RJC

RASĀYAN *J. Chem.*
Vol. 15 | No. 3 |1709-1717| July - September | 2022
ISSN: 0974-1496 | e-ISSN: 0976-0083 | CODEN: RJCABP
http://www.rasayanjournal.com
http://www.rasayanjournal.co.in

SYNTHESIS AND BIOLOGICAL ACTIVE COMPOUNDS OF NITROGEN-CONTAINING HETEROCYCLIC COMPOUNDS: A REVIEW

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ABSTRACT

Heterocyclic chemistry has a broad spectrum of applications in our day-to-day life. Heterocyclic compounds contain hetero atoms like oxygen, nitrogen, and sulphur in their structure. Among these atoms, a wide variety of heterocyclic moieties with nitrogen as hetero atoms have considerable physiological properties and useful medical applications. Nitrogen-containing heterocyclic compounds are considered a significant category due to their broad therapeutic applications like antibacterial, antimalarial, anticancer, antifungal, anti-HIV, anti-inflammatory, etc., this review article focuses on novel moieties of indole, pyrazole, and triazole compounds and its biological importance.

Keywords: Biological importance, Heterocyclic compounds, Indole, Pyrazole, Triazole.

RASĀYAN *J. Chem.*, Vol. 15, No.3, 2022

INTRODUCTION

Heterocyclic chemistry is one of the important branches of chemistry that encompass the synthesis, characteristics, and applications of hetero compounds. Heterocyclic compounds are important components of amino acids, hormones, vitamins, and drugs. These heterocyclic moieties play a remarkable role in the metabolism of all living cells. A significant number of drugs are synthesized from heterocyclic compounds. The heterocyclic compounds can be five-membered or six-membered containing one, two, or three hetero atoms. The heteroatoms may be oxygen, nitrogen, and sulphur.[1-5] Heterocyclic chemistry with nitrogen as a heteroatom is considered a significant and special class of organic chemistry with a vast quantity of research committed to the development of novel molecules. Nitrogen-containing heterocyclic compounds like pyrimidines, quinoline, pyrrole, indole, triazole, imidazole, pyrazole, and pyrazine have a prominent place in medicinal chemistry. Among these, pyrazole, indole, and triazole are considered the most important hetero moieties because of their biological and pharmacological activities.[6-11] The main aim of this article is to emphasize the importance of indole, pyrazole, and triazole derivatives in heterocyclic chemistry.

Indole

Indole is a heterocyclic compound (C_8H_7N) containing one nitrogen atom. It is a benzopyrrole that consists of benzene and pyrrole rings combined at the 2nd and 3rd positions of the pyrrole nucleus. Indole showed a large spectrum of properties like antiviral, anti-inflammatory, antioxidant, antimicrobial, antitubercular, anticancer, and anti-HIV. Indole is a scaffold that presents in natural amino acids and well-known drugs like Tryptamine, Etodolac, and sumatriptan.[12-18] A lot of synthetic routes were proposed for the synthesis of indole, a few of them are discussed below.

Significance of Indole Compounds

Deweshri R. Kerzare *et al.* have synthesized a library of 20 new indole-linked pyrazole derivatives (Fig.-1) in good yields, evaluated for anticonvulsant, anti-depressant, and anti-anxiety activity.[19] Out of all derivatives, 4-chlorophenyl containing indole moiety was proved as the most active compound against diazepam (standard drug).

http://doi.org/10.31788/RJC.2022.1536924

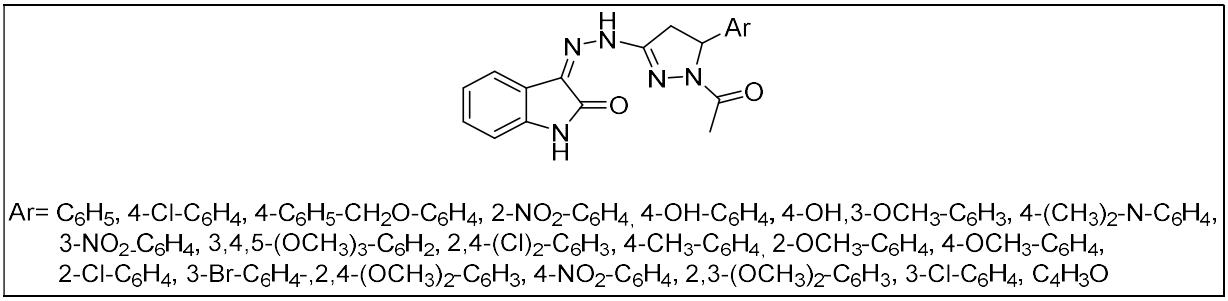

Fig.-1: Indole-linked pyrazole derivatives

Melissa M. Cadelis *et al.* have synthesized indole-3-carboxylic acid, indole-3-acetic acid, and indole-3-acrylic acid residues (Fig.-2) to be screened for enhancement of antibiotic activity towards gram -ve bacteria.[20] Two indole derivatives having 5-Bromo and 5-methoxy groups showed good antibiotic character.

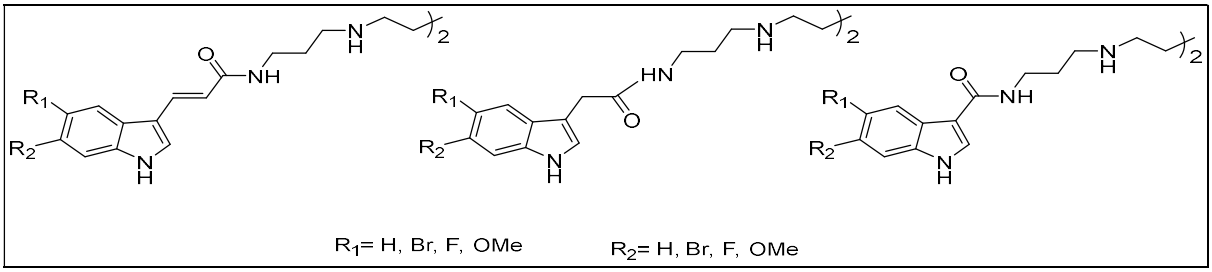

Fig.-2: Indole-3-carboxylic acid, indole-3-acetic acid, and indole-3-acrylic acid derivatives

Sonal Deswal *et al.* have prepared 5-Fluro-1H-indole-2-3-dione-triazoles derivatives (Fig.-3) through CuAAC quick reaction. The biological evaluation of antifungal and antibacterial activities was conducted and supported by the DFT and molecular docking studies.[21] It was noticed that all derivatives showed moderate to good activity against fungal and bacterial strains.

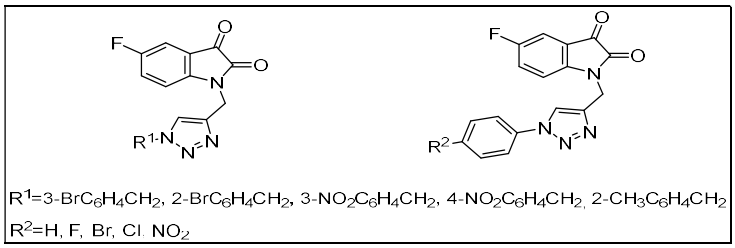

Fig.-3: 5-Fluro-1H-indole-2-3-dione-triazoles derivatives

Heba A.H Elshemy *et al.* have reported pyridyl-indole compounds (Fig.-4), screened for their *in vitro* & *in silico* antimalarial studies.[22] It is a one-pot synthesis, multicomponent reaction, and was observed that p-fluorophenyl, 3,4-difluorophenyl, and 3,4,5-trimethoxyphenyl containing indole derivatives exhibited good antimalarial activity.

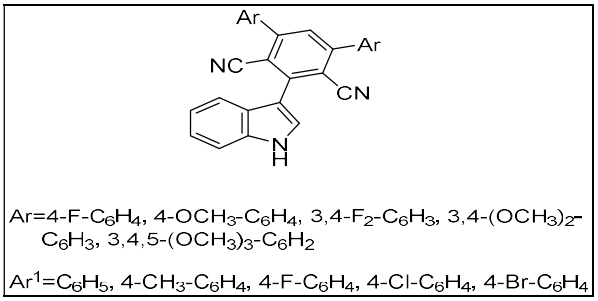

Fig.-4: pyridyl-indole compounds

Fariba Peyam *et al.* have prepared novel dihydro indolizino [8, 7-b] indole compounds (Fig.-5) and evaluated them as new α-glucosidase inhibitors.[23] All derivatives had been prepared by one-pot reaction in

mild conditions. Among all the compounds, diethyl and dimethyl derivatives showed good anti-α-glucosidase activity.

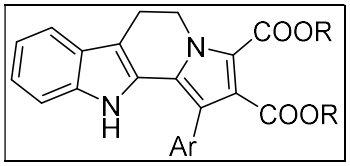

Fig.-5: Dihydro indolizino [8, 7-b] indole compounds

Navaneetha Depa and Harikrishna Erothu have synthesized 3-Aminoalkyl indole derivatives (Fig.-6) through a one-pot coupling reaction. The significance of this reaction is obtaining good yields in a short time by using a low-cost catalyst i.e., molecular iodine catalyst.[24]

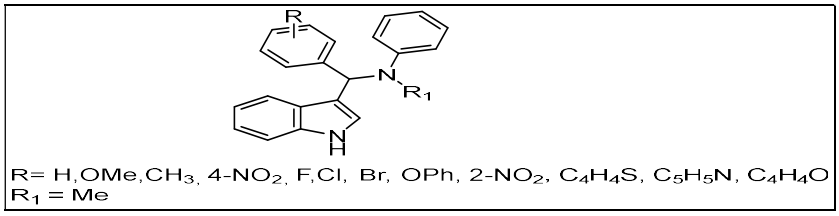

Fig.-6: 3-Aminoalkyl indole derivatives

Pyrazole

Pyrazole is a five-membered heterocyclic compound that contains 3 carbons and 2 nitrogen in adjacent positions and is even called azoles. Many numbers of compounds having pyrazole structures are synthesized and show a broad spectrum of its biological activity like antioxidant, antimicrobial, antitubercular, antifungal, antiviral, and anticancer activities.[25-31] It is considered one of the core structures for many drugs which constitutes a significant synthetic route in the field of pharmacy and few of them are discussed in this article.

Significance of Pyrazole Compounds

Wasim Akhtar *et al.* designed and prepared novel pyrazole-pyrazoline derivatives (Fig.-7) and tested them for anti-cancer and anti-inflammatory activities.[32] Out of 15 derivatives, 4-methoxy and 4-chloro containing pyrazole compounds showed good activity with 2.09 and 8.56μM IC_{50} values.

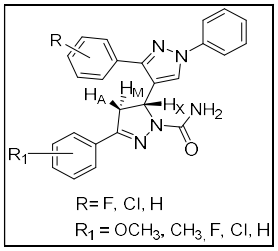

Fig.-7: Pyrazole-pyrazoline derivatives

Guda Mallikarjuna Reddy *et al.* anticipated and prepared tri-substituted pyrazole derivatives (Fig.-8) and evaluated them as antimicrobial agents.[33] Interestingly, it was found, that 4-nitrobenzylidene containing pyrazole moiety showed the highest biological activity towards microbial strains.

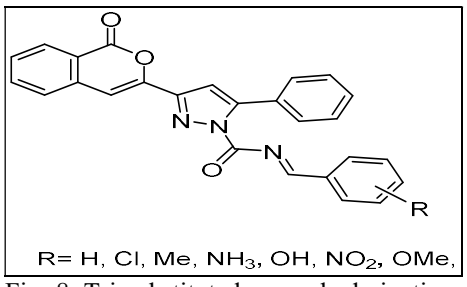

Fig.-8: Tri-substituted pyrazole derivatives

Ashraf A. Aly *et al.* have intended and synthesized novel quinoline-2-one/pyrazole compounds (Fig.-9) and evaluated them as anti-apoptotic activity, caspase-3 inhibition assay, and molecular docking.[34] Among all compounds, when R_1=H, Br, and R_2=H, CH_3 showed good anti-apoptotic activity.

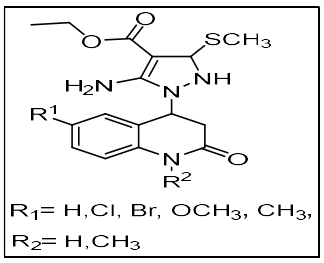

Fig.-9: Quinoline-2-one/pyrazole compounds

Archana D. Jadhav *et al.* have prepared new pyrazole moieties (Fig.-10) through Knoevenagel condensation in a simple, fast, and efficient way. These compounds were evaluated for antifungal and antibacterial activities.[35] Among all compounds, ***a*** *and* ***c*** exhibited good antibacterial activity against *S. aureus* and *b.subtilis*, a and d showed good activity upon *e.coli* and *p.vulgaris* bacteria compared to ampicillin (standard drug). Impressively, all compounds showed a good anti-fungal activity compared to itraconazole (standard drug).

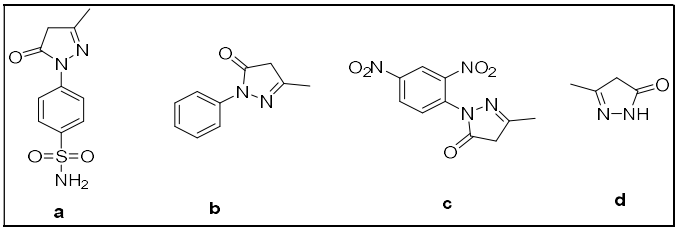

Fig.-10: Pyrazole derivatives

Ganesh Akula *et al.* have synthesized, characterized, and screened the anti-bacterial activity of novel 3,4-disubstituted pyrazoles (Fig.-11).[36] These derivatives are prepared in a two-step reaction by cyclization of aryl ethenone and hydrazine hydrate. Out of all derivatives, when R_2=H, CH_3, and R=F, OMe exhibited good anti-bacterial & anti-fungal activity.

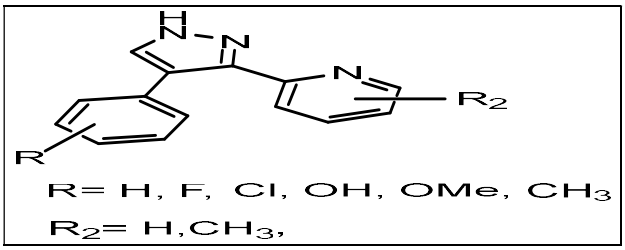

Fig.-11: 3,4-disubstituted pyrazoles

Navaneetha Depa and Harikrishna Erothu have designed, and synthesized new pyrazole/1,2,4-oxadiazole conjugate ester compounds (Fig.-12). All the molecules are screened for antibacterial activity and also studied for pharmacokinetic properties and molecular docking.[37] It was observed that unsubstituted derivatives, 4-Bromo, 4-methoxy, 4-fluoro, 2-chloro, and 3-chloro pyrazole/1,2,4-oxadiazole conjugate ester moieties showed good anti-bacterial activity contrary to gram +ve and -ve bacteria.

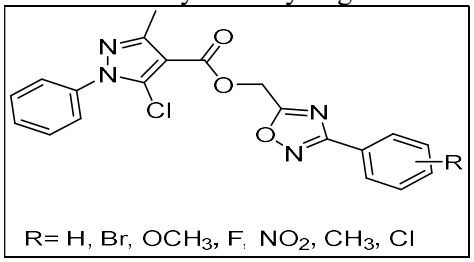

Fig.-12: Pyrazole/1,2,4-oxadiazole conjugate ester compounds

Triazole

Triazole is a five-membered heterocyclic compound also known as pyrrodiazole that consists of 3 nitrogen and 2 carbon atoms having molecular formula $C_2H_3N_3$. The 1,2,3-triazole & 1,2,4-triazole are two isomeric structures of triazole. Out of two isomeric forms, 1,2,3-troazole derivatives are considered an important heterocyclic moiety that are widely used in synthetic chemistry, and medicinal chemistry and few of them are discussed in this article. 1,2,3-triazole derivatives show biological properties such as antibacterial, antifungal, antimicrobial, anticancer, antimalarial, and antitubercular activities.[38-44]

Significance of Triazole Compounds

M Vishnuvardhan *et al.* have developed an efficient microwave-assisted synthetic route and prepared a novel P-Tolyoxyquinoline-Triazole hybrid derivative (Fig.-13). Triazole derivatives were synthesized with alkynes and azides by 1,3-dipolar cycloaddition in presence of CuI catalyst. These compounds were also evaluated for antimicrobial activity.[45] Among all compounds, phenyl, 2-nitrophenyl, and 4-nitrophenyl derivates are potent for antimicrobial study.

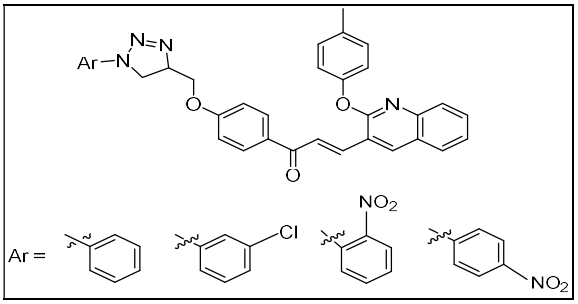

Fig.-13: P-Tolyoxyquinoline-Triazole hybrid derivatives

Mahdieh Mohammad Karbasi *et al.* have prepared new 1,2,3-triazole-dithiocarbamate compounds (Fig.-14) and analyzed their density functional theory (DFT). This method progressed to be easy, green in mild conditions with inexpensive materials.[46]

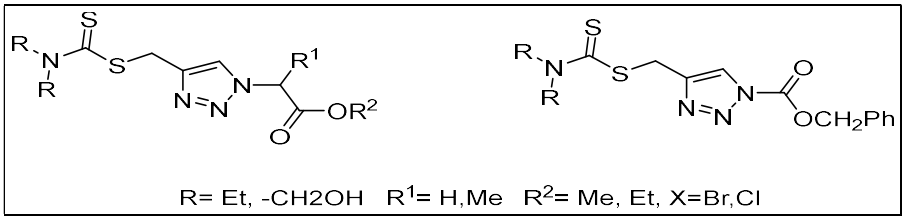

Fig.-14: 1,2,3-triazole-dithiocarbamate compounds

Kodide Santhosh Kumar *et al.* have reported novel 1,2,3-triazole-furan hybrid chalcone derivatives (Fig.-15) in a simplified, safer, and obtained good yield. Further, these compounds were tested for antimicrobial activity.[47] These derivatives are synthesized by Claisen Schmidt condensation reaction in presence of a base catalyst. The derivatives with trifluoromethyl and hydroxy phenyl groups exhibited good antimicrobial activity.

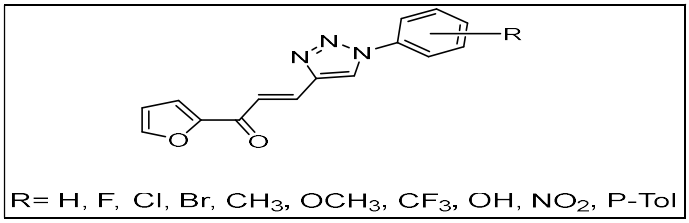

Fig.-15: 1,2,3-triazole-furan hybrid chalcone derivatives

Pramod S. Phatak *et al.* worked and prepared a novel indanol 1,2,3-triazole derivatives (Fig.-16). All compounds are tested in contrast to antimicrobial and antitubercular (*in vitro)* activities. The *in-silico* methods of molecular docking, and pharmacokinetic properties were studied and obtained acceptable drug-likeness scores.[48] The compound with a). R=2,4-Me showed excellent antitubercular activity. The

compounds with a) R=H, 2-OMe, 3-OMe, 4-OMe, 3-Me, 2,4,6-Me, 5-NO_2, 2-Br, 2F, Cl b) R=OMe have shown good antitubercular activity. Moreover, a) R=4-OMe, 2,4-Me, 5-NO_2, 2-Br, 3-Br, 3-NO_2 b) R=H, 2-OMe, 3-Cl, 3-NO_2 showed good antimicrobial action.

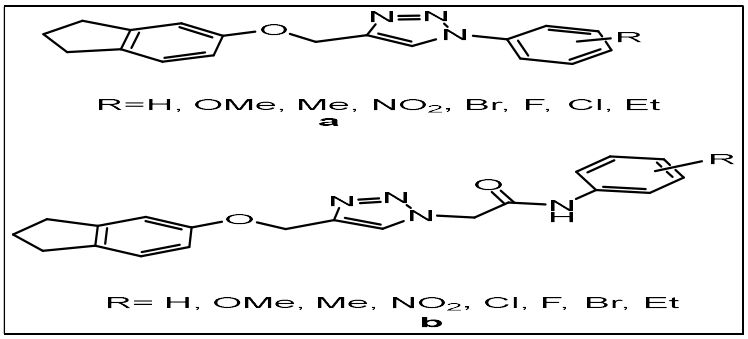

Fig.-16: Indanol 1,2,3-triazole derivatives

Ghouse Khan *et al.* have prepared novel 1,2,4-triazole derivatives (Fig.-17), screened for their antifungal, anthelmintic, antibacterial, and cytotoxic activity. Docking studies were also carried out for synthesized derivatives and examined the binding pattern of molecules. These compounds were also scrutinized for fingerprint application.[49] Among all compounds, 1f and 2b showed good antibacterial activity, 2c showed significant antifungal activity, 1d and 1f exhibited anthelmintic activity, 2a showed prominent anticancer activity, and 1d with the prominent adhesive property.

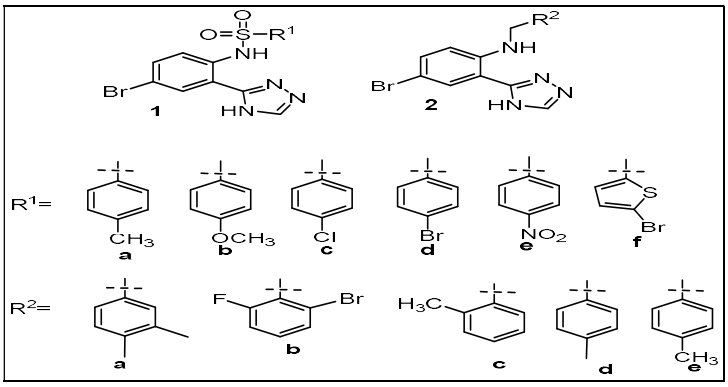

Fig.-17: 1,2,4-triazole derivatives

Tuncay Ince *et al.* have synthesized novel poly-substituted pyrrolidines linked to 1,2,3-triazoles (Fig.-18) by click chemistry in excellent yields. These compounds were screened for in vitro antiproliferative activity and DFT, acid dissociation constant and drug-likeness properties were also studied.[50] The triazole derivative containing the cyclohexylmethyl group contains good drug-likeness properties and potent towards antiproliferative activity.

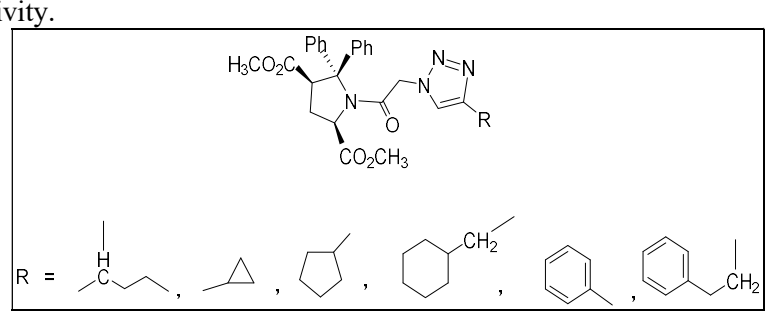

Fig.-18: Poly-substituted pyrrolidines triazole derivatives

CONCLUSION

Heterocyclic compounds containing nitrogen atoms may be considered the main class of heterocyclic chemistry as it has drawn great attention to the synthetic chemist and medicinal chemist for designing

biologically active molecules. Various heterocyclic derivatives with nitrogen atoms have potential applications for antimicrobial, anticancer, anti-inflammatory, antiallergic, antifungal, antitubercular, and other activities. This review depicts the importance of nitrogen-containing heterocyclic compounds in drug design and synthesis with broad medicinal applications.

ACKNOWLEDGEMENT

We (Navaneetha Depa and Harikrishna Erothu) are thankful to KLEF (Deemed to be University), A.P., India.

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[RJC-6924/2021]