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SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL SCREENING OF NEWER PYRAZOLE DERIVATIVES

Karumudi Bhavya Sai[1a], Nagandla Durga Deepak [2a]*

[a]Department of Pharmacy Practice,
[1]Chalapathi Institute of Pharmaceutical Sciences, Guntur, India.
[2]Hindu College of Pharmacy, Guntur, India.

***Corresponding Author: Nagandla Durga Deepak**
Department of Pharmacy Practice, Hindu College of Pharmacy, Guntur, India.

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ABSTRACT
Pyrazole is an important class of heterocyclic compound, has been shown to exhibit diverse biological and pharmacological activities such as anti-cancer, antioxidant, anti-inflammatory, antimicrobial, etc. In this study, a series of pyrazole derivatives have been synthesized. All the synthesized compounds have been characterized by using elemental analysis, FT-IR, ^{1}H NMR, ^{13}C NMR spectroscopy and further supported by mass spectroscopy. Purity of all the compounds has been checked on thin layer chromatographic plate and HPLC technique. All the synthesized compounds were tested for their analgesic and antiinflammatory activities. The compounds exhibited significant analgesic and antiinflammatory activities. These compounds can be further exploited to get the potent lead compounds. The detailed synthesis, analgesic and antiinflammatory screening of the new compounds are reported.

KEYWORDS: Pyrazole, Diphenyl, analgesic and antiinflammatory activities.

INTRODUCTION
The synthesis of heterocyclic compounds has always drawn the attention of chemists over the years mainly because of their important biological properties. Pyrazoles are five member ring heterocyclic compounds, have some structural features with two nitrogen atoms in adjacent position and are also called as Azoles. Pyrazoles and its derivatives, a class of well known nitrogen heterocycles, occupy a prime position in medicinal chemistry for their diverse biological activities. They have been known to exhibit antimicrobial[1, 2], analgesic[3,4], anticancer[5,6], anti-tubercular[7,8], anti-inflammatory[9,10], antidepressant[11], anticonvulsant[12], hypoglycemic[13], antipyretic[14], antihelmintic[15], antioxidant[16] and herbicidal properties. Considering the above observations and in connection to previous publications involving the synthesis of new biologically active heterocycles. Substitution of the heterocyclic moieties on the pyrazole ring is anticipated to have potential biological activity. In the present communication synthesis, characterization and the biological activity of various pyrazoles substituted with heterocyclic moieties are reported. Thus the efficient synthesis newer pyrazole derivatives still represent highly pursued target.

EXPERIMENTAL SECTION
Preparation of *N*-Phenyl-*N*'-(1-phenyl-ethylidene)-hydrazine
Phenyl hydrazine hydrochloride (2gm, 13.8mmol, 1.0 eq) was added to a solution of acetophenone (1.8gm, 15.2mmol, 1.1 eq) in 50 ml of ethanol at 0^{0}C followed by the slow addition of glacial acetic acid 1.5ml. The reaction mixture was then refluxed for 2hours (TLC) and cooled to room temperature, when the product precipitated out of the reaction mixture, which was filtered, washed with cold ethanol (20 ml) and dried under vacuum to obtain pure acetophenonephenylhydrazone as a yellow solid (2.8gm, 90%), M.P 104-106^{0}C.

Synthesis of 1, 3-Diphenyl-1H-pyrazole-4-Carbaldehyde
To a solution of *N, N*-Dimethylformamide (0.8gm, 11.4 mmole, 1.2eq, 0.84ml) was added to phosphorous oxychloride (1.7gm, 11.4 mmol, 1.2 eq 1.03 ml) at 0^{0}C and stirred at the same temperature for 1hr. This mixture was then slowly added to a solution of acetophenonephenylhydrazone, (2gm, 9.5 mmol, 1eq) in *N, N*-dimethylformamide (5ml) was added drop wise and the reaction mixture allowed to stir for 10min at the same temperature and then heated to 70^{0}C for 3hours (TLC). The reaction mixture was then cooled to room temperature and basified with cold and saturated

potassium carbonate, when a solid (brown color) precipitated out. The precipitate was filtered, washed with cold water (20 ml) to obtain the crude product as a colored solid.

The crude products was purified by silica gel column chromatography to obtain pure product as a (off-white) solid 2.17 gm, yield 92%, M.P; 146-148^{0}C, ^{1}H NMR: (DMSO; 400 MHz; ∂ ppm), 9.99(1H, s), 9.34(1H, s), 7.42-7.60(6H, m), 7.92-8.01(4H, m). EI MASS m/z: 249.2, Mol. Wt.: 248.28.

General Procedure for Preparation of (1, 3-Diphenyl-1H-pyrazol-4-yl)-amine derivatives

A suspension of $ZnCl_2$ (0.043gm, 0.31mmol 0.8eq) and $NaCNBH_3$ (0.03gm, 0.48 mmol, 1.2 eq) in methanol 1ml was stirred for 2 hours at room temperature and to this added a mixture of compound-2 (0.1gm, 0.4 mmol 1 eq) and the respective amine (0.4mmol, 1eq) in dichloromethane (2ml). The reaction mixture was stirred at room temperature overnight. Next day the reaction mixture was quenched with an aqueous solution of 2N NaOH (0.5ml) and extracted with dichloromethane (3 × 2ml). The organic layer was then washed with water (3ml), brine (3ml), dried with anhydrous magnesium sulphate and concentrated to obtain the crude product. The crude product was purified by silica gel column chromatography using a mixture of chloroform-methanol (1-5%) to obtain pure products.

2-(2-chlorophenyl)-N-((1, 3-diphenyl-1H-pyrazol-yl) methyl)ethanamine (TP-1)

Pale yellow solid, M.P: 135-137^{0}C; MS (m/z): 388.2 $(M+1)^+$; ^{1}H NMR (400 MHz, $CDCl_3$, ∂ppm): 7.99(1H, s), 7.74(5H, d, J=8Hz), 7.44(5H, q, J=8Hz), 7.31-7.39(2H, m), 7.26-7.31(1H, m), 7.18-7.23(1H, m), 7.13, 7.18(1H, m), 3.99(2H, s), 3.00(2H, s), 2.62(2H, s); IR (KBr, cm^{-1}): 3412.54, 1635.74, 1647.52, 772.05.

1-(1-((1, 3-diphenyl-1H-pyrazol-4-yl)methyl)piperidin-4-yl)-1H-benzo[d]imidazol-2(3H)-one (TP-2)

White solid, M.P: 184-186^{0}C; MS (m/z): 450.2 $(M+1)^+$; ^{1}H NMR (400 MHz, ∂ppm, $CDCl_3$): 8.69(1H, s), 7.94(3H, t, J=12Hz), 7.78(2H, d, J=16Hz), 7.48(4H, q, J=8Hz), 7.41(1H, t, J=12Hz), 7.29(1H, t, J=12Hz), 7.35(1H, J=8.2 Hz, d), 7.20-7.29(3H, m), 4.32-4.45(1H, m), 3.62(1H, s), 3.38(1H, t, J=12Hz), 3.20(2H, J=3.2 Hz, dd), 2.42-2.55(2H, m), 2.38(1H, t, J=20Hz), 2.23 (2H, t, J=16Hz); IR (KBr, cm^{-1}): 1695.74, 1670, 698.41.

2-(4-fluorophenyl)-N-((1,3-diphenyl-1H-pyrazol-4-yl) methyl) ethanamine (TP-3)

White solid, M.P: 148-150^{0}C; MS (m/z): 372.2 $(M+1)^+$; ^{1}H NMR (400 MHz, $CDCl_3$)∂: 8.3(1H, s), 7.63(2H, d, J=16Hz), 7.51(2H, d, J=16Hz), 7.357.47(6H, m), 7.26-7.28(1H, m), 6.84-6.97(4H, m), 4.15(2H, s), 2.98(2H, m), 2.81(2H, m).

4-phenyl-N-((1, 3-diphenyl-1H-pyrazol-4-yl) methyl) butan-2-amine (TP-4)

White solid, M.P: 153-155^{0}C; MS (m/z): 382.2 $(M+1)^+$; ^{1}H NMR (400 MHz, $CDCl_3$)∂: 8.45(1H, s), 7.70(2H, d, J=16Hz), 7.38-7.49(7H, m), 7.28(1H, d, J=16Hz), 7.08-7.18(3H, m), 6.94(2H, d, J=12Hz), 2.91(1H, b s), 2.56(1H, m), 2.39(1H, m), 2.10(2H, m), 1.96(1H, m), 1.76(1H, m), 1.13(3H, s). IR (KBr, cm^{-1}): 3030.57, 1657.86, 119.45, 696.14.

2-morpholino-N-((1, 3-diphenyl-1H-pyrazol-4-yl) methyl)ethanamine (TP-5)

White solid, M.P: 138-130^{0}C; MS (m/z): 363.2 $(M+1)^+$; ^{1}H NMR (400 MHz, $CDCl_3$)∂: 8.37(1H, s), 7.73(2H, d, J=16Hz), 7.60(2H, d, J=16Hz), 7.427.51(5H, m), 7.31(1H, t, J=10Hz), 4.32(2H, s), 3.63(4H, m), 3.16(2H, m), 2.92(2H, m), 2.36(4H, m). IR (KBr, cm^{-1}): 3067.57, 1657.21, 1203.20, 698.21.

1-benzyl-N-((1, 3-diphenyl-1H-pyrazol-4-yl) methyl) pyrrolidin-3-amine (TP-6)

White white solid, M.P: 144-148^{0}C; MS (m/z): 409.2 $(M+1)^+$; ^{1}H NMR (400 MHz, $CDCl_3$) ∂: 8.40(1H, s), 7.71(2H, d, J=16Hz), 7.54(2H, d, J=12Hz), 7.38-7.47(7H, m), 7.28-7.37(3H, m), 4.18(2H, s), 4.12(2H, s), 3.253.58(4H, m), 2.89(1H, m), 2.08-2.18(2H, m). IR (KBr, cm^{-1}): 3420.44, 1674.29, 1202.74, 771.98.

N-methyl-N-((1, 3-diphenyl-1H-pyrazol-4-yl) methyl) prop-2-yn-1-amine (TP-7)

Off white solid, M.P: 134-136^{0}C; MS (m/z): 302.2 $(M+1)^+$; ^{1}H NMR (400 MHz, $CDCl_3$)∂: 8.45(1H, s), 7.75(2H, d, J=7.2 Hz), 7.58(2H, d, 8Hz), 7.417.51(5H, m), 7.34(1H, t, J=10Hz), 4.38(2H, s), 3.80(2H, s), 2.68(3H, s), 2.34(1H, s); IR (KBr, cm^{-1}): 3434.86, 1675.30, 1200.54, 770.59.

N-Methyl-N-((1, 3-diphenyl-1H-pyrazol-4-yl) methyl) (m-tolyl) methanamine (TP-8)

White solid, M.P: 161-163^{0}C; MS (m/z): 368.2 $(M+1)^+$; ^{1}H NMR (400 MHz, $CDCl_3$)∂: 8.59(s, 1H), 7.78(2H, d, J=20Hz), 7.42-7.57(7H, m), 7.33(1H, t, J=12Hz), 7.18-7.25(2H, m), 7.04-7.11(2H, m), 4.46(1H, m),4.26(2H, m), 3.80(1H, m), 2.44(3H, s), 2.24(3H, s).

3-morpholino-N-((1, 3-diphenyl-1H-pyrazol-4-yl) methyl) propan-1-amine (TP-9)

White solid, M.P: 136-148^{0}C; MS (m/z): 377.2 $(M+1)^+$; ^{1}H NMR (400 MHz, $CDCl_3$)∂: 8.6(s, 1H), 7.80(2H, d, J=16Hz), 7.64(2H, d, J=20Hz), 7.417.52(5H, m), 7.33(1H, t, J=24, 12Hz), 4.21(2H, s), 3.36-3.42(4H, m), 3.08-3.13(2H, m), 2.53-2.60(2H, m), 2.38-2.48(4H, m), 1.89-1.96(2H, m); IR (KBr, cm^{-1}): 3407.54, 1641.75, 772.23.

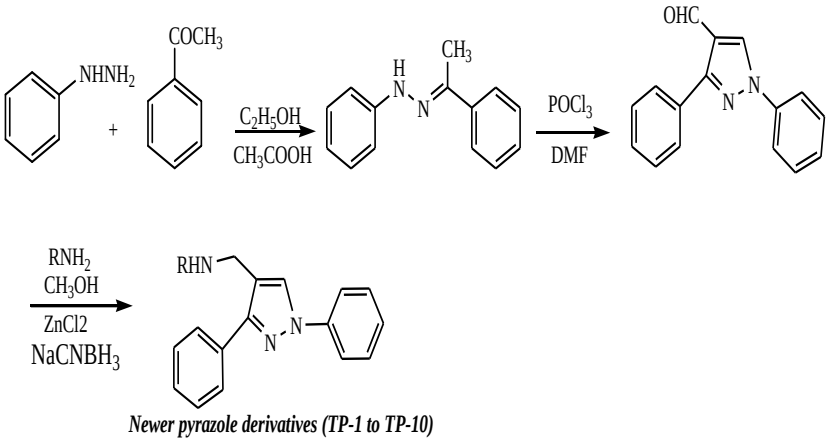
1-((1, 3-diphenyl-1H-pyrazol-4-yl) methyl) piperidin-3-ol (TP-10)

Off white solid, M.P: 110-112^{0}C; MS (m/z): 334.2 $(M+H)^+$; ^{1}H NMR (400 MHz, CDCl3)∂: 8.50(1H, s), 7.90-7.96(4H, m), 7.44-7.54(4H, m), 7.307.40(2H, m),

4.58(1H, d, J=4Hz), 3.38-3.49(2H, m), 3.29-3.32(2H, m), 2.70(2H, s), 2.18(2H, t, J=8Hz), 1.92-1.94(3H, m).

Table 1: Physical constants of newer pyrazole derivatives (TP-1 to TP-10)

Comp	R	M.F	M.W	Yield	M.P (^{0}C)
TP -1	2-chlorophenyl-N- ethanamine	$C_{24}H_{24}ClN_3$	389.92	86%	135-137
TP -2	1-piperidin-4-yl-1H-benzo[d]imidazol-2(3H)-one	$C_{28}H_{27}N_5O$	449.55	91%	184-186
TP -3	4-fluorophenyl-N-ethanamine	$C_{24}H_{22}FN_3$	371.45	95%	148-150
TP -4	4-phenyl-N-butanamine	$C_{26}H_{27}N_3$	381.51	85%	153-155
TP -5	2-morpholino-N-ethanamine	$C_{22}H_{26}N_4O$	362.47	78%	138-140
TP -6	1-benzyl-N- pyrrolidin-3-amine	$C_{27}H_{28}N_4$	408.54	80%	144-146
TP -7	N-methyl-N- prop-2-yn-1-amine	$C_{20}H_{19}N_3$	301.38	76%	134-136
TP -8	N-Methyl-N-m-tolyl-methanamine	$C_{23}H_{28}N_4O$	376.49	92%	161-163
TP -9	3-morpholino-propylamine	$C_{23}H_{28}N_4O$	376.49	75%	136-138
TP -10	1- piperidin-3-ol	$C_{21}H_{23}N_3O$	333.43	65%	110-112



Scheme 1: Synthesis of newer pyrazole derivatives (TP-1 to TP-10)

BIOLOGICAL SCREENING

ANALGESIC ACTIVITY[16]

Swiss Albino mice (weighing 20-25 gm) and Wistar rats (weighing 150-200 gm) were used for studying *in vivo* analgesic and anti-pyretic activities. Animals were maintained under standard laboratory conditions (24±2 0C; relative humidity 60-70%). Study protocol was approved by the Institutional Animal Ethics Committee before conducting the experiments (CIPS/IAEC/08/2015-2016). The mice and rats were used in the study. The animals were kept in polypropylene cages and maintained on balanced diet with free access to drinking water. All the experimental procedures were conducted in accordance with the guide for Care and Use of Laboratory Animals and in accordance with the Local Animal Care and Use Committee. The analgesic activity was carried out by Tail-flick and writhing methods.

Tail-flick method

After over-night fasting, the rats were divided into different groups (n=6) as shown in Table 3. The reaction time was measured at the end of 0, 30, 60 and 90 min after the administration of the compounds. The drugs were dispersed in 0.5% w/v of sodium carboxy methyl cellulose (sodium CMC) and administered orally. The control group (no drug) was administered with 0.5 ml of 0.5% w/v of sodium CMC. The tail-flick latency was assessed by considering the time taken by the rat to withdraw its tail from the hot water bath (55 ± 0.50C). The tail-flick latency of treated animals was compared with control animals.

Writhing method

After activity an over-night fast, the mice were distributed into different groups and treated as shown in Table 4**.** The drugs were dispersed in 0.5% w/v of sodium CMC and administered orally. The control group (no drug) was administered with 0.5 ml of 0.5% w/v of sodium CMC. The standard drug used was nimesulide (12.5 mg/ kg). One hour after the treatment, the mice were given an intraperitoneal injection of 0.7% v/v acetic acid solution (volume of injection was 0.1 ml/ 10 gm body weight). The number of writhes produced in these animals was counted for 30 min. The analgesic was evaluated in terms of the percentage of writhe inhibitions.

Table 2: Analgesic activities of newer pyrazole derivatives (TP-1 to TP-10)

Compd code	Comparative analgesic potency to Aceclofenac after time in minutes			
	10 min.	30 min.	60 min.	120 min.
TP -1	0.46 ± 0.01	0.50 ± 0.04	0.66 ± 0.06	1.30 ± 0.08
TP -2	0.54 ± 0.01	0.82± 0.05	0.95 ± 0.08	2.32 ± 0.21
TP -3	0.75 ± 0.03	0.95 ± 0.09	1.20 ± 0.11	2.20 ± 0.20
TP -4	0.42 ± 0.01	0.50 ± 0.05	0.60 ± 0.06	1.27 ± 0.16
TP -5	0.60 ± 0.01	0.82 ± 0.07	0.96 ± 0.08	2.30 ± 0.08
TP -6	0.45 ± 0.02	0.55 ± 0.05	0.72 ± 0.07	1.57 ± 0.04
TP -7	0.60 ± 0.01	0.95 ± 0.08	1.00 ± 0.01	2.20 ± 0.18
TP -8	0.65 ± 0.02	0.80 ± 0.07	1.25 ± 0.14	2.50 ± 0.14
TP -9	0.52 ± 0.02	0.54 ± 0.04	0.65 ± 0.06	1.32 ± 0.20
TP -10	0.60 ± 0.02	0.92 ± 0.03	1.00 ± 0.01	2.30 ± 0.12
Aceclofenac	1.00	1.00	1.00	1.00

All results were significantly different from the standard and normal control.
Value at P = 0.05.

ANTI-INFLAMMATORY ACTIVITY[17]

Carrageenan-induced rat paw edema method was used to determine the anti-inflammatory activity of the newly synthesized novel acridine derivatives containing pyrazole moiety.

Materials

Carrageenan required for inducing the inflammation was obtained from Himedia (Mumbai) whereas sodium CMC was of Merck grade and the required saline (Core Health Care) was purchased from a local supplier. Aceclofenac used as standard was supplied as a gift sample by Jagsonpal, New Delhi.

Preparation of sodium CMC suspension

1gm of sodium CMC was triturated in 100 ml of distilled water to give the required stock suspension of sodium CMC. This stock suspension was used for suspending all the test compounds as well as the standard drug.

Experimental procedure

Albino rats of either sex, weighing between 150-200 gm, supplied by Chalapathi Institute of Pharmaceutical Sciences, Guntur (08/IAEC/CIPS/2015-16) were divided into twenty seven groups of six animals each. All these groups were kept for fasting overnight and only allowed water adlibitum.0.05 ml of 1% carrageenan suspension was slowly injected subcutaneously into the subplantar region of the left hind paw to produce inflammation in all the groups. Groups III to XXVII were treated with 3,4,6,7-tetrahydro-3,3,6,6-tetramethyl-9-(3-(aryl)-1-phenyl-1H-pyrazol-4-yl)acridine-1,8(2H,5H,9H,10H)-diones (AP-1 to AP-10) (10mg/kg) after carrageenan administration and the time gap is at an interval of 0.5, 1, 2, 3, 4 and 6 h. Group I used as carrageenan treated control was given only 1% sodium CMC suspension (1 ml/kg) whereas group II received aceclofenac (2 mg/kg). All these doses were administered orally and the induced paw edema in each group was measured to assess the anti-inflammatory activity.

Measurement of paw thickness

Before carrageenan injection, the thickness of both the paws of each rat was measured using Zeitlin's constant load lever method. The paws thickness was also measured in a similar way after carrageenan injection at time intervals 0, 0.5, 1, 2, 3, 4 and 6 h. The dose selection for the compound in the preliminary screening is usually 5 times the dose of the standard drug aceclofenac, which was used at a dose of 2 mg/kg.

The percent increase at each time interval was determined by using the formula: Yt-Yo / Yo×100 Yt = Paw thickness at time t hours (after injection), Yo = Paw thickness at time 0 hours (before injection).

The percent inhibition of paw oedema thickness was calculated by using the formula:
Percentage inhibition = [1- Yt/Yc] × 100
Where Yt= Average increase in paw thickness in groups tested with 3,4,6,7-tetrahydro-3,3,6,6-tetramethyl-9-(3-(aryl)-1-phenyl-1H-pyrazol-4-yl)acridine-1,8(2H,5H,9H,10H)-diones (TP-1 to TP-10) and the standard.
Yc= Average increase in paw thickness in control.

The results of anti-inflammatory activity of aceclofenac and the3,4,6,7-tetrahydro-3,3,6,6-tetramethyl-9-(3-(aryl)-1-phenyl-1H-pyrazol-4-yl)acridine-1,8(2H,5H,9H,10H)-diones (TP-1 to TP-10) tested are shown in Table 3.

Table 3: Percentage inhibition in paw thickness at various time intervals

Compd code	% inhibition in paw thickness at various time intervals					
	0.5hr	1hr	2hr	3hr	4hr	6hr
TP -1	02 ± 1	06 ± 1**	37 ± 2	46 ± 1	70 ± 1	73 ± 2
TP -2	15 ± 1*	18 ± 2	50 ± 1	61 ± 1**	89 ± 1	90 ± 1
TP -3	14 ± 1	17 ± 2**	50 ± 1	61 ± 2	87 ± 2	88 ± 2*
TP -4	15± 1	17 ± 1	51± 1**	60 ± 2	88 ± 1	88 ± 1
TP -5	04 ± 1	10 ± 2*	40 ± 2	50 ± 2*	75 ± 1	80 ± 1*
TP -6	10 ± 1*	14 ± 2	47 ± 1	56 ± 2	84 ± 2	87 ± 1
TP -7	08 ± 1**	13 ± 1*	44 ± 1	54 ± 1	83 ± 1	84 ± 1
TP -8	08 ± 1	13 ± 1	46 ± 2	52 ± 2	82 ± 1	83 ± 2
TP -9	18 ± 1	20 ± 1	56 ± 1**	65 ± 1	94 ± 1	95 ± 2
TP -10	16 ± 1	19 ± 1	53 ± 1	63 ± 1*	92 ± 1	93 ± 2
Aceclofenac	22 ± 1	25 ± 1	59 ± 1	68 ± 1	98 ± 2	99 ± 1

Values are expressed as mean ± (n=6); P<0.05, P**<0.01 compared to control, Student t-test (Unpaired); Value for the control group in all the cases is zero.*

RESULTS AND DISCUSSION

The present work embodies the synthesis of various pyrazole derivatives (TP-1 to TP-10). 1, 3-diphenylpyrazole-4-carboxaldehyde was prepared in two steps. The first one was the reaction between acetophenone and phenylhydrazine. The hydrazone derivative was treated with the Vilsmeier–Haack reagent (DMF–$POCl_3$) leading to the corresponding 4-carboxaldehyde functionalizedpyrazole heterocyclic ring in mild operating conditions in good yields. First synthesis of pyrazole derivatives (TP-1 to TP-10) such as (1, 3-Diphenyl-1H-pyrazol-4-yl)-amine derivatives through reductive amination by using a suspension of $ZnCl_2$ and $NaCNBH_3$ in methanol was added to a mixture of 1, 3-diphenylpyrazole-4-carboxaldehyde and the respective amine in dichloromethane. All the compounds were subjected to analgesic and anti-inflammatory evaluation.

The analgesic activity of the newly synthesized novel acridine derivatives containing pyrazole moiety (TP-1 to TP-10) has been evaluated by using hot-plate test protocol method. Data recorded in table 2 indicating that all the tested compounds exhibited more potent analgesic activity than Aceclofenac as a reference drug. Compounds TP-2, TP-3, TP-5, TP-7, TP-8 and TP-10 showed more than twice the activity of Aceclofenac after two hours.

The anti-inflammatory activity of the newly synthesized novel acridine derivatives containing pyrazole moiety (TP-1 to TP-10) has been evaluated by using carrageenan-induced rat paw edema method. The results of the evaluation have been viewed by taking aceclofenac as the standard drug. The results of anti-inflammatory activity revealed that the compounds TP-1 to TP-10 exhibited moderate to considerable activity when compared with reference standard aceclofenac, but not at an identical dose level as the standard drug was tested at 2 mg/kg, whereas the novel acridine derivatives containing pyrazole moiety were tested at a dose of 10 mg/kg. Compounds TP-2, TP-9, TP-10 showed maximum activity and this is consistent with the literature reports that such groups enhance the lipophilic properties of the molecule. Other compounds tested in this present study also showed some degree of anti-inflammatory activity.

CONCLUSION

The main objective of the present study was to synthesize certain the pyrazole derivatives (TP-1 to TP-10). 1, 3-diphenylpyrazole-4-carboxaldehyde was prepared in two steps. The first one was the reaction between acetophenone and phenylhydrazine. The hydrazone derivative was treated with the Vilsmeier–Haack reagent (DMF–$POCl_3$) leading to the corresponding 4-carboxaldehyde functionalizedpyrazole heterocyclic ring in mild operating conditions in good yields. First synthesis of 1, 3, 4-trisubstituted pyrazoles (TP-1 to TP-10) such as (1, 3-Diphenyl-1H-pyrazol-4-yl)-amine derivatives through reductive amination by using a suspension of $ZnCl_2$ and $NaCNBH_3$ in methanol was added to a mixture of 1, 3-diphenylpyrazole-4-carboxaldehyde and the respective amine in dichloromethane. All the derivatives evaluated for their analgesic & anti-inflammatory activities. Results revealed that the compounds exhibited significant activity. All the synthesized compounds are more potent to moderate analgesic activity. The study would be a fruitful matrix for the development of the pyrazole derivatives for further bio-evaluation.

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REFERENCES

1. Gollapalli Naga Raju et al; Synthesis, characterization and antimicrobial evaluation of 5-(thiophen-2-yl)-4,5-dihydro-1H-pyrazole derivatives containing indole ring; Der Chemica Sinica, 2015; 6(6): 72-77.

2. Essam Mohamed Sharshira et al; Synthesis and Antimicrobial Evaluation of Some Pyrazole Derivatives; Molecules, 2012; 17: 4962-4971.
3. Gollapalli Naga Raju et al; Synthesis, characterization and biological evaluation pyrazole derivatives containing indole ring as a potent analgesic and anti-inflammatory agents; Der Pharma Chemica, 2016; 8(4): 301-309.
4. Nagwa M. Abd-El Gawad, Hanan H. Georgey et al, Synthesis of novel pyrazole and dihydropyrazoles derivatives as potential anti-inflammatory and analgesic agents; Archives of Pharmacal Research; May 2012; 35(5): 807–821.
5. R. S. Gouhar et al; Synthesis and anticancer screening of some novel substituted pyrazole derivatives; Der Pharma Chemica, 2013; 5(6): 225-233.
6. Abdelgawad MA et al; Design, Synthesis and Anticancer Screening of Novel Pyrazole Derivatives Linking to Benzimidazole, Benzoxazole and Benzothiazole. Med chem, 2014; 1-7.
7. Vimal I Patel and Dr.Bhavesh Patel; Synthesis and study of some pyrazole derivatives as anti tubercular agent; International Journal of Pharma and Bio Sciences; Vol.1/Issue-4/Oct-Dec.2010.
8. Hipparagi SM, Bhanushali MD; Synthesis and evaluation of anti-tubercular activity of some novel 2-pyrazoline derivatives. J Sci Soc., 2013; 40: 80-3.
9. Gollapalli Naga Raju et al; Synthesis, characterization and biological evaluation pyrazole derivatives containing indole ring as a potent analgesic and anti-inflammatory agents; Der Pharma Chemica, 2016; 8(4): 301-309.
10. Pawan Kumar et al; Synthesis and biological evaluation of some pyrazole derivatives as anti-inflammatory–antibacterial agents; Medicinal Chemistry Research, November 2012; 21(11): 3396–3405.
11. Secci D et al; The state of the art of pyrazole derivatives as monoamine oxidase inhibitors and antidepressant/anticonvulsant agents; Curr Med Chem, 2011; 18(33): 5114-44.
12. B. V. Kendre et al; Synthesis and biological evaluation of some novel pyrazole, isoxazole, benzoxazepine, benzothiazepine and benzodiazepine derivatives bearing an aryl sulfonate moiety as antimicrobial and anti-inflammatory agents; Arabian Journal of Chemistry, 2015.
13. Prasanna A. Datar and Sonali R. Jadhav; Design and Synthesis of Pyrazole-3-one Derivatives as Hypoglycaemic Agents; International Journal of Medicinal Chemistry Volume 2015.
14. Gollapalli Naga Raju et al; Synthesis and Biological Screening of Benzothiazole Derivatives with Pyrazole Moiety J. basic appl. Res, 2016; 2(2): 124-131.
15. Balaji.P.N et al; Anthelmintic and Anti-microbial activities of synthesized heterocyclic pyrazole and its derivatives from fluoro substituted hydrazino benzothiazole; Int. J. Pharm Tech Res. 2014; 6(7): 1970-1975.
16. Raju et al., Synthesis and Biological Screening of Benzothiazole Derivatives with Pyrazole Moiety J. basic appl. Res, 2016; 2(2): 124-131.
17. Gollapalli Naga Raju et al; Green synthesis, antiinflammatory and antimicrobial evaluation of novel isoxazole carboxamide derivatives; Der Pharmacia Lettre, 2016; 8(3): 135-142.