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Synthesis, anticonvulsant activity and *in-silico* study of some novel amino acids incorporated bicyclo compounds

Chandra Shekhar Sharma[1]*, Rajesh Kumar Nema[1] and Vinod Kumar Sharma[2]

Department of Pharmaceutical Chemistry, B. N. College of Pharmacy, Udaipur, (Rajasthan), India[1]
Department of Chemistry, M. L. S. University, Udaipur, (Rajasthan), India[2]

***Corresponding Author**
Chandra Shekhar Sharma
Assistant Professor
Department of Pharmaceutical Chemistry
B. N. College of Pharmacy
Udaipur-313001 (Rajasthan), India
Contact no.: (91)9828173650
E-mail: cssharma_medicinalchemistry@yahoo.com

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ABSTRACT

In the present study, some novel amino acids incorporated bicyclo compounds have been synthesized and their structure was confirmed by physico-chemical and spectral data. The title compounds were evaluated for in silico toxicity study and anticonvulsant activity by maximal electric shock method. The results showed that substitution with cysteine and glutamic acid moiety was found to increase the activity. In silico toxicity study results showed that the compounds are free of toxicity in neurotoxicity, irritability, sensitivity, immunotoxicity and oncogenecity

Key words: Maximal electrical shock method, anticonvulsant activity, i*n silico* toxicity.

INTRODUCTION

Epilepsy is a common disorder of the central nervous system (CNS). Conventional antiepileptic drugs (AEDs) are widely prescribed but induce a range of side effects specially neuro toxicity. Furthermore, there is a significant group of patients (20-30%) resistant to the currently available therapeutic agents (Ho et al., 2001). Although the current drugs provide adequate seizure control in many patients, it is roughly estimated that up to 28-30% of patients are poorly treated with the available antiepileptic drugs (AEDs). Moreover, many AEDs have serious side effects and lifelong medication may be required (Craig, 1997). Hence, with all of these factors in mind, it has been suggested that the focus of epilepsy research should be directed to identifying the underlying mechanism of epileptogenesis and the subsequent “expression” of seizure activity, rather than resorting primarily to symptom control, that is, mere suppression of seizures(McNamara, 2001).
The analogues of bicyclic systems, 8, 10-diza-bicyclo [4.3.1] decane and 3, 10-diza-bicyclo [4.3.1] decane bicyclo compounds, have been found to possess a wide range of biological activities, which include analgesic, anti inflammatory (Peter 2008, Nagaev et al., 1999, Pinna et al., 2000), muscarinic receptor antagonist (Myoung et al., 2003), antibacterial (Smirnova et al., 1995), antiviral (Miller et al., 2001), antiprotozoal (Seeacher et al., 2005) and antispasmolytic (Rajdan et al., 1987) but still no one has reported/studied, such compounds as anticonvulsants. The reason to incorporate biologically friendly amino acids into pharmacologically active moiety is not only to minimize the side effects of the metabolites of the parent compound upon metabolism in the body but also to direct the drug for specific site and in order to enhance the hydrophilicity of the synthesized candidates, like bicyclo compounds may exhibit potent anticonvulsant activity. In the same context, our objective of the study was to synthesize such compounds and to further evaluate these synthesized candidates, like bicyclo compounds that may exhibit potent anticonvulsant activity with lesser neurotoxicity. The toxicity of a molecule is highly dependent upon its structural elements. Exogenous chemicals entering a living system can undergo a number of chemical modifications by a wide array of enzymes, which use these chemicals as substrates. Rarely does a compound simply produce a single metabolite, in general, complex metabolic pattern of competitive and sequential reactions occur. Computer aided toxicity prediction provides help to anyone who would like to gain a deeper insight in to the field of metabolism and toxicity, including medicinal chemists looking for quick information on the expected metabolic fate and toxicity of compounds still in the bottleneck stage of clinical trials (Moorthy et al., 2006).

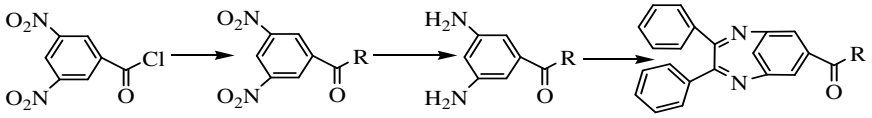
In the present work, we report the synthesis, anticonvulsant activity and *in-silico* toxicity studies of such amino acids incorporated bicyclo compounds.

MATERIALS AND METHODS

CHEMISTRY

Melting points (m.p.) were determined in open glass capillary tubes and are uncorrected. Infrared (IR) and proton nuclear magnetic resonance (1H NMR) spectra were recorded for the compounds on FT-IR Bruker Tensor 27 spectrometer and Bruker DRX-300 spectrometer, respectively. Chemical shifts are reported in parts per million (ppm) using tetramethylsilane (TMS) as an internal standard. The LC mass spectra of the compounds were recorded on Shimadzu 8201PC spectrometer. Elemental analysis (C, H and N) were undertaken with a Perkin-Elmer model 240C analyzer, and were consistent with theoretical values (within 0.4%) unless indicated. The progress of the reaction was monitored on precoated silica gel 60 F254 plates (Merck) using different solvent systems.

Scheme-1

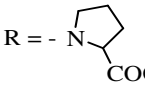


(**1a-1e**) (**2a-2e**) (**CSa-CSe**)

R = - $NHCH_2COOH$

R = - $NHCH(COOH)(CH_2)_2COOH$

R = -



R = - $NHCH(CH_2SH)\ COOH$

R = - $NH(CH_2)_4\ CH\ (NH_2)COOH$

General procedure for the preparation of compounds 1a-1e.

A solution of 3,5-dinitrobenzoyl chloride (1 mmole) in 1,4-dioxan was added to appropriate amino acid (1.2mmoles) in 0.1N sodium hydroxide (10 ml) and refluxed. The reaction mixture was allowed to cool and poured into 1N hydrochloric acid and crushed ice. The crude product was filtered, dried, recrystallized with methanol and column chromatographed on silica gel (60-120 mesh) eluting with methanol: ethyl acetate (8:2).

*2-(3, 5-Dinitrobenzamido) acetic acid (**1a**).*

Mol. Formula: $C_9H_7N_3O_7$, Yield 76%, m.p. 182˚C; IR (cm^{-1}): 1570(-NO_2), 3703(-OH), 3402(-NH_2), 2867(-CH_2), 1714, 1634(C=O), 2968(CH-Ar).

*2-(3,5-dinitrobenzamido)pentanedioic acid(**1b**).*

Mol. Formula: $C_{12}H_{11}N_3O_9$, Yield 76%, m.p. 178˚C; IR (cm^{-1}): 1571(-NO_2), 3714(-OH), 3378(-NH_2), 2863(-CH_2), 1713, 1630(C=O), 2969(CH-Ar).

*1-(3,5-Dinitrobenzoyl)-pyrrolidine-2-carboxylic acid (**1c**).*

Mol. Formula: $C_{12}H_{11}N_3O_7$, Yield 76%, m.p. 181˚C; IR (cm^{-1}): 1570(-NO_2), 3609(-OH), 2885(-CH_2), 1705, 1622(C=O), 3102(CH-Ar), 1346(tert.N).

*2-(3,5-Dinitrobenzamido)-3-mercapto propanoic acid (**1d**).*

Mol. Formula: $C_{10}H_9N_3O_7S$, Yield 76%, m.p. 202˚C; IR (cm^{-1}): 1593(-NO_2), 3752(-OH), 3605(-NH_2), 2873(-CH_2), 1698, 1645(C=O), 2978(CH-Ar), 2560(-SH).

*2-Amino-6-(3,5-dinitro-benzoyl amino)-hexanoic acid (**1e**).*

Mol. Formula: $C_{13}H_{16}N_4O_7$, Yield 76%, m.p. 196˚C; IR (cm^{-1}): 1552(-NO_2), 3409(-OH,-NH_2 merged), 2862,2842(-CH_2), 1702, 1651(C=O), 2982(CH-Ar).

General procedure for the preparation of compounds 2a-2e.

A suspension of compound ***1a-1e*** (1 mmole) and zinc dust (2.5 mmole) in methanol was stirred with 5 ml of 90% formic acid at room temperature. After completion of the reaction (monitored by TLC), the reaction mixture was filtered off. The organic layer was evaporated and the residue was dissolved in ether and washed with saturated sodium chloride (5 times) to remove of ammonium formate. Then the etheral layer was evaporated to dryness (Gowda et al., 2001). The crude

product was recrystallized with ethanol and purified by column chromatography on silica gel (60-120 mesh) eluting with chloroform: ethyl acetate (9:1).

*2-(3,5-diamino-benzamido)acetic acid (**2a**).*

Mol. Formula: $C_9H_{11}N_3O_3$, Yield 76%, m.p. 173˚C; IR (cm^{-1}): 3727(-OH), 3634(-NH_2), 2858(-CH_2), 1680, 1619(C=O), 2938(CH-Ar).

*2-(3,5-Diamino-benzamido)-pentanedioic acid (**2b**).*

Mol. Formula: $C_{12}H_{15}N_3O_5$, Yield 76%, m.p. 184˚C; IR (cm^{-1}): 3733(-OH), 3633(-NH_2), 2865(-CH_2), 1700(C=O), 2987(CH-Ar).

*1-(3,5-Diamino-benzoyl)–pyrrolidine-2-carboxylic acid (**2c**).*

Mol. Formula: $C_{12}H_{15}N_3O_3$, Yield 76%, m.p. 108˚C; IR (cm^{-1}): 3628(-OH), 3700, 3726(-NH_2), 2873(-CH_2), 1697, 1613(C=O), 2977(CH-Ar), 1342(tert.N).

*2-(3,5-Diamino-benzamido)-3-mercapto propionic acid (**2d**).*

Mol. Formula: $C_{10}H_{13}N_3O_3S$, Yield 76%, m.p. 115˚C; IR (cm^{-1}): 3732(-OH), 3618(-NH_2), 2853(-CH_2), 1618, 1702(C=O), 2934(CH-Ar), 2531(-SH).

*2-Amino-6-(3,5-diamino-benzamido)hexanoic acid (**2e**).*

Mol. Formula: $C_{13}H_{20}N_4O_3$, Yield 76%, m.p. 126˚C; IR (cm^{-1}): 3734(-OH), 3622(-NH_2), 2865(-CH_2), 1622, 1701(C=O), 2924(CH-Ar).

General procedure for the preparation of compounds CSa-CSe.

Compound ***2a-2e*** (1 mmole) was dissolved in 0.1N sodium hydroxide solution. To this, a mixture of benzil (1.1mmole) and sodium ethoxide (2.3mmole) in ethanol was dissolved with continuous stirring and refluxed. The reaction mixture was then allowed to cool and poured into 1N hydrochloric acid and crushed ice. The content was kept over night at room temperature, filtered, dried and recrystallized with methanol. The completion of the reaction was monitored by TLC and purified by column chromatography on silica gel (60-120 mesh) eluting with methanol: ethyl acetate (8:2).

*2-[(3,4-Diphenyl-2,5-diaza-bicyclo [4.3.1] deca-1(9),2,4,6(10),7-pentaene-8-carbonyl) -amino]-pentanedioic acid (**CSa**).*

Yield 76%, m.p. 83˚C; IR (cm^{-1}) : 3712(-OH), 3670(-NH_2), 2858(-CH_2), 1681(C=O), 2968(CH-Ar),1530(C=N);^{1}H NMR(DMSO) : δ 2.5 (d, 2H, CH_2), 9.03 (t, 1H, NH), 8.86 (s, 1H, COOH), 7.60-7.93 (m, 13H, ArH) ; LCMS : m/z $[M+1]^+$384.4, $[M+2]^+$ 385.4. Anal. found: C, 72.16; H, 04.57; N, 10.89. Calcd for $C_{23}H_{17}N_3O_3$: C, 72.05; H, 04.47; N, 10.96.

*2-[(3,4-Diphenyl-2,5-diaza-bicyclo[4.3.1]deca-1(9),2,4,6(10),7-pentaene-8-carbonyl)-amino]-pentanedioic acid (**CSb**).*

Yield 76%, m.p. 68˚C; IR (cm^{-1}) : 3737(-OH), 3528(-NH_2), 2888(-CH_2), 1675,1699(C=O), 3083(CH-Ar),1588(C=N); ^{1}H NMR(DMSO) : δ 1.21 (s, 1H, CH), 8.66 (s, 1H, COOH), 2.5 (m, 4H, $(CH_2)_2$), 8.88 (t, 1H, NH), 9.10 (s, 1H, COOH), 7.53-7.93 (m, 13H, ArH) ; LCMS : m/z $[M+1]^+$ 456. Anal. found: C, 69.18; H, 04.62; N, 09.31. Calcd for $C_{26}H_{21}N_3O_5$: C, 68.56; H, 04.65; N, 09.23.

*1-(3,4-Diphenyl-2,5-diaza-bicyclo[4.3.1]deca-1(9),2,4,6(10),7-pentaene-8-carbonyl)-pyrrolidine-2-carboxylic acid (**CSc**).*

Yield 76%, m.p. 55˚C; IR (cm^{-1}) : 3602(-OH), 2798(-CH_2), 1707,1546(C=O), 3098(CH-Ar),1493(C=N),1336(tert.N) ; ^{1}H NMR(DMSO) : δ 1.20 (t, 1H, CH), 3.75 (m, 4H, $(CH_2)_2$ pyrrolidine ring), 2.5 (m, 2H, CH_2), 9.0 (s, 1H, COOH), 7.23-8.02 (m, 13H, ArH) ; LCMS : m/z $[M+1]^+$424.4. Anal. found: C, 74.46; H, 04.92; N, 09.76. Calcd for $C_{26}H_{21}N_3O_3$: C, 73.74; H, 05.00; N, 09.92.

*2-[(3,4-Diphenyl-2,5-diaza-bicyclo[4.3.1]deca-1(9),2,4,6(10),7-pentaene-8-carbonyl)-amino]-3-mercapto propionic acid (**CSd**).*

Yield 76%, m.p. 73˚C; IR (cm^{-1}) : 3506(-OH), 3399(-NH_2), 2877(-CH_2), 1711, 1626(C=O), 3084(CH-Ar),1532(C=N), 2637(-SH) ; ^{1}H NMR(DMSO) : δ 1.20 (s, 1H, CH), 8.65 (s, 1H, COOH), 2.5 (d, 2H, CH_2), 9.09 (t, 1H, NH), 8.87 (s, 1H, SH), 7.27-7.93 (m, 13H, ArH) ; LCMS : m/z $[M-1]^+$428.3. Anal. found: C, 66.88; H, 04.54; N, 09.65. Calcd for $C_{24}H_{19}N_3O_3S$: C, 67.12; H, 04.46; N, 09.78.

*3,4-Diphenyl-2,5-diaza-bicyclo[4.3.1]deca-1(9),2,4,6(10),7-pentaene-8-carboxylic acid (5-amino-6-hydroxy-6-oxo-hexyl)-amide (**CSe**).*

Yield 76%, m.p. 77˚C; IR (cm^{-1}) : 3726(-OH), 3647(-NH_2), 2864(-CH_2), 1678(C=O), 2924(CH-Ar), 1569(C=N) ; ^{1}H NMR(DMSO) : δ 1.21 (t, 1H, CH), 8.66 (s, 1H, COOH), 2.5 (m, 2H, CH_2), 9.09 (t, 1H, NH), 8.88 (d, 2H, NH_2), 3.58 (m, 6H, CH_2) 7.60-7.93 (m, 13H, ArH) ; LCMS : m/z $[M+1]^+$455.4, $[M-1]^+$452.8. Anal. found: C, 70.90; H, 05.81; N, 12.42. Calcd for $C_{27}H_{26}N_4O_3$: C, 71.35; H, 05.77; N, 12.33.

PHARMACOLOGY

All the title compounds (**CSa-CSe**) were dissolved in DMSO. Wistar rats weighing 150-200gm were used for anticonvulsant activity. The animals were housed in colony cages, conditions of constant temperature (22±2℃), a 12h light/dark schedule, and allowed free access to standard diet and tap water except during the experiment. The animals were allowed to habituate to the laboratory environment for 2h before the experiments were initiated. The protocol of the study was approved by Institutional Animal Ethical Committee.

Acute toxicity study

The tested compounds were administered intraperitoneally at different dose levels in separate groups of animals. After 24 hr of the drug administration the percent mortality in each group was observed, Approximate Lethal Dose (ALD_{50}) was calculated by the karbers method (>400mg/kg).

Anticonvulsant activity

The anticonvulsant activity was carried out of all the five synthesized amino acid incorporated bicyclo compounds by maximal electric shock method using phenytoin sodium as reference drug. Animals were weighed, numbered and divided into three groups each consisting of 6 rats. One group was used as normal control received dimethyl sulphoxide i.v., second group was standard control received phenytoin sodium at dose of 25mg/kg body wt i.v. and the third group received sample treatment at dose of 25mg/kg body wt. i.v. The corneal electrodes were placed on the cornea of the animal. The whole procedures were repeated with the animals of all the three groups. After 30 min of drug treatment, the animals were subjected to a electric shock of 150 M.A. by convulsiometer for 0.2 sec. The reduction in time or abolition of tonic extensor phase of MES-convulsions was noted (Kulkarni 2005, Hosseini et al., 2005).

The data are calculated & expressed as mean extensor phase duration in sec. followed by % protection and % potency in comparison with the standard as shown in Table 1 using the following formula:

$$\textbf{\% Protection} = (MEPD_{nc} - MEPD_{sample} / MEPD) \times 100,$$

where $MEPD_{nc}$ is the mean extensor phase duration of normal control in sec. and MEPD is the mean extensor phase duration of sample or standard in sec.

$$\textbf{\% Potency} = (MEPD_{nc} - MEPD / MEPD_{nc} - MEPD_{std}) \times 100,$$

where $MEPD_{std}$ is the mean extensor phase duration of standard control in sec.

Statistical anlysis

The results are expressed as the mean±SEM per group and the data were statistically analyzed by one-way analysis of Variance (ANOVA) followed by Dunnett's test as post hoc test. P value <0.05 was considered statistically significant.

In Silico toxicity prediction

The toxicity of the compounds were predicted by computational method using Pallas version 3.1ADME-Tox prediction software and pentium IV processor (Pallas, 2000).

RESULTS AND DISCUSSION

All title compounds were synthesized as per scheme 1 and confirmed by I.R., N.M.R., L.C. Mass spectra. The anticonvulsant activity was determined by maximal shock method on Wistar rats using phenytoin sodium as reference standard as shown in table 1&2.

The *In-silico* toxicity study was performed by using Pallas 3.1 software to predict oncogenicity, mutagenicity, teratogenicity, irritability, sensitivity, immunotoxicity and neurotoxicity as shown in table 3.

Table 1. Extensor phase duration of title compounds

Animal No.	Group 1	Group 2	Group 3				
	Normal Control	***Phenytoin Sodium***	***Comp. CSa***	***Comp. CSb***	***Comp. CSc***	***Comp. CSd***	***Comp. CSe***
1.	9.1	2.1	3.7	2.9	8.9	3.2	5.1
2.	9.2	2.4	4.1	3.1	9.0	3.3	5.4
3.	8.9	1.6	4.4	3.2	9.1	3.6	5.6
4.	9.0	1.9	4.7	3.4	8.9	3.9	5.9
5.	8.8	1.8	5.1	3.6	8.8	2.9	5.6
6.	8.9	2.2	4.2	2.8	9.1	4.1	4.9
MEAN ±SEM	8.983± 0.06009	2.000 ±0.1183	4.367 ±0.1994	3.167 ±0.1229	8.967 ±0.04944	3.500 ±0.1844	5.417 ±0.1493

Table 2. Anticonvulsant activity of title compounds

Compound	Dose(mg/kg)	Extensor phase duration(Sec.)	Protection (%)	Potency (%)
Control(DMSO)	-	8.983±0.06009	-	-
Phenytoin	25	2.000±0.1183	77.74	100
CSa	25	4.367±0.1994	51.39	66.10
CSb	25	3.167±0.1229	64.74	83.29
CSc	25	8.967±0.04944	00.18	00.23
CSd	25	3.500±0.1844	61.04	78.52
CSe	25	5.417±0.1493	39.70	51.07

Table 3. Predicted toxicity of title compounds

Comp.	Toxicity	Overall toxicity	Oncogenicity	Mutagenicity	Teratogenicity	Irritability	Sensitivity	Immuno toxicity	Neuro toxicity
CSa	Not probabale	47	00	47	19	00	00	00	00
CSb	Not probabale	47	00	47	19	00	00	00	00
CSc	Highly probabale	71	00	71	17	00	00	00	00
CSd	Not probabale	19	00	00	19	00	00	00	00
CSe	Highly probabale	71	00	71	19	00	00	00	00

The results of anticonvulsant activity showed that compound **CSb** i.e. with glutamic acid substitution and compound **CSd** i.e. with cysteine substitution were found to be highly potent with 64.74% and 61.04% protection against seizers induced by shock method and moreover and substitution with glycine and lysine shows moderation activity by 66.10% & 51.07% potency respectively as compared to phenytoin sodium as in case of **CSa** and **CSe** but unfortunately the substitution with proline i.e. compound **CSc** showed very less of no activity. The result of the computational toxicity prediction shows that the Compounds **CSb**(most active compound) possess 47% overall toxicity and has 47% mutagenicity with no oncogenicity, teratogenicity, irritability, sensitivity, immunotoxicity and specially neurotoxicity. Among the all compounds tested, the compound **CSd** has over all less toxicity i.e. 19% than other compounds.

CONCLUSION

In summary, the present work concludes a simple and novel method for the synthesis of bicyclo compounds without using any costly chemicals and any drastic conditions as such, the incorporation of amino acid favors the anticonvulsant activity specially in case of glutamic acid and cysteine with no neurotoxicity.

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