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Mini-review

Present status of quinoxaline motifs: Excellent pathfinders in therapeutic medicine

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ABSTRACT

Quinoxalines belong to a class of excellent heterocyclic scaffolds owing to their wide biological properties and diverse therapeutic applications in medicinal research. They are complementary in shapes and charges to numerous biomolecules they interact with, thereby resulting in increased binding affinity. The pharmacokinetic properties of drugs bearing quinoxaline cores have shown them to be relatively easy to administer either as intramuscular solutions, oral capsules or rectal suppositories. This work deals with recent advances in the synthesis and pharmacological diversities of quinoxaline motifs which might pave ways for novel drugs development.

1. Introduction

Over the years, heterocycles are known to be one of the largest areas of research in organic chemistry [1]. Quinoxaline belongs to the heterocyclic family of benzodiazine with its nitrogen heteroatom situated at 1- and 4-positions. The microwave assisted synthesis has been recently reported to be remarkably successful approach which gave quinoxalinone-hydrazones [2] in higher yield at less reaction time compared to conventional heating method [3]. Recent updates showed that the chemistry of quinoxaline has attracted considerable attention [4] due to its diverse chemical reactivities [5–7], application in material science [8,9] and wide spectrum of biological activities [10,11]. Quinoxaline motif is known to represent a class of medicinally important compounds which are effective as antibacterial [1,4], antifungal [2,10], anticancer [11], analgesic [12], antimalarial [13], antitumor [14], antiamoebic [15], antiepileptic [16], anticonvulsant [17], antitubercular [18], antiproliferative [19], anti-HCV [20], anti-inflammatory [21] agents among others. Compounds with quinoxaline cores are used as allosteric dual Akt1 and Akt2 inhibitors, human cytomegalovirus polymerase inhibitors [22], Src-Family Kinase p56Lck inhibitors [23], SRPK-1 inhibitors [24] and monoamine oxidase A inhibitors [25]. Report has shown recently that pyrrolo[1,2-a]quinoxaline derivatives are potent and selective 5-HT_3 ligands [12].

Furthermore, quinoxaline nucleus is a common substructure of many biologically and pharmacologically active compounds [26]. For instance, echinomycin **1** (Fig. 1) is a natural depsipeptide antibiotic which is structurally related to triostin in that they both have two quinoxaline-2-carboxylic acid moieties attached to a cyclic octadepsipeptide containing a sulfur cross-linkage [27]. The quinomycin families of nonribosomal peptides, including echinomycin, triostin A, and SW-163s are important secondary metabolites which act as bisintercalators [28], inserting quinoxaline units preferentially adjacent to CG base pairs of DNA [29]. In search for new quinoxaline antibiotics, some analogues of echinomycin have been reported via some cutting-edge synthetic modifications [27]. According to data acquired by Park and coworkers, the excellent activity of echinomycin might justify its potential use against infections with *Staphylococcus aureus* strains that are resistant to vancomycin [30]. In recent development, compounds acting as the antagonists of 2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl) propanoic acid (AMPA), are now generally known to be potentially useful for the prevention and treatment of broad range of acute and chronic neurological disorders [31]. In view of this, some coded quinoxaline derivatives such as CNQX **2**, YM90K **3**, YM872 **4**, LU112313 **5** and NBQX **6** have been reported as potent AMPA receptor antagonists and were projected as good candidates for neuro-pharmacological screening (Fig. 1) [17]. In addition,

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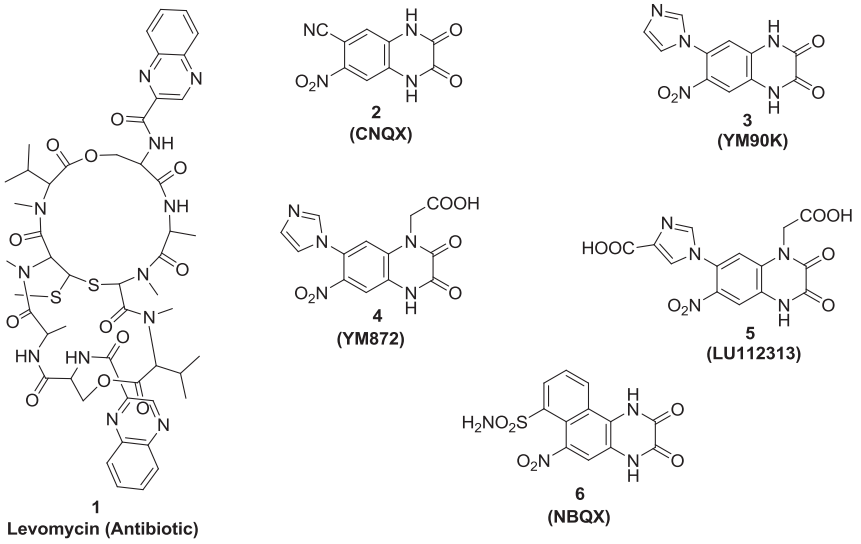

Fig. 1. Antibiotic and AMPA receptor antagonists containing quinoxaline core structures.

quinoxaline moieties also find relevant applications in agrochemicals as herbicides [32a], insecticides [32b] and pesticides [32c].

In view of the occurrence of microorganisms' resistance to drugs currently in use and the emergence of new diseases, there is a continuous need for the synthesis of new heterocyclic compounds as potential therapeutic agents. Hence, the aim of this present study is to provide recent updates in synthesis and biological diversities of quinoxaline derivatives in order to unveil new pathways for therapeutic targets in drug design and future drug discovery.

2. Chemistry

2.1. Synthesis of quinoxaline derivatives

Over the years, it has been established that quinoxaline is relatively easy to prepare and many derivatives have been synthesized with the aim of obtaining biologically active materials [1–3]. Due to high diversity, many synthetic approaches have been utilized in preparing quinoxaline and their polycyclic derivatives. Some of the recent updates for such synthesis are specifically reviewed below:

2.1.1. Heterogeneous catalysis synthetic approach

Diverse functionalized 2,3-disubstituted- and 2,3,6-trisubstituted quinoxaline derivatives **7**–**16** have been synthesized in high yields by reaction of substituted-*o*-phenylenediamines with 1,2-diketone derivatives in the presence of different efficient heterogeneous catalysts such as cellulose sulfuric acid (CSA) [33a], molecular iodine [33b], ferric perchlorate [33c], $Ga(OTf)_3$ [33d], $CuSO_4.5H_2O$ [34a], Zn[(L)proline] [34b], silica bonded *S*-sulfonic acid (SBSSA) [34c], Montmorillonite K-10 [35a], $Cu_2H_2PMo_{11}VO_{40}$ [35b] and ZrO_2/Ga_2O_2/MCM-41 [35c] (Table 1). Furthermore, other heterogeneous catalysts such as graphite [36a], Cu/SBA-15 [36b], $PdCl_2/PPh_3$ [36c], $MgSO_4.7H_2O$ [36d], $HClO_4.SiO_2$ [36e], zirconium(iv)-modified silica gel [36f], acidic alumina [36g] as well as nanomerically generated catalysts such as $MnFe_2O_4$ [37a], Ni-nanoparticles [37b], nanocrystalline CuO [37c] and γ-Maghemite–silica nanocomposite [37d] have been recently reported to provide suitable pathways to numerous quinoxaline derivatives. In addition, green approach for the synthesis of quinoxaline derivatives have also been documented using ionic liquid such as hyperpolyanion-based [38a], [2-MPyH]OTf [38b], C8 [DABCO]Br [38c], $[bmim]BF_4$ [38d–f] as the efficient catalytic. The wide applications of these ionic liquid stemmed from their special properties such as the negligible vapor pressure, tunable polarity, high thermal stability, good solvating ability, ease of recyclability and the potential to enhance reaction rates and selectivity [38e,38g].

2.1.2. Microwave-assisted approach

(a). Recently, the microwave method was found to be remarkably successful for the synthesis of a new series of quinoxaline-incorporated schiff bases **17** [39]. 3-Methylquinoxalin-2-ol was treated with ethyl chloroacetate in the presence of potassium carbonate and dry acetone to produce ethyl 2-(3-methylquinoxalin-2-yloxy)acetate, which upon hydrazinolysis in methanol gave 2-(3-methylquinoxalin-2-yloxy)acetohydrazide [39]. The condensation of methanolic solution of acetohydrazide derivative with various aromatic- and heteroaromatic aldehydes afforded the targeted Schiff bases under microwave irradiation (Scheme 1) [39].

(b). 6-Subsituted-3-(3-hydrazono-3,4-dihydroquinoxalin-2-yl) propanoic acid **18** has been synthesized in 68–79% yields by microwave irradiated hydrazinolysis of the corresponding 3-(3-oxo-3,4-dihydroquinoxalin-2-yl)propanoic acid, which was obtained from the condensation of 4-substituted-*o*-phenylenediamine with α-ketoglutaric acid in absolute ethanol (Scheme 2a) [40]. A related reaction was reported by Gris and coworkers using enzymatic action of *Saccharomyces cerevisiae* via microwave-assisted Hinsberg reaction in order to synthesize benzo-fused derivative **19** (Scheme 2b) [41]. It was in accordance with one-pot biomimetic strategy reported by Akkilagunta and coworkers using supramolecular cyclodextrin [42].

(c). The exposure of a well ground neat mixture of α-hydoxyimino ketone and *o*-phenylenediamine to microwave irradiation afforded the corresponding quinoxalines **20** as shown in Scheme 3a [43], while the plausible mechanism for the protonation of oxime group and intramolecular