ISSN: 0975-766X
CODEN: IJPTFI
Research Article

Available Online through
www.ijptonline.com

SYNTHESIS AND EVALVATION OF NEW OXCARBAZEPINE ANALOGUES FOR ANTICONVULSANT ACTIVITY

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Received on 07-06-2012 *Accepted on 25-06-2012*

Abstract

Epilepsy is one other most common ailment of man with a prevalence of approximately 1%. It is estimated that 50 millions person's worldwide may have this disorder. Although many are well controlled with available therapies, perhaps one quarter of the total continue to have seizures. Anticonvulsant drugs are the mainstay of epilepsy management and may have to be taken for life. In more than 20% of those affected, chronic in aractable (refraction) epilepsy develops. This necessitates the use of combination therapy. But the use of these drugs in combination is plagued by cognitive impairment and drug interactions with the results that only about 10% of the patients with refractory epilepsy seem to benefit substantially from polypharmacy. Thus the new viable antiepileptic molecules are urgently needed. Oxacarbazepine has developed its efficacy and its improved safety profile and is now considered as epileptic drug of first choice. To potentiate the activity of oxcarbazepine for anticonvulsant activity the oxygen group of 10^{th} position and NH_2 group of 5^{th} position were changed with different groups such as methoxy, benzyl, piprazine, dimethylamine, methylamine which possess remarkable chemical and geometrical similarities for anti-convulsant activity. About six novel derivatives of oxcarbazepine were prepared. Their identification and characterization was done by TLC, IR, NMR spectroscopy.

Keywords: Epilepsy, Oxacarbazepine, Polypharmacy.

Introduction: The term epilepsy refers to a disorder of brain function characterized by the periodic and unpredictable occurrence of seizures[1,2] . The term "seizures" refer to a transient alteration of behaviour due to abnormal excessive, hyper synchronous discharges from aggregate of CNS neurons.

Seizure can be

a) Non epileptic –when evoked in a brain by treatment such as electric shock or chemical convulsants.

b) Epileptic –when occur without evident provocation.

The epilepsy is common and frequently devastating disorder, affecting approximately 0.5% of the population. More than 40 distinct forms of epilepsy have been identified. The incidence increases again epilepsy begins before the age of 18 in over 75% population.

Seizures the characteristic event in epilepsy, is associated with the episodic high frequency discharges of impulses by a group of neurons in the brain. What starts as a local discharge may then spread to other areas of the brain. The site of primary discharge and extent of its spread determines the symptoms that are produced, which ranged from a brief lapse of attention to a full conclusive fit lasting for several minutes.

The particular symptoms produced depend on the function of the region of the brain that is affected thus involvement of the hypothalamus causes peripheral autonomic discharge and involvement of the reticular formation in the upper brain stem leads to loss of consciousness.

Objectives of the Study

Oxcarbazepine and its analogues are highly lipophilic thus easily pass the BBB and reach the site of action[3]. Hence, an attempt was made to prepare oxcarbazepine analogues by modified route and screen for anticonvulsant activity.

The Main Objectives of the Study

- ✓ Attempt was made to synthesize oxcarbazepine analogues through different routes that may give good yield with acceptable purity
- ✓ Costly raw materials were avoided to make the process economical.
- ✓ Complicated procedures were avoided to achieve simpler techniques.
- ✓ Characterization of synthesized oxcarbazepine analogues was made by TLC, IR, and NMR techniques.
- ✓ Pharmacological evaluation of oxcarbazepine by maximal electrical shock method which produce a selective anticonvulsant activity was studied.

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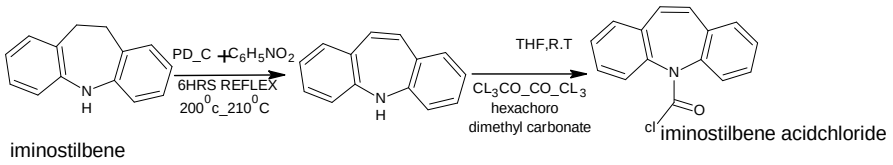

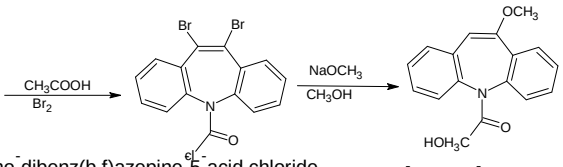

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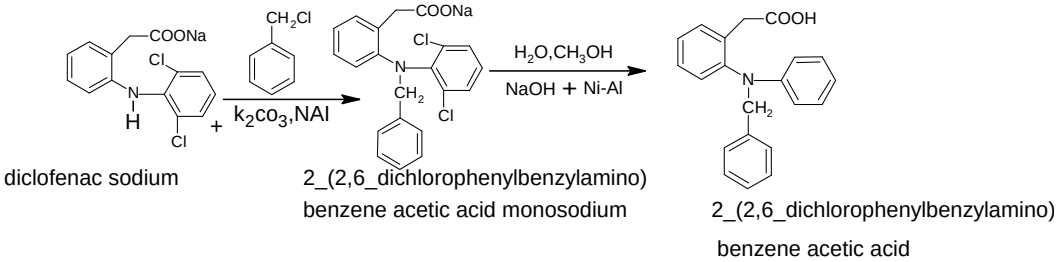

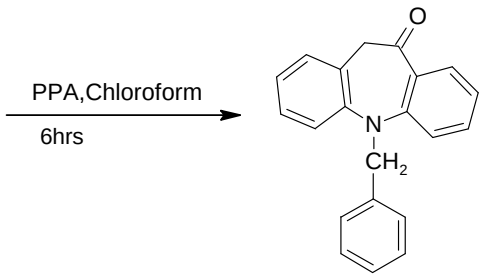

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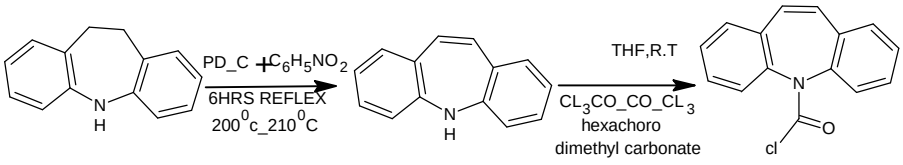

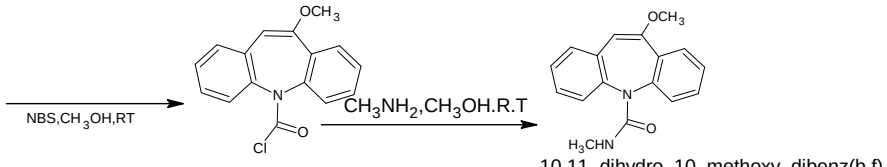

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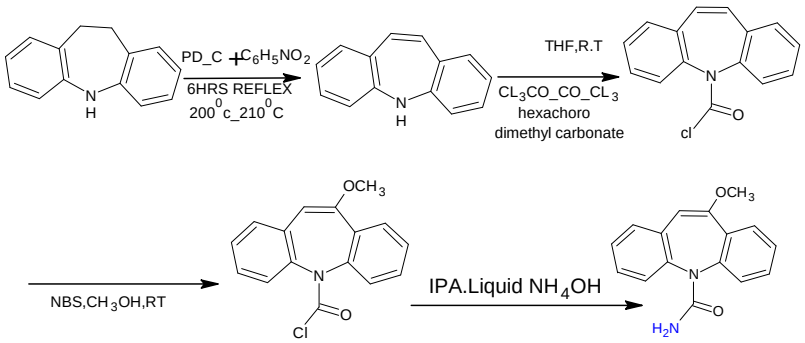
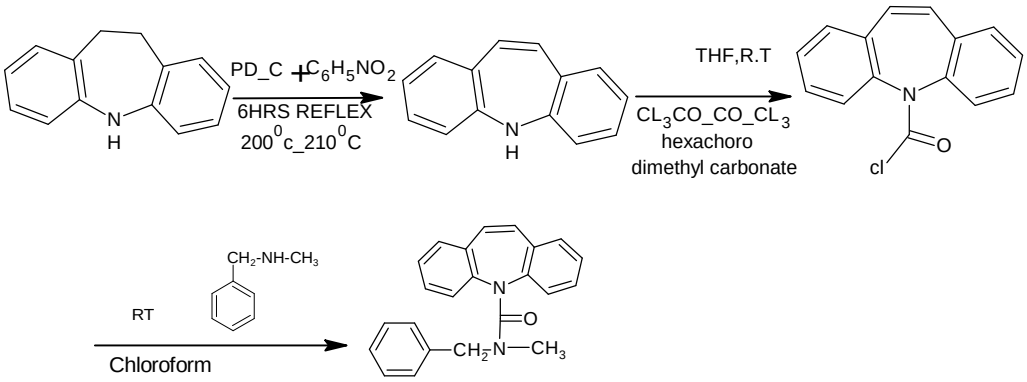


10,11_dihydro_10_methoxy_dibenz(b,f) azepine -5 -carbonyl chloride

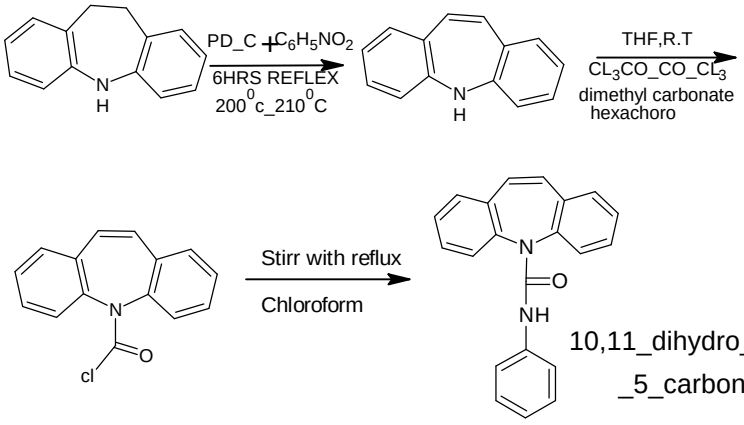
10,11_dihydro_10_methoxy_dibenz(b,f) azepine -5 -carboxamide

SYNTHESIS OF DERIVATIVE -5



10,11_dihydro_5H_dibenz(b,f)azepine_5_carbonyl(methylbenzyl)amine

SYNTHESIS OF DERIVATIVE -6



10,11_dihydro_5H_dibenz(b,f)azepine _5_carbonylphenylamine

PHYSICAL PROPERTIES (D1-D6):

The physical properties of all the synthesized derivatives are given in Table – 1.

Table No-1: The physical properties of all the synthesized derivatives.

PROPERTIES	**OBSERVATIONS**					
	Derivative-D1	**Derivative-D2**	**Derivative-D3**	**Derivative-D4**	**Derivative-D5**	**Derivative-D6**
Description	It is yellow and odourless	Yellow crystals and odourless	Brown, solid and odourless	Dark brown and odourless	Brown crystals and odourless	White crystals and odourless
Solubility	Acetone, Methanol, Ethanol, Chloroform, sparingly soluble in toluene	Ehyl acetate, Choloroform, Ethanol, Methanol Sparingly soluble in PE	EA, Chloroform, Methanol, Ethanol, Acetone, Sparingly soluble in Toluene	EA, Acetone, Methanol, Toluene, Sparingly soluble or insoluble in water	EA, Acetone, chloroform, Methanol IPA and insoluble in water	EA, Acetone, chloroform, Methanol IPA, Toluene and insoluble in water
Recrystallized by	Column Chromatography	Column Chromatography	Ethanol	Column Chromatography	Ethanol	Column Chromatography
Melting Point	130^0C-132^0C	148^0C-150^0C	128^0C-130^0C	122^0C-125^0C	105^0C-110^0C	138^0C-142^0C
% of Yield (In final stage)	90	84	80	79	90	86

I.R SPECTRA (D1-D6):

The IR spectra of the synthesized derivatives are given in Table – 2, 3 & 4.

Table-2: The IR spectra of the synthesized derivatives 1 and 2.

IR Spectrum D1 Groups	Wave Numbers (CM^{-1})	**IR Spectrum D1** Groups	Wave Numbers (CM^{-1})
C=O Str of ester	1705	C=O Str of ester	1727
C=o Str of Methoxy group	1439	Aromatic C=C Str	1611-1490
C=C Str of Aromatic ring	1589	Aromatic CH Str	3030
Aromatic out of plane CH deformation vibrations	700-800	Aromatic out of plane CH deformation vibrations	700-800
CH Str of Alkane	2390		

Table –3: The IR spectra of the synthesized derivatives 3 and 4.

IR Spectrum D3 Groups	Wave Numbers (CM^{-1})	**IR Spectrum D4** Groups	Wave Numbers (CM^{-1})
C=O Str of amide group	1661	C=O Str of amide group	1672
NH Str of amide group	3366	Asymmetric & Symmetric Str of NH_2 group of amide	3476.5 3348
Aliphatic CH Str of azepine	2930	C=C Str of Aromatic ring	1583 & 1479.3
Aromatic C=C Str	1473.5	C-H deformation vibration	756
C-O Str of methoxy group	1111.9		

Table –4: The IR spectra of the synthesized derivatives 5 and 6.

IR Spectrum D5 Groups	Wave Numbers (CM^{-1})	**IR Spectrum D6** Groups	Wave Numbers (CM^{-1})
C=O Str of amide group	1647	C=O Str of amide group	1663
CH_2 Str of benzyl group	2930	NH Asymmetric & Symmetric Str of Amide group respectively	3421 3333
Aromatic C=C Str	1400	Aromatic C=C Str	1525.8
C-H deformation vibration	741.6		

NMR SPECTRA (D1-D6):

The NMR spectra of the synthesized derivatives are given in Table – 5 & 6.

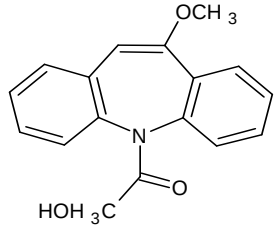
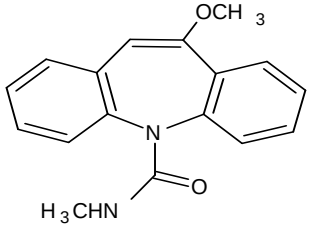
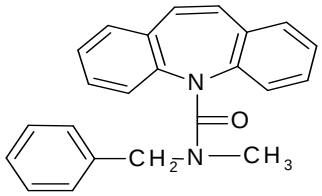
Table-5: The NMR spectra of the synthesized derivatives 1, 2 and 3.

NMR Spectrum D1	**NMR Spectrum of D2**	**NMR Spectrum D3**
Two sharp methoxy protons at 3.7 δppm	The azepine proton of 10th position and benzyl proton of CH_2 group merged and gave quintet at 3.4 δppm	Methoxy protons and Methyl protons at 3.4 and 2.9 δppm respectively
At 6.7 δppm singlet proton of azepine ring system		NH proton of amide group at 5.2 δppm
Between 7 to 8 δppm aromatic protons	Aromatic protons between 7 to 8 δppm	Aromatic proton between 7 to 8 δppm
		Proton of azepine ring at 4.2 δppm

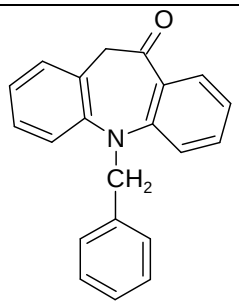
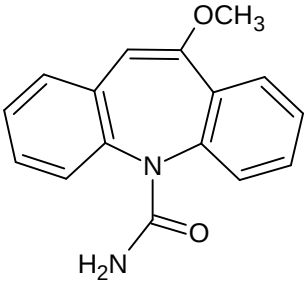
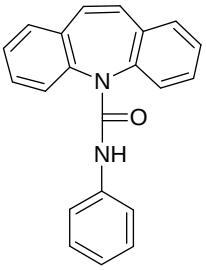
Table-6: The NMR spectra of the synthesized derivatives 4, 5 and 6.

NMR Spectrum of D4	**NMR Spectrum of D5**	**NMR Spectrum of D6**
Methoxy protons peak at 3.4 δppm	Methyl protons at 2.5 δppm	NH protons at 6.3 δppm
Amide protons at 4.7 and 5 δppm respectively	Methylene protons at 4.3 δppm	Aromatic protons between 7 to 8 δppm
Aromatic protons between 7 to 8 δppm	Aromatic protons between 7 to 8 δppm	Azepine ring protons at 6.9 δppm
Azepine ring protons at 6.9 δppm	Azepine ring protons at 6.9 δppm	

According to the IR and NMR spectral data obtained the structures of the compounds may be as follows:

DERIVATIVE-D1	**DERIVATIVE-D2**	**DERIVATIVE-D3**
		

10,11-dihydro-10 methoxy - 5H -dibenz(b,f)azepine-5-acetate. Attributed Molecular formula: $C_{17}H_{15}NO_3$	10,11-dihydro-10-methoxy-5H-dibenz (b,f) azepine-5 - carbonyl methyl amine. Attributed Molecular formula: $C_{17}H_{16}NO_2$	10,11-dihydro-5H-dibenz(b,f) azepine-5 –carbonyl (methyl benzyl) amine. Attributed molecular formula: $C_{23}H_{21}N_2O$

DERIVATIVE-D4	**DERIVATIVE-D5**	**DERIVATIVE-D6**
 10,11-dihydro-10-oxo-dibenz(b,f)azepine-5-Benzyl Attributed Molecular formula: $C_{21}H_{17}NO$	 10,11-dihydro- 0-methoxy -5H-dibenz(b,f) azepine-5-carboxamide Attributed Molecular formula: $C_{15}H_{14}NO_2$	 10,11-dihydro-5H-dibenz (b,f) azepine-5-carbonyl (phenyl) amine Attributed molecular formula: $C_{21}H_{17}N_2O$

Anticonvulsant activity of synthesized oxcarbazepine analogues by maximal electroshock method[4].

Institutional Animal Ethical Committee (IAEC) approval was taken before performing the animal studies.

In maximal electroshock (MES) electroshock is applied through the ear electrodes. The MES convulsions are divided into five phases such as

1. Tonic flexion

2. Tonic extensor

3. Clonic convulsion

4. Stupor and

5. Recovery or death

A substance is to possess anticonvulsant property if it reduces or abolished the extensor phase of MES convulsion.

Procedure: Swiss albino rats of either sex (170-250gm) were weighed and divided into 8 groups of 5 animals each. Of the 8 groups one group was used as control, to test the effect of MES alone and one group was used as STD administered with oxcarbazepine 14mg/kg[1] and remaining groups were used for synthesized oxcarbazepine analogues The suspension of the drugs were prepared in 0.5% guargum solution in distilled water. To the control animals MES was given and time for onset of clonic convulsions was recorded. To the other groups 14mg/kg[9] of oxcarbazepine was given through oral route and after 1 hour MES was given and delay in the onset of action were recorded.

To the remaining six groups, synthesized oxcarbazepine analogues were given through oral route and after one hour, the onset of convulsions were recorded. Results were statistically compared against the control.

Group no	**Body Wt**	**Treatment (dose)**	**Time(sec) in various phase of convulsions**				
			flexion	**Extensor**	**clonus**	**Stupor**	**Ror D**
I	189 190 195 192 193	Control	6 5 4 5 7	9 8 11 10 9	3 4 2 4 2	90 110 96 102 98	R D R R D
II	185 180 175 183 182	Oxcar- bazepine 14mg/kg	2 2 0 2 0	6 3 3 1 2	2 1 1 0 2	60 58 71 42 48	R R R R R
III	205 208	**D1**	2 3	8 7	2 3	80 83	R R

	207	**(14mg/kg)**	0	8	1	78	R
	203		4	8	2	75	R
	210		1	9	1	79	R
	210		3	6	4	76	R
	215	**D2**	4	7	3	78	R
IV	213	**(14mg/kg)**	3	8	2	84	R
	214		2	6	1	90	R
	215		0	8	2	70	R
	210		3	9	3	90	R
	212	**D3**	0	8	4	79	R
V	214	**(14mg/kg)**	1	6	3	80	R
	213		3	5	2	75	R
	216		2	7	1	74	R
	233		0	5	3	80	R
	236	**D4**	2	7	4	79	R
VI	240	**(14mg/kg)**	1	6	3	70	R
	235		1	9	2	78	R
	241		1	7	2	70	R
	170		4	10	5	100	R
	173	**D5**	5	11	6	110	D
VII	175	**(14mg/kg)**	7	09	7	105	R
	178		6	10	8	103	R
	180		3	12	13	115	D

VIII	210 203 207 208 205	**D6 (14mg/kg)**	1 4 3 0 4	6 7 8 6 8	3 4 3 2 1	80 79 70 78 70	R R R R R

R = Recovery, D = Death

The following table indicates the effects of synthesized oxcarbazepine and its analogues on the extensor phase of convulsions in albino rats.

S. No	Treatment dose (mg/kg)	Mean ± SEM	P value
1	Control	4.60 ± 0.748***	-
2	Oxcarbazepine (14mg/kg)	3.00 ± 0.836***	0.0002
3	D1 (14mg/kg)	8.00±0.316*	0.0479
4	D2 (14mg/kg)	7.00±0.447*	0.0076
5	D3 (14mg/kg)	7.00±0.707*	0.0249
6	D4 (14mg/kg)	6.80±0.663*	0.0145
7	D5 (14mg/kg)	10.40±0.509*	0.2029
8	D6 (14mg/kg)	7.00±0.447**	0.0076

Statistics: Unpaired 't' test n=5, *P<0.05, **P<0.01, ***P<0.001

Results

The synthesized oxcarbazepine analogues were compared with that of control for anticonvulsant activity. Among the six synthesized oxcarbazepine analogues five of them were found to be active as they reduced time of extensor phase

as compared to control and the values are statistically significant as compared to control. Remaining one analogue D5 did not show any anticonvulsant activity in the parameter tested.

Discussion and Conclusion

Oxacarbazepine has developed its efficacy and its improved safety profile and is now considered as epileptic drug of first choice. To potentiate the activity of oxcarbazepine for anticonvulsant activity the oxygen group of 10^{th} position and NH2 group of 5^{th} position were changed[8] with different groups such as methoxy, benzyl, piprazine, dimethylamine, methylamine which possess remarkable chemical and geometrical similarities for anti-convulsant activity. About six novel derivatives of oxcarbazepine were prepared. Their identification and characterization was done by TLC, IR, NMR spectroscopy. The synthesized oxcarbazepine analogues were screened for anticonvulsant activity by maximal electrical shock method (MES). The animal studies proved that D5 is not significant in its activity. D2 and D6 are said to be more significant. The animal studies have been performed with respect to oxcarbazepine as standard, using 14mg/kg[14,15]. The animal studies using 14mg/kg have proved that D1, D2, D3, D4, & D6 are significant in their activity. However LONG TERM TOXICITY STUDIES have to be carried out before any conclusion is drawn.

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