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PIPERAZINE DERIVATIVES: A POTENTIALLY TOOL FOR THE TREATMENT OF NEUROLOGICAL DISORDERS

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Abstract

The aim of this review is to compile information about the reported neurobiological effects of piperazine derivatives. Piperazine derivatives are molecules with a wide variety of neurological activity. These molecules could be a promising tool to create drugs with greater potency and less adverse effects than existing molecules.

Keywords: *piperazine, biological effects, neurological disorders, molecules.*

Introduction

Neurological disorders are diseases of the central and peripheral nervous system. These diseases are becoming a serious world health problem. Millions of people worldwide are affected by neurological disorders. According to the world health organization (WHO) around 50 million people have epilepsy worldwide. It is estimated that there are globally 47.5 million people with dementia with 7.7 million new cases every year, being Alzheimer disease the most common cause of dementia. The prevalence of migraine is more than 10% worldwide. This is the reason for looking new tools to mitigate this kind of diseases.[1] On the other hand, medicinal chemistry is a chemistry derivate science that has as main objective find, develop and improve molecules that cure or alleviate diseases.[2] Within these molecules the piperazine is a wide studied molecule for its vary biological effects, mainly on the nervous system.

Chemical considerations

Piperazine is an organic compound that posses two nitrogen atoms in opposite positions within a 6-members heterocyclic ring (figure 1).[3]

This molecule has led to synthetizes important derivatives with a wide range of uses. Several researches have reported antihelmintic, antitubercular, antimalarial, antifungal, antiviral and anticancer activity of piperazine derivatives.[4] As well in industry, piperazine derivatives have some uses in perfumes, as starting materials and agrochemical industry.[5]

Anxiolytic effect of piperazines derivatives

Anxiety disorders are the most prevalent mental disorders. Anxiety represents high health costs for several countries. In 2015, anxiety has affected to 3.6 % of worldwide population.[6] It is know that some neurological systems are involved in anxiety disorders, like GABA system. Nowadays drug research is focus in looking for new targets to treat it.[7] There is a wide variety of piperazine analogues that have shown anxiolytic effect. Several studies have suggested the involvement of 5-HT_{1A} receptors in anxiety and depressive disorders.[8] Trifluoromethylphenylpiperzine (TFMMPP) and *m*-chlorophenylpiperazine are compounds demonstrated to be agonists at 5-HT_{1A} receptors, triggering an anxiolytic effect.[9] Other target that has relation with anxiety disorder is melacortin receptor (MC). There are five subtypes of this receptor; MCR4 has been involved in this mental disorder. Two mono piperazine derivatives have demonstrated affinity for this receptor and exerting anxiolytic effect. This pipirazine derivatives were 1-[3-(6-Fluorobiphenyl-2-yl)propyl]-4-[2-(4-fluorophenyl)-2-(1-isopropylpiperidin-4-yl)ethyl]piperazine-3-hydrochloride and 1-(3-Biphenyl-2-yl-propyl)-4-[2-(4-fluorophenyl)-2-(1-isopropylpiperidin-4-yl)ethyl]piperazine-3-hydrochloride.[10] Other piperazine derivative,1-(2-(2,5-dimethylphenoxy) ethyl)-4-phenylpiperazine dihydrochloride, demonstrated activity in the four-plate test (anxiolytic-like activity) at 1.25 mg/kg.[11] The Table 1 shows some piperazine derivatives with anxiolytic effect.

Anti-epileptic activity of piperazines derivatives

Epilepsy is a neurological chronic disease characterized by the generation of epileptic seizures. The definition of epilepsy requires the occurrence of a least one epileptic seizure.[17] Seizures can be caused by a variety of pathologic conditions, including acquired injuries and genetic abnormalities. In addition, many physiologic disturbances of brain function can produce seizures.[18] Piperazines derivatives are molecules that have shown some anticonvulsant activity. A piperazine derivative, benzhydryl-4-(6-methyl-2-pyridylmethylenimino)-piperazine, showed to be effective in several experimental models of epilepsy. It also showed selectivity equal to or better than some anti epileptic drugs like phenobarbital, phenytoin and diazepam.[19]

Anti-Alzheimer disease activity of piperazines derivatives

The most common cause of dementia is the Alzheimer disease. This pathology is characterized by a decline in memory, language, problem solving and some other cognitive skills. This condition, affects the possibilities of the person to perform everyday activities In the Alzheimer disease, neuronal damage eventually affects parts of the brain that enable a person to carry out basic bodily functions such as walking and swallowing. [20]

There are some piperazine derivatives that have demonstrated anti-Alzheimer's disease. A series of N′-(4-benzylpiperidin-piperazines were evaluated. They showed affinity to dopamine transporter and also antioxidant activity, even more than α-tocopherol. [21]

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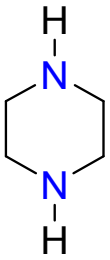

Molecular weight	86.4 g/mol
Molecular formula	$C_4H_{10}N_2$

Figure 1. Properties and chemical structure of piperazine.

Name of compound	Target
Gepirone	$5HT_{1A}$.[12, 13]
Buspirone	$5HT_{1A}$.[14]
Isapirone	$5HT_{1A}$.[14]
Aripripazole	$5HT_{1A}$.[15]
1-[1-(4-chlorophenyl)-1H-pyrazol-4-ylmethyl]-4-phenyl-piperazine	Dopamine D2.[16]
1-phenyl-4-(1-phenyl-1H-[1,2,3]triazol-4-ylmethyl)-piperazine	Dopamine D2.[16]
1-[1-(4-chlorophenyl)-1H-[1,2,3]triazol-4-ylmethyl]-4-phenyl-piperazine	Dopamine D2.[16]
N-(2-methoxyphenyl)piperazine	$5HT_{1A}$.[16]

Table 1. List of some piperazine derivatives with anxiolytic effect.

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