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A Review on Biological Activity of Imidazole and Thiazole Moieties and their Derivatives

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ABSTRACT

Heterocyclic compounds comprise the major family of organic compounds. These are enormously essential with wide range of synthetic, pharmaceutical and industrial applications and are famous for their biological activities. There is an extensive spectrum of biological activities shown by many compounds containing five membered heterocyclic rings in their structure. The high therapeutic properties of these heterocycles have encouraged the medicinal chemists to synthesize a large number of novel chemotherapeutic agents. These heterocyclic compounds have broadened scope in remedying various dispositions in clinical medicines. Imidazoles and thiazoles have been reported to show pharmacological activities. This articles aims to review the work reported, their chemistry and biological activities of imidazole and thiazole during past years.

Key words: Heterocyclic, pharmaceutical, biological, chemotherapeutic

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INTRODUCTION

Heterocycles form by far the major of classical divisions of organic chemistry and are of immense use biologically and industrially. It is well known that the heterocycles are present in all kinds of organic compounds of interest in electronics, biology, optics, pharmacology, material sciences and so on. Heterocyclic nucleus imparts an important function in medicinal chemistry and serves as a key template for the development of various therapeutic agents[1]. Mostly researchers have maintained their interest in sulfur and nitrogen-containing heterocyclic compounds through decades of historical development of organic synthesis[2] but heterocycles with other heteroatoms such as oxygen[3], phosphorus[4] and selenium[5] also appears. There are widespread therapeutic uses of synthetic heterocycles such as antibacterial, antimycobacterial, trypanocidal, anti-HIV activity, genotoxic, herbicidal, analgesic, antiinflammatory, muscle relaxants, antileishmanial agents, anticonvulsant, anticancer, antimalarial, antifungal and lipid peroxidation inhibitor, antitubercular, hypnotics, antidepressant, antitumoral, anthelmintic and insecticidal agents[6,7,8,9,10,11]. The exploration for new biologically active heterocyclic analogues continues to be an area of intensive research in medicinal chemistry.

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Structure and Pharmacological activities

Imidazole: Imidazoles are well known heterocyclic compounds having important feature of a variety of medicinal agents. Imidazole is a planar 5-membered ring. It is a highly polar compound with dipole moment of 3.61 D. It is highly soluble in water and also is soluble in other polar solvents. It exists in two equivalent tautomeric forms because the proton can be located on either of the two nitrogen atoms. Due to the presence of a sextet of π-electrons the compound is classified as aromatic. It consists of a pair of electrons from the protonated nitrogen atom and one from each of the remaining four atoms of the ring. Imidazole is amphoteric, i.e., it can function as both an acid and as a base.

The literature surveys depicts that Imidazole derivatives shows various pharmacological activities such as anti viral, anti inflammatory and analgesic, anti depressant, anti fungal and anti-bacterial, anti cancer, anti tubercular and antileishmanial activity.

Anti viral activity: Chronic infection with the Hepatitis C Virus (HCV) is a major cause for developing cirrhosis and hepatocellular carcinoma. A series of novel compounds, 5-alkynyl-1-beta-D-ribofuranosylimidazole-4- carboxamides have been synthesized and identified as broad-spectrum antiviral agents. 5-Ethynyl-1-beta-D-ribofuranosylimidazole-4-carboxamide (EICAR) 1, the most potent congener of the

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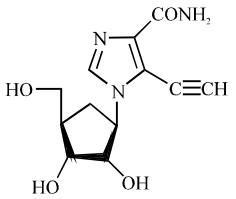
group, showed antiviral potency about 10-to 100-fold superior than that of ribavirin, 2[12]. EICAR is an antiviral drug for the treatment of pox-, toga-, arena-, reo-, orthomyxo and paramyxovirus infections.



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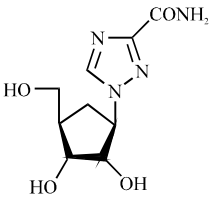

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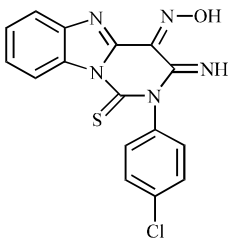
Anti inflammatory and analgesic: A new series of pyrimido [1,6-a] benzimidazole and pyrimido -imidazo [4,5-b] pyridine derivatives have been synthesized with the purpose of developing a new anti-inflammatory-antimicrobial agent with analgesic activity[13]. All the compounds were found to be potent anti-inflammatory and analgesic agents. In particular compound 3 showed the most potent anti-inflammatory and analgesic activity. Moreover docking studies of compounds that have highest anti anti-inflammatory activity showed that compound 3 displayed stronger binding interactions with the active site of the human COX-2 enzyme. Compound 4 was found to be the most active anti-microbial agent.



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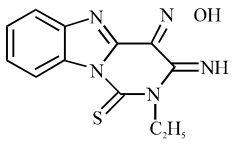

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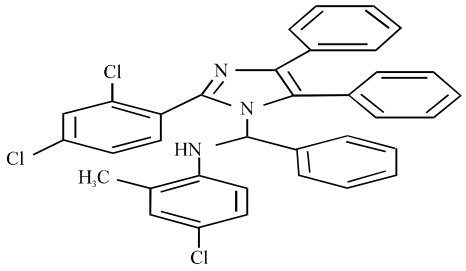
A series of N-((2-substituted phenyl)-4,5-diphenyl-1H-imidazol-1yl)(phenyl)methyl) substituted amine derivatives have been synthesized by 2-substituted 4,5-diphenyl imidazole derivatives starting from benzyl and aromatic aldehyde[14]. The newly synthesized compounds were screened for analgesic and anti-inflammatory activities by hot plate and carrageenan induced rat paw oedema methods. Compounds 5 and 6 have showed potent anti-inflammatory activity and compounds 5, 6 and 7 showed good analgesic activity.



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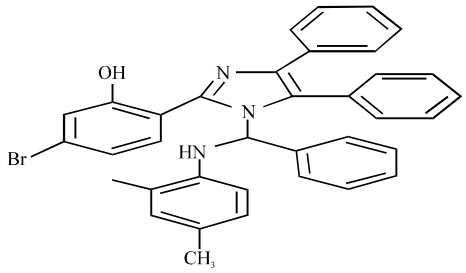

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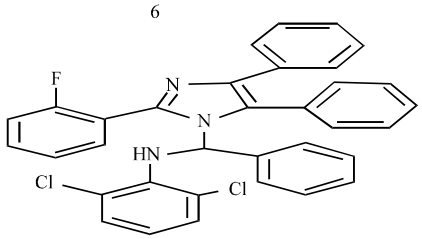

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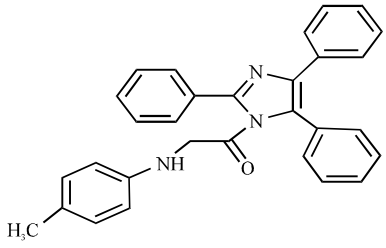
A series of 2,4,5-triphenyl-1H-imidazole-1-yl derivatives have been synthesized and tested for their antiinflammatory activity *in vitro* using Phenylbutazone as a reference drug and antimicrobial activity using clotrimazole and ciprofloxacin as a standard drug[15]. All the synthesized compounds were screened for their anti-fungal activity against *Candida albicans* and for antimicrobial activity against *B. subtilis* and *E. coli*. Compound 8 was found to be the most potent derivative of the series.



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Anti depressant activity: Three moclobemide analogues have been synthesized by replacing

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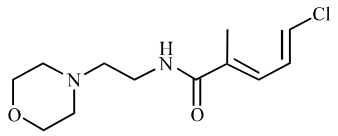
moclobemide phenyl ring with substituted imidazoles[16]. Moclobemide 9 is a selective and reversible monoamine oxidase-A inhibitor and is used as an antidepressant. So, N-[(4-morpholinyl)ethyl)]-1-benzyl-2-(alkylthio)-1H-imidazole-5-carboxamides were synthesized and studied for the antidepressant activity using forced swimming test in mice. Analogues 10, 11 and 12 were found to be more potent than moclobemide.



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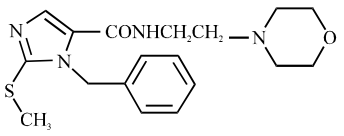

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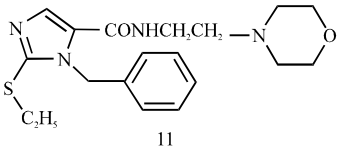

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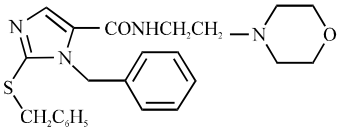

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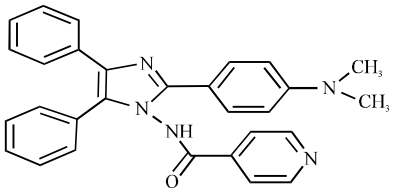
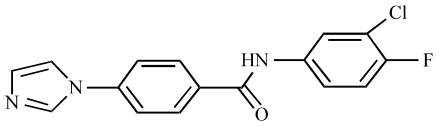
Anti cancer activity: Ten new aryl imidazoles incorporated with chemotherapeutic pharmacophores have ben synthesized and evaluated for their anti bacterial and short term anti cancer activity. All the synthesized substituted imidazoles have shown good antibacterial activity against gram negative bacterial strains *Klebsiella pneumoniae* and *Escherichia coli*. The synthesized imidazole derivatives possess significant cytotoxic activity against Ehrich's Ascites Carcinoma (EAC) cell lines and Dalton's Lyphoma Ascites (DLA) cell lines. Compound 13 showed the best anti cancer activity with CTC_{50} value of 98.56 and 31.25 $\mu g\ mL^{-1}$ against DLA and EAC cell line[17].



13

A new series of 1-substituted imidazole derivatives have been synthesized by taking different anilines and sulfonamides as substitutions[18]. The compounds were screened for their anticancer and antimicrobial activities. Compound 14 exhibited highest activity against cervical cancer. Compound 15 showed good antifungal activity while compound 16 showed good antibacterial activity.



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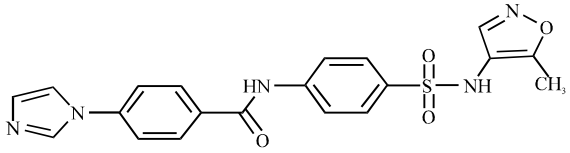

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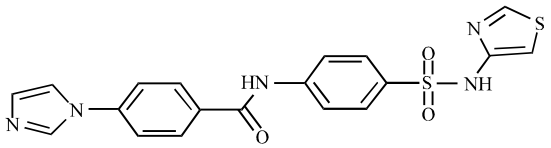
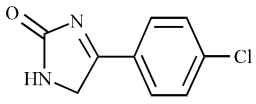


16

Antimicrobial activity: The antimicrobial activity of the synthesized heterocyclic viz 4-(substituted phenyl)-1H-imidazol-2(5H)-one/thione/imine compounds have been studied against *Staphylococcus aureus, Escherichia coli, Salmonella typhi, Proteus vulgaris*. Compounds 17, 18 and 19 are the chloro substituted analogs. The results have indicated that *P. vulgarius* is sensitive to all the synthesized heterocycles. *S. aureus* is less sensitive to the synthesized heterocycles. The imidazoles have been found to show good activity against *E. coli*, it shows average activity against *S. typhi*[19].



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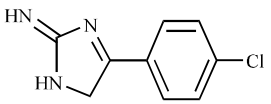

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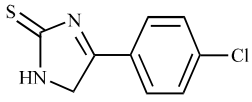

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Antileishmanial activity: A series of N,N'-disubstituted ethylenediamine and imidazolidine derivatives have been synthesized and their *in vitro*

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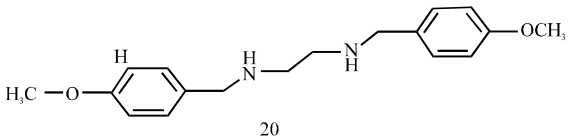
biological activities against *Leishmania* species have been evaluated. Of the nine synthesized compounds, five displayed a good activity in both *L. amazonensis* and *L. major promastigotes*. The compounds 1,2-Bis (p-methoxybenzyl) ethylenediamine 20 and 1,3-Bis (p-methoxybenzyl)imidazolidines 21 showed the best activity on intracellular amastigotes, with IC_{50} values of 2.0 and 9.4 $\mu g\ mL^{-1}$, respectively[20].



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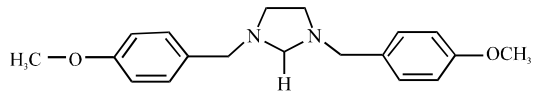

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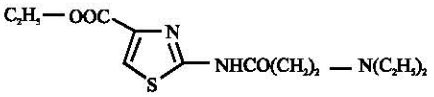
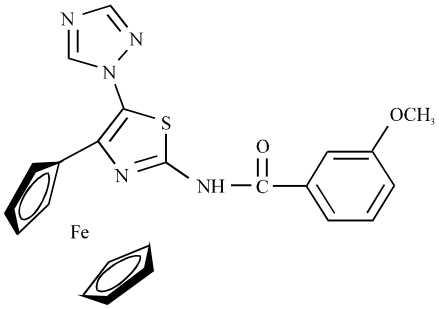
Thiazole: Thiazole, or 1,3-thiazole, is a heterocyclic compound that contains both sulfur and nitrogen; the term 'thiazole' also refers to a large family of derivatives. Thiazoles are structurally similar to imidazoles, with the thiazole sulfur replaced by nitrogen. Thiazole itself is a pale yellow liquid with a pyridine-like odor and the molecular formula C_3H_3NS. Thiazole rings are planar and aromatic. There is larger pi-electron delocalization in thiazoles as compared to corresponding oxazoles and hence have greater aromaticity which is evidenced by the chemical shift of the ring protons in proton NMR spectroscopy (between 7.27 and 8.77 ppm), clearly indicating a strong diamagnetic ring current. The thiazole ring is a component of the vitamin thiamine (B_1).

Thiazoles are important class of heterocyclic compounds, found in many potent biologically active molecules such as Sulfathiazol (antimicrobial drug), Ritonavir (antiretroviral drug), Abafungin (antifungal drug) with trade name Abasol cream and Bleomycine and Tiazofurin (antineoplastic drug)[21]. In recent times, the applications of thiazoles were found in drug development for the treatment of allergies[22], hypertension[23], inflammation[24], schizophrenia[25], bacterial[26], HIV infections [27], hypnotics [28] and more recently for the treatment of pain[29], as fibrinogen receptor antagonists with antithrombotic activity[30] and as new inhibitors of bacterial DNA gyrase B[31].

Antitumor activity: The synthesis of several new ethyl 2-substituted aminothiazole-4-carboxylate analogs have been described and the prepared compounds were tested for their in vitro antitumor activity against 60 human tumor cell lines by the National Cancer Institute (NCI) and showed potential anticancer activity. Ethyl 2-[3-(diethylamino)-propanamido]-thiazole-4-carboxylate 22 exhibited remarkable activity against RPMI-8226 leukemia cell line with GI_{50} value of 0.08 μM and a broad spectrum activity against all the tumor cell lines used with GI_{50} (MG-MID) value of 38.3 μM[32].



A series of novel ferrocenyl containing thiazole derivatives have been synthesized from 2-amino-4-ferrocenyl-5-(1H-1,2,4-triazole-1-yl)-1,3-thiazole and substituted benzoyl chloride and evaluated for their anticancer activities[33]. Thiazole 23 and 24 showed good inhibition percentages against human cancer cell lines.



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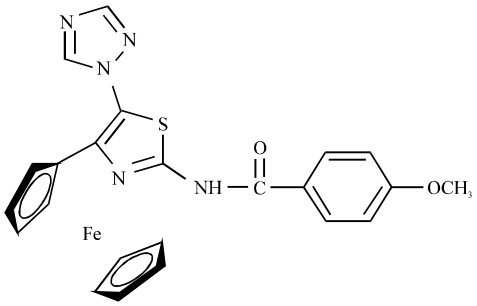

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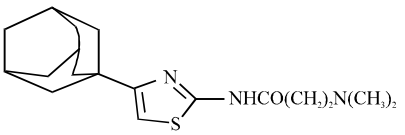
Anti-inflammatory activity: A series of adamantane derivatives of thiazolyl-N substituted amides were synthesized and tested for anti-inflammatory activity as well as lipoxygenase and cycloxygenase inhibitory actions. Among the tested compounds, 25 showed potent activity[34].



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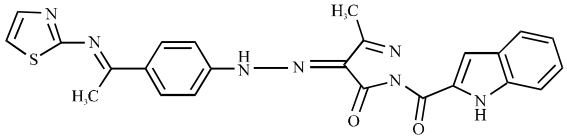
Antimicrobial activity: Six 3-methyl-1-[(5-substituted-1H-indol-2-yl)carbonyl]-4-{[4-(substitutedthiazol-2-yl)iminoethyl)phenyl] hydrazono}-2-pyrazolin-5-one derivatives were synthesized by conventional and microwave methods[35]. The synthesized compounds were tested for their antimicrobial activity against six strains of bacteria and three fungal strains. Compound 26 showed a broad spectrum of activity against bacteria and compound 27 exhibited excellent antifungal activity, while most of the other compounds showed varying antimicrobial activity.



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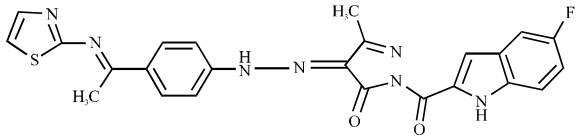

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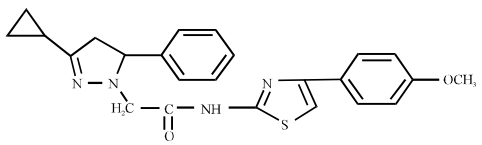
A series of thiazoles were synthesized by incorporation of pyrazoline ring at position 2 of 2-hydrazinyl-N-(4-phenylthiazol-2-yl)acetamide by treating with chalcones[36]. The structures of the newly synthesized compounds were determined on the basis of their elemental analysis and spectroscopic data such as IR and HNMR spectra. The *in vitro* antimicrobial activities of the synthesized compounds were investigated against four pathogenic representative microorganism *Staphylococcus aureus* ATCC6538P, *Pseudomonas aeruginosa* ATCC9027, *Escherichia coli* ATCC8739 and Candida albicans ATCC2091 using Ampicillin, Imipenam and Clotrimazole as standard drugs. The compounds 28, 29 and 30 showed a moderate degree of potent antimicrobial activity.



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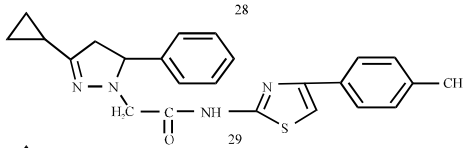

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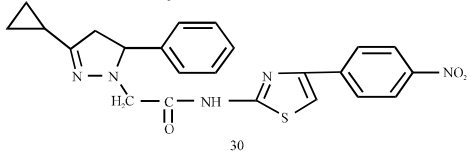

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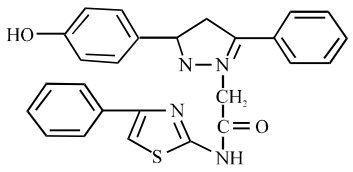
Antifungal activity: Novel thiazoles have been synthesized by incorporation of pyrazole moiety at 2nd position of 2-hydrazinyl-N-(4-phenylthiazol-2-yl) acetamide by treating with chalcones[37]. The chemical structures of the synthesized compounds were confirmed by means of IR, ^{1}H-NMR, Mass spectral and Elemental analysis. These compounds were screened for anti-bacterial (*Staphylococcus aureus* ATCC 9144, *Staphylococcus epidermidis* ATCC 155, *Micrococcus luteus* ATCC 4698, *Bacillus cereus* ATCC 11778, *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 2853 and *Klebsiella pneumoniae* ATCC 11298)) and anti-fungal (*Aspergillus niger* ATCC 9029 and *Aspergillus fumigatus* ATCC 46645) activities by paper disc diffusion technique. Most of the synthesized compounds exhibited significant anti-bacterial and anti-fungal activities. Among the synthesized compounds, 2-(5-(4-hydroxyphenyl)-3-phenyl-4,5-dihydropyrazol-1-yl)-N-(4-phenylthiazol-2 yl) acetamide 31 was found to exhibit the highest anti-bacterial activity and 2-(5-(4-hydroxy-3-methoxyphenyl)-3-phenyl-4,5-dihydropyrazol-1-yl)-N-(4-phenylthiazol-2-yl)acetamide 32 exhibited highest anti-fungal activity.



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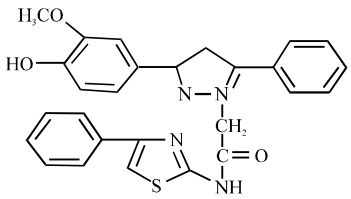
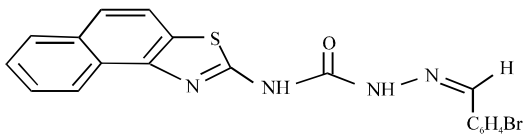


32

Anticonvulsant activity: Azam *et al.* designed and synthesized a series of N^4-(naphtha[1,2-d]thiazol-2-yl)semicarbazides 33 and evaluated for their anticonvulsant and neurotoxicity studies[38].



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Antibacterial activity: A series of 4'-(2-n-Butyl-4-chloro-5-hydroxymethyl-imidazol-1-yl-methyl-biphenyl-2-caboxylic acid- (4-phenyl/ substituted phenyl thiazole)-amide have been prepared. Compounds were

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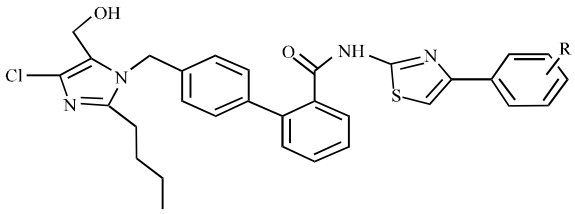
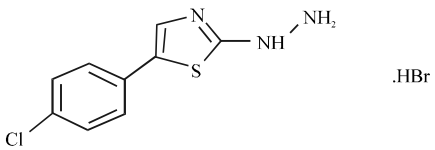
screened for their *in vitro* antibacterial activity against *S. aureus* and *B. subtilis* employing cup-plate method at the concentration of 100 μg mL^{-1} in nutrient agar media and also for *in vitro* antifungal activity against *C. albicans* and *A. niger* by cup plate method at 100 μg mL^{-1} concentration using sabouraud dextrose agar[39]. DMSO was used as solvent control for antimicrobial activity. Streptomycin and Griesuofulin were used as standard for antibacterial and antifungal activities, respectively. The structures of aminothiazole derivatives were confirmed on the basis of spectral data. The newly synthesized title compounds were screened for their *in vitro* antibacterial activity. Maximum antibacterial activity was observed in the compounds 34, 35, 36, 37 and 38. Fungicidal screening data also revealed that compounds 35, 37 and 38 showed maximum activity.



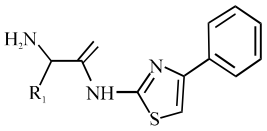
R = Cl, 34
F, 35
p-OCH_3, 36
-2,4-$(OCH_3)_2$, 37
-2,4-$(OCH_2CH_3)_2$, 38

The synthesis of 1-(5-(4-chlorophenyl)thiazol-2-yl)hydrazine hydrobromide 39 was carried out in a single step by condensation of 2-bromo-1-(4-chlorophenyl) ethanone with thiosemicarbazide in absolute ethanol[40]. The structure of the target compound was deduced by modern spectroscopic techniques including FTIR, ^{1}H and ^{13}C NMR spectroscopy and unequivocally confirmed by crystallographic data. The title compound has been screened for *in vitro* antibacterial screening by agar well diffusion method against ten different Gram positive and Gram negative bacteria and it exhibited strong efficacy against *B. subtilis* and *S. aureus*, respectively as compared to standard drug Levofloxacin.



39

Antihelmintic and insecticidal activity: Himaja *et al.*[41] synthesized a series of substituted thiazole containing N-methylated amino acids and peptides 40 and 41 by solution phase technique and subjected them to evaluation of antihelmintic and insecticidal activity[41]. Antihelmintic activities were carried out against earthworms (*Eudrilus eugeniea*) by Garg's method[42]. Insecticidal activitiy studies of the synthesized compounds were carried out against termites (*Coptotermis formasanus*) by Morita *et al*. method[43].



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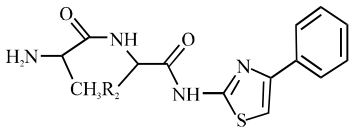

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CONCLUSION

The present review study showed that imidazole and thiazole derivatives signify an interesting class of compounds possessing a wide spectrum of biological activities. On the basis of various literature survey imidazole and thiazole derivatives show a variety of activity against antimicrobial, anti-inflammatory, analgesic, antitubercular, anticancer etc. Series of compounds can be synthesized by using same approach and further characterized and evaluated for desire pharmacological activity with high potency and low toxicity. Moreover the possible improvements in the activity can be achieved by slight modifications in the substituents on the imidazole and thiazole nucleus. Various recent new drugs developments in imidazole and thiazole derivatives show better effect and less toxicity. This has been noticed so far, that modifications on imidazole and thiazole moiety displayed important biological activities. It will be exciting to observe that these modifications can be utilized as potent therapeutic agents in future.

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