University of Tikrit
College of science

# Thiazoles: Biological activity and therapeutic application

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## *Abstract*

Thiazole, a unique heterocycle containing Sulphur and nitrogen atoms, occupies an important place in medicinal chemistry. It is an essential core scaffold present in many natural (Vitamin B1-Thiamine) and synthetic medicinally important compounds. The versatility of thiazole nucleus demonstrated by the fact that it is an essential part of penicillin nucleus and some of its derivatives which have shown antimicrobial (sulfazole), antiretroviral (ritonavir), antifungal (abafungin), antihistaminic and antithyroid activities. The synthetic importance of thiazole derivatives, its reduced forms and condensed derivatives have been increased much by their recent applications as anticancer (tiazofurin), anthelmintic.

**Key words**: Thiazoles, Biological activity

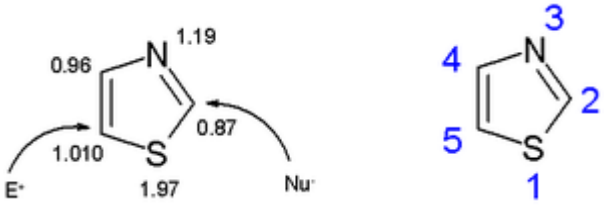
## Introduction*:*

Thiazole, or 1,3-thiazole, is a heterocyclic compound that contains both sulfur and nitrogen; the term 'thiazole' also refers to a large family of derivatives. Thiazole itself is a pale yellow liquid with a pyridine-like odor and the molecular formula $C_3H_3NS$.[1]

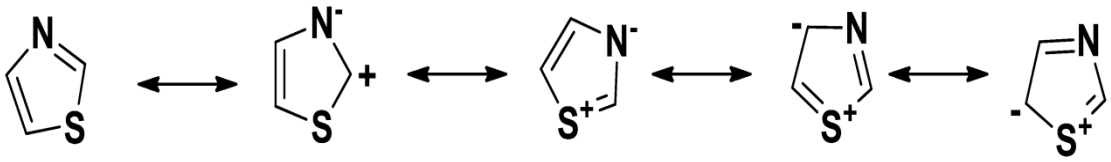
Thiazoles are members of the azoles, heterocycles that include imidazoles and oxazoles. Thiazole can also be considered a functional group. Oxazoles are related compounds, with sulfur replaced by oxygen. Thiazoles are structurally similar to imidazoles, with the thiazole sulfur replaced by nitrogen.

Thiazole rings are planar and aromatic. Thiazoles are characterized by larger pi-electron delocalization than the corresponding oxazoles and have therefore greater aromaticity. This

aromaticity is evidenced by the chemical shift of the ring protons in proton NMR spectroscopy (between 7.27 and 8.77 ppm), clearly indicating a strong diamagnetic ring current. The calculated pi-electron density marks C5 as the primary site for electrophilic substitution, and C2 as the site for nucleophilic substitution.

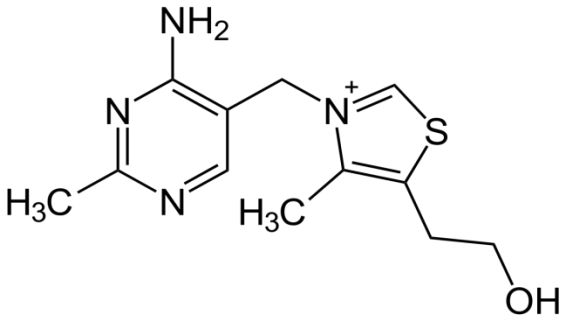



Thiazole is aromatic on the basis of delocalization of a lone pair of electrons from the sulfur atom completing the needed 6 π electrons to satisfy Huckel's rule. The resonance forms are



The p-bond orders quantified by molecular orbital methods have specified thiazole molecule to be aromatic with some dienic nature. Localization energies have projected reducing order of the nucleophilic reactivities following the order: 2 > 5 > 4 and the electrophilic reactivities as: 5 > 2 > 4. Three hydrogen atoms present in the thiazole are anticipated to have the order of acidity as H2 >> H5 > H4.

thiazole ring is found naturally in the essential vitamin B1 (thiamin).



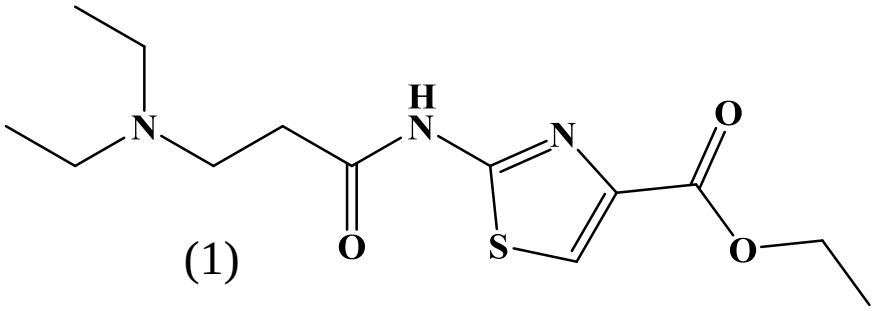
Thiamin is a water soluble vitamin that helps the body release energy from carbohydrates during metabolism. It also helps in the normal functioning of the nervous system by its role in the synthesis of acetylcholine, a neurotransmitter. Thiamin is found mostly in pasta and breads made from refined flours. It is also found in ready-to-eat cereals and in navy and kidney beans[(2)]

## Biological activities and therapeutic properties:

Thiazoles are significant class of heterocyclic compounds, found in many potent biologically active molecules such as Sulfathiazol (antimicrobial drug), Ritonavir (antiretroviral drug), Abafungin (antifungal drug) with trade name Abasol cream and Bleomycine and Tiazofurin (antineoplastic drug).

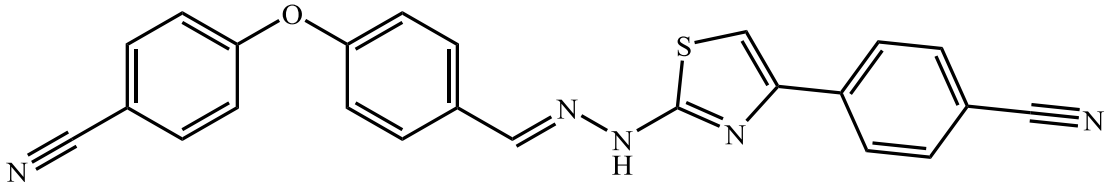
It has been noticed continuously over the years that interesting biological activities [3-4] were related with thiazole derivatives. Recently the applications of thiazoles were found in drug development for the treatment of allergies [5], hypertension [6], inflammation [7], schizophrenia [8], bacterial [9], HIV infections [10], hypnotics [11] and more recently for the treatment of pain [12], as fibrinogen receptor antagonists with antithrombotic activity [13] and as new inhibitors of bacterial DNA gyrase B. [14] A brief review of thiazoles associated with large number of biological activities is presented below

**Antitumor and anticancer activity**: The prepare of several new ethyl 2-substituted aminothiazole-4-carboxylate analogs have been described and the prepared compounds were tested for their in vitro antitumor activity against 60 human tumor cell lines by the National Cancer Institute (NCI) and showed potential anticancer activity. Ethyl 2-[3-(diethylamino)-propanamido]-thiazole-4-carboxylate (1) exhibited remarkable activity against RPMI-8226 leukemia cell line with $GI_{50}$ value of 0.08 μM and a broad spectrum activity against all the tumor cell lines used with $GI_{50}$ (MG-MID) value of 38.3 μM[15]. Also the novel compound is (E)-4-(2-(2-(4-(4-cyanophenoxy)benzylidene)hydrazineyl)thiazol-4-yl)benzonitrile (2) that synthesized by (Altıntop MD., et al) which tested on A549 and C6 cells. The synthesized compound exhibited most promising anti-cancer agent due to significant inhibitory effects on A549 and C6 cells[16].



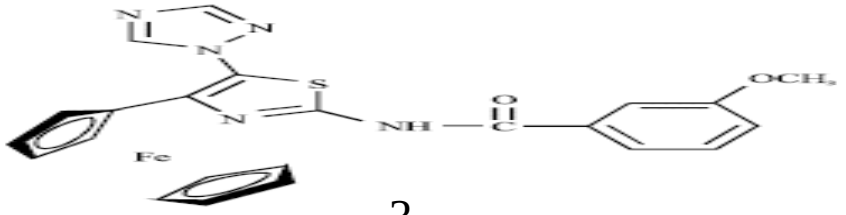

(1)

**Ethyl 2-[3-(diethylamino)-propanamido]-thiazole-4-carboxylate**



(2)

A series of novel ferrocenyl containing thiazole derivatives have been synthesized from 2-amino-4-ferrocenyl-5-(1H-1,2,4-triazole-1-yl)-1,3-thiazole and substituted benzoyl chloride and evaluated for their anticancer activities[17]. Thiazole (3) and (4) showed good inhibition percentages against human cancer cell lines.



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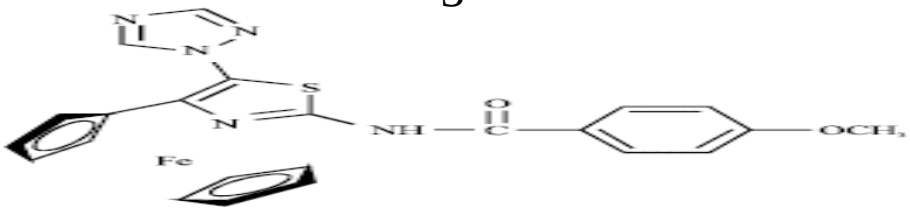

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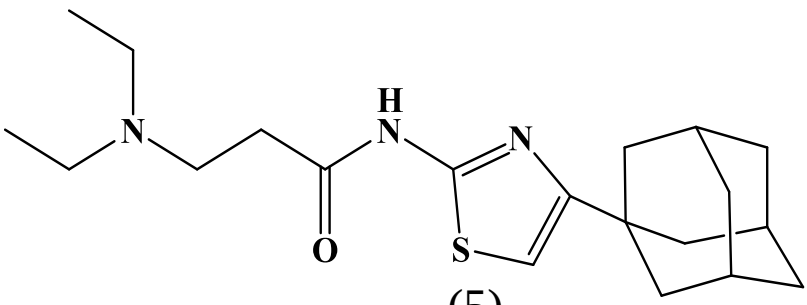
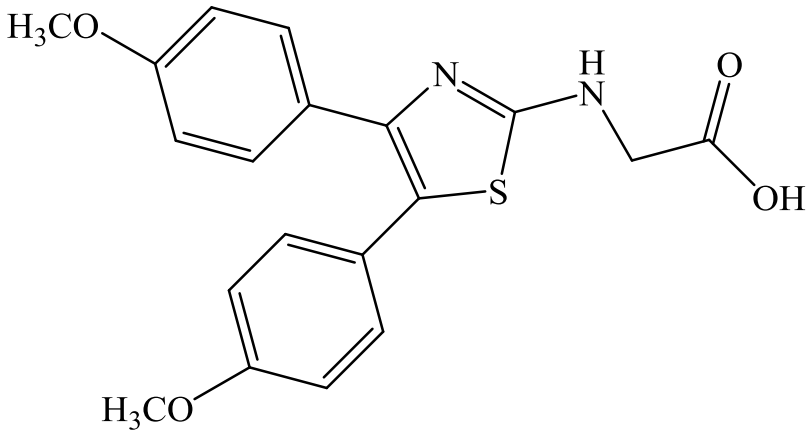
**Anti-inflammatory activity**: A series of adamantane derivatives of thiazolyl-N substituted amides were synthesized and tested for anti-inflammatory activity as well as lipoxygenase and cycloxygenase inhibitory actions. Among the tested compounds, (5) showed potent activity[18].



(5)

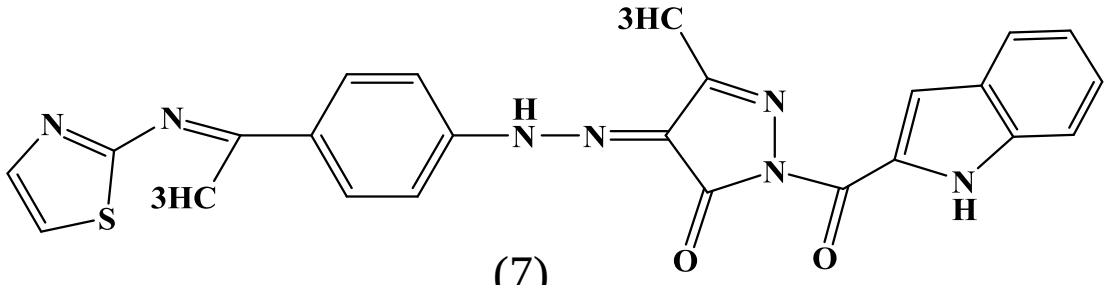
Also Ahmed H. Abdelazeem *et al.*, synthesized the novel compound of thiazole derivative 6. the new compound evaluated *in vitro* for their COXs inhibitory activity and *in vivo* for their anti-inflammatory and analgesic potentials this compound was the most potent compound against COX-1 with an inhibitory half maximal concentration (IC50) of 0.32 μM[19] .




(4,5-bis(4-methoxyphenyl)thiazol-2-yl)glycine

(6)

**Antimicrobial activity**: Six 3-methyl-1-[(5-substituted-1H-indol-2-yl) carbonyl]-4-{[4-(substitutedthiazol-2-yl)iminoethyl)phenyl] hydrazono}-2-pyrazolin-5-one derivatives were synthesized by conventional and microwave methods[20]. The synthesized compounds were tested for their antimicrobial activity against six strains of bacteria and three fungal strains. Compound (7) showed a broad spectrum of activity against bacteria and compound (8) exhibited excellent antifungal activity, while most of the other compounds showed varying antimicrobial activity.

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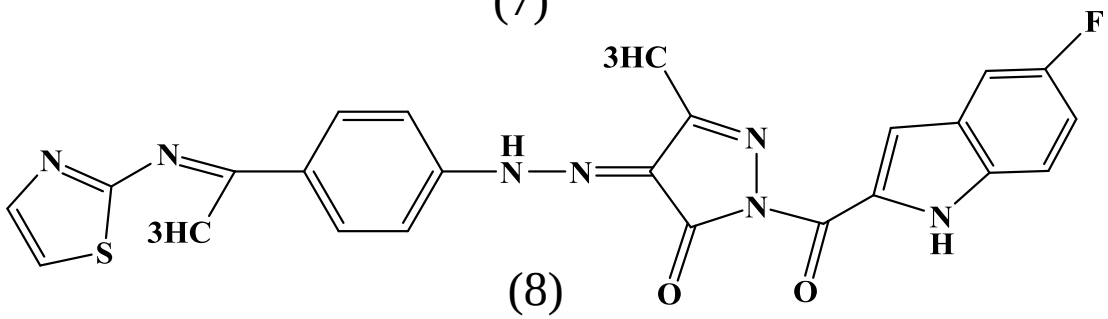
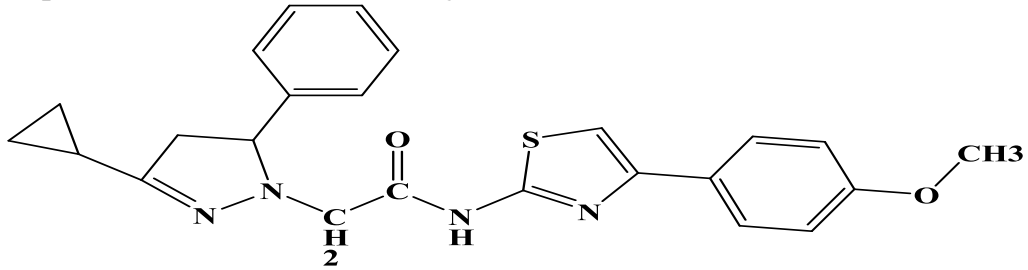



(8)

A series of thiazoles were synthesized by incorporation of pyrazoline ring at position 2 of 2-hydrazinyl-N-(4-phenylthiazol-2-yl)acetamide by treating with chalcones[21]. The structures of the novel synthesized compounds were confirmed by IR and $^{1}$H-NMR spectra. The *in vitro* antimicrobial activities of the synthesized compounds were investigated against four pathogenic representative microorganism *Staphylococcus aureus* ATCC6538P, *Pseudomonas aeruginosa* ATCC9027, *Escherichia coli* ATCC8739 and Candida albicans ATCC2091 using Ampicillin, Imipenam and Clotrimazole as standard drugs. The compounds 9, 10 and 11 showed a moderate degree of potent antimicrobial activity.

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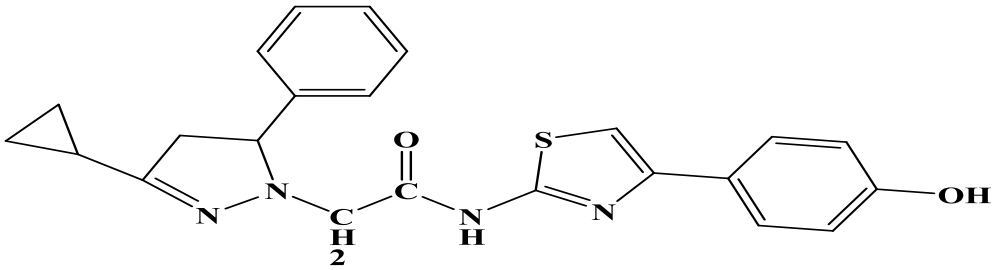


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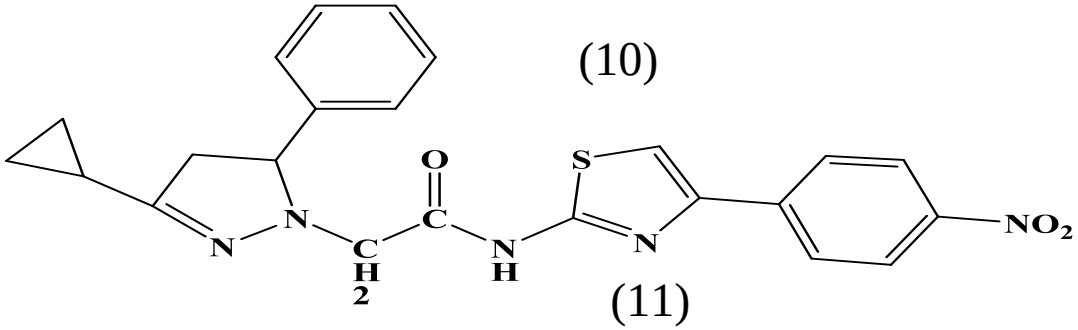
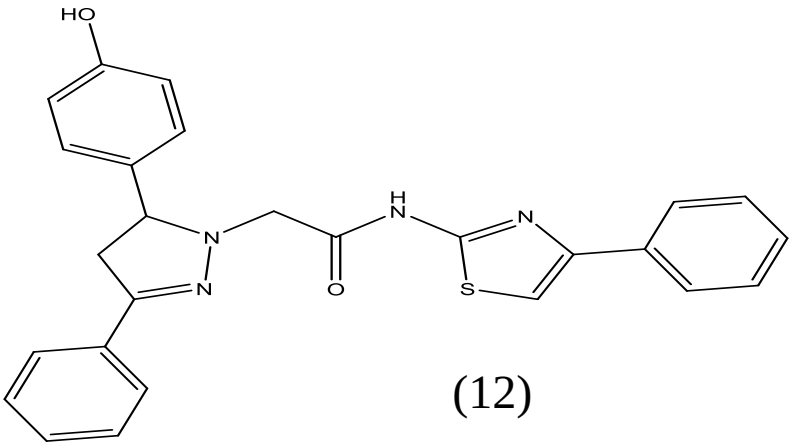



(11)

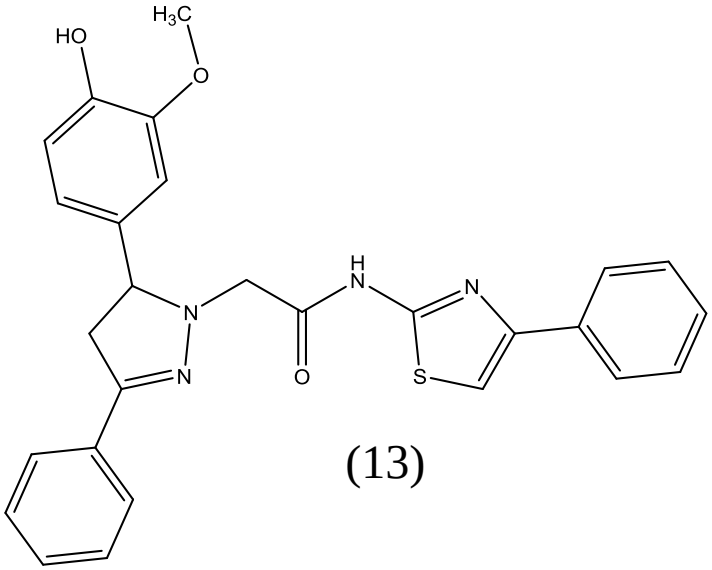
Also exhibited antimicrobial activity against *Staphylococcus aureus* and *Bacillus cereus*.

**Antifungal activity**: Novel thiazoles have been synthesized by incorporation of pyrazole moiety at 2nd position of 2-hydrazinyl-N-(4-phenylthiazol-2-yl) acetamide by treating with chalcones[22]. The chemical structures of the synthesized compounds were confirmed by means of IR, $^{1}$H-NMR, Mass spectral and Elemental analysis. These compounds were screened for anti-bacterial (*Staphylococcus aureus* ATCC 9144, *Staphylococcus epidermidis* ATCC 155, *Micrococcus luteus* ATCC 4698, *Bacillus cereus* ATCC 11778, *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 2853 and *Klebsiella pneumoniae* ATCC 11298)) and anti-fungal (*Aspergillus niger* ATCC 9029 and *Aspergillus fumigatus* ATCC 46645) activities by paper disc diffusion technique. Most of the synthesized compounds exhibited significant anti-bacterial and anti-fungal activities. Among the synthesized compounds, 2-(5-(4-hydroxyphenyl)-3-phenyl-4,5-dihydropyrazol-1-yl)-N-(4-phenylthiazol-2 yl) acetamide 10 was found to exhibit the highest anti-bacterial activity and 2-(5-(4-hydroxy-3-methoxyphenyl)-3-phenyl-4,5-dihydropyrazol-1-yl)-N-(4-phenylthiazol-2-yl)acetamide 32 exhibited highest anti-fungal activity.




(12)

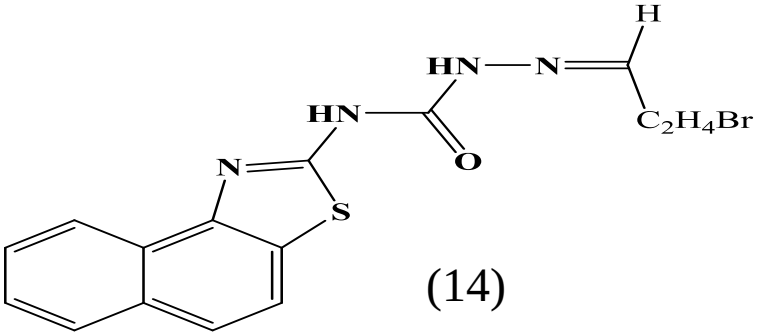
2-(5-(4-hydroxyphenyl)-3-phenyl-4,5-dihydropyrazol-1-yl)-N-(4-phenylthiazol-2 yl) acetamide




(13)

2-(5-(4-hydroxy-3-methoxyphenyl)-3-phenyl-4,5-dihydropyrazol-1-yl)-N-(4-phenylthiazol-2-yl)acetamide

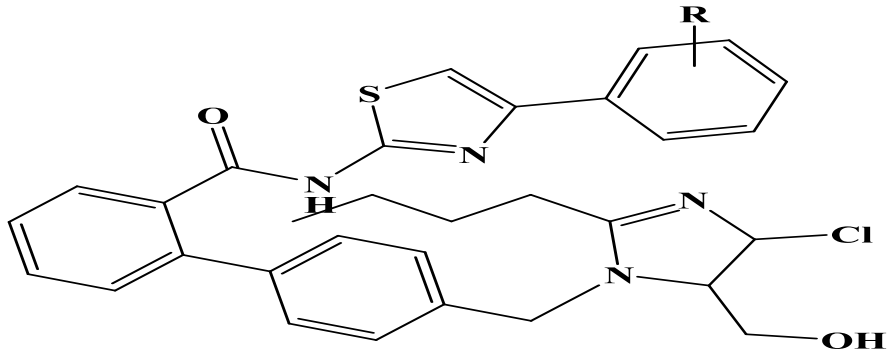
**Anticonvulsant activity**: Azam *et al*. designed and synthesized a series of $N^4$-(naphtha[1,2-d]thiazol-2-yl)semicarbazides 14 and evaluated for their anticonvulsant and neurotoxicity studies[23].




(14)

**2-(3-bromopropylidene)-*N*-(naphtho[1,2-*d*]thiazol-2-yl)hydrazine-1-carboxamide**

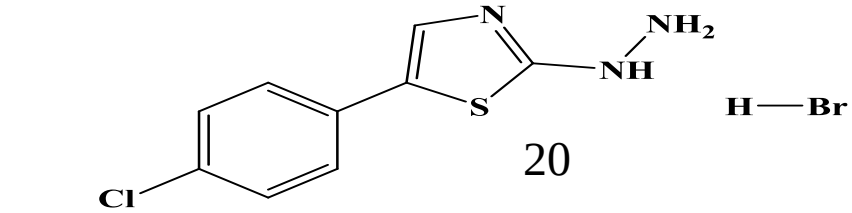
**Antibacterial activity**: A series of 4'-(2-n-Butyl-4-chloro-5-hydroxymethyl-imidazol-1-yl-methyl-biphenyl-2-caboxylic acid- (4-phenyl/ substituted phenyl thiazole)-amide have been prepared. Compounds were screened for their *in vitro* antibacterial activity against *S. aureus* and *B. subtilis* employing cup-plate method at the concentration of 100 μg $mL^{-1}$ in nutrient agar media and also for *in vitro* antifungal activity against *C. albicans* and *A. niger* by cup plate method at 100 μg $mL^{-1}$ concentration using sabouraud dextrose agar[24]. DMSO was used as solvent control for antimicrobial activity. Streptomycin and Griesuofulin were used as standard for antibacterial and antifungal activities, respectively. The structures of aminothiazole derivatives were confirmed on the basis of spectral data. The newly synthesized title compounds were screened for their *in vitro* antibacterial activity. Maximum antibacterial activity was observed in the compounds 15, 16, 17, 18 and 19. Fungicidal screening data also revealed that compounds 16, 18 and 19 showed maximum activity.




R=Cl,15
F,16
P-$OCH_3$,17
2,4 (OCH3)2 ,18
2,4(OC2H5)2, 19

The synthesis of 1-(5-(4-chlorophenyl)thiazol-2-yl)hydrazine hydrobromide 20 was carried out in a single step by condensation of 2-bromo-1-(4-chlorophenyl) ethanone with thiosemicarbazide in absolute ethanol[25]. The structure of the target compound was deduced by modern spectroscopic techniques including FTIR, $^{1}H$ and $^{13}C$ NMR spectroscopy and unequivocally confirmed by crystallographic data. The title compound has been screened for *in vitro* antibacterial screening by agar well diffusion method against ten different Gram positive and Gram

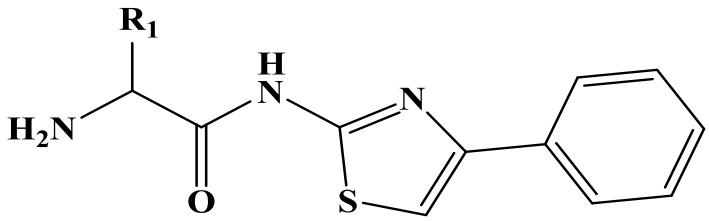
negative bacteria and it exhibited strong efficacy against *B. subtilis* and *S. aureus*, respectively as compared to standard drug Levofloxacin.




20

**1-(5-(4-chlorophenyl)thiazol-2-yl)hydrazine hydrobromide**

**Antihelmintic and insecticidal activity**: Himaja *et al*.[41] synthesized a series of substituted thiazole containing N-methylated amino acids and peptides 21 and 22 by solution phase technique and subjected them to evaluation of antihelmintic and insecticidal activity[26]. Antihelmintic activities were carried out against earthworms (*Eudrilus eugeniea*) by Garg's method[25]. Insecticidal activitiy studies of the synthesized compounds were carried out against termites (*Coptotermis formasanus*) by Morita *et al*. method[26].

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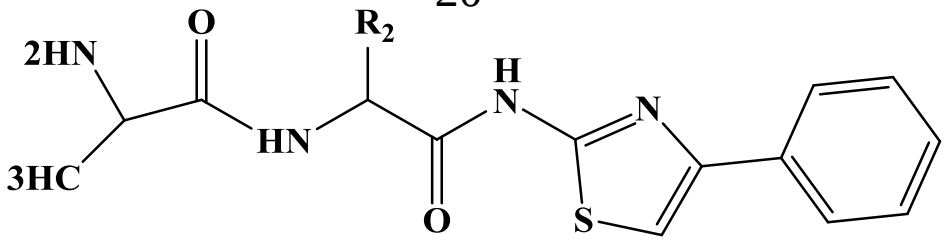


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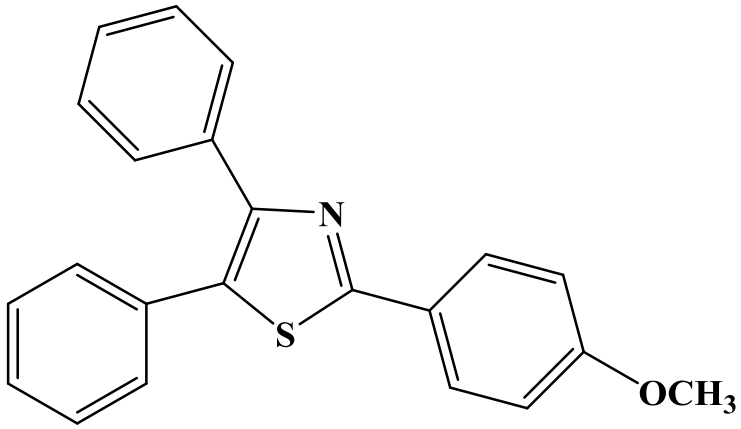
Also synthesized the novel compound of thiazole derivative 22. The anthelmintic activity of compounds was tested by utilizing the piperazine citrate as standard and showed a good anthelmintic activity [27]




**2-(4-methoxyphenyl)-4,5-diphenylthiazole**

**22**

# Conclusion:

The present review showed that thiazole derivatives important an interesting class of compounds possessing a wide spectrum of biological activities and therapeutic potency. On the basis of various literature survey thiazole derivatives exhibit a variety of activity against antimicrobial, anti-inflammatory, analgesic, antitubercular, anticancer etc.

# References:


1- Eicher, T.; Hauptmann, S. (2003). *The Chemistry of Heterocycles: Structure, Reactions, Syntheses, and Applications*. ISBN 978-3-527-30720-3.

2- Siddiqui, N., Arshad, M. F., Ahsan, W., & Alam, M. S. (2009). Thiazoles: a valuable insight into the recent advances and biological activities. *Int J Pharm Sci Drug Res*, *1*(3), 136-143.

3- Quiroga, J., Hernández, P., Insuasty, B., Abonía, R., Cobo, J., Sánchez, A., ... & Low, J. N. (2002). Control of the reaction between 2-aminobenzothiazoles and Mannich bases. Synthesis of pyrido [2, 1-b][1, 3] benzothiazoles versus [1, 3] benzothiazolo [2, 3-b] quinazolines. *Journal of the Chemical Society, Perkin Transactions 1*, (4), 555-559..

4- Hutchinson, I., Jennings, S. A., Vishnuvajjala, B. R., Westwell, A. D., & Stevens, M. F. (2002). Antitumor benzothiazoles. 16. Synthesis and pharmaceutical properties of antitumor 2-(4-aminophenyl) benzothiazole amino acid prodrugs. *Journal of Medicinal Chemistry*, *45*(3), 744-747..

5- Hargrave KD, Hess FK, Oliver JT. N-(4-Substituted-thiazolyl)oxamic acid Derivatives, New Series of Potent, Orally Active Antiallergy Agents. J Med Chem. 1983; 26:1158-1163.
6- Hargrave, K. D., Hess, F. K., & Oliver, J. T. (1983). N-(4-Substituted-thiazolyl) oxamic acid derivatives, new series of potent, orally active antiallergy agents. *Journal of medicinal chemistry*, *26*(8), 1158-1163..
7- Sharma, R. N., Xavier, F. P., Vasu, K. K., Chaturvedi, S. C., & Pancholi, S. S. (2009). Synthesis of 4-benzyl-1, 3-thiazole derivatives as potential anti-inflammatory agents: an analogue-based drug design approach. *Journal of enzyme inhibition and medicinal chemistry*, *24*(3), 890-897..
8- Jaen, J. C., Wise, L. D., Caprathe, B. W., Tecle, H., Bergmeier, S., Humblet, C. C., ... & Pugsley, T. A. (1990). 4-(1, 2, 5, 6-Tetrahydro-1-alkyl-3-pyridinyl)-2-thiazolamines: A novel class of compounds with central dopamine agonist properties. *Journal of medicinal chemistry*, *33*(1), 311-317..
9- Tsuji, K., & Ishikawa, H. (1994). Synthesis and anti-pseudomonal activity of new 2-isocephems with a dihydroxypyridone moiety at C-7. *Bioorganic & Medicinal Chemistry Letters*, *4*(13), 1601-1606.
10- Bell, F. W., Cantrell, A. S., Hoegberg, M., Jaskunas, S. R., Johansson, N. G., Jordan, C. L., ... & Morin Jr, J. M. (1995). Phenethylthiazolethiourea (PETT) compounds, a new class of HIV-1 reverse transcriptase inhibitors. 1. Synthesis and basic structure-activity relationship studies of PETT analogs. *Journal of medicinal chemistry*, *38*(25), 4929-4936.
11- Ergenc N, Capan G, Gunay NS, Ozkirimli S, Gungor M, Ozbey S, Kendi E. Synthesis and Hypnotic Activity of New 4-Thiazolidinone and 2-Thioxo- 4,5-Imidazolidinedione Derivatives. Arch Pharm Pharm Med Chem. 1999; 332:343-347.
12- Carter, J. S., Kramer, S., Talley, J. J., Penning, T., Collins, P., Graneto, M. J., ... & Zweifel, B. (1999). Synthesis and activity of sulfonamide-substituted 4, 5-diaryl thiazoles as selective cyclooxygenase-2 inhibitors. *Bioorganic & medicinal chemistry letters*, *9*(8), 1171-1174.
13- Badorc, A., Bordes, M. F., de Cointet, P., Savi, P., Bernat, A., Lalé, A., ... & Herbert, J. M. (1997). New orally active non-peptide fibrinogen receptor (GpIIb-IIIa) antagonists: identification of ethyl 3-[N-[4-[4-[amino [(ethoxycarbonyl) imino] methyl] phenyl]-1, 3-thiazol-2-yl]-N-[1-[(ethoxycarbonyl) methyl] piperid-4-yl] amino] propionate (SR 121787) as a potent and long-acting antithrombotic agent. *Journal of medicinal chemistry*, *40*(21), 3393-3401.

14- Rudolph, J., Theis, H., Hanke, R., Endermann, R., Johannsen, L., & Geschke, F. U. (2001). seco-Cyclothialidines: new concise synthesis, inhibitory activity toward bacterial and human DNA topoisomerases, and antibacterial properties. *Journal of medicinal chemistry*, *44*(4), 619-626.

15- El-Subbagh, H. I., Abadi, A. H., & Lehmann, J. (1999). Synthesis and Antitumor Activity of Ethyl 2-Substituted-aminothiazole-4-carboxylate Analogs. *Archiv der Pharmazie: An International Journal Pharmaceutical and Medicinal Chemistry*, *332*(4), 137-142.

16- Altıntop, M. D., Sever, B., Akalın Çiftçi, G., & Özdemir, A. (2018). Design, synthesis, and evaluation of a new series of thiazole-based anticancer agents as potent Akt inhibitors. *Molecules*, *23*(6), 1318.

17- Shao, L., Zhou, X., Hu, Y., Jin, Z., Liu, J., & Fang, J. X. (2006). Synthesis and evaluation of novel ferrocenyl thiazole derivatives as anticancer agents. *Synthesis and Reactivity in Inorganic and Metal-Organic Chemistry*, *36*(4), 325-330.

18- Kouatly, O., Geronikaki, A., Kamoutsis, C., Hadjipavlou-Litina, D., & Eleftheriou, P. (2009). Adamantane derivatives of thiazolyl-N-substituted amide, as possible non-steroidal anti-inflammatory agents. *European journal of medicinal chemistry*, *44*(3), 1198-1204.

19- Abdelazeem, A. H., El-Saadi, M. T., El-Din, A. G. S., Omar, H. A., & El-Moghazy, S. M. (2017). Design, synthesis and analgesic/anti-inflammatory evaluation of novel diarylthiazole and diarylimidazole derivatives towards selective COX-1 inhibitors with better gastric profile. *Bioorganic & medicinal chemistry*, *25*(2), 665-676.

20- Mostafa, M. S., Abd El-Salam, N. M., & Alothman, O. Y. (2013). Synthesis and microbial activity of novel 3-methyl-2-pyrazolin-5-one derivatives. *Journal of Chemistry*, *2013*.

21- Sharshira, E. M., & Hamada, N. M. M. (2012). Synthesis, characterization and antimicrobial activities of some thiazole derivatives. *Am. J. Org. Chem*, *2*(3), 69-73.

22- Saravanan, G., Alagarsamy, V., Pavitra, T. G. V., Kumar, G. C., Savithri, Y., Naresh, L., & Avinash, P. (2010). Synthesis, characterization and anti-microbial activities of novel thiazole derivatives. *International Journal of Pharma and Bio Sciences*, *1*(3).

23- Azam, F., Alkskas, I. A., Khokra, S. L., & Prakash, O. (2009). Synthesis of some novel N4-(naphtha [1, 2-d] thiazol-2-yl)

semicarbazides as potential anticonvulsants. *European journal of medicinal chemistry*, *44*(1), 203-211.

24- Shreenivas, M. T., Swamy, B. K., Srinivasa, G. R., & Sherigara, B. S. (2011). Synthesis and antibacterial evaluation of some novel aminothiazole derivatives. *Pharma Chemica*, *3*, 156-161.

25- Khan, I., Ibrar, A., Waqas, M., & White, J. M. (2013). Synthesis, X-ray crystallographic studies and antibacterial screening of 1-(5-(4-chlorophenyl) thiazol-2-yl) hydrazine hydrobromide. *studies*, *35*, 36.

26- Himaja, M., Gupta, N., Munirajashekhar, D., Karigar, A., & Sikarwar, M. K. (2012). Synthesis and biological evaluation of some N-methylated derivatives of thiazolyl amino acid and peptides. *J. Pharm. Scient. Innovat*, *1*(2), 33-36..

27- Lunkad, A. S., Kothawade, S. N., Darkunde, K. K., Priya, B., Bagmar, U. R., & Bhandari, D. S. (2013). Synthesis and Screening Antihelminitic Activity of Some Thiazole Derivatives. *Int. J. Chem. Sci*, *11*(2), 1146-1152..