Synthesis and Biological Activity of Conformationally Restricted Analogues of Milnacipran: (1*S*,2*R*)-1-Phenyl-2-[(*R*)-1-amino-2-propynyl]-*N*,*N*-diethylcyclopropanecarboxamide Is a Novel Class of NMDA Receptor Channel Blocker

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Conformationally restricted analogues of (±)-(*Z*)-2-aminomethyl-1-phenyl-*N*,*N*-diethylcyclopropanecarboxamide [milnacipran, (±)-**1**] were designed on the basis of its characteristic cyclopropane structure and were synthesized enantioselectively to develop efficient NMDA receptor antagonists. Among these analogues, (1*S*,2*R*)-1-phenyl-2-[(*R*)-1-amino-2-propynyl]-*N*,*N*-diethylcyclopropanecarboxamide (**2d**) had one of the most potent affinities for the receptor, with a K_i value of 0.29 μM. The blockade of NMDA receptor channels expressed by *Xenopus* oocytes by **2d** was investigated in detail, and **2d** was identified as a new class of open channel blocker against this receptor.

Introduction

Various antagonists to NMDA (*N*-methyl-D-aspartic acid) receptors have been developed[1−5] since such receptors may be involved in both chronic and acute neurodegenerative disorders.[1] Some of these antagonists have been shown to be effective in experimental models of epilepsy and stroke.[1−3] Unfortunately, currently available noncompetitive inhibitors have serious behavioral effects[4a,b] and cause neuronal vacuolization,[4c] while competitive inhibitors are often inactive in vivo because of their poor permeability through the blood−brain barrier.[5] Therefore, another type of efficient NMDA receptor antagonist is eagerly desired.

(±)-(*Z*)-2-Aminomethyl-1-phenyl-*N*,*N*-diethylcyclopropanecarboxamide [milnacipran, (±)-**1**],[6] a clinically efficient antidepressant due to competitive inhibition of the re-uptake of serotonin (5-HT) in the CNS,[7] has also been recognized as a new class of noncompetitive NMDA receptor antagonist.[8] However, the binding affinity of (±)-**1** for the NMDA receptor is not very high. We designed and synthesized four types of conformationally restricted analogues of (±)-**1** with different stereochemistries; i.e., **2** (type-1) and **3** (type-2), and their enantiomers ***ent-2*** (type-3) and ***ent-3*** (type-4), as shown in Figure 1. In these analogues, an alkyl group introduced at the α-position of the amino function of (±)-**1** restricts the location of the amino group in space, which is essential for the binding to the NMDA receptor,[8] due to steric repulsion from the diethylcarbamoyl group.[9a] Therefore, the conformation of these compounds can be limited, depending on the configuration of the alkyl group introduced, and this hypothesis has been supported by X-ray crystallographic analyses,[9a] NMR experiments,[10] and molecular orbital calculations.[9d] Biological evaluations of these compounds have shown that (1) conformational restriction can improve the activity; (2) analogues with a (1*S*,2*R*)-configuration (type-1 and type-2) are more potent than the corresponding enantiomers (type-3 and type-4), and type-1 analogues are more potent than the corresponding type-2 analogues; and (3) introduction of a substituent bulkier than an ethyl group, such as a butyl or a phenyl group, at the 1′-position significantly reduces the activity. Thus, we found that analogues with a type-1 configuration, i.e.; **2a**, **2b**, and **2c**, were potent NMDA receptor antagonists which significantly inhibited the binding of [^{3}H] MK-801, with IC_{50} values about 30-fold stronger than that of (±)-**1**.[9d]

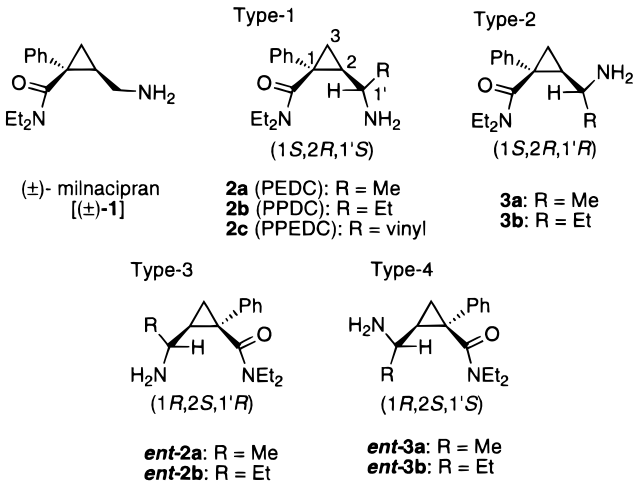

Figure 1.

In this paper, we describe the synthesis and biological evaluation of other conformationally restricted analogues of milnacipran as NMDA receptor antagonists. Considering the above findings, we designed conformationally restricted analogues with a type-1 configuration and a sterically small carbon substituent, such as an ethynyl or a cyano group, at the 1′-position, as shown

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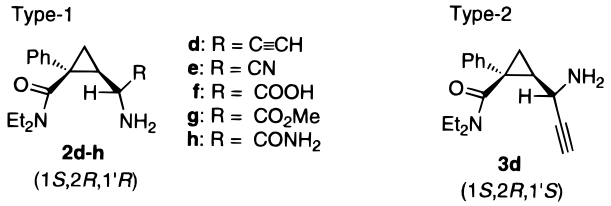


Figure 2.

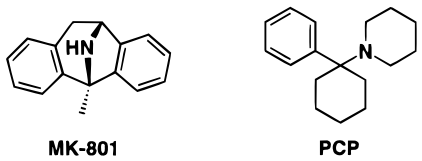
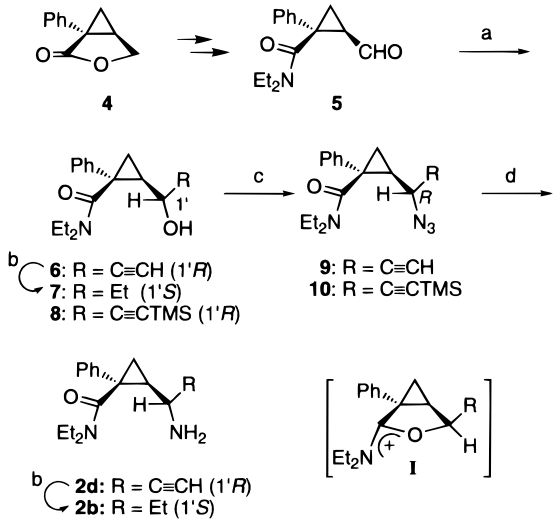


Figure 3.

Scheme 1[a]



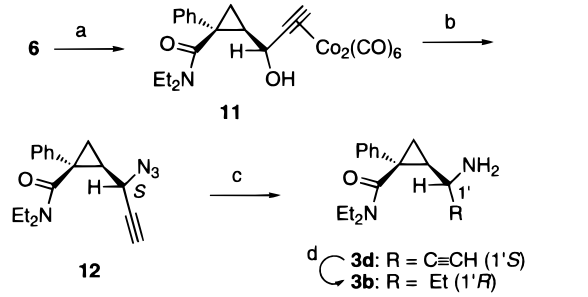
[a] Reagents: (a) RMgBr or RLi; (b) H_2, Pd-C; (c) NaN_3, CBr_4, Ph_3P; (d) Ph_3P, py, then NH_4OH.

in Figure 2. We also synthesized 1′-carbamoyl, -methoxycarbonyl, and -carboxylic acid derivatives, **2f**−**h**, to investigate the effects of the functional characteristics of the 1′-substituent on the activity. In this study, (1*S*,2*R*)-1-phenyl-2-[(*R*)-1-amino-2-propynyl]-*N*,*N*-diethylcyclopropanecarboxamide (**2d**) was identified as one of the most potent NMDA receptor antagonists among the conformationally restricted analogues. The effect of **2d** on NMDA receptor channels expressed by *Xenopus* oocytes was investigated in detail. Its selectivity for NMDA receptors among other glutamate receptor subtypes and the mechanism of its blocking effect on NMDA receptors were investigated using *Xenopus* oocytes under voltage-clamp conditions. Thus, **2d** is a new class of an open channel blocker that is different from other blockers such as MK-801 and phencyclidine (PCP) (Figure 3).

Results and Discussion

Chemistry. All of the target compounds were synthesized from an optically active cyclopropylcarbaldehyde derivative **5** with a (1*S*,2*R*)-configuration,[9a] which was readily prepared from (*R*)-epichlorohydrin via a lactone **4**[11] (Scheme 1). The Grignard reaction of **5** with HC≡CMgBr in THF at −20 °C gave 1′*R*-product **6** highly diastereoselectively in 89% yield. The stereochemistry at the 1′-position of **6** was determined to be *R*, since the catalytic hydrogenation of **6** with Pd−C in MeOH gave 1′*S*-ethyl[12] derivative **7**, the stereochemistry of which was previously determined.[9a,c] As we reported, the addition reactions of Grignard reagents on cyclopropylcarbaldehyde **5** proceed from the least-hindered si-face in the bisected s-trans conformation, which would be preferred due to the peculiar stereoelectronic effects of the cyclopropane ring, to give 1′-addition products highly stereoselectively.[9] Introduction of an azide group at the 1′-position of **6** with a $NaN_3/Ph_3P/CBr_4$ system,[13] which was effective in the synthetic route for **2a** and **2b**,[9a] did not give the corresponding azide product **9** at all. However, when (trimethylsilyl)ethynyl derivative **8a**, which was prepared by the addition reaction of lithium TMS-acetylide on **5**, was used as a substrate, the desired 1′*R*-azide derivative **10** was obtained stereoselectively in 78% yield. This reaction is thought to give the configuration-retained azide product **10** via participation of the neighboring amide group as an intermediate **I** (Scheme 1).[9a] Treatment of **10** with Ph_3P and NH_4OH in pyridine[14] afforded a 1′-ethynyl analogue with type-1 configuration **2d** in 77% yield. Catalytic hydrogenation of **2d** with Pd−C in MeOH gave the known 1′*S*-ethyl derivative **2b** (PPDC),[9a] so that the 1′-configuration of **2d** was confirmed to be *R*.

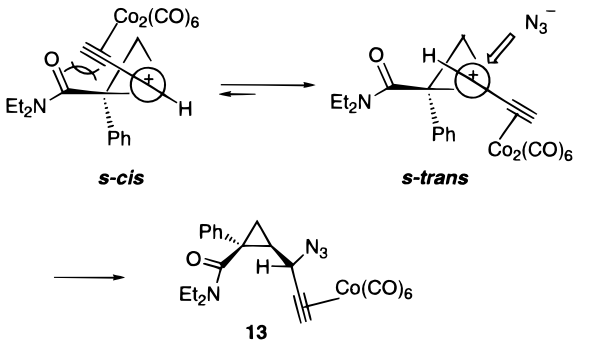
Scheme 2[a]



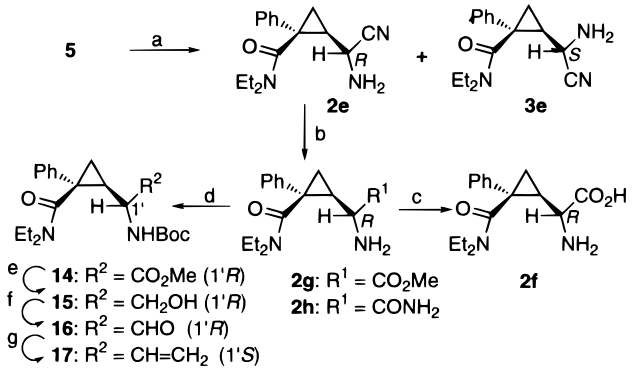
[a] Reagents: (a) $Co_2(CO)_8$; (b) 1) TFA, 2) NaN_3, 3) CAN; (c) Ph_3P, py, then NH_4OH; (d) H_2, Pd-C.

As described below, the 1′-ethynyl derivative **2d** with type-1 configuration was identified as one of the most potent NMDA receptor antagonists in this series of compounds. Therefore, we planned to synthesize its 1′-diastereomer **3d** to confirm the stereochemistry−activity relationship. Compound **3d** with type-2 configuration was synthesized via a stereoselective S_N1-type replacement reaction using an azide anion as a nucleophile (Scheme 2). It has been shown that alkynes readily form complexes with $Co_2(CO)_6$ which can be used efficiently in S_N1-type substitution reactions, since they significantly stabilize the carbocation at the adjacent position.[15] It has also been recognized that cyclopropylmethyl carbocations can be significantly stabilized by the interaction between a vacant p-orbital of the carbocation and electrons of the cyclopropane ring, which are characterized as a strong π-donor.[16] Nucleophilic substitution reactions at the cyclopropylmethyl position are facilitated by this interaction, which is maximal when the cyclopropylmethyl carbocations exist in either the bisected s-trans or s-cis conformation.[16] Considering these previous findings, we presumed that the nucleophilic substitution reaction between an azide anion and the carbocation generated from a $Co_2(CO)_6$ complex **11** would not proceed via participation of the

Scheme 3



Scheme 4[a]



[a] Reagents: (a) 1) TMSCN, Et_3N, 2) NH_3/MeOH; (b) 1) HCl/MeOH, 2) H_2O; (c) 6 M HCl; (d) Boc_2O; (e) DIBAL-H; (f) Swern ox.; (g) Ph_3PCH_3Br, BuLi.

neighboring group (**I** in Scheme 1) as mentioned above but rather via an S_N1 reaction due to effective stabilization of the 1′-carbocation by both the $Co_2(CO)_6$−alkyne complex and the cyclopropane ring. If this is the case, the reaction would stereoselectively give the desired 1′*S*-azide **12** since, with regard to the intermediate carbocation, a bisected s-trans conformation would be preferred over a bisected s-cis conformation due to steric repulsion between the cobalt-bound alkynylmethyl group and the *N*,*N*-diethylcarbamoyl group, and an azide anion would attack the intermediate at the least-hindered face to give the desired product **13** with high selectivity (Scheme 3). In fact, when complex **11**, prepared from **6** and $Co_2(CO)_8$, was successively treated with TFA and NaN_3 in CH_2Cl_2, the desired azide derivative was obtained as a sole product. Oxidative cleavage of the cobalt complex with cerium nitrite (CAN) in acetone gave the 1′*S*-azide **12** in 56% yield from **6**. Treatment of **12** with Ph_3P and NH_4OH in pyridine gave **3d** with type-2 configuration. The stereochemistry was confirmed by converting **3d** into the previously reported **3b**[9a] by catalytic hydrogenation.

The synthesis of the 1′-CN, −CO_2Me, and −$CONH_2$ analogues with type-1 configuration is summarized in Scheme 4. Treatment of aldehyde **5** with TMSCN and Et_3N in CH_2Cl_2[17] gave a 1′-diastereomeric mixture of the corresponding TMS-cyanohydrins, which was immediately heated with NH_3/MeOH in a steel tube to afford amines **2e** and **3e** from **5** in isolated yields of 64% and 32%, respectively, after silica gel column chromatography. The 1′*R*-cyano analogue **2e** with type-1 configuration was successively treated with HCl/MeOH and water to give type-1 methyl ester **2g** and type-1 amide **2h** in yields of 50% and 24%, respectively. The ester **2g** was hydrolyzed with 6 M HCl to give amino acid **2f** as a hydrochloride in 66% yield. After the amino group of **2g** was protected by a Boc group, **14** was converted to 1′-vinyl derivative **17**, the stereochemistry of which has been identified previously.[9d] Thus, the configurations of the type-1 analogues **2e**−**h** were confirmed.

Binding Affinity for NMDA Receptor. The synthesized compounds were evaluated for their binding affinity for the NMDA receptor of cerebral cortical synaptic membranes from rats with [^{3}H] MK-801 as a radioligand.[18] The binding affinity was significantly affected by the substituent at the 1′-position, and the results are shown in Table 1.

Notably, the 1′-ethynyl analogue **2d** (PPYDC) with type-1 configuration [(1*S*,2*R*)-1-phenyl-2-[(*R*)-1-amino-2-propynyl]-*N*,*N*-diethylcyclopropanecarboxamide] significantly inhibited the binding of [^{3}H] MK-801 with an IC_{50} value of 0.29 ± 0.2 μM, which is about 20-fold stronger than that of (±)-**1** (IC_{50} = 6.3 ± 0.29 μM).

Analogues with a CN, CO_2Me, or CO_2H group at the 1′-position, i.e., **2e**−**g**, were almost inactive, and the 1′-carbamoyl analogue **2h** showed weak binding affinity to the receptor (IC_{50} = 27 ± 1.8 μM). These results suggest that the electron-withdrawing effect of the 1′-substituents, which decreases the basicity of the amino group, may diminish the potency. It is especially interesting that the 1′-CN analogue **2e** with type-1 configuration is inactive, although a cyano group has steric and electronic features very similar to those of an ethynyl group.

Considering these results, we synthesized a 1′-ethynyl derivative with type-2 configuration, **3d**, and evaluated its binding affinity for the receptor. As a result, **3d** showed an only weak activity. This is consistent with a previous finding that analogues with type-1 configuration are more potent than the corresponding analogues with type-2 configuration.[9d]

As described above, **2d** (PPYDC) had the most significant affinity for the receptor among the conformationally restricted analogues.

Inhibitory Effects on the Uptake of 5-HT. The inhibitory effects of the compounds on the uptake of 5-HT by nerve terminals of cerebral cortical synaptic membrane from rats were evaluated with [^{3}H] paroxetine as a radioligand, and the results are shown in Table 1. Among the newly synthesized compounds, type-1 ethynyl derivative **2d** (PPYDC) was the most potent 5-HT uptake inhibitor (K_i = 0.19 ± 0.2 μM) although its effect was about 210-fold less than that of milnacipran [(±)-**1**, K_i = 0.0085 ± 0.0006 μM]. On the basis of these results, it appears as though the inhibitory potency of the conformationally restricted analogues with type-1 configuration against the 5-HT uptake is significantly affected by the bulkiness of the 1′-substituent (Me > C≡CH > Et).

Effect on NMDA Receptor Expressed by Oocytes. The effect of PPYDC on glutamate receptor subtypes expressed by *Xenopus* oocytes injected with total brain mRNA of the Wistar-strain rat under two-electrode voltage-clamp conditions was investigated as described previously.[19] The injected oocytes produced various glutamate receptor subtypes (metabotropic and ionotropic receptors), namely, NMDA, kainate, and

Table 1. Effects of Compounds on the NMDA Receptor Binding and the 5-HT Uptake

compd	stereochemistry	1′-substituent	NMDA receptor binding[a] (IC_{50}, μM)	5-HT uptake[b] (K_i, μM)
(±)-**1**			6.3 ± 0.3	0.0085 ± 0.0006
2a	type-1	Me	0.35 ± 0.08	0.014 ± 0.002
2b	type-1	Et	0.20 ± 0.02	24 ± 0.9
2d	type-1	C≡CH	0.29 ± 0.2	0.19 ± 0.2
2e	type-1	C≡N	96 ± 10	>100
2f	type-1	CO_2H	>100	>100
2g	type-1	CO_2Me	>100	25 ± 5
2h	type-1	$CONH_2$	27 ± 1.8	>100
3a	type-2	Me	6.5 ± 0.5	2.4 ± 0.3
3b	type-2	Et	8.2 ± 2.1	>100
3d	type-2	C≡CH	16 ± 4.8	15 ± 0.8
3e	type-2	C≡N	>100	not tested
ketamine			0.61± 0.46	not tested

[a] Assay was done with cerebral cortical synaptic membrane of rats using [^{3}H]MK-801. [b] Assay was done with cerebral cortical synaptic membrane of rats using [^{3}H]paroxetine.

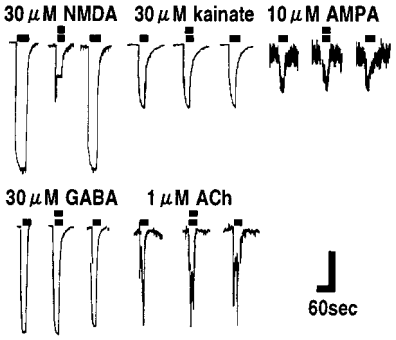


Figure 4. Effect of 10 μM PPYDC on different neurotransmitter receptor responses. Oocytes were voltage-clamped at −50 mV and stimulated with selective agonists in the presence and absence of 10 μM PPYDC. Lower bars on each current trace show the duration of stimulation, and upper bars show the duration of PPYDC application. Scale: 40 nA for NMDA; 10 nA for kainate, GABA, and ACh; and 2 nA for AMPA.

Table 2. Effect of 10 μM PPYDC (**2d**) on Different Neurotransmitter Receptors

receptor	relative response (%)[a] mean ± SD	agonist
NMDA receptors	32.1 ± 0.07[b]	30 μM NMDA + 10 μM glycine
kainate receptors	96.9 ± 0.05	30 μM kainate
AMPA receptors	100.3 ± 0.08	10 μM AMPA
$GABA_A$ receptors	99.6 ± 0.03	30 μM GABA
ACh_{M1} receptors	102.0 ± 0.05	1 μM ACh
$5HT_{2C}$ receptors	100.3 ± 0.16	0.1 μM 5HT

[a] The numerals are means and SD of relative responses obtained from 5 oocytes. [b] $p < 0.05$, paired two-tailed *t*-test.

AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionate) receptors, and other neurotransmitter receptors, such as $GABA_A$, $AChM_1$, and $5HT_{2C}$ receptors. In the presence of PPYDC (10 μM), the responses of NMDA receptors were decreased (Figure 4, Table 2). In contrast, the responses of other glutamate receptor subtypes and neurotransmitter receptors remained unchanged in the presence of 10 μM of PPYDC. PPYDC had no effect on NMDA receptor responses when it was applied prior to stimulating NMDA solution (data not shown). These results indicate that PPYDC selectively blocks opened NMDA receptor channels.

The blockade of the responses to 30 μM NMDA increased with an increase in the concentration of PPYDC (Figure 5). An IC_{50} value (the concentration of a blocker at which receptor responses are reduced by half) and an empirical Hill coefficient *n* were determined

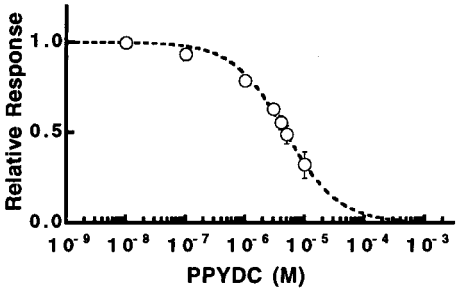


Figure 5. Suppression curve. Oocytes were stimulated with 30 μM NMDA supplemented with 10 μM glycine in the presence of different concentrations of PPYDC. Plotted relative responses are the mean ± SD of five oocytes. Holding potential, −50 mV.

by fitting the following equation to the experimental data

$$R = 1 - \{1/(1 + (IC_{50}/[PPYDC])^n)\} \quad (1)$$

where *R* is the relative response in the presence of a given concentration of PPYDC, [PPYDC].

As Figure 5 shows, eq 1 fits the plotted data points with an IC_{50} of 4.75 μM, an *n* of 0.983, and a correlation coefficient between eq 1 and the experimental data of 0.994. The *n* value was close to unity, indicating 1:1 stoichiometry; one PPYDC molecule blocks one NMDA receptor molecule.

NMDA receptor channels require both NMDA and glycine to open. PPYDC decreased the saturation levels of the concentration−response curve for NMDA supplemented with 10 μM glycine (Figure 6a) and that for glycine supplemented with 30 μM NMDA (Figure 6b) without shifting the concentration−response curves. These results indicate that PPYDC blocks NMDA receptors without competing with NMDA or glycine.

To test this conclusion, we compared the concentration−response curves shown in Figure 6 with an equation (eq 2) that assumes the uncompetitive blockade of NMDA receptors

$$R = \frac{\left\{\frac{K_d}{[A_{control}]}\right\}^n + 1}{\left\{\frac{K_d}{[A]}\right\}^n + \frac{[PPYDC]}{K_{PPYDC}} + 1} \quad (2)$$

where *R* is the relative response, $[A_{control}]$ is the con-

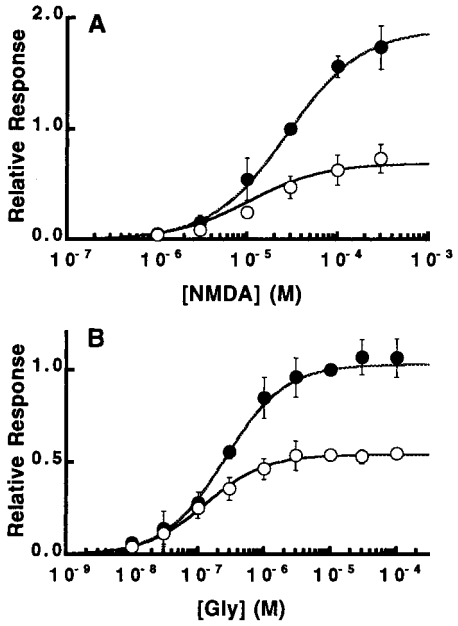


Figure 6. Concentration−response curves for NMDA (A) and glycine (B) in the absence (●) and presence (○) of 3 μM PPYDC. Different concentrations of NMDA (A) and glycine (B) were supplemented with 10 μM glycine and 30 μM NMDA, respectively. Holding potential, −50 mV. Lines were drawn using the nonlinear least-squares method following eq 2. Each point represents the mean ± SD of five oocytes.

centration of the control (30 μM NMDA in Figure 6a and 10 μM glycine in Figure 6b), [A] is a given concentration of test stimulus (NMDA in Figure 6a and glycine in Figure 6b), K_d and K_{PPYDC} are the dissociation constants for the agonist (NMDA in Figure 6a and glycine in Figure 6b) and PPYDC, respectively, [PPYDC] is a fixed concentration of PPYDC (3 μM), and n is the empirical Hill coefficient for the agonists. The Hill coefficient for PPYDC is taken as unity based on an analysis of the suppression curve shown in Figure 5.

As Figure 6 shows, the concentration curves for both NMDA and glycine are described by eq 2 using the nonlinear least-squares method, and the correlation coefficients for the fitting ranged from 0.976 to 0.999. This good fit supports the above conclusion that the mode of action is uncompetitive. These results, together with the above result that PPYDC blocked only activated NMDA receptors, indicate that PPYDC acts as an open channel blocker against NMDA receptors.

The estimated dissociation constants of PPYDC were 1.81 μM in the presence of 10 μM glycine and 3.72 μM in the presence of 30 μM NMDA; i.e., these values were comparable to each other. The estimated dissociation constants for NMDA and glycine were 27.0 μM and 0.25 μM, respectively, and the empirical Hill coefficients were 1.04 for NMDA and 0.96 for glycine.

Several potent open channel blockers against the NMDA receptor, such as MK-801 and PCP, which have similar structural and biological features, are known.[1,2,4,20] Although PPYDC may block the same site that MK-801 blocks within the NMDA channel, they typically gave different results in unblocking processes. As Figure 7 shows, the time constant for the recovery of NMDA receptors blocked by PPYDC was about 8 s, which is much shorter than the recovery time constant of MK-801-blocked NMDA receptors, which was too long

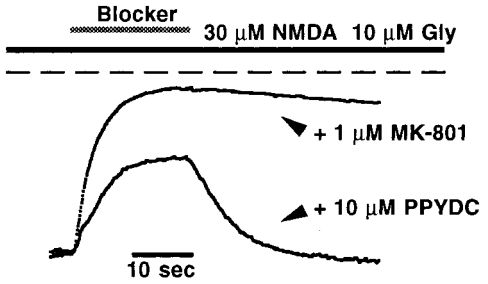


Figure 7. Blocking and unblocking by 10 μM PPYDC and 1 μM MK-801 in the continuous presence of 30 μM NMDA supplemented with 10 μM glycine. These traces were obtained from the same oocyte to eliminate differences in the open probability of NMDA receptors. Broken line, zero current level. Holding potential, −50 mV.

to measure with our present system. This difference is not surprising because the structure of PPYDC is quite different from those of other known blockers (Figure 3). The moderate recovery time constant of PPYDC suggests that its pharmacological effect on NMDA receptors is different from those of known blockers of this receptor.

In conclusion, we developed conformationally restricted analogues of milnacipran [(±)-**1**] and found a potent NMDA receptor antagonist, PPYDC (**2d**), which was identified as a new class of channel blockers against this receptor. PPYDC may be a desirable NMDA antagonist, since milnacipran, the prototype of PPYDC, has been shown clinically to be free from serious side-effects and to be transportable to the brain.[7]

Experimental Section

Melting points were determined on a Yanagimoto MP-3 micro-melting point apparatus and are uncorrected. The NMR spectra were recorded with a JEOL EX-270, -400, or Bruker AMX 500 spectrometer with tetramethylsilane as an internal standard. Chemical shifts were reported in parts per million (δ), and signals are expressed as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or br (broad). Mass spectra were measured on a JEOL JMS-D300 spectrometer. Thin-layer chromatography was done on Merck coated plate $60F_{254}$. Silica gel chromatography was done with Merck silica gel 5715. Reactions were performed under argon.

(1*S*,2*R*)-1-Phenyl-2-[(*R*)-1-hydroxy-2-propynyl]-*N*,*N*-diethylcyclopropanecarboxamide (6). A THF solution of HC≡CMgBr (0.5 M, 24 mL, 12 mmol) was added slowly to a solution of **5** (1.94 g, 7.9 mmol) in THF (20 mL) at −10 °C. The mixture was stirred at the same temperature for 3 h and was quenched with aqueous saturated NH_4Cl (20 mL). After the mixture was concentrated in vacuo, the mixture was partitioned between EtOAc and H_2O. The organic layer was washed with brine, dried (Na_2SO_4), evaporated, and purified by column chromatography (silica gel; hexane/EtOAc, 3:1) to give **6** (2.06 g, 96% as a solid): mp 77−80 °C; ^{1}H NMR (500 MHz, $CDCl_3$) 0.90 (3 H, t, J = 7.0 Hz), 1.13 (3 H, t, J = 7.0 Hz), 1.20 (1 H, dd, J = 5.5, 6.5 Hz), 1.69 (1 H, ddd, J = 6.5, 9.0, 10.0 Hz), 1.80 (1 H, dd, J = 5.5, 9.0 Hz), 2.44 (1 H, d, J = 2.5 Hz), 3.31−3.44 (3 H, m), 3.48 (1 H, dq, J = 14.0, 7.0 Hz), 3.96 (1 H, ddd, J = 2.5, 2.5, 10.0 Hz), 5.50 (1 H, d, J = 2.5 Hz), 7.21−7.32 (5 H, m); MS (EI) m/z 271 (M^+). Anal. ($C_{17}H_{21}NO_2$) C, H, N.

Catalytic Hydrogenation of 6. A mixture of **6** (30 mg, 0.11 mmol) and 10% Pd−charcoal (5 mg) in MeOH (2 mL) was stirred under atmospheric pressure of hydrogen at room temperature for 2 h, and then the catalyst was filtered off with Celite. The filtrate was evaporated, and the residue was purified by column chromatography (silica gel; hexane/EtOAc, 2:1) to give **7** (27 mg, 89% as an oil), of which spectral data were in accord with those reported previously.[9a]

(1*S*,2*R*)-1-Phenyl-2-[(*R*)-1-hydroxy-3-(trimethylsilyl)-2-propynyl]-*N*,*N*-diethylcyclopropanecarboxamide (8) and Its 1′-Diastereomer. A hexane solution of BuLi (1.64 M, 2.3 mL, 3.9 mmol) was added to a solution of TMSC≡CH (0.57 mL, 4.0 mmol) in THF (6 mL) at −78 °C, and the resulting solution was stirred at the same temperature for 1 h. To the resulting solution was added slowly a solution of **5** (490 mg, 2.0 mmol) in THF (10 mL) at −78 °C. The mixture was stirred at the same temperature for 1 h and was quenched with aqueous saturated NH_4Cl (5 mL). After the mixture was concentrated in vacuo, the mixture was partitioned between EtOAc and H_2O. The organic layer was washed with brine, dried (Na_2SO_4), evaporated, and purified by column chromatography (silica gel; hexane/EtOAc, 5:1) to give **8** and its 1′*S*-diastereomer. Physical data of **8** (585 mg, 85% as crystals) are as follows: mp 107−109 °C; ^{1}H NMR (500 MHz, $CDCl_3$) 0.17 (9 H, s), 0.91 (3 H, t, J = 7.0 Hz), 1.12 (3 H, t, J = 7.0 Hz), 1.21 (1 H, dd, J = 5.5, 6.5 Hz), 1.68 (1 H, ddd, J = 6.5, 9.0, 10.0 Hz), 1.79 (1 H, dd, J = 5.5, 9.0 Hz), 3.33−3.41 (3 H, m), 3.49 (1 H, dq, J = 14.0, 7.0 Hz), 3.95 (1 H, dd, J = 2.5, 10.0 Hz), 5.52 (1 H, d, J = 2.5 Hz), 7.20−7.31 (5 H, m); MS (EI) m/z 343 (M^+). Anal. ($C_{20}H_{29}NO_2Si$) C, H, N. Physical data of the 1′*S*-diastereomer of **8** [(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-hydroxy-3-(trimethylsilyl)-2-propynyl]-*N*,*N*-diethylcyclopropanecarboxamide, 89 mg, 13% as crystals] are as follows: mp 75−77 °C; ^{1}H NMR (500 MHz, $CDCl_3$) 0.15 (9 H, s), 0.98 (3 H, t, J = 7.0 Hz), 1.16 (3 H, t, J = 7.0 Hz), 1.65−1.72 (3 H, m), 3.15 (1 H, dq, J = 14.0, 7.0 Hz), 3.31 (1 H, dq, J = 14.0, 7.0 Hz), 3.61 (2 H, dq, J = 14.0, 7.0 Hz), 4.90 (1 H, dd, J = 5.5, 10.5 Hz), 5.96 (1 H, d, J = 10.5 Hz), 7.19−7.31 (5 H, m); MS (EI) m/z 343 (M^+). Anal. ($C_{20}H_{29}NO_2Si$) C, H, N.

(1*S*,2*R*)-1-Phenyl-2-[(*R*)-1-azido-3-trimethylsilyl-2-propynyl]-*N*,*N*-diethylcyclopropanecarboxamide (10). To a solution of **8** (343 mg, 1.0 mmol) in DMF (8 mL) at 0 °C were added NaN_3 (1.17 g, 18 mmol), Ph_3P (787 mg, 3.0 mmol), and CBr_4 (995 mg, 3.0 mmol), and the resulting mixture was stirred at room temperature for 3 h. After the addition of water, the resulting mixture was evaporated, and the residue was partitioned between brine and EtOAc. The organic layer was dried (Na_2SO_4), evaporated, and purified by column chromatography (silica gel; hexane/EtOAc, 1:10) to give **10** (287 mg, 78% as an oil): ^{1}H NMR (500 MHz, $CDCl_3$) 0.21 (9 H, s), 0.44 (3 H, t, J = 7.0 Hz), 1.07 (1 H, dd, J = 5.5, 9.0 Hz), 1.10 (3 H, t, J = 7.0 Hz), 1.78 (1 H, dd, J = 5.5, 6.0 Hz), 2.14 (1 H, ddd, J = 6.0, 9.0, 9.5 Hz), 3.02 (1 H, dq, J = 14.0, 7.0 Hz), 3.10 (1 H, dq, J = 14.0, 7.0 Hz), 3.52−3.61 (2 H, m), 3.85 (1 H, d, J = 9.5 Hz), 7.20−7.31 (5 H, m); MS (EI) m/z 368 (M^+). Anal. ($C_{20}H_{28}N_4OSi\cdot0.25H_2O$) C, H, N.

(1*S*,2*R*)-1-Phenyl-2-[(*R*)-1-amino-2-propynyl]-*N*,*N*-diethylcyclopropanecarboxamide Hydrochloride (2d). After a mixture of **10** (154 mg, 0.42 mmol) and Ph_3P (219 mg, 0.84 mmol) in pyridine (6 mL) was stirred at room temperature for 30 min, 28% NH_4OH (4 mL) was added, and the resulting mixture was stirred at room temperature for 36 h. The mixture was evaporated, and the residue was partitioned between Et_2O and water. The organic layer was separated and was washed with brine, dried (Na_2SO_4), evaporated, and purified by column chromatography (silica gel; $CHCl_3$/MeOH/28% NH_4OH, 300:10:0.1) to give **2d** as an oil (87 mg, 77%). The oil was partitioned between $CHCl_3$ and 1 M NaOH, and then the $CHCl_3$ layer was washed twice with brine, dried (Na_2SO_4), and evaporated. The residue was dissolved in MeOH (1 mL), and the solution was put on a column of Diaion WA-30 resin (2 × 8 cm, Cl^- form), which was developed with MeOH. The solvent was evaporated, and the residue was treated with Et_2O to give white crystals of **2d** (95 mg, 71% from **10** as a hydrochloride): mp 96−100 °C; $[\alpha]^{21}_D$ = +73.1 (*c* 0.840, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) 0.90 (3 H, t, J = 7.0 Hz), 1.09 (3 H, t, J = 7.0 Hz), 1.24 (1 H, dd, J = 6.0, 6.0 Hz), 1.95 (1 H, dd, J = 6.0, 9.0 Hz), 2.01 (1 H, ddd, J = 6.0, 9.0, 10.0 Hz), 2.78 (1 H, d, J = 1.5 Hz), 3.29 (1 H, dq, J = 14.0, 7.0 Hz), 3.34−3.49 (2 H, m), 3.52 (1 H, dd, J = 10.0, 1.5 Hz), 7.20−7.31 (5 H, m), 9.46 (3 H, br s); MS (EI) m/z 270 (M^+). Anal. ($C_{17}H_{23}ClN_2O\cdot0.4H_2O$) C, H, N.

Catalytic Hydrogenation of 2d. Compound **2d** (free amine, 11 mg, 0.040 mmol) was hydrogenated as described above for **6**. After the residue was purified by column chromatography (silica gel; $CHCl_3$/MeOH/28% NH_4OH, 45:5:0.1), **2b** (8 mg, 74% as an oil) was obtained, of which spectral data were in accord with those reported previously.[9d]

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-azido-2-propynyl]-*N*,*N*-diethylcyclopropanecarboxamide (12). A mixture of **6** (271 mg, 1.0 mmol) and $Co_2(CO)_8$ (380 mg, 1.0 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature for 20 min, and then TFA (770 μL, 10 mmol) was added at 0 °C. After the mixture was stirred at 0 °C for 10 min, NaN_3 (650 mg, 10 mmol) was added, and the resulting mixture was stirred at room temperature for 1.5 h. Water was added, and the resulting mixture was partitioned. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated. A mixture of the residue and CAN (274 mg, 5.0 mmol) in acetone (15 mL) was stirred at room temperature for 1 h. The resulting mixture was partitioned between EtOAc and brine, and the organic layer was dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (neutral silica gel; hexane/EtOAc, 5:1) to give **12** (165 mg, 56% as an oil): ^{1}H NMR (270 MHz, $CDCl_3$) 0.46 (3 H, t, J = 7.0 Hz), 1.11 (3 H, t, J = 7.0 Hz), 1.14 (1 H, dd, J = 5.5, 9.5 Hz), 1.74 (1 H, dd, J = 5.5, 6.0 Hz), 2.18 (1 H, ddd, J = 6.0, 9.5, 10.0 Hz), 2.65 (1 H, d, J = 2.5 Hz), 3.04 (1 H, dq, J = 14.0, 7.0 Hz), 3.13 (1 H, dq, J = 14.0, 7.0 Hz), 3.55 (1 H, dq, J = 14.0, 7.0 Hz), 3.61 (1 H, dq, J = 14.0, 7.0 Hz), 3.79 (1 H, dd, J = 2.5, 10.0 Hz), 7.20−7.35 (5 H, m); IR (neat), 2120 cm^{-1}(ν_{N3}).

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-amino-2-propynyl]-*N*,*N*-diethylcyclopropanecarboxamide Hydrochloride (3d). Compound **3d** was prepared from **12** (150 mg, 0.51 mmol) as described above for **2d**. After the residue was purified by column chromatography (silica gel; $CHCl_3$/MeOH/28% NH_4OH, 45:5:0.1) and treated with ion-exchange resin (Diaion WA-30, Cl^- form), **3d** (83 mg, 60% as crystals) was obtained as a hydrochloride: mp 95−98 °C; $[\alpha]^{23}_D$ = −24.0 (*c* 0.620, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) 0.97 (3 H, t, J = 7.0 Hz), 1.12 (3 H, t, J = 7.0 Hz), 1.73−1.86 (2 H, m), 2.05−2.10 (1 H, m), 2.55 (1 H, s), 3.25 (1 H, dq, J = 14.0, 7.0 Hz), 3.36−3.46 (2 H, m), 3.58 (1 H, dq, J = 14.0, 7.0 Hz), 4.91 (1 H, br s), 7.20−7.31 (5 H, m), 9.51 (3 H, br s); MS (EI) m/z 270 (M^+). Anal. ($C_{17}H_{23}ClN_2O\cdot1.6H_2O$) C, H, N.

Catalytic Hydrogenation of 3d. Compound **3d** (free amine, 17 mg, 0.063 mmol) was hydrogenated as described above for **6**. After the residue was purified by column chromatography (silica gel; $CHCl_3$/MeOH/28% NH_4OH, 45:5:0.1), **3b** (17 mg, 98% as an oil) was obtained, of which spectral data were in accord with those reported previously.[9a]

(1*S*,2*R*)-1-Phenyl-2-[(*R*)-aminocyanomethyl]-*N*,*N*-diethylcyclopropanecarboxamide (2e) and (1*S*,2*R*)-1-Phenyl-2-[(*S*)-aminocyanomethyl]-*N*,*N*-diethylcyclopropanecarboxamide (3e). A solution of **5** (858 mg, 3.50 mmol), TMSCN (600 μL, 4.4 mmol), and Et_3N (62 μL, 0.44 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature for 16 h. To the mixture was added NH_3/MeOH (saturated at 0 °C, 40 mL), and the whole was heated at 50 °C for 4 h in a steel tube. After the solvent was evaporated, the residue was partitioned between EtOAc and brine. The organic layer was dried (Na_2SO_4), evaporated, and purified by column chromatography (silica gel; hexane/EtOAc, 1:2, then EtOAc) to give **2e** (free amine, 605 mg, 64% as yellow crystals) and **3e** (free amine, 305 mg, 32% as a yellow oil). The hydrochlorides of the diastereomers were prepared as described above for **2d**. **2e** (hydrochloride): mp 140−142 °C; $[\alpha]^{27}_D$ = −47.7 (*c* 0.760, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) 0.87 (3 H, t, J = 7.0 Hz), 1.09 (3 H, t, J = 7.0 Hz), 1.44 (1 H, dd, J = 6.0, 6.5 Hz), 2.05 (1 H, dd, J = 6.0, 8.5 Hz), 2.16 (1 H, ddd, J = 6.5, 8.5, 10.5 Hz), 3.26 (1 H, dq, J = 14.0, 7.0 Hz), 3.31−3.47 (3 H, m), 3.95 (1 H, d, J = 10.5 Hz), 7.20−7.33 (5 H, m), 9.87 (3 H, br s); MS (EI) m/z 271 (M^+). Anal. ($C_{16}H_{22}ClN_3O$) C, H, N. **3e** (hydrochloride): mp 145−147 °C; $[\alpha]^{27}_D$ = +20.4 (*c* 0.850, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) 0.92 (3 H, t, J = 7.0 Hz), 1.16 (3 H, t, J = 7.0 Hz), 1.68 (1 H, dd, J = 6.5, 6.5 Hz), 2.02 (1 H, dd,

J = 6.5, 9.0 Hz), 2.09 (1 H, ddd, J = 5.5, 6.5, 9.0 Hz), 3.29 (1 H, dq, J = 14.0, 7.0 Hz), 3.42−3.53 (3 H, m), 5.33 (1 H, d, J = 5.5 Hz), 7.23−7.34 (5 H, m), 9.96 (3 H, br s); MS (EI) *m*/*z* 271 (M^+). Anal. ($C_{16}H_{22}ClN_3O\cdot0.3H_2O$) C, H, N.

(1*S*,2*R*)-1-Phenyl-2-[(*R*)-amino(methoxycarbonyl)methyl]-*N*,*N*-diethylcyclopropanecarboxamide (2g) and (1*S*,2*R*)-1-Phenyl-2-[(*R*)-amine(carbamoyl)methyl]-*N*,*N*-diethylcyclopropanecarboxamide (2h). HCl gas was bubbled and saturated into a solution of **2e** (free amine, 691 mg, 2.55 mmol) in MeOH (15 mL) at 0 °C, and the resulting solution was stirred at the same temperature for 1 h. After ice−water (75 mL) was added, the resulting mixture was stirred at 0 °C and was neutralized with $NaHCO_3$. The resulting mixture was extracted with EtOAc, and the organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (silica gel; $CHCl_3$/MeOH, 20:1 and then 5:1) to give **2g** (free amine, 385 mg, 50% as an oil) and **2h** (free amine, 173 mg, 24% as a solid). **2g**: ^{1}H NMR (500 MHz, $CDCl_3$) 0.81 (3 H, t, J = 7.0 Hz), 1.13 (3 H, t, J = 7.0 Hz), 1.41 (1 H, dd, J = 5.0, 6.0 Hz), 1.50 (1 H, ddd, J = 6.0, 9.0, 9.5 Hz), 1.56 (1 H, dd, J = 5.0, 9.0 Hz), 2.55 (2 H, br s), 3.21 (1 H, d, J = 9.5 Hz), 3.27 (1 H, dq, J = 14.0, 7.0 Hz), 3.29 (1 H, dq, J = 14.0, 7.0 Hz), 3.43 (1 H, dq, J = 14.0, 7.0 Hz), 3.53 (1 H, dq, J = 14.0, 7.0 Hz), 3.75 (3 H, s), 7.19−7.31 (5 H, m); MS (EI) *m*/*z* 304 (M^+). Anal. ($C_{17}H_{24}N_2O_3$) C, H, N. **2h**: mp 117−119 °C; $[\alpha]^{22}_D$ = +86.1 (*c* 0.906, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) 0.89 (3 H, t, J = 7.0 Hz), 1.13 (3 H, t, J = 7.0 Hz), 1.36 (1 H, ddd, J = 6.5, 9.0, 9.5 Hz), 1.54 (1 H, dd, J = 6.0, 6.5 Hz), 1.72 (1 H, dd, J = 6.0, 9.0 Hz), 2.32 (2 H, br s), 3.11 (1 H, d, J = 9.5 Hz), 3.28−3.43 (3 H, m), 3.50 (1 H, dq, J = 14.0, 7.0 Hz), 5.55 (1 H, br s), 7.16 (1 H, br s), 7.20−7.31 (5 H, m); MS (EI) *m*/*z* 289 (M^+). Anal. ($C_{16}H_{23}N_3O_2\cdot0.2H_2O$) C, H, N.

(1*S*,2*R*)-1-Phenyl-2-[(*R*)-aminocarboxymethyl]-*N*,*N*-diethylcyclopropanecarboxamide Hydrochloride (2f). A solution of **2g** (304 mg, 1.0 mmol) in 6 M HCl (8 mL) was stirred at room temperature for 3 days. The mixture was evaporated, and the residual powders were washed with Et_2O. The powders were treated with $CHCl_3$/hexane/benzene to give white crystals of **2f** as a hydrochloride (215 mg, 66%): mp 159−161 °C; $[\alpha]^{21}_D$ = +67.3 (*c* 0.545, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) 0.86 (3 H, t, J = 7.0 Hz), 1.07 (3 H, t, J = 7.0 Hz), 1.36 (1 H, ddd, J = 6.5, 9.0, 11.0 Hz), 1.65 (1 H, dd, J = 6.0, 6.5 Hz), 2.14 (1 H, dd, J = 6.0, 9.0 Hz), 3.23−3.42 (4 H, m), 3.57 (1 H, d, J = 11.0 Hz), 7.26−7.37 (5 H, m), 8.53 (3 H, br s), 13.8 (1 H, br s); MS (EI) *m*/*z* 290 (M^+). Anal. ($C_{16}H_{23}ClN_2O_3\cdot0.2H_2O$) C, H, N.

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-(*tert*-butoxycarbonylamino)-(methoxycarbonyl)methyl]-*N*,*N*-diethylcyclopropanecarboxamide (14). A solution of **2g** (152 mg, 0.50 mmol) and Boc_2O (0.17 mL, 0.75 mmol) in MeCN (5 mL) was stirred at room temperature for 1.5 h. After water was added, the mixture was concentrated in vacuo and then extracted with $CHCl_3$. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (silica gel; hexane/EtOAc, 1:1) to give **14** (194 mg, 96% as a foam): ^{1}H NMR (500 MHz, $CDCl_3$) 0.68 (3 H, br s), 1.10 (3 H, t, J = 7.1 Hz), 1.33−1.46 (m, 11 H), 1.88 (1 H, dd, J = 7.2, 15.8 Hz), 3.22−3.34 (2 H, m), 3.48−3.58 (2 H, m), 3.74 (1 H, m), 3.83−3.89 (2 H, m), 5.13 (1 H, br s), 5.57 (1 H, br s), 3.79 (s, 3 H), 7.20−7.31 (5 H, m); MS (EI) *m*/*z* 376 (M^+). Anal. ($C_{22}H_{32}N_2O_5\cdot0.3H_2O$).

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-(*tert*-butoxycarbonylamino)-2-hydroxyethyl]-*N*,*N*-diethylcyclopropanecarboxa- mide (15). A hexane solution of DIBAL-H (0.93 M, 0.56 mL, 0.52 mmol) was added to a solution of **14** (70 mg, 0.17 mmol) in THF (4 mL) at −78 °C, and the mixture was stirred at the same temperature for 1 h and then at room temperature for 15 h. After being quenched with aqueous saturated NH_4Cl (5 mL), the mixture was concentrated in vacuo. The mixture was partitioned between EtOAc and H_2O, and the organic layer was separated and washed with brine, dried (Na_2SO_4), evaporated, and purified by column chromatography (silica gel; $CHCl_3$/MeOH, 10:1) to give **15** (39 mg, 60% as a foam): ^{1}H NMR (500 MHz, $CDCl_3$) 0.82 (3 H, t, J = 6.5 Hz), 1.15 (3 H, t, J = 7.0 Hz), 1.41−1.58 (m, 12 H), 1.88 (1 H, dd, J = 7.2, 15.8 Hz), 3.22−3.53 (4 H, m), 3.79 (s, 3 H), 4.27 (br s, 1 H), 5.30 (br s, 1 H), 7.19−7.31 (5 H, m); MS (EI) *m*/*z* 404 (M^+).

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-amino-2-propenyl]-*N*,*N*-diethylcyclopropanecarboxamide (17). To a solution of oxalyl chloride (75 μL, 0.088 mmol) in CH_2Cl_2 (2 mL) was added slowly a mixture of DMSO (16 μL, 0.18 mmol) and CH_2Cl_2 (2 mL) at −78 °C, and the mixture was stirred at the same temperature for 30 min. To the resulting mixture was added slowly a solution of **15** (18 mg, 0.048 mmol) in CH_2Cl_2 (2 mL); the whole was stirred at the same temperature for 2 h, and then Et_3N (49 μL, 0.35 mmol) was added. After being stirred at −78 °C further for 1 h, the reaction mixture was quenched with aqueous saturated NH_4Cl, and then CH_2Cl_2 (10 mL) was added. The organic layer was separated and washed with brine, dried (Na_2SO_4), evaporated, and purified by column chromatography (silica gel; hexane/EtOAc, 1:1) to give **16** as an oil, which was used immediately in the next reaction.

To a suspension of Ph_3PCH_3Br (10 mg, 0.029 mmol) in THF (1 mL) was added a BuLi solution (1.63 M in hexane, 16 μL, 0.029 mmol) at −21 °C, and the mixture was stirred at the same temperature for 30 min. To the resulting mixture was added slowly a solution of **16** (8 mg, 0.021 mmol) in THF (1 mL) at −21 °C. The mixture was stirred at the same temperature for 1.5 h and then was quenched with aqueous saturated NH_4Cl (2 mL). After the mixture was concentrated in vacuo, EtOAc and water were added, and then the mixture was partitioned. The organic layer was washed with brine, dried (Na_2SO_4), evaporated, and purified by column chromatography (silica gel; hexane/EtOAc, 1:1) to give **17** (4 mg, 33% as on oil), of which spectral data were in accord with those reported previously.[9d]

Binding Assay. The binding affinity for the NMDA receptor was investigated according to previously reported methods.[18]

Inhibitory Effects on the Uptake of 5-HT. The assay was investigated according to the previously reprted method.[9d]

Assay with Voltage-Clamped Oocytes. The blocking effects of the compound were investigated on glutamate receptor subtypes expressed by *Xenopus* oocytes injected with total brain mRNA of the Wistar-strain rat under two-electrode voltage-clamp conditions.[19] Electrodes (∼1 MΩ) were filled with 3 M KCl, and the ground electrode was a salt bridge. Oocytes were perfused with a bathing solution (in mM: 96 NaCl, 2 KCl, 1 $CaCl_2$, 10 HEPES/NaOH, pH 7.4). Selective agonists for glutamate receptor subtypes and other neurotransmitter receptors were added to the bathing solution in the absence or presence of the compound. The stimulation intervals were ∼2 min. NMDA was added to the bathing solution together with 10 μM glycine unless otherwise noted. The NMDA-induced currents consisted of a transient current and a following steady-state current. The magnitude of the steady-state current at a holding potential of −50 mV was measured as the magnitude of the responses. The magnitude of the responses to given test solutions was calculated relative to the mean of the magnitude of the responses to 30 μM NMDA in the absence of blockers (control responses) determined before and after the application of the test solutions. When the magnitude of the control responses changed by more than 20% in the experimental period of 60 min, the preparation was discarded.

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