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Synthesis and antidepressant activity of some 1,3,5-triphenyl-2-pyrazolines and 3-(2″-hydroxy naphthalen-1″-yl)-1,5-diphenyl-2-pyrazolines

Y. Rajendra Prasad,* A. Lakshmana Rao, L. Prasoona, K. Murali and P. Ravi Kumar

University College of Pharmaceutical Sciences, Andhra University, Visakapatnam 530003, Andhra Pradesh, India

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Abstract—Five new 1,3,5-triphenyl-2-pyrazolines were synthesised by reacting 1,3-diphenyl-2-propene-1-one with phenyl hydrazine hydrochloride and another five new 3-(2″-hydroxy naphthalen-1″-yl)-1,5-diphenyl-2-pyrazolines were synthesised by reacting 1-(2′-hydroxynaphthyl)-3-phenyl-2-propene-1-one with phenyl hydrazine hydrochloride. The structures of the compounds were proved 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.1-Phenyl-3-(2″-hydroxyphenyl)-5-(4′-dimethylaminophenyl)-2-pyrazoline, 5-(4′-dimethylaminophenyl)-1,3-diphenyl-2-pyrazoline, 1-phenyl-3-(2″-hydroxynaphthalen-1″-yl)-5-(3′,4′,5′-trimethoxyphenyl)-2-pyrazoline, 1-phenyl-3-(4″-methylphenyl)-5-(4′-dimethylaminophenyl)-2-pyrazoline and 1-phenyl-3-(4″-bromophenyl)-5-(4′-dimethyl amino phenyl)-2-pyrazoline reduced immobility times 25.63–59.25% at 100 mg/kg dose level. In addition, it was found that the compounds possessing electron-releasing groups such as dimethyl amino, methoxy and hydroxyl substituents, on both the aromatic rings at positions 3 and 5 of pyrazolines, considerably enhanced the antidepressant activity when compared to the pyrazolines having no substituents on the phenyl rings.

Considerable interest has been focused on the pyrazoline structure, which has been known to possess a broad spectrum of biological activities such as tranquillizing, muscle relaxant, psychoanaleptic, anticonvulsant, antihypertensive, and antidepressant activities.[1–6] The discovery of this class of drugs provides an outstanding case history 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 (MAO) inhibitors having hydrazide, hydrazine, and amine moiety such as isocarboxazide,[7] phenelzine,[8] and meclobemide[9,10] 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 synthesised 2-pyrazoline derivatives are very similar to those of isocarboxazid (Fig. 1). 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.[11–14] As part of our efforts in this area, a series of some new 1-phenyl-3-(2″ and/or 4″-substituted phenyl)-5-(3′-and/or 4′-substituted phenyl)-2-pyrazolines and 1-(phenyl)-5-(2′- and/or 3′- and/or 4′-substituted phenyl)-3-(2″-hydroxy-naphthalen-1″-yl)-2-pyrazolines have been synthesised and evaluated for their antidepressant activities using 'Behavioural despair test'.

In the present work, 1,3-diphenyl-2-propen-1-ones ($\mathbf{1}_{a–e}$) and 1-(2′-hydroxy naphthyl)-3-phenyl-2-propene-1-ones were synthesised by condensing appropriate acetophenones with benzaldehyde derivatives in dilute ethanolic potassium hydroxide solution at room temperature according to Claisen–Schmidt condensation.[15–17] The 1,3,5-triphenyl-2-pyrazolines ($\mathbf{2}_{a–e}$) were synthesised by

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* Corresponding author. Tel.: +91 891 2504224; fax: +91 891 2525611; e-mail: dryrp@rediffmail.com

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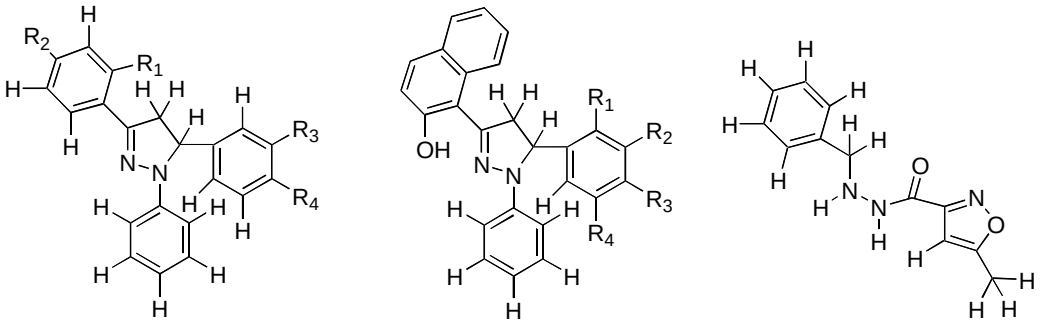


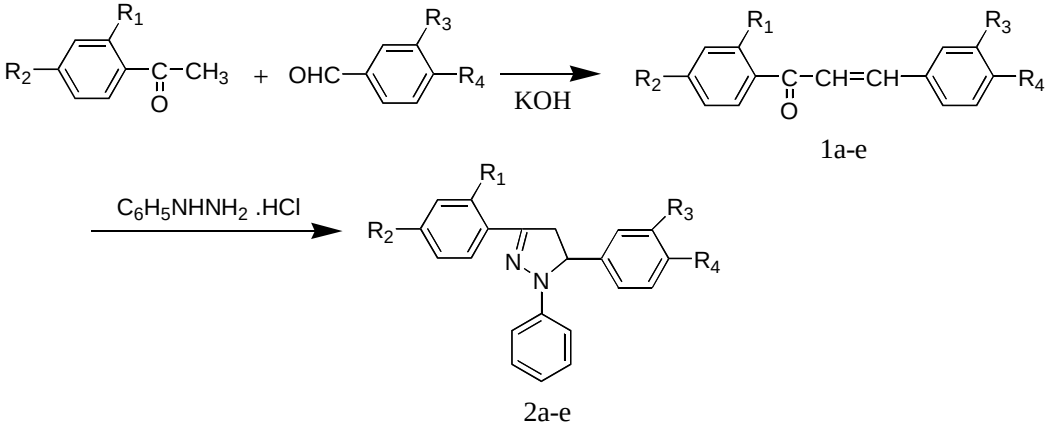
1,3,5-Triphenyl-2-pyrazolines **(2_{a-e})** 3-(2"-hydroxy napthalen-1"-yl) -1,5-diphenyl-2-pyrazolines (**4_{a-e}**) Isocarboxazid

Figure 1. Structures of 1,3,5-triphenyl-2-pyrazolines (2_{a-e}), 3-(2″-hydroxy naphthalen-1″-yl)-1,5-diphenyl-2-pyrazolines (4_{a-e}) and isocorboxazid.

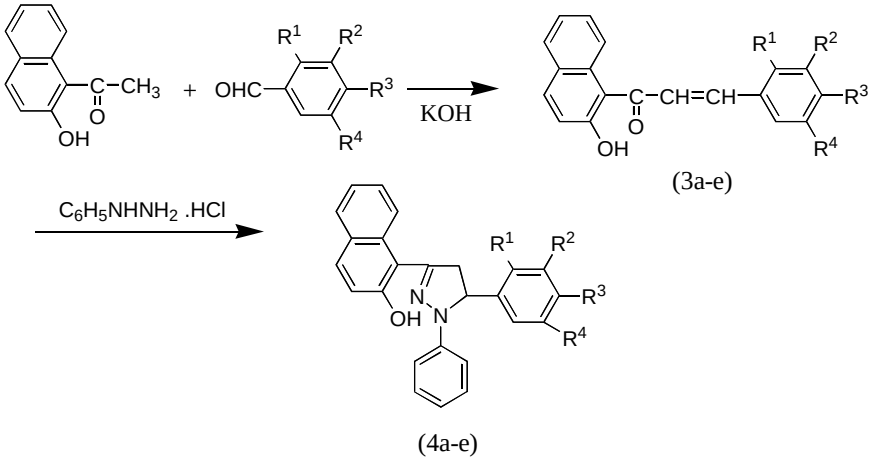
the reaction of 0.01 mol of appropriate 1,3-diphenyl-2-propen-1-one derivatives ($1_{a–e}$) in 15 ml ethanol with 0.02 mol phenyl hydrazine hydrochloride according to the condensation reaction of unsaturated ketones with hydrazines. 3-(2″-Hydroxy naphthalen-1″-yl)-1,5-diphenyl-2-pyrazolines ($4_{a–e}$) were synthesised by the reaction of appropriate 1-(2′-hydroxy naphthyl)-3-phenyl-2-propene-1-ones ($3_{a–e}$) with phenyl hydrazine hydrochloride in a similar way in yields varying from 78% to 91% (Schemes 1 and 2).

Structure and chemical data of the synthesised compounds are given in Table 1. IR spectra of the compounds showed C=N stretching band at 1590 cm^{-1}. In the ^1H NMR spectra, H_A, H_B and H_x protons of the pyrazoline ring were seen as doublet of doublets at 3.07–3.25, 3.75–3.88, and 5.15–5.30 ppm (J_{AB} = 17, J_{AX} = 7 and J_{BX} = 10 Hz). The protons belonging to the aromatic ring and substituent groups were observed within the expected chemical shift values (Table 2).

The synthesised compounds were evaluated for antidepressant activity in Adult male albino Swiss-Webster mice by using the Porsolt behavioural despair test. This test is effective in predicting the antidepressant activity of a wide variety of new molecules.[18,19] The Porsolt 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,[20] with an increase in diameter of the cylinder, mice lose 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, antihistiminics, 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

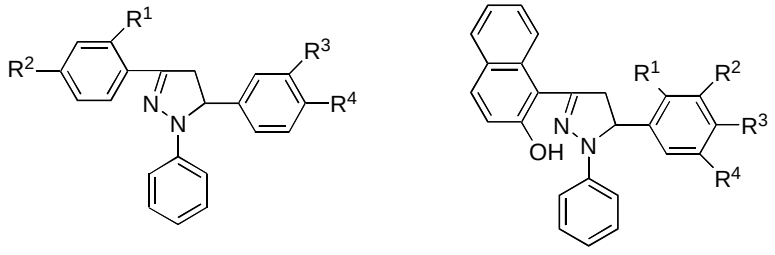


Scheme 1. Synthesis of 1,3,5-triphenyl-2-pyrazolines.



Scheme 2. Synthesis of 3-(2″-hydroxy naphthalen-1″-yl)-1,5-diphenyl-2-pyrazolines.

Table 1. Structure and chemical data of the compounds $\mathbf{2}_{a–e}$ and $\mathbf{4}_{a–e}$



(2_{a-e}) **(4_{a-e})**

Compound	R^1	R^2	R^3	R^4	Formula	Melting point (°C)	Yield (%)
$\mathbf{2}_a$	–H	–H	–H	$–N(CH_3)_2$	$C_{23}H_{23}N_3$(C,H,N)[a]	120	80
$\mathbf{2}_b$	–H	$–CH_3$	–H	$–N(CH_3)_2$	$C_{24}H_{25}N_3$(C,H,N)	140	78
$\mathbf{2}_c$	–OH	–H	–H	$–N(CH_3)_2$	$C_{23}H_{23}N_3O$(C,H,N)	178	85
$\mathbf{2}_d$	–H	–Br	–H	$–N(CH_3)_2$	$C_{23}H_{22}N_3Br$(C,H,N)	172	89
$\mathbf{2}_e$	–H	–OH	–Br	–H	$C_{21}H_{17}BrN_2O$(C,H,N)	128	79
$\mathbf{4}_a$	–H	–H	–H	–H	$C_{25}H_{20}N_2O$(C,H,N)	238	84
$\mathbf{4}_b$	–H	–H	$–OCH_3$	–H	$C_{26}H_{22}N_2O_2$(C,H,N)	240	91
$\mathbf{4}_c$	–H	–H	–Cl	–H	$C_{25}H_{19}ClN_2O$(C,H,N)	246	83
$\mathbf{4}_d$	–H	–H	–Br	–H	$C_{25}H_{19}BrN_2O$(C,H,N)	252	86
$\mathbf{4}_e$	–H	$–OCH_3$	$–OCH_3$	$–OCH_3$	$C_{28}H_{26}N_2O_4$(C,H,N)	258	90

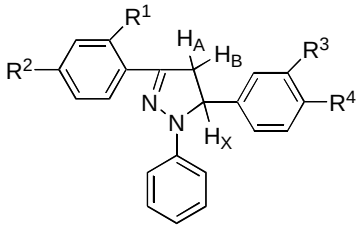
[a] Elemental analyses for C, H and N are within ± 0.4% of the theoretical values.

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-withdrawing substituents produced a lesser degree of enzyme inhibition.

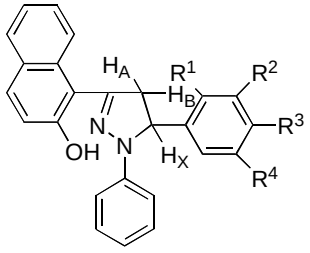
The mice (22 ± 2 g) were housed in plexiglass cages with six animals for each cage in a quiet and temperature and humidity controlled room (22 ± 3 °C and 60 ± 5%, respectively) in which a 12 h light dark cycle was maintained (08:00–20:00 h light). On the testing day, mice were assigned to different groups ($n = 6$ for each group). The synthesised compounds and the standard drug clomipramine were suspended in aqueous Tween 80 (0.2% w/v, 0.9% NaCl). All the synthesised compounds (100 mg kg^{-1}) and clomipramine (10 and 20 mg kg^{-1}) were injected intraperitoneally to mice at a volume of 0.5 ml per 100 g body weight. One hour later, 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 were measured in the next 4 min period.

From the results it may be observed that compounds 1-phenyl-3-(2″-hydroxyphenyl)-5-(4′-dimethylaminophenyl)-2-pyrazoline, 5-(4′-dimethylaminophenyl)-1,3-diphenyl-2-

Table 2. Spectral data of compounds $\mathbf{2}_{a-e}$and $\mathbf{4}_{a-e}$



$\mathbf{2}_{a-e}$



$\mathbf{4}_{a-e}$

Compound	IR (KBr, cm^{-1})	^1H NMR ($CDCl_3$, ppm)[a]
$\mathbf{2}_a$	1600, 1520 (C=C, C=N); 1065 (C–N)	2.92 (6H, s, $-N(CH_3)_2$), 3.11 (1H, dd, H_A), 3.80 (1H, dd, H_B), 5.23 (1H, dd, H_X), 6.69–7.87 (14H, m, Ar-H), (J_{AB} = 16.98, J_{AX} = 7.50, J_{BX} = 9.35 Hz)
$\mathbf{2}_b$	1595, 1522 (C=C, C=N); 1070 (C–N)	2.37 (3H, s, Ar-CH_3), 2.92 (6H, S, $-N(CH_3)_2$), 3.11 (1H, dd, H_A), 3.78 (1H, dd, H_B), 5.17 (1H, dd, H_X), 6.67–7.63 (13H, m, Ar-H), (J_{AB} = 16.50, J_{AX} = 7.80, J_{BX} = 9.90 Hz)
$\mathbf{2}_c$	3100 (–OH); 1600, 1520 (C=C, C=N); 1075 (C–N)	2.92 (6H, s, $-N(CH_3)_2$), 3.25 (1H, dd, H_A), 3.88 (1H, dd, H_B), 5.15 (1H, dd, H_X), 10.85 (1H, s, C-2-OH), 6.65–7.28 (13H, m, Ar-H), (J_{AB} = 16.92, J_{AX} = 6.98, J_{BX} = 9.80 Hz)
$\mathbf{2}_d$	1605, 1525 (C=C, C=N); 1080 (C–N); 855 (–C–Br)	2.92 (6H, s, $-N(CH_3)_2$), 3.10 (1H, dd, H_A), 3.75 (1H, dd, H_B), 5.22 (1H, dd, H_X), 6.74–7.60 (13H, m, Ar-H), (J_{AB} = 17.05, J_{AX} = 7.10, J_{BX} = 9.65 Hz)
$\mathbf{2}_e$	3100 (–OH); 1605, 1522 (C=C, C=N); 1081 (C–N); 857 (–C–Br)	3.15 (1H, dd, H_A), 3.80 (1H, dd, H_B), 5.15 (1H, dd, H_X), 6.74–7.80 (13H, m, Ar-H), (J_{AB} = 17.25, J_{AX} = 7.30, J_{BX} = 9.67 Hz)
$\mathbf{4}_a$	3100 (–OH); 1640 (C=N); 1350 (C–N)	3.07 (1H,dd, H_A), 3.85 (1H, dd, H_B), 5.30 (1H, dd, H_X), 6.80–7.95 (15H, m, Ar-H), 9.90 (1H, d, J = 9 Hz, C-8-H), 10.30 (1H, s, C-2-OH), (J_{AB} = 16.78, J_{AX} = 6.95, J_{BX} = 9.35 Hz)
$\mathbf{4}_b$	3110 (–OH); 1642 (C=N); 1355 (–C–N); 1160 ($-OCH_3$)	3.12 (1H, dd, H_A), 3.76 (1H, dd, H_B), 3.90 (3H, s, C-4-OCH_3), 5.28 (1H, dd, H_X), 9.70 (1H, d, J = 9Hz, C-8-H), (J_{AB} = 17.10, J_{AX} = 6.90, J_{BX} = 9.48 Hz)
$\mathbf{4}_c$	3050 (–OH); 1645 (C=N); 1350 (–C–N); 855 (–C–Cl)	3.08 (1H, dd, H_A), 3.78 (1H, dd, H_B), 5.15 (1H, dd, H_X), 6.90–7.90 (14H, m, Ar-H), 9.70 (1H, d, J = 9 Hz, C-8-H), (J_{AB} = 17.05, J_{AX} = 6.99, J_{BX} = 9.35 Hz)
$\mathbf{4}_d$	3050 (–OH); 1640 (C=N); 1352 (–C–N); 860 (–C–Br)	3.16 (1H, dd, H_A), 3.88 (1H, dd, H_B), 5.25 (1H, dd, H_X), 6.80–7.90 (14H, m, Ar-H), 9.50 (1H, d, J = 9 Hz, C-8-H), 13.50 (1H, s, C-2-OH), (J_{AB} = 16.88, J_{AX} = 7.89, J_{BX} = 10.25 Hz)
$\mathbf{4}_e$	3120 (–OH); 1640 (C=N); 1350 (–C–N); 1180 ($-OCH_3$)	3.11 (1H, dd, H_A), 3.86 (3H, s, $-O-CH_3$), 3.85 (1H, dd, H_B), 3.90 (6H, s, 2×-O–CH_3), 5.24 (1H, dd, H_X), 9.72 (1H, d, J = 9 Hz, C-8-H), 6.90–7.95 (12H, m, Ar-H), (J_{AB} = 17.38, J_{AX} = 7.48, J_{BX} = 9.62 Hz)

[a] s, singlet; dd, doublet of doublets; m, multiplet.

pyrazoline, 1-phenyl-3-(2″-hydroxynaphthalen-1″-yl)-5-(3′,4′,5′-trimethoxyphenyl)-2-pyrazoline,1-phenyl-3-(4″-methylphenyl)-5-(4′-dimethylaminophenyl)-2-pyrazoline and 1-phenyl-3-(4″-bromophenyl)-5-(4′-dimethyl aminophenyl)-2-pyrazoline reduced immobility times 25.63–59.25% at 100 mg kg^{-1} dose level. The results revealed that the compounds possessing electron-releasing groups such as dimethylamino, methoxy, and hydroxyl substituents, on both the aromatic rings at positions 3 and 5 of pyrazolines, considerably enhanced the antidepressant activity when compared to the pyrazolines having no substituents on the phenyl rings and this is consistent with the observation made earlier by Parmar et al.[3] (Table 3).

Statistical significance was set at $P < 0.05$ level. Changes in duration of immobilizations expressed as means ± SEM were evaluated using Dunnet's test (Pharmacological Calculation System, version 4.1).

Table 3. Antidepressant activity of the compounds

Compound[a]	Duration of immobility(s)	% change from control[b]
$\mathbf{2}_a$	22.95 ± 4.21	−59.25
$\mathbf{2}_b$	50.15 ± 5.45	−10.95
$\mathbf{2}_c$	35.85 ± 4.20	−36.34
$\mathbf{2}_d$	41.88 ± 2.86	−25.63
$\mathbf{2}_e$	32.46 ± 4.63	−42.18
$\mathbf{4}_a$	50.33 ± 6.88	−10.63
$\mathbf{4}_b$	50.78 ± 4.58	−9.83
$\mathbf{4}_c$	46.28 ± 4.39	−17.82
$\mathbf{4}_d$	25.40 ± 3.33	−54.10
$\mathbf{4}_e$	49.26 ± 4.70	−12.53
Clomipramine (10 mg/kg)	33.81 ± 3.98	−39.96
Clomipramine (20 mg/kg)	18.68 ± 2.25	−66.93
Control (Vehicle)	56.32 ± 7.14	—

[a] Compounds were tested at 100 mg kg^{-1} dose level, ip.
[b] 95% confidence limits (Dunnet's test), $n = 6$.

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