



## **EXPLORING POTENTIAL OF 4-THIAZOLIDINONE: A BRIEF REVIEW**

MULAY ABHINIT, MANGESH GHODKE, NIKALJE ANNA PRATIMA\*

*\*Y. B. Chavan College of Pharmacy, Dr. Rafiq Zakaria Campus, Aurangabad-431001, Maharashtra, India, E-mail: ana@k.st  
Received- 06 March 09, Revised and Accepted- 30 March 09*

### **ABSTRACT**

Thiazolidinone, a saturated form of thiazole with carbonyl group on fourth carbon, has been considered as a magic moiety (wonder nucleus) which possesses almost all types of biological activities. 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. Present article is sincere attempt to review chemistry, synthesis, spectral studies and applications of 4-thiazolidinone.

**Key words:** Thiazolidinone, Thiazole.

### **INTRODUCTION**

Thiazolidinones are the derivatives of thiazolidine which belong to an important group of heterocyclic compounds containing sulfur and nitrogen in a five member ring. A lot of research work on thiazolidinones has been done in the past. The nucleus is also known as wonder nucleus because it gives out different derivatives with all different types of biological activities. Numbers of methods for synthesis by using various agents are available in the references.

#### **Physical Properties**

The 3-unsubstituted 4-thiazolidinones are usually solids, often melting with decomposition, but the attachment of an

alkyl group to the nitrogen lowers the melting point. The 4-thiazolidinones that do not contain aryl or higher alkyl substituents are somewhat soluble in water<sup>1</sup>.

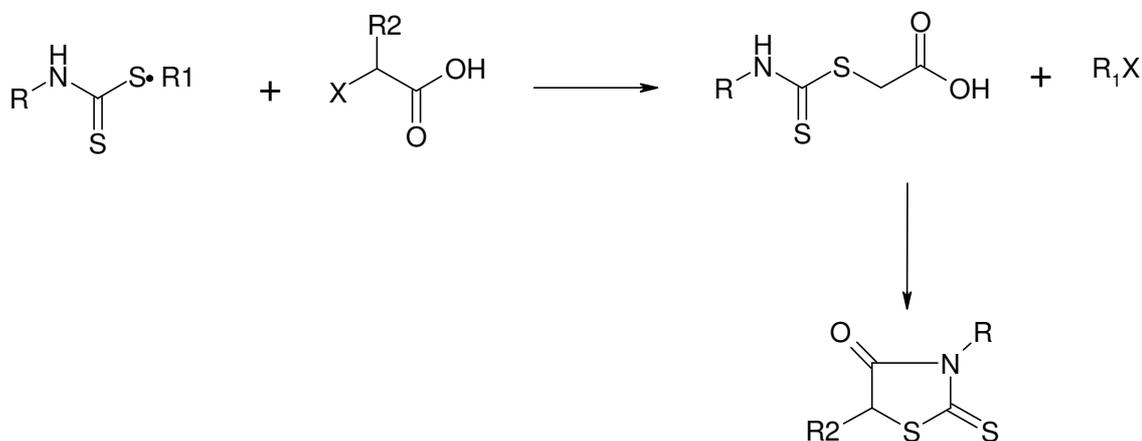
#### **Chemistry**

Considerable confusion concerning the structure of 4-thiazolidinones exist in the early literature and noncyclic formulas were at first proposed for pseudothiohydantoin and for rhodanine<sup>1</sup>. 4-thiazolidinones are derivatives of thiazolidine with a carbonyl group at the 4 position<sup>2</sup>. Substitution is possible at 2, 3 and 5 position. Various optical and geometrical isomers are reported in the references<sup>3</sup>. A series of regioselective isomers has been reported in some

works<sup>4,5</sup>. The carbonyl group of 4-thiazolidinone is highly unreactive. But in few cases 4-thiazolidinone on reaction with Lawesson's reagent gives corresponding 4-thione derivatives<sup>6</sup>. A detail study of tautomerism in 2-iminothiazolidine-4-one has been done by *Akerblom E.*<sup>7</sup>

### Syntheses of 4-thiazolidinones

Several methods for syntheses are available in literature which involve



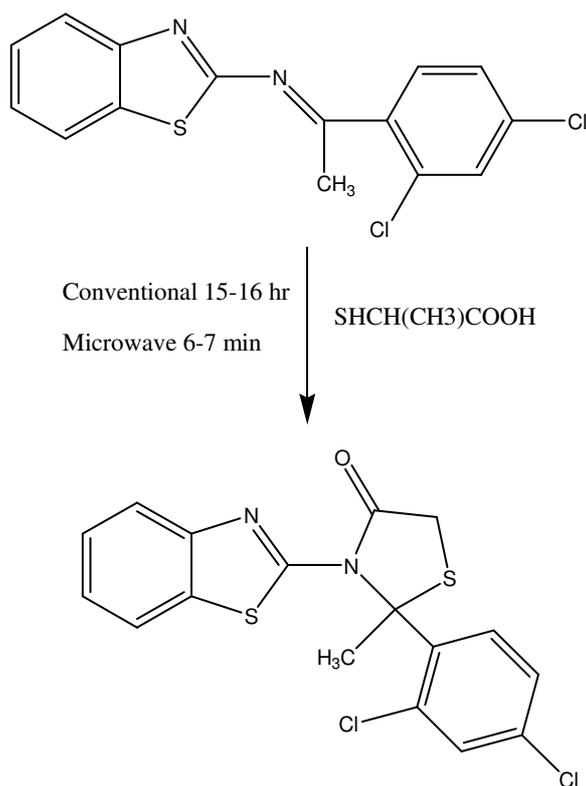
**SCHEME 1**

The synthesis of 2-imino-4-thiazolidinones-4-<sup>14</sup>C has been reported by using thiourea and sodium salt of labeled monochloroacetic acid<sup>(10)</sup>. Another method of synthesis of 4-thiazolidinones is by use of thiocyanate, alkyl isothiocyanate with hydrazide/acetamide followed by the treatment with ethyl bromoacetate and sodium acetate<sup>11</sup>. Schiff's bases obtained by the condensation of ketones and amines also react with  $\alpha$ -mercaptoacetic acid to give

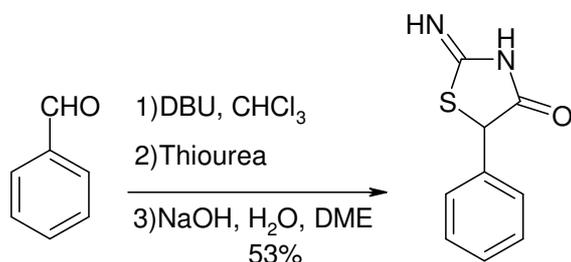
conventional one pot, two pot synthesis<sup>8,9</sup> and microwave as well as combinatorial syntheses methods. The dithiocarbamates formed by the reaction of primary amine with carbon disulfide in the presence of base react with haloalkanoic acid in the presence of NaHCO<sub>3</sub> to give substituted 2-thiono-4-thiazolidinones<sup>9</sup> as presented in the scheme 1.

2,2-disubstituted-4-thiazolidinones<sup>12</sup>.

Desai KR *et al*<sup>13</sup> has carried out the microwave assisted synthesis of thiazolidinone from the Schiff's bases (scheme 2) by using thiolactic acid. The products were synthesized by conventional and microwave synthesis and the yield were compared with each other. They concluded that the percent yield with the microwave irradiated synthesis was better than the conventional.



**SCHEME 2**



**SCHEME 3**

Use of task specific ionic liquid as synthetic equivalent of ionic liquid-phase matrices for the synthesis of small library of 4-thiazolidinone is also possible. Ethylene glycol is functionalized in good yields with 4-(formylphenoxy) butyric acid by using DCC/ DMAP catalyst. The synthesis was performed by one pot three component condensation under microwave dielectric heating<sup>18,19</sup>. Lot of

Attempt to synthesize combinatorial libraries of 4-thiazolidinones are present in the literature as reported by *Look GC et al*<sup>14</sup>. HPLC and Mass spectroscopic analysis were done for checking the purity and assure the quality derivatives<sup>15</sup>. Recently library of more than 42,000 compounds were synthesized by encoding 4-thiazolidinone library on solid phase. Three sets of 35 building blocks were combined by encoded split-pool synthesis to give a series of compounds<sup>16</sup>.

One pot three component synthesis containing aldehyde, thiourea and chloroform (scheme 3) to give 2-amino-4-thiazolidinone derivatives was also reported<sup>17</sup>. Various imino thiazolidinones were developed by using different reagents with different reaction conditions.

work has been done on the microwave dielectric heating based techniques either one step three component or two step processes<sup>20-24</sup>. Microwave method is easiest and rapid method of synthesis. The yield of product obtained is better than the conventional technique. Generally environmentally benign catalysts are used for the synthesis which helps in the less pollution and lower wastage of the reagents.

## Spectral study

### Ultra violet spectra

The U.V. spectral study in tabular form was present in earlier literature reviews<sup>1,7</sup>. The ultraviolet absorption spectra of a series of 2-(arylimino)-4-thiazolidinones containing electron donor and electron acceptor substituents in the phenyl ring were studied<sup>25</sup>. When substituents are present in the Para position of the phenyl ring, the position of characteristic thione absorption is shifted. UV spectra of the 5-aryazo derivatives of thiazolidin-4-one 5-phenylazo-2-phenyliminothiazolidin-4-One were synthesized in the literature<sup>26</sup>. The displacement of the absorption maximum of the N=N group to the long-wave part of the spectrum by 42 nm in the spectrum of 5-aryazo derivative of substituted compound caused by the presence of a nitro group in the chain of conjugated double bonds with the azo group is a confirmation of the existence of the compound in the azo form.

### Infrared Spectra

The infrared spectra of 4-thiazolidinones are helpful in determining the structure of the compounds. It is also useful in the determination of configuration of *cis* and *trans* isomers<sup>27</sup>.

The *cis* isomer is favored when H-bonding is otherwise impossible. In

other circumstances the *trans* isomer is the stable form<sup>28</sup>.

The carbonyl peak<sup>29</sup> in the 2-alkyl-4-thiazolidinone was somewhere around 1680-1740 cm<sup>-1</sup>, Characteristic N-H stretching<sup>1</sup> was in the range of 3100-3400 cm<sup>-1</sup>.

### NMR spectra

Both <sup>1</sup>H and <sup>13</sup>C NMR are important so as to confirm the structure of the derivatives and are also useful in regioselective synthesis of isomers. Some articles describe <sup>1</sup>H-NMR spectroscopic study as a method to distinguish between the intramolecular and intermolecular hydrogen bonding in (Z)-2-(5-ethoxycarbonylmethyl-4-oxothiazolidin-2-ylidene)-1-phenylethanone, being an example of the thiazolidinone series<sup>30</sup>.

Ferrocenyl-thiosemicarbazones and their S-methylated derivatives can be used for the synthesis of a variety of novel ferrocenyl-substituted S,N- and N,N-heterocycles. The intramolecular S-O and S-N close contact interactions seem to be governing factors in the cyclization reactions of thiosemicarbazone-reagents which is described with the help of <sup>13</sup>C and <sup>1</sup>H NMR<sup>31</sup>.

A series of substituted 4-thiazolidinones in CDCl<sub>3</sub> were synthesized the chemical shift and C, H spin coupling constants are given<sup>32</sup>.

## Mass Spectra

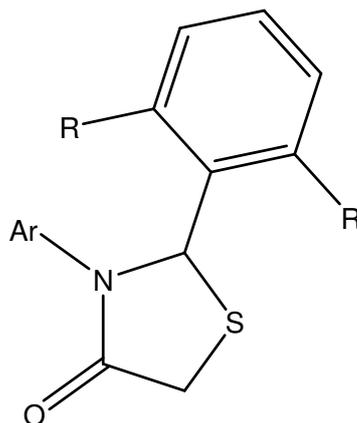
The molecular ion peaks in the mass spectra of 2-imino-4-oxothiazolidinyl-5-acetate have been assigned<sup>33</sup>. Various spirothiazolidinones and fatty acid chain-substituted thiazolidinones were synthesized and characterized. In contrast to spirothiazolidinones in which the parent peaks usually are the base peak, fatty acid chain-substituted thiazolidinones showed very low intensity  $M^+$  peaks two significant peaks  $m/z$  42 and 43, of comparatively moderate intensity are also observed in the spectra of all the three thiazolidinones<sup>34</sup>.

N-tryptophyl-4-thiazolidinones and N-tryptophyl-5-benzylidene-4-thiazolidinones were synthesized and possible fragmentation patterns of these compounds by electron impact mass spectrometry was reported<sup>35</sup>. All compounds have shown the same base peak at  $m/z$  143.

## Pharmacological uses of 4-thiazolidinones

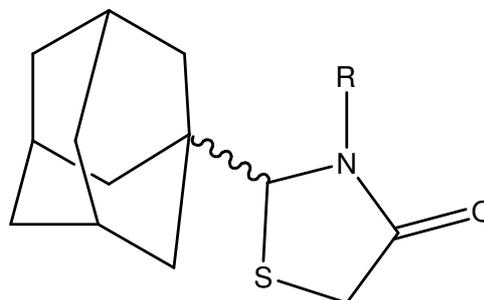
### Anti-HIV activity

The anti-HIV activity of several series of 2,3-diaryl-1,3-thiazolidin-4-ones (Fig.1) has been studied. Which are reported as a new family of antiviral agents acting as NNRTIs with minimal cytotoxicity<sup>36-38</sup>.



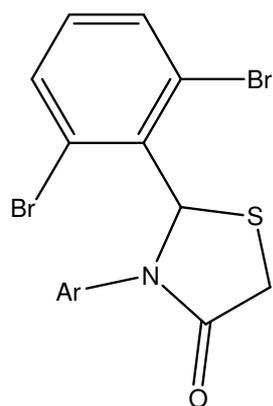
**Fig. 1: 2,3-diaryl-1,3-thiazolidin-4-ones**

2-adamantyl-substituted thiazolidin-4-ones (Fig. 2) were synthesized and evaluated for activity against HIV-1 (IIB) and HIV-2(ROD) in CEM cell cultures, by taking Nevirapine as reference compounds<sup>39</sup>.



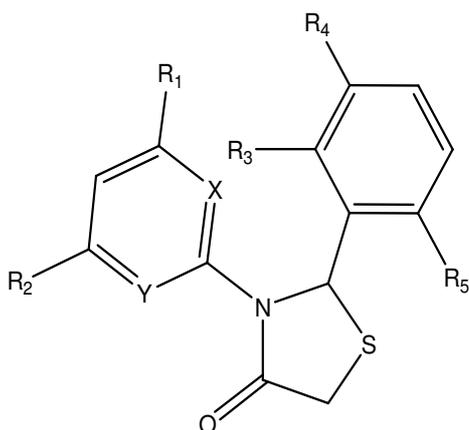
**Fig. 2: 2-adamantyl-substituted thiazolidin-4-ones as Anti-HIV agent**

Some researchers reported 2-(2,6-dibromophenyl)-3-heteroaryl-1,3-thiazolidin-4-one derivatives as shown in the Fig 3. A positive correlation between size of the halogen substituent and HIV-RT inhibitory activity was taken as logic for the synthesis<sup>40</sup>.



**Fig. 3: 2-(2,6-dibromophenyl)-3-heteroaryl-1,3-thiazolidin-4-one derivatives**

Microwave-assisted synthesis of 2,3-diaryl-1,3-thiazolidin-4-ones (Fig.4) was performed in order to achieve striking reductions in reaction times, better yields, cleaner reactions<sup>41</sup>.

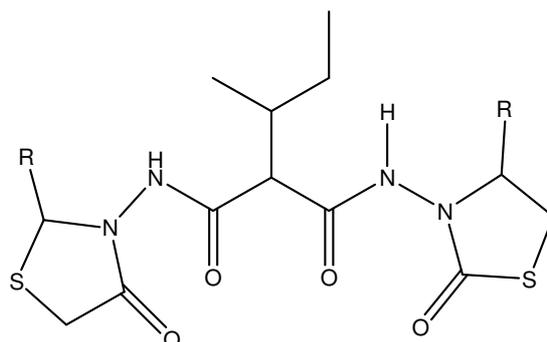


**Fig. 4. Microwave-assisted synthesis of 2,3-diaryl-1,3-thiazolidin-4-ones**

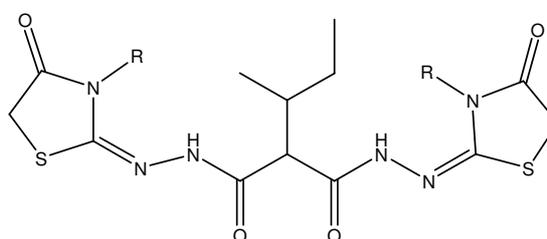
Recently prediction of Anti-HIV activity of 1,3,4-thiazolidinone derivatives were made on the basis of QSAR. CoMFA and CoMSIA were the two models used for the analysis. Based on the structures and biodata of previous thiazolidinone analogs, 3D-QSAR studies have been performed with a training set consisting of 96 molecules<sup>42</sup>.

### Anticonvulsant activity

Number of articles were found for the anticonvulsant potential of 4-thiazolidinones where substitution on 2, 3,5 positions were done. Most of the compounds were found to exhibit protection against pentylenetetrazole induced seizures<sup>43-48</sup>. Researchers reported the synthesis, characterization, and anticonvulsant evaluation of new N,N'-bis(arylidene)dihydrazide (Fig. 5) and bis(4-thiazolidinone) (Fig.6) derivatives. Upto 90% protection was observed in the pentylenetetrazole seizure<sup>49</sup>.



**Fig. 5: N,N'-bis(arylidene)dihydrazide**

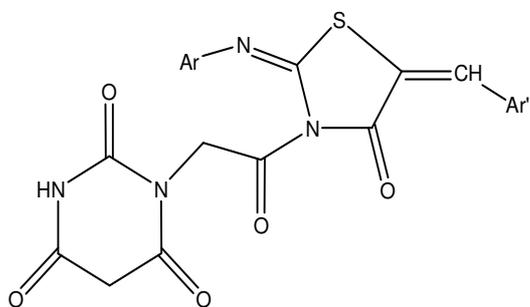


**Fig. 6: bis(4-thiazolidinone)**

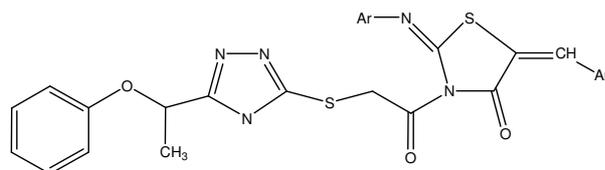
Synthesis of newer thiazolidinone and thiazolidinonyl quinazolin-4(3H)-ones was done in 2002 by Archana, kumar A<sup>50</sup>. The compounds were screened for

their anticonvulsant activity and were compared with the standard drugs, phenytoin sodium, lamotrigine and sodium valproate. Out of the 30 compounds the most active compound was 3-({4-[2-(m-methoxy-hydroxyphenyl)-4-oxo-1,3-thiazolidin-3-yl]-1,3,4-thiadiazol-2-yl}methylamino)-2-methyl-6-bromo-quinazolin-4(3H)-one.

Recently anticonvulsant activity of clubbed Thiazolidinone-barbituric acid and Thiazolidinone-triazole derivatives have been reported<sup>51</sup>. The compound in (Fig 7), substituted with different phenylthiazolidinonyl amino moieties at the 5 position of barbituric acid, has shown varying degrees of anticonvulsant activity. While 3-(2-chloroacetyl)-2-arylimino-5-[(Z)-arylmethylidene]-1,3-thiazolan-4-ones on treatment with 5-(1-phenoxyethyl)-4H-1,2,4-triazole-3-thiol in identical conditions provided a set of bulkier derivatives which have also shown the anticonvulsant potential (Fig 8).



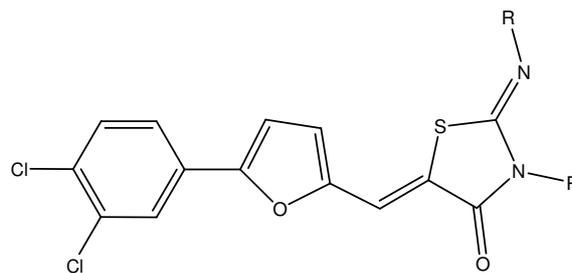
**Fig. 7**



**Fig. 8**

### Antimicrobial activity

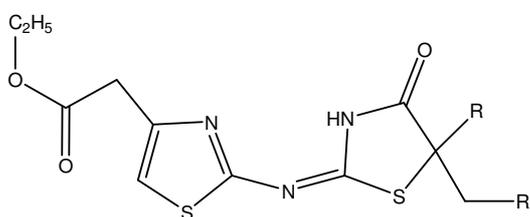
*Bhoot et al* have synthesized 2-(p-tolylimino)-3-(4-tolyl)-5-[5'-(3,4-dichlorophenyl)-2'-furylidene]-4-thiazolidinone (Fig. 9) and derivatives as an antimicrobial agents. compounds were screened *in vitro* for their antimicrobial activity towards variety of bacterial strains such as *B. mega*, *S. aureus*, *E. coli*, *P. vulgaris* and fungi such as *Aspergillus niger* at a concentration of 40 µg. And in conclusion remarkable inhibition was observed in compounds bearing R=phenyl, 2-methoxyphenyl, 2-methylphenyl, 3-methylphenyl 4-nitrophenyl substituents<sup>52</sup>.



**Fig. 9: 2-(p-tolylimino)-3-(4-tolyl)-5-[5'-(3,4-dichlorophenyl)-2'-furylidene]-4-thiazolidinone**

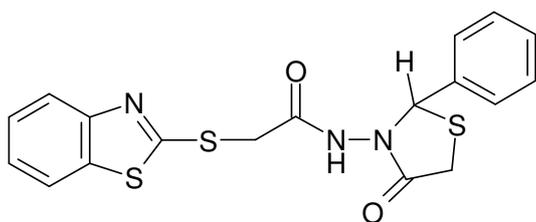
Various 5-substituted 5-(N,N-disubstituted aminomethyl)-2-[(4-carbethoxymethylthiazol-2-yl)imino]-4-thiazolidinones (Fig. 10) were synthesized by *Altintas et al.*

Derivatives were screened for their in vitro antibacterial activity against *Staphylococcus aureus* ATCC 6538, *Staphylococcus epidermidis* ATCC 12228, *Escherichia coli* ATCC 8739, *Klebsiella pneumoniae* ATCC 4352, *Pseudomonas aeruginosa* ATCC 1539, *Salmonella typhi*, *Shigella flexneri* and *Proteus mirabilis* ATCC 14153 using disk diffusion<sup>53</sup>.



**Fig. 10**

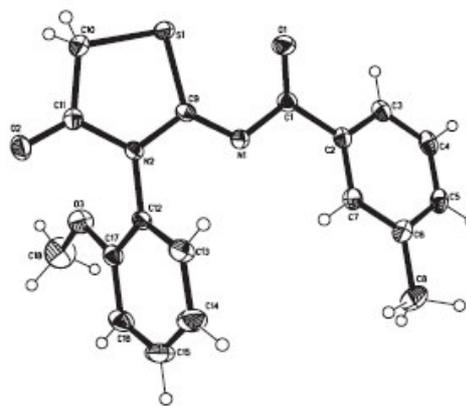
Desai KG and Desai KR have synthesized five membered sulfur-containing heterocyclic derivatives 2-(aryl)-3-[2-(benzothiazolylthio)-acetamidyl]-4-oxo-thiazolidines (Fig. 11). All the compounds have been screened for their antibacterial activity against *Escherichia coli* (Gram-ve), *Staphylococcus aureus* and *Bacillus subtilis* (Gram +ve)<sup>54</sup>.



**Fig. 11**

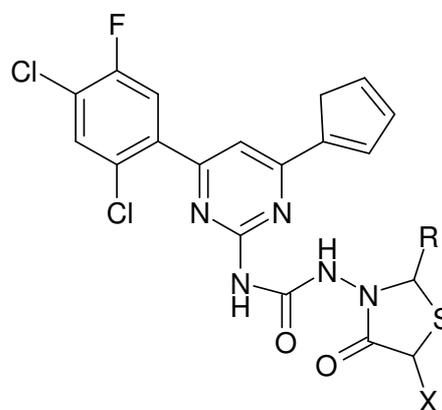
Several derivatives of 2-arylimino-3-arylthiazolidin-4-ones were prepared

and were screened for antimicrobial activity by Saeed A<sup>(55)</sup>. The compounds were characterized by spectroscopic techniques and molecular structure is shown in the following figure (Fig. 12).



**Fig. 12 : Molecular structure of 2-arylimino-3-arylthiazolidin-4-ones**

A series of 2-(substituted phenyl)-3-[4-(2,4-dichloro-5-fluorophenyl)-6-(2-thienyl)pyrimidine-2-yl-ureido]-5H/methyl/carboxymethyl-4-thiazolidinones (Fig. 13) were prepared. All the derivatives were screened for antibacterial activity<sup>56</sup>. Number of other researchers also synthesized and screened 4-thiazolidinone derivatives for antimicrobial potential<sup>57-63</sup>.



**Fig. 13**

### Follicle stimulating hormone (FSH) receptor agonist activity

Follicle stimulating hormone (FSH) is a 38 kDa protein that triggers maturation of ovarian follicles in women and spermatogenesis in men. It is released from the anterior pituitary gland, following stimulation by gonadotropin-releasing hormone (GnRH), and serves as the naturally occurring agonist of the FSH receptor.

Yanofsky SD *et al.* have shown the allosteric activation of FSH receptor, by screening unbiased combinatorial chemistry libraries of thiazolidinone derivatives (Fig. 14), using a cAMP-responsive luciferase reporter assay<sup>64</sup>. They also have shown that discrete modifications in the chemical structure of the thiazolidinone agonists produced compounds with different pharmacological properties<sup>65</sup>. This was done by preparing substituted 5-alkyl<sup>66</sup>, Gamma lactam substituted<sup>67</sup> 4-thiazolidinone derivatives.

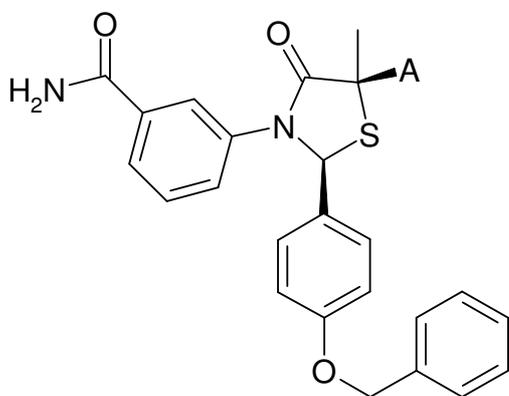


Fig. 14

Maclean *et al.* reported the FSH agonist activity of an encoded 4-thiazolidinone library<sup>68</sup>. Among the hits discovered in these studies was compound 2-chloro-4-[5-{{[2-(3H-inden-1-yl)-ethylcarbamoyl]-methyl}}-2-(4-methoxyphenyl)-4-oxo-thiazolidin-3-yl]-benzamide, which possessed moderate FSH receptor agonistic activity<sup>69</sup>.

### Anti cancer activity, antiproliferative activity

Ten cytoselective compounds have been identified from 372 thiazolidinone analogues (Fig. 15) by applying iterative library approaches. These compounds selectively killed both non-small cell lung cancer cell line H460 and its paclitaxel-resistant variant H460taxR at an IC<sub>50</sub> between 0.21 and 2.93  $\mu$ M while showing much less toxicity to normal human fibroblasts at concentrations up to 195  $\mu$ M. A pharmacophore derived from active molecules suggested that two hydrogen bond acceptors and three hydrophobic regions were common features<sup>70</sup>.

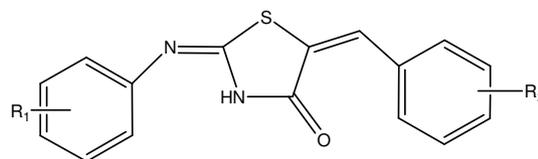


Fig. 15

Guduru have synthesized a series of 2-aryl-4-oxothiazolidin-3-yl amides and were evaluated for ability to inhibit

prostate cancer cells. Few potent compounds were detected, which were effective in killing prostate cancer cells with improved selectivity compared to serine amide phosphates<sup>71</sup>.

Various 4-thiazolidinone derivatives were synthesized for in vitro antiproliferative activity on five cell lines of human colon cancers, obtained from the American type culture collection<sup>72-76</sup>.

Thiazolidinone amides, carboxylic acids, serine amides were synthesized and tested for possible anticancer activity<sup>77</sup>.

#### Anti-inflammatory activity

Sparatore F has synthesized aromatic Schiff bases and 2,3-disubstituted-1,3-thiazolidin-4-one derivatives (Fig. 16) as anti-inflammatory agents. Both types of compounds displayed good level of activity against carrageenan induced edema in rat hind paw, while only moderate activity was observed in the writhing test in mice<sup>78</sup>.

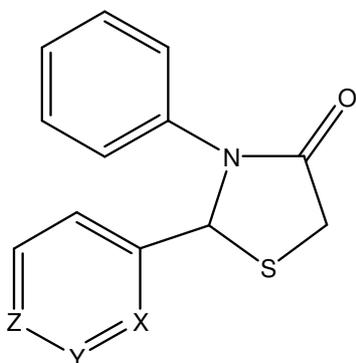


Fig. 16

Kumar A have synthesized 3-[4'-(p-chlorophenyl)-thiazol-20-yl]-2-[(substituted azetidinone/thiazolidinone)-aminomethyl] - 6-bromoquinazolin-4-ones (Fig. 17). Some of the compounds have shown satisfactory anti-inflammatory activity<sup>79</sup>.

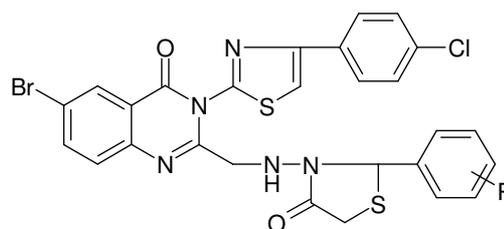


Fig. 17

A series of 4-thiazolidinone compounds, represented by LY178002 (5-[3,5-bis (1,1-dimethylethyl)- 4- hydroxyphenyl] methylene-4- thiazolidinone), have been described as potent inhibitors of cyclooxygenase and 5-lipoxygenase, also an inhibitor of phospholipase A 2 and cellular production of LTB<sub>4</sub> by human polymorphonuclear leukocytes (PMNL). The results indicate that LY178002 is more effective in suppressing bone damage than the edema<sup>80</sup>.

Ottana *et al* investigated 3,3'-(1,2-ethanediyl)-bis[2-aryl-4-thiazolidinone] derivatives, which showed interesting stereo selective anti-inflammatory/ analgesic activities, suggesting that they might preferentially interact with inducible COX-2 isoform<sup>81</sup>. Synthesized 2-imino-4-thiazolidinones and 5-arylidene-2-imino-4-thiazolidinones were tested

for in vivo anti-inflammatory activity in models of acute inflammation such as carrageenan-induced paw edema and pleurisy assay in rats<sup>82,83</sup>. All derivatives exhibited significant activity levels. In addition, the ability of such a new class of anti-inflammatory agents to inhibit COX isoform was assessed in murine monocyte/macrophage J774 cell line assay.

Newbould studied the anti-inflammatory activity of 2-[(butoxycarbonyl)methylene]-4-thiazolidinone. The compound was found to be devoid of activity against most models of acute inflammation. However it partially inhibited Carageenan induced edema in the rat and prevented completely the development of secondary lesions in the rats injected with adjuvant in the footpad<sup>84</sup>. Geronikaki AA *et al*<sup>85</sup> has performed computer aided discovery of anti-inflammatory potential of 4-thiazolidinones by using PASS (Prediction of Activity Spectra for Substances).

### **CFTR inhibitor**

The cystic fibrosis transmembrane conductance regulator (CFTR) is a cAMP-regulated chloride channel, which when mutated can produce the hereditary disease cystic fibrosis. CFTR inhibition is a potential strategy for therapy of secretory diarrheas<sup>86</sup>.

Tonghui Ma<sup>87</sup> have shown that the 4-thiazolidinones also have CFTR inhibitory potential. The purpose of the study was to identify high affinity CFTR inhibitors for application to studies of CF disease mechanisms and to the treatment of secretory diarrheas. The primary screening of 50,000 diverse compounds identified a small set of putative inhibitors of the 2-thioxo-4-thiazolidinone compound class. These compounds were unrelated structurally to known CFTR activators and to the CFTR inhibitors diphenylamine-2-carboxylate (DPC), 5-nitro-2-(3-phenylpropyl-amino) benzoate (NPPB) and glibenclamide. The most potent CFTR inhibitor identified by screening of library of structural analogs had a  $K_i$  of about 300nM for inhibition of  $Cl^-$  current in human airway cells. Inhibition was rapid, reversible and voltage dependant.

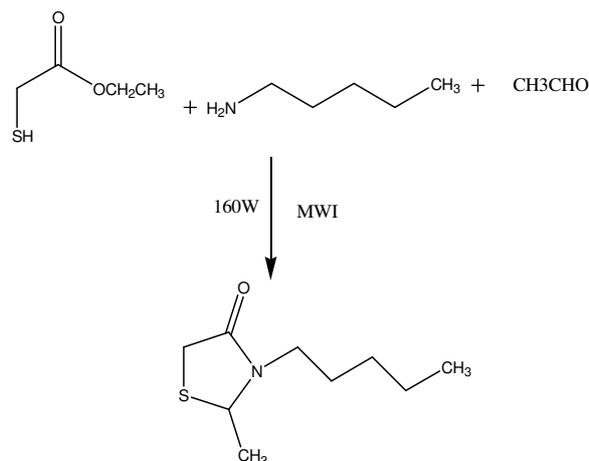
Sonawane ND<sup>88</sup>, have synthesized thiazolidinone 3-[(3-trifluoromethyl)phenyl]-5-[(4-carboxyphenyl)methylene]-2-thioxo-4-thiazolidinone (CFTRinh-172) which inhibits cystic fibrosis transmembrane conductance regulator (CFTR) chloride channel conductance with sub-micromolar affinity and blocks cholera toxin-induced intestinal fluid secretion. Greatest CFTR inhibition potency was found for 3-CF3 and polar

group-substituted-phenyl rings, and a thiazolidinone core. Two compounds with CFTR inhibition potency and solubility >180 IM(>10-fold more than CFTRinh-172) were identified: Tetrazolo-172, containing 4-tetrazolophenyl in place of 4-carboxyphenyl, and Oxo-172, containing thiazolidinedione in place of the thiazolidinone core. The same researchers and their co workers have shown the CFTR inhibitory activity of thiazolidinone derivatives using computational as well as conventional methods<sup>89,90</sup>.

#### Miscellaneous uses

Apart from pharmacological applications the 4-thiazolidinones have also been used in synthesis. One of the most older use was in the synthesis of merocyanine dyes which extend the sensitivity of silver halide emulsions to wavelengths within the visible region of the spectrum. Pawelczyk A and Zaprutko L have synthesized the 4-thiazolidinone derivatives by microwave method as a new fragrant substances and unsaturated analogs of jasmynes<sup>91</sup>. The n-pentylamine was mixed with acetaldehyde. The mixture was stirred at room temperature under condenser. After 1 h ethyl thioglycolate (or thioglycolic acid) was added. Reagents were irradiated for 5 min with 160 W by

microwaves in a flask with condenser and further treated with ethyl acetate.



#### SCHEME 4: Microwave assisted jasmine analogues.

#### CONCLUSION

The literature reveals that 4-thiazolidinone has diverse biological potential, and the easy synthetic routes for synthesis have taken attention of the chemists, pharmacologists and researchers. The anticancer and anti HIV activities are the most encouraging activities for the pharmacists. Also the research in anticonvulsant, FSH agonistic and CFTR inhibitory activity has given positive results. By the present scenario it can be concluded that 4-thiazolidinones have a great potential which remain to be disclosed till date.

#### REFERENCES

1. Frances C, Brown, 4-thiazolidinone. Chem Rev 1961;61:463
2. Horton DA, Bourne GT, Smyth ML, The combinatorial synthesis of

- Bicyclic privileged structures or privileged substructures. *Chem Rev* 2003;103: 893.
3. Knott EB, The electrophilic reactivity of alkoxyalkylidene derivatives of heterocyclic keto methylene compounds. *J Chem Soc* 1954; 1482.
  4. St Laurent DR, Gao Q, Wu DD, Regioselective synthesis of 3-(heteroaryl)-iminothiazolidin-4-ones. *Tetrahedron Letters*, 2004;45(9): 1907–1910
  5. Gursoy A, Terzioglu N, Synthesis and isolation of new regioisomeric 4-thiazolidinones and their anticonvulsant activity. *Turk J Chem* 2005;29:247-254.
  6. Kato T, Ozaki T, Tamura K, Suzuki Y, Akima M, Ohi N, Novel calcium antagonist with both calcium overload inhibition and anti-oxidant activity. 2. Structure activity relationship of thiazolidinone derivatives. *J Med Chem* 1999;42:3134.
  7. Akerblom E, 2-Aminothiazoline-4-one and 2-iminothiazolidine-4-one derivatives part II Tautomerism. *Acta Chemica Scandinavica* 1967;21:1437-1442.
  8. Singh SP, Parmar SS, Raman K, Stenberg VI, Chemistry and biological activity of thiazolidinones. *Chem Rev* 1981; 81: 175-203.
  9. Cunico W *et al.*, One-pot synthesis of 2-isopropyl-3-benzyl-1,3-thiazolidin-4-ones and 2-phenyl-3-isobutyl-1,3-thiazolidin-4-ones from valine, arenaldehydes and mercaptoacetic acid. *Tetrahedron letters* 2007;48: 6217-6220.
  10. Akerblom E, 2-Aminothiazoline-4-one and 2-iminothiazolidine-4-one derivatives. *Acta Chemica Scandinavica* 1967;21:843-848.
  11. Cesur Z, Guner H, Otuk W, Synthesis and antimycobacterial activity of new imidazo[2,1-b]thiazole derivatives. *Eur J Med Chem* 1994; 29,12: 981-983.
  12. Vicini P, Gerenikaki A, Anastasia K, Incertia M, Zania F, Synthesis and antimicrobial activity of novel 2-thiazolylimino-5-arylidene-4-thiazolidinones. *Bioorg Med Chem* 2006;14: 3859-3864.
  13. Desai KR, Mistry K, Microwave assisted synthesis of nitrogen and sulphur containing heterocyclic compounds and their pharmacological evaluation. *Ind J Chem*, 2006;45B: 1762-1766.
  14. Look GC *et al*, The identification of cyclooxygenase-I inhibitors from 4-thiazolidinone combinatorial libraries. *Bioorg Med Chem Letters* 1996; 6,6:707-712.
  15. Munson MC, Cook AW, Josey JA, Rao C, An efficient high speed synthetic route to amino substituted Thiazolidinone libraries. *Tetrahedron Letters* 1998; 39:7223-7226.

16. Maclean D *et al*, Agonists of the follicle stimulating hormone receptor from an encoded thiazolidinone library. *J Comb Chem* 2004; 6:196-206.
17. Jieping Z, Blanchet J, Reeve's synthesis of 2-imino-4-thiazolidinone from alkyl (aryl) trichloromethylcarbinol revisited, a three-component process from aldehyde, chloroform and thiourea. *Tetrahedron Letters* 2004; 45:4449–4452.
18. Dubreuil JF, Bazureau JP, Efficient combination of task-specific ionic liquid and microwave dielectric heating applied to one-pot three component synthesis of a small library of 4-thiazolidinones. *Tetrahedron* 2003; 59: 6121-6130.
19. Verma A, Saraf SK, 4-Thiazolidinone-A biologically active scaffold. *Eur J Med Chem* 2007; doi:10.1016/j.ejmech.2007.07.017
20. Dandia A, Singh R, Khaturia S, Merienne C, Morgantc G, Loupyd A, Efficient microwave enhanced regioselective synthesis of a series of benzimidazolyl/triazolyl spiro [indole-thiazolidinones] as potent antifungal agents and crystal structure of spiro[3*H*-indole-3,2'-thiazolidine]-3'(1,2,4-triazol-3-yl)-2,4'(1*H*)-dione. *Bioorg Med Chem* 2006;14:2409-2417.
21. Desai KG, Desai KR, A facile microwave enhanced synthesis of sulfur-containing 5-membered heterocycles derived from 2-mercaptobenzothiazole over ZnCl<sub>2</sub>/DMF and antimicrobial activity evaluation. *J Sulfur Chemistry* 2006; 27,4:315–328
22. Kasmi-Mir S, Djafri A, Paquin L, Hamelin J, Rahmouni M, One-Pot Synthesis of 5-Arylidene-2-Imino-4-Thiazolidinones under Microwave Irradiation. *Molecules* 2006;11:597-602.
23. Erdelyi M, Solid phase methods for the microwave assisted synthesis of heterocycles. *Top Heterocyclic Chemistry* 2006;1:79–128
24. Martins M, Frizzo CP, Moreira DN, Zanatta N, Bonacorso HG, Ionic liquids in heterocyclic synthesis. *Chem Rev* 2008;108:2015–2050.
25. Khovratovich NN, Chizhevskaya II, The problem of the tautomerism of 2-iminothiazolidin-4-one and some of its derivatives. *Khimiya Geterotsiklicheskikh Soedinenii* 1967;3(4):637-641.
26. Chizhevskaya II, Zavadskaya MI, Khovratovich NN, synthesis and spectroscopic investigation of some arylazo derivatives of thiazolidin-4-one. *Khimiya Geterotsiklicheskikh Soedinenii*, 1969;5(1):52-55.
27. Chizhevskaya II, Khovratovich NN, Kharchenko RS, Investigation of the mobility of methylene group hydrogen atoms in some derivatives of 2-iminothiazolidin-4-one. *Khimiya*

- Geterotsiklicheskih Soedinenii 1967; 3(4):642-646.
28. Popp FD, Rajopadhye MJ, J. Heterocyclic Chem, 1987;24:261
  29. Taylor PJ, Spectrochim. Acta, 1970;26A:153.
  30. Fabian B, Kudar V, Csampai A, Tibor Zs. Nagy, Pal Sohar, Synthesis, IR, NMR, DFT and X-ray study of ferrocenyl heterocycles from thiosemicarbazones. Part 21: Study on ferrocenes. J Organometallic Chemistry, 2007; 692:5621–5632.
  31. Markovi R, Shirazi AZ, Ambaski D, Baranac M, J Serbian Chemical Society, 2003; 68(1):1–7.
  32. Nagase H, Studies on fungicides XXII. Reaction of dimethyl Acetylenedicarboxylate with Dithiocarbamates, thiolcarbamates, Thiosemicarbazides and Thiosemicarbazones. Chem Pharm Bull 1973; 21: 279-286.
  33. Nagase H, Studies on fungicides: XXI. Reaction of Dimethyl acetylenedicarboxylate with thioureas. Chem Pharm Bull 1973; 21: 270.
  34. Nasirullah FA, Osman SM, Derivatization of keto fatty acids: synthesis and mass spectrometry of thiazolidinones. J American Oil and Chemical Society 1982; 59,10,1: 411.
  35. Lima WT, Lima JG, Gos AJS, Mass spectrometry of some n-tryptophyl-4-thiazolidinone and n-tryptophyl-5-benzylidene-4- thiazolidinone derivatives. Spectroscopy Letters 2002; 35,1: 137–144.
  36. Monforte P *et al*, Discovery of 2,3-diaryl-1,3-thiazolidin-4-ones as potent anti-HIV-1 agent. Bioorg Med Chem Letters, 2001;11:1793–1796.
  37. Rao *et al.*, Synthesis and anti-HIV activity of 2,3-diaryl-1,3-thiazolidin-4-(thi)one derivatives. IL Farmaco 2002;57:747-751.
  38. Rao *et al.*, Synthesis of new 2,3-diaryl-1,3-thiazolidin-4-ones as anti-HIV agents. IL Farmaco 2004; 59:33-39.
  39. Balzarini J, Orzeszko B, Maurin JK, Orzeszko A, Synthesis and anti-HIV studies of 2-admantylsubstituted thiazolidine-4-ones. Eur J Med Chem 2007; 42:993-1003.
  40. Rawal RK *et al.*, Eur J Med Chem 2008, doi:10.1016/j.ejmech. 2007:12.015
  41. Monforte P *et al*, Microwave-assisted synthesis of benzimidazole and thiazolidinone derivatives as HIV-1 RT inhibitors. ARKIVOC 2004; (v):147-155.
  42. Ravichandran V, Prashantha Kumar BR, Sankar S, Agrawal RK, Predicting anti-HIV activity of 1,3,4-thiazolidinone derivatives: 3D-QSAR approach. Eur J Med Chem 2008, doi:10.1016/j.ejmech. 2008. 05.036.
  43. Shyam R, Tiwari RC, Bull Chem Soc of Japan 1972; 49: 171.

44. Kumar R, Gupta TK, Parmar SS, J Practical Chem 1970;312: 201.
45. Dwivedi C, Gupta SS, Parmar SS, Substituted thiazolidinones as anticonvulsants. J Med Chem 1972; 15:553.
46. Parmar SS, Dwivedi C, Chaudhari A, Gupta TK, Substituted thiazolidinones and their selective inhibition of nicotinamide dependant oxidations. J Med Chem 1972; 15:99.
47. Malawska B, New anticonvulsant agents. Current Topics in Medicinal Chem 2005;5:69-85.
48. Chen *et al.*, Synthesis and biological activity of novel thiazolidin-4-ones with a carbohydrate moiety. Carbohydrate Research 2008;343: 3015-3020.
49. Ulusoy N, Ergen N, Ekinici AC, Ozer H, Synthesis and anticonvulsant activity of some new arylidenehydrazides and 4-thiazolidinones. Monatshefte fur Chemie 1996; 127:1197-1202.
50. Archana, Srivastava VK, Kumar A, Synthesis of newer thiadiazolyl and thiazolidinonyl quinazolin-4(3H)-ones as potential anticonvulsant agents. Eur J Med Chem 2002; 37: 873- 882.
51. Shiradkar MR, Nikalje AG, Synthesis and anticonvulsant activity of clubbed thiazolidinone-barbituric acid and thiazolidinone-triazole derivatives. ARKIVOC 2007; (xiv): 58-74.
52. Bhoot DP, Khunt RC, Shankhvara VK, Parekh HH, Journal of Sciences 2006;17(4): 323-325.
53. Altintas H *et al.*, Synthesis of Mannich bases of some 2,5-disubstituted 4-thiazolidinones and evaluation of their antimicrobial activities. Turk J Chem 2005; 29: 425- 435.
54. Desai KG, Desai KR, A facile microwave enhanced synthesis of sulfur-containing 5-membered heterocycles derived from 2-mercaptobenzothiazole over ZnCl<sub>2</sub>/DMF and antimicrobial activity evaluation. J Sulfur Chemistry 2006; 27(4):315–328.
55. Saeed A, Abbas N, Flörke U. J Braz Chem Soc 2007;18(3):559-565.
56. Shah TJ, Desai VA, Synthesis of some novel fluorinated 4-thiazolidinones containing amide linkages and their antimicrobial screening. ARKIVOC 2007; (xiv): 218-228.
57. Mehta PD, Sengar NP, Subrahmanyam EVS, Satyanarayana D, Synthesis and Biological Activity Studies of Some thiazolidinones and azetidiones. Ind J Pharm Sci 2006; 68 (1):103-106.
58. Hamed AE, Nadia H. Metwalli, Nagwa MM, Cycloaddition reactions of 5-(2-thienyl) methylene derivatives

- of thiazolidinone-4-thiones and their antimicrobial activities. *Archives of Pharmaceutical Research* 1990; 13(1):5-8.
59. Pawar RB, Mulwad VV, Synthesis of some biologically active pyrazole, thiazolidinone, and azetidinone derivatives. *Chemistry of Heterocyclic Compounds* 2004;40(2):219-226.
  60. Aly AA, Sayed R, *Chem Pap* 2006;60 (1): 56-60.
  61. Vicini P, Geronikaki A, Incerti M, Zani F, Deardenc J, Hewitt M, 2-Heteroarylimino-5-benzylidene-4-thiazolidinones analogues of 2-thiazolylimino-5-benzylidene-4-thiazolidinones with antimicrobial activity: Synthesis and structure-activity relationship. *Bioorg Med Chem* 2008;16:3714–3724.
  62. Cacic M, Trkovnik M, Cacic F, Has-Schon E, Synthesis and antimicrobial activity of some derivatives of (7-hydroxy-2-oxo-2h-chromen-4-yl)-acetic acid hydrazide, *Molecules* 2006; 11:134-147.
  63. Vagdevi HM, Vaidya VP, Latha KP, Padmashali B, Synthesis and pharmacological examination of some Thiazolidinone derivatives of Naphto[2,1-b]furan. *Indian J Pharm Sci* 2006; 68(6): 719-725.
  64. Yanofsky SD *et al.*, Allosteric activation of the follicle-stimulating hormone (fsh) receptor by selective, nonpeptide agonists. *J Biol Chem* 2006;281(19):13226-13237.
  65. Brian J Arey *et al* Differing pharmacological activities of Thiazolidinone analogs at the FSH receptor. *Biochemical and Biophysical Research Communications* 2008; 368: 723–728.
  66. Wrobel J *et al.*, 5-Alkylated thiazolidinones as follicle-stimulating hormone (FSH) receptor agonists, *Bioorg Med Chem* 2006;14:5729-5741.
  67. Pelletier JC *et al.*, Preparation of highly substituted gamma-lactam follicle stimulating hormone receptor agonists, *Bioorg Med Chem* 2005;13:5986–5995.
  68. Maclean D *et al.*, *J Comb Chem* 2004; 6:196-204.
  69. Albanese C *et al.*, *Mol Cell Endocrinol* 1994;101: 211-219.
  70. Hongyu Z *et al.*, Design, synthesis, cytoselective toxicity, structure–activity relationships, and pharmacophore of thiazolidinone derivatives targeting drug-resistant lung cancer cells. *J Med Chem* 2008; 51:1242–125.
  71. Gududuru V, *Bioorg Med Chem Lett* 2004;14:5289-5293.
  72. Dexter DL, Barbosa JA, P. Calabresi, *Cancer Res* 1979; 39:1020.
  73. Brattain MG, Fine WD, Khaled FM, Thompson J, Brattain DE, *Cancer Res* 1981; 41:1751.

74. Fogh J, Trempe G, Fogh JI, Human Tumor Cells in Vitro, Plenum Press, New York, 1975:115-119.
75. Tompkins WA, Watrach AM, Schmale JD, Schultz RM, Harris JA, J. Natl. Cancer Inst. 1974; 52:1101.
76. NCI-Navy Medical Oncology Branch cell line supplement, J Cell Biochem Suppl 1996; 24
77. Miller *et al.*, US 2007/ 0155807 A1,
78. Vazzana I, Terranova E, Mattioli F, Sparatore F, Aromatic Schiff bases and 2,3-disubstituted-1,3-thiazolidin-4-one derivatives as anti-inflammatory agents. *Arkivoc* 2004; (v):364-374.
79. Kumar A, Rajput CS, Bhati SK, Synthesis of 3-[4'-(p-chlorophenyl)-thiazol-2'-yl]-2-[(substituted azetidinone/thiazolidinone)-aminomethyl]-6-bromoquinazolin-4-ones as anti-inflammatory agent, *Bioorg Med Chem* 2007; 15: 3089–3096.
80. Panetta JA *et al.*, The anti-inflammatory effects of LY178002 and LY256548. *Agents and Actions*, 1989; 27: 300-302.
81. Ottana R *et al.*, *Eur J Pharmacol* 2002;448: 71-80.
82. DiRosa M, Willoughby DA, *J Pharm Pharmacol* 1971;23: 297-298.
83. Cuzzocrea S, Zingarelli B, Gilard E, Hake P, Salzman AL, Szabo C, *Free Radical Biol Med*. 1998;24: 450-459.
84. Newbould BB, *British J Pharmacology*, 1965: 24632.
85. Geronikaki AA *et al.*, Computer-aided discovery of anti-inflammatory thiazolidinones with dual cyclooxygenase/ lipoyxygenase inhibition. *J Med Chem* 2008; 51(6):1601-1609.
86. Barrett KE, Keely SJ, *Annual Review Physiology* 2000; 62: 535.
87. Tonghui M *et al.*, *J. Clinical Investigation*, 2002;110(11):1651-1658.
88. Sonawane ND, Verkman AS, Thiazolidinone CFTR inhibitors with improved water solubility identified by structure-activity analysis. *Bioorg Med Chem* 2008; 16:8187-8195.
89. Alessandro Taddei *et al.*, Altered channel gating mechanism for CFTR inhibition by a high-affinity thiazolidinone blocker, *FEBS Letters*, 2004;558:52-56.
90. Hong Yang *et al.*, *The Journal of Biological Chemistry*, 2003; 278(37):35079-35085.
91. Pawelczyk A, Zaprutko L, Microwave assisted synthesis of fragrant jasmone heterocyclic analogues *European Journal of Medicinal Chemistry*, 2006;41:586-591.