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The Effect of *N*-Substituted Alkyl Groups on Anticonvulsant Activities of *N*-Cbz-α-amino-*N*-alkylglutarimides

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In order to examine the effects of *N*-substituted alkyl group on the anticonvulsant activities of *N*-Cbz-α-aminoglutarimides as novel anticonvulsants with broad spectrum, a series of (R) or (S) *N*-Cbz-α-amino-*N*-alkylglutarimides (**1** and **2**) were prepared from the corresponding (R) or (S) *N*-Cbz-glutamic acidand evaluated for the anticonvulsant activities in the maximal electroshock seizure(MES) test and pentylenetetrazol induced seizure(PTZ) test, including the neurotoxicity. The most potent compound in the MES test was (S) *N*-Cbz-α-amino-*N*-methylglutarimide(ED_{50}=36.3 mg/kg, PI=1.7). This compound was also most potent in the PTZ test (ED_{50}=12.5 mg/kg, PI=5.0). The order of anticonvulsant activities against the MES test as evaluated from ED_{50} values for (R) series was *N*-methyl > *N*-H > *N*-ethyl > *N*-allyl ; for the (S) series *N*-methyl > *N*-H > *N*-ethyl > *N*-allyl > *N*-isobutyl compound. Against the PTZ tests, the order of anticonvulsant activities showed similar pattern ; for the (R) series, *N*-methyl > *N*-H > *N*-ethyl > *N*-allyl ; for the (S) series *N*-methyl > *N*-H > *N*-ethyl > *N*-allyl > *N*-isobutyl compound. From the above results, *N*-substituted alkyl groups were thought to play an important role for the anticonvulsant activities of *N*-Cbz-α-amino-*N*-alkylglutarimides.

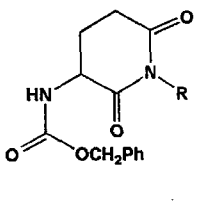
Key words : Anticonvulsant, Maximal Electroshock Seizure(MES), Pentylenetetrazole Induced Seizure (PTZ), *N*-Cbz-α-amino-*N*-alkylglutarimide, Glutarimide, Structure-activity Relationship

INTRODUTION

Approximately 1% of population are afflicted with epilepsy,making this disorder the second leading neurological disease (Harvey and Champe, 1992). Despite the optimal use of currently marketed antiepileptic drugs, 20-40% of epileptic patients fail to experience significant seizure control (Harvey and Champe, 1992).

Even though the search for antiepileptic drugs has recently been extented to various novel structures, these compounds were reported to have some limitations including narrow anticonvulsant spectrum (Harvey and Champe, 1992). Consequently, there is a need for the development of antiepileptic substances, having broader clinical spectrum and lower side effects.

Previously, we reported that *N*-Cbz-α-aminoglutarimides (**1a, b, f, 2a, b**, and **f**) in Fig. 1, combining common structures of other anticonvulsant agents such as N-CO-C-N and cyclic imide in a single molecule, showed significant anticonvulsant activities in both the maximal electroshock seizure (MES) test and the pentylenetetrazole induced seizure (PTZ) test (Lee *et al.*, 1996; Park *et al.*, 1996).The preliminary studies also indicated thatthe anticonvulsant activities of these compounds depended on their *N*-alkyl substituents. This estimates prompted us to prepare the various *N*-alkyl substituted series of this compounds as shown in Fig. 1 in order to define the effects of *N*-substituted alkyl groups on their anticonvulsant activities more precisely.



1a-f, 2a-f

1a: (R), R=H
b: (R), R=CH_3
c: (R), R=C_2H_6
d: (R), R=allyl
e: (R), R=isobutyl
f: (R), R=benzyl

2a: (S), R=H
b: (S), R=CH_3
c: (S), R=C_2H_6
d: (S), R=allyl
e: (S), R=isobutyl
f: (S), R=benzyl

Fig. 1. *N*-Cbz-α-amino-*N*-alkylglutarimides

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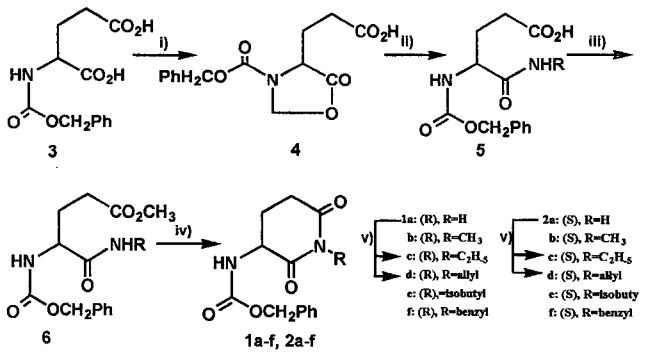
Herein we wish to report the synthesis and the anticonvulsant activities of the various *N*-alkyl substituted (R)-and (S)-*N*-Cbz-α-aminoglutarimides (**1** and **2**), focusing on the effect of *N*-substituted alkyl groups on the activities of these compounds.

MATERIALS AND METHODS

Melting points were determined by Electrothermal digital melting point apparatus and uncorrected. IR spectra were taken in KBr disks with JASCO FT/IR 200 and reported in cm^{-1}. ^1H NMR spectra were recorded in DMSO-d_6 on JNM-EX90A and chemical shifts were reported as δ values in parts per million from TMS as an internal standard. All yields referred to chromatographically and spectroscopically homogeneous materials. The pharmacological tests were carried out according to the protocol of the Antiepileptic Drug Development Program, National Institute of Neurological Disorders and Stroke (Swinyard *et al.*, 1989).

Synthesis: The compounds (**4-6**) could be prepared from the corresponding (R)-or (S)-*N*-Cbz-glutamic acid (**3**) of known absolute configuration in moderate yields by using known chemical reactions (Itho, 1969; Sandler *et al.*, 1972) as shown in Scheme 1.

The synthetic procedures for the preparation of **6** from (R)- or (S)-*N*-Cbz-glutamic acid (**3**) were as follows: The compound **4** could be quantitatively prepared from *N*-Cbz-glutamic acid by treating paraformaldehyde (1.5 eq.) and catalytic amount of *p*-toluenesulfonic acid in benzene. The treatment of **4** with excess amine in methanol gave **5** quantitatively. The compound **6** was obtained from **5** in 70-85% yields by treating with thionyl chloride in methanol and stirring at room temperature for 2-3 hrs.



i) HCHO / p-toluenesulfonic acid / benzene, reflux (Dean- stark apparatus), 8 hrs.
ii)RNH_2 (5 eq.) / methanol, room temperature 8 hrs.
iii)$SOCl_2$(1.3eq.)/methanol, room temperature 2-3 hrs.
iv)p-toluenesulfonic acid (0.5 eq.)/toluene, reflux, 8 hrs.
v)1a or 2a / alkyl bromide / NaH / DMF, 0 °C, room temperature 2-3 hrs

Scheme 1. The preparation of the *N*-Cbz-α-amino-*N*-alkyl-glutarimides

Then (R)- or (S)-*N*-Cbz-α-aminoglutarimides (**1a, b, e, f, 2 a, b, e** and **f**) were afforded by refluxing of **6** with 0.5 equivalent of *p*-toluenesulfonic acid in toluene. **1c**, **d**, **2c** and **d** were prepared by *N*-alkylation of **1a** or **2a** with corresponding alkyl halide and NaH in dry *N,N*-dimethylformamide.

(R)-*N*-Cbz-α-aminoglutarimide(1a)

(R)-*N*-Cbz-isoglutamine methyl ester(**6a**) (2.94 g, 0.01 mol) and *p*-touenesulfonic acid (954 mg, 0.05 mol) were suspended in toluene (294 ml) and this mixture was refluxed for 8 hrs by using Dean-Stark apparatus. Then the reaction mixture was evaporated under reduced pressure and the residue was diluted with EtOAc (300 ml). The EtOAc layer was washed with 5% $NaHCO_3$ solution (30 ml ×2), H_2O (30 ml ×2) and saturated NaCl solution(30 ml) successively then dried over anhydrous $MgSO_4$. The filtrate was evaporated to give a brownish solid. This crude product was purified with silica gel column chromatography (230-400 mesh; EtOAc: hexane =4:1) to afford 1.81 g (69%) of white solid. $[\alpha]_D^{25}$ = +42.78 (c=1.00, CH_3OH); mp: 112.9°C; IR (KBr) 3420, 3270, 1720, 1680 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.83-2.03 (2 H, m), 2.61-2.87 (2 H, m), 4.30-4.42 (1 H, m), 5.14 (2 H, s), 5.62-5.65 (1 H, br), 7.31 (5H, s), 8.20-8.30 (1 H, br).

By using this procedure, the following compounds were prepared from 6.

(R)-*N*-Cbz-α-amino-*N*-methylglutarimide(1b)

Yield: 73%; $[\alpha]_D^{25}$ =+57.13 (c=1.00, CH_3OH); mp: 87.8°C; IR (KBr) 3290, 1720, 1680 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.71-1.93 (2 H, m), 2.62-2.86 (2 H, m), 3.17 (3 H,s), 4.26-4.38 (1 H, m), 5.14 (2 H, s), 5.62-5.65 (1 H, br), 7.31 (5 H, s).

(R)-*N*-Cbz-α-amino-*N*-isobutylglutarimide(1e)

Yield: 80%; $[\alpha]_D^{25}$ =+42.52 (c=1.00, CH_3OH); mp: 79.8°C; IR (KBr) 3310, 1700, 1680 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.85 (6 H, d, J=6.8 Hz), 1.76-1.85 (1 H, m), 1.85-2.00 (2 H, m), 2.71-2.87 (2 H, m), 3.65 (2 H, d, J=7.0 Hz), 4.25-4.30 (1 H, m), 5.14 (2 H, s), 5.60-5.68 (1 H, br), 7.36 (5H, s)

(R)-*N*-Cbz-α-amino-*N*-benzylglutarimide(1f)

Yield: 79%; $[\alpha]_D^{25}$ =+55.22 (c=1.00, CH_3OH); mp: 118.6°C; IR (KBr) 3310, 1720, 1680 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.71-1.93 (2 H, m), 2.72-2.86 (2 H, m), 4.30-4.36 (1 H, m), 4.93 (2 H, s), 5.13 (2 H, s), 5.66-5.68 (1 H, br), 7.23-7.37 (10 H, m).

(S)-*N*-Cbz-α-aminoglutarimide(2a)

Yield: 71%; $[\alpha]_D^{25}$ =-42.66 (c=1.00, CH_3OH); mp: 113.2°C ; IR and ^1H NMR spectra were identical with **1a**.

(S)-*N*-Cbz-α-amino-*N*-methylglutarimide(2b)

Yield: 82%; $[\alpha]_D^{25}$ =-58.06 (c=1.00, CH_3OH); mp: 91.6°C ; IR and ^1H NMR spectra were identical with **1b**.

(S)-*N*-Cbz-α-amino-*N*-isobutylglutarimide(2e)

Yield: 69%; $[\alpha]_D^{25}$ =-42.02 (c=1.00, CH_3OH); mp: 86.5°C ; IR and ^1H NMR spectra were identical with **1e**.

(S)-*N*-Cbz-α-amino-*N*-benzylglutarimide(2f)

Yield: 75 %; $[\alpha]_D^{25}$ =-55.60 (c=1.00, CH_3OH); mp: 118.4°C ; IR and ^1H NMR spectra were identical with **1f**.

(R)-*N*-Cbz-α-amino-*N*-ethylglutarimide(1c)

To a suspension of NaH (96 mg, 4 mmol) in dry *N,N*-dimethylformamide (5 ml), the solution of (R)-*N*-Cbz-α-aminoglutarimide (**1a**, 522 mg, 2 mmol) in *N,N*-dimethylformamide(5 ml) was added. And the mixture was stirred for 30 min in ice bath and followed by addition of ethyl bromide (326 mg, 6 mmol). Then the reaction mixture was stirred at room temperature for 4-5 hrs. The reaction mixture was evaporated *in vacuo* and the residue was dissolved with EtOAc (250 ml). The EtOAc layer was washed with 5% $NaHCO_3$ solution (25 ml × 2), 5% HCl solution (25 ml × 2), H_2O (25 ml × 2) and saturated NaCl (25 ml × 2) successively then dried over anhydrous Mg SO_4. The filtrate was evaporated to give brown solid. This crude compound was purified with silica gel column chromatography (230-400 mesh, EtOAc: Hexane = 1:1) to afford 388 mg of white solid (67%). $[\alpha]_D^{25}$ =+9.721 (c=1.00, CH_3OH); mp: 88.7°C ; IR (KBr) 3350, 1730, 1680 cm^{-1} ; ^1H NMR (DMSO-d_6) δ 1.11 (3 H, t, J= 7.0 Hz), 1.75-1.89 (2 H, m), 2.62-2.86 (2 H, m), 3.82 (2 H, q, J= 7.0 Hz), 4.26-4.38 (1 H, m), 5.14 (2 H, s), 5.60-5.70 (1 H, br), 7.34 (5 H, s)

The following compounds were prepared according to this procedure.

(R)-*N*-Cbz-α-amino-*N*-allylglutarimide (1d)

Yield: 68%; $[\alpha]_D^{25}$ =+4.01 (c=1.00, CH_3OH); mp: 101.6°C ; IR (KBr) 3320, 1720, 1680 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.78-1.88 (2 H, m), 2.70-2.88 (2 H, m), 4.30-4.40 (3 H, m), 5.12 (2 H, s), 5.12-5.22 (2 H, m), 5.60-5.68 (1 H, br), 5.68-5.84 (1 H, m), 7.34 (5 H, s)

(S)-*N*-Cbz--amino-*N*-ethylglutarimide (2c)

Yield: 67%; $[\alpha]_D^{25}$ =-9.564(c=1.00, CH_3OH) ; mp: 83.9°C ; IR and ^1H NMR spectra were identical with **1c**.

(S)-*N*-Cbz-α-amino-*N*-allylglutarimide (2d)

Yield: 68%; $[\alpha]_D^{25}$ =-4.31(c=1.00, CH_3OH); mp: 103.3 °C ; IR and ^1H NMR spectra were identical with **1d**.

Pharmacology: The anticonvulsant tests for *N*-Cbz-α-aminoglutarimides (**1** and **2**) in the maximal electroshock seizure (MES) test and the pentylenetetrazole induced seizure (PTZ) test were carried out according to the protocol of the Antiepileptic Drug Developement Program, National Institute of Neurological Disorders and Stroke (Swinyard *et al.*, 1989) as follows: All tested compounds were dissolved in polyethylene glycol 400 and administered i.p to ICR male mice (20-25 g) at a dose of 25, 50, 75 and 100 mg/kg and anticonvulsant tests were performed at 30 min after administration in groups of 4 mice. Seizure was then artificially induced by either electric shock or pentylenetetrazole. The maximal elelectroshock seizure (MES) test was elicited with a 60-cycle a.c. of 50 mA intensity delivered for 0.2 s via corneal electrods with ECT unit (UGO Basile, Italy). A drop of 0.9% saline was instilled in the eye prior to the application of electrods. Protection in this test was defined as the abolition of hind limb tonic extension component of seizure. The pentylenetetrazole induced seizure (PTZ) test entailed the administration of 80 mg/ kg of pentylenetetrazole as a 0.5% solution subcutaneously in the posterior midline of mice. The animal was then observed for 30 min. Protection was defined as the failure to observe even a threshold seizure (single episode of clonic spasms of at least 5 sec. duration). The ED_{50} as quantitative anticonvulsant evaluations was estimated from the dose-response data. The effects of the compounds on the forced and spontaneous motor activity were evaluated in mice by the rotorod test with Rotorod treadmill for mice (UGO Basile, Italy) as follows. The previously trained animal was placed on an 1 inch diameter knurled plastic rod rotating at 6 rpm after the administration of the tested compounds. Normal mice can remain on a rod at this speed indefinitely. Neurological toxicity was defined as the failure of the animal to remain on the rod for 2 min. And the median neurotoxic dose (TD_{50}) was estimated from the dose-response data.

RESULTS AND DISCUSSION

As shown in Scheme **1**, **1a**, **b**, **e**, **f**, **2a**, **b**, **e** and **f** could be prepared from the corresponding (R)- or (S)-*N*-Cbz-glutamic acid in moderate yields by using known chemical reactions (Lee *et al.*, 1996; Park *et al.*, 1996). And **1c**, **d**, **2c** and **d** were prepared by *N*-alkylation of **1a** or **2a** with the corresponding alkyl halide and NaH in *N,N*-dimethylformamide. All products gave satisfactory spectral data. And the synthesized compounds(**1a-f** and **2a-f**) were submitted to the following anticonvulsant tests.

It was reported that the MES test was correlated to the generalized tonic clonic seizure and the PTZ test to the generalized absence seizure (Swinyard *et al.*,1989). So these two kinds of seizure test are very meaningful for clinical prediction of the anticonvulsant drug candidates. Therefore, we investigated the anticonvulsant activity for those compounds (**1** and **2**) in both the MES and the PTZ test according to the protocol of the Antiepileptic Drug Developement Program, National Institute of Neurological Disorders and Stroke (Swinyard *et al.*, 1989). The results of preliminary anticonvulsant activity were summarized in Table I and Table II.

As shown in Table I and II, all the tested compounds,

Table I. Anticonvulsant activities of (R)-N-Cbz-α-aminoglutarimides (1) in mice

Compound	Config.	R	Dose[a]	MES[b]	PTZ[c]
1a	R	H	25	4/4[d]	2/4(4/4)[e]
			50	2/4	2/4
			75	1/4[f]	1/4
			100	0/4	0/4
1b	R	CH_3	25	4/4[d]	2/4(4/4)[g]
			50	1/4	0/4
			75	0/4	0/4
			100	0/4	0/4
1c	R	C_2H_5	25	4/4	3/4(4/4)[h]
			50	2/4	2/4
			75	2/4	2/4
			100	0/4	0/4
1d	R	Allyl	50	4/4	4/4
			75	1/4	3/4
			100	0/4	2/4(0/4)[i]
1e	R	Isobutyl	50	4/4	
			100	4/4	
1f	R	Benzyl	100	4/4	4/4

[a]All compounds were dissolved in polyethyleneglycol 400 and administered i.p to ICRmale mice. Dose was denoted in mg/kg [b]The MES test : 50 mA, 60 Hz, ac, 0.2 sec., via corneal eletrods, 30 min after administration of test compounds. And the results were denoted as non-protected animals/tested animals. [c]The PTZ test: Subcutaneous pentylene-tetrazol (80 ml/kg) 30 min after administration of test compound. And the results were denoted as non-protected animals/tested animals. [d]at a dose of 30 mg/kg. [e]at a dose of 10 mg/kg. [f]at a dose of 70 mg/kg [g]at a dose of 5 mg/kg [h]at a dose of 15 mg/kg. [i]at a dose of 150 mg/kg.

Table II. Anticonvulsant activities of (S)-N-Cbz-α-aminoglutarimides (2) in mice

Compound	Config.	R	Dose[a]	MES[b]	PTZ[c]
2a	S	H	25	2/4(4/4)[d]	2/4(4/4)[d]
			50	2/4	2/4
			75	1/4	0/4
			100	0/4	0/4
2b	S	CH_3	25	4/4[d]	0/4(4/4)[e]
			50	0/4	0/4
			75	0/4	0/4
			100	0/4	0/4
2c	S	C_2H_5	25	4/4	4/4
			50	3/4	2/4
			75	2/4	1/4
			100	0/4	0/4
2d	S	Allyl	25		4/4
			50	4/4	3/4
			75	2/4	1/4
			100	0/4	0/4
2e	S	Isobutyl	25		4/4
			50	4/4	3/4
			75	3/4	3/4
			100	0/4	1/4
2f	S	Benzyl	100	4/4	4/4

[a]All compounds were dissolved in polyethyleneglycol 400 and administered i.p to ICR male mice. Dose was denoted in mg/kg [b]The MES test : 50 mA, 60 Hz, ac, 0.2 sec., via corneal eletrods, 30min after administration of test compound. And the results were denoted as non-protected animals/tested animals. [c]The PTZ test: Subcutaneous pentylenetetrazol (80 mg/kg) 30 min after administration of test compound. And the results were denoted as non-protected animals/tested animals. [d]at a dose of 20 mg/kg. [e]at a dose of 5 mg/kg.

except **1e, f** and **2f,** showed significant anticonvulsant activities in both the MES and PTZ test. The anticonvulsant activities were revealed as dose dependent pattern. According to the protocol (Swinyard *et al.*, 1989) for the development of new anticonvulsant, the compounds, showing significant anticonvulsant activities at a dose of 100 mg/kg in mice, were recomended as promising anticonvusants to submit to further investigation of quantification. So we selected the *N*-Cbz-α-aminoglutarimide (**1a-d** and **2a-e**) for the quantitative anticonvulsant evaluation, In addition, we also determined TD_{50} in rotorod test to define the neurotoxicity for these selected compounds. The results of quantitative anticonvulsant evaluation and neurotoxicity were summarized in Table III.

As shown in Table III, the *N*-Cbz-α-amino glutarimides (**1a-e** and **2a-e**) showed high anticonvulsant activities in both MES and PTZ test and the ED_{50} values were comparable to those of currently available anticonvulsants. The most active compounds among them was (S)-*N*-Cbz-α-amino-*N*-methylglutarimide (**2b**) and the ED_{50} value in the MES test was 36.3 mg/kg and the ED_{50} value in the PTZ test was 12.5 mg/kg. As evaluated from ED_{50} values, this compound was 7.5-fold more potent than valproic acid in the MES test and 11.9-fold more potent than valproic acid in the PTZ test. Table III showed that the pharmacological activities were dependent on their *N*-substituted alkyl chains as follows. The order of anticonvulsant activity against the MES test as evaluated from ED_{50} values for (R) series was *N*-methyl > *N*-H > *N*-ethyl > *N*-allyl compound; for the (S) series *N*-methyl > *N*-H > *N*-ethyl > *N*-allyl > *N*-isobutyl compound. In the case of PTZ test, the order of anticonvulsant activity showed similar pattern; for the (R) series, *N*-methyl > *N*-H > *N*-ethyl > *N*-allyl > *N*-isobutyl ; for the (S) series *N*-methyl > *N*-H > *N*-ethyl >*N*-allyl > *N*-isobutyl compound. From the above results, it was conceivable that the *N*-substituted alkyl chain might play an important role for their anticonvulsant activities and the methyl group was most appropriate among them. In addition, we found that there were differences in their pharmacological activities between the enantiomers. In the case of MES test, (S) isomer (**2**) was more active than the correspond-

Table III. The Selected Anticonvulsant Evaluation of N-Cbz-α-aminoglutarimides (1 and 2) in Mice

Compound	Config.	R	TD50[b] (mg/kg)	ED50(mg/kg)[a]	
				MES(PI)[c]	PTZ(PI)[d]
1a	R	H	122.5	56.3(2.2)	46.9(2.6)
1b	R	CH_3	120.0	47.5(2.5)	24.4(4.9)
1c	R	C_2H_5	80.0	63.8(1.3)	57.5(1.4)
1d	R	Allyl	63.1	70.0(1.3)	100.0(0.6)
2a	S	H	130.0	43.1(3.0)	42.5(3.1)
2b	S	CH_3	62.5	36.3(1.7)	12.5(5.0)
2c	S	C_2H_5	81.9	60.0(1.4)	55.6(1.5)
2d	S	Allyl	63.8	67.5(0.9)	63.8(1.0)
2e	S	Isobutyl	68.1	80.0(0.9)	90.6(0.8)
Diphenylhydantoin[e]			65.4	9.5(6.9)	f
Phenobarbital[e]			69.0	21.8(3.1)	13.1(5.3)
Ethosuximide[e]			440.8	f	130.4(3.4)
Methosuximide[e]			130.1	42.6(3.1)	34.5(3.7)
Valproic acid[e]			425.8	271.1(1.6)	148.6(2.9)
Trimethadione[e]			1070.0	704.2(1.5)	250.5(4.3)

[a]All compounds were administered ip to ICR male mice and all anticonvulsant tests were performed in groups of 4 mice 30 in after test compound administration. [b]Rotarod test for neurotoxicity in groups of 5 mice. [c]maximal electric shock seizure test: 50 mA, 60 Hz, ac, 0.2 s. and PI is protective index (TD50 /ED50) [d]Subutaneous pentylenetetrazole (80 mg/kg) induced seizure test. [e]Witak et al, 1972. [f]no effect

ing (R) isomer (**1**), the stereoisomeric pharmacological differences in the PTZ test were also displayed in a similar pattern.

We examined the rotorod test for neurotoxicity and determined the TD_{50} value for these compounds (**1a-d** and **2a-e**). The TD_{50} value of (S)-*N*-Cbz-α-amino-*N*-methylglutarimide (**2b**), showing the most potent anticonvulsant activity, was 62.5 mg/kg and the PI (Protective Index, TD_{50}/ED_{50}) was 1.7 in the MES test and 5.0 in the PTZ test. The TD_{50} values of other compounds in this study were comparable to those of other clinically used anticonvulsants.

In conclusion, the anticonvulsant activities of the glutarimides (**1** and **2**) in this study were comparable to those of currently available drugs in both the MES and PTZ test. The most active compound among them was (S)-*N*-Cbz-α-amino-*N*-methylglutarimide (**2b**). Especially, diphenylhydantoin, known as a typical anticonvulsant, was reported to be active in only MES test, so this compound was clinically limited to the treatement ofthe generalized tonic clonic seizure. But the glutarimides (**1** and **2**) in this study showed significant anticonvulsant effect in both the MES and PTZ test. Therefore, it was believed that some of the *N*-Cbz-α-aminoglutarimide (**1** and **2**) could be promising anticonvulsant drug candidates with broader clinical spectrum. Interestingly, as the size of the *N*-substituted alkyl chain increased from methyl to ethyl, allyl, isobutyl and benzyl, their anticonvulsant activities in the MES test decreased and the pharmacological differences in the PTZ test revealed a similar pattern. From this results, it was conceivable that the *N*-substituted alkyl group played an important role on the anticonvulsant activities of *N*-Cbz-α-aminoglutarimides.

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