Design and Synthesis of Novel Quinoxaline Analogues as Potential Anti-Inflammatory Agents

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***Abstract*—Quinoxaline is a nitrogen-containing fused heteroaromatic scaffold that has attracted considerable attention in medicinal chemistry because it can be chemically modified at multiple positions and can interact with diverse inflammatory targets. Recent studies indicate that quinoxaline derivatives may exert anti-inflammatory activity through inhibition of cyclooxygenase enzymes, inducible nitric oxide synthase, nitric oxide release, pro-inflammatory cytokines such as TNF-α and IL-6, and intracellular pathways including MAPK, NF-κB, PI3K/Akt, and NRF2/Keap1 signaling. A 2025 review specifically highlights quinoxaline analogues as multi-mechanistic anti-inflammatory pharmacophores and discusses their structure–activity relationships and synthetic strategies. This review summarizes the rationale for designing novel quinoxaline analogues, common synthetic routes, reported biological targets, structure–activity trends, and future directions for developing safer and more potent anti-inflammatory agents.**

***Index Terms*—Quinoxaline, anti-inflammatory agents, COX-2, iNOS, TNF-α, IL-6, molecular docking, SAR, heterocyclic synthesis.**

I. INTRODUCTION

Inflammation is a protective biological response against infection, injury, or chemical irritation. However, chronic or uncontrolled inflammation contributes to diseases such as rheumatoid arthritis, inflammatory bowel disease, psoriasis, neuroinflammation, diabetes-associated inflammation, and cancer-related inflammation. Conventional non-steroidal anti-inflammatory drugs are effective but may cause gastrointestinal, renal, and cardiovascular adverse effects, especially with long-term use. Therefore, the discovery of new anti-inflammatory scaffolds with improved selectivity and safety remains an important objective in medicinal chemistry.[1]

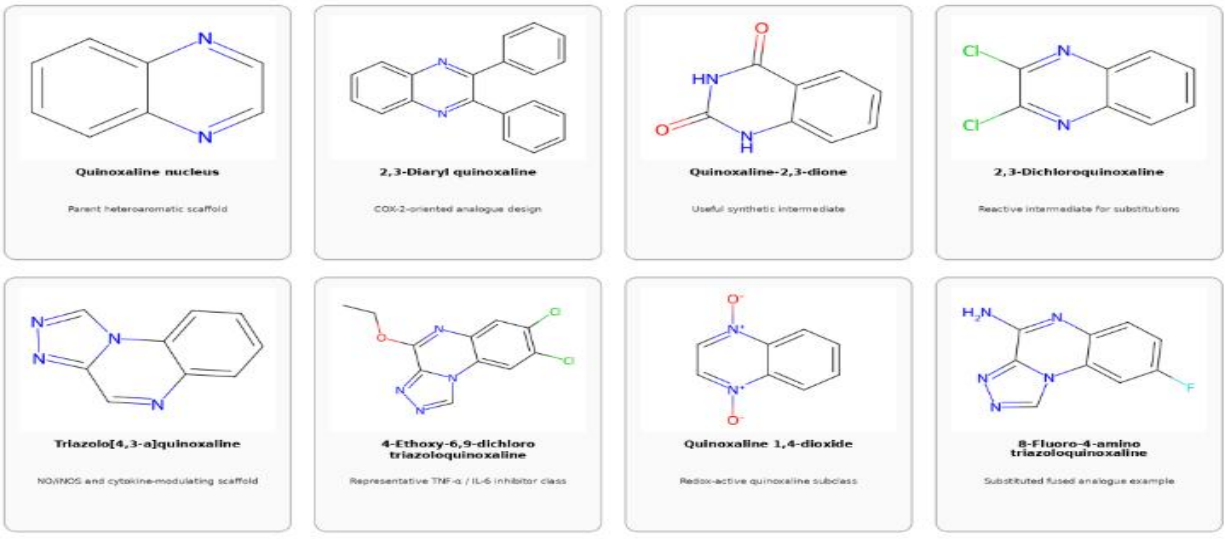


Fig: Quinoxaline Derivatives

Quinoxaline, commonly referred to as benzopyrazine, is an important nitrogen-containing fused heterocyclic compound. Structurally, it consists of a benzene ring fused with a pyrazine ring, resulting in a rigid bicyclic aromatic system. The presence of two nitrogen atoms in the pyrazine portion of the molecule gives quinoxaline distinctive chemical and biological properties. These nitrogen atoms increase the electron-deficient nature of the ring and allow the molecule to participate in several types of interactions with biological targets, including hydrogen bonding, dipole–dipole interactions, metal coordination, and π–π stacking interactions. These interactions are highly valuable in drug design because they help the molecule bind effectively to enzymes, receptors, and signaling proteins. The quinoxaline nucleus is considered a privileged scaffold in medicinal chemistry due to its structural versatility and broad pharmacological profile. Different substituents can be introduced at various positions of the quinoxaline ring, especially at the 2-, 3-, 6-, and 7-positions. These substitutions can significantly influence biological activity, lipophilicity, solubility, metabolic stability, and target selectivity. For example, electron-withdrawing groups, aryl groups, heterocyclic moieties, amide linkages, sulfonamide groups, and fused triazole systems can be incorporated to improve interaction with inflammatory targets.[2]

Quinoxaline derivatives have been extensively explored for a wide range of biological activities. Reported pharmacological properties include antibacterial, antifungal, antiviral, antitubercular, anticancer, antioxidant, analgesic, and anti-inflammatory activities. This wide spectrum of activity indicates that the quinoxaline scaffold can interact with multiple biological pathways. In the context of inflammation, quinoxaline analogues are especially interesting because they may affect several inflammatory mediators, including cyclooxygenase enzymes, inducible nitric oxide synthase, nitric oxide production, pro-inflammatory cytokines, and intracellular signaling pathways such as NF-κB, MAPK, and NRF2. A recent review emphasized the importance of quinoxaline as a valuable chemical moiety because of its diverse physicochemical and biological applications. Its planar aromatic structure, ease of synthesis, and ability to undergo chemical modification make it a useful platform for rational drug design. Therefore, quinoxaline-based compounds provide an attractive foundation for the development of novel anti-inflammatory agents with improved potency, selectivity, and pharmacokinetic properties.[3]

II. RATIONALE FOR DESIGNING QUINOXALINE-BASED ANTI-INFLAMMATORY AGENTS

The prepared reaction and structure images represent the general design and synthesis strategy for novel quinoxaline analogues as potential anti-inflammatory agents. The first reaction scheme shows the basic formation of the quinoxaline nucleus. In this route, substituted *o*-phenylenediamine reacts with a 1,2-dicarbonyl compound such as glyoxal, benzil, or substituted diketones. This condensation reaction forms the fused benzopyrazine ring system, which is the core structure of quinoxaline. By changing the substituents on the diamine or dicarbonyl compound, different quinoxaline analogues can be synthesized with modified biological properties. The second reaction scheme represents further structural modification of the quinoxaline scaffold. Functional groups such as chloro, hydrazino, amide, alkoxy, or aryl groups can be introduced at suitable positions. Hydrazinoquinoxaline intermediates may undergo cyclization to produce fused triazoloquinoxaline derivatives. These fused analogues are important because triazole rings can improve hydrogen bonding, planarity, and interaction with inflammatory targets such as COX-2, iNOS, and cytokine-regulating pathways.

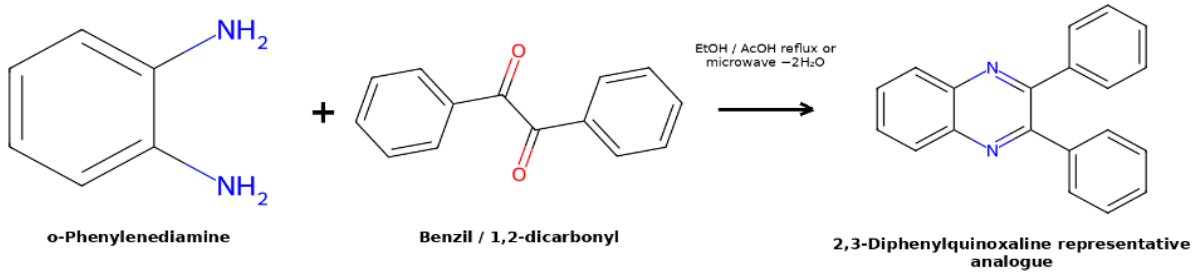
The structure panel highlights important quinoxaline-based pharmacophores, including the parent quinoxaline nucleus, substituted quinoxaline derivatives, quinoxaline-2,3-dione, quinoxaline 1,4-dioxide, and triazolo[4,3-a]quinoxaline analogues. These structures demonstrate how medicinal chemists can modify the quinoxaline ring to improve potency, selectivity, solubility, and safety. The images support the review article by visually explaining how novel quinoxaline analogues are designed and synthesized. The quinoxaline nucleus acts as a versatile scaffold, while different substituents control anti-inflammatory activity. Electron-withdrawing groups, heterocyclic rings, amide groups, and fused triazole systems may enhance activity by improving binding with enzymes

and signaling proteins involved in inflammation. Therefore, these reaction and structure images provide a clear chemical foundation for understanding quinoxaline-based anti-inflammatory drug design.[5]

III. GENERAL SYNTHETIC APPROACHES

3.1 Formation of the quinoxaline core

The most common route to quinoxaline derivatives involves the condensation of substituted *o*-phenylenediamines with 1,2-dicarbonyl compounds such as glyoxal, benzil, phenacyl derivatives, or α-ketoesters. This reaction is simple, versatile, and suitable for generating 2,3-disubstituted quinoxalines. Reaction conditions may include ethanol, acetic acid, reflux, microwave irradiation, or green catalysts depending on the desired substitution pattern.
A general synthetic scheme may be represented as:



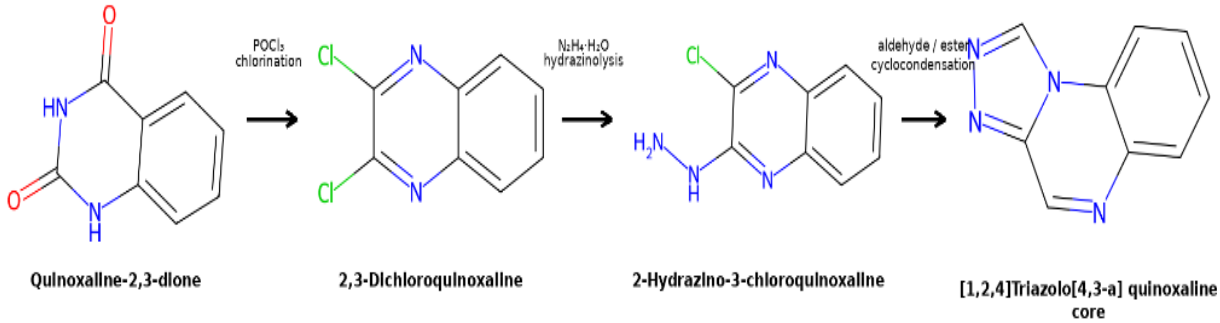
This strategy allows the introduction of electron-donating or electron-withdrawing groups on the benzene ring and aryl/heteroaryl groups at the 2- and 3-positions.

3.2 Functionalization of quinoxaline intermediates

Quinoxaline-2,3-dione or 2,3-dichloroquinoxaline intermediates are useful for preparing further analogues. Chlorinated intermediates can undergo nucleophilic substitution with hydrazine, amines, thiols, or alcohols. Hydrazinoquinoxaline intermediates can then be cyclized to fused triazoloquinoxalines, which have shown promising anti-inflammatory effects. For example, a 2022 ChemistrySelect study synthesized twelve 1,2,4-triazolo[4,3-a]quinoxaline derivatives by cyclocondensation between iminoester derivatives and 1-(quinoxalin-2-yl)hydrazine. The compounds were characterized by NMR and mass analysis and evaluated in LPS-induced RAW264.7 macrophages. [6]

3.3 Quinoxaline 1,4-dioxide chemistry

Quinoxaline 1,4-dioxides are another important subclass. A 2023 review reports that quinoxaline 1,4-dioxides possess diverse biological activities and are commonly prepared by methods such as oxidation of quinoxalines or the Beirut reaction using benzofuroxans. Although this subclass is more widely discussed for antimicrobial, antitumor, and antiparasitic activity, its chemistry is useful for medicinal-chemistry expansion because N-oxide groups can strongly influence polarity, redox behavior, and biological activity.[7]



IV. ANTI-INFLAMMATORY MECHANISMS OF QUINOXALINE ANALOGUES

4.1 COX-2 inhibition

Cyclooxygenase-2 (COX-2) is an inducible isoform of the cyclooxygenase enzyme family that plays a central role in the inflammatory process. Under normal physiological conditions, COX-2 expression is low in most tissues; however, it is rapidly upregulated in response to inflammatory stimuli such as cytokines, bacterial endotoxins, tissue injury, and oxidative stress. Once activated, COX-2 converts arachidonic acid into prostaglandins, particularly prostaglandin E2 (PGE2), which contributes to pain, fever, swelling, redness, and vascular permeability. Therefore, inhibition of COX-2 is considered an effective approach for controlling inflammation.[8]

Traditional non-steroidal anti-inflammatory drugs inhibit both COX-1 and COX-2. Although this produces anti-inflammatory and analgesic effects, inhibition of COX-1 may disturb gastric mucosal protection, platelet function, and renal homeostasis, leading to adverse effects such as gastric irritation, ulceration, and bleeding. Selective COX-2 inhibitors are designed to suppress inflammation-associated prostaglandin production while preserving COX-1-mediated protective functions. This selectivity makes COX-2 an attractive molecular target for safer anti-inflammatory drug development. Quinoxaline derivatives have emerged as promising candidates in this field because the quinoxaline nucleus is a versatile heterocyclic scaffold capable of forming strong interactions within enzyme active sites. Ahmed, Mohamed, and Omran reported novel quinoxaline derivatives with dual EGFR and COX-2 inhibitory activity. Their study combined biological evaluation, molecular docking, and physicochemical analysis to identify compounds with favorable anti-inflammatory potential. Among the synthesized molecules, compounds 4a, 5, 11, and 13 showed promising activity and were predicted to possess acceptable oral absorption properties. Docking studies suggested that these quinoxaline analogues could fit effectively into the COX-2 binding pocket through hydrophobic interactions, hydrogen bonding, and aromatic stacking. These findings support the view that quinoxaline can serve as a privileged scaffold for designing selective COX-2-directed anti-inflammatory agents with improved potency, selectivity, oral bioavailability, and therapeutic safety.[9]

4.2 iNOS and nitric oxide inhibition

Nitric oxide is an important inflammatory mediator produced by inducible nitric oxide synthase. Excessive NO production contributes to tissue damage and chronic inflammatory pathology. Triazoloquinoxaline derivatives have shown activity in NO/nitrite-based anti-inflammatory models.[10]

In the 2022 ChemistrySelect study, compound 3f showed the most notable nitrite-reducing effect, with 65.12 ± 1.62% inhibition, close to indomethacin under the reported experimental conditions. The study suggested that the activity was probably associated with iNOS inhibition based on molecular docking. Another study on 5-alkyl-4-oxo-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinoxaline-1-carboxamide derivatives found that compound 6p reduced NO, TNF-α, and IL-6 levels and involved inhibition of COX-2 and iNOS with downregulation of MAPK signaling.[11]

4.3 Cytokine inhibition: TNF-α and IL-6

TNF-α and IL-6 are important pro-inflammatory cytokines that play a major role in the development and progression of inflammation. Tumor necrosis factor-alpha (TNF-α) is mainly released by activated macrophages, monocytes, and immune cells during infection, injury, or tissue stress. It promotes inflammation by increasing vascular permeability, recruiting leukocytes to the site of injury, and stimulating the production of other inflammatory mediators. Interleukin-6 (IL-6) is another key cytokine involved in fever, acute-phase protein synthesis, immune-cell activation, and chronic inflammatory responses. Excessive production of TNF-α and IL-6 is associated with inflammatory disorders such as rheumatoid arthritis, inflammatory bowel disease, psoriasis, asthma, and autoimmune diseases.[12]

Quinoxaline derivatives, especially fused triazoloquinoxaline analogues, have shown promising effects in reducing cytokine-mediated inflammation. A study on 4-alkoxy-6,9-dichloro[1,2,4]triazolo[4,3-a]quinoxalines demonstrated that these compounds significantly inhibited the production of TNF-α and IL-6 in inflammatory cell models. This suggests that such molecules do not merely act on a single

inflammatory enzyme but may regulate deeper intracellular signaling mechanisms responsible for cytokine release.[13]

The anti-inflammatory activity of these quinoxaline derivatives was linked to modulation of important signaling pathways. The compounds inhibited ERK1/2 and JNK/c-Jun cascades, which are part of the mitogen-activated protein kinase pathway. These pathways are normally activated during inflammation and lead to the expression of inflammatory genes. Reduction of c-Fos expression further supports suppression of transcription factors involved in cytokine production.[14]

Additionally, activation of the PI3K/Akt pathway contributed to the anti-inflammatory response. This pathway can promote cell survival and regulate immune balance, helping to reduce excessive inflammatory signaling. Therefore, 4-alkoxy-6,9-dichloro triazoloquinoxaline derivatives may act as multi-target anti-inflammatory agents by lowering TNF-α and IL-6 levels and controlling intracellular pathways involved in inflammatory mediator release.[15]

4.4 MAPK, PI3K/Akt, and transcription-factor modulation

MAPK signaling pathways are important intracellular communication systems that regulate inflammatory gene expression. The major MAPK pathways include extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), and p38 MAPK. These pathways are activated when cells are exposed to inflammatory stimuli such as bacterial lipopolysaccharide, oxidative stress, cytokines, or tissue injury. Once activated, MAPK pathways transmit signals from the cell surface to the nucleus, where they regulate transcription factors responsible for the production of inflammatory mediators.[16]

ERK1/2 and JNK are especially important in controlling cytokine production. Activation of ERK1/2 can promote the expression of genes involved in cell activation, inflammation, and immune-cell response. Similarly, the JNK pathway activates c-Jun, a component of the AP-1 transcription factor complex. AP-1 regulates several inflammatory genes, including those responsible for cytokines such as TNF-α and IL-6. Therefore, excessive activation of ERK and JNK pathways can increase inflammatory mediator release and contribute to chronic inflammation.[17]

Quinoxaline derivatives have been reported to modify these signaling cascades, which may explain their cytokine-lowering effects. In particular, 4-alkoxy-6,9-dichloro triazoloquinoxaline derivatives were shown to influence ERK1/2, JNK/c-Jun, c-Fos, and PI3K/Akt pathways. Suppression of ERK1/2 and JNK/c-Jun signaling reduces the activation of transcription factors that promote inflammatory gene expression. Reduction of c-Fos expression further indicates inhibition of AP-1-mediated inflammatory responses.[18]

Interestingly, activation of the PI3K/Akt pathway may also contribute to the anti-inflammatory effect. PI3K/Akt signaling can regulate immune balance, support cell survival, and reduce excessive inflammatory activation under certain conditions. Thus, quinoxaline derivatives may act through a multi-target mechanism rather than only inhibiting a single enzyme. These findings are valuable for rational drug design. By understanding how quinoxaline analogues affect MAPK and PI3K/Akt signaling, researchers can design more potent anti-inflammatory compounds with improved selectivity, reduced cytokine production, and better therapeutic potential.[19]

4.5 NRF2/Keap1 activation

NRF2 activation is considered an important anti-inflammatory and antioxidant strategy because oxidative stress and inflammation are closely interconnected. Nuclear factor erythroid 2–related factor 2 (NRF2) is a transcription factor that regulates the expression of several antioxidant and cytoprotective genes. Under normal conditions, NRF2 remains bound to Kelch-like ECH-associated protein 1 (Keap1) in the cytoplasm, where it is targeted for degradation. During oxidative or inflammatory stress, NRF2 is released from Keap1 and moves into the nucleus. There, it activates antioxidant response element-dependent genes such as heme oxygenase-1, glutathione-related enzymes, and other detoxifying proteins. These enzymes help reduce reactive oxygen species and suppress inflammatory damage.[20]

Inflammatory stimulation, such as exposure to lipopolysaccharide in macrophages, increases the production of inflammatory mediators including

nitric oxide, prostaglandin E2, interleukin-1β, interleukin-6, and TNF-α. Excessive formation of these mediators contributes to tissue injury, chronic inflammation, and immune imbalance. Therefore, compounds that activate NRF2 can provide dual protection by reducing oxidative stress and controlling inflammatory mediator production.[21]

Kandasamy and co-workers reported a quinoxaline-based compound known as NQC as an NRF2 activator. In LPS-stimulated RAW264.7 macrophage cells, NQC significantly reduced the levels of nitric oxide, PGE2, IL-1β, IL-6, and TNF-α. These findings indicate that the compound can suppress multiple inflammatory markers rather than acting on only one pathway. Importantly, NQC also showed dose-dependent inhibition of the NRF2–Keap1 interaction, suggesting that it promotes NRF2 activation by interfering with its negative regulator. This observation broadens the therapeutic importance of quinoxaline analogues. Instead of being designed only as COX-2, iNOS, or cytokine inhibitors, quinoxaline derivatives may also be developed as antioxidant-response modulators. Such compounds could be useful in inflammatory diseases where oxidative stress plays a major pathological role.[22]

V. STRUCTURE–ACTIVITY RELATIONSHIP CONSIDERATIONS

The available studies suggest several useful SAR trends:

Electron-withdrawing groups such as chloro, fluoro, trifluoromethyl, or trifluoromethoxy substituents may improve binding to hydrophobic inflammatory targets and alter metabolic stability. Dichloro-substituted triazoloquinoxalines have been associated with inhibition of TNF-α and IL-6 production. Fused triazole rings can improve planarity, hydrogen-bonding capacity, and binding orientation. Triazolo[4,3-a]quinoxaline derivatives have shown promising nitrite-reducing and cytokine-modulating effects. Amide, carboxamide, hydrazone, and heteroaryl substituents may improve target interaction through hydrogen bonding with amino acid residues in COX-2, iNOS, or NRF2/Keap1 binding sites. In the reported triazoloquinoxaline carboxamide series, compound 6p was especially active against inflammatory mediators.

Balanced lipophilicity is important. Highly lipophilic derivatives may bind strongly to hydrophobic pockets but can suffer from poor solubility, while highly polar derivatives may show reduced membrane permeability. Therefore, future analogues should be optimized for potency, solubility, metabolic stability, and cytotoxicity together.[23]

VI. BIOLOGICAL EVALUATION METHODS

Initial screening can be performed using in vitro anti-inflammatory assays such as albumin denaturation inhibition and membrane stabilization. More mechanistic assays should include LPS-induced RAW264.7 or HL-60 macrophage models, where NO, PGE2, TNF-α, IL-1β, and IL-6 levels can be quantified. The 2022 triazoloquinoxaline study used LPS-induced RAW264.7 macrophages and measured nitrite levels after cytotoxicity evaluation by MTT assay.

Molecular docking can help predict binding to COX-2, iNOS, p38 MAPK, or NRF2/Keap1 interfaces. However, docking should not be considered proof of activity. It should be supported by enzyme inhibition, cellular assays, cytotoxicity testing, and preferably in vivo models such as carrageenan-induced paw edema.[24]

VII. CHALLENGES AND FUTURE PERSPECTIVES

Despite their promising anti-inflammatory activity, quinoxaline analogues still face several important development challenges before they can be considered suitable drug candidates. One of the major limitations is poor aqueous solubility. Many quinoxaline derivatives contain fused aromatic rings and hydrophobic substituents, which may improve interaction with biological targets but can reduce water solubility. Low solubility affects dissolution, absorption, bioavailability, and formulation development. Therefore, future molecules should be designed with a proper balance between lipophilicity and polarity. Introduction of suitable polar groups such as amides, sulfonamides, hydroxyl groups, morpholine, piperazine, or carboxamide moieties may help improve solubility without completely reducing target affinity.[25]

Another major concern is possible cytotoxicity. Since quinoxaline is a biologically active heterocyclic scaffold, some derivatives may interact with unintended cellular targets. This can lead to unwanted toxicity in normal cells. Quinoxaline 1,4-dioxide derivatives are pharmacologically interesting because of their strong biological activity; however, some compounds from this class have been associated with drawbacks such as mutagenicity, photoallergic reactions, low solubility, and resistance-related problems in certain biological systems. These issues indicate that biological potency alone is not enough. A compound must also show an acceptable safety profile, low genotoxic potential, and selective action against inflammatory pathways.

Metabolic instability is another challenge in the development of quinoxaline analogues. Some compounds may be rapidly metabolized in the liver, leading to short duration of action or formation of toxic metabolites. Substituents such as halogens, trifluoromethyl groups, or metabolically stable heterocycles may improve stability, but excessive lipophilicity can increase toxicity or poor clearance. Hence, metabolic studies should be performed early during lead optimization. In vitro liver microsomal stability, plasma stability, CYP enzyme inhibition, and metabolite identification are useful tools for selecting better candidates.

Selectivity is also a critical issue. Inflammation involves many enzymes, cytokines, and signaling pathways. Although multi-target activity can be beneficial, non-selective inhibition of essential physiological pathways may produce adverse effects. For example, selective COX-2 inhibition is preferred over non-selective COX inhibition to minimize gastric toxicity. Similarly, inhibition of iNOS should not strongly interfere with normal nitric oxide signaling required for vascular and immune functions. Therefore, future quinoxaline derivatives should be designed to target inflammatory pathways more selectively while sparing protective biological functions.[26]

Future research should focus on designing multi-target but safer quinoxaline-based anti-inflammatory agents. Promising approaches include COX-2/iNOS dual inhibitors, cytokine-suppressing triazoloquinoxalines, NRF2-activating quinoxalines, and hybrid molecules containing quinoxaline linked with sulfonamide, triazole, oxadiazole, pyrazole, or carboxamide pharmacophores. These hybrid structures may improve binding interactions, potency, and pharmacokinetic properties.

Modern computational and experimental methods should be incorporated at the early stage of drug design. ADME prediction can help estimate absorption, distribution, metabolism, and excretion properties. Toxicity prediction can identify potentially mutagenic, hepatotoxic, or cardiotoxic compounds before synthesis. Molecular docking and molecular dynamics simulations can provide insight into ligand stability within target binding sites. Finally, promising compounds should be validated through enzyme assays, cell-based anti-inflammatory models, cytotoxicity studies, and in vivo inflammation models. Through this integrated approach, quinoxaline analogues may be developed into safer, more selective, and therapeutically useful anti-inflammatory agents.[27]

VIII. CONCLUSION

Quinoxaline is a versatile heterocyclic scaffold for developing novel anti-inflammatory agents. Its synthetic accessibility, broad substitution possibilities, and ability to interact with multiple inflammatory pathways make it a valuable platform for medicinal chemistry. Recent studies show that quinoxaline derivatives can inhibit COX-2, iNOS, NO production, TNF-α, IL-6, MAPK signaling, and NRF2/Keap1 interaction. Among the most promising subclasses are triazolo[4,3-a]quinoxalines, carboxamide-substituted quinoxalines, dichloro-alkoxy quinoxalines, and NRF2-activating quinoxaline analogues. Future development should emphasize rational SAR optimization, target selectivity, low cytotoxicity, good pharmacokinetics, and validated in vivo anti-inflammatory efficacy.

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