ScienSage

Journal of Advanced Scientific Research

Available online through http://www.sciensage.info/jasr

ISSN
0976-9595
Review Article

Review on Synthesis and Various Biological Potential of Thiazolopyrimidine Derivatives

Shiv Jee Kashyap*, Pramod Kumar Sharma, Vipin Kumar Garg, Rupesh Dudhe, Nitin Kumar

Pharmaceutical Chemistry Research Lab., Department of Pharmaceutical Technology,
Meerut Institute of Engineering and Technology, NH-58, Bypass Road, Baghpat Crossing, Meerut- 250005, U.P., India
**Corresponding Author: shivjee10@gmail.com*

ABSTRACT

A number of efforts were made to synthesize a large number of heterocyclic compounds and their derivatives and screened their pharmacological activities for treating various diseases. Heterocyclic compounds having nitrogen and sulfur in their skeleton are the most fascinated compound by scientists due to their diverse biological activities. Among the various heterocyclic compounds, pyrimidine and fused pyrimidine plays an important role in the medicinal chemistry because it posses promising anticancer, antioxidant, antimicrobial, antitubercular, antiparkinsonian, anti-inflammatory, analgesic and anti-HIV activities. This review is focused on tthiazolopyrimidine and its derivatives that are now in development and screened for different activities

Keywords: Thiazolopyrimidine, Pyrimidine, Thiazole, Antiinflammatory, Antiparkinsonian, Anticancer

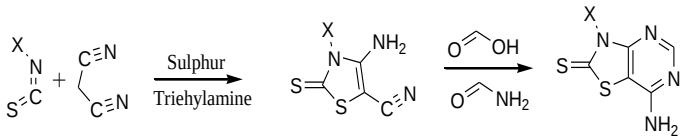
1. INTRODUCTION

Heterocyclic nucleus imparts an important role in medicinal chemistry and serves as a key template for the development of various therapeutic agents. Synthetic studies of fused pyrimidine have been reported extensively because of their structural diversity and association with a wide spectrum of biological activity. It has been observed over the years that thiazole nucleus possess different biological activities such as antihypertensive [1], anti-inflammatory [2], anti-schizophrenic [3], antibacterial [4], anti-HIV [5], hypnotic [6], anti-allergic [7] and more recently analgesic [8], fibrinogen receptor antagonists with antithrombotic activity [9], inhibitors of bacterial DNA gyrase B [10] and antitumor and cytotoxic activities. In addition, pyrimidine and fused pyrimidine derivatives are one of the most prominent structures found in nucleic acid including uracil, thymine, cytosine, adenine, and guanine are fundamental building blocks for deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). They also play an essential role in several biological processes, found in nucleoside antibiotics, anti-bacterials, and cardiovascular as well as considerable chemical reactions. Condensed pyrimidine derivatives have been reported as anti-microbial [11], analgesic, anti-viral, anti-inflammatory [12], anti-HIV [13], anti-tubercular [14], anti-tumor [15], anti-neoplastic [16], anti-malaria [17], diuretic [18], cardiovascular [19] agents and hypnotic drugs for the nervous system [20], calcium-sensing receptor antagonists [21] and also for antagonists of the human A_{2A} adenosine receptor [22]. Due to the great potential of both of the moiety, different scientists synthesized thiazolopyrimidine to evaluate their various pharmacological activities. Thiazolo[4,5-d]pyrimidine derivatives have acquired a growing importance in the field of medicinal chemistry and considered as thia-analogues of the natural purine bases such as adenine and guanine, because of their biological potential while some thiazolo[3,2-a]pyrimidines have been demonstrated to be associated with potent immunomodulating properties [23].

Thiazolo [3, 2-a]pyrimidines are also of pharmacological interest due to their anti-inflammatory [24-25] psychopharmacological [26] bactericidal [27] and antiviral activity as inhibitors of HIV-1 reverse transcriptase [28].

2. SYNTHESIS

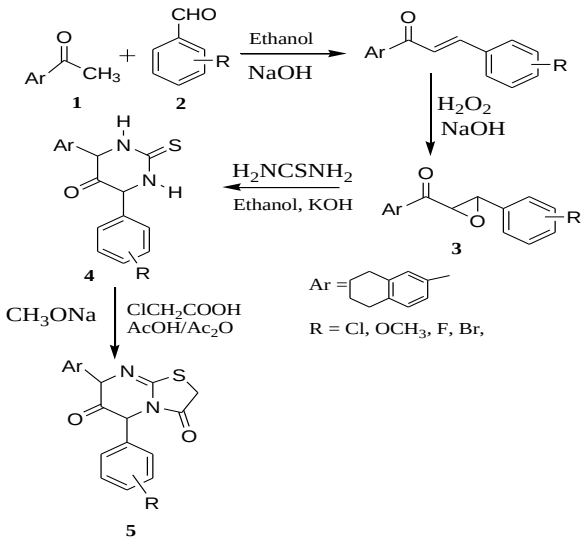
A mixture of malononitrile, phenyl/ethyl isothiocyanate and finely divided sulphur in DMF was added triethylamine very slowly with constant stirring at room temperature for three hours. The resulting compound was treated with formamide and formic acid with heating to yield 7-amino-3-phenyl/ethyl thiazolo [4, 5-d] pyrimidine-2(3H)-thione **(Scheme1)** [29].



1 **2** **3** **4**

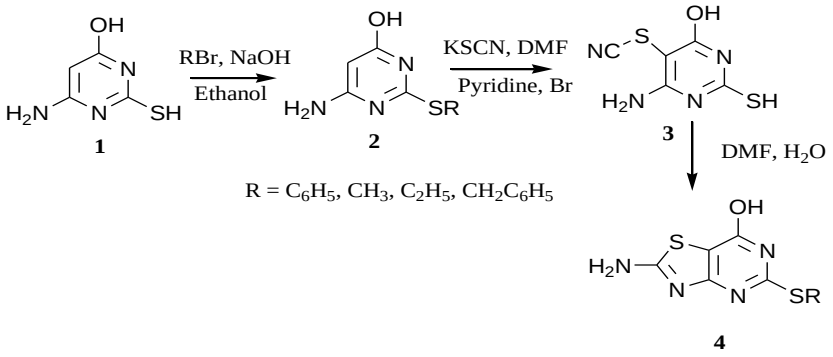
Scheme 1: Synthesis of thiazolopyrimidine 4 from malononitrile 2 and phenyl/ethyl isothiocyanate 1.

An equimolar quantity of aromatic aldehydes **1** and acetophenone **2** react in the presence of alcoholic sodium hydroxide to give chalcone derivatives by cross aldol condensation reaction which was followed by treatment of chalcone with hydrogen peroxide to produce oxirnao derivative **3**. In next step, treatment of equimolar quantity of oxirano derivatives and thiourea in the presence of HCl gives pyrimidine derivatives **4** by cyclization reaction.**(Scheme 2)** In final step, pyrimidine derivatives react with chloro acetic acid to gives thiazolo pyrimidine derivatives **5** [30].



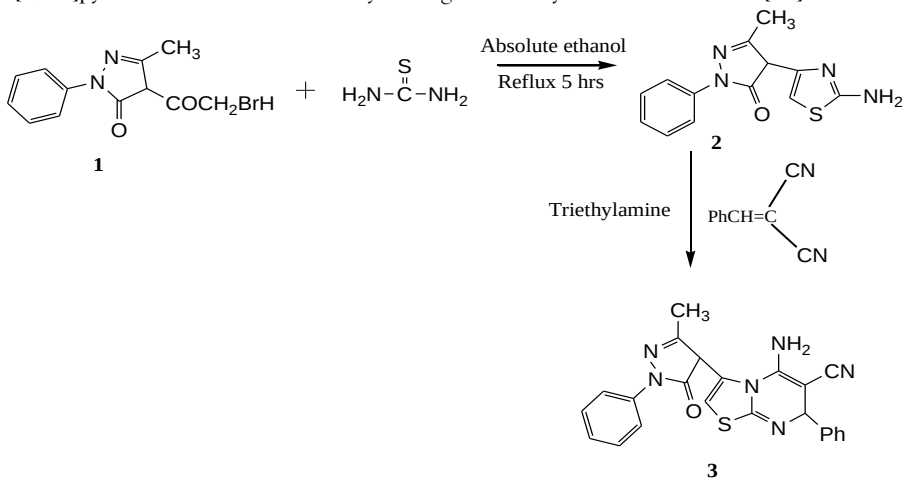
Scheme2: Synthesis of Thiazolopyrimidine derivatives 5 from aromatic aldehydes 2 and acetophenone 1

Alkylation of 6-aminothiouracil **1** followed by thiocyanation and cyclisation gave the alkyl thio thiazolopyrimidines **4 (Scheme 3)**. [31]



Scheme 3: Synthesis of alkyl thio-thiazolopyrimidines 4 from 6-aminothiouracil 1

4-(2-aminothiazol-4-yl)-3-methyl-1-phenyl-1H-pyrazol-5(4H)-one **2** was prepared by reaction of 4-bromoacetyl-3-methyl-1-phenyl-2-pyrazolin-5-one **1** with thiourea. Then resulting compound was used as a candidate for the synthesis of 5-amino-3-(3-methyl-5-oxo-1-phenyl- 2-pyrazolin-4-yl)-7-phenyl-7H-thiazolo[3,2-a]pyrimidine- 6-carbonitrile **3** by recting with benzylidene malononitrile [32].

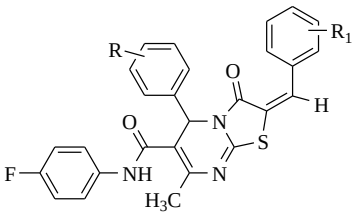


Scheme 4: Syntheis of known thiazolopyrimidine 3 from 4-bromoacetyl-3-methyl-1-phenyl-2-pyrazolin-5-one 1.

3. THIAZOLOPYRIMIDINE AS A TEMPLATE FOR VARIOUS BIOLOGICAL ACTIVITIES

3.1 Antiinflammatory and antinociceptive activity

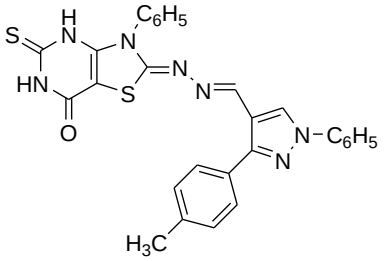
A new series of thiazolo [3, 2-a] pyrimidine derivatives was designed and synthesized by Ozair Alam *et al* [33] using 4-fluoroaniline and ethylacetoacetate as starting material. Anti-inflammatory activity was assessed by the rat paw edema method and antinociceptive activity was evaluated by thermal stimulus technique. The compounds 5-(4-chlorophenyl)-2-(4-fluorobenzylidene)-7-methyl-3-oxo-2,3-dihydro-5H-thiazolo [3,2-a] pyrimidine-6-carboxylic acid (4-fluoro phenyl) amide **(1a)** and 2-(4-chlorobenzylidene)- 5-(4-fluorophenyl)-7-methyl-3-oxo-2,3-dihydro-5H-thiazolo[3,2-a] pyrimidine-6-carboxylic acid (4-fluorophenyl)amide **(1b) (Fig.1)** were found to possess significant anti-inflammatory and antinociceptive activities.



Compounds	R	R_1
1a	4-NO_2	2-Cl
1b	4-F	4-Cl

Figure 1

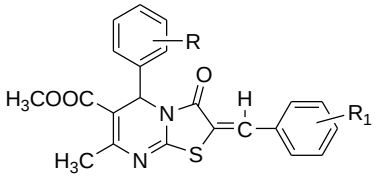
A series of some substituted 1H-Pyrazolyl thiazolo [4,5-d]-pyrimidines were **s**ynthesized by Bekhit *et al* [34] and all the synthesized compounds were evaluated for their anti-inflammatory activity by using carrageenan inducing rat paw edema method. The anti-inflammatory potency of all the tested compounds was compared with the standard drug indomethacin. The thiazolopyrimidine derivatives **(Fig.2)** showed good anti-inflammatory activity comparable to indomethacin with no or minimal ulcerogenic activity.



(2Z)-2-((E)-2-((1-phenyl-3-p-tolyl-1H-pyrazol-4-yl)methylene)hydrazono)-2,3,5,6-tetrahydro-3-phenyl-5-thioxothiazolo[4,5-d]pyrimidin-7(4H)-one

Figure 2

Mevlut Ertan *et al* [35] synthesized a series of new 2-benzylidene-7-methyl-3-oxo-5-(substitutedphenyl)-2,3-dihydro-5H-thiazolo [3, 2 a] pyrimidine-6-carboxylic acid methyl esters by reacting 1,2,3,4-tetrahydropyrimidine-2-thiones with chloroacetic acid and substituted benzaldehydes. Their structures have been established by IR, ^{1}H NMR, mass spectra and elemental analysis. The synthesized compounds were tested for their anti-inflammatory activities by using carrageenan inducing rat paw edema method. Test results observed that compounds **3a 3b**, **3c** and **3d (Fig.3)** showed moderate anti-inflammatory activity at the 100 mg/kg dose level compared with standard drug indomethacin.



Compounds	R	R_1
3a	4-Br	4-CH_3
3b	4-Br	4-OCH_3
3c	2-F	H
3d	2-F	4-OCH_3

Figure 3

3.2 Antimicrobial agents

Mohamed Salah K. Youssef *et al* [32] synthesized a series of 4-(2-Aminothiazol-4-yl)-3-methyl-5-oxo-1-phenyl-2-pyrazoline by the reaction of 4-bromoacetyl-3-methyl-5-oxo-1-phenyl-2-pyrazoline with thiourea. They evaluated these compounds for their antimicrobial activity against six fungal strains such as *Candida albicans, Geotrichum candidum, Scopulariopsis brevicaulis, Aspergillus flavus, Aspergillus niger* and *Trichophyton rubrum* and five bacterial species *Bacillus cereus (Gram positive), Staphylococcus aureus (Gram positive), Pseudomonas aeruginosa (Gram negative), Serratia marcescens (Gram negative)* and *Escherichia coli (Gram negative)*. Compound 3-(4,5-dihydro-3-methyl-5-oxo-1-phenyl-1H-pyrazol-4-yl)-6H-thia--zolo[3,2-a]pyrimidine-5,7-dione **(fig.4)** showed a wide spectrum of antifungal activity but a narrow spectrum of antibacterial activity with minimum inhibitory concentrations (MIC=5-50mg/cm^3). They also reported that Gram negative bacteria *Escherichia coli*, *Pseudomonas aeruginosa*, and *Serratia marcescens* were generally resistant to the test compounds.

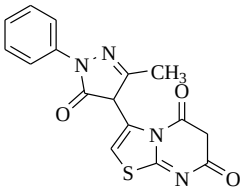
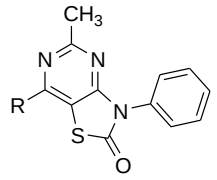


Figure 4

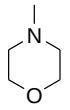
Alaa A. EI-Tombary *et al* [36] were reported the synthesis of a series of new thiazolo[4,5-d] pyrimidine derivatives, such as 7-substituted amino-5-methyl-3-phenylthiazolo[4,5-d] pyrimidine -2(3H)-thiones, ethyl 2-cyano-2-(7-substituted-5-methyl-3-phenylthiazolo[4,5-d]-pyrimidin-2(3H)-ylidene)acetates, 2-(7-substituted-5-methyl-3-phenylthiazolo [4,5-d] pyrimidin 2(3H)-ylidene)malononitriles, 5-methyl-7-morpholino-3-phenylthiazolo [4,5-d] pyrimidine-2(3H)-one, and 7-[4-(1-substituted-5-phenyl-4,5-dihydro-lH-pyrazolin-3-yl)anUino]-5-methyl-3-phenyl thiazolo [4,5-d]pyrimidine-2(3H)-thiones **(Fig.5)** and screened all the

synthesized compounds for their antimicrobial activity against *Candida albicans*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* using cup diffusion technique. Compounds 5, 6 and 7 showed both antimicrobial and antifungal activities. Compound 5, 6, 8 and 9 possess antimicrobial activity against *Escherichia coli* with inhibition zone (IZ) 18-20mm and with minimum inhibitory concentration (MIC) 62.5µg/ml which is one sixth the activity of ampicillin while compounds 5,7and 10 showed the most antifungal activity against *Candida albicans* with IZ= 20-25mm and MIC 31.25µg/ml which is one sixth of the activity of clotrimazole.

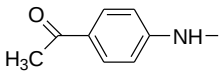


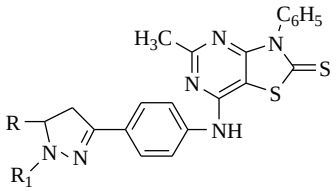
Compounds **R**

5

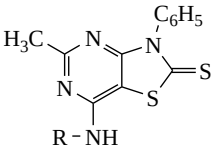


10



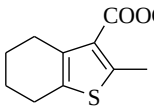


Compounds	R	R_1
6	C_6H_5,	H
7	C_6H_5,	$COCH_3$



Compounds **R**

8



9

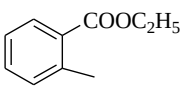


Figure 5

A series of thiazolo[3,2-a]pyrimidine derivatives such as 2,4-Bis(ethylthio)-9-(3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)-5-phenyl-5H-pyrimido[5,4-e]thiazolo[3,2-a]pyrimidine and 4Amino-2-hydroxy-9-(3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)-5-phenyl-5H-pyrimido[5,4 e] thiazolo [3,2-a]- Pyrimidine were prepared by Mohamed Salah K. Youssef *et al* [37] using 5-amino-3-(3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)-7-phenyl-7H-thiazolo [3,2-a]pyrimidine-6-carbonitrile as a starting material. All the synthesized compounds were tested for their antimicrobial activity against six fungal such as *Aspergillus flavus, Aspergillus niger, Candida albicans, Geotrichum candidum*, *Scopulariopsis brevicaulis* and *Trichophyton rubrum* and against five bacterial strains such as *Bacillus cereus, Staphylococcus aureus, Pseudomonas aeruginosa, Serratia marcescens* and *Escherichia coli*. Comparing the minimum inhibitory concentration (MIC) of all tested compounds with their reference drugs such as chlotrimazole as antifungal agent and chloramphenical as antibacterial agent. Compounds 11 **(Fig. 6)** and 12 **(Fig.7)** showed a wide spectrum of antifungal action but narrow spectrum of antibacterial effect with MIC ranging from 5-50mg/cm^3.

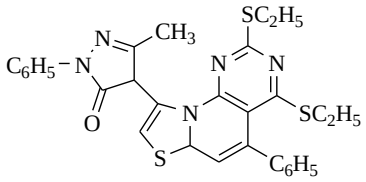


Figure 6

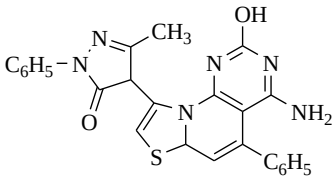


Figure 7

3.3 Antiperkinsonian activity

A series of thiopyrimidine, pyrane, pyrazoline and thiazolopyrimidine derivatives were synthesized by Abd El- Gail E. Amr *et al* [38] prepared from citrazinic acid as a starting material. They evaluated all the synthesized compounds for their analgesic and antiparkinsonian activities. Pharmacological screening of these compounds showed that they have good analgesic and antiparkinsonian activity comparable to Valdecoxib and Benzatropine as reference drugs respectively. Among all the synthesized compounds the thiazolopyrimidine derivatives 7-[(2-Chloro-6-ethoxypyridin-4-yl)-2-(phenylmethylene)-5-(2-thienyl)-2,3-dihydro-5-thiazolo[3,2-a]pyrimidine **(Fig.8)** showed most potent antiparkinsonian activity having 0.80 relative potencies compared to benzatropine. They used Tremorine and Oxotremorine to induce parkinsonian signs, such as tremor, ataxia, spasticity, salivation, lacrimation and hypothermia.

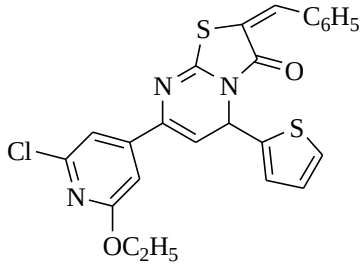
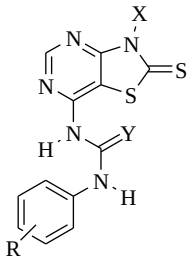


Figure 8

Faizul Azam et al [29] synthesized a series of 3-phenyl/ethyl-2-thioxo-2, 3 dihydrothiazolo [4, 5-d] pyrimidin-7-yl urea and thiourea derivatives. All the synthesized compounds were evaluated for their antiparkinsonian activity in catalepsy induced by haloperidol in mice after intraperitoneal administration. Most of the compounds exhibited significant antiparkinsonian activity. Among all the synthesized compound, compounds 13 and 14 **(Fig. 9)** showed better activity than standard drug levodopa.



Compounds	X	Y	R
13	C_6H_5	O	2-OCH_3
14	C_2H_5	S	2-OCH_3

Figure 9

3.4 Antiviral activity

A series of substituted pyrimidine, thiopyrimidine and thiazolopyrimidine derivatives were synthesized by Abd El-Galil E. Amr *et al* [30] by using 1-(5,6,7,8-tetrahydronaphthalen-2-yl)ethanone as starting material and all the synthesized compounds were evaluated for their antiviral activity against HSV-1 virus. The antiviral screening showed that many of these obtained compounds have good antiviral activities comparable to Acyclovir as reference drug. Compound 5-(3,4-Dimethoxyphenyl)-2-methyl-7-(5,6,7,8-tetrahydronaphthalen-2-yl)-2H-thiazolo[3,2-a]pyrimidine-3,6(5H, 7H)-dione **(Fig.10)** gave over 90% inhibition and considered to be most promising activity and comparing them to antiviral activity of Acyclovir.

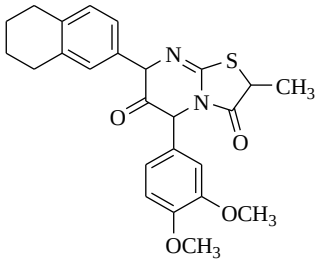


Figure 10

Revankar *et al* [39] synthesized a series of Thiazolo[4,5-d]pyrimidine derivatives from guanine analogs 5-aminothiazolo-[4,5-d]pyrimidine-2,7(3H,6H)-dione as a starting material. All the synthesized compounds were tested for their antiviral activity against human cytomegalovirus (HCMV). Compound 5-amino-3-(4-hydroxybut-2-enyl)thiazolo[4,5-d]pyrimidine-2,7(3H,6H)-dione **(Fig. 11)** possess antiviral activity against human cytomegalovirus (HCMV).

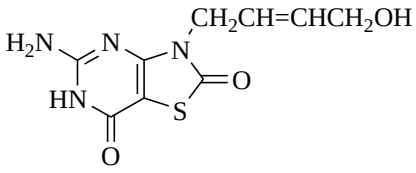


Figure 11

3.5 Anticancer activity

Fahmy *et al* [40] synthesized a series of novel fluorinated thiazolo[4,5-d]pyrimidine derivatives and sceened their anticancer activity against 60 human tumor cell lines. Compounds 15 **(Fig.12)** and 16 **(Fig.13)** showed better anticancer activity against tumor cell lines.

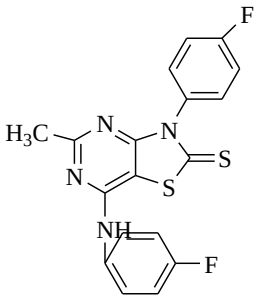


Figure 12

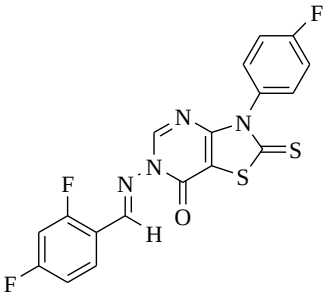
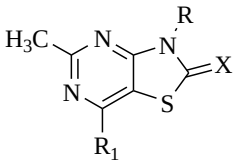


Figure 13

3.6 Antipsychotic activity

Beck *et al* [41] synthesized a series of Thiazolo [4,5-d]pyrimidinethiones and –ones and evaluated their antipsychotic activity by antagonizing the activity of corticotrophin releasing factor. Compounds 17 **(Fig. 14)** showed better antipsychotic activity.



X= O, S
R= 2-Br-4-isopropyl-C_6H_5, 2,4,6-Trimethyl-C_6H_5
R_1= morpholino, $N(C_6H_5)_2$, NEtBu, $N(CH_2CH_2OCH_3)_2$

Figure 14

4. MARKETED PRODUCT:

Ritanserin:

Chemical Name: 6-[2-[4-[Bis(4-fluorophenyl)methylene]-1-piperidinyl]ethyl]-7-methyl-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one

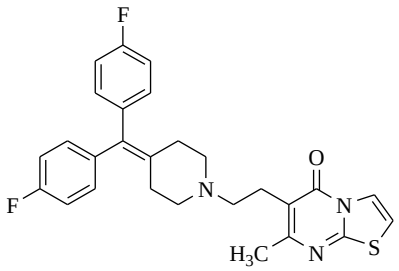


Figure: 15

5. CONCLUSION

Due to the presence of sulphur and nitrogen in the heterocyclic compounds skeleton, they show diverse biological activities. Pyrimidine and fused pyrimidine are the important heterocyclic compounds which show promising pharmacological activities i.e. anticancer, antioxidant, antimicrobial, antitubercular etc. Combination of thiazole nucleus with pyrimidine and fused pyrimidine can be a potential therapy for the treatment of large number of diseases because over the year's thiazole nucleus has been showing different biological activities such as antihypertensive, anti-inflammatory, antibacterial, hypnotic etc.

This review focus on the various synthesis and pharmacological activity of the thiazolopyrimidine could be synthesized by using malonitril, phenyl/ethyl, isothiocynates, triethylamine, aromatic benzaldehyde, acetophenone, 6-aminothiouracil as a starting reagent.

After literature review it is concluded that 5-(4-chlorophenyl)-2-(4-fluorobenzylidene)-7-methyl-3-oxo-2,3-dihydro-5H-thiazolo [3,2-a] pyrimidine-6-carboxylic acid (4-fluoro phenyl) amide and (2Z)-2-((E)-2-((1-phenyl-3-p-tolyl-1H-pyrazol-4-yl)methylene) hydrazono)-2,3,5,6-tetrahydro-3-phenyl-5-thioxothiazolo[4,5-d] pyrimidin-7(4H)-one derivatives have great potential of anti-inflammatory activity, it revaled that the substitution of substituted benzene and pyrazole moiety enhance the anti-inflammatory activity of the compounds . The series of 4-(2-Aminothiazol-4-yl)-3-methyl-5-oxo-1-phenyl-2-pyrazoline and various substituted thiazoloprimidine derivatives have efficient antimicrobial activity against various fungal and bacterial strains like *Candida albicans, Geotrichum candidum, Scopulariopsis brevicaulis, Aspergillus flavus, Bacillus cereus (Gram positive), Staphylococcus aureus (Gram positive), including gram Negative strain Pseudomonas aeruginosa, Serratia marcescens* and *Escherichia coli*. It observed that cyclic structure with minimum substitution with electron withdrawing groups like SC_2H_5, -OH and Fluoro were showed good potential activity and electron donating groups like $-NH_2$, $-CH_3$ showed less active compounds. Substitution of electron withdrawing group also showed better antiviral, anticancer and antipakinsonian activity.

6. REFERENCES

1. Patt WC, Hamilton HW, Taylor MD, Ryan M. *J Med Chem*, 1992; **35**: 2562-72.
2. Sharma RN, Xavier FP, Vasu KK, Chaturvedi SC, Pancholi SS. *J Enz Inhib Med Chem*, 2009; **24**: 890 – 897.
3. Jaen JC, Wise LD, Caprathe BW, Tecle H, Bergmeier S, Humblet CC *et al*. *J Med Chem*, 1990; **33**: 311-317.
4. Tsuji K, Ishikawa H. *Bioorg Med Chem Lett*, 1994; **4**: 1601-1606.
5. Bell FW, Cantrell AS, Hogberg M, Jaskunas SR *et al*. *J Med Chem*, 1995; **38**: 4929-4936.
6. Ergenc N, Capan G, Gunay NS, Ozkirimli S, Gungor M, Ozbey S, Kendi E. *Arch Pharm Pharm Med Chem*, 1999; **332**: 343-347.
7. Hargrave KD, Hess FK, Oliver JT. *J Med Chem*, 1983; **26**: 1158-1163.
8. Carter JS, Kramer S, Talley JJ, Penning T, Collins P, et al. *Bioorg Med Chem Lett*, 1999; **9**: 1171-1174.
9. Badorc A, Bordes MF, Cointet P, Savi P. et al. *J Med Chem*, 1997; **40**: 3393-3401.
10. Rudolph J, Theis H, Hanke R, Endermann R, Johannsen L, Geschke FU. *J Med Chem*, 2001; **44**: 619-626.
11. Desai K, Patel R, Chikhalia K. *J Ind Chem*, 2006; **45**: 773-778.
12. Amr EA, Nermien MS, Abdulla MM. *Monatsh Chem*, 2007; **138**: 699-707.
13. Fujiwara N, Nakajima T, Ueda Y, Fujita HK, Awakami H. *Bioorg Med Chem*, 2008; **16**: 9804-9816.
14. Ballell L, Field RA, Chung GAC, Young RJ. *Bioorg Med Chem Lett*, 2007; **17**: 1736-1740.
15. Wagner E, Al-Kadasi K, Zimecki M, Sawka-Dobrowolska W. *Eur J Med Chem*, 2008; **43**: 2498-2504.
16. Jean-Damien C, David B, Ronald K, Julian G, Pan L, Robert D. Vertex Pharmaceuticals Incorporated, USA, PCT Int. Appl. 2002; **22**: 608.
17. Gorlitzer K, Herbig S, Walter RD. *Pharmazie*, 1997; **52**: 670-672.
18. Ukrainets IV, Tugaibei IA, Bereznykova NL, Karvechenko VN, Turov AV. *Khimiya Geterotsiklicheskikh Soedinenii*, 2008; **5**: 718-729.
19. Kurono M, Hayashi M, Miura K, Isogawa Y, Sawai K, Kokai Tokkyo Koho JP 1987; **62**: 267-272, Chem. Abstr.**1988**,*109*, 37832.
20. Wang SQ, Fang L, Liu XJ, Zhao K. *Chinese Chem Lett*, 2004; **15**: 885-888.
21. Yang W, Ruan Z, Wang Y, Van Kirk K, Ma Z, Arey BJ. *et al*. *J Med Chem* 2009; **52**: 1204-1208.
22. Gillespie RJ, Bamford SJ, Botting R, Comer M, Denny S, *et al*. *J Med Chem*, 2009; **52:** 33-47.
23. Doria G, Passarotti C, Sala R, Magrini R, Sberze P, Tibolla M, Cesarini R, *et al*. *Il Farmaco Ed Sci*, 1985; **40**: 885–894.
24. Tozkoparan B, Ertan M, Krebs B, Lage M, Kelicen P, Demirdamar R. *Arch Pharm Pharm Med Chem*, 1998; **331**: 201.
25. Tozkoparan B, Ertan M, Kelicen P, Demirdamar R. *Farmaco*, 1999; **54**: 588.
26. Van Laar M, Volkerts E, Verbaten M. *Psychopharmacology*, 2001; **154**: 189.
27. Parmar JM, Parikh AR. *Heterocycl Commun*. 1998; **4**: 463.
28. Danel K, Pedersen EB, Nielsen C. *J Med Chem*. 1998; **41**: 191.
29. Azam F, Alkskas AI, Ahmed AM. *Eur J Med Chem*. 2009; **44**: 3889–3897.
30. Abd El-Galil, EA, Salwa FM, Eman MF, Dina N. Abd El-Shafy. *Eur J Med Chem*. 2010; **45**:1494–1501.
31. Baxter A, Cooper A, Kinchin E, Moakes K, Unitt J, Wallace A. *Bioorg Med Chem Lett*. 2006; **16**: 960–963.
32. Youssef MSK, Ahmed RA, Abbady MS, Abdel-Mohsen SA, Omar AA. *Monatsh Chem*. 2008**; 139**: 553–559.
33. Alam O, Khan SA, Siddiqui N, Ahsan W. *Med Chem Res*. 2010**; 19**: 1245–1258.
34. Bekhit AA, Fahmy HTY, Rostom SAF, Baraka AM. *Eur J Med Chem*. 2003; **38**: 27-36.
35. Ertan M, Tozkoparan B, Kelicen P, Demirdamar R. *Il Farmaco*.1999; **55**: 588–593.
36. Youssef MSK, Omar AA. *Monatshefte fur Chemie*. 2007; **138**: 989–995.
37. EI-Tombary AA, Nargues S, Habib RS, EI-Hawash SA, Shaaban OG. *Arch Pharm Res*. 2007; **30**: 1511-1520.

38. Abd GE, Amr SM, Abdulla MM. *Monatsh Chem*. 2008; **139**: 1409–1415.
39. Revankar GR, Ojwang JO, Mustain SD, Rando RF, De Clercq E, *et al. Antiviral Chem Chemother*.1998; **9**: 53-63.
40. Fahmy HTY, Rostom SAF, Saudi MN, Zjawiony JK, Robins DJ. *Arch Pharm Pharm Med Chem*, 2003; **3**: 1-10.
41. Beck JP, Curry MA, Chorvat RJ, Fitzgerald LW, Gilligan PJ, Zaczek R, Trainor GL. *Med Chem Lett*. 1999; **9**: 1185-1188.