Biological potential of thiazolidinedione derivatives of synthetic origin

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Abstract
Thiazolidinediones are sulfur containing pentacyclic compounds that are widely found throughout nature in various forms. Thiazolidinedione nucleus is present in numerous biological compounds, e.g., anti-malarial, antimicrobial, anti-mycobacterium, anticonvulsant, antiviral, anticancer, anti-inflammatory, antioxidant, anti-HIV (human immunodeficiency virus) and antitubercular agent. However, owing to the swift development of new molecules containing this nucleus, many research reports have been generated in a brief span of time. Therefore seems to be a requirement to collect recent information in order to understand the current status of the thiazolidinedione nucleus in medicinal chemistry research, focusing in particular on the numerous attempts to synthesize and investigate new structural prototypes with more effective antidiabetic, antimicrobial, antioxidant, anti-inflammatory, anticancer and antitubercular activity.

Keywords: Thiazolidinedione derivatives, Antidiabetic, Antimicrobial, Anti-inflammatory

Introduction
The number of antimicrobial drugs available in the market is vast, but there is a need to discover novel antimicrobial agents with better pharmacodynamic and pharmacokinetic properties with lesser or no side effects. Most of thiazolidinediones exhibit good bactericidal activity against various Gram-positive and Gram-negative bacteria. The bactericidal activity of thiazolidinediones derivatives depends on the substitution on the heterocyclic thiazolidine ring rather than the aromatic moiety.

Thiazolidinedione (Scheme 1) along with their derivatives draw attention as they have diverse biological as well as clinical use. Researchers focus on this moiety because it is involved in the control of various physiological activities. Heterocyclic moieties having Nitrogen and Sulfur are involved in a broad range of pharmacological processes. This created interest among researchers who have synthesized variety of thiazolidinediones derivatives and screened them for their various biological activities. In the present study, we have made an attempt to collect biological properties of thiazolidinediones and its derivatives of synthetic origin.

Biological activities of thiazolidinediones derivatives in the new millennium
Thiazolidinedione derivatives as antidiabetic agents
Diabetes mellitus (DM), also known as diabetes, is represented by the high blood sugar level over a period of prolonged time. There are three types of diabetes: (i) type 1 DM in which pancreas fails to produce insulin. Previously, it was referred as “insulin-dependent diabetes mellitus” or “juvenile diabetes”, (ii) type-2 DM a condition in which cells does not respond to insulin. Previously, it was referred as “non insulin-dependent diabetes mellitus”, (iii) gestational diabetes is the third main type and arises in pregnant women with no prior record of diabetes with high blood sugar levels [1].

The fundamental reasons of diabetes are a low production of insulin, the inability of the body to use it, or a combination of both (hormone which regulate carbohydrate, fat and protein metabolism). Normally it is a long-standing syndrome having different clinical revelation, with a number of problems such as cardiovascular, hypertension, renal, neurological. It is a disease in which pancreas does not secrete sufficient insulin or cells...
prevent reacting toward secreted insulin, that’s why cells cannot absorb blood glucose. Its symptoms are recurrent urination, tiredness, too much dehydration and hunger. It is cured by change in food habits, by regulation of proper diet; oral prescription and few situations include insulin injection [2, 3]. The thiazole moiety is a significant heterocyclic unit in drug invention. Literature survey shows that the wide-spread studies have been carried out on the production of thiazolidinediones. Thiazolidiones compounds shows a number of pharmacological activities such as antimicrobial, antitubercular, anti-tumor, anti-viral, anti-HIV, anti-inflammatory and anti-diabetic effects [4–6].

Datar et al. [7] synthesized a new series of thiazolidinediones by the reaction of thiazolidenedione with several benzaldehyde derivatives using Scheme 2. In vitro antidiabetic activity of synthesized compound was performed by SLM model. In this series compounds 1 and 2 found to be most active [5-(3,4-dimethoxy)benzylidine-2,4-thiazolidinedione,5-(3,4,5 trimethoxy)benzylidine-2,4-thiazolidinedione] due to presence of methoxy group and comparable to standard drug pioglitazone studies. The results of the most active compound are indicated Tables 1 and 2 (Datar et al. [7]).

Swapna et al. [8] synthesized novel thiazolidinediones by using Scheme 3. In vitro antidiabetic activity performed by alloxan induced tail tipping method. From this series compound 3, 4, 5 showed highest activity as comparable to standard drug metformin because of presence of electron donating group. The results of most active derivatives showed in Table 3 (Swapna et al. [8]).

Pattan et al. [2] synthesized a new series of thiazolidinediones derivatives [5-(4-substitutedsulfonylbenzylidene)-2,4-thiazolidinedione] using Scheme 4. The In vitro antidiabetic activity performed by ANOVA and Dunnet’s ’t’ test. From this series 6, 7 and 8 compound showed moderates activity and comparable to the standard drug glibenclamide. The results of active compound are given in Table 4 (Pattan et al. [2]).

Badiger et al. [9] synthesized novel thiazolidinediones derived from 4-fluorophenylacetic acid and thiourea in phosphorous oxychloride using Scheme 5. The
in vitro antidiabetic activity of synthesized compound [5-[[2-(4-alkyl/aryl)-6-arylimidazo[1,2][1,3,4]thiadiazol-5-yl]methylene]-1,3-thiazolidine-2,4-dione] were performed by alloxan induced tail tipping method. Among them, compounds 9 and 10 found to be most active due to presence of napthyl and coumarinyl groups at C5.

Table 1 Blood glucose level in experimental animals (mg/dl)

| Compounds | 0  | 30 | 60 | 90 | 120 |
|-----------|----|----|----|----|-----|
| DMSO      | 145| 150| 150| 147| 141 |
| Pioglitazone | 139| 105| 110| 112| 115 |
| 1         | 141| 112| 117| 118| 112 |
| 2         | 147| 110| 112| 107| 104 |

Table 2 Decrease in blood glucose levels by AUC method

| Compounds | 30 | 60 | 90 | 120 % reduction in blood glucose level |
|-----------|----|----|----|--------------------------------------|
| DMSO      | + 11 | + 05 | + 02 | + 04 | + 31 |
| Pioglitazone | − 34 | − 39 | − 29 | − 26 | − 23.07 |
| 1         | − 29 | − 25 | − 24 | − 27 | − 21.71 |
| 2         | − 37 | − 35 | − 28 | − 24 | − 22.84 |

Table 3 Blood glucose level (mg/dl) of synthesized thiazolidinediones derivatives

| Compounds | Blood glucose level (mean ± SE) | 0 h | 3 h | 6 h |
|-----------|---------------------------------|-----|-----|-----|
| 3         | 343 ± 5.797                    | 313.8 ± 9.411 | 303.2 ± 9.827 |
| 4         | 341.5 ± 6.158                  | 320.5 ± 6.737 | 313 ± 9.500 |
| 5         | 353.7 ± 6.026                  | 315.8 ± 8.109 | 311.2 ± 9.297 |
| Positive control | 335.7 ± 5.168              | 345.5 ± 5.488 | 354 ± 8.135 |
| Normal control | 125.0 ± 4.497                | 126.3 ± 4.047 | 127.7 ± 3.703 |
| Metformin | 343.3 ± 6.206                  | 322.8 ± 4.989 | 292.0 ± 7.767 |

Scheme 3 Synthesis of 5-[4-Substituted] sulphonyl benzylidene]-2,4-thiazolidinedione
position as compared to standard drug pioglitazone. The results of synthesized compounds presented in Table 5 (Badiger et al. [9]).

Patil et al. [10] synthesized a new series of thiazolidinedione derivatives derived from thiourea and chloroacetic acid in ethanol/DMF as presented in Scheme 6. The In vitro antidiabetic activity of synthesized compounds was performed by alloxan induced tail tipping method. From these series compounds 11, 12 and 13 showed better activities compared to pioglitazone and metformin as standard drug. The results of most active derivatives showed in Table 6 (Patil et al. [10]).

Srikanth et al. [11] synthesized an innovative sequence of thiazolidinediones using 4-fluoroaniline, methyl acrylate and thiourea using proper solvent as showed in Scheme 7. The In vitro antidiabetic activities of synthesized compounds were confirmed by tail vein method and ANOVA method. In this series compounds 14, 15, 16 and 17 showed significant activity as compared to standard drug rosiglitazone. The results of synthesized compounds presented in Table 7 (Srikanth et al. [11]).

**Table 4 Blood glucose level (mg/dl) in synthesized compounds**

| Compounds | Blood glucose level (mean ± SE) |
|-----------|---------------------------------|
|           | 0 h              | 1 h              | 3 h              | 6 h              |
| 6         | 320.5 ± 15.81    | 145.5 ± 2.26     | 137.0 ± 3.80     | 123.5 ± 1.10     |
| 7         | 213.5 ± 8.78     | 140.7 ± 3.30     | 106.3 ± 6.91     | 95.75 ± 6.06     |
| 8         | 283.5 ± 43.76    | 205.75 ± 49.7    | 166.3 ± 38.92    | 124.5 ± 13.16    |
| Standard  | 385.8 ± 21.37    | 230.8 ± 12.35    | 156.8 ± 10.87    | 93.4 ± 4.98      |

**Scheme 4** Synthesis of 5-(4-Substituted sulfonyl benzylidene)-2,4-thiazolidinedione
Nikalje et al. [12] designed few thiazolidinediones derivatives from thiazolidindione via 4-hydroxy, 3-ethoxy benzaldehyde in ethanol, benzoic acid and piperidine using Scheme 8. The In vitro antidiabetic activity of synthesized compounds was confirmed by ANOVA, alloxan induced diabetic rat model and dunnet’t test. From this series compounds 18, 19, 20, 21, and 22 showed better activity as compared to standard drug rosiglitazone. The results of synthesized compounds presented in Table 8 (Nikalje et al. [12]).

Jiwane et al. [13] synthesized a new series of thiazolidine-2,4-dione derivatives from 5-(benzylidene)thiazolidine-2,4-dione with N,N1-dimethylformamide in diethyl amino as presented in Scheme 9. The In vitro antidiabetic activity of synthesized compound [3-((diethyl amino)methyl)-5-(4-methoxybenzylidene)thiazolidine-2,4-dione] were confirmed by alloxan induced diabetic rat model. From this series, compounds 23 and 24 showed remarkable activity as that of the standard rosiglitazone, which indicates that the substitution of α-amino methyl group at position-3 show different hypoglycemic activity. The results of most active derivatives showed in Table 9 (Jiwane et al. [13]).

Grag et al. [14] designed novel thiazolidinediones derivative from 3-benzylthiazolidine-2,4-dione with selected various substituted aromatic aldehydes in ethanol, benzoic acid and piperidine using Scheme 10. In vitro antidiabetic activity of synthesized compound

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**Scheme 5** Synthesis of 5-{[2-(4-Fluorobenzyl)-6-arylimidazo[2,1-b][1,3,4]thiadiazole-5-yl)methylene]-1,3-thiazolidine-2,4-diones

**Table 5 Plasma glucose level of 3–4 at various drug doses**

| Compounds | % decrease in plasma glucose level (PG) at various drug doses (mg/kg bodyweight) |
|-----------|--------------------------------------------------------------------------------|
|           | 10 mg  | 30 mg  | 60 mg  |
| 9         | 42.48  | + 3.25 | 62.24  | + 3.42 | 70.35  | + 3.14 |
| 10        | 45.42  | + 1.25 | 58.36  | + 2.36 | 68.42  | + 2.16 |
| Pioglitazone | 47.25  | + 5.50 | 64.59  | + 5.42 | 75.43  | + 3.40 |

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**Scheme 6** Synthesis of 5-(Substituted benzylidene)-2,4-thiazolidinedione

**Table 6** Hypoglycemic effect of synthesized compounds

| Compounds          | Blood glucose level mg/dl (mean ± SE) | 0 h     | 3 h     | 6 h     | 24 h    |
|-------------------|--------------------------------------|---------|---------|---------|---------|
| 11                |                                      | 376.4 ± 21.00 | 342.8 ± 21.58 | 315.2 ± 21.66 | 276 ± 21.79 |
| 12                |                                      | 326.2 ± 25.32 | 300 ± 25.03  | 278.2 ± 25.76 | 245.2 ± 25.91 |
| 13                |                                      | 355 ± 24.59  | 322.8 ± 24.10 | 253.8 ± 23.45 | 231.4 ± 23.48 |
| Pioglitazone      |                                      | 402.2 ± 28.7  | 363.4 ± 26.08 | 302.4 ± 26.87 | 232.2 ± 20.53 |
| Metformin         |                                      | 441.8 ± 18.71 | 399.4 ± 17.72 | 289.4 ± 18.46 | 219.6 ± 18.40 |
| Vehicle control   |                                      | 304.2 ± 36.81 | 308.2 ± 36.85 | 309 ± 37.92  | 310.4 ± 39.57 |
| Diabetic control  |                                      | 322.2 ± 22.96 | 337 ± 23.59  | 347 ± 24.01  | 363.4 ± 24.0  |
| Normal control    |                                      | 120.33 ± 7.76 | 125.66 ± 2.08 | 126.66 ± 3.05 | 129.33 ± 1.52 |
5-arylidene-3-benzyl-thiazolidine-2,4-diones] was confirmed by ANOVA, alloxan induced diabetic rat model and dunnet’s test. From this series compounds 25, 26 and 27 showed highest activity because of methoxy group as compared to standard rosiglitazone. The results of synthesized compounds presented in Table 10 (Grag et al. [14]).

Bhat et al. [15] synthesized a new series of thiazolidinediones derivatives derived from 5-arylidene-2,4-thiazolidinedione using Scheme 11. The In vitro antidiabetic activity of synthesized compound [5-(4-methoxy-benzylidene)-2,4-dioxo-thiazolidin-3-yl]-acetic acid] and [5-(substituted)-2,4-dioxo-thiazolidin-3-yl]-acetic acid substituted ester were performed by alloxan induced tail tipping method and SLM. Among them compounds 28, 29, 30, 31, 32, 33, 34, 35 and 36 found to be most active or higher than rosiglitazone and metformin using as standard drug. The results of most active derivatives showed in Table 11 (Bhat et al. [15]).

Jawale et al. [16] synthesized innovative chain of thiazolidinediones derived from maleic anhydride and thiourea was treated with water using Scheme 12. The In vitro antidiabetic activity of synthesized compounds was performed by alloxan induced tail tipping method using wister rat, dunnet’s test and SLM model. Among them compounds 37, 38, 39 and 40 found to be significant activity metformin using as standard drug. The

### Table 7 Antidiabetic activities of synthesized compounds (mg/dl)

| Compounds | Blood glucose level (mean ± SE) |
|-----------|-------------------------------|
| 14        | 82.81 ± 1.115                |
| 15        | 86.31 ± 0.993                |
| 16        | 87.21 ± 1.233                |
| 17        | 97.91 ± 1.870                |
| Rosiglitazone | 65.58 ± 1.013       |
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**Scheme 8** Synthesis of 2-(4-((2,4-Dioxothiazolidin-5-ylidene)methyl)-2-methoxyphenoxy)-N-substituted acetamide derivatives

| Compounds | R |
|-----------|---|
| 18        | ![Image] |
| 19        | ![Image] |
| 20        | ![Image] |
| 21        | ![Image] |
| 22        | ![Image] |

Table 8 Evaluation of hypoglycemic activity: effect of compound on % decrease in blood glucose in diabetic mice

| Compounds | 0 h   | 2 h   | 4 h   | 6 h   | 24 h  |
|-----------|-------|-------|-------|-------|-------|
| Control   | 252.53±4.254 | 4.74±0.68   | 7.9±4.32  | 13.43±2.68  | 3.18±4.35  |
| Pioglitazone | 250.75±5.21  | 31.07±6.74  | 37.48±5.37 | 45.41±3.67 | 10.3±6.53 |
| 18        | 252.79±2.85  | 29.34±4.53  | 36.52±5.43 | 46.64±4.52 | 6.70±6.51 |
| 19        | 252.19±4.35  | 24.7±3.97   | 34.76±6.51 | 37.89±5.43 | 5.19±7.74 |
| 20        | 254.38±4.53  | 26.64±5.28  | 34.26±5.67 | 37.05±4.62 | 4.19±5.43 |
| 21        | 253.60±5.64  | 22.9±4.72   | 35.6±5.53  | 40.41±5.97  | 3.87±6.53 |
| 22        | 252.73±5.23  | 29.01±6.54  | 36.47±4.65 | 39.21±5.74  | 3.0±3.75 |

**Scheme 9** Synthesis of \(N^3\)-dialylamino methyl 5-benzylidene 2,4-thiazolidinedione derivatives

| Compounds | R     | R\(_1\) |
|-----------|-------|---------|
| 23        | \(p\)-OCH\(_3\) | \(\text{C}_6\text{H}_5\text{N}\) \(\text{C}_2\text{H}_5\) |
| 24        | \(o\)-OCH\(_3\) | \(\text{C}_6\text{H}_5\text{N}\) \(\text{C}_2\text{H}_5\) |
results of most active derivatives showed in Table 12 (Jawale et al. [16]).

**Thiazolidinedione derivatives as antimicrobial agents**

Long-ago, contagious diseases caused by multidrug-resistant microorganisms have become a serious issue, representing a growing threat to human health and being a major problem in many countries worldwide. There has been a significant increase in clinical drug resistance over the past few decades, owing to exploitation of antimicrobial agents, thus many infectious disease can no longer be treated successfully with general anti-infective agents [17]. Modern therapies and management technique such as bone marrow or solid-organ transplants, and newer much aggressive chemotherapy have resulted in a rapidly inflating number of immune-suppressed patient. So, in order to meet above mentioned challenges, there is an urgent need for the development of novel antimicrobial agents [18].

In this study, Nawale et al. [19] synthesized a new series of 5-Substituted 2,4-thiazolidinedione derivatives (Scheme 13) and evaluated for in vitro antimicrobial

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**Table 9 Hypoglycemic activity of synthesized derivatives**

| Compounds | Dose (mg/kg) | Mean blood glucose level (mg/dl) | % reduction in blood glucose level |
|------------|-------------|----------------------------------|----------------------------------|
|            |             | Before 1st dose | After 2 h | After 4 h | After 2 h | After 4 h |
| 23         | 50          | 400              | 56       | 48       | 86       | 88       |
| 24         | 50          | 275              | 63       | 79       | 72       | 65       |
| Rosiglitazone | 50        | 400              | 56       | 48       | 86       | 88       |

**Scheme 10 Synthesis of 5-Substituted-arylidene-3-substituted-benzyl-thiazolidine-2,4-dione derivatives**

| Compounds | R   | R1   |
|-----------|-----|------|
| 25        | 4-NO2 | 4-OCH3 |
| 26        | 4-Cl  | 4-OCH3 |
| 27        | 4-Cl  | 2-Cl  |

**Table 10 Hypoglycemic activity of synthesized derivatives**

| Treatment (mg/kg) | Blood glucose level (mg/dl) |
|-------------------|-----------------------------|
|                   | 0 day                      | 3rd day | 5th day | 7th day     |
| 25                | 86.11 ± 0.98               | 85.67 ± 0.58 | 84.68 ± 0.54 | 86.23 ± 0.48 |
| 26                | 188.23 ± 1.14              | 189.56 ± 0.98 | 185 ± 0.86    | 182.36 ± 1.25* |
| 27                | 189.35 ± 1.18              | 206.38 ± 0.86 | 192.30 ± 1.2  | 188.36 ± 1.23  |
| Rosiglitazone     | 194.99 ± 1.70              | 207.45 ± 0.69 | 189.64 ± 1.33 | 172.38 ± 2.24 |

* indicates high reduction in glucose level after seven days
activity against two species of Gram-positive bacteria, *Bacillus subtilis*, *Staphylococcus aureus* and Gram-negative bacteria, *Pseudomonas aeruginosa* using broth dilution method. Among the synthesized derivatives, compounds 41, 42, 43 and 44 exhibited highest activity on all tested microorganisms. The results of synthesized compounds presented in Table 13 (Nawale et al. [19]).

Nastas et al. [20] synthesized a series of novel 5-(Chromene-3-yl)methylene-2,4-thiazolidinedione derivatives as presented in Scheme 14 and tested for its in vitro antimicrobial potency towards Gram-positive bacteria (*Listeria monocytogenes*, *Staphylococcus aureus*) and Gram-negative bacteria (*Escherichia coli*, *Salmonella typhi*) pathogenic bacteria and fungi (*Candida albicans*) using broth dilution method and the disk diffusion method. Among the synthesized derivatives, compounds 45, 46 and 47 antimicrobial activity against all tested
bacteria and fungi. The results of most active derivatives showed in Table 14 (Nastas et al. [20]).

Moorthy et al. [5] synthesized a series of novel imidazolyl thiazolidinedione derivatives (Scheme 15) and screened them for their in vitro antimicrobial activity towards Gram-positive (S. aureus, S. epidermidis, M. luteus, B. cereus) and Gram-negative (E. coli, P. aeruginosa, K. pneumonia) bacteria and fungi (A. niger, A. fumigates). They were compared with standard drug ciprofloxacin and ketoconazole. Among the synthesized derivatives, compound 48 [Methyl-2-(4-((3-(2-methoxy-2-oxoethyl)-2,4-dioxothiazolidin-5-ylidene)methyl)1H-imidazol-1-yl)acetate] showed potent activities towards S. aureus, S. epidermidis, E. coli, P. aeruginosa, A. niger and A. fumigates and 49 [Methyl-2-((2,4-dioxothiazolidin-5-ylidene)methyl)-1H-imidazol-1-yl)acetate] showed potent activities towards S. aureus, S. epidermidis, E. coli, P. aeruginosa, A. niger and A. fumigates and 49 [Methyl-2-((2,4-dioxothiazolidin-5-ylidene)methyl)-1H-imidazol-1-yl)acetate], 50 [Methyl-2-(2-((3-(2-methoxy-2-oxoethyl)2,4-dioxothiazolidin-5-ylidene)methyl)1H-imidazol-1-yl)acetate] and 51 [5-(isocyanatomethyl)thiazolidine-2,4-dione] showed good activity against all microorganism. The results of synthesized compounds presented in Table 15 (Moorthy et al. [5]).

Alagawadi et al. [21] designed some novel derivatives of imidazole fused with thiazolidine-2,4-dione and evaluated them for their antibacterial activity against
Gram-positive bacteria *Staphylococcus aureus* (*S. a*), *Enterococcus faecalis* (*E. f*) Gram-negative bacteria *Escherichia coli* (*E. c.*) *Pseudomonas aeruginosa* (*P. a.*) and antifungal activity *Candida albicans* (*C. a*), *Cryptococcus neoformans* (*C. n.*), *Aspergillus flavus* (*A. f.*) and *Aspergillus niger* (*A. n.*) Among the screened compound the MIC value of compound 52 [5-[2-(3,4,5-trimethoxyphenyl)-6-(4-bromophenyl)imidazo[2,1-b][1,3,4]thiazol-5-yl] methylidene]-1,3-thiazolidine-2,4-dione], 53 [5-[2-(3,4,5-trimethoxyphenyl)-6-(4-chlorophenyl)imidazo[1-b][1,3,4]thiazol-5-yl]methylidene]-1,3-thiazolidine-2,4-dione (Scheme 16), 54 [N-[(dimethylamino)
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Scheme 14: Synthesis of 5-(Chromene-3-yl)methylene-2,4-thiazolidinediones

Table 14 Antimicrobial activity of 5-(Chromene-3-yl)methylene-2,4-thiazolidinediones

| Compounds | R   | Ar            |
|-----------|-----|---------------|
| 45        | H   | C₈H₁₀O        |
| 46        | CH₃ | C₇H₈         |
| 47        | H   | C₈H₆NO₂      |

Table 14 shows the antimicrobial activity of 5-(Chromene-3-yl)methylene-2,4-thiazolidinediones against Gram-positive, Gram-negative, and fungal strains. The compounds were evaluated at various concentrations, and the results are presented in the table.

Khan et al. [22] designed some novel biphenyl tetrazole thiazolidinedione derivatives (Scheme 18) and evaluated for their antimicrobial activity against bacterial strain...
Antimicrobial activity result indicated that among the synthesized derivatives 56 [(E)-3-((20-(1H)-tetrazol-5-yl)biphenyl-4-yl)methyl]-5-(4-chlorobenzylidene)thiazolidine-2,4-dione], 57 [(E)-3-((20-(1H)-tetrazol-5-yl)biphenyl-4-yl)methyl]-5-(2,6-dichlorobenzylidene)thiazolidine-2,4-dione] and 58 [(E)-3-((20-(1H)-tetrazol-5-yl)biphenyl-4-yl)methyl]-5-(2,6-dichlorobenzylidene)thiazolidine-2,4-dione]
showed potent in vitro antimicrobial activity. The results of most active derivatives showed in Table 17 (Khan et al. [22]).

Liu et al. [23] synthesized a series of new compound bearing 2,4-thiazolidinedione and benzoic moiety as presented in Scheme 19 and screened for their in vitro antimicrobial activity against bacterial strain (Staphylococcus aureus and Escherichia coli). Antimicrobial activity result indicated that among the synthesized derivatives, compounds 59, 60, 61, 62 and 63 showed highest in vitro growth of inhibition against bacterial strains. The results of synthesized compounds presented in Table 18 (Liu et al. [23]).

Purohit et al. [24] synthesized a series of novel 3,5-disubstituted thiazolidinediones derivatives (Scheme 20) and evaluated its antibacterial activity against Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumonia, Escherichia coli and antifungal activity was performed against Candida albicans, Aspergillus niger, Aspergillus flavus. The screening results were compared with ciprofloxacin, norfloxacin for antibacterial and fluconazole, griseofulvin for antifungal activity respectively. Among the synthesized compounds 64, 65, 66 and 67 showed highest antimicrobial potency and their structure were. The significant results of these compounds are presented in Table 19 (Purohit et al. [24]).
Sharma et al. [25] synthesized a series of novel \( N\-(5\text{-arylidene }-2\text{-}(4\text{-chlorophenyl})\text{-4-oxothiazolidin-3-yl}) \) isonicotnamide derivatives by knoevenagel condensation using Scheme 21 and assayed for antibacterial activity against *Escherichia coli*, *Staphylococcus aureus*, *Bacillus subtilis* and antifungal activity against *Candida albicans*, *Aspergillus niger*, *Saccharomyces cerevisiae* using turbidimetric method. Among the synthesized compounds 68

![Scheme 17 Synthesis of \( N\-[(\text{Dimethylamino)methylidene]-5\-[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]-6-arylimidazo[2,1-b][1,3,4]thiadiazole-2-sulfonamide \)](image)
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(N-(5-benzylidene-2-(4-chlorophenyl)-4-oxothiazolidin-3-yl)isonicotinamide), 69 (N-(2-(4-chlorophenyl)-5-(furan-2-ylmethylene)-4-oxothiazolidin-3-yl)isonicotinamide) and 70 (N-(5-(2-nitrobenzylidene)-2-(4-chlorophenyl)-4-oxothiazolidin-3-yl)isonicotinamide) result in wide spectrum antimicrobial activity against all the test bacteria and fungi using ciprofloxacin and clotrimazole as a standard drug respectively. The results of synthesized compounds presented in Table 20 (Sharma et al. [25]).

![Scheme 18 Synthesis of Biphenyl tetrazole-thiazolidinediones](image)

| Compounds | Ar |
|-----------|----|
| 56        | ![Structure](image) |
| 57        | ![Structure](image) |
| 58        | ![Structure](image) |

**Table 17 Antibacterial activities of synthesized compounds**

| Compounds | MIC ± SLM (μg/ml) |
|-----------|-------------------|
|           | E. coli           | B. subtilis       |
| 56        | 20.75 ± 1.55      | 35.41 ± 2.41     |
| 57        | 19.41 ± 1.27      | 26.00 ± 1.96     |
| 58        | 8.58 ± 0.42       | 8.42 ± 0.51      |
| Ciprofloxacin | 25.00 ± 0.95 | 50.00 ± 1.75 |
Scheme 19 Synthesis of 4-((Z)-5-((4-((E))-3-Oxo-3-phenylprop-1-en-1-yl)benzylidene)thiazolidin-3-yl)methyl)benzoic acid

| Compounds | R   |
|-----------|-----|
| 59        | H   |
| 60        | 2-Cl|
| 61        | 2-Br|
| 62        | 2-OCH₃|
| 63        | 3-OH|
The future of anti-inflammatory compound lies in the development of orally active drugs that decreases production or activities of pro-inflammatory cytokines. Anti-inflammatory compounds are normally used for curing of different infectious conditions. Therefore, the rate of incidence of disease limits its clinical use. Thus here is requirement of designing advance drugs with improved activity and long term relieve from chronic inflammatory condition [26]. The complete knowledge and understanding of the pivotal role of inflammation in seemingly untreated diseases has resulted in development of novel anti-inflammatory agents [27].

Table 18 Inhibitory activities of novel compounds against bacteria

| Compounds     | S. aureus | E. coli |
|---------------|-----------|---------|
|               |           |         |
| 59            | 1         | 2       |
| 60            | 1         | 2       |
| 61            | 2         | 4       |
| 62            | 2         | 4       |
| 63            | 2         | 4       |
| Norfloxacin   | 2         | 2       |
| Oxacillin     | 1         | 1       |

Thiazolidine-2,4-dione derivatives as anti-inflammatory agents

| Compounds | R₁ | R₂        |
|-----------|----|----------|
| 64        | H  | 4-chloro  |
| 65        | 2-hydroxy | H       |
| 66        | 4-hydroxy | 4-chloro |
| 67        | 4-hydroxy | 2-chloro |

Table 19 Antimicrobial activities of synthesized compounds

| Compounds | Minimum inhibitory concentration (MIC μg/ml) |
|-----------|---------------------------------------------|
|           | S. aureus | E. faecalis | K. pneumonia | E. coli | C. albicans | A. niger | A. flavus |
| 64        | 4         | 4           | 250          | 500     | 16          | 16       | 8         |
| 65        | 4         | 31.25       | 62.5         | 62.5    | 31.5        | 1        | 8         |
| 66        | 2         | 4           | > 500        | > 500   | 4           | 8        | 8         |
| 67        | 1         | 1           | 62.5         | 62.5    | 4           | 4        | 2         |
| Ciprofloxacin | 2  | 2            | 1           | 2       | –           | –        | –         |
| Norfloxacin  | 10    | 3.1          | 0.1         | 10      | –           | –        | –         |
| Fluconazole  | –      | –            | –           | –       | 16          | 8        | 8         |
| Griseofulvin | –      | –            | –           | –       | 500         | 100      | 7.5       |

Scheme 20 Synthesis of 3,5-Disubstituted thiazolidine-2,4-diones
Youssef et al. [26] synthesized some novel active pyrazolyl-2,4-thiazolidinedione derivatives (Scheme 22) followed by their in vitro anti-inflammatory evaluation. Among them, compounds 71 and 72 [(Z)-3-allyl-5-((3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl(methylene)thiazolidine-2,4-dione] showed moderate to good anti-inflammatory activity using celecoxib as standard and turpentine oil as control. The results of potent derivatives presented in Tables 21, 22 and 23 (Youssef et al. [26]).

Ma et al. [28] synthesized a series of novel 5-benzylidene thiazolidine-2,4-dione derivatives as presented in Scheme 23 and screened for in vitro inflammation reduction activity. Among the synthesized derivatives, compounds 73 [(Z)-2-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenoxy)-N-(3-fluorophenyl)acetamide], 74 [(Z)-N-(3-chlorophenyl)-2-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenoxy)acetamide] and 75 [(Z)-2-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenoxy)-N-(naphthalene-1-yl)acetamide] were found to be most active anti-inflammatory agent compared to indomethacin as the standard. The results of potent compounds are accessible in Table 24 (Ma et al. [28]).

**Table 20 Antimicrobial activities of synthesized compounds**

| Compounds | Minimum inhibitory concentration (MIC) in μg/ml |
|-----------|-----------------------------------------------|
|           | E. coli | B. subtilis | S. aureus | A. niger | C. albicans | S. cerevisiae |
| 68        | 1.25    | 1.25        | 0.62      | 0.62     | 0.31        | 1.25         |
| 69        | 0.62    | 0.31        | 0.62      | 0.62     | 0.15        | 0.62         |
| 70        | 0.31    | 0.62        | 0.31      | 0.62     | 0.15        | 0.31         |
| Ciprofloxacin | 0.15    | 0.25        | 0.01      | –        | –           | –            |
| Clotrimazole      | –      | –          | –        | 0.10     | 0.30        | 0.20         |

Thiazolidinedione derivatives as anticancer agents

Cancer is a genetic disorder that has always been a major threat all over the world and has been characterized by proliferation of abnormal cells and exhibiting an increasing mortality rate globally and being characterized by
such formation of abnormal cells and spreading through metastasis to different organs [29, 30]. Currently available treatment (chemotherapy and radiotherapy) for most types of cancer only provide temporary therapeutic benefits as well as being limited by a narrow therapeutic index, remarkable toxicity and acquired resistance [31]. In recent times, advance in clinical researches for anticancer agents have been increased and as neoplastic cells are the anomalous proliferation of cells in the body which cause cancer, various effective compounds derived

![Chemical structures and reactions](image)

**Scheme 22** Synthesis of 3-Substituted benzyl-5-((3-substituted-1-phenyl-1H-pyrazol-4-yl)methylene)thiazolidine-2,4-diones

| Compound | R  | R1 |
|----------|----|----|
| 71       | NO2| Cl |
| 72       | H  | Cl |

**Table 21** Cyclooxygenase inhibition activity of synthesized compound

| Compounds | Concentration (Um) (no. of experiments) | COX-1 activity (% inhibition) | COX-2 activity (% inhibition) |
|-----------|----------------------------------------|------------------------------|------------------------------|
| 71        | 10 (3)                                 | 28.4 ± 11.6                  | 19.4 ± 8.2                   |
| 72        | 10 (3)                                 | 26.5 ± 6                     | 13.6 ± 1.1                   |
| Celecoxib | 10 (3)                                 | 0.3 ± 2.5                    | 30.8 ± 5.9                   |

**Table 22** Inflammation reduction results of synthesized compounds in Formalin induced rat paw edema bioassay

| Compounds | Volume of edema (ml) |
|-----------|----------------------|
|           | 0 h      | 1 h     | 2 h     | 3 h     | 4 h     |
| 71        | 0.31 ± 0.001 | 0.44 ± 0.01 (24)| 0.44 ± 0.01 (46)| 0.46 ± 0.003 (68)| 0.46 ± 0.02 (68)|
| 72        | 0.33 ± 0.02 | 0.41 ± 0.01 (53)| 0.42 ± 0.01 (63)| 0.46 ± 0.01 (72)| 0.49 ± 0.01 (66)|
| Control   | 0.31 ± 0.01 | 0.40 ± 0.01 | 0.55 ± 0.01 | 0.78 ± 0.01 | 0.78 ± 0.008 |
| Celecoxib | 0.31 ± 0.01 | 0.41 ± 0.005 (41)| 0.43 ± 0.02 (50)| 0.50 ± 0.005 (60)| 0.48 ± 0.03 (68)|

**Table 23** Inflammation reduction results of synthesized compounds in turpentine oil induced granuloma pouch bioassay in rat

| Compounds | Volume of exudates (ml) | % inhibition |
|-----------|-------------------------|--------------|
| 71        | 1.12 ± 0.06             | 51           |
| 72        | 1.12 ± 0.06             | 50           |
| Control   | 2.28 ± 0.07             | –            |
| Celecoxib | 1.05 ± 0.10             | 54           |
from natural products have been isolated and developed as anticancer agents. These chemical compounds are formulated with a view to create effective action with minimum side effects against cancer [32].

Patil et al. [33] developed a novel class of 5-benzylidene-2,4-thiazolidinediones using Scheme 24. The synthesized derivatives were screened for the anticancer activity against K-562 (human leukemia), MCF-7 (human breast cancer), HepG-2 (human hepatoma), PC-3 (human prostate cancer), GURAV (human oral cancer) and KB (human nasopharyngeal cancer) cell lines by SRB protein assay. Among this series, 76, 77, 78 and 79 displayed the most potent anticancer activity compared with doxorubicin. The results of synthesized compounds presented in Table 25 (Patil et al. [33]).

Anh et al. [34] designed a chain of novel chromony thiazolidinediones derived from knoevenagel condensation reaction between 3-formyl-7-methoxy chromone with 4-Hydroxybenzaldehyde Thiazolidine-2,4-dione + Piperidinebenzoate Toluene $\xrightarrow{\text{DMF, K$_2$CO$_3$}}$ 5-(4-Hydroxybenzalidene) thiazolidine-2,4-dione + R$\xrightarrow{\text{Cl, EtN,CH$_2$Cl$_2$}}$ 2-Chloro chloride, 5-(4-Hydroxybenzalidene) thiazolidine-2,4-dione (76-79)

Table 24 Anti-inflammatory activities of synthesized derivatives

| Compounds | R$_1$ | R$_2$ | No inhibition (%) ± SD |
|-----------|-------|-------|------------------------|
| 73        | 3-fluro | H     | 41.5 ± 3.1             |
| 74        | 3-chloro | H     | 80.9 ± 5.0             |
| 75        | Naphthalene-1-yl | H | 70.9 ± 13.6 |
| Indomethacin |       |       | 63.2 ± 4.0             |

Scheme 24 Synthesis of 5-Benzylidene-2,4-thiazolidinedione derivatives
different thiazolidinedione derivatives as presented in Scheme 25. These synthesized derivatives were screened for their cytotoxic activity against Hep-G2 (heptocellular carcinoma), HC-60 (acute promyeloid carcinoma), KB (epidermoid carcinoma), LLC (lewis lung carcinoma), LNCaP (hormone dependent prostate carcinoma), MCF-7 (breast cancer), SW-480 (colon adenocarcinoma) cell lines using the MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide] assay. In this series compounds 80, 81 and 82 showed highest cytotoxic activity against cancer cell lines. The results of potent compounds are presented in Table 26 (Anh et al. [34]).

Kumar et al. [35] synthesized a series of novel 3-(substituted aryl)-1-phenyl-1H-pyrazolyl-2,4-thiazolidinedione derivatives using Scheme 26. These synthesized derivatives were screened for their cytotoxic activity against lung and breast cancer cell lines using standard doxil. In this series 83 and 84 showed highest cytotoxic activity against cancer cell lines. The results of potent compounds are presented in Table 27 (Kumar et al. [35]).

### Thiazolidinedione derivatives as antioxidant agent

Free radicals produced in several biochemical reactions, cellular metabolism are negotiator for several infections
### Table 26 Cytotoxicity of synthesized thiazolidinediones

| Compounds | IC₅₀ (μg/ml) | HepG₂ | HC-60 | KB | LLC | LNCaP | LU-1 | MCF-7 | SW-480 |
|-----------|--------------|-------|-------|----|-----|-------|------|-------|--------|
| 80        | > 100        |       | 82.2 ± 4.5 | 44.1 ± 3.6 | 87.4 ± 6.3 | 77.4 ± 5.8 | 52.9 ± 3.4 | 66.0 ± 2.7 | 71.4 ± 3.6 |
| 81        | 86.3 ± 6.4   |       | 75.3 ± 3.9 | 84.6 ± 4.2 | > 100        | 81.6 ± 6.3 | > 100        | 32.8 ± 1.4 | 90.1 ± 4.8 |
| 82        | 78.4 ± 5.8   |       | 92.3 ± 5.3 | 74.1 ± 5.1 | 90.1 ± 7.7 | 84.2 ± 4.1 | 65.5 ± 4.1 | 52.7 ± 3.6 | 85.4 ± 7.4 |
| Ellipticine | 1.45 ± 0.08 | 0.56 ± 0.04 | 0.43 ± 0.05 | 0.98 ± 0.04 | 0.86 ± 0.06 | 1.29 ± 0.11 | 0.49 ± 0.04 | 0.64 ± 0.05 |

### Scheme 25 Synthesis of 5-((7-Methoxy-4-oxo-4H-chromen-3-yl)methylene) substituted thiazolidine-2,4-dione

### Scheme 26 Synthesis of 3-(Substituted aryl)-1-phenyl-1H-pyrazolyl-2,4-thiazolidinediones

| Compounds | Ar |
|-----------|----|
| 83        | H₂C-        |
| 84        | [Structure] |
and diseases like atherosclerosis, tumor as well as heart disease. Free radicals are not only formed by normal cellular processes but also produced by exposure of numerous chemical substances (polycyclic aromatic hydrocarbon, cadmium, lead, etc.), radiations, cigarette smoke, and higher obese food. Usually free radical development is stopped by beneficial compounds known as antioxidant. Antioxidants deactivate free radicals before they attack the cell. Natural antioxidants are body detoxifiers and natural cleansers. They convert toxins of body to harmless waste products. They protect body from many diseases like cancer, heart attack and absorb bad cholesterol. Synthetic antioxidants such as BHT (butylated hydroxytoluene) and BHA (butylated hydroxyanisole), are effective as antioxidants are also present and are used in several industries but there use has been limited because they can cause cancer as well as other side effects. So there use is decreased in food, cosmetic and pharmaceutical products. Thus, in present there is need for the oxidation inhibitor compounds [18, 36, 37].

Hossain et al. [37] synthesized a series of novel O-prenylated and O-geranylated derivatives of 5-benzylidene 2,4-thiazolidinedione by knoeveengal condensation as showed in Scheme 27 and evaluated for their antioxidant activity. Among the synthesized derivatives, compounds 85, 86, 87, 88 and 89 were found to be most active antioxidant agent. The significant results of potent compounds are given in Table 28 (Hossain et al. [37]).

Lupascu et al. [4] designed a chain of novel thiazolidinediones containing xanthine moiety (Scheme 28) and evaluated for antioxidant potential using in vitro models such as DPPH radical scavenging assay and ABTS [2,2-azino-bis-(3-ethyl benzothiazoline-6-sulfonic acid) radical scavenging assay method. Among the synthesized derivatives 90, 91, 92 and 93 showed highest antioxidant activity. The results of potent derivatives are given in Table 29 (Lupascu et al. [4]).

**Table 27 IC50 value of synthesized derivatives against cancer cell lines**

| Compounds | A549 (μM) | MCF-7 (μM) | DU145 (μM) |
|-----------|-----------|------------|------------|
| 83        | 05.12     | 09.16      | 43.17      |
| 84        | 06.83     | 4.44       | 59.29      |
| Doxil     | 07.92     | 08.12      | 07.22      |

**Table 28 Inhibition of DPPH radical by synthesized compounds**

| Compounds | R1 | R2   | R3   | R4   | IC50 (μM) |
|-----------|----|------|------|------|-----------|
| α-Tocopherol | H  | Hydroxyl | H  | H  | 2.3       |
| 85        | Methoxy | Hydroxyl | H  | H  | 2.49      |
| 86        | Methoxy | Hydroxyl | Methoxy | H  | 2.85      |
| 87        | Methoxy | PRO     | H  | H  | 17.89     |
| 88        | Methoxy | PRO     | Methoxy | H  | 4.08      |
| 89        | H    | GRO   | H  | H  | 9.8       |

**Scheme 27** Synthesis of 5-Benzylidene 2,4-thiazolidinediones

**Scheme 28** Synthesis of 5-Benzylidene 2,4-thiazolidinediones
there is a need for new drugs targeting enzymes essential to mycobacterium survival [41, 42].

Chilamakuru et al. [42] synthesized a series of novel 3,5-disubstituted-2,4-thiazolidinediones as presented in Scheme 29 and appraised for anti-tubercular activities with pyrazinamide and streptomycin as the standard drug. Among all the synthesized derivatives, compounds 94, 95 (3-(2-amino-5-nitrophenyl)-5-(4-methoxybenzylidene)-1,3-thiazolidine-2,4-dione), 96

Table 29 Antioxidant activities of the synthesized derivatives

| Compounds | EC₅₀ mg/ml |
|-----------|------------|
| 90        | 0.025 ± 0.0012 |
| 91        | 0.022 ± 0.0013 |
| 92        | 0.033 ± 0.0014 |
| 93        | 0.026 ± 0.0028 |
| Ascorbic acid | 0.0067 ± 0.0003 |
[3-tert-butyl-5-(4-methoxybenzylidene)-1,3-thiazolidine-2,4-dione] and 97 showed the maximum antitubercular activity against *Mycobacterium tuberculosis* H37Rv strain. The results of synthesized compounds presented in Table 30 (Chliamakuru et al. [42]).

Pattan et al. [43] integrating a series of novel substituted thiazolidinediones via knoevenageal condensation reaction as presented in Scheme 30 and evaluated for their antitubercular activities by middle book 7H9 agar medium assay with streptomycin as the standard drug. Among all the synthesized derivatives, compounds 98 [(Z)-N-(3-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenoxy)-2-oxopropyl)pyrazin-2-carboxamide] and 99 [(Z)-5-(4-methoxybenzylidene)-3-(2-oxo-2-(pyrazin-2-yl)ethyl)thiazolidine-2,4-dione] showed the maximum antitubercular activity against *Mycobacterium tuberculosis* H37Rv strain. The results of synthesized compounds presented in Table 31 (Pattan et al. [43]).

### Scheme 29 Synthesis of 3,5-Disubstituted-1,3-thiazolidine-2,4-dione

### Table 30 Anti-tubercular activity of synthesized derivatives

| Compounds | MIC μg/ml |
|-----------|-----------|
| 94        | 12.5      |
| 95        | 12.5      |
| 96        | 12.5      |
| 97        | 12.5      |
| Pyrazinamide | 3.125   |
| Streptomycin | 6.25    |

### Conclusion

Appraisal of literature reports reveals that thiazolidinediones and its derivatives represent an important class of compound in the medicinal field with various therapeutic potentials, i.e., antidiabetic, antimicrobial,
anti-inflammatory, anticancer, antioxidant and antituber-
cular, antiviral, anti-malarial, anti-HIV and anti-con-
vulsant activities etc. which created immense interest
among researchers to synthesized variety of thiazolidi-
ediones. This review focuses especially on synthesized
active compounds of thiazolidinediones having different
pharmacological activities playing an important role in
the medicinal field. These most active thiazolidinediones
derivatives may be taken as leads to discover novel agents
with therapeutic potential in the future.

### Authors' contributions
PKV designed and finalized the scheme; SA performed review work and ST
wrote the paper. All authors read and approved the final manuscript.

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### Table 31 Antitubercular activity of synthesized deriv-
atives

| Compounds | 25 μg/ml | 50 μg/ml | 100 μg/ml |
|-----------|----------|----------|-----------|
| 98        | Resistant | Resistant | Sensitive |
| 99        | Resistance | Resistance | Sensitive |
| Streptomycin | Sensitive | Sensitive | Sensitive |

### Scheme 30 Synthesis of 4-Substitutedacetyl-benzylidene-2,4-thiazolidinediones

### Competing interests
The authors declare that they have no competing interests.

### Ethics approval and consent to participate
Not applicable.

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### References
1. Yang Y, Hu X, Zhang Q, Zou R (2016) Diabetes mellitus and risk of fall
in older adult: a systematic review and meta-analysis. Age Ageing
45(6):761–767
2. Pattan SR, Kekare P, Patil A, Nikalje A, Kittur BS (2009) Studies on the syn-
thesis of novel 2,4-thiazolidinedione derivatives with ant diabetic activity.
Iran J Pharm Sci 5(4):225–232
3. Rekha S, Shantharam U, Chandy V (2011) Synthesis and evaluation of
novel thiazolidinedione anti-inflammatory activity. Int Res J Pharm
2(9):1–7
4. Lupascu FG, Dragostin OM, Foia L, Lupascu D (2013) The synthesis and
the biological evaluation of new thiazolidin-4-one derivatives containing
a xanthine moiety. Lenuta Profine Mol 18:9684–9703
5. Moorthy P, Ekambaram SP, Perumal SS (2014) Synthesis, characterization
and antimicrobial evaluation of imidazoyl thiazolidinedione derivatives.
Arabian J Chem 8:1–7
6. Unlusoy MC, Dundar OB, Alanlar N, Ertan R (2006) Synthesis and antimi-
crobial activity of some new 3-substituted
benzyl-5-(4-chloro-2-piperidin-1-ylthiazole-3-yl-methylene)-thiazolidine-2,4-dione derivatives. Turk J Chem 30:355–360
7. Darat PA, Aher SB (2016) Design and synthesis of novel thiazolidine-2,4-dione as hypoglycemic agents. J Saudi Chem Soc 196–210
8. Swapan D, Sivagani B, Manasa K, Rajiga G, Alagarsamy V (2016) Synthesis and evaluation of novel thiazolidinedione derivatives for antidiabetic activity. Int Res J Pharma 15–19
9. Badiger NP, Shashidhar N, Vaidya PN (2015) Novel 5-[(2-(4-fluorobenzyl)-6-aryl-1,3,4-thiadiazol-2-yl)methyl]thiazolidine-2,4-diones as potent antidiabetic agents. Int J Sci Eng Appl 4(2):24–29
10. Patil SD, Navale SL, Balasubramaniam V (2015) Evaluation of thiazolidinedione derivatives for acute toxicity and potential antidiabetic activity. Der Pharm Chem 7(5):216–223
11. Srikanth L, Raghunandan N, Srinivas P, Reddy GA (2010) Synthesis and evaluation of newer quinoline derivatives of thiazolidinedione for their ant diabetic activity. Int J Pharm Bio Sci 1:110–131
12. Nikaljea PGA, Choudharia S, Une H (2012) Design, synthesis and hypoglycemic study. Biomed Pharmacother 83:1146–1153
13. Jiwane SK, Singh VK, Namdeo KP, Prappap SK (2009) Synthesis of some novel 2,4-thiazolidinedione derivatives and their biological screening as ant diabetic agents. Asian J Chem 21:5068–5072
14. Garg A, Chawla P, Shubhini SA (2012) Substituted-arylidene-3 substituted-benzyl-thiazolidine-2,4-dione analogues as anti-hyperglycemic agents. Int J Drug Dev Res 4(3):141–146
15. Bhat BA, Ponnala S, Sahu DP, Tiwari P, Tripathi BK, Srivastava AK (2004) Synthesis and antihyperglycemic activity profiles of novel thiazolidinedione derivatives. Bioorg Med Chem 12:5857–5864
16. Jawale DV, Pratap UR, Rahuja N, Srivastava AK, Mane RA (2012) Synthesis and antihyperglycemic evaluation of new 2,4-thiazolidinediones having bimodal sulfonylurea moieties. Bioorg Med Chem 22:436–439
17. Vivekanand B, Mahendra Raj K, Murthyuyayyaswamy BHM (2015) Synthesis, characterization, antimicrobial, DNA-cleavage and antioxidant activities of 3-(5-chloro-2-phenyl-1H-indol-3-yl)methylquinoline-2(1H-thione) and its metal complexes. J Mol Struct. 1079:214–224
18. Martin APM, Machado P, Piovesan LA, Flores AFC, De Campos MMA, Scheidt C, Bonacorsco HG, Zanatta N (2008) Microwave-assisted synthesis and antimicrobial activity of 5-trihalomethyl-3-arylisoxazoles. Monatsh-Chem 139:985–990
19. Navale SL, Dhake AS (2012) Synthesis and evaluation of novel thiazolidinedione derivatives for antibacterial activity. Der Pharma Chemica 4(6):2270–2277
20. Nastasa CM, Duma M, Pirnau A, Vlase L, Tiperciuc B, Oniga O (2016) Development of new 5-(3-(5-(4-chloro-2-piperidin-1-ylthiazole-3-yl)methylene)-thiazolidine-2,4-dione derivatives. Arabian J Chem 4:465–472
21. Alagawadi KR, Alegao GC (2011) Synthesis, characterization and antimicrobial activity evaluation of new 2,4-thiazolidinediones bearing imidazo[1,2-b][1,3]thiadiazole moiety. Arabian J Chem 4:465–472
22. Khan FAK, Jadhav KS, Patil RH, Shinde DB, Arote RB, Sangshetti JN (2016) Biphenyl tetrazole-thiazolidinediones as novel bacterial peptide deformylase inhibitors: synthesis, biological evaluations and molecular docking study. Biomed Pharmacother 83:1146–1153
23. Liu XF, Zheng CJ, Sun LP, Liu KX, Piao HR (2011) Synthesis of novel chalcone derivatives bearing 2,4-thiazolidinedione and benzoic acid moieties as potential anti-bacterial agents. Eur J Med Chem 46:3469–3473
24. Purohit SS, Alman A, Shewale J (2012) Synthesis and antimicrobial activity of a new series of 3,5-disubstitutedthiazolidine-2,4-diones. Int J Pharm Pharm Sci 4(3):273–276
25. Sharma R, Vinay V (2012) Synthesis and antimicrobial activity of thiazolidinedione derivatives. Int J Sci Res Rev 1(1):57–66
26. Youssef AM, White MS, Villanueva EB, Ashmawy IM, Klegers A (2010) Synthesis and evaluation of novel pyrazolyl-2,4-thiazolidinediones as anti-inflammatory and neuroprotective agents. Bioorg Med Chem 18:2019–2028
27. Dinarello CA (2010) Anti-inflammatory agents: present and future. Cell 140:935–950
28. Ma L, Xie C, Ma Y, Liu J, Xiang M, Ye X, Zheng H, Chen Z (2011) Synthesis and biological evaluation of novel 5-benzylidenethiazolidine-derivatives 2,4-dione derivatives for the treatment of inflammatory diseases. J Med Chem 54:211–235
29. Danu AS, Shankargur P, Devi DR, Hari BNV (2012) Evaluation of in vitro antitumor activity of hydroxyalcohol extract of Tabernamontana divaricata. Asian J Pharm Clin Res 5(3):50–61
30. Arafa RK, Hegazy GH, Piazza GA, Abadi AH (2013) Synthesis and in vitro antiproliferative effect of novel quinoline-based potential anticancer agents. Eur J Med Chem 63:826–883
31. El-Damasy AK, Seo SH, Cho NC, Kang SB, Pae AN, Kim KS, Keum G (2013) Design, synthesis, in-vitro antiproliferative activity and kinase profile of new picolinamide based 2-amido and ureido quinoline derivatives. Eur J Med Chem 101:754–768. https://doi.org/10.1016/j.ejmech.2015.07.025
32. Merina N, Chandra JK, Jibon K (2012) Medicinal plants with potential anticancer activities: a review. Int Res J Pharm 3(6):26–30
33. Patil V, Tilekar K, Munj SM, Mohan R, Ramaa CS (2010) Synthesis and primary cytotoxicity evaluation of new 5-benzylidenethiazolidine-derivatives. Eur J Med Chem 45:4539–4544
34. Anh HLT, Cuc NT, Tai BH, Yen PH, Xuan N, Thao DT, Nam NH, Minh CV, Kiem PV, Kim YH (2015) Synthesis of chromonylthiazolidines and their cytotoxicity to human cancer cell lines. Molecules 20:1151–1160
35. Kumar KS, Reddy BM, Babu VH (2014) Synthesis of some novel 2,4-thiazolidinedione incorporated pyrazole derivatives as anticancer agents. Int J Pharm Sci 62(2):831–834
36. Feng L, Lv K, Liu M, Wang S, Zhao J, You X, Li S, Cao J, Guo H (2012) Eur J Med Chem 55:125–136
37. Hossain SU, Bhattachary S (2007) Synthesis of O-phenylened and O-geranylated derivatives of 2,4-thiazolidinediones and evaluation of their free radical scavenging activity as well s effect on some phase II antioxidant/detoxifying enzymes. Bioorg Med Chem Lett 17:1149–1154
38. Junior NS, Hyarc ML, Da Costa CF, Correa TA, Taveira AF, Araujo DP, Reis PPCF, Vicente FRC, De Almeida MV (2009) Preparation and antitubercular activity of lipophilic diamines and amino alcohols. Med Inst Oswaldo Cruz 104(5):703–707
39. Illango K, Arunkumar S (2011) Synthesis, antimicrobial and antitubercular activities of some novel trihydroxybenzamidoazetidin-2-one derivatives. Trop J Pharm Res 10(2):219–229
40. Thompson AM, Blaser A, Anderson RF, Shinde SS, Franzblau SG, Ma Z, Denny WA, Palmer BD (2008) Synthesis, reduction potential and anti-tubercular activity of ring A/B analogues of the bioreductive drug (65)-2-nitro-6-(4-(fluoromethyl)benzamidoxy)-6,7-dihydro-5H-imidaz[2,1-b][1,3]oxazine. J Med Chem 52(3):637–645
41. Bate AB, Kalin JH, Fooksman EM, Amorose EL, Price CM, Williams HM, Rodig MJ, Mitchell MO, Cho SH, Wang Y, Franzblau SG (2006) Synthesis and antitubercular activity of quaternized promazine and promethazine derivatives. Bioorg Med Chem Lett 17:1149–1154
42. Chilamakuru N, Shankarananth V, Rajakshar KR, Singirisetty T (2013) Synthesis, characterization and anti-tubercular activity of some new 3,5-disubstituted-2,4-thiazolidinediones. Asian J Pharm Clin Res 6(5):29–33
43. Pattan S, Kedar M, Pattan J, Dengale S, Sanap M, Gharate U, Shinde P, Sucheta et al. Chemistry Central Journal (2017) 11:130
Page 29 of 29