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PIPERAZINE DERIVATIVES: A REVIEW OF BIOLOGICAL ACTIVITIES

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ABSTRACT

Piperazine is a vital organic scaffold that consists of a six-membered ring containing two nitrogen atoms at opposite positions in the ring and also posse's four carbon atoms. This moiety can be found in a plethora of well-known drugs with various therapeutic uses, such as antipsychotic, antihistamine, antianginal, antidepressant, anticancer, antiviral, cardio protectors, anti-inflammatory, and imaging agents. Slight modification to the substitution pattern on the piperazine nucleus facilitates a recognizable difference in the medicinal potential of the resultant molecules. The article describes a variety of molecular designs bearing piperazine entity furnishing as an anthelmintic agent, anti inflammatory agent, as an anti microbial agent, anti convulsing agent, as an anti histamic agent.

KEYWORDS: Piperazine, antihistamine, anti-inflammatory, an anthelmintic agent, anti inflammatory agent, as an anti microbial agent, anti convulsing agent.

INTRODUCTION

Piperazines were initially named for their chemical similarity with piperidine, part of the structure of piperine in the black pepper plant (Piper nigrum). Medicinal chemists have been extremely successful in the recent years in redesigning this scaffold which is vital for an exact pharmacological activity.[1]

Piperazine derivatives are a broad class of chemical compounds, many with important pharmacological properties, which contain a core piperazine heterocyclic nucleus. A trivial

change in the substitution pattern in the piperazine nucleus causes distinguishable difference in their pharmacological activities.[1]

Piperazines are a broad class of chemical compound with diverse activity. Piperazine is one of the most widely used and thoroughly explored heterocyclic compounds. Piperazine nucleus is a structural fragment of many analgesics, psychotropic and antitumor drugs etc. but it is firstly introduced as an anthelmintic.[2]

PIPERAZINE NUCLEUS DERIVATIVES ACT AS VARIOUS BIOLOGICAL AGENTS

1. ANTHELMINTIC AGENT[2]

Helminthiasis is a disease in which a part of the body is infested with worms such as pinworm, roundworm or tapeworm.[3] Typically, the worms reside in the gastrointestinal tract but may also burrow into the liver and other organs; infected people excrete helminthes eggs in their faeces, which then contaminate the soil in areas with inadequate sanitation.

The discovery of the anthelmintic properties usually is credited to Fayard (1949), but these were first observed by Boismare, a Rouen pharmacist, whose recipe is quoted in Fayard's thesis. A large number of substituted piperazine derivative exhibit anthelmintics activity, but apart from diethycarbamazine, none has found a place in human therapeutics[4] anthelmintics are drugs that have the capability of riding the body of parasitic worms or helminthes.

Piperazine is highly effective against both A. lumbricoides and E. vermicularis. The predominant effect of piperazine on ascaris is to cause a flaccid paralysis that result in expulsion of the worm by peristalsis. Affected worms recover if incubated in drug free medium. This action mediated by its agonist effects upon the inhibitory GABA (γ-amino butyric acid) receptor. Its selectivity for helminthes is because vertebrates only use GABA in the CNS and helminthes GABA receptor is a different form to the vertebrate's one.

Piperazine hydrate and piperazine citrate are the main anthelmintic piperazines. These drugs are often referred to simply as "piperazine" which may cause confusion between the specific anthelmintic drugs and the entire class of piperazine-containing compounds.[5]

Piperazine citrate (Mutifage) (figure 1), the form available in the United States is a useful and inexpensive second-choice alternative to mebendazole or pyrantel pamoate in treating combined ascariasis and enterobius infections.

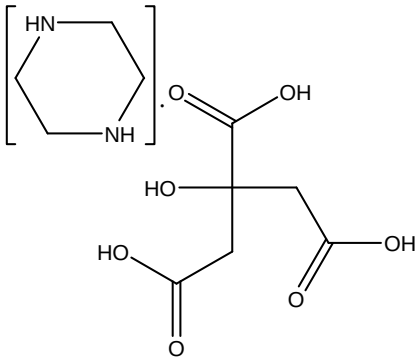

Figure 1

2. ANTI-INFLAMMTORY AGENT[2,6]

Inflammation (Latin, inflamatio, to set on fire) is the complex biological response of vascular tissues to harmful stimuli, such as pathogens, damaged cells, or irritants. It is a protective attempt by the organism to remove the injurious stimuli as well as initiate the healing process for the tissue.

G.I.Regnie[7] et. al., have been prepared thirty-seven 1,4-disubstitiited piperazines in which the 1-substituents (figure 2a) are benzyl or phenylalkyl or its mono- or polyalkoxy, alkylenedioxy, or alkoxyhydroxy derivatives, and the 4-substituents (figure 2b) are pyrimidyl and its substituted derivatives, quinazolinyl or triazinyl. Some derivatives were found to have an anti inflammatory action in rats, by the kaolin paw edema method.

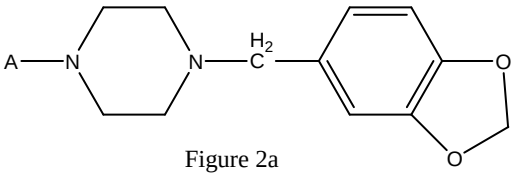

Figure 2a

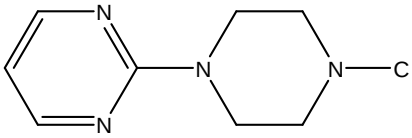

Figure 2b

[[

Hatnapure[8] et. al., have reported synthesis of a series of 6-methoxy-2-(piperazin-1-yl)-4H-chromen-4-one (figure 2c) and 5,7-dimethoxy-2-(piperazin-1-ylmethyl)-4H-chromen-4-one(figure 2d) derivatives and screened for their pro-inflammatory cytokines (TNF-a and IL-6). The series of the novel 6-methoxy-2-(piperazin-1-yl)-4H-chromen-4-one and 5,7-dimethoxy-2-(piperazin-1-ylmethyl)-4H-chromen-4-one derivatives, next in order to search for the potent compounds from these newly synthesized flavones derivatives, compounds were evaluated for in vitro anti-inflammatory activity against the pro-inflammatory cytokines (TNF-a and IL-6) by TNF-a and IL-6 inhibition assay.

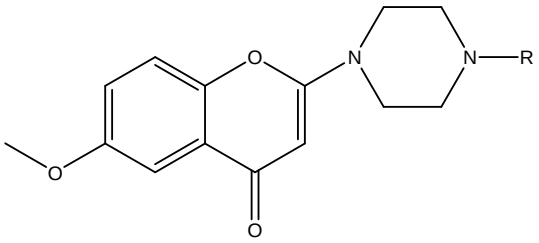

Figure 2c

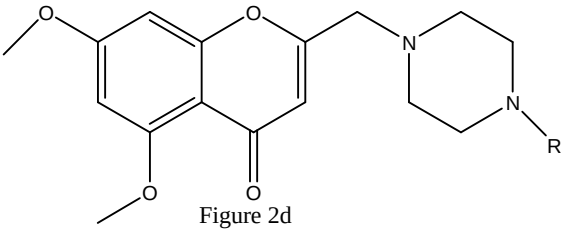

Figure 2d

3. ANTI-CONVULSING AGENT

Epilepsy is considered as one of the most common neurological disorders, afflicting around 50 million people worldwide. This condition is characterized by neuronal hyperexcitability and firing. Antiepileptic drug (AED) therapy continues to be the mainstay for treatment of epilepsy. Even with the advances in development of AEDs, approximately 20-30% of patients suffer from recurrent seizures. Search for the development of new antiepileptic agents is still going on. In this regard, several piperazine bearing anticonvulsant drugs have been developed.[9]

Two dicarboxylic piperazine derivatives, 1-(p-chlorobenzoyl)-piperazine-2,3-dicarboxylic acid(pCB-PzDA) (figure 3a) and 1-(p-bromobenzoyl)-piperazine-2,3-dicarboxylic acid (pBB-PzDA) (figure 3b), that block excitation at glutamate receptors have been evaluated as anticonvulsants in rodent models of epilepsy by i.c.v. or i.p. injection.[1,10]

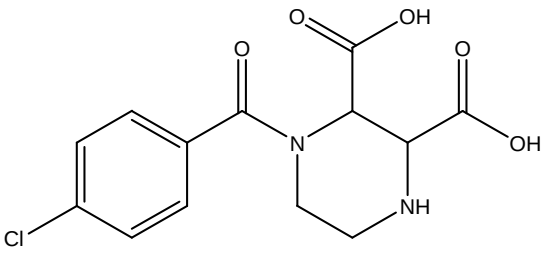

Figure 3a

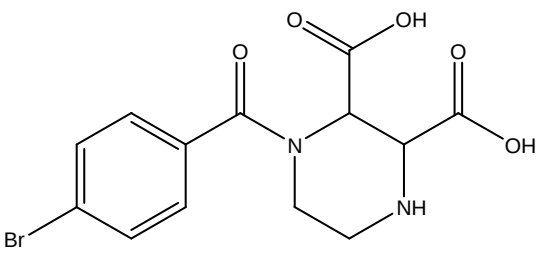

Figure 3b

NMDA antagonists, D (-) 4-(3-phosphonopropyl) piperazine-2-carboxylic acid (D-CPP) (figure 3c) and D (-) (E)-4-(3-phosphonoprop-2-enyl) piperazine-2-carboxylic acid (D-CPPene) (figure 3d) in a rodent and aprimate model of reflex epilepsy was shown anticonvulsant activity.

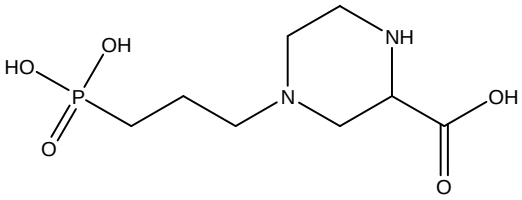

Figure 3c

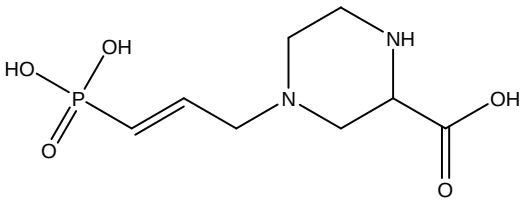

Figure 3d

Waszkielewicz[11] et. al., have designed a new series of xanthone derivatives with piperazine moiety (figure 3e) and evaluated them for their biological activity. Preclinical research and discovery of potential antiepileptic drugs rely heavily on the use of animal models of seizures. The explanation of this fact is that there is no single pathomechanism related with development of epilepsy. As a co8nsequence, most of existing antiepileptic drugs have been discovered with use of either of the anticonvulsant in vivo tests: maximal electroshock (MES) or subcutaneous metrazole (ScMet). These two methods serve as 'gold standards' in screening for potential anticonvulsants, giving premises for activity in human grand mal or petit mal epilepsy, respectively. Many antiepileptic drugs exhibit significant toxicity. Therefore, the ASP program includes a screening model for neurotoxicity-rotarod. The ability of an animal to stay on a slowly rotating rod (6 rpm) without falling is measured (3 times within 1 min). If it falls after 0.5 or 4 h of a dose of 30 mg/kg b.w. (mice, i.p.), the minimal motor impairment observed for the compound excludes it from further testing.

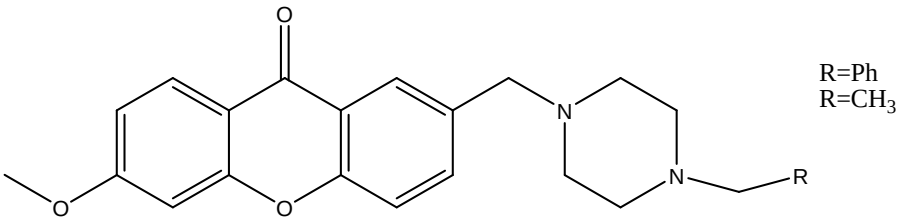

Figure 3e

4. ANTI-MYCOBACTERIAL AGENT

Bacterial infections are one of the foremost reasons for mortality and morbidity in tropical nations of the globe. Antibiotics are generally prescribed by the physicians to evade these stern and life threatening bacterial infections. Nevertheless, the emergence of resistance to the available antibacterials is a major impediment in the treatment of these bacterial infections. A number of antibacterial agents bearing piperazine moiety have been developed by numerous researchers.[9]

Rifampicin (figure 4a) is the 3-[(4-methyl-1-piperazin-yl) iminomethyl]-rifamycin SV. The Rifamycin antibiotics were discovered in 1959 as metabolite of a micro-organism originally considered to belong to the genus Streptomyces.

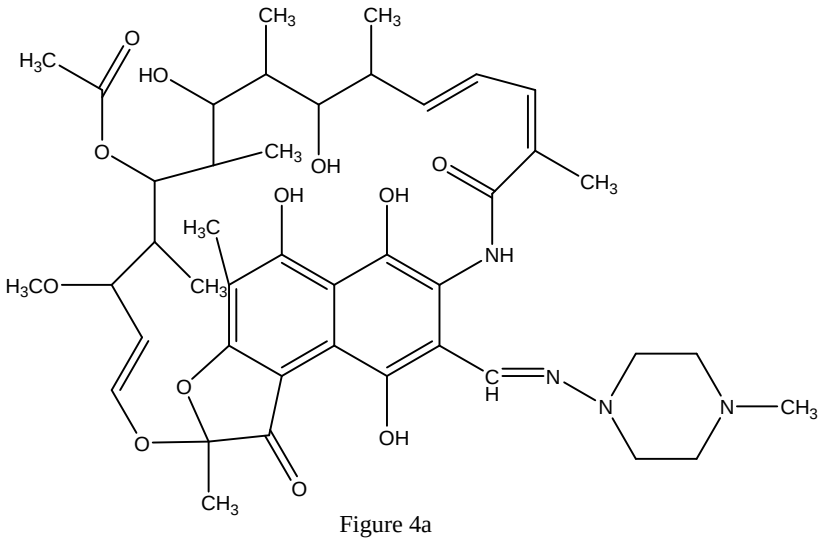

Figure 4a

Rifalazil (figure 4b) is 3'-hydroxy-5'-(4-isobutyl-1-piperazinyl) benzoxazino rifamycin. Rifalazil is more potent in-vitro and in-vivo against M. tuberculosis and M. avium complex than Rifampicin. The potent antimycobacterial activity of rifalazil is largely because of its increased ability to penetrate the mycobacterial cell wall.

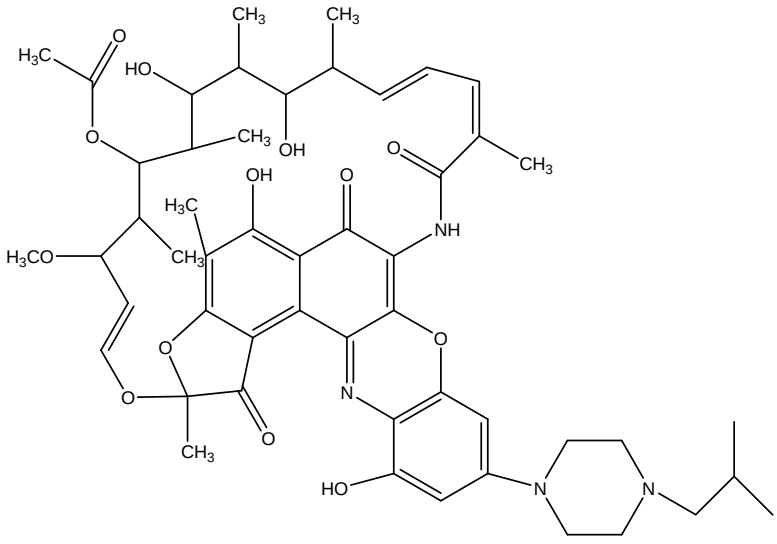

Figure 4b

Rifapentine (figure 4c) is the 3-(4-cyclopentyl-1-piperazinyl-iminomethyl)-rifamycin SV and therefore is an analog of rifampicin in which a cyclopentyl group substitutes for a methyl group on the piperazine ring. It is slightly superior against mycobacteria.

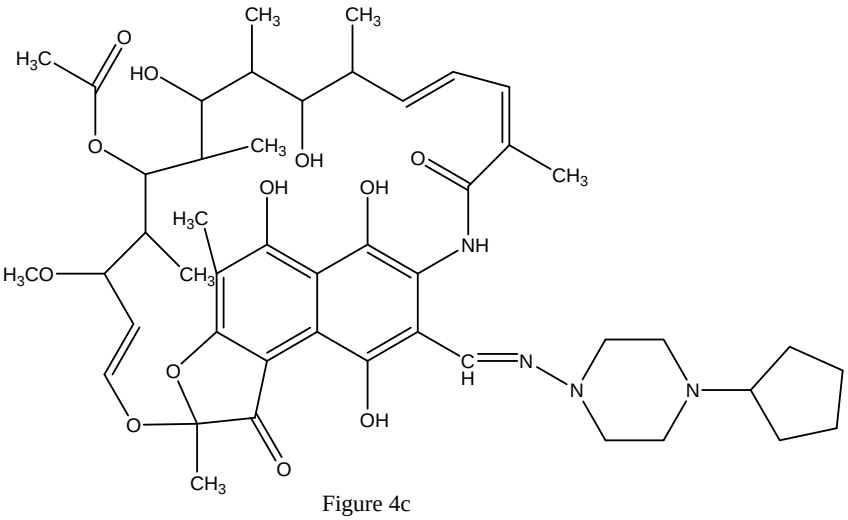

Figure 4c

Preeti Chaudhary[12] et. al., have been synthesized a series of substituted piperazine derivatives (figure 4d, 4e, 4f, 4g) and tested for antimicrobial activity. All synthesized compounds showed significant activity against bacterial strains. The in vitro antibacterial activity was tested by the disc diffusion method using pathogenic strains of S. aureus (MTCCB 737), P. aeruginosa (MTCCB 741), S. epidermidis (MTCCB 1824) and E. coli (MTCCB 1652). The concentration 30 lg/disc of compounds was impregnated on the discs. These discs were placed on the surface of the agar plates already inoculated with pathogenic bacteria. The plates were incubated at 37^0C and examined at 48 h for zone of inhibition, if any, around the discs. Gentamicin was used in the assay as a standard control drug. An additional control disc without any sample but impregnated with an equivalent amount of solvent (DMSO) was also used in the assay. The result of antibacterial activity indicated that some of the compounds exhibited mild to moderate activity.

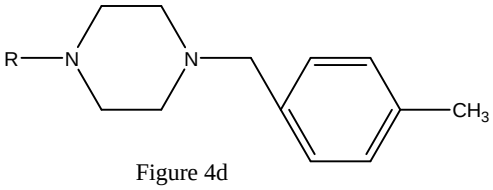

Figure 4d

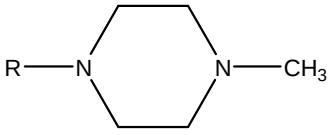

Figure 4e

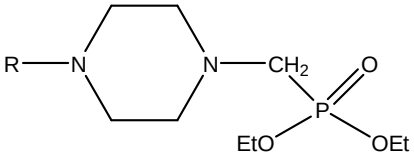

Figure 4f

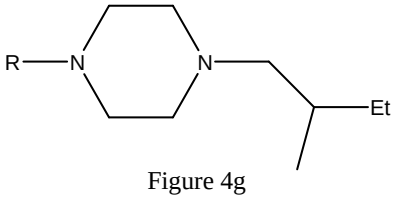

Figure 4g

K.S.Thriveni[13] et. al., were synthesized pyrimidine incorporated piperazine derivatives (figure 4h, 4i**)** and their antimicrobial activity. Some selected compounds were screened for

their in vitro antibacterial activity against Gram positive bacteria namely Staphylococcus aureus (NCIM2492), Bacillus subtilis (NCIM2088) and Gram negative bacteria Escherichia coli (NCIM2138) and Salmonella paratyphi-A (ATCC3220). The activity was carried out using the cup-plate agar diffusion method. The test compounds were dissolved in dimethyl formamide to obtain a solution of 40 µg/ml concentration. The inhibition zones of microbial growth produced by different compounds were measured in millimetres at the end of an incubation period of 48 h at 38º dimethyl formamide alone showed no inhibition zone. Choramphenicol was employed as reference standard (40 µg/ml) to evaluate the potency of tested compounds.

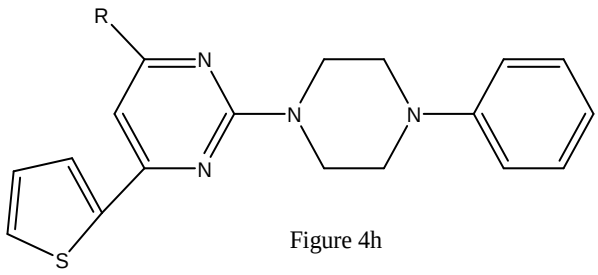

Figure 4h

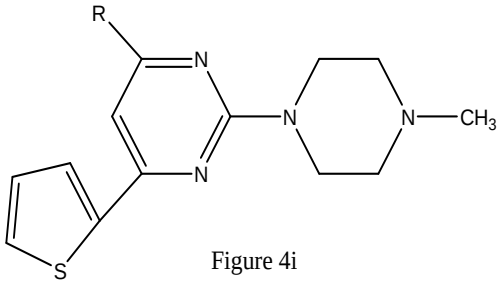

Figure 4i

5. ANTI-HISTAMINIC AGENT[14]

Histamine, discovered more than 90 years ago is a biogenic amine with a molecular weight of 112. It is an enzyme that is expressed in cells throughout the body, which includes the central nervous system neurons, gastric-mucosa parietal cells, mast cells, and basophiles. When released, histamine through four types of receptors induces diverse and complex physiological and pathological effects. It plays an important role in the pathogenesis of various allergic conditions in the skin and the airway system, and is considered as one of the most important mediators of allergy and inflammation.[15,16]

KAA-276 (figure 5a) is a novel irreversible and selective long acting histamine H1 receptor antagonist inducing constriction of ileum and trachea isolated from guinea pig**.**

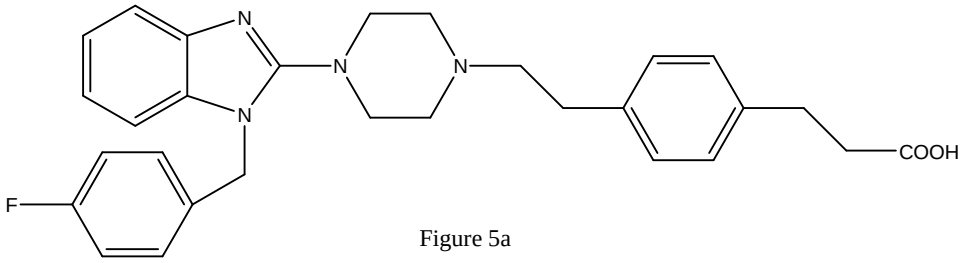

Figure 5a

Among 4-(Diphenyl methyl)-1-piperazine derivatives (figure 5b) with a terminal heteroaryl or cycloalkyl amide fragments showing antihistaminic, anticholinergic and antiallergic activities.[17,18]

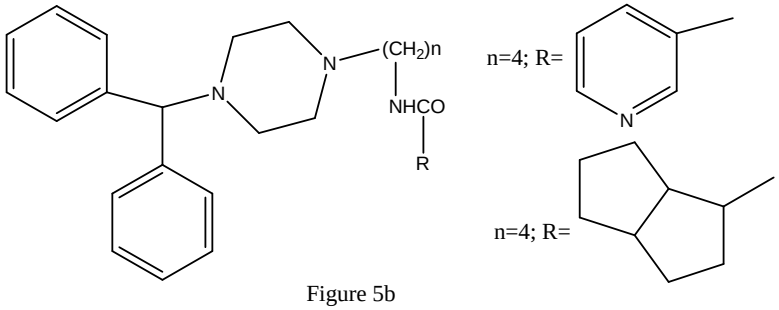

Figure 5b

Waszkielewicz[11] et. al., have designed a new series of xanthone derivatives with piperazine moiety (figure 5c) and evaluated them for their biological activity. They were subject to binding assays for α_1 and β_1 adrenergic as well as 5-HT_{1A}, 5-HT_6 and 5-HT_{7b} serotoninergic receptors. The compound 3-methoxy-5-{[4-(2-methoxyphenyl) piperazin-1-yl] methyl}-9H-xanthen-9-one hydrochloride exhibited significantly higher affinity for serotoninergic 5-HT1A receptors (Ki = 24 nM) than other substances. Piperazine moiety resulted in obtaining of compounds with increased bioavailability after oral administration.

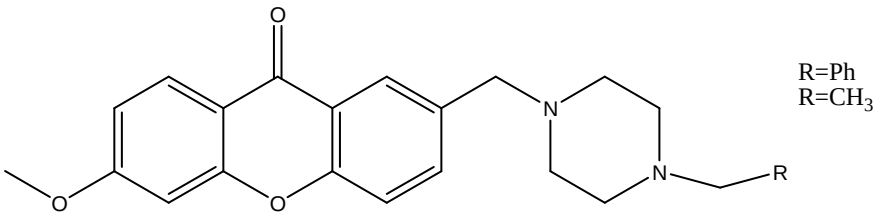

Figure 5c

Systemic antihistamines, such as Loratadine and Cetirizine hydrochloride, have proven efficacious in the control of many allergic conditions; but both induce signs and symptoms associated with ocular dryness, including increased corneal and conjunctival staining and increased ocular discomfort in healthy individuals.[19] Still Cetirizine (figure 5d) has good safety records in comparison to older antihistamines.

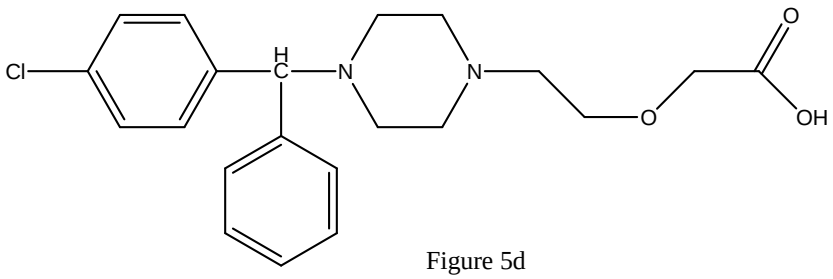

Figure 5d

CONCLUSION

This review has fulfilled significant information about biological activities of various derivatives based on piperazine moiety and also some drugs having piperazine nucleus. It may be concluded that piperazine scaffold is a resourceful and vital nuclei possessing medicinal importance and is a promising lead compound for the drug design and development of potent therapeutic agents in future.

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