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Synthesis, characterization and biological evaluation of some novel 2,4-thiazolidinediones as potential cytotoxic, antimicrobial and antihyperglycemic agents

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ABSTRACT

A series of some novel 2,4-thiazolidinediones (TZDs) (**2a–x**) have been synthesized and characterized by FTIR, ^{1}H NMR, ^{13}C NMR and LC mass spectral analysis. All the synthesized compounds were evaluated for their cytotoxicity, antimicrobial and in vivo antihyperglycemic activities. Among the tested compounds for cytotoxicity using Brine Shrimp Lethality assay, compound **2t** ((*Z*)-5-(4-((E)-3-oxo-3-(thiophen-2-yl)prop-1-enyl)benzylidene)-1,3-thiazolidine-2,4-dione) exhibited significant inhibitory activity at ED_{50} value 4.00 ± 0.25 μg/mL and this level of activity was comparable to that of the reference drug podophyllotoxin with ED_{50} value 3.61 ± 0.17 μg/mL. Antimicrobial activity was screened using agar well diffusion assay method against selected Gram-positive, Gram-negative and fungal strains and the activity expressed as the minimum inhibitory concentration (MIC) in μg/mL. From the results of antimicrobial activity compound **2s** ((*Z*)-5-(4-((E)-3-(3,5-bis(benzyloxy)phenyl)-3-oxoprop-1-enyl)benzylidene)-1,3-thiazolidine-2,4-dione) was found to be the most active against all the tested strains of microorganisms with MIC value 16 μg/mL. In vivo antihyperglycemic effect of twenty four TZDs (**2a–x**) at different doses 10, 30 and 50 mg/kg b.w (oral) were assessed using percentage reduction of plasma glucose (PG) levels in streptozotocin-induced type II diabetic rat models. From the results, the novel compound **2x** ((*Z*)-5-(4-((E)-3-(9H-fluoren-2-yl)-3-oxoprop-1-enyl)benzylidene)-1,3-thiazolidine-2,4-dione) exhibited considerably potent blood glucose lowering activity than that of the standard drug rosiglitazone and it could be a remarkable starting point to evaluate structure–activity relationships and to develop new lead molecules with potential cytotoxicity, antimicrobial and antihyperglycemic activities. In addition molecular docking studies were carried out against PPARγ molecular target using Molegro Virtual Docker v 4.0 to accomplish preliminary confirmation of the observed in vivo antihyperglycemic activity.

In recent years, the chemistry of 2,4-thiazolidinediones (TZDs) captivated importance as these compounds have been found to exhibit several biological activities, such as antihyperglycemic,[1] euglycemic,[2] anti-inflammatory,[3] antimalarial,[4] antioxidant,[5] antitumor,[6] cytotoxic,[7] antimicrobial,[8] antiproliferative,[9] PPARγ agonist,[10] dual PPARα/γ activator,[11] free radical scavenger,[12] LDL oxidation inhibitor,[13] glycogen synthase kinase (GSK) 3 inhibitor,[14] aldose reductase inhibitor,[15] cholesterol esterase inhibitor,[16] 15-hydroxyprostaglandin dehydrogenase (15-PGDH) inhibitor,[17] human β_3 agonist,[18] chymase inhibitor,[19] bacterial arylamine *N*-Acetyltransferases (NATs) inhibitor,[20] $P2X_7$ receptor antagonist,[21] thyroid hormone receptor antagonist,[22] PTP1B inhibitor,[23] human PTP1B and LMW-PTP inhibitor,[24] Raf/MEK/Extracellular signal regulated kinase (ERK1/2) inhibitor,[25] dual inhibitor of the Raf/MEK/ERK and the PI3K/Akt signaling pathways,[26] serine/threonine protein kinases Pim-1 and Pim-2 inhibitor,[27] G-protein coupled receptor 40 (GPR40) agonist,[28] MurD ligase inhibitor,[29] monoamine oxidase B (MAO-B) inhibitor[30] and neuroprotective.[31] Having such diverse range of pharmacological activities, these molecules have attracted medicinal chemists and consequently a number of strategies have been originated to synthesize them.

A series of TZDs (**2a–x**) synthesized in the present study were studied for their cytotoxicity, antimicrobial and antihyperglycemic activities. In fact, compounds having α,β-unsaturated ketone or 1,3-thiazolidine-2,4-dione moieties were earlier reported to

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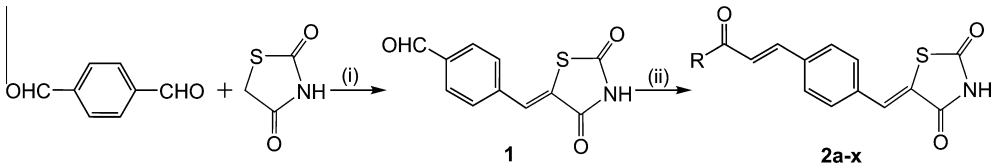
possess cytotoxicity[32–39], antimicrobial[40–47] and antihyperglycemic[48–55] activities and thus the synthesized compounds now are expected to possess synergistic effect, as both the features form part of these molecules. In the present investigation, the aim of molecular docking study of a series of TZDs (**2a–x**) against PPARγ (PDB ID: 3CS8) is to predict and compare the ligand conformation and orientation within a targeted binding site. To the best of our knowledge there is, to date, no report was published regarding the binding properties of TZDs (**2a–x**) against PPARγ 3CS8 Ligand Binding Domain (LBD).

The reaction sequence employed for the synthesis of title compounds (**2a–x**) is shown in Scheme 1, and their physical properties are depicted in Table 1. As described by Momose et al.[56] and Bruno et al.[57] 2,4-thiazolidinedione can undergo a Knoevenagel condensation with a variety of substituted aldehydes to produce 5-arylidene-2,4-thiazolidinediones. The key intermediate in the present study *(Z)*-4-((2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl)benzaldehyde **1** was prepared by Knoevenagel condensation reaction between terephthaldehyde and 1,3-thiazolidine-2,4-dione. Further, subsequent base catalyzed condensation of the **1** with appropriate substituted aromatic/heteroaromatic ketones in the presence of pulverized sodium hydroxide in boiling dimethylformamide (DMF) afforded a series of 2,4-thiazolidinediones (**2a–x**) in good yield.[58,59]

All the synthesized compounds as mentioned in Table 1 were characterized by CHN elemental analysis and spectroscopic methods such as FTIR, ^{1}H NMR, ^{13}C NMR and LC mass spectral analysis. The IR spectrum of **1** exhibited characteristic –C=C– (aliphatic) and –C=C– (aromatic) stretching bands at frequencies 1685 cm^{-1} and 1598 cm^{-1}, respectively. The ^{1}H NMR spectrum of **1** revealed characteristic peaks of 5-benzylidene (HC=C) and NH protons as two singlets, one at δ 7.86 ppm and the other one at δ 12.74 ppm (broad) providing evidence for formation of **1** and reconfirmed by the ^{13}C NMR peaks at δ 126.78 ppm and δ 115.14 ppm due to 5-methylidene carbon and carbon (C_5) of 1,3-thiazolidine-2,4-dione. The ESI mass spectrum (positive ion mode) of **1** revealed a $(M+H)^+$ ion at *m/z* 234. The geometry of all TZDs (**2a–x**) were assumed to be (*Z*) configuration because of its high degree of thermal stability of this isomer.[60]

The IR spectrum of all the compounds (**2a–x**) exhibited the characteristic absorptions at various frequencies correspondingly at 3300–3100 cm^{-1} and 1650–1735 cm^{-1} suggesting the presence of a secondary amine group and α,β-unsaturated carbonyl group, respectively. In the ^{1}H NMR spectra of TZDs (**2a–x**), a singlet integrating for one proton characteristic of the HC=C group was observed in between δ 7.72–8.10 ppm and a singlet integrating for one proton of the NH group was observed in between δ 12.5–13.5 ppm as a broad signal. The ^{1}H NMR spectrum of the compound **2a** exhibited characteristic peaks of H-α and H-β protons of α,β-unsaturated carbonyl group as two doublets, one at δ 8.01 ppm (H-β, J = 15.2 Hz) and the other one at δ 7.78 ppm (H-α, J = 15.2 Hz). The large J value clearly reveals the *trans* geometry at the double bond. In the ^{13}C NMR spectra, the presence of characteristic signals correspondingly at δ 123.36 ppm and δ 142.76 ppm indicating the presence of C-α and C-β carbon atoms of α,β-unsaturated carbonyl group confirmed the formation of



Scheme 1. Reagents and conditions: (i) Piperidine, ethanol, reflux, 8 h; (ii) dry dimethylformamide (DMF), pulverized NaOH, substituted aromatic/heteroaromatic ketones.

Table 1
Physical characterization and cytotoxicity data of TZDs (**2a**–**x**) produced via Scheme 1

Compound	R	Yield[a] (%)	Molecular weight	Molecular formula	Mp (°C)	ED_{50} (μg/mL) (mean ± SEM)
2a	C_6H_5	88	335.58	$C_{19}H_{13}NO_3S$	212–215	44.73 ± 0.12
2b	4-MeC_6H_4	84	349.40	$C_{20}H_{15}NO_3S$	179–182	19.66 ± 0.25
2c	3-OMeC_6H_4	83	365.40	$C_{20}H_{15}NO_4S$	181–184	18.72 ± 0.15
2d	4-OMeC_6H_4	91	365.40	$C_{20}H_{15}NO_4S$	218–221	16.24 ± 0.52
2e	2-OHC_6H_4	91	351.38	$C_{19}H_{13}NO_4S$	189–192	41.35 ± 0.33
2f	4-OHC_6H_4	87	351.38	$C_{19}H_{13}NO_4S$	206–209	36.20 ± 0.23
2g	2,4-diOHC_6H_3	83	367.38	$C_{19}H_{13}NO_5S$	215–218	49.21 ± 0.25
2h	2,5-diOHC_6H_3	83	367.38	$C_{19}H_{13}NO_5S$	213–216	46.71 ± 0.15
2i	2-OH,5-MeC_6H_3	90	365.07	$C_{20}H_{15}NO_4S$	125–128	39.42 ± 0.52
2j	6-OH,5-MeC_6H_3	81	365.07	$C_{20}H_{15}NO_4S$	221–224	33.12 ± 0.21
2k	3-$NH_2C_6H_4$	81	350.07	$C_{19}H_{14}N_2O_3S$	211–214	33.18 ± 0.15
2l	4-$NH_2C_6H_4$	80	350.07	$C_{19}H_{14}N_2O_3S$	231–234	28.82 ± 0.12
2m	3-$NO_2C_6H_4$	86	380.05	$C_{19}H_{12}N_2O_5S$	255–258	56.06 ± 0.25
2n	4-$NO_2C_6H_4$	84	380.05	$C_{19}H_{12}N_2O_5S$	217–220	49.28 ± 0.15
2o	3-ClC_6H_4	92	369.82	$C_{19}H_{12}ClNO_3S$	219–222	24.82 ± 0.12
2p	4-ClC_6H_4	90	369.82	$C_{19}H_{12}ClNO_3S$	206–209	12.06 ± 0.25
2q	3-FC_6H_4	93	353.05	$C_{19}H_{12}FNO_3S$	212–215	9.28 ± 0.15
2r	4-FC_6H_4	89	353.05	$C_{19}H_{12}FNO_3S$	199–203	4.32 ± 0.52
2s	3,5-di$C_7H_7OC_6H_3$	94	547.62	$C_{33}H_{25}NO_5S$	229–233	26.82 ± 0.12
2t	Thiophen-2-yl	88	341.40	$C_{17}H_{11}NO_3S_2$	207–210	4.00 ± 0.25
2u	Pyridin-2-yl	87	336.06	$C_{18}H_{12}N_2O_3S$	194–197	30.28 ± 0.15
2v	Pyridin-3-yl	84	336.06	$C_{18}H_{12}N_2O_3S$	205–208	31.42 ± 0.52
2w	Naphthalen-2-yl	81	385.08	$C_{23}H_{15}NO_3S$	216–219	48.11 ± 0.33
2x	Fluoren-2-yl	79	423.48	$C_{26}H_{17}NO_3S$	218–221	39.66 ± 0.31
Standard[b]	–	–	–	–	–	3.61 ± 0.17

[a] Crystallization solvent is ethanol.
[b] Podophyllotoxin.