**Recent Advances in Nitrogen-Containing heterocyclic compounds and Their Biological significance**

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**ABSTRACT**

Heterocyclic compounds have a role in most fields of sciences such as medicinal chemistry, biochemistry also another area of sciences. More than 90% of new drugs contain heterocycles and the interface between chemistry and biology, at which so much new scientific insight, discovery and application is taking place is crossed by heterocyclic compounds. They owe their importance in the biological system due to uniqueness in their structural Skelton parts. They are naturally found in nucleic acid, vitamins, antibiotics, hormones etc. Compounds derived from heterocyclic rings in pharmacy, medicine, agriculture, plastic, polymer and other fields.

Nitrogen containing heterocyclic compounds are an important class of heterocyclic compounds that has paid significant contribution towards medicinal chemistry. The types of compounds depend upon number of nitrogen atoms and their position. The analogs of nitrogen-based heterocycles occupy an exclusive position as a valuable source of therapeutic agents in medicinal chemistry. More than 75% of drugs approved by the FDA and currently available in the market are nitrogen-containing heterocyclic moieties. In the forthcoming decade, a much greater share of new nitrogen-based pharmaceuticals is anticipated. In this review, we consolidate the recent advances on novel nitrogen-containing heterocycles and their distinct biological activities, reported over the past one year. This review highlights the trends in the use of nitrogen-based moieties in drug design and the development of different potent and competent candidates against various diseases.

**Keywords:** Heterocycles. Nitrogen containing compounds biological activity, Triazole, Pyrazole etc.

1. **INTRODUCTION**

Nitrogen-based heterocyclic chemistry is an important and unique class among the applied branches of organic chemistry, with a significant amount of research dedicated to the development of novel molecules and composites. These molecules have received increasing attention over the past two decades. They contributed to the development of numerous organic synthesis protocols and found abundant applications in the chemical sciences. A heterocyclic compound or ring structure is a [cyclic compound](https://en.wikipedia.org/wiki/Cyclic_compound) that has atoms of at least two different [elements](https://en.wikipedia.org/wiki/Chemical_element) as members of its ring(s) (1). Heterocyclic chemistry is the branch of [organic chemistry](https://en.wikipedia.org/wiki/Organic_chemistry) dealing with the synthesis, properties, and applications of these heterocycles (2).

Examples of heterocyclic compounds include all of the nucleic acids, the majority of drugs, most biomass (cellulose and related materials), and many natural and synthetic dyes. More than half of known compounds are heterocycles (3). 59% of US FDA-approved drugs contain nitrogen heterocycles (4)

**CLASSIFICATIONS OF HETEROCYCLIC COMPOUNDS:**

The study of heterocyclic chemistry focuses especially on unsaturated derivatives, and the preponderance of work and applications involves unstrained 5- and 6-membered rings. Included are pyridine, thiophene, pyrrole, and furan. Another large class of heterocycles refers to those fused to benzene rings. For example, the fused benzene derivatives of pyridine, thiophene, pyrrole, and furan are quinoline, benzothiophene, indole, and benzofuran, respectively. The fusion of two benzene rings gives rise to a third large family of compounds. Analogs of the previously mentioned heterocycles for this third family of compounds are acridine, dibenzothiophene, carbazole, and dibenzofuran, respectively.

Heterocyclic compounds can be usefully classified based on their electronic structure. The saturated heterocycles behave like the acyclic derivatives. Thus, [piperidine](https://en.wikipedia.org/wiki/Piperidine) and [tetrahydrofuran](https://en.wikipedia.org/wiki/Tetrahydrofuran) are conventional amines and ethers, with modified steric profiles. Therefore, the study of heterocyclic chemistry focuses on unsaturated rings.

1. **RATIONAL AND SIGNIFICANCE OF STUDY:**
2. Drug discovery and development is a process aims to design safe and effective medications to improve life’s quality and to reduce suffering to minimum. However, the process is very complex, time consuming, and resource intensive, requiring multi-disciplinary expertise and innovative approaches (5).
3. Technology in medicine and health care has rapidly changed over the past decades. Biomedical Engineering development has an essential rule in solving medical problems
4. Rational drug design methods minimize the time and cost needed in drug designing process in comparison to traditional drug discovery methods. QSAR/QSPR studies can be used to design and identify new inhibitors de novo or to optimize absorption, distribution, metabolism, excretion and toxicity profile of identified molecules from various sources. Advances in computational techniques and hardware have eased the application of in silico methods in the designing process. Drug design can be divided in two groups: Structure based drug design (SBDD) and Ligand based drug design (LBDD) [12]. SBDD is the approach applying the structural information of the drug target to develop its inhibitor. While LBDD is used in the absence of the receptor 3D information and it relies on molecules bind to the biological target of interest (6-11).
5. Also, in drug discovery and environmental toxicology, QSAR models are now regarded as a scientifically credible tool for predicting and classifying the biological activities of untested compounds, drug resistance, toxicity prediction and physicochemical properties prediction. The QSAR methodology is based on the concept that the differences observed in the biological activity of a series of compounds can be quantitatively correlated with differences in their molecular structure. As a result, al biological activities and functions of molecules relate to specific molecular descriptors and specific regression techniques can be used to estimate the relative roles of those descriptors contributing to the biological effect (13)
6. **NOVEL HETEROCYCLIC COMPOUNDS AND THEIR BIOLOGICAL IMPORTANCE:**
	1. **1,2,4-TRIAZOLE**

Popat B. Mohite et al in 2014; reported Microwave Assisted Synthesis of 1-[5-(Substituted Aryl)-1H-Pyrazol-3-yl]-3,5- Diphenyl-1H-1,2,4-Triazole as Antimicrobial and analgesic agent. The synthesis of 1 -[5-(substituted aryl)-1 H-pyrazol-3- yl]-3,5-diphenyl-1H-1,2,4-triazolederivatives(S1-S10) depicted in Figure 1. The previously synthesized chalcones were cyclized with hydrazine hydrate in acidic medium to get various pyrazoles clubbed with 1,2,4- triazole (14).



**Fig-1-**The substitute Aryl shows A) Antimicrobial properties B) Analgesic activity

Rakesh Kumar et al, in 2014; Synthesis, characterization and biological evaluation of novel 1,2,4-triazole derivatives as potent antibacterial and anti-inflammatory agents. A new class of 1,2,4-Triazole have been synthesized from Biphenyl4-carboxylic acid on treatment with various chemicals & synthesized 3-(biphenyl-4-yl)-4-phenyl-1H-1,2,4-triazole- 5(4H)-thione derivatives. The synthesized compounds were characterized by FT- IR, 1H-NMR and mass
spectrometry. The Anti-inflammatory activity of test compounds was determined by Carrgeenan induced mice paw edema inhibition method. The antimicrobial Activity studies were carried out for the synthesized compounds which were also evaluated against the representative panel of Staphylococcus aureus and Bacillus subtilis gram positive *Escherichia coli* and *Pseudomonas aeroginosa* gram negative bacteria (15).



**Fig-2-** Triazole derivatives shows A) Antibacterial activity B) Anti-inflammatory properties

Narayana Rao et al., in 2014 have been synthesized and characterized a new 1,2,4-triazole derivatives. Also, they have been evaluated the biological activity 4-[(3-(4-
substituted-phenoxymethyl)-5-benzylsulfonyl)-1,2,4-triazol- 4-yl) methyl]-morpholine and all the title compounds showed good antibacterial and antifungal activities (16).



Subbarao et al. in 2014 have been evaluated a good anti- inflammatory activities of novel series of 1,2,4-triazolo [ 3,4- b] [ 1,3,4 ] thiadiazoles (17).



* 1. **IMIDAZOLE**

Fatemah elahian et al, in 2014; reported synthesis and anticancer activity of 2, 4, 5, triaryl imidazole derivatives. This study describes the synthesis of four 2, 4, 5-triarylimidazole derivatives and their anticancer activities. The target compounds were prepared from the reaction of benzaldehyde and benzoin derivatives in presence of ammonium acetate and ammonium vanadate. All the synthesized compounds were screened for anticancer activities against T47D and MDA-MB231 cell lines using the MTT assay. However, our obtained results indicated a significant difference between colchicine cytotoxicity and their homologs on treated MDA-MB231 and T47D cells; one compound (4a) showed a significant IC50 on MDA-MB231 cells in cell culture assay (18).



**Fig-3-** Imidazole derivatives show A) Anticancer activity

Zala SP et al , in 2012 have reported a synthesis of a series of 2,4,5-triphenyl-1H-imidazole-1-yl derivatives 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. 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 (19).



**Fig-3-** Imidazole derivatives show Anti-inflammatory activity

* 1. **TETRAZOLE**

Leila Zamani and Bi Bi Fatemeh Mirjalili et al, 2015; reported some 5-substituted 1-H Tetrazoles in presence of Nano-TiCl4.SiO2 having Anti-fungal activity. They investigated the synthesis of 5-substituted 1H-tetrazole in the presence of nano-TiCl4.SiO2 (20).



**Fig-4-** Tetrazoles derivatives shows A) Antifungal activity

Phoebe F. Lamie et al, 2017; reported some novel tetrazole and cyanamide derivatives as inhibitors of cyclooxygenase-2enzyme having anti-inflammatory activity. The synthetic routes of the target compounds are summarized in 1-[4–(1 H-Tetrazol-1-yl)phenyl]ethanone2 was obtained using 4-aminoacetophenone as the starting material according to the literature. Chalcone derivatives 3a and b were synthesized in high yields (79–86%) by a base catalyzed Claisen–Schmidt condensation of
acetophenone derivative 2 and substituted aryl aldehydes namely: 3,4-dimethoxybenzaldehyde and 3,4,5-trimethoxybenzaldehyde, respectively (21).



**Fig-5-** Tetrazoles and Cynamides shows A) Anti-inflammatory activities

Safaa I. Elewa et al, 2020 reported some tetrazoles and their prospective, N-(1H-tetrazol-5-yl)-1-(aryl)methanimine and 1-(4-alkoxyphenyl)-N-(1H-tetrazol-5-yl)methanimine having antibacterial and antimicrobial activity.Biological assays Activity index screening the antibacterial activity of the synthesized tetrazoles, using diffusion techniques revealed that
they apparently exhibited antibacterial activities according to
their main substituted groups together with the main skeleton activity (22).



**Fig-6-** A novel tetrazole shows A) antibacterial activity

Girdhar Pal Singh et al, 2021 reported synthesis of novel tetrazole Tetrahydrobenzo[b] Thiophene via Ugi-MCR as new antileishmanial prototype. The mechanism of synthesis of tetrazole formation has been shown in Scheme 2. The first step is the imine formation 9
by the reaction of amine and aldehydes. Imine 9 converts into
imine 10, which gave nucleophilic addition with isocyanide to
form intermediate 11. After azide insertion intermediate 11
give tetrazole. Total 11 compounds have synthesized
through route (23).



**Fig-7-** A novel tetrazole shows A) antileishmanial activity

Valery N. Kizhnyaev et al, 2022 reported tetrazole-containing polyelectrolytes based on chitosan, starch, and arabinogalactan (TEC, TES, TEAG) showing polyampholytic properties. The macromolecules of chitosan, starch, and arabinoga lactan polysaccharides, used in this work, contain the same pyranose structural fragments, but differ in func tionality and branching (Scheme 2). In each pyranose cycle, a linear chitosan macromolecule bears, along with hydroxyl groups, the amino or residual acylamino func tions, which does not participate in the studied modification reactions. Starch and arabinogalactan have only one type of reactive functional group (hydroxyl). However, the
macromolecules of these polysaccharides have a branched structure. Therefore, in the case of these polysaccharides, the tetrazole rings can be introduced both into the main and side polymer chains. It should be noted that here we aimed to reach the maximum conversion of functional (24).



**Fig-8-** A tetrazole shows A) polyampholytic properties

* 1. **1-3-4 OXADIAZOLE**

Neeraj K et al, in 2016; reported synthesis, characterization and antimicrobial evaluation of 2-phenyl propionic acid derived a new oxadiazoles.The 2-Phenyl propanoic acid and oxadiazoles are known to possess antimicrobial activity Phenyl propane hydrazide a derivative of methyl 2-phenyl propionate on crystallization with aromatic acids offered new 2-aryl-5-(1-phenylethyl) 1-3-4 oxadiazole derivative (25).



**Fig-9-** A new Oxadiazoles shows A) Antimicrobial properties

Bakshi Anjali et al, 2019; reported some oxadiazole moiety substituted oxadiazole Mannich bases showing antibacterial and anti-fungal activity.Compounds and were synthesized as shown in figure 10. Compounds were characterized by infra-red spectroscopy and1H NMR spectra. The details of synthesized compounds (K1, K2 and K3) like molecular structure, nature of compound, yield, molecular formula and molecular weight. All the synthesized compounds of oxadiazoles in the present study showed significant activity against bacteria employed at the concentration of 100µg/ml when compared with that of ampicillin as standard. All the synthesized compounds of oxadiazole in the present study showed significant activity against the fungi employed at the concentrations of 100µg/ml when compared with that of ketoconazole as standard (26).

 

 **Fig-10-** Oxadiazole moiety shows A) Antibacterial activity B) Antifungal activity

Ahmed Mutanabbi Abdula et al; in 2016, reported synthesis, antimicrobial and docking study of three novel 2, 4, 5-triarylimidazole derivatives.5-(4-Substituted phenyl)furan-2-carboxaldehyde were obtained by the reaction of the diazonium salts RPhN2+ Cl and furan-2-carboxaldehyde in the presence of cuprous chloride (Meerwein method). Novel 2-[5-(4-substituted phenyl)furan-2-yl]-4,5-diphenyl-1H-imidazole derivatives ( 2a–c) were synthesized in excellent yield by the refluxing of aldehyde compounds, benzil and ammonium acetate mixture in the
presence of glacial acetic acid (27) .



**Fig-11-** Triaryl imidazole shows A) Antimicrobial activities

* 1. **ISOXAZOLE**

M. E. Ibrahim et al, in 2016; reported Synthesis and Biological Evaluation of Some Novel Isoxazole Derivatives. The behavior of 5-amino-3-methylisoxazole (1) towards Mannich reaction. It behaves as an enamine upon reaction with a mixture of formalin and dibasic secondary amines such as 1,3-di(piperidin-4-yl)propane (2) or piperazine in a molar ratio (2:2:1) to afford 4,4′-(propane-1,3-diyl)bis(piperidine-4,1-diyl))bis(methylene)bis(3-methylisoxazol amine) (3) and 4,4′-(piperazine-1,4-diylbis(methylene))bis(3-methylisoxazol-5-amine) (4), respectively. Moreover, Mannich reaction of 1 with a mixture of formalin and monobasic secondary amines such as piperidine or dimethylamine in a molar ratio (1:1:1) afforded 5-amino-3-methyl-4-(piperidin-1- ylmethyl)isoxazole(5)and5-amino-4-[(dimethylamino) methyl]-3-methylisoxazole (6), respectively. Furthermore, we report herein a new direct and simple synthetic entry to synthesize unsubstituted isoxazolo[5,4- b]pyridine ring
systems via alkylation at position 4 with Mannich bases (28).



**Fig-12-** Isoxazoles derivatives shows A) Anticancer agents B) In biomedical studies

Vijayakumar K et al, 2017; reported some4-(1-Methyl-1H-benzo[d]imidazol-2-yl)aniline, N-(4-(1-methyl-1H-benzo[d]imidazol-2-yl)phenyl) benzamide, 4-Chloro-N-(4-(1-methyl-1H-benzo[d]imidazol-2-yl)phenyl) benzamide, N-(4-(1-methyl-1H-benzo[d]imidazol-2-yl)phenyl)-4-nitrobenzamide, 2-(4-(5-(4-Fluorophenyl)-1H-tetrazol-1-yl)phenyl)-1-methyl-1H-benzo[d] imidazole, 2-(4-(5-(4-Chlorophenyl)-1H-tetrazol-1-yl)phenyl)-1-methyl-1H-benzo[d] imidazole, 4-(1-(4-(1-Methyl-1H-benzo[d]imidazol-2-yl)phenyl)-1H-tetrazol-5-yl)benzonitrile, 1-Methyl-2-(4-(5-(4-nitrophenyl)-1H-tetrazol-1-yl)phenyl)-1H-benzo[d]imidazole having Anti-cancer activity (29).



**Fig-13-** Amides and Imidazoles shows A) Anticancer properties

Mounir Cherfi et al, 2021; synthesized and characterized new pyrazole-tetrazole derivatives ethyl 1-(cyanomethyl)-5-methyl-1H-pyrazole-3-carboxylate-2, Synthesis of ethyl 1-((2H-tetrazol-5-yl)methyl)-5-methyl-1H-pyrazole-3-carboxylate-3, (1-((2H-tetrazol-5-yl)methyl)-5-methyl-1H-pyrazol-3-yl)methanol-4, (5-methyl-1-((2-propyl-2Htetrazol-5-yl)methyl)-1H-pyrazol-3 yl)methanol-5, ethyl 1-((2-(3-bromopropyl)-2H-tetrazol-5-yl)methyl)-5-methyl-1H-pyrazole-3-carboxylate-6, ethyl 1-((2-benzyl-2H-tetrazol-5-yl)methyl)-5-methyl-1H-pyrazole-3-carboxylate-7, having vasorelaxant effect (30).



**Fig-14-** Pyrazole and Tetrazoles shows A) Vasorelaxant effects

Younas Aouine et al, 2021; reported experimental and computational studies on N- tetrazole 1,5- and 2,5-AMTs derivatives was carried out via the N-alkylation reaction starting from 5-AMT, which contains a free N-H bond.[28] The compound 5-AMT was obtained in high yield . However, the control of its purity by the Thin-Layer Chromatography (TLC) showed that there was only a very thin trail, which proved that the 5-AMT in the form of an inseparable mixture of two tautomeric forms 1*H* and 2*H*. In order to have an idea on the ratio of each resulting regioisomers from its *N*-alkylation, we performed this reaction with benzyl bromide in the presence of K2CO3 as base (31).



**Fig-15-** Tetrazoles shows A) Antibacterial properties B) Antimicrobial properties

**3.6. THIAZOLE**

G. A. Kashid et al, 2018; reported novel tetrazole, n- (substituted benzylidene) - 4- (4- substituted phenyl) thiazole- 2-carbohydrazides) gs-5i having anti-oxidant activity. Based upon the literature survey, the present investigation was designed and extensive interest has been shown in Oxadiazoles containing compounds in search of potential drugs. Oxadiazole derivatives are known to exhibit an array of biological activities. All the compounds tested and compoundswere showed moderate % inhibition and were found to be significant among all the tested compounds. Remaining compounds showing mild activity (32).



**Fig-16-** Tetrazoles and Thiazoles shows A) Antioxidant activity

* 1. **INDOLE**

Maged A. Aziz et al,2021; reported some novel 1 H-3-Indolyl derivatives like 3-(4-(thiophen-2-yl)-pyridin/pyran/pyrimidin/pyrazol-2-yl)-1H-indole derivatives (2–12) having antioxidant activity. A new series of 3-(4-(thiophen-2-yl)-pyridin/pyran/pyrimidin/pyrazol-2-yl)-1*H*indole derivatives were designed and synthesized as promising antioxidant candidates based on the introduction of equivalent reducing heterocyclic rings comparable to that
of ascorbic acid. Applying a quantitative analysis of the structure-activity relationship
(2D-QSAR) on candidates exhibited a various range of potentially promising antioxidant activities. Concerning ascorbic acid antioxidant activity, these synthesized compounds were categorized into three featured groups of antioxidants based on the results of their biological scavenging abilities against the evaluated radicals in vitro. Furthermore, the mechanism of action for the new compounds was proposed as cytochrome *c* peroxidase inhibitors via molecular docking compared to ascorbic acid as a reference standard (33).



**Fig-17-** A new Indolyl derivatives shows A) Antioxidant activity

Indole-based chalcone derivatives reported as COX-1 and COX-2 inhibitor by Ozdemir et al. Compound 3-(5- Bromo-1H-indol-3-yl)-1-(4-cyanophenyl)prop-2-en-1- one (21) and compound 3-(5-methoxy-1H-indol-3-yl)-1- (4-(methylsulfonyl)phenyl)prop-2-en-1-one (22) were found to demonstrate a significant activity (34).



Zhuang et al. reported a series of 2, 4-disubstituted furo[3,2-b]indoles for anticancer activity against the (human NCI-60 ) tumor cell lines. Among the tested compounds, compound (5-((2-(hydroxy- methyl)-4H-furo[3,2-b]indol-4-yl)methyl)furan-2- yl)methanol demonstrated the best anticancer activity. The analysis of results suggests that the fingerprint of the compound 48 is similar NSC- 754549 (35).



1. **CONCLUSION:**

Heterocyclic compounds play an important role in biological
processes. Hence, the scientists are trying to understand the
chemistry of heterocyclic in order to improve the quality of
human life. The present review summarizes and focuses on the recent developments in the synthesis, QSAR study and pharmacological evaluation of novel nitrogen heterocycles and their versatility as scaffolds in the synthesis of varied classes of compounds of medicinal perspectives, and also describes their structure-activity relationship studies. The discussion on physical properties like semiconductor, optical, and fluorescence properties explores the diverse applications in photo sensing and optical switching devices. The structure and structural optimization is promising for potential drug design and discovery, and development.

Based on the information provided in this overview, we
demonstrated that novel heterocyclic compounds act as on anti-cancer, antimicrobial, antibacterial, anti-inflammatory, antioxidant, and antifungal activities in this review may surely help, particularly the young researchers working in this area.

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