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Research Article

SYNTHESIS AND ANALGESIC ACTIVITY OF SOME 1, 3, 5-TRISUBSTITUTED-2-PYRAZOLINES

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ABSTRACT

Fifteen new 1, 3, 5-trisubstituted-2-pyrazolines were synthesized by reacting various chalcones with phenylhydrazine hydrochloride. The required chalcones were prepared by condensation of 3'-methyl-4'-hydroxyacetophenone with various substituted aromatic / heteroaromatic aldehydes in the presence of alkali. The structures of the compounds were proved by means of their IR, ^{1}H NMR spectroscopic data and microanalysis. The analgesic activity of these compounds was evaluated by tail flick method in albino rats. It was found that compounds possessing electron releasing groups on both the aromatic rings considerably enhanced the analgesic activity when compared to the pyrazolines having no substituent.

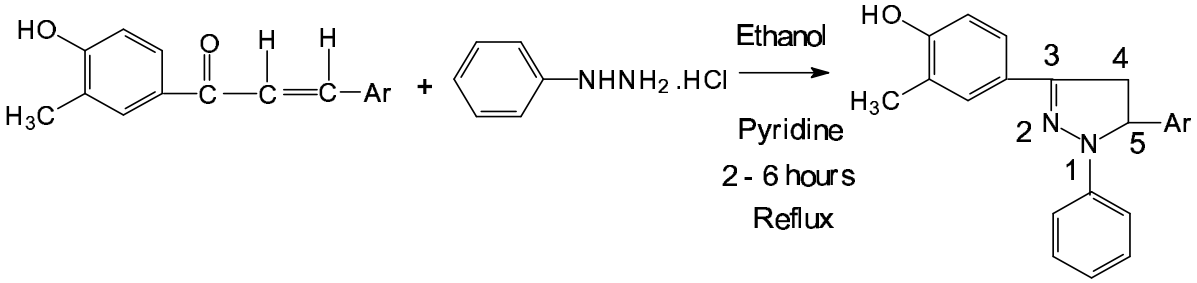
Keywords: Pyrazolines, Synthesis, Analgesic activity

INTRODUCTION

Considerable interest has been focused on the pyrazoline structure, which has been known to possess a broad spectrum of biological activities such as analgesic, anti-inflammatory, antimicrobial, tranquilizing, muscle relaxant, psycho-analeptic, anticonvulsant, antihypertensive and antidepressant activities[1-6]. A series of some new 1, 3, 5-trisubstituted-2-pyrazolines have been synthesized and evaluated for their analgesic activity.

EXPERIMENTAL

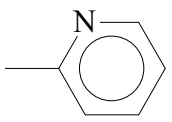
In the present work, chalcones were synthesized by condensing 3'-methyl-4'-hydroxyacetophenone with various substituted aromatic / hetero-aromatic aldehydes in ethanolic potassium hydroxide solution at room temperature according to Claisen-Schmidt condensation.[7-12]. The 1,3,5-trisubstituted-2-pyrazolines (B_1PY_1-$B_{15}PY_{15}$) were synthesized by the reaction of 0.001 mol of appropriate chalcone in 15 ml ethanol with 0.002 mol phenylhydrazine hydrochloride according to condensation reaction of unsaturated ketones with hydrazines[13,14] (Scheme1). The chemical and spectral data of the compounds (B_1PY_1- $B_{15}PY_{15}$) are given in Tables 1 and 2.



Chalcone (**B_1-B_{15}**) | Phenylhydrazine hydrochloride | 1, 3, 5- tri-substituted-2-pyrazoline

Scheme 1

Where Ar =



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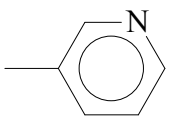

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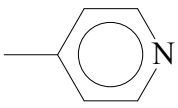

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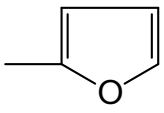

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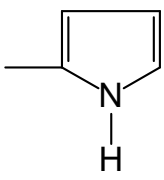

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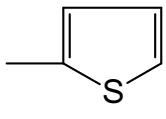

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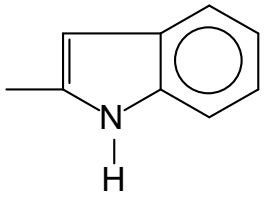

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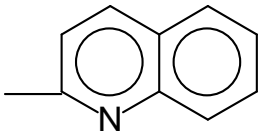

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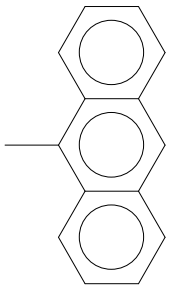

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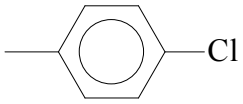
B_{10}



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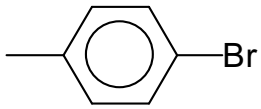

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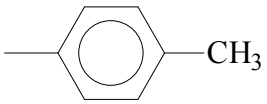

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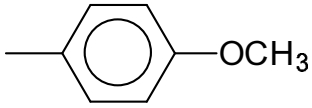
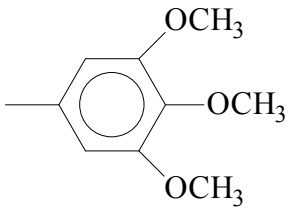


B_{14}



B_{15}

Table 1: Physical characterization data of pyrazolines

Compound	Ar	Molecular Formula	m. p (^{0}C)	Yield (%)
B_1PY_1	2''-pyridinyl	$C_{21}H_{19}N_3O$ (C,H,N)[a]	208	78
B_2PY_2	3''-pyridinyl	$C_{21}H_{19}N_3O$ (C,H,N)	213	75
B_3PY_3	4''-pyridinyl	$C_{21}H_{19}N_3O$ (C,H,N)	202	77
B_4PY_4	2''-furyl	$C_{20}H_{18}N_2O_2$ (C,H,N)	187	72
B_5PY_5	2''-pyrrolyl	$C_{20}H_{19}N_3O$ (C,H,N)	243	70
B_6PY_6	2''-thienyl	$C_{20}H_{18}N_2SO$ (C,H,N)	205	76
B_7PY_7	2''-indolyl	$C_{24}H_{21}N_3O$ (C,H,N)	226	65
B_8PY_8	2''-quinolinyl	$C_{25}H_{21}N_3O$ (C,H,N)	216	68
B_9PY_9	9''-anthracenyl	$C_{30}H_{24}N_2O$ (C,H,N)	198	67
$B_{10}PY_{10}$	4''-fluorophenyl	$C_{22}H_{19}N_2FO$ (C,H,N)	235	70
$B_{11}PY_{11}$	4''-chlorophenyl	$C_{22}H_{19}N_2ClO$ (C,H,N)	242	71
$B_{12}PY_{12}$	4''-bromophenyl	$C_{22}H_{19}N_2BrO$ (C,H,N)	249	69
$B_{13}PY_{13}$	4''-methylphenyl	$C_{23}H_{22}N_2O$ (C,H,N)	204	67
$B_{14}PY_{14}$	4''-methoxyphenyl	$C_{23}H_{22}N_2O_2$ (C,H,N)	220	66
$B_{15}PY_{15}$	3'',4'',5''-tri-methoxyphenyl	$C_{25}H_{26}N_2O_4$ (C,H,N)	255	72

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

Table 2: IR and ^{1}H NMR spectral data of pyrazolines

Compound	IR (KBr, cm^{-1})	^{1}H NMR ($CDCl_3$, ppm)*
B_1PY_1	3406 (O-H)	3.05 (1H, dd, H_A)
	1594 (C=N)	3.60 (1H, dd, H_M)
	1494 (C=C Quadrant of Ar)	5.36 (1H, dd, H_X)
	1437 (CH=CH)	2.31 (3H, s, C-3'-CH_3)
		5.50 (1H, s, Ar-OH)
		6.79 – 8.15 (12H, Ar-H)
B_2PY_2	3404 (O-H)	3.15 (1H, dd, H_A)
	1595 (C=N)	3.90 (1H, dd, H_M)
	1495 (C=C Quadrant of Ar)	5.40 (1H, dd, H_X)
	1436 (CH=CH)	2.31 (3H, s, C-3'-CH_3)
		5.50 (1H, s, Ar-OH)
		6.79 – 7.68 (12H, Ar-H)
B_3PY_3	3405 (O-H)	3.25 (1H, dd, H_A)
	1593 (C=N)	3.75 (1H, dd, H_M)
	1496 (C=C Quadrant of Ar)	5.40 (1H, dd, H_X)

	1435 (CH=CH)	2.31 (3H, s, C-3'-CH_3) 5.50 (1H, s, Ar-OH) 6.79 – 7.75 (12H, Ar-H)
B_4PY_4	3403 (O-H) 1596 (C=N) 1493 (C=C Quadrant of Ar) 1437 (CH=CH) 1205 (-C-O-)	3.15 (1H, dd, H_A) 3.85 (1H, dd, H_M) 5.30 (1H, dd, H_X) 2.31 (3H, s, C-3'-CH_3) 5.50 (1H, s, Ar-OH) 6.21 – 7.65 (11H, Ar-H)
B_5PY_5	3401 (O-H) 1594 (C=N) 1492 (C=C Quadrant of Ar) 1436 (CH=CH)	3.20 (1H, dd, H_A) 3.79 (1H, dd, H_M) 5.30 (1H, dd, H_X) 2.31 (3H, s, C-3'-CH_3) 5.50 (1H, s, Ar-OH) 6.70 – 7.62 (12H, Ar-H)
B_6PY_6	3406 (O-H) 1597 (C=N) 1495 (C=C Quadrant of Ar) 1435 (CH=CH) 690 (C-S)	3.25 (1H, dd, H_A) 3.77 (1H, dd, H_M) 5.50 (1H, dd, H_X) 2.31 (3H, s, C-3'-CH_3) 5.50 (1H, s, Ar-OH) 6.89 – 7.67 (11H, Ar-H)
B_7PY_7	3403 (O-H) 1596 (C=N) 1494 (C=C Quadrant of Ar) 1438 (CH=CH)	3.15 (1H, dd, H_A) 3.85 (1H, dd, H_M) 5.30 (1H, dd, H_X) 2.31 (3H, s, C-3'-CH_3) 5.50 (1H, s, Ar-OH) 6.79 – 7.68 (14H, Ar-H)
B_8PY_8	3407 (O-H) 1595 (C=N) 1492 (C=C Quadrant of Ar) 1437 (CH=CH)	3.15 (1H, dd, H_A) 3.85 (1H, dd, H_M) 5.38 (1H, dd, H_X) 2.31 (3H, s, C-3'-CH_3) 5.50 (1H, s, Ar-OH) 6.45 – 7.95 (14H, Ar-H)
B_9PY_9	3401 (O-H) 1597 (C=N) 1495 (C=C Quadrant of Ar) 1439 (CH=CH)	3.10 (1H, dd, H_A) 3.92 (1H, dd, H_M) 5.60 (1H, dd, H_X) 2.31 (3H, s, C-3'-CH_3) 5.50 (1H, s, Ar-OH) 6.79 – 7.69 (17H, Ar-H)
$B_{10}PY_{10}$	3405 (O-H) 1593 (C=N) 1491 (C=C Quadrant of Ar) 1439 (CH=CH) 1122 (C-F)	3.15 (1H, dd, H_A) 3.85 (1H, dd, H_M) 5.40 (1H, dd, H_X) 2.31 (3H, s, C-3'-CH_3) 5.50 (1H, s, Ar-OH) 6.79 – 7.67 (12H, Ar-H)
$B_{12}PY_{12}$	3402 (O-H) 1594 (C=N) 1493 (C=C Quadrant of Ar) 1436 (CH=CH) 1024 (C-Br)	3.40 (1H, dd, H_A) 3.90 (1H, dd, H_M) 5.40 (1H, dd, H_X) 2.31 (3H, s, C-3'-CH_3) 5.50 (1H, s, Ar-OH) 6.79 – 7.48 (12H, Ar-H)
$B_{13}PY_{13}$	3409 (O-H) 1591 (C=N) 1492 (C=C Quadrant of Ar) 1433 (CH=CH)	3.15 (1H, dd, H_A) 3.75 (1H, dd, H_M) 5.30 (1H, dd, H_X) 2.31 (3H, s, C-3'-CH_3) 2.15 (3H, s, C-4''-CH_3) 5.50 (1H, s, Ar-OH) 6.79 – 7.44 (12H, Ar-H)
$B_{14}PY_{14}$	3403 (O-H) 1592 (C=N) 1497 (C=C Quadrant of Ar) 1435 (CH=CH) 1072 (-O-CH_3)	3.15 (1H, dd, H_A) 3.50 (1H, dd, H_M) 5.40 (1H, dd, H_X) 2.31 (3H, s, C-3'-CH_3) 3.74 (3H, s, C-4''-OCH_3) 5.50 (1H, s, Ar-OH) 6.79 – 7.67 (12H, Ar-H)
$B_{15}PY_{15}$	3401 (O-H) 1598 (C=N) 1495 (C=C Quadrant of Ar) 1438 (CH=CH) 1070 (-O-CH_3)	3.20 (1H, dd, H_A) 3.65 (1H, dd, H_M) 5.20 (1H, dd, H_X) 2.31 (3H, s, C-3'-CH_3) 3.85 (9H, s, 3 x -OCH_3) 5.50 (1H, s, Ar-OH) 6.51 – 7.67 (10H, Ar-H)

***** s, singlet; d, doublet; m, multiplet; dd, doublet of doublet

Analgesic activity

A number of pyrazolines were reported to possess significant analgesic activity and infact some of the drugs currently used in therapy possessed pyrazoline structure and hence it was felt worthwhile to screen the compounds synthesized in the present study for analgesic activity by tail flick method. The working procedure is described separately and the results are given in Table 3.

Experimental

Tail immersion test method / tail flick method[15,16] was adopted for evaluation of analgesic activity of the test compounds. The tail of the control, standard and test group animals (rats) was dipped in a beaker of water maintained 55 ± 1°C and the time taken to withdraw the tail clearly out of water is taken as the reaction time.

Requirements

Animals: Albino rats of either sex

Standard drug: Ibuprofen suspension in 2% v/v Tween 80 solution administered orally at the dose of 100 mg/kg body weight.

Samples*:* Test compounds were suspended in 2% v/v Tween 80 solution and administered orally at the dose of 100 mg/kg body weight. Water was heated in a beaker and the temperature was maintained at 55 ± 1 °C.

Working procedure

85 albino rats of either sex weighing between 150-200 grams were divided into 17 groups of 5 animals each and they were numbered individually. The animals were fasted for 24 hours before administering the drug with water *ad libitum.*

Group I was administered with only 2% v/v Tween 80 solution, which served as control. Group II was administered with 100 mg/kg body weight of ibuprofen suspension orally, which served as standard. Group III to group XVII were administered with test compounds respectively, the dose being 100 mg/kg body weight selected on the basis of the standard drug used. All the animal tails were dipped into a beaker containing water maintained at 55 ± 1 °C and the time taken for the animals to flick the tail from the hot water completely is recorded at 15 minutes, 30 minutes, 1 hour, 2 hours and 3 hours respectively.

The percentage of protection in the control, standard and drug treated animals were recorded and calculated by using the formula.

% Analgesic activity (PAA) = [(Rt/Rc) - 1] x 100

Where Rt and Rc are the reaction time in test and control respectively.

The results of analgesic activity of ibuprofen and the compounds tested are shown in Table 3.

Table 3: Analgesic activity of Pyrazolines

Com-pound	Ar	% Analgesic activity (PAA)				
		15min	30min	1 hour	2 hour	3 hour
B_1PY_1	2''-pyridinyl	75±1	86±1	101±1	113±1	125±1
B_2PY_2	3''-pyridinyl	74±1	82±1	96±1	107±1	121±1
B_3PY_3	4''-pyridinyl	74±1	81±1	93±1	105±1	118±1
B_4PY_4	2''-furyl	80±1	90±1	108±1	117±1	134±1
B_5PY_5	2''-pyrrolyl	81±1	93±1	112±1	120±1	136±1
B_6PY_6	2''-thienyl	78±1	88±1	105±1	115±1	130±1
B_7PY_7	2''-indolyl	82±1	95±1	116±1	123±1	141±1
B_8PY_8	2''-quinolinyl	70±1	78±1	89±1	102±1	115±1
B_9PY_9	9''-anthracenyl	63±1	75±1	85±1	100±1	113±1
$B_{10}PY_{10}$	4''-fluorophenyl	92±1	105±1	127±1	135±1	154±1
$B_{11}PY_{11}$	4''-chlorophenyl	89±1	102±1	123±1	131±1	150±1
$B_{12}PY_{12}$	4''-bromophenyl	85±1	97±1	120±1	128±1	145±1
$B_{13}PY_{13}$	4''-methylphenyl	94±1	106±1	130±1	136±1	156±1
$B_{14}PY_{14}$	4''-methoxyphenyl	96±1	108±1	133±1	139±1	158±1
$B_{15}PY_{15}$	3'',4'',5''-tri methoxyphenyl	99±1	111±1	137±1	143±1	162±1
Ibuprofen (standard)		103±1	114±1	149±1	160±1	174±1
Control		-	-	-	-	-

Values are expressed as mean ± SEM (n=5). *p<0.05; **p<0.01; ***p<0.001 compared to controls. Students's t-test

RESULTS AND DISCUSSION

All the 2-pyrazolines tested for analgesic activity showed considerable activity when compared to the standard drug ibuprofen. It is interesting to note that compound $B_{15}PY_{15}$ having 3, 4, 5-trimethoxyphenyl, compound $B_{14}PY_{14}$ having 4-methoxyphenyl, compound $B_{13}PY_{13}$ having 4-methylphenyl ring at the 5-position of the 2-pyrazoline ring possessed the maximum activity.

It clearly indicates the favorable effect of electron releasing substituents on the analgesic activity of the 2-pyrazolines. 2-pyrazolines having these substituents both on the aromatic and the heteroaromatic rings, if synthesized and tested, may possess significant analgesic activity. Literature reports also indicated the necessity of electron releasing groups in enhancing the analgesic activity. 2-Pyrazolines with a fluorine substituent (compound $B_{10}PY_{10}$) on the aromatic ring also enhanced the activity.

Hence, compounds having fluorine and other halogens at one or more positions of the aromatic rings can be synthesized to have compounds with much better activity.

REFERENCES

1. Polevoi, l.G.; tr.Nauchn. Konf.Aspir.Ordin; 1-yi (peruyi) Mosk. Med.Inst.; Moscow, 1964, 159; *Chem.Abstr*., 65, 19147d (1996).
2. Batulin, yu.M. farmakol.Toksikal.1968, 3, 533; batulin, Yu,M. *Chem.Abstr*.,70, 2236a (1969).
3. Parmar, S.S.; Pandey, B.R.; Dwivedi, C.; Harbinson, R.D. *J.Pharm.Sci.*, 63, 1152 (1974).
4. Soni,N.;pande,K.;kalsi,R;Gupta,T.K.;Parmar,S.S.;Barthwal,J.P. *Res.Commun.Chem.Pathol.Pharm*., 56, 129 (1987).
5. Yuran-Zitouni,G.; Chevallet,P.; Kilic,F.S.; Erol,K. *Eur.J.Med.Chem*., 35, 635 (2000).
6. Erhan, P.; Mutlu, A.; Tayfun, U.; Dilek, E.*J.Med.Chem*., 36, 539 (2001).
7. Min, J., Jiaxing, H., Weiyi, H. and Hongmen, H., *Ind. J. Chem.,* 40B, 1223 (2001).
8. Dawey, W. and Tivey, D., *J. Chem. Soc.,* 1320 (1958).
9. Kohler, H.M., Chadwell, H., Gillman, H., Blatt, A.H., in: *Organic Synthesis, Wiley Interscience*, New York, (Coll. Vol.I), 78 (1967).
10. Mehra, H.S. *et al., J. Ind. Chem. Soc*., 45, 178 (1968).

11. Climent, M.J., Corma, A., Iborra, S. and Primo, J., *J. Catal.,* 151, 60 (1995) .
12. Sogawa, S., Nihro, Y., Ueda, H., Izumi, A., Miki, T., Matsumosa, H. and Satoh T.*, J. Med Chem*., 36, 3904 (1993).
13. Shivarama, H.B., Shivananda, M.K. and Veerendra, B., *Ind. J. Het. Chem.*, 12, 135 (2002).
14. Jones, D.G., Liang, X., Stewart, E.L. and Noe, R.A., *Bioorg. Med. Chem. Lett.*, 3203 (2005).
15. 1Armarego, W.L.F., in: *Physical Methods in Heterocyclic Chemistry, Academic Press*, New York, 3, 90 (1971).
16. Vanderhaeghe, H. and Claesen, M., *Bull. Sci. Chim. Belg*., 66, 276 (1957).