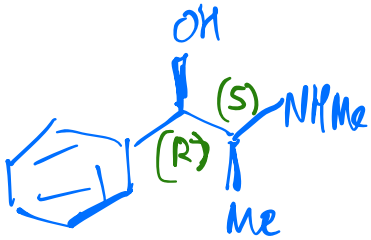
Topics in Organic Chemistry: Medicinal Chemistry (CHEM 515)

I. Introductory lecture

A. Three drug examples to illustrate drug development

1. Ephedrine



a) Folk medicine (traditional medicine)=natural product
3000 BCE
Emperor Shen Nung
-from the plant ma huang
-suppresses coughing

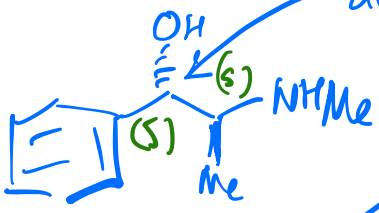
b) Acts at a receptor
-The principal mechanism of action relies on its indirect stimulation of the adrenergic receptor system by increasing the activity of noradrenaline at the postsynaptic α- and β-receptors.

Ephedrine use (from Wikipedia and internet):
- central nervous system (CNS) stimulant often used to prevent low blood pressure during anesthesia.

-treatment of asthma (bronchodilator)

- obesity but is not the preferred treatment.

Related structrues:
Pseudoephedrine

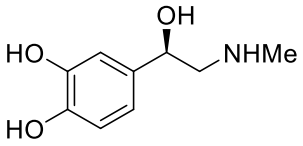
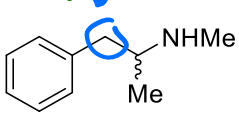
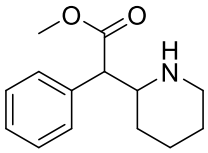


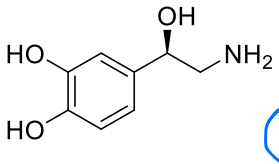
-active ingredient in over-the-counter (OTC) medications Sudafed (McNeil, J&J), Actifed (GSK), Claritin-D (Bayer), Allegra-D (Sanofi-Aventis)
NO prescription required

-now kept secure behind the counter → precursor to methamphetamine

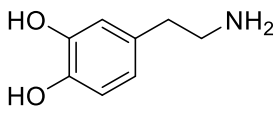
-nasal/sinus decongestant without drowsiness; has stimulant effects

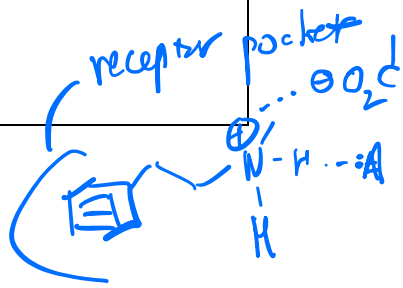
benzylic OH missing

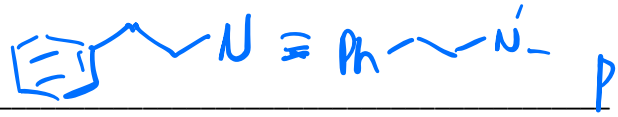
 epinephrine (adrenalin)	 methamphetamine	 Ritalin (methylphenidate)
- fight or flight response	- recreational drug - CNS stimulant - occassionally treats ADHD	- ADHD treatment


norepinephrine (noradrenaline)

loss of one C (Me)


dopamine



Common structural element:  phenethylamine

Pharmacophore= key fundamental structural unit responsible for bioactivity

2. cimetidine (Tagamet), an anti-ulcer drug

(Smith, Kline & French → GlaxoSmithKline or GSK)

-mid 1970's

-note: cimetidine= generic name; Tagamet= trade name (company name);

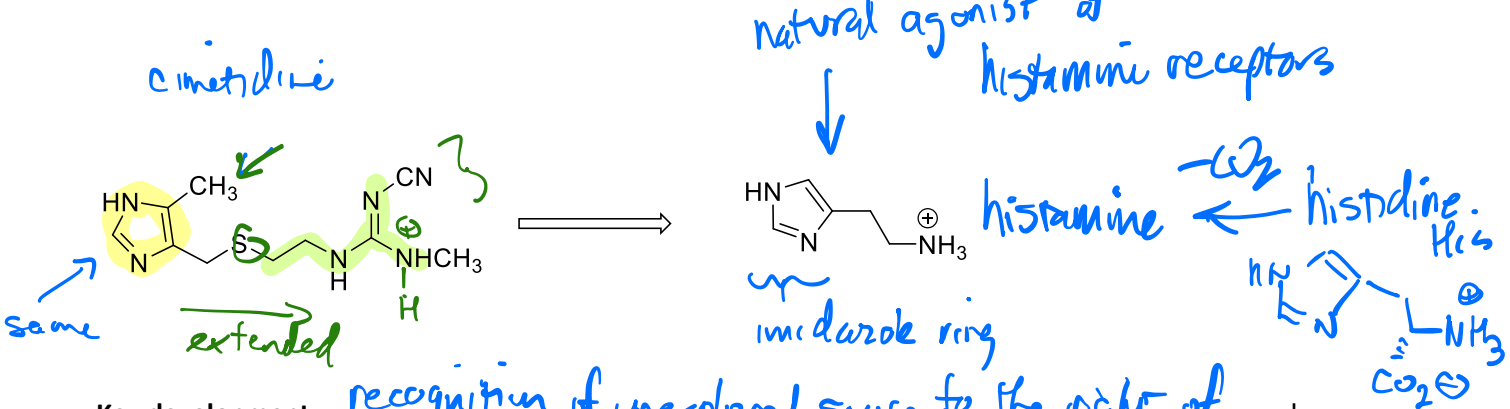
pre-clinical = e.g. GSK-1093

a) blocks H2 histamine receptors = antagonist

receptor : antagonist :: enzyme : inhibitor

receptor : agonist :: enzyme : substrate

-no H2 histamine receptor X-ray structure or related receptor structural information!

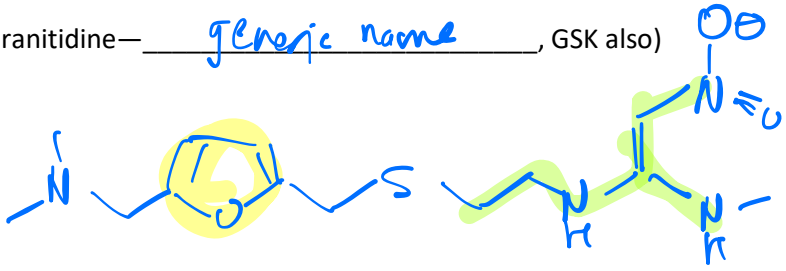


Key development: recognition of unexplored space to the right of the ammonium ion ($-NH_3^{\oplus}$)!

b) rational drug design **→evolved from modifications of natural agonist, histamine**

-1988 Sir James Black, Nobel Prize in Physiology or Medicine (also for propranolol)

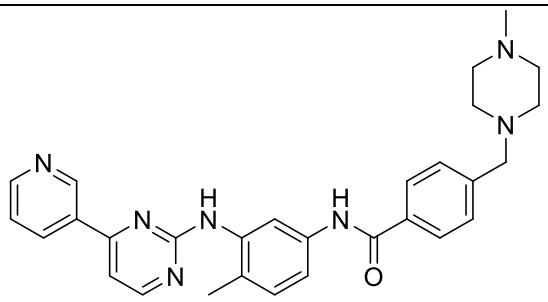
Zantac (ranitidine—generic name, GSK also)

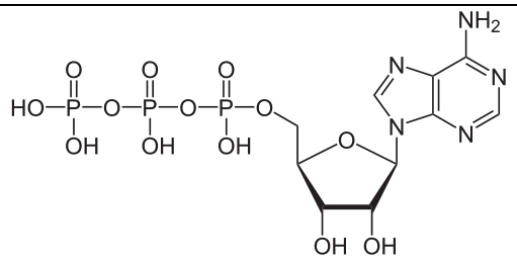


[Eventually replaced by proton pump inhibitors like Prilosec, generic name: omeprazole.]

3. Gleevec, an anti-cancer drug (Novartis)

-generic name= imatinib


imatinib


ATP

- tyrosine kinase inhibitor
- binds in ATP pocket → enzyme target

* imatinib doesn't look like ATP, which is a good thing because it might react in a lot more ATP binding sites

if it did look like ATP → selectivity achieved!

-**genetic research**→ provided target

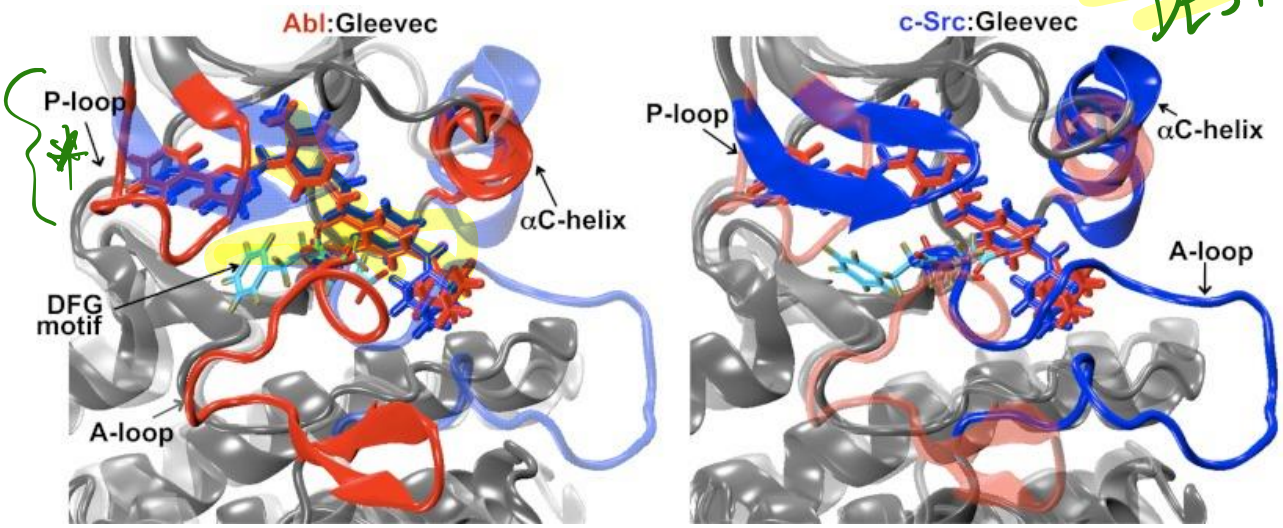
- high throughput screening (HTS) to find lead compound that was selective
- structure-activity relationship (SAR) studies optimized the lead
  = make changes to structure and assay for change in bioactivity

-genetic defect (chromosome translocation) discovered in chronic myelogenous leukemia (CML) leads to aberrant protein (Abl, a tyrosine kinase—attaches phosphate groups to proteins) that is overactive.

No crystal structure known while development occurred.

IRRATIONAL DRUG DESIGN

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3562763/figure/fig01/



Details of intermolecular interactions with target are critical to bioactivity and therapeutic optimization → X-ray information is critical

B. Drug Development: the task

1. Medicinal Chemistry=the study of bioactive chemical compounds to develop and optimize the beneficial therapeutic nature of the chemicals.

Who's involved? Teams of people.

Organic chemists (called medicinal chemists and process chemists), large scale synthesis

biochemists, crystallographers, pharmacologists, toxicologists, biologists (biophysicists)

2. All bioactive chemicals have both positive (therapeutic) and negative (toxic) effects on humans.

a) Quantifying positive vs. negative effects….

therapeutic index= ratio of undesirable effects to desireable effects

= Lethal dose 50 / effective dose 50 or LD_{50}/ED_{50}

(1) effective dose= produces maximum therapeutic effect

-ED_{50}= effective dose in 50% of test animals

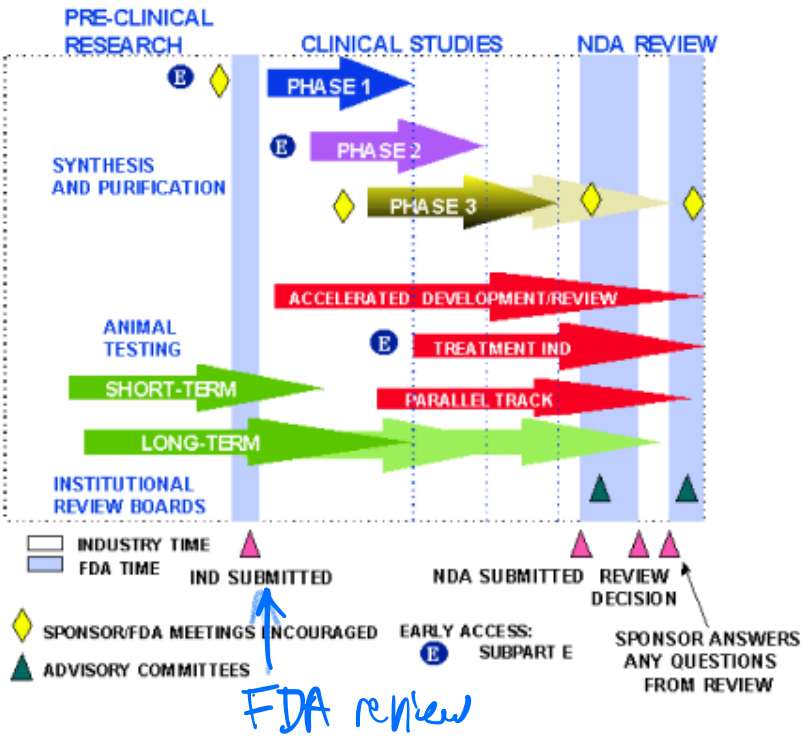
(2) LD_{50}= lethal dose in 50% of test animals

b) Goal=find a lower concentration to achieve ED_{50} and a higher concentration to obtain LD_{50}.

c) The larger the therapeutic index,… the better the drug

$\frac{LD_{50}\ \text{high}}{ED_{50}\ \text{low}} \Rightarrow$ large number

C. Drug Development process: an overview



IND = investigational new drug

NDA = new drug application

from:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/ucm053131.htm

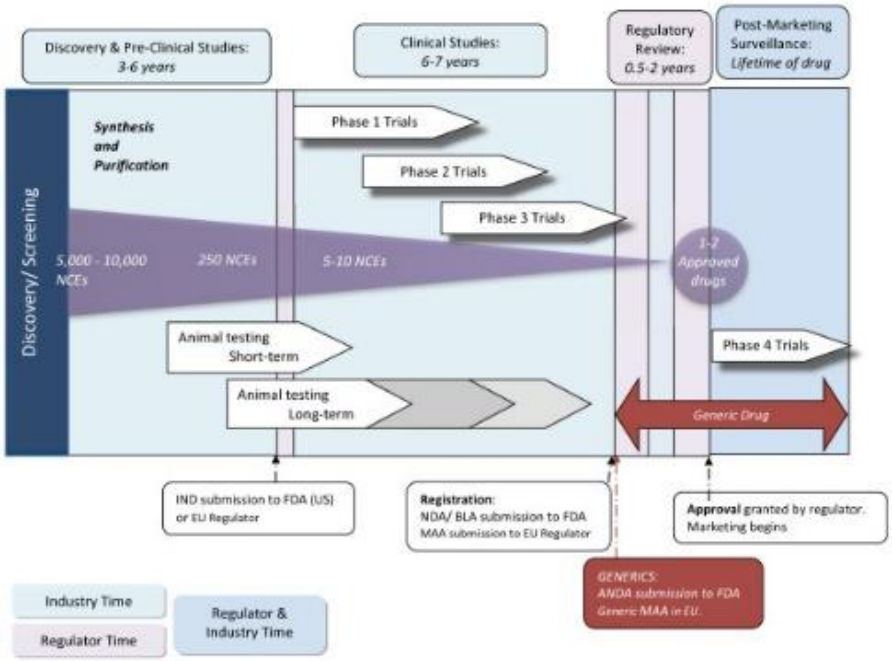


Figure from https://www.researchgate.net

1. Pre-clinical research

**our primary focus!!

a) Discovery of a biological target

-drive by molecular biologists and proteomics

-develop an assay to screen compounds; preferably amenable to HTS

-in vitro assays = isolated enzyme or receptor; cell based assays

-in vivo= animal testing (mice, rats, dogs, monkeys)

b) Discovery of a bioactive molecule or lead discovery

***start of med chem**

-random screening: High-throughput screening (~100 up to 1,000,000 compounds in a company library)

-e.g. Gleevec

-most common today!

-non-random screening: rational drug design beginning with a known substrate or agonist

-e.g. cimetidine

-other serendipitous starting points:

- folk medicine / natural products
- drug metabolism studies that reveal the true active component

-e.g. sulfa drugs from dyes

-clinical observation: side effects of another drug

-e.g. rogaine, an anti-hypertensive that lead to hair growth

-e.g. Viagra, an anti-hypertensive that leads to ....

c). Analyzing and modifying chemical structures

(1) It's all about the heteroatoms!

- heteroatoms =everything not C and H; look for N, O, S, Cl, etc.

Why? They form most important intermolecular forces !--> more next week

(2) SAR studies (structure-activity relationship)

-changes to structure are analyzed for impact on bioactivity

(i) two basic changes

-keep it the same: use isosteres/bioisosteres

Bioisosteres/Isosteres

Bioisosteres= functionality or groups with comparable chemical or physical properties and which have similar biological properties

Isosteres= atoms or groups with similar valency and equivalent chemical or physical properties

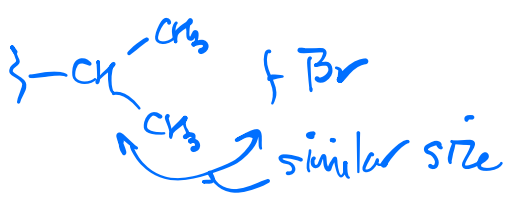
Isosteres:

1. Univalent atoms

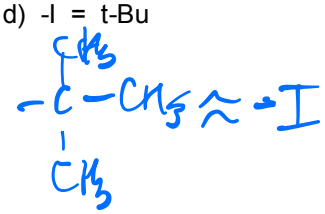
a) $-CH_3$ = $-NH_2$ = -OH = -F = -Cl = -SH (thick)

b) -Cl = -SH → 3rd energy level ≡ similar size

c) -Br = i-Pr



d) -I = t-Bu

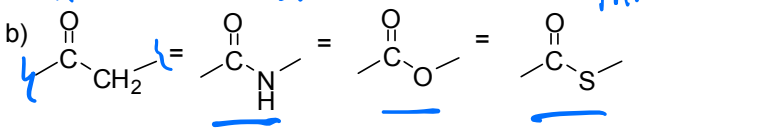


2. Bivalent atoms

methylene

a) $-CH_2-$ = -NH- = -O- =-S- = -Se-

ketone amide ester thioester

b) 

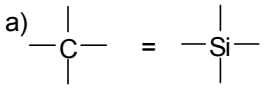
3. Trivalent atoms

methine

-CH= = -N=

4. Tetravalent atoms

allene

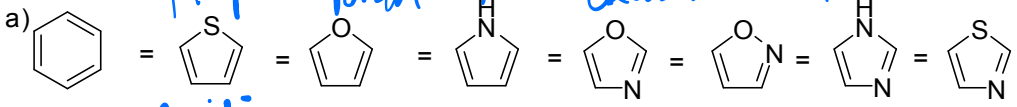
a) 

b) =C= = $=\overset{\oplus}{N}=$

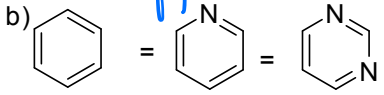
5. Ring equivalents

thiophene furan pyrrole rich ring

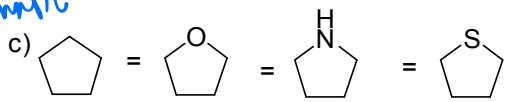
oxazole imidazole

a) 

pyridine pyrimidine

b) 

non-aromatic

c) 

<u>Bioisosteres</u> (less similar structurally)

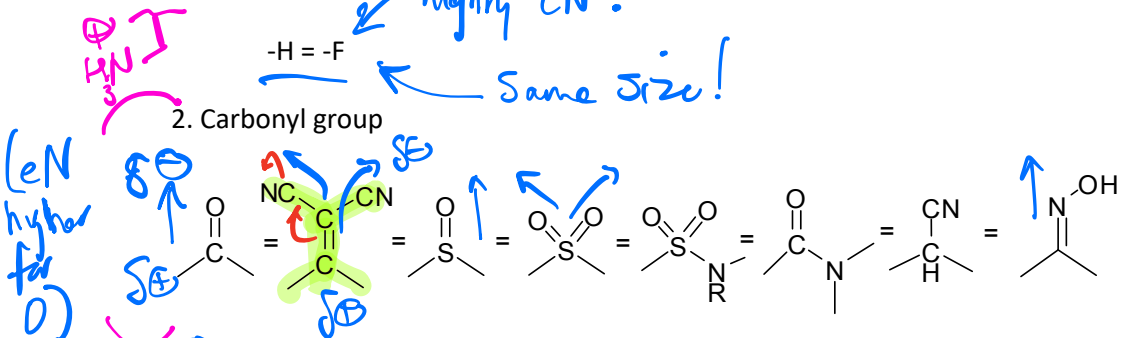
1. Hydrogen

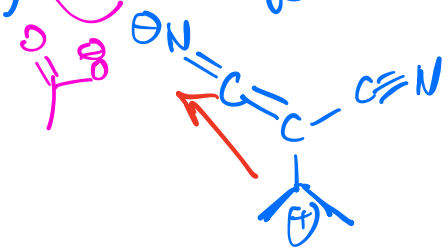
highly eN!

-H = -F

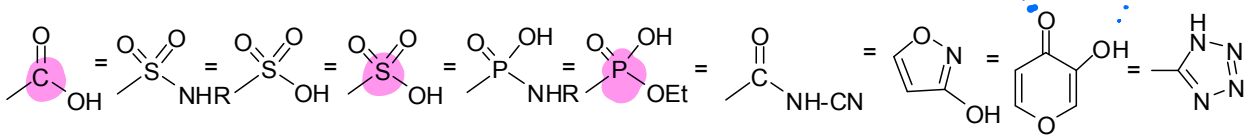
Same size!

2. Carbonyl group

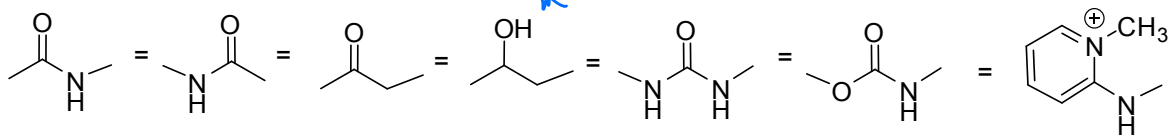




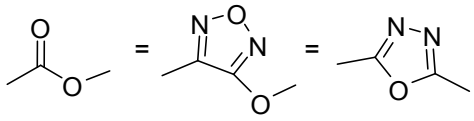
3. Carboxylic acid group



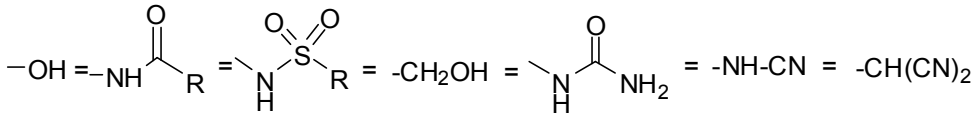
4. Amide group



5. Ester group



6. Hydroxy group

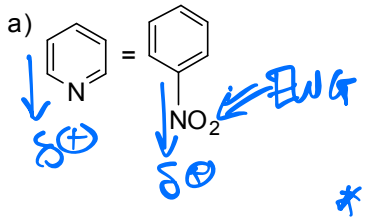


7. Halogen

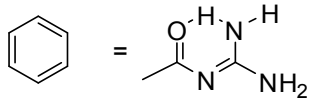
X= $-CF_3$ = -CN = $-N(CN)_2$ = $-C(CN)_3$

8. Ring equivalents

a)

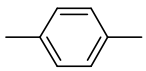


b)



9. Spacer group

$-(CH_2)_3-$ =



Key reference: **Bioisosterism: A Rational Approach in Drug Design** , George A. Patani and Edmond J. LaVoie*, *Chem. Rev.*, 1996, 96 (8), pp 3147–3176. Abstract (found 1.10.14)

More updated reference on bioisosteres: **Synopsis of Some Recent Tactical Application of Bioisosteres in Drug Design,** Nicholas A. Meanwell, *J. Med. Chem.*, 2011, 54 (8), pp 2529–2591. Abstract (found 10.16.14)

-change it up: add or delete structure

impact of additions/deletions:

(1) change flexibility or steric characteristics

(2) change solubility or lipophilicity

(3) change intermolecular forces

(4) change electronics

-these will impact both bioactivity at target and ADMET properties

THIS IS AN ITERATIVE PROCESS!

ADMET = absorption distribution metabolism excretion toxicity

***end of med chem**

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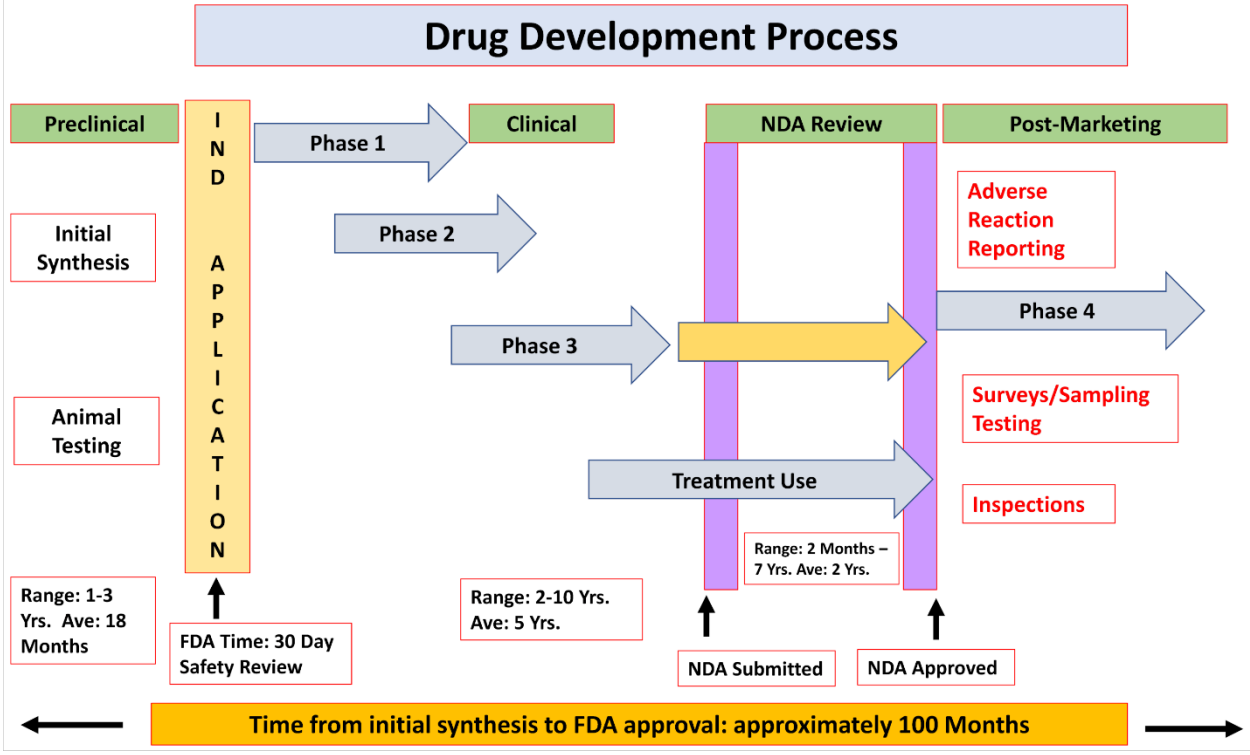
patent filing

-Investigational new drug (IND), a.k.a. new chemical entity (NCE)

2. Clinical research: Phase trials



From: Edit image, resize image, crop pictures and appply effect to your images

-phase 1: safety, 20-80 healthy "volunteers" → look for side effects

-phase 2: efficacy in diseased patients, several hundred patients

-phase 3: expand efficacy analyses to broader range of patients, increase patient diversity, hundreds to thousands of people w/ disease

-phase 4: continued monitoring after drug approved

New drug application (NDA)→ FDA approval

*entire process can take 8-12 years

-$ 1 billion

D. Other Drug Development Details

1. Reasons for drug failure

- ADME ~40% in UK study 1964-1985
- efficacy ~35% in US trials, 1981-1992
- economics ~30% (market changes) in US trials, 1981-1992

2. types of therapeutics:

a) Vaccines

b) small molecules

c) biologics, e.g. antibodies or peptides

3. How many drug targets are there?

From J. P. Overington et al. Nature Reviews Drug Discovery 2017, 16, 19-34

-893 human and pathogen-derived biomolecules

-acted upon by 1,578 US FDA-approved drugs

>>>

Therapeutic drug use statistics

see: http://www.cdc.gov/nchs/fastats/drug-use-therapeutic.htm

also: http://www.drugbank.ca/stats

Table 1.1 Important milestones in drug research

Year	Substance	Indication/Mode of action
1806	Morphine	Hypnotic
1875	Salicylic acid	Anti-inflammatory
1884	Cocaine	Stimulant, local anesthetic
1888	Phenacetin	Analgetic and antipyretic
1889	Acetylsalicylic acid	Analgetic and antipyretic
1903	Barbiturate	Sedative
1909	Arsphenamin	Anti-syphilitic
1921	Procaine	Local anesthetic
1922	Insulin	Antidiabetic
1928	Estrone	Female sex hormone
1928	Penicillin	Antibiotic
1935	Sulfamidochrysoidine	Bacteriostatic
1944	Streptomycin	Antibiotic
1945	Chloroquine	Antimalarial
1952	Chlorpromazine	Neuroleptic
1956	Tolbutamide	Oral antidiabetic
1960	Chlordiazepoxide	Tranquilizer
1962	Verapamil	Calcium channel blocker
1963	Propranolol	Antihypertensive (b-blocker)
1964	Furosemide	Diuretic
1971	L-DOPA	Parkinson's disease
1973	Tamoxifen	Breast cancer (estrogen receptor antagonist)
1975	Nifedipine	Calcium channel blocker
1976	Cimetidine	Gastrointestinal ulcer (H_2 blocker)
1981	Captopril	Antihypertensive (ACE inhibitor)
1981	Ranitidine	Gastrointestinal ulcer (H_2 blocker)
1983	Ciclosporin A	Immunosuppressant
1984	Enalapril	Antihypertensive (ACE inhibitor)
1985	Mefloquine	Antimalarial
1986	Fluoxetine	Antidepressant (5-HT-transport inhibitor)
1987	Artemisinin	Antimalarial
1987	Lovastatin	Cholesterol biosynthesis inhibitor
1988	Omeprazole	Gastrointestinal ulcer (H^+/K^+-ATPase inhibitor)
1990	Ondansetron	Antiemetic (5-HT_3 blocker)
1991	Sumatriptan	Migraine (5-$HT_{1B,D}$ agonist)
1993	Risperidone	Antipsychotic (D_2/5-HT_2-blocker)
1994	Famciclovir	Antiviral/herpes (DNA polymerase inhibitor)
1995	Losartan	Arterial hypertension (ATII antagonist)
1995	Dorzolamide	Glaucoma (carboanhydrase inhibitor)
1996	Saquinavir	HIV protease inhibitor
1996	Ritonavir	HIV protease inhibitor
1996	Indinavir	HIV Protease inhibitor
1996	Nevirapine	HIV reverse transcriptase inhibitor

Table 1.1 (continued)

Year	Substance	Indication/Mode of action
1997	Sibutramine	Obesity (uptake inhibitor)

1997 Orlistat Obesity (lipase inhibitor)
1997 Tolcapon Parkinson's disease (COMT inhibitor)
1998 Sildenafil Erectile dysfunction (PDE5 inhibitor)
1998 Montelukast Broncholytic (leukotriene receptor antagonist)
1999 Infliximab Antirheumatic (TNFa antagonist)
2000 Celecoxib Analgesic (COX-2 inhibitor)
2000 Verteporfin Macular degeneration (photodynamic therapy)
2001 Imatinib Acute myeloid leukemia (kinase inhibitor)
2002 Boscutan Arterial hypertension (endothelin-1 receptor antagonist)
2002 Aprepitant Antiemetic (neurokinin receptor antagonist)
2003 Enfuvirtid HIV fusion inhibitor (oligopeptide)
2004 Ximelagatran Coagulation inhibitor (thrombin inhibitor)
2004 Bortezomib Multiple myeloma (proteasome inhibitor)
2005 Bevacizumab Cytostatic (angiogenese inhibitor)
2006 Natalizumab Multiple sclerosis (monoclonal antibody; integrin inhibitor)
2006 Aliskiren Antihypertensive (renin inhibitor)
2007 Maraviroc HIV fusion inhibitor (CCR5 antagonist)
2007 Sitagliptin Type-II diabetes (DPPVI inhibitor)
2008 Raltegravir HIV integrase inhibitor
2009 Rivaroxaban Oral Anticoagulant (FXa inhibitor)
2010 Mifamurtide Drug against Osteosarcoma (bone cancer)
2011 Fingolimod Immunomodulating drug (multiple sclerosis treatment)

(from Drug Design: Methodology, Concepts, and Mode of Action by Gerhard Klebe, 2013)