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Table 1. *Phosphodiesterase (PDE) families: tissue specificity and therapeutic potential of PDE inhibitors*

PDE family, references	Expression pattern	Selective PDE inhibitors		Indications	
		Pipeline products*	Approved products	Pipeline products*	Approved products
PDE1 [5, 6]	(1A10) Brain (1A5, 1A6,1C) (including the corpus striatum (1B1)), smooth muscle, heart (1C), testes (1A10)	Lenrispodun	–	Parkinson's disease (motor fluctuations in patients receiving levodopa)	–
PDE2 [4, 7]	Brain (2A3), heart (2A3)	–	–	–	–
PDE3 [4, 8]	Heart (3A2), vascular smooth muscle (3A2), corpus cavernosum smooth muscle, adipocytes, thrombocytes	PCS-499	Cilostazol, levosimendan, enoximone, amrinone, milrinone, olprinone	Diabetic nephropathy	Thromboangiitis obliterans, intermittent claudication, congestive heart failure
PDE4 [4, 9]	Most tissues; predominantly, T-lymphocytes, eosinophils, neutrophils, monocytes	ART-648, difamilast, mufemilast, Hemay808, lotamilast, PF-07038124, UNI-500	Apremilast, roflumilast, crisaborole, drotaverine, ibudilast, irsogladine	Seborrhoea, bullous pemphigoid	Psoriasis, atopic dermatitis, Behçet's disease, chronic obstructive pulmonary disease, smooth muscle spasms
PDE5 [4, 10]	Most tissues (5A1, 5A2), heart (5A3), smooth muscle, including corpus cavernosum smooth muscle (5A3)	AR-1001, fadanafil, TPN-171, TPN-729	Tadalafil, sildenafil, avanafil, mirodenafil, udenafil, vardenafil	Alzheimer's disease	Erectile dysfunction, benign prostatic hyperplasia, pulmonary arterial hypertension
PDE6 [4, 11]	Retinal rods (6A, 6B) and cones (6C)	CTx-PDE6b	–	Retinitis pigmentosa	–
PDE7 [4, 12]	Most tissues (7A1), kidneys (7A2), heart, skeletal muscle (7A2), brain (7B)	–	–	–	–
PDE8 [4, 13]	Liver (8A), testes (8A), thyroid gland (8A)	–	–	–	–
PDE9 [4, 14]	Spleen (8A), small intestine (8A), brain (8A), prostate (8A), kidneys (8A), placenta (8A)	BI-409306, irsenontrine maleate, tovinontrin	–	Psychoses, schizophrenia, Alzheimer's disease, Parkinson's disease, dementia with Lewy bodies, sickle cell anaemia	–
PDE10 [4, 15]	Corpus striatum (10A), testicles (10A)	CPL-500036, MK-8189, gemlapodect, mardepodect, balipodect, Lu AF11167	–	Psychoses, schizophrenia, levodopa-induced dyskinesia, Tourette's syndrome, Huntington's disease	–
PDE11 [4, 16]	Prostate (11A4), testes (11A4)	–	–	–	–

The table is prepared by the authors using GlobalData.com

Note. *–, no data.*
** only clinical trials of phases II–III*

Table 3. *50% inhibitory concentration (IC50) data for phosphodiesterase 10A (PDE10A) inhibitors*

INN / references	Alternative names	Chemical name	IC50, nM
Mardepodect [38]	MP-10, PF-2545920	2-[4-(1-methyl-4-pyridin-4-yl-1H-pyrazol-3-yl)-phenoxymethyl]-quinoline	0,37*; 1,04*; 1,34*
– [39–41]	TP-10	2-{4-[-pyridin-4-yl-1-(2,2,2-trifluoro-ethyl)-1H-pyrazol-3-yl]-phenoxymethyl}-quinoline	0,3***; 1,0*; 1,41*
Papaverine [39]	–	1-[(3,4-dimethoxyphenyl)methyl]-6,7-dimethoxyisoquinoline	40*
Balipodect [42, 43]	TAK-063	1-(2-fluoro-4-(1H-pyrazol-1-yl)phenyl)-5-methoxy-3-(1-phenyl-1H-pyrazol-5-yl)pyridazin-4(1H)-one	0,3*
– [44]	AMG 579	1-(4-(3-(4-(1H-benzimidazole-2-carbonyl)phenoxy)pyrazin-2-yl)piperidin-1-yl)ethanone	0,1*
– [63]	JNJ-42314415	4-(3-(6-(2-methoxyethyl)pyridin-3-yl)-2-methyl-8-morpholine-4-ylimidazo(1,2-a)pyrazin	–
– [45, 46]	PQ-10, A-844337	6,7-dimethoxy-4-[3-(quinoxalin-2-yloxy)pyrrolidin-1-yl]quinazoline	16*; 64*
– [47]	PDM-042	(E)-4-(2-(2-(5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)vinyl]-6-pyrrolidin-1-yl)pyrimidin-4-yl)morpholine	0,83*; 0,82**
– [48]	FRM-6308, EVP-6308	–	0,0114
– [73]	THPP-1, DA-78439, EX-A4562	[2-(6-chloropyridin-3-yl)-4-(2-methoxyethoxy)-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl](imidazo[1,5-a]pyridin-1-yl)methanone	–
– [49]	PyP-1, GLXC-26773, PD128771	N-[(1-methyl-1H-pyrazol-4-yl)methyl]-5-{[(1S,2S)-2-(pyridin-2-yl)cyclopropyl]methoxy}pyrazolo[1,5-a]pyrimidin-7-amine	–
– [50]	BMS-843496	2-((4-chloro-6-((pyridin-3-ylmethyl)amino)pyrimidin-2-yl)amino)-N-ethyl-4-methylthiazole-5-carboxamide	2,11±0,7*
– [51, 52]	SEP-39	2-(2-(5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)ethyl)-3H-imidazo[4,5-f]quinoline	1,0*; 0,001
– [53]	ASP9436, compound 38b	1-methyl-5-(1-methyl-3-{[4-(1-methyl-1H-benzimidazol-4-yl)phenoxy]methyl}-1H-pyrazol-4-yl)pyridin-2(1H)-one	8,0*
– [83]	Lu AF33241	1-(2-chlorophenyl)-4,8-dimethyl-[1,2,4]triazolo[4,3-a]quinoxaline	–
– [54]	MK-8189	2-methyl-6-((2-(5-methylpyridin-2-yl)cyclopropyl)methoxy)-N-((5-methyl-1,3,4-thiadiazol-2-yl)methyl)pyrimidin-4-amine	1,6*
– [55]	EM-221, MR1916	N-butil-11-[(7R,8R,9S,13S,14S,16R,17S)-16-fluoro-3,17-dihydroxy-13-methyl-6,7,8,9,11,12,14,15,16,17-decahydrocyclopenta[a]phenanthrene-7-yl]-N-dimethyldecanamide	0,022***
– [55]	CPL500036	{7-[5,8-dimethyl-(1,2,4)triazolo(1,5-a)pyrazin-2-yl]-2-phenylimidazo(1,2-a)pyrimidine}	1,0*

Продолжение таблицы 3

Table 3 (continued)

INN / references	Alternative names	Chemical name	IC50, nM
– [56]	RO5545965, RG7203	2-(4-(1-methyl-4-pyridin-4-yl-1H-pyrazol-3-yl)-phenoxymethyl)quinoline	0,37
Gemlapodect [24]	RO554965, NOE-105	2-{4-[4-pyridin-4-yl-1-(2,2,2-trifluoro-ethyl)-1H-pyrazol-3-yl]-phenoxymethyl}-quinoline	0,3; 1,0; 1,41
– [57]	MT-3014	1-({2-(7-fluoro-3-methylquinoxalin-2-yl)-5-[(3R)-3-fluoropyrrolidin-1-yl]pyrazolo [1,5-α]pyrimidin-7-yl}amino)-2-methylpropan-2-ol hydrochloride	0,062– 0,357*
– [58]	T-251	2-[(E)-2-(7-fluoro-3-methylquinoxalin-2-yl)vinyl]-6-pyrrolidin-1-yl-N-(tetrahydro-2H-pyran-4-yl)pyrimidin-4-amine hydrochloride	0,05*
– [59]	T-773	1-[2-fluoro-4-(tetrahydro-2H-pyran-4-yl)phenyl]-5-methoxy-3-(1-phenyl-1H-pyrazol-5-yl)pyridazin-4(1H)-one	0,77*
– [35, 59]	T-609, compound 19e, compound 1	(1-[cyclopropylmethyl]-4-fluoro-5-[5-methoxy-4-oxo-3-(1-phenyl-1H-pyrazol-5-yl)pyridazin-1(4H)-yl]-3,3-dimethyl-1,3-dihydro-2H-indol-2-one]	0,08*
– [60]	WEB 3	8-methoxy-3-methyl-4-methylsulphonyl amino-1-propyl-imidazo-[1,5-a]pyrido[3,2-e]pyrazine	7,28*
– [60]	WEB 6	3,4-dimethyl-8-methoxy-1-propyl-imidazo[1,5-a]pyrido[3,2-e]-pyrazine	7,16*
– [56]	PBF-999	5-bromo-N-(prop-2-yn-1-yl)-2-(1H-1,2,4-triazol-1-yl)pyrimidine-4,6-diamine	8,2*
– [61]	OMS643762, OMS824	N-(3-(4-(2-(4-(trifluoromethyl)phenyl)thiazol-2-yl)thiazol-4-yl)piperidin-1-yl)propyl)-2,6-dimethylpyrimidin-4-amine	0,82*

The table is prepared by the authors

Note. *INN, international non-proprietary name; –, no data.*
** Homo sapiens, ** Rattus norvegicus, *** Mus musculus.*

Table 4. *Animal studies of phosphodiesterase 10A (PDE10A) inhibitors*

Method	Study object / model	Pharmacological effect	PDE10A inhibitor	Reference
Weighing	Wistar stock rats	–	MT-3014	[58]
Determination of plasma prolactin levels	Wistar stock rats	–		
	Sprague–Dawley stock rats	– (co-administration with haloperidol and olanzapine)	Balipodect	[62]
		–		
Body temperature measurement	Wistar stock rats	– ⇓ in body temperature (after JNJ-42314415 administration at high doses)	JNJ-42314415, PQ-10, TP-10, Mardepodect	[63]
Locomotor activity test	Wistar stock rats / prenatal alcohol exposure (model of ADHD)	⇓ in hyperactivity (open field)	Papaverine*	[64]
	Wistar stock rats / prenatal valproic acid exposure (model of fetal valproate syndrome)	⇓ in hyperactivity (open field)		[65]
	Wistar stock rats / MK-801-induced hyperactivity	⇓ in motor activity in intact animals ⇓ in hyperactivity after MK-801 administration (open field)	MT-3014	[66]
		⇓ in hyperactivity (locomotor activity cages)	T-251	[58]
		⇓ in activity	MK-8189	[54, 67]
	Wistar stock rats / scopolamine-induced hyperactivity	⇓ in hyperactivity (locomotor activity cages)	JNJ-42314415, PQ-10, TP-10, Mardepodect	[63]
	Wistar stock rats / PCP-induced hyperactivity	⇓ in hyperactivity (locomotor activity cages)		
	Wistar stock rats / d-amphetamine-induced hyperactivity	⇓ in hyperactivity (locomotor activity cages)		
	ICR stock mice	– (locomotor activity cages)	Balipodect	[68]
	ICR stock mice / KM-801-induced hyperactivity	⇓ in hyperactivity (locomotor activity cages)		[43]
	NMRI stock mice / d-amphetamine-induced hyperactivity	⇓ in hyperactivity (open field)	JNJ-42314415, PQ-10, TP-10, Mardepodect	[36]
	NMRI stock mice / SCH-23390-induced hypoactivity	⇓ in hypoactivity after SKF-82958 administration (open field)		
	NMRI stock mice / haloperidol-induced hypoactivity	– (open field)		
	C57BL/6J mice / MK-801- and methamphetamine-induced hyperactivity	⇓ in hyperactivity (locomotor activity cages)	T-609, T-773	[59]

Продолжение таблицы 4

Table 4 (continued)

Method	Study object / model	Pharmacological effect	PDE10A inhibitor	Reference
	Sprague—Dawley stock rats	— (locomotor activity cages)	Balipodect	[68]
	Sprague—Dawley stock rats / MK-801- and methamphetamine-induced hyperactivity	⇓ in hyperactivity (locomotor activity cages)	Balipodect	[62]
		⇓ in hyperactivity (locomotor activity cages)	Balipodect	[69]
		⇓ in hyperactivity (locomotor activity cages)	Mardepodect	[35]
		⇓ in hyperactivity (locomotor activity cages)	Compound 13a	[70]
	Sprague—Dawley stock rats / phencyclidine-induced hyperactivity	⇓ in hyperactivity (open field)	Compound 73, Compound 77	[71]
		⇓ in hyperactivity (open field)	SEP-39	[51]
		⇓ in hyperactivity (open field)	AMG579	[44]
	R6/2 Tg mice / Huntington's disease model	⇑ in motor activity (open field)	Balipodect	[72]
	Wistar stock rats / MK-801-induced hyperactivity	⇓ in hyperactivity (open field)	THPP-1	[73]
	Rhesus monkeys / amphetamine-induced hyperactivity	⇓ in hyperactivity (accelerometer)		[74]
	DAT-KO rats / αMPT-induced hypoactivity	⇑ in motor activity (locomotor activity cages)	Mardepodect	[75]
	Wistar stock rats / tetrabenazine-induced hypoactivity		Mardepodect, Gemlapodect	[76]
Motor impairment modelling	Cynomolgus monkeys / MPTP-induced parkinsonism	⇓ in dyskinesia incidence after levodopa administration	MR1916	[77]
	Rhesus monkeys	No induction of motor impairment (MDS scale, Klüver Board test, DENS scale) No effect on postural stability (perch test)	FRM-6308	[48]
	Tufted capuchins	Induction of extrapyramidal symptoms	Mardepodect	[78]
Tail suspension test	R6/2 Tg mice / Huntington's disease model	⇓ in the number of animals with abnormal hind-limb clasping response	Balipodect	[72]
		⇓ in the duration of abnormal hind-limb clasping response	TP-10	[79]
Rotarod test	C57BL/6J mice / MPTP-induced parkinsonism	⇑ in the time on the rotarod	Mardepodect	[80]
	R6/2 Tg mice / Huntington's disease model	—	Balipodect	[72]
		Prevention of deficit development	TP-10	[79]
Pole test	C57BL/6J mice / MPTP-induced parkinsonism	⇓ in the descending time	Mardepodect	[80]

Продолжение таблицы 4

Table 4 (continued)

Method	Study object / model	Pharmacological effect	PDE10A inhibitor	Reference
Catalepsy test	Wistar stock rats	Induction of catalepsy (bar test)	MT-3014	[66]
		No induction of catalepsy (bar test)	T-251	[58]
		No induction of catalepsy when co-administered with a D1 antagonist	JNJ-42314415, PQ-10, TP-10, Mardepodect	[70]
	Sprague—Dawley stock rats	No induction of catalepsy (bar test)	MR1916	[81]
		No induction of catalepsy (bar test)	Balipodect	[62]
		Induction of catalepsy (bar test)		[43]
		Induction of catalepsy (bar test)	PDM-042	[82]
		No induction of catalepsy (grid test)	Lu AF33241	[83]
		Induction of catalepsy (bar test)	SEP-39	[51]
	Sprague—Dawley stock rats	No induction of catalepsy (bar test)	Mardepodect	[84]
	DAT-KO rats / αMPT-induced catalepsy	⇓ in the time with the forepaws placed on the rod	Mardepodect	[75]
Y-maze	Wistar stock rats / prenatal alcohol exposure (model of ADHD)	⇑ in % spontaneous arm alteration	Papaverine*	[64]
	Wistar stock rats / prenatal valproic acid exposure (model of fetal valproate syndrome)	⇑ in % spontaneous arm alteration	Papaverine*	[65]
	ICR mice / PCP-induced cognitive deficit	⇓ in total arm entries	Balipodect	[68]
Elevated plus maze	Wistar stock rats / prenatal alcohol exposure (model of ADHD)	⇑ in % time spent in open arms and % open arm entries	Papaverine*	[64]
	Wistar stock rats / prenatal valproic acid exposure (model of fetal valproate syndrome)		Papaverine*	[65]
Radial maze	Long—Evans stock rats	⇓ in the numbers of errors produced by MK-801	Balipodect	[68]
Prepulse inhibition test	Wistar stock rats / MK-801-induced cognitive deficit	⇑ in prepulse inhibition	MT-3014	[66]
			T-251	[58]
	C57BL/6J mice	–	T-609	[59]
		⇑ in prepulse inhibition	T-773	
			Balipodect	[35]
		–	Mardepodect	
	ICR stock mice / MK-801-induced cognitive deficit	⇑ in prepulse inhibition when combined with antipsychotics at sub-effective doses	Balipodect	[62]
	Sprague—Dawley stock rats / phencyclidine-induced cognitive deficit	⇑ in prepulse inhibition	Compound 73, Compound 77	[71]
			Compound 13a	[70]
	Sprague—Dawley stock rats / MK-801-induced cognitive deficit	⇑ in prepulse inhibition	MK-8189	[67]
Conditioned avoidance response test	Wistar stock rats	Avoidance response suppression	MT-3014	[66]
			T-251	[58]
			Lu AF33241	[83]
			MK-8189	[67]

Продолжение таблицы 4

Table 4 (continued)

Method	Study object / model	Pharmacological effect	PDE10A inhibitor	Reference
	Sprague—Dawley stock rats	Avoidance response suppression	MR1916	[81]
	Wistar stock rats	Avoidance response suppression	Compound 13a	[70]
			THPP-1	[73]
Apomorphine-induced motor response test	Swiss albino mice	⇓ in sniffing and climbing	Compound 13a	[70]
	Wistar stock rats	⇓ in apomorphine-induced agitation	JNJ-42314415, PQ-10, TP-10, Mardepodect	[36]
	Wistar stock rats	⇓ in apomorphine-induced stereotypy		[63]
Ethanol self-administration behaviour	Wistar stock rats	⇓ in ethanol and saccharin self-administration behaviour without altering the ability to push the pedal	TP-10	[85]
Conditioned place aversion test	Wistar stock rats	No place preferences observed		
Forced swim test	NMRI stock mice / MK-801-induced increase in passive floating time (model of negative symptoms of schizophrenia)	⇑ in active swimming in model animals	Mardepodect, WEB 3, WEB 6	[60]
Novel object recognition test	Long—Evans stock rats / MK-801-induced cognitive deficit	⇑ in the time spent exploring a novel object	MT-3014	[81]
	Sprague—Dawley stock rats		MR1916	[81]
			PDM-042	[82]
	Long—Evans stock rats	⇑ in the time spent exploring a novel object	T-773	[59]
	Wistar stock rats / MK-801-induced cognitive deficit		T-251	[58]
	Long—Evans stock rats		Balipodect	[68]
	Lister hooded rats (stock) / sub-chronic PCP administration (cognitive impairment model)		SEP-39	[51]
	Wistar stock rats / MK-801-induced cognitive deficit (cognitive impairment model)		Lu AF33241	[83]
	Wistar stock rats / scopolamine-induced cognitive deficit (cognitive impairment model)	—	PQ-10	[86]
	Wistar stock rats	⇑ in the time spent exploring a novel object	THPP-1, MK-8189	[54, 73]
Object retrieval detour test	Rhesus monkeys / ketamine-induced cognitive deficit (cognitive impairment model)	⇑ in % successful object retrieval on the first attempt	THPP-1	[73]
			MK-8189	[67]
Five-choice serial reaction time test	Long—Evans stock rats	⇑ in the number of correct responses ⇑ in the number of omissions ⇓ in the number of premature responses	Balipodect	[68]
Attentional set-shifting test	Sprague—Dawley stock rats	⇑ in cognitive flexibility	Mardepodect	[87]
Hot plate test	Wistar stock rats / prenatal valproic acid exposure (model of fetal valproate syndrome)	⇓ in the latency to lick the paw/paw withdrawal	Papaverine*	[65]
Seizure activity evaluation	R6/2 Tg mice / Huntington's disease model	⇓ in seizure frequency	Balipodect	[72]

The table is prepared by the authors

Note. *This is the authors' own rendering of neuropsychiatric disorder models. ADHD, attention-deficit/hyperactivity disorder; αMPT, α-methyl-p-tyrosine; DAT-KO, dopamine transporter knockout rats; PCP, phencyclidine; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MDS, Movement Disorder Society; DENS, Drug Effects on the Nervous System; —, no effect; ⇑, increase; ⇑, decrease.*

** Papaverine is a relatively selective PDE10A inhibitor, albeit with significant affinity to other PDEs.*

Table 5. *Patents relevant to studying phosphodiesterase 10A (PDE10A) inhibitors*

Patent No.	Year	Inventors	Description
WO 2024/206200 A1	2024	Dinunzio James C, Harris David, Kumar Maria Sharlini, Pollitt Michael John, Radojevic Jovana, Terife Graciela	Controlled-release tablets of 2-methyl-N-((5-methyl-1,3,4-thiadiazol-2-yl)methyl)-6-(((1S,2S)-2-(5-methylpyridin-2-yl)cyclopropyl)methoxy)pyrimidin-4-amine (Compound A) and their use in the treatment of schizophrenia and other psychiatric disorders that improve the tolerability profile
WO 2022/162193 A1	2022	Garibaldi George	Methods of treating childhood-onset fluency disorder with PDE10A inhibitors
CN 118255747 A	2024	Guo Lei, Huang Hongzhe, Yuan Han, Wu Jiafei, Yang Yi, Yang Dongjing	A more selective pyrazole derivative with a longer half-life
JP 2024112854 A	2024	Mahindra Makhija	A PDE10A inhibitor (1-[2-fluoro-4-(1H-pyrazol-1-yl)phenyl]-5-methoxy-3-(1-phenyl-1H-pyrazol-5-yl)pyridazin-4(1H)-one, or a salt thereof)
WO 2022/060978 A1	2022	During Matthew	A treatment for levodopa induced dyskinesia, "off" episodes associated with Parkinson's disease, and Parkinson's disease psychosis with a PDE10A inhibitor, e.g., 1-[2-fluoro-4-(1H-pyrazol-1-yl)phenyl]-5-methoxy-3-(1-phenyl-1H-pyrazol-5-yl)-pyridazin-4(1H)-one
KR 20210148533 A	2021	Park Se Jin, Park Hyeon Bae, Kim So Yeon, Han Sang Deok, Lee Eun Seok, Kim Kyeong Min	A composition for preventing, improving, or treating cognitive dysfunction or mental disease, comprising an extract of *Dracocephalum moldavica* as an active ingredient

The table is prepared by the authors