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Invited review

4-Thiazolidinones: The advances continue…

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ABSTRACT

The diversity in the biological response of 4-thiazolidinones has attracted the attention of many researchers to explore this framework for its potential. It is, therefore, of prime importance that the study of this topic and the development of new synthetic strategies should be based on the most recent knowledge, emerging from the latest research. This review is an endeavor to highlight the progress in the chemistry and biological activity of the 4-thiazolidinones, predominantly after 2006. The last section of the review encompasses the various patents granted on 4-thiazolidinone analogs/derivatives with World Intellectual Proprietary Organization (WIPO) and United State Patent Trademark Office (USPTO), particularly in the duration of the year 2000 to the year 2012.

1. Introduction

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. Jeyaraman and Avila have reviewed the importance of heterocyclic and bicyclic compounds as intermediates in the synthesis of several physiologically active compounds [1]. These compounds are also found to be useful as intermediates for the synthesis of a variety of heterocyclic compounds [2]. 4-Thiazolidinone derivatives have attracted continuing interest over the years because of their diverse biological activities, such as anti-inflammatory, anti-proliferative, antiviral, anticonvulsant, anti-diabetic, anti-hyperlipidemic, cardiovascular, anti-tubercular, antifungal, and antibacterial. Compounds such as; ralitoline (anti-convulsant), etozoline (anti-hypertensive), pioglitazone (hypoglycemic) and thiazolidomycin (activity against streptomyces species), based on this pharmacophore are already in the market. In recent years, 4-thiazolidinone derivatives with antitumor activity on leukemia, melanoma, lung, colon, CNS, ovarian, renal, prostate and breast cancers cell lines have become a promising area of research. Different researchers have reviewed the progress on the scaffold from time to time, such as Brown in 196 [3], Newkome et al. in 1977 [4], Singh et al. in 1981 [2], Abdel-Rahman et al. in 2001 [5], Verma et al. in 2008 [6], Hamama et al. in 2008 [7] and Jain et al. in 2012 [8]. Our group has also been continuously involved in researching this nucleus through chemical modifications with encouraging results [6,9–12]. The review summarizes current propensity in the 4-thiazolidinone synthetic chemistry and divulges the utility of this potent

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pharmacophore as a rich source of new compounds having promising biological activities. This assemblage recapitulates ongoing medicinal chemistry investigations worldwide, to explore novel chemical entities that can be useful in the treatment of many ailments.

2. Chemistry

The chemistry of 4-thiazolidinone was reviewed in depth by Brown in 1961 [3]. Thiazolidinones are a saturated form of thiazole, called thiazolidine, with a carbonyl group. 1,3-Thiazolidin-4-ones are heterocycles that have an atom of sulfur at position 1, a nitrogen at position 3 and a carbonyl group at position 4. New derivatives of 4-thiazolidinones have been obtained by modifications of the parent structure in several ways:

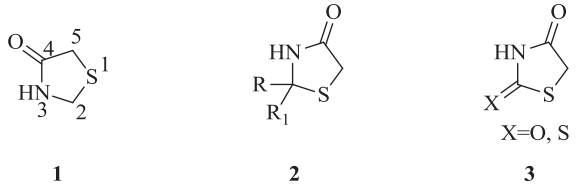
1. Substituents in the 2, 3 and 5-positions may be varied, but the greatest difference in structure and properties is exerted by the group attached to the carbon atom at the 2-position (R and R_1 in **2** or X in **3**, of Scheme 1),
2. Variations in the substituents attached to the nitrogen atom and the methylene carbon atom are possible for the structures represented by **2** and **3**,
3. The carbonyl group of 4-thiazolidinone is highly unreactive. However, in a few cases, 4-thiazolidinone on reaction with Lawesson's reagent gives corresponding 4-thione derivative [13].

The unsubstituted 4-thiazolidinones are usually solids, often melting with decomposition, but the attachment of an alkyl group to the nitrogen lowers the melting point. The 4-thiazolidinones not containing any aryl or higher alkyl substituents are somewhat soluble in water [3].

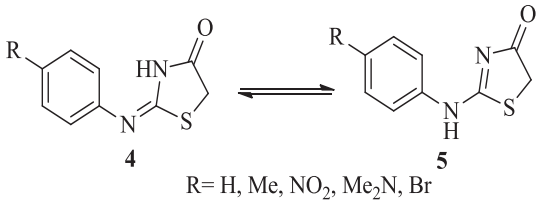
2.1. Stereochemistry

Various optical, geometrical and regioselective isomers [14–16] of 4-thiazolidinone derivatives have been reported by different workers. Ramsh et al. reported that 2-imino-4-thiazolidinone and its 2-aryl derivatives exist in the crystal state as the amino tautomers (Scheme 2) [17,18]. A detailed study of imino–amino tautomerism in 2- iminothiazolidin-4-one and its derivatives has also been reported by *Akerblom* [19]. The infrared spectroscopy data showed that in the crystal state, imino isomer is predominant whereas in the solution, amino isomer predominates [6].

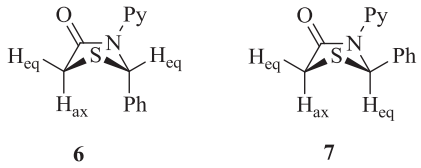
The 2,3-disubstituted 4-thiazolidinones exist as two diastereoisomers **6** and **7** (Scheme 3). Vigorita et al. conducted the conformational studies on various 2-aryl-3-(2-pyridyl)-4-thiazolidinones and found that the preferred configuration **6** is that in which the C(2) proton and one of the methylene protons are in *cis*-1,3 diequatorial relationship. This is due to the fact that the phenyl group prefers the axial orientation to avoid the steric crowding with pyridyl group [6,20].



Scheme 1. Structure of 4-thiazolidinone nucleus with substituents at various positions (**1**, **2**, **3**).



Scheme 2. Tautomerization of 2-imino-4-thiazolidinone (**4**, **5**).



Scheme 3. Stereochemistry of 4-thiazolidinones (**6**, **7**).

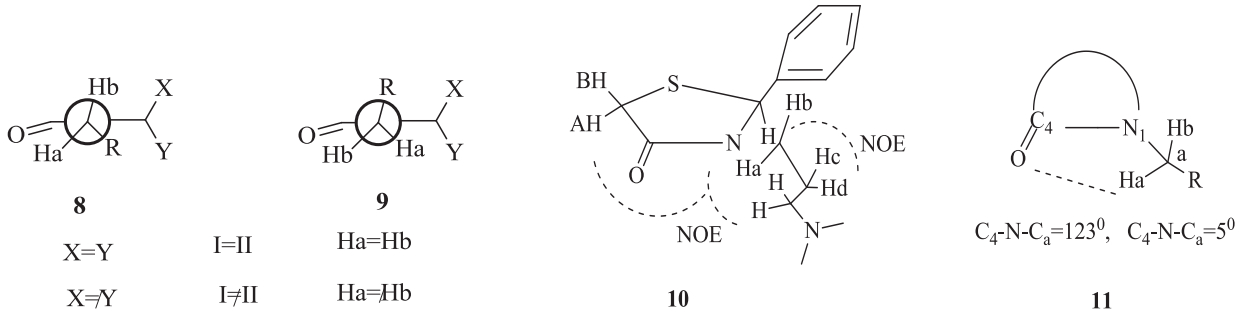
During a study on a recently synthesized series of 2-(substitutedphenyl)-3-[3-(*N*,*N*-dimethylamino) propyl]-1,3-thiazolidin-4-ones active as H_1 antagonists, 1H NMR data showed that the geminal protons of the three methylene groups, α, β, and γ, belonging to the alkylamine side chains of the series were not equivalent and were coupled to each other in a *gauche-anti* conformation. The chemical shift difference (~0.9 ppm) between the geminal α-CH_2 protons was very large and could be ascribed to an unusual intramolecular interaction, such as a hydrogen bond, between the amidic oxygen of the thiazolidinone ring and hydrogen of the α-CH_2.

Molecular mechanics calculations of the low energy conformations of all derivatives were carried out by TRIPOS force field of SYBYL (a comprehensive computational tool kit for molecular design and analysis). Geometrical optimizations were realized with the semiempirical quantum mechanical method AM1, available in the Molecular Orbital Package (MOPAC) program. Two low energy conformers, **8** and **9** (Scheme 4), showed a *gauche-anti* conformation of the alkylamine chain and the H–Cα–N3–C4=O atoms lying on the same plane in agreement with an attractive interaction between the carbonyl oxygen and α-CH_2 hydrogen. When X = Y, the two thiazolidinone planes are equal; **8** and **9** have the same energy and are equally probable, and ^{1}H NMR spectrum shows only one α-CH_2 signal. When X # Y, Ha # Hb, the two low-energy minimized conformers, **8** and **9**, contribute differently to the Ha and Hb shifts, and 1H NMR spectrum shows two α-CH_2 signals [21].

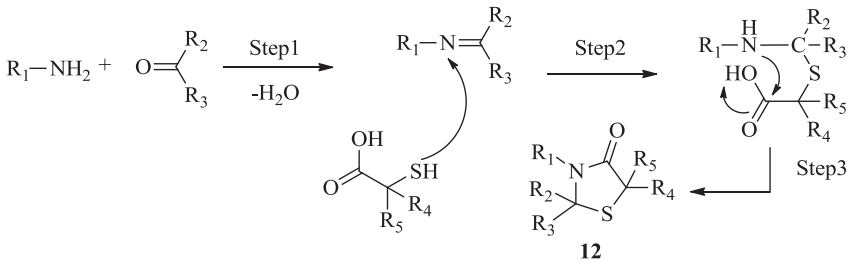
3. Synthesis

Literature survey reveals that several substituted thiazolidinones have been prepared from different synthetic routes [21–52]. The main synthetic routes to 1,3-thiazolidin-4-ones **12** involve three components (an aldehyde, an amine, and mercaptoacetic acid), either in a one or two-step process (Scheme 5). The reactions proceed by initial formation of an imine, which undergoes attack by the sulfur nucleophile, followed by intramolecular cyclization on elimination of water. The most common protocol to remove the water is by azeotropic distillation. Dicyclohexyl-carbidiimide (DCC), which is extensively used in peptide synthesis dehydration, strongly promotes the dehydration here too.

Some improved protocols have been reported by Shrivastava et al. and Rawal et al. wherein *N*,*N*-dicyclohexyl carbodiimide/2-(1H-benzotriazo-1-yl)-1,1,3,3 tetramethyluranium-hexafluorophospate is used as a dehydrating agent to accelerate the intramolecular cyclization resulting in faster reaction and



Scheme 4. Two low energy thiazolidinone conformers contributing differently to the α-CH_2 shifts (**8**, **9**); The minimum energy conformers obtained from SYBYL package showing NOE interactions detected by COSY and NOESY (**10**); Structure representing generic N-alkyl lactam structure, with C4–N-Cα and C4–N-Cα-Ha dihedral angle values (**11**).



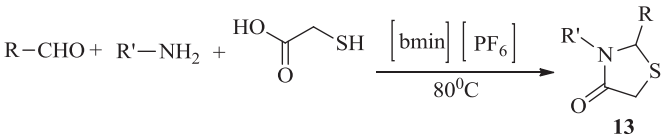
Scheme 5. Reaction mechanism for the formation of 4-thiazolidinones (**12**).

improved yields. The dicyclohexyl-carbodiimide/2-(*1H*-benzotriazo-1-yl)-1,1,3,3-tetramethyl uraniumhexafluoro-phospate mediated protocol has the advantage of mild reaction conditions, a very short reaction time and product formation in almost quantitative yields. More importantly, yield of the 4-thiazolidinones is independent of the nature of the reactants. This modification is compatible with a solid-phase combinatorial approach to generate a library of compounds [33,34].

Zhang et al. efficiently synthesized 2,3-disubstituted-1,3-thiazolidin-4-one derivatives via the three-component reaction of aldehyde, amine and mercaptoacetic acid in 1-butyl-3-methyl-imidazolium hexafluorophosphate [bmim][PF6] without any catalyst (Scheme 6). The procedure is simple, efficient and straightforward and no aqueous work-up is needed. A series of novel pyrimidine nucleoside–thiazolidin-4-one hybrids can be prepared by employing this protocol [22].

Recently, Neuenfeldt et al. synthesized 2-cyclohexanyl-3-(*N*-phenyl)-1, 3-thiazolidin-4-ones **14** via an efficient solvent-free method from the reaction of mercaptoacetic acid, aldehydes (benzaldehyde and valeraldehyde) or ketones (cyclopentanone and cyclohexanone), and hydrazines (phenylhydrazine and 2,4-dinitrophenylhydrazine) (Scheme 7). The one-pot reaction of one equivalent of phenylhydrazine, one equivalent of appropriate ketone or aldehydes with three equivalent of mercaptoacetic acid in toluene, using a Dean Stark trap for 6 h gave the thiazolidinones in good yields after purification by column chromatography [27].

An expeditious one-pot synthesis of 2,3-diaryl/2-aryl-3-heteroaryl-1,3-thiazolidin-4-ones **15** has been accomplished by



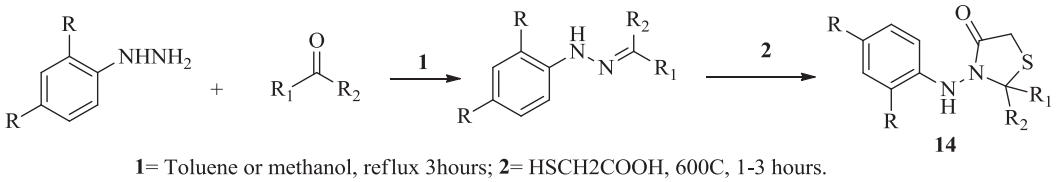
Scheme 6. Synthesis of 4-thiazolidinone derivatives under different reaction conditions (**13**).

condensing hetero/aromatic amine, 2-mercaptoacetic acid, aromatic aldehyde in ionic liquids, viz. 1-butyl-3-methyl-imidazolium tetrafluoroborate [BMIM]BF4 and 1-methoxyethyl-3-methylimidazolium trifluoroacetate [MOEMIM]TFA (Scheme 8). A microwave assisted synthesis of the same compound has been reported in toluene as the solvent. Except ionic liquid [36] promoted synthesis described here, most of the synthetic procedures are associated with harsh reaction conditions, poor yields and environmentally black-listed solvents [32].

2-[(Thiazol-2-yl)imino]thiazolidin-4-ones and 2-imino-3-(thiazol-2-yl)thiazolidin-4-ones **16**, **17** have been synthesized from chloroacetyl derivatives of 2-aminothiazoles (Scheme 9) and studied for the treatment of tumors and microbial diseases. Ostapuik et al. synthesized 2-[(5-benzyl-1,3-thiazol-2-yl)imino]-1,3-thiazolidin-4-ones **18**, **19** by the reaction of 2-chloro-acetamido/chloropropioamido-5-benzylthiazole with potassium thiocyanate, via rearrangement (Scheme 10) [23].

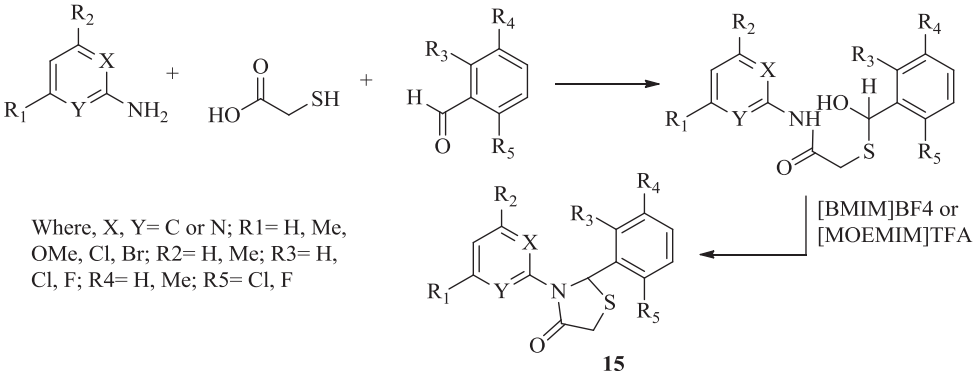
5-Arylidene-2-imino-4-thiazolidinones **21** have been synthesized by the conventional heating of 2-imino-4-thiazolidinones **20** with the appropriate aldehydes, under basic or acidic conditions. Recently, compound **21** was prepared by a one pot three component solvent-free reaction of N,N-diphenylthiourea with chloroacetic acid and benzaldehyde under microwave irradiation (Scheme 11), and was assigned the Z configuration [35–40]. The structure of the new derivative **21** was confirmed from its elemental and spectral analyses.

A three component reaction involving isatins with heterocyclic amines, that is, 3-amino-1,2,4-triazole/2-aminobenzimidazole and thioacid under MW irradiation (Scheme 12) was used to discover new thia-azaheterocycles of biocidal interest, guided by the observation that the presence of two or more different heterocyclic moieties in a single molecule often enhances the biocidal profile remarkably. Three types of conditions were explored: (i) in dry media using various solid supports (KSF montmorillonite, silica gel, acidic or neutral alumina), (ii) neat reaction without solvent and (iii) conventional methods using different solvents. The exclusive formation of spiro [indole-thiazolidinones] **22** was observed, as



14

Scheme 7. Efficient solvent free synthesis of 4-thiazolidinones (**14**).



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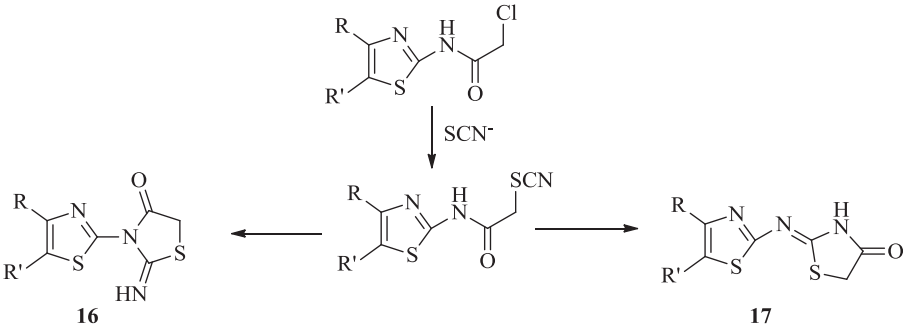
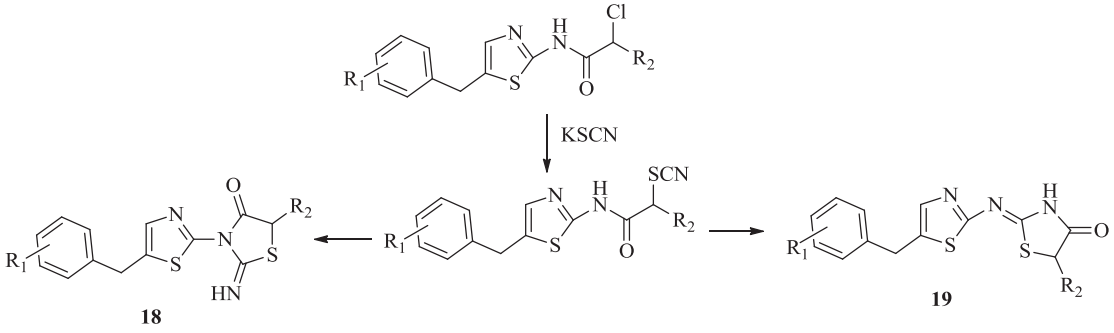
Scheme 8. One-pot synthesis of 2,3-diaryl/2-aryl-3-heteroaryl-1, 3-thiazolidin-4-ones (**15**).



16 17

Scheme 9. Synthesis of 2-[(thiazol-2-yl) imino]thiazolidin-4-ones and 2-imino-3-(thiazol-2-yl)thiazolidin-4-ones (**16**, **17**).

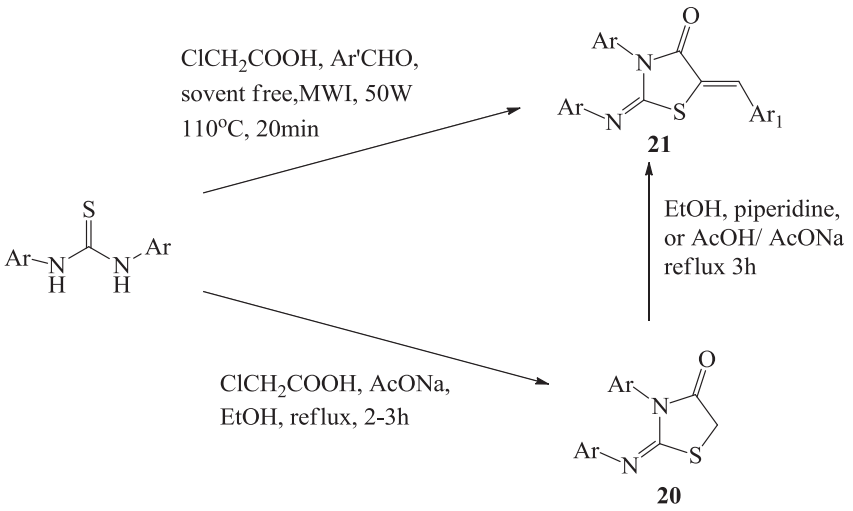


18 19

Scheme 10. Reactions of *N*-(5-benzyl-1, 3-thiazol-2-yl)-2-chloroacetamides with potassium thiocyanate (**18**, **19**).

confirmed by spectral studies and X-ray diffraction under all conditions employed. This reaction constitutes a striking example of solvent-free regioselective synthesis of thiazolidinones, greatly improving under MW irradiation. Solution-phase reaction uses high boiling hydrocarbons like toluene or benzene with continuous removal of water or requiring desiccants like anhydrous zinc chloride, sodium sulfate or molecular sieves and the use of stoichiometric amount of DCC and Hűnig base [28]. Condensation of 5-arylfurfural with any of the thiazolidinones **23** furnished the desired products, i.e. heteroarylmethylene analogs **24** and **25** in 50–95% yield. Some of the thiazolidinones are commercially available or they can be prepared in two steps from methyl isothiocyanate (Scheme 13) [24].

Whole cell biocatalysis with Baker's yeast (*Saccharomyces cerevisae*) is gaining prime importance in synthetic organic chemistry as yeast catalyzes a variety of organic transformations.



Scheme 11. Synthesis of thiazolidin-4-one derivatives under conventional thermal heating and/or microwave irradiation (**20**, **21**).

Cyclocondensation using biocatalysts has not been explored much. Lipases and Baker's yeast have the ability to catalyze the cyclocondensations leading to bioactive heterocycles such as benzimidazoles, dihydropyridines, dihydropyrimidines, polyhydr oquinolines, benzothiazoles, benzotriazoles, quinoxaline and 4-thiazolidinones. *Saccharomyces cerevisiae* catalyzed one-pot three component cyclocondensation of aryl aldehydes, amines, and thioglycolic acid, in organic medium, leading to 2,3-diaryl 4-thiazolidinones **26** (Scheme 14) was carried out for the first time by Pratap et al. [31] (Scheme 15).

cis-Jasmone, from jasmonoid group, is an important jasmine odor fragrance compound. The syntheses of new heterocyclic analogs **28** of jasmone were described by St Laurent et al. Five analogs of this compound were prepared under microwave irradiation (Scheme 16) and the results of the microwave assisted syntheses were compared with classical, thermally initiated reactions in the presence of a solvent. Three of five obtained analogs, pyrrolidinone, oxazolidinone and thiazolidinone demonstrated an interesting, specific odor which was compared with floral, typical jasmine odor of jasmone [30].

Two novel series of 4-thiazolidinone derivatives, namely 2′,4′-difluoro-4-hydroxybiphenyl-3-carboxylic acid [2-(5-nitro-2-furyl/substituted phenyl)-4-thiazolidinone-3-yl]amides and 2-(2′,4′-difluoro-4-hydroxybiphenyl-3-carbonylhydrazono)-3-alkyl/aryl-4-thiazolidinones, together with 5-(2′,4′-difluoro-4-hydroxyb iphenyl-5-yl)-2-cyclohexylamino-1,3,4-oxadiazole have been synthesized by Küçükgüzel et al. 1-(2′,4′-Difluoro-4-hydroxybiphenyl,3-carbonyl)-4-alkyl/arylthiosemicarbazides were also obtained and used as intermediates to give the title compounds [42]. Mamaghani et al. developed a convenient one-pot protocol for the synthesis of 2-imino-1,3-thiazolidin-4-ones by the reaction of amines, isocyanates, aldehydes, and chloroform in the presence of sodium hydroxide under ultrasonic conditions in high yields (75–91%) and with shorter reaction times (12–15 min) [43]. The use of 3-substituted-2-mercaptoacrylic acids, synthesized via hydrolysis of 5-ylidenerhodanines, for the preparation of 2,3,5-trisubstituted-4-thiazolidinones via a new variant of the one-pot, three component reaction has been studied by Kaminskyy et al. [53]. Propylphosphonic anhydride (T3P)-DMSO mediated oxidation of alcohols to carbonyl compounds and their subsequent cyclization with aryl/hetero aryl amines and thioglycolic acid to afford 4-thiazolidinones has been reported by Kothanahally et al. Synthesis of 4-thiazolidinones directly from alcohols has been carried out for the first time. Mild reaction conditions, wide functional group tolerance, ease of work-up, and good yields were the noteworthy features of this protocol [54].

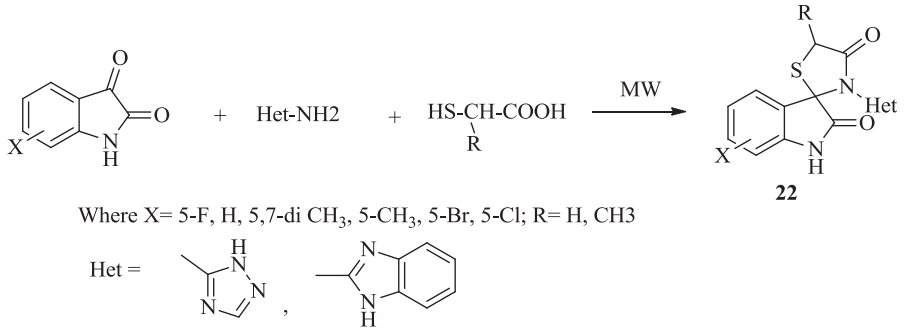
Diastereoselectivity in the oxidation of different 4-thiazolidinones **29**, **30** and **31** was achieved (Scheme 17), discussed and interpreted by Colombo et al. containing a sulfoxide. Alkylation of these compounds with benzyl bromide was also studied [44].

4. Characterization

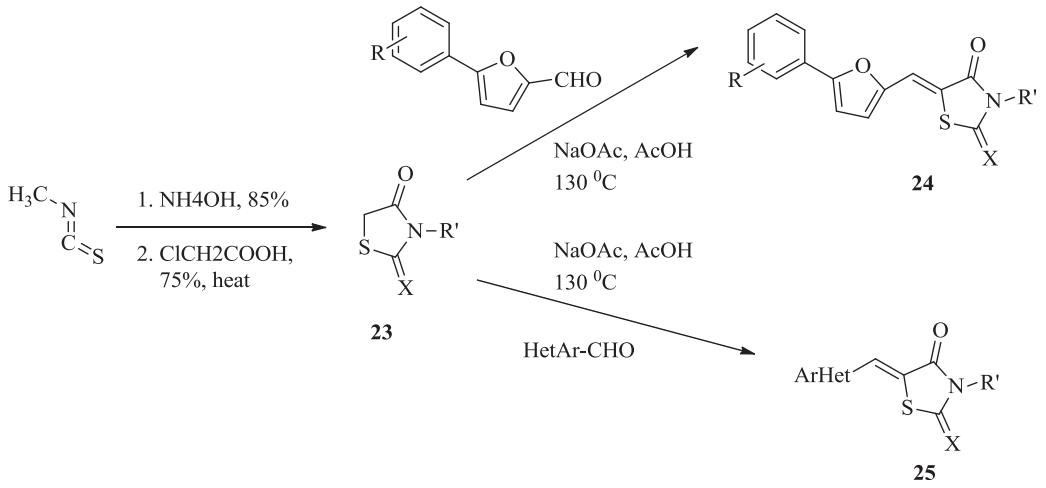
4-Thiazolidinone derivatives have been generally characterized by IR, NMR (^{1}H and ^{13}C), mass spectrometry and X-ray crystallography. A characteristic band in the infrared spectra of several 2-substituted 4-thiazolidinones was reported by Taylor et al., describing the criteria for determining the *cis* and *trans* configurations of these compounds. H-bonding favored *cis* isomer otherwise *trans* isomer was the stable form. The imino–amino tautomerism of 2-imino-4-thiazolidinones and its derivatives was studied by infrared spectroscopy. The spectral data showed that in the crystal state, the imino isomer is predominant whereas in a solution, amino isomer predominates [6,55,56].

The nature of the substituents at the C(2) and N(3) positions of the thiazolidine ring highly influences the ^{1}H NMR spectra. The 2,3-disubstituted 4-thiazolidinones have three characteristic peaks in the NMR spectrum; proton appears as a singlet or as separate doublets in the range of 5–6 ppm and 3.5–3.9 ppm, depending upon the nature of the substituent [6,56]. The ^{13}C NMR spectra of a series of substituted 4-thiazolidinones in $CDCl_3$ was studied by Nagase et al. Various constitutional isomers have been differentiated, and the configuration of trisubstituted exocyclic C=C has been established on the basis of the C,H spin coupling constants over two and three bonds [6,57]. Mass spectra of different 4-thiazolidinones were studied and reported on the basis of molecular ion peak and fragmentation pattern. The principle daughter ion peaks were determined by means of deuterium exchange and high-resolution mass spectroscopy [6,58].

According to Cremer and Pople puckering analysis [59], the conformation of the thiazolidin-4-one ring is best described as having a twisted chair conformation. The thiazolidinone and phenyl rings are nearly orthogonal to each other [27]. The structure of a thiazolidinone derivative was established by Ostapiuk et al. using X-ray crystallography [23]. The X-ray analysis showed that a



Scheme 12. Efficient microwave enhanced regioselective synthesis of a series of benzimidazolyl/triazolyl spiro [indole-thiazolidinones] (**22**).



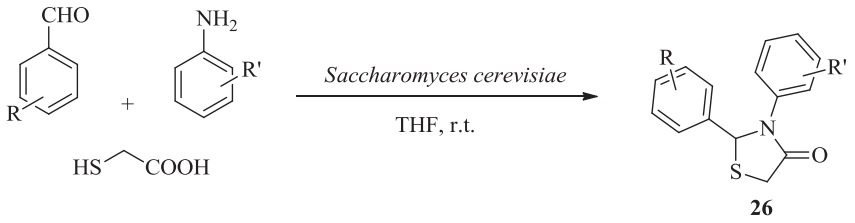
Scheme 13. Synthesis of thiazolidinone derivatives (**23**, **24**, **25**).

hydrogen atom was attached to N_3, which is in agreement with the structure containing a secondary amide in the thiazolidin-4-one ring and exocyclic imine nitrogen. The appropriateness of this observation is supported by the values of the interatomic distances, N3–C4 and C2–N3 [1.379(4) and 1.380(4) Å] as well as C2═N6 [1.292(4) Å], which are close to the mean values for the single bonds (O═)C–NH [1.357(2) Å] and NH–C(═N) [1.377(10) Å] as well as the double bond C═N [1.280(2) Å], respectively, acquired from two structures containing a 2-imino-1,3-thiazolidin-4-one moiety. The ^{1}H NMR spectra correlate with the crystallographically observed geometry of the same derivative showing a signal for the CH_2 protons at 3.96–4.20 ppm and a signal for the NH proton at 11.81–12.15 ppm. It should be noted that the resonance for the proton of the imino group at position 2 of the thiazolidinone ring would be expected to occur at ~9 ppm. Crystallographic data suggests; Empirical formula: $C_{14}H_{12}ClN_3OS_2$, formula weight: 337.84, crystal system: monoclinic, A colorless crystal (EtOH) (0.25 × 0.21 × 0.02 mm) was used to record 26307 (CuKα-radiation, $\theta_{max} = 75.6^0$) intensities on a SuperNova diffractometer [23].

5. Biological activities

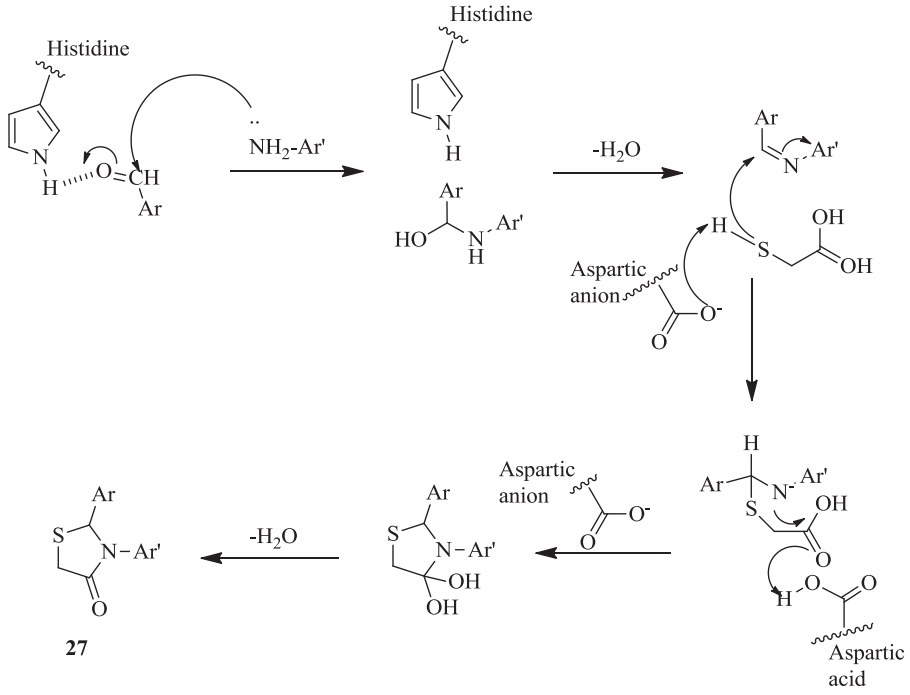
5.1. Anticancer activity

Chemotherapeutic drugs can be subdivided based on their mode of action into distinct groups: (i) drugs that interfere with DNA synthesis, (ii) drugs that introduce DNA damage and (iii) drugs that inhibit the function of the mitotic spindle, i.e. spindle poisons [60]. Drugs that interfere with the normal progression of mitosis belong to the most successful chemotherapeutic compounds currently used for anti-cancer treatment. Classically, these drugs are represented by microtubule binding drugs that inhibit the function of the mitotic spindle, in order to halt the cell cycle in mitosis, and to induce apoptosis in tumor cells. However, these compounds act not only on proliferating tumor cells but also exhibit significant side effects on non-proliferating cells, including neurons that are highly dependent on intracellular transport processes mediated by microtubules. Thus, there is a particular interest in developing novel anti-mitotic drugs that target non-microtubule structures. In fact, several novel drugs that target mitotic kinesins or the Aurora and polo-like kinases have been developed and are currently under clinical trials [61,62]. In addition, approaches of cell cycle checkpoint abrogation during mitosis and at the G2/M transition inducing mitosis-associated tumor cell death are promising new strategies for anti-cancer therapy. It is expected that this “next generation” of anti-mitotic drugs will be as successful as the classical anti-microtubule drugs, while avoiding some of the adverse side effects. The proteins that are promising targets for cancer therapy are indicated and include polo-like kinase 1 (Plk1), kinesin-spindle protein (KSP/Eg5), centromeric protein E (CENP-E), Aurora-A kinase (Aur-A), Aurora-B kinase (Aur-B) and the mitotic spindle assembly checkpoint pathway that controls the metaphase to anaphase transition. Inhibitors of the mitotic spindle (spindle poisons) are frequently used for anti-cancer treatment and inhibitors for KSP/Eg5, Plk1 and the Aurora kinases are currently in clinical development. In addition, the induction of DNA damage during mitosis by abrogation of the G2 cell cycle arrest by inhibitors of the Chk1 kinase (e.g. UCN-01) leads to a spindle checkpoint mediated

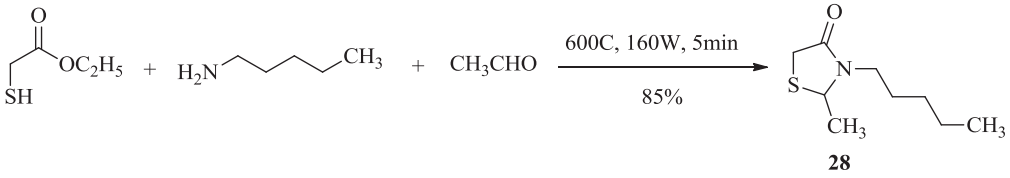


R= H, 4-OCH3, 3-Cl, 3-NO2, 4-OHand 4-Cl; R' = H, 4-CH3 and 4-Cl

Scheme 14. Baker's yeast catalyzed one-pot three component synthesis of 4-thiazolidinones (**26**).



Scheme 15. Plausible mechanism for the formation of 4-thiazolidinone (**27**) [31].

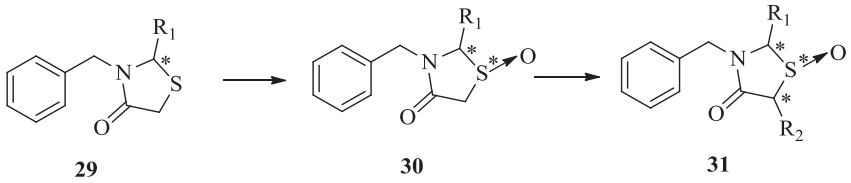


Scheme 16. Microwave synthesis of thiazolidinone analog of jasmine (**28**).

mitotic arrest followed by the induction of a mitotic form of apoptosis [63].

The increasing diversity of small molecule libraries is an important source for the discovery of new drug candidates. In this context, azolidinone heterocycles are of great importance in modern medicinal chemistry, particularly thiazolidinones (Scheme 18) [64–78]. These are peroxisome proliferator-activated (PPAR) receptors agonists showing hypoglycemic, antineoplastic and anti-inflammatory activities [79]. Recently, it was studied that PPARγ agonist troglitazone (2,4-thiazolidinedione derivative) mediated the suppression of cyclin D1 in MCF-7 breast cancer cells by facilitating proteasome facilitated proteolysis [80]. Antitumor properties of 4-thiazolidinones and related heterocycles are most probably related to their affinity to anticancer biotargets, such as JNK stimulating phosphatase-1 (JSP-1) [68], tumor necrosis factor TNFα [81], antiapoptotic biocomplex Bcl-XL-BH3 [70], integrin αvβ3 receptor [69], etc.

Several 5-benzylidene-thiazolidine- 2,4-diones and -2-thiones (rhodanines) inhibit cell growth with low micromolar GI50 mediated by inhibition of translation initiation, which involves partial depletion of intracellular Ca^{2+} stores and IF2a phosphorylation [67,68,82]. Among thiazolidinone derivatives, 2-arylaminothiazol-4-ones are one of the most promising groups in anticancer drug discovery, effectively inhibiting the growth of several human lung cancer cell lines (H460 and H460/TaxR) but not normal fibroblasts in a dose-dependent manner [83,84]. Moreover, 2-arylaminothiazol-4-ones with selectivity to NSCL cancer cell line H-460 at sub-micromolar concentrations and lower toxicity to



Scheme 17. Diastereoselective oxidation of 4-thiazolidinones (**29**, **30** and **31**).

normal human fibroblasts were discovered [85]. Among 3-substituted 2-arylimino-4-thiazolidinones, integrin avb3 antagonists were shown to be perspective novel anticancer agents [69]. 2-Phenylimino-3-alkyl-4-thiazolidinone derivatives demonstrated inhibition of the HT29 cell line (colon cancer), characterized by a high COX-2 expression [86], as well as CDK1/cyclin B inhibition [87]. These effects were achieved by the block of cell cycle progression at the G2/M phase border, in a reversible manner, and induction of apoptosis [88]. Anticancer activity profile of 5-arylidene-2-aminoazolones and SAR analysis within the series was found in accordance with anticancer activity of azolidinone derivatives and related/fused heterocyclic systems [74,89]. 5-Benzylidene-4-thiazolidinone derivatives have been reported to show marked antitumor activities with different biotargets and mechanism, such as phosphatase of a regenerating liver (PRL-3) [67], Sphingosine Kinase (SK) [90], JNK stimulating phosphatase-1 (JSP-1) [68] and nonmembrane protein tyrosine phosphatase (SHP-2) [91]. Moreover, 5-benzylidene-4-thiazolidinone derivatives exhibited potent antitumor activities against non-small cell lung cancer cell line H460, paclitaxel-resistant H460taxR, human colon cancer cell line HT-29 and human breast cancer cell line MDA-MB-231 [85,86].

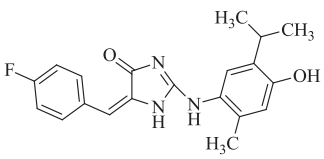
Subtel'na et al. synthesized a novel series of 5-arylidene-2-arylaminothiazol-4(5H)-ones and 2-aryl (benzyl) amino-1H-imidazol-4(5H)- ones from appropriate 2-alkylthioazol-4-ones using nucleophilic substitution in position 2 by various anilines and benzylamines and Knoevenagel reaction. X-ray structural studies of **32** (Scheme 18) revealed the structure to be intermediate between amino and imino tautomeric forms. All the target compounds were evaluated for the anticancer activity *in vitro* in standard National Cancer Institute 60 cancer cell lines assay. Majority of the compounds showed significant antitumor cytotoxicity effect at micromolar and sub-micromolar level (Mean Log GI50 ranges −5.77 to −4.35). Some of the most potent compounds, namely **33** (Scheme 18), possessed selectively high effect on all leukemia cell lines at sub-micromolar levels (Mean Log GI50 [leukemia lines], respectively, −6.41 and −6.29), which are probably associated with immune−suppressive activity. Individual cancer cell lines sensitivity to synthesized compounds and SAR studies revealed that the presence of OH-substituent at *para* position of arylamino fragment in 2-amino-4-thiazolinonesis was more favorable than in *meta* position. Effect of elimination of hydrogen bond donar (HBD), by introduction of methyl into secondary amino group gave ambiguous influence on the activity depending on the ylidene substituent in position 5 of thiazoline heterocycle. Compounds containing 2-chloro-3-(4-nitrophenyl) propenylidene substituent in combination with 4-hydroxyphenylamino moiety exhibited one of the most potent activities with specific selectivity against certain cancer cell lines. COMPARE analysis allowed to disclose probable modes of anticancer action for the synthesized compounds, in particular to the number of high correlations with activity patterns of alkylating agents (PCC ~0.606−0.731) [92].

Following the reaction of benzothiazol-2-yl-hydrazine or (2-oxo-benzothiazol-3-yl)-acetic acid hydrazide with thiocarbonyl-bis-thioglycolic acid, 3-(benzothiazol-2-ylamino)-2-thioxoth iazolidin-4-one and 2-(2-oxobenzothiazol-3-yl)-N-(4-oxo-2-thioxothiazolidin-3-yl)-acetamide was synthesized as the starting compound for obtaining new 5-arylidene derivatives in Knoevenagel condensation with aromatic aldehydes and isatins. The synthesized compounds showed antitumor activity on renal cancer, non-small cell lung cancer and ovarian cancer cell lines. The most efficient anticancer agent, 2-{2-[3-(benzothiazol-2-ylamino)-4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl]-4-chloro-phenoxy}-N-(4-methoxy-phenyl)-acetamide **34** (Scheme 18) was found to be active with average values of −5.38 and −4.45 for log GI50 and log TGI, respectively [93].

The cystic fibrosis transmembrane conductance regulator (CFTR) is a plasma membrane Cl^- channel that is involved in the electrolyte/fluid transport in various epithelial cells. Defective CFTR function causes cystic fibrosis (CF), the most common lethal genetic disease in caucasians that produces severe lung disease, pancreatic insufficiency, neonatal intestinal obstruction, and infertility [94]. CFTR is activated by cAMP-dependent phosphorylation at its R domain and modulated by interaction/hydrolysis of ATP at its two nucleotide binding domains NBD-1 and NBD-2 [95]. CFTRinh-172 blocked CFTR-dependent Cl^- currents with KiW300 nM, nearly 500-fold more potent than that of the reference CFTR blocker glibenclamide [96]. Recently, Sonawane et al. synthesized a series of 3-[(3-trifluoromethyl) phenyl]- 5-[(3-carboxyphenyl) methylene]-2-thioxo-4-thiazolidinone **35** (Scheme 18), labeled $CFTR_{inh}$-172, to identify a small-molecule CFTR inhibitor by high-throughput screening and studied SAR with improved water solubility, exploring modifications in its two phenyl rings, thiazolidinone core, and core-phenyl connectors. Greatest CFTR inhibition potency was found for 3-CF_3 and polar group-substituted-phenyl rings, and a thiazolidinone core. Two compounds with ~1 μM CFTR inhibition potency and solubility >180 μM (>10-fold more than $CFTR_{inh}$-172) were identified: Tetrazolo-172, containing 4-tetrazolophenyl in place of 4-carboxyphenyl, and oxo-172, containing thiazolidinedione in place of the thiazolidinone core. These water soluble thiazolidinone analogs had low cellular toxicity. The improved water solubility of tetrazolo- and oxo-172 makes them potential lead candidates for therapy of secretory diarrheas and polycystic kidney disease [97,98].

Some novel 2-aryl-3-[5-deoxy-1,2-o-isopropylidene-α-D-xylofuranose-5-*C*-yl] thiazolidin-4ones **36** (Scheme 18) were synthesized by Chen et al. by the three-component condensation of an amino sugar, an aromatic aldehyde and mercaptoacetic acid in the presence of DCC and DMAP at room temperature. The structures of the new compounds were determined by NMR spectroscopy and mass spectrometry (MS), and the configuration of the newly generated chiral carbon (C-2) in the thiazolidin-4-one ring was tentatively assigned based on the X-ray crystallographic structure and the comparison of their corresponding NMR signals. The antitumor (human cervical cancer cells) activity and the inhibition against the glycosidases (α-glucosidase, β-glucosidase, α-amylase) have been evaluated for the new compounds [99].

A series of sulfapyridine-polyhydroxyalkylidene (or arylidene)-imino derivatives (Schiff's bases) were prepared by condensation of 4-amino-N-pyridin-2-ylbenzenesulfonamide with different



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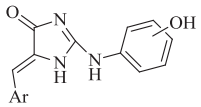

Ar = 4-(Cl)-C6H4 or
4-(NO2)-C6H4-CH=C(Cl)-CH

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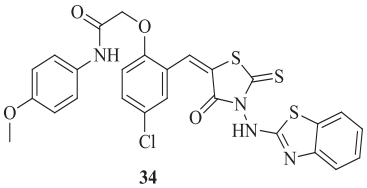

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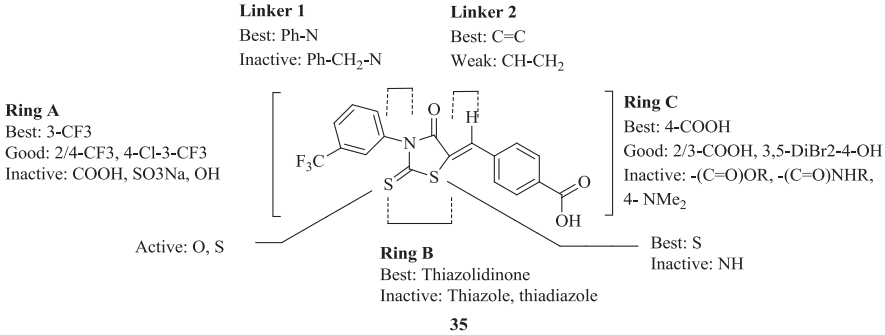

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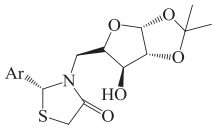

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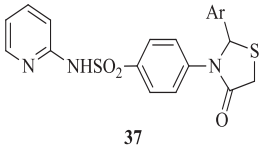

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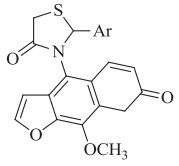

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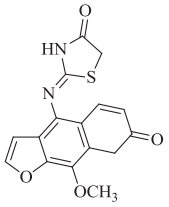

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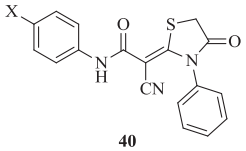

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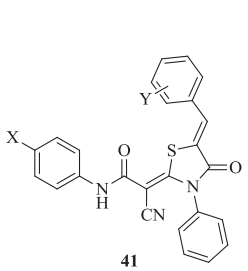

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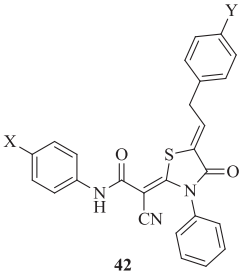

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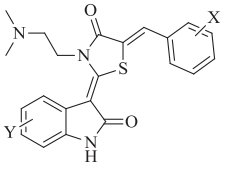

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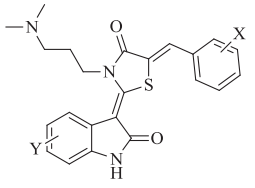

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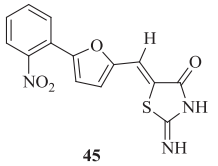

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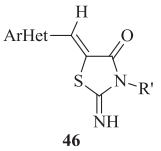

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Scheme 18. 4-Thiazolidinone derivatives showing anticancer activity (**32**–**46**).

monosaccharides or with aromatic aldehydes by Kamel et al. Treatment of these Schiff bases with thioglycolic acids afforded the corresponding 2-arylthiazolidin-4-one or 2-arylbenzothiazin-4-one derivatives **37**(Scheme 18). Some representative members of the newly prepared compounds showed considerable cytotoxic effect against breast carcinoma cell line MCF7 and cervix carcinoma cell line HELA in comparison with 5-flurouracil and doxorubicin. AutoDock molecular docking into protein tyrosine kinase (PTK) has been done for lead optimization of the compounds in study as potential PTK inhibitors. SAR of these compounds mainly depends on their main structural feature, 4-[(pyridin-2-ylamino) sulfonyl] benzene which was considered as the pharmacophoric moiety and substituent variation resulted in narrow change in activity [73].

The condensation of 4-amino-9-methoxy psoralene (4-aminoxanthotoxin) with some aromatic aldehydes led to the formation of 4-arylimine xanthotoxin derivatives, which were cyclized with mercaptoacetic acid to afford the thiazolidinone derivatives **38** (Scheme 18). On the other hand, the reaction of aminoxanthotoxin with some anhydrides afforded 4-imidione derivatives. When aminoxantho-toxin reacted with some isothiocyanates, the thiourea derivatives were obtained. The thiourea derivative was cyclized by the reaction with monochloroacetic acid in the presence of sodium acetate to give aminothiazolidinone derivative **39** (Scheme 18), but when the same reaction was carried out in the presence of pyridine, the thioxoimidazolidinone was formed. The antitumor and cytotoxic activities of synthesized derivatives were tested, which inhibited the growth of HeLa cells [100].

(2Z,5Z) 2-[(5-Arylidene-4-oxo-3-phenyl)-thiazolidin-2-ylidine]-2-cyano-N-arylacetamides **41** (Scheme 18)were stereoselectively prepared via condensation of aromatic aldehydes with 4-thiazolidinones **40** (Scheme 18), obtained via electrophilic attack of phenylisothiocyanate on 2-cyano-N-arylacetamides followed by reaction with chloroacetyl chloride under basic condition. Single crystal X-ray study allows good confirmation for the assigned structure. Additionally, 5-arylhydrazono analogs **42** (Scheme 18) were prepared via condensation of the appropriate diazonium salts with 4-thiazolidinones. Many of the synthesized compounds exhibited promising antitumor properties against colon HCT116, breast MCF7 and liver HEPG2 cell lines. 3D-Pharmacophore modeling and QSAR analysis were combined to explain the observed antitumor properties [101].

A series of novel 4-thiazolidinone and indolin-2-one hybrid derivatives **43** and **44** (Scheme 18) have been synthesized by Wang et al. and their *in vitro* cytotoxic activities were evaluated against three human cancer cell lines including HT-29 (human colon cancer), H460 (human lung cancer), MDA-MB-231 (human breast cancer) by MTT assay. Most of the prepared compounds exhibited significant antitumor activities against different human cancer cell lines. Compound **44** (IC50 ¼ 0.025 mM, 0.075 mM, 0.77 mM, 1.95 mM) was 52, 36, 4.8 and 3.3 times more active than Sunitinib (IC50 ¼ 1.3 mM, 2.7 mM, 3.7 mM, 6.47 mM) against HT-29, H460, MDA-MB-231 and SMMC-7721 cancer cell line, respectively. The preliminary SAR studies revealed that, the introduction of 5-fluoroindolinone or 6-fluoroindolinone group at 2-position of the 4-thiazolidinone scaffold enhanced antitumor activity [102].

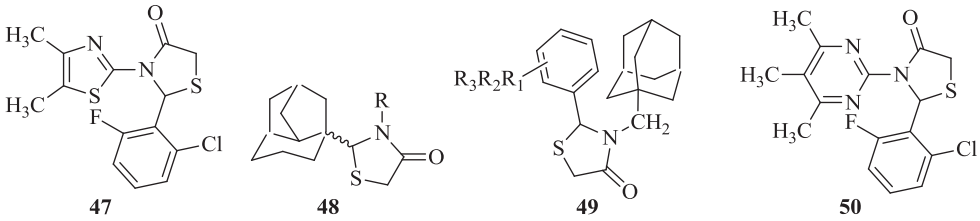
A nonsense mutation is a point mutation in a sequence of DNA that results in a premature termination codon (PTC) or a nonsense codon in the transcribed mRNA. These cause the formation of either no protein or of a truncated, unstable, nonfunctional protein. Approximately 30% of common genetic diseases result from nonsense mutations, such as in Ataxia telangiectasia (A-T), Duchenne muscular dystrophy (DMD), cystic fibrosis (CF), and spinal muscular dystrophy (SMA). High-throughput screen (HTS) of 34,000 compounds using a PTT-ELISA assay was performed by Du et al. that resulted in the identification of twelve low molecular weight compounds with PTC readthrough activity. From these, one potent lead compound, **45** (Scheme 18) was obtained [103]. A structure–activity relationship (SAR) study was carried out to identify novel, small molecular weight compounds which induce readthrough of premature termination codons. In particular, compound **46** (Scheme 18) was proposed and evaluated. Four structural changes in **46** namely: change in the heteroatom of the 2-carbonyl unit of the thiazolidin-4-one; variation of the aryl group on the furan ring; introduction of an alkyl group on the ring nitrogen of the thiazolidin-4-one; and introduction of different aryl groups as the central ring unit. In addition, hypothesizing that these compounds exhibit their activity by binding to the ribosome, hybrid analogs containing pyrimidine bases were also prepared which showed good readthrough activity [24]. 2-(4,5-Dihydropyrazol-1-yl)-thiazol-4-ones have been synthesized by Havrylyuk et al. starting from 3-phenyl-5-aryl-1-thiocarbamoyl-2-pyrazolines via [2 + 3]-cyclization with 2-bromopropionic acid, maleic anhydride, *N*-arylmaleimides, and aroylacrylic acids. The *in vitro* anticancer activity of the synthesized compounds was tested which showed selective inhibition of leukemia cell lines growth at a single concentration (10^{-5} M). The screening of antiviral activity for a broad panel of viruses revealed that *N*-(4-methoxyphenyl)-2-{2-[5-(4-methoxyphenyl)-3-phenyl-4,5-dihydropyrazol-1-yl]-4-oxo-4,5-dihydrothiazol-5-yl}-acetamide was highly active against Tacaribe TRVL 11 573 virus strain (EC_{50} = 0.71 μg/mL, selectivity index = 130) [104].

5.2. Antiviral activity

The pathogenesis of HIV-1 is due to uncontrolled viral replication in CD^{4+} T cells [105]. Several efforts have been made in the last two decades to understand and control virus replication. In this direction, HIV-1 RT has been identified as a prime target for designing inhibitors for treatment of HIV/AIDS [106,107]. The introduction of antiHIV-1 RT drugs has significantly reduced morbidity and mortality of HIV/AIDS patients.

Several 2,3-diaryl-1,3-thiazolidin-4-ones have proved to be particularly effective non-nucleoside HIV reverse transcriptase inhibitors (NNRTIs) [108]. Barreca et al. reported 2,3-diarylsubstituted-4-thiozolidinone scaffold derived from retrosynthetic opening of the imidazole nucleus of thiazolobenzimidazole (TBZ) [109], which selectively inhibit HIV-1 RT, because they contain necessary pharmacophoric elements of those HIV-1 NNRTIs, namely a benzene-fused ring, an aryl group at C-1 and the nitrogen atom of the thiazole nucleus. Structure activity relationship (SAR) studies have shown that the antiHIV activity strongly depends on the nature of substituents at C-2 and N-3 of the thiazolidinone ring. It has been demonstrated that a high antiviral activity was associated with the presence of a 2,6-dihalo-substituted phenyl ring at C-2 and pyridin-2-yl or pyrimidin-2-yl rings at N-3 [110,111]. Detailed QSAR and docking studies have revealed that the biophoric space around N-3 can accommodate a variety of heterocyclic moieties namely, pyridine, pyrimidine, and furfuryl. This provides compelling rationale for further optimization at N-3 of thiazolidinone [112,113].

Compounds having isothiourea or thiourea functional group have shown high anti-HIV-1 activity. Therefore, a series of 2-aryl-3-heteroaryl-1, 3-thiazolidin-4-ones was designed, synthesized, and evaluated for antiHIV-1 RT activity. The results of *in vitro* tests showed that the compound **47** (Scheme 19) exhibited EC50 at 0.26 l M and selectivity index of 113 and 138 in MT-4 cells and CEM cells, respectively, with minimal toxicity in MT-4 cells as compared to 0.35 l M for thiazobenzimidazole (TBZ). The introduction of a thiazol-2-yl moiety (with or without substitution) at the N-3



Scheme 19. 4-Thiazolidinone derivatives showing antiviral activity (**47**–**50**).

position of 4-thiazolidinone scaffold has led to an increase in the antiHIV-1 RT activity. Taken together these results indicate that changes at N-3 position of 4-thiazolidinone scaffolds with different heterocyclic moiety, with an appropriate lipophilic character, may provide compounds with improved activity [114].

A series of novel thiazolidin-4-ones bearing a lipophilic adamantyl substituent at position 2 and versatile substituents on the nitrogen atom of the thiazolidine ring were synthesized. Several compounds exhibited modest antiHIV-1 activity; (±)-2-adamantan-1-yl-3-(4,6-dimethyl-pyridin-2-yl)-thiazolidin-4-one **48** (Scheme 19) was endowed with a remarkable antiviral potency (EC50 ¼ 0.35 mM). The adamantane moiety played an important role in the eventual antiviral activity of the compound. This compound behaved as a typical non-nucleoside reverse transcriptase (RT) inhibitor (NNRTI) with non-competitive inhibition against RT with respect to the substrate (Ki ¼ 12 mM). Separation of the enantiomers via diastereoisomeric salts was performed for **48**. X-ray studies ascribed an S configuration to compound **48**. Furthermore, it was found that the (+)-**48** isomer was predominantly responsible for the potent antiHIV-1 activity (EC50 value of 0.178 mM), while the levo isomer was more than 60-fold less active [115]. The new series of compounds **49** (Scheme 19), with an adamantyl moiety at the 3-position of the thiazolidinone ring showed good to modest antiHIV-1 activity with pronounced cytostatic activity. X-ray studies and quantum chemical calculations revealed that the anti-HIV activity of the compounds strongly depends on their dipole moments and conformation of the thiazolidinones [116].

A series of 2-(2,6-dihalophenyl)-3-(substituted pyrimidinyl)-1,3-thiazolidin-4-ones **50** (Scheme 19) were designed on the prediction of quantitative structure–activity relationship (QSAR) studies, synthesized, and evaluated as HIV-1 reverse transcriptase inhibitors. In an attempt of correlating the identified molecular surface features related properties for modeling, the HIV-1 RT inhibitory activity resulted in some statistically significant QSAR models with good predictive ability. The results showed that compound **50** (Scheme 19) was highly active in inhibiting HIV-1 replication with EC50 values in the range of 22–28 nM in MT-4 as well as in CEM cells with selectivity indexes of >10,000. The derived models collectively suggest that the compounds should be compact, without bulky substitution on its peripheries for better HIV-1 RT inhibitory activity. These models also indicate a preference for hydrophobic compounds to obtain good HIV-1 RT inhibitory activity [117].

Hepatitis C virus (HCV) NS5B RNA polymerase is crucial for replicating the HCV RNA genome and is an attractive target for developing antiHCV drugs [118–120]. A novel series of 2,3-diaryl-1,3-thiazolidin-4-one derivatives were evaluated for their ability to inhibit HCV NS5B, which emerged as a potent agent, displaying over 95% inhibition of NS5B RNA polymerase activity *in vitro*, and an IC50 of 31.9 l M against HCV NS5B. It may be inferred from the biological activity that the anti-HCV NS5B activity is dependent on the nature of the substituent at C-2, N-3 and C-5 of the 4-thiazolidinone scaffold. In particular, a high activity level was observed for compounds possessing a halophenyl and 4-dimethylaminophenyl group at C-2, substituted/unsubstituted pyridine-2-yl, pyridine-3-ylmethyl, substituted pyrimidin-2-yl and furan-2-ylmethyl at N-3 and unsubstituted or methyl substitution at C-5. In fact, the compounds with the best combination of high potency were unsubstituted pyridine-2-yl, pyridine-3-ylmethyl or furan-2-ylmethyl substituted at N-3 of 4-thiazolidinone scaffold [121].

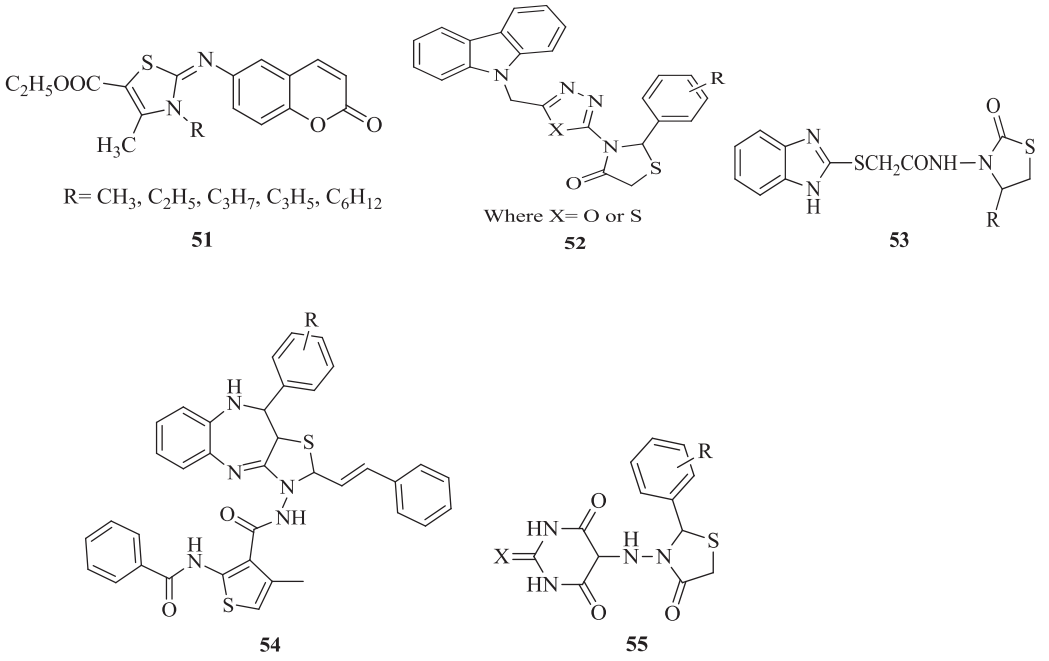
5.3. Anticonvulsant activity

Epilepsy is the most frequent neurologic affection characterized by excessive temporary neuronal discharge. Many patients with epilepsy do not respond well to currently available antiepileptic drugs (AED), which present some undesirable side effects such as vertigo, ataxia, headache, hirsutism, hepatotoxicity, gastrointestinal, and cardiovascular side effects [122,123]. In previous literature, thiazolidinones have been known to possess anticonvulsant activity [124–135]. Anticonvulsant activity of thiazolidines was observed due to their ability to inhibit oxidation of substrate of tricarboxylic acid cycle like pyruvate, α-ketogluterate, citrate and β-hydroxybutyrate. Maximum inhibition was observed with the compounds when an unsubstituted phenyl group was attached at position −2 of thiazolidinone nucleus [127].

Some new substituted coumarinylthiazolines, coumarinylthiazolidin-4-ones, and substituted chromenothiazoles were synthesized and evaluated for anticonvulsant activity against seizures induced by pentylenetetrazole (PTZ) and strychnine in mice. Compound **51** (Scheme 20) was the most active of the series against PTZ induced seizures and exhibited anticonvulsant activity (PD50 = 95 mg/kg, ip) at a dose of 200 mg/kg as compared to Phenobarbital (PD50 = 16 mg/kg, ip) at a dose of 30 mg/kg (90% protection) [136].

Novel substituted oxa/thiadiazolylazetidinonyl/thiazolidinonylcarbazoles **52** (Scheme 20) were synthesized and screened for their antipsychotic and anticonvulsant activities. It was concluded from the results that compounds having thiadiazole ring showed better biological activities than compounds having oxadiazole ring and compounds having thiadiazolylthiazolidinonyl ring at 9th position of carbazole nucleus showed good antipsychotic and anticonvulsant response when compared to the other compounds and the reference drugs [137].

Shingalapur et al. synthesized a series of 4-thiazolidinones containing 2-mercapto benzimidazole moiety **53** (Scheme 20) and screened them for their *in vivo* anticonvulsant activity using MES model and the results of the study were compared to the standard drug phenytoin. It was observed that existence of a hydrophobic unit in benzimidazole ring, an electron donar group and a hydrogen bonding domain is essential for the anticonvulsant activity. The presence of a hydroxyl function at 2 and 4 position of phenyl ring were found to be main structural requirements for the activity because when replaced by chloro or methyl group complete loss of anticonvulsant activity resulted [138].



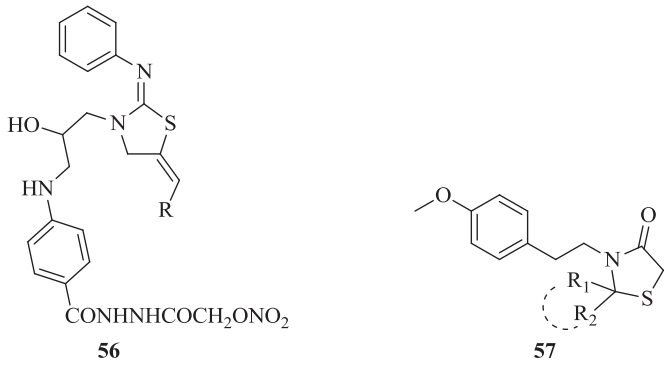
Scheme 20. 4-Thiazolidinone derivatives showing anticonvulsant activity (**51**–**55**).

A series of 9*H*,10*H*, 3-[N-methyl-2-benzamidothiophen-3-yl carbonylamino-[2-(2′-phenyl-1′ethylenyl)]-10-aryl thiazolodino [4,5b]-1,5-benzodiazepine **54** (Scheme 20) were synthesized by Ghogare et al. to meet the structural requirements for anticonvulsant activity. This was determined, after intraperitoneal administration to mice, by supramaximal electroshock seizures model and isoniazide hydrazone induced seizures model. Motor impairment was determined by actophotometer and rotarod apparatus. Active compounds were found to possess hydroxyl substituent at 2-position and methoxy position in the phenyl ring at C_5 of benzodiazepine. Results of the study conclude that a small, polar and electron rich polar group contributes significantly more than the electronegative substituents for the anticonvulsant activity [139].

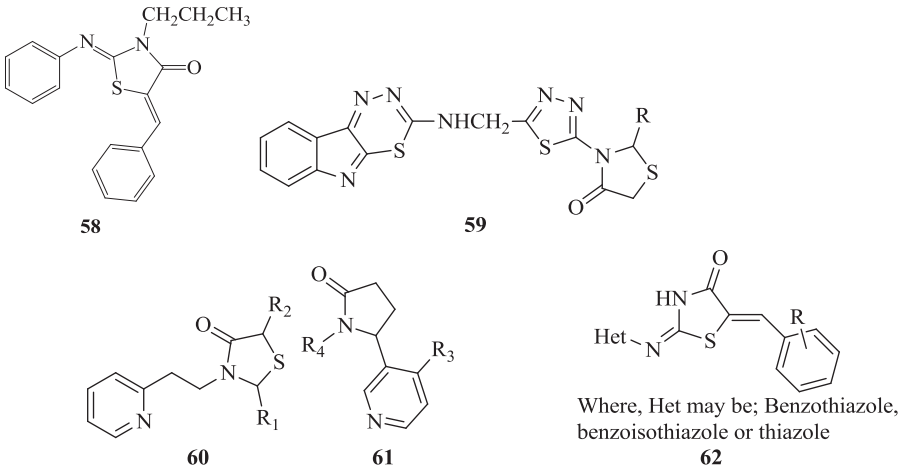
Agrawal et al. synthesized a series of 5-[(N-substituted benzylidenylimino)amino]-2-oxo/thiobarbituric acid **55** (Scheme 20) and screened them for their anticonvulsant activity and acute toxicity resulting into some potent compounds, when compared with the reference drugs phenytoin sodium, lamotrigine and sodium valproate [128].

5.4. Cardiovascular activity

In the long-term treatment of hypertension, there is no single antihypertensive drug which is able to normalize the elevated blood pressure in all hypertensive patients. β-Adrenoceptors are known to play an important role. In the regulation of the autonomic nervous system, β -blockers have been shown to be useful in the pharmacotherapy of serious and widespread cardiovascular diseases [140]. Nitric oxide (NO) donors have been used for many years in the treatment of various clinical conditions, particularly coronary arterial diseases [141]. In order to improve patient compliance, hybrid compounds were developed containing three different pharmacophores viz. propanolamine possessing the characteristics of a typical β-antagonist, thiazolidinone component responsible for antiarrythmic activity and of a 'slow NO donor', by adding NO-donor side chain. These new compounds displayed vasorelaxing effects, due to the release of NO. Therefore, hybrid molecules with vasodilating and nitric oxide (NO), which is constitutively produced by endothelial nitric oxide synthase and acts upon the guanylate cyclase–cGMP pathway, is required for the maintenance of blood-vessel homeostasis, blood pressure, and organ perfusion. Eight derivatives of general formula 2-(2-(4-(3-((5-substituted methylene)-4-oxo-2-(phenylimino) thiazolidin- 3-yl)-2-hydroxypropylamino) benzoyl) hydrazinyl)-2-oxoethyl nitrate were synthesized and tested for electrocardiographic, antiarrhythmic, vasorelaxing and antihypertensive activity as well as for *in-vitro* nitric oxide (NO) releasing ability. Compound **56** (Scheme 21), 2-(2-(4-(3-(5-benzyliden-4-oxo-2-(phenylimino) thiazolidin-3-yl)-2 hydroxypropylamino) benzoyl) hydrazinyl)-2-oxoethyl nitrate, was the most potent compound in this series. The pharmacological results suggested that the antiarrhythmic effects of these compounds were related to their adrenolytic properties which are believed to be due to the presence of the 5-(substituted) methylen-2-(phenylimino)thiazolidin-4-one moiety with less bulky, electron donating substituent on the phenyl ring at 5th position of the thiazolidin-4-one. In conclusion, most of the synthesized compounds were significantly potent as antiarrhythmic and antihypertensive; this might be due to the presence of different pharmacopores which might act at different locations with different mode of action. Further insights of the same can be obtained by doing investigation at receptor level [142].



Scheme 21. 4-Thiazolidinone derivatives showing cardiovascular activity (**56**, **57**).



58 59 60 61 62

Scheme 22. 4-Thiazolidinone derivatives showing antiinflammatory and analgesic activity (**58**–**62**).

One approach to prevent fibrillation involves increasing myocardial refractoriness by blockade of repolarizing currents carried by potassium ion (K+) channels. Most of the currently marketed antiarrhythmic agents block the hERG channel and the associated IKr repolarizing current which is present in both the atria and the ventricles. While blockade of hERG in the atria can reduce atrial arrhythmias, blockade of hERG in the ventricles leads to a prolongation of the QT interval and an increased propensity for life-threatening ventricular arrhythmias. Blockade of atrial selective K^+ channels could provide an approach for control of atrial arrhythmias that is devoid of adverse ventricular effects. One such atrial-selective channel is Kv1.5 which carries the ultra-rapid delayed rectifier current I_{Kur} [143,144]. The I_{Kur} current functions selectively, in human atrial cells, so blockade of Kv1.5 may provide a promising approach for the development of safe and effective drugs for prevention of atrial arrhythmias [145]. Several companies have pursued Kv1.5 inhibitors and much of this work has been summarized in recent reviews [146]. Blockade of the Kv1.5 ion channel is a potentially atrial-selective avenue for the treatment of atrial fibrillation and atrial flutter. The development and biological evaluation of a series of thiazolidine- based **57** (Scheme 21) blockers of Kv1.5 has been described [147].

5.5. Antiinflammatory and analgesic activity

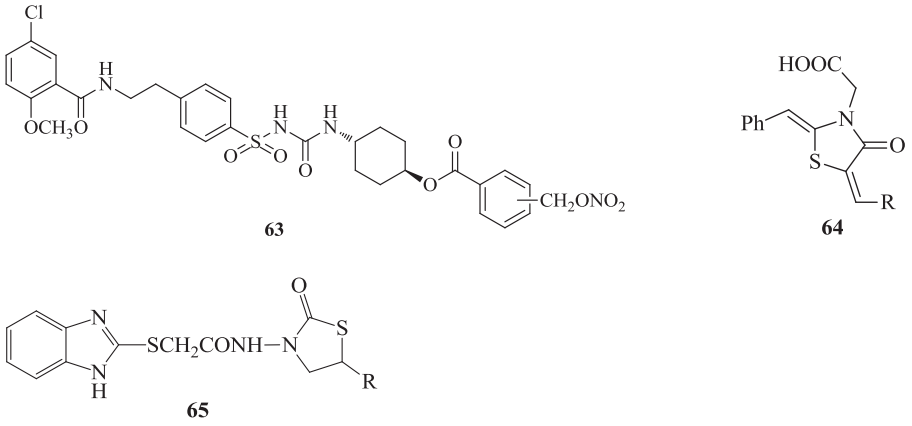
Thiazolidinone is an important pharmacodynamic heterocyclic nucleus, which when alone or when incorporated with different heterocyclic templates, has been reported to possess potent anti-inflammatory activity. 3,3′-(1,2-Ethanediyl)-bis[2-aryl-4-thiazolidinone] derivatives showed interesting stereo-selective antiinflammatory/analgesic activities together with better gastrointestinal safety profile than known NSAIDs [148–150].

In this context, the synthesis and pharmacological activity of 5-arylidene-2-imino-4-thiazolidinones **58** (Scheme 22) was described. All derivatives exhibited significant activity in models of acute inflammation, such as carrageenan induced paw and pleurisy edema in rats. In particular, 5-(3 methoxy-phenylidene)-2-phenylimino-3-propyl-4-thiazolidinone displayed high levels of carrageenan- induced paw edema inhibition, comparable to that of indomethacin. In addition, the ability of such a new class of anti-inflammatory agents to inhibit COX isoforms was assessed in murine monocyte/macrophage J774 cell line assay. 5-(4-Methoxyphenylidene)- 2-phenylimino-3-propyl-4-thiazolidinone, the most interesting compound in the experiment, was docked in the known active site of COX-2 protein which showed that its 4-methoxyarylidene moiety can easily occupy the COX-2 secondary pocket, considered as the critical interaction for COX-2 selectivity [38].

Different thiazolidin-4-one substituted bromoquinazolinone derivatives have been synthesized and screened for their anti-inflammatory and analgesic activities, at the dose of 50 mg/kg p.o., and also tested for ulcerogenic activity, the UD50 value was found to be 195.6 mg/kg p.o. The structures of all the compounds were established by elemental analysis (C, H, N) and spectral analysis (IR, 1H NMR and mass spectrometry) [151].

Various N-({5-[(arylmethylene)amino]-1,3,4-thiadiazol-2-yl} methyl) [1,3,4] thiadiazino[6,5-b]indol-3-amine, 2-aryl-3-{5-[([1,3,4] thiadiazino[6,5-b]indol-3-ylamino)methyl]-1,3,4-thiadiazol-2-yl}-1,3-thiazolidin-4-one **59** (Scheme 22), and 3-chloro-4-aryl-1-{5-[{[1,3,4]thiadiazino[6,5-b]indol-3-ylamino]methyl]-1,3,4-thiadiazol-2-yl}azetidin-2-one have been synthesized and their structures were confirmed by analytical and spectral data. These compounds were also evaluated for their antiinflammatory, ulcerogenic and analgesic activities [152].

N-type channels are located primarily at pre-synaptic nerve terminals and mediate spinal transmission of pain signals from the periphery to the central nervous system (CNS), by modulating release of nociceptive neuro-transmitters and neuropeptides. N-type channels may be essential for the development of neuropathic pain, associated with nerve injury, and control of N-type activity is important in the management of pain [153]. The recently approved pain drug Ziconotide (Prialt™) is a potent blocker of N-type Ca^{2+} channels [154]. Pre-clinical and clinical studies of Ziconotide conclude that selective blockade of the N-type channel is effective in reducing inflammatory and neuropathic pain in humans. Gabapentin was the first drug approved for post-herpetic neuralgia treatment. A series of new N-type ($C_{av}2.2$) calcium channel blockers derived from the 'hit' structures 2-(3-bromo-4-fluorophenyl)-3- (2-pyridin-2-ylethyl) thiazolidin-4-one **60** (Scheme 22) and its 2-[4-(4-bromophenyl) pyridin-3-yl]-3-isobutyl analog **61** (Scheme 22) was described. Extensive SAR studies, using a range of synthetic approaches, resulted in novel patented compounds with IC_{50} values of up to 0.2 lM in an *in vitro* IMR32 assay, and selectivities for N/L of up to 30-fold. The new compounds described have potential in the treatment of neuropathic pain [155]. Further, Panico et al. synthesized 5-arylidene-2-oxo-4-thiazolidinones and the 2-phenylimino analogs and evaluated their anti-degenerative activity on human chondrocyte cultures stimulated by IL-1β and their inhibitory



Scheme 23. 4-Thiazolidinone derivatives showing antidiabetic activity (**63**–**65**).

capability against matrix metalloproteinase-13. The results indicated that 5-arylidene- 2,4-dioxothiazolidin-3-yl acetic acids exhibited maximum anti-degenerative activity and could block multiple cartilage destruction during the osteoarthritic process. These compounds showed significant effectiveness in reducing NO release and restoring normal levels of GAGs in chondrocytes treated with IL-1β [156].

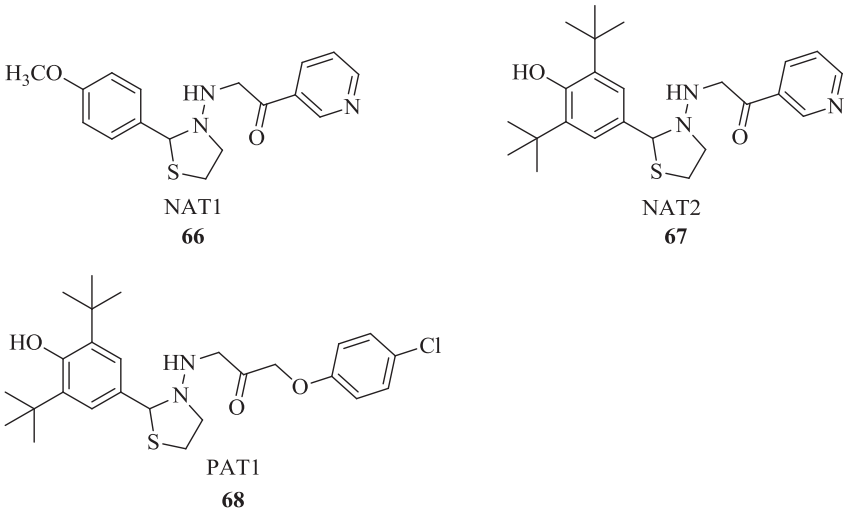
Balanced modulation of several targets is one of the current strategies for the treatment of multi-factorial diseases. Based on the knowledge of inflammation mechanisms, it was inferred that the balanced inhibition of COX-1/COX-2/lipoxigenase (LOX) might be a promising approach for the treatment of such multi-factorial disease states as inflammation. Detection of fragments responsible for interaction with the enzyme's binding site provides the basis for designing new molecules **62** (Scheme 22) with increased affinity and selectivity. A new chemo-informatics approach has been proposed and applied to create a fragment library that was used to design novel inhibitors of COX-1/COX-2/LOX enzymes. Potential binding sites were elucidated by docking. Synthesis of novel compounds, and the *in vitro/in vivo* biological testing confirmed the results of computational studies. The benzothiazolyl moiety has been proven to be of great significance for developing more potent inhibitors [157].

5.6. Antidiabetic activity

Type II diabetes mellitus is presently viewed as a multifactorial disease in which both metabolic and cardiovascular disorders coexist and are somehow correlated, although the exact mechanisms of this possible interaction are not yet completely understood [158]. Really, the metabolic aspects of this complex disease are almost always associated with microvascular complications, leading to retinopathy, neuropathy and nephropathy. Also, important macrovascular problems (myocardial ischemia, cerebrovascular accidents, hypertension, peripheral vasculopathy) accompanying (and sometimes anticipate) type II diabetes [159].

The pathogenesis of diabetic cardiovascular complication seems to involve biosynthesis and release of nitric oxide (NO) and other endothelial factors [160,161]. The examples of NO-antidiabetic molecules, that is, hybrid drugs nitrooxymethylbenzoate-derivatives of a hydroxylated active metabolite of glibenclamide **63** (Scheme 23) exhibit both, hypoglycaemic effects (due to the insulin secretagogue property, residing in the hydroxyglibenclamide portion) and further cardiovascular effects ensured by NO (released by the suitable side chains bearing the nitrooxy function) [162].

In view of the complex metabolic changes induced by hyperglycemia in which aldose reductase 2 (ALR2) is critically involved and the prominent role performed by oxidative stress, derivatives endowed with dual activity as ALR2 inhibitors and antioxidant agents could thus represent a promising way forward in the search for useful drugs to treat long-term complications associated with diabetes mellitus. A variety of structurally different compounds have already been identified as potent *in vitro* ALR2 inhibitors (ARIs) [163]. They can be classified into three general groups based on their structures: acetic acid derivatives (e.g. tolrestat and epalrestat), cyclic imides (especially spirohydantoins, e.g. sorbinil) and phenolic derivatives (e.g. quercetin). Despite being structurally different, all ARIs possess two peculiar pharmacophoric elements: (a) an acid moiety which is able to interact with the rigid anion binding site of the catalytic site (Y48, H110, W111 and the flanking cofactor NADPþ) and (b) a lipophilic scaffold which can bind to the flexible specificity pocket of the catalytic site lined with L300, W111, and T113. In spite of the numerous efforts made over recent decades, to date epalrestat is the only ARI currently available in the market. In this context, 2,4-thiazolidinediones have attracted considerable attention being ARIs designed as sorbinil analogs, that lack the hydantoin moiety which is thought to be responsible for side effects. Moreover, the introduction of 2,4-thiazolidinediones into clinical practice as antidiabetic drugs, that are able to improve glycemic control and enhance insulin sensitivity in type 2 diabetic subjects, has increased the interest in this class of compounds as potential dual purpose drugs to treat both DM and its associated complications. In recent years, a series of 5-arylidene-2,4-thiazolidinones active as ARIs has been designed. Among these, the presence of an acetic chain N-3 gave inhibitors endowed with the highest activity. The substituents on the 5-arylidene moiety in particular, the presence of a wide lipophilic moiety such; as phenoxy-benzylidene, benzyloxybenzylidene or naphthylmethylidene, favors interaction with the ALR2 lipophilic pocket. Molecular docking experiments of 2,4-thiazolidinediones into the ALR2 active site highlighted that the acetic acid group can bind the anion binding site by electrostatic and hydrogen bonds with Y48, H110 and W111 together with the nicotinamide moiety of the cofactor, while the lipophilic 5-arylidene group binds tightly to the hydrophobic binding pocket lined with W111 and L300. The insertion of the vinyl moiety as a spacer, allowed a more extensive electronic delocalization which could strengthen the affinity of inhibitors with ALR2 through different interactions over and above serve as a probe to assess the capability of the flexible lipophilic pocket of ALR2 to accommodate an enlarged arylidene moiety [164–166].



Scheme 24. 4-Thiazolidinone derivatives showing antihyperlipidemic activity (**66**–**68**).

In the search for more effective 5-arylidene-4-thiazolidinones **64** (Scheme 23) as ALRs, a new set of suitably substituted compounds were explored which proved to be interesting inhibitors of the enzyme as well as excellent antioxidant agents that were potentially able to counteract the oxidative stress associated with both, diabetic complications as well as other pathologies [167].

A study was undertaken on the basis of several reports in the literature that pancreatic beta cells were capable of replication/regeneration and also afforded protection against damage induced by streptozotocin. Nicotinamide was reported to give protection against streptozotocin-induced damage in rats. In a study, two thiazolidine-4-ones with nicotinamide substitution were administered to Swiss albino mice with streptozotocin diabetes for 15 days. Concurrently, one group received nicotinic acid. Both the test compounds reversed the hyper-glycemia in the diabetic mice. Damage to pancreatic islets was also reduced in these groups compared to diabetic control and nicotinic acid treated groups. Since these compounds have been earlier found to have antioxidant activity, one of the possible mechanisms of action could be by reducing oxidative stress in pancreas. Further, possibly by releasing nicotinamide *in vivo*, the molecules could have contributed to the NAD pool in pancreas and afforded protection. It was concluded that the test compounds had potential to be developed for multiple action in conditions like metabolic syndrome [168].

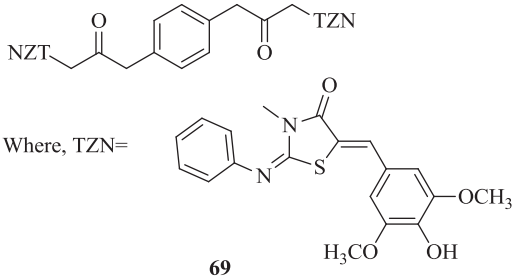
In seeking broad spectrum pharmacological activities of benzimidazole derivatives, a group reported that 4-thiazolidinones **65** (Scheme 23) exhibited antidiabetic activity in the oral glucose tolerance test (OGTT) and also, pharmacophore derived from the active molecules suggested that the presence of –OH group was a common feature in all the active compounds [138].

5.7. Antihyperlipidemic activity

Although there are effective drugs for the control of each of the conditions of the metabolic syndrome, none of them has the ability to address all the problems like dyslipidemia, hypertension, increased blood glucose, insulin resistance, pro-thrombotic state and inflammation [169]. Drugs with multiple actions could be presumed to be of high value for patients with metabolic syndrome. Previous studies led to the finding of a 4-thiazolidinone derivative (NAT1) with both, hypolipidemic and hypoglycaemic activities in rats [170,171]. Three 4-thiazolidinones, two with nicotinamide (NAT1 and NAT2) **66**, **67** (Scheme 24) and one with 4-chlorophenoxy-acetamide (PAT1) **68** (Scheme 24), side chains were evaluated for their hypolipidemic, hypoglycaemic activity in Swiss albino mice fed with a high-fat diet along with fructose administered in drinking water. NAT1 and PAT caused reduction of elevated triglycerides, cholesterol and glucose; NAT2 was effective only against triglycerides. Nicotinamide side chain might have contributed to the lipid lowering effect of both NAT1 and NAT2, but the bulky group of the latter could have affected proper binding to the receptor sites, making it ineffective against the elevated cholesterol. On the other hand, the 4-chlorophenoxyacetamide side chain of PAT might have exerted powerful hypolipidemic activity, despite the bulky substitution at C2. As antioxidants, NAT2 and PAT1 showed superior activity, compared to NAT1. The thiazolidinone ring might be responsible for the lipid lowering effect, which is however, modified by the type of substitutions at C2 and N of the ring [172].

5.8. Antimicrobial activity

4-Thiazolidinone ring system is a core structure in various synthetic pharmaceuticals displaying a broad spectrum of biological activity, including antibacterial and antifungal properties (Scheme 25) [173–181]. The emergence of multidrug-resistant gram-positive bacteria, such as methicillin-resistant *Staphylococcus aureus* (MRSA), have made treatment of infectious diseases difficult and over the last decade, become a serious medical problem. As pathogenic bacteria continuously evolve resistance to the currently used antibacterial agents, the discovery of novel and potent antibacterial agents is the best way to overcome bacterial resistance and develop effective therapies [182]. Peptidoglycan is an essential component of the cell wall of both, Gram-positive and Gram negative bacteria. 4-Thiazolidinones have been reported as novel inhibitors of the bacterial enzyme Mur B, which is a precursor during the biosynthesis of peptidoglycan [183]. A possible therapeutic solution to the problem of bacterial resistance to existing antibiotics is to discover drugs that will block pathogenic mechanisms rather than killing the infecting microbe. These pathogenic mechanisms include secretion systems, such as the type 3 secretion system (T3SS) that deliver a variety of pathogen proteins using multi-component oligomeric structures. Although many of the secreted virulence proteins are species-specific, the secretion systems are more conserved across species, indicating that disruption of such secretion systems is potentially a broad-spectrum



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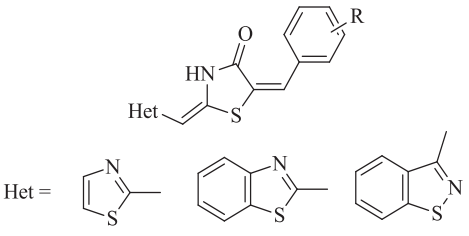

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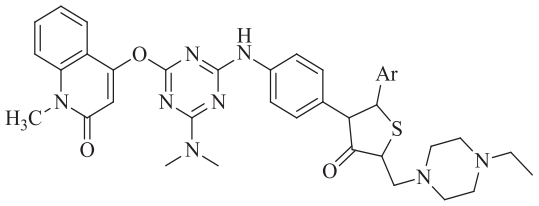

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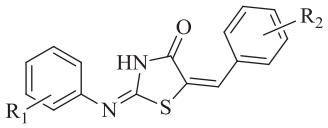
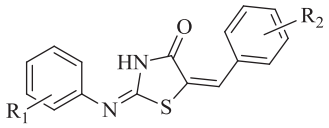


Where, R_1= 2-NO_2, 4-NO_2, R_2= H, 2-Cl, 4-Cl, 4-OH, 2-NO_2, 3-NO_2, 4-OH & 3-OCH_3

72



Where, R_1= 3-Cl & 4-F, 4-Cl, 3-Cl, R_2= H, 2-Cl, 4-Cl, 4-OH, 2-NO_2, 3-NO_2, 4-OH & 3-OCH_3

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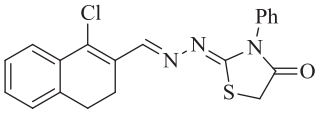

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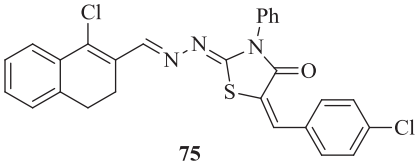

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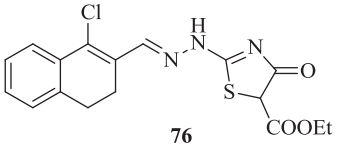

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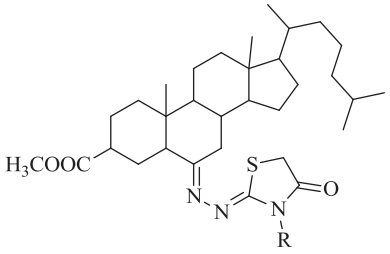

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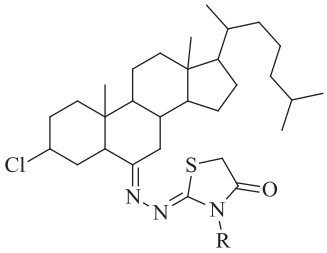

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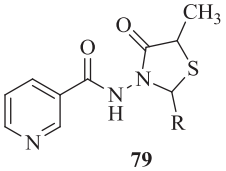

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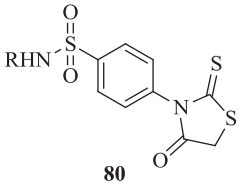

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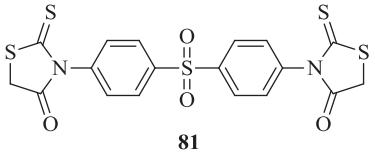

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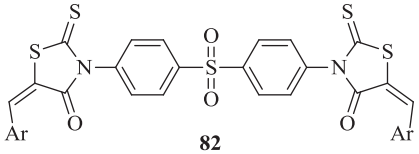

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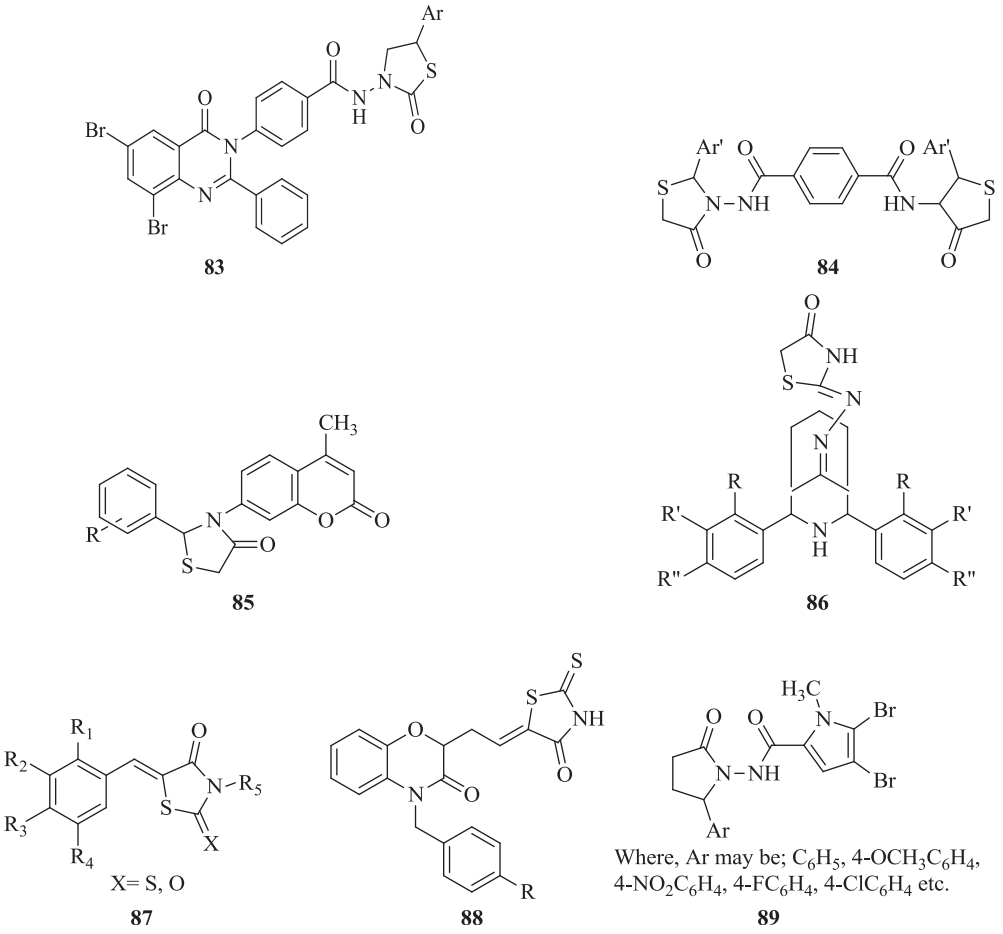
Scheme 25. 4-Thiazolidinone derivatives showing anti-microbial activity (**69**–**89**).



Scheme 25. (*continued*).

therapeutic strategy. Because the T3SS is not required for bacterial growth per se, this strategy might spare commensals and limit bacterial resistance. In contrast, antibiotics that inhibit microbial growth exert a strong selection pressure for resistance [184]. In recent years, the T3SS machinery has become an aggregate target for drug discovery [185,186]. Previously, tris-aryl substituted 2-imino- 5-arylidenethiazolidin-4-one **69** (Scheme 25), was identified as a broad spectrum inhibitor of Gram-negative bacterial secretion systems [187]. It has been demonstrated that thiazolidinone analogs, in which the heterocycle is presented as a dimer at the termini of a series of linkers, had the potential to be expanded into molecules with broad-spectrum anti-Gram negative activity. Many of these dimers inhibited the T3SS-dependent secretion of a virulence protein at concentrations lower than that of the original monomeric compound [188].

On the basis of the assumption that a benzylidene moiety at the 5-position of the 4-thiazolidinone is necessary for the antimicrobial activity, an attempt was made to rationalize the structure–activity relationship of all the 2-heteroarylimino-5-benzylidene-4-thiazolidinones **70** (Scheme 25) through a QSAR analysis. 2-Heteroarylimino-5-benzylidene-4-thiazolidinones, unsubstituted or carrying hydroxy, methoxy, nitro and chloro groups on the benzene ring, were synthesized and assayed *in vitro* for their antimicrobial activity against Gram positive and Gram negative bacteria, yeasts and mold. The antimicrobial activity of the 2-benzo [d]thiazolyl- and of the 2-benzo[d]isothiazolyl-imino-5- benzylidene-4-thiazolidinones was, on the whole, lower in comparison with the high activity detected for the derivatives of the 2-thiazolylimino- 5-benzylidene-4-thiazolidinone class. Nevertheless, most of the benzo[d]thiazole analogs displayed good inhibition of the growth of Gram positive bacilli and staphylococci, including methicillin-resistant Staphylococcus strains. Among the 2-benzo[d]isothiazole analogs, a few derivatives showed a strong and selective activity against bacilli. Moreover, it was worth noting that the replacement of the thiazole nucleus for the benzo[d]thiazole bicyclic system in the parent 2-(benzo[d]thiazol-2-ylimino) thiazolidin-4-one lead to significant antifungal properties against both yeasts and molds, properties not shown by the analogous 2-thiazolyl- and 2-benzo[d]isothiazolyl-imino)thiazolidin-4-ones [189].

Patel et al. synthesized a novel series of thiazolidinone derivatives, namely 4-(4-dimethylamino-6-{4-[5-(4-ethylpiperazin-1-ylmethyl)-4-oxo-2-phenylthiazolidin-3-yl]-phenylamino}-[1,3,5]triazin-2-yloxy)-1-methyl-1H-quinolin- 2-one **71** (Scheme 25) from the key intermediate 4-[4-(4-aminophenylamino)-6-dimethylamino- [1,3,5]triazin-2-yloxy]-1-methyl-1H-quinolin-2-one through condensation reaction with different aldehyde derivatives to obtain Schiff base derivatives, which after cyclization gave thiazolidinones and finally they were reacted with N-ethylpiperazine to get the target compounds. These compounds were evaluated for their antimicrobial activity against eight bacterial strains and four fungal strains, which ascertained that some of the newly synthesized compound containing electron withdrawing group like chloro, fluoro as substituent on phenyl ring at thiazolidinone moiety showed significant activity against both the Gram-positive as well as Gram-negative bacteria. On the other hand,

compounds having electron donating group such as methoxy as substituent on phenyl ring also showed good activity against both bacterial strains (gram-positive and gram-negative) [190].

Chawla et al. synthesized a series of 4-thiazolidinone derivatives **72** (Scheme 25), bearing 2-nitrophenyl imino and 4-nitrophenyl imino groups at position-2 and substituted arylidene groups at position-5, and evaluated for antimicrobial activity against four bacterial and one fungal strain. The success of the synthesis of compounds was confirmed on the basis of spectral analysis. All the newly synthesized compounds were obtained in high yields and exhibited good antibacterial activity; however, the antifungal potential was limited to compounds bearing 5-arylidene moiety as such or as substituted with 2-chloro, 2-nitro, 3-nitro groups [10].

Another series comprising of several 2, 5-disubstituted-4-thiazolidinone derivatives **73** (Scheme 25), bearing 3-chloro-4-fluorophenyl imino, 4-chlorophenyl imino and 3-chlorophenyl imino groups at position-2 and substituted arylidene groups at position-5 was synthesized by Chawla et al. The title compounds were obtained in high yields through Knoevenagel condensation and evaluated for antimicrobial activity against *B. subtilis*, *S. aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, and *Candida albicans*. Success of the synthesis was confirmed through spectral analysis. The newly synthesized compounds exhibited promising antibacterial activity but no antifungal activity. SAR studies revealed that the presence of a fluoro group in addition to a chloro group had a marked influence on the antibacterial activity [11].

The thiosemicarbazones and N-arylidene cyanoacetohydrazide were prepared by Bondock et al. and used as key intermediates for the synthesis of 4-thiazolidinones **74**, **75** and **76** (Scheme 25) thiazoles and thiazoline derivatives. The newly synthesized compounds were characterized by IR, ^{1}H NMR and mass spectral studies. Representative compounds were evaluated as antimicrobial agents [191].

Steroidal thiazolidinone derivatives **77** and **78** (Scheme 25) were prepared by the multistep reactions of steroid by Khan et al. from steroidal thiosemicarbazones with ethylbromoacetate in dioxane. Steroidal thiosemicarbazones were prepared by the reaction of thiosemicarbazide with steroidal ketones. The structures of the synthesized compounds were elucidated by IR, 1H NMR, mass spectrometry and their purities were confirmed by elemental analyses. The antibacterial activity of these compounds was evaluated by the disk diffusion assay against two Gram-positive and two Gram-negative bacteria and then the minimum inhibitory concentration (MIC) of the compounds was determined. The results showed that steroidal thiazolidinone derivatives were better in inhibiting the growth as compared to steroidal thiosemicarbazone derivatives against Gram-positive and Gram-negative bacterial strains. Synthesized compounds showed better antibacterial activity as compared to the standard drug Amoxycillin. The biological behavior of these compounds revealed that chloro and acetoxy substituents on the 3β-position of the steroidal thiazolidinone ring increased the antibacterial activity [192].

Sharma et al. synthesized some new N-(5-methyl-4-oxo-thiazolidin-3-yl)-nicotinamide derivatives **79** (Scheme 25) by condensation of nicotinic acid hydrazide with various aromatic or heterocyclic aldehydes to yield the Schiff bases. Cyclo-condensation of Schiff bases with 2-mercapto-propionic acid afforded 4-thiazolidinone derivatives. The structures of the newly synthesized compounds were confirmed by analytical IR, NMR and mass spectral data. All the synthesized compounds of the series elicited remarkable activity in comparison to the standard drug, ampicillin. A number of descriptors were tested to adjudge a quantitative correlation between activity and structural features. However, significant correlation emerged between activity and physicochemical parameters viz. hydrophobic parameter (log P). Moreover, results were interpreted on the basis of multiple regression analysis and cross validation methodology [193].

Syntheses of 2-thioxo-4-thiazolidinones **80** (Scheme 25) was achieved by cyclo-condensation of isothiocyanato-sulfonamides with sulfanyl acetic acid, at reflux temperature in dioxane, in the presence of triethylamine by El-Gaby et al. Cyclization of 4,40-diisothiocyanate diphenylsulfone with sulfanyl acetic acid furnished 4,40-bis (2-thioxo-4-thiazolidinone-3-yl) diphenylsulfone **81** (Scheme 25), which on treatment with excess 4-methoxybenzaldehyde, in refluxing dioxane in the presence of piperidine, yielded the bisbenzylidene derivative **82** (Scheme 25). The novel synthesized compounds were characterized by IR, ^{1}H NMR and mass spectral studies. All the synthesized compounds were screened *in vitro* for their antibacterial and antifungal activities [194].

Mohamed et al. synthesized a new series of Schiff bases and their cyclized products, oxa-diazole, pyrazoles, pyrroles, thiazolidinones **83** (Scheme 25) and other related products starting from 4-(6,8-dibromo-2-phenyl-4-oxo-(4H)-quinazolin-3-yl)-benzoic acid ethyl ester and its acid hydrazide. These compounds were screened for their antibacterial activity against Gram-positive bacteria (*S. aureus*, *Legionella monocytogenes* and *Bacillus cereus*) and Gram-negative bacteria (*E. coli*, *P. aeruginosa* and *Salmonella typhimurium*) and antifungal activity (*C. albicans* and *Aspergillus flavus*) using paper disc diffusion technique. The MICs of the compounds were also determined by agar streak dilution method. The antimicrobial activity of the synthesized compounds may be due to the presence of the versatile pharmacophores and bromine, which might increase the lipophilic character of the molecule facilitating the crossing through the biological membrane of the microorganism and thereby inhibit their growth. The data also revealed that presence of *N*-methylthioamido benzoic acid hydrazide moiety of the 2-phenyl substituted quinazolin-4(*3H*)-one exerted more influence on the anti-fungal profile than ethylamido benzoic acid hydrazide and phenylamidobenzoic acid hydrazide moieties, which might be due to the presence of sulfur atom which has anti-fungal properties [195].

Metwally et al. synthesized *N*-(2, 3, 4, 6-tetra-*O*-acetyl-β-D-glucopyranosyl) or *N*-(2, 3, 4, 6-tetra-*O*-acetyl-β-D-galactopyranosyl) 2-thioxo-4-thiazolidinone derivatives by reacting, 5-arylidene-2-thioxo-4-thiazolidinones with each of 2, 3, 4, 6-tetra-*O*-acetyl-α-D-glucopyranosyl and α-D-galactopyranosyl bromides in acetone, in the presence of aqueous potassium hydroxide at room temperature. Similarly, the reaction of 5-cycloalkylidene-2-thioxo-4-thiazolidinones gave the corresponding *N*-glucosides which were tested for their antimicrobial activities [196].

A novel series of 1,4-bis(6-(substituted phenyl)-[1,2,4]-triazolo [3,4-b]-1,3,4-thiadiazoles and 4-bis(substituted phenyl)-4-thiazolidinone derivatives **84** (Scheme 25) has been synthesized from terephthalic dihydrazide through multistep reaction sequence by Palekar et al. 1,4-Bis(5-aryl-1,3,4-oxadiazole-2yl) benzene derivatives and bis-substituted terephthalohydrazide were also synthesized from terephthalic dihydrazide by cyclization with various aromatic acids and aldehydes. Terephthalic dihydrazide was obtained from poly (ethylene terephthalate) waste by reaction with hydrazine hydrate in good yield (86%). All the synthesized compounds were screened for their antibacterial activities against various bacteria and fungi strains. Several of these compounds showed potential antibacterial activity [197].

Ronad et al. synthesized a series of 7-(2-substituted phenyl-thiazolidinyl)-benzopyran-2-one derivatives by the reaction of 7-amino-4-methyl-benzopyran-2-one with appropriate substituted aldehydes to obtain various Schiff bases, which on treatment with thioglycolic acid afforded the title compounds **85** (Scheme 25). Purity of the compounds has been confirmed by TLC. Structures of

the synthesized compounds were established on the basis of IR, 1H NMR, 13C NMR and Mass spectral data. Schiff bases and title compounds were evaluated for antibacterial and antifungal activities against various bacterial and fungal strains. The results showed that some of the compounds at a dose of 100 mg/ml, exhibited good antibacterial and antifungal activity as that of standard drugs, Ciprofloxacin and Griseofulvin. The preliminary *in vitro* antimicrobial activity evidenced that the thiazolidinone derivatives are more active than the Schiff bases [198].

Ramachandran et al. synthesized a novel series of 2-[(2,4-diaryl-3-azabicyclo [3.3.1] nonan-9-ylidene)hydrazono]-1,3-thiazolidin-4-ones **86** (Scheme 25) through 2,4-diaryl-3-azabicyclo [3.3.1] nonan-9-one thiosemicarbazones from the corresponding 2,4-diaryl-3-azabicyclo [3.3.1]nonan-9-ones, upon cyclization with ethylbromoacetate in the presence of sodium acetate–acetic acid buffer. The synthesized compounds were characterized by elemental, analytical and spectral studies. Besides, the reported compounds were screened for their antibacterial and antifungal activities against a spectrum of microbes. These studies proved that some of the synthesized compounds showed maximum inhibition potency against *S. aureus*, *Salmonella typhi*, *C. albicans* and *Rhizopus* sp. at all concentrations and the derivatives with fluorine or chlorine substituents were found to be more active against all the tested organisms [199].

5-Benzylidenethiazolidin-4-ones and 5-benzylidenepyrimidine-4, 6-diones, carrying 2,3,4-trifluoro or 3,4,5-trimethoxy groups on the benzylidene moiety **87** (Scheme 25), and rhodanine derivatives **88** (Scheme 25) were synthesized and assayed *in vitro* for their antimicrobial activity against four standard bacterial strains (*S. aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, *E. coli* ATCC 25922 and *P. aeruginosa* ATCC 27853) by Tomasic et al. Some of the synthesized compounds that were active against *S. aureus* were also tested against methicillin-resistant *S. aureus* (MRSA) ATCC 43300, *Streptococcus pneumoniae* ATCC 49619 and *Streptococcus pyogenes* ATCC 19615. (Z)-5-(2,3,4-Trifluorobenzylidene)rhodanine inhibited the growth of *S. aureus* at 0.5 mg/mL and MRSA at 32 mg/mL. Stronger antimicrobial activity against *S. aureus* was observed for compounds bearing the rhodanine ring than those containing other heterocyclic moieties. Also, the 2,3,4-trifluorobenzylidene moiety and the thiocarbonyl group on the thiazolidin-4-one ring were important for potent inhibition of *S. aureus* and MRSA growth. When 2,3,4-trifluorobenzylidene moiety was replaced by 3,4,5-trimethoxy-benzylidene moiety or when thiazolidine-2,4-dione, rhodanine- N-acetic acid, barbituric or thiobarbituric acid ring was used instead of the rhodanine ring, antimicrobial activity decreases. Neither of the compounds inhibited the growth of Gram-negative bacteria, *E. coli* or *P. aeruginosa* [200].

New 2-thiazolylimino-5-arylidene-4-thiazolidinones, unsubstituted or carrying hydroxy, methoxy, nitro and chloro groups on the benzene ring, were synthesized and assayed *in vitro* for their antimicrobial activity against Gram positive and Gram negative bacteria, yeasts and mold by Vicini et al. The compounds were very potent towards all tested Gram positive microorganisms (MIC ranging from 0.03 to 6 μg/mL in most of the cases) and Gram negative microorganism, *Haemophilus influenzae* (MIC 0.15–1.5 μg/mL). However, the compounds were not effective against Gram negative microorganism, *E. coli* and fungi up to the concentration of 100 μg/mL. The 5-arylidene derivatives showed an antibacterial efficacy considerably greater than that of the parent 2-(thiazol-2-ylimino) thiazolidin-4-one, suggesting that the substituted and unsubstituted 5-arylidene moiety plays an important role in enhancing the antimicrobial properties of this class of compounds. The remarkable inhibition of the growth of penicillin-resistant Staphylococci makes these substances promising agents also for the treatment of infections caused by microorganisms resistant to currently available drugs [40]. A new series of 2-((1-(4-(4-arylidene-2-methyl-5-oxo-4,5-dihydro-1*H*-imidazol-1-yl)phenyl) ethylidene)hydrazono)thiazolidin-4-ones were synthesized under conventional and microwave irradiation methods by Desai et al. [201]. All the compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectra. The newly synthesized compounds were screened for their antibacterial and antifungal activities on *E. coli*, *S. aureus*, *P. aeruginosa*, *Staphylococcus pyogenes*, *C. albicans*, *Aspergillus niger* and *Aspergillus clavatus* by bioassays, namely serial broth dilution. The synthesized compounds showed potent antimicrobial activity against the tested microorganisms.

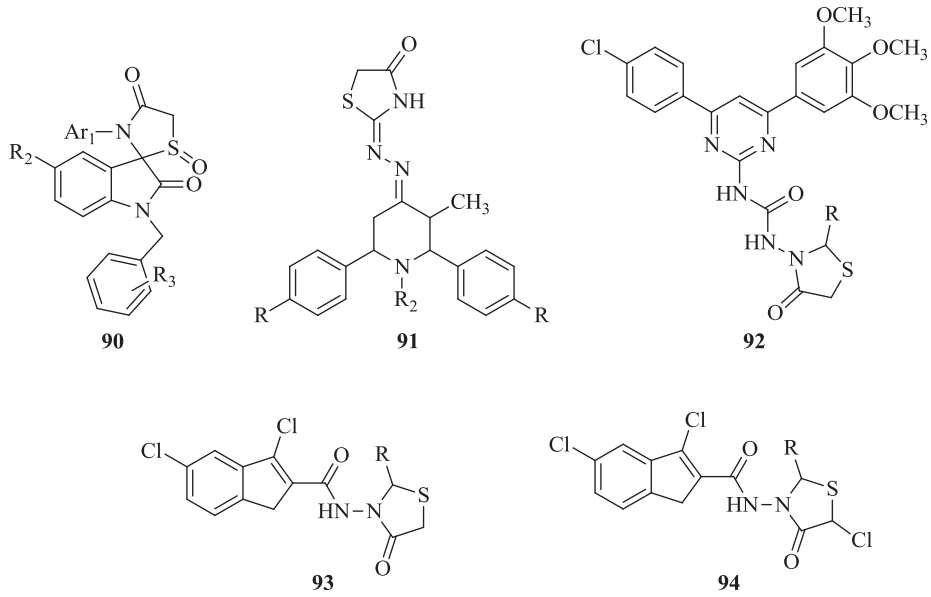
In the search for newer antimicrobial substances, it was found that bromo-pyrrole alkaloids (halogenated pyrrole derivatives), from a family of marine alkaloids represent a fascinating example of a large variety of secondary metabolites formed by marine sponges, turned attention of the researchers to naturally produced organohalogens. The activity of these kinds of natural anti-microbial substances has been modified by analog synthesis. 4-Thiazolidinones derivatives of marine bromopyrrole alkaloids **89** (Scheme 25) were synthesized as potential antibiofilm compounds. Among the synthesized compounds, some showed promising antibiofilm activity. Biological data revealed that 1,3-thiazolidin-4-one derivatives were more potent antibiofilm agents as compared to 1,3-thiazinan-4-ones, with an MIC of 0.78 μg/ml which was 3-fold superior than that of standard vancomycin [202].

5.9. Antituberculosis activity

Tuberculosis (TB), a contagious infection caused by *Mycobacterium tuberculosis*, still remains the leading cause of the worldwide morbidity and mortality among the infectious disease. Different moieties like pyrazoline, benzimidazole, purines, thiazole, flouroquinolones, quinoxaline, oxadiazole, pyrazole, thiozolidinones and azetidinones have been studied, synthesized and evaluated worldwide against *M. tuberculosis* to show their anti-tuberculosis activity [203].

Protein tyrosine phosphatases from *M. tuberculosis* are attractive targets for developing novel strategies in battling tuberculosis due to their role in the intracellular survival of *M. tuberculosis* in various infection models. The identification and further development of thiazolidinones spiro-fused to indolin-2-ones as a new class of potent and selective inhibitors of *M. tuberculosis* protein tyrosine phosphatase B (MptpB) has been reported. Detailed structure activity relationship (SAR) studies revealed that a nitro-substituted 2-oxoindole core, together with a dihalogenated anilide and a halogenated N-benzyl moiety, are essential for strong inhibitory activity against MptpB. Small structural modification of the identified compounds led to significant improvement of compound solubility and cell permeability while retaining inhibitory activity in the micromolar range. The configuration of the spiro-center was found to be crucial for the inhibitory activity and the separation of the racemate revealed the R(−)enantiomers as the biologically active components.

The reported MptpB inhibitors show excellent selectivity against a selected panel of protein tyrosine phosphatases, including MptpA (*M. tuberculosis* protein tyrosine phosphatase A), PTP1B (protein tyrosine phosphatase 1B), SHP-2 (Src homology 2 domain-containing protein tyrosine phosphatase), PTPN2, h-PTPb (human protein tyrosine phosphatase b), and VHR (Vaccinia virus VH1-related dual-specific protein phosphatase) and further highlight the identified thiazolidinones spiro-fused to indolin-2-ones **90** (Scheme 26) as a promising class of new compounds that might prove useful for chemical biology research to dissect MptpB function and eventually foster the development of next generation antibiotics [204,205].



Scheme 26. 4-Thiazolidinone derivatives showing antitubercular activity (**90**–**94**).

A stereospecific synthesis of some thiazolidinones and thiazoles was achieved conveniently through certain α-halo keto agents and reactivity of chloroacetyl chloride was successfully enhanced by CsF– Celite and sodium acetate. NMR studies revealed that the configuration of N—N bond was *anti* with respect to C-3 alkyl group while C═N bond in thiazolidinone was *trans* with respect to N—N bond. Anti-mycobacterial activity tested against *M. tuberculosis* indicated that compounds **91** (Scheme 26) exhibited two-fold enhanced potency than Rifampicin [206]. Patel et al. synthesized 2-aryl-3-[4-(4-chlorophenyl)-6-(3,4,5-trimethoxy-phenyl)pyrimidin-2-yl-ureido]-4-thiazolidinones **92** (Scheme 26) and 1-[4-(4-chlorophenyl)-6-(3,4,5-trimethoxyphenyl) pyrimidin-2-yl-ureido]-3-chloro-4-aryl-2-azetidinones and tested them for antitubercular activity against *M. tuberculosis* [207].

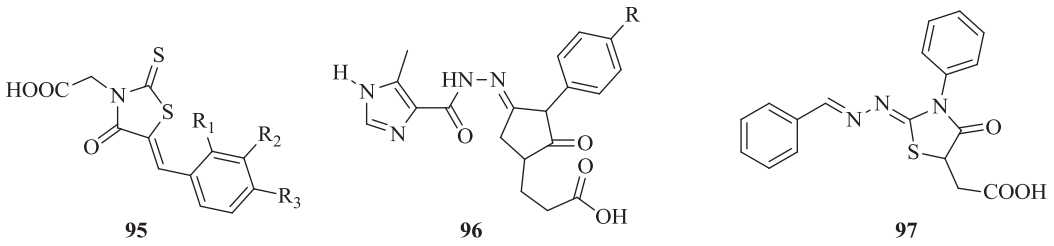
Khedekar et al. studied many substituted 1,2-dihydro compounds **93** and **94** (Scheme 26) for their antitubercular activity, which was carried out by taking into consideration various physicochemical descriptors [208]. Omar et al. synthesized a class of structurally novel 4-thiazolidinone derivatives incorporating three known bioactive nuclei such as thiazole, thiazolidinone and adamantine by a multi-step reaction protocol. NMR and Molecular Modeling techniques were employed for structure elucidation and Z/E potential isomerism configuration of the analogs. Evaluation of antibacterial and antifungal activity showed that almost all compounds exhibited better results than the reference drugs [209].

5.10. Antiparasitic activity

African sleeping sickness, also known as Human African Trypanosomiasis (HAT), is an infectious disease caused by the protozoan parasite *Trypanosoma brucei (T. brucei)* and if untreated, is invariably lethal, while with arsenical melarsoprol serious leathal side effects are observed [210,211]. The only relatively effective modern antiHAT drug against *T. brucei gambiense is*, ornithine decarboxylase inhibitor eflornithine, which is expensive and difficult to administer. The *T. brucei* parasite is covered in a dense cell-surface coat of 5 million variant surface glycoprotein (VSG) dimmers, which acts as a physical diffusion barrier for components of the innate immune system [212]. All VSG variants are linked to the trypanosomal plasma membrane via glycosyl-phosphatidylinositol (GPI) anchors. Genetic and chemical studies show that GPI anchor biosynthesis is essential for viability of the bloodstream form of *T. brucei*, thus validating it as a drug target against HAT [213]. Small molecular inhibitors of enzymes involved in GPI anchor biosynthesis therefore hold great promise as novel anti-trypanosomal agents. Recently, *T. brucei* dolicholphosphate mannose synthase (DPMS) has also been validated genetically as a drug target. Despite its promise as a therapeutic target, no inhibitors for *T. brucei* DPMS have been reported to date. The rational design of such inhibitors is complicated by the absence of a crystal structure for *T. brucei* DPMS at present. Drug-like molecules with activity against *T. brucei* are urgently required as potential therapeutics for the treatment of African sleeping sickness. Starting from known inhibitors of other glycosyltransferases, the first small molecular inhibitors of DPMS, a mannosyltransferase critically involved in glycoconjugate biosynthesis in *T. brucei* has been developed, which prevents the biosynthesis of GPI anchors, and possesses trypanocidal activity against live trypanosomes [214].

In search of a suitable lead structure for the development of DPMS inhibitors, striking structural similarities among small molecular inhibitors for other glycosyltransferases and sugar-nucleotide-dependent glycoprocessing enzymes were noticed. Several such inhibitors contain a rhodanine (2-thioxothiazolidin-4-one) scaffold, and derivatives of rhodanine-3-acetic acid **95** (Scheme 27) have been reported as inhibitors of the *E. coli* glycosyltransferase MurG and the *C. albicans* protein mannosyltransferase 1 (PMT1). It has been suggested that the thiazolidinone ring can act as a mimic of the pyrophosphate group [215,216], and that this mimicry may explain the inhibitory activity of thiazolidinone derivatives towards sugarnucleotide- dependent enzymes. As DPMS is dependent on the sugar-nucleotide donor GDP-mannose, it was reasoned that the thiazolidinone scaffold may also represent a good starting point for the development of DPMS inhibitors.

2,3-Disubstituted-1,3-thiazolidin-4-one derivatives were synthesized efficiently by Zang et al. A series of novel pyrimidine nucleoside—thiazolidin-4-one hybrids were prepared, their preliminary anti-parasitic activities were studied and it was found that some of the derivatives possessed activity against trypomastigote forms of *T. brucei* [22]. In immunocompetent patients, the infection with *Toxoplasma gondii* can cause symptoms as fever, headache or



Scheme 27. 4-Thiazolidinone derivatives showing antiparasitic activity (**95**–**97**).

myalgia. However, serious cases can result in toxoplasmic encephalitis (characterized by intra-cerebral mass lesions) with mortality rates exceeding 30% [217]. Synthesis and evaluation of anti *T. gondii* activity of 4-thiazolidinones substituted at arylhydrazone moiety with electron-withdrawing or electron-donating groups, and at N- 3 position with H, methyl, ethyl and phenyl substituents has been reported [218]. Liesen et al. synthesized and evaluated three new series of compounds from ethyl (5-methyl-1-H-imidazole-4- carboxylate): acylthio-semicarbazide analogs, 4-thiazolidinone analogs **96** (Scheme 27) and 1,3,4-thiadiazole analogs. All the synthesized compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR and HRMS. The majority of the tested compounds showed excellent anti- *T. gondii* activity when compared to hydroxyurea and sulfadiazine. [219].

A new series of 2-[(phenylmethylene) hydrazono]-4-oxo-3-phenyl-5-thiazolidineacetic acids **97** (Scheme 27) have been synthesized by de Aquino et al. using 4-phenyl-3 thiosemicarbazones substituted benzaldehyde as intermediate to give the title compounds. All the synthesized compounds were characterized by IR, 1H and 13C NMR. The *in vitro* anti-*T. gondii* and *in vitro* antimicrobial activity of synthesized compounds was evaluated and all the synthesized compounds promoted decreases in the percentage of infected cells leading to parasite elimination. These effects on intracellular parasites also caused a decrease in the mean number of tachyzoites. In addition, most of the 4-thiazolidinones showed more effective toxicity against intracellular parasites, with IC50 values ranging from 0.05 to 1 mM [220].

6. Miscellaneous activities

6.1. Follicle stimulating hormone agonist activity

Follicle-stimulating hormone (FSH) is a 38 kDa glycoprotein that is synthesized and released, as with luteinizing hormone (LH), from the anterior pituitary gland under the control of gonadotropin-releasing hormone (GnRH), act directly on the ovary to promote the development of selected follicles by stimulating granulose and theca cell proliferation and differentiation, leading to ovulation. The FSH is critical to reproductive success and is an important target for the development of novel reproductive therapies. Orally active small molecule antagonists of FSH action could lead to a new class of non-steroidal contraceptive agents [221]. Thiazolidinone-based compounds were identified as hFSHR agonists via screening of encoded combinatorial libraries [222]. One representative, 3-((2*S**, 5*R**)-2-(4-benzyloxy-phenyl)-5-{[2-(3-ethoxy-4-methoxyphenyl)-ethylcarbamoyl]-methyl}-4-oxo-thiazolidin-3-yl)- benzamide **98** (Scheme 28) was recently profiled and found to be a potent activator of human and rat FSHRs based on luciferase reporter gene screens causing hFSH-dependent cAMP accumulation, as well as estradiol secretion in rat granulosa cells. Bis sulfonic acids and monosulfonic acids were shown to be functional antagonists that displaced FSH in receptor binding assays [223]. A potent analog **99** (Scheme 28) of thiazolidinone-based follicle-stimulating hormone (FSH) agonists, containing an additional 5-alkyl substituent, was prepared and evaluated in a Chinese hamster ovary (CHO) cell line that expressed recombinant human FSH receptor (FSHR) and a luciferase reporter gene regulated by a cAMP response element (CRE) by Arey et al. Selected compounds were also tested on a CHO-cell line that over expressed the FSHR for the ability to induce cAMP production. When the 5-alkyl substituent was replaced by a methyl group, similar FSH activity (i.e. EC50 = 51 nM, 100% efficacy relative to hFSH) was observed; thus, proving that a small 5-alkyl substituent was well tolerated. New derivatives, in which the potentially hydrolytically labile secondary amide function of 1 (−CONH−) was modified to other moieties (e.g. $-CH_2NH-$, $-CH_2S-$, and $-CH_2OCONH-$), were also prepared and evaluated. These congeners also displayed good potency in the CRE-luciferase assay [224].

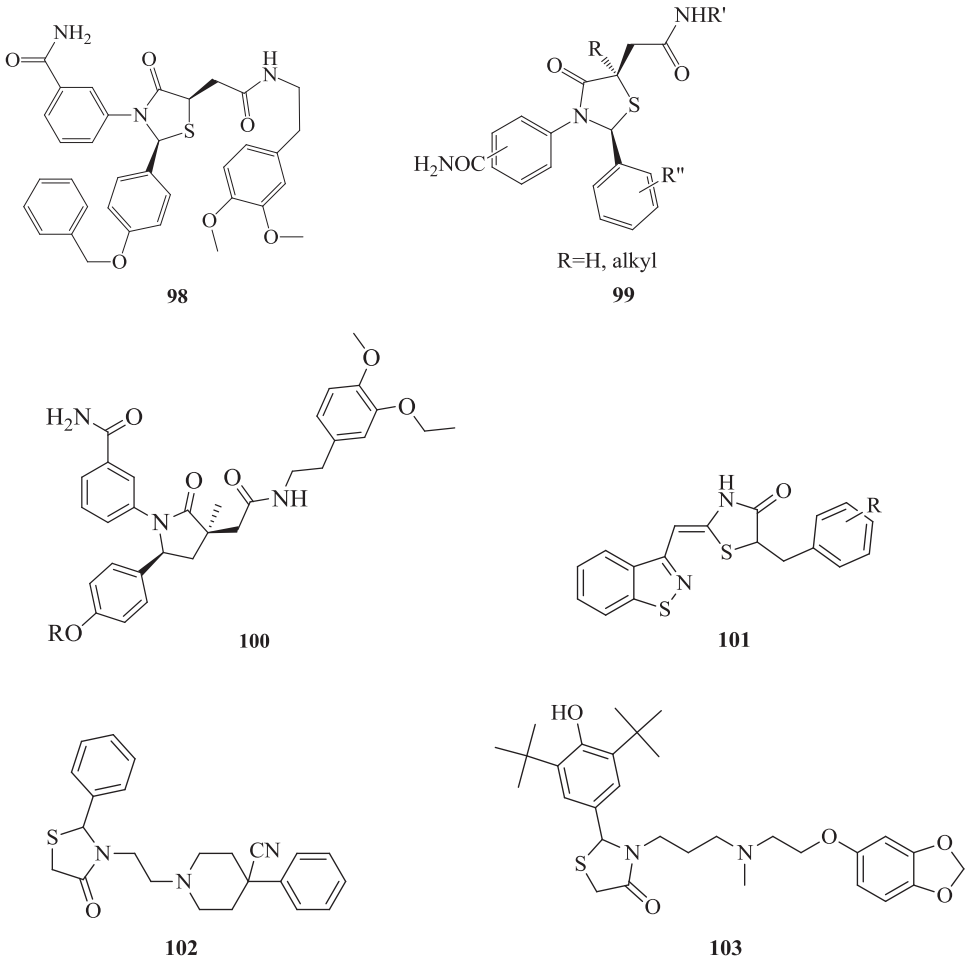
The development of thiazolidinone positive allosteric modulators of the follicle-stimulating hormone receptor was recently reported. Positive allosteric modulators activated adenylate cyclase signaling (Gs). Using an ADP-ribosylation assay, it was found that both differing glycosylated variants of human FSH (hFSH) and selected thiazolidinone allosteric modulators of the FSHR induce activation of the Gi signaling pathway. These data suggest that the pharmacological activity of thiazolidinone modulators to the FSHR may be due to the ability of these compounds to induce association of the FSHR with either Gs or Gi signaling pathways in an analog-specific manner [225].

Pelletier et al. synthesized highly substituted γ-lactam analogs of a thiazolidinone **100** (Scheme 28) by combination of Weinreb amidation and Mitsunobu lactam formation and tested them for follicle stimulation hormone receptor (FSHR) agonist activity. The analog synthesis was stereo-selective and the biological properties of the target molecules were nearly identical to those of the lead compound [226].

6.2. Antiarthritic activity

The matrix metalloproteinases (MMPs) are a family of zinc endopeptidases that have been implicated in a wide variety of biological processes and pathological conditions such as cancer, heart failure, atherosclerosis and arthritis [227-230]. Increased levels of these enzymes, that are responsible for degradation of aggrecan and collagen, have been observed in the cartilage of patients with osteoarthritis (OA) and correlate with the severity of the disease.

2-Benzo[d]thiazolyl- and 2-benzo[d]isothiazolyl-imino-5-benzylidene-4-thiazolidinone derivatives were investigated as potential metalloproteinases (MMPs) inhibitors and evaluated for their antidegenerative activity on human chondrocyte cultures stimulated by IL-1b, using an experimental model that reproduces the mechanisms involved in osteoarthritic (OA) diseases. Cell viability, the amount of glycosaminoglycans (GAGs) and the production of nitric oxide (NO) were measured. The most potent compound, 5-(4-methoxy-benzylidene)-2-(benzo[d] isothiazol-3-ylimino)-thiazolidin-4-one **101**(Scheme 28), a MMP-13 inhibitor



Scheme 28. 4-Thiazolidinone derivatives showing miscellaneous activities (**98**–**103**).

at nanomolar concentration (IC50 = 0.036 lM), could be considered as a lead compound for the development of novel clinical agents, inhibitors of cartilage degradation, for the treatment of OA [231].

6.3. Antidiarrhoeal activity

Loperamide is a well known peripherally acting opiate used for the treatment of diarrhea. A series aryl-cyano-piperidinoalkyl-thiazolidinones related to loperamide was synthesized and screened for antidiarrhoeal activity in mice by castor oil test. The synthesized compounds displayed antidiarrhoeal activity at doses ranging between 15 and 82 mg/kg. Also, to evaluate the involvement of opioid receptors for the activity, Naloxone was administered prior to the test compound, 2-phenyl-3-[2-[(4-phenyl-cyano) piperidino] ethyl]-1, 3-thiazolidin-4-one **102** (Scheme 28). The results of the study suggests that antidiarrhoeal activity of this series of thiazolidinone derivatives could involve the opioid receptor [29].

6.4. Calcium antagonists with calcium overload inhibition and antioxidant activity

Kato et al. synthesized a series of 2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-3-[3-[N-methyl-N-[2-[3,4-(methylenedioxy)-phenoxy]ethyl]amino]propyl]-1,3-thiazolidin-4-one derivatives **103** (Scheme 28), and screened them as Ca^{+2} antagonist possessing both Ca^{+2} overload inhibition and antioxidant activity. The structure activity relationship of this series of compound was studied by synthesizing the analogs and evaluating these three kinds of activities. Ca^{+2} antagonistic activities were largely determined by the lipophilicity of the phenyl ring at 2-position and the length of the alkyl chain. Antioxidant activity demonstrated that phenolic hydroxyl group is an essential structural element. Potent compounds were also evaluated for their effect on coronary blood flow *in vivo* [13,232].

7. Recent patents filed on 4-thiazolidinones

This section deals with the patents granted at WIPO and USPTO in the duration of 2000–2012 (Table S1; given under section of "supplementary material for publication online") [233–278]. These patents accentuate the synthetic advancements as well as expediency of the thiazolidinone based research molecules and drugs at some or the other stage of the diseases.

8. Conclusion

The 4-thiazolidinones continue to be one of the most researched areas in medicinal chemistry. The structural characterization of novel derivatives, together with the development of new synthetic methods and biological properties, are topics of growing interest. The new 4-thiazolidinones exhibit promising activities like anticancer, antiviral, anticonvulsant, cardiovascular, antiinflammatory and analgesic, antihyperlipidemic, anti-diabetic, antibacterial, antifungal, antituberculosis, antiparasitic etc. These activities may

be owed not only to the scaffold but also to the interaction of the pharmacophoric substituents with the biological system. The activities have been reported using various biological systems such as cell lines, bacteria, viruses, parasites, laboratory mice, rats and rabbits, and monolayer and bilayer membranes. Thus, with the passing years the advances continue and the promise of positivity holds.

The authors apologize to the researchers who, for one reason or another, have not been mentioned in this anthology.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2013.11.017

References

[1] R. Jeyaraman, S. Avila, Chem. Rev. 81 (1981) 149.
[2] S.P. Singh, S.S. Parmar, K. Raman, V.I. Stenberg, Chem. Rev. 81 (1981) 175–203.
[3] F.C. Brown, Chem. Rev. 61 (1961) 463–521.
[4] G.R. Newkome, A. Nayak, Adv. Heterocycl. Chem. 25 (1979) 83.
[5] R.M. Abdel-Rahman, Boll. Chim. Farm. 140 (2001) 401–410.
[6] A. Verma, S.K. Saraf, Eur. J. Med. Chem. 43 (2008) 897–905.
[7] W.S. Hamama, M.A. Ismail, S. Shaaban, H.H. Zoorob, J. Heterocycl. Chem. 45 (2008) 939–956.
[8] A.K. Jain, A. Vaidya, V. Ravichandran, S.K. Kashaw, R.K. Agrawal, Bioorg. Med. Chem. 20 (2012) 3378–3395.
[9] A. Verma, S.S. Verma, S.K. Saraf, J. Heterocycl. Chem. 47 (2010) 1084–1089.
[10] P. Chawla, R. Singh, S.K. Saraf, Med. Chem. Res. 21 (2011) 2064–2071.
[11] P. Chawla, R. Singh, S.K. Saraf, Med. Chem. Res. 21 (2011) 3263–3271.
[12] O.P. Agrawal, P.K. Sonar, S.K. Saraf, Med. Chem. Res. 22 (2013) 1972–1978.
[13] T. Kato, T. Ozaki, K. Tamura, Y. Suzuki, M. Akima, N. Ohi, J. Med. Chem. 42 (1999) 3134–3146.
[14] E.B. Knott, J. Chem. Soc. 22 (1954) 1482–1486.
[15] D.R. St Laurent, Q. Gao, D.D. Wu, Tetrahedron Lett 45 (2004) 1907–1910.
[16] A. Gursoy, N. Terzioglu, Turk. J. Chem. 29 (2005) 247–254.
[17] S.M. Ramsh, N.A. Smorygo, E.S. Khrabrova, Khim. Geterotsikl. Soedin. 1 (1985) 32–37.
[18] M.A. Metwally, A.A. Farahat, B.F. Abdel-Wahab, J. Sulfur Chem. 31 (2010) 315–349.
[19] E. Akerblom, Acta Chem. Scand. 21 (1967) 1437–1442.
[20] M.G. Vigorita, A. Chimirri, S. Grasso, G. Fenech, J. Heterocycl. Chem. 16 (1979) 257–261.
[21] V. Barone, A. Bolognese, G. Correale, M.V. Diurno, I. Gomez-Monterrey, O. Mazzoni, J. Mol. Graphics Model 19 (2001) 318–324.
[22] X. Zhang, X. Li, D. Li, G. Qu, J. Wang, P.M. Loiseau, X. Fan, Bioorg. Med. Chem. Lett. 19 (2009) 6280–6283.
[23] Y.V. Ostapiuk, M.D. Obushak, V.S. Matiychuk, M. Naskrent, A.K. Gzella, Tetrahedron Lett. 53 (2012) 543–545.
[24] M.E. Jung, J.M. Ku, L. Du, H. Hu, R.A. Gatti, Bioorg. Med. Chem. Lett. 21 (2011) 5842–5848.
[25] V.N. Choubey, H. Singh, Bull. Chem. Soc. Jpn. 43 (1970) 2233–2236.
[26] P.N. Bhargava, M.R. Chaurasia, J. Pharm. Sci. 58 (1969) 896–898.
[27] P.D. Neuenfeldt, B.B. Drawanz, G.M. Siqueira, C.R.B. Gomes, S.M.S.V. Wardell, A.F.C. Flores, W. Cunico, Tetrahedron Lett. 51 (2010) 3106–3108.
[28] A. Dandia, R. Singh, S. Khaturia, C. Merienne, G. Morgant, A. Loupy, Bioorg. Med. Chem. 14 (2006) 2409–2417.
[29] O. Mazzoni, A.M. di Bosco, P. Grieco, E. Novellino, A. Bertamino, F. Borrelli, R. Capasso, M.V. Diurno, Chem. Biol. Drug. Des. 67 (2006) 432–436.
[30] A. Pawelczyk, L. Zaprutko, Eur. J. Med. Chem. 41 (2006) 586–591.
[31] U.R. Pratap, D.V. Jawale, M.R. Bhosle, R.A. Mane, Tetrahedron Lett. 52 (2011) 1689–1691.
[32] A.K. Yadav, M. Kumar, T. Yadav, R. Jain, Tetrahedron Lett. 50 (2009) 5031–5034.
[33] T. Srivastava, W. Haq, S.B. Katti, Tetrahedron 58 (2002) 7619.
[34] R.K. Rawal, T. Srivastava, W. Haq, S.B. Katti, J. Chem. Res. 12 (2004) 368.
[35] S. Erol, I. Dogan, J. Org. Chem. 72 (2007) 2494–2500.
[36] P. Bonhote, A.P. Dias, N. Papageorgiou, K. Kalyanasundaram, M. Gratzel, Inorg. Chem. 35 (1996) 1168–1178.
[37] S. Gabillet, D. Lecercle, O. Loreau, M. Carboni, S. Dezard, J.M. Gomis, F. Taran, Org. Lett. 9 (2007) 3925–3927.
[38] R. Ottana, R. Maccari, M.L. Barreca, G. Bruno, A. Rotondo, A. Rossi, G. Chiricosta, R. Di Paola, L. Sautebin, S. Cuzzocrea, M.G. Vigorita, Bioorg. Med. Chem. 13 (2005) 4243–4252.
[39] G. Bruno, L. Costantino, C. Curinga, R. Maccari, F. Monforte, F. Nicolo, R. Ottana, M.G. Vigorita, Bioorg. Med. Chem. 10 (2002) 1077–1084.
[40] P. Vicini, A. Geronikaki, K. Anastasia, M. Incerti, F. Zani, Bioorg. Med. Chem. 14 (2006) 3859–3864.
[41] H.A. Abdel-Aziz, H.S. El-Zahabi, K.M. Dawood, Eur. J. Med. Chem. 45 (2010) 2427–2432.
[42] G. Kucukguzel, A. Kocatepe, E. De Clercq, F. Sahin, M. Gulluce, Eur. J. Med. Chem. 41 (2006) 353–359.
[43] M. Mamaghani, A. Loghmanifar, M.R. Taati, Ultrason. Sonochem. 18 (2011) 45–48.
[44] A. Colombo, J.C. Fernàndeza, D. Fernández-Forner, N.d.l. Figueraa, F. Albericio, P. Forns, Tetrahedron Lett. 49 (2008) 1569–1572.
[45] M.H. Bolli, S. Abele, C. Binkert, R. Bravo, S. Buchmann, D. Bur, J. Gatfield, P. Hess, C. Kohl, C. Mangold, B. Mathys, K. Menyhart, C. Muller, O. Nayler, M. Scherz, G. Schmidt, V. Sippel, B. Steiner, D. Strasser, A. Treiber, T. Weller, J. Med. Chem. 53 (2010) 4198–4211.
[46] F.M. Moghaddam, L.J. Hojabri, J. Heterocycl. Chem. 44 (2007) 35.
[47] J.R. Mali, U.R. Pratap, P.D. Netankar, R.A. Mane, Tetrahedron Lett. 50 (2009) 5025–5027.
[48] O.A. Attanasi, L.D. Crescentini, G. Favi, P. Filippone, G. Giorgi, F. Mantellini, F.R. Perrulli, D. Spinelli, Tetrahedron 64 (2008) 3837–3858.
[49] P.D. Neuenfeldt, A.R. Duval, B.B. Drawanz, P.F. Rosales, C.R.B. Gomes, C.M.P. Pereira, W. Cunico, Ultrason. Sonochem. 18 (2011) 65–67.
[50] C. Saiz, C. Pizzo, E. Manta, P. Wipf, S.G. Mahler, Tetrahedron Lett. 50 (2009) 901–904.
[51] W. Cunico, C.R.B. Gomes, M.d.L.G. Ferreira, L.R. Capri, M. Soares, S.M.S.V. Wardell, Tetrahedron Lett. 48 (2007) 6217–6220.
[52] Q. Zhang, H. Zhou, S. Zhai, B. Yan, Curr. Pharm. Des. 16 (2010) 1826–1842.
[53] D. Kaminskyy, D. Khyluk, O. Vasylenko, R. Lesyk, Tetrahedron Lett. 53 (2012) 557–559.
[54] K.S. Sharath Kumar, T.R. Swaroop, K.B. Harsha, K.H. Narasimhamurthy, K.S. Rangappa, Tetrahedron Lett. 53 (2012) 5619–5623.
[55] F.D. Popp, M.J. Rajopadhye, J. Heterocycl. Chem. 24 (1987) 261.
[56] P.J. Taylor, Spectrochim. Acta 26A (1970) 153.
[57] H. Nagase, Chem. Pharm. Bull. 21 (1973) 279.
[58] U. Vogeli, W. Philipsborn, K. Nararanjan, M.D. Nair, Helv. Chim. Acta 61 (1978) 607.
[59] D. Cremer, J.A. Pople, J. Am. Chem. Soc. 97 (1975) 1354.
[60] E. Pasquier, S. Honore, D. Braguer, Drug Resist. Updates 9 (2006) 74–86.
[61] J.R. Jackson, D.R. Patrick, M.M. Dar, P.S. Huang, Nat. Rev. Cancer 7 (2007) 107–117.
[62] N. Jiang, X. Wang, Y. Yang, W. Dai, Mini Rev. Med. Chem. 6 (2006) 885–895.
[63] M. Schmidt, H. Bastians, Drug Resist. Updates 10 (2007) 162–181.
[64] D. Kaminskyy, B. Zimenkovsky, R. Lesyk, Eur. J. Med. Chem. 44 (2009) 3627–3636.
[65] O.M. Abd Elhafez, D. El Khrisy Eel, F. Badria, D. Fathy Ael, Arch. Pharmacal. Res. 26 (2003) 686–696.
[66] V. Gududuru, E. Hurh, J.T. Dalton, D.D. Miller, J. Med. Chem. 48 (2005) 2584–2588.
[67] J.H. Ahn, S.J. Kim, W.S. Park, S.Y. Cho, J.D. Ha, S.S. Kim, S.K. Kang, D.G. Jeong, S.K. Jung, S.H. Lee, H.M. Kim, S.K. Park, K.H. Lee, C.W. Lee, S.E. Ryu, J.K. Choi, Bioorg. Med. Chem. Lett. 16 (2006) 2996–2999.
[68] N.S. Cutshall, C. O'Day, M. Prezhdo, Bioorg. Med. Chem. Lett. 15 (2005) 3374–3379.
[69] R. Dayam, F. Aiello, J. Deng, Y. Wu, A. Garofalo, X. Chen, N. Neamati, J. Med. Chem. 49 (2006) 4526–4534.
[70] A. Degterev, A. Lugovskoy, M. Cardone, B. Mulley, G. Wagner, T. Mitchison, J. Yuan, Nat. Cell. Biol. 3 (2001) 173–182.
[71] D. Havrylyuk, L. Mosula, B. Zimenkovsky, O. Vasylenko, A. Gzella, R. Lesyk, Eur. J. Med. Chem. 45 (2010) 5012–5021.
[72] D. Havrylyuk, B. Zimenkovsky, O. Vasylenko, L. Zaprutko, A. Gzella, R. Lesyk, Eur. J. Med. Chem. 44 (2009) 1396–1404.
[73] M.M. Kamel, H.I. Ali, M.M. Anwar, N.A. Mohamed, A.M. Soliman, Eur. J. Med. Chem. 45 (2010) 572–580.
[74] R. Lesyk, O. Vladzimirska, S. Holota, L. Zaprutko, A. Gzella, Eur. J. Med. Chem. 42 (2007) 641–648.
[75] Q. Li, J. Wu, H. Zheng, K. Liu, T.L. Guo, Y. Liu, S.T. Eblen, S. Grant, S. Zhang, Bioorg. Med. Chem. Lett. 20 (2010) 4526–4530.
[76] V. Patil, K. Tilekar, S. Mehendale-Munj, R. Mohan, C.S. Ramaa, Eur. J. Med. Chem. 45 (2010) 4539–4544.
[77] I. Subtel'na, D. Atamanyuk, E. Szymanska, K. Kiec-Kononowicz, B. Zimenkovsky, O. Vasylenko, A. Gzella, R. Lesyk, Bioorg. Med. Chem. 18 (2010) 5090–5102.
[78] Z. Xia, C. Knaak, J. Ma, Z.M. Beharry, C. McInnes, W. Wang, A.S. Kraft, C.D. Smith, J. Med. Chem. 52 (2009) 74–86.
[79] G.J. Murphy, J.C. Holder, Trends Pharmacol. Sci. 21 (2000) 469–474.
[80] J.W. Huang, C.W. Shiau, J. Yang, D.S. Wang, H.C. Chiu, C.Y. Chen, C.S. Chen, J. Med. Chem. 49 (2006) 4684–4689.
[81] P.H. Carter, P.A. Scherle, J.A. Muckelbauer, Proc. Natl. Acad. Sci. U. S. A. 98 (2001) 11879–11886.
[82] H. Chen, Y.H. Fan, A. Natarajan, Y. Guo, J. Iyasere, F. Harbinski, L. Luus, W. Christ, H. Aktas, J.A. Halperin, Bioorg. Med. Chem. Lett. 14 (2004) 5401–5405.
[83] F. Teraishi, S. Wu, J. Sasaki, L. Zhang, H.B. Zhu, J.J. Davis, B. Fang, J. Pharmacol. Exp. Ther. 314 (2005) 355–362.
[84] F. Teraishi, S. Wu, J. Sasaki, L. Zhang, J.J. Davis, W. Guo, F. Dong, B. Fang, Cell. Mol. Life. Sci. 62 (2005) 2382–2389.
[85] H. Zhou, S. Wu, S. Zhai, A. Liu, Y. Sun, R. Li, Y. Zhang, S. Ekins, P.W. Swaan, B. Fang, B. Zhang, B. Yan, J. Med. Chem. 51 (2008) 1242–1251.

[86] R. Ottana, S. Carotti, R. Maccari, I. Landini, G. Chiricosta, B. Caciagli, M.G. Vigorita, E. Mini, Bioorg. Med. Chem. Lett. 15 (2005) 3930–3933.
[87] S. Chen, L. Chen, N.T. Le, C. Zhao, A. Sidduri, J.P. Lou, C. Michoud, L. Portland, N. Jackson, J.J. Liu, F. Konzelmann, F. Chi, C. Tovar, Q. Xiang, Y. Chen, Y. Wen, L.T. Vassilev, Bioorg. Med. Chem. Lett. 17 (2007) 2134–2138.
[88] L.T. Vassilev, C. Tovar, S. Chen, D. Knezevic, X. Zhao, H. Sun, D.C. Heimbrook, L. Chen, Proc. Natl. Acad. Sci. U. S. A. 103 (2006) 10660–10665.
[89] R. Lesyk, B. Zimenkovsky, D. Atamanyuk, F. Jensen, K. Kiec-Kononowicz, A. Gzella, Bioorg. Med. Chem. 14 (2006) 5230–5240.
[90] K.J. French, R.S. Schrecengost, B.D. Lee, Y. Zhuang, S.N. Smith, J.L. Eberly, J.K. Yun, C.D. Smith, Cancer Res. 63 (2003) 5962–5969.
[91] A. Geronikaki, P. Eleftheriou, P. Vicini, I. Alam, A. Dixit, A.K. Saxena, J. Med. Chem. 51 (2008) 5221–5228.
[92] I. Subtel'na, D. Atamanyuk, E. Szymanska, K. Kiec-Kononowicz, B. Zimenkovsky, O. Vasylenko, A. Gzella, R. Lesyk, Bioorg. Med. Chem. 18 (14) 5090–5102.
[93] L. Mosula, B. Zimenkovsky, D. Havrylyuk, A.V. Missir, I.C. Chirita, R. Lesyk, Farmacia 57 (2009) 312–330.
[94] J.M. Pilewski, R.A. Frizzell, Physiol. Rev. 79 (1999) S215–S255.
[95] D.N. Sheppard, M.J. Welsh, Physiol. Rev. 79 (1999) S23–S45.
[96] A. Taddei, C. Folli, O. Zegarra-Moran, P. Fanen, A.S. Verkman, L.J. Galietta, FEBS Lett. 558 (2004) 52–56.
[97] N.D. Sonawane, A.S. Verkman, Bioorg. Med. Chem. 16 (2008) 8187–8195.
[98] T. Ma, J.R. Thiagarajah, H. Yang, N.D. Sonawane, C. Folli, L.J. Galietta, A.S. Verkman, J Clin. Invest. 110 (2002) 1651–1658.
[99] H. Chen, L. Jiao, Z. Guo, X. Li, C. Ba, J. Zhang, Carbohydr. Res. 343 (2008) 3015–3020.
[100] O.M. Abdel Hafez, K.M. Amin, N.A. Abdel-Latif, T.K. Mohamed, E.Y. Ahmed, T. Maher, Eur. J. Med. Chem. 44 (2009) 2967–2974.
[101] R.F. George, Eur. J. Med. Chem (2011), http://dx.doi.org/10.1016/j.ejmech.2011.1011.1006.
[102] S. Wang, G.Z.Y. Zhao, Y. Lv, N. Zhang, P. Gong, Eur. J. Med. Chem. 46 (2011) 3509–3518.
[103] L. Du, R. Damoiseaux, S. Nahas, K. Gao, H. Hu, J.M. Pollard, J. Goldstine, M.E. Jung, S.M. Henning, C. Bertoni, R.A. Gatti, J. Exp. Med. 206 (2009) 2285–2297.
[104] D. Havrylyuk, B. Zimenkovsky, O. Vasylenko, R. Lesyk, J. Heterocycl. Chem. 50 (2013) E55–E62.
[105] B.G. Turner, M.F. Summers, J. Mol. Biol. 285 (1999) 1–32.
[106] E. Arnold, K. Das, J. Ding, P.N. Yadav, Y. Hsiou, P.L. Boyer, S.H. Hughes, Drug. Des. Discov. 13 (1996) 29–47.
[107] B. Gazzard, G. Moyle, Lancet 352 (1998) 314–316.
[108] M.L. Barreca, A. Chimirri, L. De Luca, A.M. Monforte, P. Monforte, A. Rao, M. Zappala, J. Balzarini, E. De Clercq, C. Pannecouque, M. Witvrouw, Bioorg. Med. Chem. Lett. 11 (2001) 1793–1796.
[109] A. Chimirri, S. Grasso, A.M. Monforte, P. Monforte, M. Zappala, Farmaco 46 (1991) 817–823.
[110] M.L. Barreca, J. Balzarini, A. Chimirri, E. De Clercq, L. De Luca, H.D. Holtje, M. Holtje, A.M. Monforte, P. Monforte, C. Pannecouque, A. Rao, M. Zappala, J. Med. Chem. 45 (2002) 5410–5413.
[111] A. Rao, J. Balzarini, A. Carbone, A. Chimirri, E. De Clercq, A.M. Monforte, P. Monforte, C. Pannecouque, M. Zappala, Antiviral Res. 63 (2004) 79–84.
[112] R.K. Rawal, Y.S. Prabhakar, S.B. Katti, E. De Clercq, Bioorg. Med. Chem. 13 (2005) 6771–6776.
[113] Y.S. Prabhakar, R.K. Rawal, M.K. Gupta, V.R. Solomon, S.B. Katti, Comb. Chem. High Throughput Screening 8 (2005) 431–437.
[114] R.K. Rawal, R. Tripathi, S.B. Katti, C. Pannecouque, E. De Clercq, Bioorg. Med. Chem. 15 (2007) 1725–1731.
[115] J. Balzarini, B. Orzeszko, J.K. Maurin, A. Orzeszko, Eur. J. Med. Chem. 42 (2007) 993–1003.
[116] J. Balzarini, B. Orzeszko-Krzesinska, J.K. Maurin, A. Orzeszko, Eur. J. Med. Chem. 44 (2009) 303–311.
[117] R.K. Rawal, R. Tripathi, S.B. Katti, C. Pannecouque, E. De Clercq, Bioorg. Med. Chem. 15 (2007) 3134–3142.
[118] R. De Francesco, G. Migliaccio, Nature 436 (2005) 953–960.
[119] C.P. Gordon, P.A. Keller, J. Med. Chem. 48 (2005) 1–20.
[120] N. Kaushik-Basu, A. Bopda-Waffo, T.T. Talele, A. Basu, Y. Chen, S.G. Kucukguzel, Front. Biosci. 13 (2008) 3857–3868.
[121] R.K. Rawal, S.B. Katti, N. Kaushik-Basu, P. Arora, Z. Pan, Bioorg. Med. Chem. Lett. 18 (2008) 6110–6114.
[122] P. Kwan, G.J. Sills, M.J. Brodie, Pharmacol. Ther. 90 (2001) 21–34.
[123] M.A. Rogawski, Epilepsy Res. 69 (2006) 273–294.
[124] H.D. Troutman, L.M. Long, J. Am. Chem. Soc. 70 (1948) 3436–3439.
[125] R. kumar, T.K. Gupta, S.S. Parmar, J. Prackt. Chem. 312 (1970) 201.
[126] C. Dwivedi, T.K. Gupta, S.S. Parmar, J. Med. Chem. 15 (1972) 553–554.
[127] S.S. Parmar, C. Dwivedi, A. Chaudhari, T.K. Gupta, J. Med. Chem. 15 (1972) 99–101.
[128] A. Agarwal, S. Lata, K.K. Saxena, V.K. Srivastava, A. Kumar, Eur. J. Med. Chem. 41 (2006) 1223–1229.
[129] Archana, V.K. Srivastava, A. Kumar, Eur. J. Med. Chem. 37 (2002) 873–882.
[130] G. Capan, N. Ulusoy, N. Ergenc, A. Cevdet Ekinci, A. Vidin, Farmaco 51 (1996) 729–732.
[131] S.A. el-Feky, Pharmazie 48 (1993) 894–896.
[132] S.A. el-Feky, Z.K. Abd el-Samii, Arch. Pharm. (Weinheim) 324 (1991) 381–383.
[133] N. Ergenc, G. Capan, Farmaco 49 (1994) 449–451.
[134] F.A. Ragab, N.M. Eid, H.A. el-Tawab, Pharmazie 52 (1997) 926–929.
[135] S. Nagar, H.H. Singh, J.N. Sinha, S.S. Parmar, J. Med. Chem. 16 (1973) 178–180.
[136] K.M. Amin, D.E. Rahman, Y.A. Al-Eryani, Bioorg. Med. Chem. 16 (2008) 5377–5388.
[137] H. Kaur, S. Kumar, P. Vishwakarma, M. Sharma, K.K. Saxena, A. Kumar, Eur. J. Med. Chem. 45 (2010) 2777–2783.
[138] R.V. Shingalapur, K.M. Hosamani, R.S. Keri, M.H. Hugar, Eur. J. Med. Chem. 45 (2010) 1753–1759.
[139] J.G. Goghare, S.V. Bhandari, K.G. Bothara, A.R. Madgulkar, G.A. Parashar, Eur. J. Med. Chem. 45 (2010) 857–863.
[140] V. Brizzi, M. Francioli, M. Brufani, L. Filocamo, G. Bruni, P. Massarelli, Farmaco 54 (1999) 713–720.
[141] R.J. Bing, T. Yamamoto, H. Kim, R.H. Grubbs, Biochem. Biophys. Res. Commun. 275 (2000) 350–353.
[142] S.V. Bhandari, K.G. Bothara, A.A. Patil, T.S. Chitre, A.P. Sarkate, S.T. Gore, S.C. Dangre, C.V. Khachane, Bioorg. Med. Chem. 17 (2009) 390–400.
[143] S. Nattel, L. Yue, Z. Wang, Cell. Physiol. Biochem. 9 (1999) 217–226.
[144] Z. Wang, B. Fermini, S. Nattel, Circ. Res. 73 (1993) 1061–1076.
[145] M.A. Vos, J. Cardiovasc. Electrophysiol. 15 (2004) 1451–1452.
[146] J. Brendel, S. Peukert, Curr. Med. Chem. Cardiovasc. Hematol. Agents 1 (2003) 273–287.
[147] C.M. Jackson, B. Blass, K. Coburn, L. Djandjighian, G. Fadayel, A.J. Fluxe, S.J. Hodson, J.M. Janusz, M. Murawsky, J.M. Ridgeway, R.E. White, S. Wu, Bioorg. Med. Chem. Lett. 17 (2007) 282–284.
[148] R. Ottana, E. Mazzon, L. Dugo, F. Monforte, R. Maccari, L. Sautebin, G. De Luca, M.G. Vigorita, S. Alcaro, F. Ortuso, A.P. Caputi, S. Cuzzocrea, Eur. J. Pharmacol. 448 (2002) 71–80.
[149] M.G. Vigorita, R. Ottana, F. Monforte, R. Maccari, M.T. Monforte, A. Trovato, M.F. Taviano, N. Miceli, G. De Luca, S. Alcaro, F. Ortuso, Bioorg. Med. Chem. 11 (2003) 999–1006.
[150] M.G. Vigorita, T. Previtera, R. Ottana, I. Grillone, F. Monforte, M.T. Monforte, A. Trovato, A. Rossitto, Farmaco 52 (1997) 43–48.
[151] A. Kumar, C.S. Rajput, S.K. Bhati, Bioorg. Med. Chem. 15 (2007) 3089–3096.
[152] S.K. Bhati, A. Kumar, Eur. J. Med. Chem. 43 (2008) 2323–2330.
[153] H. Saegusa, T. Kurihara, S. Zong, A. Kazuno, Y. Matsuda, T. Nonaka, W. Han, H. Toriyama, T. Tanabe, EMBO J. 20 (2001) 2349–2356.
[154] G.P. Miljanich, Curr. Med. Chem. 11 (2004) 3029–3040.
[155] L.J. Knutsen, C.J. Hobbs, C.G. Earnshaw, A. Fiumana, J. Gilbert, S.L. Mellor, F. Radford, N.J. Smith, P.J. Birch, J. Russell Burley, S.D. Ward, I.F. James, Bioorg. Med. Chem. Lett. 17 (2007) 662–667.
[156] A. Panico, R. Maccari, V. Cardile, L. Crasci, S. Ronsisvalle, R. Ottana, Med. Chem. 9 (2013) 84–90.
[157] P. Eleftheriou, A. Geronikaki, D. Hadjipavlou-Litina, P. Vicini, O. Filz, D. Filimonov, V. Poroikov, S.S. Chaudhaery, K.K. Roy, A.K. Saxena, Eur. J. Med. Chem. 47 (2012) 111–124.
[158] S.M. Fitzgerald, B.K. Kemp-Harper, H.C. Parkington, G.A. Head, R.G. Evans, Am. J. Physiol. Regul. Integr. Comp. Physiol. 293 (2007) R707–R713.
[159] C.M. Clark Jr., D.A. Lee, N. Engl. J. Med. 332 (1995) 1210–1217.
[160] E. Torlone, A.M. Rambotti, G. Perriello, G. Botta, F. Santeusanio, P. Brunetti, G.B. Bolli, Diabetologia 34 (1991) 119–125.
[161] H. Drexler, B. Hornig, J. Mol. Cell. Cardiol. 31 (1999) 51–60.
[162] V. Calderone, S. Rapposelli, A. Martelli, M. Digiacomo, L. Testai, S. Torri, P. Marchetti, M.C. Breschi, A. Balsamo, Bioorg. Med. Chem. 17 (2009) 5426–5432.
[163] P. Alexiou, K. Pegklidou, M. Chatzopoulou, I. Nicolaou, V.J. Demopoulos, Curr. Med. Chem. 16 (2009) 734–752.
[164] R. Maccari, R. Ottana, C. Curinga, M.G. Vigorita, D. Rakowitz, T. Steindl, T. Langer, Bioorg. Med. Chem. 13 (2005) 2809–2823.
[165] R. Maccari, R. Ottana, R. Ciurleo, M.G. Vigorita, D. Rakowitz, T. Steindl, T. Langer, Bioorg. Med. Chem. Lett. 17 (2007) 3886–3893.
[166] M. Zentgraf, H. Steuber, C. Koch, C. La Motta, S. Sartini, C.A. Sotriffer, G. Klebe, Angew. Chem. Int. Ed. Engl. 46 (2007) 3575–3578.
[167] R. Ottana, R. Maccari, M. Giglio, A. Del Corso, M. Cappiello, U. Mura, S. Cosconati, L. Marinelli, E. Novellino, S. Sartini, C. La Motta, F. Da Settimo, Eur. J. Med. Chem. 46 (2011) 2797–2806.
[168] A. Kishore, G.K. Nampurath, S.P. Mathew, R.T. Zachariah, B.K. Potu, M.S. Rao, M. Valiathan, M.R. Chamallamudi, Chem. Biol. Interact. 177 (2009) 242–246.
[169] S.M. Grundy, Nat. Rev. Drug Discov. 5 (2006) 295–309.
[170] M.J. Joy, N. Jacob, N.G. Kutty, Indian Drugs 42 (2005) 47–51.
[171] N.K. Jacob, N.G. Kutty, Indian Drugs 41 (2004) 76–79.
[172] G.K. Nampurath, S.P. Mathew, V. Khanna, R.T. Zachariah, S. Kanji, M.R. Chamallamudi, Chem. Biol. Interact. 171 (2008) 363–368.
[173] S.G. Kucukguzel, E.E. Oruc, S. Rollas, F. Sahin, A. Ozbek, Eur. J. Med. Chem. 37 (2002) 197–206.
[174] L. Ballell, R.A. Field, K. Duncan, R.J. Young, Antimicrob. Agents Chemother. 49 (2005) 2153–2163.
[175] A.R. Kulkarni, V.H. Kulkarni, J. Keshavayya, V.I. Hukkeri, H.W. Sung, Macromol. Biosci. 5 (2005) 490–493.
[176] I.R. Siddiqui, P.K. Singh, J. Singh, J. Singh, J. Agric. Food Chem. 51 (2003) 7062–7065.
[177] C.G. Bonde, N.J. Gaikwad, Bioorg. Med. Chem. 12 (2004) 2151–2161.
[178] N. Cesur, Z. Cesur, N. Ergenc, M. Uzun, M. Kiraz, O. Kasimoglu, D. Kaya, Arch. Pharm. (Weinheim) 327 (1994) 271–273.

[179] O. Ates, H. Altintas, G. Otuk, Arzneimittelforschung 50 (2000) 569–575.
[180] O. Ates, A. Kocabalkanli, G.O. Sanis, A.C. Ekinci, A. Vidin, Arzneimittelforschung 47 (1997) 1134–1138.
[181] A. Kocabalkanli, O. Ates, G. Otuk, Arch. Pharm. (Weinheim) 334 (2001) 35–39.
[182] I. Chopra, C. Schofield, M. Everett, A. O'Neill, K. Miller, M. Wilcox, J.M. Frere, M. Dawson, L. Czaplewski, U. Urleb, P. Courvalin, Lancet Infect. Dis. 8 (2008) 133–139.
[183] C.J. Andres, J.J. Bronson, S.V. D'Andrea, M.S. Deshpande, P.J. Falk, K.A. Grant-Young, W.E. Harte, H.T. Ho, P.F. Misco, J.G. Robertson, D. Stock, Y. Sun, A.W. Walsh, Bioorg. Med. Chem. Lett. 10 (2000) 715–717.
[184] P. Keyser, M. Elofsson, S. Rosell, H. Wolf-Watz, J Intern Med 264 (2008) 17–29.
[185] A.M. Kauppi, R. Nordfelth, H. Uvell, H. Wolf-Watz, M. Elofsson, Chem. Biol. 10 (2003) 241–249.
[186] A. Negrea, E. Bjur, S.E. Ygberg, M. Elofsson, H. Wolf-Watz, M. Rhen, Antimicrob. Agents Chemother. 51 (2007) 2867–2876.
[187] H.B. Felise, H.V. Nguyen, R.A. Pfuetzner, K.C. Barry, S.R. Jackson, M.P. Blanc, P.A. Bronstein, T. Kline, S.I. Miller, Cell Host Microbe 4 (2008) 325–336.
[188] T. Kline, K.C. Barry, S.R. Jackson, H.B. Felise, H.V. Nguyen, S.I. Miller, Bioorg. Med. Chem. Lett. 19 (2009) 1340–1343.
[189] P. Vicini, A. Geronikaki, M. Incerti, F. Zani, J. Dearden, M. Hewitt, Bioorg. Med. Chem. 16 (2008) 3714–3724.
[190] D. Patel, P. Kumari, N. Patel, Eur. J. Med. Chem (2012), http://dx.doi.org/10.1016/j.ejmech.2011.1011.1041.
[191] S. Bondock, W. Khalifa, A.A. Fadda, Eur. J. Med. Chem. 42 (2007) 948–954.
[192] S.A. Khan, A.M. Asiri, M. Yusuf, Eur. J. Med. Chem. 44 (2009) 2597–2600.
[193] M.C. Sharma, N.K. Sahu, D.V. Kohli, S.C. Chaturvedi, S. Sharma, Dig. J. Nanomater. Biostruct. 4 (2009) 223–232.
[194] M.S. El-Gaby, G.A. El-Hag Ali, A.A. El-Maghraby, M.T. Abd El-Rahman, M.H. Helal, Eur. J. Med. Chem. 44 (2009) 4148–4152.
[195] M.S. Mohamed, M.M. Kamel, E.M. Kassem, N. Abotaleb, S.I. Abd El-Moez, M.F. Ahmed, Eur. J. Med. Chem. 45 (2010) 3311–3319.
[196] N.H. Metwally, M.A. Abdalla, M.A. Mosselhi, E.A. El-Desoky, Carbohydr. Res. 345 (2010) 1135–1141.
[197] V.S. Palekar, A.J. Damle, S.R. Shukla, Eur. J. Med. Chem. 44 (2009) 5112–5116.
[198] P.M. Ronad, M.N. Noolvi, S. Sapkal, S. Dharbhamulla, V.S. Maddi, Eur. J. Med. Chem. 45 (2010) 85–89.
[199] R. Ramachandran, M. Rani, S. Kabilan, Bioorg. Med. Chem. Lett. 19 (2009) 2819–2823.
[200] T. Tomasic, N. Zidar, M. Mueller-Premru, D. Kikelj, L.P. Masic, Eur. J. Med. Chem. 45 (2010) 1667–1672.
[201] N.C. Desai, V.V. Joshi, K.M. Rajpara, H.V. Vaghani, H.M. Satodiya, Med. Chem. Res. 22 (2013) 1893–1908.
[202] R.A. Rane, N.U. Sahu, C.P. Shah, Bioorg. Med. Chem. Lett. 22 (2012) 7131–7134.
[203] S. Sharma, P.K. Sharma, N. Kumar, R. Dudhe, Biomed. Pharmacother. 65 (2011) 244–251.
[204] V.V. Vintonyak, K. Warburg, B. Over, K. Hübel, D. Rauh, H. Waldmann, Tetrahedron 67 (2011) 6713–6729.
[205] V.V. Vintonyak, K. Warburg, H. Kruse, S. Grimme, K. Hubel, D. Rauh, H. Waldmann, Angew. Chem. Int. Ed. Engl. 49 (2010) 5902–5905.
[206] G. Aridoss, S. Amirthaganesan, M.S. Kim, J.T. Kim, Y.T. Jeong, Eur. J. Med. Chem. 44 (2009) 4199–4210.
[207] R.B. Patel, P.S. Desai, K.R. Desai, K.H. Chikhalia, Indian J. Chem. 45B (2006) 773–778.
[208] A.S. Narute, P.B. Khedekar, K.P. Bhusari, Indian J. Chem. 47B (2008) 586–591.
[209] K. Omar, A. Geronikaki, P. Zoumpoulakis, C. Camoutsis, M. Sokovic, A. Ciric, J. Glamoclija, Bioorg. Med. Chem. 18 (2010) 426–432.
[210] R. Pink, A. Hudson, M.A. Mouries, M. Bendig, Nat. Rev. Drug Discov. 4 (2005) 727–740.
[211] J. Pepin, F. Milord, C. Guern, B. Mpia, L. Ethier, D. Mansinsa, Lancet 1 (1989) 1246–1250.
[212] M.A. Ferguson, G.A. Cross, J. Biol. Chem. 259 (1984) 3011–3015.
[213] M.A. Ferguson, J.S. Brimacombe, J.R. Brown, A. Crossman, A. Dix, R.A. Field, M.L. Guther, K.G. Milne, D.K. Sharma, T.K. Smith, Biochim. Biophys. Acta 1455 (1999) 327–340.
[214] T.K. Smith, B.L. Young, H. Denton, D.L. Hughes, G.K. Wagner, Bioorg. Med. Chem. Lett. 19 (2009) 1749–1752.
[215] E.E. Carlson, J.F. May, L.L. Kiessling, Chem. Biol. 13 (2006) 825–837.
[216] J.S. Helm, Y. Hu, L. Chen, B. Gross, S. Walker, J. Am. Chem. Soc. 125 (2003) 11168–11169.
[217] D. Hill, J.P. Dubey, Clin. Microbiol. Infect. 8 (2002) 634–640.
[218] R.P. Tenorio, C.S. Carvalho, C.S. Pessanha, J.G. de Lima, A.R. de Faria, A.J. Alves, E.J. de Melo, A.J. Goes, Bioorg. Med. Chem. Lett. 15 (2005) 2575–2578.
[219] A.P. Liesen, T.M. de Aquino, C.S. Carvalho, V.T. Lima, J.M. de Araujo, J.G. de Lima, A.R. de Faria, E.J. de Melo, A.J. Alves, E.W. Alves, A.Q. Alves, A.J. Goes, Eur. J. Med. Chem. 45 (2010) 3685–3691.
[220] T.M. de Aquino, A.P. Liesen, R.E. da Silva, V.T. Lima, C.S. Carvalho, A.R. de Faria, J.M. de Araujo, J.G. de Lima, A.J. Alves, E.J. de Melo, A.J. Goes, Bioorg. Med. Chem. 16 (2008) 446–456.
[221] S. Chappel, D. Buckler, C. Kelton, N.E. Tayar, Hum. Reprod. 13 (Suppl. 3) (1998) 18–35 discussion 47–51.
[222] D. Maclean, F. Holden, A.M. Davis, R.A. Scheuerman, S. Yanofsky, C.P. Holmes, W.L. Fitch, K. Tsutsui, R.W. Barrett, M.A. Gallop, J. Comb. Chem. 6 (2004) 196–206.
[223] J. Wrobel, D. Green, J. Jetter, W. Kao, J. Rogers, M.C. Perez, J. Hardenburg, D.C. Deecher, F.J. Lopez, B.J. Arey, E.S. Shen, Bioorg. Med. Chem. 10 (2002) 639–656.
[224] J. Wrobel, J. Jetter, W. Kao, J. Rogers, L. Di, J. Chi, M.C. Perez, G.C. Chen, E.S. Shen, Bioorg. Med. Chem. 14 (2006) 5729–5741.
[225] B.J. Arey, S.D. Yanofsky, M. Claudia Perez, C.P. Holmes, J. Wrobel, A. Gopalsamy, P.E. Stevis, F.J. Lopez, R.C. Winneker, Biochem. Biophys. Res. Commun. 368 (2008) 723–728.
[226] J.C. Pelletier, J. Rogers, J. Wrobel, M.C. Perez, E.S. Shen, Bioorg. Med. Chem. 13 (2005) 5986–5995.
[227] D.T. Puerta, S.M. Cohen, Curr. Top Med. Chem. 4 (2004) 1551–1573.
[228] R.P. Verma, C. Hansch, Bioorg. Med. Chem. 15 (2007) 2223–2268.
[229] A.L. Clutterbuck, K.E. Asplin, P. Harris, D. Allaway, A. Mobasheri, Curr. Drug Targets 10 (2009) 1245–1254.
[230] E. Nuti, T. Tuccinardi, A. Rossello, Curr. Pharm. Des. 13 (2007) 2087–2100.
[231] A.M. Panico, P. Vicini, A. Geronikaki, M. Incerti, V. Cardile, L. Crascì, R. Messina, S. Ronsisvalle, Bioorg. Chem. 39 (2011) 48–52.
[232] T. Kato, T. Ozaki, K. Tamura, Y. Suzuki, M. Akima, N. Ohi, J. Med. Chem. 41 (1998) 4309–4316.
[233] H.S. Choi, Z. Wang, X. Zhu, X. He, K. Yang, H. Liu, W.O. Patent 2008112674, September 18, 2008.
[234] H.B. Felise, S.I. Miller, T. Kline, U.S. Patent 8252940B2, August 28, 2012.
[235] J.H. Ahn, J. Choi, D.G. Jeong, S.K. Jung, S.J. Kim, H.M. Kim, S.H. Lee, K.H. Lee, C.W. Lee, S.K. Park, S.E. Ryu, U.S. Patent 8148541 B2, April 3, 2012.
[236] S. Skubin, L.T. Stanic, R. Staric, W.O. Patent 2012045859 A1, April 12, 2012.
[237] H. Finch, C. Fox, M. Sajad, M.B.V. Neil, A. Forrest, U.S. Patent 8236786 B2, August 7, 2012.
[238] T. Irie, M. Sawa, S. Ito, C. Tanaka, S. GU Ro, C.H. Park, US Patent 8119812, February 21, 2012.
[239] T. Ma, K. Verkman, U.S. Patent 8058295B2, November 15, 2011.
[240] N.D. Sonawane, A.S. Verkman, U.S. Patent 20110105565 A1, May 5, 2011.
[241] D.W. Old, U.S. Patent 7786117B2, August 31, 2010.
[242] D.W. Old, U.S. Patent 7781465B2, August 24, 2010.
[243] K.J. Duffy, C.L. Erickson-Miller, H. Kikkawa, A.C. Maroney, U.S. Patent 0184774A1, July 22, 2010.
[244] R. Sakhardande, V. Kulkarni, N. Sachan, M. Nimbalkar, WO2010082212, July 22, 2010.
[245] J.T. Dalton, V. Gududuru, E. Hurh, D.D. Miller, U.S. Patent 7662842B2, February 16, 2010.
[246] D.W. Old, U.S. Patent 7659295B2, February 9, 2010.
[247] G. Noronha, J. Cao, C.P. Chow, J. Renick, February 26, 2009.
[248] B. Eriksson, C. Hedberg, G. Kurz, J. Westman, W.O. Patent 2008090356A1, July 31, 2008.
[249] V.R.R. Macherla, B. Nicholson, K.S. Lam, U.S. Patent 7378530B2, May 27, 2008.
[250] D.D. Miller, V. Gududuru, J.T. Dalton, E. Hurh, U.S. Patent 7307093B2, December 11, 2007.
[251] C.R. Somerville, W. Scheible, U.S. Patent 7241878B1, July 10, 2007.
[252] Q. Sun, D.J. Kyle, P. Gharagozloo, J. Yang, U.S. Patent 7169782B2, June 30, 2007.
[253] M.F. Gross, N.A. Castle, J.S. Mendoza, U.S. Patent 6395730B1, May 29, 2007.
[254] C. Binkert, M. Bolli, B. Mathys, C. Mueller, M. Scherz, U.S. Patent 0082933A1, April 12, 2007.
[255] V.B. Lohray, B.B. Lohray, B. Pandey, U.S. Patent 2006/0167061A1, July 27, 2006.
[256] Y. Han, J. Colucci, X. Billot, M. Wilson, R. Young, U.S. Patent 2006/0154899A1, July 13, 2006.
[257] V.C. Chhabada, R.R. Pandya, R.B. Rehani, R. Thennati, W.O. Patent 2005049532, June 2, 2005.
[258] A. Halama, L. Hejtmankova, J. Richter, L. Srsnova, J. Jirman, U.S. Patent 2005/0043360A1, February 24, 2005.
[259] J. Mihara, S. Nakamura, S. Narabu, S. Shirakura, A. Yanagi, Y. Yamaguchi, W.O. Patent 2005000824 A1, January 6, 2005.
[260] V.C. Chhabada, R. Rashminkumar, R.B. Rehani, R. Thennati, W.O. Patetn 2004108721, December 16, 2004.
[261] C.D. Cotterman, C. Tseng, U.S. Patent 2004/0106520A1, June 3, 2004.
[262] M. Pfahl, H.A. Al-Shamma, A.F. Giachino, D.P.M. Pleynet, H. Bao, L.W. Spruce, C.N. Cow, C. Tachdjian, J.W. Zapf, T.R. Wiemann, U.S. Patent 00097566A1, May 20, 2004.
[263] T. Ma, A. Verkman, U.S. Patent 2004/0063695A1, April 1, 2004.
[264] P.N. Gadkari, R.G. Lala, M.J. Shah, J.R. Shah, W.O. Patent 2004024059A3, March 25, 2004.
[265] A. Fiumana, C.J. Hobbs, L.J.S. Knutsen, F. Radford, W.O. Patent 2004017965, March 4, 2004.
[266] M. Orchard, W.O. Patent 2003070238A1, August 28, 2003.
[267] S.E.A. Justus, H.T. Lee, J.K. Pontrello, B.D. Roth, K.E. Sexton, M.W. Wilson, U.S. Patent 6506751B1, January 14, 2003.
[268] A.C. Chin, R. Holcomb, M.A. Piatyszek, U. Singh, R.L. Tolman, T. Akama, Y. Kanda, A. Asai, Y. Yamashita, K. Endo, H. Yamaguchi, U.S. Patent 6518268B1, February 11, 2003.
[269] M. Pfahl, C. Yachdjian, H.A. Al-Shamma, A. Fanjul, D.P.M. Pleynet, L.W. Spruce, U.S. Patent 6515003B1, February 4, 2003.

[270] G. Moinet, G. botton, E. Prugnard, L. Doare, M. Kergoat, D. Mesangeau, U.S. Patent 6437143B2, August 20, 2002.
[271] B. Hu, U.S. Patent 6410734B1, June 25, 2002.
[272] M.F. Gross, N.A. Castle, J.S. Mendoza, U.S. Patent 6395730B1, May 28, 2002.
[273] J.A. Panetta, M.L. Phillips, J.K. Reel, J.K. Shadle, S.K. Sigmund, R.L. Simon, C.A. Whitesitt, U.S. Patent 6251928B1, June 26, 2001.
[274] T.W. Kurtz, H.A. Pershadsingh, U.S. Patent 6110951, August 29, 2000.
[275] T.P. Brady, J. Wang, K. Ramnarayan, D. Rideout, S. Mong, H. Zhu, C. Niemeyer, W.O. Patent 2000032598A1, June 8, 2000.
[276] M.M. Hansen, A.R. Harkness, S.M. Reutzel, U.S. Patent 6063799 May 16, 2000.
[277] A. Esswein, W. Schaefer, C. Tsaklakidis, K. Honold, K. Kaluza, E. Hoffmann, W.O. Patent 2000018748A1, April 6, 2000.
[278] T. Antonucci, D. Lockwood, R. Norris, U.S. Patent 6046202A, April 4, 2000.