تفريغ ميديسينال

محاضرة: Antihistamin Drug and Drugs acting on GI

الصيدلاني\ة: Rahaf Tyoucl

لجان الدفعات

Soul Academy

Antihistamine Drugs and Drugs Acting on GIT

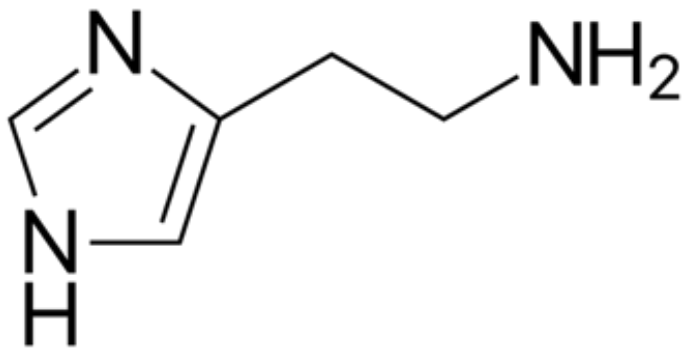
Histamine

- 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

decarboxlation بـ يصير Histadin الـ

Histamin وبـ يصير

Precursor is Histadin



Histaminic receptors

الي بصير عنده activation الـ H_1 receptor رح آلاحظ:

① بصير عنده ضيق تنفس لانه H_1 بعمل bronchoconstrition

② رح يصير عند احمرار بمنطقة الـ inflammation لانه H_1 بعمل vasodilator

③ رح يصير عنده edema لانه H_1 بزيد الـ permeability للماء

- Of Four types: H1 to H4.

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

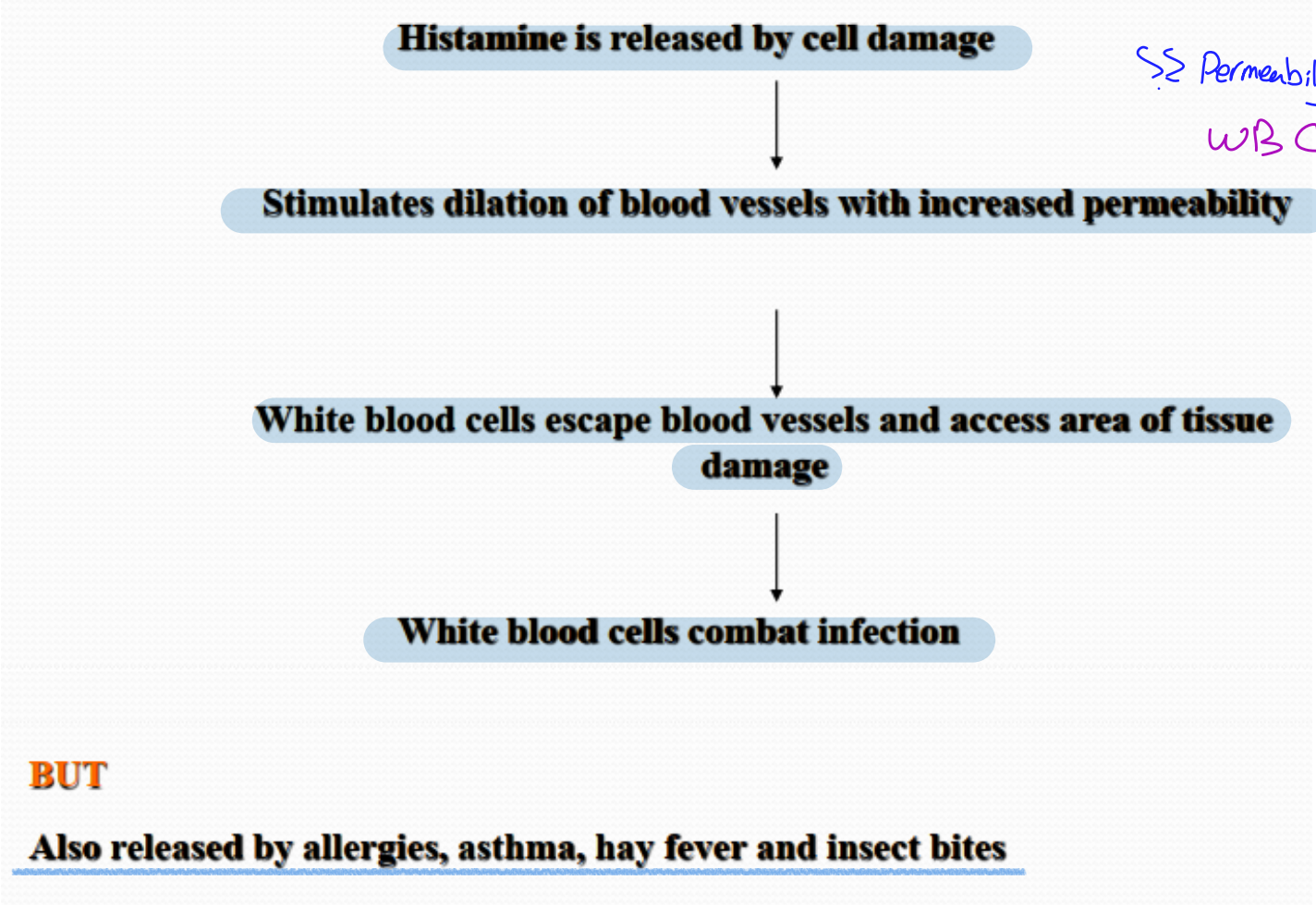
- H2-activation:
  - Gastric secretion.
  - Hypotension due to vascular dilatation.

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

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

بأدوية الـ Anti histamin رح نركز انه نعمل inactivation للـ H_1 و H_2

Histamine action

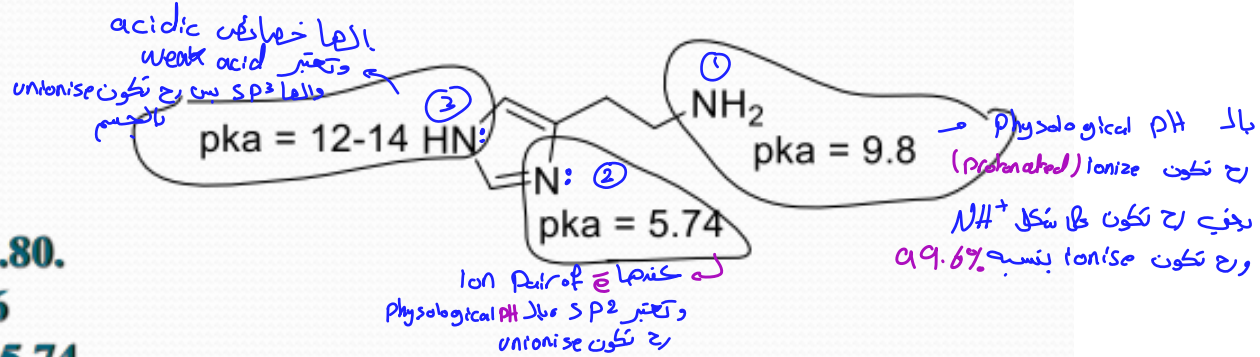


ليش رح تزيد الـ Permeability؟
عشان تسمح للـ WBC انها تدخل للمنطقة المصابة

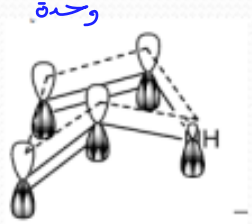
Histamine

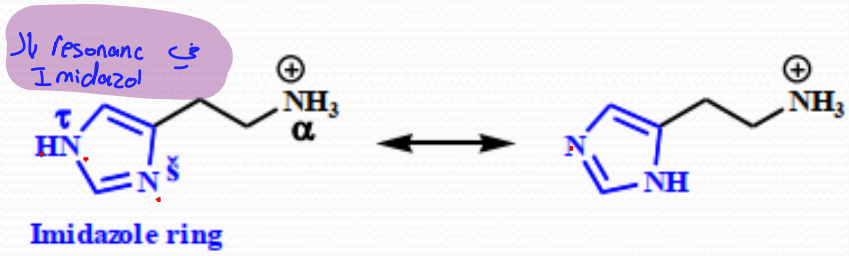
الـ Histamin كتير مهم للجسم عشان بحمي الجسم بحارب اي عدو خارجي بس مرات لما يكون في Hypersensitivity بشكل يكون sever رح تأثر على حياة المريض " Allergy " في بعض الاحيان ، وبرضه رح تأثر على الـ GI عشان هيك رح استخدم Anti histamin

- 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
- pK_a for the imidazole ring = 5.74
- Imidazole ring is not ionised at blood pH
- At physiological pH it presents as monocation. (+)charge





Imidazole ring

Anti-allergic agents

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

- 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.

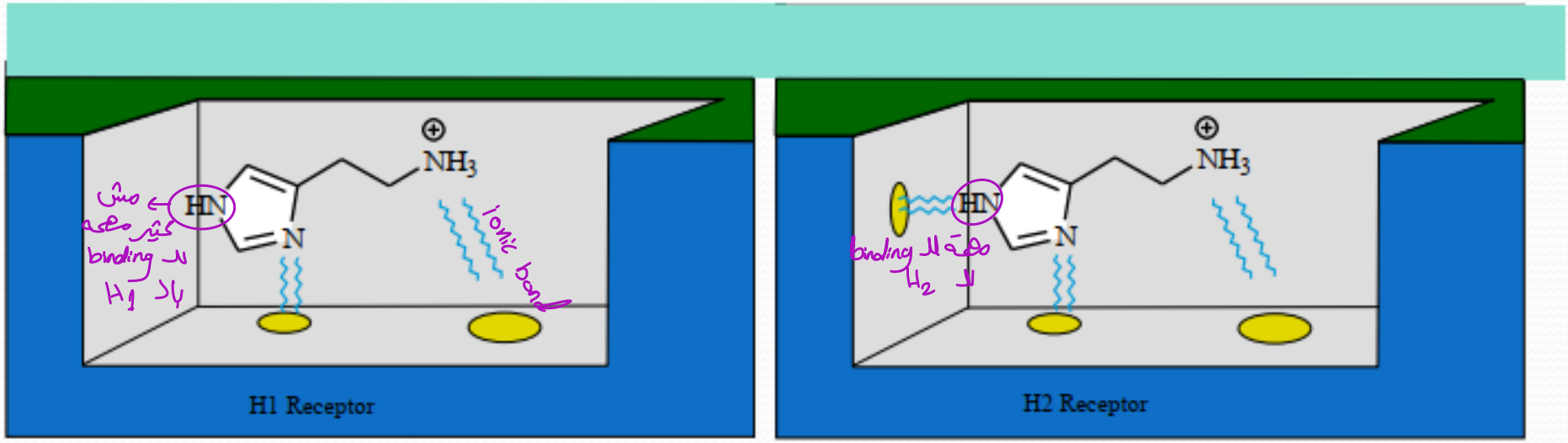
- Anti-allergic agents block some of the action of histamine.

Histamin يعني agonist

باك H_2 agonist الـ Imidazol مش معه

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**

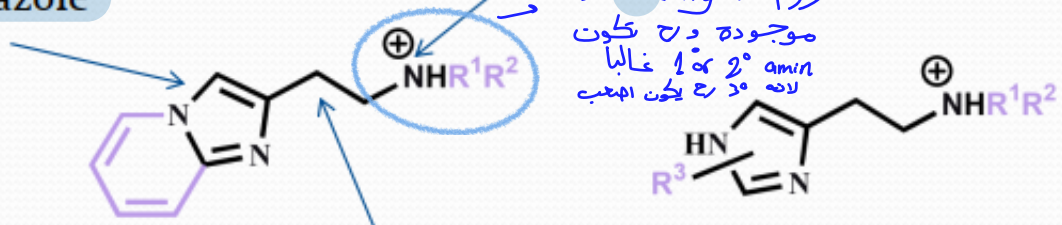


Strategies for Converting Agonists to Antagonists

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

لازم الـ +charg تكون موجودة و ح تكون غالبا 1° or 2° amin لانه 3° ح يكون اصعب

The heteroaromatic do not have to be imidazole



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

Antihistamines

الصيغة العامة

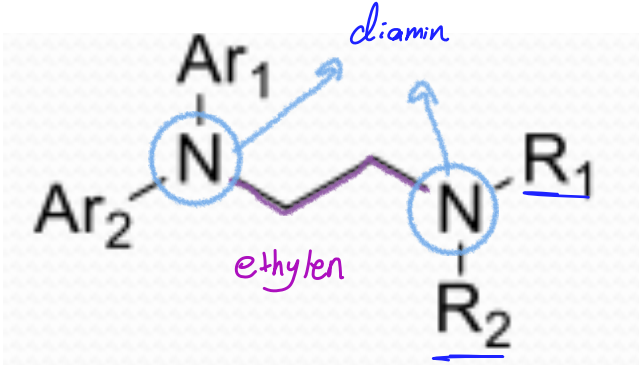
$$R - X - (CH_2)_n - Y$$

X = NH, O, CH_2

Y = $N(CH_3)_2$ (n = 2)

Ethylenediamine derivatives
H1 antagonists

- R1 and R2 should be small (CH3) for maximum H1-antagonist activity.

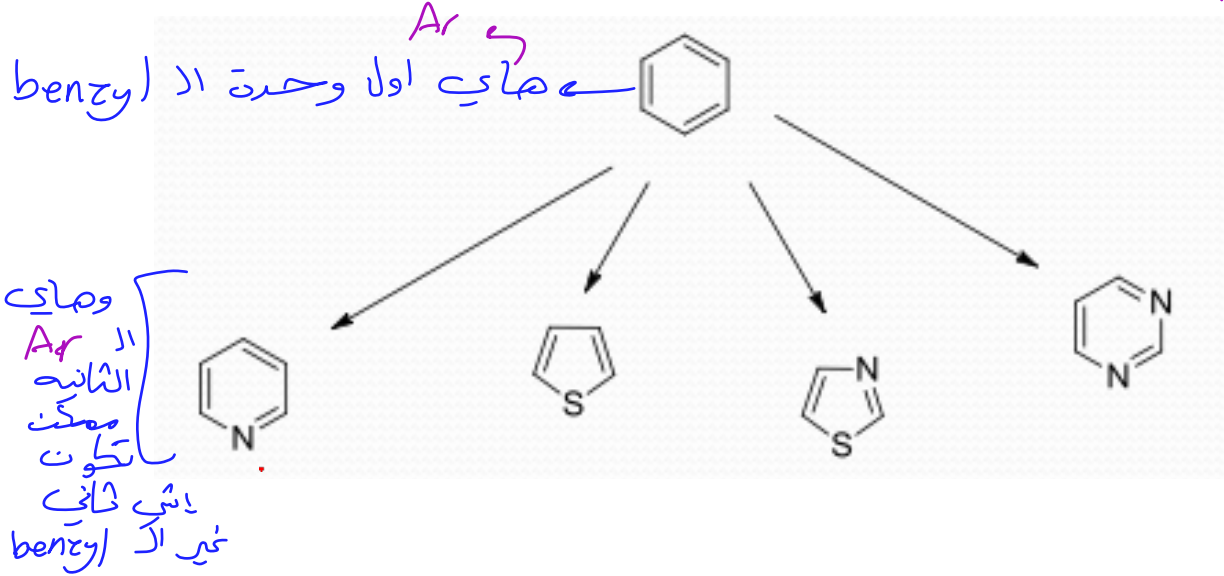


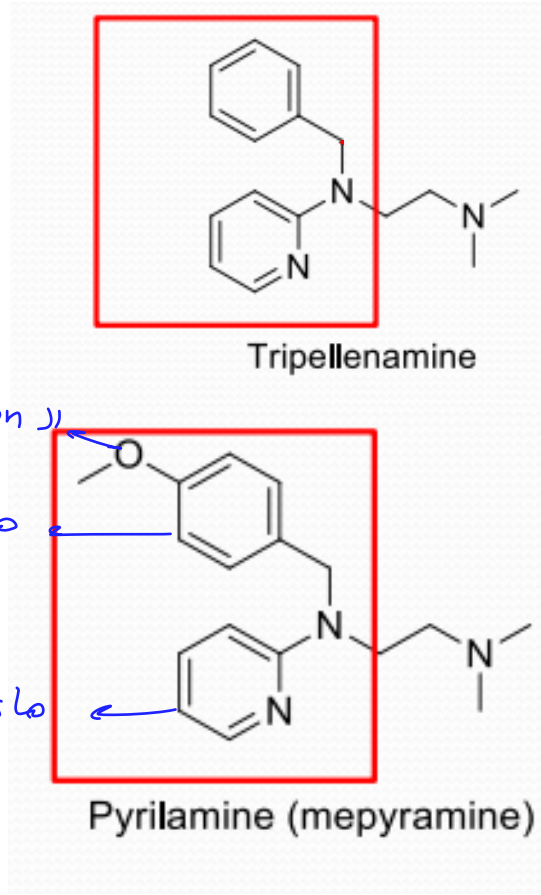
R1 + R2 small لازم يكون حجمهم
لازم وحده من Ar1 و Ar2 تكون benzyl
وال benzyl يكون عليها substituion في Para موقع

- 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:



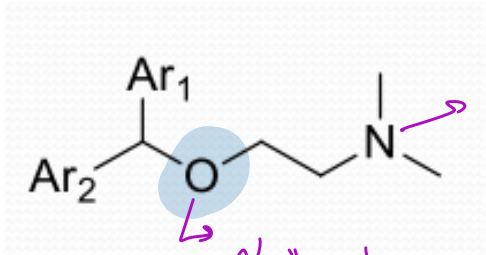


- All H1-antagonists are dispensed as water soluble salts.

Aminoalkyl ether analogues

الفرق بينهم وبين الـ ethylendiamin هو وجود O بدل الـ N والباقي نفس الإشي

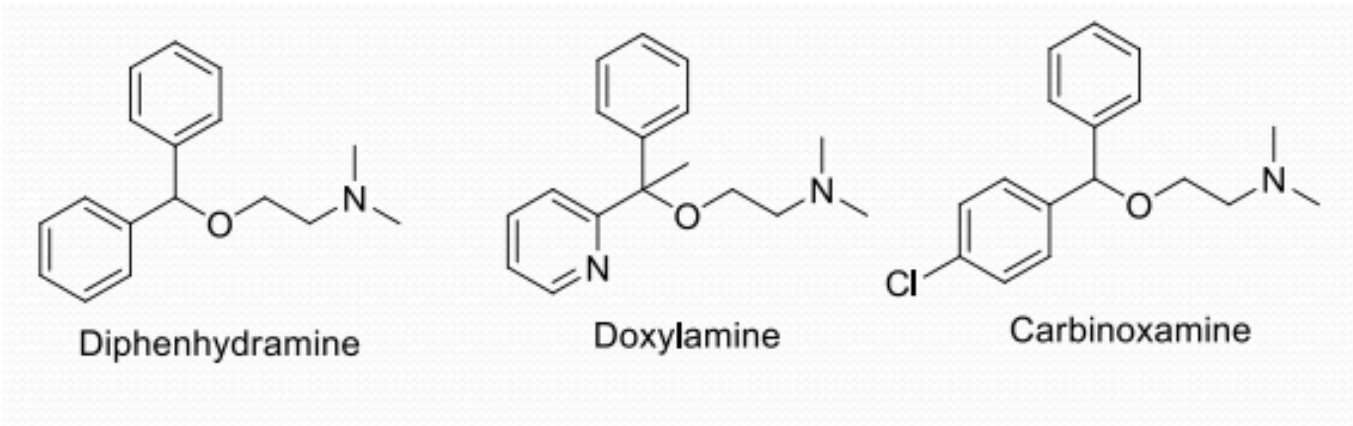
- Closely related to ethylenediamine derivatives.



صاي لازم تحفل

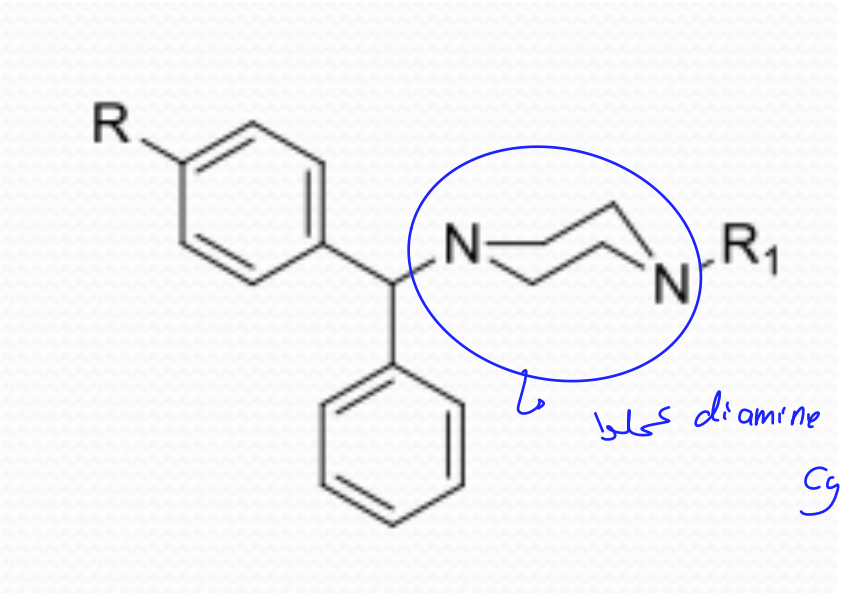
صون بدلت الـ N بـ O

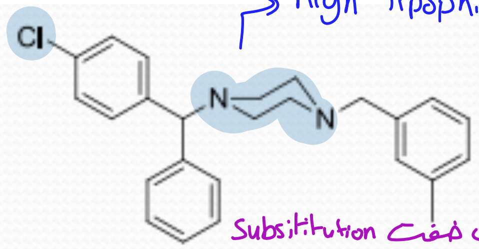
- Examples:



3 Cyclic analogues of ethylenediamine

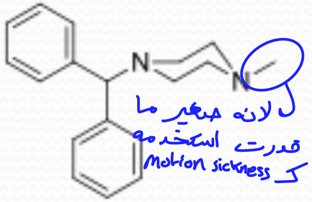
- They have mainly CNS depressant effects.
- Main uses:
  - In allergy.
  - As antiemetic agents.
  - In motion sickness.



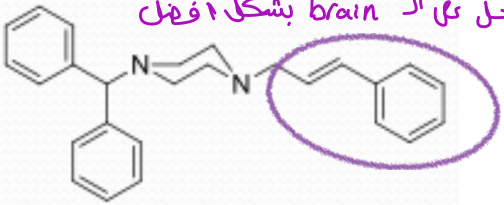


Meclizine
Potent H_1-antagonist
used in prevention of motion sickness
for nausea and vomiting

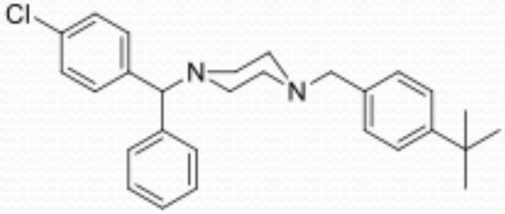
هون خفف Substitution
كبير فزادت ال Potency
اجا ال antagonist



Cyclizine
antiallergic agents



Cinnarizine
in prevention of motion sickness



Buclizine
in motion sickness

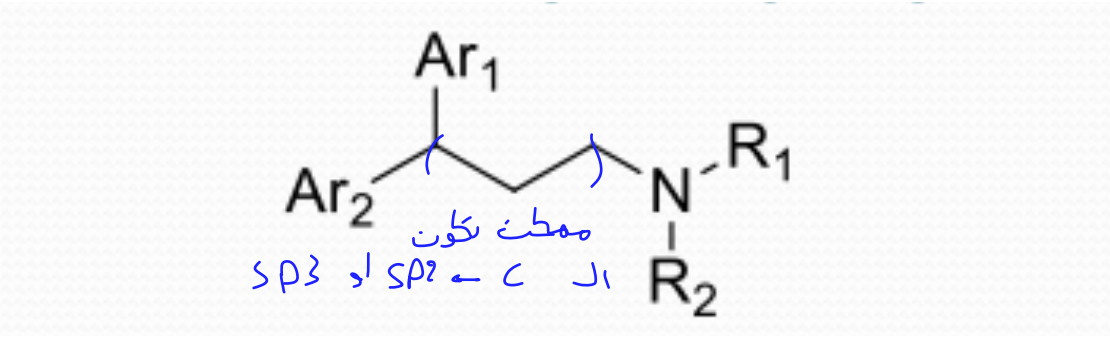
بلاحظ انه شكلهم بشبه ال Antimuscarinic

عشان هيك عنا antimuscarinic effect

- 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

٤ Propylamines

(monoaminoproprylamines) ـه ما في غير N وحده



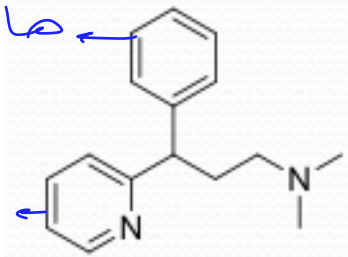
- Mainly have a phenyl and 2-pyridyl groups, and a terminal dimethylamino moiety.
  - The hydrophobic linker should have either sp2 or sp3 carbons.
  - They are less sedating compared to the ethylenediamine derivatives.
  - The *S* enantiomer is the most active form.

هذا الـ Cl هو الاختلاف عن Pheniramin

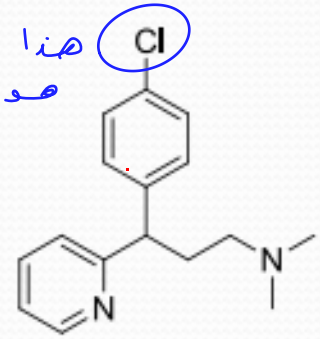
Para الـ substitution

Phenyl صاي

Pyridin

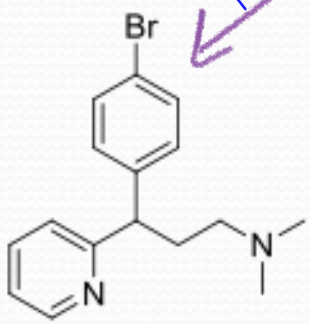


Pheniramine



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

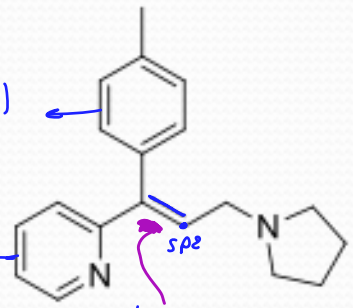
الاختلاف بدل الـ Cl في Br



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

Phenyl

Pyridin



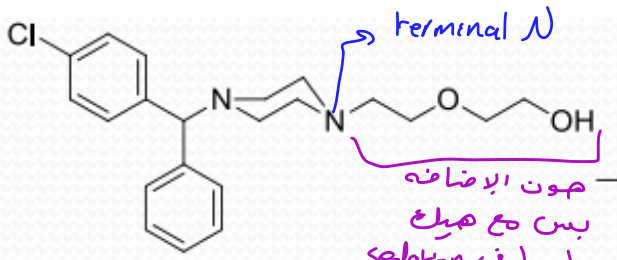
عشان Trans لازم يكون
يعطي الـ effect

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

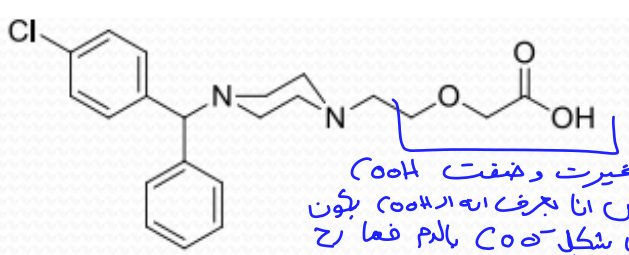
H1-antagonists with decreased sedative effects

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

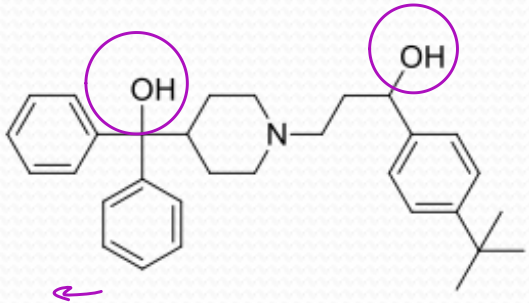
- Strategies to decrease sedation:
  - Increase selectivity to the peripheral compared to the central H1-receptors.
  - increase polarity of classic H1-antagonists to decrease the ability to penetrate the BBB.
  - These non-sedating antihistamines have greater receptor specificity, lower penetration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



Hydroxyzine
cause sedation as s/e

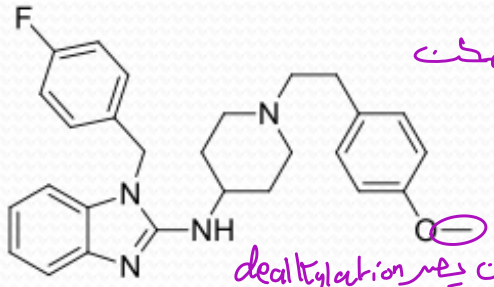


Cetirizine
presents as zwitter-ionic compound
has reduced sedative s/e

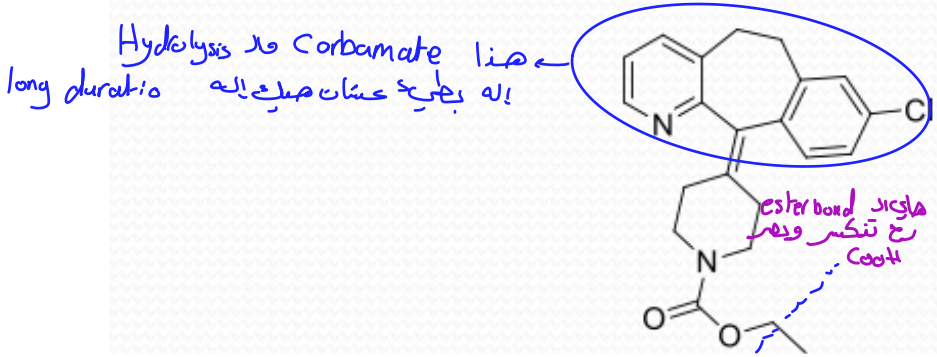


بالرغم من وجود 2OH
sedation إلا انه رح يعمل

Trefinadine

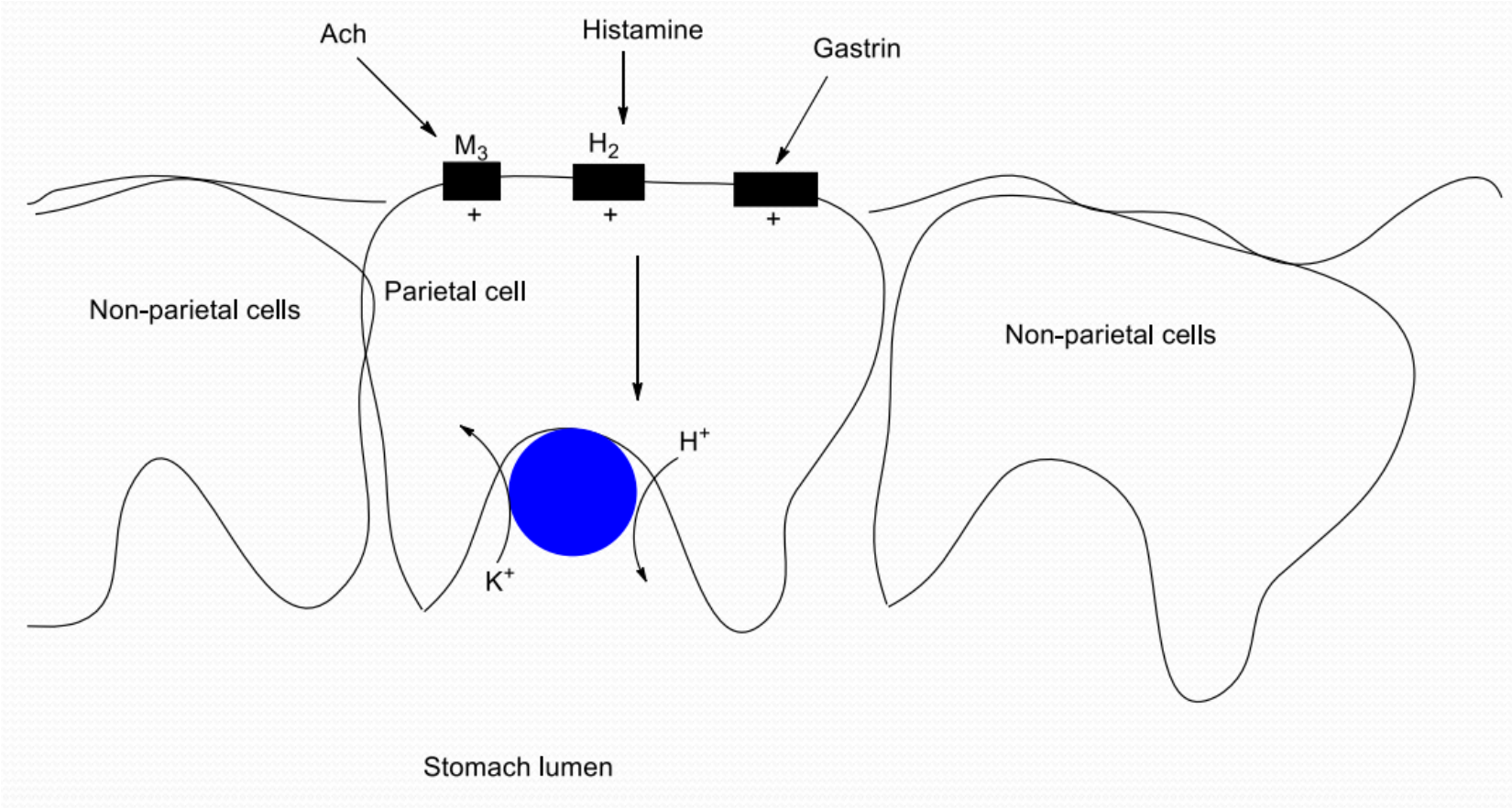


Astimizole
Has no sedative effects due to poor penetration of the BBB.
Has long duration of action because its metabolite (desmethyl) is also active.



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

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

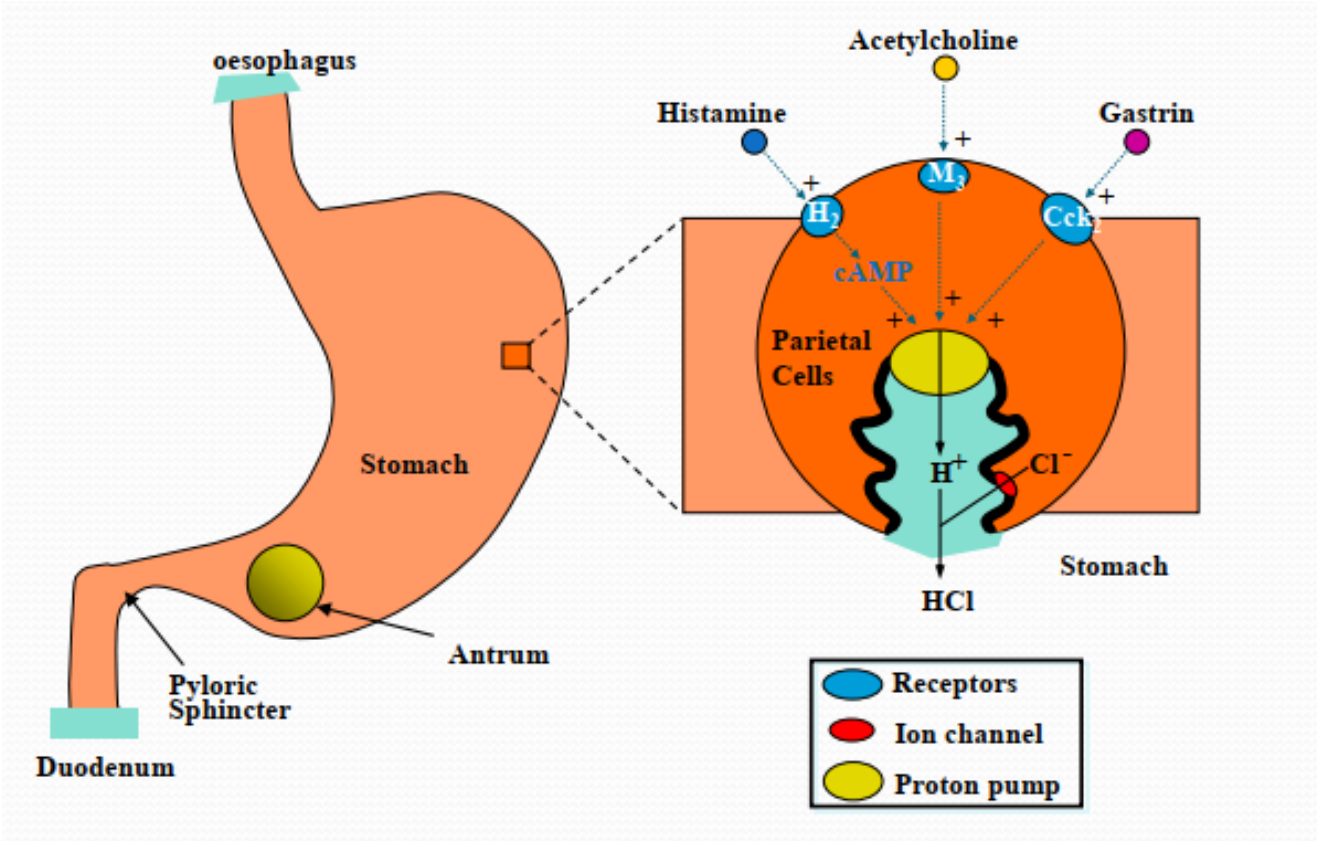
ح يزيدو لـ HCl ← Ulcer وهيك ح يصير

- Therapy of ulcer:
- Lower the level of gastric acid

- Histamine antagonists and proton pump inhibitors

- Antibacterial agents for *H. pylori*

Parietal cells and gastric acid secretion



Release of gastric acid is promoted by acetylcholine, gastrin and

كتبتهم فوق

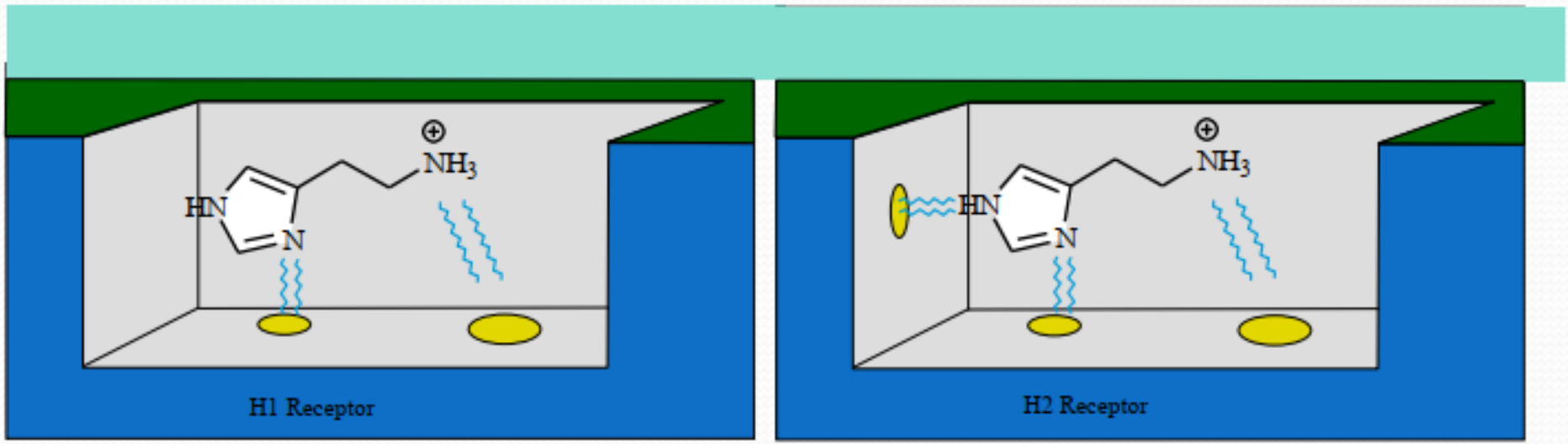
- Gastric secretion in stomach is controlled by:
  1. Acetylcholine: M3-activation which lead to the production of acid.
  2. Gastrin hormone: will be released from the G-cells in the antrum … this will interact with Cck2 receptor in the parietal cells to produce the gastric acid.
  3. Histamine: will 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.

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

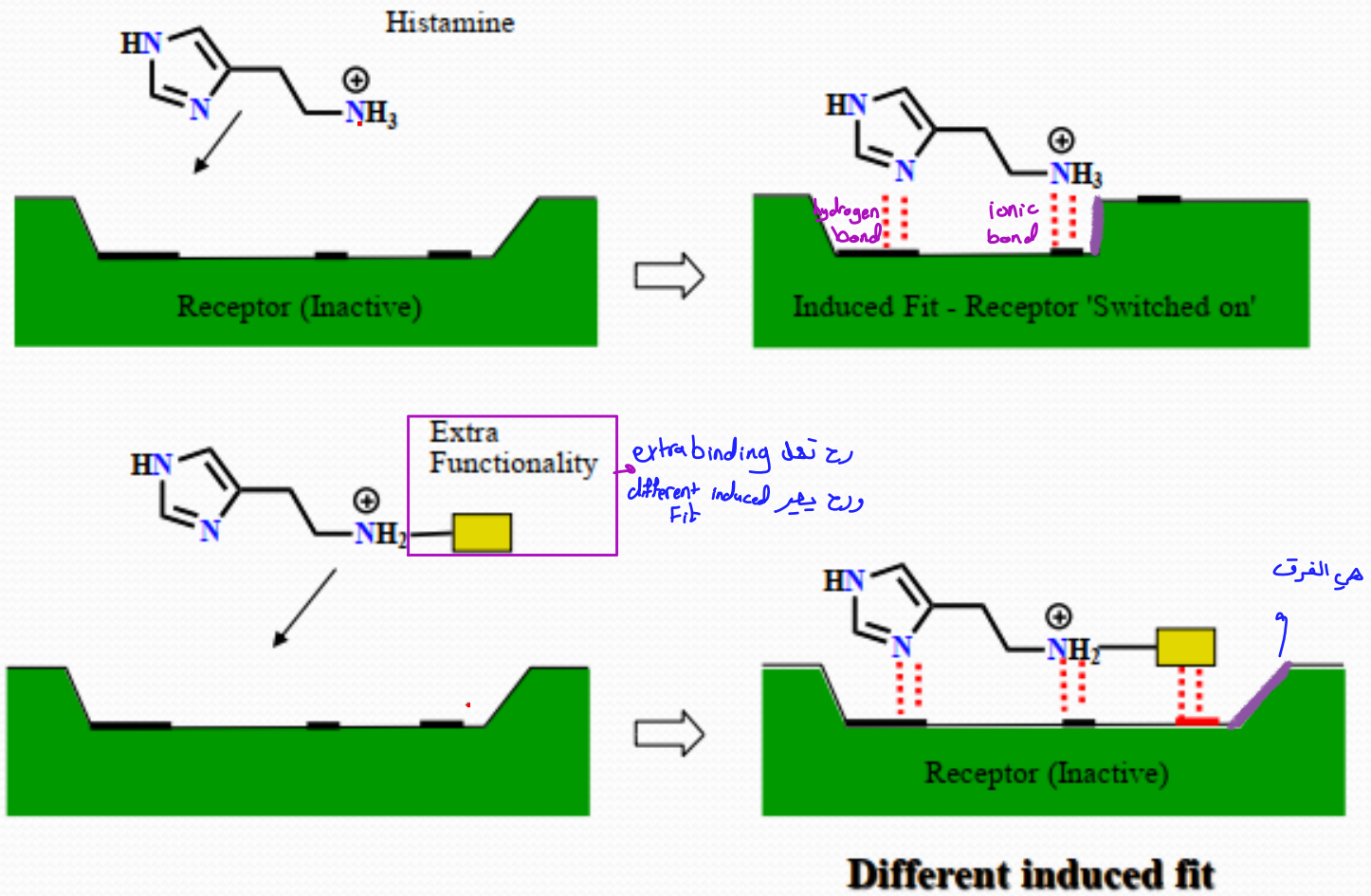
- **Two nitrogen atoms are required for H_1 agonist activity**
- **All three nitrogen atoms are required for H_2 agonist activity**

لازم يكون في imidazol حلقة — H2



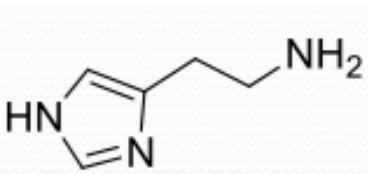
Strategies for converting agonists to antagonists

- 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

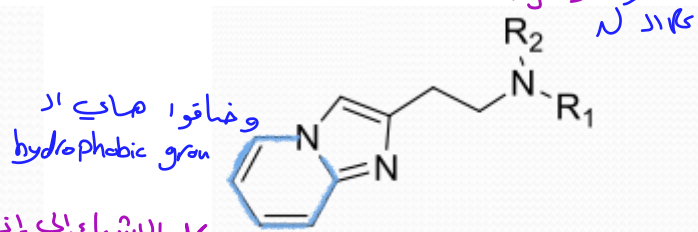

Histamine
HN
N
NH3
Receptor (Inactive)
HN
N
NH3
hydrogen bond
ionic bond
Induced Fit - Receptor 'Switched on'
HN
N
NH2
Extra Functionality
extra binding ربح تعلق
different Fit induced ربح يغير
HN
N
NH2
هي الفرق
Receptor (Inactive)
Different induced fit

- 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

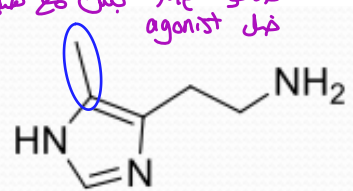
حكينا معمه لا activity



Histamine



Hydrophobic analogues
None were active



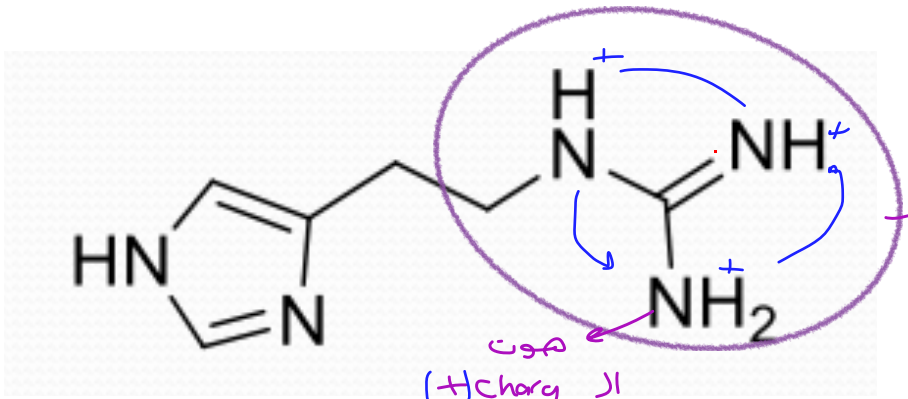
Was found to be selective H_2-agonist

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

هون قرروا يغيروا الـ Polarity لـ terminal N

- The first derivative was *N*-guanylhistamine:

وحاقوا عليها Polar group وصار Partial agonist



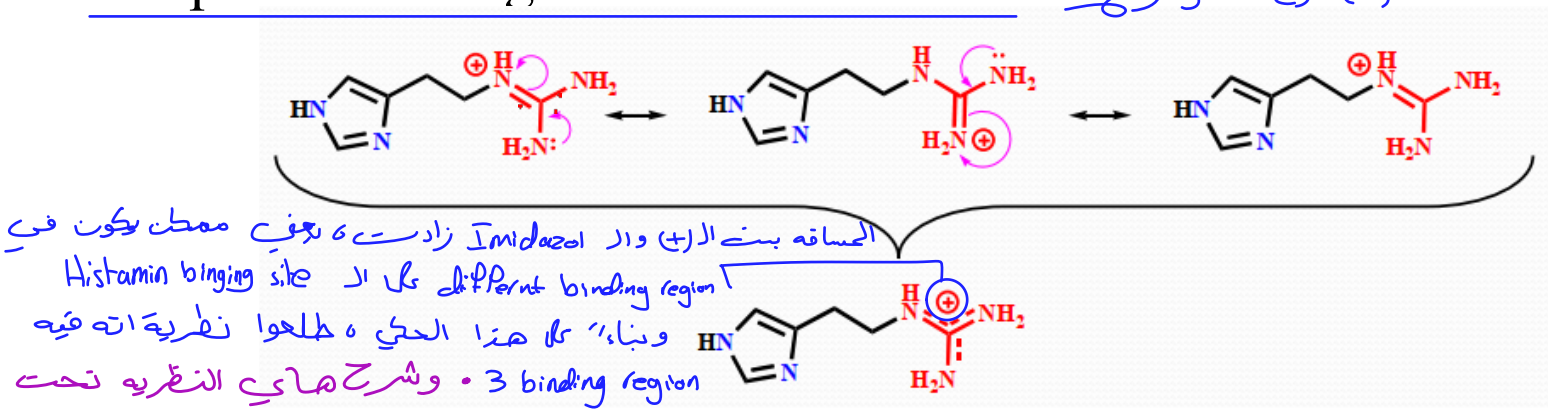
هاي الـ group اللي ضفتها اسمها guanidine وبالحط انه عليها (+)charg ورح تكون ionise بالـ Physological pH بس رح تتوزع على الـ 3 N

هون الـ (+)charg

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

Nα- guanyl histamine

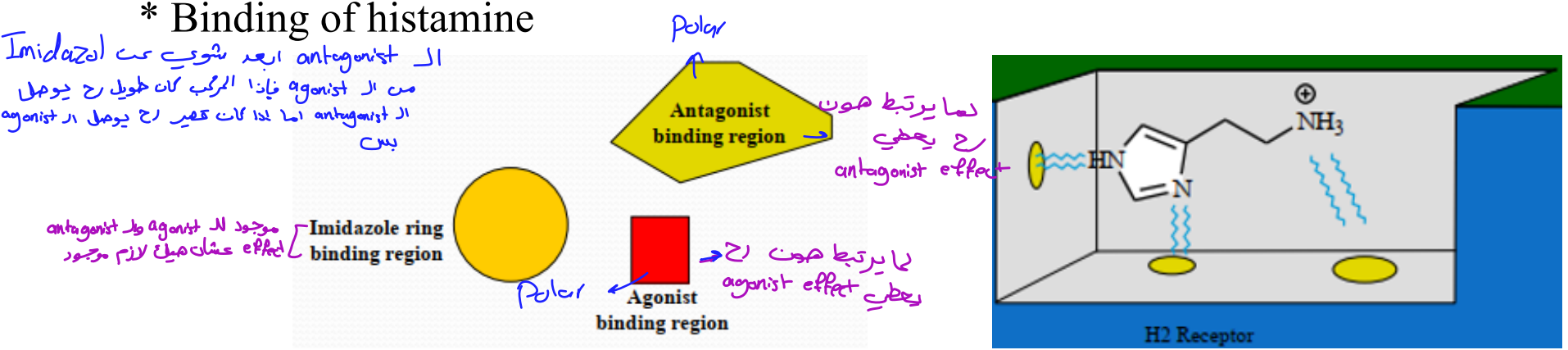
- The guanidine group is basic and ionised
- Different tautomers are possible
- The positive charge can be delocalised



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

Binding theory for agonists and antagonists

* Binding of histamine

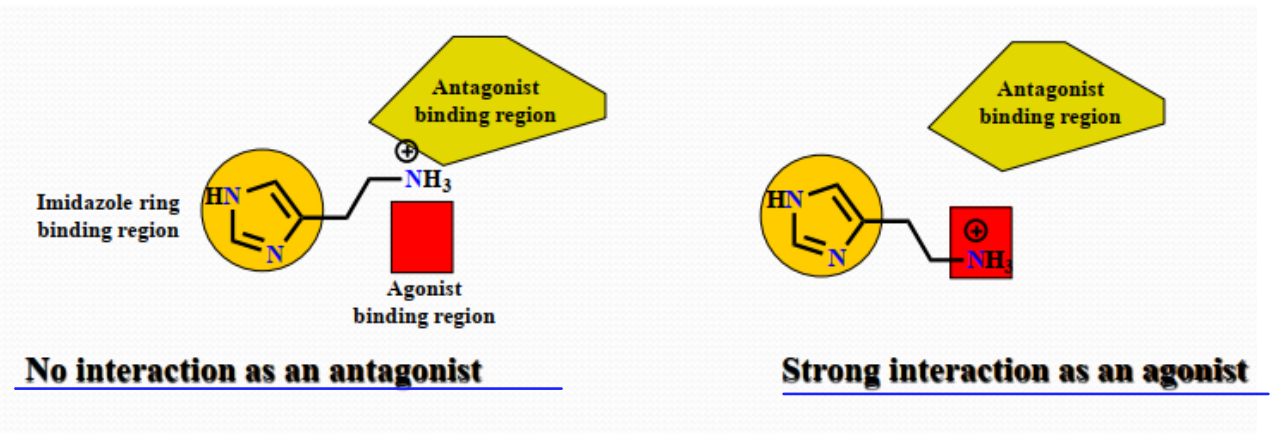


- Three binding regions are proposed for the H2 receptor; an imidazole binding region and two polar binding regions
- Two binding modes are proposed; one for agonists and the other for antagonists.
- The imidazole binding region is common to both binding modes
- One of the polar binding regions is accessed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

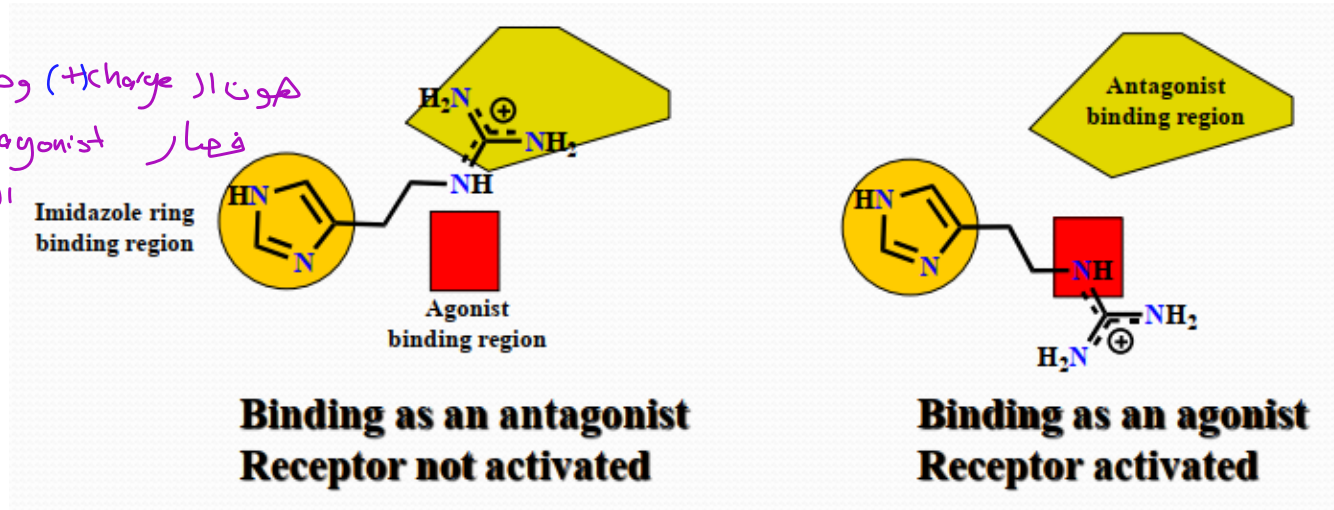
لانه قصير قدر يوصل ال agonist بس

وما بقدر يوصل ال antagonist

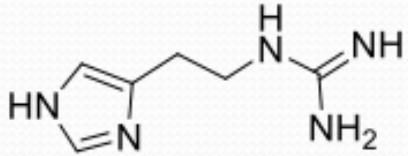


Binding of Nα-guanylhistamine

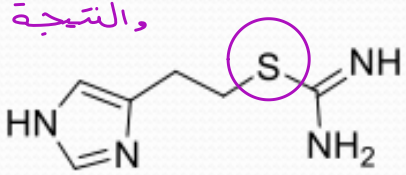
- Positive charge on the structure is more diffuse and further out
- Allows Nα - guanylhistamine to bind in two different modes (agonist and antagonist), making it a partial agonist.



N-guanylhistamine as a lead

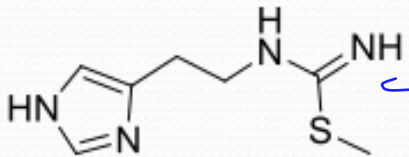


حطوا S بدل الـ N عشان يشوفوا هل الـ charg (+) ضعفة للـ antagonist ولا لأ والنتيجة ؟



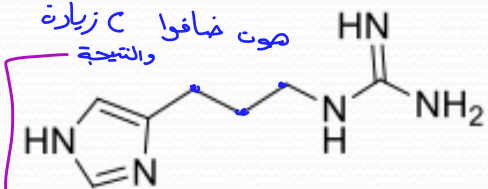
partial agonist
poor antagonist

(+) charge حكينا انه الـ ionic bond يتعطل



وهون بدلوا وحده من الـ N لـ SCH_3 وبرضه نفس الإشي

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

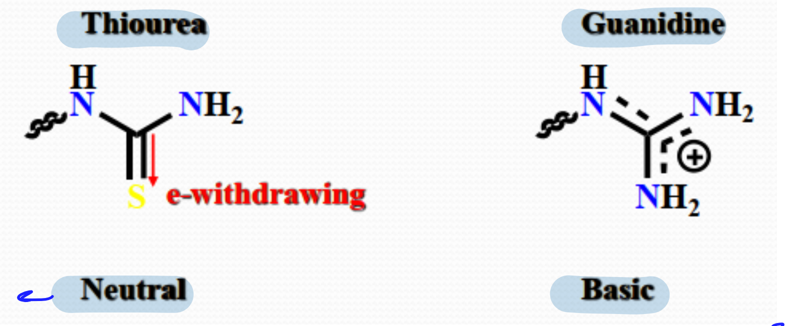


هون ضافوا C زيادة والنتيجة

antagonist activity increased

Distinguishing between the polar binding regions

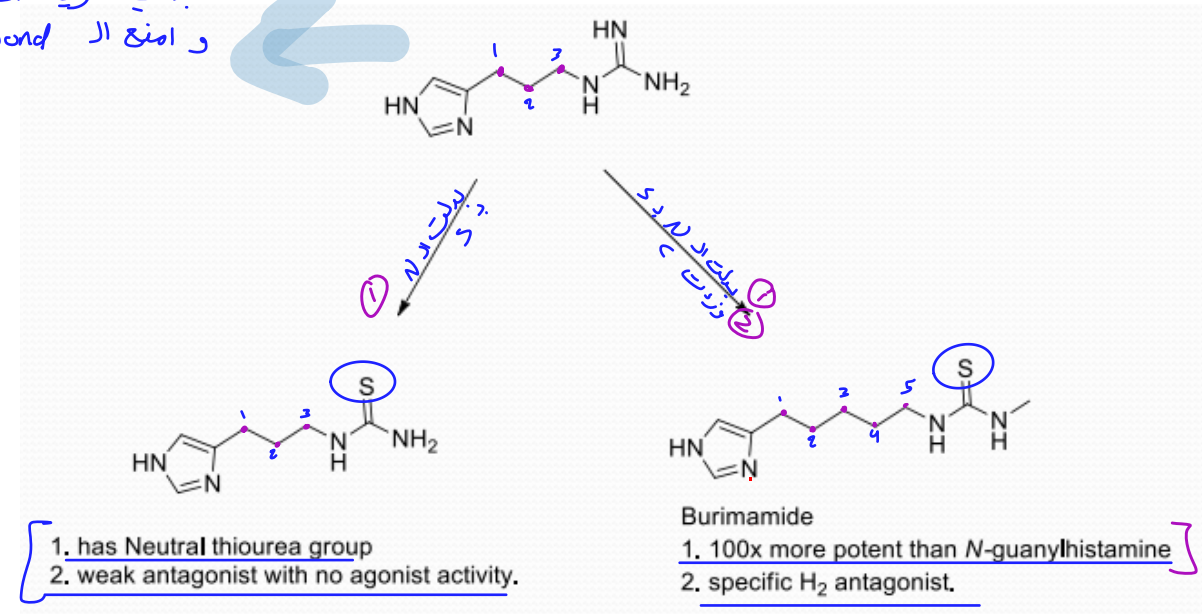
- Comparison between the thiourea and the guanidine groups
- Similarities: planetary, geometry, size, polarity, H- bonding
- Differences: thiourea is neutral while guanidine is basic and ionised



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

رح امنع الـ agonist effect

بدي ازيد الـ polarity و امنع الـ ionic bond



ماي النتيجة

- 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.

يوجد 40% من المركب رح يرتبط على الـ binding site

السبب الـ Imidazol تعتبر H-B acceptor فإذا كانت Protonated إله H-B acceptor رح يبطل ورح تصير وحده من H-B

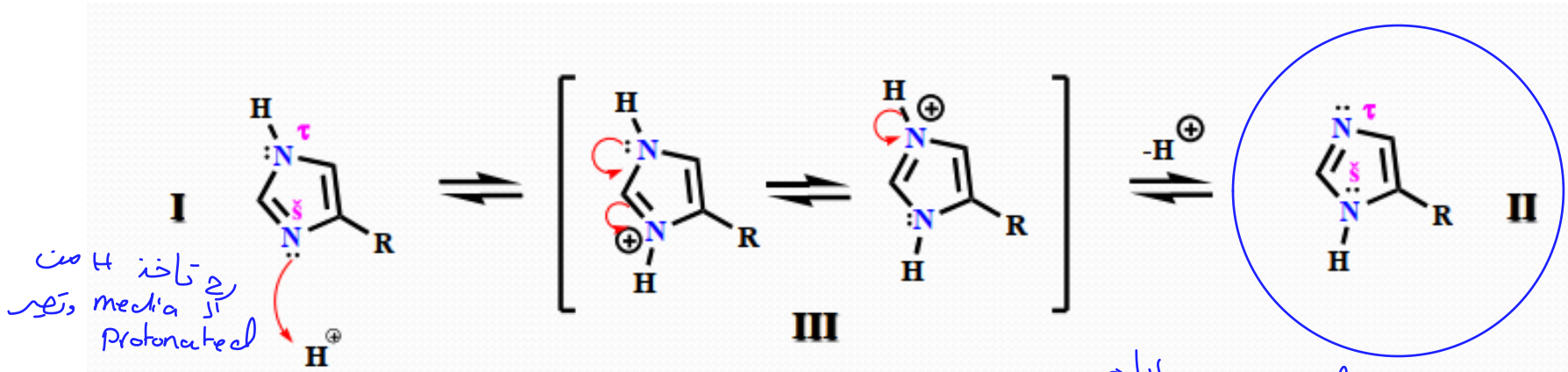
الارتفاع يسبب الـ ٢ إلي زدتها

قريب لـ Physiological

deprotonated عشان اخليه لازم اقلل الـ PKa عن طريق إضافه e withdrawing group

The imidazole ring

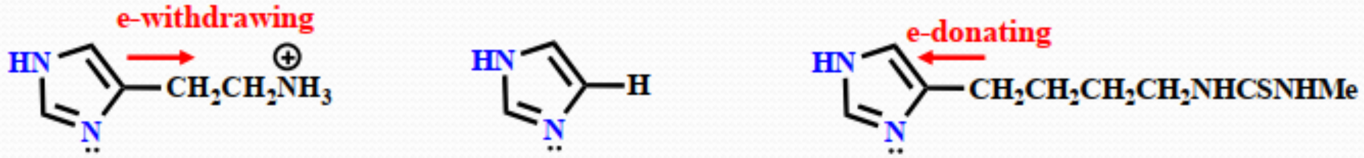
1- structure



- **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	Imidazole	Burimamide
$pK_a = 5.74$	$pK_a = 6.80$	$pK_a = 7.25$
Ionisation = 3%		Ionisation = 40%

ما بدي هاي النسبة
ال ionisation فبضيف e withdrawing group
عشان تقل ال pKa وبيطل ionize

Conclusions

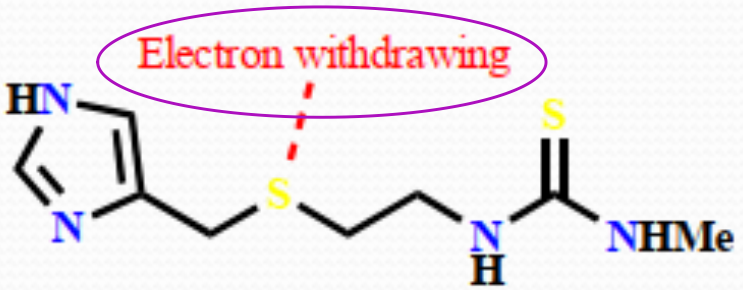
- **The imidazole ring of histamine is not ionised when it interacts with the imidazole binding region**
- **The ionised form of burimamide is unlikely to bind well**
- **Decreasing the basicity and ionisation of the imidazole ring in burimamide closer to that of histamine may increase the binding interactions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

The imidazole ring

*Varying basicity strategy

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

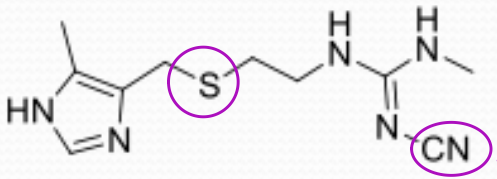
Thiaburimamide



$pK_a \equiv 6.25$

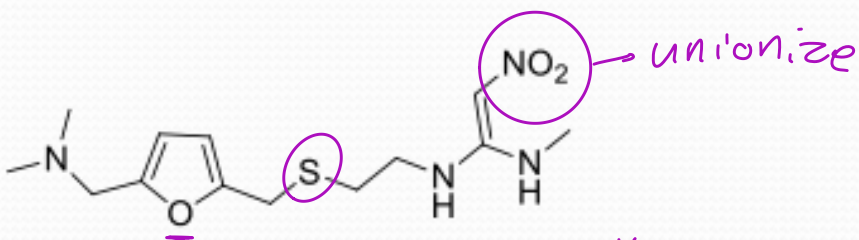
Increase in antagonist activity

Non-ionised imidazole is favoured



رح تفل unionize

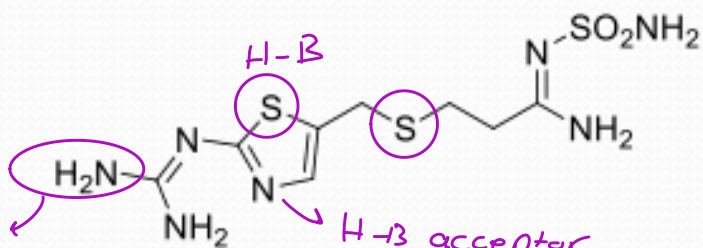
Cimetidine



unionize

another H-B

Ranitidine
Fewer s/e than cimetidine
10x more active



H-B acceptor

Famotidine
30x more active than cimetidine

هون ما حافظت
على الـ Imidazol بس
لسا الـ H-B موجودين

Cimetidine مش موجود حالياً

- 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

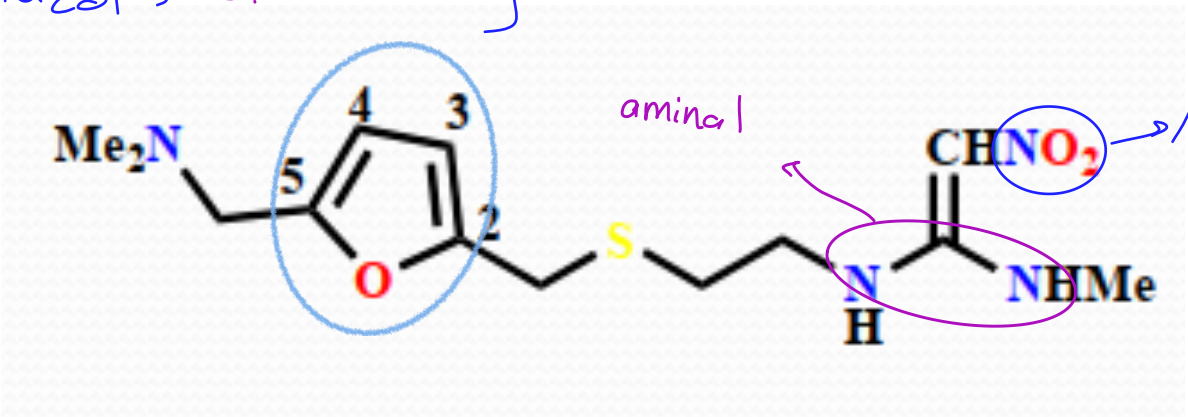
Cimetidine

*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 cyanoguanidine group is not ionised at pH 7.4

Ranitidine

Imidazol بدل Furan Ring



2N لما يكون في ٤ مرتبط عليها بسميها aminal groub

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