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SYNTHESIS CHARACTERIZATION AND ANTI-INFLAMMATORY EVALUATION OF HALOGENATED BENZOXAZINE DERIVATIVES: A REVIEW

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Abstract: This review explores the synthesis, characterization, and pharmacological evaluation of halogenated benzoxazine derivatives, focusing on their potential therapeutic applications. The synthesis of these compounds involves various methodologies, including the use of chloroacetyl chloride and different anhydrides to produce benzoxazine derivatives with diverse halogen substitutions. Characterization techniques such as melting point determination, Rf value analysis, and structural elucidation are employed to confirm the identity and purity of the synthesized derivatives. Pharmacological assessments, including anti-inflammatory and anti-diabetic evaluations, demonstrate that while some halogenated benzoxazine derivatives exhibit promising biological activities, their effectiveness varies. Notably, derivatives with iodine or bromine substitutions show significant anti-inflammatory potential, although their overall efficacy is moderate. Additionally, the evaluation of these compounds in diabetic animal models provides insights into their potential as therapeutic agents for managing diabetes. The findings suggest that halogenated benzoxazine derivatives have considerable promise as drug candidates, but further research is essential to optimize their therapeutic efficacy and safety profiles. Future studies should focus on enhancing the effectiveness of these compounds, elucidating their mechanisms of action, and ensuring their safety for clinical applications. This review provides a comprehensive overview of current advancements and highlights areas for future research in the field of benzoxazine derivatives.

Keywords: Synthesis Characterization, Pharmacological Evaluation, Medicinal chemistry and Halogenated Benzoxazine Derivatives

1. INTRODUCTION

Drugs have existed as long as illness has been part of human history. With globalization, new diseases have emerged, leading to a continuous quest for cures. Historically, drugs were derived from plants, animals, and minerals. However, due to limited efficacy, conclusive cures, and high toxicity, the development of new, less toxic drugs has become crucial. Synthesizing derivatives has significantly advanced drug development, particularly in enhancing efficacy and reducing side effects. Today, synthetic derivatives make up over 60% of medicines in clinical use, and the field of synthetic medicinal chemistry continues to grow, underscoring the vital role of drugs in modern medicine.

Medicinal chemistry is the science behind the creation of drugs, whether through observation or design. In the past century, many drugs were discovered by modifying natural substances or through chemical synthesis. With a growing understanding of disease pathophysiology,

recent years have seen more innovative approaches to the design, synthesis, and evaluation of drug candidates. The late 20th century blurred the lines between biological, chemical, and physical sciences, leading to new interdisciplinary fields like molecular biology, pharmacology, biomedicine, cellular biology, genetics, and bioinformatics, which are now of great interest to medicinal scientists.

The drug discovery process has become increasingly multidisciplinary due to the growing need for new drug molecules. Medicinal chemists now require expertise in both biological areas, like enzymology and pharmacology, and physicochemical aspects, such as thermodynamics and quantum mechanics. With advancements in enzyme/receptor principles and receptor-based assays, the approach has become more mechanistic. Lead discovery and optimization, essential in medicinal chemistry, have advanced through improvements in structural biology, combinatorial synthesis, and high-throughput screening techniques. Benzoxazines display various effects, including anti-inflammatory, analgesic, antibacterial, and neuroprotective properties. They inhibit bacterial histidine protein kinase and may aid in treating heart disease and arrhythmia. Their antimycobacterial activity and dual biological effects, like anti-inflammatory and antibacterial, are of growing interest for microbial infections. This study synthesizes compounds with these dual properties by reacting aromatic amines with substituted phenols in formaldehyde and assesses their biological activities **(Mymoona Akhter et al., 2021).**

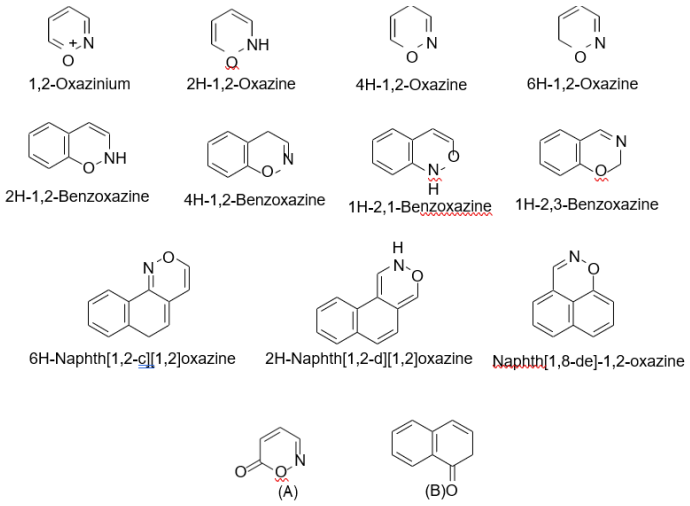

Figure 1 Example of well-known 1,2-oxazine ring system

The biological activity of 2H-1,4-benzoxazine-3-(4H)-one and 3,4-dihydro-2H-1,4-benzoxazine derivatives, including their neuroprotective potential, has been extensively studied. Our research focuses on designing and synthesizing bioactive molecules with a 5,7,8-trimethyl-1,4-benzoxazine core, resembling the antioxidant vitamin E's structure. We tested six derivatives (Figure 2) for their ability to inhibit PrPSc generation in mouse neuroblastoma cells (N2a) infected with the scrapie strain 22L. The EC50 of 2-(4-methoxyphenyl)-5,7,8-trimethyl-3,4-dihydro-2H-1,4-benzoxazine (TC121) is 1.17 µM, and the EC90 is 3.2 µM. Our results indicate that TC121 effectively reduces PrPSc levels in ScN2a cells, suggesting its potential therapeutic value.

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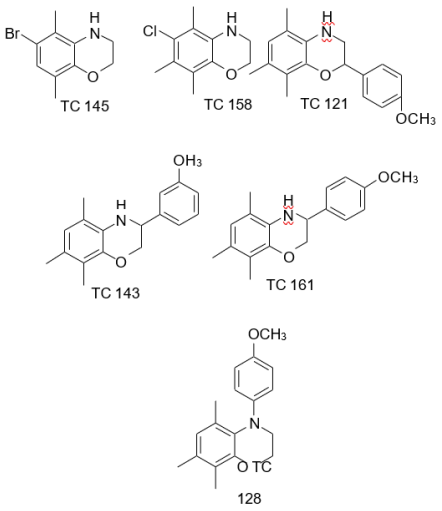

Figure 2 Tested six derivatives of Benzoxazine

Poly-benzoxazines are novel thermoset polymers with customizable properties, offering advantages over traditional phenolic resins. They are used in coatings, adhesives, microelectronics, and aerospace due to their low water absorption, dimensional stability, minimal shrinkage, thermal stability, chemical resistance, low dielectric characteristics, and flame retardance. Additionally, their polymerization is eco-friendly, producing no catalysts or toxic volatiles and using renewable feedstock. Despite their benefits, poly-benzoxazines face challenges such as limited solubility, high curing temperatures, and low fracture toughness. Research is ongoing to develop new benzoxazine monomers with improved properties and functionalities, focusing on enhancing stability and addressing existing drawbacks **(Danuta Trybu et al., 2020).**

Phenolic compounds, including phenols, hydroquinones, coumarins, flavonoids, and tannins, are widely studied for their diverse chemical and biological properties. Found in microbes, plants, and animals, phenols play a key role in proton-linked electron transfer and are used in photo-cleavable probes for mass spectrometry. Synthetic phenol derivatives exhibit various pharmacological effects: hydroquinone dimethyl ethers have anticancer and antibacterial properties, while caffeic acid and p-coumaric acid show antioxidant effects. The addition of hydroxyl or methoxy groups to phenols enhances their antioxidant activity. Phenolic compounds are also known for their antibacterial, antiviral, anti-inflammatory, and other therapeutic properties. However, antimicrobial resistance remains a significant global health challenge. To address this, we synthesized and tested new phenolic derivatives, including two novel nitrobenzyl-oxy-phenol compounds, for their antibacterial activity.

Benzo-1,3-oxazine features a bicyclic structure with an oxazine ring fused to a benzene ring. It exists in various isomeric forms depending on the oxidation state and ring system. Figure 3 shows the isomers 2H- and 4H-benz-1,3-oxazine, and 2,3-dihydro-2H-benz-1,3-oxazine. The semi-chair (A) and semi-boat (B) conformations of 3,4-dihydro-2H-benz-1,3-oxazines are also illustrated in Figure 3.1. Each conformation can exist in two forms based on the nitrogen atom's substituent orientation. Dihydro-1,3-benzoxazine monomers can be synthesized using

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Mannich condensation, cycloaddition, and other methods, with studies focusing on reactant ratios, structures, solvents, temperatures, and durations.

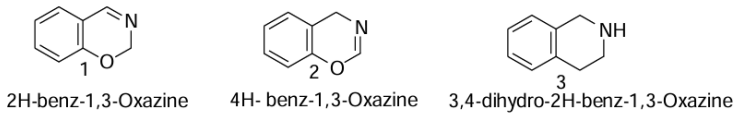

Figure 3 Chemical structure of 1,3 Oxazine

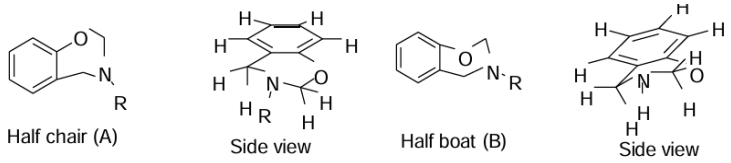

Figure 4 3,4-Dihydro-2H-benz-1,3-oxazines conformations

The benzoxazine nucleus is widely used as an intermediate in synthesizing various heterocyclic bioactive compounds and medicinally relevant molecules. Many 1,3-benzoxazines exhibit notable biological and pharmacological properties. Additionally, acetal glycosides, synthesized in plants, serve as natural defenses against insects, pests, fungi, and microbial diseases, making these derivatives valuable in natural product chemistry. This study examines the chemistry and bioactivities of 3,4-dihydro-2H-1,3-benzoxazine monomers and their derivatives **(Sharaf El Din et al., 2019).** Benzoxazines are used as fungicides, anti-inflammatory agents, anticonvulsants, DNA-binding anticancer agents, and inhibitors of human leukocyte elastase and Clr serine protease. 1,4-Benzoxazine derivatives inhibit cell proliferation and angiogenesis in chorioallantoic membrane assays. Notably, 1,2-dihydrobenzoxazine derivatives have shown promise in developing nonsteroidal progesterone-receptor agonists and have cytotoxic effects against human cancer cell lines. Benzoxazine fragments are also found in natural substances, such as antimicrobial alkaloids in the sea sponge Jaspis splendens. The antibacterial potential of 1,3-benzoxazine derivatives is of particular interest due to its practical applications **(S. P. Zahorulko et al., 2019).**

Heterocycles are valuable in pharmaceuticals due to their ability to incorporate substituents in distinct three-dimensional arrangements. Early studies focused on nitrogen and sulfur-containing heterocycles, which were integral to the development of organic chemistry and drug discovery. These compounds remain crucial in biology and industry because their structures can be finely tuned to achieve specific functions **(Dinesh Kumar Jangid et al., 2019)**. Several substances are known as NOS inhibitors, including arginates, aminopyridines, cyclic amidines, and phenylimidazoles. Specifically, 3-amino-2H-1,4-benzoxazines and 3-amino-2H-1,4-benzothiazines are effective and selective inhibitors of nitric oxide synthases, as noted in WO 98/50372 and WO 99/12915. Recent findings suggest that these newly substituted heterocyclic compounds offer advantages over existing agents and have improved medicinal efficacy **(Petro P. On et al., 2017).** The palladium-catalyzed oxidative alkoxycarbonylation of alkynes is an efficient method for creating complex heterocycles from readily available materials. We have successfully utilized this technique to produce carbonylated compounds in a one-pot process. Previously, we developed a simple method for

synthesizing novel functionalized benzo[d][1,3]oxazines by in situ deprotecting 2-(trimethylsilanyl)ethynylaniline derivatives, followed by palladium-catalyzed cyclization-alkoxycarbonylation **(Francesco Pancrazzi et al., 2017).** Substituted benzoxazinone and quinazolinone derivatives are significant due to their broad biological activities, including antitubercular, antihypertensive, anticancer, anti-HIV, antiviral, anti-inflammatory, and antifungal effects. They are also used as analgesics and inhibitors of cathepsin G, human leukocyte elastase, selective serotonin reuptake, and CIr serine protease. Additionally, compounds with aromatic sulfonate or sulfonamide groups exhibit strong acaricidal and insecticidal activities **(Mohamed Suleman Malik et al., 2016).**

The 1,4-benzoxazine nucleus is a common heterocyclic scaffold in pharmacologically active and medicinally relevant molecules. For instance, glycosides with the 2-hydroxy-2H-1,4-benzoxazine structure, found in gramineous plants, are suggested to play a role in plant resistance against microbial diseases and insects. The 1,4-benzoxazine moiety is found in various pharmaceuticals, including antibiotics, antirheumatic drugs, calcium channel antagonists, CNS drugs, and analgesics. Derivatives such as 3,4-dihydro-2H-1,4-benzoxazines have shown potassium channel opening activity in vascular smooth muscle, while some exhibit anti-Mycobacterium tuberculosis properties. Methotrexate derivatives with the benzoxazine group have shown potential as antirheumatic agents. Additionally, 2,3-disubstituted-1,4-benzoxazines are promising intermediates for synthesizing bioactive compounds. Several methods for synthesizing 1,4-benzoxazine derivatives include O-alkylation of 2-nitrophenols, intramolecular N-substitution of 2-aminophenols, microwave-assisted synthesis, copper-catalyzed coupling, and the Petasis reaction. We have successfully synthesized 2-hydroxy-1,4-benzoxazines from 2-aminophenols and aldehydes using the Petasis reaction with phenylboronic acid at room temperature **(Sara Mahdjoub et al., 2016).** Benzo [d][1,3]oxazine and benzothiazine rings are crucial in many biologically active compounds, used for antifungal, anti-inflammatory, anticonvulsant, and DNA-binding applications. For example, 2-substituted-4H-3,1-benzoxazin-4-one lowers cholesterol and triglycerides, and etifoxine, a non-benzodiazepine anticonvulsant, treats psychiatric disorders effectively. Synthesis methods include thermolysis, electrochemical cyclization, and palladium-catalyzed reactions, but face issues like toxic chemicals and low yields. Recent work has investigated α-diazocarbonyl compounds for creating various heterocycles **(B. V. Subba Reddy et al., 2014).**

Indolo[2,1-b][1,3]benzoxazines are a new class of photochromic compounds with notable molecular switching speeds and resistance to photochemical fatigue. Structurally similar to spiropyrans, these compounds feature fused indole and benzoxazine rings. UV exposure causes the [1,3]oxazine ring to open, forming two chromophoric systems. This results in a 3H-indolium cation and a 4-nitrophenolate anion with strong absorption around 430 nm. The ring reverts to its closed state within nanoseconds upon heat. Unlike spiropyrans, these compounds do not undergo slow trans-cis isomerization, allowing for rapid switching. They are also resistant to chemical deterioration and can endure thousands of switching cycles. The photochromic properties of indolo[2,1-b][1,3]benzoxazines, such as absorption spectra, switching speed, and fatigue resistance, can be modified by introducing substituents. This

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study investigates the impact of phenylic substituents on these properties. Ten new compounds were synthesized, divided into two groups: Group I has substituents at the 5th position of the indole ring, and Group II has substituents at the o-position of the phenolic ring within the [1,3] benzoxazine moiety. This is the first report of such modifications to the nitrophenolic fragment of indolo[2,1-b][1,3]benzoxazines. The novel compounds were characterized in acetonitrile (MeCN) by evaluating photochromic parameters like relaxation periods, quantum yields, and photochemical fatigue resistance, and compared with the parent compound and other related compounds **(Vladislava Voicu et al., 2014).**

Benzoxazine consists of an oxazine ring attached to a benzene ring, with oxygen and nitrogen in the ring. The three types of benzoxazines are categorized based on the ring structure, with 1,3-benzoxazines being the most notable for their biological activity. These derivatives exhibit a wide range of effects, including antibacterial, antifungal, analgesic, anti-inflammatory, and more. They have shown potential in treating conditions such as inflammation, rheumatoid arthritis, and cancer, and are effective in inhibiting acute and chronic inflammatory responses. The research aims to synthesize various benzoxazines with different substituted aldehydes and perform docking studies with cyclooxygenase-1, an enzyme involved in inflammation, to explore their potential for treating inflammatory diseases **(G. Naveen Kumar et al., 2014).** One fundamental goal of organic synthesis is to develop efficient pathways to produce common organic molecules using readily available reagents. Heterocyclic compounds, particularly oxazines, have been central to many areas of chemistry due to their broad biological and medicinal activities. Aromatic oxazines were first synthesized by Holly and Cope in 1944 using Mannich processes with phenols, formaldehyde, and amines. Oxazine derivatives are prevalent in biological and pharmaceutical applications, showing activities such as antimicrobial, anticancer, antifungal, antitubercular, antimalarial, analgesic, anti-inflammatory, antibacterial, antidiabetic, hypolipidaemic, and antiproliferative. In our research, we synthesized novel 6-chloro-2,4-diphenyl-3,4-dihydro-2H-1,3-benzoxazine derivatives from parachlorophenol, aromatic aldehyde, and methanolic ammonia, and evaluated their antibacterial properties **(Sayaji S et al., 2013)**.

Benzoxazines are key heterocyclic compounds with diverse biological activities, including antirheumatic, neuroprotective, and anticancer effects. Efavirenz, a 3,1-benzoxazine derivative, has been used since 1998 for HIV treatment. Benzoxazine derivatives also show antimicrobial, CNS activity, antitumor, and anti-inflammatory properties. Additionally, 1,3-benzoxazines can isomerize to 3,1-benzoxazines, with some derivatives offering potential treatments for Mycobacterium infections. However, synthesis methods for 1,3-benzoxazine-2,4-diones are limited compared to other benzoxazine types. The synthesis of Schiff bases and their cyclization into 1,3-benzoxazine-2,4-diones is reported. Synthetic methods for 1,3-benzoxazine-2,4-diones are rare, and to our knowledge, this is the first report on their synthesis from Schiff bases and triphosgene **(Ali Abdullah Al-Qahtani et al., 2012)**. In medicine and materials science, 2H-1,3-benzoxazines are notable for their applications as anti-inflammatory agents, photochromic compounds, and photo fading-preventive products. Derivatives of 1,3-benzoxazines I-III are effective potassium channel regulators, potentially

useful for treating hypertension, angina pectoris, asthma, and urinary incontinence. Additionally, 2,3-disubstituted-1,3-benzoxazines exhibit fungicidal activity, while hydrogenated benzo[e][1,3]oxazine and naphtha[2,1-e][1,3]oxazine fragments show antimicrobial and cytotoxic properties **(Osman M. O. Habib et al., 2012)**.

Benzoxazines are key heterocyclic compounds with diverse pharmacological and therapeutic uses. They display a range of biological activities, including antirheumatic, neuroprotective, antioxidant, anticancer, and antihypertensive effects. Efavirenz, a 3,1-benzoxazine derivative approved in 1998 as Sustiva and Stocrin, is used in HAART for HIV and has promising analogues. 1,3-benzoxazine derivatives also show antimicrobial, CNS, antitumor, antiviral, antithrombotic, anti-inflammatory, antidiabetic, and hypolipidaemic activities and can convert to their 3,1-benzoxazine isomer. Recent research highlights 1,3-benzoxazine-2,4-dione as a potential treatment for Mycobacterium infections. However, methods for synthesizing 1,3-benzoxazine-2,4-diones are limited. This study explores the synthesis of Schiff bases and their cyclization into 1,3-benzoxazine-2,4-diones. Triphosgene, a versatile and safer alternative to phosgene, is used in this process due to its reactivity and ease of handling. Schiff bases are valuable in industrial and laboratory synthesis of heterocycles and non-natural amino acids **(Ali Abdullah Al-Qahtani et al., 2012)**. Sainsbury (84CHEC-I (3)995) examined 1,2-oxazines and their benzo derivatives, focusing on 3,6- and 5,6-dihydro-1,2-oxazines as synthetic intermediates. Advancements include asymmetric synthesis of 3,6-dihydro-1,2-oxazines and characterization of 1,2-oxazinium cations. Figure 5 illustrates various 1,2-oxazine ring systems. The unique naphth[1,8-de]-1,2-oxazine is the only fully conjugated, neutral 1-oxazine derivative **(Thomas I. Gilchrist et al., 2011)**.

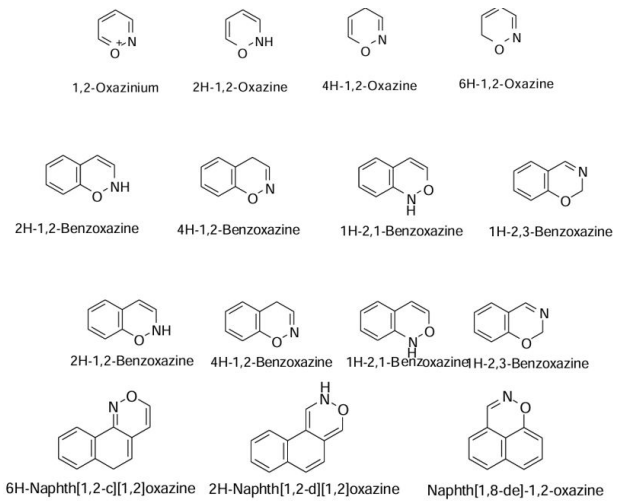

Figure 5 1, 2-oxazine ring system

Figure 6 1 Naphth [l,8-de]-1,2-oxazine ring system

The invention pertains to benzoxazine and benzothiazine derivatives, focusing on their synthesis and pharmaceutical applications. Benzoxazine derivatives, known for their diverse biological activities including antibacterial, antifungal, neuroprotective, antinociceptive, and anti-inflammatory effects, are crucial in pharmacology and natural products. They are free from severe side effects such as nephrotoxicity and reproductive toxicity. Notably, 3-amino-2H-1,4-benzoxazines and 3-amino-2H-1,4-benzothiazines are effective and selective inhibitors of nitric oxide synthases (NOS), which are involved in various disorders due to abnormal nitric oxide levels. Selective NOS inhibitors, including compounds like arginine derivatives and cyclic amidines, are used to treat diseases associated with pathological NO levels. The synthesis of novel benzoxazine derivatives involves methods like the condensation of 3-amino-2-aryl-4-quinazolone with aromatic aldehydes **(Verma Manjusha et al., 2003).** Research also highlights the significance of pyrido(4,3-b)(1,5)benzoxazepines and dibenzoxazepines, which have been studied for their central nervous system effects and antibacterial properties **(Howell et al., 1968; Hayakawa et al., 1982**). New drugs, including pyrido(1,2,3-de)(1,4)benzoxazine, have been synthesized from 8-hydroxy-1,2,3,4-tetrahydroquinolines **(Nagarajan et al., 1974; K. Nagarajan et al., 1992).** Additionally, the synthesis of 1,3-benzoxazine-2,4-diones from Schiff bases and triphosgene introduces a novel approach, with triphosgene offering advantages over phosgene due to its ease of handling and lower toxicity **(Ali Abdullah Al-Qahtani et al., 2012).** Schiff bases are also valuable for creating heterocyclic ring structures and non-natural amino acids.

2. Anti-Inflammatory Agents

The synthesis of benzoxazine and aminomethyl derivatives of phenols has been reported by Japanese researchers, highlighting their various biological activities. Benzoxazine compounds have been evaluated for their antihypertensive, antimicrobial, antifungal, antimycobacterial, analgesic, and anti-inflammatory properties. Aminomethyl derivatives, in addition to displaying antimalarial, analgesic, and anti-inflammatory effects, have also shown antibacterial, anticonvulsant, and anticancer activities. Indonesian researchers have reported that aminomethyl derivatives of eugenol, as well as benzoxazine derivatives, exhibit anticancer properties **(Kumar, G. Naveen et al., 2013)**. Inflammation, a complex physiological response to infections, irritants, and cell damage, involves biochemical cascades within the vascular system, immune system, and affected tissues. Acute inflammation is characterized by the influx of plasma and immune cells, such as neutrophils and macrophages, into the damaged area, while chronic inflammation involves ongoing tissue destruction and repair with a shift in cell types at the site of inflammation **(Ferrero-Milianiet al., 2007).**

Anti-inflammatory agents are essential for treating disorders caused by inflammation, a protective response to harmful stimuli. Medicinal plants and their isolated compounds have long been used to manage conditions like lung and skin inflammations. Essential oils, particularly monoterpenes, are noted for their anti-inflammatory properties. Research typically involves testing these agents in rats using models such as carrageenan and formalin-induced edema, along with in vitro and ex vivo studies. The concept of inflammation, described by Celsius as redness, heat, pain, and swelling, has been studied for centuries.

Traditional remedies, like willow leaf preparations, led to the development of Aspirin, a key anti-inflammatory drug. Today, many NSAIDs are available, and the role of anti-inflammatory foods and natural products, including terpenoids and flavonoids, is increasingly recognized **(Gaofeng Yuan MS et al., 2006)**. During early inflammation, leukotrienes, prostaglandins, and histamine bind to endothelial receptors, causing vasodilation, endothelial cell contraction, and increased permeability. Histamine induces P-selectin and platelet-activating factor (PAF) on venular endothelial cells, facilitating leukocyte adhesion and migration toward chemotactic signals like complement protein C5a and leukotriene B4. Activated macrophages and endothelial cells release cytokines such as tumor necrosis factor (TNF) and interleukin-1 (IL-1), which sustain the inflammatory response by upregulating E-selectin and maintaining P-selectin. E-selectin helps leukocytes cross the basement membrane toward chemokines like interleukin-8 (IL-8) and monocyte chemotactic protein-1 (MCP-1). Inflammation typically involves increased blood flow, metabolism, vasodilation, mediator release, fluid extravasation, and cellular influx. Phospholipase A2 activation during inflammation releases arachidonic acid and mediators such as cytokines, serotonin, histamine, prostaglandins, and leukotrienes, which enhance vascular permeability and facilitate leukocyte migration **(Falcao et al., 2005; Dassoler et al., 2004**).

Natural materials have been used for healing since ancient times, and their role in treating diseases such as cardiovascular disease, cancer, and inflammatory conditions remains significant. Despite advances in combinatorial chemistry, natural products continue to be crucial in drug discovery **(Puni V. et al., 2004)**. The inflammatory response, including in conditions like inflammatory bowel disease, involves various mediators that sustain gut inflammation. Effective treatment strategies often involve targeting multiple stages of the inflammatory cascade with medications such as 5-aminosalicylic acid and glucocorticoids **(Bratts R. et al., 1996).** Anti-inflammatory natural products have long been employed in folk medicine for ailments like fevers, pain, and arthritis, and their use is gaining popularity as the role of inflammation in disease becomes clearer. Terpenoids, flavonoids, and other phytochemicals are highlighted in reports for their anti-inflammatory properties **(Srivastava R. et al., 1985).**

2.1.1 Classification of Anti-inflammatory Drug

Type B adverse drug reactions, as classified by the WHO, are unpredictable and occur in susceptible individuals, including hypersensitivity reactions to NSAIDs. These should be distinguished from Type A reactions, which are predictable based on pharmacological mechanisms and occur in everyone at sufficient doses **(Kowalski ML et al., 2012)**. Hypersensitivity to NSAIDs can manifest in two ways: cross-reactive and specific. In cross-reactive NSAID hypersensitivity, symptoms arise from multiple, chemically unrelated NSAIDs that inhibit the COX-1 enzyme, and the reaction is not immunological. Conversely, some patients may only react to specific NSAIDs or those from the same chemical group, while tolerating other unrelated drugs (Table 1 provide examples of NSAIDs by chemical structure). These specific reactions are considered allergic hypersensitivity reactions and can be either immunologically mediated (IgE or T-cell) or nonimmunologically mediated (cross-reactive). The timing of reactions (immediate or delayed) and the range of reacting

medications can provide clues about the underlying mechanism, but mixed or atypical reactions may also occur in clinical practice **(Caimmi S et al., 2012)**.

Terminology such as intolerance, pseudoallergy, and idiosyncrasy, previously used to describe nonimmunologically mediated hypersensitivity reactions to NSAIDs, should be avoided. NSAIDs, including aspirin, exert their anti-inflammatory effects by inhibiting cyclooxygenases, which produce prostaglandins and thromboxanes. Historically, hypersensitivity reactions to NSAIDs were termed "aspirin-induced reactions" (e.g., aspirin-induced asthma, aspirin-induced urticaria). However, recent data indicate that non-aspirin NSAIDs are responsible for most hypersensitivity events, making the term "aspirin" less relevant. Therefore, the term "NSAIDs" is now preferred in describing these reactions **(Stevenson DD et al., 2001).** According to the EAACI/WAO nomenclature, NSAID hypersensitivity reactions are classified as either allergic (immunologically mediated) or nonallergic, based on the presence or absence of immunological mechanisms (**Rawlins MD et al., 1977).**

Table 1 NSAIDs classified according to the chemical structure

Chemical group	**Drug**
Salicylic acid derivates	Aspirin (acetylsalicylic acid) Sodium salicylate Salsalate Diflunisal Salsalate Sulfasalazine
Para-aminophenol	Acetaminophen (paracetamol)
Propionic acid derivates	Ibuprofen Fenoprofen, Flurbiprofen, Ketoprofen, Naproxen , Oxaprozin
Acetic acid derivatives	Diclofenac, Ketorolac, Indomethacin, Sulindac, Etodolac , Tolmetin, Nabumetone
Enolic acid derivatives	Pyrazolones, Phenylbutazone, Dipirone
	Oxicams: Piroxicam, Meloxicam, Tenoxicam, Lornoxicam
Fenamic acid derivatives (Fenamates)	Mefenamic acid, Meclofenamic acid, Flufenamic acid, Tolfenamic acid
Selective COX-2 inhibitors (Coxibs)	Celecoxib, Rofecoxib (withdrawn from the market)Valdecoxib (withdrawn from the market)

3. Antidiabetic Agents

Diabetes mellitus, marked by hyperglycemia due to impaired insulin function or secretion, leads to complications in the kidneys, eyes, and nerves. Type 2 diabetes (T2D) affects over 90% of diabetes patients and is often managed with a combination of drugs, as single medications rarely control blood glucose long-term. Novel treatments are needed due to the

risk of severe hypoglycemia from existing drugs. Small-molecule allosteric glucokinase (GK) activators, including Piragliatin and AZD6370, show promise in lowering glucose levels and advancing in clinical trials, though they may cause side effects like hypoglycemia. GK activators, particularly 3,5-disubstituted benzamide derivatives, are being developed to improve glucose control by enhancing interactions with GK's allosteric site **(Grewal Ajmer Singh et al., 2019).**

Alpha-glucosidases are enzymes that hydrolyze glycosidic linkages in oligosaccharides and polysaccharides to release glucose and monosaccharides. Predominantly located at the small intestine's brush border, these enzymes facilitate glucose absorption **(Moorthy NS et al., 2012).** Alpha-glucosidase inhibitors (AGIs) like acarbose and miglitol help manage Type 2 diabetes by slowing glucose absorption and release, thus reducing postprandial blood glucose levels. However, they can cause significant gastrointestinal issues **(Wardrop DJ et al., 2010).** Recent research focuses on developing new AGIs from natural glycosides, including stable glucosides and benzoxazine derivatives, to improve treatment and minimize side effects **(Macias FA et al., 2009).**

Biologically inactive glucosides are converted by β-glucosidases into active aglycones such as DIMBOA (2,4-dihydroxy-7-methoxy-2H-1,4-benzoxazin-3(4H)-one) and its desmethoxy derivative DIBOA, which exhibit anti-auxin, anti-inflammatory, and potent antibiotic activities. These aglycones spontaneously degrade into benzoxazolinones like MBOA (6-methoxy-benzoxazolin-2(3H)-one) and BOA, with degradation accelerated by electron-donating or hydroxyl groups on the benzene ring and amide linkage **(Kato-Noguchi H., 2008).** Diabetes mellitus, particularly Type 2 diabetes (T2-DM), is a major global health issue with around 300 million cases worldwide. It is linked to severe complications such as cardiovascular disease, stroke, retinopathy, kidney failure, and may lead to limb amputations. T2-DM treatment includes oral hypoglycemic agents like sulfonylureas, thiazolidinediones, incretin-based therapies, α-glucosidase inhibitors, and injectable insulin. Recent research emphasizes early management of diabetes by delaying glucose absorption and enhancing insulin secretion through α-glucosidase inhibition **(Li JM et al., 2007).**

3.1 Classification of Diabetes Mellitus:

3.1.1 Earlier classifications

The WHO published the first widely accepted classification of diabetes mellitus in 1980, which was updated in 1985. The 1980 classification included medical and predictive risk categories, defining diabetes as Type 1 (IDDM) and Type 2 (NIDDM). In the 1985 update, the terminology Type 1 and Type 2 was replaced, but IDDM and NIDDM were retained, with the addition of a new category, Malnutrition-Related Diabetes Mellitus (MRDM). The classification also covered other types of diabetes, such as Impaired Glucose Tolerance (IGT) and Gestational Diabetes Mellitus (GDM). These classifications were later incorporated into the International Nomenclature of Diseases (IND) in 1991 and the tenth revision of the International Classification of Diseases (ICD-10) in 1992. The 1985 classification remains widely accepted, providing a clinically useful framework despite not always specifying the exact etiology of diabetes, and includes considerations for both dialysis and its staging.

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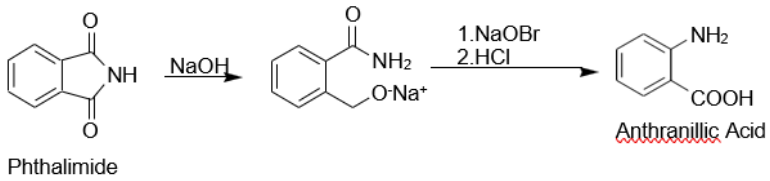
3.1.2 Revised classification

According to Kuzuya and Matsuda, the classification system for diabetes mellitus encompasses all clinical stages and etiological forms, as well as other types of hyperglycemia. This system illustrates that diabetes progresses through various clinical phases throughout its natural history, and individuals can transition between stages in any direction. Even without precise knowledge of the underlying etiology, diabetes can be classified by clinical characteristics. Antidiabetic medications aim to manage blood glucose levels, reducing some of the complications associated with diabetes by keeping blood sugar levels within or near the normal range. These drugs work by increasing insulin levels, enhancing the body's sensitivity to insulin, or decreasing glucose absorption in the intestines.

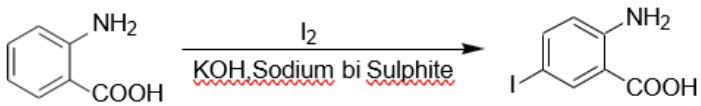
4 General Procedure Preparation of Anthranilic Acid

Dissolve 30 grams of sodium hydroxide in 120 ml of water in a 350 ml flask. Cool to 0°C or below using an ice and salt bath. Add 26.2 grams (0.16 mol) of bromine slowly, stirring until it reacts. Cool again to 0°C. Prepare a solution of 22 grams of sodium hydroxide in 80 ml of water. Add 24 grams of finely powdered phthalimide to the cold sodium hypobromite solution, stirring to form a smooth paste. Remove from the ice bath and shake for 5 minutes until a clear yellow solution forms. Add the sodium hydroxide solution quickly, heat to 80°C for 2 minutes, and filter if necessary. Cool in ice and add concentrated hydrochloric acid slowly until neutral (about 60 ml). Reserve some alkaline solution in case too much acid is added. Precipitate anthranilic acid by adding 20-25 ml of glacial acetic acid gradually. Transfer the mixture to a 1-liter beaker due to foaming. Filter, wash with cold water, recrystallize from hot water with decolorizing carbon, and dry at 100°C. The yield is 14 grams (62%) with a melting point of 145°C.



Phthalimide Anthranillic Acid

4.1 Preparation of Iodinated Anthranilic Acid



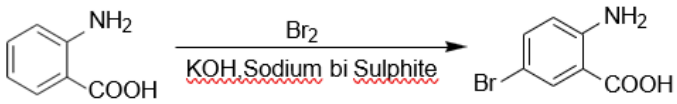
Using a mechanical stirrer, 25 grams (0.184 mol) of recrystallized anthranilic acid (melting point 145°C) was dissolved in a solution of 16.9 grams of Shick KOH in 500 ml of water within a 2-liter beaker. To this well-stirred potassium anthranilate solution, a solution of 46.5 grams (0.184 mol) of iodine in 500 ml of water containing 24.75 grams of Shick KOH was added slowly. After one minute, 100 ml of glacial acetic acid was quickly introduced, and the reaction mixture was immediately diluted with 500 ml of water. A dark precipitate began to

form almost immediately, and stirring was continued for one hour, during which the precipitate turned a light brown color.

After standing undisturbed for two hours, excess iodine was removed by adding 255 ml of 15% sodium bisulfite and stirring thoroughly. The mixture was then allowed to stand briefly before the precipitate was collected, washed repeatedly with water, and air-dried. Crystallization from dilute alcohol yielded 34.84 grams (72.2%) of a pure product with a melting point of 200-205°C. A portion of this product, when mixed with an authentic specimen of 2-amino-5-iodobenzoic acid, showed no depression in the melting point, confirming its identity. Further verification was achieved by comparing melting points with known samples. Repeating the procedure with different amounts of starting material consistently gave good yields.

Melting Point: 200-205°C , Yield: 68% , Rf Value: 0.65

4.2 Preparation of Brominated Anthranilic Acid



Using a mechanical stirrer, 25 grams (0.184 mol) of recrystallized anthranilic acid (melting point 145°C) was dissolved in a solution of 16.9 grams of Shick KOH in 500 ml of water within a 2-liter beaker. To this well-stirred potassium anthranilate solution, a solution of 46.5 grams (0.184 mol) of bromine in 500 ml of water containing 24.75 grams of Shick KOH was added slowly. After one minute, 100 ml of glacial acetic acid was quickly introduced, and the reaction mixture was immediately diluted with 500 ml of water. A dark precipitate began to form almost immediately, and stirring continued for one hour, during which the precipitate turned a light brown color.

After allowing the mixture to stand undisturbed for two hours, excess bromine was removed by adding 255 ml of 15% sodium bisulfite and stirring thoroughly. The mixture was then allowed to stand briefly before the precipitate was collected, washed repeatedly with water, and air-dried. Crystallization from dilute alcohol yielded 34.84 grams (72.2%) of a pure product with a melting point of 100-105°C. When a portion of this product was mixed with an authentic specimen of 2-amino-5-bromobenzoic acid, no depression in the melting point was observed, confirming its identity. Further confirmation was achieved by comparing melting points with known samples. Repeating the procedure with different amounts of starting material consistently yielded good results.

Melting Point: 100-105°C, Yield: 79%, Rf Value: 0.71

5 Benzoxazine Derivatives

5.1 Preparation of 7-bromo-2-(-2-chloronapthalen-6-yl)-4H-benzo[d][oxazine-4-one](K_1)

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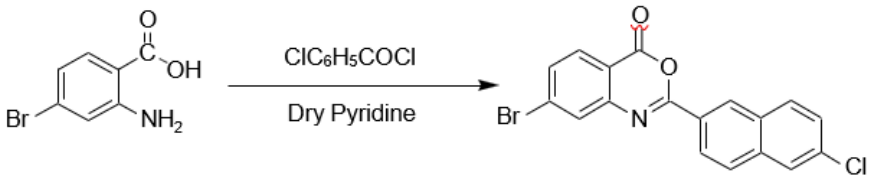
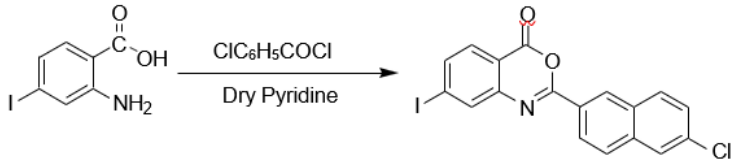


A stirred solution of 2-amino-5-bromobenzoic acid in dry pyridine was treated with para-chlorobenzoyl chloride (0.12 M) and refluxed for two hours. After refluxing, the solvent was removed under vacuum. The resulting liquid was then poured over crushed ice, leading to the formation of 7-bromo-2-(-2-chloronaphthalen-6-yl)-4H-benzo[d][oxazine-4-one]. The product was obtained with a melting point of 150-155°C and a yield of 77%. The Rf value was measured at 0.78.

5.2 Preparation of 2-(-2-chloronapthalen-6-yl)-7-iodo-4H-benzo[d][1,3]oxazine-4-one (K_2)



A stirred solution of 2-amino-5-bromobenzoic acid in dry pyridine was treated with chloro benzoyl chloride (0.12 M) and refluxed for two hours. After refluxing, the solvent was removed under vacuum, and the remaining liquid was poured onto crushed ice. This process yielded 2-(2-chloronaphthalen-6-yl)-7-iodo-4H-benzo[d][1,3]oxazin-4-one. The product had a melting point of 250-255°C and a yield of 62%. Its Rf value was 0.60.

5.3 Preparation of 2-(chloromethyl)-7-iodo-4H-benzo[d][1,3]oxazine-4-one (K_3)

A stirred solution of 2-amino-5-iodobenzoic acid in dry benzene was treated with chloroacetyl chloride (0.12 M) and refluxed for two hours. After refluxing, the solvent was removed under vacuum, and the remaining liquid was poured onto crushed ice to obtain 5-iodo-2-N-chloroanthranilic acid. This compound was then refluxed with acetic anhydride under anhydrous conditions, resulting in the formation of 2-chloromethyl-6-iodo-1,3-benzoxazine-3,4-dihydro-4-one. The product had a melting point of 220-225°C, a yield of 78%, an Rf value of 0.58, and a mass of 321.67 g/mol.

5.4 Preparation of 7-bromo-2-(naphthalene-3-yl)-4H-benzo[d][1,3]oxazine-4-one (K_4)

A stirred solution of 2-amino-5-bromobenzoic acid in dry pyridine was treated with chloro-benzoyl chloride (0.12 M) and refluxed for two hours. After refluxing, the solvent was removed under vacuum, and the remaining liquid was poured onto crushed ice to yield 7-bromo-2-(naphthalene-3-yl)-4H-benzo[d][1,3]oxazin-4-one. The product had a melting point of 50-55°C, a yield of 68%, and an Rf value of 0.76.

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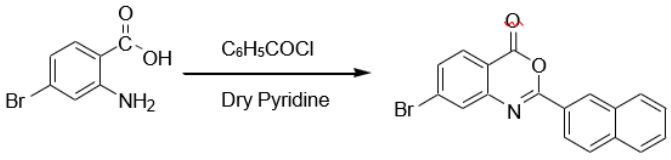
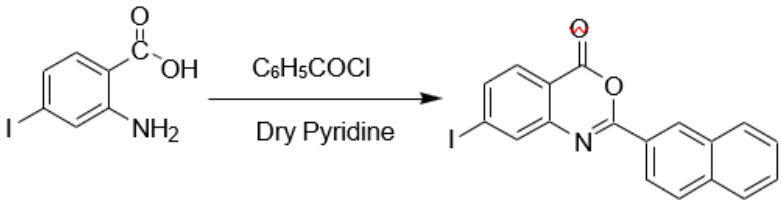
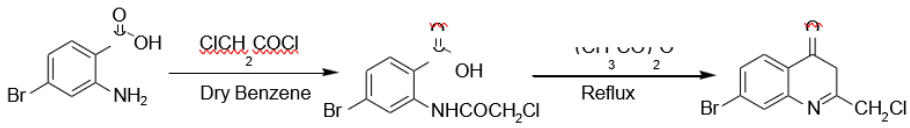


5.5 Preparation of 7-iodo-2-(naphthalen-3-yl)-4H-benzo[d][1,3]oxazine-4-one (K_5)



A stirred solution of 2-amino-5-bromobenzoic acid in dry pyridine was treated with chloro-benzoyl chloride (0.12 M) and refluxed for two hours. After refluxing, the solvent was removed under vacuum, and the remaining liquid was poured onto crushed ice, resulting in the formation of 7-iodo-2-(naphthalene-3-yl)-4H-benzo[d][1,3]oxazin-4-one. The product exhibited a melting point of 260-265°C, a yield of 58%, and an Rf value of 0.56.

5.6 Preparation of 2-(chloromethyl)-7-Bromo-4H-benzo[d][1,3]oxazine-4-one (K_6)



A stirred solution of 2-amino-5-bromobenzoic acid in dry benzene was treated with chloroacetyl chloride (0.12 M) and refluxed for two hours. After refluxing, the solvent was removed under vacuum, and the remaining liquid was poured onto crushed ice to yield 5-bromo-2N-chloro anthranilic acid. This compound was then refluxed with acetic anhydride under anhydrous conditions to produce 2-chloromethyl-6-iodo-1,3-benzoxazine-3,4-dihydro-4-one. The final product had a melting point of 230-235°C and a yield of 85%.with Rf value of 0.78.

Table Identification of Benzoxazine Derivates by Physical Parameter

Compound no.	**X**	**R**	**M.P ( ) ˚c**	**Yield (%)**	**R_f value**
K_1	Br	ClC_6H_5COCl	150-155 C。	85	0.78
K_2	I	ClC_6H_5COCl	250-255 C˚	68.2	0.60
K_3	I	$ClCH_2COCl$	220- 225˚C	58.2	0.65
K_4	Br	C_6H_5COCl	55- 55˚C	72	0.76
K_5	I	C_6H_5COCl	260-265 C。	55	0.56

K_6	Br	$ClCH_2COCl$	230-235 C。	69	0.78

6. Pharmacological Activity

6.1 Anti-Inflammatory Activity

Since benzoxazine derivatives are known for their anti-inflammatory properties, several new derivatives (K1 to K5) were synthesized and evaluated for their anti-inflammatory activity. The results showed that all these compounds exhibited only moderate to poor anti-inflammatory effects. The study identified a relationship between the structural modifications of these benzoxazine derivatives and their anti-inflammatory efficacy. Detailed findings of the activity are provided below.

6.1.1 Animals

Albino rats, weighing 200-300 g and of either sex, were used in the study. They were sourced from the Institute of Foreign Trade and Management animal house. The rats were provided with a standard chow diet and water ad libitum. They were kept in polypropylene cages under standard conditions with a 12-hour light/dark cycle. Prior to the experiment, the rats were fasted for 24 hours but had free access to water. The experimental protocol was approved by the institutional animal ethics committee.

6.1.2 Carrageenan Induced Paw Edema Method

The synthesized compounds were assessed for anti-inflammatory activity using the carrageenan-induced paw edema method. Albino rats (200-300 g) were divided into seven groups, each consisting of six animals. Group-I served as the control, Group-II as the standard, and the remaining four groups were designated as Test Groups K1 through K5. A mark was made on the left hind paw of each rat just beyond the tibio-tarsal junction to ensure consistent paw volume measurement. Initial paw volumes were recorded using the mercury displacement method.

Group-I (control) received an oral dose of 1% carrageenan solution in gum acacia (1 ml/100 g body weight). Group-II (standard) was treated with Diclofenac sodium (10 mg/kg body weight, orally). Test Groups K1, K2, K3, and K4 received synthesized compounds at a dose of 200 mg/kg body weight, orally. Thirty minutes after treatment, rats were injected subcutaneously with 0.1 ml of a 1% carrageenan solution into the plantar side of the left hind paw. Paw volume was measured using a plethysmometer at 1, 2, and 3 hours post-carrageenan injection. The percentage increase in paw volume for animals treated with synthesized compounds and the standard was compared to that of the control group. Percent inhibition was calculated using the standard formula.

% Inhibition = (1-Vt / Vc)*100

Where, Vt and Vc are the mean change in paw volume of treated and control rats respectively.

6.2 Antidiabetic Activity

6.2.1 Animals

Albino rats (200-300 g) of either sex were used in the study, sourced from the animal house at Shri Venkateshwara University. The rats were provided with a standard chow diet and water ad libitum and housed in polypropylene cages under standard conditions (12-hour light/dark cycle). They were fasted for 24 hours before the experiment, although they had free access to drinking water. The experimental protocol received approval from the Institutional Animal Ethics Committee (IAEC).

6.2.2 Experimental Induction of Diabetes

The animals were fasted for 24 hours before diabetes was induced using a single intraperitoneal injection of freshly prepared alloxan monohydrate solution (130 mg/kg) in ice-cold 0.9% saline. To counteract drug-induced hypoglycemia, the rats were immediately given 2 ml of 5% dextrose solution via an orogastric tube. After 72 hours, rats with blood glucose levels exceeding 200 mg/dL were classified as diabetic. Blood glucose levels were measured at 0, 30, 60, 90, and 120 minutes using a SUGAR SCAN Glucometer (Thyrocare), and the rats with the required glucose levels were selected for the experiment **(Kankam Sunitha et al., 2014).**

Group I: Rats served as normal- control and receives 5% gum acacia

Group II: Diabetic rats received 5% gum acacia served a diabetic control

Group III: Diabetic rats served as standard received glibenclamide (10mg/kg b.wt).

Group IV - Group VII: Rats were administered with (test compounds, 10 mg/kg b.wt) orally.

7. CONCLUSION

This review has provided a comprehensive overview of the synthesis, characterization, and pharmacological evaluation of halogenated benzoxazine derivatives. The synthesis of these compounds involves a variety of methods and reagents, including chloroacetyl chloride and various anhydrides, to yield benzoxazine derivatives with potential therapeutic applications. Characterization techniques such as melting point determination, Rf value assessment, and structural analysis have been crucial in confirming the identity and purity of these derivatives.

Pharmacological evaluations, including anti-inflammatory and anti-diabetic activities, reveal that while halogenated benzoxazine derivatives exhibit promising biological activities, the effectiveness varies significantly among different compounds. The reviewed studies highlight that certain derivatives, such as those with iodine or bromine substitutions, show notable anti-inflammatory effects, although their overall efficacy remains moderate. Additionally, the induction of diabetes in experimental models and subsequent treatment with these derivatives provides insight into their potential as therapeutic agents for managing diabetes.

Overall, the reviewed literature underscores the potential of halogenated benzoxazine derivatives as valuable candidates for drug development. However, the variations in pharmacological responses suggest that further research is necessary to optimize their

therapeutic profiles. Future studies should focus on improving the efficacy of these compounds, understanding their mechanisms of action, and evaluating their safety profiles to enhance their potential for clinical use.

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