Online Available at www.thepharmaresearch.info

THE PHARMA RESEARCH, A JOURNAL

The Pharma Research (T. Ph. Res.), (2010), 3; 257-262.
Published on- 15 June 2010

ISSN 0975-8216

Original Article

SYNTHESIS AND ANTI-CONVULSANT ACTIVITIES OF PHENOXYCHALCONES

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ABSTRACT

Some new phenoxy chalcones were prepared by condensing different aromatic aldehydes with phenoxy acetophenones. All the synthesized compounds were confirmed by ^{1}H NMR, IR and MASS spectral studies and were screened for their anticonvulsant activity. It was found that methoxy substitution in the phenoxychalcones showed significant anticonvulsant activity.

Keywords: Phenoxy Acetophenones, Phenoxy Chalcones, Anti-Convulsant, Maximal Electroshock Seizures Method, Rotarod Method.

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1.0 INTRODUCTION

Epilepsy is a disorder characterized by recurrent seizures of cerebral origin, presenting with episodes of sensory, motor or autonomic phenomenon with or without loss of consciousness. Epilepsy is the second most common chronic neurological condition seen by neurologists. It is one of the most common afflictions of the man with a prevalence of approximate 1 %. It is estimated that the 50 million-person worldwide may have this disorder [1].

Chalcone (and related compounds "chalconoids") is an aromatic ketone that forms the central core for a variety of important biological compounds, which are known collectively as chalcones [2]. They show antibacterial, antifungal, anticonvulsant, antitumor and anti-inflammatory properties [3]. Some chalcones demonstrated the ability to block voltage-dependent potassium channels. They are also intermediates in the biosynthesis of flavonoids, which are substances widespread in plants and with an array of biological activities. Chalcones, or 1,3-diaryl-2-propen-1-ones, belong to the flavonoid family. Chemically they consist of open-chain flavonoids in which the two aromatic rings are joined by a three-carbon α, β-unsaturated carbonyl system. A vast number of naturally occurring chalcones are polyhydroxylated in the aryl rings. The radical quenching properties of the phenolic groups present in many chalcones have raised interest in using the compounds or chalcone rich plant extracts as drugs or food preservatives [4]. Chalcone derivatives have also been found to inhibit several important enzymes in cellular systems, including xanthine oxidase, aldose reductase, epoxide hydrolase, protein tyrosine kinase and quinone reductase [5].

In the view of the above-mentioned facts, we intend to synthesize some substituted 4′-phenoxy chalcones and screen them for anticonvulsant activity.

2.0 Experimental Method- *Step-1*

Synthesis of phenoxy acetophenone (I)

To a cooled mixture of biphenyl ether and aluminium chloride in carbon disulphide, acetic anhydride was added and refluxed for two hours. After two hours, the reaction mixture was cooled to room temperature and poured into a mixture of crushed ice and concentrated hydrochloric acid. It was then extracted with diethyl ether. After removing the ether, the residue was recrystallized in ethanol [6].

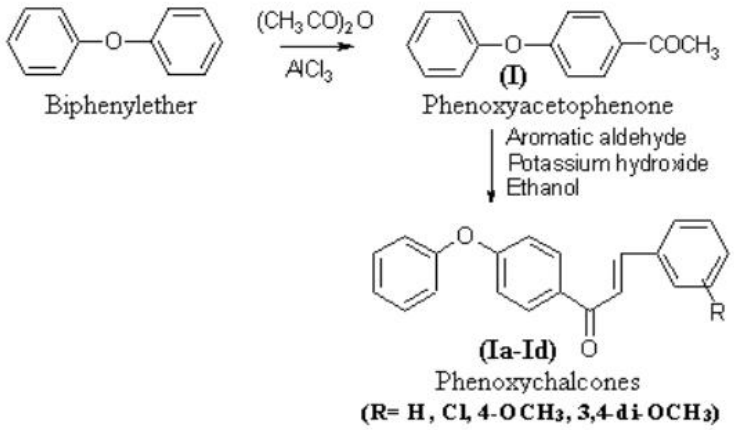
Step – 2

General synthesis of substituted 4′-phenoxy chalcones (Ia-Id)

To a stirred solution of potassium hydroxide in water and ethanol mixture, 4′-phenoxy acetophenone and aromatic aldehyde were added.

The reaction mixture was stirred vigorously for 3 hours and poured into crushed ice, a solid mass that separates out. It was filtered washed with cold water and then it was recrystallized from methanol [7].

Scheme:



Physical characteristics data of the synthesized compounds are mentioned in Table 1.

Table no. -1. Physical characteristics of the compound

S. no	Compound code	R	R_f value	M.pt (° C)	Yield (%)
1	I	--	0.92	48-50	78.72
2	Ia	H	0.83	80-82	47.46
3	Ib	Cl	0.80	76-78	64.80
4	Ic	4-methoxy	0.79	60-64	74.36
5	Id	3,4-dimethoxy	0.71	106-108	56.47

Compound I:

1-(4-phenoxyphenyl) ethanone:

To a cooled mixture of biphenyl ether and aluminium chloride in carbon disulphide, acetic anhydride was added and refluxed for two hours. After two hours, the reaction mixture was cooled to room temperature and poured into a mixture of crushed ice and concentrated hydrochloric acid. It was then extracted with diethyl ether. After removing the ether, the residue was recrystallized

in ethanol. ^{1}HNMR: δ 2.56(s, 3H, -$COCH_3$), 6.98 ~ 7.39 (m, 9H, aromatic protons), IR, KBr: 1680(C=O), 1230 (C-O-C), 1580, 740, 680; Mass: m/z 212 (M^+), 197, 141, 115, 77.

Compound Ia:

(*E*)-1-(4-phenoxyphenyl)-3-phenylprop-2-en-1-one:

To a stirred solution of potassium hydroxide in water and ethanol mixture, 4′-phenoxy acetophenone and benzaldehyde were added. The reaction mixture was stirred vigorously for 3 hours and poured into crushed ice; a solid mass was separates out. It was filtered washed with cold water and then it was recrystallized from methanol. ^{1}HNMR: δ 8.04 (d, 2H, phenoxy substituted phenyl protons), 7.82 (d, 1H, alkenyl β proton), 7.52 (d, 1H, alkenyl α proton), 7.2 ~ 7.04 (m, 12H, aromatic protons), IR, KBr: 1677 (C=O), 1470 (C-C), 1644 (C=C); Mass: m/z 300 (M^+), 272, 207, 197, 154, 103, 77.

Compound Ib:

(*E*)-3-(2-chlorophenyl)-1-(4-phenoxyphenyl) prop-2-en-1-one:

To a stirred solution of potassium hydroxide in water and ethanol mixture, 4′-phenoxy acetophenone and 2-chlorobenzaldehyde were added. The reaction mixture was stirred vigorously for 3 hours and poured into crushed ice; a solid mass was separates out. It was filtered washed with cold water and then it was recrystallized from methanol. ^{1}HNMR: δ 8.21 (d, 2H, phenoxy substituted phenyl protons), 7.90(d, 1H, alkenyl β proton), 7.71(d, 1H, alkenyl α proton), 7.4 ~ 7.61 (m, 11H, aromatic protons), IR, KBr: 1684 (C=O), 1587 (C-C), 1648 (C=C), 745 (C-Cl); Mass: m/z 336 (M^+), 231, 195, 167, 152, 77.

Compound Ic:

(*E*)-3-(4-methoxyphenyl)-1-(4-phenoxyphenyl) prop-2-en-1-one:

To a stirred solution of potassium hydroxide in water and ethanol mixture, 4′-phenoxy acetophenone and 4-methoxybenzaldehyde were added. The reaction mixture was stirred vigorously for 3 hours and poured into crushed ice; a solid mass was separates out. It was filtered washed with cold water and then it was recrystallized from methanol. ^{1}HNMR: δ 7.77 (d, 1H, alkenyl β proton), 7.55(d, 2H, phenoxy substituted phenyl protons), 7.39 ~ 7.02 (m, 10H, aromatic protons and α proton), 6.88(d, 2H, phenyl protons ortho to methoxy group), 3.78 (s, 3H, methoxy), IR, KBr: 1720 (C=O), 1486 (C-C), 1647 (C=C), 2829 (O-CH_3); Mass: m/z 330 (M^+), 237, 197, 170, 154, 77.

Compound Id:

(*E*)-3-(3, 4-dimethoxyphenyl)-1-(4-phenoxy phenyl) prop-2-en-1-one:

To a stirred solution of potassium hydroxide in water and ethanol mixture,4′-phenoxy acetophenone and 3,4-dimethoxybenzaldehyde

were added. The reaction mixture was stirred vigorously for 3 hours and poured into crushed ice; a solid mass was separates out. It was filtered washed with cold water and then it was recrystallized from methanol. ^{1}HNMR: δ 8.03 ~ 7.09 (m, 13H, aromatic protons and alkenyl protons), 6.88 (d, 1H, phenyl proton ortho to methoxy group), 3.78 (s, 3H, methoxy), IR, KBr: 1726 (C=O), 1582 (C-C), 1642 (C=C), 2826 (O-CH_3); Mass: m/z 360 (M^+), 346, 330, 267, 212, 197, 157, 77.

3.0 Biological Screening-

3.1 Anticonvulsant activity-

Anticonvulsant activity is evaluated by Maximal Electroshock Method (MES). Each compound was administered as an i.p. injection at dose level of 30 mg/kg and the anticonvulsant activity was assessed after 0.5 hr and 3 hrs intervals of administration. Maximal electroshock seizures were elicited in mice by delivering a 60 Hz, 50 mA electrical stimuli for 0.2 sec via ear clip electrodes. The maximal seizure typically consists of a short period of tonic extension of the hind limbs and a final clonic episode. Blockade of the hind limbs tonic extensor component due to the drug treatment is taken as the end point [8].

3.2 Neurotoxicity Study-

The mice were trained to stay on an accelerating rotarod that rotates at 10 revolutions /min and is 3.2 cm in diameter. Trained mice were given i.p. injection of the test compounds in dose of 30 mg/kg. Unimpaired mice can easily remain on a rod rotating at this speed. Neurological deficit e.g. ataxia, sedation, hyperexcitability is indicated by the inability of the mice to maintain equilibrium on the rod for at least 1 min in each of three concurrent trails [8].

Results of anticonvulsant activity and neurotoxicity studies are mentioned in Table no.2.

Table no. - 2. Anticonvulsant and Neurotoxicity activity of synthesized compounds.

S. No.	Comp. code	Dose	Mean ± S.E	% Protection	Neurotoxicity
1	Standard (Phenytoin)	30	0.94 ± 0.3267*	100	X
2	control	--	9.82 ± 0.3572	33.33	--
3	Ia	30	7.59±0.3320**	50.00	--
4	Ib	30	5.80 ±0.5585*	83.33	X
5	Ic	30	1.54 ± 0.558*	83.33	X
6	Id	30	3.87 ±0.6874*		X

n- Number of animals = 6, X – does not show neurotoxicity,
-- neurotoxicity - not checked, Dose- mg/kg body weight,
Route of administration - I.P., * p <0.001, **p < 0.01as compared to control.

4.0 Result and Discussion-

All the synthesized compounds were confirmed by the ^{1}HNMR, IR and MASS spectral characterization. Purity of the compounds was checked by the TLC, melting point was uncorrected and was taken by open capillary method. Results of the biological activity are mentioned in Table- 2, which shows the activity of the compound Ic and Id are very significant when compared to the standard drug phenytoin. Compoubnd Ia and Ib are less significant when compared to the standard drug. Synthesized compounds Ib, Ic and Id did not showed neurotoxicity.

Substitution of 4-methoxy (Ic) and 3, 4-dimethoxy (Id) group in the substituted ring showed significant anticonvulsant activity without neurotoxicity while hydrogen and chloro substitution does not showed the significant anticonvulsant activity.

5.0 Conclusion

On the basis of above mentioned fact it is concluded that the methoxy substitution in the phenoxychalcones showed significant anticonvulsant activity.

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