Overview of the Chemistry and Diverse Biological Functions of the Active Quinoxaline Nucleus

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Abstract: Nitrogen-bearing hetero cycles are incredible significance with a recognized track record of therapeutic advances with - inside the latest drug discovery [1] [2]. Quinoxaline nucleus - based derivatives have attracted researcher’s attention due to privileged and extensive applications in medicine, pharmaceuticals and pharmacological fields. Quinoxaline moiety is part of numerous antibiotics together with echinomycine, levomycine, actinoleutine, glecaprevir (Mavyret), voxilaprevir (Vosevi), Balversa (LO1EX16) (erdaftinib), cabadox, XK469R (NSC698215), and becampanel (AMP397). Recognizing the importance of those bioactive quinoxaline derivatives, researchers have committed their efforts to growing numerous artificial techniques for their production [3] [4].

Keywords: drug discovery, quinoxaline derivatives, therapeutic applications, antibiotics, artificial synthesis

1. Introduction

Quinoxalines also called benzoyprazines are well known and important nitrogen containing heterocyclic compounds bearing a ring complex made up of a benzene ring and a pyrazine ring [2]. Quinoxaline represents an important six-membered ring template of the benzodiazine family. These are pharmacology important compounds, displaying a wide array of interesting biological activities such as anti-bacterial, anti-tubercular, anti-malarial, anti-viral, anti-HIV, anti-inflammatory, anti-fungal, antiamoebic, anticancer, antiproliferative, antitumor, antihypertensive, anti-convulsant, kinase inhibitor, antiepileptic, anti-HCV, analgesic, anthelmintic, etc. Moreover, quinoxaline also used for crop protection in agro - industries, as a major component of insecticides, herbicides, and fungicides. Besides their medicinal and crop protection applications, These compounds have been widely used as dyes for solar cell applications, fluorescent materials, organic semiconductors and corrosion inhibitors for metals [1] [3].

The fused benzene ring in quinoxaline confers the compound extra balance through resonance. Quinoxaline is a white crystalline strong at room temperature, having a low molecular weight (130.15). The quinoxaline has a low boiling point. In industries, scale-up purification turned into executed with the aid of using distillation technique. Its present acidic nature (pKa of 0.60) in water at 20 °C and its dipole moment is 0.51 D. The photon electron spectroscopy instrument used to calculate their first and second ionization potentials which are 8.99 and 10.72 eV [1] [4].

Chemistry
Quinoxaline is naphthyridine in which the nitrogen’s are at positions 1 and 4. It is a mancude organic heterobicyclic parent, an ortho - fused heteroarene and a naphthyridine [5].

2. Synthesis

The methods of preparation of quinoxalines can be divided into two pathways [6 - 12]:

The traditional chemistry pathway, which is based on the condensation between o - phenylenediamines and dicarbonyl compounds in the presence of special conditions such as organic solvents, high temperatures, long times, or strong catalysts. Additionally, the response yield can be low and aspect merchandise can be produced. These forms of reactions have terrible consequences at the environment. 2. The green chemistry pathway, which is a cost - effective pathway through using green chemistry methodologies to produce quinoxalines. This pathway is characterized with the aid of an environmentally pleasant recyclable catalyst, a low cost, decrease intake of energy, one - pot synthesis, no aspect products, brief time, and excessive yield. It may be carried out in an aqueous medium at room temperature or with the aid of using the microwave reactor.

2.1 Traditional Chemistry Pathway

2.1.1 Condensation of o - Phenylenediamine and 1, 2 - Dicarbonyl Derivatives

Korner and Hinsberg in 1884 synthesized the first derivative of quinoxaline through a condensation of o - phenylenediamine with a 1, 2 - dicarbonyl derivative.

Synthesis of quinoxaline through the condensation technique: diamine (1 mmol), dicarbonyl (1 mmol), glycerol (five mL), water (2 mL), 90 °C, 4–6 min, yield (85–91%) [6].

2.1.2 Metal - Catalyzed Cyclization of Imines and Azides

Ketimines and azides had been used to create quinoxalines. Synthesis of quinoxalines from imines and azides: imine (1 mmol), sodium azide (3 mmol), (diacetoxyiodo) benzene (3 mmol), CuO (1 mmol), ethyl acetate, Rt, 16 h, yield (35–80%) [7, 8, 9].

2.1.3 Cyclocondensation of o - Phenylenediamine and Aromatic Alkynes

Quinoxalines have been synthesized through cyclocondensation of phenylene diamine and fragrant alkynes withinside the presence of Cu (OAc) 2 as a catalyst.

Synthesis of quinoxalines from aromatic alkynes and amines: o - phenylenediamine (0.25 mmol) in toluene, phenyl acetylene (1 mmol), Cs2CO3 (0.75 mmol), Cu (OAc) 2, H2O (10 mol % from the o - phenylenediamine), DMPA (0.75 mmol), 70 °C, 8 h, yield (86%). [10]
2.2 Green Chemistry Pathway

2.2.1 Clay - 10 Based Method
This is a green chemistry pathway for the synthesis of quinoxalines. This reaction is performed by mixing the two reagents with bentonite K - 10 at room temperature, and then it is flowed on a celite pad and ethanol. The combination is focused to 5 mL and diluted with 10 mL of water. The reaction is allowed to stand for 1 h. The clay may be recovered after formation of the product as natural crystals and may be used five instances again. Synthesis of quinoxalines with the aid of using one - pot cascade method: o - phenylene - diamine (1 mmol), benzil (1 mmol), bentonite K - 10 (three gm), ethanol 50 mL, RT, 20 min, yield (95%) [11].

2.2.2 Zinc Triflate Catalyst
Zinc triflate is a zinc salt of trifluoromethanesulfonic acid. The reactions carried out through the use of zinc triflate catalyst may be finished without solvent (solvent - free) the use of a microwave - assisted reactor or through the use of acetonitrile solvent. Quinoxaline derivatives have been organized via way of means of the response of o - phenylenediamine and α - diketones the usage of a zinc triflate catalyst at room temperature in acetonitrile. This response produced a yield as much as 90%.

Synthesis of quinoxaline by using zinc triflate catalyst: diamine (1.1 mmol), dicarboxyl (1 mmol), Zn (OTf) 4 (0.2 mmol), CH3CN (5 mL), RT, yield (85–91%) [12].

Diverse Biological Activity of Quinoxaline
Quinazolines and quinazolinones are classes of fused heterocycles that are of considerable interest because of the diverse range of their biological properties. Many substituted quinazoline and quinazolinone derivatives possess a wide range of bioactivities such as antimalarial, anticancer, antimicrobial, antifungal, antiviral, antiprotozoal, anti-inflammatory, diuretic, muscle relaxant, antitubercular, antidepressant, anticonvulsant, acaricidal, weedicide, and many other biological activities. Quinazoline and quinazolinone compounds are also used in preparation of various functional materials for synthetic chemistry and also present in various drugs molecules [13].
This figure compiles the most recent findings on the synthesis and biological properties of quinoxaline derivatives from 2015 to 2023 [14].

**Examples of Quinoxaline Based Drugs**

Some of the few examples of quinoxaline derivatives such as Echinomycin (as antibacterial, antineoplastic, and nucleic acid inhibitor), dioxidine and mequindox (as antibacterial agents), carbadox (controlling swine dysentery), desoxycarbadox (as swine growth promoter) and panadipion (as hepatoprotective agent), Varenicline, Brimonidine etc. are given below:

**Echinomycin**

Echinomycin is a cytotoxic polypeptide quinoxaline antibiotic obtained from *Streptomyces echinatus*. It possesses antibacterial, anticancer, and antiviral activities. [15]

**Dioxidine**

Dioxidine is an antibacterial drug for the remedy of suppurative infections. It is a synthetic broad-spectrum antimicrobial drug that is reserved for second- or third-line therapy in most cases. Dioxidine as a reserve drug in treating proinflammatory infections such as phlegmon, abscesses, etc., developing at lowered concentrations of oxygen [16].

**Varenicline**

Varenicline is a partial agonist at nicotinic acetylcholine receptors used as a resource in smoking cessation. It is smoking cessation aid to help people stop smoking in conjunction with education and counseling. [17]

**Brimonidine**

Brimonidine is an alpha-adrenergic agonist and 2-imidazoline derivative that turned into first added in 1996. It can be used to lower pressure in the eyes in patients who have glaucoma (high pressure in the eyes that may damage nerves and cause vision loss) and ocular hypertension (pressure in
3. Future Aspects

Quinoxaline can be considered as a privileged structure. Due to the emergence as an important chemical moiety, demonstrating a wide range of physicochemical and biological activities, Quinoxaline has become an important subject of extensive research. It possesses unique physicochemical properties that provide a huge possibility of a large number of targeted modifications. The scientific world has witnessed several researches utilizing quinoxaline scaffolds for the design and development of numerous bioactive molecules, dyes, fluorescent materials, electrofluorescent materials and organic sensizers for solar cell applications and polymeric optoelectronic materials for the last few decades. Therefore, immense effort has been taken in the development of newer synthetic strategies as well as novel methodologies to modify the quinoxaline framework with proper functional groups. These lead to develop future potent therapeutic agents with limited side effects.

4. Conclusion

The recent studies defines that the organic and medicinal chemists have great interest in the design and development of quinoxaline scaffolds bearing drugs to target a variety of diseases. The literature survey highlighted and revealed that quinoxaline and its derivatives possess a wide range of biological activities such as antimicrobial, anti - convulsant, anti - inflammatory, anti - leishmania, antitumor and anticancer properties. This review mainly focused on the prominent quinoxaline moiety, its chemistry, general synthesis scheme and most relevant examples of drugs bearing quinoxaline nucleus. The structure - based activity studies will be helpful for further modifications on the quinoxaline and its derivatives.

References


