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SYNTHESIS AND ANTICONVULSANT EVALUATION OF A SERIES OF (*R*)- AND (*S*)-*N*-Cbz-α-AMINOGLUTARIMIDE AND SUCCINIMIDE

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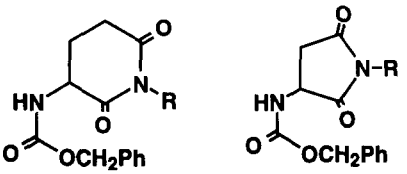
Abstract: A series of (*R*)- and (*S*)-*N*-Cbz-α-aminoimides(**1** and **2**) were synthesized and were investigated their anticonvulsant activities in the MES and PTZ test, and determined the neurotoxicities. The most active compound among them was (*S*)-*N*-Cbz-α-amino-*N*-methyl glutarimide(**1d**) and the ED_{50} value in the MES test was 36.1 mg/kg and the ED_{50} value in the PTZ test was 12.5 mg/kg. In the rotorod test for neurotoxicity, the TD_{50} value was 62.5 mg/kg.

Recent estimate indicates that 1% of population is affected by some form of epilepsy and that 20-40% of epileptic patients fail to experience significant seizure control with the drugs currently available.[1] Furthermore, the antiepileptic drugs presently used in clinical practice suffer from a broad range of adverse side effects, including sedation, tetratogenecity, cognitive dulling and liver toxicity.[2] And clinically, the epilepsy consists of various forms of seizure,[3] so there is a need for combination and repeat therapy to control the such complex convulsion.[4] Owing to this multitherapy, there is a danger of toxic and troublesome side effect. Consequently, a need currently exists for the new antiepileptic compound having broader clinical spectrum and lower toxic side effects.

Recently, there have been many trials for the development of new types of anticonvulsive compounds, including derivatives of various amino acids (e.g. alanine derivatives,[5] *N*-benzoyl- and *N*-phenylacetylglycine amide[6]), structural modification of currently used drug (e.g. hydantoin,[7] succinimdes,[8] and glutarimides[9]) and various GABA related compounds.[10] However, these compounds can not provide complete control of complex seizures. These facts led us to develop the new anticonvulsant of broad spectrum.

In connection with the studies for the development of the new anticonvulsants of broad spectrum, we examined the structural similarities of the anticonvulsants which were known to act by different pharmacological mechanisms. From the above inspection, we found that some anticonvulsant compounds included the common structural moiety such as N-CO-C-N or imide group in their structures and also some NMDA antagonists,[11] showing anticonvulsant effect, had structural similarity to aspartic acid or glutamic acid in view of bioisoster.

Based on the above fact, we designed the following compounds such as **1** and **2** in Figure 1, combining all the forementioned common moieties such as N-CO-C-N and imide in a single molecule, as new anticonvulsants of broad spectrum.



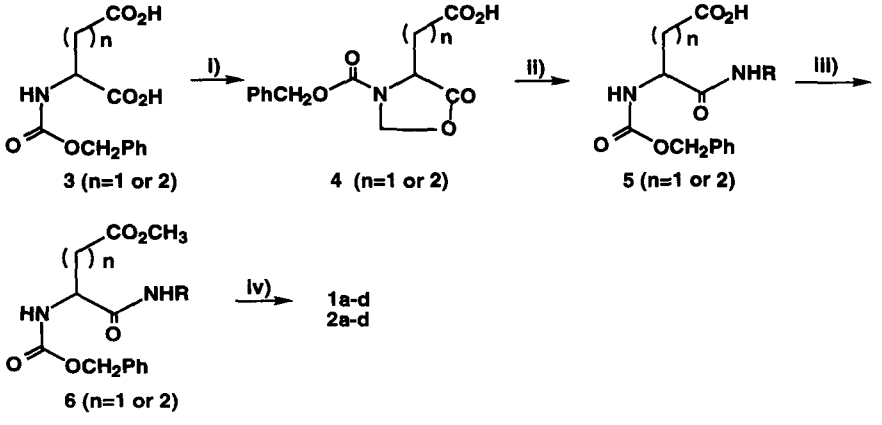
1 a: (R) R=H
b: (R) R=CH_3
c: (S) R=H
d: (S) R=CH_3

2a: (R) R=H
b: (R) R=CH_3
c: (S) R=H
d: (S) R=CH_3

Figure 1

Usually the enantiomers exhibited different pharmacological activities, so we tried to prepare both the *R* and *S* compounds in order to investigate the pharmacological differences between the enantiomers. The compounds(**1a-d** and **2a-d**) could be prepared from the corresponding (*R*)- or (*S*)-*N*-Cbz-glutamic acid and aspartic acid in moderate yields by known chemical reactions[12] as shown in Scheme 1.

Scheme 1



3 (n=1 or 2) 4 (n=1 or 2) 5 (n=1 or 2)

6 (n=1 or 2)

i) HCHO/ *p*-TsOH/ benzene, reflux(Dean-Stark apparatus), 8 hrs. ii) RNH_2(5 eq.)/ MeOH, rt, 8 hrs.
iii) H_2SO_4(catalytic amount)/ MeOH, reflux, 6hrs. iv) *p*-TsOH(0.5 eq.)/ toluene, reflux, 8hrs.
R=H or CH_3

The synthetic procedures for the preparation of (*R*)- or (*S*)-*N*-Cbz-α-aminoglutarimides(**1a-d**) and succinimides(**2a-d**) are as follows: The compound **4** could be prepared from *N*-Cbz-glutamic acid or aspartic acid by treating paraformaldehyde(1.5 eq.) and catalytic amount of *p*-toluenesulfonic acid in quantitative yield and the treatment of **4** with excess amine in methanol gave **5** quantitatively. The compound **6** was obtained from **5** in 70-85% yields by usual

esterification. Then (*R*)- or (*S*)-*N*-Cbz-α-aminoglutarimides(**1a-d**) and succinimides(**2a-d**), the target compounds, could be afforded by refluxing of **6** with 0.5 equivalent of *p*-toluenesulfonic acid in toluene in 65-82% yields. And all the products gave satisfactory spectral data and these compounds(**1a-d** and **2a-d**) 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.[13] So these two kinds of seizure test are very meaningful for clinical prediction of the anticonvulsant drug candidates. Therefore we investigated the anticonvulsant activities for **1** and **2** in both the MES test and the PTZ test, and the neurotoxicity in rotorod test according to the protocol of the Antiepileptic Drug Development Program, National Institute of Neurological Disorders and Stroke.[13] The results of anticonvulsant activity are summarized in Table 1.

Table 1. The Anticonvulsant Evaluations and Neurotoxicities of **1** and **2**

Compound	Config.	TD_{50}(mg/kg) [b]	ED_{50} (mg/kg) [a]	
			MES (PI) [c]	PTZ (PI) [d]
1a	R	122.5	56.3(2.2)	46.9(2.6)
1b	R	120.0	47.5(2.5)	24.4(4.9)
1c	S	130.0	43.1(3.0)	42.5(3.1)
1d	S	62.5	36.1(1.7)	12.5(5.0)
2a	R	178.0	125.0(1.4)	110.0(1.6)
2b	R	166.7	52.5(3.2)	82.5(2.0)
2c	S	160.8	103.0(1.6)	78.1(2.1)
2d	S	117.5	61.2(1.9)	113.3(1.0)
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)
Methsuximide [e]		130.1	42.6(3.1)	34.5(3.7)
Valproic acid [e]		425.8	271.7(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 male ICR mice and all the anticonvulsant tests were performed in groups of 4 mice 30 min after test compound administration. [b] Rotorod test for neurotoxicity in groups of 5 mice. [c] Maximal electric shock seizure test: 50 mA, 60Hz, ac, 0.2 s. and PI is protective index(TD_{50}/ ED_{50})

[d] Sc. pentylenetetrazole(80 mg/kg) induced seizure test .[e] ref.14 . [f] not effective.

As seen in Table 1, glutarimides(**1a-d**) and succinimides(**2a-d**) showed high anticonvulsant effects in both the MES test and the PTZ test. The most active compound among them was (*S*)-*N*-Cbz-α-amino-*N*-methylglutarimide(**1d**) and the ED_{50} value in the MES test was 36.1 mg/kg and the ED_{50} value in the PTZ test was 12.5 mg/kg. We also found that there were differences in their pharmacological activities according to their structures as follows. The glutarimides(**1a-d**) showed more active anticonvulsant effect than the succinimides(**2a-d**) in both the MES test and the PTZ test. In a series of glutarimides(**1a-d**), the *N*-methylated derivative(**1b** or **1d**) showed higher anticonvulsant activity than the corresponding non-methylated analog(**1a** or **1c**) in both the MES test and the PTZ test . Interestingly, the pharmacological difference was observed between their enantiomers. The *S* isomer(**1c** or **1d**) was more active than the corresponding *R* isomer(**1a** or **1b**) in both the MES test and the PTZ test. On the other hand, a series of succinimdes(**2a-d**) showed somewhat different pharmacological patterns from those of glutarimides(**1a-d**) as follows. In the case of MES test, the *N*-methylated derivative(**2b** or **2d**) was more active than the non-methylated analog(**2a** or **2c**) of the same configuration. However, in the case of PTZ test, the pharmacological results displayed the different patterns from those of MES test according to their stereochemistry. Between the compounds(**2a** and **2b**), having *R* configuration, the *N*-methylated derivative(**2b**) was more active than the non-methylated analog(**2a**), but the compounds of *S* configuration (**2c** and **2d**) exhibited the inverse phamacological pattern. In the previous papers about the anticonvulsant activity of *N*-acyl-amino acid amide[5] and α-substituted glutarimide,[9] it was reported that the *R* isomer was more active than the *S* isomer. But interestingly, the compounds (**1a-d** and **2a-d**) in this study showed different pharmacological trends as shown in Table 1. These facts suggest that the anticonvulsant mechanisms of our tested compounds(**1** and **2**) are different from each other and other related compounds.

We examined the rotorod test for neurotoxicity and determined the TD_{50} value for these compounds(**1a-d** and **2a-d**). The TD_{50} value of (*S*)-*N*-Cbz-α-amino-*N*-methylglutarimide(**1d**), showing the most active anticonvulsant activity, was 62.5 mg/kg and the PI(Protective Index, TD_{50}/ED_{50}) was 1.7 in the MES test and 5.6 in the PTZ test. The TD_{50} values of other compounds in this study were above 117.5 mg/kg.

In conclusion, the anticonvulsant activities of the glutarimides(**1**) and the succinimides(**2**) in this study were comparable to those of currently used anticonvulsants in both the MES test and the PTZ test. Especially, diphenylhydantoin,[4] known as a typical anticonvulsant, was reported to be active only in the MES test and this compound was limited to the treatement of the generalized tonic clonic seizure clinically. But the glutarimides(**1**) and the succinimides(**2**) in this study were active in both the MES test and the PTZ test as shown in Table 1. Therefore it is believed that these compounds are warrented to be promissing anticonvulsant drug candidates of the broader clinical spectrum.

Now we are currently continuing to prepare their analogs and evaluate their anticonvulsant activities in order to develop more active anticonvulsant compounds and define the structure-activity relationship more distinctly.

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was defined as the abolition of hind limb tonic extension component of seizure. The pentylenetetrazole seizure (PTZ) test entailed the administration of 80 mg/kg of pentylenetetrazole as a 0.5 % solution subcutaneously in the posterior midline of mice. And the animal was 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 effects of the compounds on forced and spontaneous motor activity were evaluated in mice by the rotorod test with Rotorod treadmill for mice(UGO Baseline, Itlay) as follows. The animal was placed on a rod an 1 inch diameter knurled plastic rod rotating at 6 rpm after the administration of the compounds. Normal mice can remain on a rod at this speed indifinitely. Neurological toxicity was defined as the failure of the animal to remain on the rod for 2 min.

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