

TABLE 14.1

SLC6 Gene Family Neurotransmitter Transporters

	Endogenous Substrates	Synthetic Substrates	Potent Inhibitors	Therapeutic Use/ Potential
Dopamine transporter (DAT)	Dopamine Norepinephrine Epinephrine	Amphetamine MPP+	CFT, GBR12,909 bentropine, mazindol, RTI-55, Cocaine, Zn ²⁺	ADHD (amphetamines), Parkinsonism? (inhibitors)
Serotonin transporter (SERT)	5-HT	p-Cl- Amphetamine MDMA ("ecstasy")	Citalopram, escitalopram, fluoxetine, paroxetine, sertraline, imipramine, cocaine, RTI-55	Depression, anxiety, OCD (inhibitors)
Norepinephrine transporter (NET)	Dopamine Norepinephrine Epinephrine	Amphetamine MPP+	Nisoxetine, nortriptyline, desipramine, duloxetine, venlafaxine, mazindol	Depression (inhibitors)
Glycine transporter 1 (GlyT-1)	Glycine	—	(R)NFPS (ALX5407), NPTS, Org24598 Zn ²⁺	Schizophrenia? Psychosis? Dementia? (inhibitors)
Glycine transporter 2 (GlyT-2)	Glycine	—	ALX1393, ALX1405 Org25543	Anticonvulsant? Analgesic? (inhibitors)
GABA transporter 1 (GAT-1)	GABA	—	Tiagabine, SKF89976A, THPO <i>exo</i> -THPO	Epilepsy (tiagabine)
GABA transporter 2 (GAT-2 equivalent to mouse GAT-3)	GABA beta-Ala	—	—	?
GABA transporter 3 (GAT-3 equivalent to mouse GAT-4)	GABA beta-Ala	—	SNAP5114	?
GABA transporter 4 (GAT-4, equivalent to BGT-1 or mouse GAT-2)	GABA Betaine	—	EF1502, NNC052090, THPO Zn ²⁺	Epilepsy? (inhibitors) EF1502

Note: The known neurotransmitter transporters belonging to the SLC6 gene family with their respective substrates, inhibitors, and potential therapeutic use.

Abbreviations: CFT, (2 β -carbomethoxy-3 β -(4-fluorophenyl)tropane; MDMA, 3,4-methylenedioxymethamphetamine; MPP+, 1-methyl-4-phenylpyridinium; (R)NFPS, *N*-[3-(40-fluorophenyl)-3-(40-phenylphenoxy) propyl]sarcosine; NPTS, (*N*-[3-phenyl-3-(40-(4-toluoyl) phenoxy)propyl]sarcosine; THPO, (4,5,6,7-tetrahydroisoxazolo[4,5-c]pyridine-3-ol); ADHD, attention-deficit hyperactivity disorder; OCD, obsessive-compulsive disorder; *exo*-THPO, 4-amino-4,5,6,7-tetrahydrobenzo[d]isoxazol-3-ol.

of these transporters is still unknown; however, a few of them have been identified as amino acid transporters, for example, the leucine transporter (LeuT) from the *Aquifex aeolicus* bacterium and the multi-hydrophobic amino acid transporter (MhsT) from *Bacillus halodurans*.

At the molecular level, the SLC6 family transporters operate as Na⁺-dependent co-transporters that utilize the transmembrane Na⁺ gradient to couple "downhill" transport of Na⁺ with "uphill" transport (against a concentration gradient) of their substrate from the extracellular to the intracellular environment. The transport process is so efficient that, for example, the serotonin transporter (SERT) can accumulate internal serotonin (5-HT) to concentrations hundreds of fold higher than the external medium when appropriate ion gradients are imposed. Most SLC6 transporters are also co-transporters of Cl⁻ and accordingly SLC6 transporters have been referred to as the family of Na⁺/Cl⁻-dependent transporters.