

SLC6 neurotransmitter transporter family in GtoPdb v.2023.1

Stefan Bröer¹ and Gary Rudnick²

1. Australian National University, Australia
2. Yale University, USA

Abstract

Members of the solute carrier family 6 (SLC6) of sodium- and (sometimes chloride-) dependent neurotransmitter transporters [32, 2, 23, 75] are primarily plasma membrane located and may be divided into four subfamilies that transport monoamines, GABA, glycine and neutral amino acids, plus the related bacterial NSS transporters [109]. The members of this superfamily share a structural motif of 10 TM segments that has been observed in crystal structures of the NSS bacterial homolog LeuT_{Aa}, a Na⁺-dependent amino acid transporter from *Aquiflex aeolicus* [137] and in several other transporter families structurally related to LeuT [49].

Contents

This is a citation summary for SLC6 neurotransmitter transporter family in the [Guide to Pharmacology](#) database (GtoPdb). It exists purely as an adjunct to the database to facilitate the recognition of citations to and from the database by citation analyzers. Readers will almost certainly want to visit the relevant sections of the database which are given here under database links.

[GtoPdb](#) is an expert-driven guide to pharmacological targets and the substances that act on them. GtoPdb is a reference work which is most usefully represented as an on-line database. As in any publication this work should be appropriately cited, and the papers it cites should also be recognized. This document provides a citation for the relevant parts of the database, and also provides a reference list for the research cited by those parts. For further details see [25].

Please note that the database version for the citations given in GtoPdb are to the most recent preceding version in which the family or its subfamilies and targets were substantially changed. The links below are to the current version. If you need to consult the cited version, rather than the most recent version, please contact the GtoPdb curators.

Database links

[SLC6 neurotransmitter transporter family](#)

<https://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=144>

[Monoamine transporter subfamily](#)

<https://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=176>

Transporters

NET

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=926>

DAT

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=927>

SERT

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=928>

GABA transporter subfamily

<https://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=177>

Transporters

GAT1

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=929>

GAT2

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=930>

GAT3

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=931>

BGT1

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=932>

TauT

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=933>

CT1

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=934>

Glycine transporter subfamily

<https://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=178>

Transporters

GlyT1

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=935>

GlyT2

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=936>

ATB^{0,+}

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=937>

PROT

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=938>

Neutral amino acid transporter subfamily

<https://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=179>

Transporters

B⁰AT1

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=939>

B⁰AT2

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=940>

B⁰AT3

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=941>

NTT5

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=942>

NTT4

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=943>

SIT1

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=944>

References

1. Ablordeppey SY, Altundas R, Bricker B, Zhu XY, Kumar EV, Jackson T, Khan A and Roth BL. (2008) Identification of a butyrophenone analog as a potential atypical antipsychotic agent: 4-[4-(4-chlorophenyl)-1,4-diazepan-1-yl]-1-(4-fluorophenyl)butan-1-one. *Bioorg Med Chem* **16**: 7291-301 [PMID:18595716]
2. Alexander SPH, Kelly E, Mathie A, Peters JA, Veale EL, Armstrong JF, Faccenda E, Harding SD, Pawson AJ and Sharman JL *et al.*. (2019) THE CONCISE GUIDE TO PHARMACOLOGY 2019/20: Transporters. *Br J Pharmacol* **176 Suppl 1**: S397-S493 [PMID:31710713]
3. Altenbach RJ, Black LA, Strakhova MI, Manelli AM, Carr TL, Marsh KC, Wetter JM, Wensink EJ, Hsieh GC and Honore P *et al.*. (2010) Diaryldiamines with dual inhibition of the histamine H(3) receptor and the norepinephrine transporter and the efficacy of 4-(3-(methylamino)-1-phenylpropyl)-6-(2-(pyrrolidin-1-

- yl)ethoxy)naphthalen-1-ol in pain. *J Med Chem* **53**: 7869-73 [PMID:20945906]
4. Amberg W, Lange UEW, Ochse M, Pohlki F, Behl B, Relo AL, Hornberger W, Hoft C, Mezler M and Sydor J *et al.* (2018) Discovery of Novel Aminotetralines and Aminochromanes as Selective and Competitive Glycine Transporter 1 (GlyT1) Inhibitors. *J Med Chem* **61**: 7503-7524 [PMID:30080045]
 5. Andersen PH. (1989) The dopamine inhibitor GBR 12909: selectivity and molecular mechanism of action. *Eur J Pharmacol* **166**: 493-504 [PMID:2530094]
 6. Anderson CM, Ganapathy V and Thwaites DT. (2008) Human solute carrier SLC6A14 is the beta-alanine carrier. *J Physiol (Lond.)* **586**: 4061-7 [PMID:18599538]
 7. Anderson CM, Howard A, Walters JR, Ganapathy V and Thwaites DT. (2009) Taurine uptake across the human intestinal brush-border membrane is via two transporters: H⁺-coupled PAT1 (SLC36A1) and Na⁺- and Cl⁻-dependent TauT (SLC6A6). *J Physiol (Lond.)* **587**: 731-44 [PMID:19074966]
 8. Arunotayanun W, Dalley JW, Huang XP, Setola V, Treble R, Iversen L, Roth BL and Gibbons S. (2013) An analysis of the synthetic tryptamines AMT and 5-MeO-DALT: emerging 'Novel Psychoactive Drugs'. *Bioorg Med Chem Lett* **23**: 3411-5 [PMID:23602445]
 9. Aubrey KR, Mitrovic AD and Vandenberg RJ. (2000) Molecular basis for proton regulation of glycine transport by glycine transporter subtype 1b. *Mol Pharmacol* **58**: 129-35 [PMID:10860934]
 10. Auerbach SS and DrugMatrix® and ToxFX® Coordinator National Toxicology Program.. National Toxicology Program: Dept of Health and Human Services. <https://ntp.niehs.nih.gov/drugmatrix/index.html>. Accessed on 02/05/2014.
 11. Baladi MG, Forster MJ, Gatch MB, Mailman RB, Hyman DL, Carter LP and Janowsky A. (2018) Characterization of the Neurochemical and Behavioral Effects of Solriamfetol (JZP-110), a Selective Dopamine and Norepinephrine Reuptake Inhibitor. *J Pharmacol Exp Ther* **366**: 367-376 [PMID:29891587]
 12. Bang-Andersen B, Ruhland T, Jørgensen M, Smith G, Frederiksen K, Jensen KG, Zhong H, Nielsen SM, Hogg S and Mørk A *et al.* (2011) Discovery of 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine (Lu AA21004): a novel multimodal compound for the treatment of major depressive disorder. *J Med Chem* **54**: 3206-21 [PMID:21486038]
 13. Belanger AM, Przybylska M, Gefteas E, Furgerson M, Geller S, Kloss A, Cheng SH, Zhu Y and Yew NS. (2018) Inhibiting neutral amino acid transport for the treatment of phenylketonuria. *JCI Insight* **3** [PMID:30046012]
 14. Ben-Daniel R, Deuther-Conrad W, Scheunemann M, Steinbach J, Brust P and Mishani E. (2008) Carbon-11 labeled indolylpropylamine analog as a new potential PET agent for imaging of the serotonin transporter. *Bioorg Med Chem* **16**: 6364-70 [PMID:18487050]
 15. Bergeron R, Meyer TM, Coyle JT and Greene RW. (1998) Modulation of N-methyl-D-aspartate receptor function by glycine transport. *Proc Natl Acad Sci USA* **95**: 15730-4 [PMID:9861038]
 16. Betz H, Gomeza J, Armsen W, Scholze P and Eulenburg V. (2006) Glycine transporters: essential regulators of synaptic transmission. *Biochem Soc Trans* **34**: 55-8 [PMID:16417482]
 17. Borden LA, Dhar TG, Smith KE, Branchek TA, Gluchowski C and Weinshank RL. (1994) Cloning of the human homologue of the GABA transporter GAT-3 and identification of a novel inhibitor with selectivity for this site. *Recept Channels* **2**: 207-13 [PMID:7874447]
 18. Borden LA, Murali Dhar TG, Smith KE, Weinshank RL, Branchek TA and Gluchowski C. (1994) Tiagabine, SK&F 89976-A, CI-966, and NNC-711 are selective for the cloned GABA transporter GAT-1. *Eur J Pharmacol* **269**: 219-24 [PMID:7851497]
 19. Boulay D, Pichat P, Dargazanli G, Estenne-Bouhtou G, Terranova JP, Rogacki N, Stemmelin J, Coste A, Lanneau C and Desvignes C *et al.* (2008) Characterization of SSR103800, a selective inhibitor of the glycine transporter-1 in models predictive of therapeutic activity in schizophrenia. *Pharmacol Biochem Behav* **91**: 47-58 [PMID:18621075]
 20. Brown A, Carlyle I, Clark J, Hamilton W, Gibson S, McGarry G, McEachen S, Rae D, Thorn S and Walker G. (2001) Discovery and SAR of org 24598-a selective glycine uptake inhibitor. *Bioorg Med Chem Lett* **11**: 2007-9 [PMID:11454468]
 21. Bröer A, Balkrishna S, Kottra G, Davis S, Oakley A and Bröer S. (2009) Sodium translocation by the iminoglycinuria associated imino transporter (SLC6A20). *Mol Membr Biol* **26**: 333-46 [PMID:19657969]
 22. Bröer A, Tietze N, Kowalczyk S, Chubb S, Munzinger M, Bak LK and Bröer S. (2006) The orphan transporter v7-3 (slc6a15) is a Na⁺-dependent neutral amino acid transporter (BOAT2). *Biochem J* **393**: 421-30 [PMID:16185194]

23. Bröer S. (2006) The SLC6 orphans are forming a family of amino acid transporters. *Neurochem Int* **48**: 559-67 [PMID:16540203]
24. Bröer S. (2008) Apical transporters for neutral amino acids: physiology and pathophysiology. *Physiology (Bethesda)* **23**: 95-103 [PMID:18400692]
25. Buneman P, Christie G, Davies JA, Dimitrellou R, Harding SD, Pawson AJ, Sharman JL and Wu Y. (2020) Why data citation isn't working, and what to do about it *Database* **2020** [PMID:32367113]
26. Böhmer C, Bröer A, Munzinger M, Kowalczyk S, Rasko JE, Lang F and Bröer S. (2005) Characterization of mouse amino acid transporter B0AT1 (slc6a19). *Biochem J* **389**: 745-51 [PMID:15804236]
27. Carland JE, Mansfield RE, Ryan RM and Vandenberg RJ. (2013) Oleoyl-L-carnitine inhibits glycine transport by GlyT2. *Br J Pharmacol* **168**: 891-902 [PMID:22978602]
28. Carlier PR, Lo MM, Lo PC, Richelson E, Tatsumi M, Reynolds IJ and Sharma TA. (1998) Synthesis of a potent wide-spectrum serotonin-, norepinephrine-, dopamine-reuptake inhibitor (SNDR1) and a species-selective dopamine-reuptake inhibitor based on the gamma-amino alcohol functional group. *Bioorg Med Chem Lett* **8**: 487-92 [PMID:9871604]
29. Carroll FI, Blough BE, Abraham P, Mills AC, Holleman JA, Wolckenhauer SA, Decker AM, Landavazo A, McElroy KT and Navarro HA *et al.* (2009) Synthesis and biological evaluation of bupropion analogues as potential pharmacotherapies for cocaine addiction. *J Med Chem* **52**: 6768-81 [PMID:19821577]
30. Carroll FI, Runyon SP, Abraham P, Navarro H, Kuhar MJ, Pollard GT and Howard JL. (2004) Monoamine transporter binding, locomotor activity, and drug discrimination properties of 3-(4-substituted-phenyl)tropane-2-carboxylic acid methyl ester isomers. *J Med Chem* **47**: 6401-9 [PMID:15566309]
31. Caulfield WL, Collie IT, Dickins RS, Epemolu O, McGuire R, Hill DR, McVey G, Morphy JR, Rankovic Z and Sundaram H. (2001) The first potent and selective inhibitors of the glycine transporter type 2. *J Med Chem* **44**: 2679-82 [PMID:11495577]
32. Chen NH, Reith ME and Quick MW. (2004) Synaptic uptake and beyond: the sodium- and chloride-dependent neurotransmitter transporter family SLC6. *Pflugers Arch* **447**: 519-31 [PMID:12719981]
33. Cheng Q, Shah N, Bröer A, Fairweather S, Jiang Y, Schmoll D, Corry B and Bröer S. (2017) Identification of novel inhibitors of the amino acid transporter B⁰ AT1 (SLC6A19), a potential target to induce protein restriction and to treat type 2 diabetes. *Br J Pharmacol* **174**: 468-482 [PMID:28176326]
34. Clausen RP, Madsen K, Larsson OM, Frølund B, Krogsgaard-Larsen P and Schousboe A. (2006) Structure-activity relationship and pharmacology of gamma-aminobutyric acid (GABA) transport inhibitors. *Adv Pharmacol* **54**: 265-84 [PMID:17175818]
35. Cohen-Kfir E, Lee W, Eskandari S and Nelson N. (2005) Zinc inhibition of gamma-aminobutyric acid transporter 4 (GAT4) reveals a link between excitatory and inhibitory neurotransmission. *Proc Natl Acad Sci USA* **102**: 6154-9 [PMID:15829583]
36. Coleman JA, Green EM and Gouaux E. (2016) X-ray structures and mechanism of the human serotonin transporter. *Nature* **532**: 334-9 [PMID:27049939]
37. Cubelos B, González-González IM, Giménez C and Zafra F. (2005) The scaffolding protein PSD-95 interacts with the glycine transporter GLYT1 and impairs its internalization. *J Neurochem* **95**: 1047-58 [PMID:16271045]
38. Cuboni S, Devigny C, Hoogeland B, Strasser A, Pomplun S, Hauger B, Höfner G, Wanner KT, Eder M and Buschauer A *et al.* (2014) Loratadine and analogues: discovery and preliminary structure-activity relationship of inhibitors of the amino acid transporter B(0)AT2. *J Med Chem* **57**: 9473-9 [PMID:25318072]
39. Dai W, Vinnakota S, Qian X, Kunze DL and Sarkar HK. (1999) Molecular characterization of the human CRT-1 creatine transporter expressed in *Xenopus* oocytes. *Arch Biochem Biophys* **361**: 75-84 [PMID:9882430]
40. Danthi SJ, Liang B, Smicker O, Coupland B, Gregory J, Gefteas E, Tietz D, Klodnitsky H, Randall K and Belanger A *et al.* (2019) Identification and Characterization of Inhibitors of a Neutral Amino Acid Transporter, SLC6A19, Using Two Functional Cell-Based Assays. *SLAS Discov* **24**: 111-120 [PMID:30589598]
41. Dawson LA and Watson JM. (2009) Vilazodone: a 5-HT1A receptor agonist/serotonin transporter inhibitor for the treatment of affective disorders. *CNS Neurosci Ther* **15**: 107-17 [PMID:19499624]
42. Dhar TG, Borden LA, Tyagarajan S, Smith KE, Brancheck TA, Weinshank RL and Gluchowski C. (1994) Design, synthesis and evaluation of substituted triaryl nipepic acid derivatives as GABA uptake inhibitors: identification of a ligand with moderate affinity and selectivity for the cloned human GABA

- transporter GAT-3. *J Med Chem* **37**: 2334-42 [PMID:8057281]
43. Dhar TGM, Nakanishi H, Borden LA and Gluchowski C. (1996) On the bioactive conformation of the GABA uptake inhibitor SK&F 89976-A. *Bioorg Med Chem Lett* **6**: 1535 -1540
 44. Dodd JR and Christie DL. (2007) Selective amino acid substitutions convert the creatine transporter to a gamma-aminobutyric acid transporter. *J Biol Chem* **282**: 15528-33 [PMID:17400549]
 45. Dreyfus N, Myers JK, Badescu VO, de Frutos O, de la Puente ML, Ding C, Filla SA, Fynboe K, Gernert DL and Heinz BA *et al.*. (2013) Discovery of a potent, dual serotonin and norepinephrine reuptake inhibitor. *ACS Med Chem Lett* **4**: 560-4 [PMID:24900709]
 46. Edington AR, McKinzie AA, Reynolds AJ, Kassiou M, Ryan RM and Vandenberg RJ. (2009) Extracellular loops 2 and 4 of GLYT2 are required for N-arachidonylglycine inhibition of glycine transport. *J Biol Chem* **284**: 36424-30 [PMID:19875446]
 47. Eulenburg V, Armsen W, Betz H and Gomeza J. (2005) Glycine transporters: essential regulators of neurotransmission. *Trends Biochem Sci* **30**: 325-33 [PMID:15950877]
 48. Fish PV, Deur C, Gan X, Greene K, Hoople D, Mackenny M, Para KS, Reeves K, Ryckmans T and Stiff C *et al.*. (2008) Design and synthesis of morpholine derivatives. SAR for dual serotonin & noradrenaline reuptake inhibition. *Bioorg Med Chem Lett* **18**: 2562-6 [PMID:18387300]
 49. Forrest LR and Rudnick G. (2009) The rocking bundle: a mechanism for ion-coupled solute flux by symmetrical transporters. *Physiology (Bethesda)* **24**: 377-86 [PMID:19996368]
 50. Froimowitz M, Gu Y, Dakin LA, Nagafuji PM, Kelley CJ, Parrish D, Deschamps JR and Janowsky A. (2007) Slow-onset, long-duration, alkyl analogues of methylphenidate with enhanced selectivity for the dopamine transporter. *J Med Chem* **50**: 219-32 [PMID:17228864]
 51. Fülep GH, Hoesl CE, Höfner G and Wanner KT. (2006) New highly potent GABA uptake inhibitors selective for GAT-1 and GAT-3 derived from (R)- and (S)-proline and homologous pyrrolidine-2-alkanoic acids. *Eur J Med Chem* **41**: 809-24 [PMID:16766089]
 52. Gabernet L, Pauly-Evers M, Schwerdel C, Lentz M, Bluethmann H, Vogt K, Alberati D, Mohler H and Boison D. (2005) Enhancement of the NMDA receptor function by reduction of glycine transporter-1 expression. *Neurosci Lett* **373**: 79-84 [PMID:15555781]
 53. Gengo PJ, Giuliano F and McKenna KE *et al.*. (2005) Monoaminergic transporter binding and inhibition profile of dapoxetine, a medication for the treatment of premature ejaculation [abstract]. *J Urol* **173**: Abstract 878
 54. Glennon RA, Lee M, Rangisetty JB, Dukat M, Roth BL, Savage JE, McBride A, Rauser L, Hufeisen S and Lee DK. (2000) 2-Substituted tryptamines: agents with selectivity for 5-HT(6) serotonin receptors. *J Med Chem* **43**: 1011-8 [PMID:10715164]
 55. Gomeza J, Armsen W, Betz H and Eulenburg V. (2006) Lessons from the knocked-out glycine transporters. *Handb Exp Pharmacol*: 457-83 [PMID:16722246]
 56. Gomeza J, Hülsmann S, Ohno K, Eulenburg V, Szöke K, Richter D and Betz H. (2003) Inactivation of the glycine transporter 1 gene discloses vital role of glial glycine uptake in glycinergic inhibition. *Neuron* **40**: 785-96 [PMID:14622582]
 57. Gomeza J, Ohno K, Hülsmann S, Armsen W, Eulenburg V, Richter DW, Laube B and Betz H. (2003) Deletion of the mouse glycine transporter 2 results in a hyperekplexia phenotype and postnatal lethality. *Neuron* **40**: 797-806 [PMID:14622583]
 58. Gu H, Wall SC and Rudnick G. (1994) Stable expression of biogenic amine transporters reveals differences in inhibitor sensitivity, kinetics, and ion dependence. *J Biol Chem* **269**: 7124-30 [PMID:8125921]
 59. Gu HH, Wall S and Rudnick G. (1996) Ion coupling stoichiometry for the norepinephrine transporter in membrane vesicles from stably transfected cells. *J Biol Chem* **271**: 6911-6 [PMID:8636118]
 60. Han X, Patters AB, Jones DP, Zelikovic I and Chesney RW. (2006) The taurine transporter: mechanisms of regulation. *Acta Physiol (Oxf)* **187**: 61-73 [PMID:16734743]
 61. Harada K, Nakato K, Yarimizu J, Yamazaki M, Morita M, Takahashi S, Aota M, Saita K, Doihara H and Sato Y *et al.*. (2012) A novel glycine transporter-1 (GlyT1) inhibitor, ASP2535 (4-[3-isopropyl-5-(6-phenyl-3-pyridyl)-4H-1,2,4-triazol-4-yl]-2,1,3-benzoxadiazole), improves cognition in animal models of cognitive impairment in schizophrenia and Alzheimer's disease. *Eur J Pharmacol* **685**: 59-69 [PMID:22542656]
 62. Harvey RJ, Topf M, Harvey K and Rees MI. (2008) The genetics of hyperekplexia: more than startle! *Trends Genet* **24**: 439-47 [PMID:18707791]
 63. Hatanaka T, Nakanishi T, Huang W, Leibach FH, Prasad PD, Ganapathy V and Ganapathy ME. (2001)

- Na⁺ - and Cl⁻-coupled active transport of nitric oxide synthase inhibitors via amino acid transport system B(0,+). *J Clin Invest* **107**: 1035-43 [PMID:11306607]
64. Heffernan GD, Coghlan RD, Manas ES, McDevitt RE, Li Y, Mahaney PE, Robichaud AJ, Huselton C, Alfinito P and Bray JA *et al.* (2009) Dual acting norepinephrine reuptake inhibitors and 5-HT(2A) receptor antagonists: Identification, synthesis and activity of novel 4-aminoethyl-3-(phenylsulfonyl)-1H-indoles. *Bioorg Med Chem* **17**: 7802-15 [PMID:19836247]
65. Heikkila RE and Manzino L. (1984) Behavioral properties of GBR 12909, GBR 13069 and GBR 13098: specific inhibitors of dopamine uptake. *Eur J Pharmacol* **103**: 241-8 [PMID:6237922]
66. Heinrich T, Böttcher H, Gericke R, Bartoszyk GD, Anzali S, Seyfried CA, Greiner HE and Van Amsterdam C. (2004) Synthesis and structure--activity relationship in a class of indolebutylpiperazines as dual 5-HT(1A) receptor agonists and serotonin reuptake inhibitors. *J Med Chem* **47**: 4684-92 [PMID:15341484]
67. Herdon HJ, Roberts JC, Coulton S and Porter RA. (2010) Pharmacological characterisation of the GlyT-1 glycine transporter using two novel radioligands. *Neuropharmacology* **59**: 558-65 [PMID:20691713]
68. Inazu M, Takeda H, Ikoshi H, Sugisawa M, Uchida Y and Matsumiya T. (2001) Pharmacological characterization and visualization of the glial serotonin transporter. *Neurochem Int* **39**: 39-49 [PMID:11311448]
69. Jensen NH, Rodriguiz RM, Caron MG, Wetsel WC, Rothman RB and Roth BL. (2008) N-desalkylquetiapine, a potent norepinephrine reuptake inhibitor and partial 5-HT1A agonist, as a putative mediator of quetiapine's antidepressant activity. *Neuropsychopharmacology* **33**: 2303-12 [PMID:18059438]
70. Jeong HJ, Vandenberg RJ and Vaughan CW. (2010) N-arachidonyl-glycine modulates synaptic transmission in superficial dorsal horn. *Br J Pharmacol* **161**: 925-35 [PMID:20860669]
71. Ju P, Aubrey KR and Vandenberg RJ. (2004) Zn²⁺ inhibits glycine transport by glycine transporter subtype 1b. *J Biol Chem* **279**: 22983-91 [PMID:15031290]
72. Karunakaran S, Umapathy NS, Thangaraju M, Hatanaka T, Itagaki S, Munn DH, Prasad PD and Ganapathy V. (2008) Interaction of tryptophan derivatives with SLC6A14 (ATB0,+) reveals the potential of the transporter as a drug target for cancer chemotherapy. *Biochem J* **414**: 343-55 [PMID:18522536]
73. Kim DI, Deutsch HM, Ye X and Schweri MM. (2007) Synthesis and pharmacology of site-specific cocaine abuse treatment agents: restricted rotation analogues of methylphenidate. *J Med Chem* **50**: 2718-31 [PMID:17489581]
74. Knutsen LJ, Andersen KE, Lau J, Lundt BF, Henry RF, Morton HE, Naerum L, Petersen H, Stephensen H and Suzdak PD *et al.* (1999) Synthesis of novel GABA uptake inhibitors. 3. Diaryloxime and diarylvinyloxy derivatives of nipecotic acid and guvacine as anticonvulsant agents. *J Med Chem* **42**: 3447-62 [PMID:10479278]
75. Kristensen AS, Andersen J, Jørgensen TN, Sørensen L, Eriksen J, Loland CJ, Strømgaard K and Gether U. (2011) SLC6 neurotransmitter transporters: structure, function, and regulation. *Pharmacol Rev* **63**: 585-640 [PMID:21752877]
76. Kvist T, Christiansen B, Jensen AA and Bräuner-Osborne H. (2009) The four human gamma-aminobutyric acid (GABA) transporters: pharmacological characterization and validation of a highly efficient screening assay. *Comb Chem High Throughput Screen* **12**: 241-9 [PMID:19275529]
77. Lapinsky DJ, Aggarwal S, Huang Y, Surratt CK, Lever JR, Foster JD and Vaughan RA. (2009) A novel photoaffinity ligand for the dopamine transporter based on pyrovalerone. *Bioorg Med Chem* **17**: 3770-4 [PMID:19442525]
78. Lapinsky DJ, Velagaleti R, Yarravarapu N, Liu Y, Huang Y, Surratt CK, Lever JR, Foster JD, Acharya R and Vaughan RA *et al.* (2011) Azido-iodo-N-benzyl derivatives of threo-methylphenidate (Ritalin, Concerta): Rational design, synthesis, pharmacological evaluation, and dopamine transporter photoaffinity labeling. *Bioorg Med Chem* **19**: 504-12 [PMID:21129986]
79. Li P, Zhang Q, Robichaud AJ, Lee T, Tomesch J, Yao W, Beard JD, Snyder GL, Zhu H and Peng Y *et al.* (2014) Discovery of a tetracyclic quinoxaline derivative as a potent and orally active multifunctional drug candidate for the treatment of neuropsychiatric and neurological disorders. *J Med Chem* **57**: 2670-82 [PMID:24559051]
80. Liu H, Altenbach RJ, Carr TL, Chandran P, Hsieh GC, Lewis LG, Manelli AM, Milicic I, Marsh KC and Miller TR *et al.* (2008) cis-4-(Piperazin-1-yl)-5,6,7a,8,9,10,11,11a-octahydrobenzofuro[2,3-h]quinazolin-2-amine (A-987306), a new histamine H4R antagonist that blocks pain responses against carrageenan-induced hyperalgesia. *J Med Chem* **51**: 7094-8 [PMID:18983139]

81. Lowe 3rd JA, Drozda SE, Fisher K, Strick C, Lebel L, Schmidt C, Hiller D and Zandi KS. (2003) [3H]-(R)-NPTS, a radioligand for the type 1 glycine transporter. *Bioorg Med Chem Lett* **13**: 1291-2 [PMID:12657266]
82. Lowe 3rd JA, Hou X, Schmidt C, David Tingley 3rd F, McHardy S, Kalman M, Deninno S, Sanner M, Ward K and Lebel L *et al.*. (2009) The discovery of a structurally novel class of inhibitors of the type 1 glycine transporter. *Bioorg Med Chem Lett* **19**: 2974-6 [PMID:19410451]
83. Madsen KK, White HS and Schousboe A. (2010) Neuronal and non-neuronal GABA transporters as targets for antiepileptic drugs. *Pharmacol Ther* **125**: 394-401 [PMID:20026354]
84. Mallorga PJ, Williams JB, Jacobson M, Marques R, Chaudhary A, Conn PJ, Pettibone DJ and Sur C. (2003) Pharmacology and expression analysis of glycine transporter GlyT1 with [3H]-(N-[3-(4'-fluorophenyl)-3-(4'phenylphenoxy)propyl])sarcosine. *Neuropharmacology* **45**: 585-93 [PMID:12941372]
85. Maryanoff BE, McComsey DF, Castanzo MJ, Setler PE, Gardocki JF, Shank RP and Schneider CR. (1984) Pyrroloisoquinoline antidepressants. Potent, enantioselective inhibition of tetrabenazine-induced ptosis and neuronal uptake of norepinephrine, dopamine, and serotonin. *J Med Chem* **27**: 943-6 [PMID:6747993]
86. Melia KF and Spealman RD. (1991) Pharmacological characterization of the discriminative-stimulus effects of GBR 12909. *J Pharmacol Exp Ther* **258**: 626-32 [PMID:1678014]
87. Mezler M, Hornberger W, Mueller R, Schmidt M, Amberg MS, Amberg W, Amberg MS, Braje W, Ochse M and Schoemaker H *et al.*. (2008) Inhibitors of GlyT1 affect glycine transport via discrete binding sites. *Mol Pharmacol* **74**: 1705-15 [PMID:18815213]
88. Mingorance-Le Meur A, Ghisdal P, Mullier B, De Ron P, Downey P, Van Der Perren C, Declercq V, Cornelis S, Famelart M and Van Asperen J *et al.*. (2013) Reversible inhibition of the glycine transporter GlyT2 circumvents acute toxicity while preserving efficacy in the treatment of pain. *Br J Pharmacol* **170**: 1053-63 [PMID:23962079]
89. Mladenova G, Annedi SC, Ramnauth J, Maddaford SP, Rakhit S, Andrews JS, Zhang D and Porreca F. (2012) First-in-class, dual-action, 3,5-disubstituted indole derivatives having human nitric oxide synthase (nNOS) and norepinephrine reuptake inhibitory (NERI) activity for the treatment of neuropathic pain. *J Med Chem* **55**: 3488-501 [PMID:22420844]
90. Newman AH, Kline RH, Allen AC, Izenwasser S, George C and Katz JL. (1995) Novel 4'-substituted and 4',4"-disubstituted 3 alpha-(diphenylmethoxy)tropane analogs as potent and selective dopamine uptake inhibitors. *J Med Chem* **38**: 3933-40 [PMID:7562926]
91. Núñez E, López-Corcuera B, Vázquez J, Giménez C and Aragón C. (2000) Differential effects of the tricyclic antidepressant amoxapine on glycine uptake mediated by the recombinant GLYT1 and GLYT2 glycine transporters. *Br J Pharmacol* **129**: 200-6 [PMID:10694221]
92. O'Neill DJ, Adedoyin A, Alfinito PD, Bray JA, Cosmi S, Deecher DC, Fensome A, Harrison J, Leventhal L and Mann C *et al.*. (2010) Discovery of novel selective norepinephrine reuptake inhibitors: 4-[3-aryl-2,2-dioxido-2,1,3-benzothiadiazol-1(3H)-yl]-1-(methylamino)butan-2-ols (WYE-103231). *J Med Chem* **53**: 4511-21 [PMID:20462211]
93. Oh J, Lee S, Kim A, Yoon J, Jang K, Lee DH, Cho S, Lee SR, Yu KS and Chung JY. (2018) Safety, Tolerability, and Pharmacokinetic Characteristics of a Novel Nonopioid Analgesic, VVZ-149 Injections in Healthy Volunteers: A First-in-Class, First-in-Human Study. *J Clin Pharmacol* **58**: 64-73 [PMID:28815639]
94. Omori Y, Nakajima M, Nishimura K, Takahashi E, Arai T, Akahira M, Suzuki T and Kainoh M. (2015) Analgesic effect of GT-0198, a structurally novel glycine transporter 2 inhibitor, in a mouse model of neuropathic pain. *J Pharmacol Sci* **127**: 377-81 [PMID:25837937]
95. Owens MJ, Morgan WN, Plott SJ and Nemeroff CB. (1997) Neurotransmitter receptor and transporter binding profile of antidepressants and their metabolites. *J Pharmacol Exp Ther* **283**: 1305-22 [PMID:9400006]
96. Pearlman RJ, Aubrey KR and Vandenberg RJ. (2003) Arachidonic acid and anandamide have opposite modulatory actions at the glycine transporter, GLYT1a. *J Neurochem* **84**: 592-601 [PMID:12558979]
97. Pechulis AD, Beck JP, Curry MA, Wolf MA, Harms AE, Xi N, Opalka C, Sweet MP, Yang Z and Vellekoop AS *et al.*. (2012) 4-Phenyl tetrahydroisoquinolines as dual norepinephrine and dopamine reuptake inhibitors. *Bioorg Med Chem Lett* **22**: 7219-22 [PMID:23084899]
98. Perry KW, Falcone JF, Fell MJ, Ryder JW, Yu H, Love PL, Katner J, Gordon KD, Wade MR and Man T *et al.*. (2008) Neurochemical and behavioral profiling of the selective GlyT1 inhibitors ALX5407 and LY2365109 indicate a preferential action in caudal vs. cortical brain areas. *Neuropharmacology* **55**: 743-

54 [PMID:18602930]

99. Pinard E, Alanine A, Alberati D, Bender M, Borroni E, Bourdeaux P, Brom V, Burner S, Fischer H and Hainzl D *et al.*. (2010) Selective GlyT1 inhibitors: discovery of [4-(3-fluoro-5-trifluoromethylpyridin-2-yl)piperazin-1-yl][5-methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methylethoxy)phenyl]methanone (RG1678), a promising novel medicine to treat schizophrenia. *J Med Chem* **53**: 4603-14 [PMID:20491477]
100. Pochini L, Seidita A, Sensi C, Scalise M, Eberini I and Indiveri C. (2014) Nimesulide binding site in the B0AT1 (SLC6A19) amino acid transporter. Mechanism of inhibition revealed by proteoliposome transport assay and molecular modelling. *Biochem Pharmacol* **89**: 422-30 [PMID:24704252]
101. Pristupa ZB, Wilson JM, Hoffman BJ, Kish SJ and Niznik HB. (1994) Pharmacological heterogeneity of the cloned and native human dopamine transporter: disassociation of [3H]WIN 35,428 and [3H]GBR 12,935 binding. *Mol Pharmacol* **45**: 125-35 [PMID:8302271]
102. Pérez-Siles G, Morreale A, Leo-Macías A, Pita G, Ortíz AR, Aragón C and López-Corcuera B. (2011) Molecular basis of the differential interaction with lithium of glycine transporters GLYT1 and GLYT2. *J Neurochem* **118**: 195-204 [PMID:21574997]
103. Raffle DM and Chen W. (2004) Binding of [3H]mazindol to cardiac norepinephrine transporters: kinetic and equilibrium studies. *Naunyn Schmiedebergs Arch Pharmacol* **370**: 9-16 [PMID:15300361]
104. Reith ME, Xu C, Zhang L and Coffey LL. (1996) Translocation of dopamine and binding of WIN 35,428 measured under identical conditions in cells expressing the cloned human dopamine transporter. *Naunyn Schmiedebergs Arch Pharmacol* **354**: 295-304 [PMID:8878059]
105. Rosenbrock H, Desch M, Kleiner O, Dorner-Ciossek C, Schmid B, Keller S, Schlecker C, Moschetti V, Goetz S and Liesenfeld KH *et al.*. (2018) Evaluation of Pharmacokinetics and Pharmacodynamics of BI 425809, a Novel GlyT1 Inhibitor: Translational Studies. *Clin Transl Sci* **11**: 616-623 [PMID:30136756]
106. Rotella DP, McFarlane GR, Greenfield A, Grosanu C, Robichaud AJ, Denny RA, Feenstra RW, Núñez-García S, Reinders JH and Neut Mv *et al.*. (2009) Tetrahydrocarbazole-based serotonin reuptake inhibitor/dopamine D2 partial agonists for the potential treatment of schizophrenia. *Bioorg Med Chem Lett* **19**: 5552-5 [PMID:19720528]
107. Rousseau F, Aubrey KR and Supplisson S. (2008) The glycine transporter GlyT2 controls the dynamics of synaptic vesicle refilling in inhibitory spinal cord neurons. *J Neurosci* **28**: 9755-68 [PMID:18815261]
108. Sabatucci JP, Mahaney PE, Leiter J, Johnston G, Burroughs K, Cosmi S, Zhang Y, Ho D, Deecher DC and Trybulski E. (2010) Heterocyclic cycloalkanol ethylamines as norepinephrine reuptake inhibitors. *Bioorg Med Chem Lett* **20**: 2809-12 [PMID:20378347]
109. Saier MH, Yen MR, Noto K, Tamang DG and Elkan C. (2009) The Transporter Classification Database: recent advances. *Nucleic Acids Res* **37**: D274-8 [PMID:19022853]
110. Schousboe A, Madsen KK and White HS. (2011) GABA transport inhibitors and seizure protection: the past and future. *Future Med Chem* **3**: 183-7 [PMID:21428813]
111. Schousboe A, Sarup A, Larsson OM and White HS. (2004) GABA transporters as drug targets for modulation of GABAergic activity. *Biochem Pharmacol* **68**: 1557-63 [PMID:15451399]
112. Semyanov A, Walker MC, Kullmann DM and Silver RA. (2004) Tonically active GABA A receptors: modulating gain and maintaining the tone. *Trends Neurosci* **27**: 262-9 [PMID:15111008]
113. Shobo M, Kondo Y, Yamada H, Mihara T, Yamamoto N, Katsuoka M, Harada K, Ni K and Matsuoka N. (2010) Norzotepine, a major metabolite of zotepine, exerts atypical antipsychotic-like and antidepressant-like actions through its potent inhibition of norepinephrine reuptake. *J Pharmacol Exp Ther* **333**: 772-81 [PMID:20223878]
114. Singer D, Camargo SM, Huggel K, Romeo E, Danilczyk U, Kuba K, Chesnov S, Caron MG, Penninger JM and Verrey F. (2009) Orphan transporter SLC6A18 is renal neutral amino acid transporter B0AT3. *J Biol Chem* **284**: 19953-60 [PMID:19478081]
115. Singh SK, Yamashita A and Gouaux E. (2007) Antidepressant binding site in a bacterial homologue of neurotransmitter transporters. *Nature* **448**: 952-6 [PMID:17687333]
116. Sloan JL and Mager S. (1999) Cloning and functional expression of a human Na(+) and Cl(-)-dependent neutral and cationic amino acid transporter B(0+). *J Biol Chem* **274**: 23740-5 [PMID:10446133]
117. Snyder GL, Vanover KE, Zhu H, Miller DB, O'Callaghan JP, Tomesch J, Li P, Zhang Q, Krishnan V and Hendrick JP *et al.*. (2015) Functional profile of a novel modulator of serotonin, dopamine, and glutamate neurotransmission. *Psychopharmacology (Berl.)* **232**: 605-21 [PMID:25120104]
118. Supplisson S and Roux MJ. (2002) Why glycine transporters have different stoichiometries. *FEBS Lett* **529**: 93-101 [PMID:12354619]

119. Sweetnam PM, Caldwell L, Lancaster J, Bauer Jr C, McMillan B, Kinnier WJ and Price CH. (1993) The role of receptor binding in drug discovery. *J Nat Prod* **56**: 441-55 [PMID:8496700]
120. Talvenheimo J, Fishkes H, Nelson PJ and Rudnick G. (1983) The serotonin transporter-imipramine "receptor". *J Biol Chem* **258**: 6115-9 [PMID:6853478]
121. Tatsumi M, Groshan K, Blakely RD and Richelson E. (1997) Pharmacological profile of antidepressants and related compounds at human monoamine transporters. *Eur J Pharmacol* **340**: 249-58 [PMID:9537821]
122. Thomsen C, Sørensen PO and Egebjerg J. (1997) 1-(3-(9H-carbazol-9-yl)-1-propyl)-4-(2-methoxyphenyl)-4-piperidinol, a novel subtype selective inhibitor of the mouse type II GABA-transporter. *Br J Pharmacol* **120**: 983-5 [PMID:9134205]
123. Trenchard A, Turner P, Pare CM and Hills M. (1975) The effects of protriptyline and clomipramine in vitro on the uptake of 5-hydroxytryptamine and dopamine in human platelet-rich plasma. *Psychopharmacologia* **43**: 89-93 [PMID:1161997]
124. Tsai G, Ralph-Williams RJ, Martina M, Bergeron R, Berger-Sweeney J, Dunham KS, Jiang Z, Caine SB and Coyle JT. (2004) Gene knockout of glycine transporter 1: characterization of the behavioral phenotype. *Proc Natl Acad Sci USA* **101**: 8485-90 [PMID:15159536]
125. Tzschentke TM, Christoph T, Kögel B, Schiene K, Hennies HH, Englberger W, Haurand M, Jahnel U, Cremers TI and Friderichs E *et al.*. (2007) (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol hydrochloride (tapentadol HCl): a novel mu-opioid receptor agonist/norepinephrine reuptake inhibitor with broad-spectrum analgesic properties. *J Pharmacol Exp Ther* **323**: 265-76 [PMID:17656655]
126. Umopathy NS, Ganapathy V and Ganapathy ME. (2004) Transport of amino acid esters and the amino-acid-based prodrug valganciclovir by the amino acid transporter ATB(0,+). *Pharm Res* **21**: 1303-10 [PMID:15290873]
127. Van Orden LJ, Van Dyke PM, Saito DR, Church TJ, Chang R, Smith JA, Martin WJ, Jaw-Tsai S and Stangeland EL. (2013) A novel class of 3-(phenoxy-phenyl-methyl)-pyrrolidines as potent and balanced norepinephrine and serotonin reuptake inhibitors: synthesis and structure-activity relationships. *Bioorg Med Chem Lett* **23**: 1456-61 [PMID:23347683]
128. Vandenberg RJ, Ju P, Aubrey KR, Ryan RM and Mitrovic AD. (2004) Allosteric modulation of neurotransmitter transporters at excitatory synapses. *Eur J Pharm Sci* **23**: 1-11 [PMID:15324920]
129. Vandenberg RJ, Shaddick K and Ju P. (2007) Molecular basis for substrate discrimination by glycine transporters. *J Biol Chem* **282**: 14447-53 [PMID:17383967]
130. Vanslambrouck JM, Bröer A, Thavyogarah T, Holst J, Bailey CG, Bröer S and Rasko JE. (2010) Renal imino acid and glycine transport system ontogeny and involvement in developmental iminoglycinuria. *Biochem J* **428**: 397-407 [PMID:20377526]
131. Vickers T, Dyck B, Tamiya J, Zhang M, Jovic F, Grey J, Fleck BA, Aparicio A, Johns M and Jin L *et al.*. (2008) Studies on a series of milnacipran analogs containing a heteroaromatic group as potent norepinephrine and serotonin transporter inhibitors. *Bioorg Med Chem Lett* **18**: 3230-5 [PMID:18468895]
132. White HS, Watson WP, Hansen SL, Slough S, Perregaard J, Sarup A, Bolvig T, Petersen G, Larsson OM and Clausen RP *et al.*. (2005) First demonstration of a functional role for central nervous system betaine/ γ -aminobutyric acid transporter (mGAT2) based on synergistic anticonvulsant action among inhibitors of mGAT1 and mGAT2. *J Pharmacol Exp Ther* **312**: 866-74 [PMID:15550575]
133. Wiles AL, Pearlman RJ, Rosvall M, Aubrey KR and Vandenberg RJ. (2006) N-Arachidonyl-glycine inhibits the glycine transporter, GLYT2a. *J Neurochem* **99**: 781-6 [PMID:16899062]
134. Wong EH, Sonders MS, Amara SG, Tinholt PM, Piercey MF, Hoffmann WP, Hyslop DK, Franklin S, Porsolt RD and Bonsignori A *et al.*. (2000) Reboxetine: a pharmacologically potent, selective, and specific norepinephrine reuptake inhibitor. *Biol Psychiatry* **47**: 818-29 [PMID:10812041]
135. Xu X, Wei Y, Guo Q, Zhao S, Liu Z, Xiao T, Liu Y, Qiu Y, Hou Y and Zhang G *et al.*. (2018) Pharmacological Characterization of H05, a Novel Serotonin and Noradrenaline Reuptake Inhibitor with Moderate 5-HT_{2A} Antagonist Activity for the Treatment of Depression. *J Pharmacol Exp Ther* **365**: 624-635 [PMID:29615471]
136. Yadav A, Shah N, Tiwari PK, Javed K, Cheng Q, Aidhen IS and Bröer S. (2020) Novel Chemical Scaffolds to Inhibit the Neutral Amino Acid Transporter B⁰AT1 (SLC6A19), a Potential Target to Treat Metabolic Diseases. *Front Pharmacol* **11**: 140 [PMID:32180718]
137. Yamashita A, Singh SK, Kawate T, Jin Y and Gouaux E. (2005) Crystal structure of a bacterial homologue

- of Na⁺/Cl⁻-dependent neurotransmitter transporters. *Nature* **437**: 215-23 [PMID:16041361]
138. Yee BK, Balic E, Singer P, Schwerdel C, Grampp T, Gabernet L, Knuesel I, Benke D, Feldon J and Mohler H *et al.*. (2006) Disruption of glycine transporter 1 restricted to forebrain neurons is associated with a procognitive and antipsychotic phenotypic profile. *J Neurosci* **26**: 3169-81 [PMID:16554468]
139. Yu XC, Zhang W, Oldham A, Buxton E, Patel S, Nghi N, Tran D, Lanthorn TH, Bomont C and Shi ZC *et al.*. (2009) Discovery and characterization of potent small molecule inhibitors of the high affinity proline transporter. *Neurosci Lett* **451**: 212-6 [PMID:19159658]
140. Zaia KA and Reimer RJ. (2009) Synaptic Vesicle Protein NTT4/XT1 (SLC6A17) Catalyzes Na⁺-coupled Neutral Amino Acid Transport. *J Biol Chem* **284**: 8439-48 [PMID:19147495]
141. Zeng Z, O'Brien JA, Lemaire W, O'Malley SS, Miller PJ, Zhao Z, Wallace MA, Raab C, Lindsley CW and Sur C *et al.*. (2008) A novel radioligand for glycine transporter 1: characterization and use in autoradiographic and in vivo brain occupancy studies. *Nucl Med Biol* **35**: 315-25 [PMID:18355687]
142. Zhang HX, Hyrc K and Thio LL. (2009) The glycine transport inhibitor sarcosine is an NMDA receptor co-agonist that differs from glycine. *J Physiol (Lond.)* **587**: 3207-20 [PMID:19433577]
143. Zhang P, Jørgensen TN, Loland CJ and Newman AH. (2013) A rhodamine-labeled citalopram analogue as a high-affinity fluorescent probe for the serotonin transporter. *Bioorg Med Chem Lett* **23**: 323-6 [PMID:23168018]
144. Zhou J, He R, Johnson KM, Ye Y and Kozikowski AP. (2004) Piperidine-based cocaine/modafinil hybrid ligands as highly potent monoamine transporter inhibitors: efficient drug discovery by rational lead hybridization. *J Med Chem* **47**: 5821-4 [PMID:15537337]
145. Zipp GG, Barbosa J, Green MA, Terranova KM, Fink C, Yu XC, Nouraldeen A, Wilson A, Savelieva K and Lanthorn TH *et al.*. (2014) Novel inhibitors of the high-affinity L-proline transporter as potential therapeutic agents for the treatment of cognitive disorders. *Bioorg Med Chem Lett* **24**: 3886-90 [PMID:25037917]