Biological Forum – An International Journal **15(5a): 665-673(2023)**

ISSN No. (Print): 0975-1130
ISSN No. (Online): 2249-3239

Exploring the Diverse World of Isoxazoles: Synthesis, Biological Activities, and Prospects

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(Received: 06 April 2023; Revised: 29 April 2023; Accepted: 05 May 2023; Published: 15 May 2023)
(Published by Research Trend)

ABSTRACT: Isoxazoles represent a class of heterocyclic compounds having remarkable diversity of biological activities, making them a subject of extensive research and interest among chemists and pharmacologists. Achieving regioselective synthesis of isoxazoles and controlling the stereochemistry can be challenging due to the presence of multiple reactive sites. Ensuring compatibility with various functional groups during synthesis is crucial for the versatility of isoxazole derivatives. This comprehensive review aims to offer a concise overview of synthesis methods and the diverse range of biological activities associated with isoxazoles. In conclusion, this review offers a comprehensive perspective on the synthesis methodologies and the extensive biological activities of isoxazoles. It underscores the significance of isoxazole-based compounds in drug discovery and medicinal chemistry, inspiring further research in this intriguing class of heterocycles.

Keywords: Isoxazoles, Synthesis, Biological Activities.

INTRODUCTION

Isoxazoles, a class of heterocyclic compounds which are five-membered containing an oxygen and nitrogen atom at adjacent positions within a ring, have captured the attention of chemists, pharmacologists, and medicinal chemists alike due to their remarkable structural diversity and wide range of biological activities (Hepworth & Wainwright 1975; Sahani *et al*., 2020; Sharma *et al*., 2021). These compounds, with their unique chemical architecture, have been the subject of extensive research and have found applications in various fields, including drug discovery, agrochemicals, and materials science (Zhu *et al*., 2018; Sysak & Obmińska-Mrukowicz 2017; Kodge *et al*., 2016; Rai *et al*., 2023).

This paper targets to provide a comprehensive exploration of isoxazoles, focusing on two primary facets: their synthesis methodologies and the diverse biological activities associated with these compounds. Isoxazoles have proven to be versatile building blocks in organic synthesis, and their synthetic methods have evolved over the years, offering numerous pathways for the construction of isoxazole-containing molecules (Agrawal & Mishra 2018; Grygorenko *et al*., 2021). From classic Huisgen 1,3-dipolar cycloadditions to more modern transition metal-catalyzed reactions and green chemistry approaches, the synthesis of isoxazoles has seen significant advancements (Xing & Wang 2012; Wang *et al*., 2016).

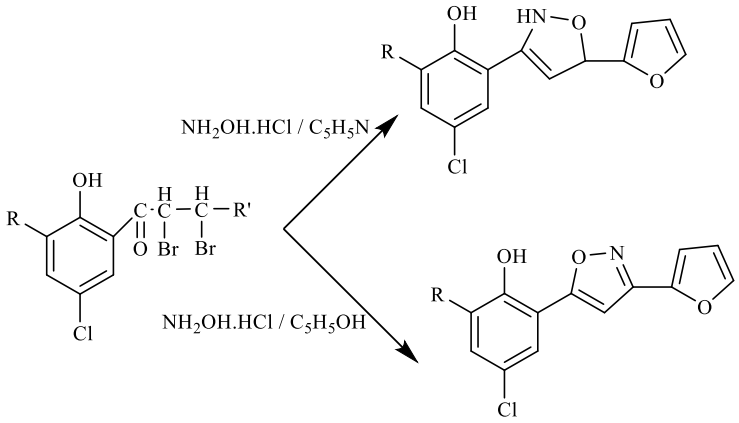
Isoxazoles are not just synthetic curiosities; they exhibit a plethora of biological activities, which makes them particularly attractive in medicinal chemistry. Compounds containing the isoxazole core have demonstrated potent pharmacological effects, including anticancer, antimicrobial, anti-inflammatory, and neuroprotective properties. Some isoxazole-based drugs have successfully made their way into clinical use, further emphasizing the significance of this class of heterocycles in drug discovery and development (Abu-Hashem & El-Shazly 2018; Al-Fayez *et al*., 2022; Agrawal & Mishra 2018; Priya & Shobana 2019).

In addition to discussing synthetic strategies and biological activities, this review will explore the structure-activity relationships (SAR) that govern the bioactivity of isoxazoles. By understanding how specific structural features influence their biological properties, researchers can design more effective compounds and target specific diseases with greater precision.

The overarching goal of this review is to provide a holistic perspective on isoxazoles, offering insights into both their synthesis and their potential applications in the realm of biology and medicine. As we delve into the synthesis methodologies and biological activities associated with isoxazoles, we aim to inspire further research and innovation in this intriguing and versatile class of heterocyclic compounds.

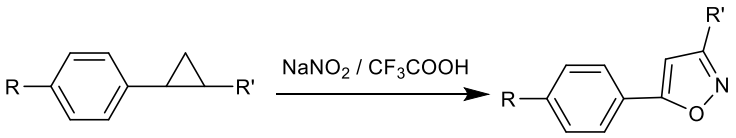
SYNTHESIS OF ISOXAZOLES

The following figure illustrates the process of cyclo-condensation of acrylophenone dibromide derivatives with hydroxylamine hydrochloride, which results in the formation of isoxazoles that correspond to the parent compound (Sahu *et al.*, 2008).



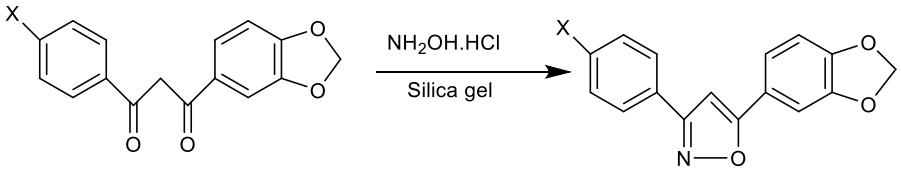
Synthesis of isoxazoles from acrylophenone dibromide

3-Alkyl, 5-aryl isoxazoles can be synthesized from aryl cycolpropanes with $NaNO_2$ in CF_3COOH (Marri *et al.*, 2018).



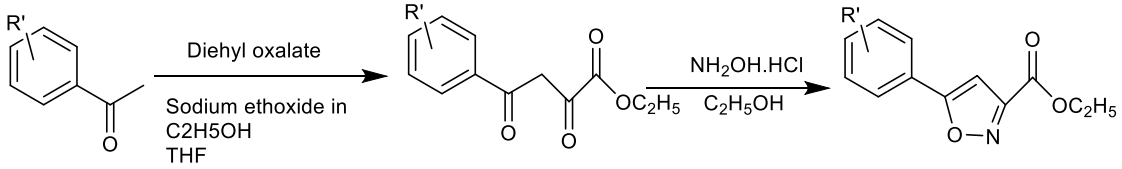
Synthesis of isoxazoles from aryl cyclopropanes

Solid phase synthesis of isoxazole derivative from di aryl1,3-diketones can be carried out in presence of hydroxyl amine hydrochloride and silica gel (Patel *et. al.*, 1997).



Solid phase synthesis of isoxazoles from diaryl-1,3-diketones

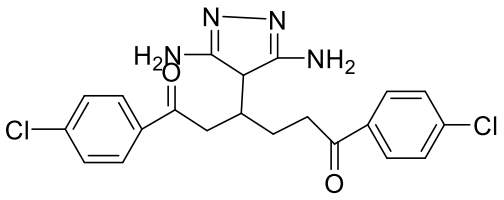
Reaction of several substituted aceto phenones with diethyl oxalate in presence of sodium ethoxide forms resulting 2,4-di keto esters which on treatment with hydroxyl amine hydro chloride furnishes substituted 3-isoxazole esters (Sunita *et al.*, 2018)



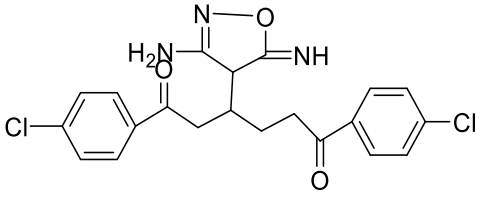
Synthesis of 3-isoxazoles from acetophenones

BIOLOGICAL ACTIVITIES OF ISOXAZOLES

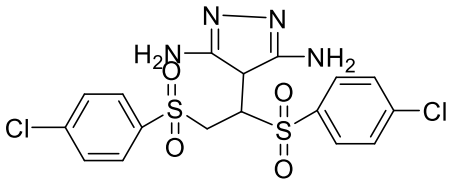
Michael adducts, 2-(1,2-diaroylethyl) malononitrile, were used to synthesize a novel class of heterocycles, including substituted isoxazoles, pyrazoles, thioxopyrimidines, and pyrimidines. Padmaja, A., *et. al.* (2009) contributed for this invention. The findings of the investigation demonstrated that compounds 1c and 2c exhibited superior activity against Gram +ve bacteria (inhibitory zone more than 28 mm), while they exhibited satisfactory activity against Gram -ve bacteria (inhibitory zone greater than 24 mm). Compounds 3c and 4c demonstrated the highest level of activity against Gram +ve bacteria (inhibitory zone greater than 30 mm), while they demonstrated sufficient action against Gram -ve bacteria (inhibitory zone greater than 25 mm). At a concentration of 100 mM, compounds 1c, 2c, 4c, and 5a demonstrated elevated levels of antioxidant activity when tested using the nitric oxide and DPPH techniques.



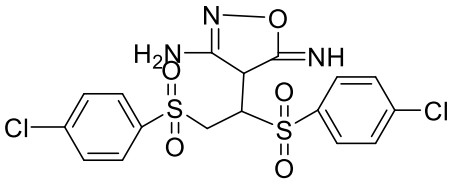
1C



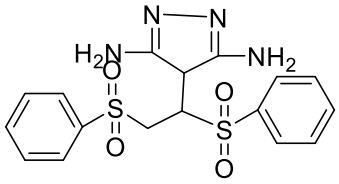
2C



3C

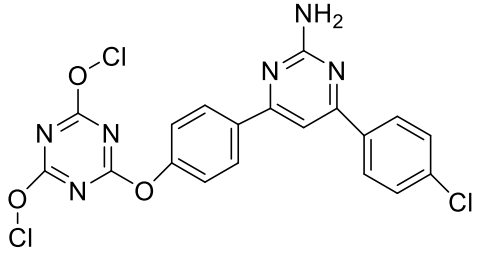


4C

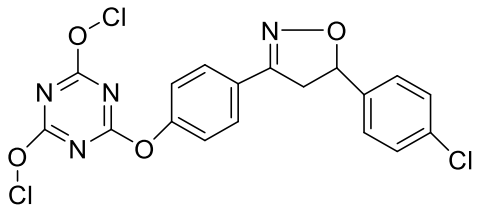


5A

Sharma *et al.* (2009) were successful in synthesis of a number of novel Phthalimidoxy derivatives of triazine that contained isoxazole and pyrimidine. The spectral and elemental analysis data associated with each of the compounds that were produced were used to describe them. During the evaluation process, antifungal and antibacterial properties of finished compounds were examined. Microorganisms such as *Bacillus subtilis, E. coli, Pseudomonas aeruginosa*, and Proteus mirabilis as well as fungal strains of Aspergillus fumigatus, and Candida albicans were utilized for the purpose of testing. Amphotericin and ciprofloxacin were utilized as the control medicines in this study. The activity of each of compounds is significantly higher than that of standard, which was utilized to combat Aspergillus fumigatus, and Candida albicans. Among all compounds that were created, it was discovered that compounds (6a) and (7a) were the most powerful.

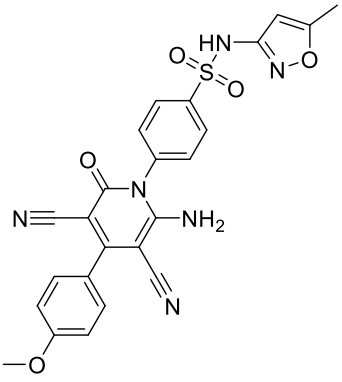


6a

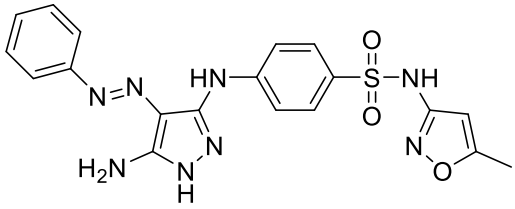


7a

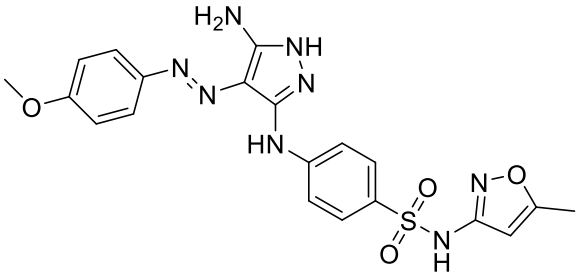
Darwish *et al.* (2014) synthesized some isoxazole based heterocycles. The in vitro antibacterial activity of newly synthesized compounds was assessed against Gram +ve bacteria, namely *Bacillis subtilis* (RCMB-010067) (BS), and Streptococcus pneumoniae (RCMB-010010) (SP) along with following Gram -ve bacteria Escherichia coli (RCMB-010052) (EC), and Pseudomonas aeruginosa (RCMB-010043) (PA). Furthermore, antifungal activity of these substances was examined in vitro against various fungal strains, including *Syncephalastrum racemosum* (RCMB-05922) (SR), *Aspergillus fumigates* (RCMB-02568) (AF), *Candida albicans* (RCMB-05036) (CA), and *Geotricum candidum* (RCMB-05097) (GC). For the purpose of determining the antibacterial activity, inhibition zone diameter in millimeters was utilized as a criteria. In order to evaluate efficacy of compounds that were evaluated under identical conditions, fungicide amphotericin B and the antibiotic sulfamethoxazole were utilized as benchmarks. The most active compounds were 8b and 9a,b,c which revealed strong inhibitory activity to the tested bacteria and fungi.



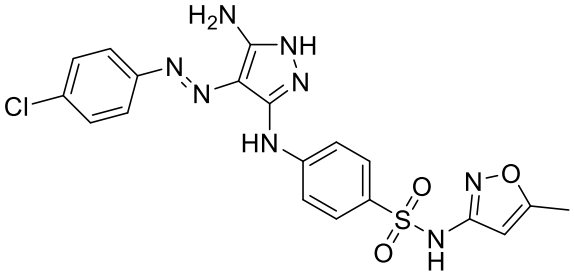
8b



9a



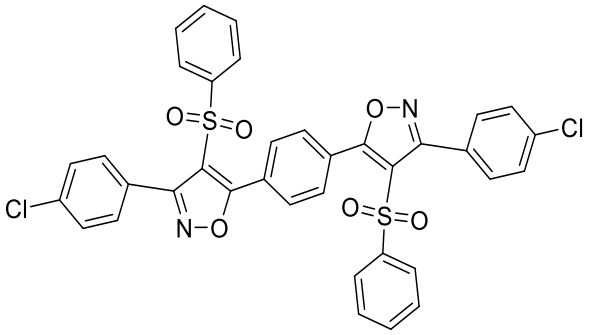
9b



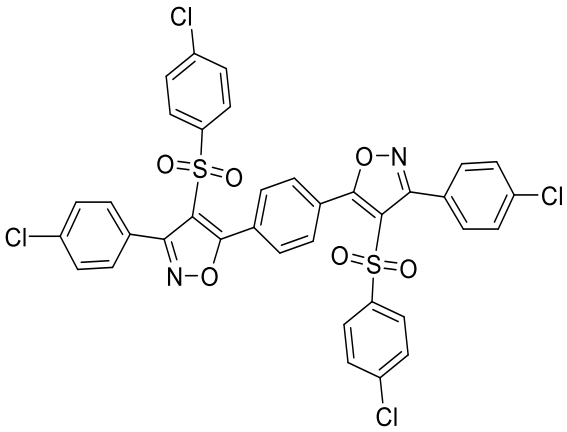
9c

Lavanya *et al.* (2014) performed a synthesis. Bis(sulfonyl) activated olefin was used to create a new class of (1,4-phenylene)bis(arylsufonylpyrazoles and

isoxazoles), and antibacterial activity of these compounds was thoroughly investigated. When compared with standard medicine Chloramphenicol, which also exhibited antibacterial action at a concentration of 38 mm at 100 µg/ml, the compound 10f demonstrated a significantly higher level of antimicrobial activity, specifically against Bacillus subtilis. Both compound 10b and compound 10f demonstrated comparable activity, notably against *Pencillium chrysogenum*, which was essentially identical to that of the conventional medication ketoconazole.

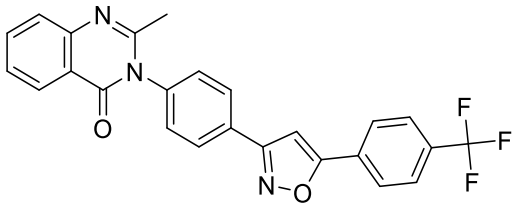


10b



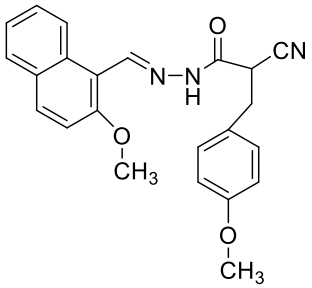
10f

A number of novel isoxazole linked quinazolin-4(3H)-one derivatives were the result of a synthesis carried out by Saravanan *et al.* (2013). The tailflick technique, the carrageenan-induced foot paw edema test, and the agar streak dilution test were carried out in order to screen for anti-inflammatory, analgesic, and in vitro antibacterial properties, respectively. Additionally, their ulcerogenicity was investigated for each and every molecule. The findings demonstrated that the complete series of compounds exhibited analgesic efficacy ranging from mild to good, anti-inflammatory activity, and antibacterial activity, with an ulcer score ranging from low to moderate. The molecule 11e had superior anti-inflammatory and analgesic activity, making it extra effective than the standard Diclofenac used as reference. This was found among the numerous compounds that were created. It is interesting to note that this derivative in question possessed approximately thirty percent of ulcer index of reference standards. In addition to this, compound 11e demonstrated remarkable antibacterial activity against a number of microorganisms that are known to cause disease.

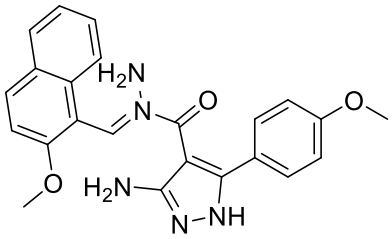


11e

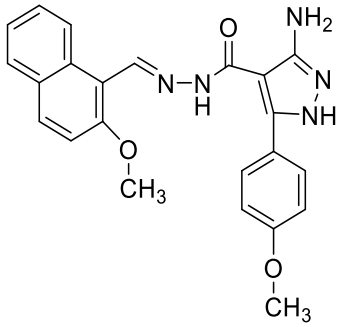
A series of pyrazole, 1,2,4-triazine, isoxazole, and pyrimidine, along with other related products that include a hydrazide moiety, were synthesized by Refat and Fadda (2015). These compounds were generated by reacting 2-cyano-N-((2-methoxynaphthalen-1-yl)methylene) acetohydrazide with the necessary chemical reagents. In addition to determining the minimal inhibitory concentration of these compounds against the majority of the organisms that were tested, antibacterial activities of these compounds were identified as well as analyzed. Antibacterial activity of compounds 12, 13, 14, and 15 was found to be exceptionally high among those that were evaluated (Beyzaei *et al.*, 2018).



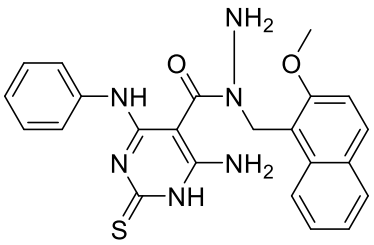
12



13



14

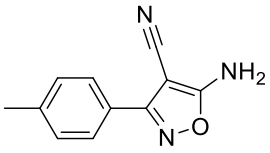


15

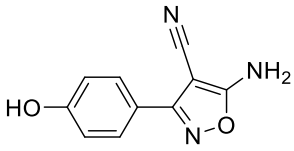
Beyzaei *et al*. (2018) developed a multicomponent process that was both environmentally friendly and very effective in order to produce some novel 5-amino-isoxazole-4-carbonitriles. Researchers investigated the antimicrobial properties of isoxazoles by testing them against a wide range of bacterial and fungal diseases. The following bacterial strains were tested for the newly synthesized compounds' *in vitro* antibacterial activity.

Gram -ve bacterial strains	**Gram +ve bacterial strains**
Pseudomonas aeruginosa (PTCC 1310)	*Staphylococcus epidermidis* (PTCC 1435)
Escherichia coli (PTCC 1399)	*Staphylococcus aureus* (PTCC 1189)
Klebsiella pneumonia (PTCC 1290)	Listeria monocytogenes (PTCC 1297)
Acinetobacter baumannii (PTCC 1855)	*Bacillus cereus* (PTCC 1665)
Shigella dysenteriae (PTCC 1188)	*Streptococcus agalactiae* (PTCC 1768)
Shigella flexneri (PTCC 1234)	*Streptococcus pneumoniae* (PTCC 1240)
	Streptococcus equines (PTCC 1445)
	Streptococcus pyogenes (PTCC 1447)
	Bacillus subtilis subsp. spizizenii (PTCC 1023)
	Bacillus thuringiensis subsp. kurstaki (PTCC 1494)
	Rhodococcus equi (PTCC 1633)

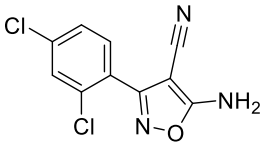
It was also determined whether or not they possessed antifungal properties in vitro against *Aspergillus fumigatus* (PTCC 5009), *Candida albicans (*PTCC 5027), and *Fusarium oxysporum* (PTCC 5115). Antimicrobial actions that were observed to be broad-spectrum were observed with isoxazoles 16a, b, and d. On the other hand, the DPPH test demonstrated that isoxazole 16i possesses antioxidant activity.



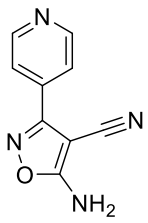
16a



16b

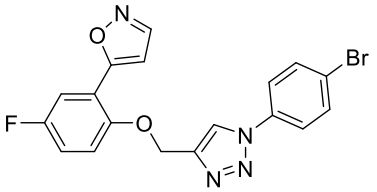


16d

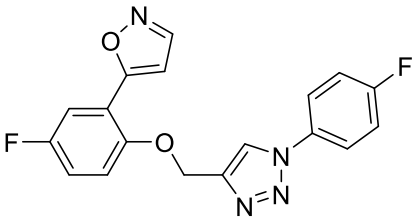


16i

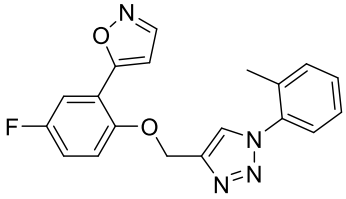
Kumar *et al*. (2019) synthesized a novel series 3-{2-[(1-aryl-1*H*-1,2,3-triazol-4-yl)methoxy]-5-fluorophenyl}isoxazoles derivatives from 1-(5-fluoro-2-hydroxyphenyl)ethanone. IR, NMR (1H and 13C), and mass spectral data are utilized to characterize all of compounds that have been synthesized. Additionally, the compounds are examined for their antibacterial efficacy against fungal AND bacterial species in vitro. All of these compounds were tested for their capability to hinder bacterial growth in vitro against Escherichia coli as well as *Staphylococcus aureus*, with ampicillin serving as standard antibiotic among compounds. There were three different concentrations of the chemicals that were tested in DMSO: 25, 50, and 100 µg/mL. There was evidence that compounds 17d and 17g exhibited antibacterial activity against all of the species that were examined. In vitro testing was performed on all of the compounds to determine whether or not they possessed antifungal properties against *Candida metapsilosis* and *Aspergillus niger*. Grieseofulvin served as the representative medication. For the purpose of screening, the compounds were examined in DMSO at doses of 25, 50, and 100 µg/mL. It was established that compounds 17f and 17g exhibited effective antifungal activity against all of the organisms that were examined.



17d



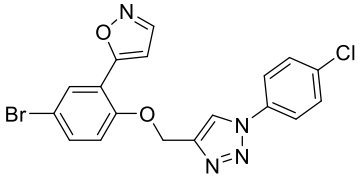
17f



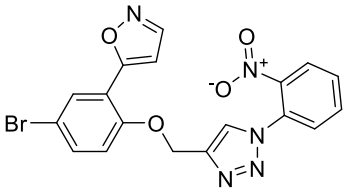
17g

A synthesis was performed by Thotla *et al*. (2019). The Click reaction was used to create a unique series of 1,2,3-triazolyl isoxazole derivatives. These derivatives were derived from matching propargylated isoxazoles and a significant number of aryl azides. Through use of

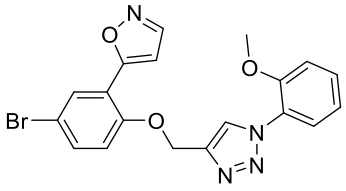
paper disc method and Norfloxacin as standard drug, 1,2,3-triazolyl isoxazoles that were synthesized were tested for their ability to inhibit growth of 4 different bacterial strains in vitro. These strains included 2 gram +ve bacteria, namely *Staphylococcus aureus*, and *Bacillus subtilis* along with two gram -ve bacteria, namely *Pseudomonas aeruginosa*, and *Escherichia coli*. All bacterial stains were successfully eradicated by the compounds 18b, 18d, and 18h, which exhibited strong antibacterial activity. The 1,2,3-triazolyl isoxazoles that were synthesized were tested for their activity against 2 different fungal strains, namely *Sclerothema rolfsii* and *Aspergillus niger*, at a concentration of 1 mg/mL. Disc diffusion method was utilized, and ketoconazole was used as reference. Antifungal activity of compounds 18d, 18e, and 18h was superior to that of any other compounds.



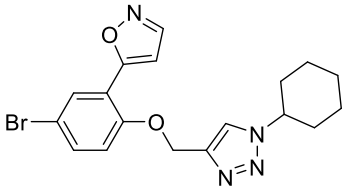
18b



18d

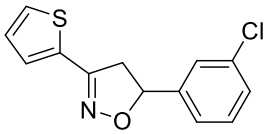


18e



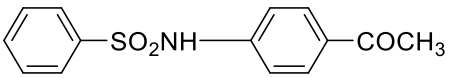
18h

Isoxazole derivatives of thiophene were synthesized by Gautam and Singh as part of their 2013 research. With the assistance of infrared and nuclear magnetic resonance spectroscopy, the chemicals that were produced were purified, and their structures were identified. We used the disc diffusion method to test the chemicals for their ability to inhibit growth of microorganisms. In vitro tests were performed on all of the compounds that were produced to determine whether or not they possessed antibacterial properties against gram +ve microbes including *Staphylococcus aureus* and *Bacillus subtilis* as well as gram -ve strains of Escherichia coli, and Pseudomonas aeruginosa. The discs that were impregnated with DMSO served as the control, while the discs that included ciprofloxacin served as the antibacterial reference method. In order to evaluate antifungal activity 19, sabouraud dextrose agar media plate disc diffusion method was utilized. Concentration of 50µg per disk was utilized for analysis. In vitro tests were performed on all of the compounds that were produced to determine whether or not they possessed antifungal properties against bacteria such as *Candida albicans* and *Aspergillus niger*. At same time that fluconazole discs served as the antifungal reference standard, discs that had been impregnated with DMSO served as the control. It was discovered that compound 19 exhibited significant antimicrobial activity against Candida albicans, *P. aeruginosa*, and *E. coli.*

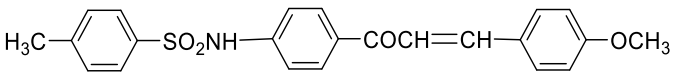


19

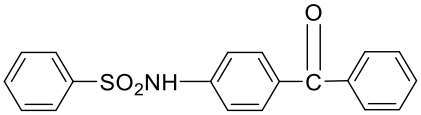
Both Moustafa and Ahmad (2010) were successful in the synthesis of a number of novel cyanopyridines, isoxazoles, pyrazoles, and pyrimidines that contained a sulfonamide component. In order to determine whether or not the newly synthesized compounds possessed antibacterial properties, they were tested against three distinct different types of bacteria. Positive for Gramme. *Bacillus subtillus, Micrococcus luteus*, Gram -ve bacteria, and *Serration rhodenil*, as well as 3 species of fungi, *Fusarium equiseti, Aspergillus fumigatus*, and *Penicllum chrysogen* were tested using filter paper technique. Zone of inhibition was measured in millimeters at a conc. of 25 micrograms per milliliter. All of the compounds shown a high level of growth inhibition against Gram +ve bacteria; however, only two compounds (20a and 21f) demonstrated a high level of growth inhibition against Gram -ve bacteria. Specifically, compound 22a had antifungal properties, meaning that it was effective against fungus.



20a

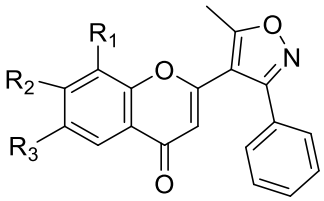


21f

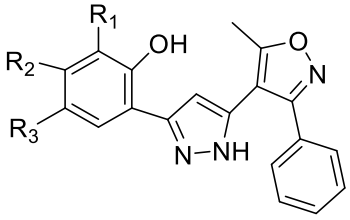


22a

Badadhe *et al.* (2013) were successful in synthesizing a number of novel chromophores and pyrazoles that contained incorporated isoxazole moieties. Infrared spectroscopy, nuclear magnetic resonance with a 1H spin, mass spectrum data, and elemental analysis have all been utilized to validate structures of all freshly synthesized compounds. The chemicals that were produced were tested for their ability to inhibit bacterial growth, namely 2 Gram -ve bacteria, *Salmonella typhimurium* (ATCC 23564), and *Pseudomonas aeruginosa* (ATCC 27853) as well as 2 Gram +ve bacteria, *Bacillus subtilis* (ATCC 6633), Staphylococcus aureus (ATCC 25923). For the purpose of evaluating the effectiveness of each chemical, Streptomycin and Ampicillin were used as benchmarks. There was a modest level of antibacterial activity demonstrated by compounds 23b, 23c, and 23g when tested against Gram-positive bacterial strains. In a similar vein, compounds 24c, 24d, and 24g demonstrated effective antibacterial action against Gram-negative bacterial strains.

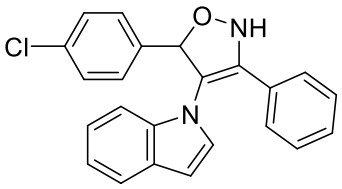


Compound	R1	R2	R3
23b	CH_3	H	H
23c	CH_3	H	CH_3
23g	H	H	Br



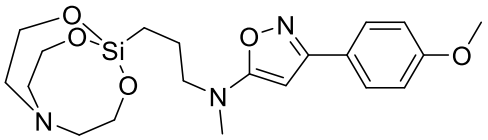
Compound	R1	R2	R3
24c	CH_3	H	CH_3
24d	H	H	Cl
24g	H	H	Br

Chauhan *et al*. (2012) synthesized various pyrazole and isoxazole derivatives and screened for antimicrobial activity. Elements of the compounds that were produced were analyzed by elemental analysis, IR spectroscopy, NMR with 1H, and mass spectroscopy. For purpose of determining whether or not the newly synthesized compounds possessed antibacterial and antifungal properties, the Cup-Plate (disk diffusion) method was utilized to test the compounds against Escherichia coli and Bacillus cereus, as well as *Macrophomina phaeolin*, and *Fusarium oxysporium*, two types of bacteria. Both streptomycin and fluconazole were utilized as reference medications in the screening investigations that were conducted for antibacterial and antifungal medication. The compound 25c had the highest level of activity against E. coli, which was higher than activity of medication that served as the reference. Compound 25c exhibits the highest level of activity against the fungus *F. oxysporium*.



25C

An entirely new family of mono- and bis-isoxazole-bridged silatranes was synthesized by Adamovich *et al.* (2020). Structure of hybrids of isoxazolesilatrane is described by elemental analysis, Fourier transform IR spectroscopy, UV spectroscopy, X-ray diffraction technique, high-resolution mass spectrometry, and NMR (1H, 13C, 29Si, and 15N) spectroscopy. Based on initial screening of synthesized silatranes for antibacterial activity against *Escherichia coli, Bacillus subtilis*, *Pseudomonas aeruginosa*, and *Enterococcus durans*, it has been determined that all of test samples are solely effective against gram +ve microbes. In comparison to the standard antibiotic gentamicin, which has MIC values of 25 and 50 µg ml−1, Silatrane 26f exhibits a minimal inhibitory concentration (MIC) of 12.5 and 6.2 µg per ml against *B. subtilis* and *E. durans*.



26f

CONCLUSIONS

In conclusion, the future of isoxazole research is marked by a convergence of synthetic innovation, biological discovery, and interdisciplinary collaboration. As our understanding of isoxazoles deepens and their diverse applications expand, these compounds are poised to make significant contributions to science, medicine, and technology in the coming years. Researchers in academia and industry are likely to continue harnessing the versatility of isoxazoles to address pressing scientific challenges and improve human well-being.

FUTURE SCOPE

The exploration of isoxazoles holds immense promise for future research and applications in various scientific domains. Several avenues of future research and development emerge from the current understanding of isoxazoles, encompassing both their synthesis and biological activities. Here are some key areas of future scope:

— **Development of Novel Synthetic Strategies:** Continual innovation in the synthesis of isoxazoles is anticipated. The development of more efficient and sustainable synthetic methods, such as catalytic processes and environmentally benign approaches, will be of great interest. Advances in asymmetric synthesis techniques to access enantiomerically pure isoxazoles are also expected.

— Structure-Activity Relationship (SAR) Studies: Further elucidation of the SAR of isoxazoles is essential to design compounds with enhanced specificity and potency. Understanding how subtle structural modifications influence their biological activities will aid in the rational design of new drug candidates targeting various diseases.

— Drug Discovery and Development: Isoxazoles will continue to play a pivotal role in drug discovery efforts. Researchers will focus on identifying new therapeutic targets for isoxazole-containing compounds, particularly in areas such as cancer, infectious diseases, neurodegenerative disorders, and inflammation. Combining isoxazoles with other pharmacophores to create multi-targeted drugs could be explored.

— Natural Product Derivatives: Investigating isoxazoles found in natural products and their derivatives may lead to the discovery of bioactive compounds with novel mechanisms of action. This could open new avenues for drug development and the search for innovative solutions to address emerging health challenges.

— Bioorthogonal Chemistry and Chemical Biology: Isoxazoles, with their bioorthogonal properties, can be employed in chemical biology studies. Future research may involve the development of isoxazole-based probes for the selective labeling and tracking of biomolecules within living systems, aiding in our understanding of complex biological processes.

— Materials Science: Isoxazole-containing compounds have shown potential in materials science applications, including the development of advanced polymers, liquid crystals, and functional materials. Future research may lead to the creation of novel materials with unique properties for various technological applications.

— Environmental and Green Chemistry: Sustainable approaches to isoxazole synthesis will become increasingly important in the context of green chemistry. Researchers may focus on developing greener synthetic methodologies and exploring renewable starting materials.

— Computational Chemistry: The use of computational tools and modeling techniques to predict the biological activities and properties of isoxazole derivatives will become more prevalent. This approach can expedite the design and optimization of potential drug candidates.

Acknowledgement. The authors are grateful to the Principal Prof. Anna Pratima Nikalje and Wilson College management for providing research laboratory facilities. We express a deep sense of gratitude to Dr. Abhijeet Kadam Department of Chemistry, John Wilson Education Society's, Wilson College (Autonomous), Mumbai, 400007, Maharashtra, India, for his assistance and providing the valuable suggestions and support.

Conflict of Interest. None.

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How to cite this article: Kishor Wani, Anna Pratima Nikalje and Harichandra A. Parbat (2023). Exploring the Diverse World of Isoxazoles: Synthesis, Biological Activities, and Prospects. *Biological Forum – An International Journal, 15*(5a): 665-673.