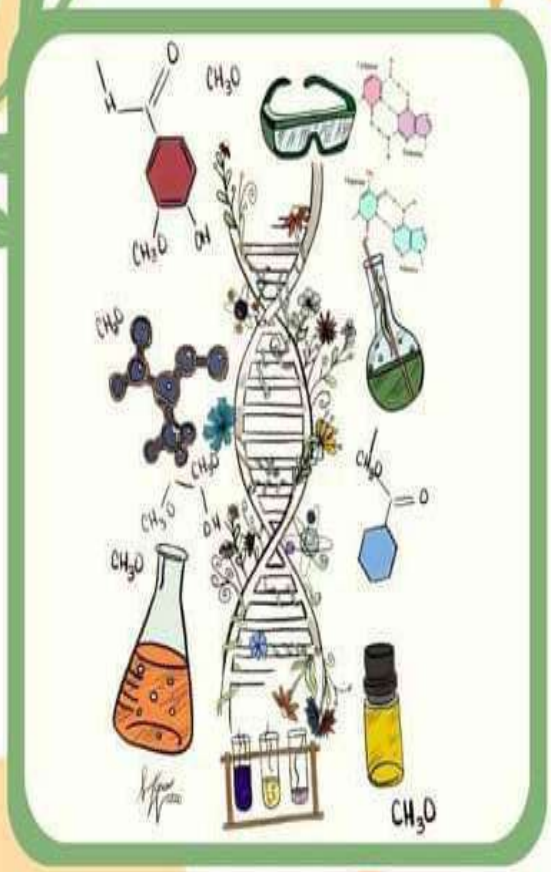
تفريغ عقاقير



اسم الموضوع: تفريغ CH_{12}

Part 2

إعداد الصيدلاني/ـة: شيماء المسلموني

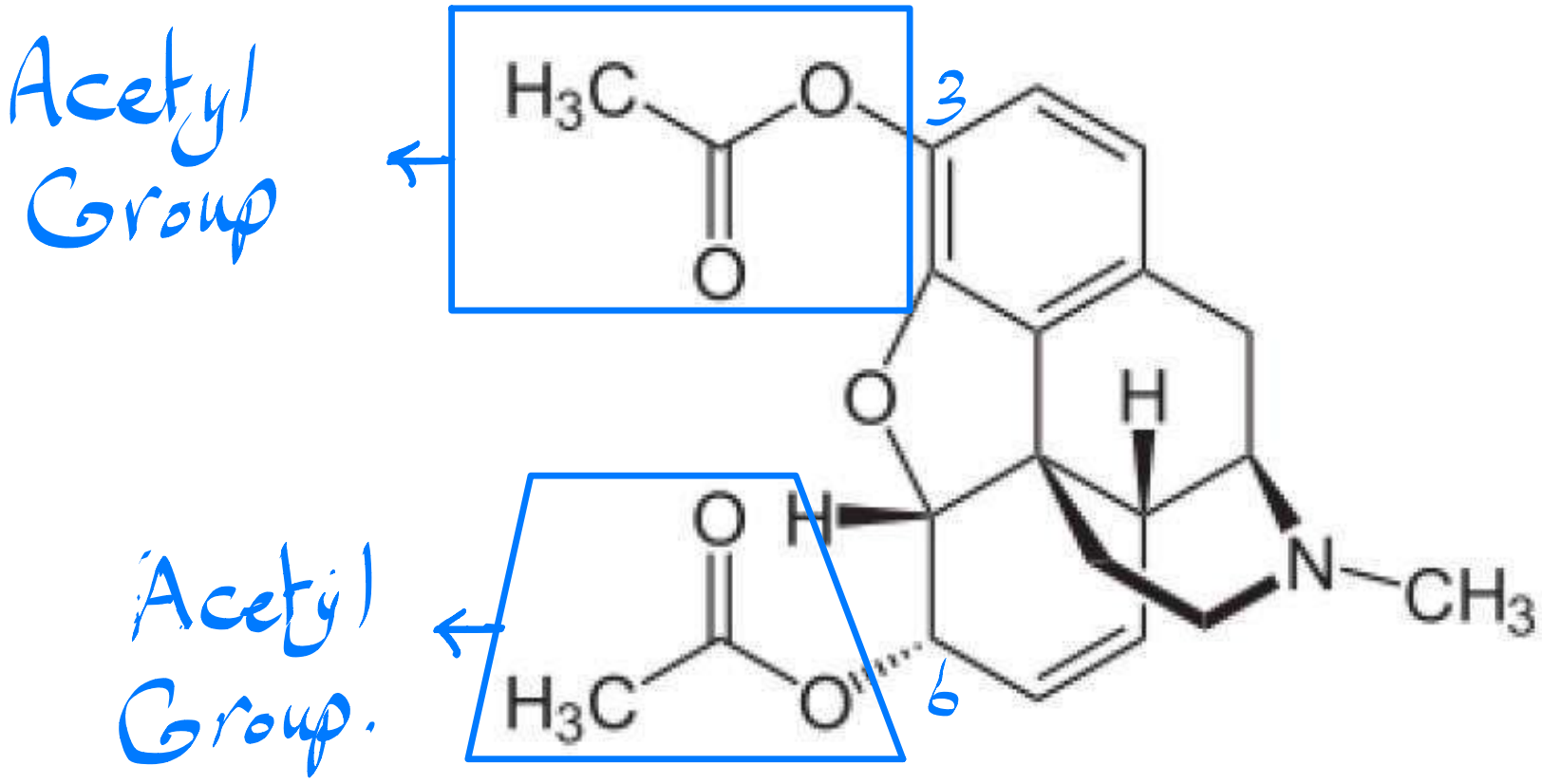
Seul Academy

لجان الدفعات

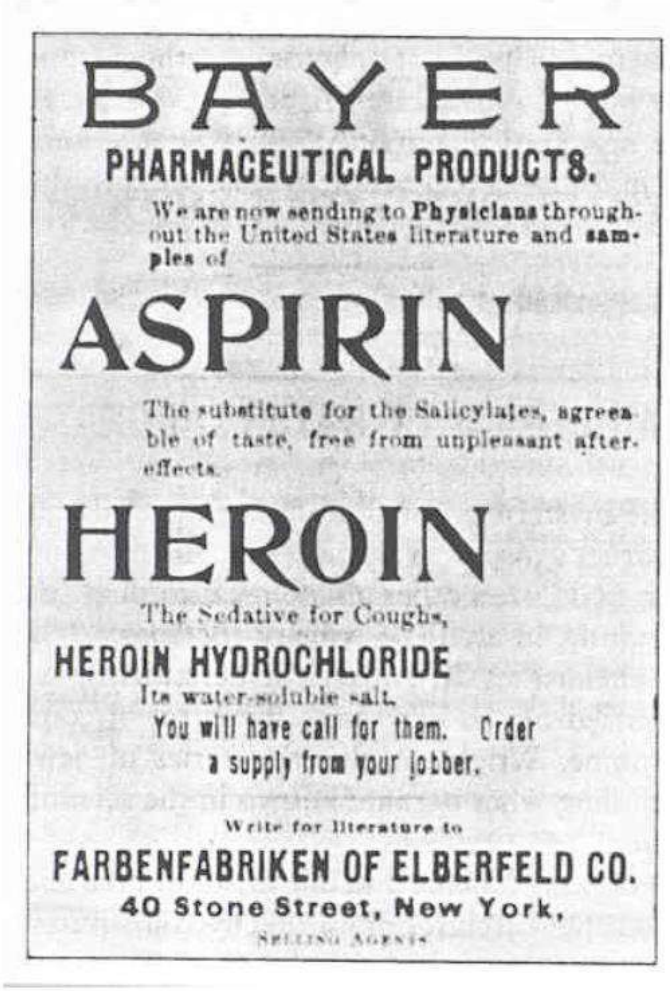
Heroin

- (it's also known as di acetyl morphine)
- This compound isn't natural occurring, it's highly addictive analgesic and hypnotic semi synthetic derivative. Heroin cause euphoria (عدم الاحساس بالمحيط الخارجي)
- - It's obtain from morphine but the difference between them is in 2 hydroxyl gp in morphine while in heroine 2 hydroxyl in morphine gps are replaced with acetate function gps (named so as diacetyl bond).
- Morphine too is addicting from the first dose.
- Heroin is more addictive and each time the body need a higher dose than the previous one (has tolerance)

Heroin ← عبارة عن Morphine وعملوا (+Acetyl group) Acetylation عليه



Derivates of Natural Products



Addiction and Dependence

الإدمان

- Drug addiction is a condition in which an individual has lost the power of self-control with reference to a drug and abuses the drug to such an extent that the individual, society, or both are harmed.

التعوّد

- Dependence refers to a state resulting from habitual use of a drug, where negative physical withdrawal symptoms result from abrupt discontinuation.

التوقف المفاجئ عن استخدام المادة

ناس بتصرفه للعلاج فقط ← ناس تستخدمه عشان السعادة ← مثل Tramadol

The key is that addiction results when the reward pathways in the brain are stimulated by drug use thereby causing dependence due at least in part to psychological reasons.

معنى الجملة أنه الإدمان يحصل وله علاقة بالأسباب النفسية لاستخدام المريض للدواء.

- Dependence implies need of the drug to avoid withdrawal symptoms, not to gain a reward response in all cases. Palliative care patients do not experience a “high” when taking an opioid and are therefore not considered to be addicted.

Mechanism of Dependence and Addiction

- Dependence occurs when, after a constant supply of the opiate, the brain shows adaptation, or changes in its circuitry. When that drug is taken away, neurons that have been inhibited start pumping out neurotransmitters again. This imbalance of chemicals in the brain interacts with the nervous system to produce the classic opiate withdrawal symptoms: nausea, muscle spasms, cramps, anxiety, fever, diarrhea.

Tolerance

كل مرة المدمن يحتاج جرعات أكبر من اللي قبلها.

- Tolerance, describes the need for a drug user to administer larger and larger doses of the drug to achieve the same psychoactive effect.
- When the body's chemical equilibrium is upset, as in habitual drug-taking, the body sets up oppositional processes to restore itself. More of the drug is needed to overcome these efficient corrective processes.
- While considerable debate exists about the mechanisms of opioid tolerance, two factors have been isolated with a degree of certainty.

مزهم

1. Receptor Downregulation- Opioid receptors in the body are actively reduced due to overexposure to opioids. This can also have an effect on endogenous opioid peptide function (i.e. regular functioning of endorphins)

يقلل عددهم

2. Antiopiates- Chemicals like neuropeptide FF, orphanin FQ/nociceptin, and Tyr-W-MIF-1 have all been found to block the function of opioids. This activity is due to the fact that these drugs can block g-protein activity.

معاد بفرزها جسم المدمن بتزيد مع حاجته للهيروين كل مرة.

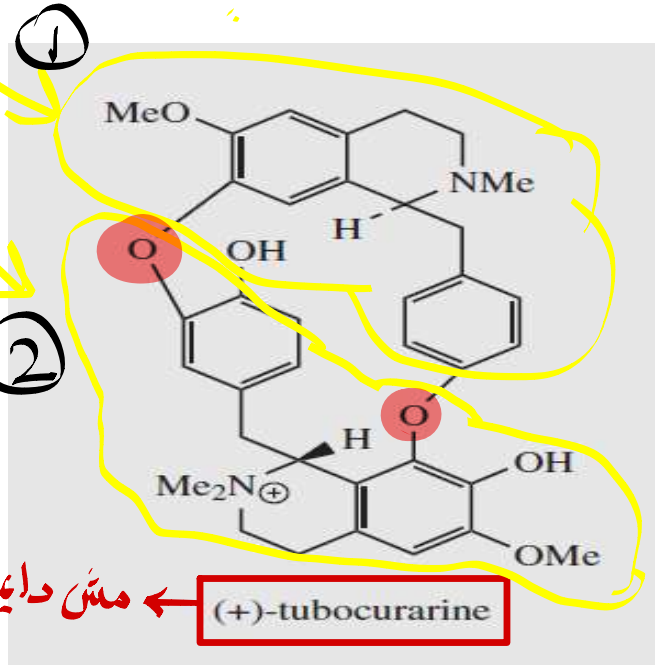
(تشنج العضلات) Spasm غالباً يصير ← Ach Receptors

- Nicotinic ← له على العضلات الهيكلية (Skeletal)
- Muscarinic ← له على العضلات الملساء اللاإرادية

هاي Receptors لما انتشلت بصير ارتخاء بالعضلات

Dimeric products of benzyltetrahydroisoquinoline alkaloids

- Two O are The Bridges Between those two ← Benzyltetrahydroisoquinoline

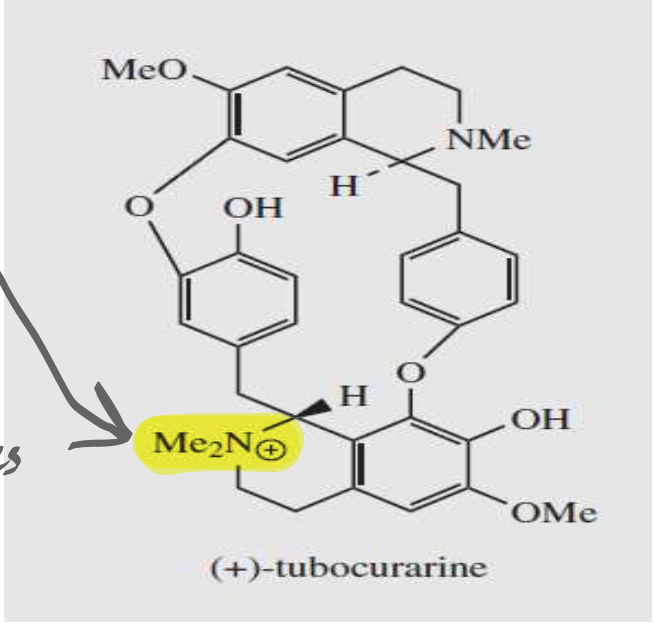


(+)-tubocurarine ← منش دايمًا موجود

Dimeric products of benzyltetrahydroisoquinoline alkaloids

- **D-tubocurarine** is a very interesting compound , although it was discovered long time before the final structure of it was found only in the late 1960s . It is **water soluble** , quaternary ammonium salt and it is a **dimeric compound**, (possessing **two nitrogen** in its structure) .

When we look at the structure of the D-tubocurarine we will recognize the two monomeric parts , we can see two groups of these (the benzyl group , the hydroxyl group and the tetrahydroisoquinoline group) . Both monomeric parts are linked via ether bridges or O Bridges The ether bridges are products of the oxidative coupling process .



(+)-tubocurarine

Dimeric products of benzyltetrahydroisoquinoline alkaloids

- D-tubocurarine is a dimmer of two N-methylcoclaurine one (S) one (R)
- it is a natural compound used widely as a muscle relaxant in many abdomen and thorax surgeries as well as in treatment of Parkinson disease , multiple sclerosis and in tetanus .
- Now there are many synthetic analogues which are currently used in different surgeries . These compounds can be ultra short acting (up to 10 minutes) , short acting (10- 20 minutes) , intermediate acting (up to 30 min) or long acting (up to two hours) depending on surgery .
- Upon toxicity they can effect of these drugs can be antagonized by artificial respiration or Anti-acetylcholinesterase drugs like physostigmine and neostigmine.

بسيطة

Anti Ach في حالات Overdose

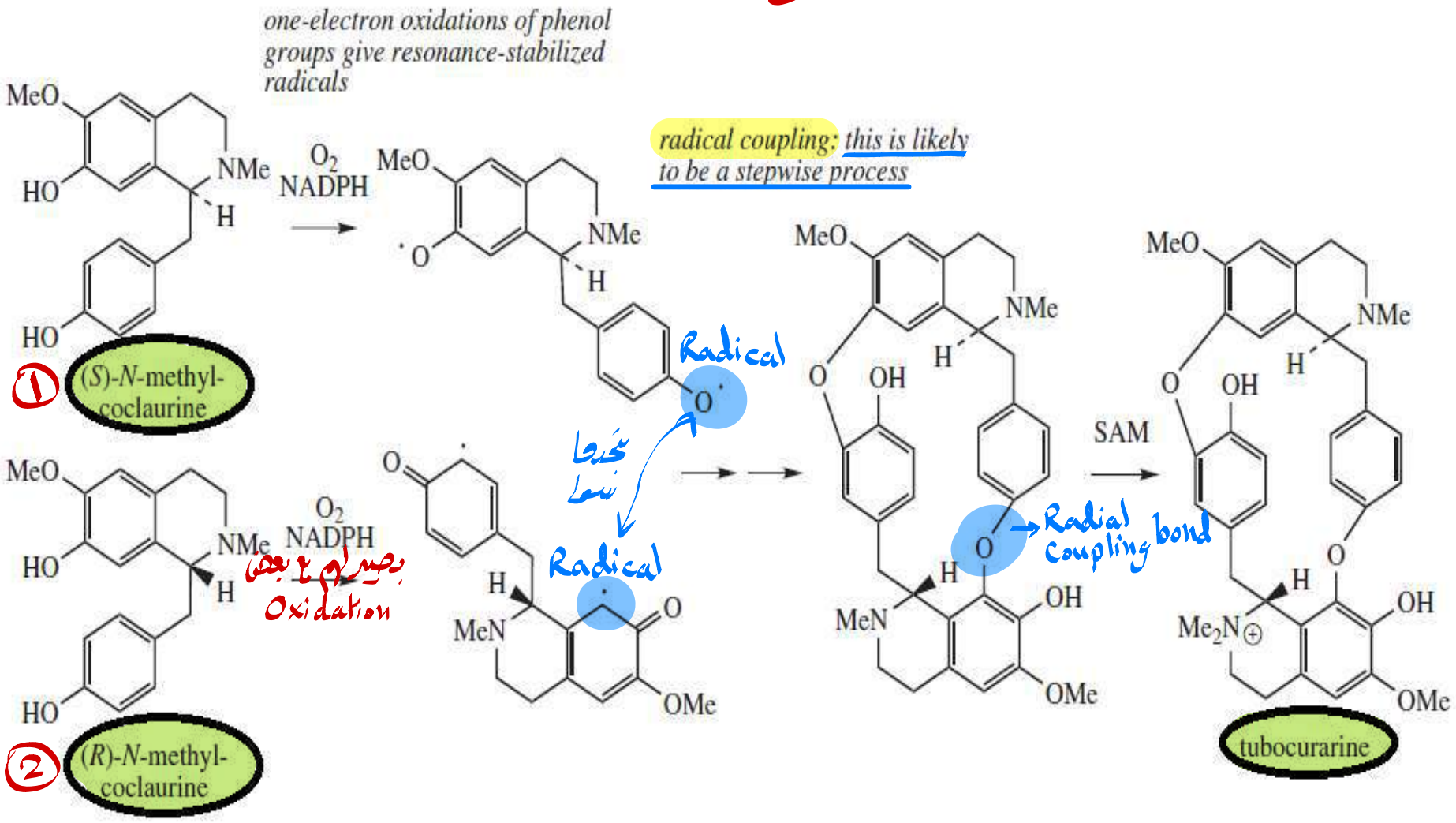
Ach estrase inhibitor بشكل مباشر Ach أعطيه ما بقدر Tubocurarine مثل

يعني لإني ما بقدر أعطيه Ach بمنع عن الاتصال تكسر Ach الموجود بالجسم

مادة مصنّعة ما بتكون بجسمنا بشكل طبيعي أبدًا.

Tubocurarine الطريقة اللي بتصنّع فيها النبتة

"Oxidative Coupling Process"



D-tubocurarine

- D-tubocurarine is not the only compound that possesses the activities that we have mentioned , other similar minor alkaloids which are found in the same plant that contains d-tubocurarine are found to have these activities too .

خلطة من عدة مواد اتخذتها القبائل قديمًا وفيها أكثر من 30 مادة

- ***Note*** → There are two different terms which you shouldn't mix between: **Curare** and **d-tubocurarine**

أحد المواد الموجودة في هذه الخلطة

- **Curare** is a collective term for the arrow poisons prepared by south American Indians and one of the compounds of these arrow poisons is d-tubocurarine , in addition to d-tubocurarine more than 30 different compounds were detected in the curare and they have the activities that we mentioned for the d-tubocurarine .

Nicotinic Receptor Antagonist

Curare :

- Arrow poisons are prepared in Amazons by different tribes and each tribe was preparing its own arrow poisons based on the plants growing in their surroundings.
- Some of these tribes were using plants belonging to the family **Menispermaceae** , while other tribes which don't have Menispermaceae in their surroundings were using plants from the family **Loganiaceae** . Other tribes they have plants from the both families so they mix them all together .
- So basically we have three different types of curare (curare from Menispermaceae , from Loganiaceae or from the two families) and all of them are used for the same purpose (for hunting or killing the animals) .

- In the case of Menispermaceae curare, the main tree which is used is the *Chondrodendron tomentosum*, the bark is scraped off , boiled with water and then they add some other plant materials to make the final product some sticky material so that it will stick to the arrows or darts . The main constituent (arrow poison) of this plant is d-tubocurarine .
- In the case of the Loganiaceae, the plants used are of the genus *Strychnos* ,the toxic ingredient in Strychnos is the toxipherons Not the strychnine . Toxipherons are Indole alkaloids not benzyl-tetrahydroisoquinoline alkaloids so we will talk about them later .
- In the case where there is a mixture of the two families , we will find the two poisons , d-tubocurarine and toxipherons .

Menispermaceae family with the main constituent d-tubocurarine :

- *Curare is only effective if it enters the bloodstream, it is inactive when given oraly.
- The potency of curare as an arrow poison is variable because of the variability of ingredients in it (e.g the extract which is obtained in summer will differ in its ingredients from the extract obtained in winter) and consequently the potency needs testing

شلل

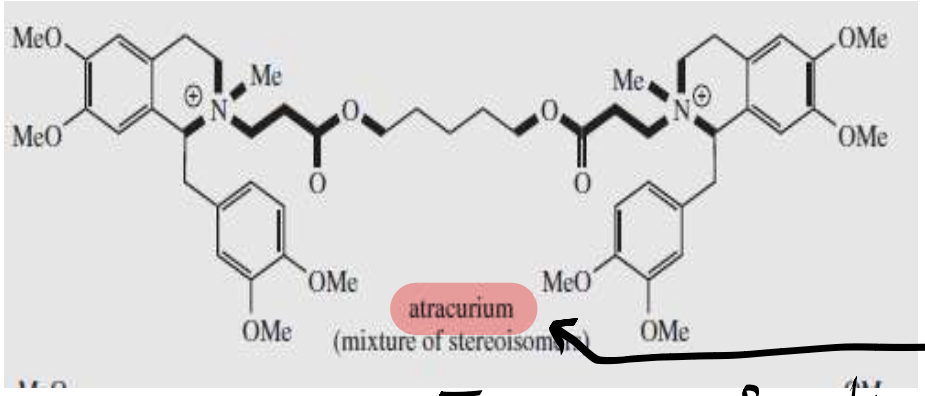
- In medicine they are utilized in the paralysis and relaxation of the voluntary muscles , muscles of the respiration will mainly stop working .

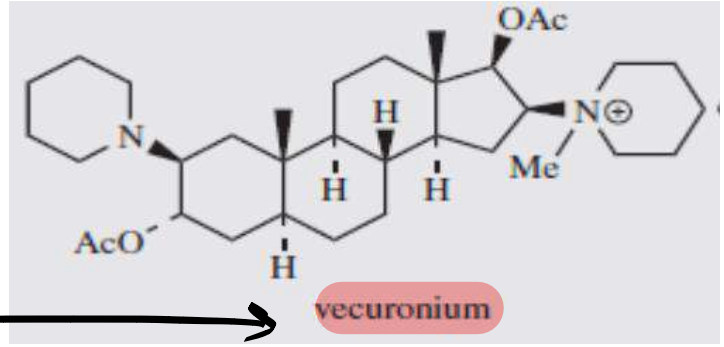
استرخاء العضلات

- We use them in Parkinson, tetanus, abdomen and tonsillectomy surgeries and the effect is counteracted by artificial respiration and Anti-acetylcholinesterase agents as we mentioned previously .

- Tubocurarine and the heterocyclic analogues are termed non-depolarizing or competitive muscle relaxants; their action may be reversed with anticholinesterase agents such as neostigmine that increase acetylcholine concentration at the neuromuscular junction by inhibiting its breakdown.

- Then synthesized analogues with heterocyclic structures like (**Atracurium**) it's like tubocurarine possessing benzyl tetrahydroisoquinoline, di-quaternary (base), atracurium is occurring as mixture of stereoisomers, later on separated in to pure isomers and Cis is the one used, the two quaternary N here separated by 13 atoms
- So they found that it's not obligatory that the distance in a physiological solution is ten atoms (14 angstroms) since 10 and 16 atoms show similar activity, also not necessary that the di-quaternary N to be separated by straight chain it may separated by a steroidal nucleus like in (**Vecuronium**) which is a **Mono-quaternary** ammonium salt where two N separated by steroidal nucleus.





[Duration of action] تختلفوا فقط في

Radix Ipecacuanha

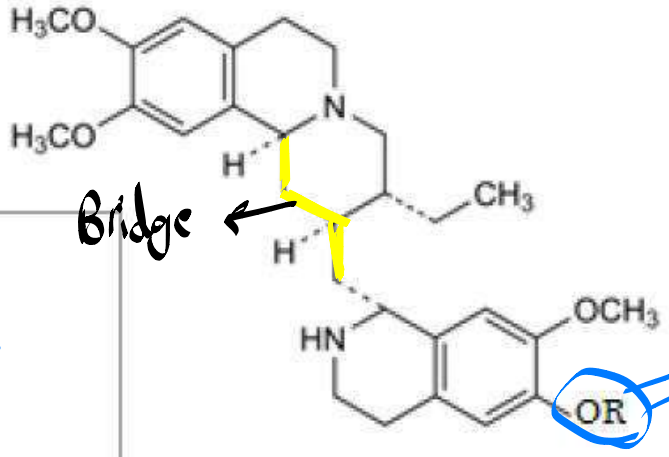
Ipecacuanha Root عرق الذهب

- We will talk about ipecac root and different constituents o ipecac root, definitely that ipecac syrup is very well known from your pharmacy practice, its obligatory part in poisoning antidote because it's emetic properties also different expectorants contains ipecac extract, so it is a plant which has quit different utilization depending on the **doses** and depending on the **purification** of the major constituents.
- Ipecac extract **Major** constituents are **cephaeline** and **emetine.**
- Ipecac extract **Minor** constituents are **psychotrine** and **O-methylpsychotrine.**

كان يعتقد انه سبب التقيؤ لكن طلع العكس .

Ipecacuanha has a group of alkaloids { most importantly **emetine** and **cephaline**} .It was believed that emetine is responsible for vomiting , but later its found that emetine has very weak emetic property and the majority of vomiting effect comes from cephaline .

emetic properties هو المسؤول فعلياً عن



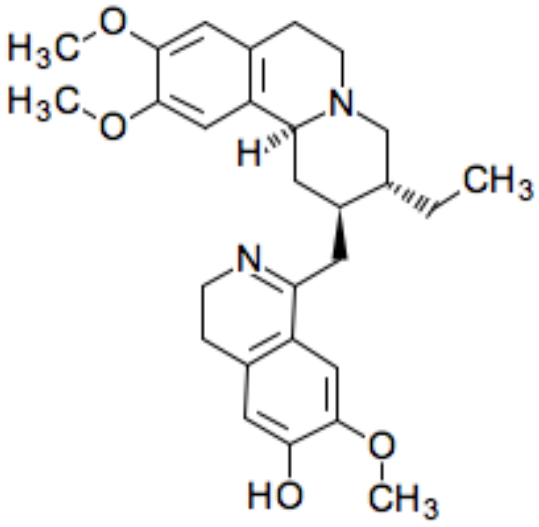
Bridge

We have 2 isoquinoline molecules attached to each other by ethyl group.

R:CH3 => Emetine

R:H => Cephaline

Emetine



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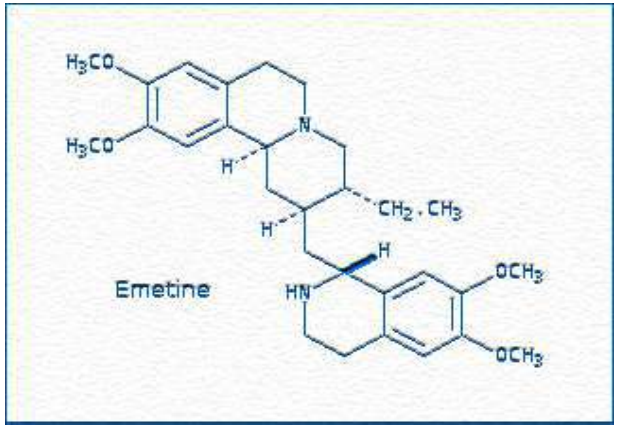
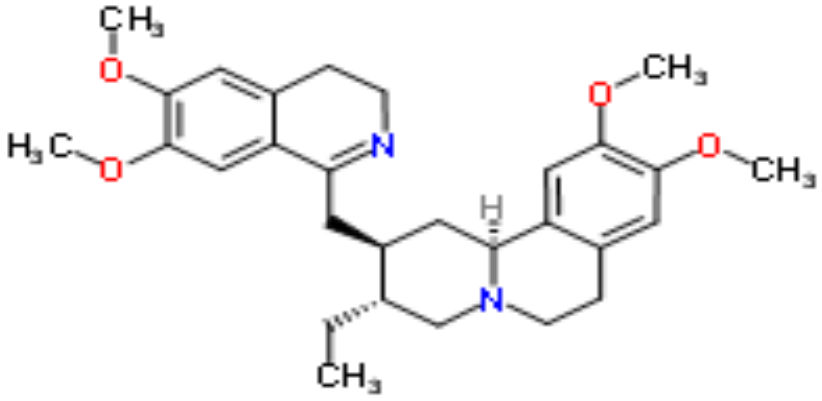


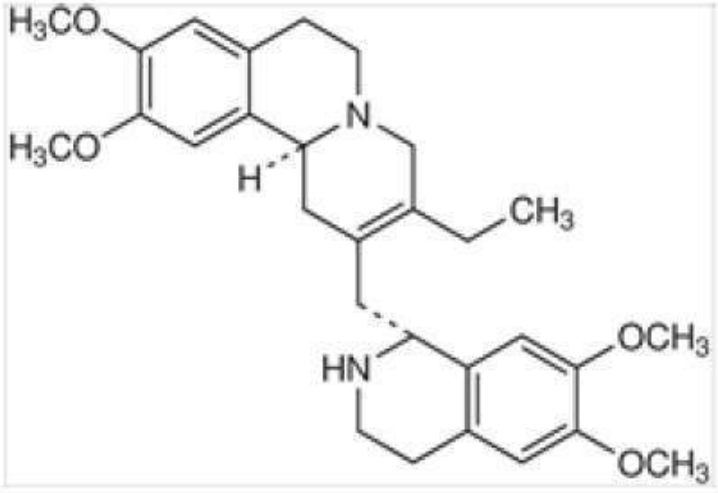
Psychotrine:



موجودين أيضًا بالنبتة
لكن بشكل أقل .

O-methylpsychotrine

(emetine) prevents the synthesis of proteins in microorganisms at the translocation stage and thus death, but it's too toxic for therapeutic use , instead we use the dehydro form .



بصنعه بطريقتين

Dehydro emetine

- Scratch
- removing 2H

completely synthetic compound and sometimes we can use emetine to produce it by removing two H's.

- It is a South American plant, main countries produce it is Brazil, the major species of this plant is Cepahalis *ipecacuanha* the emetine to cephaeline ratio might be 2:1 where as in species Cepahalis *acuminate* ratio ranges from about 1:2 to 1:1. Dehydro emetine المخلمات
- Emetine also used in: amebic dysentery, expectorant and antiviral.*
- Ipecac extract: at high doses as emetic, at small doses as expectorant.*
- Ipecac more recently mixed with powdered opium to give **Dover's powder** where the ipecac content functioned as a diaphoretic (promote perspiration).

Opioids

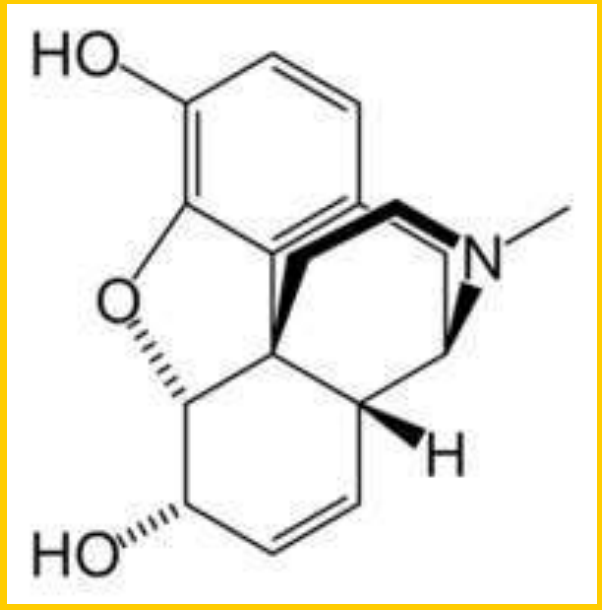
Addiction and Treatments

Shariq Chudhri
Medicinal Chemistry
Dr. John Buynak

Opioid Addiction and Treatments- Overview

- What are Opioids?
- Addiction and Dependence
- Mechanism of Dependence
- Tolerance
- Treating Addiction
  - Cold Turkey Approach
  - Traditional Drug Treatment
  - Rapid Detoxification
- Conclusions and Future Avenues For Research

What are Opioids? (A quick review!)



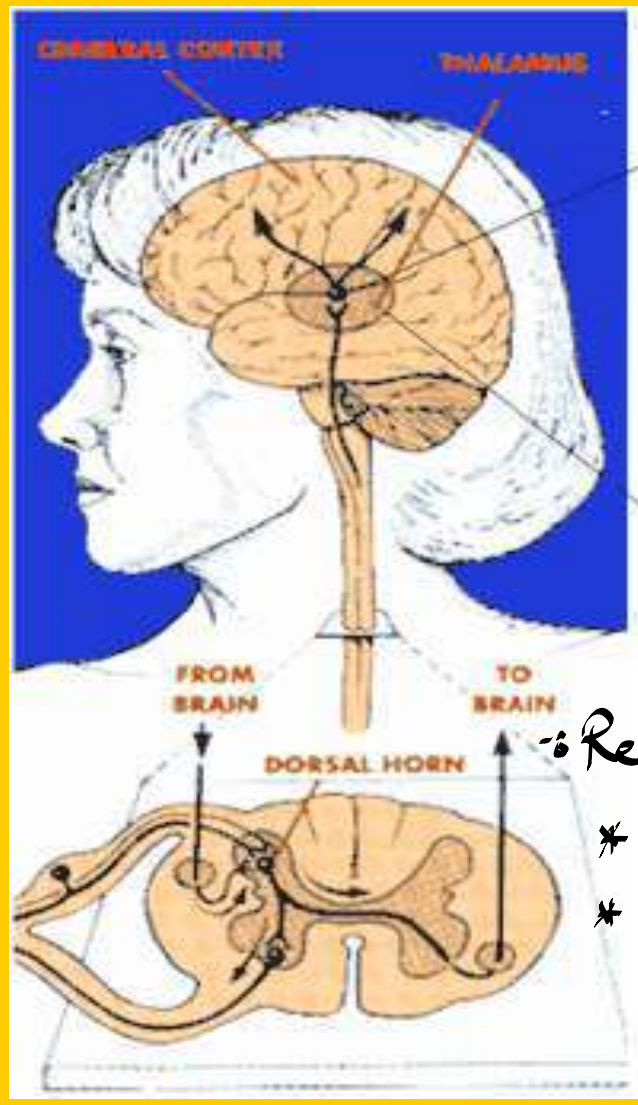
Morphine

- Opioids are a class of drugs that act primarily on the body's opioid receptors.
- Opioids are often referred to as narcotics.
- They act by blocking μ, κ, σ and possibly δ receptor classes.
- Most opioid receptors are found in the central nervous system and in the gastrointestinal tract.
- Opioids are used primarily for their analgesic effects but also for their cough suppressant properties.

Diarrhea الأعراض الإسهابية ومن Constipation الجانبية

Blocking of the Opioid G Receptor (Opioid Agonists)

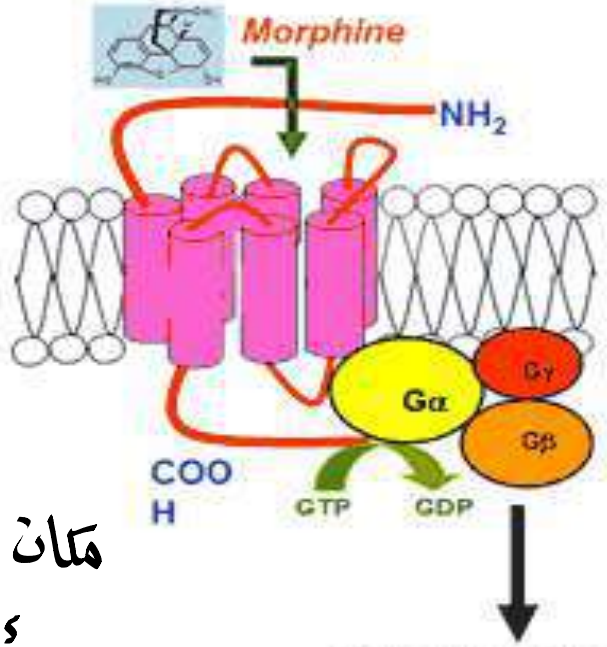
7 Trans membrane or G-Protein coupled



الدماغ بتأثر مباشرة

Mu Opioid Receptor:

located on the membrane of neuronal cells



Affect the brain reward/pain system

- Receptors مكان
  - * Thalamus
  - * Cortical Cortex

Addiction and Dependence

- Drug addiction is a condition in which an individual has lost the power of self-control with reference to a drug and abuses the drug to such an extent that the individual, society, or both are harmed.
- Dependence refers to a state resulting from habitual use of a drug, where negative physical withdrawal symptoms result from abrupt discontinuation.
- The key is that addiction results when the reward pathways in the brain are stimulated by drug use thereby causing dependence due at least in part to psychological reasons.
- Dependence implies need of the drug to avoid withdrawal symptoms, not to gain a reward response in all cases. Palliative care patients do not experience a “high” when taking an opioid and are therefore not considered to be addicted.

Mechanism of Dependence and Addiction

- Dependence occurs when, after a constant supply of the opiate, the brain shows adaptation, or changes in its circuitry. When that drug is taken away, neurons that have been inhibited start pumping out neurotransmitters again. This imbalance of chemicals in the brain interacts with the nervous system to produce the classic opiate withdrawal symptoms: nausea, muscle spasms, cramps, anxiety, fever, diarrhea.

دورة الإدمان

عدم توازن في المواد الكيميائية داخل الدماغ

الأعراض الانسحابية التي تظهر على المريض لتوقف عن التعاطي ه

Tolerance

- Tolerance, describes the need for a drug user to administer larger and larger doses of the drug to achieve the same psychoactive effect.
- When the body's chemical equilibrium is upset, as in habitual drug-taking, the body sets up oppositional processes to restore itself. More of the drug is needed to overcome these efficient corrective processes.
- While considerable debate exists about the mechanisms of opioid tolerance, two factors have been isolated with a degree of certainty.

1. Receptor Downregulation- Opioid receptors in the body are actively reduced due to overexposure to opioids. This can also have an effect on endogenous opioid peptide function (i.e. regular functioning of endorphins)
2. Antiopiates- Chemicals like neuropeptide FF, orphanin FQ/nociceptin, and Tyr-W-MIF-1 have all been found to block the function of opioids. This activity is due to the fact that these drugs can block g-protein activity.

Treatments

- Several treatments and treatment strategies exist for opioid addiction. طرق عديدة للتخلص من الإدمان

1. The Cold Turkey Approach
2. Traditional Opioid Drug Treatment → Methadone أدوية تعالج هذا الإدمان
3. Rapid Detoxification

→ يتوقف Overdose في حالات Respiratory Depression الجهاز التنفسي ويصير Naloxone مثل Opioid Antagonists يتم إسعافه

The Cold Turkey Method

- Quitting opioid use cold turkey after dependence has developed has several drawbacks but also some advantages.
- Of course, this is the cheapest method of ending dependence. This body, however, is put through a significant amount of stress during the "withdrawal" period.
- Death or seizures almost never result from opioid withdrawal unless the amount of opioid being withdrawn was extremely large. These events are more likely to occur during withdrawal from barbiturates or benzodiazepines.

The Cold Turkey Method- Withdrawal Symptoms

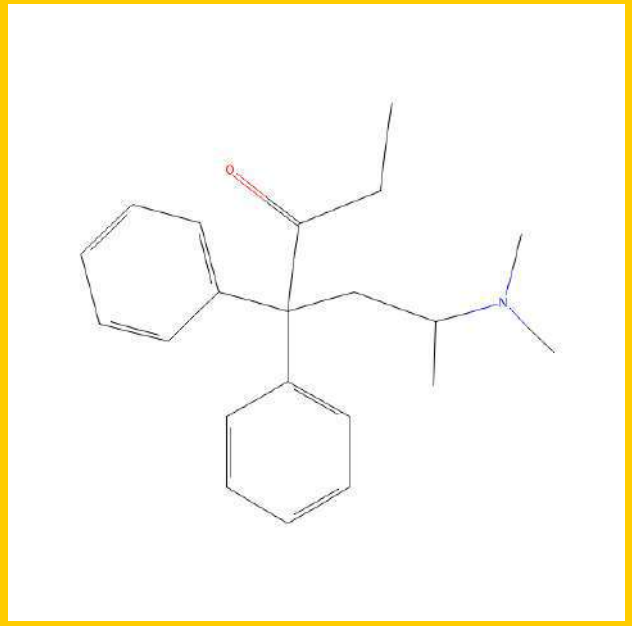
- About eight to twelve hours after the last heroin use, an addict's eyes begin to tear and he/she starts to experience flu-like symptoms: sneezing, weakness, depression, muscle cramps, nausea, vomiting, diarrhea. The symptoms increase in severity over two to three days.
- Within a week to 10 days the illness is over.
- The phrase 'cold turkey' probably comes from the appearance of goose bumps all over the body, which resembles a plucked turkey. Muscle spasms in the legs produce kicking movements, and this may be the derivation of the expression 'kick the habit.'

Traditional Drug Based Treatments

- The primary method of treating and managing opioid addiction and dependence has been with the use of other opioid drugs.
- These replacement drugs function to essentially wean the user off of opioid use.
- Most of these drugs have withdrawal symptoms lighter than those of the abused opioid (heroin, Oxycontin, morphine, etc…)

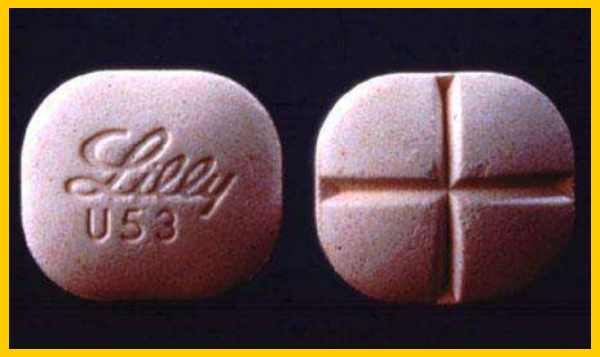
Traditional Drug Based Treatments- Methadone

- A synthetic opioid, used medically as an analgesic and in the treatment of narcotic addiction.
- Although chemically unlike morphine or heroin, methadone also acts on the opioid receptors and thus produces many of the same effects. Chemically, methadone is the simplest of the opioids.
- Methadone has a slow metabolism and very high lipid solubility, making it longer lasting than morphine-based drugs. Methadone has a typical half-life of 15 to 60 hours, in rare cases up to 190 hours. permitting the administration only once a day in heroin detoxification and maintenance programs.
- Methadone has traditionally been provided to the addiction population in a highly regulated methadone clinic, generally associated with an outpatient department of a hospital.
- Numerous clinics start addicts at 30mg and raise the dosage 10mg a day until the addict feels they are at a comfortable level of dosage.



Traditional Drug Based Treatments-

يعطى داخل المصحات فقط. ← Methadone, continued…



العرالمضفي له ضعف الهيروين [48 hr]

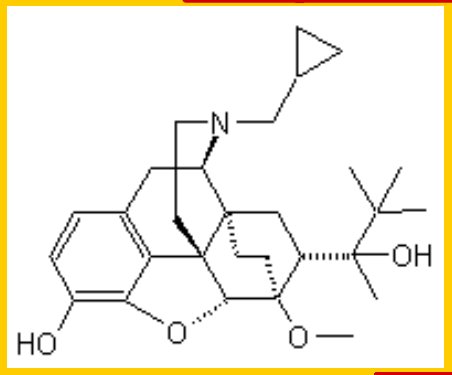
- At proper dosing, methadone usually reduces the appetite for and need to take heroin.
- However, most heroin addicts report more difficulty in quitting methadone than heroin.
- While there is much debate over the treatment schedule and duration required, treatment at a methadone maintenance clinic is intended to be for an indefinite duration.
- Many factors determine the treatment dose schedule, and some follow the philosophy that methadone maintenance treatment is not curative for heroin addiction.

Traditional Drug Based Treatments- Methadone- History

- Methadone/dolophine, was first synthesized in 1937 by German scientists Max Bockmühl and Gustav Ehrhart at IG Farben during their search for an analgesic that would be easier to use during surgery (and less potentially addictive, post-op) than morphine…)
- Methadone was introduced into the United States in 1947 by Eli Lilly and Company as an analgesic.
- A great deal of anecdotal evidence was available "on the street" that methadone might prove effective in treating heroin withdrawal and it had even been used in some hospitals. It was not until studies performed at the Rockefeller University in New York City by Professor Vincent Dole, along with Marie Nyswander and Mary Jeanne Kreek, that methadone was systematically studied as a potential substitution therapy.
- To date, methadone maintenance therapy has been the most systematically studied and most successful, and most politically polarizing, of any pharmacotherapy for the treatment of drug addiction patients.

اسم الشركة

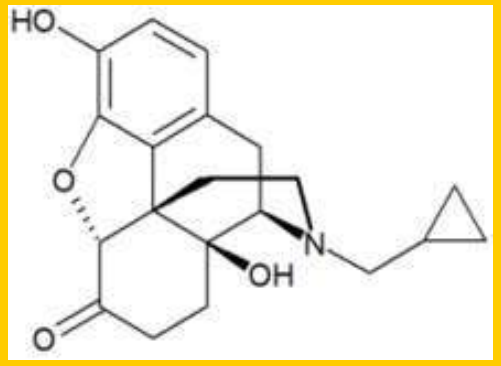
Traditional Drug Based Treatments- Buprenorphine

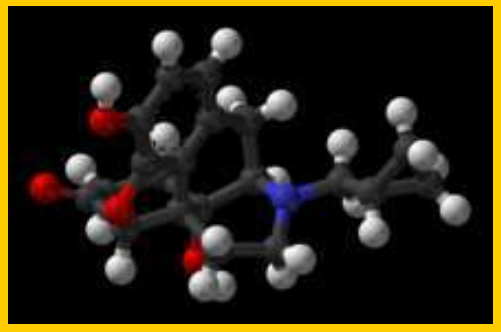


Methadone Like Drug
long half-life .
قد يُعطى خارج المصحة

- an opioid drug with partial agonist and antagonist actions.
- In October 2002, the FDA additionally approved Suboxone and Subutex, buprenorphine's high-dose sublingual pill preparations for opioid addiction.
- Belongs in the Schedule III category of drugs along with hydrocodone and anabolic steroids.
- Advantages to using buprenorphine over methadone include less restrictive availability. A patient can be prescribed the drug for self administration rather than having to receive their dose at a clinic.
- Also, it is thought that Buprenorphine has less severe withdrawal symptoms than methadone although the symptoms may last longer.

Traditional Drug Based Treatments- Naltrexone → over Dose Treatment.





- Naltrexone is an opioid receptor antagonist used primarily in the management of alcohol dependence and opioid dependence.
- Naltrexone, and its active metabolite 6-β-naltrexol, are competitive antagonists at μ- and κ-opioid receptors, and to a lesser extent at δ-opioid receptors. The plasma half-life of Naltrexone is about 4 h, for 6-β-naltrexol 13 h. The blockade of opioid receptors is the basis behind its action in the management of opioid dependence—it reversibly blocks or attenuates the effects of opioids.
- Because the drug is merely a receptor antagonist, it blocks the effects of opioids but does not reduce the craving for opioids.
- As such, Naltrexone is found to be effective mostly for treatment of people in stable social situations such as addicted health care professionals.
- Even so, compliance with treatments is a continuing problem for which implantable Naltrexone release devices are being increasingly used.

Rapid Detoxification

- A technique that aims to reduce the duration and intensity of opioid withdrawal by administering a combination of drugs while the patient is under general anesthesia.
- The process involves intubation and external ventilation of the patient coupled with the administration of opioid receptor antagonists (blockers).
- The most often used drugs are Naloxone and Naltrexone.
- Naloxone is a powerful Mu opioid receptor antagonist that is capable of rapidly displacing other opioids from the opioid receptors.
- As a result, massive withdrawal symptoms are triggered but are attenuated by the fact that the patient is under anesthesia.
- As with Naltrexone treatment alone, the Rapid Detoxification procedure cannot reduce the craving aspect of addiction and traditional drug based follow up treatments are necessary to manage the addiction although dependence has ended.

Patient undergoing Rapid Detox

Conclusions

- Opioid addictions is a serious issue that must be given more thought than at present in the scientific community as well as in politics.
- Current treatments are only partially successful in breaking the hold of addiction and dependence on the addict.
- Research can and must be done into other treatments and drugs that are more effective in not only reducing physical dependence and withdrawal symptoms but also in blocking addict's tendency to continue to crave the drug.

References

- http://opioids.com/tolerance/molecular.html
- http://en.wikipedia.org/wiki/Opioid
- http://pharmrev.aspetjournals.org/cgi/content/abstract/2/2/355
- http://en.wikipedia.org/wiki/Morphine
- http://en.wikipedia.org/wiki/Pethidine
- http://www.drug-addiction.com/opioids.htm
- http://opioids.com/tolerance/index.html- Opiate tolerance and dependence: receptors, G-proteins, and antiopiates by Harrison LM, Kastin AJ, Zadina JE Tulane University School of Medicine and Veterans Affairs Medical Center, New Orleans, LA 70112-1262, USA. *Peptides* 1998; 19(9):1603-30
- http://www.emedicine.com/emerg/topic643.htm
- http://en.wikipedia.org/wiki/Methadone
- http://en.wikipedia.org/wiki/Naltrexone

القسم الثّاني :-

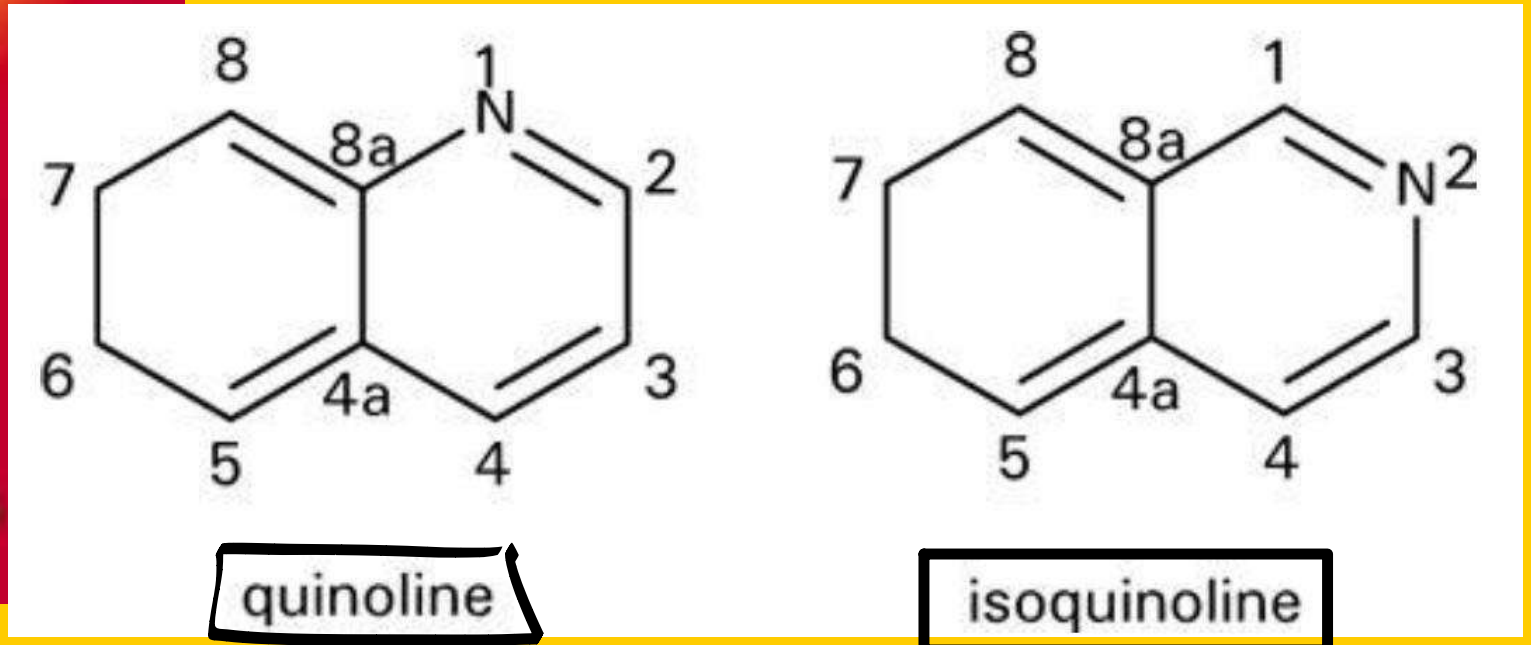
Quinoline alkaloids:

* الدكتورة حكت عنهم بأول فيديو بشكل بسيط وبس.

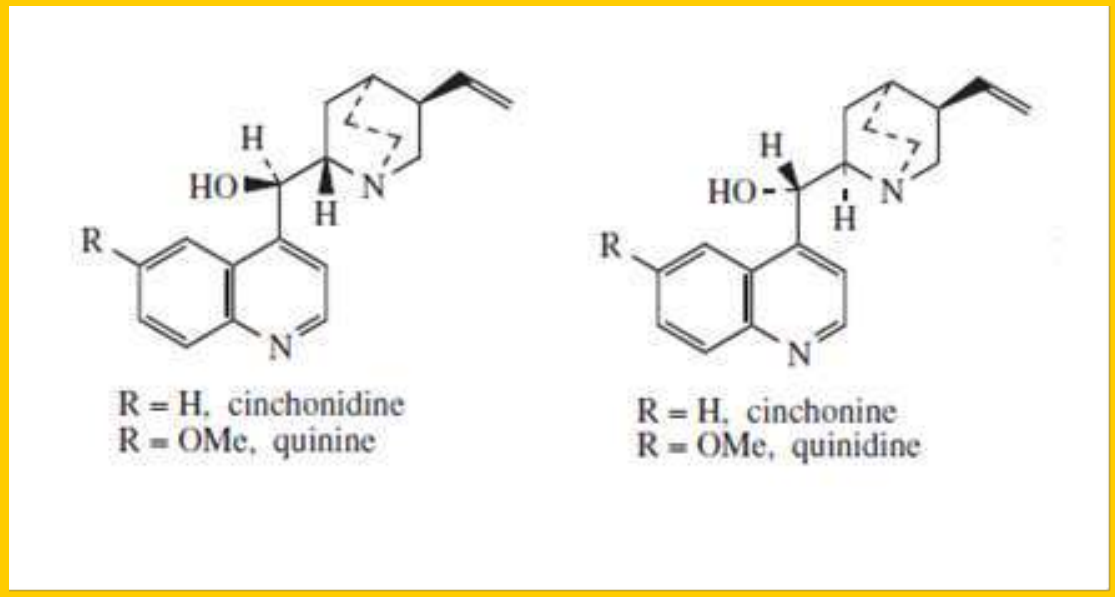
- The **most** important **quinoline** alkaloids that found in plant tissue is **cinchona alkaloids** (family: **Rubiaceae**) which in turn has **diastereoisomers**:

1. **Quinine**
2. **Quinidine**
3. **cinchonine**
4. **cinchonidine**

- We studied **isoquinoline** alkaloids that come form **tyrosine**, while **quinolines** come from **tryptophan**, the **difference** between quinoline and isoquinoline is the **nitrogen atom place**.
- **In Isoquinoline**: nitrogen atom on **C2**.
- In **Quinoline**: nitrogen atom on **C1**.



Cinchona (Rubiaceae)



- Quinine: C#8 is S and C#9 is R //// Quinidine C#8 is R and C#9 is S (quinine and quinidine have opposite stereochemistry)
- Quinine and cinchonidine are different in the presence of the methoxy group with same stereochemistry
- Quinidine and cinchonine also have the same stereochemistry and differ in the presence of methoxy group in quinidine.

- About a dozen different *Cinchona* species have been used as commercial sources, but the great variation in alkaloid content and the range of alkaloids present has favored cultivation of three main species, together with varieties, hybrids, and grafts. ***Cinchona succirubra*** provides what is called ‘red’ bark (alkaloid content 5–7%), ***Cinchona ledgeriana*** gives ‘brown’ bark (alkaloid content 5–14%), and ***Cinchona calisaya*** ‘yellow’ bark with an alkaloid content of 4–7%.

- We use **bark** of **stem** and **roots** of cinchona species:
- 1. **Cinchona calisaya**: it's **yellow** in color.
- 2. **Cinchona ledergiana:** it's **brown** in color (the **most** common), found in Africa esp. **South Africa** (تعتبر الدولة الأولى المصدّرة لهذا النبات .(
- **3. Cinchona succirubra or Cinchona pubescens:** it's **red** to **brown** in color**.**
- **NOTE: All** species have different percent of **indole** alkaloids (from **3-15%)**, and the **most** common species we use is **cinchona ledergiana.**

Cinchona-Red Cinchona Bark
(قشر الكينا)

- Cinchona succirubra
- Family: Rubiaceae.
- •**Medicinal Parts:** The medicinal part is the dried bark of 6- to 8-year-old trees.
- **Active constituents:** The bark contains alkaloids quinine; quinidine , cinchonine , cinchonidine and other alkaloids, quinamine, javanine.
- Tannin : cinchotannin.
- **Herbal Uses:**
- Quinine is **antimalarial.**
- Quinidine is **antiarrhythmic and cardiac tonic**, also used in psychic treatments. In large doses, it is sedative to CNS.
- **Quinine is toxic at over 3 g, quir**
- •Approved for:
- •**Loss of appetite**
- •Dyspeptic complaints.

- **Quinine** administered as free base or salts, continues to be used for treatment of multidrug-resistant malaria.
- larger amounts of the alkaloid are consumed in beverages. It is amusing to realize that gin was originally added to quinine to make the bitter antimalarial more palatable.
- Quinine also has a skeletal muscle relaxant effect with a mild curare-like action. It thus finds use in the prevention and treatment of nocturnal leg cramps, a painful condition affecting many individuals,especially the elderly.

- Until recently, **quinidine** was used to treat cardiac arrhymias. It inhibits fibrillation, the uncoordinated contraction of muscle fibres in the heart. However, it is rapidly absorbed by the gastrointestinal tract and overdose can be hazardous, leading to diastolic arrest. This has effectively decreased it's use.
- Quinidine, Cinchonine, and Cinchonidine also have antimalarial properties, but these alkaloids are not as effective as quinine. The cardiac effect makes quinidine unsuitable as an antimalarial. However, mixtures of total *Cinchona* alkaloids, even though low in quinine content, are acceptable antimalarial agents. This mixture, termed **Totaquine**, has served as a substitute for quinine during shortages.

- Cinchona and its alkaloids, particularly quinine, have been used for many years in the treatment of malaria, , it was used as safe analgesic up to the 50s or 60s "for common headache" with the safe drugs now its not used as analgesic anymore , Until recently, quinidine was used to treat cardiac arrhymias.
- Quinine is not a synthetic compound it's a natural compound , it's the secondary metabolite of the cinchona bark , that was first found in south America , it was cultivated world wide especially in china and the eastern part of asia .

- When this source was cut off by Japan in the Second World War, a range of synthetic antimalarial drugs was hastily produced as alternatives to quinine. Many of these compounds were based on the quinine structure. They took the quinine and substituted it with an amino group , a wide range of compounds was produced, chloroquine, primaquine, and mefloquine.
- **Primaquine** is exceptional in having an 8-aminoquinoline structure, whereas **chloroquine** and **mefloquine** retain the 4-substituted quinoline as in quinine.

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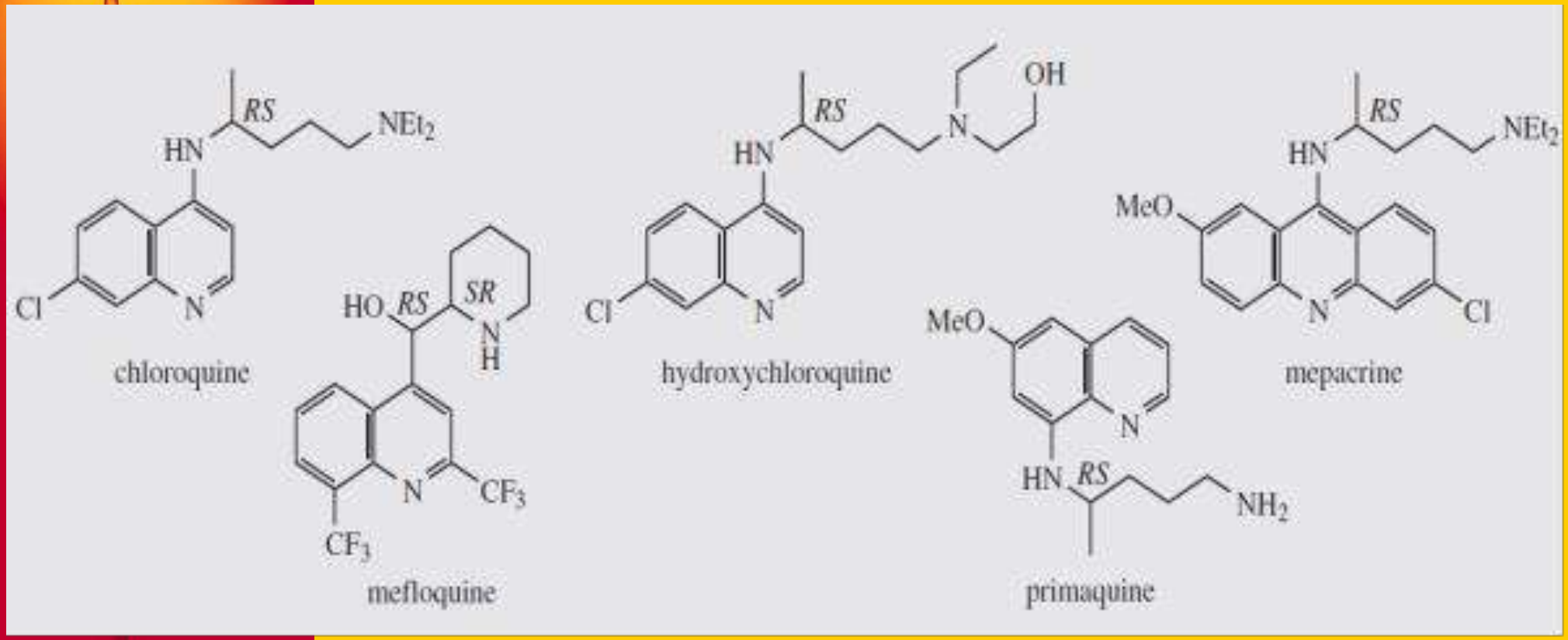
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- Long time use of quinines cause hearing impairment, particularly high-frequency loss. Although some studies suggest that this high-frequency hearing impairment is reversible, it has not been conclusively established whether such impairment is temporary or permanent .

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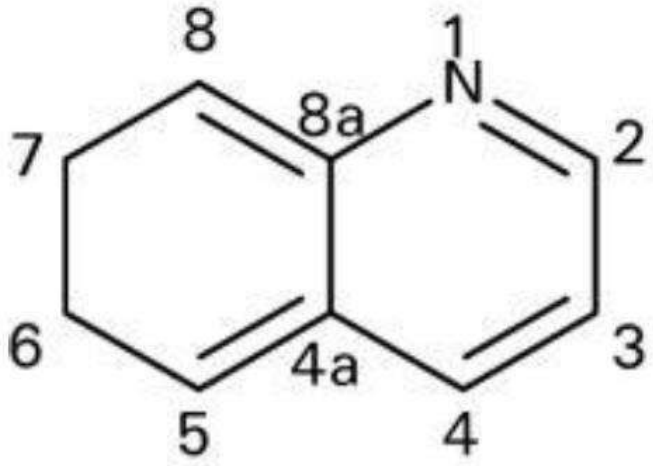
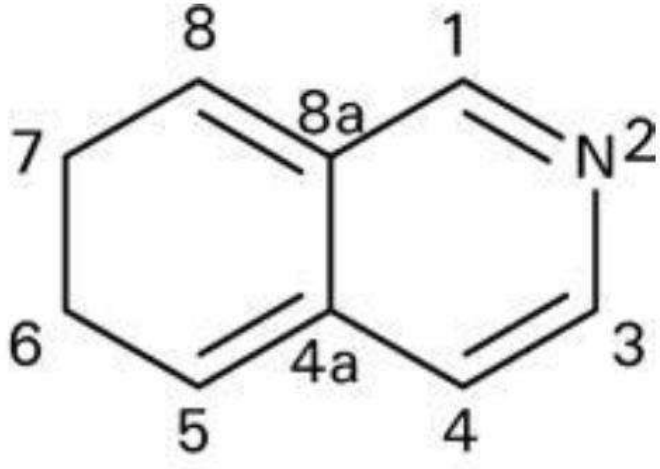


quinoline



isoquinoline

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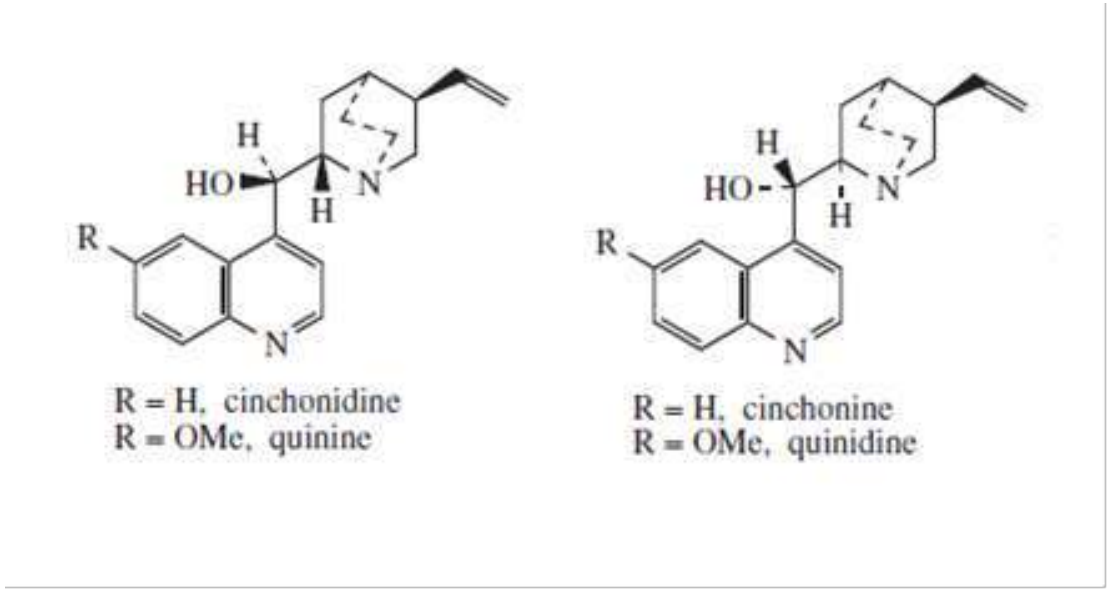

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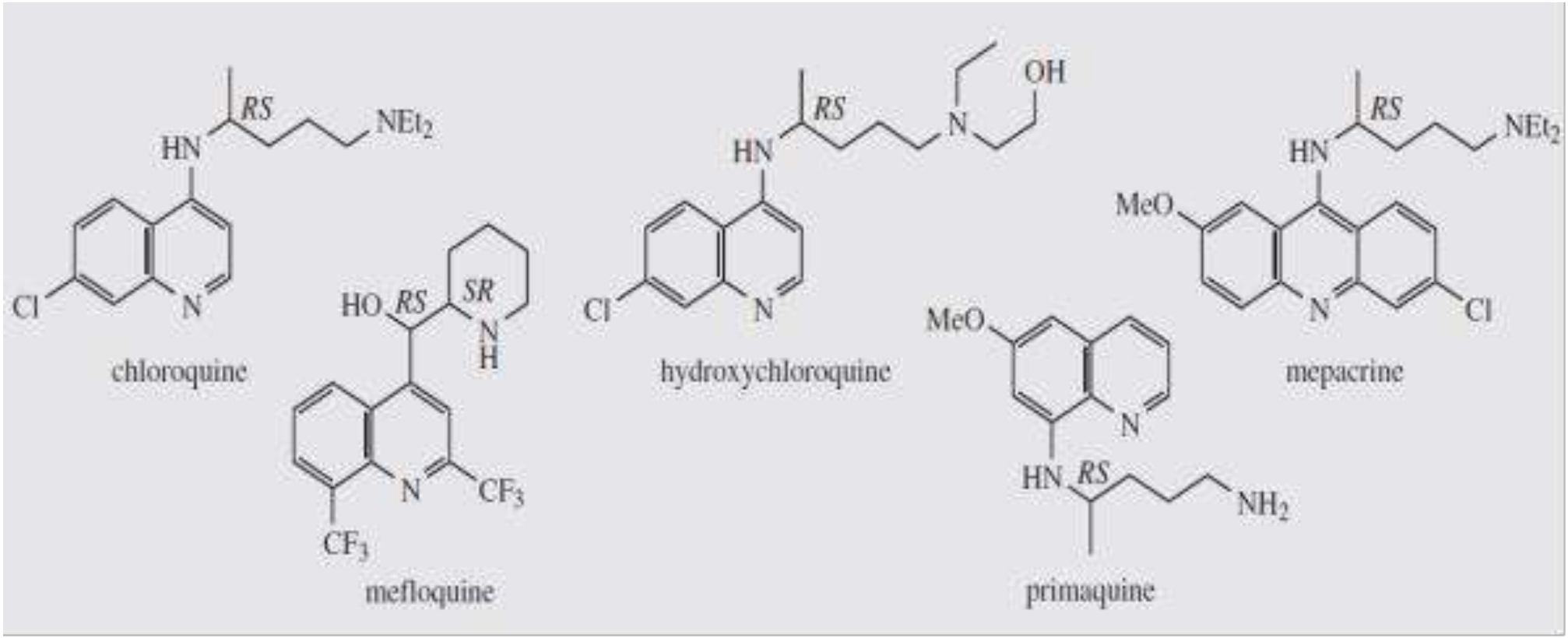
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