Synthesis and Anticonvulsant Evaluation of A Series of *N*-Cbz-α-aminoglutarimides

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(Received March 22, 1996)

Key words : Anticonvulsant, Glutarimide, Maximal electric shock(MES), Pentylenetetrazole induced seizure(PTZ)

Currently marketed anticonvulsants do not often provide complete control of epilepsy, which consists of various forms of seizure (Wilder, 1985). Furthermore, it was reported that about 20-40% of epileptic patients failed to experience significant seizure control with the such drugs currently available (Harvey and Champe, 1992).

Therefore there have been many trials for the development of new typed anticonvulsants including modification of currently used anticonvulsants such as hydantoin (Sun *et al.*, 1994; Brouillette *et al.*, 1994; Gaoni *et al.*, 1994) and succinimide (Borenstein and Dukas, 1987; Kornet, 1984), GABA related compounds (Anderson *et al.*, 1993; N'Goka *et al.*, 1991), NMDA antagonists (Heckendorn *et al.*, 1993; Hays *et al.*, 1993) and derivatives of various amino acids (Kohn *et al.*, 1994; idem, 1993). But these compounds were reported to have limitations of narrow anticonvulsant spectrum.

In connection with the developement of new anticonvulsant, we examined the structural similarities of various anticonvulsants, known to act by different mechanisms. From the above inspection, we found out the interesting facts that hydantoins and *N*-α-acylamino acid amides, showing anticonvulsant effect in maximal electric shock seizure (MES) test, had N-CO-C-N and succinimides such as phensuximide, ethosuximide and methsuximide, showing anticonvulsant effect in pentylenetetrazole induced seizure (PTZ) test, had cyclic imide as common moiety in their structures respectively.

So we designed the following structure such as 1 in Fig .1, combining all the forementioned moieties in a single molecule as new anticonvulsant of broader spectrum. Usally the stereoisomers exhibited different pharmacological activities, so we prepared all the (R) and (S) compounds in order to investigate the pharmacological differences between their stereoisomers.

Herein we wish to report the synthesis of a series of *N*-Cbz-α-aminoglutarimides (1) and their *in vivo* anticonvulsant evaluations in MES and PTZ test.

The compounds (**1a-f**) could be prepared from the corresponding (R) or (S) *N*-Cbz-glutamic acid 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 (R)- or (S)- *N*-Cbz-α-aminoglutarimide (**1a-f**) are as follows; the compound **3** could be prepared from *N*-Cbz-glutamic acid (**2**) by treating paraformaldehyde (1.5 eq.) and catalytic amount of *p*-toluenesulfonic acid in quantitative yield and the treatment of **3** with excess amine in methanol gave **4** quantitatively. The compound **5** was obtained from **4** in 70-85% yields by treating with thionyl chloride (1.3 eq.) in methanol and stirring at room temperature for 2-3hrs. Then (R)- or (S)- *N*-Cbz-α-aminoglutarimide (**1a-f**), the final products, could be afforded by refluxing of **5** with 0.5 equivalent of *p*-toluenesulfonic acid in toluene in 65-82% yields. And all products gave satisfactory spectral data as shown in Table I.

So the compounds (**1a-f**) were submitted to the fol-

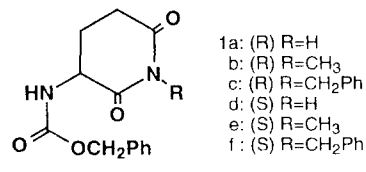
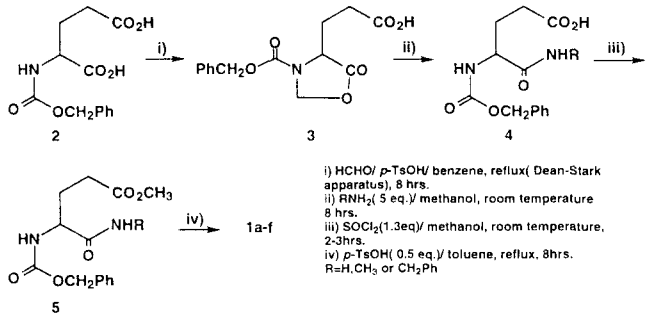


Fig. 1.



Scheme 1. The preparation of *N*-Cbz-α-aminoglutarimides (1)

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Table I. The Melting Points and Spectral Data of *N*-Cbz-α-aminoglutarimides (1)

Comp.	mp (°C)[a]	IR(cm^{-1})[b]	^1H NMR (δ in ppm)[c]
1a	112.9	3420, 3270	1.83-2.03(2H,m),
1b	87.8		2.61-2.87(2H,m)
1c	119.2	1720, 1680	4.30-4.42(1H,m),5.14(2H,s),
1d	113.2		5.62-5.65(1H,br), 7.31(5H,s),
1e	91.6		8.20-8.30(1H,br)
1f	118.4	3290, 1720, 1680	1.71-1.93(2H,m),
			2.62-2.86(2H,m), 3.17(3H, s),
			4.26-4.38(1H,m), 5.14(2H, s),
			5.62-5.65(1H,br), 7.31(5H,s)
		3310, 1720, 1680	1.71-1.93(2H,m), 2.72-2.86
			(2H,m), 4.30-4.36(1H,m), 4.93
			(2H, s), 5.13(2H, s), 5.66-5.68
			(1H,br), 7.23-7.37(10H,m)
		identical to 1a	identical to 1a
		identical to 1b	identical to 1b
		identical to 1c	identical to 1c

[a]mp were determined by Electrothermal digital melting point apparutus and uncorrected.
[b]IR spectra were taken in KBr disks with JASCO FT/IR 200 and structurally important peaks were selected.

lowing anticonvulsant tests in mice as primary screening.

It was reported that MES test was correlated to generalized tonic clonic seizure and PTZ test to generalized absence seizure (Swinyard *et al.*, 1988). So these two kinds of seizure test are very meaningful for the clinical prediction of anticonvulsant drug candidates. Therefore we investigated the anticonvulsant activity of those compounds (**1a-f**) in maximal electric shock seizure test (MES test) and pentylenetetrazole induced seizure test (PTZ test) in mice according to the protocol of the Antiepileptic Drug Developement Program, National Institute of Neurological Disorders and Stroke (Swinyard *et al.*, 1988). The results of anticonvulsant activity are summarized in Table II.

As seen in Table II, all the tested compounds, except **1c** and **1f**, showed significant anticonvulsant activities in both MES and PTZ tests. And the anticonvulsant activities were revealed as dose dependent pattern. Interestingly, *N*-benzylated glutarimides (**1c** and **1f**) exhibited no anticonvulsant activity at dose of 100 mg/kg in MES and PTZ test, so we thought that *N*-substituted alkyl chain might play an import role for the anticonvulsant effect of these compounds. And also the anticonvulsant test *in vivo* of primary screening indicated that (S) compounds (**1d** and **e**) were more active than (R) compounds (**1a** and **1b**) in MES test and (S) *N*-Cbz-α-amino-*N*-methyl glutarimide (**1e**) was most active among them. But there was no noticeable pharmacolgical difference between the stereisomers in PTZ test. In particular, diphenylhydantoin, a typical anticonvulsant, was reported to be active in only MES test, so this compound was limited to the treatement of generalized tonic clonic seizure clinically(Harvey and Champe, 1992). But the glutarimides (**1**) in this study were active in both MES and PTZ tests as seen in Table II. According to the protocol of the antiepileptic drug development program (Swinyard *et al.*, 1989), the compounds, showing significant anticonvulsant activity at dose of 100 mg/kg in mice, were regarded as promising anticonvulsant to submit to further anticonvulsant evaluation. From this estimate, we thought that the *N*-Cbz-α-aminoglutarimides (**1**) except **1c** and **1f**, could be warrented to further evaluation for their anticonvulsant effects.

Table II. Anticonvulsant Activity of *N*-Cbz-α-aminoglutarimides (1) in Mice

Compounds	config.	R	Dose[a]	MES[b]	PTZ[c]
1a	R	H	25	4/4	3/4(4/4)[d]
			50	2/4	2/4
			75	1/4	---
			100	0/4	0/4
1b	R	CH_3	25	4/4	2/4(4/4)[e]
			50	1/4	0/4
			75	0/4	0/4
			100	0/4	
1c	R	$PhCH_2$	100	4/4	4/4
			150	4/4	4/4
1d	S	H	25	2/4(4/4)[f]	2/4(4/4)[f]
			50	2/4	2/4
			75	1/4	0/4
			100	0/4	0/4
1e	S	CH_3	25	(4/4)[f]	2/4(4/4)[d]
			50	0/4	0/4
			75	0/4	0/4
1f	S	$PhCH_2$	100	4/4	4/4
			150	4/4	4/4

[a]All compounds were dissolved in polyethyleneglycol and administerd i.p. Dose is denoted in mg/kg
[b]The MES test: 60 mA, 60 Hz,ac,0.2 sec., via corneal electrods, 30min post 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 post administration of test compound. And the results were denoted as non protected animals/tested animals.
[d]at dose of 10 mg/kg
[e]at dose of 5 mg/kg
[f]at dose of 20 mg/kg

In conclusion, a series of *N*-Cbz-α-aminoglutarimides (**1a-f**), combining common structures such as N-CO-C-N and cyclic imide in a single molecule, were prepared from the (R)- or (S)- *N*-Cbz-glutamic acid and evaluated for their anticonvulsant activities in MES and PTZ tests in order to develope new and broad spectrum anticonvulsant. In this study, *N*-Cbz-α-aminoglutarimides (**1**) except **1c** and **1f**, showed significant anticonvulsant activity in both

MES and PTZ tests enough to be recomended as promising new anticonvulsant drug candidates. Now we are continuing to investigate further anticonvulsant test (quantification) for these compounds and synthesize their analogues in order to develop more active anticonvulsant and define the structure activity relationship more precisely.

ACKNOWLEDGEMENT

This work was supported by a grant of the 95' Good Health R&D Project , Ministry of Health and Welfare, R.O.K.

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