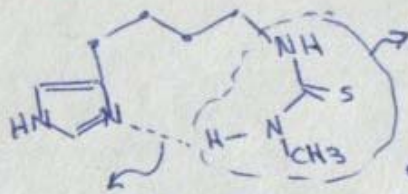
SAR

* Ring sub. on 5 pos. (CH_3)
* Side chain H atoms ē e.w.g
* Terminal atom (polar, non basic)

1st generation of H_2 AN

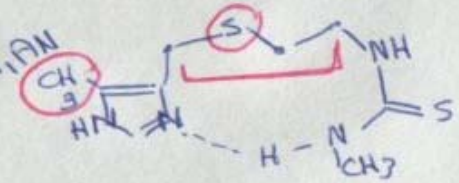
Burimamide



methyl thiourea polar not basic as H1AN

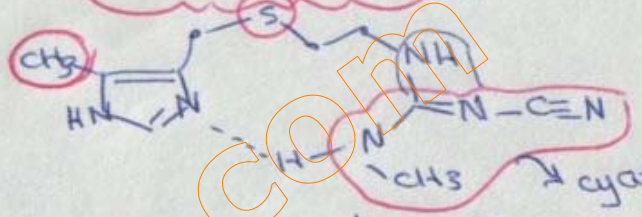
* weak H.b
* open chain conf.
* Hb breaks immediately in phys. pH
* H_3 AN

metiamide



* Acidic polar
* S only ao H.b is ↓ than cimitidine

amiftidine

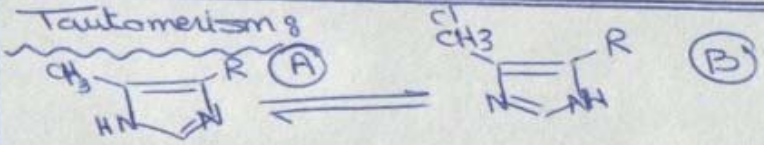


cyanoguanidine

* ↑ strong / lipophilic
* compact folded more potent
  has ↑ ability to pass cell membrane.
* ↑ e.w.g → ↑ activity → strong H.b
  as e.w.g ↑ +δ of H terminal → ↑ potency

* Antagonist of H_2 :
  - Anticholinergic
  - Anti hist
  - Anti ATPase
* Histamine has 2 roles → intrinsic, potentiating
* in cyclical conformation, polar → No CNS effect
* in H1AN, pass CNS.
* when hist is formed & ↑ (H^+) inside parietal cell ē help of gastrin & Ach, ATPase extrudes H^+ & replaces it by (K^+) → we can interrupt this hist → activate G prot → 2nd mess → synth. (H^+)

Tautomerism :

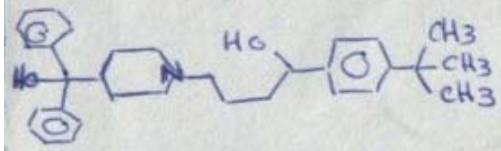


* If e.d.g (CH_3) : ē's will be on N①
  so ē's cloud on $N_1 > N_3$
  ∴ d.b bet 2 & 3
  ∴ H^+ → N①
  ∴ A predominates → active
* If e.w.g (Cl, NO_2) : ē's will be drawn from N①
  ∴ d.b N① → 2
  ∴ B predominates open chain
  no H.b → inactive

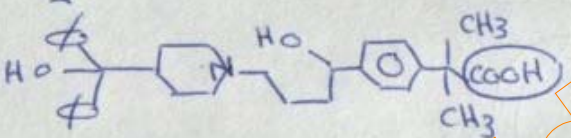
Second generation H_1 AN

Same requirements of 1st g. but differs in polarity

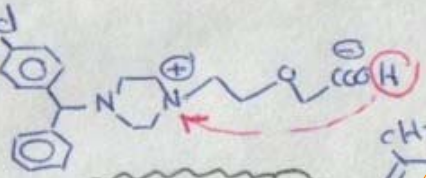
Terfenadine | Fexofenadine | cetirizine | Acrivastine | Loratidine



prototype

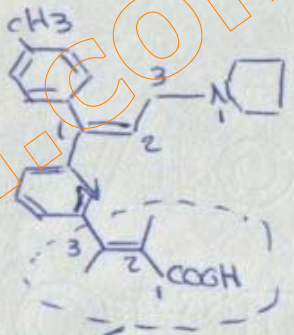


* 2 alc.-gps & COOH compensate bulky gp & protein binding

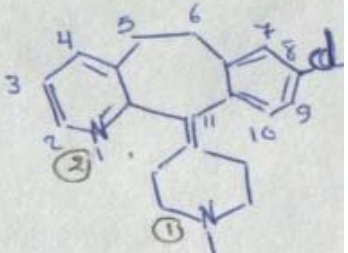


Zwitterion

highly potent
widely used
no arrythmia
polar



Carboxyethenyl moiety (propenoic acid)



① ② ③ ⇒ r. pola
no BBB
so put Cl to ↑ lipid solu.

① piperidine moiety instead of piperazine
Bioisoster.

② 2 OH ⟶ ↑ polarity
can't pass CNS

③ r- protein binding affinity of slow dissociat°

④ life threatening ⟶ arrythmia
⇒ so deleted from market.

Notes i 1st generat° & 2nd :

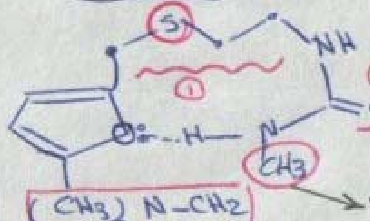
* 3 sites for attachment in hist NH2 , 2 N in imidazole ring
* 2 conformat° a- Antiperiplannar - Transoid minimal E b- Synclinal cisoid

* H_1AN : 1) change in imidazole ring
2) no change in side chain ⟶ HR ⟶ Racemic non selective.
3) bulky gp ⟶ neigh. area S(+)
4) sedatives.

* SAR : ① 3° amine ≈ CH_3 or pyrrolidine not other or st. hind. to R
② spacer - non branched unless tricyclic
③ X = O, NH, CH_2 Bioisost
④ R = phenyl 'R = phenyl - Benzyl - 2 pyridyl - thenyl
⑤ α C* ⟶ S(+) B ⟶ HR ⟶ racemic
⑥ noncoplannar ⑦ Cl, Br in P- ⟶ ↑ activity but not in TC

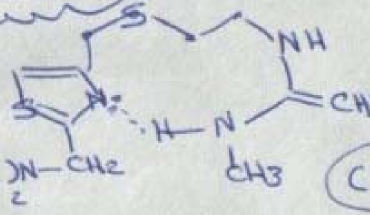
2nd generation H2AN

Ranitidine



① (chain under S)
③ e-w-g $CHNO_2$
④ $(CH_3)_2N-CH_2$ → Bioisostere
but e-w-g >> e-d-g (CH_3)

Nizatidine



$(CH_3)_2N-CH_2$ → Bioisostere
furan ⟶ thiazole

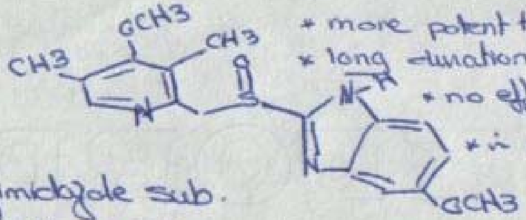
Famotidine ⟶ Amide derivative

$CH_2SCH_2CH_2 - C(=NSO_2NH_2) - NH_2$*

① 4C
② sulfamoyl
③ no Me but NH_2
↓ st-hind & H-b stronger

$(NH_2)_2C=N$ → diamino methylene
e-d-g to N
∴ ring + thiazole
most potent

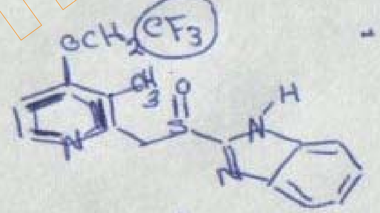
2 | Proton pump inhibitor



* more potent than H2AN
* long duration of action
* no effect on gastric secret^n
* ∴ ulcers resistant to H2AN
* rapid heal^ing

SAR
① Benzimidazole sub. by a methoxy gp on 5-position.
② sulfinyl gp
③ sub. pyridine (weak base) sub by OCH_3, CH_3

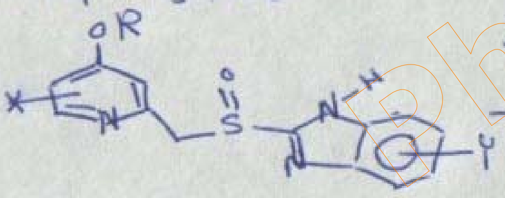
omeprazole (prototype)



* more active
* more lipid sol. (OCH_2CF_3)

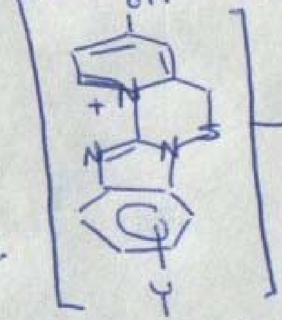
Lansoprazole.

- if taken orally ⟶ protonation in stomach ✗ no effect. so all are coated tablets to enter parietal cells.



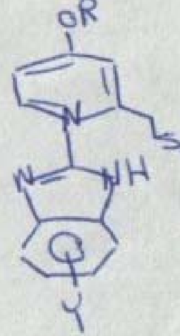
Acid Catalysis
H_3O^+

active metabolite
occurs inside parietal cells
bec. med. has ↑ conc. of H^+



∴ drug entrapped inside

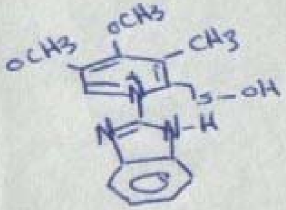
ATPase-SH (active site)



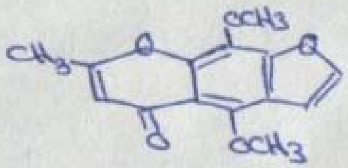
* Irrev. inhibition to ATPase by strong covalent bond
∴ prolonged action (disulfide bond)

* Antibacterial activity (for helicobacter) due to Benzimidazol

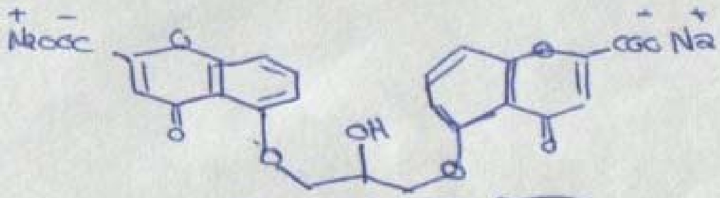
cyclizat^n
rearrang.



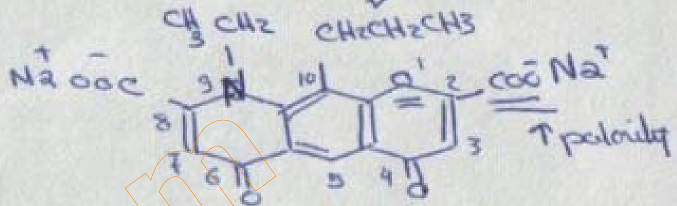
Prophylactic Anti histaminic drugs (before secret°)



Khellin



cromolyn sodium



Pyrano Quinolone

Trade® ← Nedocromil Sod.

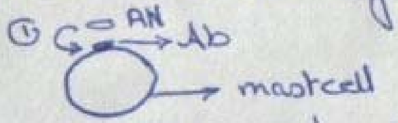
SAR:

1- 2 large rings are coplanar (2 chromones) unlike 1 generat° H_1 AN

2- Side chain should be at C_5 or C_8 → O (site for R-)
C_5 → = bond.

3- The linker chain is 3 C's to fit R (↑more or less → no fitting)

mech.: on mast cell → inhibit sensitizat°



② sensitizat° release hist

drug ≠ interference.

- As 6,6,6 ⇒ supposed to be non-coplanar but it's planar as middle ring → sat.

but more active as:
① inhibit synthesis
② inhibit immuno sys. (prevent Ab-Ag complexat°)

- Superior in potency: 2 chromone linked by 6 memb. ring using isostere (N) instead of O