Thiazole: A Remarkable Antimicrobial And Antioxidant Agents

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Summary

Antibiotics are, by definition, natural products biosynthesized by microorganisms that are toxic to other species of microorganisms. Susceptible bacteria can acquire resistance to an antimicrobial agent via new mutations. Free radicals formation leads to atherosclerosis, cancer, inflammatory joint disease, asthma, diabetes, senile dementia and degenerative eye disease. Hetero-aromatic Some novel Thiazole derivatives shows potential Antimicrobial and Antioxidant activity. So the thiazole nucleus has been attracted as a lead.

Key Words: Thiazole, Antimicrobial, Free radicals, Mutation, Resistance

Introduction

Antibiotics are, by definition, natural products biosynthesized by microorganisms that are toxic to other species of microorganisms. Sulfonamides, trimethoprim and quinolones are man-made drugs and are therefore, strictly speaking, not antibiotics, but synthetic antibacterial agents[1].

When forced to use antimicrobials, optimum programmes of use must be employed to reduce the opportunities for resistance development. Making sure the right organism is being treated, by culturing and antimicrobial susceptibility testing, using knowledge of effective drug concentrations to kill the organism in the target tissues or fluids. Going beyond the mutant selection window, also helps to improve the long term clinical effect of an antimicrobial and reduces the development of resistance[2].

The infectious disease is the second leading cause of death in the worldwide due to chemotherapeutic agent resistant microorganisms. The extensive and improper use of antibiotic led to the mutation in microorganism. Mutated bacteria have acquired gene producing novel machinery to overcome the action of many antibiotics. As a result, now with every possible bacterial infection resistant to antibiotic treatment is a common phenomenon. Hence the research still on antimicrobial agent is continuously going on to develop novel molecules[3].

Susceptible bacteria can acquire resistance to an antimicrobial agent via new mutations. Such spontaneous mutations may cause resistance by:-

(1) Barrier Mechanism: Decrased permeability, efflux pumps
   - ✓ Upregulating pumps that expel the drug from the cell (efflux of fluoroquinolones in *S aureus*).

(2) Inactivation enzymes
   - ✓ Altering the target protein to which the antibacterial agent binds by modifying or eliminating the binding site (e.g., change in penicillin-binding protein 2b in pneumococci, which results in penicillin resistance.

(3) Drug Target
   - ✓ Single Mutation in key gene

(4) Anti-TB drug resistance
   - ✓ Modification by spontaneous, predictable chromosomal mutation of key target genes
   - ✓ Stepwise accumulationof individual mutation in several independent genes

(5) Modification Downregulating or altering an outer membrane protein channel that the drug requires for cell entry (e.g., OmpF in *E coli*).

(6) Resistance is transferred from one bacterium to another by extrachromosomal R factor (DNA) that self replicate and are transferred by conjugation (Direct contact).

Bacterial resistance developed in Antimicrobial Drugs

1. Bacteria become resistant to **sulfonamides**:
   - Synthesizing large amounts of PABA. It takes 5,000 to 25,000 molecules of sulfonamide to compete with 1 molecule of PABA. Resistant cells synthesize PABA at 70x the rate of normal cells.
     - ✓ PABA from pus can compete with sulfonamides (also preformed nucleotides)
     - ✓ PABA can be produced by hydrolysis of procaine
   - Bacterial dihydropteroate synthetase is altered so that it no longer is inhibitable by sulfonamides.
   - Bacteria utilize "salvage pathway" which bypasses 1-carbon synthesis of bases Genes for sulfonamide resistance are transferred by R-plasmids. Generally, one resistance phenotype will confer resistance to all sulfonamides. Cross-resistance to sulfonamides and other drugs also occurs (multiple genes on same plasmid)
2. Bacteria become resistant to **Quinoline**:
   - Resistant bacteria appear to have an altered DNA gyrase, and/or altered drug transport properties.
3. Bacteria become resistant to **Third-Generation Cephalosporins**:
   - The acquisition of plasmid-encoded β-lactamases, such as TEM-1, TEM-2, or SHV-1, which hydrolyze and inactivate these drugs. Some *E coli* strains develop resistance to third-generation cephalosporins and monobactams (i.e., aztreonam) through the acquisition of ESBLs, commonly arising through mutation of TEM-, SHV-, or CTX-M–type enzymes.

4. Bacteria become resistant to **High-Level Vancomycin**:
   The first report of an MRSA strain with reduced susceptibility to vancomycin (MIC=8 µg/mL, reported as a vancomycin-intermediate *S. aureus* [VISA]) appeared in Japan in 1997.
   - The exact mechanism by which VISA isolates become resistant to vancomycin remains unclear, but it probably involves thickening of the organism's cell wall due to the accumulation of cell wall fragments capable of binding vancomycin extracellularly, and changes in several metabolic pathways that slow cell growth.
5. Bacteria become resistant to **Antitubercular drugs**
   - Bacteria become resistant to **Isoniazid**
     - ✓ Mutation in atleast 5 genes e.g KatG-codes for catalase – peroxidase.
   - Bacteria become resistant to **Rifampin**
     - ✓ Mutation in the target, DNA depended RNA polymerase, reduce binding of RIF to the polymerase.
   - Bacteria become resistant to **Ethambutal**
     - ✓ Single amino acid substitutions in embA gene.
   - Bacteria become resistant to **Pyrazinamide**
     - ✓ Loss of pyrazinamidase activity, Decrease formation of active moiety
     - ✓ Develops quickly if used as monotherapy.
   - Bacteria become resistant to **Streptomycin**
     - ✓ Ribosomal protein mutation
     - ✓ Develops gradually over course of therapy
   - Bacteria become resistant to **Ethionamide**
     - ✓ Mutation in inhA gene
     - ✓ Develops gradually over course of therapy
     - ✓ Possible cross resistance with Isoniazid
   - Bacteria become resistant to **Capreomycin**
     - ✓ Mutation in tlyA
   - Bacteria become resistant to **Linezolid**
     - ✓ Ribosomal RNA mutation
6. Bacteria become resistant to **Multidrugs**
   - Multidrug resistance is observed in clinical isolates of *P aeruginosa*. Multidrug resistance often reflects not one but a combination of resistance mechanisms. Efflux pumps are common components of multidrug-resistant *P aeruginosa* isolates, and prevent accumulation of antibacterial drugs within the bacterium, extruding the drugs from the cell before they have the opportunity to achieve an adequate concentrationat the site of action.
   - The 4 major efflux systems of *P aeruginosa* are MexABOprM, MexXY-OprM, MexCD-OprJ, and MexEFOprN. MexAB-OprM and MexXY-OprM contribute to intrinsic multidrug resistance, whereas overexpression of MexXY-OprM or MexCD-OprJ has been associated with acquired multidrug resistance. MexAB-OprM and MexXYOprM may also be

overexpressed. In each case, over-expression is caused by a mutation in 1 of the genes encoding a protein regulating expression of efflux system components.

- The fact that the efflux systems can mediate resistance to a variety of drug classes makes them very effective mechanisms of resistance[3-5].

Principal mechanism of action of Antimicrobial agent[5, 6]

Most antimicrobial agents used for the treatment of bacterial infections may be categorized according to their principal mechanism of action. There are 4 major modes of action:

(1) Interference with cell wall synthesis
(2) Inhibition of protein synthesis
    - Bind to 50S ribosomal subunit
    - Bind to 30S ribosomal subunit
(3) Interference with nucleic acid synthesis
    - Inhibit DNA synthesis
    - Inhibit RNA synthesis
(4) Inhibition of a metabolic pathway
(5) Disruption of bacterial membrane structure

Role of free radicals in disease

Evidence is accumulating that most of the degenerative diseases that afflict humanity have their origin in deleterious free radical reactions. These diseases include atherosclerosis, cancer, inflammatory joint disease, asthma, diabetes, senile dementia and degenerative eye disease[7]

Thiazole: Biological Aspects

Raju and coworkers[8] synthesized 2, 4-disubstituted Thiazole as antibacterial agent. Cevera and coworkers[9] synthesized 2, 5- Disubstituted 1, 3-Azoles as antibacterial compounds. Mehta and Patel[10] synthesized thiazole with thiazolidinone and azetidinone as Antibacterial compounds. Shakeel AS and coworkers[11] Synthesized Thiazole Schiff bases as Antibacterial agent. Kopnarr M and coworkers[12] synthesized New 2-Amino-4-[3-methyl-3-(5,6,7,8-tetrahydro-2-naphthyl)cyclobutyl]thiazole Derivatives as Antifungal agent. Logu and coworkers[13] reported *In vitro* Antifungal activity of 2-cyclohexylidenhydrazo-4-phenyl-thiazole against clinically isolated *Candida albicans spp.* Capan and Coworkers[14] synthesized 6-Phenylimidazo[2,1-b]thiazole Derivatives as Antifungal agents.

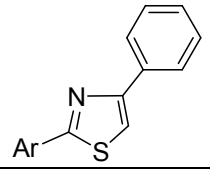
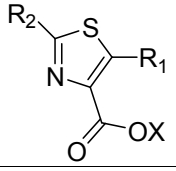
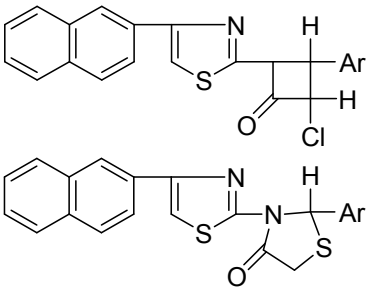
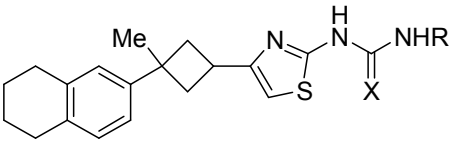
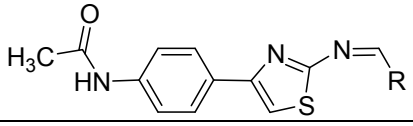
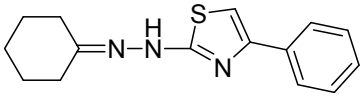
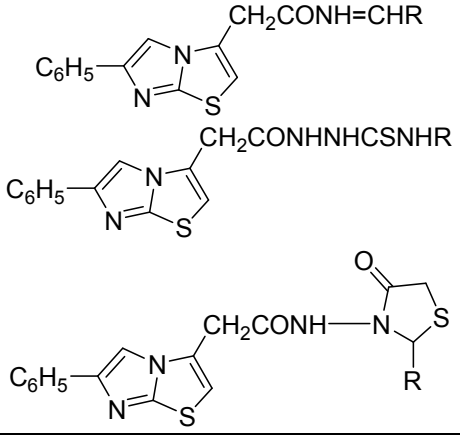
Chang li lu and coworkers[15] synthesised novel 2-methyl-4-trifluromethyl-thiazole-5-carboxamide derivatives and evaluated for fungicidal and insecticidal activity. Pattanaik JM and coworkers[16] have been synthesized a series of 3-aryl-2-(4'-aryl thiazole-2'- ylaminomethyl) quinazol-4(3H)-ones as antifungal agent. Lui HL and coworkers[17] synthesized 2-imino-3-(4-arylthiazol-2- yl)thiazolidin-4-ones and a series of their 5-arylidine derivatives and synthesized for antifungal agent. Bakar and coworkers[18] synthesized 2-substituted-4-hydroxythiazoles as antibacterial and antifungal agents. Bharti and coworkers[19] synthesized some novel schiff's bases containing 2, 4-disubstituted thiazole as antibacterial and antifungal agents. Omar and coworkers[20] synthesized Thiazole with Thiazolidinone as potent Antibacterial

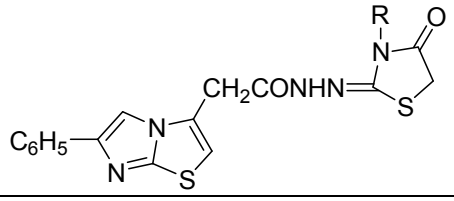
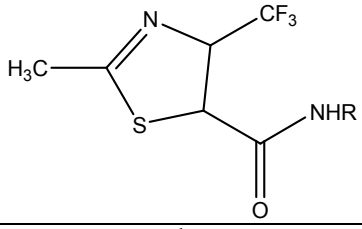
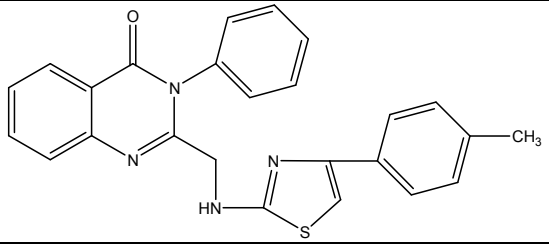
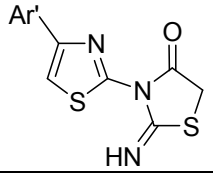
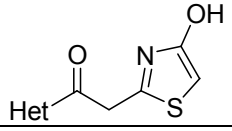
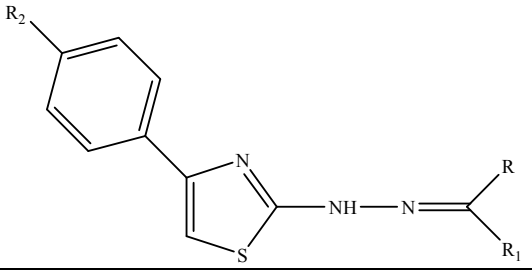
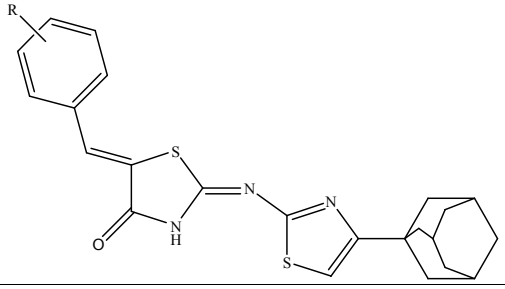
and Antifungal agents. Narayana and coworkers[21] synthesized some novel cinnolinyl thiazole derivatives as Antibacterial and Antifungal agents. Narayana and coworkers[22] synthesized some novel 4-(2-Chloropyridin-4-yl)-N-Aryl-1,3-Thiazol-2-Amine derivatives as Antibacterial and Antifungal agents.

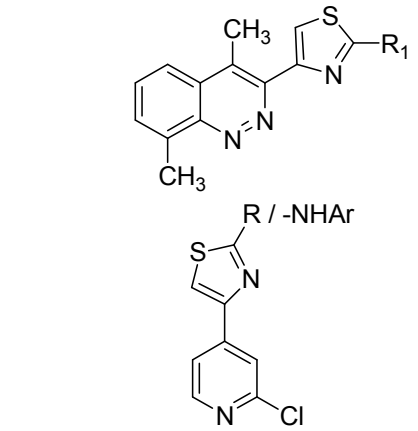
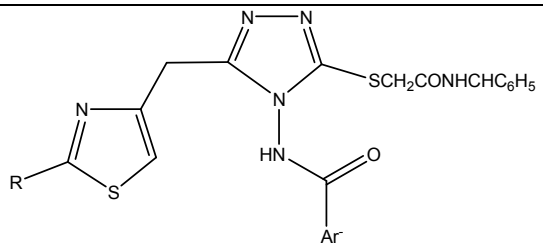
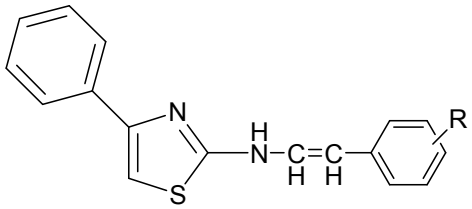
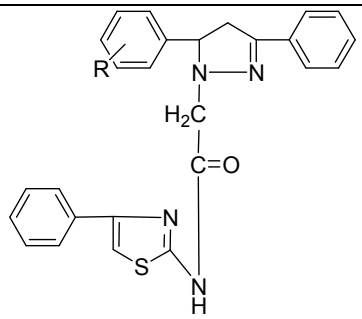
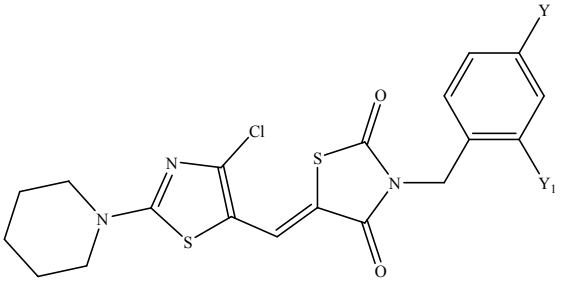
Mahendra S and coworkers[23] synthesized a series of N-{4-[(4-amino-5-sulfanyl-4H-1,2,4- triazol-3-yl)methyl]-1,3-thiazol-2-yl}-2-substituted-amide derivatives and screened for their preliminary *in vitro* antibacterial and antitubercular activity. Baviskar and coworkers[24] synthesized thiazole containing chalcones as Antimicrobial agents. Saravanan and coworkers[25] synthesized 4-phenyl-2-substituted thiazole derivatives as Antimicrobial compounds. Unlusoy and coworkers[26] synthesized Some New 3-Substituted Benzyl-5-(4-chloro-2-piperidin-1ylthiazole-5-yl-methylene)-thiazolidine-2,4-dione Derivatives as Antimicrobial compounds. Vicini and coworkers[27] synthesized thiazole with thiazolidinone as Antimicrobial compounds. Jagani and corkers[28] synthesized 3-thiazole substituted 2-styryl-4(3H)-quinazolinone derivatives as Antimicrobial agents. Kumar S and coworkers[29] synthesizes 2- aminothiazole derivatives as antimicrobial agent.

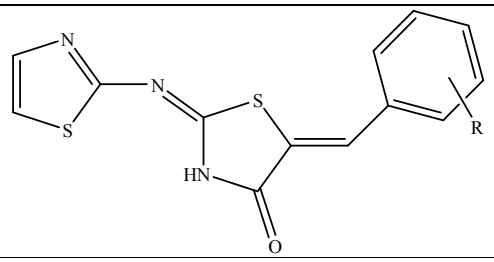
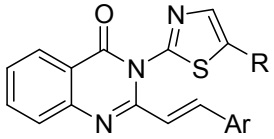
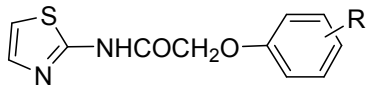
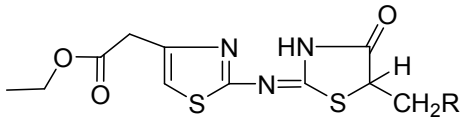
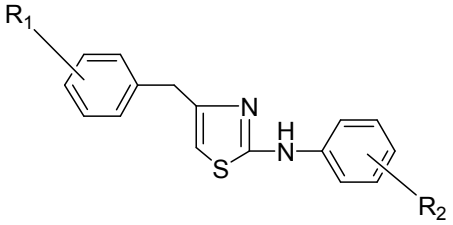
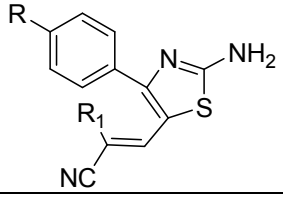
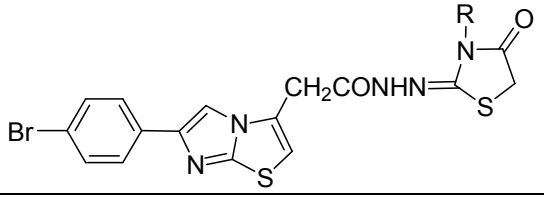
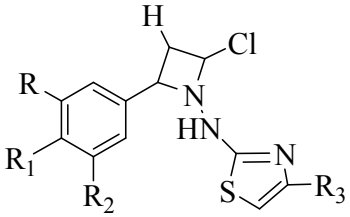
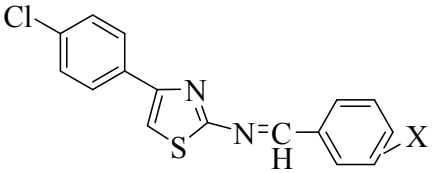
Altintas H and coworkers[30] synthesizes mannich bases of some 2-[4-carbethoxymethylthiazol-2-yl]imino-4-thiazolidinones as Antimicrobial agent. Siddiqui N and coworkers[31] synthesizes some new 1, 3-thiazole-2,4-diamine derivatives as Antimicrobial agent. Thumar and coworkers[32] synthesizes Thiazole-5-carboxaldehydes and Their Ylidenenitriles Derivatives as Antimicrobial agents. Ulusoy N and coworkers[33] synthesizes 6-(4-Bromophenyl)-imidazo[2, 1-b] thiazole Derivatives as Antimicrobial and Antimycobacterial agents. Jaishree V and coworkes[34] synthesized A series of novel N2-[2-chloro-4(3,4,5-trimethoxy phenyl azetidin-1-yl]-N4-(substituted aryl)-1,3-thiazole-2,4-diamine and screened for antioxidant activity. Kavitha PN and coworkers[35] synthesized some novel 4-(4-Chlorophenyl)2-aryl substituted metheniminothiazoles as possible antioxidant agents. Kachroo M and coworkers[36] synthesized N-[(4E)- arylidene-5-oxo-2-phenyl-4, 5-dihydro-1*H*-imidazol-1-yl]-2-(2-methyl-1, 3-thiazol-4-yl)acetamide and screened for their Antibacterial and Antioxidant Activity. Adhikari and coworkers[37] synthesized some new 2-(4-alkkylthiophenoxy)-4-substituted-1, 3-thiazole as possible anti-inflammatory and antimicrobial agents. Pattan R and coworkers[38] synthesized new series 5-[1-(4-(4-sustituted-phenylamino)-meth-(z)-ylidene]-thiazolidine-2,4-diones derivatives and screened for their antitubercular activity.
Pattan S and coworkers[39] reported a new series of N-3[4-(4-chlorophenyl thiazole-2-yl)-2-amino methyl]quinazoline-4(3H)-one and their derivatives and screened for their anti tubercular activity. Andreani A and coworkers[40] reported a number of selected imidazo[2,1-b]thiazoles derivatives and screened for anti-tubercular activity. Manian and coworkers[41] synthesized 2-substituted anilino/phenyl/benzyl/-5-substituted-4- phenylamido-(3-*o*-chlorophenyl-5-methylisoxazolyl) thiazoles and screened for *in vitro* antitubercular activity. Pattan and coworkers[42] synthesized and evaluated some of the new substituted phenyl thiazoles derivatives for anti-tubercular activities.

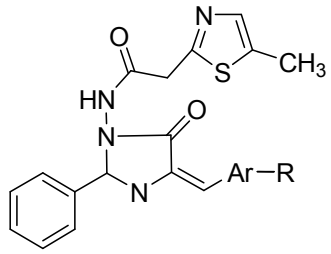
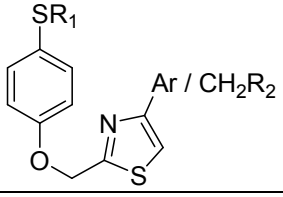
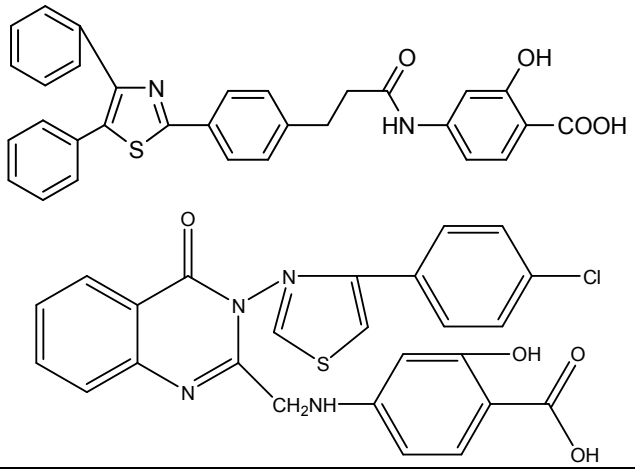
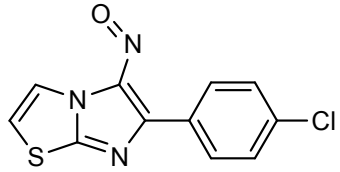
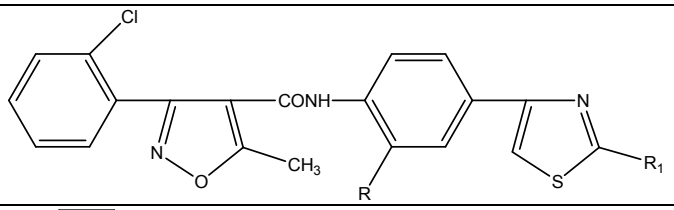
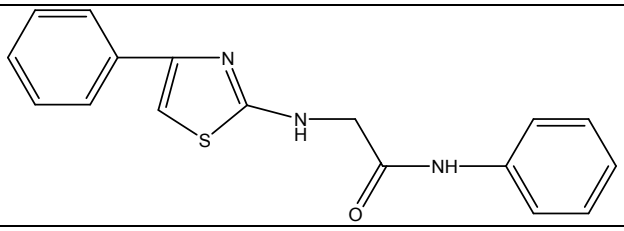
Table: 1 Enlist thiazole derivatives with their corresponding biological activity

Derivatives of Thiazole	Biological Activities	References
	Antibacterial	**[8]**
	Antibacterial	**[9]**
	Antibacterial	**[10]**
	Antibacterial	**[11]**
	Antibacterial	**[12]**
	Antifungal	**[13]**
	Antifungal	**[14]**

		
	Fungicidal	**[15]**
	Fungicidal	**[16]**
	Fungicidal	**[17]**
	Antibacterial and Antifungal agents	**[18]**
	Antibacterial and Antifungal agents	**[19]**
	Antibacterial and Antifungal agent	**[20]**

	Antibacterial and Antifungal agents	**[21]** **[22]**
	Antibacterial and Antitubercular Agents	**[23]**
	Antimicrobial	**[24]**
	Antimicrobial	**[25]**
	Antimicrobial	**[26]**

	Antimicrobial	**[27]**
	Antimicrobial	**[28]**
	Antimicrobial	**[29]**
	Antimicrobial	**[30]**
	Antimicrobial	**[31]**
	Antimicrobial	**[32]**
	Antimicrobial and Antimycobacterial agents	**[33]**
	Antioxidant	**[34]**
	Antioxidant	**[35]**

	Antioxidant and Antibacterial Agents	**[36]**
	Antimicrobial and Anti-inflammatory	**[37]**
	Antitubercular	**[38]** **[39]**
	Antitubercular	**[40]**
	Antitubercular	**[41]**
	Antitubercular	**[42]**

Conclusion

The Present review describes in brief on Bacterial Resistance and Modes of Antimicrobial agents. Thiazole is a heterocyclic aromatic compound, having wide range of biological activities like Antimicrobial, Antioxidant, Anti-inflammatory, Antiviral, Anti-HIV, Anticancer, Diuretic, Hypolipidemic etc. This review compiled Thiazole derivatives as Antimicrobial and Antioxidant activity.

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