Review Article

A Review on Five Membered Nitrogen Containing Heterocyclic Compounds with Various Biological Activities

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ABSTRACT

Heterocyclic compounds are a highly valuable and unique class of compounds. Different heterocyclic analogues have been evaluated for their diverse biological activities. Five membered heterocyclic compounds possess various pharmacological activities. Among them Nitrogen containing five membered heterocyclic compounds have crucial place in medicinal chemistry. This paper aims to review on the pharmacological activities of five membered nitrogen containing heterocyclic compounds.

Keywords: pyrazole, imidazole, pyrrole, triazole, pharmacological activities.

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INTRODUCTION

In the organic chemistry, largest families of organic compounds are belonging in the heterocyclic compounds. In our daily life heterocyclic compounds are of very essential. Among them five membered Nitrogen containing heterocyclic compounds in the wide range of medicinal chemistry such as antimicrobial, antitubercular, antiviral, anti-inflammatory, antibacterial, anti-obesity, antiparasitic, antifungal, antihistaminic, anticancer, antihypertensive, and other potential medicinal agents with their broad applications in pathology and diagnostics. This review paper high light the five membered nitrogen containing heterocyclic compounds and some of their biological activities.

Pyrazole

The term pyrazole was coined by Ludwig Knorr in 1883. Pyrazoles are a group of simple aromatic heterocyclic compounds which impart pharmacological effects on human beings. They are classified as alkaloids, although they are rare in nature. In 1959, the first natural pyrazole, 1-pyrazolyl-alanine, was isolated from seeds of watermelons. The pyrazole ring is a predominant structural moiety found in many pharmaceutically active compounds. This is mainly due to its ease of preparation and versatile pharmacological activity[1].

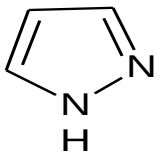


Figure 1: Pyrazole

Pyrazole, a five membered ring heterocycle, the N-atom at position 2 with two electrons are basic and therefore they are reacting with electrophiles, while as the N-atom at position 1 is acidic due to its imide nature, and pyrazole can lose this proton easily in the presence of a base. Pyrazoles are aromatic in nature due to their planar conjugated ring structure with six delocalized π-electrons [2].

Different tautomeric structures can be written for pyrazole. Unsubstituted pyrazole can be represented in three tautomeric forms.

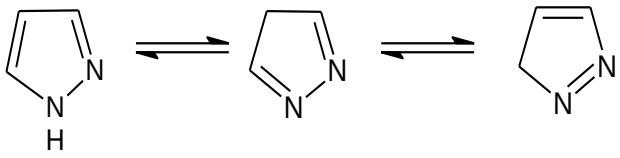


Figure 2:

Tautomeric forms of unsubstituted pyrazole.

Now a day's vast number of compounds with pyrazole nucleus have been reported to show a broad spectrum of biological activity including antimicrobial, antiviral, antitumor, anti-histaminic, anti-depressant, insecticides and fungicides. Due to its wide range of biological activity, pyrazole ring constitutes a relevant synthetic route in pharmaceutical industry. In fact, such a heterocyclic moiety represents the core structure for number of drugs[3].

Pharmacological Activities

Pyrazole as Anticancer Agents

R. Kalirajan *et al* synthesized a series of pyrazole derivatives and these derivatives show anticancer activity[4].

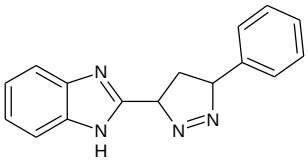


Figure 3:

L. R. S. Dias *et al* synthesized (isoindolin-2-yl) (3, 5-dimethyl-1H-pyrazol-1-yl) methanone and the synthesized compound show good antitumor activity[5].

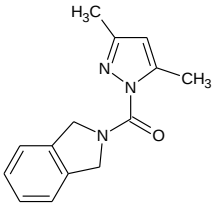
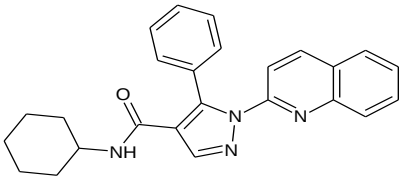


Figure 4:

Pyrazole as Antimicrobials

Arun M Isloor *et al* synthesized N-cyclohexyl-5- phenyl-1-(quinolin-2-yl)-1H-pyrazole-4-carboxamide,N-(2,6-dimethylphenyl)-5-phenyl-1-9quinolin-2-yl)-1Hpyrazole-4-carboxamide and N, N-diethyl-5-phenyl-1-(quinolin-2-yl)-1H-pyrazole-4-carboxamide and these derivatives shows good antibacterial activity[6].



N-cyclohexyl-5-phenyl-1-(quinolin-2-yl)-1H-pyrazole-4-carboxamide

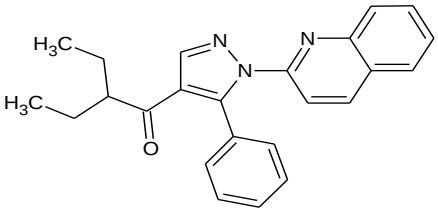


Figure 5: N, N -diethyl-5-phenyl-1-(quinolin-2-yl)-1H-pyrazole-4-carboxamide

Pyrazole as anticonvulsant activity

Anoop Singh *et al* synthesized a series of 1- [(4, 5 –dihydro-5 phenyl -3 phenyl amino) pyrazole -1 yl] ethanone derivatives and evaluated for anticonvulsant activity against electric shock induced convulsion method[7].

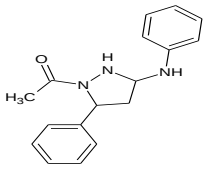


Figure 6:

Marketed formulations

Fezolamine

- It is the drug used as an antidepressant.
- Routes of administration is oral.
- IUPAC name is, 3-(3,4-diphenyl-1H-pyrazol-1-yl)-N, N-dimethylpropan-1-amine.

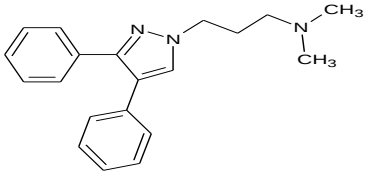


Figure 7:

Lonazolac

- It is non-steroidal anti-inflammatory drug, a non-narcotic analgesic.
- It is a monocarboxylic acid a member of pyrazoles.
- IUPAC name is, [3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl] acetic acid.

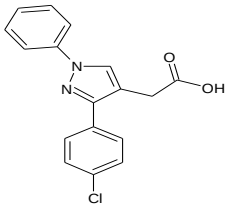


Figure 8:

Imidazole

Imidazole (1,3-diaza-2,4-cyclopentadiene) is a planar five-membered heterocyclic ring compound with 3C and 2N atom in 1 and 3 positions. The molecular formula is C3H4N2. The systemic name for the molecule is 1, 3 diazoles, one of the annular N bear a H atom and can be regarded as a pyrrole type N. It is soluble in water and polar solvents. It exists in two canonical tautomeric forms because the hydrogen atom can be located on either of the two nitrogen atoms. Imidazole is very much polar compound, as evidenced by a calculated dipole of 3.61D and is entirely soluble in water. Imidazole compound is considered as aromatic due to the presence of a sextet of π-electrons, consisting of a pair of electrons from the protonated nitrogen atom. Imidazole is amphoteric, *i.e.,* it can act as both an acid and as a base. The acidic proton is situated on N-1. The basic site is N-3[8].

Imidazoles are very important class of drug due its wide-ranging antimalarial, antibacterial, antifungal, anti-inflammatory, antiviral, antitubercular and finally anticancer activity. The development of synthesis of imidazoles moiety as well as its functionalisation at various position is still going on to increase its activity[9].

Figure 9: Imidazole

Pharmacological activities.

Imidazole as Antitubercular activity

Ramya v *et al* synthesized a series of novel 5-(bromo)-styryl-2-benzimidazole derivatives and screened for their antitubercular activity against M. tuberculosis strain. Streptomycin was used as a reference drug[10].

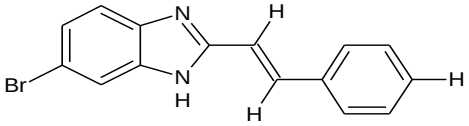


Figure 10:

Anti-cancer activity

Yusuf Ozkay *et al* synthesized many novel imidazole-(Benz) azole and imidazole epiperazine derivatives and synthesized compounds are tested for anticancer activity. All derivatives show good activity. Cisplatin was used as reference drug[11].

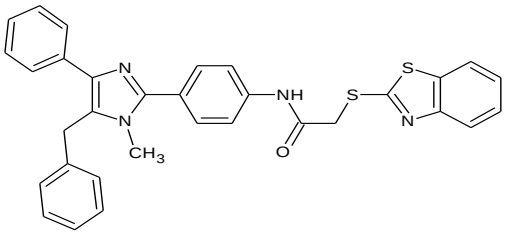
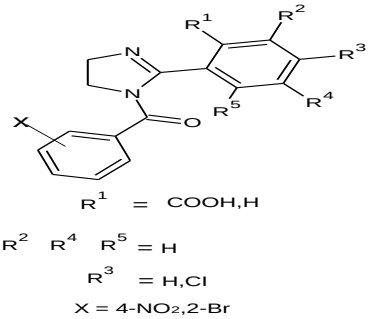


Figure 11:

Antimicrobial activity

Deepika Sharma *et al* synthesized imidazole derivatives and tested for their antimicrobial activity. All derivatives show good activity against the tested microorganism. Norfloxacin was used as standard drug[12].



R^1 = COOH,H

R^2 R^4 R^5 = H

R^3 = H,Cl

X = 4-NO_2,2-Br

Figure 12:

Marketed formulations

Dacarbazine

- Trade name: DTIC-Dome
- IUPAC name :5 (3,3 dimethyl 1thiazeno) imidazole 4 carboxamide
- Routes of administration: intravenous
- Drug type: anti-cancer chemotherapy drug

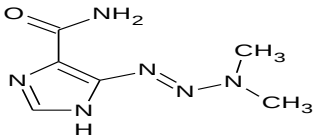


Figure 13:

Metronidazole

- It is an antibiotic and antiprotozoal medication.
- It marketed under the brand name Flagyl.
- It is an effective amebicide and the drug of choice for the treatment of all symptomatic forms of amoebiasis.

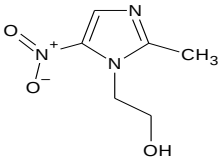


Figure 14:

Pyrrole

Pyrrole is a five membered heterocyclic aromatic organic compound with molecular formula C4H5N. It is a colorless volatile liquid that darkens readily upon exposure to air. Pyrrole is a necessary component of more complex macromolecules including porphyrins of heme, chlorophyll, chlorins etc. It was first detected by F.F Runge in 1834, as a constituent of coal tar.

Pyrrole derivatives are found in varieties of biological component as part of co-factors and natural products. Common naturally produced molecules containing pyrrole includes Vit.B12, bile pigments like bilirubin and biliverdin, porphyrins of heme, chlorophyll, chlorins, bacteriochlorin and porphyrinogens. One of the first syntheses of pyrrole containing molecule was that of haemin, synthesized by E. Fischer in 1929[13].

The pyrrole derivatives have been reported in synthetic and effective biological importance such as anti-lipidemic, antioxidants, anti- inflammatory, anti-bacterial, antitumor, anti-fungal, anti-tubercular etc.

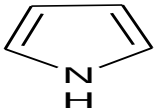
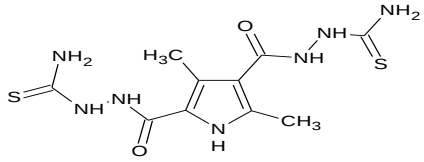


Figure 15: Pyrrole

Pharmacological Activities

Antimicrobial activity

Akbar I *et al* synthesized some new pyrrole and pyridine derivatives and tested for in vitro antibacterial and antifungal activity. This was comparable with Ciprofloxacin and Clotrimazole[14].



2,2'-[(3,5-dimethyl-1*H*-pyrrole-2,4-diyl)dicarbonyl] di(hydrazine-1-carbothioamide)

Figure 16:

Anti-inflammatory activity

Rania Helmy *et al* synthesized novel pyrrole, pyrrolopyrimidine and spiropyrrolopyrimidine derivatives and evaluated anti- inflammatory activity. Ibuprofen was used as standard drug[15].

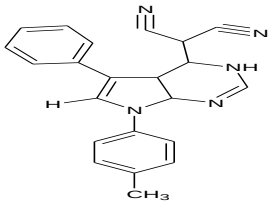
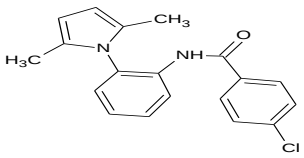


Figure 17:

Anti-tubercular activity

Shrinivas D. J *et al* synthesized novel N'-(substituted)-2-(2,5-dimethyl-1H-pyrrol-1-yl) phenyl) benzamide derivatives and screened for anti-tubercular activity by using INH as standard drug[16].



N-(2-(2,5-dimethyl-1H-pyrrol-1-yl)phenyl)-4-chloro-benzamide

Figure 18:

Marketed formulations

Tolmetin

- Tolmetin is a nonsteroidal anti-inflammatory drug (NSAID) of the heterocyclic acetic acid derivative class.
- It is used primarily to reduce hormones that cause pain, swelling, tenderness, and stiffness in conditions such as osteoarthritis and rheumatoid arthritis, including juvenile rheumatoid arthritis.
- Routes of administration: by mouth
- IUPAC name: 1-methyl-5-(4-methylbenzoyl)-1H-pyrrol-2-yl] acetic acid.

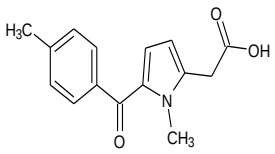


Figure 19:

Atorvastatin

- Atorvastatin oral tablet is a prescription drug. It is available as a brand-name drug called Lipitor.
- Atorvastatin is a member of the drug class known as statins, used primarily for lowering blood cholesterol and for preventing cardiovascular diseases.
- It has a role as an environmental contaminant and a xenobiotic.

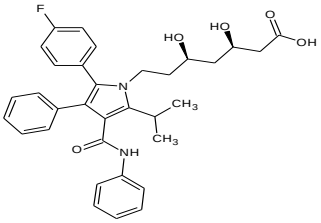


Figure 20:

Triazole

Triazoles are an important heterocyclic compound which are under study since many some years. 1, 2, 4-Triazole is one of a pair of isomeric chemical compounds with molecular formula C2H3N3, which have a five-membered ring of two carbon atoms and three nitrogen atoms, azole ring are readily able to bind with a variety of enzymes and receptors in biological system via diverse non-covalent interactions, and thus possess a large number of biological activities[17].

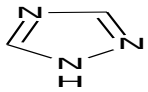


Figure 21: 1,2,4 triazole

Pharmacological Activities

Antimicrobial activity

Mohamed S B *et al* synthesized a series of 1,2,4 triazole derivatives and tested for antibacterial and antifungal activity. Tetracycline and Amphotericin B was the standard drugs used[18].

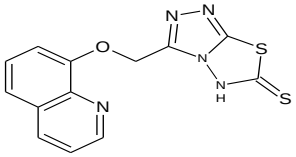


Figure 22: 3-{[(quinolin-8-yl) oxy] methyl} [1,2,4] triazolo[3,4-b] [1,3,4] thiadiazole-6(5H)- thione

Anti- inflammatory activity

Mohd. Amir *et al* synthesized 3-diphenylmethyl-6-substituted-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazoles: A condensed bridgehead nitrogen heterocyclic system and evaluated for Anti-inflammatory activity by the carrageenan induced paw oedema test in Wistar albino rats by Winter et al. (1962) method. The standard drug was ibuprofen[19].

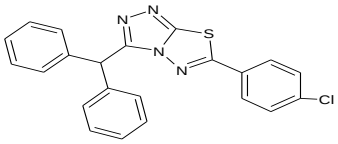


Figure 23: 6-(4-chlorophenyl)-3-(diphenyl l methyl) [1,2,4] triazolo [3,4-b] [1,3,4] thiadiazol

Anti-tumour activity

Olcay B & Nurhan G synthesized series of 3,5-diphenyl-4H-1,2,4-triazole derivatives and tested for tumour growth inhibitory activity[20].

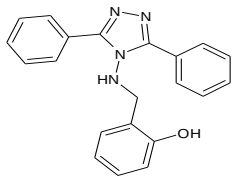


Figure 24:

Marketed formulations

Fluconazole

- Fluconazole is an antifungal medication used for a number of fungal infections.
- Trade name: Diflucan, Celozole
- Fluconazole is a first-generation triazole antifungal medication.

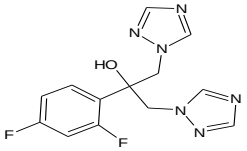


Figure 25:

Ribavirin

- Ribavirin, also known as tribavirin, is an antiviral medication
- it is used to treat RSV infection, hepatitis C and some viral haemorrhagic fevers.
- Ribavirin is taken by mouth or inhaled.

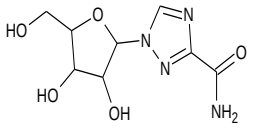


Figure 26:

CONCLUSION

Nitrogen containing five membered heterocyclic compounds have numerous applications in the pharmaceutical field which are pharmacologically and physiologically active and it is used in the treatment of various diseases. On the basis of various literature surveys these derivatives show various activities like anti-microbial, anti-inflammatory, analgesic, anti-cancer, anti-depressant, anti-viral, anti-tubercular and anti-fungal. This paper reviewed some of the biological activities of these compounds. The possible improvements in the activity can be further achieved by slight modifications in the substituents on the basic nucleus of these compounds. Thus, has been long focused for research interest in the field of medicine, due to excellent activities exhibited by its derivatives.

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