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***Research Article***



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**DESIGN, SYNTHESIS AND PHARMACOLOGICAL EVALUATION OF NOVEL PYRIMIDINES AND PYRAZOLINES OF NEW CHALCONES**

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

novel pyrazolines (5a-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 Ebra 1108 element analyzer and were within the ± 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



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**2a-p 3a-p**



















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

Yield 82%; mp 155o 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 C14 H9Cl2NO: 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 (3b):

Yield 82%; mp 167 OC; 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 C14 H10 ClNO: C, 69.13; H, 4.11; N, 5.76. Found: C, 69.12; H, 4.13; N,

5.74.





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

Yield 78%; mp 96 OC; Relative molecular mass 244; IR (KBr) 1690 (C=O), 1626

(CH=CH), 1580 (C=N), 1086 (C-Cl); 1H-NMR

### 1-(3'-pyridyl)-3-(3'', 4'', 5''-

**trimethoxyphenyl)-2-propen-1-one (3g):**

Yield 78%; mp 115 OC; Relative molecular mass 299; IR (KBr) 1690 (C = O), 1610 (HC

1

=CH), 1585 (C = N), 1210 (C- O - C); H-

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 (3d):

Yield 90%; mp 90 OC; 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 H10FNO: 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 (3e):

Yield 92%; mp 140 OC; 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 (3f):

Yield 86%; mp 156 OC; 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.

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 C17H17 N 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 (3h):

Yield 80%; mp 126 OC; Relative molecular mass 239; IR (KBr) 1684 (C=O), 1626 (CH=CH),1596 (C=N), 1165 (-OCH3); 1H-

NMR 3.86 (3H, s, -O**C**H3), 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 (3i) :

Yield 82%; mp 60 OC; 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 (3j):

Yield 87%; mp 98 OC; 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,

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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 (3k):

Yield 87%; mp 178 OC; 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 C14 H10 N2 O3: 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 (3l):

Yield 86%; mp 156 OC; 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 (3m):

Yield 75%; mp 138 OC; 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

C16 H15 N 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 (3n):

Yield 95%; mp 144 OC; 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 (3o):

Yield 95%; mp 78 OC; 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 C22 H15NO: 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 (3p):

Yield 96%; mp 162 OC; 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 C12 H9 NOS: 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].

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**(3k-p) (4a-f)**





### 2-amino-4-(3'- pyridyl)-6-(3"-nitrophenyl) pyrimidine (4a):

Yield 72%; mp 265-269 0C; 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 (4b):

Yield 65%; mp 238-242 0C; 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 (4c):

Yield 75%; mp 285-289 0C; 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 (4d):

Yield 72%; mp 265-269 0C; 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,

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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 (4e):

Yield 75%; mp 295-299 0C; 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 (4f):

Yield 62%; mp 208-212 0C; 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



**3(b,c,d,e,f,i,m,n,o,p) 5a-j**





    







**5i : Ar =**



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

Yield 85%; mp 142 oC; Relative molecular mass 317; IR (KBr) 1598 (C =N), 1323 (C-N),

1072 (C-F); 1H-NMR 3.32 (1H, dd, HA ), 3.99

(1H, dd, HB ), 5.33 (1H, dd, Hx), 6.81 – 8.13 (13H, JAB =17.72, JAX =7.80, JBX

=10.8, Ar-H). Anal.calcd for C20 H16N3F: 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 (5b):

Yield 90%; mp 121 oC; Relative molecular mass 313; IR (KBr) 1565 (C =N), 1325 (C-N); 1H-NMR 2.29 (3H, s, Ar-CH3), 3.32 (1H,

dd,HA ), 3.97 (1H, dd, HB ), 5.31 (1H, dd, HX

), 6.77 – 8.51 (13H, JAB =17.6, JAX =7.85, JBX

=10.8, Ar-H). Anal.calcd for C21 H19N3: 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 (5c):

Yield 72%; mp 98 oC; Relative molecular mass 334; IR (KBr) 1592 (C=N), 1350 (C-N),

1040 (C-Cl); 1H-NMR 3.25 (1H, dd, HA), 4.09

### 1-phenyl-3-(3'-pyridyl)-5- (4"- chlorophenyl)-2-pyrazoline (5e):

Yield 93%; mp 85 0C; Relative molecular mass 334; IR (KBr) 1590 (C=N), 1328 (C-N); 1H-NMR 3.32 (1H, dd, HA), 3.99 (1H, dd,HB),

5.33 (1H, dd, HX), 6.81-8.53 (13H, JAB =17.41,

JAX =7.89, JBX =10.22, Ar-H). Anal.calcd for C20 H16 Cl N3: 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 (5f):

Yield 93%; mp 124 0C; Relative molecular mass 378; IR (KBr) 1578 (C=N), 1320 (C-N); 1H-NMR 3.39 (1H, dd, HA), 4.10 (1H, dd,HB),

5.42 (1H, dd, HX), 7.19-8.52 (13H, JAB =17.41,

JAX =7.89, JBX =10.22, Ar-H). Anal.calcd for C20 H16 Br N3: 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 (5g):

Yield 83%; mp 203 0C; Relative molecular mass 344; IR (KBr) 1598 (C=N), 1540 (N=O,

asymmetric), 1335(N=O, symmetric), 1310

1

(C-N); H –NMR 3.07 (1H, dd, HA), 3.92

(1H, dd, HB), 5.71 (1H, dd, HX), 7.19 – 8.51 (13H, JAB =17.20, JAX =7.30, JBX =10.15, Ar-

(1H, dd, HB ), 5.48 (1H, dd, HX), 7.26-8.79 (13H, JAB =17.41, JAX =7.89, JBX =10.22, Ar-

H). Anal.calcd for C20H16ClN3: C, 71.85; H,

H). Anal.calcd for C20

H16N4

O2: C, 69.76; 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 (5d):

Yield 68%; mp 61 oC; Relative molecular mass 329; IR (KBr) 1586 (C=N), 1329 (C-N);

1H-NMR 3.74(3H, s, Ar-OCH3 ), 3.34 (1H, dd,

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 (5h):** Yield 82%; mp 129 oC; Relative molecular mass 342; IR (KBr) 1590 (C=N), 1350 (C-N),

1

1181(N(CH3)2); H-NMR 2.89 (6H, s, N

HA), 4.00 (1H, dd, HB), 5.31 (1H, dd, HX), 6.76-8.53(13H, JAB =17.10, JAX =7.6, JBX =9.8,

Ar-H). Anal.calcd for C21 H19N3O: C, 76.59;

H, 5.77; N, 12.76. Found: C, 76.62; H, 5.76;

(Me)2), 3.32 (1H, dd,HA ), 3.95 (1H, dd,HB), 5.28 (1H, dd, HX ), 6.65 – 7.64 (13H, JAB

=17.20, JAX =7.40, JBX =10.15, Ar-H).

Anal.calcd for C H N : C, 77.19; H, 6.43; N,

22 22 4

N, 12.73.

16.37. Found: C, 77.17; H, 6.44; N, 16.35.

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### 1-phenyl-3-(3'-pyridyl -5-(9"-anthracenyl)-2

**-pyrazoline (5i):**

Yield 95%; mp 204 oC; Relative molecular mass 399; IR (KBr) 1590 (C=N), 1330 (C-N); 1H-NMR 3.70 (1H, dd, HA), 4.22 (1H, dd, HB),

6.64 (1H, dd, HX), 6.96-8.56 (18H, JAB

=17.10, JAX =7.9, JBX =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 (5j):

Yield 93%; mp 194 0C; Relative molecular mass 305; IR (KBr) 1596 (C=N), 1342 (C-N),

647 (C-S); 1H-NMR 3.49 (1H, dd, HA), 3.97

(1H, dd, HB), 5.60 (1H, dd, HX), 6.82-8.53 (12H, JAB =17.41, JAX =7.89, JBX =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 intraperitonially 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.

### 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

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Where,

Yt  Y0

=

Y0

X 100

by carrageenan-induced rat paw oedema method, using aceclofenac as standard. Among the compounds tested for anti-inflammatory

Yt = paw thickness at the time‘t’ hours (After injection)

Yo = paw thickness at the time ‘0’ hours (Before injection)

activity, the order of potency for chalcones at 6th hr is; **3a** > **3c** > **3d** > **3b** > **3k** > **3e** > **3f** > **3h**

> **3i** > **3m** > **3l** > **3j** > **3n** > **3g** > **3o** >**3p** , for

pyrimidines at 6th hr is; **4a** > **4c** > **4b** > **4f** > **4e** > **4d**

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

and for pyrazolines at 6th hr is; **5g**

**> 5b**

**> 5i > 5e >**

Percentage inhibition =   Yt  X 100

1 Yc 

 

Where,

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

Yc = 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

**5j > 5h > 5d > 5a > 5c > 5f** 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.

## Acknowledgements

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

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

All values are represented as mean±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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### Table No. 02: Anti-inflammatory activity of novel pyrimidines

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **0.5 h** | **1.0 h** | **2.0 h** | **3.0 h** | **4.0 h** | **6.0 h** |
| **4a** | 19.87±0.82 | 33.09±1.21 | 59.85±1.92 | 76.82±2.26 | 91.26±2.35\* | 94.61±2.22 |
| **4b** | 17.50±0.62\* | 21.11±1.35 | 53.57±1.68 | 61.10±2.02 | 82.44±2.45\* | 89.04±2.66 |
| **4c** | 17.32±0.62\* | 21.32±1.35 | 54.57±1.68 | 62.14±2.02 | 83.47±2.45\* | 89.05±2.68 |
| **4d** | 16.23±0.86\* | 43.41±1.92\* | 61.77±1.97 | 70.79±2.42 | 83.53±2.62\* | 86.47±2.71 |
| **4e** | 20.99±0.93\* | 35.84±1.21 | 55.78±1.76 | 70.74±2.33 | 85.12±2.24\* | 87.92±2.81 |
| **4f**  **Aceclofen** | 20.33±0.91  **ac** 20.26±0.90 | 52.13±1.58  23.95±0.97 | 71.97±2.41  58.02±1.87 | 72.97±2.48  67.93±2.22 | 83.96±2.52\*  97.09±2.86 | 87.97±2.89  98.78±2.92 |

**Compound Percent inhibition ± SEM at various time intervals**

All values are represented as mean±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

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **0.5 h** | **1.0 h** | **2.0 h** | **3.0 h** | **4.0 h** | **6.0 h** |
| **5a** | 15.23±0.90 | 21.33±1.04\* | 53.54±1.75 | 60.62±2.53 | 92.54±2.62 | 94.43±2.73 |
| **5b** | 15.22±0.68\* | 20.45±1.23\* | 56.94±1.79 | 62.51±2.33 | 87.23±2.61\* | 88.39±2.65 |
| **5c** | 20.01±0.89 | 20.56±1.21 | 57.22±1.79 | 60.52±2.21 | 83.46±2.54\* | 87.75±2.61 |
| **5d** | 17.32±0.62\* | 21.32±1.35 | 54.57±1.68 | 62.14±2.02 | 83.47±2.45\* | 89.05±2.68 |
| **5e** | 20.14±0.92 | 20.57±1.47 | 57.24±1.92 | 60.25±2.35\* | 82.82±2.69\* | 93.13±2.78 |
| **5f** | 20.06±0.92 | 23.05±1.49 | 55.42±1.80 | 77.79±2.42 | 83.50±2.51\* | 87.73±2.68 |
| **5g** | 19.87±0.82 | 33.09±1.21 | 59.85±1.92 | 76.82±2.26 | 91.26±2.35\* | 94.61±2.22 |
| **5h** | 18.26±0.68 | 19.35±1.41\* | 53.32±2.01 | 62.13±2.25 | 86.99±2.62\* | 92.11±2.75 |
| **5i** | 20.38±0.91 | 20.49±1.23\* | 54.23±1.82 | 60.12±2.12 | 85.60±2.55\* | 93.32±2.75 |
| **5j**  **Aceclofen** | 20.13±1.25  **ac** 19.26±0.90 | 22.03±1.45  22.95±0.97 | 51.20±1.87  58.02±1.87 | 59.02±2.01\*  66.93±2.22 | 92.13±2.62  97.09±2.86 | 92.87±2.76  98.78±2.92 |

**Compound Percent inhibition ± SEM at various time intervals**

All values are represented as mean±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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