DOI: 10.1002/cmdc.200600097

Design, Synthesis, and In Vivo Efficacy of Glycine Transporter-1 (GlyT1) Inhibitors Derived from a Series of [4-Phenyl-1-(propylsulfonyl)piperidin-4-yl]methyl Benzamides

Craig W. Lindsley,*[a] Zhijian Zhao,[a] William H. Leister,[a] Julie O'Brien,[b] Wei Lemaire,[b] David L. Williams, Jr.,[b] Tsing-Bau Chen,[b] Raymond S. L. Chang,[b] Maryann Burno,[b] Marlene A. Jacobson,[b] Cyrille Sur,[b] Gene G. Kinney,[b] Douglas J. Pettibone,[b] Philip R. Tiller,[c] Sheri Smith,[c] Nancy N. Tsou,[d] Mark E. Duggan,[a] P. Jeffrey Conn,[b, e] and George D. Hartman[a]

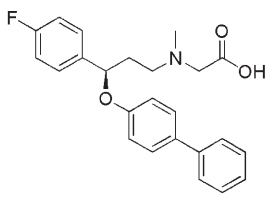
As prevalent as diabetes or Alzheimer's disease, schizophrenia affects 1% of the world's adult population. With an onset in late adolescence, schizophrenia, a complex psychiatric disorder characterized by a combination of negative (social withdrawal, blunting of emotional responses, anhedonia) and positive (hallucinations, delusions, paranoia, disorganized behavior) symptoms along with significant cognitive dysfunction, is a debilitating disease that requires lifelong, daily maintenance therapy at a cost to society of $65 billion a year.[1] The prevailing dogma by which schizophrenia has been managed for decades states that excessive dopaminergic transmission in the forebrain underlies the disease—the so-called "dopamine hypothesis" or "dopamine hyperfunction hypothesis".[2] The rationale for this hypothesis is based on the fact that all clinically relevant antipsychotic agents, both typical (haloperidol) and atypical (clozapine, olanzapine), possess significant antagonist activity at the dopamine D_2 receptor. However, these agents have a slow onset of action and mainly treat the positive symptoms of schizophrenia, with limited to no effect on the negative and cognitive symptoms, thereby representing a substantial unmet medical need.[3]

The *N*-methyl-D-aspartate (NMDA) receptor antagonist phencyclidine (PCP) has been shown to induce the positive, negative, and cognitive symptoms of schizophrenia in healthy patients, and elicit a resurgence of symptoms in stable schizophrenics.[4] In the clinic, the observation that administration of the NMDA receptor co-agonist glycine provides a modest improvement in schizophrenic patients suggests that increasing NMDA receptor activation may provide a therapeutic benefit.[5] These observations led to the NMDA receptor hypofunction hypothesis as an alternative theory for the underlying cause of schizophrenia.[6] According to this hypothesis, any agent that can potentiate NMDA receptor currents, either directly by action on modulatory sites on the NMDA receptor (such as the glycine co-agonist binding site) or indirectly by activation of GPCRs known to potentiate NMDA receptor function (such as mGluR5), has the potential to ameliorate the symptoms of schizophrenia.[7]

Glycine is a required co-agonist for the NMDA receptor and modulates NMDA-dependent excitatory neurotransmission; therefore, one approach to enhance NMDA receptor function is to pharmacologically increase synaptic glycine levels.[8] In the CNS, synaptic glycine levels are regulated by two Na^+/Cl^--dependent transporters, glycine transporter type 1 (GlyT1) and glycine transporter type 2 (GlyT2), which share 50% homology at the amino acid level.[9] Importantly, GlyT1 distribution mirrors NMDA receptor expression suggesting that GlyT1 is optimally positioned to modulate glycine levels near NMDA-receptor-expressing synapses.[10] This strategy has strong clinical support. Both glycine **1** and sarcosine **2** (a weak selective GlyT1 inhibitor) have been shown to improve the positive, negative, and cognitive symptoms of schizophrenia; however, poor brain penetration and pharmacokinetics limit their clinical utility (Figure 1).[11] The first GlyT1 inhibitors were analogues of sarcosine, such as NFPS **3**, that provided support for the NMDA receptor hypofunction hypothesis, by selectively elevating gly-

1 glycine

2 sarcosine



3 NFPS, ALX-5407

Figure 1. Structures of glycine (co-agonist of the NMDA receptor), sarcosine (a weak GlyT1 inhibitor), and NFPS (ALX-5047), the prototypical sarcosine-derived GlyT1 inhibitor.

[a] *Dr. C. W. Lindsley, Z. Zhao, W. H. Leister, M. E. Duggan, G. D. Hartman*
Department of Medicinal Chemistry, Technology Enabled Synthesis Group
Merck Research Laboratories
P.O. Box 4, West Point, PA 19486 (USA)
Fax: (+1) 215-652-6345
E-mail: craig_lindsley@merck.com

[b] *J. O'Brien, W. Lemaire, Dr. D. L. Williams, Jr., T.-B. Chen, Dr. R. S. L. Chang, M. Burno, Dr. M. A. Jacobson, Dr. C. Sur, Dr. G. G. Kinney, Dr. D. J. Pettibone, Dr. P. J. Conn*
Department of Neuroscience
Merck Research Laboratories, West Point (USA)

[c] *Dr. P. R. Tiller, S. Smith*
Department of Drug Metabolism
Merck Research Laboratories, West Point (USA)

[d] *N. N. Tsou*
Department of Medicinal Chemistry, X-Ray Crystallography, Rahway (USA)

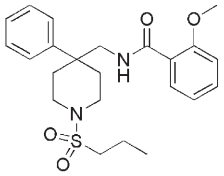
[e] *Dr. P. J. Conn*
VICB Program in Drug Discovery, Department of Pharmacology, Vanderbilt Medical Center, Nashville, TN 37232 (USA)

Supporting information for this article is available on the WWW under http://www.chemmedchem.org or from the author.

cine levels and reversing PCP-induced behaviors in preclinical animal models (Figure 1).[1,2,5] Due to a variety of side effects, many pharmaceutical companies launched efforts to identify non-sarcosine-derived GlyT1 inhibitors.[12] While the patent literature is rich with novel, non-sarcosine-derived GlyT1 inhibitors, reports in the primary literature are only now beginning to accrue.[13]

In an effort to develop new antipsychotics based on the NMDA receptor hypofunction hypothesis of schizophrenia, our laboratory initiated a program to discover potent, non-sarcosine-derived GlyT1 inhibitors. A high-throughput screening (HTS) campaign, employing a [^{14}C]glycine uptake SPA assay, identified a novel [4-phenyl-1-(propylsulfonyl)piperidin-4-yl]-methyl benzamide, **4**, as a potent, reversible inhibitor of GlyT1 (IC_{50} = 135 nM) with high selectivity against GlyT2.[14] Compound **4** was originally prepared for a potassium channel program; therefore, eliminating this ancillary pharmacology was a key objective. In this communication, we report on the optimization, pharmacology, and in vivo efficacy of advanced analogues of **4** that further validate the NMDA receptor hypofunction hypothesis in a preclinical behavioral model of prepulse inhibition where known antipsychotics provide similar, positive results.

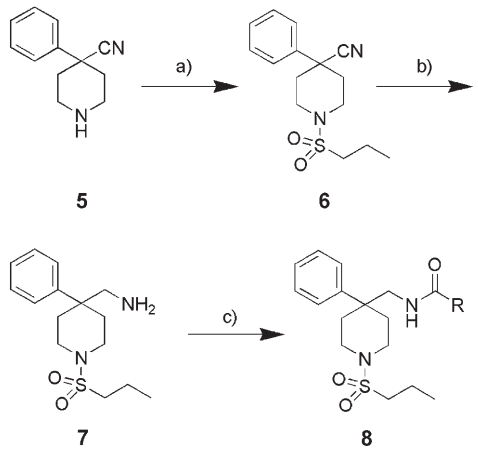
An iterative analogue library synthesis approach was employed to rapidly develop structure–activity relationships (SAR) for **4**. The initial strategy was to replace the 2-OMe benzamide moiety with a diverse assortment of functionalized benzamides



4

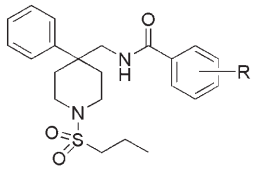
Figure 2. GlyT1 HTS lead, GlyT1 IC_{50} = 135 nM.

in an effort to improve GlyT1 potency and abolish potassium channel activity. Commercially available 4-cyano-4-phenyl piperidine **5** was converted to the sulfonamide **6** and then hydrogenated with Raney nickel to deliver the key aminomethyl intermediate **7** in excellent yields. Intermediate **7** was then acylated under standard solution phase parallel synthesis conditions to deliver over 200 benzamide analogues, **8** (Scheme 1). As shown in Table 1, a variety of functionalized benzamides are tolerated, and not only dramatically improve GlyT1 potency while maintaining high selectivity, but also abolish the ancillary potassium channel activity. Clearly, the 2-OMe benzamide moiety was the key to the undesired ancillary potassium channel activity, as unsubstituted phenyl **8a**, 2-halogen substituted analogues **8c** and **8d**, and 3-OMe and 4-OMe (data not shown), possessed no potassium channel activity. In general, a wide range of substituents on the phenyl ring was tolerated. The 6-chloroanthranilic benzamide analogue **8h** proved to be an extremely potent inhibitor (GlyT1 IC_{50} = 3.6 nM). Due to a



Scheme 1. Synthesis of [4-Phenyl-1-(propylsulfonyl)piperidin-4-yl]methyl benzamides **8**. Reagents and conditions: a) *n*-$PrSO_2Cl$, DIEA, DCM (95%); b) cat. Raney Ni, H_2, MeOH (95%); c) (1) RCOCl, PS-DIEA, DCM, (2) PS-Trisamine, or (1) RCOOH, PS-DCC, HOBt, DCM, (2) MP-CO_3^{2-} (70–99%). All compounds purified by mass-guided preparative HPLC to analytical purity (>98%).[15]

Table 1. Structures and activities of benzamide analogues **8**.



8

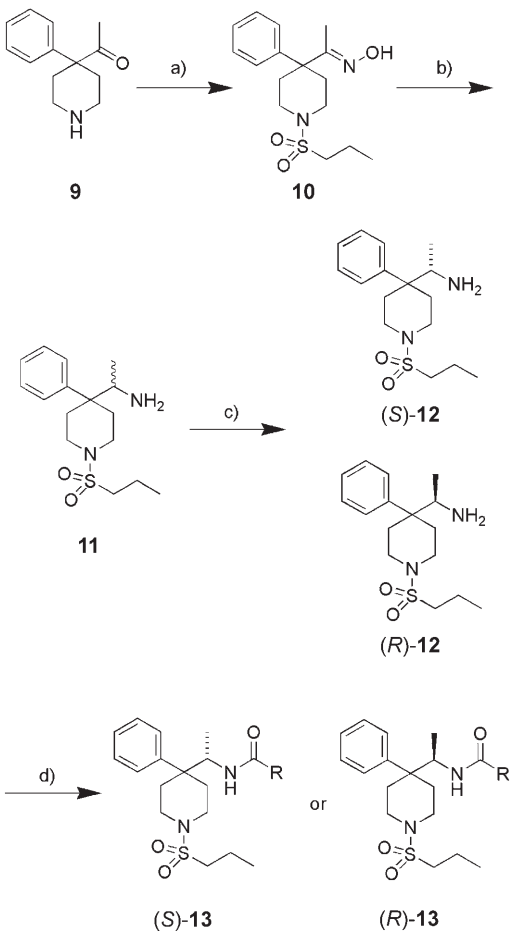
Compd	R	GlyT1 IC_{50} [nM][a]	GlyT2 IC_{50} [nM][a]	TauT IC_{50} [nM][a]	K^+ IC_{50} [nM][b]
8a	H	66.2	>30000	>30000	>30000
8b	2-OCF_3	53.4	>30000	>30000	>30000
8c	2-Cl	10.6	>30000	>30000	>30000
8d	2-F	32.6	>30000	>30000	>30000
8e	2,4-diF	32.1	>30000	>30000	>30000
8f	2,4-diCl	13.4	>30000	>30000	>30000
8g	2-NH_2, 6-F	15.3	>30000	>30000	>30000
8h	2-NH_2, 6-Cl	3.6	>30000	>30000	>30000

[a] IC_{50} values are the average of at least three determinations; TauT is the taurine transporter. [b] K^+ is the undesired potassium channel.

clean ancillary profile, **8h** was further evaluated as a potential proof of concept compound in rat behavioral models; however, **8h** was a rodent *p*-glycoprotein (P-gp) substrate and could not be developed further.[16]

In an effort to diminish P-gp susceptibility and to enhance potency, libraries were prepared that incorporated a methyl group at the α-position of the benzamide nitrogen. Commercially available 4-acetyl-4-phenyl piperidine **9** was converted into the corresponding oxime **10,** and that compound was subsequently hydrogenated with Raney nickel to provide racemic α-methyl amine **11**. Chiral preparative HPLC easily separated the two enantiomeric α-methyl amines, (*S*)-**12** and (*R*)-**12**. Absolute stereochemistry was established by single crystal X-

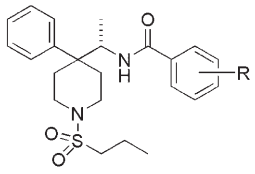
ray crystallography of a Mosher's amide analogue (**15**) of (*S*)-**12**.[17] With enantiomers (*S*)-**12** and (*R*)-**12** in hand, each chiral α-methyl amine was acylated under standard solution phase parallel synthesis conditions to deliver ~100 benzamide analogues (*S*)-**13** and (*R*)-**13** (Scheme 2).



Scheme 2. Synthesis of (1*S*)- or (1*R*)-[4-Phenyl-1-(propylsulfonyl)piperidin-4-yl]ethyl benzamides (*S*)-**13** or (*R*)-**13**. Reagents and conditions: a) (1) *n*-$PrSO_2Cl$, DIEA, DCM (95%), (2) NH_2OH, pyridine, reflux; (90%) b) cat. Raney Ni, H_2, MeOH (95%); c) Chiral HPLC; d) (1) RCOCl, PS-DIEA, DCM, (2) PS-Trisamine, or (1) RCOOH, PS-DCC, HOBt, DCM, (2) MP-CO_3^{2-} (70–99%). All compounds purified by mass-guided preparative HPLC to analytical purity (>98%).[15]

Unexpectedly, all of the (*R*)-**13** analogues were uniformly inactive (GlyT1 IC_{50} > 3000 nM). In contrast, the (*S*)-**13** analogues were either as potent as the *des*-methyl analogues **8**, or significantly more potent (up to 10-fold), yet maintained high selectivity relative to GlyT2, TauT, and the ancillary potassium channel. As shown in Table 2, the simple unsubstituted phenyl analogue (*S*)-**13a** (GlyT1 IC_{50} = 6.5 nM) is 10-fold more potent than the des-methyl analogue **8a** (GlyT1 IC_{50} = 66.1 nM, Table 1) and is uniformly potent against both rat and mouse GlyT1. Of the 100 analogues prepared, the introduction of the chiral α-methyl group afforded a number of extremely potent GlyT1 inhibitors for further evaluation, such as (*S*)-**13b** and (*S*)-**13f**. However, (*S*)-**13h**, the chiral α-methyl analogue of **8h**, did not exhibit heightened potency for human GlyT1 (IC_{50} = 2.6 nM),

Table 2. Structures and activities of (*S*)-**13** analogues.



(*S*)-**13**

Compd	R	GlyT1 (h) IC_{50} [nM][a]	GlyT1 (r) IC_{50} [nM][a]	GlyT1 (m) IC_{50} [nM][a]
(*S*)-**13a**	H	6.3	2.1	9.2
(*S*)-**13b**	2-OCF_3	11.1	6.3	23
(*S*)-**13c**	2-Cl	18.6	14.7	nd
(*S*)-**13d**	2-F	16.1	16.7	nd
(*S*)-**13e**	2,4-diF	153	25.2	nd
(*S*)-**13f**	2,4-diCl	3.7	1.8	25.2
(*S*)-**13g**	2-NH_2, 6-F	12.8	9.4	14.1
(*S*)-**13h**	2-NH_2, 6-Cl	2.6	2.1	5.1

[a] IC_{50} values are the average of at least three determinations; (h) = human; (r) = rat; (m) = mouse; nd = not determined. All compounds > 30,000 nM versus GlyT2, TauT and K^+ channel.

but provided improved inhibition of rat and mouse GlyT1 (IC_{50} = 2.1 nM and 5.1 nM, respectively).

Of these potent analogues, (*S*)-**13h** was selected for further evaluation as a proof of concept compound. Due to the P-gp issue observed with **8h**, brain penetration of (*S*)-**13h** was examined. Clearly, (*S*)-**13h** was not subject to P-gp efflux in vitro in either human or mouse P-gp assays (B-A/A-B ratios of 1.1 and 2.1, respectively) and (*S*)-**13h** displayed excellent passive permeability ($Papp = 28.0 \times 10^{-6}$ cm s^{-1}).[16] In addition, (*S*)-**13h** possessed an ideal log P (2.83) for a CNS agent, a 6.2% free fraction (protein binding = 93.8%) and displayed no significant off-target activities. Rat pharmacokinetic studies demonstrated that (*S*)-**13h** was a moderate clearance compound (Cl = 22 mL min^{-1} kg^{-1}) with a 1.2 hour half-life and modest oral bioavailability (%F = 12). Based on these data, (*S*)-**13h** was advanced into microdialysis and mouse prepulse inhibition studies.

The ability of (*S*)-**13h** to selectively increase glycine levels in the prefrontal cortex (PFC) of freely moving rats was then evaluated.[18] Average basal levels of extracellular glycine were determined to be ~5 μM. After 40 min of basal measurements, (*S*)-**13h** was administered intravenously (i.v.) at 1 mg kg^{-1}, 3 mg kg^{-1}, or 10 mg kg^{-1}. As shown in Figure 3a, a rapid and sustained increase in PFC extracellular levels of glycine was observed at all three doses of (*S*)-**13h**. At the 10 mg kg^{-1} dose, the maximal increase in glycine was observed 20 min post-dose and afforded an over threefold increase in extracellular glycine ([Gly] ~17 μM or 340% of basal control) with brain levels for (*S*)-**13h** of 1.9 μM. Importantly, (*S*)-**13h** selectively increased glycine levels and had no effect on other amino acids such as glutamate, serine, threonine, alanine and taurine (Figure 3b).

As (*S*)-**13h** selectively increased glycine in rat PFC, we then evaluated its ability to enhance prepulse inhibition (PPI) of the

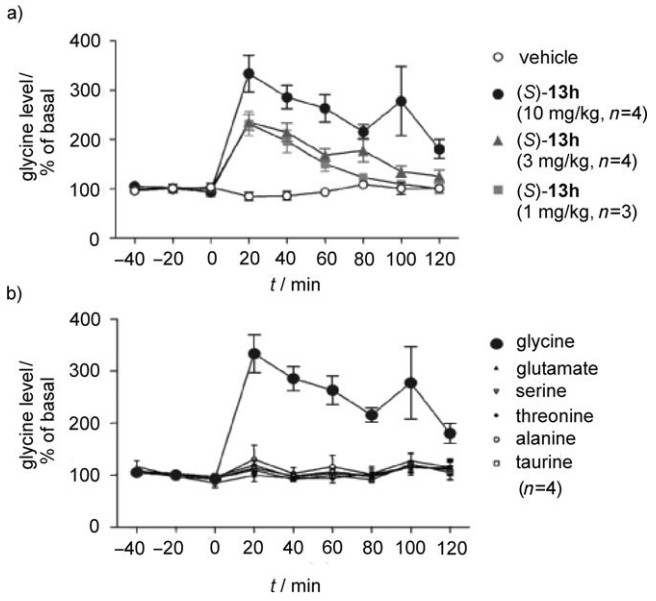


Figure 3. Increase in extracellular glycine after i.v. administration of (*S*)-**13h**. a) At three doses of (*S*)-**13h** a significant increase in PFC extracellular levels of glycine was observed. Maximal increase was observed at 20 min post-dose (340% of basal control). b) Increase in PFC extracellular levels of glycine by (*S*)-**13h** was selective, with no increase observed for other amino acids.

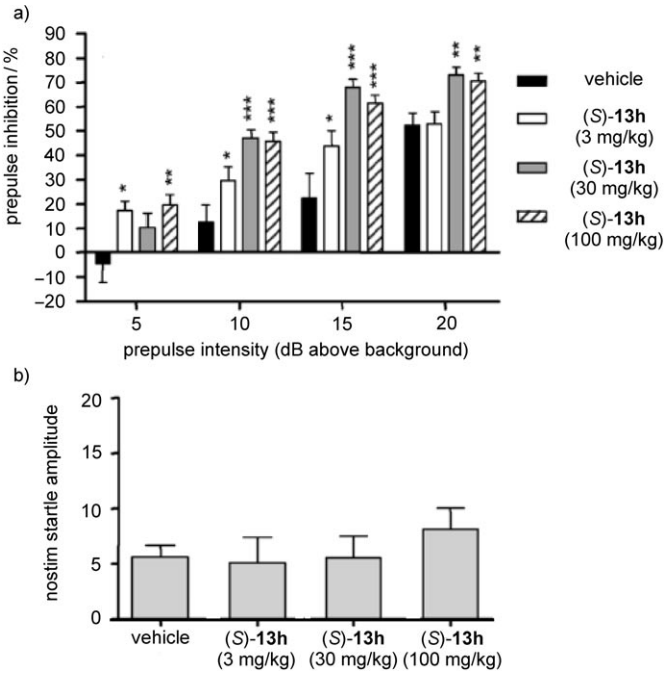


Figure 4. a) The effect of vehicle and three doses of (*S*)-**13h** (3, 10, and 100 mg kg^{-1}, s.c.) on PPI in DBA/2J mice at four prepulse intensities (5–20 dB above background). Asterisks represent a significant difference from the vehicle group: * $p<0.05$, ** $p<0.01$, *** $p<0.001$. Error bars represent SEM. $n=21$–23 per group. b) The effect of vehicle and (*S*)-**13h** on startle amplitude during no-stimulus trials with the same mice represented in a).

rodent acoustic startle response.[19] PPI is a measure of sensorimotor gating, known to be deficient in schizophrenic patients. Thus, an enhancement in PPI is consistent with an antipsychotic profile. Previous work by Kinney demonstrated that NFPS **3** enhances PPI in DBA/2J mice, a strain with low levels of basal PPI, with a level of efficacy comparable to the atypical antipsychotic clozapine.[20] In the present study, (*S*)-**13h** was found to significantly enhance PPI at three doses (3 mg kg^{-1}, 30 mg kg^{-1}, and 100 mg kg^{-1} s.c.) and at four prepulse intensities (5–20 dB above background) in DBA/2 J mice (Figure 4a). Moreover, (*S*)-**13h** had no effect on basal startle amplitude during no-stimulus trials at all three doses relative to vehicle, indicating that (*S*)-**13h** possessed no sedative properties (Figure 4b). Brain levels of (*S*)-**13h** ranged from 400 nM to 2,300 nM during the time course of the PPI experiment. Thus, (*S*)-**13h**, by selectively increasing extracellular glycine levels in the PFC through inhibition of GlyT1, enhanced performance significantly in a behavioral model of sensorimotor gating in which well characterized antipsychotics show similar effects.

In summary, an HTS campaign identified **4** as a potent, reversible and selective GlyT1 inhibitor. An iterative analogue library synthesis approach rapidly developed SAR for this series and led directly to the discovery of (*S*)-**13h**, a novel, centrally active GlyT1 inhibitor. (*S*)-**13h** selectively increased PFC extracellular glycine levels (340% of basal control levels) with no effect on other amino acids. By selective blockade of GlyT1, (*S*)-**13h** significantly enhanced PPI in DBA/2 J mice, a rodent behavioral model sensitive to antipsychotic treatment. These data provide strong support for the NMDA receptor hypofunction hypothesis of schizophrenia and the development of novel antipsychotics. Additional refinements to (*S*)-**13h** and related series of GlyT1 inhibitors are in progress and will be reported in due course.

Keywords: GlyT1 · hypoglutamatergy · NMDA hypofunction · schizophrenia · structure–activity relationships

[1] a) N. C. Andreasen, *Brain Res. Rev.* **2000**, *31*,106–112; b) M. Karayiorgou, *Clin. Neurosci. Res.* **2001**, *1*, 158–163; c) J. H. Meador-Woodruff, D. J. Healy, *Brain Res. Rev.* **2000**, *31*, 288–294.

[2] a) P. J. Marino, P. J. Conn, *Curr. Drug Targets: CNS Neurol. Disord.* **2002**, *1*, 1–16; b) A. Carlsson, M. Lindqvist, *Acta Pharmacol. Toxicol.* **1963**, *20*, 140–144; c) P. Seeman, T. Lee, M. Chau-Wong, K. Wong, *Nature* **1976**, *261*, 717–719; d) P. Seeman, T. Lee, *Science* **1975**, *188*, 1217–1219.

[3] a) A. Bertolino, A. Breier, J. H. Callicott, C. Adler, V. S. Mattay, M. Shapiro, J. A. Frank, D. Pickar, D. R. Weinberger, *Neuropsychopharmacology* **1999**, *22*, 125–132; b) M. Laruelle, A. Abi-Dargham, C. H. van Dyck, R. Gil, C. D. D'Souza, J. Erdos, E. McCance, W. Rosenblatt, C. Fingado, S. S. Zoghbi, R. M. Baldwin, J. P. Seibyl, J. H. Krystal, D. S. Charney, R. B. Innis, *Proc. Natl. Acad. Sci. USA* **1996**, *93*, 9235–9240; c) M. Laruelle, C. D. D'Souza, R. M. Baldwin, A. Abi-Dargham, S. J. Kanes, C. L. Fingado, J. P. Seibyl, S. S. Zoghbi, M. B. Bowers, P. Jatlow, D. S. Charney, R. B. Innis, *Neuropsychopharmacology* **1997**, *17*, 162–174; d) B. M. Angrist, in *Amphetamine and its analogues* (Eds.: S. Cho), Academic Press, San Diego, CA, **1994**, pp. 387–414.

[4] a) D. C. Javitt, S. R. Zukin, *Am. J. Psychiatry* **1991**, *148*, 1301–1308; b) J. W. Olney, N. B. Farber, *Arch. Gen. Psychiatry* **1995**, *52*, 998–1007.

[5] a) D. C. Javitt, I. Zylberman, S. R. Zukin, U. Heresco-Levy, J. P. Lindenmayer, *Am. J. Psychiatry* **1994**, *151*, 1234–1236; b) E. Leiderman, I. Zylberman, S. R. Zukin, T. B. Cooper, D. C. Javitt, *Biol. Psychiatry* **1996**, *39*, 213–215; c) U. Heresco-Levy, D. Javitt, M. Ermilov, C. Mordel, A. Horowitz, D. Kelly, *Br. J. Psychiatry* **1996**, *169*, 610–617; d) U. Heresco-Levy, Javitt, D.C; M. Ermilov, C. Mordel, G. Silipo, M. Lichtenstein, *Arch. Gen. Psychiatry* **1999**, *56*, 29–36; e) U. Heresco-Levy, M. Ermilov, P. Lichtenberg, G.

Bar, D. C. Javitt, *Biol. Psychiatry* **2004**, *55*, 165 – 171; f) G. Tsai, P. Yang, L. C. Chung, N. Lange, J. T. Coyle, *Biol. Psychiatry* **1998**, *44*, 1081 – 1089.
[6] J. W. Olney, J. W. Newcomer, N. B. Farber, *J. Psychiatry Res.* **1999**, *33*, 523 – 533.
[7] a) D. L. Williams, Jr., C. W. Lindsley, *Curr. Top. Med. Chem.* **2005**, *5*, 825 – 846; b) C. W. Lindsley, S. E. Wolkenberg, W. D. Shipe, C. R. Theberge, D. L. Williams, Jr., C. Sur, G. G. Kinney, *Curr. Topics Med. Chem.* in press, and references therein.
[8] a) W. Danysz, A. C. Parsons, *Pharmacol. Rev.* **1998**, *50*, 597 – 664; b) K. E. Smith, L. A. Borden, P. R. Hartig, T. Branchek, R. L. Weinshank, *Neuron* **1992**, *8*, 927 – 935.
[9] a) B. Borowsky, E. Mezey, B. J. Hoffman, *Neuron* **1993**, *10*, 851 – 863; b) Q. R. Liu, B. Lopez-Corcuera, S. Mandiyan, H. Nelson, N. Nelson, *J. Biol. Chem.* **1993**, *268*, 22 802 – 22 808; c) K. M. Kim, S. F. Kingsmore, H. Han, *Mol. Pharmacol.* **1994**, *45*, 608 – 617; d) J. A. Morrow, I. T. Collie, D. R. Dunbar, G. B. Walker, M. Shahid, D. R. Hill, *FEBS Lett.* **1998**, *439*, 334 – 340.
[10] a) F. Zarfa, J. Gomeza, L. Olivares, C. Aragon, C. Gimenez, *Eur. J. Neurosci.* **1995**, *7*, 1342 – 1352; b) F. Zafra, C. Aragon, L. Olivares, N. C. Danbolt, C. Giminez, J. Storm-Mathisen, *J. Neurosci.* **1995**, *15*, 3952 – 3969.
[11] a) B. N. Atkinson, S. C. Bell, M. De Vivo, L. R. Kowalski, S. M. Lechner, V. I. Ognyanov, C. -S. Tham, C. Tsai, J. Jia, D. Ashton, and M. A. Klitenick *Mol. Pharm.* **2001**, *60*, 1414 – 1420; b) K. R. Aubrey, R. J. Vandenberg, *Br. J. Pharmacol.* **2001**, *134*, 1429 – 1436.
[12] For excellent reviews, see: a) A. Slassi, I. Egle, *Expert Opin. Ther. Pat.* **2004**, *14*, 201 – -214; b) G. G. Kinney, C. Sur, *Neurosci. Drug Disc.* **2005**, *3*, 35 – 43, and references therein.
[13] a) For an excellent review, see: J. A. Lowe III, *Expert Opin. Ther. Pat.* **2005**, *15*, 1657 – 1662 and references therein; For recent publications on non-sarcosine-derived GlyT1 inhibitors, see: b) R. Depoortere, G. Daraganzanil, G. Estenne-Bouhtou, A. Coste, C. Lanneau, C. Desvignes, M. Ponce, M. Heaulme, V. Santucci, et al., *Neuropsychopharmacology* **2005**, *30*, 1963 – 1985; c) E. Pinard, S. M. Ceccarelli, H. Stadler, D. Alberati, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 349 – 353; d) S. M. Ceccarelli, E. Pinard, H. Stadler, D. Alberati, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 354 – 357.
[14] J. B. Williams, P. J. Mallorga, W. Lemaire, D. L. Williams, Jr., S. Na, S. Patel, J. P. Conn, D. J. Pettibone, C. Austin, C. Sur, *Anal. Biochem.* **2003**, *321*, 31 – 37.
[15] W. H. Leister, K. A. Strauss, D. D. Wisnoski, Z. Zhao, C. W. Lindsley, *J. Comb. Chem.* **2003**, *5*, 322 – 329.
[16] J. H. Hochman, M. Yamazaki, T. Ohe, J. H. Lin, *Curr. Drugs Methods Cancer Treat.* **2002**, *3*, 257 – 273.
[17] See the Supporting Information section for further details of X-ray crystal structure data. CCDC 603055 (**15**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data request/cif.
[18] K. J. Whitehead, J.-P. Manning, C. G. S. Smith, N. G. Bowery, *Brain Res.* **2001**, *910*, 192 – 194.
[19] M. A. Geyer, K. Krebs-Thompson, D. L. Braff, N. R. Swerdlow, *Psychopharmacology* **2001**, *156*, 117 – 154.
[20] G. G. Kinney, C. Sur, M. Burno, P. J. Mallorga, J. Williams, D. J. Figueroa, M. Wittman, W. Lemaire, P. J. Conn, *J. Neurosci.* **2003**, *23*, 7586 – 7591.

Received: April 14, 2006
Published online on June 29, 2006

