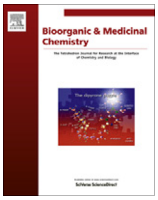
Bioorganic & Medicinal Chemistry xxx (2012) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc



Review

Recent developments and biological activities of thiazolidinone derivatives: A review

Abhishek Kumar Jain[a], Ankur Vaidya[a], Veerasamy Ravichandran[b], Sushil Kumar Kashaw[a], Ram Kishore Agrawal[a,*]

[a] Pharmaceutical Chemistry Research Laboratory, Department of Pharmaceutical Sciences, Dr. Hari Singh Gour University, Sagar 470 003, MP, India
[b] Faculty of Pharmacy, AIMST University, Semeling 08100, Kedah, Malaysia

ARTICLE INFO

Article history:
Received 2 November 2011
Revised 26 March 2012
Accepted 30 March 2012
Available online xxxx

Keywords:
4-Thiazolidinone
Antitubercular
Antibacterial

ABSTRACT

Thiazolidinone is considered as a biologically important active scaffold that possesses almost all types of biological activities. Successful introduction of ralitoline as a potent anti-convulsant, etozoline as a anti-hypertensive, pioglitazone as a hypoglycemic agent and thiazolidomycin activity against streptomyces species proved potential of thiazolidinone moiety. This diversity in the biological response profile has attracted the attention of many researchers to explore this skeleton to its multiple potential against several activities. This review is complementary to earlier reviews and aims to review the work reported on various biological activities of thiazolidinone derivatives from year 2000 to the beginning of 2011. Data are presented for active compounds, some of which have passed the preclinical testing stage.

Contents

1. Introduction

There are numerous biologically active molecules which contain various heteroatoms such as nitrogen, sulphur and oxygen, always drawn the attention of chemist over the years mainly because of their biological importance. Thiazolidinones are thiazolidine derivatives and have an atom of sulfur at position 1, an atom of nitrogen at position 3 and a carbonyl group at position 2, 4, or 5. However, its derivatives belong to the most frequently studied moieties and its presence in penicillin was the first recognition of its occurrence in nature.[1,2] Similarly 1,3-thiazolidin-4-ones are heterocyclic nucleus that have an atom of sulfur and nitrogen at position 1 and 3, respectively and a carbonyl group at position 4

---

* Corresponding author. Tel.: +91 9425027060.
E-mail address: ramkishoreagrawal@gmail.com (R.K. Agrawal).

0968-0896/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.bmc.2012.03.069

have been subjected to extensive study in the recent years. The 4-thiazolidinone scaffold is very versatile and has featured in a number of clinically used drugs. They have found uses as antitubercular, antimicrobial, anti-inflammatory and as antiviral agents, especially as anti-HIV agents. It has been extensively reported that presence of arylazo,[3] sulfamoylphenylazo[4] or phenylhydrazono[5] moieties at different positions of the thiazolidone ring enhanced anti-microbial activity and its antibacterial activity may be due to its inhibitory activity of enzyme Mur *B* which is a precursor acting during the biosynthesis of peptidoglycan.[6] Numerous reports have appeared in the literature which highlight their chemistry and pharmacological uses.[7–9]

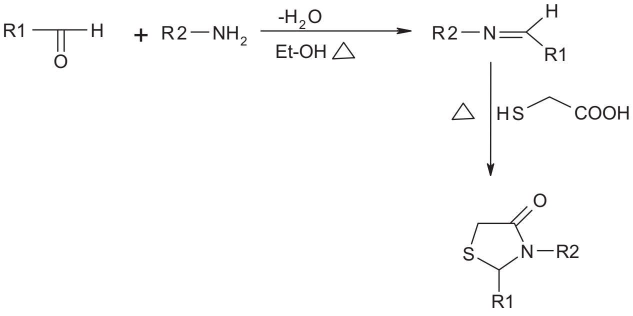
In the present review, emphasis is given on diverse pharmacological properties associated with substituted thiazolidinones and structurally related thiazolidines. The review covers advances made in the last twelve years and provides a detailed discussion on SAR.

2. Preparation of thiazolidinones derivatives

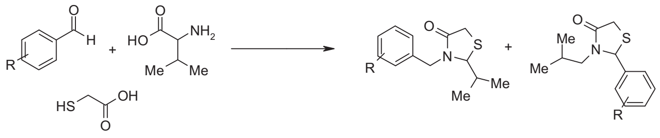
Several methods for the synthesis of 4-thiazolidinones are widely reported in the literature. The main synthetic routes to 1,3-thiazolidin-4-ones involve three components that is an amine, a carbonyl compound, and a mercapto-acid. The classical synthesis reported can be either a one-pot three-component condensation or a two-step process (Scheme 1). The reactions begin by formation of an imine (the nitrogen of amine attacks the carbonyl of aldehyde or ketone), which undergoes attack by generated sulfur nucleophile, followed by intramolecular cyclization on elimination of water.[10–12]

Eltsov et al. reported an convenient one-step cyclization reaction protocol (Scheme 2) wherein the reaction of ethyl 5-phenylthioureido-3*H*-imidazole-4-carboxylate with bromoacetic acid to afforded (imidazolylimino)thiazolidinones. The cyclization reaction proceeds by one of the nitrogen atoms of the nucleophilic centers in derivatives of 5-thioureido-3*H*-imidazole-4-carboxylic acid give the desired thiazolidinone.[13]

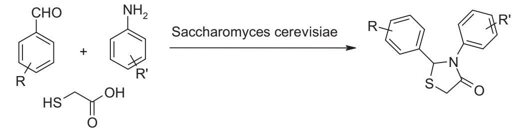
Furthermore, novel route to the synthesis of 2-isopropyl-3-benzyl-1,3-thiazolidin-4-ones and 2-phenyl-3-isobutyl-1,3-thiazolidin-4-ones by using 1:1:3 mole ratio of valine, arenealdehyde and mercaptoacetic acid was reported by Cunico et al.[14] and suggested that the insertion of strong withdrawing group, NO_2, present on benzaldehydes favored the synthesis of hetero-cycle **1** in good yields, whereas the methoxy and fluoro groups produces the type **2** thiazolidinones. In continuation of research, authors reported solvent-free synthesis of five-membered heterocyclic thiazolidinones from phenylhydrazine and 2,4-dinitrophenylhydrazine as the amino cores.[15] Pratap et al.[16] have reported another method of synthesis of 2,3-diaryl-4-thiazolidinones (**3**) wherein *Saccharomyces cerevisiae* (baker's yeast) that contained enzyme lipase was used as a catalyst which accelerated the formation of imines as well as cyclo-condensation of the aryl aldehydes, amines, and thioglycolic acid.



Scheme 1. Common synthetic route for the synthesis of 4-thiazolidinone derivatives.



(1) (2)

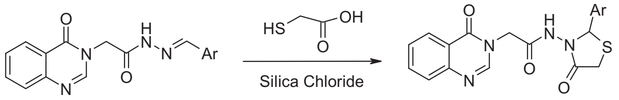


(3)

R= H, *p*-OCH_3, *m*-Cl, *m*-NO_2, *p*-OH and *p*-Cl

R' = H, *p*-CH_3 and *p*-Cl

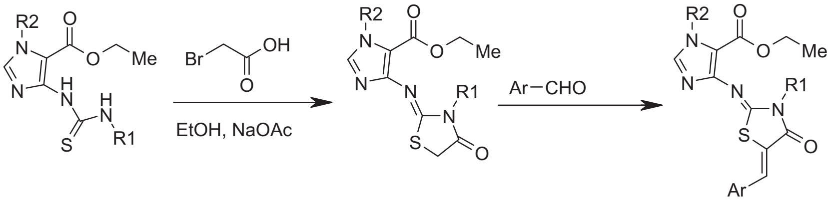
Various quinazolinyl azomethines (**4**) on treatment with mercaptoacetic acid in the presence of silica chloride that was used as a heterogeneous catalyst to accelerate the intra-molecular cyclocondensation under solvent-free condition, yield 4-thiazolidinones (**5**).[17]



(4) (5)

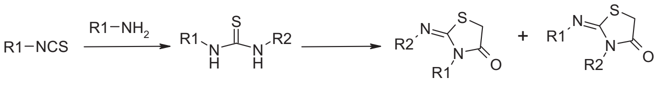
Furthermore, the reaction of aryl or alkyl isothiocyanate (**6**) with a primary amine furnished the corresponding thiourea derivative (**7**), which was directly cyclized by treating with halo acetic acid to the corresponding two isomeric 2-imino-thiazolidin-4-ones of the general structures **8** and **9**.[18]

Also, coupling reaction between α-chloro amide derivatives (**11**) with isothiocyanate in the presence of a mild base afforded the iminothiazolidinone derivatives (**12**).[19]

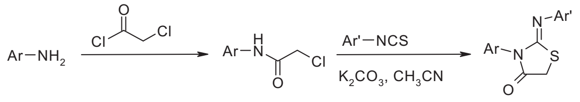


Scheme 2. Common synthetic route for the synthesis of 4-(imidazolylimino)thiazolidinones.

Please cite this article in press as: Jain, A. K.; et al. *Bioorg. Med. Chem.* (2012), http://dx.doi.org/10.1016/j.bmc.2012.03.069

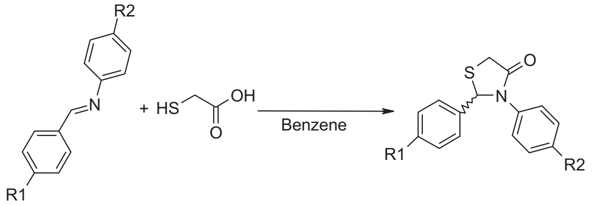


(6) **(7)** **(8)** **(9)**



(10) **(11)** **(12)**

Bolognese et al.[20] prepared a range of 1,3-thiazolidin-4-one derivatives (**14**) by the microwave-assisted reaction between benzylidene-anilines (**13**) and mercaptoacetic acid in benzene at 30 °C for 10 min. After purification by chromatography, the 1,3-thiazolidin-4-ones are isolated in 65–90% yield.



(13) **(14)**

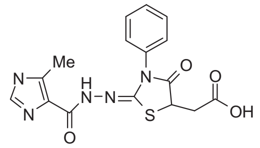
R1 = H, $-CH_3$, Cl, NO_2; R2 = H, $-CH_3$, Cl, NO_2

3. Biological activity of 4-thiazolidinones

The thiazolidinones ring has been incorporated into a broad range of known biologically active compounds, either as a substituent group or as a replacement of another ring inspired researchers to synthesize several compounds containing this moiety. There are several reports in the literature describing the thiazolidinone derivatives for their various biological activities and some of them are covered in this review.

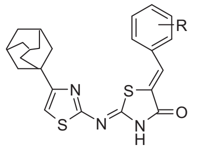
3.1. Antibacterial and antifungal activity

Thiazolidinones with C-2 and N-3 substituted positions, possess diverse degrees of inhibition against bacteria and fungi. The dramatically rising prevalence of multi-drug resistant microbial infections in the past few decades has become a serious health problem. Approximately all the positions of 4-thiazolidinone have been explored to improve the antibacterial and antifungal activity. The SAR studies of thiazolidinone derivatives showed that they are more effective on gram-negative bacteria as compared to gram-positive bacteria. The search for new antimicrobial agents will consequently remain as an important and challenging task for medicinal chemists. Liesen et al. reported 4-thiazolidinone derivatives obtained from ethyl(5-methyl-1-*H*-imidazole-4-carboxylate). The whole synthesized compounds were evaluated against variety of pathogens for their antibacterial and antifungal activity. The results showed that the tested compounds possessed weak antibacterial and antifungal activities compared to standard drugs chloramphenicol and rifampicin for antibacterial activity and ketoconazole for antifungal activity. Compound (**15**) showed MIC of 270 μg mL^{-1} against *B. subtilis.*[21]



(15)

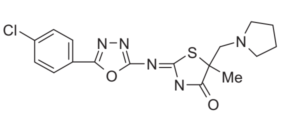
4-Adamantyl-2-thiazolylimino-5-arylidene-4-thiazolidinones (**16**) was found to exhibit a remarkable inhibition of a wide spectrum of gram positive and gram negative bacteria. The most significant activity was observed for compounds having *p*-OH and 3,5-OCH_3 group on arylidene moiety against tested strains with an MIC between 1.05 and 4.18×10^{-2} μmol/ml. It has been shown that the introduction of arylidene moieties at different positions of the thiazolidinone ring enhanced the antimicrobial activity. It is interesting to point out that the isomeric *m-Cl* substituted compound showed higher activity with respect to *o*/*p* chloro substitution. Furthermore, studies have revealed that the presence of electron-withdrawing nitro group at para and *meta* position of arylidene moiety encourages the activity profile. The introduction of methoxy group at position 3 and 3, 5 in the 4-hydroxy derivative in general lead to compounds with higher activity, whereas replacement of hydroxyl group with methoxy in 4th position usually decreased activity.[22]



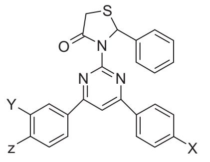
(16)

R = *p*-Cl, *m*-Cl, *o*-Cl, *p*-NO_2, *m*-NO_2, *o*-NO_2, *p*-OH, *p*-OH *m*-OCH_3, *p*-OH and 3,5-OCH_3, *p*-OCH_3

Kocabalkanli et al.[23] synthesized Mannich bases of some 2,5-disubstituted 4-thiazolidinones and evaluated their antimicrobial activity. They reported that the most active compound had a *p*-chlorophenyl group on the oxadiazole, a methyl and a pyrrolidinomethyl at the 5-position of the thiazolidinone (**17**), while the least active one has a hydrogen atom in place of a chlorine and a morpholine in place of a pyrrolidine. Further analogous of 2-phenyl-3-(4,6-diarylpyrimidin-2-yl)thiazolidin-4-ones (**18, 19**) have been synthesized by Gopalakrishnan et al.[24] and tested for their antibacterial activity against *Staphylococcus aureus, β-hemolytic Streptococcus, Vibrio cholera, Salmonella typhi, Shigella felxneri, Escherichia coli, Klebsiella pneumonia,* and *Pseudomonas aeruginosa.* Ciprofloxacin was used as standard drug. Results revealed that *p*-(OCH_3) and *p*-(CH_3) groups at phenyl ring attached to the pyrimidine ring exerted strong antibacterial activity against all the tested bacterial strains on the other hand compounds with electron withdrawing *p*-Cl and *p*-F functional group at phenyl ring attached to pyrimidine ring did not improved antibacterial activity.



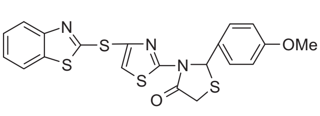
(17)



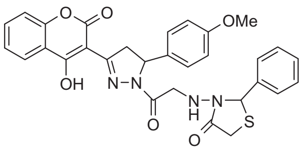
(18) X=Y= H, Z= $-OCH_3$; **(19)** X= $-OCH_3$, Y=Z= H

Please cite this article in press as: Jain, A. K.; et al. *Bioorg. Med. Chem.* (2012), http://dx.doi.org/10.1016/j.bmc.2012.03.069

Singh et al. studied substituted thiazolyl-thiazolidinylbenzothiazoles and showed that none of the compounds having 2-substituted 4-thiazolidinone ring showed any antibacterial activity but compounds were potent for insecticidal activity. Electron withdrawing group at phenyl ring such as *p*-$\mathrm{OCH_3}$ (**20**) enhanced its insecticidal activity. Compound containing the azetidinone moiety instead of thiazolidinone displayed antibacterial activity against Gram-positive bacteria *S. aureus* and *E. coli*.[25] Thiazolidinone derivatives synthesized from chalcones of 4-hydroxycoumarin (**21**) showed that compounds having the methoxy group have increased antibacterial activity while azetidinones were found to be more active than thiazolidinones.[26]

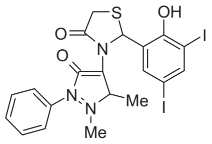


(20)



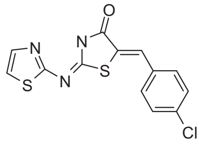
(21)

Antibacterial activity is strongly dependent on the nature of the substituents at C-2 and N-3 of the thiazolidinone ring. Compound 3-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-2-(2-hydroxy-3,5-diiodophenyl)-thiazolidin-4-one (**22**) having antipyrine at N-3 and 3-iodo substituted phenyl ring at C-2 exhibited zone of inhibition of 27, 24, 25 mm against *E. coli*, *B. subtillis* and *S. typhi*, respectively.[27]

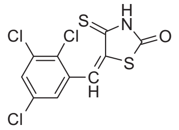


(22)

Substituted 5-arylidene moiety plays an important role in enhancing the antimicrobial properties of 2-(thiazol-2-ylimino) thiazolidin-4-one (**23**). Substitution with chloro group at second, third or forth position on benzene ring improved antibacterial activity (*p-Cl* substitution is most active) compared to arylidene derivatives substituted with hydrophilic hydroxyl or methoxy group or nitro group.[28] Recently, a series of 5-arylidene-4-thioxo-thiazolidine-2-one derivatives have been evaluated for their antimicrobial and cytotoxic activities. Majority of the tested compounds were active against Gram positive bacteria *B. subtillis*. Thiazolidine-2,4-dione was inactive for all microorganisms tested, however replacing the carbonyl group by thiocarbonyl increased the antimicrobial activity. This study demonstrated that the bioisosteric replacement of thiocarbonyl instead of carbonyl in thiazolidine ring, resulted in an enhancement of antimicrobial activity. Due to its antibacterial properties, especially against multidrug-resistant strains of clinical isolates, the 5-arylidene-4-thioxo-thiazolidine-2-ones identified may represent useful starting points for further lead optimization. In this series, derivative 5-(2,3,5 trichloro benzylidene)-4-thioxo-thiazolidine-2-one (**24**) showed a greater inhibitory capacity.[29]

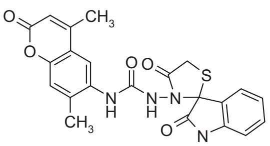


(23)

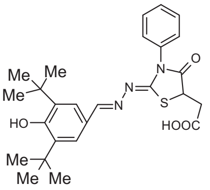


(24)

Antibacterial activity of *N*-[coumarin-6-yl] spiro-indoloazetidin-2-ones/thiazolidin-4-ones derivatives was reported by Mulwad and Mir.[30] Thiazolidinone ring instead of azetidinone did not show significant activity, coumarin ring substituted with methyl group at 4th and 7th position attached with 2-isatin-4-thiazolidinone ring (**25**) showed moderate antibacterial activity against *S. aureus* and *B. subtilis.* Aquino et al. synthesized a series of 2-[(phenylmethylene)hydrazono]-4-oxo-3-phenyl-5-thiazolidineacetic acids for their anti-*T. gondii* and antimicrobial activities. 4-Thiazolidinone derivatives were initially tested for antimicrobial activity by the disc diffusion method and it was found that compound (**26**) revealed the best activities against *S. aureus*, *S. faecalis*, *B. subtilis* reduced and the percentage of infected cells and mean number of tachyzoites per cell in 2 μM concentration.[31]

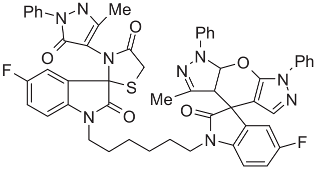


(25)

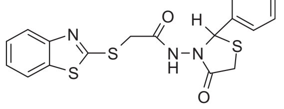


(26)

The antimicrobial activity of derivatives involving a series of novel spiro[indole-thiazolidine]spiro[indole-pyran] derivatives was studied in experiments in vitro with respect to three Gram-positive bacteria (*S. aureus, B. subtilis, and Staphylococcus epidermis*), four Gram-negative bacteria (*E. coli, P. aeruginosa, S. typhi, and K. pneumoniae*). Most of the synthesized compounds showed moderate to comparable activity, only **27** had more pronounced activity and almost equipotent to Ciprofloxacin with respect to Gram-positive and Gram-negative bacteria.[32] Desai and Desai have synthesized derivatives of 2-(aryl)-3-[2-(benzothiazolylthio)-acetamidyl]-4-oxo-thiazolidines **28**. All the compounds have been screened for their antibacterial activity against *Escherchia coli*, *Staphylococcus aureus* and *Bacillus substilis* and some of the compounds showed promising activity.[33]



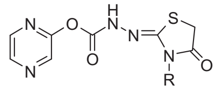
(27)



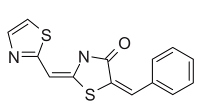
(28)

Bonde et al. prepared eight different derivatives of *N*′-[(2*Z*)-3-(4-bromophenyl)-4-oxo-1,3-thiazolidin-2-ylidene]-2-(pyrazine-2-yloxy) acetohydrazide and investigated for antimicrobial activity. They reported that thiazolidine ring was not essential for imparting the anti-bacterial activity to the compounds containing pyrazine ring. Replacement of thiazolidinone ring by disubstituted-1,3-thiazol (**29**) increased its antibacterial activity

(MIC = 3–45 μg/ml).[34] Analysis of 2-heteroarylimino-5-benzylidene-4-thiazolidinones displayed good inhibition of the growth of gram positive bacilli and staphylococci. In this series activity depended on the substituents at the 5-benzylidene moiety, on the other hand, both the bicyclic ring system benzo thiazoles and benzisothiazoles revealed decrease in antibacterial properties when compared to the corresponding thiazoles attached with substituted 4-thiazolidinone, suggesting that these bicyclic systems played a negative role on the antimicrobial effectiveness of this class. Compound 2-thiazolylimino-5-benzylidene-4-thiazolidinone (**30**) showed comparatively remarkable activity against all the tested microorganisms than other compounds.[35]

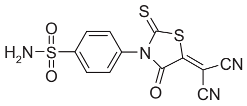


(29)

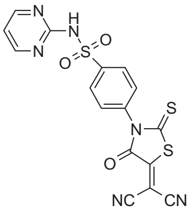


(30)

El-Gaby et al. recently synthesized a series of 2-thioxo-4-thiazolidinones and 4,4′-bis(2-thioxo-4-thiazolidinone-3-yl)diphenylsulfone derivatives. Most of the compounds were found moderate in activity against tested strain of bacteria. Thiazolidinones (**31**) with sulfamoyl and thioxo moieties were found to possess highest antibacterial activity towards *Bacillus cereus* whereas thiazolidinone derivative (**32**) bearing pyrimidine nucleus, sulfamoylphenyl and thioxo moieties revealed high activity against *S. aureus*.[36]

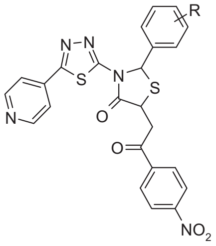


(31)

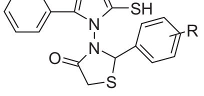


(32)

Various isoniazidothiazolidinones and their imidoxy derivatives showed moderate to significant activity against bacteria at concentration of 100 μg/ml. Compounds (**33** and **34**) in which a nitro group is present at the *meta* and *para* position of the aryl ring were shown to increase antibacterial activity and electron donating group seemed to be a non-profitable structural feature. The chlorine atom in place of nitro group being a less electron withdrawing moiety, showed less activity.[37] Dave et al. synthesized substituted thiazolidinone derivatives of 4-amino-3-mercapto-5-pyridin-3′-yl-(1,2,4)-triazole derivatives (**35**) and checked for their biological activity. They reported that most of the synthesized compounds possessed significant inhibitory activity against microbes whereas none of the compounds showed antitubercular activity at 6.25 μg/ml.[38]

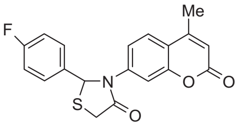


33 = R = *p*-NO$_2$, **34** = *m*-NO$_2$

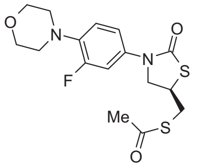


(35)

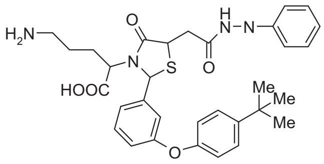
Novel 7-(2-substituted phenylthiazolidinyl)-benzopyran-2-one derivatives have been reported by Ronad et al. and were found to inhibited the growth of various bacterial and fungal strains. The results showed that most of the compounds exhibited good antibacterial and antifungal activity as that of standard antibiotics Ciprofloxacin and Griseofulvin at a concentration of 100 μg/ml. Compound **36** found to be the most active derivative with varying degree of inhibition against tested bacteria B. subtillis and S. sureus and antifungal potency against *Aspergillus niger*.[39] Sattigeri et al. observed that replacement of –O– with –S– lead to completely lost the antimicrobial activity in a series of thiazolidine-2-thione and thiazolidin-2-one derivatives (**37**).[40] 4-Thiazolidinones have been reported as novel inhibitors of the bacterial enzyme Mur *B* which was a precursor acting during the biosynthesis of peptidoglycan. Molecular modeling study on 4-thiazolidinones revealed that insertion of phenyl group at C1 position of thiazolidinone ring showed lack of bacterial enzyme Mur *B* inhibition while activity increased when *t*-butyl-*m*-phenoxy group (**38**) was employed at that position.[41]



(36)

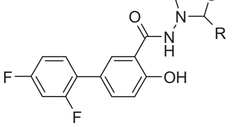


(37)

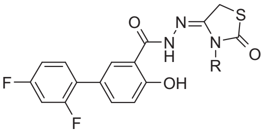


(38)

Similarly thiazolidinone derivatives of diflunisal do not show any antibacterial activity against any strain. Subtitution at position 2nd and 3rd of thiazolidinone (**39**, **40**) further did not improve its antimicrobial activity.[42]



(39)



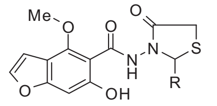
(40)

R = 5-Nitro-2-furyl, C$_6$H$_5$, *p*-Cl-C$_6$H$_4$,
o-FC$_6$H$_4$, *m*-F-C$_6$H$_4$, *p*-F-C$_6$H$_4$, *p*-CH$_3$-C$_6$H$_4$

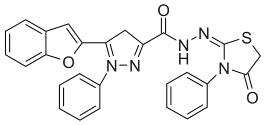
Hassaneen et al. synthesized oxadiazole, thiazolidinone, *N*-phthalimidoamino carbonyl and arylidene derivatives and checked their antimicrobial activity. Incorporation of substituted 4-thiazolidinone ring attached with benzofuranol (**41**) showed loss of activity while attachment of pthalamide group surprisingly increased antimicrobial activity against tested strain.[43] Several benzofurans bearing various substituents at the C-2 position were widely tested for different biological activities. Compound 5-(benzofuran-2-yl)-*N*9-(4-oxo-3-phenylthiazolidin-2-ylidene)-1-phenyl-1*H*-pyrazole-

Please cite this article in press as: Jain, A. K.; et al. *Bioorg. Med. Chem.* (2012), http://dx.doi.org/10.1016/j.bmc.2012.03.069

3-carbohydrazide (**42**), that contained thiazolidinone ring showed zone of inhibition of 40 mm against *Bacillus subitilis* which was superior in activity than standard drug amoxicillin.[44]



(41)

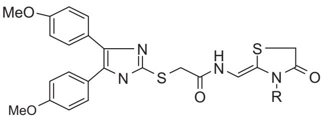


(42)

R = Ph, *p*- OCH_3- C_6H_4 , C_6H_2 $(OCH_3)_3$-3,4,5,

C_6H_2-F (*p*) Cl (2,6)

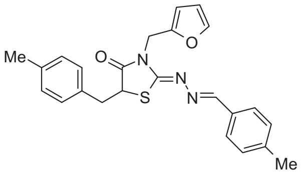
Synthesis and antimicrobial evaluation of novel derivatives of hydrazide-hydrazones, thiosemicarbazides and thiazolidinones had been performed by Gihsoyl et al. All the synthesized compounds were tested for antibacterial, antifungal and antimycobacterial activity against different bacteria (*S. aureus* ATCC 6538, *S. epidermidis* ATCC 12228, *K. pneumoniae* ATCC 4352, *P. aeruginosa* ATCC 1539, *E. coli* ATCC 8739, *Shigella jlexneri*, *S. typhi*, *Proteus mirabilis*, *Mycobacterium tuberculosis* H37Rv) and *C. albicans* ATCC 10231. They noted that none of the compounds (**43, 44**) showed significant activity against the selected microorganisms.[45]



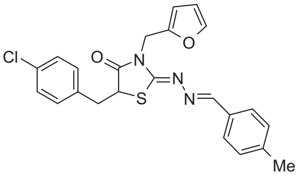
43 = R = -C_3H_5 ,**44** = R= -C_6H_5

Novel 5-(R^1-benzyl)-2-(R^2-benzylidenehydrazono)-3-(2-furylmethyl) thiazolidin-4-one derivatives were synthesized and evaluated for their antimicrobial activity by Tsyalkovsky et al.

Their findings revealed that methyl group at 4th position of benzyl group was essential for activity while replacement of methyl group by halogen (**45, 46**) resulted in the loss of antimicrobial activity.[33]

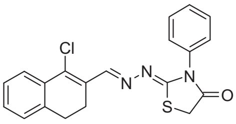


(45)

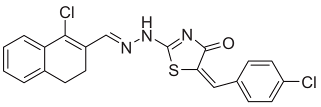


(46)

Bondock et al. synthesized thirteen compounds and screened for antimicrobial activities against *B. subtilis*, *B. megaterium*, *E. coli*. Most of the prepared thiazolidinone derivatives (**47**, **48**) revealed comparable activity against tested strains by taking ampicillin and chloramphenicol in a concentration of 25 mg/mL as a reference drug.[46]

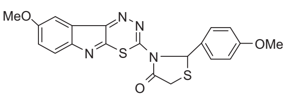


(47)

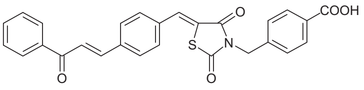


(48)

A variety of new indolylthiadiazino-azetidinones and indolylthiadiazino-thiazolidinone derivatives were synthesized by Kumar et al. Out of eight indolylthiadiazino-thiazolidinone derivatives only 5-methoxy-2,3-[2′-(2″-methoxy-phenyl-4″-oxo-1″,3″-thiazolidin-3″-yl)-1′,3′,4′-thiadiazino]indoles (**49**) showed moderate antibacterial activity, but none of the compounds was found to be more active than 5-methoxy-2,3-[2′-(3″-chloro-2″-oxo-4″-methoxy-phenyl-1″-azetidinyl)-1′,3′,4′-thiadiazino]indoles.[47] A number of chalcone derivatives bearing the 2,4-thiazolidinedione and benzoic acid moieties has been evaluated for antimicrobial activity against six Gram-positive bacteria and tested compounds did not exhibited any activity against Gram-negative strains. From this series compound **50** was the best against multidrugresistant Gram-positive bacterial strains (MRSA CCARM 3167, 3506; QRSA CCARM 3505, 3519) with MIC values in the range of 0.5–2 μg/mL, that showed eight-fold more potency than norfloxacin and 64-fold more activity than oxacillin. SAR study explained that free carboxyl group at *para* position and Cl, Br and $–OCH_3$ groups at *ortho* position seem to be enhanced antibacterial activity.[48]

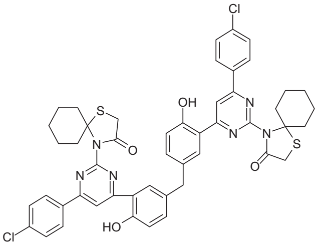


(49)

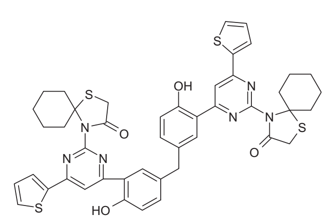


(50)

Biological screening of methylene-bis-pyrimidinyl-spiro-4-thiazolidinones showed that these compounds demonstrated relatively good activity against the human pathogenic bacteria *E. coli*, *K. pneumoniae*, *S. dysentriae* and *S. flexnei* and antifungal activity against *A. niger*, *C. albicans*, *Aspergillus flavus* and *Rhizopus oryzae.* 4-[4-(4-chlorophenyl)-6-(5-{3-[6-(4-chlorophenyl)-2-(3-oxo-1-thia-4-azaspiro[4.5]dec-4-yl)-4-pyrimidinyl]-4-hydroxybenzyl}-2-hydroxyphenyl)-2-pyrimidinyl]-1-thia-4-azaspiro[4.5]decan-3-one (**51**) showed high activity against all tested bacterial organisms and compound 4-[4-(2-hydroxy-5-{4-hydroxy-3-[2-(3-oxo-1-thia-4-azaspiro-[4.5]dec-4-yl)-6-(2-thienyl)-4-pyrimidinyl]benzyl}phenyl)-6-(2-thienyl)-2-pyrimidinyl]-1-thia-4 azaspiro[4.5]decan-3-one (**52**) was highly active against all the tested fungal strains.[49]



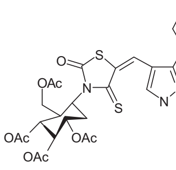
(51)



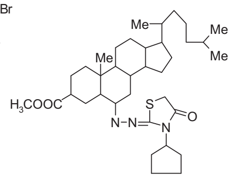
(52)

Compound *N*-(2,3,4,6-tetra-*O*-acetyl-b-D-glucopyranosyl)-5-[(3-(4-bromophenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene]-2-thioxo-4-thiazolidinone (**53**) exhibited MIC of 143 μg/mL against *E. coli*.[50] Khan and Yusuf synthesized steroidal (cholesterol) derivatives of thiazolidinone and evaluated against bacteria such as *S. aureus*, *S. pyogenes*, *S. typhimurium* and *E. coli*. Compounds having acetoxy (**54**) and chloro (**55**) substituents on the 3β-position of the steroidal thiazolidinone ring showed maximum potency.[51]

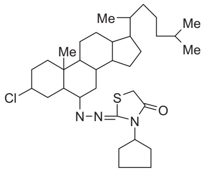
Please cite this article in press as: Jain, A. K.; et al. *Bioorg. Med. Chem.* (2012), http://dx.doi.org/10.1016/j.bmc.2012.03.069



(53)

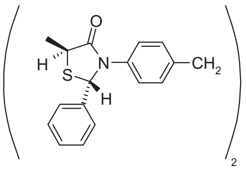


(54)

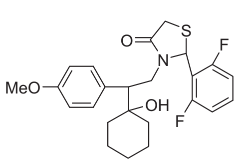


(55)

Fungicidal activity of 4,4′-bis(2″-aryl-5″-methyl/unsubstituted-4″-oxo-thiazolidin-3″-yl) bibenzyl had been studied by Siddiqui et al. against *Fusarium oxysporium* and *Penicillium citrinum.* The results demonstrated that the presence of 5-methyl oxothiazolidine nucleus with the bibenzyl nucleus (**56**) caused complete inhibition of mycelial growth of the test fungi and enhanced the fungicidal activity of these compounds. Further substitution on phenyl ring on thiazolidinone did not improve its fungicidal activity.[52] Presence of two fluorine atoms at 2nd and 6th positions of 2-phenyl-thiazolidin-4-one (**57**) bearing a venlafaxine moiety represented more potent antibacterial and antifungal agents.[53]

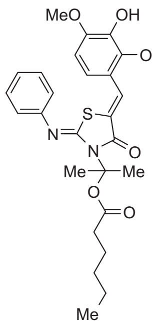


(56)

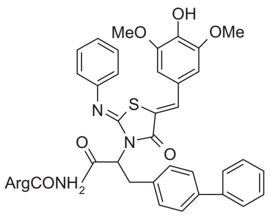


(57)

Some Gram-negative bacteria secrete proteinous toxins and virulence factor that are responsible for creating and maintain infection. Kline et al. have carried out the synthesis of some novel tris-aryl substituted 2-imino-5-arylidenethiazolidin-4-one derivatives and evaluated for their inhibitory activity of bacterial type III secretion in *Salmonella enterica.* The results indicated that compound **58** and **59** acted directly to disrupt a protein-protein interaction. Analogous having *N*-3 carbalkoxy substituent (**58**) was shown to have significant degree of SipA inhibition at concentrations of 1 μM or less and the activity of compound **59** was due to the presence of combination of a cationic group and a functional group having the potential for hydrophobic interactions.[54]

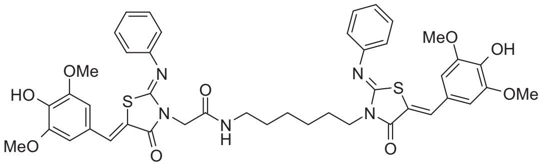


(58)

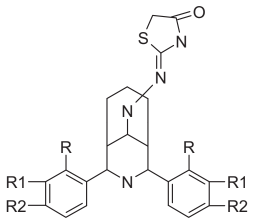


(59)

Dimerization of compound **58** showed a substantial increases its activity. Many of the synthesized dimers (**60**) inhibited the type III secretion system reliant secretion of a virulence protein at concentrations lower than that of the original monomeric compounds.[55] A series of 2,4-diaryl-3-azabicyclo[3.3.1]nonan-9-one thiosemicarbazones upon cyclization with ethylbromoacetate in the presence of sodium acetate–acetic acid buffer afforded novel 2-[(2,4-diaryl-3-azabicyclo[3.3.1]nonan-9-ylidene) hydrazono]-1,3-thiazolidin-4-ones. From this series, two compounds were found to be most active against *E. coli* and *S. aureus*, while some derivatives were moderately active in antifungal assay. Results revealed that the compounds with fluorine or chlorine substituents (**61**) were found to be more active against all the tested bacterial and fungal strains.[56]



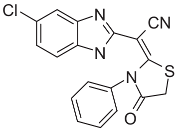
(60)



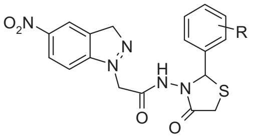
(61)

R= H, Cl , R1 = H, F, OCH$_3$, R2 = H, F, Cl, CH$_3$, OCH$_3$

An attempt to prepare active compounds in the 2-substituted benzimidazole derivatives was unsuccessful. Introducing a substituted or unsubstituted 4-oxothiazolidin at 2nd position on benzimidazole had no significant impact on activity while 5-chloro or 5-unsubstituted carboxylic acid group on 5th position of benzimidazole ring (**62**) was favourable for the activity.[57] Upadhyay et al. synthesized *N*-[(4-oxo-2-substitutedaryl-1,3-thiazolidine)-acetamidyl]-5-nitroindazole derivatives by using microwave method and screened them for antibacterial activity against *E. coli, B. subtilis* and *S. typhi* at 50 and 100 μg/mL concentrations and antifungal activity against *A. flavus, P. citrinum* and *F. oxysporum* at the same concentrations by filter paper disk technique. Compounds **63** and **64** in which a nitro group was present at *ortho* and *meta* positions of the aryl ring, respectively possessed stronger antibacterial and antifungal activity against all tested strains.[58]

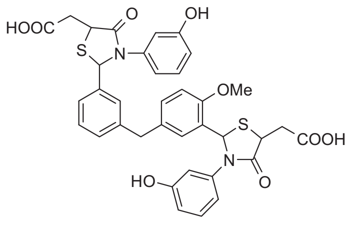


(62)

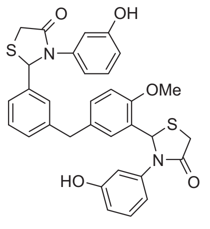


63 = R= *m*-NO$_2$, **64** = *o*-NO$_2$

Srinivas et al. reported that compounds **65** and **66** shows LD$_{50}$ values of 210 and 240 ppm against *D. myceliophagus* and *C. elegans*, respectively and were highly active against *B. subtilis*, *S. aureus* and *E. coli* .[59]

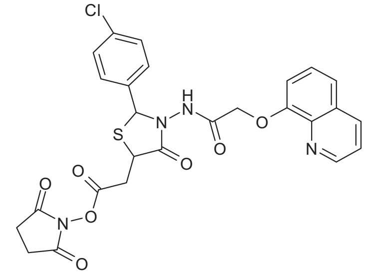


(65)

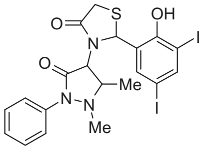


(66)

Antimicrobial activity of succinimido(2-aryl-4-oxo-3-{[(quinolin-8-yloxy) acetyl]amino}-1,3-thiazolidin-5-yl) acetates with respect to five bacteria species *S. aureus*, *S. albus*, *S. faecalis*, *K. pneumoniae* and *P. aeuroginosa and* antifungal activity against *C. albicans* and *A. fumigates* showed compound **67** as highly active against all tested strains.[60] The antimicrobial activity of 2,3-diaryl-1,3-thiazolidin-4-ones was studied. Most of synthesized compounds 2,3-diaryl-1,3-thiazolidin-4-one derivatives having a 2,6-dichlorophenyl, antipyrine, or 1,2,4-triazole ring at N-3 and variously substituted 3-iodo-or 3-bromo-phenyl rings at C-2 exhibited a marked degree of activity against bacteria at the minimum inhibitory concentration (MIC) of 50 μg/ml. Compound **68** exhibited a zone of inhibition of 27, 24, 25 mm against *E. coli, B. subtillis, S. typhi,* respectively.[61]



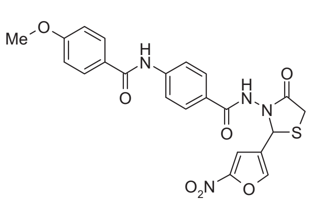
(67)



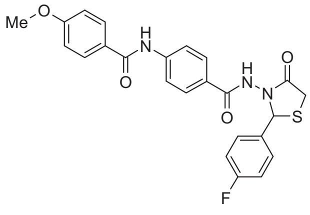
(68)

3.2. Antitubercular activity

Kucukguzel et al. reported antimycobacterial activity of substituted 4-thiazolidinones and found that only compounds **69** and **70** showed 90 and 98% inhibitions at 6.25 μg mL^{-1}, respectively.[62]

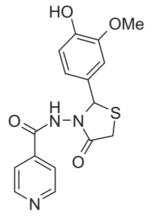


(69)

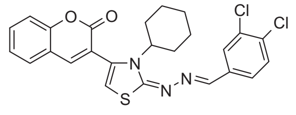


(70)

Jaju and co-workers had synthesized isonicotinylhydrazide derivatives and screened their in vitro antimycobacterial activity against *M. tuberculosis* $H37_{Rv}$ using alamar-blue susceptibility test. They found that the antitubercular activity was considerably affected by various substituents on the aromatic ring of 4-thiazolidinone and it was proved by the fact that compounds with no substitution at the aromatic ring did not show any considerable activity. The hydroxyl and methoxyl group on aromatic ring substituted compound **71** was found to be more active (MIC = 0.31 μg/mL).[63] Karali et al. tested 4-(3-coumarinyl)-3-cyclohexyl-4-thiazolin-2-one benzylidene hydrazone derivatives for antitubercular activity. Most of the compounds showed less than 90% inhibition and considered to be inactive and compound **72** showed maximum inhibition of 42%.[64]

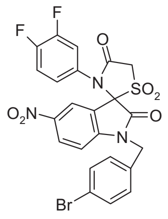


(71)

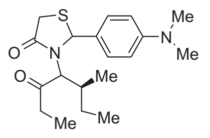


(72)

Protein tyrosine phosphatases A (MptpA) and B (MptpB) secreted into the host cell by growing *Mycobacterium tuberculosis* potently to be active selectively showed a target for the treatment of tuberculosis. Vintonyak et al. designed a novel series of indolin-2-one-3-spirothiazolidinones as a new class of potent and selective inhibitors of MptpB. They studied the modification on phenyl substituent on the thiazolidinone and 2-indolinone positions. The SAR studies suggested that two fluorine atoms or a fluorine and a chlorine atom in *meta* and *para* positions of the phenyl ring attached to thiazolidinone were found to be more potent than analogues bearing mono or dialkyl substituents. Introduction of sulfonamide, trifluoromethoxy or methoxy group led to loss of inhibitory activity. Compound **73** was found to be highly active against *M. tuberculosis* protein tyrosine phosphatase B enzyme (IC_{50} 1.1 μM).[65] Babaoglu et al. reported the activity of 1,3-thiazolidin-4-ones (**74**) against *M. tuberculosis* by inhibition of dTDP-rhamnose synthesis in an attempt to find new inhibitors of the enzymes in the essential rhamnose biosynthetic pathway. A virtual library of 2,3,5-trisubstituted-4-thiazolidinones was created. Synthesized compounds were then docked into the active site cavity of 6-hydroxyl; dTDP-6-deoxy-D-xylo-4-hexulose 3,5-epimerase (RmlC) from *M. tuberculosis*.[66]

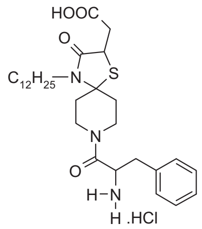


(73)

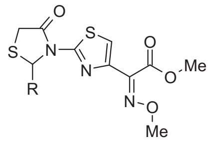


(74)

4-Dodecyl-3-oxo-8-phenyl-alanyl-1-thia-4,8-diazaspiro[4.5] dec-2-yl) acetic acid hydrochloride (**75**) showed inhibition of 97%.[67] Thiazolidinone derivatives (**76**) were found to be inactive or poorly active against *M. tuberculosis* $H_{37}RV$.[68]

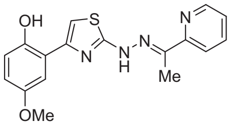


(75)



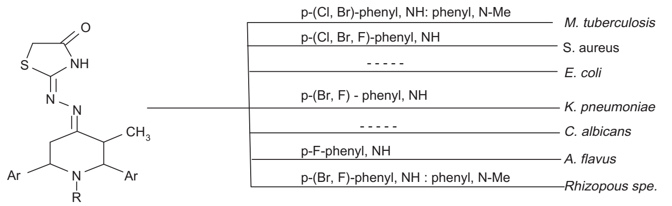
(76)

Zitouni et al. reported the synthesis of *N*-pyridyl-*N*′-thiazolylhydrazine derivatives. Compound **77** showed high antituberculosis activity (IC_{50}: 6.22 µg/mL and IC_{90}: 6.78 µg/mL), its structural details revealed that 2-pyridyl and 2-hydroxy-5-methoxyphenyl group are essential for antimycobacterial activity while 3-pyridyl, 4-pyridyl group were unfavorable for activity.[69]



(77)

Series of 2-[3-methyl-2,6-substituted-4-hydrazono]-1,3-thiazolidin-4-one (**78**) with respect to acid-resistant mycobacteria showed investigated compounds to have pronounced activity with respect to the mycobacteria of tuberculosis of the human type (the $H_{37}R_v$) strain and few of the synthesized compounds showed comparable activity with Rifampicin. It was also reported that all compounds were found to be less active than isoniazid.[70]

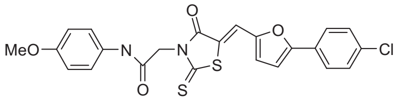


(78)

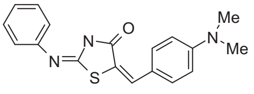
Ar = Phenyl, *p*- (F/Cl/Br/OMe/Me)-phenyl; R= H, Me

3.3. Anticancer activity

Chandrappa et al. reported the synthesis of 2-(5-((5-(4-chlorophenyl)furan-2-yl) methylene)-4-oxo-2-thioxothiazolidin-3-yl) acetic acid derivatives and evaluation of their cytotoxic activity. It was noticed that the compounds with electron donating groups at C-terminal of the phenyl ring resulted in an increase in activity by inducing cell death while compounds with electron withdrawing groups (CN, F, CF_3) exhibited decreased activity. Compound **79** was identified as the most potent one since it displayed the most prominent cytotoxicity which could be attributed to its electron donating methoxy group. Compound **79** also displayed DNA fragmentation of chromosomal DNA at 50 µM.[71] In searching for better anticancer agent Zhou et al. reported design, synthesis, cytoselective toxicity, structure–activity relationships and pharmacophore of thiazolidinone derivatives. Primary screening was performed at a concentration of 10 µM against the cell panel. Changes in cell numbers and cell morphology in 96-well plates at 24 and 48 h had been detected. Compounds that exhibited toxicity to both cancer cell lines but not to normal cells were selected for the secondary confirmation assays. For a secondary screening, the concentration (which was used in the primary screening) was screened in triplicate. As a result, eleven compounds were identified as potent agents for inducing cytoselective toxicity. Substitution on nitrogen atom in thiazolidinone ring and the –NMe_2 group at the 4-position of phenyl ring did not show any cytoselective toxicity. Compound (2*E*,5*E*)-5-(4-(dimethylamino)benzylidene)-2-(phenylimino)thiazolidin-4-one (**80**) showed IC_{50} of 0.50 and 0.21 µM against H460 and $H460_{taxR.}$[72]

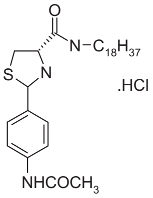


(79)

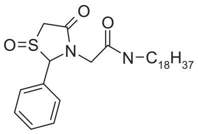


(80)

Gududuru et al. tested a series of 2-arylthiazolidine-4-carboxylic acid amides for possible cytotoxic activity in prostate cancer. Compound **81** was found to be most potent and selective cytotoxic agent with IC_{50} of 0.55 µM and 38-fold selectivity in PPC-1 cells. The SAR study showed that as the chain length increased from C7 to C18, the potency also increased but further increase in the alkyl chain by one carbon unit caused a significant loss of activity, so alkyl chain with C18 unit was optimal for effectiveness of thiazolidine analogues. Replacement of the phenyl ring with an alkyl or cyclohexyl group reduced the potency while replacement with furanyl ring derivative showed equivalent cytotoxicity.[73] The same research group designed new series of 2-aryl-4-oxo-thiazolidin-3-yl amides (**82**) and all synthesized compounds were evaluated against five human prostate cancer cell lines. They reported that increase in the alkyl chain enhanced the antiproliferative activity while replacement of the alkyl chain with aryl group reduced the biological activity.[74]

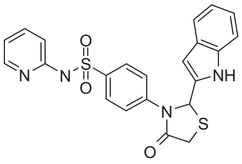


(81)

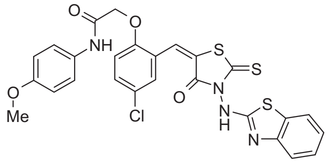


(82)

Compound 2-(3-indolyl)-3-[4-(pyridin-2-ylamino)sulfonyl] phenyl]thiazolidin-4-one (**83**) showed IC_{50} of 1.97 and 1.07 µg/mL, respectively against HELA and MCF7. The activity mainly dependent on 4-[(pyridin-2-ylamino) sulfonyl]benzene pharnmmacophoric moiety while thiazolidi-4-one ring attached to pharmacophoric moiety played a minor role. Docking study of above compound exhibited the lowest binding free energy (ΔGb: −9.07 kcal/mol) which exhibited one hydrogen bonds with Thr670, and RMSD: 0.99 Å.[75] 4-Thiazolidinones containing benzothiazolyl moiety had been synthesized by using reactions of (benzothiazole-2-yl)hydrazine with trithiocarbonyl di-glycolic acid or 6-methyl-2 amino benzo-thiazole with 2-carbethoxymethylthio-2-thiazoline-4-one. Among tested compounds, 2-{2-[3-(benzothiazol-2-ylamino)-4-oxo-2-thioxothiazolidin-5-ylidenemethyl] -4-chlorophenoxy}-*N*-(4-methoxyphenyl)-acetamide (**84**) was found to be the most active candidate with average log GI$_{50}$ and log TGI values as −5.38 and −4.45, respectively. The SAR study revealed that anticancer activity of compound **84** was affected by the nature of substituent in position 5 of 4-thiazolidinone cycle and introduction of 4-chlorophenoxy-*N*-(4-methoxyphenyl)-acetamide group in 5-position of 4-thiazolidinone core enhanced potency.[76]

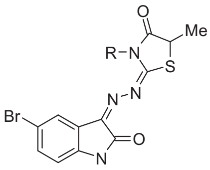


(83)



(84)

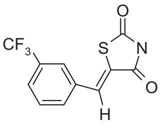
A number of 5-bromo-3-[(3-substituted-5-methyl-4-thiazolidinone-2-ylidene)hydrazono]-1*H*-2-indolinones (**85**) had been investigated for their primary cytotoxic activity against 3-cell line panel consisting of NCI-H460 (Lung), MCF7 (Breast), and SF-268 (CNS). It was observed that thiosemicarbazone derivatives of indolinones showed promising cytotoxicity activity.[77]



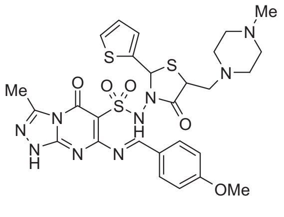
(85)

R = CH_2-CH=CH_2, *n*-C_4H_9, Cycl-C_6H_{11}, C_6H_5, *p*-CH3-C6H4, *p*-Br-C_6H_4, *p*- Cl-C_6H_4, *p*- F-C_6H_4, *p*- NO_2-C_6H_4

Cyclooxygenase (COX) is a well-known enzyme that is responcible for prostaglandins formation. COX-2 is over expressed in several human tumors and production of Prostaglandin of the E series is significantly increased in malignant tissue during the development of colorectal cancer. Compound **86** did not interect with COX enzyme and inhibited the growth of HT29 cell line that do not express COX-2, attained activity levels with IC$_{50}$ ranging between 38.8 and 59.7 μM.[78] Hafez et al. synthesized a series of substituted triazolo[4,3-*a*]pyrimidin-6-sulfonamide with an incorporated thiazolidinone moiety and reported for their antitumor activity. Most of the synthesized compounds were found moderate in activity and compound **87** displayed a good growth inhibitory activity on all tested 60 cell lines showing GI$_{50}$ values between 5.89 and 37.1 × 10^{-6} μM. In fact, the presence of 4-methylpiprazin/morpholine on C-5 and thienyl group at C-2 of thiazolidinone seems to be very important for anticancer activity.[79]

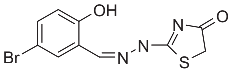


(86)

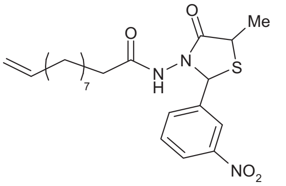


(87)

2-(2-(5-Bromo-2-hydroxybenzylidene)hydrazinyl)thiazol-4(5*H*)-one (**88**) displayed IC$_{50}$ = 0.09 μm for EGFR and IC$_{50}$ = 0.42 μm for HER-2 kinase inhibitors. Compounds with aromatic ring showed better inhibitory activity than those substituted with aliphatic ring.[80] Compound **89** was screened against nine types of human cancer cells and showed significant cytotoxic activity in case of lung cancer, melanoma and renal cancer, where the reduction in growth was found to be 75%, 97% and 84%, respectively, at the concentration of 1.0 × 10^{-4} μm.[81]

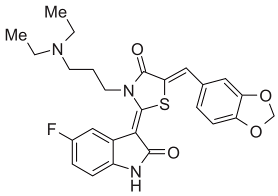


(88)

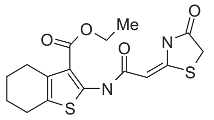


(89)

Compound **90** was screened against three human cancer cell lines (HT-29, H460 and MDA-MB-231) by MTT assay and exhibited IC$_{50}$'s of 0.025, 0.075 and 0.77 μM, respectively. The SAR study showed that substitution with smaller electron-withdrawing fluorine atom at 5-position of the indolin-2-one ring and 3-(diethylamino) propyl group at the 3-position of 4-thiazolidinone ring had positive contribution for increasing antitumor activity.[82] Gouda et al. reported DNA degraditive capacity of thiazolidinone derivatives (**91**). Only few of synthesized derivatives showed complete degradation of the calf thymus DNA.[83]

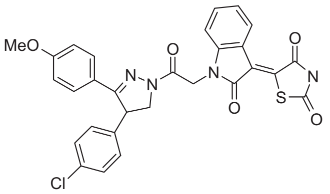


(90)



(91)

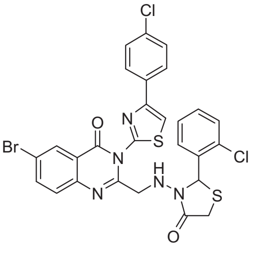
A number of isatin-based thiazolidines conjugates (**92**) have been investigated as anticancer activity, their affinity to tyrosine kinase, cyclin-dependent kinases and carbonic anhydrase isozymes suggested their potential as novel anticancer agents. None of the thiazolidinone conjugates showed greater activity than 1,3-dihydroindol-2-one conjugates with 3,5-diaryl-4,5-dihydropyrazolyne derivatives.[84]



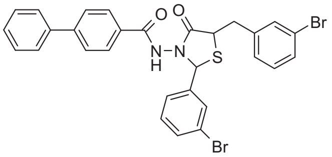
(92)

3.4. Antiinflammtory and analgesic activity

Inflammation constitute a complex biological response to the harmful stimuli and is linked with many pathophysiological conditions. In response to inflammatory stimuli, macrophages release various pro-inflammatory molecules, including the short-lived free radical nitric oxide (NO). Arylalkanoic acids constitute the basis for the widely used nonsteroidal anti-inflammatory agents naproxen and ibuprofen, these drugs inhibit the COX enzyme that catalyzes the biosynthesis of prostaglandins and tromboxane from arachidonic acid. The mode of action of these drugs is correlated with unwanted side-effects such as gastrointestinal and renal toxicities. To overcome the above mentioned side effects anti-inflammatory and analgesic activity of new series of quinazolinone derivatives having thiazolidinone at 2nd position was reported by Kumar et al. Interestingly compound **93** which was substituted with chloro group at 2nd position of phenyl ring, showed almost equal anti-inflammatory activity to that of phenylbutazone at 50 mg/kg.[85] In another study biphenyl-4-carboxylic acid 5-(arylidene)-2-(aryl)-4-oxo-thiazolidin-3-yl amide derivatives exhibited significant anti-inflammatory activity. Compound **94** with a substitution of bromine on both the aromatic rings showed percentage inhibition of 44.59 and 55.73 at 2 and 4 h, respectively.[86]

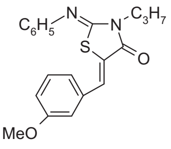


(93)

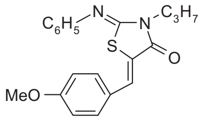


(94)

Series of 5-arylidene-2-imino-4-thiazolidinones exhibited significant activity levels in carrageenan-induced paw and rats pleurisy edema models of acute inflammation. 5-(3-methoxy phenylidene)-2-phenylimino-3-propyl-4 thiazolidinone (**95**) showed inhibition level (85% at the 3rd h) similar to that of indomethacin. Moving the methoxy group from 3rd position to 4th and substitution with 4-SCH_3, $4\text{-SO}_2\text{CH}_3$ indicated that sulfur oxidation was slightly detrimental to the anti-inflammatory activity. 5-(4-Methoxyphenyl)methylidene-2-phenylimino-3-propyl-4-thiazolidinone (**96**) revealed high levels of carrageenan-induced paw edema inhibition comparable to those of indomethacin. Docking study of compound **96** showed that 4-methoxyarylidene moiety can easily occupy the vicinity of the COX-2 secondary pocket and make hydrogen-bonds interaction with Arg513, Arg 120 and Tyr 355.[87]

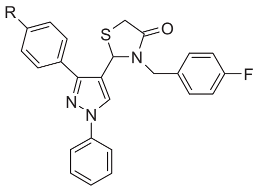


(95)

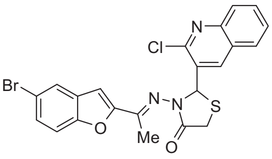


(96)

2-(3-Aryl-1-phenyl-1*H*-pyrazole-4-yl)-3-(4-fluorobenzyl)-4-oxo-thiazolidine derivatives (**97**) was found to be associated with lesser degree of anti-inflammatory activity compared to indomethacin, while thiazolidine carboxamide derivatives and thiazolidine carboxylic acid derivative appeared to exhibit higher anti-inflammatory activity.[88] Compound 3-([1-(5-bromo-1-benzofuran-2-yl) ethylidene]amino)-2-(2-chloroquinolin-3-yl)-1,3-thiazolidin-4-one (**98**) showed significant analgesic activity against carageenan induced rat paw edema test.[89]

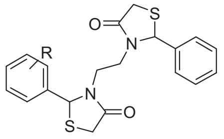


(97)

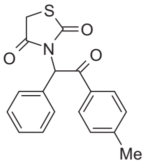


(98)

Ottana et al. investigated 3,3′-(1,2-ethanediyl)-bis[2-aryl-4-thiazolidinone] derivatives (99), which showed interesting stereo selective anti-inflammatory/analgesic activities and suggested that these derivatives might preferentially interact with inducible COX-2 isoform.[90] Absence of 5-arylmethylidene moiety in 3-[2-(4-methylphenyl)-2-oxo-l-phenylethyl]-2,4-thiazolidinedione (**100**) enhanced its anti-inflammatory activity and decreased the analgesic activity. Bulkiness at NH group of 2,4-thiazolidinedione ring either decreased or abolished the anti-inflammatory activity.[91]

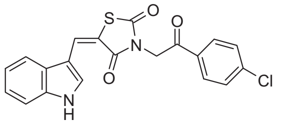


(99)

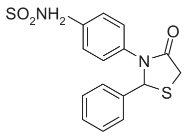


(100)

Compound (5*Z*,*E*)-3-[2-(4-chlorophenyl)-2-oxoethyl]-5-(1*H*-indol-3-ylmethylene)-thiazolidine-2,4-dione (**101**) showed 67.2% inhibition of inflammation at 3 mg/kg dose and attained peak plasma concentrations between 0.5 and 1 h.[92] Good level of anti-inflammtory activity against carrageenan induced rat paw edema was observed in compound **102** with 78% edema inhibition compared to celecoxib at the same dosage producing 45% inhibition.[93]



(101)

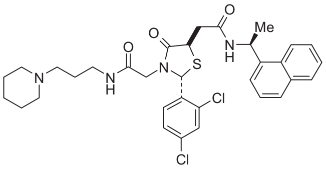


(102)

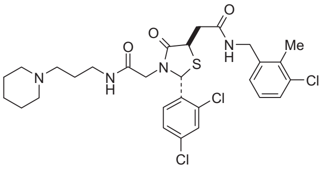
The CCR4 is a kind of receptor which is expressed on Th2-type CD4+ T-cells which play a major role in allergic inflammation. Allen et al. synthesized trisubstituted thiazolidinones as a CCR4 antagonists for the treatment of allergic inflammation. Compounds **103** and **104** showed $IC_{50} = 0.11$, 0.14 µM, respectively and the activity of those compound was due to presence of 2, 4-dichlorophenyl ring in the central position and terminal piperidine on the

Please cite this article in press as: Jain, A. K.; et al. *Bioorg. Med. Chem.* (2012), http://dx.doi.org/10.1016/j.bmc.2012.03.069

left side along with α-methyl naphthyl and 3-chloro-2-methylphenyl moieties on the right side for strong CCR4 receptor binding.[94]

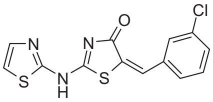


(103)



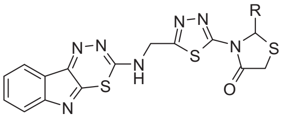
(104)

Compound 2-(thiazole-2-ylamino)-5-(*m*-chlorophenylidene)-4-thiazolidinone (**105**) showed highest COX-1 and COX-2 inhibitory activity while changing the position of chloro group from *meta* to other positions decreased the activity in a series of 2-thiazolylimino/heteroarylimino-5-arylidene-4-thiazolidinones. Substitution with hydroxy group at the *para* position or nitro group at the *meta* or *para* position appears to be non-favorable for their COX selective activity and decreased the efficacy of substituted compounds.[95]



(105)

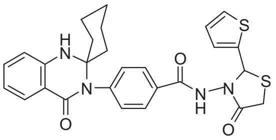
The anti-inflammatory properties of 2-aryl-3-{5-[([1,3,4]thiadiazino[6,5-*b*]indol-3-ylamino)methyl]-1,3,4-thiadiazol-2-yl}-1,3-thiazolidin-4-one (**106**) were studied using carrageenan induced rat′s paw edema method. Bhati and Kumar noted that azetidinones possessed more potent anti-inflammatory and analgesic activities than that of their corresponding thiazolidinone compounds.[96]



(106)

R = C_6H_5, *o*-Cl-C_6H_4, *p*-Cl-C_6H_4, *o*-OCH_3 C_6H_4, *p*-OCH_3 C_6H_4,
p-OHC_6H_4, *p*-$N(CH_3)_2$ C_6H_4, *p*-CH_3-C_6H_4

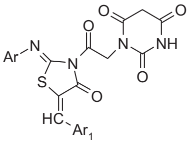
Amin et. al prepared several spiro [(2*H*,3*H*) quinazoline-2,1′-cyclohexan]-4(1*H*)-one derivatives. These compounds were evaluated for their antiinflammatory, ulcerogenic and analgesic activities. Compound **107** with 2-thiophene substitution at C-2 of thiazolidinone has shown most active anti-inflammatory activity and considerable analgesic activity.[97]



(107)

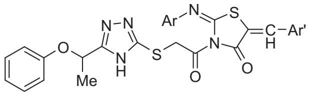
3.5. Anticonvulsant and antidepressant activity

A new series of clubbed thiazolidinone–barbituric acid (**108**) and thiazolidinone–triazole derivatives (**109**) has been synthesized by Shiradkar et al. to study the effect of a hydrophobic unit, hydrogen bonding domain and electron-donor group on the compounds on its anticonvulsant activity. Their findings revealed that the presence of –OH function at the 4-position of the phenyl ring is essential for anticonvulsant activity, the removal or replacement of –OH function by a –Cl, CH_3 or –NO_2 moieties responsible for loss of activity. The replacement of the hydroxyl group responsible for hydrogen bonding resulted in lack of a HBD (hydrogen bonding domain) leading to abolishment of the activity.[98] In a series of thiazolidinonyl 2-oxo/thiobarbituric acids derivatives compound having *p*-methoxyphenyl (**110**) substitution at C-2 of thiazolidinone ring was found to be favorable for activity and exhibited more potent anticonvulsant activity as compared to standard drug sodium phenytoin.[99]



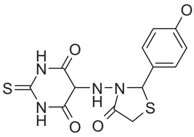
(108)

Ar, Ar´ = -2-OHC_6H_4 , -2-OHC_6H_4
Ar, Ar´ = -2-OHC_6H_4 , -4-$CH_3C_6H_4$



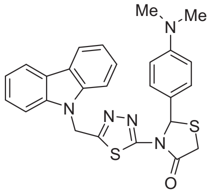
(109)

Ar, Ar´ = -2-OHC_6H_4, -2-OHC_6H_4
Ar, Ar´ = -2-OHC_6H_4 , -4-$CH_3C_6H_4$

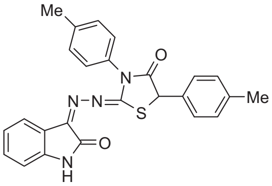


(110)

A number of substituted thiazolidinonyl carbazol derivatives are potent antipsychotic and anticonvulsant agent. Compounds having thiazolidinone ring demonstrated more potent antipsychotic as well as anticonvulsant activities as compared to compounds having azetidinone ring. Among these, compound **111** exhibited very good response against psychotic disorders by recording their responses towards amphetamine induced stereotyped, cataleptic behavior by Rota rod performance and MES test for anticonvulsant activity.[100] Series of 3-[(3-substituted-5-methyl-4-thiazolidinon-2 ylidene) hydrazono]-1*H*-2-indolinone derivatives (**112**) are evaluate for CNS Depressant Activity. Compound **112** having *p*-CH_3-C_6H_4 on thiazolidinone ring exhibited some anticonvulscant activity.[101] Replacement of *p*-CH_3-C_6H_4 with allyl group was found to increase its antidepressant activity.



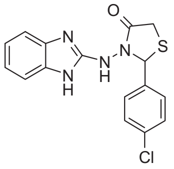
(111)



(112)

Please cite this article in press as: Jain, A. K.; et al. *Bioorg. Med. Chem.* (2012), http://dx.doi.org/10.1016/j.bmc.2012.03.069

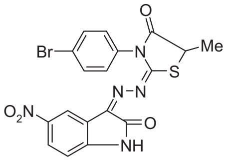
Akula et al. synthesized 3-[1*H*-benzimidazole-2-yl-amino]-2-phenyl-1,3-thiazolidin-4-one derivatives and compound with 4-chloro (**113**) on phenyl ring showed promising depressant activity among all the tested compounds.[102]



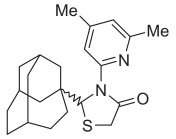
(113)

3.6. Antiviral/anti-HIV activity

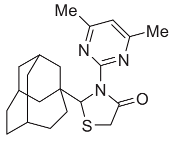
The activity of new 3-hydrazono-5-nitro-2-indolinone derivatives with various substituents at 3rd and 5th position of thiazolidinone ring was screened against the yellow fever virus and bovine viral diarrhea virus (BVDV).[103] The presence of methyl group at C-5 of the thiazolidinone ring was found to be responsible for measurable levels of antiviral activity. 5-Non substituted 4-thiazolidinone derivative exhibited no change in activity when compared to substituted thiazolidinone. The EC_{50} values of compound **114** was found to be 13 µg/mL against BVDV. Structure activity relationship (SAR) studies on thiazolidinone ring revealed that substituent's at C-2 and N-3 of the ring are responsible for the anti-HIV activity. Some 2-adamantyl-substituted thiazolidin-4-ones derivatives which is structurally related to TBZs have been studied by Balzarini et al. They found that compound 2-adamantan-1-yl-3-(4,6-dimethyl-pyridin-2-yl)-thiazolidin-4-one (**115**) represent $EC_{50} = 0.35$ µM against typical non-nucleoside reverse transcriptase. The activity of compound was due to the presence of adamantyl moiety better at C-2 while instead of other derivatives bearing the same N-substituent (i.e. 4,6-dimethyl-2-pyridyl), but lacking the adamantyl moiety, was devoid of antiviral activity.[104] In other report 2-adamantan-1-yl-3-(4,6-dimethylpyrimidin-2-yl)-thiazolidin-4-one (**116**) showed $EC_{50} = 0.67$ µM. The thiazolidinone contain 4,6-dimethylpyrimidinyl group was only two times less potent than the derivative bearing pyridin-2-yl (98).[105]



(114)



(115)



(116)

Using QSAR study it has been observed that thiazolidin-4-ones bearing a lipophilic adamantyl substituent has exhibited good anti-HIV activity and for a series of 2-(2,6-dihalophenyl)-3-(4,6-dimethyl-pyrimidin-2-yl)thiazolidin-4-ones (**117**) have been observed higher anti-HIV activity compared to the other aryl substituted ones (Fig. 1).[106–109]

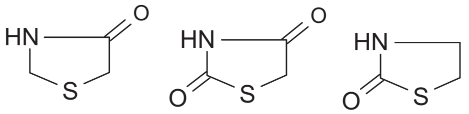
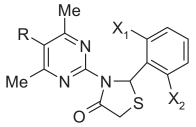


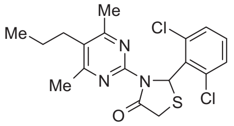
Figure 1. Thiazolidinone structures.



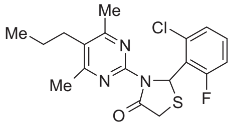
$X_1 = X_2 = F$, $X_1 = X_2 = Br$, $X_1 = X_2 = Cl$, $X_1 = Cl$ $X_2 = F$, R = H, CH_3

(117)

Chen et al. prepared various 2-(2,6-dihalophenyl)-3-(4,6-dimethyl-5-(un)substituted-pyrimidin-2-yl)-thiazolidin-4-ones. The structures of these newly synthesized compounds were confirmed by their analytical and spectral data. These compounds were also evaluated for their HIV-RT inhibitory activity. It was stated that HIV-RT inhibitory activity would be majorly affected by high value of hydrophobicity. It was reported that compound **118** and **119** having ethyl group at 5-position on N-3 position of pyrimidine ring were the most potent ones with the IC_{50} value of 0.26 and 0.23 µM, respectively. Their findings suggested that overall hydrophobicity of the analogues, and steric and electronic features of *meta*/*para*-substituents of 3-hetero-aryl moiety on thiazolidin-4-one led to a substantial increase in antiviral activity.[110]

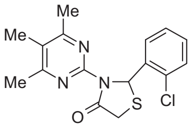


(118)



(119)

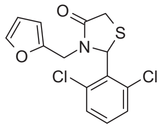
In a series of 2-aryl-3-(4,5,6-trimethylpyrimidin-2-yl) thiazolidin-4-ones, HIV-RT inhibitory activity greatly affected by substitution at C-5 (unfavorable) and enhanced by introducing chlorine atom on the phenyl at C-2. Compound **120** exhibited remarkable anti-HIV-RT activity ($IC_{50} = 2.95$ µM).[111]



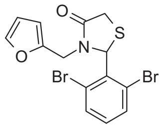
(120)

It should be noted that 2-aryl-3-heteroaryl-2-ylmethyl-1,3-thiazolidin-4-one derivatives were evaluated for human immunodeficiency virus type-1 (HIV-1) reverse transcriptase (RT) inhibitory activity. It was found that some of compounds were effective inhibitors of HIV-1 reverse transcriptase enzyme at micromolar concentrations with less cytotoxicity. Compounds **121** and **122** showed activity at 0.20 and 0.21 µM concentration compared to 0.35 µM concentration of TBZ-1 lead molecule in MT-4 cells. Activity of this series is dependant on substitution at C-2 and N-3 of the 4-thiazolidinone scaffold and a high activity level was observed for compounds that contain a 2,6-dihalophenyl group at C-2 and a pyridine-2-yl or pyrimidine-2-yl ring at N-3.[112]

Please cite this article in press as: Jain, A. K.; et al. *Bioorg. Med. Chem.* (2012), http://dx.doi.org/10.1016/j.bmc.2012.03.069

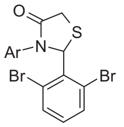


(121)



(122)

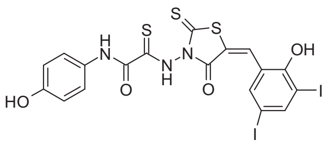
Replacement of furan ring at N-3 with 4-methyl-pyrimidin-2-yl and 4,6-dimethyl-pyrimidin-2-yl **123** was found to enhance reverse transcriptase (RT) inhibitory activity by 1.25-to 2.5-fold more than nevirapine in MT-4 cells.[113] In other way SAR of rhodanine derivatives has been studied by Ramkumar et al. It was reported that electron-donating substituents in ring A and strong electron-withdrawing substitution in substructure B of thiazolidinone is favorable for HIV-1 Integrase inhibitory activity. Compound **124** having hydroxyl groups at position 4 of ring A and strong electron-withdrawing and hydrophobic substitutions 3,5-diiodophenol in substructure B showed IC_{50} value of 7 ± 3 μM and 3 ± 2 for 3′-processing and strand transfer, respectively.[114]



Ar = 4-methyl-pyrimidin-2-yl

and 4,6-dimethyl-pyrimidin-2-yl

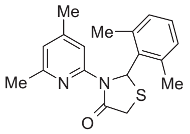
(123)



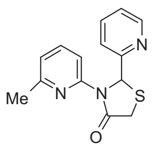
(124)

Ar = 4-methyl-pyrimidin-2-yl and 4,6-dimethyl-pyrimidin-2-yl

1,3-Thiazolidinone-4-one derivatives were prepared by Ravichandran et al. and their antiviral activity against Herpes simplex virus-1 (KOS), Herpes simplex virus-2 (G), Influenza A H3N2 subtype and Influenza B was evaluated. Compound **125** was found to be most active with an EC_{50} of 130.24, 161.38, 249.15 and 263.31 μM, respectively. They concluded that combination of 1,3-thiazolidin-4-one and 2-pyridinyl ring (substituted) at N-3 with an aromatic system namely 2,6-disustituted phenyl or 2-pyridinyl ring at C-2 has enhanced the anti-viral effect. Compound **126** having 2-pyridinyl substituent at C-2 and methyl group at the 6 position of the pyridin-2-yl of N-3 of thiazolidinone was found to be most active with an EC_{50} of 0.0078 μM against wild-type HIV-1.[115]



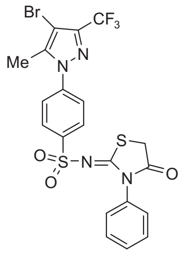
(125)



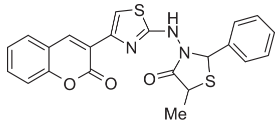
(126)

3.7. Antidiabetic activity

3-Subsituted-2-[*p*-(4-bromo-3-trifluoro-5-substituted-pyrazol-1-yl)benzenesulfonylimino]-4-oxothiazolidine derivatives (**127**) were evaluated for their hypoglycemic activity using alloxan-treated female albino mice.[116] Kini and Ghate studied the oral hypoglycemic activity of 3-[5′-methyl-2′-aryl-3′-(thiazol-2″-yl amino) thiazolidin-4′-one]coumarin derivatives (**128**) and reported that electro-negativity seemed to be responsible for variation in hypoglycemic activity.[117]

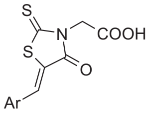


(127)

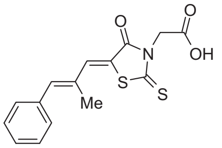


(128)

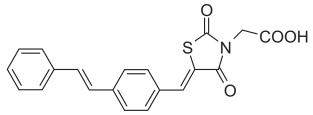
Aldose reductase, is an enzyme that is in general found in many parts of the body, and catalyzes the pathway that is responsible for fructose formation from glucose. Aldose reductase activity increases as the glucose concentration while its inhibition explore a attractive molecular target to build up drugs able to prevent the inception and succession of secondary pathologies associated with DM, even in the presence of defective control of glycaemia. In a series of 5-arylidene-2-thioxo-4-thiazolidinone derivatives (**129**) most of the compounds were found to be moderate in aldose reductase inhibitory effects at low micromolar doses and two of them exhibited higher potency than epalrestat (**130**). Based on the results structure–activity relationship (SAR) it was concluded that acetic chain on N-3 position favored the activity and make a strongest interactions to the polar recognition region of the ALR2 active site while removal of the acetic chain on N-3 of the thiazolidinedione ring decrease its potency towards active site. Effect of 5-arylidene moiety on the inhibitory activity could become less evident and replacement of the carbonyl group in position 2nd of the 2,4-thiazolidinedione scaffold with the bioisoster thiocarbonyl group can improve inhibitory efficacy.[118] Similarly introduction of vinyl moiety between the two aromatic rings or between the methylidene group and the aromatic ring of the arylidene moiety has been introduced in some derivatives to improve the activity profile. Unsubstituted derivative (**131**) at *para* position of the distal phenyl ring proved to be most active in this series.[119]



(129) Ar = 3-O-C_6H_5-C_6H_5, 4- O-C_6H_5-C_6H_5, 3-O-CH_2-C_6H_5-C_6H_4, 4-O-CH_2-C_6H_5-C_6H_4, 3-OCH_3-C_6H_4



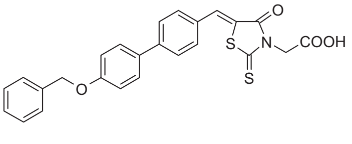
(130)



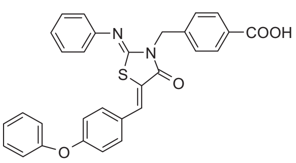
(131)

Protein tyrosine phosphatase 1B (PTP1B) is an important enzyme that is responsible for down-regulating of the insulin signaling through dephosphorylation of the insulin receptor. Inhibitors of PTP1B normalize the increased plasma glucose level by increases the insulin sensitivity and thus are useful therapeutic agents for the treatment of diabetes. In view of above, Liu et al. studied a series of novel PTP1B inhibitors containing a thiazolidinone-substituted biphenyl scaffold and reported that introduction of the 4-

oxothiazolidine-2-thione moiety showed better inhibitory activity against PTP1B. Substitution with polar group at N of thiazolidinone ring and alkyl group at the 4′-position of the biphenyl scaffold led to unfavorable for bioactivity. Compound **132** have benzyl group lowered the fasting glucose levels and showed IC_{50} value of 0.48±0.07 μmol/L.[120] Replacement of carbonyl group in position 2 of the 2,4-thiazolidinedione scaffold with a phenylimino moiety enhanced its PTP1B as well as LMW-PTP inhibitory activity. Ottana et al. reported that substitution with lipophilic arylidene moiety in position 5 particularly favored the activity; phenoxy and benzyloxy groups in the *para* and *meta* positions of the 5-benzylidene group found to be better substituents for enzyme inhibition. Compound 4-{[4-oxo-5-(4-phenoxy-benzylidene)-2-phenylimino-thiazolidin-3-yl]methyl} benzoic acid (**133**) showed PTP1B and LMW-PTP inhibition at IC_{50} = 1.1, 3.1 μM, respectively.[121]

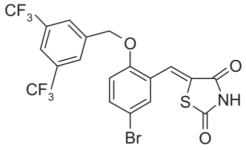


(132)

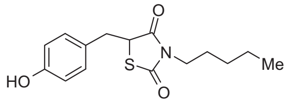


(133)

In a series of benzylidene-2,4-thiazolidinedione, compound **134** substituted with 5-(2-(3,5-bis(trifluoromethyl) benzyloxy)-5bromobenzylidene) at C-5 to the TZD ring was more potent in PTP1B inhibition.[122] Several derivatives of thiazolidine-2,4-diones derivatives having carboxylic ester moieties at N-3 and benzyl and heteroaryl substituents at C-5 have been also screened for their anti-hyperglycemic activity. Compound **135** emerged as the most promissory anti-hyperglycemic activity.[123]



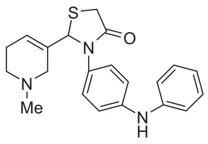
(134)



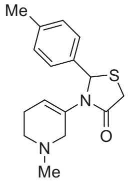
(135)

3.8. Muscarinic receptor 1 agonist

M1 selective muscarinic agonists are highly lipophilic and are capable of crossing the blood–brain barrier.[109] Most of the potent muscarinic agonists show central and peripheral adverse side effects, and non-selective or M2 > M1 selective. They decreases Ach release due to its M2 autoreceptors inhibitory activity. *N*-alkyl/aryl substituted thiazolidinone arecoline analogues were tested for muscarinic receptor 1 agonist in Alzheimer's dementia models. Among all the synthesized compounds, four derivatives showed high affinity for binding with receptor from its binding site. Compound 2-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-3-(4-phenylamino-phenyl)-thiazolidin-4-one (**136**) (IC_{50} = 6.23 μM) was found to be most potent ligand having biphenyl amine attached to nitrogen of thiazolidinone arecoline. Other compounds substituted with *n*-butyl chain at nitrogen atom of biphenyl amine increases its activity and further increases in chain length consequently decreased its activity towards muscarinic receptor.[124] Chandra et al. findings revealed that, affinity and potency of arecoline thiazolidinone molecules dependent on the length of carbon chain. As the length of carbon chain increases affinity and potency of these molecules towards M1 receptor decreases. The most active compound among aromatic derivatives **137** which contain one electron donating methyl group at *para* position of aromatic ring showed significant affinity and potency towards M1 receptor (K_i = 26 μm and IC_{50} = 143 μm).[125]



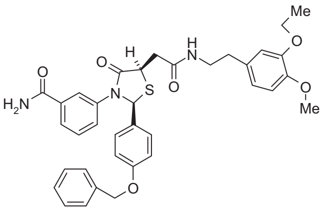
(136)



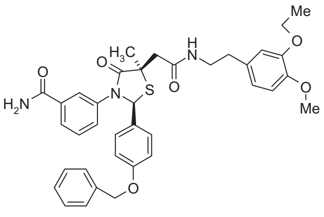
(137)

3.9. FSH receptor agonist

Follicle-stimulating hormone receptor is a G-protein coupled receptor that provides a surface for FSH binding which stimulate adenylyl cyclase for its activity. Some of the thiazolidinone based compounds have been found to be hFSHR agonists.[126] Jetter et al.[127] evaluated few 5-alkylated thiazolidinones derivatives as FSH receptor agonist. They reported that replacement of the 5-hydrogen (**138**) with a 5-methyl moiety (**139**) lead to increased agonist activity while replacement with allyl moiety displayed full agonist efficacy. Oxidation of sulphur of thiazolidinone moieties gave highly unstable and rapidly degradable compound.

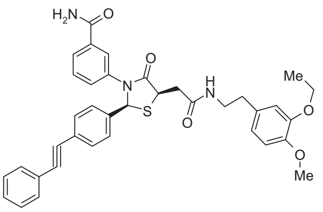


(138)

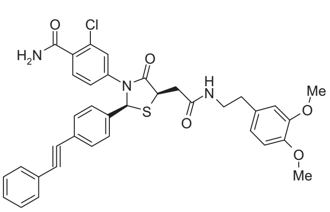


(139)

Several thiazolidinone analogs have been synthesized and shown to have positive allosteric modulators of the follicle-stimulating hormone receptor. Modification on aryl group at the 3rd and 5th position of thiazolidine was found to effect functional activity of compounds which produces positive and negative allosteric modulators. The leading compound **140** displayed full agonistic activity in both the cAMP bioassay and aromatase bioassay with EC_{50} were of approximately 80 and 50 nM for the cAMP and aromatase bioassay, respectively.[128] Allosteric activation of the Follicle-stimulating Hormone (FSH) Receptor by compound **141** showed EC_{50} = 1 nM.[129]



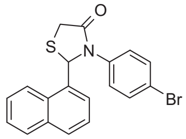
(140)



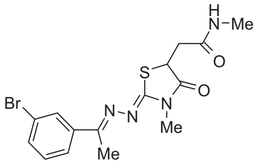
(141)

3.10. Trypanocidal (anti-epimastigote) activity

A number of new 3-aryl-2-(α-naphtyl)-4-thiazolidinones has been synthesized and tested for their biological activity. The synthesized thiazolidin-4-one derivatives were screened for trypanocidal (anti-epimastigote activity, %AE), trichomonacidal activity (growth inhibition,%GI) and unspecific cytotoxicity (expressed as cytotoxicity percentage –%C) to macrophages. All synthesized compounds exhibited a trypanocidal activity ranging from 79.4% to 100% at the higher concentration assayed (100 μg/mL). The compounds also showed unspecific cytotoxicity to macrophages at this concentration. Compound 3-(4-bromophenyl)-2-(*a*-naphthyl)-1,3-thiazolidin-4-one (**142**) showed 91.4% anti-epimastigote activity which is lower than that shown by Nifurtimox.[130] Similarly compound **143** represented best selectivity (60%) as anti-*T. cruzi*. Docking study revealed that these compound did not inhibit cruzipain enzyme site and is independent on the cystein protease activity.[131]



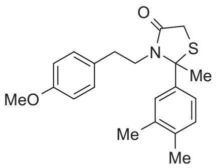
(142)



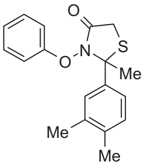
(143)

3.11. Antiarrhythmic activity

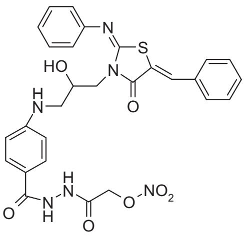
The most common features of cardiac arrhythmias are atrial flutter and atrial fibrillation which are associated with an increase in heart failure, stroke, and mortality. Blockade of the Kv1.5 ion channel is a potentially atrial-selective avenue for the treatment of atrial fibrillation and atrial flutter. Jackson et al. reported synthesis and biological evaluation of thiazolidinone-based blockers of Kv1.5. The 3,4-dimethyl derivatives **144** (IC$_{50}$ = 0.069 μM) and **145** (IC$_{50}$ = 0.270 μM) were found to be the most potent compounds of this series.[132] In 2009, Bhandari and co-workers discovered 2-(2-(4-(3-((5-substituted methylene)-4-oxo-2-(phenylimino)thiazolidin-3-yl)-2-hydroxypropylamino) benzoyl) hydrazinyl)-2-oxoethyl nitrate derivatives and evaluated them for electrocardiographic, antiarrhythmic, vasorelaxing and antihypertensive activity as well as for in-vitro nitric oxide (NO) releasing ability and found that some of these heterocycles are very potent. Compound 2-(2-(4-(3-(5-benzyliden-4-oxo-2-(phenylimino) thiazolidin-3-yl)-2-hydroxy propylamino) benzoyl) hydrazinyl)-2-oxoethyl nitrate (**146**), was found to be the most potent in this series.[133]



(144)



(145)



(146)

4. Conclusion

The potency of 4-thiazolidinone nucleus is cleared from the clinically used drugs. Though the antibacterial and antitubercular, antiviral and antidiabetic (PTP1B inhibitors) are the four major areas of clinical use, other potential targets are still to be explored. Most of the positions were explored to improve the antibacterial and antitubercular profile of 4-thiazolidinone but still none of the derivatives showed promising antitubercular activity. However, few derivatives with C-2 and N-3 substituted positions and the presences of electron-withdrawing substitution on aromatic ring on C-2 position of 4-thiazolinone presenting varied degrees of inhibition against Gram-positive and Gram-negative bacteria showing inhibition as good as to the standard drugs used. The activity of the compounds depends upon the nature and position of the substituents at the aryl moiety attached with thiazolidinone ring. Hence further investigation in this direction may yield fruitful results. No concerted conclusion has emerged regarding SAR and potency of the reported derivatives. Hence further study in this direction may be quite rewarding. From these observations, the importance of the nucleus is highlighted. But there is much scope in this promising moiety as a number of different molecular targets is available for 4-thiazolidinone. The literature revealed that 4-thiazolidinone has diverse biological potential, and the easy synthetic routes for synthesis have taken attention of the researchers.

Acknowledgement

One of the authors Mr. Abhishek K. Jain is grateful to AICTE for providing National Doctoral fellowship.

References

1. Singh, S. P.; Parmar, S. S.; Raman, K.; Stenberg, V. I. *Chem. Rev.* **1981**, *81*, 175.
2. Brown, F. C. *Chem. Rev.* **1961**, *61*, 463.
3. Samarin, A. S.; Loslcutov, V. A. *Tr Tomsk. Gos. Utiiv. Ser. Khim.* **1965**, *170*, 157.
4. Meher, S. S.; Naik, S.; Behera, R. K.; Nayak, A. *J. Indian Chem. Soc.* **1981**, *58*, 274.
5. Mandlik, J. V.; Patwardham, V. A.; Nargund, K. S. *J. Univ. Poona. Sci. Technol.* **1966**, *32*, 39.
6. Bronson, J. J.; DenBleyker, K. L.; Falk, P. J.; Mate, R. A.; Ho, H. T.; Pucci, M. J.; Snyder, L. B. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 873.
7. Cunico, W.; Gomes, C. R. B.; Vellasco, W. T., Jr. *Mini Rev. Org. Chem.* **2008**, *5*, 336.
8. Verma, A.; Saraf, S. K. *Eur. J. Med. Chem.* **2008**, *43*, 897.
9. Hamama, W. S.; Ismail, M. A.; Shaaban, S.; Zoorob, H. H. *J. Heterocycl. Chem.* **2008**, *45*, 1.
10. Markovic, R.; Stodanovic, M. *Heterocycles* **2005**, *56*, 2635.
11. Pawar, R. B.; Mulwad, V. V. *Chem Heterocycl. Compd.* **2004**, *40*, 219.
12. Ocal, N.; Aydogan, F.; Yolacan, C.; Turgut, Z. *J. Heterocycl. Chem.* **2003**, *40*, 721.
13. Eltsov, O. S.; Mokrushin, V. S.; Belskaya, N. P.; Kozlova, N. M. *Rus. Chem. Bull., Int. Edn.* **2003**, *52*, 461.
14. Cunico, W.; Gomes, C. R. B.; Ferreira, M.; Capri, L. R.; Soares, M.; Wardell, S. M. S. V. *Tetrahedron Lett.* **2007**, *48*, 6217.
15. Neuenfeldt, P. D.; Drawanz, B. B.; Siqueira, G. M.; Gomes, C. R. B.; Wardell, S. N. S. V.; Flores, A. F. C.; Cunico, W. *Tetrahedron Lett.* **2010**, *51*, 3106.
16. Pratap, U. R.; Jawale, D. V.; Bhosle, M. R.; Mane, R. A. *Tetrahedron Lett.* **2011**, *52*, 1689.
17. Mali, J. R.; Pratap, U. R.; Netankar, P. D.; Mane, R. A. *Tetrahedron Lett.* **2009**, *50*, 5027.
18. Bolli, M. H.; Abele, S.; Binkert, C.; Bravo, R.; Buchmann, S.; Bur, D.; Gatfield, J.; Hess, P.; Kohl, C.; Mangold, C.; Mathys, B.; Menyhart, M.; Meuller, C.; Nayler, O.; Scherz, M.; Schmidt, G.; Sippel, V.; Steiner, B.; Strasser, D.; Treiber, A.; Weller, T. *J. Med. Chem.* **2010**, *53*, 4198.
19. Moghaddam, F. M.; Hojabri, L. J. *J. Heterocycl. Chem.* **2007**, *44*, 35.
20. Bolognese, A.; Correale, G.; Manfra, M.; Lavecchia, A.; Novellino, E.; Barone, V. *Org. Biomol. Chem.* **2004**, *2*, 2809.
21. Liesen, A. P.; Aquino, T. M.; Carvalho, C. S.; Lima, V. T.; Araujo, J. M.; Lima, J. G.; Faria, A. R.; Melo, E. J. T.; Alves, A. J.; Alves, E. W.; Alves, A. Q.; Goes, A. S. *Eur. J. Med. Chem.* **2010**, *45*, 3685.
22. Omar, K.; Geronikaki, A.; Zoumpoulakis, P.; Camoutsis, C.; Sokovic, M.; Ciric, A.; Glamoclija, J. *Bioorg. Med. Chem.* **2010**, *18*, 426.
23. Kocabalkanli, A.; Ates, A.; Otuk, G. *Arch. Pharm. Pharm. Med. Chem.* **2001**, *334*, 35.
24. Gopalakrishnan, M.; Thanusu, J.; Kanagarajan, V. *J. Enz. Inhib. Med. Chem.* **2009**, *24*, 1088.
25. Singh, T.; Srivastava, V. K.; Saxena, K. K.; Goel, S. L.; Kumar, A. *Arch. Pharm. Chem. Life Sci.* **2006**, *339*, 466.
26. Pawar, R. B.; Mulwad, V. V. *Chem. Heterocycl. Comp.* **2004**, *40*, 219.
27. Sayed, M.; Mokle, S.; Bokhare, M.; Mankar, A.; Surwase, S.; Bhusare, S.; Vibhute, Y. *ARKIVOC* **2006**, *II*, 187.

28. Vicini, P.; Geronikaki, A.; Anastasia, K.; Incerti, M.; Zani, F. *Bioorg. Med. Chem.* **2006**, *14*, 3859.
29. Gouveia, F. L.; Oliveira, R. M. B.; Oliveira, T. B.; Silva, I. M.; Nascimento, S. C.; Sena, K. X. F. R.; Albuquerque, J. F. C. *Eur. J. Med. Chem.* **2009**, *44*, 2038.
30. Mulwad, V. V.; Mir, A. A. *J. Kor. Chem. Soc.* **2008**, *52*, 649.
31. Aquino, T. M.; Liesen, A. P.; Silva, R. E. A.; Lima, V. T.; Carvalho, C. S.; Faria, A. R.; Araujo, J. M.; Lima, J. G.; Alves, A. J.; Melo, E. J. T.; Goes, A. J. S. *Bioorg. Med. Chem.* **2008**, *16*, 446.
32. Sakhuja, R.; Panda, S. S.; Khanna, L.; Khurana, S.; Jain, S. C. *Bioorg. Med. Chem* **2011**, *21*, 5465.
33. Tsyalkovsky, V. M.; Kutsyk, R. V.; Matiychuk, V. S.; Obushak, N. D.; Klyufinskaya, T. I. *Pharm. Chem. J.* **2005**, *39*, 245.
34. Bonde, C. G.; Gaikwad, N. J. *Bioorg. Med. Chem.* **2004**, *12*, 2151.
35. Vicini, P.; Geronikaki, A.; Incerti, M.; Zani, F.; Dearden, J.; Hewitt, M. *Bioorg. Med. Chem.* **2008**, *16*, 3714.
36. El-Gaby, M. S. A.; El-Hag Ali, G. A. M.; El-Maghraby, A. A.; Abd El-Rahman, M. T.; Helal, M. H. M. *Eur. J. Med. Chem.* **2009**, *44*, 4148.
37. Sharma, R.; Nagda, D. P.; Talesara, G. L. *ARKIVOC* **2006**, *1*, 1.
38. Dave, T. K.; Purohit, D. H.; Akbari, J. D.; Joshi, H. S. *Ind. J. Chem.* **2007**, *46B*, 352.
39. Ronad, P. M.; Noolvi, M. N.; Sapkal, S.; Dharbhamulla, S.; Maddi, V. S. *Eur. J. Med. Chem.* **2010**, *45*, 85.
40. Sattigeri, V. J.; Soni, A.; Singhal, S.; Khan, S.; Pandya, M.; Bhateja, P.; Mathur, T.; Rattan, A.; Khanna, J. G.; Mehta, A. *ARKIVOC* **2005**, *2*, 46.
41. Andres, C. J.; Bronson, J. J.; D'Andrea, S. V.; Deshpande, M. S.; Falk, P. J.; Grant-Young, K. A.; Harte, W. E.; Ho, H.; Misco, P. H.; Robertson, J. G.; Stock, D.; Sun, Y.; Walsh, A. W. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 715.
42. Kucukguzel, G.; Kocatepe, A.; Clercq, E.; Sahin, F.; Gulluce, M. *Eur. J. Med. Chem.* **2006**, *41*, 353.
43. Hassaneen, H. M.; Atta, S. M. S.; Fawzy, N. M.; Ahmed, F. A.; Hegazi, A. G.; Abdalla, F. A.; Abd El Rahman, A. H. *Arch. Pharm. Pharm. Med. Chem.* **2002**, *6*, 251.
44. Abdel-Wahab, B. F.; Abdel-Aziz, H. A.; Ahmed, E. M. *Arch. Pharm. Chem. Life Sci.* **2008**, *341*, 734.
45. Gihsoyl, A.; Terzioglul, N.; Otuk, G. *Eur. J. Med. Chem.* **1997**, *17*, 181.
46. Bondock, S.; Khalifa, W.; Fadda, A. A. *Eur. J. Med. Chem.* **2007**, *42*, 948.
47. Kumar, V.; Sharma, S. K.; Singh, S.; Kumar, A.; Sharma, S. *Arch. Pharm. Chem. Life Sci.* **2010**, *343*, 98.
48. Liu, X.; Zheng, C.; Sun, L.; Liu, X.; Piao, H. *Eur. J. Med. Chem.* **2011**, *46*, 3469.
49. Srinivas, A.; Nagaraj, A.; Reddy, C. S. *J. Heterocycl. Chem.* **2008**, *45*, 1121.
50. Metwally, N. H.; Abdalla, M. H.; Nabi Mosselhi, M. A.; El-Desoky, E. A. *Carbohyd. Res.* **2010**, *345*, 1135.
51. Khan, S. A.; Yusuf, M. *Eur. J. Med. Chem.* **2009**, *44*, 2597.
52. Siddiqui, I. R.; Singh, P. K.; Singh, J.; Singh, J. *J. Agric Food Chem.* **2003**, *51*, 7062.
53. Kavitha, C. V.; Basappa, S.; Swamy, N.; Mantelingu, K.; Doreswamy, S.; Sridhar, M. A.; Prasad, J. S.; Rangappa, K. S. *Bioorg. Med. Chem.* **2006**, *14*, 2290.
54. Kline, T.; Felise, H. B.; Barry, K. C.; Jackson, S. R.; Nguyen, H. V.; Miller, S. I. *J. Med. Chem.* **2008**, *51*, 7065.
55. Kline, T.; Barry, K. C.; Jackson, S. R.; Felise, H. B.; Nguyen, H. V.; Miller, S. I. *Bioorg. Med. Chem.* **2009**, *19*, 1340.
56. Ramachandran, R.; Rani, M.; Kabilan, S. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2819.
57. Refaat, H. M. *Eur. J. Med. Chem.* **2010**, *45*, 2949.
58. Upadhyay, A.; Srivastava, S. K.; Srivastava, S. D. *Eur. J. Med. Chem.* **2010**, *45*, 3541.
59. Srinivas, A.; Nagaraj, A.; Reddy, C. H. *J. Heterocycl. Chem.* **2008**, *45*, 999.
60. Ahmed, M.; Sharma, R.; Nagda, D. P.; Jat, J. L.; Talesara, G. L. *ARKIVOC* **2006**, *11*, 66.
61. Sayyed, M.; Mokle, S.; Bokhare, M.; Mankar, A.; Surwase, S.; Bhusare, S.; Vibhute, Y. *ARKIVOC* **2006**, *2*, 187.
62. Kucukguzel, S. G.; Oruc, E. E.; Rollas, S.; Sahin, F.; Ozbek, A. *Eur. J. Med. Chem.* **2002**, *37*, 197.
63. Jaju, S.; Palkar, M.; Maddi, V.; Ronad, P. K.; Mamledesai, S.; Satyanarayana, D.; Ghatole, M. *Arch. Pharm. Chem. Life Sci.* **2009**, *342*, 723.
64. Karali, N.; Kocabalkanlı, A.; Gursoy, A.; Ates, O., II *Farmaco* **2002**, *57*, 589.
65. Vintonyak, V. K.; Warburg, K.; Kruse, H.; Grimme, S.; Hubel, K.; Rauh, D.; Waldmann, H. *Angew. Chem.* **2010**, *122*, 6038.
66. Babaoglu, K.; Page, M. A.; Jones, V. C.; McNeil, M. R.; Dong, C.; Naismith, J. H.; Lee, R. E. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3227.
67. Srivastava, T.; Gaikwad, A. K.; Haq, W.; Sinha, S.; Katti, S. B. *ARKIVOC* **2005**, *2*, 120.
68. Parekh, H. H.; Parikh, K. H.; Parikh, A. R. *J. Sci. Islm. Rep. Iran* **2004**, *15*, 143.
69. Turan-Zitouni, G.; Kaplancikli, Z. A.; Ozdemir, A. *Eur. J. Med. Chem.* **2010**, *45*, 2085.
70. Aridoss, G.; Amirthaganesan, S.; Kim, M. S.; Kim, J. T.; Jeong, Y. T. *Eur. J. Med. Chem.* **2009**, *44*, 4199.
71. Chandrappa, S.; Kavitha, C. V.; Shahabuddin, M. S.; Vinaya, K.; Anandakumar, C. S.; Ranganatha, S. R.; Raghavan, S. C.; Rangappa, K. S. *Bioorg. Med. Chem.* **2009**, *17*, 2576.
72. Zhou, H.; Wu, S.; Zhai, S.; Liu, A.; Sun, Y.; Li, R.; Zhang, Y.; Ekins, S.; Swaan, P. W.; Fang, B.; Zhang, B.; Yan, B. *J. Med. Chem.* **2008**, *51*, 1242.
73. Gududuru, V.; Hurh, H.; Dalton, J. T.; Miller, D. D. *J. Med. Chem.* **2005**, *48*, 2584.
74. Gududuru, V.; Hurh, H.; Dalton, J. T.; Miller, D. D. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5289.
75. Kamel, M. M.; Ali, H. I.; Anwar, M. M.; Mohamed, N. A.; Soliman, A. M. *Eur. J. Med. Chem.* **2010**, *45*, 572.
76. Havrylyuk, D.; Mosula, L.; Zimenkovsky, B.; Vasylenko, O.; Gzella, A.; Lesyk, R. *Eur. J. Med. Chem.* **2010**, *45*, 5012.
77. Karali, N.; Terzioglu, N.; Gursoy, A. *Arch. Pharm. Pharm. Med. Chem.* **2002**, *8*, 374.
78. Ottana, R.; Carotti, S.; Maccari, R.; Landini, I.; Chiricosta, G.; Caciagli, B.; Vigorita, M. G.; Mini, E. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3930.
79. Hafez, H. N.; El-Gazzar, A. B. A. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4143.
80. Lv, P.; Zhou, C.; Chen, J.; Liu, P.; Wang, K.; Mao, W.; Li, H.; Yang, Y.; Xiong, J.; Zhu, H. *Bioorg. Med. Chem.* **2010**, *18*, 314.
81. Rahman, V. P. M.; Mukhtar, S.; Ansari, W. H.; Lemiere, G. *Eur. J. Med. Chem.* **2005**, *40*, 173.
82. Wang, S.; Zhao, Y.; Zhang, G.; Lv, Y.; Zhang, N.; Gong, P. *Eur. J. Med. Chem.* **2011**, *46*, 3509.
83. Gouda, M. A.; Abu-Hashem, A. A. *Arch. Pharm. Chem. Life Sci.* **2011**, *11*, 170.
84. Havrylyuk, H.; Kovach, N.; Zimenkovsky, B.; Vasylenko, O.; Lesyk, R. *Arch. Pharm. Chem. Life Sci.* **2011**, *344*, 514.
85. Kumar, A.; Rajput, C. S.; Bhati, S. K. *Bioorg. Med. Chem.* **2007**, *15*, 3089.
86. Deep, A.; Jain, S.; Sharma, P. C. *Acta Poloniae Pharmaceutica - Drug Res.* **2010**, *67*, 63.
87. Ottana, R.; Maccari, R.; Barreca, M. L.; Bruno, G.; Rotondo, A.; Rossi, A.; Chiricosta, G.; Paola, R.; Sautebin, L.; Cuzzocrea, S.; Vigorita, M. G. *Bioorg. Med. Chem.* **2005**, *13*, 4243.
88. Bekhit, A. A.; Fahmy, H. T. Y.; Rostom, S. A. F.; Bekhit, A. *Eur. J. Med. Chem.* **2010**, *45*, 6027.
89. Bhovi, V. K.; Bodke, Y. D.; Biradar, S.; Swamy, B. E. K.; Umesh, S. *Phosphorus, Sulfur Silicon Relat. Elem.* **2010**, *185*, 110.
90. Ottana, R.; Mazzon, E.; Dugo, L.; Monforte, F.; Maccari, R.; Sautebin, L.; De Luca, G.; Vigorita, M. G.; Alcaro, S.; Ortuso, F.; Caputi, A. P.; Cuzzocrea, S. *Eur. J. Pharmacol.* **2002**, *448*, 71.
91. Ali, A. M.; Saber, G. E.; Mahfouz, N. M.; El-Gendy, M. A.; Radwan, A. A.; Hamid, M. A. *Arch. Pharm. Res.* **2007**, *30*, 1186.
92. Uchoa, F.; Silva, T.; Lima, M.; Galdino, S.; Pitta, I.; Costa, T. D. *J. Pharm. Pharmacol.* **2009**, *61*, 339.
93. Vazzana, I.; Terranova, E.; Mattioli, F.; Sparatore, F. *ARKIVOC* **2004**, *V*, 364.
94. Allen, S.; Newhouse, B.; Anderson, A. S.; Fauber, B.; Allen, A.; Chantry, D.; Eberhardt, C.; Odingo, J.; Burgess, L. E. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1619.
95. Geronikaki, A. A.; Lagunin, A. A.; Hadjipavlou-Litina, D. I.; Eleftheriou, P. T.; Filimonov, D. A.; Poroikov, V. V.; Alam, A.; Saxena, A. K. *J. Med. Chem.* **2008**, *51*, 1601.
96. Bhati, S. K.; Kumar, A. *Eur. J. Med. Chem.* **2008**, *43*, 2323.
97. Amin, K. M.; Kamel, M. M.; Anwar, M. M.; Khedr, M.; Syam, Y. N. *Eur. J. Med. Chem.* **2010**, *45*, 2117.
98. Shiradkar, M. R.; Ghodake, M.; Bothara, K. G.; Bhandari, S. B.; Nikalje, A.; Akula, K. C.; Desai, N. C.; Burange, P. J. *ARKIVOC* **2007**, *XIV*, 58.
99. Agarwal, A.; Lata, S.; Saxena, K. K.; Srivastava, V. K.; Kumar, A. *Eur. J. Med. Chem.* **2006**, *41*, 1223.
100. Kaur, H.; Kumar, S.; Vishwakarma, P.; Sharma, M.; Saxena, K. K.; Kumar, A. *Eur. J. Med. Chem.* **2010**, *45*, 2777.
101. Karall, N.; Gursoy, A.; Terzioglu, N.; Ozkurml, S.; Ozer, H.; Ekinci, A. C. *Arch. Pharm. Pharm. Med. Chem.* **1998**, *331*, 254.
102. Akula, G.; Srinivas, B.; Vidyasagar, M.; Kandikonda, S. *Int. J. Pharm. Tech. Res.* **2011**, *3*, 360.
103. Terzioglu, N.; Karalı, N.; Gursoy, A.; Pannecouque, C.; Leysen, P.; Paeshuyse, J.; Neyts, J.; Clercq, E. *ARKIVOC* **2006**, *I*, 109.
104. Balzarini, J.; Orzeszko, B.; Maurin, J. K.; Orzeszko, A. *Eur. J. Med. Chem.* **2007**, *42*, 993.
105. Balzarini, J.; Orzeszko-Krzesinska, B.; Maurin, J. K.; Orzeszko, A. *Eur. J. Med. Chem.* **2009**, *44*, 303.
106. Rawal, R. K.; Srivastava, T.; Haq, W.; Katti, S. B. *J. Chem. Res.* **2004**, *5*, 368.
107. Rawal, R. K.; Tripathi, R.; Katti, S. B.; Pannecouque, C.; De Clercq, E. *Bioorg. Med. Chem.* **2007**, *15*, 3134.
108. Rawal, R. K.; Prabhakar, Y. S.; Katti, S. B.; De Clercq, E. *Bioorg. Med. Chem.* **2005**, *13*, 6771.
109. Rawal, R. K.; Tripathi, R. K.; Katti, S. B.; Pannecouque, C.; De Clercq, E. *Med. Chem.* **2007**, *3*, 355.
110. Chen, H.; Bai, J.; Jiao, L.; Guo, Z.; Yin, Q.; Li, X. *Bioorg. Med. Chem.* **2009**, *17*, 3980.
111. Chen, H.; Guo, Z.; Yin, Q.; Duan, X.; Gu, Y.; Li, X. *Front. Chem. Sci. Eng.* **2011**, *5*, 231.
112. Rawal, R. K.; Tripathi, R.; Kulkarni, S.; Paranjape, R.; Katti, S. B.; Pannecouque, C.; De Clercq, E. *Chem. Biol. Drug. Des.* **2008**, *72*, 147.
113. Rawal, R. K.; Tripathi, R.; Katti, S. B.; Pannecouque, C.; De Clercq, E. *Eur. J. Med. Chem.* **2008**, *43*, 2800.
114. Ramkumar, K.; Yarovenko, V. N.; Nikitina, A. S.; Zavarzin, I. V.; Krayushkin, M. M.; Kovalenko, L. V.; Esqueda, A.; Odde, S.; Neamati, N. *Molecules* **2010**, *15*, 3958.
115. Ravichandran, V.; Jain, A.; Kumar, K. S.; Rajak, H.; Agrawal, R. K. *Chem. Biol. Drug Des.* **2011**, *78*, 464.
116. Faidallah, H. M.; Khan, K. A.; Asiri, A. M. *J. Fluor. Chem.* **2011**, *132*, 131.
117. Kini, D.; Ghate, M. *Eur. J. Chem.* **2011**, *8*, 386.
118. Maccari, R.; Corso, A. D.; Giglio, M.; Moschini, R.; Mura, U.; Ottana, R. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 200.
119. Ottana, A.; Maccari, R.; Giglio, M.; Corso, A. D.; Cappiello, M.; Mura, U.; Cosconati, S.; Marinelli, M.; Novellino, E.; Sartini, S.; La-Motta, C.; Settimo, F. D. *Eur. J. Med. Chem.* **2011**, *46*, 2797.
120. Liu, Z.; Chai, Q.; Li, Y.; Shen, Q.; Ma, P.; Zhang, L.; Wang, X.; Sheng, L.; Li, J.; Li, J.; Shen, J. *Acta Pharmacol. Sin.* **2010**, *31*, 1005.

Please cite this article in press as: Jain, A. K.; et al. *Bioorg. Med. Chem.* (2012), http://dx.doi.org/10.1016/j.bmc.2012.03.069

121. Ottana, R.; Maccari, R.; Ciurleo, R.; Paoli, P.; Jacomelli, M.; Manao, G.; Camici, G.; Laggner, C.; Langer, T. *Bioorg. Med. Chem.* **1928**, *2009*, 17.
122. Bhattarai, B. R.; Kafle, B.; Hwang, J.; Khadka, D.; Lee, S.; Kang, J.; Ham, S. W.; Han, I.; Park, H.; Cho, H. *Bioorg. Med. Chem.* **2009**, *19*, 6161.
123. Bhat, B. A.; Ponnala, S.; Sahu, D. P.; Tiwari, P.; Tripathi, B. K.; Srivastava, A. K. *Bioorg. Med. Chem.* **2004**, *12*, 5857.
124. Sadashiva, C. T.; Narendra Sharath Chandra, J. N.; Kavitha, C. V.; Thimmegowda, A.; Subhash, M. N.; Rangappa, K. S. *Eur. J. Med. Chem.* **2009**, *41*, 1.
125. Narendra Sharath Chandra, J. N.; Malviya, M.; Sadashiva, C. T.; Subhash, M. N.; Rangappa, K. S. *Neurochem. Int.* **2008**, *52*, 376.
126. Maclean, D.; Holden, F.; Davis, A. M.; Scheuerman, R. A.; Yanofsky, S.; Holmes, C. P.; Fitch, W. L.; Tsutsui, K.; Barrett, R. W.; Gallop, M. A. *J. Comb. Chem.* **2004**, *6*, 196.
127. Wrobel, J.; Jetter, J.; Kao, W.; Rogers, J.; Di, L.; Chi, J.; Peréz, M. C.; Chen, G.; Shen, E. S. *Bioorg. Med. Chem.* **2006**, *14*, 5729.
128. Arey, B. J.; Yanofsky, S. D.; Perez, M. C.; Holmes, C. P.; Wrobel, J.; Gopalsamy, A.; Stevis, P. E.; Lopez, F. J.; Winneker, R. C. *Biochem. Biophy. Res. Comm.* **2008**, *368*, 723.
129. Arey, B. J.; Yanofsky, S. D.; Perez, M. C.; Holmes, C. P.; Wrobel, J.; Gopalsamy, A.; Stevis, P. E.; Lopez, F. J.; Winneker, R. C. *Biochem. Biophy. Res. Commun.* **2008**, *368*, 723.
130. Kouznetsov, V.; Rodriguez, W.; Stashenko, E. *J. Hetero. Chem.* **2004**, *41*, 995.
131. Pizzo, C.; Saiz, C.; Talevi, A.; Gavernet, L.; Palestro, P.; Bellera, C.; Blanch, L. B.; Benítez, D.; Cazzulo, J. J.; Chidichimo, A.; Wipf, P.; Mahler, S. G. *Chem. Biol. Drug Des.* **2011**, *77*, 166.
132. Jackson, C. M.; Blass, B.; Coburn, K.; Djandjighian, L.; Fadayel, G.; Fluxe, A. J.; Hodson, S. J.; Janusz, J. M.; Murawsky, M.; Ridgeway, J. M.; White, R. E.; Wu, S. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 282.
133. Bhandari, S. V.; Bothara, K. G.; Patil, A. A.; Chitre, T. S.; Sarkate, A. P.; Gore, S. T.; Dangre, S. C.; Khachane, C. V. *Bioorg. Med. Chem.* **2009**, *17*, 390.

Please cite this article in press as: Jain, A. K.; et al. *Bioorg. Med. Chem.* (2012), http://dx.doi.org/10.1016/j.bmc.2012.03.069