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SYNTHESIS OF NEWLY SUBSTITUTED PYRAZOLE DERIVATIVE AND THEIR ANTI-INFLAMMATORY ACTIVITY

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ABSTRACT

A series of novel pyrazole derivatives have been synthesized by the reaction of substituted chalcones with phenylhydrazine. The starting materials were prepared by reaction of acetophenone with substituted aldehydes in presence of sodium hydroxide. The structure of newly synthesized compounds has been characterized by using elemental analysis and IR and ^{1}HNMR spectral analysis. The melting points of synthesized compounds were determined in open capillaries with the help of thermonic melting point apparatus and the homogeneity of newly synthesized compounds was checked by TLC. The synthesized compounds have been evaluated to determine their anti-inflammatory activity. The anti-inflammatory activity of synthesized compounds was compared by phenylbutazone. In this series compound 2j showed better anti-inflammatory activity than standard drug.

KEYWORDS: Pyrazole, anti-inflammatory activity, phenylbutazone.

INTRODUCTION

Clinically biological activity is the result of a chemical compound's interaction with a human organism. Heterocyclic compounds are one of the main groups of organic compounds possessing wide range of applications in various areas of science and high technologies. Pyrazole is a simple aromatic ring of heterocyclic series which is a five member ring skeleton composed of three carbon and two nitrogen atoms. Pyrazole ring is an important structural moiety found in numerous pharmaceutically active compounds. Several pharmacological activities like anti-inflammatory[1-6], analgesic[7-9], anticancer[10-12], antifungal[13], antimicrobial[14-18], antibacterial[19], antimalaria[20] and anticonvulsant[21] activities have been attributed to pyrazoles. In view of these observations and as a continuation of our efforts in synthesizing bioactive pyrazoles, it was thought worthwhile to synthesize a series of novel pyrazole derivatives and screen them for anti-inflammatory activity.

MATERIAL AND METHODS

Chemistry

The melting points of compounds were determined in open capillaries with the help of thermonic melting point apparatus and were uncorrected. The homogeneity of newly synthesized compounds was routinely checked by thin layer chromatography (TLC). Elemental analysis (C, H, N) of the synthesized compounds were determined by perkin-Elmer 2400 elemental analyzer, and results were found within the ± 0.4% of theoretical values. The IR spectra were recorded on a Beckman Acculab-10 Spectrometer (ν max in cm^{-1}) and the ^{1}HNMR spectra were recorded by Brucker DPX-300MHz using $CDCl_3$ as solvent. The animal research study was approved by the animal ethical committee (CPCSEA). The synthesis of the target compounds was accomplished according to the reaction sequence illustrated in Scheme 1.

Pharmacological study

Preliminary study at the entire three tested dose (25, 50, 100 mg/kg) were compared with standard drug, phenyl butazone. These compounds were administered either by oral or intraperitoneal route. Rats of either sex weighing 60-130 were divided into groups of 6 animals each. A freshly prepared suspension of carrageenan (1.0% in 0.9% saline) 0.05 ml, was injected under the planter aponeurosis of right paw of the rat by the method of Winter et al.[22] One group was kept as control and the animals of other group were pretreated with the test drugs given orally 1 h before the carrageenan injection. The volume of foot was measured before one and 3 h after carrageenan treatment with the help of a Plethysmometer. The mean increase of paw volume in each group was measured and percentage anti-inflammatory activity was calculated according to the formula given below-

Percentage of inhibition of oedema = $(1-V_t/V_c) \times 100$

RESULT AND DISCUSSION

All the newly synthesized compounds 2a-j were tested in vivo in order to evaluate their anti inflammatory activity.

Table 1: Anti–inflammatory activity data of compounds 2a-j.

Compound No.	Dose (mg/kg p.o.)	Anti-inflammatory activity % oedema inhibition relative to control.
2a	50	18.5
2b	50	23.9
2c	50	26.5
2d	50	30.3
2e	50	24.6
2f	50	25.3
2g	50	29.4
2h	50	28.6
2i	50	30.2
2j	25 50 100	16.3 37.1 66.4
Phenylbutazone	25 50 100	17.6 36.3 65.6

These compounds were screened for their anti-inflammatory activities at a dose of 50 mg/kg p.o. exhibited substantive anti-inflammatory activity of varying degree from 18.5-36.3 are given in table-1. The characteristic feature of this series is substituted phenyl moiety at fifth position of pyrazole nucleus. It was observed that compound 2j showed maximum anti-inflammatory 36.3% inhibition of oedema. This compound showed better anti-inflammatory activities than standard drug phenyl butazone at the three graded doses of 25, 50 and 100 mg/kg p.o.

Preparation of (E)-Chalcone (1a)

A mixture of acetophenone (0.1 mol) and aromatic aldehyde (0.1 mol) was dissolved in ethanol (40 ml) and sodium hydroxide solution (20 ml and 40%) was added to make it alkaline. The reaction mixture was stirred for 8 hr at room temperature. The solid obtained was filtered, washed with ethanol, dried and recrystallized from ethanol.

Yield 73% (ethanol); m.p. 135^{0}C. IR (KBr ν_{max} in cm^{-1}): 1560 (C=C), 1610 (C-C of aromatic ring), 1689 (C=O); ^{1}HNMR ($CDCl_3$ + DMSO-d_6)δ in ppm: 6.55 (d, 1H, CO-CH=), 6.82 (d, 1H, =CH-Ar), 7.51-8.51 (m, 10H, Ar-H); Anal. Calcd. for $C_{15}H_{12}N_3O$: C, 86.51; H, 5.81; Found: C, 86.55; H, 5.84%.

The following compounds (1b-j) were prepared using a similar procedure described for compound 1a. The physical and spectral data of compounds (1b-j) are giving below.

(E)-3-(2-chlorophenyl)-1-phenylprop-2-en-1-one (1b)

Yield 72% (methanol); m.p. 148^{0}C. IR (KBr ν_{max} in cm^{-1}): 762 (C-Cl), 1562 (C=C), 1611 (C-C of aromatic ring), 1680 (C=O); ^{1}HNMR ($CDCl_3$ + DMSO-d_6)δ in ppm: 6.52 (d, 1H, CO-CH=), 6.84 (d, 1H, =CH-Ar), 7.52-8.53 (m, 9H, Ar-H); Anal. Calcd. for $C_{15}H_{11}ClO$: C, 74.23; H, 4.57; Found: C, 74.25; H, 4.54%.

(E)-3-(4-chlorophenyl)-1-phenylprop-2-en-1-one (1c)

Yield 70% (ethanol); m.p. 152^{0}C. IR (KBr ν_{max} in cm^{-1}): 766 (C-Cl), 1568 (C=C), 1610 (C-C of aromatic ring), 1687 (C=O); ^{1}HNMR ($CDCl_3$ + DMSO-d_6)δ in ppm: 6.54 (d, 1H, CO-CH=), 6.87 (d, 1H, =CH-Ar), 7.50-8.52 (m, 9H, Ar-H); Anal. Calcd. for $C_{15}H_{11}ClO$: C, 74.23; H, 4.57; Found: C, 74.21; H, 4.55%.

(E)-3-(2,6-dichlorophenyl)-1-phenylprop-2-en-1-one (1d)

Yield 69% (methanol); m.p. 165^{0}C. IR (KBr ν_{max} in cm^{-1}): 762 (C-Cl), 1563 (C=C), 1614 (C-C of aromatic ring), 1688 (C=O); ^{1}HNMR ($CDCl_3$ + DMSO-d_6)δ in ppm: 6.50 (d, 1H, CO-CH=), 6.85 (d, 1H, =CH-Ar), 7.52-8.51 (m, 8H, Ar-H); Anal. Calcd. for $C_{15}H_{10}Cl_2O$: C, 65.01; H, 3.64; Found: C, 65.03; H, 3.65%.

(E)-3-(2-bromophenyl)-1-phenylprop-2-en-1-one (1e)

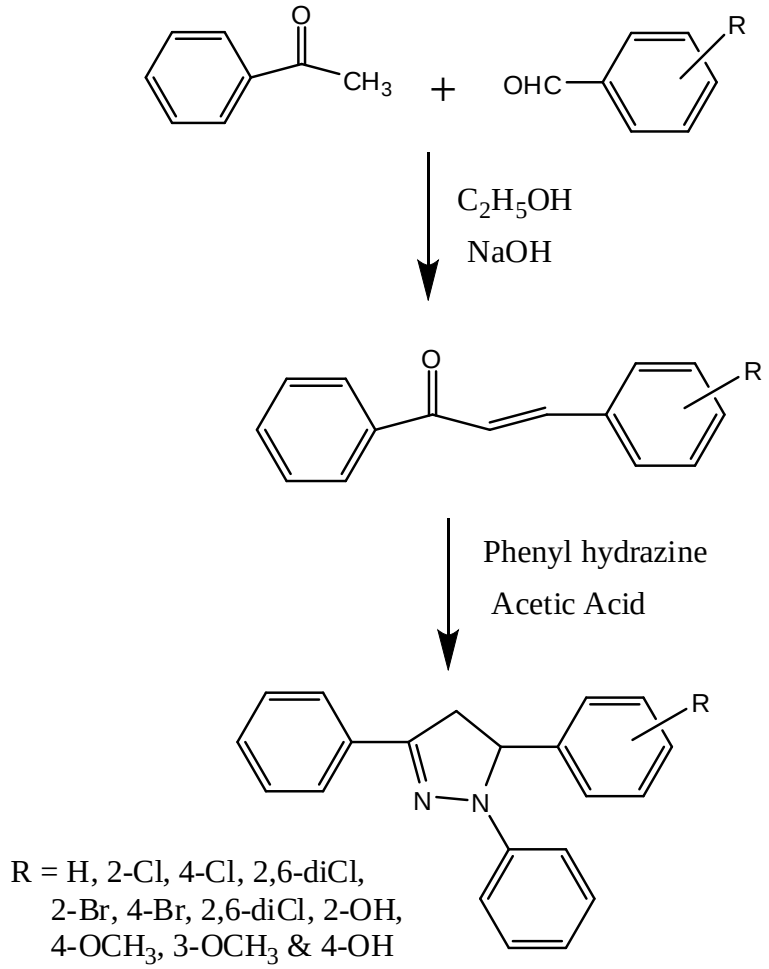
Yield 67% (acetone); m.p. 146^{0}C. IR (KBr ν_{max} in cm^{-1}): 613 (C-Br), 1565 (C=C), 1613 (C-C of aromatic ring), 1685 (C=O); ^{1}HNMR ($CDCl_3$ + DMSO-d_6)δ in ppm: 6.57 (d, 1H, CO-CH=), 6.89 (d, 1H, =CH-Ar), 7.50-8.52 (m, 9H, Ar-H); Anal. Calcd. for $C_{15}H_{11}BrO$: C, 62.74; H, 3.86; Found: C, 62.76; H, 3.84%.

(E)-3-(4-bromophenyl)-1-phenylprop-2-en-1-one (1f)

Yield 65% (ethanol); m.p. 155^{0}C. IR (KBr ν_{max} in cm^{-1}): 614 (C-Br), 1561 (C=C), 1616 (C-C of aromatic ring), 1682 (C=O); ^{1}HNMR ($CDCl_3$ + DMSO-d_6)δ in ppm: 6.57 (d, 1H, CO-CH=), 6.86 (d, 1H, =CH-Ar), 7.52-8.50 (m, 9H, Ar-H); Anal. Calcd. for $C_{15}H_{11}BrO$: C, 62.74; H, 3.86; Found: C, 62.77; H, 3.85%.

(E)-3-(2,6-dibromophenyl)-1-phenylprop-2-en-1-one (1g)
Yield 68% (methanol); m.p. 176^{0}C. IR (KBr ν_{max} in cm^{-1}): 610 (C-Br), 1565 (C=C), 1619 (C-C of aromatic ring), 1687 (C=O); ^{1}HNMR ($CDCl_3$ + DMSO-d_6)δ in ppm: 6.53 (d, 1H, CO-CH=), 6.82 (d, 1H, =CH-Ar), 7.52-8.51 (m, 8H, Ar-H); Anal. Calcd. for $C_{15}H_{10}Br_2O$: C, 49.22; H, 2.75; Found: C, 49.24; H, 2.74%.

(E)-3-(2-hydroxyphenyl)-1-phenylprop-2-en-1-one (1h)
Yield 64% (methanol); m.p. 159^{0}C. IR (KBr ν_{max} in cm^{-1}): 1563 (C=C), 1613 (C-C of aromatic ring), 1680 (C=O), 3420 (OH); ^{1}HNMR ($CDCl_3$ + DMSO-d_6)δ in ppm: 6.54 (d, 1H, CO-CH=), 6.89 (d, 1H, =CH-Ar), 7.51-8.53 (m, 9H, Ar-H), 12.15 (s, 1H, OH exchangeable with D_2O); Anal. Calcd. for $C_{15}H_{12}O_2$: C, 80.34; H, 5.39; Found: C, 80.36; H, 5.37%.



Scheme - 1

1(a-j)
2(a-j)

(E)-3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one (1i)
Yield 62% (ethanol); m.p. 164^{0}C. IR (KBr ν_{max} in cm^{-1}): 1567 (C=C), 1610 (C-C of aromatic ring), 1683 (C=O); ^{1}HNMR ($CDCl_3$ + DMSO-d_6)δ in ppm: 4.42 (s, 3H, OCH_3), 6.58 (d, 1H, CO-CH=), 6.85 (d, 1H, =CH-Ar), 7.52-8.52 (m, 9H, Ar-H); Anal. Calcd. for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92; Found: C, 80.67; H, 9.54%.

(E)-3-(4-hydroxy-3-methoxyphenyl)-1-phenylprop-2-en-1-one (1j)
Yield 62% (acetone); m.p. 173^{0}C. IR (KBr ν_{max} in cm^{-1}): 1569 (C=C), 1615 (C-C of aromatic ring), 1685 (C=O), 3420 (OH); ^{1}HNMR ($CDCl_3$ + DMSO-d_6)δ in ppm: 4.48 (s, 3H, OCH_3), 6.52 (d, 1H, CO-CH=), 6.89 (d, 1H, =CH-Ar), 7.52-8.53 (m, 8H, Ar-H) 12.10 (s, 1H, OH exchangeable with D_2O); Anal. Calcd. for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55; Found: C, 75.54; H, 5.53%.

Preparation of 1,3,5-triphenyl-4,5-dihydro-1H-pyrazole (2a)

A mixture of compound 1a (0.1 mol), phenyl hydrazine (0.5 mol) and acetic acid (40 ml) was refluxed for 3hr. Then poured into ice cold water. The precipitate was separated by filtration, washed free of acid to offered 2-pyrazolines, dried and recrystallized from ethanol.

Yield 60% (ethanol); m.p. 190^{0}C. IR (KBr ν_{max} in cm^{-1}): 1284 (N-N), 1530 (C=N), 1561 (C=C), 1616 (C-C of aromatic ring); ^{1}HNMR ($CDCl_3$ + DMSO-d_6)δ in ppm : 3.62 (s, 2H, CH_2 of pyrazole 6.50 (t, 1H, CH-Ar), 7.52-8.51 (m, 15H, Ar-H),; Anal. Calcd. for $C_{21}H_{18}N_2$: C, 84.53; H, 6.08; N, 9.39; Found: C, 84.55; H, 6.04; N, 9.37%.

The following compounds (2b-j) were prepared using a similar procedure described for compound 2a. The physical and spectral data of compounds (2b-j) are giving below.

5-(2-chlorophenyl)-1,3,diphenyl-4,5-dihydro-1H-pyrazole (2b)

Yield 61% (methanol); m.p. 195^{0}C. IR (KBr ν_{max} in cm^{-1}): 763 (C-Cl), 1288 (N-N), 1532 (C=N), 1567 (C=C), 1619 (C-C of aromatic ring),; ^{1}HNMR ($CDCl_3$ + DMSO-d_6)δ in ppm: 3.68 (s, 2H, CH_2 of pyrazole 6.57 (t, 1H, CH-Ar), 7.50-8.50 (m, 14H, Ar-H); Anal. Calcd. for $C_{21}H_{17}ClN_2$: C, 75.78; H, 5.15; N, 8.42; Found: C, 75.75; H, 5.14; N, 8.45%.

5-(4-chlorophenyl)-1,3,diphenyl-4,5-dihydro-1H-pyrazole (2c)

Yield 58% (ethanol); m.p. 198^{0}C. IR (KBr ν_{max} in cm^{-1}): 766 (C-Cl), 1287 (N-N), 1534 (C=N), 1569 (C=C), 1619 (C-C of aromatic ring),; ^{1}HNMR ($CDCl_3$ + DMSO-d_6)δ in ppm: 3.65 (s, 2H, CH_2 of pyrazole 6.53 (t, 1H, CH-Ar), 7.51-8.52 (m, 14H, Ar-H); Anal. Calcd. for $C_{21}H_{17}ClN_2$: C, 75.78; H, 5.15; N, 8.42; Found: C, 75.76; H, 5.12; N, 8.44%.

5-(2,6-dichlorophenyl)-1,3,diphenyl-4,5-dihydro-1H-pyrazole (2d)

Yield 57% (acetone); m.p. 215^{0}C. IR (KBr ν_{max} in cm^{-1}): 761 (C-Cl), 1282 (N-N), 1538 (C=N), 1562 (C=C), 1610 (C-C of aromatic ring),; ^{1}HNMR ($CDCl_3$ + DMSO-d_6)δ in ppm: 3.67 (s, 2H, CH_2 of pyrazole 6.56 (t, 1H, CH-Ar), 7.53-8.53 (m, 13H, Ar-H); Anal. Calcd. for $C_{21}H_{16}Cl_2N_2$: C, 68.68; H, 4.39; N, 7.68; Found: C, 68.65; H, 4.36; N, 7.65%.

5-(2-bromophenyl)-1,3,diphenyl-4,5-dihydro-1H-pyrazole (2e)

Yield 54% (methanol); m.p. 196^{0}C. IR (KBr ν_{max} in cm^{-1}): 615 (C-Br), 1283 (N-N), 1532 (C=N), 1568 (C=C), 1615 (C-C of aromatic ring),; ^{1}HNMR ($CDCl_3$ + DMSO-d_6)δ in ppm: 3.65 (s, 2H, CH_2 of pyrazole 6.51 (t, 1H, CH-Ar), 7.53-8.51 (m, 14H, Ar-H); Anal. Calcd. for $C_{21}H_{17}BrN_2$: C, 66.85; H, 4.54; N, 7.43; Found: C, 66.82; H, 4.56; N, 7.45%.

5-(4-bromophenyl)-1,3,diphenyl-4,5-dihydro-1H-pyrazole (2f)

Yield 52% (ethanol); m.p. 207^{0}C. IR (KBr ν_{max} in cm^{-1}): 619 (C-Br), 1289 (N-N), 1536 (C=N), 1560 (C=C), 1617 (C-C of aromatic ring),; ^{1}HNMR ($CDCl_3$ + DMSO-d_6)δ in ppm: 3.60 (s, 2H, CH_2 of pyrazole 6.54 (t, 1H, CH-Ar), 7.53-8.51 (m, 14H, Ar-H); Anal. Calcd. for $C_{21}H_{17}BrN_2$: C, 66.85; H, 4.54; N, 7.43; Found: C, 66.81; H, 4.55; N, 7.43%.

5-(2,6-dibromophenyl)-1,3,diphenyl-4,5-dihydro-1H-pyrazole (2g)

Yield 50% (methanol); m.p. 218^{0}C. IR (KBr ν_{max} in cm^{-1}): 612 (C-Br), 1289 (N-N), 1534 (C=N), 1560 (C=C), 1617 (C-C of aromatic ring),; ^{1}HNMR ($CDCl_3$ + DMSO-d_6)δ in ppm: 3.62 (s, 2H, CH_2 of pyrazole 6.56 (t, 1H, CH-Ar), 7.52-8.52 (m, 13H, Ar-H); Anal. Calcd. for $C_{21}H_{16}Br_2N_2$: C, 55.29; H, 3.54; N, 6.14; Found: C, 55.27; H, 3.56; N, 6.15%.

2(-1,3,diphenyl-4,5-dihydro-1H-pyrazol-5-yl)phenol (2h)

Yield 48% (acetone); m.p. 220^{0}C. IR (KBr ν_{max} in cm^{-1}): 1280 (N-N), 1536 (C=N), 1568 (C=C), 1611 (C-C of aromatic ring), 3420 (OH); ^{1}HNMR ($CDCl_3$ + DMSO-d_6)δ in ppm: 3.67 (s, 2H, CH_2 of pyrazole 6.53 (t, 1H, CH-Ar), 7.51-8.50 (m, 14H, Ar-H), 12.12 (s, 1H, OH exchangeable with D_2O); Anal. Calcd. for $C_{21}H_{18}N_2O$: C, 80.23; H, 5.77; N, 8.91; Found: C, 80.22; H, 5.75; N, 8.93%.

5-(4-methoxyphenyl)-1,3,diphenyl-4,5-dihydro-1H-pyrazole (2i)

Yield 46% (ethanol); m.p. 225^{0}C. IR (KBr ν_{max} in cm^{-1}): 1284 (N-N), 1530 (C=N), 1563 (C=C), 1610 (C-C of aromatic ring),; ^{1}HNMR ($CDCl_3$ + DMSO-d_6)δ in ppm: 3.63 (s, 2H, CH_2 of pyrazole), 4.43 (s, 3H, OCH_3), 6.57 (t, 1H, CH-Ar), 7.52-8.53 (m, 14H, Ar-H); Anal. Calcd. for $C_{22}H_{20}N_2O$: C, 80.46; H, 6.14; N, 8.53; Found: C, 80.42; H, 6.16; N, 8.55%.

4-(1,3,diphenyl-4,5-dihydro-1H-pyrazol-5-yl)-2-methoxyphenol (2j)

Yield 43% (methanol); m.p. 135^{0}C. IR (KBr ν_{max} in cm^{-1}): 1287 (N-N), 1534 (C=N), 1565 (C=C), 1613 (C-C of aromatic ring), 3421 (OH); ^{1}HNMR ($CDCl_3$ + DMSO-d_6)δ in ppm: 3.65 (s, 2H, CH_2 of pyrazole), 4.49 (s, 3H, OCH_3), 6.54 (t, 1H, CH-Ar), 7.50-8.52 (m, 13H, Ar-H), 12.10 (s, 1H, OH exchangeable with D_2O); Anal. Calcd. for $C_{22}H_{20}N_2O_2$: C, 76.72; H, 5.85; N, 8.13; Found: C, 76.74; H, 5.87; N, 8.15%.

CONCLUSION

A new series of pyrazole derivatives were synthesized and characterized by elemental analysis and spectral analysis. The synthesized compounds were screened for their in vivo anti-inflammatory activity. Some of the synthesized compounds i.e. 2d, 2g, 2i and 2j exhibited significant anti-inflammatory activity.

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