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NITROGEN CONTAINING BENZOXAZINE BASED HETEROCYCLIC COMPOUNDS: A KEY TO MODERN DRUG DESIGN

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Abstract:
Heterocyclic compounds consist of at least two elements other than carbon in a pentagonal or hexagonal ring structure, such as nitrogen, oxygen, and sulphur. Nitrogen-based heterocyclic compounds play an essential role in modern drug design. Nitrogen-containing heterocyclic compounds are primarily used because it helps in drug design. We found some types of drugs, such as diazepam, isoniazid, chlorpromazine, metronidazole, barbituric acid, captopril, chloroquine, azidothymidine, and antipyrine. All of these compounds play a significant role in medicinal chemistry as well. Benzoxazines are among the essential heterocyclic compounds containing a benzene ring fused to an oxazine (Hexagonal ring structure). In benzoxazine, the leading functional group is responsible for various biological activities, including anticancer (lavoflaxin), anti-inflammatory (fulnoxaprofen), anti-microbial (anguslureine), anti-HIV activity (Efavirenz) etc.. The objective of the article is to assess the therapeutic properties of derivatives of Benzoxazine.

Key words:
Heterocyclic compounds, Benzoxazine derivative, Biological Activity, Drugs design, Green Chemistry

Introduction:
Nitrogen-containing heterocyclic compounds are an important portion for biological active compounds**.** Nitrogen containing heterocycles are found to various product and natural product to investigate drug design (Figure 1).[i] They play an important role in biological investigation such as anticancer, anti-inflammatory, antibacterial, antifungal, anti-malarial activity. Benzoxazine is a versatile and important class of compounds in organic chemistry due to its unique structure and reactivity.[ii] Nitrogen-containing heterocyclic compounds play crucial roles in various fields, including medicinal chemistry, materials science, and organic synthesis. Benzoxazines can be used as key building blocks in the synthesis of nitrogen-

containing heterocycles, offering several important roles and advantages.[iii-v] Benzoxazines are indeed important compounds with diverse applications across various fields.

Benzoxazines have gained significant attention in the field of medicinal chemistry due to their ability to interact with various biological targets and their potential therapeutic applications. These compounds have demonstrated promising activities against a variety of diseases, including cancer, inflammation, microbial infections, and neurological disorders, among others. The presence of the nitrogen atom in the heterocyclic ring system enhances the compounds' ability to form hydrogen bonds and interact with specific amino acid residues in target proteins, which is crucial for their biological activity.[vi]

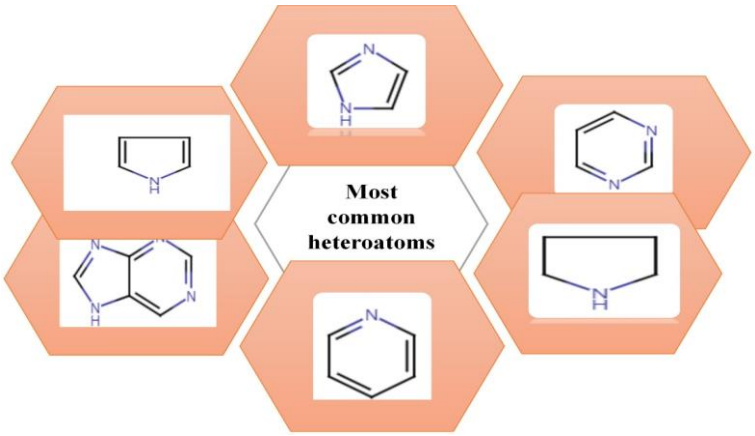

Figure 1: Structures of N-containing heterocyclic compounds

Moreover, the benzoxazine scaffold provides a stable and rigid structure that can be further functionalized with various substituents to optimize their pharmacokinetic properties and target specificity. This flexibility in structural modification allows medicinal chemists to design and synthesize novel benzoxazine derivatives with improved potency, selectivity, and drug-like properties.

Properties of nitrogen containing heterocyclic compounds:

Nitrogen-containing heterocyclic compounds indicate various properties and are broadly present in various natural substances. These compounds occurs special characteristics due to the presence of nitrogen among their ring structures.

Some properties are as follows:

Biological Importance: Nitrogen containing heterocyclic compounds play vital role in biological material. Most of the nitrogen containing heterocyclic are used to design drug.

Aromaticity: Some nitrogen-containing heterocycles express aromatic properties due to their ring structures and delocalized electrons.

Functional Groups: Nitrogen heterocyclic compound contain various functional groups attached to the ring structure such as amide, amine, hydroxyl etc.

Medicinal chemistry: Nitrogen containing heterocyclic compound containing drug design.

Benzoxazine:

Benzoxazines (Figure 2) are the type of heterocyclic compounds containing an oxazine ring other than benzene ring. They occur special properties that make them precious in various fields, in polymer chemistry, more thermal stability, less water absorption.[vii] It is also used in various industries like coating, composites and resin.

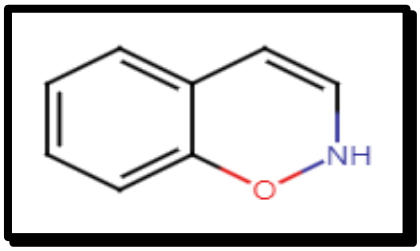

Figure 2: Structure of benzoxazine

Benzene is a chemical compound having hexagonal ring structure. It is used as starting material of pharmaceutical industries like drug design and dyes.

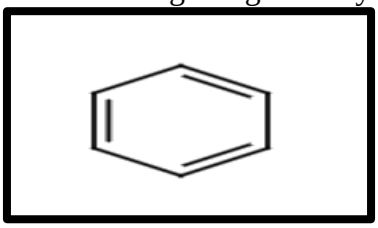

Figure 3: Benzene ring

Oxazine (Figure 3) are the class of nitrogen containing heterocyclic compound contain hexagonal ring structure of five carbon atoms and one oxygen atom[viii]. Oxazine is a saturated heterocyclic compound having both nitrogen and oxygen atoms.

It can be found in natural products, dyes and other compound.

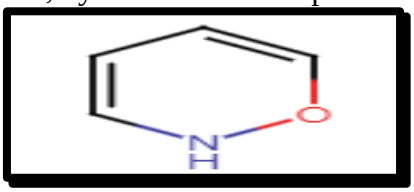

Figure 4: Structure of Oxazine

Biological activity:

Benzoxazine acts as anticancer activity: Benzoxazine compounds have presented huge range of biological activities, inclusive power anticancer properties in some studies. Cancer is occurring due to uncontrolled cell division and multiplication. Several methods exist for eliminating tumor cells, and the use of anticancer drug agents is crucial for efficiently removing tumors without harming healthy tissues,[ii] while numerous drugs are available to inhibit the growth of cancer cells, Benzoxazine derivatives, as a distinct class of compounds, hold significant importance in the fields of biological and medicinal chemistry.

Anti-cancer activity of benzoxazine is observed in vivo in mice, specifically in the case of Benzoxazine derivatives 6-allyl-3-benzyl-8-methoxy-3,4-dihydro-2H-benzo(e)(1,3)-oxazine and 6-allyl-3-(furan-2-methyl)-8-methoxy-3,4-dihydro-2H-benzo(e)(1,3)oxazine. For the study, male mice were randomly divided into different groups. The first group served as the negative control and received only CMC-Na. The second group was administered the test compound at a dose of 30 mg/Kg, the third group received the test compound at a dose of 50 mg/Kg, and the fourth group was given the test compound at a dose of 90 mg/Kg body weight. The fifth group received test compound at a dose of 10 mg/Kg, the sixth group received test compound at a dose of 50 mg/Kg, the seventh group received test compound at a dose of 90 mg/Kg, the eighth group received test compound at a dose of 30 mg/Kg, the ninth group received test compound at a dose of 50 mg/Kg, and the tenth group received test compound at a dose of 90 mg/Kg. The eleventh group received test compound at a dose of 30 mg/Kg, and the twelfth group received test compound at a dose of 50 mg/Kg daily for each month. Earlier, every two days (five times within ten days), the mice were administered 0.3

mg of benzopyrene in 0.2 ml of olive oil through subcutaneous injection in the scapular area.[vii-x] The mice were maintained on the same diet for a period exceeding two months.

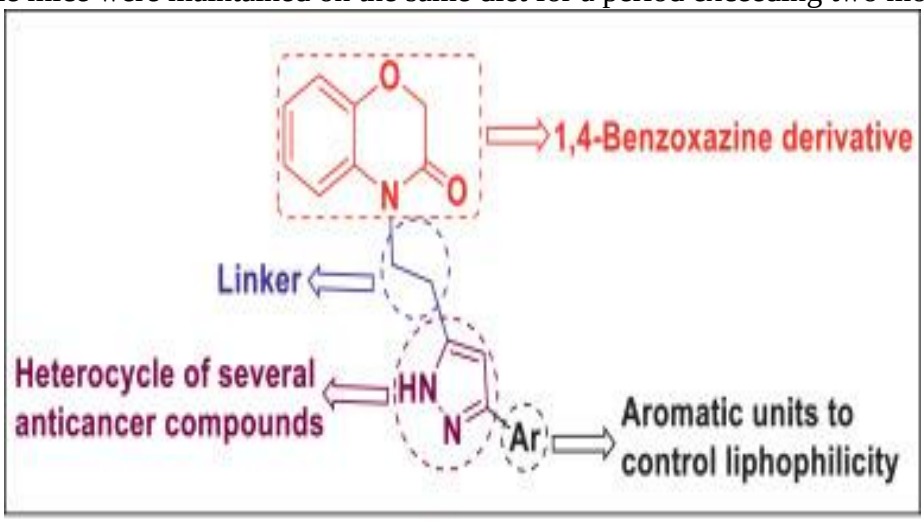

Figure 5: Structure of Benzoxazine derivative as anticancer compound

Benzoxazine derivatives act as antimicrobial agent: The reaction of benzoxazine aminomethylation with different nitrogen and oxygen-containing nucleophiles leads to the formation of heterocyclic systems known as benzoxazine derivatives.[xi] These derivatives were evaluated for their antimicrobial activity. This review seeks to identify the functional groups responsible for the antimicrobial properties exhibited by benzoxazine derivatives. The antimicrobial activity was tested against bacterial strains such as *E. coli*, *S. aureus*, and *B. subtilis*, as well as against *A. Niger*, using the cup plate technique with ofloxacin and fluconazole as controls.[xi, xii] The series of creative primary amine methylation benzoxazine derivatives showed acceptional antimicrobial activities.

Antimicrobial protection has vital role for providing hygienic for various industries by antimicrobial agents like growth of microbes such as bacteria, fungi, protozoa, algae. Benzoxazines derivatives have been evaluate for their potential in medical techniques due to their compatible and melodious properties.[xiii] While their starting technique revolve around materials science and some research has explored their antimicrobial effects.[xiv] Some antimicrobial drug has been used in benzoxazine as antimicrobial agent like quaternary ammonium compound; Metal based antimicrobial agents, organic antimicrobial agent etc. Further research is being done on Benzoxazine compound to know the drug which can be better for antimicrobial activity. To culminate, researchers suggest that benzoxazine compounds with a more potent effect will be generated.

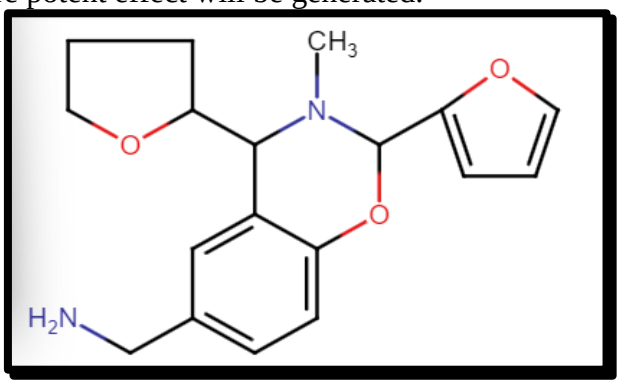

Figure 6: Metal based compound of Benzoxazine ligand

Benzoxazine acts as antihypertensive agent: Hypertension, also known as high blood pressure, is said to be when a blood (blood vessels) in human body is too high generate hypertension. Hypertension occurs due to irregular exercise and eats unhealthy food. Various types of diseases occur due to hypertension like heart attack, stroke, brain problems, and kidney diseases. Benzoxazine derivatives have been employed for their antihypertensive properties. Benzoxazine derivatives have been utilized due to their abilities to lower blood pressure as antihypertensive agents. A number of benzoxazines contain a similar functional unit—the amide group—that enhances the efficacy of these antihypertensive medications in achieving optimal blood pressure reduction.[xv-xvi]

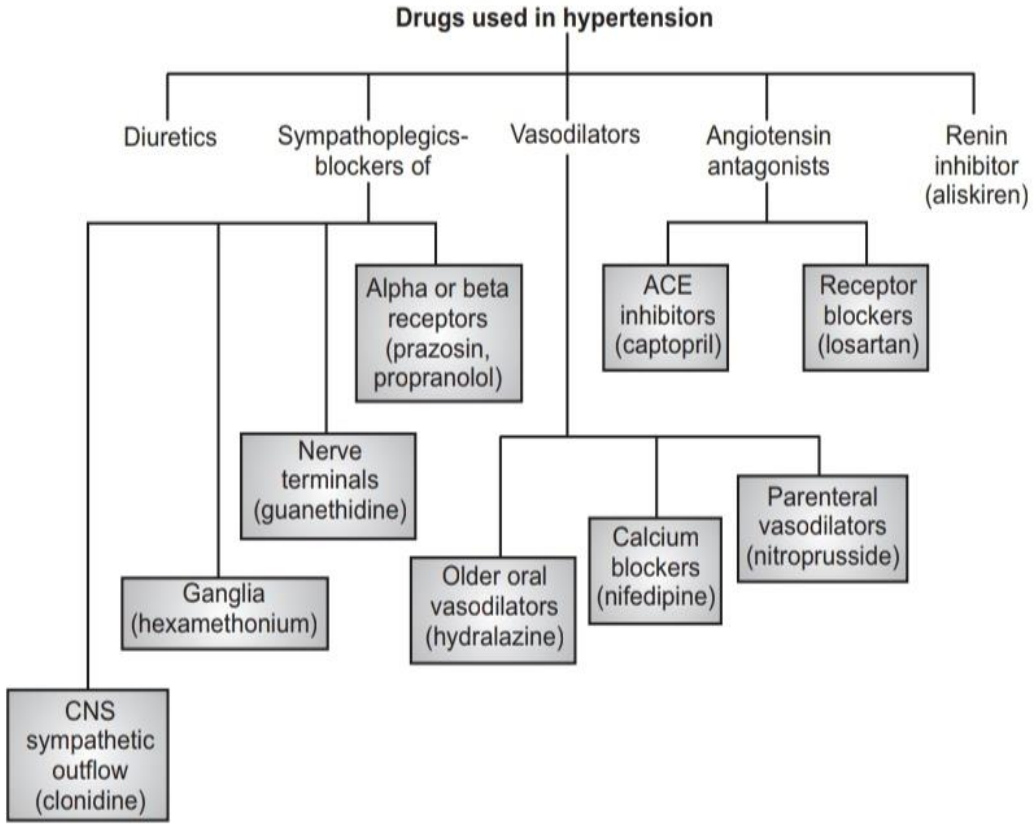

Figure 7: Classification of drugs used in hypertension

Modern and green chemistry approaches:

Recent advances have introduced more efficient and environmentally friendly synthesis methods for benzoxazines. Green chemistry approaches aim to reduce the use of hazardous reagents and solvents, minimize waste, and improve reaction efficiency. Some modern methods include:

- *Microwave-Assisted Synthesis:* This method accelerates the reaction time and improves yield by using microwave radiation to heat the reactants.
- *Solvent-Free Reactions*: Performing reactions without solvents reduces the environmental impact and simplifies the purification process.
- *Catalyst Development:* New catalysts, such as ionic liquids or metal-organic frameworks, have been developed to enhance reaction rates and selectivity.

Synthetic scheme:

The synthesis of benzoxazines typically involves the condensation of ortho-amino phenols with aldehydes or ketones. This reaction can be catalyzed by various acids or bases, leading

to the formation of benzoxazine rings. The reaction conditions and the choice of reagents can be tailored to produce benzoxazines with different substitutions, which can significantly affect their biological properties.[xvii-xviii]

Mannich-condensation based benzoxazine synthesis: This synthesis occurs in formaldehyde and amine groups along with compound containing proton. Benzoxazine compound are important class of organic chemistry due to their mechanical properties.[viii] In the case of benzoxazines, employing the Mannich condensation may lead to the synthesis of novel benzoxazine derivatives with altered characteristics or improved properties.

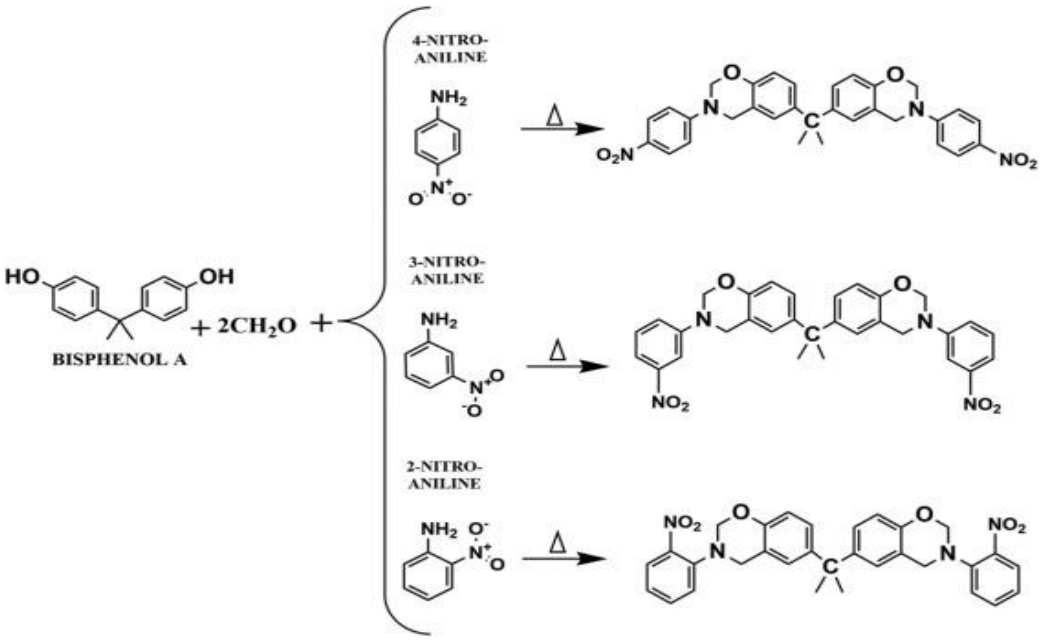

Figure 8: Synthetic routes of benzoxazines by Mannich-condensation

Benzoxazine synthesis through cycloaddition: In this reaction synthesis occurs in the presence of phenol, formaldehyde and primary amines. It's pivotal to note that the same conditions, reagents, and procedures may vary depending on the especial benzoxazine compound being synthesized and the esteemed substituents.[xix-xx] This general procedure outlines the steps take in the cycloaddition synthesis of benzoxazines. Researchers invent this approach or use other methods based on their specific requirements.

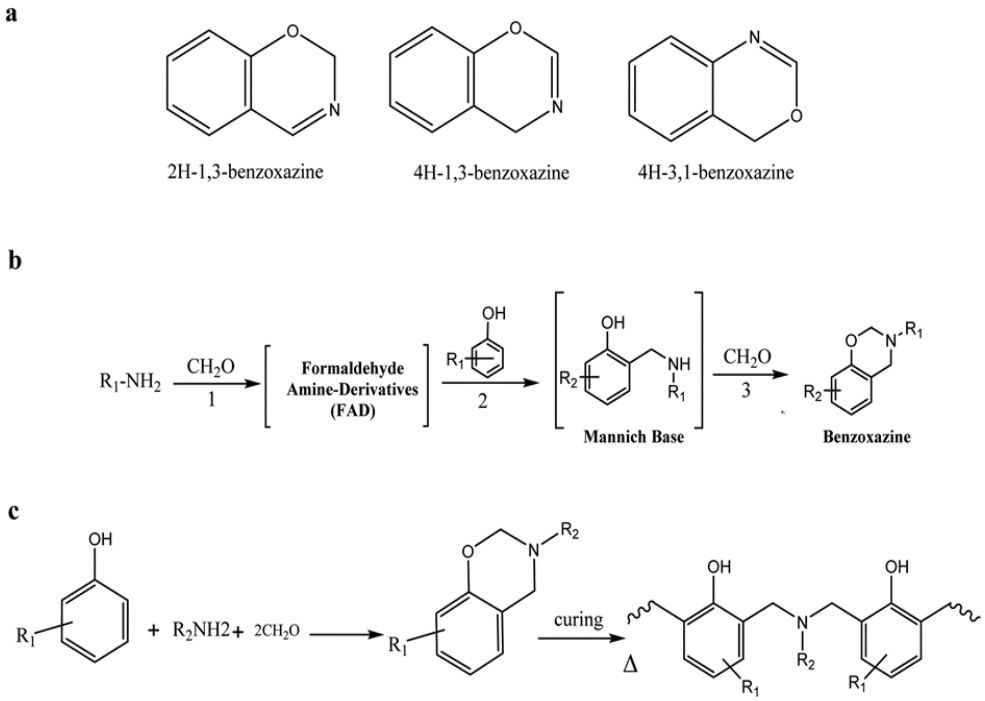

Figure 9: Synthetic routes of benzoxazines by cycloaddition

Applications of benzoxazine compounds:

Benzoxazine have their unique properties and application. There are some applications:

1. Composite material
2. Coating
3. Electronic appliances
4. Pharmaceutical application
5. Fuel cell

Composite material: Benzoxazine compound are used as composite substance and they show some mechanical properties and low shrinkage.

Coating: Benzoxazine provide coating to reduce corrosion and chemical resistance.

Electronic appliances: Benzoxazine are used as electronic appliances such as microelectronic and insulating material.

Pharmaceutical appliances: Benzoxazine compounds are used in various pharmaceutical industries includes drug design and biological importance.

Fuel cell: Benzoxazine polymers have been explored for their use in proton exchange membrane and another component.

Challenges in drug development:

Synthetic Challenges:

While the synthesis of benzoxazines has been well-established, challenges remain in optimizing reaction conditions, improving yields, and reducing the use of hazardous reagents. Streamlining synthetic processes and developing new methodologies are essential for the efficient production of benzoxazine-based drugs.[xxi]

Selectivity and Toxicity:

Achieving high selectivity for specific biological targets while minimizing off-target effects and toxicity is a major challenge. SAR studies and structure-based drug design approaches can help in identifying compounds with improved selectivity and reduced adverse effects.

Pharmacokinetics and Bioavailability:

The pharmacokinetic properties of benzoxazine-based drugs, including their absorption, distribution, metabolism, and excretion, need to be carefully evaluated. Enhancing

bioavailability and ensuring optimal drug delivery are crucial for achieving therapeutic efficacy.

Resistance Mechanisms:

For antimicrobial and anticancer agents, resistance mechanisms can limit the effectiveness of benzoxazine-based drugs.[xxii] Understanding these mechanisms and developing strategies to overcome resistance are critical for maintaining drug efficacy.

Future directions:

Development of Novel Benzoxazine Derivatives

Future research should focus on developing novel benzoxazine derivatives with improved biological activity, selectivity, and safety profiles. Exploration of new substitutions, functional groups, and ring modifications can lead to the discovery of more effective drugs.[xxiii]

Integration with Modern Drug Design Techniques

Incorporating advanced drug design techniques, such as computational modelling, high-throughput screening, and structure-based drug design, can enhance the efficiency of benzoxazine-based drug development. These techniques can provide insights into molecular interactions and optimize drug candidates.

Exploration of New Therapeutic Areas

Benzoxazines have shown potential in various therapeutic areas, but further research is needed to explore their applications in additional fields, such as cardiovascular diseases, metabolic disorders, and rare diseases. Expanding the scope of research can lead to new therapeutic opportunities.[xxiv]

Collaboration and Interdisciplinary Research

Collaboration between chemists, biologists, and pharmacologists is essential for advancing benzoxazine-based drug development. Interdisciplinary research can provide a holistic understanding of drug properties, mechanisms of action, and potential applications.

Conclusions:

In the research benzoxazine derivative shows several new structure by using synthetic scheme and green chemistry. Benzoxazine compounds holds huge significance due to their biological activities for drug development in pharmaceutical area and further research is going on in this field. Nitrogen-containing benzoxazine-based heterocyclic compounds represent a valuable class of molecules in modern drug design. Their unique chemical structure and diverse biological activities make them promising candidates for developing new therapeutic agents. Ongoing research into their synthesis, biological properties, and pharmacokinetics will be crucial for advancing benzoxazine-based drugs. By addressing current challenges and leveraging modern drug design techniques, benzoxazine-based compounds have the potential to contribute significantly to the advancement of medical treatments and the fight against various diseases. The ability to modify these compounds allows researchers to optimize their pharmacological properties, enhancing efficacy while minimizing side effects. Furthermore, advancements in synthetic methodologies, particularly greener approaches, facilitate the efficient production of these compounds, making them viable candidates for pharmaceutical development. As research in this field continues to progress, nitrogen-containing benzoxazines are poised to contribute significantly to innovative drug discovery, addressing unmet medical needs and advancing therapeutic options. Their importance in pharmacology underscores the vital intersection of chemistry and biology in developing effective medical solutions.

Statement and declaration:

Author contribution statement:

Barkha Sharma: Conceptualization, Data curation, Investigation, Methodology, Visualization, Writing –original draft. **Chandra Mohan**: Visualization, Writing – review & editing, Project administration, Resources. **Noushi Zaidi**: Conceptualization, Methodology. **Sunil Kumar**: Writing – review & editing, Resources.

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***Declaration of competing interest*:** None

Data availability:

The authors do not have any data to share as this is the review article.

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