
Research Article



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**DESIGN, SYNTHESIS AND PHARMACOLOGICAL EVALUATION OF
NOVEL PYRIMIDINES AND PYRAZOLINES OF NEW CHALCONES***¹Jyothi M V, ²Rajendra Prasad Y, ³Venkatesh P, ⁴Subas Chandra Dinda¹Raghavendra Institute of Pharmaceutical Education and Research, K.R.Palli cross, Anantapur,
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Abstract

Inflammation is defined as a localized protective reaction of tissue to irritation, injury, or infection, characterized by pain, redness, swelling, and sometimes loss of function. Several drug molecules with heterocyclic moieties were reported as anti-inflammatory drugs. Chalcones either natural or synthetic and their heterocyclics are known to exhibit various biological activities. Pyrimidines are the parent substances of a large group of heterocyclic compounds and play a vital role in many biological processes and possess various therapeutic activities. The pyrazoline nucleus is a ubiquitous feature of various therapeutically active compounds. Some of the novel molecules with pyrimidine or pyrazoline moiety were reported to possess anti-inflammatory activity. In the present study an attempt is made to synthesize novel pyrimidines and novel pyrazolines from chalcones which provide an easy route of synthesis. All these compounds were characterized by means of their IR, ¹H NMR, ¹³C NMR, and mass spectral data. These compounds were evaluated for antiinflammatory activity by carrageenan induced rat paw oedema model.

Keywords: Chalcone, Pyrimidine, Pyrazoline, Inflammation, Carrageenan induced rat paw oedema model.

Introduction

The reaction of 3-acetylpyridine with different aromatic aldehydes was performed (2_{a-p}) to form chalcones (3_{a-p}) in the presence of alkali following claisen-schmidt condensation. The resulting chalcones have been successfully converted into novel pyrimidines (4_{a-f}) by reaction with guanidine hydrochloride and

novel pyrazolines (5_{a-j}) by reaction of chalcones with phenyl hydrazine hydrochloride in absolute ethanol. All these compounds were characterized by means of their IR, ¹H NMR, ¹³C NMR, and mass spectral data. The compounds were tested for anti-inflammatory activity by carrageenan induced rat paw oedema model^[1].

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^{2]} employing Zeitlin's apparatus to measure the paw thickness.

Materials and Methods

Melting points were determined on a capillary melting point apparatus and are uncorrected. ¹H NMR and ¹³C NMR spectra were recorded in the indicated solvent on Bruker AMX 400 MHz spectrophotometer using TMS as an internal standard. Infrared spectra were recorded in KBr on Perkin-Elmer BXF1 spectrophotometer. Microanalyses were performed on Carlo Erba 1108 element analyzer and were within the $\pm 0.5\%$ of the theoretical values. Column chromatography was performed on silica gel (Merck, 100-200 mesh).

All the materials used in this experiment are of analytical grade. Carrageenan was procured from Hi-media. Sodium CMC (E. Merck), Saline (Core Health Care) were purchased from the local supplier. Aceclofenac sample was the gift sample from Jagsonpal, New Delhi.

Preparation of sodium CMC suspension

Stock suspension of sodium CMC was prepared by triturating 1g of sodium- CMC in 100 mL of distilled water and used for suspending the test compounds and standard drug.

Preparation of carrageenan suspension

1 % suspension of carrageenan sodium salt was prepared by sprinkling 100 mg of carrageenan powder in 10 mL of saline (0.9 % NaCl) solution and set aside to soak for 1 hr. A homogenous suspension was then obtained by thorough mixing with a magnetic stirrer.

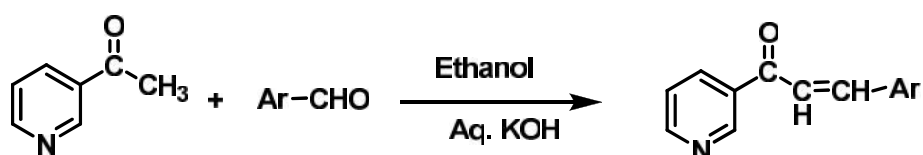
Ethical approval

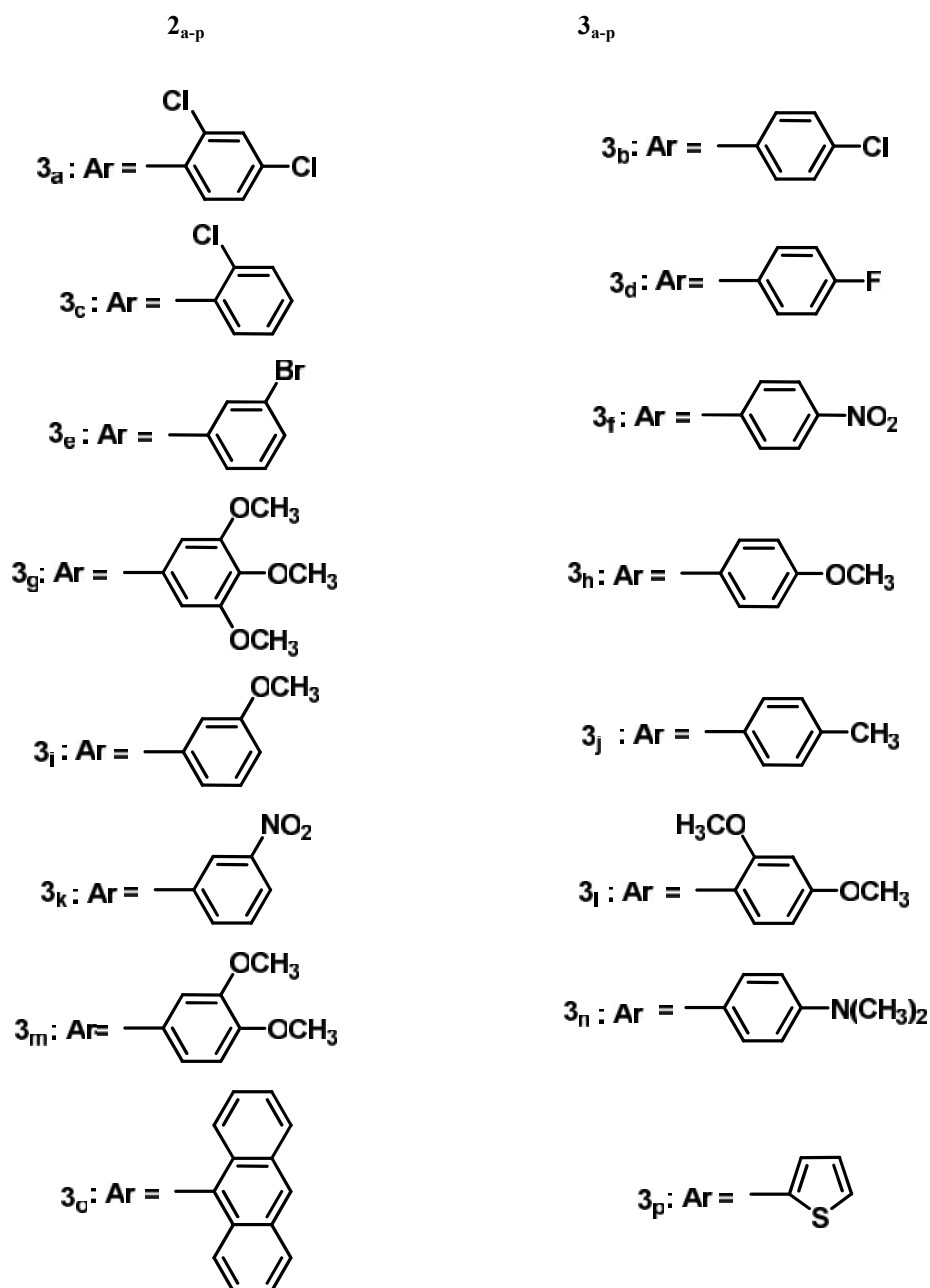
The Institutional Animal Ethics Committee (878/ac/05/CPCSEA/023/2011) has approved the experimental protocol at Department of pharmacology, Raghavendra Institute of Pharmaceutical Education and Research, Anantapur, Andhra Pradesh, India.

General procedure for the synthesis of chalcones:

Equimolar quantity (0.001mol) of 3-acetylpyridine and respective aldehydes were mixed and dissolved in minimum amount of alcohol. To this, 40 % aqueous potassium hydroxide solution (15 ml) was added slowly and mixed occasionally for 24 hrs, at room temperature. Completion of the reaction was identified by TLC using Silica gel-G. After completion of the reaction, the reaction mixture was poured into crushed ice, if necessary acidified with dil.HCl. The solid separated was filtered and dried. It was purified by column chromatography on silica gel (100-200 #, Merck), using ethylacetate and hexane mixture (1:1) as mobile phase to get the desired novel substituted chalcones ^[3-5].

Reaction





1-(3'-pyridyl)-3-(2'',4''-dichlorophenyl)-2-propen-1-one (3_a):

Yield 82%; mp 155 °C; Relative molecular mass 277; IR (KBr) 1673 (C=O), 1607 (HC = CH), 1584 (C = N), 1096 (C - Cl); ¹H-NMR 7.47 (1H, d, J=17 Hz, =CH-Ar), 7.2 (1H, d, J=17 Hz, -CO-CH=), 7.57 - 8.76 (7H, Ar-H). Anal. calcd for C₁₄H₉Cl₂NO: C, 60.64; H, 3.25; N, 5.05. Found: C, 60.62; H, 3.23; N, 5.06.

1-(3'-pyridyl)-3-(4''-chlorophenyl)-2-propen-1-one (3_b):

Yield 82%; mp 167 °C; Relative molecular mass 243; IR (KBr) 1672 (C = O), 1610 (HC = CH), 1596 (C = N), 1090 (C - Cl); ¹H-NMR 7.41 (1H, d, J=17 Hz, -CO-CH=), 7.70 (1H, d, J=17 Hz, =CH- Ar), 7.1 - 8.7 (8H, Ar-H). Anal. calcd for C₁₄H₁₀ClNO: C, 69.13; H, 4.11; N, 5.76. Found: C, 69.12; H, 4.13; N, 5.74.

1-(3'-pyridyl)-3-(2''-chlorophenyl)-2-propen-1-one (3_c):

Yield 78%; mp 96 °C; Relative molecular mass 244; IR (KBr) 1690 (C=O), 1626 (CH=CH), 1580 (C=N), 1086 (C-Cl); ¹H-NMR 7.26 (1H, d, J=17 Hz, -CO-CH=), 7.42 (1H, d, J=17 Hz, =CH- Ar), 7.49– 8.74 (8H, Ar-H). Anal.calcd for C₁₄ H₁₀ ClNO: C, 69.13; H, 4.10; N, 5.76. Found: C, 69.10; H, 4.09; N, 5.77.

1-(3'-pyridyl)-3-(4''-fluorophenyl)-2-propen-1-one (3_d):

Yield 90%; mp 90 °C; Relative molecular mass 226; IR (KBr) 1680 (C=O), 1610 (CH=CH), 1584 (C=N), 1110 (C-F); ¹H-NMR 7.26 (1H, d, J=17 Hz, -CO-CH=), 7.47 (1H, d, J=17 Hz, =CH - Ar), 7.08 – 8.74 (8H, Ar-H). Anal.calcd for C₁₄ H₁₀ FNO: C, 74.33; H, 4.42; N, 6.19. Found: C, 74.30; H, 4.40; N, 6.17.

1-(3'-pyridyl)-3-(3''-bromophenyl)-2-propen-1-one (3_e):

Yield 92%; mp 140 °C; Relative molecular mass 288; IR (KBr) 1680 (C=O), 1610 (HC=CH), 1580 (C=N), 1170 (C-Br); ¹H-NMR 6.67 (1H, d, J=17 Hz, -CO-CH=), 7.3 (1H, d, J=17 Hz, =CH-Ar), 6.99 – 8.76 (8H, Ar-H). Anal.calcd for C₁₄ H₁₀ BrNO: C, 58.33; H, 3.47; N, 4.86. Found: C, 58.34; H, 3.48; N, 4.84.

1-(3'-pyridyl)-3-(4''-nitrophenyl)-2-propen-1-one (3_f):

Yield 86%; mp 156 °C; Relative molecular mass 254; IR (KBr) 1690 (C=O), 1618 (CH=CH), 1596 (C=N), 1520 (N=O, asymmetric), 1340 (N=O, symmetric); ¹H-NMR 7.20 (1H, d, J=17 Hz, -CO-CH=), 7.45 (1H, d, J=17 Hz, =CH -Ar), 7.4 -8.53 (8H, Ar-H). Anal.calcd for C₁₄H₁₀N₂O₃: C, 66.56; H, 3.93; N, 11.02. Found: C, 64.54; H, 3.92; N, 11.00.

1-(3'-pyridyl)-3-(3'', 4'', 5''-trimethoxyphenyl)-2-propen-1-one (3_g):

Yield 78%; mp 115 °C; Relative molecular mass 299; IR (KBr) 1690 (C=O), 1610 (HC=CH), 1585 (C=N), 1210 (C-O-C); ¹H-NMR 3.95 (9H, 3xOCH₃), 7.20 (1H, d, J=17 Hz, -CO-CH=), 7.26 (1H, d, J=17 Hz, =CH-Ar) 7.20 – 7.28 (6H, Ar-H). Anal.calcd for C₁₇H₁₇N O₄: C, 68.22; H, 5.68; N, 4.68. Found: C, 68.20; H, 5.66; N, 4.67.

1-(3'-pyridyl)-3-(4''-methoxyphenyl)-2-propen-1-one (3_h):

Yield 80%; mp 126 °C; Relative molecular mass 239; IR (KBr) 1684 (C=O), 1626 (CH=CH), 1596 (C=N), 1165 (-OCH₃); ¹H-NMR 3.86 (3H, s, -OCH₃), 6.96 (1H, d, J=17 Hz, -CO-CH=), 7.26 (1H, d, J=17 Hz, =CH - Ar), 6.95-8.75 (8H, Ar-H). Anal.calcd for C₁₅H₁₃NO₂: C, 75.31; H, 5.43; N, 5.85. Found: C, 75.29; H, 5.41; N, 5.83.

1-(3'-pyridyl)-3-(3''-methoxyphenyl)-2-propen-1-one (3_i):

Yield 82%; mp 60 °C; Relative molecular mass 239; IR (KBr) 1680 (C=O), 1625 (CH=CH), 1586 (C=N), 1190 (C-O-C); ¹H-NMR 3.87 (3H, s, C-4'', OCH₃), 6.98 (1H, d, J=17 Hz, -CO-CH=), 7.94 (1H, d, J=17 Hz, Ar-CH=), 6.94 – 9.04 (8H, Ar-H). Anal.calcd for C₁₅H₁₃NO₂: C, 75.31; H, 5.43; N, 5.85. Found: C, 75.29; H, 5.41; N, 5.86.

1-(3'-pyridyl)-3-(4''-methylphenyl)-2-propen-1-one (3_j):

Yield 87%; mp 98 °C; Relative molecular mass 223; IR (KBr) 1690 (C=O), 1610 (CH=CH), 1590 (C=N); ¹H-NMR 7.2 (1H, d, J=17 Hz, -CO-CH=), 7.46 (1H, d, J=17 Hz, =CH- Ar), 7.2 – 8.75 (8H, Ar-H), 2.45 (3H, s, C-4''-CH₃). Anal.calcd for C₁₅H₁₃NO: C, 88.33; H, 6.10; N, 5.57. Found: C, 88.30; H, 6.08; N, 5.55.

80.71; H, 5.82; N, 6.27. Found: C, 80.70; H, 5.81; N, 6.25.

1-(3'-pyridyl)-3-(3''-nitrophenyl)-2-propen-1-one (3_k):

Yield 87%; mp 178 °C; Relative molecular mass 254; IR (KBr) 1690 (C=O), 1610 (CH=CH), 1590 (C=N); ¹H-NMR 7.50 (1H, d, J=17 Hz, -CO-CH=), 7.86 (1H, d, J=17 Hz, =CH-Ar), 7.65 – 9.20 (8H, Ar-H). Anal.calcd for C₁₄H₁₀N₂O₃: C, 64.56; H, 3.94; N, 11.02. Found: C, 64.57; H, 3.95; N, 11.04.

1-(3'-pyridyl)-3-(2'', 4''-dimethoxyphenyl)-2-propen-1-one (3_j):

Yield 86%; mp 156 °C; Relative molecular mass 269; IR (KBr) 1690 (C=O), 1618 (CH=CH), 1596 (C=N); ¹H-NMR 3.90 (6H, s, 2 x OCH₃), 7.50 (1H, d, J=17 Hz, -CO-CH=), 8.07 (1H, d, J=17 Hz, =CH-Ar), 6.50 -9.20 (8H, Ar-H). Anal.calcd for C₁₆H₁₅NO₃: C, 71.37; H, 5.57; N, 5.20. Found: C, 71.39; H, 5.55; N, 5.19.

1-(3'-pyridyl)-3-(3'', 4''-dimethoxyphenyl)-2-propen-1-one (3_m):

Yield 75%; mp 138 °C; Relative molecular mass 269; IR (KBr) 1684 (C=O), 1610 (CH=CH), 1590 (C=N), 1210 (C-O-C); ¹H-NMR 3.90 (6H, s, 2xOCH₃), 7.01 (1H, d, J=17 Hz, -CO-CH=), 7.38 (1H, d, J=17 Hz, Ar-CH=), 6.85 – 8.7 (7H, Ar-H). Anal.calcd for C₁₆H₁₅N O₃: C, 71.34; H, 5.57; N, 6.28. Found: C, 71.40; H, 5.59; N, 6.26.

1-(3'-pyridyl)-3-(4''-N, N-

dimethylaminophenyl)-2-propen-1-one (3_n):

Yield 95%; mp 144 °C; Relative molecular mass 252; IR (KBr) 1696 (C=O), 1620 (-CH=CH), 1180 (-N-(CH₃)₂), 1586 (C=N); ¹H-

NMR 3.05 (6H, s, N Me₂), 6.69 (1H, d, J=17 Hz, -CO-CH=), 7.10 (1H, d, J=17 Hz, =CH-Ar), 7.25 -8.73 (8H, Ar-H). Anal.calcd for C₁₆H₁₆N₂O: C, 76.19; H, 6.34; N, 11.11. Found: C, 76.17; H, 6.32; N, 11.10.

1-(3'-pyridyl)-3-(9''-anthracenyl)-2-propen-1-one (3_o):

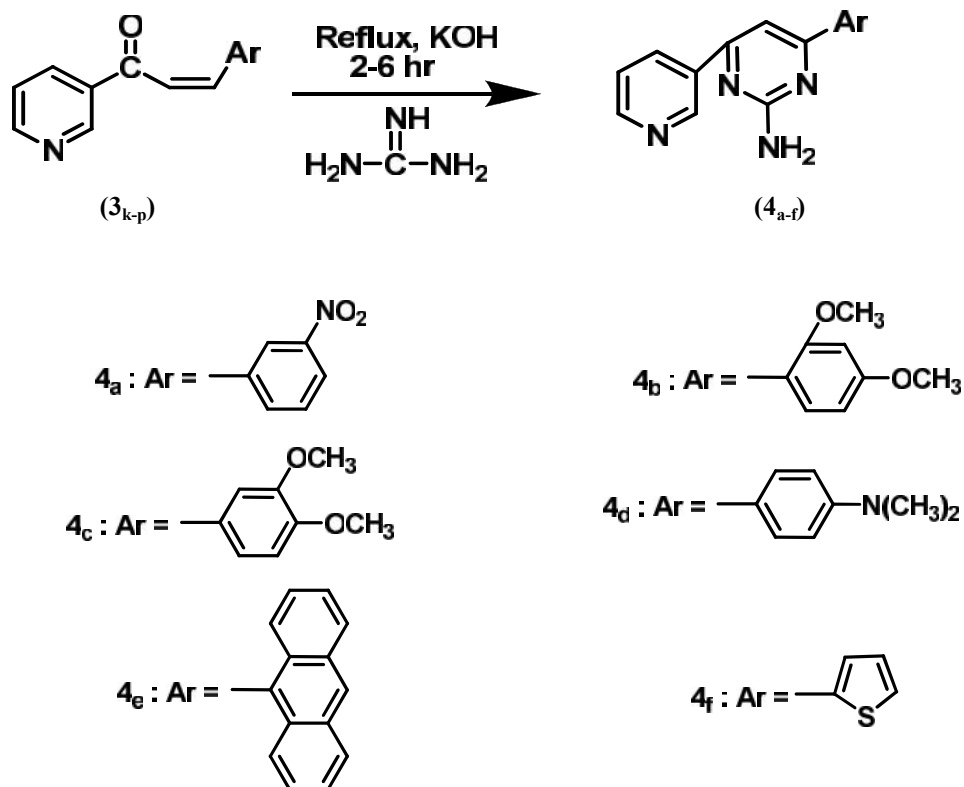
Yield 95%; mp 78 °C; Relative molecular mass 309; IR (KBr) 1695 (C=O), 1610 (CH=CH), 1528 (C=C), 1592 (C=N); ¹H-NMR 7.46 (1H, d, J=17 Hz, =CH-Ar), 7.24 (1H, d, J=17 Hz, -CO-CH=), 7.2 - 8.94 (13H, Ar-H). Anal.calcd for C₂₂H₁₅NO: C, 85.43; H, 4.85; N, 4.53. Found: C, 85.41; H, 4.83; N, 4.52.

1-(3'-pyridyl)-3-(2''-thienyl)-2-propen-1-one (3_p):

Yield 96%; mp 162 °C; Relative molecular mass 215; IR (KBr) 1696 (C=O), 1620 (CH=CH), 650 (C-S), 1590 (C=N); ¹H-NMR 7.07 (1H, d, J=17 Hz, -CO-CH=), 7.39 (1H, d, =CH-Ar), 7.20-8.73 (7H, Ar-H). Anal.calcd for C₁₂H₉NOS: C, 66.97; H, 4.18; N, 6.51. Found: C, 66.94; H, 4.15; N, 6.50.

General procedure for the synthesis of pyrimidines:

A mixture of chalcones (obtained by the above method) of 3-acetylpyridine (0.001 mol) and guanidine hydrochloride (0.001 mol) in absolute ethanol (10 ml) were refluxed on a water bath for 6 hours. The solvent was completely evaporated and the residue was poured into ice cold water, the precipitated solid was collected by filtration and crystallized from a suitable solvent to give the desired substituted pyrimidines [6-9].



2-amino-4-(3'-pyridyl)-6-(3''-nitrophenyl) pyrimidine (4_a):

Yield 72%; mp 265-269 °C; Relative molecular mass 293; IR (KBr) 3342 (NH₂), 1642 (C=N), 1586 (C=C), 1358 (C-N); ¹H-NMR 7.20 (1H, s, C-5-H), 5.52 (2H, s, C-2-NH₂), 7.40-8.70 (8H, Ar-H). Anal.calcd for C₁₅H₁₁N₅O₂: C, 61.43; H, 3.75; N, 23.89. Found: C, 61.45; H, 3.79; N, 23.91.

2-amino-4-(3'-pyridyl)-6-(2'', 4''-dimethoxyphenyl) pyrimidine (4_b):

Yield 65%; mp 238-242 °C; Relative molecular mass 308; IR (KBr) 3316 (NH₂), 1680 (C=N), 1570 (C=C), 1340 (C-N), 1210 (C-O-C); ¹H-NMR 7.36 (1H, s, C-5-H), 5.52 (2H, s, C-2-NH₂), 7.26-8.60 (7H, Ar-H). Anal.calcd for C₁₇H₁₆N₄O₂: C, 65.59; H, 5.14; N, 18.00. Found: C, 65.60; H, 5.13; N, 18.01.

2-amino-4-(3'-pyridyl)-6-(3'',4''-dimethoxyphenyl) pyrimidine (4_c):

Yield 75%; mp 285-289 °C; Relative molecular mass 311; IR (KBr) 3340 (NH₂), 1632 (C=N), 1579 (C=C), 1356 (C-N), 1208 (C-O-C); ¹H-NMR 7.30 (1H, s, C-5-H), 5.58 (2H, s, C-2-NH₂), 3.95 (6H, 2 x OCH₃), 6.90 – 8.69 (7H, Ar-H). Anal.calcd for C₁₇H₁₆N₄O₂: C, 65.59; H, 5.14; N, 18.00. Found: C, 65.57; H, 5.12; N, 18.02.

2-amino-4-(3'-pyridyl)-6-(4''-dimethylaminophenyl) pyrimidine (4_d):

Yield 72%; mp 265-269 °C; Relative molecular mass 266; IR (KBr) 3342 (NH₂), 1642 (C=N), 1586 (C=C), 1358 (C-N), 1108 (-N-(CH₃)₂); ¹H-NMR 7.30 (1H, s, C-5-H), 5.30 (2H, s, C-2-NH₂), 3.10 (6H, -N-(CH₃)₂) -6.80–9.10 (8H, Ar-H). Anal.calcd for C₁₇H₁₇N₅: C,

70.10; H, 5.84; N, 24.05. Found: C, 70.06; H, 5.82; N, 24.02.

2-amino-4-(3'-pyridyl)-6-(9''-anthracenyl) pyrimidine (4_e):

Yield 75%; mp 295-299 °C; Relative molecular mass 348; IR (KBr) 3340 (NH₂), 1640 (C=N), 1580 (C=C), 1358 (C-N); ¹H-NMR 7.30 (1H, s, C-5-H), 5.60 (2H, s, C-2-NH₂), 7.10-8.75 (13H, Ar-H). Anal.calcd for C₂₃H₁₆N₄: C, 79.31; H, 4.59; N, 16.09. Found: C, 79.28; H, 4.56; N, 16.10.

2-amino-4-(3'-pyridyl)-6-(2''-thienyl) pyrimidine (4_f):

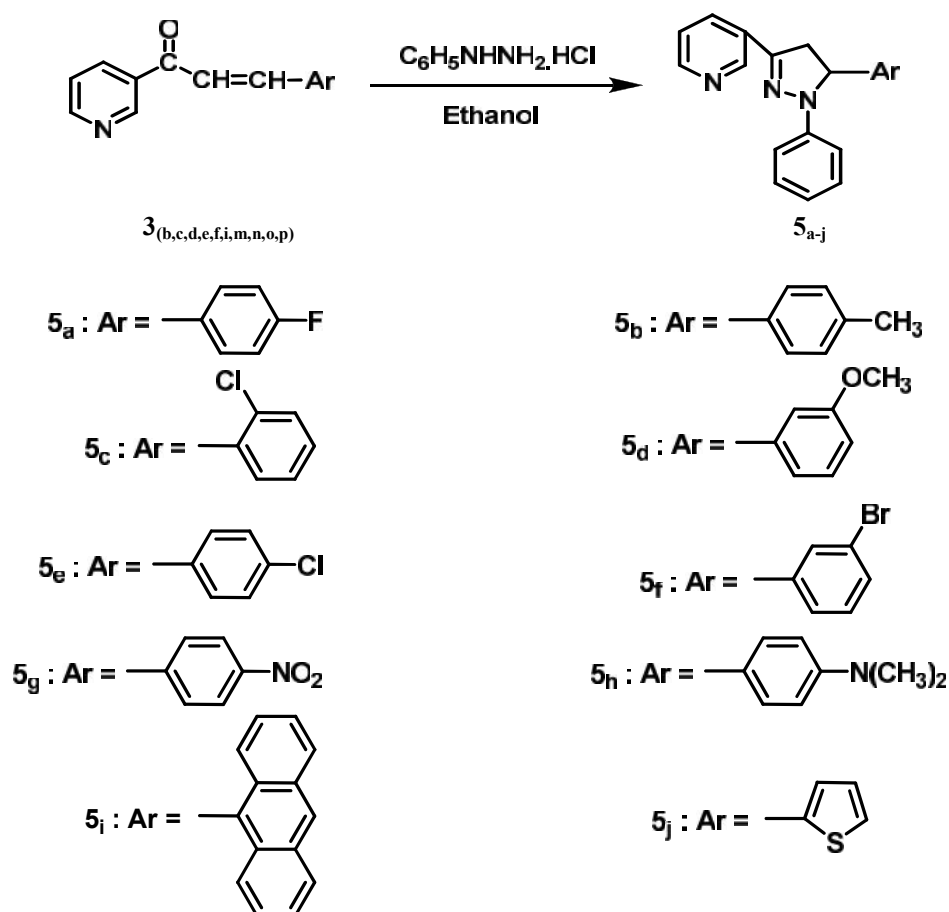
Yield 62%; mp 208-212 °C; Relative molecular mass 254; IR (KBr) 3308 (NH₂), 1632 (C=N), 1579 (C=C), 1358 (C-N), ¹H-NMR 7.20 (1H, s, C-5-H), 5.30 (2H, s, C-2-NH₂), 7.10 – 8.80 (7H, Ar-H). Anal.calcd for

C₁₃H₁₀SN₄: C, 61.41; H, 3.93; N, 22.04. Found: C, 61.38; H, 3.90; N, 22.01.

General procedure for the synthesis of pyrazolines:

Chalcone was (0.001 mol) dissolved in absolute ethanol (20 ml) and phenyl hydrazine hydrochloride (0.001 mol) was added to it. After that the mixture was refluxed for 5-6 hr and the solvent was evaporated completely. The reaction mixture was poured into ice-cold water and the solid mass that separated out was filtered, dried and purified by column chromatography with ethyl acetate/hexane and recrystallized from chloroform to give the desired substituted pyrazolines [10-14].

Reaction



1-phenyl-3-(3'-pyridyl)-5-(4''-fluorophenyl)-2-pyrazoline (5_a):

Yield 85%; mp 142 °C; Relative molecular mass 317; IR (KBr) 1598 (C=N), 1323 (C-N), 1072 (C-F); ¹H-NMR 3.32 (1H, dd, H_A), 3.99 (1H, dd, H_B), 5.33 (1H, dd, H_X), 6.81 – 8.13 (13H, J_{AB}=17.72, J_{AX}=7.80, J_{BX}=10.8, Ar-H). Anal.calcd for C₂₀H₁₆N₃F: C, 79.94; H, 5.06; N, 13.29. Found: C, 75.92; H, 5.04; N, 13.26.

1-phenyl-3-(3'-pyridyl)-5-(4''-methylphenyl)-2-pyrazoline (5_b):

Yield 90%; mp 121 °C; Relative molecular mass 313; IR (KBr) 1565 (C=N), 1325 (C-N); ¹H-NMR 2.29 (3H, s, Ar-CH₃), 3.32 (1H, dd, H_A), 3.97 (1H, dd, H_B), 5.31 (1H, dd, H_X), 6.77 – 8.51 (13H, J_{AB}=17.6, J_{AX}=7.85, J_{BX}=10.8, Ar-H). Anal.calcd for C₂₁H₁₉N₃: C, 80.51; H, 6.07; N, 13.41. Found: C, 80.49; H, 6.06; N, 13.39.

1-phenyl-3-(3'-pyridyl)-5-(2''-chlorophenyl)-2-pyrazoline (5_c):

Yield 72%; mp 98 °C; Relative molecular mass 334; IR (KBr) 1592 (C=N), 1350 (C-N), 1040 (C-Cl); ¹H-NMR 3.25 (1H, dd, H_A), 4.09 (1H, dd, H_B), 5.71 (1H, dd, H_X), 7.19 – 8.51 (13H, J_{AB}=17.20, J_{AX}=7.30, J_{BX}=10.15, Ar-H). Anal.calcd for C₂₀H₁₆ClN₃: C, 71.85; H, 4.79; N, 12.58. Found: C, 71.89; H, 4.81; N, 12.60.

1-phenyl-3-(3'-pyridyl)-5-(3''-methoxyphenyl)-2-pyrazoline (5_d):

Yield 68%; mp 61 °C; Relative molecular mass 329; IR (KBr) 1586 (C=N), 1329 (C-N); ¹H-NMR 3.74(3H, s, Ar-OCH₃), 3.34 (1H, dd, H_A), 4.00 (1H, dd, H_B), 5.31 (1H, dd, H_X), 6.76-8.53(13H, J_{AB}=17.10, J_{AX}=7.6, J_{BX}=9.8, Ar-H). Anal.calcd for C₂₁H₁₉N₃O: C, 76.59; H, 5.77; N, 12.76. Found: C, 76.62; H, 5.76; N, 12.73.

1-phenyl-3-(3'-pyridyl)-5-(4''-chlorophenyl)-2-pyrazoline (5_e):

Yield 93%; mp 85 °C; Relative molecular mass 334; IR (KBr) 1590 (C=N), 1328 (C-N); ¹H-NMR 3.32 (1H, dd, H_A), 3.99 (1H, dd, H_B), 5.33 (1H, dd, H_X), 6.81-8.53 (13H, J_{AB}=17.41, J_{AX}=7.89, J_{BX}=10.22, Ar-H). Anal.calcd for C₂₀H₁₆ClN₃: C, 71.85; H, 4.79; N, 12.57. Found: C, 71.83; H, 4.77; N, 12.55.

1-phenyl-3-(3'-pyridyl)-5-(3''-bromophenyl)-2-pyrazoline (5_f):

Yield 93%; mp 124 °C; Relative molecular mass 378; IR (KBr) 1578 (C=N), 1320 (C-N); ¹H-NMR 3.39 (1H, dd, H_A), 4.10 (1H, dd, H_B), 5.42 (1H, dd, H_X), 7.19-8.52 (13H, J_{AB}=17.41, J_{AX}=7.89, J_{BX}=10.22, Ar-H). Anal.calcd for C₂₀H₁₆BrN₃: C, 63.49; H, 4.23; N, 11.11. Found: C, 63.45; H, 4.21; N, 11.13.

1-phenyl-3-(3'-pyridyl)-5-(4''-nitrophenyl)-2-pyrazoline (5_g):

Yield 83%; mp 203 °C; Relative molecular mass 344; IR (KBr) 1598 (C=N), 1540 (N=O, asymmetric), 1335(N=O, symmetric), 1310 (C-N); ¹H-NMR 3.07 (1H, dd, H_A), 3.92 (1H, dd, H_B), 5.48 (1H, dd, H_X), 7.26-8.79 (13H, J_{AB}=17.41, J_{AX}=7.89, J_{BX}=10.22, Ar-H). Anal.calcd for C₂₀H₁₆N₄O₂: C, 69.76; H, 4.65; N, 16.27. Found: C, 69.79; H, 4.62; N, 16.25.

1-phenyl-3-(3'-pyridyl)-5-(4''-dimethylaminophenyl)-2-pyrazoline (5_h):

Yield 82%; mp 129 °C; Relative molecular mass 342; IR (KBr) 1590 (C=N), 1350 (C-N), 1181(N(CH₃)₂); ¹H-NMR 2.89 (6H, s, N(Me)₂), 3.32 (1H, dd, H_A), 3.95 (1H, dd, H_B), 5.28 (1H, dd, H_X), 6.65 – 7.64 (13H, J_{AB}=17.20, J_{AX}=7.40, J_{BX}=10.15, Ar-H). Anal.calcd for C₂₂H₂₂N₄: C, 77.19; H, 6.43; N, 16.37. Found: C, 77.17; H, 6.44; N, 16.35.

1-phenyl-3-(3'-pyridyl)-5-(9''-anthracenyl)-2-pyrazoline (5_i):

Yield 95%; mp 204 °C; Relative molecular mass 399; IR (KBr) 1590 (C=N), 1330 (C-N); ¹H-NMR 3.70 (1H, dd, H_A), 4.22 (1H, dd, H_B), 6.64 (1H, dd, H_X), 6.96-8.56 (18H, J_{AB} =17.10, J_{AX} =7.9, J_{BX} =10.32, Ar-H). Anal.calcd for C₂₈H₂₁N₃: C, 83.20; H, 5.26; N, 10.52. Found: C, 83.23; H, 5.27; N, 10.55.

1-phenyl-3-(3'-pyridyl)-5-(2''-thienyl)-2-pyrazoline (5_j):

Yield 93%; mp 194 °C; Relative molecular mass 305; IR (KBr) 1596 (C=N), 1342 (C-N), 647 (C-S); ¹H-NMR 3.49 (1H, dd, H_A), 3.97 (1H, dd, H_B), 5.60 (1H, dd, H_X), 6.82-8.53 (12H, J_{AB} =17.41, J_{AX} =7.89, J_{BX} =10.22, Ar-H). Anal.calcd for C₁₈ H₁₅S N₃: C, 70.81; H, 4.91; N, 13.77. Found: C, 70.83; H, 4.88; N, 13.73.

Experimental procedure

1. Acute toxicity^[15]:

Healthy and adult male albino swiss mice weighing between 20-25g were used in this investigation. Animals were fasted for 24 hours and divided into groups of five animals each for all categories of compounds. The test compounds suspended in sodium carboxy methyl cellulose solution (1 %) were administered intraperitoneally in doses of 100 mg to 1000 mg per kg body weight. The control group of animals received only the vehicle (1 % sodium CMC).

The animals were observed for 48 hours from the time of administration of test compounds to record the mortality.

2. Anti-inflammatory activity:

Albino rats (M/S Ghosh Enterprises, Calcutta, West Bengal, India) of either sex, weighing

between 200-250 gm were used in the experiment. They were divided into groups of six animals each. 18 groups for chalcones, 8 groups for pyrimidines and 12 groups for pyrazolines were used. All groups were fasted for overnight and allowed following treatment to water *ad libitum*.

Inflammation was induced by injecting 0.05 mL of 1 % carrageenan suspension subcutaneously into the sub plantar region of the right hind paw and 0.05 mL of saline was injected into the subplantar region of the left hind paw for all groups. One hour prior to carrageenan injection, the groups III to XVIII were treated with novel chalcones, the groups III to VIII with novel pyrimidines (10 mg/kg)^[16-18] and groups III to XII treated with novel pyrazolines (10 mg/kg)^[19-20]. 1 % sodium CMC gel (1 mL/kg), was given to group-I used as carrageenan treated control and the standard drug aceclofenac (2 mg/kg) was administered to group-II. All the doses were administered orally. Anti-inflammatory activity was evaluated by measuring carrageenan induced paw oedema^[21].

Measurement of paw thickness

The thickness of the both paws of each rat was measured before carrageenan injection and after carrageenan injection at time intervals 0.5, 1, 2, 3, 4 and 6 hours using Zeitlin's constant load lever method^[22-23] consisting of a graduated micrometer combined with a constant loaded lever system to magnify the small changes in paw thickness during the course of the experiment. The percent increase of paw oedema thickness^[24] was determined at 0.5, 1, 2, 3, 4 and 6 hrs after induction of inflammation.

Percentage increase in paw thickness

$$= \frac{Y_t - Y_0}{Y_0} \times 100$$

Where,

Y_t = paw thickness at the time 't' hours (After injection)

Y_0 = paw thickness at the time '0' hours (Before injection)

The percent inhibition of paw oedema thickness is calculated using the formula,

$$\text{Percentage inhibition} = \left[1 - \frac{Y_t}{Y_c} \right] \times 100$$

Where,

Y_t = Average increase in paw thickness in groups tested with test compounds

Y_c = Average increase in paw thickness in control

The results and statistical analysis of anti-inflammatory activity of aceclofenac and the compounds tested are shown in Tables 1, 2 and 3.

Results and Discussion

In acute toxicity studies, all the novel chalcones, novel pyrimidines and novel pyrazolines employed in the pharmacological screening have been found to be free from toxicity as well as toxic symptoms even at a high dose of 1000 mg/kg (b.w), intraperitoneally. The anti-inflammatory activity all the compounds has been evaluated

by carrageenan-induced rat paw oedema method, using aceclofenac as standard. Among the compounds tested for anti-inflammatory activity, the order of potency for chalcones at 6th hr is; $3_a > 3_c > 3_d > 3_b > 3_k > 3_e > 3_f > 3_h > 3_i > 3_m > 3_l > 3_j > 3_n > 3_g > 3_o > 3_p$, for pyrimidines at 6th hr is; $4_a > 4_c > 4_b > 4_f > 4_e > 4_d$ and for pyrazolines at 6th hr is; $5_g > 5_b > 5_i > 5_e > 5_j > 5_h > 5_d > 5_a > 5_c > 5_f$ and the results are comparable to that produced by the standard drug aceclofenac, but not at an identical dose level since the compounds were tested at 10 mg/kg, where as the drug tested at 2 mg/kg body weight. All these chalcones, pyrimidines and pyrazolines showed considerable anti-inflammatory activity even at 3rd and 4th hr. All the chalcones, pyrimidines and pyrazolines synthesized and tested in the present study possessed some degree of anti-inflammatory activity and were free from toxicity.

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Table No. 01: Anti-inflammatory activity of novel chalcones

Compound	Percent inhibition \pm SEM at various time intervals					
	0.5 h	1.0 h	2.0 h	3.0 h	4.0 h	6.0 h
3_a	20.20 \pm 2.34*	23.50 \pm 2.82*	57.90 \pm 2.75*	67.53 \pm 1.82	97.00 \pm 1.95	99.95 \pm 1.76
3_b	18.08 \pm 0.78*	23.05 \pm 0.99*	55.57 \pm 1.65*	64.97 \pm 1.66*	95.38 \pm 2.01	98.54 \pm 1.99
3_c	17.15 \pm 0.65	22.56 \pm 1.12*	54.23 \pm 1.36*	63.93 \pm 1.67	94.75 \pm 2.32	98.40 \pm 2.32
3_d	19.10 \pm 0.75*	23.07 \pm 0.89	57.47 \pm 1.45*	66.91 \pm 1.33*	96.84 \pm 1.88	98.80 \pm 2.53
3_e	16.88 \pm 2.82*	22.40 \pm 2.86*	54.11 \pm 1.34	62.62 \pm 1.80	94.30 \pm 1.85	97.22 \pm 1.47
3_f	16.93 \pm 3.92**	23.62 \pm 3.92**	55.72 \pm 2.92*	64.42 \pm 3.75**	95.57 \pm 1.82	98.38 \pm 1.92
3_g	13.49 \pm 3.85*	20.40 \pm 1.64**	50.98 \pm 4.73*	60.52 \pm 2.73	88.69 \pm 1.60	89.36 \pm 1.72
3_h	16.50 \pm 0.91	22.64 \pm 1.01	53.94 \pm 1.53	63.11 \pm 1.25	93.65 \pm 1.98	96.05 \pm 2.22
3_i	16.30 \pm 3.75**	22.86 \pm 4.32*	52.98 \pm 2.62*	62.37 \pm 3.75	92.32 \pm 1.82	94.27 \pm 1.87
3_j	12.57 \pm 0.34	20.22 \pm 2.75*	50.31 \pm 1.43	61.67 \pm 1.62	88.55 \pm 1.82	89.12 \pm 1.72
3_k	16.88 \pm 0.77*	23.47 \pm 0.92*	55.14 \pm 1.35	64.45 \pm 1.81*	94.10 \pm 2.95	97.65 \pm 3.25
3_l	15.26 \pm 4.47*	21.49 \pm 3.34**	53.09 \pm 1.48**	62.70 \pm 2.44*	91.58 \pm 1.48	94.01 \pm 1.98
3_m	15.57 \pm 0.34	21.64 \pm 2.75*	53.31 \pm 1.43	61.67 \pm 1.62	91.69 \pm 1.82	94.12 \pm 1.72
3_n	11.49 \pm 3.85*	21.39 \pm 1.64**	51.95 \pm 4.73*	60.48 \pm 2.73	88.22 \pm 1.60	89.54 \pm 1.72
3_o	10.56 \pm 0.92	20.43 \pm 0.99	50.12 \pm 1.52*	60.34 \pm 1.67	86.94 \pm 1.85	88.35 \pm 1.84
3_p	10.09 \pm 0.53	20.11 \pm 0.65	51.01 \pm 1.54	60.42 \pm 2.73	80.02 \pm 1.82	87.40 \pm 1.76
Aceclofenac	20.26 \pm 0.90	23.95 \pm 0.97	58.00 \pm 1.52	67.93 \pm 1.68	97.09 \pm 1.97	99.98 \pm 2.00

All values are represented as mean \pm SEM (n=6). *P<0.01 compared to reference standard aceclofenac. Student's t-test. Dosage : Aceclofenac-2 mg/kg and test compounds-10 mg/kg body weight of rat.

Table No. 02: Anti-inflammatory activity of novel pyrimidines

Compound	Percent inhibition \pm SEM at various time intervals					
	0.5 h	1.0 h	2.0 h	3.0 h	4.0 h	6.0 h
4 _a	19.87 \pm 0.82	33.09 \pm 1.21	59.85 \pm 1.92	76.82 \pm 2.26	91.26 \pm 2.35*	94.61 \pm 2.22
4 _b	17.50 \pm 0.62*	21.11 \pm 1.35	53.57 \pm 1.68	61.10 \pm 2.02	82.44 \pm 2.45*	89.04 \pm 2.66
4 _c	17.32 \pm 0.62*	21.32 \pm 1.35	54.57 \pm 1.68	62.14 \pm 2.02	83.47 \pm 2.45*	89.05 \pm 2.68
4 _d	16.23 \pm 0.86*	43.41 \pm 1.92*	61.77 \pm 1.97	70.79 \pm 2.42	83.53 \pm 2.62*	86.47 \pm 2.71
4 _e	20.99 \pm 0.93*	35.84 \pm 1.21	55.78 \pm 1.76	70.74 \pm 2.33	85.12 \pm 2.24*	87.92 \pm 2.81
4 _f	20.33 \pm 0.91	52.13 \pm 1.58	71.97 \pm 2.41	72.97 \pm 2.48	83.96 \pm 2.52*	87.97 \pm 2.89
Acceclofenac	20.26 \pm 0.90	23.95 \pm 0.97	58.02 \pm 1.87	67.93 \pm 2.22	97.09 \pm 2.86	98.78 \pm 2.92

All values are represented as mean \pm SEM (n=6). *P<0.01 compared to reference standard aceclofenac. Student's t-test.

Dosage : Aceclofenac-2 mg/kg and test compounds-10 mg/kg body weight of rat.

Table No. 03: Anti-inflammatory activity of novel pyrazolines

Compound	Percent inhibition \pm SEM at various time intervals					
	0.5 h	1.0 h	2.0 h	3.0 h	4.0 h	6.0 h
5 _a	15.23 \pm 0.90	21.33 \pm 1.04*	53.54 \pm 1.75	60.62 \pm 2.53	92.54 \pm 2.62	94.43 \pm 2.73
5 _b	15.22 \pm 0.68*	20.45 \pm 1.23*	56.94 \pm 1.79	62.51 \pm 2.33	87.23 \pm 2.61*	88.39 \pm 2.65
5 _c	20.01 \pm 0.89	20.56 \pm 1.21	57.22 \pm 1.79	60.52 \pm 2.21	83.46 \pm 2.54*	87.75 \pm 2.61
5 _d	17.32 \pm 0.62*	21.32 \pm 1.35	54.57 \pm 1.68	62.14 \pm 2.02	83.47 \pm 2.45*	89.05 \pm 2.68
5 _e	20.14 \pm 0.92	20.57 \pm 1.47	57.24 \pm 1.92	60.25 \pm 2.35*	82.82 \pm 2.69*	93.13 \pm 2.78
5 _f	20.06 \pm 0.92	23.05 \pm 1.49	55.42 \pm 1.80	77.79 \pm 2.42	83.50 \pm 2.51*	87.73 \pm 2.68
5 _g	19.87 \pm 0.82	33.09 \pm 1.21	59.85 \pm 1.92	76.82 \pm 2.26	91.26 \pm 2.35*	94.61 \pm 2.22
5 _h	18.26 \pm 0.68	19.35 \pm 1.41*	53.32 \pm 2.01	62.13 \pm 2.25	86.99 \pm 2.62*	92.11 \pm 2.75
5 _i	20.38 \pm 0.91	20.49 \pm 1.23*	54.23 \pm 1.82	60.12 \pm 2.12	85.60 \pm 2.55*	93.32 \pm 2.75
5 _j	20.13 \pm 1.25	22.03 \pm 1.45	51.20 \pm 1.87	59.02 \pm 2.01*	92.13 \pm 2.62	92.87 \pm 2.76
Acceclofenac	19.26 \pm 0.90	22.95 \pm 0.97	58.02 \pm 1.87	66.93 \pm 2.22	97.09 \pm 2.86	98.78 \pm 2.92

All values are represented as mean \pm sem (n=6).

*P<0.01 compared to reference standard aceclofenac. Student's t-test.

Dosage : Aceclofenac-2 mg/kg and test compounds-10 mg/kg body weight of rat.

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