Pharmaceutical Chemistry Two.

< Course Summary >

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Lecturer: **Prof. Usama Abu-mohsen**

Semester: **Second Semester of the year 2022/2023**

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lec 1

Anti Fungle

Date. No.

- what is the Ch.Ch of Fungle cells?

- Euckaryot (تحوي على نواة)
- hetelrotraphs (غيبية)
- multicelluleur

Note * Peptidoglycan is the principle componant in Bacterial cell wall

while In Fungle **Chitine** is the principle componant

* Cholesterol in Animal cell membrane

while **ergosterol** in Fungle cell membrane.

So AntiBacterial doesn't affect Fungi.

* Types of infection caused by Fungi :-

systemic ↔ superficial

↳ affect internal organ ↳ on skin " Topically"

* Fungistatic: inhibition of the growth

Fungicidal :- killing Fungi

Date. No.

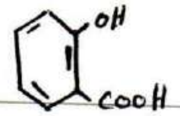
Classification of Antifungle.

Depend on MoA "pharmacological" → Chemical Structure

1. Cell wall synthesis : Capsofungin
2. Membran Function : Amphotericin B
3. Nuclic acid synthesis : Flucytosine
4. Lanosterol synthesis : Terbinafine
5. ergosterol synthesis : Azole.

1. Acid derevative : Biphenamine , salicylanalid , Buclozamid
2. halogen derevative : clorphenaline , proklonol
3. Azole → Imidazole : Econazole (spectrazole), Miconalole, isoconalole, Clotrimazole (medicinal), ketoconazole (Mineral)
   - Triazole ;

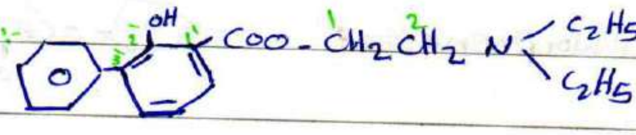
remeber:



- salicyclic acid
- ortho hydroxy Benzoic acid

For chemical classification of AntiFungle :-

II) Acid Derivatives:-

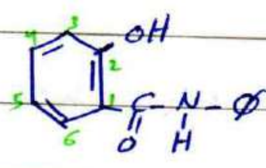


① Biphen amine

2 [(N,N diethyl amino) Ethyl] 3'-phenyl salicylate

انتبه ester ، لما سمي الشق الكحولي اولاً.

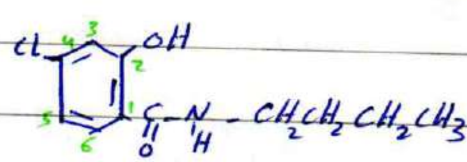
② Salicylanilide



N-phenyl-2-hydroxy Benzamide.

↳ Butyl

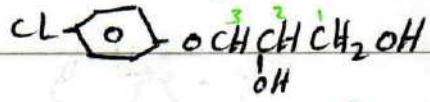
③ Buclozamit



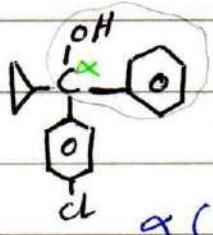
N-Butyl-2-hydroxy 4-Chloro Benzamide.

Date. No.

2- Halogen derivatives:- Halogen + OH.

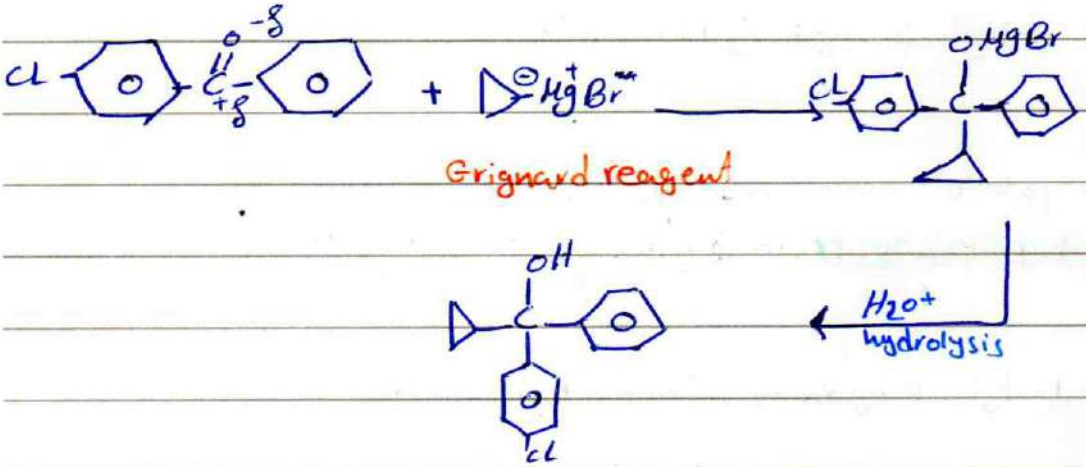
① chlorpheneZine 

3[p-chloro phenoxy] 1, 2 propan diol.

②  Proklonol 3° alcohol

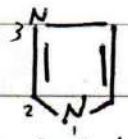
α (cyclopropyl) α (p-chloro phenyl) benZyl alcohol

preperation:



Date. No.

3- Azole ; Imidazole , Triazole.

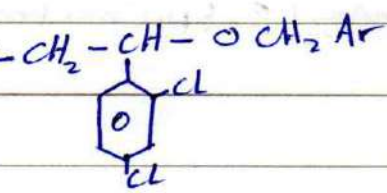


1,3 diazole

1,2,4 Triazole

azole ; unsaturated Five 5 membre ring.

Drug contain Imidazole

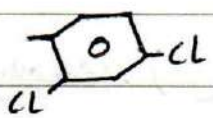


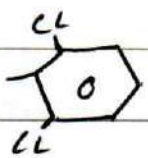
topically

Ar :

1-  : econazole → specta zole ®

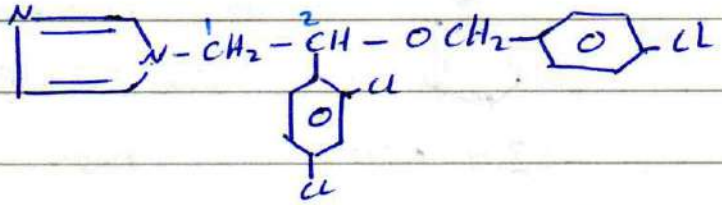
P- Chlorophenyl

2-  Miconazole

3-  isoconazole

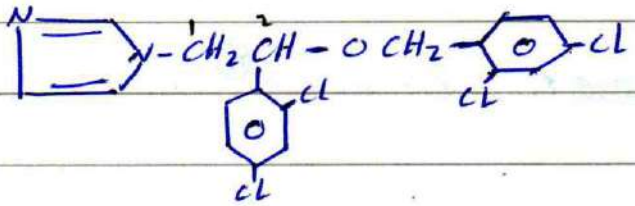
Date. No.

Nomenclature:



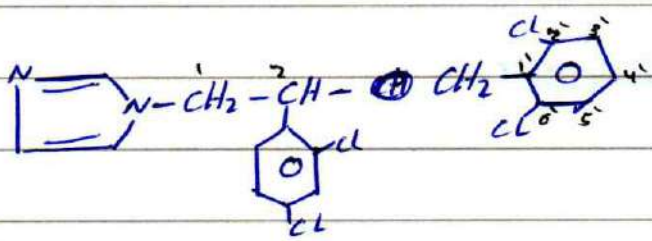
econazole

N [2 [o, p dichlorophenyl] 2- (p-Chlor phenyl Methoxy) ethyl] Imidazole.



Miconazole

N [2 (o, p dichlorphenyl) 2- (o, p dichlorphenyl) Methoxy] ethyl] Imidazole.

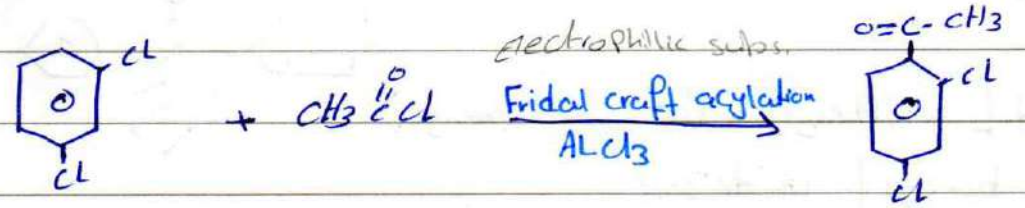


isoconazole

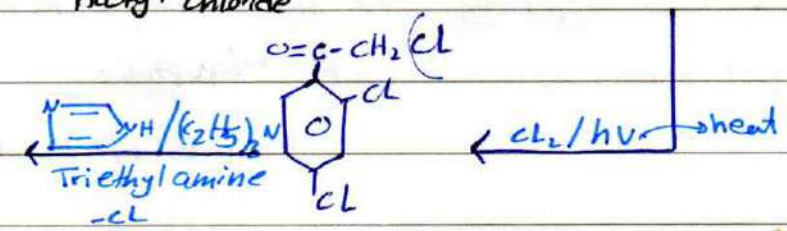
N [2 (o, p dichlorophenyl) 2- (2`, 6` dichlorophenyl) Methoxy] ethyl] Imidazole

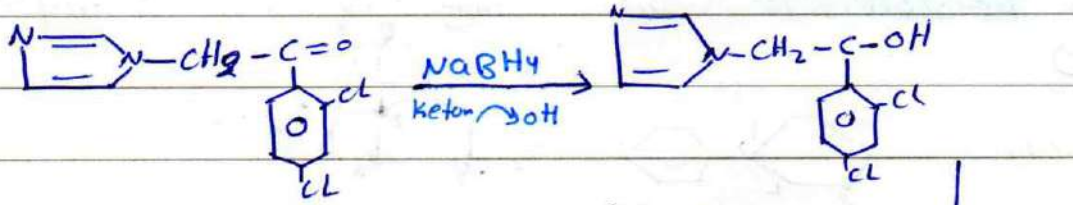
Date. No.

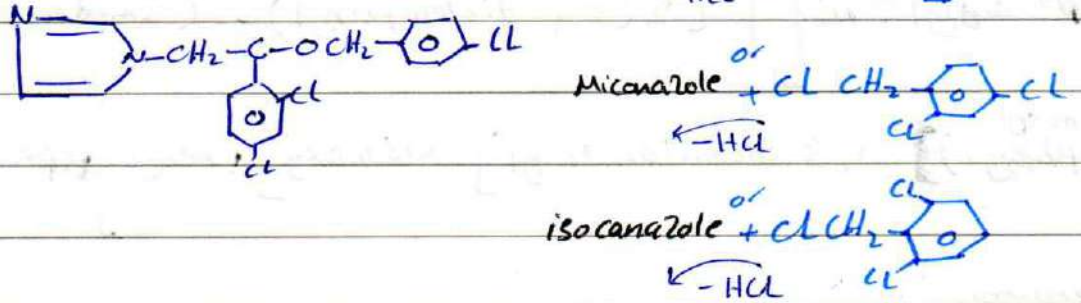
preperation of econazole: Ar عند آخر خطوة تتكلم بـ



1, 3 dicloro Benzen Acetyl chloride



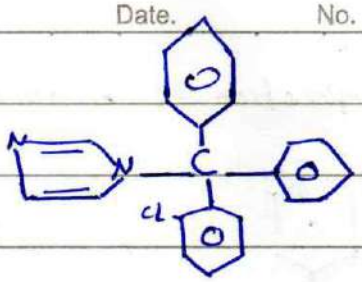




- Are used Topically, to treat superficial Dermatophytic and yeast infection

Date. No.

4. Clotrimazole Hedisint®



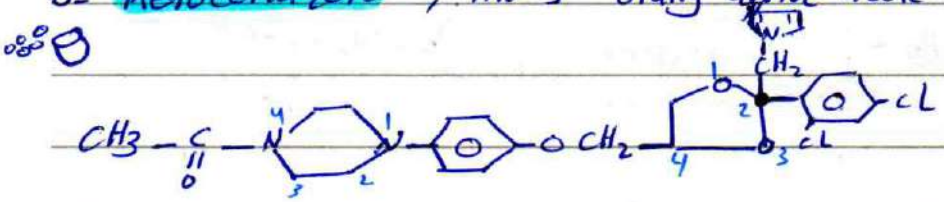
N [α (Phenyl) α (O-Chlorophenyl) benzyl] Imidazole.

- used Topically, to treat Tinea infection and candidasis

not used systemically → Lipophilic

→ ↑ P.B (protein Binding)

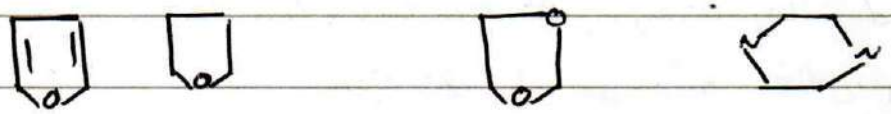
5. *** Ketoconazole, The 1st orally active azole. Nizoral®



N^4 acetyl - N^1 [[[2 (O,P dichlorophenyl) -2 (Imidazole

~~Phenyl~~ methyl) 1,3 dioxalan 4 yl] Methoxy] phenyl] piperazine

remeber:



Furan Tetrahydro Furan 1,3 dioxalane Pipirazine.

Date. No.

Not clinicaly used ; due to its side effect from the present of keto group i.e as :-

1. Hepato toxicity
2. ↓ Androgen Hormon
3. ↓ cyp 3A4

The ch. Ch of ketoconazole :

- Low water solubility
- Drug - Drug interaction as H_2 Antagonist, Antaci
- All it's metabolized Are inactive.
- $t_{1/2}$ = 6-9 h.

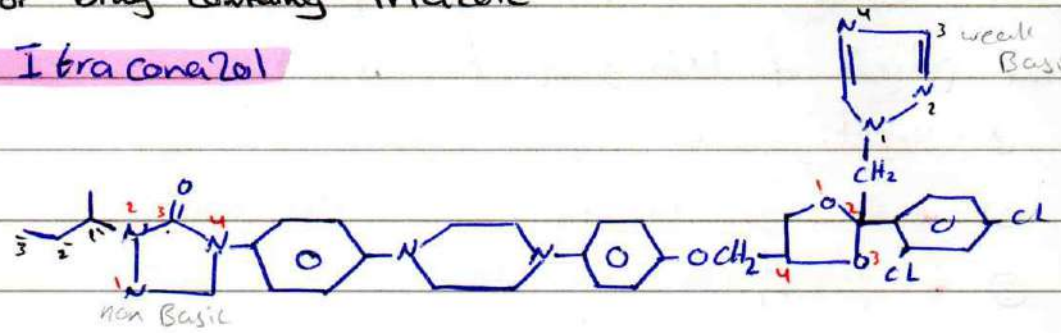
Now days it's used Topically.

Date. No.

→ more polar than imidazole

For Drug containg Triazole

1) Itraconazol



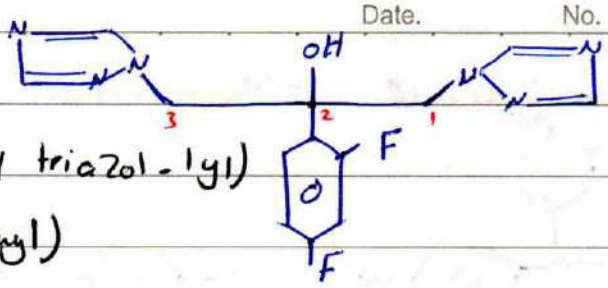
N4 [[[[[[2-(o,p dichlor phenyl)-2-(1,2,4 triazol-1-methyl)-1,3-dioxolan-4 yl] Methoxy] phenyl] piperazinyl] phenyl] 2,4 dihydro (1`methyl propyl) 1,2,4 Triazole 3-one.

Ch.ch of Itraconazole:

- compared to Imidazole, triazole more save, less side effect.
- Broad spectrum
- Non polar, so not affected to Fungal meningitis (need Polar)
- orally active
- $t_{1/2}$ = 20-30 h
- Not affected by food or antacid.
- NO hepatotoxicity side effect.
- Two tricalol ring.

Date. No.

2. Fluconazole.



1, 3 di or bis (1, 2, 4 triazol-1yl)

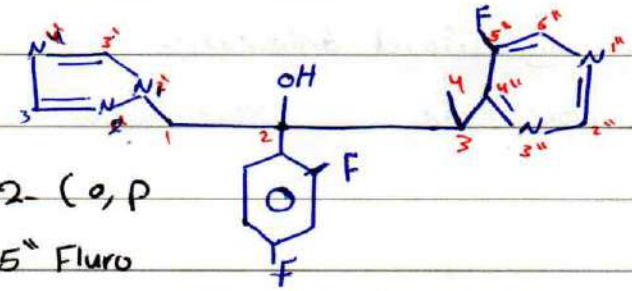
2-(o, p di Fluro Phenyl)

Propan-2-ole.

Ch.ch of Fluconazole:

- Polar → cross BBB, For menigitis in specicl case called cryptococcocal menigitis
- $t_{1/2}$ = 25-30 h, Not affected by food or Antacid
- Broad spectrum.

3. voriconazole



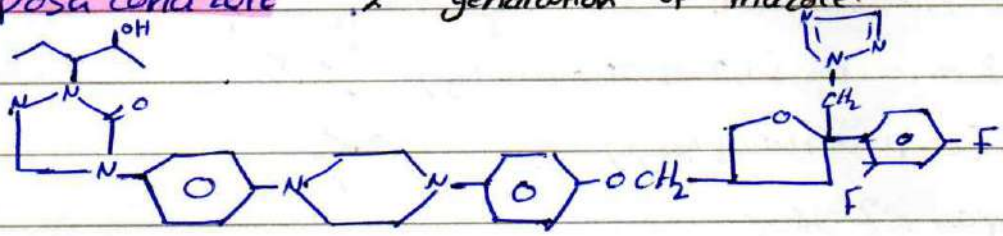
1(1', 2', 4' triazol-1'-yl)-2-(o, p difluro phenyl)-3-(5" Fluro pyrimidine 4"yl) but-2-ole.

- Lipophilic, Broad spectrum
- use alternative for amphotericin B (polyenes)
- For Invasive → aspergillosis, candiasis

note: Itraconazole, Fluconazole, voriconazole } 1st generation

Date. No.

4. Posaconazole 2ed generation of triazole.



- The Broadest spectrum of Azoles.
- Most expensive $
- inhibit cyp
- used in clinical Zygomycete Fungitis.

usually Triazol derivatives:-

- More safe - More Active - ↓ side effect

Date. No.

SAR For AZoles :- either for TriaZole / ImidaZole.

- N^3 in ImideZole must be free
  N^4 in TriaZole must be free.

The other ~~in~~ N is Bind to hydrophobic ~~tha~~ such as Phenyl (has 2 substitution F, cL)
But F >> cL in the activity.

- FlucocinaZole : only drug dosn't contain hydrophobic grou
  ✓BBB , water soluble.

MoA :

Ergosterol Biosynthesis inhibition.

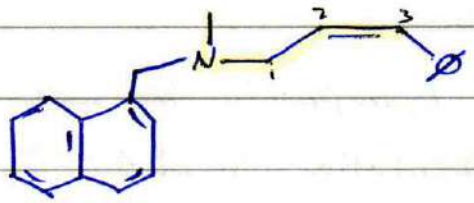
squalene
↓ squalene 2,3 epoxidation ⊣ allyl amines.
Lanosterol
↓ 14 α demethylas ⊣ AZole
Is has free Fe^{+3} orbital
Ergosterol

The free position in N^3 ImideZole, N^4 TriaZole will Bind to Fe^{+3} free orbital in 14 α demethylase ∴ Cordination Bon thus prevent ergosterol synthesis

sulfur (fine), Amine derivatives. Date. No.

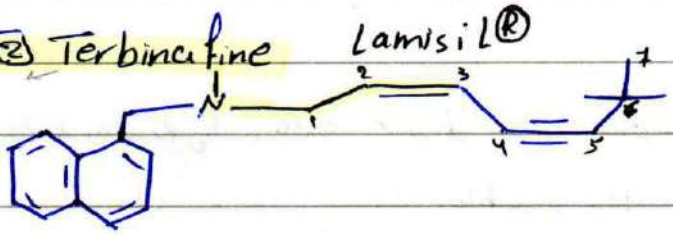
4- Allyl Amines: (H_2N) less activity than Azoles.

① Naftifine (naphthalin) Topically for Tenea infection.



N (methyl) N (naphthaline methyl) N (3-phenyl prop-2-enyl) amine.

② Terbinafine Lamisil®



10-100 more activ than Naftifine

N (naphthaline methyl) N (methyl) N (6,6 dimethyl hept-2-en-4yne yl) amine.

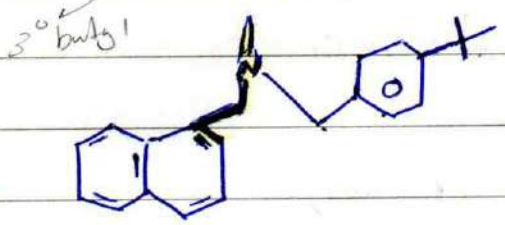
- used Topically and systemically
  - Tinea pedis
  - Tinea corporis
  - Tinea Cruris

↳ Nail infection "Dermatophyllic onychomycosis" ringworm of Nails.

contraindicated / For pregnant + lactating ; it accumulates in Breast Milk.

Date. No.

3. Butenafine , Not containing allyl amin But same MoA.



N(methyl) N(naphthalin Methyl) N(p 3° butyl benzyl Methyl) amine

- From Benzyl amine derivatives
- MoA

Inhibition squelene 2,3 epoxidase, thus lanosterol is inhibited.

Fungi. squelene تراكم *
Toxic.

⑤ Polyenes :

Both has 38 C , Amphoteric , Large Macrolides.

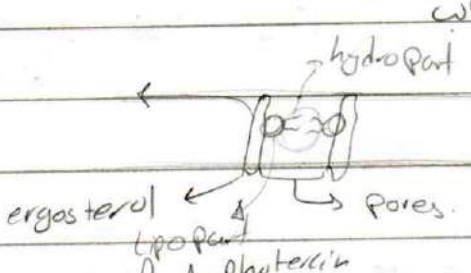
Nystatin	Amphotercin B
- Contain 6 double Bond only 4 Bond conjugated - Topically, Not absorbed GIT	- 7 double bond , All - All are conjugated. - As injection (locally) in the joint in Fungal arthritis. + systimic ca - can't cross BBB - More use , less side effect (conj) - Cause nephrotoxicity. - More active , expensive

Date. No.

- Amphotercin B is directly injected in Subconjuctiva
For myocotic coreneal ulcers. + Keratits.

- Both Amphotercin B, Nystatin (Polyenes)
Binds w ergasterol in cell membrane and during
Binding it cause pores, lead to leakage of
K^+ and small molecule, thus Fungal cell death.
"Fungicidal"

- Amphotercin is Polyene Macrolide (GIT)



Amphotericin B
→ Amphoteric
part lipophyli
part hydroph
Bind to ergosterol
Bind to wate
thus make po

6- Echino candins : " Fungin" 

[1] CapsoFungin [2] MicaFungin [3] AnidulaFungin

it's group of cyclic peptide with long side chain.

MoA:

Inhibition of cell wall biosynthesis by inhibition of
β 1,3 glycan synthase

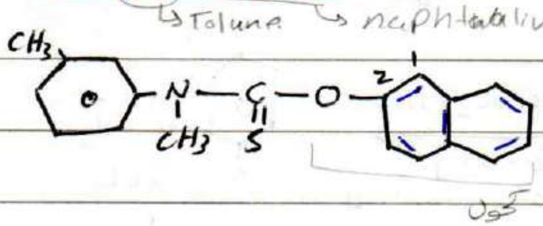
it's Ch.ch:

[1] Long $t_{1/2}$ [3] used for Azole resistant [5] used I.V.
[2] Broad spectrum [4] orally inactive

[7] others

[1] Tolnaftate :-

↳ Toluene ↳ naphthalin



O- 2 - ~~napht~~ naphthyl - N- Methyl - N (meta M - Methyl phenyl) ~~Fo~~ Thiocarbamate

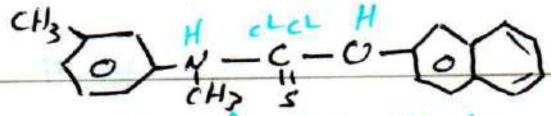
Note/

$NH_2-C(=O)-OH$ Carbamic Acid

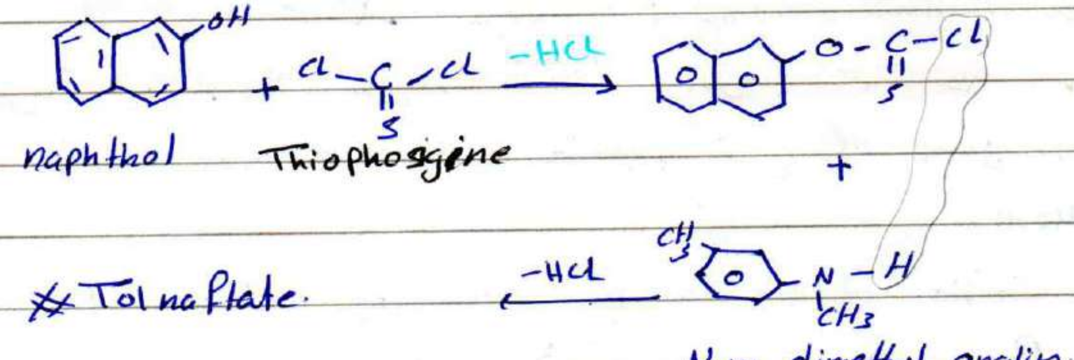
$NH_2-C(=S)-OH$ → لو تم إزالة H يصبح ester Thio carbamic acid

عند التسمية نبدأ بالشق الكحولي أي المرتبط بـ O

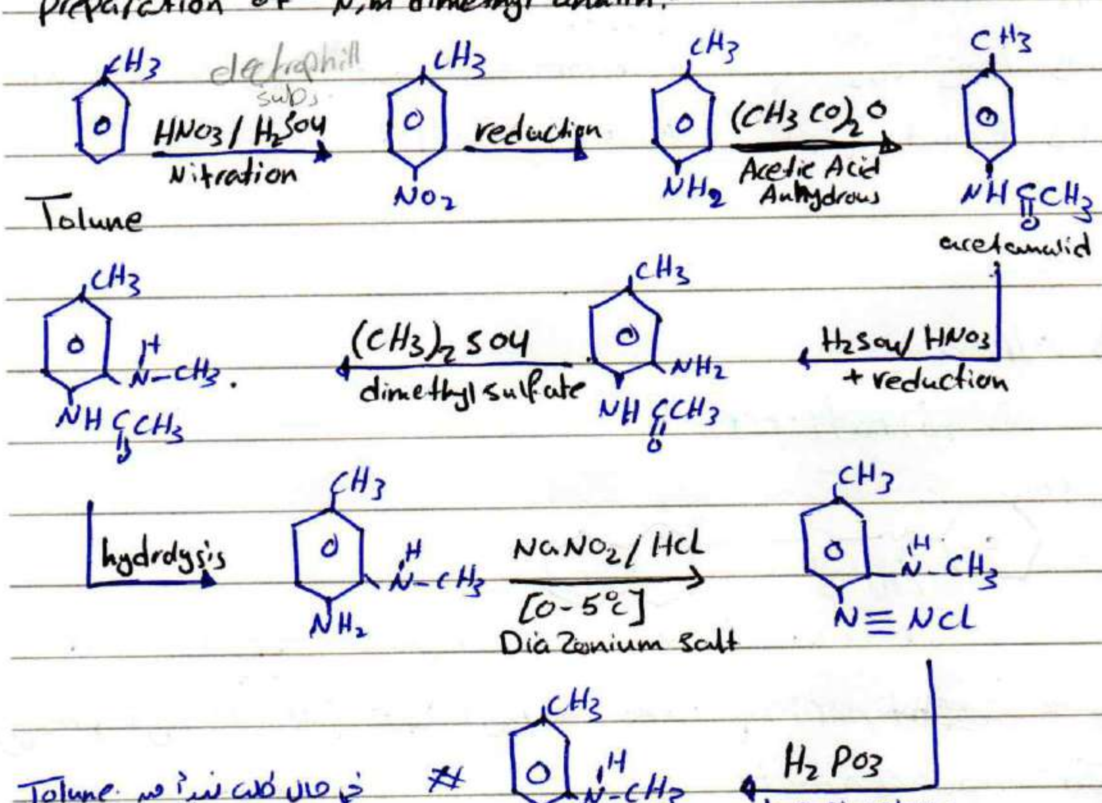
وآخر التسمية نضع (-ate)



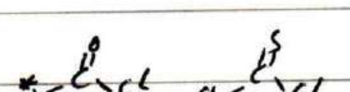
Preperation of Tolnaftate:-



preparation of N,m dimethyl analin:

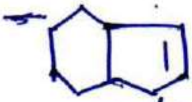


Tolune. في حال طلب نبدأ من

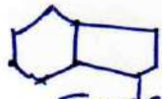


Phosigin Thio phosigin.

Indol



Inden



Indan.

Date. No.

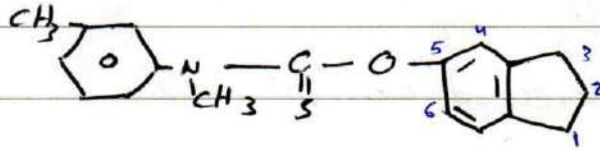
→ Tolune

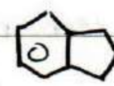
[2] Tolindate

↳ Indan

بعض الكتب تدرجه تحت allyl Amin

لأن نفس الـ MoA





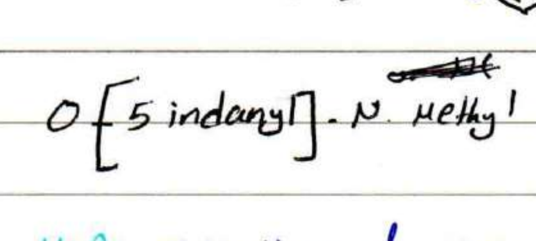
Indan ring

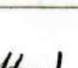
O [5 indanyl] - N Methyl - N (m-methyl phenyl) Thiocarbamate

MoA: Inhibition of ~~Z/S~~ squalene 2,3 epoxidase thus lanosterol is inhibited.

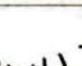
- Used for (Topically): Tinea → Pedis / Corporis / Crunis.

[3] Griseofulvine, sporofulvine®





Furan



Benzofuran

2`, 4, 6 trimethoxy - 7 - Chloro - 6` methyl spiro [2, 3 dihydro benzofuran (2) (1`) cyclohex-2`-ene] 3, 4" diones.

keton الــ

MoA/ ↓ inhibition of Mitosis, by binding to Tubulines which ↓ Miotic spindle formation

Thus No Mitosis, No daughter Nucles separation

Fungistatic ~~a~~ effect

Date. No.

Uses/

① systemically Not Topically

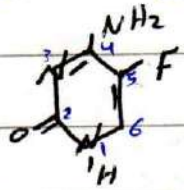
② Affected by food, increased absorption ∵ Lipophilic food. (fatty food)

Ch.Ch/

- Need 6-12 month
- Not relive the affected fiber but form new fiber.

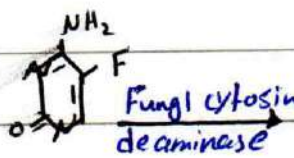
لهذا لا يعالج الجزء المصاب إذا يمنع كلوه العضل في الانسان الجديدة.

④ Flucytosine



- Anti metabolite (anti cancer)
- prospectrum [used for fungi + human]
- ↓ DNA synthesis.

4-Amine-5-Fluro-1,2 dihydro pyrimidine-2-one



5Fu

5-Fluro uracyle

→ 5FDUMP

5 Fluro deoxy uridin Monophosphate

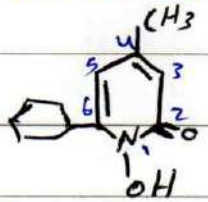
DUMP → (Thymidlate synthase) → DTMP

DTMP need for False Nucleotid DNA synthesis.

* Thymidlic Acid is essintial compound for DNA synthesis

Date. No.

[5] Ciclopirox



6- cyclohexyl - 1- hydroxy- 4-Methyl 1,2 dihydropyridin - 2- one.

used : Topically , shampo

- For seborrheic dermatitis
- For Tinea → pedis, corporis, cruris
- For Tinea versi color.

MoA/

By chelation "complexation" of polyvalnt cations as Al^{+3}, Fe^{+3} that affect from complex :-

① energy production

② electron transfer of Mitochondria.

Analgesic

Lec: 5

Date.

No.

Drug Bringing about insensibility to pain without consciousness.

Analgesic

Strong

- Natural
  - Morphine
- semisynthetic
  - Codein
  - Dionine
  - Heroine
  - hydromorphone
  - hydrocodone
  - oxymorphone
  - oxycodone
  - morphinane
  - Antagonist
    - Nalophrine
    - Naloxone
    - Naltrexone
    - levallorphane
- synthetic
  1. pelidine → Meperidine
     - A) Large group N
       - anilteridine
       - Phenoridine
       - Piminodine
       - Benzibidine
       - Diphenoxylate
     - B) ester → Keton
       - Ketobemidone
     - c) sub. ring
       - prodineα
     - D) to Azipem
       - Ethoheptazin.
  2. Methadone
     - Dipanone
     - L-α ~~Amino~~ Acetyl Methadol
     - Dextropropyphen
     - Dextromoramide
  3. Benzomorphene
     - Methazosine
     - Phenazosine
     - pentazosine
     - cyclazosine

Week

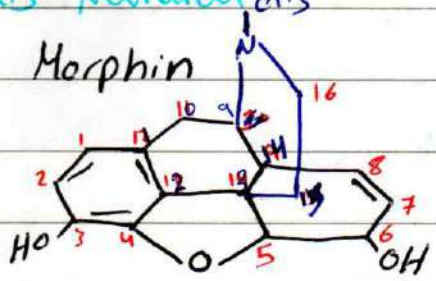
1. Salicyclic Acid derivative
2. Anilin ≤
3. Indol ≤
4. Aryl Acetic Acid ≤
5. Aryl Propioic Acid ≤
6. anthranilic Acid ≤
7. Pyrazolone + Pyrazolidine ≤
8. others.
   - others/ Tramadol

Strong Analgesic.

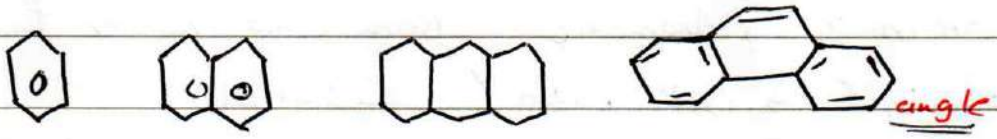
Date. No.

1) Natural

● Morphin

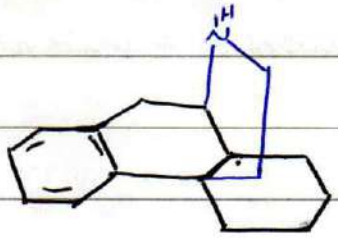


3,6-dihydroxy-4,5 epoxy-N-Methyl 7,8 didehydro Morfinane



Benzen naphthelin anthracin phenanthren

single



Morfinane or Morphinane (No epoxy group)

Ch.Ch of Morphine/

- Amphoteric, has $\overset{OH}{\underset{3^{o}N^{3}}{\leftrightarrow}}$
- has chiral centers [5, 6, 9, 13, 14] thus 2^{n} (n=5) = 32 isomer
  But it has just 8 isomers and the others are epimere (just differ in configuration)
- it has T-shape conformation in space.
- orally absorption is low

Date. No.

it's absorption improve by adding HCl salt, sulfate

- slowly cross BBB
- it's L-isomer active ✓
  D-isomer inactive ✗
- Biotransformation :
  - 3-O-glucoronid
  - 6-O Glucoronid.
  - OH in 3 → Aromatic
    OH in 6 → cyclic Alcohol
    > Both could transfer for O-sulfate.

* By Morphin we could get Both synthetic + semisynthetic Analgesic.

*

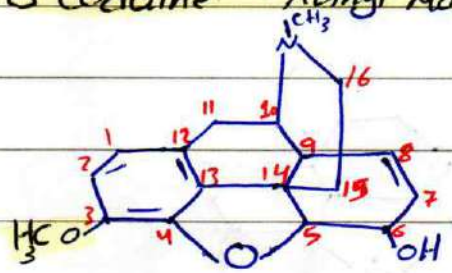
Date. No.

[2] Semisynthetic All are Amphoteric.

- Either Chang OH in 3, 6 position
- or remove = in 7, 8
  or add OH in 14
  or remove of epoxid in 4, 5.

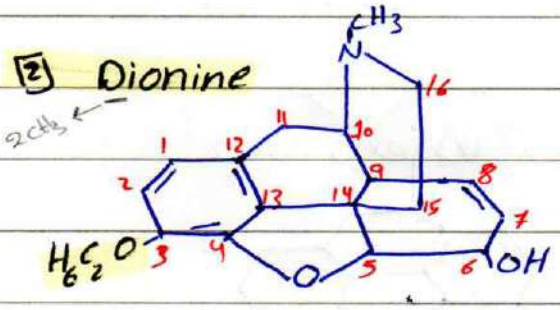
[1] Codaine "Methyl Morphine"

- Antitussive
- ↓ Analgesic effect.



N-methyl - 6-hydroxy - 4,5 epoxy - 3-Methoxy 7,8 didehydro Morphinane.

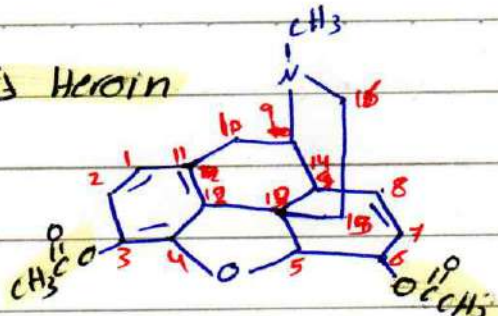
[2] Dionine



3- ethoxy - 6-hydroxy - 4,5 epoxy - N-methyl 7,8 didehydro Morphinane.

Date. No.

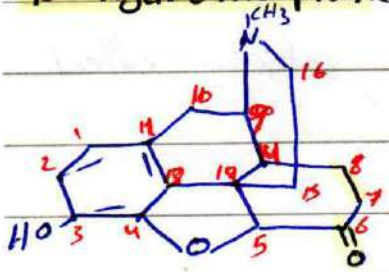
[3] Heroin



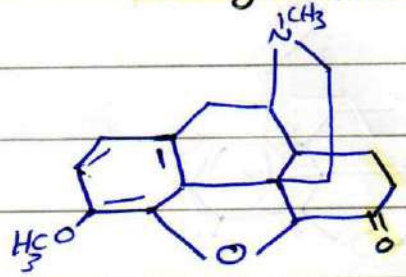
- more Analgesic than Morphin
- ↑ side effect
- ✓ BBB.

3,6 di acetyl oxy - 4,5 epoxy - N methyl didehydroMorphinane

4. hydromorphone



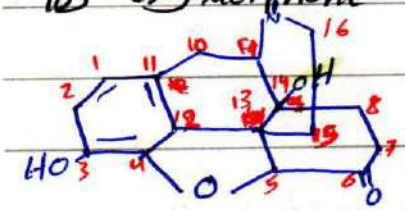
[5] hydrocodone



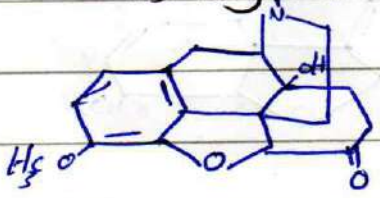
↑ Analgesic effect
(3-hydroxy - 4,5 epoxy - N-Methyl 6oxo Morphinane)

- = morphin Analgesic effect
But less than hydromorphone
- Anti tussive.

[6] oxy Morphone



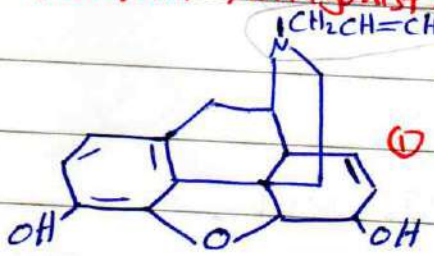
[7] oxy codone



More Analgesic than Morphin
3,14 dihydroxy - 4,5 epoxy - 6oxo
N-Methyl Morphinane

Date. No.

Morphin Antagonist:-

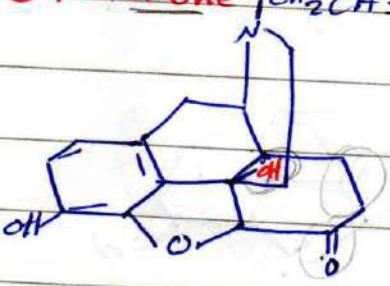


$CH_2CH=CH_2$ → allyl amine H_2N

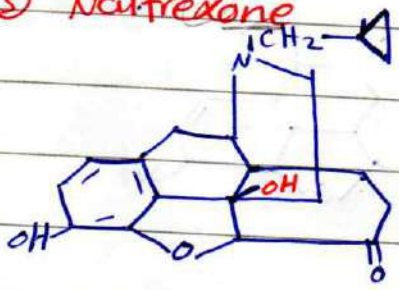
① Nalorphine (semi synthetic Antagonist)

"Nalopharm"R

② Naloxone



③ Naltrexone



* For synthic they teck pharmacophore groups from ~~Semi~~ Morphin then make modification.

Date. No.

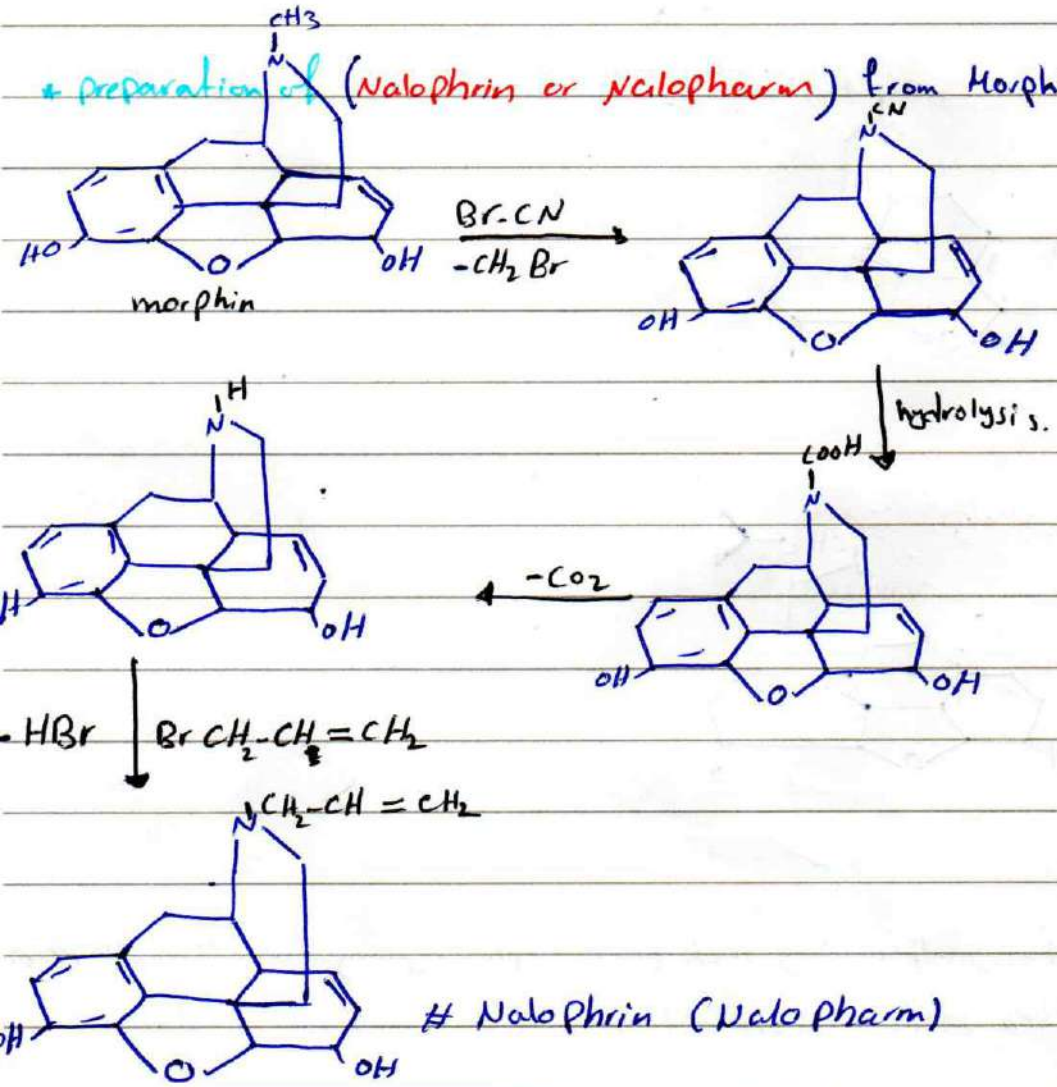
- There are 3 receptor for analgesic drug:

μ (Mu) — K (Kubbu) — delta (Fever)

(most popular)

- These receptor found in CNS, GIT, so Theres type of Analgesic would cause diarrhea, Colic.

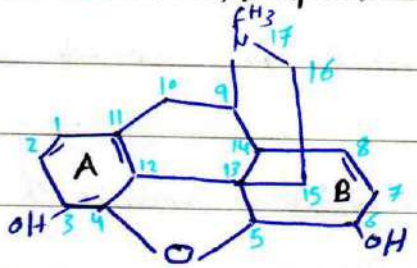
* preparation of (Nalophrin or Nalopharm) from Morphine



Nalophrin (Nalopharm)

SAR "Morphin"

Date. No.



[A] phenol ring if removed or reduced → loss activity

- The presence of hydroxy in position 3 requried for give activity.
- if OH in 3 convert to OCH_3 → ↑ Lipophilicity ↑ oral Bioavilability.

as in codein ↓ Analgesic effect, ↑ Antitussive

- OCH_3 in 6 position in hydrocodain → isomer for codain

[B] ring

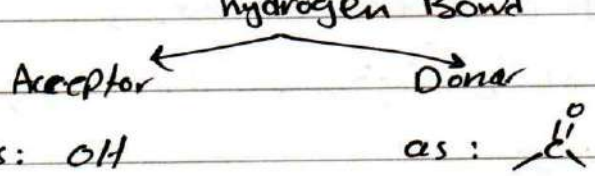
- OH in position 6 is Not requried for activity.
- if OH in position 6 converted to H →

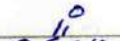
↑ Binding to μ receptor, ↑ activity 10 time higher.

- if it replaced $\bar{w}$ CH_3 or $=CH_2$ (Methelene) als ↑ Binding to μ receptor
- if replaced $\bar{w}$ (=O) $\bar{w}$ prescence of double bond in (7-8) ↓ activity to 1/3 due to weak connection or Binding $\bar{w}$ receptor

Date. No.

- if OH in 6 converted to (=O) without presence of double bond in (7-8), The Activity is increased. Due to conformation of cyclo Alkan that responsible of strength the Binding w the receptor.



* if the group of OH in 3, 6 converted to (acetyl oxy)  The activity and toxicity are increased: Heroin

* on position 14 (14 β-OH), presence of OH in 14 increased or stimulate binding to M receptor ↑ activity, ↑ effectiveness (2 or 3 times) higher than Morphin ↓ Antitussive effect.

thus

* oxycodone >> hydrocodone (in Activity) (orally)

oxyMorphone >> hydroMorphone (in Activity) I.v

(Bioisosterism)

Date No.

* N in position 17, if replaced to CHR → Inactive
or replaced ῶ oxidation (N-oxide) → Inactive.
or it becom Quatery  → Inactive.

if CH_3 on N converte to H → reducess activity by 75% or 3/4 or three quarters. "Normorphine"
↳ No CH_3

R

CH_3
C_2H_5
C_3H_6 — As increased in R, ↓ activity.

C_4H_9 → No activity At all

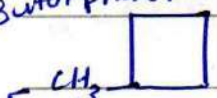
C_5H_{11}
Hexyl C_6H_{12}
phenyl ethyl $CH_3-CH_2-\phi$ or Aryl alkyl
— increased activity for 14^{14} times.

* if R on N is unsaturated ($CH_2CH=CH_2$) or Nalorone Nalophrin
or carbocyclic (cyclopropyl Methyl CH_2-△) Naltrexone
Both are pure Antagonist.

Date. No.

in case R replaced ~~w~~ cyclo butyl Methyl

Butorphenol



or dimethyl allyl 

Nasal spray or injection

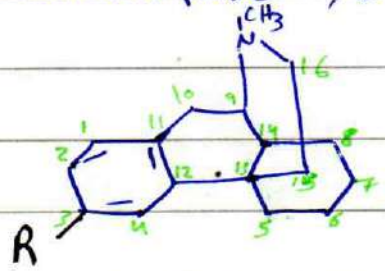
Not orally

They give Mixed Agonist Antagonist

↑ at Kaba receptor

at M receptor

- epoxy group, the ether link is not essintal for activity as in Morphinane ↑ more potent, Longer activty Than Morphine, but has ↑ toxicity.



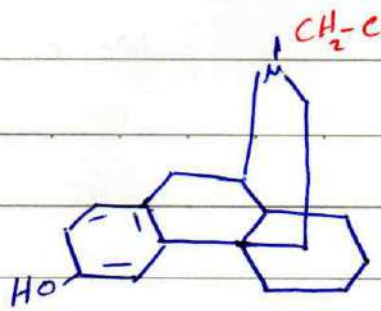
Morphinane

- DoA 6 to 8 h
- called Tetracyclin opoid
- used as Tartarte (salt)
- levo form active
- it's 7.5 time more active than Morphin as Analgesic.

if R : OH ⟶ "levorphanol"

OCH_3 ⟶ Dextro Methorphan Dm®

(Antitussive)



Date. No.

Levallorphan

Antagonist.

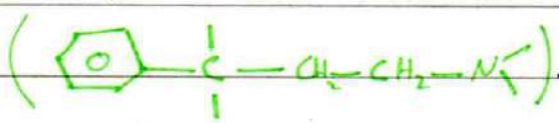
5 time higher than Nalorphen.

Natural ✓ semiSynthetic ✓

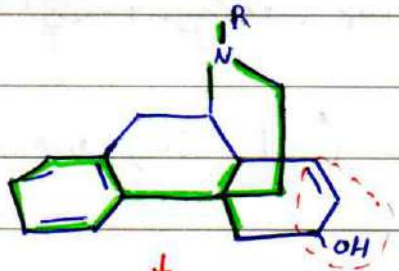
* Narcotic Drug → Any Drug induce sleep.
* opoid → strong Analgesic
  - bind to 3 recepta (μ, K, delta)
  - many form. → Natural / synthetic / semi synthet

* All Drug except Morphin (befor) is Semisynthetic.
* synthetic Drug. for strong Analgesic

They take pharmacophor group (phenyl propyl amine)



→ in all Drug ⇄ synthetic / semi synthetic / Natural.



→ not important for activity.

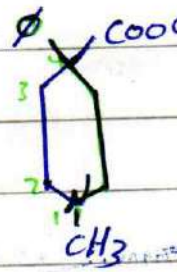
↓ epoxy not important

Date. No.

- Synthetic Strong Analgesic :-

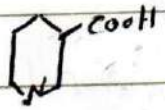
1. Petidine = Mepredine
2. Methadone
3. Benzomorphine.

① Petidine = Mepredine. Dolantine ®

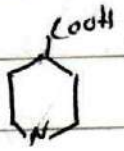


ethyl → (1-Methyl-4-phenyl) isonepecotate ester
or Piperidine-4-carboxylic acid

Piperidine



nipecotic Acid



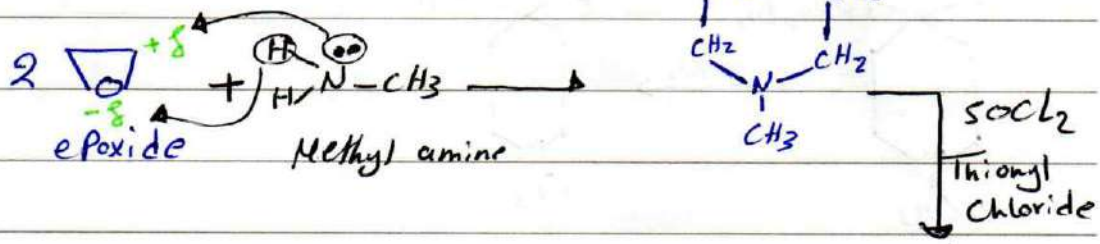
iso nipecotic Acid

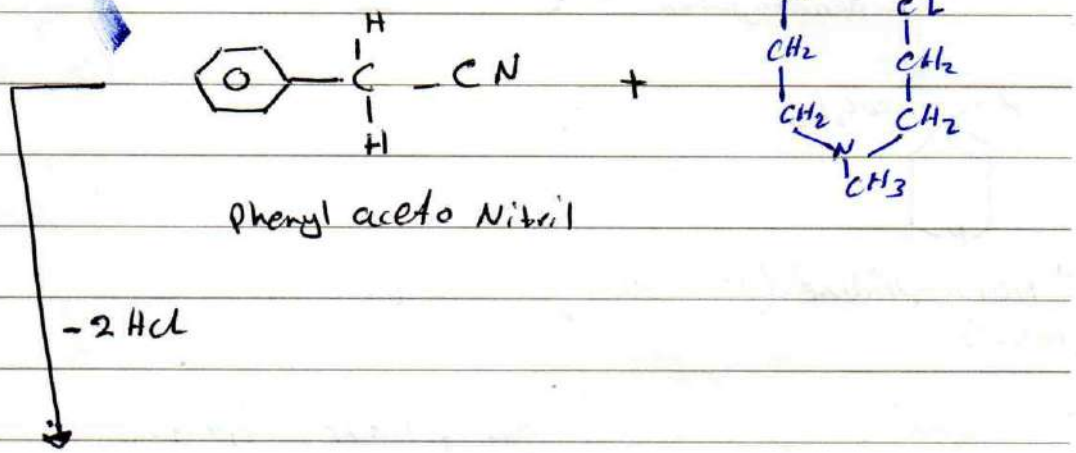
has the Pharmacophor group (Phenyl propyl amine)

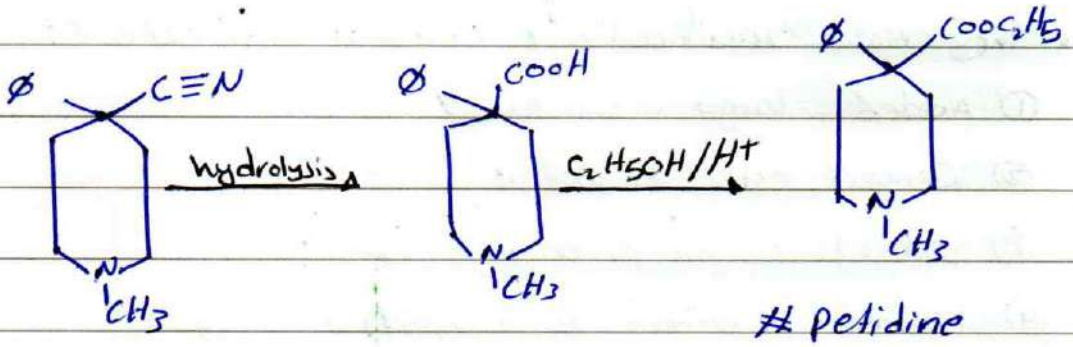
* Petidin effect To Morphin (1 - 10) weeker than morphine
- used in Obstetrics
- Rapid onset + short duration.
- used orally or I.v.

Date. No.

preparation of ~~##~~ pethidine :-





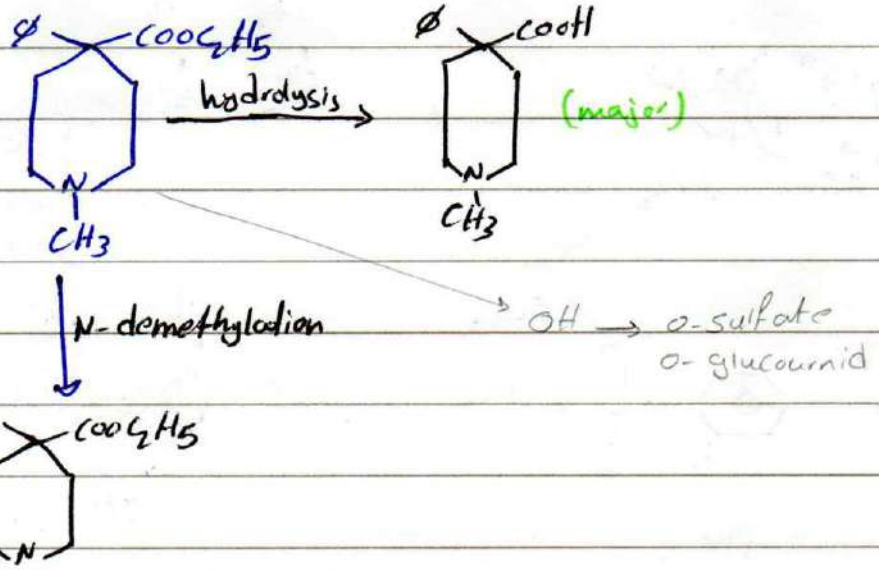


pethidine

make Neurotoxcity.

Date. No.

Biotransformation of pitidine



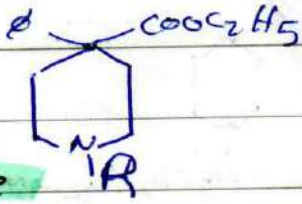
"Normepridine" (Neurotoxicity)
(major)

* They Make Modification on pitidine / Mepridine, To avoid side effect:
  1. Added large group on N
  2. Convert ester to Keton
  3. substitution on piperidine ring.
  4. Convert piperidine to azepine

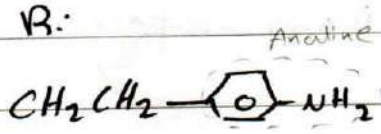
* after modification it becom has rapid duration, rapid onset

Date. No.

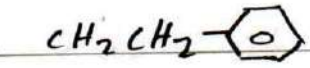
① Added large group on N.

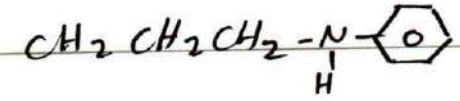


R:

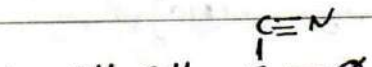
1. 

Aniteridine

2.  pheneridine

3.  piminodine "alvodine" ®

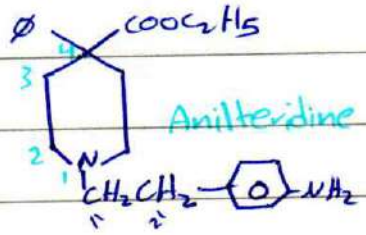
↕ Bioisosterism.

4.  Bin zetidine

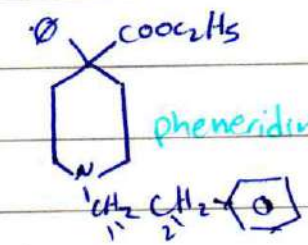
5. Diphenoxylate.

All are more Lipophilic, cross BBB. ✓

- nomenclature /



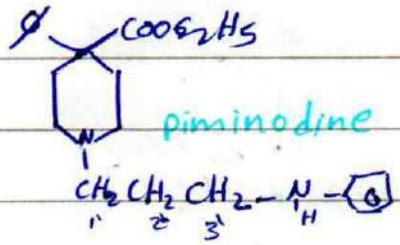
ethyl ((2-cinaline ethyl) - 4- phenyl) isonepcotate.



ethyl ((2-phenyl ethyl) - 4- phenyl) isonepcotate

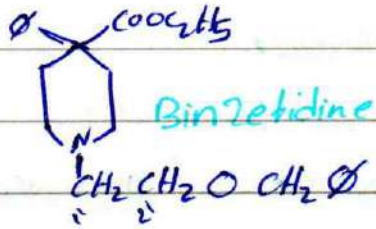
(1-Benzyl methyl)

Date. No.



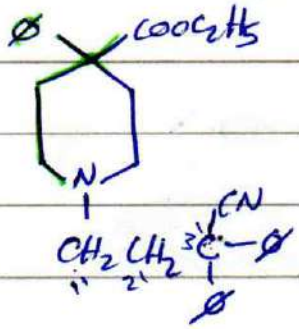
Piminodine

ethyl (3-(4-phenyl Amino propyl))-4-phenyl isonepcotate



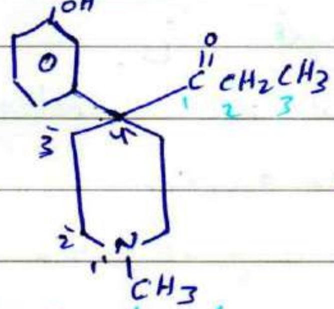
Bintetidine

ethyl (1-Benzyl oxy ethyl)-4-Phenyl isonepcotate.
or Phenylmethyl



ethyl [3-(3,3 diphenyl cyano) propyl]-4-phenyl isonepcotate.

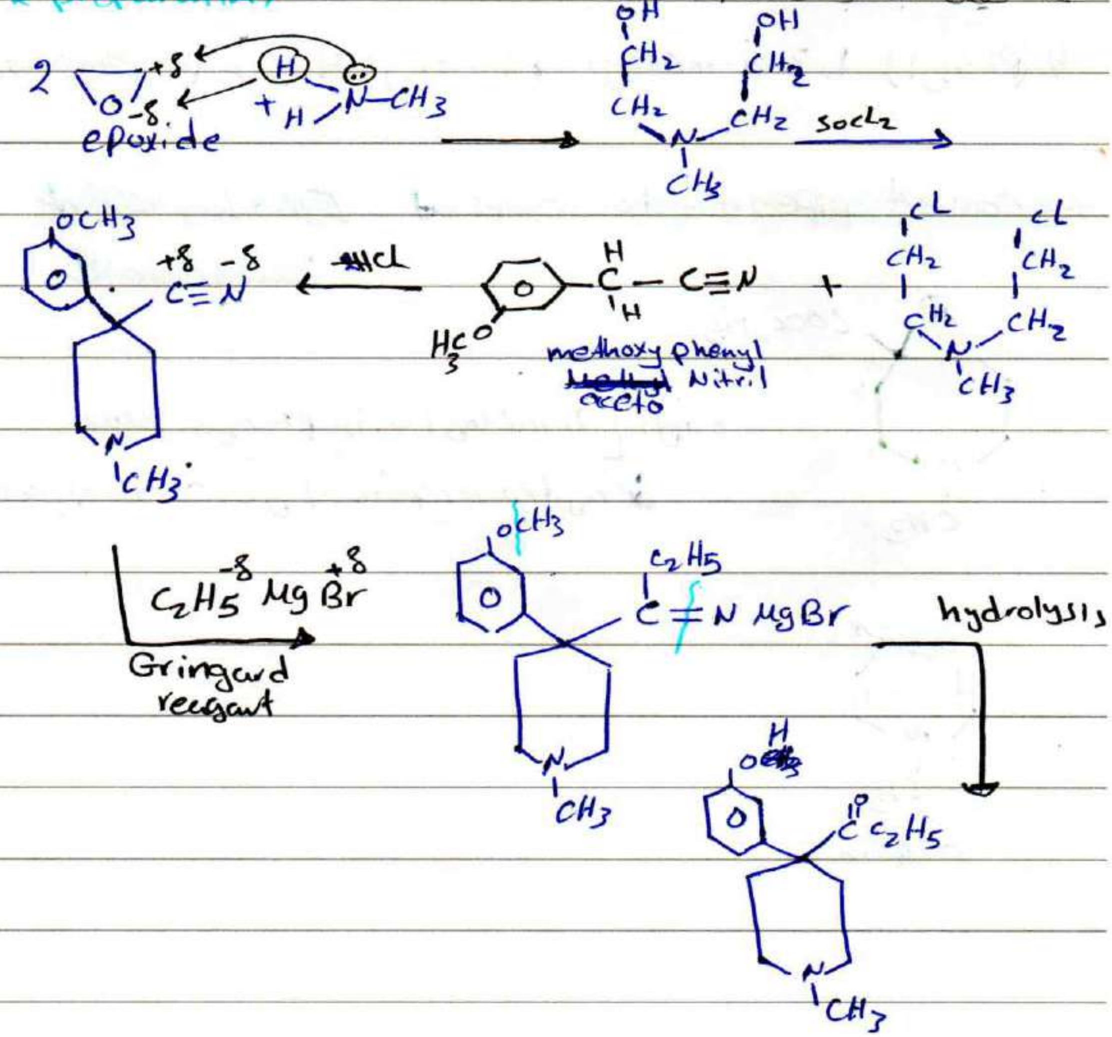
② convert ester to keton. Ketobemidone
Ketogane®



1 [4`-meta hydroxy phenyl - 1`- methyl pipredin-4`yl] propone.

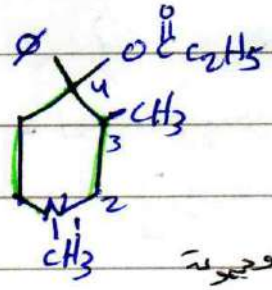
* preparation/

عند تفاعل أمين و ePoxide



Date. No.

③ Substitution on piperidine Prodine



Both CH_3 are in same direction.

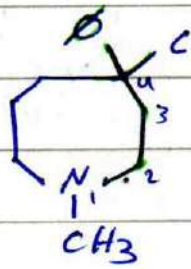
Nisentil ®

* نلاحظ أنه الشق الكحولي اختفى منه ذرة وحيدة

4-(Phenyl) 1,3 dimethyl piperdinyl 4 yl} propanoate

4- Convert piperidin to Azipene Ethoheptazine

Zactane ®

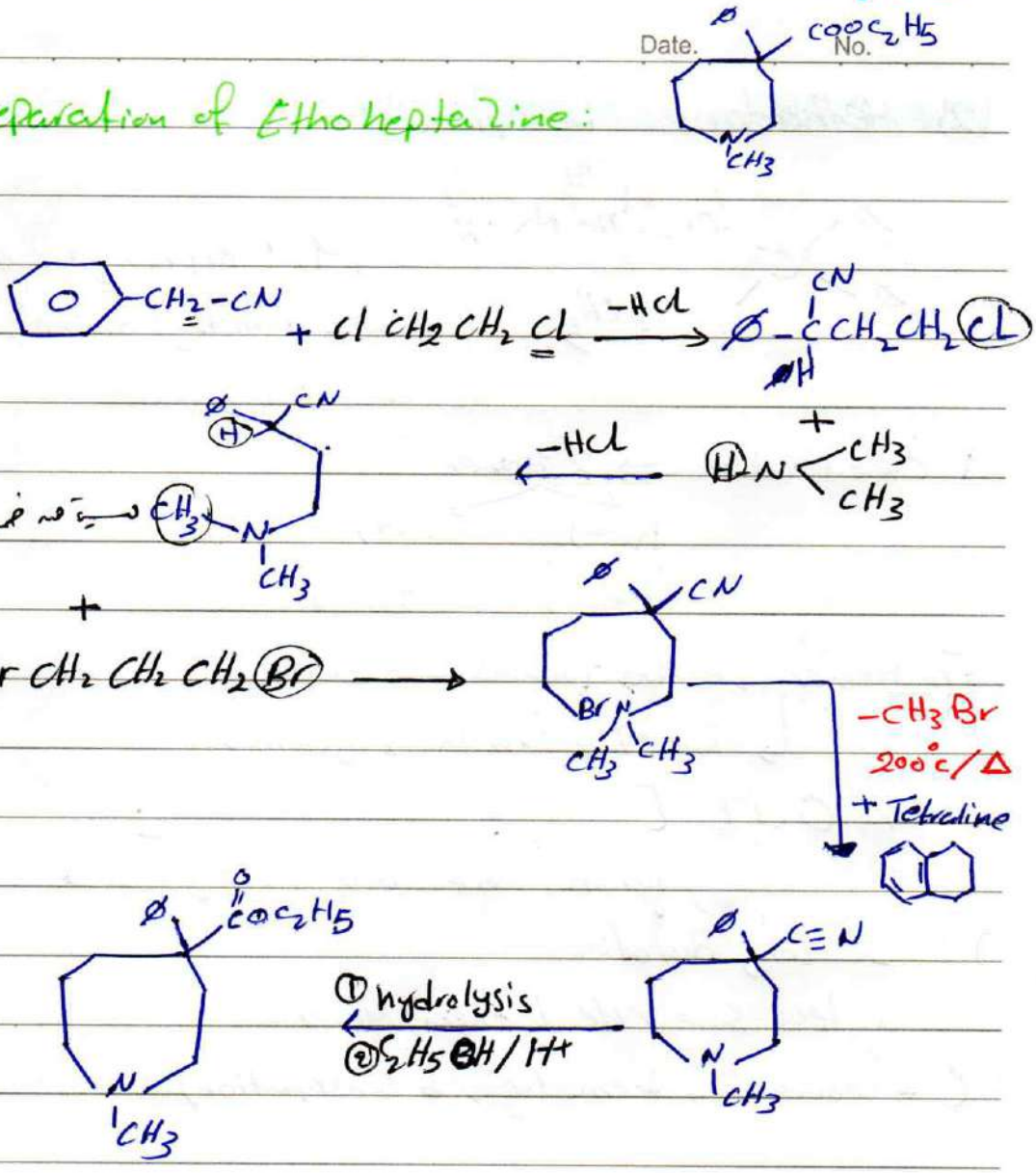


ethyl [1-methyl-4-phenyl hexa hydro Azepim 4 yl] carboxylate.

azepim

Date. No.

preparation of Ethoheptazine:



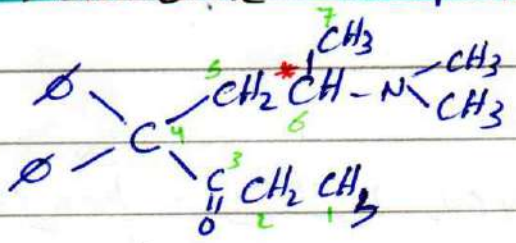
~~Pethidine~~ ✓

Ethoheptazine

or Zaetan ®

Date. No.

[2] Methadone Dolophine®



4,4 diphenyl - 6- (N,N dimethyl amino) heptan 3-one

1- Chiral center ⟹ 2 isomer

R(-) S(+)

Active ✓ InActive ✗

Enatiomer → Active formula ⟶ Eutomer
→ Inactive formula → dystomer.

uses/ OUD [opoid use disorders]

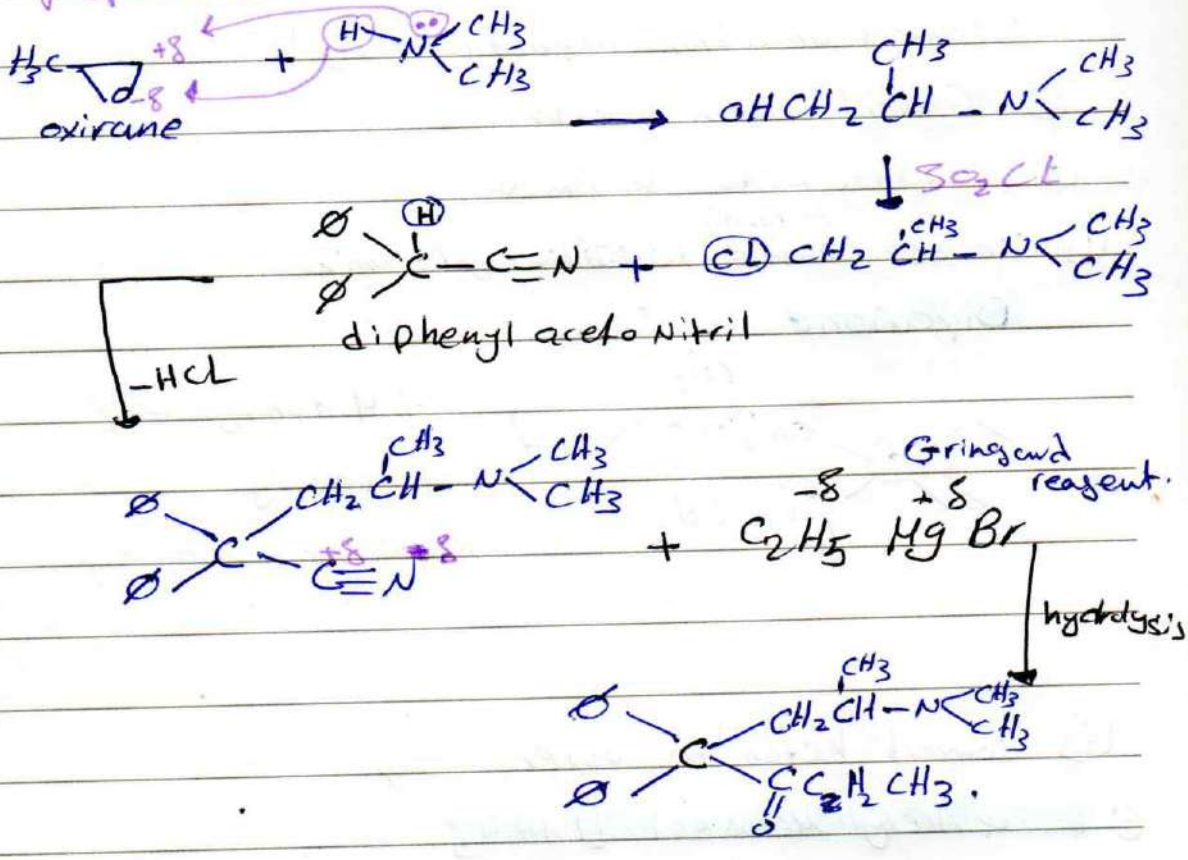
heroin. مستخدم في حالات الإدمان خاصة

- long duration
- less side effect than Morphin

(↓ sedation , ↓ emetic , ↓ constipation).

Date. No.

preparation of Methadone:



Note : if CN want to convert to C.A $\overset{O}{\overset{\|}{C}}OC_2H_5$

add C_2H_5OH/H^+

if convert to Keton add Grignard reagent

C_2H_5MgBr.

Date. No.

* Modification of Methadone:

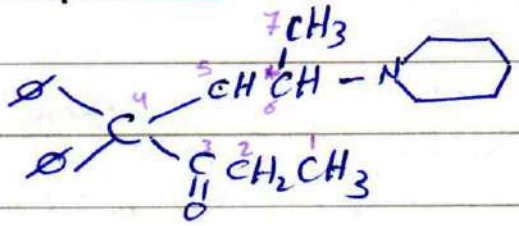
① convert amin from Aliphatic to cyclic.

② Convert keton to ester.

③ Convert keton to Amide

[1] convert amine (Aliphatic) to ~~keton~~ cyclic Amine.

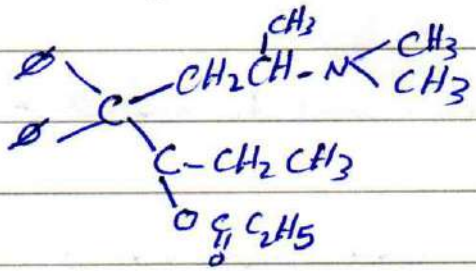
Dipanone



4, 4. diphenyl
6-piperedenyl
heptan 3 one.

[2] convert keton to ester

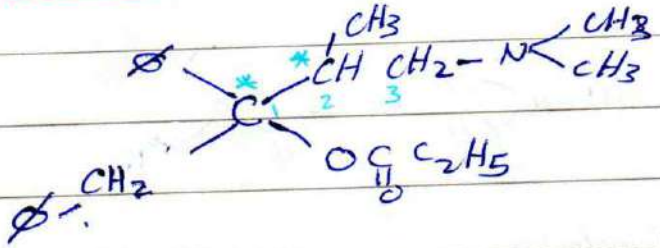
① **L- α Acetyl Methadol [LAAM]**



* more effective for OUD than Methadone
* long duration (٣٥ ساعة)

Date. No.

② Dextropropoxy phen:



2 chiral center, 4 isomer.

- 2R, 3S → Antitussive
- 2S, 3R → Analgesic

* cardiotoxcity. side effect.

(1-(phenyl)-1-(Benzyl)-2-Methyl-3-N,N dimethyl amino) propanoate.

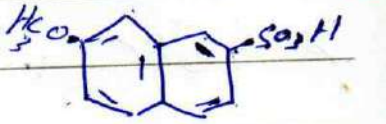
propane.

Darvan® HCl

Darvan N® (napsylate)

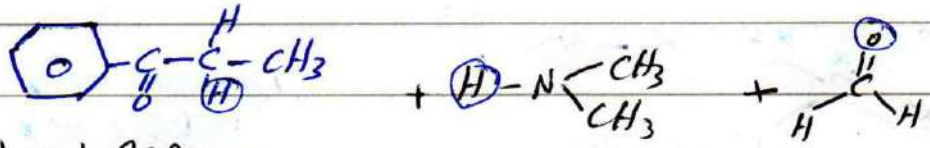
↳ salt non soluble in water.
To prevent addiction

* napsylate

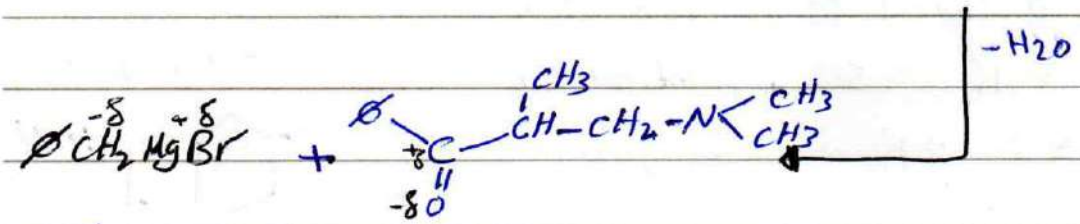


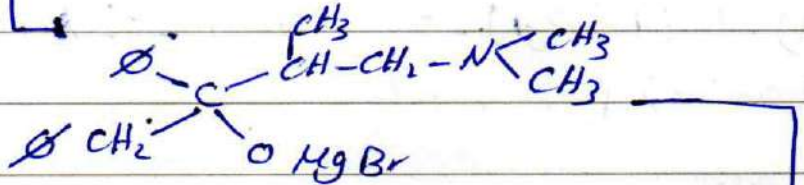
Date. No.

preparation of Dextropropoxyphen:



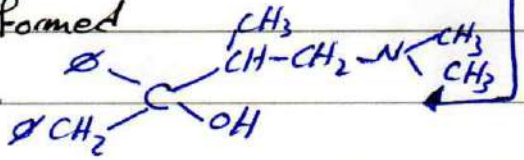
Phenyl Propanon or phenyl ethyl Keton. Dimethyl amin. formaldehyde.





hydrolysis.

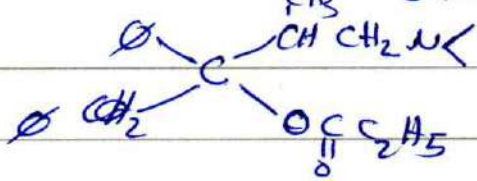
more than 1 isomer formed for seprate / isolate



Add to Champhor sulfonic Acid

→ D form → Acetic Acid anhydrous ($(CH_3CO)_2O$)

Dextropropoxyphen



Date. No.

Dextropropoxyphen usea as compination:-

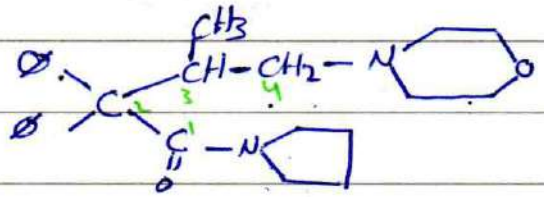
① Dextropropoxyphen + paracetamol → Dologesic®
Paragesic®

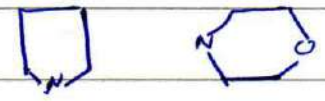
② ≤ + Mefamic Acid → ponsan fort®

③ ≤ + caffine + paracetamol + Diazepam → proxan®

④ ≤ + Aspirin + acetominophen (paracetamol) + caffine → Rogeon®

⑤ Dextromoramide → morpholine [3] convert keton to amide.





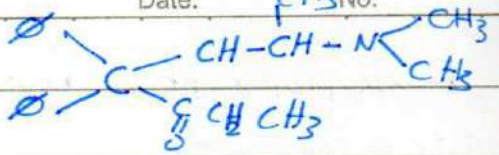
Pyrrolidine Morpholi

1-Pyrrolidinyl-2,2 diphenyl-3-methyl-4-morpholine butanone.

lec. 9.

Date. No.

SAR of Methadone :-



① phenyl ring must be unsubsituted to give activity.

② Aliphatic amine → to → cyclic Amine ↑activity
as Dipanone

③ convert Keton → ester ↑activity L-Acetyl Methadol [LAAM]
Keton → Amide ↑activity as Dextromoramide

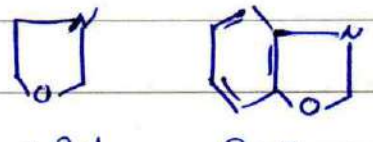
④ Transfer of methyl from position 1 → 2 ↑activity

⑤ it must has the pharmaco phor group
" phenyl propyl amine "

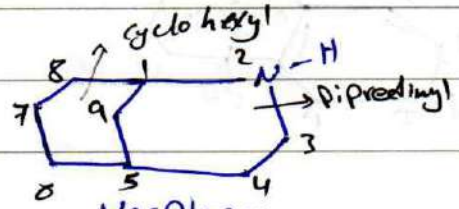
phenyl ... Amine ...

Date. No.

[3] Benzomorphane.



oxazol Benzoxazole



Morphan

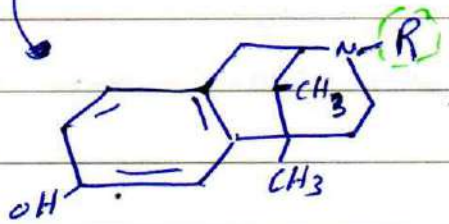
2-Aza Bicyclo (3,3,1) no

Note

Morphine → 5 ring

Morphinone → 4 ring

Benzo Morphane → 3 ring



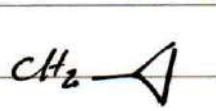
* side effect → Psycohotomimet
→ Hallucinogenic.
→ less addictive
→ less Tolerance

* All end with Zosine.

(R)

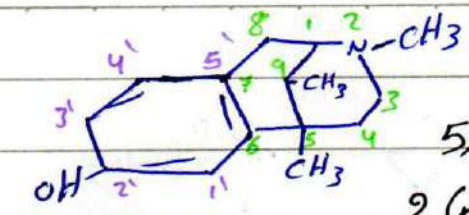
- CH_3 → Metha Zosine = Morphin
- $CH_2CH_2\emptyset$ → Phena Zosine = 4x Morphin
  Aryl alkyl / ethyl phenyl

$CH_2CH=C(CH_3)(CH_3)$ → Penta Zosine — Mixed Agonist Antagonist
Dimethyl allyl
K receptor (Partial / Full)
↳ M receptor (weak)



→ Cyclo Zosine Antagonist

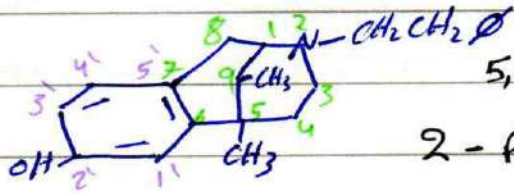
Date. No.



Methazosine

5,9 dimethyl - 2' - hydroxy

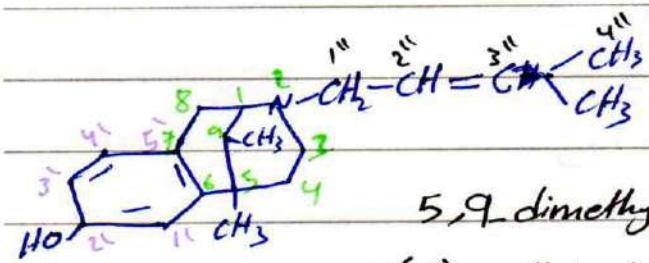
2 (methyl) benzomorphan



phenazosine

5,9 dimethyl - 2' - hydroxy -

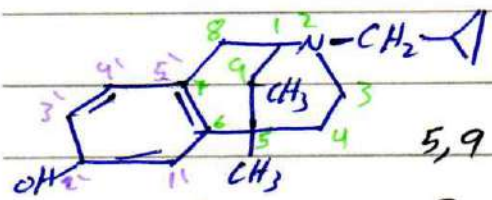
2 - phenyl ethyl benzomorphan



pentazosine

5,9 dimethyl - 2' - hydroxy

2 (3" methyl - but - 2" enyl) benzomorphan



Cyclazosine

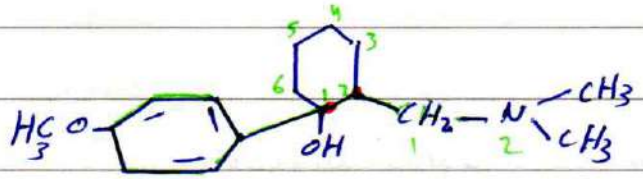
5,9 dimethyl - 2' hydroxy -

- 2 - (cyclopropyl methyl)

Benzomorphan.

Date. No.

Others: Tramadole, Tramal®



✓ Pharmacophore group

"Phenyl propyl amine"

1(p-Methoxy phenyl)-2-((N,N dimethyl amino) methyl) cyclo hexanole.

C_1, C_2 → chiral center.

(+)enatiomer 30 fold activity than (-) enantiomer

- Tramal → on salt or HCl salt form
  - orally active.
- O-demethylation By CYP-2D6 — same enzyme for codaine

OCH_3 → OH

active → increased Activity. + give active metabolite.

- Has Dual mechanism, stimulation M receptor and inhibition for Noradrineline. (Norepiniphrin)
- it's potancy is .1 of morphin (weak)
- The metabolite, Enantomer cause (Proconvulsive)

for knowledge:

- Tapentadol → No pharmacophor ↓ from others

Strong Analgesic

. lec. 10 .

Date. No.

Analgesic

Strong
- Narcotic "induce sedation"
- All contain pharmacopher group
- Activity related to structure

week "Mild"
- Non Narcotic
- No pharmacopher.
- Drug Activity Not related to structure.
- called "NSAIDs"

Non steroided Antiinflammatory Drugs.

- Analgesic, Antipyrtic
  - affect on Thermoregulation center in hypothalamus.
- Analgesic, Antiinflammatory

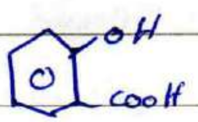
* Inflammation: A Normal protective response to tissues injury, caused by noxious chemical, physical trumen or microbilogical Agent.
* Autocoids: As Histamin, Serotenins, Prostaglandin, leucotryins (release of these medicators lead to immune response).
* All NSAIDs, has different structure but same Action.

Date. No.

NSAIDs inhibits cycloxygenase [cox] pathway.
That lead to inhibit prostaglandine.

read chapter 2 (prostaglandine) Text Book of Medicinal Che.
- Type of Ps, Biosynthesis, Function
- class of cox inhibitor.
- Type of cox.

* Eicosanoids:
it compounds that derived from Arachidonic Acid (20C)
as : Thromboxan, Lipoxin, Leukotrins.
* classification of week Analgesic:-
I) Salicylic Acid derivative : "Salicylate" 1st
- From [spirea plant] جريه
- The plant has salicine $\xrightarrow{ox.}$ salicylic Acid
* Not used directly : ① gastric irritation, ulceration
② Bad taste



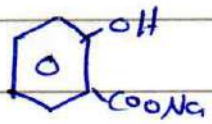
ortho hydroxy benzoic Acid
Salicylate / Salicylic Acid

Date. No.

So they make salt form of Salicyclic Acid.

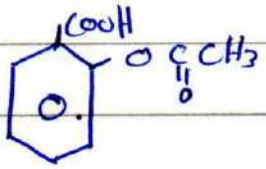
Thus : ① ↓ gastric irritation

② ↓ Analgesic.



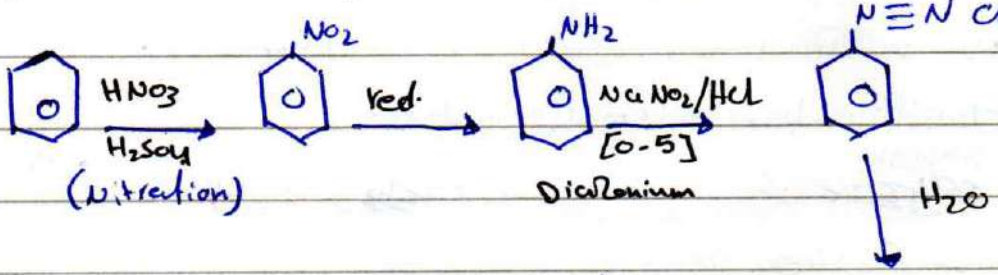
Sodium Salicylate

① Aspirin , Aspirin®, Baby Aspirin®, Godmed®, Rhonal®

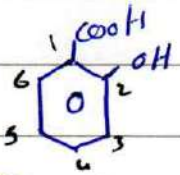


Acetyl Salicylic Acid

* preperation of Aspirin : Koble shmith RXN.



Date. No.



① OH in ortho, but if convert to (m,p) loss Activity

② 5 position if has withdrowal group [Cl⁻, F⁻..]

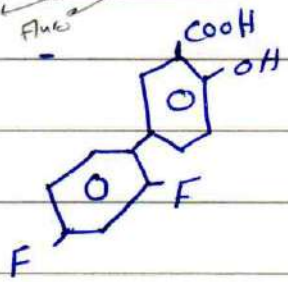
↑ Antiinflammatory effect. but ↑ toxicity.

A) So they make modification instead of put Direct Cl or F⁻

They put Phenyl group with orther, para Floro.

[1] Diflunisal Dolobid®

Di Fluo

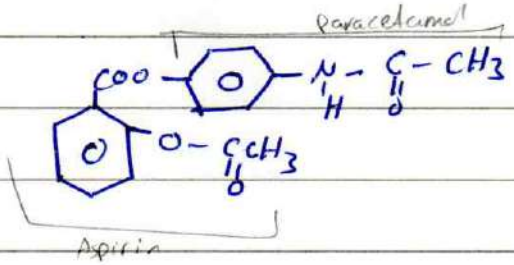


- Absorbed in intestin.
- ↑ Potency
- has Longer DoA

Due to Enterohepatic circulation cycle.

B) second modification.

Benorylate [esterification of Paracetamol and Aspirin]



salicylate

N(acetyl) amino phenyl Acetyl Salicylate.

↙ ester

Date. No.

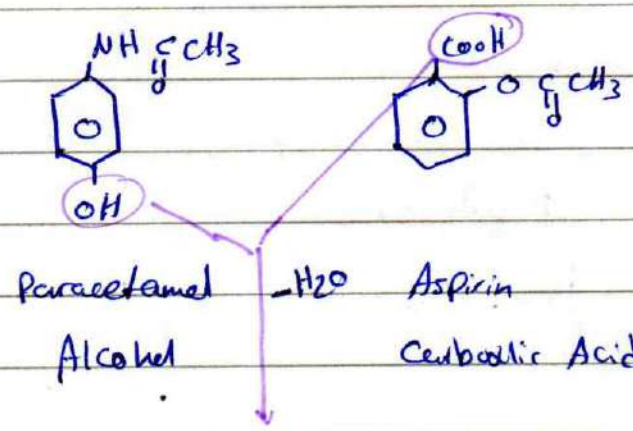
goals of All Modifications:

① ↑ Activity.

② ↑ stability

③ ↓ side effect in GIT

in this case ↓ side effect in GIT so less gastric problem



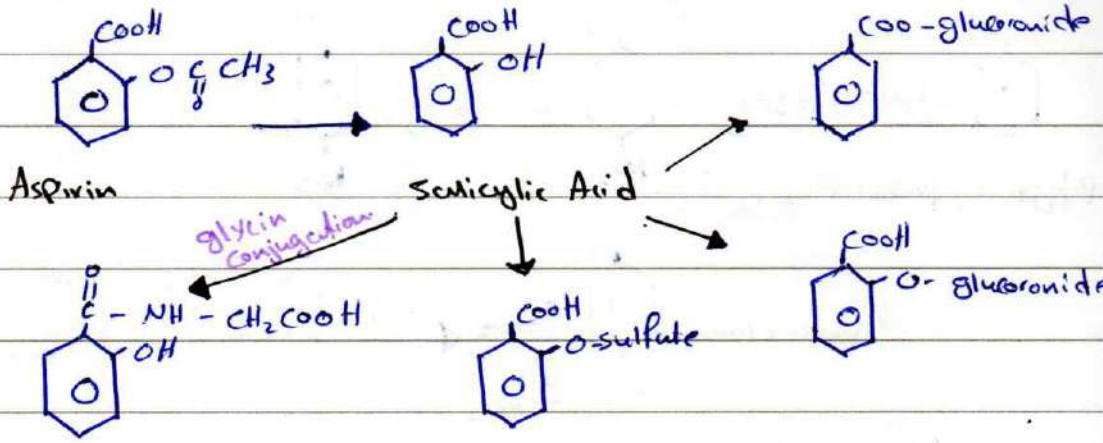
Estrification

↓

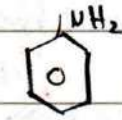
Benorylate.

Date. No.

Biotransformation of Aspirin.

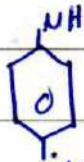


[2] Analine Derivative :- 2ed



Anali

① Paracetamol. Dexamol®, Acamol®, Paramol®
Autamol®



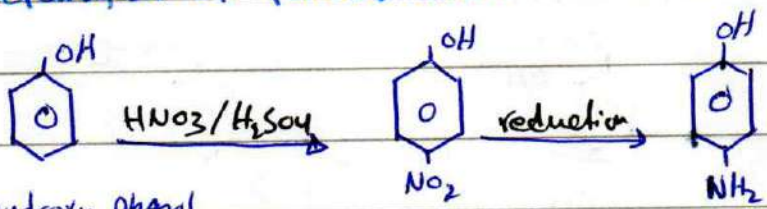
p-hydroxy Acet ~~Acid~~ Anilin.

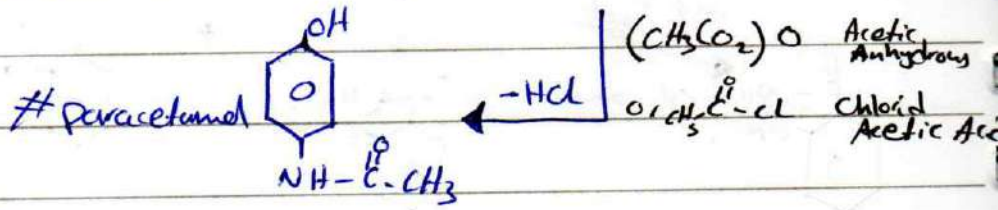
or N-Acetyl p-hydroxy Anilin.

- weak inhibitor for COX_1, COX_2.
- No Antiinflammatory effect.
- Not affected on Platlete aggregation.
- inhibito COX_3 ⇒ give Analgesic + Antipyritic eff

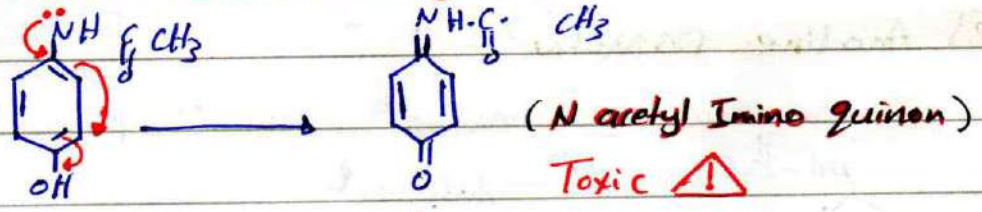
Date. No.

Preparation of paracetamol:-

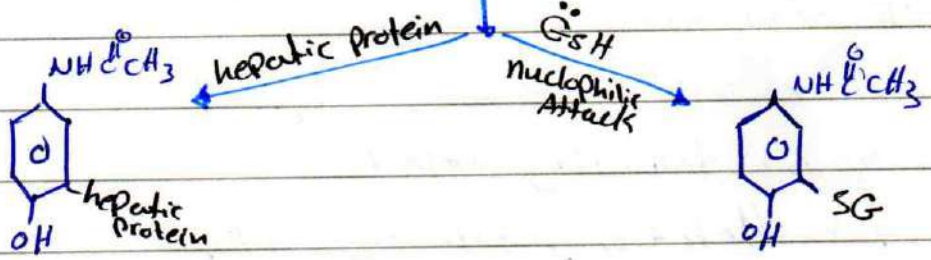




Side effect: Hepatic toxicity How ??

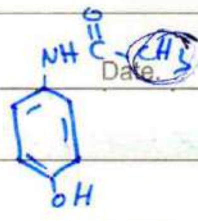


To remove toxicity



Note: Acetylcysteine act as Antidote of high Dose of paracetamol, because it has a source of GSH

SAR of paracetamol :-



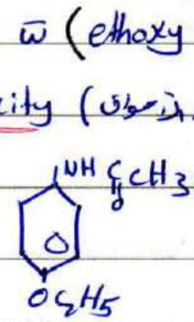
(1) Methyl group , if replaced $\bar{w}$ Phenyl → ↓ activity.

(2) OH in para , if replaced $\bar{w}$ alkyloxy (Methoxy OCH_3 , Propoxy OC_3H_7) → ↑ side effect.

But

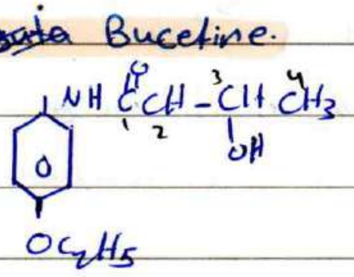
if replaced $\bar{w}$ (ethoxy OC_2H_5) → become Prodrug of paracetamol $\bar{w}$ ↑ toxicity (تم سحبه من السوق).

as :-



Phenacetine (Prodrug). ⚠

* Bucetine.



N(P-ethoxy Phenyl) - 3-hydroxy butanamide or butiramide.

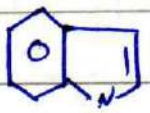
$CH_3 \overset{O}{\overset{\|}{C}} - NH$
acet amid

$CH_3 \overset{O}{\overset{\|}{C}} NH$ (phenyl)
N-phenyl acetamide

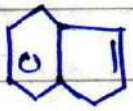
3rd

Date. No.

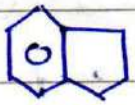
[3] Indol derivative :- [Aryl hetero Aryl Acetic Acid or Aryl Alkanoic Acid]



Indol

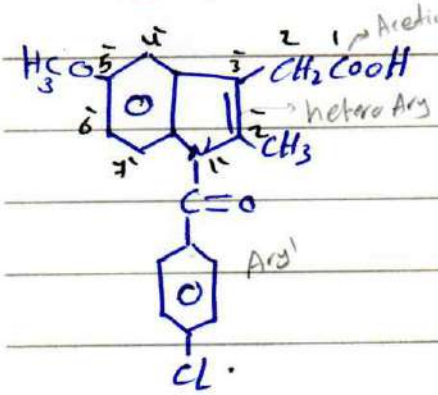


Inden



Indan.

① Indomethacin Indomed® Indocine® Indovis®



* Non-selective cox inhibitor
* Antipyrtic higher than Aspirn and Paracetamol
* has 2 cyclic
  - Phenol
  - Indol
* Aryl hetro Aryl Acetic Acid

2 [1' (p-Chloro benzyl) - 2- methyl - 5- methoxy indol-3-yl] acetic acid.

* side effect /
  1. Indol Lipophylic ring → pentrate CNS → CNS side effect Due to N
  2. GI irritation.

Date. No.

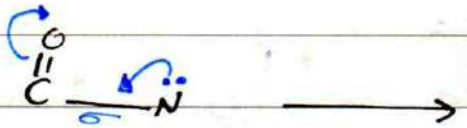
تبقى على نفس المستوى

* 2 cyclic in Indomethacin are [Non-coplanner] why ??

① Due to conversion of single bond of Amide to double bond

in which single bond (more easy in rotation)

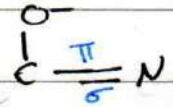
But double bond (Lower flexability, break when rotate).



single bond

as Alkan, cyclo Alkan

easy in rotation



double bond

- break in rotation
- Lower flexability.

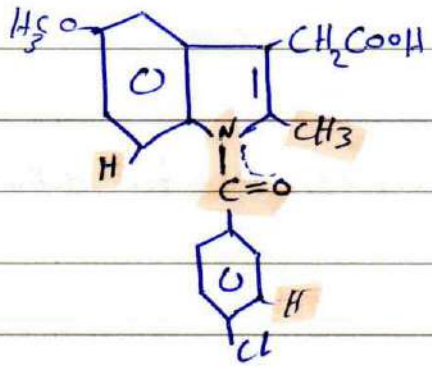
and give → cis Z active ✓

→ Tran E inactive ✗

② CH_3 on 2

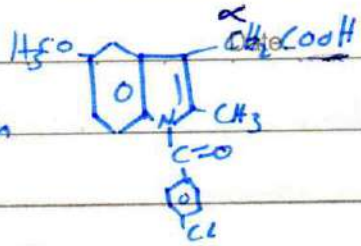
③ H on 7

④ H on ortho on P-Chloro ~~Pho~~ benzoyl.



No.

SAR of Indomethacin



① Carboxlic Acid if replaced w Bio isostresm

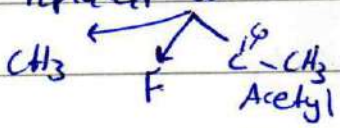
as • Amide ⟶ inactive

• Alcohol ⟶ ↓ activity · (CH_2OH)

② Cl in p- chloro benzoyl if replaced with → CF_3 (Tribro methy) ↑ activity

→ 5-CH_3 (Methy thio)

③ o CH_3 in positim 5, if replaced w still active.



④ p. cl benzoyl if replaced phenyl with CH_3 inactive

⑤ ∝ carbon, if attached to methy, it becom Chiral carbon.

This lead to

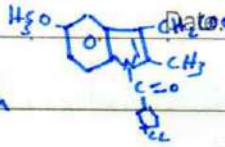
S-isomer R-isomer → inactive ∝

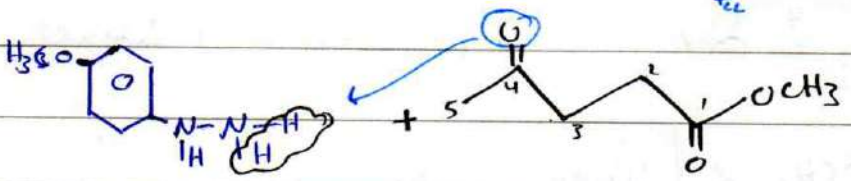
Active as Antiinflammatory ✓

⑥ N in indol, it's excistance not essintial for Activity.

Date: No.

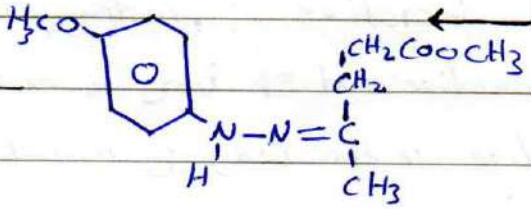
preparation of Indomethacin



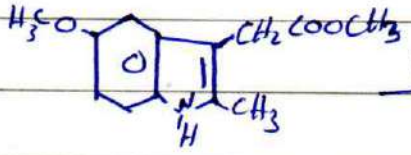


P-Methoxy phenyl hydrazin Methyl 1,4 oxo pentanoate.

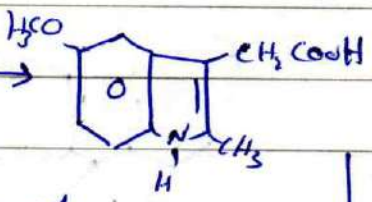
$-H_2O$

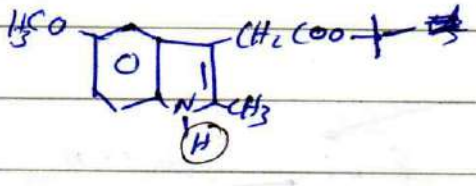


Fisher Indol cyclization.

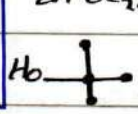


hydrolysis

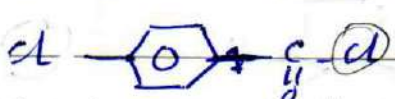




Zn Cl_2/DCC

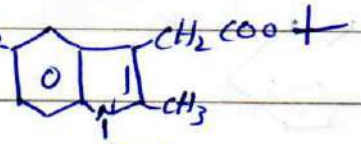


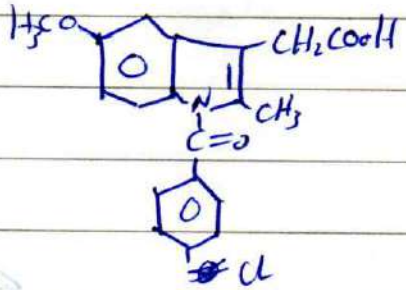
+



P-Chlorbenzyl Chloride

$-HCl$ / NaH





Pyrolysis

without water

but hydrolysis vi water.

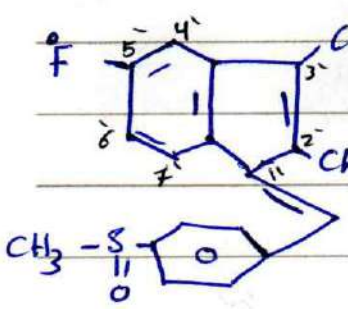
Indomethacine

Date. No.

2- Sulindace (sulfonyl) Clinoril®

Indan → Inden

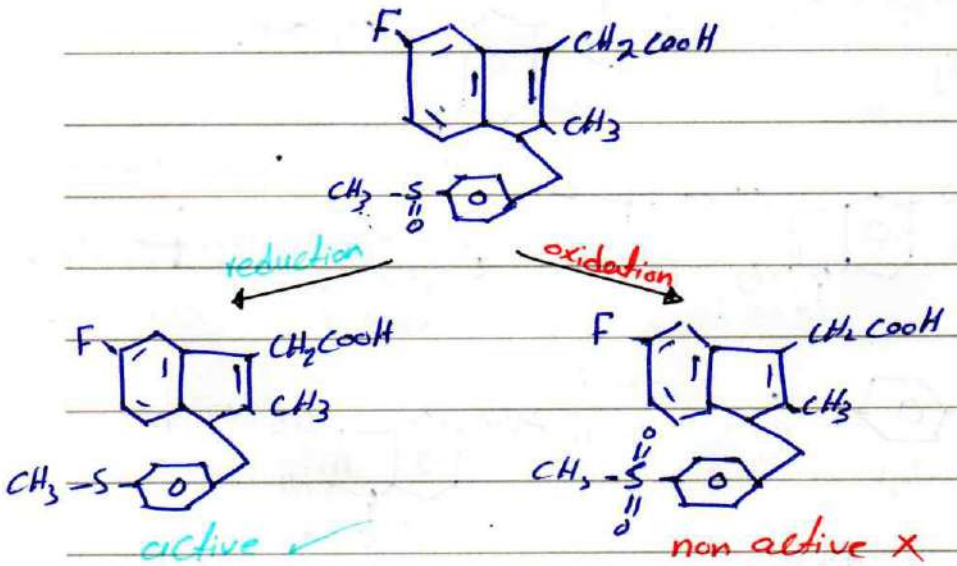
* Bioisosterism of Indomethacin



2 [(methyl sulfonyl phenyl ideny l) 2` methyl - 5` Fluro] Inden 3` yl] acetic acid

* It's inactive (Prodrug)
* Inactive out of body in oxidation form
* active in the body by metabolism in a reduced form.

- The metabolism:

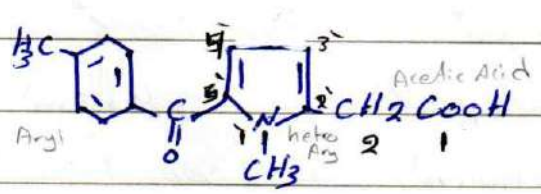


Date. No.

Note

- in 5` position if F replaced with CH_3 (methyl thio) give same activity.
- CH_3-S (methyl thio) ↑ activity.
- in the middle double bond Z > E
  Z is mor active as Anti inflammatory than E.
- removing N (Indan → Indene) • make ↓ side effect. on GI, CNS. , ↓ Activity!
- Indomethacine > sulindace (Anti inflammatory)
- The goal of Bioisosterism is Lowering side effect.
- give Long Duration.

3- Tolmetine, Tolectine® (Aryl hetero Aryl acetic Acid)



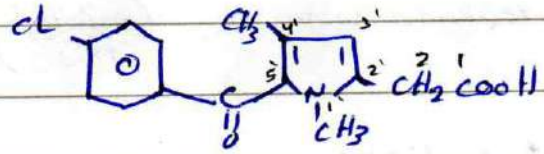
* The rings are Non Co-planner

2[5`(p-methyl benzoyl)-1`-methyl Pyrrol-2`-yl] Acetic Acid

- short duration of Action Methyl $\xrightarrow{\text{metabolism}}$ CH_2OH
- Non selective cox inhibitor
- Analgesic, Antipyritic, Antiinflammatory

Date. No.

4- Zomepirac , Zomex® (Aryl hetero Aryl A.A)

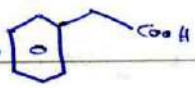


2[5`(p chloro benzoyl) - 1`, 4` dimethyl Pyrrol-2`-yl]

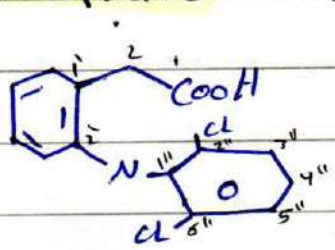
Acetic Acid

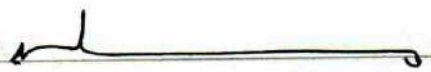
- 4 time higher than Tolmetine
- Anaphlyfic shock RxN side effect
- Long DoA CH_3 → Cl (in Tolmetine)

* 4th Phenyl Acetic Acid Derevatives.



1- Diclophenic in salt Form





$COO^- Na^+$

- Diclophen®
- voltaren®
- Bettaran®
- ABitren®

↑ absorption
as upjohn

$COO^- K^+$

- cataflam®
- Anaflam®

* For HTN
rapid absorption
↓ liss duration
in body.

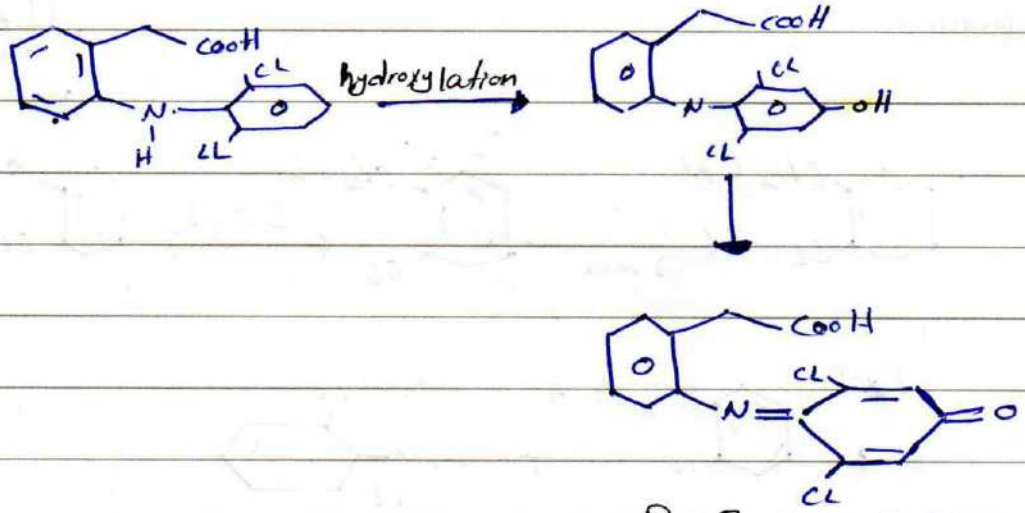
- more potent
then Indomethacin
and Aspirin

Date. No.

• 2[[2`(2",6" dichlorophenyl] amino] phenyl] A.A (or anilino)

hepatotoxic ; due to metabolism.

The metabolism /



Benzo imino quinon

toxic ⚠

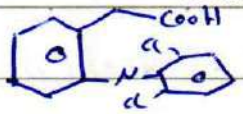
• we could remove the toxicity by Adding

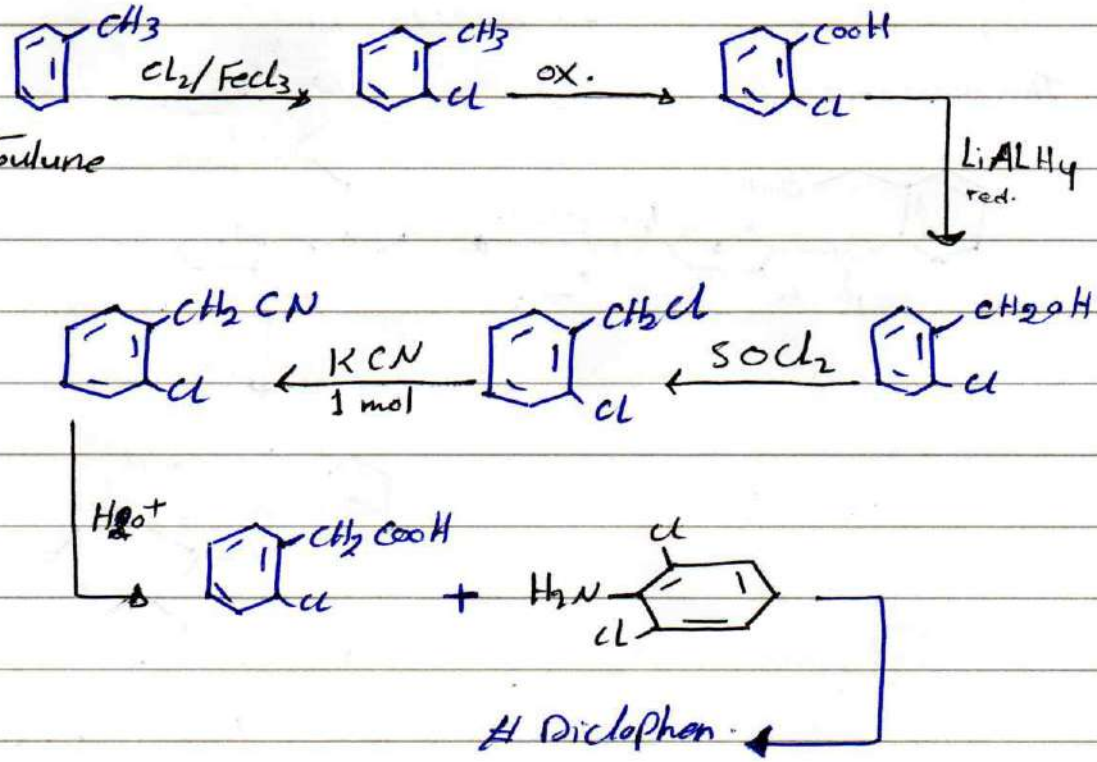
- OsH
- heptatic Protein.

★ Diclophen is the most spread and use in weak analgesic.

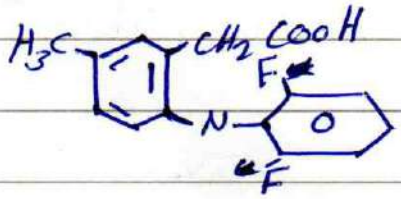
Date. No.

preperation of Diclophen:





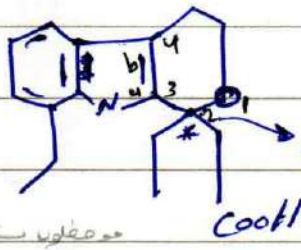
2. Lamira coxib



- Selective COX_2 inhibitor.
- Has been used in 2004
  But removed from the marked 2007
  Due to it's side effect on the liver.

Date. No.

3. Etodolac.



Pyran.

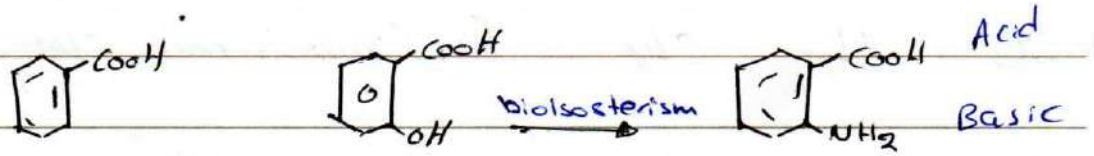
Fused ring

Pyrano [3,4-b] Indol Derivative.

Chiral center.

- S(+) active
- selective COX_2 inhibitor.
- 1/3 effect as Antiinflammatory compared to indomethacine.
- less GI side effect.

5th Anthranillic Acid derivative.

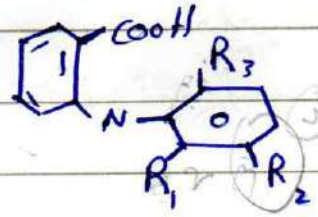


benzoic Acid — o-hydroxy benzoic Acid — o-Amino benzoic Acid "Anthranillic Acid"

Amphoteric.

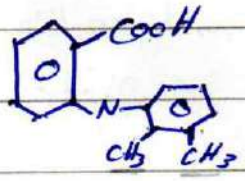
Date. No.

General Structure For Anthranillic Acid derivatives /



	R_1	R_2	R_3	
1.	CH_3	CH_3	H	Mefenamic Acid → Ponstan®, Ponstal®
2.	H	CF_3	H	Flufenamic Acid arelf®
3.	Cl	CH_3	Cl	Meclofenamic acid Meclomen®
4.	CH_3	Cl	CH_3	Tolfenamic Acid Clotam®

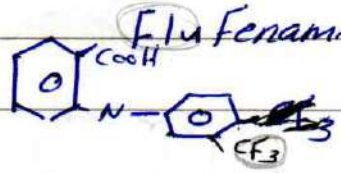
① Mefenomic Acid Ponstan®, Ponstal®



N[(o,m dimethyl) phenyl] anthranillic Acid.

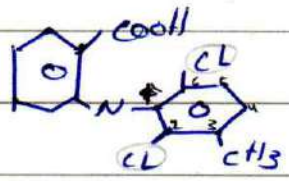
Date. No.

2- Flufenamic Acid



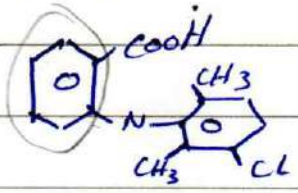
N[m- Trifluro phenyl] anthranillic Acid

3- Meclofenamic Acid



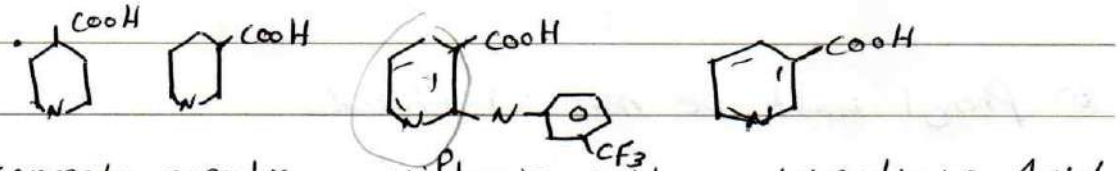
N[(2, 6 dichloro - 3- methyl) Phenyl] anthranillic acid

4. Tolfenemic acid



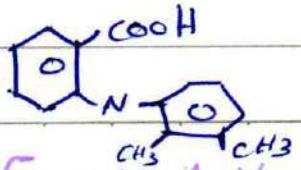
N[(2, 6 dimethyl - 3- Chloro) Phenyl] anthranillic Acid

Note



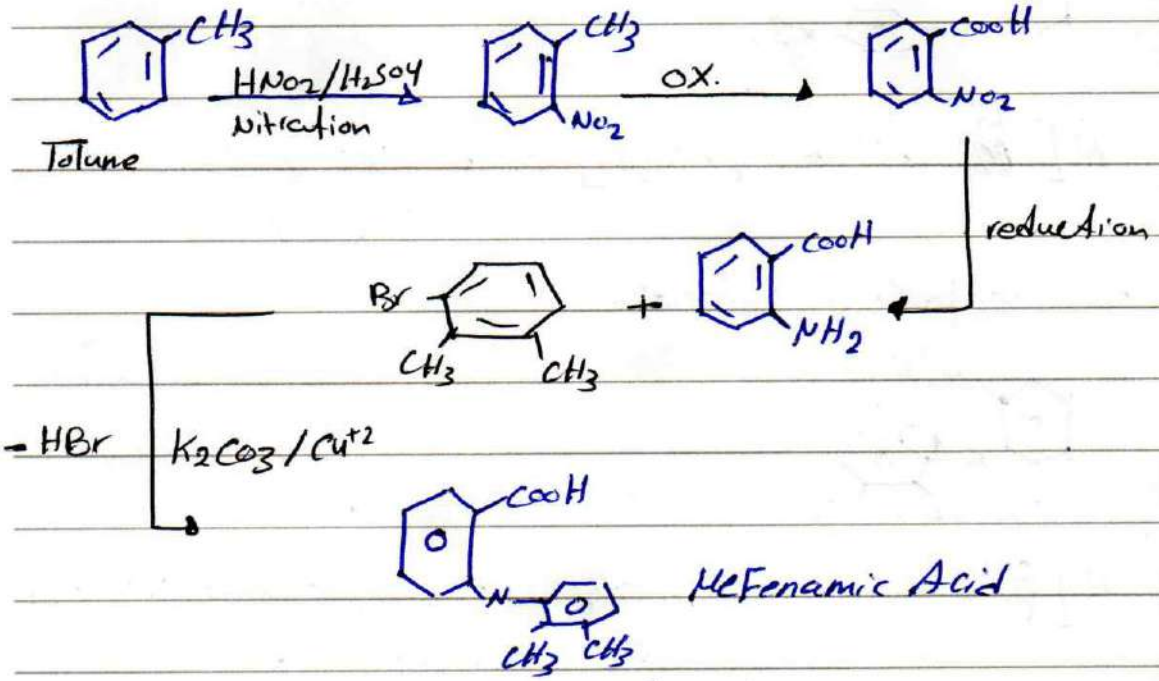
Isonicotic Acid Nicotic Acid Niflumic Acid Nicotinic Acid.

Is Bioisostesm of Flufenamic acid.

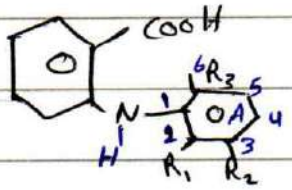


Date. No.

Preparation of Mefenamic Acid From Tolune &



SAR/



① COOH, is improtent for give activity
if replaced ω tetrazole still active.

② Phenyl must be non substituted

Date. No.

③ $\underset{H}{N}$ if replaced ~ O, CH_2, S, $\overset{O}{\underset{O}{S}}$ (sulfoxid), $N-CH_3$ (methyl amin), $N-C(=O)-CH_3$ (Acetyl Amino)

↓ Activity

④ NH must be in ortho position to give activity if replaced to m, p → inactive.

⑤ Phenyl Ring (A) must has substitute to give activity best position :- 3 > 2 > 4

⑥ if 2 substituted present at the same type. must be in (2,3) or (2,6) → more active than (2,3)

.ex/ Antiinflametory effect in Meclofenamic Acid (2,6) Cl is higher 25 time as Antiinflammatory than Metanemic acid (2,3).

(2,6) TolFenamic acid.

∴ Meclofenamic Acid or TolFenamic Acid > Metenamic Acid

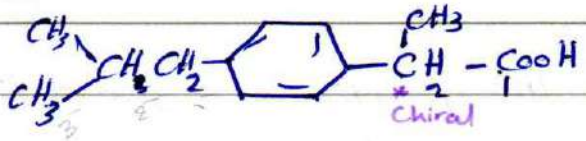
25 time As Antiinflammatory

Date. No.

6th Phenyl propanoic Acid derivatives.

ends ~~w~~ profen.

① ~~Ibo~~ **Ibuprofen** Advil®, Trofen®, Ibufen®, isofen®



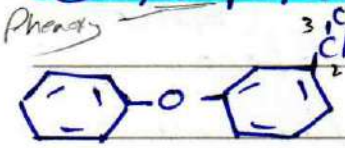
R(-) 2[[[p(2'methyl) propyl] phenyl]] propanoic Acid.

or iso butyl

* 1 Chiral center → S(+) active
→ R

* inside the body R —epimerization→ S (Prodrug)

② **Fenoprofen Nalfon®**

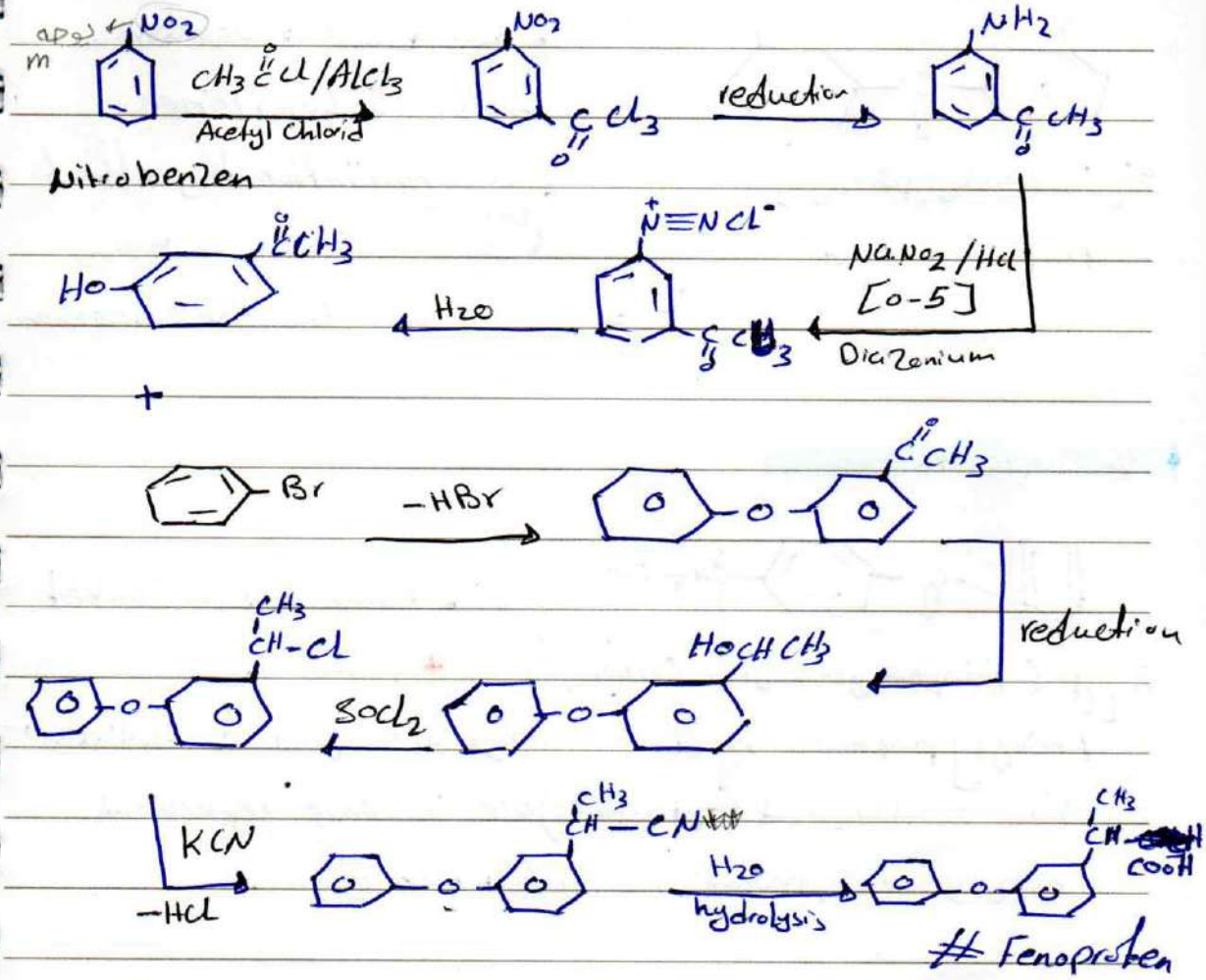


2[[[(m phenoxy) Phenyl]] propanoic Acid

- has ↓ Antiinflamatory effect than others.
- Bus Same Antipyrtic, Analgesic effect.

Date. No.

preperation of Fenoprofen.

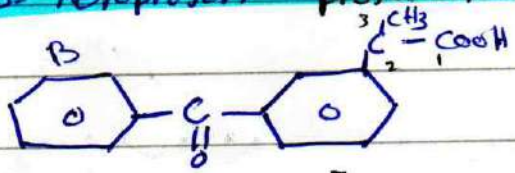


Note

- we don't start ~~w~~ Tolune  cause it direct ortho. and para because CH_3 is donating group
- But Nitro benzen  has NO_2 (withdrawl group) it direct m only

Date. No.

3- Ketoprofen profencil ®



2 [(m-benzoyl)Phenyl]
Propanoic Acid

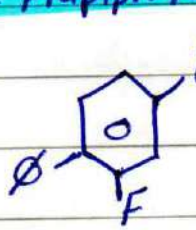
- has Duel mechanism ↓Ps, ↓ Lukotrines.
- Less Antiinflamatory effect. due to
  - No substitution on B ring
  so loss the non coplanner.

4- Suprofen

2 [[p (thiophenyl-2-yl) carbonyl]
Phenyl] propanoic Acid

- removed from Market ↑ Iodic
- Today used just as Antiinflam~
  For ocular (ophtalmic) use in Lense replacement surgery to prevent iris inflammation.

5- Flupiprofen



- due to presence of F it has non coplanner
- For ophthamic use.

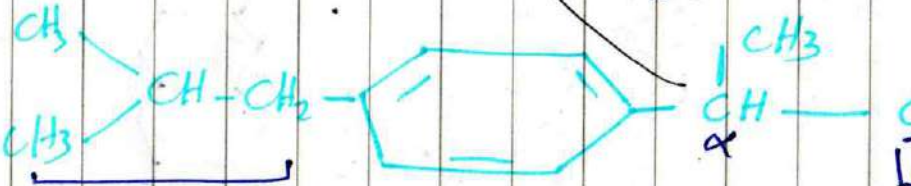
2 (m-Fluro-p-Phenyl) Phenyl propanoic Acid

SAR

α-carbon must bind to CH_3
To ↑ inflammatory effect
↓ side effect.

if not bind to methyl → has ↓ Antiflammatory

Acetic Acid der.
Ibufenac
hepatotoxic ⚠



* isobutyl must be in para position.
* if Phenoxy (As in Fenoprofen)
  - it should be in m
  - if replaced in o, p. ↓ activity
  - if replaced ω benzoyl still active as in Ketoprofen

if it has Cl, F (withdrawal) ↑ activity.

- C.A, ↑ inflammatory effect
- if replaced ω ester, Amid Azole ↓ Activity

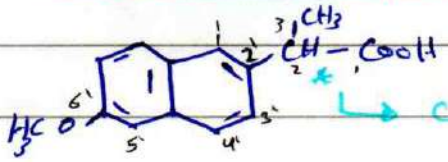
Date.

No.

Part 2 of Propanoic Acid derivative Date. No.

Now ⬡ replaced with ⬡⬡ naphtalin

6- Naprodine Naproxye®, Naroline®, Naxyn®

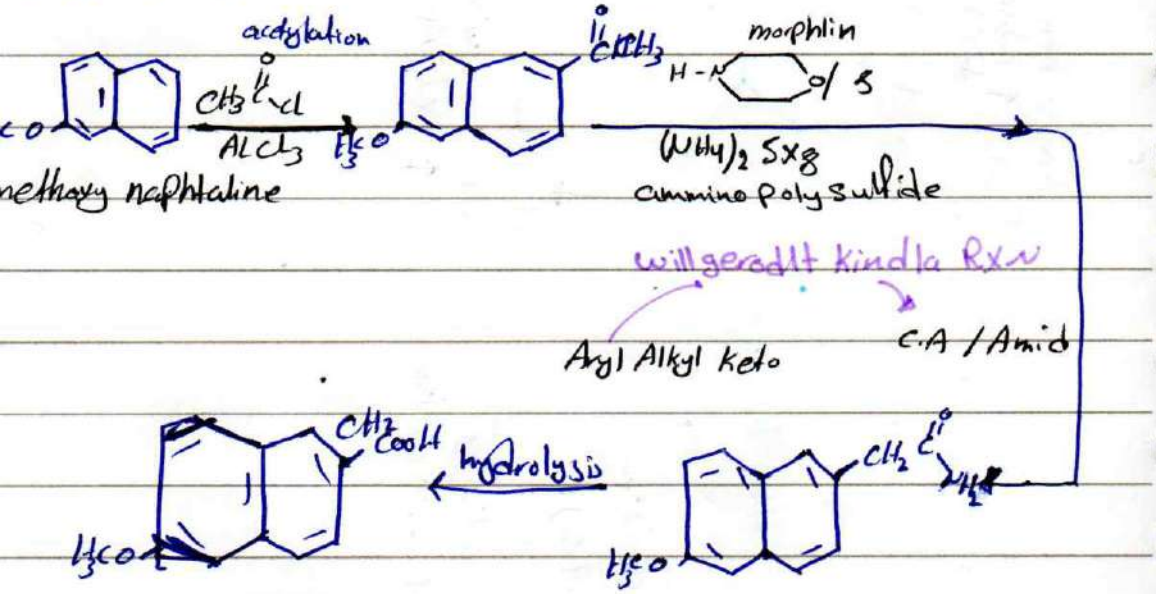


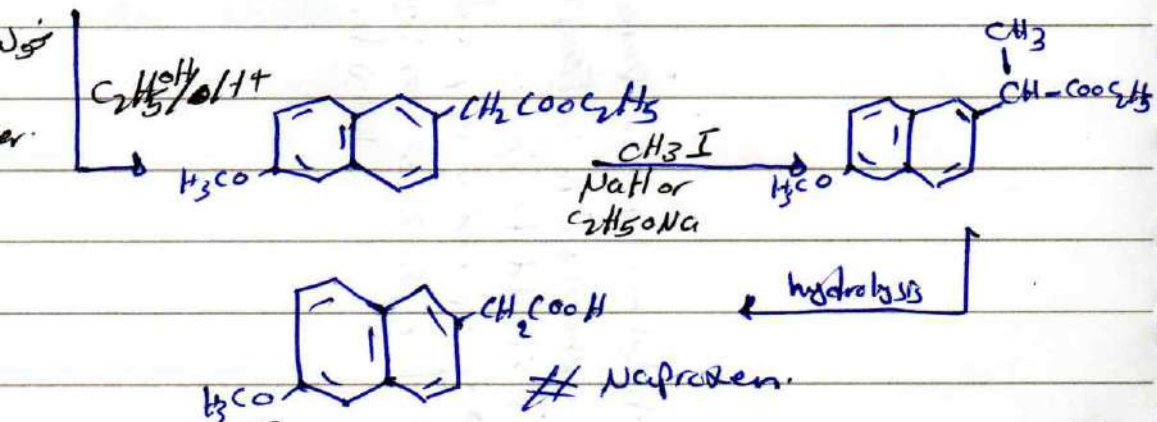
↳ chiral S(-) active.

↑ Antiinflammatory.

2[6'methoxy naphthal 2'yl] propanoic Acid

Preparation/

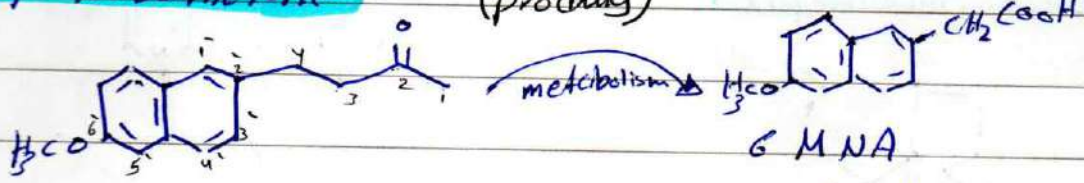




↳ sideffect ↑ Antinflamatory

Date. No.

7- Nabumetone. (prodrug)



6 MNA
(active)

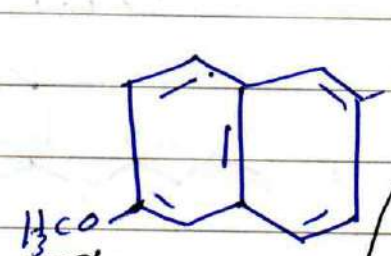
4 [6-methoxy naphth-2-yl] but-2-one.

- pretential Cox2 inhibitor (Not selective)

* GMNP (6- methoxy naphthyl Acetic Acid)
  - ↑ $t_{1/2}$ ≈ 24 h.
  - less GI side effect.

Not acid

SAR.



C.A if replaced ω
(Alchol, ester, aldehyde
still same activity
CH_2OH, $COOCH_3$, CHO

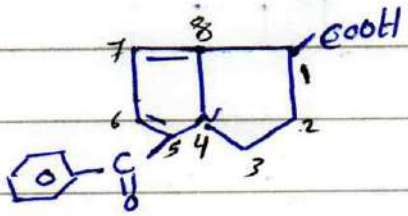
if removed ↓ activity

if replaced ω
[Cl, $(5\text{-}CH_3)$ $(6\text{-}CHF_2)$] (Difluoro methoxy)
still active

if replaced ω large group ↓ activity.

Date. No.

8- ketorolaee spirx

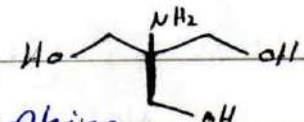


5-benzoyl-2,3 dihydro-pyrrolizidin-1-C.A.

Ch. Ch/

- Acidic
- use as Salt Form called Tromethamine (I.V only) → narcotic.

by adding base to it.

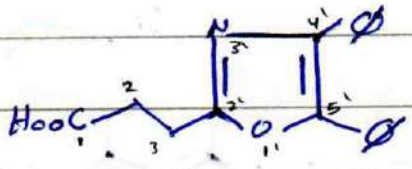


15-30 mg equal 12 mg morphine

So it's used as Alternative for Narcotic Analgesic.

- Non selective. cox_1, cox_2 inhibita

9- oxaprozine



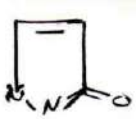
3[(4',5'-diphenyl) oxazol-2'-yl] propanoic Acid.

- long DOA → once daily
- side effect :- rash, mild photosensitivity


Imidazol


1,2 N Pyrazol

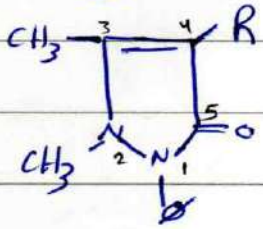

2,3 dihydro Pyrazol


2,3 dihydropyrazolone.

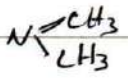
Date. No.

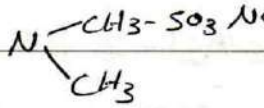
7th

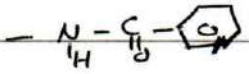
⑦ Pyrazolone + pyrazolidiones derivatives.

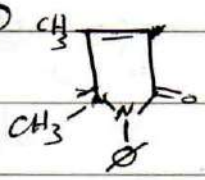


R: H Antipyrine Phenazone ®

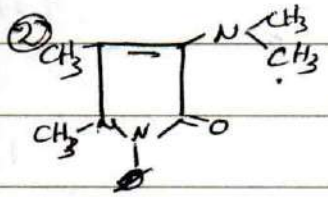

Aminopyrine.


Novalgine Dipyrone ® Oplagin ®


Niphenazone.

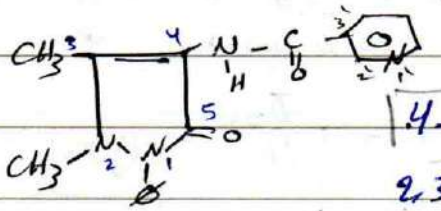
① 
Antipyrine

(2, 3 dimethyl - 1 Phenyl 2, 3 dihydro Pyrazolone 5-one.).

② 
Aminopyrine

(2, 3 dimethyl - 1- Phenyl - 4- N,N dimethyl amino 2,3 dihydropyrazol 5-one)

③ Niphenazone



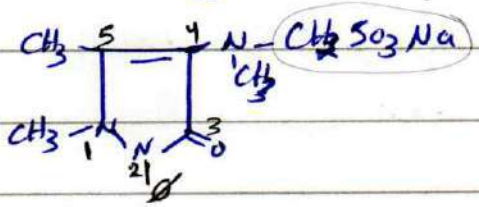
(2,3 di~~p~~methyl - 1- Phenyl - 4- Pyridin-3-yl carbonyl amino 2,3 dihydro Pyrazol 5-one)

Nicotinyl

اکثر فی ای مرکب صو ا زنی

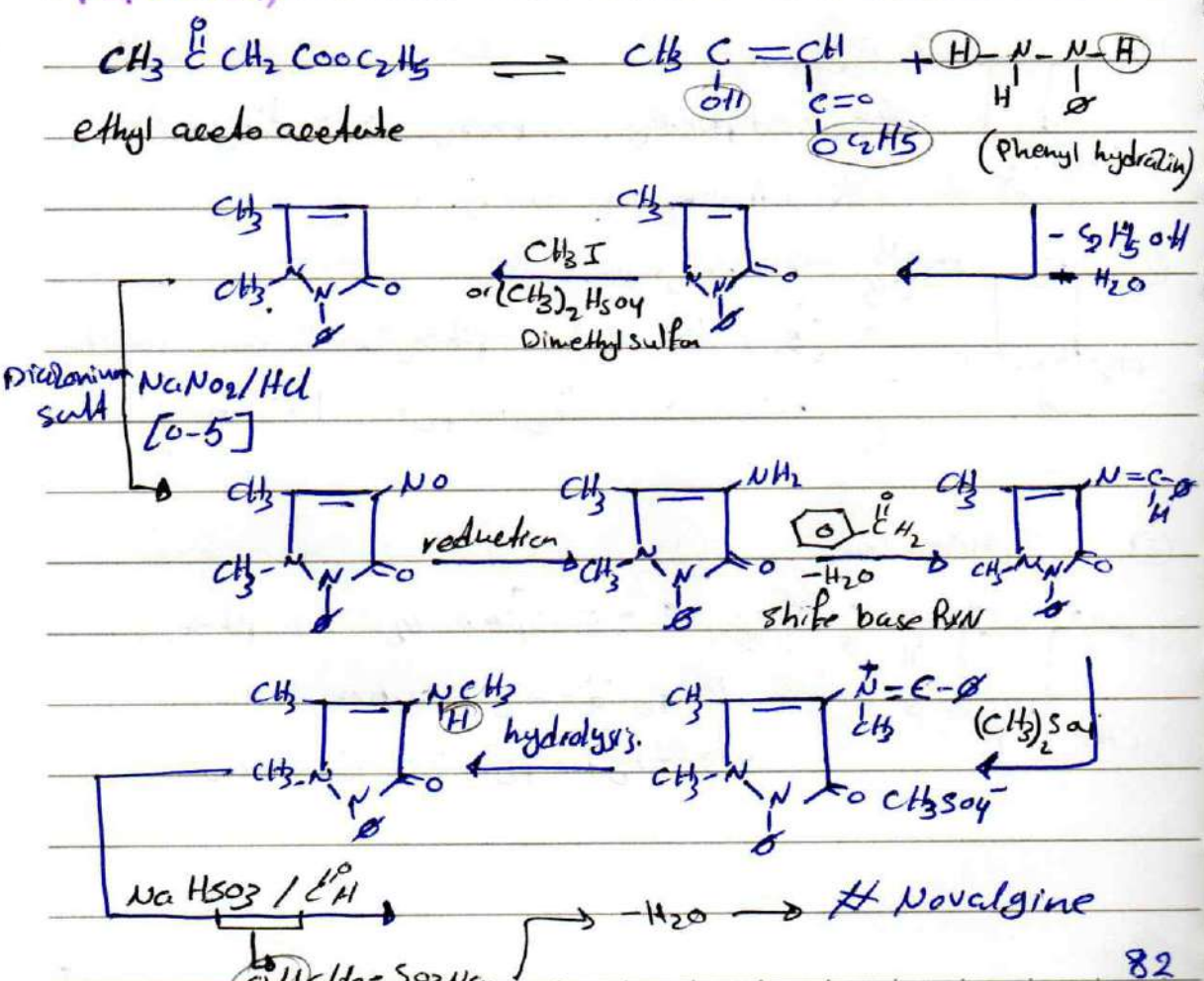
Date. No.

Novalgine



N-methyl [(1,5-dimethyl-2-phenyl-3-oxo-2,3-dihydro pyrazol-4-yl) amino] methanesulfonic acid Sodium salt.

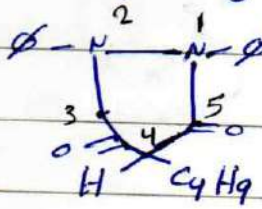
Preparation/



Date. No.

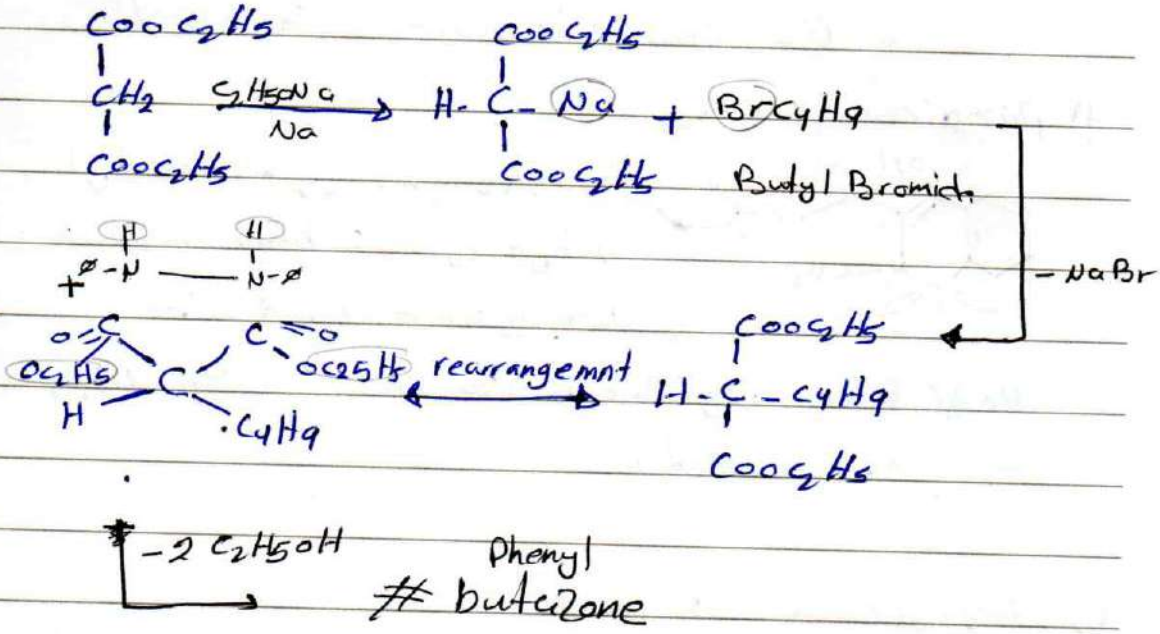
Pyrazolidinediones.

Phenyl butazon.



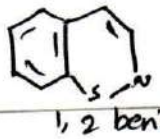
(4- butyl - 1,2- diphenyl Pyrazolidin 3-5 dione.).

Preparation /

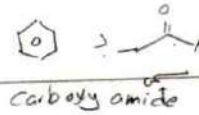


$\xrightarrow{-2\ C_2H_5OH}$ Phenyl # butazone

thiazin



1, 2 benzo thiazin

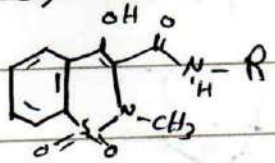


carboxy amide

Date. No.

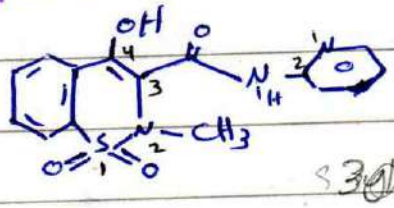
Others "selective COX_2 inhibitor" → oxicam, coxib

① oxicam · (1, 2 benzo thiazin derivative)



in general
- No Free COOH
- Acidic group is Enole
- Long t1/2, once daily
- For osteoarthritis OA
- GI, CNS disturbance "side effect"

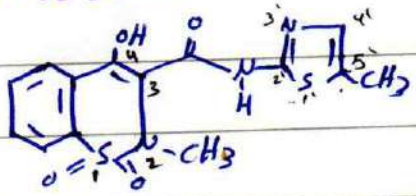
A) Piroxicam. R- pyridine



N(pyridin-2-yl) -2- methyl 4- hydroxy - 1, 2 benzothiazine 3 carboxyamid 1,1 dioxide

MoA/ Reversibly inhibits cox enzyme (COX_1, COX_2) "non selective".

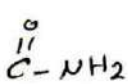
B) Meloxicam R- Thiazol.



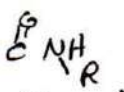
N (5-methyl thiazol 2-yl)- -4- hydroxy -2- methyl- ~~carboxy~~ 1,2 benzo thiazin carboxy amid 1,1 dioxide

MoA/ - selectively inhibits COX_2

Note



amide

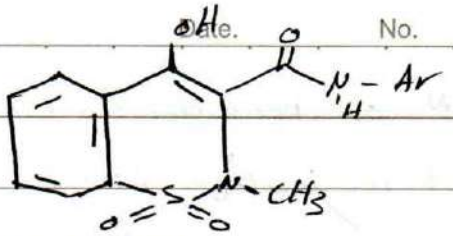


1° amide

2° amid.

Date. No.

SAR of oxicam

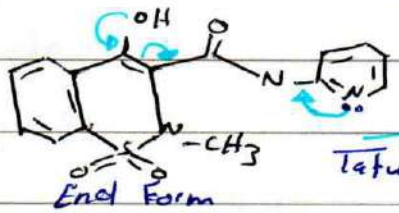


[1] 1° amide > 2° amide (more active)

[2] Heterocyclic on Ar is more potant (active) than Aryl [7 times] as pyridine, Thiazol.

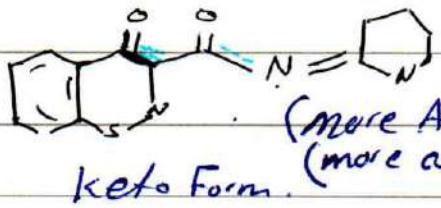
To ↑ acidity. ↑ Pka ↑ absorption.

- How??



End Form

Tatumerization



keto Form. (more Acidic) (more active)

* N is base so it take H and double bound is move and E is move thus ↑ acidity (4-6 Pka) so N heterocyclic is more Acidic (Active) than N-Aryl carboxyamide

[3] on hetrocyclic ring. best position for substitution is m >>> p and best is ct

[4] if hetero aryl replaced with methyl / Allyl ↓ Activity

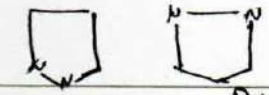
[5] 1,2 benzothiazin. if replaced by its bioisostrism phenyl → Thiophen [1,3] → Thioenoxicam = Thioxin more active.

Date. No.

6) N on benzothiazin ring must be substituted best is methyl CH_3

7) $O=S=O$ with drawing group must still with drawing.

8) Tatumerism Form is more active than Aspirin and indomethacin about 200 time.



Imidazol
1, 2

Pyrazol
3, 4.

Lec. 16

Date. No.

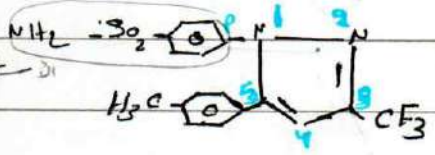
② coxib : selective cox_2 inhibitors.

• has ↑ side effect : • GI ulceration, bleeding, perforation of stomach and intestine

• MI, stroke. (cardiovascular)

in this group we will Note that it has Five membered ring attached with 2 Aryl ring one of them at least must has substitution.

① cele coxibe celebrex®

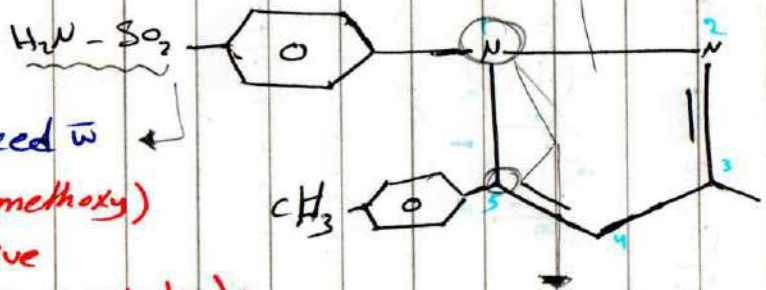


P-[5-(p-methyl phenyl)-3-(trifluro methyl) Pyrazol] benzen sulfonamide

No.

Date.

Parallel to give activity must be present.



if replaced ⊼
(OCH_3 methoxy)
Inactive
so loss of selectivity

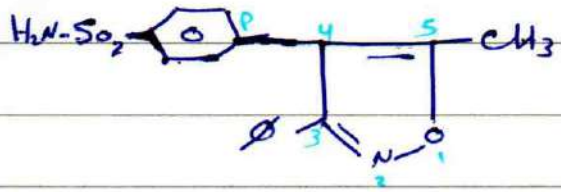
-1,5 position:
Both has Aryl one of them at Least must has substitution on para (p) Position

- best substitution
NH_2SO_2 / CH_3SO_2
↳ sulfonamide ↳ methyl sulfonyl
↳ if replaced ⊼ (SH Thiol) ↓ activity ↓ selectivity.

- if replaced with CHF_2 (Di Fluro methyl) same activity
- but if replaced ⊼
CH_2F , CH_3 ↓ Activity ↓ selectivity

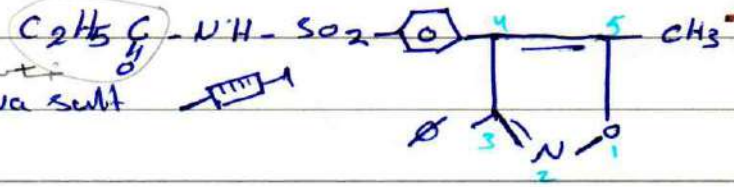
Date. No.

② valde coxibe (Active)



P [5-methyl-3-phenyl-isoxazol 4yl] benzen sulfonam

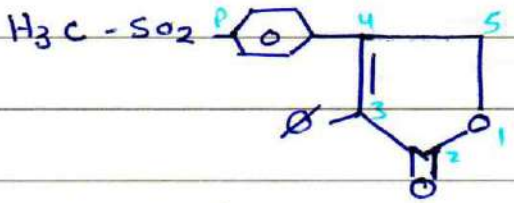
② pare coxibe (pro drug)

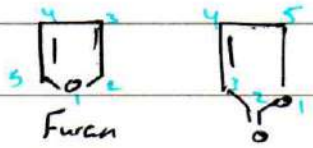


as Na salt

N [3-phenyl-5-methyl isoxazol 4yl] phenyl sulfonyl propanamide

③ Forecoxibe.





Furan

2,3,4,5 3,4

2,5 dihydro.

4 [p(methyl sulfonyl) phenyl] - 3-phenyl - 2,5 dihydro Furan-2-one.

Weak analgesic Done :) !

Anti Cancer

Date.

No.

Lec. 17

Date. No.

* Chemical classification of Anticancer :

1) Alkylating agent.

1) N-mustard : mechloretamine, Chlorambucil, melphalan, cyclophosphamide
2) Thiotepa : Aziridine
3) Nitrosoureas : carmustine, lamustine, Nimustine
4) Triazene : Dacarbazine
5) hydrazine : procarbazine
6) methyl sulfonate ester : Busulfan, 7) Pt organometalic : Cisplatin + carboplatin

2) Antimetabolite

3) Antibiotic

4) plant alkaloid
5) hormon Antagonist
6) Others.

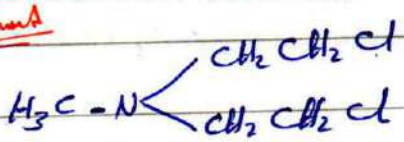
1st Alkylating agent

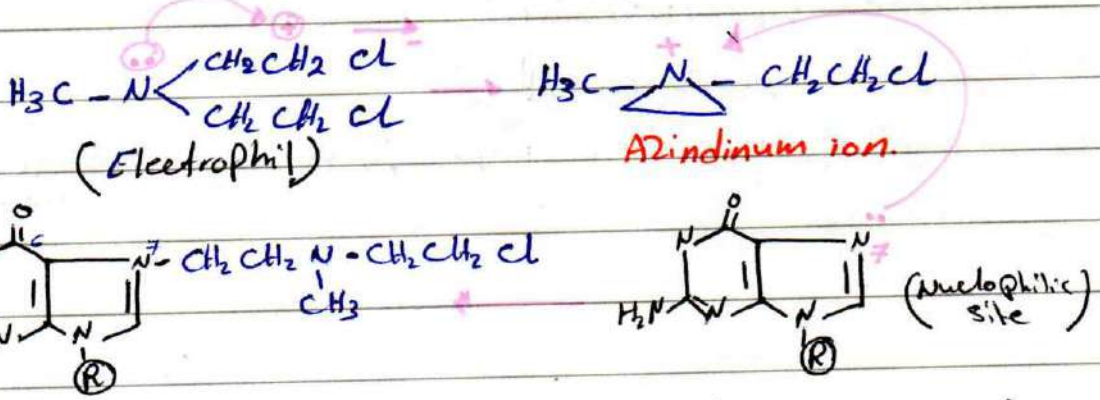
Date. No.

① alkylating agent / has ⚡ group

1 ⑤ Nitrogen mustard 1) Mechloretamine I.V

4 compound





Date. No.

- The attack by guanin on Azidinum ion occure 2 time (Bifunctional).
- There is types of Alkylating agent that has monofunctional.

Monofunctional	Bifunctional
- Nitrosourea	- N-mustard
- Decarbazide or Triazine "DNA methylator"	- Thiotepa or Aziridine
	- platinium(II) complexes.
- Form one covalent bond $\bar{c}$ DNA	- Busulfan.
	- Form 2 covalent bond $\bar{c}$ DNA Intrastrand- cross linkage+ enzyme.

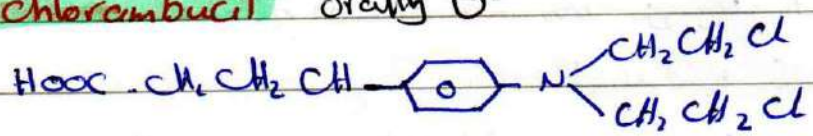
- N- musterd → بالاصل الخردل جودي S كله تم تحويله N.
- MoA/ of Alkylating agent
  - prevent DNA replication. and RNA trancription.
  - The fregmentation DNA.
- Alkylating agent / capable of covalently attaching an alkyl group to a biomolecule (DNA) under physiological condition.

* All agent are Electrophile
That attacks Nucleophillic site.

N7 Guanine > N1 Adenine > N3 Cytosine > N3 Thymine.

Date. No.

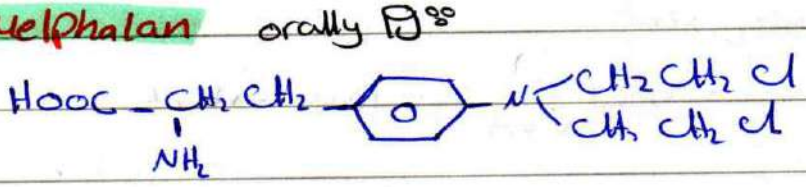
2) Chlorambucil orally ☺



[Butanoic Acid Derivative]

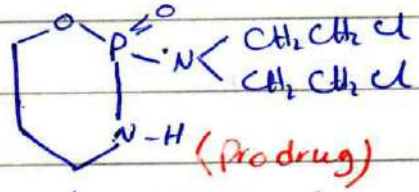
* binding of N to phenyl Lead to make resonance thus ↓ nucleophilicity around N, which lead to ↓ binding (or slowing it) to Aziridinium ion. thus ↓ effet ω Long effect.

3) Melphalan orally ☹



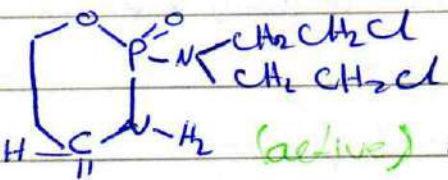
[2-Amino Propanoic Acid deriv]

4) cylophosphamide



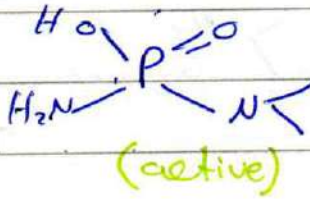
(Prodrug) cyclophosphamide

↓ N-dealkylation



(active) aldophosphamide

↓ o-dealkylation

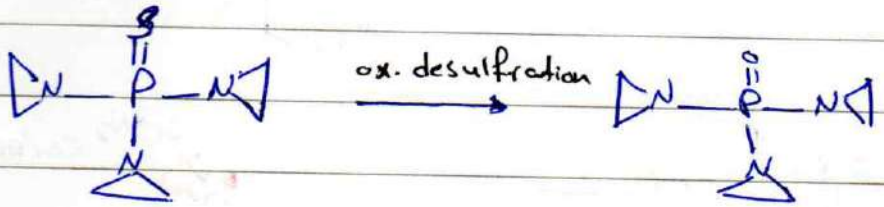


Phosphoramid (Anticancer)

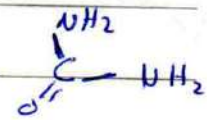
(active)

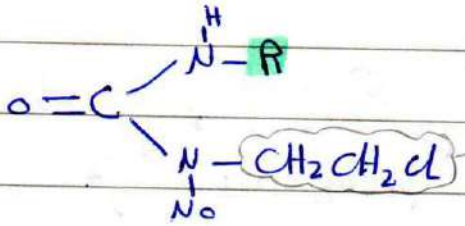
Date. No.

2) Thiotepa, Aziridines.



3) Nitroso urea. "mustine" sulfur urea

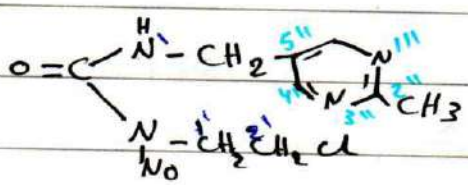




R : • CH_2CH_2Cl → **carmustine**

• → **Lamustine**

• → **Nimustine**



Nimustine ✓ BBB

For Brain tumor.

N (2` Chloro ethyl) N`[(2"-methyl pyrimidin-5`yl) methyl] N- Nitrosourea.

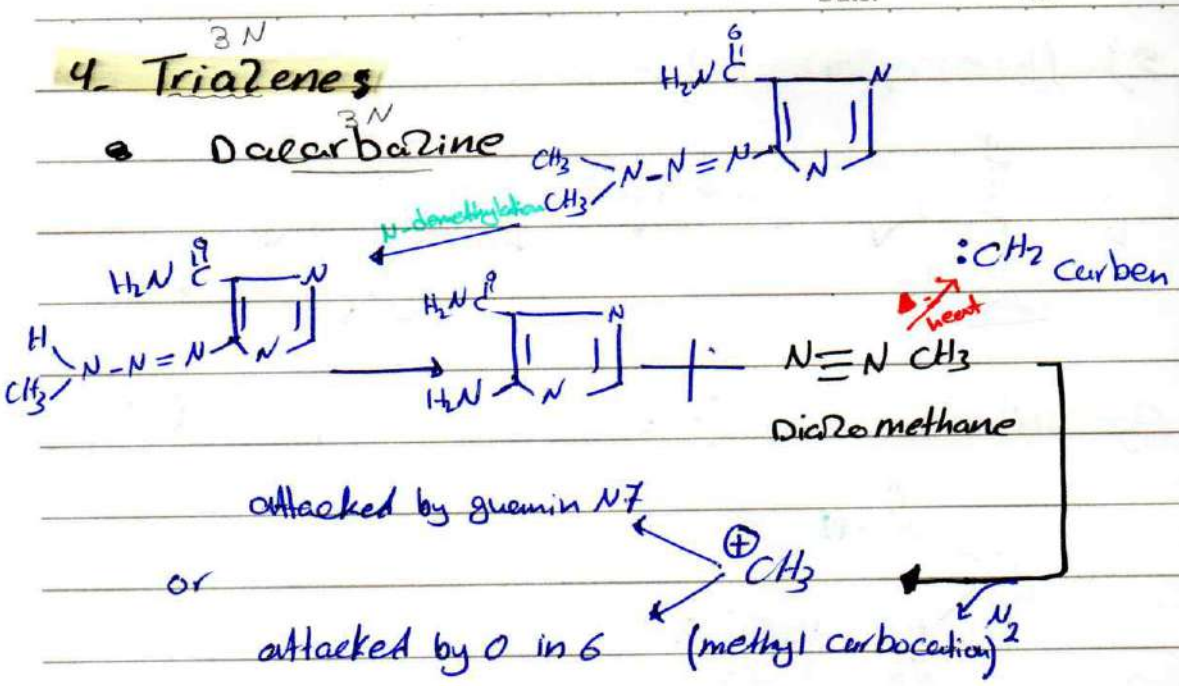
Date. No.

4. Triazenes

3 N

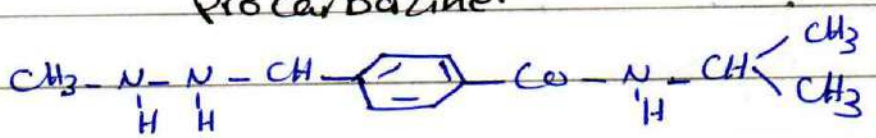
- Dacarbazine

3 N



5. Hydrazine (NH_2-NH_2)

Procarbazine.



6) methyl sulfonate ester

Busulfan

Thus it's Bifunctional

2 carbocation.

Is good leaving group give carbocation which attack by guanin.

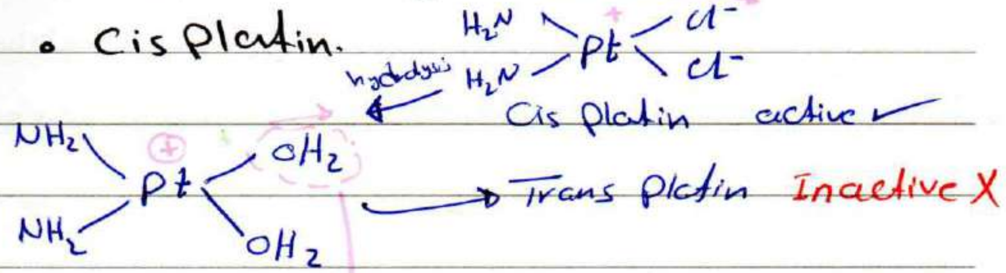
2 time

* بعضهم يصنفو ضمن other والأخر ضمن Alkylating Agent.

Date. No.

7) platinium pt (II) organometalic :- *

- Cis Platin.

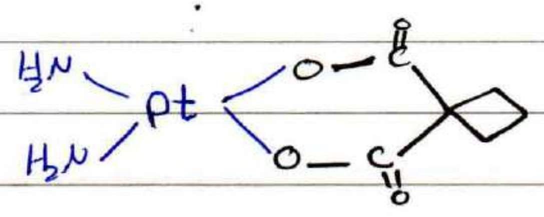


hydronium ion, good leaving group form cation → attack by guanin. in N7

side effect ① Nephrotoxcity

② Neurotoxcity

To remove toxocity, we remove Cl^- and adding dicarboxylic Acid, which will has hydrolysis less than Cl^- so ↓ side effect.



carboplatin.
↓ side effect.

2ed Antimetabolit

Lec. 15

Date. No.

1) DNA Polymerase inhibitor.

prodrugs. ← { Cytarabine, Fludarabine, Clofarabine }

* Enter the cell by Active transport

The active form Triphosphate nuclotide

2) purin Antagonist

Prodrugs { Azathioprin (produg) → 6-mercaptopurin (produg) → Thioguanine }

6-mercaptopurin → (active form) Phosphoribosyl

أول خطوة في تصنيعة purin

MoA / ↓ inhibiton of Amidophosphorribosyl transferase

3) Pyrimidine Antagonist.

Direct inhibiter of Thymidlate synthase

- Flurourasyl
- Floxuridine
- capececetabin

} prodrugs

Indirect inhibiter of Thymidlate synthase

- Methoterexate
- pemetrexate

* called / Antifolate ;
- DHFR inhibitor.

DHFR : Dihydrofolate reductase

(MoA)

Direct inhibitor as/ Flurouracyl

Date. No.

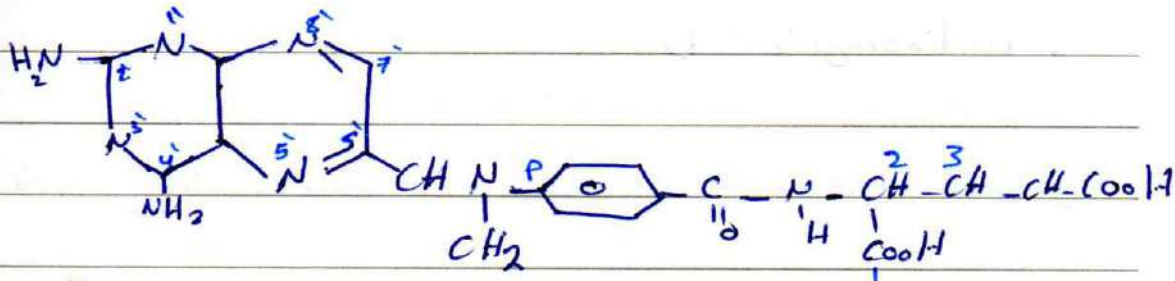
DUMP $\xrightarrow{\text{Thymidlate synthase}}$ DTMP → needed For DNA Sysuthesis

* Transfear methyl group
* Cofactor : Tetrahydro folic Acid
(5, 10 methylen THF (active form))

DHF $\xrightarrow{\text{DHFR inhibitor}}$ THF

indirect inhibitor of Thymidlat synthase here inhibit THF the cofactor of

* Methotrexate :-



2 [N [P [2`, 4`- diamino petridine - 6`yl] methyl N- methyl amino] benzoyl amino] 1, 5 pentadioic Acid

- Methotrexate Baesity is higher than Folic Acid thus its Binding to Thymidlat synthase is higher.

3rd Antibiotic.

Date. No.

1) Anthracyclines — MoA

Doxorubicin — [1], [2], [3]

Daunorubicin

~~Ida~~ Idarubicin

side effect / Cardiotoxic.

2) Anthraquinone — [1] [2] [3]

Mitoxantrone

3) Polypeptide — [1], [2], [3]

- Bleomycine [BLM]
- Actinomycine D

4) ~~Act~~ Mitomycin C. — Alkylating DNA

too

Date. No.

MoA /

[1] interacalate double stranded DNA

[2] Topoisomerase II inhibitor

[3] Generation of cytotoxic free radicles.

[4] Alkylating DNA

كيمياء صيدلانية ‖ تمت بحمد الله

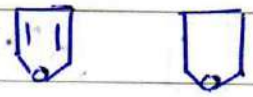
- "ربي اغفرلي وارحمني وعافني واهدني

وارزقني وارفعني واجبرني"

- " والله ولي التوفيق "

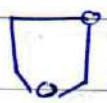
marah isam Felit ...

Date. No.



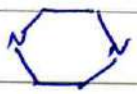
Furan

2,4 ~~thi~~tetrahydroFuran

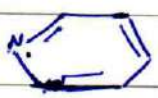


1,3 dioxalane

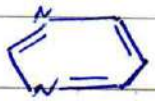
Salicylic Acid



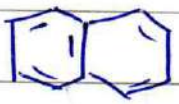
Pipraline



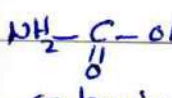
Pyridine



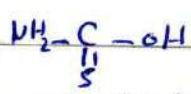
Pyrimidine



naphtheline

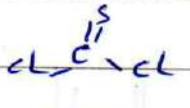


carbamic acid

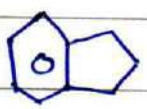


Thio carbmic Acid

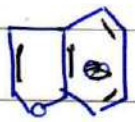
Phosigin



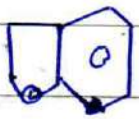
Thiophosigin



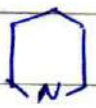
Indan ring



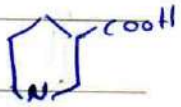
Benzofuran



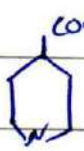
2,3 dihydro Benzo Furan



Piperidine



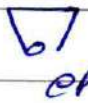
nepcotic Acid



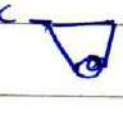
iso nepcotic Acid

Azepin

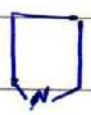
hexahydro Azepin



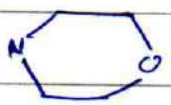
epoxid.



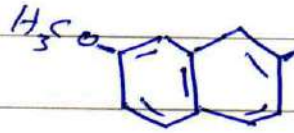
oxirane



Pyrrolidine



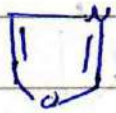
Morpholin.



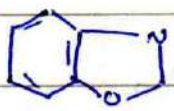
napsylate

Pyrrol

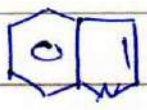
Date. No.



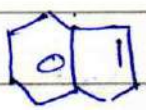
oxazol



Benzoxazol



Indol



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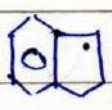
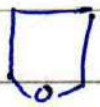


Indan.

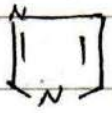
Furan



Tetrahydrofuran

Pyran.

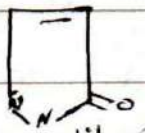
Thiophan



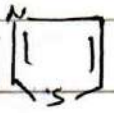
Imidazol

Pyrazol

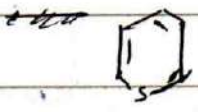
2,3 dihydro Pyrazol



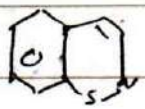
2,3 dihydro Pyrazolone.



Thiazol



Thiazin



1,2 benzo thiazin

Date. No.

Econazole	specta zole®
Clotrimazole	Hedisint®
Ketoconazole	Nizoral®
Terbinafine	Lamisile®
Griseofulvine	sporofulvine®
Nalophrine	Nalopharm®
Pethidine/Meperidine	Dolantine®
Piminodine	Alvodine®
Ketopemidone	Ketogan®
Prodine	Nisentil®
Ethoheptazine	Zactan®
Methadone	Dolophene®
Dextropropoxyphen	Darvon HCl®, Darvon N® (napsylate)

Date. No.

Aspirin	Aspirin®, Baby Aspirin®, Godmed®, Rhonal®
Diflusinal	Dolobid®
Paracetamol	paramol, Acanol, Autamol, Dexamol
Indomethacine	Indomed, Indovis, Indocine.
sulindace	Clinoril
Tolmetine	Tolectine
Zomepirace	Zomex
Diclophenic	COO^{Na^+} : Diclophen, Voltaren, ABitren, Beflaram
	COO^{K^+} : Bateflam, Anaflam
• Mefanemic Acid	Ponstan, Ponstel.
• Flufenamic Acid	arelf
• Meclofenamic Acid	Hedomen
• Tolfenamic acid	Clotam.
Ibuprofen	Trofen, Ibufen, isofen, Advil
Fenoprofen	Nalphon / Nalfon
Ketoprofen	profenil
Naproxen	Naprosy, Naprocin, Naxyn.