1. INTRODUCTION

Antihistamines are the drugs which compete with histamine at the histamine receptors. These are the antagonists of the H_1 receptor and serves to decrease or eliminate the effects mediated by histamine released upon allergic reactions like rhinitis, conjunctivitis, urticaria, pruritis, anaphylactic etc. The therapeutic effect of these agents is mediated by negative modulation of histamine receptors.

In general the term "antihistamines" indicate only to H_1 antagonists, they are also called as H_1 receptor antagonists and H_1 antihistamines. It has been found that these H_1 antagonists are inverse agonists at the histamine H_1 receptor rather than antagonists. Clinically they are used in allergic rhinitis, conjunctivitis, contact dermatitis, urticaria, pruritis and in anaphylatic reaction as adjunct.

Histamine was first detected as uterine stimulants in extracts of ergot, from which it is subsequently isolated. It was soon observed by Dale and Laidlaw,[1] discovered histamine stimulating host smooth muscles and had an intense vasodepressor action. In 1927, Best[2] *et. al.,* isolated histamine from fresh samples of liver, it is a natural constituent of many mammalian tissues and hence the name histamine coined from Greek word '*histos'* means tissues.

The histamine release from basophils during immediate type allergy is of clinical interest, as well as levels of histamine in biological fluids (plasma and urine) and cell culture supernatants after allergen challenge. The discovery and development in the 1940, histamine antagonists capable of reducing the severity of an immediate hypersensitivity response firmly established the physiological importance of histamine.

Histamine is a biogenic amine generated by humans, plants and micro-organisms during normal metabolism. In humans, histamine is found in nearly all tissues and is mainly stored in the metachromatic granula of mast cells and in basophilic leukocytes. Histamine acts predominantly on smooth muscles and blood vessels. Furthermore, it acts through more than one of the histamine receptors like H_1, H_2, H_3 and recently discovered H_4.[3-6] Among these, H_1 receptors are activated by the biogenic amine histamine is expressed throughout the body, to be specific, in smooth muscles, on vascular endothelial cells, in the heart and are activated by endogenous histamine, which is released by neurons. Furthermore, they are blocked selectively by the classical "antihistamines" such as pheniramine, helps against severe allergies.

The first generation antihistamines penetrate blood brain barrier and also possess anticholinergic properties. This has lead to the development of second generation antagonists known

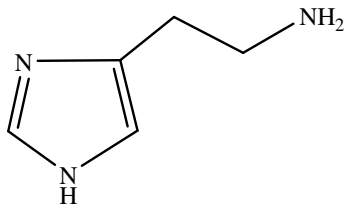
as non sedating antihistamines. i.e. the second generation antihistamines do not penetrate the blood brain barrier and as such do not cause drowsiness.

The histamine interacts with H_2 receptors stimulates stomach secretions, heart rhythm regulation, immunological reactions, etc. Since, H_2 histamine receptors are basically found in the partial cells of the gastric mucosa. The active metabolites of first and second generation antihistamines are not metabolized further (e.g. Cetirizine derived from hydroxyzine or Fexofenadine from terfenadine) lead to development of third generation antihistamines. H_3 receptors were discovered as presynaptic auto receptors on histamine containing neurons that mediate feedback inhibition of the release and synthesis of histamine. The H_4 receptors are closely resemble to the H_3 receptors but, it is different from other histamine receptors like H_1 and H_2. These are expressed in cells of hematopoietic linkage; the availability of H_4 specific antagonist[7] has anti-inflammatory and analgesic properties.

1.1 Chemistry of histamine

Histamine (β-Aminoethyl imidazole or [2-(imidazol-4-yl)ethylamine]) is a hydrophilic molecule consisting of an imidazole ring with amino group connected by two methylene groups. Analogs of histamine activated the four classes of

histamine receptors (H_1, H_2, H_3 and H_4). 2-Methylhistamine and 4(5)-Methyl histamine have a preferential effect on H_1 and H_2 receptors respectively. A chiral analog of histamine with restricted conformational freedom (*R*)-α-methyl histamine is the preferred strong and weak agonist of the H_3 and H_4 receptors respectively.[8]



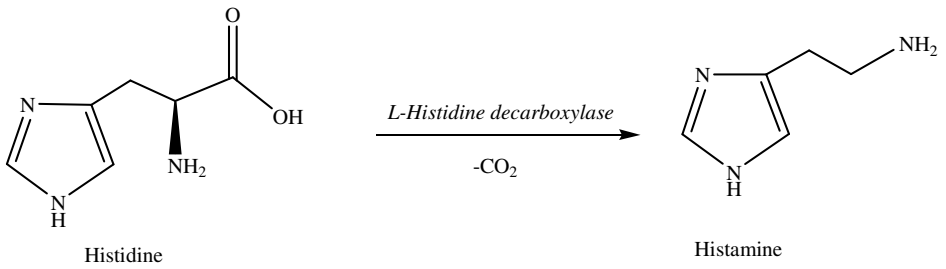
Histamine

1.2 Distribution

Histamine is widely distributed in animal kingdom and is presented in venoms, bacteria and plants. Almost all mammalian tissues contain histamine in amounts ranging from less than 1 to more than 100 µg/g. Particularly tissues having high concentration of histamine and that contain large number of mast cells such as skin, bronchial tree mucosa and intestinal mucosa.

1.3 Synthesis, storage and metabolism of Histamine

Histamine is a dibasic vasoactive substance formed from the decarboxylation of the amino acid histidine by the enzyme *L-histidine decarboxylase*.



Histidine Histamine

The main site of histamine storage in most tissues is the mast cells and basophil in the blood. In these cells, histamine is synthesized and stored in secretory granules that are then carried through the axons and stored in nerve terminals located in the median eminence or posterior pituitary gland. Histamine is positively charged with the pH of approximately 5.5, and ionically complexed with negatively charged acidic groups on other constituents of the secretory granule.[9] Non-mast cell sites of histamine formation or storage include the epidermis, gastric mucosa, neurons within the Central Nervous System (CNS) and cells in regenerating or rapidly growing tissues. Histamine is released continuously rather than stored because of rapid turnover at non-mast cell sites. Non-mast cell sites of histamine production contribute significantly to the daily excretion of histamine metabolites in the urine. Histamine normally ingested or formed by bacteria in the gastro intestinal tract (GIT), which is metabolized rapidly and eliminated through the urine. Histamine is metabolized by *histaminase* or methylating enzyme *Imidazole-N-methyl transferase.*

1.4 Release and functions of endogenous Histamine

Histamine in the body tissues is found in mast cells. Mast cells are granulated cells of hematopoietic origin localized to tissues. Mast cells play a role in innate and adaptive defense to pathogens as well as in various inflammatory and immunoregulatory responses. Its liberation takes place during antigen-antibody reactions with prior sensitization of the organism with specific antigen. Mechanical stimuli like injury to the tissue, cold, heat and ultraviolet rays also cause release of histamine.

Histamine establishes three species like at pH values between 6.5 and 8.5 the predominant species is the monocation, at pH values lower than 5, the predominant species is the dication and at pH values greater than 10, the predominant species is the free-base. When, histamine is a free base, it is bound to acid group like carboxyl, thiol and phosphate of the cellular proteins. Any free base species stronger than monocation and dication species, histamine, antigen, snake, spider, bee bites, bacterial toxins, acids, alkalies, proteolytic enzymes (trypsin), detergents, macromolecules like dextran and polyvinyl pyrrolidone displaces histamine from the bound form in plasma proteins. Drugs containing tertiary and quaternary nitrogen atoms particularly various compounds like *d*-

tubocurarine, morphine, codeine and atropine also cause the release of histamine in the body.

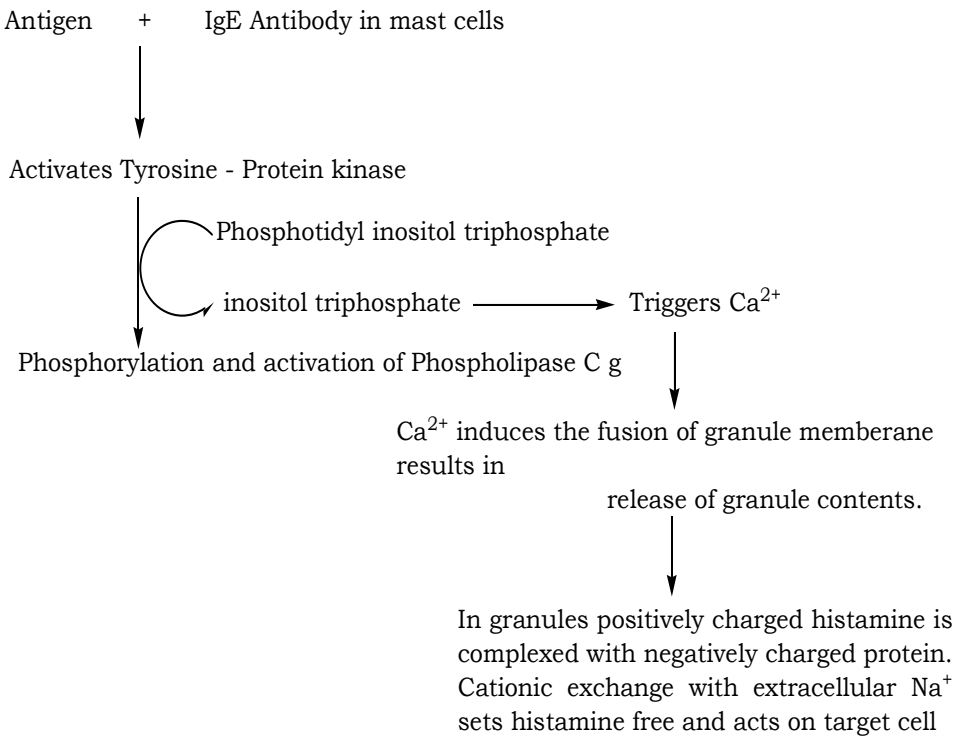


Figure 1: Histamine formation

Histamine plays a central role in neurotransmission, immunomodulation, hematopoiesis, wound healing, day-night rhythm and the regulation of histamine and polyamine induced cell proliferation, angiogenesis in tumor models and intestinal ischemia, because the molecule of histamine derived from the decarboxylation of the amino acid histidine. The actions of histamine on bronchial smooth muscle and blood vessels account for many of the symptoms of the allergic response. In addition, histamine has a major role in the regulation of gastric

acid secretion, which can causes dilation of capillaries, constriction of bronchial smooth muscle and decreased blood pressure and also mediates the neurotransmitter release.

1.5 Role in allergic responses

The main target cells of immediate hypersensitivity reactions are in mast cells and basophil.[10] The allergic responses are caused by either an immune response to a normally innocuous substance, which comes in contact with lymphocytes specific for that substance or antigen or a free-floating IgE (an immunoglobulin associated with allergic response) antibodies. These are bind to the surfaces of mast cells and basophils *via* high affinity F_c receptors, which are more specific for IgE.

1.6 Release of other autacoids

Release of histamine in the human bodies provides a partial knowledge on all biological effects because of production of other autacoids that ensure from immediate hypersensitivity reactions. Stimulation of IgE receptors also activates phospholipase A_2 (PLA_2) leading to the production of a host mediators including Platelet-Activating Factor (PAF), metabolites of arachidonic acid and Leukotriene D_4. Histamine generated in this way is a potent contractor of the smooth muscle of the bronchial tree.

1.7 Histamine release by drugs, peptides, venoms and other agents

Many compounds including a large number of therapeutic agents that are stimulating the release of histamine from mast cells directly and without prior sensitization. Responses of are most likely to occur by I.V of certain categories of substances particularly organic bases such as amides, amidines, quarternary ammonium compounds, pyridinium compounds, piperidines and alkaloids.[11]

Histamine injected intradermally causes triple response described by Sir Thomas Lewis. Reddening from local vasodilation is caused by release of specific mediators, it is responsible for redness and warmth at sites of tissue injury followed by Wheal by direct action on blood vessel are reversible after mild injury, within several minutes to hours, extravascular fluid is cleared through lymphatics and Flare from an axon reflex in sensory nerves, that are is mediated by both neurogenic and chemical mediator systems and usually resolves within seconds to minutes.

1.8 Mechanism of histamine releasing agents

Histamine exerts its actions by combining with specific cellular histamine receptors. Mast cell generate IgE antibodies binds to Fc receptor on granule surface leads to activation of *Tyrosine protein kinase*, it activates the *phospholiphase* helps in conversion of phosphotidyl inositol biphosphate to inositol triphosphate, which triggers the intra cellular release of calcium ion, causes exocytosis release of histamine with transfer of Na^+ ions from extra cellular space. Histamine secretion is caused by rise in cystolic Ca^{2+} ions.[12]

1.9 Receptor-effector coupling and mechanism of action

Histamine receptors are G-Protein Coupled Receptors (GPCRs). The H_1 histamine receptors couple to $G_{q/11}$ and activate the PLC-IP_3-Ca^{2+} pathway and its many possible sequence including activation of *Protein kinase C* (PKC), Ca^{2+} calmodulin dependent enzymes (eNOS and various protein kinases) and PLA_2. H_2 receptors link to G_s to activate the *Adenylyl cyclase cyclic AMP-protein kinase A* (PKA) pathway, whereas H_3 and H_4 receptors couple to $G_{i/o}$ to inhibit *Adenylyl cyclase.*

1.10 Mode of action of antihistamines

Mast cells release the histamine and it binds with histaminergic receptors (H_1, H_2, H_3 or H_4) to elicit a series of events mediates the characteristic response through second messenger systems. All histaminergic receptors are G-protein coupled type. The activation of H_1 receptors coupled with *phospholipase-C*, leads to formation of IP_3 and DAG respectively from phospholipids in cell membrane. Rapid release of Ca^{2+} from endoplasmic reticulum is due to formation of IP_3. DAG activates the the *protein kinase C*, altogether turnover of Ca^{2+} and *protein kinase-C* activates Ca^{2+}/calmodulin dependent *protein kinase* and *phospholipase* A_2. H_1 antagonist binds with H_1 receptors, it decreases the production of *phospholipase-C* and activates the IP_3 and DAG thereby blocks the characteristic response of histamine.

H_2 receptor produces cAMP-dependent *protein kinase* to elicit the response in GIT. The H_2 receptor bound reversibly by H_2 antagonist and reduces the cAMP formation. Further, it is responsible for the activation of proton pump and subsequently reduces the gastric acid secretion in GIT.

H_3 receptors are also G-protein coupled receptors, unlike H_1 and H_2. The receptors produce a decreased Ca^{2+} influx. H_3 receptors function as feedback inhibitors for histamine and

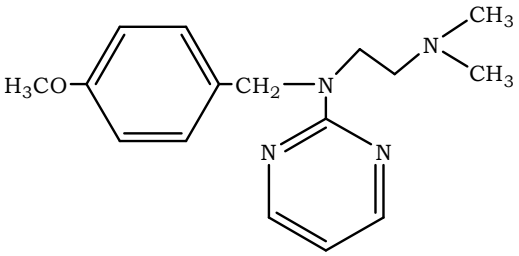
other neurotransmitter by decreasing the Ca^{2+} influx into the cells in CNS and GIT. Further, these receptors reduce the secretion of gastric and down regulate histamine through auto regulatory effect.

1.11 Commonly used antihistamine drugs

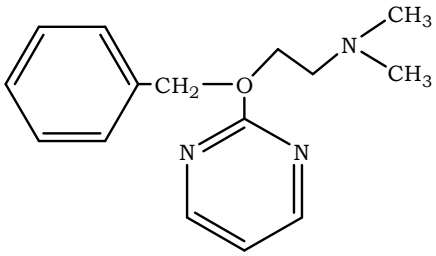
I. H_1 antihistamines

1) First generation H_1 antihistamines

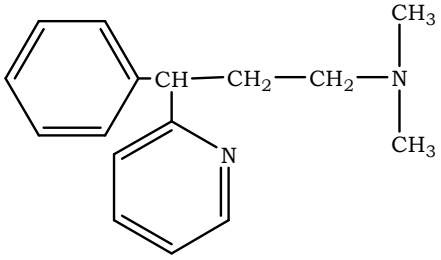
Thonzylamine



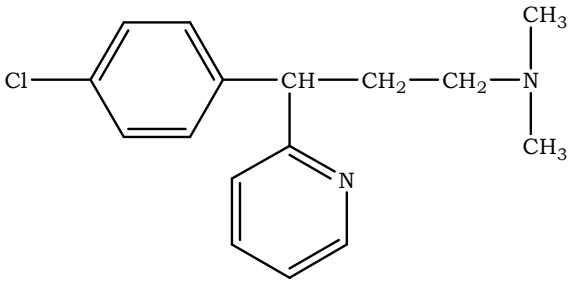
Diphenhydramine



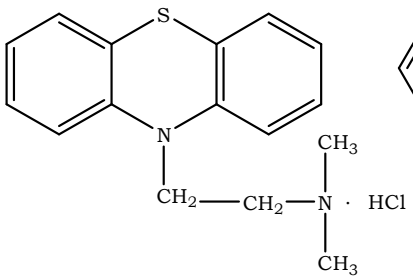
Pheniramine



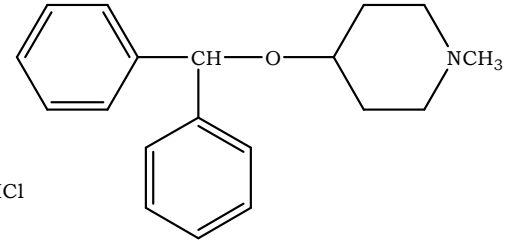
Chlorpheniramine



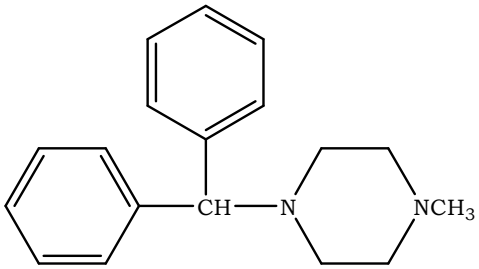
Promethazine HCl



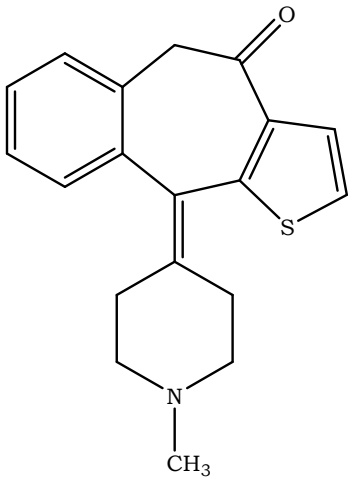
Diphenylpyraline



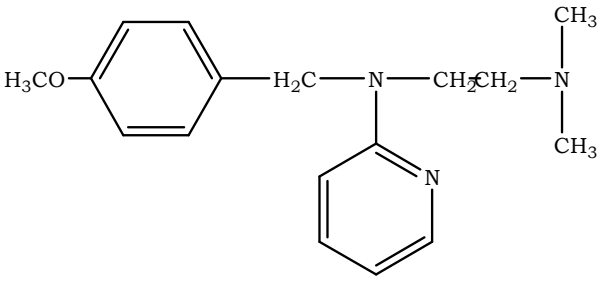
Cyclizine



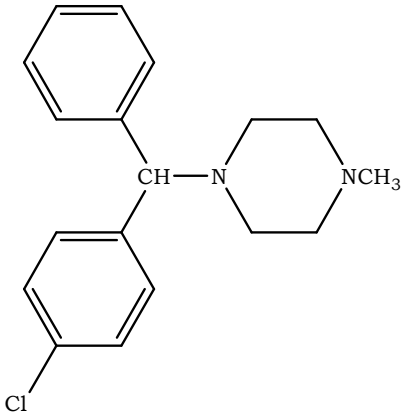
Ketotifene



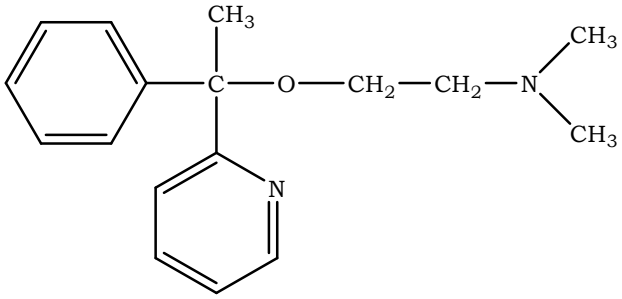
Mepyramine



Chlorcyclizine

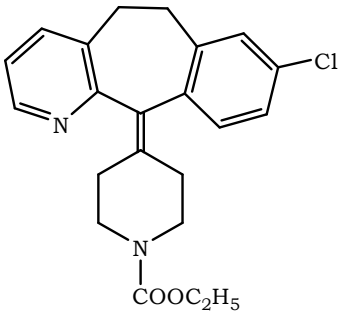


Doxylamine

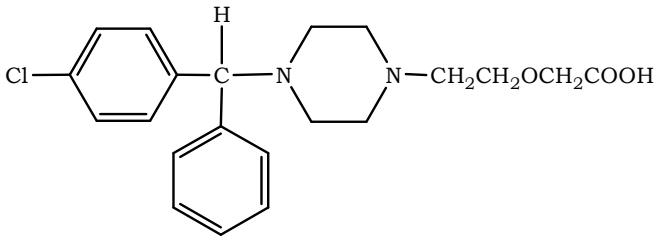


2) Second generation H_1 antihistamines

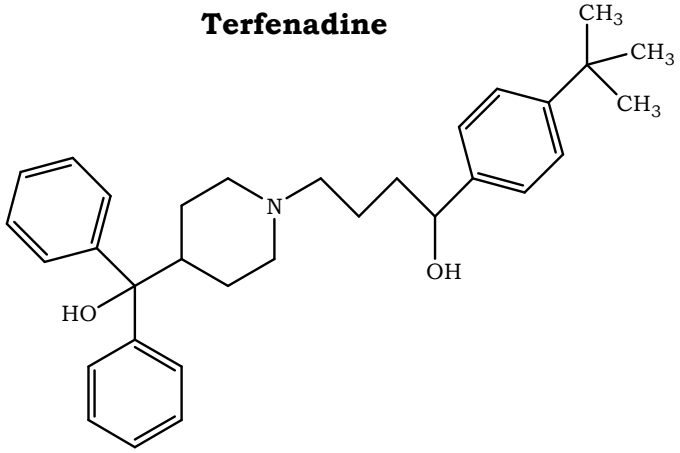
Loratadine



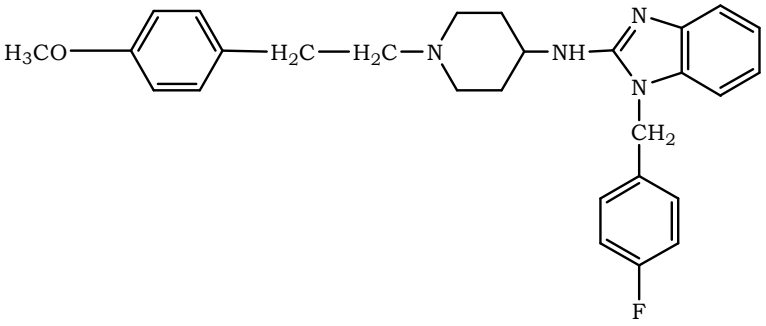
Cetirizine



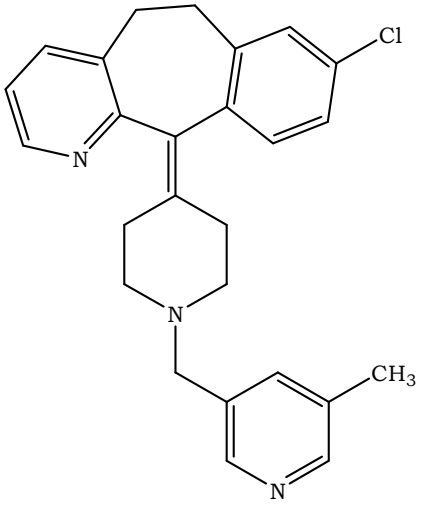
Terfenadine



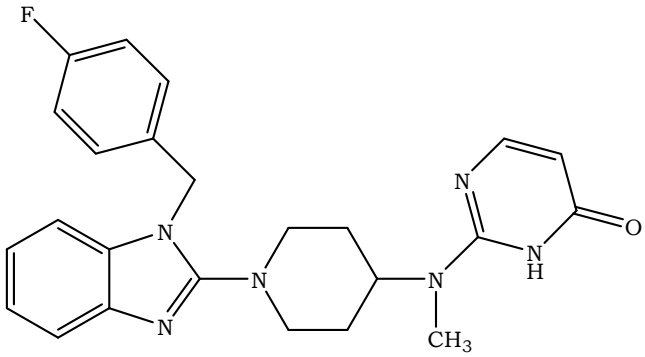
Astemizole



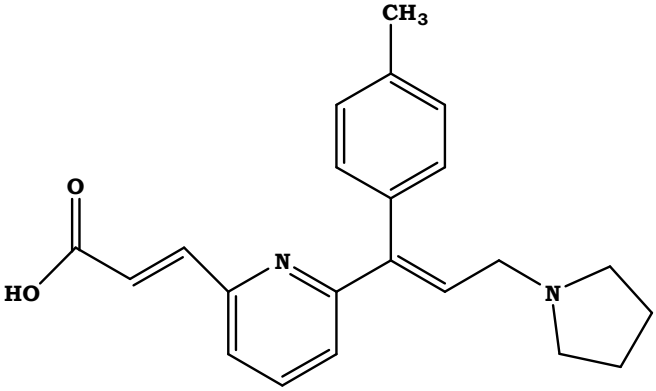
Rupatadine



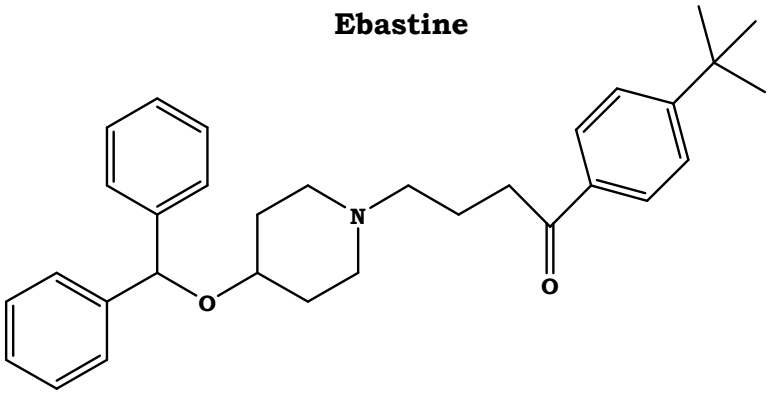
Mizolastine



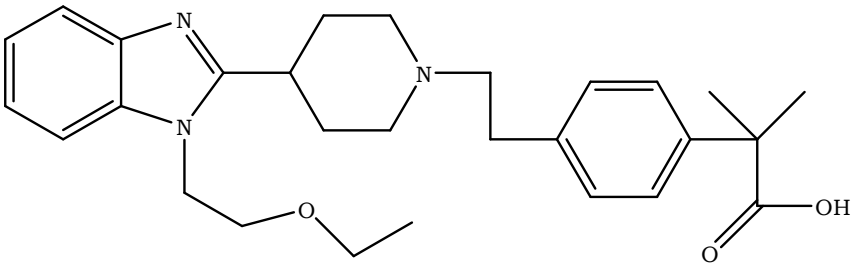
Acrivastine



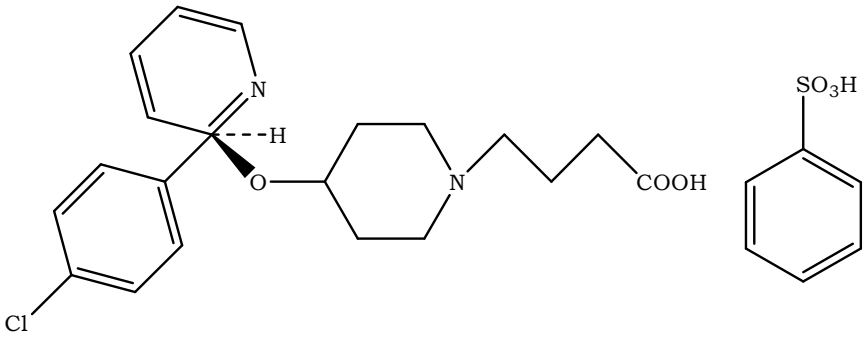
Ebastine



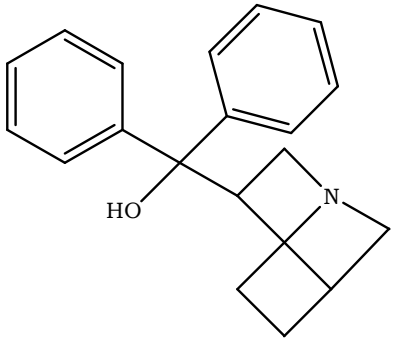
Bilastine



Bepotastine besilate

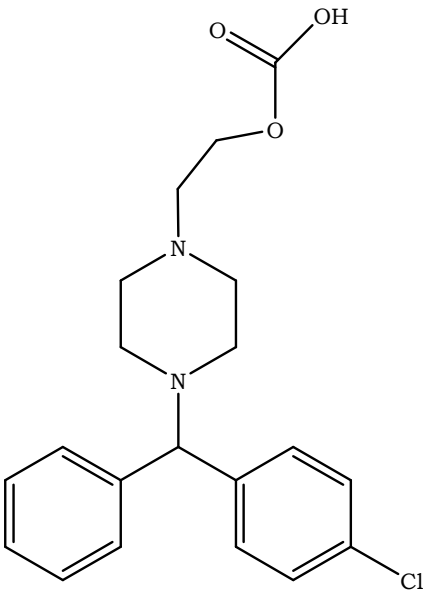


Quifinadine

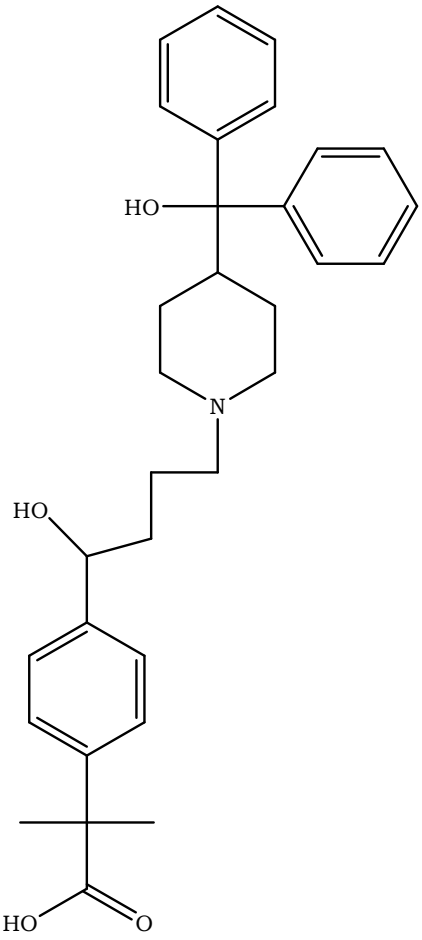


3) Third gereration H_1 antihistamines

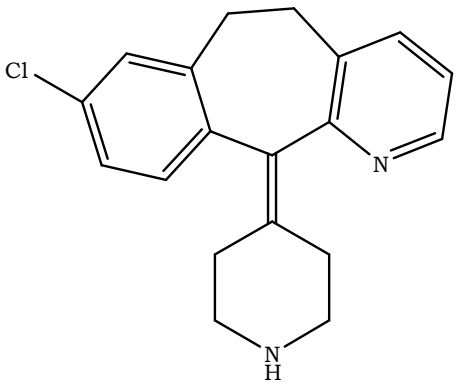
Levocetrizine



Fexofenadine

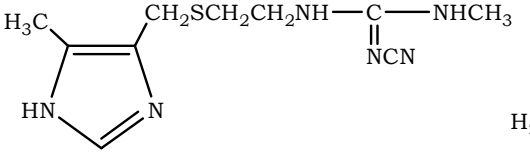


Desloratadine

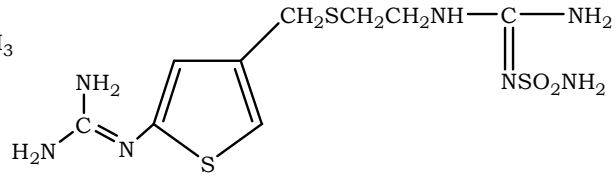


II. H_2 receptor antagonists

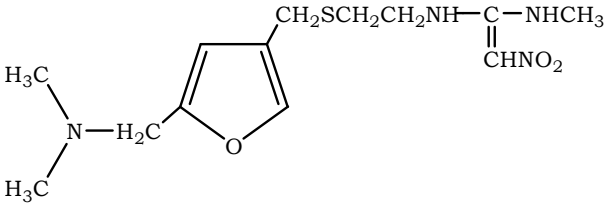
Cimetidine



Famotidine

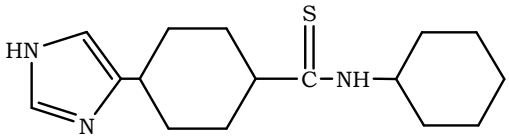


Ranitidine

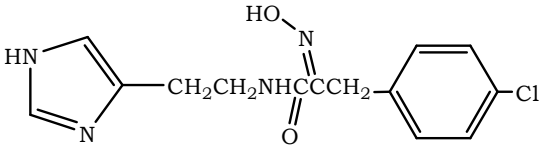


III. H_3 receptor antagonists

Thioperamide



Verongamine



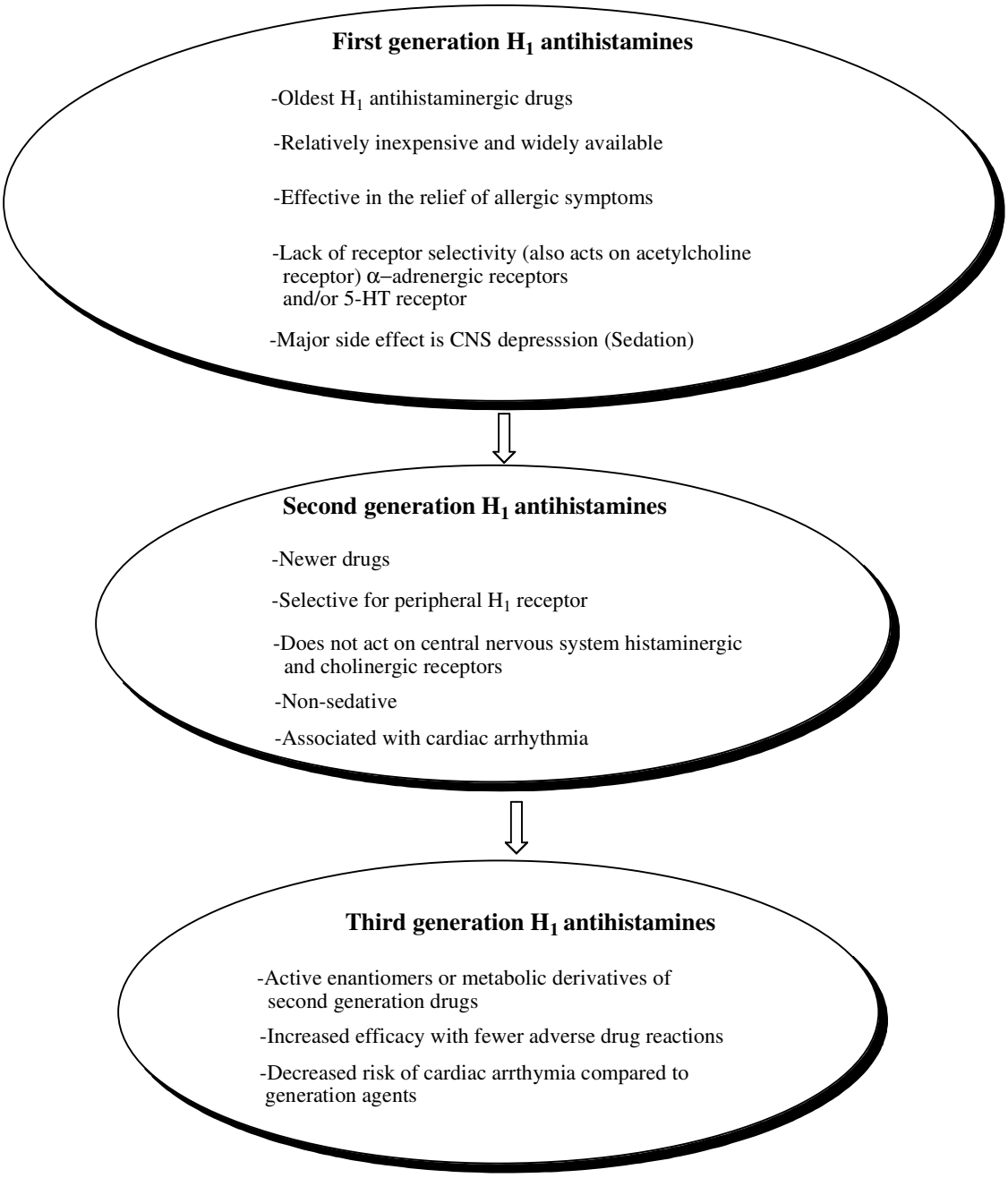


Figure 2: Development of Antihistamines