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Research Article

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Synthesis and anticonvulsant activity of some chalcone derivatives

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ABSTRACT

A new series of chalconesemicarbazones was synthesized and evaluated for anticonvulsant activity by MES Method. Most of the compounds were found to be more or comparable potent than the reference standard drug in the acetic acid-induced writhing test.

Keywords: chalcones**,** Claisen Schmidt reaction, semicarbazone, anticonvulsant activity.

INTRODUCTION

The chalcones are α-β unsaturated ketones containing the reactive keto ethylenic group – CO – CH = CH –. Presence of α-β- unsaturated carbonyl system in chalcone makes it biologically active. Some substituted chalcones and their derivatives have been reported to possess some interesting biological properties such as antibacterial, insecticidal, anaesthetic, analgesic, ulcerogenic etc[1-4].

Chalcones are well known intermediates for synthesizing various heterocyclic compounds. The compounds with the backbone of chalcones have been reported to possess various biological activities such as anti-inflammatory, antiplatelet, antiulcerative, antimalarial, anticancer, antiviral, antileishmanial, antioxidant, antitubercular, antihyperglycemic, immunomodulatory, inhibition of chemical mediators release, inhibition of leukotriene B4, inhibition of tyrosinase and inhibition of aldose reductase activities[5-21].

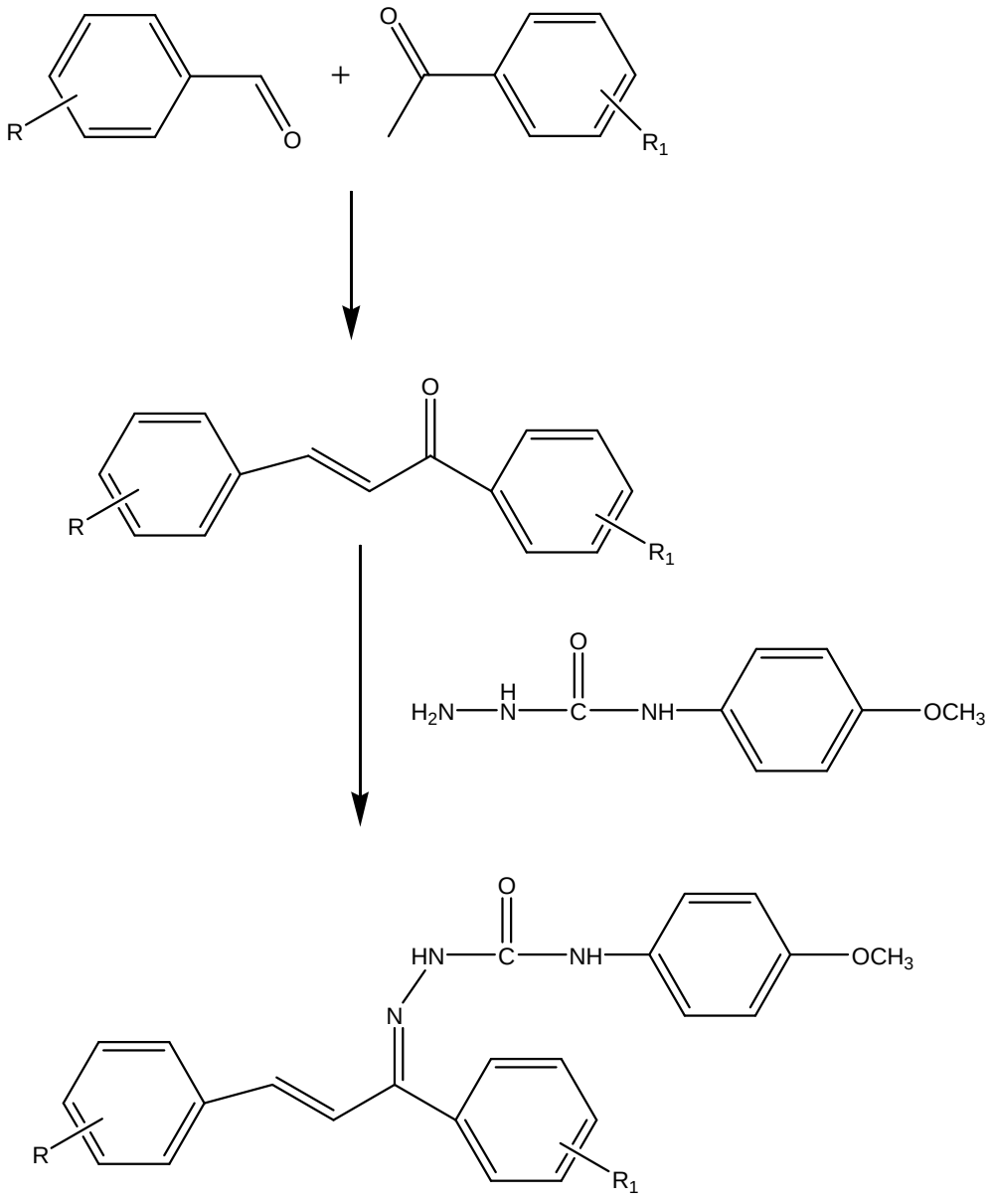
Although each new drug introduced has its unique advantage, disadvantages are still there. Thus, none has proved to be the ultimate drug for epilepsies and need for better, novel AEDs is still there. Application of rational drug design models has led to certain new leads, which are undergoing various preclinical and clinical trials10. On the basis of knowledge of the characteristics of different receptor sites, and by means of identification of the minimal requirements associated with the pharmacophoric pattern for a manifested activity at the targeted sites, several of them would undoubtedly become meaningful addition to the neurobiologist's pharmacological armamentarium. The discovery of this compound was also based on the rational considerations of pathophysiological mechanisms of epileptic syndrome, in conjugation with detailed understanding of central excitability mechanisms and logical principles of drug design. Unlike other classes these are all structurally and mechanically unique and not possible to discuss them as a single class of agents. Hence, the endeavor of the century is to develop antiepileptic drugs with 100% efficacy, safety and tolerability.

Recently benzylidene hyrazides have been explored as newer chemical entities with potential anticonvulsant effects. benzylidene hyrazides is their structural dissimilarity to the existing antiepileptic drugs. So an attempt is made to synthesize such novel compounds with better efficacy and lesser side effects.

EXPERIMENTAL SECTION

Melting points of the synthesized compounds were determined in open capillary tubes and are uncorrected. IR absorption spectra were recorded on Bruker Tensor-27/Jasco FT/IR-470 PLUS, KBr diffuse reflectance, ^{1}H-NMR spectra were recorded on the Bruker DPX-400 instrument at 400 and 100 MHz, respectively. The ^{1}H chemical shifts are reported as parts per million (ppm) downfield from TMS (Me_4Si). ^{1}H-NMR, IR and Mass spectra were consistent with the assigned structures. Purity of the compounds was checked by thin layer chromatography (TLC). The elemental analysis (CHN analysis) was done on a CHN rapid analyzer. All the compounds gave satisfactory analysis within ±0.4% of the theoretical values. The LC mass spectra of the compounds were recorded on Shimadzu 8201PC spectrometer.

Scheme 1



General method for the synthesis of chalcone (1a-1f, 2a-2e)

A solution of appropriate substituted benzaldehyde (0.1 mol) in methanol was mixed with appropriate substituted acetophenone (0.1 mol) and an aqueous solution of potassium hydroxide (60%) was added to it till, further no turbidity occurs. The reaction mixture was stirred and kept overnight at room temperature and then it was poured into crushed ice and acidified with dilute hydrochloric acid. The crude product so obtained was filtered and recrystallized from methanol and dried at room temperature. The completion of reaction was monitored by running TLC.

Table 1

Compound No	IR Wave No.(cm^{-1})	^{1}H NMR Chemical Shift (δ, ppm)	Mass (M/Z)	Elemental analysis	
				Calculated	Found
Y1aM	3370(-NH), 1594(C=O), 1443(CH=CH), 1345(Ar. C=C), 2922, 2877(CH Str.), 1282(C-N), 1220(C-O)	10.51 (s, 1H, NHCO), 8.88 (s, 1H, NHCO), 7.19-7.68 (m, 14H, Ar-H), 7.00 (d, 1H, CH), 6.97 (d, 1H, CH), 3.79 (s, 3H, OCH_3)	371.2 (M), 372.2 (M+1)	C, 74.37 H, 5.70 N, 11.31	C, 74.07 H, 5.96 N, 11.02
Y1bM	3310(-NH), 3216 (OH Str.), 1655(C=O), 1548(CH=CH), 1485(Ar. C=C), 2927 (CH Str.), 1357(C-N), 1247(C-O)	10.15 (s, 1H, NHCO), 9.38 (s, 1H, NHCO), 8.69 (s, 1H, OH), 6.79-7.50 (m, 11H, Ar-H), 6.67 (d, 1H, CH), 6.59 (d, 1H, CH), 6.71-6.81 (m, 2H, Ar-H) , 3.69 (s, 3H, OCH_3)	387.2 (M), 388.2 (M+1)	C, 71.30 H, 5.46 N, 10.85	C, 70.96 H, 5.32 N, 10.61
Y1cM	3392(-NH), 1670(C=O), 1527(CH=CH), 1480(Ar. C=C), 2932 (CH Str.), 1352(C-N), 1227(C-O)	9.91 (s, 1H, NHCO), 8.95 (s, 1H, NHCO), 6.99-7.60 (m, 13H, Ar-H), 6.84 (d, 1H, CH), 6.55 (d, 1H, CH), 3.80 (s, 3H, OCH3), 2.88 (s, 6H, $N(CH_3)_2$)	414.2 (M), 415.2 (M+1)	C, 72.44 H, 6.32 N, 13.52	C, 72.01 H, 6.02 N, 12.96
Y1dM	3335 (-NH), 1687 (C=O), 1505(CH=CH), 1517(Ar. C=C), 3091, 2829(CH Str.), 1301(C-N), 1230(C-O)	9.82 (s, 1H, NHCO), 8.88 (s, 1H, NHCO), 7.14-7.54 (m, 14H, Ar-H), 6.92 (d, 1H, CH), 6.83 (d, 1H, CH), 3.72 (s, 3H, OCH_3)	405.1 (M), 407.1 (M+2), 406.1 (M+1)	C, 68.06 H, 4.97 N, 10.35	C, 67.90 H, 4.58 N, 10.11
Y1eM	3364(-NH), 1692(C=O), 1591(CH=CH), 1526(Ar. C=C), 2929, 2723(CH Str.), 1392(C-N), 1278 (C-O)	10.48 (s, 1H, NHCO), 9.02 (s, 1H, NHCO), 6.81-7.43 (m, 14H, Ar-H), 6.79 (d, 1H, CH), 6.59 (d, 2H, CH), 6.49 (d, 1H, CH) , 3.64 (s, 3H, OCH_3)	397.2 (M), 398.2 (M+1)	C, 75.54 H, 5.83 N, 10.57	C, 75.13 H, 5.62 N, 10.33
Y1fM	3334 (-NH), 3148(OH Str.), 1652(C=O), 1589(CH=CH), 1513(Ar. C=C), 2972, 2825(CH Str.), 1383(C-N), 1280(C-O)	9.77 (s, 1H, NHCO), 8.83 (s, 1H, NHCO), 8.47 (s, 1H, OH), 6.86-7.47 (m, 13H, Ar-H), 6.74 (d, 1H, CH), 6.58 (d, 1H, CH), 3.66 (s, 3H, OCH_3)	387.2 (M), 388.2 (M+1)	C, 71.30 H, 5.46 N, 10.85	C, 71.12 H, 5.03 N, 10.56
Y2aM	3367(-NH), 3208(OH Str.), 1681(C=O), 1535(CH=CH), 1490(Ar. C=C), 2921, 2828(CH Str.), 1356(C-N), 1283(C-O)	10.02 (s, 1H, NHCO), 8.95 (s, 1H, NHCO), 8.38 (s, 1H, OH), 7.00-7.50 (m, 13H, Ar-H), 6.96 (d, 1H, CH), 6.80 (d, 1H, CH) , 3.81 (s, 3H, OCH_3)	387.2 (M), 388.2 (M+1)	C, 71.30 H, 5.46 N, 10.85	C, 70.86 H, 5.41 N, 10.52
Y2bM	3410(-NH), 3278(OH Str.), 1656(C=O), 1530(CH=CH), 1460(Ar. C=C), 2942, 2832(CH Str.), 1350(C-N), 1246(C-O)	9.78 (s, 1H, NHCO), 8.71 (s, 1H, NHCO), 8.33 (s, 1H, OH), 6.76-7.37 (m, 12H, Ar-H), 6.66 (d, 1H, CH), 6.50 (d, 1H, CH), 3.75 (s, 3H, OCH_3), 2.84 (s, 6H, $N(CH_3)_2$)	430.2 (M), 431.2 (M+1)	C, 69.75 H, 6.09 N, 13.01	C, 68.68 H, 5.93 N, 12.82
Y2cM	3350(-NH), 3211(OH Str.), 1661(C=O), 1565(CH=CH), 1454(Ar. C=C), 2948, 2810(CH Str.), 1360(C-N), 1225(C-O)	9.94 (s, 1H, NHCO), 9.67 (s, 1H, NHCO), 9.14 (s, 1H, OH), 8.32 (s, 1H, OH), 6.76-7.57 (m, 12H, Ar-H), 6.72 (d, 1H, CH), 6.53 (d, 1H, CH) , 3.80 (s, 3H, OCH_3)	403.2 (M), 404.2 (M+1)	C, 68.47 H, 5.25 N, 10.42	C, 67.93 H, 5.12 N, 10.22
Y2dM	3426(-NH), 3214(OH Str.), 1653(C=O), 1588(CH=CH), 1486(Ar. C=C), 2952, 2830(CH Str.), 1355(C-N), 1228(C-O)	10.36 (s, 1H, NHCO), 9.34 (s, 1H, NHCO), 8.74 (s, 1H, OH), 7.06-7.65 (m, 12H, Ar-H), 7.04 (d, 1H, CH), 6.88 (d, 1H, CH), 3.85 (s, 3H, OCH_3)	421.1 (M), 423.1 (M+2), 422.1 (M+1)	C, 65.48 H, 4.78 N, 9.96	C, 64.82 H, 4.91 N, 9.70
Y2eM	3431(-NH), 3316(OH Str.), 1657(C=O), 1586(CH=CH), 1486(Ar. C=C), 2930, 2820(CH Str.), 1390(C-N), 1245(C-O)	10.05 (s, 1H, NHCO), 9.00 (s, 1H, NHCO), 8.42 (s, 1H, OH), 7.01-7.49 (m, 13H, Ar-H), 6.86-6.89 (d, 2H, CH), 6.81-6.84 (d, 2H, CH) , (s, 3H, OCH_3)	421.1 (M), 423.1 (M+2), 422.1 (M+1)	C, 65.48 H, 4.78 N, 9.96	C, 64.96 H, 4.60 N, 9.62

Synthesis of 4-methoxyphenylurea(XM)
4-Methoxyaniline (0.1mol) was dissolved in 40 ml of glacial acetic acid. To this, 0.1 mole of sodium cyanate (6.5 gm) in about 100ml of hot water was added with vigorous stirring. Then the reaction mixture was allowed to stand for 1 hour, cooled by means of ice and filtered. The crude product so obtained was thoroughly washed with ice cold water and dried and recrystallized from methanol. The completion of reaction was monitored by running TLC.

Synthesis of 4-methoxyphenyl semicarbazide (X1M):
A solution of 4-methoxyphenylurea (0.1 mol) in methanol was refluxed with 99% hydrazine hydrate (1.6 mol) for 70-72 hours. After the completion of reaction, the reaction mixture was allowed to cool at room temperature and poured into crushed ice. The crude white product was filtered, thoroughly washed with water, dried and recrystallized from methanol. The completion of reaction was monitored by running TLC.

General method for the synthesis of chalconyl semicarbazone(Y1aM- Y1fM, Y2aM- Y2eM):
A mixture of 4-methoxyphenyl semicarbazide (0.01 mol) and appropriate substituted chalcone (0.01 mol) in methanol was stirred at 60-70^{o}C in the presence of 2-3 ml of conc. hydrochloric acid. The reaction mixture was poured into a beaker containing crushed ice and allowed to stand for two hours. The precipitate so formed was filtered and washed with ice cold water followed by ice cold methanol. The crude product was dried and recrystallized from chloroform. The completion of reaction was monitored by running TLC.

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 (>300 mg/kg).

Anticonvulsant activity
Animal were weighed and numbered and divided into two groups each consisting of 4-5 mices. One group were used as control and the other for sample compound treatment. The corneal electrodes were placed on the cornea of the animal and the prescribed current were applied. The readings of different stages of convulsions i.e. (a) tonic flexion, (b) tonic extensor phase, (c) clonic convulsions, (d) stupor and (e) recovery or death were noted. The time (sec) spend by the animal in each phase of the convulsions were noted. The whole procedure were repeated with other animals of control group also. The sample compound were injected intraperitoneally to a group of 4-5 mice. After 30 min, the animals were subjected to electroconvulsions as described in step2. The reduction in time or abolition of tonic extensor phase of MES- convulsions were noted[22].

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

% Protection = ($MEPD_{nc}$ – $MEPD_{sample}$/ MEPD) X 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.

Statistical analysis
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.

RESULTS AND DISCUSSION

The synthesis of title compounds was started with when Substituted aryl aldehyde was reacted with various aryl ketones to yield chalcone derivatives via Claisen Schmidt reaction. Then synthesized chalcone derivatives were reacted with (4-methoxyphenyl urea) semicarbazides to give the title compounds.

The structure of title compounds was confirmed by physico-chemical (T.L.C and m.p.) and spectral data (I.R., N.M.R, Mass and elemental analysis) as shown in table 1. The synthesized title compound were screening for antimicrobial activity as shown in table 2.

Table 2: Extensor phase duration of synthesized title compounds (Sec.)

Compound	Dose mg/Kg	Mean ± SEM	% Protection
Control (DMSO)	-	8.700 ± 0.07303	-
Phenytoin (STD)	25	1.733± 0.04216	80%
Y1aM	30	6.015±0.036	30.86%
Y1bM	30	6.897±0.431	20.72%
Y1cM	30	4.608±0.201	47.03%
Y1dM	30	5.975±0.153	31.32%
Y1eM	30	4.778±0.198	45.08%
Y1fM	30	1.868±0.132	78.52%
Y2aM	30	1.505±0.096	82.70%
Y2bM	30	3.573±0.093	58.93%
Y2cM	30	4.917±0.142	43.48%
Y2dM	30	3.907±0.149	55.09%
Y2eM	30	5.662±0.113	34.91%

All the synthesized compounds (Y1aM-Y1fM, Y2aM-Y2eM) were subjected for *in vivo* anticonvulsant activity using MES method using Phenytoin sodium as standard drug.

The compound Y1fM and Y2bM have shown significant protection as 78.52% and 58.93% respectively where as compound Y2aM have shown 82.70% protection which was even more against seizures as compared to the standard drug Phenytoin Sodium used i.e. 80%.

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