

Antidepressants: Current and Future Targets

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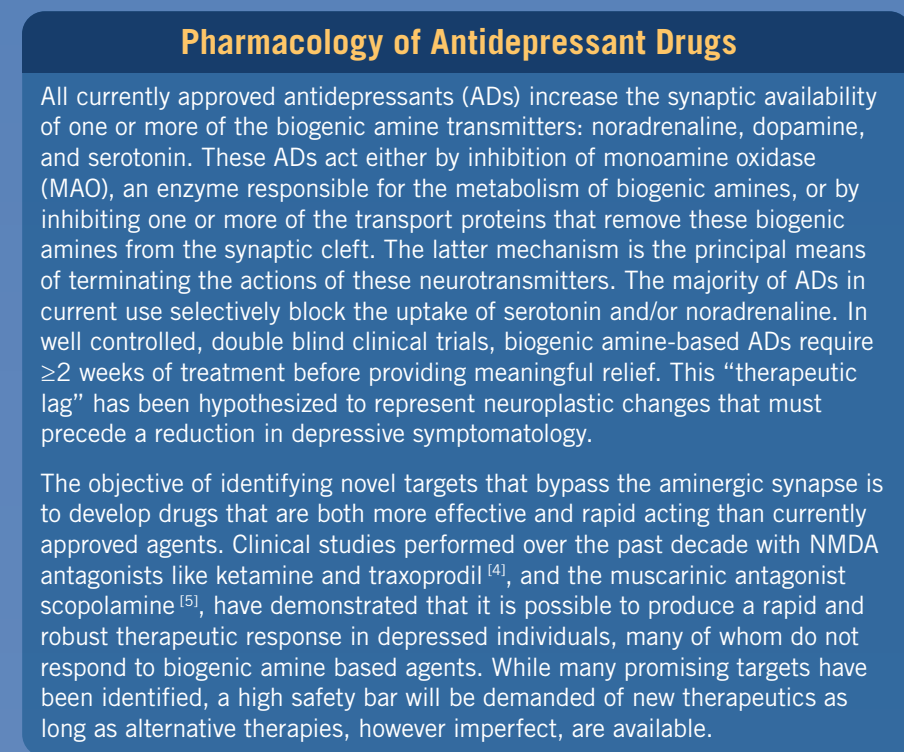
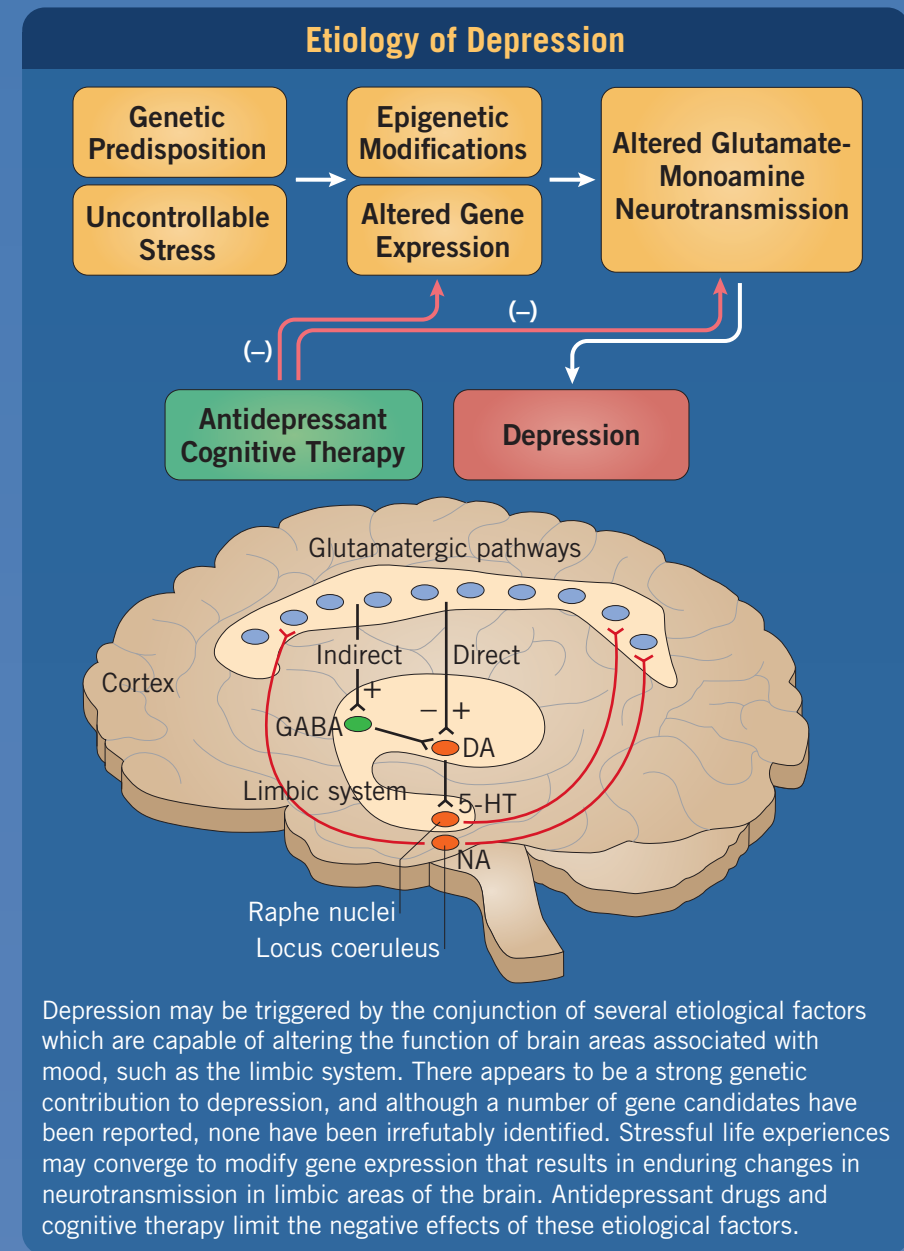
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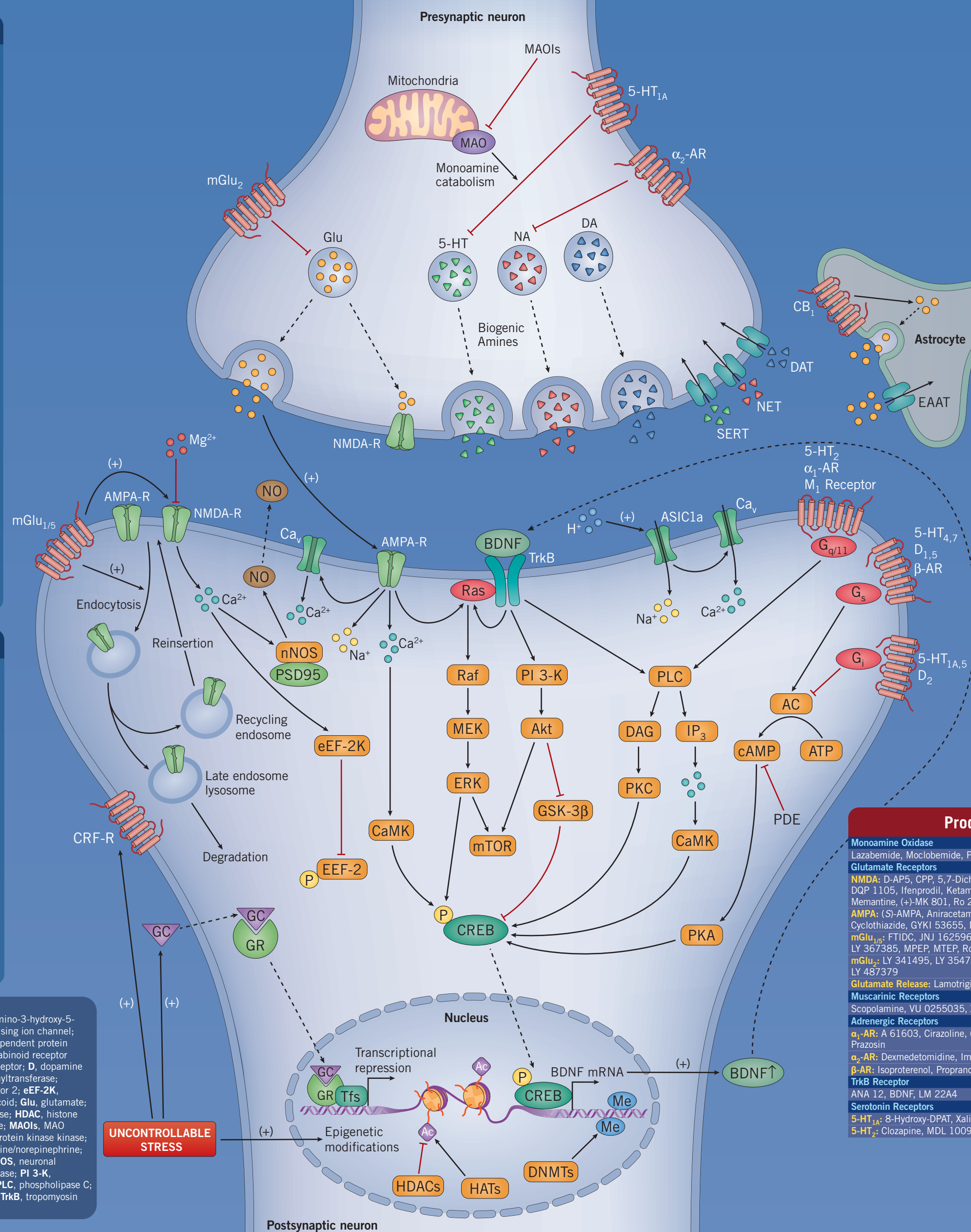
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Major depressive disorder (MDD), often referred to as major depression, is characterized by the core symptoms of depressed mood and a loss of interest and/or pleasure. Other symptoms that may be manifested include significant weight changes (loss or gain), sleep disturbances (insomnia or hypersomnia), fatigue, diminished ability to think or concentrate, feelings of worthlessness or guilt, recurrent thoughts of death or suicide, and psychomotor agitation or retardation. In addition to producing clinically significant distress, a major depressive episode is almost uniformly accompanied by some degree of social and/or occupational impairment, negatively impacting quality of life and contributing to the societal burden associated with loss of work and health care costs. In developed countries approximately 15% of the population has been affected by MDD in their lifetime and around 5% has suffered a major depressive episode during the last year^[1]. The risk of developing MDD is almost twice as high in women^[2] and the majority of people affected with MDD do not receive standard treatment^[3].



Abbreviations

5-HT, serotonin; Ac, acetylation; AC, adenyl cyclase; Akt/PKB, protein kinase B; AMPA-R, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; AR, adrenoceptor/adrenergic receptor; ASIC, acid-sensing ion channel; ATP, adenosine triphosphate; BDNF, brain-derived neurotrophic factor; CaMK, Ca^{2+} /calmodulin-dependent protein kinase; cAMP, cyclic adenosine monophosphate; Ca_v , voltage-gated calcium channel; CB₁, cannabinoid receptor type 1; CREB, cAMP response element-binding protein; CRF-R, corticotropin-releasing factor receptor; D, dopamine receptor; DA, dopamine; DAG, 1,2-diacylglycerol; DAT, dopamine transporter; DNMT, DNA methyltransferase; EAAT, excitatory amino acid transporter/glutamate transporter; EEF-2, eukaryotic elongation factor 2; eEF-2K, eukaryotic elongation factor-2 kinase; ERK, extracellular signal-regulated kinase; GC, glucocorticoid; Glu, glutamate; GR, glucocorticoid receptor; GSK-3 β , glycogen synthase kinase 3 β ; HAT, histone acetyltransferase; HDAC, histone deacetylase; IP₃, inositol 1,4,5-trisphosphate; M, muscarinic receptor; MAO, monoamine oxidase; MAOIs, MAO inhibitors; MAPK, mitogen-activated protein kinase; Me, methylation; MEK, mitogen-activated protein kinase kinase; mGlu, metabotropic glutamate receptor; mTOR, mammalian target of rapamycin; NA, noradrenaline/norepinephrine; NET, noradrenaline/norepinephrine transporter; NMDA-R, N-methyl-D-aspartic acid receptor; nNOS, neuronal nitric oxide synthase; NO, nitric oxide; NR2B, NMDA receptor subtype 2B; PDE, phosphodiesterase; PI 3-K, phosphatidylinositol-4,5-bisphosphate 3-kinase; PKA, protein kinase A; PKC, protein kinase C; PLC, phospholipase C; PSD95, postsynaptic density protein 95; SERT, serotonin transporter; Tfs, transcription factors; TrkB, tropomyosin receptor kinase B



Targets for the Development of Antidepressants

Presynaptic targets:

- Receptors that regulate neurotransmitter release such as the 5-HT_{1A}, α_2 adrenoceptor, mGlu₂ and NMDA receptor.
- MAO, an enzyme that catabolizes monoamines.
- Neurotransmitter transporters, exemplified by biogenic amine transporters. Inhibiting these transporters increases the availability of neurotransmitter at the synaptic cleft, a key action in the mechanism of most currently prescribed antidepressants.

Postsynaptic targets:

Targets for antidepressant action include both ionotropic and metabotropic receptors, as well as the signal transduction pathways activated by these receptors. These pathways converge in regulating gene expression, release of neurotrophic factors, and synaptic plasticity that may contribute to the mechanism of antidepressant action.

mGlu_{1/5} receptors regulate NMDA receptor function by modulating its trafficking and cell surface expression. The NMDA receptor is blocked by Mg²⁺ at resting membrane potential; when the membrane is depolarized, this block is relieved, allowing Ca²⁺ to enter the cell. Ca²⁺ participates in a number of cellular cascades, including nitric oxide synthesis, which functions as a retrograde neuronal messenger. Ca²⁺ can also enter the cell via voltage-dependent Ca²⁺ channels (Ca_v) where it activates CaMK. Ca_v function can be modulated by other ion channels sensitive to glutamate such as the AMPA receptor. Both AMPA receptors and the TrkB receptor (the receptor for BDNF) influence the activity of signal transduction pathways, which may be involved in the mechanism of action of certain antidepressant drugs.

Other metabotropic receptors such as 5-HT₂, α_1 adrenoceptors and M₁ muscarinic receptors, stimulate PLC and second messengers through G_{q/11} signaling. G_i and G_s proteins are activated by β -adrenoceptors, D_{1,2,5} receptors and 5-HT_{1A,4,5,7} receptors. These G proteins modulate AC activity, which regulates the level of cAMP and thus PKA activity. cAMP concentrations are also affected by drugs that influence PDE enzymatic activity. Scopolamine is a muscarinic receptor antagonist that inhibits M₁-M₅ with similar affinity; studies with both knock-out mice and selective pharmacological agents^[6] indicate that the M₁ and to a lesser extent M₂ receptor subtypes may be responsible for the rapid and robust antidepressant effects of this drug.

Many of these signal transduction pathways (CaMK, ERK, GSK-3 β) appear to converge in phosphorylating transcription factors such as CREB, a transcription factor that binds to DNA sequences (cAMP response elements (CRE)), before inducing transcription and the expression of certain genes in the nucleus of the neuron. Such changes in gene expression induced by antidepressants can modify the genetic and epigenetic alterations caused by inescapable life experiences, as well as other genetic factors that are believed to be involved in the pathophysiology of depression. For example the rapid acting antidepressants (ketamine, scopolamine) have been associated with rapid changes in synaptic morphology, including increases in spine density and spine head diameter^[7].

Compounds clinically validated or with preclinical evidence:

- Acetylcholine muscarinic receptor antagonists: **scopolamine**
- NMDA ion channel blockers: **AZD 6765**, **ketamine**, **mefenazine**, **Zn²⁺**
- NMDA receptor (glycine site) partial agonists: **ACPC**, **D-cycloserine**, **Glyx-13**, **HA-966**
- NMDA receptor (glycine site) antagonists: 4-chlorokynurenine, 5,7-dichlorokynurenic acid, L-701,324
- Selective NR2B antagonists: **CP 101, 606** (traxoprodil), eliprodil, ifenprodil, **MRK-0657**

Compounds highlighted in bold are clinically validated

Products available from Tocris acting on antidepressant pathways

Monoamine Oxidase Lazabemide, Moclobemide, Pirlindole	5-HT₂ : BIMU 8, GR 113808, GR 125487, RS 67333	Vasopressin Receptors [Arg8]-Vasopressin, SR 49059
Glutamate Receptors NMDA: D-AP5, CPP, 5,7-Dichlorokynurenic acid, DQP 1105, Ifenprodil, Ketamine, L-689,560, Memantine, (+)-MK 801, Ro 25-6981	5-HT_{1A} : SB 699551	Tachykinin Receptors GR 73632, L-733,060, RP 67580
Dopamine Receptors AMPA: (S)-AMPA, Aniracetam, CX 546, Cyclothiazide, GYKI 53655, Naspim, S 18986	5-HT_{2B} : SCH 23390, SCH 39166, SKF 81297	Signal Transduction AC: Forskolin, NKH 477, SQ 22536
Neurotransmitter Transporters mGlu _{1/5} : FTIDC, JNJ 16259685, LSN 2463359, LY 367385, MPEP, MTEP, Ro 67-7476	D₂ : L-741,626, (-)-Quinpirole, Sumanitrol	Akt : API-1, 10-DEBC, GSK 690693
SERT : Citalopram, Fluoxetine, Sertraline	Ca²⁺ Signaling : A23187, Ionomycin	CaMK : A 484954, KN 93, STO-609
DAT : Bupropion, GBR 12909	PKC : GSK-3, BIO, SB 216763, SB 415286	DNMTs : Decitabine, SGI 1027, Zebularine
mGlu₂ : LY 341495, LY 354740, LY 379268, LY 487379	HDACs : FK 228, SAHA, Trichostatin A	MEK : BIX 02189, PD 0325901, PD 98059, SL 327, U0126
Glutamate Release : Lamotrigine, Riluzole	PKA : KT 5720, PKI 14-22	mTOR : KU 0063794, Rapamycin, Temsirolimus, Torin 1
Muscarinic Receptors Scopolamine, VU 0255035, Xanomeline	ERK : SCH 773154, SCH 773154	NO : N ^G -Propyl-L-arginine, SNAP
Adrenergic Receptors α_1 -AR: A 61603, Cirazoline, (R)-(-)-Phenylephrine, Prazosin	PKC : GSK-3, BIO, SB 216763, SB 415286	PDE : IBMX, Rolipram, Sildenafil
α_2 -AR: Dexmedetomidine, Imiloxan, RS 79948	PKA : KT 5720, PKI 14-22	PI 3-K : LY 294002, Wortmannin, 740 Y-P
TrkB Receptor ANA 12, BDNF, LM 224A	PLC : D609, U 73122	Raf : GW 5074, SB 590885
Serotonin Receptors 5-HT _{1A} : 8-Hydroxy-DPAT, Xaliproden	FGFR PD 173074, SU 5402, SU 6668	
5-HT ₂ : Clozapine, MDL 100907, TCB-2		

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