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Research Articles

New 1,2,3-Triazole-Tethered Thiazolidinedione Derivatives: Synthesis, Bioevaluation and Molecular Docking Study

Mubarak H. Shaikh, Dnyaneshwar D. Subhedar, Satish V. Akolkar, Amol A. Nagargoje, Ashish Asrondkar, Vijay M. Khedkar & ...show all

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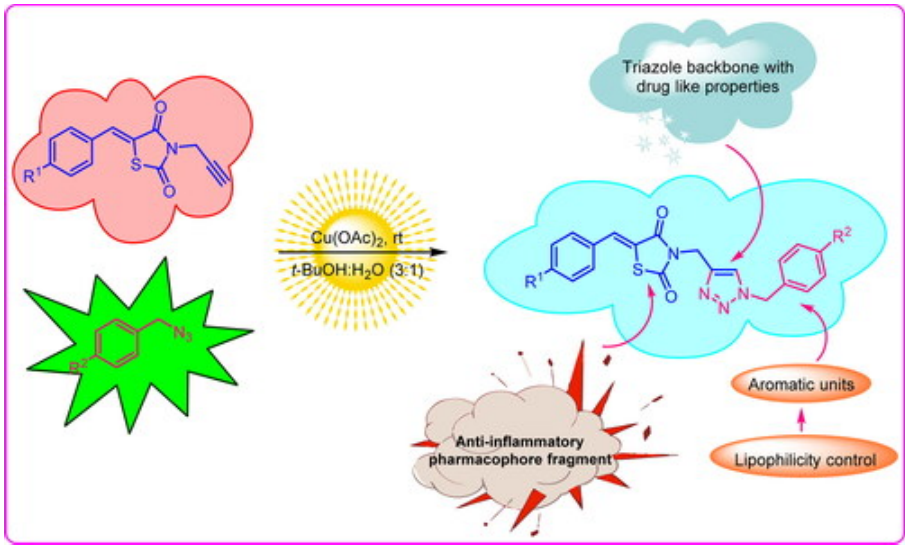
Abstract

In search of new active molecules, a small focused library of 1,2,3-triazoles based 2,4-thiazolidinedione derivatives has been efficiently prepared *via* the click chemistry approach. Several derivatives were exhibited excellent anti-inflammatory activity compared to the standard drug. Further, the synthesized compounds were found to have potential antioxidant activity. Furthermore, to rationalize the observed biological activity data, the molecular docking study has also been carried out against the active site of inflammation enzyme PPARγ, which revealed a significant correlation between the binding score and biological activity for these compounds. The results of the *in vitro* and *in silico* study suggest that the triazole incorporated

development of novel therapeutic agents.

Graphical Abstract



Keywords: Click chemistry 1,2,3-triazoles anti-inflammatory activity antioxidant activity 2,4-thiazolidinedione

Introduction

There are numerous biologically active molecules with nitrogen, sulfur and oxygen heteroatoms that have always drawn the attention of chemists over the years mainly because of their biological importance, therefore, extensive research is still needed to improve their properties and to reduce their adverse effects. Thiazolidinone is considered as a biologically important active scaffold that possesses almost all types of biological activities.[1] Thiazolidine-2,4-dione (TZDs) are a class of insulin sensitizing drugs which include ciglitazone, pioglitazone and rosiglitazone. Apart from their known antidiabetic activity,[2] the ability of TZDs to contribute to cancer therapy has been evidenced by numerous *in vitro* and *in vivo* studies,[3] antibacterial and antifungal activity,[4] aldose reductase inhibitory activity,[5] antimicrobial activity,[6] anti-inflammatory activity,[7] oncostatic,[8] anti-cancer activity[9] and tuberculostatic activity.[10]

The involvement of PPARγ in inflammatory processes was first suggested by the antagonism between the activities of proinflammatory cytokines and PPARγ. Additionally, macrophage

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target for the development of anti-inflammatory agents due to its key roles at various stages in the inflammatory process. The two thiazolidines share a common thiazolidine-2,4-dione structure that is responsible for the majority of their pharmacological effects, including anti-inflammatory effects.[12] It has been shown that PPARγ trans-represses the expression of pro-inflammatory mediators at the transcriptional level, by inhibiting inducible nitric oxide synthase (iNOS), NF-κB, STAT and activation protein-1 (AP-1) signaling.[13] Thus, drugs with anti-inflammatory properties such as TZDs (clubbed with triazole) can probably reduce the risk of inflammation-induced problems.

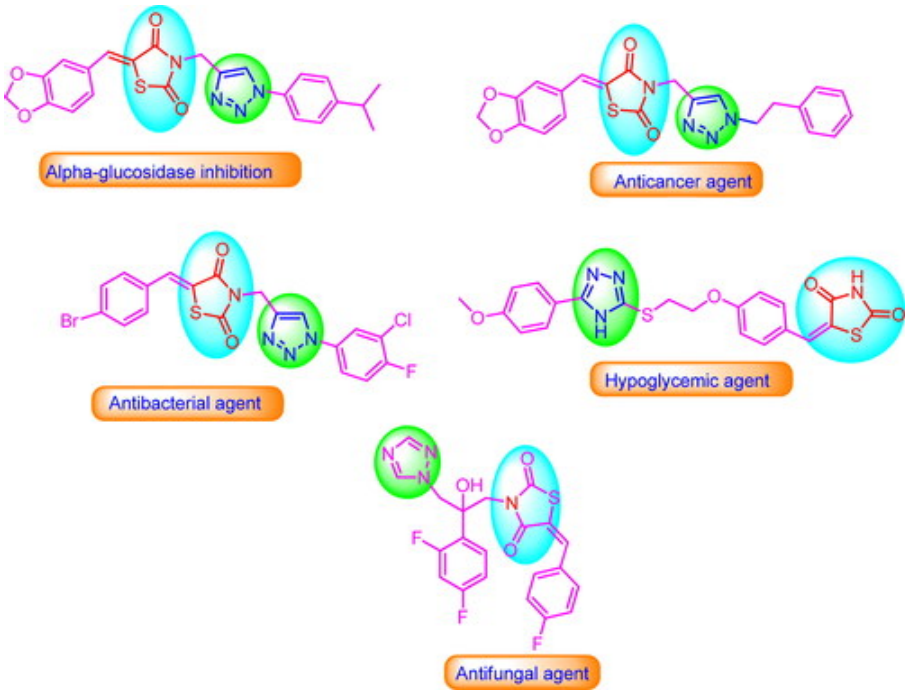
Antioxidant therapies are gaining importance due to their ability to retard disease progression by reducing the damage caused by free radical oxidative stress in a patient.[14] Physiological levels of reactive oxygen species (ROS) play a vital role as signaling molecules to mediate numerous biological functions causing alterations in cell growth, gene expression and host defence.[15] Under inflammatory conditions, the presence of excess reactive oxygen species (O_2, OH^-, H_2O_2, NO, $ONOO^-$) can initiate damage to nucleic acids, proteins, carbohydrates and lipids in many types of cells including macrophages.[16] Increased oxidative stress-induced production of ROS, overwhelming the antioxidant defence system, has been implicated in the pathogenesis of various disorders including atherosclerosis,[17] cancer,[18] asthma,[19] rheumatoid arthritis,[20] ischemia-reperfusion injury,[21] neurodegenerative diseases,[22] inflammation,[23] myocardial infarction and also aging.[24]

Triazoles are stable to acidic/basic hydrolysis and also reductive/oxidative conditions, indicative of a high aromatic stabilization. This moiety is relatively resistant to metabolic degradation. Over the past two decades, 1,2,3-triazole and its derivatives have attracted continued interest in the medicinal field and are reported to possess a wide range of biological activities such as antifungal,[25] antitubercular,[26] antiallergic,[27]a anti-HIV activity,[27]b α-glycosidase inhibitor,[9] antimicrobial,[28] anticoccidiostats,[29] anticonvulsant,[30] antimalarial,[31] antiviral[32] and antimycobacterial,[33] antitumor,[34] antiproliferative efficacy[35] and anticancer activity.[36] Similarly, copper oxide chitosan nanocomposite has been used for green regioselective synthesis of [1,2,3]triazoles.[37] Triazole has been used to improve the pharmacokinetic properties of the desired drug.[38]

Barros et. al., synthesized arylidene-thiazolidine-2,4-diones and assayed in vivo to investigate their anti-inflammatory activities.[39] These compounds showed considerable biological efficacy

library of thiazolidinedione derivatives conjugated with triazole skeleton was synthesized and proved to possess different bioactivity such as α-glucosidase inhibition,[9] anticancer,[9] hypoglycemic,[40] antibacterial,[41a] and antifungal activity[41b] (Figure 1).

Figure 1. Thiazolidinedione derivatives clubbed with triazole shows different biological activity.



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The search for new anti-inflammatory and antioxidant agents will consequently remain as an important and challenging task for medicinal chemists. The combination of two pharmacophores into a single molecule is an effective and commonly used direction in modern medicinal chemistry for the exploration of novel and highly active compounds. In continuation of our earlier work[42] on the synthesis and biological properties of various heterocyclic moieties, herein, a small focused library of 1,2,3-triazole incorporated molecules have been efficiently prepared by click chemistry. Considering the biological importance of 2,4-thiazolidinediones and 1,2,3-triazoles, we construct conjugated thiazolidinedione with 1,2,3-triazoles in one molecular framework through a methylene linkage to enhance the anti-inflammatory activity with minimizing the side effects. In addition to this, we have also performed molecular docking study and *in silico* ADME prediction for the synthesized compounds.

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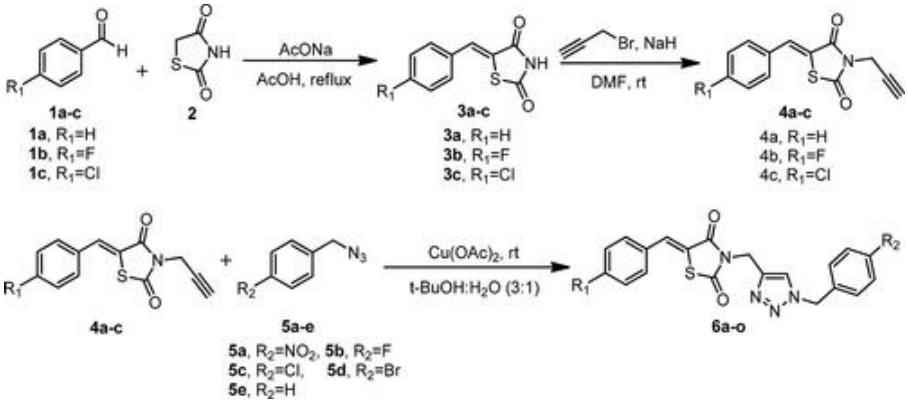
Chemistry

We have described a protocol for the syntheses of a series of new (*Z*)-5-benzylidene-3-((1-(4-substitutedbenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)thiazolidine-2,4-diones **6a-o** as a potential anti-inflammatory and antioxidant agents from commercially available starting materials (Scheme1). These compounds were formed by the fusion of substituted (*Z*)-5-benzylidene-3-(prop-2-yn-1-yl)thiazolidine-2,4-dione **4a-c** and benzyl azides **5a-e** *via* click chemistry (Scheme 1). The substituted (*Z*)-5-benzylidene-3-(prop-2-yn-1-yl)thiazolidine-2,4-diones **4a-c** were prepared in two steps, in the first step, (*Z*)-5-benzylidenethiazolidine-2,4-diones **3a-c** were prepared by Knoevenagel condensation reaction between benzaldehydes **1a-c** and 2,4-thiazolidinedione **2** under reflux conditions in acetic acid using sodium acetate as the base. In the second step, (*Z*)-5-benzylidene thiazolidine-2,4-dione **3a-c** have been alkylated with propargyl bromide in the presence of K_2CO_3 as a base in *N, N*-dimethylformamide (DMF) afforded the corresponding (*Z*)-5-benzylidene-3-(prop-2-yn-1-yl)thiazolidine-2,4-diones **4a-c** in good to excellent yield.

Scheme 1. Synthesis of 1,4-disubstituted-1,2,3-triazole based 2,4-thiazolidinedione derivatives.



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Finally, the Huisgen's CuAAC reaction has been performed on (*Z*)-5-benzylidene-3-(prop-2-yn-1-yl)thiazolidine-2,4-dione **4a-c** and benzyl azides **5a-e** in the presence of $Cu(OAc)_2$ in *t*-BuOH-H_2O (3:1) at room temperature for 22-30 h gave the corresponding 1,4-disubstituted-1,2,3-triazole based 2,4-thiazolidinedione derivatives **6a-o** in quantitative isolated yield (90-92%) (Scheme 1).

The formation of compounds **6a-o** was confirmed by physical data and spectral analysis. In the ^{1}H NMR spectrum of compound **6 b**, the two methylene groups attached to nitrogen showed singlet at δ 4.89 and 5.55 ppm. In addition to this, the signal observed at δ 8.18 ppm indicates

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37.2 and 52.6 ppm indicate the presence of methylene carbon attached to the nitrogen of 2,4-thiazolidinedione and triazole ring, respectively. Furthermore, two characteristics carbon signals exhibited at δ 165.7 and 167.5 ppm due to the -N-C = O and -S-C = O groups, respectively. The formation of compound **6 b** has been confirmed by the HRMS spectrum. For compound **6 b**, the calculated mass for $[M + H]^+$ is 395.0978 and in HRMS, the $[M + H]^+$ peak was observed at 395.0981. Furthermore, to expand the series, 1,4-disubstituted-1,2,3-triazole-2,4-thiazolidinedione derivatives **6a-o** with various substituents have been prepared by the cycloaddition reaction of (*Z*)-5-benzylidene-3-(prop-2-yn-1-yl)thiazolidine-2,4-dione **4a-c** and benzyl azides **5a-e** (Scheme 1 and Table 1) under similar reaction condition in good to excellent yields.

Table 1. *In vitro* anti-inflammatory activity and antioxidant activity of compounds **6a-o**.

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Biological evaluation

Anti-inflammatory activity

The newly synthesized 1,2,3-triazole incorporated 2,4-thiazolidinedione derivatives **6c**, **6d**, **6e** and **6o** (EC_{50} range = 0.6483 ± 0.221-0.8519 ± 0.281 µg/mL) exhibited excellent anti-inflammatory activity as compared to the standard drug diclofenac sodium (Table 1).

Remaining compounds were found to show less anti-inflammatory activity. Compound **6c** (EC_{50} = 0.8519 ± 0.281 µg/mL), **6d** (EC_{50} = 0.7034 ± 0.349 µg/mL) and **6e** (EC_{50} = 0.6483 ± 0.221 µg/mL) from **6a-e** were found to be display more anti-inflammatory activity than standard drug DFS. When NO_2 group at R^2 in compound **6a**, (EC_{50} = 8.668 ± 2.63 µg/mL) and *fluoro*- at R^2 in compound **6 b** (EC_{50} = 11.66 ± 1.22 µg/mL) did not show any significant change in activity. Replacement of R^2 = Cl group led to increase in activity (compound **6c**, EC_{50} = 0.8519 ± 0.281 µg/mL). Again, when *bromo*- group is at R^2 in compound **6d** (EC_{50} = 0.7034 ± 0.349 µg/mL) further increases the anti-inflammatory activity compared to the standard DFS. Surprisingly, the compound **6e** (EC_{50} = 0.6483 ± 0.221) in which R_1 = H and R_2 = H exhibited excellent anti-

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Among the **6f-j** series, all the five compounds (EC_{50} range = 31.43 ± 0.192-57.80 ± 0.224 µg/mL) have shown less potent anti-inflammatory activity compared with standard drug DFS. There is no significant variation observed while varying the substituent like, NO_2, Cl, F and Br on the phenyl ring system (Table 1). Compound **6o** (EC_{50} = 0.8416 ± 0.239 µg/mL) from **6k-6o** series bearing R^1 = Cl and R^2 = H group was found to be display excellent anti-inflammatory activity compared to the standard drug DFS. Replacement of *nitro*- group at R^2 in compound **6k**, (EC_{50} = 65.93 ± 0.180 µg/mL), *fluoro*- at R^2 in compound **6 l** (EC_{50} = 17.76 ± 0.350 µg/mL) and *bromo*- at R^2 in **6n** (EC_{50} = 10.96 ± 0.182 µg/mL) did not show any significant change in the activity. In compound **6 m**, (EC_{50} = 6.630 ± 0.241 µg/mL), the replacement of the *chloro*- group at a R^2 led to decrease in the activity.

Antioxidant activity

According to the DPPH assay, compounds **6d** (IC_{50} = 16.3 µg/mL), **6f** (IC_{50} = 16.78 µg/mL), **6 g** (IC_{50} = 12.53 µg/mL), **6 h** (IC_{50} = 15.19 µg/mL) and **6j** (IC_{50} = 13.82) show excellent antioxidant activity compared to the standard antioxidant drug BHT (IC_{50} = 16.47 µg/mL) (Table 1). Compound **6d** (IC_{50} = 16.3 µg/mL) from **6a-e** series bearing R^2 = Br group was found to be display more antioxidant activity than standard drug BHT. Replacement of R^2 = F group led to decrease in activity by two-fold (compound **6 b**, IC_{50} = 39.43 µg/mL). Replacement of NO_2 group at R^2 in compound **6a**, (IC_{50} = 30.2 µg/mL) and *chloro*- at R^2 in compound **6c** (IC_{50} = 27.3 µg/mL) did not show any significant change in activity. When hydrogen is at R^2 in compound **6e** (IC_{50} = 20.41 µg/mL) exhibited satisfactory antioxidant, activity compared to the standard BHT. Among **6f-j** series, all the five compounds (IC_{50} range = 12.55-19.2 µg/mL) have shown good activity when compared with standards. There is no significant variation observed while varying the substituent like, NO_2, Cl, F and Br. Compound **6 g** (IC_{50} = 12.55 µg/mL) bearing R^1 and R^2 = F group was found to be most active antioxidant agent among synthesized compounds than standard drug BHT. From **6k-o** series, all compounds (IC_{50} range = 17.18-33.3 µg/mL) except **6k** (IC_{50} = 17.18 µg/mL) showed less potent activity when compared with standards.

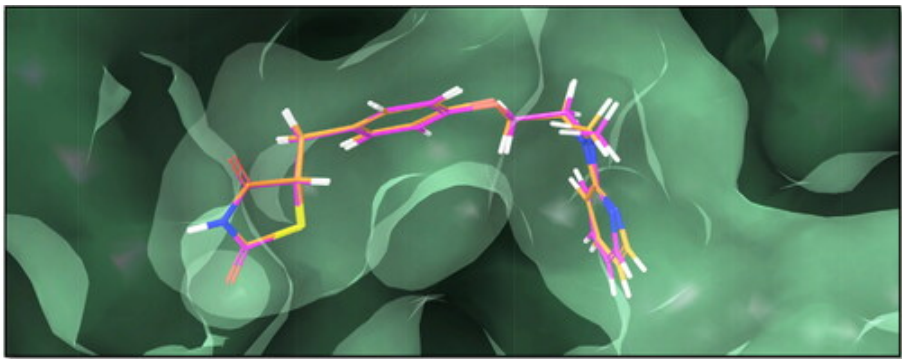
Computational study

Molecular docking study

The most appropriate approach for gauzing the accuracy of a docking protocol is to monitor

experimentally observed binding mode in the PDB. The molecular docking protocol adopted in the current study was validated by extracting the native ligand from the crystal structure and re-docking it to the binding site of PPARγ. The root means square deviation (RMSD) between the X-ray conformation of native ligand and the conformation predicted by docking into crystal structure was found to be less than 1 Å, validating the reliability of and reproducibility of the docking procedure in reproducing the experimentally observed binding mode for molecules investigated herein. The overlay of the experimentally observed binding mode of the native ligand over its best docked conformation is shown in Figure 2.

Figure 2. Overlay of the best scoring poses for the co-crystallized ligand-Rosiglitazone obtained by docking (orange carbon) against the X-ray bound conformation (pink carbon).



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The level of anti-inflammatory activities demonstrated by 2,4-thiazolidinedione-1,2,3-triazole derivatives motivated us to gain an insight into molecular interactions that govern the binding of these molecules with the target enzyme PPARγ. In the absence of available resources to carry out the enzyme-based experimental studies, molecular docking study has gained significant attention to identify the targets for different ligands and provides an alternative approach to understand the thermodynamic events involved in the binding of molecules to the active site of the target enzyme which thereby helps to rationalize their experimentally observed biological activity.

Molecular docking study revealed that all the 1,2,3-Triazole incorporated 2,4-Thiazolidinedione derivatives investigated herein, snugly fitted into the active site of PPARγ with very similar orientations occupying coordinates very close to that of the native ligand in the crystal structure and their resulting complexes were stabilized by a network of steric and electrostatic

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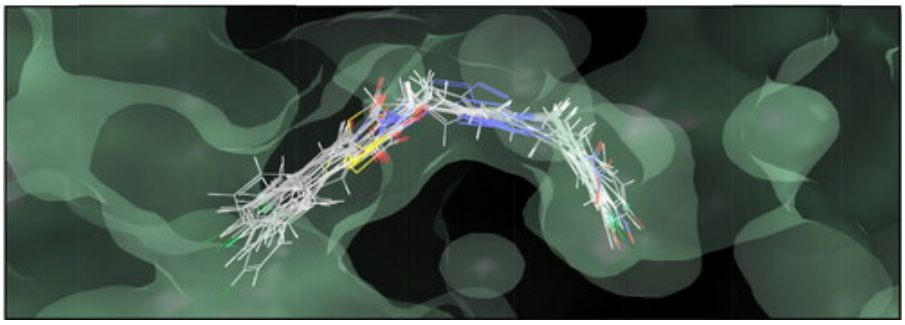
−50.869 kcal/mol to −27.09 kcal/mol while the docking score ranged from −8.51 to −6.21. The docking score for the native ligand Rosiglitazone was found to be −9.511 with a binding energy of −58.26 kcal/mol. We could observe a statistically significant correlation between the experimental anti-inflammatory activities and the molecular docking scores wherein the active analogues exhibited higher docking scores while those with relatively low inhibition were also predicted to have a lower score.

Figure 3. Binding modes of 1,2,3-Triazole incorporated 2,4-Thiazolidinedione Derivatives into the active site of human peroxisome proliferator-activated receptor gamma (PPARγ).



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Furthermore, a detailed per-residue interaction analysis between the enzyme and the docked 1,2,3-Triazole incorporated 2,4-Thiazolidinedione derivatives were carried out to identify the most significantly interacting residues and provide an explanation for the observed difference in binding affinity for these molecules through which we can speculate regarding the detailed binding patterns in the cavity. For the sake of brevity, we have illustrated this analysis only for the most active analogue **6e** (Figure 4) while the results for other derivatives and their binding modes shown in **(**Table 2**)** and molecular docking images shown in Figure 5.

Figure 4. Binding mode of **6e** into the active site of human peroxisome proliferator-activated receptor gamma (PPARγ) (the π-π stacking interaction has been represented using green lines).

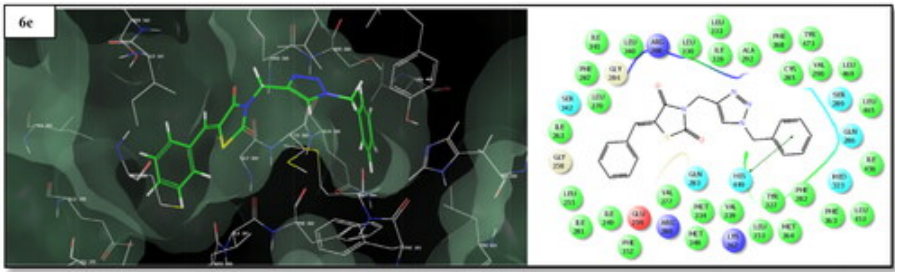

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Figure 5. Binding mode of compounds into the active site of human peroxisome proliferator-activated receptor gamma (PPARγ) (the π-π stacking interaction has been represented using green lines).

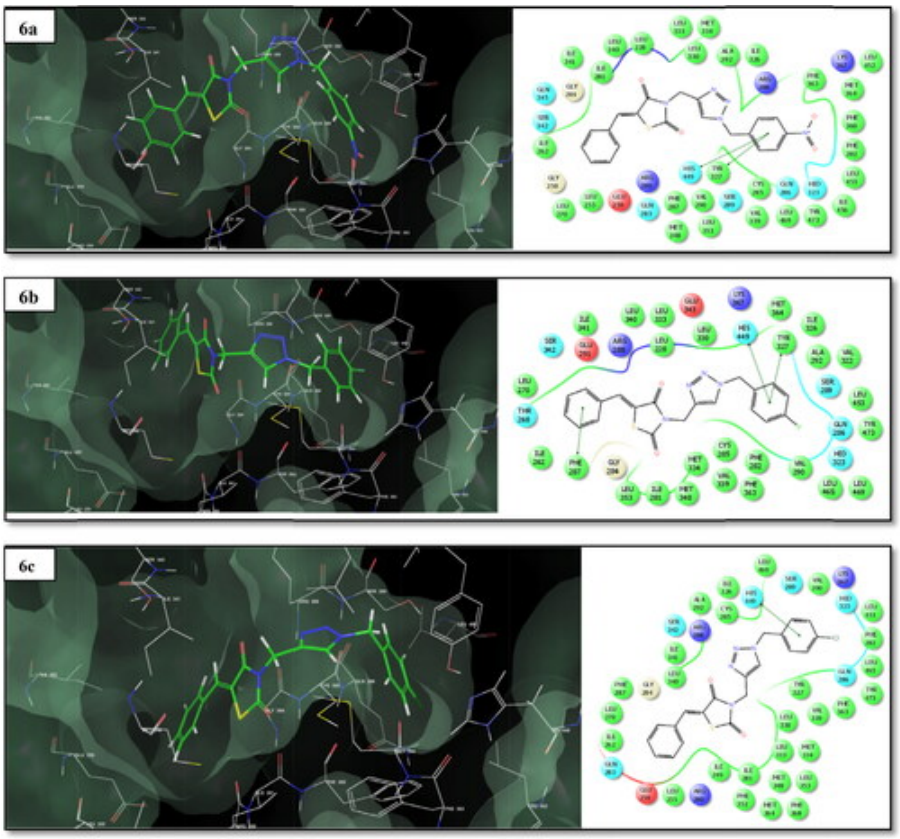

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Figure 5. Continued.

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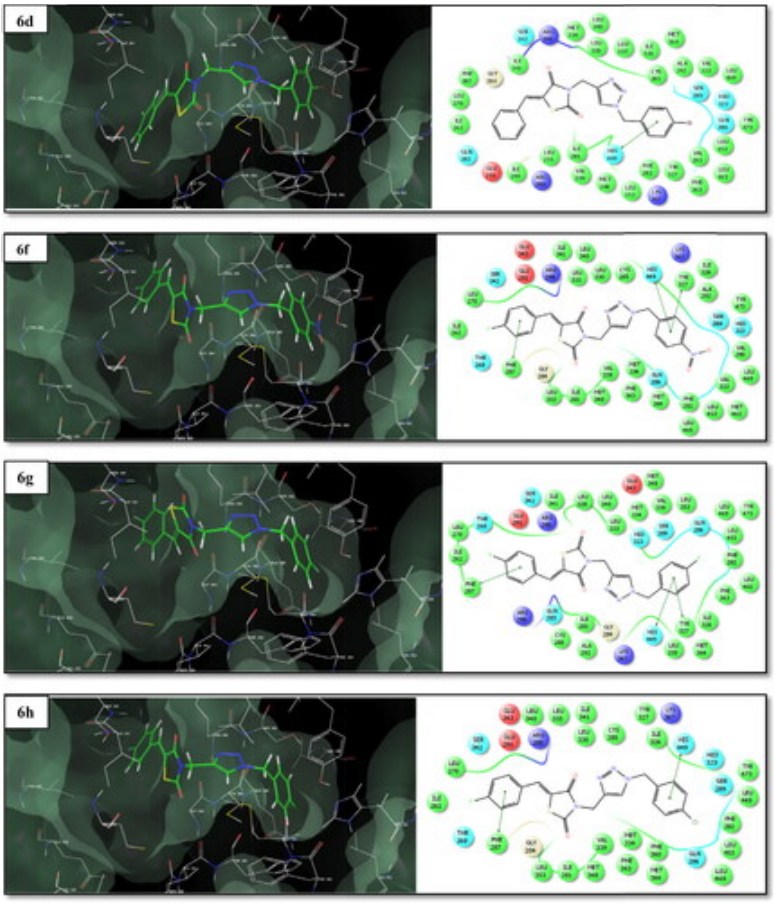

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Figure 5. Continued.

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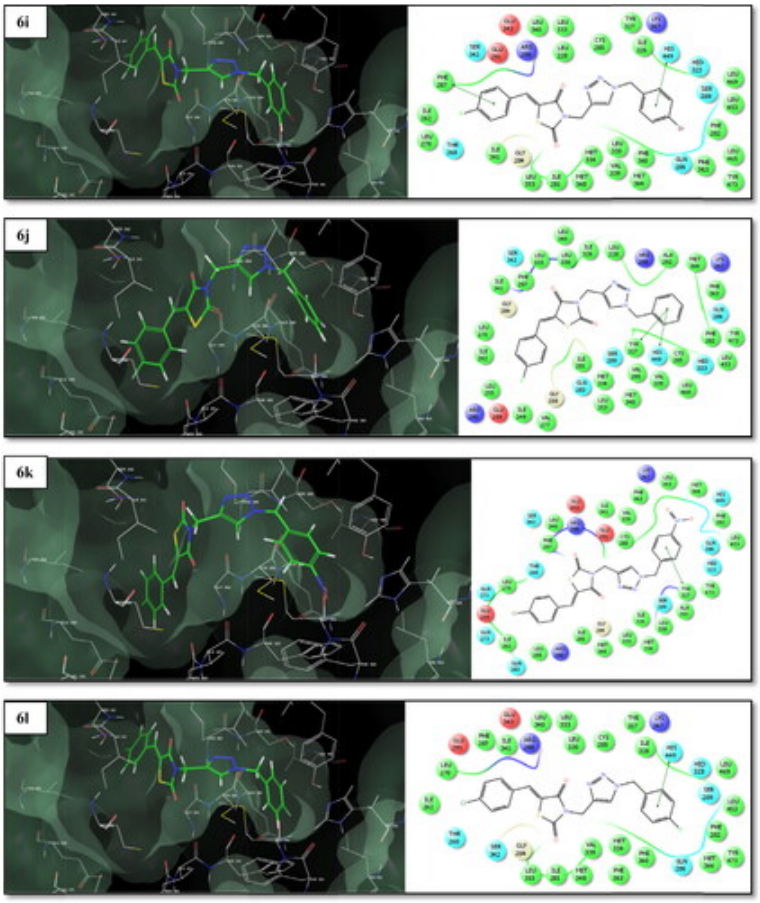

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Figure 5. Continued.

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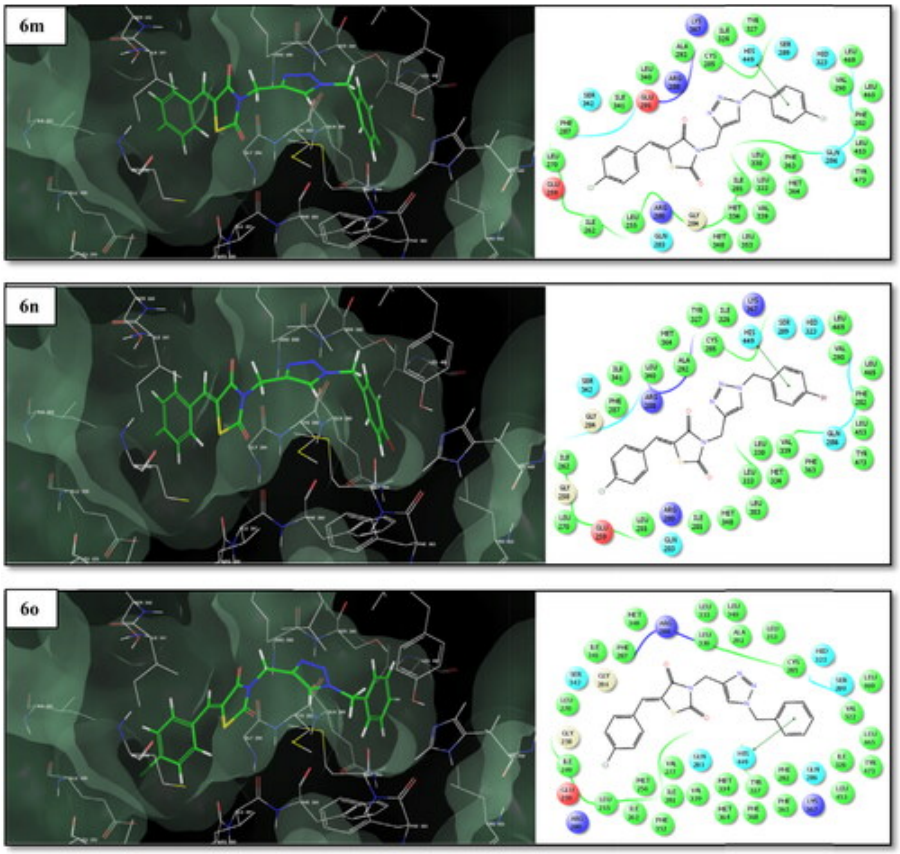

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Table 2. Results of the per-residue interaction analysis for the 2,4-thiazolidinedione-1,2,3-triazole derivatives with the active site of human PPARγ.

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The lowest energy docking pose of the most active analogue **6e** into the active site of PPARγrevealed that it binds to the enzyme with a significantly higher binding affinity (docking score: −8.51, binding energy: −50.869 kcal/mol) which can be explained in terms of the specific bonded and non-bonded per-residue interactions with the residues shaping the active site. The per residue-ligand interaction energy distribution showed that the compound is stabilized within the active site of PPARγthrough an extensive network of van der Waals interactions with Met348(-1.80 kcal/mol), Ile341(-3.74 kcal/mol), Leu330(-2.90 kcal/mol), Arg288(-4.51 kcal/mol), Gly284(-3.41 kcal/mol), Ile281(-2.87 kcal/mol) and Arg280(-1.04 kcal/mol) residues through

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component was engaged in favorable van der Waals interactions with Tyr473 (-1.28 kcal/mol), Leu453(-1.18 kcal/mol), His449(-2.14 kcal/mol), Met364(-2.75 kcal/mol), Tyr327(-2.85 kcal/mol), Ile326(-2.74 kcal/mol), His323(-1.51 kcal/mol), Ser289(-2.39 kcal/mol), Gln286(-3.15 kcal/mol), Cys285(-8.85 kcal/mol), Phe282(-2.25 kcal/mol) residues. Analysis of the polar contacts i.e. electrostatic interactions revealed multiple closed contacts with Lys367 (-1.21 kcal/mol), Met364(-1.02 kcal/mol) and Arg288(-4.86 kcal/mol) residues. The enhanced binding affinity of **6e** is also attributed to its position in the π-interaction space (π- π stacking) of His449(2.46 Å). This type of the π-π stacking interaction serves as an "anchor", guiding the 3 D orientation of the ligand in the active site of the enzyme and thereby aid the steric and electrostatic interactions within. Thus, a strong network of thermodynamic interactions observed with PPARγ account for its good *in silico* affinity and provides a clue for its significant *in vitro* anti-inflammatory activity.

A similar network of thermodynamic interaction was consistently observed for other 1,2,3-Triazole incorporated 2,4-Thiazolidinedione derivatives investigated herein as well but decreasing gradually with their observed anti-inflammatory activity. The per-residue interaction energy distribution revealed that the primary driving force for mechanical interlocking was the steric complementarity between the ligand and the active site residues of PPARγ which is reflected in the relatively higher number of favorable van der Waals interaction over other components contributing to the overall binding scores. The binding pattern predicted by docking and the per-residue interaction energy distribution along with the glide score and the glide energy indicates that these 1,2,3-Triazole incorporated 2,4-Thiazolidinedione derivatives have a good affinity toward the active site of PPARγ enzyme making them pertinent starting points for further structure-based design efforts.

ADME properties

The success of a drug is determined not only by good efficacy but also by an acceptable ADME (absorption, distribution, metabolism and excretion) profile. A computational study of all the synthesized compounds was performed for the prediction of ADME properties and the value obtained is presented in Table 3. It is observed that compounds exhibited a good % ABS (% absorption) ranging from 69.11 to 85.02%.

Table 3. Pharmacokinetic parameters were important for good oral

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Furthermore, none of the synthesized derivatives violates Lipinski's rule of five (miLog $P \leq 5$). A molecule likely to be developed as an orally active drug candidate should not show more than one violation of the following four criteria: miLog *P* (octanol-water partition coefficient) ≤ 5, molecular weight ≤ 500, number of hydrogen bond acceptors ≤ 10 and number of hydrogen bond donors ≤ 5.[43] The larger the value of the drug-likeness model score, the higher is also the probability that the particular molecule will be active. All the tested compounds followed the criteria for orally active drugs and therefore, these compounds may have a good potential for eventual development as oral agents.

Conclusion

In conclusion, we have synthesized new 1,2,3-triazole based thiazolidinone derivatives *via* click chemistry approach and evaluated them for biological activity. The synthesized 1,2,3-Triazole incorporated 2,4-Thiazolidinedione derivatives exhibited promising anti-inflammatory activity. Compounds **6d** and **6e** display higher anti-inflammatory activity compared to the standard drug diclofenac sodium. Similarly, all the synthesized compound displays promising antioxidant activity as compared to the standard drug. Compounds **6d**, **6 g**, **6 h** and **6j** shows potential antioxidant activity (IC_{50} = 12.55-16.30 µg/mL) when compared with standard drug BHT. In addition to this, molecular docking study of 1,2,3-Triazole incorporated 2,4-Thiazolidinedione derivatives have a high affinity toward the active site of enzyme PPARγ which provides a strong platform for new structure-based design efforts. Furthermore, analysis of the ADME parameters shows good drug-like properties and can be developed as an oral drug candidate. Thus, suggesting that compounds from the present series can be further optimized and developed as a lead molecule. Further work on the utilization of triazole incorporated thiazolidinedione derivatives leading to useful bioactive compounds is in progress.

Experimental section

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All the solvents and reagents were purchased from commercial suppliers, Spectrochem Pvt. Ltd., Rankem India Ltd. and Sigma Aldrich which was used without further purification. The progress of each reaction was monitored by ascending thin layer chromatography (TLC) using TLC aluminum sheets, silica gel F_{254} precoated, Merck, Germany and locating the spots using UV light as the visualizing agent or Iodine vapors. Melting points were taken in the open capillary method and are uncorrected. ^{1}H NMR spectra were recorded (DMSO-d_6) on Bruker Avance 400 NMR Spectrometer. ^{13}C NMR and DEPT 135 spectra were recorded (DMSO-d_6) on Bruker Avance 100 NMR Spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) using tetramethylsilane (TMS) as an internal standard. The splitting pattern abbreviations are designed as singlet (s); doublet (d); double doublet (dd); triplet (t); quartet (q) and multiplet (m). The mass spectra were recorded on Q-TOF micromass (YA-105) spectrometer in the ESI (Electrospray Ionization) modes.

General procedure for the synthesis of (Z)-5-benzylidenethiazolidine-2,4-dione (3a-c)

A mixture of aldehyde (10 mmol) **1a-c**, glacial acetic acid (10 mL), 2,4-thiazolidinedione **2** (10 mmol), and fused sodium acetate (20 mmol) was refluxed for 4-5 hr with constant stirring. The progress of the reaction was monitored by thin layer chromatography (*n*-Hexane/EtOAc 9:1). After completion of reaction indicated by TLC, it was allowed to cool at room temperature. Then ice cold water (50 mL) was added to it and whole reaction mass was stirred for 10 min and then filtered. The solid appeared was collected by simple filtration and washed with cold water. The crude compound was recrystallized using the ethanol/ethylacetate.

General procedure for synthesis of (Z)-5-benzylidene-3-(prop-2-yn-1-yl)thiazolidine-2,4-dione (4a-c)

To the stirred solution of (*Z*)-5-benzylidenethiazolidine-2,4-dione (10 mmol) in *N,N*-dimethylformamide (DMF) (10 mL), K_2CO_3 (20 mmol) was added. The reaction mixture was stirred at room temperature for 30 minutes, which results in the corresponding anion. To this mixture, propargyl bromide (10 mmol) was added and stirred for 2 h. The progress of the reaction was monitored by TLC using ethyl acetate:hexane as a solvent system. The reaction was quenched by crushed ice. The obtained solid product was filtered and crystallized using ethanol/ethylacetate. The crystallized products were taken for the next step.

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triazol-4-yl)methyl)thiazolidine-2,4-dione (6a-o)

To the solution of (*Z*)-5-benzylidene-3-(prop-2-yn-1-yl)thiazolidine-2,4-dione **(4a-c)** (1 mmol), benzyl azides **5a-e** (1 mmol) and copper diacetate ($Cu(OAc)_2$) (20 mole %) in *t*-BuOH-H_2O (3:1, 8 mL) and the resulting mixture was stirred at room temperature for 22-30 h. The progress of the reaction was monitored by TLC using ethyl acetate:hexane as a solvent system. The reaction mixture was quenched with crushed ice and extracted with ethyl acetate (2 × 25 mL). The organic extracts were washed with brine solution (2 × 25 mL) and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to afford the corresponding crude compounds. The obtained crude compounds were crystallized using ethanol and ethyl acetate.

(Z)-5-Benzylidene-3-((1-(4-nitrobenzyl)-1H-1,2,3-triazol-4-yl)methyl)thiazolidine-2,4-dione (6a)

The compound **6a** as a off white solid and was obtained *via* 1,3-dipolar cycloaddition between (*Z*)-5-benzylidene-3-(prop-2-yn-1-yl)thiazolidine-2,4-dione (**4a)** and 1-(azidomethyl)-4-nitrobenzene (**5a)** using 20 mol% of $Cu(OAc)_2$ in 26 h with 92% yield. Mp. 190 °C.

(Z)-5-Benzylidene-3-((1-(4-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)thiazolidine-2,4-dione (6 b)

The compound **6 b** as a off white solid and was obtained *via* 1,3-dipolar cycloaddition between (*Z*)-5-benzylidene-3-(prop-2-yn-1-yl)thiazolidine-2,4-dione (**4a)** and 1-(azidomethyl)-4-fluorobenzene (**5 b)** using 20 mol% of $Cu(OAc)_2$ in 26 h with 92% yield. Mp. 178-179 °C. IR (KBr) $\tilde{\nu}$: 653.6-783.8 (monosubstituted aromatic C-F stretching), 1599.8 (C = C stretching), 1685.52 (carbonyl carbon CN), 1754.21(Carbonyl carbon CS), 2965.7 (Ar-H stretching). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 4.89 (s, 2H, CH_2, methylene bridge between TZD and Triazole), 5.55 (s, 2H, CH_2, methylene bridge between Triazole and phenyl ring), 7.18-7.38 (m, 2H, Ar-H at ortho position with respect to fluorine on phenyl), 7.39-7.49 (m, 2H, Ar-H at ortho position with respect to fluorine on phenyl), 7.50-7.56 (m, 3H, Ar-H fused with TZD), 7.62-7.64 (d, 2H, Ar-H fused with TZD), 7.95 (s, 1H, Ar-H of triazole) and 8.18 (s, 1H, β-H of carbonyl). ^{13}C NMR (100 MHz, DMSO-d_6, ppm): δ 37.2, 52.6 (methylene carbon between Triazole and phenyl ring), 116, 116.2, 121.6, 124.2, 129.9, 130.7, 130.8, 130.9, 131.3, 132.7, 133.4, 133.9, 141.9, 161.2, 163.6, 165.7 (Carbonyl carbon attached to the nitrogen) and 167.5 (Carbonyl carbon attached to the sulfur). HRMS calculated $[M + H]^+$ for $C_{20}H_{16}N_4O_2SF$: 395.0978, found: 395.0981; $[M + Na]^+$ for $C_{20}H_{15}N_4O_2SFNa$: 417.0798, found: 417.0802.

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The compound **6c** as a off white solid and was obtained *via* 1,3-dipolar cycloaddition between (*Z*)-5-benzylidene-3-(prop-2-yn-1-yl)thiazolidine-2,4-dione (**4a)** and 1-(azidomethyl)-4-chlorobenzene (**5c)** using 20 mol% of $Cu(OAc)_2$ in 26 h with 94% yield. Mp. 196 °C. ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 4.44 (s, 2H, CH_2, methylene bridge between TZD and Triazole), 5.29 (s, 2H, CH_2, methylene bridge between Triazole and phenyl ring), 7.48-7.88 (m, 9H, Ar-H), 8.26 (s,1H, Ar-H of triazole) and 8.56 (s, 1H, β-H of carbonyl). ^{13}C NMR (100 MHz, DMSO-d_6, ppm): δ 36 (methylene carbon between TZD and Triazole), 55.2 (methylene carbon between Triazole and phenyl ring), 141.5, 144.7, 151.1, 151.9, 152.6, 152.8, 156.2, 158.7 (Carbonyl carbon attached to the nitrogen) and 166.8 (Carbonyl carbon attached to the sulfur).

(Z)-5-Benzylidene-3-((1-(4-bromobenzyl)-1H-1,2,3-triazol-4-yl)methyl)thiazolidine-2,4-dione (6d)

The compound **6d** as a off white solid and was obtained *via* 1,3-dipolar cycloaddition between (*Z*)-5-benzylidene-3-(prop-2-yn-1-yl)thiazolidine-2,4-dione (**4a)** and 1-(azidomethyl)-4-bromobenzene (**5d)** using 20 mol% of $Cu(OAc)_2$ in 28 h with 92% yield. Mp. 204-205 °C. ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 4.43 (s, 2H, CH_2, methylene bridge between TZD and Triazole), 5.26 (s, 2H, CH_2, methylene bridge between Triazole and phenyl ring), 7.39-7.41 (d, 2H, Ar-H at ortho position with respect to bromine on phenyl), 7.71-7.87 (m, 7H, Ar-H), 8.26 (s, 1H, Ar-H of triazole) and 8.55 (s, 1H, β-H of carbonyl). ^{13}C NMR (100 MHz, DMSO-d_6, ppm): δ 36 (methylene carbon between TZD and Triazole), 55.2 (methylene carbon between Triazole and phenyl ring), 141.5, 142, 144.9, 151.9, 152.8, 153, 153.6, 154.7, 156.2 (Carbonyl carbon attached to the nitrogen) and 159.3 (Carbonyl carbon attached to the sulfur). HRMS calculated $[M + H]^+$ for $C_{20}H_{16}N_4O_2SBr$: 455.0177, found: 455.0172.

(Z)-3-((1-Benzyl-1H-1,2,3-triazol-4-yl)methyl)-5-benzylidenethiazolidine-2,4-dione (6e)

The compound **6e** as a off white solid and was obtained *via* 1,3-dipolar cycloaddition between (*Z*)-5-benzylidene-3-(prop-2-yn-1-yl)thiazolidine-2,4-dione (**4a)** and (azidomethyl)benzene (**5e)** using 20 mol% of $Cu(OAc)_2$ in 22 h with 95% yield. Mp. 190 °C. ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 4.82 (s, 2H, CH_2, methylene bridge between TZD and Triazole), 5.66 (s, 2H, CH_2, methylene bridge between Triazole and phenyl ring), 7.82-8.26 (m, 10H, Ar-H), 8.65 (s, 1H, Ar-H of triazole) and 8.93 (s, 1H, β-H of carbonyl). ^{13}C NMR (100 MHz, DMSO-d_6, ppm): δ 36.3 (methylene carbon between TZD and Triazole), 56.4 (methylene carbon between Triazole and phenyl ring), 141.9, 145.1, 150.4, 150.6, 151.3, 152.1, 153.1, 156.5, 157.1, 160.3 (Carbonyl carbon

+ H]$^+$ for $C_{20}H_{17}N_4O_2S$: 377.1072, found: 377.1073.

(Z)-5-(4-Fluorobenzylidene)-3-((1-(4-nitrobenzyl)-1H-1,2,3-triazol-4-yl)methyl) thiazolidine-2,4-dione (6f)

The compound **6f** as a off white solid and was obtained *via* 1,3-dipolar cycloaddition between (*Z*)-5-(4-fluorobenzylidene)-3-(prop-2-yn-1-yl)thiazolidine-2,4-dione (**4 b)** and 1-(azidomethyl)-4-nitrobenzene (**5a)** using 20 mol% of $Cu(OAc)_2$ in 28 h with 94% yield. Mp. 178-179 °C. ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 4.90 (s, 2H, CH_2, methylene bridge between TZD and Triazole), 5.75 (s, 2H, CH_2, methylene bridge between Triazole and phenyl ring), 7.36-7.52 (m, 4H, Ar-H), 7.68-7.71 (m, 2H, Ar-H at meta position with respect to nitro on phenyl), 7.96 (s,1H, Ar-H of triazole) and 8.21-8.25 (t, 3H, 1 β-H of carbonyl and 2 Ar-H at ortho position with respect to nitro on phenyl). HRMS calculated [M + H]$^+$ for $C_{20}H_{15}N_5O_4SF$: 440.0829, found: 440.0831.

(Z)-3-((1-(4-Fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)-5-(4-fluorobenzylidene) thiazolidine-2,4-dione (6 g)

The compound **6 g** as a off white solid and was obtained *via* 1,3-dipolar cycloaddition between (Z)-5-(4-fluorobenzylidene)-3-(prop-2-yn-1-yl)thiazolidine-2,4-dione (**4 b)** and 1-(azidomethyl)-4-fluorobenzene (**5 b)** using 20 mol% of $Cu(OAc)_2$ in 27 h with 92% yield. Mp. 198-200 °C.

(Z)-3-((1-(4-Chlorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)-5-(4-fluorobenzylidene) thiazolidine-2,4-dione (6 h)

The compound **6 h** as a off white solid and was obtained *via* 1,3-dipolar cycloaddition between (*Z*)-5-(4-fluorobenzylidene)-3-(prop-2-yn-1-yl)thiazolidine-2,4-dione (**4 b)** and 1-(azidomethyl)-4-chlorobenzene (**5c)** using 20 mol% of $Cu(OAc)_2$ in 29 h with 90% yield. Mp. 135-136 °C.

(Z)-3-((1-(4-Bromobenzyl)-1H-1,2,3-triazol-4-yl)methyl)-5-(4-fluorobenzylidene) thiazolidine-2,4-dione (6i)

The compound **6i** as a off white solid and was obtained *via* 1,3-dipolar cycloaddition between (*Z*)-5-(4-fluorobenzylidene)-3-(prop-2-yn-1-yl)thiazolidine-2,4-dione (**4 b)** and 1-(azidomethyl)-4-bromobenzene (**5d)** using 20 mol% of $Cu(OAc)_2$ in 28 h with 92% yield. Mp. 154-156 °C. ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 4.43 (s, 2H, CH_2, methylene bridge between TZD and Triazole), 5.26 (s, 2H, CH_2, methylene bridge between Triazole and phenyl ring), 7.38-7.41 (d, 2H, Ar-H at ortho position with respect to fluorine on phenyl), 7.53-7.59 (m, 2H, Ar-H at meta position with respect

phenyl), 7.93-7.97 (m, 2H, Ar-H at ortho position with respect to bromine on phenyl), 8.27 (s, 1H, Ar-H of triazole) and 8.55 (s, 1H, β-H of carbonyl). ^{13}C NMR (100 MHz, DMSO-d_6, ppm): δ 36.3 (methylene carbon between TZD and Triazole), 55.5 (methylene carbon between Triazole and phenyl ring), 136, 136.3, 141.4, 142.2, 145.2, 152.3, 152.4, 153.2, 155, 156.2, 159.5 (Carbonyl carbon attached to the nitrogen) and 167.1 (Carbonyl carbon attached to the sulfur). HRMS calculated $[M + H]^+$ for $C_{20}H_{15}N_4O_2SBr$: 473.0083, found: 473.0082.

(Z)-3-((1-Benzyl-1H-1,2,3-triazol-4-yl)methyl)-5-(4-fluorobenzylidene)thiazolidine-2,4-dione (6j)

The compound **6j** as a off white solid and was obtained *via* 1,3-dipolar cycloaddition between (*Z*)-5-(4-fluorobenzylidene)-3-(prop-2-yn-1-yl)thiazolidine-2,4-dione (**4 b)** and (azidomethyl)benzene (**5e)** using 20 mol% of $Cu(OAc)_2$ in 26 h with 93% yield. Mp. 174-176 °C. ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 4.80 (s, 2H, CH_2, methylene bridge between TZD and Triazole), 5.64 (s, 2H, CH_2, methylene bridge between Triazole and phenyl ring), 7.80-7.95 (m, 7H, Ar-H), 8.29-8.34 (m, 2H, Ar-H at meta position with respect to fluorine on phenyl), 8.64 (s, 1H, Ar-H of triazole) and 8.90 (s, 1H, β-H of carbonyl). ^{13}C NMR (100 MHz, DMSO-d_6, ppm): δ 36 (methylene carbon between TZD and Triazole), 56.2 (methylene carbon between Triazole and phenyl ring), 135.7, 136, 141.1, 144.8, 150.1, 150.3, 151.1, 152.1, 155.5, 155.9, 160 (Carbonyl carbon attached to the nitrogen) and 167 (Carbonyl carbon attached to the sulfur). HRMS calculated $[M + H]^+$ for $C_{20}H_{16}N_4O_2SF$: 395.0978, found: 395.0981.

(Z)-5-(4-Chlorobenzylidene)-3-((1-(4-nitrobenzyl)-1H-1,2,3-triazol-4-yl)methyl) thiazolidine-2,4-dione (6k)

The compound **6k** as a off white solid and was obtained *via* 1,3-dipolar cycloaddition between (*Z*)-5-(4-chlorobenzylidene)-3-(prop-2-yn-1-yl)thiazolidine-2,4-dione (**4c)** and 1-(azidomethyl)-4-nitrobenzene (**5a)** using 20 mol% of $Cu(OAc)_2$ in 30 h with 94% yield. Mp. 184 °C.

(Z)-5-(4-Chlorobenzylidene)-3-((1-(4-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl) thiazolidine -2,4-dione (6 l)

The compound **6 l** as a off white solid and was obtained *via* 1,3-dipolar cycloaddition between (*Z*)-5-(4-chlorobenzylidene)-3-(prop-2-yn-1-yl)thiazolidine-2,4-dione (**4c)** and 1-(azidomethyl)-4-fluorobenzene (**5 b)** using 20 mol% of $Cu(OAc)_2$ in 30 h with 94% yield. Mp. 180 °C. ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 4.87 (s, 2H, CH_2, methylene bridge between TZD and Triazole), 5.54 (s,

(m, 2H, Ar-H) , 7.60-7.62 (m, 4H, Ar-H phenyl with chlorine), 7.93(s, 1H, Ar-H of triazole) and 8.17 (s, 1H, β-H of carbonyl). ^{13}C NMR (100 MHz, DMSO-d_6, ppm): δ 36.7 (methylene carbon between TZD and Triazole), 52.1 (methylene carbon between Triazole and phenyl ring), 115.5, 121.9, 123.7, 129.5, 130.4, 130.5, 131.8, 132.1, 132.2, 132.5, 135.4, 141.3, 160.7, 163.1, 165.1 (Carbonyl carbon attached to the nitrogen) and 166.7 (Carbonyl carbon attached to the sulfur).

(Z)-3-((1-(4-Chlorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)-5-(4-chlorobenzylidene) thiazolidine -2,4-dione (6 m)

The compound **6 m** as a off white solid and was obtained *via* 1,3-dipolar cycloaddition between (*Z*)-5-(4-chlorobenzylidene)-3-(prop-2-yn-1-yl)thiazolidine-2,4-dione (**4c)** and 1-(azidomethyl)-4-chlorobenzene (**5c)** using 20 mol% of $Cu(OAc)_2$ in 28 h with 92% yield. Mp. 168 °C. ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 4.98 (s, 2H, CH_2, methylene bridge between TZD and Triazole), 5.56 (s, 2H, CH_2, methylene bridge between Triazole and phenyl ring), 7.31-7.33 (d, 2H, Ar-H), 7.41-7.43 (d, 2H, Ar-H), 7.58-7.65 (q, 4H, Ar-H), 7.94 (s, 1H, Ar-H of triazole) and 8.18 (s, 1H, β-H of carbonyl). HRMS calculated $[M + H]^+$ for $C_{20}H_{15}N_4O_2SCl_2$: 445.0293, found: 445.0300.

(Z)-3-((1-(4-Bromobenzyl)-1H-1,2,3-triazol-4-yl)methyl)-5-(4-chlorobenzylidene) thiazolidine-2,4-dione (6n)

The compound **6n** as a off white solid and was obtained *via* 1,3-dipolar cycloaddition between (*Z*)-5-(4-chlorobenzylidene)-3-(prop-2-yn-1-yl)thiazolidine-2,4-dione (**4c)** and 1-(azidomethyl)-4-bromobenzene (**5d)** using 20 mol% of $Cu(OAc)_2$ in 27 h with 90% yield. Mp. 176-178 °C.

(Z)-3-((1-Benzyl-1H-1,2,3-triazol-4-yl)methyl)-5-(4-chlorobenzylidene)thiazolidine-2,4-dione (6o)

The compound **6o** as a off white solid and was obtained *via* 1,3-dipolar cycloaddition between (*Z*)-5-(4-chlorobenzylidene)-3-(prop-2-yn-1-yl)thiazolidine-2,4-dione (**4c)** and (azidomethyl)benzene (**5e)** using 20 mol% of $Cu(OAc)_2$ in 26 h with 93% yield. Mp. 168-169 °C. ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 4.87 (s, 2H, CH_2, methylene bridge between TZD and Triazole), 5.54 (s, 2H, CH_2, methylene bridge between Triazole and phenyl ring), 7.28-7.34 (m, 5H, Ar-H), 7.58-7.62 (m, 4H, Ar-H), 7.93 (s, 1H, Ar-H of triazole) and 8.16 (s, 1H, β-H of carbonyl). ^{13}C NMR (100 MHz, DMSO-d_6, ppm): δ 36.8 (methylene carbon between TZD and Triazole), 52.9 (methylene carbon between Triazole and phenyl ring), 121.9, 123.8, 128, 128.2, 128.8, 129.5, 132.1, 135.4, 135.9, 141.3, 165.1 (Carbonyl carbon attached to the nitrogen) and 166.7 (Carbonyl

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411.0684.

Experimental protocol for biological activity

Anti-inflammatory activity

Thiazolidinedione binding with PPARγ has been suggested to play a down regulatory role in the treatment of inflammatory disorders. Thiazolidinedione gives potential anti-inflammatory activity by inhibiting monocyte/macrophage activation and expression of inflammatory molecules, i.e. interleukin (IL)-1β, IL-6, tumor necrosis factor (TNF-α), inducible nitric oxide synthase and gelatinase B.[44] Anti-inflammatory agents act by either inhibiting lysosomal enzymes or by stabilizing lysosomal membranes, and HRBC membranes are similar to these lysosomal membrane components. Hence, the lysis of an HRBC membrane is taken as a measure of anti-inflammatory activity. *In vitro* anti-inflammatory activity was studied *via* the HRBC membrane stabilization method against the standard drug diclofenac sodium (DFS).[45] Blood is collected from healthy volunteers. Fresh whole human blood was collected and it was mixed with equal volumes of sterilized Alsever's solution (Dextrose 2%, Sodium citrate 0.8%, Citric acid 0.05%, Sodium chloride 0.42% and Distilled water 100 mL). This blood solution was centrifuged for 10 mins at 3000 rpm and then washed three times with an equal volume of normal saline. The volume of the blood is measured and reconstituted as 10% v/v suspension with normal saline. The reaction mixture consists of 1.0 mL of the test sample of different concentrations in normal saline and 0.5 mL of 10% HRBC suspension, 1 mL of 0.2 M phosphate buffer, 1 mL hypo saline were incubated at 37 °C for 30 min and centrifuged for 30 min at 3000 rpm. The hemoglobin content of the supernatant solution was estimated at 560 nm spectrophotometrically. Each experiment was performed in triplicate and distilled water as control in this study. Where the blood control represents 100% lysis or zero percent stability, the percentage of HRBC hemolysis calculated by formula,

$$\%\,\mathrm{Haemolysis} = \left(\mathrm{O.D.ofControl} - \mathrm{O.D.ofTestsample} \,/\, \mathrm{O.D.ofControl}\right) \times 100$$

The concentration of a compound where 50% of its maximal effect is observed (EC_{50}) using graph pad prism was measured.

DPPH radical scavenging activity

diphenyl-2-picrylhydrazyl (DPPH) radical scavenging assay.[46] Butylated hydroxytoluene (BHT) has been used as a standard drug for the comparison of antioxidant activity. The hydrogen atom or electron donation ability of the compounds was measured from the bleaching of the purple-colored methanol solution of 1,1-diphenyl-1-picrylhydrazyl (DPPH). The spectrophotometric assay uses the stable radical DPPH as a reagent. 1 mL of various concentrations of the test compounds (5, 10, 25, 50 and 100 µg/mL) in methanol was added to 4 mL of 0.004% (w/v) methanol solution of DPPH. After a 30 min incubation period at room temperature, the absorbance was measured against blank at 517 nm. The percent inhibition (I %) of free radical production from DPPH was calculated by the following equation.

$$\%\,\text{ofscavenging} = \left[\left(\text{Acontrol} - \text{Asample}\right) / \text{Ablank}\right] \times 100$$

Where 'A control' is the absorbance of the control reaction (containing all reagents except the test compound) and 'A sample' is the absorbance of the test compound. Tests were carried at in triplicate.

Computational study

Molecular docking study

Grid-Based Ligand Docking with Energetics (Glide) module integrated with in the Small Drug Discovery Suite of Schrodinger molecular modeling software was used to study the binding mode of the title compounds into the active site of human peroxisome proliferator-activated receptor gamma (PPARγ).[47]

Grid-Based Ligand Docking with Energetics (Glide) module integrated in the Small Drug Discovery Suite of Schrodinger molecular modeling software was used to study the binding mode of the title compounds into the active site of human peroxisome proliferator-activated receptor gamma (PPARγ). With this purpose, the three-dimensional X-ray structure of human peroxisome proliferator-activated receptor gamma (PPARγ) in complex with Rosiglitazone (PDB code: 2PRG) was obtained from the Protein Data Bank (PDB) (http://www.rcsb.org/pdb). The *Protein Preparation Wizard* integrated in the software package was used to preprocess the enzyme structure for docking simulation which involved omitting the crystallographically observed water molecules (since no water molecule was observed to be conserved), the addition of missing hydrogens and side chain atoms and assigning the appropriate charge and

appropriate ionization states for the acidic and basic amino acid residues in the enzyme. Thereafter, the structure was subjected to energy minimization using the OPLS-2005 force field to relieve the steric clashes among the residues caused due to addition of hydrogen atoms until the RMSD (root mean square deviation) constraint was reached to 0.3 Å.

The 3 D structures of the title compounds (**6a-o**) were sketched through the *build* panel in Maestro and optimized using the *LigPrep* utility which involves the addition of hydrogen atoms, adjusting realistic bond lengths and angles, correcting the chirality and generating several low energy 3 D structures with various ionization states, tautomer's, stereo chemistries, and ring conformations from each molecule input followed by assignment of partial atomic charges using the OPLS-2005 force-field. The ligand structures thus obtained were finally refined by subjecting to energy minimization until it reached a RMSD cutoff of 0.01 Å.

After ensuring that the structures of both enzyme and ligands were in the correct form, the active site of the PPARγ enzyme was defined using the *receptor grid generation* panel in Glide which generates two cubical boxes having a common centroid for organizing the calculations: a larger enclosing and a smaller binding box. With the non-covalently bound native ligand-Rosiglitazone in place, the active site grid was defined by a 12 × 12 × 12 Å box (centred on the centroid of Rosiglitazone) which was large enough to explore a large surface of the enzyme. The co-crystallized ligand serves as the reference coordinate as it signifies the active site of a molecule concerning the target. The optimized ligand structures were then subjected to docking simulations against the defined active site using with extra precision (i.e. GlideXP) scoring function to gauze their binding affinities. The output files generated in the form of the docking poses were visualized and analyzed for the key elements of interaction with the active site residues using the Maestro's Pose Viewer utility.

ADME prediction

In this study, we calculated molecular volume (MV), molecular weight (MW), logarithm of the partition coefficient (miLog *P*), number of hydrogen bond acceptors (n-ON), number of hydrogen bonds donors (n-OHNH), topological polar surface area (TPSA), number of rotatable bonds (n-ROTB) and Lipinski's rule of five[48] using Molinspiration online property calculation

model score (a collective property of physic-chemical properties, pharmacokinetics and pharmacodynamics of a compound is represented by a numerical value) was computed by MolSoft software.[51]

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Disclosure statement

No potential conflict of interest was reported by the authors.

Additional information

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