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BIOLOGICAL PROSPECTIVE OF 4-THIAZOLIDINONE: A REVIEW

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Keywords: 4-Thiazolidinone, chemistry of 4-thiazolidinone, Biological Potential

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ABSTRACT

Plan: *Biological prospective of 4-thiazolidinone*
Prologue*: 4-Thiazolidinones are derivatives of thiazolidine with a carbonyl group in the 4th position. Substitution on the 2nd, 3rd and 5th positions may be varied, but the greatest difference in the structure and properties is exerted by the group attached to the carbon atom on the 2nd position.*
Methodology: *4-Thiazolidinones exhibited broad spectrum of biological activities viz: anticancer, antimicrobial, antimycobacterial, antiviral, anti-HIV, analgesic, anti-inflammatory, antioxidant, anticonvulsant, antidiabetic, antimalarial, anti-hypertension, antiarrhythmic, antiprotozoal, hypolipidemic, etc.*
Outcome*: This study is an attempt to address the various biological potential of 4-thiazolidinone. Information provided in this manuscript may be useful for further investigations on this scaffold.*

1. INTRODUCTION

Design and synthesis of biologically active molecules is one of the main challenges in medicinal chemistry[1]. The importance of heterocyclic compounds has long been recognized in the field of medicinal chemistry. Heterocyclic compounds are an integral part of the chemical and life sciences and constitute a considerable quantum of the modern research that is being currently pursued throughout the world[2].

An essential component of the search for new leads in a drug designing program is the synthesis of molecules, which are novel yet resemble known biologically active molecules by virtue of the presence of some critical structural features. Certain small heterocyclic molecules act as highly functionalized scaffolds. 4-Thiazolidinone and its derivatives are important class of bioactive molecules[3]. 4-Thiazolidinone derivatives have attracted continuing interest over the years because of their diverse biological activities as described in the present review.

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2. Chemistry of 4-thiazolidinone

4-Thiazolidinones are derivatives of thiazolidine with a carbonyl group in the 4th position and formed by the attack of sulphur nucleophile on imine carbon followed by intramolecular cyclisation with elimination of water. Substituents in the 2nd, 3rd and 5th positions may be varied (Fig-I), but the greatest difference in the structure and properties is exerted by the group attached to the carbon atom in the 2nd position[4].

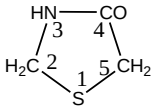
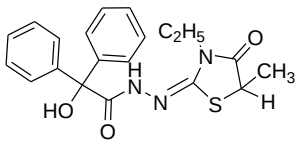


Fig-I 4-Thiazolidinone

3. Biological activities of 4-thiazolidinones

3.1. Antimicrobial activity

Guzeldemirci *et al.* synthesized a new 4-thiazolidinone derivatives and evaluated their antibacterial and antifungal activities against *S. aureus* ATCC 29213, *P. aeruginosa* ATCC 27853, *E. coli* ATCC 25922, *C. albicans* ATCC 10231, *C. parapsilosis* ATCC 22019, *C. krusei* ATCC 6258, *T. mentagrophytes var. erinacei* NCPF 375, *M. gypseum* NCPF 580 and *T. tonsurans* NCPF 245. Compounds **1** and **2** showed the highest antifungal activity against *C. parapsilosis* ATCC 22019 (MIC=16 µg/mL), *T. tonsurans* NCPF 245 (MIC=16 µg/mL) and compound **1** was most active against *M. gypseum* NCPF 580 (MIC=16 µg/mL)[5].



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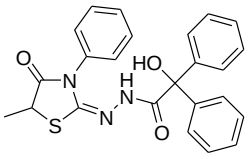
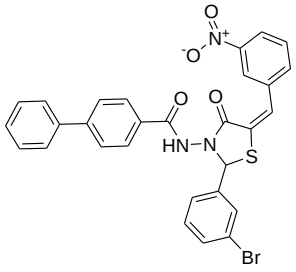


2

Novel derivatives of 4-thiazolidinone was synthesized by Deep *et al.* and evaluated for their *in vitro* antimicrobial activity against two Gram negative strains (Escherichia coli and Pseudomonas aeruginosa) and two Gram positive strains (Bacillus subtilis and Staphylococcus aureus) and fungal strain Candida albicans and Aspergillus niger. Among the synthesized derivatives, compound **3** (biphenyl-4-carboxylic acid [2-(3-bromophenyl)-5-(3-nitrobenzylidene)-4-oxo-thiazolidin-3-yl]-amide) and compound **4** (biphenyl-4-carboxylic acid [5-(3-bromobenzylidene)-2-(3-bromophenyl)-4-oxo-thiazolidin-3-yl]-amide) were found to be most effective antimicrobial compounds[6].



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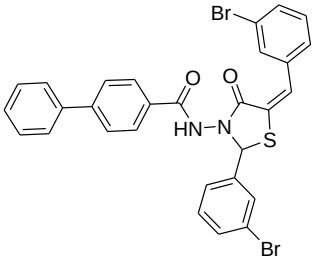
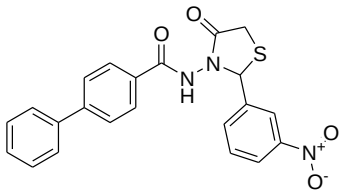


4

A series of biphenyl-4-carboxylic acid 2-(aryl)-4-oxo-thiazolidin-3-yl –amide were synthesized by Madhukar *et al.* and screened for its antimicrobial activity against two Gram negative strains (Escherichia coli and Pseudomonas aeruginosa) and two Gram positive strains (Bacillus subtilis and Staphylococcus aureus) and also against fungi Candida albicans and Aspergillus Niger. Among the synthesized derivatives, compound **5** was found to be most active one at 0.31 µg/mL[7].

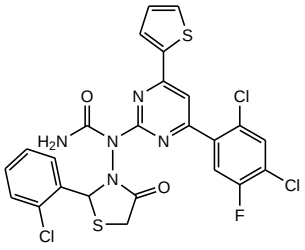


5

A series of 2-(substituted phenyl)-3-[4-(2,4-dichloro-5-fluorophenyl)-6-(2-thienyl) pyrimidine-2-yl-ureido]-5*H*/methyl/carboxymethyl-4-thiazolidinones were prepared by Shah *et al*.

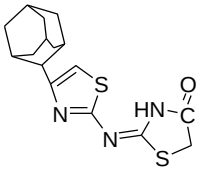
All the synthesized compounds were screened for their *in vitro* antibacterial activity against *Escherichia coli* (ATCC 8739), *Pseudomonas aureginosa* (ATCC 1539) and *Staphylococcus aureus* (ATCC 6538), *Bacillus substilis* (ATCC 6633) using the cup-plate agar diffusion method. The compounds were also tested for their antifungal activity using *Candida crusei* (ATCC 14243) and *Candida albicans* (ATCC 64550).

Streptomycin and griseofulvin were used as antibacterial and antifungal reference drugs respectively for comparison. The degree of inhibition varied with the test compound as well as with the bacterium. On the basis of the antibacterial activity data it could be concluded that some of the compounds possess considerable antibacterial activity due to the presence of methoxy, fluoro and chloro groups. However the activity of the tested compounds is less than that of streptomycin. On the basis of the antifungal activity data it could be concluded that some of the compounds possess good activity. Compound **6** was found to be most effective against all the microorganisms tested. However, none of the compounds was superior to standard used against them[8].



6

Omar *et al.* synthesized a class of structurally novel 4-thiazolidinone derivatives and tested their antimicrobial activity. As far as fungi are concerned, the majority of compounds showed the worst activity against *A. versicolor*, while *F. flavum* was the most sensitive species. All the compounds tested showed fungistatic activity at 0.52–2.38 x 10^{-2} µmol/ml and fungicidal at 1.05–3.35 x 10^{-2} µmol/ml against all the fungi tested. Compound **7** inhibited fungal growth at 0.60–2.38 x 10^{-2} µmol/ml while fungicidal activity was achieved at 2.38–3.35 x 10^{-2} µmol/ml. This compound showed the lowest antifungal activity, expressed as minimal inhibitory concentration (MIC) against *Penicillium funiculosum* (MIC 1.79 x 10^{-2} µmol/ml) *Aspergillus flavus* (MIC 1.79 x 10^{-2} µmol/ml) and *Aspergillus versicolor* (MIC 2.38 x 10^{-2} µmol/ml), moderate activity against *Trichoderma viride*, *Aspergillus fumigatus*, *Aspergillus niger* with MIC 1.19 x 10^{-2} µmol/ml, whereas it exhibited a strong effectiveness towards *Penicillium ochrochloron and Fulvia fulvum* (MIC 0.60 x 10^{-2} µmol/ml). In all cases, activity of compound **8** was better than activity of two reference drugs, bifonazole and ketoconazole. Compound **8** exhibited the highest antifungal potential with MIC at 0.52–1.57 x 10^{-2} µmol/ml and MFC at 1.05–2.09[9].



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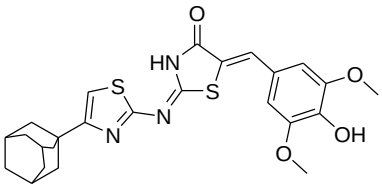
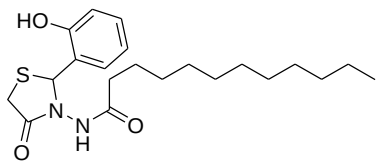


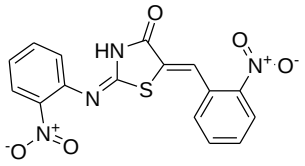
8

Ten new 4-thiazolidinone derivatives have been synthesized from the alkanoic acids and were evaluated for their *in vitro* antimicrobial activity against two Gram negative strains (*Escherichia coli* and *Pseudomonas aeruginosa)* and two Gram positive strains *(Bacillus subtilis* and *Staphylococcus aureus)* and fungal strain *Candida albicans* and *Aspergillus niger*.Among the synthesized derivatives, compound **9** was found to be most active one with MIC=1.25 µg/mL[10].



9

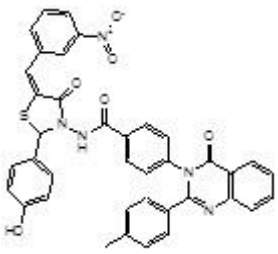
Chawla *et al.* designed and synthesized two series of novel 4-thiazolidinone derivatives and were screened for their *in vitro* antimicrobial activity against two Gram positive bacteria viz. *Bacillus subtilis* (MTCC 121), *Staphylococcus aureus* (MTCC 96), two Gram negative bacteria viz. *Escherichia coli* (MTCC 739), *Pseudomonas aeruginosa* (MTCC 2453), and one fungal strain viz. *Candida albicans* (MTCC 227). Compound **10** showed remarkable activity against *Candida albicans*[11].



10

Desai *et al.* synthesized a series of *N*-{5-[(2-chlorophenyl) methylene]-2-(4-hydroxyphenyl]-4-oxo(1,3-thiazolidin-3-yl)}{4-[2-(4-methylphenyl)-4-oxo(3-hydro quinazolin-3-yl)]phenyl} carboxamides and screened for its *in vitro* antibacterial and antifungal activities on *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Staphylococcus pyogenes*, *Candida albicans*, *Aspergillus niger*, and

Aspergillus clavatus. The results of antimicrobial activity revealed that compound **11** showed excellent activity against the *Escherichia coli* (25µg/ml) and *Staphylococcus aureus* (50µg/ml). Compound **12** was found to be active against *S.* p*yogenes* (50µg/ml) and (100µg/ml) *A. clavatus* respectively[12].



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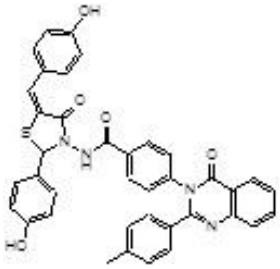

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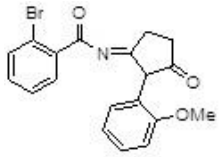
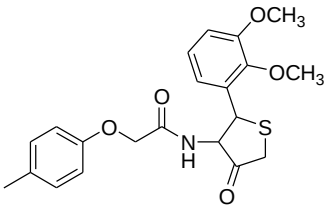


13

Saeed *et al.* synthesized some 2-aroylimino-3-aryl-thiazolidin-4-ones and were assayed *in vitro* for their antimicrobial activity against Gram positive and Gram negative bacteria. Compound **13** (towards *B. subtilis*: 34mm and *P. aueroginosa*: 33mm was found to exhibit promising activity and was better than standard drug, tetracycline[13].

Kumar *et al.* synthesized new derivatives of aryloxy-4-thiazolidones and studied their antimicrobial activity of synthesized compounds against bacteria- *Staphylococcus aureus, Bacillus subtilis, Escherichia coli* and *Pseudomonas aeruginosa,* and fungi- *Candida albicans* and *A. niger* using ampicillin and griseofulvin as reference drugs for bacteria and fungi. Compound **14** proved to be excellent antifungal agent against *A. niger* and was better than griseofulvin with zones of inhibition 17 mm and 15 mm respectively[14].



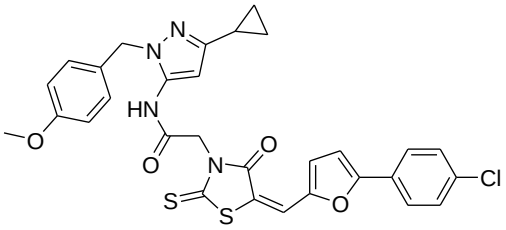
14

3.2. Anticancer activity

Chandrappa *et al.* (2010) synthesized a series of novel thioxothiazolidin-4-one derivatives and investigated their anticancer potential using mouse Ehrlich Ascites Tumor (EAT) as a model system.

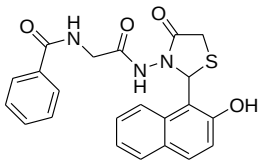
Results demonstrated that the compounds significantly reduced ascites tumor volume, cell number, and increased the life span of EAT-bearing mice. In addition, the compounds manifested strong antiangiogenic effects and suppressed tumor induced endothelial proliferation in the mice peritoneum.

Among the derivatives, *N*-(1-(4-methoxybenzyl)-3-cyclopropyl-1*H*-pyrazol-5-yl)-2-(5-((5-(4-chlorophenyl)furan-2-yl) methylene)-4-oxo-2-thioxothiazolidin-3-yl)acetamide (**15**) exhibited maximum tumor growth inhibition (56.25%) due to the presence of pyrazole with cyclopropyl ring[15].



15

Deep et al. synthesized a series of 4-thiazolidinone derivatives and tested *in vitro* for its antimicrobial and anticancer potential. Anticancer screening results indicated that compound **16** (IC_{50} = 15.18 µM) was the most active anticancer agent and was more potent than the standard drug, carboplatin (IC50 > 100 µM). Antimicrobial activity results indicated that **17** was the most active antimicrobial agent (pMICec = 2.14 µM)[16].



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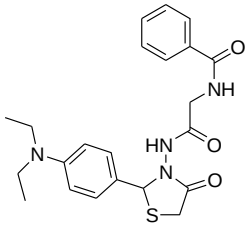
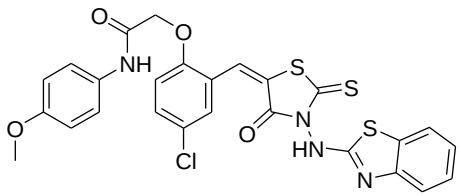


17

Havrylyuk *et al.* synthesized a novel series of 4-thiazolidinones with benzothiazole moiety and evaluated their anticancer activity using leukemia, melanoma, lung, colon, CNS, ovarian, renal, prostate and breast cancers cell lines. Among the tested compounds, 2-{2-[3-(benzothiazol-2-ylamino)-4-oxo-2-thioxothiazolidin-5-ylidenemethyl]-4-chloro phenoxy}-*N*-(4-methoxyphenyl)-acetamide (**18**) and 2-(4-chloro-2-((*E*)-((*E*)-2-(6-methylbenzo[d]thiazol-2-ylimino)-4-oxothiazolidin-5-ylidene) methyl)phenoxy)-*N*-(4-methoxyphenyl)acetamide (**19**) were found to be the most active candidates with average $logGI_{50}$ and logTGI values -5.38 and -4.45 and $logGI_{50}$ and logTGI values -4.97 and -4.20 respectively. The SAR study revealed that introduction of 4-chlorophenoxy- *N*-(4-methoxyphenyl)-acetamide group (compounds **18, 19**) in 5-position of 4-thiazolidinone core enhanced potency[17].



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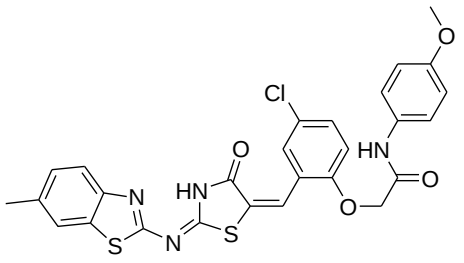
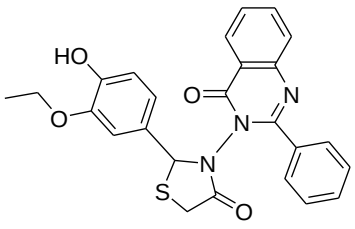


19

A new class of 4-thiazolidinones clubbed with quinozolinone nucleus has been synthesized by Deep et al. and were screened for their *in vitro* antimicrobial and anticancer potentials. Results of antimicrobial and anticancer study revealed that compounds **20** (pMICam = 1.69 μM/ml) and **21** (IC50 =12.83 μM) were found to be the most potent antimicrobial and anticancer agents respectively[18].



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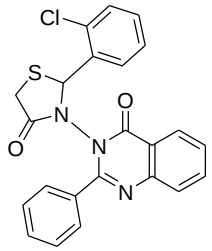
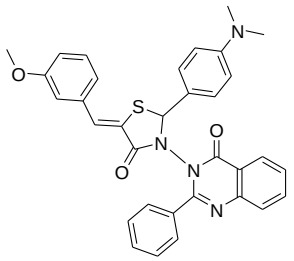


21

A series of 3-(5-(arylidene)-2-(aryl)-4-oxothiazolidin-3-yl)-2-phenylquinazolin-4(3*H*)-one derivatives was synthesized by Deep et al. and were evaluated for their *in vitro* antimicrobial and anticancer potentials. Antimicrobial properties of the title compounds were investigated against Gram positive and Gram negative bacterial as well fungal strains. 3-(5-(3-Methoxybenzylidene)-2-(4-(dimethylamino) phenyl)-4-oxothiazolidin-3-yl)-2-phenyl quinazolin-4(3*H*)-one (**22,** pMICam = 1.71 _M/ml) was found to be the most active antimicrobial agent. The anticancer evaluation of synthesized compounds against human colon (HCT116) cancer cell line indicated that 3-(5-(4-bromobenzylidene)-2-(3-chlorophenyl)-4-oxothiazolidin-3-yl)-2-phenylquinazolin-4(3*H*)-one (**23)** IC50 = 5.27 μM was the most active anticancer agent and was more potent than standard drug, 5-fluorouracil (IC50 = 6.00 μM) [19].



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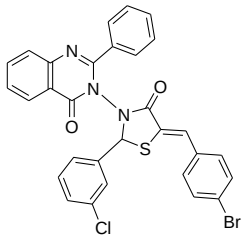
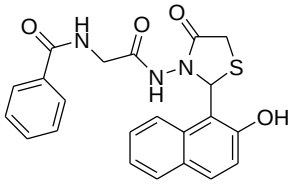


23

Deep et al. synthesized a series of 4-thiazolidinone derivatives and tested *in vitro* for its antimicrobial and anticancer potential. Synthesized compounds were found to be more potent antimicrobial agents than anticancer agents. Anticancer screening results indicated that compound **24** (IC_{50} = 15.18 µM) was the most active anticancer agent and was more potent than the standard drug, carboplatin (IC_{50} > 100 µM). Antimicrobial activity results indicated that **25** was the most active antimicrobial agent (pMICec = 2.14 µM) and may serve as an important lead for the discovery of novel antimicrobial agents[20].



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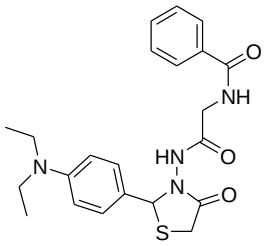
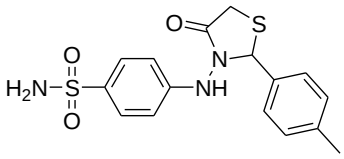


25

3.3. Analgesic and anti-inflammatory activity

In order to develop new selective cyclooxygenase-2 inhibitors, Unsal-Tan *et al.* synthesized a series of novel 2-aryl-3-(4-sulfamoyl/methylsulfonylphenylamino)-4-thiazolidinones. Their COX-1/COX-2 inhibitory activities were evaluated *in vitro*, using Screening Kit NS-398 and indomethacin as reference compounds. *In vitro* COX-1/COX-2 inhibition studies showed that the synthesized compounds inhibited COX-2 enzyme with a wide range of IC_{50} values (14-121 µM). Compounds possessing methyl group on the phenyl ring *i.e.* 2-(4-methylphenyl)-3-(4-aminosulfonylphenylamino)-4-thiazolidinone (**26**) and 2-(4-Methylphenyl)-3-(4-methylsulfonylphenylamino)-4-thiazolidinone (**27**) exhibited highly COX-2 inhibitory selectivity and potency (IC_{50} = 24.5 and 14.4 µM for **26** and **27** respectively)[21].



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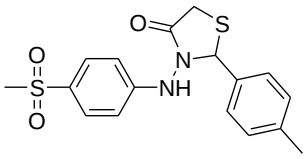
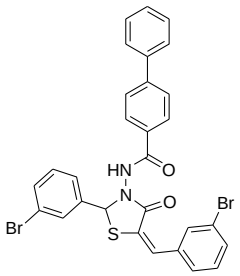


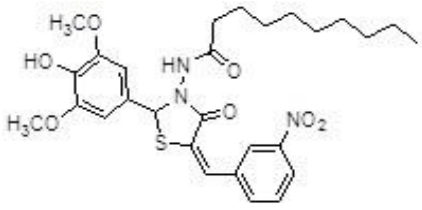
27

Deep et al. synthesized novel derivatives of biphenyl-4-carboxylic acid 5-(arylidene)-2-(aryl)-4-oxothiazolidin-3-yl amide and evaluated for anti-inflammatory activity. All compounds were screened for anti-inflammatory activity employing carrageenan test at the dose of 10 mg/kg and exhibited significant activities. The compound **28**, with a substitution of bromine on both the aromatic rings, was found to be the most potent anti-inflammatory agent with percentage inhibition of 44.59 and 55.73 at 2 h and 4 h, respectively[22].



28

Kumar *et al.* synthesized a series of decanoic acid [2, 5-disubstituted-4-oxo-thiazolidin-3-yl] amides and were evaluated for their anti-inflammatory, analgesic and antioxidant activities. The anti-inflammatory activity of the synthesized compounds was determined using the carrageenan-induced paw oedema method. All the compounds exhibited moderate to significant anti-inflammatory activity. Compound **29** with its electron releasing group substituents (four methoxy and two hydroxyl groups) was the most active compound of the series with a percentage activity of 44.84 (p value <0.01). Analgesic screening was performed using the acetic acid induced abdominal writhing test using Swiss albino mice. All the compounds exhibited significant analgesic activities. Compound **30** demonstrated the most potent activity with 69.82% (p value < 0.01) inhibition of writhing. The evaluation of antioxidant activities was carried out by the method of scavenging of hydrogen peroxide. All the synthesized compounds exhibited potent hydrogen peroxide scavenging activities. Decanoic acid [2-(3-nitro phenyl)-5-(3-nitro benzylidene)-4-oxo-thiazolidin-3-yl]amide (**31)** with two nitro groups was the most active with scavenging of hydrogen peroxide of 54.18 at 500 microgram per mL concentration[23].



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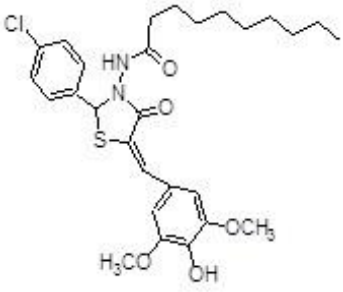

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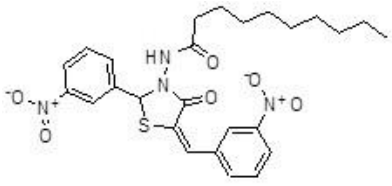
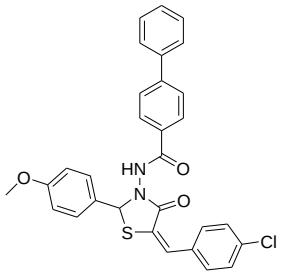


31

A series of novel *N*-[5-(arylidene)-2-(aryl)-4-oxo-thiazolidin-3-yl]-4-biphenylcarboxamide derivatives was synthesized by Deep *et al.* and evaluated for analgesic and anti-inflammatory activity. *N*-[5-(4-Chloro-benzylidene)-2-(4-methoxy-phenyl)-4-oxothiazolidin-3-yl]-biphenyl-4-carboxamide (**32)** showed comparatively good percentage of inhibition of edema than the other synthesized compounds. Similarly, all synthesized compounds were evaluated for analgesic activity. In the acetic acid-induced writhing, the entire test compounds showed the significant analgesic activity as compared to the standard drug. *N*-[2-(3-Nitro-phenyl)-5-(4-chlorobenzylidene)-4-oxothiazolidin-3-yl]-biphenyl-4-carboxamide (**33**) and N-[5-(4-Chloro-benzylidene)-2-(4-fluoro-phenyl)-4-oxothiazolidin-3-yl]-biphenyl-4-carboxylic acid amide (**34**) bearing two electron withdrawing groups *i.e.*, chloro and nitro **(33)** and fluoro and chloro **(34)** were found to be most potent with percentage protection of 46.25.[24]



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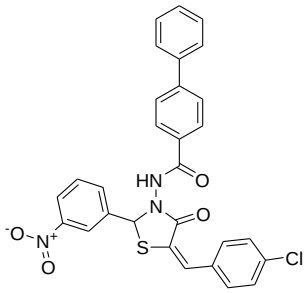

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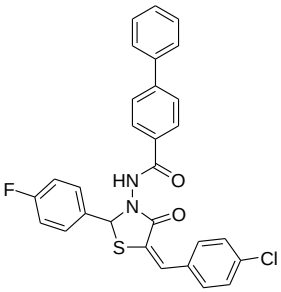
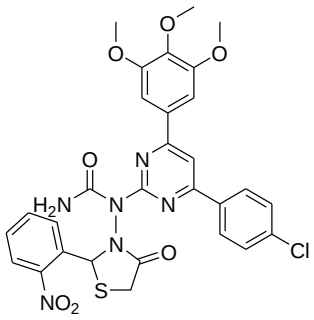


34

3.4. Antimycobacterial activity

Patel *et al.* synthesized a series of 2-aryl-3-[4-(4-chlorophenyl)-6-(3, 4, 5-trimethoxy-phenyl) pyrimidin-2-yl-ureido]-4-thiazolidinones and tested their antibacterial, antifungal and antituberculosis activities against different microorganisms. These derivatives were not active up to 100 to 200 µg/mL against *C. albicans* and H37Rv strain of *M. tuberculosis*. Among the synthesized derivatives, compounds **35, 36** and **37** showed very good zone of inhibition on different type of microorganisms. Compound **35** showed 20mm, 16mm and 21mm zone of inhibition for *E. coli*, *S. paratyphi* B and *Enterobacter*. Compound **36** showed 22 mm zone of inhibition for *S. aureus* and compound **37** showed 15mm zone of inhibition for *P. vulgaris*[25].



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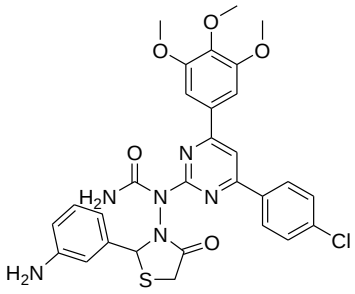

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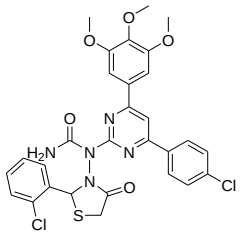
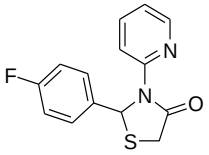


37

3.5. Antiviral activity

Hepatitis C virus (HCV) NS5B RNA polymerase is crucial for replicating the HCV RNA genome and is an attractive target for developing anti-HCV drugs. A novel series of 2, 3-diaryl-1, 3-thiazolidin-4-one derivatives was synthesized by Rawal *et al.* and evaluated for its ability to inhibit HCV NS5B. Among the synthesized derivatives, 2-(4-fluoro-phenyl)-3-pyridin-2-yl-thiazolidin-4-one (**38**) and 2-(2,6-dichlorophenyl)-3-(furan-2-ylmethyl)thiazolidin-4-one (**39**) emerged as most potent, displaying over 95% inhibition of NS5B RNA polymerase activity *in vitro*. Compounds **38** and **39** exhibited an IC_{50} of 31.9 µM and 32.2 µM, respectively, against HCV NS5B. All other derivatives also exhibited greater than 60% NS5B RdRp inhibition. Results indicated that changes at C-2, N-3 and C-5 position of 4-thiazolidinone scaffold with appropriate substitution may provide compounds with improved potency[26].



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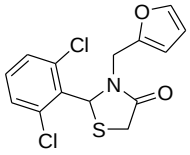
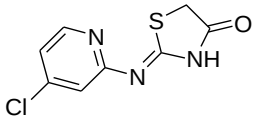


39

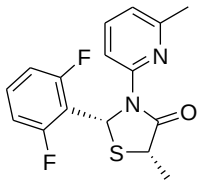
Kulabaş *et al.* performed the antiviral assays of 4-thiazolidinone derivatives against *Murine norovirus*, *Yellow fever virus*, *Enterovirus* and *Chikungunya* virus strains. EC_{50} values for all strains of these compounds were determined higher than 0.3 µM. Among the synthesized derivatives, compound 40 was found to be most active one[27].



40

3.6. Anti-HIV activity

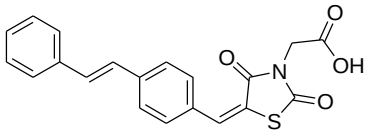
Rao *et al.* synthesized a novel series of 5-methyl-2,3-diaryl-1,3-thiazolidin-4-one derivatives and tested for its anti-HIV activity by determining their ability to inhibit the replication of HIV-1 (IIIB) or -2 (ROD) in MT-4 cells. Among the synthesized derivatives, cis-2-(2,6-difluorophenyl)-3-(6-methyl-pyridin-2-yl)-5-methyl-1,3-thiazolidin-4-one (**41**) was the most potent compound with EC_{50} = 1.90 (µM)[28].



41

3.7. Antioxidant activity

Ottana *et al.* synthesized a series of 5-arylidene-4-thiazolidinone derivatives and evaluated their antidiabetic and antioxidant activities. The *in vitro* aldose reductase (ALR2) inhibitory activity of compounds was assessed using the highly purified enzyme from bovine lens. D,L-glyceraldehyde was employed as substrate while sorbinil and epalrestat were used as reference drugs. The *in vitro* inhibition data show that the tested compounds proved to inhibit ALR2. Of these, (5-arylidene-2,4-dioxothiazolidin-3-yl)acetic acids were the best inhibitors, with IC_{50} values 0.25 µM (**42**) and 0.30 µM (**43**) thus confirming the crucial role played by the acetic acid group in the interaction with the enzyme. All compounds were more active than sorbinil. Compounds **42** and **43**, proved to be interesting inhibitors of the enzyme as well as excellent antioxidant agents that are potentially able to counteract the oxidative stress associated with both diabetic complications as well as other pathologies[29].



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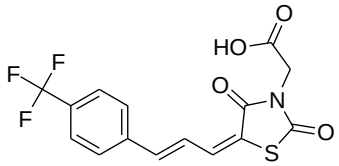
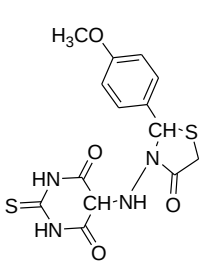


43

3.8. Anticonvulsant activity

Agarwal *et al.* synthesized a series of 5-[(2′-substituted -phenyl-4′-oxothiazolidin-3′-yl) amino]-2-oxo/thiobarbituric acid and the synthesized compounds were screened, *in vivo* for their anticonvulsant activity and acute toxicity studies. Compounds **44**, **45** and **46** having [2′-(*p*-methoxy)phenyl-4′-oxothiazolidin-3′-yl)amino], [2′-(m-methoxy-p-hydroxy) phenyl-4′-oxothiazolidin-3′-yl)amino]and 5-(2-(4-(dimethylamino)phenyl)-4-oxothiazolidin-3-ylamino)-2-thioxo-dihydropyrimidine-4,6(1*H*,5*H*)-dione substitution at fifth position of thiobarbituric acid have shown most potent response against MES test *i.e.* 90% ,80% and 70% protection as compared to the reference drugs phenytoin sodium, lamotrigine and sodium valproate. Compound substituted with two electron repelling group (m-methoxy-p-hydroxyphenyl-substituted) *i.e.* compound **46** showed better response towards pentylene tetrazole (PTZ) model than substituted with one electron repelling group (p-methoxy-substituted phenyl) *i.e.* compound **45** [30].



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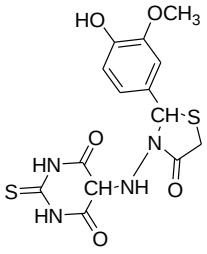

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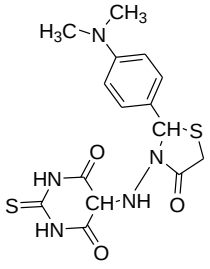
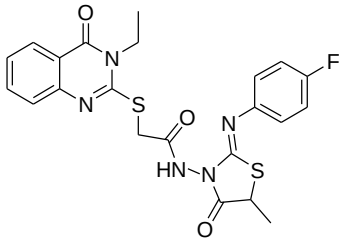


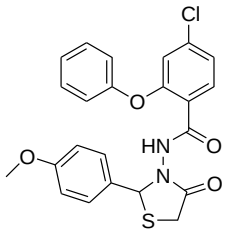
46

Two regioisomer series, 2-(3-ethyl-4(3*H*)-quinazolinone-2-ylmercaptoacetyl hydrazono)-3-alkyl/3-aryl-5-methyl-4-thiazolidinones and 2-arylimino-3-(3-ethyl-4(3*H*)-quinazolinone-2-ylmercaptoacetylamino)-5-methyl-4-thiazolidinones were synthesized by Gursoy *et al.* and were subjected to anticonvulsant activity tests using the maximal electroshock seizure (MES) and subcutaneous pentylenetetrazol seizure (ScMet) tests. Among the synthesized compounds, 4-fluorophenyl substituted thiazolidinone derivative (*Z*)-2-(3-ethyl-4-oxo-3,4-dihydroquinazolin-2-ylthio)-*N*-(2-(4-fluorophenyl imino)-5-methyl-4-oxothiazolidin-3-yl) acetamide **47** being promisingly active, showed 66% protection at 100 mg/kg[31].



47

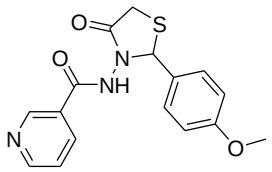
A new series of 4-chloro-N-(2-(substitutedphenyl)-4-oxothiazolidin-3-yl)-2-phenoxybenzamide derivatives were designed, synthesized by Faizi et al. and biologically evaluated as anticonvulsant agents. Compound **48**, 4-chloro-N-(2-(4-methoxyphenyl)-4-oxothiazolidin-3-yl)-2-phenoxybenzamide, with the best activity was selected for evaluation of other benzodiazepine pharmacological effects. This compound induced significant sedative-hypnotic activity. However, it does not impair the learning and memory in the experimental condition[32].



48

3.9. Antidiabetic activity

Two compounds (**49** and **50**) (*N*-[2-(4-methoxyphenyl)-4-oxothiazolidin-3-yl] nicotinamide) and (*N*-[2-(3,5-di-tert-butyl-4- hydroxy phenyl)-4-oxothiazolidin-3-yl]nicotinamide) were synthesized by Kishore *et al.* (2007) and were administered to Swiss albino mice with streptozotocin diabetes for 15 days. Concurrently, one group received nicotinic acid. In streptozotocin diabetic mice, both NAT1 (**49**) and NAT2 (**50**) produced a significant reduction in fasting blood glucose after 15 days' treatment. While the mean blood glucose was 205.9±7.9mg/dl before treatment, 15 days of treatment with NAT1 and NAT2 reduced it, respectively, to 100.1±6 and 124.9±8.6 mg/dl. In the diabetic control and nicotinic acid treated groups, the blood glucose levels after 15 days' treatment were 164.3±11 and 158±13 mg/dl respectively[33].



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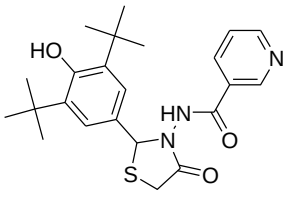
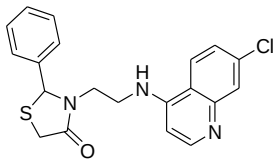


50

3.10. Antimalarial activity

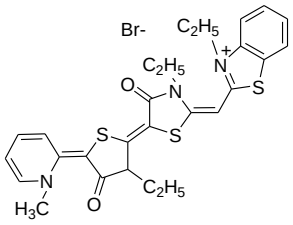
A series of new chloroquine heterocyclic hybrids containing either benzylamino fragment or *N*-(amino alkyl)thiazolidin-4-one moiety were synthesized by Rojas *et al.* (2011) and screened for their antimalarial activity against chloroquine (CQ)-sensitive 3D7 and multidrug-resistance Dd2 strains of *Plasmodium falciparum.* Although no compounds more active than CQ against 3D7 was found. Among the synthesized derivatives, 3-(2-((7-chloroquinolin-4-yl)amino)ethyl)-2-phenylthiazolidin-4-one (**51**), was more active than CQ (IC_{50} = 0.50 µM), with IC_{50} value 0.36 µM. Compound **51**, showing no more than 30% of cytotoxicity, has a selective activity against the parasite, and therefore good candidates for the *in vivo* test. A preliminary *in vivo* assay (4-day suppressive test) against *P. berghei* ANKA using 7-chloroquinoline-thiazolidinone hybrids at a dose of 10 mg/kg/day was carried out. Compound **51** was selected because this was the most active compounds and, at the same time, did not show nonspecific cytotoxicity. Compounds **51** inhibited 80% the parasite growth in infected mice[34].



51

Pudhom *et al.* synthesized 4-thiazolidinone derivatives of rhodacyanine and their *in vitro* antimalarial activities against *Plasmodium falciparum* K1 (chloroquine-resistant strain) as well as their *in vivo* activities against *P. berghei* in mice were determined.

The novel rhodacynines, **52** and **53**, possessing a benzothiazole moiety, were shown to have highly promising antimalarial activities. These substances are highly active *in vivo* with suppressions of parasitemia that approach 89% at dosages of 25 mg/kg/d (ip) [35].



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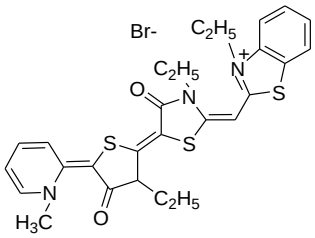
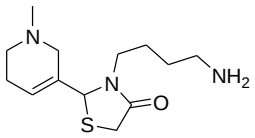


53

3.11. Antialzheimer activity

A series of novel *N*-alkyl/aryl substituted thiazolidinone arecoline analogues were designed and synthesized by Sadashiva *et al.* (2009) and subjected to *in vitro* muscarinic receptor binding studies using male Wistar rat brain membrane homogenate and extended to *in vivo* pharmacological evaluation of memory and learning in male Wistar rats (Rodent memory evaluation and plusmaze studies) to ascertain their applicability in dementia. Structure–activity relationship (SAR) can be drawn from the *in vitro* assay for the synthesized derivatives. Among all the synthesized compounds, four derivatives **54, 55, 56** and **57** showed greater affinity and potency towards the M1 receptor.



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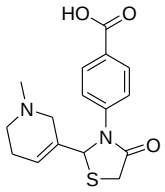

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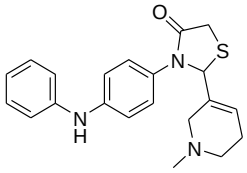

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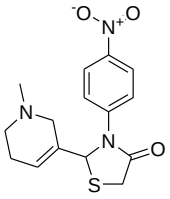
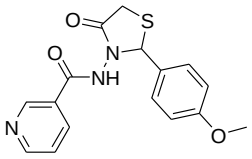


57

The remaining derivatives did not show any agonistic activity. The most potent compound **56** (Ki= 19 ± 1.97 µM and IC_{50}= 48 ± 6.23 µM) was one which was having biphenyl amine attached to nitrogen of thiazolidinone arecoline[36].

3.12. Hypolipidemic activity

Nampurath *et al*. synthesized three 4-thiazolidinones, two with nicotinamide (**58** and **59**) and one with 4-chlorophenoxyacetamide (**60**) side chains and evaluated their hypolipidaemic, hypoglycaemic activity in Swiss albino mice. Compounds **58** and **59** caused reduction of elevated triglycerides, cholesterol and glucose; **59** was effective only against triglycerides. Nicotinamide side chain might have contributed to the lipid lowering effect of both **58** and **59,** but the bulky group of the latter could have affected proper binding to the receptor sites, making it ineffective against elevated cholesterol. On the other hand, 4-chlorophenoxyacetamide side chain of **60** might have exerted powerful hypolipidaemic activity, despite the bulky substitution at C2. As antioxidants, **58** and **60** showed superior activity, compared to **59**. The thiazolidinone ring might be responsible for the lipid lowering effect, which was however, modified by the type of substitutions at C2 and *N* of the ring. After 20 days treatment, the serum triglyceride levels reduced significantly by 39.7, 41.6, 46 and 34.5%, respectively in **58, 59, 60** and nicotinic acid treated groups when compared to the high-fat control group. These groups had serum triglyceride levels similar to normal mice. The elevated serum cholesterol levels were brought back to normal by **58, 60** and nicotinic acid (by 29.2, 35.1 and 29.8%, respectively). However, **55** failed to reduce cholesterol. None of the treatments had any appreciable effect on serum HDL[37].



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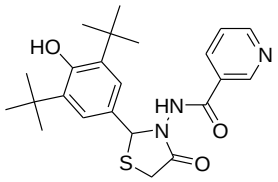

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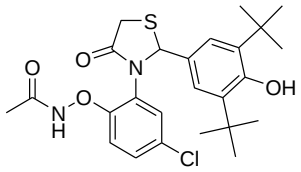

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4. CONCLUSION

This study is an attempt to address the various biological activities viz: anticancer, antimicrobial, antimycobacterial, antiviral anti-HIV, analgesic, anti-inflammatory, antioxidant, anticonvulsant, antidiabetic, antimalarial, anti-hypertension, antiarrhythmic, antiprotozoal, hypolipidemic, etc. Information provided in this manuscript may be useful for further investigations on this scaffold.

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