# Rational Drug Design lecture 5

Łukasz Berlicki

## Analogs

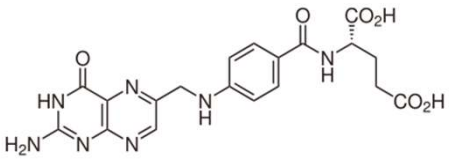
- **Analog** – from d with similar chemical and/or original compound.

## Analogs in drug discovery

- Analogs of natural ligands (including substrates and products of enzymatic reactions)
- Analogs of known bioactive compounds (inhibitors/agonists/antagonists) – property optimisation
- Analysis of biological activity of analogs allows construction of knowledge database concerning structure-activity relationships (SAR).

## Metotrexate – folic acid analog

- Sidney Farber studied influence of folic acid (vitamin $B_9$) on patients with leukemia.
- Folic acid cause faster development of the disease.
- Deficiency of folic acid should inhibit leukemia.

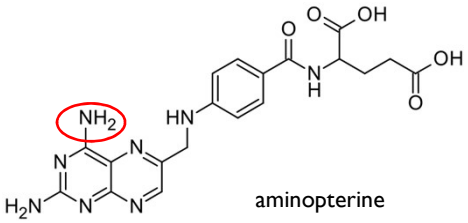



Folic acid

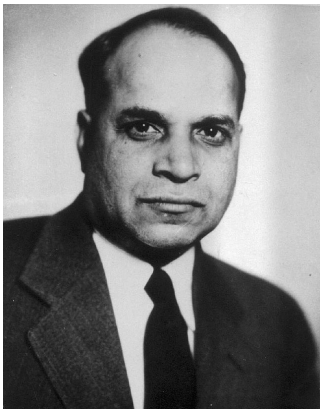
Sidney Farber

## Metotrexate – folic acid analog

- Y. Subbarow has obtained folic acid and a group of its analogs.
- S. Farber (1948) proved that analog of folic acid – aminopterine inhibits development of leukemia in children.



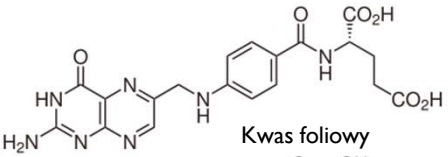

aminopterine



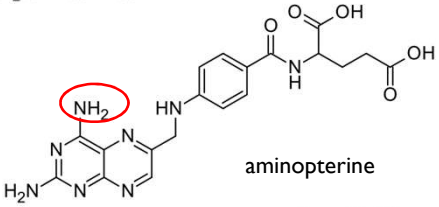
Yellapragada Subbarow

## Metotrexate – folic acid analog

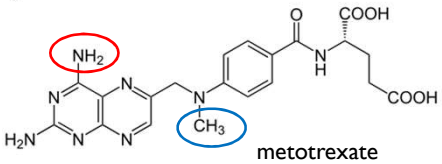
- In 1950, it was evidenced that metotrexate is equally efficient to aminopterine, but less toxic.
- In 1951, Jane Wright showed efficiency of metotrexate in case of other cancers (eg. breast cancer).




Kwas foliowy



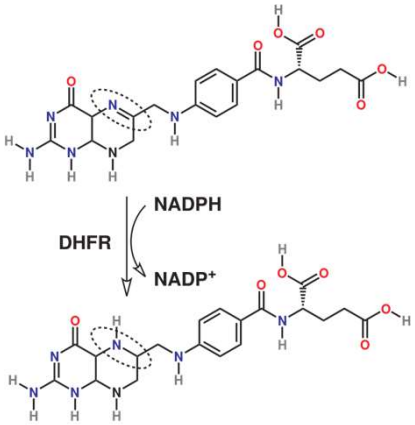

aminopterine




metotrexate

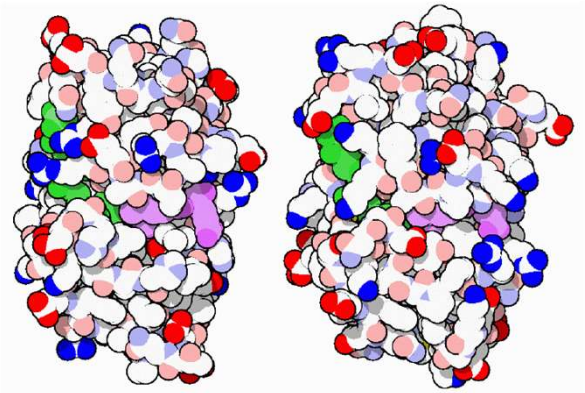
## Metotrexate – mode of action

- Metotrexate is competitive inhibitor of dihydrofolate reductase
- Metotrexate binds ca. 10 000 times stronger to enzyme than substrate.
- Tetrahydrofolate is indispensable to tymidine synthesis and subsequently DNA and RNA.




## Metotrexate – mode of action

- Mode of binding of folate and metotrexate is very similar, but compounds differ substantially in energy of binding to the enzyme.



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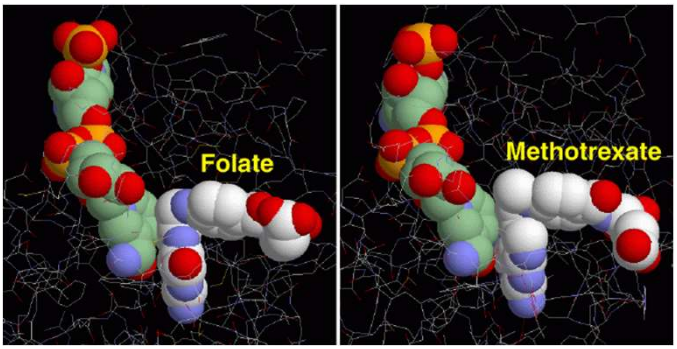
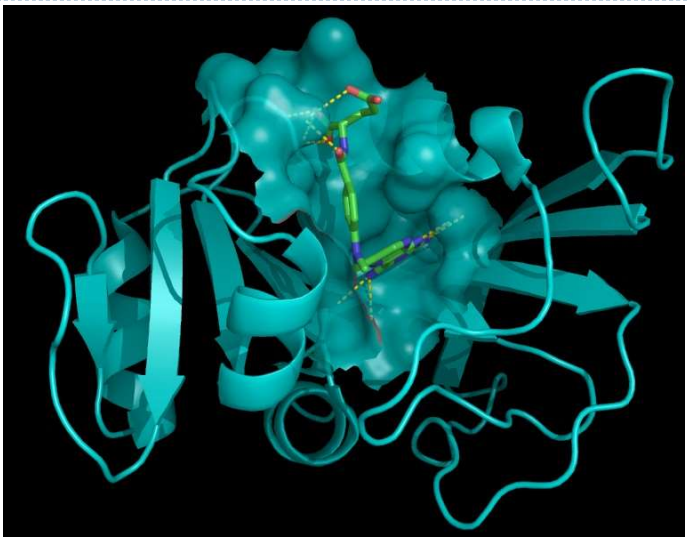



## Metotrexate – mode of action



## Analogs

- Even without knowledge concerning the structure of molecular target, rational development of analogs with considerable better properties:
  - activity;
  - selectivity;
  - Physicochemical properties;
  - Drug metabolism;
  - toxicity;
- Additionally, studies on analogs allows circumvention of patent rights.

## Types of analogs

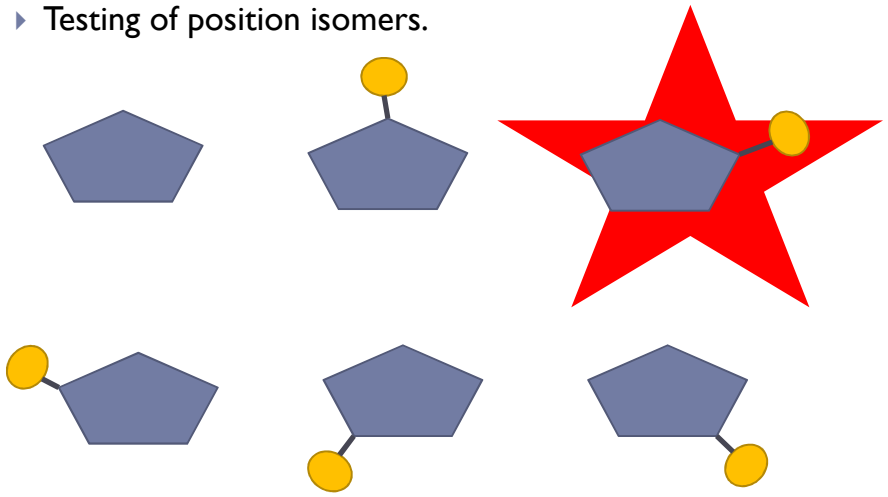
- Homologs
- Position isomers
- Optical isomers
- Isosteric compounds
- Transformation of cyclic systems

## Analogs

- Homologs are compounds differing by constant unit, typically $CH_2$
- vinylogs – compounds differing by vinyl group -CH=CH-
- Position isomers (regioisomers) – compounds, where functional groups are positioned at different places of the scaffold.

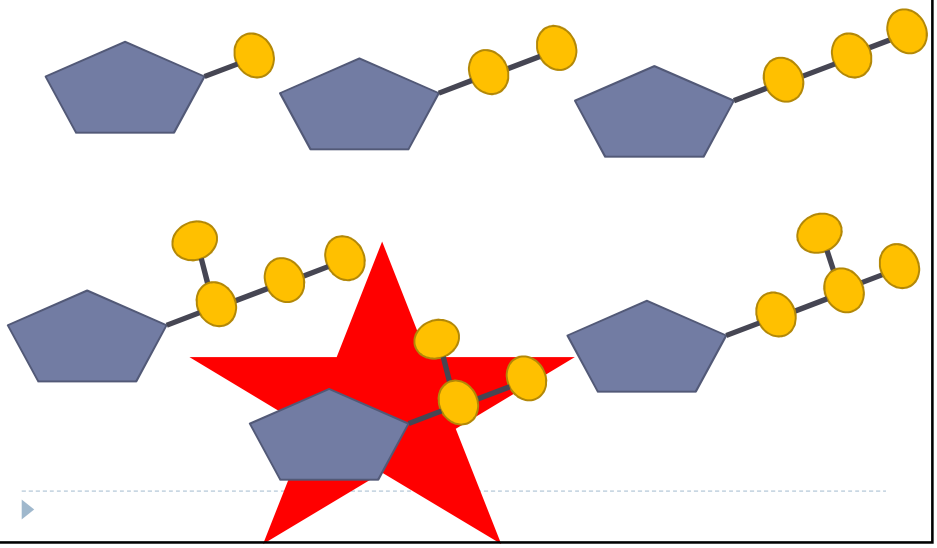
## Analogs

- Testing of position isomers.



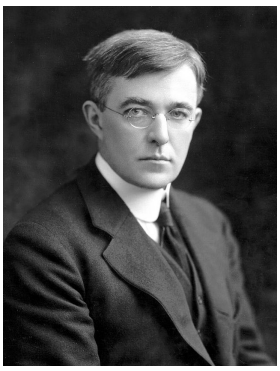
## Analogs

- Testing of homologs



## Isosteric compounds

- Isosteric compounds – (Langmuir, 1919), compounds or group od atoms which have the same number of atoms and electrons.
  - $N_2$ i CO
  - $N_2O$ i $CO_2$
  - $N_3^-$ i $NCO^-$



Irving Langmuir

## Isosteric compounds

- Grimm (1925):

„Atoms anywhere up to four places in the periodic system before an inert gas change their properties by uniting with one to four hydrogen atoms, in such a manner that the resulting combinations behave like pseudoatoms, which are similar to elements in the groups one to four places respectively, to their right."

| C | N | O | F | Ne | Na |
|---|---|---|---|---|---|
| | CH | NH | OH | FH | – |
| | | $CH_2$ | $NH_2$ | $OH_2$ | $FH_2^+$ |
| | | | $CH_3$ | $NH_3$ | $OH_3^+$ |
| | | | | $CH_4$ | $NH_4^+$ |

## Isosteric compounds

- Erlenmayer:
  - Compounds or groups of atoms with the same number of valence electrons.

| no. of peripheral electrons | | | | |
|---|---|---|---|---|
| 4 | 5 | 6 | 7 | 8 |
| $N^+$ | P | S | Cl | ClH |
| $P^+$ | As | Se | Br | BrH |
| $S^+$ | Sb | Te | I | IH |
| $As^+$ | | PH | SH | $SH_2$ |
| $Sb^+$ | | | $PH_2$ | $PH_3$ |

## Bioisosteric compounds

- Bioisosteric compounds – compounds or groups of atoms with similar chemical and physical properties and exhibiting similar biological activity
- Parameters related to bioisosteric replacement:
  - Size, conformations, inductive and mesomeric effects, polarizability, possibility of hydrogen bonds formation, acidity, solubility, hydrophobicity, reactivity and stability.

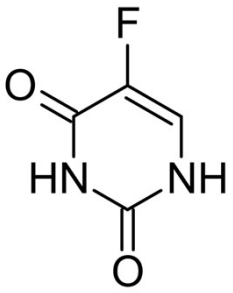
## Classical bioisosteric replacement

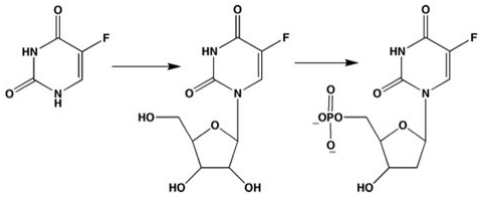
- H – F replacement
- Fluorine atom has similar size to hydrogen atom but considerably different properties.

| | H | F | Cl | $CH_3$ | $CF_3$ |
|---|---|---|---|---|---|
| Van der Waalsa diameter | 1.2 | 1.35 | 1.8 | 2 | 2 |
| Moleclar refraction 1.03 | 0.92 | 6.03 | 5.65 | 5.02 | |
| Indctive effect | - | 3.08 | 2.68 | 0.0 | 2.85 |
| Resonace effect | 0.0 | -0.34 | -0.15 | -0.13 | 0.19 |

## Fluorouracil

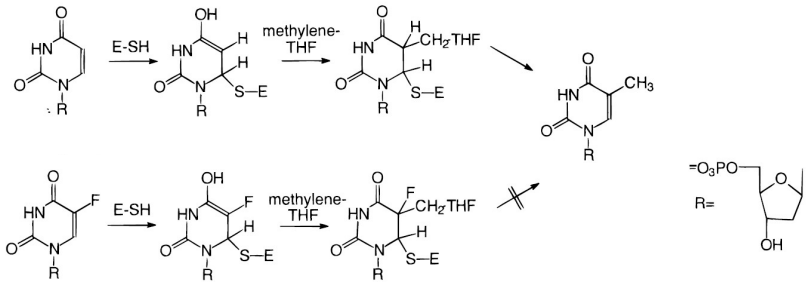
- Anticancer drug
- Irreversible inhibitor of timidylate synthase
- Inhibition of this enzyme causes inhibition of DNA synthesis
- First steps of its metabolism are similar to uracil.



## Fluorouracil

- Increase activity of fluoro-derivative (related to inductive effect) causes irreversible binding to the enzyme - tymidylate synthase



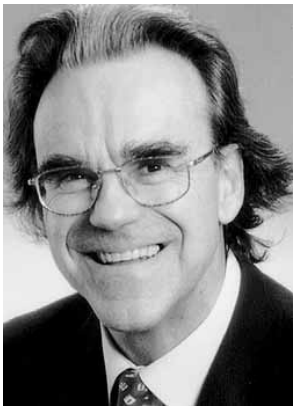

THF - tetrahydrofolate

## Bioisosteric replacements

- Monovalent group replacement
  - $-NH_2$ i -OH
  - -SH i -OH
  - -F, -OH, $-NH_2$ i $-CH_3$
  - -Cl, -Br, -SH i –OH
- Bivalent group replacement
  - C=C, C=N, C=O, C=S
  - $–CH_2–$, –NH–, –O–, –S–
- Trivalent group replacement
  - –CH=, –N=
- Tetravalent group replacement
  - $R_4C$, $R_4Si$, $R_4N+$

## Bisphosonates

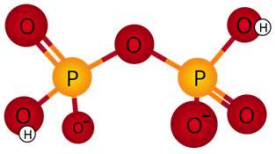
- Herbert Fleisch showed that there are some compounds in blood and urine, which inhibits precipitation of inorganic phosphates (e.g. Calcium phosphate).
- This is pyrophosphate
- He assumed that pyrophoasphates are responsible for mineralisation and demineralisation of bones
- Such compounds could be used in diseases related to such processes e.g. osteoporosis.



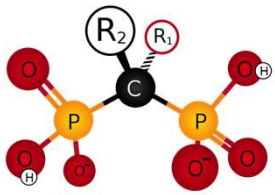
Herbert Fleisch

## Bisphosphonates

- Pyrophosphates showed too low stability and and are metabolized rapidly in living organism.
- H. Fleisch has proposed highly stable analogs of pyrophosphates – bisphosphonates.



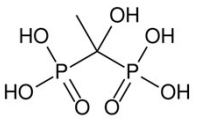
pyrophosphate



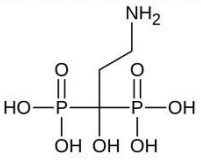
bisphosphonate

## Bisphosonates

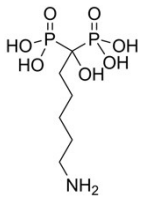
- Bisphosphonates are effective against osteoporosis
- Further side chain modifications allowed for effective optimization of the activity
- Zoledronate is 10,000 times more effective than etidronate.



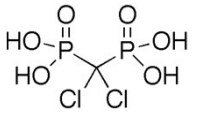
Etidronate



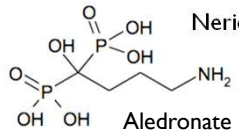
Pamironate



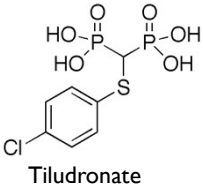
Neridronate



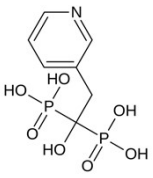
clodronate



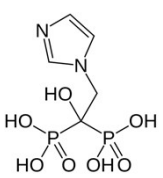
Aledronate



Tiludronate



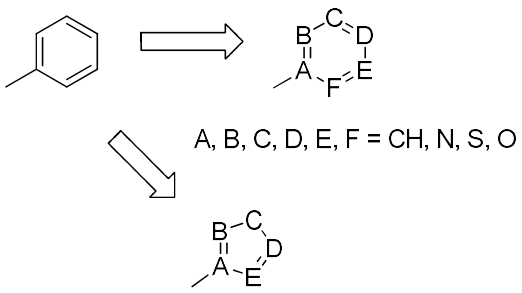
Rizedronate



Zoledronate

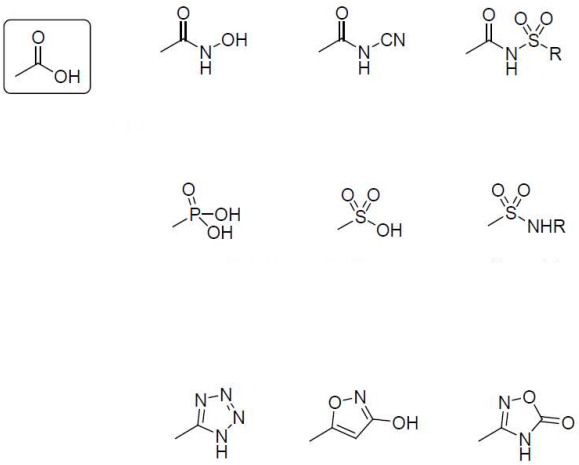
## Bioisosteric replacement

- Aromatic ring replacement



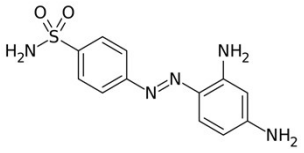

## Bioisosteric replacement

- Replacement of COOH



## Sulfonamide antibiotics

- Bayer's laboratories tested the dyes for antibacterial properties.
- In 1932, Gerhard Domagk discovered that a compound called Prontosil has antibacterial properties in vivo tests (mice).

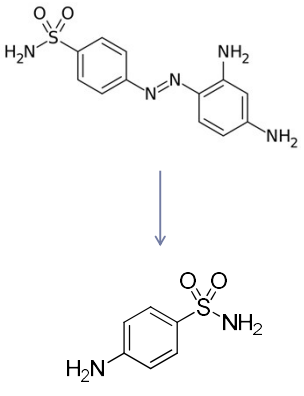



Prontosil

Gerhard Domagk

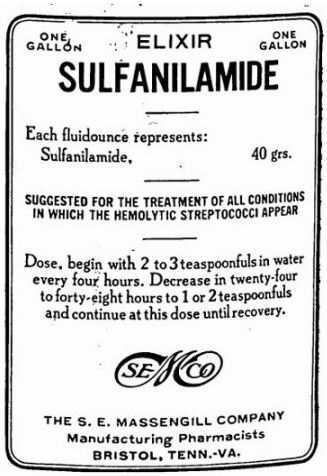
## Sulfonamide antibiotics

- Prontosil was the first sulfonamide drug and significantly improved the treatment options for bacterial infections.
- Gerhard Domagk received the Nobel Prize (1939) for this discovery
- The Ernest Fourneau Group (Pasteur Institute, 1935) has shown that Prontosil is metabolised to sulfanilamide which has antibacterial properties.



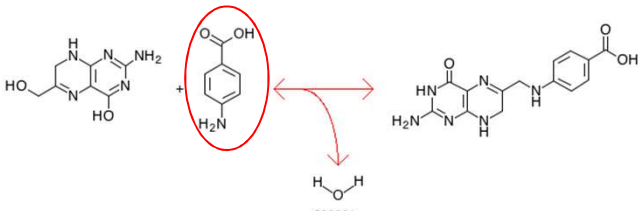
## Sulfonamide antibiotics

- Prontosil became famous after the successful therapies of famous people: Franklin Roosevelt Jr. and Winston Churchill.
- There have been many formulations of the drug. 'Elixir Sulfanilamide' proved to be highly toxic due to the use of ethylene glycol.
- This has led to the need for closer control of drug production - the Food and Drug Administration has been established.



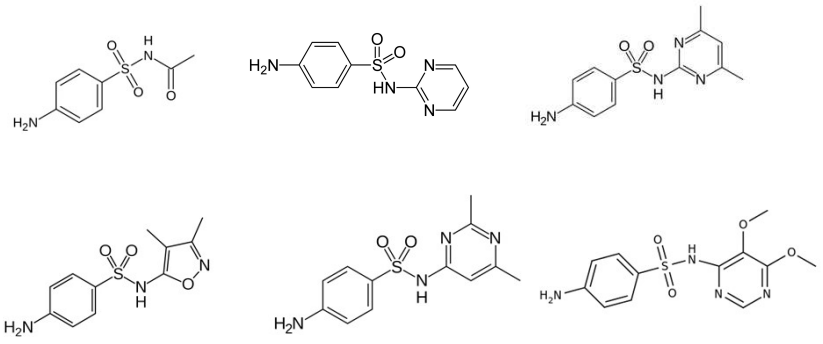

## Sulfonamide antibiotics

- Sulanilamides are competitive inhibitors of dihydrofolate synthesis
- Sulfanilamides are structural analogues of *p*-aminobenzoic acid.



## Sulfonamide antibiotics

- A wide spectrum of antibacterial sulfamide drugs is currently being used.



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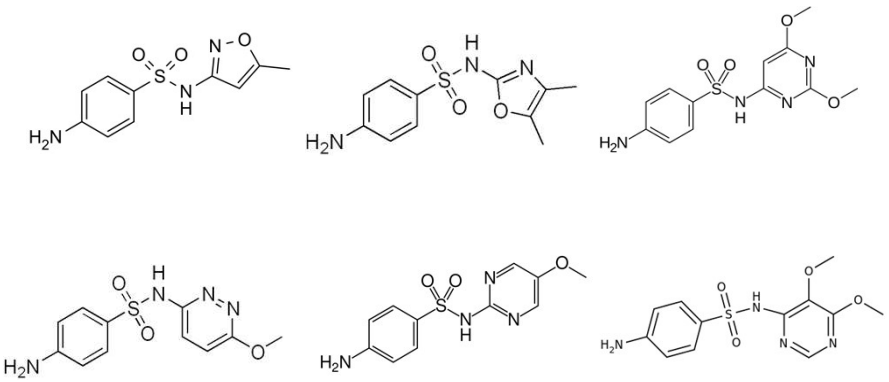
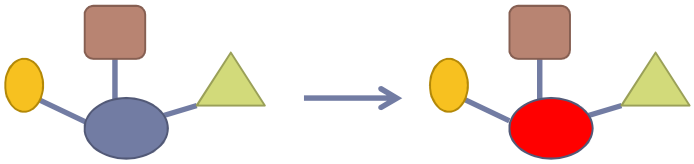


## Scaffold hopping

- *‚Scaffold hopping'* – A methodology to find new structurally differentiated classes of compounds by altering the central part of the active molecule.
- *Scaffold hopping* may influence:
  - polarity,
  - metabolism,
  - stiffness,
  - biological activity.

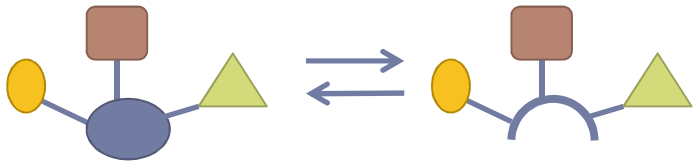
## Scaffold hopping

- Types:
  - Exchange of heterocycles:
    - high probability of success;
    - easy design;
    - A small range of possible changes in compound characteristics.



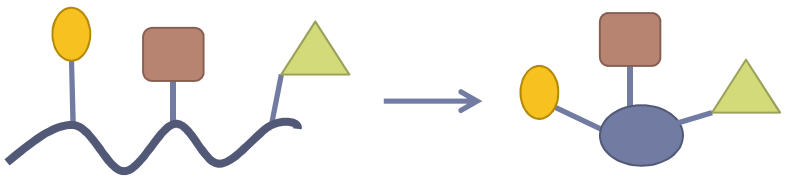
## Scaffold hopping

- Types:
  - Closing/opening of cyclic systems:
    - can increase activity and/or stability;
    - may impair solubility and synthetic accessibility.



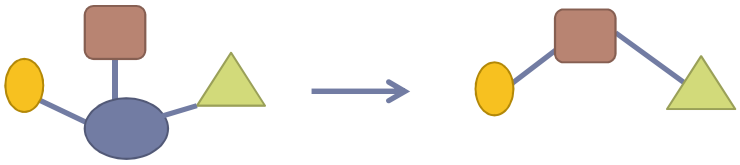
## Scaffold hopping

- Types:
  - peptidomimetics
    - known peptides with biological activity;
    - problems with metabolic stability.



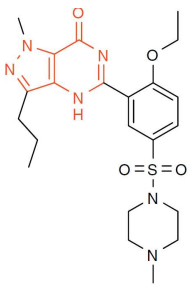
## Scaffold hopping

- Types:
  - Changes based on topology
    - significantly new structural motif that can lead to interesting properties;
    - non-trivial design.

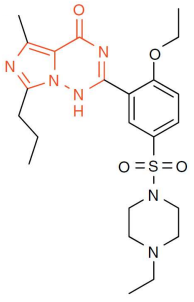


## Modification of the heterocyclic system

- Inhibitors of phosphodiesterase type 5, PDE5



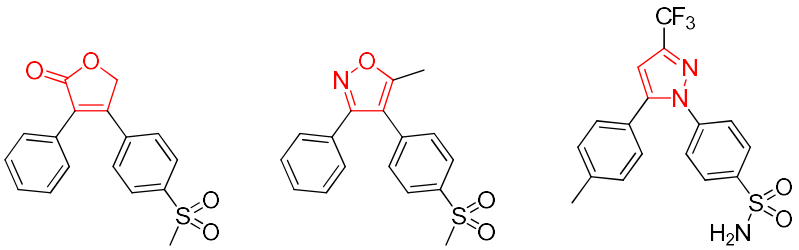
Sidenafil
(Viagra)



Vardenafil
(Levitra)

## Modification of the heterocyclic system

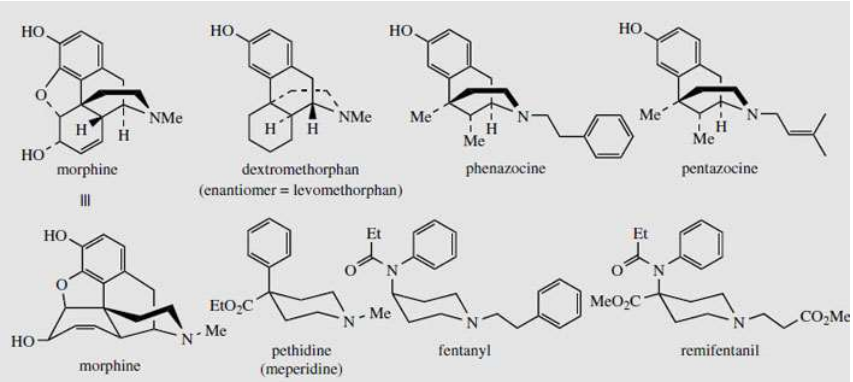
- Non-steroidal anti-inflammatory drugs– inhibitors of COX-2



Vioxx Bextra Celebrex

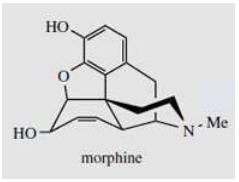
## Ring opening

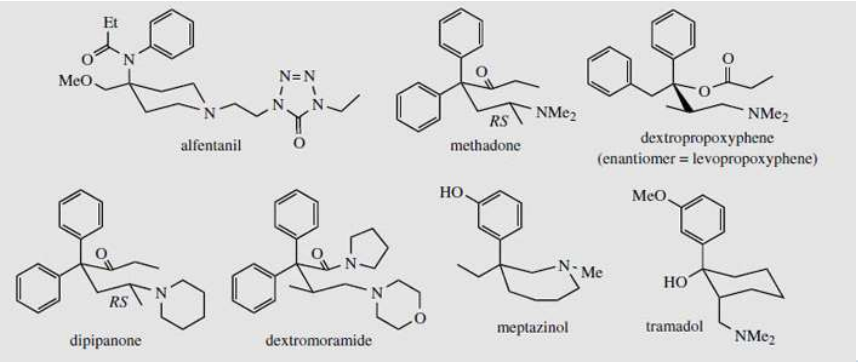
- Morphine analogs



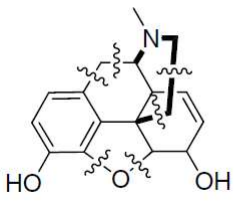
## Painkillers

- Morphine analogs

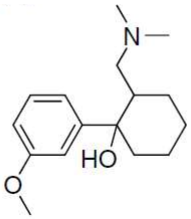



## Painkillers




morphine




tramadol

## Summary

- Examination of the analogues of the hit is one of the basic methods for finding compounds with optimal properties.
- The construction of analogs can be rational.