Studies on Cerebral Protective Agents. IX. Synthesis of Novel 1,2,3,4-Tetrahydroisoquinolines as *N*-Methyl-D-aspartate Antagonists[1)]

Mitsuru OHKUBO,*[,a] Atsushi KUNO,[a] Kiyotaka KATSUTA,[a] Yoshiko UEDA,[a] Kiyoharu SHIRAKAWA,[a] Hajime NAKANISHI,[a] Isao NAKANISHI,[b] Takayoshi KINOSHITA,[c] and Hisashi TAKASUGI[a]

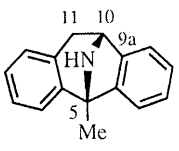
New Drug Research Laboratories,[a] R & D Information,[b] and Analytical Research Laboratories,[c] Fujisawa Pharmaceutical Co., Ltd., 1–6 Kashima 2-chome, Yodogawa-ku, Osaka 532, Japan.
Received April 21, 1995; accepted August 31, 1995

A series of 1,2,3,4-tetrahydroisoquinoline derivatives were synthesized and evaluated for anticonvulsant activity against intracerebro-ventriculas (i.c.v.) *N*-methyl-D-aspartate (NMDA)-induced seizures in mice. Among these compounds, (+)-1-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline hydrochloride ((+)-1a, FR115427) was the most effective anticonvulsant, and also protected CA1 hippocampal neurons from ischemia-induced neuronal degeneration in rats at 32 mg/kg i.p. In addition, (+)-1a showed anti-hypoxic activity in mice at 3.2—32 mg/kg i.p. The absolute configuration at the C-1 position of the isoquinoline ring was determined to be *S* by a single-crystal X-ray analysis of (+)-1a (+)-di-*p*-toluoyl-D-tartrate. Structure–activity relationships with regard to the anticonvulsant activity of this series of compounds are discussed, and the three-dimensional structures of (*S*)-(+)-1a and MK801 are compared.

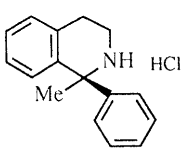
Key words 1,2,3,4-tetrahydroisoquinoline; *N*-methyl-D-aspartate antagonist; structure–activity relationship; FR115427

The *N*-methyl-D-aspartate (NMDA) receptor, an excitatory amino acid (EAA) receptor subtype,[2)] has been proposed to be responsible for neuronal degeneration following cerebral ischemia,[3)] and the search for therapeutically useful cerebral protective agents has been stimulated by the discovery of NMDA antagonists. MK801 (5*S*,10*R*)-(+)-5-methyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine: dizocilpine) (Fig. 1), a non-competitive NMDA antagonist,[4)] was reported to prevent ischemia-induced neuronal degeneration both *in vitro* (preventing degeneration of cultured neurons under hypoxic conditions)[5)] and *in vivo* (protecting CA1 hippocampal neurons from ischemia-induced neurodegeneration and reducing infarct volume following middle cerebral artery occlusion).[6,7)] However, MK801 induced unwanted side-effects such as central sympathomimetic effects[8)] and phencyclidine (PCP)-like stereotypy.[9)] We have therefore searched for new cerebral protective agents with NMDA antagonist activity distinct from these unwanted side-effects.

We have already reported that (+)-1-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline hydrochloride ((+)-**1a**: FR115427) (Fig. 1), a conformationally less restrained analog of MK801, acted as a non-competitive NMDA receptor antagonist (a K_i value of 35.4±3.8 nM for the inhibition of [^{3}H]MK801 binding using rat cortical membranes).[10)] In this report, we describe the synthesis of (+)-**1a** and some racemic derivatives and the structure–activity relationship (SAR) with regard to *in vivo* NMDA antagonist activities, which were assessed by evaluation of anticonvulsant activities against intracerebro-ventriculas (i.c.v.) NMDA-induced seizures in mice. Furthermore, (+)-**1a** was evaluated for anti-hypoxic activity in mice and neuroprotective activity in a model of ischemia-induced CA1 hippocampal damage in rats. The absolute configuration at the C-1 of the isoquinoline ring of (+)-**1a** was determined by a single-crystal X-ray analysis, and the three-dimensional structures of (+)-**1a** and MK801 are compared.



MK801



(+)-**1a**
(FR115427)

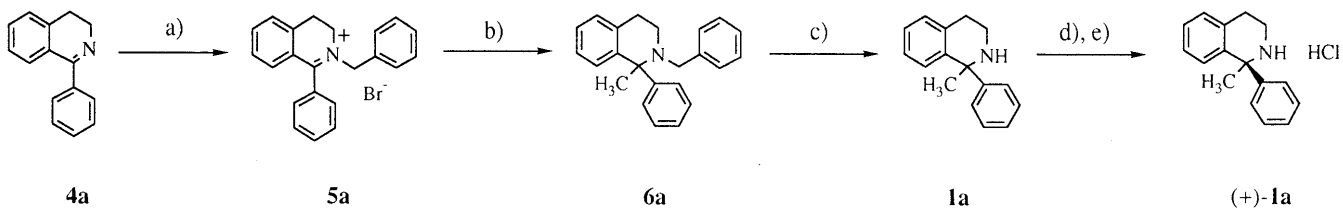
Fig. 1

Chemistry

(+)-1-Methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline ((+)-**1a**) and its racemic derivatives were synthesized by the routes shown in Chart 1.

The 3,4-dihydroisoquinoline (**4a**), prepared by means of the Bischler–Napieralski reaction,[11)] was alkylated with benzyl bromide (BzlBr) to produce *N*-benzyl-3,4-dihydroisoquinolinium bromide (**5a**). Alkylation at the C-1 position of **5a** *via* the Grignard reaction produced *N*-benzyl-1-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline (**6a**), which was reduced by using catalytic hydrogenation and converted to (±)-1-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline hydrochloride (**1a**). Optical resolution of salt-free **1a** using (+)-di-*p*-toluoyl-D-tartaric acid as the resolving agent afforded the (+)-enantiomer, which was converted to the hydrochloride salt (+)-**1a**, and (−)-**1a** was also obtained by using (−)-di-*p*-toluoyl-L-tartaric acid. Other (±)-1,2,3,4-tetrahydroisoquinoline derivatives (**1b—t**, Table 1) were prepared from the corresponding substituted 3,4-dihydroisoquinolines according to the route described for the preparation of **1a**. Optical resolution of **1p** was also performed by the same procedures as employed for separation of **1a**. The absolute configuration at the C-1 position of the isoquinoline ring of (+)-**1a** was determined to be *S* by a single-crystal X-ray

* To whom correspondence should be addressed.



4a **5a** **6a** **1a** **(+)-1a**

a) BzlBr / CH_3CN; b) CH_3MgBr / THF; c) H_2, 10%Pd-C / AcOH; d) (+)-di-*p*-toluoyl-D-tartaric acid / EtOH; e) HCl / EtOH

Chart 1

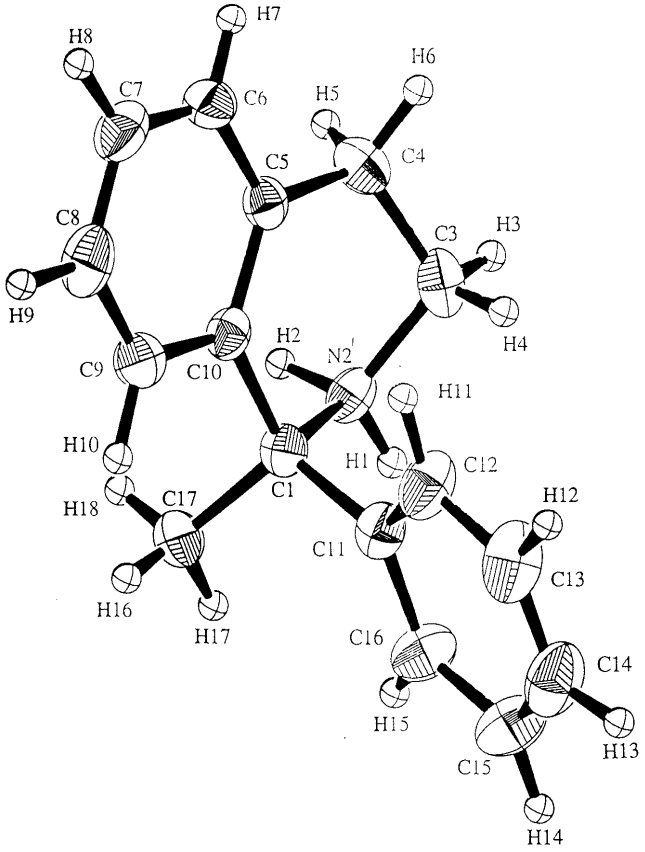


Fig. 2. X-Ray Crystal Structure of (+)-**1a**

analysis of (+)-**1a** (+)-di-*p*-toluoyl-D-tartarate (Fig. 2).

The 1,2,4,5-tetrahydro-3*H*-2-benzazepine derivative (**3**) (Table 1) was prepared from 1-phenyl-4,5-dihydro-3*H*-2-benzazepine[12] according to the route described for the preparation of **1a**. The isoindoline derivative (**2**) was also prepared by a known procedure.[13]

Pharmacological Results and Discussion

The prepared compounds were tested for anticonvulsant activities against seizures induced by i.c.v. NMDA (0.32 μg) in mice. Test compounds were administered i.p., and the results were expressed as the latency (s) of the initial seizure. The anticonvulsant activities of the racemates of the 1,2,3,4-tetrahydroisoquinolines (**1a**—**t**, **6a**—**e**), the isoindoline (**2**) and the 1,2,4,5-tetrahydro-3*H*-2-benzazepine (**3**) are summarized in Table 1.

Compound **1a**, which is a conformationally less restrained analog of MK801 (Fig. 1), showed significant anticonvulsant activity at 32 mg/kg i.p. In contrast, the isoindoline (**2**), which is an alternately analog of MK801, showed diminished activity. The 2-benzazepine (**3**), which was derived by expansion of the isoquinoline ring system of **1a**, also showed diminished activity. The results demonstrated that an isoquinoline ring system was optimal for the expression of anticonvulsant activity.

Among the C-1 substituents (**1a**—**c**) of the isoquinoline ring, optimum activity was obtained with a methyl group (**1a**). Addition of substituents on the C-1 phenyl group (**1d**—**f**) and the isoquinoline ring (**1g**—**o**) mostly resulted in diminished activity, and only **1j** with a methoxy group at the C-6 position retained activity comparable to that of **1a**. The results for **1p**—**t** showed that the C-1 phenyl group was exchangeable with a benzyl group (**1p**). However, the cyclohexyl (**1t**) and methyl (**1s**) derivatives showed diminished activity. The presence of an aromatic moiety at the C-1 position appeared to be favorable for the expression of anticonvulsant activity. Among *N*-substituted derivatives (**6a**—**e**), the *N*-methyl derivative (**6b**) was comparable in activity to **1a**, but potency decreased as the size of the substituent was increased (**6a**, **c**, **d** *versus* **6b**).

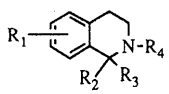
The stereoisomers of **1a** and **1p** were also evaluated for anticonvulsant activities (Table 2).

The potency of (+)-**1a** was increased three-fold compared with the racemate, while (−)-**1a** showed diminished activity. Compound (+)-**1p** also showed increased activity, while (−)-**1p** was less potent. The results showed that the NMDA antagonist activity of these isoquinoline derivatives is stereoselective.

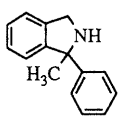
It is interesting that (*S*)-(+)-**1a** shows potent NMDA antagonist activity, although the *R* isomer of **1a** would be derived by severing the C9a–C10 bond of MK801 (Fig. 1). Overlays of (*S*)-(+)- and (*R*)-(−)-**1a** onto MK801, with the nitrogen atoms and the aromatic rings superimposed, are shown in Fig. 3a, b, respectively.[14] The C-1 phenyl group of (*S*)-(+)-**1a** was rotated from the X-ray structure to best fit the aromatic ring of MK801. The ring conformation of (*R*)-(−)-**1a** was derived from the inverted coordinates of the X-ray structure of (*S*)-(+)-**1a**. A high degree of overlap between (*S*)-(+)-**1a** and MK801 (Fig. 3a) suggested that (*S*)-(+)-**1a** could interact with the NMDA receptor in a similar fashion to MK801, while the spatial positions of the C-1 methyl and phenyl groups of (*R*)-(−)-**1a** were distinctly different from those of MK801 (Fig. 3b), and the difference may be responsible for the weaker NMDA antagonist activity of (*R*)-(−)-**1a**.

Compound (+)-**1a** (FR115427) was further evaluated for i.c.v. and i.p. anticonvulsant activity against i.c.v. NMDA (0.1 μg)-induced seizures in mice, neuroprotective

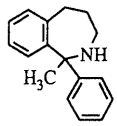
Table 1. Physical Properties and Anticonvulsant Activities of 1,2,3,4-Tetrahydroisoquinolines (**1a—t, 6a—e**), Isoindoline (**2**) and 2-Benzazepine (**3**)



1a—t, 6a—e



2



3

Compd. No.	R_1	R_2	R_3	R_4	Yield (%)	mp (°C) (Recryst. sol.)	Formula	Analysis (%) Calcd (Found) C	H	N	Anticonvulsant activity[a] (s) (mg/kg, i.p.) 32	100	320
1a	H	CH_3	Ph	H	96.2	274—276 (Et$_2$O–EtOH)	$C_{16}H_{17}N \cdot HCl \cdot 0.1H_2O$	73.47 (73.55	7.01 6.98	5.35 5.28)	32[e]	>600[f]	
2	—	—	—	—	65.3	194—195[b] (EtOH)	$C_{15}H_{15}N \cdot HCl$	73.31 (73.33	6.56 6.57	5.69 5.65)	15[e]	38[e]	
3	—	—	—	—	76.1	275—277 (Et$_2$O–EtOH)	$C_{17}H_{19}N \cdot HCl \cdot 0.1H_2O$	74.09 (74.05	7.39 7.78	5.08 5.05)	10	25[e]	
1b	H	H	Ph	H	21.9	94—97[c] (*n*-hexane)	$C_{15}H_{15}N$	86.08 (85.99	7.22 7.47	6.69 6.76)	9	108	
1c	H	C_2H_5	Ph	H	95.5	288—290 (Et$_2$O–EtOH)	$C_{17}H_{19}N \cdot HCl$	74.58 (74.57	7.36 7.42	5.12 5.08)	6	34[e]	260
1d	H	CH_3	2-ClPh	H	81.7	264—265 (Et$_2$O–EtOH)	$C_{16}H_{16}ClN \cdot HCl \cdot 0.5H_2O$	63.38 (63.78	5.98 6.14	4.62 4.37)	8	11	
1e	H	CH_3	3-ClPh	H	50.0	265—267 (Et$_2$O–EtOH)	$C_{16}H_{16}ClN \cdot HCl$	65.32 (65.10	5.82 5.65	4.76 4.78)	6	16[e]	
1f	H	CH_3	4-ClPh	H	66.0	286—287 (Et$_2$O–EtOH)	$C_{16}H_{16}ClN \cdot HCl \cdot 0.1H_2O$	64.92 (65.11	5.86 6.23	4.73 4.65)		8	
1g	5-Cl	CH_3	Ph	H	69.0	315—317 (Et$_2$O–EtOH)	$C_{16}H_{16}ClN \cdot HCl$	65.32 (65.18	5.82 5.80	4.76 4.56)	7	13	
1h	6-Cl	CH_3	Ph	H	51.2	335—336 (Et$_2$O–EtOH)	$C_{16}H_{16}ClN \cdot HCl \cdot 0.2H_2O$	64.52 (64.50	6.43 6.16	4.70 4.50)		11[e]	489[f]
1i	7-Cl	CH_3	Ph	H	85.7	319—320 (Et$_2$O–EtOH)	$C_{16}H_{16}ClN \cdot HCl \cdot 0.3H_2O$	64.13 (64.05	5.92 5.99	4.67 4.50)	16[e]	89[f]	183[f]
1j	6-MeO	CH_3	Ph	H	82.8	284—286 (Et$_2$O–EtOH)	$C_{17}H_{19}NO \cdot HCl \cdot 0.25H_2O$	69.38 (69.63	7.13 7.13	4.76 4.88)	11	>600[g]	
1k	7-MeO	CH_3	Ph	H	89.7	264—265 (Et$_2$O–EtOH)	$C_{17}H_{19}NO \cdot HCl \cdot 0.2H_2O$	69.59 (69.91	7.01 7.39	4.77 4.75)	13[e]	58[e]	
1l	6,7-MeO	CH_3	Ph	H	67.2	260—262 (Et$_2$O–EtOH)	$C_{18}H_{21}NO_2 \cdot HCl \cdot 0.15H_2O$	67.03 (67.32	6.97 7.36	4.34 4.23)	9	12	
1m	6-OH	CH_3	Ph	H	36.9	299—300 (Et$_2$O–EtOH)	$C_{16}H_{17}NO \cdot HCl \cdot 0.25H_2O$	68.56 (68.91	6.65 6.65	4.99 4.99)	35	369[f]	
1n	6-Me	CH_3	Ph	H	65.7	309—310 (Et$_2$O–EtOH)	$C_{17}H_{19}N \cdot HCl \cdot 0.1H_2O$	74.09 (74.12	7.34 7.43	5.08 5.11)	11	142[f]	
1o	4-Me	CH_3	Ph	H	79.6	245—247 (Et$_2$O–EtOH)	$C_{17}H_{19}N \cdot HCl$	74.58 (74.34	7.36 7.12	5.12 5.15)	10	12	
1p	H	CH_3	CH_2Ph	H	59.8	214—216 (Et$_2$O–EtOH)	$C_{17}H_{19}N \cdot HCl \cdot 0.1H_2O$	74.08 (74.20	7.38 7.10	5.08 5.02)	44[g]	>600[g]	
1q	H	C_2H_5	CH_2Ph	H	85.2	229—230 (Et$_2$O–EtOH)	$C_{18}H_{21}N \cdot HCl \cdot 0.5H_2O$	72.83 (73.20	7.81 8.21	4.72 4.48)	10	70[f]	
1r	6-MeO	CH_3	CH_2Ph	H	65.5	264—265 (Et$_2$O–EtOH)	$C_{18}H_{21}NO \cdot HCl \cdot 0.5H_2O$	69.50 (69.69	7.38 7.31	4.50 4.43)	9	18	
1s	H	CH_3	CH_3	H	50.3	207—208[d] (Et$_2$O–EtOH)	$C_{11}H_{15}N \cdot HCl$	66.82 (66.79	8.15 8.46	7.08 6.82)	15		
1t	H	CH_3	Cyclohexyl	H	80.0	280—281 (Et$_2$O–EtOH)	$C_{16}H_{23}N \cdot HCl \cdot 0.05H_2O$	72.05 (72.21	9.11 9.51	5.25 5.17)	12	20[g]	
6a	H	CH_3	Ph	$PhCH_2$	61.0	102—103 (*n*-hexane)	$C_{23}H_{23}N$	88.14 (87.93	7.40 7.53	4.47 4.49)	7	7	
6b	H	CH_3	Ph	CH_3	88.5	39—40 (*n*-hexane)	$C_{17}H_{19}N$	86.03 (85.99	8.06 8.36	5.90 5.88)	17	>600[f]	
6c	H	CH_3	Ph	C_2H_5	74.3	193—194 (Et$_2$O–EtOH)	$C_{18}H_{21}N \cdot HCl \cdot 0.25H_2O$	73.95 (74.21	7.75 7.44	4.79 4.80)	11[f]	368[f]	>600[f]
6d	H	CH_3	Ph	$PhCH_2CH_2$	28.4	255—256 (Et$_2$O–EtOH)	$C_{24}H_{25}N \cdot HCl \cdot 0.1H_2O$	78.81 (78.77	7.22 7.30	3.82 3.79)	9	10	9
6e	6-MeO	CH_3	Ph	CH_3	70.8	68—70 (*n*-hexane)	$C_{18}H_{21}NO \cdot HCl \cdot 0.25H_2O$	80.31 (80.37	7.93 7.80	5.20 5.16)	12	11	253[e]

a) Convulsions were induced by i.c.v. NMDA (0.32 μg). Each value represents the mean of 5 animals. *b*) Ref. 13, mp 202—203 °C. *c*) Ref. 24, mp 225—226 °C obtained as the hydrochloride. *d*) Ref. 28, bp 125—126 °C (23 mmHg) obtained as the free base. *e*) $p<0.05$. *f*) $p<0.01$. *g*) $p<0.001$. Values without superscripts are not statistically significantly different from the control.

Table 2. Physical Properties and Anticonvulsant Activities of Stereoisomers of 1,2,3,4-Tetrahydroisoquinolines (**1a**, **1p**)

Compd. No.	Yield (%)	mp (°C) (Recryst. sol.)	$[\alpha]_D^{20}$ [a] (°)	Formula	Analysis (%) Calcd (Found)			Anticonvulsant activity[b] (s) (mg/kg, i.p.)		
					C	H	N	10	32	100
(+)-**1a**	11.8	302—303 (EtOH)	+12.0	$C_{16}H_{17}N \cdot HCl$	73.98 (73.76	6.98 6.58	5.45 5.31)	18	434[c]	>600[c]
(−)-**1a**	16.7	300—301 (EtOH)	−13.3	$C_{16}H_{17}N \cdot HCl$	73.98 (74.06	6.98 6.95	5.45 5.37)	9	9	140[d]
(+)-**1p**	9.4	220—221 (EtOH)	+4.4	$C_{17}H_{19}N \cdot HCl \cdot 0.2H_2O$	73.60 (73.74	7.41 7.09	5.04 4.94)		270[d]	>600[c]
(−)-**1p**	10.2	220—221 (EtOH)	−6.0	$C_{17}H_{19}N \cdot HCl$	74.57 (74.59	7.36 7.65	5.11 5.06)	7	10	16

a) $c = 1.0$ in EtOH. *b*) Convulsions were induced by i.c.v. NMDA (0.32 μg). Each value represents the mean of 5 animals. *c*) $p < 0.001$. *d*) $p < 0.01$. Values without superscripts are not statistically significantly different from the control.

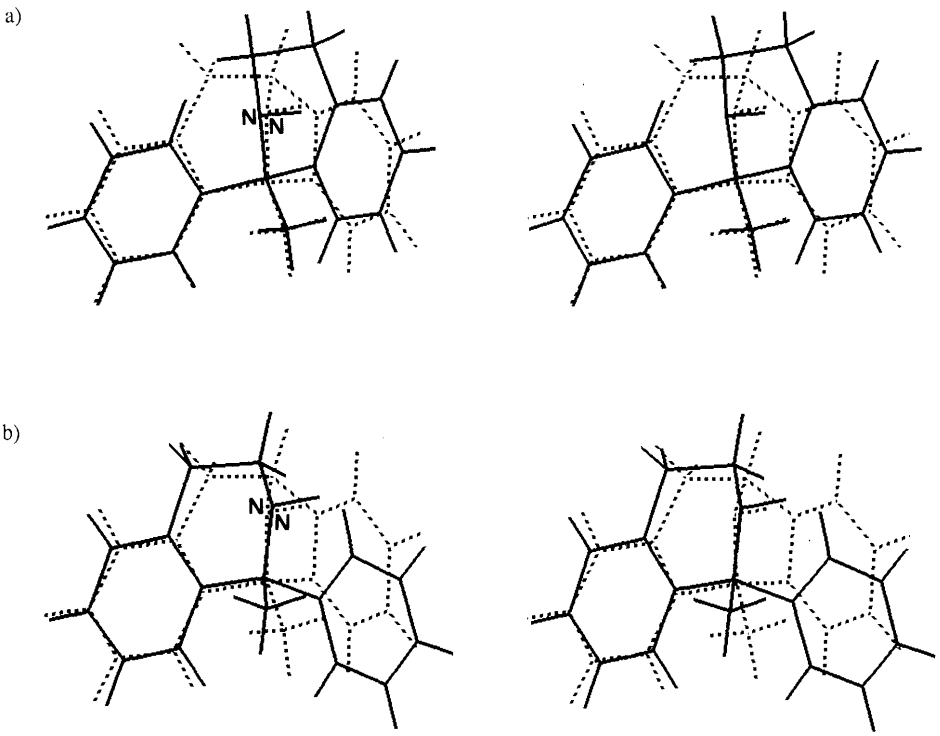


Fig. 3. Molecular Superpositions

a) Stereoview of the overlay of (*S*)-(+)-**1a** (solid line) onto MK801 (dashed line). *b*) Stereoview of the overlay of (*R*)-(−)-**1a** (solid line) onto MK801 (dashed line).

Table 3. Protective Activity of (+)-**1a** and MK801 on Ischemia-Induced CA1 Hippocampal Neurodegeneration in Rats

Group	Dose (mg/kg, i.p.)	Number of CA1 neurons[a] (/mm)
Sham-operated		128.4± 3.2
Control		20.6± 7.8
(+)-**1a**	10	31.4±16.4
	32	107.2±16.9[b]
Control		20.6± 7.8
MK801	3.2	44.4±18.3
	10	34.6±22.3
	32	94.3±33.5[c]

a) Each value represents as the mean ± S.E. of 3 animals. *b*) $p < 0.01$. *c*) $p < 0.05$. Values without superscripts are not statistically significantly different from the control.

activity against ischemia-induced CA1 hippocampal neurodegeneration in rats,[15] anti-hypoxic activity in mice, and acute toxicity in mice. The results for (+)-**1a** together with MK801 are presented in Tables 3 and 4.

Comparison of the results for i.c.v. and i.p. anticonvulsant activity of (+)-**1a** and MK801 showed that permeability of (+)-**1a** into the brain was comparable to that of MK801. Compound (+)-**1a** protected CA1 hippocampal neurons from ischemia-induced neuronal damage at 32 mg/kg i.p., which is comparable to the effective dose of MK801 (Table 3), although (+)-**1a** was almost 7-fold less potent than MK801 as an anticonvulsant (Table 4). Interestingly, (+)-**1a** also showed anti-hypoxic activity at 3.2—32 mg/kg i.p., while MK801 significantly reduced the survival time at 32 mg/kg i.p. (Table 4). The results suggested that the anti-hypoxic activity of (+)-**1a** could enhance its neuroprotective effect. In addition, (+)-**1a** showed reduced ability to induce the unwanted side effect of PCP-like stereotypy as compared with MK801 (Table 4).[16]

In conclusion, (+)-**1a** (FR115427), a novel non-

Table 4. Pharmacological Data for (+)-**1a** (FR115427) and MK801

Compound	[^{3}H]MK801[a] K_i, nM	Anticonvulsant activities[b] ED_{50}		Anti-hypoxic activities[c] (% of control) (mg/kg, i.p.)				PCP-like stereotypy[d] MED (mg/kg, i.p.)	Acute toxicity[e] LD_{50} (mg/kg, i.p.)
		μg, i.c.v.	mg/kg, i.p.	1	3.2	10	32		
(+)-**1a** (FR115427)	35.4 ±3.8	0.12	8.7	111	120[f]	119[g]	153[h]	10	200
MK801	3.57±0.4	0.017	1.2	105	95	94	87[f]	0.32	110

a) Ref. 10. *b*) Convulsions were induced by i.c.v. NMDA (0.1 μg). The ED_{50} value indicates a dose which inhibits the initial seizure to overy 300 s. *c*) Each value represents the mean of 5 animals compared with the control group. *d*) Ref. 17. MED indicates a minimum effective dose of inducing PCP-like stereotypy, such as turning and head moving. *e*) LD_{50} values are calculated from the lethality within 7 d after an i.p. administration of a test compound. *f*) $p<0.05$. *g*) $p<0.01$. *h*) $p<0.001$. Values without superscripts are not statistically significantly different from the control.

competitive NMDA antagonist, showed anticonvulsant activity against i.c.v. NMDA-induced seizure, anti-hypoxic activity, and neuroprotective activity against ischemia-induced degeneration of CA1 hippocampal neurons. These results indicate that FR115427 has potential cerebral protective activity with weaker unwanted side effects, such as PCP-like stereotypy. Further experiments on the neuroprotective activities of FR115427 in other ischemic animal models have been reported elsewhere.[17]

Experimental

Melting points were determined using a Thomas–Hoover capillary melting point apparatus and are uncorrected. ^{1}H-Nuclear magnetic resonance (^{1}H-NMR) spectra were obtained on a Varian EM-390 NMR (90 MHz) or a Bruker AC-200P (200 MHz) spectrometer using tetramethylsilane as an internal standard. Infrared (IR) spectra were recorded on a Hitachi 260-10 spectrophotometer. Mass spectral (MS) measurements were made on a Hitachi M-80 or a JEOL-D300 mass spectrometer.

2-Benzyl-1-phenyl-3,4-dihydroisoquinolinium Bromide (5a) Benzyl bromide (175.9 ml, 1.48 mol) was added dropwise to a solution of 1-phenyl-3,4-dihydroisoquinoline (**4a**)[18] (292.0 g, 1.41 mol) in CH_3CN (3.0 l) and the mixture was refluxed for 1 h, then allowed to cool to room temperature. It was concentrated to 500 ml *in vacuo*, and ether (1.0 l) was added. The mixture was stirred at 0 °C, and the crystalline precipitates were collected by filtration and washed with ether to give **5a** (471.2 g, 88.3%) as a pale yellow solid, mp 181—183 °C. IR (Nujol): 1620, 1600, 1560 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.25 (2H, t, J=7.5 Hz), 4.14 (2H, t, J=7.5 Hz), 5.03 (2H, s), 6.86—7.84 (14H, m). Compounds **5b**—**s** were prepared by the same procedures as employed for the preparation of **5a** and were not further purified or analyzed before use in the next step.

2-Benzyl-1-phenyl-4,5-dihydro-3*H*-2-benzazepinium Bromide (**5b**): **5b** was prepared from 1-phenyl-4,5-dihydro-3*H*-2-benzazepine[12] in 73.4% yield as a pale yellow solid, mp 236—238 °C (CH_3CN–ether). IR (Nujol): 1610, 1595, 1565 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.93—2.00 (2H, m), 2.87—3.04 (2H, m), 3.86—3.92 (2H, m), 5.35 (2H, s), 7.01 (1H, d, J=7.3 Hz), 7.31—7.84 (13H, m).

2-Benzyl-1-(2-chlorophenyl)-3,4-dihydroisoquinolinium Iodide (**5c**): **5c** was prepared from 1-(2-chlorophenyl)-3,4-dihydroisoquinoline[19] and benzyl iodide in 92.8% yield as a yellow solid, mp 181—182 °C (CH_3CN–ether). IR (Nujol): 1620, 1600, 1565 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.31—3.39 (2H, m), 4.14—4.44 (2H, m), 5.03 (1H, d, J=14.7 Hz), 5.26 (1H, d, J=14.7 Hz), 7.04—7.08 (1H, m), 7.04—7.08 (1H, d, J=7.8 Hz), 7.44—7.53 (6H, m), 7.64 (1H, d, J=7.5 Hz), 7.73—7.91 (4H, m), 8.04—8.10 (1H, m).

2-Benzyl-1-(3-chlorophenyl)-3,4-dihydroisoquinolinium Iodide (**5d**): **5d** was prepared from 1-(3-chlorophenyl)-3,4-dihydroisoquinoline[19] and benzyl iodide in 85.5% yield as a yellow solid, mp 191—192 °C (CH_3CN–ether). IR (Nujol): 1615, 1600, 1560 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.26—3.50 (2H, m), 4.14—4.40 (2H, m), 5.12 (2H, s), 7.18 (1H, d, J=7.0 Hz), 7.50—8.04 (13H, m).

2-Benzyl-1-(4-chlorophenyl)-3,4-dihydroisoquinolinium Iodide (**5e**): **5e** was prepared from 1-(4-chlorophenyl)-3,4-dihydroisoquinoline[20] and benzyl iodide in 41.3% yield as a yellow solid, mp 188—189 °C (THF–ether). IR (Nujol): 1615, 1600, 1565 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.28—3.35 (2H, m), 4.13—4.20 (2H, m), 5.09 (2H, s), 7.07 (1H, d, J=7.5 Hz), 7.41—7.51 (6H, m), 7.60 (1H, d, J=7.4 Hz), 7.81—7.88 (5H, m).

2-Benzyl-5-chloro-1-phenyl-3,4-dihydroisoquinolinium Iodide (**5f**): **5f** was prepared from 5-chloro-1-phenyl-3,4-dihydroisoquinoline[21] and benzyl iodide in 77.2% yield as a yellow solid, mp 244—246 °C (ether). IR (Nujol): 1620, 1560 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.32—3.39 (2H, m), 4.17—4.25 (2H, m), 5.11 (2H, s), 7.02 (1H, d, J=7.1 Hz), 7.41—7.52 (6H, m), 7.67—7.97 (5H, m), 7.99 (1H, d, J=7.2 Hz).

2-Benzyl-6-chloro-1-phenyl-3,4-dihydroisoquinolinium Bromide (**5g**): **5g** was prepared from 6-chloro-1-phenyl-3,4-dihydroisoquinoline[19] in 38.4% yield as a pale yellow solid.

2-Benzyl-7-chloro-1-phenyl-3,4-dihydroisoquinolinium Iodide (**5h**): **5h** was prepared from 7-chloro-1-phenyl-3,4-dihydroisoquinoline[22] and benzyl iodide in 62.8% yield as a yellow solid, mp 236—237 °C (ether). IR (Nujol): 1620, 1555 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.27—3.51 (2H, m), 4.18—4.38 (2H, m), 5.17 (2H, s), 6.98 (1H, d, J=2.2 Hz), 7.48—7.52 (5H, m), 7.74—7.96 (7H, m).

2-Benzyl-7-methoxy-1-phenyl-3,4-dihydroisoquinolinium Iodide (**5i**): **5i** was prepared from 7-methoxy-1-phenyl-3,4-dihydroisoquinoline[23] and benzyl iodide in 81.3% yield as a yellow solid, mp 190—191 °C (ether). IR (Nujol): 1620, 1600, 1560 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.18—3.26 (2H, m), 3.34 (3H, s), 3.67 (3H, s), 4.11—4.19 (2H, m), 5.08 (2H, s), 6.40 (1H, d, J=2.2 Hz), 7.40—7.58 (7H, m), 7.75—7.76 (5H, m).

2-Benzyl-6,7-dimethoxy-1-phenyl-3,4-dihydroisoquinolinium Iodide (**5j**): **5j** was prepared from 6,7-dimethoxy-1-phenyl-3,4-dihydroisoquinoline[24] and benzyl iodide in 78.4% yield as a pale yellow solid, mp 176—178 °C (ether). IR (Nujol): 1620, 1600, 1560 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.18—3.25 (2H, m), 3.35 (3H, s), 3.50 (3H, s), 3.97 (3H, s), 4.06—4.14 (2H, m), 5.00 (2H, s), 6.36 (1H, s), 7.30 (1H, s), 7.40—7.42 (5H, m), 7.72—7.74 (5H, m).

2-Benzyl-4-methyl-1-phenyl-3,4-dihydroisoquinolinium Iodide (**5k**): **5k** was prepared from 4-methyl-1-phenyl-3,4-dihydroisoquinoline[25] and benzyl iodide in 86.3% yield as a yellow solid, mp 195—197 °C (ether). IR (Nujol): 1610, 1595, 1565 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.14 (3H, d, J=7.0 Hz), 3.98 (1H, dd, J=7.4, 14.6 Hz), 4.28 (1H, dd, J=7.4, 14.6 Hz), 4.99—5.20 (2H, m), 7.05 (1H, d, J=7.2 Hz), 7.44—7.53 (6H, m), 7.65 (1H, d, J=7.6 Hz), 7.77—7.92 (6H, m).

1,2-Dibenzyl-3,4-dihydroisoquinolinium Bromide (**5l**): **5l** was prepared from 1-benzyl-3,4-dihydroisoquinoline[18] in 71.6% yield as a pale yellow solid, mp 184—186 °C (CH_3CN–ether). IR (Nujol): 1620, 1600, 1570 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.09—3.23 (2H, m), 4.04—4.11 (2H, m), 4.99 (2H, s), 5.56 (2H, s), 7.24—7.39 (5H, m), 7.43—7.55 (7H, m), 7.72—7.79 (1H, m), 8.17 (1H, d, J=7.8 Hz).

1,2-Dibenzyl-6-methoxy-3,4-dihydroisoquinolinium Bromide (**5m**): **5m** was prepared from 1-benzyl-3,4-dihydro-6-methoxyisoquinoline[26] in 32.7% yield as a pale yellow solid, mp 149—150 °C (CH_3CN–ether). IR (Nujol): 1620, 1600, 1560 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.13—3.20 (2H, m), 3.91 (3H, s), 3.97—4.04 (2H, m), 4.90 (2H, s), 4.45 (2H, s), 7.03—7.11 (2H, m), 7.29—7.40 (10H, m), 8.16 (1H, d, J=8.8 Hz).

2-Benzyl-1-cyclohexyl-3,4-dihydroisoquinolinium Bromide (**5n**): **5n** was prepared from 1-cyclohexyl-3,4-dihydroisoquinoline[27] in 70.4% yield as a pale yellow solid, mp 162—164 °C (ether). IR (Nujol): 1600, 1560 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.39—2.08 (11H, m), 3.07—3.14 (2H, m), 3.97—4.04 (2H, m), 5.50 (2H, s), 4.45 (2H, s), 7.42—7.61 (7H, m), 7.75—7.83 (1H, m), 8.34 (1H, d, J=7.8 Hz).

2-Methyl-1-phenyl-3,4-dihydroisoquinolinium Iodide (**5o**): **5o** was prepared from 1-phenyl-3,4-dihydroisoquinoline[18] and methyl iodide in

75.5% yield as a yellow solid, mp 185—186 °C (ether). IR (Nujol): 1640, 1600, 1565 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.28—3.51 (2H, m), 3.52 (3H, s), 4.22—4.38 (2H, m), 6.95 (1H, d, J=7.8 Hz), 7.33—7.86 (8H, m).

2-Ethyl-1-phenyl-3,4-dihydroisoquinolinium Iodide (**5p**): **5p** was prepared from 1-phenyl-3,4-dihydroisoquinoline[18] and ethyl iodide in 88.5% yield as a pale yellow solid, mp 165—166 °C (ether). IR (Nujol): 1620, 1600, 1565 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.35 (3H, t, J=7.0 Hz), 3.34—3.45 (2H, m), 3.78 (2H, t, J=7.0 Hz), 4.28—4.36 (2H, m), 6.92 (1H, d, J=7.8 Hz), 7.38—7.83 (8H, m).

2-Benzyl-6-methoxy-1-phenyl-3,4-dihydroisoquinolinium bromide (**5q**), 2-benzyl-6-methyl-1-phenyl-3,4-dihydroisoquinolinium iodide (**5r**) and 2-phenethyl-1-phenyl-3,4-dihydroisoquinolinium bromide (**5s**) were not isolated before use in the next step.

2-Benzyl-1-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline (6a) A solution of 2.0 M CH_3MgBr (700 ml, 1.4 mol) in THF was added dropwise to a suspension of **5a** (353.1 g, 0.93 mol) in THF for 1 h at room temperature. The mixture was stirred for an additional 1 h, then a solution of NH_4Cl (300 g, 5.6 mol) in water (650 ml) and ethyl acetate (3.5 l) were added at 0 °C. The organic layer was separated, washed with water (1.0 l) and brine (1.0 l), dried over $MgSO_4$, and evaporated *in vacuo*. The residue was recrystallized from EtOH (500 ml) to give **6a** (254.0 g, 87.1%) as a white solid. Compounds (**6b—v**) were prepared by the same procedures as employed for the preparation of **6a** and were not further purified or analyzed before use in the next step. Physical properties and spectral data for **6a—e** are listed in Tables 1 and 5.

2-Benzyl-1-methyl-1-phenyl-1,2,4,5-tetrahydro-3*H*-2-benzazepine (**6f**): **6f** was prepared from **5b** in 79.8% yield as a white solid, mp 134—135 °C (*n*-hexane). IR (Nujol): 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.11—1.29 (1H, m), 1.72—1.90 (1H, m), 1.89 (3H, s), 2.56—2.84 (3H, m), 3.34 (2H, m), 3.78 (1H, d, J=15.3 Hz), 7.05—7.44 (14H, m). MS *m/z*: 312 ($M^+ - CH_3$).

2-Benzyl-1-ethyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline (**6g**): **6g** was prepared from **5a** and EtMgBr in 54.7% yield as a white solid, mp 96—97 °C (*n*-hexane). IR (Nujol): 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.85 (3H, t, J=7 Hz), 2.12 (1H, dd, J=7, 14 Hz), 2.46—3.05 (5H, m), 3.88 (1H, dd, J=7, 14 Hz), 6.70—7.30 (14H, m). MS *m/z*: 327 (M^+).

2-Benzyl-1-(2-chlorophenyl)-1-methyl-1,2,3,4-tetrahydroisoquinoline (**6h**): **6h** was prepared from **5c** in 95.6% yield as a colorless oil. ^{1}H-NMR (DMSO-d_6) δ: 2.10 (3H, s), 3.20—3.67 (4H, m), 3.88—4.15 (2H, m), 6.57 (1H, d, J=7 Hz), 7.15—7.80 (12H, m). MS *m/z*: 347 (M^+).

2-Benzyl-1-methyl-1-(3-chlorophenyl)-1,2,3,4-tetrahydroisoquinoline (**6i**): **6i** was prepared from **5d** in 92.4% yield as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.81 (3H, s), 2.78—3.17 (4H, m), 3.24—3.75 (2H, m), 6.62 (1H, d, J=7 Hz), 7.02—7.70 (12H, m). MS *m/z*: 347 (M^+).

2-Benzyl-1-(4-chlorophenyl)-1-methyl-1,2,3,4-tetrahydroisoquinoline (**6j**): **6j** was prepared from **5e** in 73.5% yield as a white solid, mp 134—135 °C (*n*-hexane). ^{1}H-NMR ($CDCl_3$) δ: 1.82 (3H, s), 2.60—3.05 (4H, m), 3.28 (1H, d, J=14 Hz), 3.65 (1H, d, J=14 Hz), 6.72 (1H, d, J=7 Hz), 6.94—8.16 (12H, m). MS *m/z*: 347 (M^+).

2-Benzyl-5-chloro-1-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline (**6k**): **6k** was prepared from **5f** in 53.8% yield as a white solid, mp 98—100 °C (*n*-hexane). IR (Nujol): 1570 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.80 (3H, s), 2.73—2.95 (4H, m), 3.26 (1H, d, J=13.9 Hz), 3.55 (1H, d, J=13.9 Hz), 6.60 (1H, d, J=7.8 Hz), 6.90 (1H, dd, J=7.8, 7.8 Hz), 7.10—7.33 (10H, m), 7.53—7.59 (1H, m).

2-Benzyl-6-chloro-1-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline (**6l**): **6l** was prepared from **5g** in 83.1% yield as a colorless oil. IR (film): 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.77 (3H, s), 2.62—3.09 (4H, m), 3.27 (1H, d, J=13.8 Hz), 3.56 (1H, d, J=13.8 Hz), 6.60 (1H, d, J=8.4 Hz), 6.90—7.34 (11H, m), 7.55—7.60 (1H, m). MS *m/z*: 347 (M^+).

2-Benzyl-7-chloro-1-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline (**6m**): **6m** was prepared from **5h** in 61.4% yield as a white solid, mp 96—97 °C (*n*-hexane). IR (Nujol): 1600 cm^{-1}.

^{1}H-NMR ($CDCl_3$) δ: 1.85 (3H, s), 2.60—3.15 (4H, m), 3.30 (1H, d, J=14 Hz), 3.62 (1H, d, J=14 Hz), 6.73 (1H, d, J=2 Hz), 7.04—7.74 (12H, m). MS *m/z*: 347 (M^+).

2-Benzyl-6-methoxy-1-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline (**6n**): **6n** was prepared from **5q** in 38.9% yield as a white solid, mp 81—82 °C (MeOH). IR (Nujol): 1600, 1570 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.75 (3H, s), 2.42—2.95 (4H, m), 3.20 (1H, d, J=14 Hz), 3.55 (1H, d, J=14 Hz), 3.67 (3H, s), 6.48—6.62 (3H, m), 7.08—7.70 (10H, m).

2-Benzyl-6,7-dimethoxy-1-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline (**6o**): **6o** was prepared from **5j** in 74.3% yield as a white solid, mp 100—101 °C (*n*-hexane). IR (Nujol): 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.80 (3H, s), 2.57—2.66 (2H, m), 2.80—2.85 (2H, m), 2.94—3.09 (2H, m), 3.30 (1H, d, J=13.8 Hz), 3.55 (1H, d, J=13.8 Hz), 3.58 (3H, s), 3.83 (3H, s), 6.12 (1H, s), 6.53 (1H, s), 7.13—7.32 (8H, m), 7.57—7.61 (2H, m).

2-Benzyl-1,6-dimethyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline (**6p**): **6p** was prepared from **5r** in 100.0% yield as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.79 (3H, s), 2.24 (3H, s), 2.56—3.24 (4H, m), 3.38 (1H, d, J=13.8 Hz), 3.55 (1H, d, J=13.8 Hz), 6.57 (1H, d, J=8.0 Hz), 6.78—6.88 (2H, m), 7.13—7.32 (8H, m), 7.58—7.63 (2H, m). MS *m/z*: 327 (M^+).

2-Benzyl-1,4-dimethyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline (**6q**): **6q** was prepared from **5k** in 71.9% yield as a white solid, mp 125—126 °C (*n*-hexane). IR (Nujol): 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.22 (3H, d, J=7.0 Hz), 1.76 (3H, s), 2.49—3.05 (3H, m), 3.18 (1H, d, J=13.3 Hz), 3.63 (1H, d, J=13.3 Hz), 6.64 (1H, d, J=7.2 Hz), 6.92—7.35 (11H, m), 7.62—7.66 (2H, m). MS *m/z*: 327 (M^+).

1,2-Dibenzyl-1-methyl-1,2,3,4-tetrahydroisoquinoline (**6r**): **6r** was prepared from **5l** in 89.9% yield as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.66 (3H, s), 2.65—2.80 (4H, m), 3.36 (2H, s), 3.72 (1H, d, J=14 Hz), 4.27 (1H, d, J=14 Hz), 6.85—7.45 (14H, m). MS *m/z*: 328 (M^++1).

1,2-Dibenzyl-1-ethyl-1,2,3,4-tetrahydroisoquinoline (**6s**): **6s** was prepared from **5l** and EtMgBr in 95.7% yield as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, t, J=7.2 Hz), 1.92—2.24 (2H, m), 2.44—2.86 (4H, m), 3.14 (1H, d, J=14.4 Hz), 3.21 (1H, d, J=14.4 Hz), 4.09 (1H, d, J=14.6 Hz), 4.25 (1H, d, J=14.6 Hz), 6.78—6.90 (4H, m), 7.00—7.28 (6H, m), 7.54—7.92 (4H, m).

2-Benzyl-1-cyclohexyl-1-methyl-1,2,3,4-tetrahydroisoquinoline (**6t**): **6t** was prepared from **5n** in 100.0% yield as a colorless oil. IR (Nujol): 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.16—2.10 (11H, m), 1.54 (3H, s), 2.72—2.84 (4H, m), 3.28 (1H, d, J=14 Hz), 4.22 (1H, d, J=14 Hz), 7.12—7.54 (9H, m).

2-Benzyl-7-methoxy-1-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline (**6u**) and 1,2-dibenzyl-1-methyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline (**6v**) were not isolated before use in the next step.

1-Methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline Hydrochloride (1a) A mixture of **6a** (190.9 g, 0.61 mol) and 10% Pd–C (10 g) in acetic acid (3.0 l) was hydrogenated at atmospheric pressure of hydrogen for 4 h. Insoluble materials were removed by filtration, and the filtrate was concentrated *in vacuo*. The residue was dissolved in a mixture of ethyl acetate (2.0 l) and water (1.0 l), and the solution was adjusted to pH 10 with 4 N aqueous NaOH. The organic layer was separated, and then washed with water (1.0 l) and brine (1.0 l), dried over $MgSO_4$, and evaporated *in vacuo* to give salt-free **1a** (140.1 g, 100.0%) as a pale yellow oil. The salt-free **1a** (5.0 g) was dissolved in EtOH (50 ml), and a solution of 6 N HCl in EtOH (5 ml) was added. The crystalline prepicitates were collected by filtration, and washed with EtOH to give **1a** (5.2 g, 89.3%) as a white solid. Compounds **1b—t** and **3** were prepared from **6f—v** by the same procedures as employed for the preparation of **1a**. Physical properties and spectral data for these compounds are listed in Tables 1 and 5.

(+)-1-Methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline Hydrochloride ((+)-1a) A solution of (+)-di-*p*-toluoyl-D-tartaric acid (298.3 g, 0.77 mol) in EtOH (2.98 l) was added slowly to a solution of salt-free **1a** (172.4 g, 0.77 mol) in EtOH (1.72 l), and the mixture was allowed to stand for 2 d at room temperature. The crystalline precipitates were collected by filtration, washed with cold EtOH, and suspended in a mixture of ethyl acetate (1.0 l) and water (500 ml). The mixture was adjusted to pH 10 with 4 N aqueous NaOH, and then the organic layer was separated, washed with water (500 ml) and brine (500 ml), dried over $MgSO_4$, and evaporated *in vacuo*. The residue was dissolved in EtOH (500 ml), and a solution of 6 N HCl in EtOH (45 ml) was added. The mixture was stirred for 1 h at 0 °C, and the white crystals were collected by filtration and washed with cold EtOH to give (+)-**1a** (39.0 g, 22.7%). The enantiomeric excess of (+)-**1a** was determined to be 99.5% ee by treatment of (+)-**1a** with succinimide *l*-(−)-1-phenylethylcarbamate and triethylamine to obtain the urea derivative, which was analyzed by HPLC using a C-18 column with CH_3CN–H_2O (3:2) at 220 nm. Enantiomer (−)-**1a** was separated by the use of (−)-di-*p*-toluoyl-L-tartaric acid as a resolving agent, and its enantiomeric excess was determined to be 99.1% ee. Optical resolution of **1p** was also performed by the same procedures as employed for the separation of **1a**, and the values of enantiomeric excess of (+)- and (−)-**1p** were determined to be 94.1 and 91.1% ee, respectively. Physical properties and spectral data for these compounds are listed in Table 2.

Table 5. Spectral Data for 1,2,3,4-Tetrahydroisoquinolines (**1**, **6**) and 2-Benzazepine (**3**)

Compd. No.	MS *m/z*	IR (Nujol) cm^{-1}	Solvent[a]	^{1}H-NMR (ppm)[b]
1a	222	1585	A	2.10 (3H, s), 2.80—3.50 (4H, m), 7.05—7.45 (9H, m), 9.80 (1H, s), 10.40 (1H, s)
1c	236	1580	A	0.98 (3H, t, J=7 Hz), 2.56—3.36 (6H, m), 7.16—7.36 (4H, m), 9.65—10.26 (2H, br)
1d	257	1580	A	2.26 (3H, s), 3.10—3.67 (4H, m), 6.59—6.77 (1H, m), 7.13—7.38 (3H, m), 7.50—7.67 (4H, m), 7.87—8.18 (1H, br), 8.25—8.55 (1H, br)
1e	257	1580	A	2.13 (3H, s), 2.90—3.55 (4H, m), 7.05—7.50 (8H, m)
1f	257	1580	A	2.26 (3H, s), 2.80—3.50 (4H, m), 7.00—7.53 (8H, m), 10.12 (1H, br), 10.55 (1H, br)
1g	257	1575	A	2.16 (3H, s), 2.90—3.40 (4H, m), 7.05—7.56 (8H, m)
1h	257	1580	A	2.12 (3H, s), 3.01—3.49 (4H, m), 7.15—7.46 (8H, m), 9.82 (1H, br), 10.46 (1H, br)
1i	257	1585	A	2.24 (3H, s), 3.10—3.40 (4H, m), 7.38—7.62 (8H, m)
1j	252	1605, 1580	A	2.13 (3H, s), 2.88—3.52 (4H, m), 3.80 (3H, s), 6.78—7.12 (3H, m), 7.26—7.36 (4H, m), 9.87 (1H, br), 10.03 (1H, br)
1k	252	1615, 1585	A	2.25 (3H, s), 3.05—3.34 (4H, m), 3.76 (3H, s), 6.74 (1H, d, J=2 Hz), 7.04 (1H, dd, J=2, 8 Hz), 7.38 (1H, d, J=8 Hz), 7.44—7.53 (4H, m), 10.12 (1H, br), 10.60 (1H, br)
1l	283	1610, 1580	A	2.16 (3H, s), 2.95—3.25 (4H, m), 3.66 (3H, s), 3.82 (3H, s), 6.67 (1H, s), 6.90 (1H, s), 7.39—7.45 (4H, m), 9.92 (1H, br), 10.40 (1H, br)
1m	238	1620, 1580	A	2.09 (3H, s), 2.93—3.22 (4H, m), 6.78—6.92 (3H, m), 7.37—7.48 (4H, m), 9.96 (1H, br), 10.25 (1H, br)
1n	237	1580	A	2.09 (3H, s), 2.31 (3H, s), 2.81—3.28 (4H, m), 6.95—7.12 (3H, m), 7.28—7.35 (4H, m)
1o	237	1585	A	1.25 (3H, d, J=7 Hz), 2.22 (3H, s), 3.20—3.78 (3H, m), 7.26—7.62 (9H, m), 10.00—10.72 (2H, br)
1p	237	1585	A	1.61 (3H, s), 2.06—2.17 (4H, m), 3.38 (2H, s), 7.24—7.28 (9H, m)
1q	250	1590	A	1.06 (3H, t, J=7 Hz), 2.09 (2H, q, J=7 Hz), 2.81—3.46 (6H, m), 6.97—7.30 (9H, m), 9.20 (1H, br), 10.15 (1H, br)
1r	267	1605, 1580	A	1.60 (3H, s), 3.01—3.49 (6H, m), 3.75 (3H, s), 6.75—6.84 (3H, m), 7.16—7.28 (4H, m), 9.28 (1H, br), 9.95 (1H, br)
1t	228	1590	A	1.00—2.35 (11H, m), 1.71 (3H, s), 2.80—3.55 (4H, m), 7.22—7.40 (4H, m)
3	237	1580, 1480	A	1.70—1.85 (2H, m), 2.22 (3H, s), 2.38—2.91 (2H, m), 3.20—3.38 (2H, m), 7.23—7.55 (10H, m)
6a	313	1600, 1580	B	1.78 (3H, s), 2.58—3.10 (4H, m), 3.22 (1H, d, J=14 Hz), 3.56 (1H, d, J=14 Hz), 6.60—7.65 (14H, m)
6b	237	1600, 1580	B	1.71 (3H, s), 2.13 (3H, s), 2.72—3.24 (4H, m), 6.65—7.46 (9H, m)
6c	251	1580	A	1.21, 1.25 (total 3H, t, J=7 Hz), 2.03, 2.34 (total 3H, s), 2.87—3.70 (6H, m), 6.62—7.70 (9H, m)
6d	312	1600, 1580	A	2.14, 2.48 (total 3H, s), 3.18—3.35 (4H, m), 3.73—3.88 (4H, m), 7.25—7.90 (14H, m)
6e	267	1600, 1580	B	1.66 (3H, s), 2.17 (3H, s), 2.92—3.10 (4H, m), 3.78 (3H, s), 6.60—6.73 (3H, m), 7.24—7.48 (4H, m)

a) A, DMSO-d_6; B, $CDCl_3$. *b*) Listed as chemical shifts (number of protons, multiplicity, coupling constant).

Biological Activities. Anticonvulsant Activities against NMDA Induced Seizures in Mice Five ICR male mice of the same age were used per group. One group of mice was administered i.p. with a test compound dissolved in saline, and another group was administered with saline 30 min before the experiment. NMDA (0.1 or 0.32 μg) dissolved in saline (0.5 μl) was injected i.c.v. to each mouse. Each mouse was then placed in a plastic cage and observed for 10 min to confirm the occurrence of clonic and tonic seizures, and the latency of initial seizure (s) was measured.

Anti-hypoxia (98% N_2–2% O_2) Activities in Mice Two mice were maintained in a closed glass chamber in which a mixture of 98% nitrogen and 2% oxygen was circulated, and their survival time was measured. One mouse was pre-treated i.p. with a test compound dissolved in saline, and the other with saline 30 min before the experiment. Five mice were used in each group, and the mean values of the survival times of each group were compared.

Effects on Ischemia-Induced Delayed CA1 Hippocampal Neurodegeneration[15] Three male Wistar rats were used per group. The vertebral arteries were cauterized within the alar foramina and the common carotid arteries were exposed and looped with surgical suture under anesthesia with sodium thiopental (50 mg/kg, i.p.). Next day, both carotid arteries were occluded with an aneurysm clip for 20 min under ether anesthesia. One group of rats was administered i.p. with a test compound suspended in 0.5% methylcellulose 10 min prior to ischemic insult, and the other group was administered i.p. with 0.5% methylcellulose. Seven days later, rats were perfusion-fixed with fixative consisting of 1.5% glutamic dialdehyde and 1.0% paraformaldehyde in 0.1 M phosphate buffer (pH = 7.4). Perfusion was performed at a pressure of 160 cm H_2O. Neuronal cell damage was assessed by counting the number of pyramidal neurons appearing normal in a 1 mm length of CA1 pyramidal cell layer from each hippocampus in coronal sections (3—4 μm) stained with cresyl violet corresponding to 1.9—2.1 mm posterior to the bregma.

Table 6. Crystal Data for (+)-**1a** (+)-Di-*p*-toluoyl-D-tartrate

Formula	$C_{16}H_{17}N \cdot C_{20}H_{18}O_8$
Formula weight	609.67
Crystal color, habit	Colorless, prismatic
Crystal dimensions (mm)	0.25 × 0.10 × 0.10
Crystal system	Monoclinic
Space group	$P2_1$
Lattice parameters: a (Å)	7.882
b (Å)	12.115
c (Å)	16.471
β (°)	94.24
V (Å^3)	1568.4
Z value	2
Density (Calcd) (g/cm^3)	1.291

X-Ray Structure Determination Colorless prisms of (+)-**1a** (+)-di-*p*-toluoyl-D-tartrate were grown from ethanol. Diffraction measurements were performed on a Rigaku AFC-5R diffractometer using graphite-monochromated Mo$K\alpha$ radiation (λ=0.71069 Å). Crystal data are listed in Table 6. A total of 4083 reflections (3782 unique reflections) were collected using the $\omega-2\theta$ scan technique within a 2θ range of 55°. The structure was solved by a direct method and refined by a full-matrix least-squares procedure using 2788 reflections ($I_o > 2.5\sigma I$). The final refinement converged to R=0.041 and Rw=0.030.

Acknowledgements The authors wish to thank Mr. K. Imai of the Exploratory Laboratories for helpful advice on the calculation of

three-dimensional structures, and the staff members of the Analytical Research Laboratories for elemental analysis and measurement of NMR spectral data.

References and Notes

1) Takasugi H., Kuno A., Ohkubo M., *Eur. Pat. Appl.* EP336228 (1989) [*Chem. Abstr.*, **112**, 178706*d* (1990)].
2) For a recent review of NMDA receptor function, see: Cotman C. W., Iversen L. L., *Trends Neuroscience*, **10**, 263—302 (1987).
3) Meldrum B., Garthwaite J., *Trends Pharmacol. Sci.*, **11**, 379 (1990).
4) Thompson W. J., Anderson P. S., Britcher S. F., Lyle T. A., Thies J. E., Magill C. A., Varga S. L., Schwering J. E., Lyle P. A., Christy M. E., Evans B. E., Colton C. D., Holloway M. K., Springer J. P., Hirshfield J. M., Ball R. G., Amato J. S., Larsen R. D., Wong E. H. F., Kemp J. A., Tricklebank M. D., Singh L., Oles R., Priestly T., Marshall G. R., Knight A. R., Middlemiss D. N., Woodruff G. N., Iversen L. L., *J. Med. Chem.*, **33**, 789 (1990).
5) Olney J., Price M., Salles K. S., Labruyere J., Friedrich G., *Eur. J. Pharmacol.*, **141**, 357 (1987).
6) McDonald J. W., Silverstein F. S., Johnston M. V., *Eur. J. Pharmacol.*, **140**, 359 (1987).
7) Gill R., Brazell C., Woodruff G. N., Kemp J. A., *Br. J. Pharmacol.*, **103**, 2030 (1991).
8) Clineschmidt B. V., Martin G. E., Bunting P. R., *Drug. Devel. Res.*, **2**, 123 (1982).
9) Willett J., Balster R. L., *Fed. Proc.*, **46**, Abst. 2297 (1987).
10) Sherriffs H. J., Shirakawa K., Kelly J. S., Olverman H. J., Kuno A., Okubo M., Butcher S. P., *Eur. J. Pharmacol.*, **247**, 319 (1993).
11) Bischler A., Napieralski B., *Chem. Ber.*, **26**, 1903 (1893).
12) Trybulski E. J., Fryer R. I., Reeder E., Vitone S., Todaro L., *J. Org. Chem.*, **51**, 2191 (1986).
13) Gast G., Schmutz J., Sorg D., *Helv. Chim. Acta*, **60**, 1644 (1977).
14) The isoquinoline rings of (*S*)-(+) and (*R*)-(−)-**1a** were overlaid onto the part of the isoindoline ring and the isoquinoline ring in MK801, respectively.
15) Pulsinelli W. A., Brierley J. B., Plum F., *Ann. Neurol.*, **11**, 491 (1982).
16) Nakanishi H., Katsuta K., Ueda Y., Takasugi H., Kuno A., Ohkubo M., Ogita K., Yoneda Y., Shirakawa K., Yoshida K., *Psychopharmacology*, **117**, 172 (1995).
17) *a*) Katsuta K., Nakanishi H., Shirakawa K., Yoshida K., Takagi K., Tamura A., *J. Cereb. Blood Flow and Metab.*, **15**, 345 (1995); *b*) Nakanishi H., Katsuta K., Koide T., Ueda Y., Shirakawa K., Yoshida K., *Jpn. J. Pharmacol.*, **64**, 189 (1994).
18) Yamada S., Omar A.-M. M. E., *Chem. Pharm. Bull.*, **12**, 249 (1964).
19) This compound was prepared by using the Bischler–Napieralski reaction[11] from the amide which was obtained from the appropriate 2-arylethylamine and benzoyl chloride, and was not purified or analyzed before use in the next step.
20) Zhou Z., Gu K., Shen X., Chen Z., Lin J., Song G., *Shanghai Yike Daxaue Xuebao*, **14**, 15 (1987) [*Chem. Abstr.*, **108**, 94357 (1988)].
21) Suzuki Y., Tsukamoto K., Mikami T., Hasegawa Y., Satoh M., Yamamoto N., Miyasaka K., Mikami T., Funakoshi S., *Eur. Pat. Appl.* EP13411 (1980) [*Chem. Abstr.*, **94**, 139635 (1981)].
22) Takacs K., Puskas M. E., Marmarosi M. T., Simay A., Ajzert I. K., Pap M. H., Literati N. P., Toth L., *Hung. Teljes.* HU25548 (1983) [*Chem. Abstr.*, **100**, 51462 (1984)].
23) Lantos I., Bhattacharjee D., Eggleston D. S., *J. Org. Chem.*, **51**, 4147 (1986).
24) Georgiev V. S., Carlson R. P., Inwegen R. G. V., Khandwala A., *J. Med. Chem.*, **22**, 348 (1979).
25) Govindan C. K., Taylor G., *J. Org. Chem.*, **48**, 5348 (1983).
26) Stambach J. F., Jung L., *Tetrahedron*, **41**, 169 (1985).
27) Gray N. M., Cheng B. K., Mick S. J., Lair C. M., Contreras P. C., *J. Med. Chem.*, **32**, 1242 (1989).
28) Bailey D. M., DeGrazia C. G., Lape H. E., Frering R., Fort D., Skulan T., *J. Med. Chem.*, **16**, 151 (1973).