A TEXT BOOK OF

MEDICINAL CHEMISTRY-II

For

B. Pharm., Semester - V

As Per PCI Regulations

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Price ₹ 385.00

NIRALI PRAKASHAN
ADVANCEMENT OF KNOWLEDGE

N3976-A

MEDICINAL CHEMISTRY-II **ISBN 978-93-88897-87-7**

Sixth Edition : April 2025

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Published By :
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Abhyudaya Pragati, 1312, Shivaji Nagar,
Off J.M. Road, Pune – 411005
Tel - (020) 25512336/37/39
Email : niralipune@pragationline.com

Polyplate

Printed By :
YOGIRAJ PRINTERS AND BINDERS
Survey No. 10/1A, Ghule Industrial Estate
Nanded Gaon Road
Nanded, Pune - 411041

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PREFACE

In the last two decades, the phases of ever-growing volume and ever-changing nature of the drug information are witnessed. This is mainly due to an increase in the rate of introduction of new drugs and an increase in the number and depth of published work on both, new as well as existing drugs. Above facts necessitated addition of all recent information wherever it deserves, while presenting the first edition of this book.

The book was appreciated in all corners of the profession. It has now attained the reputation as a class-room text book for undergraduate and post-graduate students of pharmacy. However, our aim remains the same as to present a review of basic principles of medicinal chemistry and to explain the effects of structural modifications of the lead nucleus on the selectivity of action, duration of action and on the intensity and frequency of adverse-effects.

Each chapter is revised thoroughly to meet the needs of future facts and fantacies. Since this book is written basically for degree students, a backbone understanding in basic disciplines is assumed.

I wish to place on record my sincere thanks to the publisher Mr. D. K. Furia for his kind cooperation. I am greatly indebted to my colleagues for their generous help and criticism. I also wish to acknowledge indebtedness to all who have assisted for the completion of the book.

Suggestions from all corners of the profession are welcome. I am responsible for any deficiencies or errors that might have remained and would be grateful if readers would call them to my attention.

Pune ***Author***

SYLLABUS

Study of the development of the following classes of drugs, Classification, mechanism of action, uses of drugs mentioned in the course, Structure activity relationship of selective class of drugs as specified in the course and synthesis of drugs superscripted (*).

UNIT I (10 Hrs.)

Antihistaminic agents: Histamine, receptors and their distribution in the human body.

H_1–antagonists: Diphenhydramine hydrochloride*, Dimenhydrinate, Doxylamines cuccinate, Clemastine fumarate, Diphenylphyraline hydrochloride, Tripelenamine hydrochloride, Chlorcyclizine hydrochloride, Meclizine hydrochloride, Buclizine hydrochloride, Chlorpheniramine maleate, Triprolidine hydrochloride*, Phenidamine tartarate, Promethazine hydrochloride*, Trimeprazine tartrate, Cyproheptadine hydrochloride, Azatidine maleate, Astemizole, Loratadine, Cetirizine, Levocetrazine Cromolyn sodium.

H_2-antagonists: Cimetidine*, Famotidine, Ranitidin.

Gastric Proton pump inhibitors: Omeprazole, Lansoprazole, Rabeprazole, Pantoprazole.

Anti-neoplastic agents:

Alkylating agents: Meclorethamine*, Cyclophosphamide, Melphalan, Chlorambucil, Busulfan, Thiotepa.

Antimetabolites: Mercaptopurine*, Thioguanine, Fluorouracil, Floxuridine, Cytarabine, Methotrexate*, Azathioprine.

Antibiotics: Dactinomycin, Daunorubicin, Doxorubicin, Bleomycin.

Plant products: Etoposide, Vinblastin sulphate, Vincristin sulphate.

Miscellaneous: Cisplatin, Mitotane.

UNIT II (10 Hrs.)

Anti-anginal:

Vasodilators: Amyl nitrite, Nitroglycerin*, Pentaerythritol tetranitrate, Isosorbide dinitrite*, Dipyridamole.

Calcium channel blockers: Verapamil, Bepridil hydrochloride, Diltiazem hydrochloride, Nifedipine, Amlodipine, Felodipine, Nicardipine, Nimodipine.

Diuretics:

Carbonic anhydrase inhibitors: Acetazolamide*, Methazolamide, Dichlorphenamide.

Thiazides: Chlorthiazide*, Hydrochlorothiazide, Hydroflumethiazide, Cyclothiazide,

Loop diuretics: Furosemide*, Bumetanide, Ethacrynic acid.

Potassium sparing Diuretics: Spironolactone, Triamterene, Amiloride.

Osmotic Diuretics: Mannitol

Anti-hypertensive Agents: Timolol, Captopril, Lisinopril, Enalapril, Benazepril hydrochloride, Quinapril hydrochloride, Methyldopate hydrochloride,* Clonidine hydrochloride, Guanethidine monosulphate, Guanabenz acetate, Sodium nitroprusside, Diazoxide, Minoxidil, Reserpine, Hydralazine hydrochloride.

UNIT III (10 Hrs.)

Anti-arrhythmic Drugs: Quinidine sulphate, Procainamide hydrochloride, Disopyramide phosphate*, Phenytoin sodium, Lidocaine hydrochloride, Tocainide hydrochloride, Mexiletine hydrochloride, Lorcainide hydrochloride, Amiodarone, Sotalol.

Anti-hyperlipidemic agents: Clofibrate, Lovastatin, Cholesteramine and Cholestipol.

Coagulant & Anticoagulants: Menadione, Acetomenadione, Warfarin*, Anisindione, clopidogrel.

Drugs used in Congestive Heart Failure: Digoxin, Digitoxin, Nesiritide, Bosentan, Tezosentan.

UNIT IV (08 Hrs.)

Drugs acting on Endocrine system: Nomenclature, Stereochemistry and metabolism of steroids.

Sex hormones: Testosterone, Nandralone, Progestrones, Oestriol, Oestradiol, Oestrione, Diethyl stilbestrol.

Drugs for erectile dysfunction: Sildenafil, Tadalafil.

Oral contraceptives: Mifepristone, Norgestril, Levonorgestrol.

Corticosteroids: Cortisone, Hydrocortisone, Prednisolone, Betamethasone, Dexamethasone

Thyroid and antithyroid drugs: L-Thyroxine, L-Thyronine, Propylthiouracil, Methimazole.

UNIT V (07 Hrs.)

Antidiabetic agents: Insulin and its preparations

Sulfonyl ureas: Tolbutamide*, Chlorpropamide, Glipizide, Glimepiride.

Biguanides: Metformin.

Thiazolidinediones: Pioglitazone, Rosiglitazone.

Meglitinides: Repaglinide, Nateglinide.

Glucosidase inhibitors: Acrabose, Voglibose.

Local Anesthetics: SAR of Local anesthetics

Benzoic Acid derivatives; Cocaine, Hexylcaine, Meprylcaine, Cyclomethycaine, Piperocaine.

Amino Benzoic acid derivatives: Benzocaine*, Butamben, Procaine*, Butacaine, Propoxycaine, Tetracaine, Benoxinate.

Lidocaine/Anilide derivatives: Lignocaine, Mepivacaine, Prilocaine, Etidocaine.

Miscellaneous: Phenacaine, Diperodon, Dibucaine.*

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UNIT I

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ANTI-HISTAMINIC AGENTS

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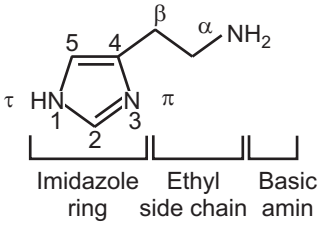
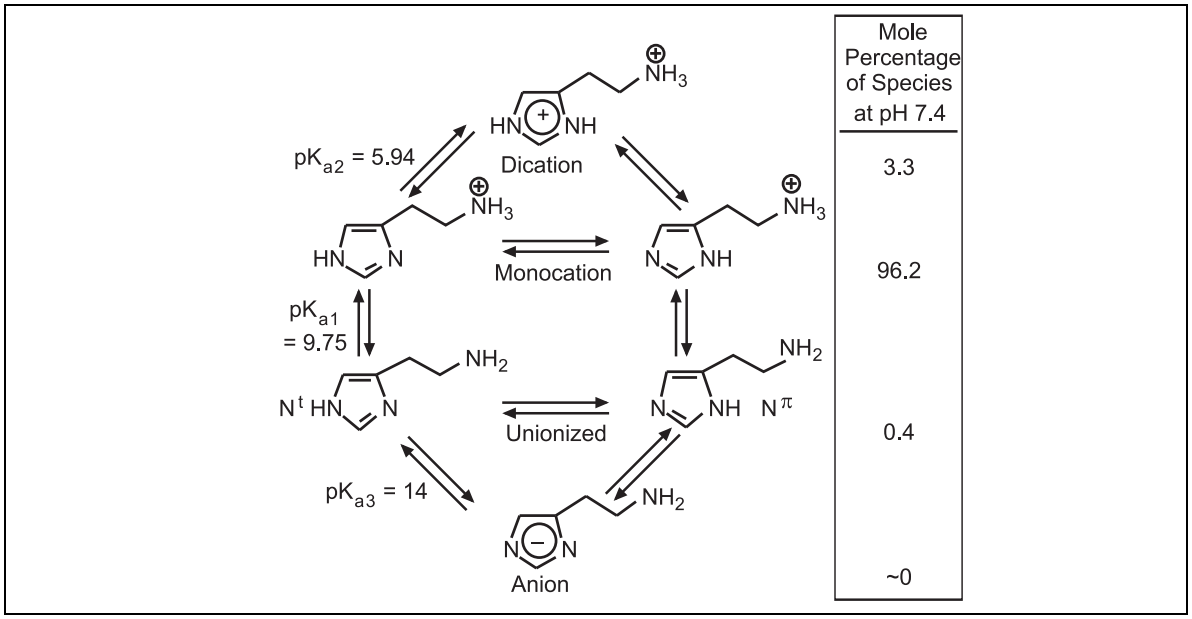
1.1 INTRODUCTION

A number of substances with widely differing structures and with diversified pharmacological activities are normally present in the body. These include histamine, serotonin, prostaglandins, angiotensin, endothelins, nitric oxide eicosanoids bradykinin, kallidin etc. Since, their pharmacological activities do not permit to call them as hormones or neurohormones, they are grouped together in a class, known as **autacoid** [Greek word: autos (self) and akos (medicinal agent or remedy)]. Though autacoids play an important role in the body's economical system, their physiological functions can not be stated with assurance.



Histamine is widely distributed in plants and animal tissues. Due to its wide-spread occurrence in body tissues, it was named histamine which means 'tissue amine'. It was first discovered in 1907 by Windaus and Vogt. Its vasodepressor effect was reported in 1910 by Dale et al. In 1927, it was first isolated from liver and lung tissues. It is found to be involved in the diversified physiological processes. It is released in body usually, in response to tissue injury, inflammation, and allergic or hypersensitivity reactions.



Histamine is comprised of an imidazole ring connected to an amino group through ethylene bridge. Both, imidazole ring and amino group are basic and get protonated under acidic condition. Chemically, it is β-imidazolyl ethylamine. The structural features of histamine permit it to exist in ionic, tautomeric and conformeric forms which constantly get interconverted to each other. These forms differ mainly in the electronic charge distribution and in the position of hydrogen atoms.

There are many drugs with histamine like properties. These drugs may contain the following molecular fragments.

$$—N = C — CH_2 — CH_2 — NH_2$$

or

$$= N — \overset{\overset{||}{}}{C} — CH_2 — CH_2 — NH_2$$

These fragments seem to be necessary for attack of histamine on receptor centers of target cells.

1.2 BIOSYNTHESIS, STORAGE AND CATABOLISM

The major source of histamine in body appears to be decarboxylation of the naturally occurring amino acid, histidine, under the influence of L-histidine decarboxylase. It is highly specific enzyme whose activity is governed by histamine itself, through negative feedback inhibition mechanism. This conversion utilises pyridoxal-5-phosphate as a coenzyme. Histidine is also converted to histamine by a pathway of minor importance that is catalysed by non-specific enzyme, aromatic L-amino acid decarboxylase (dopa decarboxylase). Almost all mammalian tissues contain varying amounts of histidine, L-histidine decarboxylase and enzymes that metabolise histamine. The higher concentration of histamine, however, is found in the skin, intestinal mucosa, lungs and bone marrow. These are the organs which are exposed to external environment. In brain, histamine is present in significant amount.

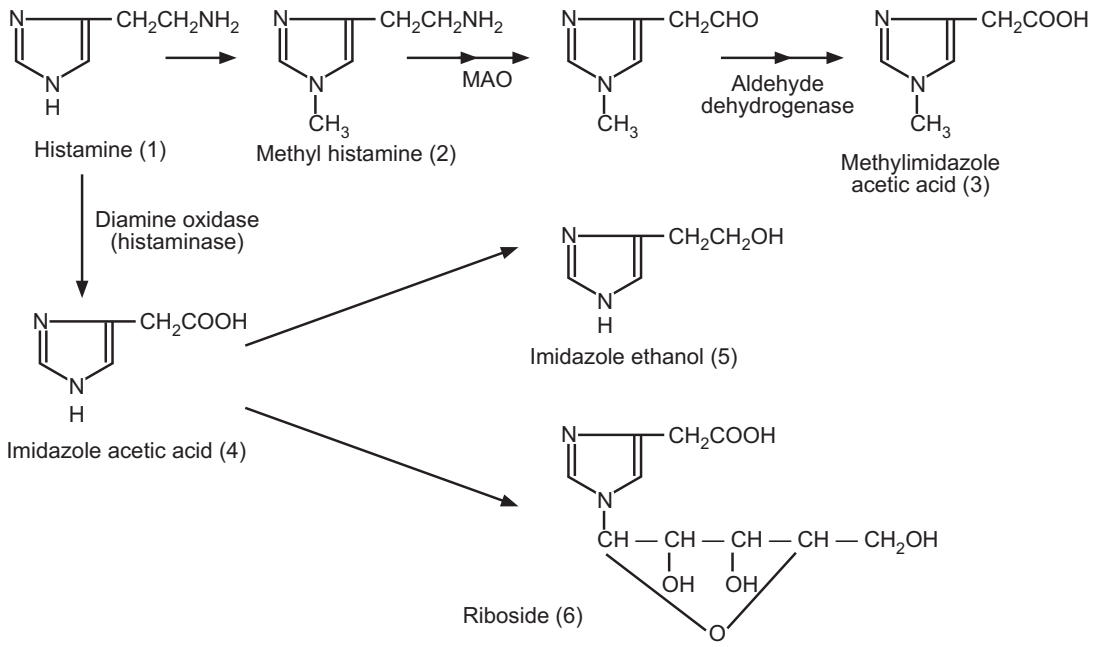


Fig. 1.1 : Histamine inactivation in body

The tissue fixed mast cells and blood basophils (circulating counterparts of mast cells) are the principal cells where histamine is synthesised and is stored in secretory granules. Besides mast cells, histamine is also present in skin, gastric mucosa and CNS where it is biosynthesized and stored in non-mast cells. Here histamine usually undergoes rapid turnover and is released, rather than stored. It is histamine which is probably of greater physiological importance.

Some histamine is also synthesized in the gut lumen by bacteria. But most of it is inactivated during absorption in the gastrointestinal mucosa, liver and lungs to N-acetyl histamine.

Fig. 1.1 shows the principal pathways by which histamine is inactivated in the body.

Except (2) and (3), rest of the metabolites of histamine retain little or no physiological activity. In general, conjugation reactions rarely utilise ribose as a substrate. Histamine seems to be among such rare compounds, which are biotransformed through the conjugation with ribose moiety. Acetylation and N-demethylation are other metabolic pathways of minor importance. Urine serves as the principal vehicle for the excretion of these inactive products.

Specific as well as non-specific enzymes are involved in the inactivation of liberated histamine into the body. Imidazole-N- methyl transferase is present in the tissues but not in blood whereas diamine oxidase is present in high concentration in intestine, kidney, liver and thoracic duct lymph. It also utilises other diamines as its substrates. It is mainly inhibited by antimalarial drugs.

1.3 HISTAMINE RELEASE

Under normal conditions, much of the body's store of histamine remains in an inactive form within the tissues. The tissue bound mast cells and basophils are the principal cells for histamine storage. Thus almost every organ is supplied with blood containing histamine, released by basophils. Within the secretory granules of mast cells and basophils, histamine is stored with a heparin-protein complex, to which it is loosely bound with ionic forces. The sensitisation of mast cell is caused by an antigen when it interacts (through bridge formation) with two membrane-bound antibody (immunoglobin) molecules resulting into initiation of a chain of events that ends into an expulsion of the contents of secretory granules by the process of exocytosis. It is Ca^{++} and Mg^{++} ion dependent and energy required metabolic process. Histamine is released from its heparin-protein complex by an exchange program, probably involving calcium ions. Cyclic AMP inhibits the release of histamine, presumably by closing the calcium channels while c-GMP facilitates the calcium influx and induces histamine release.

The concentration of c-AMP is governed by the membrane-bound adenylate cyclase enzyme which is activated by norepinephrine (α-adrenergic agonist), epinephrine (β-adrenergic agonist), prostaglandins and by histamine (negative feedback inhibition by activation of H_2-receptor) itself, while the concentration of c-GMP is governed by another membrane bound guanylate cyclase enzyme which is activated by cholinergic agonists. Both these second messengers control the breakdown of phosphatidyl-inositides and the generation of phosphorylated derivatives of inositol which are involved in the regulation of calcium channels.

The intracellular concentration of free calcium is important for the exocytotic release of histamine. In certain cases, non-exocytotic mechanism may also be involved in the release of histamine. These include morphological changes in the mast cells resulting into mast cell lysis or physical displacement of histamine. Chlorpromazine may cause the histamine release from mast cells by a cytotoxic mechanism.

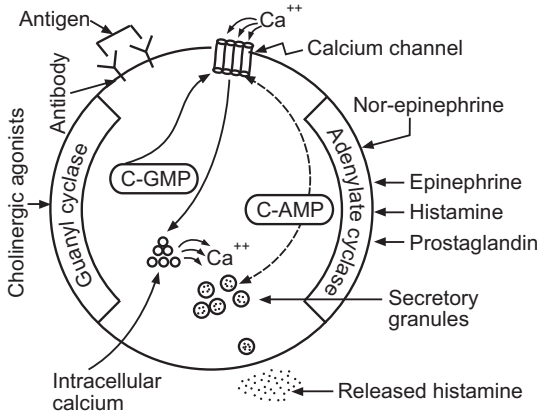


Fig. 1.2: Histamine release from mast cells

Since, activation of H_2-receptor sites on mast cell membrane, results into elevation of c-AMP, all physiological actions of histamine that are initiated by H_2-receptor activation, will be associated with elevated intracellular c-AMP level. Similarly the physiological actions of histamine that are due to H_1-receptor activation in general may then be associated with elevated intracellular c-GMP levels.

In hypersensitivity reaction, the mast cell is sensitised by an interaction of specific antigen with the cell bound antibody (IgE or reagin), resulting into degranulation and subsequent release of granular contents. Histamine is released along with other autacoids like, plasmakinins, angiotensin, prostaglandins, serotonin, platelet activating factor, slow releasing substance of anaphylaxis (SRS-A) and eosinophill chemotactic factor. These chemical mediators lead to pathologic responses such as increased vascular permeability, change in smooth muscle tone and increased secretion of mucous.

There are two different mechanisms that trigger the release of mediators from mast cells. The first triggering mechanism is atopic or IgE-mediated. This mechanism involves allergen specific IgE antibodies attached to receptor sites on mast cells (and also basophils) thereby sensitising them. These cell-bound IgE antibodies act like a trigger or fuse.

The other broad category of mast cell triggering mechanism is called non-atopic or non-immune. These non-IgE mediated mechanisms act directly or indirectly on the mast cells or target cell membrane to bring about the same results-release of histamine and other mediators and consequent pathologic responses as occur with atopic triggering. Some of the non-immune triggers are acetylcholine, complement components, oestrogen, prostaglandins, chemicals, drugs, conditions and events such as weather changes, respiratory infections, air pollution, anxiety and stress.

1.4 HISTAMINE LIBERATION

Histamine release may be increased in urticarial reactions, mastocytosis and basophilia. Similarly in certain patients, many drugs may produce hyper-sensitivity reactions by sensitising mast cells. In some cases, these drugs or their metabolic products may act as antigen while few of them can directly or indirectly activate the calcium ion channel. This may result into an eventual expulsion of the granular contents of the mast cells which include heparin and other mediators of anaphylaxis along with histamine.

Chlortetracycline, morphine, pethidine, amphetamine, tolazoline, d-tubocurarine and atropine are some of the drugs which cause the histamine release. Hence, these drugs are termed as histamine liberators. They do not deplete histamine stores from non-mast cells.

1.5 PHYSIOLOGICAL ACTIONS OF HISTAMINE

(1) An ability of histamine to dilate the capillaries and to increase their permeability, suggests its basic role in the beginning of the inflammatory reactions.

(2) In allergic reactions, (antigen-antibody), histamine plays a role along with other autacoids.

(3) Histamine exerts a variety of actions on the cardiovascular system.

(4) A "nascent" histamine refers to biosynthesis of histamine that can be provoked when needed. It is made but not stored. It may play a role in anabolic processes.

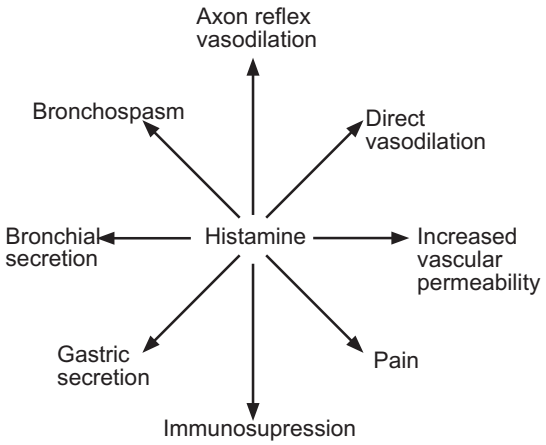


Fig. 1.3: Physiological actions of histamine

(5) Histamine is unevenly distributed in the brain and may also act as a central neurotransmitter.

(6) Histamine stimulates sensory nerves in the skin and if these sensory impulses continue into CNS to sufficient intensity, this results into itching or pain sensation.

(7) By causing the dilation of intracranial blood vessels, histamine causes an intense headache.

(8) It causes contraction of smooth muscles of GIT. This action, coupled with its stimulatory action on the secretion of gastric hydrochloric acid, causes epigastric distress, nausea, vomiting and diarrhoea.

(9) Excessive histamine release may cause peptic ulceration and asthmatic conditions.

(10) Histamine when injected into the skin, it produces dilation of both the capillaries and the neighboring arterioles which is associated with an increased permeability of these vessels and the increased exudation of tissue fluid (giving rise to a weal). These three effects i.e., dilation of capillaries, formation of weal and dilation of the arterioles constitute the term '*triple response*'.

1.6 ANTIALLERGIC AGENTS (CLASSIC ANTI-HISTAMINES)

Histamine binding to the H_1-receptor can cause stimulation of smooth muscle and produce allergic and hypersensitivity reactions such as hay fever, pruritus (itching), contact and atopic dermatitis, drug rashes, urticaria (oedematous patches of skin) and anaphylactic shock. Antihistamines are used widely to treat these symptoms.

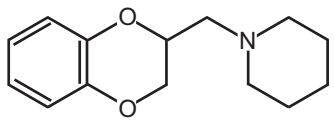
1.6.1 First Generation Agents

According to the chemical features they share, these agents are classified as:

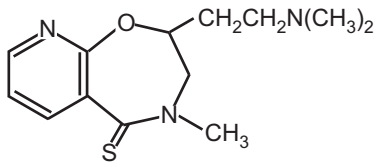
1. Ethylenediamine derivatives
2. Aminoalkyl ether analogues
3. Cyclic basic chain analogues
4. Monoaminopropyl analogues
5. Tricyclic ring system
6. Newer agents.

Classical H_1-Receptor Antagonists:

Research on antihistaminic drugs was initiated in 1933 in France by Bovet (Rome, Italy) and Fourneau who reported that piperoxan protects the animals from bronchial spasm induced by aerosolized histamine. Rocastine has been described as a rapid acting, non-sedating H_1-antagonist where no CNS activity was observed.

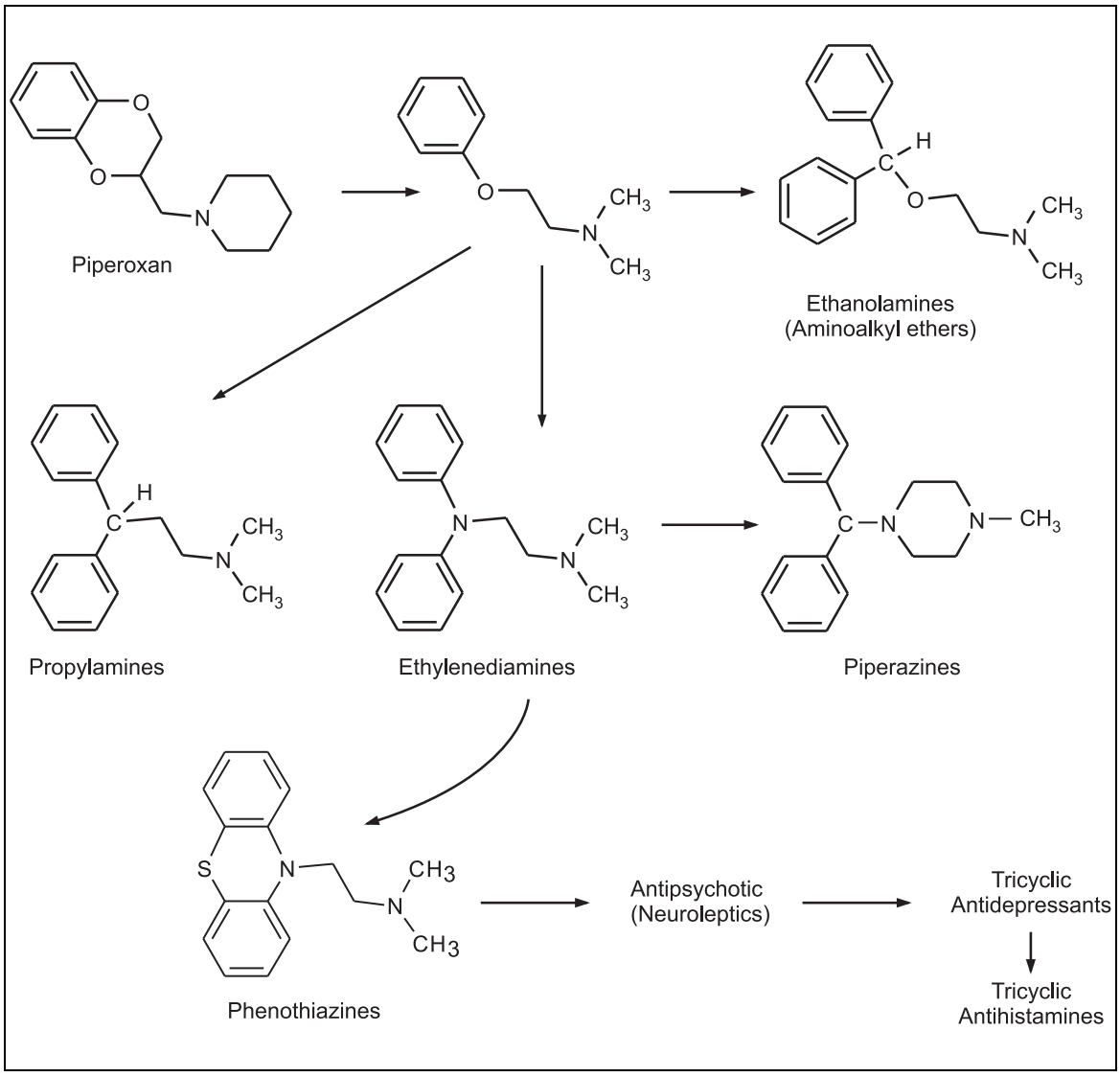


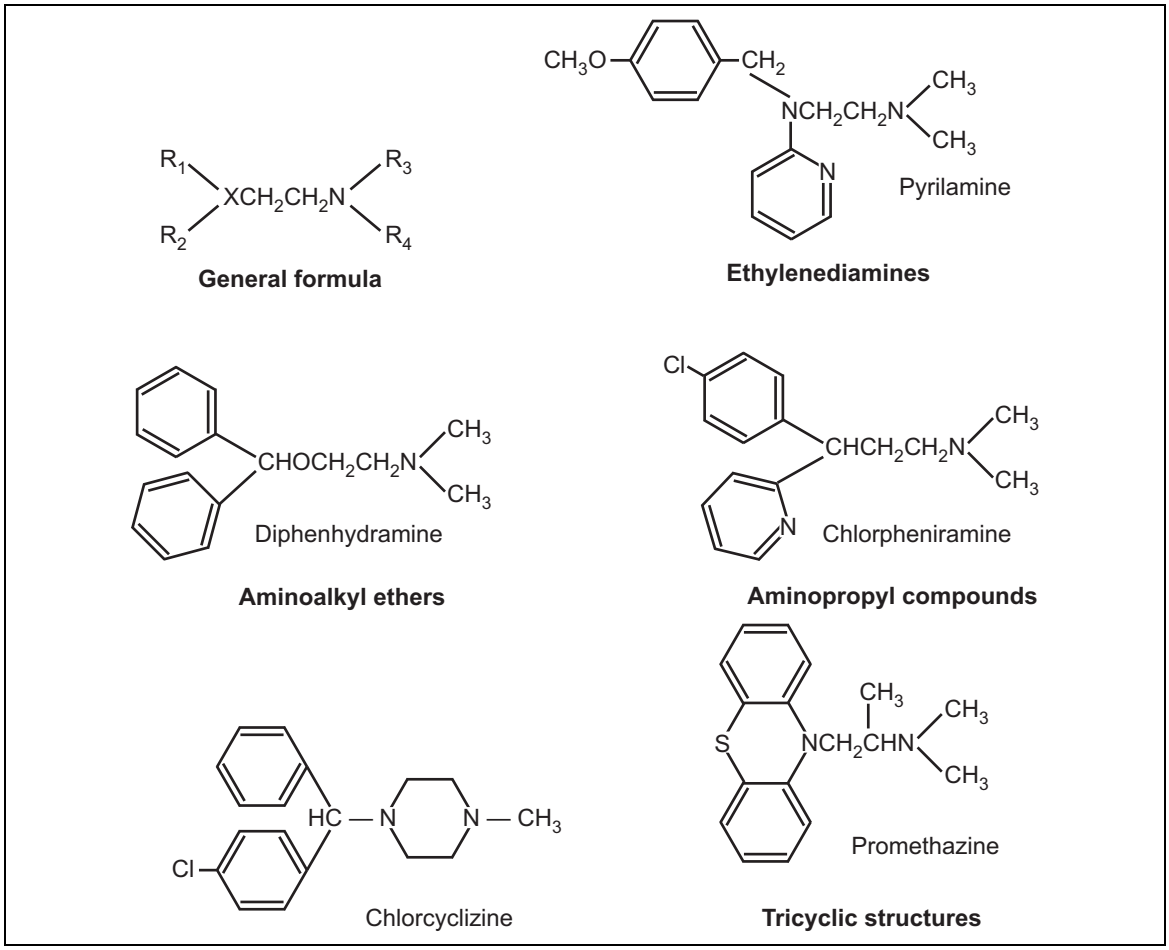
Piperoxan



Rocastine

Genesis:



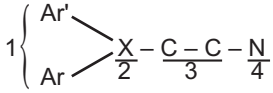


A disubstituted terminal group (usually a dimethylamino group) is connected to an atom X via a short carbon chain. The chain can be saturated, unsaturated, branched or part of a ring system, whereas X can be an oxygen, nitrogen or carbon atom; X links the side-chain to an "aromatic head". This aromatic head generally contains two aromatic rings (e.g. phenyl, benzyl, 2-pyridyl), which may be fused.

Substitution of the aromatic ring can influence the H_1-receptor antagonistic activity. Whereas ortho-substitution is highly undesirable, meta-substitution is either ineffective or unfavourable, and para-substitution in only one of the rings can increase the biological activity if the substituent is lipophilic (e.g. Cl, CH_3) or has electron-releasing properties (e.g. OCH_3).

Structure-Activity Relationship:

Like histamine, most of the classic antihistamines may be described by a substituted ethylamine moiety i.e.,



(1) Aryl groups:

In the above structure, Ar is aryl (including phenyl and heteroaryl group like 2-pyridyl) and Ar' is aryl or aryl methyl group.

Sometimes, the two aromatic rings are bridged, which constitutes tricyclic ring derivatives.

(2) Nature of X:

The nature of 'X' provides the basis of chemical classification of classic anti-histamines e.g.,

when X = Oxygen (Aminoalkyl ether analogue)

when X = Nitrogen (Ethylene-diamine derivative)

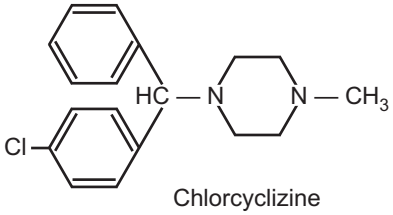
when X = Carbon (Mono aminopropyl analogue)

(3) The alkyl chain:

Most of the structures of classic antihistamines contain an ethylene chain. Extension or branching of this chain results in a less active compound (promethazine is possibly an exception). Homologation has played an important role in the development of neuroleptic and tricyclic anti-depressants from anti-histaminics. All contain, in general, the chain –C–C–NR_2, and although some of them have a neuroleptic component, antipsychotic activity is not unveiled in most cases until the carbon chain is lengthened to C_3 – NR_2.

(4) Terminal nitrogen atom:

In general, the terminal N atom should be a 3° amine for maximum activity. Unlike many anticholinergics and local anaesthetics, here the dimethylamine derivatives are found to possess better antagonist activity. The terminal nitrogen may be a part of heterocyclic ring as in antazoline and in chlorcyclizine, and still retains high antihistaminic activity.



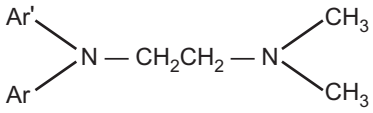
Chlorcyclizine

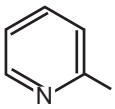
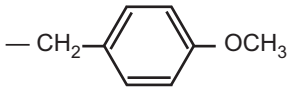
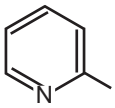
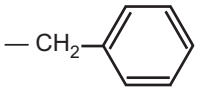
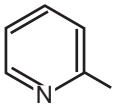
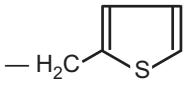
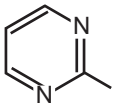
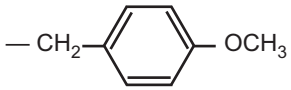
However, substitutions on the Ar groups, replacement of the aliphatic dimethylamino group with small basic heterocyclic rings, increased branching on ethylene chain and substitutions between X and N, all modify the potency, metabolism, ability to reach the site of action, toxicity and side reactions *in-vivo*.

(5) Since the structures of anti-histamines have a close resemblance with structures of cholinergic blocking agents, most of the classic anti-histamines do exhibit anticholinergic activity. The reverse is also true.

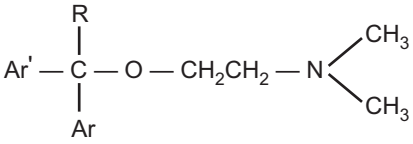
Table 1.1: Antiallergic agents or Classic Anti-histamine agents

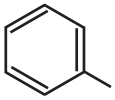
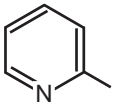
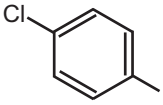
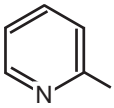
(1) Ethylenediamine derivatives:

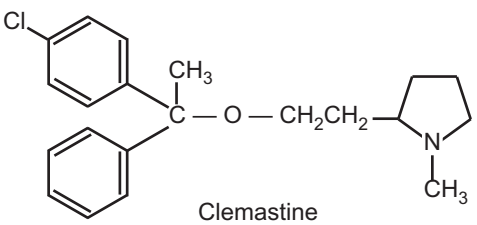


Name	Ar'	Ar
1. Pyrilamine		
2. Tripelennamine		
3. Methapyrilene		
4. Thonzylamine		

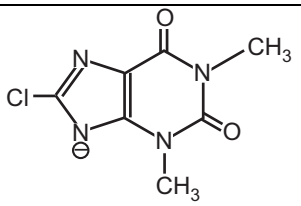
(2) Aminoalkyl ether analogues:



Name	Ar'	Ar	R
1. Diphenhydramine (Benadryl; 1946)	– C_6H_5	– C_6H_5	H
2. Bromodiphenhydramine	– C_6H_5	p-bromophenyl	H
3. Doxylamine			– CH_3
4. Carbinoxamine			H



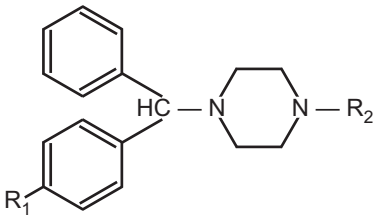
Clemastine

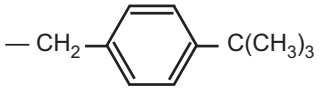
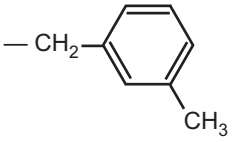
Diphenhydramine + 

8-chlorotheophylline

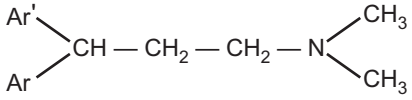
Dimenhydrinate (8-chlorotheophylline added to counteract drowsiness)

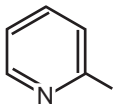
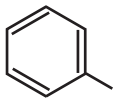
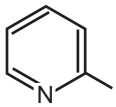
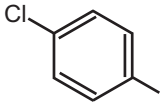
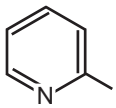
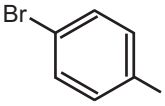
(3) Cyclic basic chain analogues:



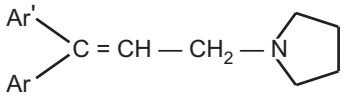
Name	R_1	R_2
1. Cyclizine	H	$-CH_3$
2. Chlorocyclizine	– Cl	$-CH_3$
3. Buclizine	– Cl	
4. Meclizine	– Cl	

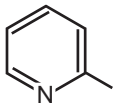
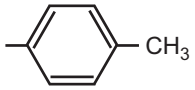
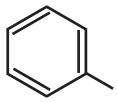
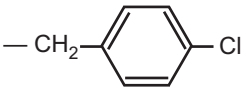
(4) Monoaminopropyl analogues:

(a) 

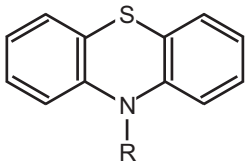
Name	Ar'	Ar
1. Pheniramine		
2. Chlorpheniramine		
3. Brompheniramine		

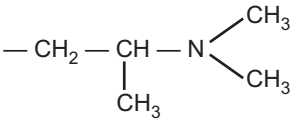
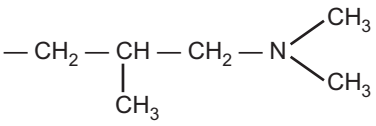
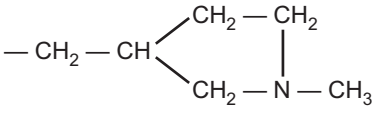
(b)



Name	Ar'	Ar
1. Triprolidine		
2. Pyrrobutamine		

(5) Tricyclic ring systems: (Phenothiazine analogues):

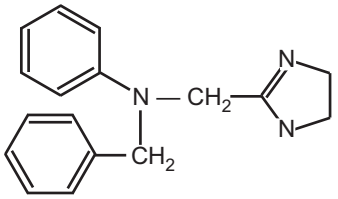


Name	R
1. Promethazine	
2. Trimeprazine	
3. Methdilazine	

Phenothiazines: Extension of dialkylaminoethylene chain to dialkylaminopropylene is not conclusive to antihistaminic activity but promotes neuroleptic activity. In chlorprothixene, trans-isomer in which the amino alkyl group lies on the side of unsubstituted aromatic ring is more anti-histaminic than the cis isomer, while reverse is true for neuroleptic activity.

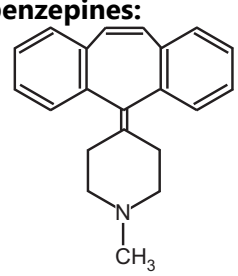
(6) Miscellaneous agents:

(a)



Antazoline

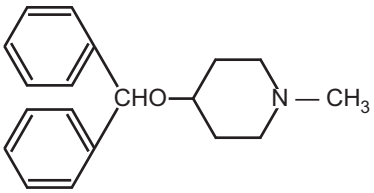
(b) Dibenzepines:



Periactin (Cyproheptadine)

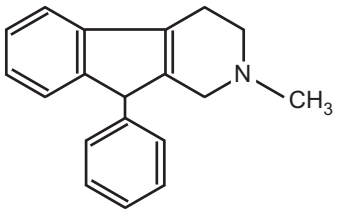
It has antihistaminic, anticholinergic and local anasthetic properties.

(c)



Diphenylpyraline

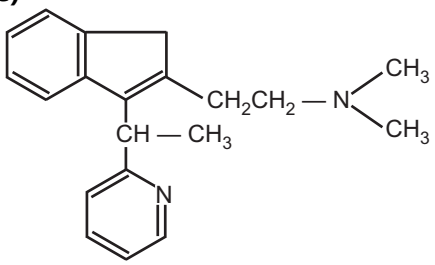
(d)



Phenindamine
(1940)

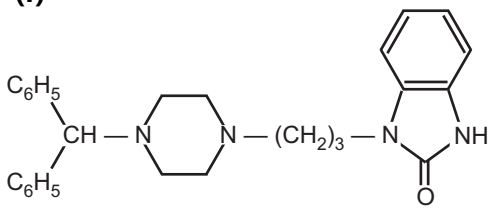
In diphenylpyraline, the basic side-chain of diphenhydramine is tied back so as to link the benzhydryl ether group with N-methyl piperidine in the 4th-position.

(e)



Dimethindene

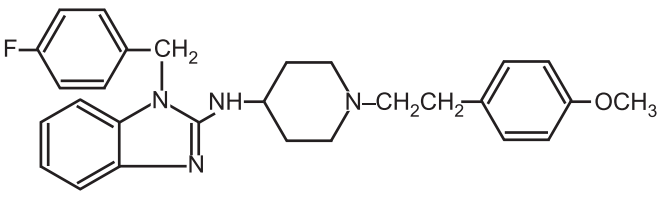
(f)



Oxatomide
(Janssen pharma, 1975)

An innovative drug with a combined H_1-5HT-leukotriene antagonism is oxatomide. It is usable in asthma, where ordinary H_1-antagonists are not appropriate.

(g) Astemizole (1977) Astemizole is also metabolized by CYP3A4 and has similar problems of cardiotoxicity (QT interval prolongation and arrhythmias) when administered with CYP3A4 inhibitors and has been removed from the market (1999).

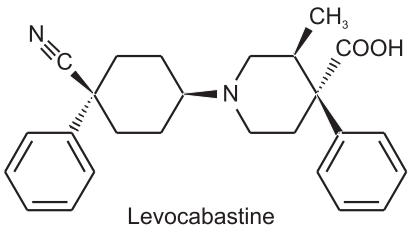


Astemizole

Astemizole and terfenadine are non-sedative H_1-blockers. These are quite polar molecule and cannot cross BBB to reach central H-receptors. Astemizole is especially long acting.

(h) Levocabastine (1979):

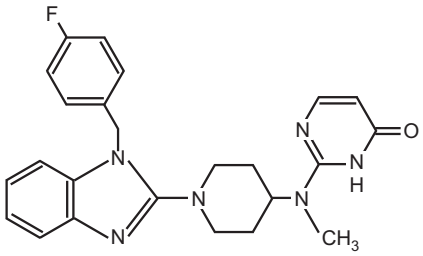
Astemizole's profile led to research on compounds containing the 4–phenyl piperidine ring (like terfenadine). Unlike Astemisole, it has a fast onset and a long duration.



Levocabastine

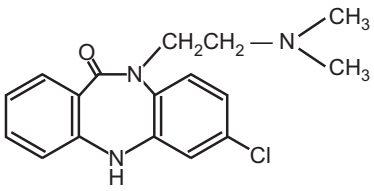
(i) Mizolastine:

It is a non-sedative antihistamine. It is effective in allergic rhinitis and urticaria by single daily dose. It blocks H_1-receptors.

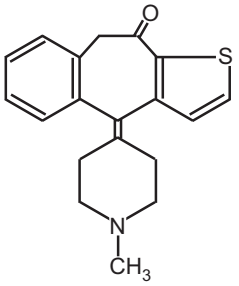


Mizolastine

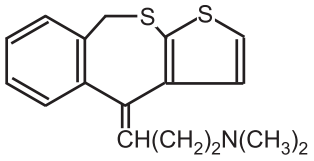
(7) Newer agents under investigation:



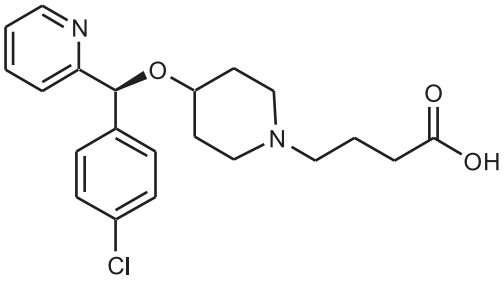
Tarpane



Ketotifene



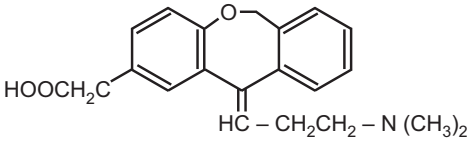
Dithiadene



Bepostatine

Bepostatine (Bepreve) is a relatively new drug in this class approved in Japan for systemic (oral) use for the treatment of allergic rhinitis and uriticaria/puritus in July 2000 and January 2002, respectively.

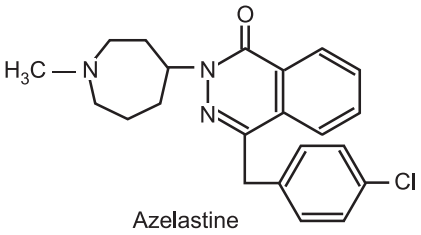
Olopatadine: It is an antihistaminic and mast cell stabilizer. It is used to treat iching associated with allergic conjunctivitis.



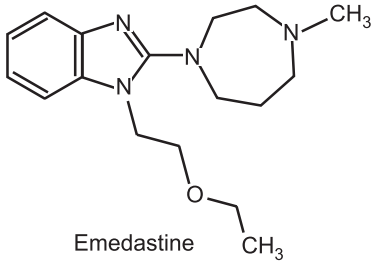
Olopatadine

(j) Azelastine:

Azelastine is a potent second generation selective H_1-receptor antagonist used to treat allergic rhinitis (nasal spray) and allergic conjunctivities (eye drop). It has (1) Antihistaminic effect, (2) Mast cell stabilizing and (3) Anti-inflammatory effect.



Azelastine

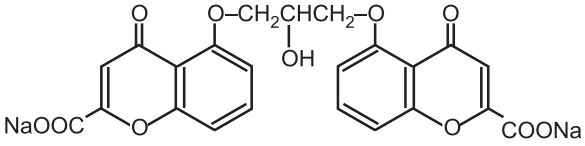


Emedastine

Emedastine is an ophthalmic H_1 antagonist, mast cell stabilizer.

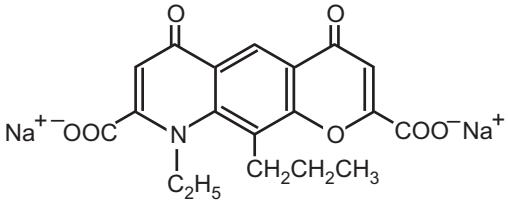
(k) Cromolyn Sodium:

It is a derivative of khellin, a vasodilatory benzopyrone isolated from the umbelliferous plant Ammivisnaga. Cromolyn belongs to a completely novel class of compounds which bring about their antihistaminic effects by the suppression of release of autacoids during antigen-antibody interaction.



Cromolyn Sodium

It bears neither a structural relationship to other commonly used anti-histaminic compounds nor it possesses a smooth muscle relaxant or bronchodilatory activity.



Nedocromil-Na

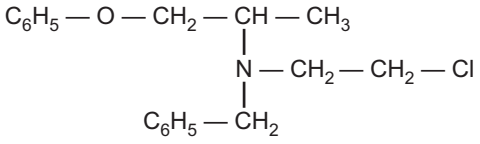
It is structurally related to cromolyn but has superior and broader pharmacological actions in the treatment of asthma. It is a massed cell stabilizer. Nedocromil - Na and Na-cromoglycate seem to act by phosphorylating a mast cell protein and thereby stabilise the cell, preventing its disruption.

Bronchial asthma and allergic rhinitis are diseases where sodium chromoglycate is the only drug for prophylaxis. Being a mast-cell stabiliser, it can be used only in the adults, that too in inhalation form only. Ketotifene is an orally active agent with similar action, having prophylactic properties. It is a tricyclic derivative of benzocyclo heptathiophine skeleton. It is useful in cases of bronchial asthma with Type I hypersensitivity as well as allergic rhinitis. It has a limited use in acute attack. It has got antiallergic, antiasthmatic and anti-anaphylactic properties.

It inhibits antigen induced release of chemical mediators, especially SRS-A, histamine.

Optimization of β_2-receptor expression by reducing its tachyphylaxis results into asthma prophylactic activity while optimisation of H_1-blockade activity results into anti-allergic action.

The structures of various classic anti-histaminic agents reveal the fact that the agents from other therapeutic class also exhibit considerable anti-histaminic activity e.g., Phenoxybenzamine (an adrenaline blocking agent), many local anaesthetics, tranquillisers (phenothiazines) and diphenylmethane derivatives (atropine like drugs and the antiparkinsonian agents).



Phenoxybenzamine

Forced by limited usefulness due to unwanted side-effects, non-sedative H_1-antagonists were developed. These new non-sedative H_1-antagonists originate from several classical H_1-antagonists but sometimes also comprises new and unexpected structural elements. In contrast to the classical H_1-antagonists, the new developed compounds do not easily cross the blood brain barrier and therefore act only peripherically. Some of the new H_1-antagonists (e.g. astemizol, etirizine, loratadine) are now in clinical use and appear to be of value for treating allergic conditions.

Sedation is the side-effect of the first generation H_1-antihistamines. Several antihistaminics have been derived from classical structures that have reduced ability to penetrate the CNS. They have little or no sedative side effects. These are collectively referred to as the second generation (non-sedating) H_1-receptor antagonists.

1.6.2 Second Generation Agents

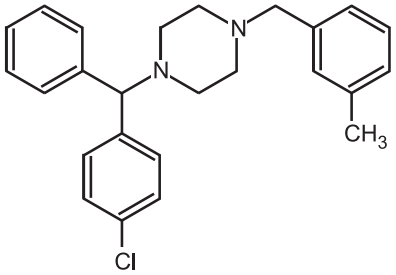
(Non-sedative Antihistaminics)

The advantages of this class include:

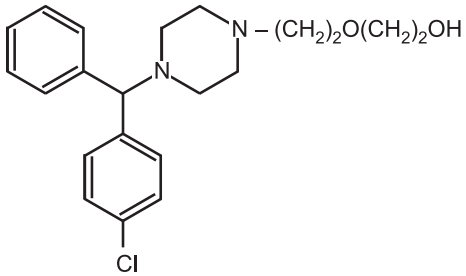
(i) Poor CNS penetration (ii) Reduced sedation

(iii) Prolonged duration of action (iv) Lacks anticholinergic side effects.

(a) Piperazines:



Meclizine

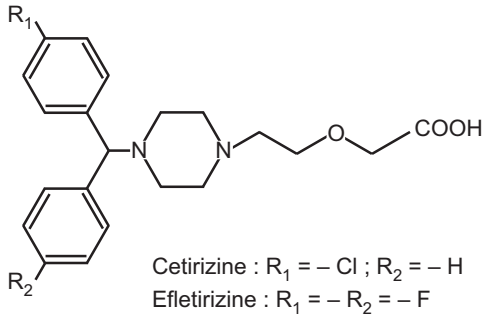


Hydroxyzine

Both nitrogens are basic; the terminal nitrogen is more basic due to less steric hindrance and no electron withdrawing groups in the vicinity.

They have moderate potency with a slow onset and prolong duration of action, moderate sedation and low anticholinergic effects.

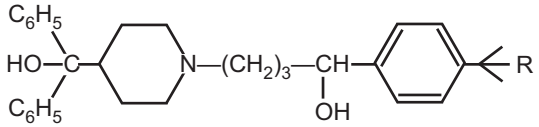
They also possess peripheral and central antinausea activity, thus they are used as antiemetic, antivertigo and antinausea products.



Cetirizine : R_1 = – Cl ; R_2 = – H
Efletirizine : R_1 = – R_2 = – F

Cetirizine is an excellent example of the second generation histamine H_1-receptor antagonist which is carboxylated metabolite of hydroxyzine. It is a long acting drug and free from central sedation and antimuscarinic activity. It is used for the symptomatic relief of hypersensitivity reactions.

(b) Piperidines:



Terfenadine : R = –CH_3 (1985)
Fexofenadine: R = –COOH

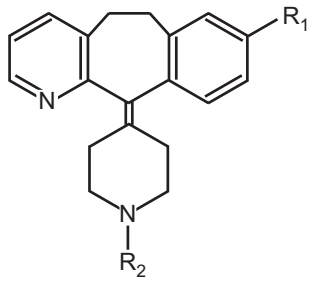
It is a butyrophenone derivative having anti-histaminic activity without sedative action used in the treatment of seasonal and perennial allergic rhinitis.

Terfenadine 1985 was discontinued when it became apparent that there was a high frequency of heart arrythmia associated with the drug. In patients with compromised liver metabolism or when the presence of other drugs limit the metabolism of terfenadine, persistent levels result in the observed arrythmias.

Fexofenadine is a metabolite and is the activated form responsible for antihistamine activity. Therefore, the fexofenadine replaced terfenadine (1997).

Azatadine (1983; I^{st} generation) is cyproheptadiene analog where a phenyl has been replaced by a 2–pyridyl and the double bond has been saturated. It also has antiserotonin and high anticholinergic potency and thus similar side effects.

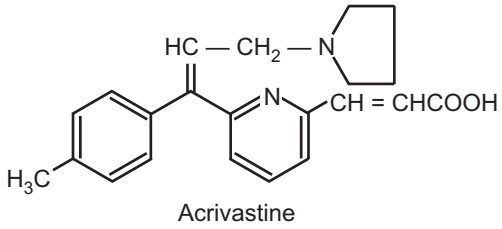
Loratadine: It is a second generation H_1-receptor antagonist used in the treatment of allergic rhinitis and urticaria. Unlike most classical antihistamines, it is devoid of CNS depressant (e.g., drowsiness) effect. It is a prodrug, metabolized to an active metabolite, desloratadine.



Azatadine: R_1 = – H; R_2 = – CH_2

Loratadine: R_1 = – Cl, R_2 = – $COOC_2H_5$

Acrivastine is a non-seditive second generation H_1-receptor antagonist used in the treatment of allergies and hay fever.



Acrivastine

(2^{nd} generation drug)

1.7 MECHANISM OF ACTION OF CLASSIC ANTI-HISTAMINIC AGENTS (ANTIALLERGIC AGENTS)

Since histamine alone is not responsible for allergic and anaphylactic conditions, the antihistamines do not necessarily antagonise all the symptoms of above reactions.

Anti-histamines seem to act as antiallergic agents by more than one mechanism

(i) By those whose pharmacological actions are opposite to that of histamine.

(ii) Those that prevent the access of histamine to its receptors by competitive antagonism.

Some anti-histamines also antagonise serotonin and bradykinin which are released along with histamine during anaphylaxis reaction. The classic anti-histamines act competitively. Some of them probably fit fairly snugly on the histamine receptor but others can only occupy the minimal area of the receptor-surface thereby, preventing the access of histamine through the steric hindrance. The receptor antagonist complex, like receptor histamine complex is a reversible reaction but unlike the latter, when antagonist binds to the receptor, it has no intrinsic activity. These competitive antagonists are not very effective if they are given after an anaphylactic attack has begun, hence substances whose actions are opposite to histamine's, like adrenaline, are much more useful in these conditions.

It is also possible that histamine and its antagonists do not bind with the same site on the receptor. Such binding is called as allosteric binding and may cause a small reversible molecular perturbation in the receptor, resulting into a change in structural and chemical nature of the active site to which histamine normally binds. In such case, histamine may not be able to bind the changed active site or, if it does bind, it may not exhibit an intrinsic activity.

1.8 FATE OF ANTI-HISTAMINES IN THE BODY

Metabolite formation depends upon the chemical nature of anti-histamine and age, sex and animal species in which the drug is studied. Generally small animals exhibit simpler excretion patterns. Metabolism occurs through typical metabolic reactions like N-dealkylation, deamination, side chain degradation, ring hydroxylation and oxidation. Prolonged administration leads to an enhanced activity of liver microsomal enzymes, resulting into increased metabolism of the anti-histamines.

1.9 SIDE-EFFECTS

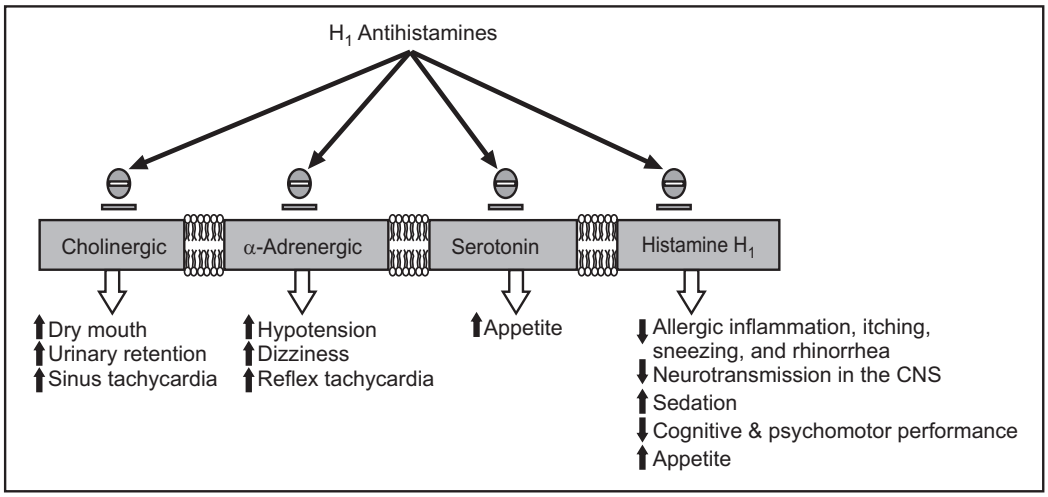


Fig. 1.4

1.10 THERAPEUTIC USEFULNESS OF CLASSIC ANTI-HISTAMINES

(1) Histamine-induced contraction of smooth muscle and increase in capillary permeability can be antagonised via H_1-receptor blockade, resulting in an improvement of asthmatic conditions and a reduction in formation of oedema and cutaneous wheal. The classical H_1-receptor antagonists, however, are usually ineffective in bronchial asthma, but they can successfully be employed in the treatment of allergic rhinitis (allergic inflammation of nasal airways), conjunctivitis and dermatitis (rash or irritation of skin) effects.

(2) As hypnotic and rarely as local anaesthetics, e.g., promethazine and diphenhydramine.

(3) In the treatment of Parkinsonism, e.g., orphenadine and diphenhydramine.

(4) In motion sickness.

(5) In cardiac arrhythmias, e.g., antazoline, diphenhydramine.

(6) As antiemetic in cases where, vomiting is caused by histamine liberation from the damaged cells.

(7) Due to their atropine-like action, they have been used in cough mixtures.

Even though the general term, anti-histaminic implies the inhibition of the actions of histamine, certain prominent actions of histamine such as, the stimulation of gastric acid secretion, relaxation of uterus and positive inotropic effect on heart (i.e., increase in force of contraction and heart rate) of guinea pig were not blocked by the classic anti-histamines.

Histamine is a powerful stimulator of hydrochloric acid secretion by the oxyntic cells of gastric mucosa. The large doses of histamine also augment the secretion of pepsin and serves as a chemical mediator for the secretary action of substances like gastrin and methylxanthines. It has been established that gastric mucosa possesses high levels of histamine.

In 1966 Ash and Schild hypothesized (on the evidence parallel to the Ahlquist's hypothesis for the existence of two different adrenaline receptors) that histamine should act via atleast two distinct receptor subtypes. James W. Black and co-workers from Glaxo Smith Kline (foremely SK & F) suggested that the histamine responses which are blocked by classic anti-histamines be classified as H_1-receptor responses while those blocked by newer agents (or not blocked by classic antihistamines) be classed as H_2 responses. These H_2-receptor antagonists of histamine are also termed as anti-secretory drugs.

1.11 ANTI-SECRETORY DRUGS (H_2-Antagonists)

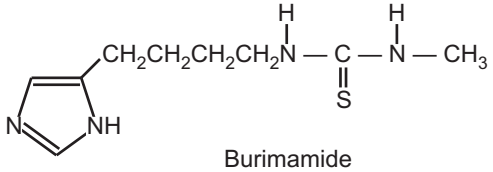
One of the compounds showing weak H_2-antagonist activity, guanylhistamine, was the point of departure in the development of these drugs. Extension of the side chain was found to increase the H_2-blocking activity, but some agonist effects were retained. When the very basic guanidino group was replaced by the neutral thiourea, burimamide was obtained. Although effective, it lacks oral effectiveness. The addition of a 4-CH_3 group further improved binding to H_2-receptor. Introduction of electron withdrawing sulphur atom into the side-chain reduced the ring pKa. The proportion of the cationic form was decreased and the tele-tautomer became predominant. Reduced ionisation improved the membrane permeability of molecule. Oral absorption (metiamide) was excellent. It is 10 times potent than burimamide. However, metiamide still showed some side effects, in the form of haematological and kidney damage, which were attributed to thiourea group.

Since 4-methyl histamine shows a weak but noticeable inhibition of the secretion of gastric acid, it was chosen to study the proton tautomerism in its imidazole ring as well as the steric interaction between 4-CH_3 group and α-CH_2 of side chain. The personal experience of investigators with guanidines suggested the replacement of thiourea group by a guanidine unit [– NHC (= NH) NHR] but it increases basicity and reduces activity. Hence, basicity would be decreased by introducing an electron withdrawing group into the guanidine group e.g. – NHC (= NNO_2) NHR or – NHC (= N – CN) NHR. Hence, cyanoguanidine [H_2NC (= NCN) NH_2] was compared directly with thiourea. Such a side-chain was introduced into 4-methyl imidazole resulting into cimetidine.

A satisfactory replacement was found by substituting another electron withdrawing group on guanidine while retaining appropriate pKa. A cyano group proved suitable and resulted into development of safe and effective cimetidine. Lately, it has become clear that an imidazole nucleus is not absolutely necessary for H_2-blocking activity. The furan derivative ranitidine and famotidine were found to be more active.

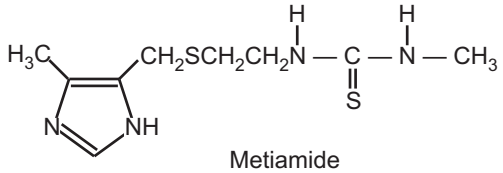
Since none of these compounds is lipid soluble, they do not produce any sedative action, as they cannot cross BBB.

Burimamide was the first selective H_2-antagonist produced by modification of histamine (Black et al 1972).



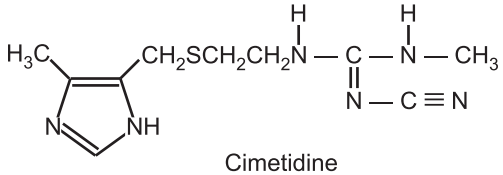
Burimamide

Burimamide was poorly absorbed orally and better absorption and higher activities were achieved by introducing a methyl group in the ring to yield metiamide.



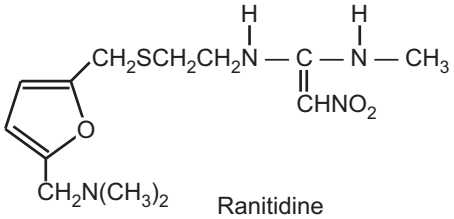
Metiamide

Replacement of the thione (=S) sulphur atom of metiamide by a cyanoimino group yielded a potent H_2-antagonist, cimetidine.



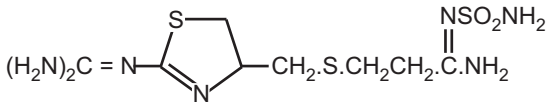
Cimetidine

Another recently introduced potent H_2-antagonist is ranitidine.



Ranitidine

Ranitidine is a nitroethane derivative of furan and on molar basis, it is five times more potent than cemitidine.



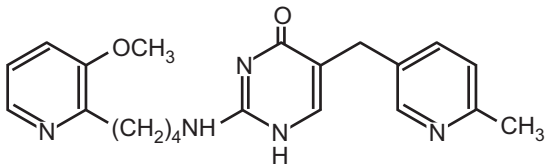
Famotidine

It differs in having a thiazole nucleus rather than a furan or imidazoline ring. It is 20 times more potent than cimetidine and 7.5 times more potent than ranitidine in inhibiting basal and pentagastrin stimulated gastric acid secretion.

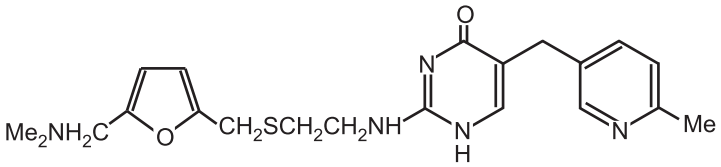
H_2-blockers are generally very polar compounds with pronounced H-bonding ability. They are very hydrophilic and don't enter the brain in more than tiny amounts.

The first brain-penetrating H_2-blocker is Zolantidine (SK & F 95282). However, the physiological role of CNS H_2-receptors is not known.

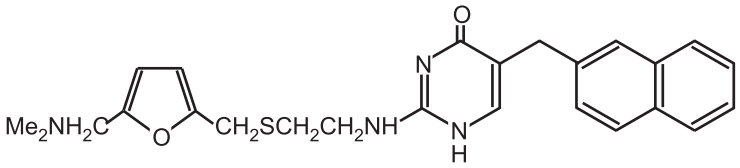
Other H_2-blockers:



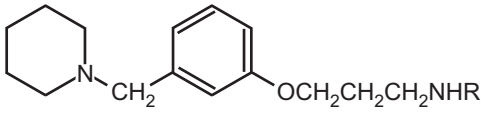
Icotidine

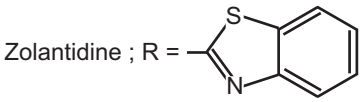


Lupitidine

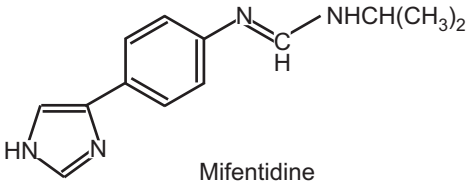


SK & F 93619

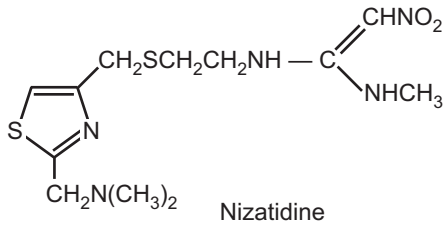




Roxatidine; R = —$COCH_2OCOCH_3$

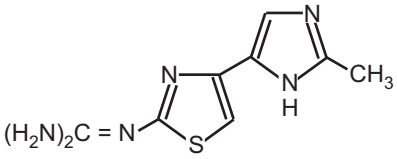


Mifentidine

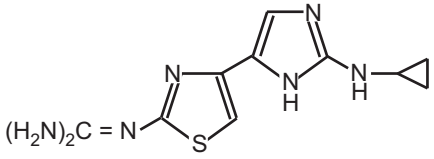


Nizatidine

Nizatidine is a (thiazole instead of furan) derivative of Ranitidine.

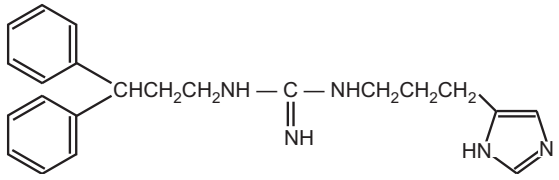


Zaltidine



III-195

Schunack described a new class of compounds in which H_1-receptor antagonism is combined with histamine H_2-receptor agonism (e.g. VUF 8531).



VUF 8531

The compounds concerned are derivatives of the potent H_2-receptor agonist impromidine, in which the 5-methylimidazole moiety has been replaced by the aromatic part of the classical H_1-receptor antagonists.

1.12 MECHANISM OF ACTION

Mucus secreted by the gastric mucous cells combined with surface epithelial bicarbonate secretion contributes to a barrier (the mucus - bicarbonate barrier) that prevents gastric acid and pepsin from damaging the gastric mucosa. While the luminal pH is acidic, the pH adjacent to the epithelial cell membrane is near neutral due to epithelial bicarbonate production and the presence of the mucus layer.

In humans, the parietal cell secretion is estimated to contain approximately 149 meq / litre HCl.

The parietal cell is pyramidal or triangular in shape, relatively large (approximately 25 µm in diameter) and the basal side bulges into the lamina propria. H^+/K^+ -ATPase is located within the cell membrane. The parietal cell also contains an unusually large number of mitochondria occupying approximately 30 - 40% of the cytoplasm. These are necessary for the high level of oxidative function involved in gastric acid secretion.

The gastric mucosa also secretes small quantities of HCO_3. At the luminal membrane there is a Cl^-/HCO_3^- exchange stimulated by glucagon as well as active HCO_3^- transporter that is chloride independent and stimulated by prostaglandins and c-AMP. Hydrogen ions are secreted into the gastric lumen by an active transport pump, the H^+/ K^+ ATPase pump. H^+ ions for the pump are made available by carbonic anhydrase which catalyses the formation of H_2CO_3 from CO_2 and H_2O. The H_2CO_3 dissociates to $H^+ + HCO_3^-$. To maintain intracellular neutrality as H^+ is secreted into the canaliculus (from where H^+ is released through H^+/K^+-ATPase pump). HCO_3^- is exchanged for Cl^- across the basolateral membrane. The resulting increased intracellular Cl^- drives through chloride conductive pathways across the luminal surface of the cell. The overall process generates HCl secretion that is followed by passive H_2O flow.

Since, the parietal cell secretes H^+ ions from the intracellular canaliculus using H^+/ K^+-ATPase pump, intracellular K^+ concentration develops. High intracellular K^+ and Na^+ concentrations are maintained by Na^+ - K^+-ATPase at the basolateral membrane, while K^+ also moves through conductive pathways into the lumen thereby providing K^+ for H^+/ K^+-ATPase.

Three separate receptors have been identified on the parietal cells that mediate HCl secretion. These receptor types interact with histamine, gastrin and acetylcholine. Stimulation of parietal cell function is linked to either c-AMP-dependent (e.g. H_2-receptor) or calcium-dependent mechanisms.

The cholinergic and gastrin stimulation are associated with increase in intracellular calcium. Proglumide which blocks the gastrin receptor, has anti-secretory properties *in-vitro* but its *in-vivo* potency is low.

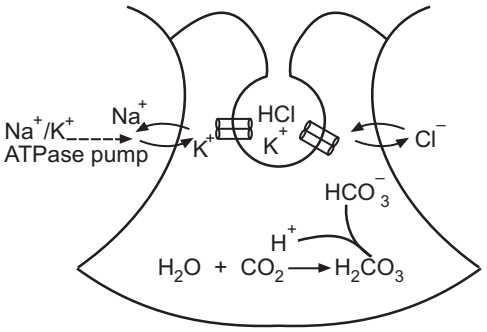


Fig. 1.5

Since H_2-receptor antagonists are potent inhibitors of all stimulants of gastric acid secretion, histamine may be considered as a single common final mediator of acid secretion on the parietal cells.

The current hypothesis states that the H_2-antagonists simply inhibit the direct actions of histamine (by forming some sort of reversible complex with the H_2-receptors) on acid secretion. The responses to stimulation of histamine H_2-receptors are mediated through the activation of adenylate cyclase, providing yet another analogy between histamine H_2- and adrenaline β-receptors.

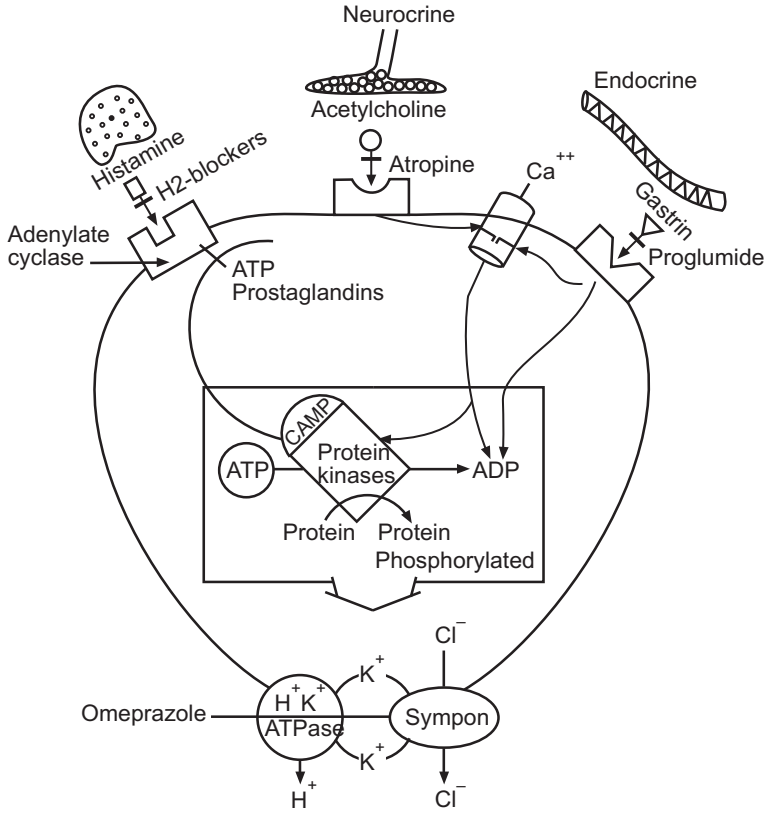


Fig. 1.6: A model of the parietal cell representing the pathways of acid secretion