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Synthesis and Pharmacological Activities of 3-(4-Substituted phenyl)-1-phenyl-1*H*-pyrazole-4-carboxaldehyde and Its Aldimines Derivatives

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A new series of heterocyclic compounds were achieved by the synthesis of 3-(4-substituted phenyl)-1-phenyl-1*H*-pyrazole-4-carboxaldehyde ($\mathbf{II}_{i\text{-}iv}$) was synthesized from 4-substituted acetophenone phenylhydrazone ($\mathbf{I}_{i\text{-}iv}$) by Vilsmeier-Haack reaction compound ($\mathbf{II}_{i\text{-}iv}$), which was further functionalized by condensation. The reaction with various substituted anilines in refluxed ethanol with trace of conc. acetic acid to give corresponding aldimines derivatives ($\mathbf{III}_{i\text{-}xii}$). The synthesized compounds were screened of their *in vivo* analgesic and anxiolytic activities in mice by acetic acid induced writhing test, elevated plus maze and light & dark exploration test in mice. The compound $\mathbf{III}_{vii}$, $\mathbf{III}_{ix}$ and $\mathbf{III}_{xii}$ showed very good anxiolytic activity, while compound no. $\mathbf{III}_{vi}$, $\mathbf{III}_{vii}$ and $\mathbf{III}_{x}$ showed very good analgesic activity.

Key Words: Substituted pyrazoles, Aldimines derivatives, Analgesic, Anxiolytic.

INTRODUCTION

The pyrazole nucleus in general its chemistry has found considerable attention during decades due to outstanding biological activities and pharmacological activities such as antianxiety[1], antipyretic, analgesic, antiinflammatory[2-4], as well as good antibacterial and antifungal properties[5-9]. These finding prompted us to synthesis new series of aldimines derivatives of 3-(4-substituted phenyl)-1-phenyl-1*H*-pyrazole-4-carboxaldehyde compounds ($\mathbf{III}_{i\text{-}xii}$) and screened for their pharmalogical activities. Several methods have been developed for the synthesis of pyrazole-4-carboxaldehyde. Kira *et al.*[10] reported the formation of pyrazole-4-carboxaldehyde by treating acetophenone phenylhydrazone with DMF/$POCl_3$ complex. It was two step reactions in which Vilsmeier-Haack reagent was used for cyclization.

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EXPERIMENTAL

Melting points were taken on Electro thermal digital melting point apparatus and are uncorrected. Single spotted TLC determined completion of reaction. IR spectra were recorded using KBR disc on a Jasco FTIR-410. ^{1}H NMR spectra were recorded in $CDCl_3$ solution on FT NMR, Varian mercury 300 MHz and proton chemical shift are relative to tetramethylsilane as internal standard.

Synthesis of 4-substituted acetophenone phenylhydrazone ($\mathbf{I_{i-iv}}$): Concentrated acetic acid (1 mL) and phenylhydrazine hydrochloride (0.028 mol) were added to solution of 4-substituted acetophenone (0.019 mol) in 60 mL of ethanol. The reaction mixture was then refluxed for 1 h. The precipitate was filtered, washed with ethanol and dried in vacuum. The analytical data of the synthesized compounds ($\mathbf{I_{i-iv}}$) are given in Table-1.

TABLE-1
ANALYTICAL DATA OF 4-SUBSTITUTED ACETOPHENONE PHENYLHYDRAZONE ($\mathbf{I_{i-iv}}$)

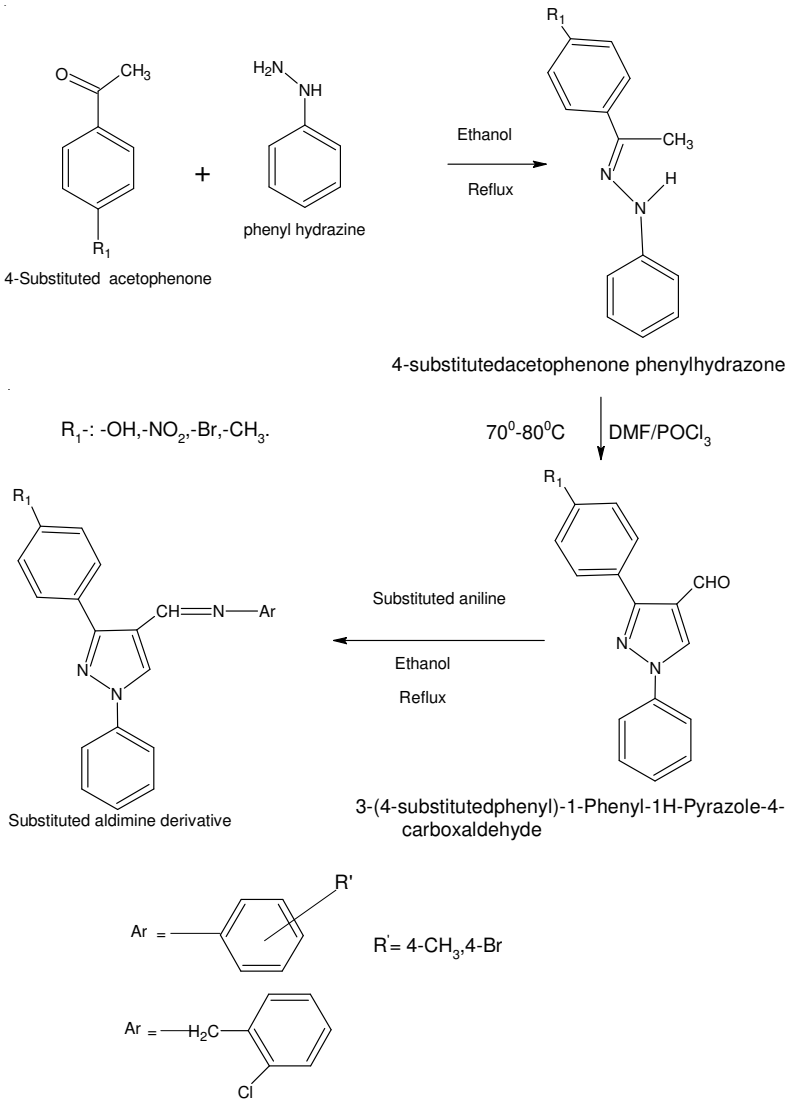
Compd.	R_1	Yield (%)	m.f.	m.p. (ºC)	R_f value
$\mathbf{I_i}$	-OH	63	$C_{14}H_{14}N_2O$	133	0.57
$\mathbf{I_{ii}}$	-Br	68	$C_{14}H_{13}N_2Br$	148	0.72
$\mathbf{I_{iii}}$	$-NO_2$	71	$C_{14}H_{13}N_3O_2$	143	0.67
$\mathbf{I_{iv}}$	$-CH_3$	74	$C_{15}H_{16}N_3$	109	0.62

Synthesis of 3-(4-substituted phenyl)-1-phenyl-1*H*-pyrazole-4-carboxaldehyde ($\mathbf{II_{i-iv}}$): A solution of **I** in DMF was added dropwise to the Vilsmeier-Haack reagent, which was then warmed at room temperature and refluxed for 8 h. After cooling at room temperature, the mixture was basified with a K_2CO_3 solution. The precipitate was filtered, washed thoroughly with water and recrystallized from ethanol. The analytical data of the synthesized compounds ($\mathbf{II_{i-iv}}$) are given in Table-2.

TABLE-2
ANALYTICAL DATA OF 3-(4-SUBSTITUTED PHENYL)-1-PHENYL-1*H*- PYRAZOLE-4- CARBOXALDEHYDE ($\mathbf{II_{i-iv}}$)

Compd.	R_1	Yield (%)	m.f.	m.p. (ºC)	R_f value
$\mathbf{II_i}$	-OH	63	$C_{16}H_{12}N_2O_2$	149	0.62
$\mathbf{II_{ii}}$	-Br	68	$C_{16}H_{11}N_2OBr$	159	0.67
$\mathbf{II_{iii}}$	$-NO_2$	71	$C_{16}H_{11}N_3O_3$	165	0.71
$\mathbf{II_{iv}}$	$-CH_3$	74	$C_{17}H_{14}N_2O$	97	0.58

General procedure for the preparation of aldimine derivatives of 3-(4-substituted phenyl)-1-phenyl-1*H*-pyrazole-4-carboxaldehyde (III_{i-xii}): Compound **II** (0.5 mmol) was dissolved in hot ethanol and to it 0.2 mL of glacial acetic acid was added. Further (0.5 mmol) substituted anilines were added and reaction mixture was refluxed for 7 h. After cooling reaction mixture at room temperature, the precipitate of the aldimine derivatives were obtained which further recrystallized in suitable solvents. The analytical data of the synthesized compounds ($\mathbf{III_{i-xii}}$) are given in Table-3. The reactions were monitored with TLC (**Scheme-I**).



Scheme-I

TABLE-3
ANALYTICAL DATA OF ALDIMINE DERIVATIVES OF 3-(4-SUBSTITUTED PHENYL)-1- PHENYL-1*H*-PYRAZOLE-4-CARBOXALDEHYDE ($\mathbf{III_{i-xii}}$)

Compd.	m.p. (ºC)	m.f.	Yield (%)	R_f value
$\mathbf{III_i}$	286	$C_{22}H_{16}N_3OBr$	48	0.71
$\mathbf{III_{ii}}$	243	$C_{23}H_{19}N_3O$	58	0.67
$\mathbf{III_{iii}}$	136	$C_{23}H_{18}N_3OCl$	78	0.60
$\mathbf{III_{iv}}$	158	$C_{22}H_{15}N_3Br_2$	63	0.68
$\mathbf{III_v}$	177	$C_{23}H_{18}N_3Br$	53	0.63
$\mathbf{III_{vi}}$	179	$C_{22}H_{17}N_3BrCl$	68	0.64
$\mathbf{III_{vii}}$	253	$C_{22}H_{15}N_4Br$	56	0.72
$\mathbf{III_{viii}}$	162	$C_{23}H_{18}N_4O_2$	61	0.69
$\mathbf{III_{ix}}$	116	$C_{23}H_{17}N_4Cl$	74	0.62
$\mathbf{III_x}$	138	$C_{23}H_{18}N_3Br$	62	0.58
$\mathbf{III_{xi}}$	285	$C_{24}H_{21}N_3$	58	0.69
$\mathbf{III_{xii}}$	109	$C_{24}H_{20}N_3Cl$	68	0.64

Spectral data

N-(4-Bromophenyl)-{[3-(4-hydroxy phenyl)-1-phenyl-1*H*-pyrazole-4-yl]methylene}amine ($\mathbf{III_i}$): IR (KBr, ν_{max}, cm^{-1}): 3061 (Ar, C-H), 1610 (Ar, C=N), 1502 (Ar, C=C), 1339 (Ar, C-N); ^{1}H NMR ($CDCl_3$) δ (ppm): 2.542 (s, 1H, P-OH, 3-phenyl), 6.895 (s, 4H, 3-phenyl), 7.202-7.244 (m, 3H, N-phenyl), 7.325-7.59 (m, 3H,$_{3,4,5}$, 1-phenyl), 7.688-7.784 (m, 2H,$_{2,6,}$ 1-phenyl), 8.423 (s, 1H, pyrazole), 8.500 (s, 1H, CH=N).

N-(4-Methylphenyl)-{[3-(4-hydroxyphenyl)-1-phenyl-1*H*-pyrazole-4-yl]methylene}amine ($\mathbf{III_{ii}}$): IR (KBr, ν_{max}, cm^{-1}): 3050 (Ar, C-H), 1620 (Ar, C=N), 1449 (Ar, C=C), 1344 (Ar, C-N); ^{1}H NMR ($CDCl_3$) δ (ppm): 2.575 (s, 1H, P-OH, 3-phenyl), 2.368-2.441 (d, 3H, -CH_3, N-phenyl), 7.208-7.268 (m, 3H, N-phenyl), 7.302-7.613 (m, 3H,$_{3,4,5}$, 1-phenyl), 7.692-7.793 (m, 2H,$_{2,6,}$ 1-phenyl), 8.501 (s, 1H, pyrazole), 9.327 (s, 1H, CH=N).

N-(2-Chlorobenzyl)-{[3-(4-hydroxy phenyl)-1-phenyl-1*H*- pyrazole-4-yl]methylene}amine ($\mathbf{III_{iii}}$): IR (KBr, ν_{max}, cm^{-1}): 2920 (Ar, C-H), 1636 (Ar, C=N), 1411 (Ar, C=C), 1333 (Ar, C-N), 1105 (Ar, C-Cl); ^{1}H NMR ($CDCl_3$) δ (ppm): 2.612 (s, 2H, CH_2-phenyl), 6.814 (s, 4H,$_{2,3,5,6}$, 3-phenyl), 7.218-7.272 (m, 3H, N-phenyl), 7.302-7.546 (m, 3H,$_{3,4,5}$, 1-phenyl), 7.589-7.774 (m, 2H,$_{2,6,}$ 1-phenyl), 8.434 (s, 1H, pyrazole), 8.574 (s, 1H, CH=N).

N-(4-Bromophenyl)-{[3-(4-bromophenyl)-1-phenyl-1*H*-pyrazole-4-yl]methylene}amine ($\mathbf{III_{iv}}$): IR (KBr, ν_{max}, cm^{-1}): 3048 (Ar, C-H), 1598 (Ar, C=N), 1448 (Ar, C=C), 1339 (Ar, C-N), ^{1}H NMR ($CDCl_3$) δ (ppm) 7.115-7.233 (m, 8H,$_{2,3,5,6}$-phenyl and N-phenyl), 7.372-7.480 (m, 3H,$_{3,4,5}$, 1-phenyl), 7.606-7.802 (m, 2H,$_{2,6,}$ 1-phenyl), 8.372 (s, 1H, pyrazole), 8.882 (s, 1H, CH=N).

N-(4-Methylphenyl)-{[3-(4-bromophenyl)-1-phenyl-1*H*-pyrazole-4-yl]methylene}amine (III_v): IR (KBr, ν_{max}, cm^{-1}): 3444 (Ar, C-H), 1594 (Ar, C=N), 1445 (Ar, C=C), 1338 (Ar, C-N), ^1H NMR ($CDCl_3$) δ (ppm) 2.612 (S, 2H, CH_2-phenyl), 6.814 (s, $4H_{2,3,5,6,}$ 3-phenyl), 7.218-7.272 (m, 3H, N-phenyl), 7.302-7.546 (m, $3H_{,3,4,5}$, 1-phenyl), 7.685-7.674 (m, $2H_{,2,6,}$ 1-phenyl), 8.424 (s, 1H, pyrazole), 8.893 (s, 1H, CH=N).

N-(2-Chlorobenzyl){[3-(4-bromophenyl)-1-phenyl-1*H*- pyrazole-4-yl]methylene}amine (III_{vi}): IR (KBr, ν_{max}, cm^{-1}): 3158 (Ar, C-H), 1594 (Ar, C=N), 1445 (Ar, C=C), 1335 (Ar, C-N), 1107 (Ar, C-Cl). ^1H NMR ($CDCl_3$) δ (ppm) 2.354 (s, 2H, CH_2-phenyl), 7.157-7.392 (s, $4H_{2,3,5,6}$, 3-phenyl), 7.353-7.489 (m, $3H_{,3,4,5}$, 1-phenyl), 7.591-7.780 (m, $2H_{,2,6}$, 1-phenyl), 8.449 (s, 1H, pyrazole), 8.773 (s, 1H, CH=N).

N-(4-Bromophenyl)-{[3-(4-nitrophenyl)-1-phenyl-1*H*- pyrazole-4-yl]methylene}amine (III_{vii}): IR (KBr, ν_{max}, cm^{-1}): 3132 (Ar, C-H), 1598 (Ar, C=N), 1505 (Ar, N=O), 1481 (Ar, C=C), 1336 (Ar, C-N), ^1H NMR ($CDCl_3$) δ (ppm) 7.711 (S,$4H_{,2,3,5,6}$, 3-phenyl), 7.380-7.497 (m, $7H_{,2,3,5,6}$, N-phenyl and $H_{,3,4,5}$, 1-phenyl), 7.793-7.816 (m, $2H_{,2,6}$, 1-phenyl), 8.545 (s, 1H, pyrazole), 8.630 (s, 1H, CH=N).

N-(4-Methylphenyl){[3-(4-nitrophenyl)-1-phenyl-1*H*-pyrazole-4-yl] methylene}amine (III_{viii}): IR (KBr, ν_{max}, cm^{-1}): 3450 (Ar, C-H), 1594 (Ar, C=N), 1445 (Ar, C=C), 1337 (Ar, C-N), ^1H NMR ($CDCl_3$) δ (ppm) 2.24-2.29 (m, 3H, P-CH_3, N-phenyl), 7.254-7.268 (m, $4H_{,2,3,5,6}$, N-phenyl), 7.601 (S, $4H_{,2,3,5,6}$, 3-phenyl), 7.341-7.490 (m, $3H_{,3,4,5}$, 1-phenyl), 7.165-7.793 (m, $2H_{,2,6}$, 1-phenyl), 8.512 (s, 1H, pyrazole), 8.890 (s, 1H, CH=N).

N-(2-Chlorobenzyl)-{[3-(4-nitrophenyl)-1-phenyl- 1*H*-pyrazole-4-yl]methylene}amine (III_{ix}): IR (KBr, ν_{max}, cm^{-1}): 2917 (Ar, C-H), 1633 (Ar, C=N), 1409 (Ar, C=C), 1334 (Ar, C-N), 1043 (Ar, C-Cl). ^1H NMR ($CDCl_3$) δ (ppm) 2.022 (s, 2H, -CH_2 phenyl) 7.238 (m, 4H, N-CH_2 phenyl), 7.359-7.472 (m, $3H_{,3,4,5}$, 1-phenyl), 7.501 (s, $4H_{,2,3,5,6}$, 3-phenyl), 7.752 (m, $2H_{,2,6}$, 1-phenyl), 8.460 (s, 1H, pyrazole), 8.557 (s, 1H, CH=N).

N-(4-Bromophenyl)-{[3-(4-methylphenyl)-1-phenyl-1*H*-pyrazole-4-yl]methylene}amine (III_x): IR (KBr, ν_{max}, cm^{-1}): 3060 (Ar, C-H), 1594 (Ar, C=N), 1451 (Ar, C=C), 1340 (Ar, C-N), 1043 (Ar, C-Cl). ^1H NMR ($CDCl_3$) δ (ppm) 2.427 (s, 1H, P-CH_3, 3-phenyl), 7.197 (s, $4H_{,2,3,4,5}$, 3-phenyl), 7.243-7.281 (m, 4H, N-phenyl), 7.306-7.609 (m, $3H_{,3,4,5}$, 1-phenyl), 7.690-7.761 (m, $2H_{,2,6}$, 1-phenyl), 8.461 (s, 1H, pyrazole), 8.708 (s, 1H, CH=N).

N-(4-Methylphenyl)-{[3-(4-methylphenyl)-1-phenyl-1*H*-pyrazole-4-yl]methylene}amine (III_{xi}): IR (KBr, ν_{max}, cm^{-1}): 2912 (Ar, C-H), 1610 (Ar, C=N), 1504 (Ar, C=C), 1438 (Ar, C-N). ^1H NMR ($CDCl_3$) δ (ppm) 2.317-2.401 (s, 6H, 2(-CH_3), N-phenyl and 3-phenyl), 6.797-6.963 (m, 8H, N-phenyl and 1-phenyl) 7.367-7.459 (s, $3H_{,3,4,5}$, 1-phenyl), 7.647-7.778 (m, $2H_{,2,6}$, 1-phenyl), 8.342 (s, 1H, pyrazole), 8.721 (s, 1H, CH=N).

N-(2-Chlorobenzyl)-{[3-(4-methylphenyl)-1-phenyl-1*H*-pyrazole-4-yl]methylene}amine (III_{xii}): IR (KBr, ν_{max}, cm^{-1}): 3409 (Ar, C-H), 1596 (Ar, C=N), 1443 (Ar, C=C), 1334 (Ar, C-N), 1051 (Ar, C-Cl). ^1H NMR ($CDCl_3$) δ (ppm) 2.416 (s, 2H, CH_2-phenyl), 7.199-7.237 (s, $4H_{2,3,5,6}$, 1-phenyl), 7.255-7.280 (m, 4H, N-phenyl), 7.301-7.577 (m, $3H_{,3,4,5}$, 1-phenyl), 7.677-7.789 (m, $2H_{,2,6}$, 1-phenyl), 8.509 (s, 1H, pyrazole), 8.614 (s, 1H, CH=N).

Pharmacological screening

Anxiolytic activity: Male swiss mice (20-25 g), in a group of six, were used throughout experiments. Mice were housed in plastic cages and kept in 30 m^2 room with controlled 12 h light/dark cycle and at constant temperature (22 ± 2 ºC).

As drug is completely soluble in DMSO, DMSO is taken as a control vehicle. The test drug was used in concentration of 10 mg/Kg in IP dose. Acute toxicity studies revealed that all the compounds were non-toxic up to the dose as high as 50 mg/kg body weight. Synthesized derivatives were used with the conc. of 10 mg/kg intra-peritoneal for each mice, where diazepam (2 mg/kg, I.P.) used as positive control.

Elevated plus maze test: The elevated plus maze for mice two open arms (37 cm × 5 cm) and two enclosed arms (37 cm × 5 cm × 12 cm) with 12 cm high wall arranged so that the arms of the same type were opposite to each other, with central square of 5 cm. The apparatus was wooden and was elevated to a height of 25 cm above the floor. The apparatus similar to that described by Pellow *et al.*[11] was used. The number of entries and the time spent in the open and closed arms were recorded during a 5 min test period as described[12]. The percentage of open arm entries (100 × open/total entries) was calculated for each animals[13].

Light and dark exploration test: This model is based on natural aversion of mice to brightly light places[14]. The apparatus consist of two compartment box, one dark and the other brightly light. A typical apparatus consist of a wooden box (45 cm × 27 cm × 27 cm). The box is open topped and dimly illuminated (10 W white bulb). Mice were placed individually in the centre of the light compartment and observed for the next 5 min for the time spent in the light and dark compartment.

Analgesic activity

Writhing test: All the compounds were screened using the method of ghosh[15]. Albino mice (20-25 g) of either sex were used for the study. Percentage protection exhibited by the test compounds administered at a dose of 20 mg/kg in DMSO solution intraperitonially against the acetic acid (0.6 % w/w) induced writhing or stretching syndrome was recorded. Indomethacin (10 mg/kg body weight) was employed as reference standard under similar conditions.

RESULTS AND DISCUSSION

In the study of anxiolytic activity by elevated plus maze test in mice intraperitonial administration of aldimine derivatives increases the number of entries and time spent (s) in open arm (Table-4).

TABLE-4
ANXIOLYTIC EFFECT OF ALDIMINES DERIVATIVES OF 3-(4-SUBSTITUTED PHENYL)-1-PHENYL-1H-PYRAZOLE-4-CARBOXALDEHYDE COMPOUNDS ($\mathbf{III}_{i\text{-}xii}$) ON ELEVATED PLUS MAZE TEST IN MICE

Compd.	Dose	No. of entries (n)		Time spent (s)	
		Open arm	Closed arm	Open arm	Closed arm
Control	10 mL/kg	6.9 ± 0.60	8.9 ± 0.4	95.5 ± 1.6	203.1 ± 1.6
Standard	2 mg/kg	11.8 ± 0.60	5.7 ± 0.3	156.8 ± 2.2	140.0 ± 3.2
$\mathbf{III}_{i}$	10 mg/kg	7.5 ± 0.42	6.3 ± 0.5	135.3 ± 3.4	174.3 ± 2.7
$\mathbf{III}_{ii}$	10 mg/kg	7.8 ± 0.40	5.6 ± 0.4	129.5 ± 3.0	170.6 ± 2.1
$\mathbf{III}_{iii}$	10 mg/kg	9.6 ± 0.49	7.1 ± 0.5	141.1 ± 3.9	160.8 ± 3.9
$\mathbf{III}_{iv}$	10 mg/kg	6.5 ± 0.42	5.2 ± 0.7	121.6 ± 2.5	176.7 ± 3.4
$\mathbf{III}_{v}$	10 mg/kg	9.1 ± 0.47	7.8 ± 0.4	138.3 ± 3.0	161.4 ± 3.2
$\mathbf{III}_{vi}$	10 mg/kg	9.5 ± 0.34	7.5 ± 0.4	144.4 ± 2.9	153.3 ± 2.5
$\mathbf{III}_{vii}$	10 mg/kg	9.0 ± 0.36	6.6 ± 0.4	147.7 ± 3.9	150.5 ± 2.1
$\mathbf{III}_{viii}$	10 mg/kg	10.3 ± 0.42	8.3 ± 0.5	153.2 ± 3.0	144.6 ± 3.2
$\mathbf{III}_{ix}$	10 mg/kg	10.8 ± 0.66	7.1 ± 0.5	159.6 ± 3.1	141.5 ± 2.2
$\mathbf{III}_{x}$	10 mg/kg	8.8 ± 0.30	8.1 ± 0.5	131.5 ± 2.8	168.3 ± 3.4
$\mathbf{III}_{xi}$	10 mg/kg	8.5 ± 0.42	7.8 ± 0.5	133.3 ± 3.4	164.1 ± 2.8
$\mathbf{III}_{xii}$	10 mg/kg	9.8 ± 0.30	6.1 ± 0.5	147.5 ± 2.4	160.0 ± 2.7

Diazepam (2 mg/kg IP) is used as a standard, increase the number of entries *i.e.* 11.8 ± 2.1 and time spent (s) is 157 ± 8.9 in open arm as compare to control DMSO 6.9 ± 0.5 and 95 ± 2.1, respectively, whereas compound no. $\mathbf{III}_{vii}$, $\mathbf{III}_{ix}$ and $\mathbf{III}_{xii}$ increases the number of entries in open arm 10.3 ± 0.42, 10.8 ± 0.66 and 9.8 ± 0.30, respectively compared to control. Also these compound shows significant increase in time spent by 153.2 ± 3.0, 159.6 ± 3.1 and 147.5 ± 2.4 compare to control. These compounds shows significant anxiolytic activity.

In the light and dark exploration method, diazepam (2 mg/kg IP) increases the number of entries by 5.2 ± 0.6 and time spent by 137.9 ± 5.7 in light compartment, respectively compared to control DMSO (3.1 ± 0.4) and 51 ± 2.6, respectively. Compound no. $\mathbf{III}_{iii}$, $\mathbf{III}_{vii}$, $\mathbf{III}_{viii}$ and $\mathbf{III}_{ix}$ shows significant increases the number of entries 4.7 ± 0.66, 4.3 ± 0.49, 4.8 ± 0.54 and 5.1 ± 0.47 and these compounds shows significant increases in the time spent in light compartment 111.0 ± 4.2,115.0 ± 5.0 and 120.8 ± 3.38, respectively compared to control. These compounds showed significant anxiolytic activity (Table-5).

TABLE-5
ANXIOLYTIC EFFECT OF ALDIMINES DERIVATIVES OF 3-(4-SUBSTITUTED PHENYL)-1-PHENYL-1H-PYRAZOLE-4-CARBOXALDEHYDE COMPOUNDS ($\mathbf{III}_{i\text{-}xii}$) ON LIGHT AND DARK EXPLORATION TEST IN MICE

Compd.	Dose	No. of entries (n) in light	Time spent (s)	
			Light	Dark
DMSO	10 mL/kg	3.1 ± 0.40	51.0 ± 1.90	248.0 ± 2.3
Diazepam	2 mg/kg	5.1 ± 0.40	137.8 ± 1.60	162.6 ± 2.3
$\mathbf{III}_{i}$	10 mg/kg	3.5 ± 0.42	70.6 ± 2.00	229.0 ± 1.3
$\mathbf{III}_{ii}$	10 mg/kg	4.1 ± 0.70	78.0 ± 1.90	220.0 ± 1.5
$\mathbf{III}_{iii}$	10 mg/kg	4.7 ± 0.66	107.8 ± 1.00	191.3 ± 1.3
$\mathbf{III}_{iv}$	10 mg/kg	3.8 ± 0.60	77.5 ± 2.40	122.3 ± 1.4
$\mathbf{III}_{v}$	10 mg/kg	3.7 ± 0.55	72.1 ± 1.40	126.3 ± 0.7
$\mathbf{III}_{vi}$	10 mg/kg	4.1 ± 0.70	109.1 ± 3.60	191.5 ± 1.6
$\mathbf{III}_{vii}$	10 mg/kg	4.3 ± 0.49	111.0 ± 4.20	187.3 ± 0.9
$\mathbf{III}_{viii}$	10 mg/kg	4.8 ± 0.54	115.0 ± 5.00	183.8 ± 1.3
$\mathbf{III}_{ix}$	10 mg/kg	5.1 ± 0.47	120.8 ± 3.38	180.5 ± 1.4
$\mathbf{III}_{x}$	10 mg/kg	4.2 ± 0.47	85.8 ± 3.40	213.5 ± 0.8
$\mathbf{III}_{xi}$	10 mg/kg	4.1 ± 0.70	81.0 ± 3.30	218.3 ± 0.6
$\mathbf{III}_{xii}$	10 mg/kg	3.9 ± 0.47	90.8 ± 3.70	208.3 ± 0.6

From observation Table-6, present investigation was undertaken with objective to evaluate analgesic activity of aldimine derivatives of 3-(4-substituted phenyl)-1-phenyl pyrazole-4-carboxaldehyde by acetic acid induced writhing test respectively. Compound No. $\mathbf{III}_{iv}$, $\mathbf{III}_{vii}$, $\mathbf{III}_{x}$ showed good analgesic activity compare to indomethacin as a standard.

TABLE-6
ANALGESIC ACTIVITY OF 3-(4-SUBSTITUTED PHENYL)-1-PHENYL-1H-PYRAZOLE-4-CARBOXALDEHYDE COMPOUNDS ($\mathbf{III}_{i\text{-}xii}$)

Compd.	Dose	No. of writhing (± SEM)	Decrease in writhing (%)
Control (DMSO)	10 mL/kg	31.8 ± 0.30	0
Standard (Indomethacin)	10 mg/kg	2.5 ± 0.56	92.13
$\mathbf{III}_{i}$	20 mg/kg	14.1 ± 0.83	55.56
$\mathbf{III}_{ii}$	20 mg/kg	19.5 ± 0.95	38.70
$\mathbf{III}_{iii}$	20 mg/kg	15.3 ± 0.94	51.88
$\mathbf{III}_{iv}$	20 mg/kg	9.6 ± 0.33	69.62
$\mathbf{III}_{v}$	20 mg/kg	11.8 ± 0.26	62.79
$\mathbf{III}_{vi}$	20 mg/kg	11.6 ± 0.61	63.33
$\mathbf{III}_{vii}$	20 mg/kg	10.6 ± 0.57	66.67
$\mathbf{III}_{viii}$	20 mg/kg	12.1 ± 0.26	61.94
$\mathbf{III}_{ix}$	20 mg/kg	12.8 ± 0.72	59.65
$\mathbf{III}_{x}$	20 mg/kg	11.4 ± 0.61	63.96
$\mathbf{III}_{xi}$	20 mg/kg	19.0 ± 0.57	40.25
$\mathbf{III}_{xii}$	20 mg/kg	15.1 ± 0.23	52.32

REFERENCES

1. A.F. Heald and R.A.L. Wildonger, US Pat. 4,364,348; *Chem. Abstr.*, **98**, 89358 (1983).
2. D.J. Wustrow, T. Capiris and R. Rubin, *Bioorg. Med. Chem. Lett.*, **8**, 2067 (1998).
3. A.I. Eid, M.A. Kira and H.H. Fahmy, *J. Pharm. Belg.*, **33**, 303 (1978); *Chem. Abstr.*, **90**, 152073 (1979).
4. G. Menozzi, L. Mosti and P. Fossa, *J. Heterocycl. Chem.*, **34**, 963 (1997).
5. D.D. Penning, J.J. Talley and S.R. Bertenshaw, *J. Med. Chem.*, **40**, 1347 (1997).
6. R.B. Pathak and S.C. Bahel, *J. Indian Chem. Soc.*, **57**, 1108 (1980).
7. A.W. Raut and A.G. Doshi, *Orient. J. Chem.*, **12**, 79 (1996).
8. V.M. Barot, *Asian J. Chem.*, **8**, 565 (1996).
9. S. Devi, P. Mitro, S.B. Mishra and A.S. Mittra, *J. Indian Chem. Soc.*, **60**, 679 (1983).
10. M.A Kira, M.O. Abdel-Rehman and K.Z. Gadalla, *Tetrahedron Lett.*, 109 (1969).
11. S. Pellow, P. Chopin, S.F. File and M. Briley, *J. Neurosci. Methods*, **14**, 149 (1985).
12. R.G. Lister, *Psychopharmacol.*, **92**, 78 (1987).
13. S. Pellow and S.E. File, *Pharmacol. Biochem. Behav.*, **24**, 525 (1986).
14. J.N. Crawley, *Pharmacol. Biochem. Behav.*, **15**, 695 (1981).
15. M.N. Ghosh, Fundamentals of Experimental Pharmacology, Scientific Book Agency, Calcutta, p. 153 (1981).

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