Preparation and antidepressants activities of a number of 2-pyrazoline derivatives

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***Abstract*—Ten novel 2-pyrazoline derivatives derivatives were synthesised by react 1,3-diphenyl-2-propen-1-one with hydrazine hydrate. The substance structures of the compounds were prove by means of their FT-IR, ^{1}H-NMR spectroscopic data and micro-analyses. The antidepressant activities of these compounds were investigated by the 'Porsolt Behavioural Despair Test' on Swiss–Webster mice. 3-(4-chlorophenyl)-5-(2-chloro-3,4-dimethoxyphenyl)-2-pyrazoline,3-(4-ethoxyphenyl)-5-(3,4-dimethoxyphenyl)-2-pyrazoline, and 3-(4-methoxyphenyl)-5-(2-chloro-3,4-dimethoxyphenyl)-2-pyrazoline 3-(4-chlorophenyl)-5-(2-chloro-3,4-dimethoxyphenyl)-2-pyrazoline reduced 40.91–49.62% immobility times at 100 mg kg^{-1} dose level. In addition, it was found that 4-methoxy and 4-chloro substituents on the phenyl ring at position 3 of the pyrazoline ring raised the antidepressant activity; the substituted of these groups by Bromo and Methyl substituents reduced activity in mice**

***Index Terms*—Microanalyses, 4-Methoxy, Pyrazoline, FT-IR, Hydrazine hydrate**

1. INTRODUCTION

Considerable attention has been alert on the pyrazole structure, which has been known to possess a broad spectrum of biological activities including tranquillizing, muscle relaxant, psycho analeptic, anticonvulsant and antihypertensive activities [1–5]. The detection of this class of drugs supply an outstanding case the past of modern drug development and also points out the unpredictability of biological activity from structural modification of a prototype drug molecule. Prodrug-based monoamine oxidase inhibitors have hydrazide, hydrazine and amine moiety like isocarboxazid [6], phenelzine [7] and moclobemide [8, 9] show prominent antidepressant activity in laboratory animals and man. furthermore, tranylcypromine-like MAO inhibitors are mechanismbased inactivators and they are metabolised by MAO with one electron of the nitrogen couple and to make an imines, the other residing on a methylene carbon (R_C_NH_2 +). The structures of 3-aryl-2-pyrazoline derivatives are very like to those of isocarboxazid (Figure-1) and these compounds metabolize easily and show their activity as prodrugs. Earlier studies by Parmar et al. [3] and Soni et al. [4] demonstrated monoamine oxidase inhibitory activities of 1,3,5-triphenyl-2-pyrazolines, and we reported some 1,3,5-triphenyl -2 - pyrazolines, 1 - thiocarbamoyl - 3,5 - diphenyl-2-pyrazolines and bicyclic pyrazolines 8-thiocarbamoyl-7,8-diazabicyclo[4.3.0]non-6-ene derivatives to be active in the behavioural despair test [10–13]. As part of our continuing efforts in this area, a series of some new 3-(4-substituted phenyl)-5-(3,4-dimethoxy- and/or 2-chloro-3,4-dimethoxyphenyl)-2-pyrazolines have been synthesized and assess for their antidepressant activities using 'Behavioural Despair Test'.

2. EXPERIMENTAL

2.1 Materials and Characterization: -
All chemicals were supplied by SD Fine Chemicals (Nasik, Maharashtra, India) and Aldrich Chemical Co. (Nasik, Maharashtra, India). Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. Fourier transform infra-red (FT-IR) spectra were obtained on a Perkin–Elmer 1720X FT-IR spectrometer (KBr pellets). Microanalyses of the compounds were performed at the Scientific and Technical Research Council of Turkey.
2.2 1,3 -Diphenyl-2 -propen-1 -ones (3A-J) :-

1,3-Diphenyl-2-propen-1-one derivatives were synthesized by condensing appropriate acetophenones (1.0) with 3,4-dimethoxy- and/or 2-chloro-3,4-dimethoxy- enzaldehyde (2.0) according to Claisen–Schmidt condensation [14–16].

Table 1. Antidepresent activities of the compounds.

Compound	Duration of immobility(s)	(%) Change from control
4-A	35.8	17.53
4-B	34.4	20.76
4-C	36.8	15.21
4-D	28.3	34.79
4-E	25.2	41.94
4-F	37.5	13.59
4-G	24.5	43.55
4-H	38.9	10.37
4-I	28.9	33.41
4-J	22.3	48.62
Clomipramine (10 $mgkg^{-1}$)	26.8	38.25
Clomipramine(20 $mgkg^{-1}$)	12.4	71.43
Tranylcypromin e (10 $mgkg^{-1}$)	23.0	47.00
Tranyl cypromine(20 $mgkg^{-1}$)	9.6	77.80
Control(vehicle)	43.4	nil

2.3. 3,5 -Diphenyl-2 -pyrazolines (4A–J):-

To the solution of 0.01 mol of the proper (4A–J) derivative in 15 mL of ethanol, 0.02 mol hydrazine hydrate (80.0 %) was extra added and the reaction mixture was refluxed for 4 h and left overnight. The reaction mixture was cooled to −18 °C and the solid mass separated out was filtered, washed with cold ethanol and purified from suitable solvents.

2.4. Pharmacology: -

Mature male albino Swiss–Webster mice (23.0) were used as subjects in the revise. They were housed in a quiet and temperature and humidity-controlled room (22.0 °C and 60.0 %, correspondingly) in which a 14 h light/dark cycle was maintained (09:00–21:00 h light). Food and water intake of the subjects was not restricted during the revise. Clomipramine and tranyl-cypromine were supplied by SD Fine Chemicals.

2.5 Test procedure: -

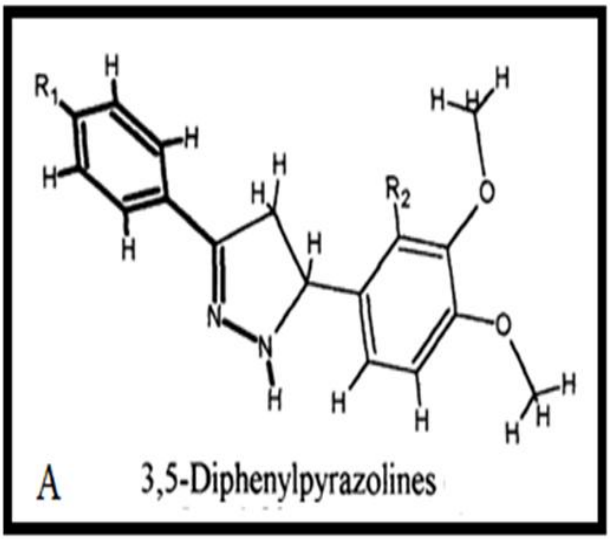
The mice were housed in Plexi-glass cages with 6.0 animals for every enclose. 'Porsolt Forced Swimming Test', a behavioural despair test, was use for evaluate if the compounds have antidepressant activity. On the testing day, mice were assigned into different groups (n=6 for every group). The synthesized compounds, clomipramine and tranylcypromine were suspended in aqueous Tween 80 (0.2% w/v, 0.9 % sodium chloride). All the synthesised compounds (0.100 g kg−1), clomi-pramine and tranyl-cypromine (10 and 20 mg kg−1) were injected intraperitoneally to mice at a volume of 0.5 ml per 100 g body weight. 60 min afterward, the mice were dropped one at a time into a Plexiglass cylinder (25.0 cm height, 30.0 cm diameter, containing 20.0 cm height of water at 22–24 °C) and left for 7.0 min. At the end of the first 2.0 min the animals showing initial vigorous struggling were im-mobile. Then, the immobility times of each mouse was measured in the period of 4 min.

2.6 Statistical analysis: -

Statistical significance was set at $P<0.05$ level. Changes in duration of im-mobilisations expressed as mean±SEM were evaluated using by Dunnet's test (Pharmacological Calculation System,).

3. CHEMISTRY

Chalcones (1,3-Diphenyl-2-propen-1-ones) (3A–J) were preparation by condensing appropriate acetophenones with benzaldehyde derivatives in dil ethanolic sodium hydroxide solution at room temperature. The 3,5-diphenyl-2-pyrazolines (4A–J) were preparation by the reaction of appropriate 1,3-diphenyl-2-propen-1-one derivatives (3A–J) and hydrazine hydrate according to the condensation reaction of unsaturated ketones with hydrazines in yield varying from 75.00 to 94.50% (Figure 2.0).



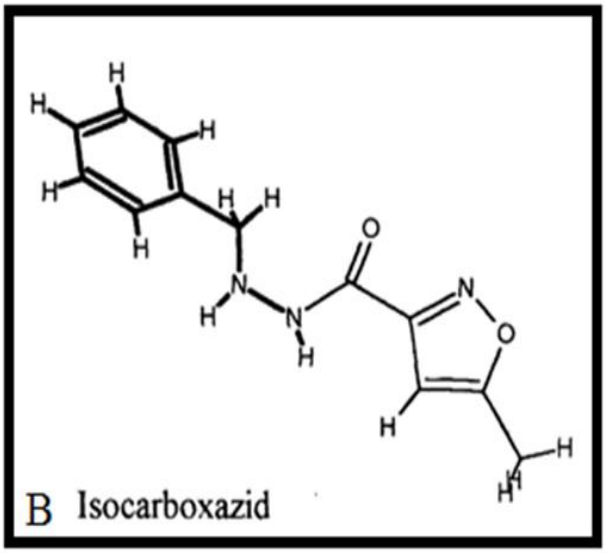


Figure 1. Structures of (A) 3,5-diphenyl-2-pyrazolines and (B) isocarboxazid

4. PHARMACOLOGY

The 3,5-diphenyl-2-pyrazoline derivatives (4A–J) were screened for their antidepressant activities using a Modified Porsolt Forced Swimming (behavioural despair) test. The synthesised compounds (0.100 g kg−1), and the reference antidepressants clomipramine and tranylcypromine (0.010 and 0.020 g kg−1) were suspended in Tween 80 and injected intraperitoneally to mice. 60 min later, the mice were dropped one at a time into a Plexiglass cylinder containing water and left for 6 min. At the end of the first 2 min the immobility times of each mouse was measured in the period of 4 min.

5. RESULTS AND DISCUSSION

The formula, melting points(0C), yields(%), purification solvents and microanalysis of the compounds are listed in Table 1.0 FT-IR spectra of the compounds showed C-N stretching band at 1590 cm−1. The Porsolt behavioural despair test is effective in predicting the activity of a wide variety of antidepressants for new molecules [17, 18]. Porsolt forced swimming induced behavioral despair model is capable of predicting a variety of potential anti-depressants, yet it is not devoid of biases. on the other hand, its validity is unclear, for the reason that, it gives false-positive results in cylinders with 10 cm diameter central nervous system (CNS) stimulants, anticholinergics and antihistaminics. Moreover, mice in the 10 cm chambers.

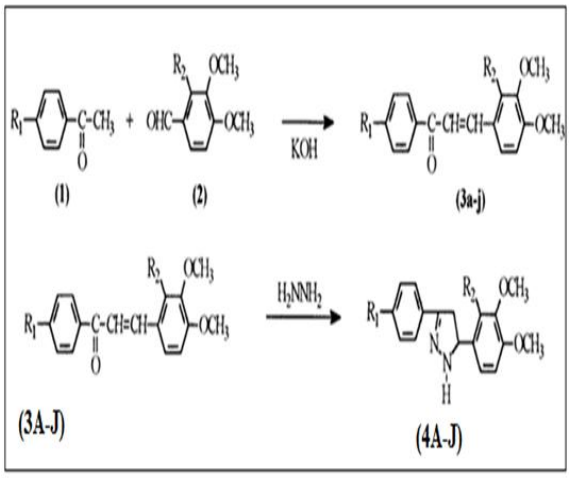


Figure 2. Synthesis of the compounds.

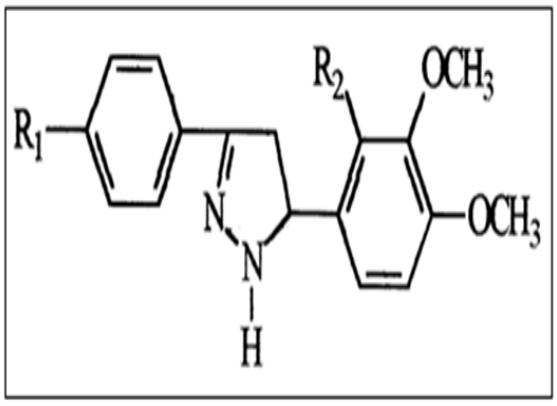


Table I. Structure and chemical data of the compounds 4A–J.

Compound no.	R1	R2	la	Melting point °C)	Yield (%)	Purification
4A	H	H	$C_{17}H_{18}N_2O_2$ (C, H, N) a	85–88	0.1	Ethanol
4B	Cl	H	$C_{17}H_{17}ClN_2O_2$ (C, H, N)	79–82	89.	Ethanol–Propnone
4C	Br	H	$C_{17}H_{17}BrN_2O_2$ (C, H, N)	75–81	90.5	Ethanol–Propnone
4D	CH3	H	$C_{18}H_{20}N_2O_2$ (C, H, N)	67–69	78.4	Ethanol
4E	OCH3	H	$C_{18}H_{20}N_2O_3$ (C, H, N)	101–107	86.5	Ethanol–Propnone
4F	H	Cl	$C_{17}H_{17}ClN_2O_2$ (C, H, N)	96–99	79.9	Ethanol–Propnone
4G	Cl	Cl	$C_{17}H_{16}Cl_2N_2O_2$ (C, H, N)	56–58	94.7	Ethanol–Propnone
4H	Br	Cl	$C_{17}H_{16}BrClN_2O_2$ (C, H, N)	65–67	87.9	Ethanol–Propnone
4I	CH3	Cl	$C_{18}H_{19}ClN_2O_2$ (C, H, N)	79–83	75.5	Ethanol–Propnone
4J	OCH3	Cl	$C_{18}H_{19}ClN_2O_3$ (C, H, N)	71–74	91.8	Ethanol–Propnone

6. CONCLUSION

The study presents a detailed account of the synthesized compounds, including their melting points, yields, purification solvents, and elemental analyses as listed in Table 1.0. The FT-IR spectra confirmed the presence of C–N stretching at 1590 cm^{-1}, supporting the structural identity of the compounds. The Porsolt behavioral despair test was employed to evaluate potential antidepressant activity. While the test is commonly used and effective in screening a broad range of antidepressants, its limitations must be acknowledged. Specifically, the model may yield false positives, particularly in 10 cm diameter chambers, due to non-specific activity from CNS stimulants, anticholinergics, and antihistamines. These factors highlight the need for complementary behavioral and biochemical assays to validate antidepressant potential more reliably.

7. ACKNOWLEDGEMENTS

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