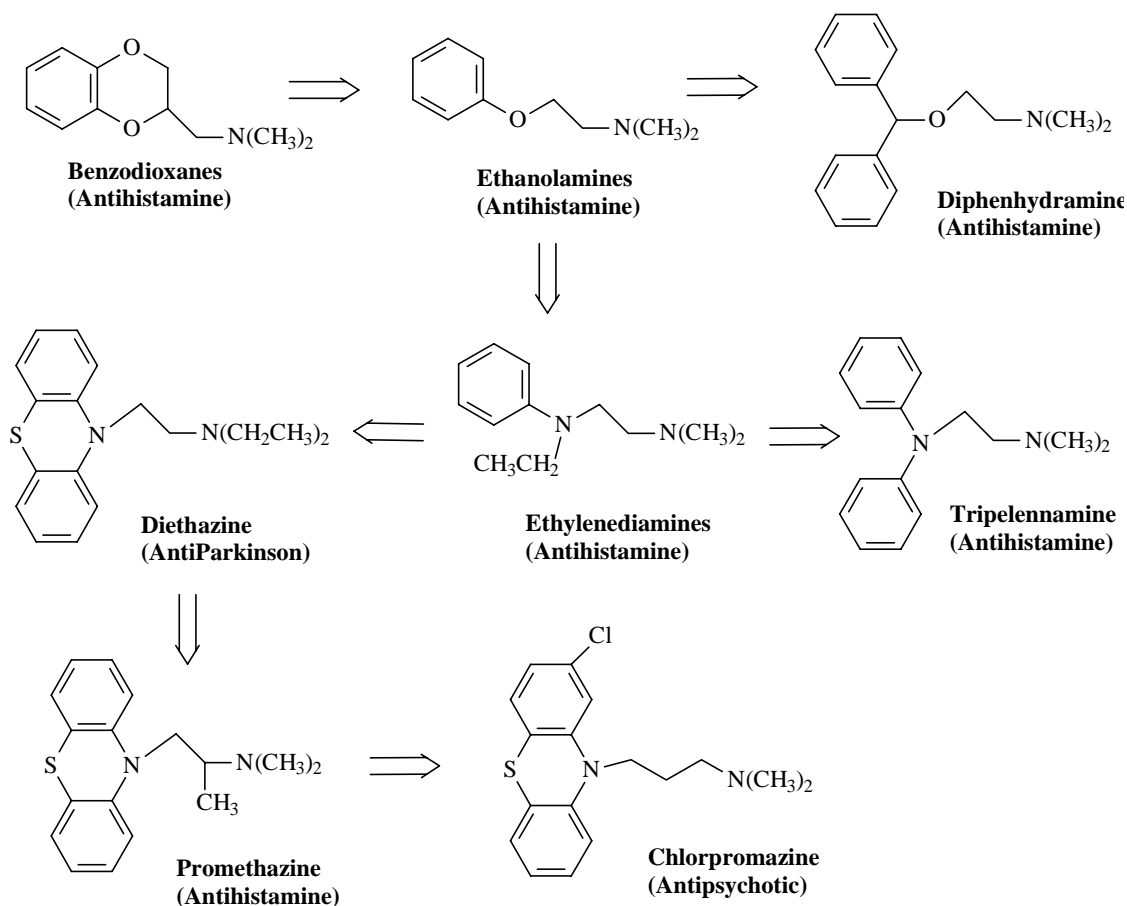


HISTAMINE H₁-RECEPTOR ANTAGONISTS: ANTIHISTAMINIC AGENTS

I. INTRODUCTION

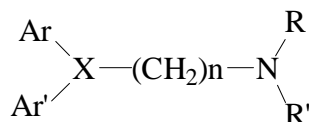
The term antihistamine historically has referred to drugs that antagonize the actions of histamine at H₁-receptors rather than H₂-receptors. The development of antihistamine drugs began more than 5 decades ago with the discovery that piperoxan was able to protect animals from the bronchial spasm induced by histamine. This finding was followed by the synthesis of a number of N-phenylethylenediamines with antihistaminic activities superior to piperoxan. Further traditional structure-activity studies in this series based largely on the principles of isosterism and functional group modification led to the introduction in the 1940s to 1970s of a variety of H₁-antagonists containing the diarylalkylamine framework. These H₁-antagonists, referred to now as the first generation or classical antihistamines, are related structurally and include a number of aminoalkyl ethers, ethylenediamines, piperazines, propylamines, phenothiazines and dibenzocycloheptenes. In addition to H₁-receptor antagonism, these compounds display an array of other pharmacological activities which contribute toward therapeutic applications and adverse reactions. More recently, a number of second generation or “non-sedating” antihistamines have been developed and introduced. The second generation agents bear some structural resemblance to the first generation agents, but have been modified to be more specific in action and limited in their distribution profiles.



II. MECHANISM OF ACTION AND GENERAL STRUCTURE-ACTIVITY RELATIONSHIPS

H₁-antagonists may be defined as those drugs that competitively inhibit the action of histamine on tissues containing H₁-receptors. The structural features required for effective interaction with these receptors is discussed below. It should be noted that some H₁-antagonists also block histamine release. However the concentrations required to do so are considerably greater than those required to produce significant histamine receptor blockade. The H₁-antagonists do not block antibody production or antigen-antibody interactions.

The H₁-antagonists are now commonly subdivided into two broad groups - the first generation or classical antihistamines and the second generation or “non-sedating” antihistamines - based primarily on their general pharmacological profiles. The differences between these two series are discussed in more detail in the sections that follow. It is important to note, however, that most detailed structure-activity analyses for H₁-antagonists that have been published focus on the structural requirements for the first generation agents. From these studies the basic structural requirements for H₁-receptor antagonism have been identified as shown below:



- Ar is aryl (including phenyl, substituted phenyl, and heteroaryl groups such as 2-pyridyl), Ar' is a second aryl or arylmethyl group. This diaryl substitution pattern is present in both the first and second generation antihistamines and is essential for significant H₁-receptor affinity. Furthermore several SAR studies suggest that the two aryl moieties must be capable of adopting a non-coplanar conformation relative to each other for optimal interaction with the H₁-receptor. The two aromatic systems may be linked as in the tricyclic antihistamines (phenothiazines, dibenzocycloheptanes and heptenes, etc.), but again they must be non-coplanar for effective receptor interaction. Most H₁-antagonists contain substituents in one of the aryl rings (usually benzene), and these influence antihistamine potency, as well as biodisposition as is discussed for individual classes of compounds in the sections that follow.
- A basic, terminal amine function which in many of the first generation or classical antihistamines the terminal nitrogen atom is a simple dimethylamino moiety. However, the amine may also be part of a heterocyclic structure, as illustrated by the piperazine, some propylamines (pyrrolidines and piperdines), some phenothiazines, the dibenzocycloheptenes and the second generation antihistamines. In all cases the amino moiety is basic with pK_as ranging from 8.5 to 10 and thus presumed to be protonated when bound on the receptor. The moiety is also important in the development of stable, solid dosage forms through salt formation.
- X is a connecting atom of O, C or N. The X connecting moiety of typical H₁-antagonists may be a saturated carbon-oxygen moiety or simply a carbon or nitrogen atom. This group, along with the carbon chain appear (see below) to serve primarily as a spacer group for the key pharmacophoric moieties. Many of the antihistamines containing a carbon atom in the connecting moiety are chiral, and exhibit stereoselective receptor binding. For example, in the pheniramine

series and carbinoxamine, this atom is chiral and in vitro analyses indicate that those enantiomers with the S-configuration have higher H₁-receptor affinity.

- The (CH₂)_n group represents a carbon chain which in typical H₁-antagonists consists of two or three atoms. The (CH₂)_n group and connecting atom results in a distance between the central point of the diaryl ring system and the terminal nitrogen atom in the extended conformation of the antihistamines ranging from 5 to 6 angstroms (a "spacer" group). A similar distance between these key moieties is observed for those antihistamines with less conformational freedom. In some series branching of the carbon chain results in a reduction of antihistaminic activity. However, there are exceptions as evidence by promethazine which has a greater activity than its nonbranched counterpart. When the carbon adjacent to the terminal nitrogen atom is branched, the possibility of asymmetry exists. However, stereoselective H₁-receptor antagonism typically is not observed when chirality exists at this site. Also, in those compounds which possess an asymmetrically substituted unsaturated carbon chain (pyrrobutamine and triprolidine), one geometric isomer typically displays higher receptor affinity than the other.

Generally, the first and second generation antihistamines are substantially more lipophilic than the endogenous agonist histamine (or the H₂-antagonists). This lipophilicity difference results primarily from the presence of the two aryl rings, and the substituted amino moieties, and thus may simply reflect the different structural requirements for antagonist versus agonist action at H₁-receptors.

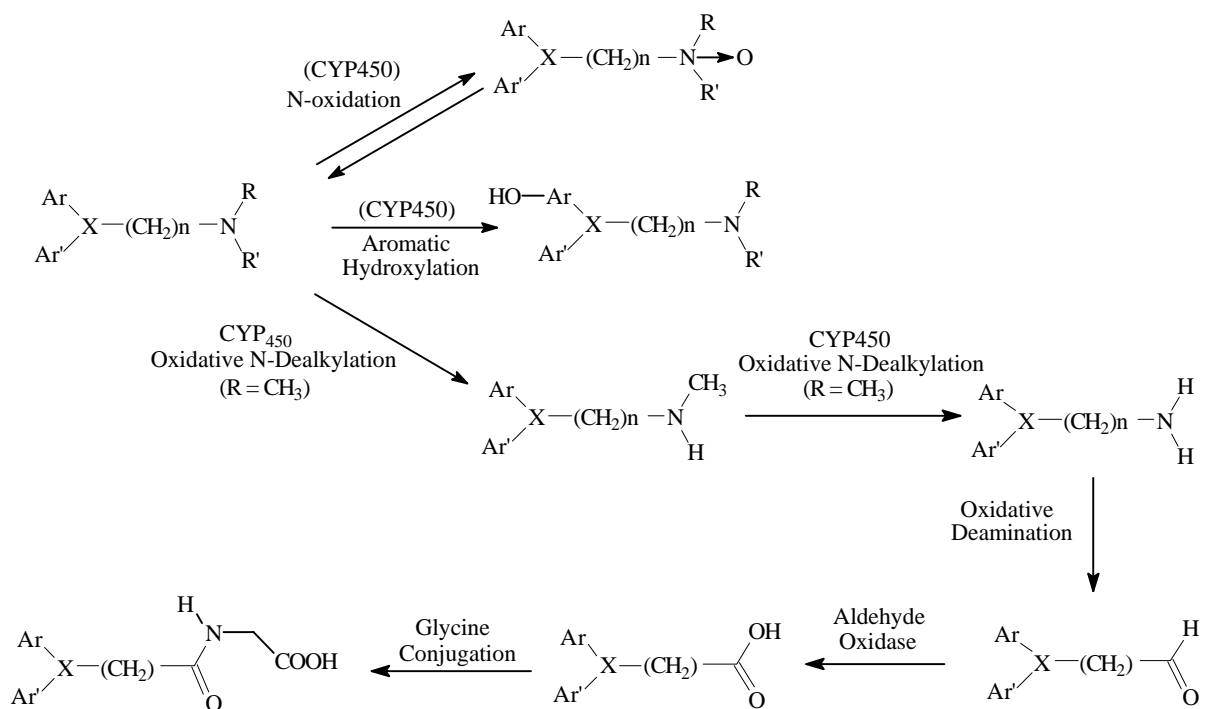
The nature of the connecting moiety and the structural nature of the aryl moieties have been used to classify the antihistamines as indicated in the sections that follow. Furthermore variations in the diaryl groups, X connecting moieties and the nature of substitution in the alkyl side chain or terminal nitrogen among the various drugs accounts for differences observed in antagonist potency as well as pharmacologic, biodisposition and adverse reaction profiles. The ability of these drugs to display an array of pharmacologic activities is due largely to the fact that they contain the basic pharmacophore required for binding to muscarinic as well as adrenergic, serotonergic receptors. The relationships of antihistamine structure to these overlapping actions (H₁-antagonist, anticholinergic, and local anesthetic) are described below.

III. GENERAL PHARMACOLOGIC CONSIDERATIONS

- Antihistaminic Action: The classical antihistamines have been used extensively for the symptomatic treatment (sneezing, rhinorrhea, and itching of eyes, nose, and throat) of allergic rhinitis (hay fever, pollinosis), chronic idiopathic urticaria and a number of other histamine-related diseases. These uses are clearly attributable to their antagonism of the action of histamine at peripheral H₁ receptors. Although the symptoms of the common cold might be modified by antihistamines, these agents do not prevent or cure colds nor do they shorten the course of the disease.²³ The antihistamines also are of little or no value in diseases such as systemic anaphylaxis and bronchial asthma, in which autacoids other than histamine are important.¹⁸
- Other Therapeutic Actions: A number of the antihistamines, particularly the phenothiazines and aminoalkyl ethers, have antiemetic actions and thus may be useful in the treatment of nausea, vomiting and motion sickness. Those agents which produce pronounced sedation have

applications as nonprescription sleeping aids. Several of the phenothiazines have limited utility in Parkinson-like syndromes as a result of their ability to block central muscarinic receptors. A number of antihistamines including promethazine, pyrilamine, tripeleennamine and diphenhydramine display local anesthetic activity that may be therapeutically useful.

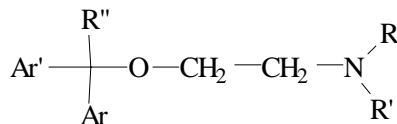
- As the general pharmacologic profiles above suggest, the majority of antihistamines are capable of interaction with a variety of neurotransmitter receptors and other biomacromolecular targets. This is most evident among the first generation agents many of which function as antagonists at muscarinic receptors and, to a lesser extent, adrenergic, serotonergic and dopamine receptors. While some of these non-target receptor interactions may be of some therapeutic value (as discussed above), more frequently they are manifested as adverse reactions that limit drug use. This is particularly true of the peripheral anticholinergic effects produced by these drugs, and interactions with a number of neurotransmitter systems in the CNS that result in sedation, fatigue and dizziness.
- The primary objective of antihistamine research over the past 20 years has centered on development of new drugs with higher selectivity for H₁-receptors and lacking undesirable CNS actions. The pronounced sedative effects of some of the first generation agents were thought to result from the ability of these drugs to penetrate the blood-brain barrier, due to their lipophilic nature, and then block cerebral H₁-receptors and possibly other receptors.¹⁶ Thus research efforts were initiated to design novel antihistamines with reduced ability to penetrate the CNS and decreased affinity for central histamine receptors. These efforts led to the introduction the second generation antihistamines which are non-sedating and have little antagonist activity at other neurotransmitter receptors at therapeutic concentrations The pharmacologic properties of these agents are discussed in more detail later in this chapter.
- Surprisingly little information is available concerning the pharmacokinetic and biodisposition profiles of the first generation antihistamines. Generally the compounds are orally active and well absorbed, but oral bioavailability may be limited by first pass metabolism. The metabolites formed depend on drug structure to a large extent, but commonly involve the tertiary amino moiety. This functionality may be subject to successive oxidative N-dealkylation, deamination, and amino acid conjugation of the resultant acid. The amine group may also undergo N-oxidation, which may be reversible, or direct glucuronide conjugation. Those first generation agents with unsubstituted and activated aromatic rings (phenothiazines) may undergo aromatic hydroxylation to yield phenols, which may be eliminated as conjugates.
- The H₁-antagonists display a variety of significant drug interactions when co-administered with other therapeutic agents. For example, monoamine oxidase inhibitors prolong and intensify the anticholinergic actions of the antihistamines. Also, the sedative effects of these agents may potentiate the depressant activity of barbiturates, alcohol, narcotic analgesics and other depressants. In recent years it has been discovered that several of the second generation antihistamines may produce life-threatening arrhythmias when coadministered with drugs that inhibit their metabolism. These interactions are discussed in more detail in the sections that follow.



IV. FIRST GENERATION H_1 -ANTAGONIST DRUG CLASSES

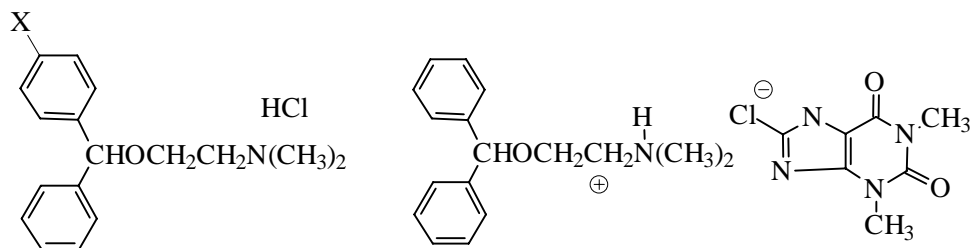
A. Aminoalkyl Ethers (Ethanamines):

- The aminoalkyl ether antihistamines are characterized by the presence of a CHO connecting moiety (X) and a two or three carbon atom chain as the linking moiety between the key diaryl and tertiary amino groups. Clemastine and diphenylpyraline (see structures below) differ from this basic structural pattern in that the basic nitrogen moiety and at least part of the carbon chain is part of a heterocyclic ring system, and that there are three carbon atoms between the oxygen and nitrogen atoms.



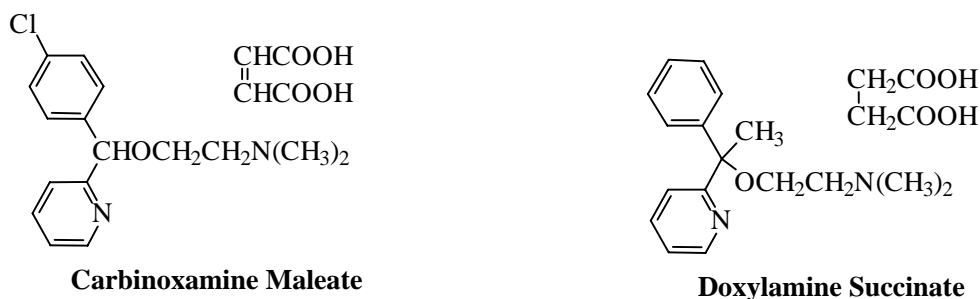
General Structure

- The simple diphenyl derivative diphenhydramine was the first clinically useful member of the ethanolamine series and serves as the prototype. In addition to antihistaminic action, diphenhydramine exhibits anticholinergic, antidyskinetic, antiemetic, antitussive, and sedative properties. Diphenhydramine is not a highly active H_1 -antagonist. Conversion to a quaternary ammonium salt does not alter the antihistaminic action greatly, but does increase the anticholinergic action. Dimenhydrinate is the 8-chlorotheophyllinate (theoclate) salt of diphenhydramine and is recommended for the nausea of motion sickness and for hyperemesis gravidarum (nausea of pregnancy).

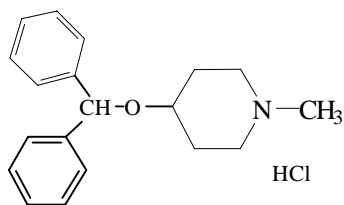


X = H: Diphenhydramine HCl
X = Br: Bromodiphenhydramine HCl

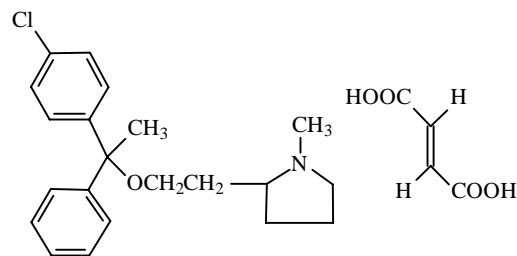
- Other therapeutically useful derivatives of diphenhydramine have been obtained by para substitution of methyl (methyldiphenhydramine), methoxy (medrylamine), chloro (chlorodiphenhydramine) or bromo (bromodiphenhydramine) of one of the phenyl rings. These derivatives are reported to have superior therapeutic profiles relative to diphenhydramine as a result of reduced side effects. For example, bromodiphenhydramine is more lipid-soluble and is twice as effective as diphenhydramine as an antihistamine
- Replacement of the one of the phenyl rings of the diphenhydramine with a 2-pyridyl group as in doxylamine and carbinoxamine results in an enhancement antihistaminic activity of 40 and 2 times greater, respectively, than diphenhydramine. Doxylamine succinate is a good nighttime hypnotic when compared with secobarbital.



- As a result of an asymmetrically substituted benzylic carbon, many of the aminoalkyl ethers are optically active. Most studies indicate that the individual enantiomers differ significantly in antihistaminic activity, with activity residing predominantly in the S-enantiomer.²¹
- Diphenylpyraline is structurally related to diphenhydramine with the aminoalkyl side chain incorporated in a piperidine ring. It is a potent antihistaminic, and the usual dose is 2 mg three or four times daily. Clemastine Fumarate is structurally related to chlorodiphenhydramine with the aminoalkyl side chain incorporated in a pyrrolidine ring, and it has an additional benzylic methyl group. This compound has two chiral centers, each of which is of the (R) absolute configuration in the dextrorotatory product. A comparison of the activities of the antipodes indicates that the asymmetric center close to the side chain nitrogen is of lesser importance to antihistaminic activity. This member of the ethanolamine series is characterized by a long duration of action, with an activity that reaches a maximum in five to seven hours and persists for 10 to 12 hours (see Table).



Diphenylpyraline HCl

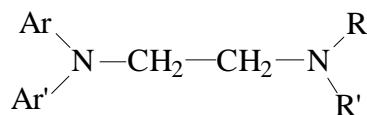


Clemastine Fumarate

- Drowsiness is a side effect common to the tertiary aminoalkyl ethers, presumably as a result of the ability of these compounds to penetrate and BBB and occupy central H₁-receptors. Although this side effect is exploited in over-the-counter (OTC) sleeping aids, it may interfere with the patient's performance of tasks requiring mental alertness.
- The diaryl tertiary aminoalkyl ether structure that characterizes these compounds also serves as a pharmacophore for muscarinic receptors. As a result the drugs in this group possess significant anticholinergic activity, which may enhance the H₁-blocking action on exocrine secretions.
- The frequency of gastrointestinal side effects in this series of antihistamines is relatively low compared to the ethylenediamine antihistamines covered later.
- In spite of their extensive use, pharmacokinetic data on this series of compounds is relatively limited. Most members of this series appear to be extensively metabolized by pathways including N-oxidation, and successive oxidative N-dealkylation followed by amino acid conjugation of the resultant acid metabolites.

B. Ethylenediamines:

The ethylenediamines were among the first useful antihistamines and are characterized by the presence of a nitrogen connecting atom (X) and a two carbon atom chain as the linking moiety between the key diaryl and tertiary amino moieties as shown below. All compounds in this series are simple diarylethylenediamines except for antazoline in which the terminal amine and a portion of the carbon chain are included as part of an imidazoline ring system. Because it differs significantly in its pharmacologic profile, antazoline is not always classified as an ethylenediamine derivative.

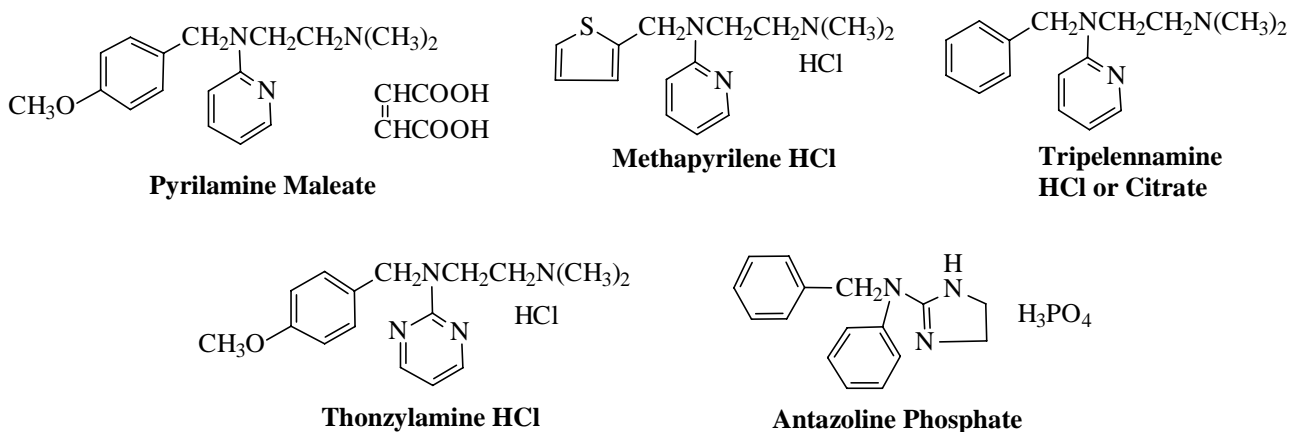


General Structure

- Phenbenzamine was the first clinically useful member of this class and served as the prototype for the development of more effective derivatives. Replacement of the phenyl moiety of phenbenzamine with a 2-pyridyl system yielded tripeleminamine, a significantly more effective

histamine receptor blocker. Substitution of a para methoxy (pyrilamine or mepyramine), chloro (chloropyramine) or bromo (bromtripelennamine) results in a further enhancement in activity.

- Replacement of the benzyl group of tripeleennamine with a 2-thienylmethyl group provided methapyrilene, and replacement of tripeleennamine's 2-pyridyl group with a pyrimidinyl moiety (along with p-methoxy substitution) yielded thonzylamine, both which function as potent H₁-receptor antagonists.

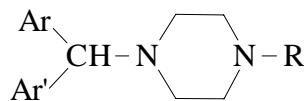


- In all of these compounds the aliphatic or terminal amino group is significantly more basic than the nitrogen atom bonded to the diaryl moiety; the non-bonded electrons on the diaryl nitrogen are delocalized by the aromatic ring and the resultant reduction in electron density on nitrogen decreases basicity. Thus the aliphatic amino group in the ethylenediamines is sufficiently basic for the formation of pharmaceutically useful salts.
- The ethylenediamines also display a relatively high frequency of central nervous system depressant (sedation) and gastrointestinal side effects. The anticholinergic and antiemetic actions of these compounds is relatively low compared to most other classical antihistamines. The piperazine and phenothiazine-type antihistamines also contain the ethylenediamine moiety, but these agents are discussed separately because they exhibit significantly different pharmacologic properties.
- Relatively little information is available concerning the pharmacokinetics of this series of compounds. Tripeleennamine is known to be metabolized in man by N-glucuronidation, N-oxidation and pyridyl oxidation followed by phenol glucuronidation. It is anticipated that other members of this series are similarly metabolized.

C. Piperazines (Cyclizines):

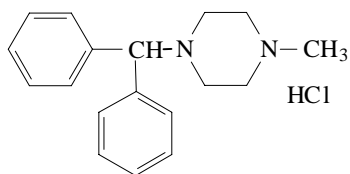
The piperazines or cyclizines can also be considered to be ethylenediamine derivatives or cyclic ethylenediamines (cyclizines), however in this series the connecting moiety (X) is a CHN group and the carbon chain, terminal amine functionality as well as the nitrogen atom of the connecting group are all part of a piperazine moiety as shown below. Both nitrogen atoms in these compounds are aliphatic and thus display comparable basicities. The primary structural differences within this series

involves the nature of the para aromatic ring substituent (H or Cl) and, more importantly, the nature of the terminal piperazine nitrogen substituent.

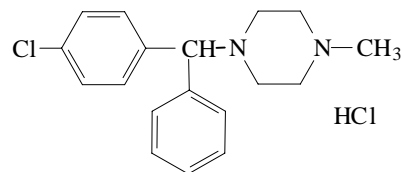


General Structure

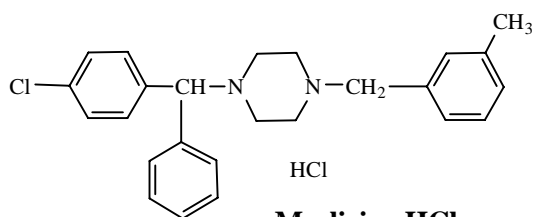
- Cyclize and chlorcyclizine are simple N-methylpiperazines. Cyclizine HCl is used primarily in the prophylaxis and treatment of motion sickness. The lactate salt (Cyclizine Lactate Injection) is used for intramuscular injection because of the limited water solubility of the hydrochloride. Chlorcyclizine HCl has an additional ring Cl substituent which **reduces** activity. Chlorcyclizine is indicated in the symptomatic relief of urticaria, hay fever, and certain other allergic conditions.



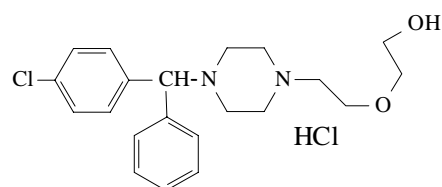
Cyclizine HCl or Lactate



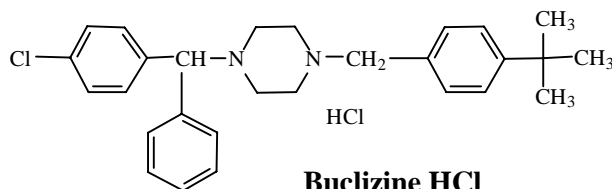
Chlorcyclizine HCl



Meclizine HCl



Hydroxyzine HCl



Buclizine HCl

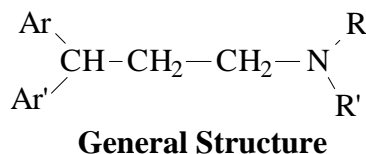
- Meclizine HCl and Buclizine HCl are N-benzyl substituted piperazines. Although it is a moderately potent antihistaminic, meclizine is used primarily as an antinauseant in the prevention and treatment of motion sickness and in the treatment of nausea and vomiting associated with vertigo and radiation sickness. Buclizine Hydrochloride, is highly lipid-soluble and has central nervous system depressant, antiemetic, and antihistaminic properties.
- The piperazines are moderately potent antihistaminics with a lower incidence of drowsiness. The activity of the piperazine-type antihistaminics is characterized by a slow onset and long duration of action. These agents exhibit peripheral and central antimuscarinic activity and this may be re-

responsible for the antiemetic (medullary chemoreceptor trigger zone) and antiverigo (diminish vestibular stimulation) effects. Thus as a group, these agents are probably more useful as antiemetics and antinauseants and in the treatment of motion sickness.

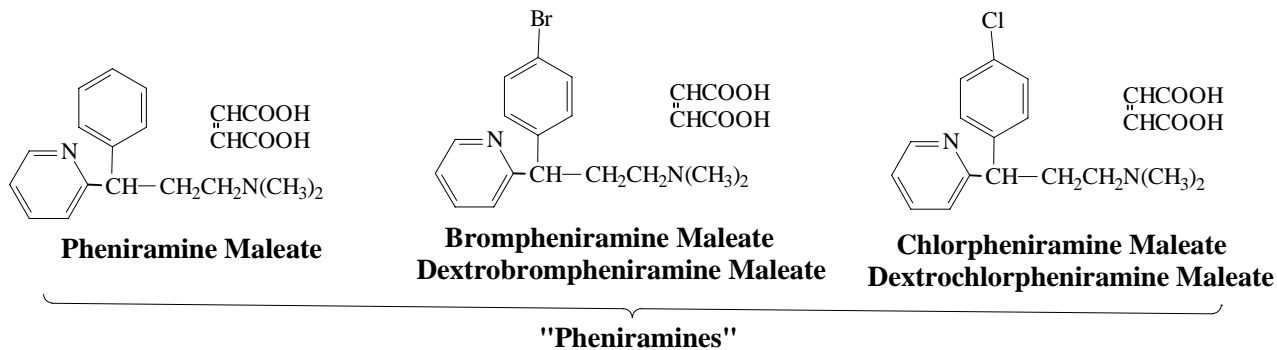
- Some members of this series have exhibited a strong teratogenic potential, inducing a number of malformations in rats. Norchlorcyclizine, a metabolite of these piperazines, was proposed to be responsible for the teratogenic effects of the parent drugs.
- Metabolic studies in this series of compounds have focused primarily on cyclizine and chlorcyclizine, and these compounds undergo similar biotransformation. The primary pathways involve N-oxidation and N-demethylation, and both of these metabolites are devoid of antihistaminic activity.

D. Propylamines (Monoaminopropyl Derivatives):

The propylamine antihistamines are characterized structurally by an sp^3 or sp^2 carbon connecting atom with a carbon chain of two additional carbons linking the key tertiary amino and diaryl pharmacophore moieties as shown below.

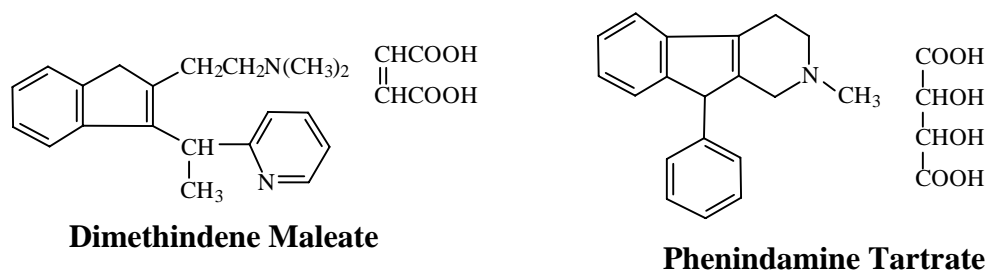
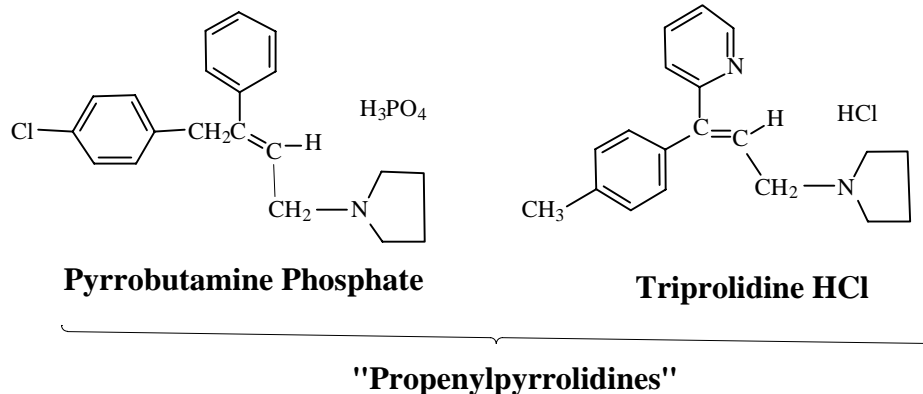


- Those propylamines with a saturated carbon connecting moiety are commonly referred to as the pheniramines. All of the pheniramines consist of a phenyl and 2-pyridyl aryl groups, and a terminal dimethylamino moiety. These compounds differ only in the phenyl substituent at the para-position; H (pheniramine), Cl (chlorpheniramine) and Br (brompheniramine). The halogenated pheniramines are significantly more potent (20-50 times) and have a longer duration of action than the parent pheniramine. All of pheniramines are chiral molecules and are marketed as racemates or the individual active dextro-enantiomers as indicated below. The halogen-substituted derivatives have been resolved by crystallization of salts formed with d-tartaric acid and antihistaminic activity resides almost exclusively in the *S*-stereoisomers.



Those propylamines with an unsaturated connecting moiety include the open derivatives pyrrobutamine and triprolidine, and the cyclic analogues dimethindene and phenindamine. The

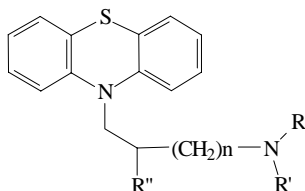
conformational rigidity of the unsaturated propylamines has provided a useful model to determine distances between the key diaryl and tertiary pharmacophoric moieties in H₁-receptor antagonists, a distance of 5-6 angstroms. For pyrrobutamine and triprolidine the E-geometric isomers (shown) are active. The relative potency of triprolidine is of the same order as that of dexchlorpheniramine. Phenindamine can be regarded as an unsaturated propylamine derivative in that the rigid ring system contains a distorted, trans alkene. Dimethindene is marketed as a racemate and its antihistaminic activity resides mainly in the levorotatory isomer.



- The antihistamines of the propylamine group are among the most active H₁-antagonists. The agents of this class also produce less sedation than the other classical antihistamines (yet a significant proportion of patients do experience this effect), and have little antiemetic action. They do, however, exhibit a significant degree of anticholinergic activity, albeit less than the aminoalkyl ethers and phenothiazines.
- In the propylamine series the pharmacokinetics of chlorpheniramine have been studied most extensively in humans. Oral bioavailability is relatively low (30-50%) and may be limited by first pass metabolism. The primary metabolites for this compound, and other members of this series, are the mono- and di-N-dealkylation products. Complete oxidation of the terminal amino moiety followed by glycine conjugation has also been reported for brompheniramine. Chlorpheniramine plasma half-lives range from about 12 hours to 28 hours, depending on the route of administration (oral versus IV).

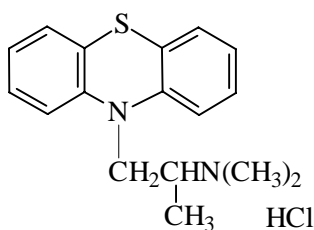
E. Phenothiazines:

Beginning in the mid-1940s, several antihistaminic drugs have been discovered as a result of bridging the aryl units of agents related to the ethylenediamines. The search for effective antimalarials led to the investigation of phenothiazine derivatives in which the bridging entity is sulfur as shown below. In subsequent testing, the phenothiazine class of drugs was discovered to have not only antihistaminic activity, but also a pharmacologic profile of its own, considerably different from that of the ethylenediamines. Thus began the era of the useful psychotherapeutic agent.

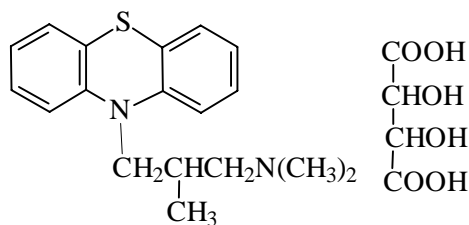


General Structure

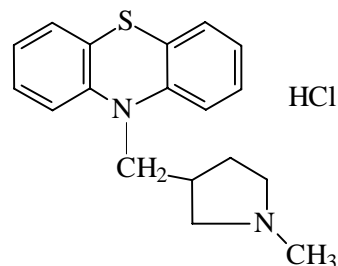
The phenothiazine derivatives that display therapeutically useful antihistaminic actions contain a two or three carbon atom, branched alkyl chain between the ring system and terminal nitrogen atom. This differs significantly from the phenothiazine antipsychotic series in which an unbranched propyl chain is required. The phenothiazines with a three carbon bridge between nitrogen atoms are more potent *in vitro*. Also, unlike the phenothiazine antipsychotics, the heterocyclic ring of the antihistamines is unsubstituted.



Promethazine HCl



Trimeprazine Tartrate



Methdilazine HCl

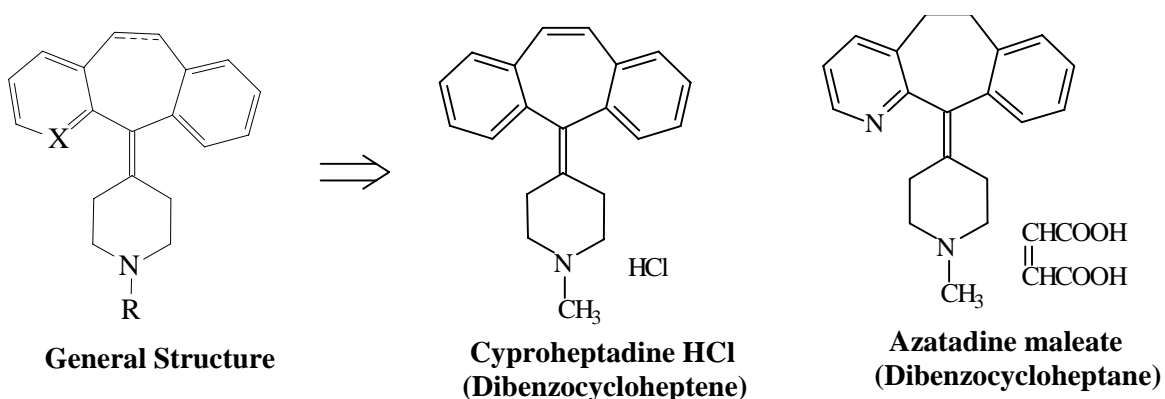
- Promethazine, the parent member of this series, is moderately potent by present-day standards with prolonged action and pronounced sedative side effects. In addition to its antihistaminic action, it is a potent antiemetic, anticholinergic and sedating agent, and significantly potentiates the action of analgesic and sedative drugs.²³ The other members of this series display a similar pharmacologic profile and thus may cause drowsiness and so may impair the ability to perform tasks requiring alertness. Also concurrent administration of alcoholic beverages and other central nervous system depressants with the phenothiazines should be avoided. In general, lengthening of the side chain and substitution of lipophilic groups in the 2-position of the aromatic ring results in compounds with decreased antihistaminic activity and increased psychotherapeutic properties.
- The enantiomers of promethazine have been resolved and have similar antihistaminic and other pharmacologic properties as described below.³³ This is in contrast with studies of the pheniramines and carbinoxamine compounds in which the chiral center is closer to the aromatic

feature of the molecule. Asymmetry appears to be of less influence on antihistaminic activity when the chiral center lies near the positively charged side chain nitrogen.

- While little pharmacokinetic data is available for the phenothiazine antihistamines, the metabolism of the close structural analogue promethazine has been studied in detail.²² This compound undergoes mono and di-N-dealkylation, sulfur oxidation, aromatic oxidation at the 3-position to yield the phenol and N-oxidation. A number of these metabolites, particularly the phenol, may yield glucuronide conjugates. It is expected that the phenothiazine antihistamines would display similar metabolic profiles.

F. Dibenzocycloheptenes/heptanes:

The dibenzocycloheptene and heptane antihistamines may be regarded as phenothiazine analogues in which the sulfur atom has been replaced by an isosteric vinyl group (cyproheptadine) or a saturated ethyl bridge (azatadine), and the ring nitrogen replaced by an sp^2 carbon atom as shown below. The two members of this series are closely related in structure; azatadine is an aza (pyridyl) isostere of cyproheptadine in which the 10,11-double bond is reduced.



- Cyproheptadine HCl possesses both an antihistamine and an antiserotonin activity and is used as an antipruritic agent. Sedation is the most prominent side effect, and this is usually brief, disappearing after three or four days of treatment.
- Azatadine maleate: A potent, long-acting antihistaminic with antiserotonin activity.

V. SECOND GENERATION H_1 -ANTAGONIST DRUG CLASSES

A. Introduction

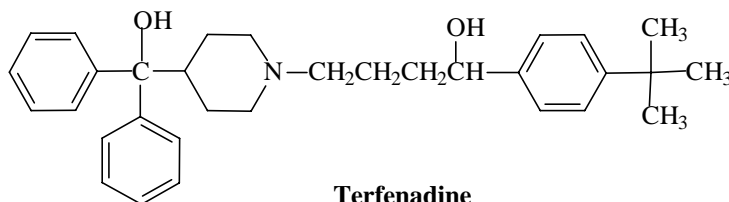
The second generation antihistamines are more similar pharmacologically than structurally. Structurally they are all diaryl substituted piperazines (cetirizine) or piperidines (all others). As discussed earlier in this chapter, these compounds were developed as selective H_1 -receptor antagonists with relatively high potency. Most of these compounds also produce prolonged antihistaminic effects as a result of slow dissociation from H_1 -receptors, and the formation of active metabolites with similar receptor binding profiles. The second generation agents have little affinity

for muscarinic, adrenergic or serotonergic receptors and therefore display a lower degree of side effects associated with antagonism at these receptors, but their affinities for these receptors is somewhat variable as indicated below. Generally, the large aralkyl groups or polar groups linked to the piperidine/piperazine rings of these compounds reduces their affinity for muscarinic or adrenergic receptors.

Perhaps most importantly, all of these compounds are devoid of sedating effects at therapeutic concentrations due to poor CNS penetration, and possibly lowered affinities for central histaminic, cholinergic and adrenergic receptors. While these compounds offer several advantages over the classical antihistamines, widespread use has revealed a number of therapeutic limitations. This is probably most true for terfenadine and astemizole (since withdrawn) which have been found to produce life-threatening arrhythmias when used concurrently with drugs that inhibit their metabolism. These drug interactions have been most evident with the imidazole antifungals ketoconazole, itraconazole and fluconazole, and the macrolides erythromycin, clarithromycin and troleandomycin which inhibit the metabolism of terfenadine and astemizole, resulting in elevated levels of the parent drugs which are proarrhythmic. This adverse is evident by prolongation of QTc intervals

B. Piperidine Second Generation Antihistamines

1. Terfenadine. Alpha-[4-(1,1-Dimethylethyl)phenyl] -4-(hydroxydiphenylmethyl)-1-piperidinebutanol (*Seldane*[®]) is a reduced butyrophenone derivative of an aminoalcohol-type antihistaminic. Terfenadine was developed during a search for new butyrophenone antipsychotic drugs as evident by the presence of the N-phenylbutanol substituent. It also contains a diphenylmethylpiperidine moiety analogous to that found in the piperazine antihistamines. Terfenadine is a selective, long-acting (>12 hours) H₁-antagonist with little affinity for muscarinic, serotonergic or adrenergic receptors (SEE Table at the end of this chapter). The histamine receptor affinity of this compound are believed to be related primarily to the presence of the diphenylmethylpiperidine moiety. The prolonged action results from very slow dissociation from these receptors. The lack of anticholinergic, adrenergic or serotonergic actions appears to be linked to the presence of the N-phenylbutanol substituent. This substituent also limits distribution of terfenadine to the CNS.

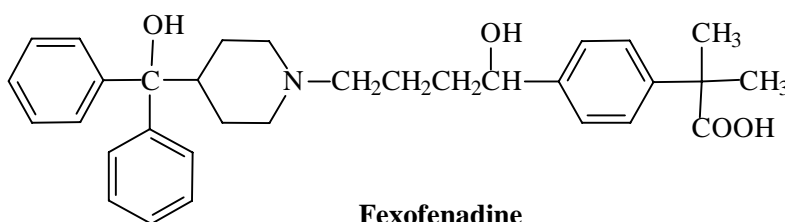


Terfenadine is rapidly absorbed producing peak plasma levels in 1-2 hours. The drug undergoes significant first pass metabolism with the predominant metabolite being fexofenadine, an active metabolite resulting from methyl group oxidation. When drugs that inhibit this transformation, such as the imidazole antifungals and marolides, are used concurrently, terfenadine levels may rise to toxic levels, resulting in potentially fatal heart rhythm problems. This resulted in withdrawal of this drug product! Terfenadine is highly plasma protein bound (97%) and has a half-life of about 20

hours. Terfenadine is widely distributed in peripheral tissues, with highest concentrations in the liver. The major route of elimination of terfenadine and its metabolites is in the feces and elimination is biphasic. The mean elimination half-life is 16-23 hours.¹⁸

2. Fexofenadine Hydrochloride. (+/-)-4-[1-hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperinyl]-butyl- α,α -dimethylbenzeneacetic acid (Allegra[®]). This compound is marketed as a racemate and exists as a zwitterion in aqueous media at physiological pH.

Fexofenadine is a primary metabolite of terfenadine. It was developed based on studies that revealed when terfenadine's hepatic conversion to the fexofenadine was blocked by other drugs or disease, levels of the parent drug (terfenadine) rise resulting in heart rhythm problems. Subsequent clinical trials demonstrated that fexofenadine was not only active and effective in allergic disorders, but less cardiotoxic than terfenadine. This led to the approval of fexofenadine as an alternative to relieve the symptoms of seasonal allergies.

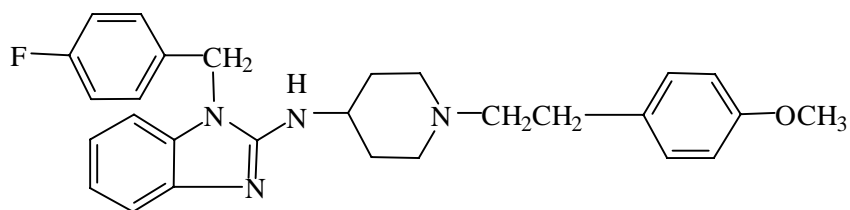


Fexofenadine is a selective peripheral H₁-receptor blocker that, like terfenadine, produces no clinically significant anticholinergic effects or α_1 -adrenergic receptor blockade at therapeutic doses (SEE Table at the end of this Chapter). The lack of anticholinergic, adrenergic or serotonergic actions appears to be linked to the presence of the N-phenylbutanol substituent which limits binding to these receptors. No sedative or other CNS effects have been reported for this drug and animal studies indicate that fexofenadine does not cross the blood-brain barrier. In vitro studies also suggest that, unlike terfenadine, fexofenadine does not block potassium channels in cardiocytes. Furthermore in drug interaction studies no prolongation of the QTc interval or related heart rhythm abnormalities were detected when administered concurrently with erythromycin or ketoconazole.

Fexofenadine is rapidly absorbed after oral administration producing peak serum concentrations in about 2.5 hours. Fexofenadine is 60-70% plasma protein bound. Unlike its parent drug, only 5% of the total dose of fexofenadine is metabolized. The remainder is excreted in the bile and urine and the mean elimination half-life is about 14 hours.

3. Astemizole, USP. 1-(4-Fluorobenzyl)-2-((1-(4-methoxyphenyl)-4-piperidyl)amino)benzimidazole (Hismanal[®]). Astemizole was developed from a series of diphenylbutylpiperidine antihistamines in an effort to extend the duration of action.^{16,39} During development it was discovered that this compound produced little sedation or autonomic side effect. Astemizole is a selective and long-acting H₁-antagonist with little affinity for muscarinic, serotonergic, adrenergic receptors or H₂-receptors. Generally, both the diaryl system and large aralkyl group linked to the piperidine nitrogen appears to reduce its affinity for muscarinic or adrenergic receptors. The piperidino-aminobenzimidazole moiety appears to be required for H₁-receptor affinity, and contributes

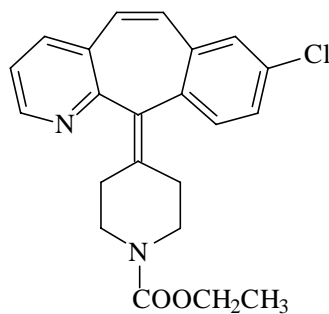
significantly to the persistent receptor binding that results in prolonged action. Astemizole is more potent and longer acting than terfenadine. It does not penetrate the CNS readily, thus sedation and other CNS side effects (dizziness, drowsiness, fatigue) are minimal. Astemizole also has no local anesthetic actions. It is used for seasonal allergic rhinitis and chronic urticaria. It has a slow onset of action (2 to 3 days).



Astemizole

Astemizole is rapidly and completely absorbed orally and should be administered 1 hour before meals. Peak plasma levels are observed within 1-4 hours. Astemizole is widely distributed in peripheral tissues, with highest concentrations attained in the liver, pancreas and adrenal glands. It undergoes extensive first pass metabolism by processes including aromatic hydroxylation, oxidative dealkylation and glucuronidation. The main metabolites are desmethylastemizole, 6-hydroxy desmethylastemizole and norastemizole. The desmethyl metabolite has antihistaminic activity comparable to the parent drug, and thus contributes to the prolonged duration of action. Astemizole is highly protein bound (96%) and has a plasma half-life of 1.6 days. The apparent half-life of the desmethyl metabolite ranges from 10-20 days, depending on frequency of dosing of the parent drug. The primary route of elimination is in the feces.¹⁶

4. Loratadine, USP. 4-(8-chloro-5,6-dihydro-11H-benzo[5,6]-cyclohepta[1,2-b]pyridin-11-ylidene-1-carboxylic acid ethyl ester. Loratadine is structurally related to the antihistamines azatadine and cyproheptadine. It differs from azatadine in that a neutral carbamate group has replaced the basic tertiary amino moiety, and the phenyl ring has been substituted with a chlorine atom. The replacement of the basic group with a neutral functionality is believed to preserve antihistaminic action while reducing CNS effects. Loratadine is also structurally related to a number of tricyclic antidepressants.



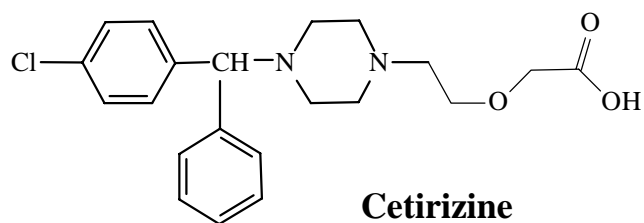
Loratadine

Loratadine is a selective peripheral H₁-antagonist with a receptor binding profile like the other members of this series, except that it has more antiserotonergic activity. Thus it produces no substantial CNS or autonomic side effects. Loratadine displays potency comparable to astemizole and greater than terfenadine.

Loratadine is rapidly absorbed after oral administration producing peak plasma levels in about 1.5 hours. This drug is extensively metabolized, primarily to the descarboethoxy metabolite which retains some antihistaminic activity. Both the parent drug and metabolite have elimination half-lives ranging from 8-15 hours. The metabolite is excreted renally as a conjugate.

C. Piperazine Second Generation Antihistamines

1. Cetirizine: [2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]acetic acid (*Zyrtec*[®]). This compound is a racemic compound. Cetirizine is the primary acid metabolite of hydroxyzine resulting from complete oxidation of the primary alcohol moiety. This compound is zwitterionic and relatively polar and thus does not penetrate the blood-brain barrier readily. Prior to its introduction in the US cetirizine was one of the most widely prescribed H₁-antihistamines in Europe. It is highly selective in its interaction with various hormonal binding sites and highly potent (» terfenadine) as well.



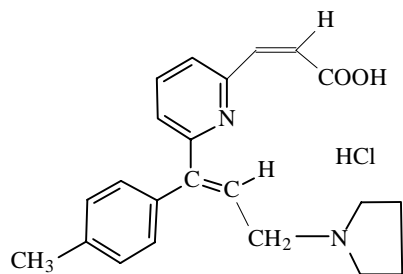
The advantages of this compound appear to be once-daily dosing, a rapid onset of activity, minimized CNS effects and a lack of clinically significant effects on cardiac rhythm when administered with imidazole antifungals and macrolide antibiotics. The onset of action is within 20 to 60 minutes in most patients. Cetirizine produces qualitatively different effects on psychomotor/psychophysical functions compared to the first generation antihistamines. However the most common adverse reaction associated with cetirizine is dose-related somnolence and thus patients should be advised that cetirizine may interfere with the performance of certain psychomotor/psychophysical activities. Other effects of this drug include fatigue, dry mouth, pharyngitis and dizziness. Because the drug is primarily eliminated by a renal route, its adverse reactions may be more pronounced in individuals suffering from renal insufficiency. No cardiotoxic effects, such as QT prolongation, are observed with the new drug when used at its recommended or higher doses or when coadministered with imidazole antifungals and macrolide antibiotics. However, other typical drug interactions of H₁-antihistamines apply to cetirizine. Concurrent use of this drug with alcohol and other CNS depressant should be avoided.

Dose proportional C_{max} values are achieved within 1 hour of oral administration of cetirizine. Food slows the rate of cetirizine absorption but does not affect the overall extent. Consistent with the polar nature of this carboxylic acid drug, less than 10% of peak plasma levels have been measured in the brain. Cetirizine is not extensively metabolized and »70% of a 10 mg oral dose is excreted in the

urine (>80% as unchanged drug) and 10% recovered in the feces. The drug is highly protein bound (93) and has a terminal half-life of 8.3 hours. The clearance of cetirizine is reduced in elderly subjects as well as in renally and hepatically impaired patients.⁴⁵

D. Pyrrolidine “Second Generation” Antihistamines

1. Acrivastine, USP. (E,E)-isomer This is fixed combination product of the antihistamine acrivastine (8 mg) with the decongestant pseudoephedrine (60 mg). Acrivastine is an analogue of triprolidine



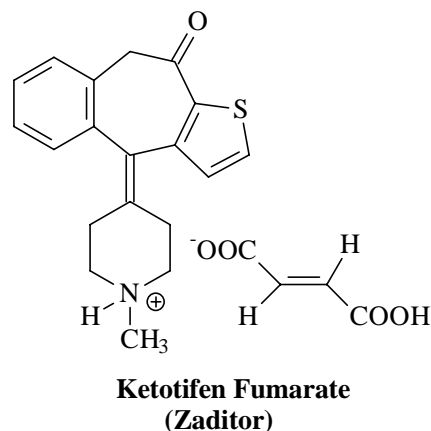
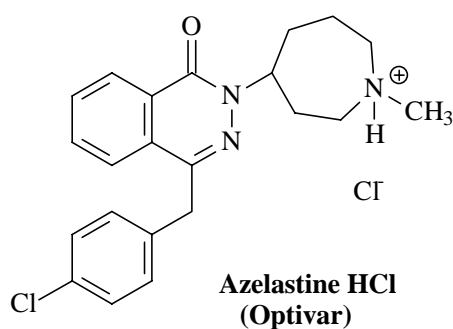
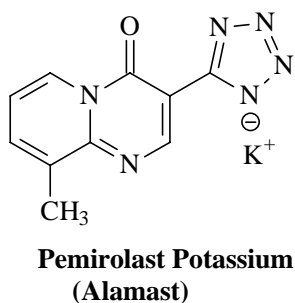
Acrivastine HCl

containing a carboxyethenyl moiety at the 6-position of the pyridyl ring. Acrivastine shows antihistaminic potency and duration of action comparable to triprolidine. Unlike triprolidine, acrivastine does not display significant anticholinergic activity at therapeutic concentrations. Also, the enhanced polarity of this compound resulting from carboxyethenyl substitution limits BBB penetration and thus this compound produces less sedation than triprolidine.

Limited pharmacokinetic data is available for this compound. Orally administered drug has a half-life of about 1.7 hours and a total body clearance of 4.4 mL/min/Kg. The mean peak plasma concentrations are reported to vary widely, and the drug appears to penetrate the CNS poorly. The metabolic fate of acrivastine has not been reported.

VI. “DUAL-ACTING” ANTIHISTAMINES:

Compounds that block the release of histamine from mast cells (MCS) **and** antagonize the actions of histamine at H₁-receptors. Compound introduced in this class over the past several years include azelastine, ketotifen and permirolast and others (see pharmacology notes). These agents have utility as ocular antihistamines and for other indications:



The properties of these agents include:

- Selective antagonism of H₁-receptors versus other neurotransmitter receptors (low antimuscarinic activity)
- MCS activity greater than cromolyn and blocks release of histamine and other inflammatory mediators such as leukotrienes, PAF, etc
- Most available as ophthalmic solutions for allergic rhinitis (azelastine also available as nasal spray)
- ADRs: local irritation (burning, stinging), headache, dizziness, etc.

- Pharmacologic Properties of Selected “Antihistamines”

Antihistamine	Dose (mg)	Dosing Int. (hrs)	Sedative effects	Anti-H1 activity	Anti-M activity	Anti-emetic
First Generation: Propylamines						
Brompheniramine	4	4 to 6	+	+++	++	-
Chlorpheniramine	4	4 to 6	+	++	++	-
Dexchlorpheniramine	2	4 to 6	+	+++	++	-
Triprolidine	2.5	4 to 6	+	++/+++	++	-
Phenindamine	25	4 to 6	±	++	++	-
First Generation: Ethanolamines (Aminoalkyl ethers)						
Clemastine	1	12	++	++	+++	++/+++
Carbinoxamine	4 to 8	6 to 8	++	+/++	+++	++/+++
Diphenhydramine	25 to 50	6 to 8	+++	+	+++	++/+++
First Generation: Ethylenediamines						
Pyrilamine	25 to 50	6 to 8	+	+/++	±	-
Tripelennamine	25 to 50	4 to 6	++	+/++	±	-
First Generation: Phenothiazines						
Promethazine	12.5 to 25	6 to 24	+++	+++	+++	++++
Trimeprazine	2.5	6	++	++/+++	+++	++++
Methdilazine	8	6 to 12	+	++/+++	+++	++++
First Generation: Piperazines (Cyclizines)						
Hydroxyzine	25 to 100	4 to 8	+++	++/+++	++	+++
First Generation: Dibenzocycloheptenes/heptanes						
Azatadine	1 to 2	12	++	++	++	-
Cyproheptadine	4	8	+	++	++	-
First Generation: Phthalazinone						
Azelastine	0.5	12	±	++/+++	±	-
Second-Generation (Peripherally selective): Piperazine						
Cetirizine	5 to 10	24	±	++/+++	±	-
Second-Generation(peripherally selective): Piperidines						
Astemizole	10	24	±	++/+++	±	-
Fexofenadine	60	12	±	-	±	-
Loratadine	10	24	±	++/+++	±	-

KEY: +++++ = very high, +++ = high, ++ = moderate, + = low, -± = low to none. — = No data.

Structure-Activity Summary for “Classic” (Non-sedating!) Antihistamines):

- Relatively low H₁ potency: Ethanolamines (except pyrrolidine and pyridyls), ethylenediamines and piperazines
- Relatively “high” H₁ potency: Propylamines (except phenindamine), pyridyl and pyrrolidine ethanolamines (clemastine and carbinoxamine), dibenzocycloheptenes/anes and phenothiazines
- Relatively low sedation: Propylamines, ethylenediamines and piperazines and cyproheptadine
- Relatively low antimuscarinic activity: Ethylenediamines
- Relatively high antiemetic activity: Phenothiazines and ethanolamines