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Brief Article

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Synthesis and Biological Evaluation of 3-Biphenyl-4-yl-4-phenyl-4*H*-1,2,4-triazoles as Novel Glycine Transporter 1 Inhibitors

Takashi Sugane,*[,†] Takahiko Tobe,[†] Wataru Hamaguchi,[†] Itsuro Shimada,[†] Kyoichi Maeno,[†] Junji Miyata,[†] Takeshi Suzuki,[†] Tetsuya Kimizuka,[‡] Atsuyuki Kohara,[†] Takuma Morita,[§] Hitoshi Doihara,[†] Kyouko Saita,[†] Masaki Aota,[†] Masako Furutani,[†] Yoshiaki Shimada,[†] Noritaka Hamada,[†] Shuichi Sakamoto,[⊥] and Shin-ichi Tsukamoto[†]

[†]*Drug Discovery Research, Astellas Pharma Inc., 21, Miyukigaoka, Tsukuba-shi, Ibaraki 305-8585, Japan,* [‡]*Intellectual Property, Astellas Pharma Inc., 2-3-11, Nihonbashi-Honcho, Chuo-ku, Tokyo 103-8411, Japan,* [§]*Astellas Research Technologies Co., Ltd., 21, Miyukigaoka, Tsukuba-shi, Ibaraki 305-8585, Japan, and* [⊥]*Technology, Astellas Pharma Inc., 3-17-1, Hasune, Itabashi, Tokyo 174-8612, Japan*

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We describe the preparation and evaluation of a novel series of glycine transporter 1 (GlyT1) inhibitors derived from a high-throughput screening hit. The SAR studies resulted in the discovery of 3-biphenyl-4-yl-4-(2-fluorophenyl)-5-isopropyl-4*H*-1,2,4-triazole (**6p**). A pharmacokinetic study was also conducted and revealed that **6p** had excellent oral bioavailability and ameliorated learning impairment in passive avoidance tasks in mice.

Introduction

In the central nervous system (CNS[a]), specific sodium/chloride-dependent transporters regulate glycine levels in the synapse. The actions of glycine are terminated by reuptake via two high affinity glycine transporters referred to as glycine transporter 1 (GlyT1) and glycine transporter 2 (GlyT2).[1,2] GlyT1 has a widespread distribution in forebrain areas such as cortex and hippocampus. GlyT1 is thought to be colocalized with the *N*-methyl-D-aspartate (NMDA) receptors,[3] controlling NMDA receptor function. The expression of GlyT2 is limited to the spinal cord, brain stem, and cerebellum, and GlyT2 is therefore thought to control the function of the strychnine-sensitive glycine receptor.

The hypofunction of NMDA receptors is related to various human diseases. For example, the functional deterioration of the NMDA receptors may have a role in schizophrenia with clinical studies demonstrating that positive, negative, and cognitive symptoms in schizophrenic patients are ameliorated with glycine, D-serine (a glycine site agonist of the NMDA receptors), and sarcosine (a weak GlyT1 inhibitor) when added to conventional therapy.[4]

The NMDA receptors are also associated with memory and learning.[5] For example, the activation of the NMDA receptors is involved in the formation of long-term potentiation (LTP), which is considered one of the mechanisms of memory and learning at the neuronal level.[6]

These findings suggest that medications aimed at inhibiting the activity of GlyT1 and thereby activating the function of the NMDA receptors may be useful as therapeutic agents for schizophrenia, dementia, and related disorders.

N-[3-(4′-Fluorophenyl)-3-(4′-phenylphenoxy)propyl]sarcosine (**1**),[7] an analogue of sarcosine, was reported as a selective glycine transporter inhibitor (Figure 1), with preclinical in vivo studies in rodents demonstrating **1** to have similar efficacy as clinically useful antipsychotics,[8,9] and therefore, many sarcosine analogues were subsequently synthesized and reported in the literature.[2,10−13] Pharmaceutical companies, however, recently launched new efforts to investigate nonsubstrate based inhibitors, and a wide variety of compounds without a carboxylate group have subsequently been disclosed.[2,10−13] Among these compounds, [4-(3-fluoro-5-trifluoromethylpyridin-2-yl)piperazin-1-yl][5-methanesulfonyl-2-((*S*)-2,2,2-trifluoro-1-methylethoxy)-phenyl]methanone (**2**)[14] was reported to show a beneficial effect in schizophrenic patients in a recent phase II clinical trial.

Here, we report the identification of structurally novel non-sarcosine derived GlyT1 inhibitors useful for studying the effects of GlyT1 inhibition in vivo. We also describe the detailed structure−activity relationships (SARs) that we have established on our novel GlyT1 inhibitors. Our initial effort began with the high-throughput screening (HTS) campaign, which led to the discovery of 3-biphenyl-4-yl-4-(2-methoxy-phenyl)-5-methyl-4*H*-1,2,4-triazole (**3**) with a novel structure. Compound **3** was selected as a lead for the following SAR studies.

Chemistry

The 1,2,4-triazole derivatives were prepared as illustrated in Schemes 1−3, with Scheme 1 showing the first general method in which the 1,3,4-oxadiazole derivatives were utilized as intermediates. 4-Phenylbenzoyl hydrazide (**4**) was first converted to diacyl hydrazides. Subsequent cyclization using $POCl_3$ gave 1,3,4-oxadiazoles **5**. Reactions of **5** with amines under acidic conditions produced the corresponding 1,2,4-triazole derivatives **6a**−**q**.[15]

*To whom correspondence should be addressed. Phone: +81-29-863-6678. Fax: +81-29-852-5387. E-mail: takashi.sugane@jp.astellas.com.

[a] Abbreviations: ACSF, artificial cerebrospinal fluid; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; CNS, central nervous system; GABA, γ-aminobutyric acid; GlyT, glycine transporter; HTS, high-throughput screening; NBS, *N*-bromosuccinimide; NMDA, *N*-methyl-D-aspartate; PAMPA, parallel artificial membrane permeability assay; SAR, structure−activity relationship; 5-HT, 5-hydroxytryptamine.

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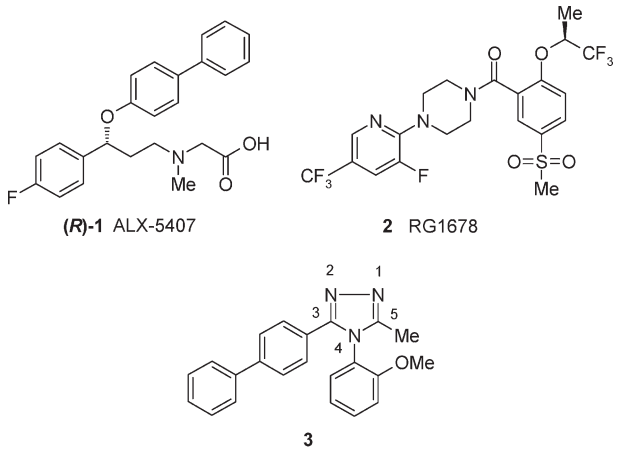
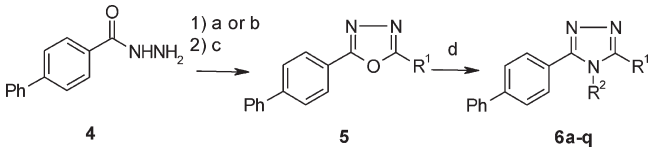


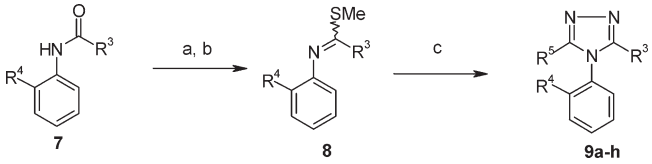
Figure 1. GlyT1 inhibitors.

Scheme 1. Synthesis of 1,2,4-Triazole Derivatives via 1,3,4-Oxadiazoles[a]



[a] Reagents and conditions: (a) $(R^1CO)_2O$, pyridine; (b) R^1COCl, Et_3N, THF; (c) $POCl_3$, 100 °C; (d) R^2-NH_2, $TsOH \cdot H_2O$ or (1*S*)-10-camphorsulfonic acid, 160 °C.

Scheme 2. Synthesis of 1,2,4-Triazole Derivatives via Methyl Thioimidates[a]



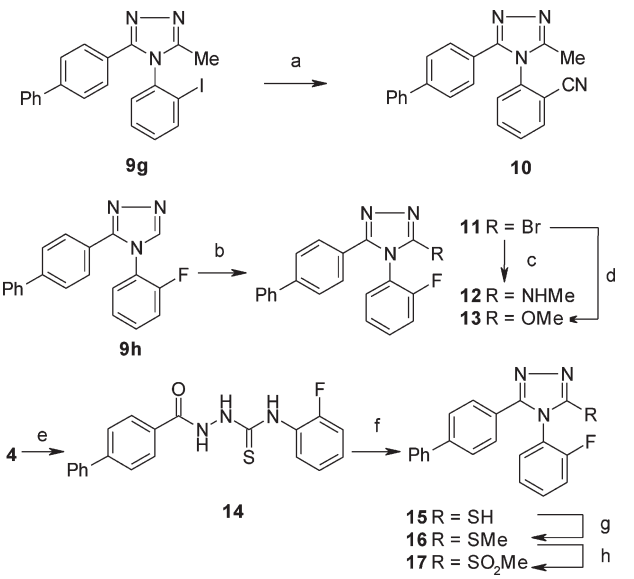
[a] Reagents and Conditions: (a) Lawesson's reagent, toluene, 110 °C; (b) MeI, K_2CO_3, CH_3CN, 50 °C; (c) $R^5CONHNH_2$, $TsOH.H_2O$ or (1*S*)-10-camphorsulfonic acid, DMF, 160 °C.

The second general method utilizes the reaction of thioimidates with acyl hydrazides as shown in Scheme 2. Amides **7** were reacted with Lawesson's reagent to afford thioamides, which were then treated with MeI and K_2CO_3 in acetonitrile to obtain thioimidates **8**. These compounds were coupled with acyl hydrazides and heated under acidic conditions to produce the desired 1,2,4-triazole derivatives **9a**−**h**. Compounds **10**, **12**, **13**, **16**, and **17** were prepared as shown in Scheme 3.

Results and Discussion

We prepared analogues of **3**, incorporating changes that would aid in elucidating the structural features required for inhibiting GlyT1. Assays for the inhibitory activities of GlyT1 were performed according to reported protocols utilizing [^{3}H]glycine uptake into rat C6 glioma cells.[16] This method was validated using the published GlyT1 inhibitors; for example, compound **1** showed potent inhibitory activity (IC_{50} = 0.0089 μM). The GlyT2 inhibitory activities were evaluated in a manner similar to the GlyT1 assay using rat brainstem cells. The typical GlyT2 inhibitor 4-benzyloxy-3,5-dimethoxy-*N*-[1-(dimethylaminocyclopentyl)methyl]benzamide (Org-25543)[17] showed potent activity (IC_{50} = 0.022 μM) on this assay.

Scheme 3. Synthesis of 1,2,4-Triazole Derivatives[a]



[a] Reagents and conditions: (a) $Pd(PPh_3)_4$, $Zn(CN)_2$, DMF, 140 °C; (b) NBS, AcOH, CCl_4, reflux; (c) $MeNH_2/H_2O$, sealed tube, 200 °C; (d) NaOMe, MeOH, reflux; (e) 2-fluorophenylisothiocyanate, EtOH; (f) NaOH aq., reflux; (g) MeI, K_2CO_3, CH_3CN; (h) Oxone, MeOH, H_2O, 70 °C.

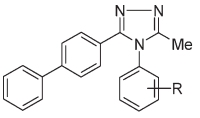
We investigated the influence of the 2-methoxyphenyl moiety on the 4-position of the triazole ring (Table 1). Removal of methoxy group of **3** resulted in the retention of GlyT1 inhibitory activity (**6a**, IC_{50} = 0.88 μM). We therefore subsequently examined the necessity of the phenyl group on the 4-position of the triazole ring by replacing it with a cyclohexyl or isopropyl group. The cyclohexyl substituted analogue showed a 5-fold loss of activity (**6b**, IC_{50} = 5.2 μM), and the isopropyl derivative showed far less activity (**6c**, IC_{50} = 35 μM) compared to **6a**, suggesting that the aromatic group at 4-position of the triazole is important for GlyT1 inhibition.

Having elucidated the necessity of the benzene ring, we then investigated the effect of substitution at the ortho, meta, and para positions of the phenyl group using fluoro analogues **6d**−**f**. While meta and para substituted analogues **6e** and **6f** showed less potent activity (**6e**, IC_{50} = 3.0 μM; **6f**, IC_{50} > 30 μM), the ortho substituted analogue **6d** showed a 4-fold improvement in activity (**6d**, IC_{50} = 0.19 μM) compared to the unsubstituted analogue **6a**.

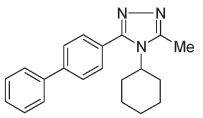
These results directed us to investigate other ortho substituents for the phenyl group on the 4-position of the triazole. Interestingly, many compounds showed equipotent GlyT1 inhibitory activity compared to **6d**. While both electron-withdrawing groups (**6g**, **6h**, and **10**) and electron-donating groups (**6i**, **6j**) were well tolerated (IC_{50} = 0.10−0.39 μM), when we added several alkyl groups to the structure, activities decreased in order of steric bulkiness (**6k**−**m**, **9a**). These results suggest that smaller rather than larger functional groups are favorable for conferring activity, whereas the electrostatic factor of the substituents is not as important. Despite obtaining some potent GlyT1 inhibitors, none of the compounds in Table 1 showed high selectivity against the GlyT2 isoform, with compound **6d**, for example, showing equipotent inhibitory activity for GlyT2 (IC_{50} = 0.34 μM; selectivity GlyT2/GlyT1 = 1.8).

We therefore turned our attention toward modification of other positions of the triazole. With the 2-fluorophenyl group

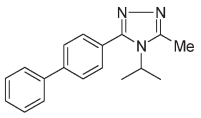
Table 1. In Vitro GlyT1 Inhibitory Activities of 1,2,4-Triazole Derivatives **3**, **6a**−**m**, **9a**, **10**



3, 6a, 6d-m, 9a, 10



6b

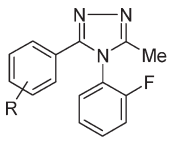


6c

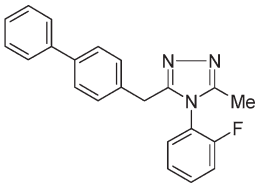
compd	R	IC$_{50}$ (μM)[a] rGlyT1	rGlyT2	selectivity[b]
3	2-OMe	1.8 ± 0.30	1.7 ± 0.46	0.94
6a	H	0.88 ± 0.11	1.4 ± 0.41	1.6
6b		5.2 ± 1.9	ND[e]	ND[e]
6c		35 ± 4.9	ND[e]	ND[e]
6d	2-F	0.19 ± 0.073	0.34 ± 0.11	1.8
6e	3-F	3.0 ± 1.2	ND[e]	ND[e]
6f	4-F	> 30 (42%)[c]	ND[e]	ND[e]
6g	2-Cl	0.19 ± 0.050	0.28 ± 0.049	1.5
6h	2-CF$_3$	0.39 ± 0.070	0.60 ± 0.020	1.5
10	2-CN	0.10 ± 0.028	0.26 ± 0.092	2.6
6i	2-OH	0.24 ± 0.090	0.68 ± 0.25	2.8
6j	2-Me	0.30 ± 0.075	0.78 ± 0.13	2.6
6k	2-Et	0.92 ± 0.10	ND[e]	ND[e]
6l	2-(*n*-Pr)	3.8 ± 0.66	ND[e]	ND[e]
6m	2-(*i*-Pr)	11 ± 0.74	ND[e]	ND[e]
9a	2-Ph	> 10 (15%)[d]	ND[e]	ND[e]

[a] Values are the mean ± standard error for three experiments. [b] Ratio of the IC$_{50}$ (μM) values for rGlyT2/rGlyT1. [c] % inhibition at 30 μM (solubility limit). [d] % inhibition at 10 μM (solubility limit). [e] ND: not determined.

Table 2. In Vitro GlyT1 Inhibitory Activities of 1,2,4-Triazole Derivatives **6d**, **9b**−**f**



6d, 9b-e



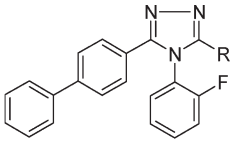
9f

compd	R	rGlyT1 IC$_{50}$ (μM)[a]
6d	4-Ph	0.19 ± 0.073
9b	H	> 100 (22%)[b]
9c	4-(*c*-C$_6$H$_{11}$)	9.8 ± 0.20
9d	2-Ph	62 ± 6.8
9e	3-Ph	70 ± 15
9f		27 ± 0.88

[a] Values are the mean ± standard error for three experiments. [b] % inhibition at 100 μM (solubility limit).

fixed at the 4-position of the triazole ring, variation around the biphenyl moiety of **6d** was explored (Table 2). Removal of the terminal phenyl group (**9b**, IC$_{50}$ > 100 μM) and replacement with a cyclohexyl group (**9c**, IC$_{50}$ = 9.8 μM) reduced activity. Likewise, translocation of a phenyl group to ortho (**9d**, IC$_{50}$ = 62 μM) and meta (**9e**, IC$_{50}$ = 70 μM) positions and insertion of a methylene linker between the triazole ring and biphenyl moiety (**9f**, IC$_{50}$ = 27 μM) were found to be detrimental to activity.

Table 3. In Vitro GlyT1 Inhibitory Activities of 1,2,4-Triazole Derivatives **6d**,**n**−**q**, **9h**, **12**, **13**, **16**, **17**



6d, 6n-q, 9h, 12, 13, 16, 17

compd	R	IC$_{50}$ (μM)[a] rGlyT1	rGlyT2	selectivity[b]
6d	Me	0.19 ± 0.073	0.34 ± 0.11	1.8
9h	H	2.3 ± 0.85	ND[d]	ND[d]
12	NHMe	0.083 ± 0.014	0.11 ± 0.030	1.3
13	OMe	0.51 ± 0.068	0.99 ± 0.18	1.9
16	SMe	1.0 ± 0.090	ND[d]	ND[d]
17	SO$_2$Me	6.5 ± 0.79	ND[d]	ND[d]
6n	CF$_3$	> 10 (11%)[c]	ND[d]	ND[d]
6o	Et	0.22 ± 0.050	0.23 ± 0.092	1.0
6p	*i*-Pr	0.37 ± 0.020	3.3 ± 0.53	9.2
6q	*t*-Bu	2.6 ± 0.72	ND[d]	ND[d]

[a] Values are the mean ± standard error for three experiments. [b] Ratio of the IC$_{50}$ (μM) values for rGlyT2/rGlyT1. [c] % inhibition at 10 μM (solubility limit). [d] ND: not determined.

Table 4. In Vitro Membrane Permeability Study (PAMPA)[a]

compd	P_e (10^{-6} cm/s) at pH 5.0[b]	at pH 6.5[b]
3	39	34
12	44	42
13	39	43
6o	37	35
6p	44	53

[a] pION membrane lipid was used. [b] pH of donor buffer.

Considering the results summarized in Tables 1 and 2, we assumed that 3-biphenyl-4-yl-4-phenyl-4*H*-1,2,4-triazole was an essential structure for this class of GlyT1 inhibitors, and with the exception of ortho substitution of the phenyl group at the 4-postion of the triazole, it was quite sensitive to modification.

SAR studies around the 5-position of the triazole were then conducted (Table 3). Removal of the methyl group resulted in a 10-fold loss of activity (**9h**, IC$_{50}$ = 2.3 μM). We therefore prepared some derivatives with electron-donating groups, and interestingly, introduction of a methylamino moiety led to a slight improvement in GlyT1 inhibitory activity (**12**, IC$_{50}$ = 0.083 μM). While **12** was the most potent compound in this series, it showed no selectivity against GlyT2 (GlyT2/GlyT1 = 1.3). Further, while some other electron-donating groups such as methoxy (**13**) and methylsulfanyl groups (**16**) were introduced, they showed a 2- to 5-fold loss of GlyT1 inhibitory activity (**13**, IC$_{50}$ = 0.51 μM; **16**, IC$_{50}$ = 1.0 μM) and replacement with electron-withdrawing groups such as SO$_2$Me or CF$_3$ was also unsuccessful (**17**, IC$_{50}$ = 6.5 μM; **6n**, IC$_{50}$ > 10 μM).

While Et and *i*-Pr analogues **6o**, **6p** maintained GlyT1 inhibitory activity (**6o**, IC$_{50}$ = 0.22 μM; **6p**, IC$_{50}$ = 0.37 μM), replacement with a *t*-Bu group resulted in > 10-fold loss of activity (**6q**, IC$_{50}$ = 2.6 μM). Interestingly, the *i*-Pr derivative **6p** had moderate selectivity for GlyT1 against GlyT2 (GlyT2/GlyT1 = 9.2), suggesting that GlyT2

Table 5. Pharmacokinetic Parameters for Compound **6p**[a]

species	route	dose (mg/kg)	$t_{1/2}$ (h)	AUC (ng·h/mL)	V_d (L/kg)	CL (mL/(min·kg))	C_{max} (ng/mL)	F (%)
mouse	iv	1	4.2	783	7.8	21		
	po	3	2.0	1419			365	60

[a] Each value is the mean for $n = 3$ measurements.

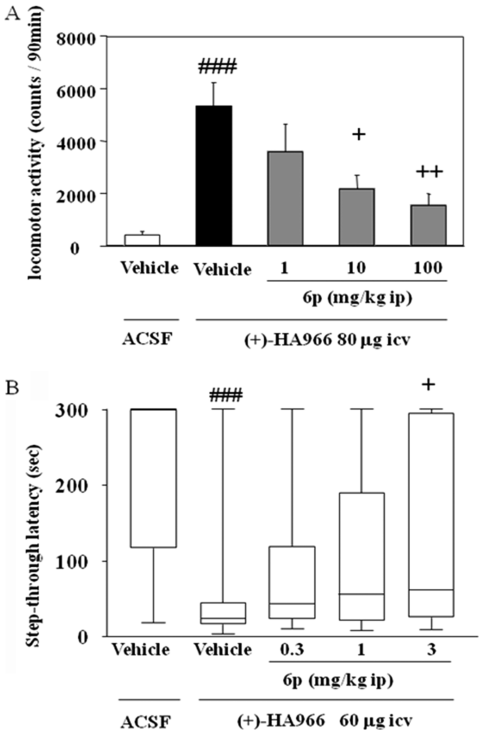


Figure 2. (A) Effect of **6p** on (+)-HA966-induced hyperlocomotion in monoamine-depleted mice. (+)-HA966 was administrated intracerebroventricularly (icv). The data represent the mean ± SEM ($n = 16$ in each group): (###) $p < 0.001$ vs (ACSF + vehicle) group (Student's t test); (+) $p < 0.05$, (++) $p < 0.01$ vs [(+)-HA966 + vehicle] group (ANOVA followed by Dunnett's test). (B) Effect of **6p** on (+)-HA966-induced learning impairment in passive avoidance tasks in mice. (+)-HA966 was administrated intracerebroventricularly. Upper and lower whiskers represent the highest and lowest values in each group, respectively. Upper and lower bars in boxes represent 75 and 25%ile values in each group respectively. The bars in boxes represent median values in each group ($n = 29-32$): (###) $p < 0.001$ vs (ACSF + vehicle) group (Wilcoxon rank sum test); (+) $p < 0.05$ vs [(+)-HA966 + vehicle] group (two-tailed Steel test).

inhibitory activity was more sensitive for steric bulkiness around the 5-position of the triazole than that of GlyT1.

During the SAR studies of these novel GlyT1 inhibitors, we derived **6p**, which showed improved GlyT1 inhibitory activity and moderate selectivity against GlyT2 compared to the HTS hit **3**. We also investigated other off-target activities of **6p** where a panel of receptors (NMDA, AMPA, strychnine-sensitive Gly, dopamine D_2, 5-$HT_{1A/1B/2A}$, and vasopressin V_{1A} receptors) and transporters (glutamate, GABA, dopamine, norepinephrine, and 5-HT transporters) were screened, with **6p** showing less than 30% affinity or inhibitory activity in all assays at 10 μM.

Compound **6p** was then profiled in an in vitro membrane permeability study (Table 4). The parallel artificial membrane permeability assay (PAMPA) has been widely used in the pharmaceutical industry as a high-throughput permeability assay to predict oral absorption.[18] Evaluation by PAMPA revealed that **6p** has a high membrane permeability ($P_e = 53 \times 10^{-6}$ cm/s at pH 6.5), with the other 1,2,4-triazole derivatives **3**, **12**, **13**, and **6o** also showing high membrane permeability, suggesting that this series of GlyT1 inhibitors exhibits a high potential for oral absorption by passive transcellular diffusion.

We next examined **6p** in a single dose in vivo pharmacokinetic (PK) study in mice (Table 5), and as expected from the results of the PAMPA, **6p** showed high oral bioavailability ($F = 60\%$). In addition, **6p** also showed good brain permeability (brain/plasma ratio: 1.5−2.1) in mice.

The good brain permeability of **6p** directed us to assess the in vivo behavioral effects on hyperlocomotion induced by (+)-3-amino-1-hydroxypyrrolid-2-one [(+)-HA966, an antagonist for Gly binding sites on the NMDA receptors][19] in monoamine-depleted mice. As shown in Figure 2A, **6p** dose-dependently attenuated the locomotor activity,[20] suggesting that **6p** increases the extracellular level of glycine, which indirectly replaces the antagonist from glycine binding sites of the NMDA receptors. Compound **1** also blocked the hyperlocomotion at a dose of 10 mg/kg ip in this assay,[21] showing equipotent activity to **6p**. Considering in vitro GlyT1 inhibitory activities between **1** and **6p**, the good CNS permeability of **6p** may have contributed to its in vivo behavioral potency.

Lastly, we evaluated the effect of **6p** on (+)-HA966-induced learning impairment in passive avoidance tasks in mice. The step-through latency (the time required for the mice to cross the sensor of the dark room from the opening of the door) was measured and adopted as an indicator of learning ability. As shown in Figure 2B, **6p** prolonged the step-through latency at a dose of 3 mg/kg ip, indicating that **6p** ameliorated learning impairment induced by (+)-HA966. This in vivo result supports the view that GlyT1 inhibitors may be effective for treatment of cognitive dysfunction based on the hypoglutamatergic theory of schizophrenia.

Conclusion

Through the iterative processes of synthesis and biological evaluation starting from the HTS hit compound **3**, we successfully established the SARs in this series of GlyT1 inhibitors, demonstrating that the 3-bipheny-4-yl-4-phenyl-4*H*-1,2,4-triazole moiety is an essential core for this novel class of non-sarcosine-derived GlyT1 inhibitors. Among the compounds prepared in this series, **6p** had improved GlyT1 inhibitory activity and selectivity against GlyT2 compared to the HTS hit compound **3**. In addition, **6p** had high membrane permeability, high oral bioavailability in mice and displayed good CNS penetration. Furthermore, **6p** effectively antagonized (+)-HA966-induced hyperlocomotion in monoamine-depleted mice and ameliorated learning impairment induced by (+)-HA966.

Experimental Section

Chemistry. General. Melting points were determined using a Büchi B-545 or Yanaco MP-500D micromelting apparatus and

were uncorrected. ^{1}H NMR spectra were recorded on a JEOL JMN-LA-300 or JEOL JMN-EX-400, and the chemical shifts were expressed in δ (ppm) values with trimethylsilane as an internal reference (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad peak). Mass spectra (MS) were recorded on a Hitachi M-80 or JEOL JMS-LX2000 spectrometer. HPLC analyses were conducted on Hitachi L-7000 system using a TSKgel ODS-80TM column with UV 254 nm detection. Elemental analyses were performed with Yanaco MT-5 (C, H, N), Elementar Vario EL III (C, H, N), and Dionex DX-500 (S, halogene) instruments, and results were within ±0.4% of theoretical values. The purities of tested compounds were found to be above 95% as determined by elemental analyses.

3-Biphenyl-4-yl-4-(2-fluorophenyl)-5-methyl-4*H*-1,2,4-triazole (6d). To a mixture of 2-(4-biphenyl)-5-methyl-1,3,4-oxadiazole (3.00 g, 12.7 mmol) and 2-fluoroaniline (3.70 mL, 38 mmol) was added *p*-toluenesulfonic acid monohydrate (0.300 g, 1.60 mmol), and the resultant mixture was stirred at 160 °C for 72 h. After cooling at room temperature, the mixture was purified by column chromatography on silica gel ($CHCl_3$/MeOH = 97/3) to give crude **6d** as a brown solid. The solid was recrystallized from EtOAc−hexane to give **6d** (3.24 g, 78%) as a colorless powder: mp 162−164 °C; ^{1}H NMR (DMSO-d_6) δ 2.37 (3H, s), 7.21−7.44 (6H, m), 7.48−7.57 (7H, m); MS (FAB) *m*/*z* 330 (MH^+). Anal. ($C_{21}H_{16}N_3F$) C, H, N, F.

Compounds **6a**−**c**, **6e**−**q** were prepared by a method similar to that described for **6d**.

3-Biphenyl-4-yl-4-(2-fluorophenyl)-5-isopropyl-4*H*-1,2,4-triazole (6p). Mp 201−204 °C; ^{1}H NMR (DMSO-d_6) δ 1.15 (3H, d, *J* = 6.8 Hz), 1.28 (3H, d, *J* = 6.8 Hz), 2.69−2.84 (1H, m), 7.34−7.56 (7H, m), 7.63−7.72 (6H, m), 7.82 (1H, ddd, *J* = 9.3, 7.7, 1.7 Hz); MS (FAB) *m*/*z* 358 (MH^+). Anal. ($C_{23}H_{20}N_3F$) C, H, N, F.

4-(2-Fluorophenyl)-3-methyl-5-phenyl-4*H*-1,2,4-triazole (9b). A mixture of methyl N-(2-fluorophenyl)ethanimidothioate (300 mg, 1.64 mmol), benzohydrazide (223 mg, 1.64 mmol), (1*S*)-10-camphorsulfonic acid (57.0 mg, 0.250 mmol), and *N*,*N*-dimethylformamide (DMF, 0.5 mL) was stirred at 160 °C for 1 h. After cooling at room temperature, the mixture was partitioned between $CHCl_3$ and water and the organic layer was then washed with $NaHCO_3$ (aq), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH = 20/1) to give crude **9b** as a brown solid. The solid was recrystallized from EtOAc−hexane to give **9b** (140 mg, 34%) as a colorless powder: mp 139−141 °C; ^{1}H NMR (DMSO-d_6) δ 2.24 (3H, s), 7.33−7.72 (9H, m); MS (FAB) *m*/*z* 254 (MH^+). Anal. ($C_{15}H_{12}N_3F$) C, H, N, F.

Compounds **9a**, **9c**−**h** were prepared by a method similar to that described for **9b**.

Supporting Information Available: Synthesis of **10**, **12**, and **13**−**17**; analytical data for final compounds; additional behavioral studies; biological evaluations. This material is available free of charge via the Internet at http://pubs.acs.org.

Note Added after ASAP Publication. This manuscript published ASAP on December 9, 2010 with an error in Scheme 3. The correct version was published on December 14, 2010.

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(20) We did not observe any significant change in locomotor activity of the naive mice treated only by compound **6p** (10−100 mg/kg ip). See Supporting Information.

(21) See Supporting Information.