

STRUCTURE and ACTIVITY of DRUGS - practical aspects I.

György Domány

Scientific adviser
Gedeon Richter Plc.

What is the goal of the pharmaceutical industry?

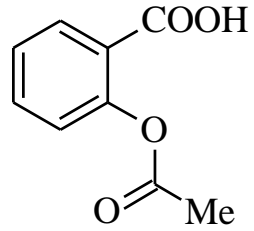
What is the goal of (industrial) drug research?

„We try to remember that medicines are for the patient. We try never to forget that medicine is for the people. It is not for profit. The profits follow and if we've remembered that, they have never failed to appear. The better we have remembered it, the larger they have been.“

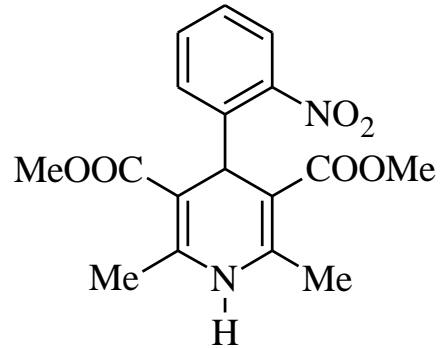
George W. Merck,
former president of Merck & Co.

STRUCTURE

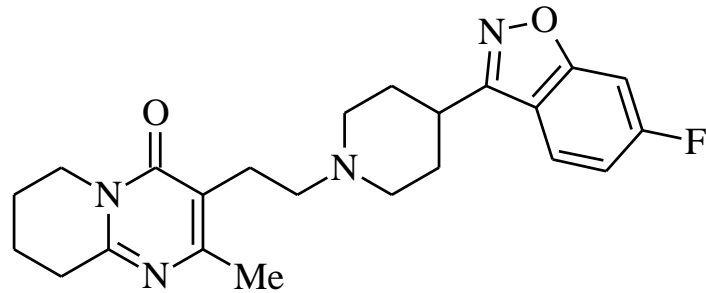
aspirin



nifedipine



risperidone



ACTIVITY

analgetic, antipyretic, antiinflammatory

antihypertensive, antianginal

antipsychotic



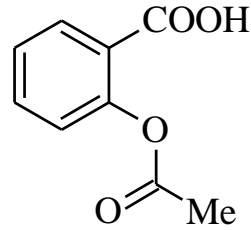
Paul Ehrlich 1854-1915

*„Corpora non agunt nisi fixata
(drugs will not act unless they
are bound)“*

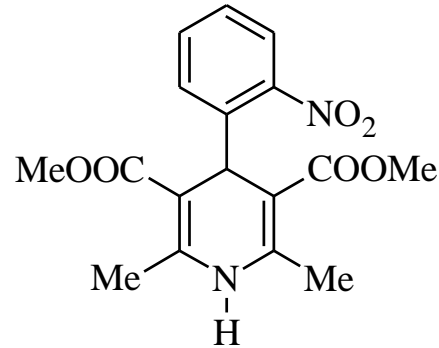
Paul Ehrlich

STRUCTURE

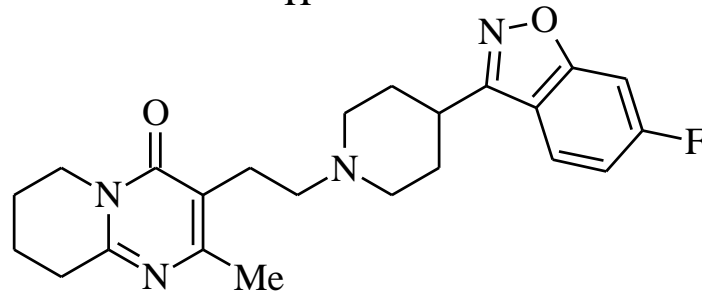
aspirin



nifedipine



risperidone



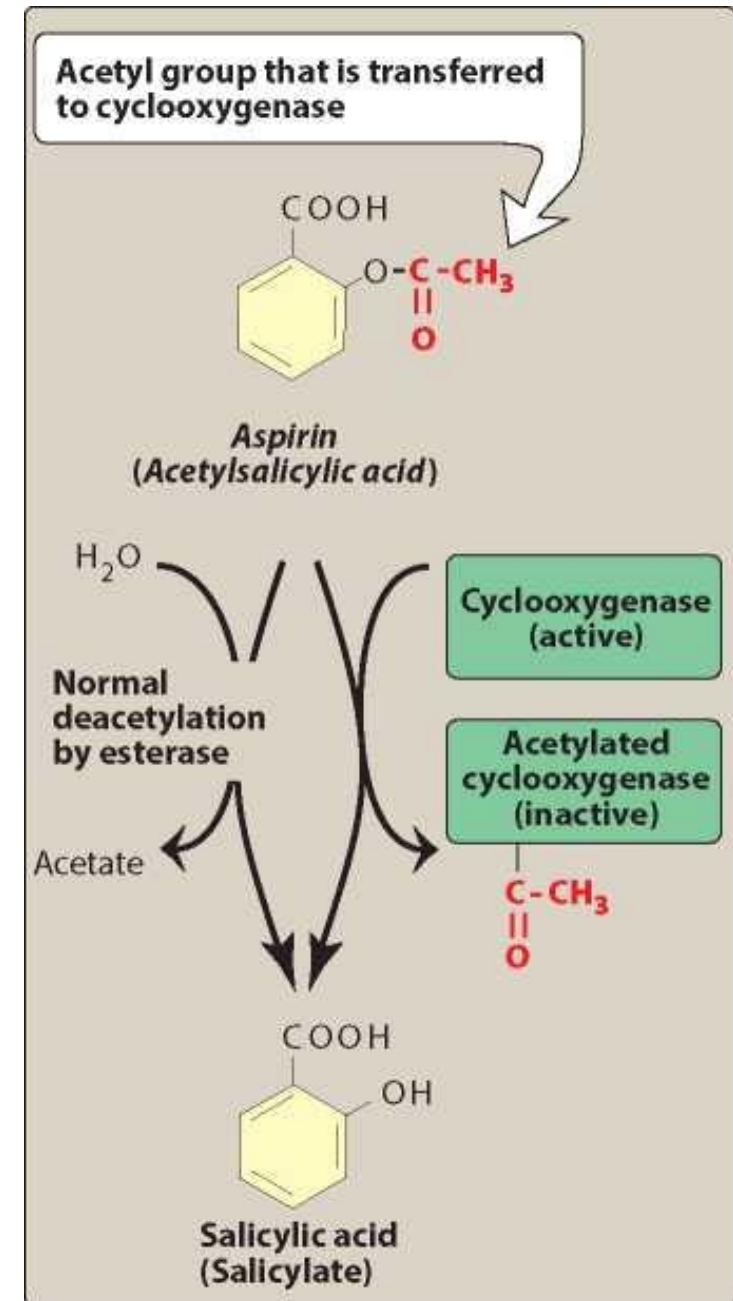
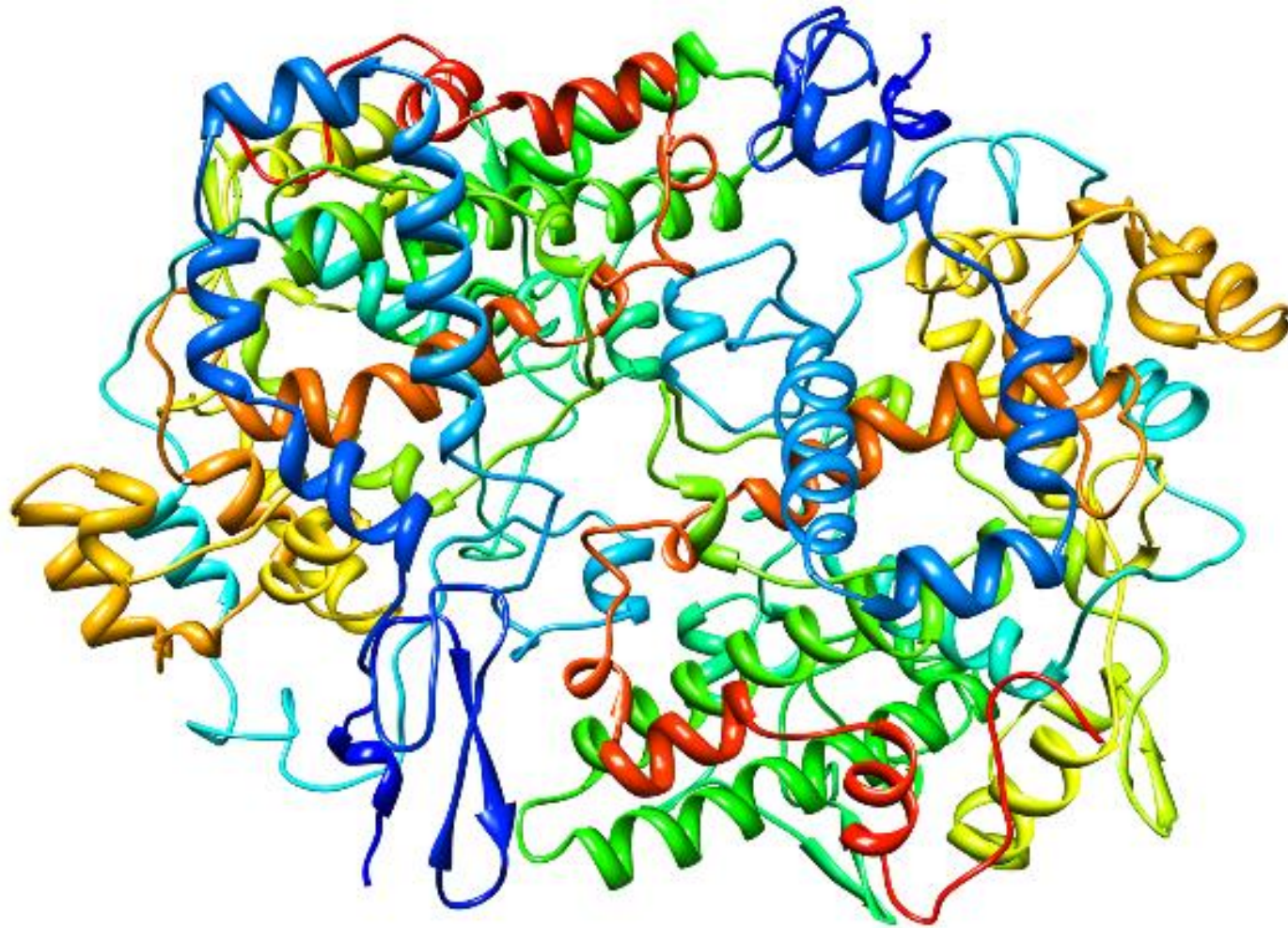
ACTIVITY

analgetic, antipyretic, antiinflammatory
cyclooxygenase (COX) inhibitor

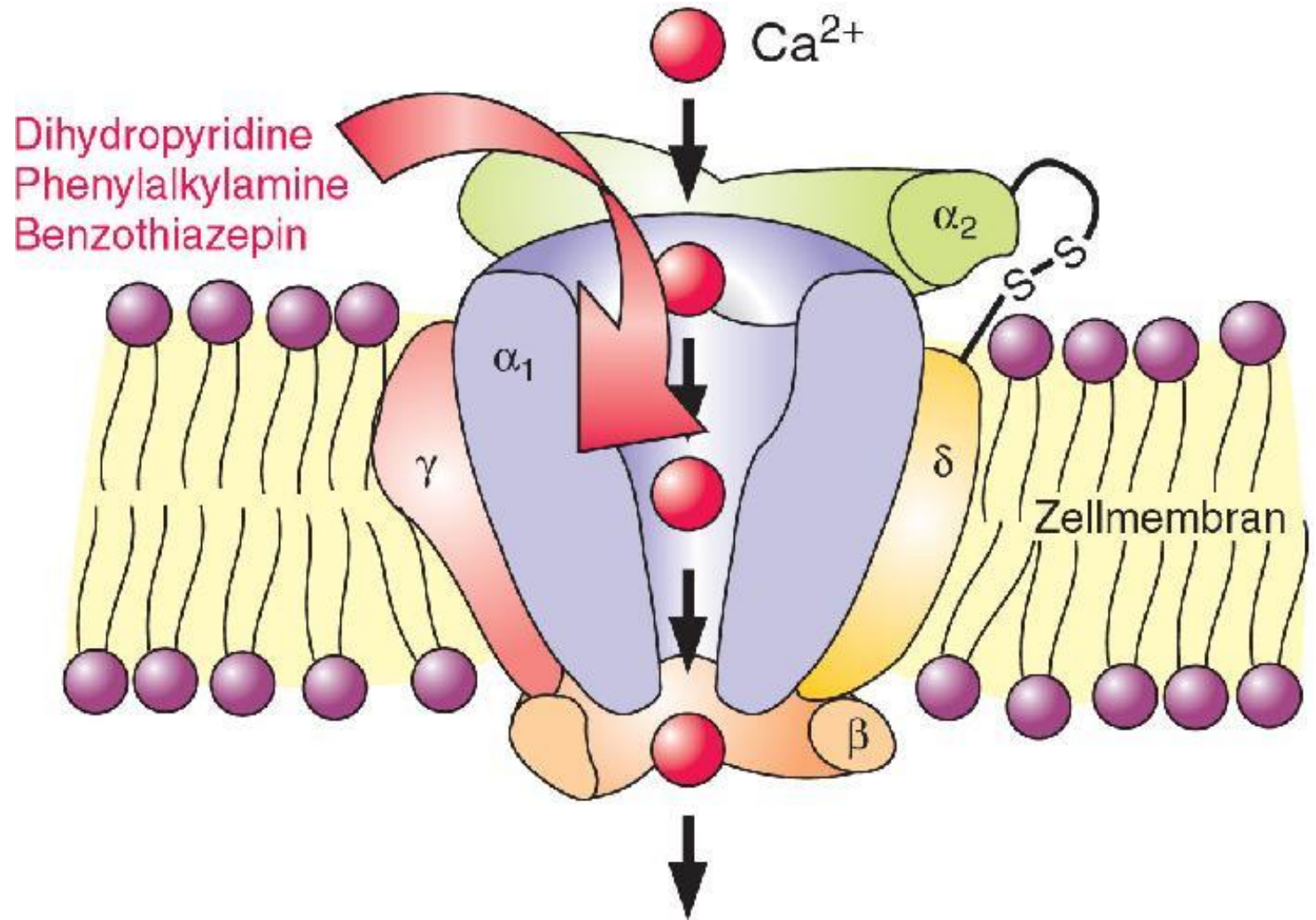
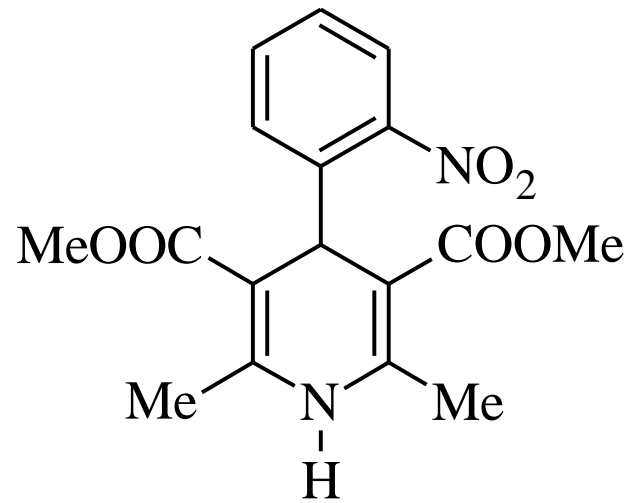
antihypertensive, antianginal
L-type Ca-channel blocker

antipsychotic
dopamine D₂ receptor antagonist

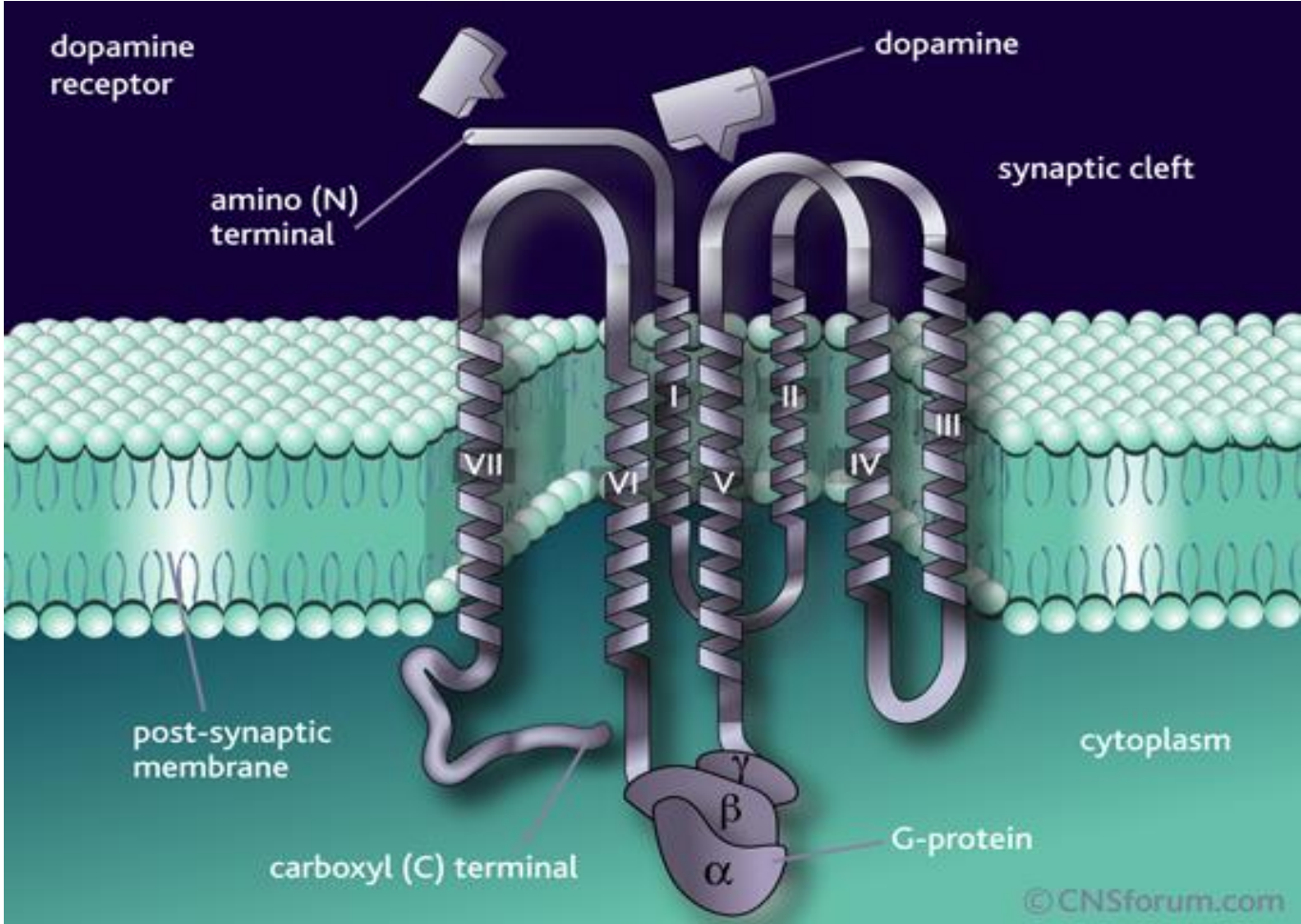
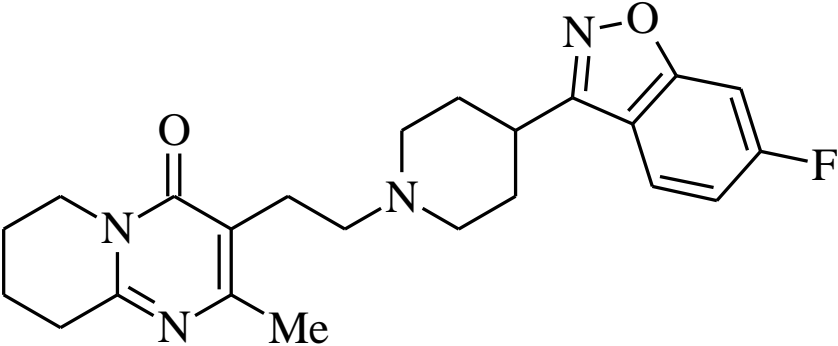
Cyclooxygenase (COX)



Calcium channel



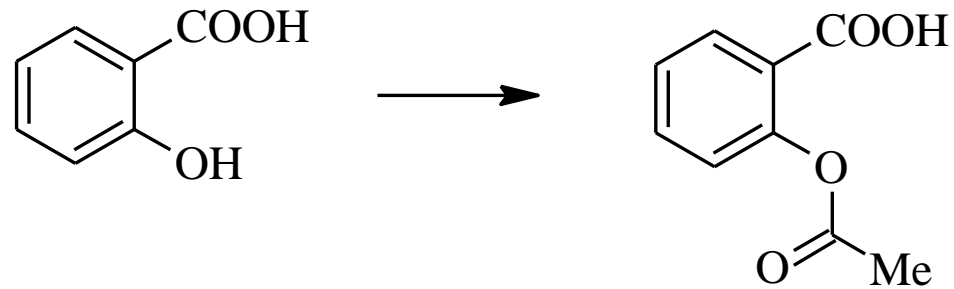
Dopamine D₂ receptor



STRUCTURE,
MoA/BIOLOGICAL
TARGET,
ACTIVITY

The discovery of aspirin

- 400 B.C. Hippocrates recommended a brew made from willow leaves to treat labour pains.
- 1763 Reverend Edward Stone described the benefits he observed after giving ground up willow bark to 50 parishioners suffering from rheumatic fever.
- 1897 Felix Hoffmann/Arthur Eichengrün of Bayer developed the process of synthesizing the acetyl salicylic acid named later as aspirin.



- 1970s the British scientist Professor John Vane discovered that aspirin blocks cyclooxygenase needed for the production of prostaglandins.

How to find a new and
better antiinflammatory
drug?

Symptoms of inflammation

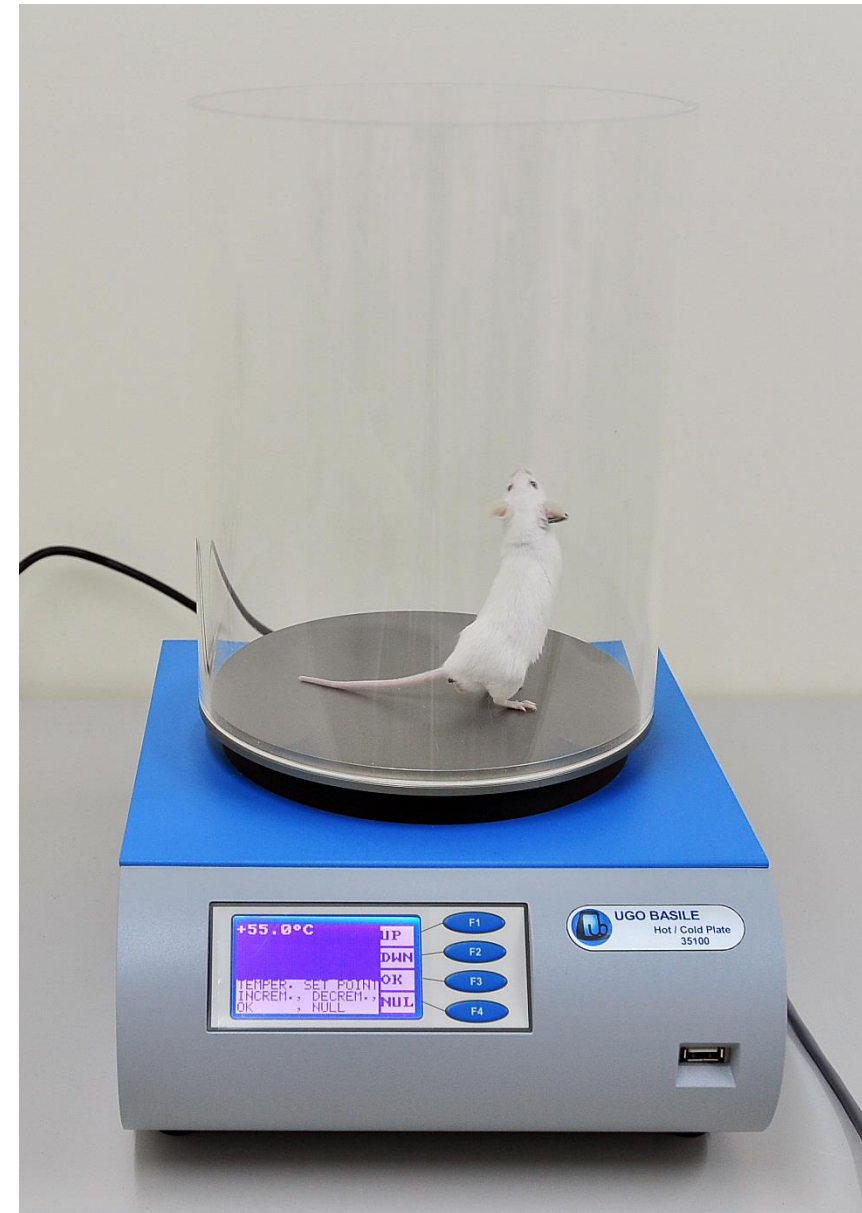
„calor“	heat
„dolor“	pain
„rubor“	redness
„tumor“	swelling
„functio laesa“	loss of function

Phenotypic drug discovery
(PDD)

Synthesis of new compounds



Testing on the hot-plate



A **phenotype** is the composite of an organism's observable characteristics or traits, such as its morphology, development, biochemical or physiological properties, behavior, and products of behavior (such as a bird's nest).

A phenotype results from the expression of an organism's genetic code, its genotype, as well as the influence of environmental factors and the interactions between the two.

Target based drug discovery
(TDD)

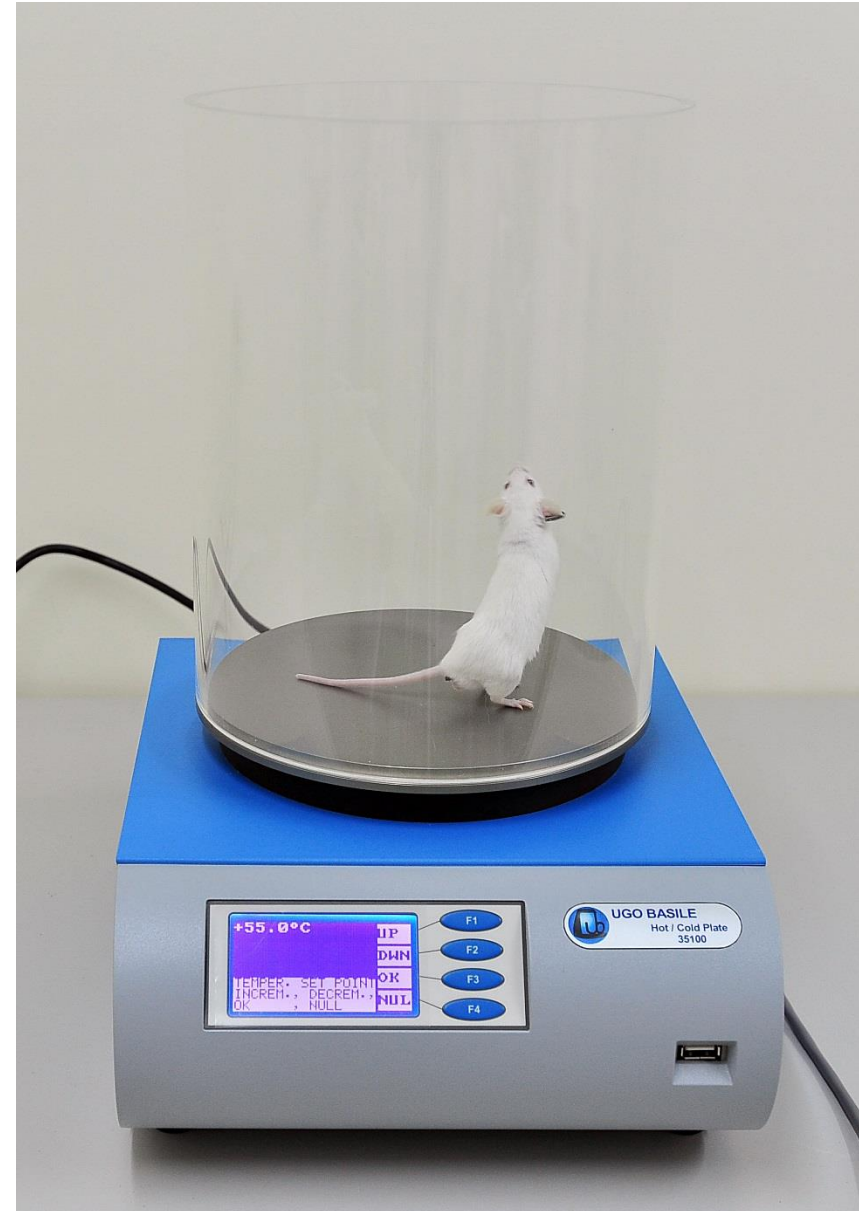
Synthesis of new compounds



Screening COX inhibition



Testing on the hot-plate



PDD & TDD

Synthesis
Analysis

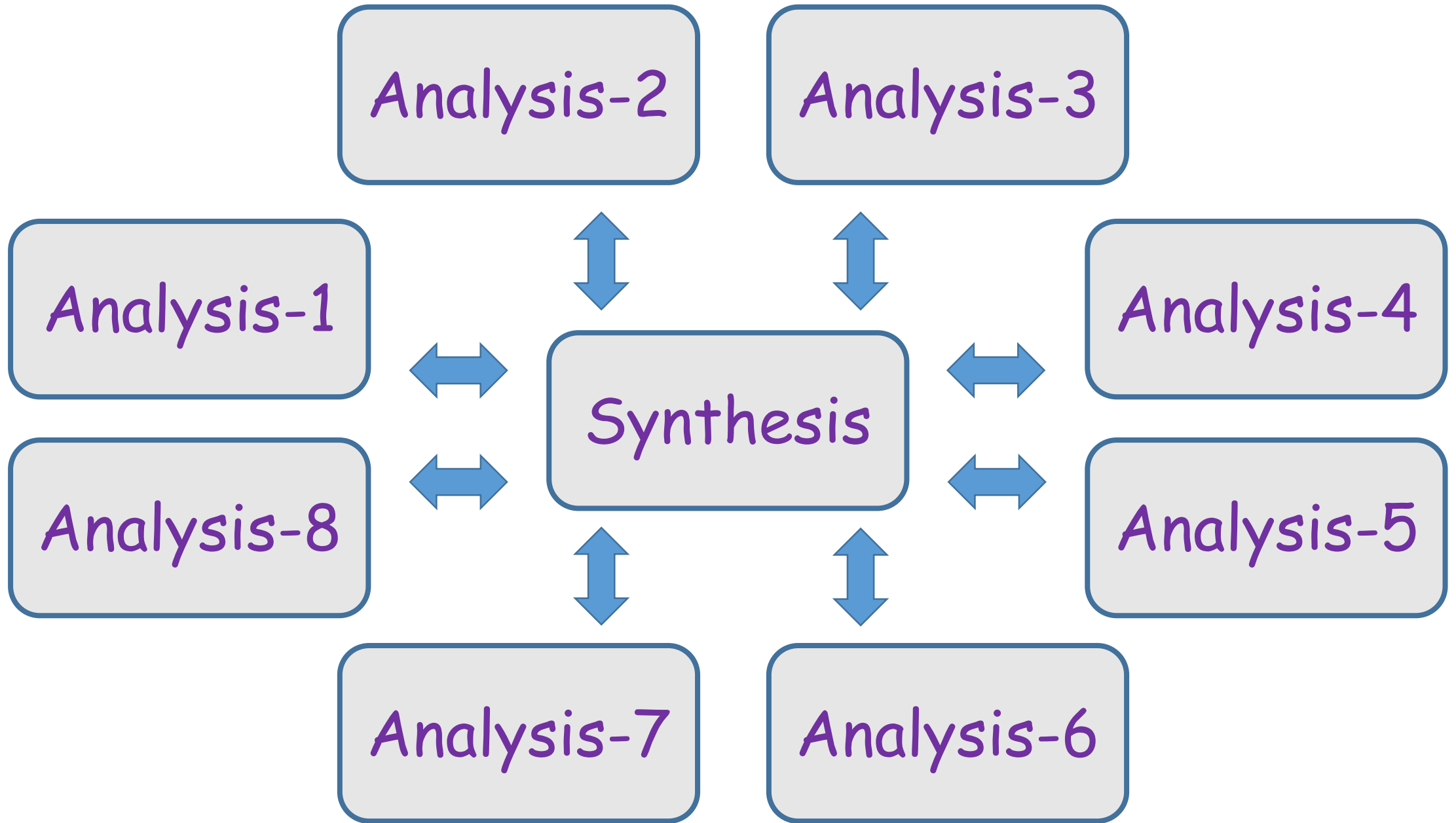


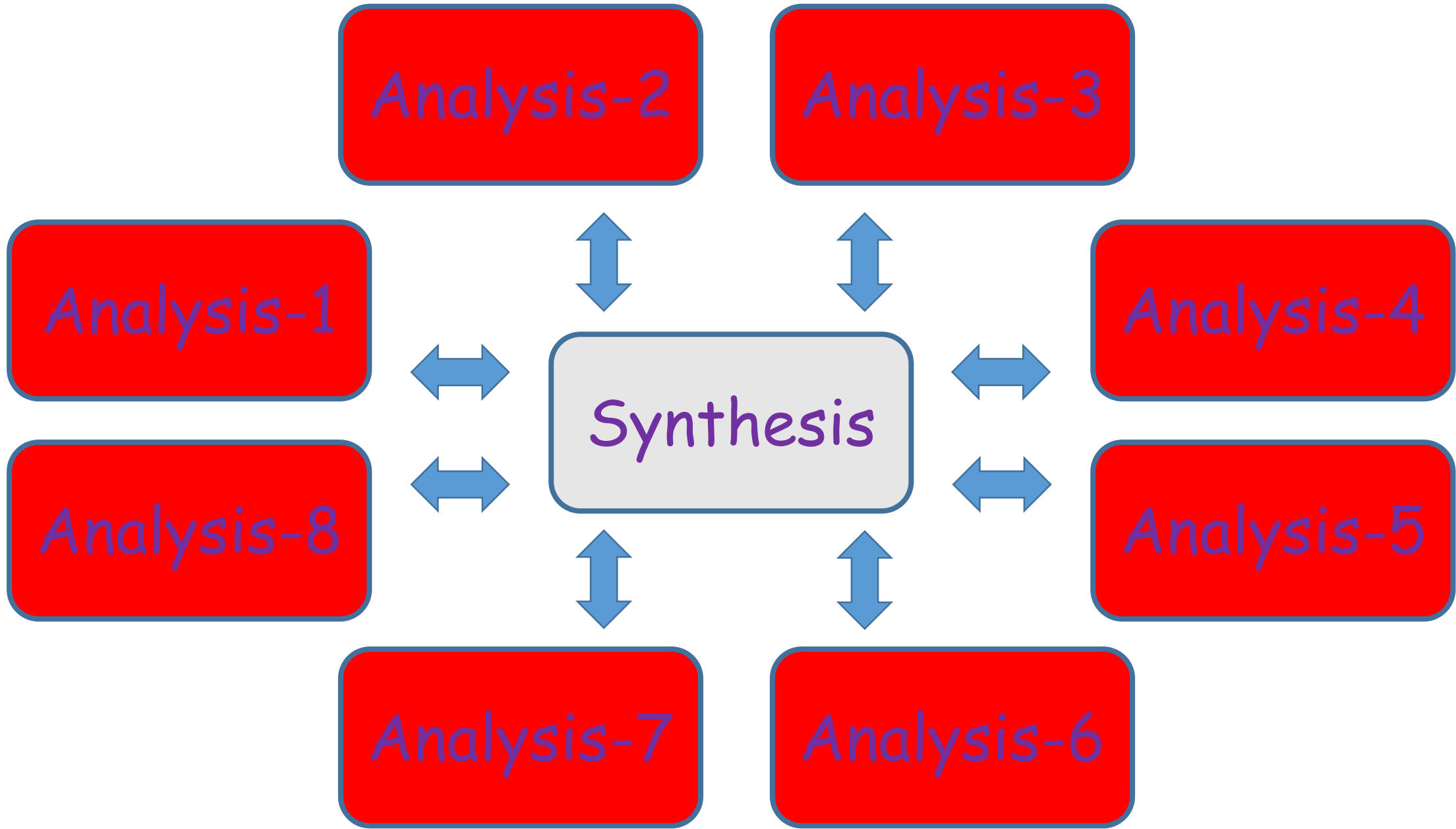
Synthesis

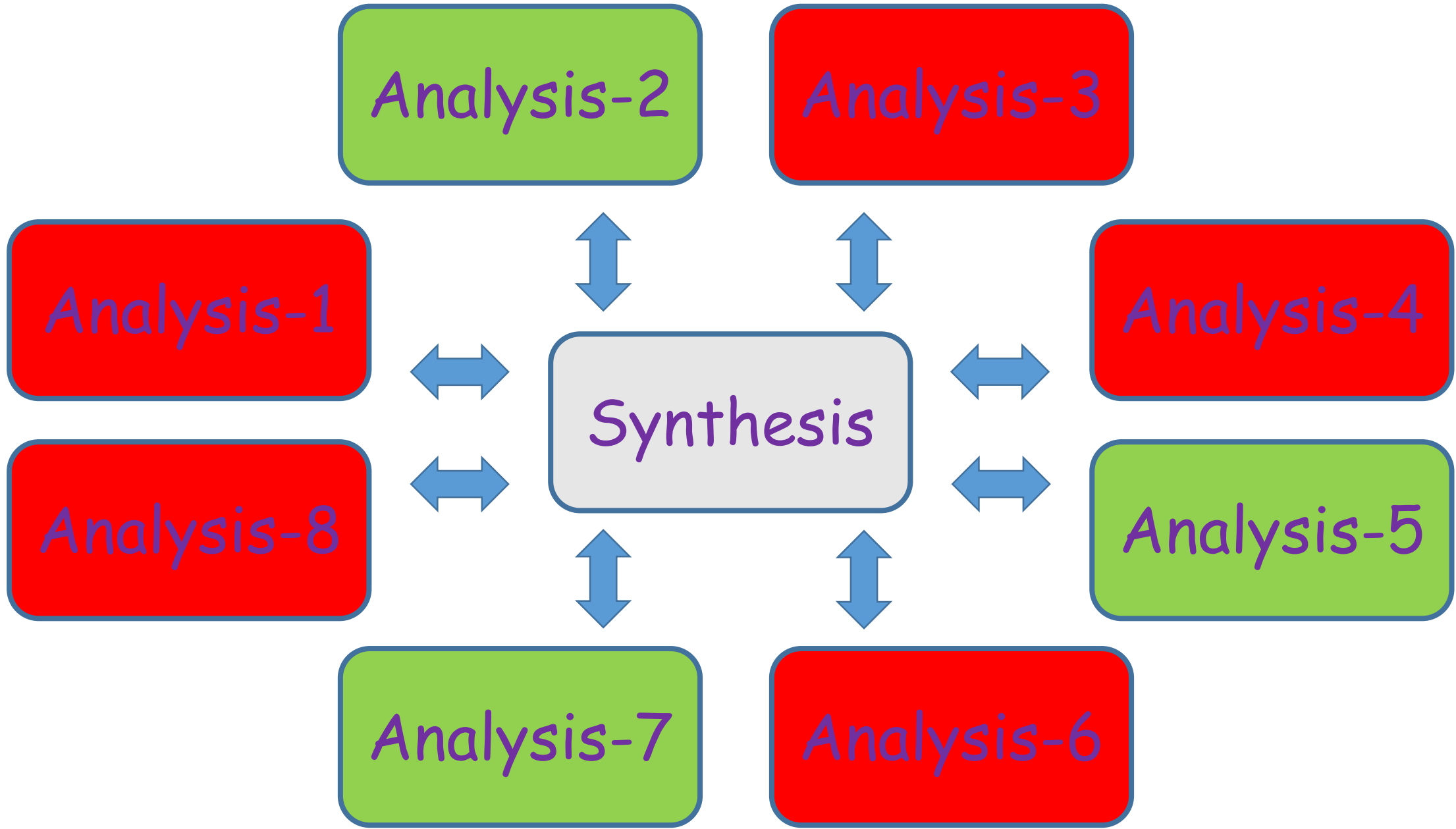


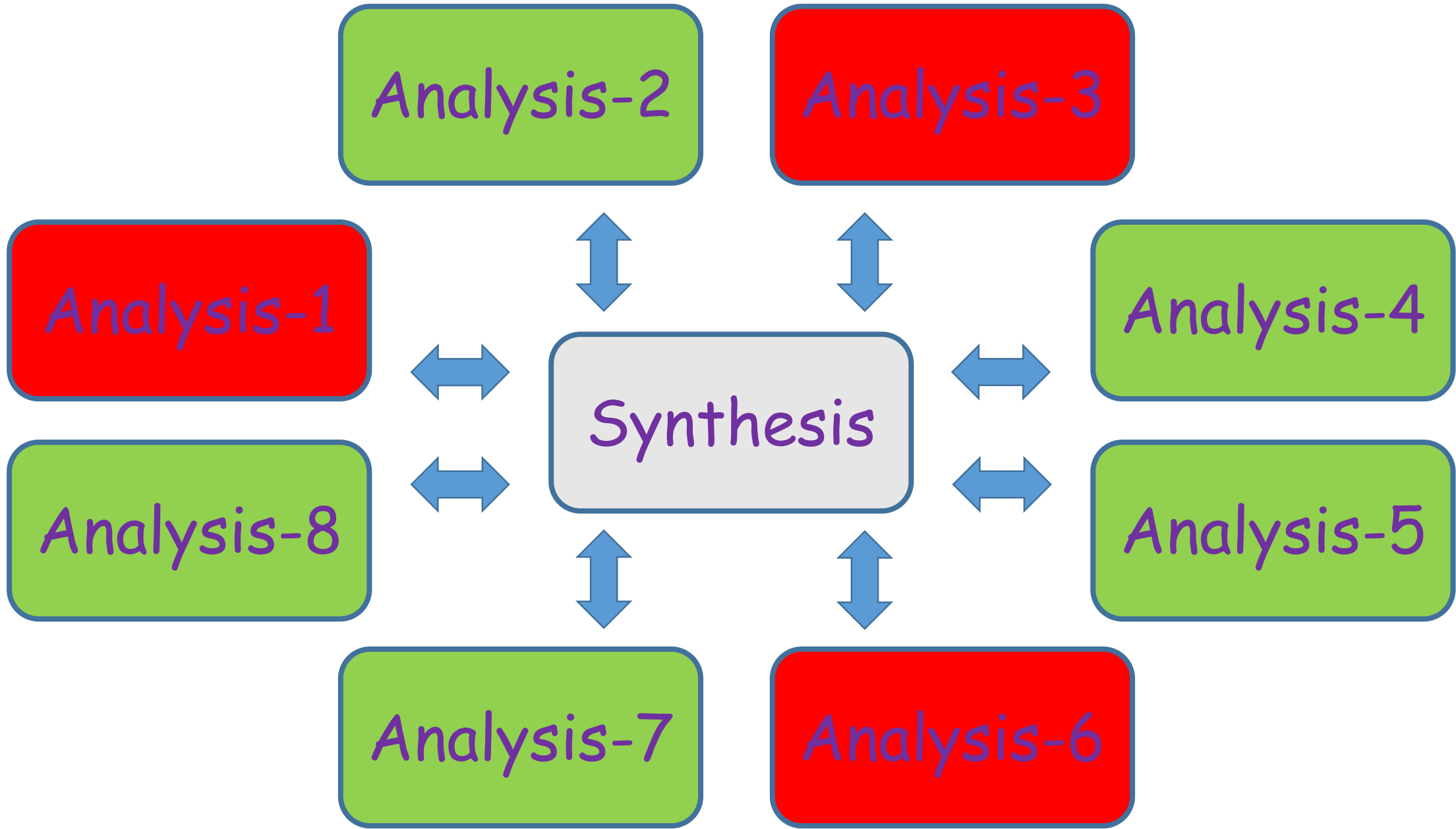
Analysis

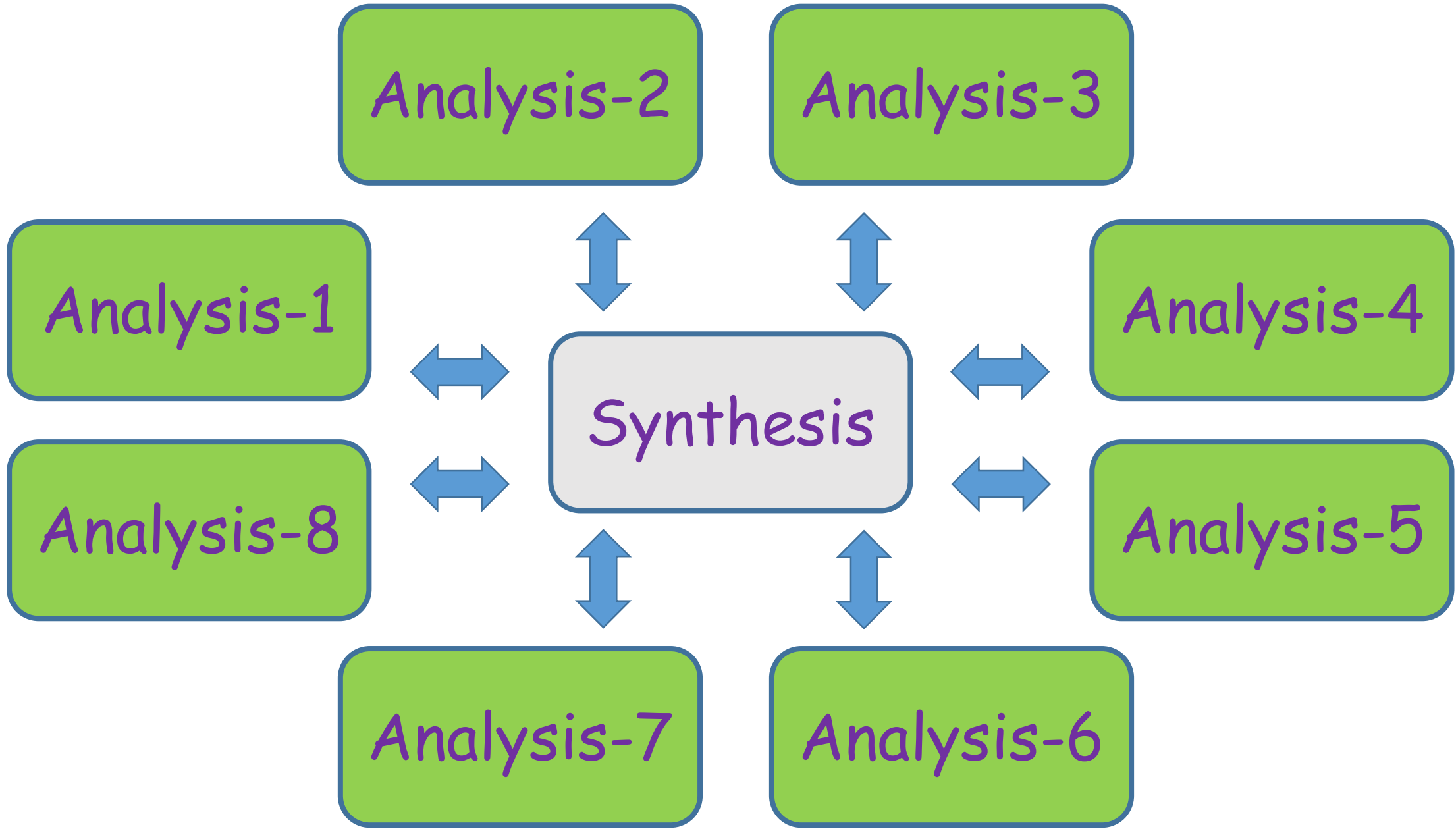


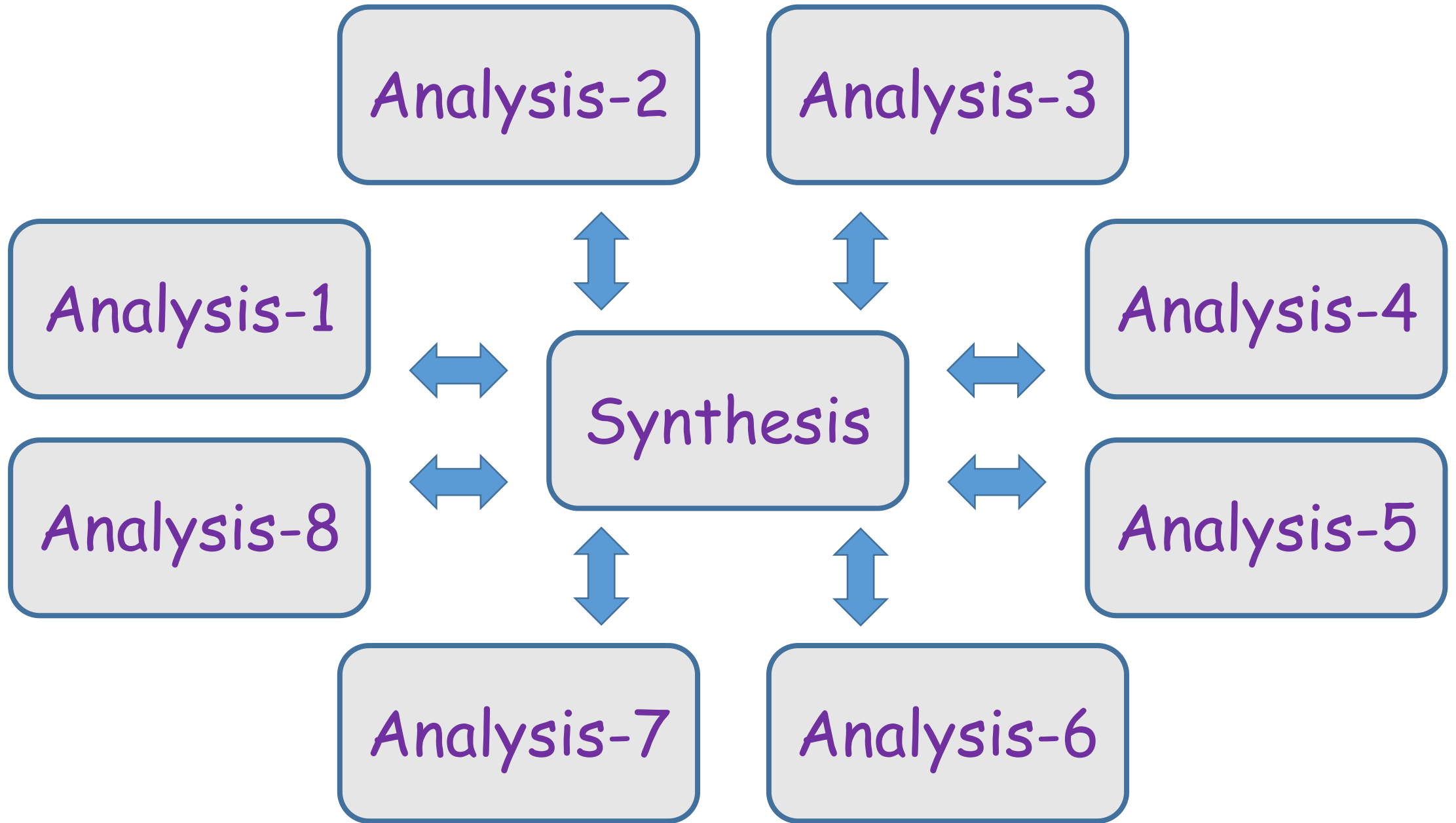


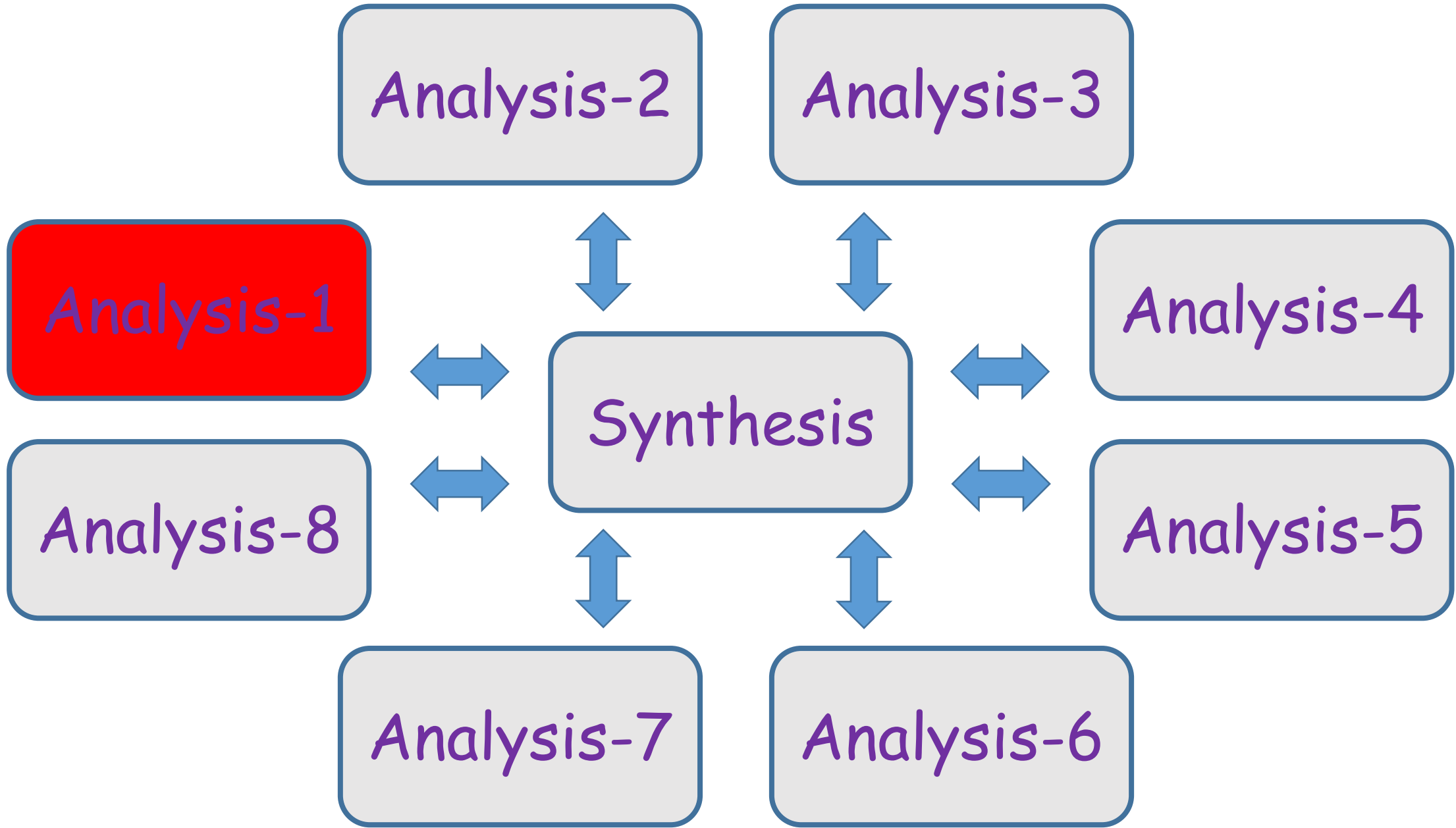


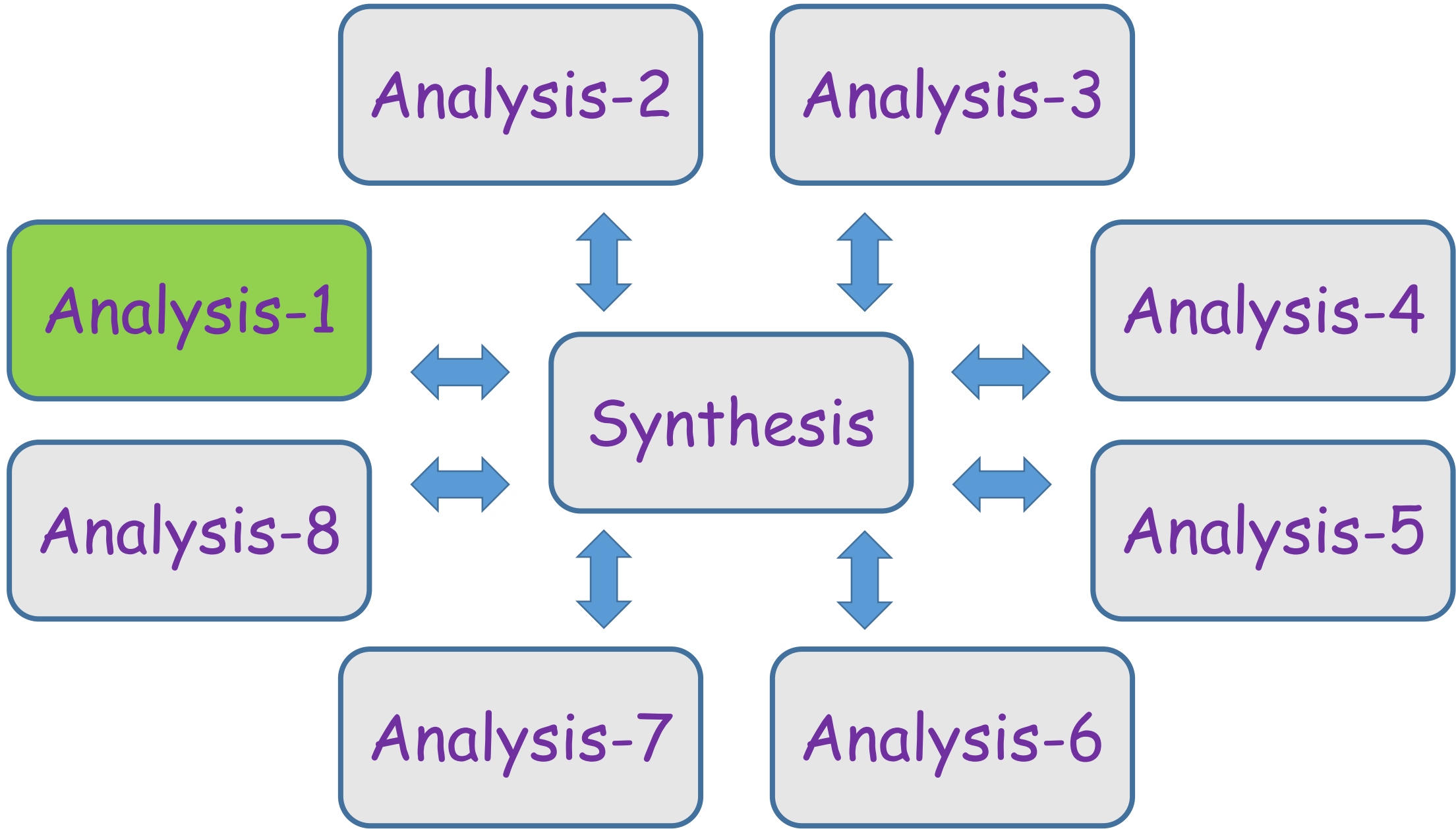


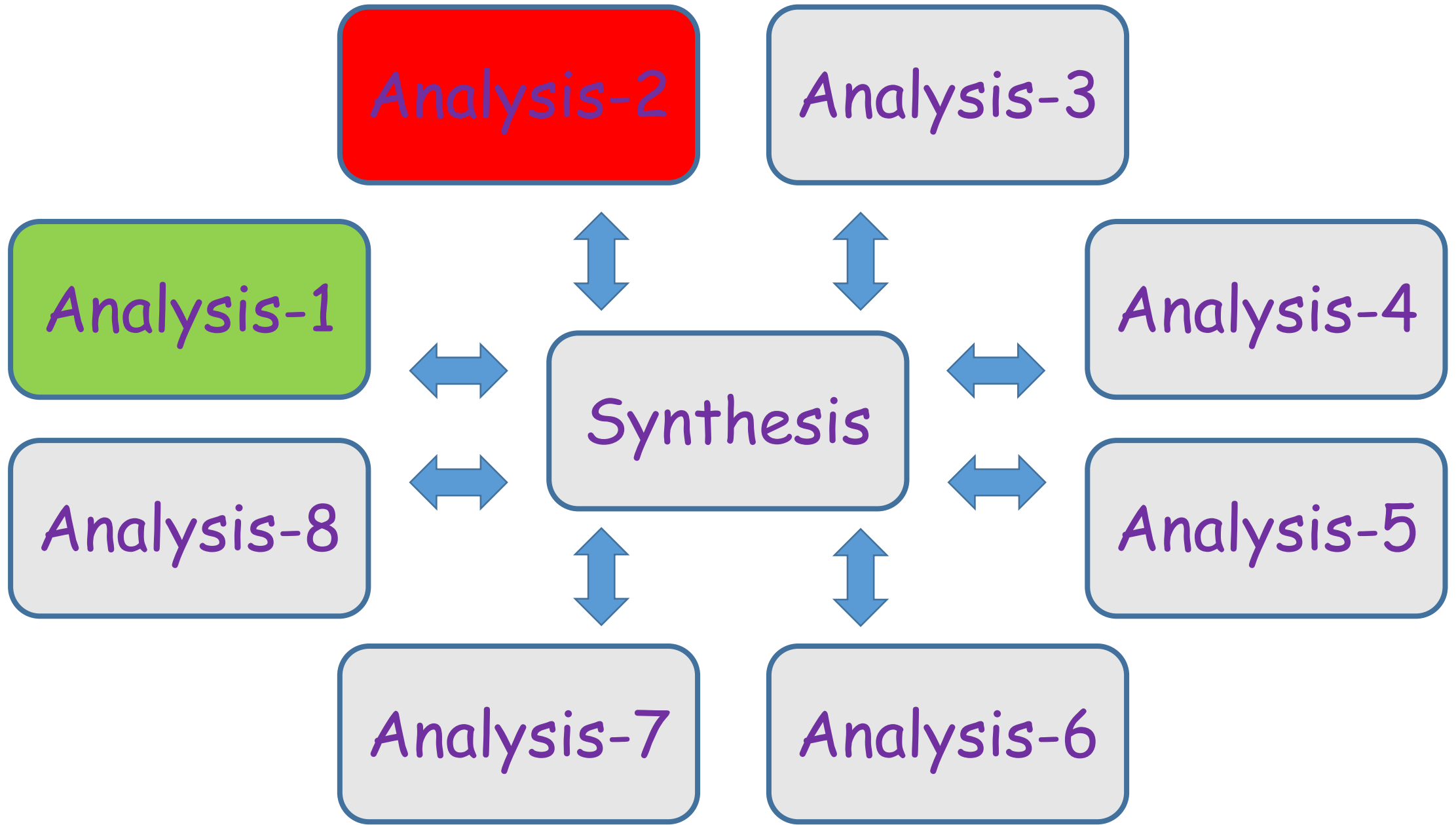


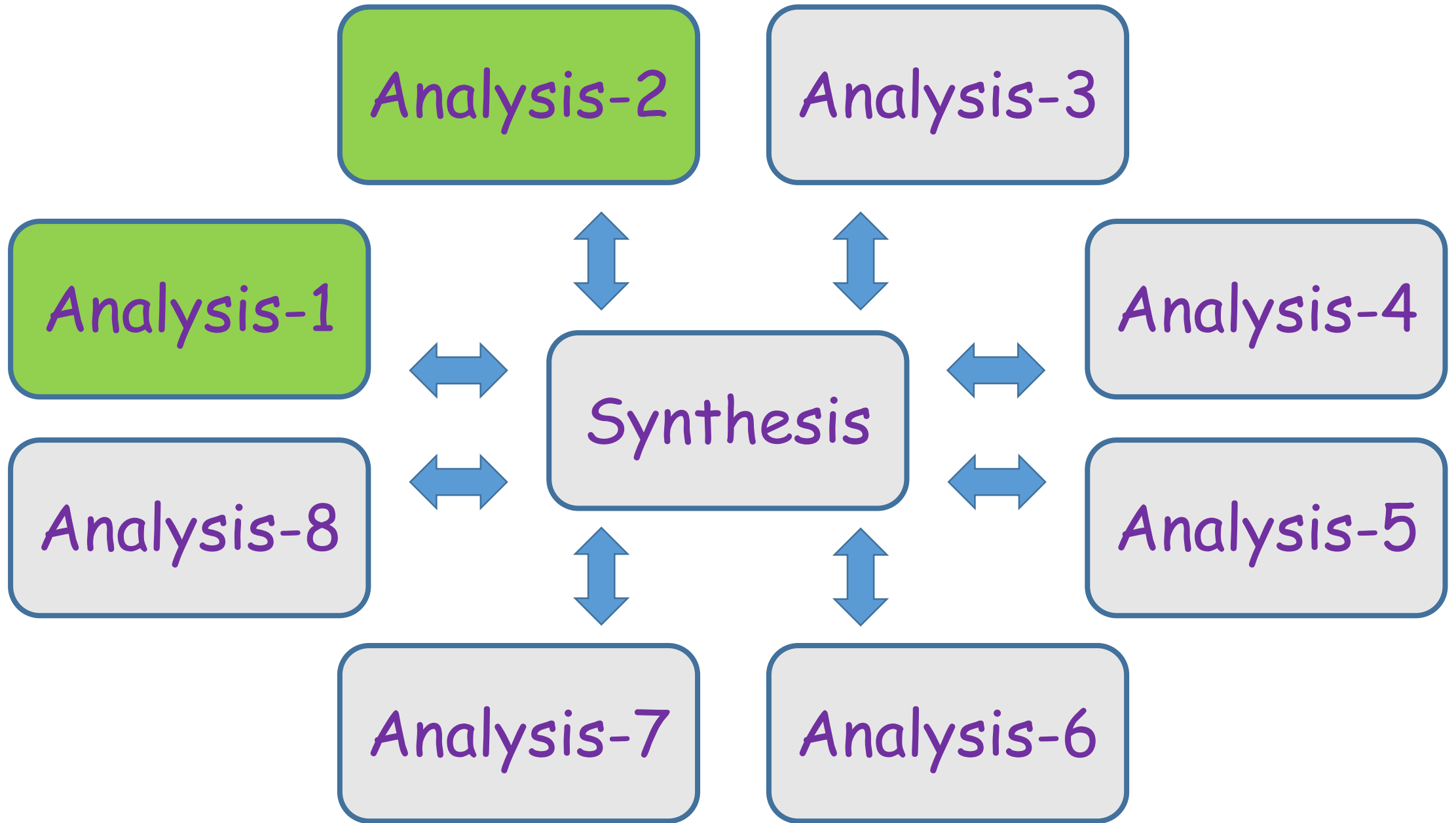


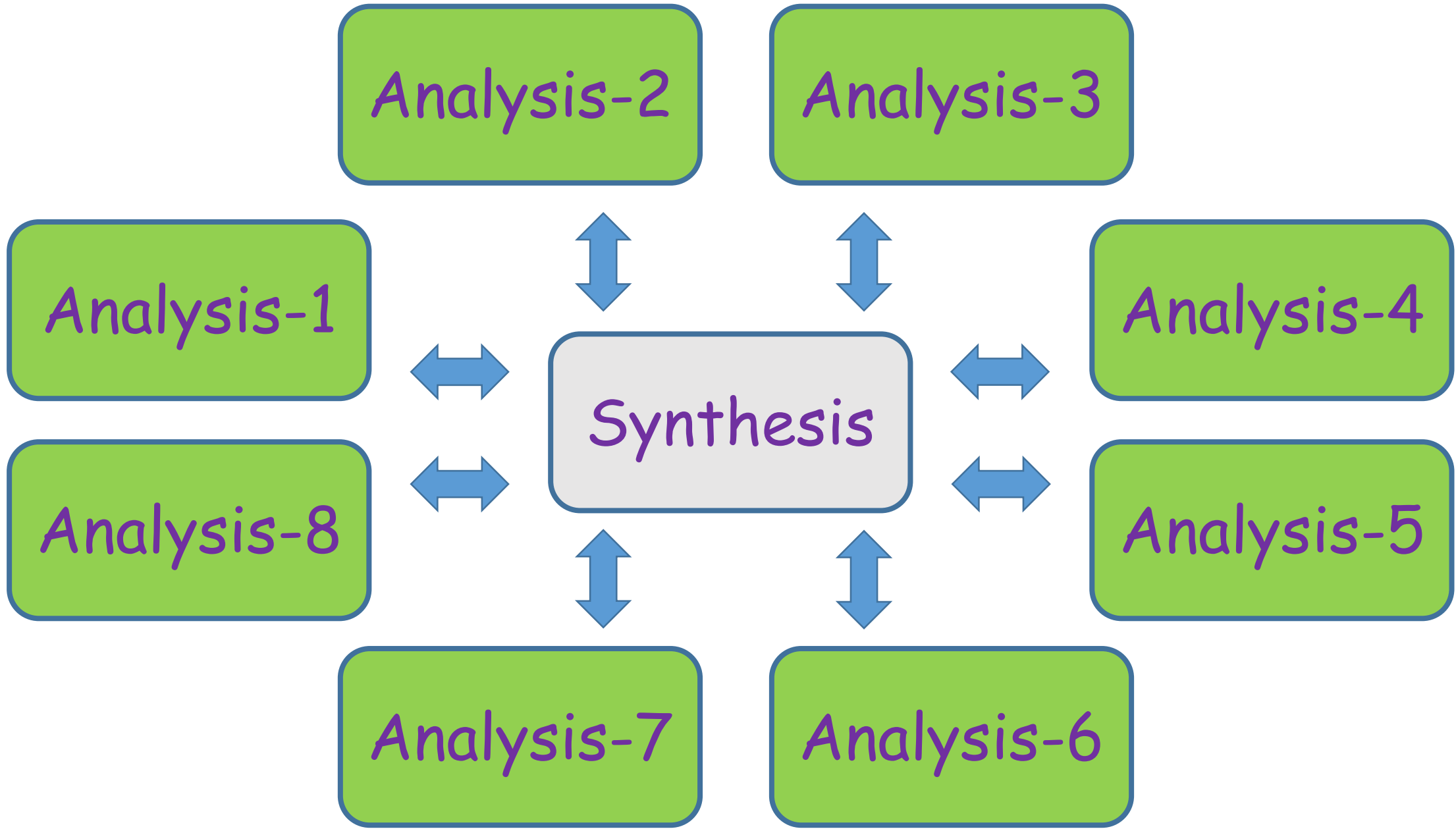


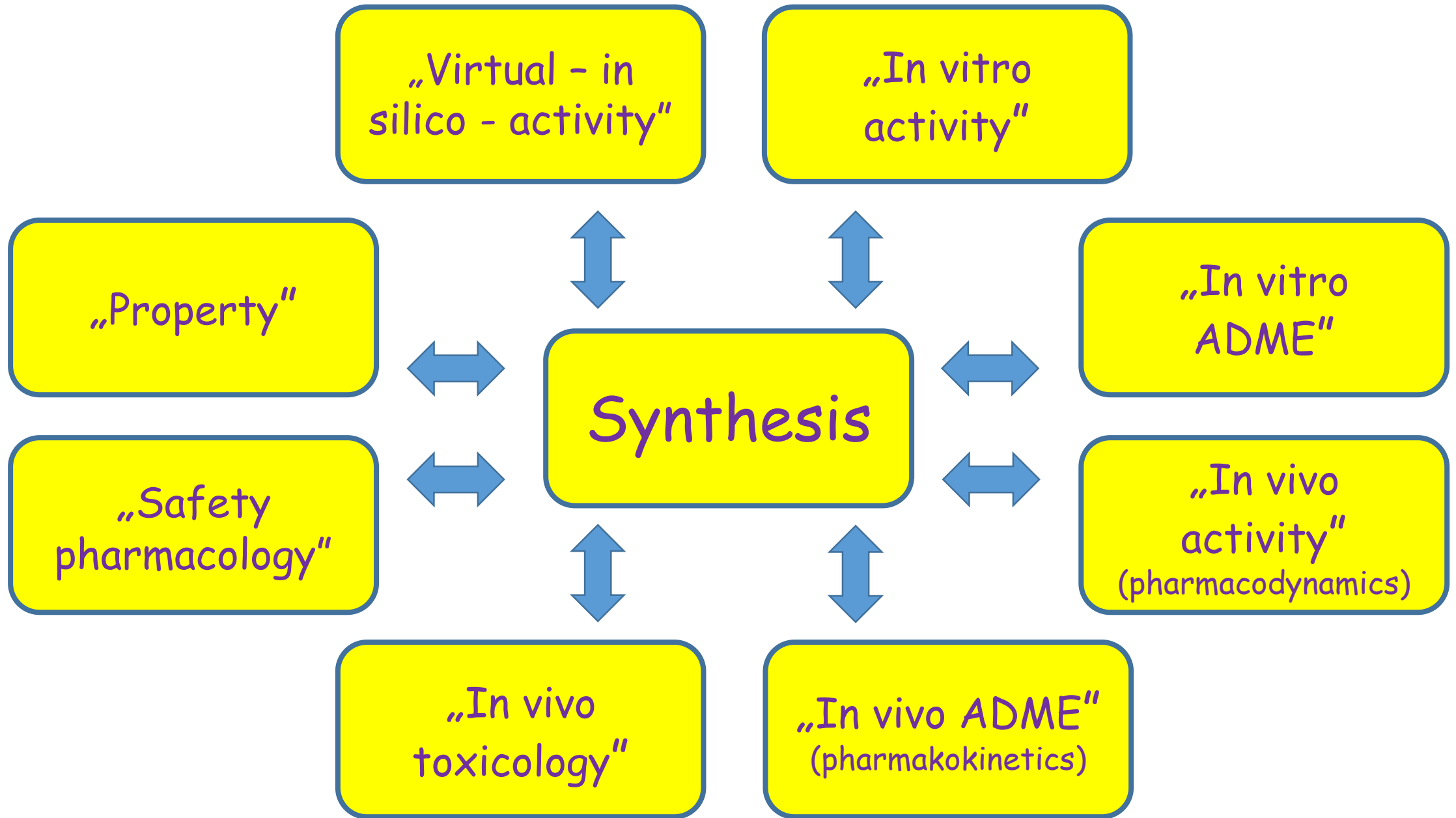












PRIMARY SCREEN/ in vitro efficacy

1st STEP: Basic in vitro screen: rmGluR5

- receptor binding: inhibition/ >70% tested at 1 μ M;
- K_i determinations on rmGlu5/ K_i<100nM;

2nd STEP: Functionality screen: rmGluR5

- inhibition of DHPG stimulated Ca²⁺ release at native cortical cells/ IC₅₀<10xK_i of binding

3rd STEP: In vitro ADME I.:

- metabolic stability (human & rat μ somes)/ F_M>70, 60%;
- in vitro inhibition of CYP enzymes/ <70% tested at 100 μ M

SECONDARY SCREEN/ in vivo efficacy

4th STEP: Basic in vivo screen:

-Vogel conflict model ip./ MED \leq 10 mg/kg

5th STEP: In Vitro ADME II.:

human intestinal permeability model

-Caco-2 permeability, out/inward ratio, cytotoxicity

/permeability \geq 1.0x 10⁻⁶

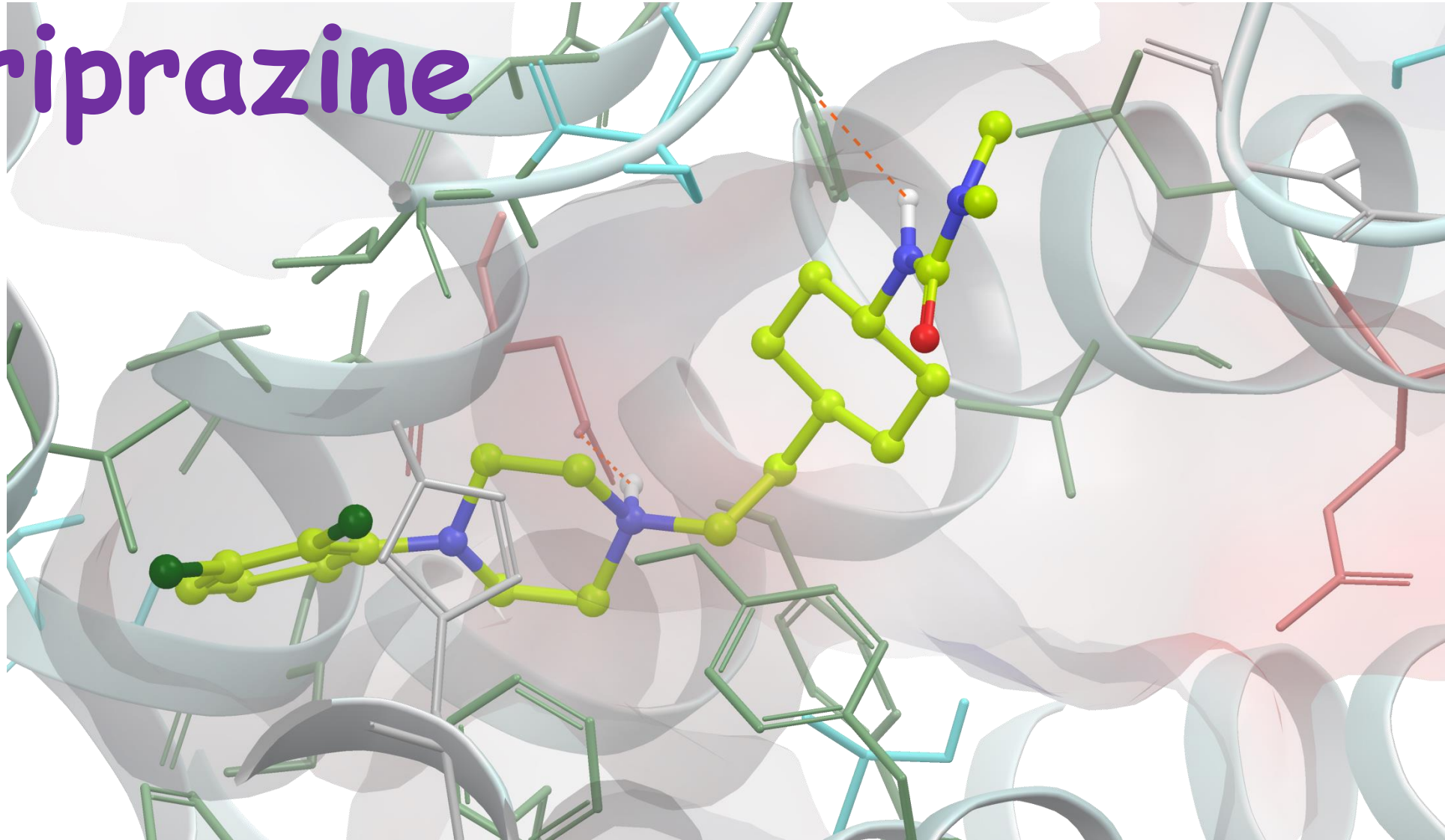
6th STEP: ADME III.:

CYP enzyme induction in rats at 3x100 mg/kg p.o./ no significant induction

SCREENING CASCADE



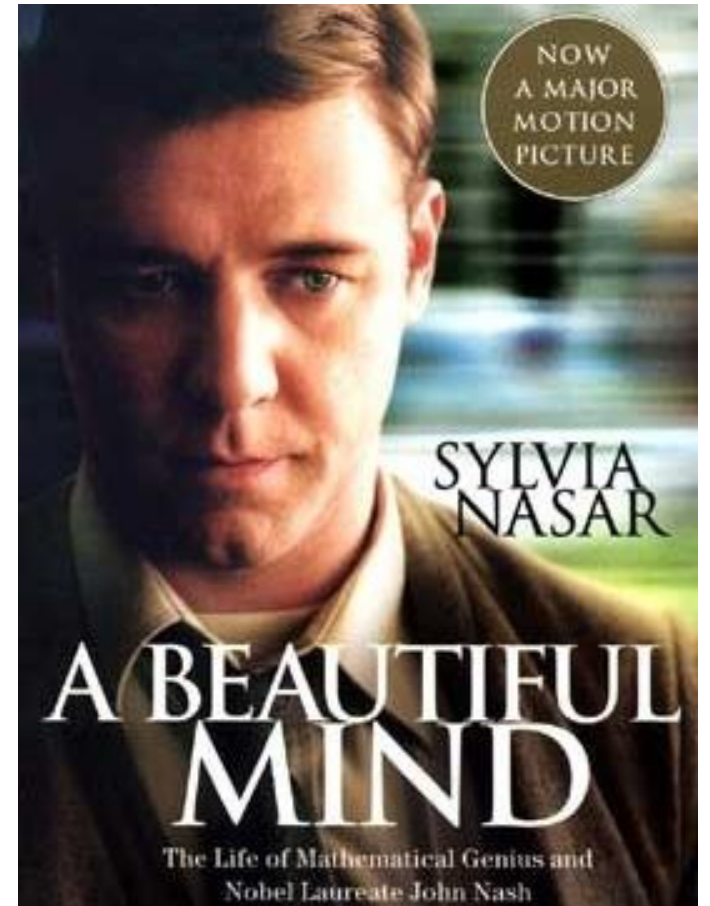
Cariprazine



„antipsychotic, dopamine D₃/D₂ receptor functional antagonist“

Psychosis is an abnormal condition of the mind that results in difficulties telling what is real and what is not. Symptoms may include false beliefs and seeing or hearing things that others do not see or hear. Other symptoms may include incoherent speech and behavior that is inappropriate for the situation. There may also be sleep problems, social withdrawal, lack of motivation, and difficulties carrying out daily activities.

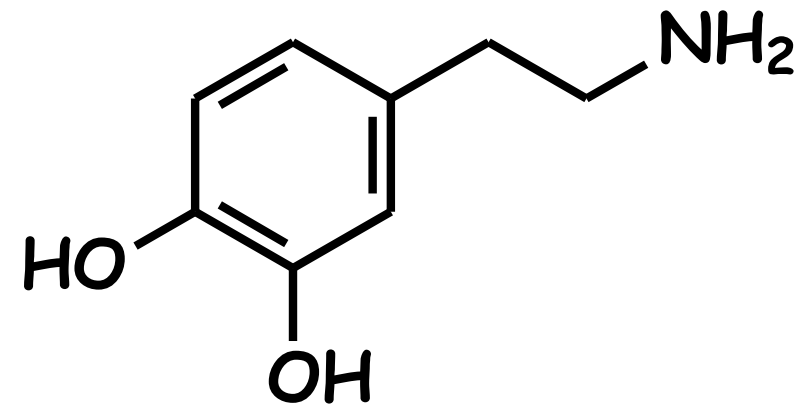
<https://en.wikipedia.org/wiki/Psychosis>



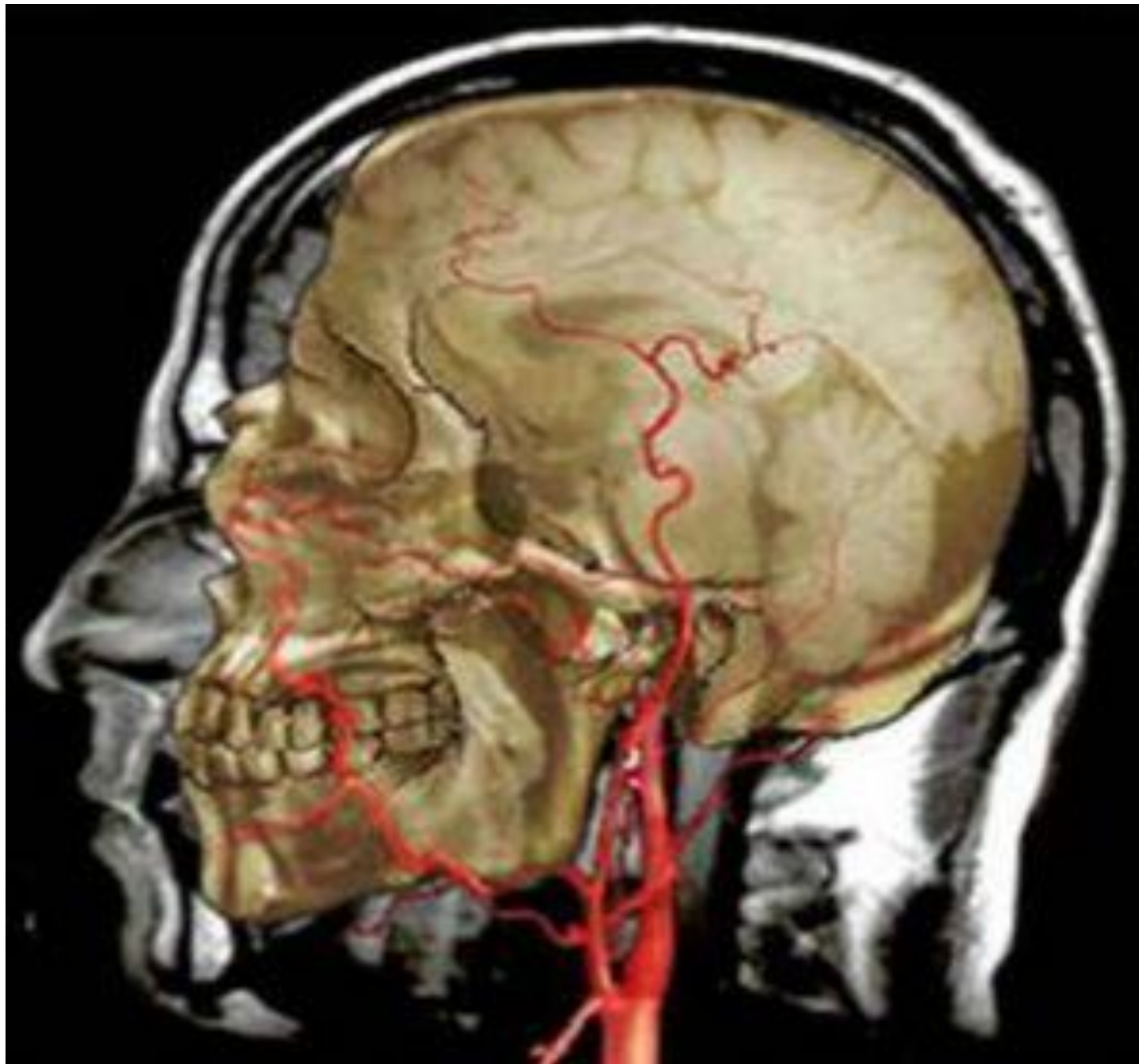
Dopamine theory of psychosis

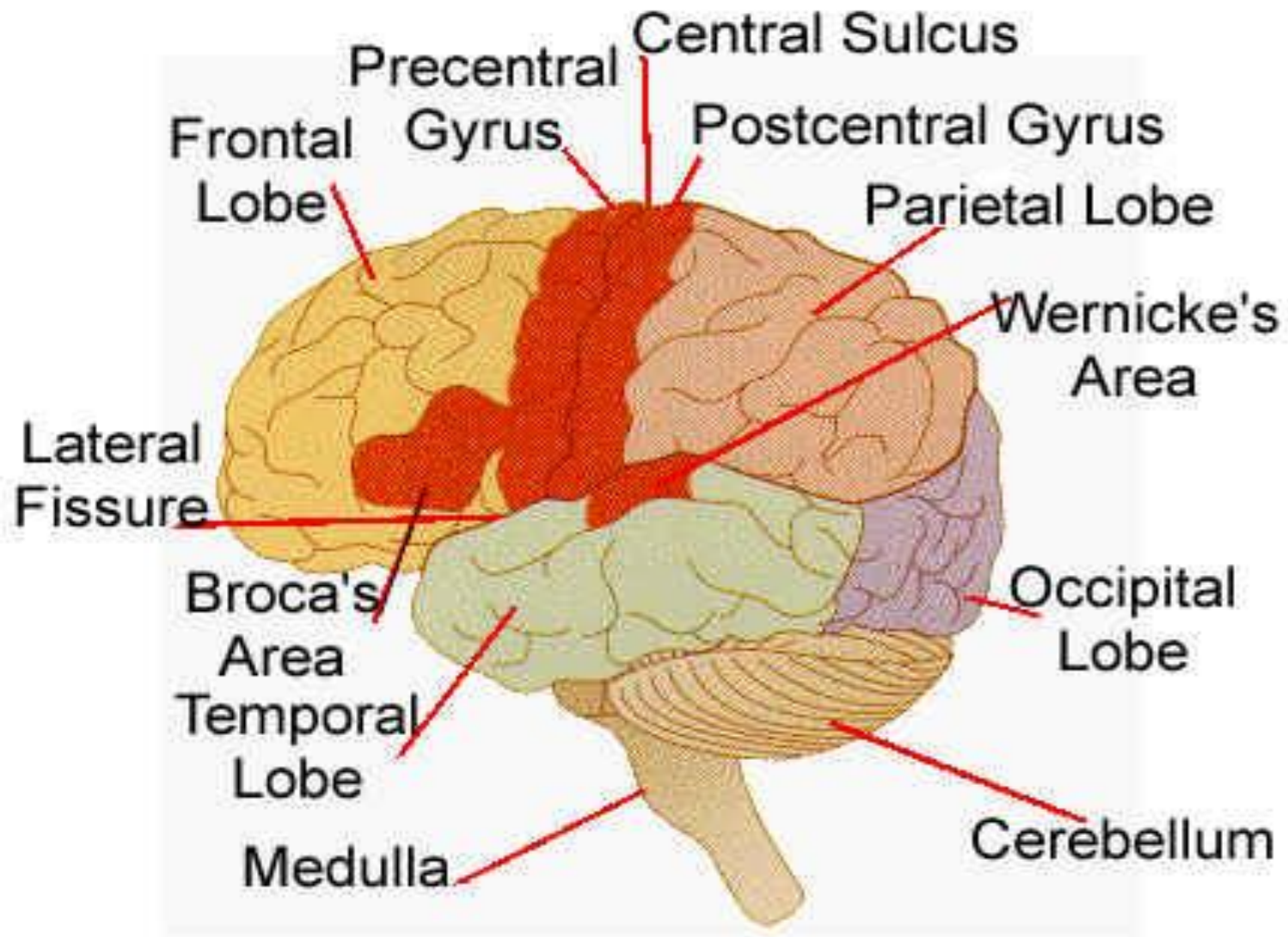
Contemporary pathophysiological models assume that psychotic symptoms are triggered by a **dysregulation of dopaminergic activity in the brain**, a theory that is tightly linked to the serendipitous discovery of the first effective antipsychotic agents in the early 1950s.

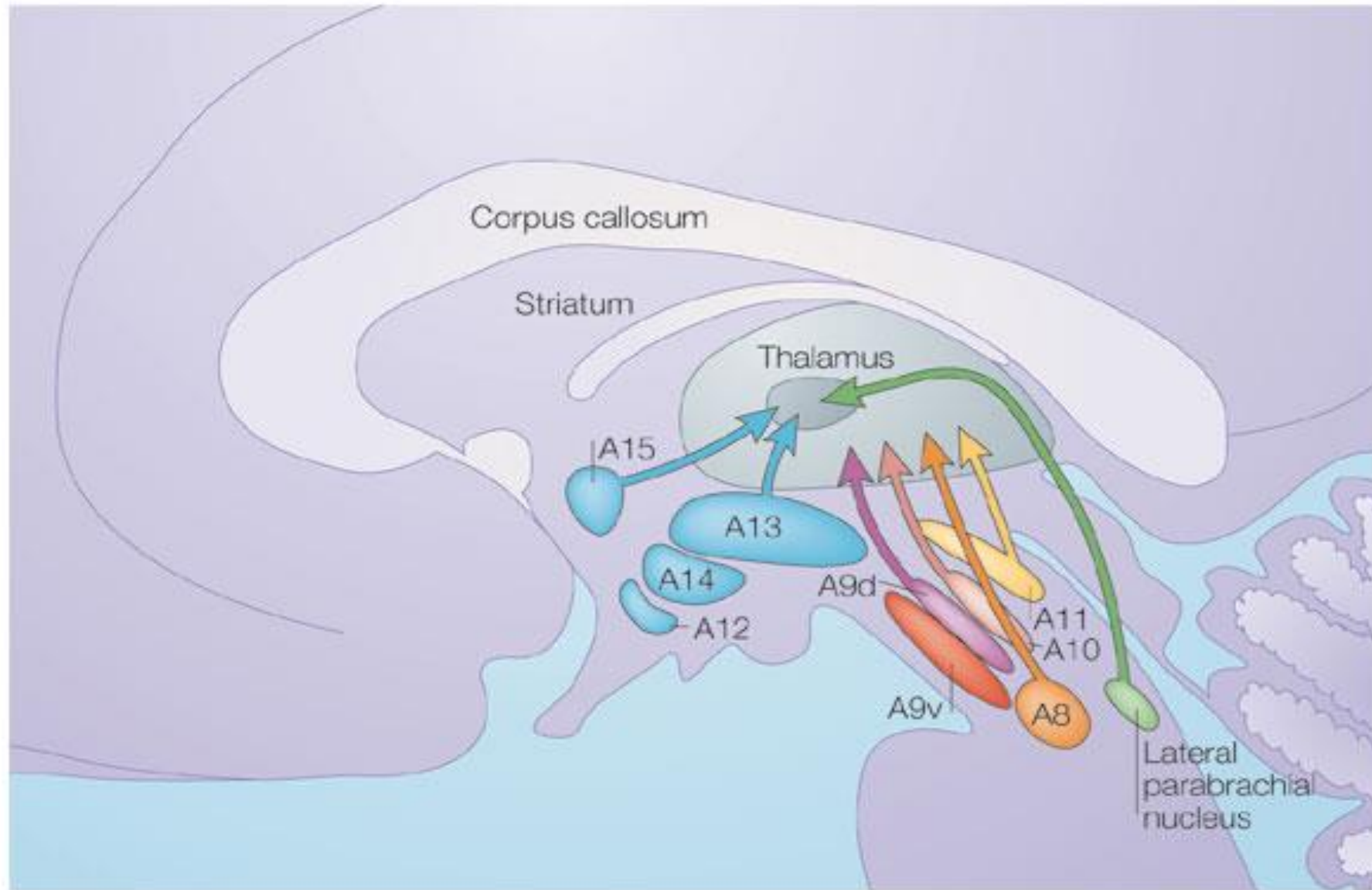
Tost, H. et al. *Neurosci. Biobehav. Rev.* (2010) 34 (5), 689-700.

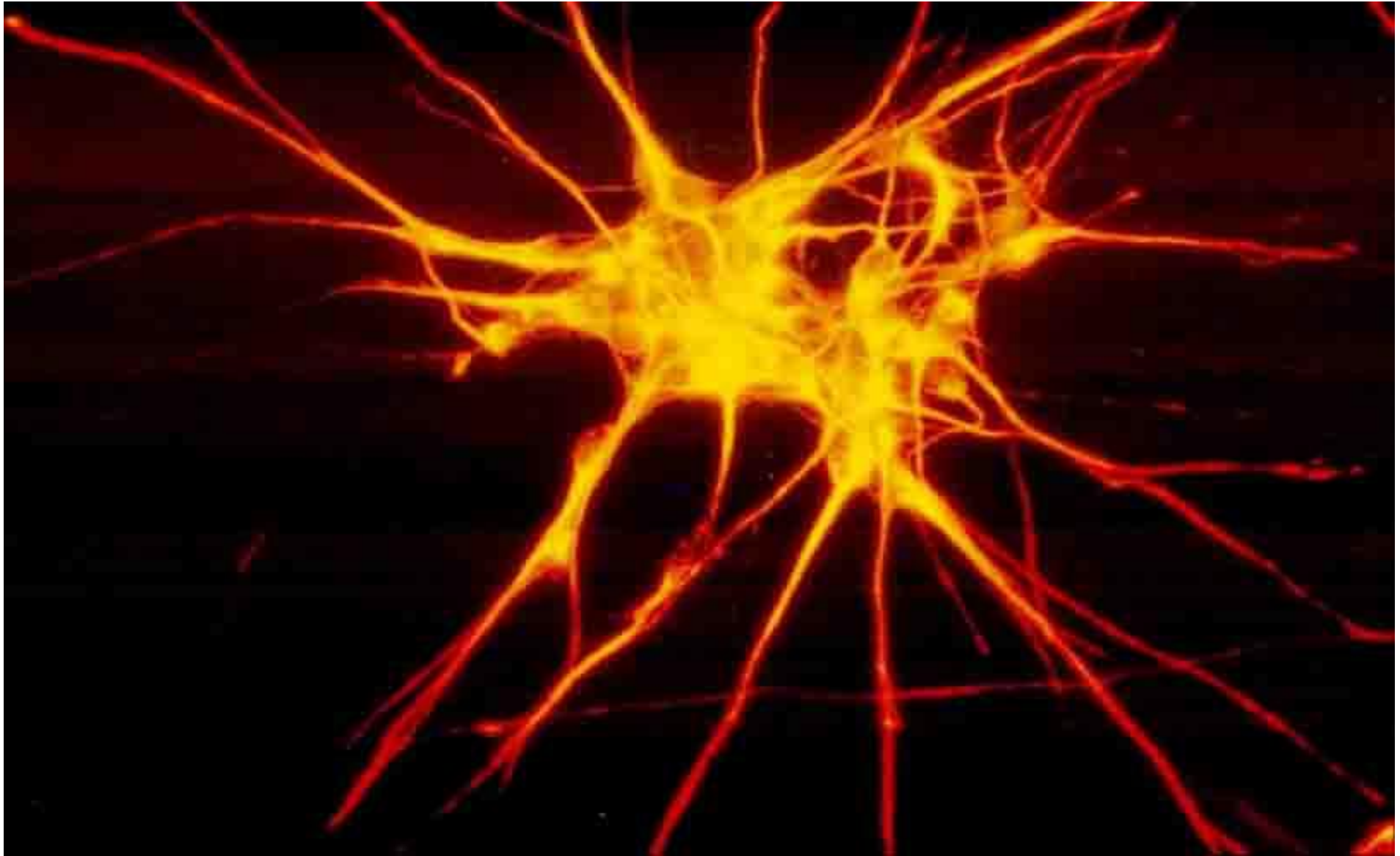


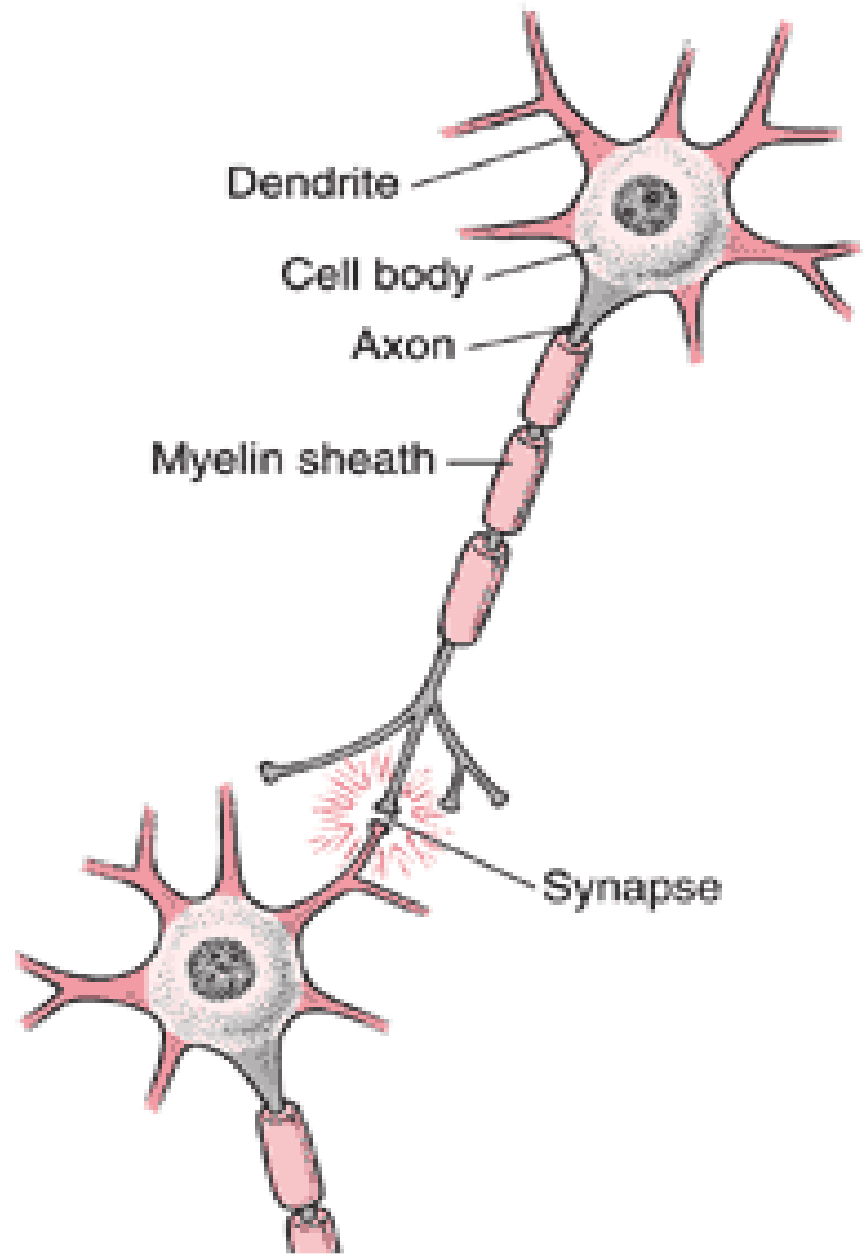
dopamine

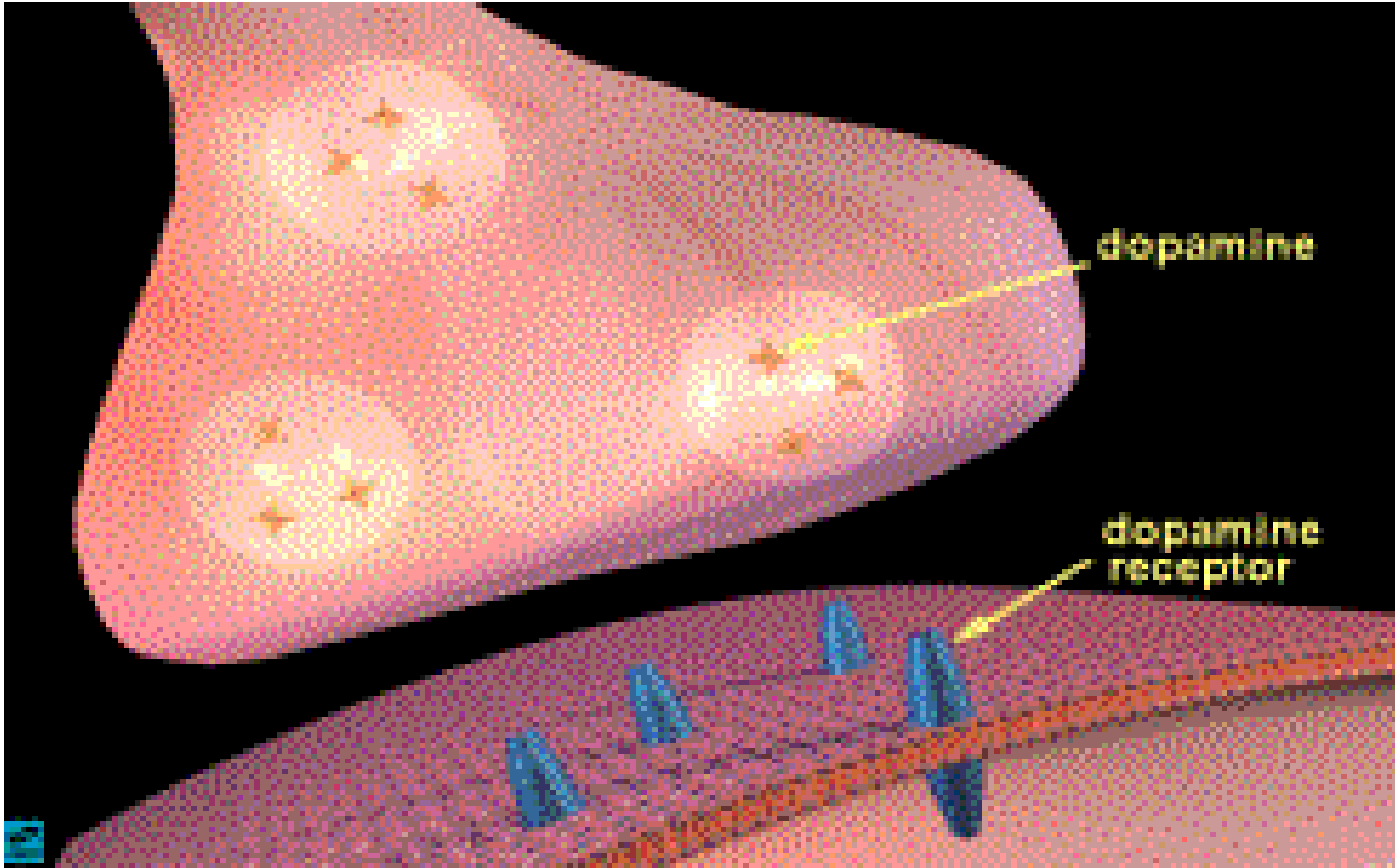


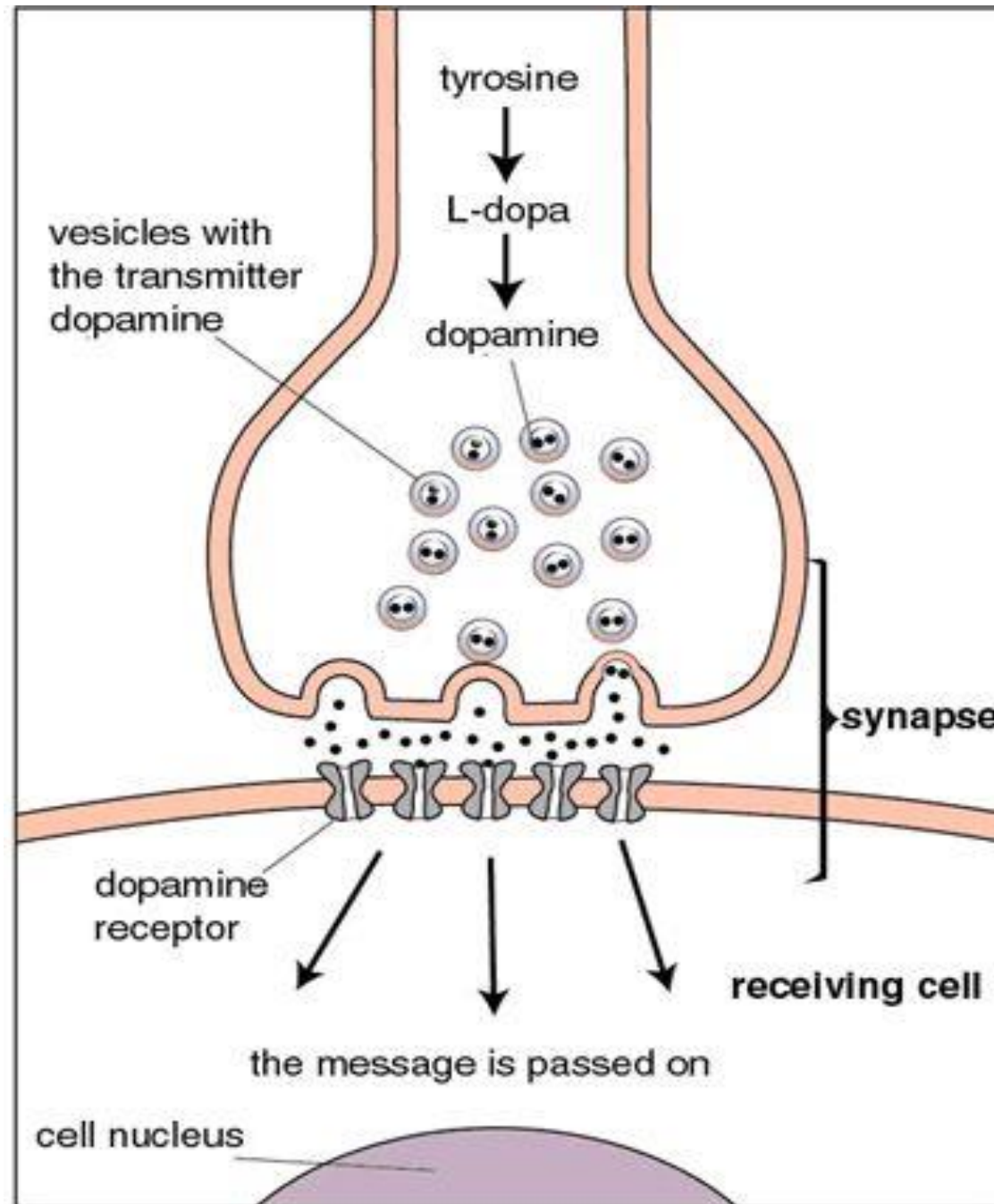


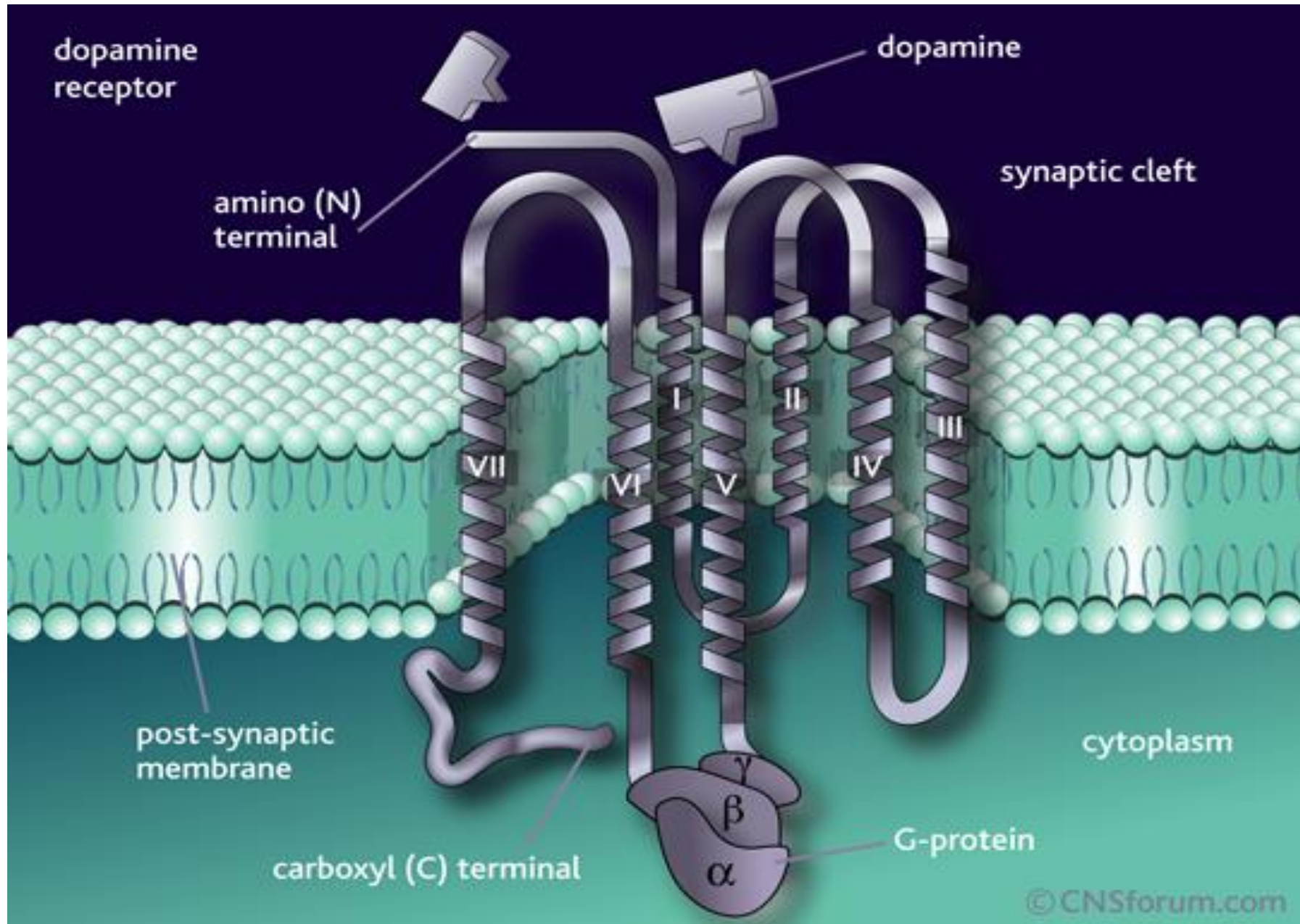


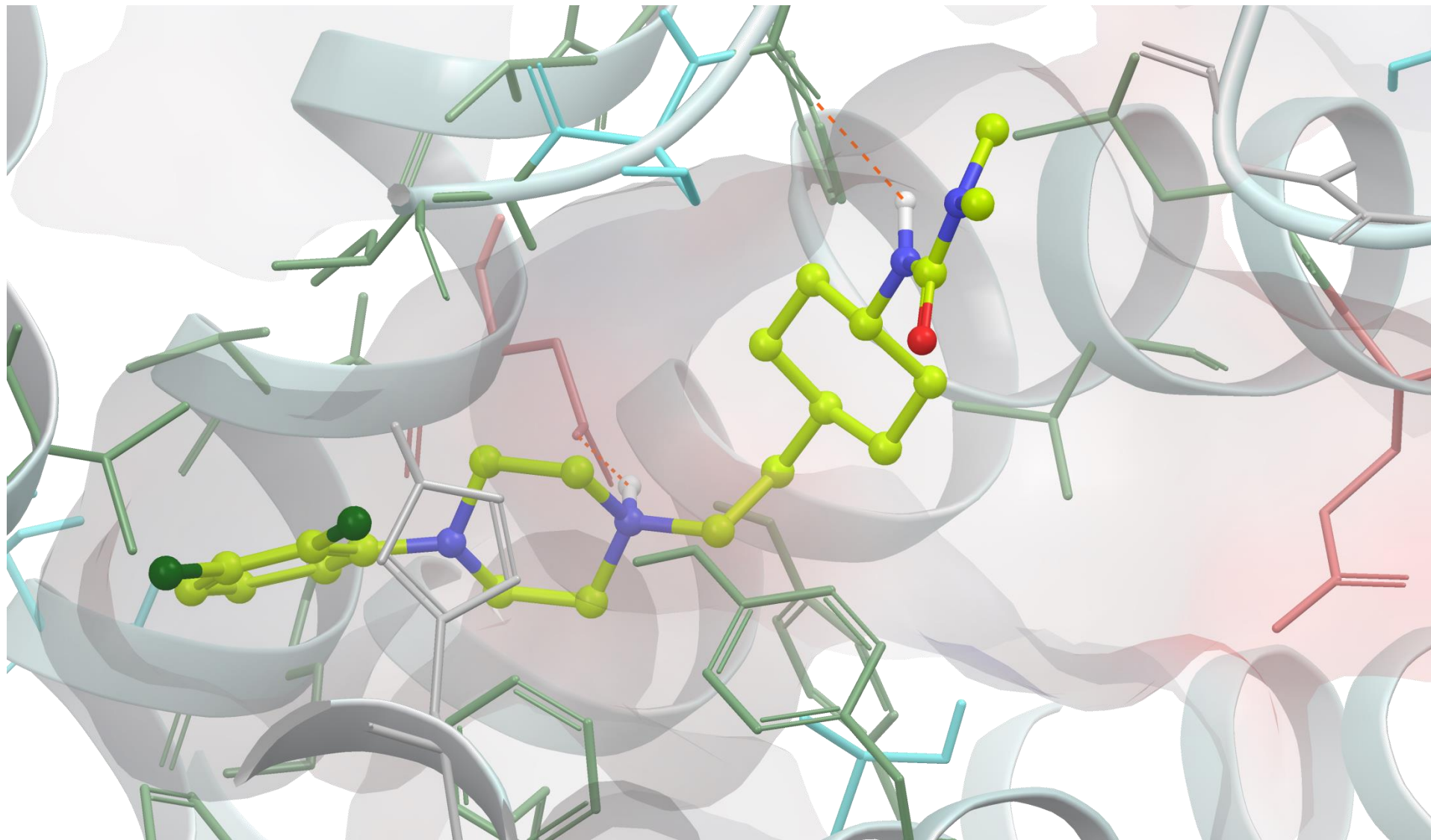








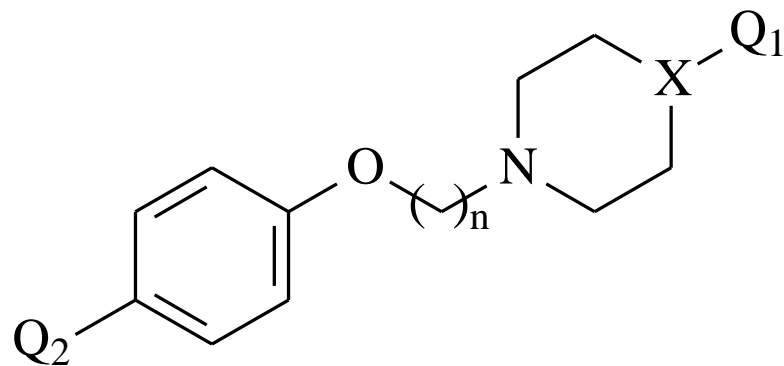




The first project: 1990s

Goal: at first „Cavinton follow-up“, then antipsychotic

CUF/ADD/MADD/APP



Q_1 : substituted phenyl or benzyl

X: N or CH

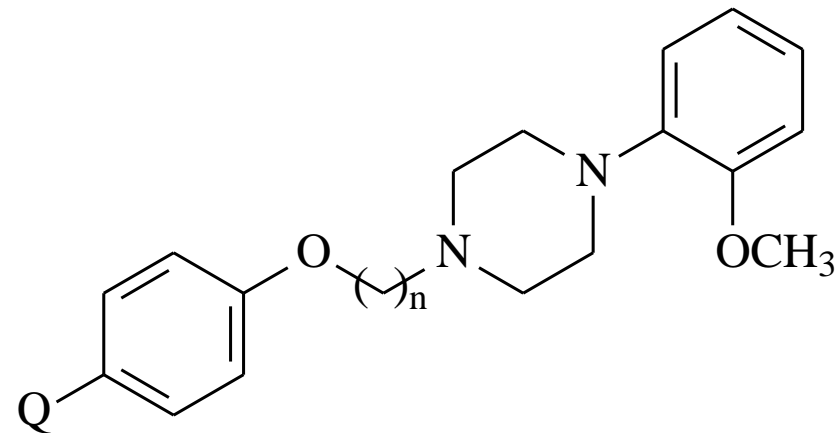
n: 2-5

Q_2 : heterocycle or heterobicycle

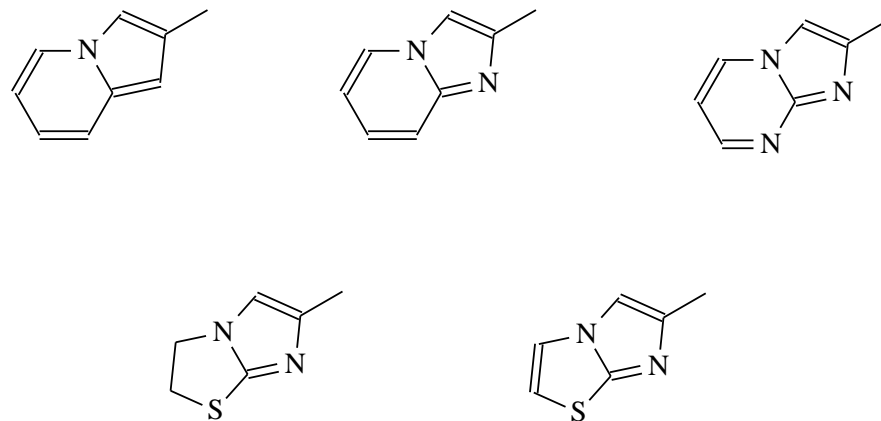
Combinatorial approach

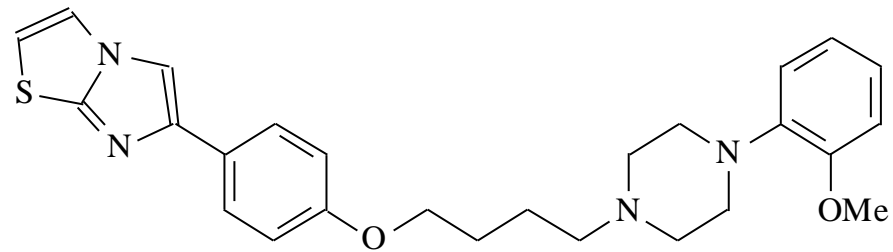


The first compound library



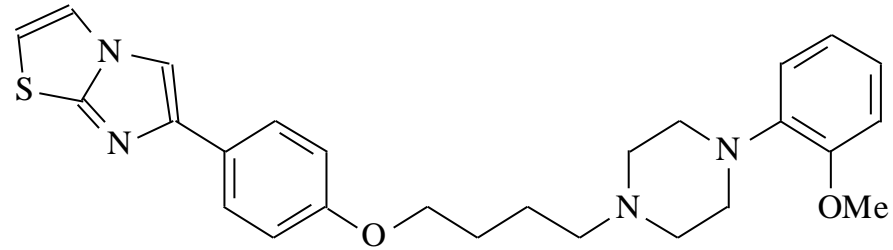
n: 2-4





RGH-1756

D_3 - IC_{50} : 2.6 nM; D_2 - IC_{50} : 20 nM
BA: 21%; „climbing“- ED_{50} : 16 mg/kg



RGH-1756

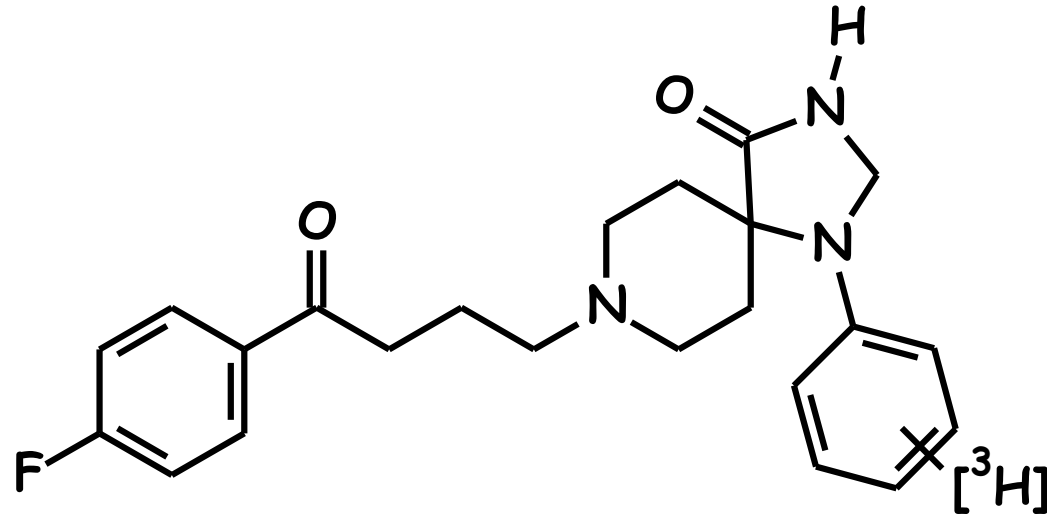
D_3 - IC_{50} : 2.6 nM; D_2 - IC_{50} : 20 nM
BA: 21%; „climbing“- ED_{50} : 16 mg/kg

„In vitro
activity“

„In vivo ADME“
(pharmakokinetics)

„In vivo
activity“
(pharmacodynamics)

Receptor binding assay

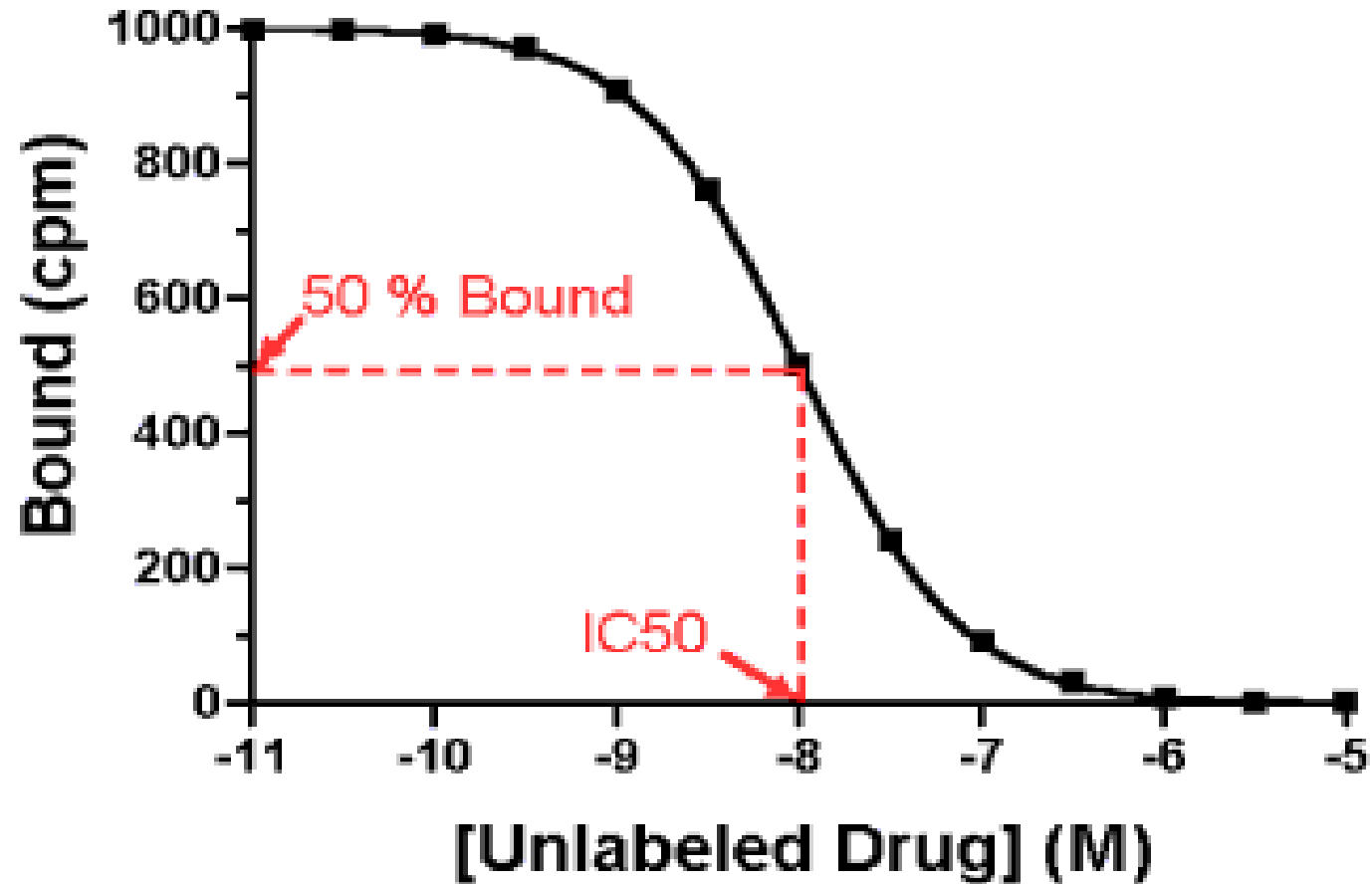


spiperone

Receptor binding assay (in vitro)

1. preparation of the receptors
2. addition of the radioligand and the drug
3. incubation
4. filtering
5. measurement
6. evaluation

Competition



IC_{50} is defined as the concentration of the inhibitor causing 50% inhibition of radioligand binding

K_i

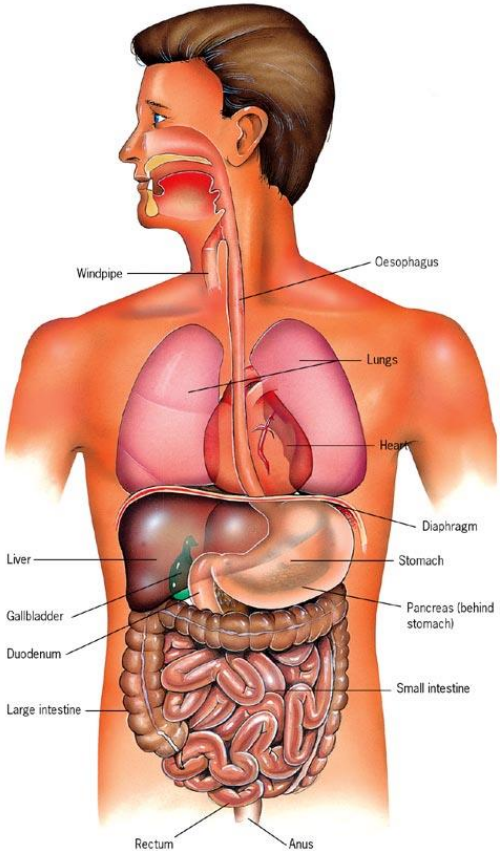
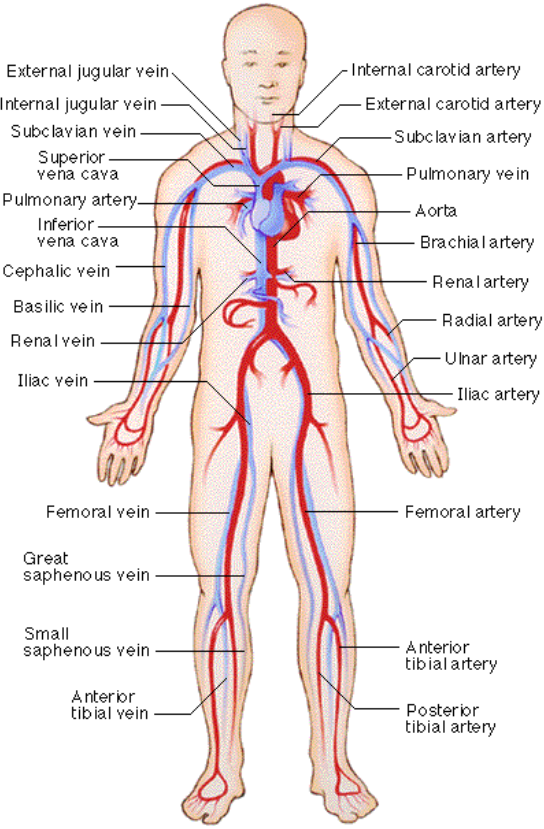
The inhibition constant for a drug; the concentration of competing ligand in a competition assay which would occupy 50% of the receptors if no radioligand were present. Whereas the IC_{50} value for a compound may vary between experiments depending on radioligand concentration, the K_i is an absolute value. It is calculated from the IC_{50} using the Cheng-Prusoff equation:

$$K_i = \frac{IC_{50}}{1 + ([L]/K_D)}$$

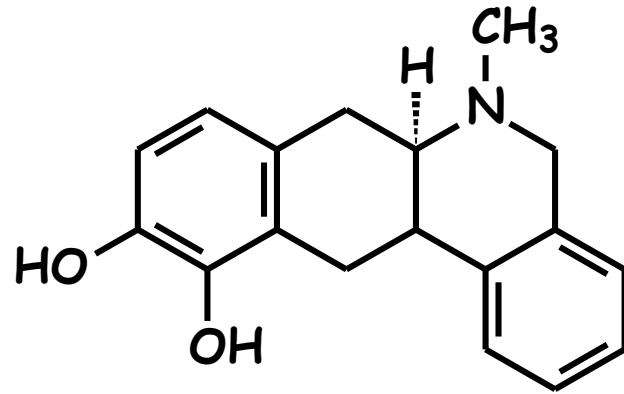
where $[L]$ = the concentration of free radioligand used in the assay, and K_D = the dissociation constant of the radioligand for the receptor.

Bioavailability (BA)

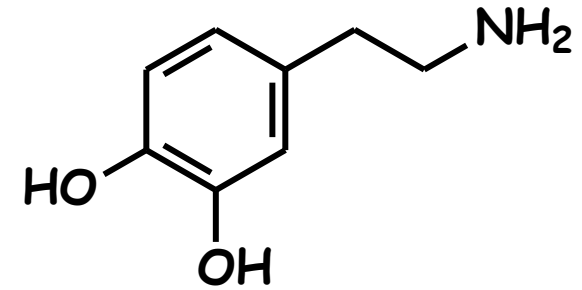
Bioavailability is a measure of the amount of an administered dose that reaches the bloodstream.



Climbing behavior in mice (in vivo)



apomorphin



dopamin

Climbing behavior in mice (in vivo)

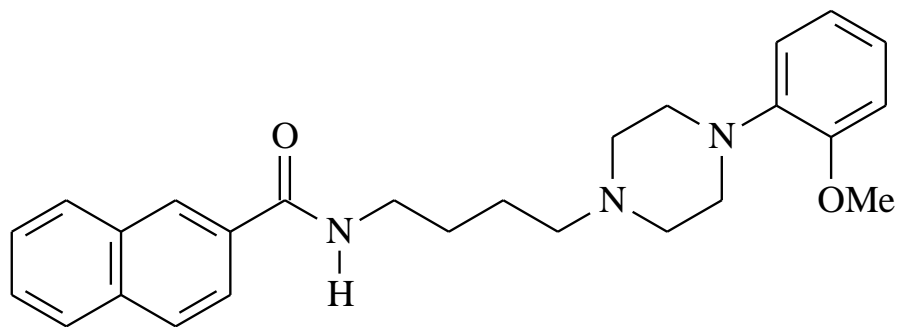
ED₅₀ is a dose that produces the desired effect in 50 per cent of a population.



IC₅₀, K_i, BA, ED₅₀

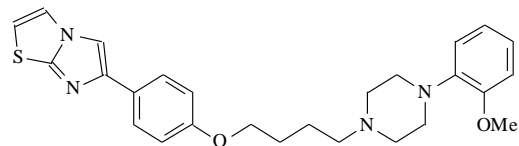
The second project: 1999-2000

Goal: treatment of cocaine abuse

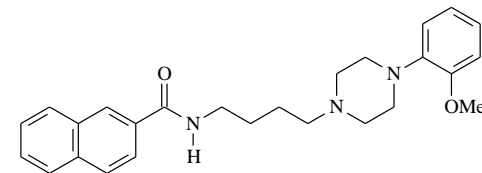


BP-897

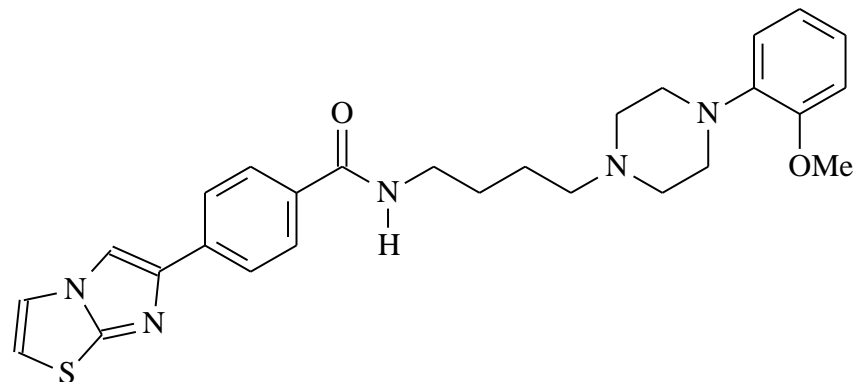
D_3 -IC₅₀: 0.6 nM; D_2 -IC₅₀: 115 nM; α -1-IC₅₀: 30 nM



RGH-1756

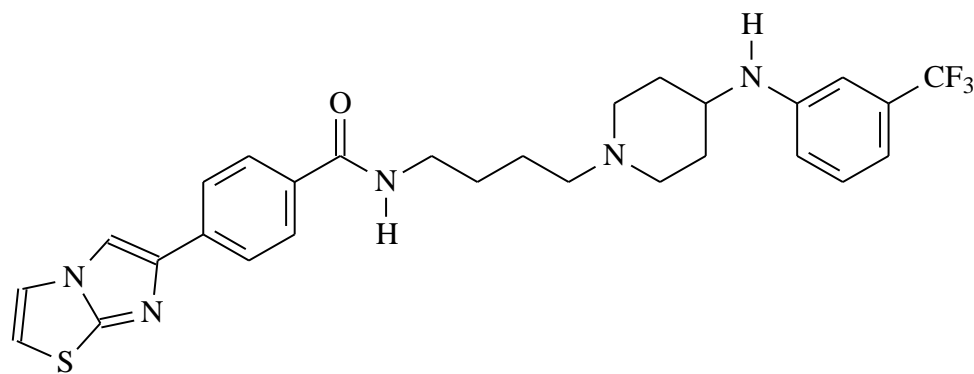


BP-897



1

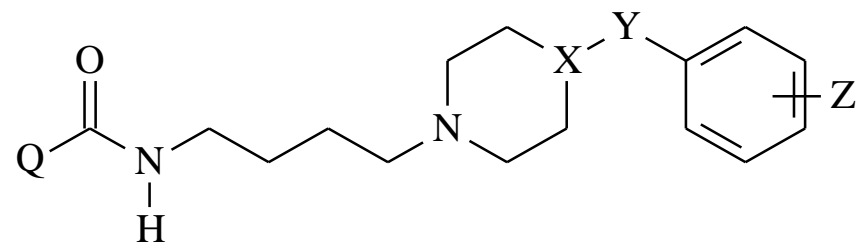
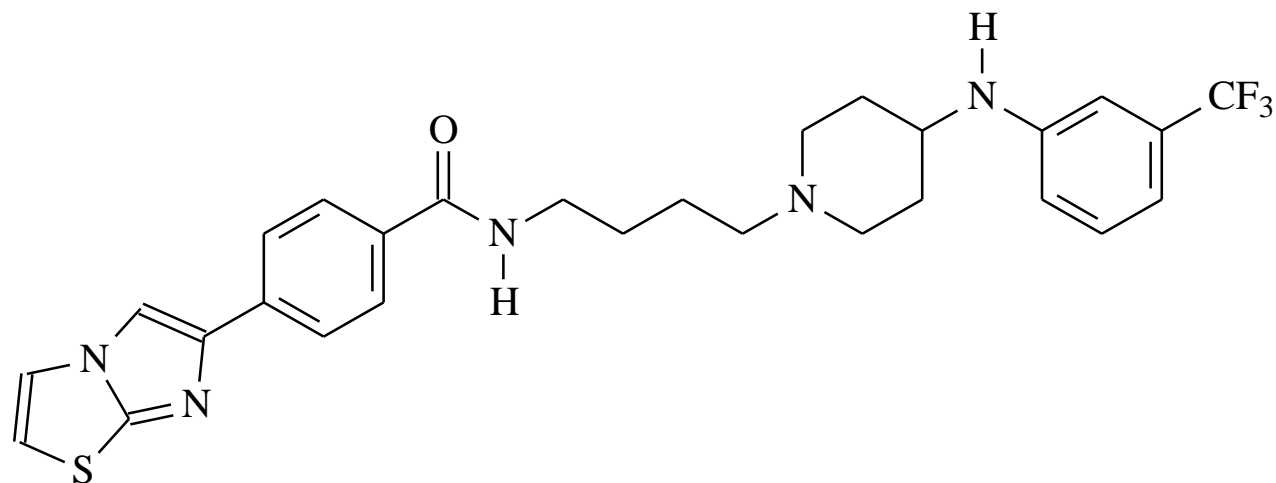
D_3 -IC₅₀: 0.13 nM; D_2 -IC₅₀: 108 nM; α -1-IC₅₀: 4.3 nM



2

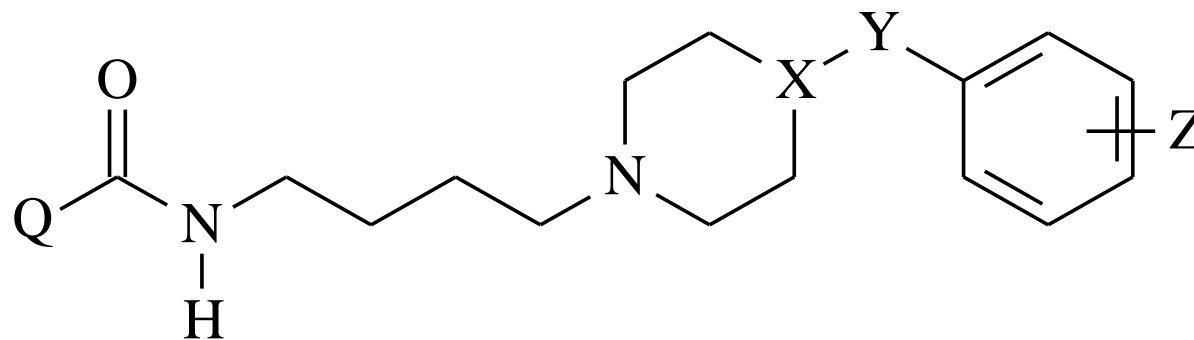
D_3 -IC₅₀: 1.0 nM; D_2 -IC₅₀: 584 nM; α -1-IC₅₀: 2829 nM

CHEMICAL
STARTING POINT,
LEAD COMPOUND



where Q mostly aromatic carbo- or heterocycle,
 X means N or CH,
 Y single bond, O, NH or CH₂,
 while Z may be one or more alkyl, alkoxy, halogen, nitril etc.
 on any carbon atom of the phenyl ring.

The second compound library



Aromatic carboxylic acids
272

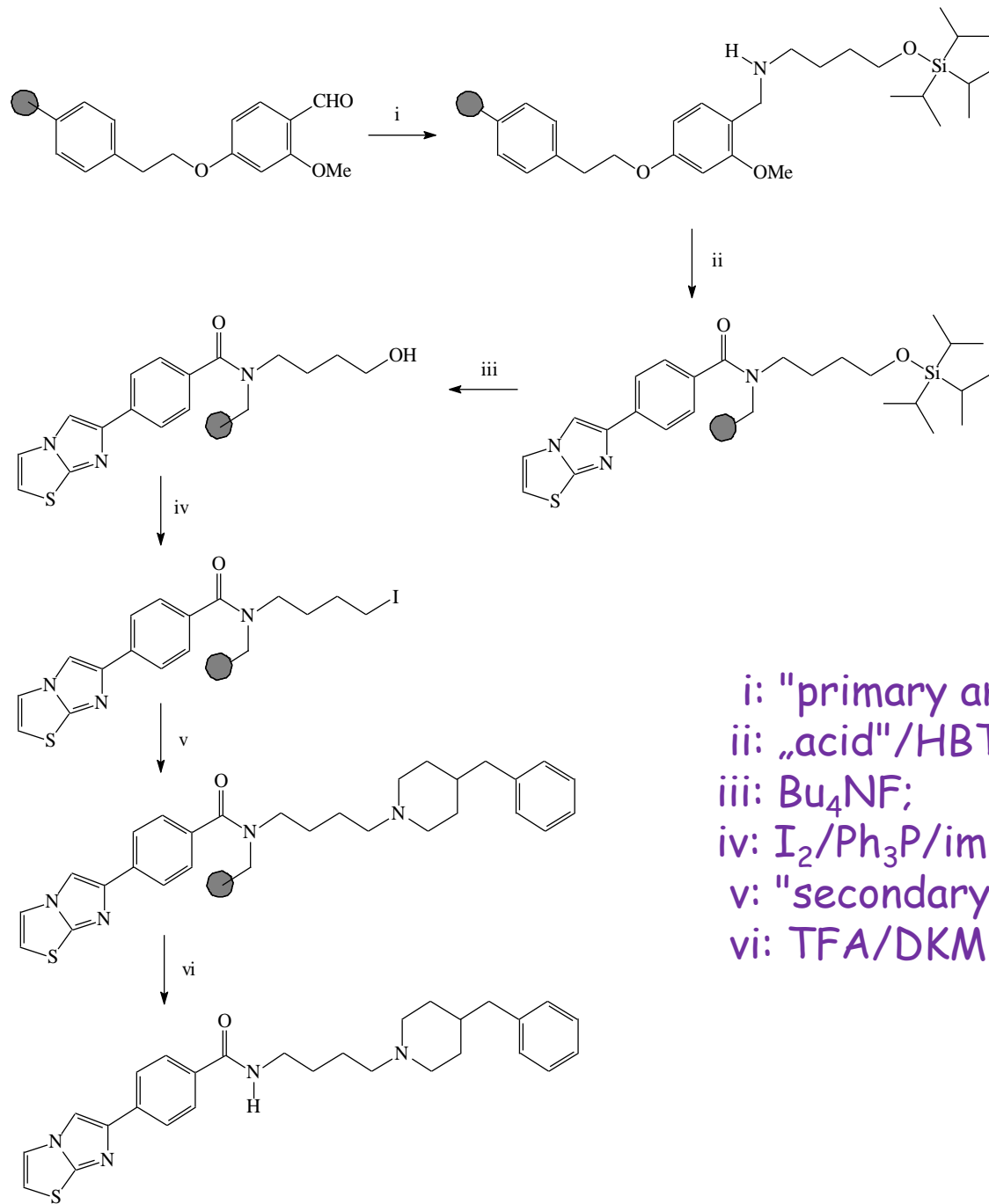
Cyclic secondary amines
46

12512 membered virtual compound library

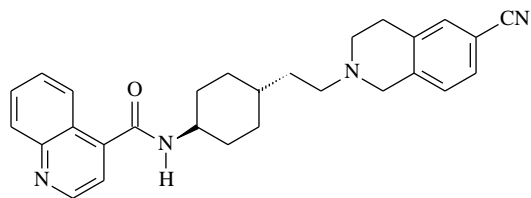
Pharmacophore screening
CoMFA focussing

Reactivity screening

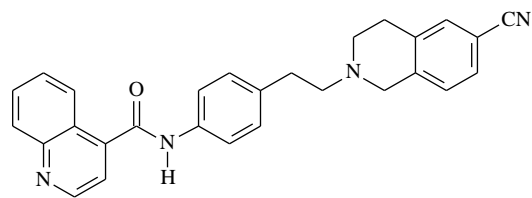
Synthesis of 480 membered focussed compound library



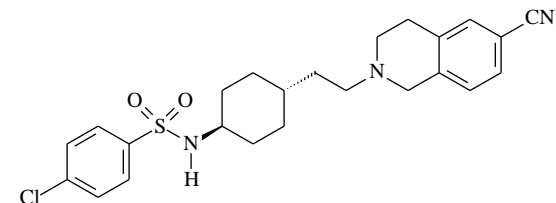
SAR: structure activity relationship



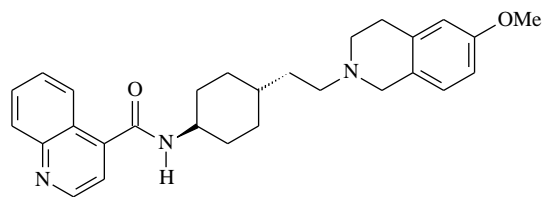
3 (SB-277011)
D₃-IC₅₀: 6.4 nM, BA: 63%



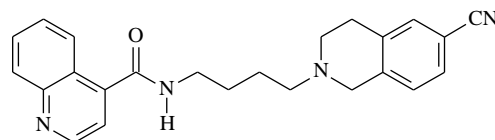
4
D₃-displ.: <<70%, BA: 18%



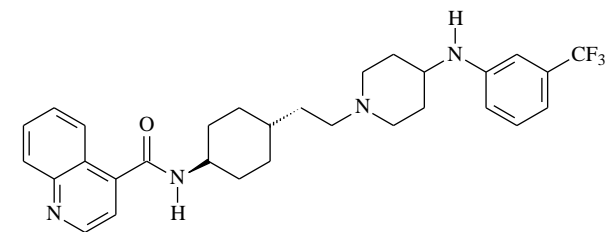
5
D₃-IC₅₀: 3.4 nM, BA: 80.4%



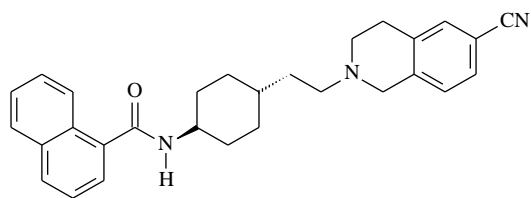
6
D₃-IC₅₀: 1.3 nM, BA: 16.7%



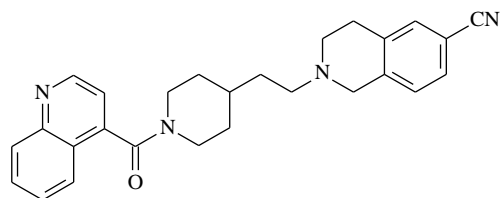
7
D₃-displ.: <<70%, BA: 11%



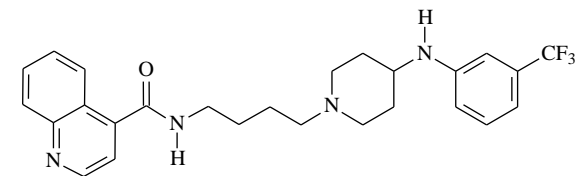
8
D₃-IC₅₀: 3.4 nM, BA: 35.5%



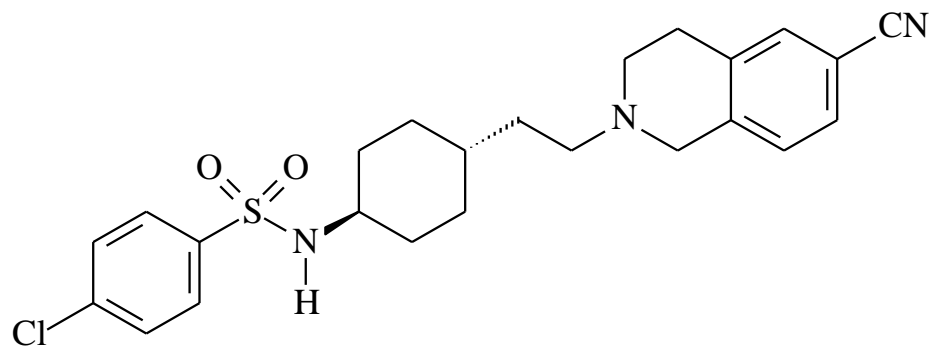
9
D₃-IC₅₀: 6.7 nM, BA: 4.9%



10
D₃-displ.: <<70%, BA: 54.6%

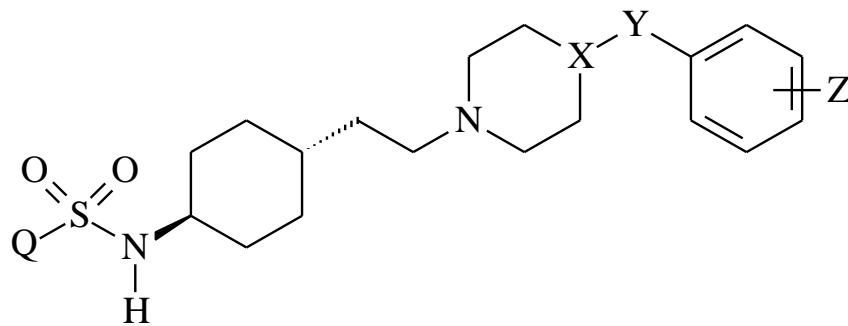


11
D₃-IC₅₀: 4.2 nM, BA: 40.6%

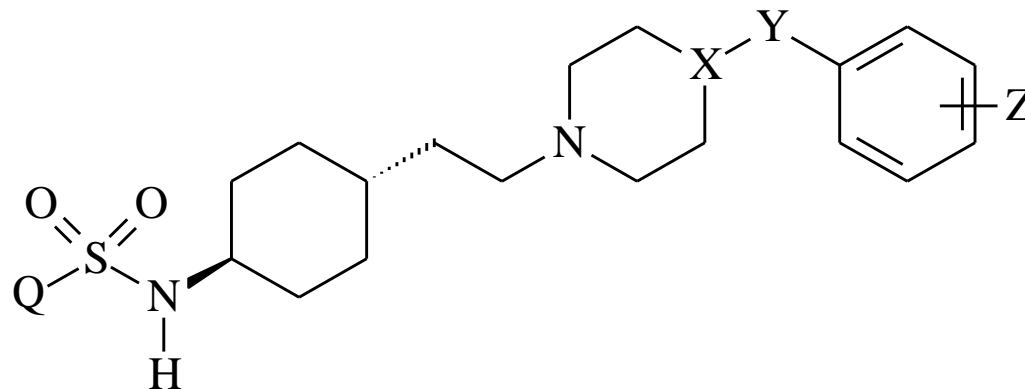


5

D₃-IC₅₀: 3.4 nM, BA: 80.4%



The third compound library



Aromatic sulfonyl chlorides
28

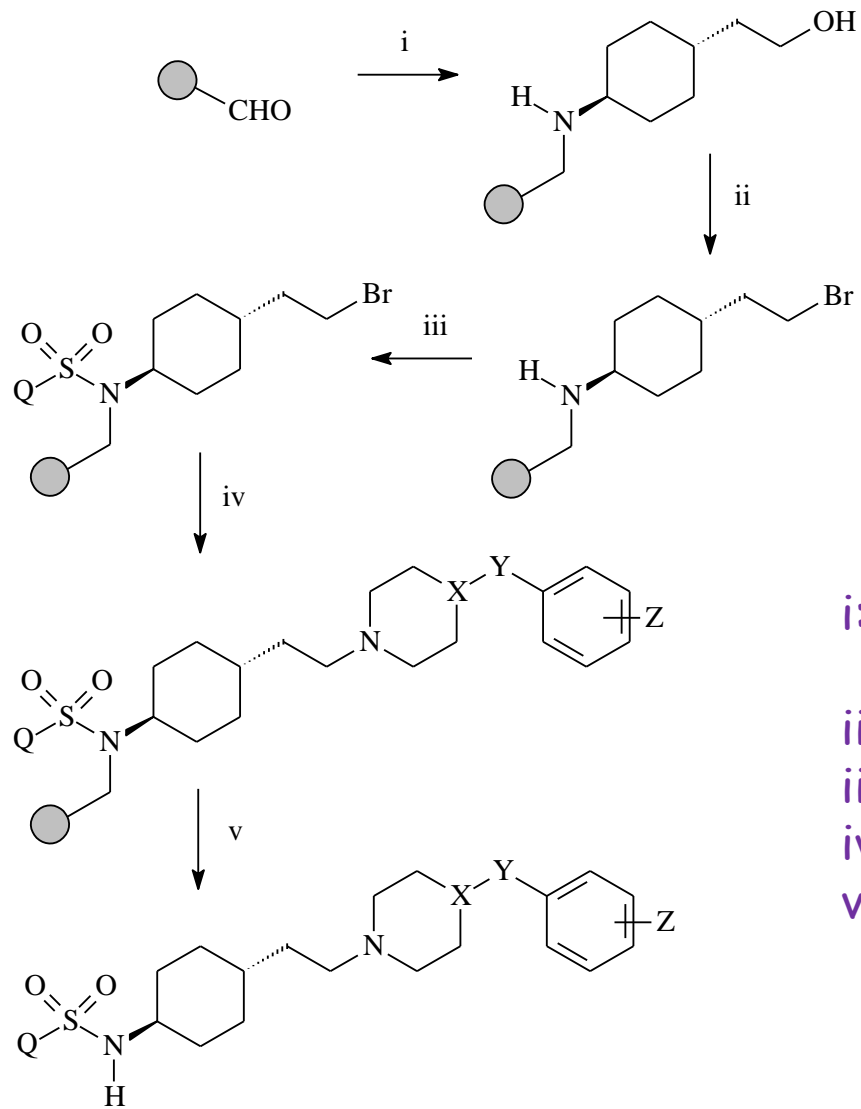
Cyclic secondary amines
46

1288 membered virtual compound library

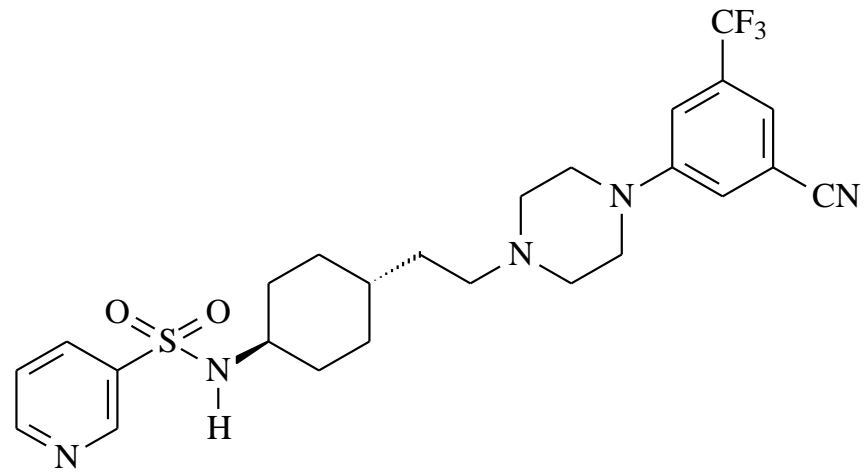
Pharmacophore screening
CoMFA focussing

Reactivity screening

Syntheses of 288 membered focussed compound library



i: *trans*-4-aminociklohexylethanol/
 $\text{NaBH}(\text{OAc})_3/\text{CH}_2\text{Cl}_2/\text{AcOH}$;
 ii: $\text{PPh}_3.\text{Br}_2/\text{imidazole}/\text{CH}_2\text{Cl}_2$;
 iii: $\text{QSO}_2\text{Cl}/\text{TEA}/\text{THF}$;
 iv: cyclic amine/ KI/DMF ;
 v: $\text{TFA}/\text{CH}_2\text{Cl}_2$.



12

D₃-IC₅₀: 0.6 nM; D₂-IC₅₀: 83 nM
BA: 55%; „climbing“- ED₅₀: 22 mg/kg

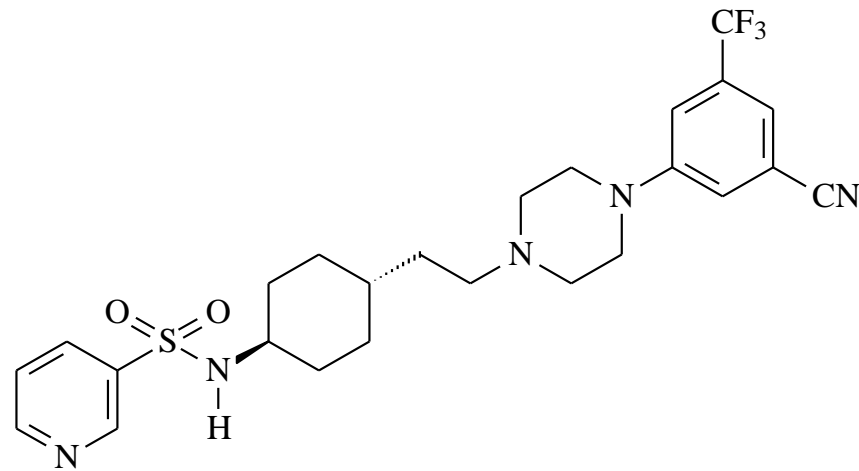
LEAD OPTIMIZATION

The third project: since 2001

Goal: antipsychotic

Starting hypotheses

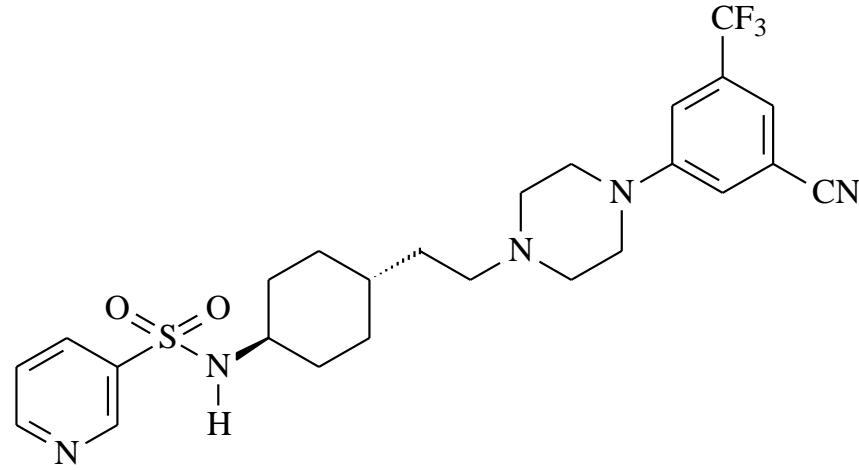
- Blocking the D₂ receptors is necessary.
- Concomitant blocking the dopamin D₃ receptors may cause further advantages.
- In order to achieve good pharmacological activity compounds should bind better to D₃ receptors than to D₂ receptors.



12

D₃-IC₅₀: 0.6 nM; D₂-IC₅₀: 83 nM
BA: 55%; „climbing“- ED₅₀: 22 mg/kg

But CYP1A induction and QT prolongation!



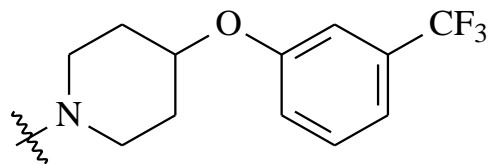
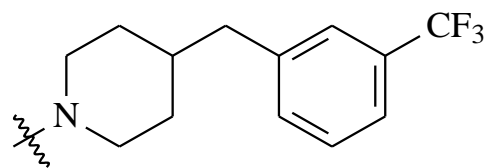
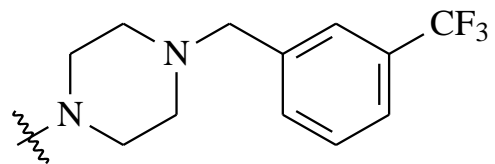
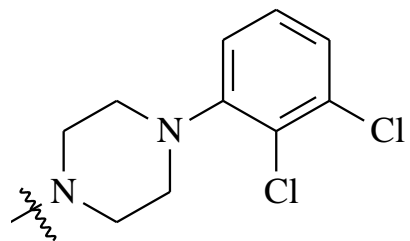
12

D₃-IC₅₀: 0.6 nM; D₂-IC₅₀: 83 nM
BA: 55%; „climbing“- ED₅₀: 22 mg/kg

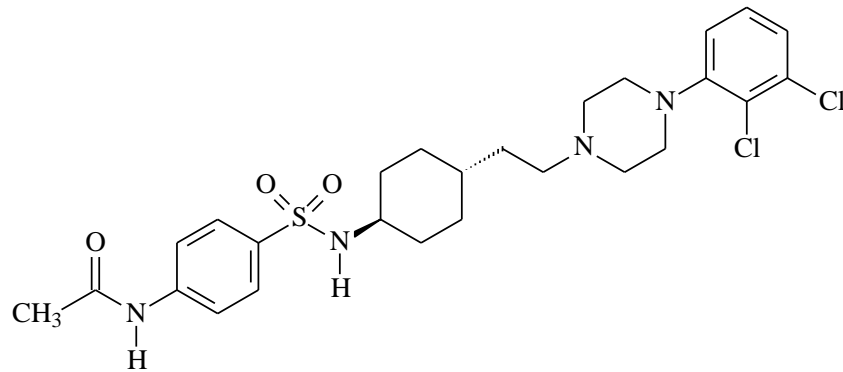
But CYP1A induction and QT prolongation!

„In vitro
ADME“

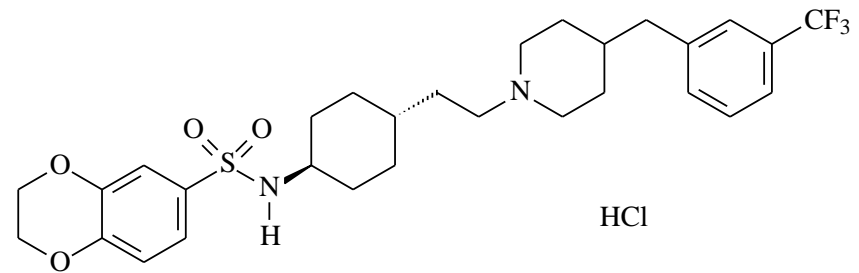
„Safety
pharmacology“



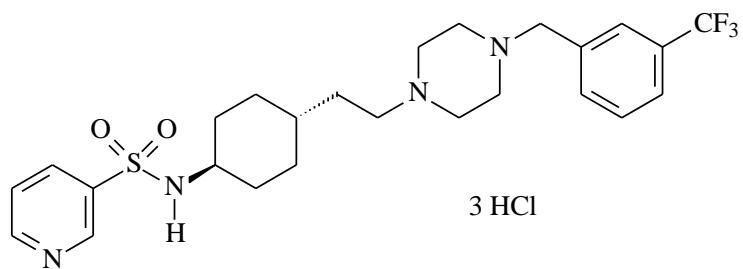
„climbing“ ED₅₀ < 10 mg/kg



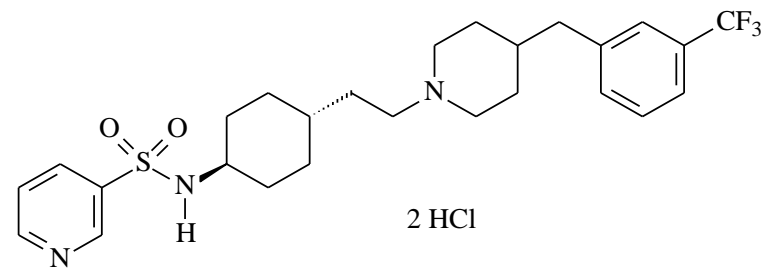
13



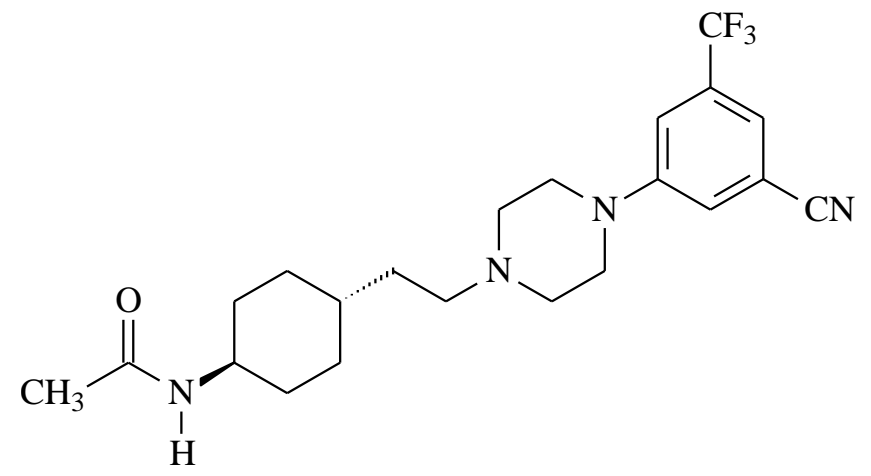
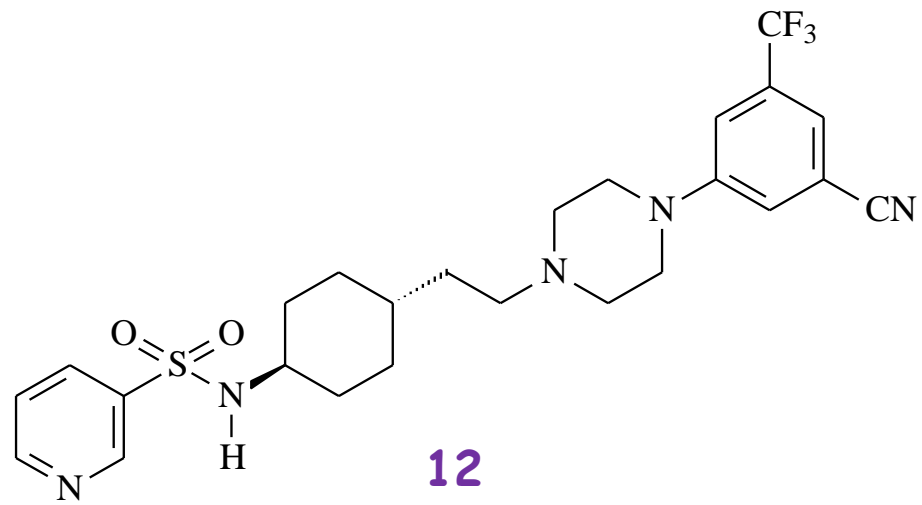
14



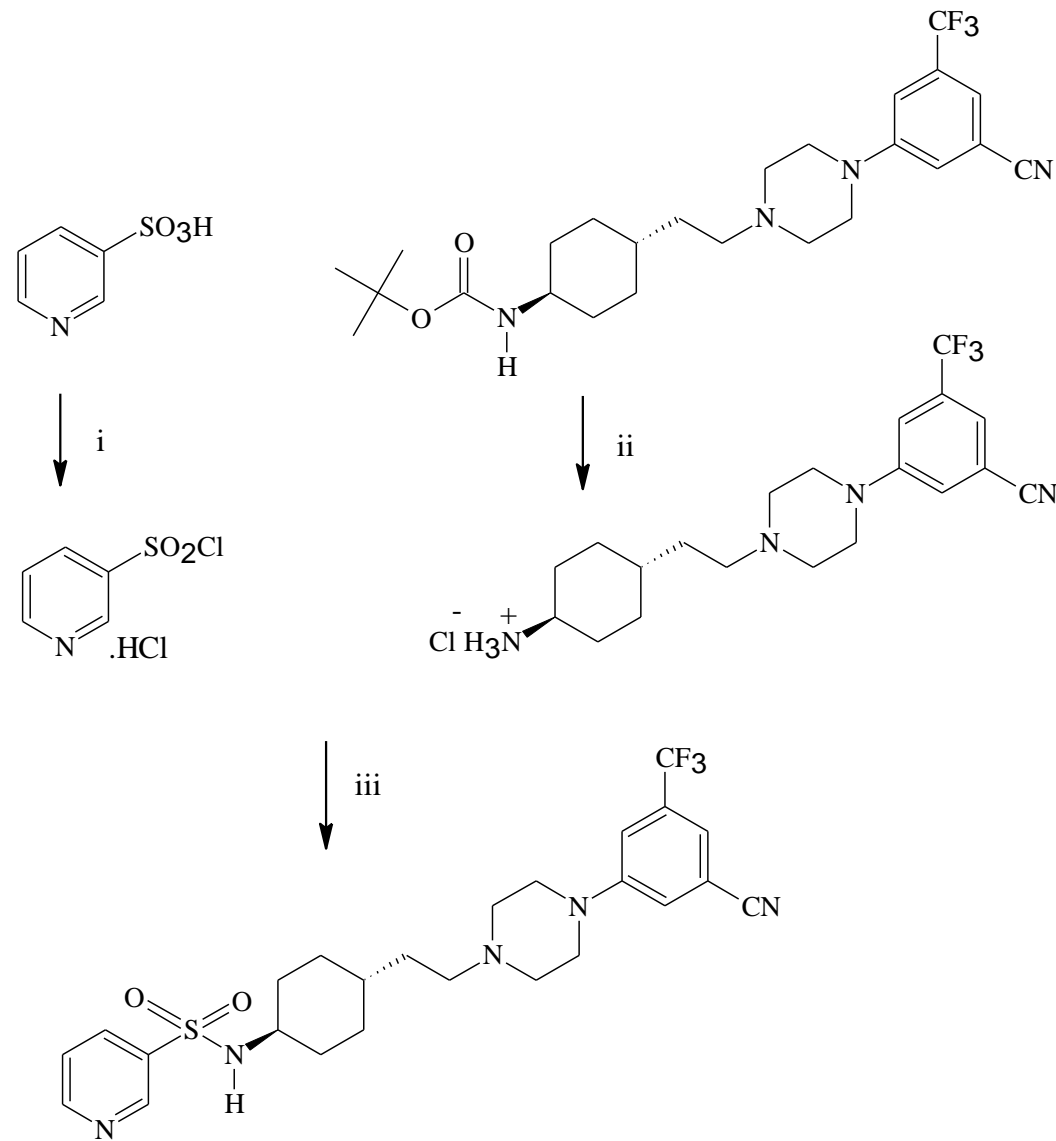
15



16

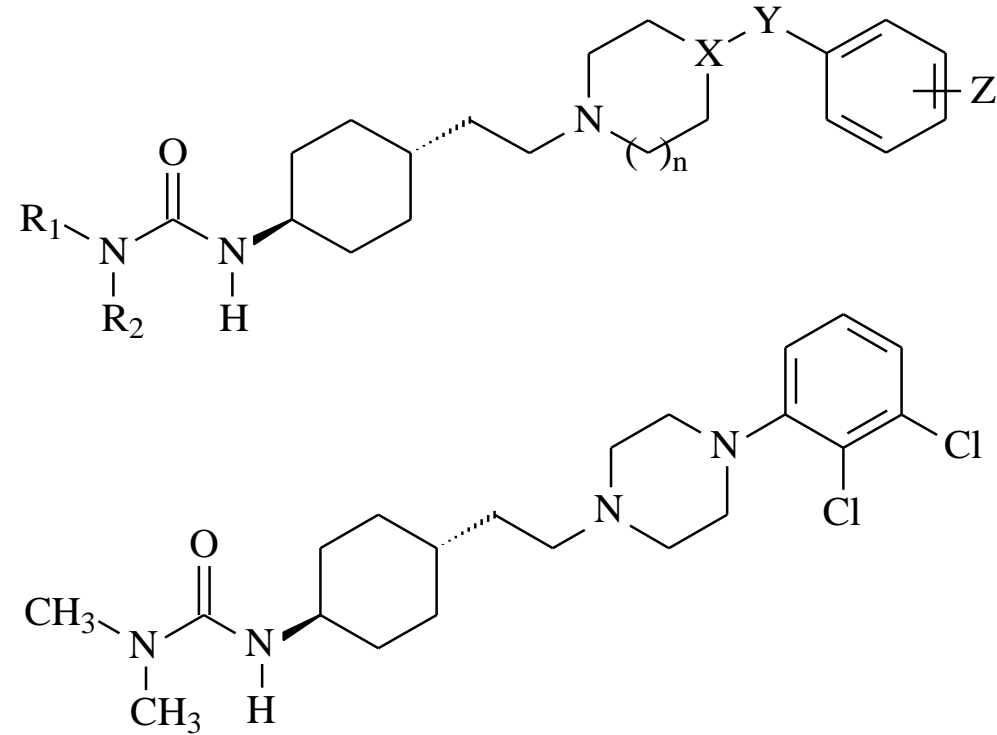


D_3 -IC₅₀: 1.9 nM; D_2 -IC₅₀: 143 nM; α -1-IC₅₀: > 10000 nM;
ind.:1408%; „climbing“- ED₅₀: 1.54 mg/kg



i: PCl_5 ; ii: HCl/EtOAc ; iii: $\text{TEA/CH}_2\text{Cl}_2$

The fourth compound library



18

D₃-IC₅₀: 1.6 nM, D₂-IC₅₀: 16 nM, α-1-IC₅₀: 508 nM,
BA: 30%, „climbing“- ED₅₀: 0.27 mg/kg

CLINICAL CANDIDATE

Allergan Announces U.S. Availability of VRAYLAR™ (cariprazine) for Treatment of Bipolar Mania and Schizophrenia in Adults

DUBLIN, March 16, 2016 /PRNewswire/

Allergan plc (NYSE: AGN), a leading global pharmaceutical company, announced today that VRAYLAR™ (cariprazine), a once-daily oral atypical antipsychotic, is now available by prescription in pharmacies throughout the U.S.

Budapest, Hungary - 19 July 2017 - Gedeon Richter Plc. ("Richter") announces that the European Commission (EC) has granted marketing authorization to Reagila[®] (cariprazine) a novel antipsychotic for the treatment of schizophrenia in adult patients.

6.11. A vezető termékek forgalma

	MFt				M€			
	2017	2016	Változás		2017	2016	Változás	
	1-12. hó		%		1-12. hó		%	
Orális fogamzásgátlók	90.576	87.002	3.574	4,1	292,9	279,3	13,6	4,9
Cavinton	30.832	28.760	2.072	7,2	99,7	92,3	7,4	8,0
Esmya®	28.757	21.504	7.253	33,7	93,0	69,0	24,0	34,8
Mydeton	20.042	17.647	2.395	13,6	64,8	56,7	8,1	14,3
Panangin	16.799	13.150	3.649	27,7	54,3	42,2	12,1	28,7
Vraylar™ / cariprazine	13.986	4.980	9.006	180,8	45,2	16,0	29,2	182,5
Verospiron	12.925	12.239	686	5,6	41,8	39,3	2,5	6,4
Bemfola®	10.706	3.292	7.414	225,2	34,6	10,6	24,0	226,4
Lisopress	10.210	10.344	-134	-1,3	33,0	33,2	-0,2	-0,6
Groprinosin	8.355	9.108	-753	-8,3	27,0	29,3	-2,3	-7,8
Vezető termékek összesen	243.188	208.026	35.162	16,9	786,3	667,9	118,4	17,7
Összes árbevétel	364.840	323.839	41.001	12,7	1.179,7	1.039,7	140,0	13,5
A 10 legnagyobb forgalmú termék részesedése %					66,7	64,2		

6.11. A vezető termékek forgalma

	MFt				MEUR			
	2018	2017	Változás		2018	2017	Változás	
	1-6. hó		%		1-6. hó		%	
Orális fogamzásgátlók	45.644	46.714	-1.070	-2,3	145,2	151,0	-5,8	-3,8
Cavinton	18.304	13.812	4.492	32,5	58,2	44,6	13,6	30,5
Vraylar® / Reagila® / cariprazine	9.707	6.256	3.451	55,2	30,9	20,2	10,7	53,0
Mydeton	9.257	10.271	-1.014	-9,9	29,4	33,2	-3,8	-11,4
Panangin	7.658	9.365	-1.707	-18,2	24,4	30,3	-5,9	-19,5
Bemfola®	6.841	5.461	1.380	25,3	21,8	17,6	4,2	23,9
Esmya®	6.361	13.647	-7.286	-53,4	20,2	44,1	-23,9	-54,2
Verospiron	5.992	6.929	-937	-13,5	19,1	22,4	-3,3	-14,7
Lisopress	5.132	5.292	-160	-3,0	16,3	17,1	-0,8	-4,7
Aflamin	4.905	3.682	1.223	33,2	15,6	11,9	3,7	31,1
Vezető termékek összesen	119.801	121.429	-1.628	-1,3	381,1	392,4	-11,3	-2,9
Összes árbevétel	183.662	187.990	-4.328	-2,3	584,3	607,5	-23,2	-3,8
A 10 legnagyobb forgalmú termék részesedése %					65,2	64,6		

STRUCTURE - MoA/BIOLOGICAL TARGET - ACTIVITY

PDD & TDD

SCREENING CASCADE

IC₅₀, BA, ED₅₀

CHEMICAL STARTING POINT, LEAD COMPOUND

LEAD OPTIMIZATION

CLINICAL CANDIDATE