RESEARCH ARTICLE

Synthesis, Characterization and Anti-Convulsant Activity of Some Novel Substituted Chalcone Derivatives

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Received: 28th February, 2022; Revised: 24th April, 2022; Accepted: 05th May, 2022; Available Online: 25th June, 2022

ABSTRACT

Objective: Present work emphasized on the search the some new chalcone derivatives and planned to screen for their anti-convulsant activity with potency and lesser adverse effect. The synthesized derivatives were screened for anticonvulsant activity.

Method: The benzaldehyde derivative and acetophenone derivative were measured accurately and placed in a mortar in the presence of alkali the mixture was turned yellow and pasty after a few times of grinding. Product was mixed properly with the water using the spatula solid product was dislodged from the mortar's wall and filtered and all the synthesized compounds were purified by recrystallization. Melting points were determined by using open capillary method and finally screened derivatives for anti-convulsion activity.

Results: The pharmacological screening of the synthesized compounds showed anti convulsant activity ranging 65.23 to 76.3% inhibition of epileptic seizures in mice, where as the standard drug Phenytoin showed 83.95% inhibition of epileptic seizures in mice.

Conclusion: The compound C2, C3 and C5 from each group was found to be nearly potent to Phenytoin which is used as standard drug. Compounds C6 shown less % of inhibition of epileptic seizures in mice than Phenytoin (standard drug).

Keywords: Aromatic aldehyde, Anti-convulsant, Chalcone, Hydroxy acetophenone.

International Journal of Drug Delivery Technology (2022); DOI: 10.25258/ijddt.12.2.7

How to cite this article: Jain K, Jain NK. Synthesis, Characterization and Anti-Convulsant Activity of Some Novel Substituted Chalcone Derivatives. International Journal of Drug Delivery Technology. 2022;12(2):502-509.

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

Around the world, roughly 40-50 million individuals experience the ill effects of epilepsy, an indication of extreme brief neuronal release, described by discrete intermittent episodes, in which there is an unsettling influence of development, sensation, conduct insight as well as cognizance. Every year around 250000 new cases are added to this fig., Epilepsy is a cerebrum issue in which an individual has rehashed seizures (spasms) over the long haul. Epilepsy happens when super durable changes in mind tissue make the cerebrum be excessively volatile or unsteady. The cerebrum conveys unusual signs. This outcome in rehashed, unusual seizures.2 Symptoms fluctuate from one individual to another. Certain individuals might have straightforward gazing spells, while others have rough shaking and loss of readiness.[1-3]

Trimethodione, found in 1944, was the main AED explicit for the treatment of nonattendance seizures. The anticonvulsants are an assorted gathering of drugs utilized when it comes to the management of status epilepticus ,types of drugs are also increasingly used to treat of bi-polar disorder, as most of them appear to act as mood stabilisers, as well as in the therapy of cancer. An anticonvulsant's goal is to stop the rapid and excessive termination of neuron that cause a seizure.[4] Effective anticonvulsant would stop the seizure from spreading inside the brain and provide protection vs any oxidative stress effects that might cause brain damage. A few investigations have referred to that anticonvulsants themselves are connected to bring down IQ in youngsters.[3,5]

The therapeutic goal is maximizing seizure control while minimizing adverse drug effects, thus improving the life.Older agents as exemplified by phenytoin, carbamazepine, valproate, the benzodiazepines, ethosuximide, Phenobarbital, primidone, and trimethadione. Newer agents consisting of vigabatrin, gabapentin, felbamate, amotrigine, carbazepine, zonisamide, tiagabine, topiramate, and levetiracetam.[4,6]

Chalcones and their subordinates show antiulcerative, against angiogenic, pain relieving, calming, anticancer and cell reinforcement because of essence of extremely receptive vinylenic bunch yet frequently In culture, they are toxic. Cell reinforcing characteristics are determined by the presence of hydroxide and propyl groups. Certain chalcones subordinates have antibacterial, antiviral, and fungicidal characteristics. A

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few of the chalcones' derivatives have anti - cancer properties.[7] In addition, chalcones subordinates are additionally viewed as another class of successful enemy of TB applicants attributable to their potential enemy of TB exercises. chalcones, similar to isoniazid (INH), act by hindrance of the development of microorganisms by obstructing lipid biosynthesis or potentially extra instruments, which are perhaps the most appealing techniques for creating viable enemy of TB agent.[7,8] Chalcone is an aromatic ketone and an enone that forms the central core for a variety of important biological compounds, which are known collectively as chalcones or chalconoids. Alternative names for chalcone include benzylideneacetophenone, phenyl styryl ketone, benzalacetophenone, *β*-phenylacrylophenone, *γ*-oxo-*α*,*γ*-diphenyl-*α*-propylene, and *α*-phenyl-*β*-benzoylethylene.

MATERIALS AND METHODS

All synthetic substances were given from our Institute. All solvents were redistilled before use. Reaactions were regularly checked by TLC and spots were pictured by openness to iodine fume or UV light. Every one of the blended mixtures were decontaminated by recrystallization. Melting not entirely set in stone by utilizing open hairlike method. Fourier Transform Infra-Red spectra (FTIR) were recorded on Shimadzu FTIR-8400S spectrophotometer utilizing potassium bromide pellets and sodium chloride cell. Atomic Magnetic Resonance spectra (1H-NMR) were recorded on JEOL-300 MHz spectrophotometer in $CDCl_3$ involving TMS as an inside norm. Substance shifts (δ) are communicated in parts per million (ppm). Mass spectra were recorded on HEWLETT 180017, PACKARD GCD System mass spectrophotometer utilizing electron ionization indicator and anticonvulsant movement checked by electroconvulsometer.

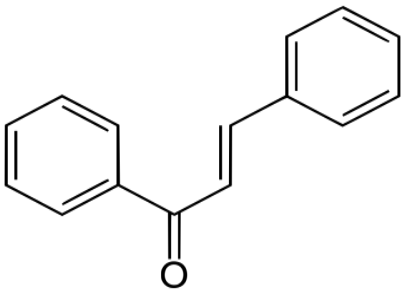


Figure 1: Structure of chalcone

METHODS

Synthesis of 2,4-dihydroxyacetophenone:

Dried resorcinol (approx.5.5 gm) were mixed at 140°C with constant agitation after crystalline powder zinc chloride (8.25) were soaked with ethyl acetate (18ml) via steaming over a hot soil. This mixture was then heated till it started boiling, then maintained at 150°C for twenty minutes. Diluted Hydrochloric then mixed and cooled down to 5°C before filtering and washing using dil. HCL (1:3) crystallised from heated water containing a small amount of HCl.[9]

General Procedure for Synthesis of Chalcone Derivatives

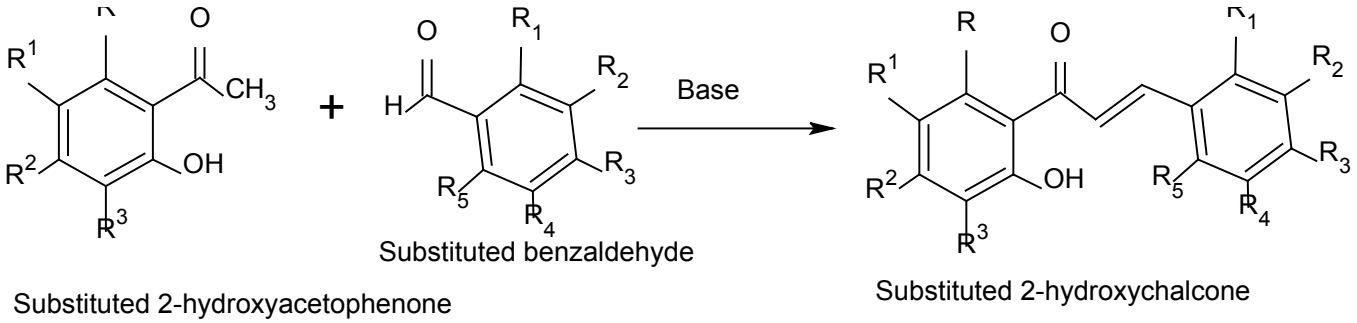
2.5 mmol acetaldehyde minor with 2.5 mmol acetophenone minor are calculated and placed in a mixer. 3 NaOH granules were added to the mix (7.5 mmole). The mixture were processed in about five minute to ten minute . After a number of smashing sessions, this mixture turned yellowish and pallid. Crushing was carried out until the mixture transformed it in to a solid lump, which then was fined. ten mL H2O was poured into the mixer with no minutes to waste before the crushing process began. Using the scraper, the item was properly combined with the water before being removed from mixer's divider and separated.[10]

Table 1: Physicochemical characterization of starting materials

Sr. No.	Compound	Mol. Formula	Mol. Weight	M.P./ B.P.
1	2-Hydroxyacetophenone	C8 H8 O2	136.14	213 °C
2	2,4-Dihydroxyacetophenone	C8H8O3	152.14	143°C
3	Salicylaldehyde	C_7H_6O2	122.12	-
4	4-Methylbenzaldehyde	C8H8O2	120.15	-
5	4-Isopropylbenzaldehyde	$C_{10}H_{12}O$	148.20	235 °C

Table 2: Substitution with Aromatic Aldehyde

Compound Code	*Hydroxy acetophenone*	*Aromatic aldehyde*
C1	2-hydroxyacetophenone	Salicylaldehyde
C2	2-hydroxyacetophenone	4-Isopropylbenzaldehyde
C3	2-hydroxyacetophenone	4-Methylbenzaldehyde
C4	2,4-dihydroxyacetophenone	Salicylaldehyde
C5	2-hydroxyacetophenone	4-Isopropylbenzaldehyde
C6	2-hydroxyacetophenone	4-Methylbenzaldehyde



SYNTHETIC SCHEME

ANTI-CONVULSANT ACTIVITY

Before being administered to people, all anti - epileptic medications (AEDs) are rigorously tested in animals, particularly rats. The physician will benefit from seeing drugs were sorted separately, because the screening system seems critical in forecasting the type convulsions in which medication will be successful, as well as determining the component medication's anti-seizure effectiveness. Merritt and Putnam, using the electroshock-activated seizure model, were the first to identify the emotional revelation of phenytoin's anti-seizure characteristics in 1938.

Animals

Among animals utilised in testing, white rats weighing 18-30 grams have been used. All animals are maintained in settlement bounds (six mouse apiece), fed a regular pellets meal containing freshwater, allowed to acclimate for two days prior to test meeting. All foodstuff was taken away the day before the test, but unfettered access to water was allowed. The recommended moral guidelines for the consideration of research facility creatures are applied to every experiments.

Laboratory Conditions

Among animals utilised in testing, white rats weighing 18-30 grams have been used. All animals are maintained in settlement bounds (six mouse apiece), fed a regular pellets meal containing freshwater, allowed to acclimate for two days prior to test meeting. All foodstuff was taken away the day before the test, but unfettered access to water was allowed. The recommended moral guidelines for the consideration of research facility creatures are applied to every experiments.[11] The anticonvulsant activity was done by maximal electrical shock prompted spasm strategy in pale skinned person mice.

Creatures in utilization: white rat
Creatures utilized a bunch: six rats
Portion test compound: half millilitre or hundred grams
Portion standard medication: half millilitre or hundred grams (Phenytoin)
Course organization: Intraperitoneal (one percentage to eighty percentage)

Requirements

Equipment: Electroconvulsiometer
Chemicals: Tween-80
Typical medication: Water mixture of propranolol (twenty five grams) was made to utilize tween-80 mixture like a colloidal suspension.
Compound suspensions was produced and delivered intraperitoneally in the same way as normal drugs.
Apparatus: Syringes (1 mL, 2 mL), sample tubes.

Experimental Design and Procedure

Creatures are weighed as well as counted. Rats are divided into seven groups, each with six creatures. Bunch One being provided with solution (2 percent v/v Tween 80), bunch two with conventional medicine phenytoin (25 mg/kg, i.p.), and bunches three to seven with newly designed Chalcone subordinates (25 mg/kg, I. p.). The animals were electro shocked for 0.2 seconds by hearing working electrode of eighty milliAmps by electrical convulsiometer 1 hr after infusion, duration of textensible reaction were observed, as well as the movement is communicated as far as percent security.[14,15] Every one of the outcomes are communicated in percentage hindrance determined utilizing recipe,Percent (%) protection = VC – VT/VC X 100,VT- Mean time in test group, VC-Mean time in control group.[16]

RESULTS AND DISCUSSIONS

Physical Characteristics

All the synthesized compounds were light creamish to brown coloured crystalline solids. Most of the compounds are freely soluble in chloroform and other solvents like methanol, ethanol. The melting point of the compounds was in the range of 152ºC to 251ºC.

Physical and Spectral Characteristics of Substituted Chalcone Derivatives

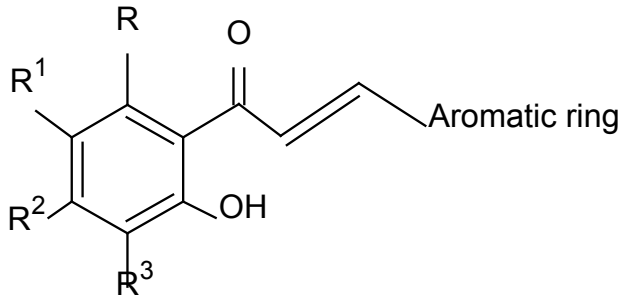


Table 3: General structure of chalcone derivatives

Compound code	*Compound Name*	*Substituents X*	*R*	*R¹*	*R²*	*R³*
C1	1,3 (2-hydroxyphenyl)-2 –propen- 1-one	2 – Hydroxyphenyl	H	H	H	H
C2	1-(2-hydroxyphenyl)-3-(4- isopropylphenyl)- 2 –propen-1- one	4 – Isopropylphenyl	H	H	H	H
C3	1-(2-hydroxyphenyl)-3-*p*- tolylprop-2en-1-one	4 – Methylphenyl	H	H	H	H
C4	1-(2,4-dihydroxyphenyl)-3-(2- hydroxyphenyl)prop-2-en-1-one	2 – Hydroxyphenyl	H	OH	H	H
C5	1-(2,4-dihydroxyphenyl)-3-(4- isopropylphenyl)prop-2-en-1-one	4 - Isopropaylphenyl	H	OH	H	H
C6	1-(2,4-dihydroxyphenyl)-3-*p*- tolylprop-2-en-1-one	4 – Methylphenyl	H	OH	H	H

Table 4: Physical characteristics of substituted chalcone derivatives

Property	*Results*					
Comp. Code	*C1*	*C2*	*C3*	*C4*	*C5*	*C6*
Meltingpoint	89^0C	92^0C	160^0C	190^0C	150^0C	150^0C
Yield	80.4 %	91%	94.20%	90.03%	88.8%	88.8%
Rf value	0.69	0.8	0.73	0.59	0.69	0.69
Molecular formula	$C_{15}H_{12}O_3$	$C_{18}H_{18}O_2$	$C_{16}H_{14}O_2$	$C_{15}H_{12}O_4$	$C_{18}H_{18}O_3$	$C_{16}H_{14}O_3$
Molecular weight	240	266	238	256	282	254

SPECTRAL ANALYSIS

FTIR Spectral characteristic

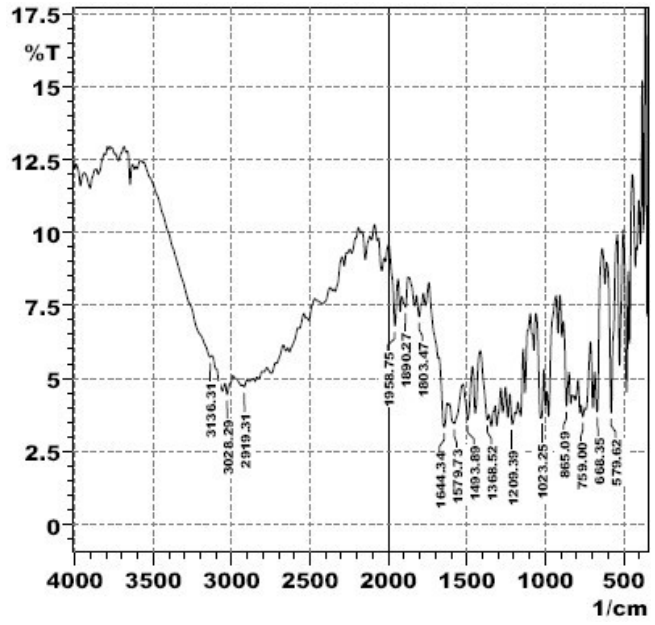


Figure 2: IR Spectra of Compound C1

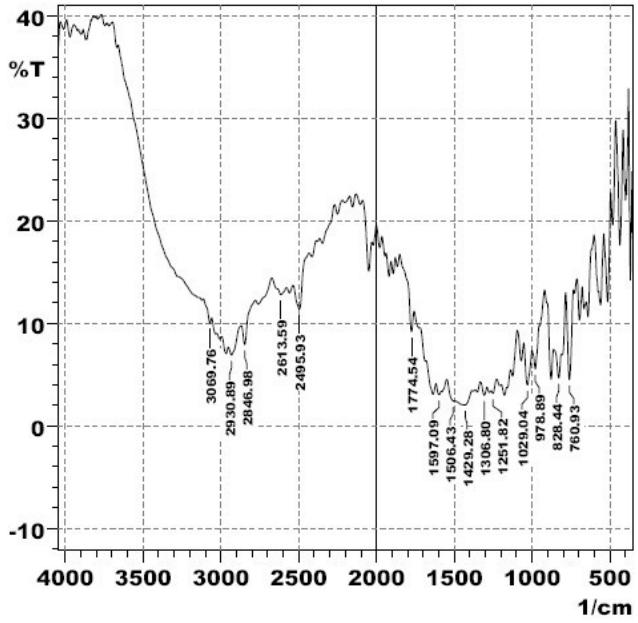


Figure 3: IR Spectra of Compound C2

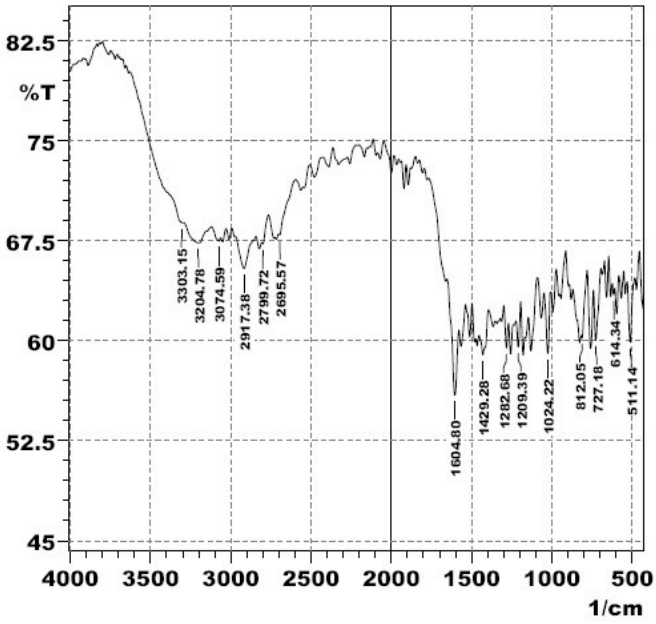


Figure 4: IR Spectra of Compound C3

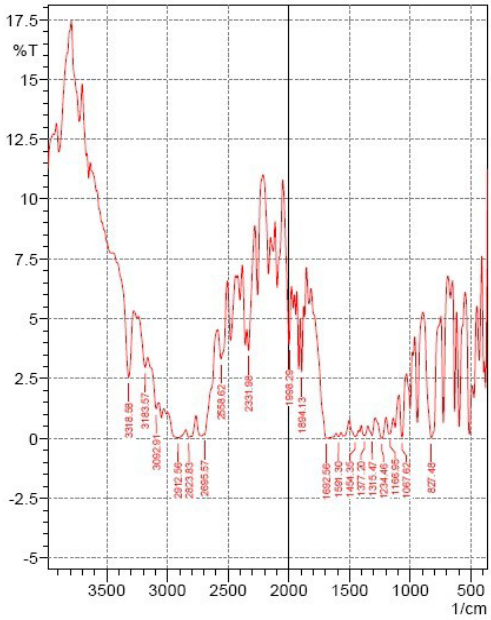


Figure 5: IR Spectra of Compound C4

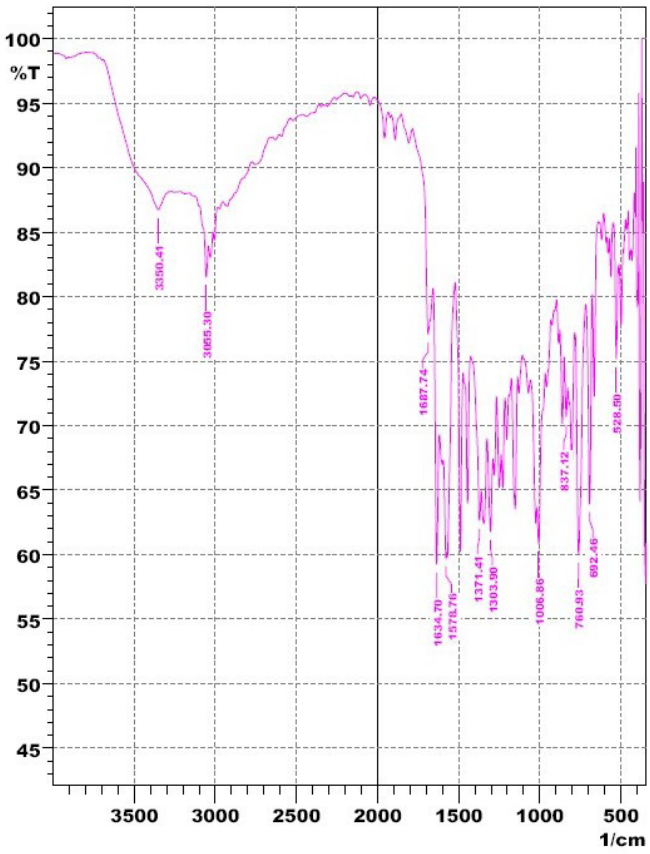


Figure 6: IR Spectra of Compound C5

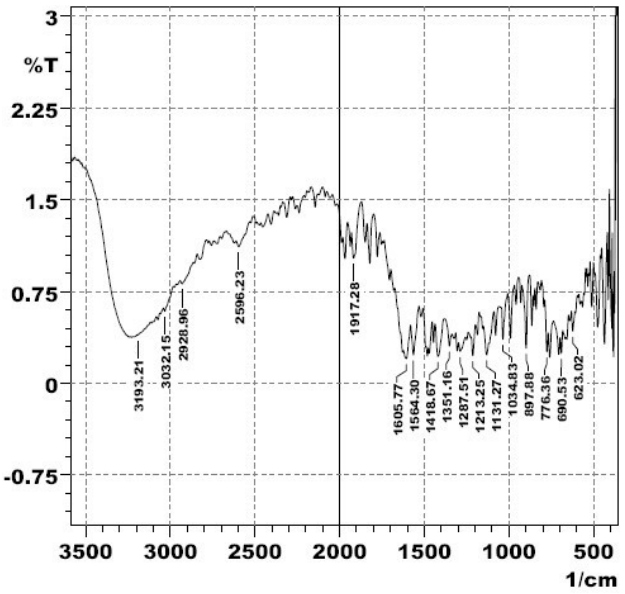


Figure 7: IR Spectra of Compound C6

Table 5: I R spectral data

	Group frequency in Wave number (cm^{-1})					
Functional group assigned	*C1*	*C2*	*C3*	*C4*	*C5*	*C6*
C=O	1645	1774	1604	1662	1634	1634
O-H	3030	3069	3074	3092	3065	3065
C=C	1300-1400	1300-1400	1300-1400	1300-1400	1300-1400	1300-1400
C-H (aromatic)	600-900	600-900	600-900	600-900	600-900	600-900
C-N	-	-	3301	-	-	-

NMR Spectral Characteristic

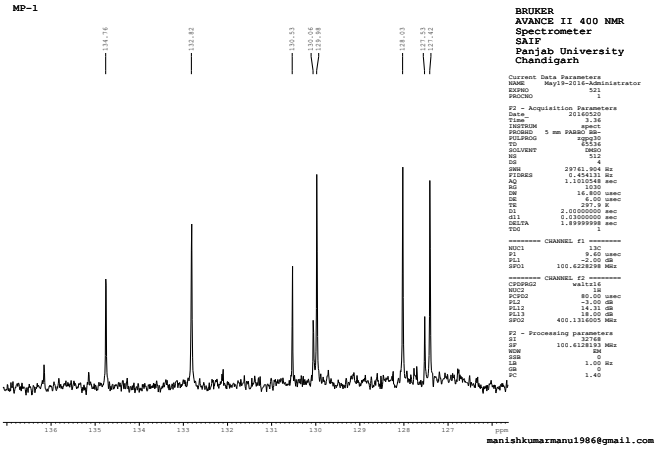


Figure 8: ^{13}C-NMR OF C1

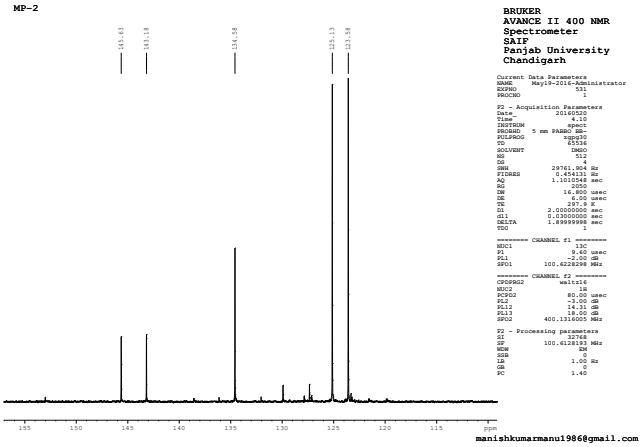


Figure 9:^{13}C-NMR OF C2

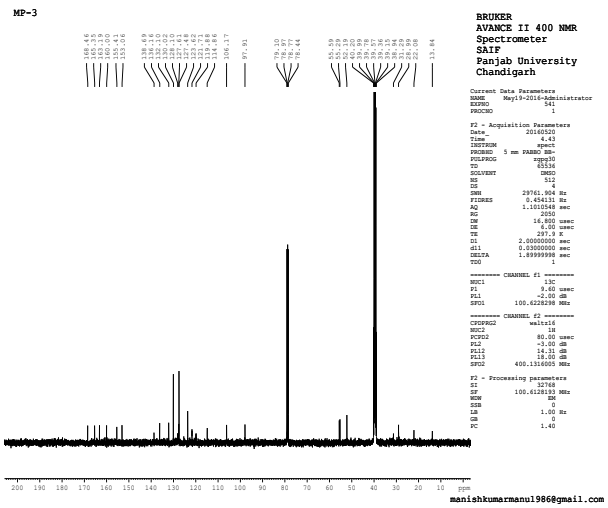


Figure 10: ^{13}C-NMR OF C3

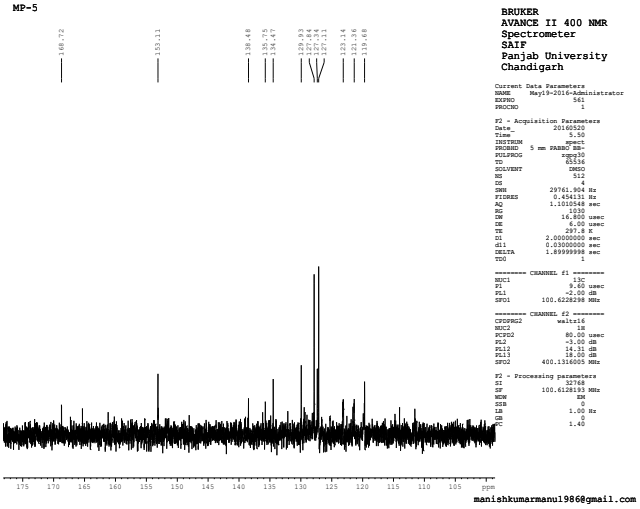


Figure 12: ^{13}C-NMR OF C5

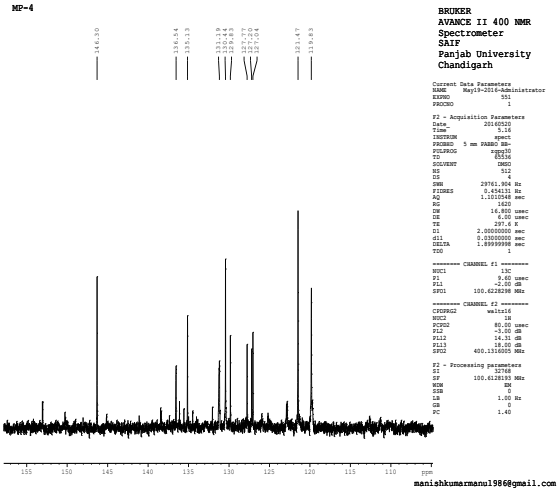


Figure 11: ^{13}C-NMR OF C4

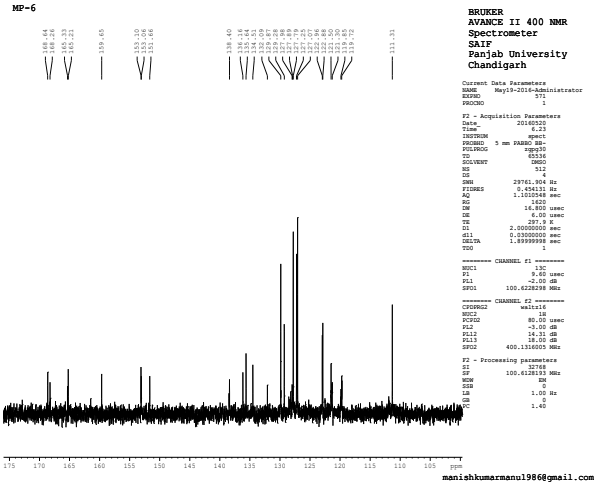


Figure 13: ^{13}C-NMR OF C6

Mass Spectral Characteristic

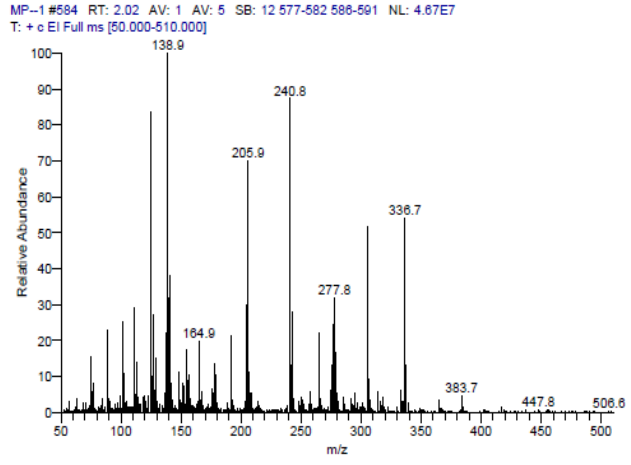


Figure 14: Mass spectra of C1

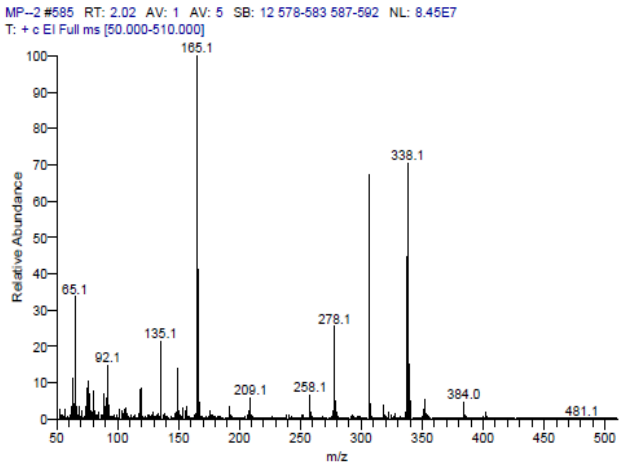


Figure 15: Mass spectra of C2

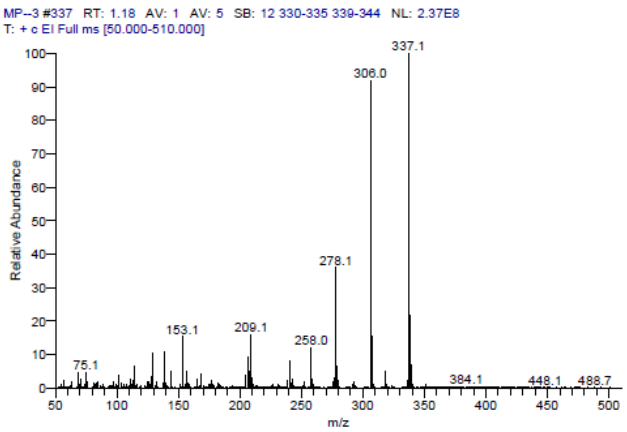


Figure 16: Mass spectra of C3

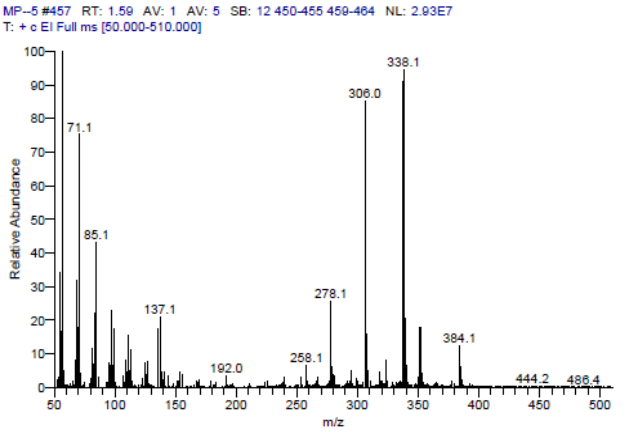


Figure 18: Mass spectra of C5

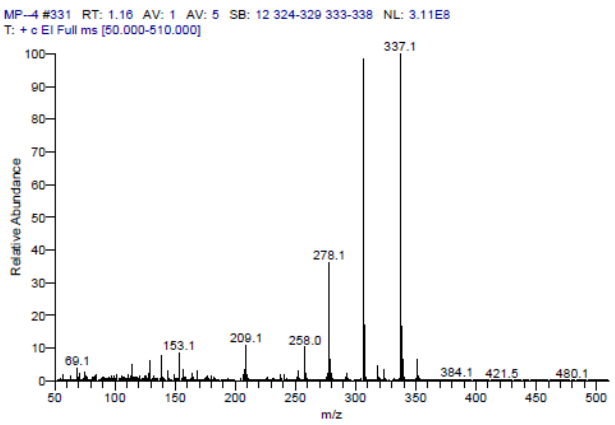


Figure 17: Mass spectra of C4

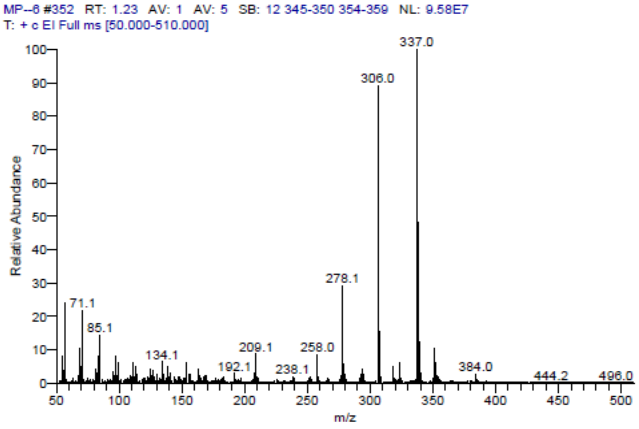


Figure 19: Mass spectra of C6

SCREENING OF ANTI-CONVULSANT ACTIVITY

Table 6: Screening of anti-convulsant activity in albino mice

	Duration (Mean ± SEM, Sec)					
Compound Code	*Flexion*	*Extension*	*Clonus*	*Stupor*	*Recovery*	*% Protection*
Control	12.75±0.3	15.85±0.23	27.50±0.19	96.0±0.09	Recovered	
Standard (Phenytoin)	9.80±0.08	11.83±0.19	3.07±0.05	1.91±0.03	Recovered	83.95 %
C1	9.5±0.12	11.5±0.13	5.5±0.07	20.5±0.02	Recovered	76.3%
C2	10.5±0.08	12.0±0.14	7.0±0.10	15.5±0.06	Recovered	75.2%
C3						
C4	9.9±0.10	13.5±0.20	7.1±0.05	24.8±0.05	Recovered	71.3%
C5	13.0±0.09	14.0±0.12	8.0±0.14	31.7±0.06	Recovered	73.2%
C6	10.1±0.11	14.4±0.25	16.5±0.15	22.5±0.11	Recovered	65.23%

CONCLUSION

The pharmacological screening of the incorporated mixtures showed against convulsant action going 65.23 % to 76.3 % restraint of epileptic seizures in mice, whereas the standard medication Phenytoin showed 83.95 % hindrance of epileptic seizures in mice.

The compound C2, C3 and C5 from each gathering was viewed as almost intense to Phenytoin which is utilized as standard medication. Intensifies C6 shown less % of restraint of epileptic seizures in mice than Phenytoin (standard medication). Structure looks like in above compound have important to standard medications were structure having substitute chalcone ring with hydroxyl bunch give better enemy of convulsant movement.

ACKNOWLEDGEMENTS

This work was supported by Faculty of Pharmacy, Oriental University Indore.

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