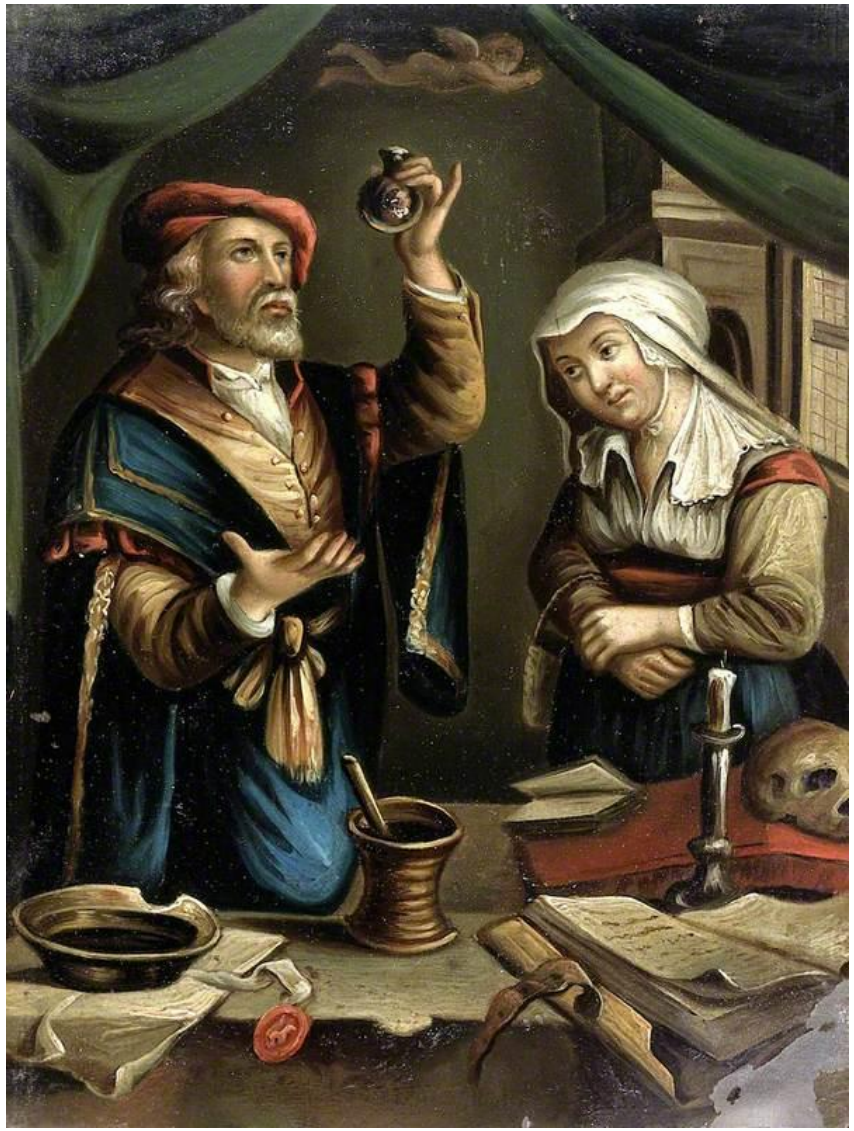
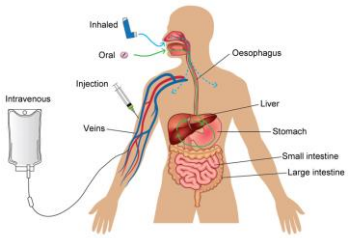
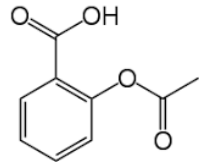
higher level international baccalaureate chemistry

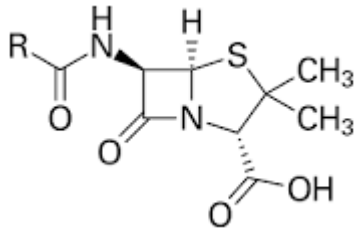


medicinal chemistry

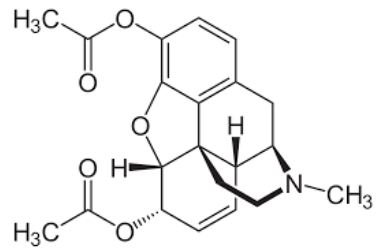


1. medicines and the human body



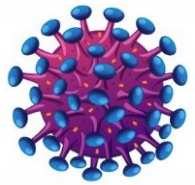


2. aspirin and penicillin



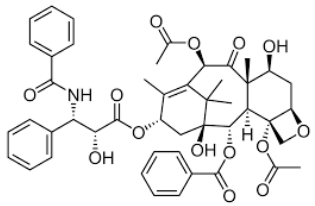
3. opiates

4. drugs and your stomach

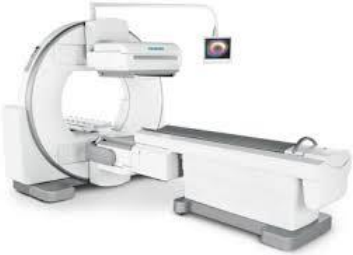


5. antivirals

6. drugs and the environment



7. taxol



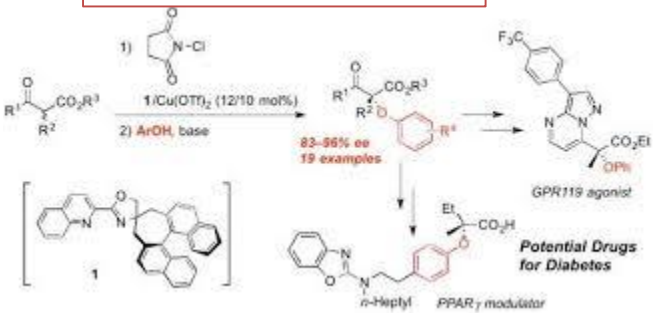
8. nuclear medicine

9. the drug making process

introduction to medicines

history

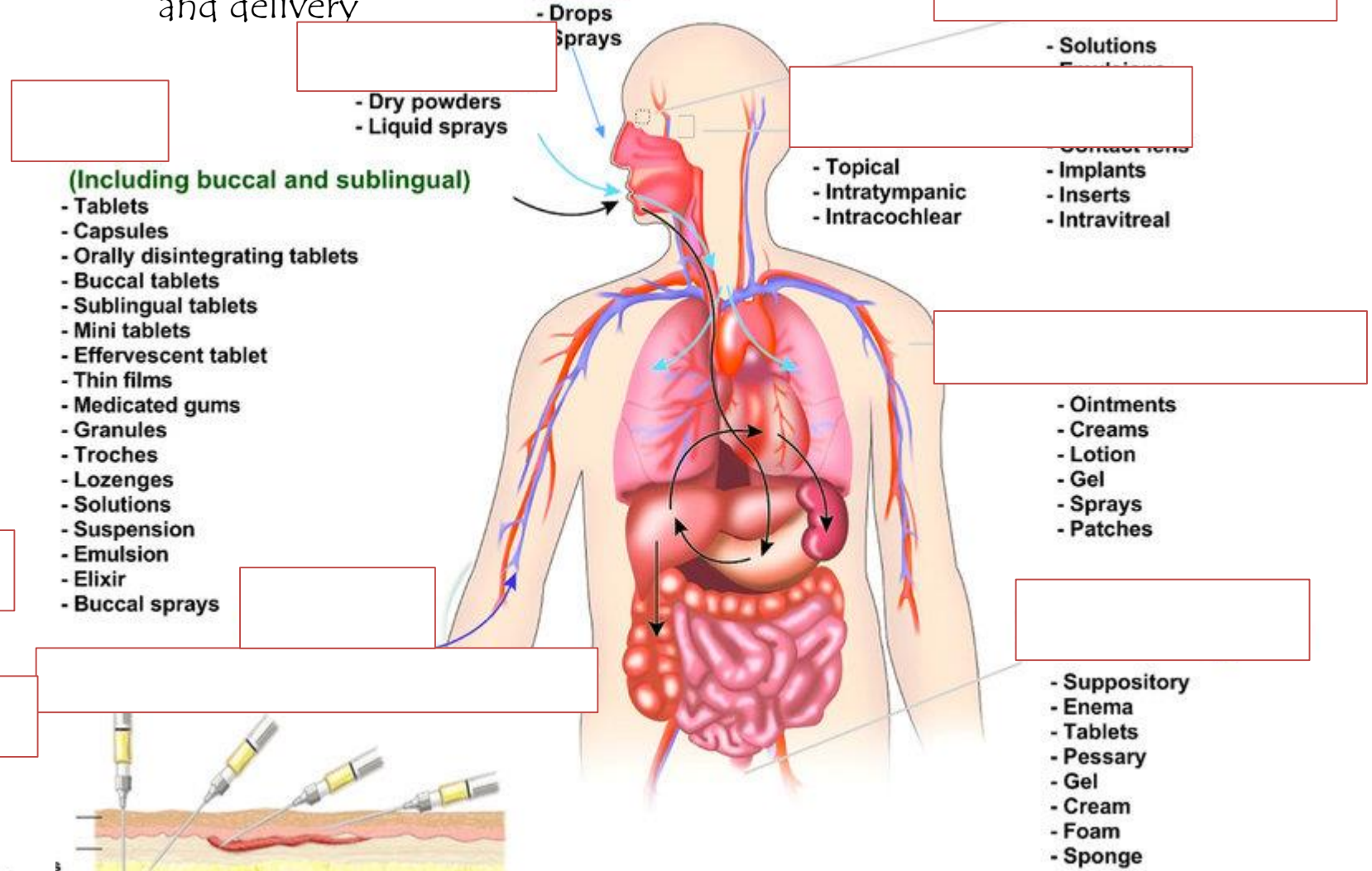
prior to 1900:

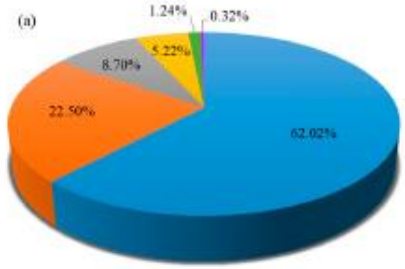


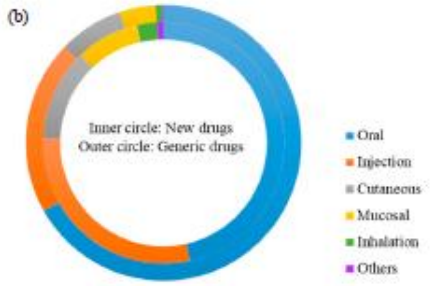
most drugs are now

drugs = medicines, though the term drugs may be

and delivery







pharmacology

medicinal modes of action, effects and uses

Lipinski's rule of 5

% of drug that enters the bloodstream

first pass bioavailability

IV:

oral:

oral to brain:

1. H-bond donors ≤ 5 (expressed as the sum of OHs and NHs)

2. Molecular weight ≤ 500 DA

Good *in vivo* drug absorption and permeation

most drugs are pH:

getting them to a receptor can be tough. The digestive system may treat them as _____; our defense systems may treat them as _____. Medicinal chemists deals with this using

3. log P ≤ 5

4. H-bond acceptors ≤ 10 (expressed as the sum of Ns and Os)

Once in the bloodstream other issues are possible:

if you have it worked out you are in the

therapeutic index:

high =

low =

these are measured in various ways (mg/kg body weight)

for 50% of population

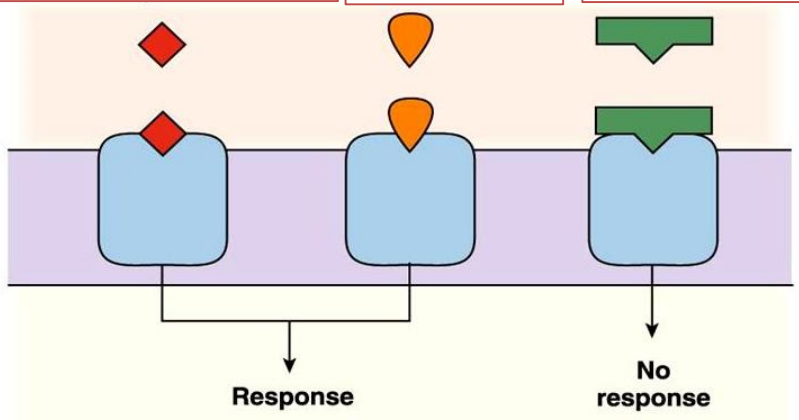
ED_{50}

TD_{50} (for humans)

LD_{50} (for animals)

medicinal chemistry: models and making it to the market

receptor model of drug activity



financial considerations & strategies

USA drug development and the FDA

Clinical Trials

Testing in Humans

PHASE	NUMBER OF PATIENTS	LENGTH	PURPOSE	PERCENTAGE OF DRUGS SUCCESSFULLY TESTED
Phase 1	20 to 100	Several months	Mainly safety	70 percent
Phase 2	100 to 500	Several months to 2 years	Some short-term safety, but mainly effectiveness	33 percent
Phase 3	1,000 to 5,000	1 to 4 years	Safety, effectiveness,	25 to 30 percent

medicine creation strategies

assay natural products with receptor plates

design substances from receptor (make the key fit)

assay the entire library

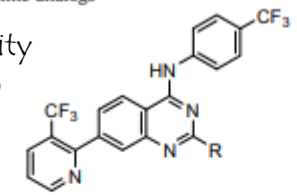
optimize structure by structure activity studies

goal:
maximize
minimize

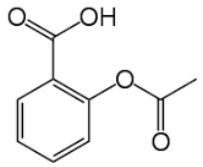
example: SAR of activity and solubility for an experimental pain medication (structure-activity relationship)

result:

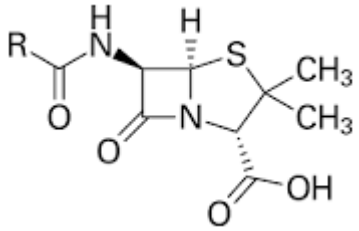
Table 1
2-Alkoxyalkyl quinazoline analogs



Compound	R	hTRPV1-cap[a] (nM)	HTSol[b] (μg/mL)
2	H	0.8 ± 0.07	0 [pK_a 4.54][c]
16	Me	0.5 ± 0.13	0
17	CH_2OH	4 ± 1.20	0.6
18	CH_2OMe	1.5 ± 0.20	0.2 [pK_a 3.7]
19	CH_2OEt	0.9 ± 0.16	0.6
20	CH_2O^iPr	0.3 ± 0.08	0.04
21	CH_2OCH_2Ph	0.5 ± 0.11	0.1
22	CH_2OPO_3H	46 ± 14	>138
23	$CH_2OCH_2CO_2H$	81 ± 22	125
24	$(CH_2)_2OMe$	2 ± 0.54	0
25	$(CH_2)_2OH$	22 ± 5.0	0.02
26	$(CH_2)_3OH$	25 ± 7.4	0.06
27	$(CH_2)_2CO_2H$	1627 ± 578	125
28	$(CH_2)_2SO_2Me$	36 ± 9.5	0.2



aspirin and penicillin



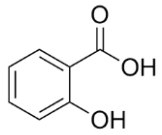
history

400 BCE

chewing willow bark relieves pain

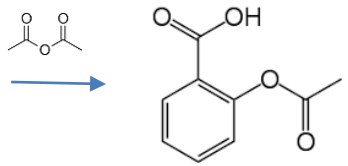
1870

active ingredient: salicylic acid



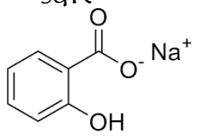
1890

esterified to reduce stomach irritation



1900's

increase bioavailablily by making sodium salt



history

1870-1930

various toxic drugs kill bacteria: arsenic, industrial dyes, sulfonamides

1928

the mold *penicillum notatum* kills bacteria

1941

active ingredient isolated (Hodgkin et al)

1950-present

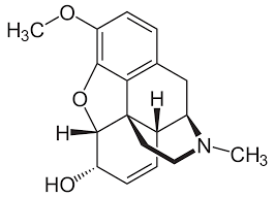
bacteria evolve: penicillinase

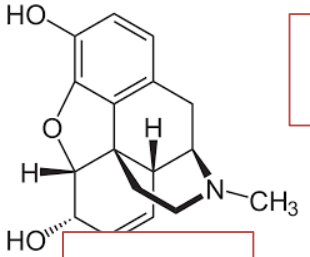
modified penicillins: methicillin oxacillin amoxicillin…

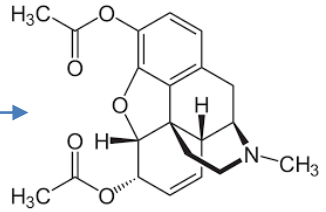
hard to make?		
class of drug		
primary target		
actual receptor target		

opiates

3 examples







history

5000 BCE

1805

1832

1874

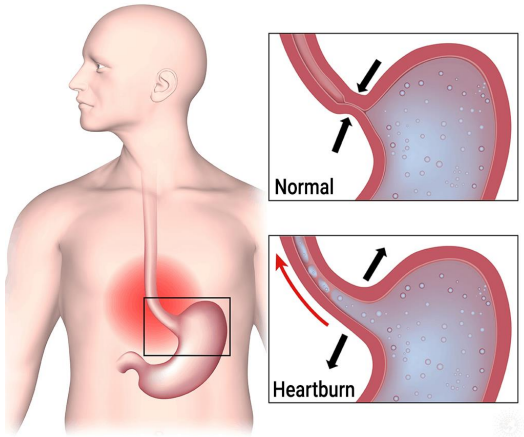
hard to make?

class of drug

activity

receptor

location



dyspeptics

dyspeptics treat dyspepsia, which is typically

some dyspeptics are buffered which means

buffers review: two components of a buffer system:

example:

Your stomach maintains a pH of

by using gastric glands to adjusting the concentration of

this can be adjusted directly with

these will resist a change in pH since they exist in solution simultaneously in equilibrium

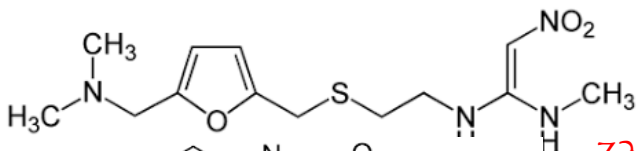
$CH_3CO_2H + H_2O \leftrightarrows CH_3CO_2^- + H_3O^+$

the pH of a buffer system can be calculated rapidly using the Henderson-Hasselbalch equation:

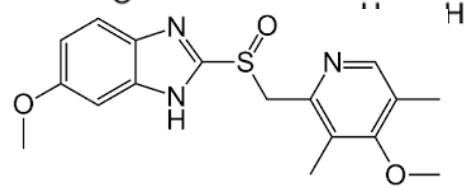
gastric gland activity can be modulated by

$CaCO_3$

tums

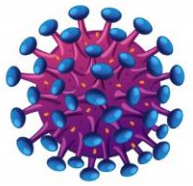


zantac



prilosec

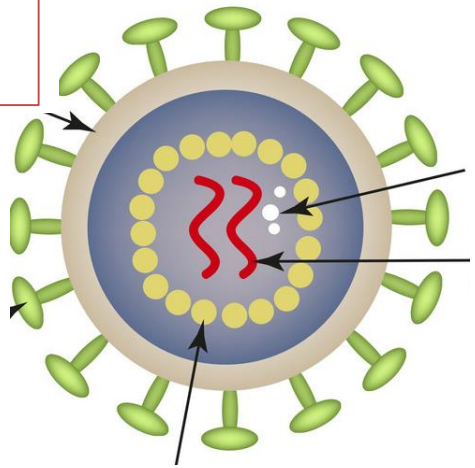
applying this to our 1M buffer system above where acetic acid has a K_a of 1.76×10^{-5}, above we find it has a pH of



a virus is a tiny:

particle that invade a host to make more

identify the main parts of a virus



antivirals

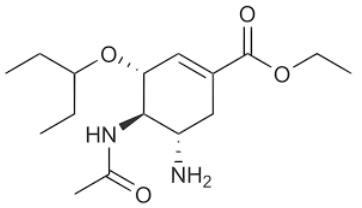
drugs for

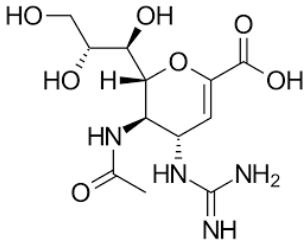
antivirals and the flu virus

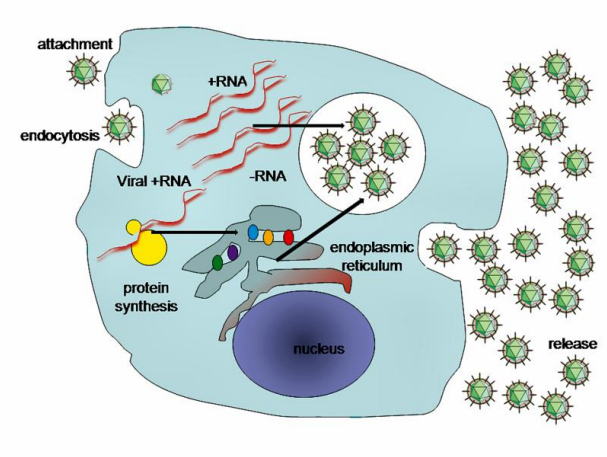
antivirals typically target

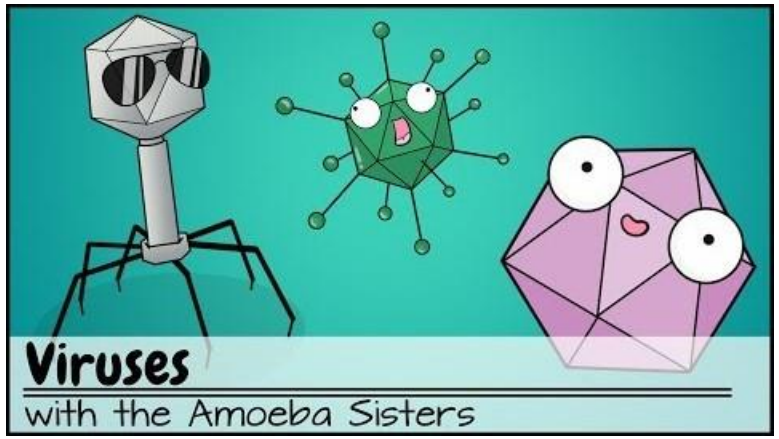
in the case of the flu virus

two medications target a specific flu enzyme:









AIDS

first diagnosed in

is due to an RNA-based virus, therefore a

transmitted through

but notably is not transmitted through

in 2018 it is estimated that the number of infected people is

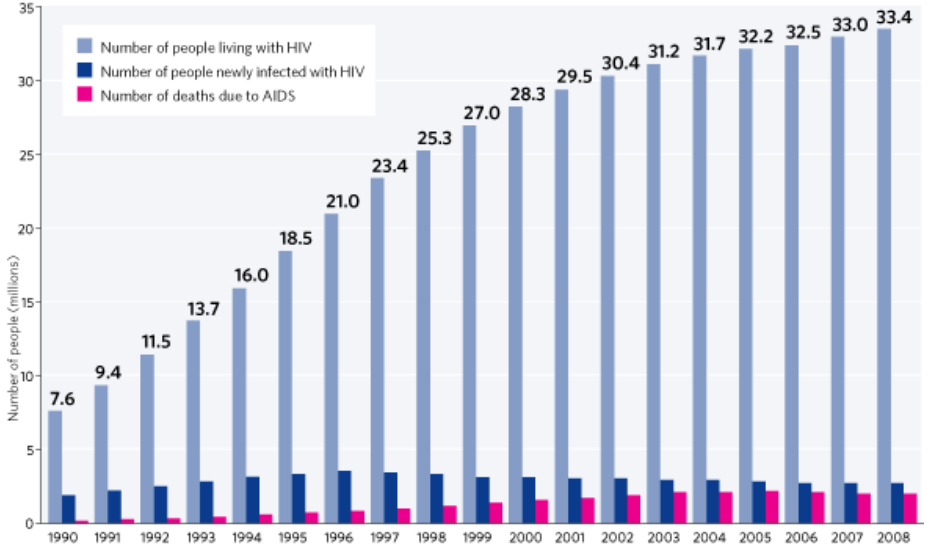
HIV attacks specific cells:

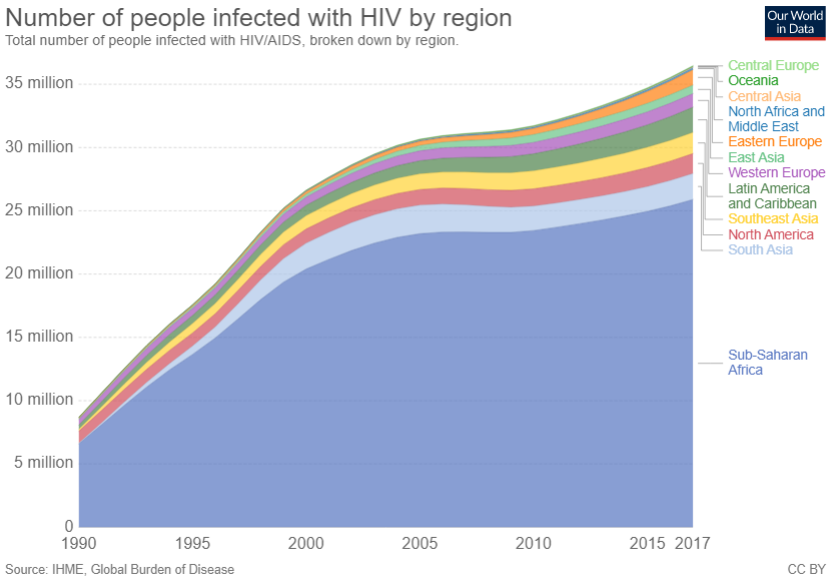
these cells are an important part of our:

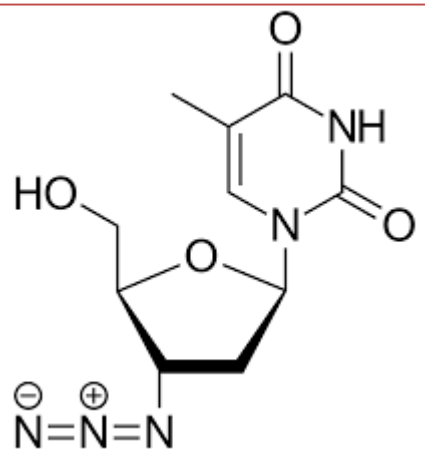
antiretrovirals often target the HIV enzyme

the first to be approved was

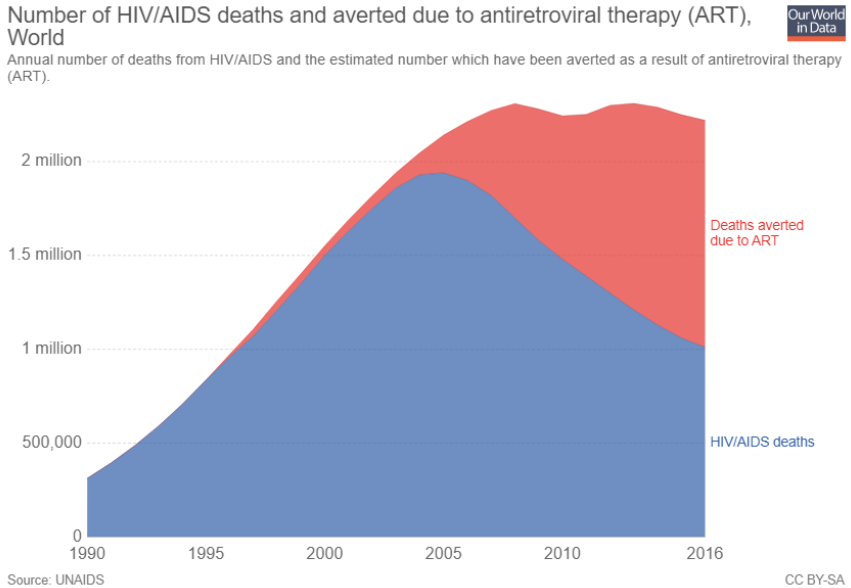
which was discovered by



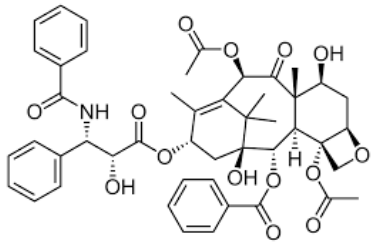




taken as a "cocktail" with other drugs current costs for a patient are



taxol



used for:

mechanism:

current source

1971

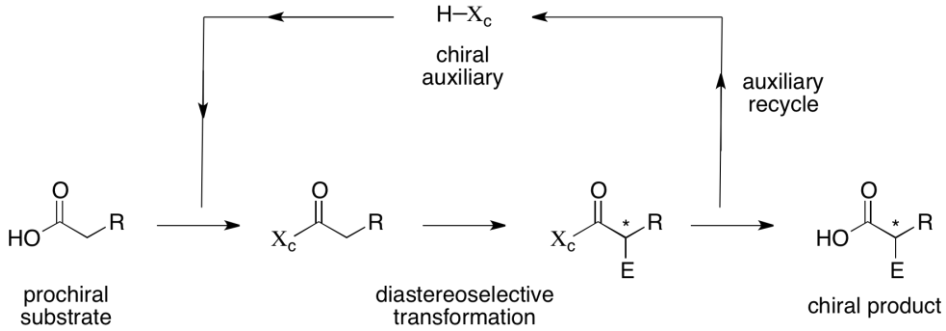
1992

initial source:

10-Deacetylbaccatin

Taxol

those 4 steps maintain chiral centers through the use of



suggested reading

Taxol's Next Stand
by Jonathan Fahey, Forbes Magazine (2001)

Paclitaxel and its evolving role in the management of ovarian cancer by Kampan et al (2015)

nuclear medicine: background

nuclear medicine relies on

for both

background:

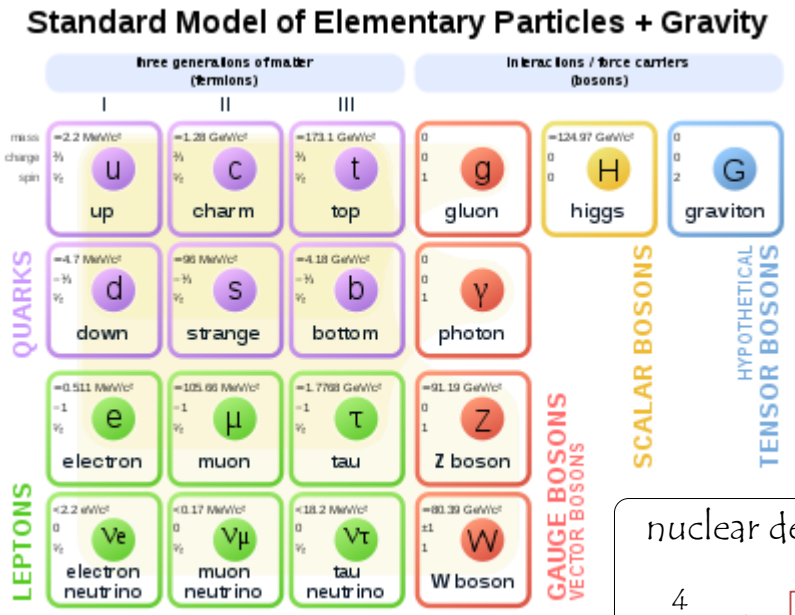
atoms consist of

the electron is an

protons and neutron are composed of

the standard model consists of 12

and 5



unstable nuclei are called

they are generally observed to be nuclei with excessive

and include all isotopes of all elements with

as well as all isotopes of

nuclear decay particles

$^{4}_{2}He^{2+}$

$^{0}_{-1}e$

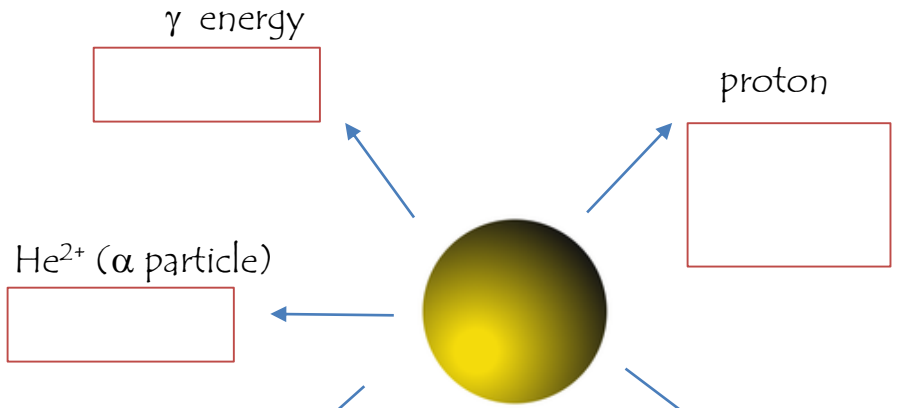
$^{0}_{0}\gamma$

$^{0}_{+1}e$

$^{1}_{0}n$

$^{1}_{1}p$

types of nuclear decay by what is ejected

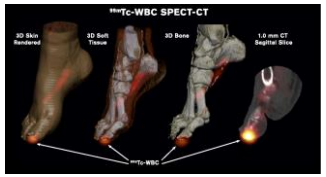
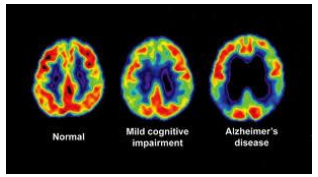
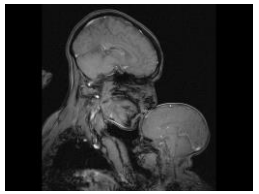
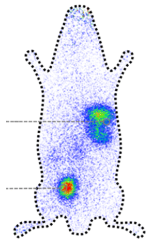
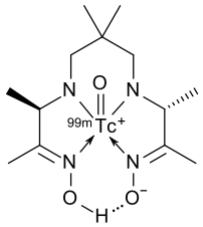
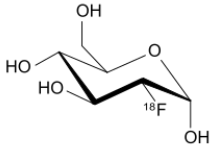


rate of nuclear decay

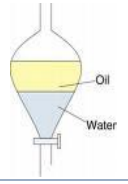
= k (N)

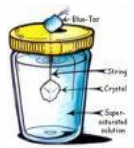
k = constant N = concentration

nuclear imaging and radiotherapy

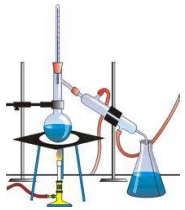
					
name	SPECT	PET scanning	MRI	radiotherapy	TAT Targeted alpha therapy
	single photon emission computed tomography	Positron Emission Tomography	Magnetic Resonance Imaging		
imaging or therapy?	imaging	imaging	imaging	external radiotherapy	internal radiotherapy
common radionuclide:	Tc-99 complexes	F-18 compounds	none	Co-60	Pb-212 bound to cancer specific antibodies ("warhead")
	ceretec  brain	myoview  heart			
		fluorodeoxyglucose			
type of emission	low energy gamma	positron	(nuclear magnetic)	beta: includes high energy gamma	alpha
nuclear reaction	$^{99}_{42}Mo \rightarrow {}^{99}_{43}Tc + {}^{0}_{-1}e$ $^{99}_{42}Tc \rightarrow {}^{99}_{43}Tc + \gamma$	$^{18}_{9}F \rightarrow {}^{18}_{8}O + {}^{0}_{+1}e$	none	$^{60}_{27}Co \longrightarrow {}^{60}_{28}Ni + {}^{0}_{-1}e + \gamma$	$^{212}_{82}Pb \rightarrow {}^{208}_{80}Tc + {}^{4}_{2}He$
application	soft tissue	tumor visualization	similar to x-ray but good for soft tissue	solid tumor treatment	non-solid tumors
advantages	Tc-99: good $T_{1/2}$: 6 hours low gamma energy emitter easily forms complexes transportable as Mo-99	F-18 can be seen systemically including cancer cells	same principles as NMR: maps all H atoms non-hazardous		α emission:high energy short range targeted bomblets

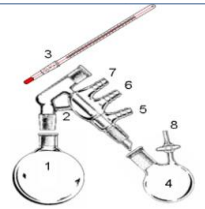
purification methods



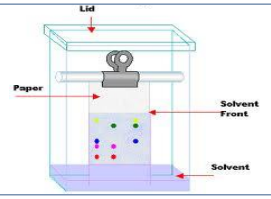


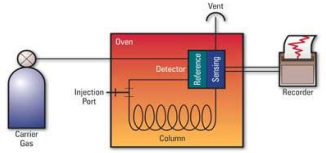
still in use

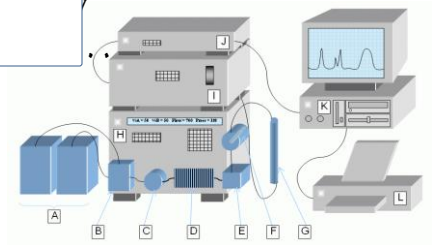




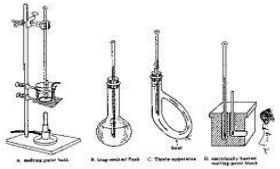
se s

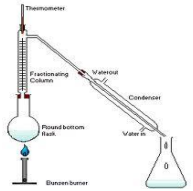






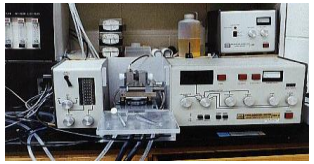
classical identification methods

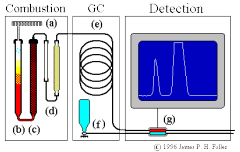


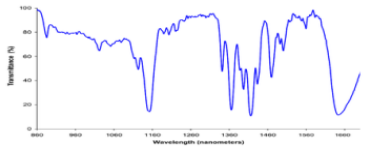


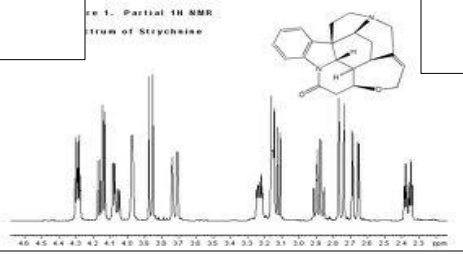
still in use

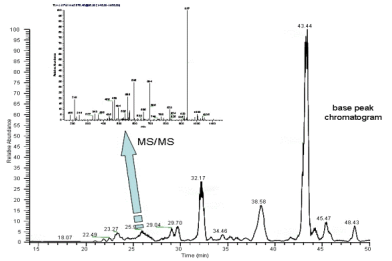
modern identification methods











how to identify an unknown substance

purify it

analyze it (mostly spectroscopically)

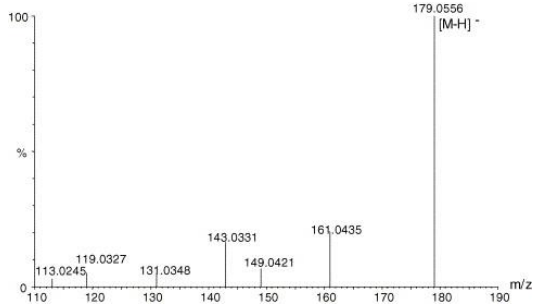
melting point
294-295 (d)

atomic absorption spectrum:

empirical formula
CH_2O

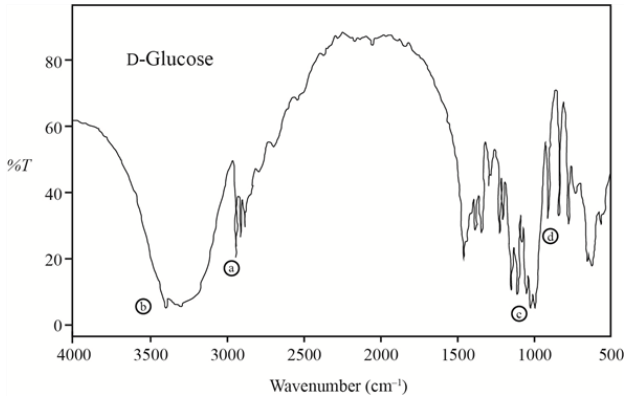
IHD = 1

mass spectrum:
180 g/mol



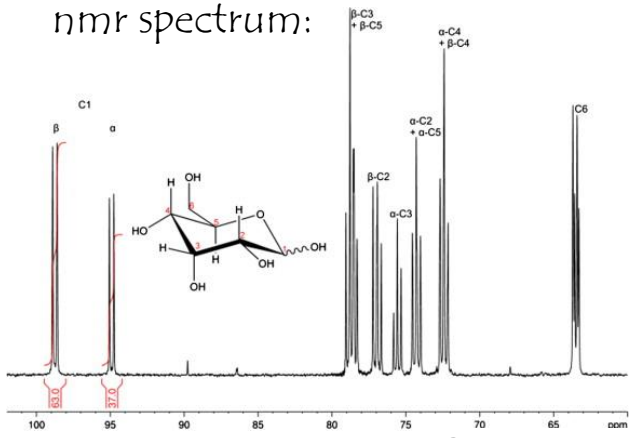
molecular formula:
$C_6H_{12}O_6$

infrared spectrum:



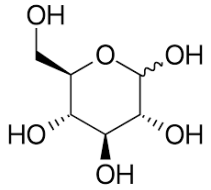
alcohol, not aromatic, no other functional groups.

nmr spectrum:



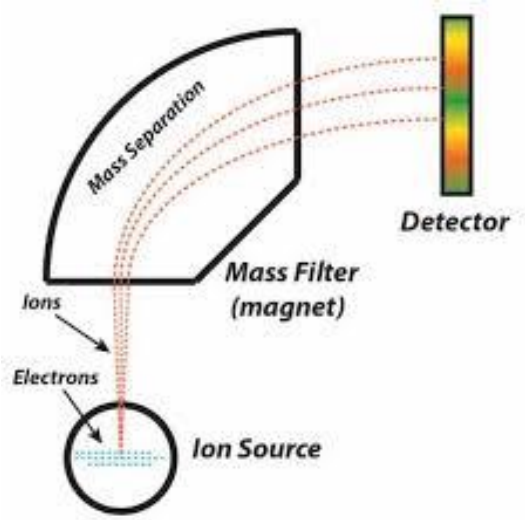
identity:

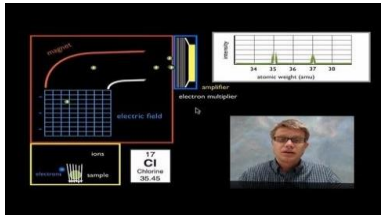
glucose

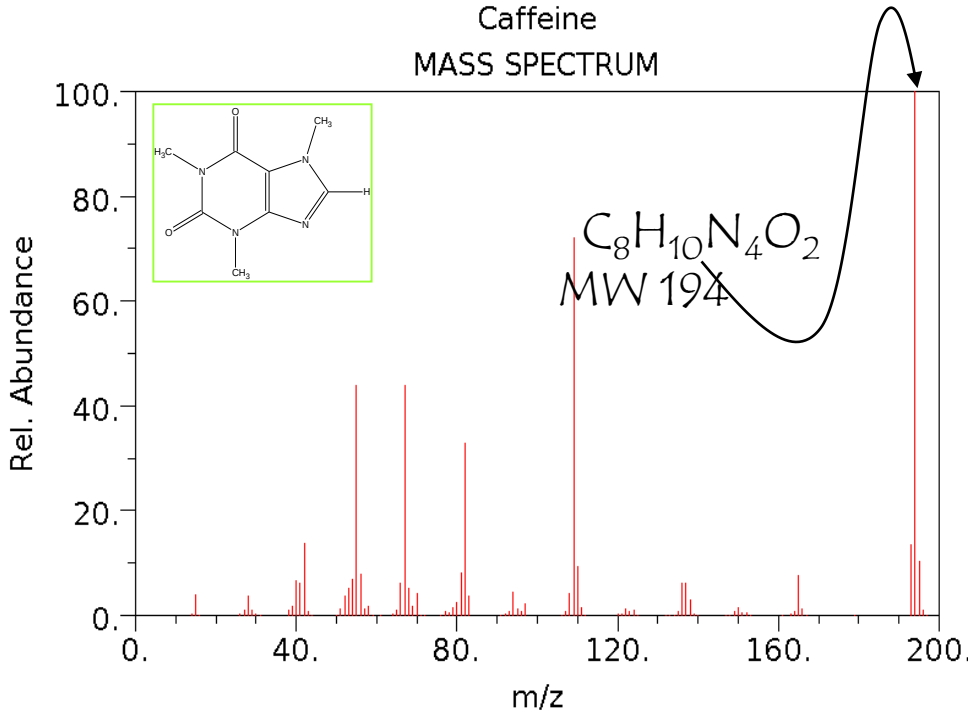


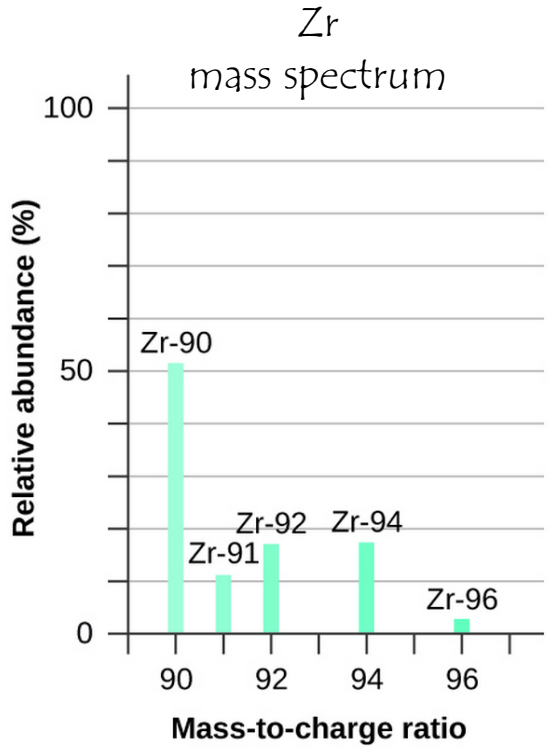
mass spectrometry

$M + e^- \rightarrow M^+ + 2e^-$

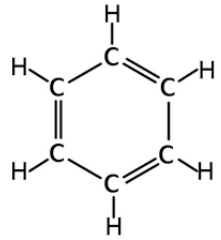


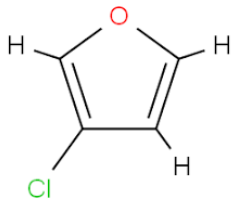






IHD = 0.5(2C+2-H-X+N)





IHD = ?

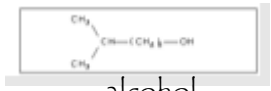
Isotope	Zr-90	Zr-91	Zr-92	Zr-94	Zr-96
Atomic mass (u)	89.905	90.906	91.905	93.906	95.908
Relative abundance (%)	51.45	11.22	17.15	17.38	2.80

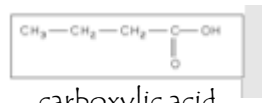
average atomic mass Zr =

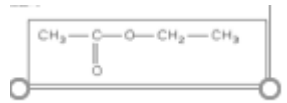
infrared spectroscopy

a device that plots the infrared absorption of a substance (typically organic)

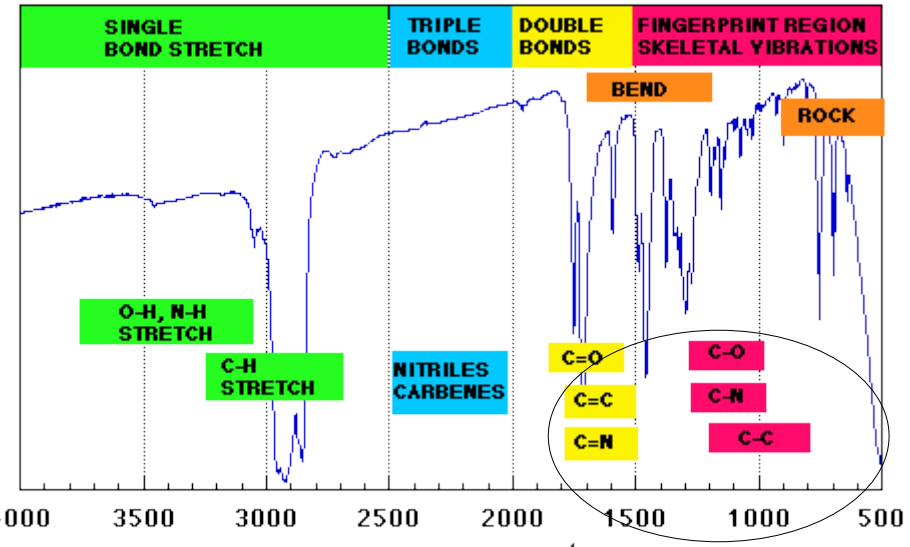
try some!


alcohol


carboxylic acid


ester


primary amide



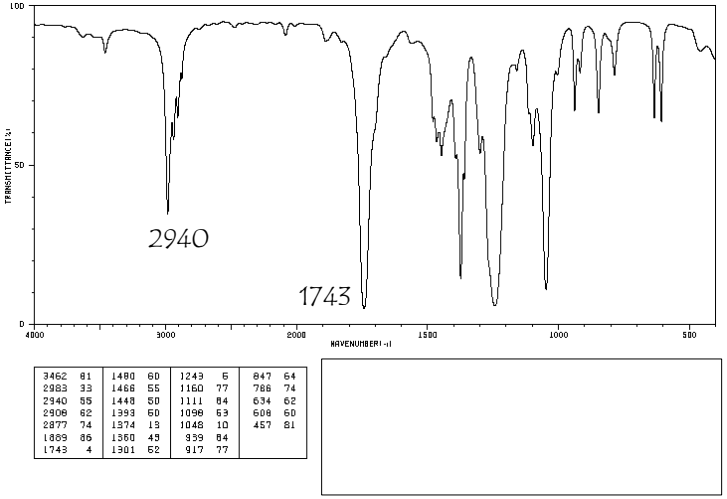
big blobs usually- watch out for water (OH)
2 peaks for NH_2
1 peak for NH, OH

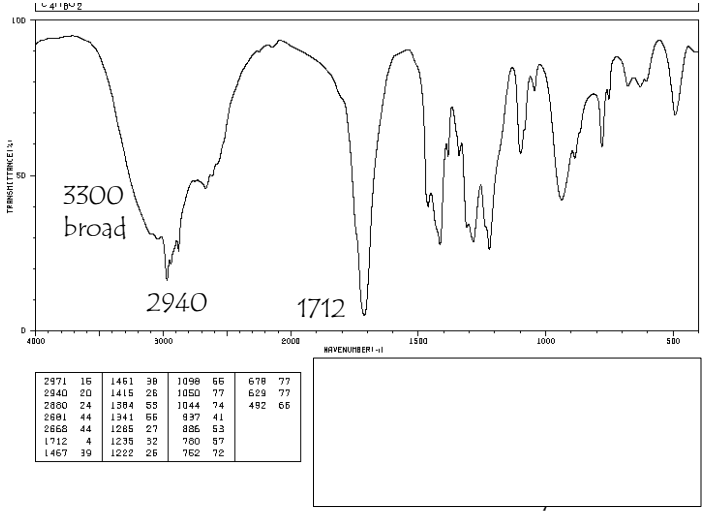
sharp, rare

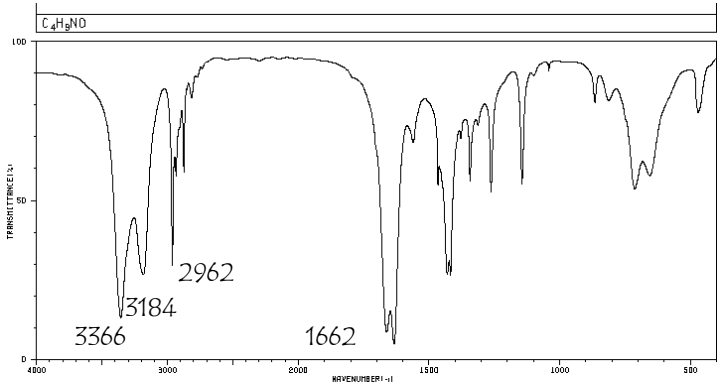
>3000 = aromatic
<3000 = aliphatic

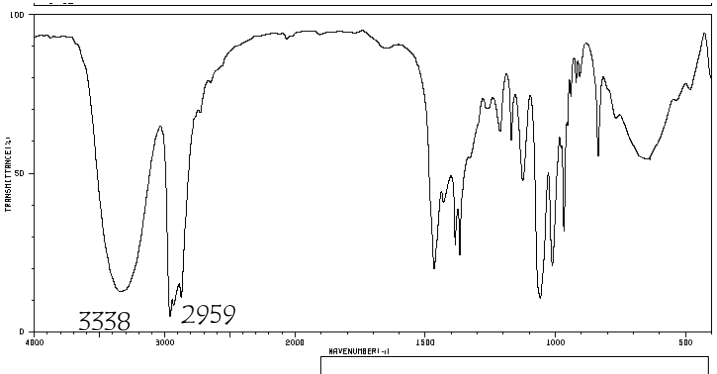
1850-1650: carbonyl (C=O) big and

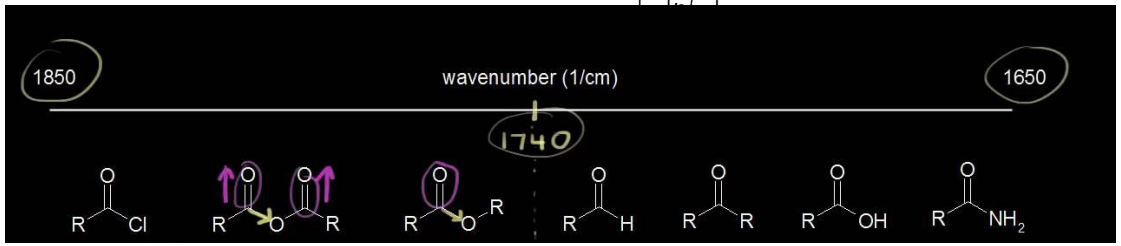
fingerprint region only- use to get a match









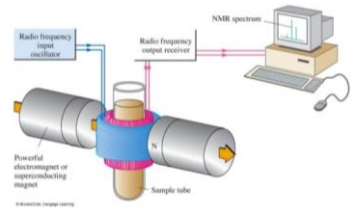


nmr spectroscopy

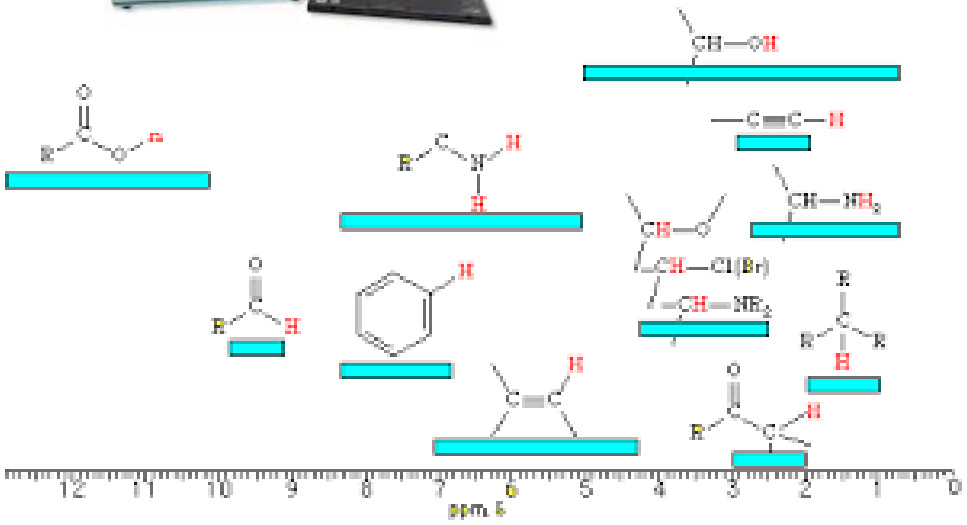
nuclear magnetic resonance

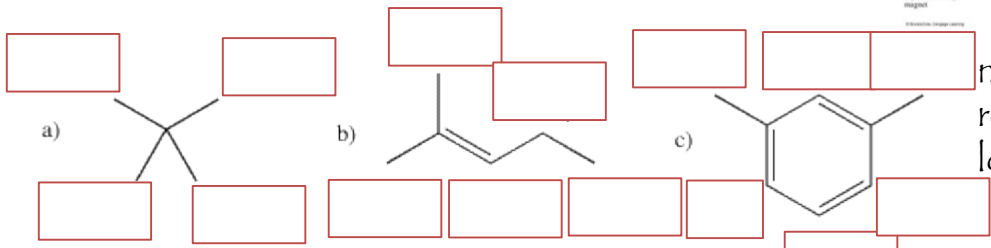
a device most commonly used to map hydrogen atom groups on a molecule

Drug Detection and analysis



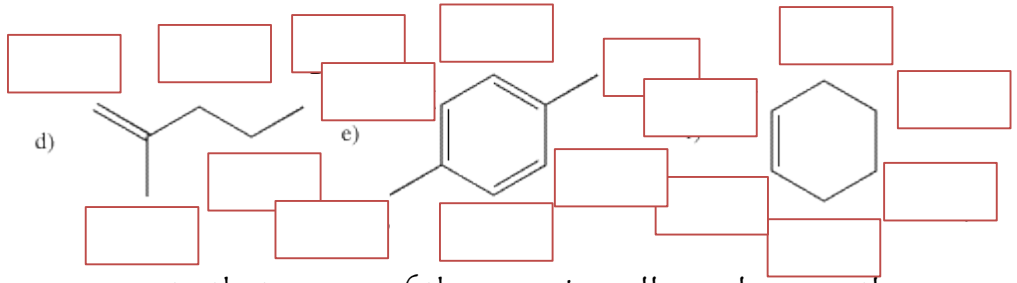
try some! size and splitting





magnet aligns spins

relaxation is highly location-dependent



note that many of these peaks will overlap exactly

cyclic and multiple-bond structures are spin-locked and will be more complex

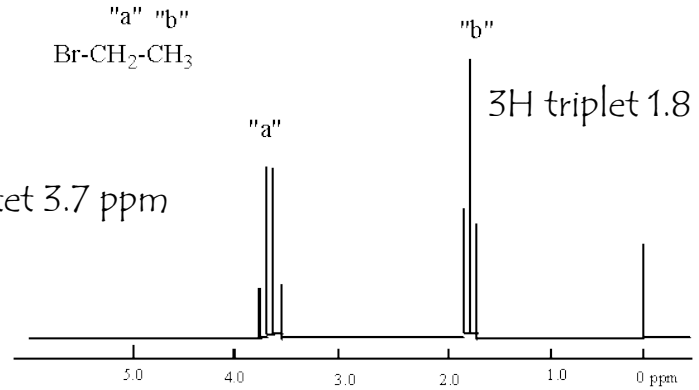
1. area of each peak proportional to # of H- do this first

2. splitting = neighboring H + 1

3. watch out for exactly overlapping regions

1 singlet
2 doublet
3 triplet
4 quartet
5 pentet
6 hextet
7 heptet
8 Octet
…multiplet

draw nmr spectrum of CH_3CH_2OH and $CH_3COCH_2CH_3$



3H triplet 1.8 ppm

2H quartet 3.7 ppm

area of peak: 2 3 for calibration (ignore)

medicinal waste

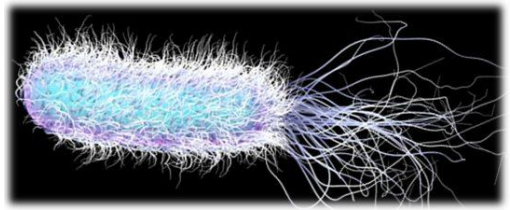
preferred treatment

undesirable

preferred

high level

low level



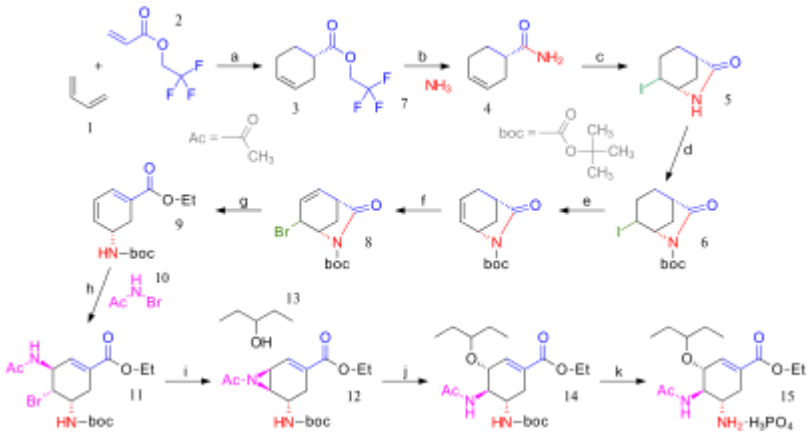
pseudomonas aeruginosa

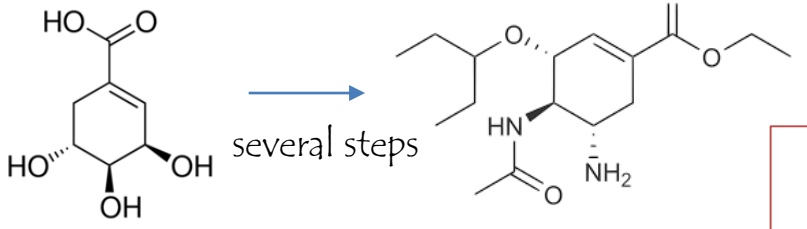
sources;

minimization:

green chemistry case study: tamiflu

total synthesis





tamiflu

shikimic acid: from Chinese star anise

minimization