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THIAZOLE AND ITS DERIVATIVES: MEDICINAL IMPORTANCE AND VARIOUS ROUTES OF SYNTHESIS

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ABSTRACT:

In medicinal research area the search for new antibacterials is always an objective of many researchers. But the major problem associated with it is that antibacterials sometime cause side effects and resistance also develops to them in course of time. So it is need of time that there should be continuous research for antibacterials as well as drugs of other properties too. Thiazole and its derivatives are the category of heterocyclic compounds showing various biological activities. The purpose of this review paper is to orient the researchers for the design and synthesis of some new compounds containing thiazole core and developing more efficient and safer drugs. Many efforts are done for synthesising compounds containing thiazole core having enhanced biological activities and synthesising them in high yield to make medicinal studies and clinical uses. Molecules containing the thiazole core possess wide range of biological properties like anti-cancer, anti-inflammatory anti-bacterial , Diuretic activity, antithelmintic etc. This review briefs the pharmacological importance and various synthetic routes regarding the synthesis of thiazoles and their derivatives.

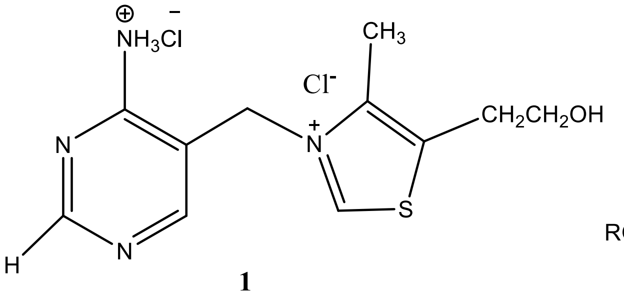
Keywords: ***Thiazole, anti-inflammatory, antibacterial, anti-cancer, antithelmintic.***

INTRODUCTION:

Although a wide range of compounds are already synthesised that are commercially available as medicines, but still there is a regular need to synthesize new compounds of pharmacological importance, as drug resistance is consistently increasing. Out of the long list of already existing biologically active compounds, heterocyclic compounds having nitrogen, oxygen or sulphur had received a great attention of scientists working with organic synthesis.

Thiazole and its derivatives are the category of heterocyclic compounds showing various biological activities. Some thiazole derivatives have been found to show multi-therapeutic effect including anti-cancer, anti-inflammatory and inhibition of the parasites like Leishmania and the fungi such as Candida [1-4]. Moreover, the anti-bacterial effects of these compounds have been proven on a wide range of pathogens like Bacillus subtilis, Staphylococcus aureus, Pseudomonas aeruginosa, and Klebsiella aerogenes so that their potency and broad spectrum activity have promised the researchers to replace them with outdated drugs to which the bacteria are resisting [5].

Diuretic activity has been reported in a number of thiazole derivatives [6-13]. Thiazole ring forms an integral ingredient of vitamin B1,(Thiamine hydrochloride) **1** [8]. Penicillins **2**, a well known antibiotics that contains reduced thiazole ring [9]. A large number of drugs contain thiazole ring e.g. sulphathiazole **3** [10]. 2-(4’-chlorophenyl)-4-thiazoleacetic acid **4** possesses anti-inflammatory activity [11,12]. Thiabendazole **5** [13], a potent antithelmintic drug, is also a thiazole derivative.



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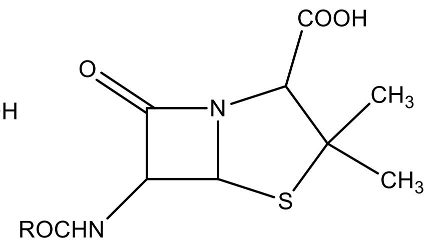

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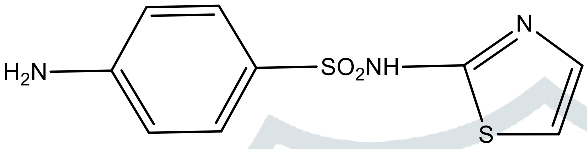

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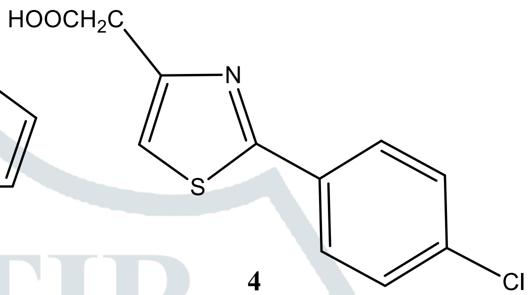

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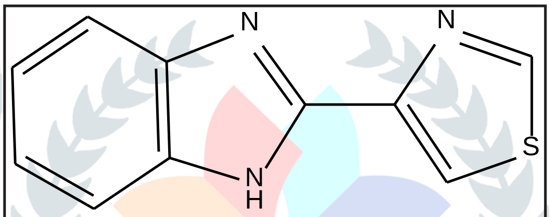

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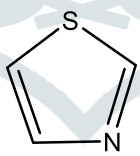
Thiazole also known as 1,3-thiazole, is a heterocyclic five membered ring having both nitrogen and sulphur atoms **6**. The term 'thiazole' is also used for a large family of its derivatives. Thiazole is a pale yellow liquid with a Pyridine like odour and its molecular formula is C_3H_3NS.



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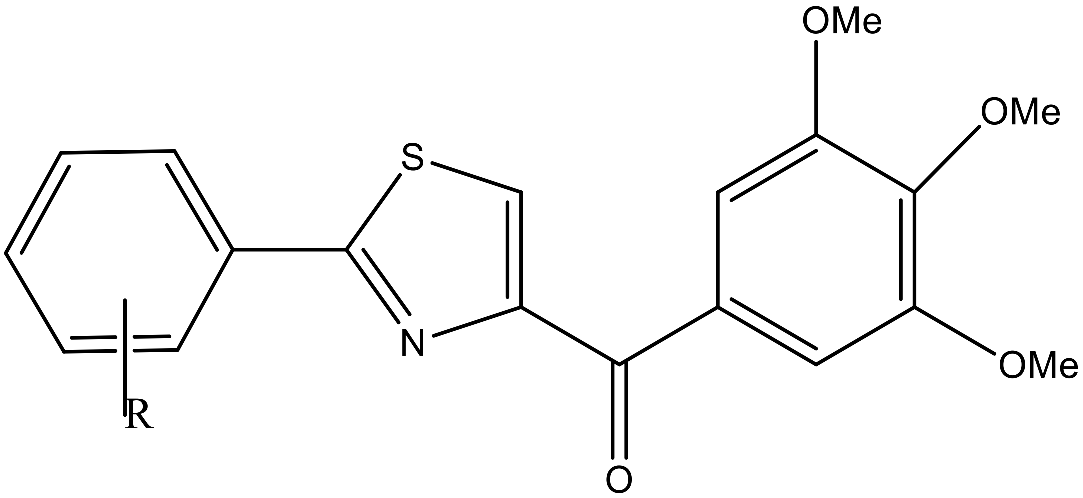
The shape, size, conformation and configuration of thiazole is nearly an average of thiophene and 1,2,3 triazole. The mass spectra of thiazole show high intensity of molecular ion, showing aromatic character of ring.

The thermodynamic study of thiazole shows its self association tendency in liquid state. At room temperature thiazole is completely soluble in water. Thiazole is found to be miscible with most of the organic solvents. Many physicochemical properties of thiazole shows the aromatic character of heterocyclic ring. The chemical properties of thiazole are similar to that of pyridine as well as thiophene. Thiamine (Vitamin B1) is the most important thiazole derivative that was found naturally occurring. Enzymatic decarboxylation of pyruvate into acetaldehyde is done in the presence of coenzyme thiamine pyrophosphate. Penicillin is one more naturally found thiazolidine derivative that is produced from cultures of mutant strains of Penicillium chrysogenom.

Thiazole ring is found as a common structural unit in various molecules of biological activity [14]. Various 1,3-thiazole derivatives were found to behave as anticancer agents. For example, 1,3-thiazole derivative structures **7** and **8** [15, 16] showed considerable anticancer activity against many cancer types [17].



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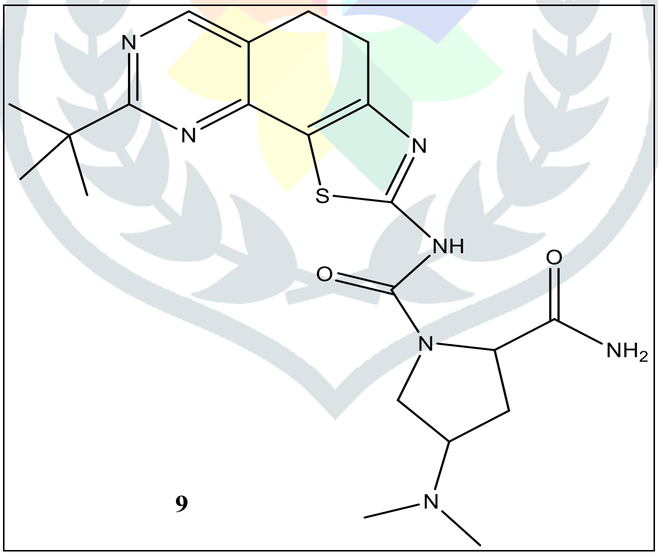
Various derivatives of thiozole having 2-carboxamide pyrrolidine urea skeleton for example, **9** and **10** were noticed by Novartis in 2011 [18] and 2012 [19]. These compounds were possessing noticeable pharmacological properties like these compounds were suitable for treating proliferative diseases like tumors and leukaemias. While studying new thiazole derivatives, Gloxo , Smithkline in 2012 [20] reported indazole based compounds for example, **11**. Activity of these compounds were studied and these were found very useful in treating disorders of respiratory system (like asthma, chronic obstructive pulmonary disease (COPD), diseases related to allergies (atopic dermatitis, allergic rhinitis), autoimmune diseases (multiple sclerosis, rheumatoid arthritis), Cardiovascular problems (thrombosis and atherosclerosis) Cystic fibrosis, Inflammatory problems, Kidney disorders, Pain related to Osteoarthritis, back pain, Cancer, Sperm motility, transplantation rejection etc.



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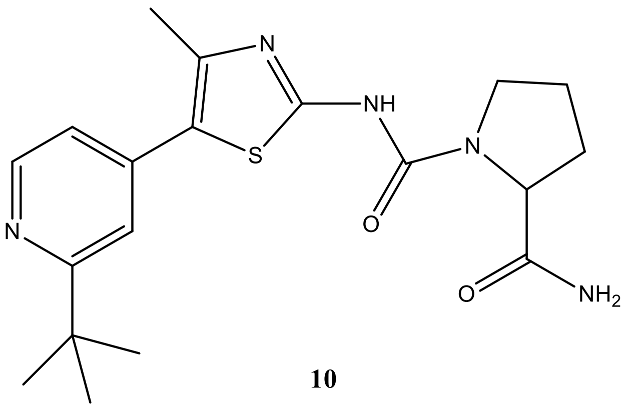

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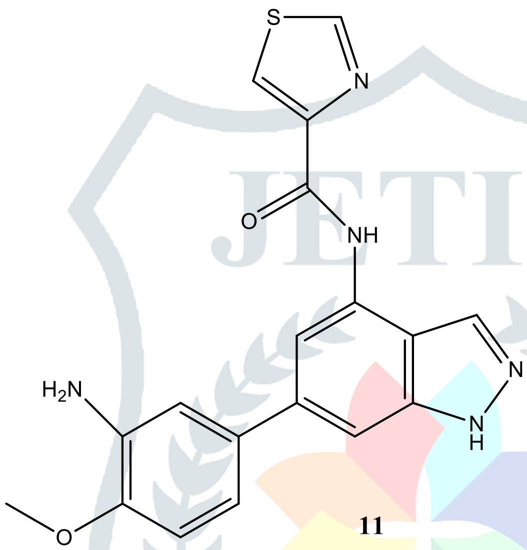

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In addition to this thiazolidin-4-ones were also reported to show various biological activities [21], like anticancer [22-25], anticonvulsant [26, 27], anti-inflammatory [28, 29], and anti-tubercular activities [30, 31].

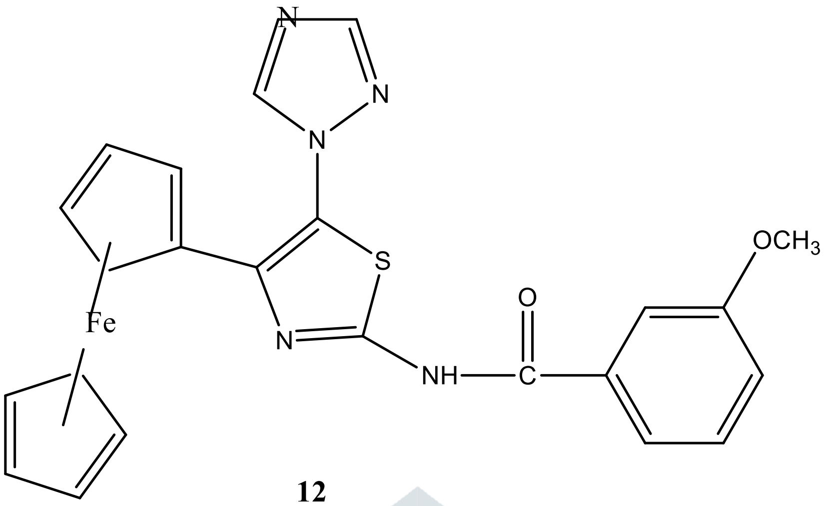
A large variety of naturally found flavones and various aroma of foods also contain the thiazole nucleus [32]. The thiazole nucleus has high thermal stability. This property induced for synthesizing polymers having this structure with good thermal stability [33]. Regarding medicinal uses also, thiazole moiety or its derivatives has got much consideration [34-36].

The preparation and medicinal uses of a new group of diaminothiazoles were described by Goff et al. [37] in 2008. These thiazole derivatives were useful in inhibiting the activity of Ax1, a receptor protein kinase. AX1 is a receptor-linked kinase (RTK) that was reported in various variety of solid tumors. Various thiazole derivatives were found to be RTK inhibitors that were useful against cancer and used for treatment of psoriasis, alzheimer's disease, rheumatoid arthritis. The preparation of such thiazole derivatives was patented by Marinier et al. [38].

The synthesis of thiazole kinase inhibitors and their use in treating cancer was also described in many patents by Adjabeng et al. [39].

Thiazole molecules were found to be present in various pharmacologically active molecules like ritonavir (antiretroviral drug), sulfathiazole (antimicrobial drug), abafungin (antifungal drug) available with name abasol cream and tiazofurin (antineoplastic drug) [40]. Thiazole systems were used in development of many drugs used for treatment of inflammation [41], hypnotics [42], allergies [43], hypertension [44], HIV infections [45], schizophrenia [46], treatment of pain [47], as inhibitor for bacterial DNA gyrase B [48] and as fibrinogen receptor antagonists with antithrombotic activity [49].

Anticancer activities of a series of ferrocenyl substituted thiazole derivatives were analysed [50]. Compound **12** and **13** showed inhibition against human cancer cell lines.



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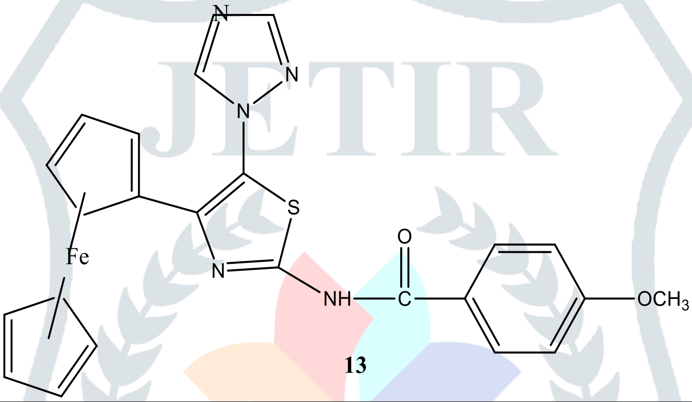

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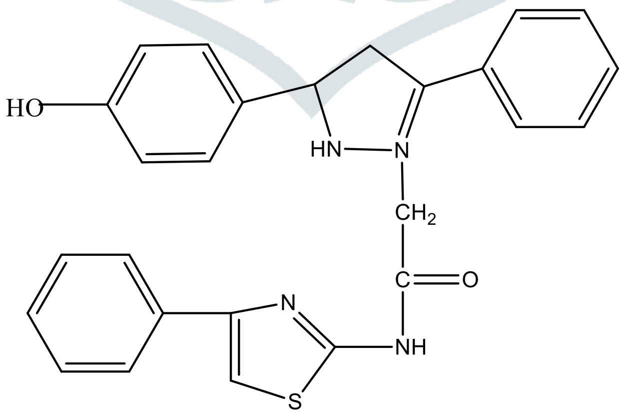
Few novel thiazole were reported to be synthesized by incorporating pyrazole system at 2nd position of 2- hydrazinyl-N-(4-phenylthiazol-2-yl) acetamide by reacting it with chalcones [51]. These compounds were then tested for their antibacterial activity against Staphylococcus aureus, Bacillus cereus, Staphylococcus epidermidis, E. colli and also for their antifungal activities. These compounds showed considerable antibacterial and antifungal activities. Compound **14** showed highest antibacterial activity and compound **15** showed highest antifungal activity.



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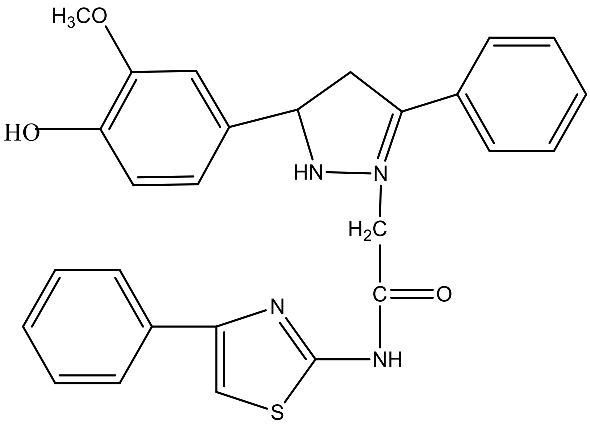

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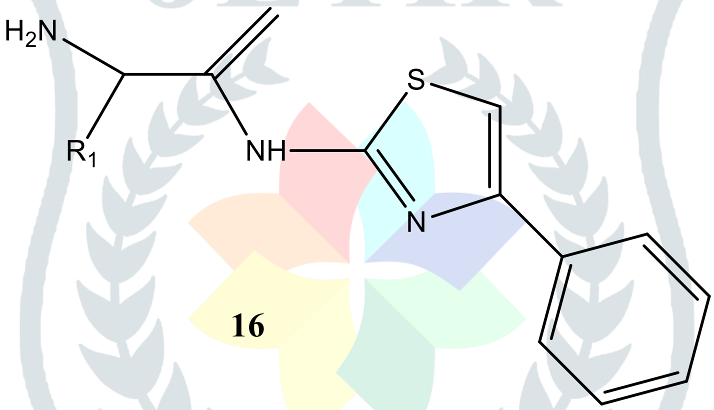
A series of N-methylated amino acids **16** and peptides **17** having substituted thiazole moiety were synthesised by Himaja et al. [52]. These compounds were analysed for insecticidal and antihelmintic activity [52]. Garg's method was used for antihelmintic activity studies against earthworms [53]. Morita et al. method [54] was performed for insecticidal activities that were done against termites.



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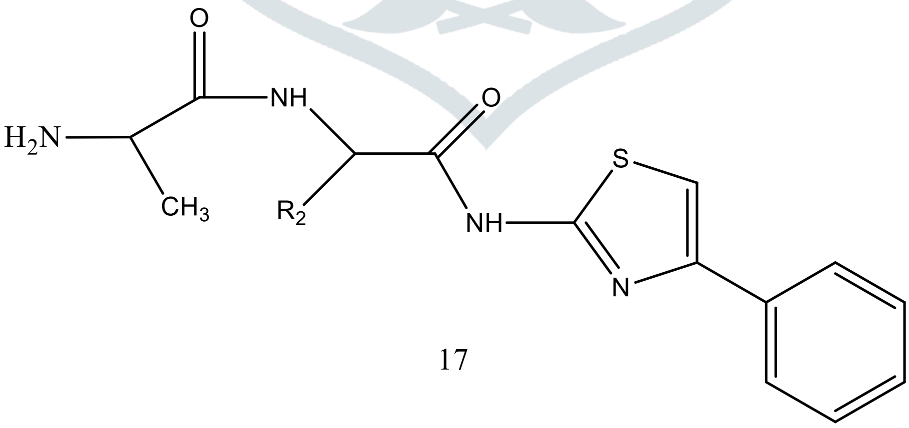

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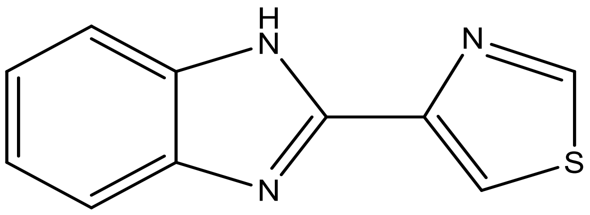
Thiazole ring containing compounds are also found as structural unit in insecticides, for example tricyclazole, thifluzamide and tiabandazole **18** which is antiparasitic and antifungal [55, 56].



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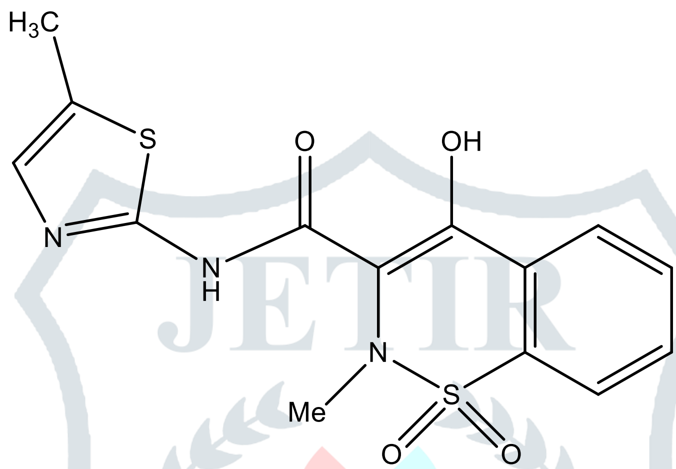
Thiazole is found to be present in meloxicam **19** which is an anti-inflammatory nonsteroidal drug. It is used for reducing pain and inflammation in osteoarthritis and rheumatic diseases [57].



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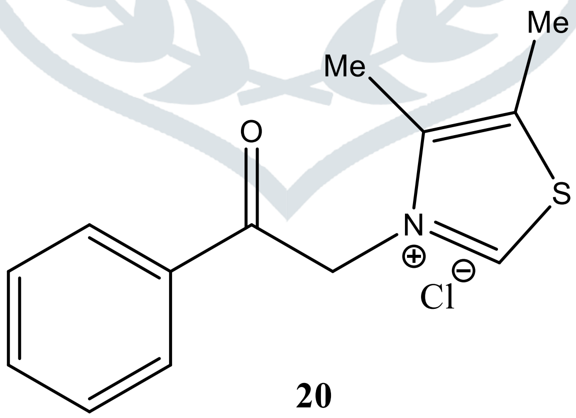
Algebrium **20** was found effective for reducing blood vessel wall stiffing, reducing systolic blood pressure, reversing aging [58].



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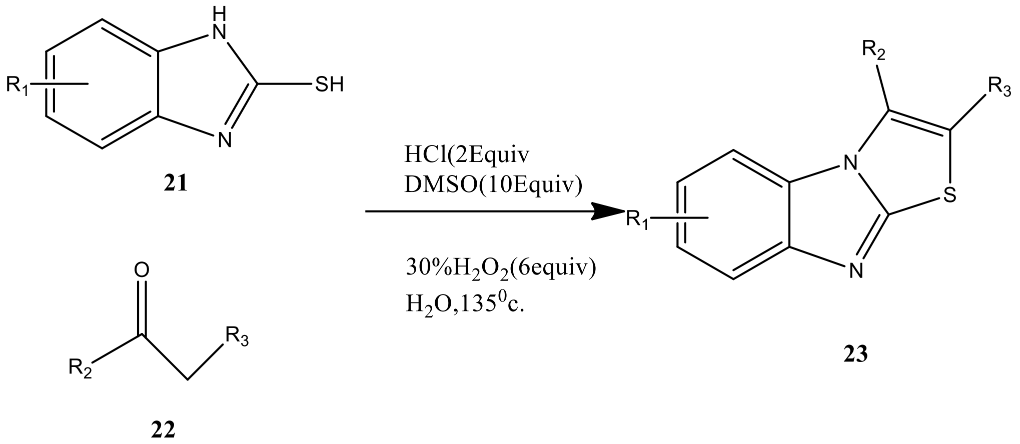
SYNTHESIS OF THIAZOLE DERIVATIVES:

Organic chemists are studying various methods for preparation of novel derivatives of thiazoles for quite a long time. Various synthetic methods towards thiazole derivatives are summarized [59-63]. Few methods are described as follows:-

Zhao et al. [64] synthesized thiazolo[3,2-a]benzimidazole structure using DMSO-H2O2 in water. Substituted-2-mercaptoben-zimidazole **21** and ketones **22** were taken as substrate and thiazolo[3,2-

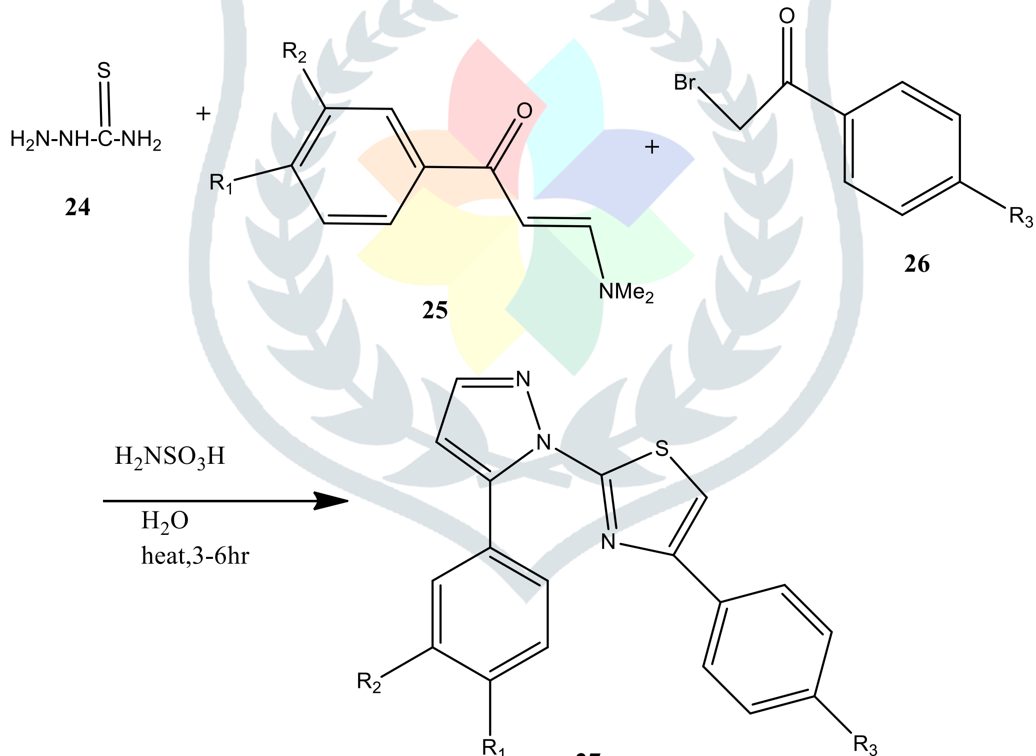
a]benzimidazole **23** was produced (Scheme-1).



R_1=Cl,Me,OMe,NO_2
R_2,R_3=Ar,Me,Et,iso-Bu,n-pr,n-C_5H_{11}

Scheme:1

Sridevi et al. [65] synthesized a series of pyrazolylthiazole **27** from hydrazine carbothioamide **24**, (E)-1-aryl-3-(dimethylamino)-2-propen-1-ones **25** and substituted 2-bromoacetophenone **26** (Scheme- 2).



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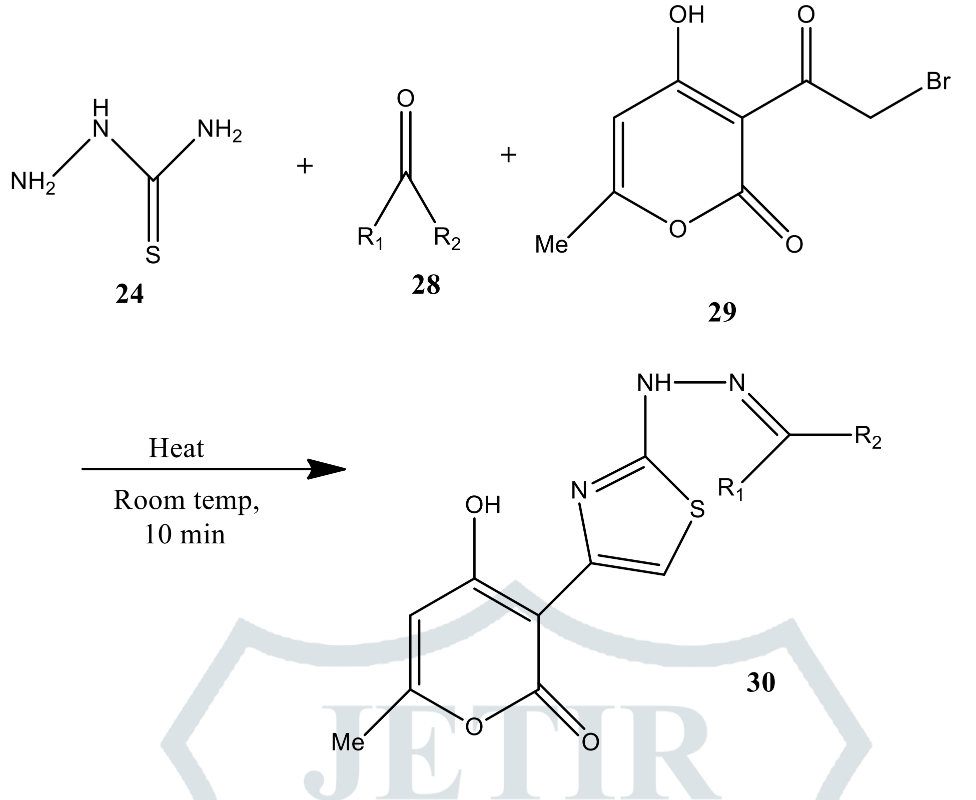
R_1=Me,OMe,Cl,CF_3,NO_2;R_2=H,NO_2
R_3=H,Me,OMe,Cy,Cl,NO_2

Scheme:2

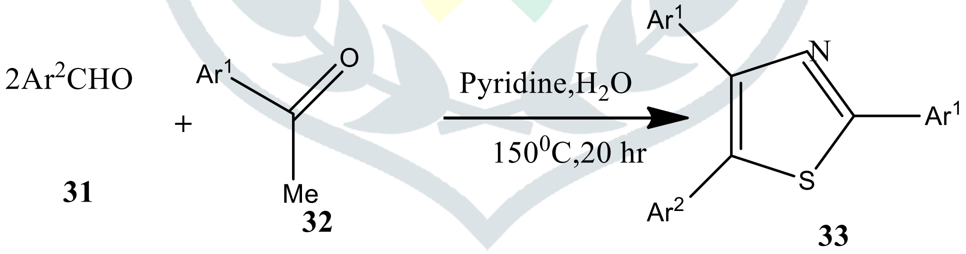
Penta and Rao Vedula [66] synthesized few substituted thiazoles **30** by reacting hydrazine carbothioamide **24**, carbonyl compounds **28** and 3-(2-bromoacetyl)-4-hydroxyl-6-methyl-2H- pyran-2-one **29** under stirring at room temperature. This was a one pot reaction producing lesser by products as compared to multi-step synthetic methods (Scheme-3).



R_1,R_2=Me,Et,Ph,4-MeC_6H_4, 2-CHOC_6H_5

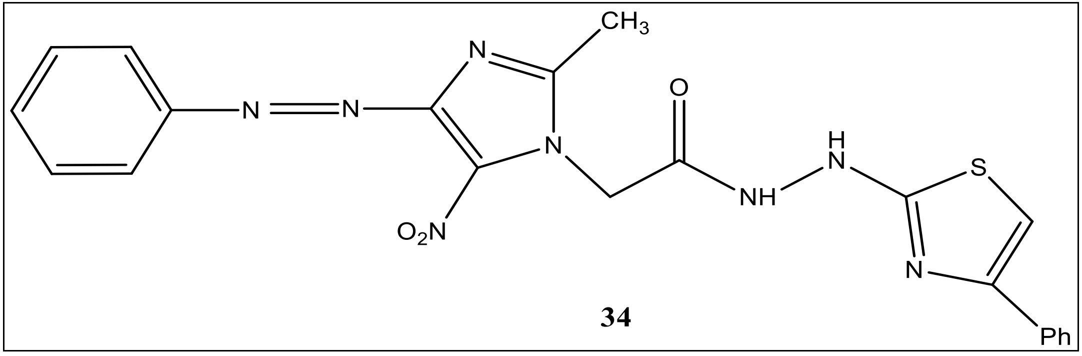
scheme:3

Jiang et al. [67] synthesized polysubstituted thiazole **33** from easily available chemicals, aldehydes **31**, ketones **32** and elemental sulphur. Pyridine was used as reaction medium that enhanced the yield (Scheme-4).



Scheme-4

Saravanan [68] synthesized new thiazole derivatives by introducing pyrazole based ring on 2nd position of 2-hydrazinyl-N-(4-phenylthiazol-2-yl)- acetamide **34**. The pyrazole ring was introduced by treating the compound **34** with chalcones.

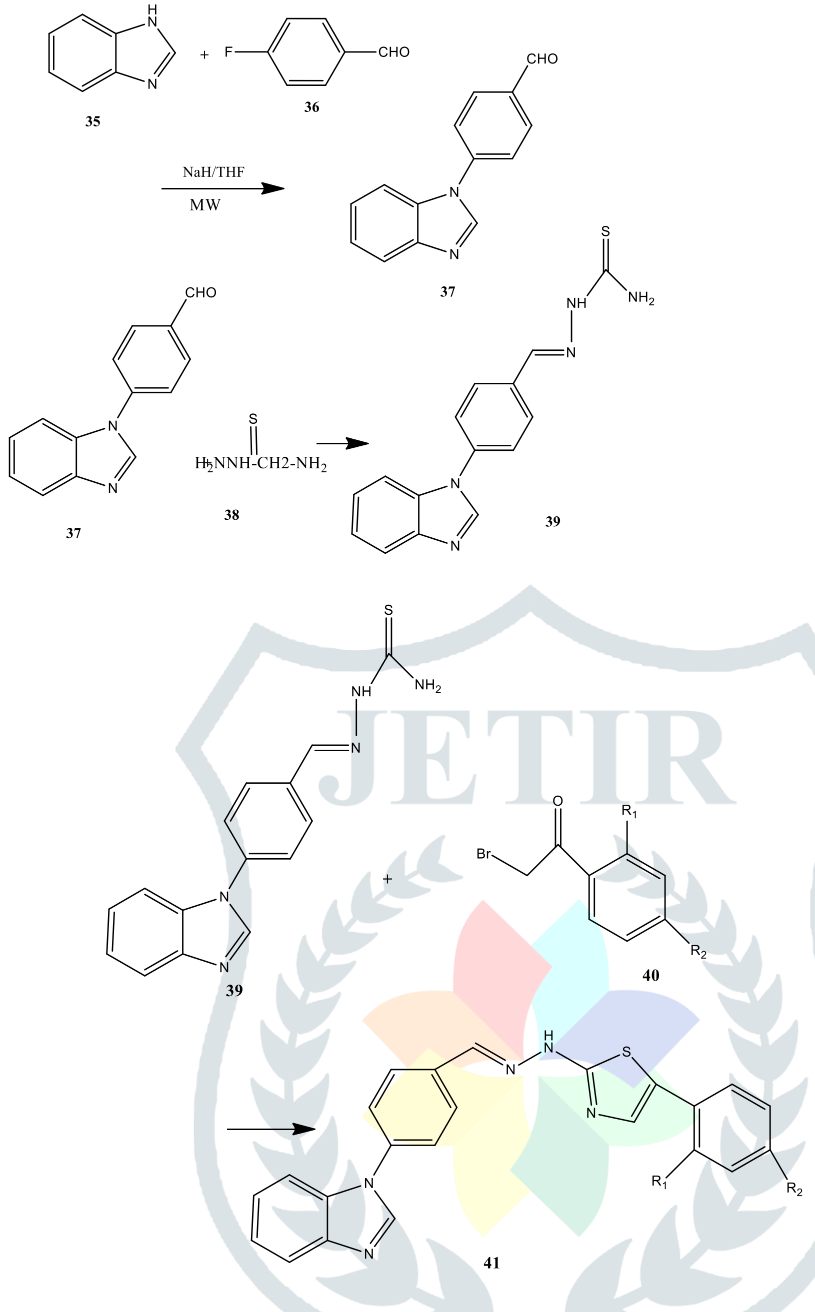


34

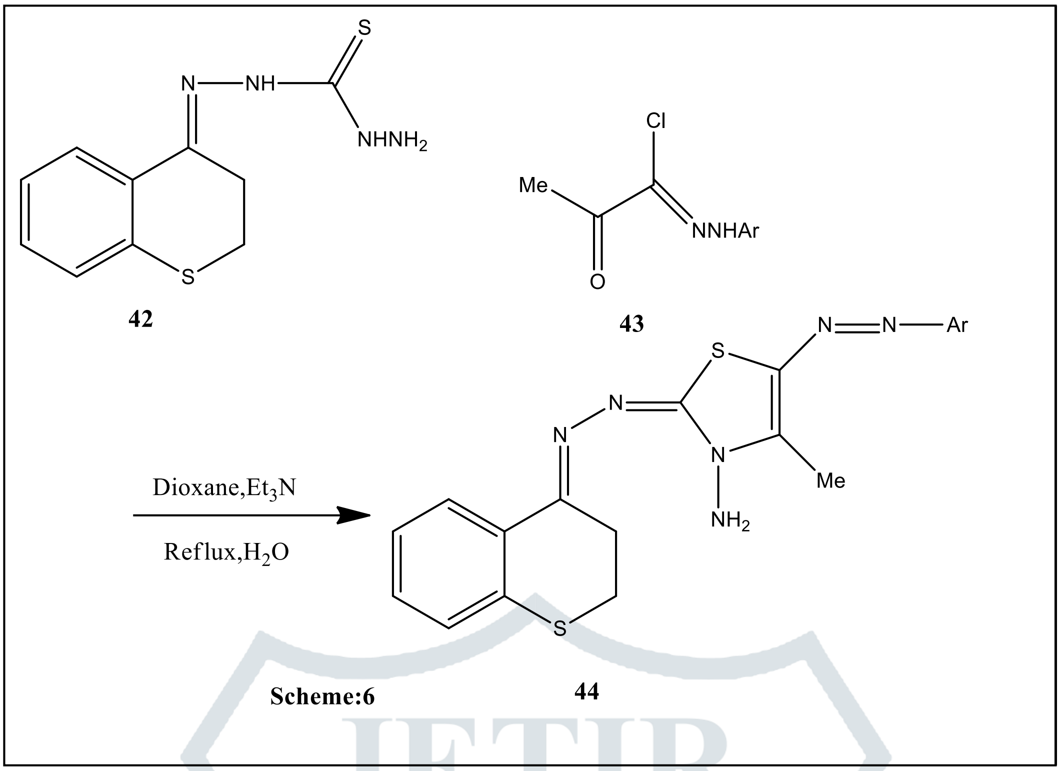
Kaplancikli et al. [69] synthesized new benzimidazole-thiazole derivatives **41** by an easy three step reaction. 1H-benzimidazole **35** and 4-fluorobenzaldehyde **36** were reacted under microwave irradiation when 4-(1H-benzimidazole-1-yl)benzaldehyde **37** was formed. Compound **37** was reacted with hydrazine carbothioamide **38** to give 2-(4-1H-benzimidazol-1-yl)benzylidenehydrazine-1-carbothioamide **39**, which then reacted with 2-bromoacetophenone **40** to give target compound **41** (Scheme-5).

Farghaly et al. [70] synthesized new thiazole derivatives **44** by reacting thiochroman-4-thiocarbohydrazone **42** with derivatives of hydrazonyl chloride **43** in presence of triethylamine as catalyst (Scheme-6).

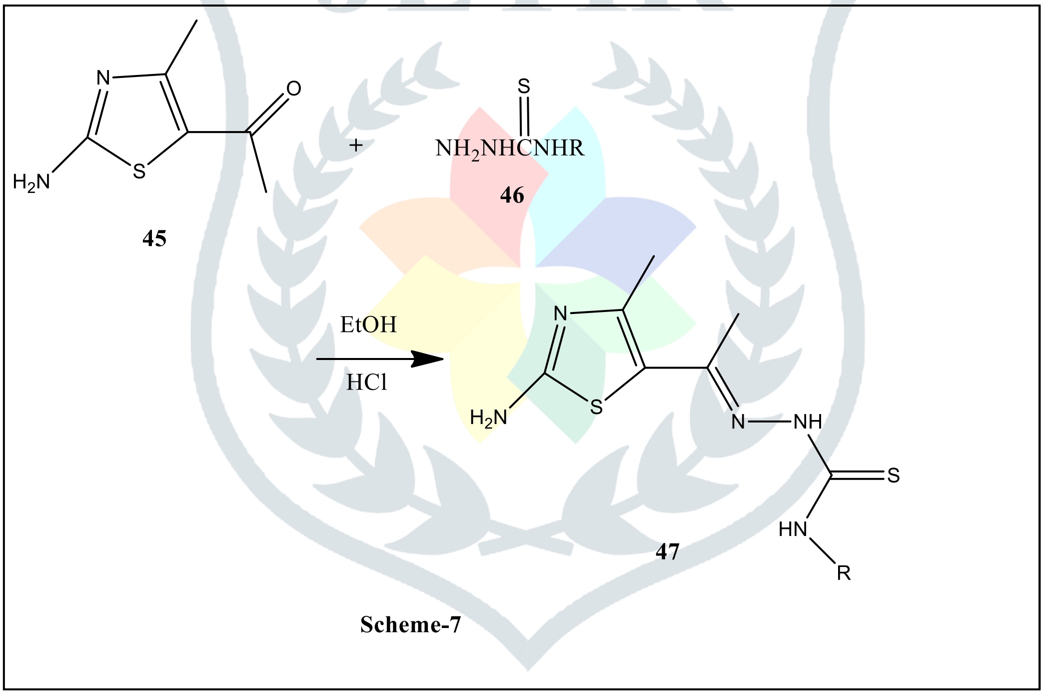
Gomha et al. [71] reacted 5-acetyl-2-amino-4-methylthiazole **45** with thiocarbohydrazide **46** in ethanol and concentrated HCL as catalyst to synthesise new thiazolyl-thiazole derivatives **47** (Scheme-7).



Scheme-5



Scheme:6



Scheme-7

CONCLUSION:

A large variety of thiazoles and its derivatives have been synthesized and examined for their biological activities. Various modifications can be done with thiazole moieties to develop compounds of potential biological importance.This paper develops an interest of researchers to explore many more new compounds of medicinal importance having this system.

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