



## REVIEW

### Thiazolopyrimidines: A Retrospective Study of Synthesis, Structure-Activity Relationship and Diverse Pharmacological Actions

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Thiazolopyrimidine is a nitrogen and sulphur containing heterocyclic aromatic molecule. The bicyclic compound is made by fusing two aromatic rings, thiazole and pyrimidine and replacing one carbon atom with nitrogen and sulphur. The current present work covers a wide range of methods for synthesizing thiazolopyrimidine and its derivatives using a variety of catalysts, solvent medium and microwave irradiation with a goal of achieving a high yield and rapid separation of the product. This article describes the evolution of thiazolopyrimidine as antimicrobial, antiviral, anti-Parkinson, anticancer, anti-inflammatory as well as its structure-activity relationship and potential mode of action for future research. It also includes a list of current patents filed/granted linked to various pharmacological activities in the previous few years.

**Keywords:** Thiazolopyrimidine, Synthesis, Pharmacological activities, Docking targets, Mechanism of action.

## INTRODUCTION

In the family of heterocyclic compounds, the condensed structure of thiazole and pyrimidine play an important role in biology due to its organic processes [1]. Thiazole consists of 5-membered ring containing sulphur and nitrogen atom placed at 1,3-positions in the heterocyclic ring (Fig. 1). Thiazoles are important structural units for medicinal chemistry and several biologically active molecules have been reported, such as thiamine (vitamin B), as well as antibiotics such as penicillin [2,3] and a variety of thiazole derivatives exhibit strong medicinal and pharmacological behaviours such as antibacterial and antifungal, anti-inflammatory [4], analgesic [5], antitubercular [6], central nervous system [7], activity against human immunodeficiency virus [8], etc.

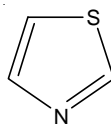


Fig. 1. General structure of thiazole

Pyrimidine is 1,3-diazine, which is identical to benzene and pyridine and has nitrogen at the 1,3-position (Fig. 2). It has a broad variety of biological functions [9] such as anti-HIV, anti-inflammatory, anticancer [10], antimicrobial action and in calcium channel modification [11]. The presence of heterocyclic nitrogenous bases cytosine and thymine are present in DNA, while uracil replaces thymine in RNA [12].

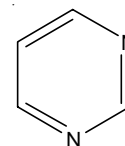


Fig. 2. General structure of pyrimidine

Thiazolopyrimidine and its analogues are a major class of fused pyrimidines and thiazoles. Thiazolopyrimidine and its derivatives have received special attention. Because they are bioisosteric analogues of purines and possible bioactive molecules, they are widely regarded as a biologically useful system [13,14]. Thiazolopyrimidine is a category of bicyclic

heterocyclic system, in which the [5,4-*d*] isomers is purine isostere. The [3,2-*a*] isomer with bridge-head nitrogen has gained a lot of interest in terms of its interesting biological properties and chemical reactivity. The existence of 5*H*- and 7*H*-forms gives it a very unique feature [15]. The ring system of thiazolopyrimidine was found to have a biological activity such as antimicrobial activity [16] and found to be an effective insecticide [17] and have also been reported to have antitumor activity [18], anti-inflammatory and analgesic agent [19], antiparkinsonian [20], antiproliferative agent [21] and antioxidant activity [22].

Ritanserin and setoperone are two of the most frequent used thiazolopyrimidine (Fig. 3). Ritanserin works by blocking the 5HT2 serotonin receptor, whereas setoperone has anti-schizophrenic properties [23]. Fig. 4 exhibits some fused structures of thiazolopyrimidine and its analogues.

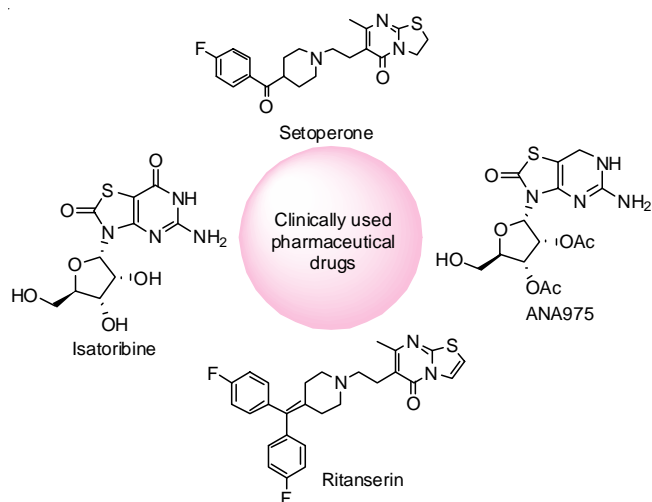


Fig. 3. Structures of clinically used pharmaceutical drugs

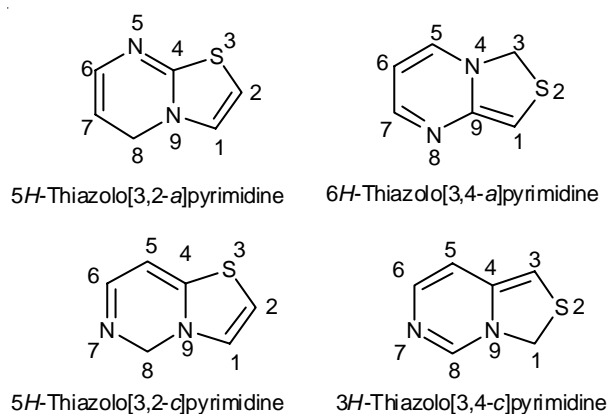
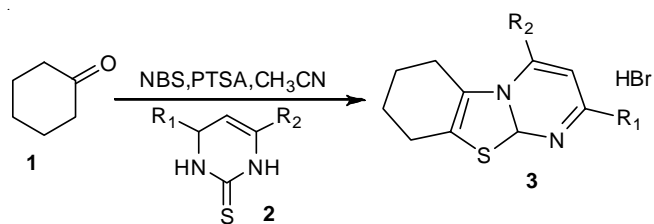


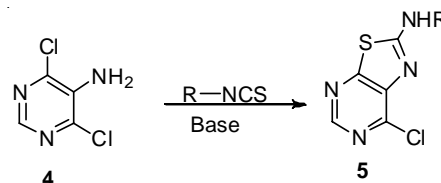
Fig. 4. Structures of thiazolopyrimidine analogues

**Synthesis of thiazolopyrimidine derivatives:** Several synthetic routes have been reported in the literature for thiazolopyrimidine derivatives, which are summarized as follows:

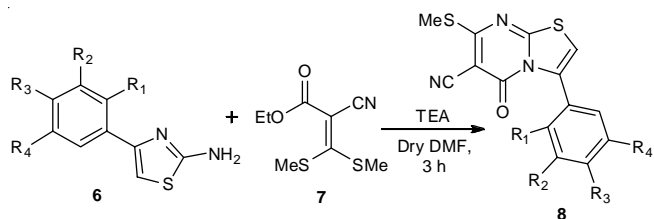
(i). The  $\alpha$ -halogenation of oxocyclohexane (**1**) with *N*-bromosuccinimide (NBS) followed by cyclization with thiopyrimidines (**2**) with *p*-toluene sulfonic acid (PTSA) and in acetonitrile solvent medium proceed to synthesize 2,4-diaryl-6,7,8,9-tetrahydro-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine hydrobromide derivatives (**3**) [24].



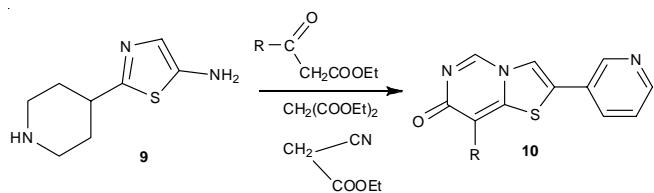
(ii). Under mild conditions, 7-chloro-derivatives (**5**) were produced by stirring and heating the isothiocyanates with 5-amino-4,6-dichloro pyrimidine (**4**) at 50 °C [25].



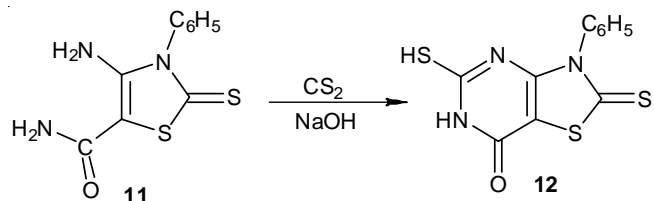
(iii). An equimolar amount of 4-(substituted phenyl)-thiazol-2-amine (**6**) and cyanoketene dithioacetal (**7**) by the addition of triethylamine (TEA) was heated for 3 h in dry DMF to obtain 3-cyano-2-methylthio-4-oxo-4*H*-thiazolo[3,2-*a*]pyrimidine (**8**) [26].



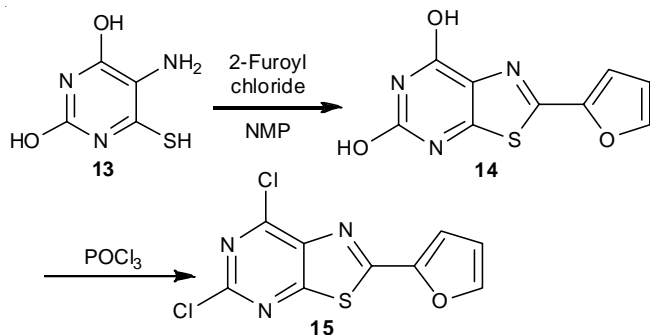
(iv). Condensation of 2-amino-4-(3-pyridyl)thiazole (**9**) with certain active methylene compound, ketoesters diethyl malonate and ethyl cyanoacetate in acetic acid yielded 7-substituted-3-(pyridine-3-yl)-5*H*-thiazolo-[3,2-*a*]pyrimidine-5-one (**10**) [27].



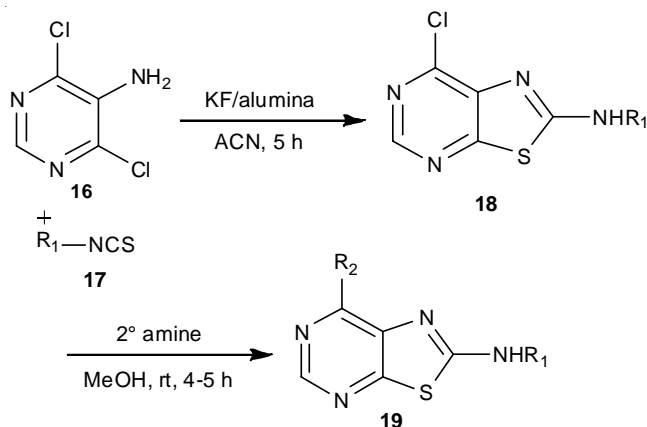
(v). Cyclization of 4-amino-3-phenyl-2-thioxo-2,3-dihydrothiazole-5-carboxamide (**11**) to 5-sulfanyl-3-phenyl-2-thioxo-2,3-dihydrothiazolo[4,5-*d*]pyrimidin-7-(6*H*)-one (**12**) by the addition of carbon disulfide with sodium hydroxide [28].



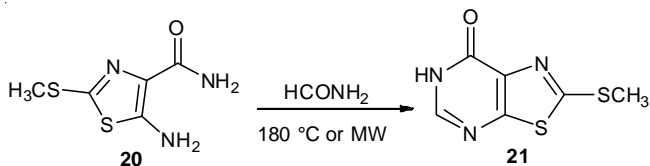
(vi). 2-(Furan-2-yl)thiazolo[5,4-*d*]-pyrimidine-5,7-diol (**14**) was achieved by refluxing 5-amino-6-sulfanyl pyrimidine-2,4-diols (**13**) with acyl chloride of furan at 150 °C, followed by refluxing with POCl<sub>3</sub> to yield compound **15** [29].



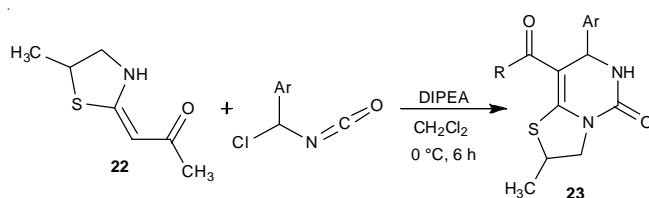
(vii). 4,6-Dichloropyrimidine-5-amine (**16**) was reacted with isothiocyanate (**17**) by the addition of KF/alumina catalyst to yield thiazolo[5,4-*d*]pyrimidine (**18**) subsequently reaction with 2°-amine was executed to achieve disubstituted thiazolo[5,4-*d*]pyrimidine (**19**) [30].



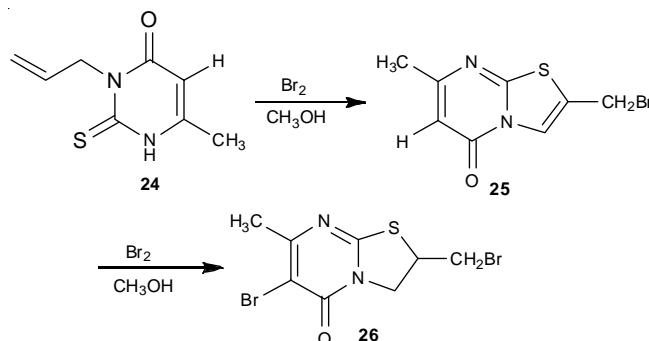
(viii). The cyclization with formamide of 5-amino-2-methylsulphonyl thiazole-4-carboxamide (**20**) to 2-methyl sulphonyl thiazolo[5,4-*d*]pyrimidine-7(6*H*)-one (**21**) was directly carried out. Another route for the synthesis of 2-methyl sulphonyl thiazolo[5,4-*d*]pyrimidine-7(6*H*)-one (**21**) using microwave-assisted organic reaction was applied to obtain formamide cyclization [31].



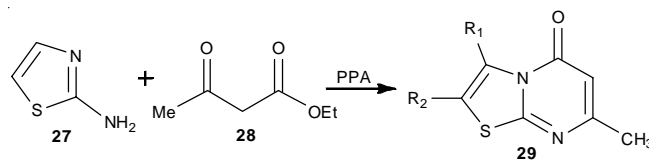
(ix). The reaction of (*E*)-1-(5-methylthiazolidin-2-ylidene)propan-2-one (**22**) with 4-chlorobenzyl isothiocyanates in the presence of a base diisopropylethylamine (DIPEA) was carried out in a CH<sub>2</sub>Cl<sub>2</sub> solution and led to the formation of diastereomeric 8-acetyl-2-methyl-7-phenyl-2,3,6,7-tetrahydro-5*H*-thiazolo[3,2-*c*]pyrimidine-5-ones (**23**) [32].



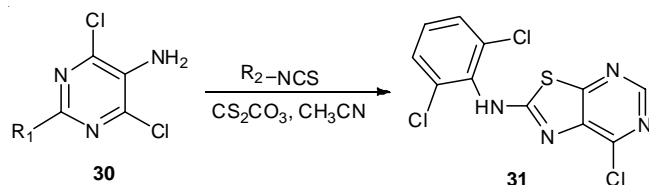
(x). Equimolar amount of 3-allyl-2-mercapto-6-methylpyrimidin-4(3*H*)-one (**24**) and bromine have resulted in the formation of 2-(bromomethyl)-7-methyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidine-5-one (**25**). Excess bromine resulted in the electrophilic substitution to 6-bromo-(2-bromomethyl)-7-methyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidine-5-one (**26**) [33].



(xi). 7-Methyl[1,3]thiazolo[3,2-*a*]pyrimidine-5-one (**29**) was synthesized by reacting 1,3-thiazolo-2-amine (**27**) with ethyl acetylacetonate (**28**) in acetic acid [34].

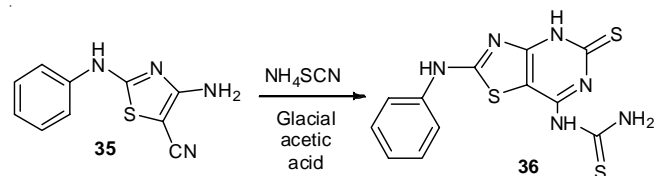
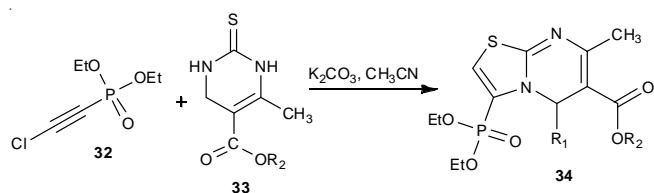


(xii). 1,3-Dichloro-2-isothiocyanatobenzene with CS<sub>2</sub>CO<sub>3</sub> and acetonitrile at 50 °C, 5-amino-4,6-dichloropyrimidine (**30**) was added to obtain 7-chloro-*N*-(1,3-dichlorobenzene)thiazolo[5,4-*d*]pyrimidin-2-amine (**31**) [35].

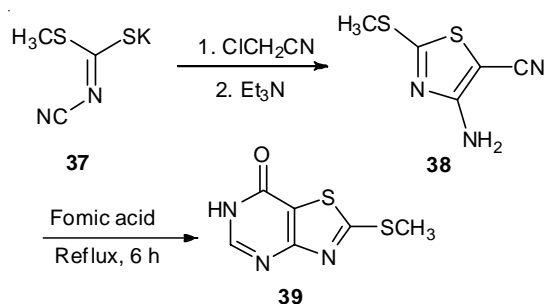


(xiii). The reaction of diethyl chloroethynylphosphonate (**32**) and ethyl-4-substituted-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**33**) along with K<sub>2</sub>CO<sub>3</sub> and methyl cyanide yielded 3-phosphorylated thiazolo[3,2-*a*]pyrimidine-6-carboxylate (**34**) in anhydrous acetonitrile at room temperature [36].

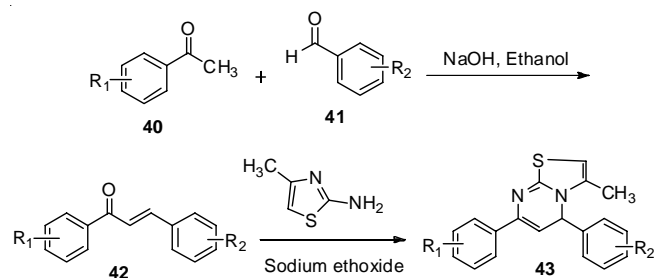
(xiv). To obtain 1-(thiazolopyrimidine-7-yl)thiourea (**36**) analogues, 2-(phenylamino)-4-amino-5-cyanothiazole (**35**) was refluxed with ammonium isothiocyanate in glacial acetic acid [37].



(xv). Chloroacetonitrile reacts with potassium methyl (*E*)-cyanocarbonimidodithioate (**37**), followed by treatment with triethylamine to yield 4-amino-2-methyl sulphonyl thiazole-5-carbonitrile (**38**). This compound yielded 2-methyl-6*H*-thiazolo[4,5-*d*]pyrimidin-7-one (**39**) when heated with formic acid [38].

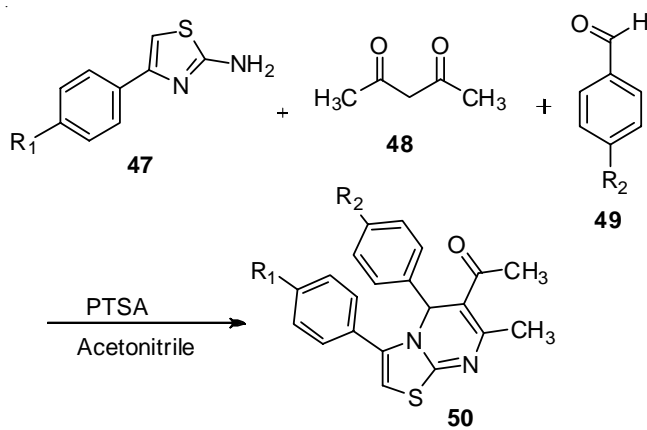
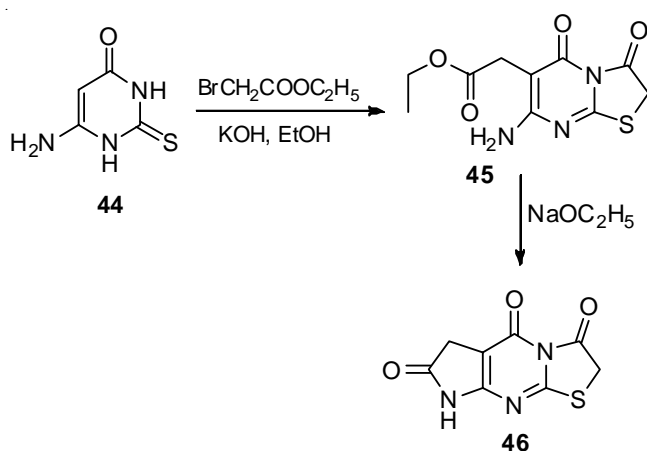


(xvi). Monoarylidene derivative (**42**) was formed in the ethanolic solution of NaOH by reaction of 3,4-substituted (or 4-disubstituted)acetophenone (**40**) with different substituted benzaldehyde derivatives (**41**). Thiazolo[3,2-*a*]pyrimidine (**43**) was prepared by reacting 2-aminothiazole or its derivatives with  $\alpha,\beta$ -unsaturated ketones in sodium ethoxide [39].



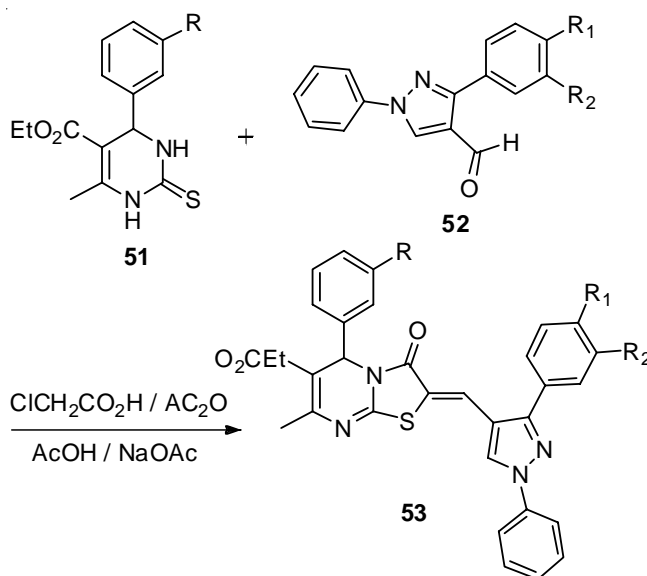
(xvii). 6-Amino-2-thiouracil (**44**) undergo cyclocondensation on boiling under reflux with ethyl bromoacetate by using ethanolic KOH as a catalyst for a long period of time to obtain ethyl 2-(7-amino-3,5-dioxo-2,3-dihydro-5*H*-thiazolo-[3,2-*a*]pyrimidin-6-yl) acetate (**45**). The compound was cyclocondensed to 6,8-dihydropyrrole[2,3-*d*]thiazolo[3,2-*a*]pyrimidine-3,5,7(2*H*)-trione (**46**) when treated with sodium ethoxide [40].

(xviii). Synthesis of bicyclic 1-(7-methyl-3,5-diphenyl-5*H*-thiazolo[3,2-*a*]pyrimidine-6-yl) ethanone derivatives (**50**) by refluxing 4-phenylthiazolo-2-amine (**47**), acetylacetone (**48**)



and various aldehyde (**49**) with PTSA and under a solvent medium of acetonitrile was achieved [41].

(xix). Synthesis of thiazolo[2,3-*b*]dihydropyrimidinone (**53**) was achieved by refluxing ethyl-6-methyl-4-(substituted phenyl)-2-thioxo-1,2,3,4-tetrahydro pyrimidine-5-carboxylate (**51**) and 3-(substituted phenyl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde (**52**) with anhydrous sodium acetate and chloroacetic acid under acetyl acetate-glacial acetic acid-acetic solvent medium [42].



**Pharmacological action:** Thiazolopyrimidines have been focussed due to its potential transfer from antibacterial to anti-cancer activity due to its mechanical similarities and sequence homologies for targeting DNA gyrase. In addition to anticancer and antimicrobial activities, thiazolopyrimidines are also very effective against viruses, inflammation, tuberculosis, anxiety and Parkinson's disease. It also exhibits antioxidant action (Fig. 5).

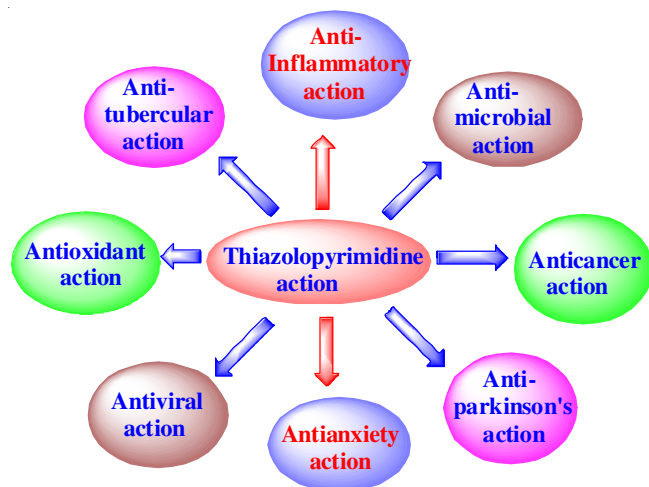
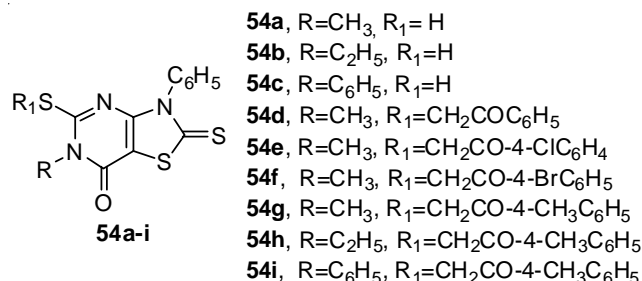


Fig. 5. Pharmacological activities of thiazolopyrimidine

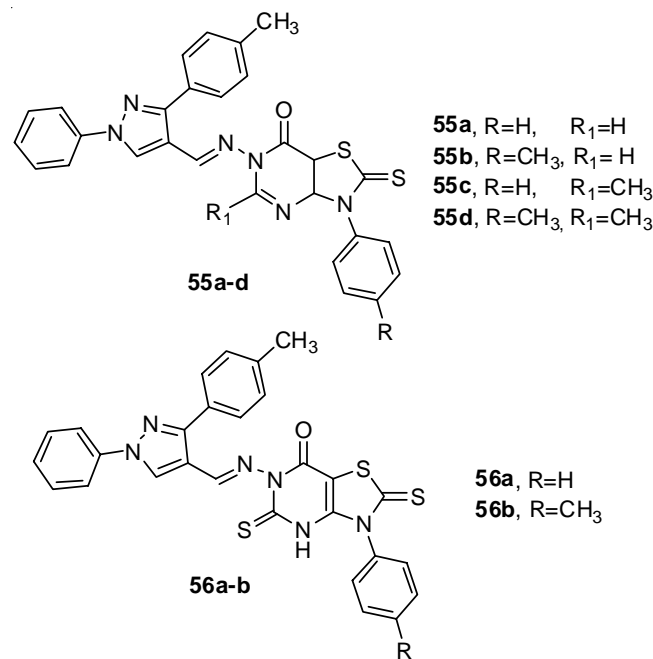
**Anti-inflammatory action:** The most effective pharmaceutical agents used in the treatment of aching and joint inflammation are non-steroidal anti-inflammatory medicines (NSAIDs) [43]. Their therapeutic potency is closely linked to their capability to suppress prostaglandin-endoperoxide synthase or COX enzymes [44]. The product of COX-1 being released constitutively is the formation of gastroprotective prostaglandin (PG) in the alimentary tract and accumulation of thromboxane in thrombocytes [45]. The expression of COX-2 is reversible, short-term and activated by pro-inflammatory mediators including lipopolysaccharides, cytokines and mitogens [46].

For the determination of gastric toxicity, Wistar rats were used and for the evaluation of analgesic activity, a writhing test was also used. The analgesic properties of compounds **54a** and **54i** were shown to be similar to those of acetylsalicylic acid. Except for **54d** and **54h**, which were considered to be as strong as phenylbutazone, all compounds displayed moderate anti-inflammatory activity [47].



**COX inhibitors:** Bekhit *et al.* [48] prepared a sequence of thiazolo[4,5-*d*]pyrimidine containing pyrazole ring, which

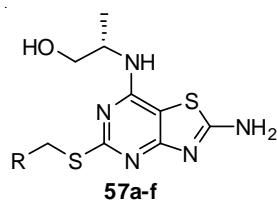
exhibited anti-inflammatory action. Indomethacin was used as a standard drug in the cotton-pellet granuloma method in mice to check the anti-inflammatory activity. Compounds **55d** and **56b** showed a mild anti-inflammatory responses. In addition, the ulcerogenic capacity in rats and inhibitory action against human enzymes COX-2 and COX-1 were also studied. Compound **55c** demonstrated superior inhibition of COX-2 in contrast to others. However, no ulceration was found in compound **56b**.



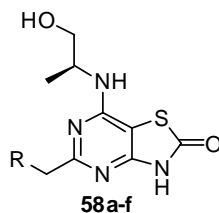
**Chemokines antagonist:** Chemokines are a type of small proteins characterized by four conserved residues of cysteine. These proteins stimulate G protein-coupled receptors *via* a concentration gradient, cause cells to migrate [49].  $\alpha$ -Chemokines are chemokines for neutrocytes while  $\beta$ -chemokines are chemokines for leukocytes and a short percentage of lymphocytes. Increased chemokines are linked to chronic obstructive lung disease, irritation, inflammatory bowel disease and stiffness [50,51].

Walters *et al.* [52] reported 5-thio and 7-amino thiazolo[4,5-*d*]pyrimidine IL8RB antagonists (**57a-f**), which came through high-throughput hit rate studies (HTS). The compound had a strong antagonist effect, but the bioavailability of rats was surprisingly weak. The structural activity relationship led the progression to newer derivatives. The substitution at position 5 led to the development of an effective compound **58d** and also 3-chlorophenyl-2-fluoro (**58a**) and 2,3-difluorophenyl (**58b**), which have enhanced potency while retaining appropriate bioavailability in rats.

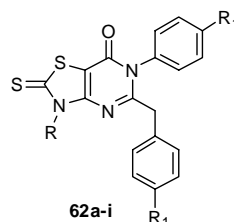
**Fractalkine receptor antagonists:** The special component of the fourth category of chemokines (CX3C) is fractalkine and comes in two forms, a membrane-bound and a soluble form, each mediating different biological activity [53]. Substituted 7-aminothiazolo[4,5-*d*]pyrimidine (**59a-i**, **60a-d**, **61a-h**) is an effective and selective fractalkine receptor (CX3CR1) antagonists [54]. In order to investigate the substituent outcomes at positions 7 and 5, structural-related properties were created.



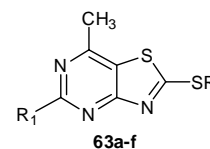
- 57a**, R= 2-F-3-ClC<sub>6</sub>H<sub>5</sub>  
**57b**, R= 2,3-diFC<sub>6</sub>H<sub>3</sub>  
**57c**, R= 2-FC<sub>6</sub>H<sub>4</sub>  
**57d**, R= C<sub>6</sub>H<sub>5</sub>  
**57e**, R= 2-furanyl  
**57f**, R= 4-(1,3thiazoyl)



- 58a**, R= 2-F-3-ClC<sub>6</sub>H<sub>5</sub>  
**58b**, R= 2,3-diFC<sub>6</sub>H<sub>3</sub>  
**58c**, R= 2-FC<sub>6</sub>H<sub>4</sub>  
**58d**, R= C<sub>6</sub>H<sub>5</sub>  
**58e**, R= 2-furanyl  
**58f**, R= 4-(1,3thiazoyl)



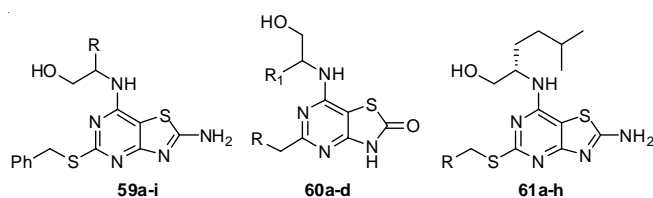
- 62a** R=C<sub>2</sub>H<sub>4</sub>, R<sub>1</sub>=4-OCH<sub>3</sub>  
**62b** R=C<sub>6</sub>H<sub>5</sub>, R<sub>1</sub>=4-OCH<sub>3</sub>  
**62c** R=C<sub>6</sub>H<sub>5</sub>, R<sub>1</sub>=2-OCH<sub>3</sub>  
**62d** R=C<sub>6</sub>H<sub>5</sub>, R<sub>1</sub>=4-CH<sub>3</sub>  
**62e** R=4-CH<sub>3</sub>-O-C<sub>6</sub>H<sub>4</sub>, R<sub>1</sub>=2-OCH<sub>3</sub>  
**62f** R=4-CH<sub>3</sub>-O-C<sub>6</sub>H<sub>4</sub>, R<sub>1</sub>=4-Br  
**62g** R=2-CH<sub>3</sub>O-C<sub>6</sub>H<sub>4</sub>, R<sub>1</sub>=2,6-diCH<sub>3</sub>  
**62h** R=3-Cl,4-F-C<sub>6</sub>H<sub>3</sub>, R<sub>1</sub>=4-OCH<sub>3</sub>  
**62i** R=4-Br-C<sub>6</sub>H<sub>4</sub>, R<sub>1</sub>=4-OCH<sub>3</sub>



- 63a**, R=CH<sub>3</sub>, R<sub>1</sub>=Cl  
**63b**, R= C<sub>2</sub>H<sub>5</sub>, R<sub>1</sub>=Cl  
**63c**, R= CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>, R<sub>1</sub>=Cl  
**63d**, R= CH<sub>2</sub>CN, R<sub>1</sub>=Cl  
**63e**, R= CH<sub>2</sub>COCH<sub>3</sub>, R<sub>1</sub>=Cl  
**63f**, R= C<sub>2</sub>H<sub>5</sub>, R<sub>1</sub>=morpholinyl

The SAR study shows that the lipophilic replacement in the benzene ring was accepted at position 5. As in compound **59e**, more polar groups (like nitrile) produce a 2-3 fold decrease in potential. In contrast to the unsubstituted compound **59e**, the affinity of 2-Br derivative (**61a**) was 12-times greater.

The SAR study shows a small rise in efficiency in compound **59a** by substituting the methyl group *via* an ethyl or isopropyl group at position 7, while a substantial increase in efficacy was achieved by replacing it with large groups like *n*-propyl or isobutyl. Usually, more lipophilic group produce a more effective compound at this position and the *R*-enantiomer binds to the CX3CR1 receptor more preferably than *S*-enantiomer.

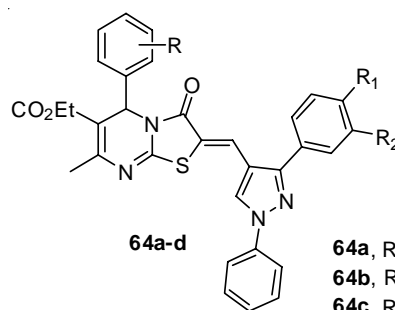


- 59a**, R= Me (R)  
**59b**, R= Et (R)  
**59c**, R= *i*-Bu (R)  
**59d**, R= *i*-Bu (S)  
**59e**, R= Ph (R)  
**59f**, R= *i*-Pr (R)  
**59g**, R= Pr (R)  
**59h**, R= *t*-Bu (R)  
**59i**, R= *t*-Bu (R)  
**60a**, R= Ph, R<sub>1</sub>= Me (R)  
**60b**, R= Ph, R<sub>1</sub>= Et (R)  
**60c**, R= Ph, R<sub>1</sub>= *t*-Bu (R)  
**60d**, R= 2,3-diF-phenyl, R<sub>1</sub>= *t*-Butyl  
**61a**, R= 2-Br-phenyl  
**61b**, R= 2-Cl-phenyl  
**61c**, R= 2-F-phenyl  
**61d**, R= 2-Me-phenyl  
**61e**, R= 2-CN-phenyl  
**61f**, R= 2-MeO-phenyl  
**61g**, R= 3-Br-phenyl  
**61h**, R= 3-CN-phenyl

**Antimicrobial action:** Chhabria *et al.* [55] synthesized and tested a sequence of derivatives for their properties against fungal infections. *In vitro* testing was done on every derivative for antifungal action against *Aspergillus clavatus*, *Aspergillus niger* and *Candida albicans*. The most active compound among all fungal strains is compound **62b**, which has a phenyl ring in the third position and a 4-methoxyphenyl ring in the fourth position. Compounds **62e** and **62i** showed significant activity against *Aspergillus niger*, while compounds **62b**, **62f** and **62h** showed good activity against *A. clavatus*.

Rahimizadeh *et al.* [56] prepared several thiazolo[4,5-*d*]pyrimidine compounds. The antibacterial efficacy of all substances using streptomycin as a standard drug against *S. aureus*, *H. bacillus*, *E. coli* and *P. aeruginosa* was measured. All the derivatives showed good action against *H. bacillus* and *P. aeruginosa* and poor activity against *S. aureus*. Compounds **63c-d**, **63f** displayed strong activity against *E. coli*.

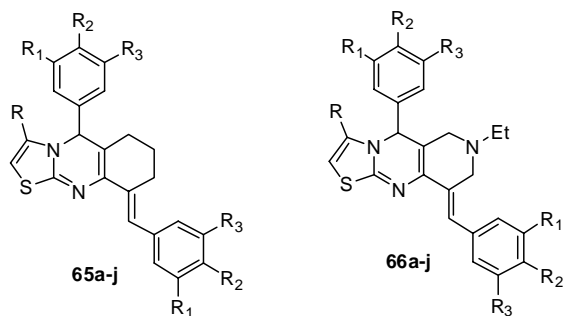
Viveka *et al.* [42] synthesized thiazolo[2,3-*b*]dihydropyrimidinone and performed *in vitro* evaluation for antimicrobial activity. Compound **64a** displayed strong antibacterial action and the pyrazole ring contained electron-withdrawing group 3,4-dichloro phenyl. The highest activity for compound **64a** was observed among all compounds.



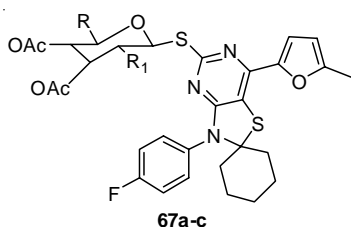
- 64a**, R=3F-4-CH<sub>3</sub> R<sub>1</sub>=Cl R<sub>2</sub>=Cl  
**64b**, R=2,5-(OCH<sub>3</sub>)<sub>2</sub> R<sub>1</sub>=Cl R<sub>2</sub>=Cl  
**64c**, R=H R<sub>1</sub>=Cl R<sub>2</sub>=Cl  
**64d**, R=4-OCH<sub>3</sub> R<sub>1</sub>=Cl R<sub>2</sub>=Cl

**Anticancer action:** One of the world's most significant death factors is cancer. Despite the development of innovative diagnostic techniques to aid in early diagnosis, new successful antitumor agents are still urgently needed to determine available targets [57]. No drug was found to date to kill malignant cells without damaging healthy tissues. Any anticancer agent must be evaluated in terms of a combination of advantage and toxicity [58].

The *in vitro* antitumour efficacy of synthesized compounds was examined and the results showed that compounds **65i**, **66e**, **66g** and **66h** showed significant broad-spectrum antitumour activity. The activity of compounds **65i** and **66e** was almost 9 times that of 5-fluorouracil [59]. The *in vitro* evaluation of compounds for their antitumour activity was accomplished by using the MTT assay against (HepG-2) human hepatoma of the liver, (PC-3) human prostate cancer and (HCT-116) human rectal malignancy cells. In three types of carcinogenic cells, all compounds exhibited dose-dependent anticancer action. Compounds **67a** and **67b** displayed strong anticancer activity in HCT-116 malignancy cells, with an IC varying from 92.2 to 120.1. The inhibitory effect of compounds **67a** and **67b** indicate the significance of linking glycosyl group with thiazolo-pyrimidine [60].

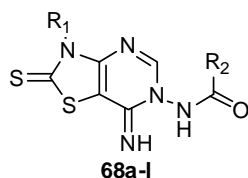


- 65a** R, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> = H  
**65b** R = CH<sub>3</sub>, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> = H  
**65c** R, R<sub>1</sub>, R<sub>3</sub> = H, R<sub>2</sub> = Cl  
**65d** R = CH<sub>3</sub>, R<sub>1</sub>, R<sub>3</sub> = H, R<sub>2</sub> = Cl  
**65e** R, R<sub>1</sub>, R<sub>3</sub> = H, R<sub>2</sub> = OCH<sub>3</sub>  
**65f** R = CH<sub>3</sub>, R<sub>1</sub>, R<sub>3</sub> = H, R<sub>2</sub> = OCH<sub>3</sub>  
**65g** R<sub>1</sub>, R<sub>3</sub> = OCH<sub>3</sub>, R<sub>2</sub> = H  
**65h** R = CH<sub>3</sub>, R<sub>1</sub>, R<sub>2</sub> = OCH<sub>3</sub>, R<sub>3</sub> = H  
**65i** R = H, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> = OCH<sub>3</sub>  
**65j** R = CH<sub>3</sub>, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> = OCH<sub>3</sub>
- 66a** R, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> = H  
**66b** R = CH<sub>3</sub>, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> = H  
**66c** R, R<sub>1</sub>, R<sub>3</sub> = H, R<sub>2</sub> = Cl  
**66d** R = CH<sub>3</sub>, R<sub>1</sub>, R<sub>3</sub> = H, R<sub>2</sub> = Cl  
**66e** R, R<sub>1</sub>, R<sub>3</sub> = H, R<sub>2</sub> = OCH<sub>3</sub>  
**66f** R = CH<sub>3</sub>, R<sub>1</sub>, R<sub>3</sub> = H, R<sub>2</sub> = OCH<sub>3</sub>  
**66g** R<sub>1</sub>, R<sub>2</sub> = OCH<sub>3</sub>, R<sub>3</sub> = H  
**66h** R = CH<sub>3</sub>, R<sub>1</sub>, R<sub>2</sub> = OCH<sub>3</sub>, R<sub>3</sub> = H  
**66i** R = H, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> = OCH<sub>3</sub>  
**66j** R = CH<sub>3</sub>, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> = OCH<sub>3</sub>



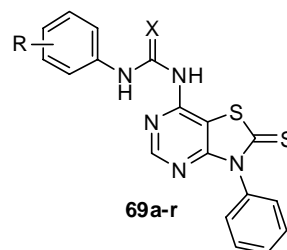
- 67a** = R = CH<sub>2</sub>OAc, R<sub>1</sub> = OAc  
**67b** = R = CH<sub>2</sub>OH, R<sub>1</sub> = OH  
**67c** = R = H

**Antiparkinson action:** Dopaminergic neuron degeneration is a symptom of Parkinson's neurodegenerative disease in the nigrostriatal brain region and indicated by lack of nimbleness or quickness slow motion, stiffness and loss of reflexes. The new compounds were synthesized which inhibits cyclic adenosine monophosphate (cAMP) by combining with A<sub>2A</sub> adenosine receptor. At nanomolar concentration, all urea derivatives (**68a-g**) exhibited chemical attraction to A<sub>2A</sub> receptors. Compound **68b** showed relatively strong selectivity of A<sub>2A</sub> binding over A<sub>1A</sub>. The urea derivatives (**68a-g**) have also been strong and more precise than furosemide derivative (**68h-l**) as per receptor binding sequence, which suggests that bonding with hydrogen is an essential part of the receptor-binding [61].



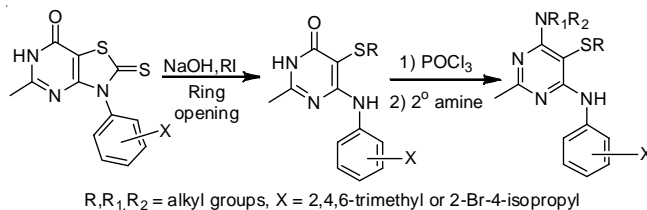
- 68a**, R = C<sub>2</sub>H<sub>5</sub>, R<sub>2</sub> = NH<sub>2</sub>  
**68b**, R = C<sub>3</sub>H<sub>7</sub>, R<sub>2</sub> = NH<sub>2</sub>  
**68c**, R = C<sub>4</sub>H<sub>9</sub>, R<sub>2</sub> = NH<sub>2</sub>  
**68d**, R = C<sub>3</sub>H<sub>5</sub>, R<sub>2</sub> = NH<sub>2</sub>  
**68e**, R = C<sub>6</sub>H<sub>5</sub>, R<sub>2</sub> = NH<sub>2</sub>  
**68f**, R = C<sub>4</sub>H<sub>4</sub>l, R<sub>2</sub> = NH<sub>2</sub>  
**68g**, R = CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>, R<sub>2</sub> = NH<sub>2</sub>
- 68h**, R = C<sub>2</sub>H<sub>5</sub>, R<sub>2</sub> = furfuryl  
**68i**, R = C<sub>3</sub>H<sub>7</sub>, R<sub>2</sub> = furfuryl  
**68j**, R = C<sub>4</sub>H<sub>9</sub>, R<sub>2</sub> = furfuryl  
**68k**, R = C<sub>3</sub>H<sub>5</sub>, R<sub>2</sub> = furfuryl  
**68l**, R = C<sub>3</sub>H<sub>5</sub>, R<sub>2</sub> = furfuryl

A sequence of urea and thiourea derivatives were prepared and evaluated for their antiparkinsonian function. Studies found that compounds **69c**, **69l**, were strong and that haloperidol induced catalepsy was greatly antagonized. It was proposed that since oxidative damage of dopaminergic neurons in the dense part of the basal ganglia is regarded as one of the evidences of neurodegeneration in Parkinson's disorder, antioxidants can help to protect dopaminergic neurons from oxidative damage. The usage of this compound substantially removed oxidative damage before 0.5 h haloperidol injection and restored glutathione levels [62].



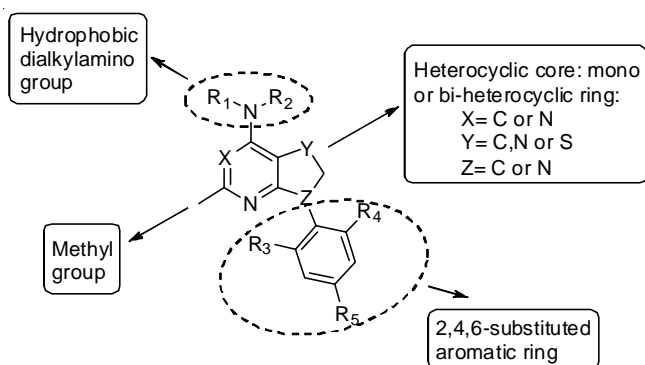
- 69a**, R = H, X = O  
**69b**, R = 4-OCH<sub>3</sub>, X = O  
**69c**, R = 2-OCH<sub>3</sub>, X = O  
**69d**, R = 2-F, X = O  
**69e**, R = 4-F, X = O  
**69f**, R = 2-Cl, X = O  
**69g**, R = 4-Cl, X = O  
**69h**, R = 2-NO<sub>2</sub>, X = O  
**69i**, R = 4-NO<sub>2</sub>, X = O
- 69j**, R = H, X = S  
**69k**, R = 4-OCH<sub>3</sub>, X = S  
**69l**, R = 2-OCH<sub>3</sub>, X = S  
**69m**, R = 2-F, X = S  
**69n**, R = 4-F, X = S  
**69o**, R = 2-Cl, X = S  
**69p**, R = 4-Cl, X = S  
**69q**, R = 2-NO<sub>2</sub>, X = S  
**69r**, R = 4-NO<sub>2</sub>, X = S

**Antianxiety action:** Corticotropin-releasing hormone (CRH) is a hypothalamus-release neurohormone which is important in incorporating the total stress response to the body. In response to stimulus, like chronic stress, CRH is released in the organism for mounting behavioural, physiological and endocrinology reaction causing stress in the body. CRH<sub>1</sub> and its role in tension and neurological conditions indicate that a new class in neuropsychiatric medication could be a new CRH<sub>1</sub> antagonist in the therapy of multiple stress-related problems, including addictive behaviour, anxiety and depression [63,64]. It was found that the opening of thiazole group of thiazolo[4,5-d]pyrimidine has another significant sequence of CRH-1 based pyrimidine antagonists. It was found that these substituted pyrimidines have excellent binding affinities compared to antalarmin [65].



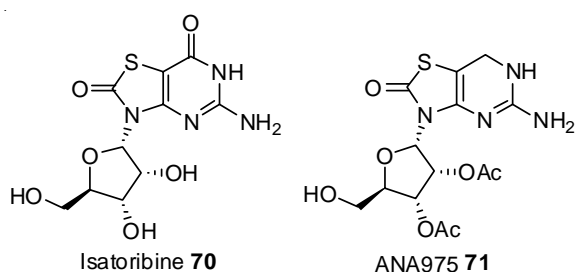
The interaction with the structure of the non-peptide CRH<sub>1</sub> antagonist and its receptors revealed that the antagonist CRH<sub>1</sub> is usually made up of three-part: the hydrophobic part upward, a proton-acceptor part in the centre and an aromatic part down-

ward. Therefore, it was proposed that the specific pharmacophore is a unicyclic or bicyclic heterocyclic, which has a non-polar dialkylamino group on a single side and generally has 2-, 4- and 6-positions substituted on aryl ring [66].

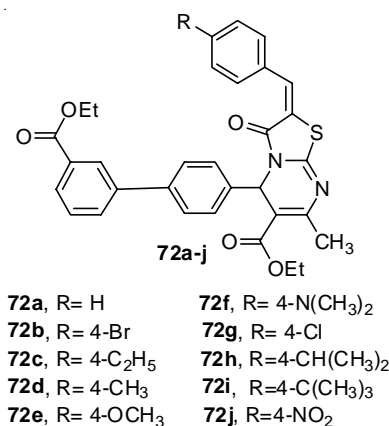


**Antiviral action:** Herpes-simplex virus (HSV) disease is found all over the world and symptoms vary from moderate disease in the majority of patients to intermittent, serious and life-threatening disease in few cases [67]. Acyclovir is used to treat it but because of its widespread and regular use [68], resistant cases have emerged; resistance has also occurred to 5-10% of immune-compromized patients [69]. It is clear from this that new antiviral compounds which can also overcome resistant strains must be tested [70].

Isatoribine is a selective toll-like receptor 7 (TLR7) agonist and native immunity is activated. In clinical trials, IV injection of isatoribine was administered to chronic HCV-infected patients once or twice a day over a week led to reduced HCV RNA levels. This was related to improving interferon response gene expression. Compound **70** had a low pharmaceutical use, to improve pharmacokinetics issues and to improve the palatability of old isatoribine, ANA975 (**71**) an isatoribine prodrug was synthesized which is transformed to isatoribine by hydrolysis of esterase and then oxidation by aldehyde oxidase, offering bioavailability of more than 85% [71].



**Antioxidant action:** Maddila *et al.* [72] synthesized and screened a series of biphenyl-3,5-dihydro-2*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxylate analogues for antioxidant activity. The entire synthesized compound displayed mild to strong antioxidant activity. Because of the addition of an aliphatic group on the benzene ring, compounds **72j**, **72i** and **72a** have shown higher potency as compared to reference ascorbic acid. Antioxidant activity is strong in derivatives containing an aliphatic group on the benzene ring. Compounds **72a**, **72b**, **72d**, **72f**, **72g** and **72h** shows medium to higher antioxidant activity.



**Antitubercular action:** Cai *et al.* [73] synthesized and screened the derivatives of 5*H*-thiazolo[3,2-*a*]pyrimidin-5-ones as antitubercular agent. Using broth microdilution method, the antitubercular efficacy *in vitro* against *M. smegmatis* were screened. Compounds **73a-d**, which has a substituted benzamide at the C-7 position, is effective towards *M. smegmatis*.

**Mechanism of action:** Thiazolopyrimidine exhibits a variety of biological characteristics. Thiazolopyrimidine may block topoisomerase of mammalian DNA, while it is 100 times more vulnerable to DNA gyrase prokaryotic. The development of thiazolopyrimidine drugs has lately gained considerable interest because of the molecular similarities of sequence homologies for the targeting of eukaryotic topoisomerase enzymes. The mechanism of action of thiazolopyrimidine is depicted in Fig. 6 [49,52,54,66,74,75].

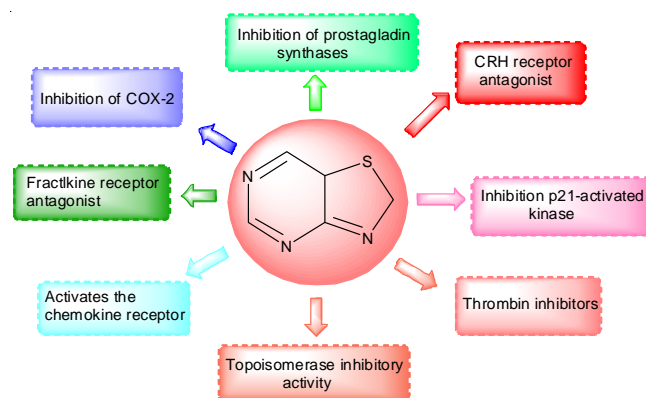


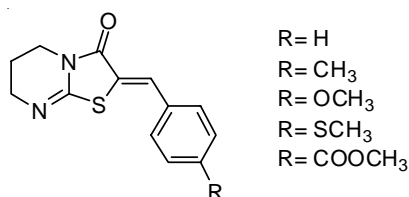
Fig. 6. Mechanism of action of thiazolopyrimidine

**Relationship between thiazolopyrimidine analogues and fraction V:** Serum albumins are an important element in biological processes predominantly present in the circulatory system [76,77]. Various ligands like fatty acids, proteins, steroids, antibiotics, pharmaceuticals and transition metals are the most essential physiological characteristic of this group of proteins in the bloodstream. Furthermore, they can help to maintain colloid oncotic blood pressure and blood pH [78,79]. The binding of serum albumin can affect the pharmacokinetic properties of the drug and its interactions with tissues [80,81]. Thus, drug-serum albumin interactions are important to understand the body's storage, transportation and distribution and to explain the action mechanism, pharmacodynamics and pharmaco-



kinetics of drug serum [82,83]. Fraction V is chosen as a protein model because of its high homology and sequence and conformation resemblance with human serum albumin (HSA).

Spectrofluorometry and UV-visible absorption spectroscopy were analyzed in the relationship between thiazolopyrimidine analogues and fraction V. To study the quenching process, the Stern-Volmer constant and UV-visible absorption parameters were used. The association constant ( $K_a$ ), binding distance ( $r$ ) were estimated along with binding sites ( $n$ ). The potential subdomain on fraction V that binds thiazolopyrimidine was identified by using a displacement experiment. The molecular configurations of five synthesized thiazolopyrimidines are shown below:



**Mechanism of fluorescence quenching of fraction V by thiazolopyrimidine:** In presence of thiazolopyrimidine, the fluorescence was quenched by a shift in the emission spectrum. When there are only methyl groups or no substituents on the benzene ring, the  $\lambda_{max}$  of fluorescence emission of fraction V showed red shift, while for the other three compounds, the blue shift will occur at the  $\lambda_{max}$  of fraction V. This phenomenon indicates that after adding thiazolopyrimidine, the microenvironment of the fraction V chromophore has changed [84,85].

Under closely regulated temperature and pH parameters, collisional quenching and contact quenching are potential causes of fluorescence quenching. The Stern-Volmer equation was used to test the fluorescence results to determine a precise quenching mechanism [86].

$$\frac{F^0}{F} = 1 + K_q \tau_0 [Q] = 1 + K_{sv} [Q] \quad (1)$$

$F^0$  and  $F$  = in the absence and presence of quencher, the relative fluorescence intensity of fraction V.  $K_{sv}$  = the collisional quenching constant;  $K_q$  = the bimolecular rate constant of the quenching;  $Q$  = concentration quenching.

**Binding parameters of thiazolopyrimidine and fraction V:** The binding dimensions between fraction V and thiazolopyrimidine can be calculated using eqn. 2, while the quenching process is constant:

$$\log \frac{F^0 - F}{F} = \log K_A + n \log [Q] \quad (2)$$

The values of 'n' are around 1 and demonstrate that the fraction V to thiazolopyrimidine molar ratio is 1:1. The binding constants of fraction V and thiazolopyrimidine interaction decreases in the following order  $2 > 5 > 3 > 4 > 1$ , the binding capacity from compound 2 to fraction V is greatest and the binding capacity from compound 1 to fraction V is weakest. Thiazolopyrimidine alkyl group will interact with the amino acid group, thereby enhancing fraction V and thiazolopyrimidine binding affinity with any substitutions on the benzene ring [78,87].

**Force acting between thiazolopyrimidine with fraction V:** Thermodynamic variables like change in entropy ( $\Delta S$ ), enthalpy changes ( $\Delta H$ ) and change in free energy ( $\Delta G$ ) are measured for determining the force. The H-bonds, Coulomb force, hydrophobic interaction and intermolecular forces are the most commonly acting forces in the relationship between small molecules and macromolecules. When the temperature is less, the values of  $\Delta H$  can be stabilized. Therefore, the thermodynamic variables of temperature may be calculated using the equations [88,89]:

$$\ln K = -\frac{\Delta H}{RT} + \frac{\Delta S}{R} \quad (3)$$

$$\Delta G = \Delta H - T\Delta S \quad (4)$$

**Distance between thiazolopyrimidine and fraction V:** The Foster theory state that the energy conversion takes place when the combination fits the following conditions (a) fluorescence can be produced by a donor, (b) the donor's fluorescence emission spectra and the acceptor absorbance spectra overlap, (c) the distance is less than 7 nm between donor and acceptor [90]. The separation between the receiver and supplier determines the ability of energy transfer as well as the crucial energy conversion distance. As a result, the energy conversion efficiency  $E$  is determined by the following equation:

$$E = \frac{R_0^6}{R_0^6 + r^6} \quad (5)$$

**A glimpse of recent patents issued or submitted:** For years, thiazolopyrimidine drugs have been useful in antimicrobial treatment, but they are currently being studied as potential anticancer and cytotoxic agents. Similarly, various patents for the use of thiazolopyrimidine have been issued or submitted as shown in Table-1.

TABLE-1  
REPORTED PATENTS OF THIAZOLOPYRIMIDINE

Patent number	Title	Date	Ref.
W020180854841	Fused thiazolopyrimidine derivatives as MNKS inhibitors	26-05-2018	[92]
US20150038494A1	Thiazolopyrimidine modulators as immune suppressive agents	05-02-2010	[93]
US8637527B2	Imidazolo-oxazolo and thiazolopyrimidine modulators of TRPV1	28-01-2014	[94]
US8901132B2	Thiazolopyrimidine modulators as immune suppressive agents	02-12-2014	[95]
EP2224929A1	Imidazolo, oxazolo and thiazolopyrimidine modulators of TRPV1	08-10-2010	[96]
US7893060B2	Thiazolopyrimidine and their use as inhibitors of phosphatidylinositol-3-kinase	22-02-2011	[97]
W02009042607A1	Thiazolopyrimidine Phosphoinositide-3-kinase inhibitor compounds and methods of use	02-04-2009	[98]
W02002072585A2	Substituted pyrazolopyrimidine and thiazolopyrimidine	19-09-2002	[99]

## Conclusion

This review article had emphasized the recent progress in the rapidly growing field of thiazolopyrimidine chemistry. In the context of synthetic methods to the pharmacological activities of condensed thiazolopyrimidine, references gathered were regarded to be reviewed and summarized. Their significant pharmacological potential provided a good foundation for the systematic exploration of these compounds in the synthesis and functioning of condensed thiazolopyrimidine.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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