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New Quinoxalines with Biological Applications

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In search of alternatives to antimicrobial agents currently in use, and in order to respond to the landscape of loss of efficacy due to the emergence of resistance, several research groups are evaluating several familiesof compounds, among them the quinoxaline derivatives family, which presented several other potential biological applications.

Quinoxaline derivatives are an important class of heterocyclic compounds, where N replaces some carbon atoms in the ring. Quinoxaline molecular formula is $C_8H_6N_2$ and is formed by two aromatic rings, benzene and pyrazine. It is rare in natural state, but their synthesis is easy to perform [1]. Modifying its structure is possible to obtain a wide variety of compounds with different biological properties.

In the last two decades, several quinoxaline derivatives have been tested and presented antimicrobial activity, as antifungal [2-4] and antibacterial agents [2-13]. The antibacterial activity observed covers both Gram-negative and Gram-positive bacteria [6,8,11-13], including *Mycobacterium* species [4,7,9,10,14,15]. There are also data pointing to activity against multidrug resistant *Mycobacterium tuberculosis* [15]. Several studies have been described, concerning synthesis and biological activity of a large amount of quinoxalines. Some quinoxaline 1,4-di-N-oxide derivatives have been shown to inhibit *M. tuberculosis* to a rate of 99 to 100% [9,16].

Antifungal activity for quinoxaline derivatives has been tested against *Candida albicans* [17,18]. Thieno[*2,3-d*]-pyrimidines and pyrrolo[*3,4-b*]-quinoxalines were among the synthesized compounds that presented this kind of biological activity. Researchers also reported some 2-sulphonyl quinoxalines and 3-[(alkylthio) methyl] quinoxaline-1-oxide derivatives as compounds with high antifungal activity [4], and also pyrazolo quinoxalines which were observed to be active against fungal infections [19].

There are quinoxaline derivatives that present anti-protozoan activity [20,21], especially anti-amoebic [22-24], against *Plasmodium* and *Leishmania* species (strain MHOM/BR/76/LTB-012A) [21,25]. Compounds with one halogenous group in position 6 and 7 of the quinoxaline core provide an efficient approach for further development of antimalarial and antileishmanial agent [21].

Quinoxaline derivatives present other biological properties. Anti-cancer activity has been already studied [26-28], and results obtained are very promising. Recently, our research group has demonstrated anti-proliferative activity in several cancer cell lines.

Antioxidant and anti-inflammatory activity has also been explored for quinoxaline derivatives [29-31]. Some compounds presented anti-inflammatory effect similar to the reference drug used, indomethacin [29].

Some cooper and zinc quinoxaline derivative complexes have presented antidiabetic activity [32] and N-arylcarbamoyl and N-aryl thiocarbamoyl derivatives revealed hypoglycemic behavior in Wister rats.

Quinoxaline-5,8-diones derivatives were tested for their inhibitory activity on rat aortic smooth muscle cell proliferation and results revealed good proliferation inhibition.Thus the quinoxaline-5,8-diones were found as promising anti-atherosclerotic agents [16,19,33].

New series of structurally novel 3-substituted-2-carboxamides quinoxaline exhibited 5-HT_3 (serotonin) receptor antagonism, and some of them showed antagonism greater than the standard TCA (Tricyclic anti-depressant) drugs [34].

A series of 7-heterocycle-substituted quinoxaline carboxylic acids were tested for their neuroprotective efficacy. One of the synthesized compounds was found to possess high neuroprotective effect *in vitro* and showed excellent *in vivo* activity [35].

Due to the wide range of applications, quinoxaline derivative compounds have aroused the interest of the scientific community, especially in the last decade. Given the ability to design different structures from the quinoxaline core, improvement of biological activities may be achieved, as well as new applications.

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