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Synthesis And Medicinal Attributes Of Thiazole Derivatives: A Review

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ABSTRACT

Thiazoles are important five-membered heterocyclic ring due to their broad spectrum of activities. The aim of the study, to summarize the medicinal effects and current approaches adopted for the synthesis of the thiazole and thiazole derivatives using different aspects. The medicinal significance of the thiazoles such as antibiotics, antimicrobials, antineoplastic, anti-inflammatory, diuretics and anti-thyroids. These routes are classified semisynthetic, synthetic or natural products for thiazole derivatives.

Keywords: Thiazoles, antibiotics, antimicrobials, semisynthetic, natural products.

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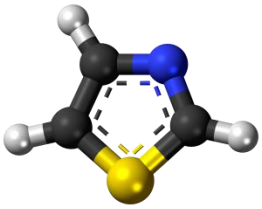
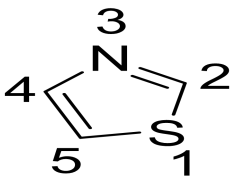
INTRODUCTION

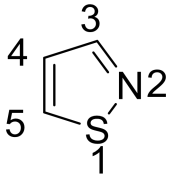
Thiazole (1,3 thiazole), a unique 5-membered heterocyclic ring containing sulphur and nitrogen atoms, occupies an important place in chemistry (Sobhi, et.al., 2016; Alrazzak, 2018). Thiazole and thiazole derivatives are found in many heterocyclic products with a wide range of activities, such as antibiotics (Kumar, et.al., 2017), antimicrobials (Ismail, et.al., 2019), anticancer (Gartel, et.al., 2008), anti-inflammatory (Derek J. Mc, 2018), anticonvulsants (Zeitschrift für K, 2016).

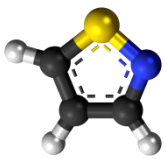




Thiazole (1,3-thiazole) 3-D structure of thiazole

Thiazole chemistry approaches by different methodologies, synthetic (Nour, et.al., 2017), natural plants (Marcus V.& Nora de S., 2005), marines (Sunil K. &Ranjana A., 2019), and different green chemistry, (including use of green solvents, catalysts, solid phase synthesis, microwave irradiation- and ultrasonication-mediated processes) (Shelly P & Ravindra K. R., 2020). The 1,2 thiazole is known as isothiazole.





3-D structure of isothiazole Isothiazole (1,2-thiazole)

The 2- amino thiazole has an important component effect of the
pharmacophores of a large number of broad spectrum of activity (Rodislav V.K.& Vladimir P.,2002).

RESONANCE OF THIAZOLE

The resonance of the subsequent resonating thiazole structures as shown in (Figure 1). The p-bond orders quantified by molecular orbital methods have specified thiazole molecule to be aromatic with some dienic nature (Sammes P.G., 1979).

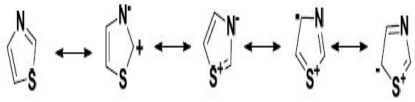
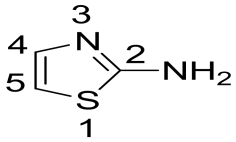


Figure 1: Resonance of Thiazole

In general, Aminothiazoles are well-known for being ligands of estrogen receptors as well as a innovative type of adenosine receptor antagonists (Behzad, Hamid & Hadi, 2015; Alsryfy, et.al (2015)). The 2- aminothiazole (2-Thiazolamine, or Thiazole-2- amine) is the famous chemical compound present in the medicinal chemistry with wide range of biological activities. The resonance of 2-amonothiazole in Figure 2.



3-D structure of 2- aminothiazole 2-Aminothiazole

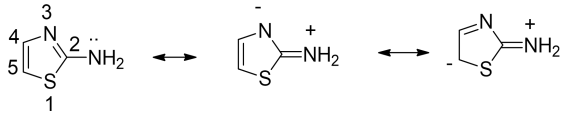


Figure 2: Resonance of 2-Aminothiazole

LITERATURE REVIEW

ANTIOBIOTICS

Thiazole as nucleus or fused ring is an essential part of the natural penicillin drug nucleus known as antibiotic(Kumar., et.al., 2017). These group of antibacterial drugs that attack a wide range of Gram positive bacteria, it was discovered by Alexander Fleming in 1928. The general chemical structure

of penicillin as a model of fused ring thiazole as shown in Figure 3:

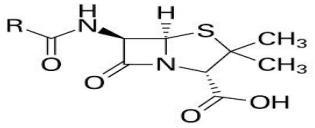


Figure 3: General chemical structure of Penicillin

Recently, 2-aminothiazole was found in many chemical structure of cephalosporin derivatives (e.g. Cefdinir) as shown in Figure 4(Stella., et.al., 2020).

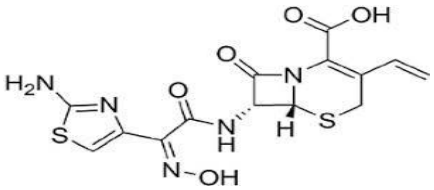


Figure 4: The chemical structure of Cefdinir

Cefdinir is a semisynthetic 3rd generation cephalosporin with a broad spectrum of activity towards Gram (+)ve and Gram(-)ve bacteria. In 2007 a new 2-aminothiazole derivatives as 4th generation cephalosporin were introduced as shown in Figure 5. The activity was showed towards Gram (-)ve more than Gram (+)ve bacteria(Stella., et.al., 2020).

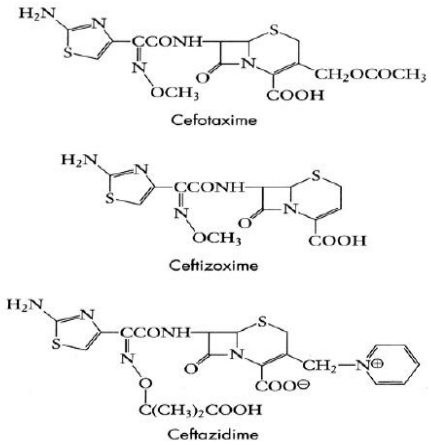


Figure 5. The chemical structures of 4th generation cephalosporin

Finally, the semisynthetic 5th generation of cephalosporin are active against Methicillin resistant *staphylococci auras* (MRSA). The ceftaroline i is a best example for this type and had Gram (-)ve avtivity more than Gram(+)ve bacteria.The N-pyridinium ion is the substituted at 4 position of thiazole ring, the chemical structure as shown in Figure 6 (Stella., et.al., 2020).

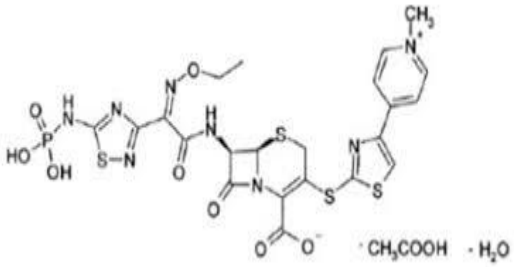


Figure 6. The chemical structure of Ceftaroline fosamil.

ANTIMICROBIAL EFFECTS

Thiazole and 2-aminothiazole derivatives have good antibacterial (Sulfthiazole) and antifungal as well as antiviral activities (Kumar, et.al., 2017). The sulfthiazole is refer to short acting sulfa drug as an antimicrobial agent, the chemical structure in Figure 7. Also, thiazole and

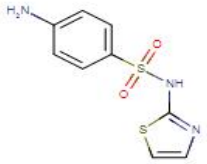


Figure 7. The chemical structure of Sulfthiazole

Its derivatives seems to be good antifungal activity against different types of candidiasis cases are caused by *Candida albicans*, however non-*C. albicans*, such as *Candida glabrata*, *Candid parapeilosis.Canditroppicals and Candida krusei* has recently been found an important of pathogenic group. As regards to the chemical structure of the compounds, the substituents on the phenyl ring are different (Lino.et.al., 2018). According to the antifungal screening results, the most active thiazole derivatives indicated similar antifungal activity to ketoconazole and fluconazole against all *Candida* strains. Several studies have been conducted aiming to synthesize thiazole derivatives with excellent antifungal activities. Also, these derivatives with polyoxygenated phenyl module have exhibited encouraging anti-fungal activity, the abafungia agent as an example for this type of activity as shown in Figure 8. Recently , thiazole and its derivatives were linked with chitosan forming Chitosan-Thiazole nanoparticles, Chitosan-Thiazole[NPs] can be used antimicrobial agent(activities (Kumar, et.al., 2017).

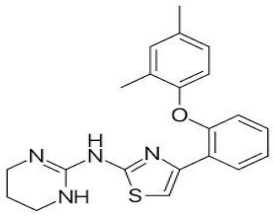


Figure 8. The chemical structure of Abafungia

Furthermore, the thiazole derivatives have been found to be potent as antiviral agent, against different types of viruses such as CVB, SARS, RSV, HCV, HRV, VZV, TMV, FMDV, DENV, YFV, influenza virus [17]. Ritonavir as protease inhibitor enzyme, it can be used to treat HIV/AIDS as an antiretrovirial agent, the chemical structure as shown in Figure 9 (Inder , Shiv & Sanjay, 2020).

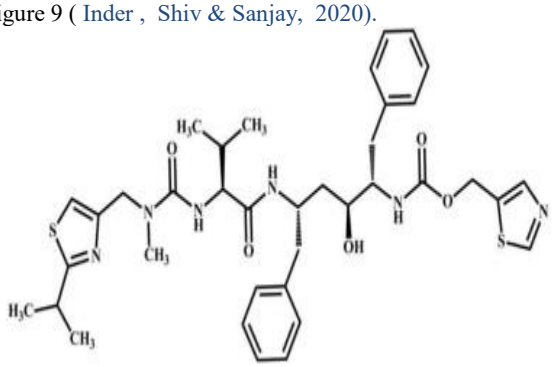


Figure 9. Thee chemical structure of Ritonavir

ANTICANCER AGENTS

There are many natural or synthetic antineoplastic agents. Bleomycin is an antibiotic anticancer agent, can be used for many types of cancers (Gartel., et.al., 2008). Chemically, it is a complex glycopeptide conjugated with bimolecular thiazole rings. On other side, two heterocyclic rings were conjugated pyrimidine and imidazole rings as shown in Figure 10 (Mahesh., et.al., 2016).

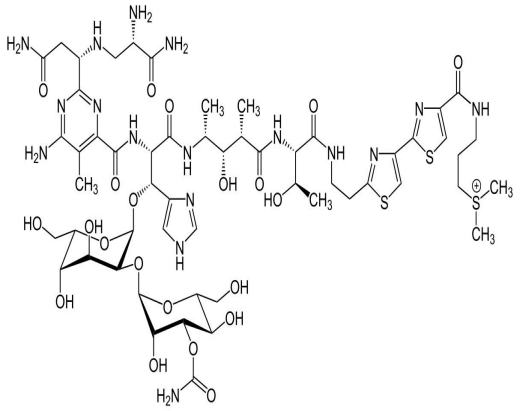


Figure 10. The chemical structure of Bleomycin

The other antibiotic anti-neoplastic drugs. Tiazofurin, Epothilone A , Epothilone B. Now, the importance of the heterocyclic nucleus in drug design and development of new chemical entities with a special emphasis on thiazole nucleus. Different methodologies have been synthesized on the base of thiazole derivatives and are used for the treatment of a wide variety of cancer diseases (Gartel., et.al., 2008).Tiazofurin is 2-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-1,3-thiazole-4-carboxamide, is the synthetic nucleoside analogue and classified as antimetabolite anti-neoplastic agent as shown in Figure 11.

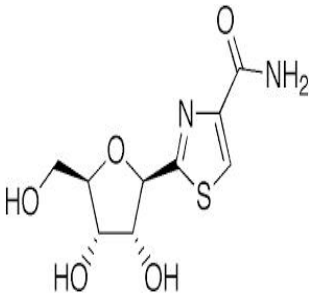


Figure 11. The chemical structure of Tiazofurin

Another example of thiazole derivative bearing anti-cancer agent, Dasatinib, previously known as BMS-354825, the chemical structure in Figure 12.

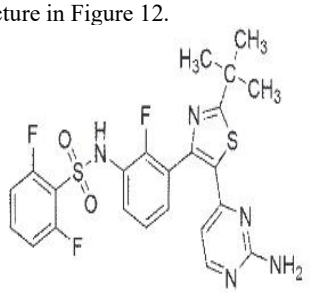
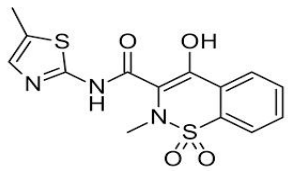


Figure 12. Chemical structure of Dasatinib

ANTI-INFLAMMATORYEFFECTS

In search for new of non -steroidal anti-inflammatory drugs (NSAIDs) (Derek J. Mc., 2018) the cyclooxyengenase (II) (COX-II) as a common drug used for treat the symptoms of arthritis, Meloxicam as a model for thiazole derivatives used to treat pain , inflammation in rheumatic and osteoarthritis diseases, the chemical structure of

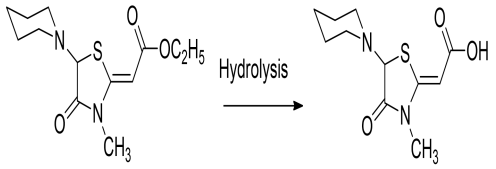


meloxicam as shown in Figure 13 (Derek J. Mc., 2018).

Figure 13. The chemical structure of Meloxicam.

DIURETIC EFFECTS

Etozolin is a prodrug of Qzolinone as new direct drug, the (L) isomer is the active chemical form and not the (D) isomer, the ozolinone is a tautomeric form thiazolidine(Kumar, 2017). The metabolism via enzymatic hydrolysis via phase (I) metabolism as shown in the equation:

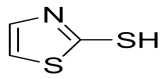


Etozolin

Ozolinone
L- isomer (active)
D-siomer (Inactive)

ANTI-THYROID EFFECTS

Previous study, 2-Metcaptothiazole was prepared by Searle, Lawson and Morley as anti-thyroid activity as thiazole derivative (Mahesh., et.al., 2016).



2-Mercaptothiazole

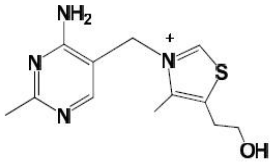
THIAZOLE NATURAL PRODUCTS IN BOTH ALKALOIDS & MARINS.

Natural products containing thiazole derivatives occur in plants and marines, because animal cant synthesis thiazole or thiazole derivatives(Shelly & Ravindra, 2020).

Thiazole derivatives in the plant kingdom are secondary metabolite products, their biological effects including, vitamins, chlorophyll & alkaloids.

VITAMIN

The famous thiazole derivative is a Thiamine as vitamin B1, and play an essential cofactor role in several metabolic pathways (Kumar, 2017).



Thiamine

ANTIFUNGAL EFFECTS

Thiazole derivatives have attracted the interest of pharmaceutical and agrochemical anti-fungal research since the development of fungicide Oxathiapiprolin was developed by DuPont in 2007 as a piperidinyl thiazole isoxazoline fungicide targeting at oxysterol binding protein (PcORP1) against *Peronospora belbahrii*, *Phytophthora parasitica* var. *Nicotianae*, the chemical structure of Oxathiapiprolin in Figure 14 (Beuchet., et.al, 1999).

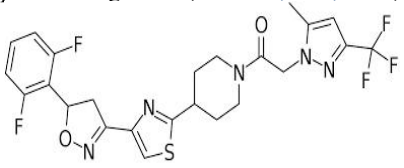


Figure 14. The chemical structure of Oxathiapiprolin.

CYTOTOXIC EFFECTS

An example of a natural compound in which both indole and thiazole rings are linked is 3-thiazol-2-yl-indole known as Camalexin (Böttcher., et.al., 2014), a phytoalexin produced in different plant leaves, the chemical structure of the natural product Camalexin in Figure 15.

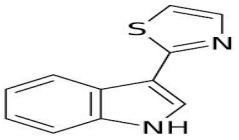
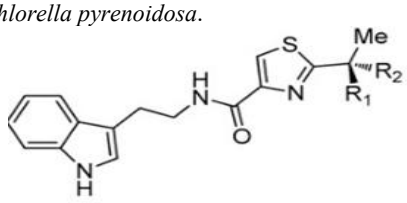


Figure 15. The chemical structure of Camalexin.

ANTIBIOTIC EFFECTS

New antibiotic was extracted and isolated from a marine (marine natural product) *Bacillus endophyticus* from toxic algal bloom. Chemically, it is 3- substituted indole derivative(Böttcher et.al., 2014). It has a powerful algicidal effect against different types of red tide algae *Skeletonema costatum* and *Gymnodinium catenatum*, and three freshwater harmful algae *Mycrocycti aeruginosa*, *Scenedesmus obliquus*, and *Chlorella pyrenoidosa*.



Bacillamide A, R_1, R_2 = O
Bacillamide B, R_1 = H, R_2 = OH
Bacillamide C, R_1 = H, R_2 = NHAc
Alkaloid (**1**), R_1 = H, R_2 = NH_2

SCOPE OF THE SYNTHETIC ASPECTS OF THIAZOLE DERIVATIVES

The heterocyclic chemistry of the thiazole and thiazole derivatives have been developed via different routes. Hofmann (Hoffman A.B 1879& 1980), and Hantzsch & Coworkers(Hantzsch, Weber & Ueber, 2014) were started in the synthesis of thiazoles. In the present review, we describes the main pathways. Two main routes of synthetic thiazole, addition reaction or cyclization reaction using different catalysts and techniques.

THE ADDITION REACTION ARE REPORTED VIA MANY DIFFERENT PATHWAYS

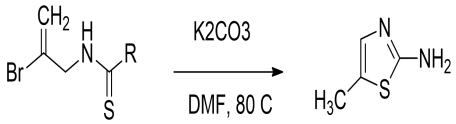
1) 1,3 (N-C-S) was added to 1,2 (C- C), this reaction known as Hantzsch method(Hantzsch, Weber & Ueber, 2014) .
2)1,3 (N-C-C) was added to 1,2 (S-C), this reaction known as Cook & Heilborn method (Cook, Heilbron & Stern, 1948).
3) 1,3 (C-C-S) was added to 1,2 (N-C), this condensation reaction known as Erlenmeyer method (Erlenmeyer, Baumann& Sorkin,1948).4) 1,2 (C-C), 1,2 (N-C) was added to sulphur, this condensation reaction known as Erlenmeyer method (Erlenmeyer, Baumann& Sorkin,1948).5) 1,4 (C-N-C-S) was added to carbon, this condensation reaction known as Hartke & Seib (Hartke, 1970).6) 1,4 (C-S-C-C) was added to nitrogen, this condensation reaction known as Kilkelj & Urleb (Kilkelj, & Urleb, 2002).Finally, the cyclization reaction 1,5 (N-C-C-S-C), this reaction known as Gabriel method (Robinson, R., 1909).

SYNTHETIC PATHWAYS OF SOME THIAZOLE DERIVATIVES.

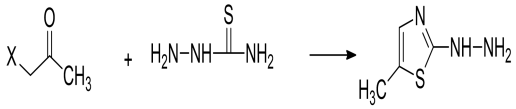
2-Aminothiazole derivatives (Shelly P& Ravindra K. R., 2020).

THERE ARE MANY SYNTHETIC METHODS USED FOR PREPARING 2-AMINOTHIAZOLE

A) 2- Aminothiazole from acetophenone and thiourea as shown:
B) 2-Aminothiazole from chloroacetaldehyde with thiourea as shown:
C) 2-Aminothiazole from bromoacetophenone with thiourea as shown:
D) 2-Aminothiazole from propargyl bromide with thiourea as shown:
E) 2-Aminothiazole from *N*-(2-bromoprop-2-enyl)thioamides via intramolecular nucleophilic substitution reaction as shown:

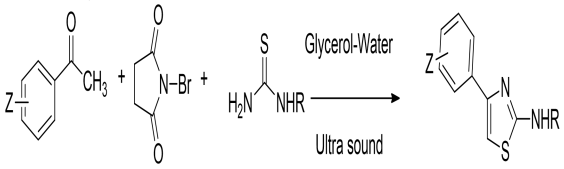


F) 2-Aminothiazole from α-halo acetone with thiosemicarbazide as shown:

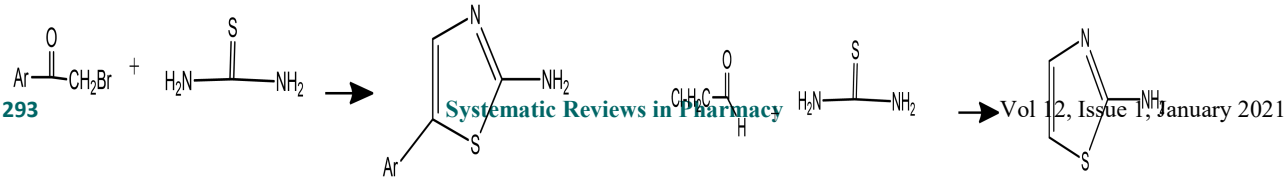


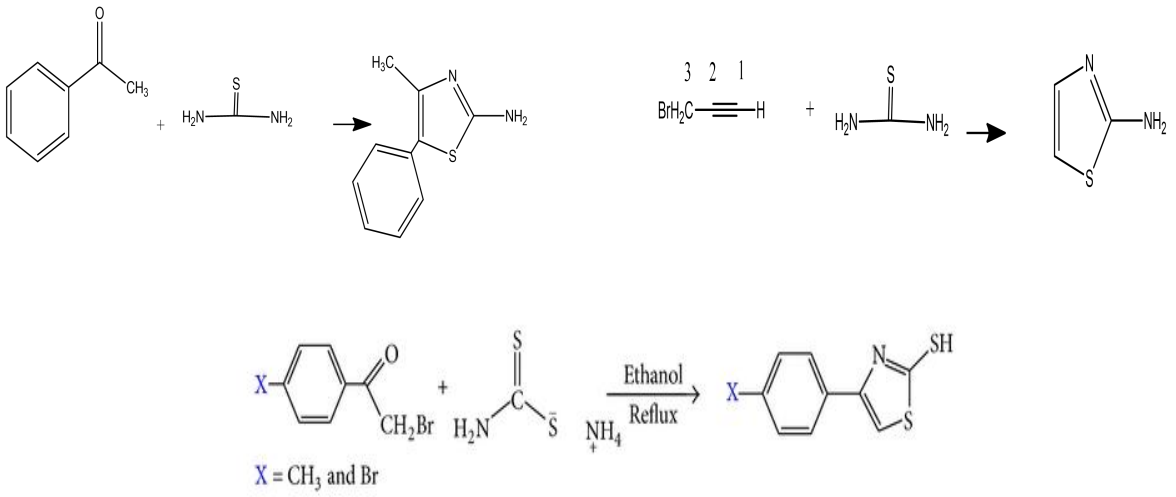
alpha-haloacetone hydrazinecarbothioamide 2-hydrazinyl-5-methylthiazole

J) 2-Aminothiazole from acetophenone, N-bromosuccinimide and thiourea in glycerin-water at room temperature (Green Reaction)



2- Mercaptothiazole derivatives (Shelly P. & Ravindra K. R.,2020).
This reaction was takes place from condensation of bromoacetophenone derivatives with ammonium dithiocarbamate in ethanol to five the corresponding 2-mercaptothiazole derivatives. Other thizole derivatives or fused heterocyclic rings are less common medicinally.





CONCLUSION

This review covers some of the literatures of the triazole derivatives in the field of organic medicinal chemistry. These five-membered ring heterocyclic compounds which possess diverse biological activities and play an important roles.

ACKNOWLEDGMENTS

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