).^1H -NMR (400 MHz, DMSO-d_6) (ppm) δ_H: 12.35 (br, s, 1H, N_1-H), 8.26 (s, 1H, C_1-H), 8.08 (d, 1H, $C_{4'}$-H, J_m=2Hz), 7.90-7.89 (d, 1H, $C_{2'}$-H, J_m=2.8Hz), 7.75-7.73 (dd, 2H, $C_{3''}$ -H, $C_{5''}$ -H, J_o=8.4Hz), 7.56-7.52(m, 3H, $C_{2''}$ – H, $C_{6''}$ -H, $C_{7'}$ –H), 7.28-7.25 (dd, 1H, $C_{6'}$ -H, J_m= 2Hz), 4.98 (s, 2H, N_3-H of TZD). ^{13}C-NMR (100MHz, DMSO-d_6) (ppm) δ_C: 167.55 and 165.722 (C=O), 140.9, 135.2, 130.9, 128.73, 128.51, 126.65,126.43, 126.043,123.7, 118.71, 114.66, 114.49, 110.72, 40.5, LC-MS ($C_{20}H_{12}ClF_3N_2O_2S$) calculated m/z : 436.83, Found: M+2: 438.9, Anal. Calcd for $C_{20}H_{12}ClF_3N_2O_2S$: C, 54.99; H, 2.77; N, 6.41; S, 7.34; Found: C, 54.97; H, 2.93, N, 6.55, S, 7.28%.

(*Z*)-5-((5-Chloro-1*H*-indol-3-yl)methylene)-3-(pyridine-2-ylmethyl) thiazolidine-2,4-dione, 4b

Yellow solid,Yield: 30.3%, melting range: 244.2-257.5°C, FT- IR [KBr in cm^{-1}] V_{max}: 3124(-NH), 2924 (C-H vinylic), 1667 and 1597 (-C=O), 1324 (C-N), 1481 (C=C), 537 (C-S). ^1H -NMR (400 MHz, DMSO-d_6) (ppm) δ_H: 12.34 (br, s, 1H, N_1-H), 8.49-8.47 (dd, 1H, $C_{6''}$, J_o=7.2Hz), 8.24(s, 1H, C_1-H), 8.08-8.07 (d, 1H, $C_{3''}$-H, J=1.6Hz), 7.91-7.90 (d, 1H, $C_{2'}$-H, J_m=2.4Hz), 7.82 (t, 1H, $C_{6''}$-H, J_o =6Hz), 7.54-7.52 (dd, 1H, $C_{5''}$-H J_o = 8.4Hz) 7.42-7.40 (dd, 1H, $C_{4''}$-H J_o =8Hz) 7.32-7.30 (t, 1H, $C_{7'}$,J_o =4.8Hz) 7.29-7.25 (dd, 1H, $C_{4'}$-H, J_m-2Hz), 4.988(s 2H, N_3-H of TZD),^{13}C-NMR (100MHz, DMSO-d_6) (ppm) δ_C: 167.49 and 165.80 (C=O), 154.72, 149.62, 137.42, 135.20, 130.77, 128.54, 126.38, 126.23, 123.16, 121, 118.73, 115.04, 114.47, 110.76 and 45.94, LC-MS ($C_{18}H_{12}ClN_3O_2S$) calculated m/z: 368.82 and Found M+2: 372, Anal. Calcd $C_{18}H_{12}ClN_3O_2S$: C, 58.46; H, 3.27; N, 11.36; S, 8.67; Found C, 57.85, H, 3.32, N, 11.05; S, 8.41%.

(*Z*)-5-((5-Chloro-1-(pyridine-2-ylmethyl)-1*H*-indol-3yl)methylene)-3-(pyridine-2-ylmethyl)thiazolidne-2,4-dione, 5b

Yellow solid,Yield: 50mg, melting range: 218-223°C, FT- IR [KBr in cm^{-1}] V_{max}: 3122 (C-H Vinylic), 1672 and 1589 (-C=O), 1521 (C=C), 1361 (C-N), 545 (C-S),^1H -NMR (400 MHz, DMSO-d_6) (ppm) δ_H: 8.52-8.42(dd, 2H, $C_{6'}$-H, C6$_{'''}$-H, J=8.4Hz and J=0.8Hz), 8.24 (s, 1H, $C_{1''}$H vinylic), 8.15(s, 1H, $C_{2'}$-H), 8.13-8.12 (d, 1H, $C_{3'}$-H, J_m=2Hz), 7.80 (q, 2H, C5''-H, C5'''-H, J_m = 3.2Hz), 7.57-7.55(dd, 1H, $C_{7'}$-H, J_o =8.8Hz) 7.43-7.41 (dd, 1H, $C_{6'}$-H, J_o =8Hz), 7.32-7.25 (m, 4H, $C_{4'}$-H, $C_{4'}$'-H, $C_{4'''}$-H, $C_{3'''}$-H), 5.72 (s, 2H, N_1-H of indole), 4.99 (s, 2H, N_3-H of TZD),^{13}C-NMR (100MHz, DMSO-d_6) (ppm) δ_C:167.43 and 165.78 (C=O), 156.33, 154.69, 149.99, 149.63, 137.77, 137.43, 135.28, 134.09, 129.19, 126.90, 125.62, 123.83, 123.48, 123.17, 122.12, 121.95, 119.08, 115.49, 113.43, 110.33, 52.15, 45.96, LC-MS ($C_{24}H_{17}ClN_4O_2S$): calculated m/z 460.94 and Found M+2 : 463.1, Anal. Calcd $C_{24}H_{17}ClN_4O_2S$: C,62.54; H,3.72; N, 12.16; S,6.96; Found: C, 63.04; H,3.552, N,12.19, S, 6.784%.

(*Z*)-5-((5-Chloro-1*H*-indol-3-yl)methylene)-3-(2-methylbenzyl) thiazolidine-2,4-dione, 4c

Yellow solid,Yield: 20.5%, melting range: 260-277°C, FT- IR [KBr in cm^{-1}] V_{max}: 3279 (br, indole-NH), 2924 (C-H vinylic), 1667, 1605 (C=O),^1H -NMR (400 MHz, DMSO-d_6) (ppm) δ_H: 12.35 (br, s, 1H, N_1-H, of Indole), 8.26 (s, 1H, $C_{1''}$-H Vinylic) 8.09 (d,1H, $C_{2'}$-H, J_m=2Hz), 7.91-7.90(d, 1H, $C_{6'}$-H, J_m=2.8Hz), 7.28-7.25 (dd, 1H, $C_{5''}$-H, J_o =10.8Hz), 7.23-7.16 (m, 3H, $C_{6''}$, $C_{3''}$, $C_{4''}$-H), 7.05-7.04 (dd, 1H, C4''-H, J_O=6.8Hz); LC-MS ($C_{20}H_{15}ClN_2O_2S$): calculated m/z: 382.86 and Found: M+2: 385.

(*Z*)-4-((5-((5-Chloro-1*H*-indol-3-yl)methylene)-2,4-dioxothiazolidin-3-yl) methyl)benzonitrile, 4d

Yellow solid,Yield: 19%, melting range: 250-265°C, FT- IR [KBr in cm^{-1}] V_{max}: 3295 (br, Indole-NH), 3123 (aromatic CH), 2931(C-H vinylic), 2231 (CN -Nitrile),1669, 1602 (-C=O), 1375 (C-N), ^1H -NMR (400 MHz, DMSO-d_6) (ppm) δ_H: 12.38(br, s, 1H, N_1-H, of Indole) 8.26(s 1H, $C_{1''}$-H, Vinylic) 8.08 (d,1H, $C_{2'}$-H, J_m=2Hz), 7.90-7.89(d, 1H, $C_{6'}$-H, J_m=2.8Hz), 7.85-7.83 (dd, 2H, $C_{6''}$-H, $C_{2''}$-H, J_m=2Hz, J_m=1.6Hz) 7.54-7.50 (m, 3H, $C_{7'}$-H, $C_{3''}$-H, $C_{4''}$-H), 7.28-7.27(dd, 1H, $C_{6'}$, J_m= 2Hz), 4.93 (s, 2H, N_3-H of TZD), LC-MS ($C_{20}H_{12}ClN_3O_2S$), : calculated m/z 393.85, Found: M-2: 392.

(*Z*)-5-((5-Chloro-1*H*-indol-3-yl) methylene)-3-(3-nitrobenzyl) thiazolidine-2,4-dione, 4e

Yellow solid, Yield: 45.5%,melting range: 219.5-241.5°C, FT- IR [KBr in cm^{-1}] V_{max}: 3300(br,Indole-NH),3097.39(aromaticCH),2933.93(C-H,vinylic),1669,1600(C=O),1570.73 (N-O), ^1H -NMR (400 MHz, DMSO-d_6) (ppm) δ_H: 12.359 (br, s, 1H, N_1-H of Indole), 8.277(s, 1H, $C_{1''}$-H, Vinylic), 8.206-8.164 (dd, 2H, $C_{2''}$-H, $C_{6''}$-H, *J*=1.6Hz), 8.09-8.09(d, 1H, C2'-H, *J*=1.6Hz), 7.90-7.89(d,1H, $C_{6'}$-H, J_m=2.8Hz), 7.80-7.79 (dd, 1H, $C_{4''}$-H, J_o =7.2Hz), 7.70-7.66 (t, 1H, $C_{5''}$-H, *J*=8.4Hz) 7.53-7.50 (dd, 1H, $C_{2''}$-H, J_m=2Hz, 3.2Hz), 7.27-7.26 (dd, 1H, $C_{7'}$-H, J_m=2Hz, 3.2Hz), 4.99 (s, 2H, N_3-H of TZD), LC-MS ($C_{19}H_{12}ClN_3O_4S$) : calculated m/z: 413.83 and Found m/z: M-2: 412.

(*Z*)-5-((5-Chloro-1*H*-indol-3-yl) methylene)-3-ethylthiazolidin-2,4-dione, 4f

Yellow solid,Yield: 24.4 %, melting range: 217.7-225.7°C, FT- IR [KBr in cm^{-1}] V_{max}: 3205.58 (br, Indole-NH), 2937.72 (C-H vinylic), 1727.44, 1651.29 (C=O),^1H -NMR (400 MHz, DMSO-d_6) (ppm) δ_H: 12.31 (s, 1H, N_1-H of Indole), 8.21 (s, 1H, $C_{1''}$-H, Vinylic), 8.07(d, 1H, $C_{2'}$-H, J_m=1.2Hz), 7.86(s,1H, $C7_{4'}$-H), 7.53-7.51(dd,1H, $C_{7'}$-H, J_o=8.8Hz), 7.27-7.25(dd,1H, $C_{6'}$-H, J_m=1.6Hz), 3.72-3.66(q, 2H, $C_{2''}$-H, *J*=7.2Hz),1.19-1.15(t, 3H, $C_{3''}$-H, *J*=7.2Hz), LC-MS ($C_{14}H_{11}ClN_2O_2S$): calculated m/z : 306.76, Found: M+2: 309.

(*Z*)-5-((5-Chloro-1*H*-indol-3-yl)methylene)-3-(cyclopropylmethyl) thizolidine-2,4-dione, 4g

Yellow solid,Yield: 22.5 %, melting range: 181.5-195.9°C, FT- IR [KBr in cm^{-1}] V_{max}: 3097.5 (br, Indole-NH), 2933.97 (C-H vinylic), 1730.04 (C=O), 1668.7(C=O),^1H -NMR (400 MHz, DMSO-d_6) (ppm) δ_H: 12.329(br, s, 1H, N_1-H of Indole), 8.23 (s, 1H, $C_{1''}$-H,) 8.08 (d, 1H, C2'-H, J_m=2Hz), 7.87(d, 1H, $C_{7'}$-H, *J*=2.8Hz), 7.54-7.51 (dd, 1H, $C_{6'}$-H, J_o =8.8Hz), 7.25-7.25(dd, 1H, $C_{4'}$-H, J_m=2Hz), 3.55-3.53 (d, 2H, N_3-H of TZD $C_{2''}$-H, J_o =7.2Hz), 1.16-1.12(q, 1H, $C_{3''}$-H, *J*=4.8Hz), 0.52-0.47 (q, 2H, $C_{4''}$-H, *J*=4.4Hz), 0.36-0.32 (q, 2H, $C_{5''}$-H, *J*=4Hz), LC-MS ($C_{16}H_{13}ClN_2O_2S$): calculated m/z: 332.80, Found: M-2: 331.

Conclusions

Understanding and controlling indole-thiazolidine 2,4-dione N-alkylation site selectivity is critical to many medicinal chemistry programs.This study has demonstrated that the N-alkylationon (*Z*)-5-((5-chloro-1*H*-indol-3-yl)methylene)thiazolidine-2,4-dioneresulted alkylated at N_3 position of thiazolidine-2,4-dione ring.Interestingly, we have notobserved alkylation reaction towards indole-NH ring(N_1).This was further confirmed by performing 2D NMR studies on the isolated compounds.The molecular docking studies revealed that compounds 4a, 4b, 4c and 4d, would be better inhibitors for COX-2 and PPAR-γ, respectively. The above results indicated that the(*Z*)-5-((5-chloro-1*H*-indol-3-yl)methylene)thiazolidine-2,4-dionederivatives may enhance the efficacy towards the antidiabetic and anti-inflammatory activities. Further *in vitro* or *in vivo* assay will warranty the pharmacological activity against diabetic with an inflammatory condition.

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