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A RETROSPECTIVE STUDY ON THIAZOLE DERIVATIVES SYNTHESIS AND THEIR ANTIMICROBIAL ACTIVITY

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Abstract

Thiazole derivatives serve as potent antimicrobial agents, structural activity relationships revealed the correlation to the effect of number and type of substituents on the nucleus. Most of the derivatives possess the broad-spectrum activity and are mostly antifungal and antibacterial in nature. The derivatives show more prominent action against gram-positive bacteria followed by a fungus, while action against gram-negative bacteria is mostly is comparatively moderate to very weak. There are some thiazoles showed excellent activities against reference drug-resistant bacteria like methicillin-resistant *Staphylococcus aureus,* hence attributing to the case of thiazole derivatives as future antimicrobial agents against multidrug-resistant microorganisms. Few of the classes have shown potency which is even better than reference drugs currently employed. Cytotoxicity studies have been reported for fewer classes only where results have shown them to be fit for human consumption and nontoxic to human cells. Herein we discussed the potential of thiazole derivative as antibacterial and antifungal properties along with illustrations of the synthetic routes.

***Keywords*:** Thiazole, antimicrobial, antibacterial, antifungal, anticancer, cytotoxic.

Introduction

There has been a significant improvement in the health status of human since the development and discovery of therapeutically active antimicrobial agents. But till to date, the microbial multidrug resistance has been prominent, and primarily due to the drug abuse as well as due to inappropriate usage of these antimicrobial agents. Also, there has been a progression of emerging newer infectious diseases. It has, therefore, become a necessity to develop new drug approaches to evade this problem. Thus, there is an immediate need to develop novel drugs lasses with non-identical mechanistic actions, so that there is no incidence of cross-resistance with other drugs and effective treatment can be achieved. Thiazole belongs to a class of heterocyclic compounds which are blessed with a range of biological activity. These analogs have also served as precursors for the synthesis of many biologically active compounds. Several methods for developing new thiazole derivatives have been developed via heterocylization. Thiazole nucleus is also a fundamental part of natural products like vitamin B_1 and antibiotic class penicillin's which has revolutionized the treatment of microbial infections (Kashyap *et al.,* 2018). Thiazoles have been reported to possess therapeutic application as anti-allergic, antimicrobial, anticancer, analgesic, cardiotonic, etc agents (Abu-Melha *et al.,* 2019). In this review, we have given an in-detail report regarding the synthesis approaches and the consequent antimicrobial effects possessed by these thiazole derivatives.

Thiazole derivatives

Various novel thiazole derivatives possessing promising antimicrobial property are discussed and detailed structure activity relationship (Table 1) for different thiazole derivatives which include:

- 2-phenylamino-thiazole derivatives
- 5,6- dihydroimidazo[2,1-*b*] thiazole derivatives
- 2-(3-pyridyl)-4,5-disubstituted thiazoles derivatives
- N'-(4-(arylamino)-6-(thiazol-2-ylamino)-1,3,5-triazin-2yl) isonicotinohydrazides
- Ethyl 2-(2-(4-Substituted) acetamido)-4substituted-thiazole-5-carboxylate derivatives
- 3,5-diphenyl-6-(5-p-toly1-1,3,4 thiadiazol-2yl)-3,3a,5,6 tetrahydro-2H pyrazolo[3,4-d] thiazole derivatives.
- Thiazole-based chalcones - (*E*)-1-[4-methyl-2-(methylamino) thiazol-5-yl)-3-phenylprop-2-en-1-ones
- Thiazole clubbed 1-oxa-3,4-diazacyclopentadiene derivatives
- 5- arylidene thiazole derivatives
- Arylazothiazole derivatives
- Tetrahydrothiophene-3-one based thiazoles
- (*E*)-2-(2-(cyclohexylmethylene) hydrazinyl)-4-(4-substitutedphenyl) thiazoles
- 4-aryl -2-(2,3,5-trichlorophenyl)-1,3-thiazoles
- Methylsulfonyl benzothiazoles
- 7-methylbenzo[d]thiazolehydrazones

2-phenylamino-thiazole derivatives (Bikobo *et al.,* 2017)

2-phenylamino-thiazole derivatives (Figure 1) can be synthesized using the Hantzsch synthesis method where various thioamides are condensed with various haloketones as shown in Scheme 1. The derivatives have shown to possess better antibacterial action against gram-positive bacterium with minimum inhibitory concentrations (MIC) experimentally found to be even lower than that of standard reference drug like spectinomycin. The action has been

prominent against gram +ve bacteria like *E. faecalis*and*S. aureus;* indicating possible treatment for urinary tract infections, endocarditis, and upper respiratory disorders (Tong *et al.,* 2015). The antifungal action has also been excellent with MICs comparable to fluconazole. However, the action against gram-negative bacterium has been found to be comparatively weaker.

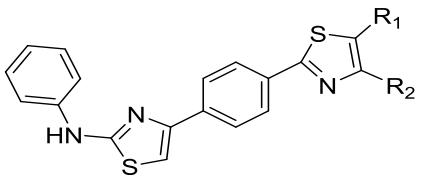
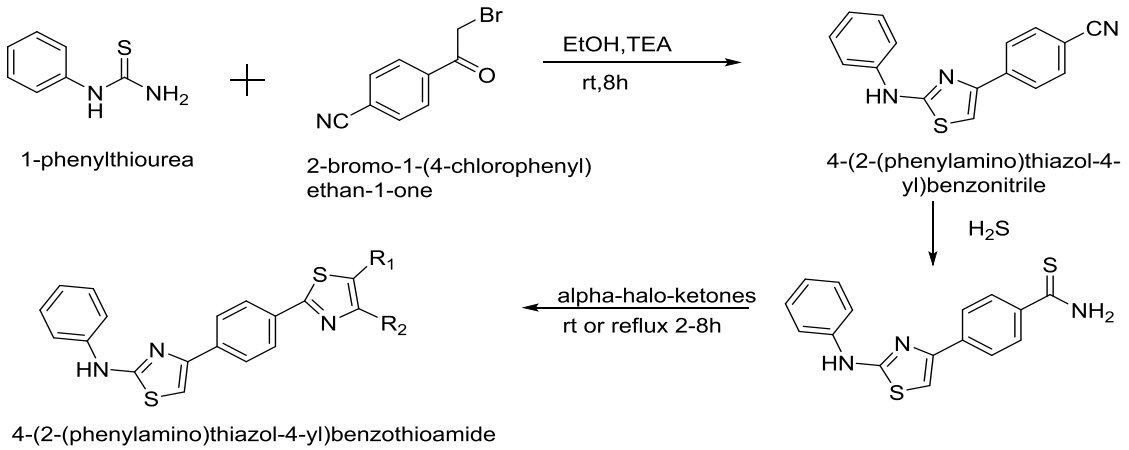


Fig. 1: 2-phenylamino-thiazole derivatives.



Scheme 1: Synthetic scheme of 2-phenylamino-thiazole derivatives.

5,6- dihydroimidazo[2,1-*b*] thiazole derivatives (Bionda *et al.*, 2016)

5,6- dihydroimidazo [2,1-*b*] thiazole derivatives (Figure 2) have shown to be effective against gram +vebacteria; notably against *S. aureus* which has been reported to be methicillin-resistant. The derivatives have proven to be safer for human consumption as they possess extremely low cytotoxicity toward human cell lines. DNA gyrase supercoiling assays have been performed on them solely due to the assumption that the compounds possessed structural similarity to benzimidazole urea compounds which were known DNA gyrase inhibitors. The assay results have proved the dose-dependent inhibition of DNA gyrase supercoiling action.

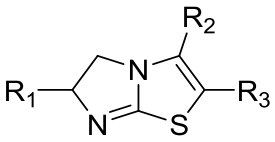


Fig. 2: 5,6- dihydroimidazo[2,1-*b*] thiazole derivatives.

2-(3-pyridyl)-4,5-disubstituted thiazoles derivatives (Bonsock *et al.*, 2013)

2-(3-pyridyl)-4,5-disubstituted thiazoles(Figure 3) can be synthesized using Hantzsch reaction via reaction of pyridine-3-carbothioamide with various ***α***-halogen substituent ketones using ethanol as refluxing solvent and triethylamine as a catalyst as shown in Scheme 2. The derivative having 5-methylcarbonyl-4-methyl-2-(3-pyridyl)thiazole has shown to possessed two folds activity against gram-positive bacteria in comparison to ampicillin, equipotent activity against fungi in comparison to reference antifungal drug amphotericin –B. Specifically, the derivatives have shown excellent action against gram +ve bacteria like *E. faecalis, S. epidermidis, S. pyogenes, S. aureus,* etc. (Tong *et al.*,2015, Vu *et al.,* 2011). Hence, they could be used as promising therapeutic agents against acute infections like pharyngitis, rheumatic fever, tonsillitis, urinary tract infections, endocarditis upper respiratory disorders and also against diseases of intravascular medical devices. Their excellent vitro antifungal activity proved them effective against *C. albicans, A.clavatus*, *P. marneffei*, *A. fumigates* and *G.candidum.* However, activity against gram-negative bacteria was not up to the mark.

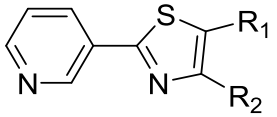
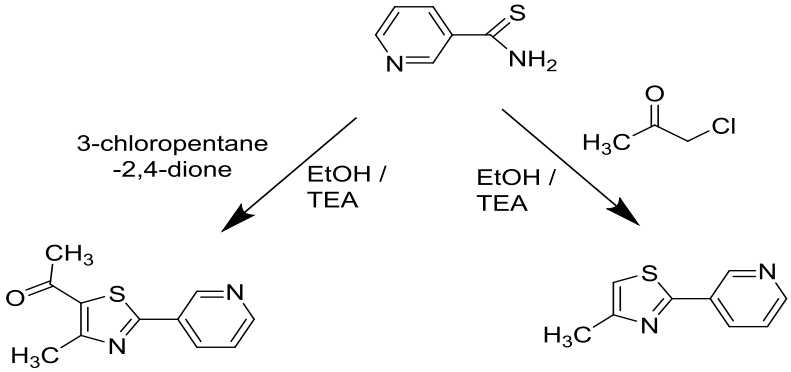


Fig. 3 : 2-(3-pyridyl)-4,5-disubstituted thiazoles derivatives general structure



Scheme 2: Synthetic scheme of 2-(3-pyridyl)-4,5-disubstituted thiazoles derivatives.

N'-(4-(arylamino)-6-(thiazol-2-ylamino)-1,3,5-triazin-2yl) isonicotinohydrazides (Desai *et al.*,2016)

N'-(4-(arylamino)-6-(thiazol-2-ylamino)-1,3,5-triazine-2yl) isonicotinohydrazides (Figure 4) can be synthesized using Scheme 3. The derivatives having electron-withdrawing substituents on the aromatic ring exhibit excellent antibacterial and antifungal activity, which are even better than the standard drugs. The derivatives have been proved to possess antimicrobial activity against Gram-ve bacteria like*E. Coli* and the infectious encapsulated *P. aeruginosa*, Gram +ve bacteria like *S. pyogenes* and *S. aureus*, Fungi-like *A. niger*, *A. Clavatus*, and the pathogenic yeast living in our gut *C. albicans*, Its excellent activity against *E. coli* makes it a possible agent against *Hemolytic uremic syndrome*, urinary tract infections (Dupont *et al.*, 1971). The derivatives could be used for the treatment of endocarditis, meningitis, pneumonia, skin and soft tissue infections, pharyngitis, tonsillitis, etc due to their excellent activity against above-mentioned bacteria's. (Tong *et al.*, 2015; Vu *et al.*, 2011). It could pave the way for better treatment of hypersensitivity pneumonitis which is also known as 'Malt Worker's Lung' due to their very good action against *A. clavatus* (Ellis *et al.*, 1981).

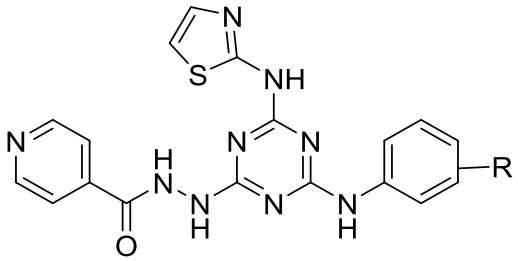
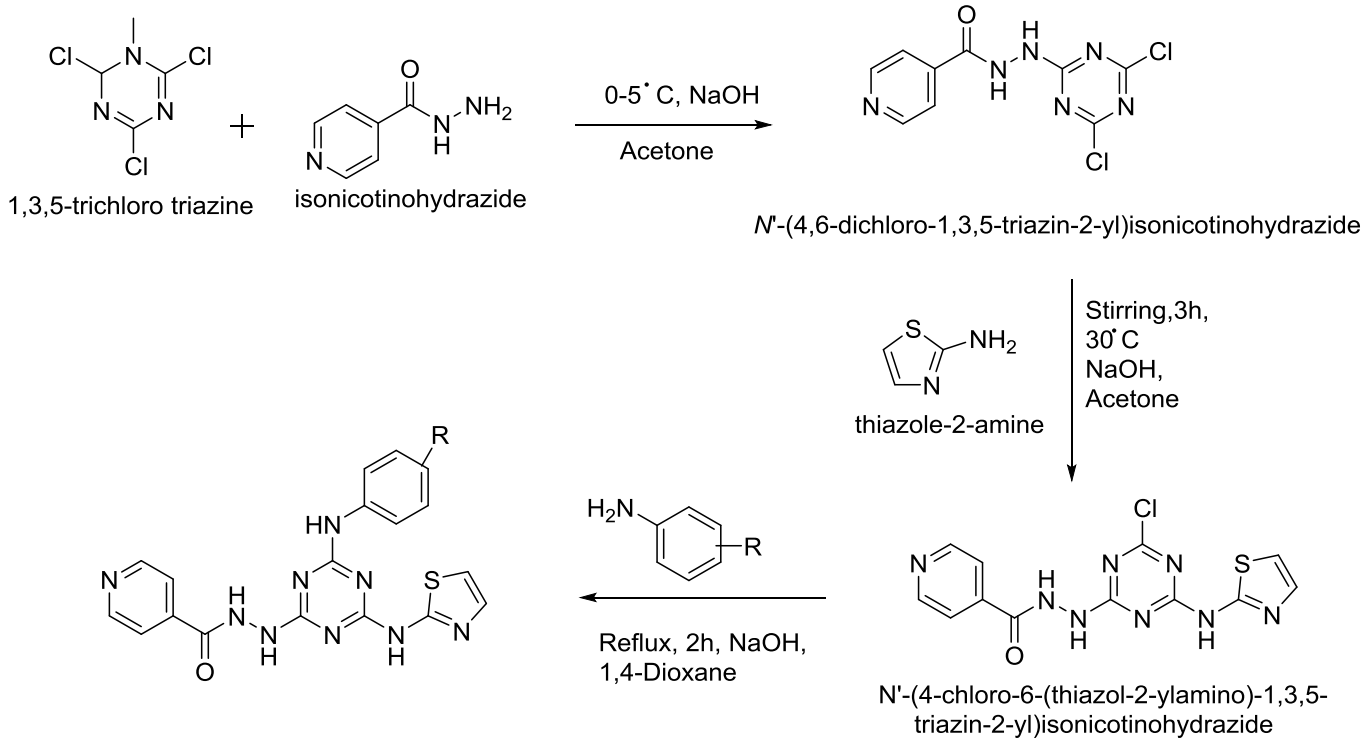


Fig. 4: N'-(4-(arylamino)-6-(thiazol-2-ylamino)-1,3,5-triazin-2yl) isonicotinohydrazides.



Scheme 3: Synthetic scheme of N'-(4-(arylamino)-6-(thiazol-2-ylamino)-1,3,5-triazin-2yl) isonicotinohydrazides.

Ethyl 2-(2-(4-substituted) acetamido)-4-substituted-thiazole-5-carboxylate derivatives (Pawar *et al.*, 2016)

Ethyl 2-(2-(4-Substituted) acetamido)-4substituted-thiazole-5-carboxylate derivatives (Figure 5) can be synthesized using Scheme 4, as described by Pawar *et al.* The derivatives possessing a bulky alkyl and ester substitution show excellent potency against both bacterial and fungal strains. The derivatives have been demonstrated to be effective against all type of bacteria, irrespective of whether they are gram-positive or gram-negative like against *B. subtilis*, *S. aureus*, and *E. coli*. Hence, they represent a possible approach for the treatment of soft tissue-skin diseases and urinary tract infections (Tong *et al.*, 2015; Vu *et al.*, 2011; Dupont *et al.*, 1971). Also, courtesy of their excellent antifungal property which is comparable to standard drugs like fluconazole and miconazole; they could be used for vaginal infections as they are particularly effective against *C. albicans* (Kabir et *al.*,2013).

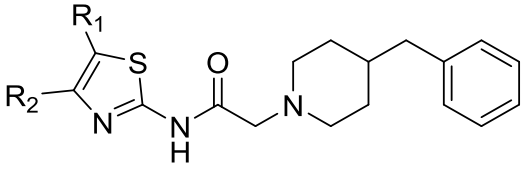
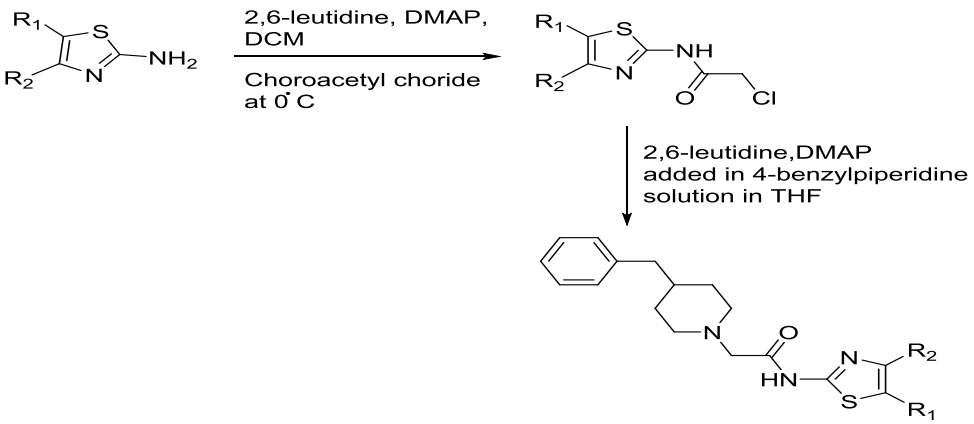


Fig. 5: Ethyl 2-(2-(4-Substituted) acetamido)-4substituted-thiazole-5-carboxylate derivatives.



Scheme 4: Synthetic scheme of ethyl 2-(2-(4-substituted) acetamido)-4-substituted-thiazole-5-carboxylate derivatives.

3,5-diphenyl-6-(5-p-toly1-1,3,4 thiadiazol-2yl)-3,3a,5,6 tetrahydro-2H pyrazolo[3,4-d]thiazole derivatives (Seelam *et al.*,2016)

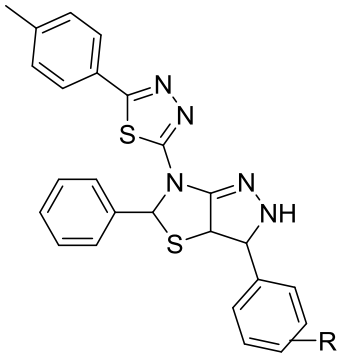
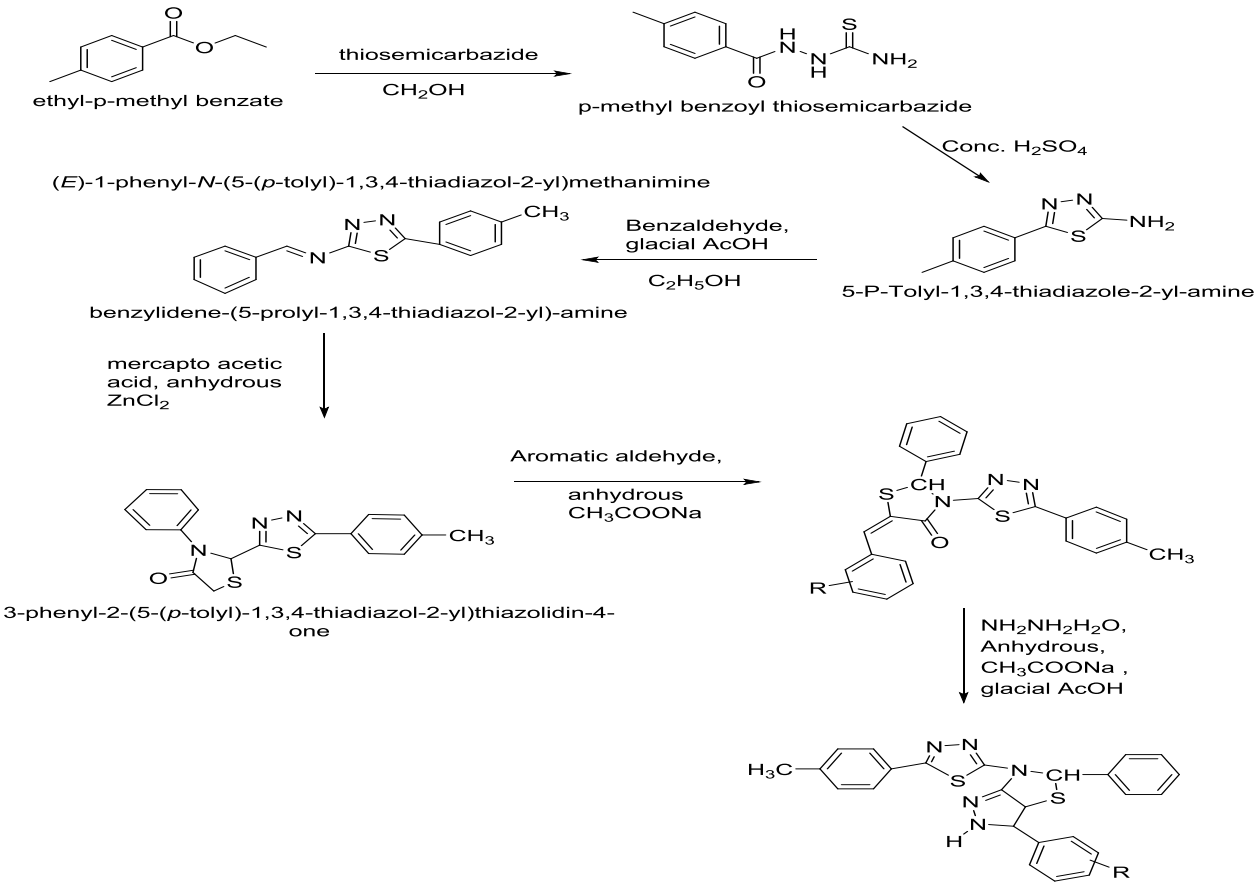


Fig. 6: 3,5-diphenyl-6-(5-p-toly1-1,3,4 thiadiazol-2yl)-3,3a,5,6 tetrahydro-2H pyrazolo[3,4-d]thiazole derivatives.

These derivatives can be prepared by reaction of hydrazine hydrate with benzalacetophenone derivatives of 1,3,4 thiadiazol-2-yl)-thiazolidine-4-one (Figure 6), as per the synthetic route illustrated below in Scheme5. The derivatives possessing p-halo phenyl nucleus on thiazolo-pyrazole moiety have been found to be broad spectrum and possess excellent potency which is comparable with standard drugs. These found active against fungi like *B. fabae* and *F. oxysporum* which make them an excellent candidate for the treatment of plant pathogenic disorders (Gordon *et al.*, 2017). In fact, they could also be used for the treatment of tuberculosis as derivatives possessing resonance dominated electron withdrawing and inductive effect dominated electron donating groups have proven to possess very good anti-TB activity.



Scheme 5: Synthetic scheme of 3,5-diphenyl-6-(5-p-toly1-1,3,4 thiadiazol-2yl)-3,3a,5,6 tetrahydro-2H pyrazolo[3,4-d]thiazole derivatives.

Thiazole-based chalcones - (E)-1-[4-methyl-2-(methylamino)thiazol-5-yl)-3-phenylprop-2-en-1-ones (Liaras *et al.*,2008)

These thiazoles (Figure 7) are based on chalcones and can be synthesized by cross-aldol condensation of 1-(4-methyl-2-(methylamino) thiazol-5-yl)ethanone with appropriate aldehydes which are aromatic in nature as shown in Scheme 6. One of the most striking features of chloro substituted derivative is its activity against *Enterococcus faecalis* which is 3 times better than the standard drug currently used ampicillin. Hence chloro substituted derivative can be a promising therapeutic solution for fatal diseases like urinary tract infections, endocarditis, and wound infections.[7]The derivatives also possess good action against fungi like *Fusarium sporotrichoides* which is the leading cause of head blight in wheat and other plant diseases. Hence, they could have notable agriculture importance in future (Leslie *et al.*,2008).

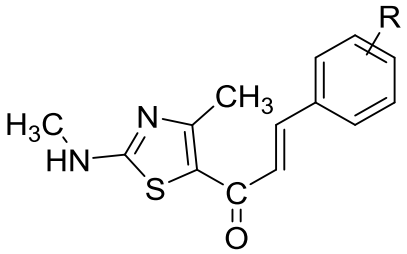
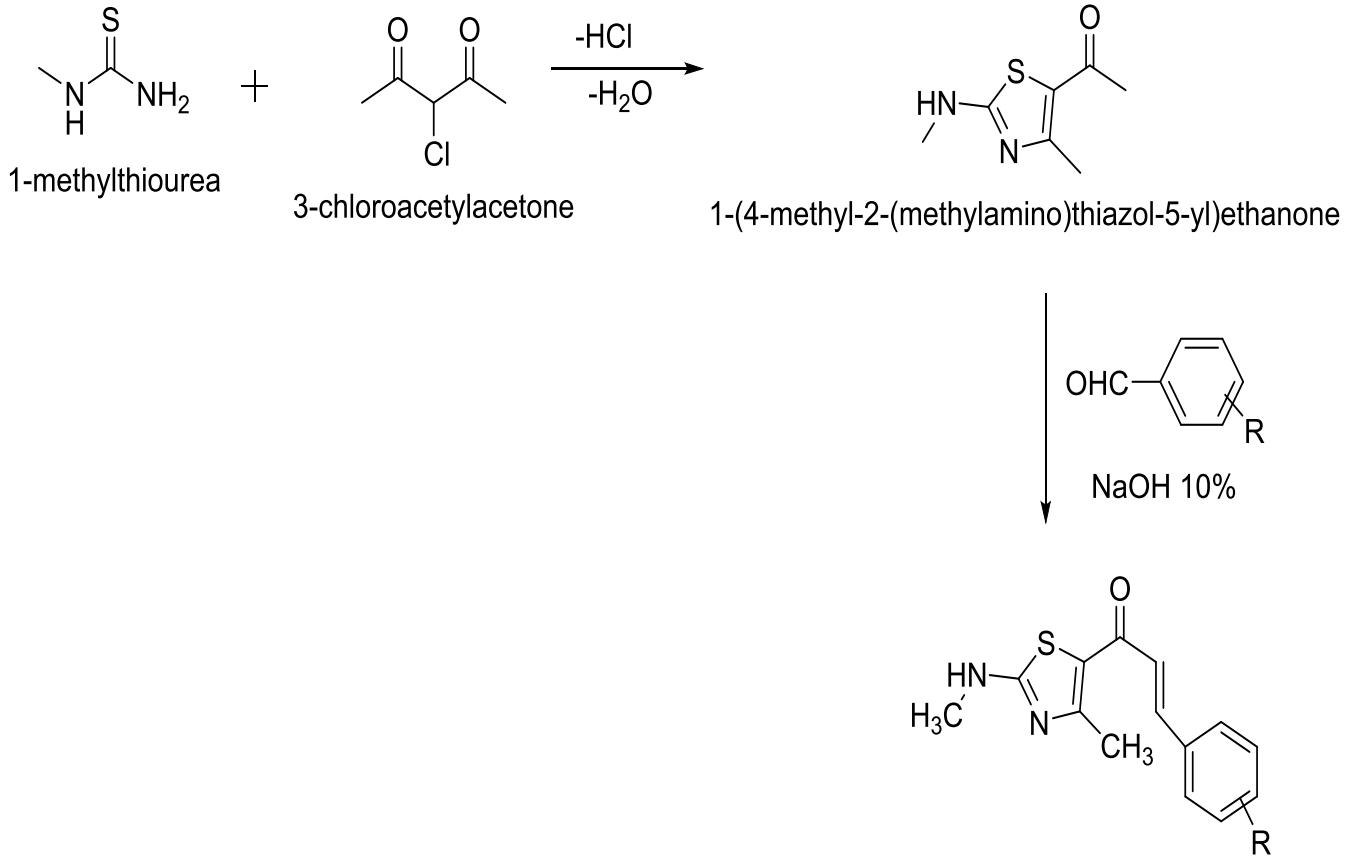


Fig. 7: Thiazole based chalcones - (E)-1-[4-methyl-2-(methylamino)thiazol-5-yl)-3-phenylprop-2-en-1-ones.



Scheme 6: Synthetic scheme of thiazole-based chalcones - (*E*)-1-[4-methyl-2-(methylamino)thiazol-5-yl) -3-phenylprop-2-en-1-ones.

Thiazole clubbed1-Oxa-3,4-diazacyclopentadiene derivatives (Desai *et al.*, 2013)

Thiazole clubbed 1-oxa-3,4-diazacyclopentadiene derivatives (Figure 8) can be synthesized using Scheme 7. These derivatives which possess electron withdrawing group at para position yield highly active antibacterial compounds with activity even 2-4 times more than standard drug chloramphenicol. Para-substitution with electron releasing group yields good antifungal agents. The derivatives have shown excellent action against *Staphylococcus aureus* and *Streptococcus pyogenes* indicating possible treatment for dermatological disorders like abscesses (boils), furuncles, acne and ailments like pharyngitis, tonsillitis, scarlet fever, and rheumatic fever (Tong *et al.,* 2015; Gordon *et al.*,2017). The derivatives have shown to fit for human consumption after MTT cytotoxicity assays on HeLa cells have shown low cytotoxicity.

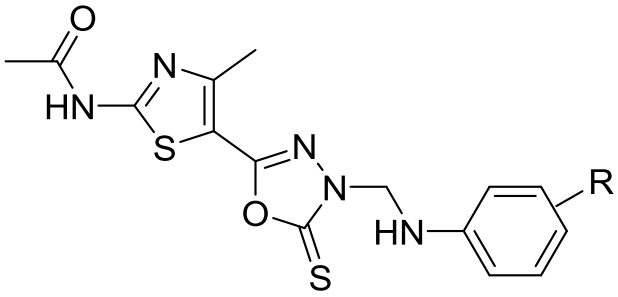
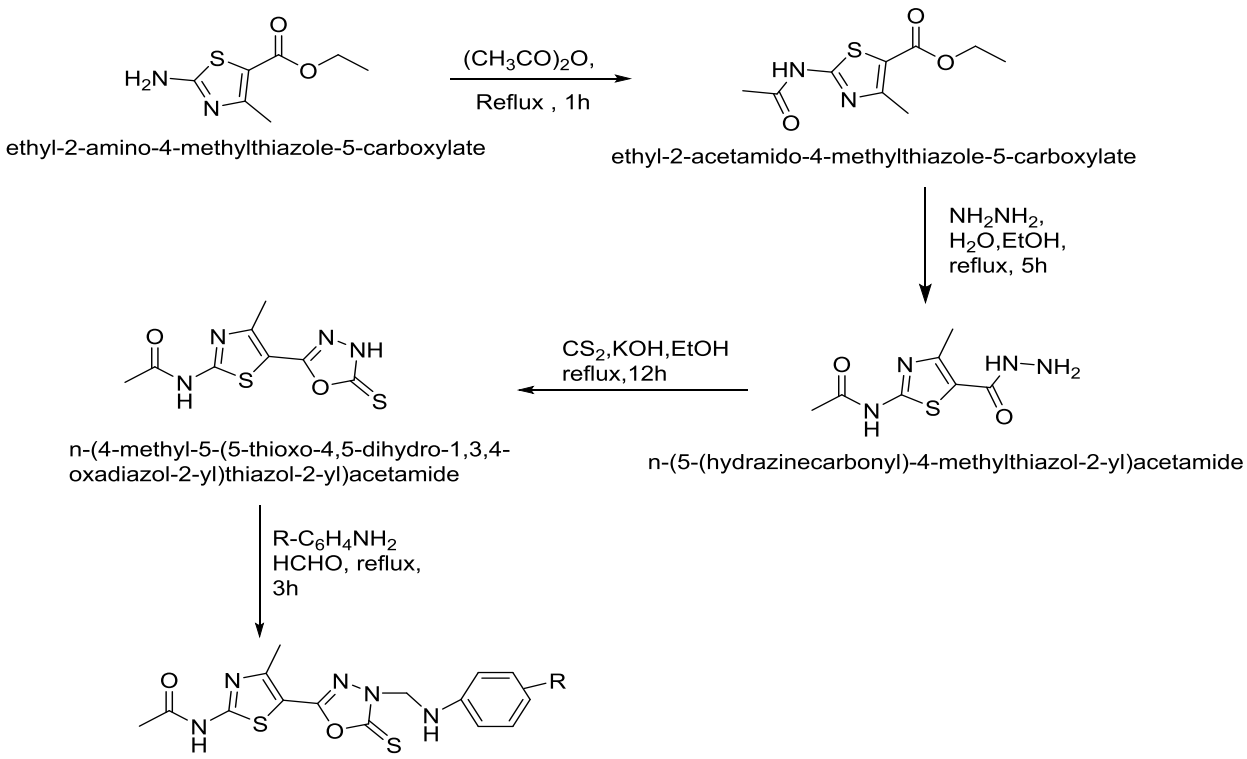


Fig. 8: Thiazole clubbed 1-oxa-3,4-diazacyclopentadienederivatives.



Scheme 6: Synthetic scheme of thiazole clubbed 1-oxa-3,4-diazacyclopentadiene derivatives.

5- arylidene thiazole derivatives (Desai *et al.*,2013)

These derivatives (Figure 9) can be synthesized by subjecting 4-fluoro-N-(4-methyl-5-(2-(4-oxo-3-phenylthiazolidin-2-ylidene)hydrazinecarbonyl)thiazol-2-yl)benzamide to modified aldol condensation or *Knoevenagel condensation* with appropriate aldehydes possessing aromaticity as shown in Scheme 7. The derivatives having an electron donating group substitution like alkyl e.g methyl and methoxy possess excellent activity against both gram +ve and gram –ve bacterial strains like *S. aureus*, *S. pyogenes*, *E. coli*, and *P. aeruginosa*. Hence they could be beneficial for patients suffering from disorders like UTI infections, dermatological disorders, endocarditis, meningitis, pharyngitis, tonsillitis, etc (Tong *et al.*, 2015, Dupont *et al.*, 1971, Gordon *et al.*,2017). Derivatives having Substitution on the phenyl ring by an electron donating group possesses very good antifungal property; notably against *Candida* and *Aspergillus* species suggesting possible treatment for vaginal fungal infections and other chronic pulmonary disorder caused by *Aspergillus* (Kousha *et al.*,2011).

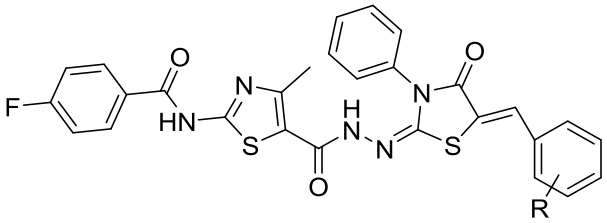
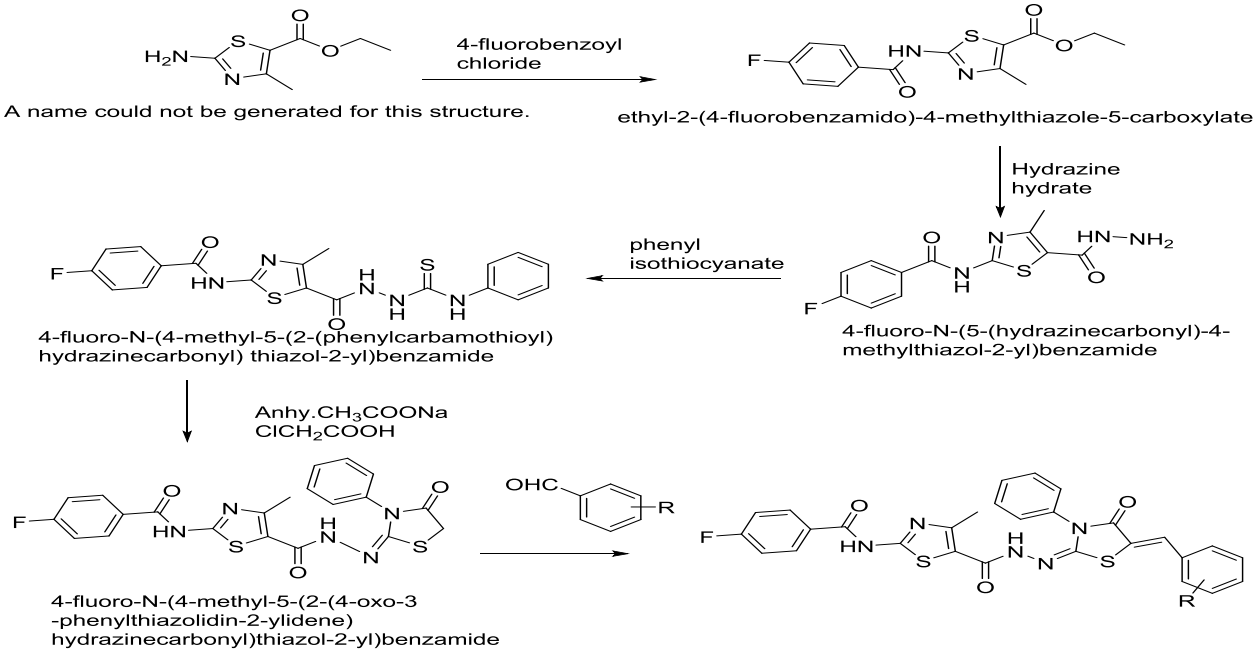


Fig. 9 : 5- arylidene thiazole derivatives.



Scheme 7: Synthetic scheme of 5- arylidene thiazole derivatives.

Arylazothiazole derivatives (Ouf *et al.*,2018)

The arylthiazole derivatives (Figure 10) are effective against cutaneous fungi. The derivatives with R as aromatic have an excellent antifungal activity which is comparable with fluconazole, which is the standard antifungal reference drug. They have shown action against fungal strains like *C. albicans*, *M. gypseum*, and *T. mentagrophytes.* Its activity could be crucial in treating dermatophytosis in AIDS patients (Inamadar *et al.,* 2013). While, activity against *C. albicans* and *T. mentagrophytes* could pave way for the treatment of athlete's foot and other skin disorders (Mala *et al.,* 2017).

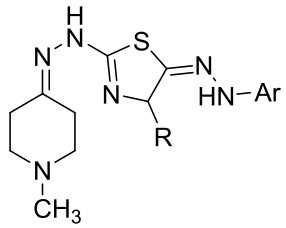


Fig. 10: Arylazothiazole derivatives.

Tetrahydrothiophene-3-one based thiazoles (Lackowaski *et al.*,2018)

Tetrahydrothiophene-3-one based thiazoles (Figure 11) are derived from dihydrothiophene-3(2*H*)-one. The synthesis involves heating dihydrothiophene-3(2*H*)-one with thiosemicarbazide yield hydrazine carbothioamide which on reaction with various *Para*-substituted bromoacetophenones yield the desired product. The synthesis scheme is illustrated in Scheme 8. The derivatives possess excellent antifungal activity against Candida species such as *Candida albicans* and *Candida krusei.* Hence, they could be used for the treatment of 'thrush' which the candidacies that develops in the throat and vaginal infections (Akpan *et al.,* 2002). *Candida krusei*is resistant to common antifungal drugs like fluconazole, therefore these derivatives could be helpful in counteracting the resistance (Berkow *et al.,*2017).

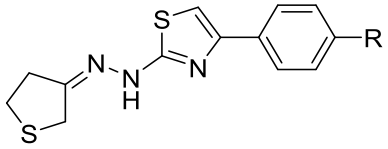
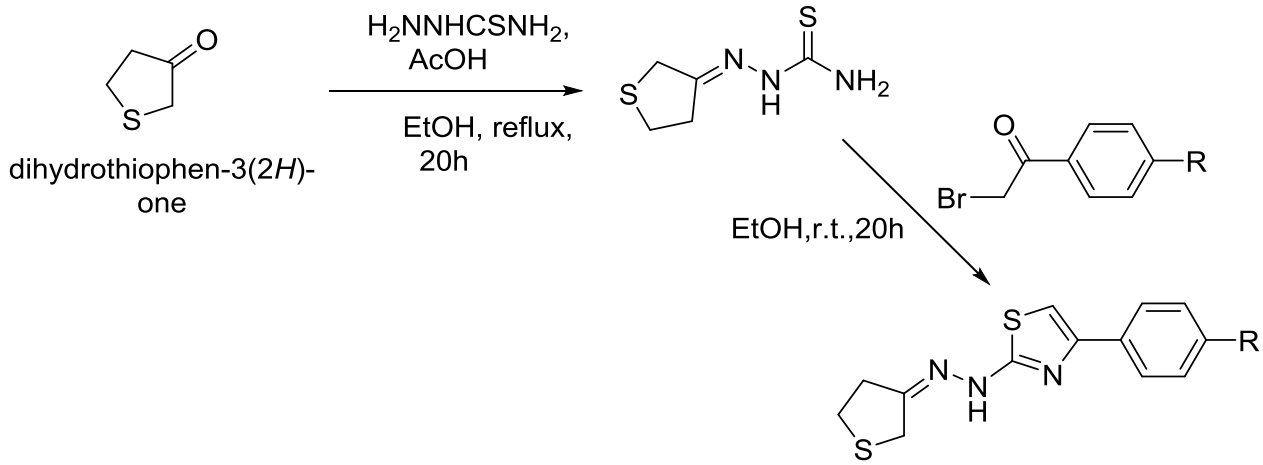


Fig. 11: Tetrahydrothiophene-3-one based thiazoles.



Scheme 8: Synthetic scheme of tetrahydrothiophene-3-one based thiazoles.

(*E*)-2-(2-(cyclohexylmethylene)hydrazinyl)-4-(4-substituted phenyl)thiazole (Laczkowski *et al.,* 2016)

(*E*)-2-(2-(cyclohexylmethylene)hydrazinyl)-4-(4-substituted phenyl)thiazoles (Figure 12) can be synthesized via cyclohexanecarbaldehyde thiosemicarbazone 's Hantzsch cyclization reaction with required para-substituted bromoacetophenones. The whole synthesis scheme is illustrated in Scheme 9. These possess strong antifungal action against Candida fungal strains such as *Candida parapsilosis* and *Candida albicans.* It's a very good activity against the later fungi could pave way for better treatment for life-threatening tissue infections in patients with a very weak immune system (Kabir *et al.,* 2013). Also, they could be used for candiasis infections and other fungal infections.

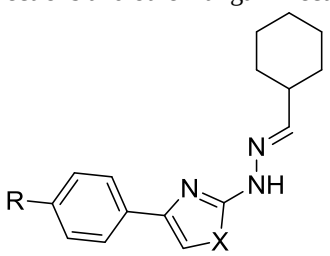
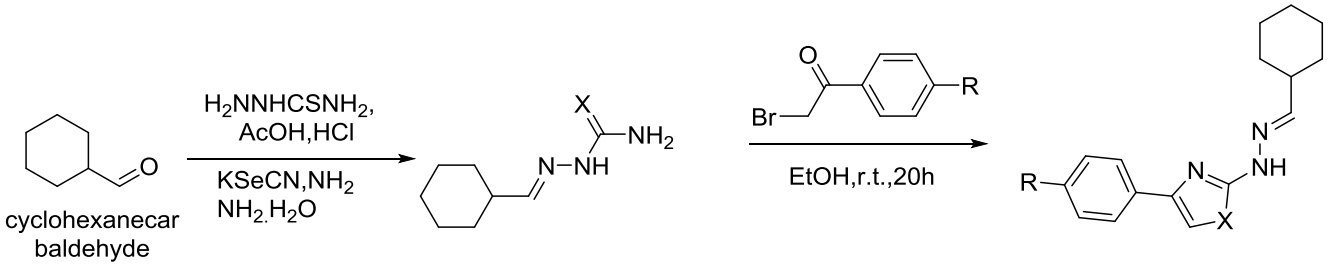


Fig. 12: (*E*)-2-(2-(cyclohexylmethylene)hydrazinyl)-4-(4-substituted phenyl)thiazoles.



Scheme 9: Synthetic scheme of (*E*)-2-(2-(cyclohexylmethylene)hydrazinyl)-4-(4-substituted phenyl)thiazoles.

4-aryl -2-(2,3,5-trichlorophenyl)-1,3-thiazoles (Karegoudar *et al.*,2008)

4-aryl -2-(2,3,5-trichlorophenyl)-1,3-thiazole derivatives (Figure 13) can be synthesized by reacting appropriate phenacyl bromides with 2,3,5 trichlorobenzene carbothioamide as shown in Scheme 10. These derivatives have shown good to moderate antibacterial and antifungal action.

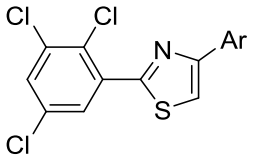
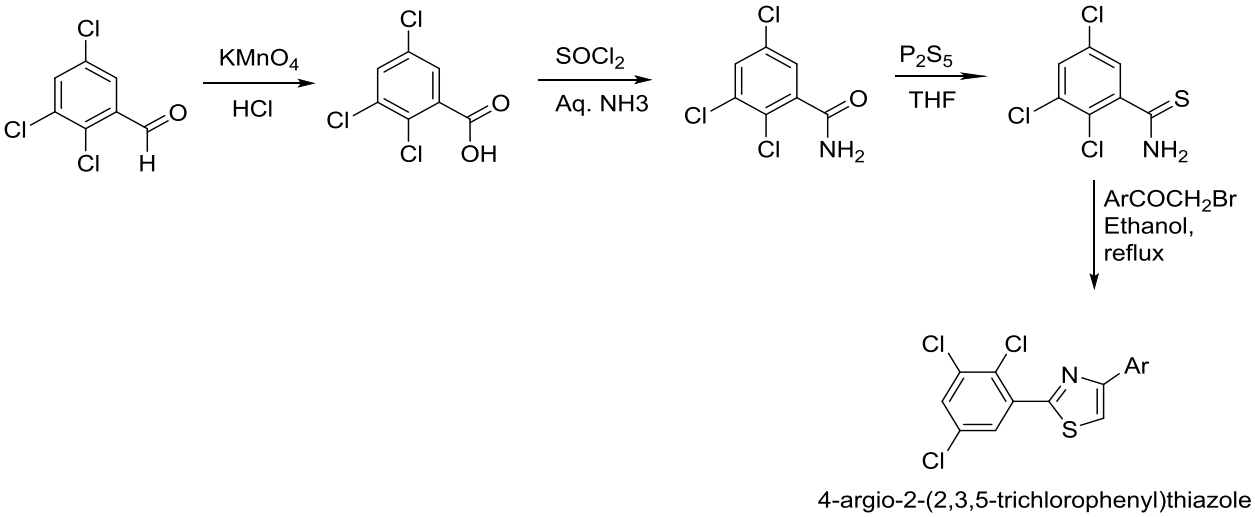


Fig. 13: 4-aryl -2-(2,3,5-trichlorophenyl)-1,3-thiazoles



Scheme 10: Synthetic scheme of 4-aryl -2-(2,3,5-trichlorophenyl)-1,3-thiazoles.

Methylsulfonyl benzothiazoles (Lad *et al.*, 2017)

Methylsulfonylbenzothiazoles (Figure 14) are synthesized by Sandmeyer reaction of commercial5-ethoxy-1,3-benzothiazole-2-amine, the product obtained i.e 2-chloro derivative is further reacted with sodium methane sulfinate to yield 5-ethoxy-2-(methylsulfonyl)benzo[d] thiazole. Later it is reacted with chlorosulphonic acid to produce 4-sulfonic acid derivative, which on treating with thionyl chloride under the catalysis of DMF yields 4-sulfonylchloride derivative. The later on reaction with require substituted amines under the catalysis of TEA yield the required sulphonamide derivatives. The whole synthesis scheme is illustrated in Scheme 11. The sulphonamide derivatives possess moderate activity against bacteria like *E. coli* and *Candida* species. The activity is promising and further structural modifications could potentially lead to better active derivatives.

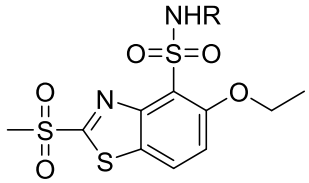
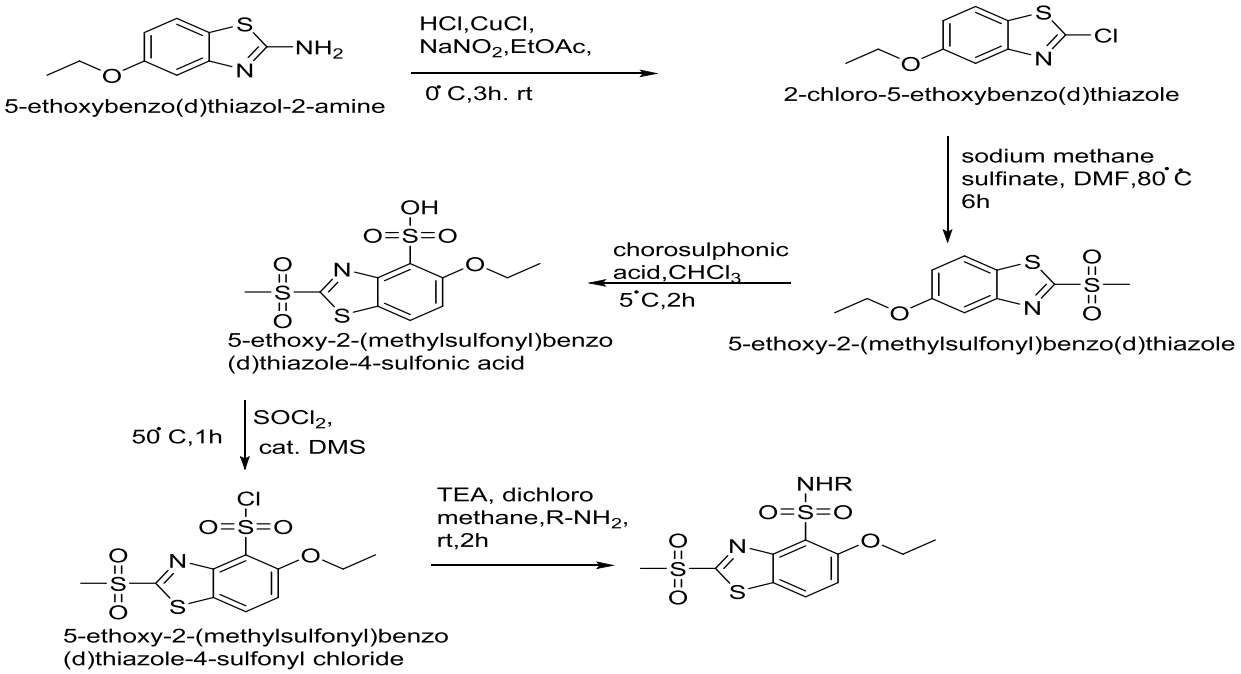


Fig. 14: Methylsulfonyl benzothiazoles.



Scheme 11: Synthetic scheme of Methylsulfonyl benzothiazoles.

7-Methylbenzo[d]thiazolehydrazones (Zha *et al.*, 2017)

7-Methyl benzo[d]thiazolehydrazones (Figure 15) can be synthesized by reacting (7-Methyl-1, benzothiazol-2-yl) hydrazine with appropriate aldehydes under the catalytic action of acetic acid as shown in Scheme 12. The derivatives with electron donating substituents possess superior activity against all bacteria, irrespective whether they are gram +ve or gram –ve bacteria as compared to reference drugs like chloramphenicol and rifampicin. These have been found to possess excellent action against methicillin-resistant *S. aureus***,** *B. subtilis, and E. coli.* Hence these could be used for skin and soft tissue infections like boils, cellulitis, Urinary tract infections, and traveler's diarrhea.

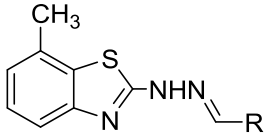
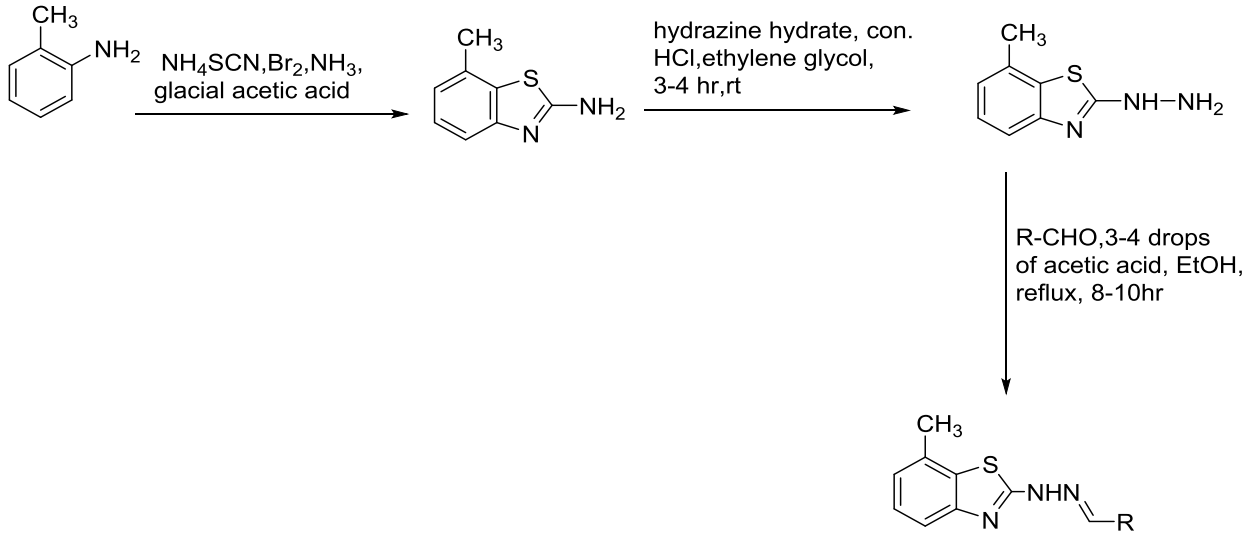


Fig. 15: Methylsulfonyl benzothiazoles.



Scheme12: Synthetic scheme of methylsulfonyl benzothiazoles.

Table 1: Structure-activity relationship and general features of thiazole classes (Bikobo *et al.,* 2017; Zha *et al.,* 2017)

Thiazole derivatives	Structure-activity relationship (SAR)	Possible therapeutic applications
2-phenylamino-thiazole derivatives	Both electrons accepting and electron donating group substitution positively affect the antibacterial activity	Antibacterial against gram-positive bacteria
5,6- dihydroimidazo[2,1-*b*]thiazole derivatives	No study performed according to our best knowledge	Antibacterial against gram-positive bacteria; low cytotoxicity; DNA gyrase inhibitor
2-(3-pyridyl)-4,5-disubstituted thiazoles derivatives	Smaller substitutions at position 4 and 5 of thiazole nucleus increased activity; increasing the bulkiness of substituent at position 4 and 5 of the thiazole nucleus decreased the activity; substitution at position 5 by an electron withdrawing group andposition 4 substitutions by a smaller sized electron donating group increases the antimicrobial activity considerably; the antibacterial activity is independent of any type of substitutions on the benzene ring of chalcone moiety	Antibacterial against gram-positive bacteria; antifungal
N'-(4-(arylamino)-6-(thiazol-2-ylamino)-1,3,5-triazin-2yl)isonicotinohydrazides	Electron-withdrawing substituent's on aromatic ring increases both antifungal and activity against bacteria; the presence of hydrophobic substituent at position 4 on the phenyl moiety increases the antimicrobial potency	Antibacterial; antifungal
Ethyl 2-(2-(4-Substituted) acetamido)-4substituted-thiazole-5-carboxylate derivatives	A bulkier alkyl substitution on the thiazole ring increases the antimicrobial activity	Antibacterial; antifungal
3,5-diphenyl-6-(5-p-toly1-1,3,4 thiadiazol-2yl)-3,3a,5,6 tetrahydro-2H pyrazolo[3,4-d]thiazole derivatives.	p-halo phenyl nucleus on thiazolo-pyrazole moiety produced broad-spectrum activity and possessed excellent potency.	Antibacterial; antifungal; antitubercular
Thiazole based chalcones - (*E*)-1-[4-methyl-2-(methylamino)thiazol-5-yl)-3-phenylprop-2-en-1-ones	Substitution with larger electron accepting groups like nitro and chloro enhance the activity against bacteria.	Antibacterial; antifungal

Thiazole clubbed 1-oxa-3,4-diazacyclopentadiene derivatives	The presence of electron accepting groups like halogen and nitro at p- position of aromatic phenyl ring yields the most potent compounds. (para> meta > ortho); the presence of an electron releasing group on the aromatic phenyl ring decreases or abolishes the antibacterial activity; substitution at the para position of phenyl ring by methoxy group yields good antifungal agents; since the methoxy group is electron releasing in nature, we can conclude that structural requirements for binding differ for bacterial and fungal cells	Antibacterial; antifungal
5- arylidene thiazole derivatives	The presence of electron withdrawing group i.e. halogen like F atom at the position four of the Bz group is required for the antibacterial activity. Electron donating group like alkyl, hydroxide or methoxy group, when substituted on the phenyl ring, results in compounds with activity even better than reference drugs. Substitution with bulky electron accepting groups like $NO_2$and halogen groups (-Cl; inductively) diminishes the antibacterial property.	Antibacterial; antifungal
Arylazothiazole derivatives	The antifungal activity is more pronounced when both Ar and R are aromatic as against compounds where R is aliphatic which are furthermore than when both Ar and R are non-substituted. The activity is lowest when aromatic substitution is with halogen or NO_2.	Antifungal
Tetrahydrothiophene-3-one based thiazoles	Electron donating substitutions like halogens (mesomerically), alkyl, methoxy, etc enhances the antifungal activity	Antifungal
(*E*)-2-(2-(cyclohexylmethylene) hydrazinyl)-4-(4-substituted phenyl)thiazoles	Electron donating substitutions like halogens, alkyl, methoxy, etc. at 4^{th} position enhances the antifungal activity	Antifungal
4-aryl -2-(2,3,5-trichlorophenyl)-1,3-thiazoles	Established SAR not available	Antifungal; antibacterial
Methylsulfonyl benzothiazoles	Established SAR not available	Antibacterial; antifungal; anticancer
7-methylbenzo[d] thiazolehydrazones	Presence of electron donating groups in the molecule like hydroxyl and methoxy group increases the antibacterial activity. Presence of thiophene moiety could attribute towards better antibacterial action since thiophenes have been reported to inhibit bacterial FA synthesis process. More the number of phenolic groups on the phenyl ring more is the antibacterial activity. More the number of methoxy groups on the phenyl ring more is the antibacterial activity. If an electron accepting substituents like a halogen or NO_2 is present, it gives inactive compounds. If both electrons accepting and electron donating substitution is present, then the antibacterial activity decreases.	Antibacterial

Conclusion

In this review, we have reported synthesis schemes of thiazole derivatives possessing antimicrobial action. Altering the structural features and incorporation of different type of substituents vastly affect the antibacterial and antifungal potency of the thiazole derivatives. Most of the derivatives are more active against gram-positive bacteria like 2-phenylamino-thiazole derivatives; as compared to action against gram-negative bacteria and fungus. Cytotoxicity studies have been reported for only a few classes like 5,6-dihydroimidazo[2,1-*b*]thiazole derivatives, revealing them to be safe for the human cell line. Hence more cytotoxic studies need to be performed. Further investigations, advancements, and improvements in the chemistry of these derivatives could potentially lead to design novel and nonresistant antimicrobial agents.

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