Valley International Journals
Open Access Journal

*International journal of medical science and clinical Invention*
*Volume 1 issue 1 2014 page no.15-24 ISSN: Applied*

# A Novel B, B -Diphenyl Propionic Acid Amide Derivatives Showing Anti-Inflammatory And Anticonvulsant Activity

***Semwal Amit****

Shree Dev Bhoomi Institute of Science Education and Technology, Dehradun, 248001.India.
"*For Correspondence" Mr. Amit semwal Assistant Professor Shree Dev Bhoomi Institute of Science Education and Technology, Dehradun, 248001.India.

E-mail: semwal_amit@rediffmail.com

**Abstract**

A series of β,β-Diphenyl Propionic acid amides were synthesized in order to obtain new compounds with potential anti-inflammatory and anticonvulsants activity. The structures of new compounds are supported by IR and $^{1}$HNMR spectral data. These derivatives were then tested for a general profile of activities as anti – inflammatory using carrageenan induced rat paw edema method and anticonvulsants activity using maximal electroshock seizures method and in this investigation a significant level of anti-inflammatory and anticonvulsants activity was illustrated.

**Key words:** Diphenyl Propionic acid amides, anti-inflammatory, anticonvulsants activity

## Introduction

Epilepsy is a common neurological condition, affecting 0.5 to 1% of the population worldwide (45-100 million people)[1].Conventional antiepileptic drugs (AEDs) phenobarbital, primidone, phenytoin, carbamazepine, ethosuximide and benzodiazepine are widely used but exhibit an unfavorable side effect profile and failure to adequately control seizures. In the recent years several new drugs (oxcarbazepine, lamotrigine, topiramate, gabapentin,zonisamide, tiagabine, fosphenytoin, vigabatrin and felbamate) have been added to the list of therapeutic agents against epilepsy. However, there is a significant group of patients (up to 30%) who are resistant to

the available antiepileptic drugs. The long-established AEDs control seizures in 50% of patients developing partial seizures and in 60-70% of those developing generalized seizures [2,3,6]. Hence, there is an urgent need to develop new AEDs [7].

These seizures are transient signs and/or symptoms due to abnormal, excessive or synchronous neuronal activity in the brain. Incidence of epilepsy in developed countries is approximately 50 per 100,000 while that of developing country is 100 per 100,000 (WHO, 2006). It has been observed that the presently available antiepileptic drugs are unable to control seizures effectively in as many as 25% of the patients. As majority of antiepileptic drugs are consumed life long, concomitant administration of other drugs predisposes to the risk of drug interaction. However, newer antiepileptics like gabapentin, vigabatrin, lamotrigine, etc are used supplemental to the conventional agents Thus, it is necessary to investigate for an antiepileptic agent that is highly efficacious as well as safe in items of drug related toxicity. The aim of treating an epileptic is not only to abolish the occurrence of seizures but also to lead a self sustained life[8].

Diphenyl alkylamides chemically synthesized which possess beneficial pharmacological properties (anticonvulsant activity) useful for treatment of neurological disorder, such as, for example, epilepsy, convulsions, and seizure disorders[9]. β,β -diphenyl propanamide and structurally related amide and acid compounds use in treating a symptom of convulsions. Thus, there is a clear and persistent need for the development of new clinical entities with improved side effect profiles and efficacy for the treatment of convulsive states or conditions.

An inflammatory reaction is a local, generally nonspecific,defensive response to cellular or tissue injury by chemical/physical irritants or a microbial infection. In mammals, it normally initiates the elimination of noxious agents and disposal of damaged tissue in order to promote wound healing. This is achieved by a succession of chemical signals (autocoids) playing the role of local hormones that prompt the incoming blood leukocytes and surrounding tissues to establish healing processes[10]. Discovery of the wide

variation among chemical mediators has clarified the apparent paradox that an anti-inflammatory drug may interfere with the action of a particular mediator important in one type of inflammation but be without effect in inflammatory processes not involving the drug's target mediators[11].

## Materials and Methods

### Experiental:

Melting points of the synthesized compounds were determined by open capillary method and are uncorrected. Thin layer chromatography was performed on pre-coated silica gel $G_{254}$ plates and visualized in iodine or UV. The IR spectra of synthesized compounds were recorded in potassium bromide discs on Schimadzu FTIR Spectrophotometer 8300. The $^1H$ NMR spectra of the synthesized compounds were recorded in DMSO and $CDCl_3$ using AV-300 Broke Jeol Spectrophometer.

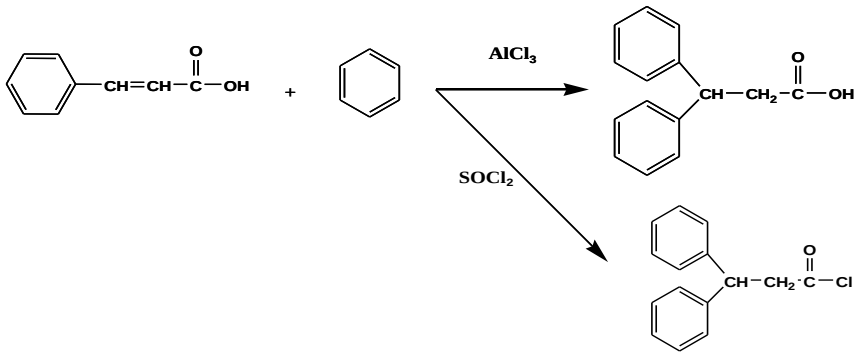
### Synthesis of β,β- Diphenyl Propionic Acid:

Cinnamic acid 30g and dry benzene 160 ml were taken in a 1-1 three necked RBF equipped with a mechanical stirrer and reflux condenser. This was surrounded with a mixture of ice-salt and anhydrous $AlCl_3$ (40g) was added in small lots when addition was over, the contents of the flask were stirred for 3 hrs. at 40-45 ºC. The $AlCl_3$ complex formed was decomposed with ice & HCl and excess of benzene was removed by steam distillation. The solid so obtained was collected by filtration, washed with water & was purified by dissolving in aq. Sodium bicarbonate sol (10%) followed by reprecipitation with dil.HCl. The product was recrystallized from ethanol.

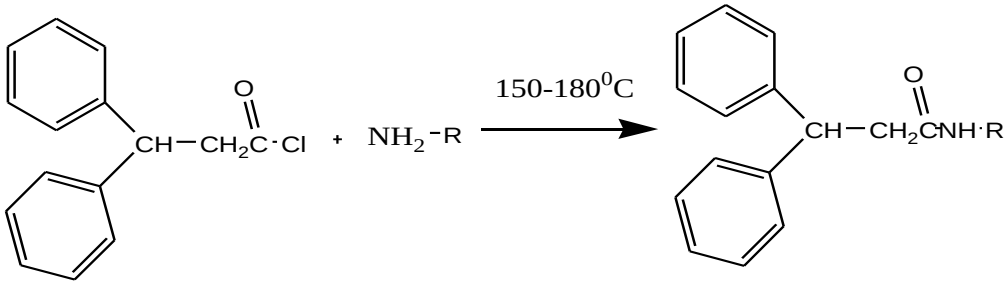
### Synthesis of 3,3-diphenylpropanamide ($AS_1$):

β,β- Diphenyl propionic acid 2.5 g, urea 3g, were added to 250 mL RBF & refluxed for 2 hr. in oil bath at 180-200ºC. After the heating period content of RBF were cooled to room temp. Dil.HCl about 30 ml (prepared by adding 5ml conc. HCl to 50ml water) was added to RBF to remove excess amine. The resultant solid was filtered, washed with water and was recrystallised from ethanol. Pure 3,3-diphenylpropanamide was obtained. The compounds II-VIII were also synthesized. The %yield and melting point are listed in the

Table 1.




**Cinnamic acid** **Benzene** **β,β- Diphenyl Propionic Acid**




**β,β- Diphenyl Propionic acid** **Amines** **β,β-diphenylpropionic Acid Amide**

**Table 1: Physical constants of different β,β- Diphenyl Propionic Acid Amides from different amines**

| S.NO | Compound | R | Meltng point(°c) | % Yield | Molecular Formula |
|---|---|---|---|---|---|
| 1. | $AS_1$ | H | 125-126 | 48 | $C_{15}H_{16}ON$ |
| 2. | $AS_2$ | $C_6H_5$ | 125-126 | 45.18 | $C_{21}H_{19}ON$ |
| 3. | $AS_3$ | $C_6H_{11}$ | 185-186 | 44.25 | $C_{21}H_{25}ON$ |
| 4. | $AS_4$ | p.$(CH_3O)C_6H_4$ | 70-72 | 26.38 | $C_{22}H_{21}O_2N$ |

| | | | | | |
|---|---|---|---|---|---|
| 5. | $AS_5$ | 2-$C_5H_4N$ | 68-69 | 35.92 | $C_{20}H_{18}ON_2$ |
| 6. | $AS_6$ | $2COOCH_3.C_6H_4$ | 127-128 | 34 | $C_{23}H_{21}O_3N$ |
| 7 | $AS_7$ | $SO_2NH_2C_6H_4$ | 156-157 | 83.78 | $C_{21}H_{20}O_3NS$ |
| 8. | $AS_8$ | -NH-$CH_2$-COOH | 70-72 | 86.26 | $C_{17}H_{17}O_3N$ |

**3,3-diphenylpropanamide ($AS_1$):**

**IR (KBr) $cm^{-1}$ :** 3500-3350(N-H str.), 3050-3000(C-H aromatic str.), 1600-1450 (C=C, str.), 900-700( C-H def.), 1690(C=O); **$^1$H-NMR (400 MHz, $CDCl_3$) δ (ppm) :** 7.05 δ ( 2H, $NH_2$), 7.07-7.27 δ ( 10H, Ar-H), 4.97 δ (H, CH),2.4 δ ( 2H, $CH_2$).

**N,3,3- triphenyl propanamide ($AS_2$):**

**IR (KBr) $cm^{-1}$ :** 3500-3350(N-H str.), 3050-3000(C-H aromatic str.), 1600-1450 (C=C, str.), 900-700( C-H def.), 1690(C=O); **$^1$H-NMR (400 MHz, $CDCl_3$) δ (ppm) :** 5.78-6.32 δ (15H, Ar-H), 7.8 δ (s, 1H, NH), 2.61 δ (2H, $CH_2$), 3.51 δ (H, CH).

**N-cyclohexyl-3,3-diphenylpropanamide ($AS_3$):**

**IR (KBr) $cm^{-1}$ :** 3500-3350(N-H str.), 3050-3000(C-H aromatic str.), 1600-1450 (C=C str), 900-700( C-H def.), 1690(C=O),1350-1280(C-N aromatic str),1442-1449(C-H N-cyclohexane str); **$^1$H-NMR (400 MHz, $CDCl_3$) δ (ppm) :** 7.07-7.27 δ ( 10H, Ar-H), 4.28 δ (H, CH), 2.80 δ (2H, $CH_2$), 1.39-1.78 δ (11H, CH).

**N-(4-methoxyphenyl)-3,3-diphenylpropanamide ($AS_4$):**

**IR (KBr) $cm^{-1}$ :** 3500-3350(N-H str.), 3050-3000(C-H aromatic str.), 1600-1450 (C=C, str.), 900-700( C-H def.), 1690(C=O),1350-1280(C-N aromatic str),1247(C-O str);**$^1$H-NMR (400 MHz, $CDCl_3$) δ (ppm) :** 6.75-7.21 δ (15H, Ar-H), 4.28 δ (H, CH), 2.85 δ (2H, $CH_2$), 3.73 δ (3H, $CH_3$).

**3,3-diphenyl-N(pyridin 2-yl) propanamide ($AS_5$):**

**IR (KBr) $cm^{-1}$ :** 3500-3350(N-H str.), 3050-3000(C-H aromatic str.), 1600-1450 (C=C, str.), 900-700( C-H def.), 1690(C=O),1350-1280(C-N aromatic str), 1250-1020(C-N aliphatic str); **NMR**

**(400 MHz, $CDCl_3$) δ (ppm) :** 7.08-7.21 δ ( 10H, Ar-H), 4.28 δ (H, CH), 2.80 δ (2H, $CH_2$), 8.0 δ ( 1H, NH),7.18-8.49 δ (4H, 2-Pyridine).

**Methyl-2-(3,3-diphenylpropanamido) benzoate ($AS_6$):**

**IR (KBr) $cm^{-1}$ :** 3500-3350(N-H str.), 3050-3000(C-H aromatic str.), 1600-1450 (C=C str.), 900-700( C-H def.), 1690(C=O), 1350-1280(C-N aromatic str), 1250-1020(C-N aliphatic str),1200(C-O),2875(C-H str); **NMR (400 MHz, $CDCl_3$) δ (ppm) :** 7.08-7.45 δ ( 14H, Ar-H), 4.28 δ (H, CH), 2.85 δ (2H, $CH_2$), 8.0 δ ( 1H, NH), 3.88 δ (3H, $CH_3$).

**N-(4-Sulfonamidophenyl)-3,3-diphenylpropanamide ($AS_7$):**

**IR (KBr) $cm^{-1}$ :** 3500-3350(N-H str.), 3050-3000(C-H aromatic str.), 1600-1450 (C=C str.), 900-700( C-H def.), 1690(C=O), 1350-1280(C-N aromatic str), 1250-1020(C-N aliphatic str), 700-600 $cm^{-1}$(C-S),1070-1030(S=Ostr),3390-3330(N-H str,Sulphonamide); **NMR (400 MHz, $CDCl_3$) δ (ppm) :** 7.08-7.92 δ (14H, Ar-H), 4.28 δ (H, CH), 2.85 δ (2H, $CH_2$), 8.0 δ (s, 1H, NH), 2.0 δ (s, 2H, $NH_2$).

**2-(3,3-diphenylpropanamido) acetic acid ($AS_8$):**

**IR (KBr) $cm^{-1}$ :** 3500-3350(N-H str.), 3050-3000(C-H aromatic str.), 1600-1450 (C=C, str.), 900-700( C-H def.), 1690(C=O), 3000-2500 (O-H, str.), 1250-1020(C-N aliphatic str); **NMR (400 MHz, $CDCl_3$) δ (ppm) :** 7.07-7.27 δ ( 10H, Ar-H), 4.28 δ (H, CH), 2.80 δ (2H, $CH_2$), 8.0 δ (1H, NH), 4.14(2H,$CH_2$),11.0(1H,OH).

**Anticonvulsant activity** [9-12]

**Maximal Electroshock seizure Test (MES):** The Maximal Electroshock seizure Test was done by the method of Toman et al. The mice were prescreened 24 hrs. before by delivering supramaximal electroshock (60 mA; 0.2 sec. duration ) by means of ear clips. Only those mice showing hind limb tonic extensor response were selected. These were then divided into twelve group of eight animals each. The test compounds (30 mg/kg) suspended in 0.5 % CMC was administered orally to ten groups. After an hour electroshock was again applied and the absence of hind limb extensor response after test compounds

treatment, was considered as the protective index of the anticonvulsant activity. The control study, which was done with the vehicle (CMC 0.5%) Showed hind limb extensor response. The result the Table 2.

were compared with the activity shown by the clinically useful anticonvulsant drug Phenytoin. The results are reported in

**Table 2: Anti-Convulsant effect of synthesized compounds**

| S.No | Drug Treatment | Dose/Kg | % Protection MES (n) |
|---|---|---|---|
| 1. | $AS_1$ | 30 mg | 50.0 |
| 2. | $AS_2$ | 30 mg | 25 |
| 3. | $AS_3$ | 30 mg | 20 |
| 4. | $AS_4$ | 30 mg | 15 |
| 5. | $AS_5$ | 30 mg | 20 |
| 6. | $AS_6$ | 30 mg | 15 |
| 7. | $AS_7$ | 30 mg | 10 |
| 8. | $AS_8$ | 30 mg | 00.0 |
| 9. | Phenytoin | 25 mg | 98** |
| 10. | Control | 10 ml | 00.0 |

** P< 0.001 n – no of animals MES - Maximal electroshock seizures

**Anti-inflammatory activity**[13]

The Synthesized compounds were evaluated for its anti-inflammatory activity by Carrageenan Induced Paw edema method. The albino rats (200-300 gm) were divided into six groups of six animals each. One group named as Control (Group-I), another was Standard (Group-II) and remaining four groups were used for test groups, named as Test Group I, Test group II, Test group III and Test group IV. A mark was made on left hind paw of each rat just beyond tibio-tarsal junction, so that every time the paw could be dipped in the column up to the fixed mark to ensure constant paw volume. The initial paw volume of each rat was noted by mercury displacement method. The Group-I, serving as control, was administered 5% acacia solution in a volume of 1 ml/100g, body weight, orally. Group-II, serving as standard, was administered Indomethacin (10 mg/kg, body weight, orally). Test Group I, Test group II, Test group III and Test group IV, serving as test was administered synthesized compounds in the dose of 100 mg/kg

body weight, orally.One hour after the oral administration of control, standard and test drug, 0.1 ml of 1% carrageenan in normal saline was injected into the plantar aponeurosis of the left hind paw of each rat. The volume of the paw was measured by a plethysmometer in 1, 2, 3 and 4 hour after carrageenan suspension injection. The percentage increase in paw volume in animals treated with standard, synthesized compounds were compared with the increase paw volume of animals of control group after 1, 2, 3 and 4 hour. The percent inhibition was calculated by following formula-

% Inhibition = (1-Vt / Vc)*100

Where, Vt and Vc are the mean change in paw volume of treated and control rats respectively. The results are reported in the Table 3

**Table 3: Anti-inflammatory effect of synthesized compounds by carrageenin induced paw edema**

| S.No | Compound applied | Weight (g) | Dose (mg/ Kg bw) | Paw vol. before adm. Carrageenan ( mm) | Paw vol. After adm. Carrageenan (hrs) | | | | Paw vol. mean | % inhibition |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 0.5 | 1 | 2 | 3 | | |
| 1. | Control | 200 | - | 3.0 | 3.5 | 4 | 5 | 5 | 1.37 | -- |
| 2. | Standard | 190 | 25 | 4.0 | 4 | 5 | 4 | 4 | 0.25 | 81.25 |
| 3. | $AS_1$ | 200 | 100 | 2 | 2.5 | 2.5 | 3 | 3 | 0.75 | 45 |
| 4. | $AS_2$ | 180 | 100 | 3 | 3 | 3.5 | 3 | 3 | 0.125 | 90 |
| 5. | $AS_3$ | 190 | 100 | 4 | 3.5 | 4 | 4.5 | 4.5 | 0.125 | 90 |
| 6. | $AS_4$ | 170 | 100 | 2 | 2 | 2.5 | 3 | 3 | 0.625 | 54.37 |
| 7. | $AS_5$ | 180 | 100 | 0.5 | 3.5 | 4 | 4.5 | 5 | 0.75 | 45.25 |
| 8. | $AS_6$ | 200 | 100 | 2 | 2 | 2.5 | 3 | 3.5 | 0.75 | 45.25 |
| 9. | $AS_7$ | 160 | 100 | 3 | 3 | 3.5 | 4 | 4 | 0.625 | 54.37 |
| 10 | $AS_8$ | 180 | 100 | 3 | 3 | 4 | 4 | 4.5 | 0.875 | 36.13 |

**Result and discussion:**

The compounds were evaluated for anticonvulsants activity using maximal electroshock seizures method, ($AS_1$, $AS_2$, $AS_3$, $AS_4$, $AS_5$, $AS_6$, $AS_7$, $AS_8$) showed mild to moderate anticonvulsant activity ranging from 00.0 % to 50 %, whereas the standard drug indomethacin showed 98 % protection. The same synthesized compounds were evaluated for anti-inflammatory activity using carragennin induced

paw edema method, showed mild to moderate anti-inflammatory activity ranging from 36.13% to 90 % after 3 hrs, whereas the standard drug indomethacin showed 81.25 % inhibition. So all of them induced significant reduction in inflammation as compare to control.

**Acknowledgement**

The author would like to thank Mr. SN Nautiyal, Chairman, Shree Dev Bhoomi Institute of Science, Education and Technology, Dehradun for his immense support and constant encouragement.

**Reference**

1 Bell G.S., Sander J.W., (2002) The epidemiology of epilepsy: The size of the problem. *Seizure*, 11 A: 306-314.

2 Lima J.M., (2000) The new drugs and strategies to manage epilepsy. *Curr. Pharmac. Design*, *6*: 873-878.

3 Perucca E., (2002) Marketed new antiepileptic drugs: Are they better than old-generation agents? *Ther. Drug Monit.*, *24*: 74-80.

4 Berk et al, (2001) Emerging options in the treatment of bipolar disorders. *Drug*, *61*:1407-1414.

5 Duncan J.S., (2002) The promise of new antiepileptic drugs. *Brit J Clin Pharmacol*, *53*:123-131.

6 Eadie M.J., (2001) Can anticonvulsant drug therapy 'cure' epilepsy? *CNS Drugs*, *15*: 679 - 690.

7 Szelenyi et al, (2003) The treatment of epilepsy: future possibilities. *Drugs Fut.*, *28*: 925-936.

8 Duraisami et al, (2009) Anticonvulsant activity of bioflavonoid gossypin. *Bangladesh J Pharmacol*, 4: 51-54.

9 Balandrin et al, (2003) Anticonvulsant And Central Nervous System-depressing bis(flurophenyl)alkylamides and their uses, United States Patent 661735 Sep.9,.

10 Michael W., (2005) Drugs to treat inflammation: A Historical Introduction. *Current Med Chem*; 12: pp 2931-2942.

11 Vogel G.H., Drug Discovery and Evaluation Pharmacological Assays, 2nd edition, Springer-Verlag Berlin

Heidelberg, New York. 759-762 &697-699.

12 Swinyard E.A, Brown W.C., Goodman L.S., (1952)Comparative assay of antiepileptic drugs in mice and rats. *J Pharmacol Exp Ther*, 106:319-30.

13 Vgzquez et al, (1997) Synthesis and anti-inflammatory activity of 2-(2,3-dihydro-1,4-benzodioxin)propionic acid and its R and S enantiomers. *Eur J Med Chem*., 32:529-534.