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MICROWAVE ASSISTED SYNTHESIS AND ANTIDEPRESSANT ACTIVITY OF SOME 1, 3, 5-TRIPHENYL- 2-PYRAZOLINES

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ABSTRACT

A series of 1,3,5-triphenyl-2-pyrazoline derivatives were synthesized through microwave assisted condensation of 1,3-diphenyl-2-propene-1-one (chalcones) with phenylhydrazine using dry acetic acid as cyclizing agent and evaluated for antidepressant activity. The chemical structures of the compounds were confirmed by means of their IR, GC-MS and ^{1}H NMR spectroscopic data. The antidepressant activity of these compounds were screened by porsolt behavioral despair test using imipramine as a reference drug. All synthesized 2-pyrazoline derivatives were found to possess significant antidepressant activity. It has been observed that 1,5-diphenyl-3- (4-methoxyphenyl)-2-pyrazoline showed maximum antidepressant activity, comparable with imipramine. A methoxy substituent on the phenyl ring at position 3 of the pyrazoline ring was found to enhance antidepressant activity. The replacement of the methoxy group by methyl and any other electron-withdrawing group decreases antidepressant activity.

Key words: Microwave effect, 2-Pyrazolines, Chalcones, Antidepressant activity

INTRODUCTION

Novel approaches to ecofriendly chemistry demands usage of domestic microwave oven for the synthesis of heterocycles, a practically convenient and rapid methodology[1, 3]. Industrial chemistry in the new millennium is widely adopting the concept of "Green Chemistry" to meet the fundamental scientific challenges of protecting the human health and environment while maintaining commercial viability.

In the last few years, 'Microwave induced Organic Reaction Enhancement

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Chemistry' (MORE) chemistry has gained popularity as a non-conventional technique for rapid organic synthesis and many researchers have described accelerated organic reactions and a large number of papers have appeared proving the synthetic utility of MORE chemistry in routine organic synthesis[3-5]. It can be termed as 'e-chemistry' because it is easy, effective, economical and ecofriendly and is believed to be a step towards green chemistry[3].

Various substituted pyrazolines and their derivatives are important biological agents and a significant amount of research activity has been directed towards this class. Increasing evidences suggest that pyrazoline derivatives possess broad spectrum of biological activities including antimicrobial[6], cardiovascular[7], antidepressant[8] and anticonvulsant[9]. The pyrazoline function is quite stable and has inspired chemists to utilize this stable fragment in bioactive moieties to synthesize new compounds and possessing biological activities. Chalcones are the α,β-unsaturated ketonic compounds, the presence of α,β-unsaturated keto function in chalcones is found to be responsible for their different pharmacological activities such as antimicrobial[10], antifungal[11], lipid peroxidation inhibitor[12] and aldose reductase inhibitor[13]. Chalcones are the important synthons for the synthesis of wide variety of heterocycles[14]. Conventionally, the preparation of chalcones were achieved with base as well as acid catalyzed condensation of different acetophenones with benzaldehydes[15,16]. In microwave methods, chalcones were reported to be prepared by using sodium hydroxide[17] and lithium chloride[18].

Among the methods employed in synthesis of pyrazolines, condensation of variety of substituted chalcones with hydrazine and its derivatives is commonly used.[7-9, 19]

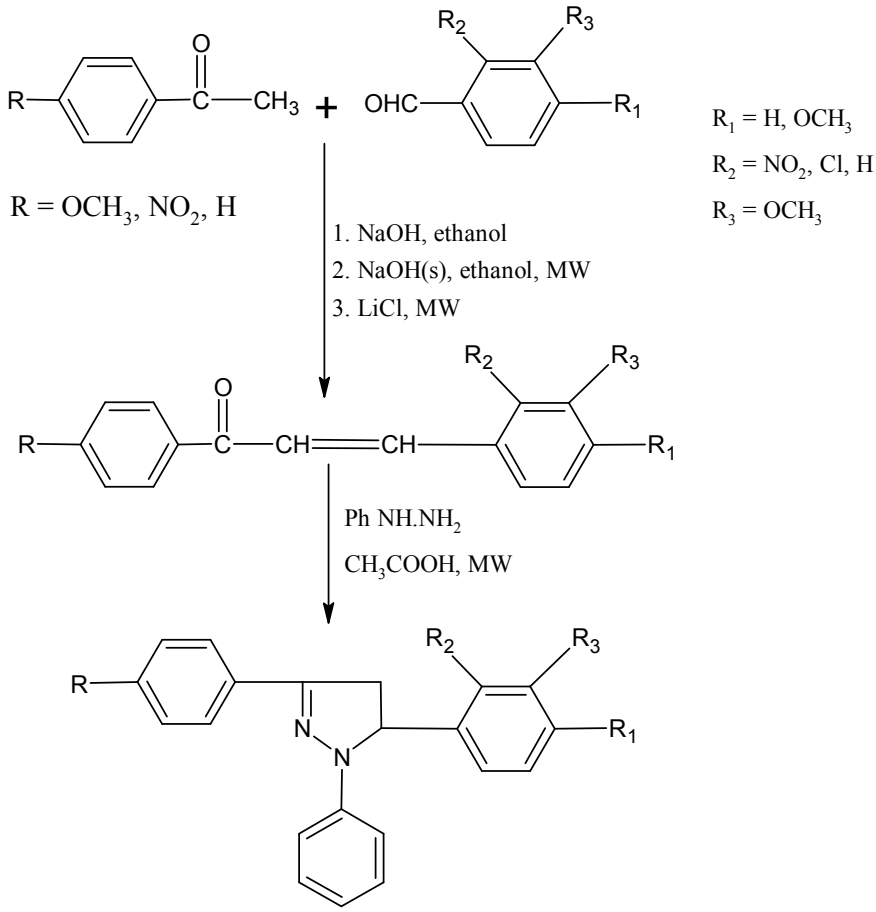
The 1,3,5-triphenyl-2-pyrazoline derivatives were screened for their antidepressant activity using a porsolt forced swimming (behavioral despair) test.[20] The porsolt behavioral despair test is effective in predicting the activity of wide variety of antidepressant for new molecules.

Literature survey revealed that very little research work has been carried out regarding synthesis of 2-pyrazoline using microwave. Present investigation deals with preparation and evaluation of antidepressant activity of various derivatives of 1,3,5-triphenyl-2-pyrazolines using microwave oven.

EXPERIMENTAL

Melting points were determined in open capillary tube using Elico Melting Point

Apparatus and were uncorrected. IR spectra were recorded of compounds were recorded on 'Schimadzu IR 48' Spectrophotometer. ^{1}H NMR spectra were recorded on BROOT Spectrophotometer using duteriochloroform as solvent and tetramethylsilane as an internal standard. GC-MS spectra were recorded on 'Perkin Elmer Auto System' excel gas chromatography. Analytical thin layer chromatography was performed on Merck 60F-254 silica gel plates. All microwave reactions were carried on 'Raga's Electromagnetic System' with automatic power setting from P-1 to P-10.



Substituted pyrozolines

Scheme

1,3-Diphenyl-2-propen-1-one

1,3-Diphenyl-2-propen-1-one derivatives were synthesized by condensing

appropriate acetophenones with substituted benzaldehydes according to the Claisen-Schmidt condensation[15,17,18].

1,3,5-Triphenyl-2-pyrazolines

The appropriate 1,3-diphenyl-2-propen-1-one derivatives (Chalcones) (0.1mol) were dissolved in glacial acetic acid (10 mL). Phenyl hydrazine (0.12 mole) was added in the mixture and subjected to microwave heating at power P-3 and at 120^0C for several minutes to afford pyrazolines. The reaction was monitored for completion of the reaction using TLC. The product obtained was filtered and washed with warm methanol in order to remove adhered acetic acid and recrystallized from ethanol to yield pure compounds.

Antidepressant activity

The porsolt forced swimming test (behavioral despair test) was employed. Local breed, male mice (20 ± 2 g) having free access to food and water were used. Mice were housed in a group of five. On the test day, mice were dropped one at a time into a cylinder (40 cm height x 15 cm diameter) containing 30 cm water column (24 ± 1° C temperature).

Test procedure

The synthesized compounds (100 mg/kg), imipramine (10 mg/kg) suspended in polyethylene glycol 400 were injected intraperitonially (ip) [n = 5]. After 30 min, the mouse was dropped into the glass cylinder (40 cm height x 15 cm diameter) containing 30 cm water column (24 ± 1°C temperature). Water was replaced between every trial and animal left for 6 min. At the end of the first 2 min, the animals showing initial vigorous struggling were immobile. The immobility times of each mouse was measured over the period of 4 min. Immobility– floating passively in the water and making slight movements to keep its head above the water line[20].

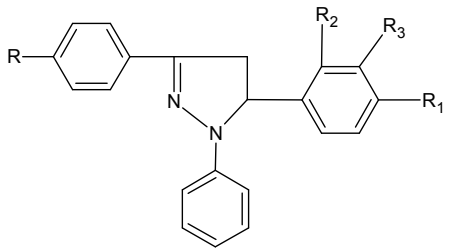
Statistical analysis

One-way ANOVA followed by Dunnet's test was used to evaluate the results.

RESULTS AND DISCUSSION

The reaction time, melting point and percentage yield of all the synthesized products are given in the Table 1. All the results of the antidepressant activity are given in Table 2 and Fig. 1.

Table 1. Reaction time, percentage yield and melting point of 1, 3, 5-triphenyl- 2-pyrazoline derivatives

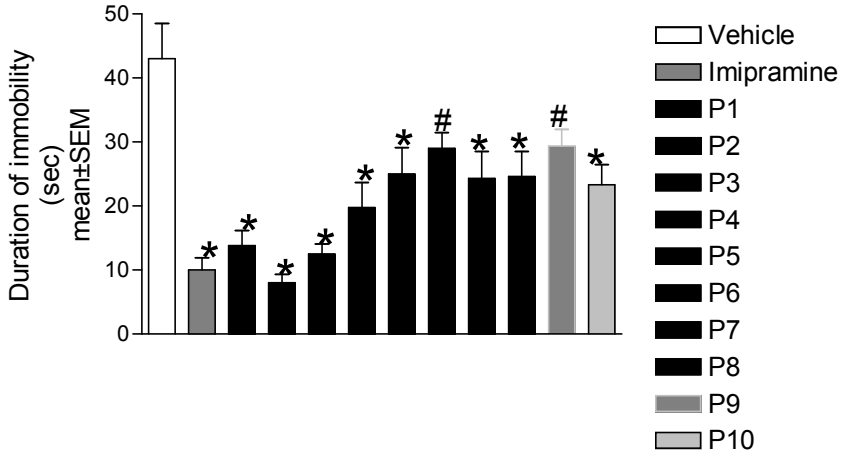


Codes	R	R_1	R_2	R_3	Reaction time (min.)	Yield (%)	Melting point (°C)
P_1	-H	-H	-H	-H	2.3	88.62	135-137a
P_2	$-OCH_3$	-H	-H	-H	1.3	79.83	140-141b
P_3	-H	$-OCH_3$	-H	-H	3.2	86.39	120-121c
P_4	-H	-H	$-NO_2$	-H	14.0	89.91	111-113
P_5	$-OCH_3$	-H	-Cl	-H	11.4	81.65	104-106
P_6	$-CH_3$	-Cl	-H	-H	10.5	76.51	156-158
P_7	-H	$-OCH_3$	-H	$-OCH_3$	7.3	83.97	132-133d
P_8	-H	-H	-Cl	-H	3.5	72.45	136-137e
P_9	$-NO_2$	$-OCH_3$	-H	-H	2.0	78.29	170-172
P_{10}	$-OCH_3$	$-OCH_3$	-H	-H	2.4	92.67	135-138

Lit. m. p. (^{0}C) a. 136-137, b. 141-142, c. 121-122, d. 131-133, e. 137.5.

We have realized a very simple, fast and useful method for the preparation of substituted triphenyl-2-pyrazoline derivatives using microwave. The notable advantages offered by this protocol are the reduced reaction times, high purity and better yields of the products. All synthesized 2-pyrazoline derivatives were found to possess significant antidepressant activity in forced swimming test. Among different compounds 1, 5-diphenyl-3- (4-methoxyphenyl)-2-pyrazoline (P2) showed maximum antidepressant activity. A methoxy substituent on the phenyl ring at position 3 of the pyrazoline ring enhances antidepressant activity while the replacement of the methoxy group by methyl and any other electron-withdrawing group decreases antidepressant activity. In present study we found that all compounds decrease the immobility and increased climbing behavior (vertical movement) in forced swimming test. Results obtained provide enough

evidence that behavioral effects of all synthesized compounds in forced swimming test is due to noradrenergic mechanism.



Antidepressat effect of different 2-pyrazolines (100mg/kg) in mice using forced swimming test

n = 5, $^{*}P < 0.001$, $^{\#}P < O.05$ compaired to vehicle treated group

one way ANOVA followed by Dunnet's test

Fig. 1: Antidepressant effect of different 2-pyrazoline derivatives

Table 2. Antidepressant effect of different 2-pyrazolines (100 mg/kg i.p.) in mice using forced swimming test

Code No.	Duration of immobility (sec.)
Vehicle	43.0 ± 5.51
Imipramine	10.0 ± 1.92
P_1	13.8 ± 2.39
P_2	8 .0 ± 1.30

Cont…

Code No.	Duration of immobility (sec.)
P_3	12.5 ± 1.55
P_4	19.75 ± 3.92
P_5	25.0 ± 4.10
P_6	29.0 ± 2.48
P_7	24.3 ± 4.2
P_8	24.6 ± 3.91
P_9	29.34 ± 2.64
P_{10}	23.32 ± 3.16
Values are in mean ± SEM, n = 5	

Spectral analysis

The IR spectrum showed absence of carbonyl C=O stretching vibrations at 1670-1710 and presence of a strong C=N stretching vibrations at 1590-1605 which is characteristic of 2-pyrazolines. Spectral analysis of the representative compounds is given below –

(i) Compound P_1

IR data (nujol): 1600, 1220, 1370, 3005 cm^{-1}

EIMS data: 298 (M^+), 299 (M+1), 221, 117, 104, 91, 77, 65 mass fragments.

NMR data: δ Values (ppm)

3.10 – 3.18 (dd, 1Ha)

3.79 – 3.89 (dd, 1Hb)

5.24 – 5.30 (dd, 1Hx)

6.75 – 7.74 (complex multiplet aromatic protons, 15 H)

(ii) Compound P_3

IR data (nujol): 1605, 1250, 1340, 1008, 3010 cm^{-1}

EIMS data: - 328 (M^+), 329(M+1), 297,251,237,221,91,77,65 mass fragments.

NMR data:-δ Values (ppm)

3.07 – 3.15 (dd, 1Ha)

3.75 – 3.85 (dd, 1Hb)

5.19 – 5.26 (dd, 1Hx)

3.77 (s, 3H, overlapping)

6.75 – 7.74 (complex multiplet aromatic protons, 14H)

(3) Compound P_4

IR data (nujol); 1600, 1530, 1300, 1220 cm^{-1}

EIMS data: 343 (M^+), 344 (M+1), 311, 297, 267, 221, 220, 105, 91, 77, 65 fragments.

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