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Design and synthesis of 6-amino-1,4-oxazepane-3,5-dione derivatives as novel broad spectrum anticonvulsants

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Abstract—Based on the structural estimations of the typical anticonvulsant drugs, a series of 6-amino-1,4-oxazepane-3,5-dione derivatives, novel structures of 7-membered heterocyclic imides, which were hybridized with pharmacophores such as cyclic imide and N-CO-C-N group in their molecule were designed and synthesized. Their anticonvulsant activities were evaluated by the maximal electroshock induced seizure (MES) and subcutaneous pentylenetetrazole (PTZ) tests. Almost all the designed compounds except **1c** and **1f** showed comparable anticonvulsant activities in at least one of the anticonvulsant tests. Moreover, some of the tested compounds exhibited moderate anticonvulsant activities in both MES and PTZ tests. From these results, 6-amino-1,4-oxazepane-3,5-dione derivatives could be recommended as novel structures of broad spectrum anticonvulsants.

About 1% of the population worldwide is affected by epilepsy, convulsive disease.[1] 20–40% of epileptic patients fail to experience significant seizure control with the drugs in clinical use.[2] Clinically, epilepsy consists of various forms of seizure. Therefore, combination of various antiepileptic drugs (AEDs) is used for the treatment of epilepsy.[3] Owing to the limitations of currently used AEDs, there is still need for the development of new AEDs of broader spectrum.

Recently, there have been various trials for the development of new anticonvulsants, including derivatives of amino acids,[4,5] structural modification of conventional AEDs,[6,7] GABA related compounds,[8,9] and NMDA antagonists.[10]

In view of the development of new anticonvulsant drugs, we examined the structural characteristics of typical anticonvulsant compounds, such as hydantoins,[3] oxazolidinediones,[3] succinimides,[3] and *N*-acyl-α-amino acid amide.[4,5] The structural inspection showed that these compounds included cyclic imides or N-CO-C-N moiety in their molecules as shown in Figure 1. Thus, these groups such as cyclic imide and N-CO-C-N play an important role on their anticonvulsant activities as pharmacophores. Interestingly, hydantoins and *N*-acyl-α-amino acid amide, which are used for the generalized

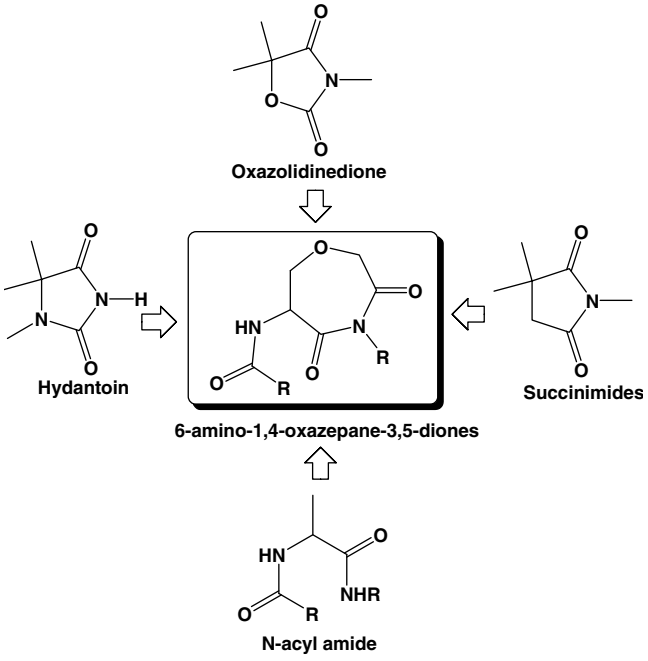

Figure 1. Structural characteristics of 6-amino-1,4-oxazepane-3,5-diones.

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seizure, have N-CO-C-N group, and oxazolidinedione and succinimide, having cyclic imide in their molecules, are used for the absence seizure in clinical practice.[3–5]

Based on these structural characteristics, it was assumed that the compound which hybridized both cyclic imide and N-CO-C-N moiety in a single molecule could be a broad spectrum anticonvulsant. In view of this structural estimation, the 6-amino-1,4-oxazepane-3,5-dione derivatives, which are 7-membered heterocyclic imides and also include N-CO-C-N moiety in their molecule, were designed as novel structure of broad spectrum anticonvulsants. The structural characteristics and similarities of 6-amino-1,4-oxazepane-3,5-diones to some anticonvulsants are shown in Figure 1.

The present work focuses on the design, synthesis and anticonvulsant evaluation of 6-amino-1,4-oxazepane-3,5-dione derivatives.

A series of 6-amino-1,4-oxazepane-3,5-dione derivatives **1a–l** were designed and prepared from (*S*)-*N*-Cbz-serine **2** by usual synthetic procedure. The synthetic procedures are outlined in Scheme 1.

The general synthetic procedures are as follows:

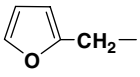
The methyl ester of (*S*)-*N*-Cbz-serine **3** was obtained by usual acid catalyzed esterification. Compound **4** was prepared by *O*-alkylation of compound **3** with ethyl bromoacetate and NaH in acetonitrile in good yields. A series of tested compounds **1a–l** could be afforded by treating the corresponding amine with compound **4**. All the tested compounds **1a–l** gave satisfactory spectral data[11] and were submitted for the following anticonvulsant evaluation.

The anticonvulsant activities are usually evaluated by both the MES and PTZ tests.[12] The MES test is related to the generalized tonic–clonic seizure and PTZ test to the absence seizure.[2,3,12] Thus, these two kinds of anticonvulsant tests are meaningful for the clinical prediction of the anticonvulsant drug candidates and evaluation of their anticonvulsant spectrum.[3,12] Therefore, the anticonvulsant evaluation for the tested compounds was carried out by both the MES and PTZ tests according to the protocol of the antiepileptic Drug Development program, National Institute of Neurological Disorder and Stroke.[12]

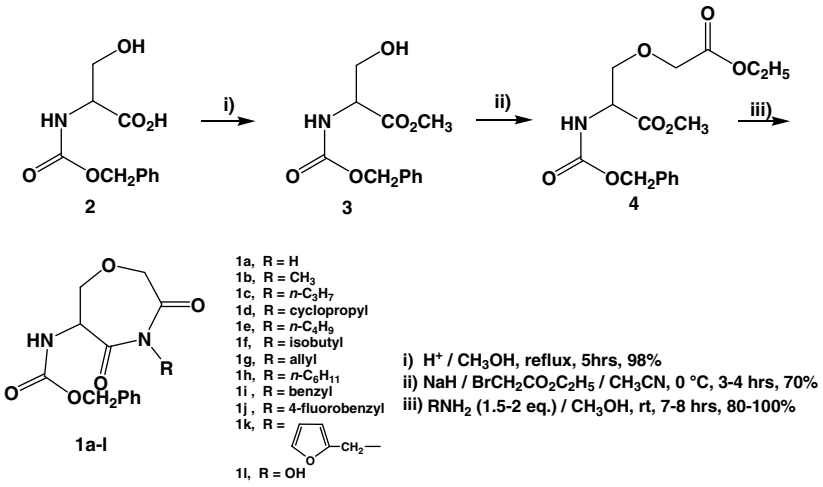
The results of anticonvulsant activities for these tested compounds are summarized in Table 1.

As seen in Table 1, **1a, 1b, 1d, 1e, 1g, 1h**, and **1l** compounds among the tested compounds exhibited considerable anticonvulsant activities in the MES test, and

Table 1. The anticonvulsant activities of 6-amino-1,4-oxazepane-3,5-dione derivatives (**1a–l**)

Compound	R	ED_{50} (mg/kg)[a]	
		MES[b]	PTZ[c]
1a	H	81.25	55.08
1b	CH_3	68.75	41.02
1c	*n*-C_3H_7	>100	>100
1d	Cyclopropyl	87.5	26.97
1e	*n*-C_4H_9	93.75	34.77
1f	Isobutyl	>100	>100
1g	Allyl	70.31	37.11
1h	*n*-C_6H_{11}	87.5	35.56
1i	Benzyl	>100	64.06
1j	4-Fluorobenzyl	>100	53.91
1k		>100	64.06
1l	OH	93.75	96.88
Diphenylhydantoin[d]		9.5	—
Methosuximide[d]		42.6	34.5
Valproic acid[d]		271.1	148.6
Trimethadione[d]		704.2	250.5

[a] All compounds were administered ip to ICR male mice and all anticonvulsant tests were performed in groups of four mice 30 min after test compound administration.
[b] Maximal electric shock seizure test: 50 mA, 60 Hz, ac, 0.2 s.
[c] Subcutaneous pentylenetetrazole (80 mg/kg) induced seizure test.
[d] Ref. 13.



Scheme 1. The preparation of 6-amino-1,4-oxazepane-3,5-diones derivatives (**1a–l**).

their ED_{50} values were 68.75–93.75 mg/kg. These pharmacological results were comparable to those of anticonvulsants in clinical use. The most active compound among the tested compounds was *N*-methylated compound **1b** (ED_{50} = 68.75 mg/kg). As evaluated from the ED_{50}, **1b** was 3.9 times more active than valproic acid, typical antiepileptic drug of broad spectrum in clinical practice. The order of anticonvulsant activities as judged from ED_{50} values is **1b > 1g > 1a > 1d = 1h > 1e = 1l.** In the case of PTZ test, all the tested compounds except **1c** and **1f** showed moderate anticonvulsant activities, and their ED_{50} values were 26.97–96.88 mg/kg. These results were also comparable to those of clinically used antiepileptic drugs. The most active compound in the PTZ test was *N*-cyclopropylated compound **1d** (ED_{50} = 26.97). Compound **1d** was 5.5 times more active than valproic acid as evaluated from ED_{50}. The order of anticonvulsant activities in the PTZ test as judged from ED_{50} values is **1d > 1e > 1h > 1g > 1b > 1j > 1a > 1i = 1k > 1l**. Especially, **1a**, **1b**, **1d**, **1e**, **1g**, **1h**, and **1l** exhibited significant anticonvulsant activities in both the MES and PTZ tests. As mentioned above, this result, showing anticonvulsant activities against these two kinds of tests, suggested that the designed compounds could be recommended to develop as anticonvulsant drug candidates of broad spectrum.

In conclusion, a series of 6-amino-1,4-oxazepane-3,5-dione derivatives, novel structures of 7-membered heterocyclic imides, were designed, synthesized, and their anticonvulsant activities were evaluated by both the MES and PTZ tests. The 6-amino-1,4-oxazepane-3,5-diones were designed as broad spectrum anticonvulsant by hybridizing important pharmacophores such as cyclic imide and N-CO-C-N group in a single molecule. This was based on the inspection of the structural characteristics in typical anticonvulsants in clinical practice. The ED_{50} values for the designed compounds were comparable to clinically used antiepileptic drugs. Moreover, some of the designed compounds in this study exhibited considerable anticonvulsant activities in both the MES and PTZ tests. These pharmacological activities were sufficient for them to develop as Broad Spectrum Anticonvulsants. Therefore, it was concluded that 6-amino-1,4-oxazepane-3,5-dione derivatives were recommended as novel structures of broad spectrum anticonvulsants.

Acknowledgment

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11. The spectral data and physical properties for the compounds **1a–l** are given below. **1a**: White solid. Yield: 100%; mp: 97–99 °C; R_f: 0.3 [ethyl acetate/hexane (1:2)]; IR (KBr) cm^{-1}: 1215, 1402, 1438, 1666, 1703, 1739, 3000; ^1H NMR (400 MHz, $CDCl_3$): δ 3.77 (d, 2H, CH_2), 4.13 (d, 1H, J = 3.12, CH_2), 4.32 (d, 1H, J = 3.12, CH_2), 5.01 (m, 1H, CH), 5.20 (s, 2H, CH_2), 7.32 (s, 1H, NH), 7.35 (s, 5H, Ph), 7.46 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 59.9, 65.9, 71.1, 81.0, 127.2, 127.7, 129.0, 141.2, 156.0, 170.7, 175.2. **1b**: White solid. Yield: 100%; mp: 107–109 °C; R_f: 0.5 [ethyl acetate/hexane (1:2)]; IR (KBr) cm^{-1}: 1214, 1346, 1403, 1438, 1667, 1703, 1739; ^1H NMR (400 MHz, $CDCl_3$): δ 2.98 (s, 3H, CH_3), 3.73 (m, 2H, CH_2), 4.28 (d, 1H, J = 3.12, CH_2), 4.32 (d, 1H, J = 3.12, CH_2), 5.05 (m, 1H, CH), 5.18 (s, 2H, CH_2), 7.34 (s, 1H, NH), 7.35 (s, 5H, Ph). ^{13}C NMR ($CDCl_3$): δ 27.3, 57.4, 65.9, 71.4, 78.5, 127.2, 127.7, 129.0, 141.2, 156.0, 174.6, 176.6. **1c**: Light yellow viscous product. Yield: 100%; R_f: 0.55 [ethyl acetate/hexane (1:2)]; IR (KBr) cm^{-1}: 1217, 1342, 1400, 1436, 1654, 1706, 1740; ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, 3H, CH_3), 1.51 (m, 2H, CH_2), 3.21 (t, 2H, CH_2), 3.70 (m, 2H, CH_2), 4.24 (d, 1H, J = 3.12, CH_2), 4.28 (d, 1H, J = 3.12, CH_2), 5.00 (m, 1H, CH), 5.18 (s, 2H, CH_2), 7.32 (s, 1H, NH), 7.35 (s, 5H, Ph). ^{13}C NMR ($CDCl_3$): δ 11.2, 20.5, 42.1, 57.7, 65.9, 71.4, 78.8, 127.2, 127.7, 129.0, 141.2, 156.0, 174.3, 176.3. **1d**: Light yellow viscous product. Yield: 100%; R_f: 0.6 [ethyl acetate/hexane (1:2)]; IR (KBr) cm^{-1}: 1209, 1311, 1406, 1671, 1705, 1743; ^1H NMR (400 MHz,$CDCl_3$): δ 0.52 (m, 1H, CH_2), 0.65 (m, 1H, CH_2), 0.77 (m, 1H, CH_2), 0.91(m, 1H, CH_2), 2.67 (m, 1H, CH), 3.76 (d, 2H, CH_2), 4.12 (d, 1H, J = 3.12, CH_2), 4.23 (d, 1H, J = 3.12, CH_2), 5.00 (m, 1H, CH), 5.19 (s, 2H, CH_2), 7.33 (s, 1H, NH), 7.36 (s, 5H, Ph). ^{13}C NMR ($CDCl_3$): δ 4.9, 26.0, 58.0, 65.9, 71.4, 79.1, 127.2, 127.7, 129.0, 141.2, 156.0, 174.0, 176.0. **1e**: Light yellow viscous product. Yield: 100%; R_f: 0.6 [ethyl acetate/hexane (1:2)]; IR (KBr) cm^{-1}: 1217, 1275, 1342, 1400, 1436, 1655, 1706, 1740; ^1H NMR (400 MHz, $CDCl_3$): δ 0.93 (t, 3H, CH_3), 1.26 (m, 2H, CH_2), 1.46 (m, 2H, CH_2), 3.50 (m, 2H, CH_2), 3.68 (d, 2H, CH_2), 4.14 (d, 1H, J = 3.12, CH_2), 4.28 (d, 1H, J = 3.12, CH_2), 5.00 (m, 1H, CH), 5.18 (s, 2H, CH_2), 7.32 (s, 1H, NH), 7.35 (s, 5H, Ph). ^{13}C NMR ($CDCl_3$): δ 13.8, 19.9, 29.6, 39.6, 57.7, 65.9, 71.4, 78.8, 127.2, 127.7, 129.0, 141.2, 156.0, 174.3, 176.3. **1f**: White solid. Yield: 100%; mp: 73–75 °C; R_f: 0.4 [ethyl acetate/hexane (1:2)]; IR (KBr) cm^{-1}: 1213, 1294, 1403, 1666, 1703, 1742; ^1H NMR (400 MHz,$CDCl_3$): δ 0.88 (dd, 6H, CH_3), 3.09 (m, 1H, CH), 3.34 (m, 2H, CH_2), 3.75 (d, 2H, CH_2), 4.18(d, 1H, J = 8.96, CH_2), 4.30(d, 1H, J = 8.96, CH_2), 5.00 (m, 1H, CH), 5.19 (s, 2H, CH_2), 7.34 (s, 1H, NH), 7.38 (s, 5H, Ph). ^{13}C NMR ($CDCl_3$): δ 20.3, 26.0, 48.7, 57.7, 65.9, 71.4, 78.8, 127.2, 127.7, 129.0, 141.2, 156.0, 174.3, 176.3. **1g**:

White solid. Yield: 100%; mp: 56–58 °C; R_f: 0.5 [ethyl acetate/hexane (1:2)]; IR (KBr) cm^{-1}: 1214, 1348, 1403, 1438, 1663, 1703, 1741; ^1H NMR (400 MHz,$CDCl_3$): δ 3.67 (d, 2H, CH_2), 4.13(d, 2H, CH_2), 4.30(d, 2H, CH_2), 5.00 (m, 1H, CH), 5.20 (s, 2H, CH_2), 5.22 (d, 1H, J = 2.88, CH), 5.24 (d, 1H, J = 2.88, CH), 5.67 (m, 1H, CH), 7.34 (s, 1H, NH), 7.38 (s, 5H, Ph). ^{13}C NMR ($CDCl_3$): δ 41.0, 57.8, 65.9, 71.4, 78.9, 127.2, 127.7, 129.0, 134.3, 141.2, 156.0, 174.3, 176.3. **1h**: White solid. Yield: 100%; mp: 48–50 °C; R_f: 0.75 [ethyl acetate/hexane (1:2)]; IR (KBr) cm^{-1}: 1211, 1346, 1403, 1437, 1665, 1702, 1742; ^1H NMR (400 MHz,$CDCl_3$): δ 0.87 (t, 3H, CH_3), 1.24 (m, 2H, CH_2), 1.26 (m, 2H, CH_2), 1.28 (m, 2H, CH_2), 1.48 (m, 2H, CH_2), 3.48 (m, 2H, CH_2), 3.70 (d, 2H, CH_2), 4.14 (d, 1H, J = 3.12, CH_2), 4.29 (d, 1H, J = 3.12, CH_2), 5.01 (m, 1H, CH), 5.20 (s, 2H, CH_2), 7.32 (s, 1H, NH), 7.35 (s, 5H, Ph). ^{13}C NMR ($CDCl_3$): δ 14.1, 22.8, 26.5, 27.4, 31.6, 39.9, 57.7, 65.9, 71.4, 78.8, 127.2, 127.7, 129.0, 141.2, 156.0, 174.3, 176.3. **1i**: White solid. Yield: 100%; mp: 113–115 °C; R_f: 0.5 [ethyl acetate/hexane (1:2)]; IR (KBr) cm^{-1}: 1211, 1348, 1404, 1437, 1665, 1702, 1742; ^1H NMR (400 MHz,$CDCl_3$): δ 3.51 (d, 2H, CH_2), 4.29 (m, 1H, CH_2), 4.89 (s, 2H, CH_2), 4.93 (m, 1H, CH), 5.19 (s, 2H, CH_2), 7.27 (dd, 1H, Ph), 7.30 (d, 2H, Ph), 7.31 (d, 2H, Ph), 7.33 (s, 1H, NH), 7.37 (s, 5H, Ph). ^{13}C NMR ($CDCl_3$): δ 42.4, 57.7, 65.9, 71.4, 78.8, 126.8, 127.0, 127.2, 127.7, 128.6, 129.0, 141.2, 156.0, 174.6, 176.6. **1j**: Yellow solid. Yield: 100%; mp: 68–70 °C; R_f: 0.4 [ethyl acetate/hexane (1:2)]; IR (KBr) cm^{-1}: 1214, 1403, 1662, 1704, 1739; ^1H NMR (400 MHz, $CDCl_3$): δ 3.53 (d, 2H, CH_2), 4.26 (m, 1H, CH_2), 4.81 (s, 2H, CH_2), 4.96 (m, 1H, CH), 5.19 (s, 2H, CH_2), 7.02 (d, 1H, CH), 7.20 (d, 1H, CH), 7.36 (s, 1H, NH), 7.37 (s, 5H, Ph). ^{13}C NMR ($CDCl_3$): δ 42.4, 57.7, 65.9, 71.4, 78.8, 115.3, 127.2, 127.7, 128.6, 129.0, 137.3, 141.2, 156.0, 160.9, 174.6, 176.6. **1k**: White solid. Yield: 100%; mp: 97–99 °C; R_f: 0.5 [ethyl acetate/hexane (1:2)]; IR (KBr) cm^{-1}: 1214, 1347, 1403, 1438, 1665, 1703, 1742; ^1H NMR (400 MHz, $CDCl_3$): δ 3.65 (d, 2H, CH_2), 4.15 (d, 1H, J = 3.12, CH_2), 4.30(d, 1H, J = 3.12, CH_2), 4.53 (m, 2H, CH_2) 5.00 (m, 1H, CH), 5.19 (s, 2H, CH_2), 6.29 (d, 1H, J = 0.92, CH), 6.33 (d, 1H, J = 0.92, CH), 7.26 (d, 1H, CH), 7.34 (s, 1H, NH), 7.36 (s, 5H, Ph). ^{13}C NMR ($CDCl_3$): δ 42.1, 57.7, 65.9, 71.4, 78.8, 106.7, 110.6, 127.2, 127.7, 129.0, 141.2, 142.1, 148.8, 156.0, 174.3, 176.3. **1l**: Oily product. Yield: 80%; R_f: 0.3 [ethyl acetate/hexane (1:2)]; IR (KBr) cm^{-1}: 1214, 1348, 1403, 1663, 1703, 1741, 3300; ^1H NMR (400 MHz,$CDCl_3$): δ 2.04 (s, 1H, OH), 3.72 (d, 2H, CH_2), 4.10 (m, 2H, CH_2), 4.87 (m, 1H, CH), 5.14 (s, 2H, CH_2), 7.32 (s, 1H, NH), 7.34 (s, 5H, Ph).; ^{13}C NMR ($CDCl_3$): δ 53.7, 71.4, 74.8, 127.2, 127.7, 129.0, 141.2, 156.0, 164.0, 168.5.

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