تفريغ ميديسينال

محاضرة: Antihistaminic and drugs acting on GIT

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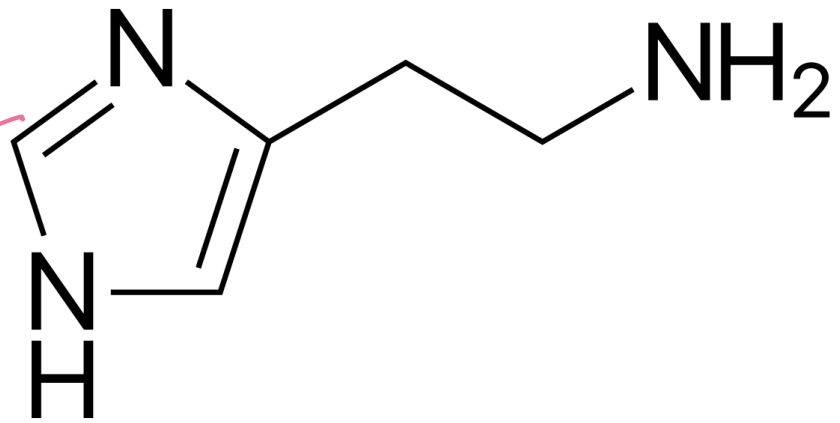
لجان الدُّفعات

Soul Academy

Antihistaminic and drugs acting on GIT

Histamine

- Histamine is an important chemical messenger.
  - Histamine is synthesized in Golgi apparatus of its principal storage cells, mast cells, and basophils.
  - Histamine is formed from the naturally occurring amino acid L-hisitidine
  - Histamine is released as a result of antigen-antibody reaction
  - After release Histamine interact with certain receptors called histaminic receptors



Histaminic receptors

- Of four types:H1 to H4.

- H1-activation:
  - Smooth muscle contraction in GIT, uterus and bronchi.
  - Relaxation of capillaries..... Increase permeability... results in edema.

- H2-activation:
  - Gastric secretion. →
  - Hypotension due to vascular dilatation.

- H3-activation:
  - Most important in CNS: regulate histamine in the body, by inhibiting the further synthesis of histamine.

- H4-activation:
  - regulate the levels of white blood cell release from bone marrow

Histamine action

بجعز افراز الhistamine

Histamine is released by cell damage

↓

Stimulates dilation of blood vessels with increased permeability

↓

White blood cells escape blood vessels and access area of tissue damage

↓

White blood cells combat infection

عشان نسمح للـ WBC انها تقدر تقدي الـ blood vessels وتدخل الـ site of damage وبترافق عنا مع الـ escape لكميات الـ water عشان هيك بصير عندي swelling و edema

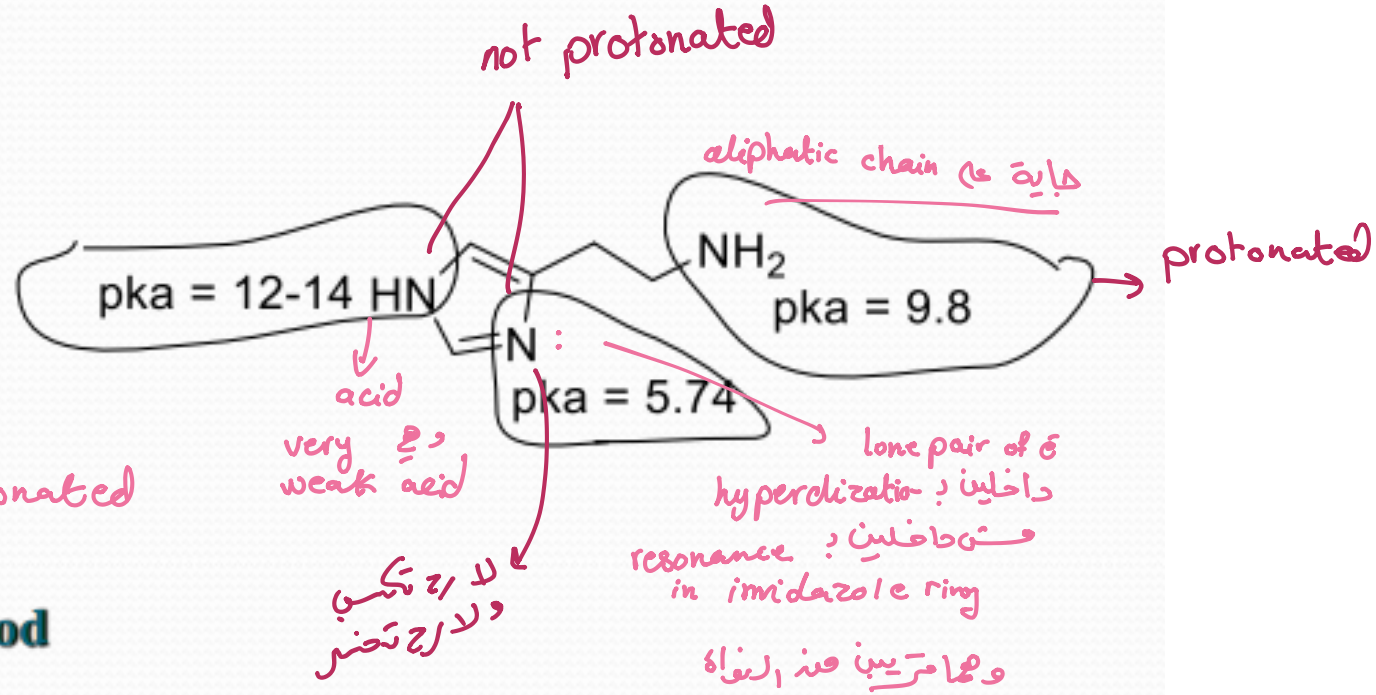
BUT

Also released by allergies, asthma, hay fever and insect bites

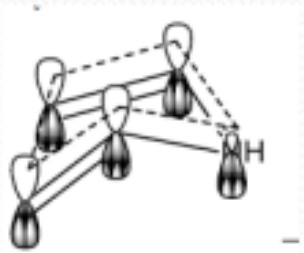
انتاج الhistamine حتى بس من الـ damage cell وكمان بكون نتيجة الـ fever و allergies و asthma

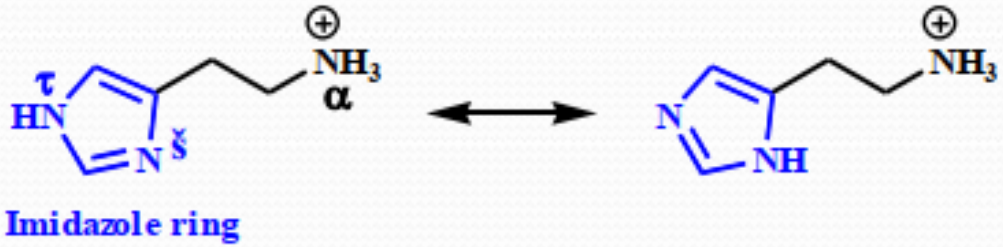
Histamine

- It has two basic centers.



- **Two possible tautomers**
- **pK_a for the α-NH_2 group = 9.80.**
- **% ionisation at pH 7.4 = 99.6** protonated
- **pK_a for the imidazole ring = 5.74**
- **Imidazole ring is not ionised at blood pH**
- **At physiological pH it presents as monocation.**





Imidazole ring

Anti-allergic agents

الـ histamine تعتبر مادة مهمة عشان الجسم يحارب اي عدو خارجي
ولكن مرات بصير عنا hypersensitivity او allergy

- Allergy: An allergy is a state of special sensitivity to a particular environmental substance, or allergen.

اشي مفيد للجسم
اذا كانت mild ولكنة اذا كانت severe ح تهدد حياة المريض

- An allergic reaction is the body's response to exposure to an allergen.

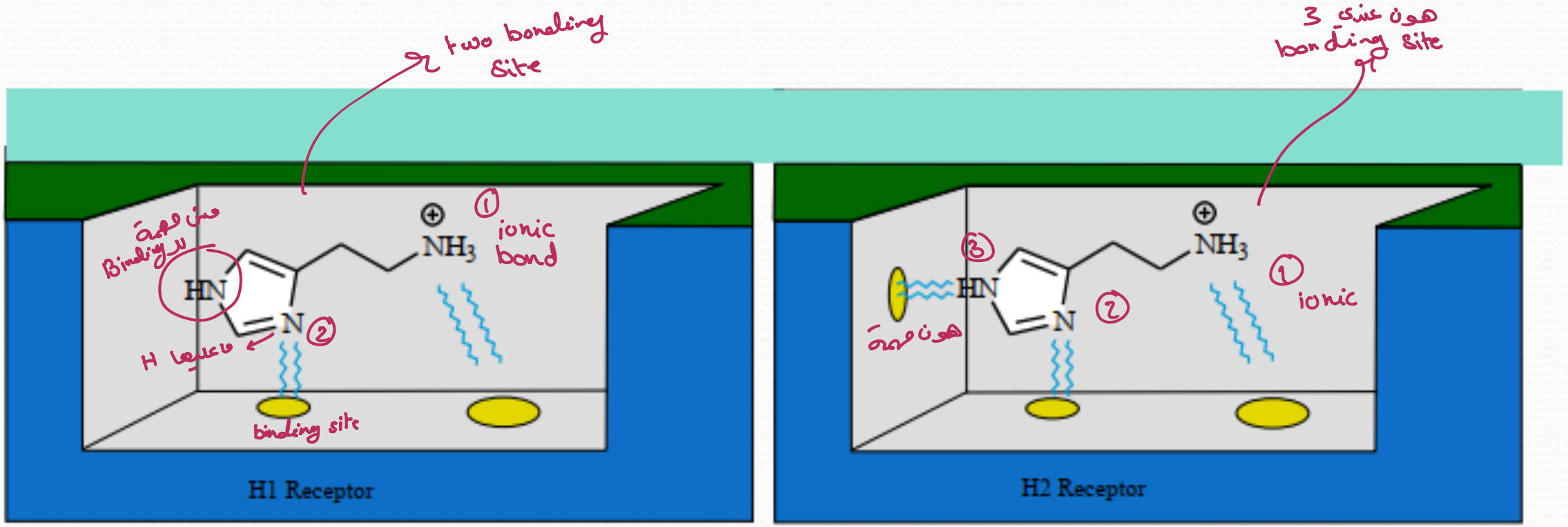
- An allergic reaction can be so mild that it is barely noticeable or so severe that it is life-threatening. An extremely severe allergic reaction, called *anaphylactic shock*, is marked by breathing difficulties (from swelling of the throat and larynx and narrowing of the bronchial tubes), itching skin, hives, and collapse of the blood vessels, as well as by vomiting, diarrhoea, and cramps. This condition can be fatal if not treated immediately.

كل هاي الأعراض اذا ما قدرت اعالجها immediately ح تكون مميتة

- Anti-allergic agents block some of the action of histamine.

SAR for the H1 and H2 Agonist

- Two nitrogen atoms are required for H_1 agonist activity
- All three nitrogen atoms are required for H_2 agonist activity



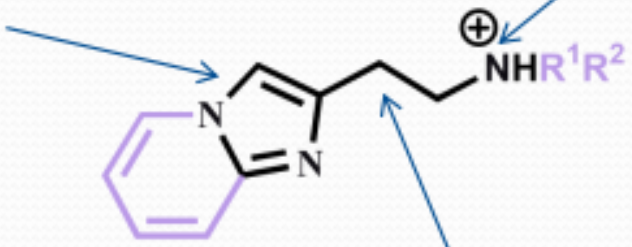
Strategies for Converting Agonists to Antagonists

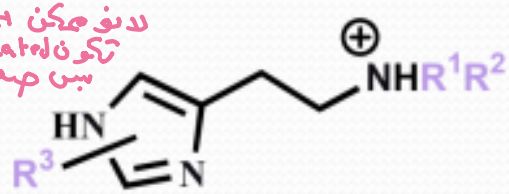
لازم تكون موجبة

The amino group should be positively charged and attached to at least one hydrogen atom.

The heteroaromatic do not have to be imidazole

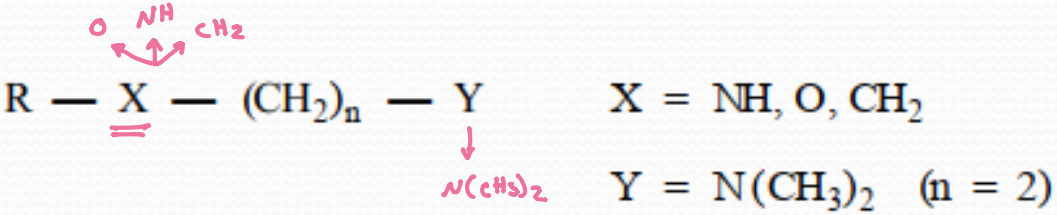
يعني مسموح ال amine تكون 1° و 2° وال 3° لا تكون موجبة لانو ممكن H وحدة protonated تكون بين موجبة.





It should have flexible chain between the amino and the aromatic ring.

Antihistamines

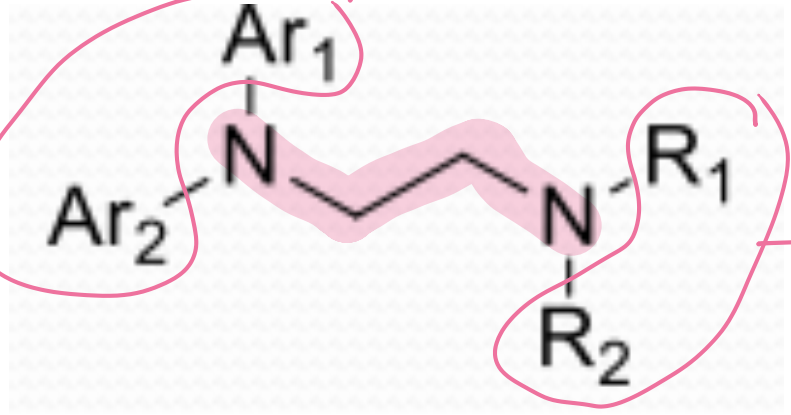


ال H1 ↓ Ring ال حتى شرط تكون imidazole

كيف حولت المركب من agonist ↓ antagonist يعني antihistamine

Ethylenediamine derivatives
H1 antagonists

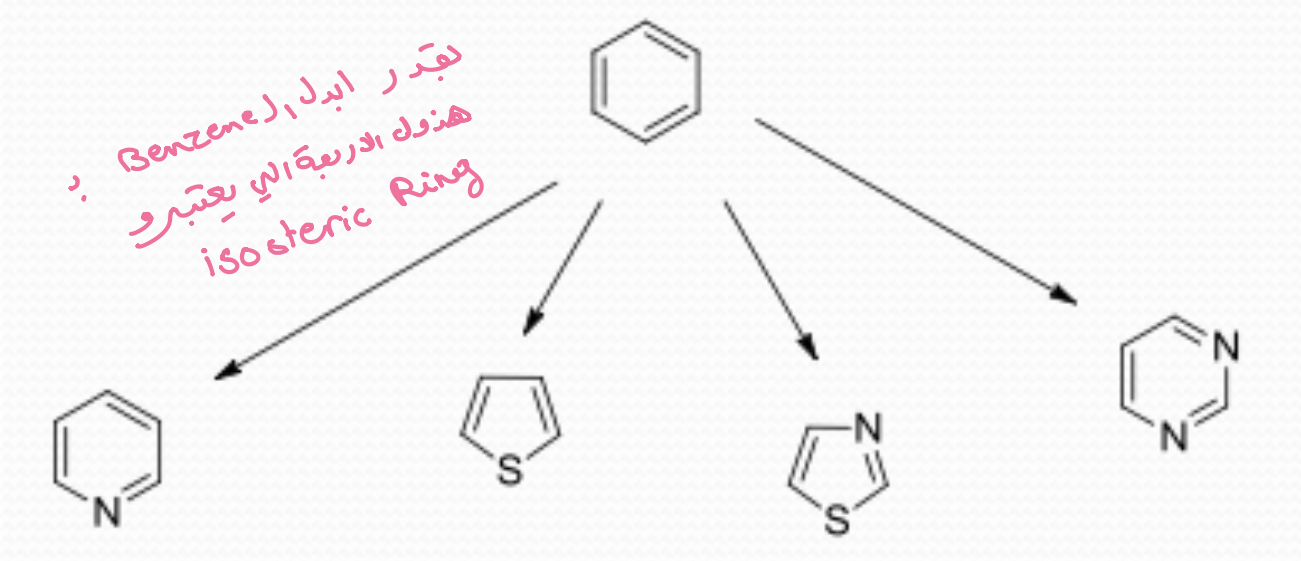
- R1 and R2 should be small (CH_3) for maximum H1-antagonist activity.

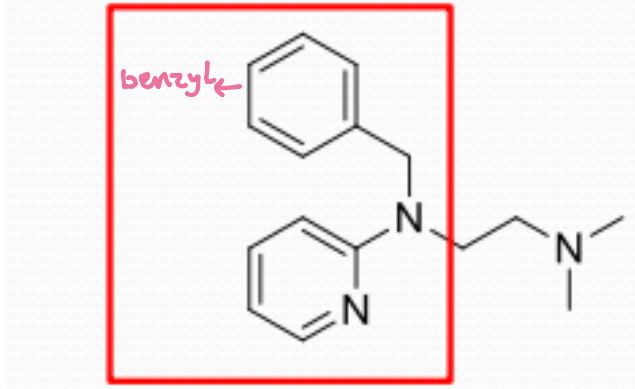


- Ar1 and Ar2 can be benzene ring or any other isosteric rings such as heterocycles.
- One of the aromatic rings should be benzyl for better activity which has *P*-substitution.

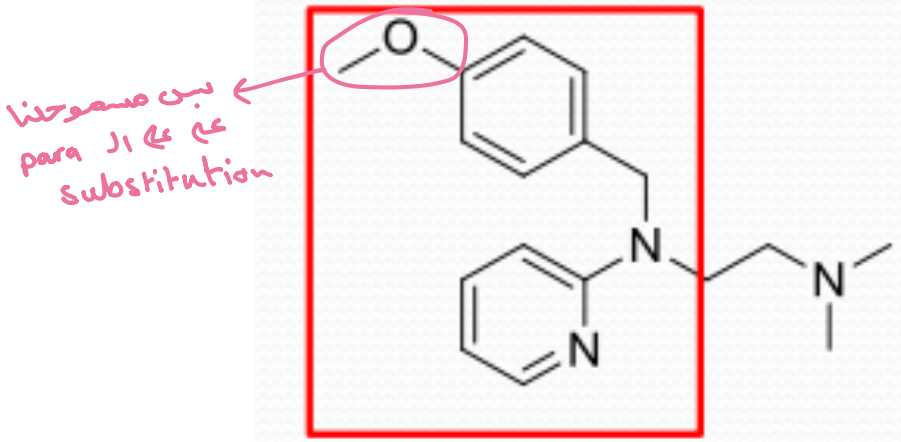
Ethylenediamine derivatives

- Isosteric rings to benzene:





Tripellenamine

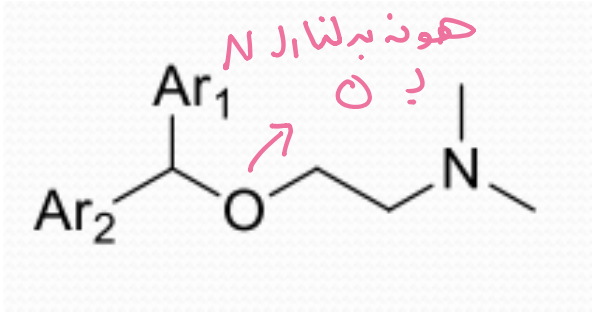


Pyrilamine (mepyramine)

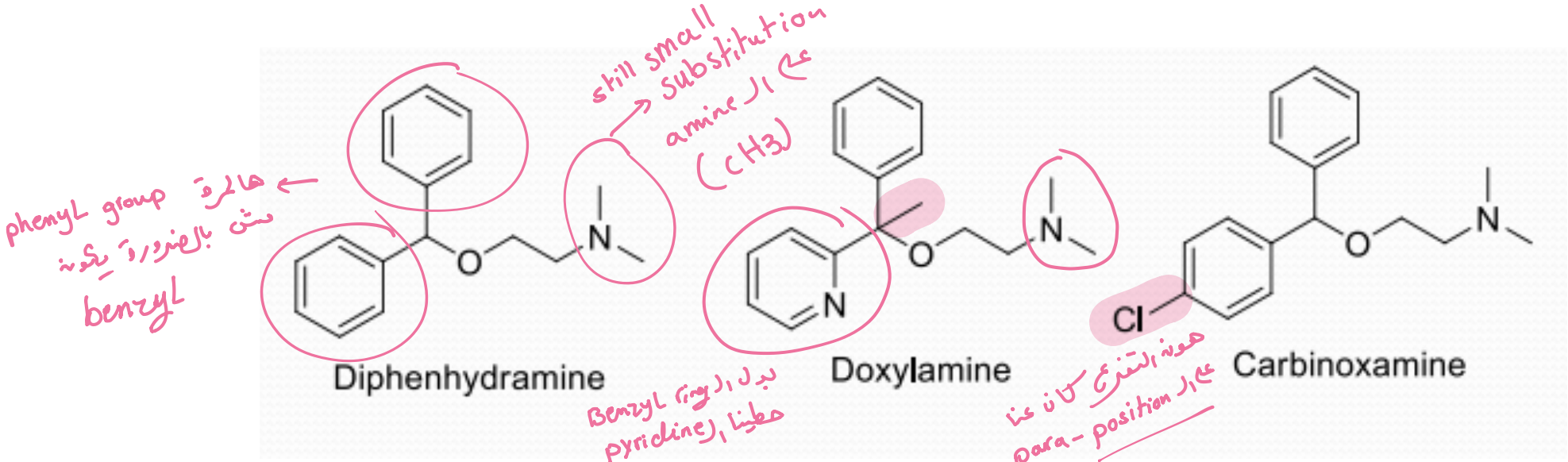
- All H1-antagonists are dispensed as water soluble salts.

Aminoalkyl ether analogues

- Closely related to ethylenediamine derivatives.

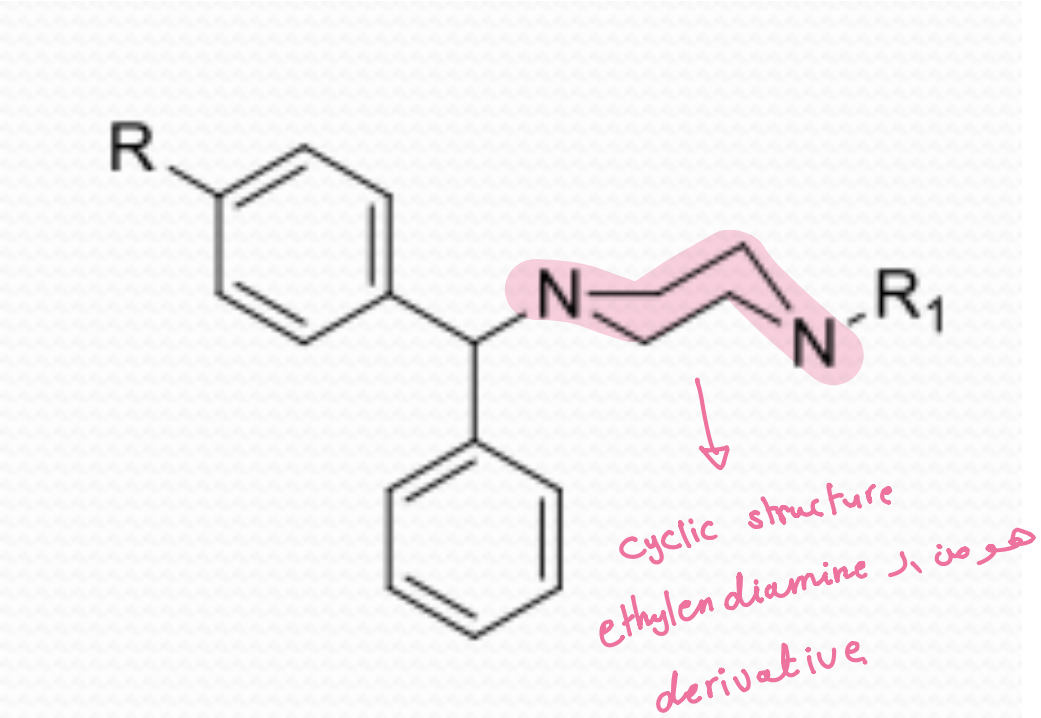


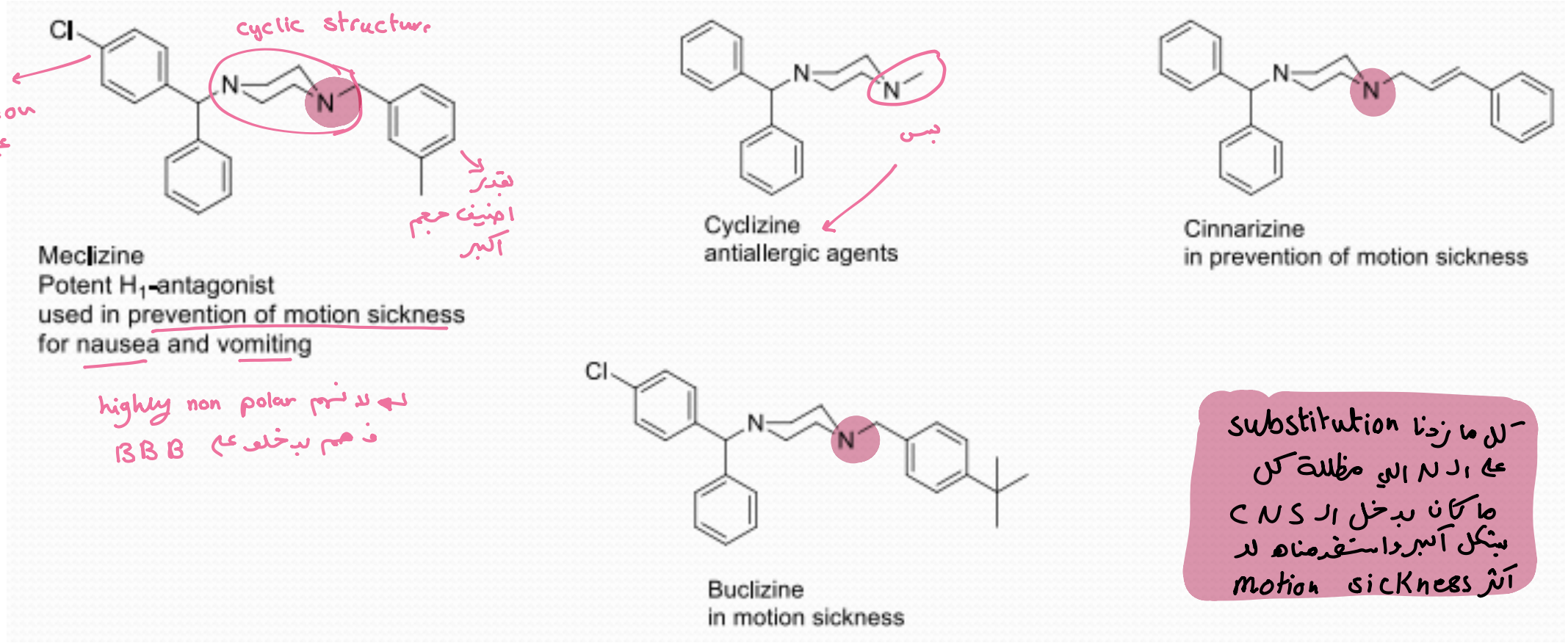
- Examples:



Cyclic analogues of ethylenediamine

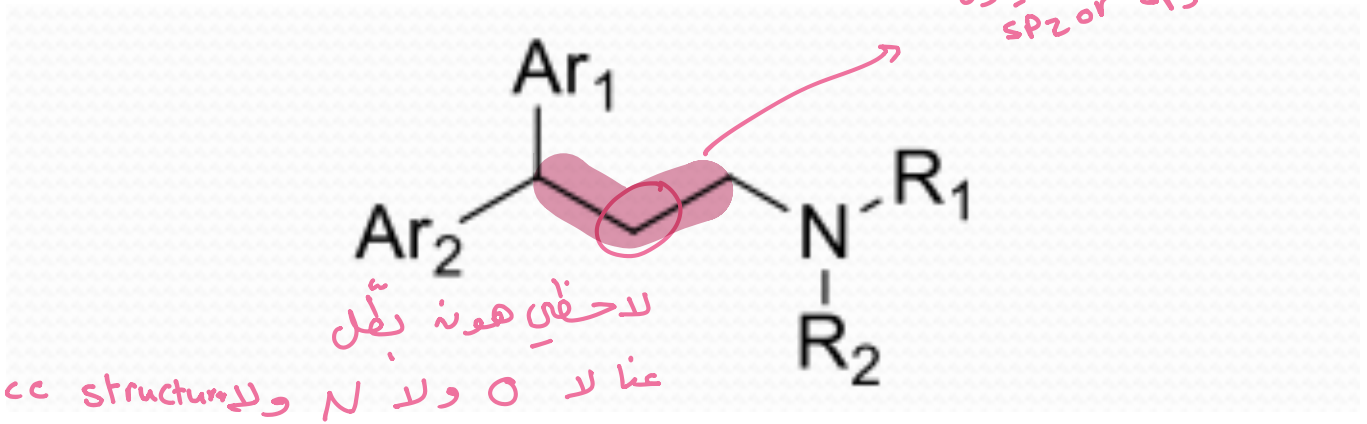
- They have mainly CNS depressant effects.
- Main uses:
  - In allergy.
  - As antiemetic agents.
  - In motion sickness.



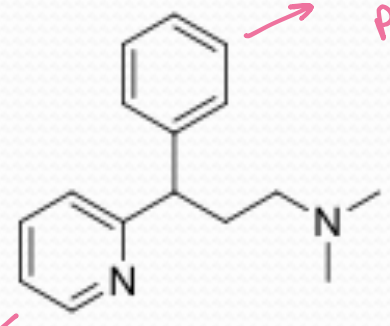


- All have hydrophobic group attached to the terminal amino group for better activity compared to ethylenediamine derivatives
- They have a rigidified ethylenediamine structure.
- They have antimuscarinic activity

Propylamines (monoaminoproprylamines)



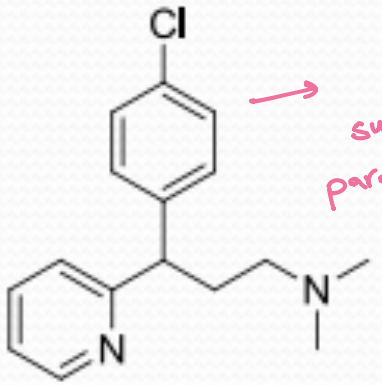
- Mainly have a phenyl and 2-pyridyl groups, and a terminal dimethylamino moiety.
  - The hydrophobic linker should have either sp2 or sp3 carbons.
  - They are less sedating compared to the ethylenediamine derivatives.
  - The *S* enantiomer is the most active form.



الدائرة الثانية phenyl group

pyridine

Pheniramine

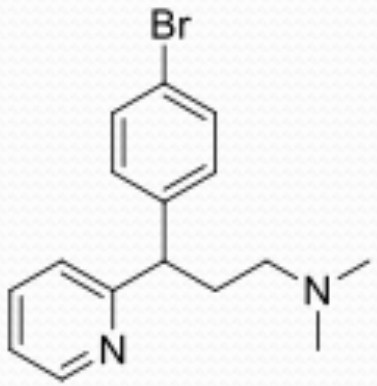


phenyl group substitution-ها في para position

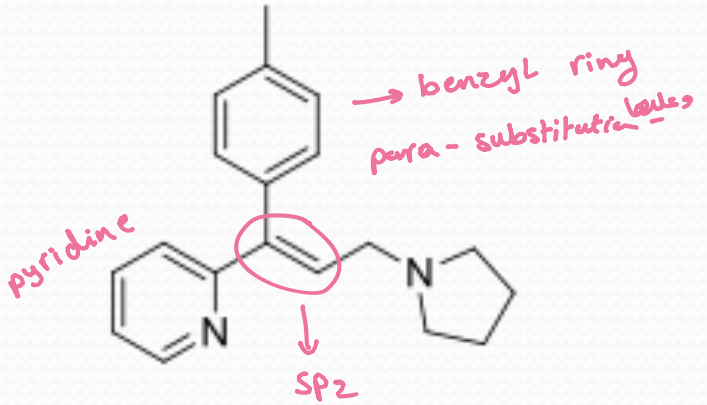
pyridine

Chlorpheniramine
20-50% more potent than pheniramine
longer duration of action
t1/2 = 12hrs

كل هذول المركبات بدخلو مع الـ CNS والمهم sedation في احنا بدهنا sedation بيطل في عنا ↓ وراح نشرح بالسلايد اللي تحت



Brompheniramine
longer duration of action (t1/2 = 25hrs)
same potency as chlorphinarmine



benzyl ring para-substitution

pyridine

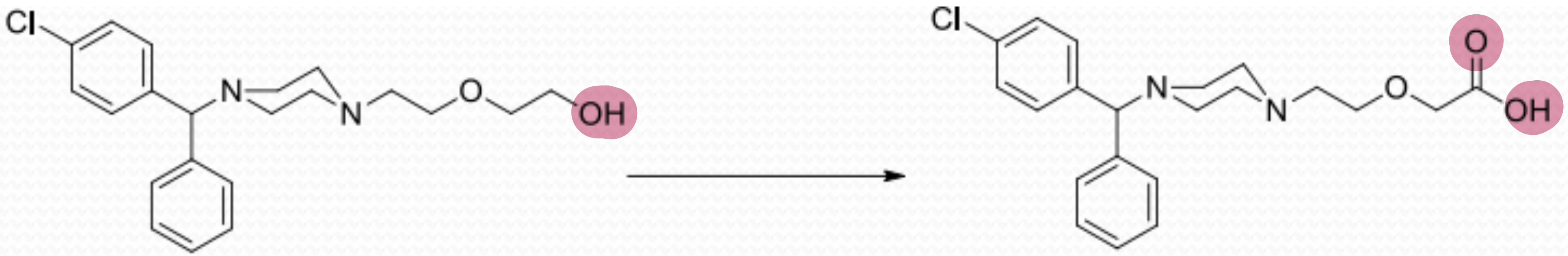
Triprolidine
pyridyl and the pyrrolidinomethyl should be trans to each other for superior activity

trans لازم يكونو activity عشان يعطينا

H1-antagonists with decreased sedative effects

- The major side effect of H1-antagonists is sedation due to the interaction with cerebral H1 and H3 -receptors.

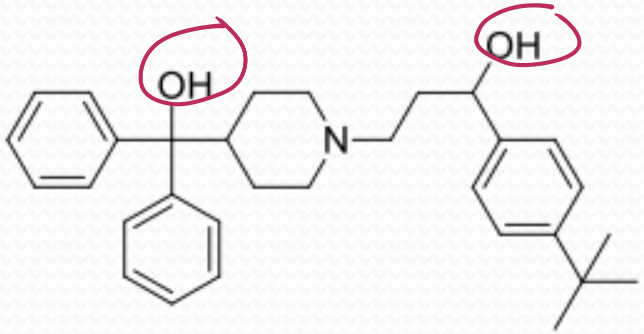
- Strategies to decrease sedation:
- Increase selectivity to the peripheral compared to the central H1-receptors.
- increase polarity of classic H1-receptors to decrease the ability to penetrate the BBB.
- These non-sedating antihistamines have greater receptor specificity, lower penetration of blood-brain barrier, and are less likely to cause drowsiness



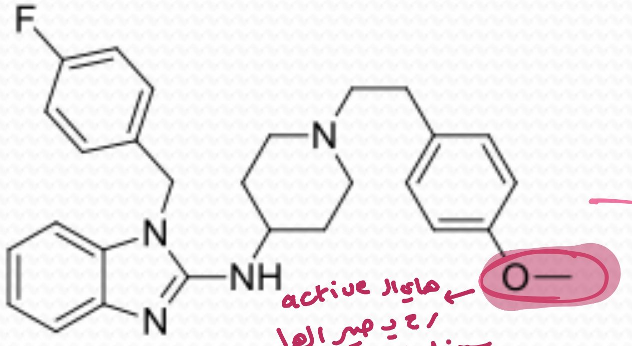
Hydroxyzine
cause sedation as s/e

Cetirizine
presents as zwitter-ionic compound
has reduced sedative s/e

بدل الكحول حطينا الحمض carboxyl acid
ف قلل ال sedation



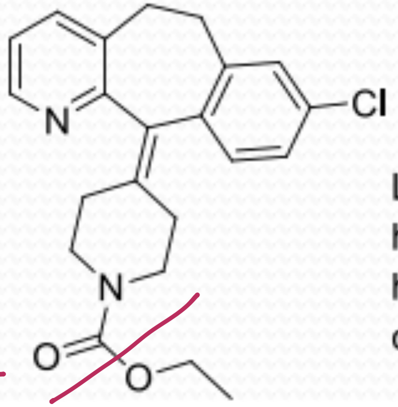
Trefinadine



هون عدل N ←
Long duration ال of action

active هاد ←
رح يصير الها dealkylation or demethylation

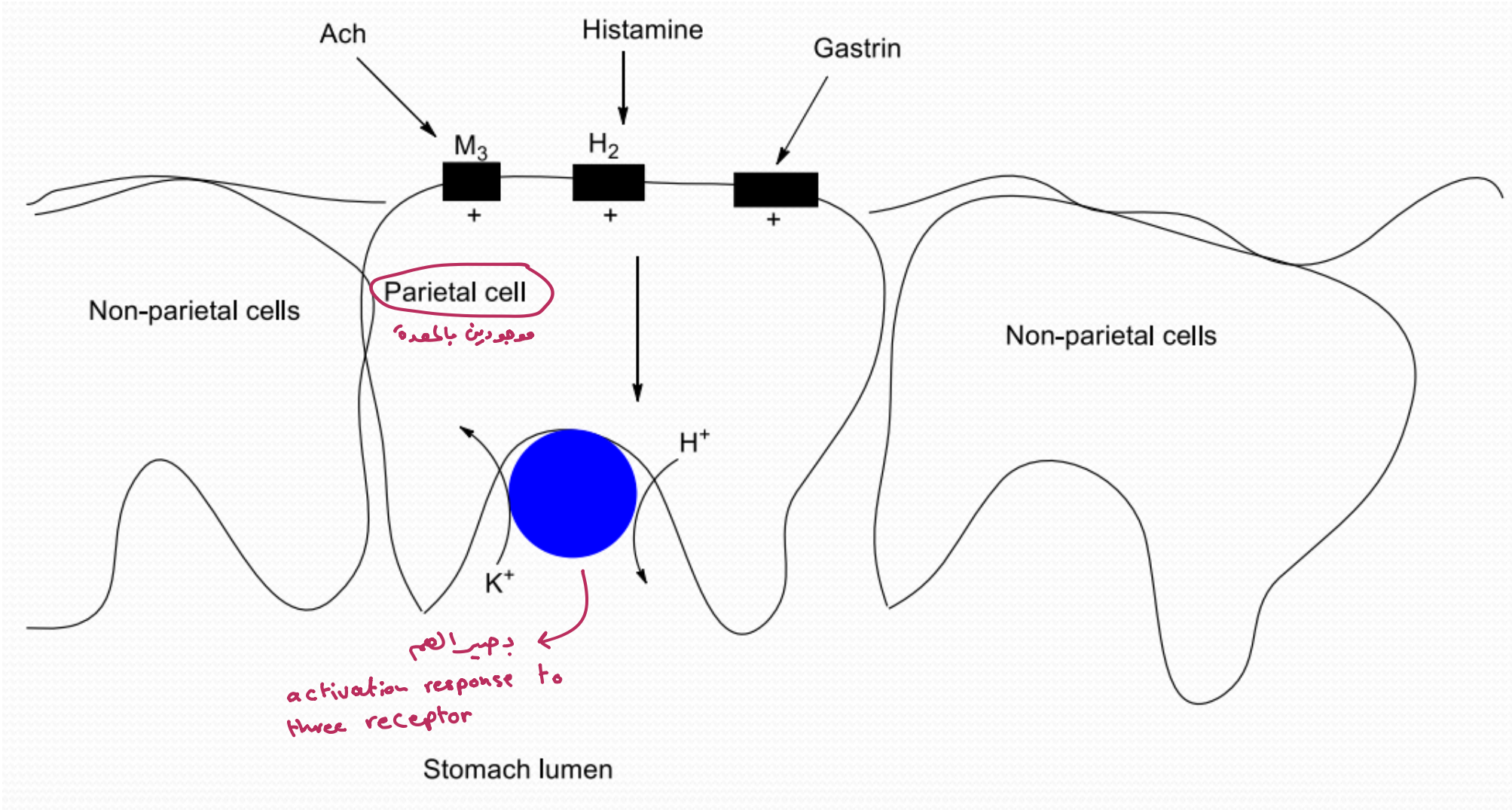
Astimizole
Has no sedative effects due to poor penetration of the BBB.
Has long duration of action because its metabolite (desmethyl) is also active.



Loratidine
higher affinity for peripheral H_1-receptors.
has long duration of action due to the lipophilic nature and the stable carbamate group.

at physiologic pH
رح تنكسر الرابطة استر وتعطينا
carboxylic acid وتعطينا

H2-antagonists: Anti-ulcer agents

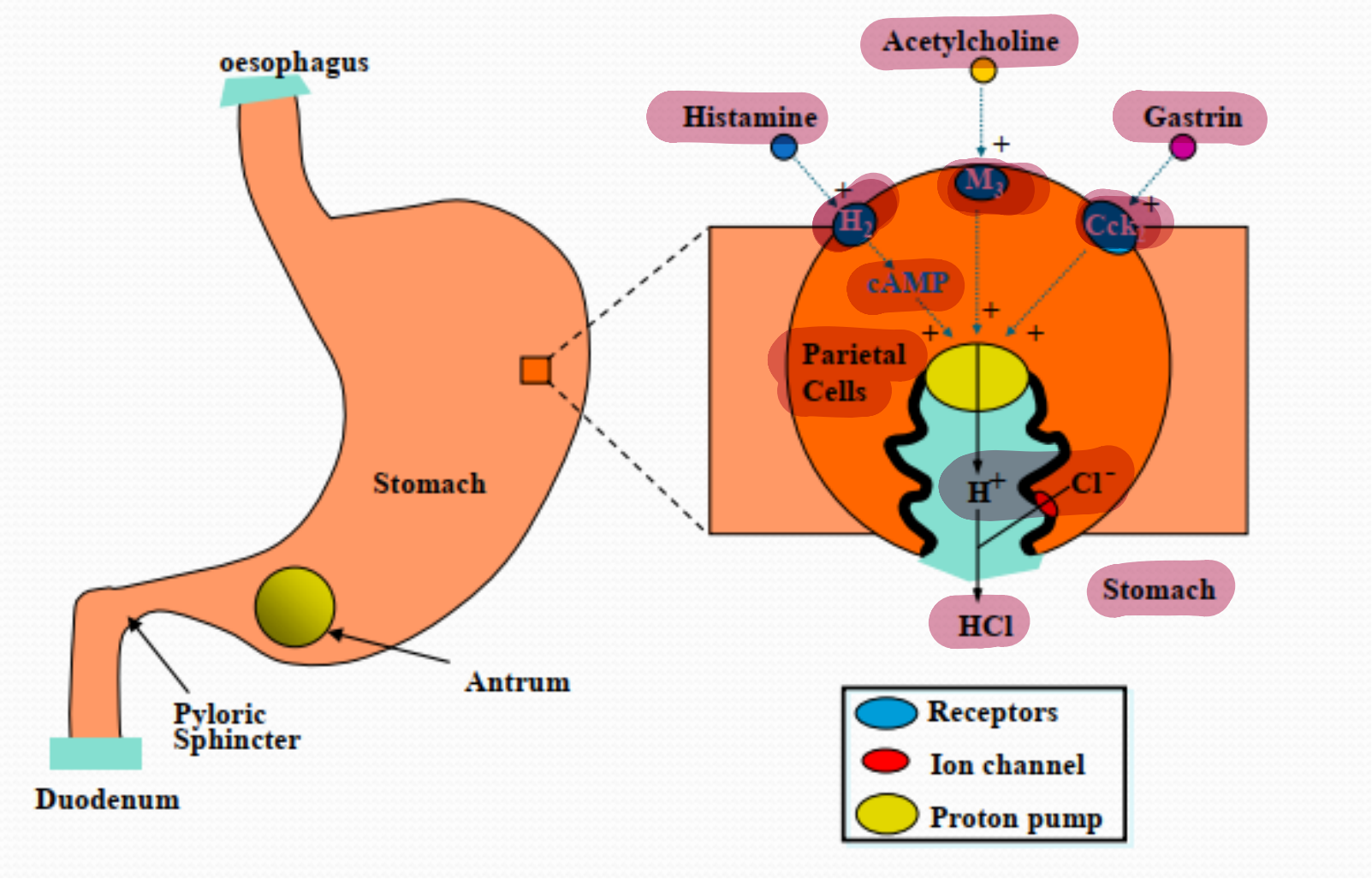


Introduction

- Ulcers
- Localised erosions of the mucous membranes of the stomach and duodenum.
- Potentially fatal if untreated
- Caused by stress, infection (*H. pylori*) and drugs (NSAIDs)
- Aggravated by gastric acid (HCl) in the stomach

- Therapy of ulcer:
- Lower the level of gastric acid
- Histamine antagonists and proton pump inhibitors
- Antibacterial agents for *H. pylori*
- Increasing the pH of the stomach

Parietal cells and gastric acid secretion



هيك بنغزز عنا
اد HCl بالمعدة .

Release of gastric acid is promoted by acetylcholine, gastrin and histamine

هذا كل تلخيص

- Gastric secretion in stomach is controlled by:
  1. Acetylcholine: M3-activation which lead to the production of acid.
  2. Gastrin hormone: will be released from the G-cells in the antrum … this will interact with Cck2 receptor in the parietal cells to produce the gastric acid.
  3. Histamine: will bind to the H2-receptors… gastric acid production.
  4. The proton pump: will pump the formed acid (H+) out of the Parietal cells into the stomach lumen.

للازم نعالجها و نقلع ال pain
ونمنع ال complication
+ recurrence

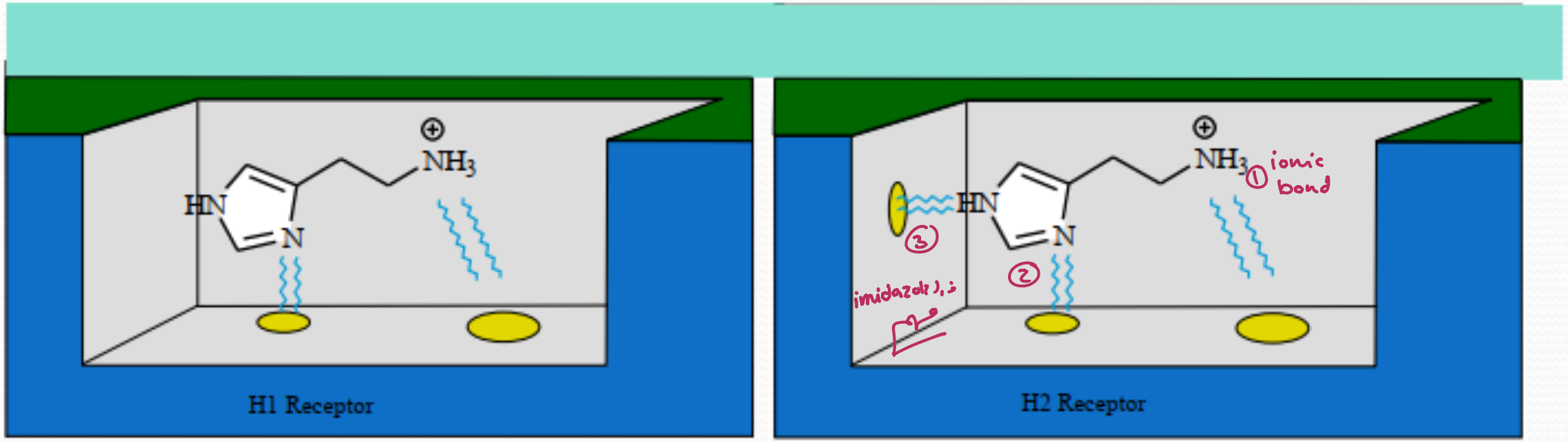
- The goals of PUD therapy are to promote healing, relieve pain, and prevent ulcer complications and recurrences.

General treating

- Medications used to heal or reduce ulcer recurrence include antacids, histamine H2-antagonists, protective mucosal barriers, proton pump inhibitors (PPIs), prostaglandins, and bismuth salt and combinations of these drugs with antibiotics to eradicate *H. pylori* infection.

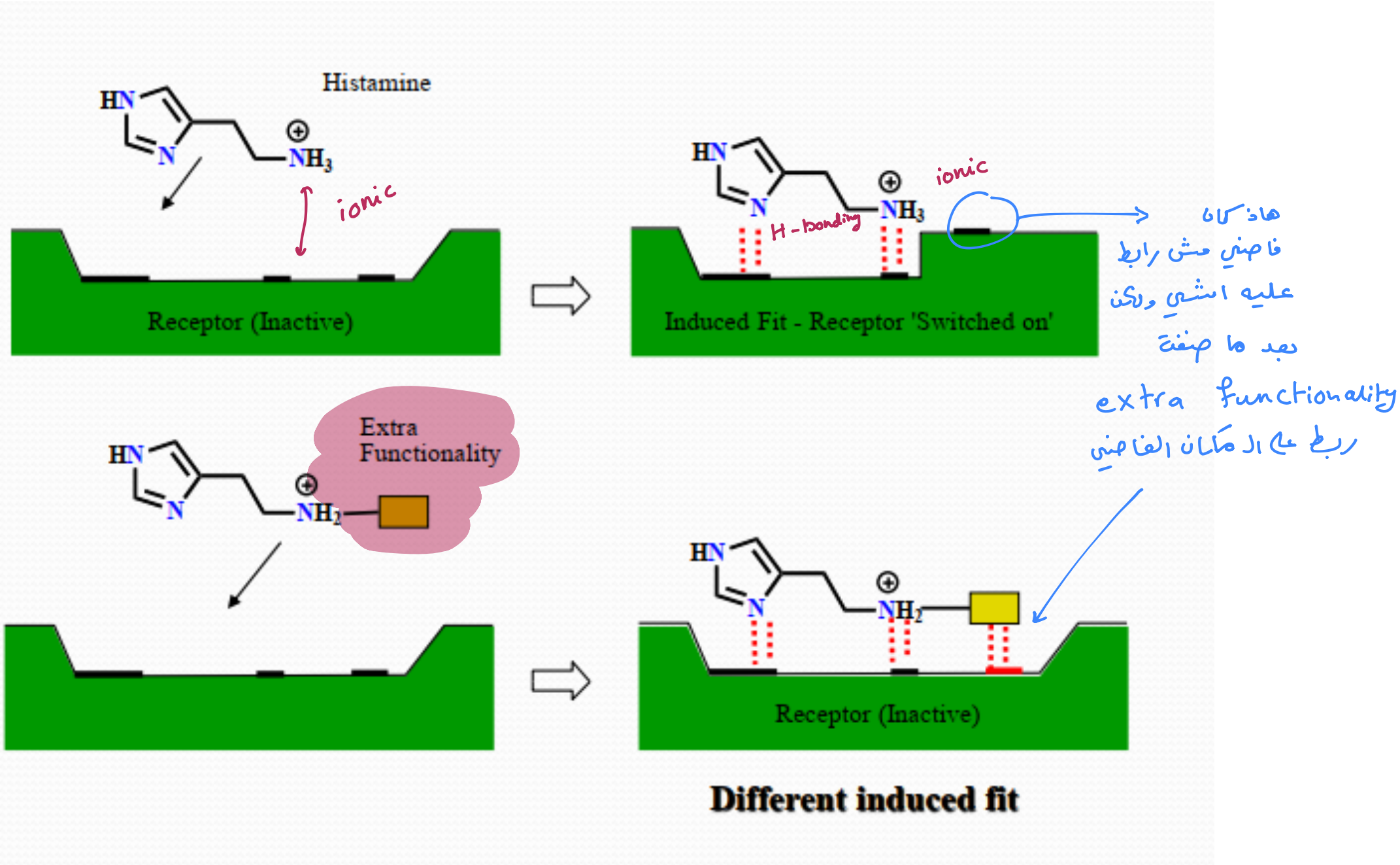
SAR for the H1 and H2 Agonist

- Two nitrogen atoms are required for H_1 agonist activity
- All three nitrogen atoms are required for H_2 agonist activity



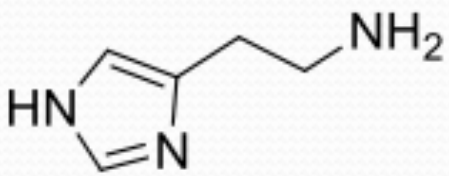
Strategies for converting agonists to antagonists

- Add an extra functional group to find extra binding interactions with the binding site.
- Extra binding interactions may result in a different mode of binding resulting in a different induced fit for the receptor.
- Different induced fit may fail to activate the receptor.
- As a result, analogue binds but fails to activate the receptor
- Analogues are likely to bind more strongly than agonists

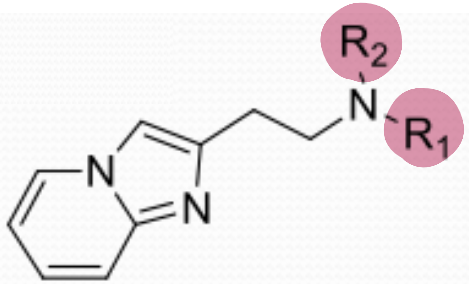

Histamine
HN
N
NH3
ionic
Receptor (Inactive)
Induced Fit - Receptor 'Switched on'
H-bonding
ionic
هاذ كان فاضي مش رابط عليه اشي ولكن بعد ما صفنة
extra functionality ربطت على المكان الفاضي
Extra Functionality
NH2
Receptor (Inactive)
Different induced fit

- The First approach in synthesizing H2-antagonists was the use of Histamine as the lead compound to produce antagonist activity.
- Can be done by:
  - Adding extra hydrophobic group to the structure.
  - Varying the polar amino group.
  - Make extension to the ethyl linker between the amino and the imidazole ring

ما غيرنا فيها ولا قربنا عليها لانها ممتازة بـ H2

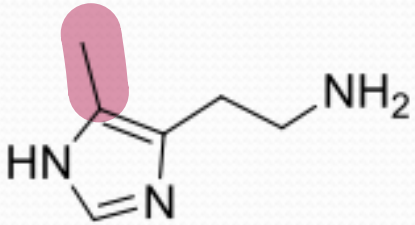


Histamine



Hydrophobic analogues
None were active

active ما كان فعالة

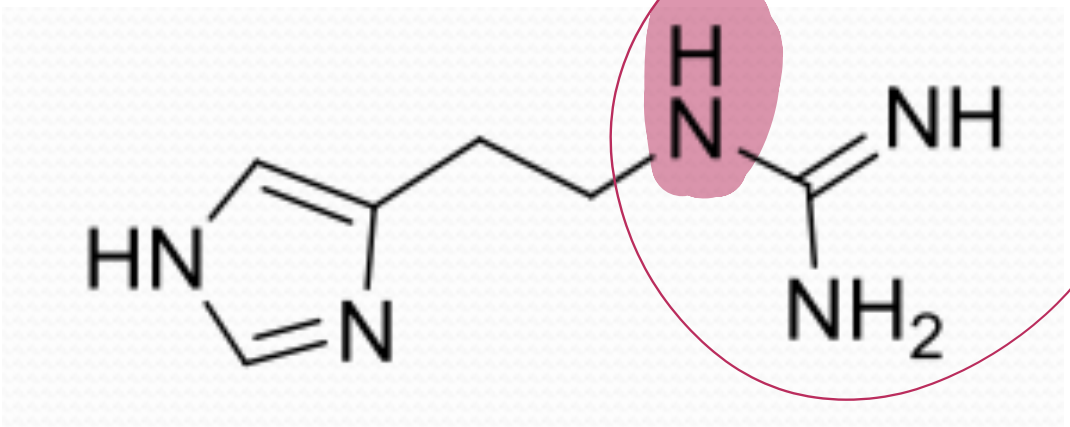


Was found to be selective H_2-agonist

- The next approach was to vary the polar groups in histamine with other polar functional groups.

polarity عزدو ب

- The first derivative was *N*-guanylhistamine:



imidazole ال صفتنا على ال
او ال N الطرفية فافاد

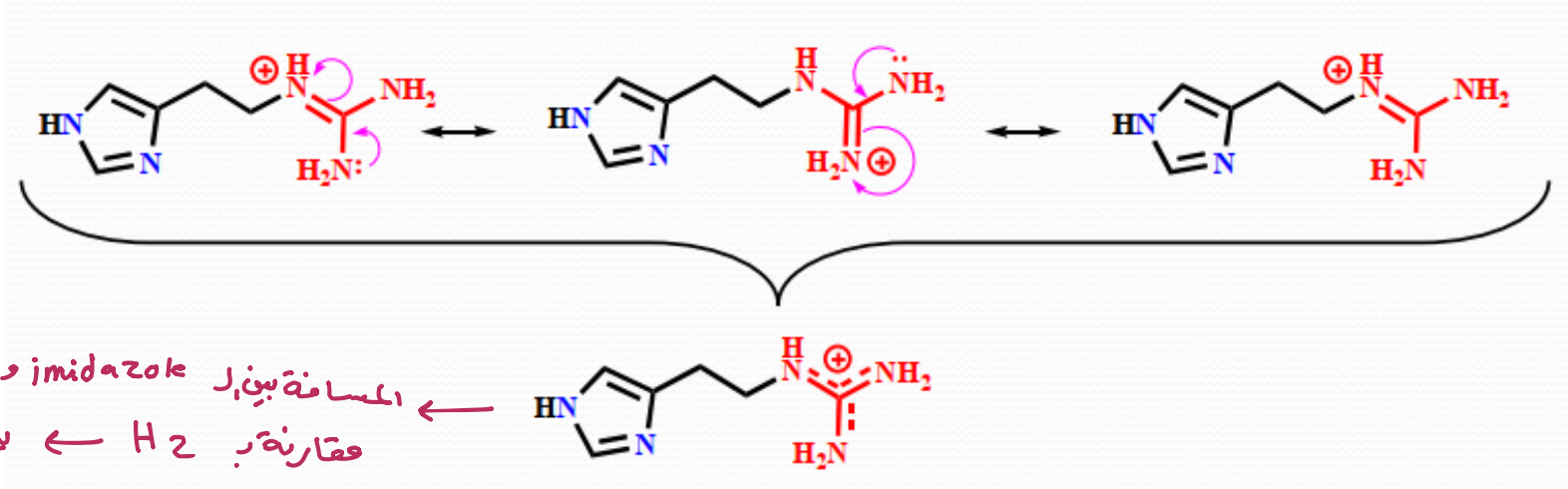
ف شو عملت ؟؟
guanyl group بدلت ال NH2 ب
ف زدت ال polarity

+ charge ال
ز تكون متوزعة على
N ال ٣
و هي ز تكون protonated
at physiological pH

- Has a weak H2-antagonist (partial agonist). يعني بلشنا نزود ال antagonist
- The guanidine moiety has a positive charge at physiological pH which will be distributed over the three nitrogen atoms.

Nα- guanyl histamine

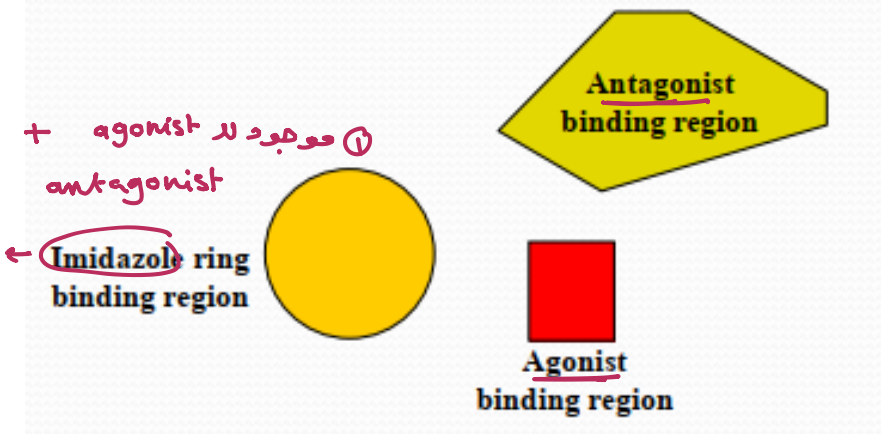
- The guanidine group is basic and ionised
- Different tautomers are possible
- The positive charge can be delocalised

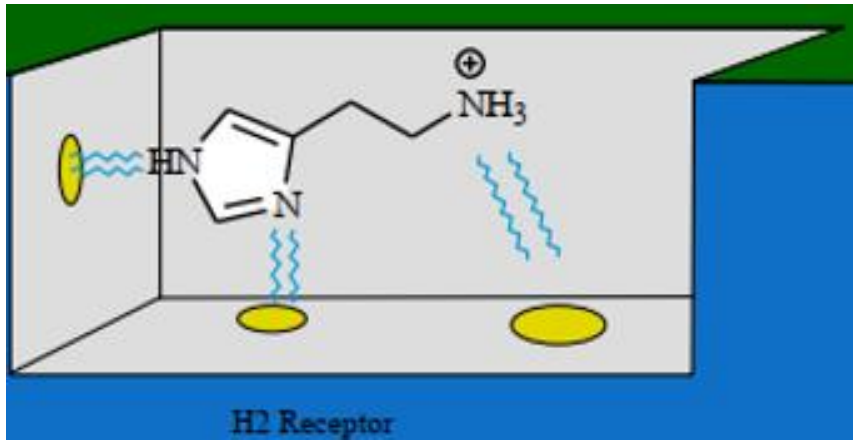


- The positive charge is more diffuse and can be further away from the imidazole ring

Binding theory for agonists and antagonists

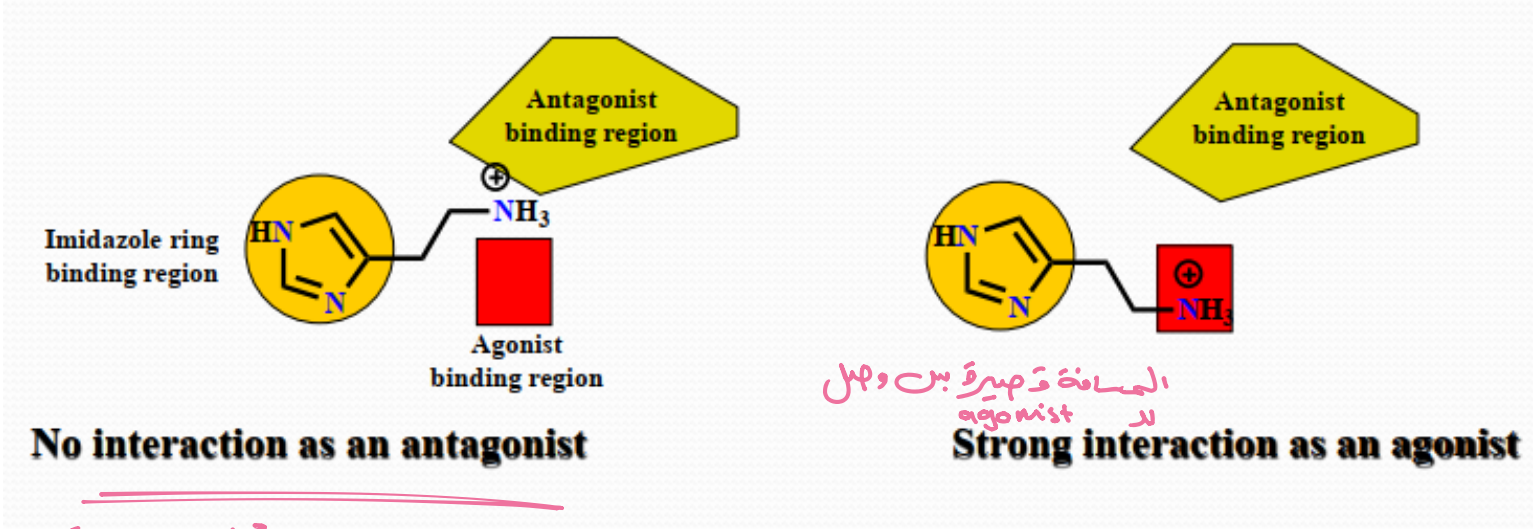
* Binding of histamine





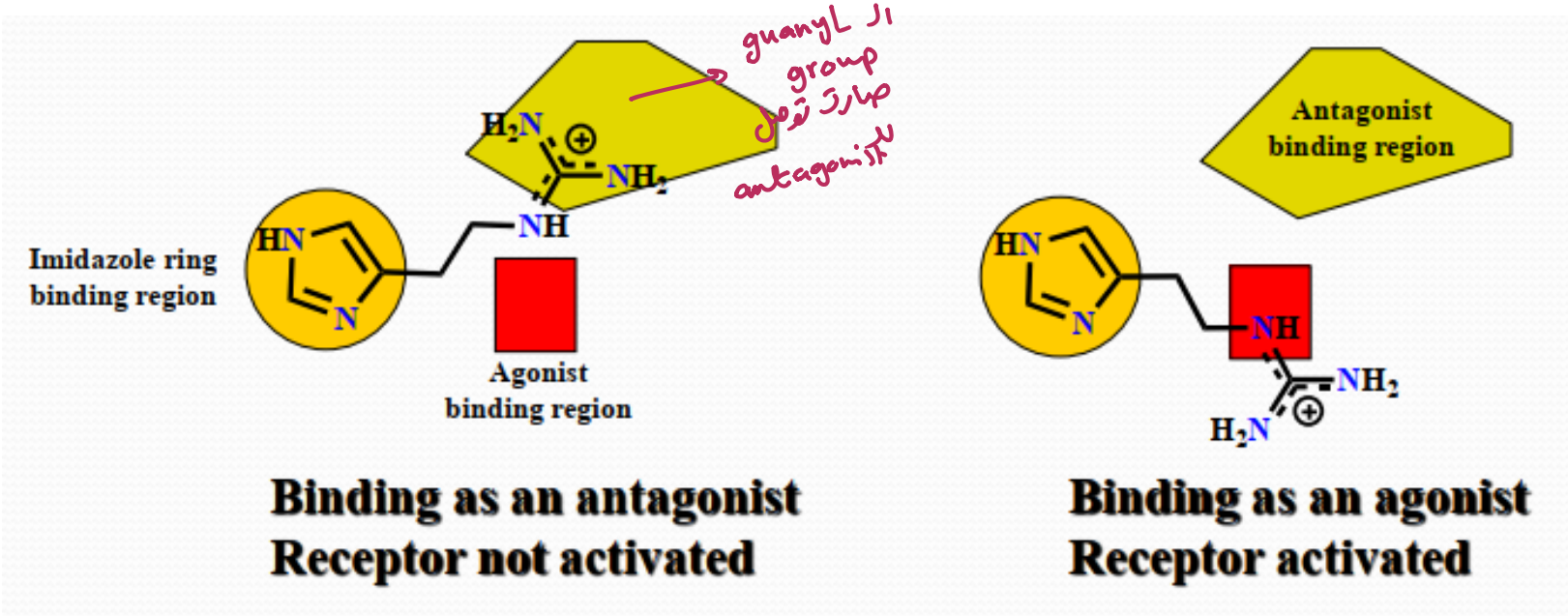
- Three binding regions are proposed for the H2 receptor; an imidazole binding region and two polar binding regions
- Two binding modes are proposed; one for agonists and the other for antagonists.
- The imidazole binding region is common to both binding modes
- One of the polar binding regions is accessed by agonists and the other by antagonists
- The antagonists polar regions is further from the imidazole binding region

- Histamine has a short chain
- Charged α-nitrogen can only reach the polar agonist region
- The antagonist binding region is out of range
- Histamine can only bind as an agonist
- Histamine acts as a pure agonist

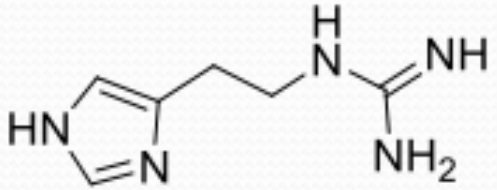


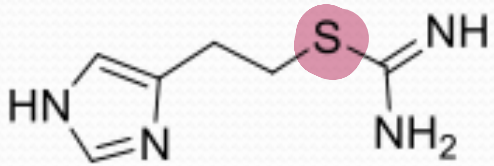
Binding of Nα-guanylhistamine

- Positive charge on the structure is more diffuse and further out
- Allows Nα - guanylhistamine to bind in two different modes (agonist and antagonist), making it a partial agonist.

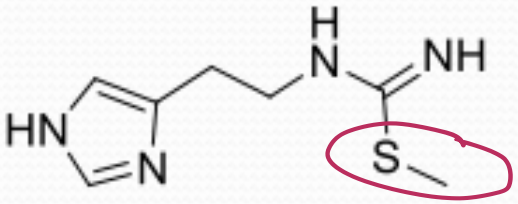


N-guanylhistamine as a lead

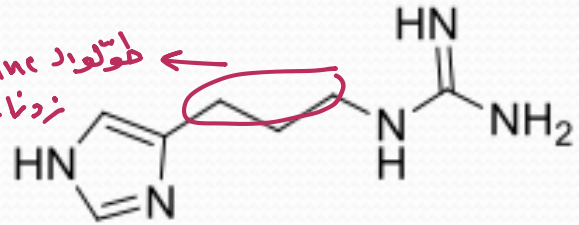




partial agonist
poor antagonist



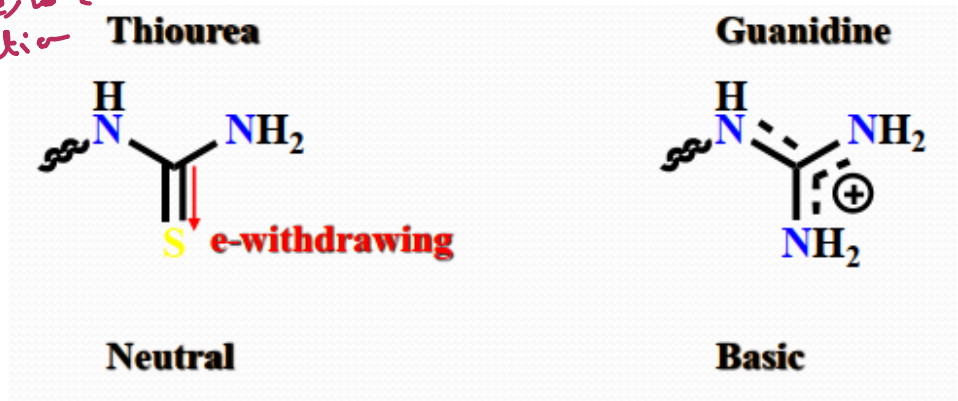
1. partial agonist
2. poor antagonist
3. this means that both terminal amines are essential for activity.



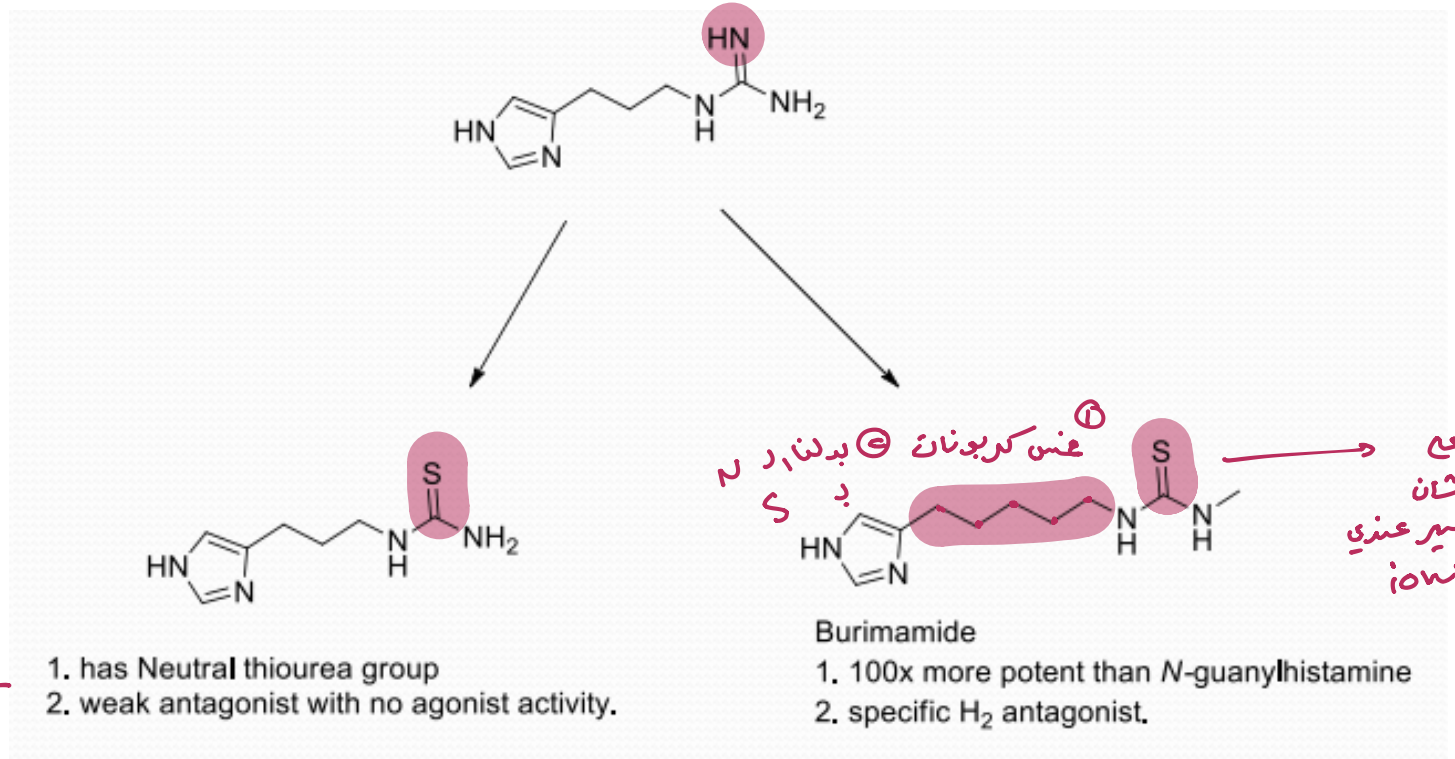
antagonist activity increased

Distinguishing between the polar binding regions

- Comparison between the thiourea and the guanidine groups
- Similarities: planetary, geometry, size, polarity, H- bonding
- Differences: thiourea is neutral while guanidine is basic and ionised



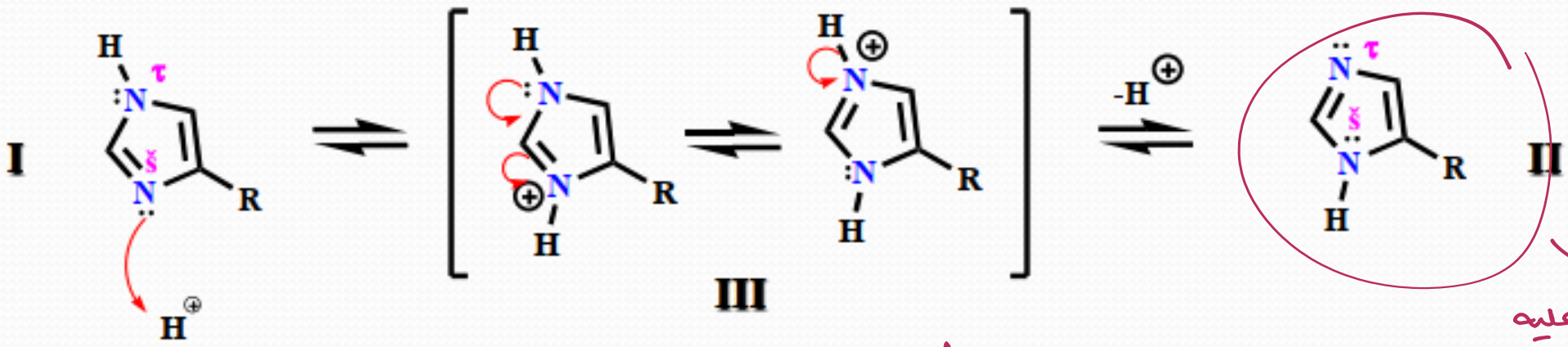
- Conclusion:
- Agonist polar region involves ionic and H-bond interaction
- Antagonist polar region may not require ionic interaction. H-bond may be sufficient



- The imidazole ring proofed to be important for both agonist and antagonist binding. So the pka of this ring should be closer to the histamine one (5.74).
- The pka of imidazole from burimamide is 7.25 which means that around 40% of the imidazole ring is ionized.
- The side chain of burimamide should be electron withdrawing to make the pka of The ring close to 5.74.

The imidazole ring

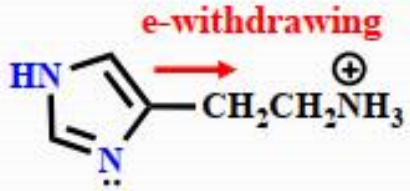
1- structure



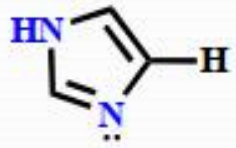
- **Imidazole ring can exist as two tautomers (I) and (II) as well as two ionised forms (III)**
- **Which of these is preferred?**

The imidazole ring

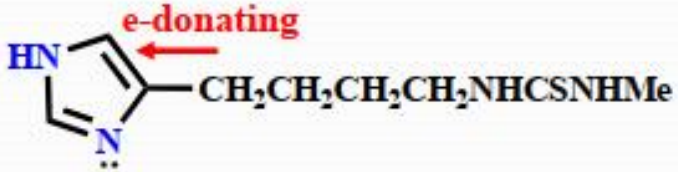
2- basicity



Histamine
pK_a = 5.74
Ionisation = 3%



Imidazole
pK_a = 6.80



Burimamide
pK_a = 7.25
Ionisation = 40%

ما بدي اياهم
ذبروح بصنف
EWG

Conclusions

- **The imidazole ring of histamine is not ionised when it interacts with the imidazole binding region**
- **The ionised form of burimamide is unlikely to bind well**
- **Decreasing the basicity and ionisation of the imidazole ring in burimamide closer to that of histamine may increase the binding interactions to the imidazole binding region**

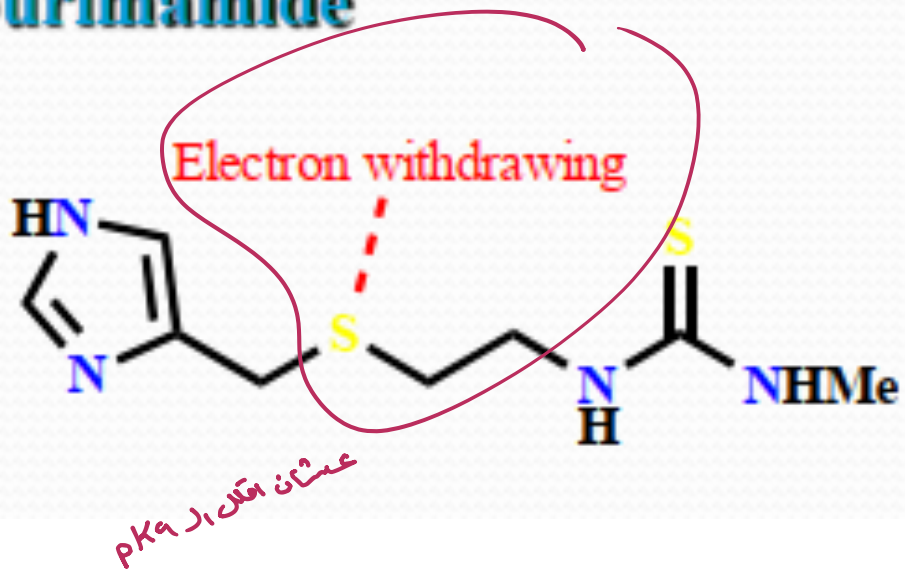
The imidazole ring

2- varying basicity

Strategy

Convert the side chain of burimamide to an e-withdrawing group

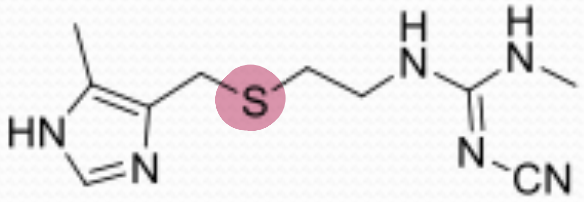
Thiaburimamide



pK_a = 6.25

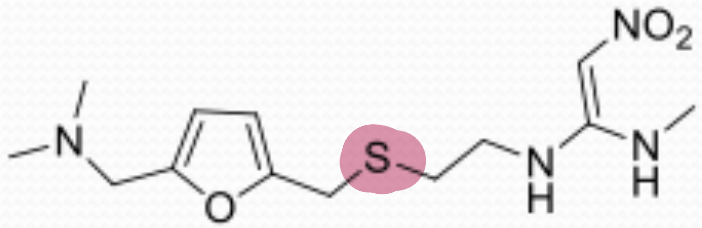
Increase in antagonist activity

Non-ionised imidazole is favoured

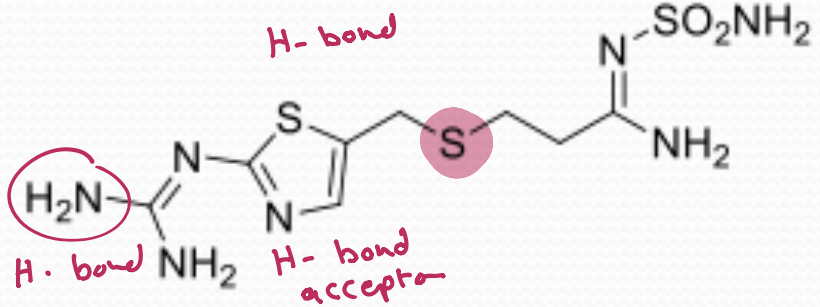


Cimetidine

mild — non ionized



Ranitidine
Fewer s/e than cimetidine
10x more active



Famotidine
30x more active than cimetidine

Cimetidine

- Properties
- Comparable activity to metiamide
- Less side effects
- Drug-drug interactions with diazepam, lidocaine and warfarin Inhibits cytochrome P450 enzymes
- Metabolically stable
- Marketed in 1976
- Biggest selling prescription drug until ranitidine
- Inhibits H2-receptors and lowers levels of gastric acid released

فعاليتواعلى مع SE اقل

SE اقل Ranitidine
وبطلو يستخدموا
Cimetidine

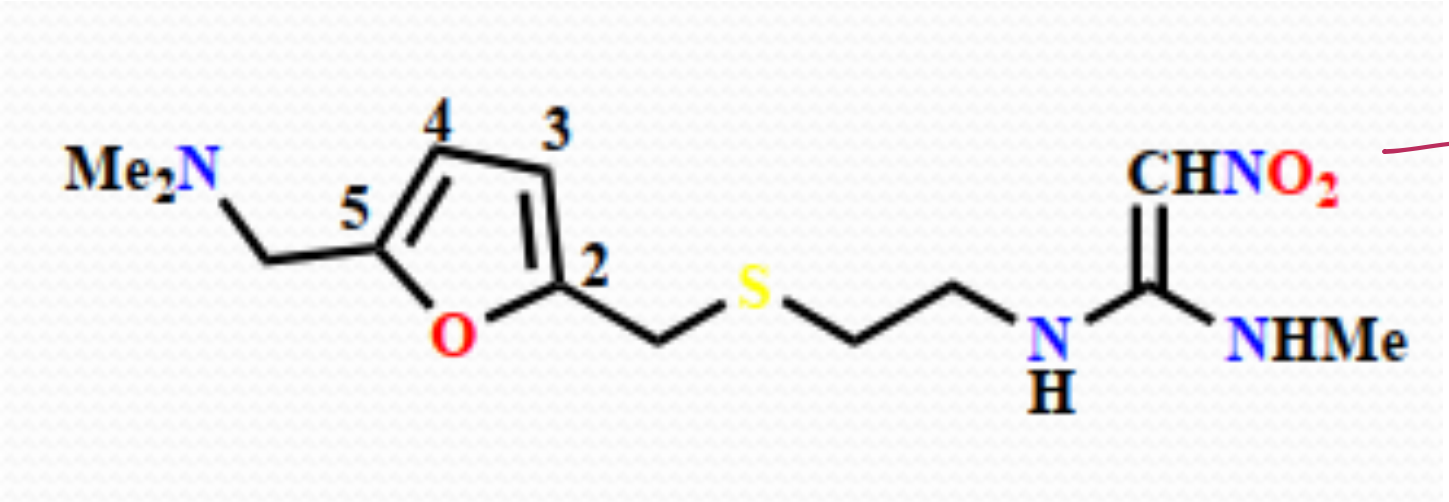
Cimitidine

*The Cyanoguanidine Moiety

- Acts as a bio-isostere for the thiourea group
- Both groups are planar and of similar geometry
- Both groups have high dipole moments
- Both groups are polar but essentially neutral
- Both groups have low partition coefficients
- The cyanoguanidine group is weakly acidic and weakly basic - amphoteric
- The cyanogaunidine group is not ionised at pH 7.4

Ranitidine

هو اختلاف عن Cimetidine



nitroketenen aminal

- Different heterocyclic ring
- Contains a nitroketene aminal group
- Took over from cimetidine as the most widely sold prescription drug in the world