Choline

Overview: The high affinity, hemicholinium-3-sensitive, choline transporter (CHT, provisional nomenclature) is a member of the solute carrier family 5 (SLC5) of sodium-dependent transporters that, in mammals, includes the Na^+/substrate co-transporters for glucose, *myo*-inositol and iodide (Ferguson and Blakely, 2004; Wright and Turk, 2004). CHT contains 13 putative TM domains with an extracellular N-terminus and cytoplasmic C-terminus (Apparsundaram *et al*., 2000). CHT is expressed mainly in cholinergic neurones (keratinocytes being an additional location) and through recapture of choline generated by the hydrolysis of ACh by acetylcholinesterase serves to maintain ACh synthesis within the presynaptic terminal (Ferguson and Blakely, 2004). Homozygous mice engineered to lack CHT die within one hour of birth as a result of hypoxia arising from failure of transmission at the neuromuscular junction of the skeletal muscles that support respiration (Ferguson *et al*., 2004). A low affinity choline uptake mechanism that remains to be identified at the molecular level may involve multiple transporters. In addition, a family of choline transporter-like (CTL) proteins with weak Na^+ dependence have been described (Traiffort *et al*., 2005).

Nomenclature	CHT
Other names	CHT1, SLC5A7
Ensembl ID	ENSG00000115665
Endogenous substrates	Choline
Selective inhibitors (K_i)	HC-3 (1–5 nM)
Probes (K_D)	[^{3}H]-HC-3 (4–6 nM)
Stoichiometry	2–3 Na^+: 2–3 Cl^-: 1 choline

K_i and K_D values for hemicholinium-3 listed in the table are for human CHT expressed in *Xenopus laevis* oocytes (Okuda and Haga, 2000), or COS-7 cells (Apparsundaram *et al*., 2000). Hemicholinium mustard is a substrate for CHT that causes covalent modification and irreversible inactivation of the transporter.

Abbreviation: HC-3, hemicholinium-3

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GABA

Overview: Plasma membrane located GABA transporters (provisional nomenclature as adopted for human GABA transporters) are members of the solute carrier family 6 (SLC6) of sodium- and chloride-dependent neurotransmitter receptor transporters that includes the monoamine and glycine transporters (Chen *et al*., 2003). The members of this superfamily share a structural motif of 12 TM segments (Palacín *et al*., 1998) that has been confirmed by the recent crystal structure of a bacterial homolog ($LeuT_{Aa}$) of the Na^+/Cl^- dependent neurotransmitter transporters from *Aquiflex aeolicus* (Yamashita *et al*., 2005). The activity of GABA-transporters located upon both neurones and glia serves to terminate GABA-ergic transmission, maintain low ambient extracellular concentrations of GABA, and recycle GABA for reuse by neurones. A structurally and functionally distinct vesicular transporter representing the SCL32 family [VGAT/VIAAT (ENSG00000101438); McIntire *et al*., 1997; Sagne *et al*., 1997; Gasnier, 2003], subject to inhibition by vigabatrin, is responsible for concentrating GABA (and glycine) within synaptic vesicles.

Nomenclature	GAT-1	GAT-2	GAT-3	BGT-1
Other names	mGAT-1, SLCA1	mGAT3, SLCA16	mGAT4, GAT-B, SLCA11	mGAT2, SLCA12
Ensembl ID	ENSG00000157103	ENSG00000010379	ENSG00000132164	ENSG00000111181
Endogenous substrates	GABA	GABA, β-alanine	GABA, β-alanine	GABA, betaine
Selective inhibitors (IC_{50})	NNC-711 (0.04 μM), SKF89976A (0.13 μM), CI-966 (0.26 μM), tiagabine (0.8 μM), EF1500 (2 μM) (*R*)-EF1502 (4 μM), LU32176B (4 μM), (*S*)-EF1502 (120 μM)	—	SNAP-5114 (6.6 μM)	NNC052090 (1.4 μM), (*R*)-EF1502 (22 μM), (*S*)-EF1502 (34 μM), LU 32176B (> 100 μM)
Probes	[^{3}H] Tiagabine	—	—	—
Stoichiometry	$2Na^+$: $1Cl^-$: 1GABA	—	$\geqslant 2Na^+$: $2\ Cl^-$: 1GABA	$3Na^+$: 1 (or 2) Cl^-: 1GABA

SNAP-5114 is only weakly selective for GAT-3, with IC_{50} values in the range 20 to > 30 μM at GAT-1, GAT-2 and BGT-1, whereas NNC052090 has at least an order of magnitude selectivity for BGT-1 [see Schousboe *et al*. (2004b) and Clausen *et al*. (2006) for reviews]. (*R*)-(1-{2-[tris(4-methoxyphenyl)methoxy]ethyl}pyrrolidin-2-yl)acetic acid is a recently described compound that displays 20-fold selectivity for GAT-3 over GAT-1 (Fülep *et al*., 2006). In addition to the inhibitors listed, EGYT3886 is a moderately potent, though non-selective, inhibitor of all cloned GABA transporters ($IC_{50} = 26$–46 μM; Dhar *et al*., 1994). Diaryloxime and diarylvinyl ether derivatives of nipecotic acid and guvacine that potently inhibit the uptake of [^{3}H]GABA into rat synaptosomes have been described (Knutsen *et al*., 1999). Several derivatives of *exo*-THPO (*e.g. N*-methyl-*exo*-THPO and *N*-acetyloxyethyl-*exo*-THPO) demonstrate selectivity as blockers of astroglial, *versus* neuronal, uptake of GABA [see Schousboe *et al*. (2004a) and Clausen *et al*. (2006) for reviews]. GAT-3 is inhibited by physiologically relevant concentrations of Zn^{2+} (Cohen-Kfir *et al*., 2005).

Abbreviations: **CI966**, [1-[2-[bis-4(trifluromethyl)phenyl]methoxy]ethyl]-1,2,5,6-tetrahydro-3-pyridinecarboxylic acid; **EF1500**, *N*-[4,4-bis (3-methyl-2-thienyl)-3-butenyl]-3-hydroxy-4-amino-4,5,6,7-tetrahydrobenzo[*d*]isoxazol-3-ol; **EF1502**, *N*-[4,4-bis(3-methyl-2-thienyl)-3-butenyl]-3-hydroxy-4-(methylamino)4,5,6,7,tetrabenzo[*d*]isoxazol-3-ol; **EGYT3886**, (-)-2-phenyl-2-[(dimethylamino)ethoxy]-(1*R*)-1,7,7-trimethyl-bicyclo[2.2.1]heptane; ***exo*-THPO**, 3-hydroxy-4-amino-4,5,6,7-tetrahydro-1,2-benzisoxazol; **LU32-176B**, *N*-[4,4-bis(4-fluorophenyl)-butyl]-3-hydroxy-4-amino-4,5,6,7-tetrahydrobenzo[d]isoxazol-3-ol; **NNC052090**, 1-(3-(9*H*-carbazol-9-yl)-1-propyl)-4-(2-methoxyphenyl)-4-piperidinol; **NNC711**, 1-2-(((diphenylmethylene)amino)oxy)ethyl)-1,2,5,6-tetrahydro-3-pyridinecarboxylic acid hydrochloride; **SKF89976A**, 1-(4,4-diphenyl-3-butenyl)-3-piperidinecarboxylic acid

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Glutamate (excitatory amino acid)

Overview: Plasma membrane located glutamate transporters (nomenclature proposed by Amara and Arriza, 1993) are members of the solute carrier family 1 (SLC1) of sodium-dependent transporters that also includes the neutral amino acid transporters ASCT1 and ASCT2 (Palacín *et al*., 1998; Kanai and Hediger, 2003, 2004; Beart and O'Shea, 2007). Glutamate transporters present the unusual structural motif of 8TM segments and 2 re-entrant loops (Grunwald and Kanner, 2000). The crystal structure of a glutamate transporter homologue (Glt_{Ph}) from *Pyrococcus horikoshii* supports this topology and indicates that the transporter assembles as a trimer, where each monomer is a functional unit capable of substrate permeation (Yernool *et al*., 2004; Boudker *et al*., 2007). This structural data is in agreement with the proposed quaternary structure for EAAT2 (Gendreau *et al*., 2004) and several functional studies that propose the monomer is the functional unit (Ryan *et al*., 2004; Grewer *et al*., 2005; Koch *et al*., 2007; Leary *et al*., 2007). The activity of glutamate transporters located upon both neurones (predominantly EAAT3, 4 & 5) and glia (predominantly EAAT 1 & 2) serves, dependent upon their location, to regulate excitatory neurotransmission, maintain low ambient extracellular concentrations of glutamate (protecting against excitotoxicity) and provide glutamate for metabolism including the glutamate-glutamine cycle. Enhanced expression of EAAT2 resulting from administration of β-lactam antibiotics (*e.g.* ceftriaxone), or the neuroimmunophilin GPI-1046, is neuroprotective (Rothstein *et al*., 2005; Ganel *et al*., 2006). In addition, a thermodynamically uncoupled Cl^- flux, activated by Na^+ and glutamate (Kanner and Borre, 2002; Kanai and Hediger, 2003; Grewer and Rauen, 2005) (or aspartate in the case of Glt_{Ph}, Ryan and Mindell, 2007), is sufficiently large, in the instances of EAAT4 and EAAT5, to influence neuronal excitability (Veruki *et al*., 2006). In the kidney, EAAT3 located in the apical membrane of proximal tubular cells is responsible for the reabsorption of glutamate (Hediger, 1999). Three structurally and functionally distinct vesicular glutamate transporters (VGLUT1, 2 & 3) of the SLC17 family are responsible for concentrating glutamate within synaptic vesicles (Reimer and Edwards, 2004).

Nomenclature	EAAT1	EAAT2	EAAT3
Other names	GLAST, SLC1A3	GLT1, SLC1A2	EAAC1, SLC1A1
Ensembl ID	ENSG00000079215	ENSG00000110436	ENSG00000106688
Endogenous substrates	L-glutamate, L-aspartate	L-glutamate, L-aspartate	L-glutamate, L-aspartate
Inhibitors (K_B or K_i)	DL-TBOA (9 μM)	WAY-213613 (IC_{50} = 130 nM), DL-TBOA (0.12 μM), (2*S*,4*R*)-4-methylglutamate (3.4 μM), dihydrokainate (9 μM), *Threo*-3-methylglutamate (18 μM)	NBI-59159 (IC_{50} = 25 nM), DL-TBOA (IC_{50} = 8 μM)
Probes	[^{3}H]-ETB-TBOA (K_D = 15.5 nM), [^{3}H]-[(2*S*,4*R*)-4-methylglutamate, [^{3}H]-D-aspartate, [^{3}H]-L-aspartate	[^{3}H]-ETB-TBOA (K_D = 16.2 nM), [^{3}H]-[(2*S*,4*R*)-4-methylglutamate, [^{3}H]-D-aspartate, [^{3}H]-L-aspartate	[^{3}H]-ETB-TBOA (K_D = 320 nM), [^{3}H]-D-aspartate, [^{3}H]-L-aspartate
Stoichiometry	—	$3Na^+$: $1H^+$: 1glutamate (in): $1K^+$ (out)	$3Na^+$: $1H^+$: 1glutamate (in): $1K^+$ (out)

Nomenclature	EAAT4	EAAT5
Other names	SLC1A6	SLC1A7
Ensembl ID	ENSG00000105143	ENSG00000162383
Endogenous substrates	L-glutamate, L-aspartate	L-glutamate, L-aspartate
Inhibitors (K_B or K_i)	DL-TBOA (4.4 μM), *Threo*-3-methylglutamate (50 μM)	DL-TBOA (3.2 μM)
Probes	[^{3}H]-ETB-TBOA (K_D = 24.8 nM), [^{3}H]-D-aspartate, [^{3}H]-L-aspartate	[^{3}H]-ETB-TBOA (K_D = 29.5 nM), [^{3}H]-D-aspartate, [^{3}H]-L-aspartate

The K_B (or K_i) values reported, unless indicated otherwise, are derived from transporter currents mediated by EAATs expressed in voltage-clamped *Xenopus laevis* oocytes (Vandenberg *et al*., 1997; Shimamoto *et al*., 1998; Eliasof *et al*., 2001; Shigeri *et al*., 2001). K_B (or K_i) values derived in uptake assays are generally higher (*e.g.* Shimamoto *et al*., 1998). In addition to acting as a non-transportable inhibitor of EAAT2, (2*S*,4*R*)-4-methylglutamate, also known as SYM2081, is a competitive substrate for EAAT1 (K_M = 54 μM; Vandenberg *et al*., 1997) and additionally is a potent kainate receptor agonist (Zhou *et al*., 1997) which renders the compound unsuitable for autoradiographic localisation of EAATs (Apricò *et al*., 2007). Similarly, at concentrations that inhibit EAAT2, dihydrokainate binds to kainate receptors (Shimamoto *et al*., 1998). WAY-855 is a non-transportable inhibitor with selectivity for EAAT1, *versus* EAAT2, or EAAT3 (Dunlop *et al*., 2003) whereas WAY-213613 is a competitive inhibitor with selectivity for EAAT2 *versus* EAAT1, or EAAT3 (Dunlop *et al*., 2005). NBI-59159 is a non-substrate inhibitor with modest selectivity for EAAT3 over EAAT1 (>10-fold) and EAAT2 (5-fold) (Coon *et al*., 2004; Dunlop, 2006). Similarly, L-β-*threo*-benzyl-aspartate is a competitive non-substrate inhibitor that preferentially blocks EAAT3 *versus* EAAT1, or EAAT2 (Esslinger *et al*., 2005). [^{3}H]-[(2*S*,4*R*)-4-methylglutamate demonstrates low affinity binding ($K_D \cong 6.0$ μM) to EAAT1 and EAAT2 in rat brain homogenates (Apricò *et al*., 2001) and EAAT1 in murine astrocyte membranes (Apricò *et al*., 2004), whereas [^{3}H]-ETB-TBOA binds with high affinity to all EAATs other than EAAT3 (Shimamoto *et al*., 2007). *Threo*-3-methylglutamate induces substrate-like currents at EAAT4, but does not elicit heteroexchange of [^{3}H]-aspartate in synaptosome preparations, inconsistent with the behaviour of a substrate inhibitor (Eliasof *et al*., 2001). In addition to the agents listed in the table, DL-*threo*-β-hydroxyaspartate and L-*trans*-2,4-pyrolidine dicarboxylate act as non-selective competitive substrate inhibitors of all EAATs. Zn^{2+} and arachidonic acid are putative endogenous modulators of EAATs with actions that differ across transporter subtypes (reviewed by Vandenberg *et al*., 2004).

Abbreviations: DL-TBOA, DL-*threo*-β-benzyloxyaspartate; **GPI-1046**, (3-(3-pyridyl)-1-propyl (2*S*)-1-(3,3-dimethyl-1, 2-dioxopentyl)-2-pyrrolidinecarboxylate; **ETB-TBOA**, (2*S*, 3*S*)-3-{3-[4-ethylbenzoylamino]benzyloxy}aspartate; **NBI-59159** (also known as WAY-209429), (*N*-4-(9*H*-fluoren-2-yl)-L-asparagine; **WAY-855**, 3-amino-tricyclo[2.2.1.$0^{2,6}$]heptane-1, 3-dicarboxylic acid; **WAY-213613**, *N*(4)-[4-(2-bromo-4, 5-difluorophenoxy)phenyl]-L-asparagine

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Glycine

Overview: Plasma membrane located glycine transporters (provisional nomenclature) are members of the solute carrier family 6 (SLC6) of sodium- and chloride-dependent neurotransmitter receptor transporters that includes the monoamine and GABA transporters (Chen *et al*., 2004). The members of this superfamily share a structural motif of 12 putative TM segments (Palacín *et al*., 1998) that has been confirmed by the recent crystal structure of a bacterial homolog of the Na^+/Cl^- dependent neurotransmitter transporters from *Aquiflex aeolicus* ($LeuT_{Aa}$) (Yamashita *et al*., 2005). Two gene products, GlyT1 and GlyT2, are known that give rise to transporters that are predominantly located on glia and neurones, respectively. Five variants of GlyT1 (a,b,c,d & e) differing in their N- and C-termini are generated by alternative promoter usage and splicing, and three splice variants of GlyT2 (a,b & c) have also been identified (see Supplisson and Roux, 2002; Eulenberg *et al*., 2005; Betz *et al*., 2006; Gomeza *et al*., 2006 for reviews). GlyT1 transporter isoforms expressed in glia surrounding glutamatergic synapses regulate synaptic glycine concentrations influencing NMDA receptor-mediated neurotransmission (Bergeron *et al*., 1998; Gabernet *et al*., 2005), but also are important, in early neonatal life, for regulating glycine concentrations at inhibitory glycinergic synapses (Gomeza *et al*., 2003a). Homozygous mice engineered to totally lack GlyT1 exhibit severe respiratory and motor deficiencies due to hyperactive glycinergic signalling and die within the first postnatal day (Gomeza *et al*., 2003a; Tsai *et al*., 2004). Disruption of GlyT1 restricted to forebrain neurones is associated with enhancement of EPSCs mediated by NMDA receptors and behaviours that are suggestive of a promnesic action (Yee *et al*., 2006). GlyT2 transporters localised on the axons and boutons of glycinergic neurones appear crucial for efficient transmitter loading of synaptic vesicles but may not be essential for the termination of inhibitory neurotransmission (Gomeza *et al*., 2003b). Mice in which GlyT2 has been deleted develop a fatal hyperekplexia phenotype during the second postnatal week (Gomeza *et al*., 2003b) and mutations in the human gene encoding GlyT2 (*SLC6A5*) have been identified in several patients with hyperekplexia (Rees *et al*., 2006). A structurally and functionally distinct vesicular transporter [VGAT/VIAAT (ENSG00000101438); McIntire *et al*., 1997; Sagne *et al*., 1997], subject to inhibition by vigabatrin, is responsible for concentrating glycine (and GABA) within synaptic vesicles.

Nomenclature	GlyT1	GlyT2
Other names	SLC6A9	SLC6A5
Ensembl ID	ENSG00000117413	ENSG00000165970
Endogenous substrates	Glycine	Glycine
Selective inhibitors (IC_{50})	(*R*)-NFPS (ALX 5407) (0.8–3 nM), NFPS (3 nM), SSR504734 (18 nM), NPTS (37 nM), Org 24598	ALX 1393, ALX 1405, Org 25543 (20 nM)
Probes (K_D)	[^{3}H]-(*R*)-NPTS (1 nM), [^{3}H]-NFPS (7–21 nM)	—
Stoichiometry	$2Na^+$: $1Cl^-$: 1 glycine	3 Na^+: $1Cl^-$: 1 glycine

In addition to the inhibitors listed, sarcosine is a selective transportable inhibitor of GlyT1, but has no affect on GlyT2. This difference has been attributed to a single residue glycine residue in transmembrane domain 6 (serine residue in GlyT2) (Vandenberg *et al*., 2007). Inhibition of GLYT1 by NFPS is non-competitive (Mallorga *et al*., 2003). IC_{50} values for Org 24598 reported in the literature vary, most likely due to differences in assay conditions (Brown *et al*., 2001; Mallorga *et al*., 2003). The tricyclic antidepressant amoxapine weakly inhibits GlyT2 (IC_{50} 92 μM) with approximately 10-fold selectivity over GlyT1 (Nunez *et al*., 2000). The endogenous lipids arachidonic acid and anandamide exert opposing effects upon GlyT1a, inhibiting ($IC_{50} \sim 2$ μM) and potentiating ($EC_{50} \sim 13$ μM) transport currents, respectively (Pearlman *et al*., 2003). N-arachidonoyl-glycine has recently been described as a non-competitive inhibitor of GlyT2a, but not GlyT1b (Wiles *et al*., 2006). Protons (Aubrey *et al*., 2000) and Zn^{2+} (Ju *et al*., 2004) act as non-competitive inhibitors of GlyT1b, with IC_{50} values of ~100 nM and ~10 μM respectively, but neither ion affects GlyT2 (reviewed by Vandenberg *et al*., 2004).

Abbreviations: ALX 1393, O-[2-benzyloxyphenyl-3-flurophenyl]methyl-L-serine; **ALX 1405**, structure not available; **NFPS**, N-[3-(4′-fluorophenyl)-3-(4′-phenylphenoxy)propyl]sarcosine; **NPTS**, (*N*-[3-phenyl-3-(4′-(4-toluoyl) phenoxy)propyl]sarcosine; **Org 24598**, *R*-(−)-*N*-[3-[(4-triflouromethyl)phenoxy]-3-phenyl-propylglycine; **Org 25543**, 4-benzyloxy-3,5-dimethoxy-*N*-[1-(dimethylaminocyclopentyl) methyl] benzamide; **SSR504734**, 2-chloro-[*N*-(*S*)-phenyl[(2*S*)-piperidin-2-yl]methyl]-3-trifluoromethyl benzamide

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Monoamine

Overview: Plasma membrane located monoamine transporters (provisional nomenclature) transport the hormone/transmitters adrenaline, noradrenaline, dopamine and 5-hydroxytryptamine, and are members of the solute carrier family 6 (SLC6) of sodium- and chloride-dependent neurotransmitter transporters that includes the GABA and glycine transporters (Chen *et al*., 2003). The members of this superfamily share a structural motif of 12 putative transmembrane segments (Palacín *et al*., 1998). A high resolution structure of a bacterial homologue of these transporters has been reported recently (Yamashita *et al*., 2005).

Nomenclature	DAT	NET	SERT
Other names	DAT1, SLC6A3	NAT1, SLC6A2	5-HTT, SERT1, SLC6A4
Ensembl ID	ENSG00000142319	ENSG00000103546	ENSG00000108576
Endogenous substrates	Dopamine, adrenaline, noradrenaline	Noradrenaline, adrenaline, dopamine	5-HT
Synthetic substrates	Amphetamine, methamphetamine, MPP^+	Amphetamine, methamphetamine, MPP^+	*p*-Chloroamphetamine, MDMA
Selective inhibitors	Mazindol (8.0), WIN35428 (7.9), GBR12935 (7.6)	Mazindol (8.9), nisoxetine (8.4), nomifensine (8.1)	Paroxetine (9.6, Tatsumi *et al*., 1997), sertraline (9.1), fluoxetine (8.5, Tatsumi *et al*., 1997)
Probes	[^{3}H]-GBR12935 (3 nM, Pristupa *et al*., 1994), [^{3}H]-WIN35428 (10 nM, Pristupa *et al*., 1994)	[^{3}H]-Mazindol (0.5 nM), [^{3}H]-nisoxetine (4 nM)	[^{3}H]-Paroxetine (0.2 nM), [^{3}H]-citalopram (5 nM)
Predicted stoichiometry	1 Dopamine:1–2 Na^+:1 Cl^- (Gu *et al*., 1994)	1 Noradrenaline: 1 Na^+:1 Cl^- (Gu *et al*., 1996)	1 5-HT:1 Na^+:1 Cl^- (in), +1 K^+ (out) (Talvenheimo *et al*., 1983)

[^{125}I]-RTI55 labels all three transporters with affinities between 0.5 and 5 nM. Cocaine is an inhibitor of all three transporters with pK_i values between 6.5 and 7.2. Potential alternative splicing sites in non-coding regions of SERT and NET have been identified. A bacterial homologue of SERT shows allosteric modulation by selected anti-depressants (Singh *et al*., 2007).

Abbreviations: GBR12935, 1-(2-[diphenylmethoxy]ethyl)-4-(3-phenylpropyl)piperazine; **MDMA**, 3,4-methylenedioxymethamphetamine; **MPP^+**, 1-methyl-4-phenylpyridinium; **RTI55**, 2β-carbomethoxy-3β-(4-iodophenyl) tropane (also known as β-CIT); **WIN35428**, 2β-carboxy-methy-3β-(4-fluorophenyl)tropane (also known as β-CFT)

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Nucleoside

Overview: Nucleoside transporters are divided into two families, the equilibrative, solute carrier family 29 (SLC29) and the sodium-dependent, solute carrier family 28 (SLC28), where the endogenous substrates are nucleosides. Structurally, SLC29 family members appear to be composed of 11 transmembrane segments, while the SLC28 family members have 13 transmembrane segments, both with cytoplasmic N-termini and extracellular C-termini.

Nomenclature	ENT1	ENT2
Other names	*es*, NBTI-sensitive, SLC29A1	*ei*, NBTI-insensitive, SLC29A2
Ensembl ID	ENSG00000112759	ENSG00000174669
Endogenous substrates	Adenosine, guanosine, inosine, uridine, thymidine, cytidine	Adenosine, guanosine, inosine, uridine, thymidine, hypoxanthine
Synthetic substrates	2-Chloroadenosine, dideoxyinosine, formycin B, tubercidin, vidarabine, cytarabine, AZT, cladribine, pentostatin, zalcitabine, didanosine, floxidine, gemcitabine	2-Chloroadenosine, formycin B, tubercidin, cytarabine, cladribine, vidarabine, gemcitabine
Selective inhibitors	NBTI (9.7), draflazine (9.5), KF24345 (9.4, Hammond & Archer, 2004), NBTGR (9.3), dilazep (9), dipyridamole (8.5)	—
Probes	[^{3}H]-NBTI (0.5 nM)	—
Predicted stoichiometry	Equilibrative	Equilibrative

The affinities of draflazine, dilazep, KF24345 and dipyridamole at ENT1 transporters are species dependent, exhibiting lower affinity at rat transporters than at human transporters (Sundaram *et al.*, 1998; Hammond and Archer, 2004). Additional members of the family have been identified (including ENT3 [SLC29A3, ENSG00000156604] and ENT4 [SLC29A4, ENSG00000164638]), which have been reported to be intracellular purine nucleoside transporters (Baldwin *et al.*, 2005).

Nomenclature	CNT1	CNT2	CNT3
Other names	N2/*cit*, SLC28A1	N1/*cif*, SPNT, SLC28A2	N3/*cib*, SLC28A3
Ensembl ID	ENSG00000156222	ENSG00000137860	ENSG00000099118
Endogenous substrates	Uridine, cytidine, thymidine, adenosine	Adenosine, guanosine, inosine, thymidine	Uridine, cytidine, thymidine, adenosine, guanosine, inosine
Synthetic substrates	AZT, zalcitabine, gemcitabine	Formycin B, cladribine, fludarabine, vidarabine, didanosine	AZT, zalcitabine, didanosine, formycin B, 5-fluorouridine, 5-fluoro-2′-deoxyuridine, zebularine, gemcitabine, cladribine, fludarabine
Predicted stoichiometry	1 : 1 Na^+	1 : 1 Na^+	1 : 2 Na^+

A further two Na^+-dependent (1 : 1 Na^+ stoichiometry) nucleoside transporters have been defined on the basis of substrate and inhibitor selectivity: CNT4 (N4/*cit*, which transports uridine, thymidine and guanosine) and CNT5 (N5/*csg*, which transports guanosine and adenosine, and may be inhibited by NBTI).

Abbreviations: **AZT**, 3′-azido-3′-deoxythymidine; **NBTI**, nitrobenzylthioinosine (also known as NBMPR); **NBTGR**, nitrobenzylthioguanosine; **KF24345**, 3-(1-[6,7-diethoxy-2-morpholinoquinazolin-4-yl]piperidin-4-yl)-1,6-dimethyl-2,4(1*H*, 3*H*)-quinazolinedione hydrochloride

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