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Role of Nitrogen-Containing Natural Heterocyclic Compounds in Medical Science: A Mini Review

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ABSTRACT

Heterocyclic compounds constitute the largest and most varied family of organic compounds. Nitrogen-containing heterocyclic compounds are an important class of heterocyclic compounds that have paid the significant contribution towards medicinal chemistry, biochemistry, material science and also another area of science. N-heterocycles show a large number of biological activities such as antifungal, anti-inflammatory, antibacterial, antioxidant, anticonvulsant, anti-allergic, enzyme inhibitors, herbicidal, anti-HIV, anti-diabetic, anticancer, insecticidal etc. This paper reviews the most biological active N-heterocyclic compounds which were synthesized or extracted from the plants.

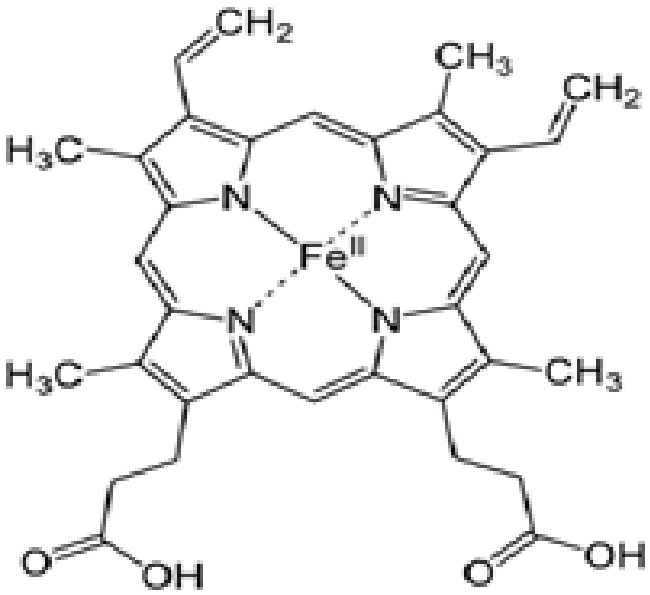
Keywords: Heterocyclic compounds, medicinal chemistry, biological activity, indole, imidazole.

I. INTRODUCTION

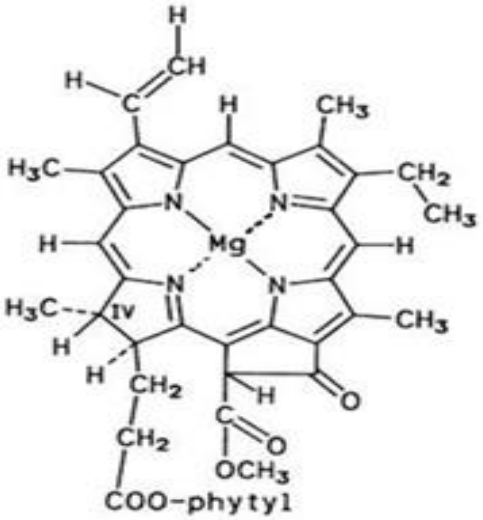
Nitrogen-containing heterocyclic compounds are key building blocks to develop compounds of biological or medicinal interest for chemists. Heterocyclic building blocks also have important uses as components in dyestuffs, antioxidants, copolymers, bases and ligands. Most of the heterocyclic compounds which contain nitrogen show better biological activities than non-nitrogen compounds. N-containing heterocycles play a significant role for human and animal health because it is a constitutional unit of various bioactive natural products such as vitamins, hormones, nucleic acids, antibiotics, alkaloids, glycosides, haem pigments and many more compounds [1]. These N-heterocycles also occurs in anthocyanin, flavones and chlorophyll. The N-heterocycle is core structure in many natural drugs such as quinine, papaverine, emetine, theophylline, atropine, codeine, morphine and reserpine [2, 3]. Therefore, N-containing heterocycles are a ‘‘exclusive’’ structures for the synthesis and development of new drugs [4, 5]. N-heterocyclic compounds are of particular importance as they are associated with a wide variety of physiological activities. A good number of synthetic and naturally occurring N-heterocyclic systems are used in medicine, pesticides, agrochemicals, polymers etc. Many N-heterocyclic compounds are useful in various common diseases such as, Triazine derivatives have been used as antimicrobial herbicides, urinary antiseptics and anti-inflammatory agents. Benzimidazole derivatives have been reported to possess a wide range of biological activities such as antibacterial, antifungal, antiviral and anthelmintic etc. [6]. Many N-containing heterocyclic derivatives such as indoles, imidazoles, thiazoles, indolylimidazole, oxadiazoles, triazoles and indazoles were marked as important bioactive and many valuable commercial products. It is therefore planned to synthesize the nitrogen-based novel heterocycles and study their pharmaceutical importance.

N-heterocycle Porphyrins [7-9] are found the backbone of many major compounds and some of

their derivatives are fundamental biomolecules such as haem [10] **(I)**, chlorophylls [11]**(II & III)** and vitamin B12 **(IV)**.

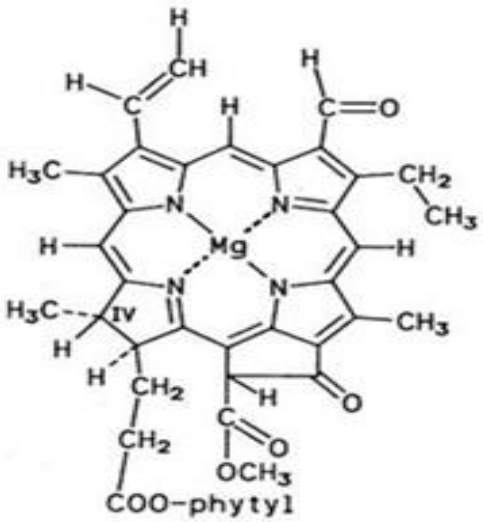


I



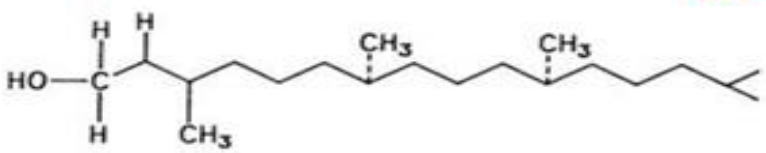
Chlorophyll a

II

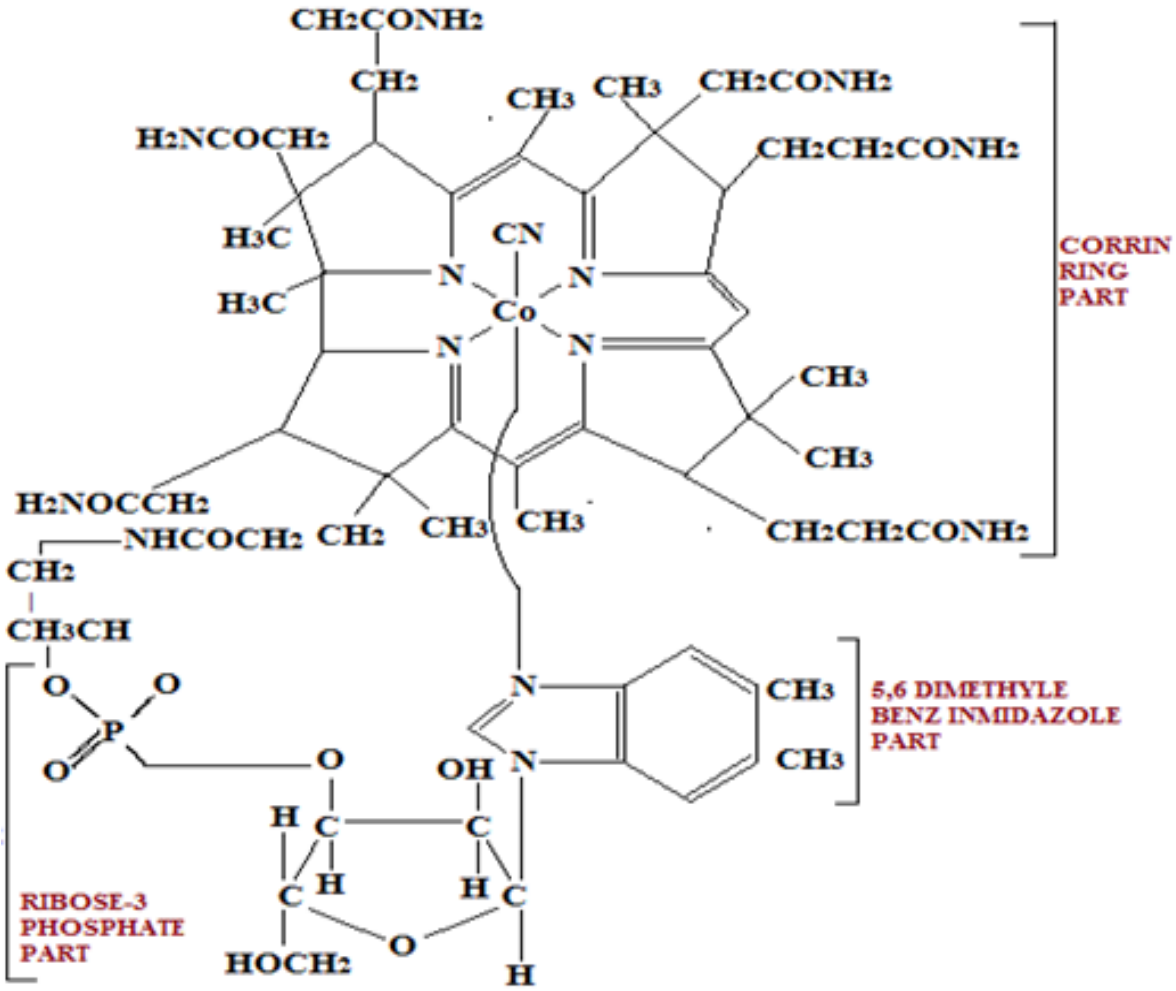


Chlorophyll b

III



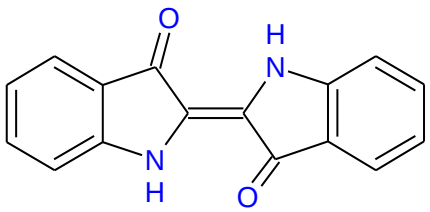
(phytol)



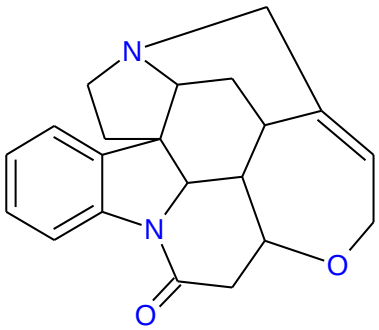
Vitamin B12

IV

Plant originated Indigo blue **(V)** dyestuff was used as fabric dye. A poison of detective novel fame was strychnine [12] **(VI)** obtained from the plant resin curare.

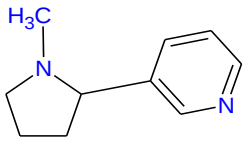


Indigo (V)

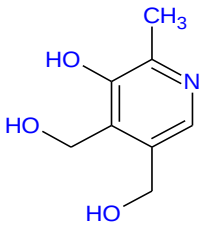


Strychnine (VI)

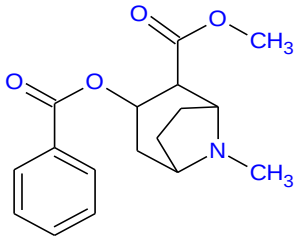
Pyridine or Piperidine derivatives containing natural products such as Nicotine **(VII)** [13], Pyridoxine **(VIII)** [14], Cocaine **(IX)** [15] and Morphine **(X)** [16] and synthesized products such as Nifedipine **(XI)** [17], Paraquat **(XII)** [18] are heterocyclic compounds which show most biological activities.



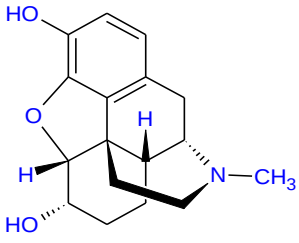
Nicotine (VII)



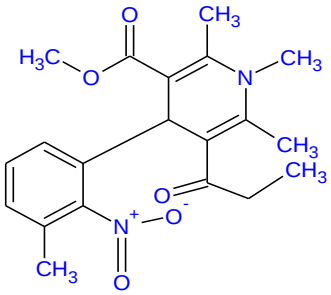
Pyridoxine (VIII)



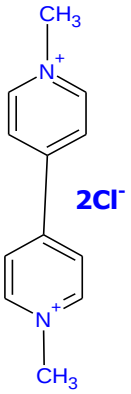
Cocaine (IX)



Morphine (X)

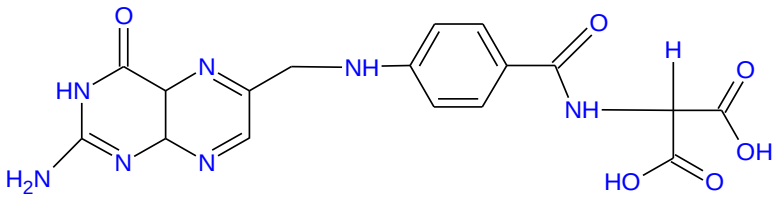


Nifedipine (XI)

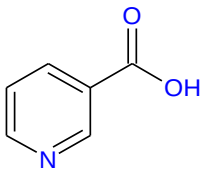


Paraquat (XII)

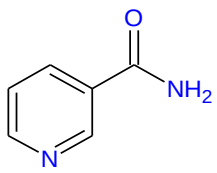
Many vitamins [19] such as folic acid **(XIII)**, vitamin B5, nicotinic acid **(XIV)**, nicotinamide **(XV)**, vitamin B6, pyridoxine **(XVI),** pyridoxal **(XVII)** and pyridoxamine **(XVIII)** are well known N-containing heterocyclic compounds.



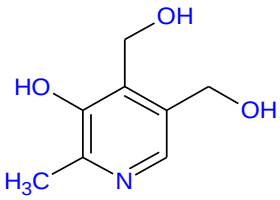
(XIII)



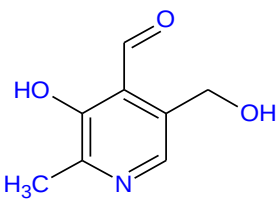
(XIV)



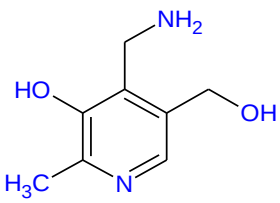
(XV)



(XVI)



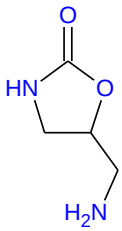
(XVII)



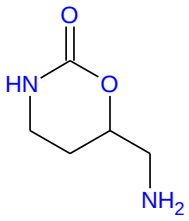
(XVIII)

(S)-5-aminomethyl-2-oxazolidinone **(XIX)** was found the core structure in antibacterial agent linezolid **(XX)** [20, 21] which was the first member of the synthetic oxazolidinone antibiotics [22-26] and effective against the

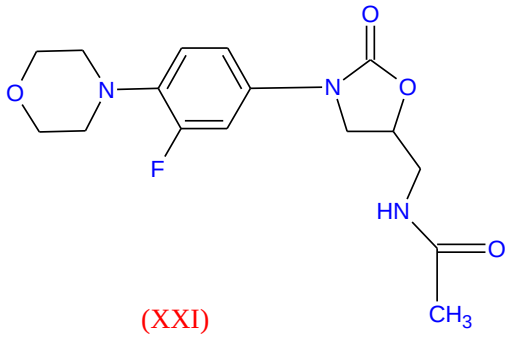
resistant Gram-positive bacterial infection. 1,3-oxazinan-2-one **(XXI)** derivatives also show anti-inflammatory [27], anti-thrombotic [28], and antibacterial activities [29].



(XIX)

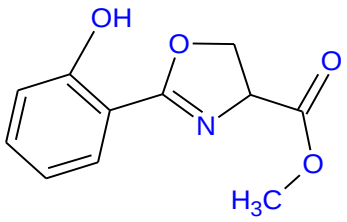


(XX)

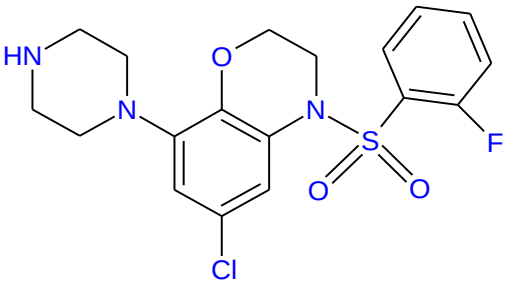


(XXI)

The oxazolines heterocycle derivatives **(XXII)** have shown antibiotic [30], neuro-protective [31] and cytotoxic activities [32]. The homologous oxazines have shown specific properties such as important synthetic intermediates [33]. 1,4-oxazine **(XXIII)** was a human 5-HT6 receptor inhibitor [34] and can be developed as an anti-depressant. It has been reported that many other oxazines show good bioactivities and are being used as drugs against hereditary obesity by inhibiting cholesteryl ester transfer proteins [35], anti-cardiovascular disease activity by inhibition of the thromboxane A2 (TXA2) receptor [36] and antibacterial agents [37,38].

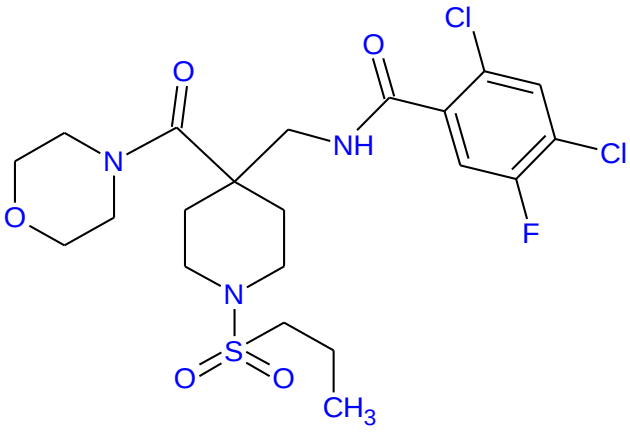


(XXII)

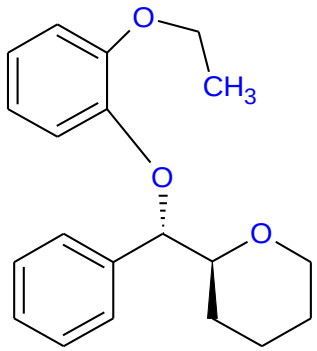


(XXIII)

Morpholine and morpholinone-containing molecules have also shown very interesting biological activities. The antibiotic Linezolid contains a morpholine cycle that is important for its biological properties. Other molecules such as **(XXIV)** have displayed an anti-schizophrenic activity [39] via interaction with the N-methyl-D-aspartate (NMDA) receptor in the brain. Reboxetine **(XXV)** is a commercially available anti-depressant that contains a morpholine cycle essential to its activity [40]. Morpholinone cycles were found in many biologically active molecules and the reported properties include thrombin inhibitors [41], selective T-type calcium channel blockers [42], HIV-protease inhibitors [43] and important intermediate in vitamin B5 synthesis [44] as well as antibacterial compounds synthesis [45]. Besides being used as synthetic intermediates and displaying interesting biological properties, many small heterocyclic molecules, notably 2-oxazolidinones, 1,3-oxazinan-2-ones and 2-oxazolines were very useful as chiral auxiliaries in asymmetric synthesis [46-48] or as a form of protecting groups [49] for amino alcohols.

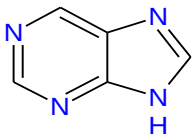


(XXIV)

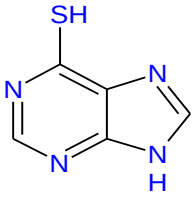


(XXV)

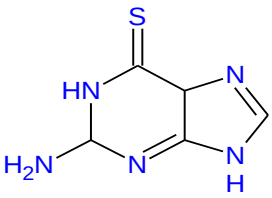
Bioactivity of Penicillin and cephalosporin are increased on introducing a pyrazolidine ring in place of the β-lactam ring [50]. Purine **(XXVI)** analogs were widely used against various diseases, particularly cancer.



Purine
(XXVI)

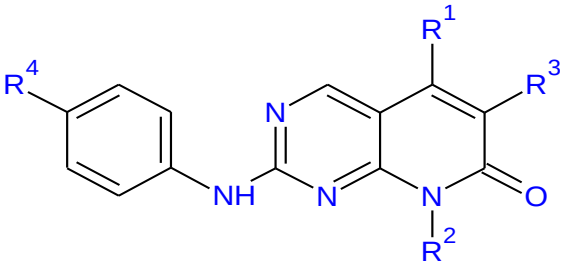


6-Mercaptopurine
(XXVII)

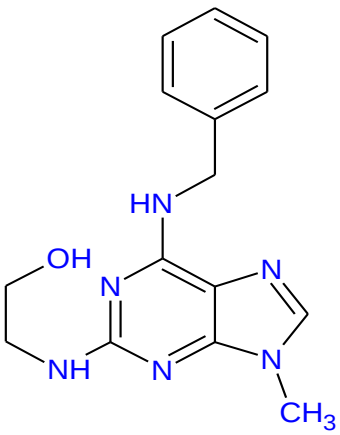


Thioguanine
(XXVIII)

The clinical applications of 6-Mercaptopurine **(XXVII)** and Thioguanine **(XXVIII)** [51, 52] in cancer treatment and the development of potent purine based inhibitors, such as Purvalanols **(XXIX)** [53], Olomoucine **(XXX)** [54, 55], Roscovitine **(XXXI)** [56] have been reported.

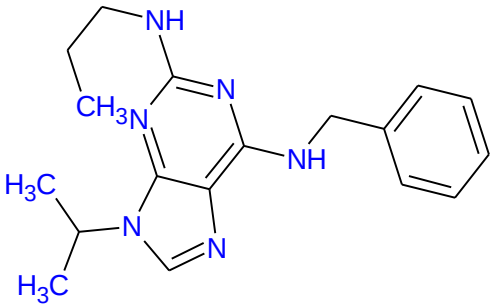


Purvalanols (XXIX)

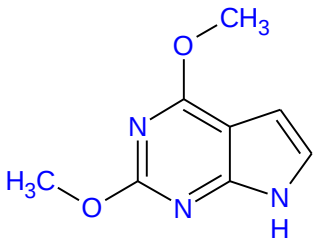


Olomoucine (XXX)

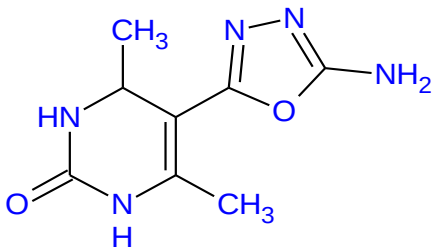
Many Purine base N-heterocycles were used as anti-tumour such as pyrrolo-pyrimidines **(XXXII)** [57], pyrazolo-pyrimidines **(XXXIII)**, indolo-pyrimidines **(XXXIV)** [58] and triazolo-pyrimidines **(XXXV)** [59].



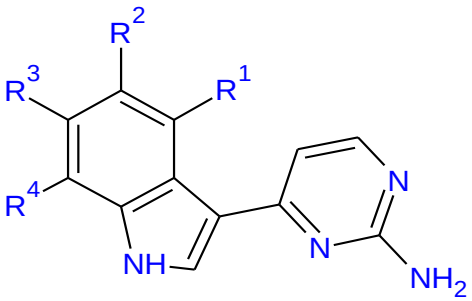
Roscovitine (XXXI)



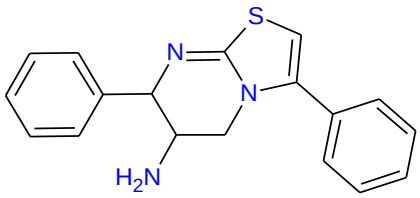
Pyrrolo-Pyrimidine (XXXII)



Pyrazollo-Pyrimidine (XXXIII)



Indolo-Pyrimidine (XXXIV)



Triazolo-Pyrimidine (XXXV)

II. CONCLUSION

N-containing heterocyclic compounds have an important place in the medicinal field because of their wide spectrum of pharmacological activities as reported in the reviewed article. Many bioactive natural and synthesized compounds have been reported which contain the important structural moiety of N-heterocycles. The drugs which contain the core of N-heterocycles skeleton show antifungal, anti-inflammation, anti-bacterial, antioxidants, anticonvulsant, anti-allergic, herbicidal and anticancer activities.

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