Pharmaceutical & Med. Chemistry Three.

< Course Summary >

Student: **Marah Isam Falit**

Lecturer: **Prof. Ihab Almasri**

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Date. No.

⇒ To get best knowledge of medicinal chemistry you have:

- Class and sub class.
- Action
- MoA
- General structure
- SAR

⇒ Course outline :-

[1] CNs acting Drugs.

- CNs Depressant
  - sub class.
  - 1 - General Anesthetic [Parenteral + inhalation]
  - 2 - Sedative and hypnotic (BNZ, Barbiturate) GABA
  - 3 - Anti seizures (Anti-convulsant, Anti epileptic)
    - ~~Psychomotor~~ Anti parkinson.
  - 4 - Psychotherapy agent (Anti Physcotic, Ant-depressant) Dopamin
  - 5 - Anxiolytic. GABA

CNs Stimulant
↳ counteracting depressant

[2] Cholinergic Drug (Direct, indirect), Anti cholinergic
sympathomimetic sympatholytic
[3] adrenergic and Anti adrenergic. (Anti muscrnic Anti Nicotinic)

[4] cardiovascular Drug.

1. Anti anginal, vasodilator
2. Anti arrythmic
3. Anti hypertensive Drug
4. ACE - inhibitor
5. ARB Drug.
6. Renin inhibitor.

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⇒ Now each sub class of the General class has its own Action (indication) and MoA.

For example.

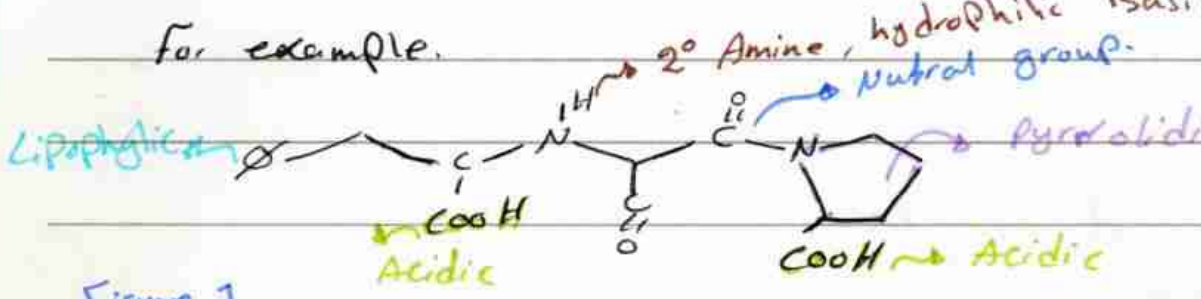


Figure 1

- The compound has many R or functional groups.
- For any Drug to give action must bind to target and befor binding to it, it must has good transporter.
- The Drug with its R must has some of Balanced bw functional group ; to give ability to be easily transported throughout the body.

For example /

- As we know the Blood is aqueous (aq) so hydrophillic Drug are best choic in this situation
- For CNs Drug to cross BBB it must be Lipophillic.
- for the drug (preveous structur) Figure 1.

General class : cardiovascular Drug (RAAs)

sub class : 3'd generation ACEIs

Name : Enalaprate

Action: Antihypertensive.

Date. No.

Note/ you have to know Basics of Physical properties of Drug as Lipophilicity, hydrophilicity, Acidity, Basicity...

- Now from the structure we have to predict the Action

- in previous Drug Enalaprilat, it's non soluble. why?
  - Due to precense of 3 ionized group.

  COOH which convert to COO^- (2 group)

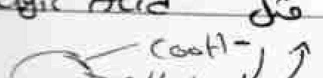
  NH which convert to $\overset{H}{N}^+$ (1 group)

- we said befor that Balance is important.
- so the Drug here has Bad physiochemical properties. becaus it has high hydrophilicity which mean hydrated in H_2O thus lead to poor absorption.
- also presence of $CO\bar{O}H$ near to $\overset{+}{N}H$ make higher stabilization. and more acidic, more ionized. (this is bad for absorption)

So we converte it to ester. (easy to break by alot of esterase enzyme in our body) which make it ↑ Lipophilic, ↓ ionized, ↓ hydrophilic,

so we make prodrug Enalpril ester form that converted to enalprilat.

ملاحظة اي مجموعات تكون جنب بعض بتعمل ↑ stabilization مثل salicylic Acid



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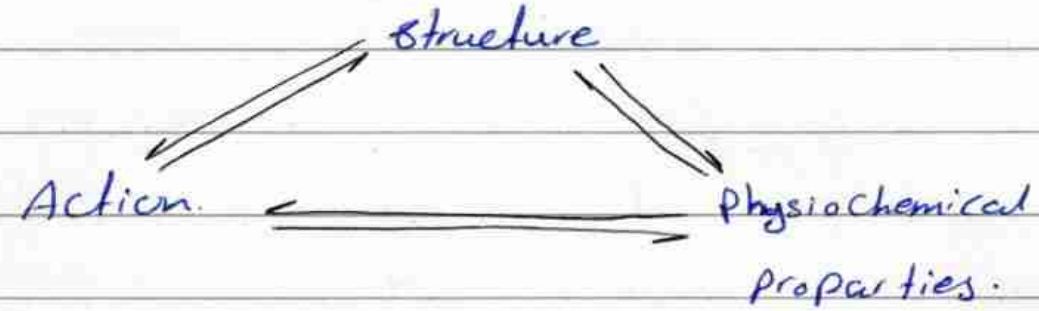
So we could make improvement of Drug properties by change in their structure.



for any drug an integration of structure, Action and physio chemical propetis must be existence.

CNS Depressants

Date. 1/10 No. Sunday

⇒ Substances that can slow or depress Normal function of brain

so it could be usfule in anxiety , sleep disorders , epilepsy ...

at ↑↑ dose → General anesthesia.

• electrophysiology of Nerve cells.

	Excitatory neuron	inhibitory neuron
Channle.	1) Na^+ Channel , ↑ Na^+ inflex 2) Ca^{++} Channel , ↑ Ca^{++} inflex	1) Cl^- Channle , ↑ Cl^- inflex 2) K^+ Channle, ↑ K^+ eflux.
Ligand or Neurotransmitter control channel's opening / closed	Excitatory neurotransmitter/ 1) Glutamic Acid which bind to NMDA thus ↑ Na influx. 2) Aspartic Acid.	Inhibitory Neurotransmitter/ 1) GABA$_A$ bind to it's receptor thus Open Cl Channle , ↑ Cl^- influx. (→ wide spread in CNS) 2) glycin. (less common) Localized
eflux	Neuron depolarization Lead to Stimulation CNs	Neuron hyperpolirization leed to depress CNs.
• Agonism	Excitatory	depression.
• Antagonism	depression	Excitatory.

Date. No.

5 class of CNs depressant :-

1. General Anesthetic
2. Sedative and hypnotic
3. Anxiolytic
4. Anticonvulsant (Antiepileptic)
5. Antipsychotics. (unique)

1st 4 group has similarity in chemical features of structur, same mode of Action and have common class.

↳ Dopamine receptor/release has differ MoA.

⇒ General MoA/ for CNs depressant especially 1st group/

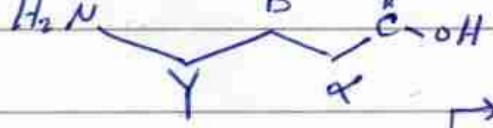
- one of the most common MoA is GABA activation
- by binding of GABA to GABA binding site or receptor. Stimulate or Potentiate the opening of Cl channel
- Most groups of CNs depressant acts by binding to allosteric site. (near to GABA binding site).

as/ Barbiturate, Benzodiazepine., General anesthis. lead to ~~Et~~ increase Cl^- channle opening ↑ Cl^- influx lead to CNs depression # (potentiate GABA effect)

⇒ GABA (gamma amino butyric Acid)

- most common type is GABA A (most inhibitory Neuron)

↳ ionotropic Cl^- channel



Binding to GABA receptor
- ionotropic ⇒ control ionic channel
- direct (active site)
- indirect (allosteric)
  - metabotropic → bind to G-protein coubled receptor, thus activate 2eA messenger, give intracellular signal

Date. No.

another MoA for depression

- inhibition of glutamic Acid (An excitatory Neuron)
- Agonism of A_2 receptor (Adenosin receptor)
- ↓ Neuronal flux of Ca^{++}, Na^{+} (direct effect on channels)

⇒ MoA of action of antipsychotics. (unique)

- Blocking of dopamine receptor D_2, D_3, D_4 mostly D_2. (Post synaptic)
- may be selective to presynaptic DA receptor agonists.
- By depleting neuronal DA (prevent release of Dopamine)
- or having more than one mechanism lead to give a Net effect of which is ↓ release of DA. into synapse
- or depletion neuronal DA (after release) ~~Post~~ in storage vessels in dopaminergic nerve ↓DA action

1) General Anaesthesia.

it's loss of sensation ω reversible loss of conciousness and depression of defense and muscle relaxent.

- it cause partial or total loss of sensation.

* stages of anesthesia produced by General Anesthesia :-

1. Stage 1 → Analgesia. (↓Pain analgesia, euphoria)
2. Stage 2 → Delirium (Excitment, Delirium) • ↑HR/B.P • muscle reflux • salivation
3. Stage 3 → surgical Anesthesia (maintenance) (unconsciousness, regular respiration)
4. Stage 4 → respiratory paralysis (No eye movement respirator, cardic arrest) (Toxic) ⚠

Date. No.

best Anaesthesia Drug which has very rapid duration of stage 1 and 2. and move on directly to stage 3.

. So it must has rapid induction phase

stage 1, 2 → induction phase

stage 3 → Needed (need maintance)

stage 4 → Avoided (toxic).

Thare different drugs involve in general Anaesthesia as :.

1) premedication. (To prevent Brady cardia, Bronchial secretion and muscle spasm) which mostly occure in stage 2 (as in stage II)

- Benzodiazepine. (Diazepam)
- Narcotic analgesic.
- Anti Cholinergic drug (scopolamine) ↓ Sativa secreation
- Skeletal muscle relaxant. (CNS) ↓ muscle spasm.

Type of Anesthetic drug. :

2) inducing agent (rapidness/accelerate of stage 1, 2 to reach stage 3 rapidly) using I.V anesthesia

normally IV anaesthetic. (usually its toxic and limited use for induction phase alone ; have narrow therapatic window) as

- Barbiturate (thiopentone)
- Non Barbiturate (propofol, Ketamine)

Liquid

Date. No.

3) Maintaining anaesthesia.

more safe usually as inhaled gas. (continous)

as/ - halogeneted hydrocarbon and ethers.

- Nitrous oxide N_2O

4 - Anti emetic (may requier after post-anaesthesia or post surgical)

MoA of Anesthesia → excitatory receptor or neurotransmitter effect

1) Blocking of NMDA (N-methy-D-aspartate) receptor which ~~Glu~~ glutamic acid bind to it.

as/ Ketamine → Blocking NMDA → CNs Depression

2) Activation of the inhibitory GABA receptor. which lead to open Cl^- channel and ↑ Cl^- influx and result in hyperpolarization of neuron.

as/ Halothan , isoflurane

also BZs and Barbiturate (allosteric site) → ↑ Cl^- channel opening

so it enhance GABA effect , by prevent distruction of GABA in synapses thus ↑ it's concentration and ↑ effect of CNs depression

** broaden therapeutic range, give small doses from several substances, ↓ toxic, side effect.
So insted of given 1 agent $\bar{w}$ ↑ doses, give many agents $\bar{w}$ low doses (same effect $\bar{w}$ lower side effect)

Date. No.

Depending on rout of adminstration, general anesthetic are classified to

stage 3 ← لكي نقلل الأعراض

Inhaled (pulmonery)	IV	combination **
• Gas, vapor of volatile liquid, mixture $\bar{w}$ O_2	→ Liquid, non-volatile	↳ prefered
• for maintance in stage 3 (فقط stage 3)	→ - used in induction phase for inhalation	↳ 1st IV ↳ 2nd inhal
• more safe.	→ Rapid onset, offset	
	→ less safe. (can't given $\bar{w}$ ↑ doses) as Barb. / BZs	
Ex /	Ex /	مدرسة

depending on physical properties that has be known from chemical structure, we could classifie any drug to either Iv. or Inhaled.
in which inhalation drug usually has
(↓ Mwt, simple carbon no., No hydrogen bond, depend on vanderval force and lipophilic)
But For Iv usually its solid and could prepare solution or emulsion.
→ easily volatile liquid by knowing it B.P ex/ ether B.P is 30°C.

• * ideal properties in table
بالسلايد

- oil - gas partion coefficient → in inhalation anesthetic For potency
- Blood-gas partion coefficient → indicate onset, action & Drug and offset

Date. No.

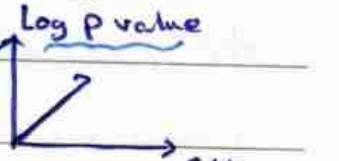
structure
Action ⇌ physical properties* critical

⇒ Due to presence of BBB (the Drug must be Lipophylic to cross BBB)

⇒ we make expression of to Lipophilic ch.ch by parameter called partion coefficient. "Log P"**

↑ Log P ↑ Lipophillicty. ↑ Potency

↓ Log P ↓ Lipophillicty. ↓ Potency



$$\text{Log P} = \frac{\text{Conc. of Drug in oil}}{\text{Conc. of Drug in } H_2O}$$

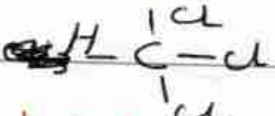
in 19 century

⇒ befor the used to use as general Anaesthetic ether

C-C-O-C-C

- volatile, explusive

Chloroform



hepatotoxic

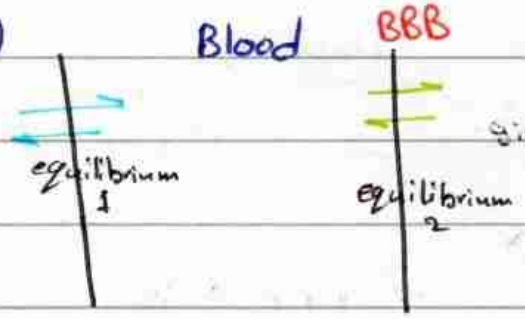
⇒ So Nowdays they make halogeneted form to ↓ toxicity ↓ flam ↓ explusive.

as/ - halogended hydrocarbon (best)

- hydrocarbon * ↑
- halogenated ether
- ether * All are simple compound used in hospital - except ether
- N_2O (Nitrous oxid)

if the Drug has Low Blood solubility, give rapid equilibrium bw Lung - Blood and rapid saturation, and also rapid equilibrium bw Blood - Brain because the drug will out from Blood quickly thus pentrate CNs rapidly ⇒ rapid onset of action.

Date. No.



when take any Anesthetics Drug (ideal properties)

⇒ must has rapid equilibrium [short period or time in Blood this indication of ↑ Lipophillicity]

the parameter that indicate the onsete of Action is Blood gas partion coefficient (B-G) ∝ Lipophilicity = $\frac{\text{Conc. Blood}}{\text{Conc. gas}}$

↳ the Low value indicate that the gas dosen't like blood, thus it's more Lipophillic and pentrate CNs more fast (the more the value is less, the more it's rapid)

كل قلت القيمة زادت سرعة.

⇒ in recovary must be rapid removed from CNs.

also ↓ Blood gas partion coef. ↑ recovary. يتم التخلص منه عن طريق الزفير

⇒ Potent inhalation anesthetic is prefered;

- to minimize the dose
- and let some space for O_2 or hypoxia will occure.

So onset of Action control by → Blood-gas Part. Coef.

potency → Log P Part Coef

↳ ↙

MAC: minimum Alveolar Concentration. measure at 1 atmospher press
it's mean conc in the Alveoli required to produce patient immobility
in response to painful stimulie in 50% of patient

Date. No.

=> any change in chemical structure. will change
- Blood-gas p.c thus chang onset of Action.
- Log p or p.c thus change potency

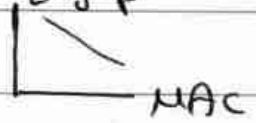
we could measur potancy by MAC (IC50)

MAC: main Alveoli conc of Inhaled anesthesia that lead to loss of mobility in 50% of patient.

ex/ Drug A is 3% MAC, Drug B 10% MAC.
So Drug A is more potant; just 3% is capable to produce immobility compared by 10% of other Drug.

=> ↓ value of MAC ↑ log.p (more potent Drug)

[↑ MAC → less potant
↓ MAC → more potant]



always choose Drug w ↓ MAC and ↑ Log.P.

So we have 3 main Physiochemical Parameter that could control potancy and kintec of G.A

1) MAC (minimum alveoli conc.)
2) Log.P (Lipophilicty of compound) or Partion coefficient.
or Lipid solubility
3) Blood-gas partion coefficient

↑ Blood-gas p.c → hydrophillic → slow onset → slow offset
↓ Blood gas p.c → lipophillic → rapid onset → rapid offset

• halogen is more Lipophillic then hydrocabon → carcinogenic
→ flamable
→ toxic
→ ↓ Potent
→ slow induction
→ ↓ safe (irritant)
→ explusive.

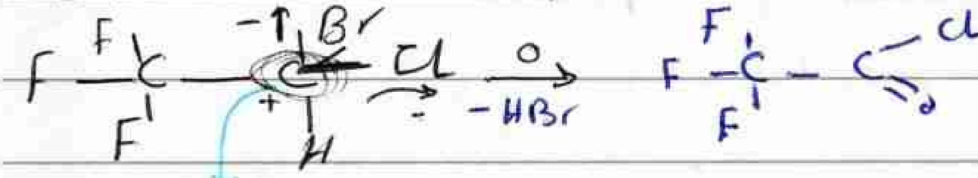
chloroform , ethe تلائم مع استثنى سبب فشا •

both alkan and ethe are substituted with halogenated form as (especilly F) → ↓ Flamability
↑ stability
↑ potancy

• halagencted hydrocabon (halothem)
• halogenated ethes.

thus ↑ potency ↑ safty and due to the stability b̄w halogen and carbon bound it's more stable this mean ↓ Blood-gas pc → Lipophillic → rapid onset of Action

* Halothen make immune Rx lead to hepatitis due to it's metabolit.



acyl chloride
very reactive

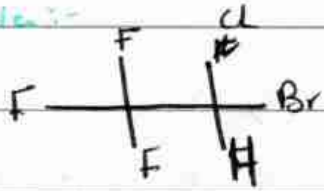
Surround by 2 halogen ↓ ē condencity so easy to be oxidized

will react ē protein, carbs --- → attack any nucleophilic sub.
so give glutathione as defense mech.

Date. No.

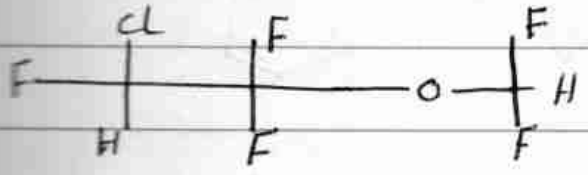
Example of Inhaled Anesthesia:-

- Halogenated hydrocarbon

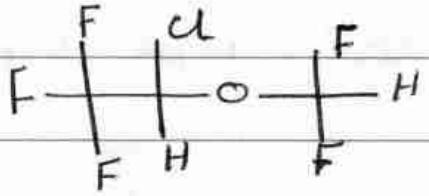


Halothane

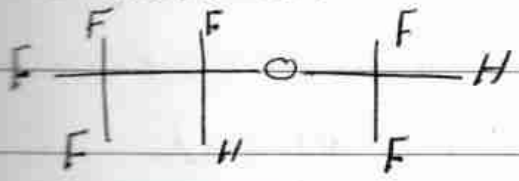
- Halogenated Ether.
  - Enflurane



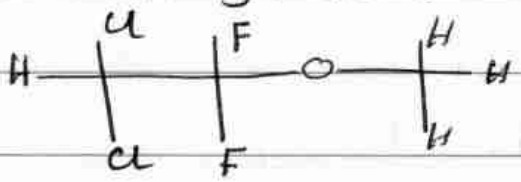
  - isoflurane



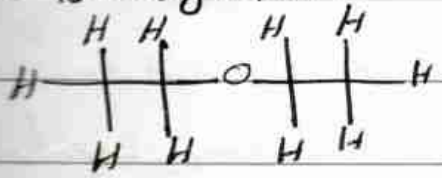
  - Desflurane



  - methoxy Flurane



- Non halogenated (ether)
  - Diethyl ether.



  - Nitrous oxide

↳ ~~gas~~

  - cyclo propane

↳ ↑ side effect
↳ very potent

Hydrocarbon < Cyclic / Acyclic

- cyclocarbon propane or propane

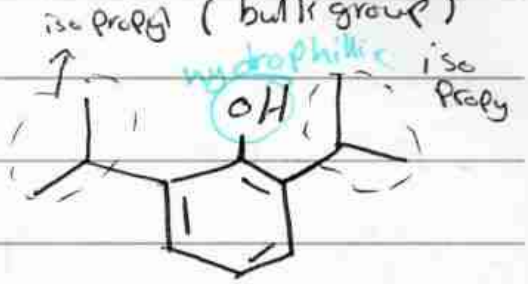
Date. No.

IV Anesthetics. (for induction Anesthetics)

Class / 1) miscellaneous : propofol , ketamin Hcl

2) Benzodiazepine

3) Barbiturate.



1) propofol ~~Diprivan~~ (Diprivan)

⇒ phenol , 2 iso propyl

↳ cause tissue distruction and general toxicity due to OH

good for biological properties of OH.

→ simple compound , very lipophyllic. , act on GABA

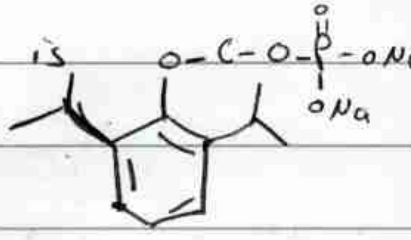
⇒ has ↑ Logp (lipid / water partition coefficient)

so rapid onset of action and low duration.

⇒ due it's high lipid solubility we can't prepare an 1-2% aqueous form solution , so it's has been disolved in oil (soya oil) to produce emulsion but this is Painful during injection.

⇒ another way of modifying on propofol is (to ↑ solubility)

making prodrug called phosphopropofol



we add PO_4^{-2} to ↑ water solubility

and ↓ pain but its ~~easily~~ breake by phosphatase enzyme thus.

its has slow onset compared to propofol (rapid onset)

delay ← non-painful ↑ soluble

painful ↓ soluble

Date. No.

Note!

- presence of 2 isopropyl is important to make shield on oH group and prevent any Hydrogen bound.
- so if change site of bulk group, ↓ Lipophilicity.

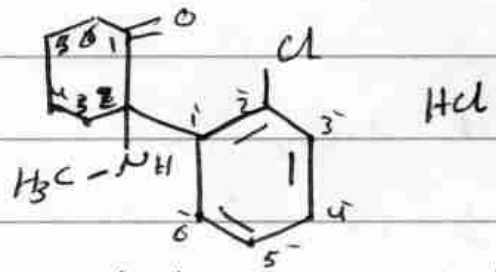
So for any drug that give I.v and non-soluble we could/

1) modifying of formulation (less cost, time)
2) modifying structure (more time, cost)
3) make pro drug (No time need, just added a group to enhance solubility)

Date. No.

2) Ketamine Hcl.

Keton, cyclohexan + amin



2 (2-Chloro phenyl) - 2- methyl amino cyclo hexanone

→ Blocke of NMDA glutamic acid recepte

→ make Hcl salt to improve solubility.

→ make dissociation from event

→ Could make upuse (limited in hasptal)

→ used as induction espacily ≤ 16 year.

→ Low incidence of hallow cinetic.

Sedative and Hypnotics

Date. 3/3/20 No. Lec. 3

⇒ sedative (at ↓ dose) → ↓ activity, excitement of the patient mild depression without drowsiness or sleep. (calm)

⇒ hypnotic (↑ dose) → produce drowsiness and forcing sleep.

* Both sedative, hypnotics are similar but differ in (degree of depression) ↑ Dose:

↑ Dose	
	small dose → sedation (calmens)
	moderate dose → hypnosis (sleep)
	high ~~strong~~ dose → depressant (surgical anesthia)

* So they are indicated for / anxity, insomnia, GA, Anti convulsant.

in which:

⇒ sedative → used for various of Anxity

- OCD: obsessive - compulsive disorder
- PTSD → post-traumatic stress disorder.
- social anxety disorder. and specific phopic.

⇒ hypnotic → used for insomnia

Date. No.

Ideal properties of hypnotics /

1) Temporary decrease in level of consciousness without any alteration in sleep cycle.
2) No decrees or arrest of respiration even in ↑ dose
3) Non. addictive, tolerance or dependance.

⇒ // each neurotransmiter in brain has induction a role in sleep cycle as :- (must has balanced)
(Ach, dopamine, histamine, serotonin, Adenosin, Adrenalin

For ex / - Anti histamine inhance sedation
- SSRIs remove Anxity
- Antipsychatic block dopamine.

⇒ Drug classification. (pharmacological + Chemical)

1) GABA(A) receptor activation on allosteric site (agonist) (Pharm

(Chemical) Class.
a) Barbiturate old
b) Benzodiazepine → (a) ज्यादा
c) Non-Benzodiazepine ↓ New
↳ called Z drug start with Z
↳ Differ in chemical structure from Ba
but has same MoA, effect

② modulation hypothalamic < histamine / melatonin Date. No.

Hypothalamus

Anterior

- has Nucleus SCN
if we make depression to SCN lead to sleep by Action of Melatonin hormon. which binds to Melatonin receptor. So if we make Agonism to melatonin receptor → activation of sleep. SCN → melatonin → sleep (agonist)

② Melatonin Receptor Activation (MRA)

posterior.

- in THN in which histamine work on it lead to alertness so if we make H_1 blocking by Anti histamine. lead to sleep. or sedation.

③ Anti histamine.

So we have 3 MoA to get CNs depressant

1) GABA (A) activation
2) MRA (melatonin receptor agonist)
3) Anti-histamine. as Doxylamine

Date. No.

For chemical classification :-

1) Barbiturate : phenobarbitone

GABA (A) agonist

2) Benzodiazepines : Alprazolam, Diazepam, Nitrazipam and lorazepam.

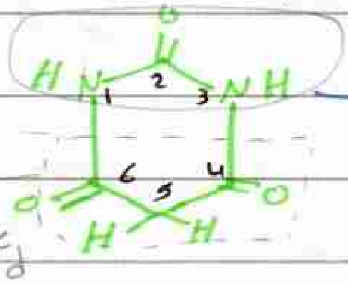
3) Non Benzodiazepine : Zolpidem, zopiclone

4) other : paraldehyde, chloralhydrate, Glutethimide.

5) herbal valerian, passiflora, Ashwagandha

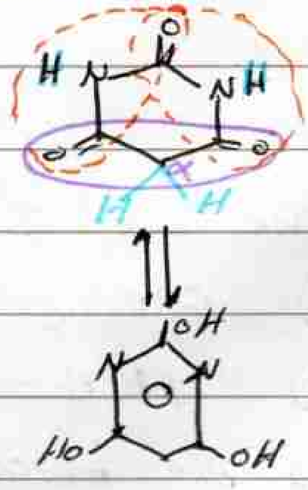
① Barbiturate

↳ has No CNS activity
↳ Acidic



→ • Barbituric Acid.
2,4,6 trioxo hexahydro Pyrimidine

Physiochemical properteis for Barbituric Acid :-



1) Acidic.

a) has 2 Imide group (acidic group)

b) has α carbon

c) has 4 H

d) by resonance make strong Acid

2) pKa = 4 → ↑ ionized very strong Acid

3) hydrophillic ; O, N that make hydrogen bond.

4) so No CNS activity ; less pentration, less log P

it's inactive No cross BBB and ↑ ionized

بشرط وجود كل الجروبات الوظيفية ، orientation وترتيب 8 لهات action.

لكن يلزم good pentration to CNS

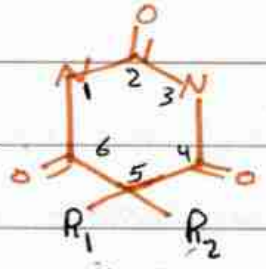
Disadvantages/
- Addiction potential < Physical / Psychological
- ↓ Therapeutic index → ↑ dose ; toxicity
- Potent CYP 450 induce → ↑ DDI

} replaced by Benzodiazepin → Barb. limit use

used as < anxiolytic / hypnotic / Anticonvulsant / analgesic

Date. No.

* Barbiturate



- it's 5, 5 di substituted Barbituric acid
- So to give activity on CNS we add R_1, R_2 For / → Lipophillic
  - less acidic, ↓ resonance, ↓ ionized

so easily transported and good penbration and GABA activation

  - pka ≈ 7, unionized, easy to be transported
  - ↑ Lipophillicity ↑ Log p.

thus change in chemical structure lead to change in physiochemical properties and action.

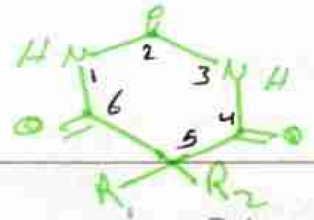
⇒ Both Barbiturate and Benzodiazepine has different Binding site (Allosteric site on GABA ⊕ receptor) thus has different SAR and different interaction.

⇒ To let Barbiturate give sedation. it must has Balanced Acidic – Lipophillic ch. Ch.

For ex/ Acidity 7 - 8 and lipophillicty log p > 1.5 For Both it must be optimum. Transport + solubility → R_1+R_2 = 7-9 Carbon

* if increase lipophillicty very high → or it will stay in Blood No good transporter.

Acidic Not strongly and not ionized



SAR of Barbiturate

Date. No.

For position 5 on R_1, R_2 which is important for Acidic and lipophillic ch. ch.

1) if we remove one of R groups on 5 postion. lead to imbalance bw Acidic - lipophillic.

2) To has sufficiently lipophillic ch.Ch. the sumation (sum) ~~of~~ no. of carbon for both (R_1+R_2) must be bw [4-9] for ex/ R_1: ethy (2 C) R_2 ethyl (2 C) = 4 C minimum.

This will control

- ~~potency~~ onset of Action. (potency)
- ~~t½~~ DoA

① ↑ sum no. of carbon in R_1, R_2 lead to :-

1) Shorter DoA; ↑ Lipophillicty that lead to increasing ↑ metabolizm rate ↑ excreation from the body.

2) rapid onsed and offset of action., During transpotel throught Blood and petration to CNS.

thus 4 - 9 carbon → give Acidic - lipophilic Balanced Short DoA.

LogP>1.5 minimal Lipophillic → increasing no of carbon, rapid onsed

② unsaturation group alkyl or cyclic on R_1, R_2 lead to ↑ metabolic rate, shorter duration; it become more valnerable to ~~be~~ oxidation. (more potent)

يعني ع ↓ الاعطاء قادر ينبه دوائي مو لازمة onset /DoA

= اول شي بعد الكربونات ← الخطوط = Branching

→ alkene is better then alkan in excreation (↑ metabolism and oxidation process

Note/ ↑ Lipophilic ↑ diffusion to BBB → rapid onset and due to rapid equilibrium b/w Brain Blood its reversible action also rapid (to Blood) thus ↓DoA as in thiopental < rapid onset / offset

I.V has short DoA than I.M & oral { ↑ Lipophilic < ↓DoA / ↑ onset of Action.

Date. No.

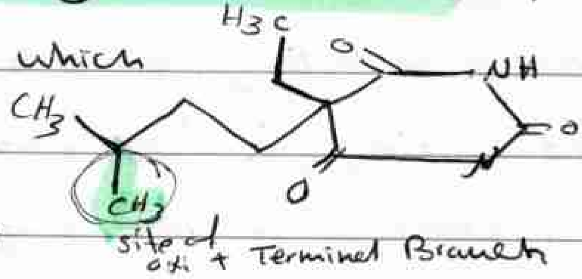
③ Branching. depending on it's site.

a) - Branching in site of oxidation will ↓ metabolism rate thus ↑ DoA

أسرع بـ metabolism

For ex/ intermediate acting : Amobarbital — ابعد من الحلقة

has terminal Branching in which it's common to be more vulnerable to have omega oxidation. this lead to ↓ metabolism ↑ DoA due to Branching in oxidation site.



* intermediate جعله Branching على الرغم من أنه 7 كربون لكن تأثير وجود not short.

أقرب للحلقة

b) Branching a way from oxidation site (acts as unsaturation in R_1 R_2) that ↑ metabolism rate ↓ DoA.

For ex/ short acting – Secobarbital

non-terminal Branching, away from oxidation, ↑ metabolism rate ↓ DoA

على الرغم أنه 5 كربون بوجود تفرعين لكن صار short مش intermed

وكان وجود unsaturation له هذا الكلام

④ in R_1 and R_2 can't be both aryl. either aryl / alkyl or both alkyl

* Branching, unsaturated → ↑ metabolism ↓ action.

Date. No.

* classification of Barbiturate depending on DoA :-

DoA ↑ → no. of carbon

1) Long acting barbiturates, > 6 h, has 4 carbon. long DoA (Slowest on)

2) intermediate acting, 3 - 6 h, 5 - 7 carbon

3) short acting, < 3 h, 7 - 9 → ω additive effect (give e)

4) ultra short < 1 h, [alot of modification]
↳ For induction anesthesia. Extra modification not only 9 carbon.

④ by ↑ Lipophilicity, ↑ potency.

the substitution on R_1, R_2 has role in < Potency / DoA

So don't add hydrophilic on R_1, R_2

we can add cyclic just 1 cyclic to ↑ potency.

but not 2 cyclin on both R_1, R_2.

cyclic aromatic as phenobarbiturate or

Non - aromatic

Note/ when we make substitution on position 5, we still have 2 H on N in position 1, 3 (Both give acidity) to give activity we must at least have 1 H on N. and another could be methylated but can't make double substituted on N

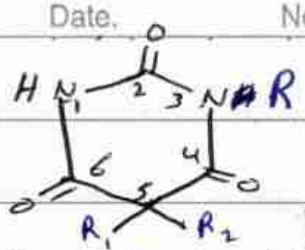
Balanced Acidic chch

Balanced Lipophilic → loss 5:5 H on position 5 and sub. ω R_1, R_2

↑ pKa ↓ acidity

Date. No.

For position 3 No methylation

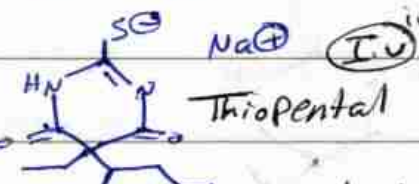


NH on 3 position could convert ↑ potency

to NR ; ↑ lipophillicty , ↓ DoA , ↓ Acidity ↓ ionized

so to make drug sufficiently acidic, both or at least one of 2 Nitrogen must be unsubstituted or it will loss acidity.

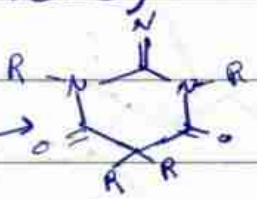
For position 2



we could substitude O → polar w its isostero atom which is S → 2 Thio Barbiturate. (IV anesthetic)

Lipophilic → ↑ Lipophillicty ↓ DoA < rapid in rapid out

Not (N) → ~~non~~ ionized. ~~Non~~ Inactive



also inclusion more sluphr in C_2, C_6 ↓ activity ∴

↳ more than upper limite

Note/ - Phenyl group not conside as 6 C ;

it has bi electron and make polarization. +δ, -δ

when it aromatic cyclic

~~Not~~ equel to 2- 3 carbon so its long DoA ↓ lipo.

but as potency its very potant.

So not counting aromatic ~~or~~ as no. of carb.

as in Phenobarbital.

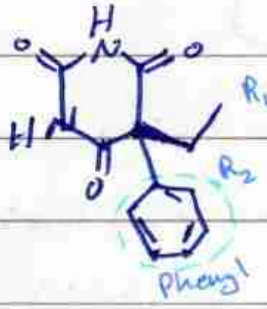
cyclic > Aliphatic as potency

↳ Aliptic potent

Aromet

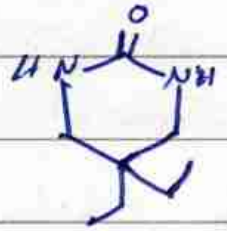
Date. No.

Ex of Barbiturate /



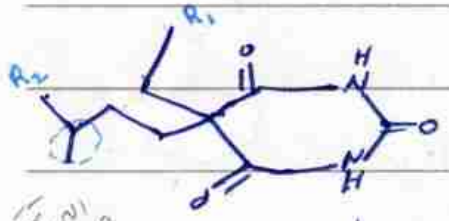
Phenobarbital. log ≈ 1.46

- long acting
- has 2 C (Phenyl not consider hydrocarbon)
- ↓ LiPo ↑ DoA



Barbital log < 1.5

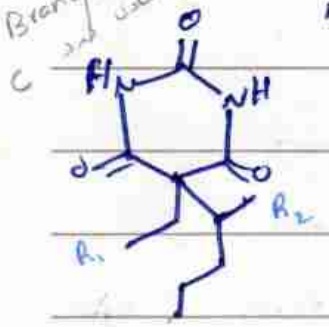
2 ethyl, 4 C, long acting., ↓ LiPo ↑ DoA



Amobarbital log ≈ 2.07

- terminal Branching ↓ metabol ↑ DoA
- 7 C → intermediate

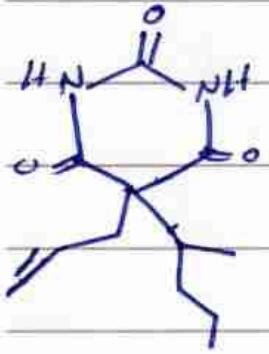
hard metabolism



Pentobarbital Log P ≈ 2.10

Short acting 7 carbon.

Branch away from site of ox. ↑ metabolism rate

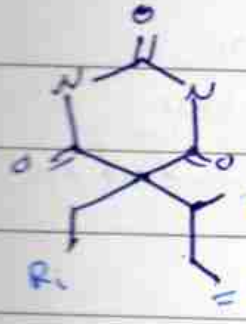


secobarbital log 2.36

Short acting., 8 C

Branching away from ox. site ไม่มี unsaturation

Date. No.



Buta barbital Log 1.6

intermediate 6 carbon.

- So if $\log P < 1.5$ → give long acting
- we named drug depending on R_2 ($R_1 \approx$ ethyl)

→ PhK
→ PhD
→ Lipophillicity
→ DoA
→ Potancy
→ onset of Acti

Date: No.:

So we have 3 position which Focus on

1) 5,5 substitution (no. of carbon)
2) N substitution
3) O substituted ~ S

Barb.
- used in → hypnotic
  → sedative
  → Anti convulsant
  → induction of Anesthesia

hydrophilic
* if we substited position 5 with ① OH / NH_2 on R grou
will ↓ activity ↓ Lipophillicity

② with halogen (Lipophillic) ↑ lipophillicity (could ↑ toxicity)

- MOA
- metabolism
- SAR
- General classification < pharmacological / chemistry
- Example

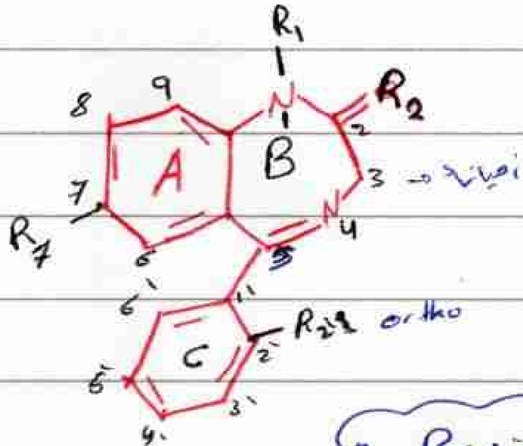
Benzodiazepines

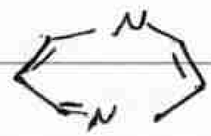
→ used as / 1) ~~anxiolytic~~ anxylotic 2) sedative / hypnotic 3) Anticonvulsant 4) muscle relaxant 5) induction of anesthesia.

⇒ General structure :-

Benzodiazepine → benzen ring | Two N | 7-membered ring contain one nitrogen

Two N + 7-membered ring → 7 membred c̄ 2 N and 3 = called diazepine



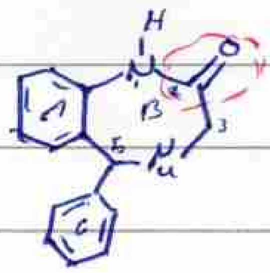


Basic nuclease is or General structure

① The core is Fused Benzen + diazepine ring
↳ 1,4 Benzodiazepin ring system

② all BZs has Phenyl ring on Position 5

③ Keton group in Position 2



ثم بعد ذلك نقوم بعمل substitution

safe
↑ therapeutic index Date. No.

- it's more safe (less addiction) than barb.

⇒ MoA:

1) main MoA as barbiturate, has positive allosteric effect on $GABA_A$ receptor, increase binding of GABA neurotransmitter to it's receptor thus opening Cl^- channel and inhibition CNs activity.
it bind at a different site than GABA or barbiturate.

2) Block reuptake of Adenosine (sedative neurotransmitter) thus left Adenosin in synaptic cleft. causing CNs depression

3) Block Acetylcholin (Ach) receptor in hippocampus and causing amnesia

⇒ metabolism:

- give idea about side effect of Drug
- responsible of phk propeites. which lead to understand the pharmacolgical and clinical uses.

back to slide on metabolism Date. No.

- in Diazepam For example / (Lipophilic)
- it has Cl on position 7 and methy on N_1

thus N-demethylation dealkylation is one route of metabolism which convert to Nordazepam or dismethyldiazepam

* CH_3 is not critical for activity thus Nordazepam still active

But still become long duration $t_{1/2}$ ~~duty~~ why ??

~~due to N-demethylation~~

on position 3 in Nordazepam which is α Carb. located two 2 withdrowal group, become more vaeunable for oxidative metabolism.

but it's very slow ; thus having long $t_{1/2}$.

and also still active (oxazepam) has short $t_{1/2}$ and thus lead to glucuronidation. and excretion

- Both Nordazepam - oxazepam are active

thus ↑ DoA of Diazepam.

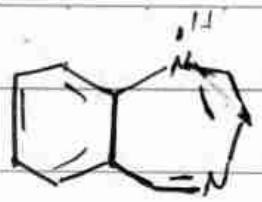
also prazepam, Halazepam, Clorazepam similar to Diazepam.

all has N-demethylation (except Chlorazepam has decarboxylation) and converte to Nordazepam and slowely to oxazepam

so All have long DoA

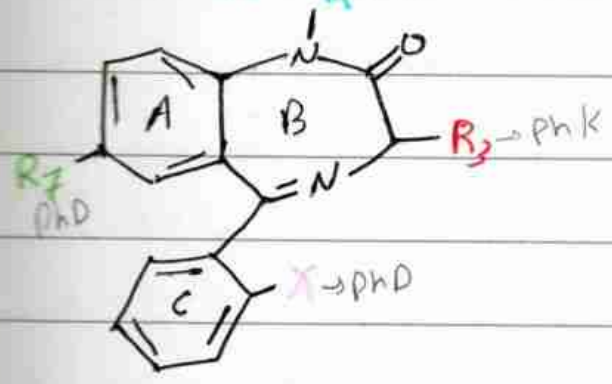
SAR of 1,4 Benzodiazepine

Date. No.



There are 2 class of BNZs

Class A

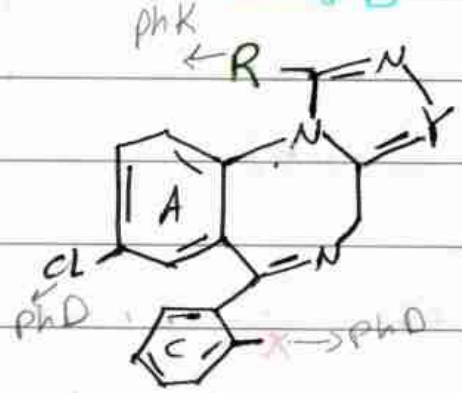


- Bicyclic Fused system
- 6, 7 cycles.
- ↑ DoA
- usually end ῶ pam

Diazepam, oxazepam ...

- Both has same Binding and MoA

Class B



- Tricyclic Fused system
- 6, 7, 5 cycles
- addition 5 cycle ῶ N Fused in position 1, 2 in Benzdiazepin ring.
- Short DoA, ↑ Potency
- end ῶ <u>zolam</u>

as/. Alprazolam

- Triazolam
- Midazolam

PhK → DoA

PhD → Binding

Date. No.

* SAR Map (give indication on PhK and PhD)
in which position you will change either give you
an PhK / PhD changes. as follow /

Class A

R_1 → on N PhD

R_3 on 7 Position → PhD

other Position ? → PhD

R_3 → phenyl

Class B

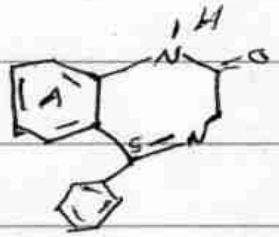
R → PhK

X → PhD

Cl → PhD

* The Basic Backbone is

5-phenyl-1,4 benzodiazepine-2-one backbone



one position 5 → phenyl

on position 2 → keto

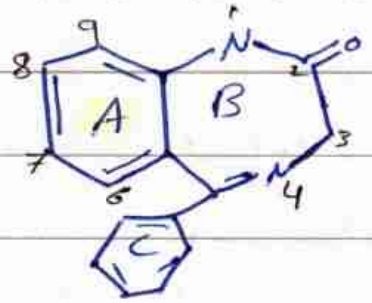
1,4 benzodiazepin

are required for BNZ, activity.

Now changes on substitution for change PhK and activity

Date. No.

Ring A/



1. mustn't has any substitution except on position 7
2. ~~Ther~~ phenyl is best form for aromaticity of ring A (if replaced w/ hetero aromatic or it's isostere as thiophene reduce activity).
~~it~~ phenyl is important due to π-π stacking (Lipophillic) and has a role in Binding and agonistic activity on GABA receptor.
3. position 6, 8, 9 prefered not having substitution. due to significant reduce in activity.
4. position 7 is the only position allowed to have substitution

Steric or electronic effect ??

bulky small withdrawal Donating

BNZs acting centraly, ~~so~~ it must has ↑ Log P ↑ LiPophill & thus avoid any polar group as possible and increase Lipophillic group ; ↑ penetration

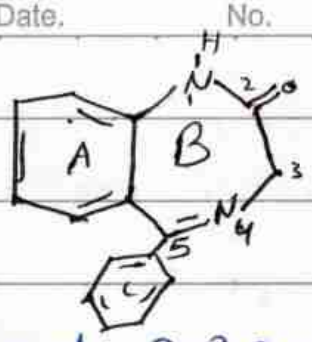
* So electrowithdrawing group w/ Lipophillic charachte is prefered on position 7 (↑ activity PhD)

ex/ halogen (F), Nitro

as in diazepam has Cl on position 7 in ring A

Date. No.

Ring B



- Diazepen ring system
- NH on position 1 substitution is not critical (still active as discussed in Diazepam...)

* but if we want to add lipophillic substitution to ↑ Log p value to enhance activity it must be tolerable group ~~bulky~~ (small lipophillic group is tolerable)
* bulky group can't be affored in this position, to activity
* linear long chain don't much reduce the activity but ~~long~~ ethyl chain (don't take much space) still active
  ↳ small alkyl (not bulk) → good activity but not required, not essintial; removed by N- demethylation in metabolism and still active

Position 2

- need hydrogen banding group (O, N...)

if replaced O ~~with~~ its isostere S → active (thiobenzodiazep
convert inside body by oxidative desulfuration and back to O and still active

Date. No.

• but optimum activity is = O (carbonyl) -C-

• position 3 Phk Propurity.

- not Preferred

- Few tolerable group could be substituted on position 3 mainly hydroxyl group OH → give active compound, won't notice a notable change in ↑ or ↓ in activity but change from Long Acting to short acting rapid Low log P why ?

position 3 OH → make it more valunrable to rapid metabolism by glucrindation and thus elimenation as oxzepam

- alkyl group ↓ activity on position 3

* Double bond in 4-5 position

• movment or cancle d double bond lead to ↓ activity in vetro

• but 5mire group if be saturated, won't affect so much on anxiolytic activity in vivo

because inside body, oxidation occure thus give = again and give activity

• = protect Geometry in ring C, any change in = affect optimume Geometry of ring C preferred

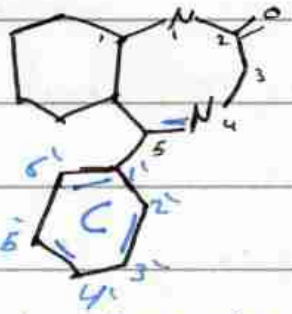
Non-Coplanner

Date. No.

Position 4

- no substitution is preferred except ^{N} oxide N=O tolerable as in Chlordiazepoxide

Ring C

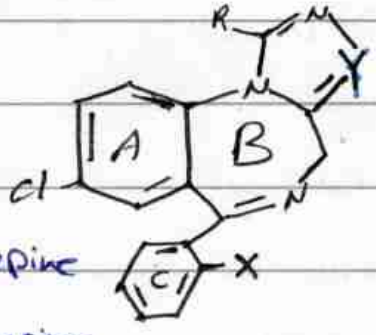


- has a role in GABA$_A$ agonistic effect
- give hydrophobic or steric interaction
- in ortho position on 2`, 6` or 2`+6`

if adding withdrawal group ↑ activity (Lipophillic) ~~not~~ as halogen Cl^-, F^- ↑ activity

- if ~~Not~~ add substitution on position 4` → ↓ activity due to steric interaction (Not recommended)

Class B



- 3'd ring diffused could be either

Y=C Imidazol  Imidazobenzodiazepine

X=N Triazole  Triazolobenzodiazepine

Both ring (as CO in Class A (carbonyl)) has ability to make hydrogen bond acts as strong proton acceptore so has same activity Plus ↑ Lipophillicity ↑ potanet electrone ē rich (act as proton acceptor) active ex/ Triazolam, Estazolam

Nonbenzodiazepine $GABA_A$ Agonist.

Date. No.

* Drug discovery and development:

- Barb as sedative, hypnetic it's use becam ↓
- Drug company to discover new Drug try to enhance PhK, PhD properities as: ↑ activity ↓ S.E and toxicity ↑ safty PhK as ↑↓ duration pentration absorption and biowildbility.

So For Barb.'s

it has ↓ therapeutic index, hapeutation dependence, tolerance, ↑ CNS and respiratory depression.

* so to transform from bad PhD and PhK to better phk. and PhD need many stratiges General stratiges as/

① Change binding site or target

Fo Barb. to change to BND.

BZDs has Allosteric binding site differ from Barb. this lead to change in PhD properities. and result in new chemical class or group ⇨ different binding site. (↓ S.E, ↓ Physical depen ↑ safty, ↓ tolerance

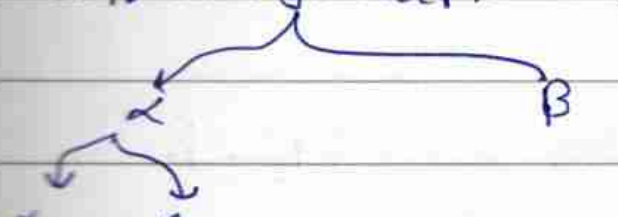
Date. No.

other strategy:

① Selectivity

- Sometimes b s.E result from ↑ selectivity.
- selectivity need special type of recepter that has subtype.

ex/. adrenergic receptor has α, β



- Histamin receptor { H_1 sub types, H_2 sub types, H_3 sub types }
- So in general when Drug act on many targets result in s.E
- the more selective the Drug is the less is side effect.

when we say is selective, it doesn't mean then it doesn't bind to other subtype, but it's more affened (↑potency ↑efficacy) more than its potency to other subtypes.

- So more affinity more selectivity
- when given drug with { ↓dose → ↑selectivity ; ↑dose → ↓selectivity.

selectivity في الأول غيرنا binding site في الثاني

Date. No.

- Non-BZDs has :
  - safety properties (↓ S.E , ↓ tolerance , ↓ addictive) than BZDs. (due to selectivity) on $GABA_A$ receptor
  - bitter PhKs properities : Fast onset & Action on ↓ DoA
    ↳ due to other strategy.

* How selectivity is come?
  - GABA has 5 ~~subtype receptor~~ subunit. $2\alpha_1, 2\beta_2, \gamma_2$
  - each unit (α, β, γ) has different class subunits
    ~~GABA(A)~~ has 6 subtypes of α subunit.
    GABA(A) → 4 different β subunit
    → 3 different γ subunit.

GABA(A) → contain α_1 subunit → involve sleep (hypnotic)
→ contain α_2 or α_3 → involve anxiety

[- Anti-convulsant
- muscle relaxant
- amnesics]

Date. No.

$GABA_A$ α_1 selective hypnotics.

- BZDs can binds to α_1, α_2, α_3, α_5 result in different effect of BZDs as
  - Smooth muscle relaxation
  - sedation
  - Anxiolytic
  - Alcohol potentiation Action
- Zolpidem and Zaleplon and Es Zopiclone → lower selectivity to α_1 subunit.
  These called Z-Drugs: → b.s.E, Non BZD, better PhK-PhD, Properitie

- Advantages For Z-Drug over BZDs as
  - relatively short $t_{1/2}$ → so No "hangover" effect
  - Fast onset → Gabber effect
  - less side effect.
  - give natural sleep
  - less addiction
  - less withdrawal symptom
  - less tolerance.

hangover in BZDs as
- residual morning sedation
- confusion
- cognetive, meomery impairmen

Date. No.

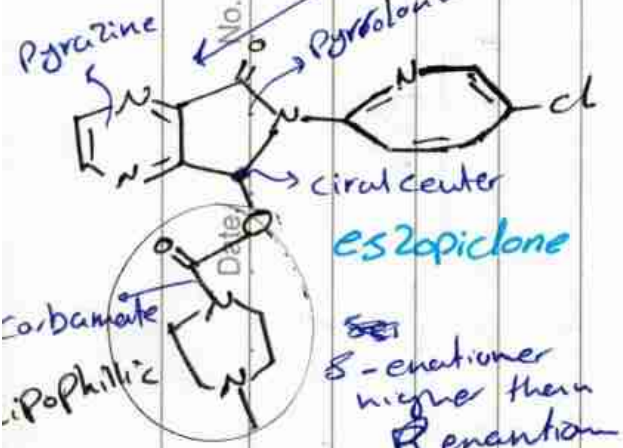
* Z-Drug and BZDs has same binding site → MoA

which activate GABA-A receptor

* but BZDs, Barb different Allosteric site

New selective hypnotics Z Drugs.

Z-Drugs, same Binding site.



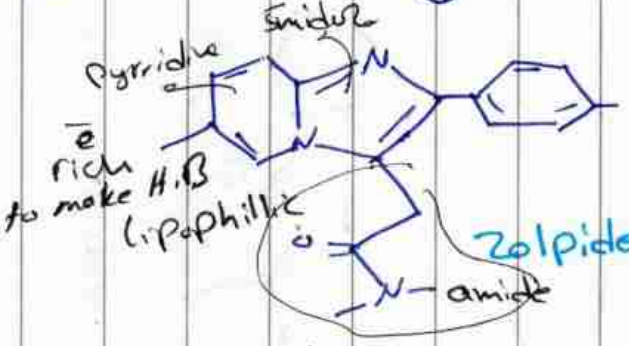
eszopiclone

S-enantiomer higher than R enantiom

Pyrrolopyrazin

or cyclopyrolone

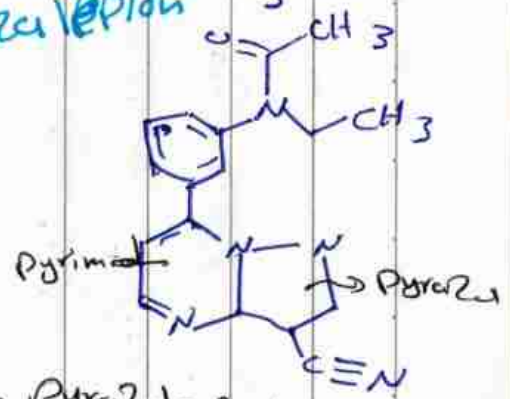
- S- better than R
- less sedative
- No tolerance
- Safe
- moderate DoA (t1/2 6h)
- Non-selective on GABA α_1



Zolpidem

- Imidazopyridine
- ↑ Lipophilicity
- ↑ selectivity on GABA α_1
- Shorter t1/2 (2.5h)
- ↑ Log P (Bioavailability higher than Zoleplon)

Zaleplon



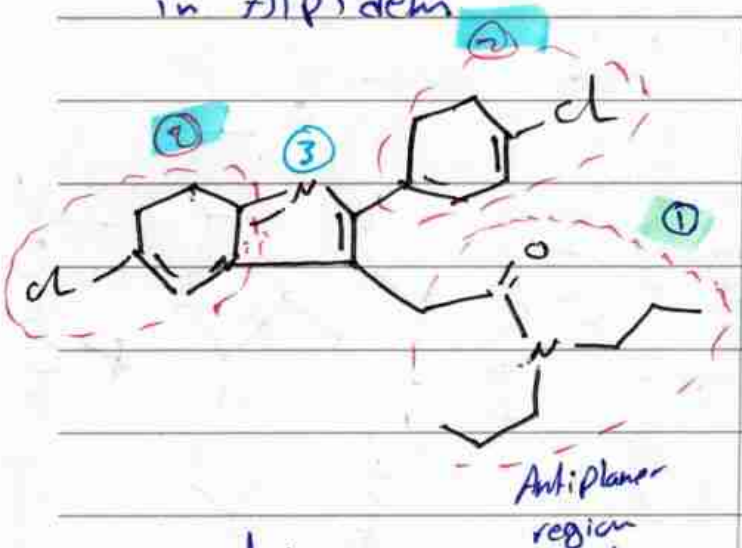
- Pyrazolopyrimidine
- Selective on GABA α_1
- Shorter t1/2 (1h)
- rapid onset
- ~~Less LogP~~

Date. No.

Zolpidem ... ←

From Alpidem → hepatoxic Drug not used
↳ was used as Anxyolytic not hypnotic
Then make Zolpidem which is Anxyolytic+hypnotic

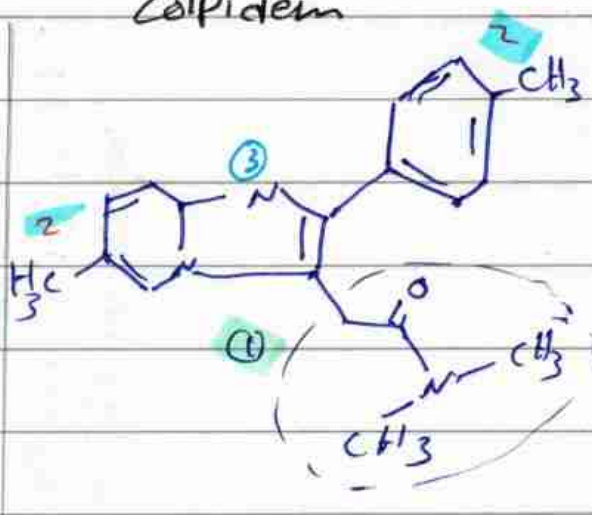
in Alpidem



① ↑ size of bulk group loss of selectivity on α_1 which result in anxyolytic effect only

2 Cl on aromatic ring result
- make deactivation for metabolism (resistance metabolism)
- long DoA (PhK)

Zolpidem



① ↓ size of bulk group ↑ selectivity on α_1 which lead to have sedative + hypnotic Action

2 H_3C on Aromatic ring result
• benzylic methyl vulnerable to rapid oxidation → OH alcohol
Then to carboxyl COOH then result in loss of activity
So it has short DoA (PhK)

Date. No.

control selectivity. ← size of bulk group : التحكم .1

2. طريقة substitu on aromatic ring

• also methyl group has role in selectivity on α_1 sub type

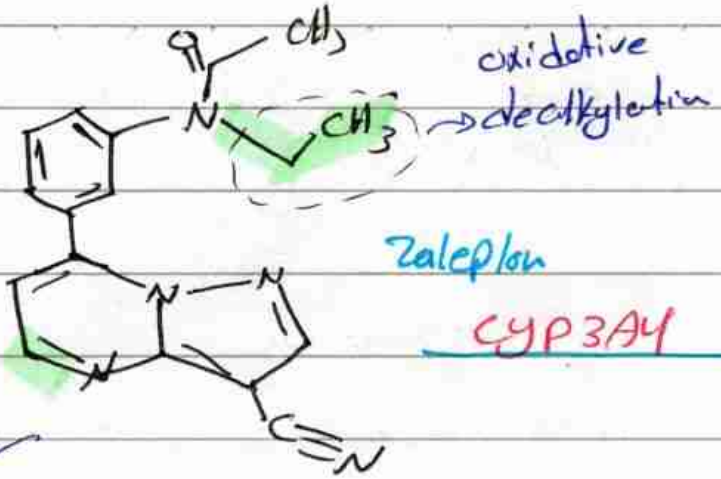
③ in both Alpidem and Zolpidem, Imidazopyridine ring has role in binding site, which is Lipophillic

Aromatic ring make Lipophillic interaction, make good penetration to BBB, reach site of action rapidly result in rapid onset.

and N work as Hydrogen Bond accepter (Nitrogen rich) if we convert it to Hydrogen Bond donor (loss selectivity)

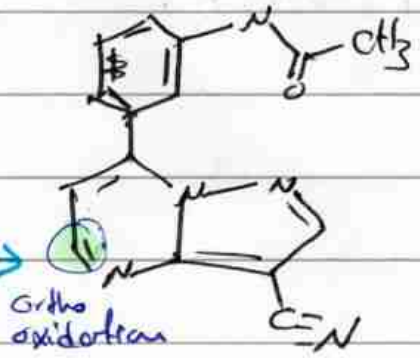
~~and~~ so selectivity by ① CH_3 ← DoA بيقلل ② N acceptor H.B ③ small size group

Date. No.



Zaleplon

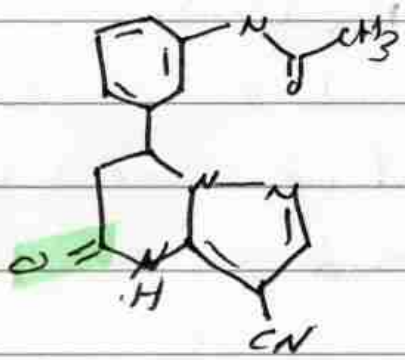
CYP3A4



N-Desethyl Zaleplon

Aldehyde oxidase

Tautomerization



5-oxo Zaleplon

has 2 site which have rapid metabolism so result in loss of Activity

Short DoA

∴ ↓ ~~selectivity~~ SE by ↑ selectivity ∴

better PhK by control metabolism rate and prevent formation of active metabolite thus result in rapid elemination

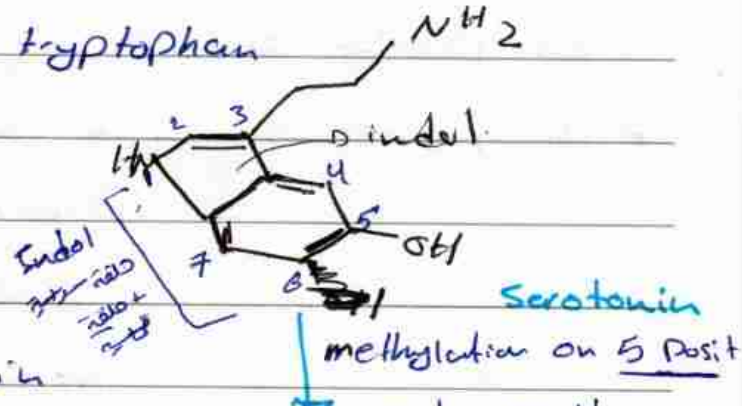
Melatonin Receptor Agonists

Date. No.

Melatonin: هرمون عصبي يفرز من الغدة الصنوبرية

neurohormon primarily synthesized in the pineal gland from it's precursor Seratonin

- Melatonin is Seratonin Analouge
- Seratonin syntesied from tryptophan
  ↳ 5-OH tryptamine

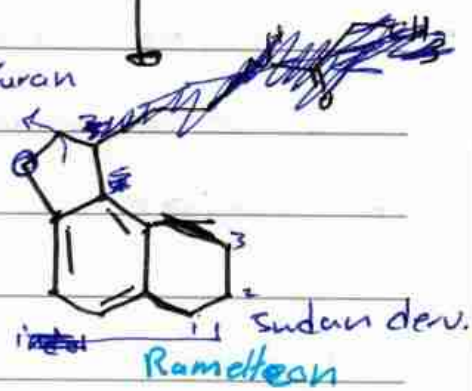


* Melatonin
- sleeping promoting
- circadian effect on Melatonin
  - MT-1 receptor: Sleep
  - MT-2 receptor: circadian rythem

* nature ligand for MT is Melatonin
* agonist for Melatonin same to Melatonin

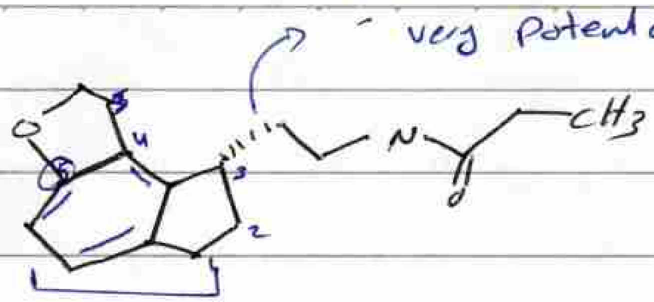
Ramelteon

- sleep agent bind to MT_1, MT_2 selectivity in SCN.
- speed onset of sleep
- alter total amount of sleep a person gets



(Rozerem)

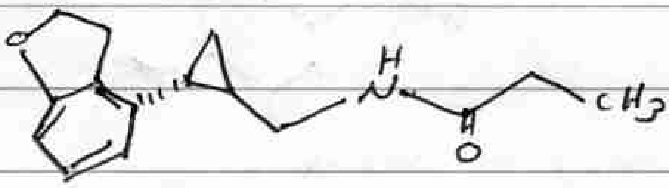
. S isomer Ramelteon >500 than R
- very potent active.



S-Ramelteon

Indan deriv.

. Indan derivative → ~~hydrop~~ Lipophillic
. on position 5 → hydrogen bond
• on position 3 → 2 C then amide c̄ H.B
propamide
acetamide ← Melato في
ما صار تغيرات كتير ع Melatonin
ضل حافظة distance بين N و O

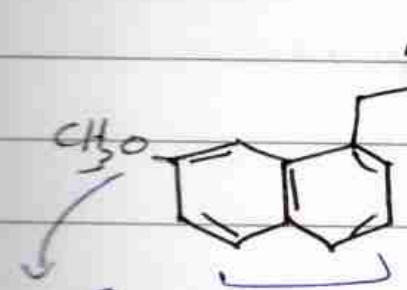


Tasimelteon

• Lipophillic ring system → to make biosatic ω̄ recepter
• O → hydrogen bond
• Amide ω̄ hydrogen bond

Date. No.

Then we make Isosteric replacement for indole in Melatonin to naphthaline



Agomelatine

Amide

MoA :-

- ① A Typical Antidepressant
- ② treat major depressive disorder has Dual MoA

has ability to bind to Melatonin receptor (A)

③ work on 5-oH tryptamine 2 c receptor (B) 5-HT2C

(Serotonergic receptor) Antagonist

which lead to improve mood (↑ release of norepinephrin and epinephrin, dopamin)

Melatonin يحتوي في تركيبه على

H.B group في الموقع 5 في Aromatic ring

Histamin H_1 - receptor Antagonist

Date. No.

1st generat Anti histamin ⇒ - induce sleep
- cross BBB
- high Lipophilic.

but 2ed generation → can't cross BBB.

They Block H_1 receptor in Brain in TMN nucleus result in sedation.

take at sleep ; due to drowsiness, tolerance
low cognition

1st generation as : Anti histamin

has ⟨ peripheral → ⇒ to acting
central → sleep

Diphenhydramin Doxylamin -

Date. No.

Doxepin: centrally acting

- Tricyclic Antidepressant histamin وله

- Act as H_1 histamin receptor antagonist

. as hypnotic at lower dose than those P-o depression

* BZDs 1st choice for Anxiolytic

لانه

* Z-Drug has no Anxiolytic effect (weak) due to high selectivity on GABA α_1 subtyp thus ↓ sedation

Miscellaneous Anxiolytic Agents

5HT-1A agonists and partial agonist

→ 5-hydroxy tryptamin-1A agonist

Thes are less effective not 1st choice

MoA of Azapirone

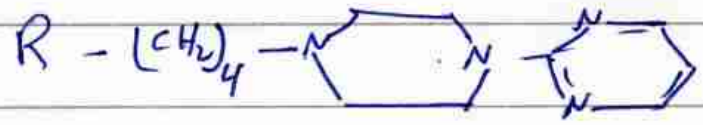
- has partial effect on 5HT-1A receptor, give Anxiolytic Action and modulate Anxiety

These called Azapirones Family

① Buspirone →

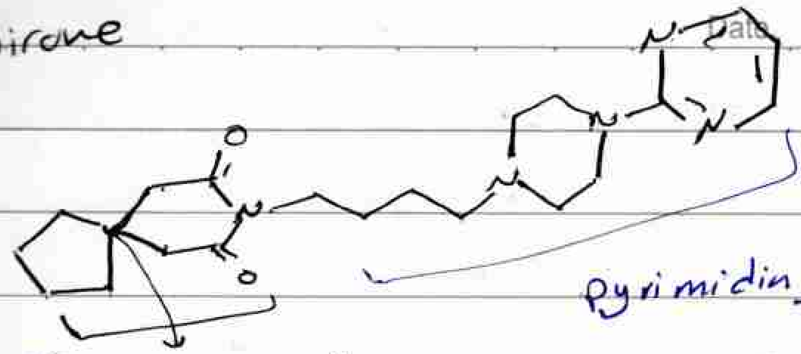
- has Azapirone system
- Anxiolytic – Antidepressant – Antipsycotic
- has spiro system

Azapiron General structure



(pyrimidinyl butyl Piperazine)

Buspirone



pyrimidinylbutyl piperazine

spiro system

called ~~spiro decan~~ Aza spiro decandione

لهيك سميناه Azapiron

- اللي بترتبط بـ butyl دائماً ⟸ N ، مع ذرتي 2 Keton
or 2 group of H.B

* Gepirone : has ↑ affinity (potent) activite 5HT-1A
but neglegable dopamin.

* isa ipsapirone

Anti-Seizure Drugs

Introduction/ Date. No.

- Anti seizures = Anti convulsante - Anti-epileptic.

* Epilepsy/ abnormal Firing of neurons in the brain.
  Lead to symptoms of convulsion
  ① Strange sensation, Emotion, behavior
  ② Convulsion تشنجات بالوجه تظهر تارة أو بمفرد
  ③ muscle spasm
  ④ loss of consciousness.

* classification of ~~seizures Drugs~~ epilepsy Depend on number of neurons affected (small - whole brain).

Epilepsy

partial (Local, Focal)
- small num. of neurons
- affected area (Focal)
- but spread to adjunct areas

Generalized
- entire brain is affected.

Date. No.

* General MoA For Anti-seizures Drug or Pharmacological target of Anti-Seizures Drug.

[a] GABA system: (not only $GABA_A$)

* by increase inhibitory neurotransmitte system.

by Allosteric Activation of $GABA_A$ receptor

1. GABA-modulating agent: Brab. → BZDs (Allostric activator)
2. Drug that inhibit GABA degradation: vigabatrin
3. Drug inhibit the reuptake of GABA: tigabine
4. Drug that enhance the biosynthesis of GABA: gabapentin, pregablin, VPA

[b] Glutamate system

by Decrease excitatory neurotransmitte system.

[c] Ion channels: by Block voltage-gated (Na^+ or Ca^+) or Excitatory or depolarizing ion channel

Ca^+ inhibition	Na^+ inhibition	
• Ethosuximide	• carbamazepine	• lamotrigine
• Trimethadione	• phenytoin	• valproate
• valproate	• topiramate	• zonisamide

Date. No.

* Many AEDs act via multiple MoA on different target as valproate on → Ca^+, Na^+, GABA

- multi Drug activity (Non-selectivity) could have more side effect but be effective in different types of epilepsy with partial or complex Generalized due to its broad spectrum activity.

1 GABA system < BZDs, Barbs.

① GABA modulating agents : BZDs, Barbs.

* BZDs : • Enhance the effect of inhibitory neurotransmitter GABA on GABA@ Cl^- Channel. (Allosteric site.

• Decrease Na^+, Ca^{+2} current (Ion Channel not GABA)

Ex BZDs/

Ⓐ Diazepam IV, IM, Doc For (Status epilepticus) Cemergency case

Seizures that last For > 5 minutes

or more than 5 Sizures occure close together & btw and person don't recover btw one and other. (Fatel), could have permenant brain damage

Date. No.

[2] Clorazepate

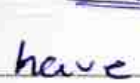
has COOH that make it prodrug (decarboxylate in stomach) and give Nordazepam (long acting).

* BARBiturates.

→ chemical classification

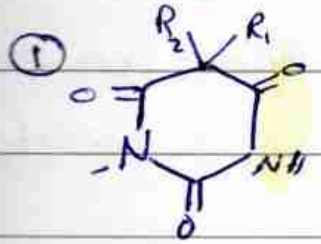
* ureide structure * ureide mean (urea / carbonyl)

or Acyl urea. or ureal derivative

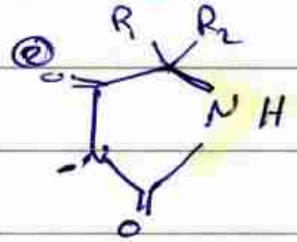
- All have Acidic Imide  Acidic Imide.

= All are isostere. of ureal or Acyl urea.

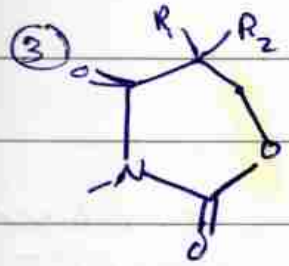
have same General structure but different MoA



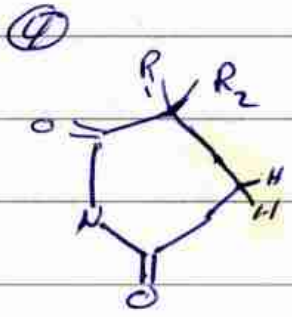
Barbiturate



Hydantoins



Oxazolidinediones



Succinimides

Date. No.

* R_1, R_2 essintial Lipophillic to enhance CNs penetration

How to differ bw Drug treat < Partical / Generalize sizeure?

- if R_1, R_2 alkyl groupes (lower group ethyl, propyl) No cromatic ring exist, active aginst Absence sizures or Petit mal
- if one of R are Aryl group active aginst grand mal Generalize tonic-clonic and partical and Not active against absence sizures

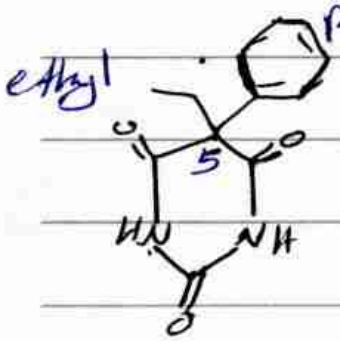
* Ureide Derivatives :-

① Barbiturates

major MoA/ - Allosteric activation For GABA(A) recepto thus ↑↑ opening of ct channels leading to CNs depr

- Also Blocke Na+ channeles.

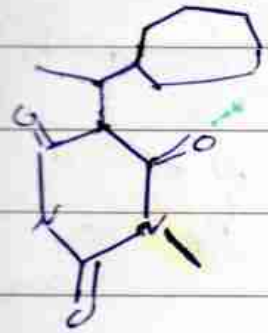
Ex/ Phenobarbital



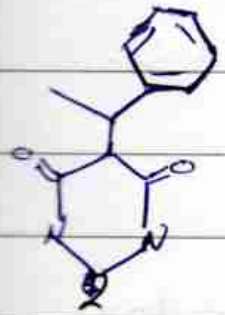
- very potent sedative hypnotic
- Anti epliptic Drug
- Due to phenol / Aromatic Drug
- S.E / sedating action, Enzyme inducer CYP450, DOIs

Date. No.

other example For Barbitals.



- mephobarbital
- more lipophillic than phenobarbital
- metabolism: Demethylation → phenobarbital (active)

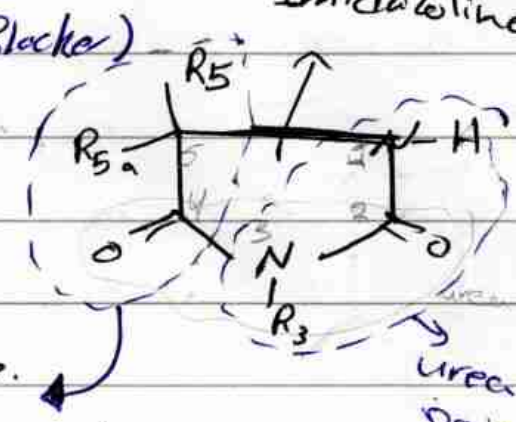


- Primidone (2-deoxy phenobarbital)
- metabolism: oxidation on position 2
- less effective, less S.E (less sedating)
- less potent, less toxic (adv advantage)

Partially convert to Phenobarbital by cyp450 but major is oxi on position 2 then hydrolysis given PEMA (Phenyl Ethyl malonyl Amide) → Major → mass Anti-epliptic activity but less active grand mal

Date. No.

② Hydantoins : (Na⁺ channels Blocker)



- Differ from Barb. that it don't have O on position 6.
- 2 Keto on 2 N on 5 → subs.
- ~~called~~ Glycolic acid derivative.

So it called Glycolyl urea ; due to its formation from condestion of urea w glycolic acid.

For / Generalized Tonic-Clonic Seizures.

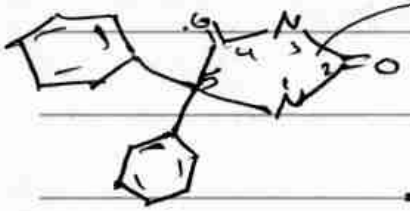
Not For autoabsence.

Ex/ ① phenytoine ② Mephenytoin ③ Ethotoin.

more used. ↵

MoA / Na⁺ channel Blocker.

- **Phenytoine** , 5,5 diphenyl hydantoins.



→ Hydantoin ring, is weakly acidic

- pka ≈ 8  weak acid
- due to 2 phenyl ring → ↑ Lipophilicity
- problem: very low H2O soluble

lead to incomplete absorption from site of ~~Adm~~ administration

either IM, IV, orally → or unpredictable / irritic absorption incomplete absorption

Solution / Na⁺ salt (phenytoin Na⁺ injection IM / IV)

but due to very H2O soluble , upone injection IM

(need pH ≥ 11 to convert to Na⁺ salt)

also absobed CO_2 from media arround it, thus neutrize occure ⇒ Tirubidity, precipitation

Date. No.

on partial neutrulization occure, thus precipitaion and crystalization in muscle → pain full

ẅ repeated injection → tissue damage / muscle necrosis

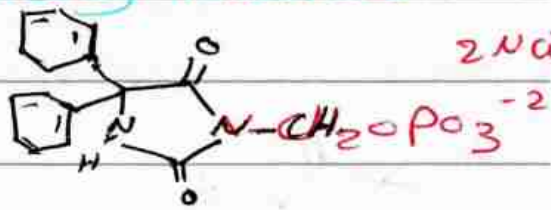
and ẅ I.v injec → ~~bacome to~~ vein irritation.

due to dilution then neutrilization For alkalin condition thus crystalization due to very low solubility in H_2O.

So Solution is /

To improve H_2O solubility ⇒ Prodrug Formation

as Phosphenytoin



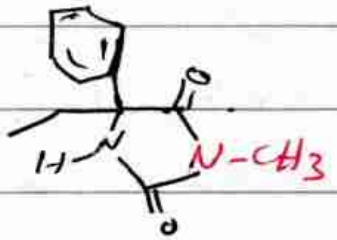
- it's solubility dosn't depend on pH

So could be give I.v / I.M

- No S.E , More Stable.
- Complete absorption (No irritic or unpredictable, uncomplea-)
- metabolism : by phosphatase enzyme → degradation

↓ methyl PO_3^{-2}

★ Mephenytoin



- replaced one of Phenyl ẅ ethyl

to ↑ Lipophilicty

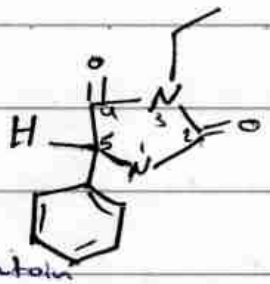
- add methyl → metabolism / Dealkylation

give demethy Mephenytoin (active) toxic ↑ Sedating

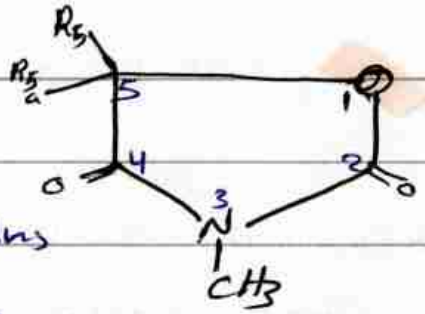
Not used.

Date. No.

* Ethotoin

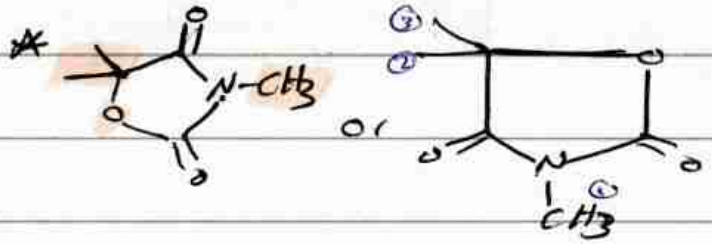


- less effective
- less toxic tha mephentoin
- No antiarrythemic (compard to pheytoin)
- more sedating.



③ Oxazolidinediones: rare used

- isosteric replacement For hydantoins
- oxazolidine-2,4 diones system.

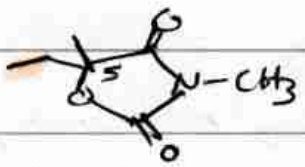


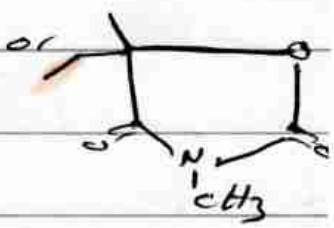
Trimethadione

more used

- Replaced R with 2 ~~dff~~ small alkyl group methyl
- So used For absence sizures
- Due to changes on ring system change MoA
- * MoA/ Blocking T-Type Ca^{+2} channels in thalamic neurons. ↓ Firing.

* paramethadione





- Ethyl methyl paramethadion

Trimethadion → inactive (N-De-methyl, Position 3) Dimethadion (active)

$t_{1/2}$ ≥ 1 day — Short $t_{1/2}$

$t_{1/2}$ 6-13 Days — very long $t_{1/2}$

S.E of oxazolidiones :

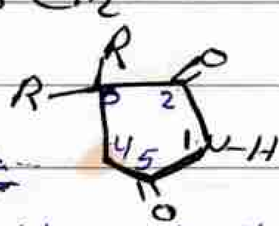
- Aplastic Anemia
- nephrosis
- teratogenic

تم اكتشافها 1946 لأنه ما كان في دوا يؤخذ فكان هي الدواء المعتمد لكنه بعد مدة تعديلات واكتشاف أدوية أخرى قلل

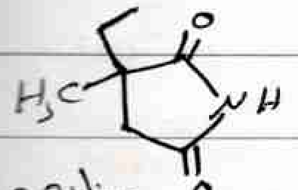
So rarly used.

(4) succinimides. replaced O → CH_2

حلقة خماسية

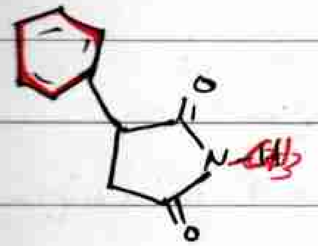


- replaced O → CH_2 (isostere) ↓ toxicity of oxa.. (شكل الحلقة)
- 2,5 Dioxo Pyrrolidine " Succinimide system"



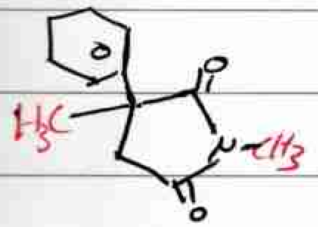
* Ethosuximide
- MoA / T-type Ca^{+2} channels Blocker.
- has CH_3 → For absence sizures. (شكل الحلقة)

oxazolidine عكس الموقع 5 المتعادل



* Phensuximide

*

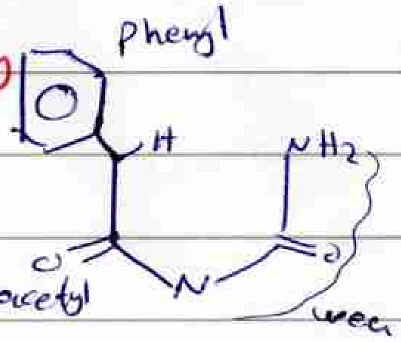


* Methsuximide

Date. No.

⑤ Ureas and Monoacylureas:

- Not used due to ↑↑ toxicity
- open ring system
- phenyl acetyl urea
- has genel structure requirement for Anti-epliePtic Drugs
- Broad - spectrum action.



personality changes, Blood, renal and skin Disoders.

تكلم باقي الأدوية التي تقلل GABA System Pharmacology.

b) GABA analogues, Drugs that enhance biosynthesis GABA (Chemestry)

- affect GABA inderictly (without Bind to GABA)
- It enhance Biosynthesis of GABA

MoA ولا

[GABA synthesis is mediated by many enzyme as Glutamic acid Decarboxylase these Drug ↑ this enzyme ↑ biosynthesis ↑ inhibitory effect]

- it's Same to GABA structure so its chemical subclass// GABA analogues.

* في بداية تصنيع عادةً تكون Lipophilic GABA mimitic بحيث تعطي التأثير ع GABA لكن هذه الأدوية لا ترتبط انما تزيد تأثيرها بطرق أخرى

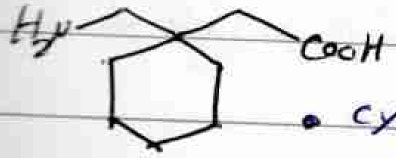
as trigeminal neuralgia

GABA 

γ amin Butric acid

neuropathic Pain as/DN

* Gabapentin good pentration + For partial sizures + GABA [illegible] GABA [illegible]

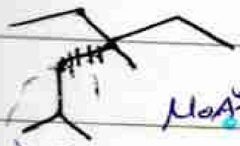


[illegible] cyclohexane 5c [illegible] Pentin [illegible]

- cyclohexan γ amin butric Acid. (GABA)
- Lipophillic GABA analouge.

MoA [illegible] . work on Ca^{+} channel (voltage-Depented) α2δ

* Pregabalin good pentration + For partial sizures + neuro Pathic Pain

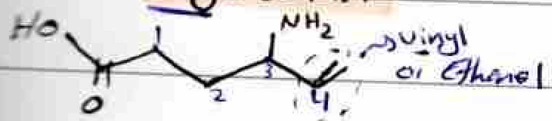


- isobutyl GABA Deivative.

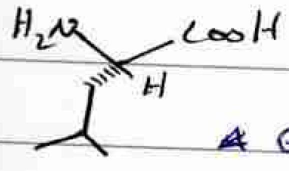
MoA [illegible] work on Ca^{+2} channel (voltage Depented α-2δ lead to inactivation of Ca^{+2} channels, + neurotrans...

CNS Depress Anti-epileptic

* Vigabatrin



- vinyl GABA.

* 

L- leucine

* Gabapentin + bregabalin use L leucin as transporter Protein. thus inhance absorption, pentration as it's A.A.

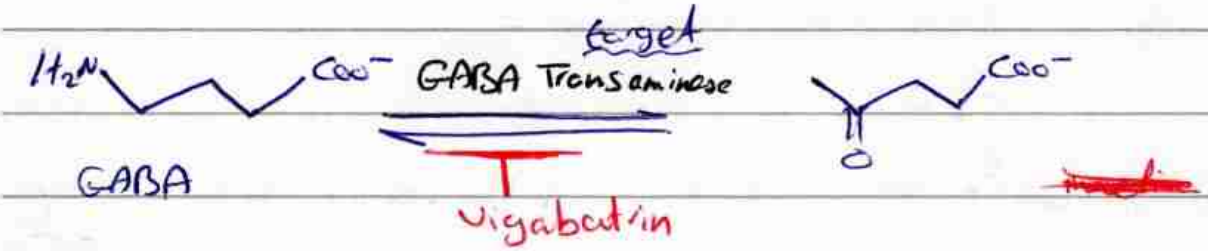
* it's thought that leucine is Ligand for these Drugs.

Date. No.

c) inhibition of GABA degradation :-

★ Vigabatrin

make irreversible inhibition of GABA-Transaminase or GABA ~~Tran~~ aminetransferase (responsible of GABA degradation) thus ↑ GABA levels

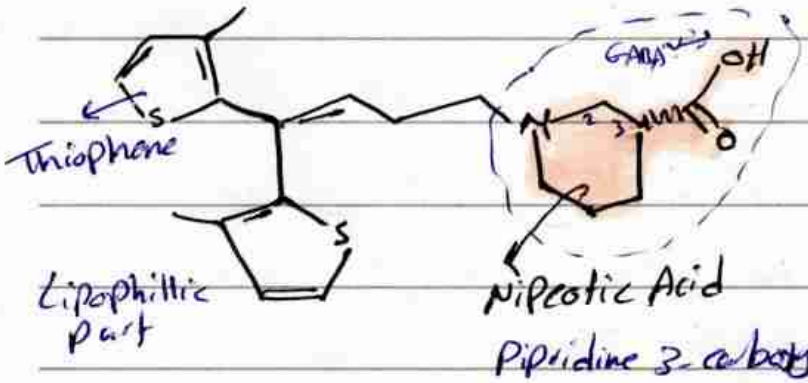


D) GABA re-uptake inhibitors :-

- when GABA ~~Ends~~ its effect either its ← Degradation / reuptake inside neuron

★ Tiagabine : R(-)-enantiomer.

↳ for GABA system



★ Nipecotic Acid was know that it Block protein responsible for GABA-reuptake, but found that it can't cross BBB so add 2 thiophen group ∵ 2 Lipophilic che- Lipophilic

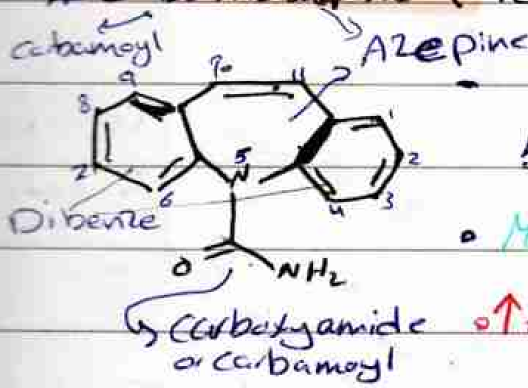
so it become more Lipophilic and able to cross BBB.

- also it's a potent GAT_1 inhibitor. (GABA Transporter 1) responsible of reuptake of GABA.

هيك حافظنا ع GABA

2 Iminostibenes / Dibenzazepine chemical class

* carbamazepine (Tegretol® Novartis)



5.carboxamid Dibenze azepine

- MoA/ Na^+ channel Blocker.
- ↑ ~~hepatotoxic~~ hematological toxicity
- Generalized Tonic - clonic (grand mal), Partial Sizures.

Dibenazepine has 3 generation

- standard/old : carbamazepine dependence, habituation & S.E
- 2ed : oxacarbazepine
- 3'd : Eslicarbazepine.

(Note) in standard or old Drug as /

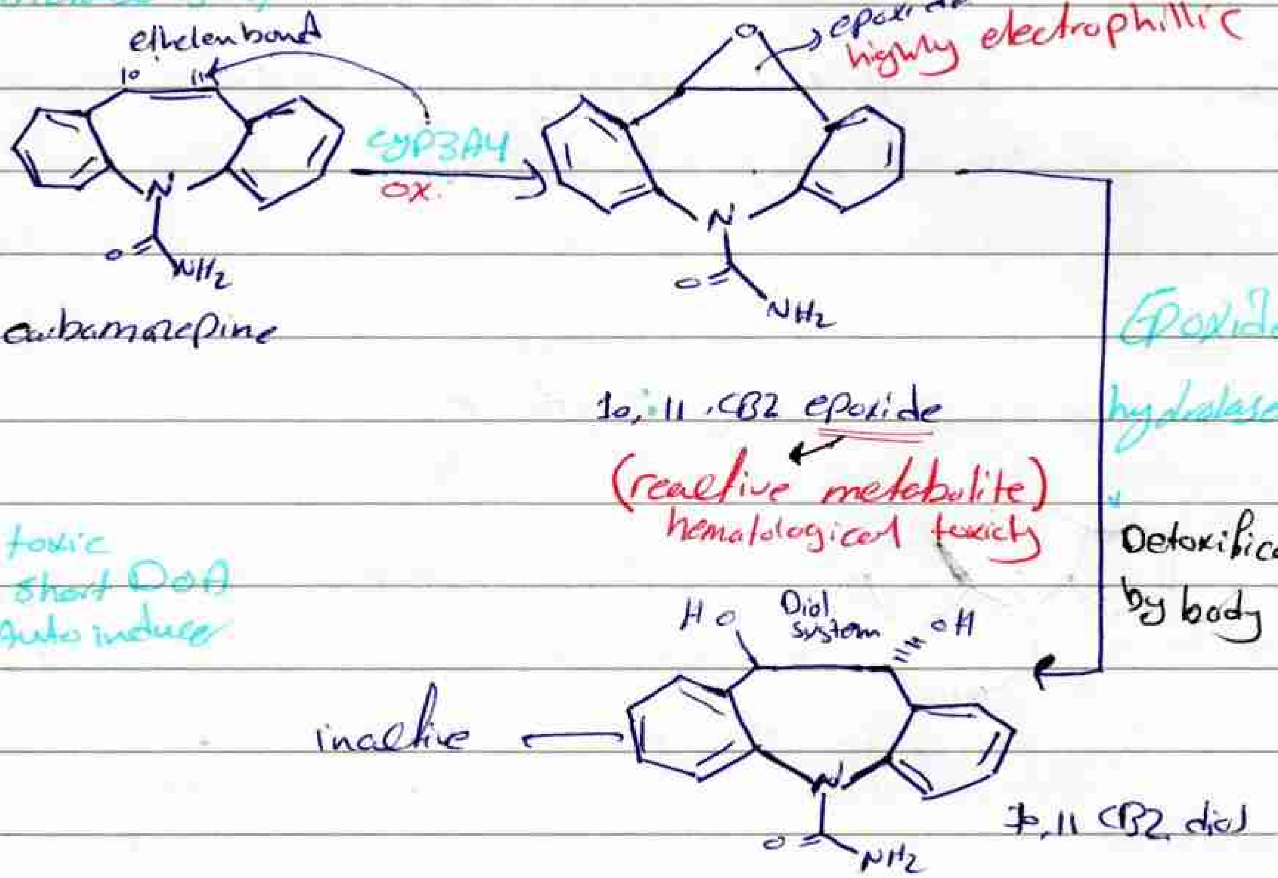
- carbamazepine, phenytoin, phenobarbital [enzyme inducer] has DDI,
- Barbital, BZDs → sedating, tolerance, withdrawl symp.

(Note) : toxicity of Drug result from either

① it's metabolite ② non-selective action (multiple binding)

↳ as carbamazepine

metabolism/



- toxic
- short DOA
- Auto inducer

Now we need to make improvement on CB2 to:

① ↓ toxicity of hematlogical (more safe)

② prevent Autoinduction (prevent DDIs)

③ CB2 have multiple adminstration 3-4 time / day ↓ compliance (↑ compliance)

الآن عند التطوير عرفنا سبب toxicity هو 10 11 الآن أحلله فيصير

Dose = essintial for CB2 activity Anti-epileptic Drugs or Not

yes

NO . Delet = and No toxicity occur

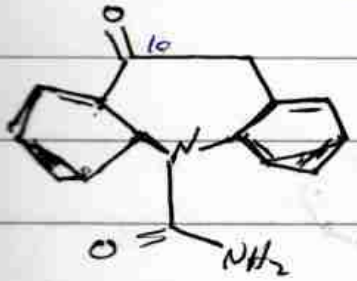
Date. No.

activity يعطي مثل لكن اكسجين

exist ↓ hydrogen bond acceptor. as O to give better Drug have activity ↑ ↓ toxic.

So we have many Drug as/

* **Oxcabazepine**



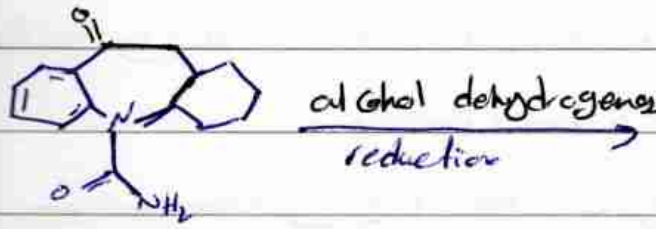
- 10-keto analog of CBZ
- ∴ 10 oxo carbamazepine.
- No epoxide formatio No hematological toxic
- No Auto inducer No DDIs
- give twic daily ↓ longe $t_{1/2}$. No =

So it has improve Phk and PhD properties.

For trigeminal neuralgia

MoA/ Na^+ channel Blocker.

Note most way to discover new Drug is studying ↓ metabolites. as also in Diazepam → oxazepam. also in OXcarbazepine



oxc (oxcarbazepine)

(S) CBZ (10-ol)

∴ 10-oH CBZ. Can be active metabolite. Licarbazepine

Anti-epileptic

Eslicarbazepine

71

Aptiom®

Date. No.

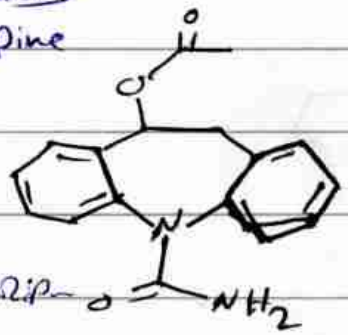
ox carbaz → Eslicarbazepine from S-CB2 Io ol

- Prodrug (converted) → S-Licarbazepine (S-enantiomer)
- ↑ tolerance, ↑ penetration BBB, better metabolic profile
- DoA 24 h once daily. Safe
- its licarbazepine (CB2-Io-ol) (hydroxy)

S → active ES licarbazepine

- exist as ester form

So it's Eslicarbazepin Acetate

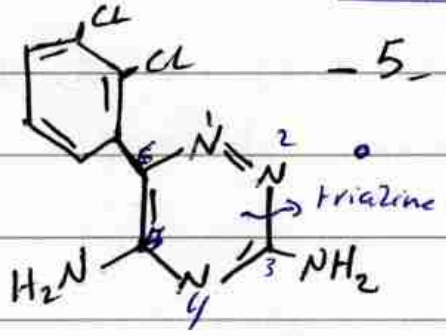


hydrolysis in GI → Eslicarbaz-

Na⁺ Channle Blocker

Lamotrigine (Lamictal®)

- has different chemical Derivative.



→ 5-phenyl-1,2,4-triazine Derivative

- 2 ring system Aromatic
- ↑↑ Lipophilicity
- Cl → ↑↑ penetration ability to BBB

MoA/ ① Block Na⁺ channel

Anti-epileptic Drug ② ↓ glutaminergic excitatory transmission

③ ↓ Nicotinic acetylcholine receptor

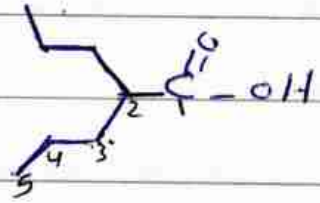
For absence seizures.

Date. No.

Broad spectrum Anticonvulsants

"acts on multiple target" Micillinouse.

* **Valproic Acid.** (Dipoken)



Dipropylacetic Acid
or 2 propyl pentanoic Acid

- MoA/

① increase the inhibitory effect of GABA

By — Activate glutamic Acid decarboxylase (+ Biosynthesis)
— inhibition of GABA-transaminase (degradation)

② Decrease GABA-reuptake

③ Blockage of T-type Ca^{+2} channel

So it has very Broad Action/

① Typical + ATypical absence sizures.

② Absence sizures ⇨ Generalized tonic-clonic sizures.

Missillinous
Date. No.

Newer AEDs or Adjunct Drug :-

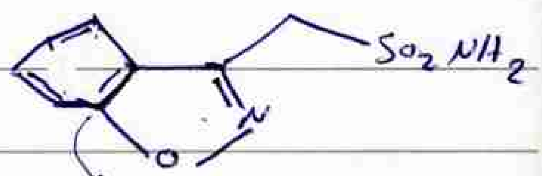
السادس

* Topiramate :

- it's Saccaride Deriv. ⇒ sulphamate-substituted
- ⇒ Monosaccharide Der. Fructose
- Simillar to ~~Fructos~~ Fructose.
- MoA / Glutamate + GABa recepter
  ↳ Broad + potent AED.
- good oral bioavalibity   very hydrophilic لأنه زي
  لكنه يتم التعامل معه بخطر انه سكر فركتوز
- L-leucine زي A.A بيتعرفوا كأنهم Gabapent Pregabalin مش
- has 2 ketal system to ↑ hydrophillicity.

* Zonisamide

- sulfonamide type AED.
- MoA / ⊖Na^+ , Ca^{+2} Blocker ion channel,
- for Partial siezures.



benze-isoexazone

Date. No.

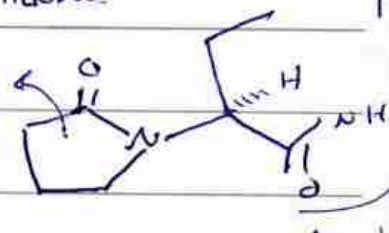
racetam

Pyrrolidone

★ LEV: levetiracetam:

- Pyrrolidone deriv.
- MoA / Kainite / AMPA modulating
  → (these are glutamic acid receptors)

  thus ↓ excitation of Glutamate receptor.



CNS Stimulant

+ Antidepressant
  - central synaptic agent
  - or Amphytamin Analogy

Date. No.

CNs stimulant or Analeptics :

- medication used to treat depression, Attension hyperactivity disorder and respiratory depression

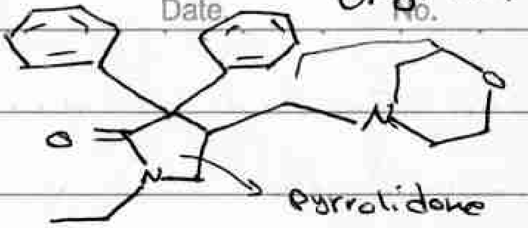
In the past :

- Traditioned Analeptic was group of potent & relatively non-selective CNs Stimulant
  - Thus it was dangerous, very toxic.
  - its CNs stimulant dose lies near their convulsion dose.
  - So they are obsolete (لم تعد تستخدم)
  - Ex/ picrotoxinin + pentylenetetrazole

research tool, تعتبر الأدوية, Animal أصبحت مركبات للتجارب في

* Then thye alternate to
- Newer agents with
  - selectivity as (modafinil and doxapram)
  - not high CNs stimulant property
  - For narcolepsy sleep disorder which xss sleep.
  - respiratory stimulant

(1) CNS Stimulant Drugs :-



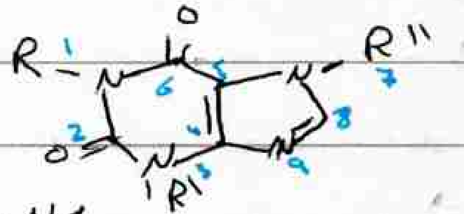
[1] Doxapram

- Pyrrolidone derivative
- good selectivity as respiratory stimulant

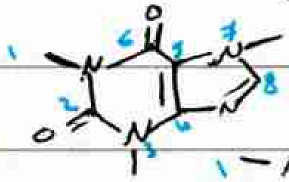
MoA / stimulate the chemoreceptors in the carotid arteries, which stimulate the respiratory center in the brain stem.

- Could be given injection For hypocapnea

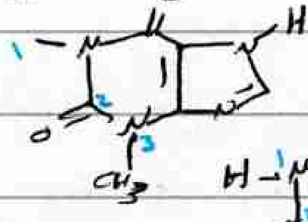
(2) Methylxanthines



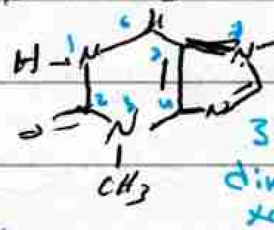
- purine derivative or (xanthin)
- differ in substitution on N_1, N_3, N_7
- ex/. caffine



  - Theophylline

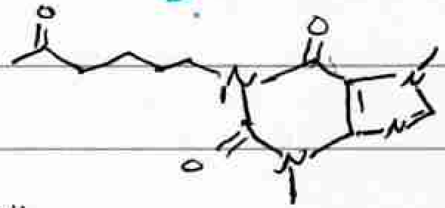


  - Theobromine



- caffiene → CNS stimulant
- Theophyllin → bronchial asthma therapy
- Theobromine → its deriv. Trental® for intermittent claudation ↳ pentoxifylline

نقص تروية بالاطراف مع ازرقاق دم



↳ Thiobromin deriv.
↳ ⊕ perfusion to prephiral
↳ ⊕ morphology of Blood cells
+ Symptoms of Pain

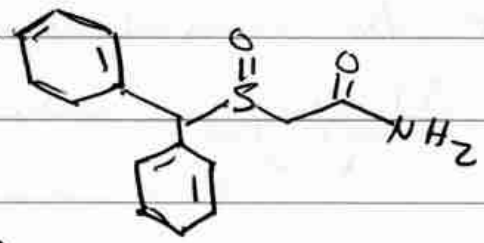
Date. No.

- it's problem lacke of selectivity . . work on many different system ~ different tightness
- so it has high S.E
- Especilly on heart
- its use as drug is limited

MoA
- Phospho diesterase inhibitor
- Adenosine Antagonist

So we replace methylxanthin → Doxapram
- modafinil

sulfoxide diphenly Amide systeme



3) Modafinil

- good selectivity
- promot wakefulness (alterness ⊕)
- Similar to central sympathominetic (amphitamine)
- MoA not well known could be
  - Atypical α, NE receptor stimulant
  - For daytime sleep or narcolepsy
  - less poteintial for abuse
  + Antioxidant properties (neuro protective effect) → مضاد
  So its good for elderly ~ disorder in Brain

② central sympathomimetic agent (psychomotor stimulant)
CSA

Date. No.

- Drug that affect adrenergic in general, could be devided to
  - Anti-Adrenergic
  - sympatholytic
    - Centrally
    - Peripheral
- adrenergic stimulant
  or give effect similar to stimulation of sympathetic N.S
- Symapthomentic → 
  - Centrally
  - Peripherally
    - Adrenalin
    - Noradrenaline

β Phenyl ethyl amin derivative or β aryl ethyl amin

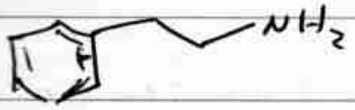
* For Sympathomimteic Drug it has 2 genral MoAe.

① Affect on adrenergic receptor (α → α_1, α_2 ; β → β_1, β_2)
activation Binding
agonist
Direct

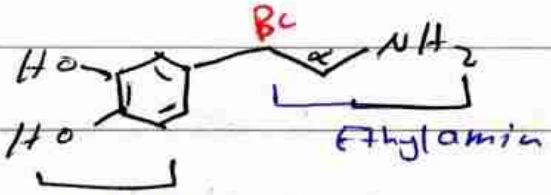
② affect life cycle of adrenergic Neurotransmitter which include (NE, EP) its synthesis, storge, release reuptake and metabolism. Indirect
catecolamin

Date. No.

* β-phenyl ethyl amin is derivative from catecholamin nucluse.

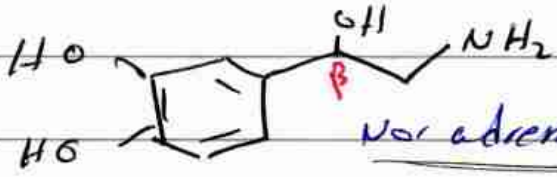


Phenyl ethyl amine

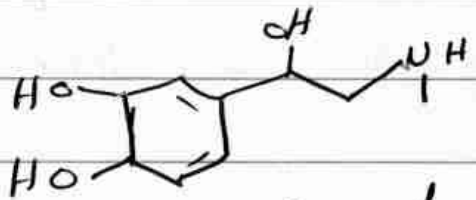


catecholamine

Dopamine.



Nor adrenaline



adrenaline

* catecolamin when given orally they can't reach CNs ; rapid metabolism , rapid clearance and can't cross BBB ; due to ↑ polarity . they could give prophral not central sympathomimeti

Date. No.

• To let them act centrally we make Structu change on phenyl ethyl amine to pentrate CNS :

PhK Problem

① . The goal is to let compound resist metabolism
. No rapid inactivation. , No clearance by enzymes for catecholamin [Mono amino oxidase] (MAO)

① which remove NH_2 $\xrightarrow{\text{ox. deamination}}$ Aldehyde

② COMT (catechol o methyl transferase) which make methylation for Meta O (4b) on position 3

② reduce polarity and increase non-polarity to have good difusion to CNS. by remove OH ? + β OH from catechol (OH Not critical for sympatho mimtic activity) but essintial for Direct sym. mimtic) which make it polar.

Date. No.

(CSA) effect :

- CNs Stimulant [excitation. alertness, wakefulness

- anorexiant مانع للشهية For obesity (habituation S.E)
abuse

MoA For central.... :-

- mainly effect Nor-adrenergic neurotransmission (increas
and less degree on dopaminergic and serotenorgiec.

. effect of Anorexiant is yield by serotergic effect

SAR/

1. Phenyl ethyl amine could act on pre + post synaptic
NA system either α_1, α_2 as adrenaline, noradrenaline

2. adren. + NA has preipheral not centrally ;
metabolism by MAO very rapid ↑ clearance
so Solution/
. remove OH from catechol + OH from β carbon
and prevent it's metabolism by COMT
. deamination بتمنع MAO انه قادرة تعمل
ـ تزود metabolism

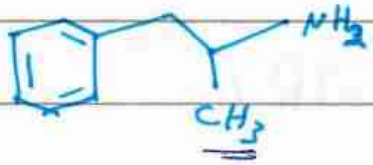
Date. No.

Solution For MoA

- NH_2 is essential for activity For Sympathomimet
[Phenyl 2 C amine or critical For activ

- MOA prefer oxi deamination when C behine
NH_2 is not branched ῶ I° amine 

So when we make branching on CH_3 we
disable enzyme MoA from oxi deamyination
and resist MoA metabolism.



Amphetamine :

- branching by adding CH_3
- which increase Lipophillicty
- resist metabolism by MAo (retardation metabolism
- α-methyl phenyl ethyl amine deivative
- has ability for CNs pentration
- central not p-ephral activity.

* Not / • The Branching must occur ῶ small alkyl group (↑ large alkyl ↓ activity)

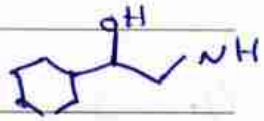
Date. No.

- has ciral central alte branching

Dextro(S) > Leva (R)

10 times

→ used for (ADHD) Attention - deficit hyperactivity disorder



- if we make hydroxylation on β position

Decrease activity & pentration

so it's preferred for Amphitamine not have hydroxyletion on either catechol or side chain

- increasing ~~hyd~~ hydrophobicity by halogenation of Aromatic F, Cl, Br decrease Sympathomimtic activity but it Strong central Sertonergic activity and neurotoxic which leaf distruction and damage Nerve.

MoA of Amphitamine:

- act indirect by increase release of NE from synaphic storage cleft (main)
- inhibition of re uptake (minmal)

Date. No.

∴ - present of OH ← aromatic side chain increase direct effect

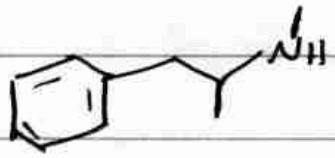
- delete / remove of OH ← aromatic β side chain . increase indirect mechanism
. ↑ release

SAR

3. methoxyl substitution on ring → psychomimetic or hallucinating agent (controlled)

4. For amine group :-

- adding methyl convert from 1° to 2° give methamphitamine



① methamphitamine > dextro HCl more potent.

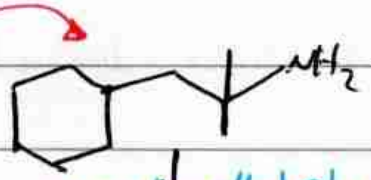
N- methyl cyclonyse for dextro amphitamin

∴ methamphitamin > dextroamphitan > amphitamin

due to increase in Lipophillicity ⊕ pentration to BBB

② phenteramine ; ↑lipo ↑ penta ↑ to CNS stimulant

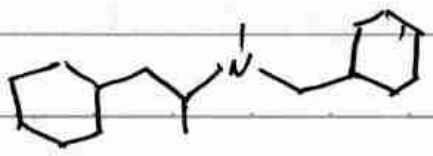
- but dimethylation ↓ activity use as anorexiant



α, α dimethyl phenethyl amine

- if substituted ω group large than methyl as benzyl will ↓ CNS activity as excitatory property but retain anorexiant property

③ benzamphitamine HCl



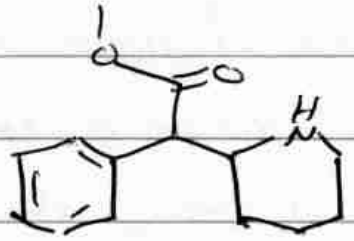
85

Date. No.

∴ nature of substitution on N, give indication for it use :

Ex : if substution was

- small alkyl (methyl) ⟶ CNS stimulant
- bulk group ⟶ ↓ excitatory, ⊕ anorexiant effect by serotonin not adrenergic
  → abuse, habituation



④ methyl phenidate HCl

- N in cycle 2° amine (pipridine ringsystem)
- phenyl ethylamin ω ester group
- its metabolite p-OH metabolit active ~~and~~
  and . block NE reuptake ~~ate~~
  - Postsynaptic agonist
  - depletion NE pools as reserpine release ~~ac~~
  - For ADHD

Anti_depressant Drugs

Date. No.

- Depression :

mental illness ch.ch pathological changes in moode ch.ch by :

loss of conc., loss energy, sleep Problem

Thought of death...

Cause of depression (Theory)

① Monoamin theory (most commen)

- it's thought that depression is due to deficiency of ~~HAs in Brain~~ mono amino neurotransmitter as (Serotonin (5-HT), NE, DA) which has arole in depression and can initiate symptomes in depression and regulation of Mood and behavour

. low activity at least in one of them → depression.

ttt goal /

- counteracting this low or abnormal monoamine activity, ↑ at leat one of 5HT3 or NE or DA

- So our Drug aim to ↑ level of Mono amin neuro transmitter

NTM neurotransmitter

classification of Antidepressant

Date.:- No.

we aim to ↓ elimination of NTM, working on life cycle :- and clearance or termination

⇒ There's 2 major way for elimination of NTM

by ① MAO (mono Amine oxidase) ~~degradation~~

② reuptake of NTM by - $5HT_3$ reuptake

- DA reuptake

So classification for Antidepressant

[1] MAO I : Pheneli2ine, Moclobemide

[2] mono amin reuptake inhibitor depend on selectivity for NTM

- TCA tri and tetra cycle : Imipramine, Doxepine, Amoxpeine Amitriptyline
non-selective

- SSRIs : Fluoxtein, sertaline, citaloPram
Selective

- Selective NE reuptake Inhibitor : Reboxetine
Selective

- Dopamin + NE reuptake inhibitor (DNRI) : Bupropion

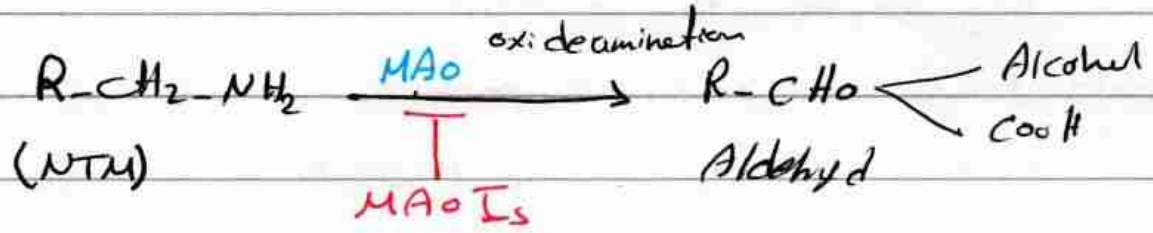
[3] Mood stabilizer : Li^{+3} carbonate
PPD
and electroshock therapy

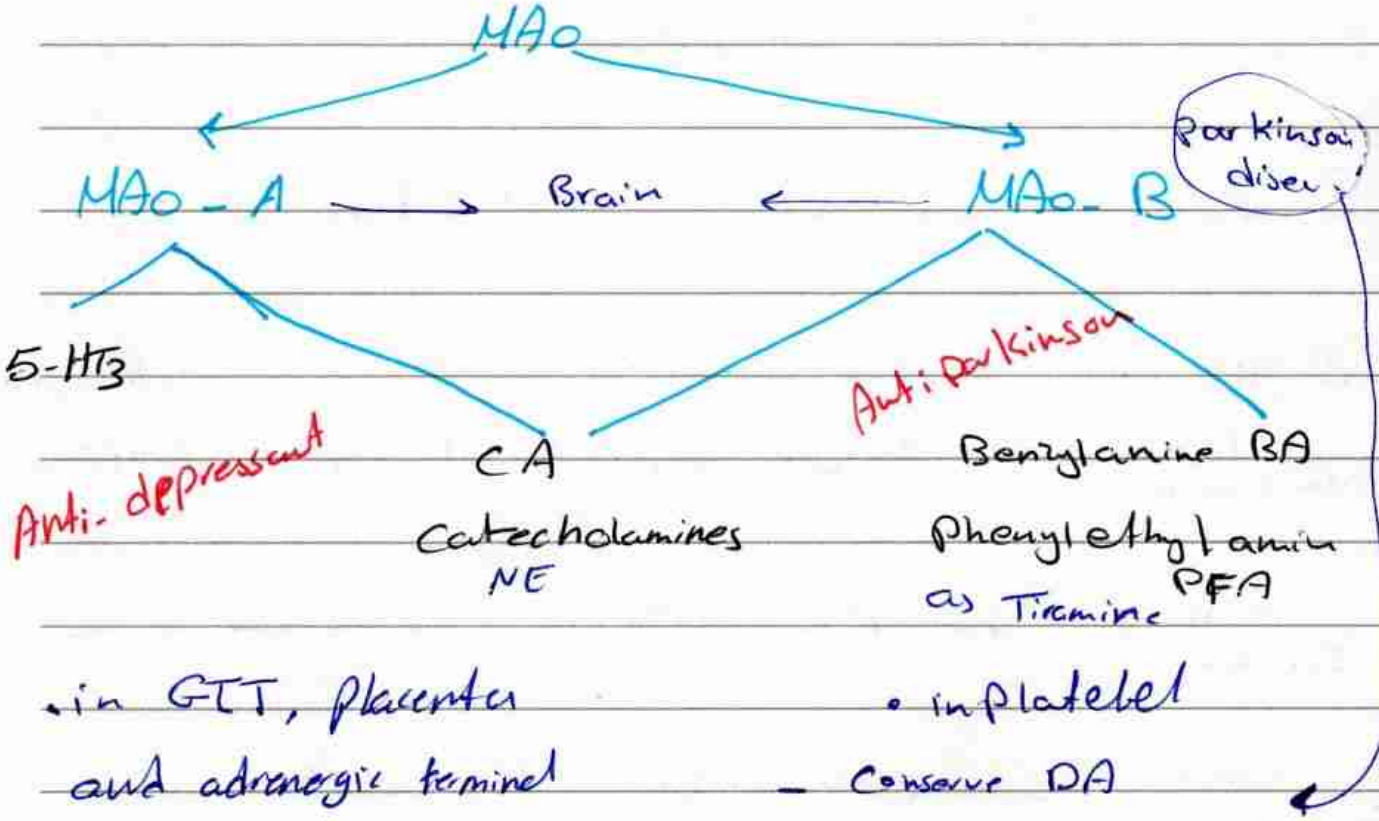
88

Date. No.

I) MOAIs

- Works as metabolic protective agent For NTM





MAOIs

selective

Non-Selective

Cardiovascular

Date. No.

MAOIs was found by:

Anti-T.B drug in past was isoniazide, Iproniazide (isopropylisoniazide)

- isoniazid (hydrazide derivative)
- Iproniazide (isopropyl der. of Niazide) can make CNS stimulation ω T.B by inhibiting MOA enzyme which lead to Alertness, improve apetite - Physic -

This lead to discover 1st group Hydrazin derivative

this called (re-purpose) كان يستخدم لمرض اصبح يستخدم

then Iproniazid used as lead compound لمرض آخر

to get more derivative.

MOAIs

reversible — irreversible

- covalent bond formation.
- suicide inhibition or mechanism based enzyme inhibition.

Date. No.

meaning of suicide inhibitor :-

. a compound ū substrate analogue (has Aryl phenyl amine) or catechol analogue

This analogue can't be metabolize by enzyme

. when oxi deamination start to occur a very reactive substance (~~[illegible]~~ Electrophilic speciese) which bind to nucleophile inside enzyme and attack it result in covalent bond

as in case ū Tranylcypromin

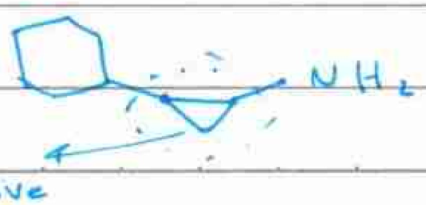
which cyclopropyl amphitamine make covalent either ū enzyme MOA or its cofactor FAD leading to covalent bond irriversible inhibition

* mechanism based inhibition

تشتغل آلية عمل الانزيم في oxidation لل α C بجانب NH2

to give reactive speices and covert compound form chemically not reactive → reactive

which make covalent bond ū enzyme or cofactor and irreversble Block for enzyme.

Tranylcypromin 

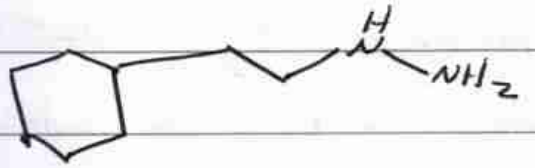
hypertensive criss → from tyramin dietary accumulation
This called cheese effect
Monoamine

Date. No.

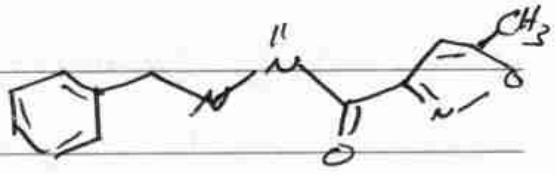
ex of irreversible group △, ═, hydrazine

MAOIs:
behind the
rational effect → ↑ level of Monoamin in synapse.
↑ level of 5HT3, NE or both. So use as
Anti-depressant
S.E → espacilly non-selective irreversible type has
as hypertensive crisis, seve hedache, intracranial bleeding
This S.E limite it use so it's Not 1't choic Anti-depress.
as/
- phenelzine (Phenyl ethyl hydrazine)
-
- isocarboxazid (Analoge for phenelzine)
- Tranyl cypromine

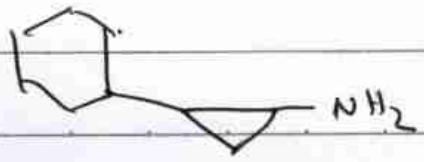
non-selective
irrersible MAOIs
old generation



1. phenlzine
Phenyl Ethyl hydrazine



2. isocarboxazid.



3.

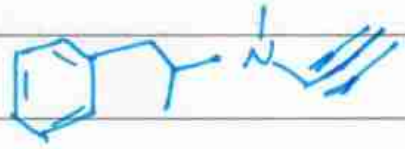
Tranyl cypromin

So in general MAO are non selective either on $5HT_3$ or NE.

MAOI

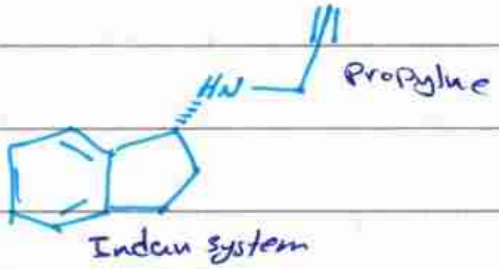
Date. No.

Selective MAO I ~~Non selective MAO~~



① selegiline (irreversible)

- It is similar to methyl amphitamine ie propyne 3C on N group
- methyl amphitamin derivative
- propyne make covalent bond (irreversible, suicide inhibitor)
- has selectivity to MAO-B → value parkinson disease
-



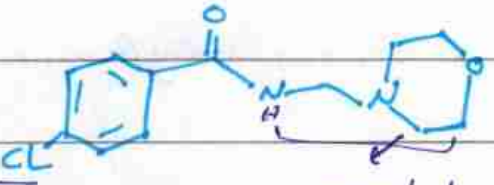
② Rasagiline

- selective irreversible suicid inhibitor
- Selective MAO B > MAO-A 14 time

New MAO

③ Moclobemide Selective reversible

- RIMA: Reversible inhibtor MAO-A
- effective Anti-depressant
- reversible → detachmint from enzyme
- permit dietary tyramine (No hypertensive S.E)



thus ↓ Food-Drug interaction and Drug, Drug interaction

have

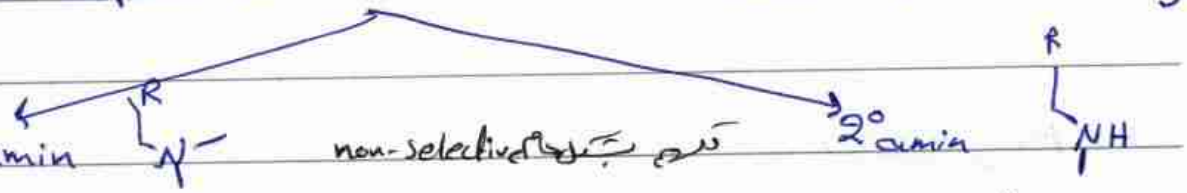
Date. No.

[2] Monoamine Reuptake inhibitors.

make competitive inhibition of binding of the MonoAmine to substrate_binding compartment.

A **A) Tricyclic Antidepressants (TCA's): (old)**

- non-selective, block NE and 5-HT$_3$ irreversible.
- Tricyclic system 6.7.6 or 6.6.6 ring system
- Due to ↑ lipophilicity ↑ High volume of distibution ↑ V_d
  ↑ protein binding and CNs depressant.
- TCAs depend on termineal amine (basic Aliphatic Amine)



Dimethyl	mono methyl
• relativly high selectivity on 5-oH Tryptamin (5HT) than NE reuptake Block. 5HT > NE	• high selective for NE > 5-HT reuptake Block.
• usually sedative action; ↑Anti-histamin	• has stimulant, lower sedative
• high Anti-cholenergic s.E (constipation, Blurred vesion, urinery retension) use for Bed weting	•
• α-Anti adrenegic s.E	
- has oxiditive demethylation result is monomethyl compound accumulation	

Date. No.

- Both has No affinity for DA transporter
- used mainly for major depression ← failed SSRIs or SNRI, (not 1st line choice, ↓ therapeutic window index ↑ toxicity ↑ S.E
- cardiotoxicity on Na channel

→ D.

- Discovery of TCA's :

- parent compound ⇒ Chlorpromazine ← راجع السلايد
← try to make isostere for sulfur

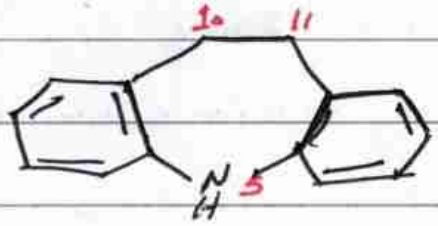
* Ring system in TCA's :-

most common 6,7,6 give optimum Geometry for TCA's ← angle 100 - 110 give optimum binding for Aromatic ring. away from planarity system.

1) dihydrodibenzazepine

as) imipramin, clomipramine

or ↳ Imino stelpin derivative



or Dibenzazepine

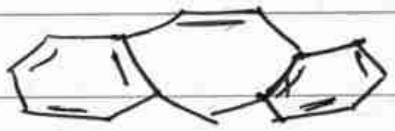
لا يؤثر = مضاد اكتئاب

Anti-depressant

remove N → C

Date. No.

② dibenzocycloheptene or heptadiene

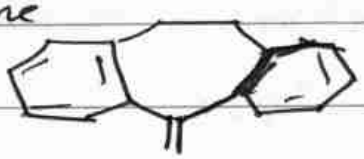


or

or dihydro dibenzocycloheptene

as amitriptyline

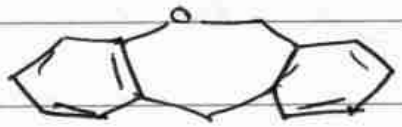
nortriptyline



C → O

③ dibenzoxepine

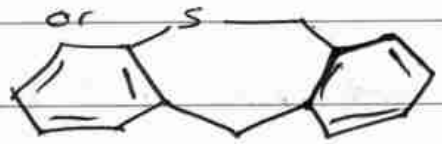
doxepin



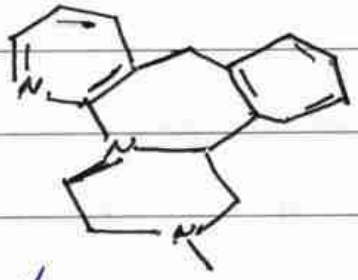
or S

dibenzthiepins

dothiepin.



④ pyrazinopyridobenzazepine



TCAs nature not affect Anti depressive with or without =, homo or hetero cyclic

⑤ Nor TCAs

bupropion, Fluoxetine, trazodone

Date. No.

SAR for TCA's :

① large bulky group include - 2 aromatic ring
activity الكلمة السابقة اللي بالأحمر ليس صحيحة لتعطي
but it's important for orientation and Geometry of
2 aromatic ring.
- must has 2 aromatic not 1 for blocking NE / 5HT3
. Preferably skewed not planner orientation
. has angle btw them given them orientation ...
and some time ↑ lipophilicity.

2 . connected chain that bind TCAs with prephiral amine
- mostly 3 C atom
- sometimes 2 C chain
-

③ in TCA's
- so, 11 position we could put
2 C, or O, S, N,

④ R on Ⓝ
- mono methyl 2° Amine دول مقارنة سابقا
- dimethyl 3° Amine
3° > 2° > 1°
lower

Date. No.

* For TCAs

- Ring substitution is not important

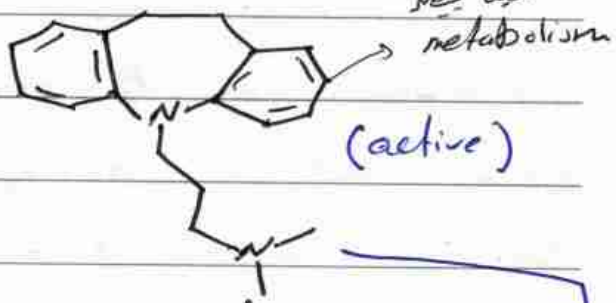
it present ↓ activity.

- Branching on side chain ↓ activity.

* TCAs are ↑↑ Lipophillic → ↑ tissue bound outside CNS

Ex on TCAs':

(1) Imipramine Tofranil®



• 3° amine dimethyl amino propyl

- dibenzazepine derivative

10,11 dihydro

- 3° amine → ↑ Anticholinergic ↑ sedative action

use for bed wetting

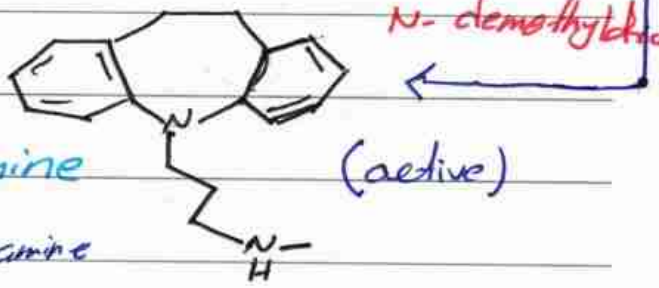
→ high $5HT_3$ > NE block ration So called (SERTI)

selective serotonin reuptake I inhibitor

. ... Selectivity ...

* metabolism:-

- N- demethylation



(2) Norimipramine or desimipramine

• has ↓ Anti Cholengic 2° amine

↓ sedative

more stimulatory SNERI selective NE reuptake inhibitor

NE > $5HT_3$

98

Overall the effect for both is Non-selective.

Date. No.

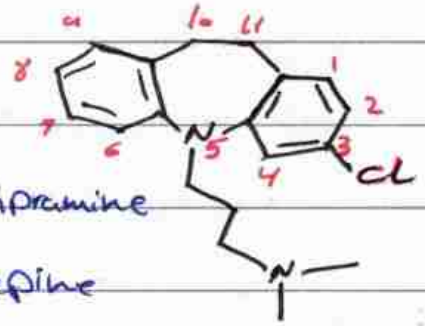
• Note

- MoAIs has slow onset of action! 2-3 week
- effect also high especially in irreversible.

also TCAs

• has slow onset up to 3 week

③ clomipramine



- non-selectiv TCAs
- more potent 50 time than imipramine
• Cl or C≡N in dihydrodibenzeazepine increase selectivity and affinity more on 5-HT3 receptor
• Cl increase potancy by ↑ Lipophilicity and distrubution For CNs
• Dihydrodibenzeazepin deravetive
• used For OCD obsessive-Compulsive disorder.

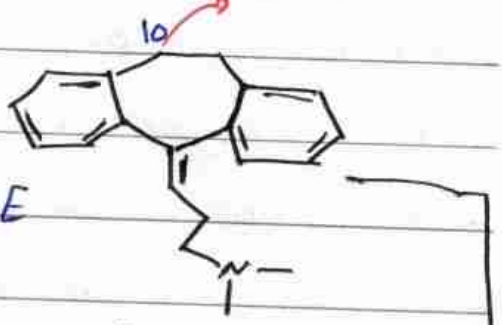
Note one of the major pathways for metabolism for imipramine is on para position on aromatic ring by hydroxylation then conjugation and then N-dealkylation

Date. No.

dibenzecycloheptene or dihydrodibenzecycloheptene.

Amitriptyline + Nortriptyline

① Amitriptyline

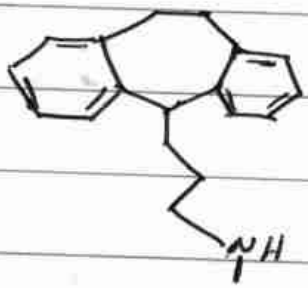


- Carbocyclic ring system
- most Anti-Cholergic + sedative S.E and Anti histamin

As Anticholinergic → Amitriptyline is most
As Antihistamin → Doxepin is most

- when we remove N on position 5, lack the ring ē rich and thus less depend on metabolism pathway induced by N presence to the other pathway. which is N-demethylation.
or benzylic carbon hydroxylation or oxidation on position 10

Nortriptyline

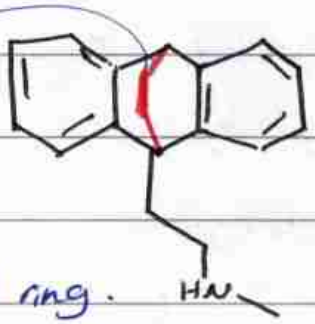


2° amine give ↓ Anti cholinergic ↓ sedative more stimulant than amitriptyline its SNERI
- both are non-selective

③ Tetra cyclic Date. No.

Maprotiline

- tetracyclic
- dibenzobicyclooctadiene
- has ethylene bridged central ring.



- 2° amine —N-demethylation→ active
- ↳ also ↑ affinity + selectivity for NE SNERI
- cause sedation to patient

So in general TCA's

Non-selective reuptake inhibitor (NSRIs - TCAs) 3° amine

selective NE reuptake inhibitor (SNRIs - TCAs) 2° amine

① Non Selective reuptake inhibitor.

Date. No.

(3 dimethyl)

Trimipramine, Dihydrodibenzazepine

- Branching on side chain

↓ reuptake inhibition potency

For NE and $5HT_3$.

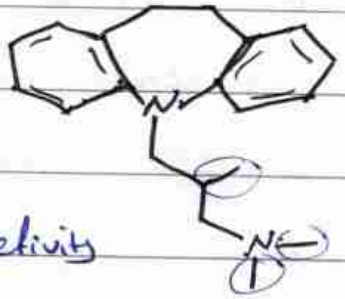
- effective Antidepressant w anxiolytic activity

and ↑ Anti-histamenergic activity.

- ✱ Antagonistic on $5HT_3$ 2A seretonin receptor.

even it's weak reuptake inhibitor but work on another-

seratonin receptor



Note

Imipramine, Clomipramine, Trimipramine

all are analoge. also Lofepramine

Lofepramine, Dihydrobenzazepine

- p-cl phenyl acyl group

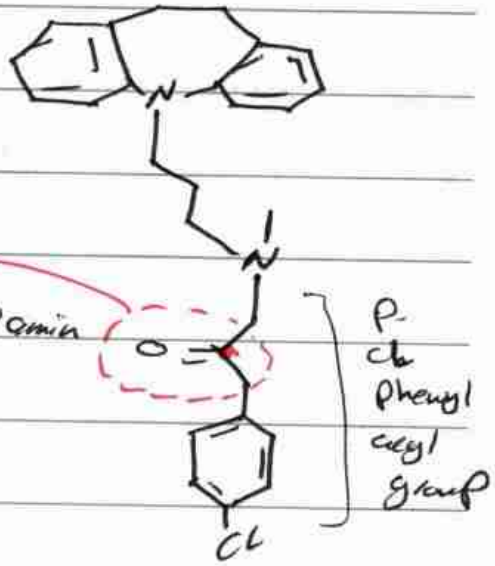
↳ ↑ Lipophillicty and improve

distribution on Brain. or pentration.

very reactive more vurnerable for ← oxidative dealkylation and convert to 2°amin

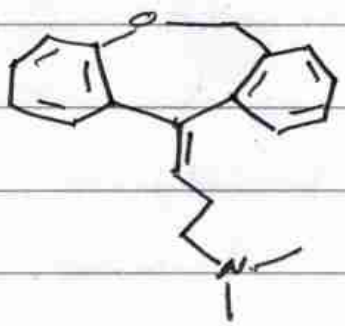
desimpramine inside body

↳ more selective NE, ↓ S.E.



Date. No.

Doxepine, Dibenzoxepine

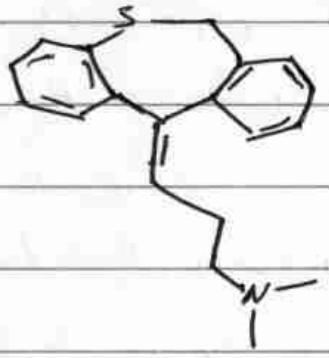


- Antidepressant ῶ high potency as Anti-histamine activity
- due to = present ῶ O has 2 Geometric isomer.

Trans	Cis
85%	15%
• more active for NE reuptake inhibition.	• high activity for 5-HT$_3$ reuptake inhibition
• large degree of metabolism to 2° amine ~~by N-de~~ ῶ ↓ SE	

O —isostere→ S

Dosulepin Dibenzothiepin



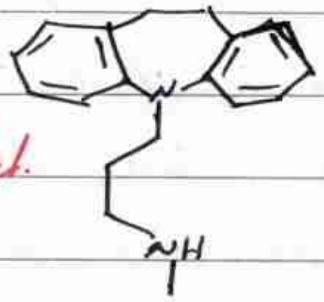
Date. No.

[2] Selective NE reuptake inhibitor (SNRIs – TCAs)

↓ S.E on cholinergic ↓ Antih--- ↓ sedative.

A) Desimpramine

Dihydrodibenzazepine

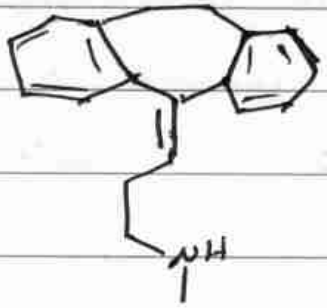


weakest antihistamin & Anticholinergic effect.

B) Nortriptyline

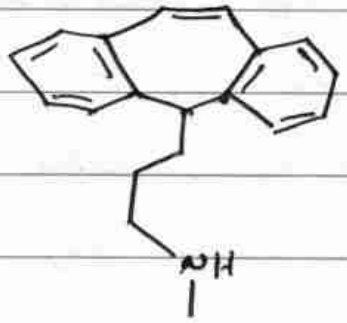
Dibenzocycloheptene

dihydro.



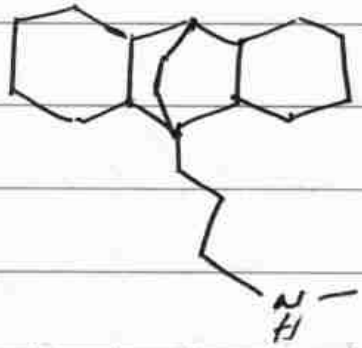
C) Protriptyline

Dibenzocycloheptriene



c) Maprotiline

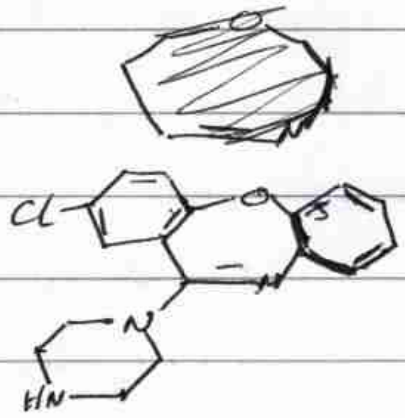
- Dibenzobicyclooctadiene
- selective NE reuptake ↓



Date. No.

Amoxepine

Dibenzoxacepine



N → O

- Antipsycotic Activity lower and Anti depressan
- Fasta onset 4-7 days
- Piprazin system
- D_2 recepto Antagonst
- Shorted elimenetia $t_{1/2}$ 8h

Note

* TCAs was effective as Antidepressant but it
  - ↑ toxcity ; lower therapeutic index
  - high S.E ; binA to many diffe recepter (lacke seleetivity as adrenergic Blocking, Anticholinegic Blocking, Anti-histamin Blocking).
* 5HT3 play or Seratonin play a significant role in depression. So why we can't make SSRIs ??. For selective seratonin w lower side effect, leave effect on Na^+ channle and low cardiotoxcity, and for ↑ affinity and seleetivity for seratonin and prevat reuptake

NET: Neuroepinephrin transpoiter.

• No side effict from ← Anti histamin
Anti Cholinergic
Anti adrenergic.

but still has S.E → sexuel dysfunction Date. No.

B) SSRIs

. To have selectivity and high affinity on 5HT3 without NET.

we know from TCAs SAR:

- we have 2 aromatic ring in 5HT3 Geometric arrengment and the middle ring either 6 or 7 member ring and the bridge in 10-11 ethylene bridge could have = or Not. and could alte O S N

• and the bridge is not essintial for transporter blocking activity also 7-membe is not essintial for activity.

nav system. ... ...

. The idea get from lead compound Anti-histamin for SSRIs. espacilly phenaramin → Starting point from phenaramin → Cis-Zimeldine (Z-Zimeldine)

by subsitution on • Para position substitution on aromatic ring

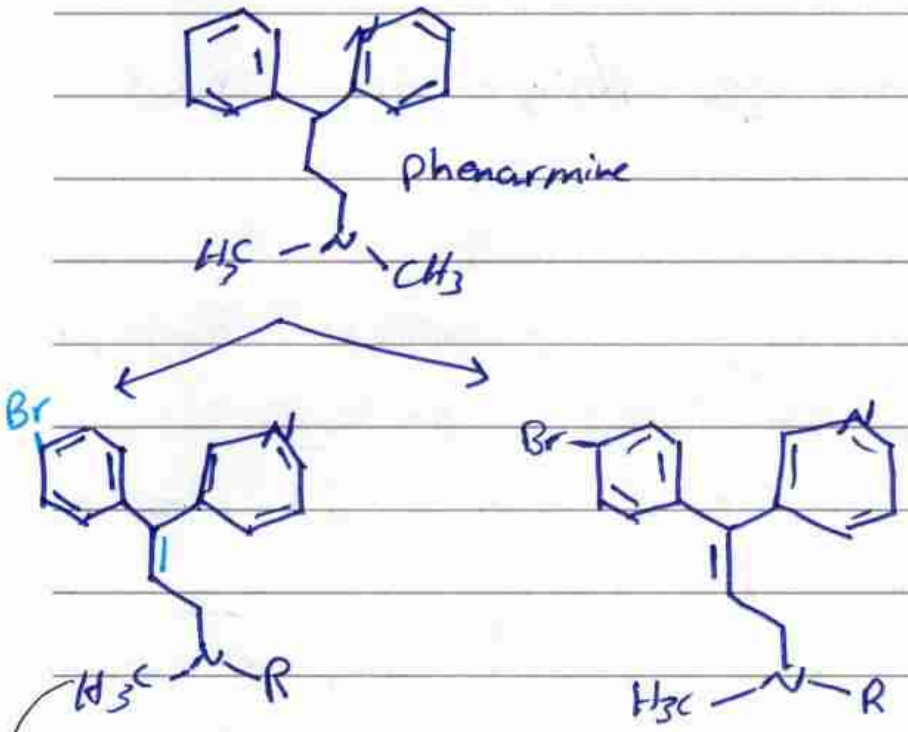
• add = on bridge

• sp3 → sp2

So SSRIs come from Diphenyl propyl amine derivative
or Phenyl ethyl amine derivati
or B-aryl amine group

are basic transporter for Neurotransmitter.

Date. No.



cis

2- Zimilidine (R=CH_3)

2-NorZimildine (R=H)

E- Zimeldine (R=CH_3)

E- NorZimeldine (R=H)

• hass SSRIs (more selective)

but ∵ ↑ toxic not use

Clinically as Anti-depressant

لكن تم التطوير من خريات

Note :-

as in TCAs, Anti depressant to give activity need

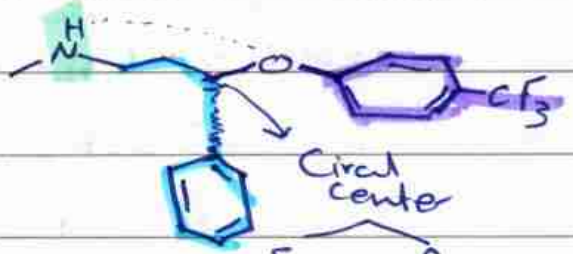
- aromatic ring
- alkyl bridge
- Basic or aliphatic amine (completely ionized at pH)

↳ it called β-aryl amine system

Date. No.

- ~~the~~ So if it has Basic nuclese is good for Blocking transpote.; fit and mimic Monoamin neurotrans.
- For more efficinet Blocking need another aromatic ring for lipophillic bulk group.
- TCAs is not essintial but 2 ~~ring~~ rings → 1 aromatic, 1 lipophillic
  Both melce complete blocking for receptor.
- Then we malle deivative from 2 Zimeldine

① Fluoxetine



- more efficient
- less side effect
- Phenoxy phenyl allyl propyl amine
- Protonated amine or Basic amine very essintial for activity (critical)
- alkyl bridge then aromatic or β-aryl amine like group which is responsible for Binding
- Then lipophillic aryl group aids in Blocking and Strong Binding w target

$5HT_3$ ← Selective 300 fold

R Poten in inhibition of Transporter

↳ For lipophillic aromatic, optimum Geometric is important optimum Geometric is thought to be from 2° amine which is protenated inside our body, which make hydrogen Bonding w O (ether), this closing bw N and O

Date. No.

yeild in optimum Geometry and proper distance to make fitting inside transporters.

- 2 aromatic ring not in necessary be planno for optimal transporte inhibition.

- Fluoxetine has Chiral center (Racemic mixture)

- S enantiomer is more active and more selective but R is more Potent than S on transporter

Note

- so here we delete the bridge 1o, II → Bicycle

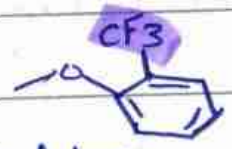
TCA

- To distinguish bw SSRIs and SNERIs

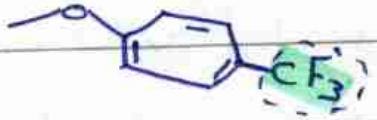
↳ Look for aromatic substitution, on para position electron withdrawing make it SSRIs

But

if ē withdrawl on ortho



it become SNERIs selectivity ↑↑



- CF_3 is good as withdrawl and Lipophillic substitution

- major metabolic pathwathy is:

N_ demethylation

2° amine — more active

1° amine NH_2 - less active

- active

- Very long $t_{1/2} \approx 50$ hrs.

substitution on 2,4 bb selectivity

o' 3,4

109

Date. No.

[redacted]

Quote

as we see in Fluoxetine has { S → more selective ; R → more potent }

So there's no parallel relationship or direct relationship between Selectivity and potency.

So it Drug could be high selective but Not potent and could be high potent but Non selective

Ex/

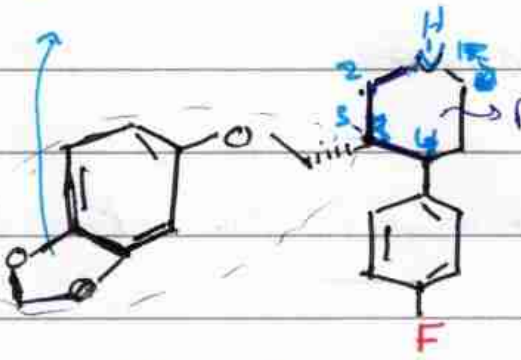
- Citalopram is highest selectivity
- paroxetin is highest potency.

So selectivity as parameter differ from potancy.

Diaryl methelen Bridge

Date. No.

② Paroxetine:



- They diffe from Fluoxetine that instead of propyl amine free flexable chain
- and make Displacement more clos to amine on pipridine ring

- make N enclosed to pipredine ring Basic 2° amine and on para position (F) → good for affinity cos e with drawal group on
- has 2 circl centre

3 active form S ⟷ 4 active form R

- paroxetine is constrain analoge of Fluoxetine
- when displace phenoxy to pipridine, hydrogen Bonding could occur bw O and H → give suitable orientation and proper binding w transporter.
- has potent activity on 5HT3 transporter
- effective Anti-depressant, Anxiolytic Drug.

SERT : $5HT_3$ Transporter

Date. No.

* Changes on paroxetine could lead to ↓ activity :

① Transform from 2° amine → 3° amine

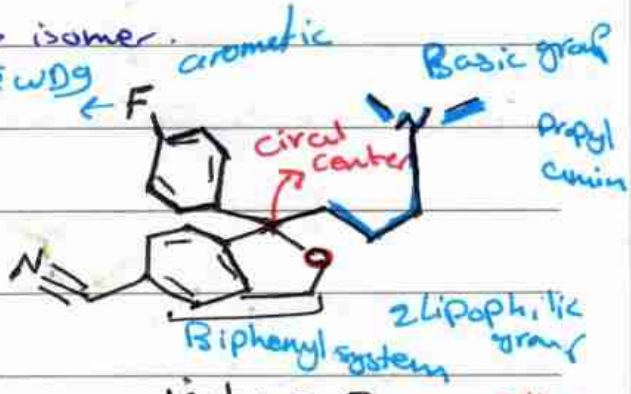
② Chang F → H or CH_3 donating group.

③ Change dioxy metholen bridge → ~~Dioxy~~ 4- methoxy

④ Chang from H → ortho position.

Citalopram and Escitalopram :-

pure isomer.



- Racimic mixture
- very selective on SERT

Most selective SSRIs.

- has ciral center

S ↔ R

S → active form. Escitalopram.

* major metabolism: N- monodemethylated compound (3° amin → 2° amine)

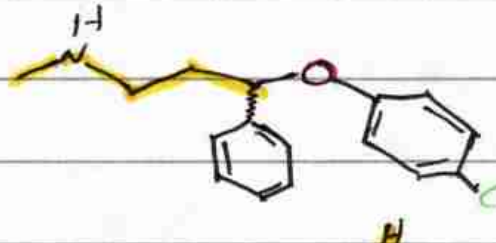
but as selective ← less potant

- aryl substitution are important For activity
- ether also is important For activity
- O in Furan probaply interact w the protonated amino group to make H.B and give suitable shape For SERT binding (intramolecular hydrogen Bond) enhance geometry For transport inhibition

Phenoxy phenyl alkyl amine

SSRIs Structures

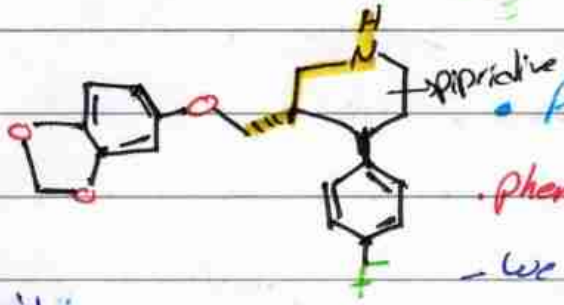
Date. No.



- Fluoxetine

Phenoxyphenyl alkylamines.

- without tricyclic system



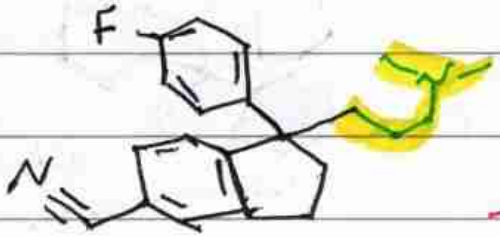
- Paroxetine

- phenoxyl phenyl alkyl amine

- we make cyclization or constricted

Constra'd

Constrain form on amine included in pipredine cycle

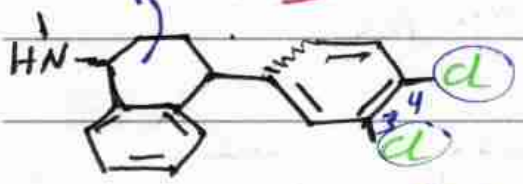


- citalopram

- phenoxyl phenyl amine.

- un non aromatic Basic ring

↑ selectivity



- sertraline

- phenylaminotertraline

↳ For tetrahydro naphtaline

- has 3,4 EWDg which improve activity on SERT selectivity

- amine binds and 2° amine on partially saturated naphtheline ring (non aromatic cyclo hexa bind to aromatic ring) if it Fully aromatic non active and non Basic.

Basic.

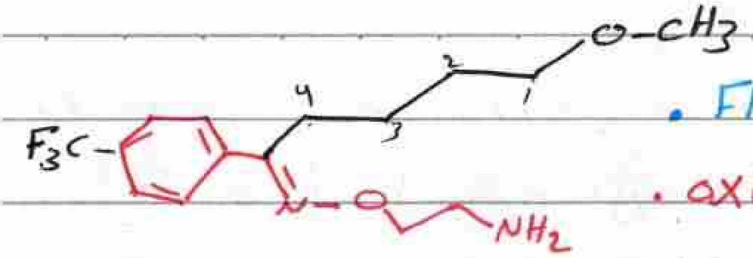
Tetrahydro naphtheline group

Date. No.

- note that there's No O in sertraline ; we make ~~orientation~~ orientation to phenyl ring by restricted rotation to Bi-cycles Compered with bete Drug which has flixable rotation but need to Fixed it by making hydrogen Bonding to have good geomitry but in sertraline there's no need to hydrogen Bond formation due to it's restricted filxability. which is Fixed good oriented aromatic ring in optimal geomitry that result in good optimal binding to the target.

- has 2 ciared center { 1 Position / Para Position } (1S, 4S)
has betta selectivity

Date. No.



- Fluvoxamine
- oxime ether derivative
- No bi aryl system
- has aromatic aliphatic Lipophilic system.

_ remeber /
- For essintial activity need 1 aryl ring aromatic amine and the other is for lipophillic interaction (Bulk inter ῶ transporter).

In Fluvoxamine
we save aromatic ring ῶ CF_3 (~~both~~ very Lipophilic
and ē WDG has vital role in SSRIs activity

_ have Basic amine ῶ Fixed orintation by oxime (N—O)
- N—OH oxime
- N—O⌄⌃NH2 oxime ether.

- 4 carbon connected to $O-CH_3$ make lipophilic interaction
- has cis geiometry E isomer active form make folding → give correct geiometry

β-aryl amine derivative for transporter inhibition

2 aryl system or bi phenyl ~~system~~ systeme لكن مو فيه   β-aryl amine general structure مو محقق

Date. No.

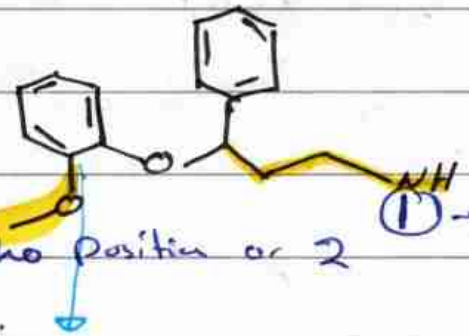
c SNERIs : . Selective Norepinephrine Reuptake inhibitors.

. we say that Phenoxy Phenyl alkyl amine its important group which determine selectivity for transporter depend on substitution on phenyl ring in para / ortho position.

. if we make ortho substitution on aryl ring insted of para substituted make selective for NERIs.

Nisoxetine

. same to fluoxetine but insted of CF_3 or para substituted (EWD) we put phenoxy group on ortho position or 2 which ↑↑ NERIs selectivity.



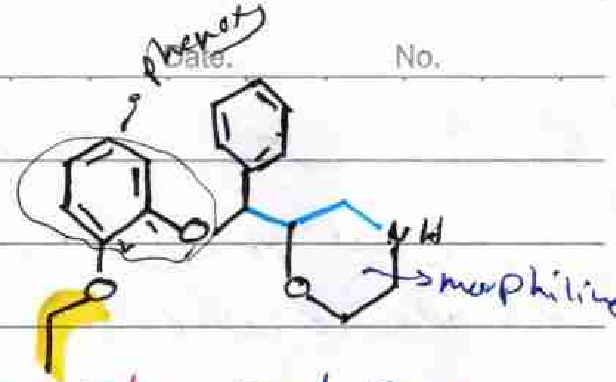
. if we put lipophilic Bulk group as CH_3 on position 2 become more active. prevent Free movement of the phenyl ring (CH_3 or S-CH_3)

. NH → prefer methyl subs. more active, if large subs. → inactive.

. Not clinically used

Reboxetine — Nisoxetine

- insted of methoxy → ethoxy
- make restriction included



in morpholine system as in paroxetine and same Basicity of N

• selectivity is due to ortho position because it make strong H.B with target NET H.B donor.

This type of H.B interaction exist in NET Not SERT

* has 2 chiral center

• active one is Racemic mixture ̄c S,S more active

S,S > R,R   الفرق د activity مش كبير

لهيك عم بستخدم Racemic

major metabolism :- by de ethylation or oxidative ~~de ethylati~~ de alkylation on ortho position on phenyl ring.

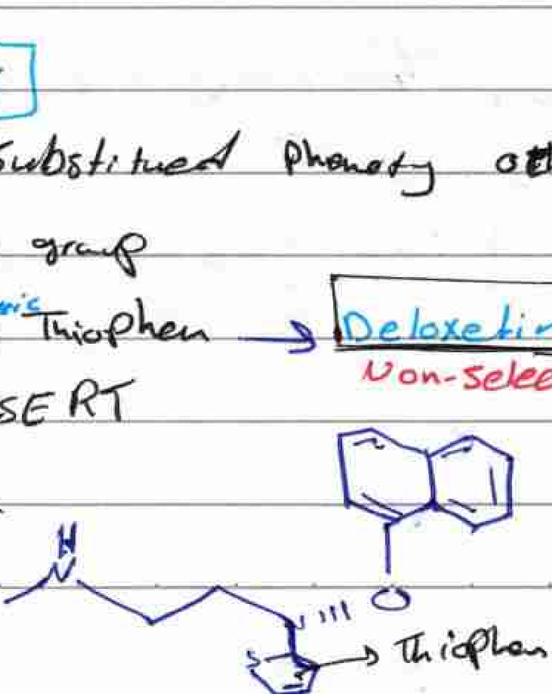
SAR For SNERIs:

- if in Nisoxetine if we substitued phenoxy OCH3 to bulk group naphthaloxy group and insted of phenyl → (isosteric) Thiophen → Duloxetine (Non-selective)

~~NET~~ NSNERIs + NSERT

No para / ortho substitution

Nisoxetine



Date. No.

. The type and position of ring substitution is very critical to determine the selectivity of these agent for NET or SERT inhibition.

• unsubstituted phenoxy ring  weak NET & SERT inhibit.

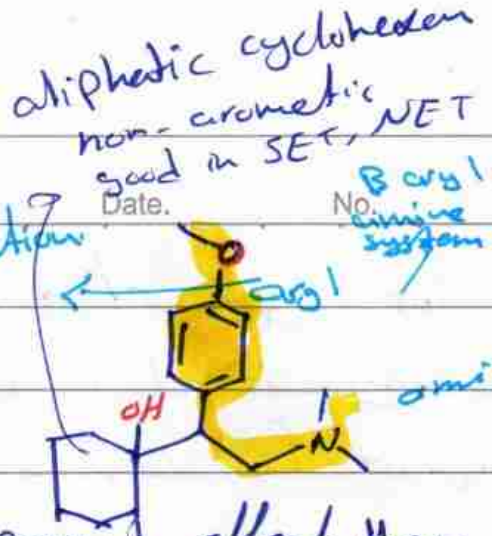
• ortho 2. substitution into the phenoxy ring except (trifluromethyl) is creating compounds that are NET selective

• Para 4-substitution will give compounds that are SERT selective ; where the trifluoromethyl is the most active. as in Fluoxetine.

D. Newer (Nontricyclic) Nonselective 5-HT and NE reuptake inhibitors.

. we try to b tricyclic system to b Anti-cholinergic and Anti-histamine, Na⁺cardiotoxcity of TCA. , Anti Adrenergic effect. so to b S.E.

• it has β-aryl amine system.

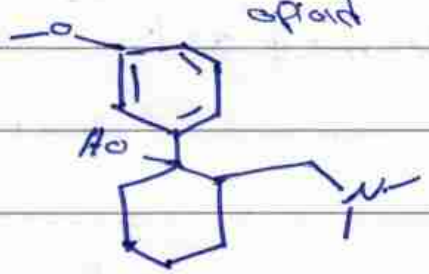


Venlafaxine

- is a serotonin-norepinephrine reuptake inhibitors. (SNRI)
- generate Faster and greater antidepressant effect than SSRIs alone
- TCA, MAOIs, SSRIs, ... All have delay onset of Action could affect patient in Antidepressant in which suicidal attemp could happend.

So we need Drug have Fast onset of Action as venlafaxine by 4 days Stat have effect in accelerating dose as Antidepressant activity.

Tramadol ترامادول



- major metabolite :-

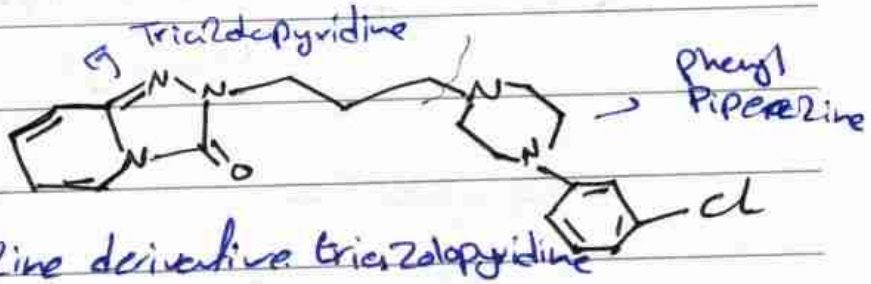
O-desmethyl (Desvenlafaxine)

- also active
- narrow therapeutic index.
- greater, Faster effect

Date. No.

E. SSRIs and 5HT2A antagonists.

Remember Antipsycotic has ability on 5HT2A and dopamine that able to treat Negative symptomes of phycosis or sechizophrinics.

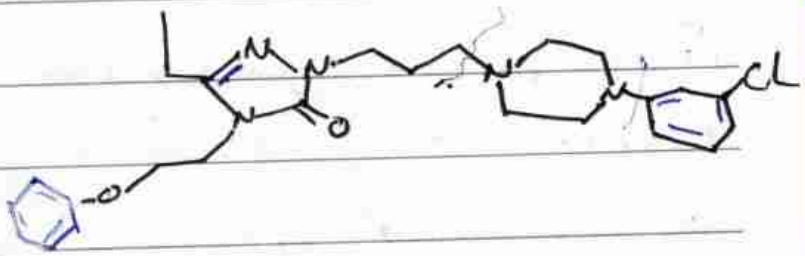


• Trazodone

its aryl a Phenyl piperazine derivative triazolopyridine

• Trazo Too my → Sedative-hypnotic.

↳ Tirazolpyridine



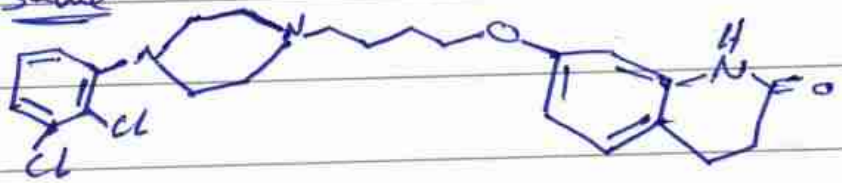
Nefazodone

• its Phenylpiperazine-triazolone derivative.

SSRIs

* Both Trazodone, Nefazodone give same metabolite by N-dealkylation lead to Phenyl piprazine metabolite

• other ring disappears and substituted w other Lipophillic substution activity. same



Aripiprazole

- Arylpiperazine deriv.

- partial agonist on 5HT1A and dopamine 2.

- its Atypical Antipsychotic.

Date. No.

- structure below derives from Fluorobutyrophenone antipsychotis.
- have β. aryl amine structure → bind SERT, 5HT2A antagonist (Dual mechanism)

could be used as → Anti-depressant, anxiolytic activity

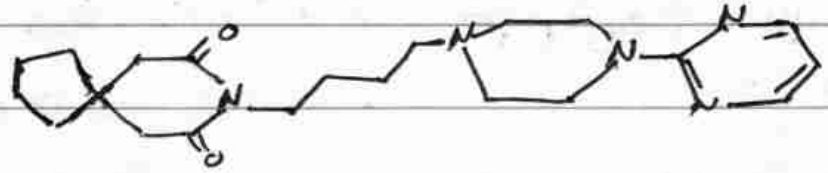
F. $5HT_{1A}$ Agonist + partial Agonists

Buspirone

Anxiolytic

~~anxylotic~~

Antidepressant



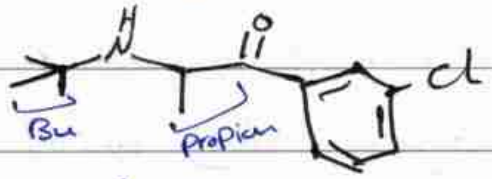
it has partial agonist, can stimulate postsynaptic receptor when 5HT level are low in the synapes as in case of depression.

Note: partial agonist. when Neurotransmitter high partial agonist ↓ NTM
and when ↓ NTM, partia agonist ↑ NTMs

Date. No.

D- NE + DA reuptake inhibitors :-

Bupropion :-



- MOA / Block reuptake of DA and NE and induces release of DA + NE

- has phenyl ethyl amine has Basic nucleus
  methamphetamine + cathinone
- used as 1st-line for smoking cessation
- if SSRIs side effect not tolerated as sexual dysfunction we could use Bupropion

Adrenergic Agents

Date. No.

⇒ general classification for drug that affecting adrenergic / sympathetic system:

- Adrenergic drug excert their therapeutic effect by

Sympathomimetic agents
↑ sympathetic activity
- activate CNS activity
- adrenergic stimulant / Agonist

Sympatholytic agents
↓ sympathetic activity
- reducing CNS activity
- Anti-Adrenergics / Antagonist

* Both of them occure by affecting various component of sympathetic system. most important ARs (Adrenoreceptor) most drugs Acts directly on ARs either as < agonist / Antagonist

OR

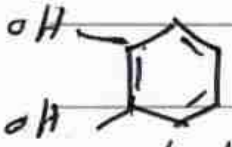
* we could affect life cycle of NTM indirectly

(biosynthesis → storge → release → fate after release)
fate after release: elimination (metabolism or reuptake)

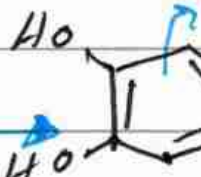
⇒ Adrenergic neurotransmitters :-

2 main ones are • adrenaline (Epinephrin)
• Noradrenaline (Nor-epinephrine)

General structure



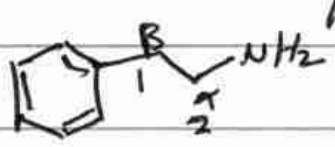
catechol



ethylamine

weak acidic → weak basic

and completly ionize at Physiological pH



B. phenyl ethyl amine

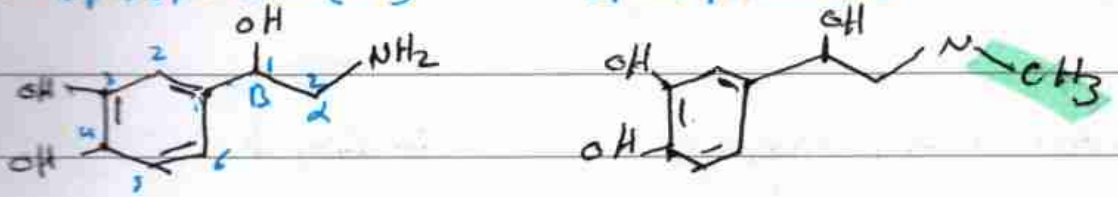
catechol

⊖ catecholamine
Dopamine (DA)

endogenous catechol amine

Date. No.

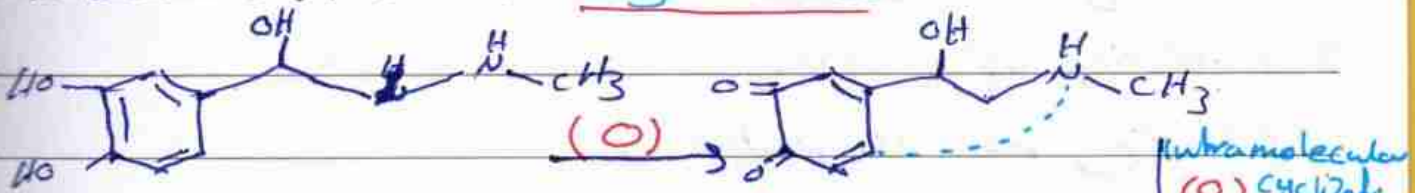
Norepinephrine (NE) Epinephrine (E)



Agonist for E and NE :- Exogenous (synthetic) catecholamine

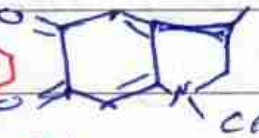
isoproterenol (iso)

* Both E, NE are easily oxidize



Epinephrin (E) A quinon Analog

Aware of there's Advertising injekt ~~Colored~~ Colorless



and change its color to dark color Adrenochrome

colorless → Dark color.
oxidize
Adrenochrome (inactive metabolite)

So we add for ampule inside it Anti oxident as Na2So3 Sodium bisulfid or Ascorbic Acid

Date. No.

- Adrenergic drug work in 2 mech. in general ↓

Direct effect on adrenoreceptor — sympathomimetic / sympatholytic

indirect — Life cycle

- Termination of NE is done by:
  - uptake ← to neuron or extra neuronal tissues
  - Diffusion away from synaps
  - Metabolism.

* general targets for Adrenergic Drugs /

1. Affecting NE synthesis
2. Affecting NE storage
3. Affecting NE reuptake

} pre synaptic

4. Affecting NE release
5. Affecting MAO or COMT — in synaptic cleft
6. Affecting NE interaction w receptors. post-synaptic.

1) Sympathomimetics Agents :-

- Direct: ↓ adreno receptor
- Mixed: ↓ adrenoreceptor + release of NE
- InDirect: release ↓ of NE or Life cycle

Date. No.

- To Fully understand SAR for Adrenergic Agonist, Easson-Stedman hypothesis is a model explain most important requirement for Binding, Activation and interaction either for α, β.
- This model is based on major group that has ability to bind to Adrenoreceptor: β phenyl ethyl amine. derivative most important are catechol amine NE, E. or Antagonist
- when we need to make drug has Agonistic effect sometimes we make mimicing For Natural Ligands

- if you have target (receptor) able to distinguish bw R, S, on least this Drug make 3 binding with spot inside target.
- There's R, S NE (R more active) and since adrano receptor is able to distinguish bw R NE, SNE

So at least there's 3 important interaction bw ligand and target.

⇒ one of these interaction / for Agonist + Antagonist

① Amine group NH_3 which is completely ionized and make Strong ionic interaction

So when you need binding inside Adre. receptor you need aliphatic Amine completely ionizable at pH Physiological 7.26

Similar to Ligand

Date. No.

② Lipophillic interaction b/w 2 aromatic ring.
Bi - Bi interaction or static. for Agonist + Antagonist

③ distance b/w Amine and aromatic by ethyl group
give optimum distance

④ Fiture (for Agonistic activity) OH on position β
make hydrogen Bond.
if in R isomer OH → optimal make strong H.B
if S isomer OH → not optimal loss H.B
اذا تغيرت orientation يتغير geometry فيتغير الارتباط

Agonist effect
⑤ OH in catechole involve for 2 H.B

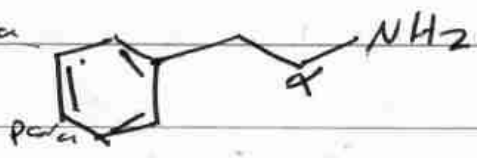
① Direct sympathomimetics :-

SAR

has a general structure (scaffold structure) has ability to act as sympathomimetics by Direct mechanism

Date No.

most general famous one :- Phenyl ethyl amine derivative.



→ main 3 components

① aromatic Ring, Pi to Pi static.

② amine group, ionic interaction

③ distance bw Aromatic / Amine (ethyl bridge) optimal geometry.

* changes occure on 4 sites which give effect on → activity, selectivity, Agonistic on Adreno receptor

① position α

② position β

③ Aromatic substitution in meta, para position

④ substitution on Amine

* To have potent direct effect catechol ring ① is important

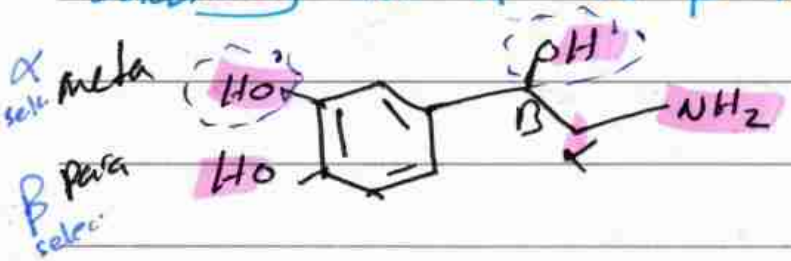
* β-OH ② group also important For potent direct agonistic activity in correct stereochemical configuration in R Geometry. or will be destructive activity.

* substitution on amine ③ → Small or Large alkyl → Bulk substitution → selective for β-receptor ⑦ For selectivity

* substitution on α position ⑤ ↑ stability / effect selectivity ↓ activity

Date. No.

selectivity for α v.s β receptor :-



There's 3 main site that affect selectivity ← Direct agonist α / Direct agonist β

① OH is important as position & orientation

① substitution on amine group. , by adding Bulk group be more selective to β ⇒ ↑ heart

② small substitution on α → α selective ⇒ ↑ Blood vessels
↑ selectivity to activity. activity ↓ as ↑ α

③ OH in catechol ring β selective in which meta if one OH is present ⇒ more active on α
para more active to → β receptor.

Date. No.

Remember!

- There's 2 general nucleus structure we could da. from it, or consider it as basis for sympathomimtic or direct agonist
adrenergic

- These 2 nucleus are: ① B. Phenyl ethyl amine which is represent by natural Catechol amine as EN, NE, and synthetic analouge isopretend.

② imidazoline derivative or acyl imidazoline derivative

- Knowing basic nucleus aid in prediction of activity.

- For B. phenyl ethyl amine to have max Adrenergic direct
Moiety : max activity on adrenergic receptor

① B. position ew OH subs. in suitable Geometry (correct) R
B-phenyl ethyl amine

② Catechol ring ~ 2 OH on 3, 4 position

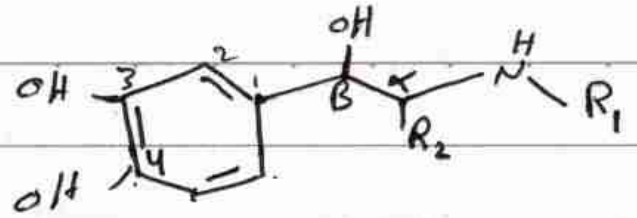
we could make modification will affect < selectivity / activity mainly

- For selectivity we have 3 position :-

① Bulkness of substitution on amine group K β selective

② substitution on α position α receptor

③ change catechol ring < β_2 / α



Date. No.

For N or R_1 substitution on N :-

- ↑ size R_1 → - ↑ β activity (PhD parameter/ratio)
  - ↓ α activity
  - ↓ degradation by MAo (which prefer 1° amine, thus Bulkness around amine group, could ↓ ox. deamination by MAo thus ↑ Metabolic stability ↑ DoA.)

  PhK effect

  So size has 2 effect ← PhD, PhK.
- nature of substitution ↓
  - ↑ Bulk, ↑ more selective $\beta_2 > \beta_1$
    as ǂ 3° butyl > iso propyl
- ↑ Lipophillicity for substitution on N too much large substitution not just reduce α activity, but Blocking α very very selective ↓ β

For R_2 Substitution on α position ↓ ← methyl, ethyl

- any substitution on α ① ↓ direct acting for β, α ← affinity
  So its not preferred but we put it to ↓ DoA
  ② metabolic stability, Bulkness ↓ ox. deamination more resistance for MAo, ↑ DoA as in amphetamine by puting methyl on α position, resist MAo

Date. No.

① selectivity for α > β (opposite to amine)

- ↑ Lipophillic action → improve CNs activity. ↑DoA as in amphitamine if remove methyl No CNS activity.
- better absorption. No 1st Pass metabolism. ↑DoA. ↓ox.d deamination by MAO
- need small group < methyl / ethyl good oral activity.
- methyl in S ointation → more α_2 selective.

So methyl alted < selectivity / metabolic stability.

Aromatic Ring Substitution:

- oH in 3, 4 has good agonistic activity on α, β
- Catechol ring and oH in 3, 4 make compound easily metabolised by COMT: catechol o methyl Transferase which make methylation on Position 3 on oH → short DoA and poor oral activity. more hydrophilic activity, Poor CNs activity higher Polarity

& we need modification: (as good CNs activity, more selective to either α, β, more resistance to metabolism)

∴ oH is good Position to make modification to have

① ↑ selectivity ② ↑ metabolic stability

③ improve oral activity and Bioavilability

④ ↑ hydrophobicity / Lipophilicity to ↑ CNs activity.

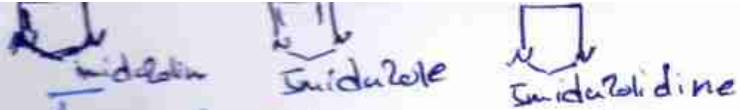
Change substitution position Date. No.

- we could change e in position insted of 3,4 → 3,5 (resolsenol)
  - more metebolic stable . No COMT cetivity.
  thus ↑ DoA good oral activity.
  - selectivity for β receptor

- we could get rid of catechol and let OH on position 3 → ~~OH~~ CH_2OH methyl alchol not Phenyl alchol thus this save hydroga Bonding Ch. Ch
  This will
  ↑ selectivity for B_2
  ↓ metabolism by COMT. ↑ oral activity ↑ DoA.

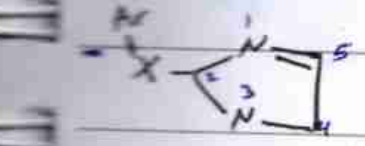
- ~~Both~~ OH are important for Both α, β agonist. but ~~OH~~ 4- OH activity more β but ↓ affinity.
  3-OH = = α

- if OH is removed ↓ direct activity on α, β and could convert drug from Direct → indirect
- if reduce no. of OH (shift) → mixed effect.



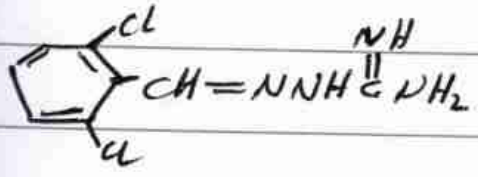
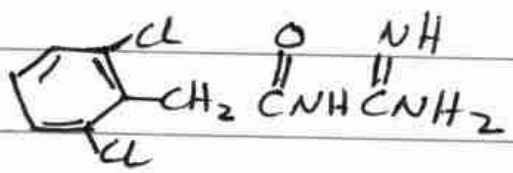
Imidazoline α_2 adrenergic receptor agonists :
or aryl Imidazoline

Date. No.

- Imidazoline has α adrenoreceptor (α_1, α_2) — catechol 없음
- 
- Basic ring pKa 9 - 11, completly ionize, make ionic interce
- bridging unit usually 1 - 2 atom. not exss 2 atom
- aryl.

* B acting agent is limited to β-phenylethanolamine but α-acting agent is has more diverse variety of activity.
- most Imidazoline has fixed aromatic ring the changes slightly in variety of bridging or Aryl substitution
  ↳ ring
  ↳ many have minimal changes but still active
- So to let it active we prefer ring without substitution.

Exception opining of Imidazoline ⟹ Lucinidine.
opening analog for imidazoline active compound.
as Guanabenz , Guanfacine

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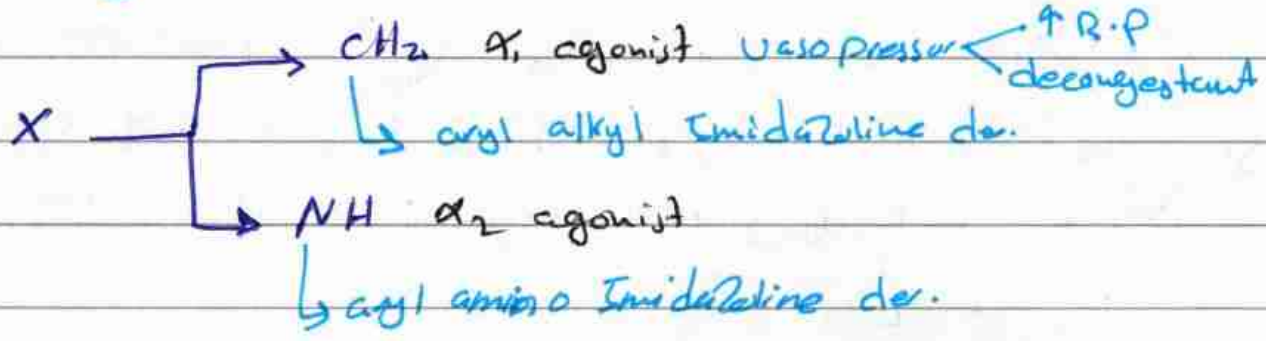
bridging unit :-



For aromatic ring:

- There's flexibility for substitution more than B. phenylamine
- best substitution is in ortho position.
- Cl, CH_3 is small group.
- * if we compare bw phenylephrine, Methoxamine w epinephrine which is more potent on α receptor

Date. No.

⇒ Aminoimidazolines

How would changes in physiochemical propeties affect the or differ b/w 2 simillar structure

as noted that All Aryl alkyl imidazoline are vaso contrictive

. if we make physiochemical change we could have for example/ Antihypertensive drugs. and change the site of binding in receptor from prephral to central acting effect which would give opossite Pharmacological effect from the same familly

in other for Aryl Alkyl imidazoline

. CH_2 and imidazline ring طبيعة تواجدهم وترابطهم مع بعض make it Imadazoline ring pka very high (10 – 11) completely ionization at Physiological pH.

which make CNS pentration week and it's major action is preiphiral action

from Naphazoline — tetrahydrozoline — to Clonidine why ??

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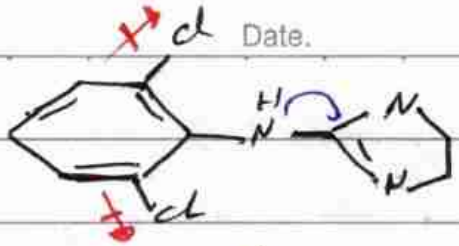
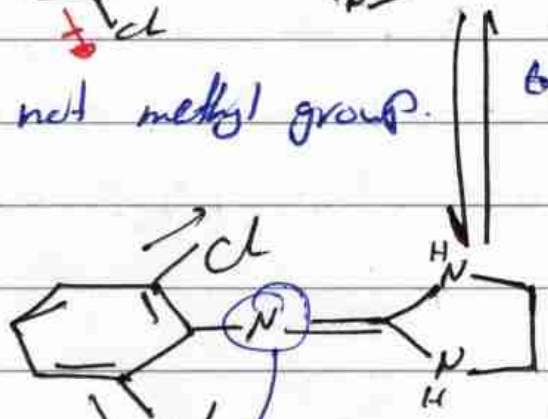


Clonidine

- N- bridging unit
- Cl group on ortho position not methyl group.



~~Cyclic~~ aliphatic
- guanidine basic group
- Cl has 2 electronegativity withdrawal effect from central N which has a vital role in Basicity of guanidine or Imidazoline ring so this will ↓ pKa and ↓ Basicity instead of pKa 10-11 → pKa = 8

This will ↓ degree of ionization

- having aliphatic guanidine Basic group.

* When we remove CH_2 from the bridging unit b/w aromatic & imidazoline ring ?

⇒ ~~There~~ When CH_2 exist there wasn't conjugation or direct connection b/w aromatic & Imidazoline

⇒ So when we remove CH_2 and replace it with N the we have 3 N in conjugation

Date. No.

and Basic guanidine has direct connect to aromatic group

This give resonance effect (ē of N is move ē

ē of aromatic ring

⇒ presence of 2 Cl in ortho position not meta position

To be closed to in guanidine (group to be affected)
and they are lipophillic

so inductive + resonance effect together let pH
down from 11 or 10 —to→ 8 < ↓ Bascity
↓ degree of ionization

so clonidine —Part→ to unionized → important for pentration
→ can pentrate CNS
→ ionized inside Brain
make agonistic α_2 in Brain
↓ sympathetic flow from CNS
and give vasodilation
and Antihypertensive.

↙ ionizable
→ important for binding

→ Centrally more than Peripherally

oxylometazoline

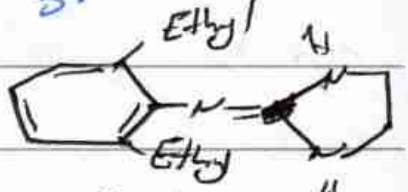
So this lead to

- central action
- preiphral action
- α_2 agonist
- ⊖ W D in ortho → ↓ pka ↓ ionized ⊕ CNS pentration

Date. ST. 9 No.

-inted of cl → ethyl (lipophillic)

*ethyl is donating not withdrawl group which would ↑ Basicity of guanidine group and wouldn't acting centrally and work peripirally



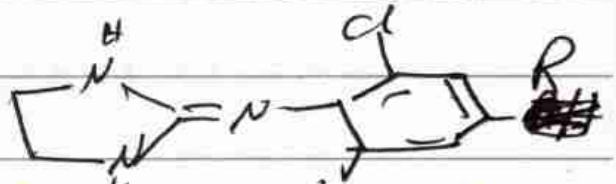
STAT

- has high affied to α_2 but No Antihypertensive in vitro

: it not nescessary for streche to have potent action on receptor but the important is to reach receptor

if R = OH

4- hydroxy clonidine



it's one of the metabolite of clonidine, has good affinity on α_2 receptor but not effective Anti-hypertensive. Why?? strong conducting effect

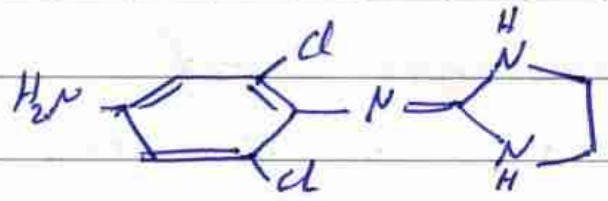
because of ↓ lipophilicity, and it's beyond the withdrawing effect of Cl^-

this ↑ pKa ↑ ionization ↓ penetration

thus work Periph not centrally

Date. No.

Apraclonidine

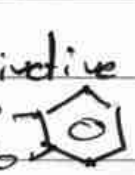


has amine group in para position, which give hydrophilic charcter that ↑ pKa+ and hydrophilic & CNS Penetrat and ↑ pKa from 8 to 9.22 not cross BBB and give priphiral actin. by α_2 agonistic effect

B_2 agonist → chemical class ← catechol deriv.
→ DoA

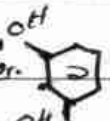
For Chemical classes of

Catechol derivative
- coltherol
- Bitoltherol
- isoPropetrderal
- isoetharine
- has & DoA
↑ metabolism by COMT



To improve DoA

Resorcinol der.



- Metaproterenol
- terbuterline

Methyl alcohol der.
- salbutamol or Albuterol

Date. No.

From DoA Aspect :-

① old generation hey short DoA called (SABA)
Short Acting Beta 2 Agonist. (3-6) h
- as Resorcinol der. and catechol der.
- need Frequant adminsteration

② "LABA" Long Acting Beta$_2$ Agonist 12 h and more

③ Altra LABA up 24 h
once daily.

Strategy used to develop B_2 agonist to have extend Action :-

① Prodrug Strategy (old strategy)

② change in Function group / Drug.

Date. No.

3 Contribution Factor that Lead to Extend DoA of Salmeterol : or LABA group :-

① Presence of Large Lipophilic group

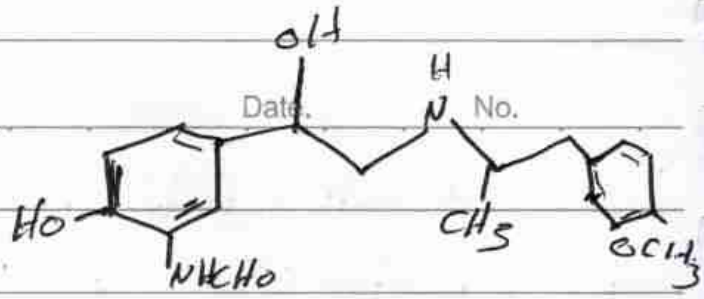
"N-phenyl butoxyhexyl substituent" which bind in very close ~~site~~ site from Active site of β-receptor.

So it has ability to make extra binding (tight Binding) this result in that association and dissociation in β_2 receptor become slow. (association slowe and dissociation more slowe). This result in ↑ DoA.

• in general LABA slow onset and more slow offset so it's not used for rapid relief of Asthmas Attack !! but it's used for regular administration for ↓ no. and severity of Asthma attack.

So it's effective in protection of Asthma

② Presence of Long chain this enable Drug either penetrate intracellular (A resivoir) or ~~in~~incorporate inside Lipid membrane of lung cell which make it stay or ↑ resident time in cells.



⑦ Formoterol

- remove catechol
- put formyl/amino group NHCHO
- still OH in para to have potency.
- formyl group have ability to make H.B so good potency

Position 13

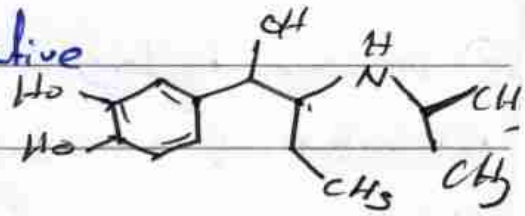
- large Lipophillic group on N, Extend DoA by isopropyl + Phenyl This w Formyl give selectivity and B_2 agonist.
- has 2 ciral center so has 4 stero isomer

(S, S) (R, R) (S, R) (R, S)

- 2 fold greater potency than racemic mixture
- ↑ affinity on B-receptor 1000 time than S, S
- so its active form.

⑧ isoetharine : catechol derivative

old generation catechol



- its ethyl isopreterol
  - has selectivity on B_2
  - Potent B_2 agonist ← isopreterol: ethyl group; isoproprle
- when adding ethyl — selectivity
  - protect against MAO → ↑ DoA

latest LABA derivative : Ultra

New LABA :- or Ultra LABA Date. No.

⑨ vilanterol

- very lipophilic

اذا اضفنا ٣ حلقة ستنوية كيف تم التعبير عنها

① by Change Catechol ↷ resoscinol

② Chang substitution on N by very large LPL

③ Prodrug

Bi ester Tolnic Acid

⑩ Bi Coltetrol (pro drug)

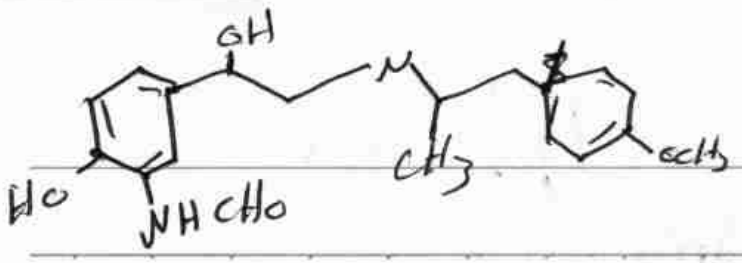
- Colterol its old generation catechol derivative it's selective B_2 due to presence of 3° butyle as in salbutamol or albuterol .

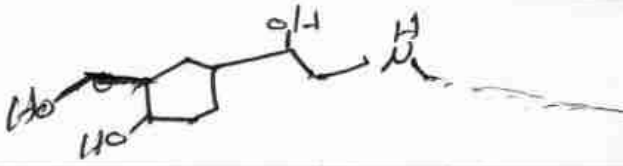
but problem in colterol is Catechol ring that it's vulnerable to metabolism thus has short DoA.

- So prolongation was needed with Saving selectivity.

by make prodrug . by adding 2 Tolnic Acid in 2 OH on catechol By Bieste

- it's has long DoA; because until esterase reach and make breaking to ester bond this process need time





Date No.

Salmeterol

Formoterol v.s ~~Isoetharine~~

- substitution in Formoterol is lower than Salmeterol
  so it's less lipophilic Salmeterol
  This effect PhK
  ↙
- onset of Action : Formoterol is faster than Salmeterol
  because it's less lipophilic thus
  has rapid dissociation from receptor
  or it's entry to cells not very high
  and Potent activity

So ester Prodrug ⇄ Protect from COMT
⇄ better absorption
↘ long DoA

DoA ≈ 8h

B-agonist

B. 1 agonist

B_2

B_3

Dobutamine

Lung — in asthma & COPD

Uterus — ① ritodrine → for premature labour

Indirectly Acting or Mix.

Date

also

No.

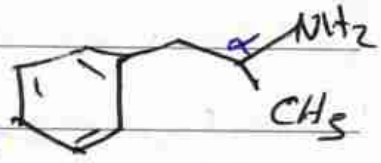
- Phenylisopropyl amine or phenylalkyl amine
- Phenyl Propanol amine
- Phenyl Propanol derivative

- Indirect Acting or
- mean Not acting directly on adreno receptor either α, β but it enhance release of endogenous NE

- These agent could be taken at the nerve ending by ~~beam~~ active catechol transport system (uptake.) and make replacment or displacement NE from these visicles and give sympathomimtic.

Phenylisopropyl amines:

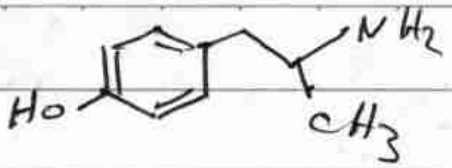
① Amphetamine (by MAO against metabolism)



- Presence of α-methyl give ~~Stability~~ and enhance ~~stability~~ penetration to CNS
- loss of OH on Phenyl and β-Position, loss its ability on direct acting and make it indirect acting
- ↑ release of catechol or Hone amine transmitter in CNS so its CNS Stimulant

Date. No.

③ hydroxy amphetamine :-



- Para OH → ↑ hydrophilic
  - ↓ lipophillic less than Amphitamine
  - make it indirect.

∴ Basic + ionizable less CNS stimulant
↓ CNS penetration, may give peripheral action as dilate pupil

2] Phenyl propanelamines :-

- has OH on β position.

(OH on β position are important for direct acting in correct geometry, presence OH in β position in phenyl ethyl amine ↓ indirect mechanism effectivness and ↑ direct mechanism.

⇒ correct orintation for β-OH ⇒ R ← ↑ direct, ↓ indirect

⇒ in opposit to α-CH_3 ← ↑ indirect, ↓ direct

- Presence of large substitution on N ↓ effectivness by indirect mech. but CH_3 is tolarible

N → 3° → ~~infe~~ inefffective as indirect

→ 2° → indirect mech

* There's 2 natural < ephidrine / pseudoephidrine

① L-(+) pseudoephedrine

• β-OH and α-methyl give 2 ciral center and 4 isomer → 2 enansiomer / 2 diasteroisomer

natural (-) ephidrine → levo tator → R-OH / S-CH_3 → has Mixed mechanism → Direct / indirect — correct position → OH r's

on opposite to (+) pseudoephidrine L isomer → S-OH / S-CH_3 incorrect orientation for OH. has just one indirect mechanism

erthro isomer

(+) ephidrine, erthroephidrine why called erthro ??
when H at the same position of 2 ciral centers.

Sympatholytic Drugs

Date. No.

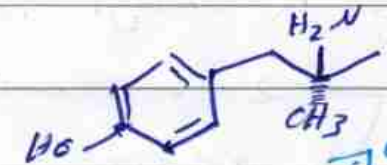
Adrenergic receptor Antagonists:-

Direct

indirect
- ↓ Synthesis
- Storage
- release

For indirect mechanism:-

Metyrosine:



→ affect CA's Biosynthesis

- affect life cycle of Neurotransmitter
- same methyldopa but lacks OH on position 3.
- Metyrosine has vital role in synthesis of catecol

tyrosin —hydroxylase→ L DopA —decarboxylase→ Dopamine —hydroxylase on β→ NE

- So we make Analogue to tyrosin → methtyrosin which is Methyl tyrosine that work substrate analogue
- So it inhibit any of 3 enzyme thus ↓ catechol

substrate competitive analogue
- tyrosin hydroxylase
- DopA decarboxylase
- dopamine β-hydroxylase

- Thus metyrosine compete with natural molecule for binding with enzyme ↓ CA syn.

Use: has counter current effect for agonist vasopressor so used for vasodilating and ↓ B.P in Management of Pheochromocytomas

Date. No.

⇒ affect CAs Storage & release:

1) reserpine

from Rauwolfia serpentine

Chemistry: indole Alkaloide

MOA:

Binds extremely tightly & irreversibly blocks VMAT → to transport of CAs cytoplasm into the storage vesicles → retained NE will be metabolized by mitochondrial MAO within cytoplasm.

- thus depletion of NE release in sympathetic cleft
- blood vessels will relax and dilate → ↓ B.P
- PNS, CNS, adrenal medulla and also depletes storage of serotonin and DA.

Uses as Antihypertensive but it has suicidal attempts and depression.

Other drug affecting storage and release of CAs.

Sympathomimetic ← aryl imidazolin derivative ← open imidazoline

pKa = 7 → can penetrate CNS

α_2 agonist centrally

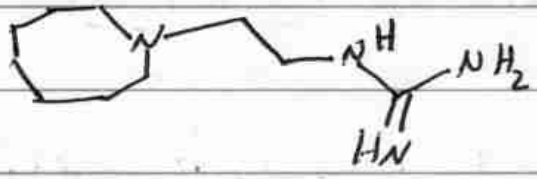
Date. No.

Drugs preventing Noradrenaline release from neuronal storge vesciles. and stabilize the membrane that store CAs. and when nerve impulse reach nerve. No release occure.

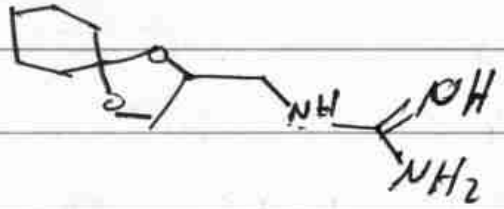
give Anti hypertensive effect

as

Guanethidine



Guanadrel



- These are very Basic (pKa = 12)
- highly ionizable (completly protonated
- No CNS penetration → peripheral
- use in hypertension.

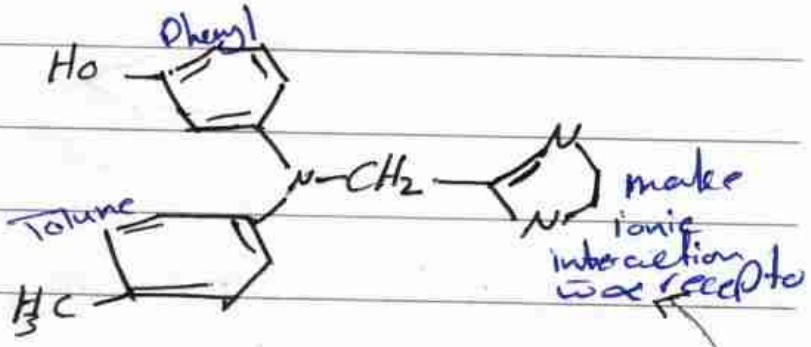
Not used , there is much more drug more safe.

Date. No.

① Non-selective α-adrenergic Antagonists

irreversible
- make covalent Bond
- called haloalkyl amines
- as phenoxybenzamine and Diberamine.

reversible
- as phentolamin Tolazoline.



① reversible

remember
- For Blocking α_1 → aryl alkyl Imidazoline
- For Blocking α_2 → aryl Iminoimidazoline

To make Blocking we need to
- ↑ Bulkiness and Lipophilicity.

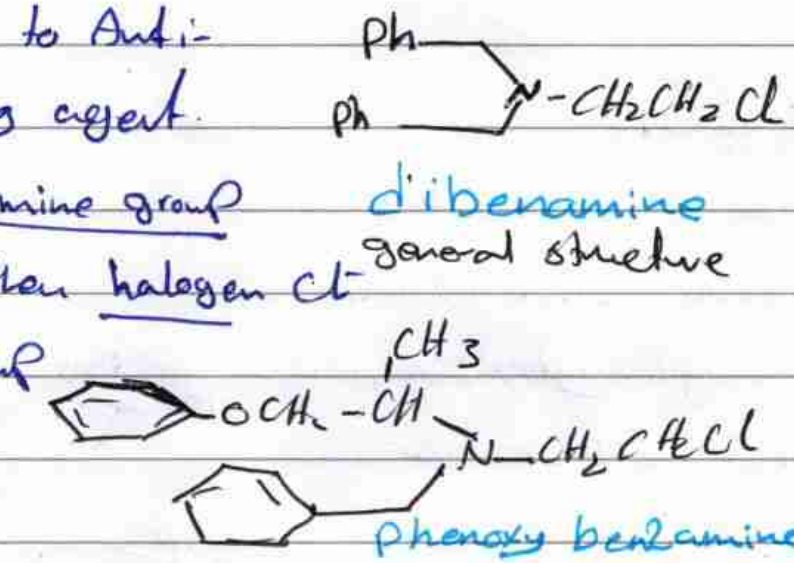
Phentolamine
we add another aromatic group on N, this ↑ Liophillicity and make Convertion from aryl imidazoline agonist to Bi aryl imidazoline Antagonist

Tachycardia S.E ; α_2 receptor Presynaptic Blocking lead ↑CA and cardic stimulation lead to Tachycardia
used for pheochromocytoma

Date. No.

② Irreversible (β-Haloalkylamine)

- dibenamine related to Anti-cancer drug alkylating agent.
- MoA/ depand on amine group Han ethyl bridge then halogen Cl⁻ as good leaving group



dibenamine general structure

Phenoxy benzamine

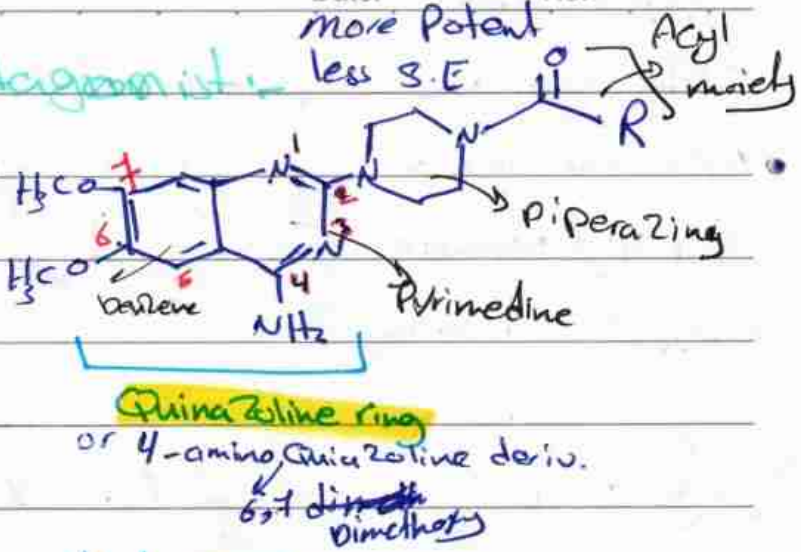
- haloalkylamine enable Drug to convert to active form Covelent bond forming Aziridinium ion.

- S.E / Tachycardia , ↑ C.O , hypotension miosis , Nasal stiffness

not use but use to diagnosis / tbt Pheochromocytoma

Selective α_1 Antagonist:-

New Drug
Date. No.
more Potent
less S.E



Quinazolines: derivative

- highly selective α_1 (Not acting on α_2, so No Tachycardia S.E)
- reversible

as/ Prazosin, Terazosin and Doxazosin.

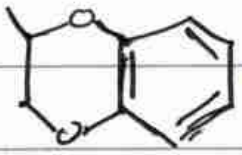
* Quinazolin ring: important for α_1 receptor affinity
* piprazine bridging: could have replacment to other hetero cycle moiety. as Piperidine

not very important just give suitable distance

* Acyl moiety: very important, has role in pkk prop. depending on R attached to Acyl

if R =  → Furan → Prazosin. short DoA

R =  saturated → Tetrahydrofuran → Terazosin long DOA

R =  → Dioxan ω benzen benzodioxan → Doxazosin Longer DoA

All day

has 2 major Clinical Application:

① Antihypertensive mild, Moderate ② For BPH

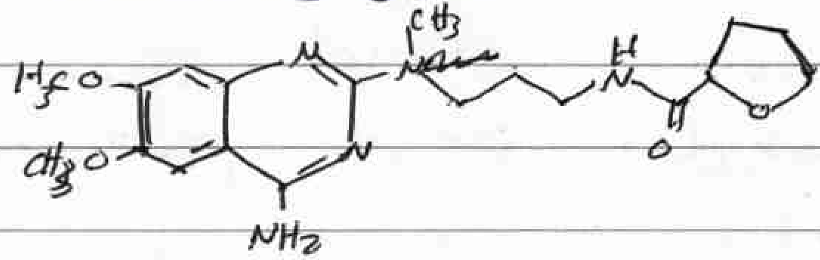
Quinazoline ج.ح

/

Alfuzosin

Alfuzosin has open piprazin ring system

- replace piprazin → with propyl diamine
- propylendiamine.



Note: Drug. Derived from 4 amino Quinazolin has azo — prazosin → selective α_1 antagonist

prazosin, Terazosin, Doxazosin ← α_1 selective Antagon من الجيل الأول :: يستعملوا لـ hypertension, BPH

especially long acting as Terazosin Doxazosin

S.E → syncop, orthostatic hypotension; has 1st dose phenomene ; due to α_1 blocking that lead to sudden, sever fall in B.P especially when rise up; or 1st dose effect

exist as sustained release — نفس استخدام الأدوية الـ ٣ السابقة

لكن الاختلاف عن Alfuzosin هذه الأدوية تستخدم to ttt BPH ∵ lower effect on cardic system.

at bed time يعطى . initial low dose تبدأ بجرعة

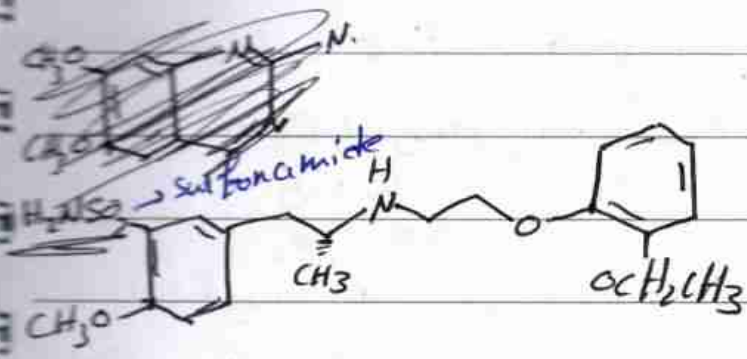
or CAs derivative / Analogue

Phenyl ethyl amine derivative analogue

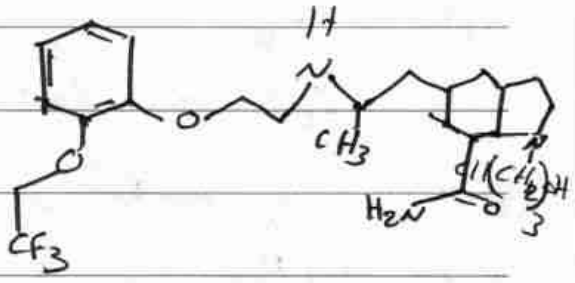
Date. No.

most selective

Tamsulosin α_{1A}



Silodosin ⇒ α_{1A}



- These agents has more selective on α adrenergic in Bladder neck and prostate with thus become more specialize to BPH and less to B.P and lower 1st dose effect.
- Note: Not use for HTN.

we said that if we put aromatic ring on N in Phenyl ethyl amine give Antagonistic (α Blocking)

- we Back to CAs Analog / Phenyl ethyl amine in try to be more selective

α

- α 1A
  - in prostate
  - Bladder neck.
- α 1B
  - major in Blood vessels
  - when Blocked → vasodilation
  - for Antihypertensive

→ sulfonamide

Date. No.

Tamsulosin → α selective

- phenyl ethyl amine or CAs sulfonamide drivative
- has lipophillic chain on N [ethoxy phenyl + ether] give selectivity ↓ and Block α_1
- give α_{1A} activity.
- For BPH ↙ So
- on aromatic ring there's 2 group hydrogen Banding
  - → H_2NSO_2 → sulfonamide
  - → CH_3O → vital for H.B

Silodosin

- The most selective α_{1A} receptor in Bladder neck, prostate
- low S.E
- For BPH
- has 2 H.B → NH_2 → astoste of sulfonamide
  - → pure N → amide
- aromatic → indol carboxamide
-

α_{1A} selectivity silodosin > Tamsulosin > Alfuzosin

BPH ↑ ↓ ↓

Date. No.

α_2 Blockers:

Yohimbine (natural)

- indol alkaloid
- ↑ H.R ↑ B.P, has central (CNS) effect
- used to treat male erectile impotance.

Mertazepine (synthetic)

- Tetracyclic
- Same to Tetracyclic Antidepressant.
- ~~too~~ act α_2 presynaptic → Blocked → ↑ NE release, ↑ serotonin
- Anti depressant (mainly)

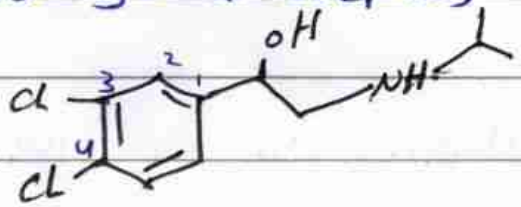
has phenyl ethyl amine System

B- Blocker

Date. No.

Use to → Antihypertensive
→ glucomer
→ Anticarythmeat

- B-Blocke Antagonist was developed by B_2 agonist isopretenol which have selectivity on B receptor, due to isopropyl on amine.

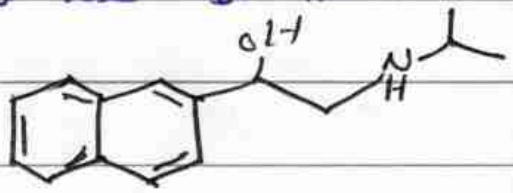


① Dichloroisoproterenol (DCI)

- isoprotenol analoge
- oH in 3,4 displace more Lipophillic Cl
- So oH is removed which was important for agonistic effect
- and become from Full agonist → partial agonist and ↓ intrinsic activity.
- Full Antagonist

Lipophillicity

② pronethalol



- napthaline
- has Antagonistic activity
- has lowe intrinsic activity.
- not used → tumor in Animal

Date. No.

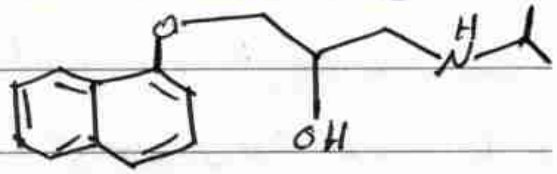
Save ← pronethalol ← Potent B-Blocker

① change substitution position from 2 → 1

② and put distance by methoxy group or oxymethylene

∴ in Binding site we save → Position N that ionic interaction

→ OH that make H.B



propranolol

- 1st effective compound
- potent Antagonistic activity
- No carcinogenic effect as in pronethalol
- Save and potent drug.
- Aryloxy propanol amines → B-Blocker تكون فيه
  - → 2 Aryl → lipophillic important, important for Blocking + Binding
- non-selective
  - B_1 → Anti arrythmeic, Anti-hypertensive
  - B_2 → cause Asthma
- adding methoxy group convert from aryl ethanol amin → aryloxy propanol amine

This ↑ Potency and remove carcinogenicity

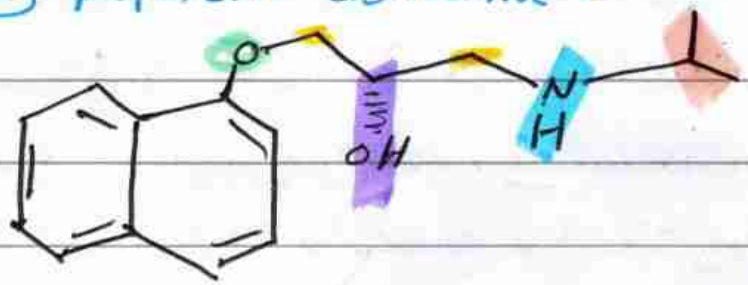
SAR

B-Blocker

Date. No.

→ prototype

SAR for propanolol as lead for B-Blocker or aryl oxy propanolol deivcative :-



- 2° amine is important for activity, affinity for ionic interaction
- Branch alkyl group very good for Antagonistic (3° butyl or isopropyl direct to B-receptor).
- OH important for hydrogen bond as in agonist
- substitution on 2 carbon of propanolol should not be present or it low activity.
- O in ether are important for hydrogen Bonding
- naphthelin → Bulk group important for hydrophobic interaction and Antagonistic activity.

---

① nature of Aromatic ring ② substitution which primarly determinant for β_2 Antagonistic activity.

and ③ Position of substitution

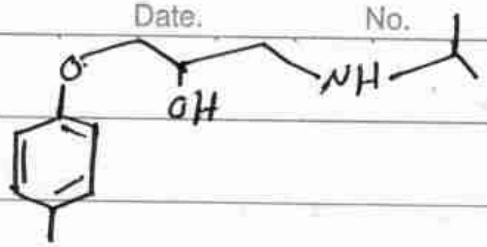
- Beta agonist
- selectivity ← B_1 / B_2
- PhK + PhD
- Physicochemical property

161

Aryloxy propanol amine

Date. No.

Practolol



- Chiral substitution on aromatic ring
- If aromatic ring has substitution on para position and its size is not too large subicunt this result in selective B-Blocker.

So

- presence of Para substitution w suitable size without meta substitution give selective B1 Blocker (cardioselective)

But.

- if substitution on meta / ortho position without para position result in non-selective B-Blocker.

- So Practolol is selective β_1-Blocker. cardio selective
- amino group is 2° for optimal activity
- due to its S.E is not used there is much more saver agent

* Note: Propanolol has CNS S.E higher than practolol? Propanolol has high Lipophilicty log P > 3 . While practolol log P < 1 , this relativity make propanolol more lipophilic, more pentration to CNS → CNS S.E Por ex Fatigue, sleep disorders, lethargy, depression, night mares hallucination

Date. No.

Note

- aryloxy propanolol amine higher potency than arylethanol amine as protanol v.s propranolol

- stereochemistry affect activity

OH must have proper orintation to make H.B

in case of CAs → R active form.

OH of CAs + B. Blocker → same orintation (R) ~~less~~ risk

But For aryloxyamine

active form is → (S) 100 Fold > R

Don't differ but due to presence of O atoms that has high priority

B-Blocker

- Nonselective: propanolol
- B_1 selective: practorolol
- B.Blocker + α_1 receptor

Date. No.

Non selective β-Blocker :-

① Propranolol

- prototypical β-adrenergic receptor antagonist
- non-selective
- CI in patient w Asthma
- ↓ CO. ↓ renin releas in kidney ⇒ Antihypertensive
- uses used as
  - Angina pectories . Antiarrythmic . Antihypertensive
  - MI . prophylaxis migrain . Anti-Anxity.

due to its ↑ lipophilic $\log P > 3$

~~Key CNS S.E~~ ~~Calming~~

- due to its lipophilicity → cleaved by liver to be more hydrophilic so need dose adjusment in Liver disease

② Nadolol

- less lipophillic so major clearence is by kidney

- ③ Pindolol

Date. No.

Ex of non-selective β-Blocke

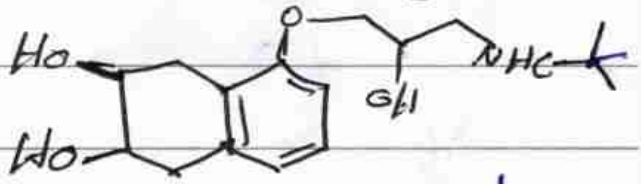
need general requirement of SAR's

① Aryloxy group

② Propanol amine group and (2° amine ~ 3° butyl / isopropyl)

③ lipophilic substitution (Para / meta) to know its selectivity.

② Nadolol



Same to propanolol → live clearance

just diff from naphtalin → tetrahydronaphthalin do.

~ 2 OH that ↓lipophilicity & ↑hydrophilicity

result in lower CNS S.E

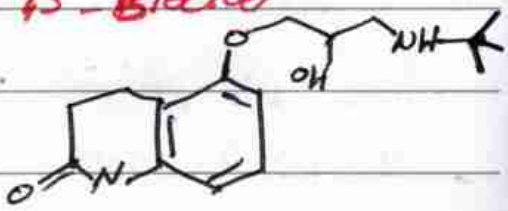
- Shift clearnes. live → kidney. unchang in urin

- So it has longest $t_{1/2}$ not metabolism by live ≈ up to 20 h.

- no substitution in

Para position so its non-selective β-Blocker

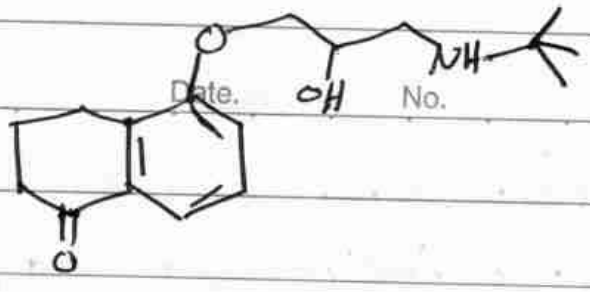
③ Carteolol



- No Para sub. → non-selective

- partially saturated Quinoline ring system.

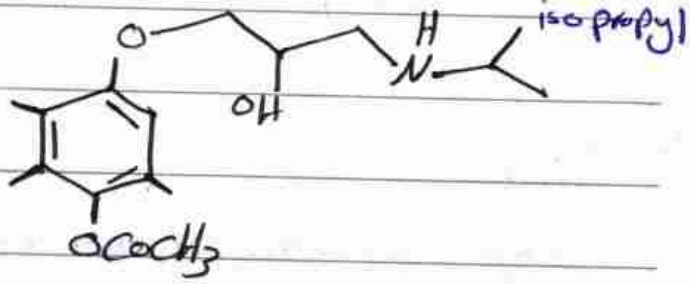
④ Levobunolol (3° butyl)



- No para substitution

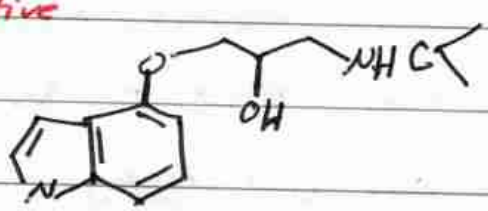
non selective β-Blocker

⑤ Metipranolol (isopropyl)



- Has 2 methyl group on meta position.
- ester subs. on para position → este ↓ DoA
- ∵ meta + para → non selective

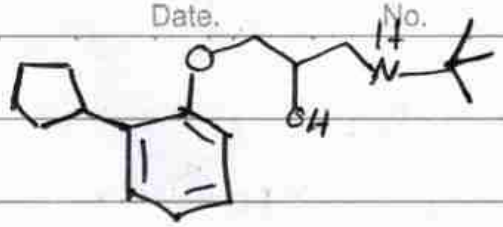
⑥ Pindolol (isopropyl)



- indol derivative
- Lipophillic without para substitution → non-selective.
- has intrensic sympathomimtic activity mean acts as partial agonist. ~~An~~ and Partial Antagonist and ch.ch that not cause sever cardic depression. So could be use in patient with Sever Bradycardia becaus it not slow heart totally and has membrain stabilizing activity which could be use in Arrythmia & add on drug for depression; Block 5HT$_{1A}$ so could be use in combination ~~with~~ SSRIs

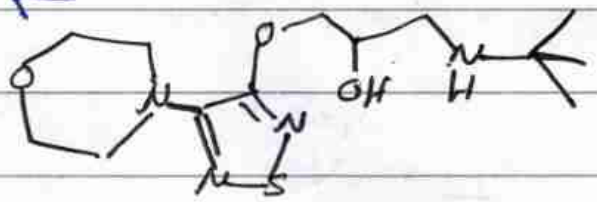
Date. No.

⑦ Penbutolol → cyclopentyl, → 3° butyl



- substitution on ortho not para

non-selective β-Blocker



⑧ Timolol

- isostere replacement for Phenyl to Thiadiazol
- ortho substitution → non-selective. (morpholin ring system)

β_1 - Selective Blockers :- cardioselective

- has affinity to β_1 in heart more than other tissue
- This give many advantages :-

① absance of Blocking on vascular β_2 receptor (β_2 cause vasodilation) so if Blocke ↑↑ prephiral resistance which countercurrent Anti-hypertensive effect of β_1 Blocke and ↑ preload and afterload thy resist it's good effect on heart so it ↓ prephiral resistance result from non selective and Blocking of β_2.

② good for patient w Bronchial ~~Asmtic~~ Asthma ; Blocking of β_2 → cause Bronchoconstriction

③ in case w priphral vascular diseases, β_2 Blocke met. vasoconstriction

Date. No.

potential in case ↓ DM, B_2 has role in regulation of Glucose level.

* given more than non-selective; due to its benifite.

- Ex of selective B_1 Blocker:

SAR :- all are aryloxypropanol amine derivative

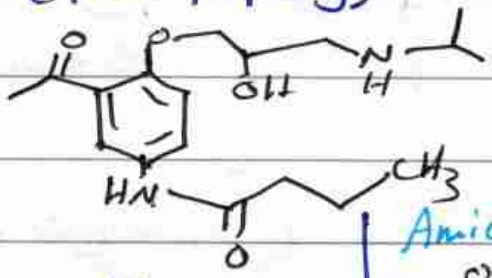
↓ Branched subs on 2° amine

- all has subs. on para without meta, which give indication on its selectivity.

- we can change DoA of Drug by change nature of substitution on aromatic ring. (Phk property)

* Acebutolol

5 Acetyl



- has ortho, para → selecti

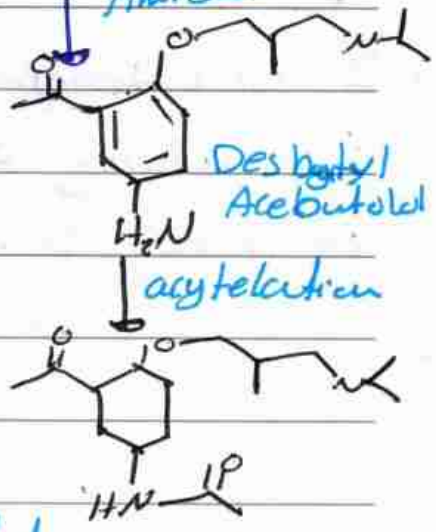
- in para → has amide (butanoic acid)

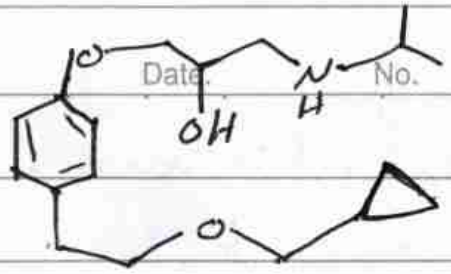
- has 1st pass effect metabolism

hydrolysis of amid group by amidase enzyme result in Desbutyl Acebutolo then acytelation occure → Diacetolol

which is active metabolite B_1 selative

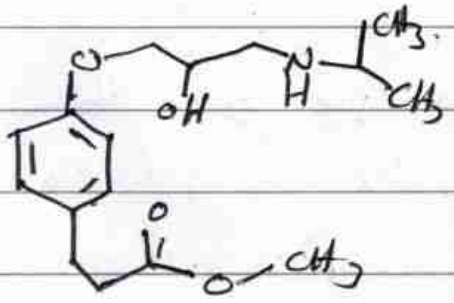
has longer $t_{1/2}$, partial Agonistic effect





② Betaxolol

- has ether on para position
- Lipophilic chain
- the longest $t_{1/2} \approx 22h$



③ betaxolol

Esmolol

- Lipophillic esto group make H.B.
- ~~esto~~ has Terminal ester so it's varuneble to metabolism and very rapid clearnce by esterase
- Very short DoA. called: Soft or Anti Drug. $t_{1/2} = 9$ min

Soft drug X Prodrug

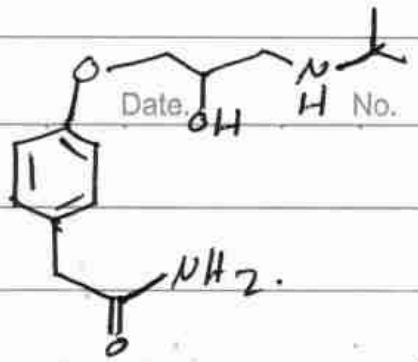
active outside, inactive inside ← | → inactive outside, active inside

- So it convert to carboxylic Acid de. ⇒ inactive

DoC used as infusion in emergency, Surgury to short term controlling of heart as Antiarrythmic Drug. to control ventricular H.R, in atrial Fibrillation or Sinus Tachycardia.

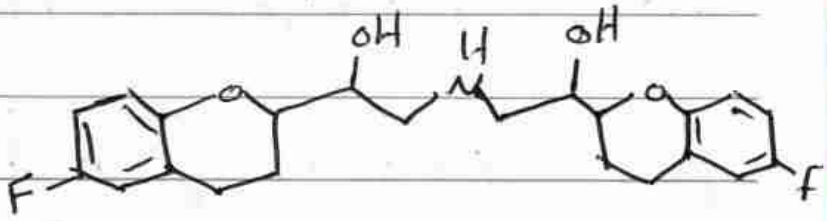
Date. No.

Atenolol



- amide in para position

Nebivolol



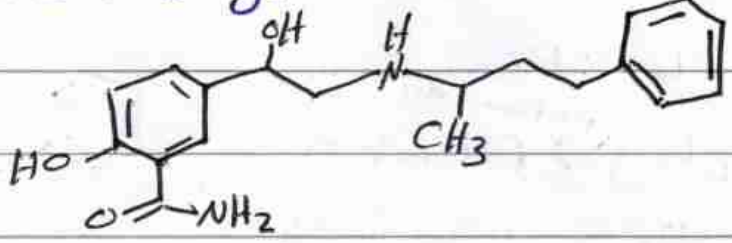
- aryloxy → propanol do pyran system
- 2 copies. mirror image.
- para position → F.
- ortho position → cycle ether. not affect selectivity
- B_1 selective
- large group subs.
- Block B_1 + potentiate for Nitric oxide effect (NO) thus lead to vasodilation. → good for Anti-hypertensive effect.

Date. No.

β-Blocker with α_1-receptor Antagonist or Dual β & α_1 Blocking activity:-

effective Antihypertensive Drugs.

Labetalol

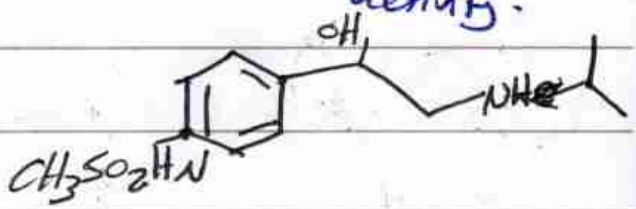


- non-selective on β
  - ↳ meta + para substi
- very large Lipophilic on N give α_1 Blocking.
- aryl ethanol amine derivative

Carvedilol

- No Para substitution → non-selective β
- benzo indol derivative
- ~~Tri~~ Tricyclic lipophilic system Carbazol ring system
- aryl oxy propanol amine
- N. substitution as in Tamsulosin give α_1 Blocking activity.

Sotalol



- ~~Para substitution~~ بدل Para Position
- ~~aryloxypropanol~~ aryloxypropanol amine

This drug is not aryloxy ~~propanol~~ deri but it's phenyl ethyl amin or aryl ethanol amine. Para بدل meta

- non-selective β-Blocker
- effective anti-arrhythmics

Date. No.

used in tht of Atrial Fibrillation and Ventricular arythmia ; ~~also~~ ~~B~~ adding to β- Blocking activity it also has ability to make K^+ & enby Blocking thus delay cardic reporilizetion. and ↓ arythmia

so it has Dual MoA.

* synthesis of aryl oxy propanol amine derivative.

2 step

① naphthol + epichlor hydrine → alcohol ether de. of naphthalin

② make other RNH with nucleophil to give isopropyl part

ACEIs

تأخر اكتشاف Renin عن اكتشاف RAAs أول وآخر اكتشاف

Date. No.

- How discover enzyme inhibitors : as ACEI,
- knowing of enzyme action.
- knowing how substrate binds to enzyme, aid in making substrate analoge which can block and acts as competitive inhibitors.
- Knowing Transition state
- because enzyme work as catalyse in chemical RXN

  substrate ⟶ product

  ~~ACE~~ Angiotensin 1 $\xrightarrow{ACE}$ ANigotensin II
- during converting substrate to product it pass through transition state which need stabilization
- sometimes we make inhibitorse same to product and sometimes related to ~~product~~ substrate, Transition state.
- if we able to make Transition state Analoge inhibitors usually result in very potent inhibitors.

  (usually we can't know Transition state ; unstable, in very short t1/2 and move rapidly to lower state or product).

Date. No.

⇒ some interaction could be done that can replace substrate and make Blocking for Active site and prevent hydrolysis of Angiotensin 1 or Blocking binding of substrate Angiotensin to ACE or

① Need Acidic group that make strong ionic interaction with Basic Amino Acid as Arginin (Arg^{+})

② Lipophilic interaction to S_2

③ H.B group close to carboxy group terminal

④ 2ed lipophilic group on S_1

⑤ inhibition for metallo enzyme ACE, by to Zn through Binding Zinc (Zinc Binding group)

⑥ Lipophilic group to S_1

So those are requirement or Functional group that must be exist to give potent ACE Inhibitors.

What is requirement for any inhibitor
or what functional group should be exist to let it
make inhibition for substrate Analogue

Date. No.

Substrate Analogue Model

from data that benifit from ACE Is, is that
- ACE is carboxy dipeptidase
- and inside body there's many carboxypeptidase
- Carboxypeptidase A1 is zinic metallopeptide and ~~not~~ acts in same pathway of ACE
- also they benfit at their understand of enzyme of inhibitor of carboxy peptidase A1 in making ~~carboxy~~ inhibitor for carboxydipeptidase ACE.

The only difference is that
carboxy dipeptidase break 2 A.A
and carboxy peptidase break 1 A.A
in sum MoA Zn catalyses

=> lead compound (or starting point) is Succinyl proline: from
① carboxy peptidase and its inhibitors from venom
② nature of substrate Binding (Angiotensin)
but succinyl proline has lower potency

↓ dose used ↑ selectivity ↓ S.E

Date. No.

⇒ optimization of lead compound : (↑ potency)

- proline → Lipophilic interaction not strong
- H.B

succinyl Prolin
weak activity

Then Zn Binding group

(we said here is S_1, S_2, S_2 lipophilic group)

here in succinyl proline there just one lipophilic

⇒ So we add small Lipophilic group CH_3

methyl succinyl Prolin.

methy succinyl Prolin

↑ Potency improve activity

How to reach Max. potency??

- carboxyl ⊖ Zn are not ↑ strong interaction
- Carboxyl is ionized inside body and ↑ hydrated and to bind to Zn need dehydration which need energy absorption and form bond and total energy of Binding is low that affinity.
- So replace carboxyl → sulfhydryl then nanopeptide in Snake Venom improve activity more

tight Bind ⊖ Zn

Potent ACE Is ⟹ Captopril

↳ S.E due to sulfhydreal

- metalic taste, loss of taste.
- sensitization, ↓ Patient Compliance
- short DoA; rapid metabolism

Date. No.

so after reaching required potency, we can modifie phk, phD property.

2ed generation

- SH group make S.E as in penicillin amin so there's need to change it that give potent binding but without captopril SE.

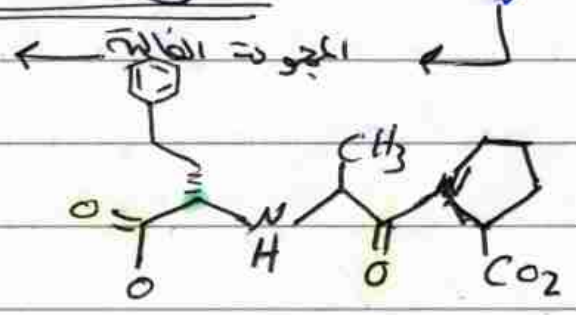
This lead to appearnce non-sulfhydryl containg ACE Is

They back to carboxyl ↓activity good binding not tight bind ∝ Zn / No S.E

but if we add another Lipophilic interaction that compansate weak binding and give potent ACE I.

as in Enalprilate (Dicarboxylate ACE Is)

- once daily ↑ DoA
- ↓ S.E
- ↑ compliance.



- enter amin group as a A.A for glycin w benzen and save phenyl ethyl group to make lipophillic interaction
- make carboxyl insted of binding to SP_2 ⟶ SP_3

Date. No.

So to compensate weak activity we add.

-phenyl ethyl group

thus we have • lipophillic interaction done by [Pyrrolidine] methyl CH_3 / Phenyl ethyl

• ionic interaction from carboxyl that make tight binding to Zn.

potent ✓ ↓ S.E ✓

Note

Both Succinyl prolin & captopril consider as dipeptid product

but Enalpril Consider as Transition State Analyse.

or lisinopril → Dicarboxylate peptidase.

Summerizing for SAR :-

① aliphatic ring containing N, not aromatic ring and this ring must have COOH

نكمل في المحاضرة

Note. Phosphinat $-\overset{OH}{\underset{O}{\overset{|}{P}}}-$ هذا اللي بستخدم / Phosphonat $O-\overset{|}{P}-O$ Phosphate $O-\overset{|}{\underset{O}{P}}-O$

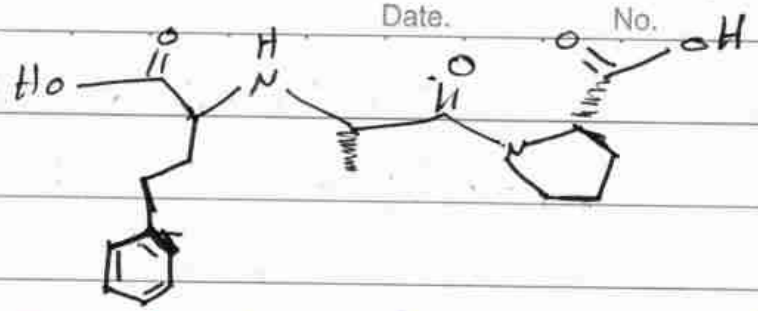
⇒ Ex on ACEIs — SH ACEI sulfahydryl ACEI; $\overset{CO_2H}{CH}$ Dicarboxylate ACEI; $-\overset{OH}{\underset{O}{P}}-$ Phosphinate ACEIs.

① captoprile

Transition State analogues : as Enalpril
• ↳ usually more potent than substrate / product
Analoge as capotpril
• Zn^{+2} binds to $\overset{O}{C}$ and withdrawal its ē
then OH attack the $\overset{O}{C}$ lead to tetrahydral
c insted of triangul (intermediate unstable e
syitem due to N, O, OH all are withdrawed)
• rearrangment is occure double bond is formed
and beak NH bond and cleavege peptide.
but in enalpriliate
we add another carboxyl, thus tetrahydral
C hold carboxy that bind to Zn group.
This called transition state. that convert to product
potency ↑ due to
① ↑ Liophillic interaction; by adding phenylethyl group
② add another carboxyl that make tight Binding to ACE

Date. No.

② Enalapril



- Dicarboxylate ACEIs
- has many ionic group
  - ① main COOH in (S) Geometry to make optimum binding to Zn and mimic natural A.A
  - has 3 Chiral center (S,S,S) correct Geometry.
  - ② NH ; so could use as injection
  - Enalaprilate is highly hydrophillic to make it oral available need to convert to prodrug.

3 group cause ↑ hydrophilicity & Lipophilicity

- COOH on Prolin
- NH basic COOH
- COOH Zn bind group.

- need make masking to one of them as Prodrug need most hydrophilic one and most affect hydrophilicity
- Pick group that it's easily synthesis which is COOH ester that breaked by esterase enzyme.

So which to pick ← COOH on Prolin ؟؟
COOH Zn Binding

- which has more hydrophilic ؟؟

COOH Zn Binding is more hydrophilic & pKa than COOH on prolin

Date. No.

When convert COOH in Binding to ester.
improve lipophilicity and oral bioavilability
- by masking most hydrophilic group COOH pK very low
- and when COOH is free is found that NH pKa 7>8
high Basic, very ionized and when make masking
pKa of N is reduced pKa = 5.5 ↓ ionization.
So COOH ↑ basicity of NH_2
and NH_2 ↑ acidity of COOH
This make intramolecular interaction and stabilization

Date No.

Lisinopril has oral absorption, not prodrug

- only Exception that doesn't need prodrug.
- Note [we said that bond bw CooH and NH is called Alanin A.A]
- if replace Alanin A.A → lysin A.A (butyl Amine side chain instead of methyl)

this lead to potent ACEIs.

- and not need to convert to prodrug, it has orally active Bioavailability
- This is due to
  - 2 Basic group (2 N) ⊕
  - 2 CooH group. 2 ⊖

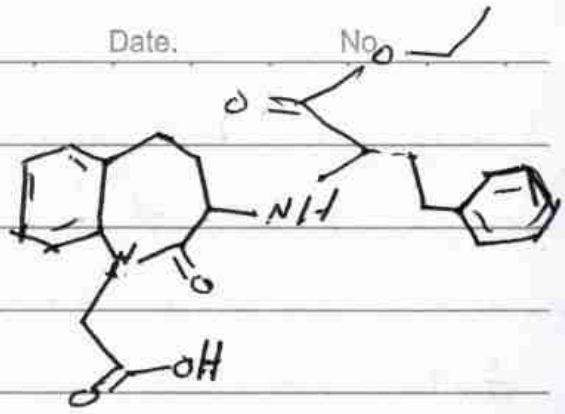
  ] Disphite ion intramolecular neutralization thus enhance it's absorption.
  - thus lead to ↑ absorption

Other prodrugs of Dicarboxylate ACEIs venom no ← Prolin der.

- before it's Prolin derivative (from venom).
- if we ↑ Lipophillicity and use large cycle contained N give more Lipophillic interaction and potency ↑DoA, once daily bbb thus cheap Phk & phD

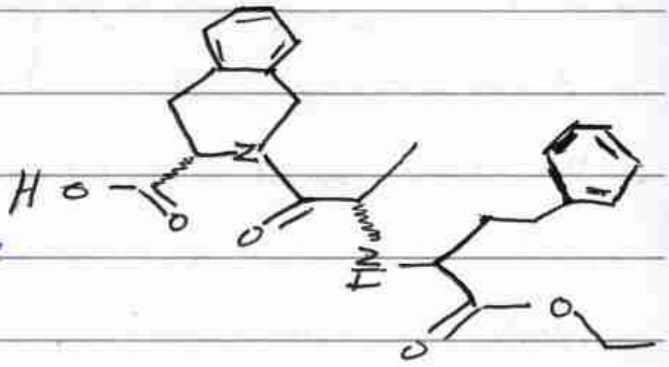
Date. No.

Benazepril → ACE Is



- Benzazepine ring
- we said cooH must exist in ring contained N
- other E for HMB
- 2n Binding group esterified → prodrug
- ethyl phenyl group
- more potent than Enelapril

Quinapril



- partially saturated isoquinoline
- ↑ lipophilicity
- near to N must be cooH
- ester prodrug

Fosinopril

- add cyclohexyl prolin on position 4
- phosphinate group and carboxylate make it poor oral Bioavailability thus need → prodrug

So

Fosinprelate (active drug) ← Fosinipril (Prodrug)

Date. No.

- instead of making direct ester on O → hard hydrolysis due to presence of bulk group on right + left thus esterase can't approach to it.

so make <u>double ester</u> as carbonate ester + isopropyl ester

- prodrug Fosinopril has the most hydrophobic in ACEIs, Logp = 6.5 ← cyclohexyl prolin, phenyl butyl group

ARBs

Date. No.

AT_1 → Angiotensin receptor 1
↳ is a g-protein coupled receptor
↳ Angiotensin II is an octapeptide

الطريقة الاولى نعمل Peptide مشابه هو تغيير بعض AA
↳ Ex/

- Saralasin

Differ from Ang II by 3 A.A < 1st, middle, last

main problem common Draw back of peptide as Drug
↳ No oral Bioavailability
↳ Neurogenic → ⊕ Antibody release
↳ Short DoA
↳ Partial week agonist not Full Antagonist
  ↳ قد تعمل لو كان القلق ↓ Level of Ang II
  lead to ↓ B.P

• لكن لو كان عنده Lower Angio II level
lead to ↑ B.P → hypertension

Date. No.

In Drug Discovery, when there's target most easy is to syntless peptide Analyse

replace phenyl alanin → Alanin

valin → isolusin

Terminal Aspatic Acid → ~~Sarcosin~~ Sarcosin

due to its S.E ← bad oral bioavilability
short DoA
Partial Agonist Activity.

The need to Synthesis small organic molecules that have → good oral Bioavilability
→ good Potency
→ good PhK + PhD

They found molecule that have 5- Imidazoline Acetic Acid.

These are starting point has week but selective ANG II.

- priority is for ↑ Potency.
- best effect is when add acidic group on para position. this is 10 time better then befor lead compound.
- so Imidazolin 5- Acetic Acid

Date. No.

To understem SAR → what is basic Function group that must be exist to get high affinety binding to AT1 receptor.

1st we have to understand Ligand Binding thus we will know basic groups that must be exist in inhibitors !!

in 2D structure :

- it's ANG II
  - has Acedic teminel stat w phenyl anatin than prolin then histidin then isolucine, tyrosin, valin, Arginin, Aspartic Acid. [octa peptide]
  - it's recognize that there's 4 or 5 sites that are essintial Binding & give high affinty for Binding AT1
    - ① Phenyl alanin → benzen ring → lipophillic interact
    - ② in ortho positin → Carboxy teminel in phenyl alanin For Ionic interaction
    - Then space / Distance
    - ③ lipophillic group → isolucine
    - ④ imidazolin ring → H.B → Lipophillic interaction

These groups if compared to losartem

186

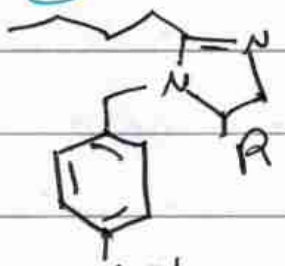
Date. No.

- in Losartan
  - → Terminal Phenyl system, in ortho position tetrazole (in Biphenyl system)
    in losartan (represint phenyl alanin and its carboxyl) are important for lipophilic interaction and ionic interaction
  - → middle Phenyl group can make lipophyllic interact but it acts as spacer bw Imidazol / phenyl ring
  - → Tetrazole or carboxyl must be in ortho position. To make optimum ionic interaction.
- 2 group above represent → Phenyl system
  - ortho position represent → imidazol
  - → imidazol represent prolin
  - → substitution on Imidazol < Cl / alkyl ethe → repre → isolucin mark Lipophillic inter.
  - → H.B group OH on Imidazol aids in tight Binding. in ortho must < Lipophillic H.B group < OH Acetic group
  - →

Date. No.

By comparsion bw losart / Arg
we know what is key / hot spot that must be exist to make potent inhibition.

SAR for ARBs



Acidic group

- Imidazole has substution on ortho (ethyl / Butyl)
- benzyl → has Acidic group on para

① Acidic group on ortho Phenyl para Need affinity and activity, mimic carboxlic group of Terminal A.A Phenyl Alanin which make ionic interaction

For Acidic group

To make ANG Blocker has 3 properaty

① Carboxyl directly connect to para of 1st phenyl

② ↳ as in lead compound 6155 >>> 6803

[But the best is to have biphenyl system and Acetic group binds in ortho in 2nd Phenyl

This ↑↑ lipophillic ↑↑ Potency more than 1 Phenyl system and have have 2 properclity of

① COOH

② tetrazole [has advantages in ARBs → ↑ Lipophillicity < oral Bioavailability stability metabolic]

188

Date. No.

For Imidazole :

- equivelant (mimic) to Histidine (in ANGII) this give (lipophilic + H.B)

Substitution on Imidazole :

- at position 2 → Lipophilic (butyl chain as in Losartan) (propyl / ethyl) make hydrophobic inte and mimic isoleucin AA in ANGII

* most site has variability position 5 .. could be

① carboxyl direct to Imidazol
② Acetic Acid CH_2COOH
③ methyl Alcohol CH_2OH
④ Keton
⑤ benze imidazol ring.

→ These group has ability to make . ion dipole interact
. Dipole - Dipole interact.
. H.B or ionic interactio.
in general polar group.

Ex/

1- losartan 1st discover

. has 3 main groups :

- Biphenyl system → Lipophilic interaction
- tetrazole → Acidic ionic interaction.
- Imidazole +sub. → lipophilic.

irbesartan > Telmisartan

in oral Bioavilabd

Date. No.

② Telmisartan has 2 benze imidazole.

- benze imidazole ⇒ lipophillic inter.
- unlike benze imidazole ⇒ H.B formation
  → very hydrophobic
- has oral Bioavilability (highest) + irbesartan >60%
- if we make on ortho position in Biphenyl system tetra zole this ↑ lipophillicity + ↓ water solubl
  (Acidic group

thus Problem in oral bioavilability

- Only Drug that have cooH Acidic group in Biphenyl Not tetra zole

cooH give: not metabolic stable ionic Pka 3-4 completly ionized
tetra zole → Pka = 6
hydrophillic
low oral bioavilabl

→ but in Telmisartan is preferred; due to presence of many aromatic ring that make drug very lipophillic thus give lipophillic – hydrophillic Balance that aids in distribution or dissolution inside body.

190

Date. No.

③ irbesartan: highest lipophilic, 60-80% oral Bioavilabl

- has Biphenyl system
- ~~Ethanol~~ tetrazole as Acidic group in ortho
- Imidazole in position 5 equivelent ~~OH~~ in Losartan to make H.B.
- butyl lipophilic interaction
- very lipophilic not contained ⇔ COOH

④ olmesartan:

- Biphenyl tetrazole → on ortho
- Imidazole → on ② has COOH ↑ ionizable group → ↑ hydrophillicity
  - or ④ Propyl alcohol →
- ↓↓ Lipophilic

↑ affinity ↓ oral Bioavilability need Prodrug to improve Bioav. oral

⑤ candesartan:

- Biphenyl system (tetrazole on ortho)
- benzimidazole has COOH → H.B → ↓ Bioavilabil
  - ethyl ether → Lipophillic

* losartan & valsartan ⇒ ↓↓ affinity

affinity olmsart > candes > val > lost

Date. No.

⑥ Valsartan Valin not Imidazolin derivative

- only drug not have Imidazole ring system
- has valin A.A. ⇒ This ~~Why~~ called Valsartan
- valin make Amide bond ω butyl chain
- COOH → H.B / ionic ↑ affinity but not as olmisart / candesata as it equivelant to Imidaz. ring and isopropyl make lipophilic interaction.
- Eprosartan:

~~Only~~

- Theres No Biphenyl system.
- has Imidazolone + Lipophilic chain
- COOH → ionic / H.B

has Thiophen ring to compansate Lipophilicity of Biphenyl system

- Acidic group (2 Phenyl) thus in para position

Somtime need prodrug to ↑ lipophilicity and improve oral Bioavilability and go to group that mostly affect hydrophilicity and make masking

Renin inhibitors

Date. No.

- Renin is rate limiting step in RAAs system
- 1st enzyme in RAAs cascade.
- Why go to ACE I ARBs then Renin ??

① nature of renin substrate & active site of renin make discovery of renin system is hard

why its important ??

① Renin is rate Limiting step

② Renin has Biochemical selectivity (not have any other role in Body thus ↓↓ S.E)

③ if we inhibite ACE it will prevent conversion

Ang I → Ang II

↓↓ of ANGII make Feeback mechanism and ↑↑ level of plasma Renin conc. and thus more conversion of ~~Ang I → Ang II~~ Angiotensinogen → Ang I and when ↑↑ ANG I make Partial overcome for inhibition of ACEIs and cycle move on even if there ACEIs.

So when make Block ACE there's compensate ~~step~~ step counter ACE effect

also when Block ARBs = = = → ARBs

Date. No.

→ because Renin is enzyme and inhibition is needed we as known need to make substrate Analogue which is Angiotensinogen that's large protein > 400 A.A thus have very large Binding site !!
this way having Difficulty in Discovery

Dual Angiotensin receptors - Neprilysin inhibitor (ARNIs)

- Entresto (mixture solid)
is 2 Drug co-crystallized complexed contained Sacubitril + valsartan in a 1 - 1 molar ratio
- Sacubitril → neprilysin inhibitors.
- Valsartan → ARBs

* Sacubitril

① Same to valsartan in that it contain Bi-phenyl system but valsartan contain in ortho position Acidic group tetrazol
- Acidic group is not essintial for ARNIs
② Both has Amide Bond, but sacubitril has 2 Acidic group (COOH, COOH) has 2 ionizable group

Date. No.

- So need to make prodrug → Sacubitril (from Sacubitrilate) ethyl ester prodrug to ⊕ oral Bioavailability

- Sacubitril (prodrug) —hydrolysis of ester→ Sacubitrilate.

- So in chemical comparsion:

- Chain has 2 Acidic group vital for activity (Sacubitril) while in valsartan has 1 Acidic group (could be replace) also Biphenyl (but has 1 essential Acidic group tetrazole)

- Entresto is contained powder for Both (valsartan / Sacubitril) in 1-1 ration in which it contained usually:-

6 molecule of Sacubitril | 6 molecule of valsartan | 18 Na | 15 H_2O

* What is Neprilysin ??

- when there's overload on heart, muscles of heart Atrum releas vasoactive compound atrial Naturtic Peptide (ANP) its goal to ↓ preload and after load on heart by ↑ excreation of Na^+ / H_2O, ↓ Blood volum. ↓ load on heart

Date. No.

Thus ANP X RAAs.

- ↑ Na/H2o excretion
- ↓ Blood volum
- ↓ Blood pressure
- ↓ Sympathetic tone
- ↓ release of Aldosteron
- Vasodilation
- ↓ H.F
- Short t1/2 ??
  - Due to Neprilysin enzyme that inhibit or degrades ANP

- vasoconstriction
- ↑ B.P
- ~~↑ ADH~~ ↑ Na / H2o retention
- ↑ Sympathetic tone
- ↑ Aldosteron
- ↑ Fibrosis / ↑ hypertrophy

- So if we ↓↓ Neprilysin ⇒ prolong for ANP
  - by Sacubitrilate has 2 carboxylate one of them is marked to make prodrug and improve oral Bioavilability

* Why we can't use ~~ANP~~ Neprilysin inhibitor alone ??

- Neprilysin degrades ANP also Neprilysin degrades ANGII, thus it's non-selective to ANP alone.
- So when making inhibition by Sacubitrilate to Neprilysin this will ↑↑ Level of ANGII and active for long time, thus induce RAAs and counter effect of ANP

Date. No.

- thus you will ↑ Duration ANP by ↓ Neprilysin but at same time you will ↑ level of ANG II that opposite effect of ANP.
- ANP X aldosteron

thus if ↑ Aldosteron due ↑ ANGII this will ↓ Neprilysin inhibitor

- So Combination is needed to avoid activation of Neprily involved in 2 pathways < ANP system / RASS and prevent effect of ANGII if Neprilysin is inhibited

* why don't make combination bw Sacubitril + ACEIs to prevent formation of ANGII ?2

- clinically ACEIs is not good Alternative ; because Neprylisin also involved in degradation of Bradykinin
- so if Neprylisin Blocke, ↑ Bradykinin

and if ACEIs also ↑↑ Bradykinin so the net result is that ↑ level of Bradykinin and ↑ risk of Angioedema S.E

So we use ARBs instead of ACEIs to avoid S.E.

Date. No.

5. Finerenone

- RAAs is ended by Aldosteron, which responsible of Na+H2o retention and ↑B.P and complicated H.F
- Blocking of Aldosteron receptor "mineralo corticoide receptor".
- So they think about Inhibition of this receptor to avoid synthesis of Aldosteron and ↑ Na / H2o excretion and to Heart load and good in H.F
- Both eplerenone + spironolactone are steroidal
  - → mineralo corticoid receptor Antagonist and Diuretics.
  - → its nucleus is steroids
  - → spironlaction has ↑ S.E due to its steroided nucleus + lacke of selectivity (ability to work on progesteron recep / Androgen re
  - thus lead to Gynecomastia
  - Importance

Thus they Develop

Eplerenone

- 2nd generation of spironolacton
- lower activity more selective

So they think of Drug ∵ non-steroidal nucleus + selective

Date. No.

Thus they develop

Finerenone

- its Dihydropyridine derivative w Fused Pyridin ring
- potent, non-steroidal
- has advantages on steroidal corticosteroid Antagonist in that No S.E and equivalent potency to eplerenon spironola
- used in H.F.

-

6-Osilodrostat

- we can inhibit Aldosteron either Direct inhibition to it's recept or stop synthesis. S.E does not
- so stop synthesis is MoA of osilodrostate
- has Pyrrolidine Imidazole system
- Single structure, oral active, Non-steroidal Corticoste ~~inhibitor~~ Biosynthesis inhibitors.
- prevent → cortisol synthesis by ↓ 11 β synthase
  → aldosteron synt by ↓ aldosteron synthase
- For H.F, HTN
- used for ~~HTN~~ is not approved by FDA. but due to its ↑ potency in inhibition cortisol synthe its approve for HTN just ~~in the~~ case of pituitary ACTH HTN + cushing's syndrom