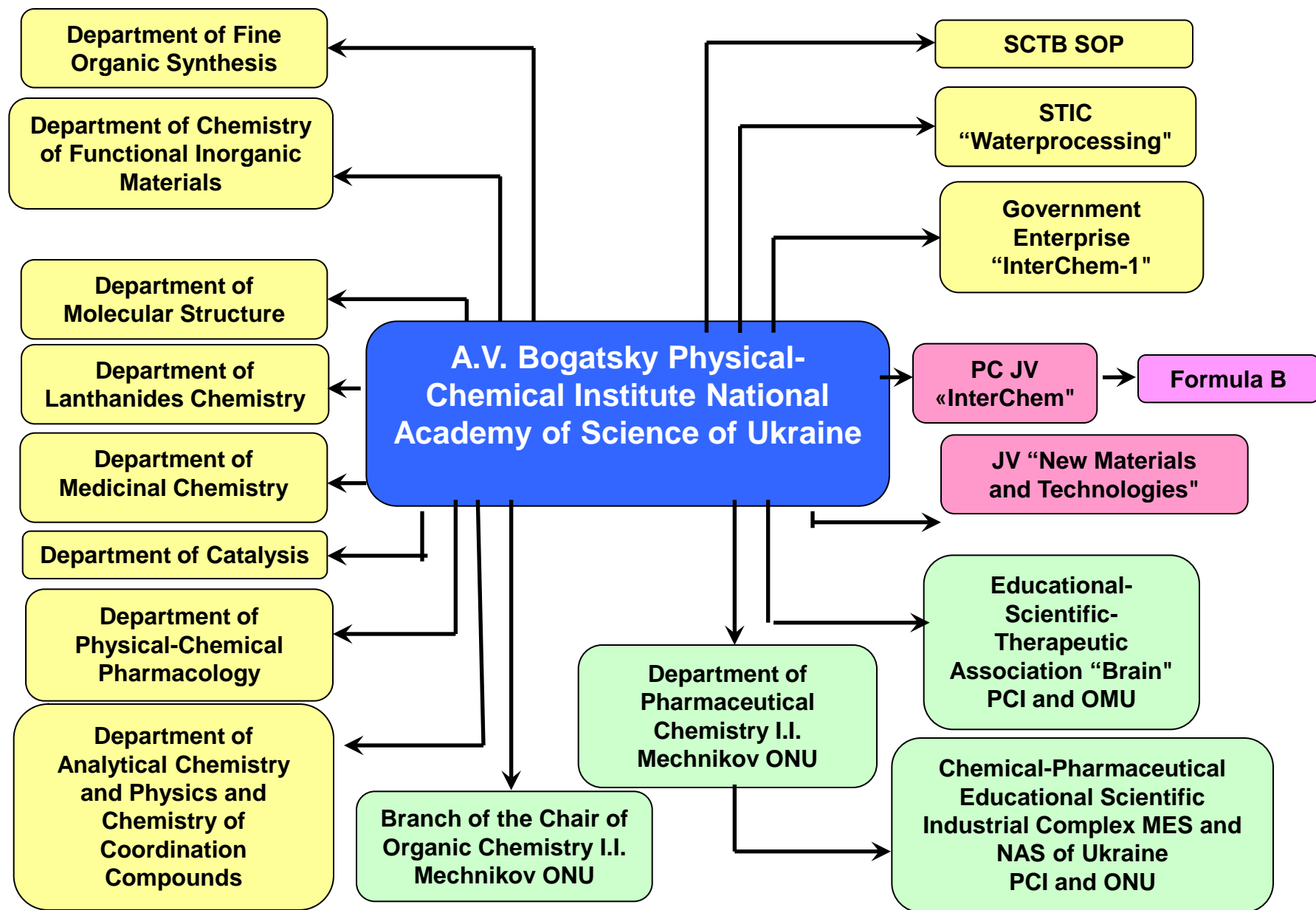
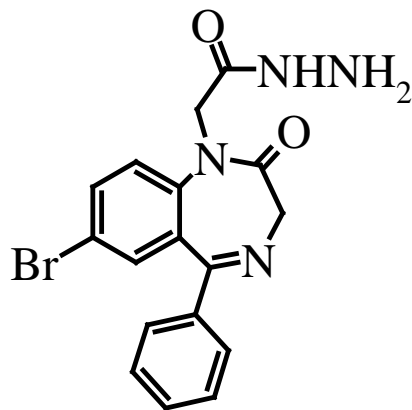
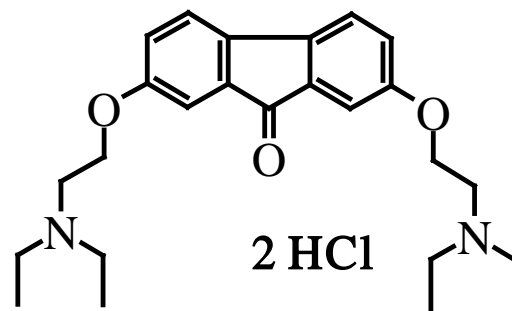


# The Structure of Scientific and Technical Complex "A.V. Bogatsky Physical-Chemical Institute NAS of Ukraine"

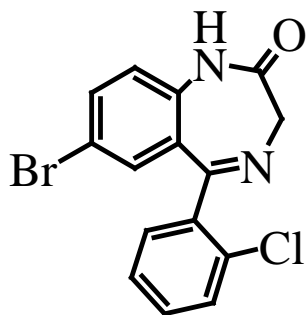




**Gidazepam**



**Amiksin**



**Phenazepam**

# Area of Complete Medicinas Manufacturing. JV “Interchem”



# Premises of Granulated Material Preparation



# Blistering Premises





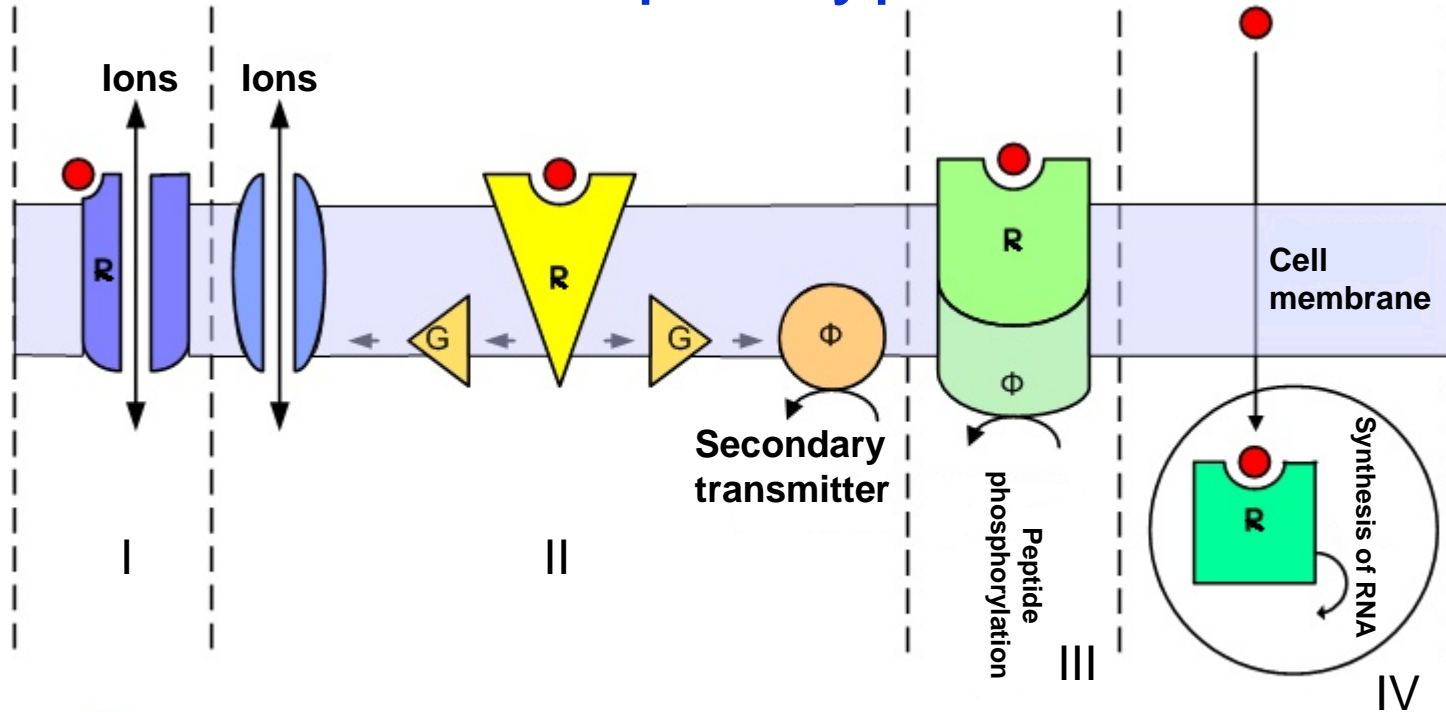
# **Ligands of Serotonin Receptors. Structure, Ligand-Receptor Recognition, Functions, Properties, QSAR**

***Sergey A. Andronati, Victor E. Kuzmin***

A.V.Bogatsky Physico-Chemical Institute  
of the National Academy of Sciences of Ukraine  
*86 Lustdorfskaya doroga, 65080 Odessa, Ukraine*

**Katciveli (Ukraine), 21-24 September 2009**

# Receptor types



● = Agonist, R = Receptor, G = G-proteins, Φ = enzymes

*Principles of the agonist action/effect on processes controlled by receptors*

- I – direct influence/effect on ion channels penetration (N-cholinoreceptors, GABA<sub>A</sub>- receptors);
- II – mediated influence (through G-proteins) either on the ion channels penetration or on the activity of enzymes regulating formation of secondary transmitters (M-cholinoreceptors, adrenoreceptors);
- III – direct influence on the activity of effector tyrosine kinase enzyme (insulin receptors, receptors of series of growth factor);
- IV – influence on the DNA transcription (steroidal hormones, thyroid hormones).

# Internal Activity

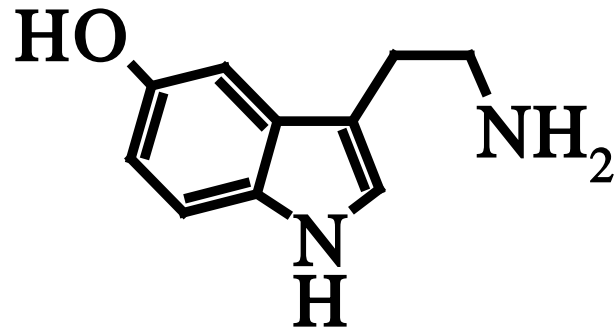
**Internal activity (IA)** – it is ligand ability to provoke receptor conformation changes, leading to signal transformation into physiological response.

High positive **IA**  $\Rightarrow$  Full agonists

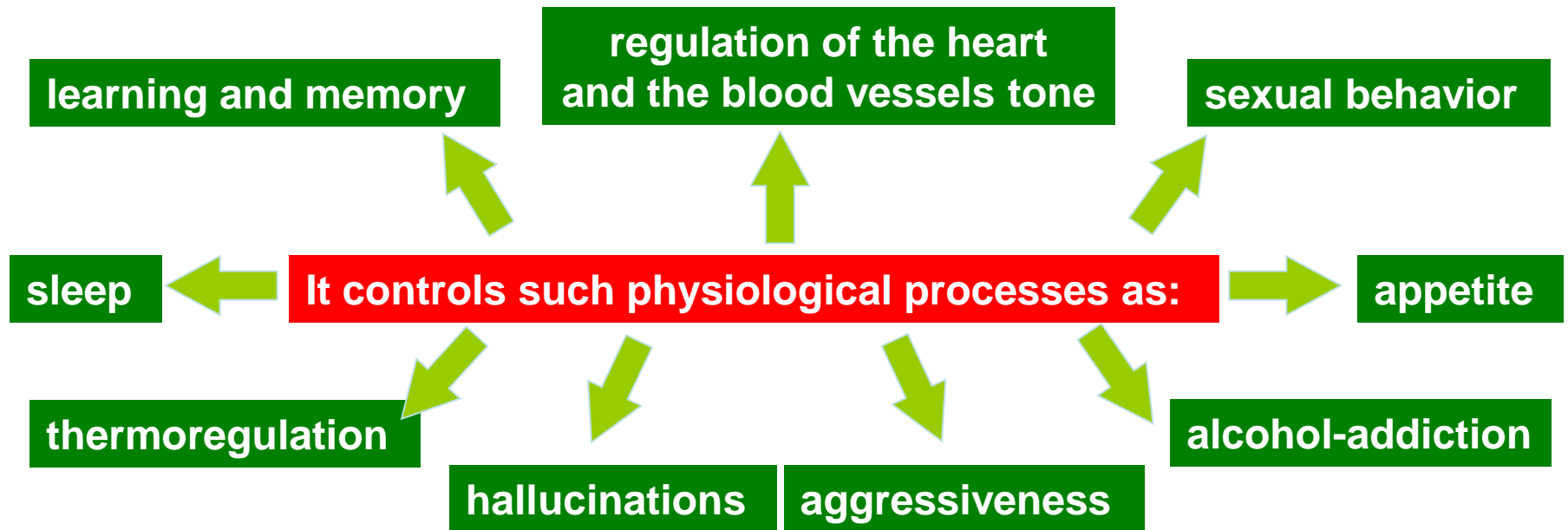
High negative **IA**  $\Rightarrow$  Inverse agonists

**IA = 0**  $\Rightarrow$  Agonists

# Serotonin (5-Hydroxytryptamine, 5-HT)



*Neuromediator and epiphysis hormone. Ligand of large family of serotonin receptors*



😊 Good mood hormone 😊

# Serotonin

**Involved in the pathogenesis:**

**state of anxiety**

**depression**

**migraines**

**schizophrenia**

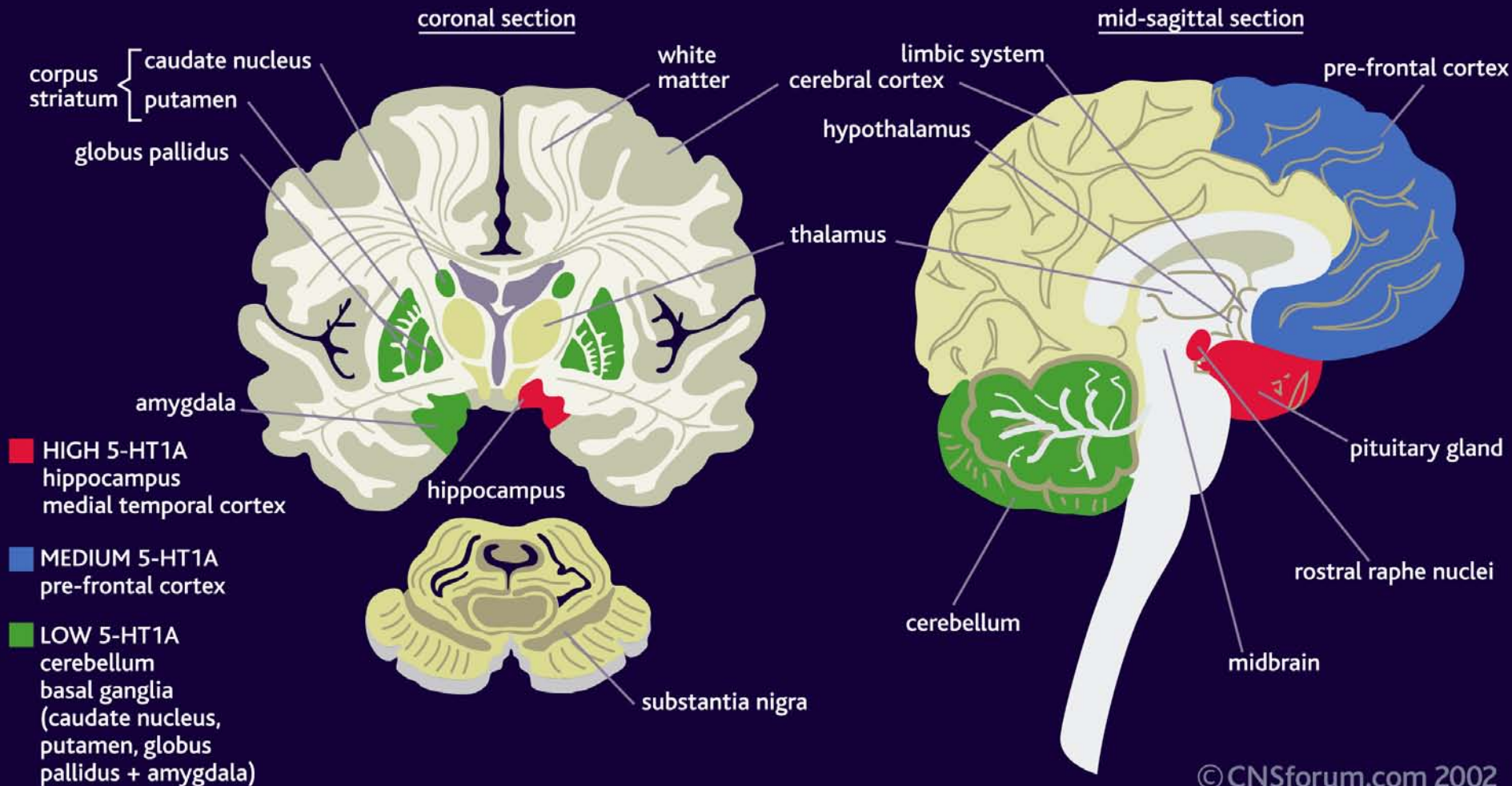
**neurodegenerative disorders  
(Parkinson's disease, Alzheimer's, Huntington's chorea)**

*It operates in the central and peripheral nervous system  
in a number of internal organs and tissues*

# 5-HT RECEPTORS CHARACTERISTICS

Receptors	Structures	Effectors	Agonists	Antagonists	Pharmacological activity
5-HT <sub>1A</sub>	422aa,7TM	G <sub>i/o</sub>	8-OH-DPAT	WAY100635	anxiolytic, antidepressive
5-HT <sub>1B</sub>	390aa,7TM	G <sub>i/o</sub>	sumatriptan L694247	GR55562, SB216641	antidepressive
5-HT <sub>1D</sub>	377aa,7TM	G <sub>i/o</sub>	sumatriptan L694247	BRL15572	antimigraine
5-HT <sub>1E</sub>	365aa,7TM	G <sub>i/o</sub>	-	-	
5-HT <sub>1F</sub>	366aa,7TM	G <sub>i/o</sub>	LY334370	-	antimigraine
5-HT <sub>2A</sub>	471aa,7TM	G <sub>q/11</sub>	α-Me-5-HT	Ketanserin, MDL100907	anxiolytic, antidepressive, hypotensive
5-HT <sub>2B</sub>	481aa,7TM	G <sub>q/11</sub>	BW723C86, α-Me-5-HT	SB200646, SB204741	anxiolytic vasoconstrictor
5-HT <sub>2C</sub>	458aa,7TM	G <sub>q/11</sub>	α-Me-5-HT		hypnotic
5-HT <sub>3</sub>	478aa, α-subunit, homopentamer	cation channel	SR57227, <i>m</i> -chlorophenylbiguanide	Mesulergine, SB242084, RS102221	neuroleptic, antiemetic, antidepressive, analgetic
5-HT <sub>4</sub>	387aa,7TM	G <sub>s</sub>	BIMU8, RS67506, ML10302	Granisetron, ondasetron, tropisetron	antiarrhythmic, cognitive
5-HT <sub>5A</sub>	357aa,7TM	unknown	-	GR113808, SB204070, RS100235	
5-HT <sub>5B</sub>	370aa,7TM	unknown	-	-	
5-HT <sub>6</sub>	440aa,7TM	G <sub>s</sub>	-	RO046790	Antipsychotic, sedative
5-HT <sub>7</sub>	445aa,7TM	G <sub>s</sub>	-	SB258719	

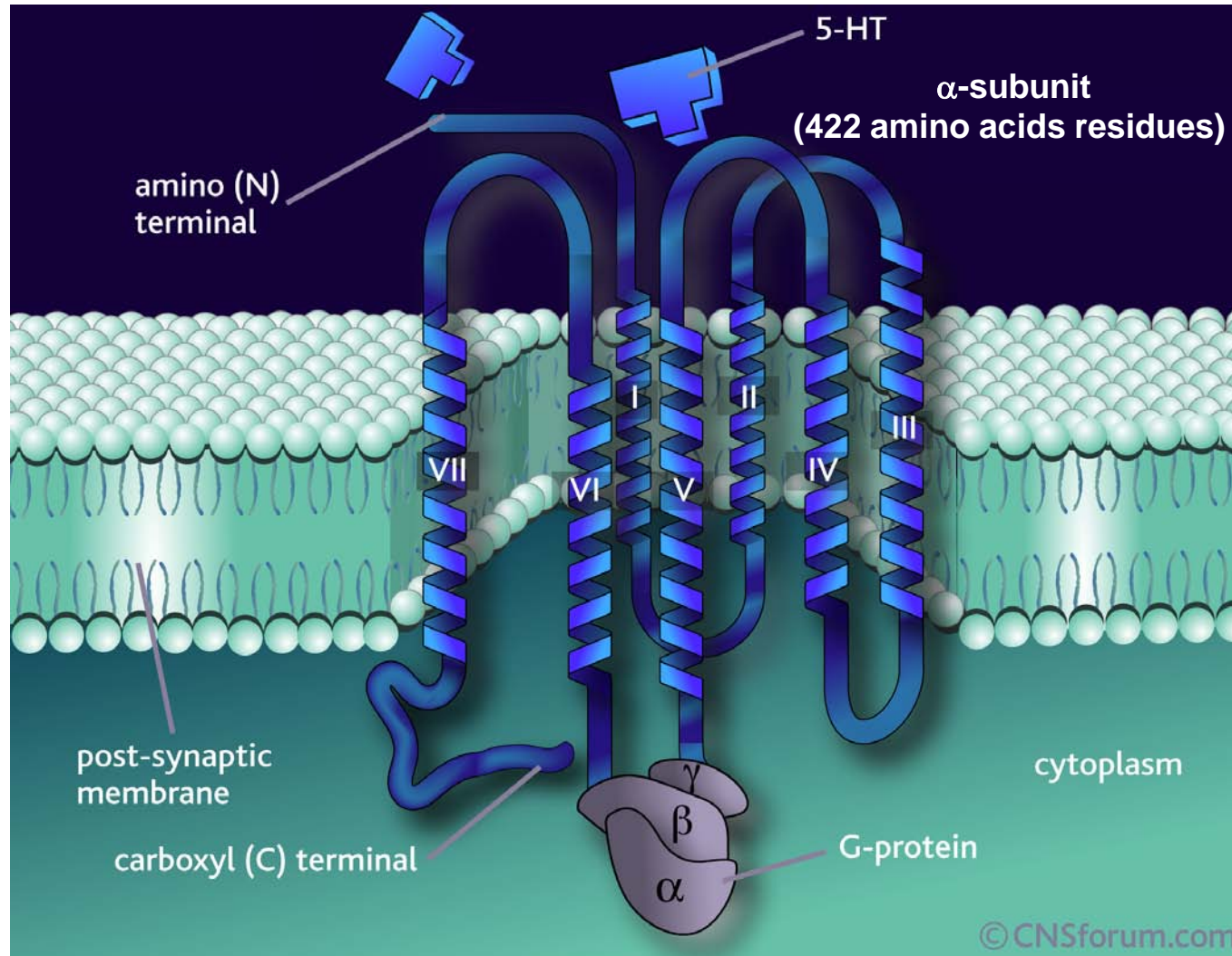
# Distribution of 5-HT<sub>1A</sub> receptors in the normal brain



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# TRANSMEMBRANE TOPOLOGY OF 5-HT<sub>1A</sub> R

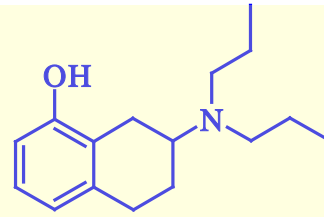
Residues Tr-343 and Val-344 are responsible for the conjunction of  $\alpha$ -subunit with the G<sub>i</sub>-protein



Fundamental importance in the recognition of ligands have residues of the Asp-116, Ser-199 and Phe-336

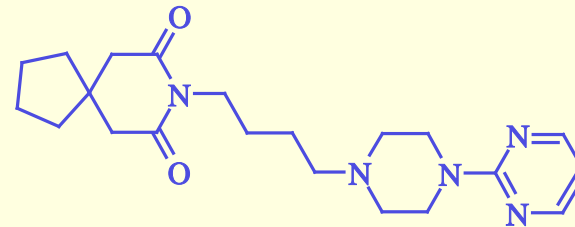
# LIGANDS OF 5-HT<sub>1A</sub> RECEPTOR

FULL AGONIST



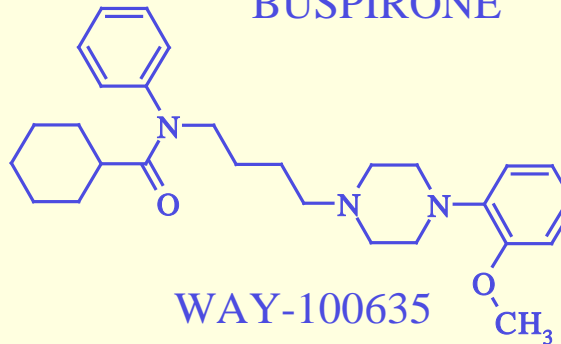
8-OH-DPAT

PARTIAL AGONIST



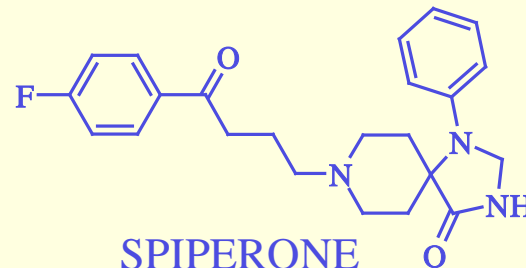
BUSPIRONE

ANTAGONIST



WAY-100635

INVERSE AGONIST

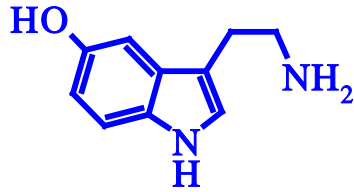


SPIPERONE

# Pharmacological properties and application of ligands 5-HT R

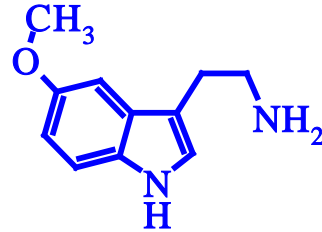
## Agonists:

Serotonin



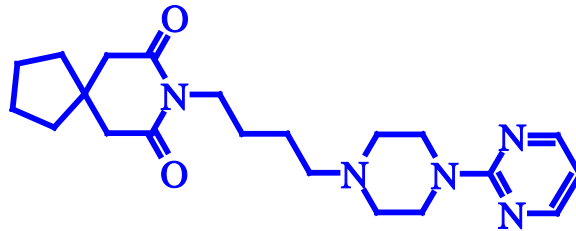
Antihemorrhoids effect  
(due to the vasoconstrictor action,  
stimulation of platelet aggregation)

5-Methoxytryptamine  
(Mexamine)



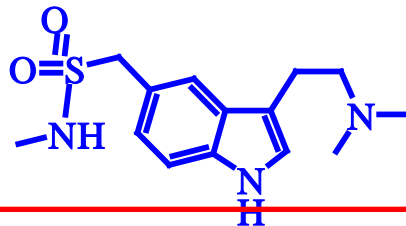
Radioprotective substance at radiotherapy  
(due to the vasoconstrictor action)

Buspirone



Anxiolytic, antidepressant

Sumatriptan

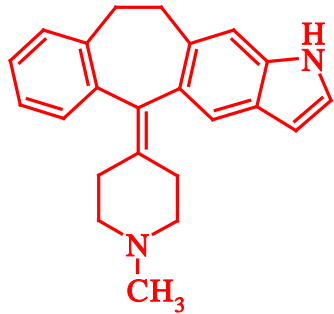


Selective agonist 5HT<sub>1D</sub> R.  
The first highly efficient antimigraine agent

# Pharmacological properties and application of ligands 5-HT R

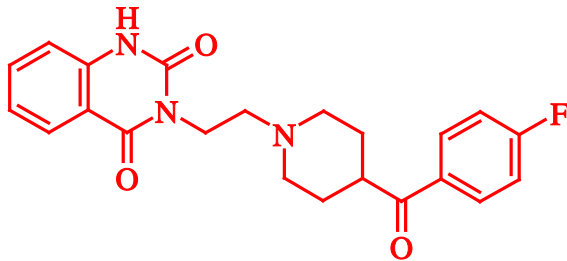
## Antagonists:

Pizotifen



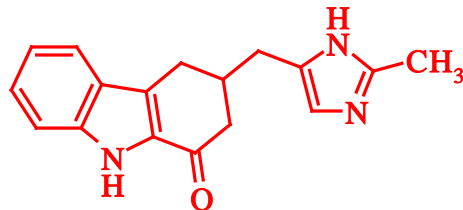
Antagonist 5-HT<sub>1A</sub>R. Antiemetic, antidepressant, antimigraine properties, stimulation of appetite

Ketanserin



Antagonist 5-HT<sub>2</sub>R. Blocks effects of serotonin, dilates blood vessels (vasodilatation), antihypertensive activity

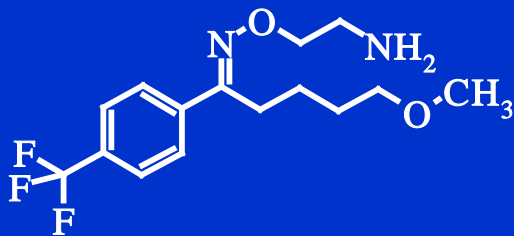
Ondasetron



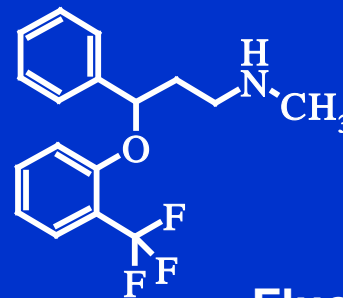
Antagonist 5-HT<sub>3</sub>R. Antipsychotic, anxiolytic and antiemetic properties

# Inhibitors of serotonin reuptake

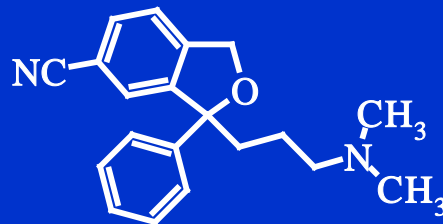
## Antidepressants of III<sup>rd</sup> generation



Fluvoxamine

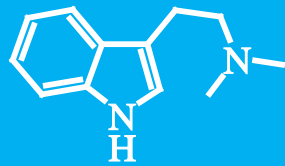


Fluoxetine



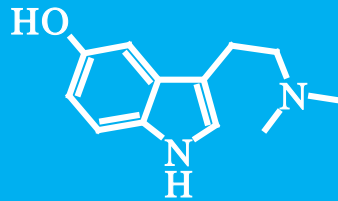
Citalopram

# Psychotomimetics (hallucinogens)



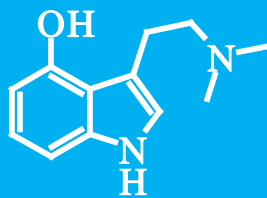
From the South American plant *Peptadenia peregrin*

Dimethyltryptamine

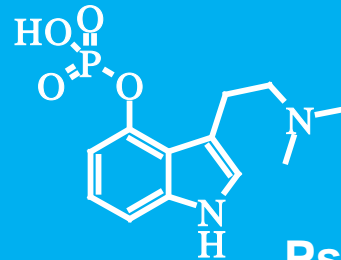


From the secrets of toads and some plants

Bufotenin



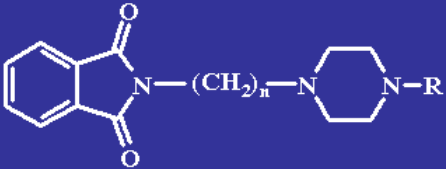
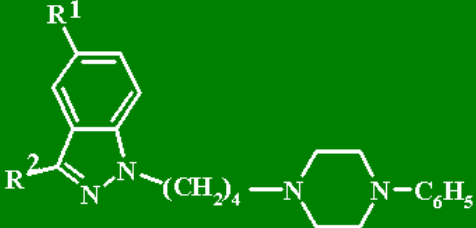
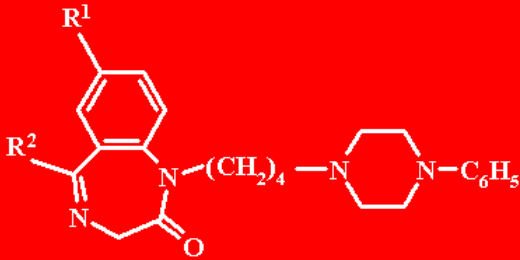
Psilocin



Psilocibin

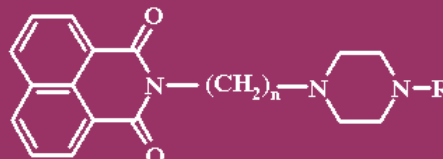
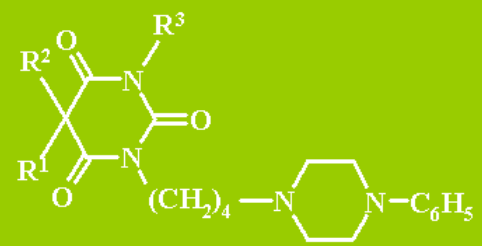
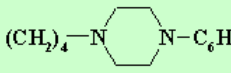
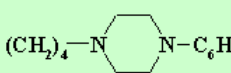
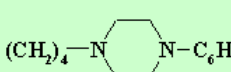
From the Mexican mushroom *Teonankate*

# Arylpiperazines derivatives affinity for 5-HT<sub>1A</sub> R

#	Compounds		K <sub>i</sub> , nM	#	Compounds		K <sub>i</sub> , nM
							
	<b>n</b>	<b>R</b>			<b>R<sup>1</sup></b>	<b>R<sup>2</sup></b>	
1	1	C <sub>6</sub> H <sub>5</sub>	>10000	25	Cl	C <sub>6</sub> H <sub>5</sub>	2800
2	2	C <sub>6</sub> H <sub>5</sub>	>9600	26	Br	C <sub>6</sub> H <sub>5</sub>	5500
3	4	C <sub>6</sub> H <sub>5</sub>	10	27	Br	O-C <sub>6</sub> H <sub>4</sub>	6100
4	4	<i>o</i> -ClC <sub>6</sub> H <sub>4</sub>	5,2	28	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	447
5	4	<i>m</i> -ClC <sub>6</sub> H <sub>4</sub>	182,4				
6	5	<i>o</i> -ClC <sub>6</sub> H <sub>4</sub>	6,8		<b>R<sup>1</sup></b>	<b>R<sup>2</sup></b>	
7	5	<i>o</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	13,1				
8	6	<i>o</i> -ClC <sub>6</sub> H <sub>4</sub>	14,0				
9	6	<i>o</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	91,5				
10	6	<i>m</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	243,7	29	Cl	C <sub>6</sub> H <sub>5</sub>	2200
				30	Br	C <sub>6</sub> H <sub>5</sub>	1690
				31	Br	<i>o</i> -ClC <sub>6</sub> H <sub>4</sub>	890
11	6	<i>n</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	440	32	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	1500

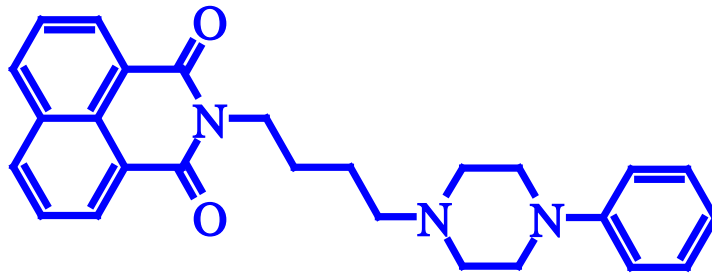
S.A. Andronati, S.Yu. Makan. Nitrogen-containing Heterocycles and Alkaloids; Moskow, 2001, Iridium Press. p. 33 - 43

# Arylpiperazines derivatives affinity for 5-HT<sub>1A</sub> R

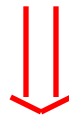
#	Compounds		Ki, nM	#	Compounds			Ki, nM
								
	n	R			R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	
12	3	C <sub>6</sub> H <sub>5</sub>	53,8	33	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	H	1,63
13	3	<i>o</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	2440	34	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub>	4,78
14	3	<i>o</i> -ClC <sub>6</sub> H <sub>4</sub>	72,6	35	C <sub>2</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	H	14,6
15	4	C <sub>6</sub> H <sub>5</sub>	2,9	36	C <sub>2</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>	17,1
16	4	<i>o</i> -ClC <sub>6</sub> H <sub>4</sub>	25,9	37	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>		358
17	4	<i>o</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	1280					
18	4	<i>m</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	38,5					
19	4	<i>m</i> -ClC <sub>6</sub> H <sub>4</sub>	30,5	38	C <sub>2</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>		106
20	4	<i>n</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	4120					
21	4	<i>n</i> -ClC <sub>6</sub> H <sub>4</sub>	38,7					
22	5	C <sub>6</sub> H <sub>5</sub>	43,4	39	C <sub>2</sub> H <sub>5</sub>	CH(CH <sub>3</sub> )C <sub>3</sub> H <sub>7</sub>		584
23	5	<i>o</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	1640					
24	6	C <sub>6</sub> H <sub>5</sub>	22,9					

S.A. Andronati, S.Yu. Makan. Nitrogen-containing Heterocycles and Alkaloids; Moskow, 2001, Iridium Press. p. 33 - 43

# Neuropharmacological profile of **MX-1207** action



Concentration of 50% inhibition of specific binding [<sup>3</sup>H] – 8-OH-DPAT with 5-HT<sub>1A</sub>R IC<sub>50</sub> = 3.5 ± 1.0 nM  
It has no anxiolytic properties! It blocks pharmacological effects of buspiron and 8-OH-DPAT!

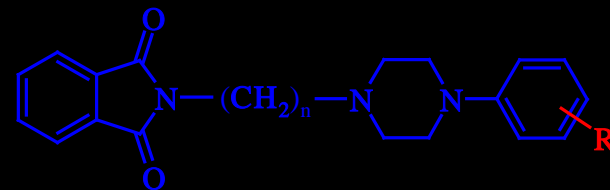


**Antagonist 5-HT<sub>1A</sub>R**

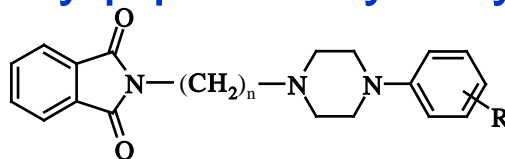
S.A. Andronati, V.M. Varava, S.G. Soboleva, A.Ya. Korneev, T.A. Voronina, S.B. Seredenin. Reports of Academy of Sciences, 1992, 327, p. 341-344

T.L. Karaseva, B.A. Lobasiuk, S.G. Soboleva, E.A. Kostenko, S.A. Andronati. Neurophysiology, 2000, 32, p.11-15

# The relationship “affinity-anxiolytic activity” of the Arylpiperazinylalkylphthalimides

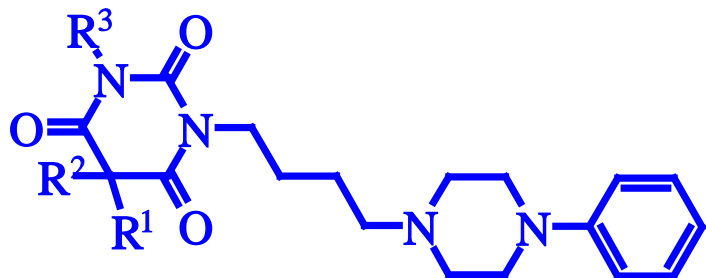


# Affinity to 5-HT<sub>1A</sub> and D<sub>2</sub> rats head brain receptors and anxiolytic activity of N-(arylpiperazinyllalkyl)phthalimides



NN comp	R	n	Affinity (K <sub>i</sub> ), nM		Selectivity	Anxiolytic activity (number of punished water intakes)
			5-HT <sub>1A</sub> R	D <sub>2</sub> R		
1	H	3	746,2±31,7	907,8±91,0	1,3	
2	H	4	10,1±0,9	187,8±11,8	18,6	52 ± 11,1
3	<i>o</i> -Cl	4	5,2±0,5	226,7±20,0	43,6	54,1 ± 11,4
4	<i>o</i> -CH <sub>3</sub>	4	73,1±0,8	693,3±57,2	9,5	37,3 ± 15,4
5	<i>m</i> -CH <sub>3</sub>	4	128±10,6	413,0±39,0	3,2	27,1 ± 7,4
6	<i>p</i> -CH <sub>3</sub>	4	371,5±36,2	710,0±70,0	1,91	
7	<i>o</i> -Cl	5	6,9±0,5	627,4±58,2	92,3	70 ± 17,3
8	<i>o</i> -CH <sub>3</sub>	5	13,1±0,9	743,5±69,7	56,9	68,8 ± 19,7
9	<i>m</i> -CH <sub>3</sub>	5	252±19,8	300,0±21,0	1,0	22,8 ± 6,9
10	<i>p</i> -CH <sub>3</sub>	5	163±13,5	198,0±13,1	1,2	27,4 ± 6,6
11	<i>o</i> -Cl	6	14,3±1,3	411,6±40,8	29,0	67,2 ± 15,4
12	<i>o</i> -CH <sub>3</sub>	6	91,5±7,2	534,0±54,7	5,8	
Buspirone			16 ± 2			53 ± 17
Control						11 ± 5

# Phenylpiperazinybutylbarbituric acids

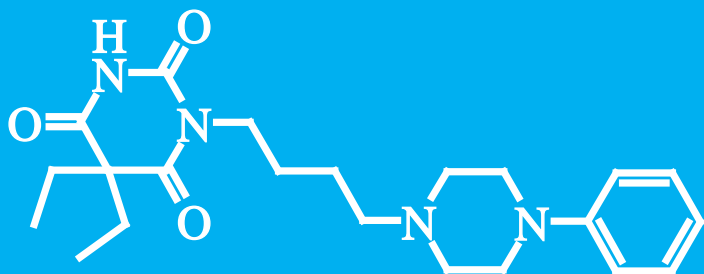


R<sup>1</sup> = CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>;

R<sup>2</sup> = C<sub>2</sub>H<sub>5</sub>, CH(CH<sub>3</sub>)C<sub>3</sub>H<sub>7</sub>, C<sub>6</sub>H<sub>5</sub>;

R<sup>3</sup> = H, CH<sub>3</sub>,  $-(\text{CH}_2)_4-\text{N}$ -piperazine-phenyl

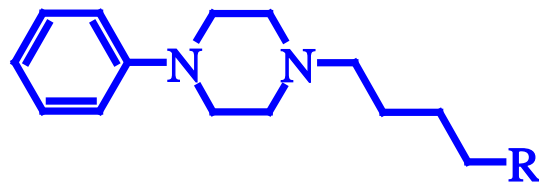
Maximum affinity for 5-HT<sub>1A</sub> R (K<sub>i</sub> = 1.26 nM)  
and anxiolytic activity (107 ± 8.1 number of  
punished water intakes)



Anticonvulsant activity (pentamethylbutetrazol)  
ED<sub>50</sub> = 135 (122.5 – 142.0) mg/kg

Hypnotic activity ED<sub>99</sub> = 80 mg/kg

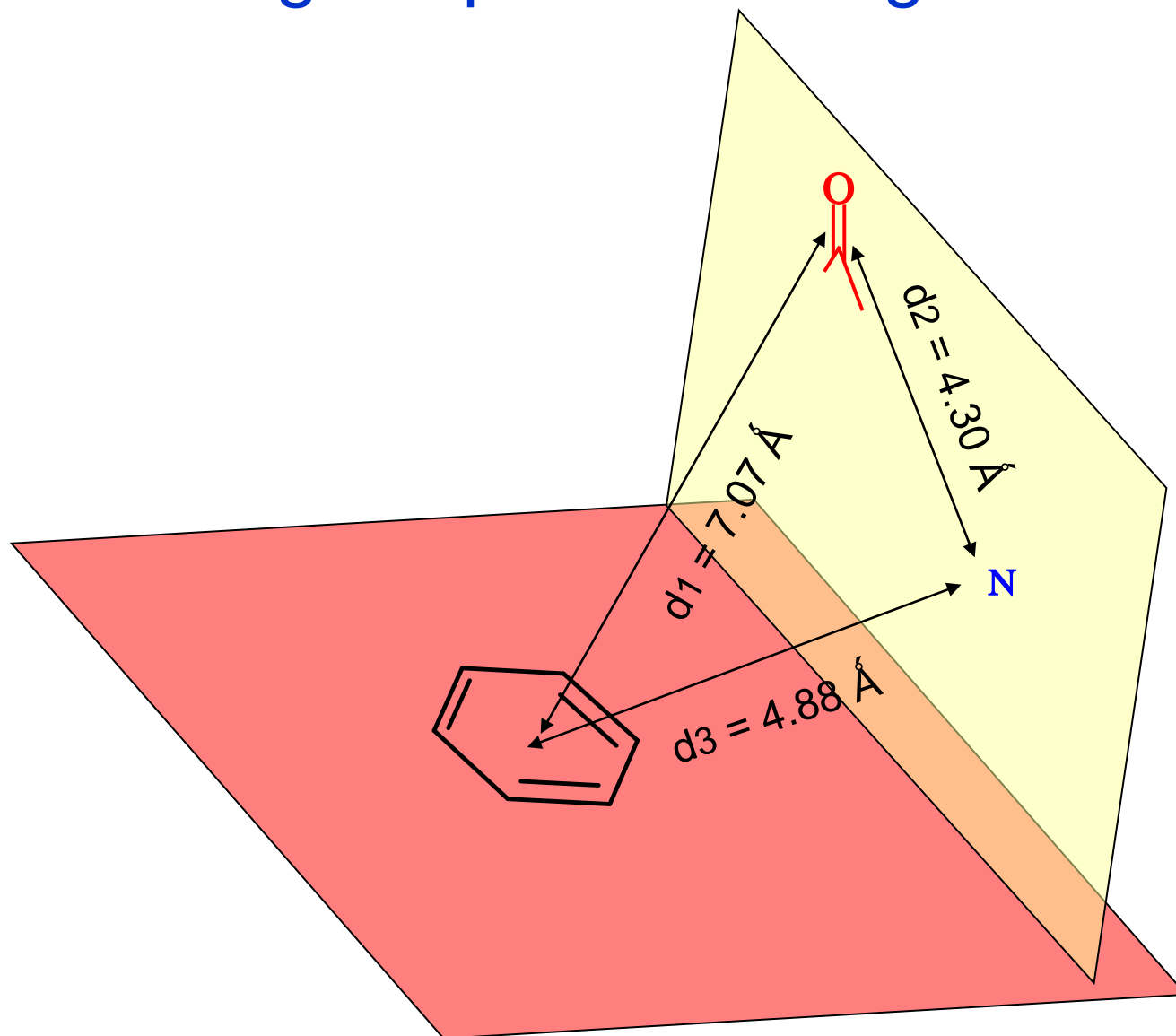
# Lipophilicity and affinity for CNS receptors of Phenylpyperazinyllalkyl – Heterocyclic compounds



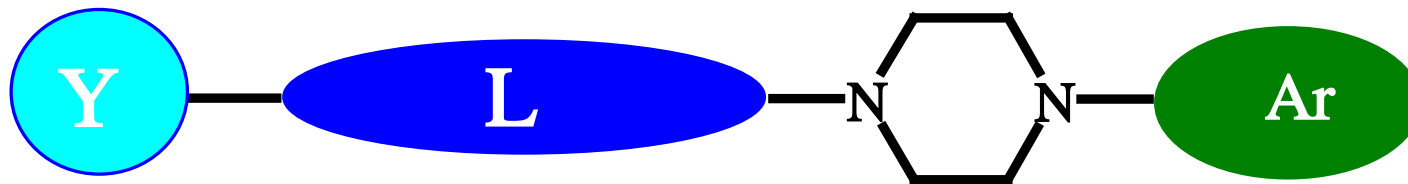
R	log P	K <sub>i</sub> , nM			
		5-HT <sub>1A</sub>	D <sub>1</sub>	D <sub>2</sub>	BD
	3.97±0.43	10.0			
	5.20±0.43	2.9			
	3.50±0.41	144±11			
	2.29±0.74	96±7			
	6.79±0.54	2800	294	225	
	5.77±0.64	5500	151	63	

R	log P	K <sub>i</sub> , nM			
		5-HT <sub>1A</sub>	D <sub>1</sub>	D <sub>2</sub>	BD
	7.44±0.61	6100	111	47	
	5.02±0.57	447	970	300	
	5.38±0.59	2200		540	216
	5.84±0.69	1680 (?)		169	96.5
	6.01±0.64	890 (?)		82	7.2
	4.90±0.58	1500		821	359

# Three-point model of the pharmacophore for binding buspirone analogs at 5-HT<sub>1A</sub> R



# Analysis of “structure-affinity” relationship of 5-HT<sub>1A</sub> receptor ligands (QSAR of 5-HT<sub>1A</sub> receptor ligands)



**Y – different mono- and polycyclic carbo- and heterocycles, which are bonded to L by amido, carbonyl, ureido and carboxylic groups**

**L – polymethylene chain with number of CH<sub>2</sub>-groups from 1 to 6**

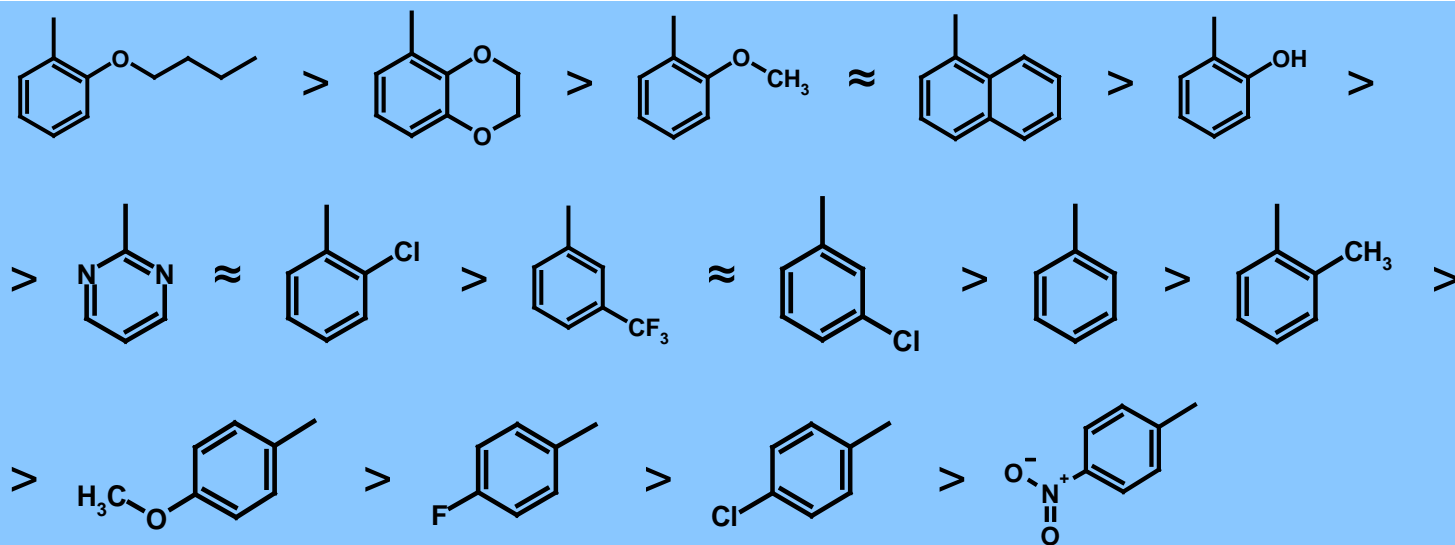
**Ar – phenyl comprising different substituents, pyridine-2-yl, pyrimidin-2-yl, benzyl, 2,3-dihydrobenzodioxin-5-yl, benzofuran-7-yl, naphthyl**

*Extended 346 compounds set*

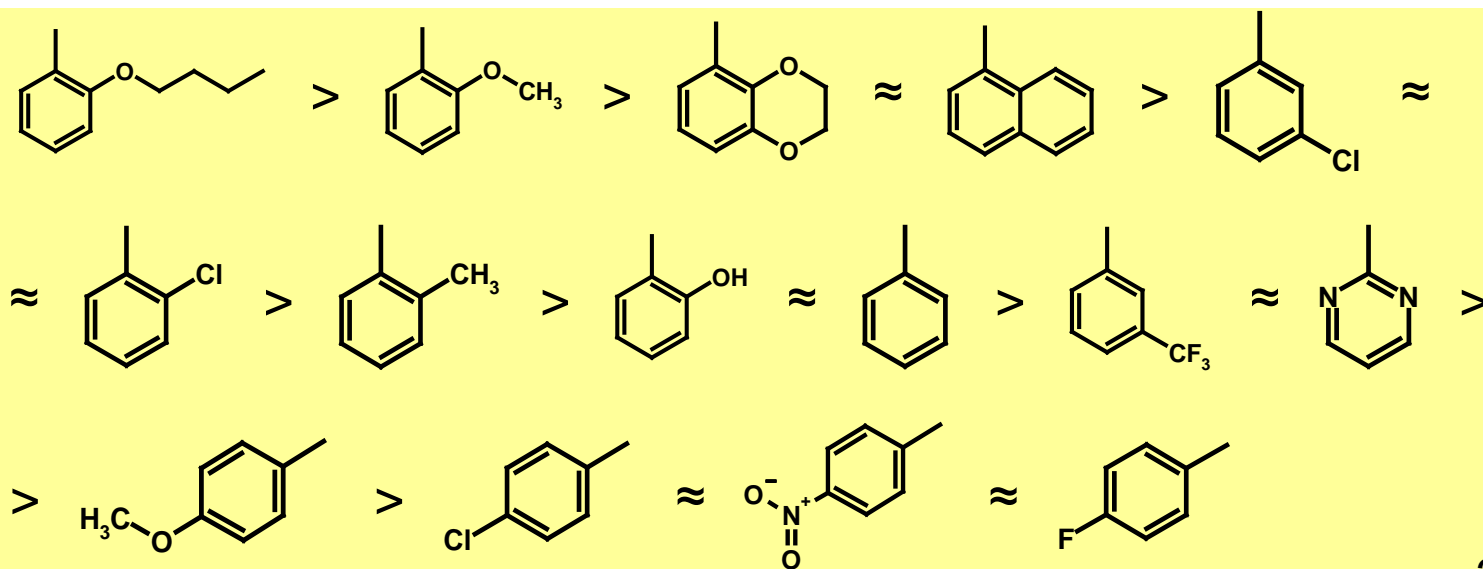
P.G. Polischuk, V.E. Kuzmin, A.G. Artemenko, S.Yu Makan, S.A. Andronati.  
Reports of the National Academy of Sciences of Ukraine. 2008, №3, p.138-144

# Relative influence of Ar fragments on affinity for 5-HT<sub>1A</sub> receptors

PLS model

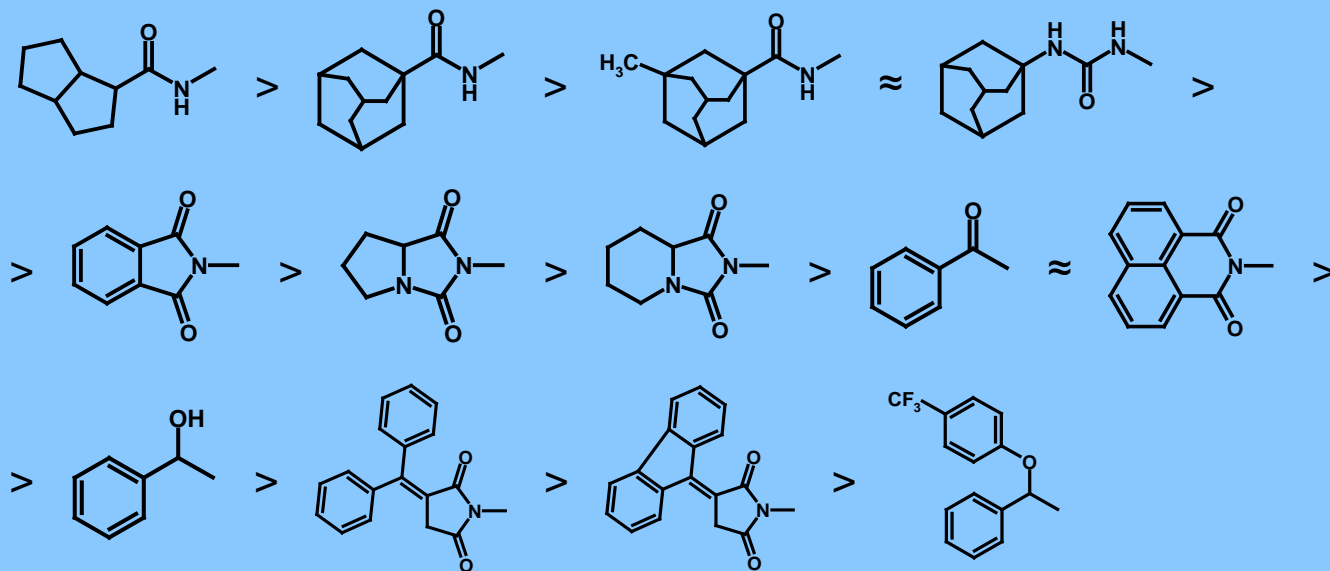


CART model

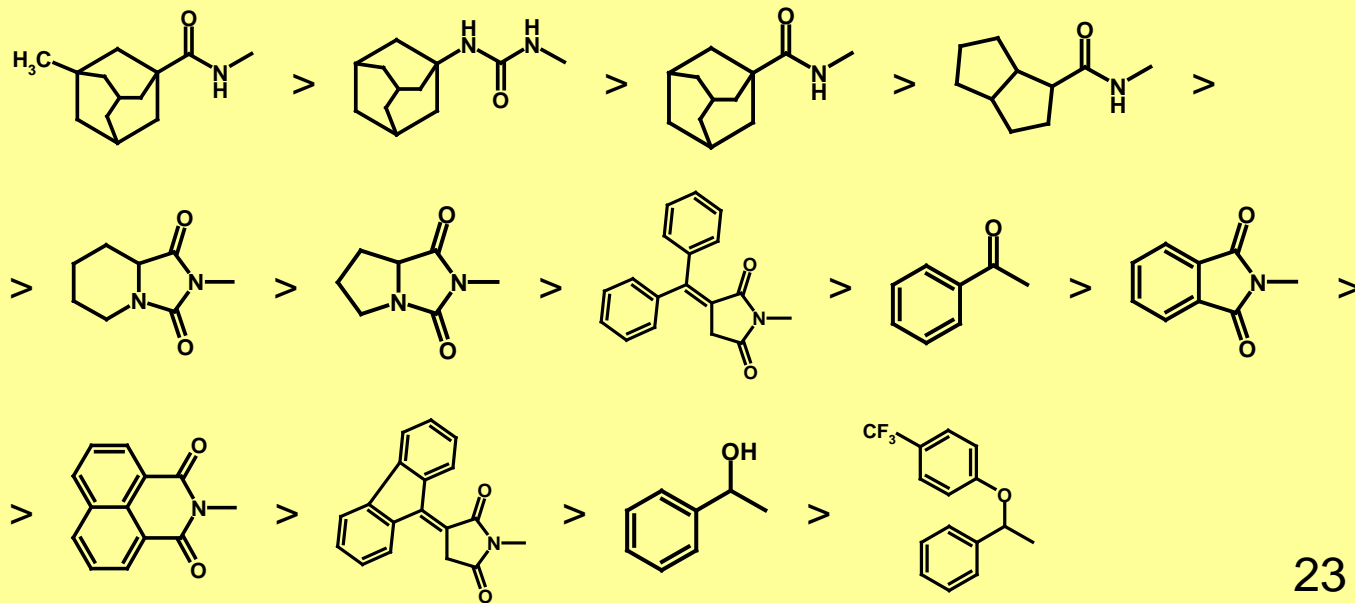


# Relative influence of Y fragments on affinity for 5-HT<sub>1A</sub> receptors

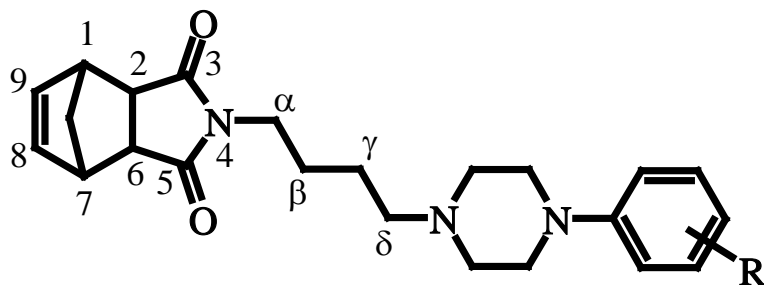
PLS model



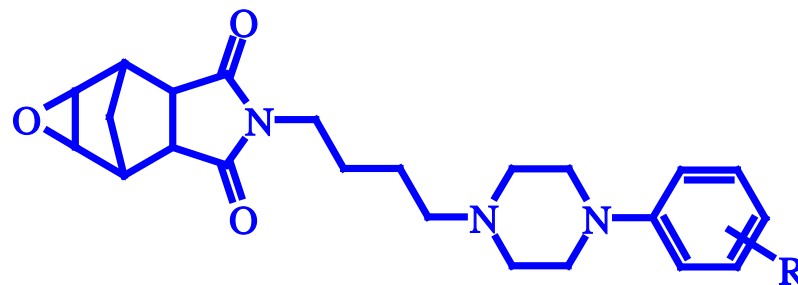
CART model



# N-(aryl)piperaziny]butylimides of bicyclo[2.2.1]hept-5-en-endo,endo-2,3-dicarboxylic acid and their epoxide derivatives



R	$K_i$ , nM
H	$16.2 \pm 2.0$
<i>o</i> -Cl	$0.60 \pm 0.08$
<i>m</i> -Cl	$3.5 \pm 0.5$
<i>o</i> -CH <sub>3</sub>	$8.3 \pm 0.9$
<i>m</i> -CH <sub>3</sub>	



R	$K_i$ , nM
<i>o</i> -Cl	$0.70 \pm 0.08$
<i>o</i> -CH <sub>3</sub>	$8.9 \pm 1.0$

**Buspiron,  $K_i = 15.05 \pm 1.5$  nM**

S.Yu. Makan, D.I. Tcimbai, S.G. Soboleva, I.N. Tarabara, L.I. Kasiyan, S.A. Andronati.  
J. General Chem. 2009, 79, p. 303 - 307