Pharmaceutical Chemistry One.

*** Course Summary ***

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

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

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لـ د. حسن (1) رحمة سس، بحاجة/هناء لغليت

دعواتكم لها بالرحمة.

Date. No. ..

Reference:

1. principle of Medicenal chemistry [Foye]
2. Text book of medicinal chemistry (parimoo)
3. *** Text book of organic Medicinal Pharmaceutical chemistry (Gisvold)
4. Burger's medicinal chemistry (Burger)

* Pharmaceutical Chemistry :-

Branch of chemistry concerd with the chemical compound that used in treatment → Drug: natural, synthetic, semisynth

* Main goal for ph.ch.

- Make new compound
- Then study the pharmacological activity

This compound must be:

1. ↑ high pharmacological activity
2. low side effect

* Branch of ph.ch:-

1. Deal with synthesize
2. Structure activity relationship (SAR)
3. Drug design

Date. No.

Types of drugs :-

[1] Drug activity ↑ not related to structure 20%

[2] Drug activity is related to structure 80%

① Drug activity is Not related to structure 20%

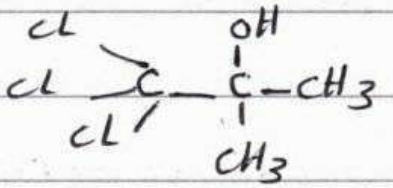
ⓐ Any change in the structure will not affect Pharmacolgico affect or activity

ⓑ To be active concentration should be high

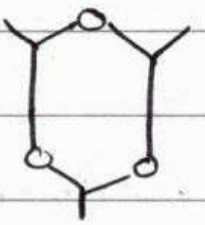
ⓒ Related to physicochemical properties

Ex :- Hypnotics , General ansethetic

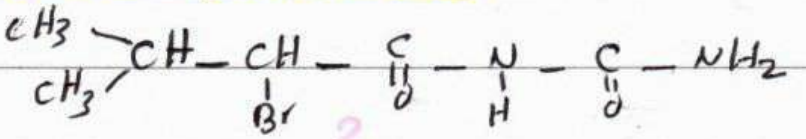
→ [a] alcohol : Chlorobutanol



→ [b] aldehyde :- paraldehyde



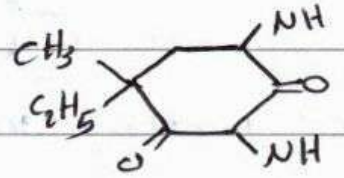
→ [c] Amide :- bromural



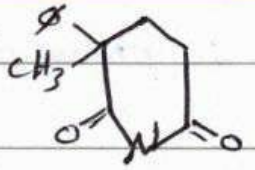
الأدوية للتوضيح فقط ليس للحفظ

Date. No.

[d] barbeturate: Phenobarbital



[e] piperidinediones: Glutimmide



ونلاحظ من خلال تركيبات السابقة أنه كل مركب مختلف عادةً عن المركب الآخر (أو لا يوجد تشابه كبير)

لأن هذه المجموعة تعتمد على Physicochemical Pro. وليس على Structure

[2] Drug activity is related to structure 80%

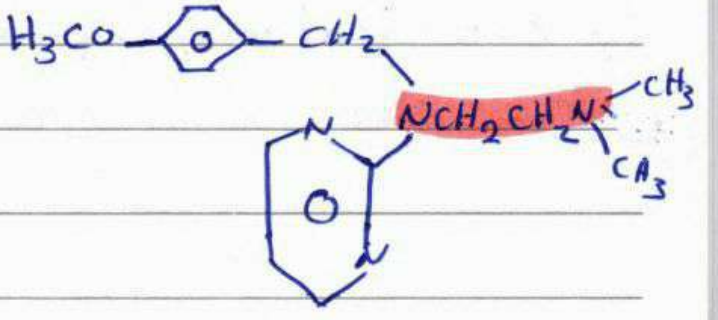
(a) Drug activity is related to structre

(b) Any change in the structure will affected Pharmacolgical activity

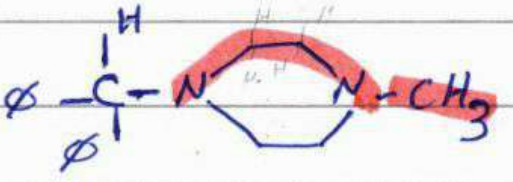
(c) To be active concentration should be Low

Ex: Antihistaminic agent, Analgesic, Local Anesthic

(a) ethylendiamine derivative: Tonzylamine



(b) Piperazine: cyclizine



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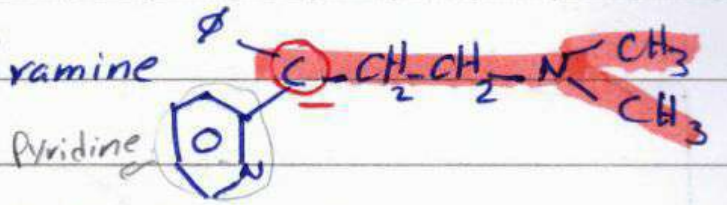
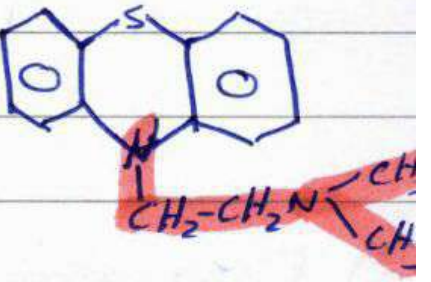
© propylamine: Pheniramine



(d) ethanol amine: Diphenhydramine

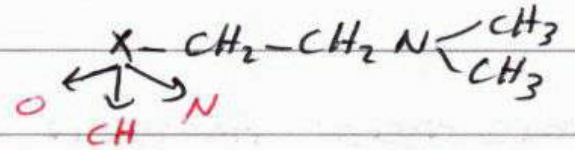
(e) phenothiazine: Phenalizine



• نلاحظ وجود مجموعة $NCH_2CH_2N(CH_3)_2$ مشتركة بين الجميع هي المسؤولة

↳ Pharmacological activity → [Pharmacophor group]

The part of structure responsible of the pharmacological activity as



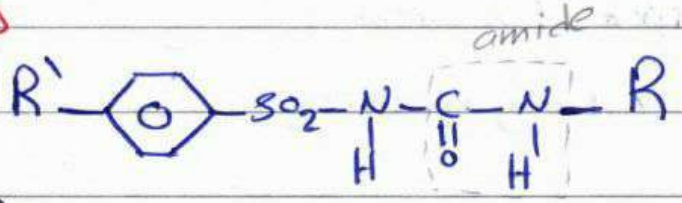
• [Bioisosterizem] وهنا يصف $\begin{matrix} C \\ O \end{matrix} \rightleftarrows N$ حدة استبدال بين

↳ substitution group with another in which will give same pharmacolgical effect.

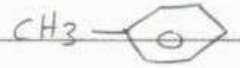
Date. No.

* Any change in the structure will be effect activity :-

[1]



(a)

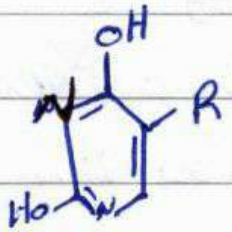
R' : CH_3 →  Toluine → Tolbutamide

R : C_4H_9 (butyl) → [short hypoglycemic]

(b) R' : Cl Chlor → Chloropromide

R : C_3H_7 Propyl → [Long hypoglycemic]

[2]

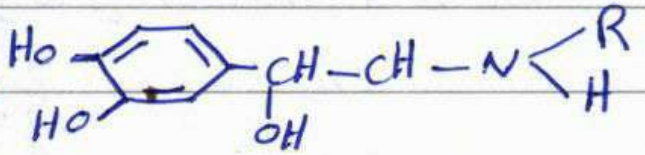


R : CH_3 Thymine [metabolite]

R : F 5-Flurourasyl [Anti-metabolite] Antagonist

Grim concept

[3]



R : CH_3 epinefrine [hypertinsive agent] (adrenaline)

R : $CH(CH_3)_2$ (isopropyl) Iso proterenol [hypotensive agent]

- Drug arrives to target [receptor, protein, enzyme, DNA/RN…, Lipid, ion channel ......]
- The Factor Affecting a Drug activity

Physicochemical properaties → solubility, Ionization

chemical proparetis → stero chemistry

[A] physicochemical properaties:

① solubility:

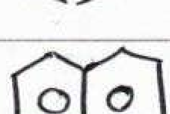
* why solubility is important for drug activity ??

a - give understand of pharmacokintics of drugs [ADME]

b - To produce ~~stab~~ sutibble dosage form [sus., emul. Li ....]

* solubility depends on polarity which depends on [EN]

↑ Increasing solubility in water, more hydrophilic

COO^-	salt	CH_3
COOH	carboxlic acid	C_2H_5
OH	alcohol	C_3H_7
R-C(=O)-H	aldehyde	C_4H_9
R-C(=O)-R	keton	
C(=O)-NH_2	1° amide	
C(=O)-N(H)(R)	2° amide	
C(=O)-N(R)(R)	3° amide 6	
COOR	ester	

↓ Increase Liposolubility, more lipophilic.

$$pH = pka + \log \frac{[A^-]}{[HA]}$$ Date. No.

For weak acid :- $$pH - pka = \log \frac{I}{unI}$$

$$10^{pH-pka} = \frac{I}{unI}$$

$$I\% = \frac{100}{1 + Antilog(pka - pH)}$$

For weak base : $$10^{pH-pka} = \frac{unI}{I}$$

$$I\% = \frac{100}{1 + Antilog(pH - pka)}$$

pH : acidity of media
pka : acidity of drug
A^- : ionized part
HA : unionized part

↑ Ka ↑ acidity ↑ H^+

↑ pka ↓ H^+

• so any drug The ionization depend on pH, pka

* we couldn't modify or improve pH of the media because its constant, but we can with pka

* The drug must be lipophilic to cross cell membrane so unionized must be >>> ionized to cross and must be hydrophilic to be active.

* Ionization gives us indication for the best place that drug will absorbed there في مثال لقدام

The Factor affecting on pka for drugs :-

① The ch.ch of atom conjugated to H :-

ⓐ size for the same group هنا سهل تفقد H ، الحجم الأكبر أسهل

$H-F < HCl < HBr \ll HI$ more acidic — more acidic يعني حجم كبير ما ضل ē يهداله غلباه فصرف

ⓑ EN for same period

$CH_4 < NH_3 < H_2O \ll HF$ —— increasing EN →

هنا زاد الـ EN لهنيه الثاني غلباه مش معه شي — decreasing EN ↓

ⓒ Hybridization = Σσ + Σ lone pair

$H-\overset{*}{C}\equiv C-H$, $H_2\overset{*}{C}=CH_2$, $H-\overset{*}{C}H_2-H$

$sp \gg sp^2 > sp^3$

قوة الجذب بينه و بين النواة عالية لأنه أقرب للنواة فما ضل ē يهداله كلما سهل فقده

50% S ch.ch 33% S ch.ch 25% S ch.ch.

② The ch.ch of negibouring Atom conjugated to H

ⓐ Inductive effect (I) +I → ↑ no. of ē in ring

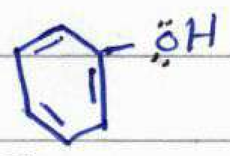
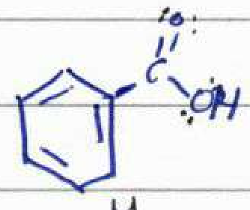
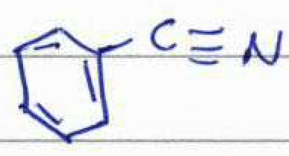
occure b/w σ bonds −I → ↓ no. of ē in Ring

All groups are −I [expet alkyl group (+I)] donating group

ⓑ Mesomeric effect (M) resonance

occure in π bonds +M → ↑ no. ē

M >>> I −M → ↓ no. ē

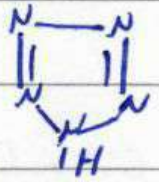
  

−I , +M −I , −M −I , −M

Date. No.

Acidic Drugs

1.  carboxlic acid
2. alcohol
3. sulphoni acid
4.  sulfonamide
5.  Imide
6.  Nitrile
7.  α carbon

 acidic ch.Ch.

Tetrazole

Basic Drugs (amine group)

- For amin group

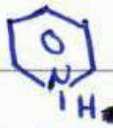
1° amine (NH_2) < 2° (NHR) << 3° (R_2N-R)

Basicity. زادت alkyl زادت.

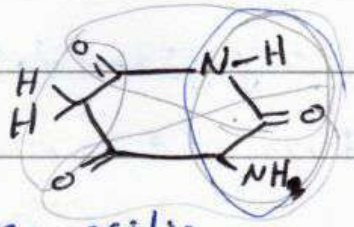
- Alphiatic amine group

$R-NH_2$, $R-N(H)(R)$, $R-N(R)(R)$

- aromatic amine
- tetrazole



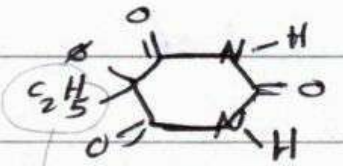
- cyclic amine



more acidic

Imide ✓ , α C ✓

pka = 4



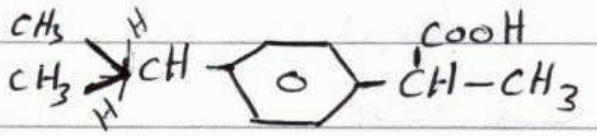
acidic

Alkyl group add some basisty

pka = 7.9

Amoxicillin ??

Date. No.



Iuproten pKa=5.5

weak acid / Analgesic

In stomach pH=3.5

$$pH = pKa + \log \frac{I}{unI}$$

$$10^{pH-pKa} = \frac{I}{unI}$$

$$10^{3.5-5.5} = \frac{I}{un}$$

$$10^{-2} = \frac{I}{unI}$$

$$\frac{1}{100} \leq \frac{I}{unI}$$

unI >> I

✓ cross stomach cell membran.

✓ good absorption

in Blood Plasma pH=7.5

$$10^{pH-pKa} = \frac{I}{unI}$$

$$10^{7.5-5.5} = \frac{I}{unI}$$

$$10^{2} = \frac{I}{unI}$$

$$\frac{100}{1} = \frac{I}{unI}$$

∴ I >> unI

unable to cross blood plasma

Date. No.

Drug Acid + base ⟶ salt

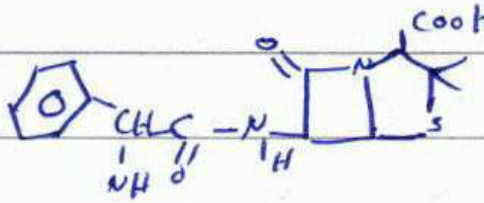
Drug basic + Acid ⟶ salt.

If we add to the Drug

- organic
  - Acid + Basic Drug
    - citric acid
    - Maleic acid
    - Acetic Acid
  - base + Acid Drug
    - procaine
    - dimethylamine
  - gives ⟶ organic salt
- Inorganic
  - Acid + Basic Drug
    - HCl
    - H_2SO_4
  - base + Acidic drugs
    - KOH
    - NaOH
  - ⟶ Inorganic salt

∴ If we need to ↑ hydrophilicity of the Drug, we add In organic Acid / Base ex: Amoxicilline and give as IV injection (rapid)

- If we need to ↑ Lipophilicty of the Drug, we add organic acid / Base ex: Ampicilline and give as depot injection (long action)



+ procaine ⟹ depot inj

organic Base

Ampicilline

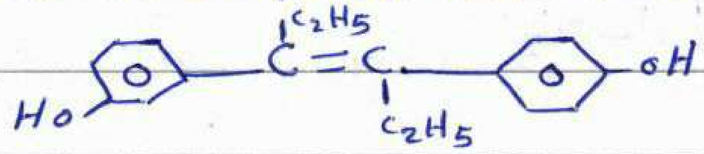
Acidic

[B] chemical Factors :-

sterochemistry (3D)

[1] Geometric

occure in compound has C=C ;  cycloalkan



Diethyl stilbesterol [Anti cancer]

Trans form → active (93% نعطي فعالية)

Cis form → inactive (7% لا نعطي فعالية)

[2] optically

must contain chairal center M − C − K (with L above and N below C)

- يتم الترتيب حسب MWt و Atomic No [أصغر مجموعة لا تدخل في الحساب مثل H]

نتبع ٣ مجموعات اذا كان الترتيب مع عقارب الساعة [R]

اذا كان عكس عقارب الساعة [S]

اذا كانت أصغر مجموعة فرضاً H vertical عمودي نتبع R R

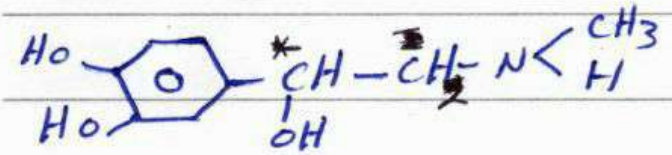
ولا نعكس الاتجاه لكن اذا لم تكن vertical نعكس الاتجاه R → S or S → R

• اذا كان اتجاه polarized يسار left (−)

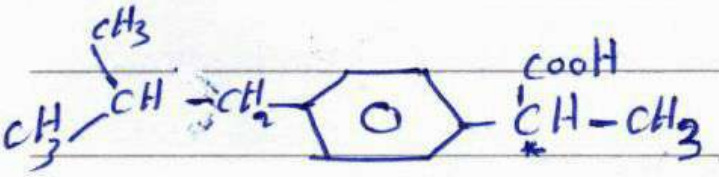
(+) right يمين

* يتم حساب عدد isomer حسب 2^n n: no. of chairal center

Date. No.



- epinephrine (hypertensive agent)
- (-) active (receptor یرتباط کامل)
  (+) inactive



(Iupo profen)

S → active

R → inactive.

* Drug $\xrightarrow{\text{receptor}}$ [D-R] Complex $\longrightarrow$ response → active agonist / Block Antagonist

↳ Kemofunchinal group: process of Binding of Drug with receptor By chemical Bonds:

* Types of chemical Bonds:

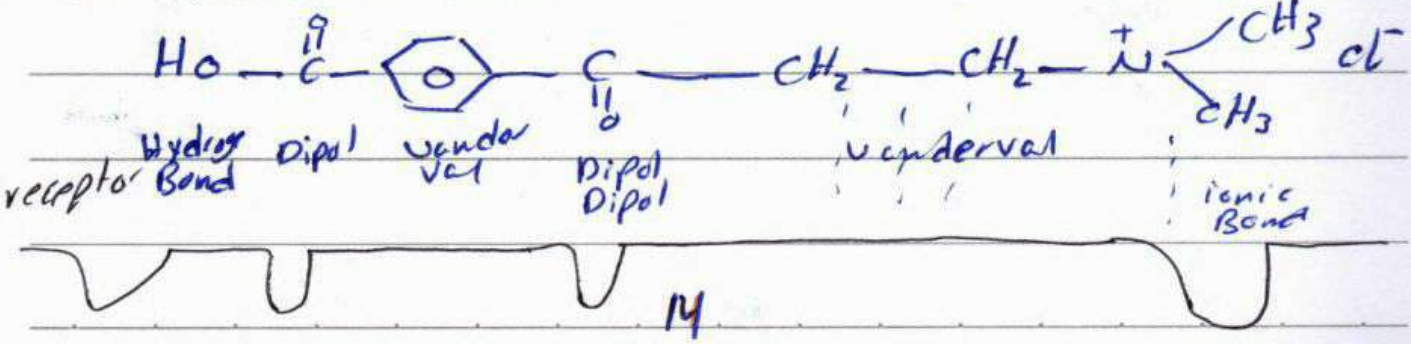
① hydrogen bonds H to N, O, F

② Dipole_Dipole in carbony $\overset{+\delta}{C}=\overset{-\delta}{O}$

③ vander val in non-polar

④ Ionic Bonds

⑤ covalent bond



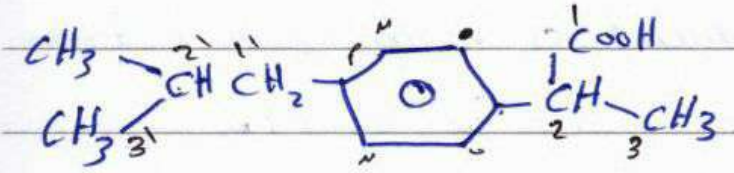
Date. No.

* Any drug has 3 names:

(1) Trade Name

(2) Chemical Name = IUPAC Name

(3) Generic Name = scientific Name.



Ibuprofen → scientific Name

2 [[p(2' Methy) propyl] Penyl] Propanoic acid.

IUPAC Name / chemical Name

Bioisosterism

Date. No.

Replacment of atom or group to another to produce new compound with the same activity. or antagonist.

* Some important Theory of Bioisosterism

[1] Grim Concept " hydride displacment concept "

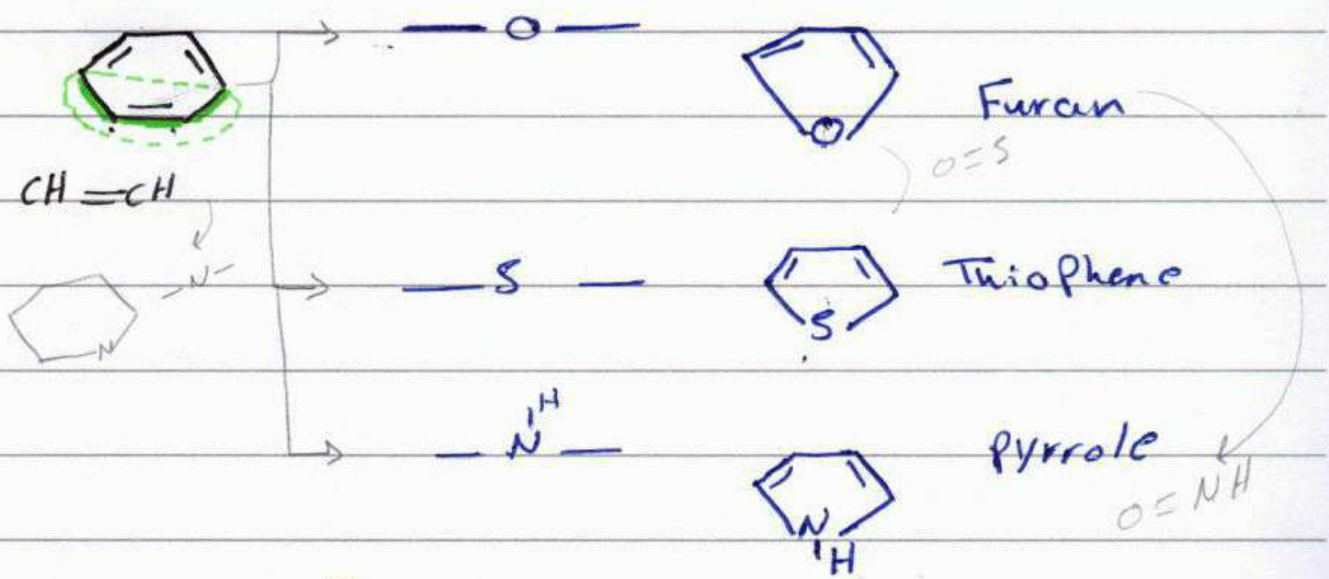
Each of ($\bar{e}$) replacment of Atom with hydrogen and the Atomic number must be equal.

C N O F

CH NH CH_2

OH NH_2 CH_3

[2] Heinsberg concept :- " Ring equivalen"

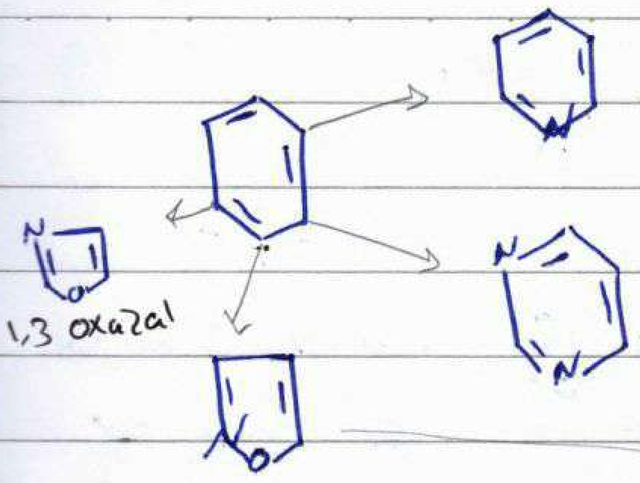


B C N O F Ne

Si P S Cl

As Se Br

I



Pyridine N → CH

نلاحظ مع O يقل عدد الحلقة بـ 2C

واحدة لـ O وأخرى بسبب فقدها H

pyrimidine اضافة N

تبقى الحلقة سداسية

1,2 isoxazole ← N–CH, O → CH_2

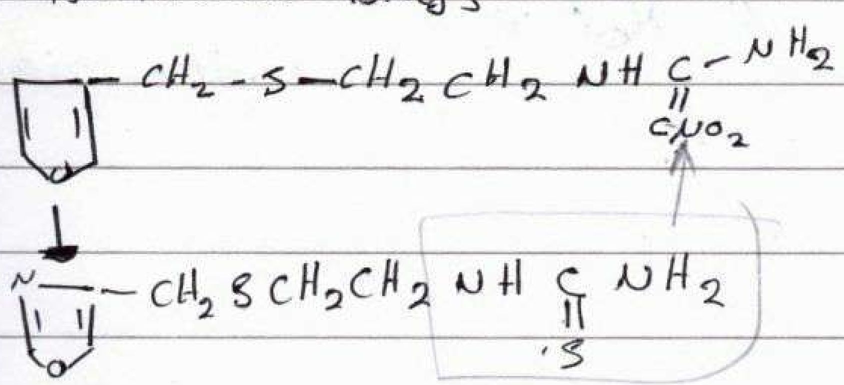
Type of Bioisoterizm

Classical — Grim, Hinsberg

non-classical — Throug experimental, contain 10 groups

Ex: thiowea $NH_2-C(=S)-NH_2$ → $NH-C(=C-NO_2)-NH_2$

As Anti-ulcer Drugs



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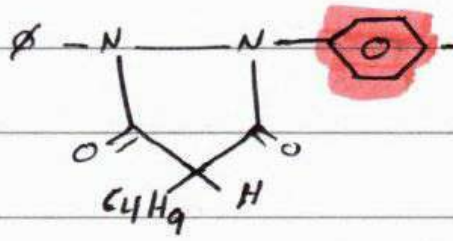
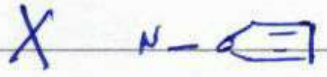
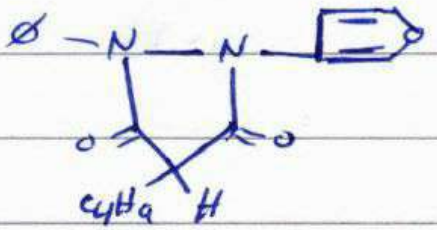
Note :



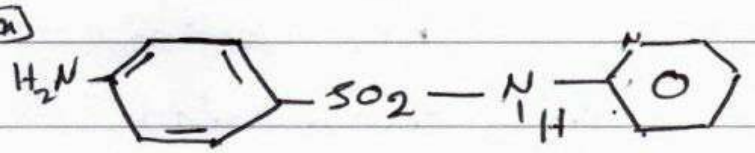
✗  لكنه لا يرتبط.  هنا كلمة تتبدل فتلاً بـ heteroatom: يجب الربط بعيداً عن



✓

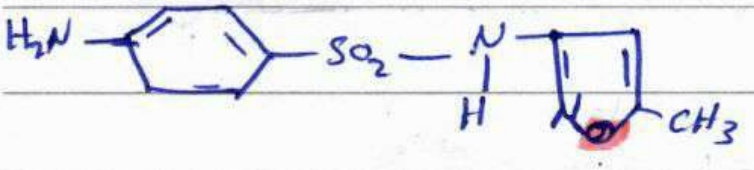
* Example of Bioisostrizm yield Agonist

(a)



sulfapyridine
" AntiBacterial "

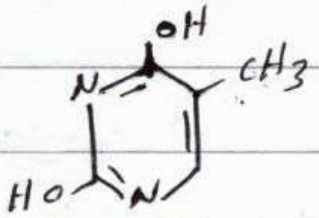
sulfadiazine
" AntiBacterial "



sulfa Metha oxazole
" AntiBacterial "

Date. No.

For Antagonist :-



CH_3 → Thymine "Metabolite"

F → 5-fluorouracyl "Anti-Metabolite"

Biotransformation : "

Detoxification
Drug Metabolism" تحويل الدواء

- The process of conversion of drug in to metabolite by enzyme in the body.
- effect Pharmacodynamic ADME ← Metabolism.

* The aim of Biotransformation:

1. Drug become more polar so
2. easy to excretion
3. ↓ reduce toxicity. (detoxification).

Biotransformation

depend on the Possition

- Microsomal
  liver → 90% of process
- non-microsomal
  in other position

Date. No.

depend on the RxN

Phase I "Functionalization"

enter of functional group

R [COOH, SH, NH, OH] ↑polarity

[1] oxidation

[2] Reduction

[3] hydrolysis.

Drug as R دخول

(Functional group دخول)

Direct ↓ oxidation of functional group

Indirect → Modification of existing group ↓ reduction, hydrolysis

• $R\overset{O}{\overset{\|}{C}}-OR \xrightarrow{hydrolysis} R\overset{O}{\overset{\|}{C}}-OH + R-OH$

"ester" (carboxlic acid) alcohol

• $R-NO_2 \xrightarrow{reduction} R-NH_2$

"Nitro" (1° amine)

Drug become more polar ← Phase I في*

بسبب دخول F.g مركب

OH
COOH
SH
NH_2

Phase II "conjugation"

- some drug pass to phase I the excreation

- some pass phase I the II then excreation

- Some pass II directly (containg functional group) then excreation.

Types of conjugation:

① conj with Glucoronic acid
② " " sulfate
③ " " amino acid as glycine
④ " " Glutathion

(↑Polar — Drug becom)

⑤ Methylation
⑥ acylation

(Drug becom less toxic)

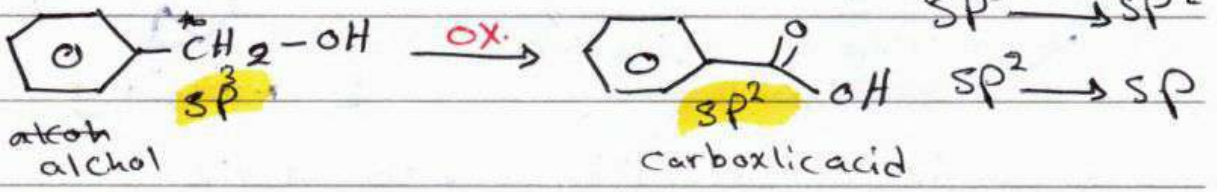
Date. No.

1) Oxidation Reaction :-

التأكسد

[1] introduction of O_2 to the drug.

[2] change in hyperidization.



Where oxidation RxN occur ??

[1] ox. of Aromatic compound [Ar. Hydroxylation]

[2] ox. of olefines "alkenes"

[3] ox. of aliphatic carbon

[4] ox. of benzylic carbon sp^3

[5] ox. of alcohols and aldehydes

[6] ox. of carbon bw carbonyl $\overset{O}{\overset{\|}{C}}$ and Imines $=N$

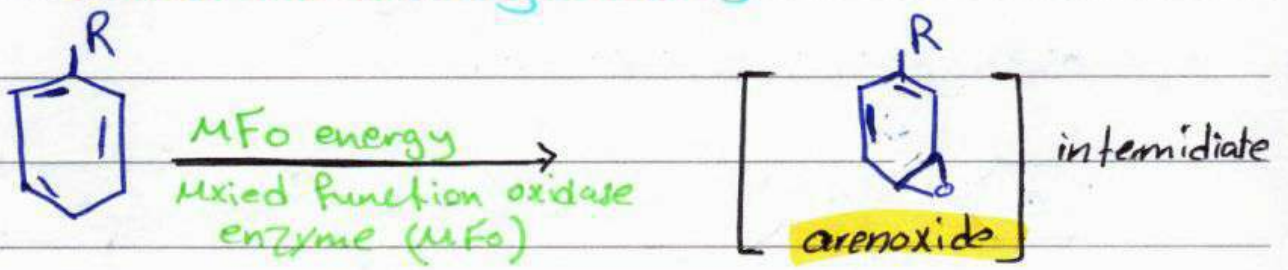
[7] ox. of carbon hetero atom system

[8] ox. of others → oxidative aromitization
→ oxidative dehalogenation.

Date. No.

1) oxidation of Aromatic compound

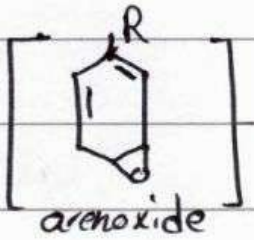
[Aromatic hydroxylation]



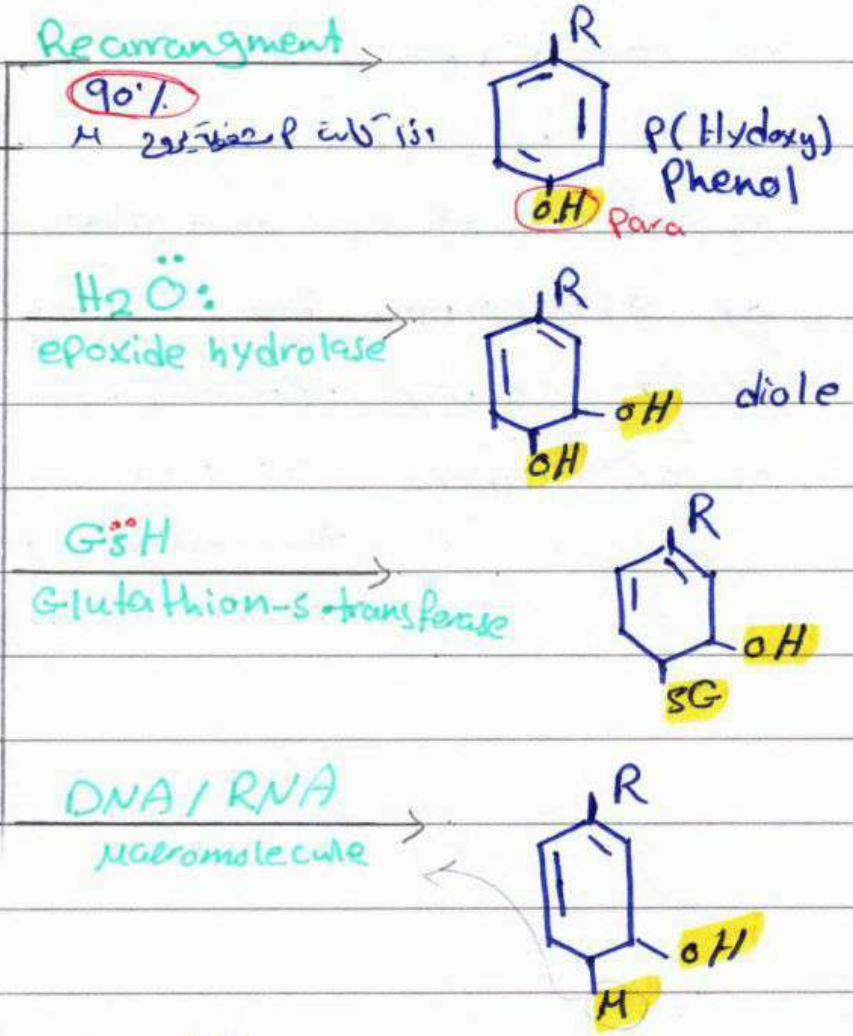
Properetes of arenoxide :
- very active
- short life

electrophilic sub so it attak neuclophili sub.

(Glutathion, RNA/DNA, SH, OH)



Polarity

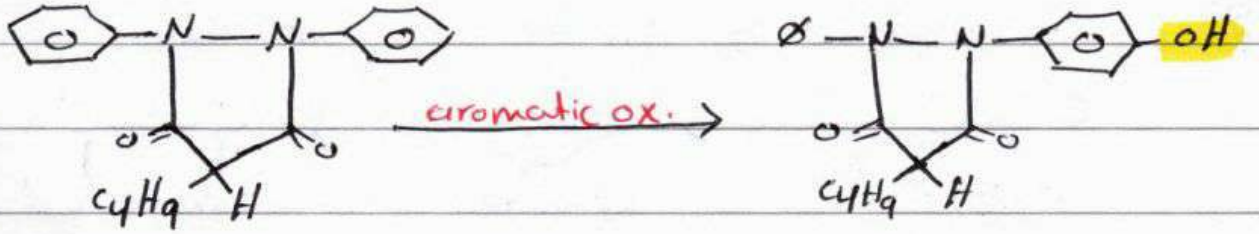


Date. No.

Notes: $\rightarrow [CF_3, NO_2, COOH, X]$ No oxidation

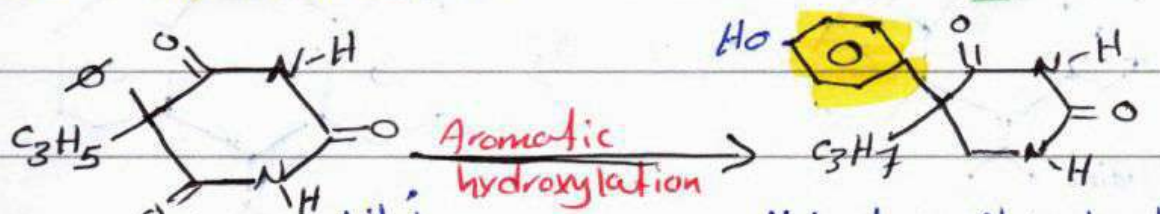
① if R is withdrawing group it will ↓ oxidation
R is donating group it will ↑ oxidation.
Alkyl group ↓

② if there's more than one aromatic group, oxidation occure just on one of them



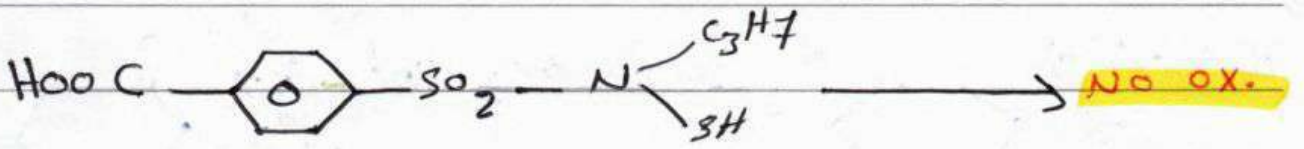
Phenyl butazone — 4-hydroxy Phenyl butazone.

③ if there is aromatic and aliphatic, oxidation occure on aromatic.



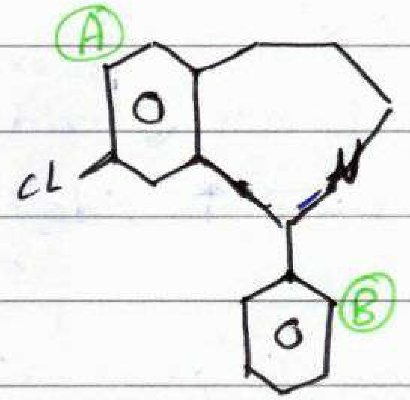
Phenoberbital — 4-hydroxy Phenobarbital

④ $C(=O)OH$ (COOH) is withdrawing so No oxidation



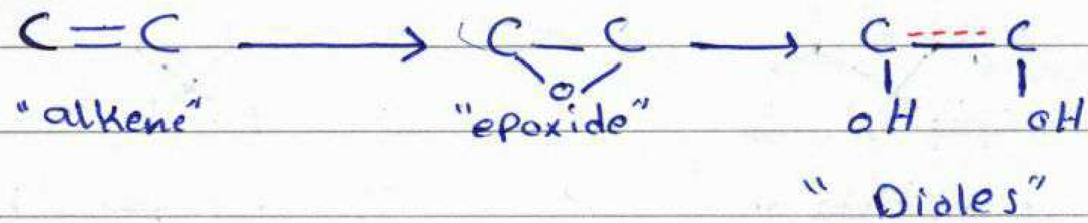
withdrawing group — Position Para

Date. No.



تحدث الأكسدة في B
لأن حلقة A تحوي Halogen
↳ withdrawing subs.

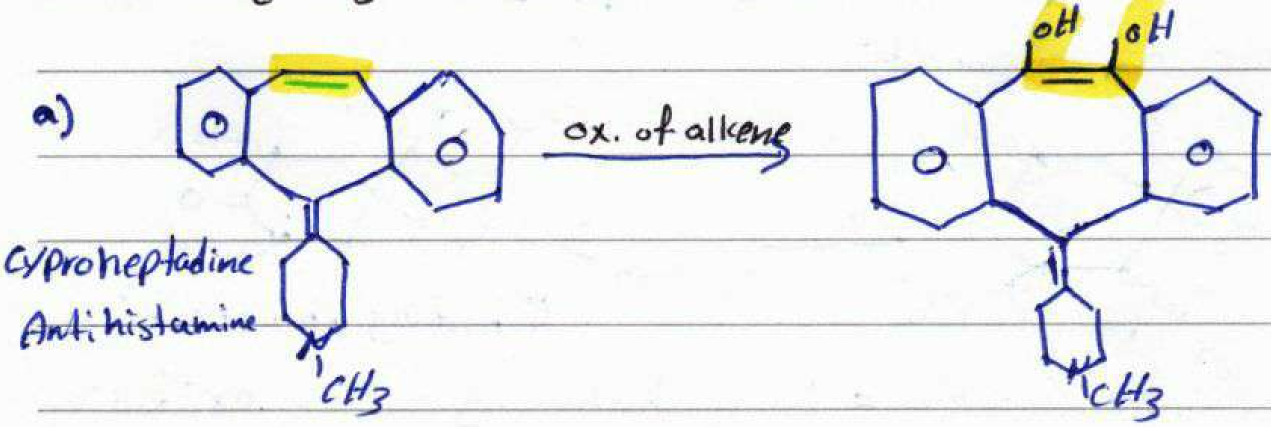
② oxidation of alkenes "Olfenes"



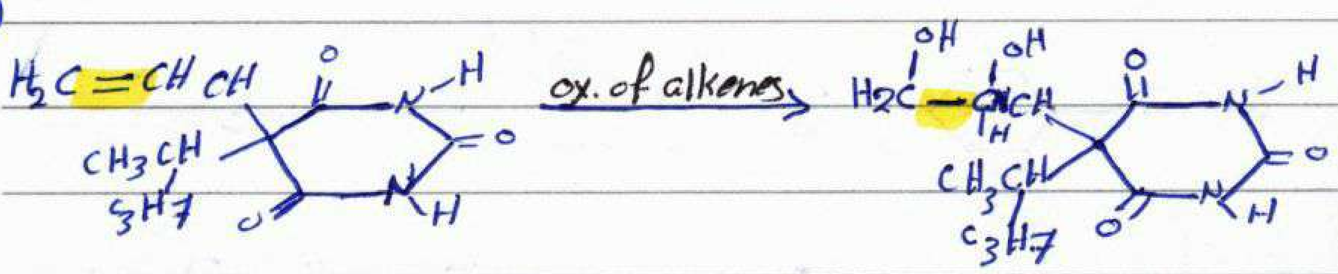
• اذا وجدت = داخل cycle ⬡ تبقى = ثابتة مع حدوث diole

• اذا وجدت = داخل aliphatic تتحول إلى single مع حدوث diole

a)



b)



seco barbitale.

→ Are Same.

Date. No.

3. oxidation of aliphatic carbon
4. oxidation of benzylic carbon → sp^3 C مرتبطة مباشرة بـ ⌬
5. oxidation of alcohol and aldehyde

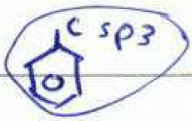
- For aliphatic carbon

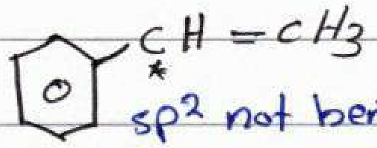
C — C — C — C — C (ω, ω-1)

عملية .ox في الأغلب تحدث على ω

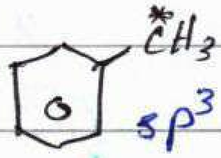
تحصل على ω-1 (أقل حدوث) بسبب تأثير steric hedrance (الإعاقة الفراغية)

- CH_2OH --- → $C(=O)H$ --- → $C(=O)OH$ ---
  (alcohol) (aldehyde) (carboxlic acid)

- For benzylic → 



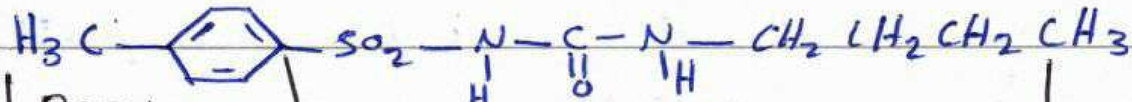
sp^2 not benzylic — No oxidation



sp^3 benzylic — ✓ oxidation

- $R-CH_3 \rightarrow R-CH_2OH \rightarrow RC(=O)H \rightarrow RC(=O)-OH$
- $Ar-CH_3 \rightarrow Ar\ CH_2OH \rightarrow Ar\ C(=O)-H \rightarrow Ar\ C(=O)-OH$.

اضفناه قبل الركب



H_3C—⌬—SO_2—N(H)—C(=O)—N(H)—$CH_2CH_2CH_2CH_3$

↓ Benzylic carbon oxidation

↓ موقع para مشغول من oxi Aromatic لا تحدث

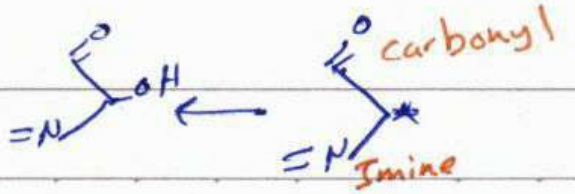
Tolubutamide

↓ ω carbon oxidation

CH_2OH ---
↓
$C(=O)H$ ---
↓
$C(=O)OH$ ---

enzyme حسب

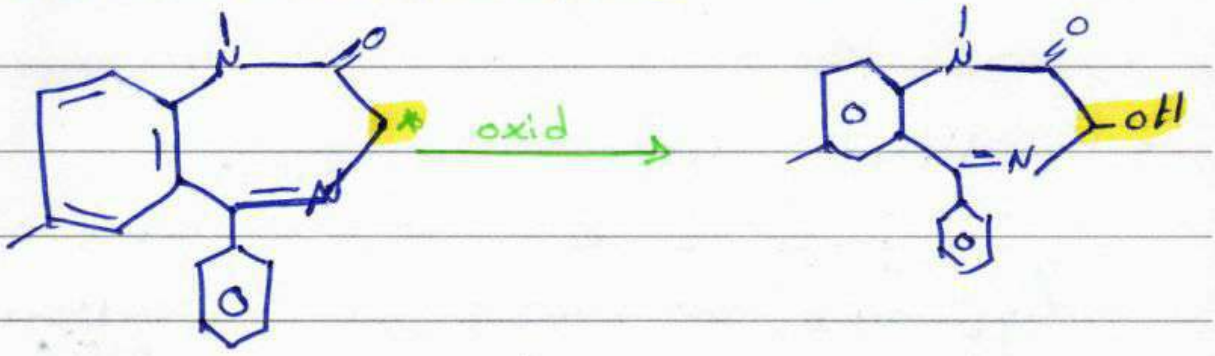
CH_2OH
↓
$C(=O)H$
↓
$C(=O)OH$



Date. No.

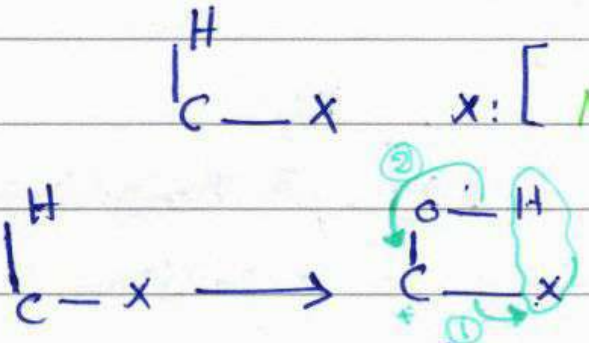
[6] oxidation of carbon bw carbonyl and Imine

This occure in Benzodiazapines



[7] oxidation of carbon-hetero atomes system

same mechanism



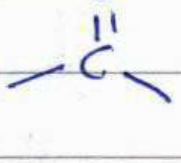
- شرط أساسي كون ox. في هذه الحالة

أن تكون C المجاورة لـ X تحوي على H ، بحيث H ← OH

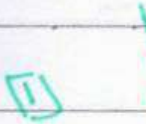
ثم تحدث ox. و ترتبط H بـ X

ox. إذا لم تتواجد H لا تحدث

* بالاعتماد على العنصر المتصل الموجود



Date. No.

[I] 

ذرة كربون — المجاورة لـ N

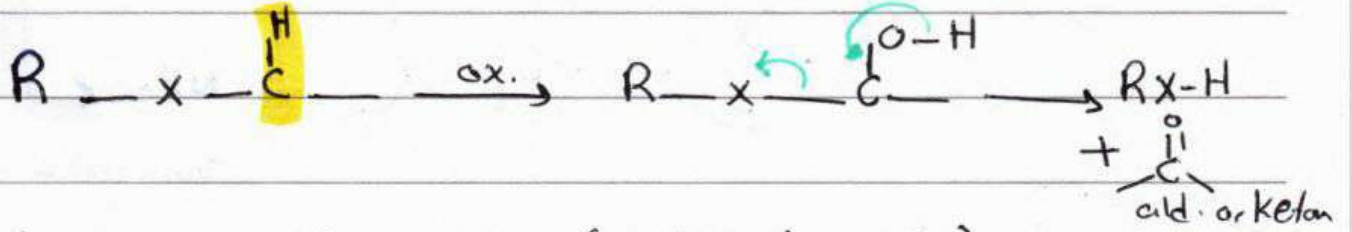
a) N, N dealkylation حذف مجموعة alkyl بشرط تكون H على C

b) oxidative deamination نزع amine بشرط تكون H على C

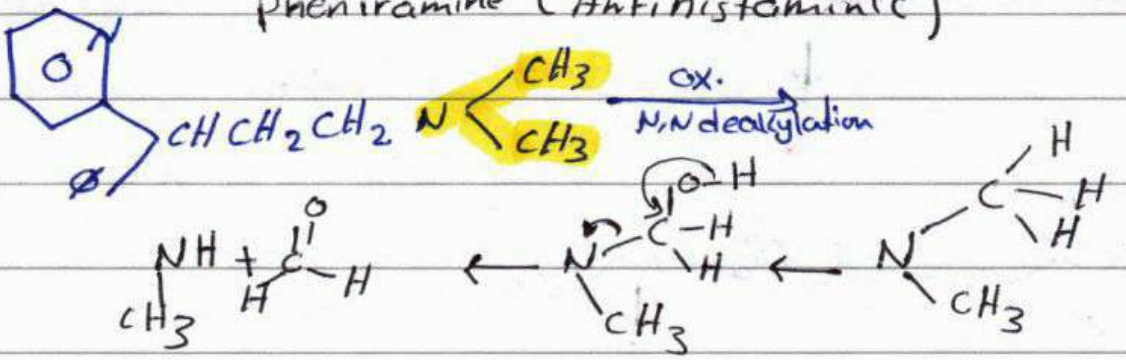
c) N- oxidation

يلزم C هجارة لـ N تكون H.

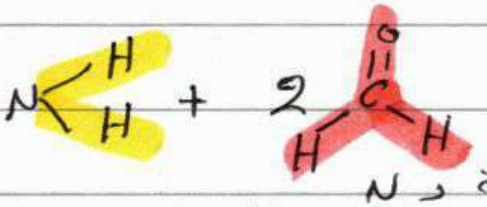
a) N, N dealkylation اذا مجموعة alkyl مجاورة لـ N تنزع وافضل ما تكون اكثر من alkyl يتم نزع alkyl الأخرى المرتبطة بـ N



Pheniramine (Antihistaminic)

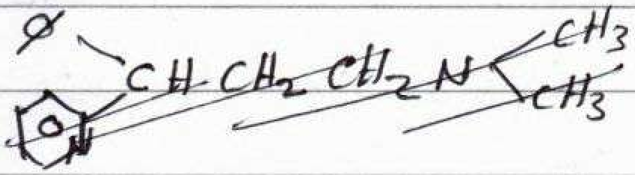


يتم نزع الأخرى ↓



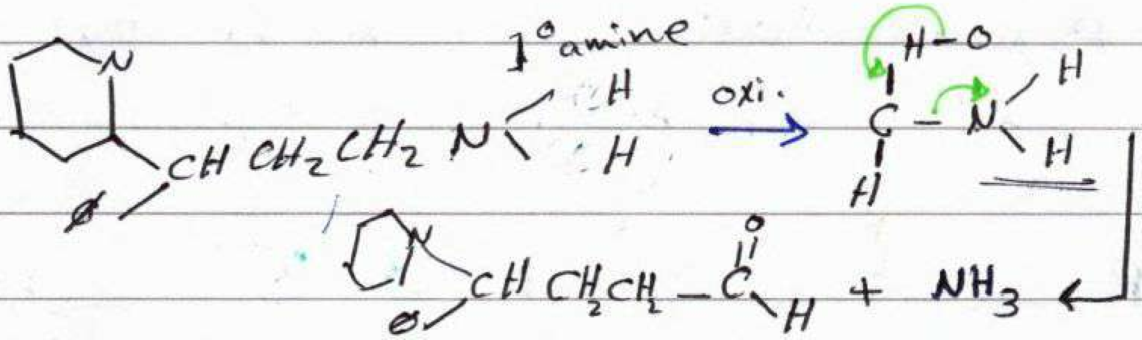
وهما كانت المجموعة المرتبطة بـ N يوضع محلها H وهي تخرج مع O=C

~~N,N dealkylation of~~



b) oxidation deamination

ذرة C مجاورة لamines تحوي H

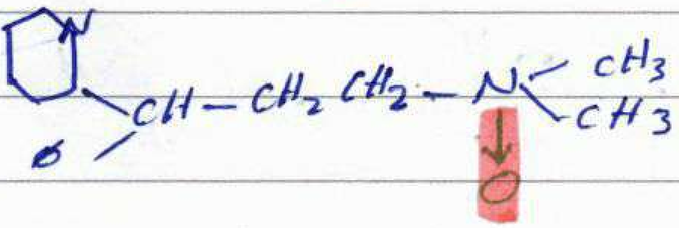


ammonia.

C) N- oxidation

occure in 3° amine.

لعدم وضوح Mech. نعبر عنه كالآتي ↓O



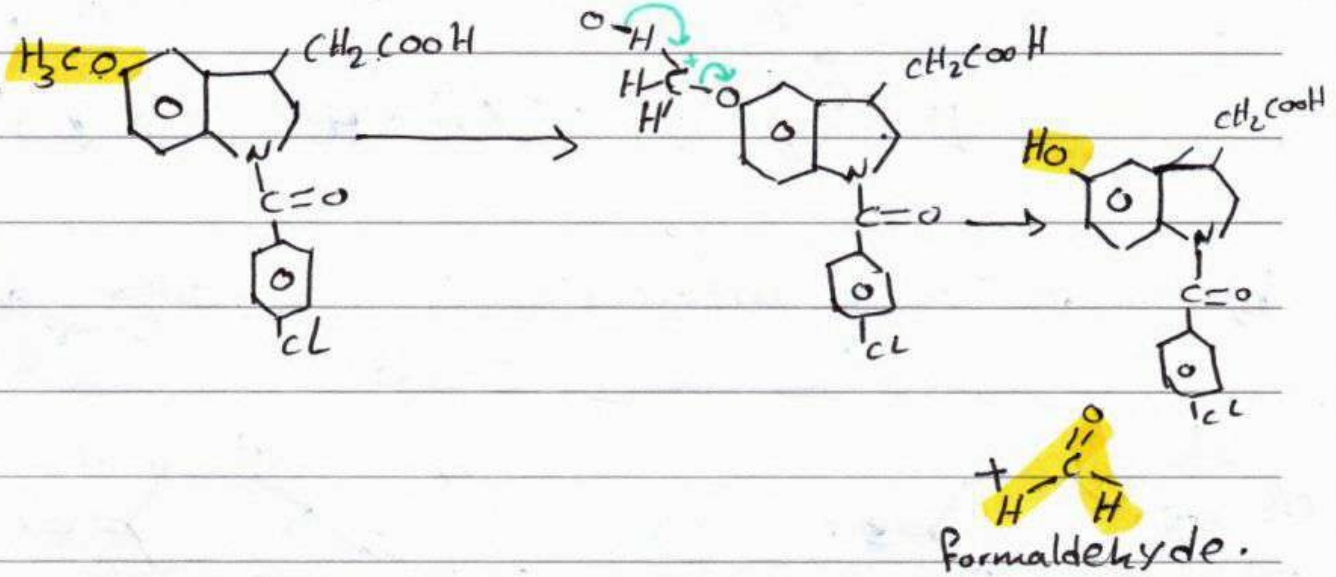
Date. No.

2- C—O تحدث في عملية واحدة ، نفس Mech.

O- dealkylation تزعى alkyl وترتبط O ، C الرابطة

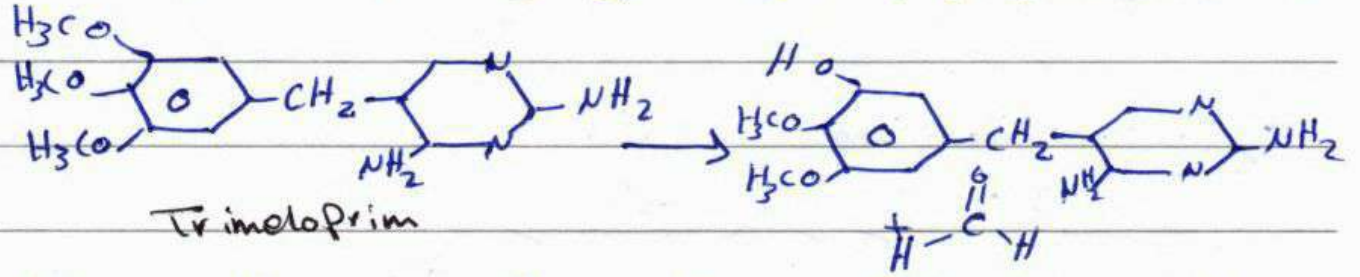
في توى H

R O ⇒ alkyl oxy. ⇒ alokxy.



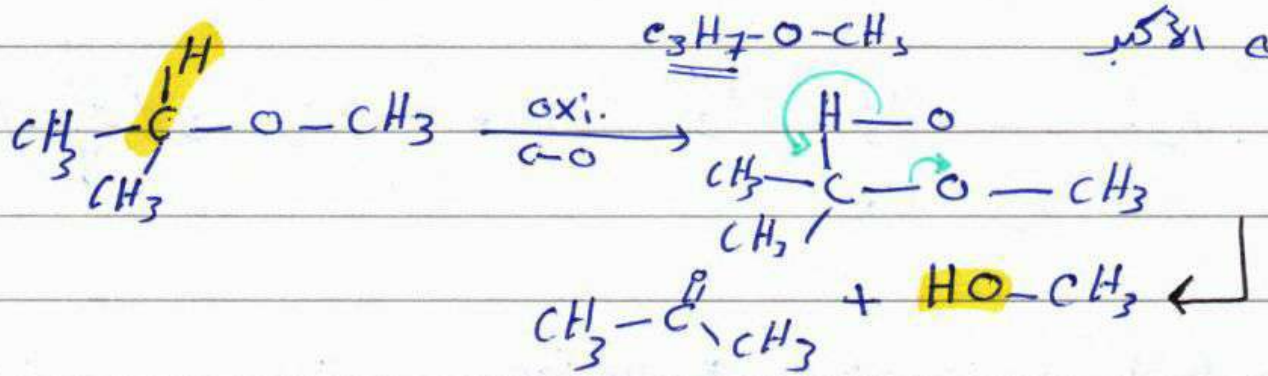
Formaldehyde.

• اذا وجد في المركب أكثر من مجموعة alkoxy فإن oxi تحدث واحدة فقط



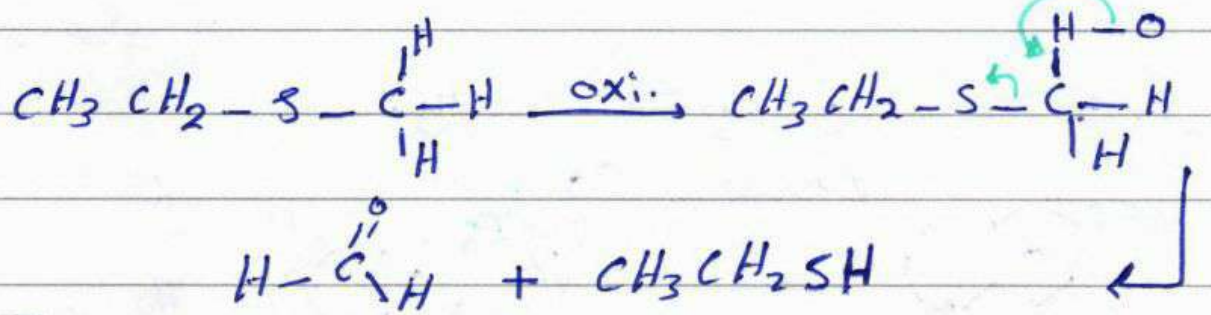
Trimeloprim

• اذا وجد في المركب مجموعتين alkoxy مختلفتين فإن ox. تحدث في الأكبر $C_3H_7-O-CH_3$

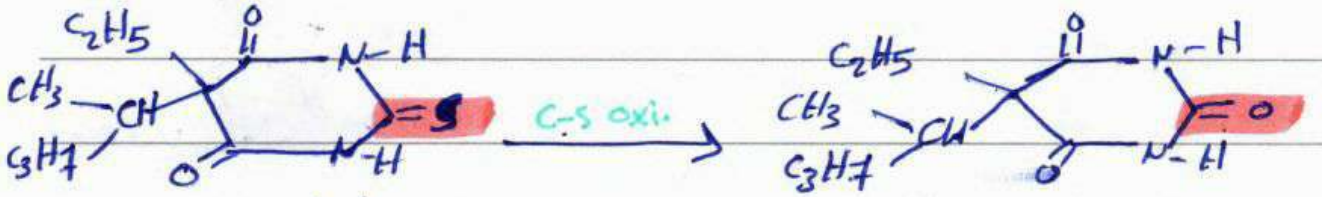


[3] C–S → S-dealkylation
→ oxidative desulfuration C=S → C=O
→ S-oxidation or oxide

a) S-dealkylation same to N, O

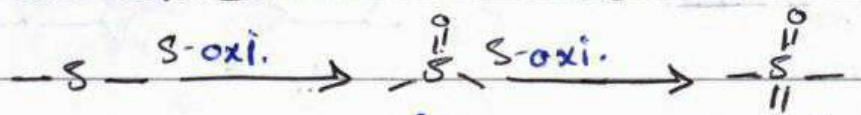


b) oxidative desulfuration sulfur group

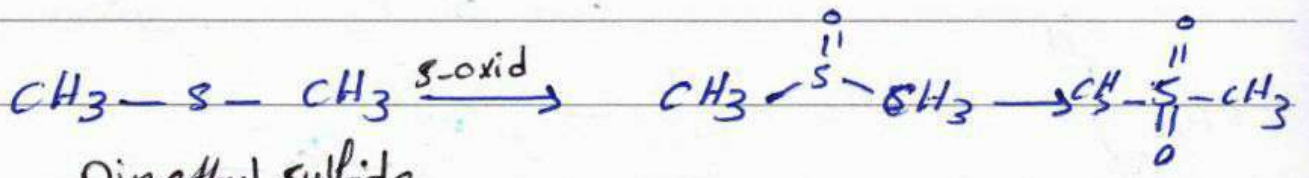


Thiopental

c) S-oxidation or oxide



sulfoxide sulfone



Dimethyl sulfide

- R-S-R → Thioether or sulfide
  called

Date. No.

8- others :-

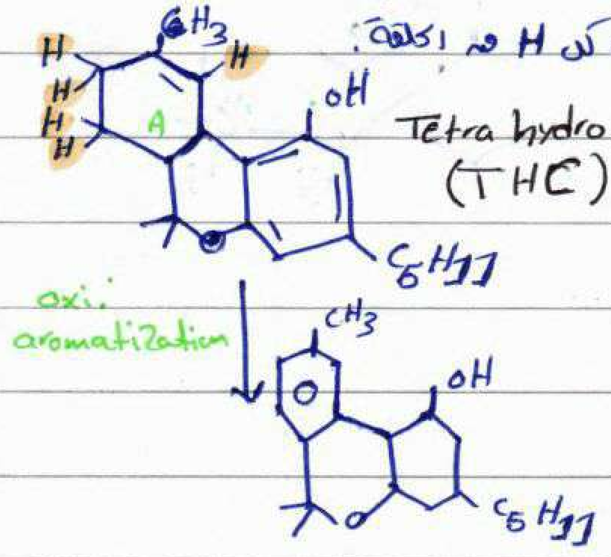
oxidative aromatization

[oxidative dehydrogenation]

⬡ non-Ar يعني الحلقة

تحولت إلى ⌬ Ar

حذف كل H من الحلقة.

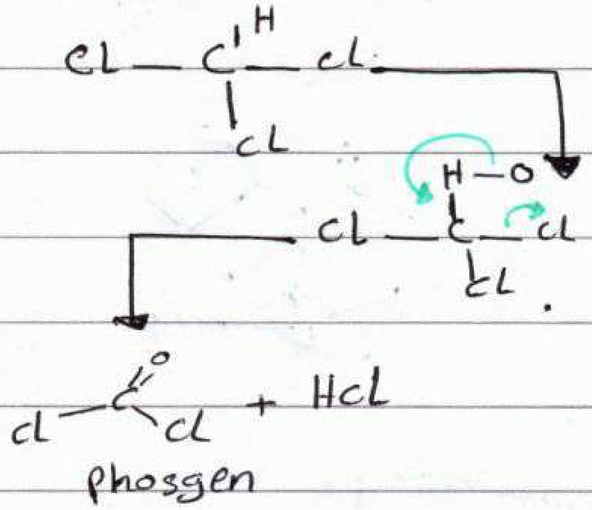


Tetra hydro canni (THC)

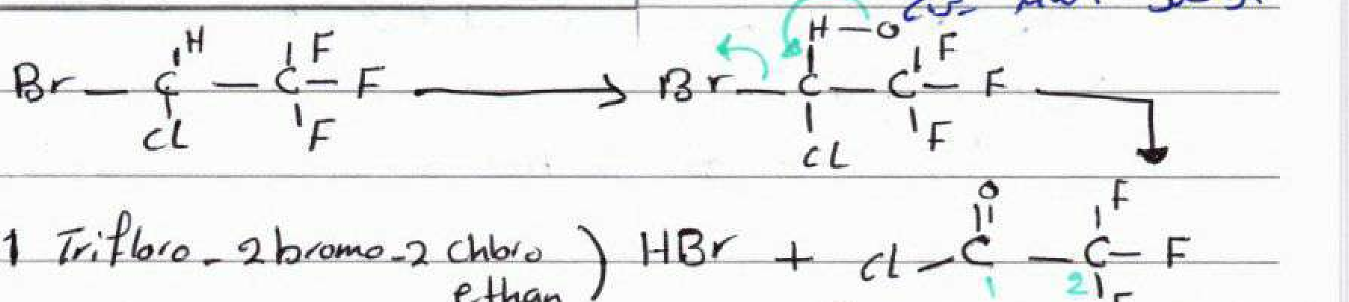
oxidative dehalogenation

تنزع هالوجين بحيث الذرة C المجاورة لـ تحوي أقل شيء H واحدة

• $CHCl_3$ [chloroform]



• اذا احتوت على C ذرتين هالوجين مختلفين الأكثر MWt يخرج



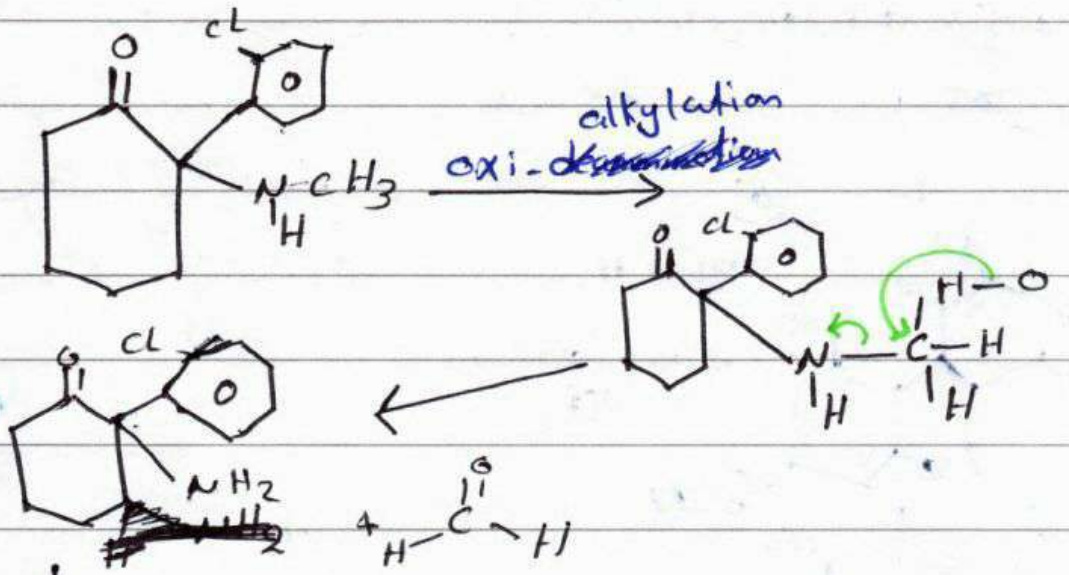
(1,1,1 Trifloro - 2 bromo - 2 chloro ethan)

(2,2,2 tri Floro Acetyl chloride)

Date. No.

نوع الإجابة المطلوب

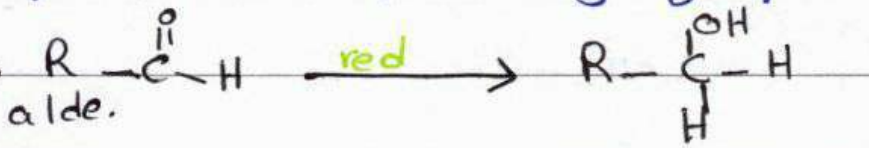
2 [O - Chlorophenyl] - 2 Methyl amino cyclohexanone undergoes oxidative deamination to yield ?



Date. No.

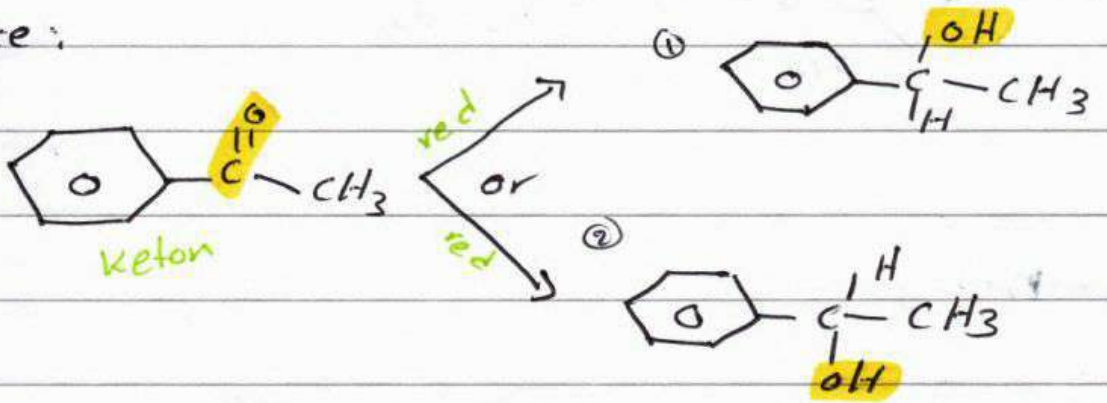
2- Reduction RxN :-

1) reduction of carbonyl group. " alde, keton"

- 

- 

Note :

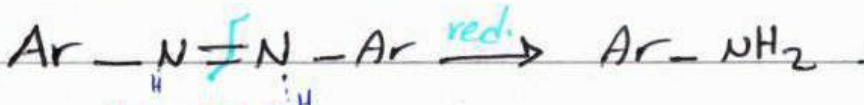


Racemic mixture ⟶ optically inactive .

واحد منهم S ، والآخر R وكل منها يلغي الآخر

2) Reduction of Nitro and diazo compound

$RNO_2 \rightarrow RNH_2$ جزيء أمين واحد.



∴ diazo $\xrightarrow{red.}$ 2 $Ar-NH_2$ بعض تركيب وسط

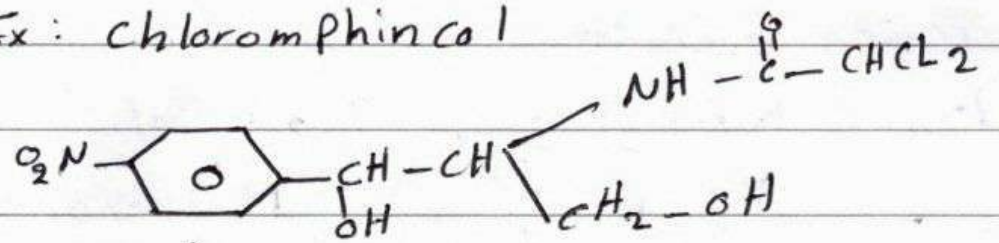
33

$Ar-\underset{H}{N}-\underset{H}{N}-Ar$

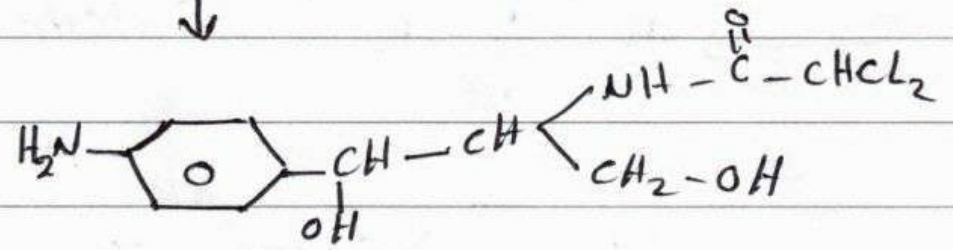
Hydrazo

Date. No.

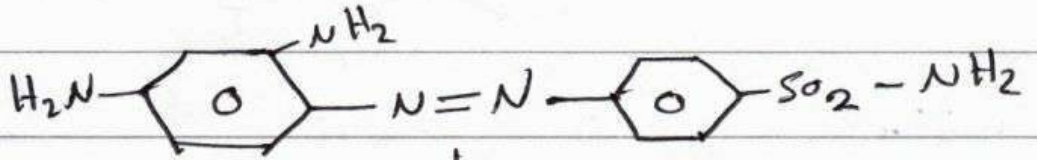
a) Ex: Chloromphincol



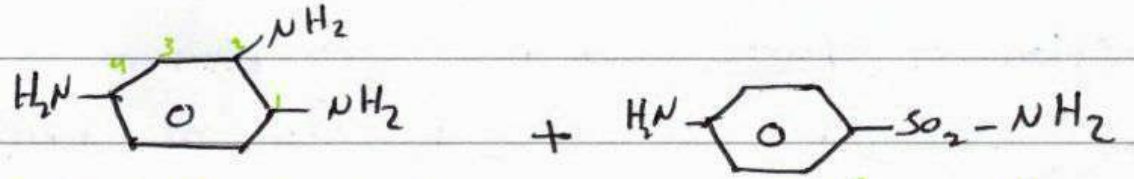
red. of nitro group



b) prontosyl



red. of diazo group



1,2,4 triamin benzene + sulfonamide

Date. No.

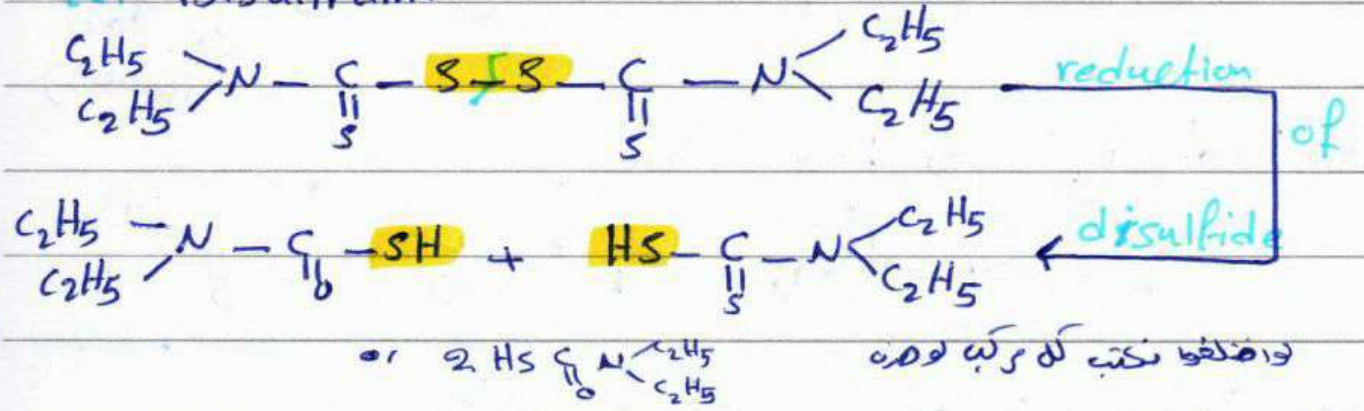
3) reduction of sulfoxide and disulfide

- $\underset{\text{sulfoxide}}{\overset{|}{S}=O} \xrightarrow{red} \underset{\text{sulfide}}{-S-}$

- $-S-S- \xrightarrow{red.} \underset{=}{2}\,SH$

disulfide

Ex: Disulfram



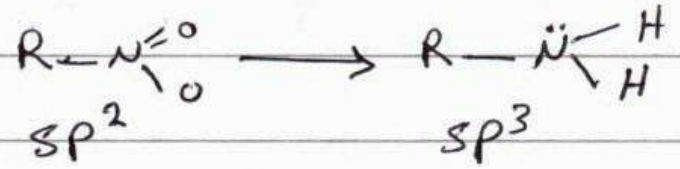
or $2\,HS-C(=S)-N(C_2H_5)_2$ واضافوا نكتب كل مركب لوحده

- $CH_3-\underset{\underset{O}{\|}}{S}-CH_3 \xrightarrow[\text{sulfoxide}]{\text{reduc. of}} CH_3-S-CH_3$

Dimethyl sulfoxide — Dimethyl sulfide

* ما الادلة التي تشير لحصول reduction RXN ؟

- convert From $sp^2 \longrightarrow sp^3$



sp^2 sp^3

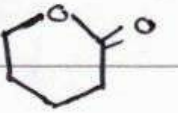
نكسي oxi $sp^3 \rightarrow sp^2$

Date. No.

3- Hydrolysis RXNs:-

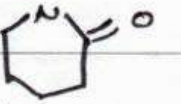
[1] hydrolysis of ester $R-\overset{\overset{O}{\|}}{C}-OR$

[2] hydrolysis of lactone "cyclic of ester"



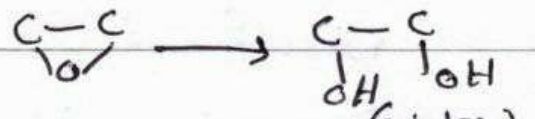
[3] hydrolysis of amide $R-\overset{\overset{O}{\|}}{C}-NH_2$

[4] hydrolysis of lactame "cyclic of amid"

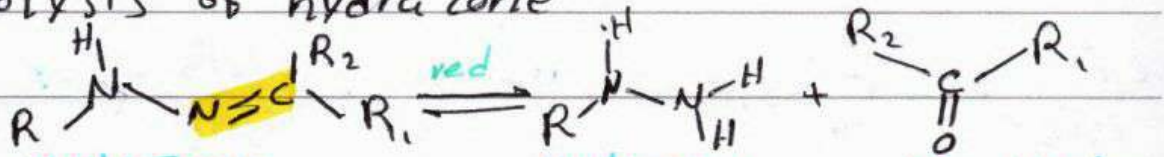


[5] hydrolysis of peptide " amino acid bond"

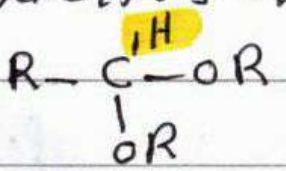
[6] hydrolysis of epoxide



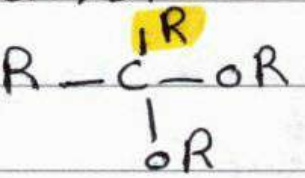
[7] hydrolysis of hydrazone



[8] hydrolysis of acetal or ketal

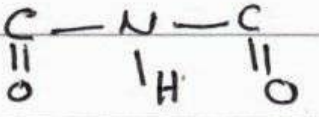


(acetal)



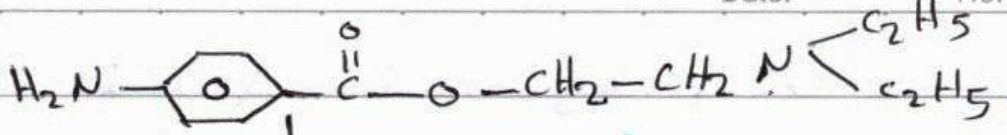
(ketal)

[9] hydrolysis of "emide"



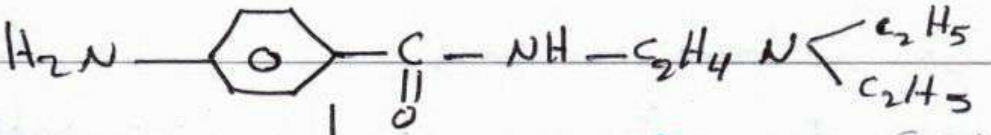
Date. No.

a)

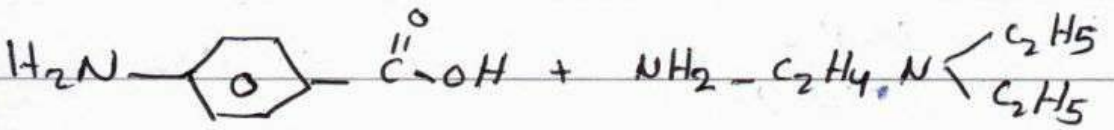
Ex: 

hydrolysis of ester

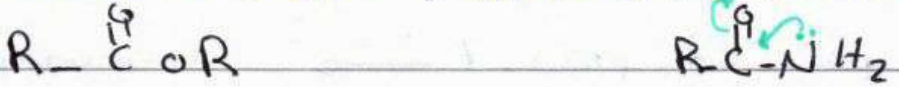
b)



hydrolysis of Amide

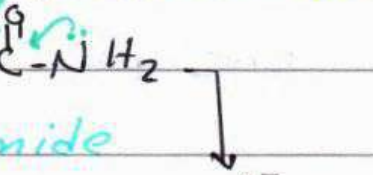


* which is Faster, hydrolysis of ester or amid??



ester is Faster than amide

- ester hydrolysis occures relativly easily but amide resist hydrolysis because: more resonance amides are the most stable and the least reactive; N is a effective donor of $\bar{e}$ to the carbonyl group " more resonance ", thus in compersion to ester, where the O_2 atom need only stabilize one carbonyl group



NH_2 More donating group

Date. No.

- The result of passing the Drug phas 1

activation Inactivation

- but if it pass phas 1 then phas II → Inactivation

Drug → phase 1 (to get funtioonal group) —if it exist / Directly→ phase II "conjugation"

activation inactivation

Directly

Inactivation.

Phase II "conjugation"

- Some Drug passes to phase 1 absorption excretion
- " " " to Phase 1 → phase II → excretion
- " " " directly to phase II (R) → excretion

Types of conjugation: To make Drug becom more polar

1. Conjugation with Gluconic acid
2. " " sulfate SO_3H
3. " " Amino acide ie glycine
4. " " Glutathion.
5. acetylation
6. Methylation.

less ~~oxidation~~ toxicity

D Gluc —enzyme→ Glucoronic acid → not bind with bilirubin → hyperbilirubinemia

Date. No.

[1] Conjugation with Glucoronic acid 90%

D-Glucose —enzyme→ Glucoronic acid الحصول عليه سهل
↳ by food. Major %. لأنه من الأكل

Why 90% ?? Major ?? occure in Adult more children وذلك بسبب عدم اكتمال الانزيم الكحول عند الاطفال

[1] easy to accept from D-Glucose

[2] easy to conjugation with different funcional group.

O-glucuronic acid [COOH / OH], N-Gluc → NH, S-Glu → SH

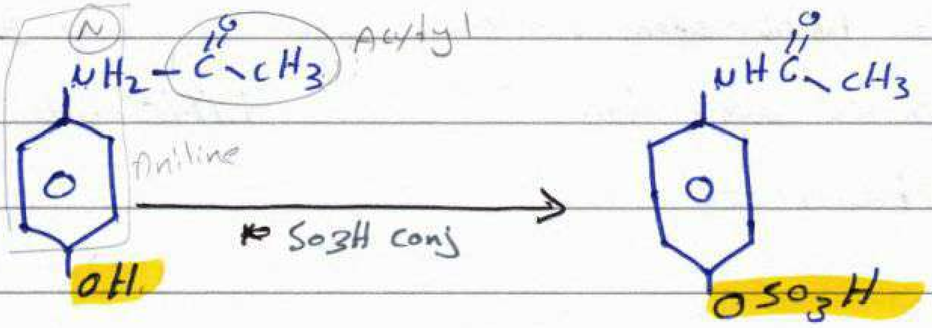
[3] More Polar [Contein OH] لو الارتباط بيصير → يسهل عليه اخراجه

[4] so it become easy to eliminate as: bilirubine + Gluc. → excretion

اذا تراكم بيصير hyperbilirubinimea صفوي عند بعض الولادات اللي بيحول enzyme بسبب

[2] Conjugation with sulfate [SO3H] تدخل على المركب

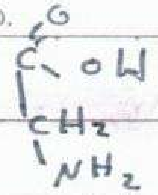
[Drug must contain OH, NH2]

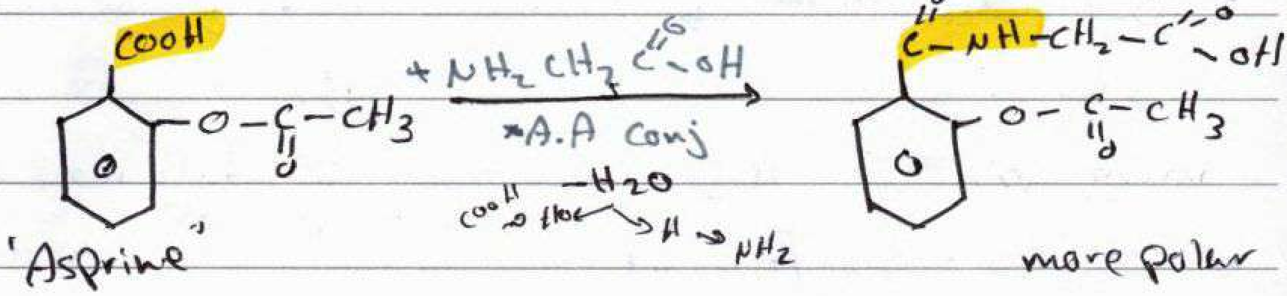


N-Acetyl-p-hydroxy Aniline more Polar.
"Paracetamole"

A.A أحمض Date. ← No.

[3] Conjugation with Amino Acid ie. glycine





* يحدث مع Drug فيه CooH

[4] Conjugation with Glutathion (GSH) → مكونه من 3 a.a (Glycine, cystine, Glutamic acid)

GSH → contain lone pair of ē

So it neucleophilic subs

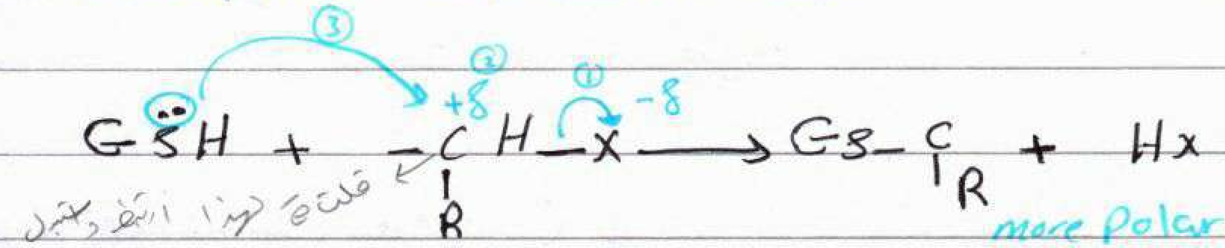
thus binds with electrophilic subs. By 2 Mech.

a) Neucleophilic displacment to an ē deficient carbon or heteroatom. hetero / C اما بـ ē في نقص

b) Neucleophilic addition to an ē difficient double bond =.

Date. No.

(I) Neucleophilic displacment mech.



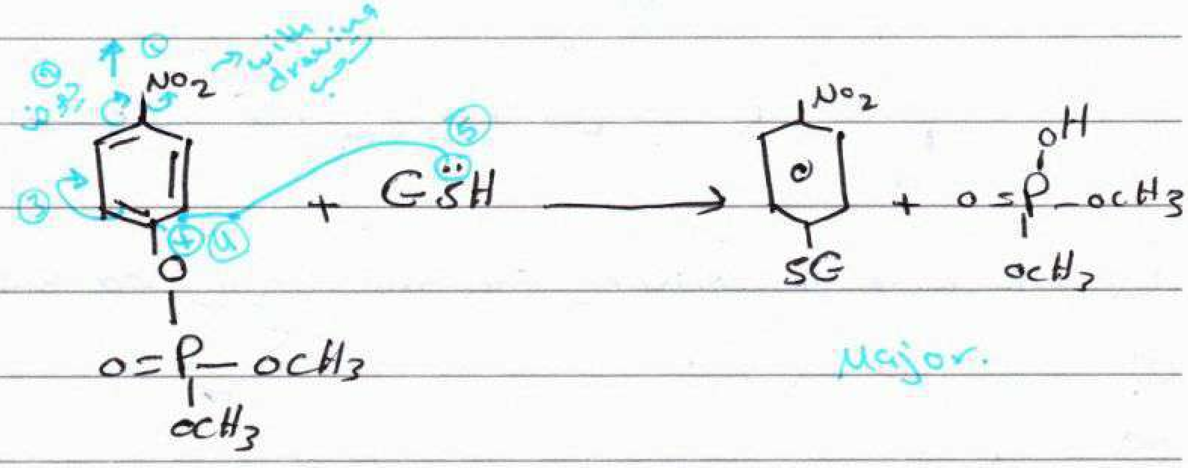
more Polar.

x: [Cl, Br, F] [R O=P—OR, OR]
withdrawing
alkyl group, Ar, aliphatic.

① سحب المجموعة الساحبة ē ويعطي $^{+\delta}C$ يهاجمه GSH

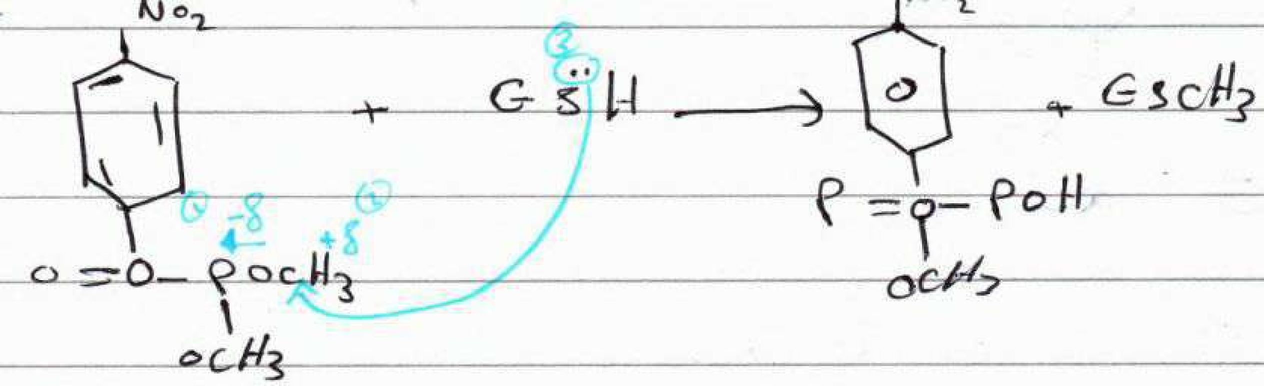
نلاحظ 2 Compound gives 2 Compound.

ex:



Major.

or



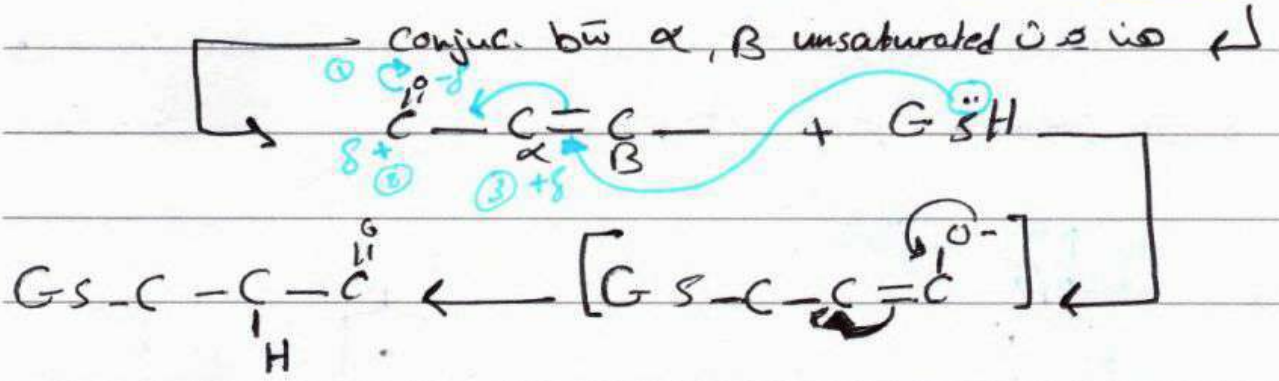
Date. No.

② Nucleophilic addition = في تفاعلات الإضافة

- "occur in conjugated system"

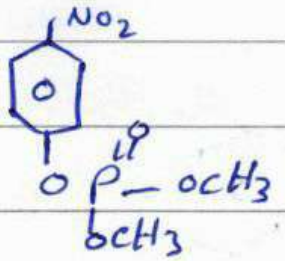
Note

- C=C=C=C ⟶ (called commulatied sys.)
- C=C–C–C–C–C=C ⟶ (isolated)
- C=C–C=C–C=C–C ⟶ (conjugated)



Q: which of the following compound conjugated with GSH?

① CH = CH – CHO

② 

③ 

④ All of the above

⑤ 1 + 2

CH=CH–CHO ①
✓ conj
✓ O ، O–CH3 ②
conj. بس with ③
X ④
✓ ⑤
∴ 1+2

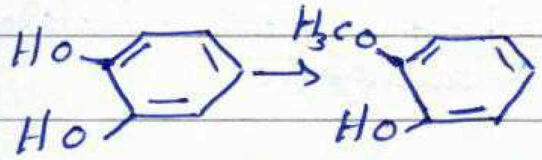
→ To reduces Toxicity

Date. No.

5 Methylation :

- Drug must contain
  OH $\xrightarrow[\text{إلى}]{\text{تتحول}}$ OCH_3

-



"catecole" ↓ toxicity

- يتم العملية على واحدة من Ho **فقط**
- لكي يسمى catecol لازم OH يكونوا جنب بعض

6 Aceylation

- Drug must contain
  1° amine NH_2

$NH_2 \xrightarrow{\text{تتحول}} NH\overset{}{\underset{O}{\underset{\|}{C}}}-CH_3$

"Amine" acetyl amine

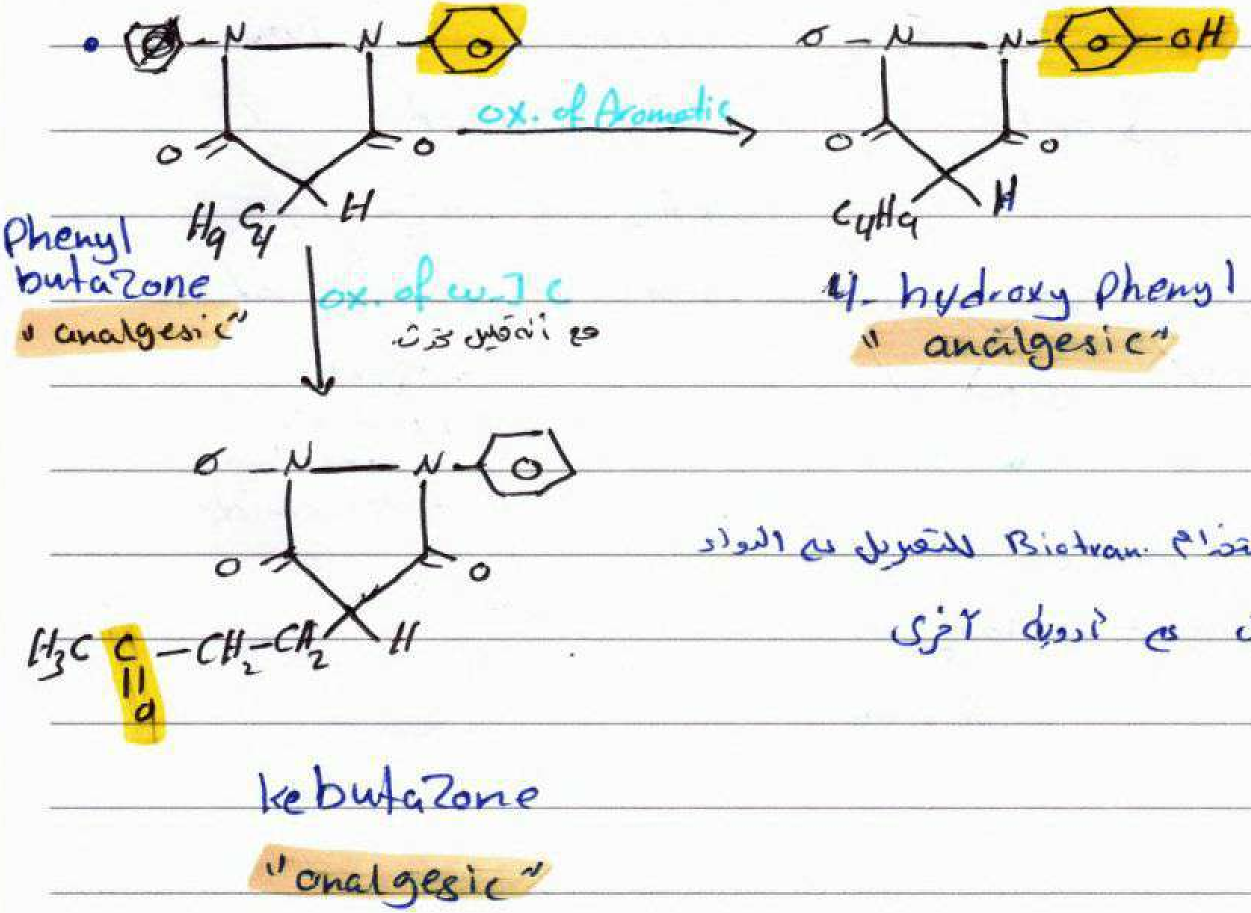
aliphetic
Aromatic
hydrazine
sulfonamide

- صدقنا يا جميل الملاح ألله يصح :
- هيا نبكي على الأطلال .

lec. 8

Drug Devolopment

- The Benifit of Biotransformation



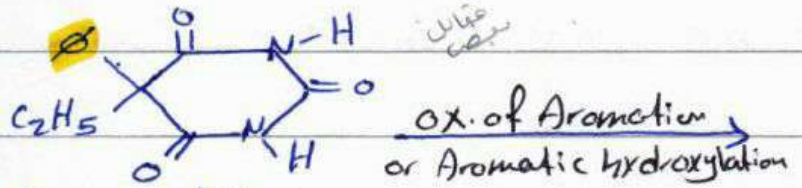
∴ تم استخدام Biotran. للتحويل بين المواد للحصول على أدوية أخرى

* Result of Biotransformation :-

1. Inactivation
2. Activation
3. less toxicity
4. Change in the pharmacological activity.

Date. No.

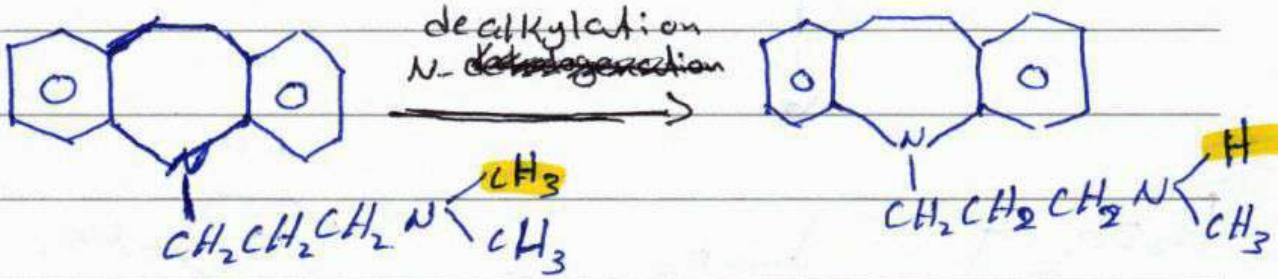
(1) Inactivation



Phenobarbital

4-hydroxyphenobarbital

(2) Activation active → active



Imipramine "Antidepressant"

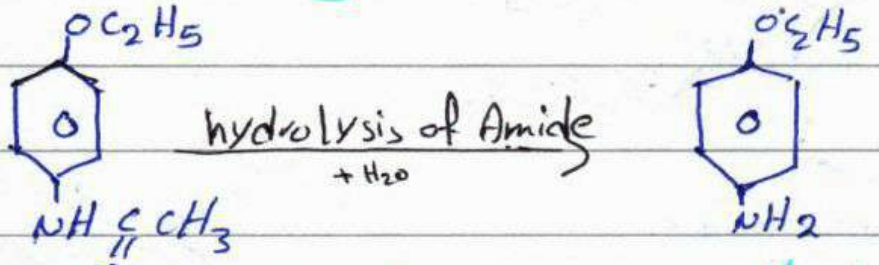
Active

desimpramine

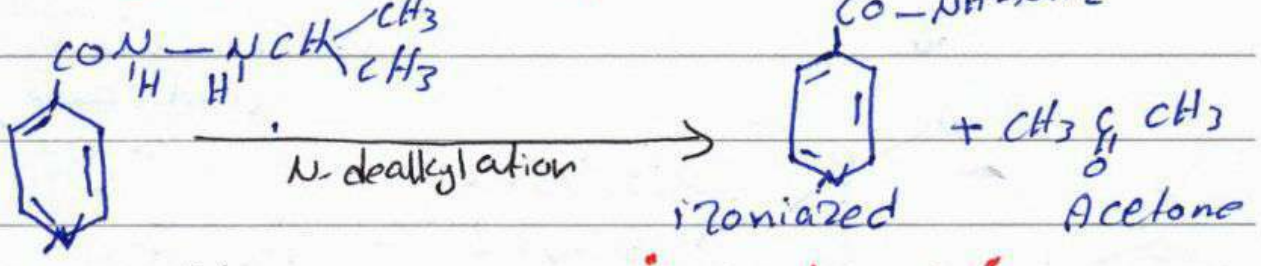
"Antidepressant"

↑ Active ↑ Doc.

(3) Less toxicity



(4) Change in the Pharmacological effect



Iproniazide

"Antidepressant"

Isoniazed

"Antitubercular"

Acetone

• ملاحظة عند المركب الناتج من N-dealkylation ، بالعادة يخرج 2 مركبين لكن هنا لأن المركب cyclic نتج واحد.

$P^{15}: 1s^2\ 2s^2\ 2p^6\ 3s^2\ 3p^3\ 3d$

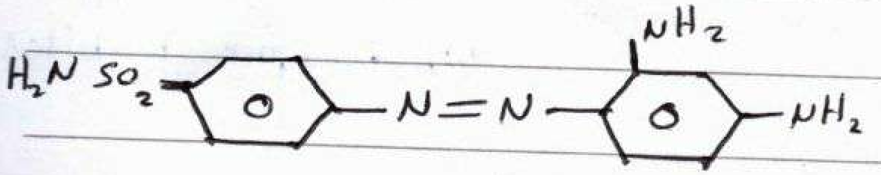
• ملاحظة / (back bond) مالك " empty لـ d

- عناصر الدورة الثالثة وما بعد تشذ عن القاعدة الثمانية 8 وتتخطاها لأن لها d وتستطيع عمل back bond

Date. No.

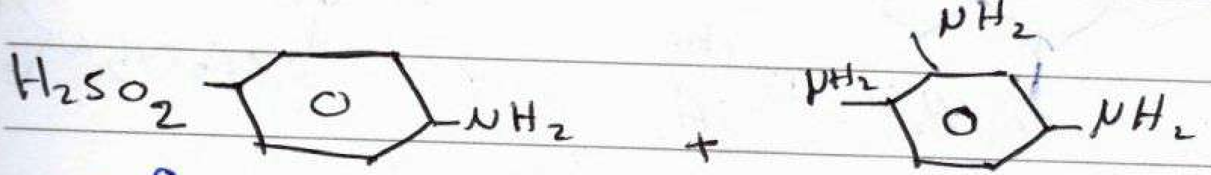
• **Prodrug :-** Inactive substance , After biotransformation the substance become active Inactive → active

Ex: [1]



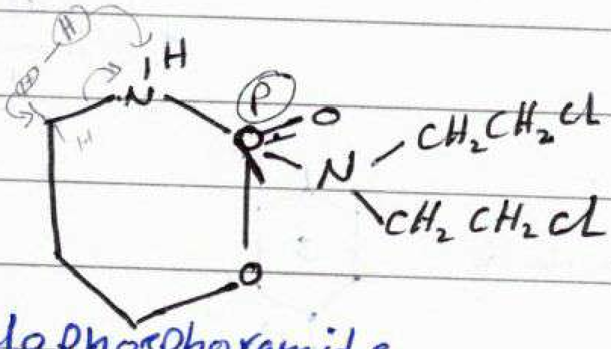
Prontosyl "inactive"

↓ reduction of diazo



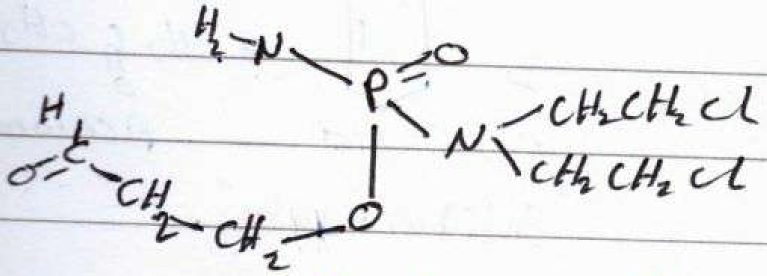
Sulfonamide " Antibacterial ".

[2]



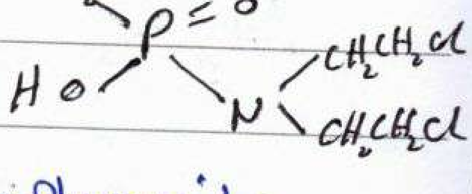
cyclophosphoramide (inactive)

↓ N, dealkylation



Aldophosphoramide (inactive)

→ o- dealkylation



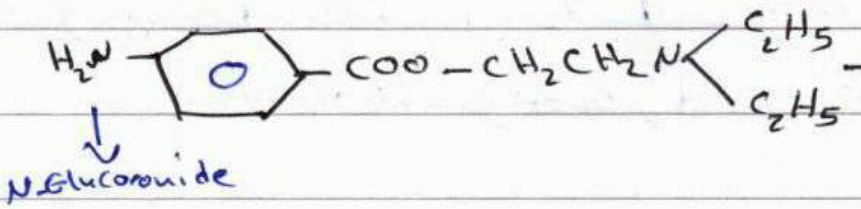
Phospharamide (Anticancer) (active)

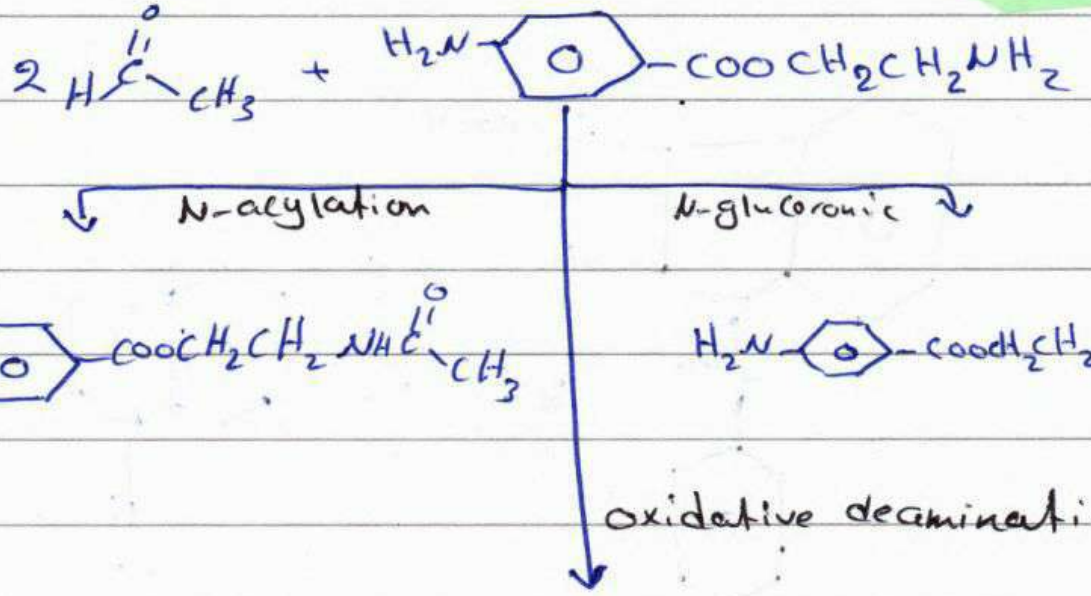
46

نوعية التفاعل الذي يحدث :

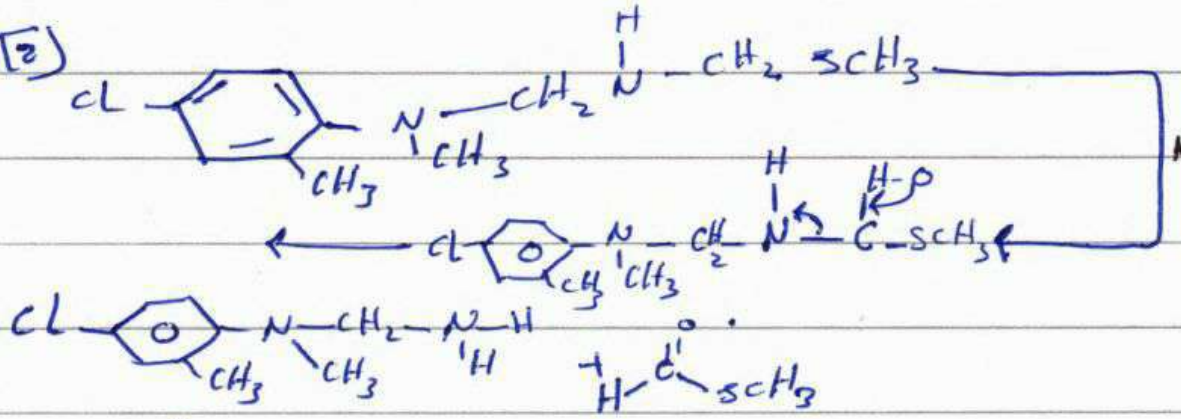
Date. No.

(1)



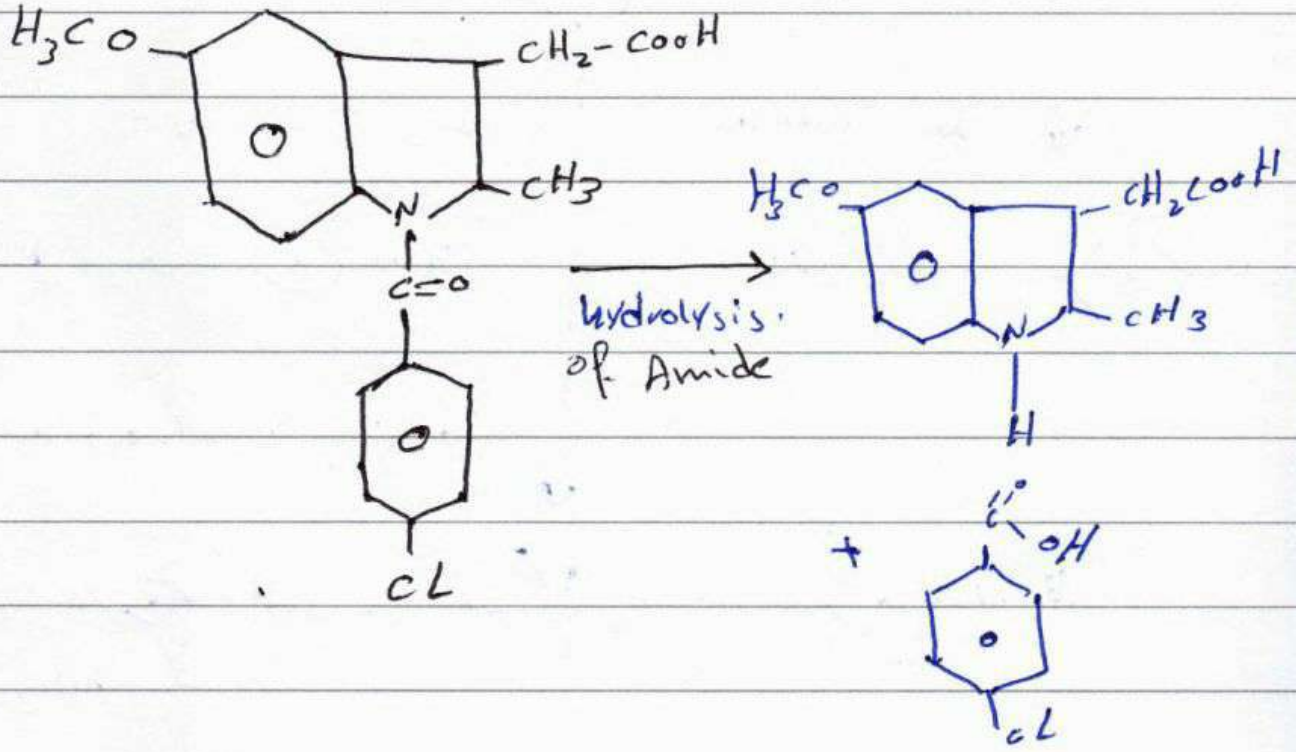


(2)



Date. No.

5-Methoxy-2-Methyl-1-1-(p-chloro benzyl) Indole-3 acetic acid, undergo hydrolysis to yield :



Anti-Bacterial Agent lec. 9

Date. No.

- Natural or synthetic agent that kill or inhibit the growth of bacteria or microorganisms.

* what is the difference b/w Antibiotic, Antibacterial?

- Antibiotic → Natural or partilly Natural source
  ← حتى لو جزء بسيط Natural فيه ←
- Antibacterial → synthetic source أعم وأشمل

  * so Antibiotic is part of Antibacterial (synth or Natural)

[Note]:-

- Bactericidal : Killing Bacteria , Bacteriostatic: inhibition
- Narrow spectrum: selective (G+ or G-) , prood spectrum: non-selective (G+ + G-)
- selective toxicity :- More toxic to microorganism than the patient (↓ side effect on patient).

synthetic agent for UTI :-

1. Sulfonamide ⎫ more used
2. Quinolones ⎭
3. Nitrofurans
4. Methanamine

Date. No.

- propervities for synthetic agent must have to be active and give it's effect?

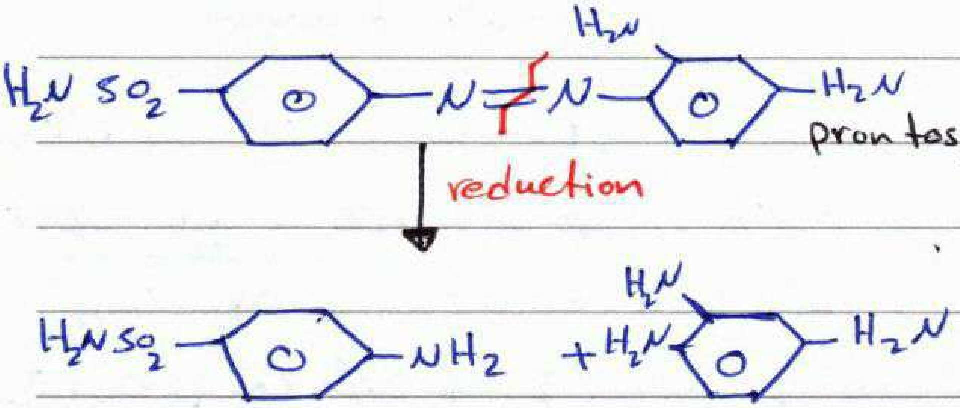
[1] Dissolution of these agent in urinary tract

[2] More polar

[3] To be excreated in urin

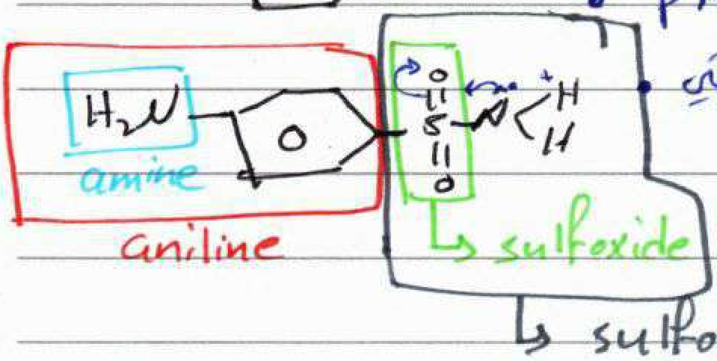
[4] selective toxicity.

[II] Sulfonamide = sulfanilamide . 1950 by domagk



sulfonamide "active"

- Acidic ch.ch → $NHSO_2R$, $R\overset{O}{\underset{O}{S}}-NH_2$
- pka = 10.4
- يتم فقد احدى H وليس كلاهما لكي تعطي الأخرى activity



p-amino benzen sulfonamide / sulfonamid / sulfonilamide

Date. No.

pH urine = 6 , pKa = 10.4 Acidic

$10^{PH-pKa} = \frac{I}{unI}$, $10^{6-10.4} = \frac{I}{unI}$ ⇒ unI >> I

lead to ppt in kideny then destruction of neforn. and thus cause crystal uria

To avoid crystal uria? 1st Modification on sulfonamide

* - we increased acidity of drug "Modification" by substitution of one of H with a withdrawing group to become more easy to loss and ↑ acidity

هذا قبل حدوث الكارثة نحاول استبدال واحد من H بمجموعة ساحبة لزيادة حموضة الدواء لكنه بعد حدوث الكارثة ننصح بشرب الكثير من الماء.

• Proplems of sulfonamide:- (unI >> I)

[1] Low potency [2] low water solubility.

• reduction use of sulfonamide after a while of many uses ? أول ما تم اكتشافه استخدم بكثرة ثم توقف

[1] Rapid resistance

[2] Appearence of penicilline which is → more safe, → high potency.

* Note that due to ↑ pKa of sulfonamid (Acidic) pH=6 urine, ⇒

sulfisoxazole 5. pKa
sulfAcetamide 5.4
sulf Methoxazole 6.1
sulfdiazine 6.5
sulf. Merazine 7.1

هنا لكي تزيد فرق موسم الدكتور

Date. No.

$pKa = 10 \quad pH = 6$

$$pH = pKa + \log \frac{A^-}{HA}$$

$$6 = 10 + \log \frac{A^-}{HA} \Rightarrow \log \frac{I}{unI} = -4$$

$$10^{-4} = \frac{I}{unI} \Rightarrow unI \gg I \quad \text{or} \quad \text{Acidic form} \ggg \text{salt form}$$

unionized is poorly soluble in water, thus it will ppt and cause crystalluria.

How to reduce it?

1. larg intake of fluid
2. Modifying pKa values nearer to pH of urin
   → structural Modification ↑ salt form ↑ solubility in water
3. ↑ pH of urin by urinary alkanisers like $NaHCO_3$
4. use of triple sulfas.

(2) $pH = pKa + \log \frac{A^-}{HA} \Rightarrow 6 - 6 = \log \frac{A}{HA}$

$A^- = HA$
salt 50% I — acid 50% unI

اكل الأنسب أنه يتم تعليل pKa كذ مستوى الامتصاص (6-7.4)

هذا مستوى مناسب للامتصاص في UT عن طريق استبدال H بمجموعة ساحبة

يؤدي الى تسهيل فقد H+

Anilin. يتم تحضيره من

How to prepare Sulfonamide ? $H_2N-C_6H_4-SO_2NH_2$

Date. No.

very active make it poly substituted

1) Nitration (NO_2)
2) reduction

Anilin

$(CH_3CO)_2O$ acetic acid Anhydrous

acetanilide

$ClSO_3H$ Chlorosulfonic acid

p-Chloro sulfonide

NH_3 (amonia) $-HCl$

N-acetamide benzen-sulfonyl chloride

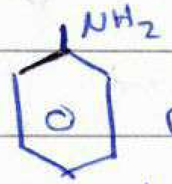
N-acetamide benzen sulfonamide

hydrolysis of Amide 100% NaOH

sulfonamide ✗✗

يتم استخدامه لتحضير مركبات أخرى.

لماذا لم يتم إضافة $ClSO_3H$ مباشرة على Aniline ؟؟



"non-selective"

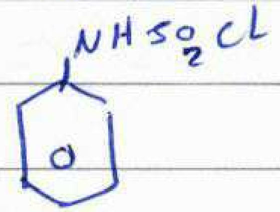
اذا صار تفاعل تفاعل Directly مع NH_2

ونه فعلا المركب very active وبيخص نه

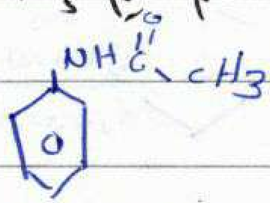
poly substituted بالتالي له يتم

توجيه $\overset{O}{\underset{O}{\overset{\|}{\underset{\|}{S}}}}$ على موقع para

↓ $ClSO_3H$



هذا ليس المطلوب



"acetanalide"

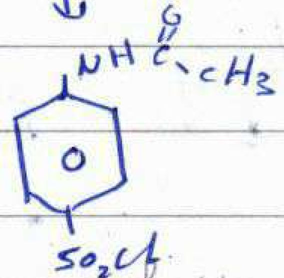
(selective)

يتم التوجيه على para لأنه

NH محمي بواسطة acetic acid anhydrous

ولأنه less active مقارنة مع Anilin

↓ $ClSO_3H$



p-chloro sulfonide

or N acetamide-benzen sulfonyl chloride

↓

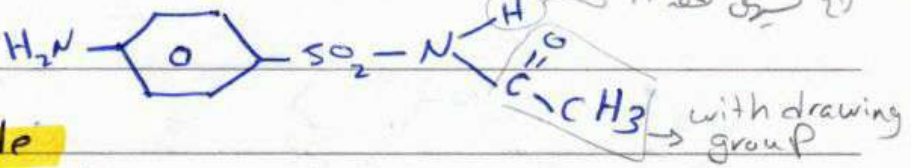
precouser for other Modification

يعني مثل جدار الحماية

* كل المشتقات تنتمي لـ O.y

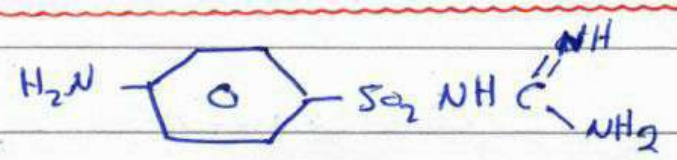
Modification of sulfonamide to obtain less pKa

Date. No.

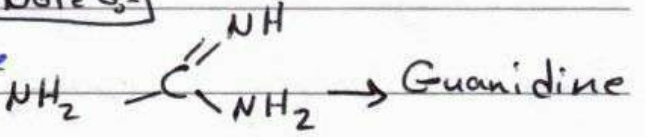
(1) H →  

- Sulf acet amide
- N- Acetyl sulfonamide
- used as ophthalmic infection, D

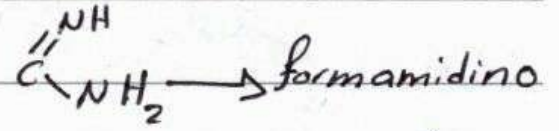
---

(2) H →  

Note ⊖-

N- paracamino Phenyl sulfanyl Guanidine 

or N- formidino sulfonamide

← تكتب هيك . 

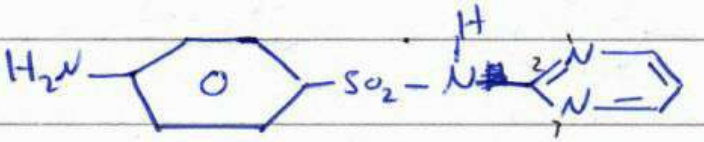
N- guanidio sulfonamide ✗ → لم تكتب هيك N ترتيب

---

(3) H →  "pyrimidine" heterocyclic ring

Sulfadiazine

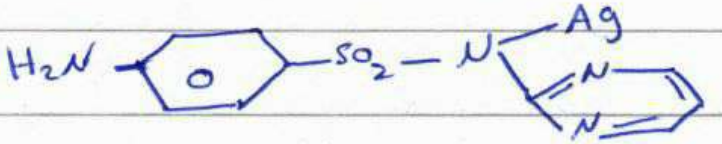
pKa = 6.5



N(2-pyrimidine) sulfonamide

or pyrimin-2-yl sulfonamide

Ag تم استبدال H الأزرق بـ



Sulfadiazine silver Basic

55

use in war → Burning

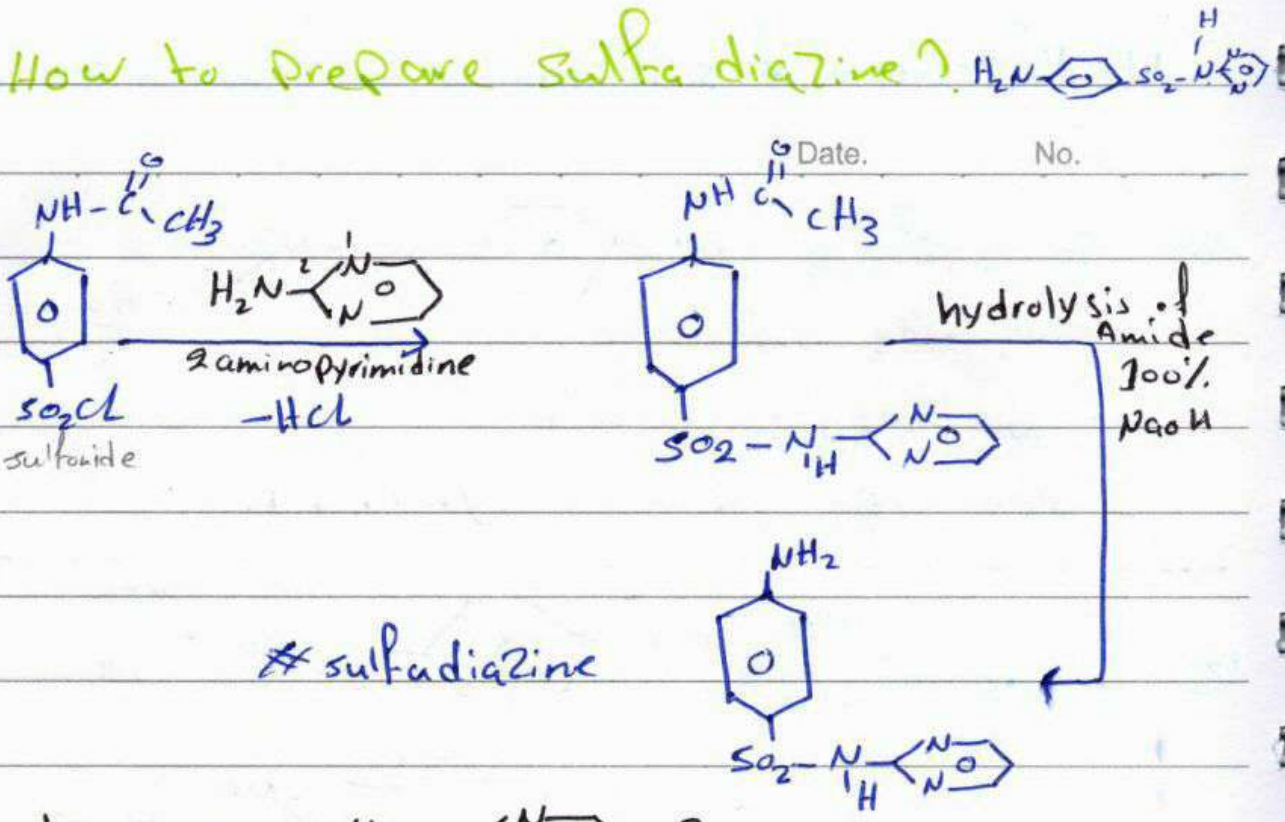
Anti Bacterial Inactivation ←

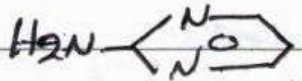
Gram سلبي

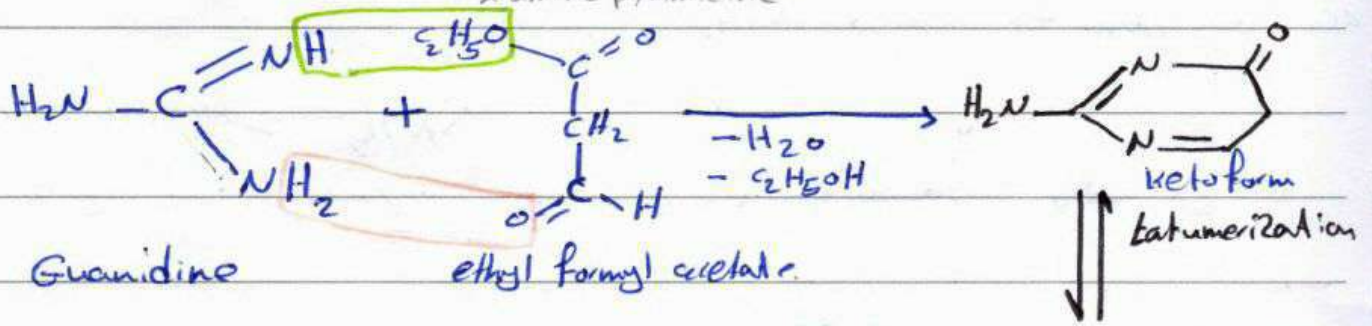
N = CH

pyridin

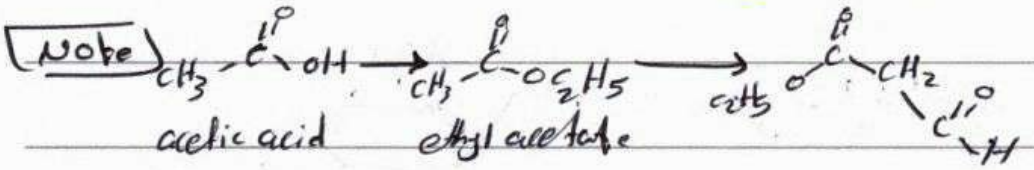
How to prepare sulfa diazine?

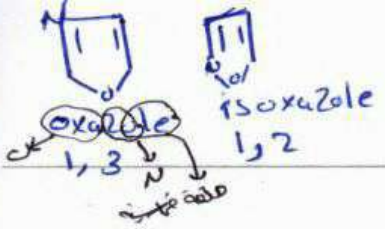


How to prepare 

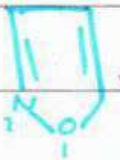


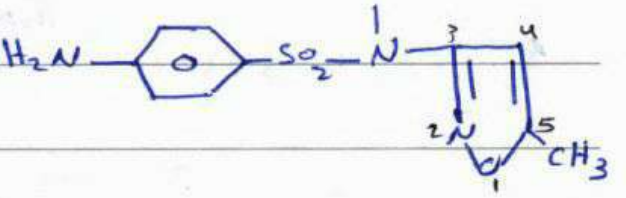
Note





Date. No.

(4) H ⟶  isoxazole.

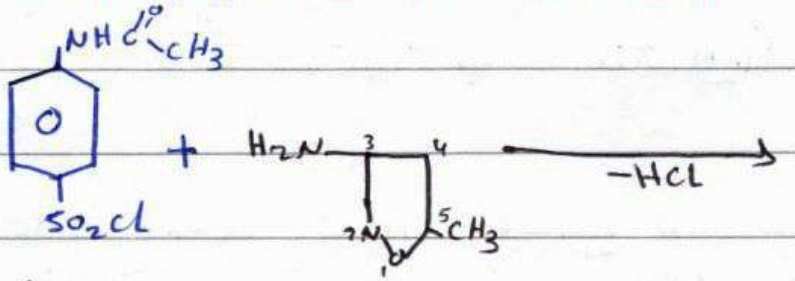


pKa = 6.1

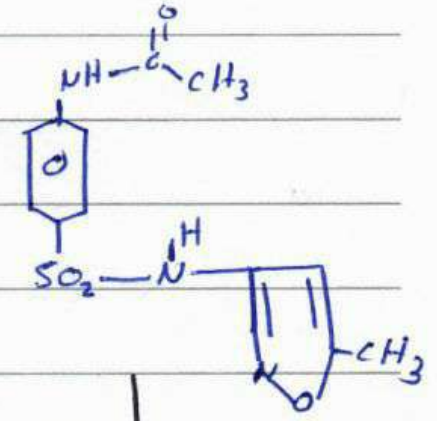
Sulfamethaoxazol

N [5-Methyl isoxazole-3yl] sulfonamide

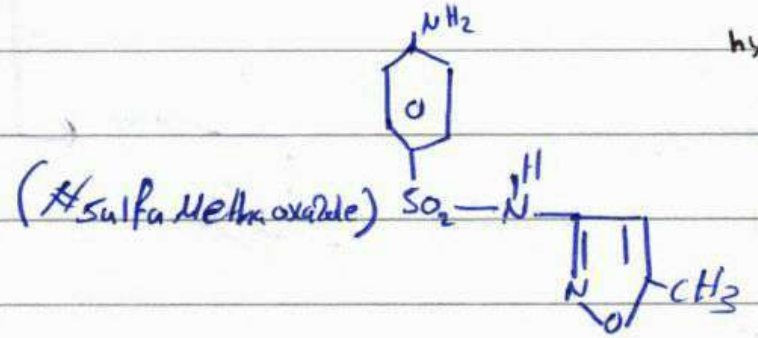
* How to prepare sulfa Methaoxazole



P chlorosulfonid (3-Amino, 5 Methoxy isoxazole)

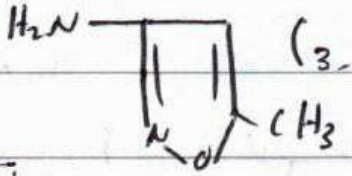


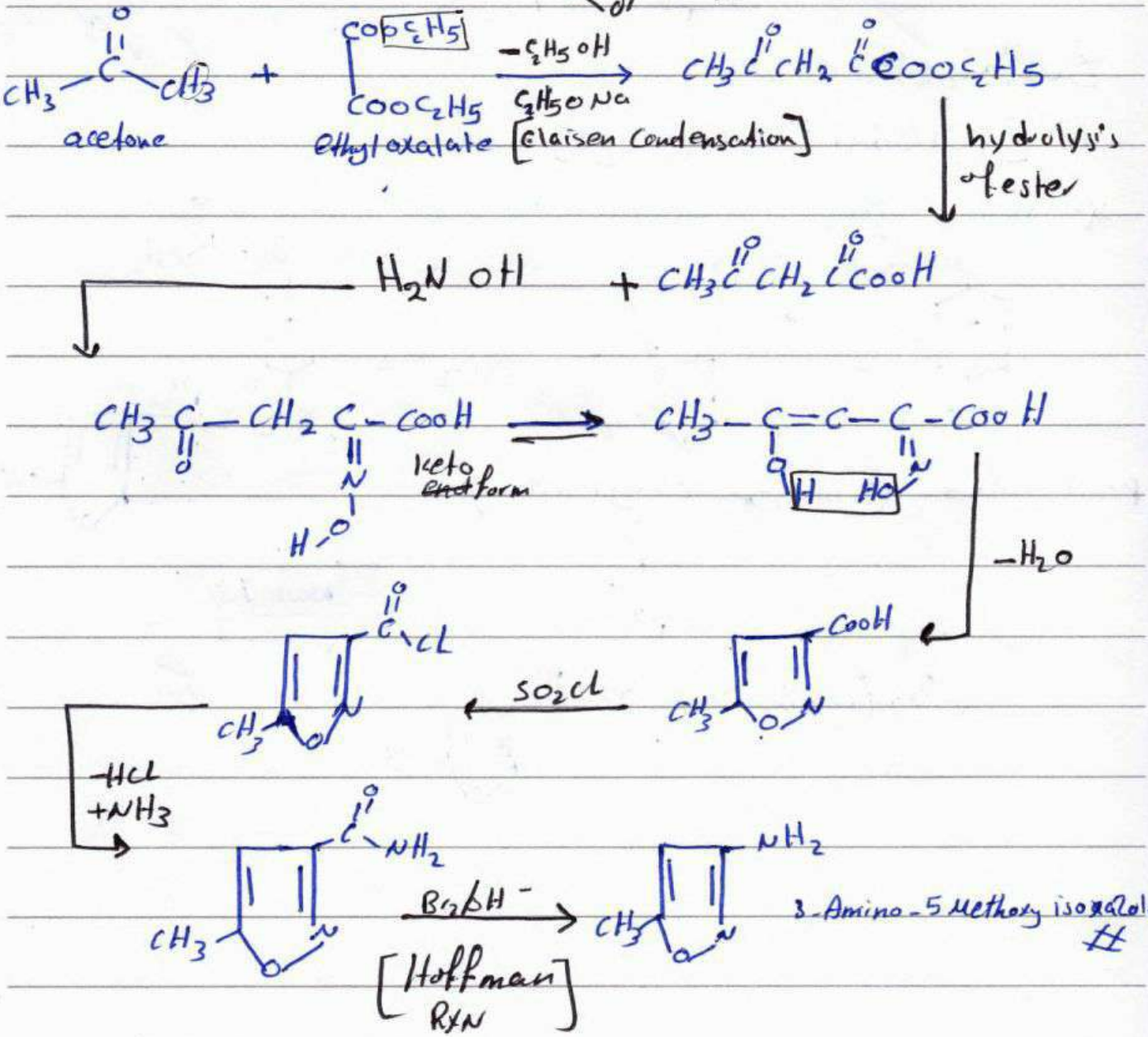
hydrolysis NaOH Boy.



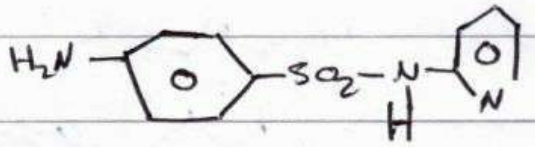
(#Sulfa Methoxazole)

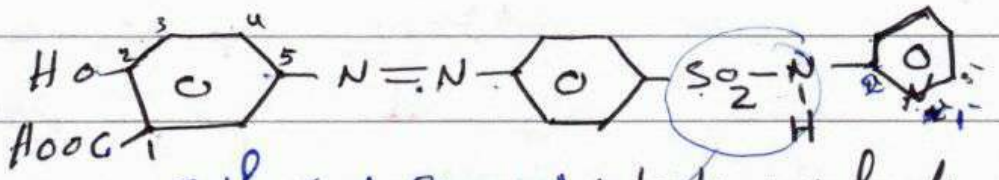
Date. No.

* How to prepare  (3-Amino-5-Methoxy isoxazole)



Date. No.

-  N(2pyridinyl)sulfonamide.

- 

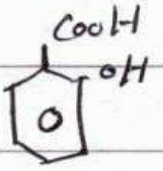
sulfasalazine "intestinal infection"

5 [[[EN(2' pyridinyl) sulfamoyl] phenyl] diazo] salicyclic acid

or hydroxy benzoic acid.

* Note :-

Benzoic acid



2-hydroxy benzoic acid.
or salicyclic acid.

* SO_2-NH → sulfamoyl

MoA :-

- Make inhibition for THF "Tetra hydro folic acid" which syntheside by Bacteria. , which make transfere of CH_3 from compound to another.

DUMP —THF→ dTMP

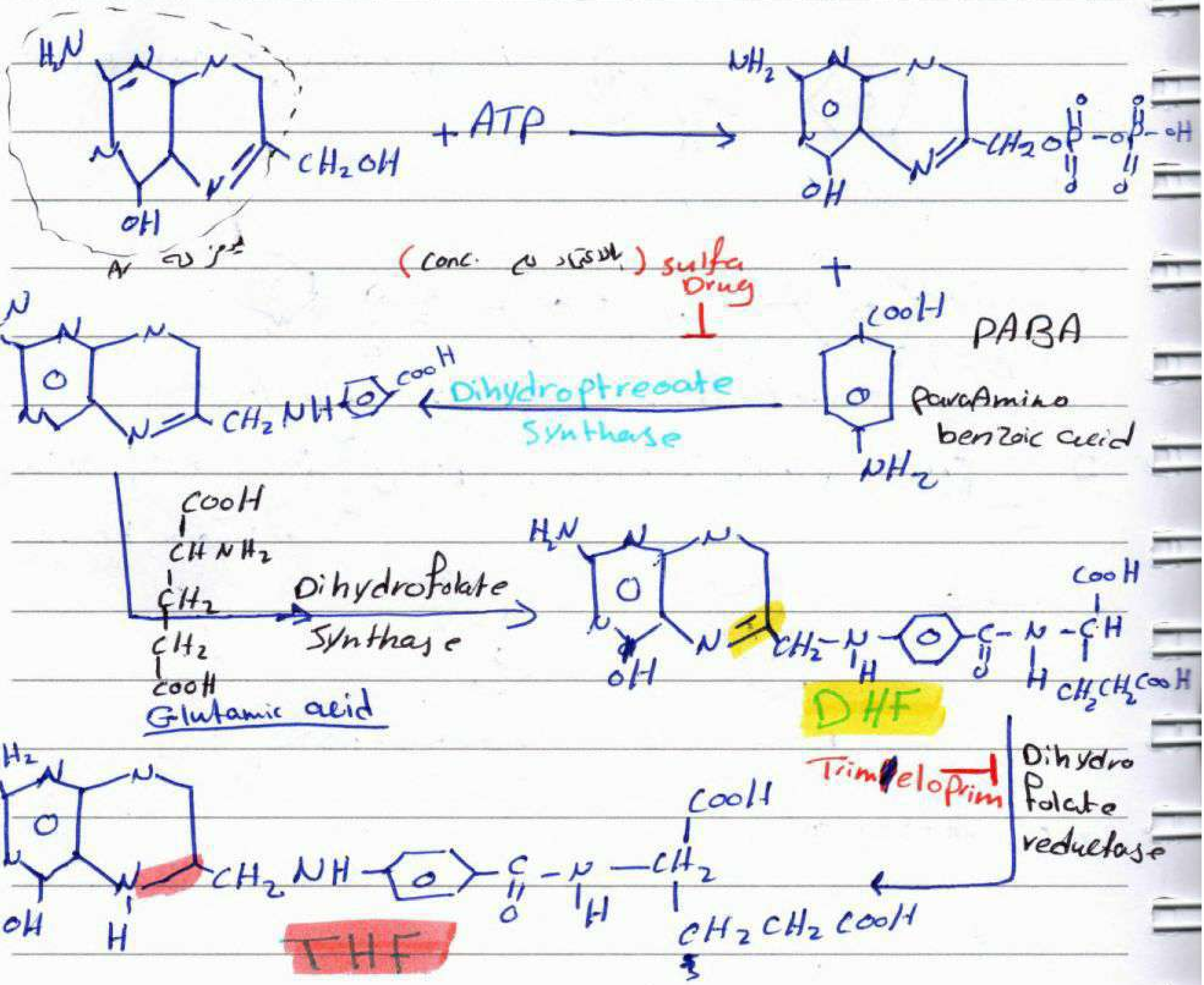
(dioxy uridine Monophosphate) (deoxy Thymidine mono phosphate)

In DNA / RNA

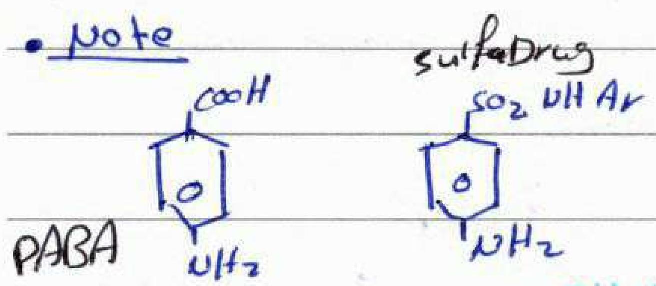
بالتالي لا يتكون وتموت البكتيريا

آلية تكوين THF في البكتيريا.

Date. No.



• Note



* تقريباً يوجد شبه كبير في structure

ويصير بينهم [compatitive Antagonist]

• الأكثر تركيزاً هو الي يرتبط.

ويعمل عليه الإنزيم Dihydropteroate Synthase (Dps)

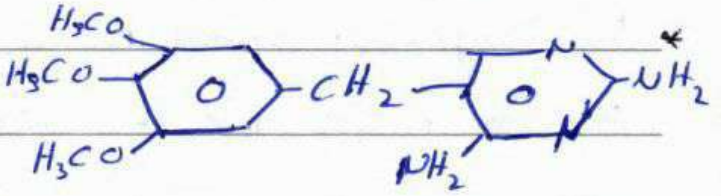
كل ما كان تركيز PABA أعلى تقوم البكتيريا بإكمال العملية من البداية

لكن لو كان sulfa Drug أعلى يتحفل عليه الانزيم DPS ويمنع التكوين

* O-dealkylation هو مسار

Date. No.

فرضاً قامت البكتيريا بمقاومة وأفرزت كميات كبيرة من PABA
حتى قامت بتكوين DHF . في هذه الحالة نعمل Combination بين Sulfa Drugs + Trimeloprim تبني تمنع تكوين THF



أو

Sulfamethaoxazole + Trimeloprim

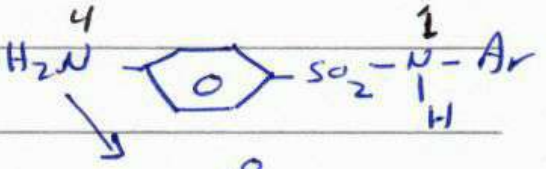
→ Sulfatrim®

→ Resprim® M.R. BSS

→ Sulprim®

→ Megaprim®

→ Bactil®



• Biotransformation " Metabolism"

* 90% of Metabolism is acylation

• SAR: structure activity relation ship

• if NH_2 in para position if replaced with NO_2, NH_2OH activity reduces, but if replaced with N=N activity is same as in Sulfasalazine

• Aromatic ring must be non-substution [-exept-P-position]; O, M position substitution → inactive

Date. No.

3. SO_2NH [sulfamoyL] if it replaced with Amide [$\overset{O}{C}-NH$] the activity reduced ↓

4. compound must be acidic ch.ch , if H (in N 1) which responsable of acidity is replaced with alkyl it become Inactive

* uses of sulfa Drugs : الاستخدام في التركيبة

① AntiBacterial ② AntiDiabetic ③ diurtics

Quinolones

1958

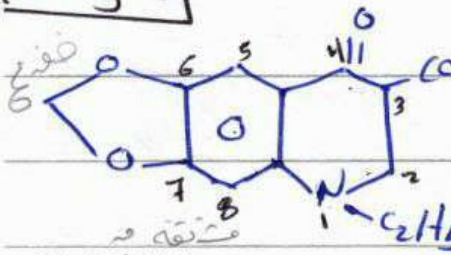
Date. No.

- Discoverd in the spread of Malaria. as Anti-malaria
- 1st Drug used as Anti-malaria is Nalidixic acid - Negram®
but show Narrow spectrum, Low potency.
- After Modification of Nalidixic we get 1st, 2ed, 3rd, 4th generation of Quinlons.

First Generation of Quinolones. low potency

- high protein binding.

Drugs:

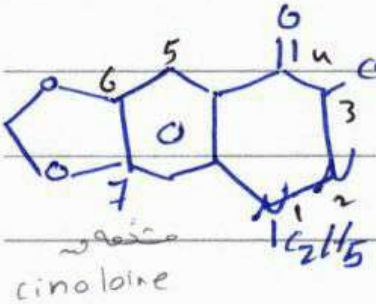


مشتق من Quinolons

Oxolinic acid

1-ethyl-4-oxo-6,7 (Methylenedioxy)
1,4 dihydroquindine-3-carboxlic acid.

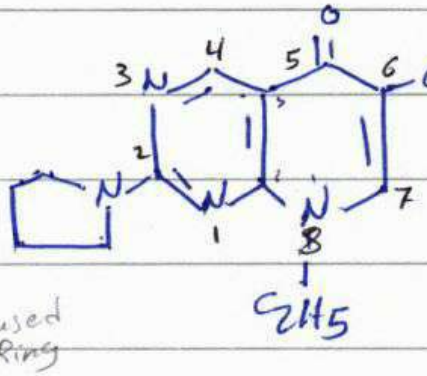
cinnoxacine



مشتق من cinoloine

1-ethyl-4-oxo-6,7 (Methylenedioxy)
1,4 dihydro cinnoline-3-carboxlic acid

Promidic Acid

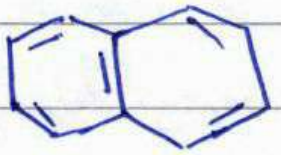


fused Ring

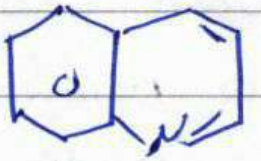
8-ethyl-5-oxo-2-(pyrrolidnyl)
5,8 pyrido [2,3-d] pyrimidine
dihydro
6-~~CA~~ carboxlic acid.

Date. No.

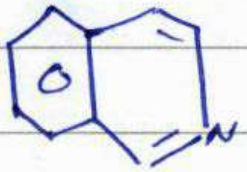
∴ no 1st Gen تتفاعل ثم



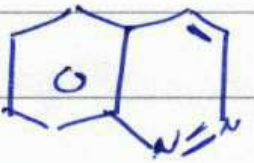
nephthalin



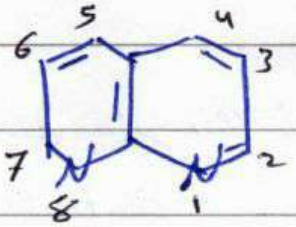
Quinoline



isoquinoline



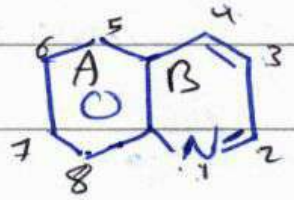
cinnoline
1, 2



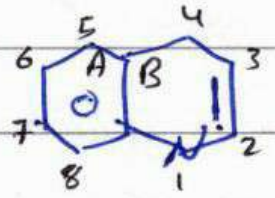
1, 8 naphthyridine

All are bioisoterism

Note:-



1, 2, 3, 4 → B في = مواقع حلقات A في استبدال



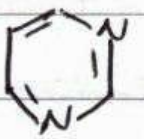
2, 3 2H بـ استبدال

1, 4 ↓ hydro quinoline
dihydro

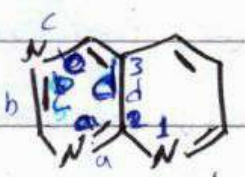
no. of fused ring

Date. No.

Pyridine



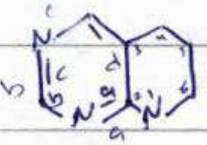
Pyrimidine



pyrido [2,3-d] pyrimidine

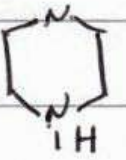
* الأكثر hetero atom هي Pyrimidine نعتبرها الأساس ، وطبعاً Pyridine مستبعد

نرقم حلقة الأساس أرقام داخلية ، الحلقة الأساس بالحرف



Pyroil

Pyrodine



piperazinyl

Date. No.

1° For Gram (-) but not pseudmonas species

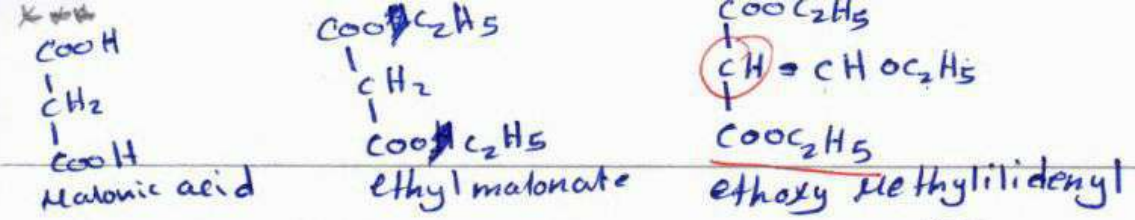
2° For → Gram (-) included pseudomonas species
→ some Gram(+) (S. aureus) and some atypical

3° same to 2° with extended Gram (-) and Atypical converge.

4° same of 3° with broad anaerobic converge

Note :-

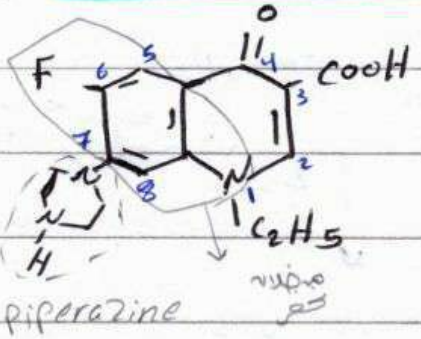
- Pseudomonas Quregonsa is the most potent Baeteria that cause UTI
- 2°, 3°, 4° → called Fluro Quinolones
  - Not highly Protein Binding
  - wide distribution to urine and other tissues
  - it's ch.ch
- But 1° generation has ch.ch.
  - Low potency
  - highly protien Binding. → لذا هي سيئة تتقرر.
  - Narrow spectrum



Date. No.

Second Generation of Quinolons :-

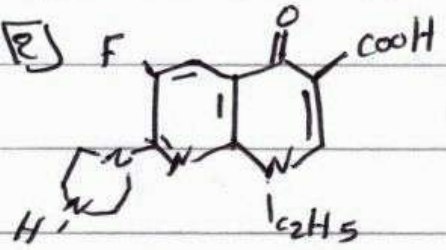
1) NorFloxacine , Apirol ®



6- Fluro - 7 - piperazinyl - 1 - ethyl - 4 - oxo - 1, 4 dihydro Quinolons - 3 C.A.

Bioisosterizm

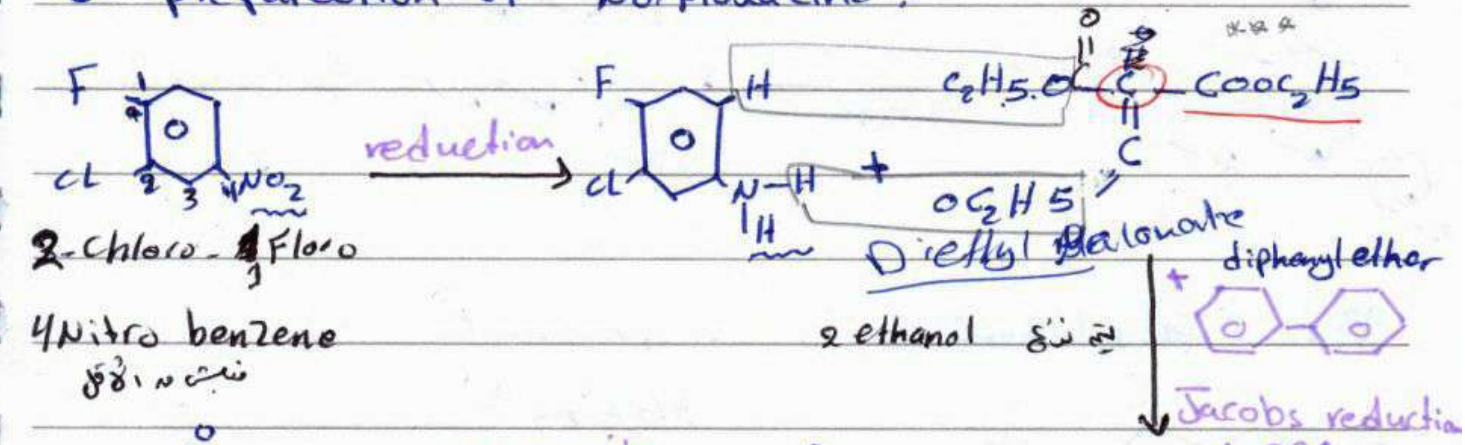
2) enoxacine

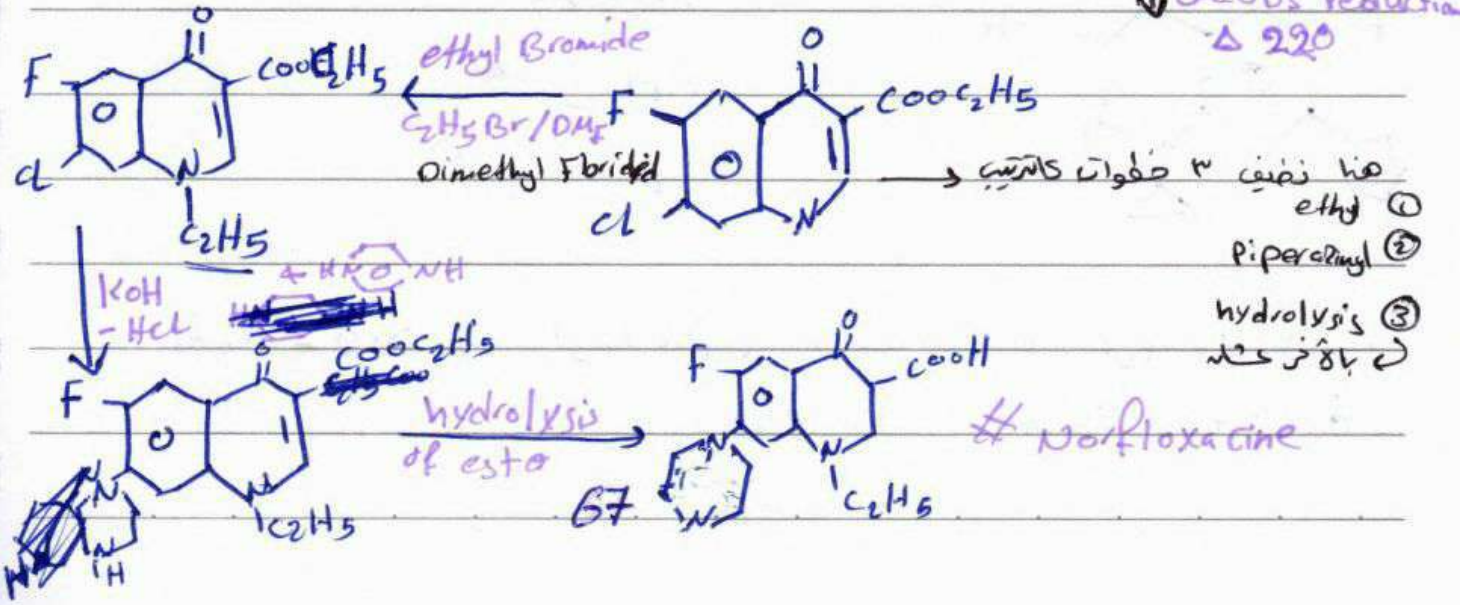


6-Fluro - 7- piperazinyl - 1-ethyl 4. oxo - 1,8 naphtridine - 3- C.A.

dihydro

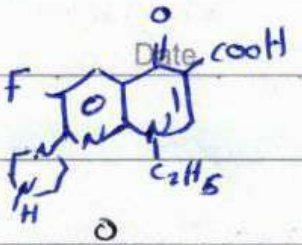
- preparation of Norfloxacine :-



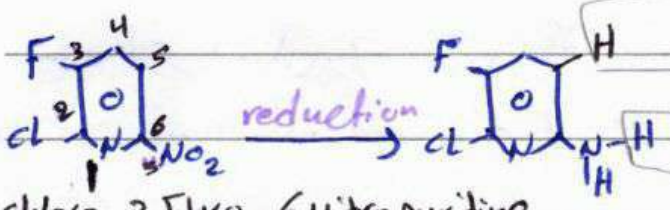


Date No.

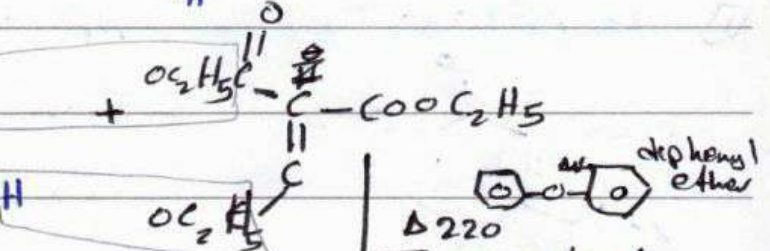
* Preparation of enoxacine :

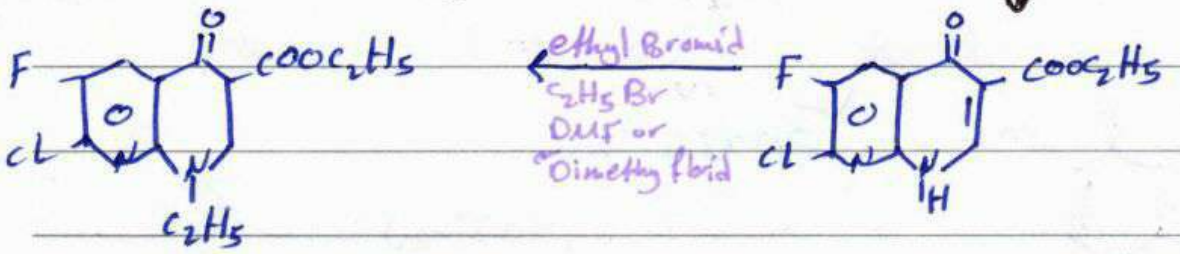


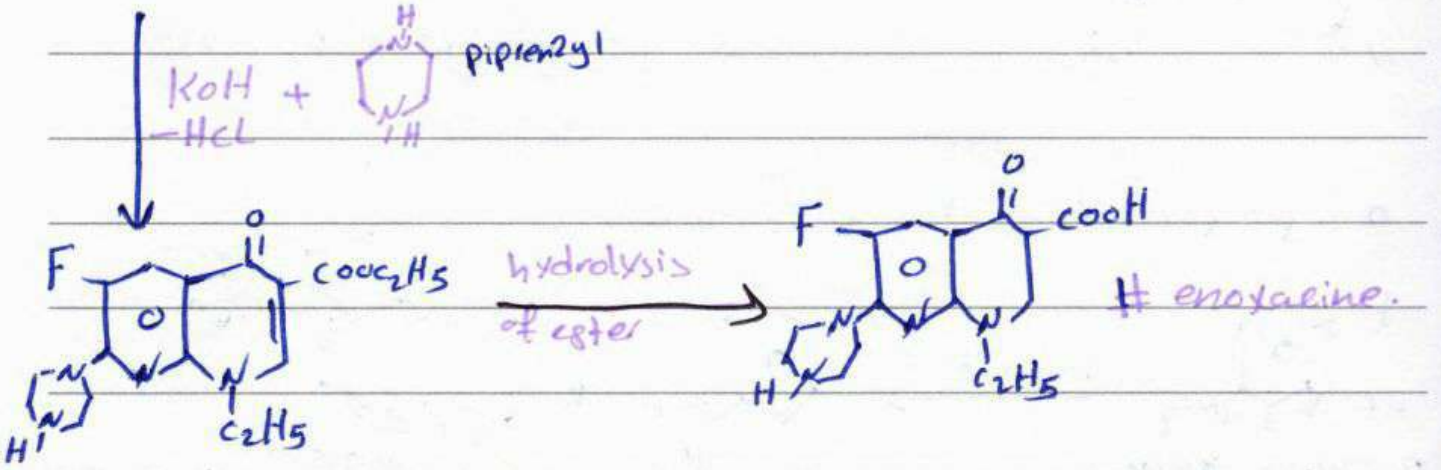
Start with



2-Chloro-3 Floro-6 Nitro pyridine

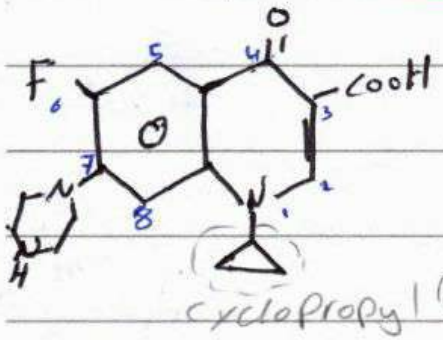






[3] CiproFloxacine :

- .ciproCare®
- Floxine®
- Ciprogis®
- cipro cine®



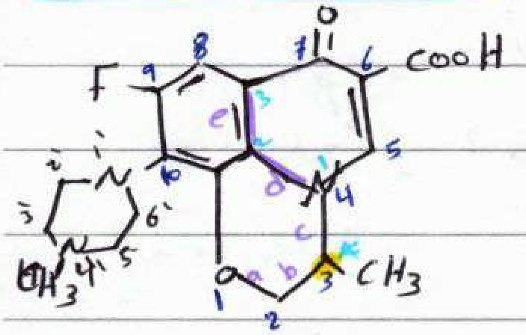
cyclopropyl ↑ potency ↓ enzyme copuso

1-Cyclopropyl-6-Floro-7-piperazinyl-4-oxo-1,4 dihydro Quinolons-3-C.A

غير مشتق من اي مركب

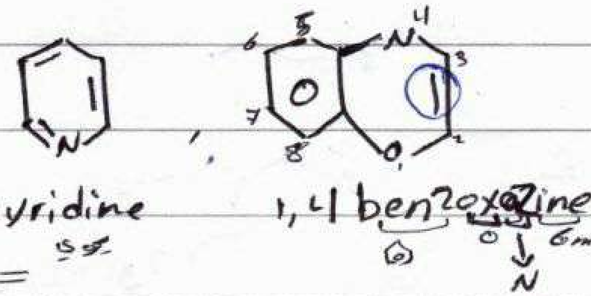
4- oFloxacine, Travide® Tarivid®, Oflocine®, wtracine®

or levofloxacine → 3rd



10 [N- Methyl piperazinyl] - 9- Floro - 3- Methyl - 7- oxo - 4, 7 dihydro - 2- 3- dihydro pyrido [1, 2, 3- d,e] 1,4 benzoxazine - 6. C.A

Note: * تم الاختيار بطريقة

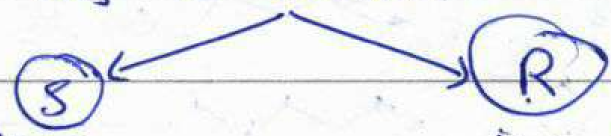


pyridine , 1,4 benzoxazine

3 =

ofloxacin contain a chiral carbon on position 3*

So it has 2 isomers.

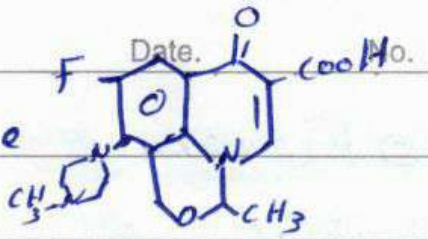


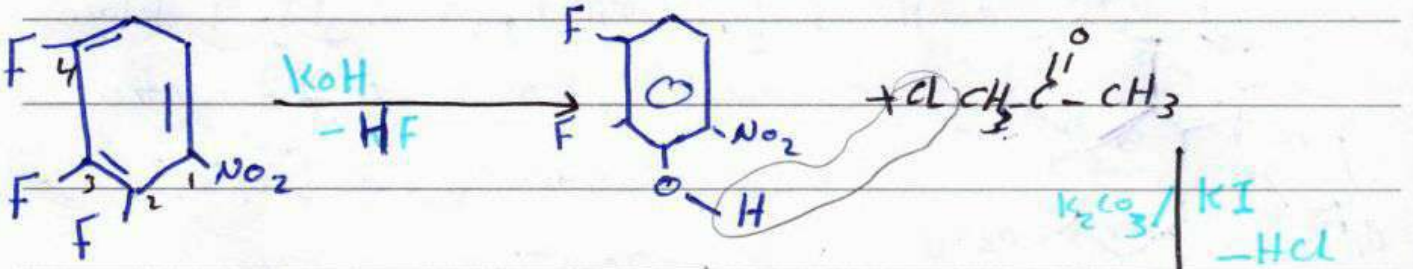
levofloxacine
3rd generation

isolation عن طريق

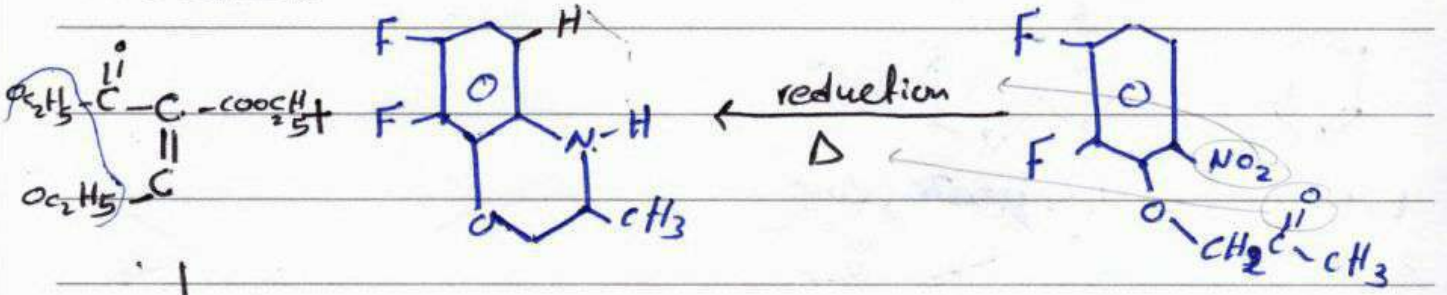
Date. No.

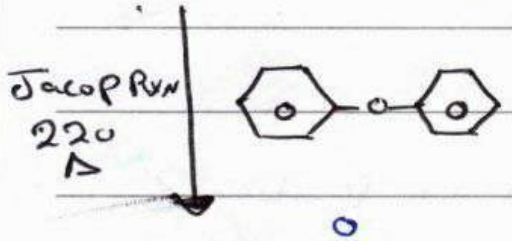
preparation of oflaxacine

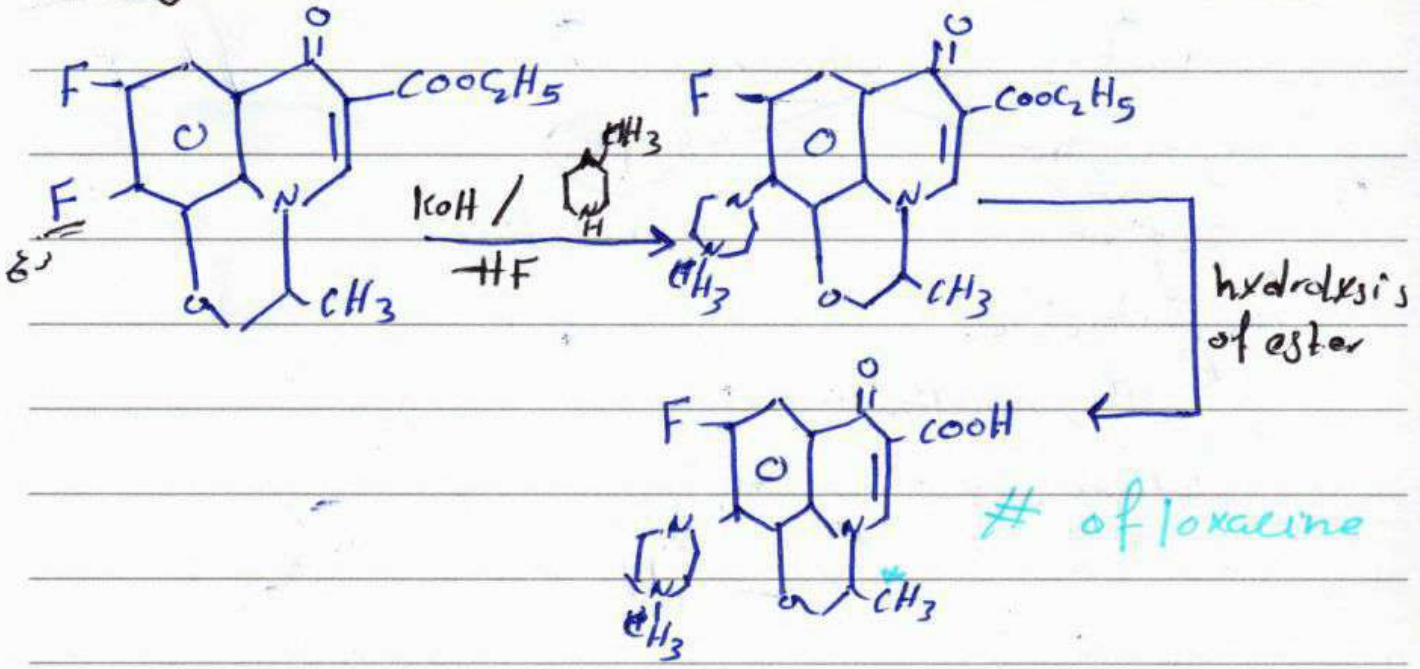




2, 3, 4 tri Floro. Nitro benzene





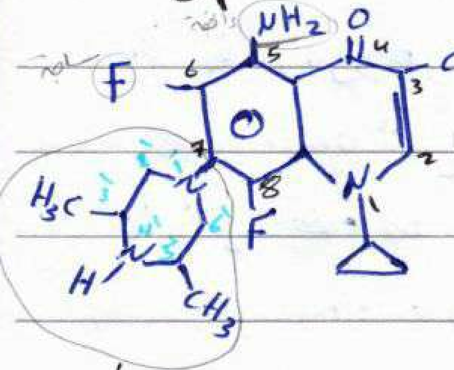


oflaxacine

3rd generation of Quinolons.

levofloxacine ✓

II sparofloxacine



6, 8 di Floro - 7 [3`, 5` dimethy piperazinyl) - 5 - amino - 1 - cyclo propyl - 4 - oxo - 1, 4 dihydro quinolons - 3 - C.A.

- Give long duration due to piperazinyl
- exist of methy make it more and more long duration [from 4 in day to one tablet] ↑DoA
- Position effect on potency and pharmacokintics

* F → make photosensitivity

كلهم فيهم F 2, 3, 4

ليش خلو sparofloxacin يقللوا F بروح مع بعض F.

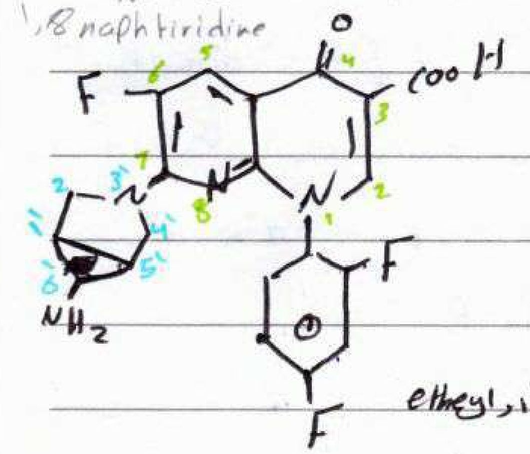
* NH_2 has H (resonance effect) → make less ~~Photosensivity~~. side effect

* in cyclopropyl compound also in (ciprofloxcine)
  → it will inhibit cyp 450 [cytochrom p 450] which is respersobile of Biotransform of warfaine (Anticoagulants)

So if they were given togather it will cause bleeding

4th generation: Broad Anearobic → due to group on position 1

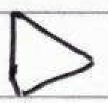
Trova floxacine



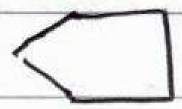
1 (o,p difloro phenyl) - 4 - oxo - 6 - Fluro - 7 - [6' amino - 3' aza bicyclo [3,1,0] hex-3'-yl] 1,4 dihydo 1,8 naphtiridine - 3 - CA

* في كل المركبات التي مرت معنا مكان [1] يحوي ◁ او ethyl لكن هنا Ar ، كذلك position [7] لم يعد يحوي N heterocyclic.

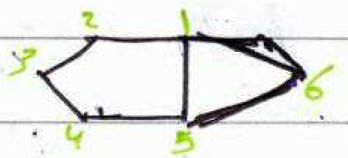
Notes:



cyclo propyl



cyclo pentan



Bicyclic compound not fused ring

No heter atom ← اذا وجد تسمى كمستبدل

كيفية تسميتها : ① من احدى نقطتي الالتقاء ، بنرقم

② ثم نتجه نحو الحلقة الكبرى حتى نصل الى نقطة الالتقاء الأخرى ثم نكمل نحو الصغرى

توضيح مسبقا bicyclo [3 , 1 , 0] hexane.

← ٣ نقاط بين نقاط الالتقاء الحلقة الكبرى

← نقطة واحدة بين نقاط الالتقاء للحلقة الصغرى

بين نقطتي الالتقاء لا يوجد اي التقاء

Quinolons

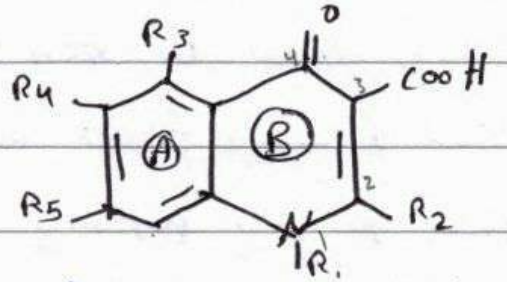
Date. No.

MOA:

DNA Chain $\xrightarrow[\text{or Grays enzyme}]{\text{DNA Topo isomerase II}}$ DNA helix

Quinolons inhibits (DNA Grays or DNA topisomerase II) so DNA will not be form and bacterial cell also will not form.

* SAR:



① if cycle B become Aromatic it will be non active

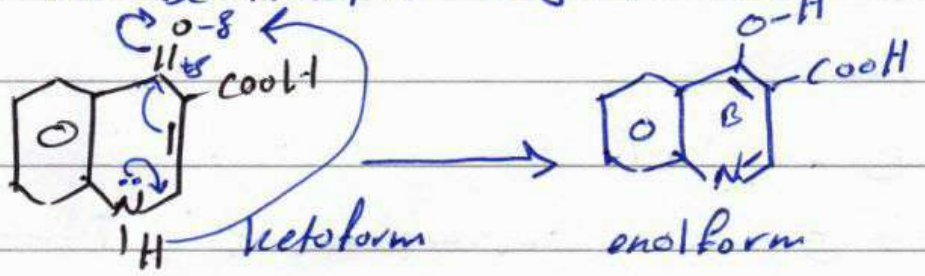
② 1,4 dihydro Quinolons or its Bioisostaism → cinnoline, 1,8 naphitiridi

③ keton on position ④ must be to give activity.

④ in position 1 it must has substition

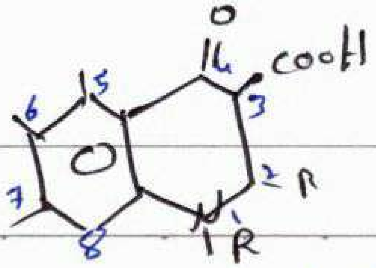
best ← cyclopropyl > ethyl > methyl

⑤ in position 1 in case if there is no substitution it will be inactive why!?



so B become Aromatic

and loss of 1,4 dihydro, loss C=O



Date. No.

[6] position 2 non substituted

[7] position 3 best is C.A or ester that will give in the end C.A. لوحتى لومو لا لا لازم C.A

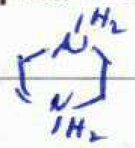
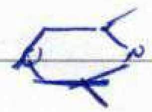
[8] keton must be to give active.

Because the inhibition of enzyme is done by C=O in 3, 4

[9] position 5 must be non substituted # sparo: has NH_2

[10] position 6 → F or with drawal group

[11] position 7 → potency
→ Pharmacokintics

either  or  or 

[12] position 8 either N, CH.

Note: [Biotransformation
→ All has COOH will mak O-glu.

Side effects:-

[1] crystaluuria-

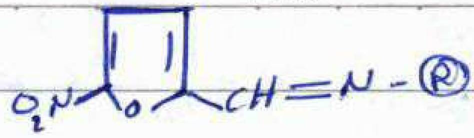
[2] Photo sensation-

[3] CNS toxicity → GABA

[4] bleeding [if given with compound has △] ↑ warfrine (ccpro, sapro)

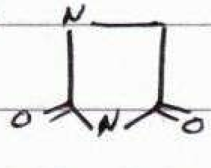
Those Drugs not given with food contain [Milk, Al^{+3}, Mg^{+2}, Ca^{+2}] insoluble متصيبس

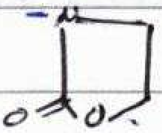
[3] Nitrofuran



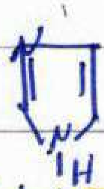
Prodrug

If R is $NH\overset{O}{\overset{\|}{C}}-NH_2$ → NitroFurazone

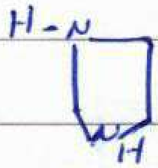
→ is  → Nitrofurantion

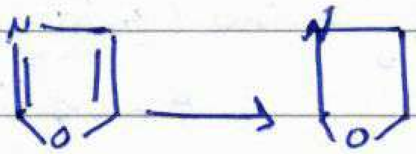
→  → Nitro Furazolidone

* $NH_2\overset{O}{\overset{\|}{C}}NH_2$ → urea , $H_2N-NH\overset{O}{\overset{\|}{C}}NH_2$ → semicarbazone


Imidazole


Imidazoline
نزعنا -

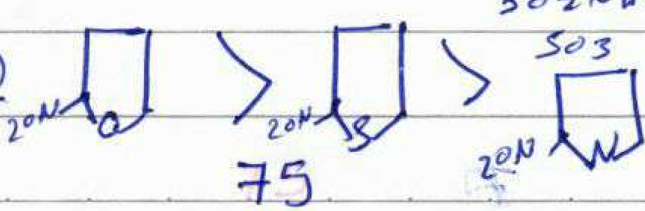

Imidazolidine
نزعنا =


oxazole → oxazolidine

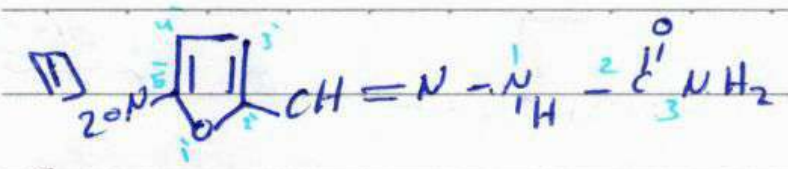
SAR:

هذه المركبات بالأصل prodrug لا تتحول ل active ai ثم
→ NO_2 also convert to hydroxy amine $\underset{|}{N}-OH$ (H)
and it's active metabolite. or form of nitrofuran

* if NO_2 replaced with CN, COOH, SO_2NH_2 | decrease in activity ↓

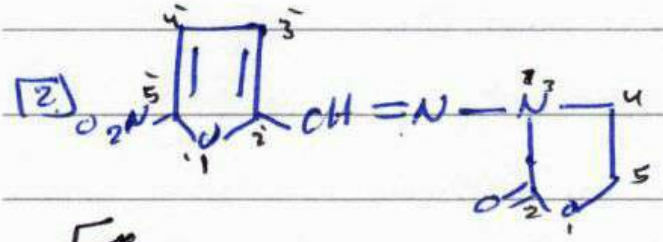
effect of 

Date. No.

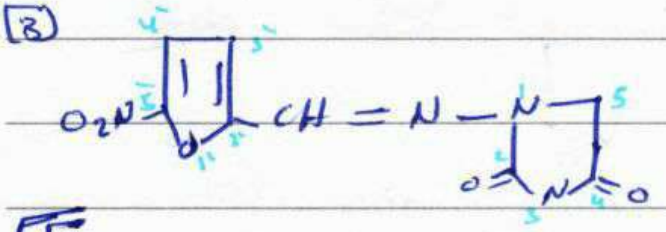
1)  Nitro Furazone

[[(5` Nitro Furan 2`yl) methylidenyl] amino] urea

Semi carbazone

2)  Nitro Furazolidone

3 [[(5` Nitro Furan 2`yl)] methylidenyl] amino] - 1, 3 oxazolidine - 2 one.

3)  Nitrofurfuration.

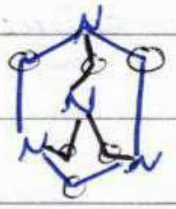
[[(5`nitro Furan 2`-yl) methylilidenyl] amino] imidazolidine - 2,4 dione

or 2,4 dioxoimidazolidine.

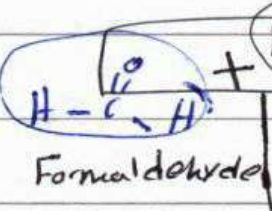
Contain Amine
from protine

Date. No.

[4] Methanamine → prodrug.



Acidic media
N convert to →

NH_3 + 

Formaldehyde

Protein

hexa methylene tetra amine

It's inactive that need acidic media for activation it.

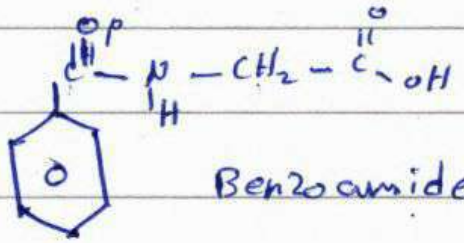
Binding to Protine

give antibacterial effect ← schiff base

$H-C(H)=N-P-$ (P: Protein)

Methamine hippurate

* Methamine give with Hipparic acid "acidic media"
antibacterial effect, يعطي تأثير schiff base يكون هذا



Benzoamide acetic acid or Happuric acid.

هذا هو الشكل المنشط.

AntiBiotics : "Natural AntiBacterial" or semisynthetic

lec. 13

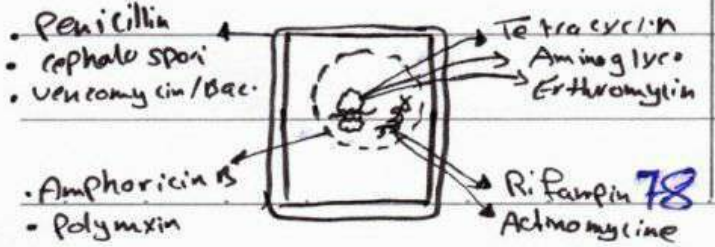
Date. No.

- Produce by Microorganism which has a capacity of inhibiting and even destroying of other microorganisms. in low conc.

Classified depending on

MoA

1. Affecting on cell wall :
   - Cephalosporines
   - Penicillines
   - Bacitiracines + vancomycine
2. Affecting on cytoplasmic membrane :
   - Amphotericin B
   - polymxine
3. protein synthesis :-
   - Aminoglycosides
   - Tetracycline
   - Erthromycines
4. ON DNA & RNA
   - Rifampine
   - Actinomycine

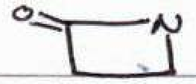


Chemical composition

1. β-Lactam → Penicillins, cephalosporins
2. Tetracyclines
3. chloramphenicol
4. Aminoglycosides
5. others → Macrolide, Polypeptide

Date. No.

B_lactam



[amide ring]

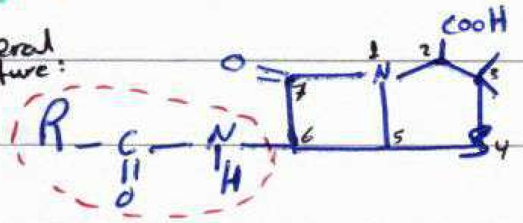
A) penicillins B) cephalosporines

- Both contain β-Lactam ring, but they differ in chemical composition

A) Penicillines

: All are same but they differ in position 6

General structure:



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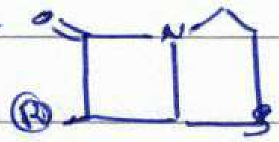
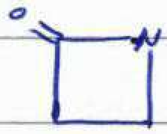
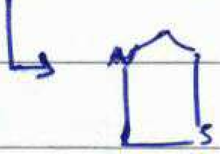




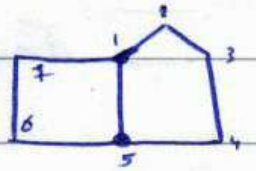
Penam Thiazide β-lactam



Thiazolidine
S N ين حلقة خماسية غير مشبعة
دم = تدل

* Nomenclature :-

Date. No.



bicyclo [3, 2, 0] heptan.

① كم حلقة ؟ 2 ← Bicyclo

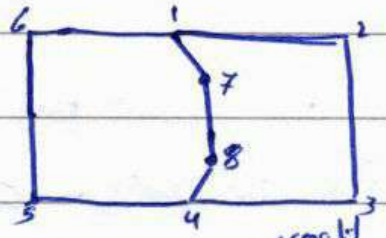
② نرقم من إحدى النقاط التركة والاتجاه هو الحلقة الأكبر . نبدأ بالأصغر

③ ← عدد النقاط في الحلقة الأكبر عدا النقاط التركة

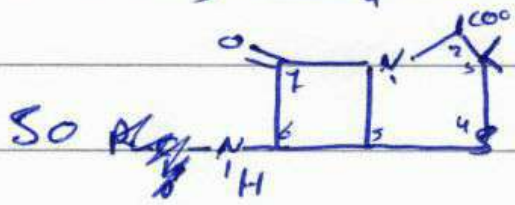
← عدد النقاط في الحلقة الأصغر عدا النقاط التركة

← عدد النقاط بين النقاط المشتركة

ex

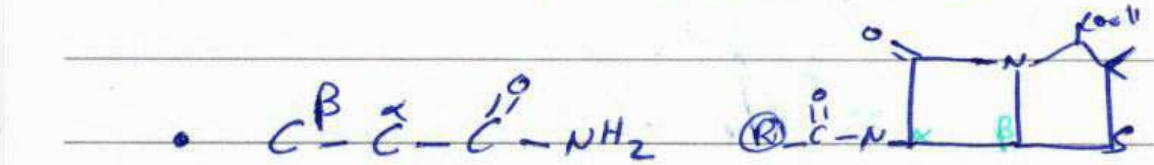


bicyclo [2, 2, 2] octane



So

ex 7 oxo - 1 A2a - 4 thia - 3,3 dimethyl - 6 amino bicyclo [3, 2, 0] heptan - 2 c.A.



• Bosition that Lactam connect to Thiazolidine. on β So its called β-Lactam ring.

Date. No.

• MoA for penicillines and cephalosporin which affect on cell wall of Bacteria.

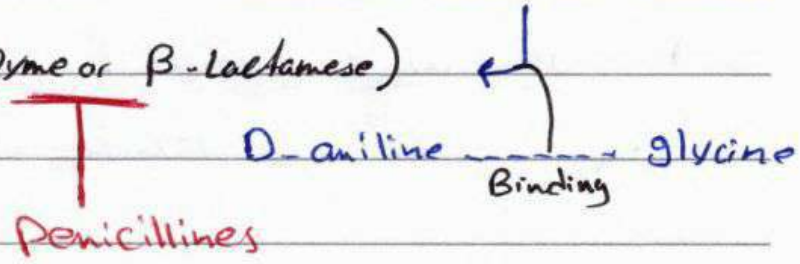
- The cell wall of bacteria consist of Dipeptidoglycan that give :

① Rigidity ② strength ③ maintain osmotic pressure

* Dipeptidoglycan contain D-amino acid such as :

D-aniline , D-glycine.

These aminoacids are connected together to give cell wall by enzyme : Trans peptidase (By Trans peptidase enzyme or β-Lactamese)



So penicillines inhibits Trans peptidase or β-Lactamase

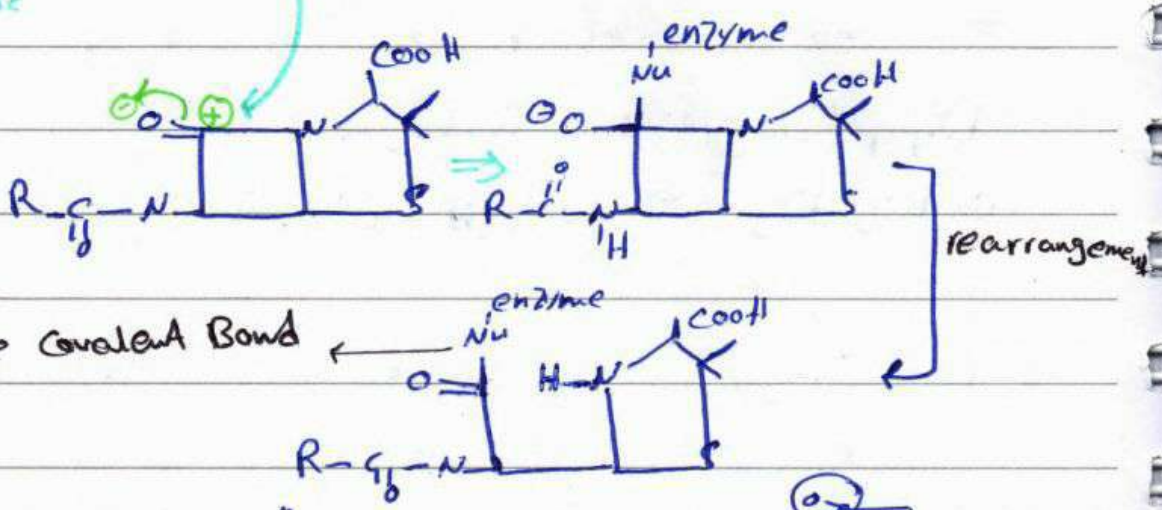
So No formation of cell wall , result in entering of water to the Bacteria cell → swelling → rapture

→ By Binding to it with irreversible covalent Bond bw penicilline and enzyme

Date. No.

The process of binding bw enzyme + penicillines.

β lactames Enzyme — Nu [nucleophilic substance]
or Transpeptidase



why enzyme binds to $\overset{\oplus}{C}$ on β-lactam ?  positon 7

not $\overset{\oplus}{C}$ in $R\overset{\oplus}{C}-N$

- Due to angle strain [توتر الزاوية] 

$sp^3 \rightarrow 109°$, $109 - 90 = 19$ For Ring $\overset{\oplus}{C}$

- But in α $\overset{\oplus}{C}$ is aliphatic so its stable.

more stable وكلما قل الفرق كانت

↑ angle strain ↑ unstable ↑ more reactive

Date. No.

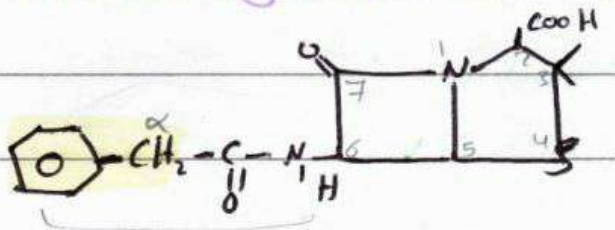
Chemical classification of penicillins :

1) Benzyl penicillines: penicilline G
2) Phenoxy penicillines: penicilline V
3) α- amino penicillines : Amoxicilline , Ampicilline
4) α- carboxy penicillines: → carbenicilline
(Anti-pseudomonas penicillins) → Ticarcilline
→ Carindacilline
5) β- lactamase resistance penicillines (Anti- staph. penicillins)
methicilline , cloxacilline , dicloxacilline , Flucloxacilline.
6) acylcurido penicillines (extended spectrum penicillin)
↳ pipericilline , Azlocilline , Mezlocilline
7) others : cyclacilline

or acetyl amino

Date: تاريخ No.

[1] Benzyl penicillines : penicilline G , Bepan®



6 [α-(phenyl) acetamido]

7- oxo - 1-aza - 4- thia

3,3 dimethyl bicyclo

[3, 2, 0] heptan - 2- C.A

Note carboxlic acid Not included in ring ⇒ carboxlic acid

heptan-2-oic acid تقول لو كانت في الحلقة

ex.. $CH_3CH_2CH_2\overset{O}{\overset{\|}{C}}-OH$ ⇒ butyl oic acid.

⇒ benzyl carboxlic acid.

Ch.Ch of penicillineG :

[1] short duration : each 4h give P.G

[2] Acid unstable → or sensitive ⇒ so not given orally X IV ✓ due to highly reactive of β-lactam ring

[3] Given by I.v injection

[4] Low water solubility.

[5] β-lactames sensitive

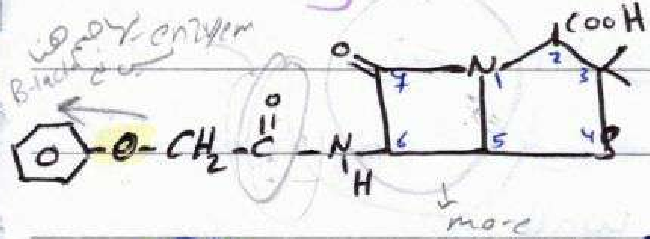
* They solve the short duration by given

- penicillines G + procaine each 1 month
- penicillines G + Benzethine each 3 weeks

* and add COO^-Na^+ to solve water solubility

1st orally penicilline ←

2- Phenoxy penicillines : Penicilline V , Rafapen®



6 [α (phenoxy) acetamido] 7-oxo - 1-aza - 3,3 dimethyl - 4-thia - bicyclo [3,2,0] heptan - 2 - Carboxlic acid.

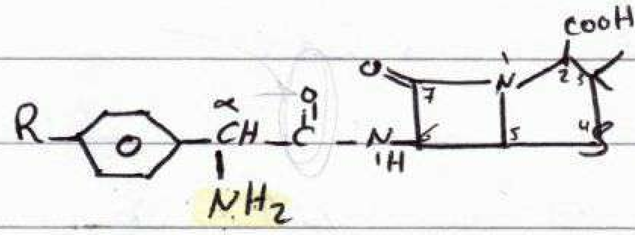
more stable

orally

↳ Acid stable.
↳ resistance to break down in gastric acid

وجود O قلل Nucleophilicity تبع C=O في ring وزاد solubity of lactam ring.

3- α amino penicillines : acid stable, orally



R: H → Ampicilline
Bradacilline®
Ampipharm®
Ampen® , Penibrim®

Ampicilline

6 [α (amino) α phenyl) acetamido] 7-oxo - 1-aza - 4-thia - 3,3 dimethyl bicyclo [3,2,0] heptan - 2 C.A

OH → Amoxicilline
Amoxicare® , Amoxim®
Amoxipham® , Amoxitid®
Moxypen® , Hiconcil®

Amoxicilline

6 [α (hydroxy phenyl) acet amido] 7-oxo - 1-aza - 4-thia 3,3 dimethyl - bicyclo [3,2,0] heptan - 2 - C.A
(α amino - α (p-hydroxy phenyl))

نتذكر انه هذه مجموعة الدول التي تحتاج Bodygard كبير ؛ لأنه م side chain ما بتحميها من Acid ولا من B-lactamase .

Date. No.

Ampicilline and Amoxicilline

- Acid ~~sensitive~~ resistance → They take only orally
- β-lactamase: ~~sensitive~~ ~~resistance~~ sensitive
- Poor absorption in gut wall, cell

Why they became acid ~~sensitive~~ resistance ??

- exist of NH_2 [hydrophilic Ch.ch] affect on Nucleophilicity of carbonyl $\overset{\delta+}{C}$ [↓ Nucleophilicity of $\overset{\delta+}{C}$] so make β-lactam ring stable → Acid ~~sensitive~~ resistant

- also NH_2 has effect on G⊖ more than G⊕ by ↑ Penetration through Pores.

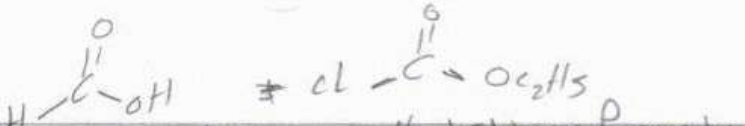
Haemophilus influenza, E.coli, Proteus

H E L P S to clear entrococca G⊕

Listeria G⊕, Salamonilla G⊖

- Ampicilline — Amoxicillin (Good absorption, more polar)
  - Phenyl (Poor absorption)
  - -OH p-hydroxy-Phenyl

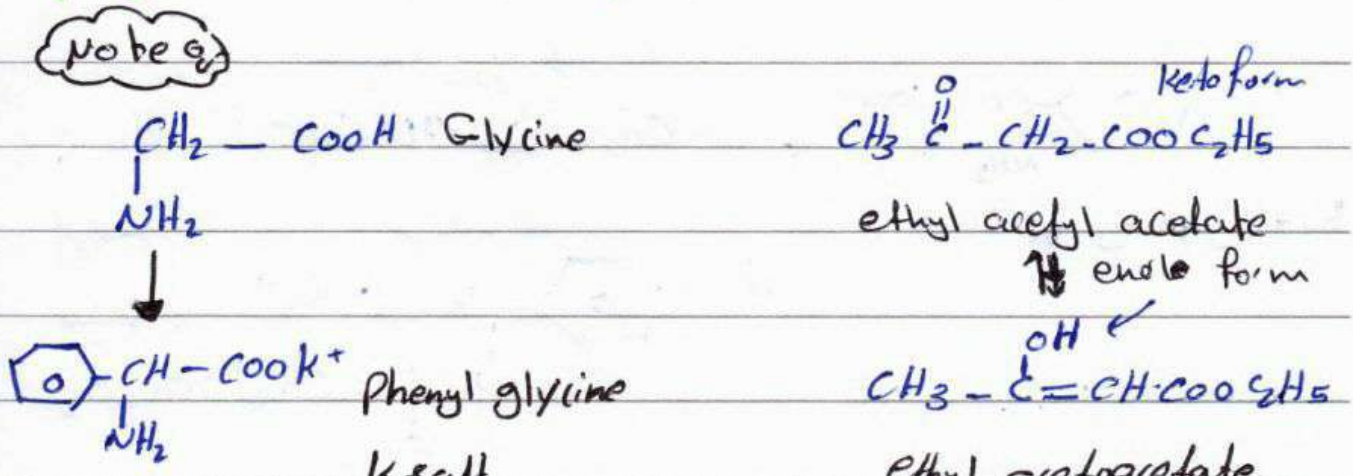
Absorption of Amoxicilline is 80% better than Ampicilline due to presence of OH

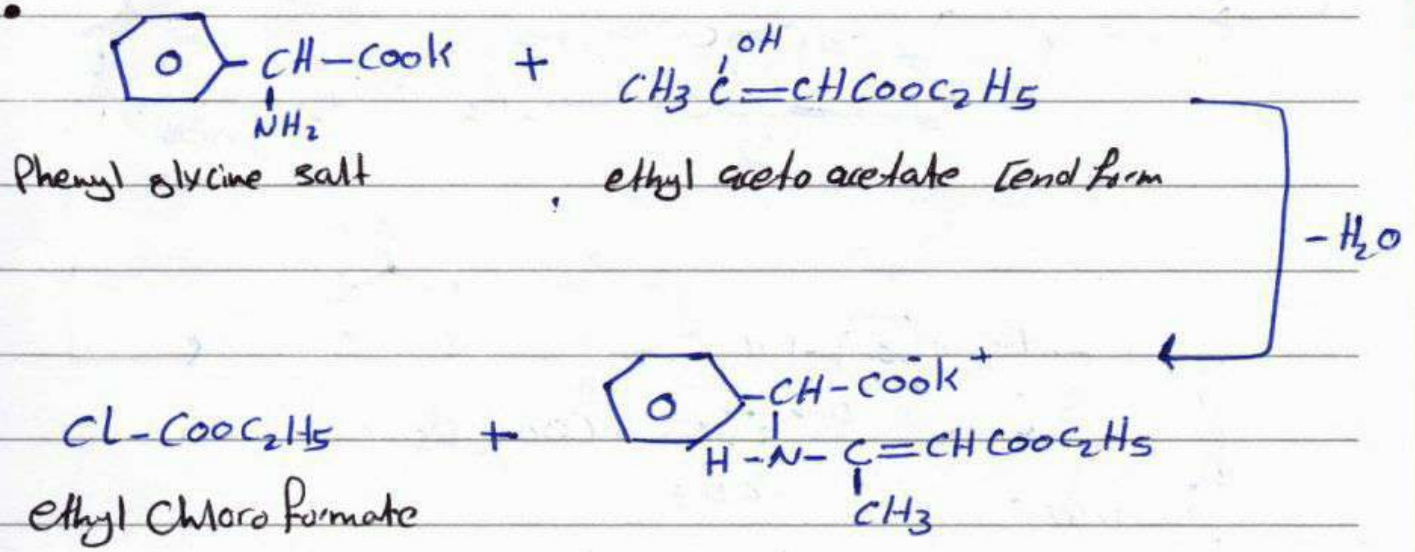


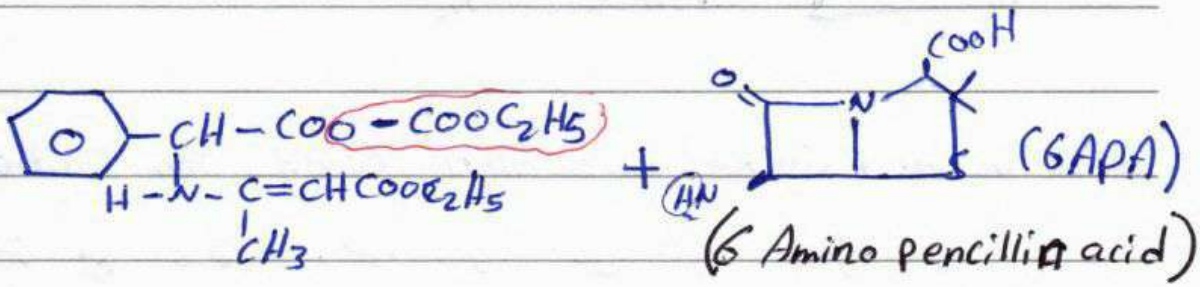
Date. No.

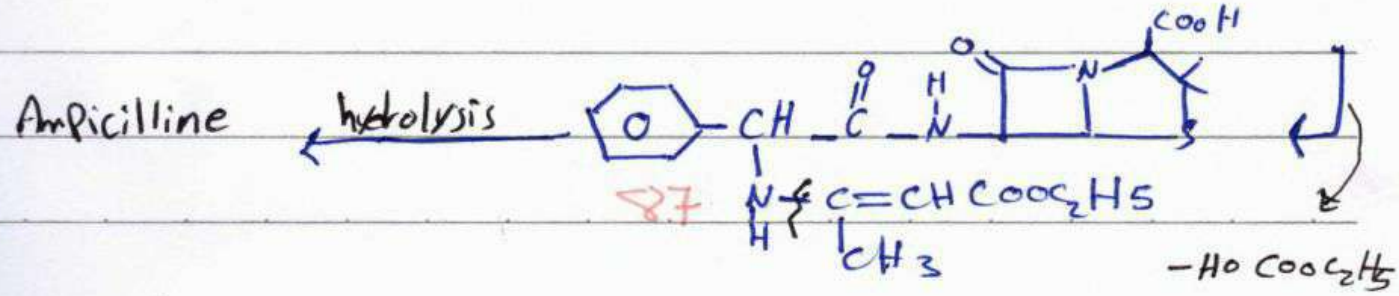
preparation of Ampicillin :

No be Q



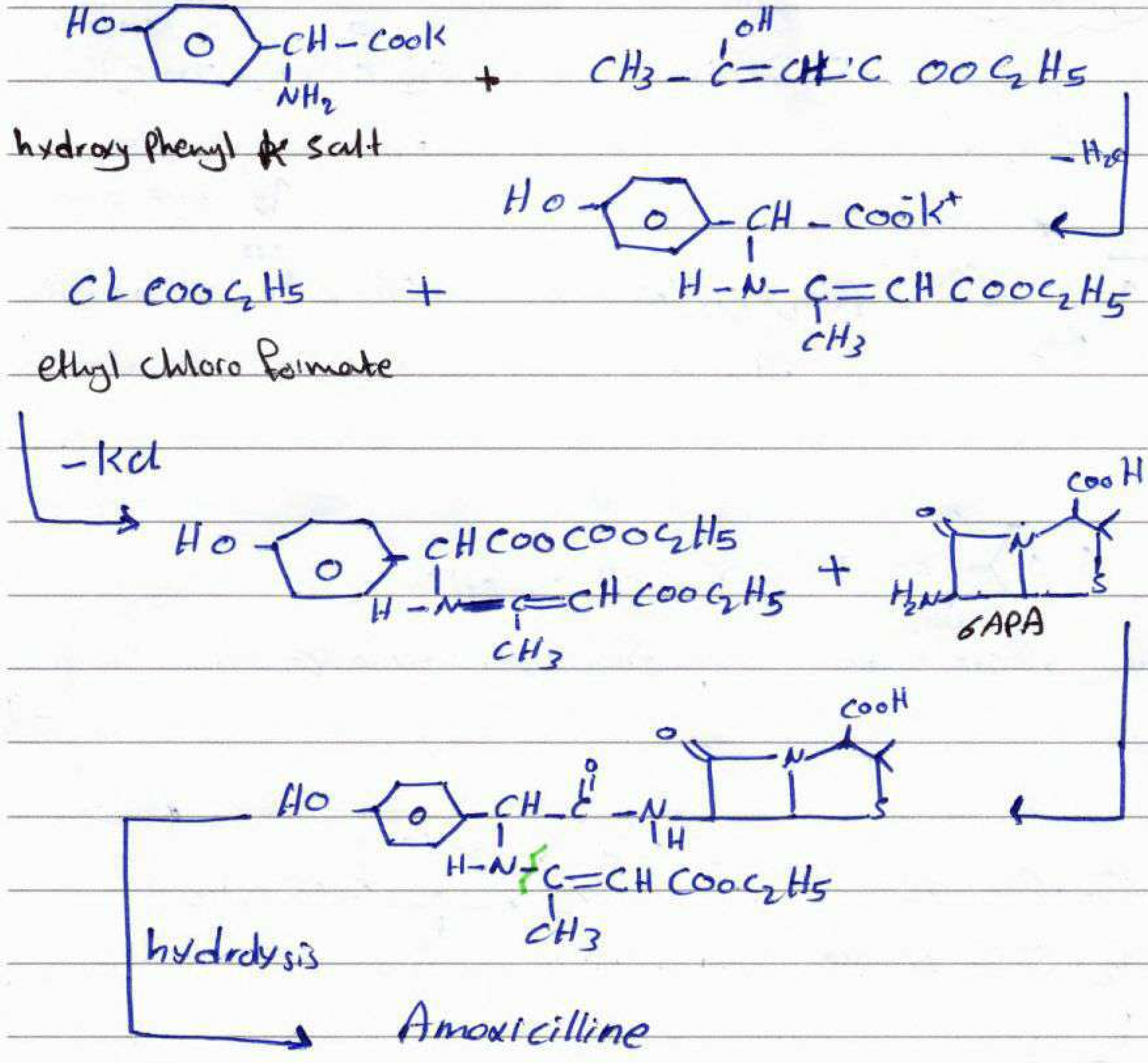






Date. No.

Preparation of Amoxicilline :-



* Both Ampicilline , Amoxicilline Called semiSynthetic

لأنه جزء يتم تحضيره ، جزء آخر نحصل عليه جاهز

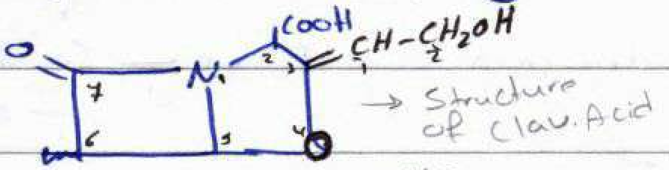
Date. No.

- because Ampicilline and Amoxicilline are bothe β-lactamase sensitive

so we make a combination using other Drug to protect β-lactam ring from degradation by β lactamase or Transpeptidase enzyme.

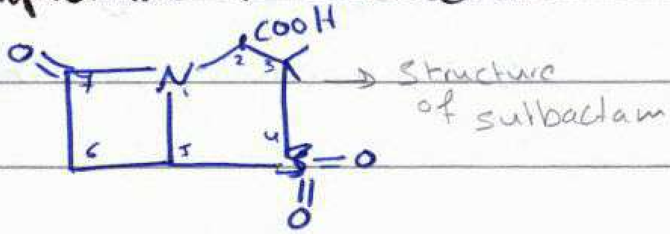
[1] Amoxicilline + Clavulanic acid (C.A) — Clamoxine®, Ogmine®, curan®, Agumentine®, Amoxiclav®, Betamox®

- C.A → has No Antibacterial effect
- it ↓ β-lactamase sensivity.



1-aza-7-oxo-4-oxa-3(2-hydroxy ethylidinyl) bicyclo [3,2,0] heptan-2-C.A.

[2] Ampicilline + sulbactam — Docuid®, Sulbampicilline®

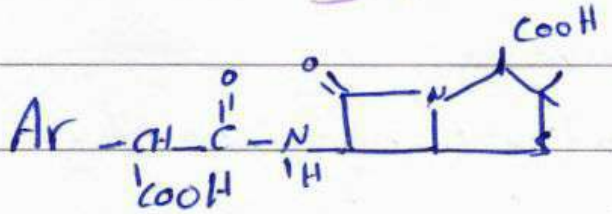


1-Aza-7-oxo-4-thia-3,3 dimethyl bicyclo[3,2,0] heptan-2-carboxlic acid-4,4 dioxide not sulfone

لو كانت free بس دون علاقة

Date. No.

4- α- carboxy penicilline :- (Anti-psedomonus penicilline)



Ar: → Carbenicillin

Ar: Ticarcilline

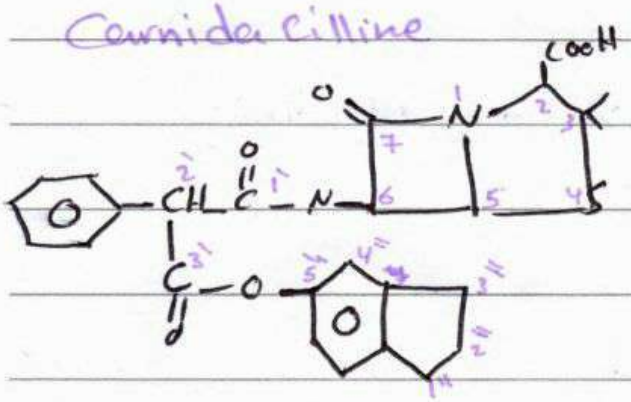
↳ called Thiophen

Thienyl تسمى

Note :-

- COOH has also hydrophilic ch.ch , ↑ effect on G⊖ more than G⊕
- Acid sensitive , in gastric Acid loose of COOH → Co_2 وتتجمع تحت CH

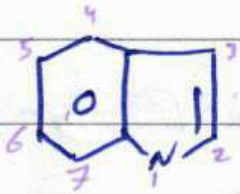
Carnidacilline



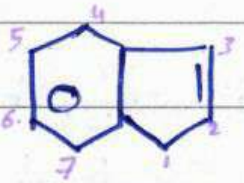
6[[2`(phenyl) [3`(Indan-5``-yl) oxy⁻] 1`,3`dioxo propyl] amino] 1-aza-4-thia-7-oxo-3,3 dimethyl-bicyclo [3,2,0] heptan-2-C.A.

ether

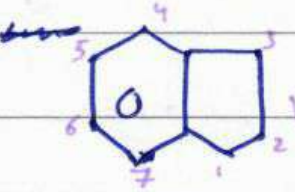
Note :-



Indol



Inden



Indan

نزحم في موقع N

ضد لو تم ازالتها

↙

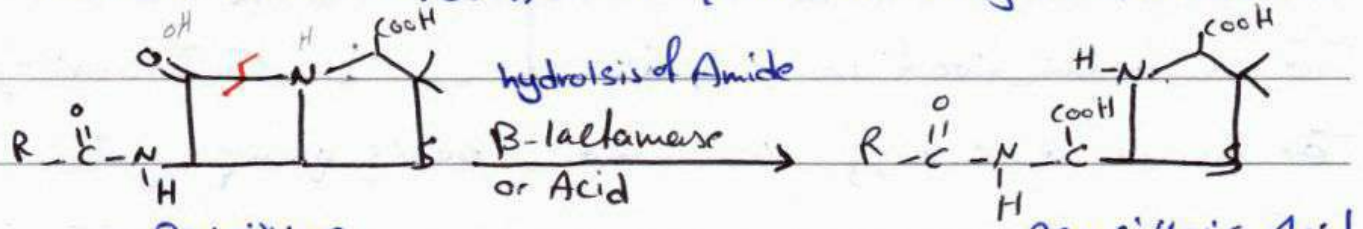
or 2,3 dihydro Inden

Date. No.

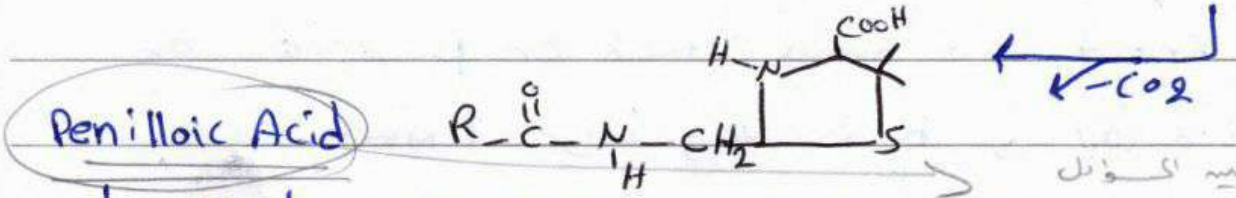
5- β- lactamase resistant penicilline

(Anti - staphilococcus penicillin)

- β- Lactamase is enzyme secreted by Bacteria, which make hydrolysis of β- lactam ring in Penicillin.



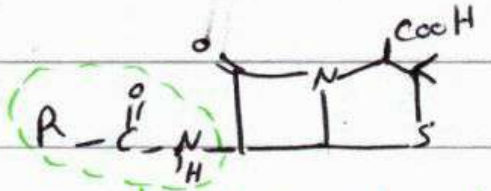
Penicilline → Pencilloic Acid



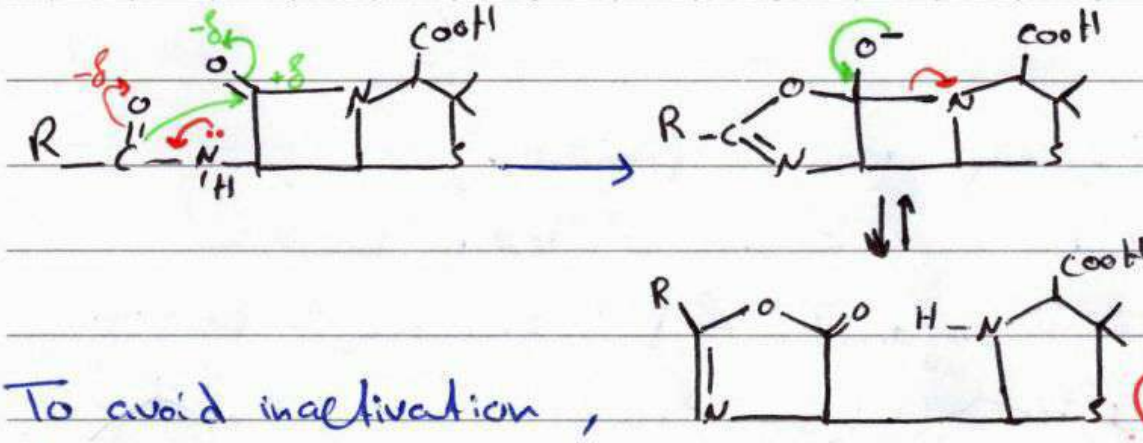
↳ Binds with protien ⟹ cause allargy

* pentilloic acid responsible of penicilline allargy for some people

* β- Lactam must be stable, in case it become unstable the penicillines become inactive



↳ Acyl side chain has effect on stability of β- Lactam



To avoid inactivation, (Inactive)

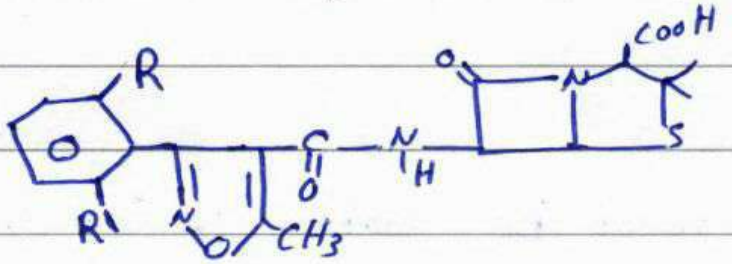
and/or To avoid allergy, we add a bulky group

To protect β-lactam ring., because it will make

Steric sheid and avoid attack on β lactam on position (6) → R is very large ↑ MWt.

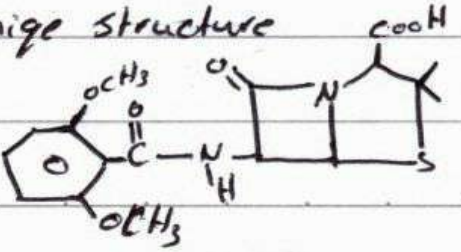
↳ and with drawal group

- General structure of β-lactamase resistant penicilline :



R	R'	
H	H	oxacilline
Cl	H	Cloxacilline . Cloxan®, loxavit®, orbind®
Cl	Cl	dicloxacilline
Cl	F	Flucloxacilline

Methicilline has unige structure

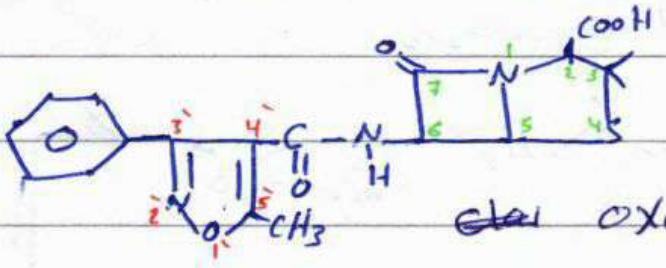


chain ... ...

Date. No.

Note :-

- Cl ⟶ ↑ absorption
- F ⟶ ↓ plasma protein Binding , ↑ leve of free drug
- cloxacilline + Ampicilline ⟶ Mega cure ®
  Megna cilline ®
- cloxa cilline + Amoxicilline ⟶ cloxabalforle ® بلفورن



~~Cloxa~~ oxacilline

- 6 [[3`- Phenyl - 5` Methy isoxazole - 4`- yl] amido (carbonyl)] - 7 - oxo 1 - Aza - 4 - thia - 3,3 dimethyl - bicyclo [3,2,0] heptan - 2 - C.A.

- All are prepared in the same way , just differ in start unit [add on Benzal aldehyde the substituted wanted]

Cloxacilline ⟶ 6`` chloro benzaldehyde ③ ... ...

dicloxacilline ⟶ 2``, 6`` dichloro benzaldehyde

Flucloxacilline ⟶ 2`` chloro - 6` Fluro benzaldehyde ؟؟

Cl - F ...

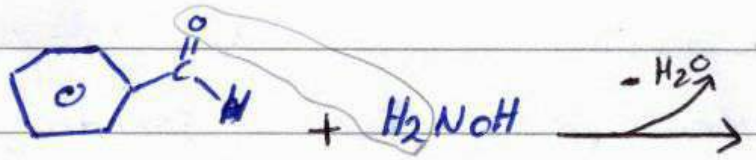
93

ethyl acetyl aceto acetate ← Isomethoxazole في Sulfa drug في استخدمت

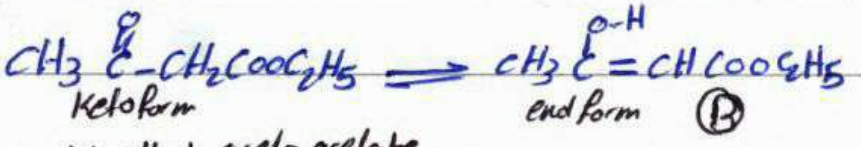
Lec. 15

Date. No.

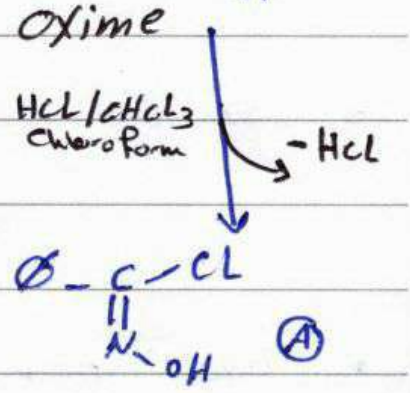
Preparation of β-Lactamase :-

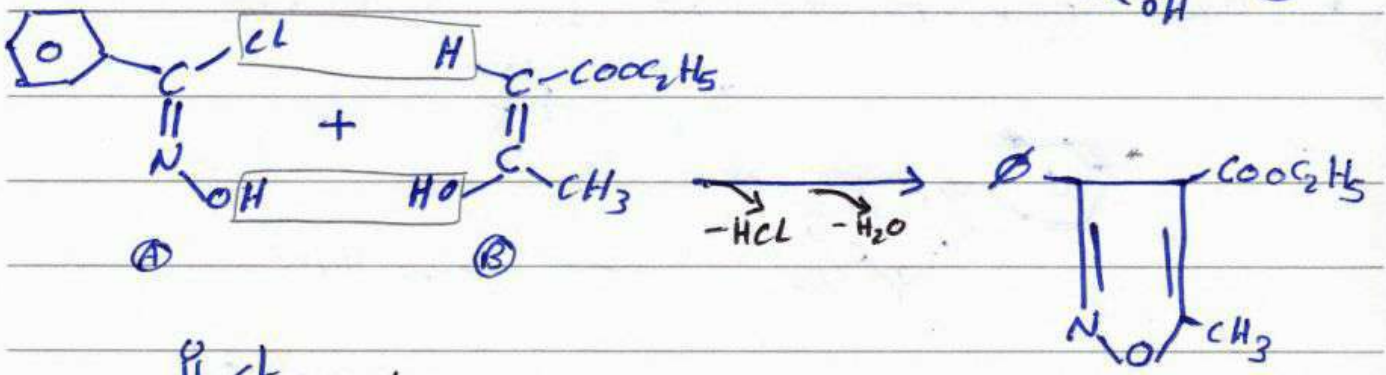


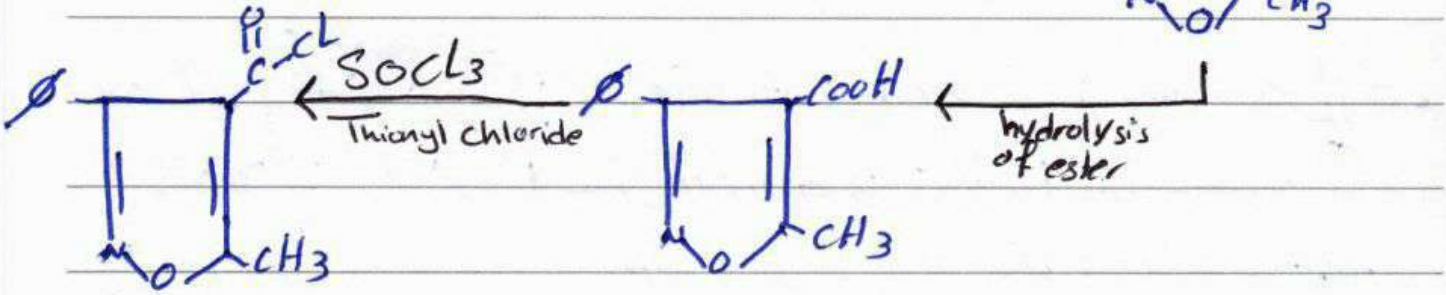
Benzaldehyde Hydroxy amine Oxime

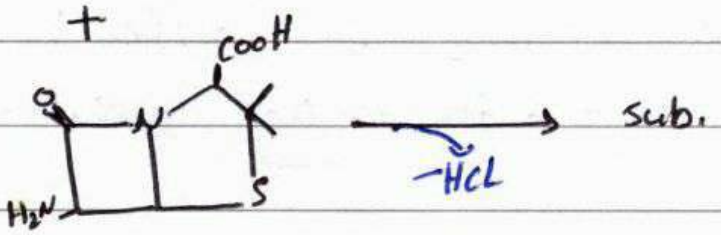


acetyl ethyl aceto acetate







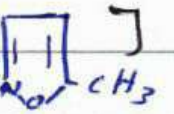


6APA

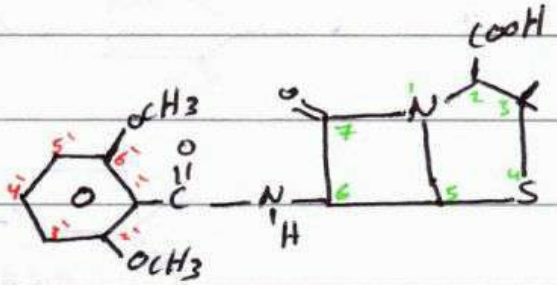
(6 Amino Pencilic Acid)

Date. No.

Methicilline. (not clinicaly used) هذا لم يعد يستخدم

- belong to β-lactamese resistance penicilline.
with unique structure. [no present of ]

- not clinically used ⟹ cause intersical nephrosis.



6 [(2`,6` dimethoxy benzoamide)] - 1- A2a - 7- oxo-

4- thia - 3,3 dimethyl bicyclo [3, 2, 0] heptan -2-c.A

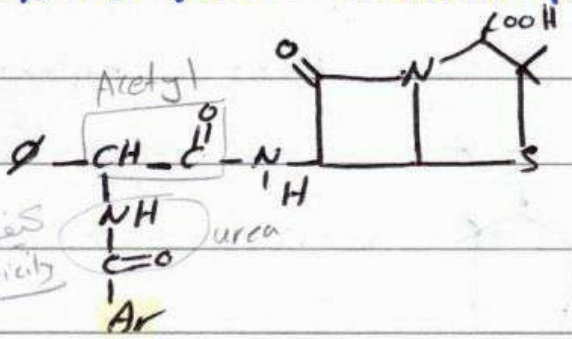
- OCH_3 → Acid unstable so not given orally X
but Iv. injection ✓
- short duration
- Low potency.

Date. No.

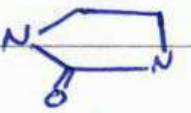
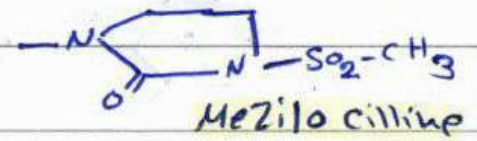
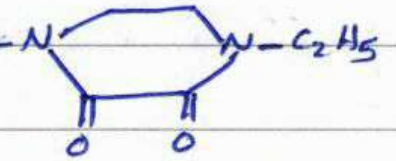
6- Acyl uredio penicilline [Extended spectrum penicilline]

↳ Acetyl ↳ urea

- Modifeded from α-amino penicillines.



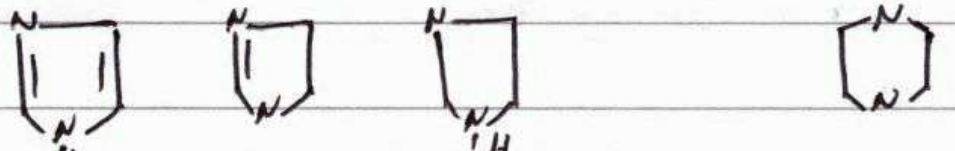
Ar:

-  Azilocilline
-  Mezilocilline
-  Piperacilline ↳ most use

- Acid unstable

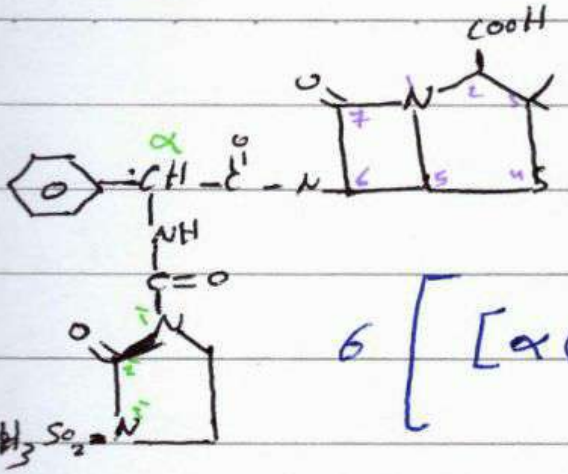
↳ so given by Iv injec.

remeber :



$\alpha \rightarrow$ in Chain not in cyclic

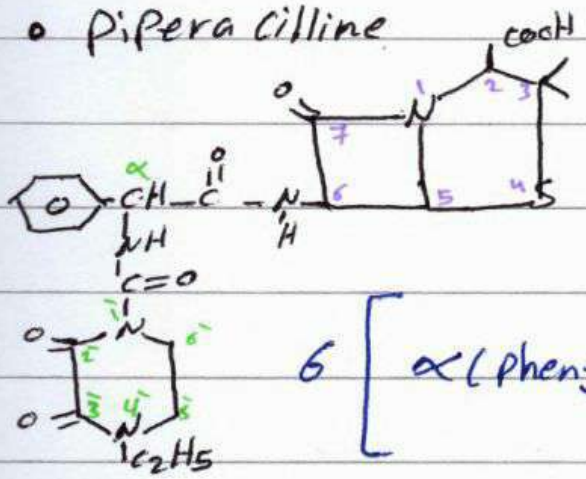
Date. No.



Mezilocilline

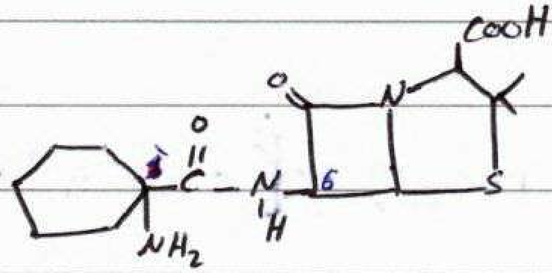
6 [[α (Phenyl) α [3`- Methyl sulfonyl - 2`- oxo - [imidazolidine) carbonyl amido] acetamido - 1-Aza - 4- thia - 7- oxo - 3,3 dimethyl - bicyclo [3,2,0] heptan - 2 C.A.

- Piperacilline



6 [α (phenyl) α [(4`-ethyl) 2`,3` dioxo piperazinyl carbonyl amido] acetamido] - 7-oxo - 4- thia 3,3 dimethyl bicyclo [3,2,0] heptan - 2- C.A.

7. others :- Cycla cilline



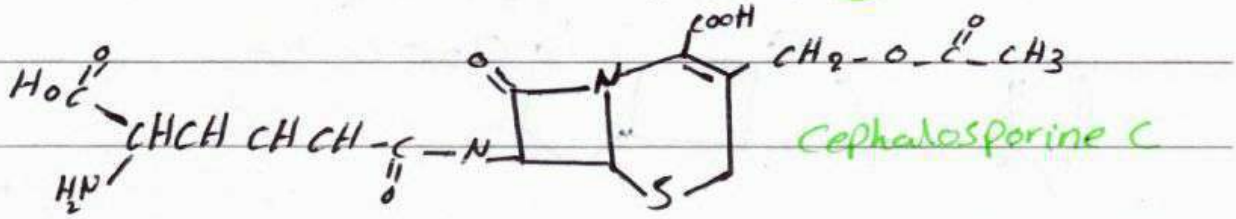
6 [1 amino [cyclohexanyl carbonyl amino] - 7 oxo - 4 - thia 3,3' dimethyl bicyclo [3,2,0] heptan - 2. C.A .

كل المركبات الاختلاف يكون مع position [6] بعد C=O

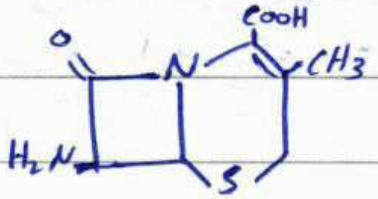
Date. No.

B) Cephalosporine

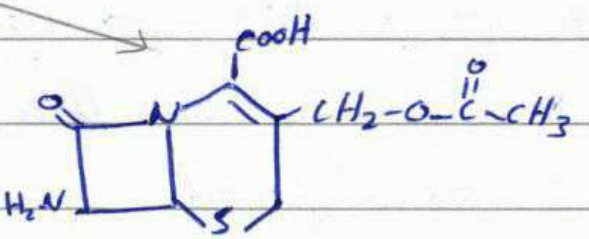
excreted From Cephalosporium acremonium Mold which yield cephalosporine P, N, C is used



Cephalosporine C



7-Amino desacetyl cephalosporinic Acid (7 ADCA).



7-Amino cephalosporonic acid [7ACA]

Note: • Both has B-lactam ring

• Bothe B-lactams, cephalosporines work on Cell wall.

• They differ in:

• β lactam has 5 ring member  (penam)

• cephalosporine has 6 ring member  3-cephem or Δ^3 cephem

• ring in cephalosporin contain = = تشبه كوتع

but penicillins not.

• in position 3 → dimethyl in penicilline but in cepalosporin an ester form

• acyl in penicillin → 6

in cep. → 7

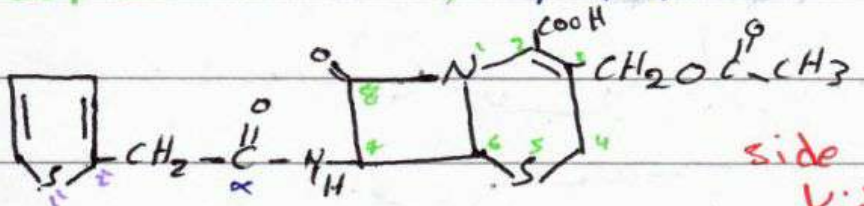
1st Generation of Cephalosporins :-

Date. No.

- Cephalosporines devided depend on there appeew. (classified)

To 1st, 2ed, 3rd, 4th Generations.

① Cephalothine , Kefline®

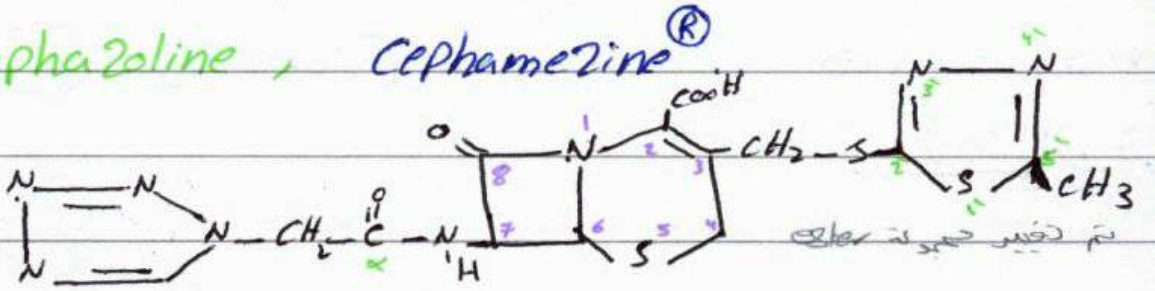


Thiophene

side effect:
Kidney toxicity.

7 [α(2`-thienyl) acetamido]-3-[acetyl oxy methyl]
1-aza-8-oxo-5-thia bicyclo [4,2,0] oct-2-en-
2-carboxylic acid.

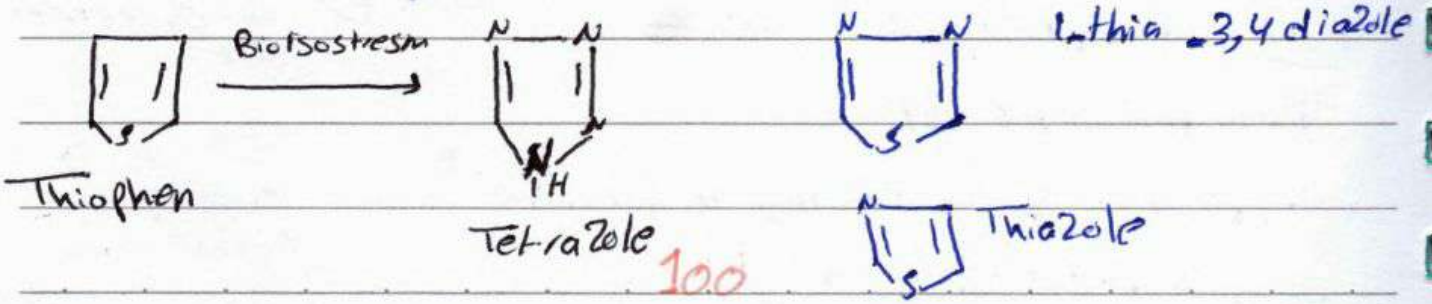
② Cephazoline , Cephamezine®



تم تغيير جزيئة علاج

7 [α(tetrazoyl) acetamido]-3-[[5`-methyl-1`thia-3`,4`
diazo-2`-yl]* thio methyl]-8-oxo-4-thia-1-Aza
bicyclo [4,2,0] oct-2-en-2 C.A.

Note



100

Thio غلط Thia انكليزية دائما الكلمة

Thiophene.

Date. No.

Note :-

- In cephalothin it's composition from

Ampicillin + Flucloxacillin
mega cure®
megnacillin®

oxacillin + Amoxicillin
cloxabalfort®

- In 1st generation the modification occur on position [3] ~~and~~ or [7]

affect on pharmacokintic properaties.

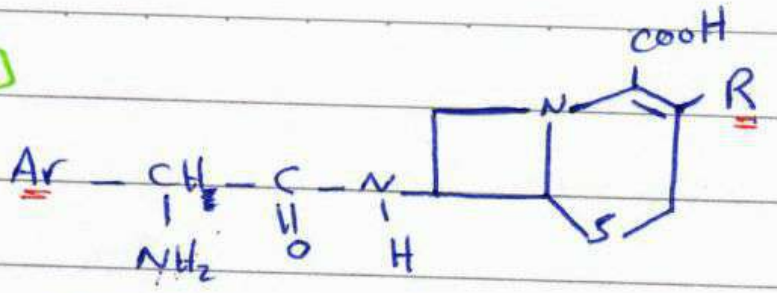
affect on β-Lactamase resistance.

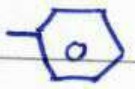
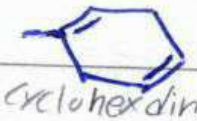
* in some compamed affect on Both position

in (2nd) cephazoline
∵ sturcture dosen't contain any hydrophilic
so it's β-lactamase sensitive

Date. No.

B)



	Ar	R		
1		CH_3	cephalexine	Jeflex ®, Keflex ®, cephaline ®, cephacare ®, cephalex ®
2		CH_3	cephadroxine or cephadroxyl	cephadrox ®
3	 cyclohexdine	CH_3	cepharadine	cephadrine ® or cephadrine fort velosef ®
4		Cl	Cephachlor	ceclar ®

Note

① ~~cephadroxine~~ cephalexine same to ampicilline ← But Add 7ADCA instead of 6APA في الصيدلة قبل الأخيرة

cephadroxyl same to amoxicilline

② This group ch.Ch by Acid stability so given orally because No ester is there and the ester is replaced with Cl or CH_3

البحث وتحضير أدل

7ADCA ← 6APA اثنين بدل

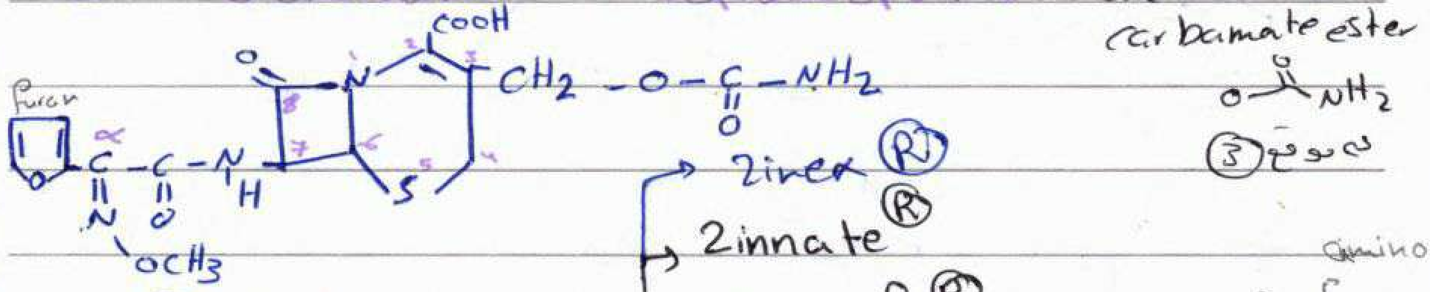
Date. No.

③ also it's β-lactamase resistant, due to (NH_2) which will ↓ nucleophilicity for ($\ddot{C}^{O}$) so reduce the attack of $\ddot{C}^{O}$ on β-lactam ring.

and the β-lactamase enzym on the ring.

2ed Generation of cephalosporine

* All 2ed generat are carbamate ester



① Cephuroxime → Zinex®, Zinnate®, Zinacef®

7 [α (2'-furanyl) - α (methoxy imino) acetamid 3 (amido oxy methyl) - 8 - oxo - 5 - thia - 1 - aza bicyclo [4, 2, 0] oct - 2 - ene - 2 C.A.

- In position 3 insted of ester → Amide

Amid hydrolysis < ester hydrolysis orally ✓

so Amid ↑ Duration of Action, ↑ absorption

- C=N → give isomer E, (Z)

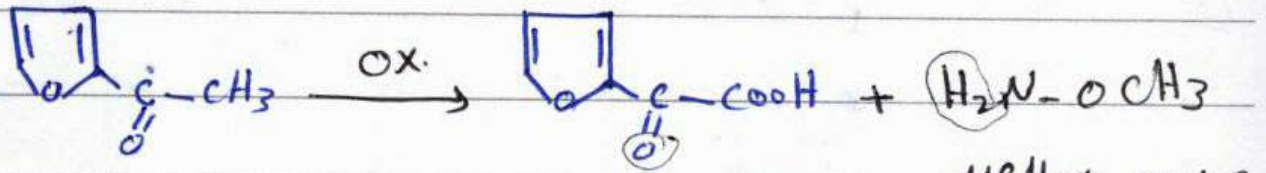
E ↓ inactive ✗

(Z) → Active form toward β-lactame resistance

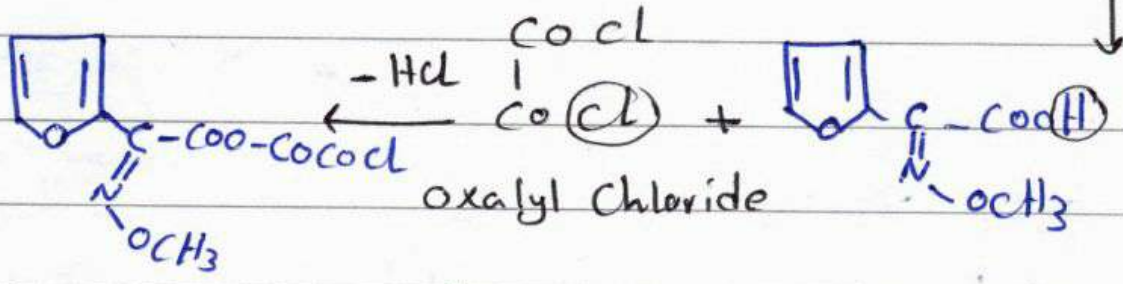
وجود ($NOCH_3$) (methoxy amino) مجموعة ساحبة بالتالي تقلل تأثير nucleophilicity لـ مجموعة C=O وبالتالي زيادة استقرار β-lactam ring

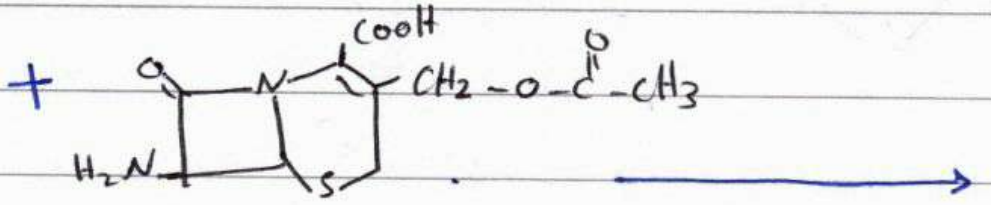
COOH
|
COOH
oxalic acid

preparation of cephuroxime :- Date. No.

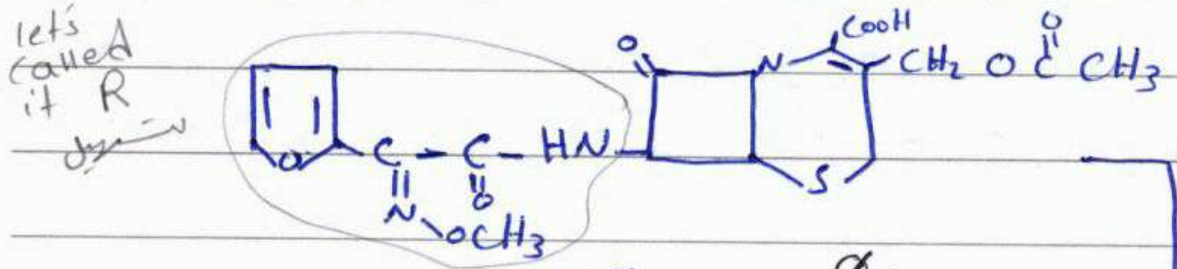


2- Acetyl furan

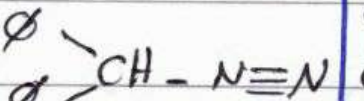


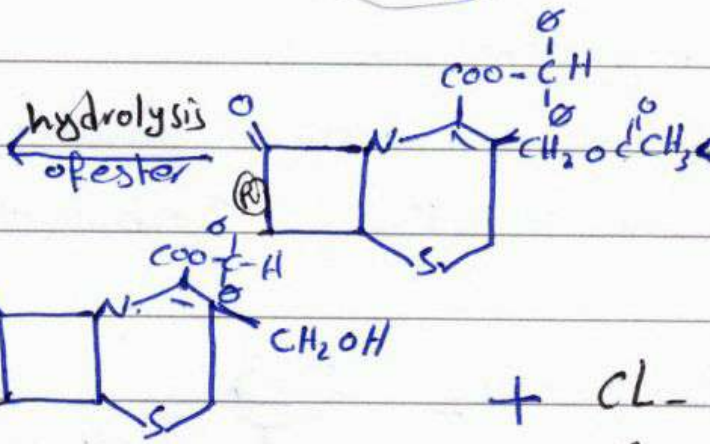


-OH CO-COCl



ester → amid

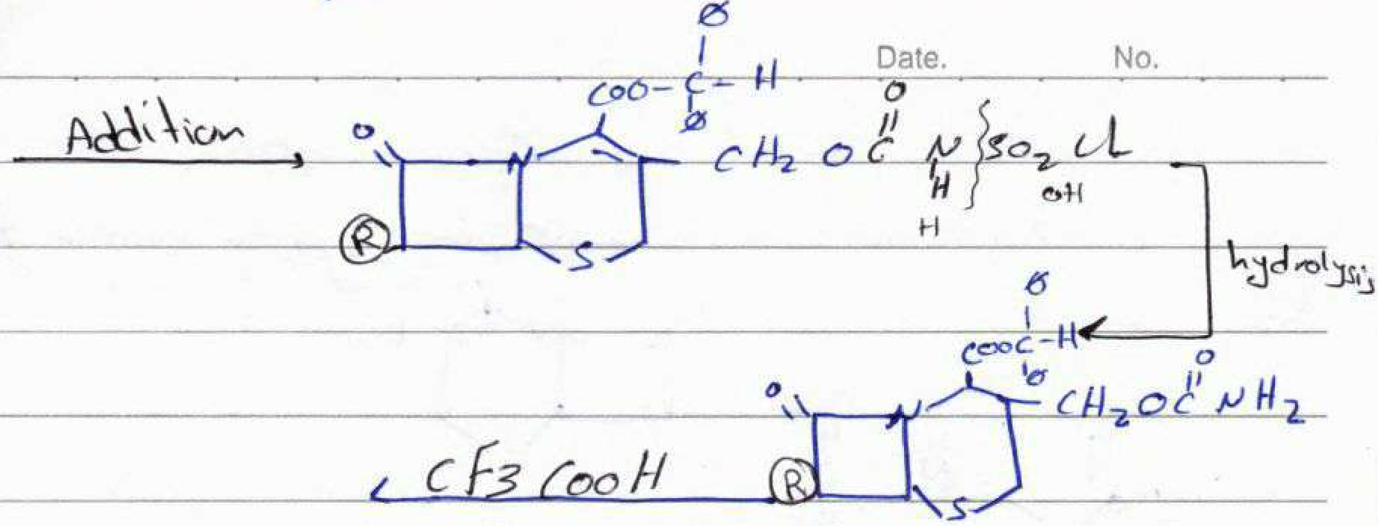




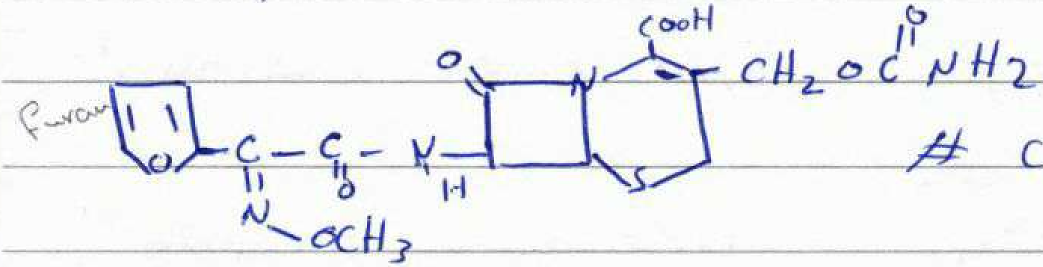
+ Cl-SO2-N=C=O
(Chloro sulfonyl isocyanide)

وجود S في موقع 7 احدى الحلقات

Thiophene G +ve اكثر من G +ve بحملها



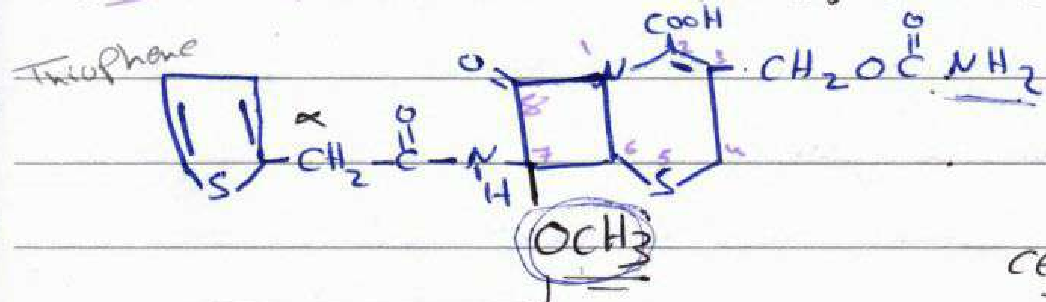
Tri floro acetic acid
hydrolysis



Cephuroxime

Cephamycine

[2] cephoxitine (Mefoxine)®



protect B-lactam

7 مكان رقم
methoxy يحتوي على

→ Cephamycine
- cephoxitine ↓ mefoxien
- cephaletan

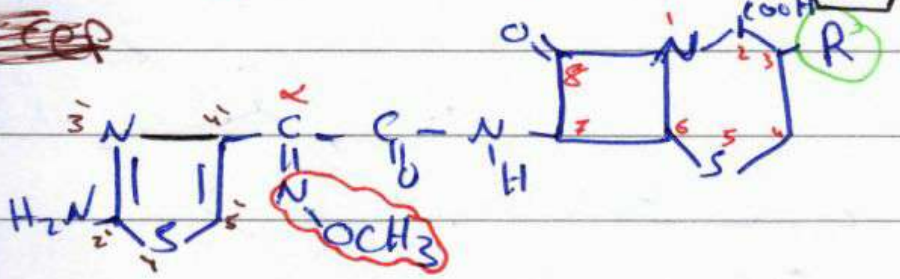
↑↑ stability of B lactam ring

7 [α (2`- thienyl) acetamido] - 7- Methoxy - 3- (amido oxy methyl) - 8 - oxo- 1-aza - 5- thia bicylo [4, 2, 0] octa 2-ene - 2 - C.A

Date. No.

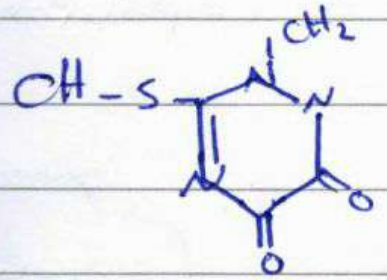
(3) 3rd Generation of cephalosporine

[Oxy amino cephalosporines] ← on position 7 کی وجہ سے



R

(1) CH_2OCCH_3 (O) cephotaxime Claforan®

(2)  cephotriaxone Rocephine®

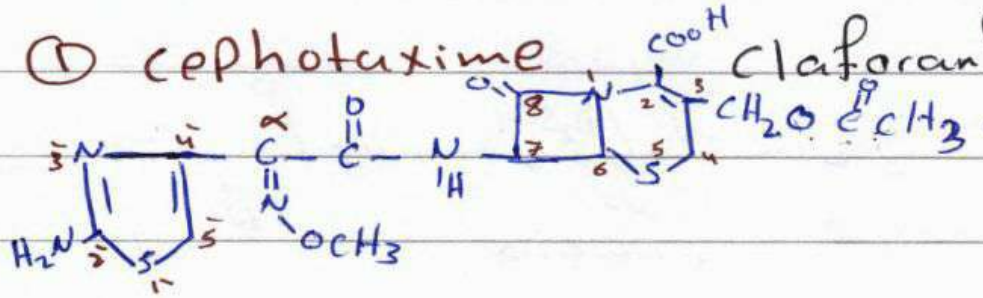
Due to $C=N$ in Both of them

They have 2 isomer E, Z

But 2 is active form

Date. No.

① cephotaxime Claforan®



7 [α (2- amino Thiazol-4'yl)-α (Methoxy imino) acetamido) 3-(acetyl oxy methyl)-1-aza-8-oxo-5-thia-Bicyclo [4, 2, 0] oct-2-ene-2-C.A

Ch. Ch. of cephotaxime :-

① on position (3) → ester → ↑hydrolysis
So not given orally X, but injectable ✓

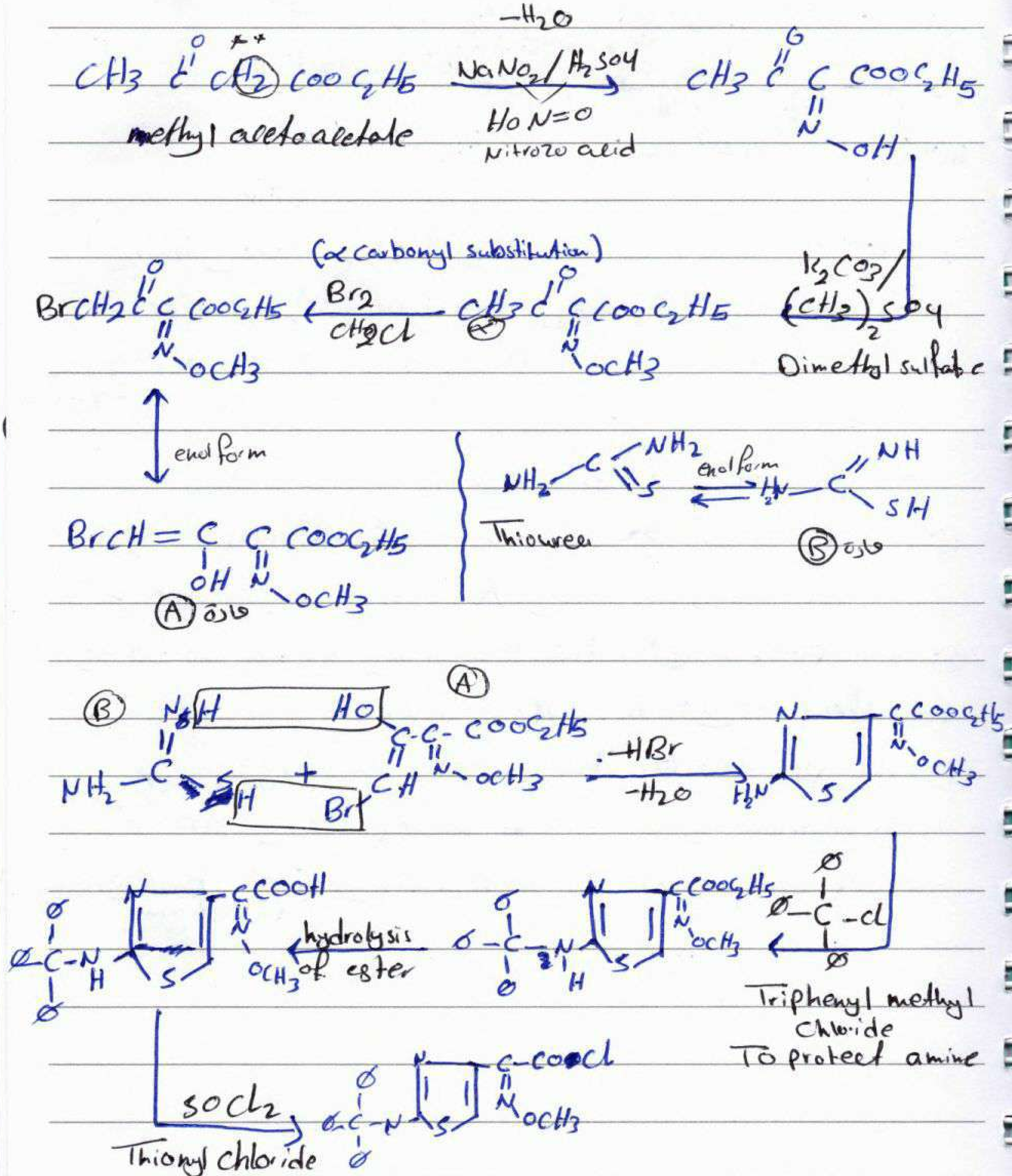
② at position (7) thiazole ring render the drug to affect G(-ve) more than Gram +ve

③ at position (7) the presence of methoxy imino is withdrawal group so ↓ nucleophilicity of C=O and ↑ stability of β lactam ring. (as bulk group) protect ring

هنا H واقعه بين مجموعتين الـ Carbonyl ألـ ابتلاع سهل نزعها لذلك * more acidic

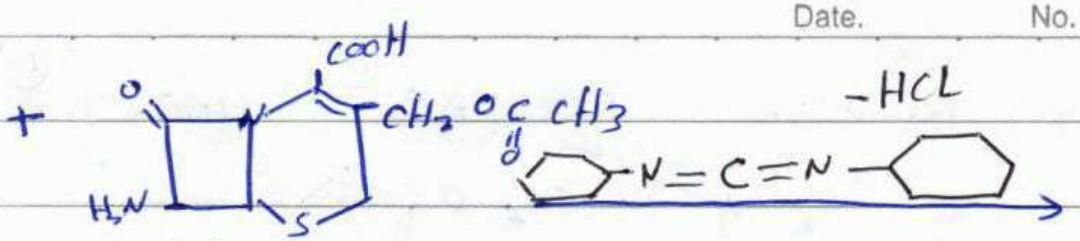
lec. 17

Cephotaxime preparation



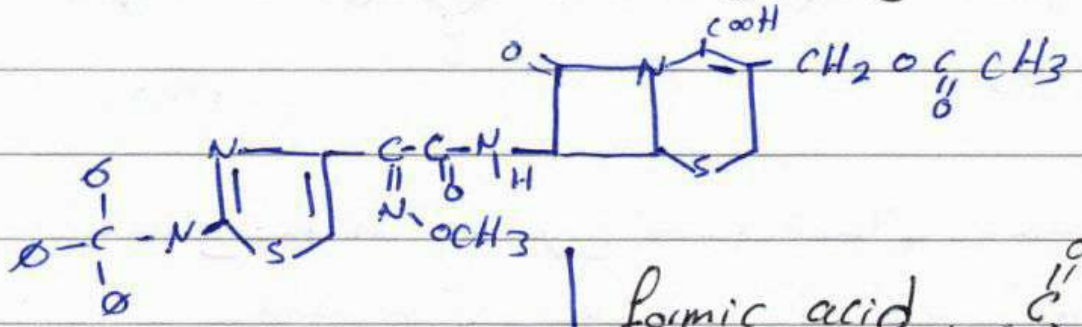
Acid halid ← C.A حولنا

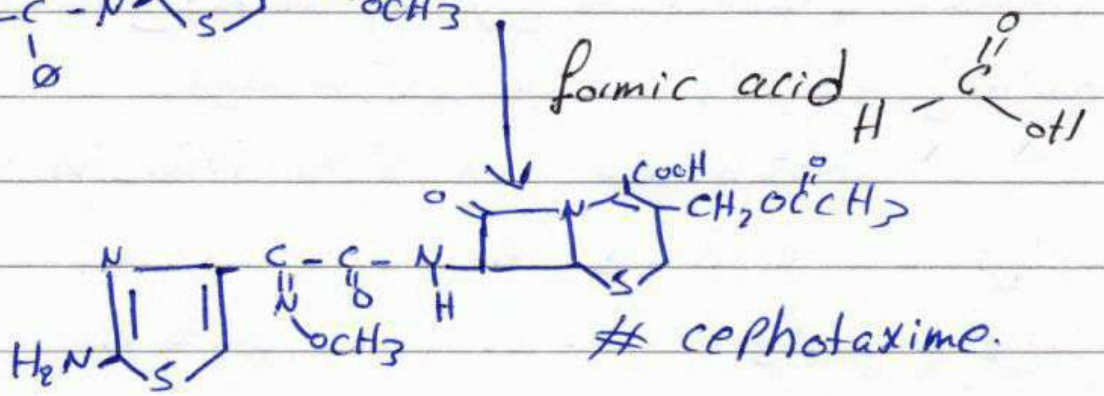
Date. No.



7 ACA

Dicyclohexyl imide



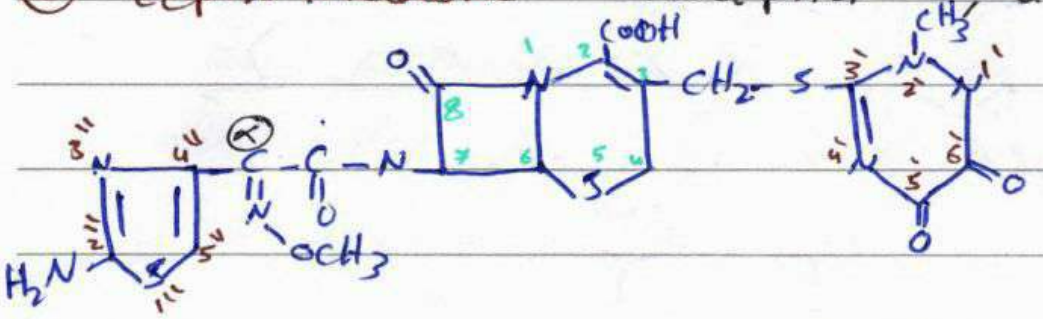


cephotaxime.

injectable

Date. No.

② Cephotriaxone Rocephen® unacef®

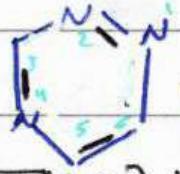


↑ DoA
↑ Plasma Protein Binding
Pentrant CNS

7 [α (2`amino - Thiazol - 4" yl) - α - Methoxy imino) acetamido] - 3 - [5`, 6` dioxo - 2" Methyl - 1", 2', 5', 6' Tetrahydro - 1", 2", 4" triazin 3`-yl] Thiomethyl - 1 - aza - 5 - thia - 8 - oxo - Bicyclo [4, 2, 0] - oct - 2 - ene - 2 - C.A

فقرة تعبير هيروغليفية .

Note

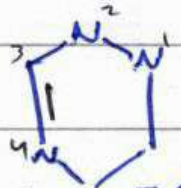


1, 2, 3, 4, 5, 6 = double bond it give Long Duration

1, 2, 4 Triazine

Triazine = in ⬡ , but ole in ⬠ So given once daily

3 Nitrogen — Nitrogen



~~3~~ 3, 4 =

→ so → 1, 2, 5, 6 tetra hydro

1, 2, 5, 6 Tetrahydro 1, 2, 4 triazin

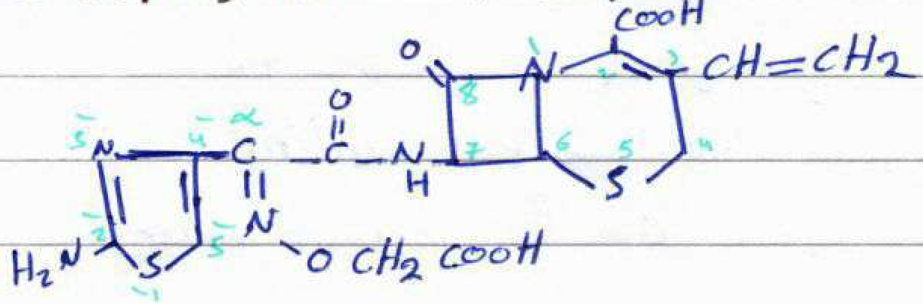
③ Due to

الآن يجب تخفيف oxo في amino مع R ③ → لهيك orally

80 orally

Date. No.

③ cephixime , supran®



7 [α (2`- amino Thiazol - 4`-yl) - α (carboxy Methoxy imino) acetamido] - 3 - ethenyl - 1- aza - 8 - oxo - 5- thia - 2- ene - Bicyclo [4, 2, 0] - oct - 2. C A

In All 3rd generation

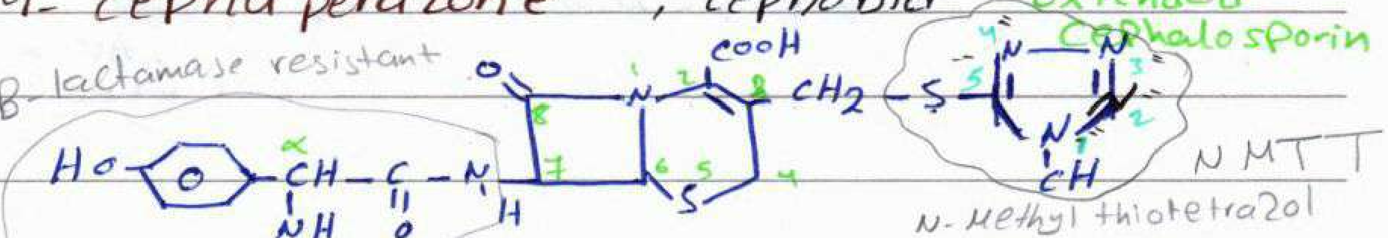
- Note :- ✱ (2` - amino thiazol ring) has ability to pentrate G-ve membrane

G+ve + G-ve

4- cephaperazone , cephobid®

Extended cephalosporin

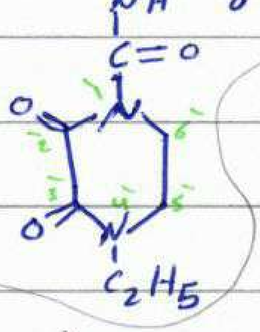
β-lactamase resistant



NMTT

N- Methyl thiotetrazol

من الاسيل Acyl ureido penic pipreclline



7 [α (p hydroxy phenyl) - α (4`- ethyl - 2`, 3` dioxo piprezinyl') carbonyl amino acet amido] - 3 - [(1`` - Methyl tetrazole - 5`` - yl) thio methyl] - 1- aza - 8 - oxo - 5- thia - bicyclo [4, 2, 0] oct - 2 - ene - 2 - C.A.

Date. No.

Cephaperazone

- on position 7 , the group is same to
  Acyl uriedo penicilline → piperacilline
  and it's for protection for β-lactam ring

- on position 3 :-
  NMTT (N-Methyl thiotetrazole) or MTT
  ↳ extended spectrum → has ability to penetrate Pseudomonas Aurgenesa (G-ve) membrane
  ↳ ↑ high potency , ↑ high half life t½
  ↑ PPB (plasm protein Binding) → so

Side effect:-

① bleeding (hypoprothrombonemia)

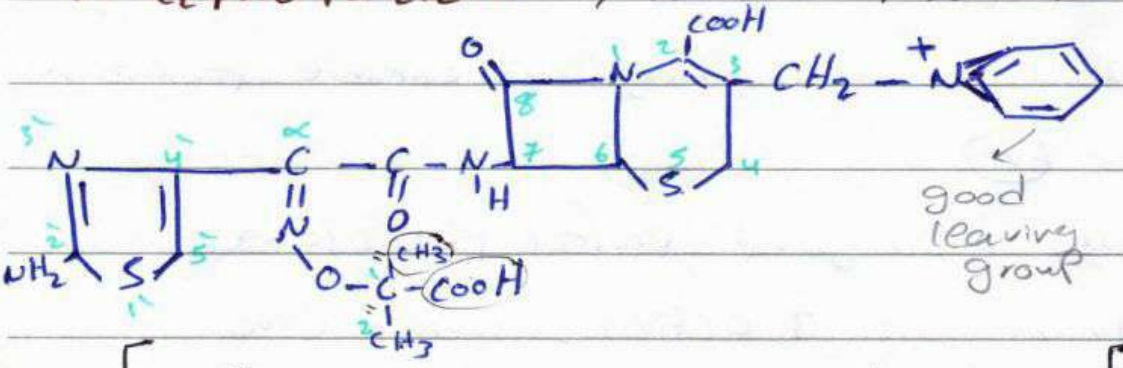
② Inhibition for aldehyde dehydrogenase (Alcohol intolerance)

pyridine

pyridinum salt

Date. No.

5- Cephotazidim , Fortum®, Fortax® Salt form



N [7 [α (2`-amino Thiazol -4`-yl) -α- [(1``-carboxy-1``-Methyl) ethoxy imino] acet amido] - 1- Aza - 8- oxo - 5- thia - bicyclo [4,2,0] oct - 2- ene [3-yl 2-Carboxy methyl]] pyridinium salt

. Note : • COOH, pyrimidine make it more Polar mean that more effect on grame (-ve) and they are ↑ Anti pseduomonas arugenusa ~~argin~~ So used for Meningitis.

The salt form

① Take by injection

② Excellent for Ps. arug.

③ cross BBB

④ For meningitis.

Date. No.

Ch.Ch of cephotazidim

① Due to amino thiazol ring, it enhance pentration to grame (-ve)

② Methoxy imino group protect β-lactam

③ Pyridinum salt ↑ activity toward G-ve espacially ps. orgenusa

Q : why cephotazidim has excellent activity towared ps. aureguna

① Pyridinum salt

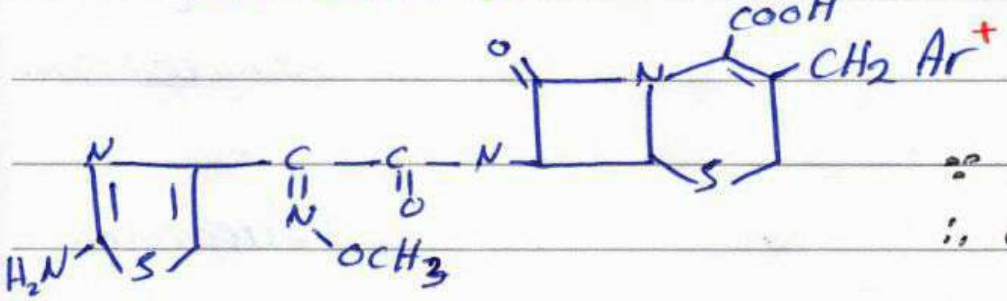
② COOH on position (7) as isO butric acid

Note In 3rd generation, we get rid of ester group (unstable group) and replace it. with more stable group - [cephotaxime] have ester

Date. No.

4th generation of cephalosporin

on salt form charged



∴ salt

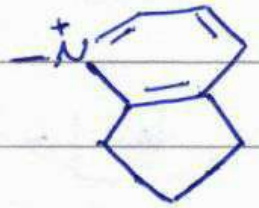
∴ charged

∴ for pseudomona aruginosa.

All 4th Generation have ⊕ good leaving group when it bind β-lactamase.

Ar

cephopim



cephopirome

Ch.Ch.

① Because of ⊕ charge in position (3) → polar

good pentration to -Gram

② Anti Pseudomonase

③ good PPB ~~but~~ less than 3rd

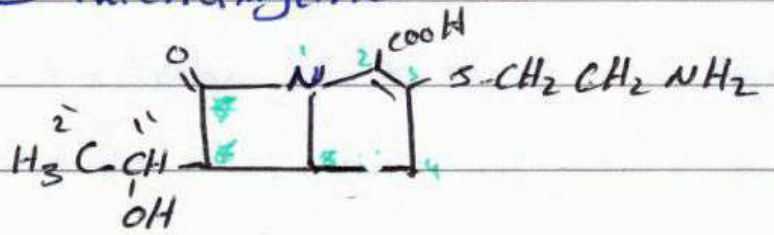
Pyrrole Pyrroline Pyrrolidine

Date. No.

New β-lactam

- Carbapenem
  - Thienamycine
  - Imipenem
- Monobactam
  - A2 tebonam

(1) Thienamycine



6 [1`-hydroxy ethyl] - 3- [[2``ethyl amino] thio] - 7- Oxo - 1- A2a - bicyclo [3,2,0] hept-2-ene 2- C.A.

* Same to penicilline but differ in

① in pencillin it contain S inside ring. here no

② in position 6 there's acyl here no

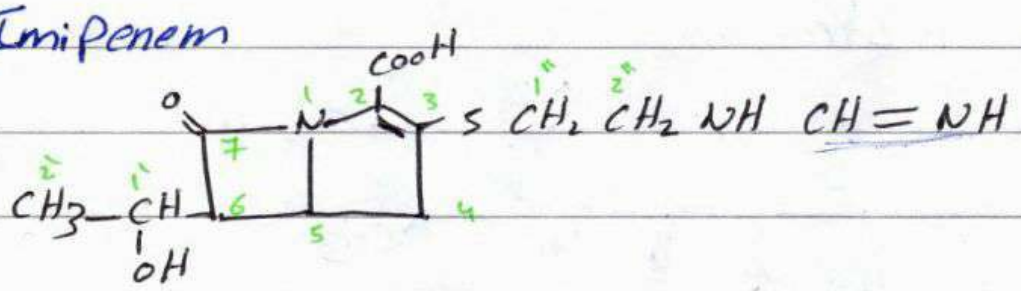
③ in penicillin it contain dimethyl → on C_3 here another group

④ btw 2, 3 there's =, in penicill no

⑤ This compound is stable (resonance)

Date. No.

[2] Imipenem



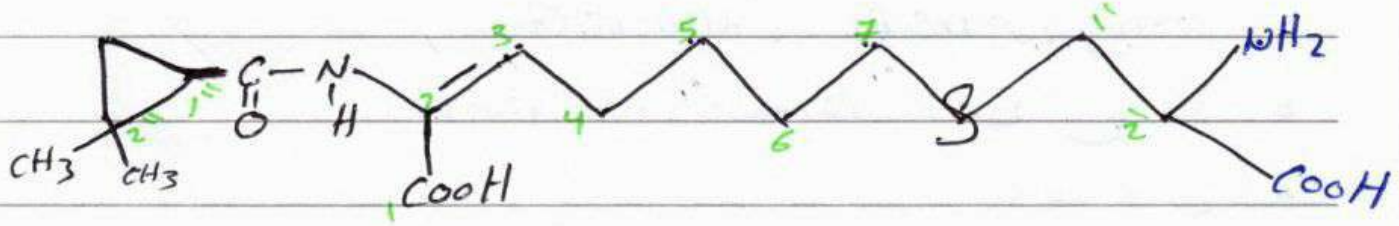
6 [1-hydroxy ethyl] - 3 [(2"- iminomethyl amino) ethyl thio] - 7- oxo - 1- Aza - bicyclo [3,2,0] hept - 2- ene - 2- C.A.

Combination :-

Imipenem + cilastatin → primexine

Inhibition For Renal dihydropeptidase enzyme I

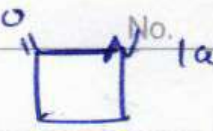
structure of cilastatin :



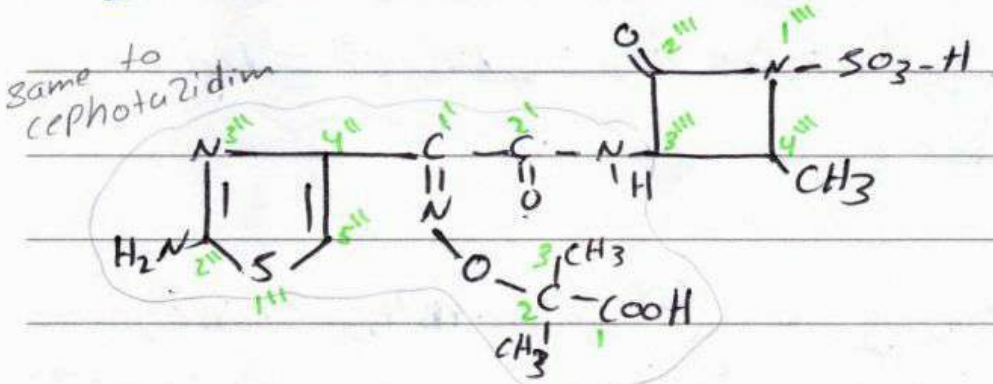
7- [(2- amino - 2- carboxy) ethyl thio] - 2 - [(2,2" dimethyl cyclo propyl) carbonyl amino] hept - 2-en - oic acid.

~~[3] AZtreonam (I.V)~~ COOH يزيد الذوبان

Date. No.

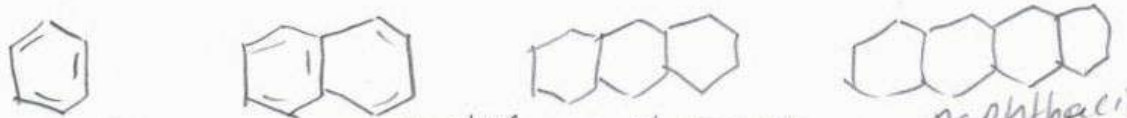


(3) Aztronam I.V



2 [[1`(2"-amino thiazol-4"-yl)-2`-(1"'-sulfonyl-2"'-oxo-4"'-methyl azetidine-3"'-yl] amino] 2`-oxo ethylidenyl imino oxy] 2-methyl propanoic acid

- Totaly synthetic (Monobactam)
- highly β-lactamase resistant.
- give I.V.



lec. 18

Date. No.

Tetracyclins = Tetracine

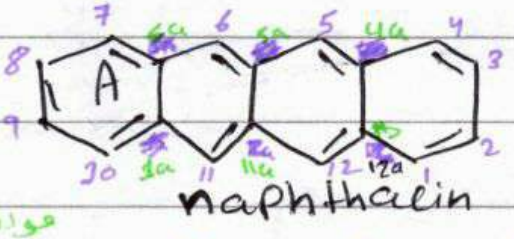
- Bacteriostatic, Broad spectrum
- Atypical Balteria
- MoA:- protein synthesis inhibitor

erthromycin ←
Tetracyclin
Amino glycoside
Chloramphinicol
Macrolides.

A Bacteriostatic.

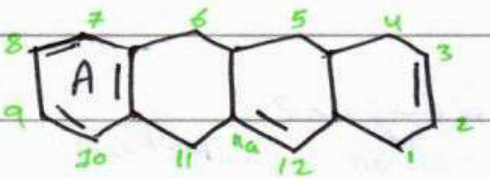
prevent protein chain elongation by inhibition of the peptidyl transferase activity of the bacterial ribosoms. specially bind to A_2451 and A_2452 residus in the 23S rRNA of 50s ribosomal subunits, prevent peptidel bond formation.

"Bind to 30S + interfer ~~w~~ Binding ~~of~~ tRNA to ribosmal complex"



$-4 = -8H$

1, 2, 3, 4, 4a, 5, 5a, 6, 6a
7, 8, 9, 10, 10a, 11, 11a, 12, 12a

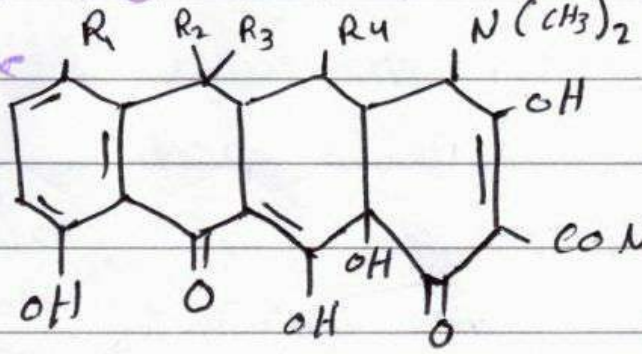


Octa hydro naphthacine.

2, 3 ; 11a, 12 = مواقع

1, 4, 4a, 5, 5a, 6, 11, 12a octa hydro naphthacine

General structure:-



Tetracycline Ring

- 4 Ring Fused
- present in 3D

Linear not planner

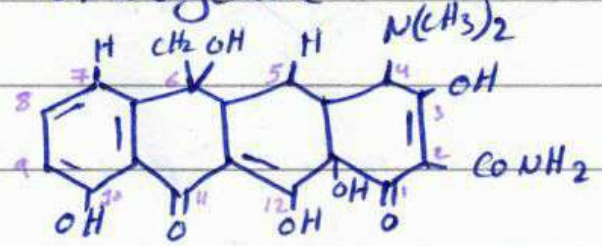
R_1	R_2	R_3	R_4		
H	CH_3	OH	H	Tetracyclin	Brimocyclin®
Cl	CH_3	OH	H	Chlorotetracyclin	
H	CH_3	OH	OH	oxytetracyclin	

↳ Natural Tetracyclin

H	$=CH_2$		OH	Methacyclin	
H	H	CH_3	OH	Doxycyclin	→ Doxal®, Doxacine®, Doxytrim®, Doxypharm®, Vibramycine®, Doxyline
$N(CH_3)_2$	H	H	H	Minocycline	→ Minocycline®, Minocine®

↳ semisynthetic

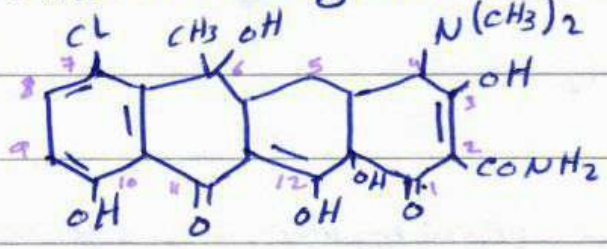
II Tetracycline



1, 11 Dioxo - 3, 6, 10, 12, 12a penta hydroxy 4-(N,N dimethyl amino) - 6- Methyl - 1, 4, 4a, 5, 5a, 6, 11, 12a octa hydro naphthacine - 2- Carboxamide

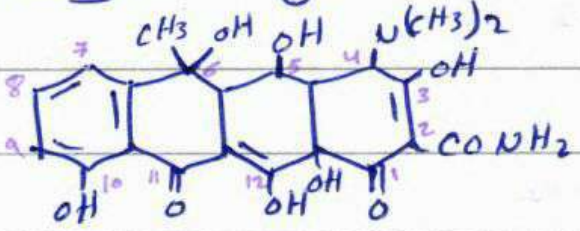
Date. No.

(2.) Chlorotetracyclin



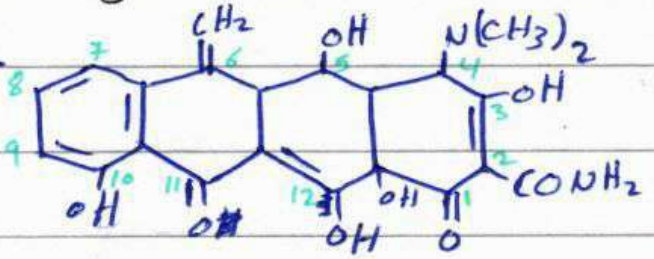
1, 11 dioxo - 3, 6, 10, 12, 12a pentahydroxy - 4-(N, N dimethyl amino) - 6 - Methyl - 7 - Chloro - 1, 4, 4a, 5, 5a 6, 11, 12a octahydro napthacine - 2 - carboxamide.

(3.) oxytetracycline



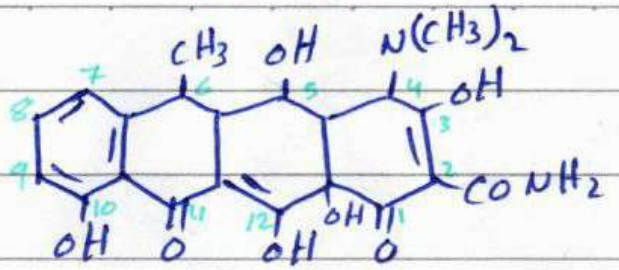
1, 11 dioxo - 3, 5, 6, 10, 12, 12a hexahydroxy - 4 (N, N dimethyl amino) - 6 - Methyl - 1, 4, 4a, 5, 5a, 6, 11, 12a octhydro naphthacin - 2 - carboxamide.

(4.)



1, 11 dioxo - 3, 5, 10, 12, 12a pentahydroxy - 4 - (N, N dimethyl amino) - 6 - Methyllidenyl - 1, 4, 4a, 5, 5a, 6, 11, 12a octhydro naphthacine - 2 - carboxamide.

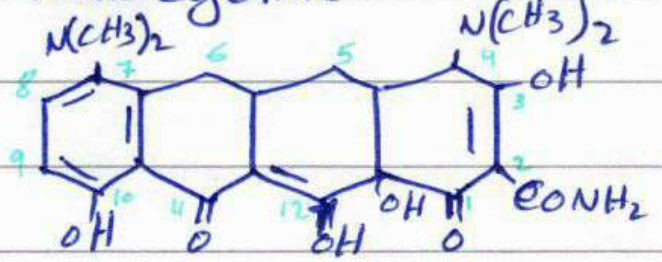
Date. No.

(5) 

Doxycycline

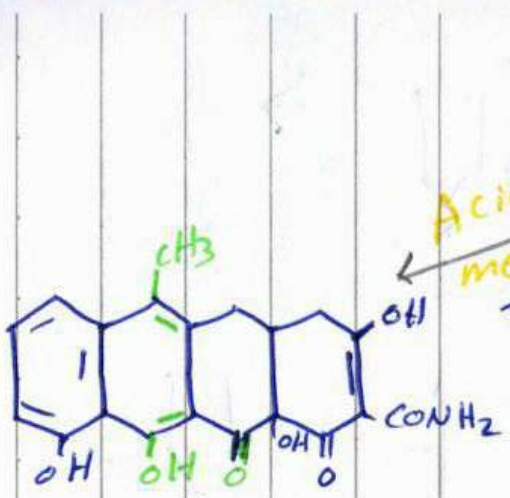
1, 11 dioxo - 3, 5, 10, 12, 12a pentahydroxy - 4. (N, N dimethyl amino) - 6 - Methyl - 1, 4, 4a, 5, 5a, 6, 11, 12a oct hydro napthacin - 2 - carboxamide.

(6) Minocycline



1, 11 dioxo - 3, 10, 12, 12a tetrahydroxy - 4, 7 di (N, N dimethyl amino) - 1, 4, 4a, 5, 5a, 6, 11, 12a oct hydro naphthacine - 2 - carboxamide.

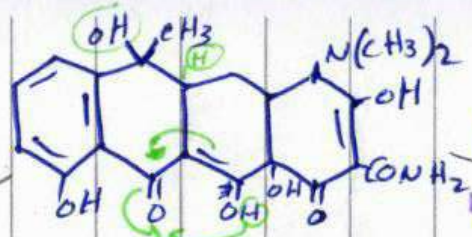
Chemical degradation of Tetracycline.



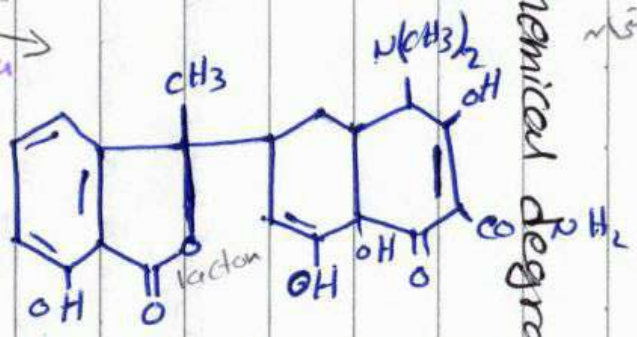
Anhydro tetracycline
(Inactive)

[Due to imparid of octahydro naphthacine system]

Acidic media $-H_2O$



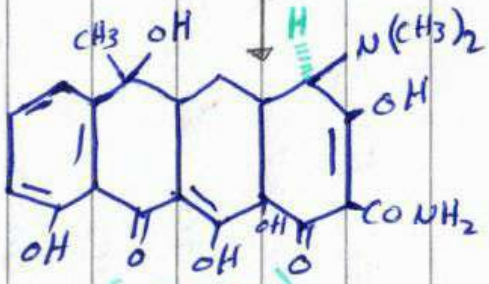
Basic media



Izo tetracycline
(Inactive)

Pharmacophore

Neutral media



(epimer)
epitetracycline

Less active than tetracyclin

H became in the back.

(Active)

- So All compound From chemical degradation of Tetracycline are inactive except epitetracycline.

123

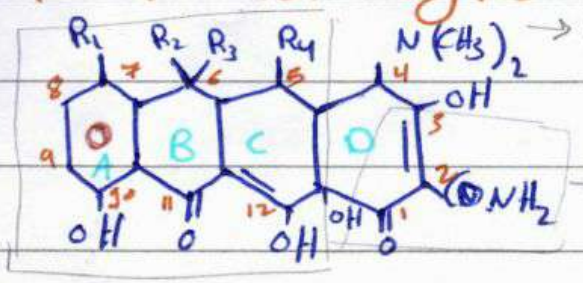
Date.

No.

SAR

Date. No.

SAR of Tetracycline :



1. Octahydro naphtacine to give activity it must not Chang to Aromatic B, C, D. ex: As in Acidic media B → Aromatic

a) so if B, C, D ring become Aromatic → inactive

B) 4 ring must be 3D Linear not planner → inactive

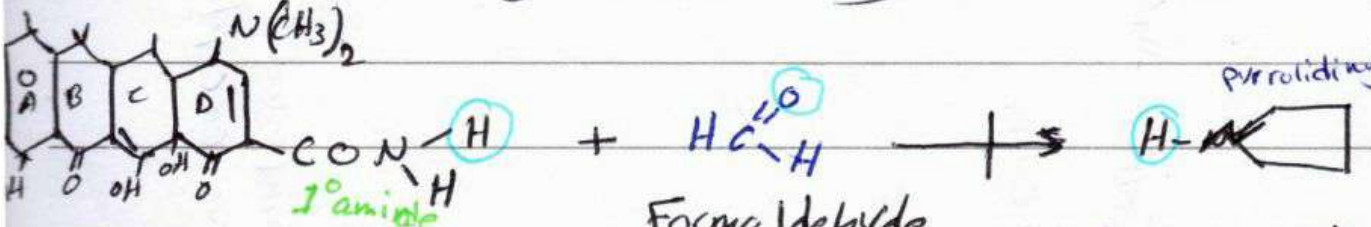
2. a) Amide group in C_2 is important for activity, when the amide replaced to CN (cyano), or aldehyde → ↓ activity.

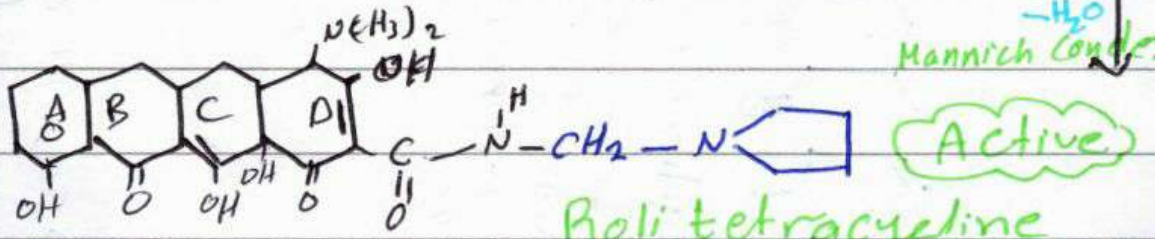
b) 1° amide in C_2 if converte to 2ed, 3° amide → inactive

So it must be just primary

c) All N, alkylation on amide → inactive

except pyrrolidinyl alkylation by Mannich condestation



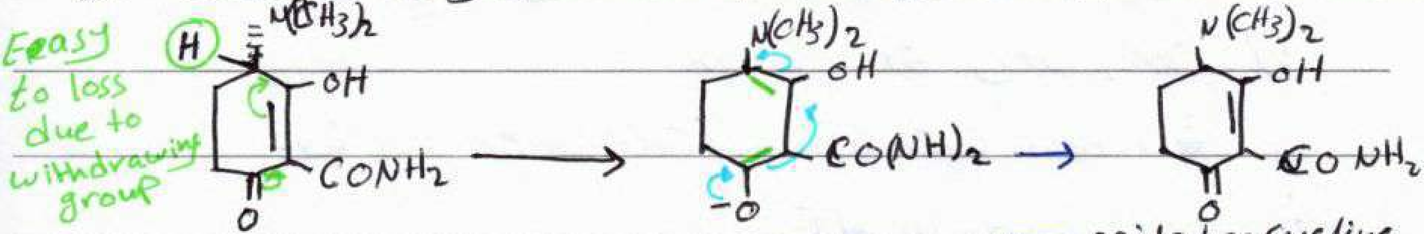


Date. No.

تقل و لا تنعدم.

3) In C4 3° amine if convert to 2°, 1° → ↓ activity.
and 3° amine must be in (α position / orintaion or S - configuration) if it converte to β - position or R - configuration by epimerization → ↓ activity

Ex: chemical degradation of tetracycline in neutral media



epitetracycline
↓ Activity

نوت 150 . دطبيعي ، وضع يرجع 50% ←

* To prevent epimerization of teracycline.

a) Good storge for tetracycline

b) prepeared in Dry solid dosage form

c) increase the dose of Drug (15%) in tablete in case of near expire date. due to degradation.

4) H in 4a, OH in 12a → cis form.

.rember:-

Ciz and Tranz are found in → ① Double bond = / → ② cyclo alkene

if it converte to Tranz → inactive

Date. No.

5 at position C_5 it could be H / OH

6 C_6 must not be OH , And the compound that Dosen't contain OH called [6- deoxy tetracycline] which is semisynthetic , it's Ch.Ch is :-

a) high plasma protein Binding ↑ PPB

b) completely absorption

c) ↓ renal excreation / clearance ↓ Cl_r

d) not used in UTI

. so natural tetracycline (contain OH) is less activity than semisynthetic teracycline

. OH make loss of octahydro naphthacine if put in acidic / Basic media

7 at C_7 has Electronic properaties → with drawal ↓ activity / Donating ↑ activity

The relation bw electronic properties and Pharmaceutical activity is called para polyic relationship

8 position 5, 6, 7 has relation to phK "kinitic"

But 8, 9 " " phD Dynamic

9 position 8, 9 are unsubstuted

Date. No.

[10] Recently they put glycin on C9 ↑ activity and called glycyl cycline

[11] at 10, 11, 12 the drug is Hydrophilic, which is a part of the activity of Drug and not changed thus it's less Lipophilic

[12] A C_{12a} All ester are inactive - [except Formyl ester]

By Adding C.A to alcohol → ester

[13] Tetracycline not given to, with ♂

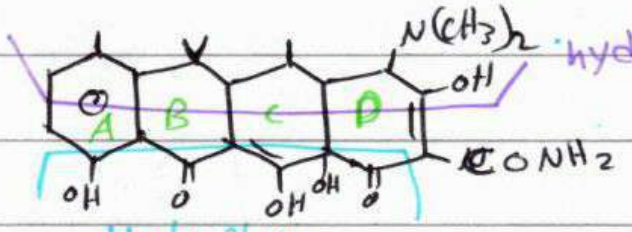
a) pregnant + lactating women

b) Children < 8 y → coloration of teeth ← Ca^{+2} ← tetracycline or ortho phosphat

c) with Food containg [Ca^{+2}, mg^{+2}, Fe^{+3}, Milk].

D) Infant → Bone disorders.

[14] Ch. Ch of tetra cycline



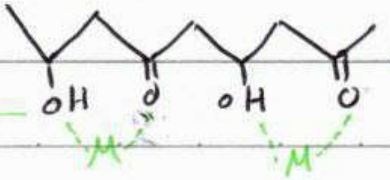
hydrophopic part

Hydrophilic Part

Due to complexation Rxn

↓

insoluble in water

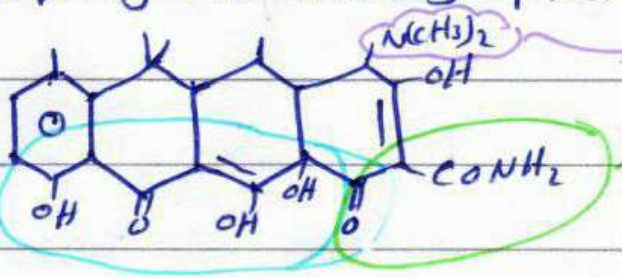


Complex ←

C=O

Date. No.

① Tetracyclin has 3 pKa



→ Basic part

→ Amide Acidic part

more acidic + strong part

Acidic part

So tetracyclin is amphoteric nature → Acidic + Basic

② make salte → water soluble

Tetracycline + HCl

Acidic salt

water soluble

stable salt

orally

Capsules

↳ not tablet

Due to bitter taste from

$N(CH_3)_2$.

Tetracycline or KOH + NaOH

Basic salt

water soluble

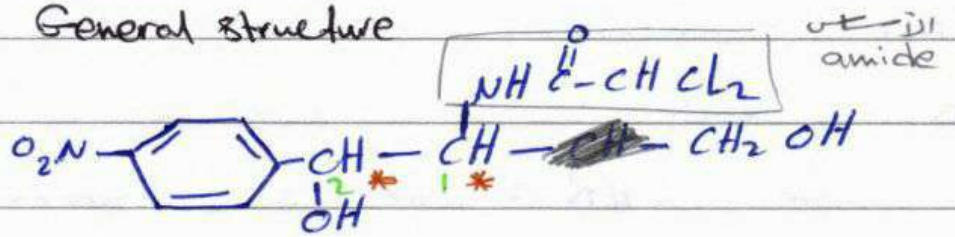
Not stable

Atypical Bacteria

Date. No.

Chloramphenicol In eye infection

- 1st choice of DoC For Thyphoid + parathyphoid
- For salamonila typhie. G⁻
- Baeteriostatic AntiBiotic.
- * General structure



D-Threo (2 chiral center)

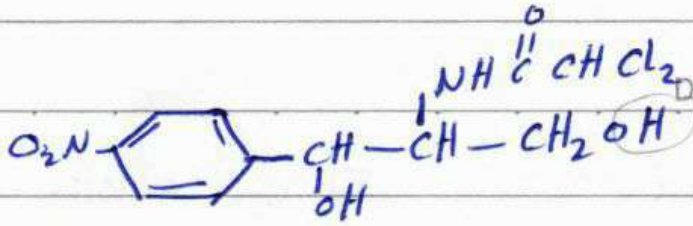
N[1(hydroxy methyl)-2(hydroxy)-2-(p-Nitro Phenyl) ethyl] α, α dichloro acetamide.

- MoA: inhibition of protein synthesis by Binding to 50S and inhibition the formation of peptide bond.
- ∵ Contain 2 chiral center → has 4 isomers 2^n $2^2=4$

Threo Configuration → Both R,S or SR

Erthro configuration → Both RR or SS

- All isomer are inactive — except D-Threo

SAR: 

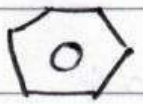
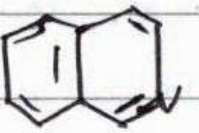
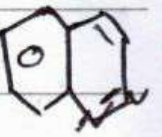
Date. Terminal OH

[1] NO_2 Nitro give activity

- But in case of substitution For
  - SO_2NHR sulfonamide
  - $NH\overset{O}{\overset{\|}{C}}R$ 2° amide
  - NR_2 3° amine, NHR 2° amine, NH_2 1° amine
  - Cl, Br, I, F halogen

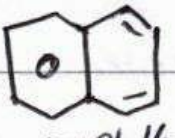
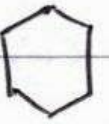
  became inactive
- SO_2-CH_3 "methyl sulfonyl" → Thiamphenicol
- CH_2-SH "mercabto"

  became active

[2]  if substituted with   

became inactive

Isoquinilone Quinilone Cinnoline

  cyclohexen

naphthaline

But with  active

Thiophene

[3] NO_2 on position para if converte to

Meta → inactive 130

Date. No.

④ OH (terminal OH) must be free

⑤ α, α di chloro acetamid if substituted with $NH\overset{O}{\overset{\|}{C}}CF_3$ → active

(Trifloro acetamid)

Biotransformation:-

a) 90% of chloramphenicol bind with OH (Free) result in O-Glucuronide.**

b) 10% by oxidative dehalogenation

**

D-glucose —(Glucoronyl Transferase)→ Glucoronic Acid

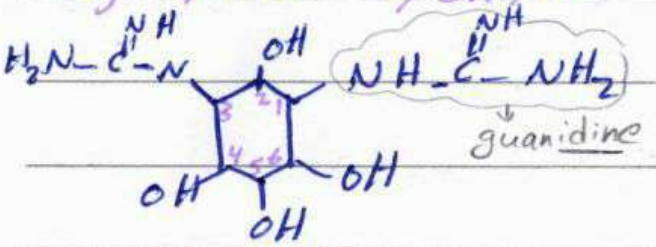
The enzyme is not exist in children (infant) and recent delevered babies, thus Chloramphenicol not given to them or it will cause Gray's baby syndrom

Date. No.

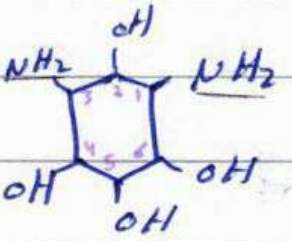
Amino glycoside : Bacterocidal.

- Consist of
  a) Amino cyclitole
  b) Amino sugar "pentose hexose" } Both binds with glycosid Bond.

a) Amino cyclitole



streptidine



streptamine

- Most Aminoglycoside contain
  2-Deoxy streptamine
  (not contain OH on position 2.)
- They differ in Amino suger (5 ↔ 6), Binding site (4,5 ↔ 4, 5 ↔ 4, 6)
- Ch. Ch. of Aminoglycosides:

① low GIT absorption (polar) ; hydrophilic ch.ch thus not given orally but given I.V injection.
② and its has salt form
③ has Basic ch.ch.

Date. No.

④ limited use + limited Dose due to it's ↑ S.E
less dose possible, for optimum activity
and it's last choice.

⑤ MoA / protein ihibitor,
Bind to 30s, and causes mRNA codon to be misread; intefere with the initiation complex of 30s and 50s with mRNA

⑥ side effect (S.E)
① nephro and oto toxicity.
② Contraindicated with β-lactam (Penicilline) due to NH_2
NH_2 has ⊖ negative effect on

Drugs of Aminoglycoside:-
- Streptomycine
- Tobramycine
- Kenamycine
- Paramycine
- Netilmycine
- Neomycine (Neomycine®)
- Gentamycine { Genticine®, Zetamycine®, Cidomycine® }

Date. No.

⑤ others → a) macrolides
→ b) poly peptides.

A) Macrolides :- → Big larg ring + laeton.

- Contain [1] macrocyclic laeton [12, 14, 16] atom
  Double bond one. [2] Amino sugar.
- 1st Drug discoverd was picromycine but it's Not clinically used.
- 1st Drug used clinically Erthromycine
  - erthro Teva ®
  - erthro bal ®
  - erthroped ®
  - erthro Pharm ®
  - erthro mycine ®
  - Pedia zole ®

But it has many problem :-

a) Short duration (4 time per day)

b) low water solubility ; so to increase it they make salt form. this → improve water solubility
→ get red of bitter taste.

c) bitter taste

d) given befor food

e) use for upper + lower Respiratory tract and G +ve

f) Limited use + limited Dose.

Salt

Hydrophilic Salt (I.v)

ADD → • Glucoheptanoic Acid
→ • ~~Lactobionic~~ lacto biotonic Acid

↑↑ water solubility

Lipho Philic Salt (suspension)

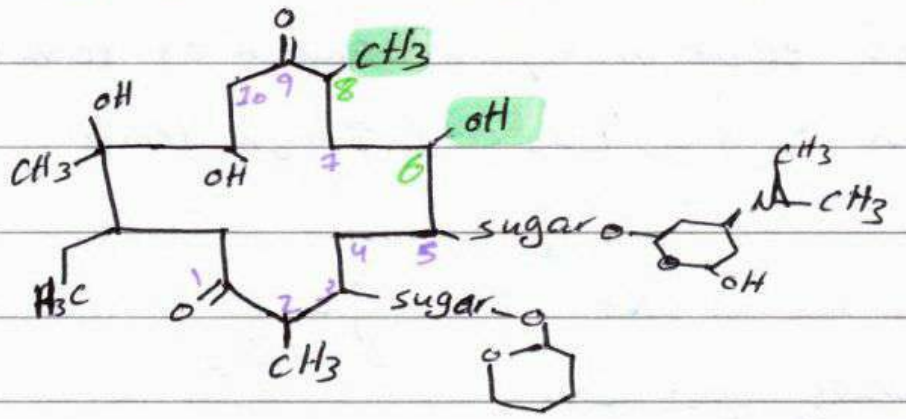
→ • Stearic acid (18C)
→ • Lauryl sulfate

↓ water solubility

orally

Date. No.

Structure of Macrolide :- تركيب الماكروليد



RXN بـ
↳ OH + C=O

- OH in C_6 and $\overset{O}{\overset{\|}{C}}$ in C_9 make hemiketal

This make intestinal cramps

* So they make modification ① They replace OH on C_6 (primarly) or C_{12} to O CH_3 [ether]

The Drug result from ether prevent fromation of hemiketa its called clarithromycin, Claricare ®
which is Acid stable → given orally ↳ Long Duration ↳ one per day.

② The 2ed modification.

replace $\overset{O}{\overset{\|}{C}}$ (ketone) in C9 → to $\underset{\underset{N-CH_3}{|}}{CH_3}$ (amine) ⇒ Azitromycine

has long Duration + 1 per day

↳ Azicare ®
↳ Azimax ®
↳ Azitra ®

③ replace CH_3 at C_8 with F (withdrawal) affect polarizability of $\overset{O}{\overset{\|}{C}}$ and preven hemiketal formation

⇒ Flurithromycine

↳ The only Drug that Don't inhibit CYP450.

Note :-

- macrolides stable in aquous solution at room temp.
- unstable in acidic / Basic / ↑ high temp.

b) Poly peptides :- C(=O) — N(H)

① Not given orally just I.V.

② Gram (-) or cell membrane.

③ has nephro and neuro toxicity.

④ Polypeptide

- → Acidic
  - ↳ Bacitracine A
- → neutral
  - ↳ vencomycine
- ↳ Basic
  - ↳ polymixine B

الامتحان
- MCQ
- T, F
- Match → الأسماء التجارية
- Table struc } IUPAC
- تصميم .

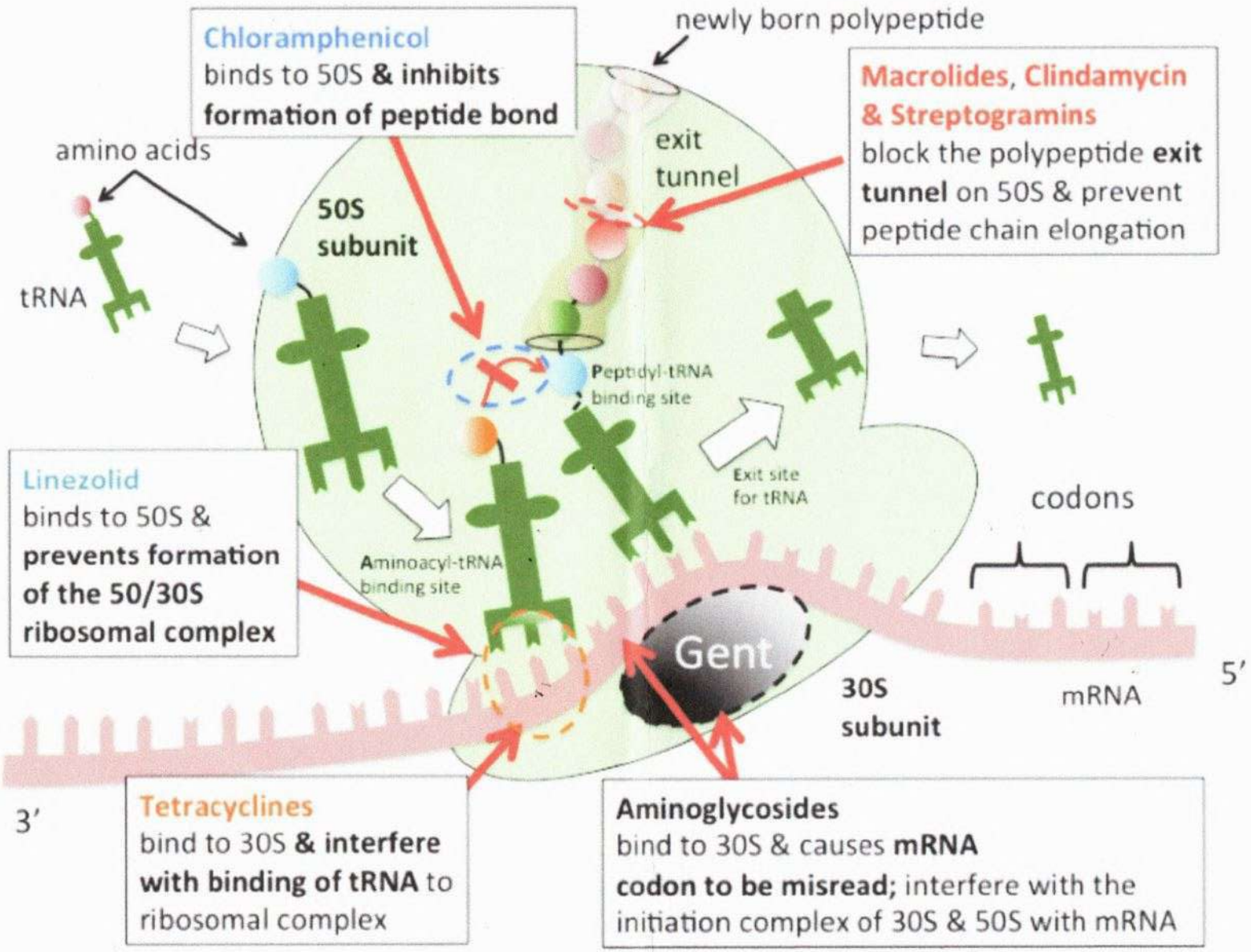
. والله ولي التوفيق .

" عسى ربي أن يهديني سواء السبيل "

. لا تنسَ أنك البناء لنهضة الأمة ومن كان بناءً فعليه ألا يستريح

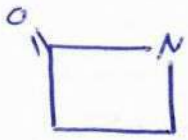
. تذكر وردد دائمًا " أليس الله بكافٍ عبده " .

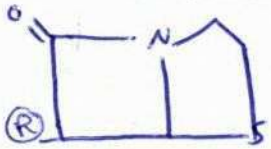
الله المستعان وعليه التكلان . الحمد لله .


Chloramphenicol
binds to 50S & inhibits formation of peptide bond
newly born polypeptide
Macrolides, Clindamycin & Streptogramins
block the polypeptide exit tunnel on 50S & prevent peptide chain elongation
amino acids
exit tunnel
50S subunit
tRNA
Peptidyl-tRNA binding site
Exit site for tRNA
Linezolid
binds to 50S & prevents formation of the 50/30S ribosomal complex
codons
Aminoacyl-tRNA binding site
Gent
30S subunit
mRNA
5'
3'
Tetracyclines
bind to 30S & interfere with binding of tRNA to ribosomal complex
Aminoglycosides
bind to 30S & causes mRNA codon to be misread; interfere with the initiation complex of 30S & 50S with mRNA

• main groups To know :-

ine ... ole → ... dine → = ...
S. → Thia ... Thio ...

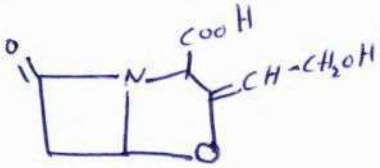

B-lactam

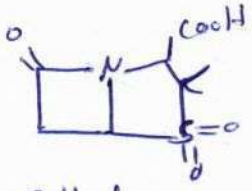

penam

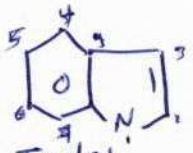

Thiazide

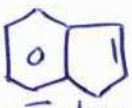

Thiazolidine

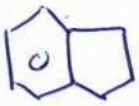

• sulfone → free
• Thia → ... dioxid


Clavulanic Acid


Sulbactam


Indol


Inden


Indan / 3,4 dihydro Inden.

O → ... oxo ... oxy


Oxazole


Isoxazole


Isoxazolidine

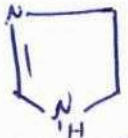

Oxazolidine


Imidazole


Imidazidine

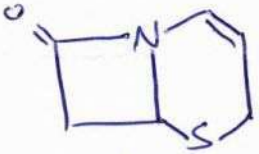

Imidazoli


Imidazole


Imidazoline


Imidazolidine


Pprazen

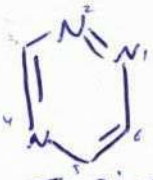

Cepham

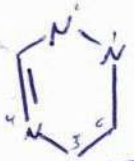

Pyrrole


Thiazole


1-Thia-3,4 diazole


Furan

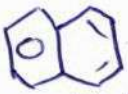

Triazine


1,2,5,6 Tetrahydro 1,2,4 Triazine

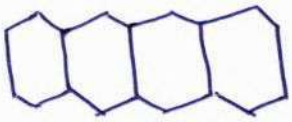

Pyrroline


Azetidine

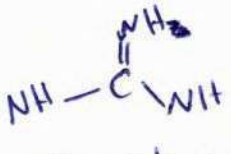

benzen

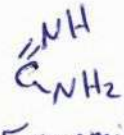

naphtaline

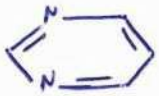

anthrecine


napthacin


Pyrrolidine


Guanidine


Formamidine


Pyrimidine


Pyridine

Benzoic Acid

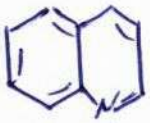
salicylic Acid

SO_2NH
sulfomanyl

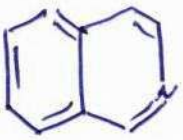
$N=N$
Diazo

Pyrido[2,3-d]pyrimidine

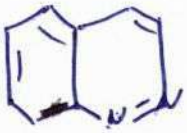
~~naphthalene~~
naphthaline



Quinoline

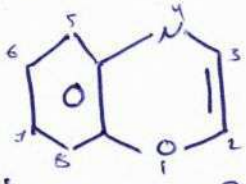


isoquinoline

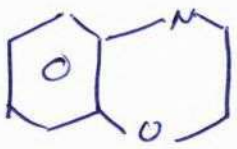


Cinnoline

1,8 naphtridine



1,4 benzoxazine



1,4 dihydrobenzoxazine

Sci name	Trade name
Penicilline G	Bepen®
Penicillin V	Rafapen®
Ampicillin	Ampen , Peniprim , Bradacillin , Ampipharm
Amoxicillin	moxypen , Amoxicare , Amoxim , Amoxipharm , Amoxitid , Hiconcil
Amoxicillin + Clavulanic acid	clamoxin , ogmine , Augmantine , Amoxiclave , Betamox , Curan
Ampicillin + sulbactam	Sulbampicillin , Docuid.
Cloxacilline	cloxan , Loxavit , ore bind
cloxacilline + Ampicilline	Mega care , Megnacilline
cloxacilline + Amoxicilline	cloxabactorle.
1st cephalothine	Kefline®
cephazoline	cephamezine®
cephalexine	cephalex , Jeflex , keflex , cephaline , cephacare.
cephadroxin	cephadrox
cepharadine	cephadrine , cephadrine fort , veloset
cephaclor	ceclar
2nd cephuroxime	Zinnate , Zinnex , Zinacef.
cephoxitine	Mefoxine
3rd cephotaxime	claforan
cephotriaxone	Rocephine , unacef
cephixime	supran
cephaperazone	cephobide
cephotazidim	Fortum , Fortax.

sulfamethoxazole + Trimeloprim	Bactil, sulfaprim, resprim, sulfatrim
NorFloxacine	Apirol
Cipro Floxacine	Ciprocare, ciprogis, ciprocine, Floxine
oFloxacine	Travid, Tracine, uTracine.
Tetracycline	Brimocycline
Doxycycline	Doxal, Doxyline, Doxypharm, Doxytrim, Doxacine, Vibramyc
Minocycline	Minocycline, Minocyne