General introduction

Histamine is a β-imidazolylethyamine derivative and essentially present in all mammalian tissues, especially abundant in the lung tissue and in the skin. Also it occurs in the marrow and in the sub cortex. A large quantity of histamine is produced and deposited in the mast cells of connective tissue; where it is stored in abound state as a protein-heparin complex. It is produced in large amounts in the blood plasma and other biological fluids. Dale and Lailaw outlined the principal pharmacological activities of histamine from 1910-1919. after more than half a century of painstaking study, several physiological roles had been proposed for histamine. Histamine probably plays a basic role in the beginning of the inflammatory response of tissue to injury by dilating the capillaries and increasing their permeability. The usefulness of this effect usually leads to a "walling off" of the area of injury. Histamine exerts a verity of action on the cardio-vascular system, plays a role in anabolic processes, acts as a central neurotransmitte, and plays a role in gastric section

In general, histamine appears to be necessary for many physiological processes. Possibly, histamine has a homeostatic role and the histamine-forming capacity of various tissues is responsive to alterations in the concentration of the amine. However, certain condition may lead to excessive production or release of the autacoids (self medicinal agent) that causes expansion of capillaries, probably by constricting the smaller veins and causes a local edema and an increase in the volume of the vascular bed. The resulting drop in blood pressure, if sever enough, may induce shock. Less drastic action of histamine are implicated in other diseases, such as peptic ulceration and asthmatic condition. Therefore, these and other actions of histamine have been studied for the purpose of developing

drugs that will block selectively certain actions of histamine. Because the antihistamine, inhibited some but not all of the actions of histamine, there be must be more than one type of histaminic receptor

Blacket al. could differentiate the histamine receptors into H_1 – receptors and H_2 – receptors. Briefly, the pharmacological distinction of histamine receptors rests upon the action of histamine and its antagonists. Histamine stimulates the contraction of smooth muscle from various organs such as the gut and bronchi. Because low concentration of antihistaminic drugs suppress this effect, the pharmacological receptors that mediate this response are referred to as H_1 –receptors and the drugs are said to be H_1–antagonists. Also, histamine stimulates the secretion of acid by the stomach, increases the heart rate, and inhibits concentrations in the rate uterus. Because the classical antihistaminic do not antagonize these effects, the receptors that mediate these action are said to be H_2 –receptors. Likewise, drugs that inhibit these responses to histamine are classified as H_2. antagonists.

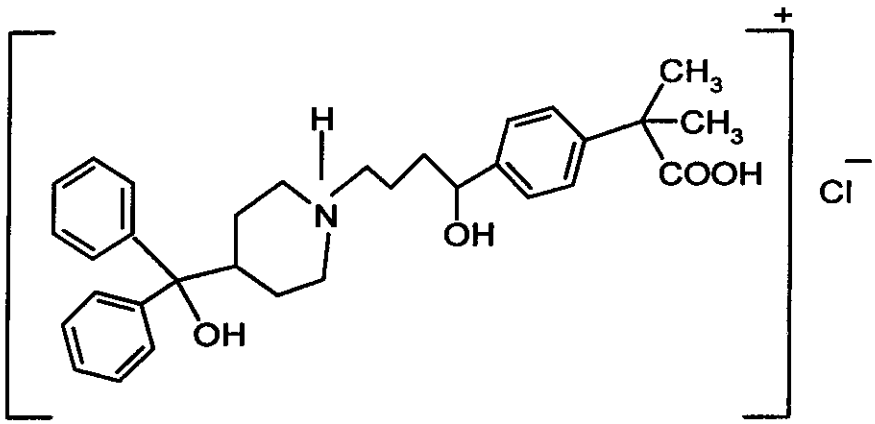
In 1992, leurs et al. pointed out the most recently histamine H_3 – receptors, which has been described to play a role as a general regulatory receptor system, modulating not only the release and synthesis of histamine but also the release of other neurotransmitters. Studies with different experimental agents suggest that H_3 –receptor agents might provide new therapeutics for central nervous system (CNS), airway, and gastrointestinal disorders. In our work, we will concentrate on the antagonists.

1..1. Investigation of the studied drugs

1. 1.1. Fexofenadine Hydrochloride

Fexofenadine, an active metabolite of terfenadine, is a non –sedating antihistamineH_1-receptor antagonist. It does not possess significant sedative or antimuscarinic actions. Fexofenadine is used as the hydrochloride in the symptomatic relief of allergic conditions including seasonal allergic rhinitis and urticaria.[1]

Chemical Structure:



Empirical formula : $C_{32}H_{39}NO_4$,HCl

Chemical Name : α,α-Dimethyl-4-[4-(hydroxydiphenylmethyl) -1-piperidinyl]benzene acetic acid

Molecular Weight : free base 501.7 and its hydrochloride 538.2

Appearance : a white to off-white crystalline powder

Melting range : 142° to 143°C

Solubility : freely soluble in methanol, ethanol; slightly soluble in chloroform and water; insoluble in hexane.