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A REVIEW ON THE BIOLOGICAL APPLICATIONS OF IMIDAZOLE, THIAZOLE AND THEIR DERIVATIVES

Syed Muzaffar Ahmad[1] and Mohd Syeed Shah[2]

[1,2] Department of Chemistry, Amar Singh College Srinagar J& K (India)

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 heterocyclic have encouraged the medicinal chemists to synthesize a large number of novel chemotherapeutic agents.

Keywords: *Heterocyclic, pharmaceutical, industrial applications, chemotherapeutic agents.*

Address for Correspondence:

Syed Muzaffar Ahmad and Mohd Syeed Shah

Department of Chemistry,

Amar Singh College, Srinagar, J& K (India).

syedmuzafar05@gmail.com

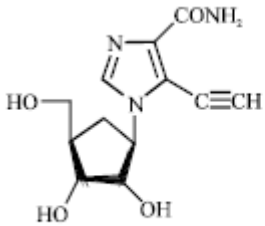
INTRODUCTION:

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 heterocyclic with other heteroatoms such as oxygen, phosphorus and selenium also appears. There are widespread therapeutic uses of synthetic heterocyclic such as antibacterial, ant mycobacterial, trypanocidal, anti-HIV activity, genotoxic, herbicidal, analgesic, anti-inflammatory[3-5], muscle relaxants, antileishmanial agents, anticonvulsant, anticancer, antimalarial, antifungal and lipid peroxidation inhibitor, ant tubercular, hypnotics, antidepressant, antitumor, anthelmintic and insecticidal agents[6]

Structure and Pharmacological activities of 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.

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 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 [7-8]



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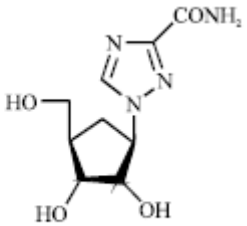

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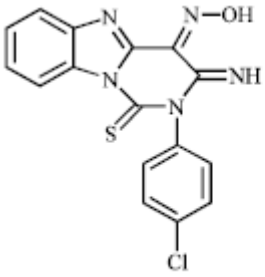
Anti-inflammatory and analgesic:

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[9]. 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 [10].



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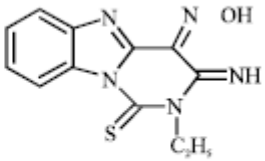

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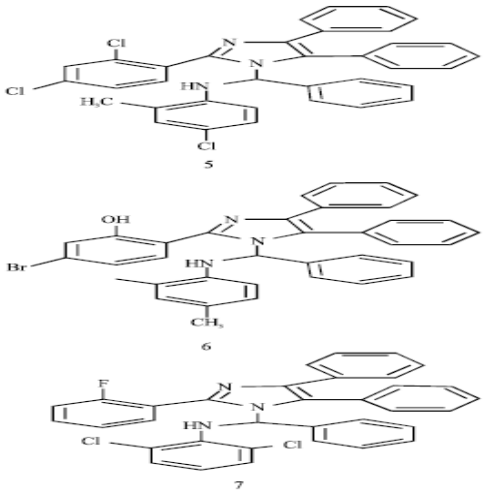
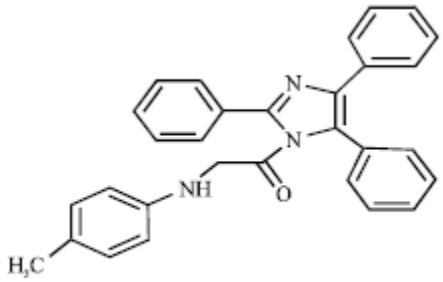
A series of N-((2-substituted phenyl)-4,5-diphenyl-1H-imidazol-1yl)(phenyl)methyl) substituted amine derivatives have been synthesized by 2-substituted 4,5-diphenyl imidazole derivatives starting from benzyl and aromatic aldehyde. The newly synthesized compounds were screened for analgesic and anti-inflammatory 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.



A series of 2,4,5-triphenyl-1H-imidazole-1-yl derivatives have been synthesized and tested for their anti-inflammatory activity *in vitro*using Phenylbutazone as a reference drug and antimicrobial activity using clotrimazole and ciprofloxacin as a standard drug[11]. 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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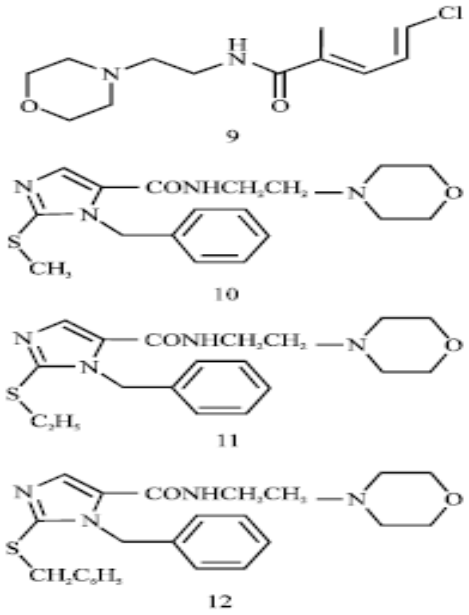
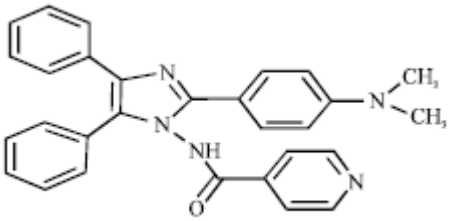
Anti-depressant activity: Three moclobemide analogues have been synthesized by replacing moclobemide phenyl ring with substituted imidazoles [12]. Moclobemide is a selective and reversible monoamine oxidase-A inhibitor and is used as an antidepressant. So, N-[(4-morpholinyl)ethyl)]-1-benzyl-2-(alkylthio)-1H-imidazole-5-carboxamides 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.



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 µg mL^{-1} against DLA and EAC cell line [13].



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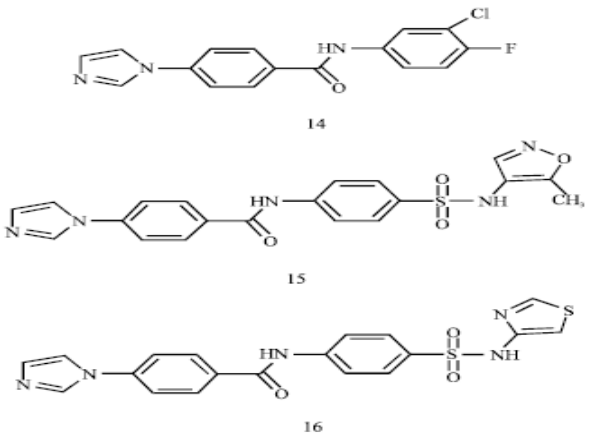
A new series of 1-substituted imidazole derivatives have been synthesized by taking different anilines and sulfonamides as substitutions [14]. The compounds were screened for their anticancer and antimicrobial activities. Compound 14 exhibited highest activity against cervical cancer. Compound 15 showed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



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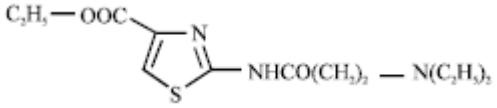
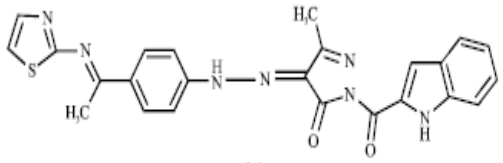
Thiazole: Thiazole, or 1,3-thiazole, is a heterocyclic compound that contains both sulfur and nitrogen; the term 'thiazole' also refers to a large family of derivatives. Thiazoles are structurally similar to imidazoles, with the thiazole sulfur replaced by nitrogen. Thiazole itself is a pale yellow liquid 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) [15].

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)[16]. In recent times, the applications of thiazoles were found in drug development for the treatment of allergies, hypertension, inflammation, schizophrenia, bacterial, HIV infections, hypnotics and more recently for the treatment of pain, as fibrinogen receptor antagonists with antithrombotic activity and as new inhibitors of bacterial DNA gyrase B [17-19].

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[20].



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[21]. 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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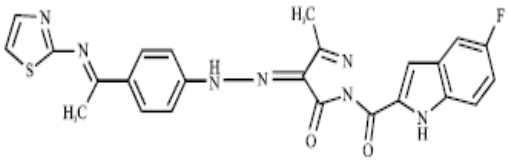

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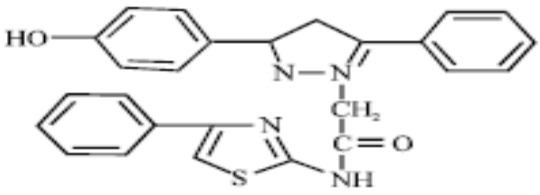
A series of thiazoles were synthesized by incorporation of pyrazoline ring at position 2 of 2-hydrazinyl-N-(4-phenylthiazol-2-yl) acetamide by treating with chalcones[22]. The structures of the newly synthesized compounds were determined on the basis of their elemental analysis and spectroscopic data such as IR and HNMR spectra. The *in vitro* antimicrobial activities of the synthesized compounds were investigated against four pathogenic representative microorganism *Staphylococcusaureus* ATCC6538P,*P seudomonasaeruginosa* ATCC9027, *Escherichia coli* ATCC8739 and Candida albicans ATCC2091 using Ampicillin, Imipenam and Clotrimazole as standard drugs[23].

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[24]. 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[24-25].



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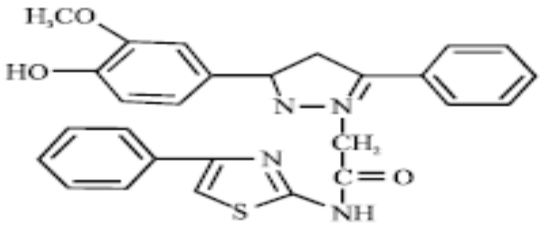

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CONCLUSION:

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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