Asian Journal of Chemistry Vol. 19, No. 6 (2007), 4790-4798

Synthesis and Antidepressant Activity of Some 3-(3''-Coumarinyl)-1,5-diphenyl-2-pyrazolines and 3-(2''-hydroxy naphthalen-1''-yl)-1,5-diphenyl-2-pyrazolines

Y. RAJENDRA PRASAD*, P. RAVI KUMAR, CH. ASHA DEEPTI and M.VENKATA RAMANA
Pharmaceutical Chemistry Division, AU College of Pharmaceutical Sciences
Andhra University, Visakhapatnam-530 003, India
Fax: (91)(891)2525611; Tel: (91)(891)2504224; E-mail: dryrp@rediffmail.com

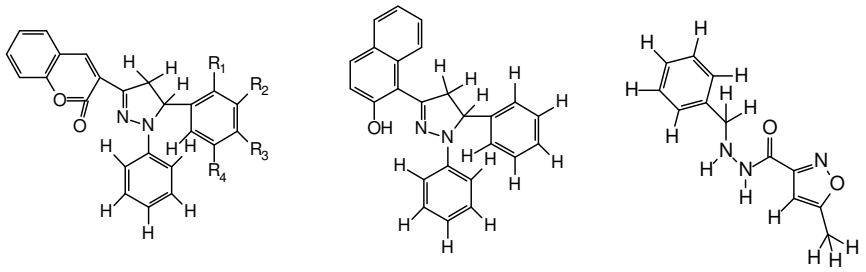
Five new 3-(3''-coumarinyl)-1,5-diphenyl-2-pyrazolines (**3**$_{a-e}$) were synthesised by reacting 3-[1-oxo-3-(substituted phenyl)-2-propenyl]-2H-1-benzopyran-2-ones (**2**$_{a-e}$) with phenyl hydrazine hydrochloride and another five new 3-(2''-hydroxy naphthalen-1''-yl)-1,5-diphenyl-2-pyrazolines (**5**$_{a-e}$) were synthesized by reacting 1-(2'-hydroxynaphthyl)-3-phenyl-2-propene-1-one (**4**$_{a-e}$) with phenyl hydrazine hydrochloride. All these compounds were characterized by means of their IR, ^{1}H NMR spectroscopic data and microanalyses. The antidepressant activity of these compounds was evaluated by the Porsolt behavioural despair test on Swiss-Webster mice. 3-(3''-coumarinyl)-1-phenyl-5-(2',4',5'-trimethylphenyl)-2-pyrazoline (**3**$_a$), 3-(3''-coumarinyl)-1-phenyl-5-(4'-hydroxy-3'-methoxyphenyl)-2-pyrazoline (**3**$_d$), 1-phenyl-3-(2''-hydroxy-naphthalen-1''-yl)-5-(2',4',5'-trimethoxyphenyl)-2-pyrazoline (**5**$_c$) and 1-phenyl-3-(2''-hydroxynaphthalen-1''-yl)-5-(4'-dimethylaminophenyl)-2-pyrazoline (**5**$_a$) reduced 36.59-59.65 % immobility times at 100 mg kg^{-1} dose level. It was observed that some of the 2-pyrazolines derived from 3-acetyl coumarin showed grater activity than those derived from 2-hydroxy-1-acetonaphthone. In addition it was found that the compounds possessing electron releasing groups such as dimethyl amino, methoxy and hydroxyl substituent, on both the rings at position 3 and 5 of pyrazolines, considerably enhanced the antidepressant activity when compared to the pyrazolines having no substituents on the rings.

Key Words: Synthesis, 2-Pyrazolines, Antidepressant activity, Forced-swimming test.

INTRODUCTION

Compounds with a pyrazoline structure are known to possess tranquilizing, muscle relaxant, psychoanaleptic, anticonvulsant, antihypertensive and antidepressant activities[1-6]. Coumarins are members of the class of compounds called benzopyrones and display a variety of pharmacological properties[7,8] depending on their substitution pattern. Some coumarin derivatives of natural[9] and synthetic origin[10] have been characterized as MAO-inhibitors. Prodrug-based monoamine oxidase (MAO) inhibitors

having hydrazide, hydrazine and amine moiety such as isocarboxazide[11], phenelzine[12] and meclobemide[13,14] show prominent antidepressant activity in laboratory animals and human. Additionally, tranylcypromine-like MAO inhibitors are mechanism-based inactivators and they are metabolized by MAO with one electron of the nitrogen pair and to generate an imine, the other residing on a methylene carbon (R-C=NH_2+). The structures of the synthesized 2-pyrazoline derivatives are very similar to those of isocarboxazide (Fig. 1).



3_{a-e} **5_{a-e}** Isocarboxazide

Fig. 1. Structures of 3-(3"-Coumarinyl)-1,5-diphenyl-2-pyrazolines (**3_{a-e}**), 3-(2"-hydroxy naphthalen-1"-yl)-1,5-diphenyl-2-pyrazolines (**5_{a-e}**) and Isocarboxazid

Earlier studies by Parmar *et al.*[3] and Soni *et al.*[4] demonstrated monoamine oxidase inhibitory activities of some 1,3,5-triphenyl-2-pyrazolines, 1-thiocarbamoyl-3,5-diphenyl-2-pyrazolines and bicyclic pyrazolines in behavioural despair test[15,16]. Since coumarins are also reported to have antidepressant activity apart from 2-pyrazolines, we planned to prepare a series of 2-pyrazolines having a coumarin substituent at position-3 in order to obtain compounds with better antidepressant activity. Hence some new 3-(3"-coumarinyl)-1,5-diphenyl-2-pyrazolines and 3-(2"-hydroxy naphthalen-1"-yl)-1, 5-diphenyl-2-pyrazolines have been synthesized and evaluated for their antidepressant activities using Porsolt behavioural despair test.

EXPERIMENTAL

Chemicals and solvents were reagent grade and used without further purification. Melting points were determined on a capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra was recorded in the indicated solvent on Bruker WM 400 MHz spectrometer with TMS as internal standard. Infrared spectra were recorded in KBr on Perkin-Elmer AC-1 spectrophotometer. Microanalyses were performed on Carlo Erba EA-1108

element analyzer and were within the ± 0.4 % of the theoretical values. Column chromatography was performed on silica gel (Merck, 60-120 mesh).

IR spectra of the 2-pyrazolines showed (C=N) absorption at 1590 cm^{-1}. In ^1H NMR spectra, H_A, H_B and H_x protons of the pyrazoline ring were seen as doublet of doublets at 2.90-3.78, 3.30-4.39 and 5.11-5.60 ppm (J_{AB} = 17, J_{AX} = 7, J_{BX} = 10 Hz).The protons belonging to the aromatic ring and substituent groups were observed with in the expected chemical shift values.

General procedure for the preparation of 2-pyrazolines (3_{a-e} and 5_{a-e})

To the solution of the appropriate chalcones derivative (1 mmol) and phenyl hydrazine HCl (500 mg) in ethanol (20 mL), pyridine (0.3 mL) was added as a catalyst. The mixture was refluxed for 4-6 h and the solvent was evaporated completely. The reaction mixture was poured into ice cold water and the solid mass that separated out was filtered, dried and purified by using column chromatography.

3-(3″-Coumarinyl)-1-phenyl-5-(2′,4′,5′-trimethoxyphenyl)-2-pyrazoline (3_a): Yield 74 %; m.p. 220-222°C; IR (KBr, ν_{max}, cm^{-1}) 1720 (CO), 1590 (C=C), 1510 (C=N), 1230 (C-O-C), 1150 (OCH_3), 1060 (C-N); ^1H NMR (400 MHz, $CDCl_3$) δ 8.39 (1H, s, C_4-H), 7.10-7.70 (9H, m, Ar-H), 6.62 (IH, s, Ar-H), 6.59 (1H, s, Ar-H), 5.60 (1H, dd, H_X), 4.10 (1H, dd, H_B), 3.93 (3H, s, -OCH_3), 3.91 (3H, s, -OCH_3), 3.62 (3H, s, -OCH_3), 3.30 (1H, dd, HA), (J_{AB} = 16.98, J_{AX} = 7.68, J_{BX} = 9.86 Hz) Anal. Calcd. for $C_{27}H_{25}N_2O_5$: C, 70.96; H, 5.51; N, 6.12. Found: C, 70.28; H, 5.12; N, 5.89.

3-(3″-Coumarinyl)-1-phenyl-5-(3′, 4′-dimethoxyphenyl)-2-pyrazoline (3_b): Yield 76 %; m.p. 236-238°C; IR (KBr, ν_{max}, cm^{-1}) 1722 (CO), 1595 (C=C), 1520 (C=N), 1240 (C-O-C), 1140 (OCH_3), 1065 (C-N); ^1H NMR (400 MHz, $CDCl_3$) δ 8.59 (1H, s, C_4-H), 6.80-7.80 (12H, m, Ar-H), 5.12 (1H, dd, H_X), 4.39 (1H, dd, H_B), 3.71 (1H, dd, H_A), (J_{AB} = 17.34, J_{AX} = 7.62, J_{BX} = 9.92 Hz) Anal. Calcd. for $C_{26}H_{23}N_2O_4$: C, 73.05; H, 5.42; N, 6.55. Found: C, 73.41; H, 5.12; N, 6.26.s

3-(3″-Coumarinyl)-1-phenyl-5-(3′-nitrophenyl)-2-pyrazoline (3_c): Yield 82 %; m.p. 244-246°C; IR (KBr, ν_{max}, cm^{-1}) 1725 (CO), 1585 (C=C), 1515 (C=N), 1235 (C-O-C), 1340 (C-N); ^1H NMR (400 MHz, $CDCl_3$) δ 8.49 (1H, s, C_4-H), 6.80-7.80 (13H, m, Ar-H), 5.45 (1H, dd, H_X), 4.20 (1H, dd, H_B), 3.41 (1H, dd, H_A), (J_{AB} = 17.04, J_{AX} = 7.60, J_{BX} = 10.02 Hz) Anal. Calcd. for $C_{24}H_{17}N_3O_4$: C, 70.13; H, 4.16; N, 10.22. Found: C, 70.32; H, 4.28; N, 10.03.

3-(3″-Coumarinyl)-1-phenyl-5-(4′-hydroxy-3′-methoxyphenyl)-2-pyrazoline (3_d): Yield 86 %; m.p. 210-212°C; IR (KBr, ν_{max}, cm^{-1}) 3085

(OH), 1715 (CO), 1610 (C=C), 1520 (C=N), 1255 (C-O-C), 1180 (OCH_3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (1H, s, C_4-H), 6.94-7.65 (7H, m, Ar-H), 5.96 (1H, s, -OH) 5.11 (1H, dd, H_X), 4.38 (1H, dd, H_B), 3.94 (3H, s, -OCH_3), 3.70 (1H, dd, H_A), (J_{AB} = 17.05, J_{AX} = 7.50, J_{BX} = 9.76 Hz) Anal. Calcd. for $C_{25}H_{20}N_2O_4$: C, 72.88; H, 4.89; N, 6.79. Found: C, 72.63; H, 4.65; N, 6.58.

3-(3″-Coumarinyl)-1-phenyl-5-(3′-bromophenyl)-2-pyrazoline (3_e): Yield 78 %; m.p. 226-228°C; IR (KBr, ν_{max}, cm^{-1}) 1725 (CO), 1615 (C=C), 1525 (C=N), 1250 (C-O-C), 855 (C-Br); $_1$H NMR (400 MHz, $CDCl_3$) δ 8.48 (1H, s, C_4-H), 6.79-7.80 (13H, m, Ar-H), 5.45 (1H, dd, H_X), 4.20 (1H, dd, H_B), 3.40 (1H, dd, H_A), (J_{AB} = 17.16, J_{AX} = 7.34, J_{BX} = 10.12 Hz) Anal. Calcd. for $C_{24}H_{17}N_2O_2Br$: C, 64.77; H, 3.85; N, 6.29; Br, 17.95. Found: C, 64.98; H, 3.63; N, 6.08; Br, 17.43.

5-(4′-Dimethylaminophenyl)-3-(2″-hydroxynaphthalene-1″-yl)-1-phenyl-2-pyrazoline (5_a): Yield 78 %; m.p. 260-262°C; IR (KBr, ν_{max}, cm^{-1}) 3115 (OH), 1642 (C=N), 1350 (C-N); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.65 (1H, s, C-2″ -OH), 9.45 (1H, d, *J* = 16 Hz, C-8″-H), 6.90-7.80 (14H, m, Ar-H), 5.20 (1H, dd, H_X), 4.10 (1H, dd, H_B), 3.29 (1H, dd, H_A), (J_{AB} = 17.12, J_{AX} = 7.30, J_{BX} = 10.14 Hz) Anal. Calcd. for $C_{27}H_{25}N_3O$: C, 79.56; H, 6.18; N, 10.31. Found: C, 79.38; H, 6.08; N, 10.22.

5-(2′-Chlorophenyl)-3-(2″-hydroxynaphthalene-1″-yl)-1-phenyl-2-pyrazoline (5_b): Yield 83 %; m.p. 244-246°C; IR (KBr, ν_{max}, cm^{-1}) 3050 (OH), 1645 (C=N), 1350 (C-N), 855 (C-Cl); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.50 (1H, s, C-2″ -OH), 9.70 (1H, d, *J* = 8 Hz, C-8″-H), 6.70-7.95 (14H, m, Ar-H), 5.15 (1H, dd, H_X), 3.30 (1H, dd, H_B), 3.00 (1H, dd, H_A), (J_{AB} = 17.10, J_{AX} = 7.20, J_{BX} = 10.12 Hz) Anal. Calcd. for $C_{25}H_{19}N_2OCl$: C, 75.27; H, 4.80; N, 7.02. Found: C, 75.58; H, 4.38; N, 7.36.

5-(2′,4′,5′-Trimethoxyphenyl)-3-(2″-hydroxynaphthalene-1″-yl)-1-phenyl-2-pyrazoline (5_c): Yield 68 %; mp 294-296°C; IR (KBr, ν_{max}, cm^{-1}) 3120 (OH), 1640 (C=N), 1360 (C-N), 1180 (OCH_3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.50 (1H, s, C-2″-OH), 9.72 (1H, d, *J* = 8 Hz, C-8″-H), 6.90-7.95 (12H, m, Ar-H), 5.30 (1H, dd, H_X), 3.30 (1H, dd, H_B), 2.90 (1H, dd, H_A), (J_{AB} = 17.38, J_{AX} = 7.48, J_{BX} = 9.62 Hz) Anal. Calcd. for $C_{28}H_{26}N_2O_4$: C, 73.99; H, 5.76; N, 6.16. Found: C, 73.72; H, 5.29; N, 6.56.

5-(4′-Nitrophenyl)-3-(2″-hydroxynaphthalene-1″-yl)-1-phenyl-2-pyrazoline (5_d): Yield 86 %; mp 266-268°C; IR (KBr, ν_{max}, cm^{-1}) 3050 (OH), 1645 (C=N), 1350 (C-N); ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.50 (1H, s, C-2″ -OH), 9.50 (1H, d, *J* = 8 Hz, C-8″-H), 6.80-7.80 (14H, m, Ar-H), 5.30 (1H, dd, H_X), 3.40 (1H, dd, H_B), 3.10 (1H, dd, H_A), (J_{AB} = 16.88, J_{AX} = 7.89, J_{BX} = 10.25 Hz) Anal. Calcd. for $C_{25}H_{19}N_3O_3$: C, 73.33; H, 4.67; N, 10.26. Found: C, 73.72; H, 5.09; N, 10.49.

5-(4′-Methylphenyl)-3-(2″-hydroxynaphthalene-1″-yl)-1-phenyl-2-pyrazoline (5_e): Yield 76 %; m.p. 202-204°C; IR (KBr, ν_{max}, cm^{-1}) 3100 (OH), 1642 (C=N), 1355 (C-N); ^1H NMR (400 MHz, $CDCl_3$) δ 12.35 (1H, s, C-2″-OH), 9.60 (1H, d, *J* = 8 Hz, C-8″-H), 6.80-8.00 (14H, m, Ar-H), 5.25 (1H, dd, H_X), 4.31 (1H, dd, H_B), 3.78 (1H, dd, H_A), 2.40 (3H, s, $-CH_3$), (J_{AB} = 16.80, J_{AX} = 7.85, J_{BX} = 10.20 Hz) Anal. Calcd. for $C_{26}H_{22}N_2O$: C, 82.51; H, 5.85; N, 7.40. Found: C, 82.38; H, 5.66; N, 7.53.

Pharmacology: The Porsolt forced swimming test was employed. Adult male albino mice (20 ± 2 g) were used with free access to food and water in the study. The mice were housed in plexiglass cages with 6 animals for each cage in a quiet and temperature and humidity controlled room (20 ± 3°C and 62 ± 5 %, respectively) in which a 12 h light dark cycle was maintained (08:00-20:00 h light). Clomipramine and tranylcypromine were supplied by Sigma Chemical Co.

On the testing day, mice were assigned into different groups (n = 6 for each group). The synthesized compounds, clomipramine and tranylcypromine were suspended in aqueous Tween 80 (0.2 % w/v, 0.9 % NaCl). All the synthesised compounds (100 mg/kg), clomipramine and tranylcypromine (10 and 20 mg/kg) were injected intraperitoneally to mice at a volume of 0.5 mL per 100 g body weight. After 1 h, the mice were dropped one at a time into a plexiglass cylinder (25 cm height, 30 cm diameter containing water to a height of 20 cm at 21-23°C) and left for 6 min. At the end of the first 2 min the animals showing initial vigorous struggling were immobile. Then the immobility times of each mouse was measured in the next 4 min period.

Statistical analysis: Statistical significance was set at $p < 0.05$ level. Changes in duration of immobilizations expressed as mean ± SEM were evaluated using Dunnet's test (Pharmacological calculation system, version 4.1).

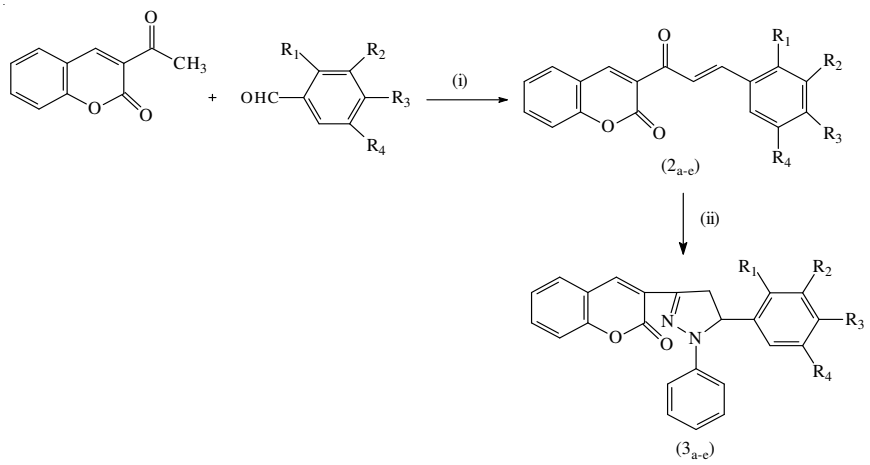
RESULTS AND DISCUSSION

3-[1-Oxo-3-(substituted phenyl)-2-propenyl]-2H-1-benzopyran-2-ones (**2**$_{a-e}$) were synthesized by refluxing 3-acetylcoumarin with aldehydes in the presence of piperidine in ethanol.

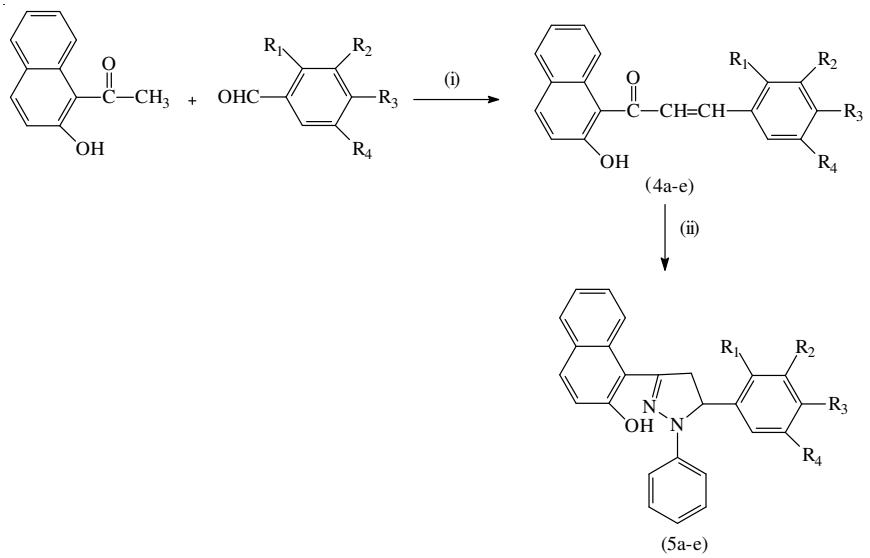
1-(2'-Hydroxy naphthyl)-3-phenyl-2-propene-1-ones (**4**$_{a-e}$) were synthesised by condensing 2-hydroxy-1-acetonaphthone with benzaldehyde derivatives in dilute ethanolic KOH solution at room temperature according to Claisen-Schmidt condensation[17-19].

3-(3"-Coumarinyl)-1,5-diphenyl-2-pyrazolines (**3**$_{a-e}$) and 3-(2"-hydroxy naphthalen-1"-yl)-1,5-diphenyl-2-pyrazolines (**5**$_{a-e}$) were synthesised by the reaction of appropriate chalcone derivatives (**2**$_{a-e}$ and **4**$_{a-e}$) with phenyl hydrazine hydrochloride in ethanol according to the condensation reaction

of unsaturated ketones with hydrazines.The synthetic routes of compounds is outline in **Schemes I and II**.



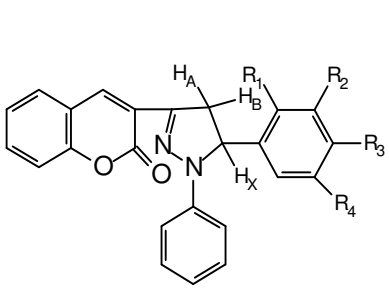
Scheme I. Reagents and conditions: (i) piperidine, absolute ethanol, refluxing for 7 h: (ii) $C_6H_5NHNH_2$·HCl, pyridine, absolute ethanol, refluxing for 7 h



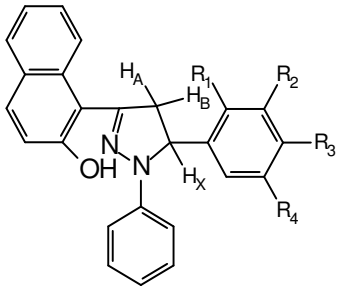
Scheme-II Reagents and conditions: (i) 40 % aq. KOH, absolute ethanol, 24 h at r.t. (ii) $C_6H_5NHNH_2$·HCl, pyridine, absolute ethanol, refluxing for 7 h

Antidepressant activity: The synthesized compounds were evaluated for antidepressant activity in adult male albino Swiss-Webster mice by using Porsolt behavioral despair test. This test is effective in predicting the antidepressant activity of a wide variety of new molecules[20-22]. Porsolt

TABLE-1
STRUCTURE AND ANTIDEPRESSANT ACTIVITY OF
THE COMPOUNDS ($\mathbf{3}_{a-e}$ AND $\mathbf{5}_{a-e}$)



$\mathbf{3}_{a-e}$



$\mathbf{5}_{a-e}\mathbf{3}$

Compd.[a]	R_1	R_2	R_3	R_4	Duration of immobility(s)	%Change from control
$\mathbf{3}_a$	$-OCH_3$	-H	$-OCH_3$	$-OCH_3$	22.80 ± 4.19	-59.65
$\mathbf{3}_b$	-H	$-OCH_3$	$-OCH_3$	-H	38.73 ± 3.09	-31.46
$\mathbf{3}_c$	-H	$-NO_2$	-H	-H	46.15 ± 3.78	-18.33
$\mathbf{3}_d$	-H	$-OCH_3$	-OH	-H	25.41 ± 2.84	-55.03
$\mathbf{3}_e$	-H	-Br	-H	-H	48.48 ± 6.16	-14.20
$\mathbf{5}_a$	-H	-H	$-N(CH_3)_2$	-H	35.83 ± 4.26	-36.59
$\mathbf{5}_b$	-Cl	-H	-H	-H	50.75 ± 4.29	-10.19
$\mathbf{5}_c$	$-OCH_3$	-H	$-OCH_3$	$-OCH_3$	32.48 ± 4.80	-42.52
$\mathbf{5}_d$	-H	-H	$-NO_2$	-H	49.35 ± 4.44	-12.67
$\mathbf{5}_e$	-H	-H	$-CH_3$	-H	41.75 ± 2.53	-26.11
Clomipramine (10mg/kg)	–	–	–	–	33.58 ± 4.90	-40.57
Clomipramine (20 mg/kg)	–	–	–	–	18.80 ± 1.59	-66.73
Tranylcypromine (10 mg/kg)	–	–	–	–	27.55 ± 5.16	-51.24
Tranylcypromine (20 mg/kg)	–	–	–	–	15.66 ± 2.36	-72.28
Control (vehicle)	–	–	–	–	56.51 ± 5.25	–

[a]Compounds were tested at 100 mg/kg dose level, i.p.

[b]95 % Confidence limits (Dunnet's test), n = 6

forced swimming induced behavioural despair model is capable of predicting a variety of potential antidepressants, yet it is not devoid of biases. However, its validity is unclear, because, it gives false-positive results in cylinders with 10 cm diameter in the case of central nervous system (CNS) stimulants, anticholinergics and antihistaminics. Moreover, mice in the 10 cm chambers touch the cylinder wall and bottom with their fore and hind paws. Therefore the data may not reflect the true immobility times. In the modified behavioural despair test method[23], with an increase in diameter of the cylinder, mice loss their chance to touch the sides and the bottom of the cylinder and thus, are forced to swim and the duration of immobility in 30 cm diameter cylinders was significantly lower than in 10 cm cylinders. The most striking result obtained by increasing the diameter of the cylinder was that the anticholinergics, antihistaminics and CNS stimulants did not give false-positive results when the duration of immobility was used as the criterion. Parmar *et al.*[3] investigated the ability of some substituted pyrazolines to inhibit rat brain MAO and indicated that the presence of electron donating substituent on the phenyl ring present at position 5 of the pyrazoline ring produced a relatively higher degree of MAO Inhibition while electron with drawing substituents produced a lesser degree of enzyme inhibition.

In general most of the compounds showed significant antidepressant activity in mice at 100 mg/kg dose level. Compounds 3-(3''-coumarinyl)-1-phenyl-5-(2',4',5'-trimethylphenyl)-2-pyrazoline (**3**$_a$), 3-(3''-coumarinyl)-1-phenyl-5(4'-hydroxy-3'-methoxyphenyl)-2-pyrazoline (**3**$_d$) , 1-phenyl-3-(2''-hydroxynapthalen-1''-yl)-5-(2',4',5'-trimethoxyphenyl)-2-pyrazoline (**5**$_c$), 1-phenyl-3-(2''-hydroxynaphthalen-1''-yl)-5-(4'-dimethylamino phenyl)-2-pyrazoline (**5**$_a$) reduced 36.59-59.65 % immobility times at 100 mg/kg dose level. It was observed as expected that some of the 2-pyrazolines derived from 3-acetyl coumarin showed grater activity than those derived from 2-hydroxy-1-acetonapthone. In addition it was found that the compounds possessing electron releasing groups such as dimethyl amino, methoxy and hydroxyl substituent, on both the rings at position 3 and 5 of pyrazolines, considerably enhanced the antidepressant activity when compared to the pyrazolines having no substituents on the rings. The antidepressant evaluation of the compounds is presented in Table-1.

ACKNOWLEDGEMENTS

The authors thank the Head, Sophisticated Instrumentation Facility, Indian Institute of Sciences, Bangalore for ^{1}H NMR spectra and to Sipra Laboratories Hyderabad for IR spectra and financial support. Acknowledgement are also due to Dr. A. Annapurna, Associate Professor in Pharmacology in carrying out the antidepressant activity.

REFERENCES

1. L.G. Polevoi, Tr. Nauchn. Konf. Aspir. Ordin.: 1-yi (Peruyi) Mosk. Med. Inst.: Moscow, 159 (1964); *Chem. Abstr.*, **65**, 19147d (1996).
2. Y.M. Batulin, *Farmakol. Toksikol.*, **3**, 533 (1968); *Chem. Abstr.*, **70**, 2236a (1969).
3. S.S. Parmar, B.R. Pandey, C. Dwivedi and R.D. Harbinson, *J. Pharm. Sci.*, **63**, 1152 (1974).
4. N. Soni, K. Pande, R. Kalsi, T.K. Gupta, S.S. Parmar and J.P. Barthwal, *Res. Commun. Chem. Pathol. Pharm.*, **56**, 129 (1987).
5. G. Turan-Zitouni, P. Chevallet, F.S. Kilic and K. Erol, *Eur. J. Med. Chem.*, **35**, 635 (2000).
6. E. Palaska, M. Aytemir, I.T. Uzbay, T. Uzbay and D. Erol, *Eur. J. Med. Chem.*, **36**, 539 (2001).
7. J.R.S. Hoult and M. Payd, *Gen. Pharmacol.*, **27**, 713 (1996).
8. G. Carmela, C. Marco, L. Francesco, W. Peter, C.P. Alain, A. Cosimo, C. Angelo, T. Bernard, *J. Med. Chem.*, **43**, 4747 (2000).
9. C.F. Hossain, E. Okuyama and M. Yamazaki, *Chem. Pharm. Bull.*, **44**, 1535 (1996).
10. B. Rendenbach-Muller, R. Schlecker, M. Traut and H. Weifenbach, *Bioorg. Med. Chem. Lett.*, **4**, 1195 (1994).
11. R.I. Shader and D.J. Greenblatt, *J. Clin. Psychopharm.*, **19**, 105 (1999).
12. L.J. Urichuk, K. Allison, A. Holt, A.J. Greenshaw and G.B. Baker, *J. Affec. Disord.*, **58**, 135 (2000).
13. A. Fitton, D. Faulds and K. Goa, *Drugs*, **43**, 561 (1992).
14. M. Ferigolo, H.M. Barros, A.R. Marquardt and M. Tanhauser, *Pharmacol. Biochem. Behav.*, **60**, 431 (1998).
15. A.A. Bilgin, E. Palaska and R. Sunal, *Arzneim. Forsch. (Drug Res).*, **43**, 1041 (1993).
16. A.A. Bilgin, E. Palaska, R. Sunal and B. Gumusel, *Pharmazie*, **49**, 67 (1994).
17. W. Dawey and D.J. Tivey, *J. Chem. Soc.*, 1320 (1958).
18. E.P. Kohler and H.M. Chadwell, in eds.: H. Gilman and A. H. Blatt, Organic Syntheses Coll, John Wiley and Sons, New York, Vol. 1, pp. 78 (1967).
19. H.S. Mehra, *J. Indian. Chem. Soc.*, **45**, 178 (1968).
20. R.D. Porsolt and A. Bertin, *Arch. Int. Pharmacodyn.*, **229**, 327 (1977).
21. R.D. Porsolt, in: eds.: S.J. Enna, J.B. Malick and E. Richelson, Antidepressants: Neurochemical, Behavioral and Clinical Perspectives, Raven Press, New York, p.121 (1981).
22. E. Palaska, D. Erol and R. Demirdamar, *Eur. J. Med. Chem.*, **31**, 43 (1996).
23. R. Sunal, B. Gumusel and S.O. Kayaalp, *Pharmacol. Biochem. Behav.*, **49**, 891 (1994).

(*Received*: 14 August 2006; *Accepted*: 24 April 2007) AJC-5624